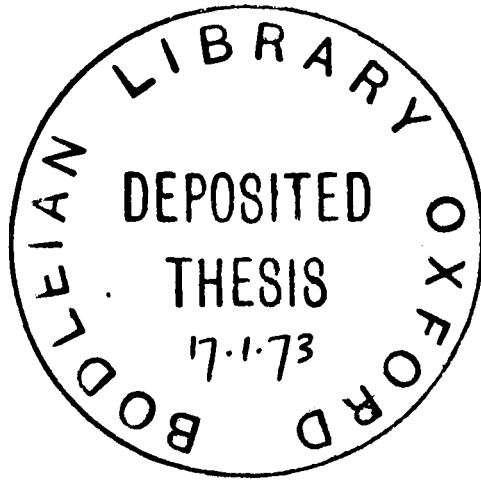


To M.



Studies of Rotational Isomerism

A

Thesis

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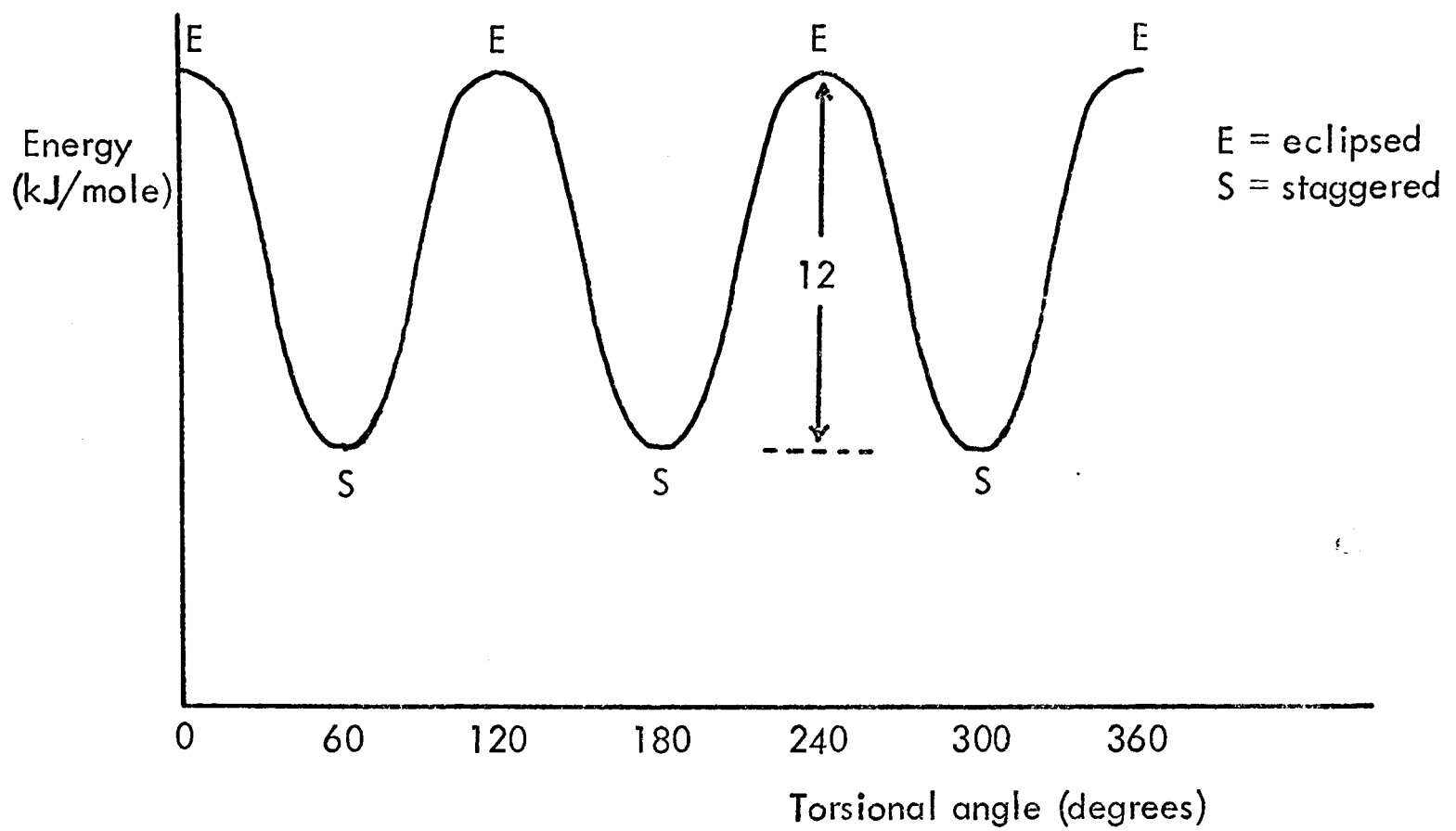
INTRODUCTION

The existence of energy barriers hindering internal rotation in molecules was proposed by Pitzer,¹ who observed that the measured thermodynamic parameters of ethane did not agree with those calculated using statistical mechanics unless a barrier to rotation about the carbon-carbon bond of some 12 kJ/mole was assumed. Figure 1 is a representation of the potential energy of an ethane molecule as a function of the torsional angle and demonstrates the existence of energy minima and maxima corresponding to "staggered" and "eclipsed" conformations, respectively.

In substituted ethanes, the staggered conformations are not all of the same energy and they are then referred to as "rotational isomers". Depending on the magnitude of the energy barriers between rotational isomers, three situations can arise:

- (i) barrier $\gg$ thermal energy; this allows the isolation of individual, kinetically stable isomers, e.g., 2,2'-dicarboxy-6,6'-dinitrobiphenyl;
- (ii) barrier $\approx$ thermal energy; there exists a dynamic equilibrium between the isomers; individual isomers cannot be isolated, e.g., 6-aryl- and 6-alkyl-phenanthridinium 5-vinyloxides;² and,
- (iii) barrier $\ll$ thermal energy; rotation is restricted only at very low temperatures: this is a widely-occurring situation for rotation about formal single bonds, e.g., furan-2-carbaldehyde, and is the basis of this investigation.

There is no simple explanation for the magnitudes of energy barriers since these depend upon the combination of several variables including repulsions between non-axial bonds, forces between non-bonded atoms, and changes in



Torsional angle	Conformation
0	
60	
120	
180	
240	
etc.	

Fig. 1

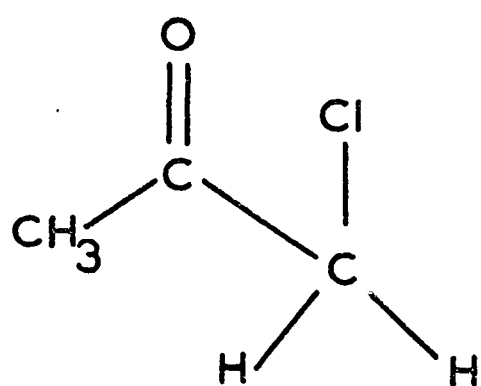
electron distribution and molecular distortion, during rotation. The theories which have been proposed to explain, and the methods which are used to measure energy barriers have been reviewed by Dale,³ Lowe,⁴ and Pethrick and Wyn-Jones.⁵

The existence of rotational isomers (or "rotamers") may have a significant effect upon the infra red (i.r.), Raman, microwave, and nuclear magnetic resonance (n.m.r.) spectra of a molecule. Thus, in molecules which are capable of existing in two rotameric forms and which contain carbonyl groups in close proximity to other polar atoms or groups (usually oxygen or halogen), the i.r. carbonyl stretching bands often appear as doublets. Arguments based upon intramolecular field effects and dipole moments are used to assign a particular doublet component band to a particular rotamer, the areas of the component bands then providing information about the relative proportions of the rotameric forms. Because the rate of isomerisation in a simple rotameric equilibrium is slow compared with the i.r. time scale, separate parameters (i.e., band areas or positions) for each rotamer can often be observed. The relative slowness of the n.m.r. time scale does not usually allow this unless a rotameric equilibrium is "frozen" by cooling to very low temperatures (-100°C or lower): at room temperature, a single time-averaged parameter "p" given by:

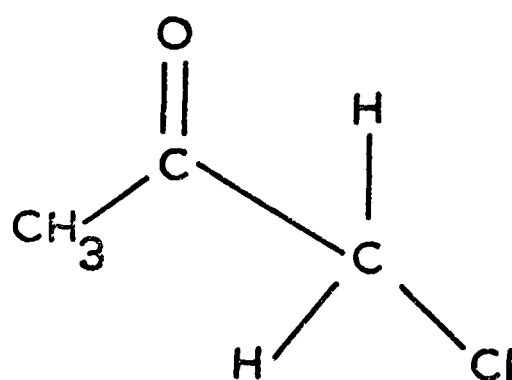
$$p = c_A p_A + c_B p_B \quad (1)$$

is usually observed, where p_A and p_B are the isomeric parameters (chemical shifts or coupling constants) and c_A and c_B are concentration fractions. In favourable cases, p_A and p_B may be measured from low-temperature spectra.

An early example^{6,7} of the use of the i.r. method is provided by chloroacetone (I), in carbon tetrachloride solution, in which the two carbonyl stretching bands may be assigned to rotamers (Ia) and (Ib).



(Ia)



(Ib)

Table 1 illustrates the widespread occurrence of band-doubling which has been ascribed to the existence of rotational isomerism.

Compound type	References
α -Haloketones	8, 17, 18, 19
α -Haloesters	8, 13, 14
α -Alkoxyesters	15
α -Hydroxyesters	11
Glycidic esters	10
α -Haloamides	8
α -Ketoethers	9
Ketoalcohols	11, 16
α -Haloacid chlorides	20

Table 1

There exists, however, a range of molecules, all of which display carbonyl band multiplicity, in which rotational isomerism either cannot, or can only in part, be the explanation for the observed multiplicity. Some examples are given in Table 2 along with possible explanations for the observed carbonyl-bands.

Compound	Explanation
Acetic acid	Dimer formation ²¹
Acetic anhydride	Coupling between carbonyl vibrations ²²
Cyclopentanone	Fermi resonance ^{23, 24}
Benzoyl chloride	Fermi resonance ²⁵
<u>p</u> -Benzoquinone	Fermi resonance ²⁵
Furan-2-carbonyl chloride	Fermi resonance and Rotational Isomerism ²¹

Table 2

Other, less common, causes of carbonyl band multiplicity include the fortuitous occurrence of hot bands, combination bands, and overtones in the carbonyl region. In a particular case, it is straightforward to distinguish band multiplicity due to dimer formation, hot bands, and coupling between carbonyl vibrations from that due to Fermi resonance and rotational isomerism, but to distinguish between the last two phenomena is much more difficult.

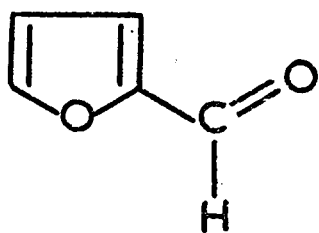
Fermi resonance²⁶ occurs when two molecular vibrations of the same symmetry type are of approximately the same energy. A mixing of eigen-functions

then occurs leading to perturbations of the energy levels and of the transition probabilities. Since the Fermi coupling coefficient depends upon the anharmonicity of the vibrations involved and upon their energies, profound solvent and temperature effects are often observed, and these may be used diagnostically. The absence of dramatic effects does not, however, imply the absence of Fermi resonance. Furthermore, it has been reported²⁷ that Fermi resonance does not occur in the carbonyl overtone region and that if a doublet in the carbonyl region remains a doublet in the first overtone region, then Fermi resonance must be absent from the fundamental vibrations. That this is not a reliable criterion is demonstrated by the work of the present author and co-workers.²⁸ The most reliable method for diagnosing Fermi resonance in a particular case involves the synthesis of functional and isotopic analogues and a comparison of their carbonyl absorptions with those of the parent compound. Because of the synthetic difficulties inherent in specific isotopic labelling, this method, though powerful, has not been widely applied: it provides the theme for much of this Thesis.

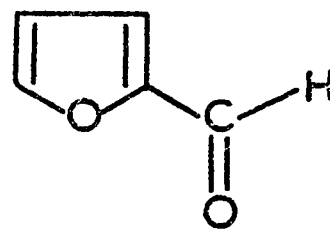
Because of the interpretational problems discussed above, widespread disagreement between different workers can develop in particular cases. This is exemplified by the 2-oxo derivatives of furan and thiophene which comprise the subject matter of much of this Thesis.

Twin i.r. bands in the carbonyl region of the furan-2-carbaldehyde spectrum were first observed by Mirone²⁹ who noted that the relative intensities of the two bands were concentration-dependent. Glusker and Thompson³⁰ observed that a linear relationship existed between the logarithm of the dielectric constant of the solvent and the ratio of the optical densities of the bands, and

that with increase in temperature the higher wavenumber component increased in intensity relative to that at lower wavenumber. The fact that the doublet collapsed in the vapour phase and that the shift to lower frequencies on passing from the vapour to the liquid was much greater than that observed for other bands, led these authors to believe that some form of intermolecular interaction existed in solution; early cryoscopic work by Getman³¹ was cited in support of this conclusion. Allen and Bernstein³² examined the i.r. and Raman spectra of furan-2-carbaldehyde in the solid, liquid, and solution phases, and noted band doubling in spectral regions other than the carbonyl; thus, they deduced that a rotameric equilibrium existed [(IIa) $\rightleftharpoons$ (IIb)]. Claverie et al.³³ re-examined



Anti (IIa)



Syn (IIb)

the cryoscopic behaviour of furan-2-carbaldehyde, in dilute carbon tetrachloride solution, and found that Raoult's law was obeyed to within the limits of experimental error; combining this with i.r. evidence based on qualitative temperature and solvent studies, these authors assigned the weaker carbonyl band at 1682 cm^{-1} to the syn rotamer (IIb). Gas-phase, microwave studies support this assignment³⁴ whereas dipole moment measurements either oppose the assignment³⁵ or are inconclusive.³⁶

Chiorboli and Drusiani³⁷ were the first workers to observe twin carbonyl bands in the thiophen-2-carbaldehyde Raman spectrum, and explained their

observations in terms of intermolecular association. Andrieu et al.³⁸ have prepared thiophen-2-deuteriocarbaldehyde and thiophen-2-carbaldehyde enriched with ^{18}O and have observed (in both compounds) alterations (but not simplifications) in the carbonyl band envelopes; although unable to rationalise completely the complexities of the carbonyl absorption in thiophen-2-carbaldehyde, they are led to the conclusion that Fermi resonance is responsible, at least in part, for the band multiplicity. Dipole moment measurements suggest that the predominant form is syn in benzene, dioxan, and carbon tetrachloride solutions, whereas gas-phase, microwave studies³⁴ oppose this assignment.

Both furan- and thiophen-2-carbaldehydes have been studied intensively by n.m.r. Below -90°C , the aldehydic proton resonance in furan-2-carbaldehyde appears as two doublets of intensity ratio 8:1 which observation, along with spin-decoupling studies, indicates that there is stereospecific long-range spin-coupling between the furan ring proton, 4-H, and the aldehydic hydrogen in one rotamer, and between the 5-H and the aldehydic hydrogen in the other rotamer. The main point of discord concerns the nature of this coupling. Thus, Dahlqvist and Forsen⁴⁰ originally considered that the main aldehydic coupling was to the 4-H in the syn rotamer and to the 5-H in the anti rotamer leading them to the conclusion that the predominant isomer in dimethyl ether solution was the anti form; later work by them⁴¹ was inconclusive and recent observations by others⁴² suggest reversed assignments. The aldehydic coupling in thiophen-2-carbaldehyde in acetone solution is virtually invariant between -80°C and $+40^{\circ}\text{C}$ and it has been proposed that although an equilibrium between rotameric forms may exist, the molecule exists almost exclusively in the syn conformation.⁴¹

The nuclear Overhauser effect (an enhancement of the absorption intensities

of certain protons on irradiation of other protons in close proximity within a molecule) has recently been used to investigate the conformations of 2-furyl methyl ketone and the 4,5-dibromo-, 4-bromo-5-deuterio-, and 4,5-dideuterio- derivatives,⁴⁴ 4-bromofuran-2-carbaldehyde, 4-bromothiophen-2-carbaldehyde, and of 2-(4,5-dibromothieryl) methyl ketone, and apparently unequivocal conformational assignments have been made; these are summarised in Table 3:

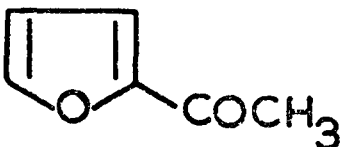
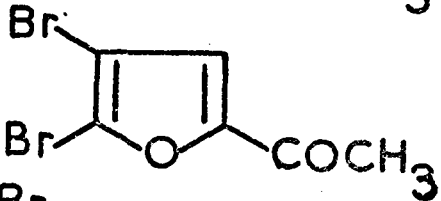
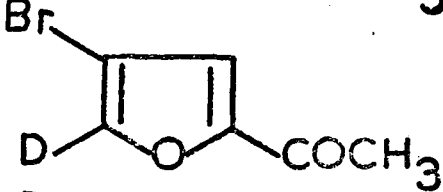
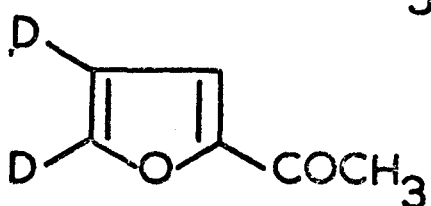
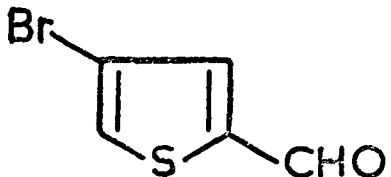
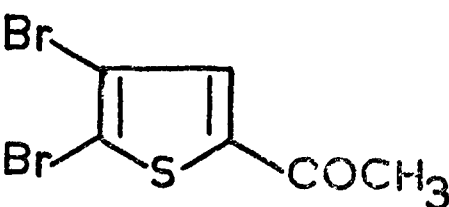
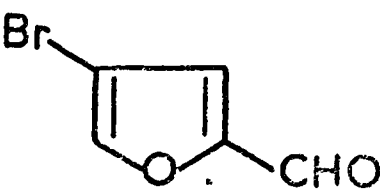
Compound	Solvent	Conclusion
		
	CD ₃ OCD ₃	At -120°C, mixture of <u>syn</u> and <u>anti</u> , with former predominating
		
		
	CDCl ₃ and T.H.F.-D ₈	At ambient temperature, single (<u>syn</u>) rotamer
		
	T.H.F.-D ₈	At -90°, mixture of <u>syn</u> and <u>anti</u> , former predominating

Table 3

Finally, X-ray crystal structure investigations of 4-bromothiophen-2-carbaldehyde, 2-(5-bromothieryl)methyl ketone, and 4-bromofuran-2-carbaldehyde⁴⁵ suggest that in the solid state these compounds exist in the syn conformation.

The aims of the present work are:

- (i) to assign to particular conformations (if possible) the twin carbonyl bands of furan-2-carbaldehyde;
- (ii) to investigate, generally, the occurrence of rotational isomerism and Fermi resonance in 2-oxo-furans and -thiophens, and thus to reconcile the results of n.m.r., i.r., and X-ray studies;
- (iii) to devise synthetic routes to specifically-deuterated furans and thiophens with a view to aim (ii);
- (iv) to investigate, in 2-oxo-furans known [from (ii)] to display rotational isomerism, the steric and electronic effects of substituents on a rotameric equilibrium;
- (v) to set up or to modify computer programs for the digital resolution of overlapping i.r. curves, to set up a digital data-logging facility, and to compare the results so-obtained with those from analogue and other methods;
- (vi) to examine the theoretical basis of the i.r. method for the determination of the energy and entropy differences between rotamers, and
- (vii) to devise computer programs for data processing based upon the results of investigations into aims (v) and (vi).

The theory of i.r. band shapes and curve resolution, and of previous workers' approaches to data processing, is described in the following section. The ways in which the aims listed above have been achieved are described in the "Experimental" and "Discussion" sections.

THEORETICAL CONSIDERATIONS

The Shapes of Infra Red Bands

The principal factors which determine the spectral line width of an i.r. band are: (i) the "natural" line width; (ii), the Doppler effect; (iii) collision broadening, and (iv) instrumental effects.⁴⁶

The natural line width arises from the energy spread of the upper and lower energy states involved in a vibrational transition; it is therefore a consequence of the Heisenberg uncertainty principle. Broadening by this mechanism is extremely small ($< 10^{-6} \text{ cm}^{-1}$) and can be neglected in the present work.

Doppler broadening arises from the thermal motion of the molecules and, because of the Maxwellian velocity distribution, produces a Gaussian band profile. Broadening by this mechanism is small ($< 10^{-3} \text{ cm}^{-1}$) and, although observable in vapour phase spectra, it is relatively unimportant for condensed state systems.

Collision broadening, the principal factor influencing the shapes of i.r. bands of liquids, results from the perturbation of the energy levels of the absorbing molecules caused by the close approach of other molecules. In the original treatment, Lorentz⁴⁷ assumed that a molecule absorbs at a discrete frequency, that radiation stops abruptly on collision, the energy becoming wholly kinetic, and that the effect of the collision is to destroy all previous orientation: the time intervals between collisions were considered to be large compared with the duration of collision. Lorentz also assumed that after

collision the molecules were randomly oriented with respect to the radiation field, but Van Vleck and Weisskopf⁴⁸ have suggested that the molecules would tend to retain a low-energy orientation with respect to the field. A detailed mathematical treatment leads to the equation:

$$\alpha_{\nu} = k \frac{1}{\pi} \left[\frac{\frac{1}{2} \Delta \nu_{\frac{1}{2}}}{(\nu - \nu_0)^2 + (\frac{1}{2} \Delta \nu_{\frac{1}{2}})^2} \right] \quad (II)$$

where "k" is a constant for a particular band, " α_{ν} " is the absorption coefficient at wavenumber " ν ", " ν_0 " is the natural wavenumber, and " $\Delta \nu_{\frac{1}{2}}$ " is the full width at half maximum of the band. This equation is of the Lorentzian (or, more generally, Cauchy) form:

$$y = \frac{a}{b^2 + x^2} \quad (III)$$

The observed i.r. band shape may be regarded as a convolution of the "true" shape with an "instrument function", $K(\nu)$ where

$$T_{\nu} = K(\nu) I_{\nu} \quad (IV)$$

I_{ν} and T_{ν} being the true and apparent band intensities when the spectrometer is set at wavenumber ν . The instrument function is a mathematical representation of the instrumental factors which can distort the true band shape including diffraction at the slits, the effect of using finite slit widths, aberrations in, and misalignment of, the optical system, and the effects of the finite time constant of the amplifier, mechanical distortion, and radiation scattering. It is usually assumed⁴⁹ that the instrument function is Gaussian or triangular, although the

amplifier time constant component can introduce an asymmetric element. The contribution of radiation at wavenumber ν to the measured intensity at ν_i is related to $(\nu - \nu_i)$ by the "spectral slit function" and increases as $(\nu - \nu_i)$ tends to zero. Writing the instrument function in the more specific form, $k(\nu - \nu_i)$, and representing the profile of the true absorption band by $g(\nu)$, the intensity contributed from ν will be given by:

$$I_{\nu_i}^{\nu} = g(\nu) \cdot k(\nu - \nu_i) \cdot \Delta\nu \quad (V)$$

being proportional to the total energy transmitted at ν , and to the band width $\Delta\nu$. Account is taken of contributions from all ν by constructing a folding integral known as the Voigt convolution:

$$f(\nu_i) = \int_{-\infty}^{+\infty} g(\nu) \cdot k(\nu - \nu_i) d\nu \quad (VI)$$

Thus, isolated i.r. absorption bands of condensed phase systems are of Lorentzian profile upon which physical and instrumental factors impose a Gaussian perturbation: this is represented mathematically by the Voigt convolution. Davies and Vaughan,⁵⁰ using such a convolution, have constructed tables giving the ratios of the widths of Voigt profiles at specific height fractions to the widths at half-height as functions of the magnitudes of the Lorentzian and Gaussian proportions. For a Voigt profile, analyses at different height fractions should yield consistent proportions of the two distributions.

Curve Analysis

Because the i.r. bands of rotamers often overlap, it is necessary for

quantitative studies to decompose observed profiles into constituent bands or into quantities proportional to the areas of constituent bands. The commonly employed methods are: (i) graphical separation; (ii) analogue computer separation (as in the Du Pont 310 Curve Resolver), and (iii) digital computer separation.

(i) Graphical Methods. Because of their simplicity, these methods have been widely used.⁵¹ They may be broadly classified under the headings: the wing method; the methods of the minimum and mid-point, and the method of outer halves.

The wing method is the least precise and involves a subjective estimate of the contribution made by a small band to a wing of a large band situated some distance away. The method becomes highly inaccurate when the band separation is small or when the component bands are of comparable intensity.

The methods of the minimum and mid-point involve the dropping of a perpendicular either from the minimum between, or from a point mid-way between, the maxima of two overlapped curves and integrating the areas so obtained. It is claimed that the methods are precise, partly as a result of compensating errors, and can be used to a precision of $\pm 4\%$.

The method of outer halves, which involves taking the leading edge of the higher band and the trailing edge of the lower as being proportional to the respective band areas, has been shown to produce large errors for overlapping Lorentzian bands with peak separations less than two to three half band widths: the errors for Gaussian curves, however, approach zero at a peak separation of only $1\frac{1}{2}$ half band widths. As the peak separation decreases, the errors become very large in a negative sense and measured enthalpies tend to zero. The use of

apparent optical densities (peak heights) as quantities proportional to band areas gives results similar to those from the outer halves method.

(ii) Analogue Computer Methods. The instrument used by the author, a Du Pont 310 Curve Resolver, is an analogue computer partially programmed for the purpose of resolving contours consisting of up to ten overlapping bands. Each of these bands is synthesised in a distinct "function generator channel" and the bands are then summed on an oscilloscope to provide a theoretical contour. A semi-silvered mirror system allows superimposition of theoretical and experimental contours. The shapes, heights, and positions of the bands are individually adjusted until the fit of the synthesised and experimental contours is optimised, the areas of the component bands relative to any standard area then being read from an integrator meter. Facilities are available for skewing curves and for fitting to contours recorded over non-linear base-lines.

The synthesised bands are composed of 26 straight-line segments, 13 for each side of a band, the positions and lengths of 24 of which are determined by 6 "breakpoint" controls which are common to all channels; the remaining 2 segments, which provide the wings of the bands, do not require a breakpoint control. In addition, each channel has 7 "diode matrix controls" which determine the slopes of the straight-line segments. Thus, the breakpoint controls, in conjunction with the diode matrix controls of the individual channels, determine the shapes of the individual distribution functions. The settings for the various controls are determined by fitting a curve generated, in turn, by each channel to a specimen experimental curve known, by measurement of half widths, to be single and undistorted: thus, it is not necessary to know the mathematical forms of the component bands. The precision of fit to a band contour and of curve area

measurement is judged to be $\pm 1\%$ in favourable cases (e.g., the carbonyl bands of t-butyl furan-2-carboxylate; Figure 15); for strongly overlapping bands the precision is not so good.

(iii) Digital Computer Methods. The basic mathematical problem is the application of least squares analysis to non-linear functions, using iteration to achieve an acceptable fit. The Lorentzian and Gaussian shape functions are commonly expressed⁵² in the form:

$$A(\nu)_L = a[b_L^2 + (\nu - \nu_o)^2]^{-1} \quad (VII)$$

and

$$A(\nu)_G = a \cdot b_G^{-2} \cdot \exp[-(\nu - \nu_o)^2 \cdot \ln 2 \cdot b_G^{-2}] \quad (VIII)$$

in which ν_o is the position of the band centre, $2b$ is the width of the band at half maximum, and a/b^2 is the peak height. For the least squares analysis, the variables are generalised as $x_1, x_2, \dots, x_n$ where x_1 is identified with the peak height, x_2 with the position of the peak centre, and x_3 and x_4 with band width parameters. Putting $x_3 = b_L^{-1}$ and $x_4^2 = \ln 2 \cdot b_G^{-2}$, equations (VII) and (VIII) transform to:

$$A(\nu)_L = x_1 \cdot [1 + x_3^2(\nu - x_2)^2]^{-1} \quad (IX)$$

and

$$A(\nu)_G = x_1 \cdot \exp[-x_4^2(\nu - x_2)^2] \quad (X)$$

and the Voigt product convolution becomes:

$$A(\nu)_P = x_1 [1 + x_3^2(\nu - x_2)^2]^{-1} \exp[-x_4^2(\nu - x_2)^2] \quad (XI)$$

$A(\nu)_P$ is usually expressed in absorbance units. However, because the signal to

noise ratio is approximately constant throughout the transmittance scale whereas on an absorbance scale it increases at high absorbance values, the optimisation program uses the transmittance function:

$$(T/T_o)_\nu = \exp -2.30258 \left\{ \Phi + \sum_{p=1}^M x_{1(p)} [1 + x_{3(p)}^2 (\nu - x_{2(p)})^2]^{-1} \cdot \exp [-x_{4(p)}^2 (\nu - x_{2(p)})^2] \right\} \quad (XII)$$

" Φ " is a baseline displacement measured in absorbance units and "M" is the number of component bands. The values of $(x_1 \dots x_4)_p$ and Φ are varied to minimise " ω " where:

$$\omega = \sum f_i^2 \quad (XIII)$$

and

$$f_i = (T/T_o)_{\nu, \text{obs.}} - (T/T_o)_{\nu, \text{calc.}} \quad (XIV)$$

The mathematical approaches to this minimisation have been reviewed by Pitha and Jones⁵² who conclude that it is possible to generate analytical expressions which will fit the contours of i.r. band envelopes with a precision approaching that of the statistical uncertainty of the data measurements.

Thermodynamic Treatment of Results

Part of the present work involves the determination of thermodynamic parameters for an equilibrium between two rotational isomers "h" and "l" (the barrier to rotation being assumed to be small compared with kT). If the proportions of the isomers are of the same order of magnitude and if h and l each has a characteristic i.r. absorption band, h giving a band at higher wavenumber than l,

the following treatment is usually applied.⁵³

- Let $A_{\underline{h}}$ = band area of rotamer $\underline{h}$,
 $\alpha_{\underline{h}}$ = integrated absorption coefficient of $\underline{h}$,
 $c_{\underline{h}}$ = concentration in gl^{-1} of $\underline{h}$,
 p = cell path length in cm,
 K = equilibrium constant for $\underline{h} \rightleftharpoons \underline{l}$,
 ΔH° = enthalpy change for $\underline{h} \rightleftharpoons \underline{l}$,
 ΔS° = entropy change for $\underline{h} \rightleftharpoons \underline{l}$, and
 ΔG° = free energy change for $\underline{h} \rightleftharpoons \underline{l}$.

Then: $A_{\underline{h}} = \alpha_{\underline{h}} c_{\underline{h}} p$

and: $K = c_{\underline{l}}/c_{\underline{h}} = A_{\underline{l}}\alpha_{\underline{h}}/A_{\underline{h}}\alpha_{\underline{l}}$

By the van't Hoff isochore, using base 10 logarithms:

$$\log_{10} \frac{A_{\underline{l}}}{A_{\underline{h}}} = \frac{-\Delta H^{\circ}}{2.303R} \cdot \frac{1}{T} + \frac{\Delta S^{\circ}}{2.303R} + \log_{10} \frac{\alpha_{\underline{l}}}{\alpha_{\underline{h}}} \quad (\text{XV})$$

and a plot of $\log_{10} (A_{\underline{l}}/A_{\underline{h}})$ against $1/T$ has a slope $-\Delta H^{\circ}/2.303R$, if the ratio $\alpha_{\underline{l}}/\alpha_{\underline{h}}$ is independent of temperature. In order to measure entropy and free energy, the ratio of α 's must be known because:

$$\Delta G^{\circ} = -RT \ln \left[\left(\frac{A_{\underline{l}}}{A_{\underline{h}}} \right) \cdot \left(\frac{\alpha_{\underline{h}}}{\alpha_{\underline{l}}} \right) \right] \quad (\text{XVI})$$

and

$$\Delta S^{\circ} = (\Delta H^{\circ} - \Delta G^{\circ})/T \quad (\text{XVII})$$

It is often assumed that $\alpha_{\underline{h}} = \alpha_{\underline{l}}$. However, Hall and Wilson⁵⁴ have shown that this assumption is invalid in a case where a priori it might be expected to apply.

Thus, the integrated absorption coefficient of the equatorial C-Cl stretching vibration in 4-t-butylcyclohexyl chloride is reported to be 47% greater than the coefficient of the axial vibration.

An alternative approach is to use the equation:

$$A_{\underline{h}} = -(\alpha_{\underline{h}}/\alpha_{\underline{l}})A_{\underline{l}} + \alpha_{\underline{h}}\underline{p}c \quad \text{(XVIII)}$$

which follows from:

$$c = c_{\underline{h}} + c_{\underline{l}}$$

and

$$c = \frac{A_{\underline{h}}}{\alpha_{\underline{h}}\underline{p}} + \frac{A_{\underline{l}}}{\alpha_{\underline{l}}\underline{p}}$$

where "c" is the total concentration of compound in gl^{-1} . If each of the α values is independent of temperature, a plot of $A_{\underline{h}}$ against $A_{\underline{l}}$ should be linear with a slope $-\alpha_{\underline{h}}/\alpha_{\underline{l}}$. It has been suggested, however,^{21,55,56} that the generally observed decrease in extinction coefficient of bands with increase in temperature is not entirely balanced by an increase in the band width, neither can it be explained by thermal dilation of the cell nor by density changes in the solvent. Thus the indiscriminate application of Equation (XVIII) may lead to serious errors in $\Delta\dot{G}^{\circ}$ and $\Delta\dot{S}^{\circ}$, but as long as the α -ratio is independent of temperature, the calculated $\Delta\dot{H}^{\circ}$ value will be valid. (This problem is considered further in the "Discussion" section of this Thesis.) It follows that the use of extinction coefficients as measures of band areas and hence of concentrations

of species responsible for the bands in a rotameric equilibrium is incorrect because the former are not necessarily proportional to the latter and because $\alpha_{\underline{h}}$ is not, in general, equal to $\alpha_{\underline{l}}$.

Karabatsos et al.⁵⁷ have noted that ΔH° values for rotameric equilibria are unreliable when obtained from the temperature variation of n.m.r. coupling constants in a solvent whose dielectric constant (usually high) has a large temperature coefficient. It is thus desirable to examine the effect of the variation in dielectric constant of carbon tetrachloride with temperature upon the measured ΔH° value. To do this,²¹ the ratios of band areas at a constant temperature are measured using as solvents mixtures of carbon tetrachloride and acetonitrile for which Kalliorinne⁵⁸ has determined the dielectric constants. The assumption is then made that:

$$\ln\left(\frac{A_{\underline{l}}}{A_{\underline{h}}}\right) = m\epsilon + c + m'\left(\frac{1}{T}\right) + c' \quad (\text{XIX})$$

where " ϵ " is the dielectric constant, " m, m' " are slopes and " c, c' " are constants. Using Kalliorinne's results, linear regression analysis (see below) of ϵ against $1/T$ gives:

$$\epsilon = 175.27 (1/T) + 1.64$$

with a correlation coefficient of 0.996, and thus to a good approximation:

$$\ln\left(\frac{A_{\underline{l}}}{A_{\underline{h}}}\right) = m[175.27 \left(\frac{1}{T}\right) + 1.64] + c + m'\left(\frac{1}{T}\right) + c' \quad (\text{XX})$$

Thus, when $\ln(A_{\underline{l}}/A_{\underline{h}})$ is plotted against $1/T$, the measured slope is given by

(175.27m + m'). The value of m is determined by plotting $\ln(A_l/A_h)$ against ϵ , and hence m', the corrected slope for ΔH° calculations, is obtained. Although there is no reason to expect a linear dependence of the equilibrium constant between rotamers on the dielectric constant of the solvent, if the fit of the experimental data is good then it would appear that the assumptions inherent in Equation (XX) are justified. The conclusion from such studies is that the dielectric variation effect is negligible for carbon tetrachloride solutions in the temperature range used in this work.

Statistical Methods and Errors

All linear plots listed in the "Experimental-Spectroscopic" section were estimated by linear regression⁵⁹ using an I.C.L. 1906A computer (vide "Discussion"), the best fit being determined by minimising the sum of the squares of the deviations of the data points from the lines.

If, for a particular measurement of the independent variable, x_1 , the corresponding measurement of the dependent variable (or response) is y_1 , then the function to be minimised is:

$$\sum_{i=1}^n (y_i - a - bx_i)^2$$

where "n" is the number of pairs of observations, "b" is a slope and "a" is an intercept. The values of a and b for minimisation are:

$$b = T_1/T_2$$

$$a = \frac{\sum y}{n} - \frac{b \sum x}{n}$$

where:

$$T_1 = \sum xy - \frac{(\sum x)(\sum y)}{n} \quad [= \sum (x - \bar{x})(y - \bar{y})]$$

$$T_2 = \sum x^2 - \frac{(\sum x)^2}{n} \quad [= \sum (x - \bar{x})^2]$$

In order to assess the precision of the estimates, an Analysis of Variance Table is constructed; the total variation in the response can then be broken down into two components: (i) the variation in y which is left unexplained when the best line has been fitted, and (ii) the variation in y which can be attributed to its dependence on x . A measure of the total variation in the response is given by the Total Sum of Squares:

$$\sum_{i=1}^n (y_i - \bar{y})^2$$

The Residual Sum of Squares is obtained by calculating the vertical deviation of each point from the best straight line, squaring these deviations, and then summing the squared deviations:

$$\sum_{i=1}^n (y_i - a - bx_i)^2$$

The proportion of the Total Sum of Squares of the response which may be attributed to the effect of the independent variable is given by:

$$(\text{Total Sum of Squares}) - (\text{Residual Sum of Squares})$$

that is:

$$\sum (y_i - \bar{y})^2 - \sum (y_i - a - bx_i)^2 = b \sum (y_i - \bar{y})(x_i - \bar{x}) = b \left[\sum xy - \frac{(\sum x)(\sum y)}{n} \right]$$

The Analysis of Variance Table is then constructed as shown:

Source of Variation	Degrees of Freedom	Sum of Squares	Mean Square
Due to regression	1	$A = b \sum_{i=1}^n (y_i - \bar{y})(x_i - \bar{x})$	$M_o = A$
About regression (residual)	$n - 2$	$B = \sum_{i=1}^n (y_i - a - bx_i)^2$	$M_1 = \frac{B}{n-2}$
Total	$n - 1$	$C = \sum_{i=1}^n (y_i - \bar{y})^2$	

M_1 is the best estimate of the residual variance, and $\sqrt{M_1}$ is called the Residual Standard Deviation. If x is having no effect upon y , then M_o will also be an estimate of the residual variance, but if y really is affected by x , M_o will be much larger than M_1 . Thus, if the true slope of the line equals zero, then the ratio M_o/M_1 will be comparatively small.

For linear plots in which both variables are subject to similar errors (e.g., A_h against A_l), the least squares fit is not always the best. In these cases, the plots were repeated using the method of means.⁶¹ Thus, the n plotted points are divided into three groups, the equal numbers in the two extreme groups being chosen to be as near $n/3$ as possible. The join of the mean coordinates $\bar{x}_1, \bar{y}_1$ and $\bar{x}_3, \bar{y}_3$ for the extreme groups provides the straight line.

The errors in each of the thermodynamic quantities were calculated assuming that the error in $\underline{K}$, the equilibrium constant, is random and can be described by the Gauss error function. If the error in $\underline{K}$ is $\pm q$, it follows⁶⁰ that the error in $\Delta \underline{H}^\circ$ is $\pm R t q / \underline{K}$, the error in $\Delta \underline{G}^\circ$ at temperature $\underline{T}_i$ is $\pm R \underline{T}_i q / \underline{K}$, and that in $\Delta \underline{S}^\circ$ at $\underline{T}_i$ is $\pm \frac{R q}{\underline{K}} (1 + \frac{t}{\underline{T}_i})$, where:

$$t = \sqrt{\left[\frac{1}{\sum (\frac{1}{\underline{T}_i^2}) - \frac{1}{n} (\sum \frac{1}{\underline{T}_i})^2} \right]}$$

EXPERIMENTAL - SPECTROSCOPIC

A. Infra Red Investigations

All the infra red spectra, the results of which are presented in this section, were recorded by the author using a Perkin-Elmer 521 grating spectrophotometer fitted with a linear absorbance attachment and purged continuously with dry air. The instrument was operated in the absorbance mode (scale linear to within 1%) at a spectral slit width of 1.7 cm^{-1} and a scanning rate of $5 \text{ cm}^{-1}/\text{min}$. The calibration, which was to 0.5 cm^{-1} , and the resolution, were checked regularly during the course of the investigations against water vapour bands.

Digitized i.r. spectra were obtained in binary-coded decimal, on eight track paper tape, with even parity, using a Stogate Data Logger. This provides a four-digit record, in units of transmittance $\times 10,000$, at a punch rate of one record per second or slower. The input d.c. voltage was eighty millivolts maximum, and the linearity was to 0.005%. The input voltage is derived from a read-out potentiometer which is clamped mechanically on to the transmitting potentiometer of the spectrophotometer: there is thus a mechanical link between the read-out potentiometer and the optical attenuator. [This mode of operation is preferred to an alternative approach in which the a.c. signal from the pen follow-up potentiometer is used since (i) the low impedance of the Data Logger tends to cause a perturbation of the signal; (ii) recording is then in the absorbance mode and the linearity of the spectrophotometer absorbance attachment becomes the limiting error, and (iii) there is no a priori reason why the signal from the

potentiometer should be linearly related to the movement of the optical attenuator.]

Variable temperature spectra were recorded using a Research and Industrial Instruments Corporation TEM-1 temperature controller with a VLT-2 variable temperature probe. The latter operates on a Dewar principle in which the i.r. cell is in direct thermal contact with the base of a steel refrigerant vessel. The vessel is inserted into an outer jacket provided with heated sodium chloride windows, and the space between the refrigerant vessel and outer jacket is evacuated to a pressure of 0.05 mm Hg. The high vacuum prevents condensation of water on to the cell windows during low temperature operation, and prevents rapid boiling of the refrigerant. The temperature of the i.r. cell is recorded on the TEM-1 via a chromel-alumel thermocouple. The current supplied to heaters located on either side of the sample cell, and hence the cell temperature, are controlled by the TEM-1. For temperatures below ambient, a refrigerant was used (20° to -70°C : acetone/solid carbon dioxide; below -70°C : liquid nitrogen). The accuracy of the temperature measurement, in the temperature range used most frequently (-15° to $+75^{\circ}\text{C}$), was checked by comparing the temperatures recorded by the TEM-1 with those recorded by a thermometer checked at the National Physical Laboratory: a calibration curve was thereby obtained, allowing an accuracy of $\pm 0.5^{\circ}\text{C}$. Because of its sensitivity to thermal shock, sodium chloride was used as a cell window material only for spectra recorded at room temperature. For variable temperature spectra, a vacuum-tight cell (nominal path length 1.0 mm) with silver chloride windows was used, silver chloride having the advantages of being relatively insensitive to thermal shock and having a low absorbance over the frequency range employed.

Carbon tetrachloride (dielectric constant 2.25 at 30°C) was used as the solvent for variable temperature work in the range -15°C to +75°C because of its low absorbance in the region 1800 to 1600 cm⁻¹, and the low variation of its dielectric constant with temperature (cf. theoretical section). For very low temperature studies, carbon disulphide was used. Gross variations in solvent dielectric constant were achieved by using chloroform, bromoform, or methyl cyanide as solvents; the ethanol added as a stabiliser to chloroform and bromoform was removed by passage of the solvents through alumina. The relative efficiencies of desiccants (phosphorus pentoxide, anhydrous potassium carbonate, anhydrous magnesium sulphate, anhydrous calcium chloride, and B.D.H. molecular sieves types 3A and 4A) in carbon tetrachloride were investigated by monitoring the magnitude of the i.r. water band at 3720 cm⁻¹. The most efficient desiccant was found to be B.D.H. molecular sieve type 3A (1/16" pellets) and all solvents (of analytical purity) were dried in this way for 24 h before use. The compounds examined in this section were either distilled in vacuo (liquids) or sublimed in vacuo (solids) immediately before use; their purity was checked, where appropriate, by t.l.c. and g.l.c.

In the tables below, the same conventions that are described in the Discussion section are used. Thus, "A" represents the area of an i.r. band, "D" represents the optical density of a band, "T" represents the absolute temperature, and the subscripts "l" and "h" refer to the lower- and higher-frequency bands in a rotamer carbonyl doublet.

Optimisation of spectrophotometer settings

Experiment 1. The hydroxyl stretching band of t-butanol was examined at 303°K in carbon tetrachloride solution (0.500 mg/g solvent). The amplifier gain and attenuator speed settings were varied to find the optimum working conditions consistent with the production of a symmetrical OH band (ν_{OH} 3616.0 cm⁻¹). A constant slit program setting of 1000 was used with the slit width set at twice the programmed value. The various settings were investigated by measuring the ratios of the leading to trailing half-widths at various fractions of the band height. The settings which gave minimum overall distortion of the band were chosen as the optimum settings.

Furan-2-carbaldehyde C=O band assignment*

Experiment 2. The carbonyl region of furan-2-carbaldehyde in carbon tetrachloride solutions was examined at various concentrations at 20°C and the areas of the bands at 1700 and 1681 cm⁻¹ were measured (vide Table 4).

Concentration (gl ⁻¹)	A _h %	A _l %	A _l /A _h
8.59	71.5	28.5	0.399
1.72	71.5	28.5	0.399
0.86	71.5	28.5	0.399
0.43	71.5	29.0	0.409
0.09	72.0	28.0	0.389

Table 4

* Tables 4 and 5 involve a re-examination of previous work by the author. ²¹

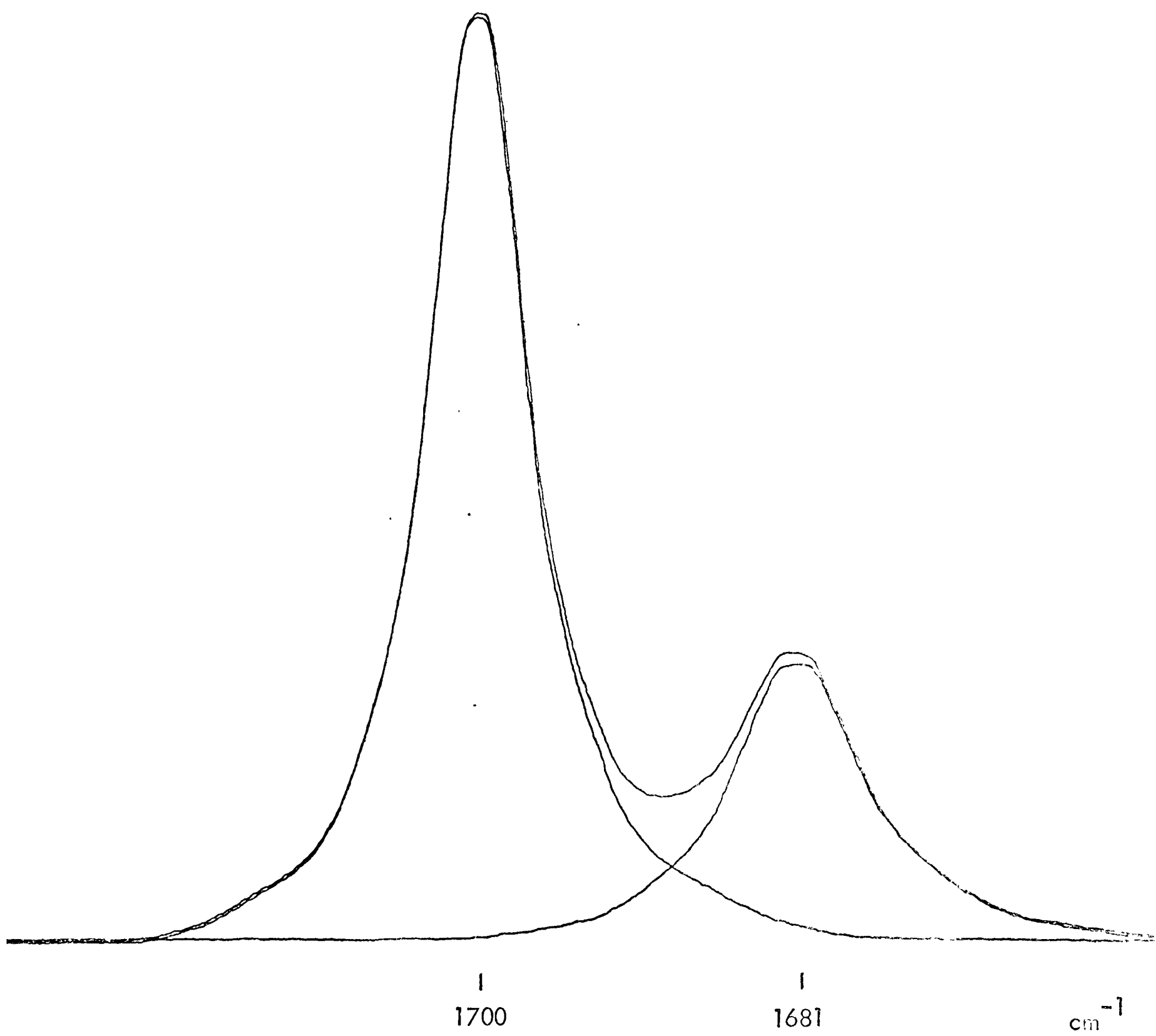


Figure 2

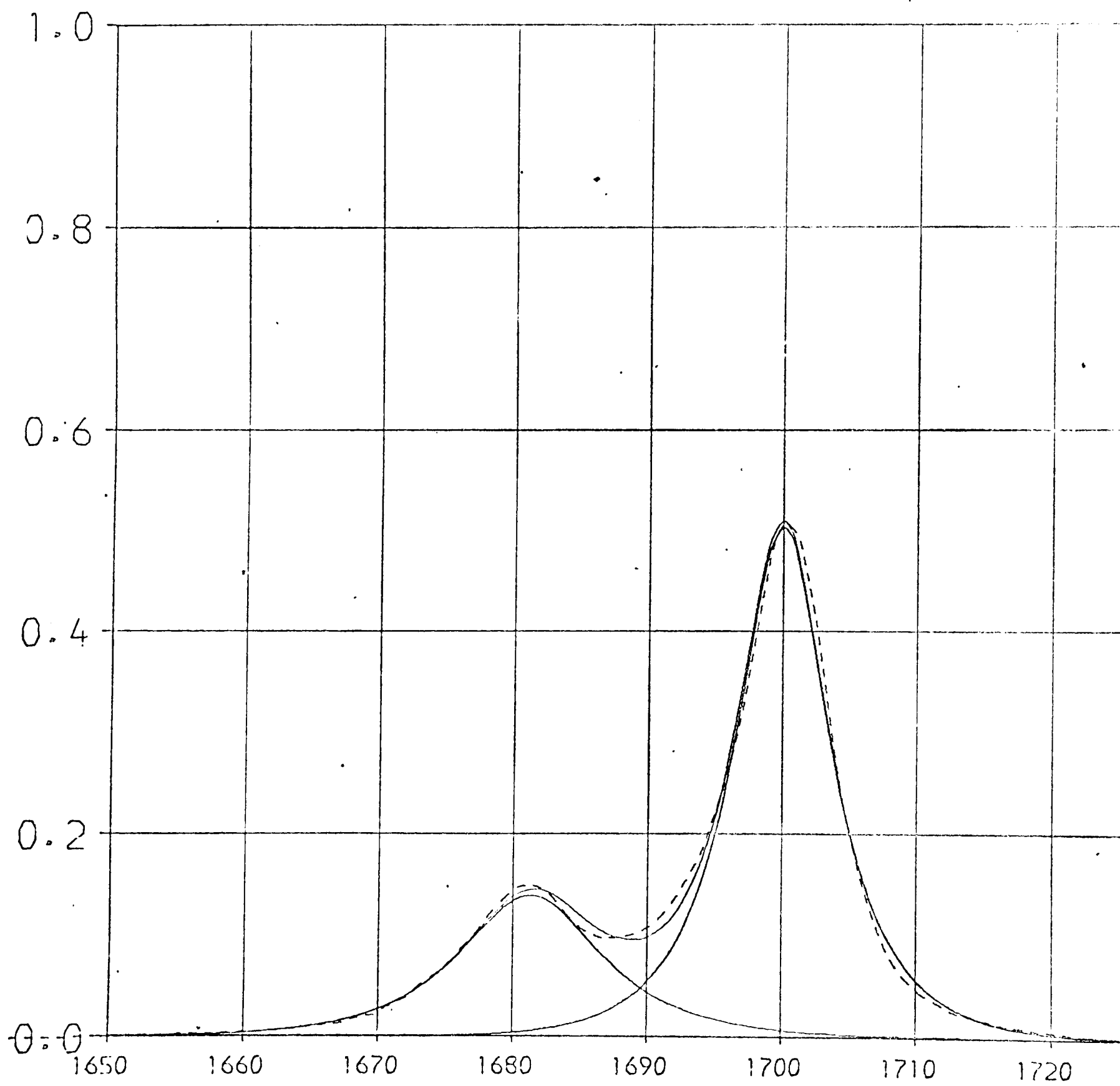


Figure 3

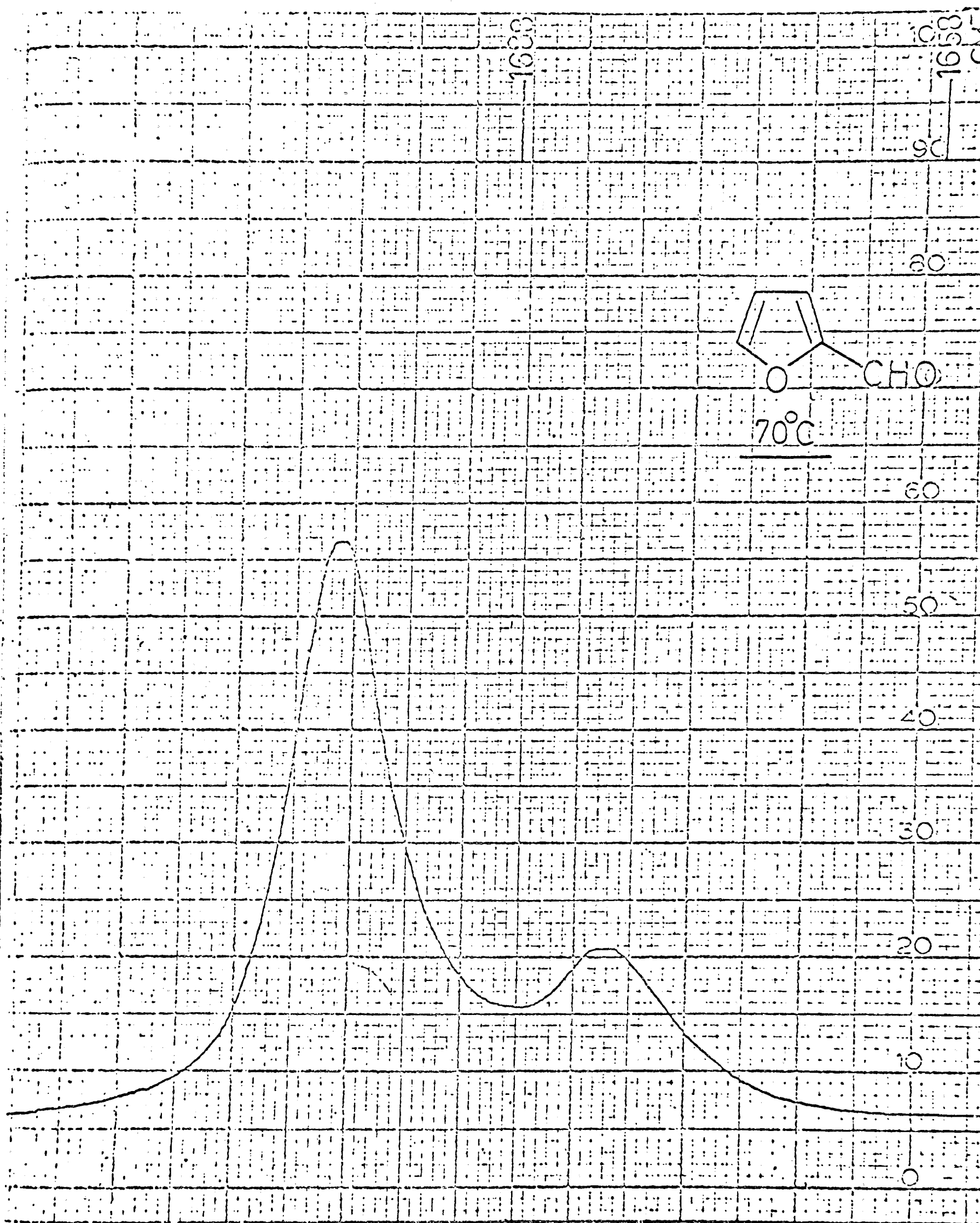


Figure 4

The aldehyde was then examined as a thin film, the optical density ratio

$D_{1690.0}/D_{1672.5}$ being measured as 0.874.

The aldehyde was next examined in carbon tetrachloride solution (3.915 mg in 7.904955 g solvent) from -20° to 70°C , and the bands at 1700 and 1681 cm^{-1} were recorded. A specimen analogue curve resolution is included as Figure 2, a digital curve resolution (for program details see later) as Figure 3, and a specimen spectrum as Figure 4. For complete curve resolution, it was necessary to include a small contribution from a third band between the major bands: its contribution has been removed from the areas quoted in Table 5.

T	Total Area	A_h	A_l
253	100.0	65.5	34.5
263	96.5	64.5	32.0
277	92.5	63.0	29.5
283	91.0	63.0	28.0
293	90.0	64.5	25.5
303	89.0	64.5	24.5
313	86.5	63.0	23.5
323	82.5	60.5	22.0
333	81.0	60.0	21.0
343	80.0	60.0	20.0

Table 5

The aldehyde was then examined as solutions in chloroform, bromoform, and carbon disulphide, and the last solution was examined at temperature below ambient down to -110°C . In chloroform, two bands were observed in the carbonyl

region at 1693 (D 0.52) and 1676 cm^{-1} (D 0.73) with a slight shoulder at 1696 cm^{-1} ; in bromoform, two bands were again observed at 1692 (D 0.39) and 1674 cm^{-1} (D 0.62) with a slight shoulder at 1698 cm^{-1} ; in carbon disulphide below 0°C , three distinct bands could be observed at 1696.5 (D 0.39), 1692.0 (D 0.63), and 1676.4 cm^{-1} (D 0.53).

The aldehyde was next examined in a 5 cm silica cell, as a carbon tetrachloride solution, in the region 3450 to 3300 cm^{-1} (the carbonyl overtone region). Three bands were observed at 3400 (D 0.17), 3371 (D 0.55), and 3355 cm^{-1} (D 0.32).

The aldehyde was finally examined in the vapour phase using a Research and Industrial Instruments Corporation 9 cm heated gas cell. Spectra in the carbonyl region were recorded in the temperature range 75° to 185°C . At all temperatures, a complex band envelope, which had the appearance of a pair of heavily overlapped doublets centred at 1719.5 and 1710.0 cm^{-1} , was obtained.

Experiment 3. The carbonyl region of 4-isopropylfuran-2-carbaldehyde (III), in carbon tetrachloride solution, was examined from -20° to $+75^{\circ}\text{C}$. At all temperatures, one major band was observed (1688.5 cm^{-1} at 30°C) with a small shoulder to higher wavenumber (1706 cm^{-1} at 30°C). Small frequency shifts to higher values and small decreases in optical density for the major band with increasing temperature were observed.

The carbonyl region of the aldehyde was also examined (at 30°C) using a chloroform solution. One major band was again observed (at 1677 cm^{-1}) along with a very minor band at 1705 cm^{-1} .

Experiment 4. The carbonyl region of 3-isopropylfuran-2-carbaldehyde (VII) in carbon tetrachloride solution was examined at 30°C. A single, major band was observed at 1686 cm⁻¹ with a very slight shoulder at 1698 cm⁻¹.

The carbonyl region of the aldehyde was also examined (at 30°C) using a chloroform solution. Two major bands were observed at 1678 (D 0.37) and 1667 cm⁻¹ (D 0.44).

Experiment 5. The carbonyl regions of 5-isopropylfuran-2-carbaldehyde (XVII) and of 4,5-diisopropylfuran-2-carbaldehyde (XI) in carbon tetrachloride solutions were examined at 30°C. A single band was observed in each case, centred at 1686 cm⁻¹ in the mono-alkylated aldehyde and at 1685 cm⁻¹ in the di-alkylated aldehyde. Single bands centred at 1672.5 cm⁻¹ (mono-alkylated aldehyde) and 1672 cm⁻¹ (di-alkylated aldehyde) were also observed when chloroform was used as solvent.

Experiment 6. The carbonyl regions of 2-furyl methyl ketone (XIII), ethyl 2-furyl ketone (XIV), and ethyl 2-(3-methyl)furyl ketone (XIX) were examined in carbon tetrachloride and chloroform solutions at 30°C. The observations are summarised in Table 6.

Compound	Band in CCl ₄ at: (cm ⁻¹)	Band in CHCl ₃ at: (cm ⁻¹)
Methyl ketone	1683.5 and 1711 (very minor)	1674
Ethyl ketone	1685	1674
Ethyl 2-(3-methyl) ketone	1678.5	1667.5

Table 6

The u.v. maxima of the ketones are compared with the maximum of furan-2-carbaldehyde in Table 7.

Compound	$\lambda_{\text{max.}}$ (nm)	
Furan-2-carbaldehyde	268	17,500
Methyl ketone	262	14,000
Ethyl ketone	262	14,000
Ethyl 2-(3-methyl) ketone	263	15,000

Table 7

Solid State Studies

Experiment 7. The carbonyl regions of 5-chlorofuran-2-carbaldehyde (XVI), 5-bromofuran-2-carbaldehyde (XLIII), 2-(5-chlorofuryl) methyl ketone (XXX), 2-(5-bromofuryl) (4-methoxyphenyl) ketone (XXXV), and 2-furyl (2,4,6-trimethylphenyl) ketone (XVIII) were examined in carbon tetrachloride solutions and in the solid state, using potassium bromide discs. The observations are summarised in Table 8, where the positions of major bands are underlined and those of minor bands are bracketted.

Compound	CCl_4 (cm^{-1})	KBr (cm^{-1})
(XVI)	<u>1690.5</u> (1718)	<u>1677.5; 1668.5</u> (1712.5)
(XLIII)	<u>1689</u> (1713.5)	<u>1674.5; 1663.5</u> (1707.5)
(XXX)	<u>1685.5</u>	<u>1656</u>
(XXXV)	<u>1643</u> (broadened to high ν)	<u>1626</u> (1639)
(XVIII)	<u>1663</u>	<u>1643</u> (1659)

Table 8

Experiment 8. The carbonyl regions of 5-phenylfuran-2-carbaldehyde (XXI), 5-(4-chlorophenyl)furan-2-carbaldehyde (XXIII), 5-(4-bromophenyl)furan-2-carbaldehyde (XXV), 5-(1-naphthyl)furan-2-carbaldehyde (XXVII), and 5-(2-naphthyl)furan-2-carbaldehyde (XXIX) were examined in carbon tetrachloride solutions, and (excepting 5-phenylfuran-2-carbaldehyde and 5-(1-naphthyl)furan-2-carbaldehyde) in the solid state using potassium bromide discs. The observations are summarised in Table 9 using the convention of Table 8.

Compound	CCl_4 (cm^{-1})	KBr (cm^{-1})
(XXI)	<u>1683.5</u>	-
(XXIII)	<u>1685</u>	<u>1681</u> (1661)
(XXV)	<u>1684</u>	<u>1678.5</u> (1670); (1657.5)
(XXVII)	<u>1683</u>	-
(XXIX)	<u>1681</u>	<u>1667</u> ; <u>1663</u>

Table 9

Fermi Resonance Studies

Experiment 9. The carbonyl region of furan-2-carbonyl chloride (XXXII) was examined, in carbon tetrachloride, solution, over the temperature range -15° to 75° . Four bands were observed, at 1797 (D 0.17), 1780 (D 0.37), 1756 (D 0.25), and 1744 cm^{-1} (D 0.44); the intensity of the band at 1756 cm^{-1} increased greatly as the temperature was lowered. An analogue curve resolution is included as Figure 5. No gross alterations in the appearance of the band envelope were observed over a hundred-fold change in concentration.

In chloroform and bromoform solutions, two major bands were observed in the carbonyl region in both cases [at 1779.5 (D 0.21) and 1745.5 (D 0.69), chloroform, and 1776 (D 0.20) and 1742.5 (D 0.58)]; slight shoulders could be discerned on the leading edges of the bands at higher wavenumber and on the trailing edges of the bands at lower wavenumber.

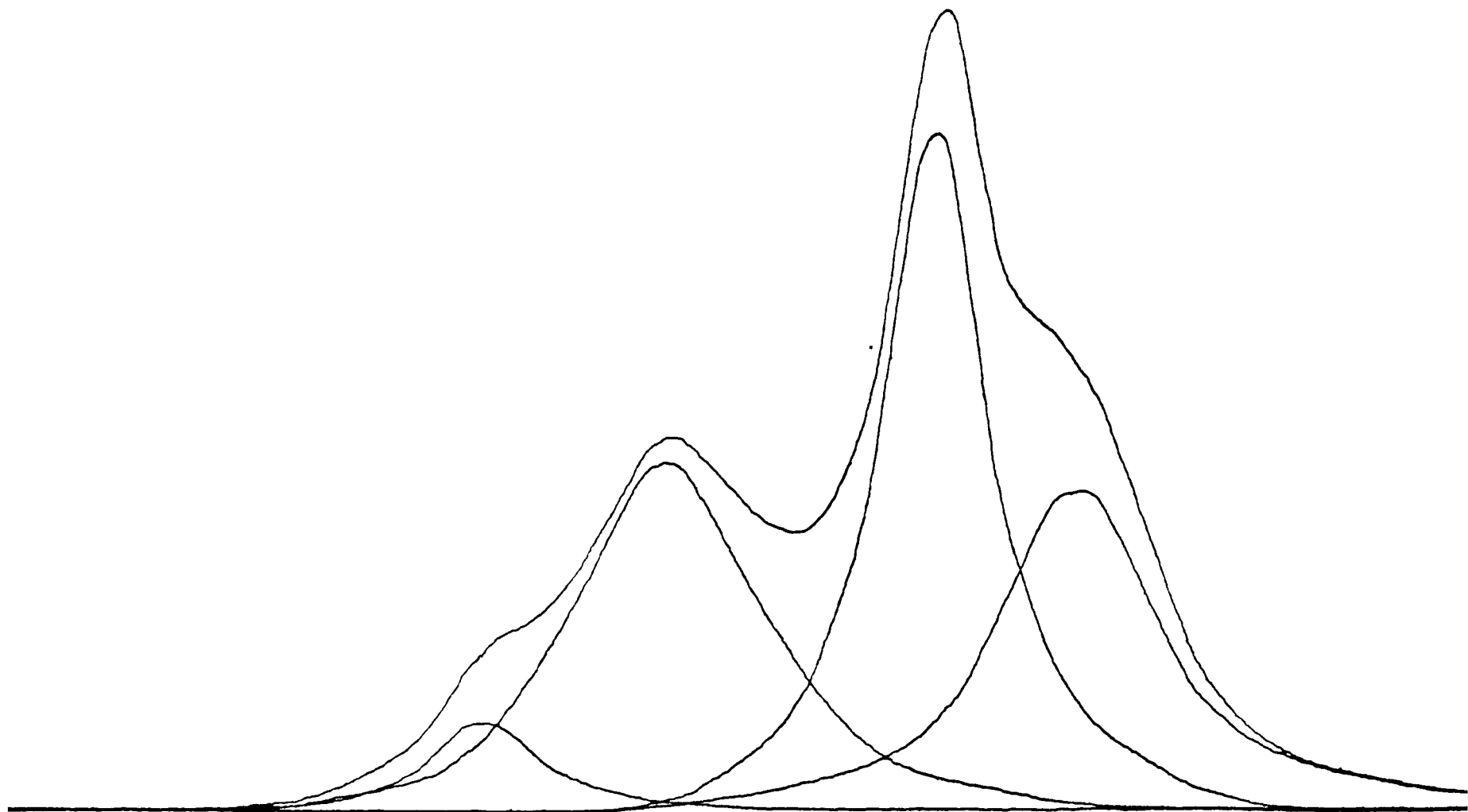


Figure 5

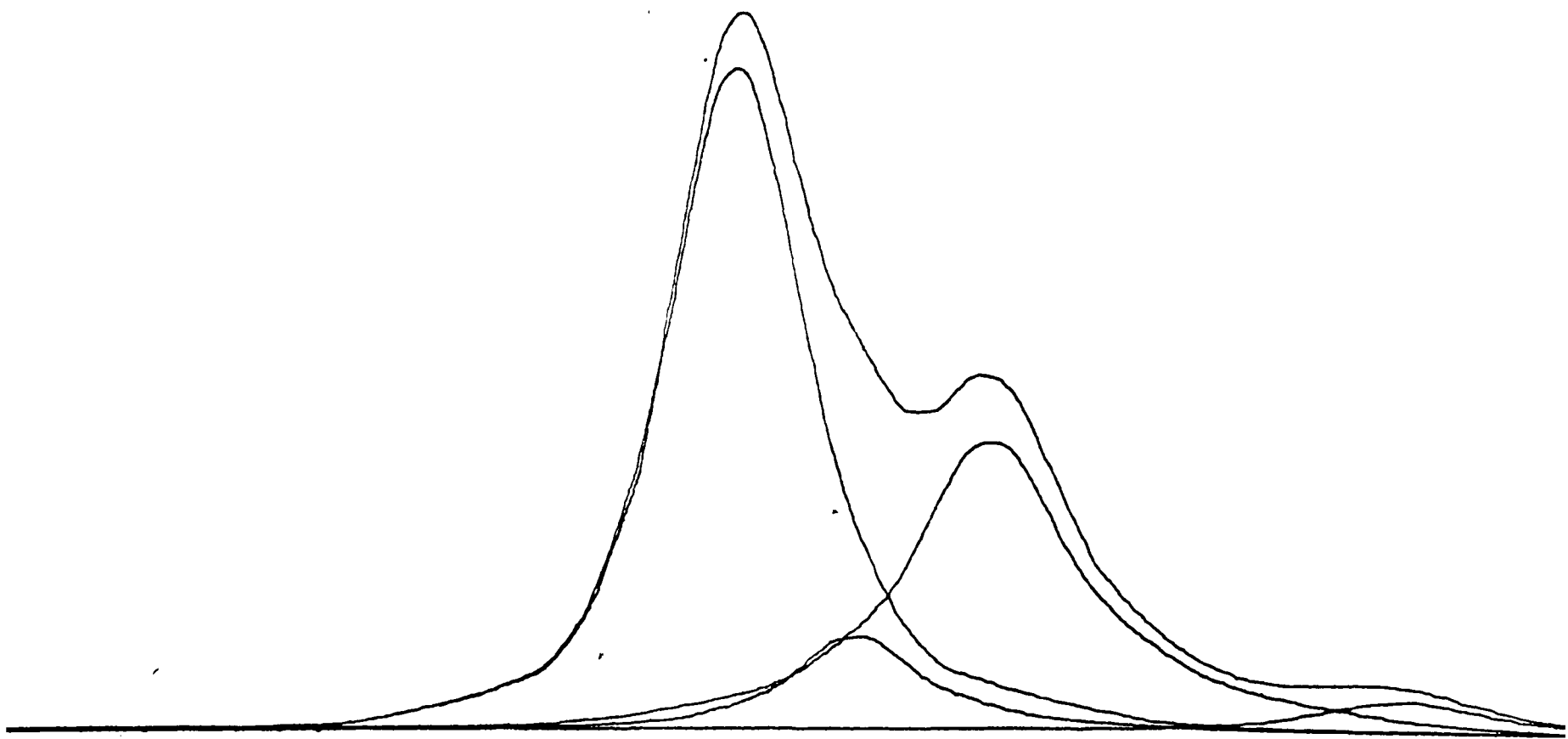


Figure 6

The acid chloride was next examined in a 5 cm silica cell, as a carbon tetrachloride solution, in the carbonyl overtone region. Three distinct maxima were observed at 3524 (D 0.47), 3501 (D 0.51), and 3476 cm^{-1} (D 0.35).

The acid chloride was finally examined in the vapour phase, at 150°C, using a 9 cm heated gas cell. A complex band envelope was observed in the carbonyl region having two distinct maxima, of approximately equal intensity, at 1794 and 1767 cm^{-1} , and shoulders at 1807, 1775, and 1756 cm^{-1} .

Experiment 10. The carbonyl regions of furan-2-carbonyl bromide (XXXIII) and furan-2-carbonyl fluoride (XXXIV), as carbon tetrachloride solutions, were examined at 30°C. In the former case, two major bands [at 1780 (D 0.45) and 1769 cm^{-1} (D 0.31)] were observed, with a broad, minor band at 1746 cm^{-1} (D 0.09). In the latter case, two major bands [at 1828.5 (D 0.70) and 1816 cm^{-1} (D 0.42)] were observed, with a shoulder at 1807 cm^{-1} (D 0.20).

Experiment 11. The carbonyl regions of thiophen-2-carbonyl chloride (XXXVI) and thiophen-2-carbonyl fluoride (XXXVII) as carbon tetrachloride solutions were examined at 30°C. In the former case, a single band was observed at 1751.5 cm^{-1} with a slight shoulder at 1760 cm^{-1} ; in the latter case, a single band was observed at 1807.5 cm^{-1} with a slight shoulder at 1813 cm^{-1} .

Experiment 12. The carbonyl regions of 5-deuteriofuran-2-carbonyl chloride (XLVIII) and 5-deuteriofuran-2-carbonyl fluoride (LXXXI), as carbon tetrachloride solutions, were examined at 30°C. The acid chloride showed two bands at 1767 (D 0.82) and 1756 cm^{-1} (D 0.51), and the acid fluoride two bands at 1828.5 (D 0.61) and 1816 cm^{-1} (D 0.39). For the acid chloride, in chloroform

solution, a broad band centred at 1751 cm^{-1} with a shoulder at 1760 cm^{-1} was observed.

The carbonyl region of the acid chloride, as a carbon tetrachloride solution, was also examined in the temperature range -15° to 75°C . An intensification of the higher frequency band relative to that at lower frequency was observed with decrease in temperature.

Experiment 13. The carbonyl region of thiophen-2-carbaldehyde (LIII), as a carbon tetrachloride solution, was examined over the temperature range -15° to 75°C . Three distinct maxima were observed at 1687.5 (D 0.61), 1677 (D 0.30), and 1659.5 cm^{-1} (D 0.04) (at 30°C). With increase in temperature, the intensity of the band at 1677 cm^{-1} decreased relative to that of the 1687.5 cm^{-1} band. A specimen analogue curve resolution is included as Figure 6; for complete curve resolution, it was found necessary to include a small contribution from a fourth band. No gross alterations in the appearance of the band envelope were observed over a hundred-fold change in concentration.

In chloroform solution, three bands were observed in the carbonyl region at 1687 (D 0.33), 1675 (D 0.65) and 1663.5 cm^{-1} (D 0.43).

The aldehyde was finally examined in a 5 cm silica cell, as a carbon tetrachloride solution, in the carbonyl overtone region. Two distinct maxima, at 3355 (D 0.59) and 3343 cm^{-1} (D 0.68), were observed.

Experiment 14. The carbonyl region of 5-deuteriothiophen-2-carbaldehyde (XL), as a carbon tetrachloride solution, was examined over the temperature range -15° to 75°C . Two distinct maxima were observed at 1688 (D 0.41) and 1672 cm^{-1} (D 0.07). With increase in temperature, the intensity of the band at 1672 cm^{-1}

decreased relative to that of the 1688 cm^{-1} band.

In chloroform solution, three bands were observed in the carbonyl region at 1709 (D 0.09), 1683 (D 0.53), and 1668 cm^{-1} (D 0.65).

Experiment 15. The carbonyl regions of 5-deuteriofuran-2-carbaldehyde (XLIX), 3,4,5-trideuteriofuran-2-carbaldehyde (LXXI), and 3,4-dideuteriofuran-2-carbaldehyde (LXXVI), as carbon tetrachloride solutions, were examined at 30°C . The mono- and tri-deuterated aldehydes showed singlets at 1694 cm^{-1} , and the di-deuterated aldehyde a doublet (with the components having approximately equal intensities) at 1696 and 1690 cm^{-1} .

In chloroform solution, the mono-deuterated aldehyde showed a singlet at 1682 cm^{-1} ; in acetonitrile solution, the tri-deuterated aldehyde showed a singlet at 1682 cm^{-1} , and the di-deuterated aldehyde a doublet at 1681.5 and 1688 cm^{-1} .

The aldehydes were then examined in the vapour phase, at 150°C , using a 9 cm heated gas cell. Complex band envelopes were observed, in the carbonyl region, in each case. The mono-deuterated aldehyde showed three maxima, of approximately equal intensities, at 1718 , 1711 , and 1705 cm^{-1} , the di-deuterated aldehyde two maxima, of approximately equal intensities, at 1722 and 1707 cm^{-1} , and the tri-deuterated aldehyde three maxima, of approximately equal intensities, at 1720 , 1710 , and 1704 cm^{-1} .

In the C-H stretching and bending regions, the mono-deuterated aldehyde showed five maxima between 2700 and 2900 cm^{-1} and three maxima between 1350 and 1400 cm^{-1} , the di-deuterated aldehyde three maxima between 2700 and 2900 cm^{-1} and four distinct maxima between 1350 and 1400 cm^{-1} , and the

tri-deuterated aldehyde four distinct maxima between 2700 and 2900 cm^{-1} and two distinct maxima between 1350 and 1400 cm^{-1} .

Experiment 16. The carbonyl regions of 3-bromofuran-2-carbaldehyde (LVII), 4-bromofuran-2-carbaldehyde (LXI), and 4-bromo-5-deuteriofuran-2-carbaldehyde (LXVII), as carbon tetrachloride and acetonitrile solutions, were examined at 30°C. Single, major bands, broadened to high wavenumber, were observed for the 3-bromo-aldehyde at 1691 cm^{-1} (carbon tetrachloride) and 1681 cm^{-1} (acetonitrile). For the 4-bromo-aldehyde, two bands were observed in each solvent, at 1705.5 (D 0.57) and 1690.5 cm^{-1} (D 0.42) (carbon tetrachloride), and 1701 (D 0.21) and 1686 cm^{-1} (D 0.43) (acetonitrile): the acetonitrile spectrum showed a distinct shoulder at 1708 cm^{-1} . Single bands were observed for the 4-bromo-5-deuterio-aldehyde at 1697 cm^{-1} (carbon tetrachloride) and 1689.5 cm^{-1} (acetonitrile).

The carbonyl regions of 4-bromofuran-2-carbaldehyde and 4-bromo-5-deuteriofuran-2-carbaldehyde were examined in the solid state, using potassium bromide discs. For the 4-bromo-aldehyde, a broad band centred at 1675 cm^{-1} with a distinct shoulder at 1700 cm^{-1} was observed. For the 4-bromo-5-deuterio-aldehyde, a broad band centred at 1676 cm^{-1} was observed.

Digital Computer Studies

Experiment 17. A copy of a digital computer program for the decomposition into constituent bands of an i.r. envelope consisting of up to twenty overlapped bands was acquired. The program so-obtained was written in FORTRAN IV for the IBM System/360, and all of the input, output, and format statements were therefore re-written in the Egdon system for an English Electric KDF-9 computer. [It was known that a changeover would eventually have to be made from the KDF-9 to

an International Computers Limited (ICL) 1906A computer, and the seven hundred program steps were therefore punched on to cards using ICL 1900 code.] The program as used initially required data points encoded as transmittance $\times 1000$ and wavenumber in $\text{cm}^{-1} \times 10$, recorded at constant wavenumber intervals in diminishing sequence, on punched cards. The program was tested using data points which were derived from a simulated four band spectrum, the run time (four minutes) being observed to be approximately twice that for an IBM 360 (50) computer.

Experiment 18. A program was written for a Hewlett-Packard programmable calculator for the evaluation of the Voigt product convolution, given the output indices (x_1 to x_4) from the band decomposition program, and for the integration of a band using Simpson's 1/3 rule. Using integration steps of 0.1 cm^{-1} , integration of a single band by this method was observed to take approximately ten minutes. An increase in the width of the integration step to 0.2 cm^{-1} produced no change in the value of the integral (to four decimal places) and halved the calculation time.

Experiment 19. Absorbance values, measured by eye at 0.8 cm^{-1} intervals, of the carbonyl bands of furan-2-carbaldehyde at -20° and 70°C were converted (manually) to transmittance values and punched on to cards. The bands were decomposed using the basic curve resolution program and integrated using the Hewlett-Packard calculator. The results are compared with those from the analogue curve resolver in Table 10.

	Position	Absorbance	A (%)	A_l/A_h
Digital	1698.1	0.54	64.2	0.56
-20°	1680.4	0.26	35.8	
Analogue	1698.4	0.54	65.5	0.53
-20°	1680.6	0.26	34.5	
Digital	1700.0	0.50	71.4	0.40
+70°	1681.2	0.14	28.6	
Analogue	1700.2	0.50	75.0	0.33
+70°	1681.2	0.14	25.0	

Table 10

A computer program was then written using the graphical output subroutines of the KDF-9 and the computed curves, their sum, and the input data for furan-2-carbaldehyde were plotted. The plot is shown earlier in this section as Figure 3.

Experiment 20. The program-terminating checks of the iterative loops of the curve-fitting program, which are based upon the rate of convergence to optimum fit between synthesised and experimental data, were removed. No improvement in curve-fitting was obtained by thus allowing more iterations, and the checks were re-introduced.

Experiment 21. With the advent of an ICL 1906A computer, the KDF-9 control commands were replaced by their 1906A equivalents. Because of the availability of disc storage, it then became possible to store the curve-fitting program as card images and as a binary, compiled program; storage in the latter format allowed a considerable reduction in computing time for a particular curve resolution.

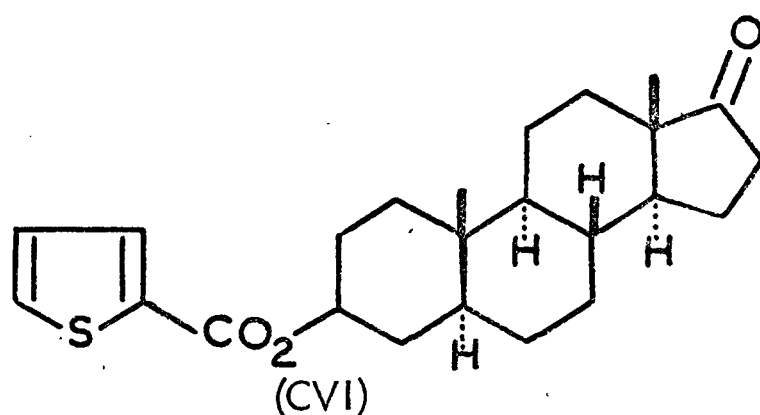
The input statements and control commands of the curve-fitting program were then altered to allow the input data to be presented in units of transmittance x 10,000 on punched paper tape. The program was also modified so that the positions (in cm^{-1}) of each data point were evaluated in the program from a starting position and a common difference. The program was then run with the same input data but allowing different common differences: the area ratios so obtained were identical in all cases.

Experiment 22. The times (in seconds) for successive 100 cm^{-1} scans (from 1700 to 1600 cm^{-1}) of the 521 i.r. spectrophotometer were measured: the results are summarised in Table 11.

Run	Time (secs)	Comment
1	1207.3	Runs recorded on same day without chart drum connected.
2	1206.9	
3	1205.8	
4	1207.0	
5	1204.9	With drum connected.
6	1204.0	
7	1203.6	
8	1206.5	Runs recorded on following day with drum connected.
9	1205.5	
10	1202.6	
11	1202.0	

Table 11

Experiment 23. The carbonyl bands of methyl m-chlorobenzoate (CIV), methyl 3-methyl-2-furyl ketone (CV), and 5 α -androstan-17-one-3 β -yl thiophen-2'-carboxylate (CVI), were recorded, as carbon tetrachloride solutions, in the temperature range -15° to 75°C, with digital encoding of transmittance $\times 10,000$ at a rate of one record per two seconds. A computer program was written for the integration of the band envelopes so obtained (using Simpson's rule, assuming tangential base-lines) and is included as Appendix A.



The results are summarised in Tables 12, 13, and 14.

Methyl m-chlorobenzoate (0.835 mg in 1.287980 g carbon tetrachloride),

$\nu_{30^\circ\text{C}} 1731 \text{ cm}^{-1}$.

Temperature (°C)	A	A%	No. of points
-15	2.45747	100.0	441
0	2.21935	90.3	450
15	2.27960	92.7	441
30	2.27831	92.7	441
45	2.12374	86.4	441
60	2.11055	85.9	441
75	1.98702	80.8	441

Table 12

Methyl 3-methyl-2-furyl ketone (1.310 mg in 1.223505 g carbon tetrachloride),

$\nu_{30^\circ\text{C}}$ 1676.5 cm^{-1} .

Temperature ($^\circ\text{C}$)	A	A%	No. of points
-15	2.93718	100.0	396
0	2.86635	97.6	396
15	2.99793	102.1	396
30	2.82972	96.4	423
45	2.90278	98.8	396
60	2.80398	95.5	396
75	2.66825	90.8	396

Table 13

5 α -Androstan-17-one-3 β -yl thiophen-2'-carboxylate (2.730 mg in 1.484980 g

carbon tetrachloride), $\nu_{30^\circ\text{C}}$ 1741.5 and 1710.5 cm^{-1} .

Temperature ($^\circ\text{C}$)	A	A%	No. of points
-15	8.78229	100.0	702
0	8.33938	95.0	702
15	8.13236	92.5	720
30	7.89358	90.0	729
45	7.51294	85.5	693
60	7.25734	82.6	693
75	6.87244	78.2	720

Table 14

The data for the three compounds was then re-analysed using the curve-fitting

program (examples of the fits are shown in Figures 7, 8, and 9 which were obtained

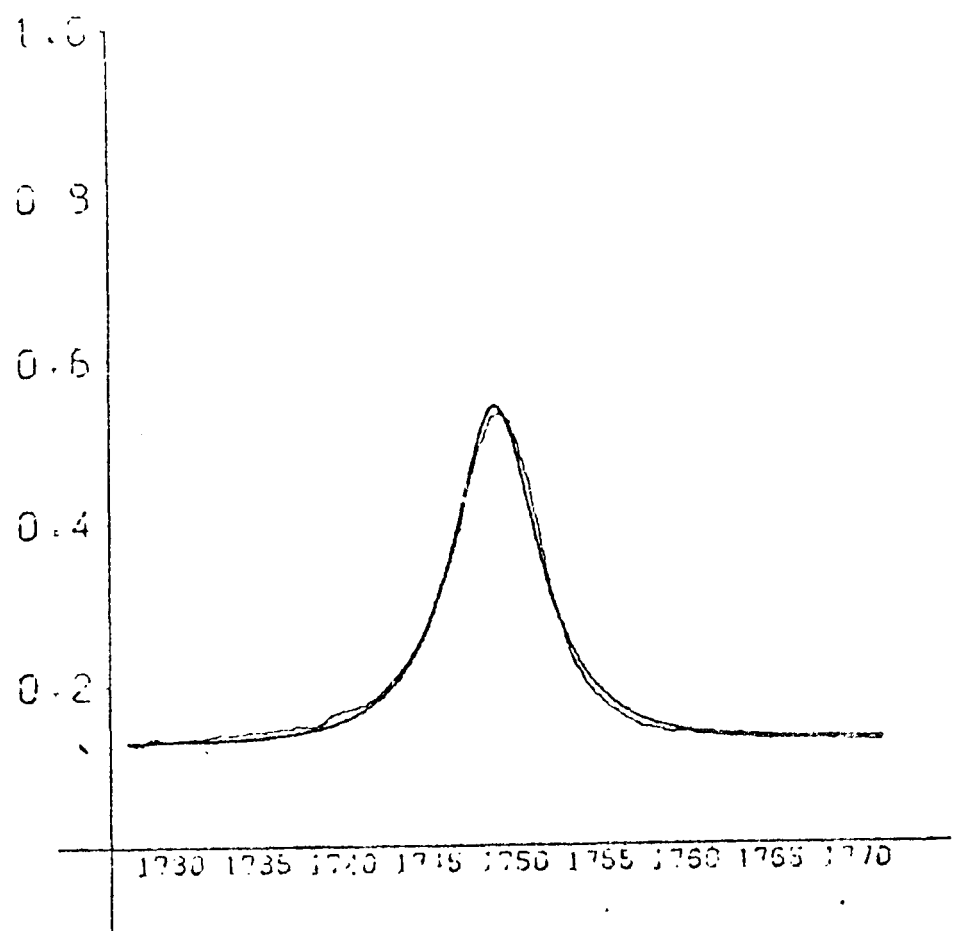


Figure 7 (dummy ν -values)

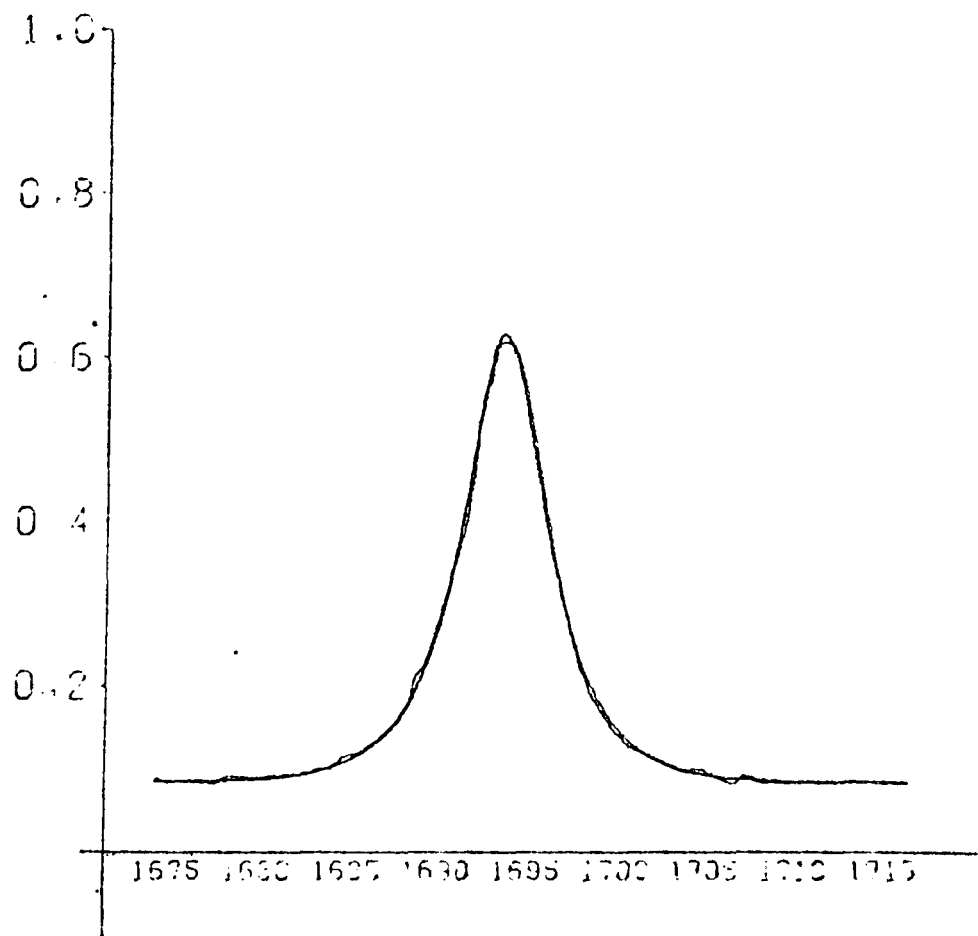


Figure 8 (dummy ν -values)

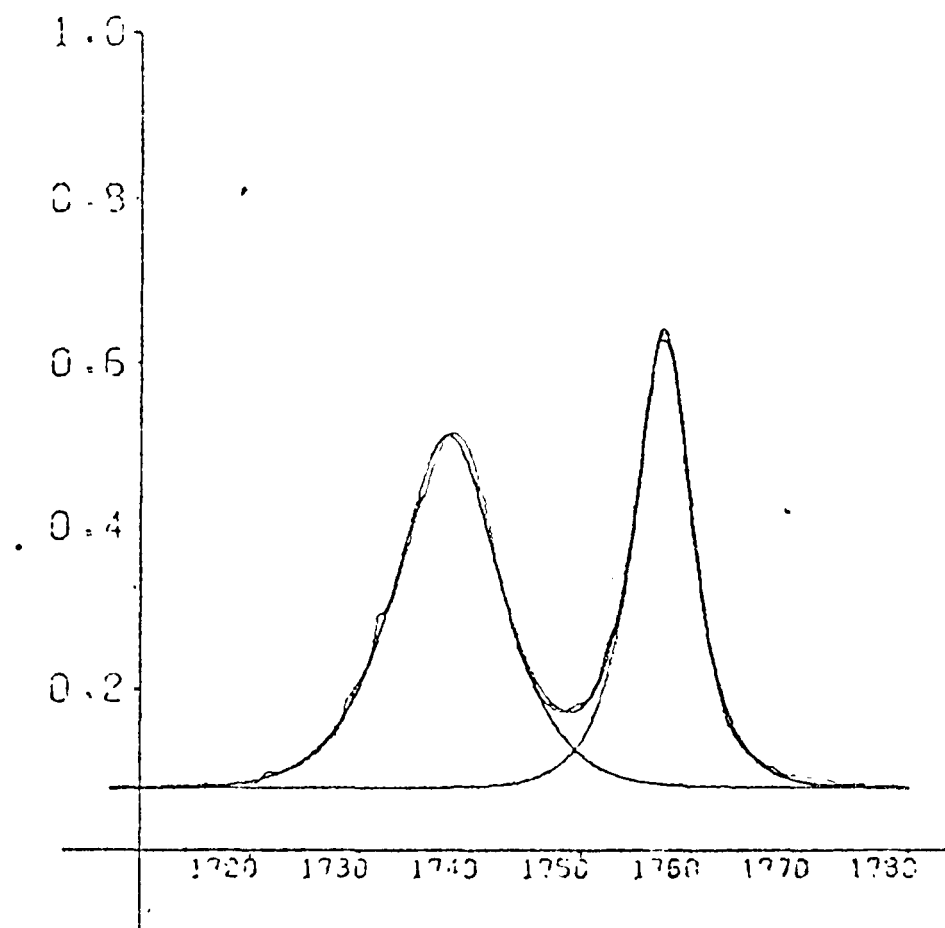


Figure 9 (dummy v -values)

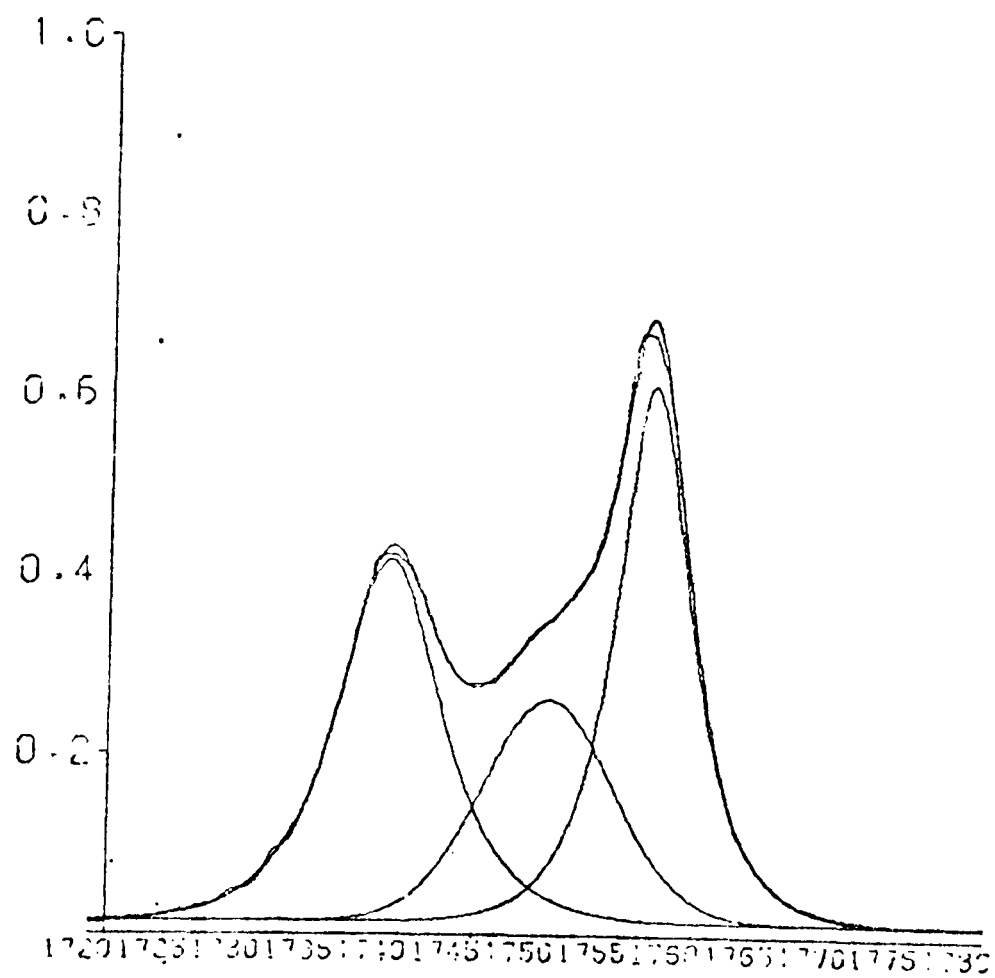


Figure 10 (dummy v -values)

from a program written for the ICL 1906A plotting subroutines: the program is included as Appendix B). Integration of the bands was achieved by including a subroutine in the basic curve-fitting program: originally, a computing laboratory subroutine was used, which proved to be unreliable; this was replaced by a subroutine based on the program originally written for the integration of band envelopes (Appendix A). The results are summarised in Tables 15, 16, and 17.

Methyl m-chlorobenzoate

Temperature (°C)	A	A%	Shape ($\frac{ x_3 }{ x_3 + x_4 }$)
-15	3.28389	100.0	0.743
0	3.15264	96.0	0.753
15	3.07859	93.7	0.782
30	3.02146	92.0	0.785
45	2.88533	87.9	0.788
60	2.82104	85.9	0.792
75	2.73759	83.4	0.815

Table 15

Methyl 3-methyl-2-furyl ketone

Temperature (°C)	A	A%	Shape
-15	4.03786	100.0	0.714
0	3.92344	97.2	0.734
15	3.88689	96.3	0.765
30	3.72664	92.3	0.769
45	3.65534	90.5	0.783
60	3.63522	90.0	0.791
75	3.58295	88.7	0.826

Table 16

5α-Androstan-17-one-3β-yl thiophen-2'-carboxylate

Temperature (°C)	A _{1741.5}	A%	Shape	A _{1710.5}	A%	Shape
-15	4.47054	100.0	0.700	5.97601	100.0	0.593
0	4.36484	97.6	0.719	5.79868	97.0	0.610
15	4.20310	94.0	0.715	5.68738	95.2	0.630
30	4.19692	93.9	0.743	5.55422	92.9	0.648
45	4.00170	89.5	0.752	5.30376	88.8	0.662
60	3.84182	85.9	0.752	5.17682	86.6	0.696
75	3.73537	83.6	0.768	4.99144	83.5	0.713

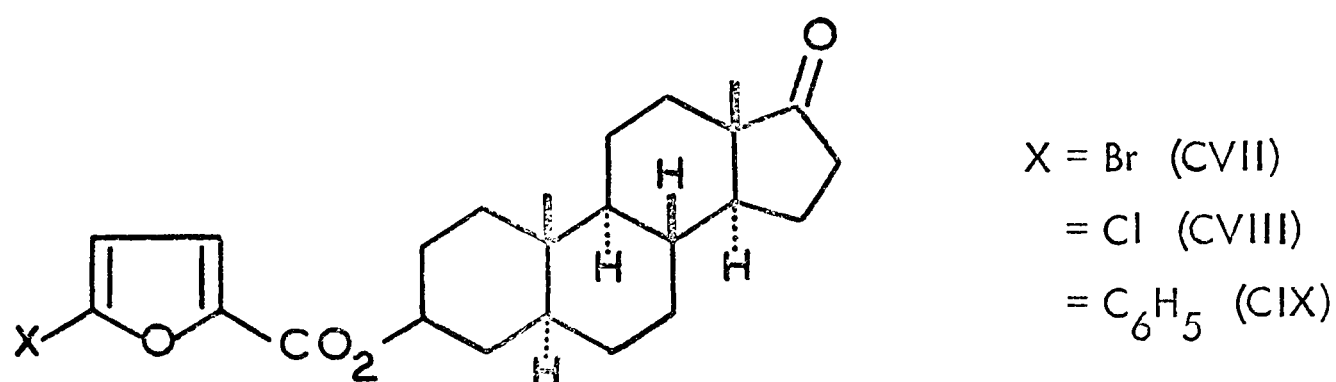
Table 17

The band envelopes (recorded as absorbance curves) were finally examined by curve fitting with the analogue curve resolver, from which the band areas were read directly. The results are listed in Table 18.

Temperature (°C)	(CIV)	(CV)	(CVI)	
-15	100.0	100.0	100.0	100.0
0	96.5	95.0	95.5	95.5
15	91.0	92.0	92.5	92.0
30	89.0	89.0	89.0	89.0
45	85.0	85.0	86.5	85.0
60	81.0	81.5	81.5	82.0
75	78.5	76.5	78.5	79.0

Table 18

Experiment 24. The carbonyl bands of 5 α -androstan-17-one-3 β -yl 5'-bromo-2'-furoate (CVII), the 5'-chloro-compound (CVIII), and the 5'-phenyl-compound (CIX), were recorded, as carbon tetrachloride solutions, in the temperature range -15° to 75°C, with digital encoding of transmittance $\times 10,000$.



The band envelopes were resolved and the individual bands were integrated by the digital method. The results are listed in Tables 19, 20, and 21, and computer plots are included as Figures 10, 11, and 12.

5 α -Androstan-17-one-3 β -yl 5'-bromo-2'-furoate (2.289 mg in 1.000 g carbon tetrachloride), $\nu_{-15^\circ\text{C}}$ 1739.5, 1727, and 1709.5 cm⁻¹.

Temperature (°C)	$A_{\text{isol.}}$	$A_{\text{i}}\%$	A_{h}	A_{l}
-15	3.2265	100.0	1.9106	3.0713
0	3.1013	96.1	1.9258	2.8900
15	2.9904	92.7	1.8540	2.7612
30	2.8904	89.6	1.8359	2.6560
45	2.8501	88.3	1.7823	2.5364
60	2.6212	81.2	1.8663	2.4032
75	2.4864	77.1	1.8099	2.2272

Table 19

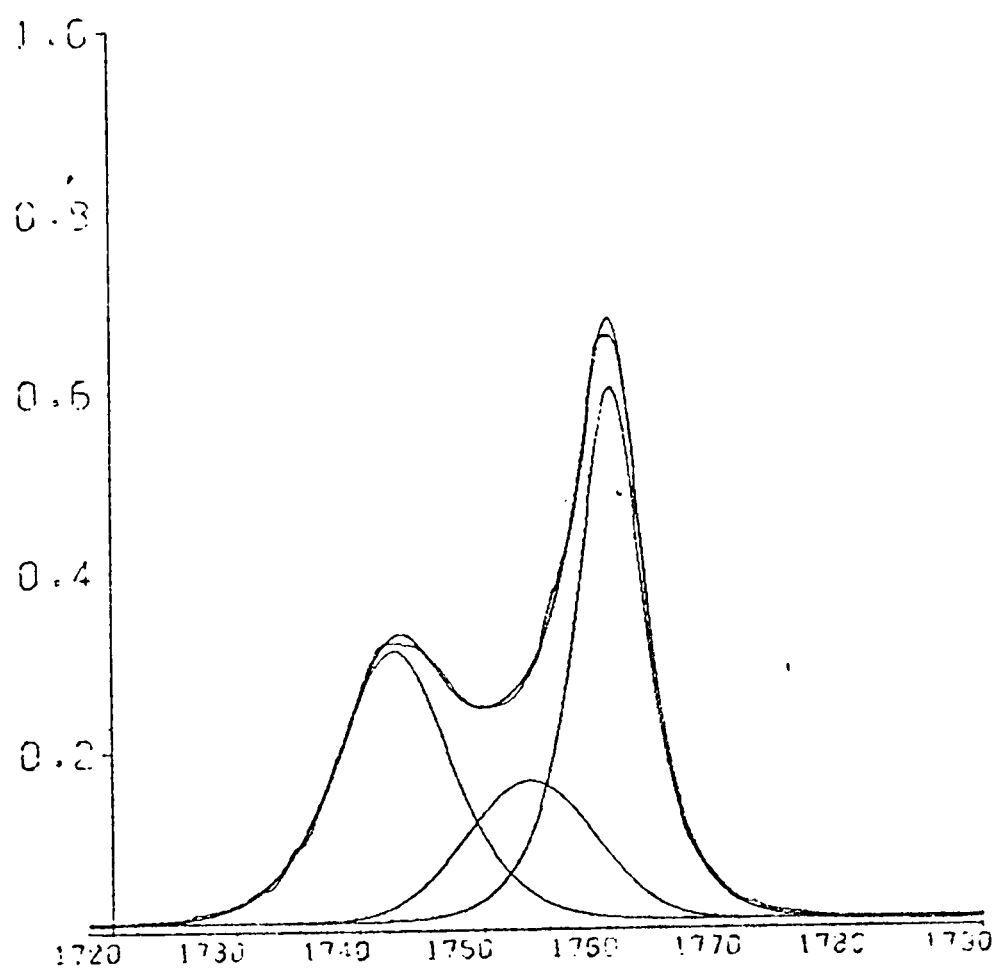


Figure 11 (dummy ν -values)

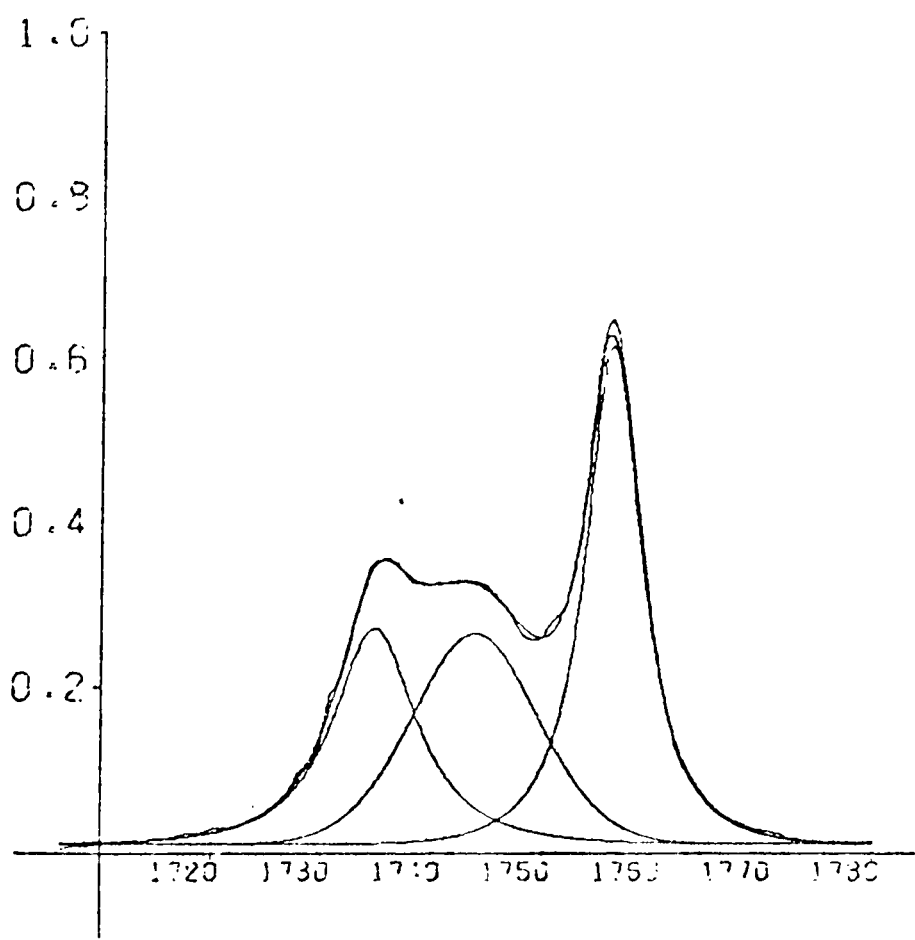


Figure 12 (dummy ν -values)

5 α -Androstan-17-one-3 β -yl-5'-chloro-2'-furoate (1.863 mg in 1.000 g carbon tetrachloride), $\nu_{-15^{\circ}\text{C}}$ 1739, 1723, and 1708 cm^{-1} .

Temperature ($^{\circ}\text{C}$)	$A_{\text{isol.}}$	$A_{\text{i}}\%$	A_{h}	A_{l}
-15	4.9267	100.0	3.2393	2.9876
0	4.9665	100.8	2.9744	3.1282
15	4.7731	96.9	2.6623	3.1924
30	4.6259	93.9	2.0147	3.6700
45	4.1590	84.4	1.9080	3.8923
60	3.9268	79.7	1.9278	3.8581
75	3.5988	73.1	2.1583	3.8208

Table 20

5 α -Androstan-17-one-3 β -yl 5'-phenyl-2'-furoate (2.115 mg in 1.000 g carbon tetrachloride), $\nu_{-15^{\circ}\text{C}}$ 1739, 1717.5, and 1703 cm^{-1} .

Temperature ($^{\circ}\text{C}$)	$A_{\text{isol.}}$	$A_{\text{i}}\%$	A_{h}	A_{l}
-15	5.2986	100.0	4.0370	3.9012
0	5.1692	97.6	3.9312	3.7244
15	4.9087	92.6	3.7913	3.5957
30	4.8062	90.7	3.8128	3.2820
45	4.7749	90.1	3.7052	3.0035
60	4.5721	86.3	3.4614	2.9213
75	4.5456	85.8	3.3821	2.9193

Table 21

Conformations of Esters: Analogue and Digital Resolutions

Experiment 25. The carbonyl regions of methyl (CX), ethyl (CXI), and t-butyl (CXII) furan-2-carboxylates were recorded, as carbon tetrachloride solutions, in the temperature range -15° to 75°C , with digital encoding of transmittance $\times 10,000$. The band envelopes were resolved and the individual bands were integrated by both analogue and digital methods. Specimen resolutions are included as Figures 13, 14, and 15. The results of the analogue resolutions are listed in Tables 22, 23, and 24, and of the digital resolutions in Tables 25, 26, and 27. The contributions made by very minor bands required for complete resolution in the methyl ester case have been excluded from the Tables.

Methyl furan-2-carboxylate (2.100 mg in 2.643210 g carbon tetrachloride),
 $\nu_{30^{\circ}\text{C}}$ 1740 and 1725 cm^{-1} .

Temperature ($^{\circ}\text{C}$)	A_{h}	A_{l}
-15	49.0	43.0
0	48.0	43.0
15	46.0	41.5
30	45.5	40.0
45	44.0	38.0
60	43.5	35.5
75	44.0	35.0

Table 22

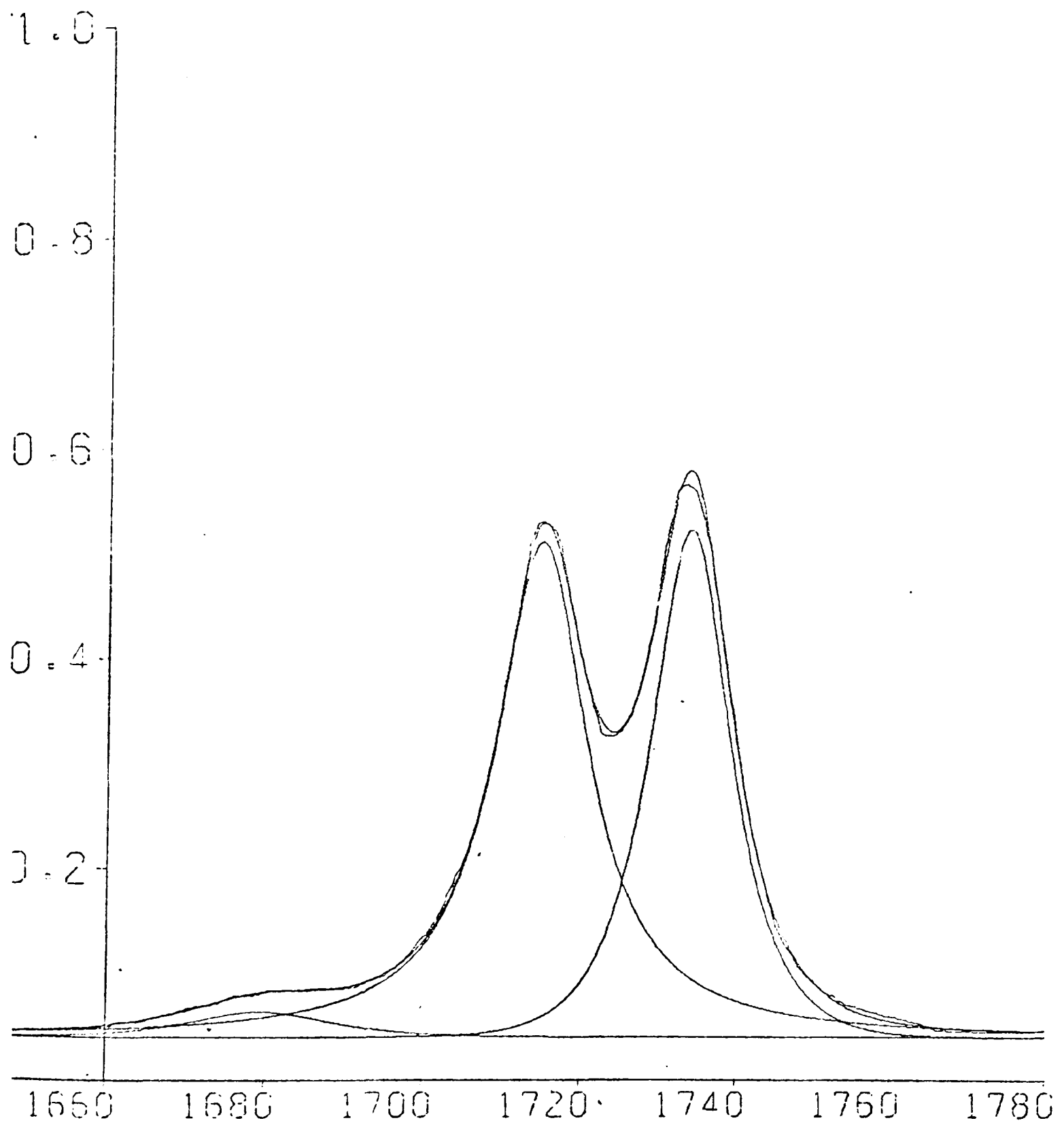


Figure 13 (dummy ν -values)

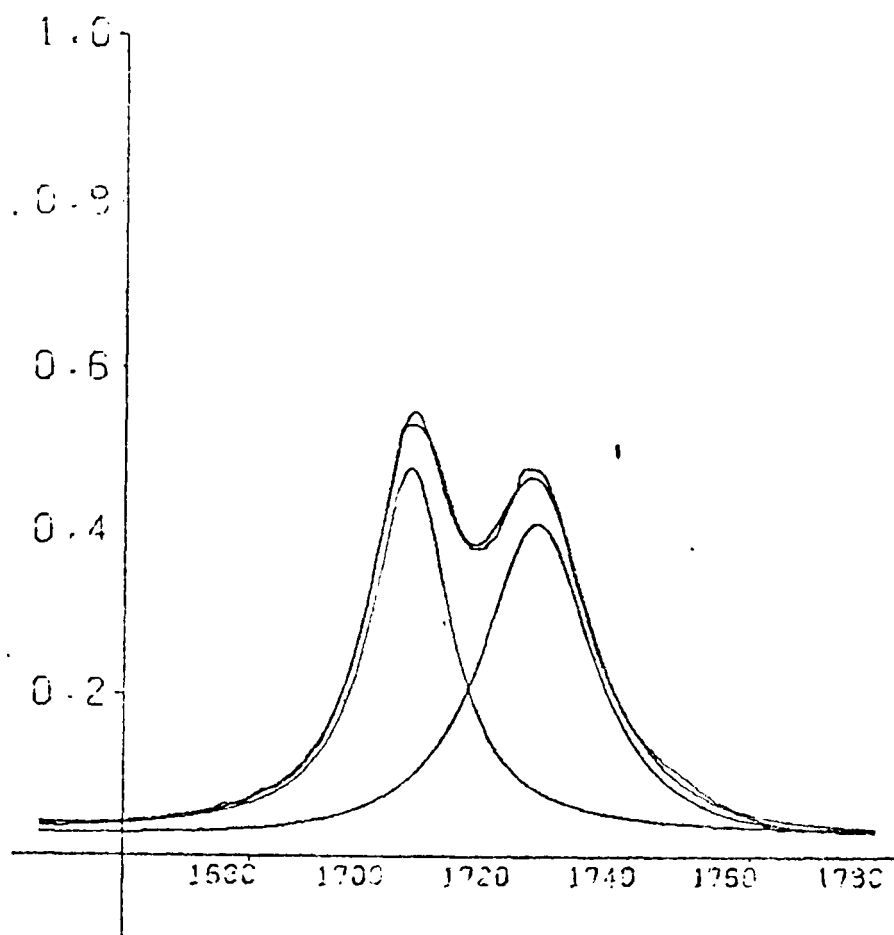


Figure 14 (dummy ν -values)

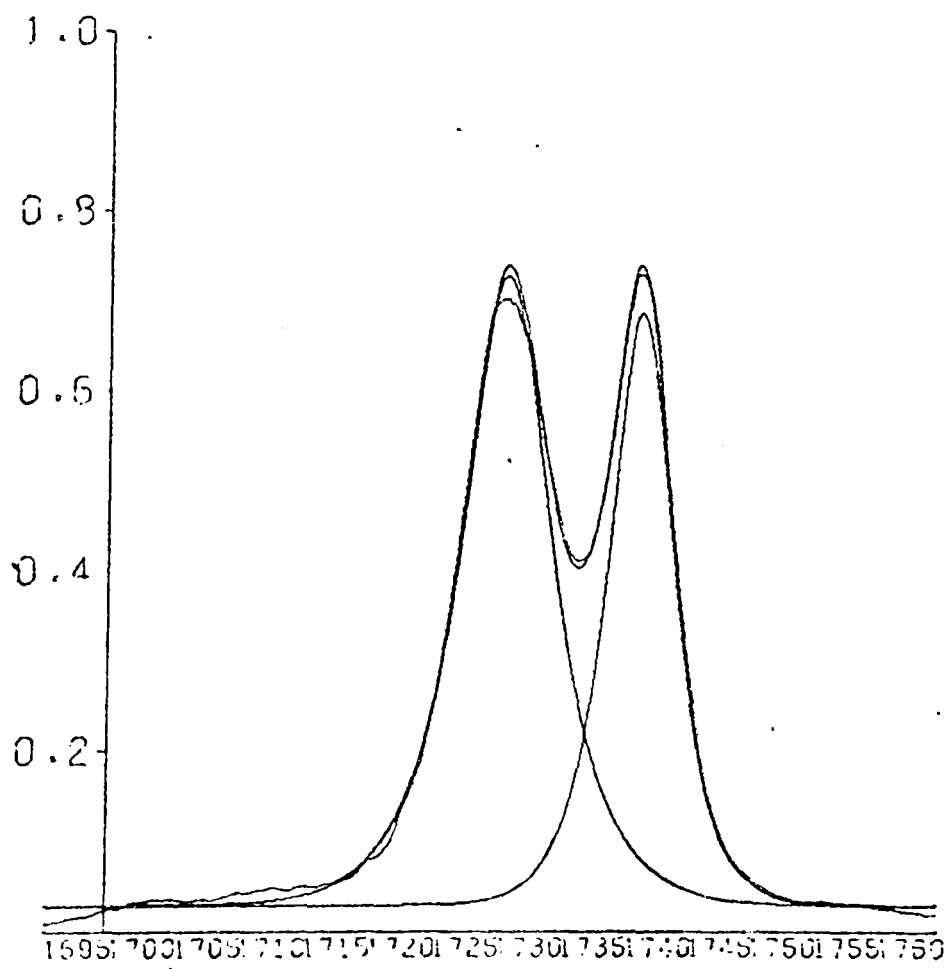


Figure 15 (dummy ν -values)

Ethyl furan-2-carboxylate (0.725 mg in 0.901475 g carbon tetrachloride),

$\nu_{30^{\circ}\text{C}}$ 1734 and 1718 cm^{-1} .

Temperature ($^{\circ}\text{C}$)	$A_{\underline{h}}$	$A_{\underline{l}}$
-15	45.0	55.0
0	42.0	54.0
15	40.5	54.5
30	39.0	53.5
45	37.0	53.0
60	35.0	52.5
75	34.0	52.5

Table 23

t-Butyl furan-2-carboxylate, $\nu_{30^{\circ}\text{C}}$ 1729 and 1711 cm^{-1} .

Temperature ($^{\circ}\text{C}$)	$A_{\underline{h}}$	$A_{\underline{l}}$
-15	40.0	60.0
0	40.5	57.0
15	40.5	53.5
30	40.5	52.0
45	41.0	48.0
60	41.0	47.5
75	41.5	46.5

Table 24

Methyl ester

Temperature (°C)	A_h	Shape	A_l	Shape
-15	7.3301	0.652	11.5167	0.972
0	7.3759	0.691	10.8403	0.964
15	7.2687	0.712	10.6563	0.980
30	7.0576	0.733	10.2998	0.995
45	6.6219	0.774	9.8993	0.999
60	6.7218	0.759	9.1286	0.971
75	6.2149	0.725	8.8971	0.984

Table 25

Ethyl ester

Temperature (°C)	A_h	Shape	A_l	Shape
-15	7.0964	0.824	8.0844	0.995
0	6.8957	0.817	7.5674	0.987
15	6.7232	0.799	7.1600	0.978
30	6.6366	0.781	7.0195	0.996
45	6.2827	0.744	6.8617	0.987
60	6.0713	0.721	6.3842	0.953
75	5.7806	0.698	6.3344	0.989

Table 26

t-Butyl ester

Temperature (°C)	A_h	Shape	A_l	Shape
-15	3.2586	0.559	5.5695	0.819
0	3.1420	0.638	5.0008	0.716
15	3.1247	0.689	4.8210	0.753
30	3.1177	0.696	4.5789	0.736
45	3.0679	0.709	4.3764	0.741
60	3.0525	0.728	4.2052	0.740
75	2.9730	0.762	4.3970	0.851

Table 27

As chloroform solutions, the three esters gave broad, single carbonyl bands at 1725 (methyl), 1716 (ethyl), and 1708 cm^{-1} (t-butyl), with shoulders to higher wavenumber at 1730.5 (methyl), 1725 (ethyl), and 1719 cm^{-1} (t-butyl).

No gross alterations in the appearance of the band envelopes were observed over hundred-fold changes in concentration.

The esters were finally examined in a 5 cm silica cell, as carbon tetrachloride solutions, in the carbonyl overtone region. The positions of bands, and their relative optical densities (in brackets) are given in Table 28.

Compound	Bands at (cm^{-1})
Methyl ester	3469 (1.1), 3437 (1.1), 3424 (1)
Ethyl ester	3453 (1), 3422 (1.2)
t-Butyl ester	3440 (1), 3408 (1.2)

Table 28

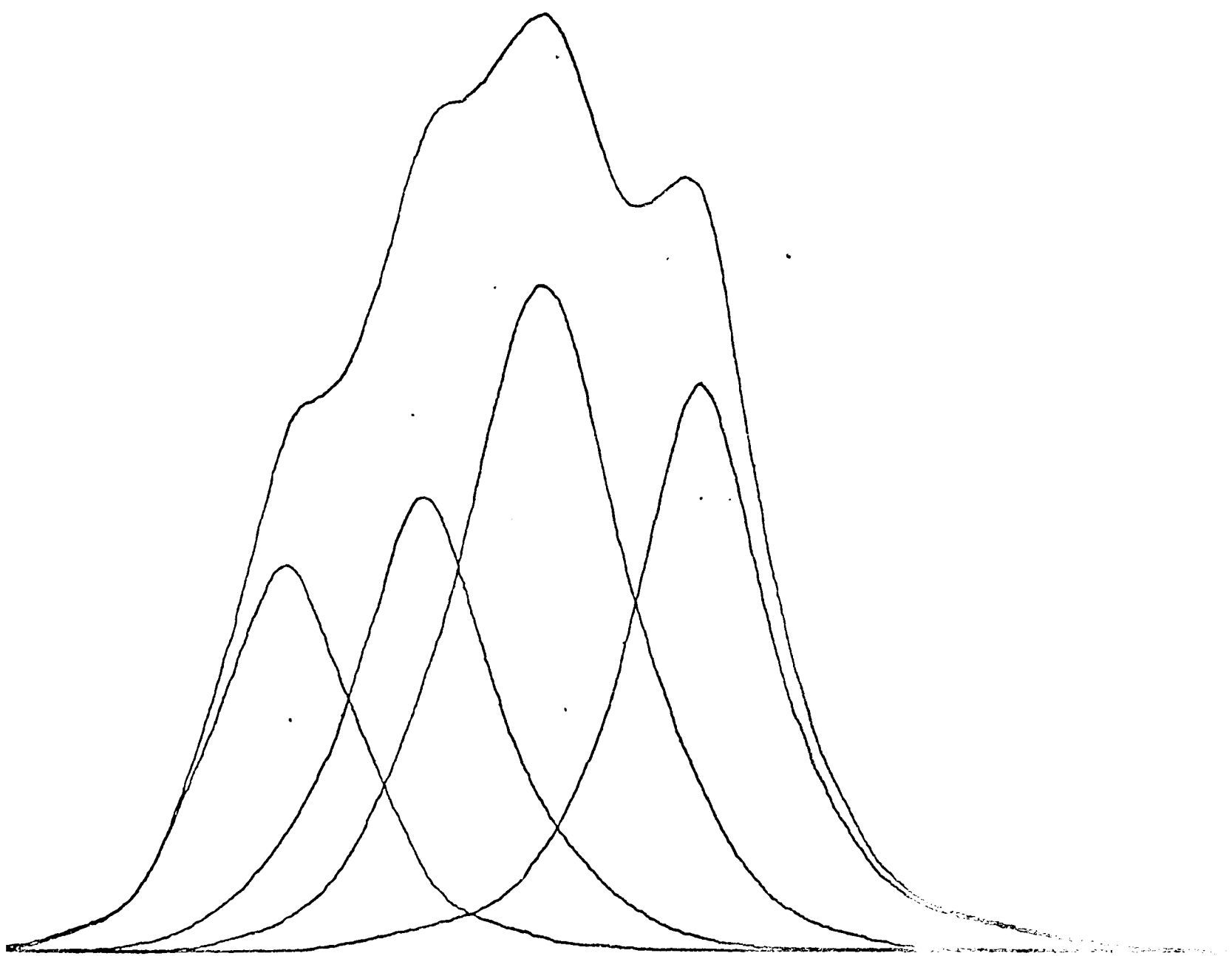


Figure 16

Experiment 26. The carbonyl regions of methyl (LXXXII), ethyl (LXXXIII), and t-butyl (LXXXIV) 5-bromofuran-2-carboxylates were recorded, as carbon tetrachloride solutions, in the temperature range -15° to 75°C . For the methyl ester, a complex band envelope was observed (vide Figure 16), having four distinct maxima at 1748 (D 0.40), 1738.5 (D 0.62), 1731.5 (D 0.69), and 1720 cm^{-1} (D 0.58) (at 30°C); the intensity of the band at 1720 cm^{-1} showed a marked increase with decrease in temperature. The ethyl and t-butyl esters showed doublets in the carbonyl regions at 1735, 1719 and 1731, 1712.5 cm^{-1} respectively, and the band envelopes were resolved and the individual bands integrated using the digital method. Specimen resolutions are included as Figures 17 and 18, and the results are listed in Tables 29 and 30.

Ethyl 5-bromofuran-2-carboxylate

Temperature ($^{\circ}\text{C}$)	$A_{\underline{h}}$	Shape	$A_{\underline{l}}$	Shape
-15	3.8931	0.662	5.0759	0.884
0	3.8878	0.675	4.6254	0.816
15	3.8406	0.665	4.3638	0.799
30	3.8823	0.701	4.1182	0.757
45	3.5962	0.670	4.1234	0.785
60	3.5022	0.678	4.0047	0.771
75	3.3331	0.677	3.9389	0.755

Table 29

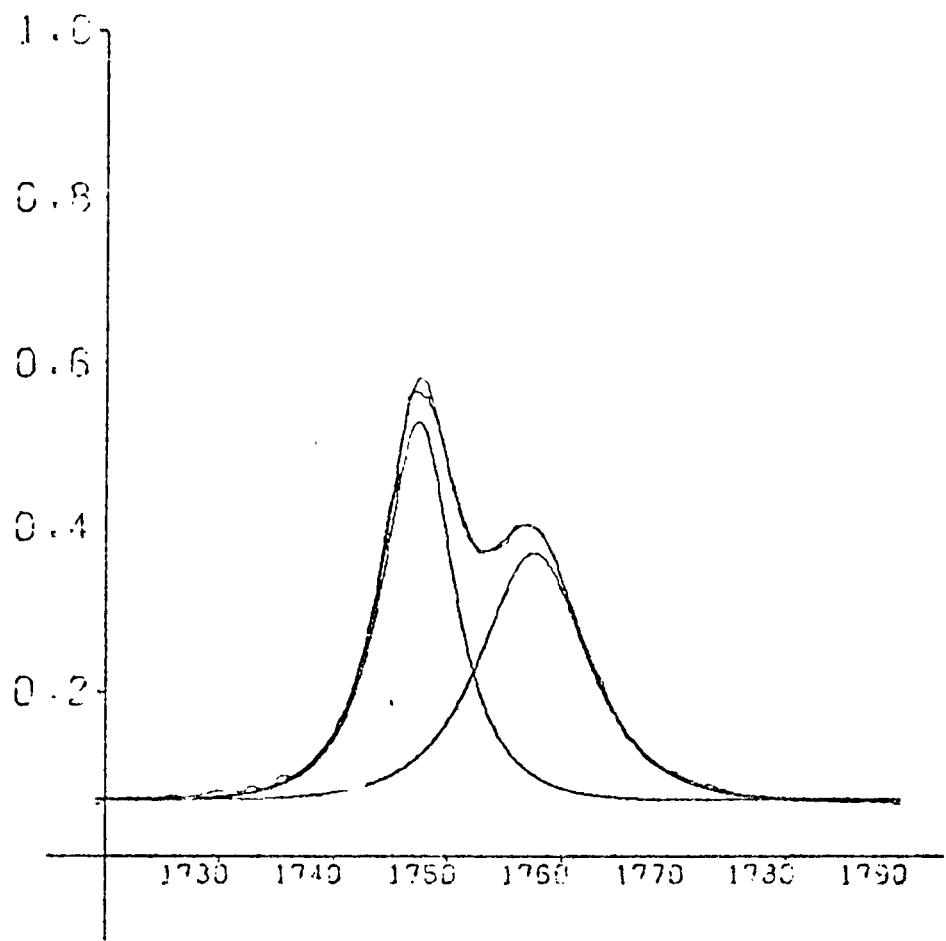


Figure 17 (dummy ν -values)

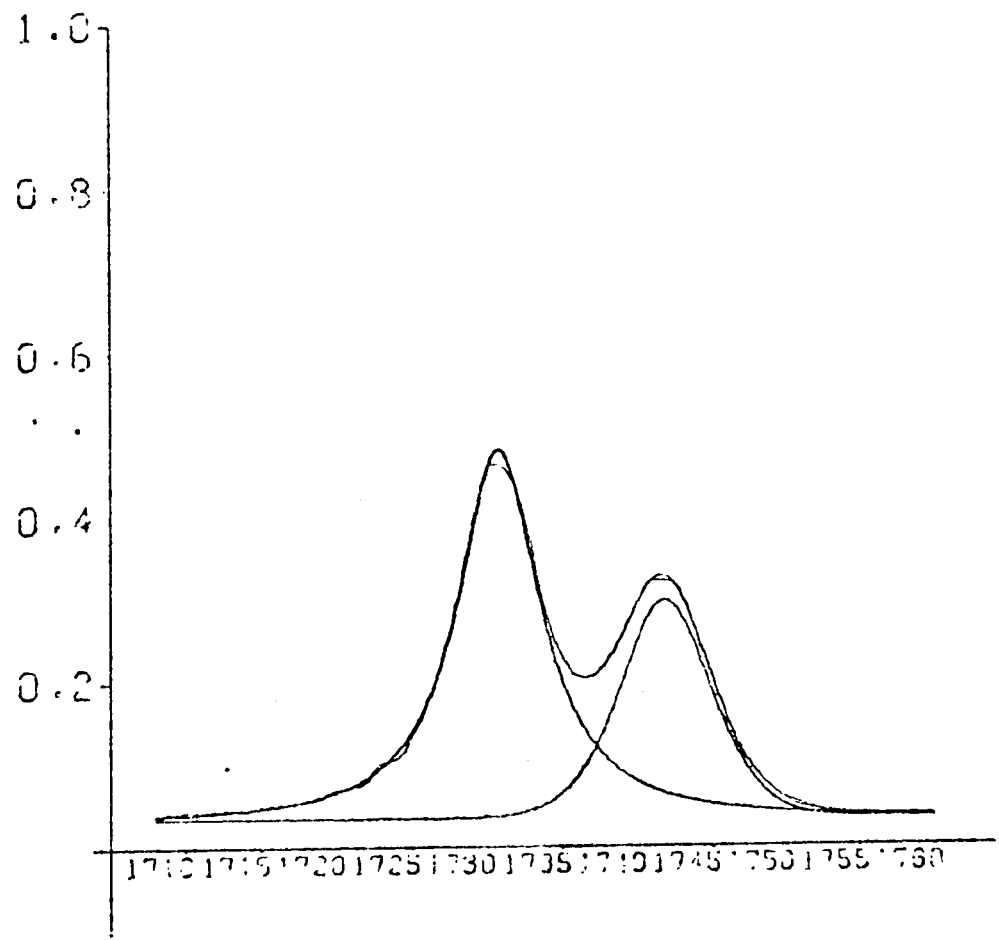


Figure 18 (dummy ν -values)

t-Butyl 5-bromofuran-2-carboxylate

Temperature (°C)	$A_{\underline{h}}$	Shape	$A_{\underline{l}}$	Shape
-15	2.1423	0.582	5.0894	0.823
0	2.1756	0.518	4.8505	0.916
15	2.0987	0.515	4.5533	0.860
30	2.0704	0.523	4.0258	0.888
45	1.9765	0.548	3.7992	0.878
60	1.9493	0.555	3.9990	0.975
75	1.9332	0.515	3.1203	0.880

Table 30

As acetonitrile solutions, the esters each gave doublet carbonyl absorptions. The positions of bands, and their relative optical densities (in brackets) are given in Table 31.

Compound	Bands at (cm ⁻¹)
Methyl ester	1731.5 (1.5), 1719.5 (1.0)
Ethyl ester	1726.5 (1.2), 1716.0 (1.0)
t-Butyl ester	1721.5 (1.1), 1710.5 (1.0)

Table 31

The esters were finally examined in a 5 cm silica cell, as carbon tetrachloride solutions, in the carbonyl overtone region. The positions of bands, and their relative optical densities (in brackets) are given in Table 32.

Compound	Bands at (cm ⁻¹)
Methyl ester	3466 (1), 3431 (1.4)
Ethyl ester	3455 (1), 3423 (1.6)
t-Butyl ester	3446 (1), 3409 (1.7)

Table 32

Experiment 27. The carbonyl regions of methyl (LXXXVI), ethyl (LXXXVIII), and t-butyl (LXXXIX) 4-bromofuran-2-carboxylates, as carbon tetrachloride solutions, were recorded in the temperature range -15° to 75°C, with digital encoding of transmittance x 10,000. The band envelopes were resolved and the individual bands were integrated by the digital method. Specimen resolutions are included as Figures 19, 20, and 21. The results of the resolutions are listed in Tables 33, 34, and 35.

Methyl 4-bromofuran-2-carboxylate, $\nu_{30^\circ\text{C}}$ 1746 and 1728.5 cm⁻¹.

Temperature (°C)	A _h	Shape	A _l	Shape
-15	5.4071	0.752	6.3453	0.698
0	5.6051	0.794	6.0297	0.734
15	5.6178	0.811	5.7318	0.758
30	5.7802	0.868	5.5331	0.784
45	5.6982	0.883	5.3269	0.801
60	6.1235	0.961	5.0278	0.808
75	5.9653	0.961	4.8431	0.815

Table 33

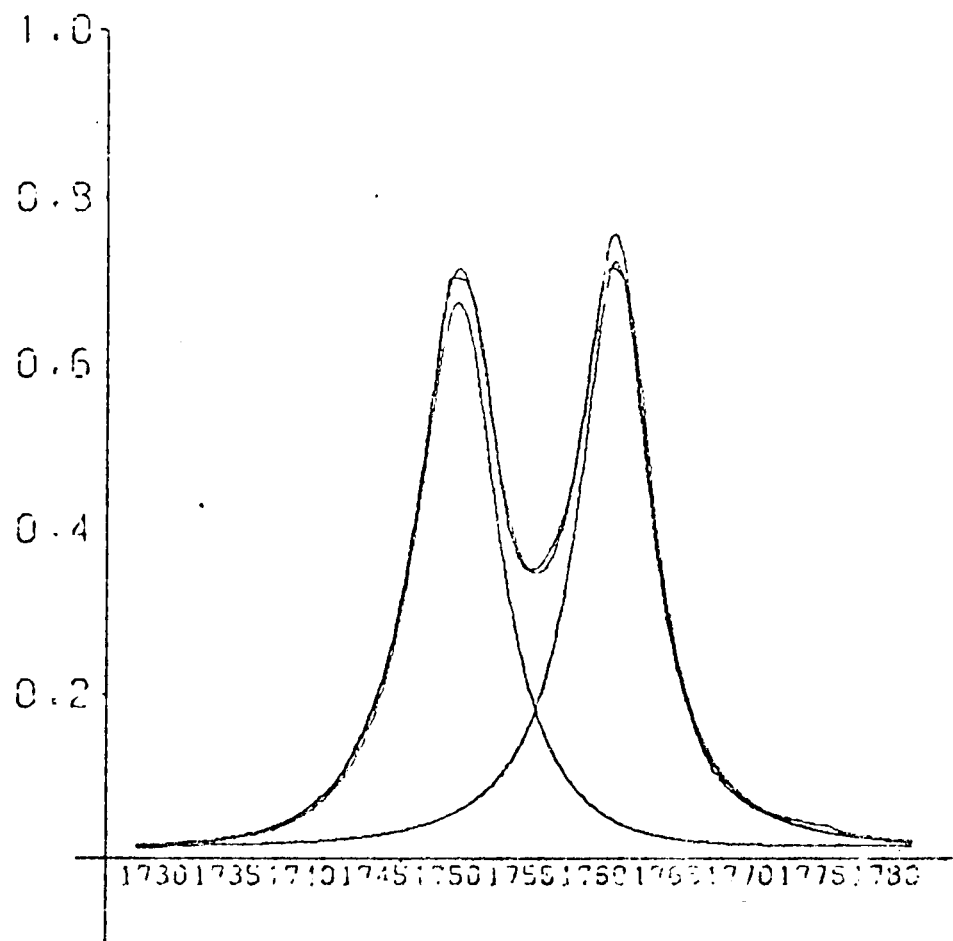


Figure 19 (dummy ν -values)

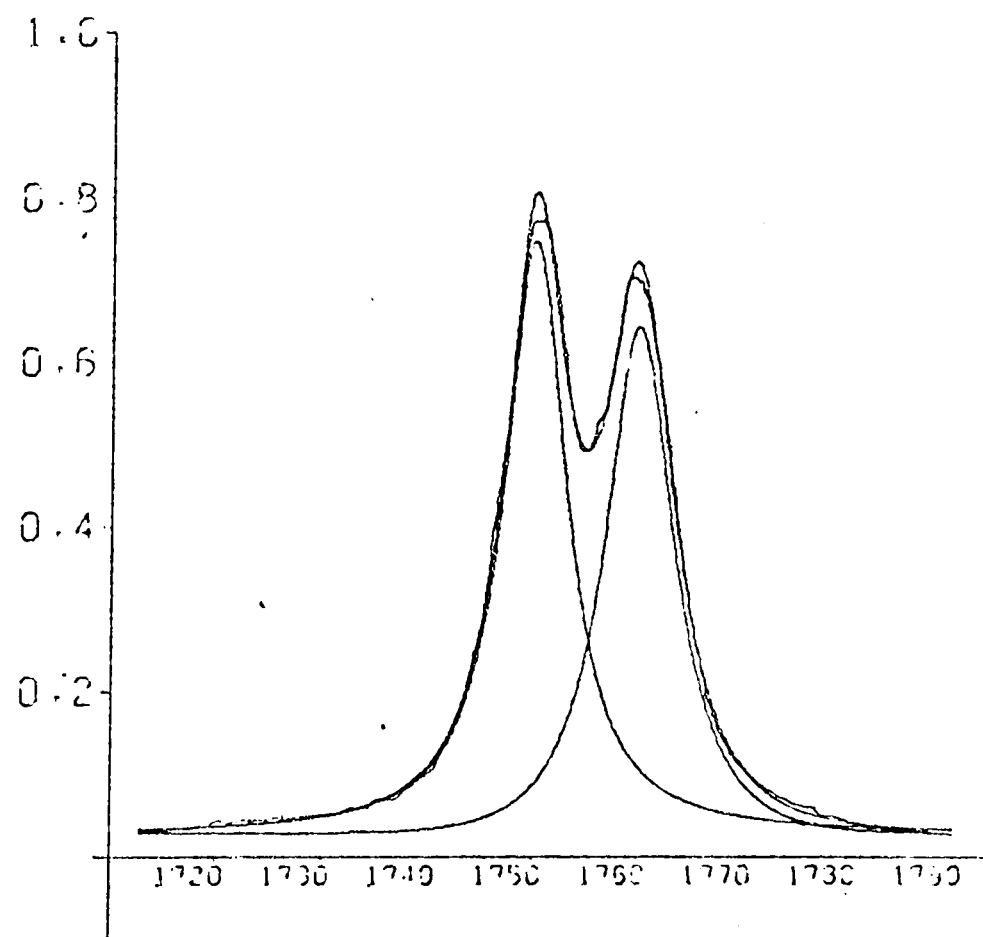


Figure 20 (dummy ν -values)

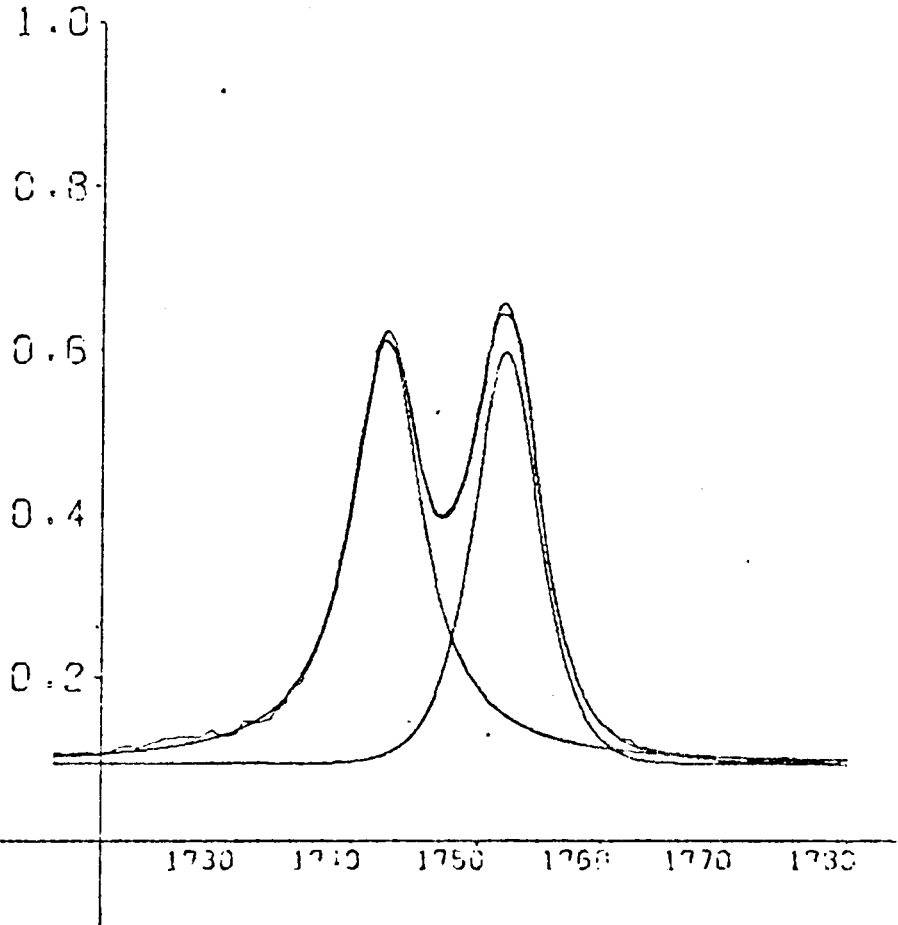


Figure 21 (dummy ν -values)

Ethyl 4-bromofuran-2-carboxylate, $\nu_{30^\circ\text{C}}$ 1739.5 and 1724 cm^{-1} .

Temperature ($^\circ\text{C}$)	$A_{\underline{h}}$	Shape	$A_{\underline{l}}$	Shape
-15	6.7263	0.689	8.2474	0.935
0	6.5788	0.710	8.1109	0.935
15	6.5196	0.771	7.3232	0.879
30	6.3205	0.779	6.6378	0.792
45	6.0215	0.786	7.4817	0.947
60	5.9124	0.793	7.0257	0.937
75	5.7518	0.803	6.7682	0.929

Table 34

t-Butyl 4-bromofuran-2-carboxylate, $\nu_{30^\circ\text{C}}$ 1734 and 1718 cm^{-1} .

Temperature ($^\circ\text{C}$)	$A_{\underline{h}}$	Shape	$A_{\underline{l}}$	Shape
-15	3.8389	0.539	6.4051	0.994
0	3.8281	0.585	5.8092	0.999
15	3.6179	0.620	5.6794	0.996
30	3.6036	0.653	5.5997	0.997
45	3.5847	0.709	5.3052	0.999
60	3.5595	0.720	5.1147	0.999
75	3.5371	0.739	4.8690	0.993

Table 35

In acetonitrile solutions, the three esters showed doublets at 1738 (D 0.55) and 1727.5 cm^{-1} (D 0.65) (methyl ester), 1730 (D 0.56) and 1722 cm^{-1} (D 0.46)

(ethyl ester), and 1724 (D 0.76) and 1717 cm^{-1} (D 0.58) (t-butyl ester).

Experiment 28. The carbonyl regions of methyl (XCII), ethyl (XCIII), and t-butyl (XCIV) 3-bromofuran-2-carboxylates, as carbon tetrachloride solutions, were recorded at 30°C. The methyl ester showed a single band centred at 1733 cm^{-1} with a slight shoulder at 1712 cm^{-1} , and the ethyl and t-butyl esters single bands at 1727.5 and 1723.5 cm^{-1} respectively, both of which were broadened to low frequency.

In acetonitrile solutions, the methyl ester showed a single band centred at 1727.5 cm^{-1} with a shoulder at 1720 cm^{-1} , the ethyl ester a band at 1721 cm^{-1} , broadened to low frequency, and the t-butyl ester a single band centred at 1713.5 cm^{-1} .

Experiment 29. The carbonyl regions of methyl (LXXVII), ethyl (LXXVIII), and t-butyl (LXXIX) 5-deuteriofuran-2-carboxylates, as carbon tetrachloride solutions, were recorded at 30°C. Doublets were observed for each of the esters at 1740.5 (D 0.87) and 1725.5 cm^{-1} (D 0.81) (methyl ester), 1734 (D 0.50) and 1718 cm^{-1} (D 0.54) (ethyl ester), and 1729 (D 0.40) and 1711 cm^{-1} (D 0.41) (t-butyl ester).

Experiment 30. The carbonyl regions of methyl (XCVII), ethyl (LXXIII), and t-butyl (XCVIII) 5-bromo-3,4-dideuteriofuran-2-carboxylates, as carbon tetrachloride solutions, were recorded at 30°C. Doublets were observed for each of the esters at 1743 (D 0.30) and 1729.5 cm^{-1} (D 0.38) (methyl ester), 1736 (D 0.54) and 1719 cm^{-1} (D 0.84) (ethyl ester), and 1731 (D 0.44) and 1712.5 cm^{-1} (D 0.67) (t-butyl ester).

In acetonitrile solutions, the methyl ester showed a single band centred

at 1731 cm^{-1} , broadened to low frequency, and the ethyl and t-butyl esters doublets at 1727 (D 0.30), 1716.5 cm^{-1} (D 0.26) and 1721 (D 0.48), 1711 cm^{-1} (D 0.46), respectively.

Experiment 31. The carbonyl regions of methyl (CII) and t-butyl (CIII) N-methylpyrrole-2-carboxylates, as carbon tetrachloride and chloroform solutions, were recorded at 30°C . Single bands were observed in all cases, in carbon tetrachloride at 1709 (methyl ester) and 1702 cm^{-1} (t-butyl ester) and in chloroform at 1700 and 1693 cm^{-1} , respectively.

Experiment 32. The carbonyl regions of 5- (LXXXV), 4- (XC), and 3- (XCV) bromofuran-2-carbonyl chlorides, and of 5-bromo-3,4-dideuteriofuran-2-carbonyl chloride (XCIX), as carbon tetrachloride and acetonitrile solutions, were recorded at 30°C . The results are summarised in Table 36, in which the positions of distinct maxima are followed (in brackets) by relative optical densities.

Compound	Solvent	Bands at (cm^{-1})
(LXXXV)	Carbon tetrachloride	1761.5 (1.4), 1745 (1)
(")	Acetonitrile	1756 (shoulder), 1747.5
(XC)	Carbon tetrachloride	1795 (1), 1764 (3.9), 1746.5 (2.5)
(")	Acetonitrile	1793 (1), 1756 (7), 1748 (shoulder)
(XCV)	Carbon tetrachloride	1755.5
(")	Acetonitrile	1749.5
(XCIX)	Carbon tetrachloride	1774 (shoulder), 1761 (1.4), 1747 (1)
(")	Acetonitrile	1756 (shoulder), 1747.5

Table 36

The acid chlorides were also examined, as carbon tetrachloride solutions, in the carbonyl overtone region. The results are summarised in Table 37 using the conventions of Table 36.

Compound	Bands at (cm^{-1})
(LXXXV)	3555 (1), 3505 (3.9), 3475 (2.2)
(XC)	3516 (1.5), 3478 (1)
(XCV)	3495 (1.4), 3473 (1)
(XCIX)	3530 (1.6), 3509 (1.7), 3475 (1)

Table 37

Approaches to Data Processing: "All-Purpose" Digital Computer Program

Experiment 33. A program was written for the ICL 1906A computer which, given as input data values of $A_{\underline{h}}$ and $A_{\underline{l}}$ at stated temperatures for a rotameric equilibrium, carries out all of the mathematical operations required for the evaluation of thermodynamic parameters (and of their errors) correcting, where possible, for the "natural decrease" (vide "Discussion") and for the plotting of the linear graphs involved.

The program, which is included as Appendix C, has five segments. Statements 1 to 15 of the main segment (the "Master" segment) are concerned with data input. Statements 16 to 23 allow the calculation of the least squares straight line fit for the $A_{\underline{h}}$, $A_{\underline{l}}$ plot and the graphical presentation of the plot, by invoking two other segments of the program (subroutines "Leastsq" and "Plotitout"). Depending on whether the α -ratio so-obtained is positive or negative, the program

then branches. If the ratio is negative, a message informing the user that the α -correction cannot be made is printed, and the program then allows the calculation and printing of the straight line fit for the A_h, A_l plot by the "means" method (vide "Theoretical Considerations") using subroutine "Means". If the α -ratio is still negative, the program continues with the calculation and printing of the least squares fit for the $\log_{10}(A_l/A_h)$ vs. $1/T$ plot by once more invoking the subroutines Leastsq and Plotitout. The thermodynamic parameters (ΔH , ΔG , and ΔS) are then calculated by a call of the subroutine "Deltah". If the α -ratio is originally positive, the program allows the calculation of the least squares fit for the $\log_{10}(\alpha_h A_l / \alpha_l A_h)$ vs. $1/T$ plot and the evaluation of the thermodynamic parameters by calls of the subroutines Leastsq and Deltah. The A_h, A_l plot is then re-examined by the "means" method (by a call of subroutine Means), and, if the α -ratio is still positive, a further set of α -corrected thermodynamic parameters is evaluated (by a call of subroutine Deltah). It is to this step that branching occurs, from earlier in the program, if the α -ratio is negative in the Leastsq plot but positive in the Means plot. The program then continues by testing if the band areas have been "corrected" for the "natural decrease" (vide Discussion). If the correction has already been made, the program terminates with the evaluation of the errors in the thermodynamic parameters. If the correction has not been made, it is applied after a test has been made to ascertain whether the band areas are derived from analogue or digital curve resolutions. Depending on their origin, the areas are corrected to differing extents. The sequence of calculations described above is then repeated using the corrected areas, after which, the program terminates with the evaluation of errors.

Subroutine Plotitout, which is called from the master segment whenever

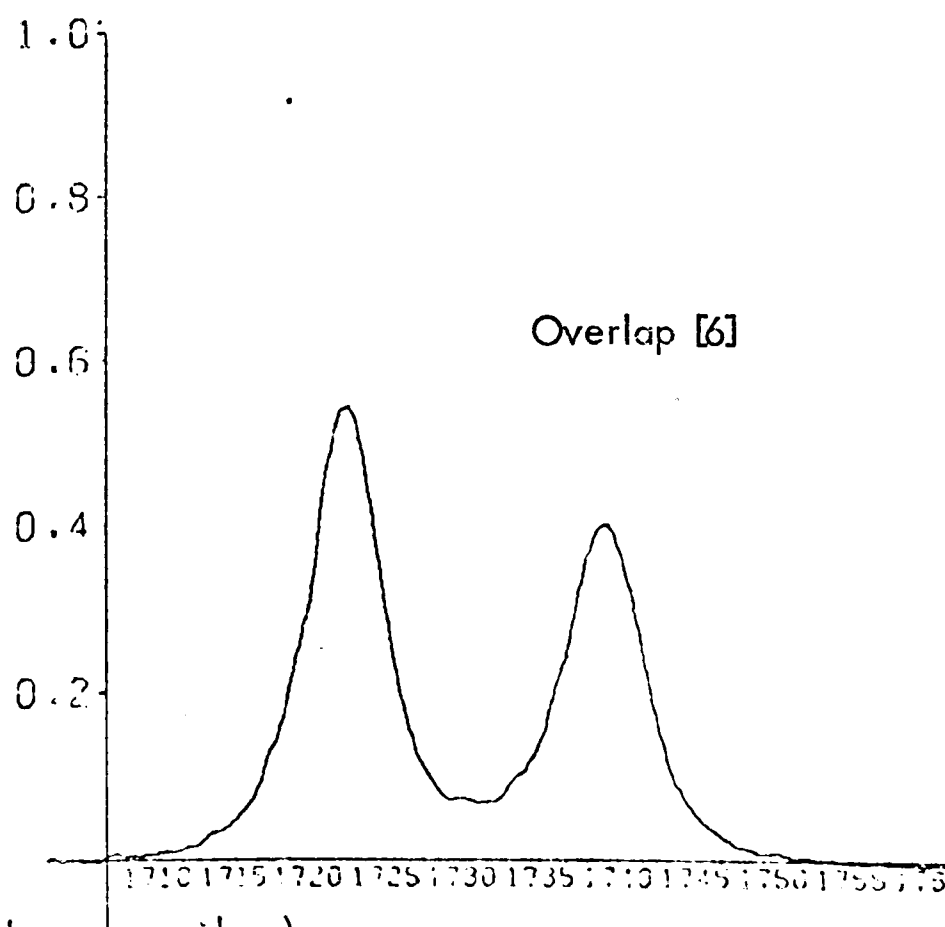
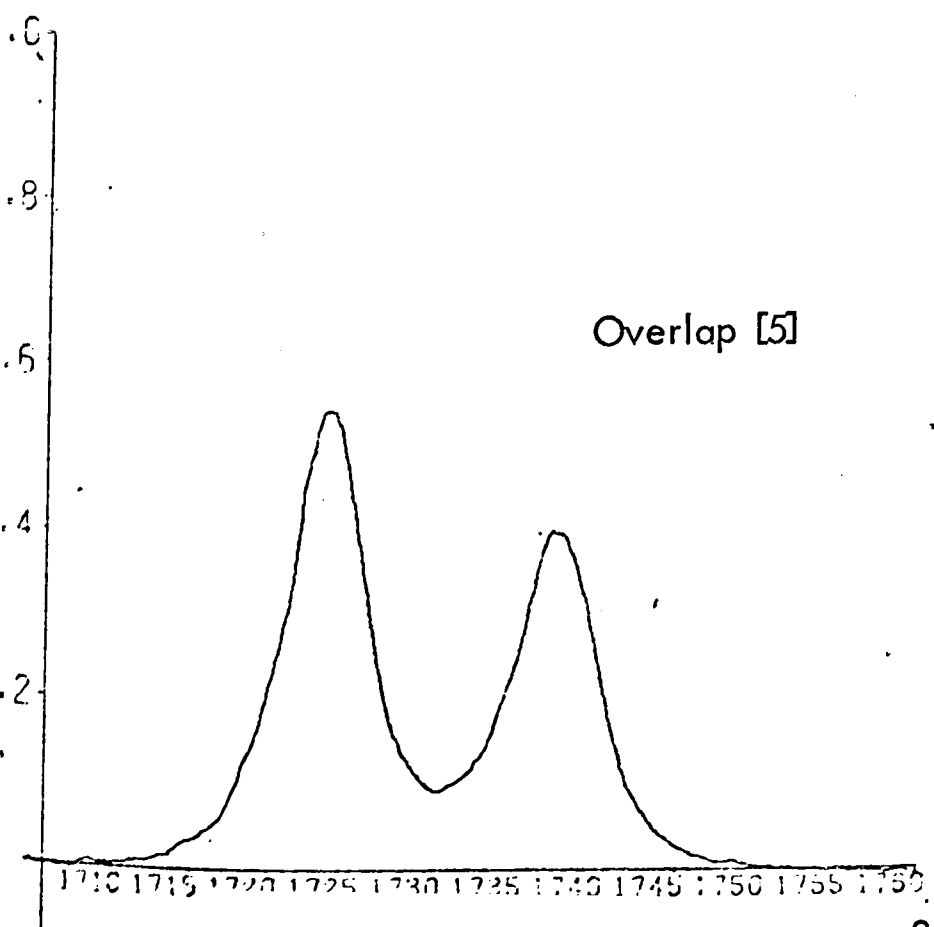
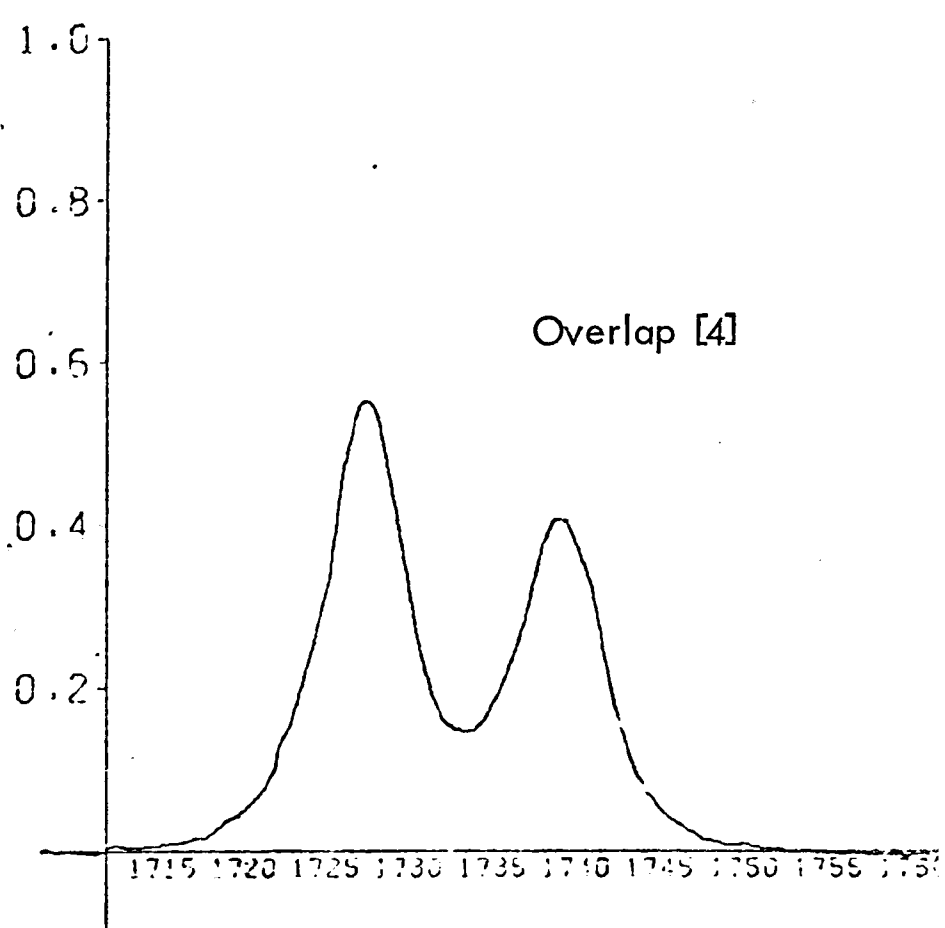
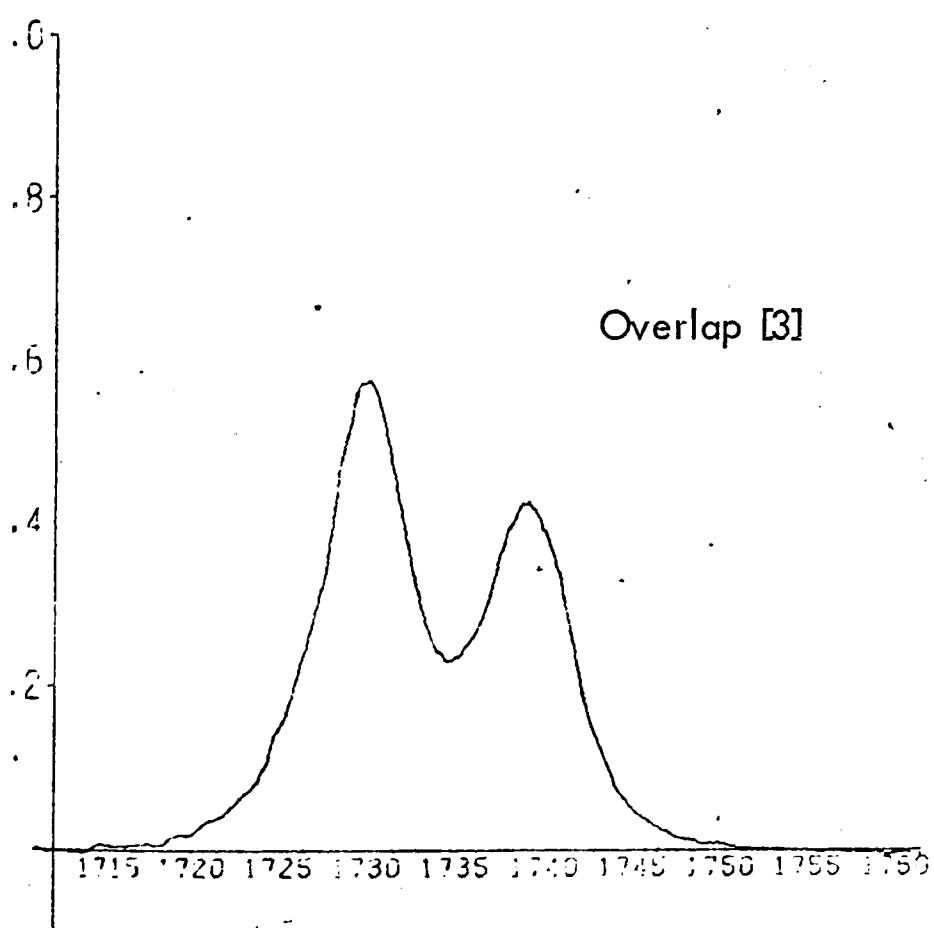
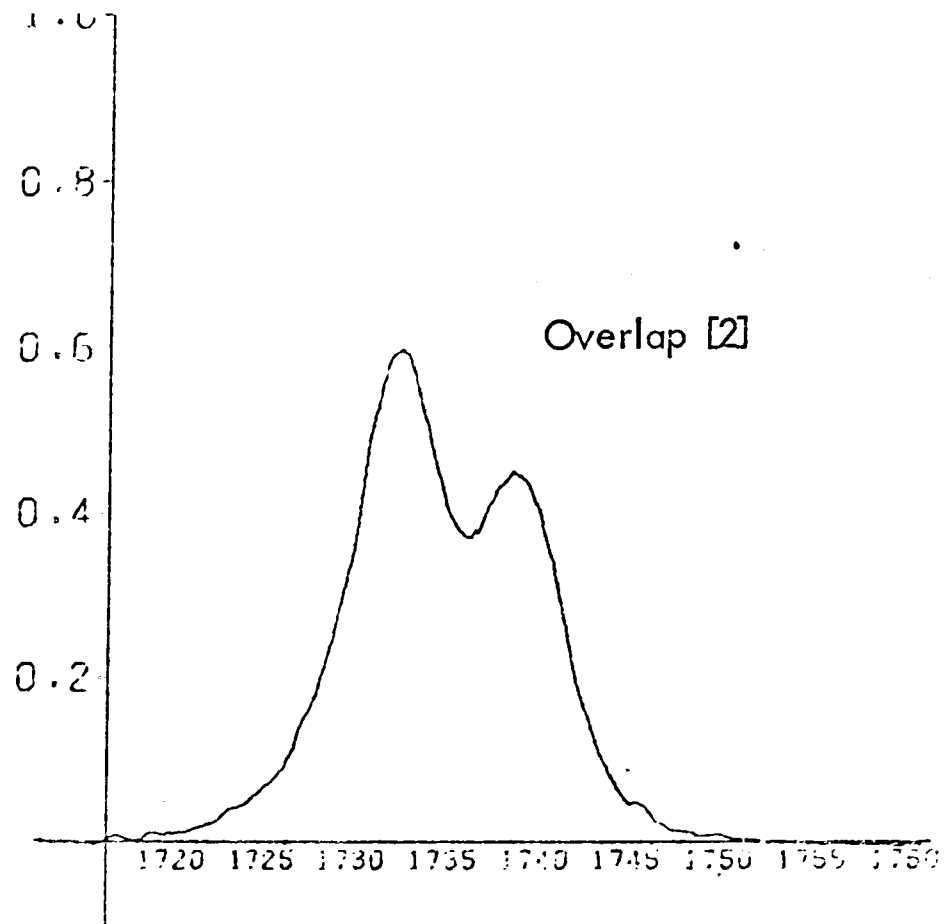
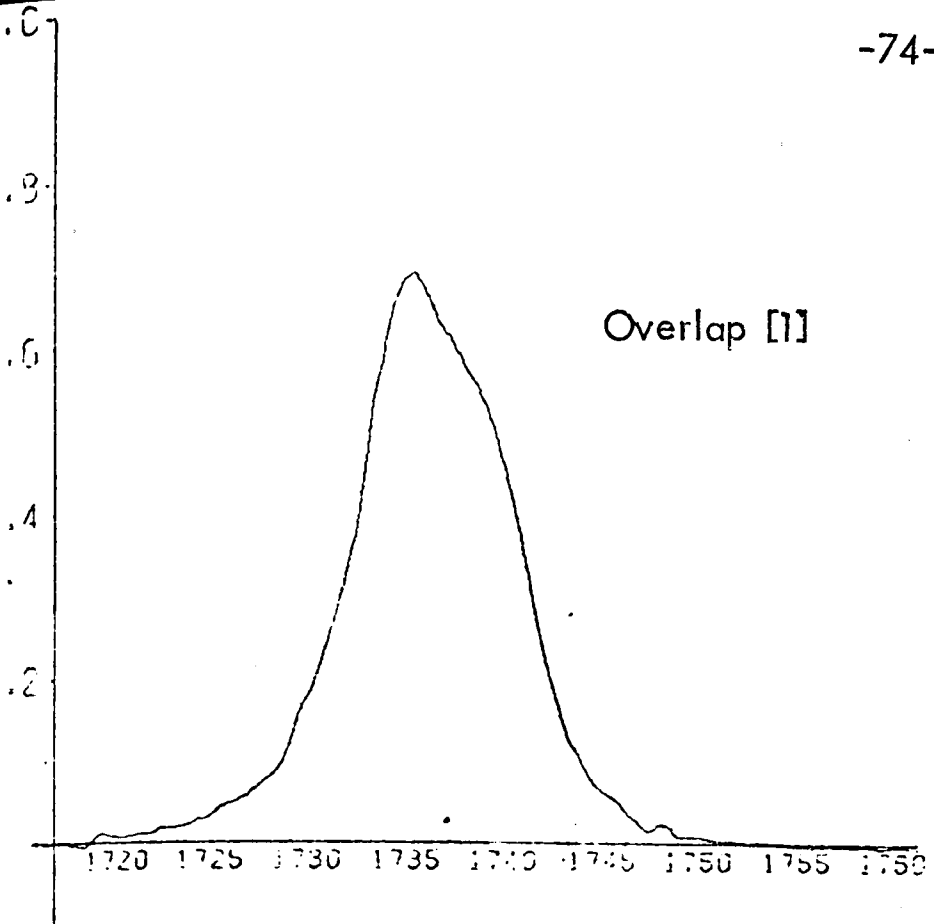
a graph has to be plotted, uses the graphical output subroutines of the ICL 1906A. The plotting limits are determined in the subroutine by a scan of the arrays containing x and y values, for the minimum and maximum values. Plotting is terminated by a variable, the value of which is set in the master segment.

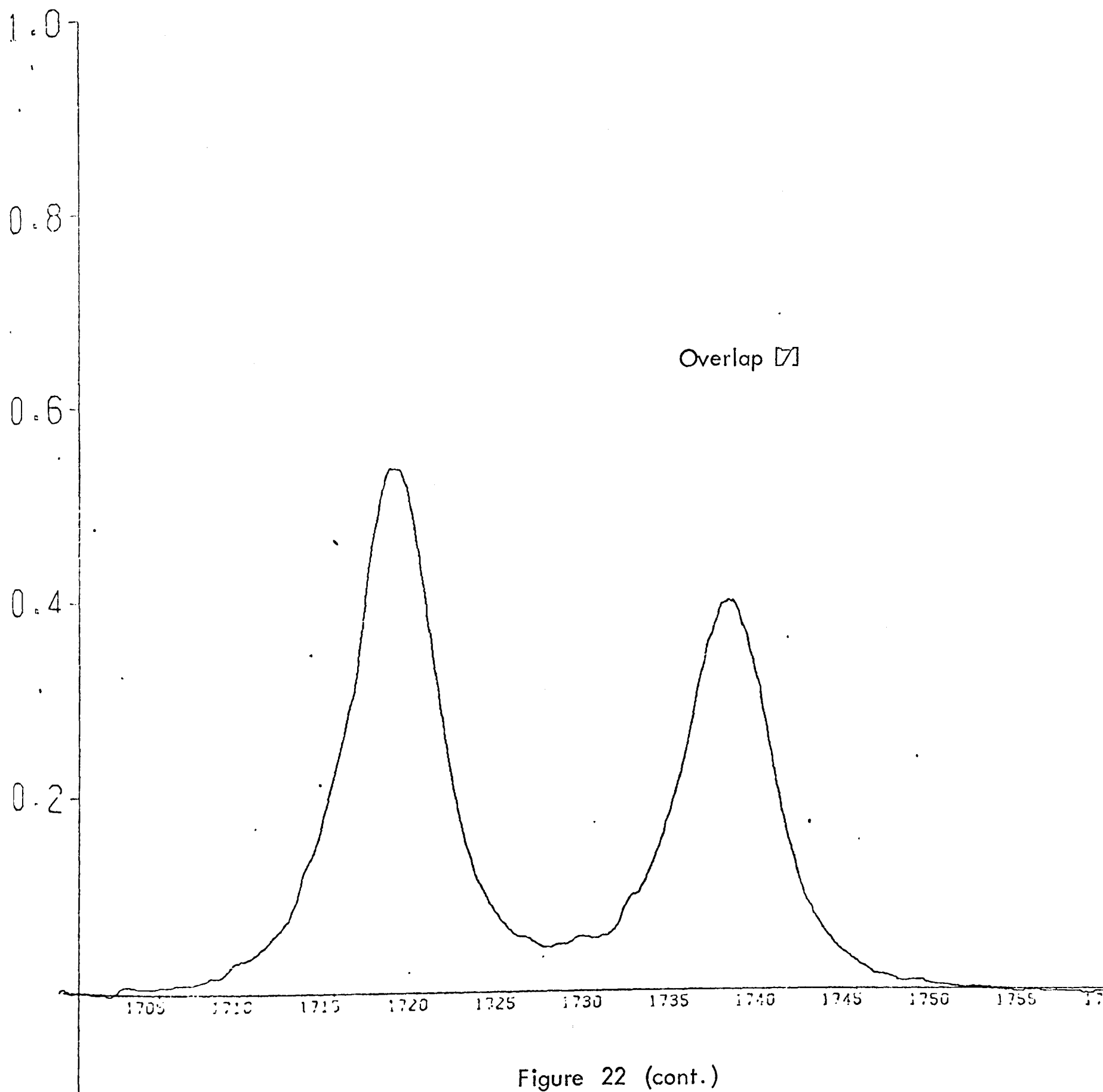
Subroutine Deltah, which is called from the master segment whenever thermodynamic parameters are to be calculated, is entirely straightforward and requires no further comment.

Subroutine Leastsq, which is called from the master segment whenever a least squares linear plot is to be evaluated, is based upon the theory described in "Theoretical Considerations". The subroutine is responsible for the printing not only of slopes and intercepts but also of Analysis of Variance tables.

Subroutine Means, which is called from the master segment whenever a linear plot is to be made by the method of means, is straightforward and requires no further comment.

Experiment 34. A program was written for the ICL 1906A computer which, given as input data the intensities of two single i.r. bands recorded as transmittance x 10,000 values punched at regular intervals, will overlap the bands to seven differing extents, starting with an overlap of 400 data points and decreasing by steps of 25 points: the program is dimensioned for a maximum of 2000 data points for each curve. The program produces two graphs for each overlap, the larger being suitable for use with an analogue curve resolver: the overlapped profile, but not the individual curves are recorded thus. A paper tape record of the profiles, suitable for subsequent digital curve resolution, is also produced. The program, which invokes the graphical output subroutines of the ICL 1906A, is





straightforward, and requires no discussion: it is included as Appendix D.

Using this program, the carbonyl bands of methyl m-chlorobenzoate and methyl 3-methyl-2-furyl ketone at 30°C were overlapped: the resulting envelopes are included as Figure 22. The individual band areas were then estimated by five methods: (1) analogue; (2) digital; (3) outer halves; (4) minimum, and (5) mid-point. Methods (3) to (5) are the so-called graphical methods which were discussed earlier (vide "Theoretical Considerations"): all of the integrations for all of the methods involved Simpson's rule. The results are summarised in Table 38 where the figures given correspond to the ratio $A_{\underline{h}}/A_{\underline{l}}$, except in column 6 where the figures correspond to $D_{\underline{h}}/D_{\underline{l}}$.

Overlap	Methods					
	(1)	(2)	(3)	(4)	(5)	(6)
1	0.57	0.40	Methods cannot be applied			
2	0.59	0.56	0.72	0.62	0.76	0.75
3	0.60	0.65	0.64	0.74	0.73	0.74
4	0.66	0.70	0.65	0.71	0.74	0.74
5	0.75	0.72	0.77	0.76	0.76	0.74
6	0.72	0.74	0.66	0.75	0.76	0.74
7	0.74	0.75	0.76	0.79	0.77	0.75

Table 38

B. Nuclear Magnetic Resonance Investigations

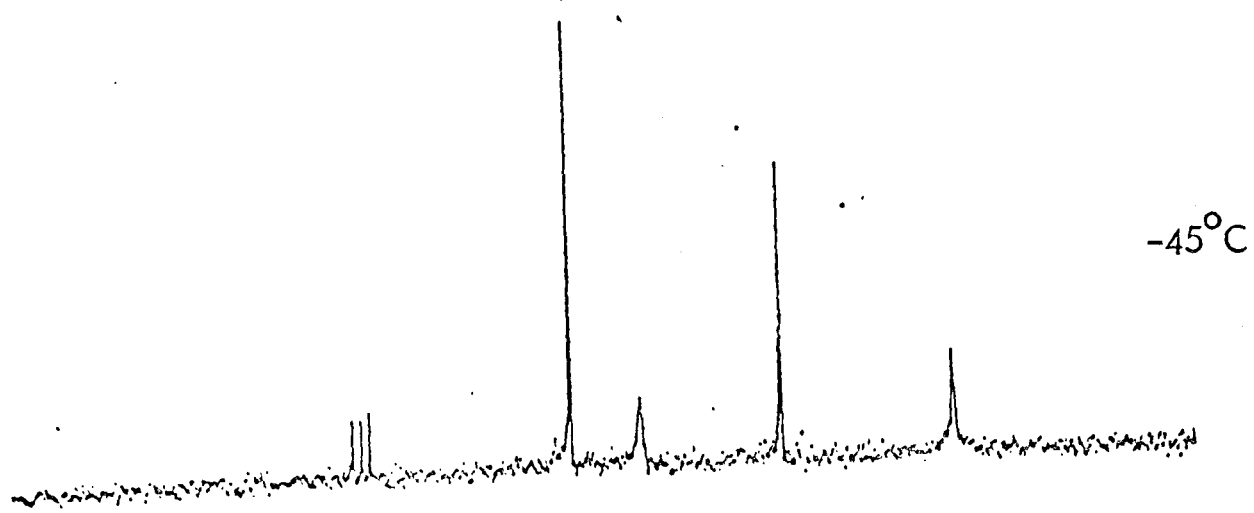
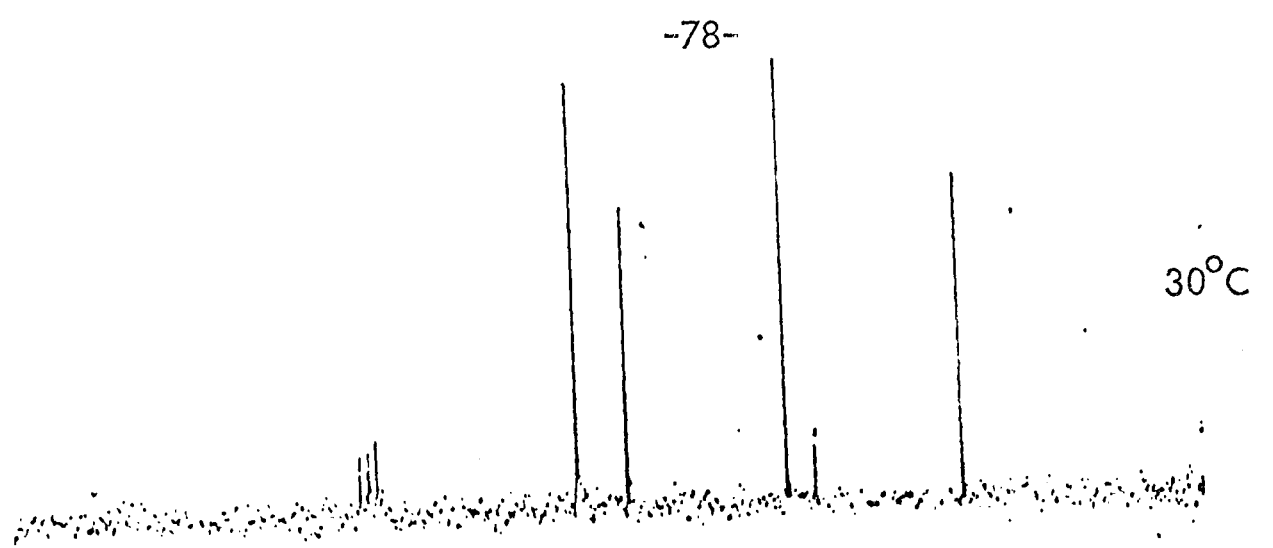
Routine n.m.r. spectra were recorded by the author on either a Perkin-Elmer R10 (60 MHz) or R14 (100 MHz) spectrometer; the results are listed, compound by compound, in the Experimental-Preparative section.

Variable temperature proton n.m.r. spectra were recorded on a Perkin-Elmer R10 spectrometer fitted with a variable temperature probe. The temperature calibration was accurate to $\pm 1^{\circ}\text{C}$, and the stability to $\pm 1^{\circ}\text{C}$. Variable temperature C-13 n.m.r. spectra were recorded for the author on a Brücker 90 MHz Fourier-transform spectrometer with wide band decoupling.

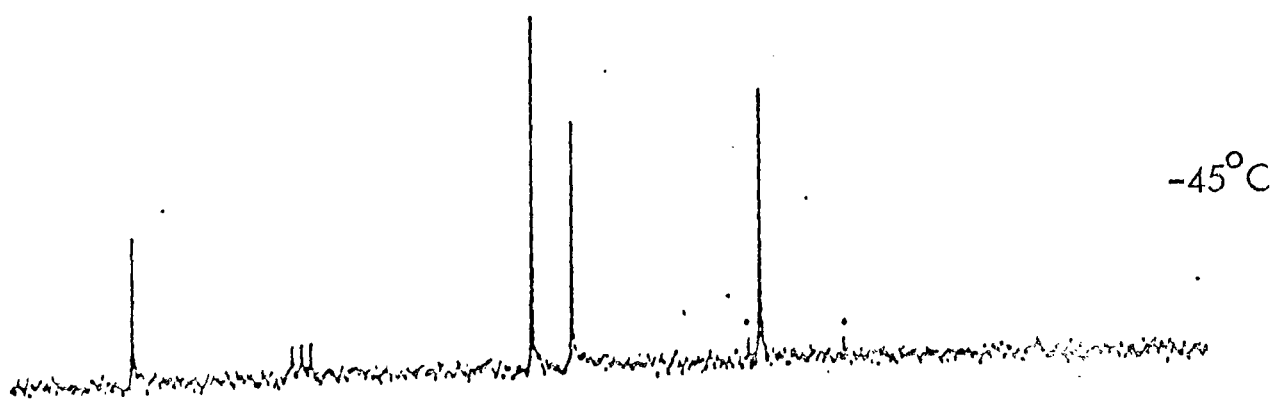
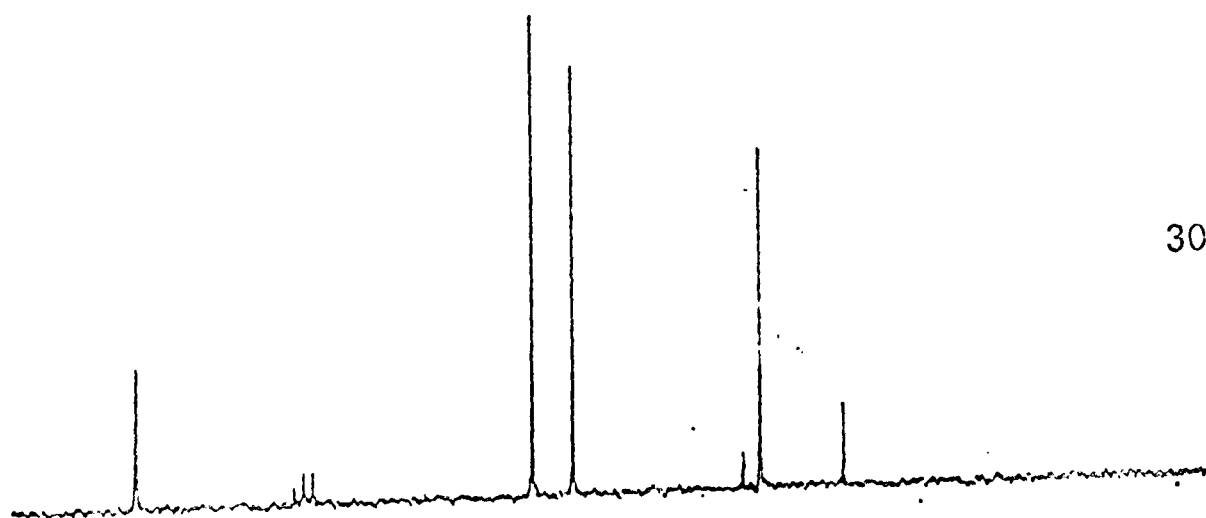
Experiment 35. The n.m.r. spectrum of furan-2-carbonyl fluoride was recorded at 30°C with carbon tetrachloride as solvent and over a range of temperatures between -70°C and 30°C using 1,2-dichloroethane as solvent.

At 30°C , the ring protons appear as three groups of signals, each consisting of eight lines, at τ 2.26 ($\underline{J}$ 0.8, 1.6, and 2.5 Hz; 5-H), 2.62 ($\underline{J}$ 3.6, 0.8, and 0.6 Hz; 3-H), and 3.39 ($\underline{J}$ 0.8, 1.6, and 3.6 Hz; 4-H). The apparent coupling constants for the signals corresponding to the 4- and 5-protons are summarised below:

Temperature ($^{\circ}\text{C}$)	4-H (Hz)	5-H (Hz)
+10	0.7, 1.9, 3.6	0.7, 1.9, 2.5
-10	0.6, 1.9, 3.6	0.6, 1.9, 2.6
-30		0.7, 1.7, 2.4
-45	0.4, 1.7, 3.7	
-50	0.3, 1.7, 3.8	0.8, 1.7, 2.7
-70	<0.2, 1.6, 3.5	



Furan-2-carbaldehyde



Methyl furan-2-carboxylate

Experiment 36. The carbon-13 n.m.r. spectra of furan-2-carbaldehyde and of methyl furan-2-carboxylate, as deuteriochloroform solutions, were recorded at 30°C and -45°C. Photographs of the spectra are included as Figure 37. The chemical shifts of major resonances in p.p.m. from the centre resonance of the deuteriochloroform triplet are summarised below:

Compound	t (°C)	Shifts (p.p.m.)
Furan-2-carbaldehyde	30	0.10×10^3 ($\underline{\text{C}}=\text{O}$)
		0.71×10^2 (5-C)
		0.44×10^2 (3-C)
		0.35×10^2 (4-C)
Furan-2-carbaldehyde	-45	0.10×10^3 ($\underline{\text{C}}=\text{O}$)
		0.71×10^2 (5-C)
		0.47×10^2 (3-C)
		0.36×10^2 (4-C)
Methyl furan-2-carboxylate	30	0.69×10^2 (5-C)
		0.41×10^2 (3-C)
		0.35×10^2 (4-C)
		-0.25×10^2 ($\underline{\text{CH}}_3$)
Methyl furan-2-carboxylate	-45	0.82×10^2 ($\underline{\text{C}}=\text{O}$)
		0.69×10^2 (5-C)
		0.41×10^2 (3-C)
		0.35×10^2 (4-C)
		-0.25×10^2 ($\underline{\text{CH}}_3$)

Collapse and broadening of the signals assigned to the carbonyl carbon atom and

to the carbon atom at the 3-position is observed, with decrease in temperature, for furan-2-carbaldehyde, but a similar phenomenon is not observed for methyl furan-2-carboxylate.

EXPERIMENTAL - PREPARATIVE

General Directions

All products were checked for purity by gas-liquid chromatography (g.l.c.) or thin-layer chromatography (t.l.c.). G.l.c. was carried out on a Pye Argon Chromatograph using a 1-metre column of 10% polypropylene adipate on "Embacel" with a gas pressure of 10 p.s.i. For t.l.c., 20 x 5 cm glass plates coated with a 0.1 mm layer of unbaked Kieselgel HF₂₅₄₊₃₆₆ were eluted with acetone-petrol mixtures (unless otherwise stated) and viewed under u.v. light.

Preparative thin-layer chromatography (p.t.l.c.) was carried out on 20 x 20 cm glass plates coated with a 1 mm layer of Kieselgel PF₂₅₄₊₃₆₆: the plates were eluted once with methanol before use. The mixture to be separated (up to 100 mg) was applied, in chloroform solution, by continuous flow from a syringe, mounted in a moving carriage above the plate. The flow rate was regulated (by varying the air pressure above the solution) so that the band formed by the solution was ca. 5 mm wide. The plate was maintained at 50°C during the application, and the carriage rate so adjusted that the solvent from one pass of the syringe was evaporated before more solution was applied. After repeated development of the plates with standard solvent systems, the bands of separated materials were located by inspection of the plates under u.v. light. The appropriate sections were scraped from the plates and extracted with ether or ethyl acetate, usually using a Soxhlet apparatus.

Column chromatography was carried out using silica (H.B.L. 60 mesh) or alumina (Laporte "Type H") as adsorbents. "Light petroleum" refers to the fraction boiling in the range 40-60°C (column chromatography) or in the range 60-80°C (t.l.c. and p.t.l.c.), unless stated otherwise: both fractions were distilled prior

to their use for chromatographic purposes.

Melting points were determined on a Kofler hot stage using polarised light, and are corrected. Temperatures are expressed as degrees Celsius.

Microanalyses were performed under the supervision of Dr. Strauss.

Routine infra red (i.r.) spectra were recorded with a Perkin-Elmer 257 grating spectrophotometer using dilute carbon tetrachloride or chloroform solutions in sodium chloride cells of path lengths 1 mm and 0.1 mm. Ultra violet (u.v.) spectra were measured on a Cary 14 spectrophotometer using hexane or ethanol solutions in 1 mm or 1 cm silica cells. Nuclear magnetic resonance (n.m.r.) spectra were recorded on either a Perkin-Elmer R10 (60 MHz) or a Perkin-Elmer R14 (100 MHz) spectrometer using carbon tetrachloride as solvent, unless otherwise stated, with tetramethylsilane as internal standard. Mass spectra (m.s.) were recorded on an A.E.I. MS9 or a Varian CH7 spectrometer, the six most intense peaks being reported.

4-Isopropylfuran-2-carbaldehyde (III).⁶² - A mixture of isopropyl chloride (78.8 g) and furan-2-carbaldehyde (freshly distilled in vacuo at 72°/50 mm; 96.0 g) was added during 0.5 h at 25° to a stirred slurry of finely-powdered, anhydrous aluminium chloride (160.2 g) and carbon disulphide (analytical quality, dried over anhydrous magnesium sulphate; 200 ml). After stirring at 25° for 1 h, the mixture was poured, with vigorous stirring, on to crushed ice (1 kg) and the organic layer was separated and washed with water (200 ml) and saturated, aqueous sodium acetate solution (200 ml). The organic solution was mixed with saturated, aqueous sodium acetate solution (200 ml) and the mixture was distilled in steam for 6 h. The distillate was extracted with dichloromethane (3 x 250 ml) and the combined organic extracts were washed with water (250 ml), saturated aqueous sodium hydrogen carbonate solution (250 ml), and brine (250 ml), and dried over anhydrous magnesium sulphate. The residue from the distillation in steam (a black oil) was also extracted with dichloromethane (250 ml) and the extract was washed and dried as above. T.l.c. (20% acetone in light petroleum) on the distillate extract showed three components R_F 's 0.30 (major), 0.43, and 0.63 (minor) (cf. furan-2-carbaldehyde R_F 0.30). Removal of solvent gave a red oil which was distilled in vacuo; the fraction boiling in the range 106-110°/30 mm was collected as crude 4-isopropylfuran-2-aldehyde (16.0 g). A small sample was further purified by p.t.l.c. (4 x 5% acetone in light petroleum); g.l.c. (column at 100°) of this material showed two minor impurities (about 5% of total peak area), and the material was examined again by p.t.l.c. (6 x 5% acetone in light petroleum); g.l.c. (column at 100°) showed that one of the impurities had been removed. The material was finally purified again by p.t.l.c. using a different solvent system (8 x 5% ether in light petroleum); this gave a sample which was pure by g.l.c.

$\lambda_{\text{max.}}$ 284 nm (ϵ 4774); $\nu_{\text{max.}}$ 1692, 2974, and 1145 cm^{-1} ; τ 0.34 (singlet; CHO), 2.53 (multiplet; 5-H), 2.86 (quartet, J 0.5 and 1.0 Hz; 3-H), 7.13 (septet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.75 (doublet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$).

The residue from the distillation in steam (after removal of solvent) was shown by n.m.r. to consist mainly of 4,5-diisopropylfuran-2-carbaldehyde; τ 0.52 (singlet; CHO), 3.00 (singlet; 3-H), 7.03 (septet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.79 (doublet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$).

The preparation was repeated using dichloromethane instead of carbon disulphide as solvent: very little product could be detected.

4-Isopropylfuran-2-carboxylic acid (IV). Attempted preparation.⁶³ -

Copper (I) oxide (1.0 g) was suspended in a 2.5% aqueous sodium hydroxide solution (25 ml) and a solution of silver nitrate (0.05 g) in water (2 ml) was added with rapid stirring. The brown slurry was heated to 55°, oxygen was passed through, and 4-isopropylfuran-2-carbaldehyde (13 g) and a solution of sodium hydroxide (4.0 g) in water (10 ml) were added separately but simultaneously to the slurry at a rate such that the temperature of the mixture was maintained at 55° without external heating. Vigorous stirring and passage of oxygen were continued until the temperature of the mixture had dropped to below 40°. The catalyst was removed by filtration and the aqueous solution extracted with ether (2 x 10 ml). Removal of ether gave a black oil (9.0 g) which t.l.c. showed to be chiefly unreacted starting material.

The preparation was repeated using the recovered aldehyde and double quantities of the catalyst. A considerable amount of starting material was again recovered. The combined aqueous solutions from the two experiments were acidified with 30% aqueous sulphuric acid and extracted with ethyl acetate

continuously for 8 h. Removal of solvent gave a black oil (0.5 g), t.l.c. and i.r. of which indicated the presence of an acid. Decarboxylation using quinoline and copper bronze (for details of the method vide infra) was attempted but failed to give a recognisable product: the preparation was thus abandoned.

4-Isopropylfuran-2-carboxylic acid (IV).⁶² - Solutions of silver nitrate (12.0 g) in water (30 ml) and sodium hydroxide (12.0 g) in water (30 ml) were mixed with rapid stirring, and aqueous ammonia solution (density 0.88 g ml^{-1}) was added until the solution just cleared. 4-Isopropylfuran-2-carbaldehyde (5.0 g) was added, and the mixture was stirred at 35° for 2 h. Filtration, acidification of the filtrate with 30% aqueous sulphuric acid, continuous extraction with ethyl acetate for 12 h, and removal of solvent gave 4-isopropylfuran-2-carboxylic acid (3.5 g) as a golden oil which crystallised on standing. Recrystallisation of a portion from ethanol/water gave white crystals, m.p. $73-75^{\circ}$ (lit.⁶² $76-77^{\circ}$); λ_{max} 257 nm (ϵ 8844); ν_{max} 1700, 2970, and 1292 cm^{-1} ; τ (deuteriochloroform) -2.24 (singlet; OH), 2.54 (multiplet; 5-H), 2.70 (multiplet; 3-H), 7.16 (septet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.77 (doublet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$).

3-Isopropylfuran (VI).⁶² - Quinoline (dried by distillation from anhydrous barium oxide; 20.0 g), 4-isopropylfuran-2-carboxylic acid (10.0 g), and finely-powdered copper bronze (2.0 g) were mixed in a round-bottomed flask (50 ml) attached to a 30 cm Vigreux column and distillation apparatus, the receiver flask being cooled in ice/salt. The mixture was maintained at 250° for 2.5 h, using a Wood's metal bath, during which time the product distilled. Towards the end of the reaction, the temperature of the metal bath was increased until the temperature of the distilling vapour rose rapidly to above 100° : collection of product was then discontinued. The crude material was distilled and fractionated,

the fraction distilling in the range 110-112° being collected as 3-isopropylfuran (5.5 g) (lit.⁶² b.p. 111-112°), pure by g.l.c. (column at 50°); $\lambda_{\text{max.}}$ 230 nm (ϵ 1335); $\nu_{\text{max.}}$ 2975 and 874 cm^{-1} ; τ 2.73 (multiplet; 5-H), 2.88 (multiplet; 3-H), 3.78 (octet, J 0.5, 1.0, and 2.0 Hz; 4-H), 7.23 (septet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.82 (doublet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$).

3-Isopropylfuran-2-carbaldehyde (VII). - Dimethylformamide (5.1 g) was added with stirring to phosphoryl chloride (10.7 g), cooled in ice/salt, at a rate such that the temperature of the mixture did not rise above 10°. 3-Isopropylfuran (5.5 g) was then added, keeping the temperature of the mixture below 20°. The mixture was stirred at 0° for 1 h, warmed to 40°, and poured on to ice (60 g). After neutralisation with sodium carbonate (18 g) and extraction with ether (2 x 100 ml), g.l.c. (column at 75°) demonstrated the presence of a major and two minor components. These were separated by p.t.l.c. (15 x 2% acetone in light petroleum) to give 3-isopropylfuran-2-carbaldehyde (Found: C, 69.8; H, 7.3. $\text{C}_8\text{H}_{10}\text{O}_2$ requires C, 69.5; H, 7.3%); $\nu_{\text{max.}}$ 1686, 1468, and 1090 cm^{-1} ; τ 0.30 (doublet, J 0.5 Hz; CHO), 2.55 (quartet, J 1.8 and 0.5 Hz; 5-H), 3.53 (multiplet; 4-H), 6.42 (septet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.76 (doublet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$); m.s. peaks at m/e 138 (M^+ , 98), 123 (100), 41 (43), 43 (35), 67 (34), and 109 (28). The product formed a 2,4-dinitrophenylhydrazone, m.p. 172-174.5° (after recrystallisation from methanol) (Found: C, 52.6; H, 4.5; N, 17.4. $\text{C}_{14}\text{H}_{14}\text{N}_4\text{O}_5$ requires C, 52.8; H, 4.4; N, 17.6%).

Attempted mono-isopropylation of methyl-2-furoate.⁶² 4,5-Diisopropylmethyl-2-furoate (VIII). - Methyl-2-furoate (freshly distilled in vacuo; 18.9 g) and isopropyl chloride (11.9 g) were added, with stirring, separately but simultaneously, during 0.5 h, to a slurry of finely-powdered, anhydrous aluminium

chloride (20.0 g) in dry carbon disulphide (200 ml), cooled to 0° in ice/salt. The mixture was stirred at 25° for 12 h, warmed to 50° during 10 min, and poured on to ice (500 g) with vigorous stirring. The organic layer was separated, the aqueous layer extracted with ether (2 x 100 ml), and the combined organic layers were washed (water and saturated aqueous sodium carbonate solution) and dried (anhydrous sodium sulphate). Removal of solvent gave a red oil (20 ml) which g.l.c. (column at 125°) and t.l.c. (20% acetone in light petroleum) showed to contain at least four components R_F 's 0.74 (major), 0.48, 0.43, and 0.31 (starting material). Distillation in vacuo (20 mm) gave three fractions boiling in the ranges: 78-84°, 84-85°, and 118-124° (major). The third fraction was redistilled in vacuo and a portion purified further by p.t.l.c. (firstly, using 5 x 2% acetone in light petroleum; secondly, using 4 x 10% acetone in light petroleum). The product so obtained was 4,5-diisopropylmethyl-2-furoate; $\nu_{\max}$. 1731 and 1720 cm^{-1} ; τ 3.10 (singlet; 3-H), 6.24 (singlet; CH_3), 7.09 (septet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.67, 8.78 and 8.89 (overlapped doublets, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$); cf. τ (benzene) 8.82, 8.93, 8.97, and 9.08. N.m.r. analysis of other fractions demonstrated the presence of only very small amounts of mono-isopropylated material.

The reaction was repeated using conditions similar to the above with the alterations that only half of the required amount of isopropyl chloride was added and, in the work-up, the mixture was not heated. G.l.c. analysis of the products showed that, as before, very little mono-isopropylated material had been formed. The reaction was therefore abandoned.

4,5-Diisopropylfuran-2-carboxylic acid (IX). - 4,5-Diisopropylmethyl-2-furoate (9.5 g) was heated at 80° for 0.5 h with a 20% solution of potassium

hydroxide (3.2 g) in methanol. After pouring on to ice (300 g), acidifying with 50% aqueous sulphuric acid, continuously extracting for 12 h with ethyl acetate and drying of the extract over anhydrous sodium sulphate, removal of solvent gave 4,5-diisopropylfuran-2-carboxylic acid (6.0 g) as a golden oil which could not be induced to crystallise; $\nu_{\text{max.}}$ 2972 cm^{-1} ; τ -2.10 (singlet; OH), 2.91 (singlet; 3-H), 7.10 (septet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.64, 8.75, 8.86 (overlapped doublets, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$).

2,3-Diisopropylfuran (X). - The method used was similar to that described for 3-isopropylfuran (vide supra). Quinoline (dried by distillation from anhydrous barium oxide; 10.0 g), 4,5-diisopropylfuran-2-carboxylic acid (6.0 g) and finely-powdered copper bronze (1.5 g) were heated at 250° for 2.5 h, during which time the product distilled. Redistillation gave a product shown by g.l.c. (column at 75°) and n.m.r. to be mainly 2,3-diisopropylfuran (2.5 g); τ 2.92 (doublet, J 2.5 Hz; 5-H), 3.91 (doublet, J 2.5 Hz; 4-H), 7.14 (septet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.73, 8.84, and 8.95 (overlapped doublets, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$).

4,5-Diisopropylfuran-2-carbaldehyde (XI). - The method used was similar to that described for 3-isopropylfuran-2-carbaldehyde (vide supra). Dimethylformamide (1.1 g) and phosphoryl chloride (2.2 g) were mixed at 0°, and 2,3-diisopropylfuran (1.5 g) was added, keeping the temperature of the mixture below 20°. After stirring at 0° for 1 h, work-up as before [ice (15 g), sodium carbonate (5 g), ether (3 x 100 ml), and drying of the extracts over anhydrous magnesium sulphate] gave, after removal of solvent, a golden oil of which g.l.c. (column at 100°) demonstrated the presence of dimethylformamide, quinoline, three further minor components, and one major component. T.l.c.

(20% acetone in light petroleum) indicated at least five components R_F 's 0.23 (quinoline), 0.37, 0.40, 0.47, and 0.52. P.t.l.c. (12 x 2% acetone in light petroleum) gave three significant fractions, the major one being 4,5-diisopropylfuran-2-carbaldehyde (Found: C, 73.03; H, 8.95. $C_{11}H_{16}O_2$ requires C, 73.30; H, 8.95%); $\nu_{\max}$. 1685 cm^{-1} ; τ 0.56 (singlet; $\underline{\text{CHO}}$), 3.01 (singlet; 3-H), 7.03 (septet, $\underline{\text{J}}$ 7.0 Hz; $\underline{\text{CH}}(\text{CH}_3)_2$), and 8.63, 8.74, and 8.86 (overlapped doublets, $\underline{\text{J}}$ 7.0 Hz; $\underline{\text{CH}}(\text{CH}_3)_2$). The minor components from the p.t.l.c. were identified by n.m.r. as 3-isopropylfuran-2-carbaldehyde and 5-isopropylfuran-2-carbaldehyde (vide infra).

2-Isopropylfuran (XII). Attempted preparation. (a) - Lithium (extruded into wire; 1.54 g) was cut into small pieces and stirred, under dry nitrogen, with ether (dried over sodium; 15 ml). n-Butyl bromide (dried over molecular sieve; 40 drops) was added at 20° and, when reaction had commenced, the remaining halide (12.0 g) was added in ether (dried over sodium; 20 ml) at a rate such that the ether boiled gently under reflux. After addition was complete, the mixture was boiled under reflux for 1 h. The solution of n-butyl lithium in ether so prepared was filtered through a canula plugged with glass wool into furan (purified by passing through an alumina column; 6.8 g), the mixture was boiled under reflux for 3 h and then allowed to stand at 25° for 12 h. To the resulting orange solution of 2-furyl lithium in ether was added isopropyl chloride (7.9 g) in ether (dried over sodium; 15 ml) and the mixture was boiled under reflux for 3 h. Pouring on to ice (50 g), extraction of the dark red aqueous solution with ether (3 x 100 ml), washing of the organic extracts with water (100 ml), dilute sulphuric acid (100 ml), and brine (100 ml), and drying of the extracts over anhydrous potassium carbonate gave, after removal of solvent at 50° , a red liquid (4 g) which did not contain

any furan material (n.m.r.): the preparation was thus abandoned.

Attempted preparation. (b) - n-Butyl bromide (dried over molecular sieve; 27.4 g) in tetrahydrofuran (purified and dried by passing through an alumina column and then distilling from lithium aluminium hydride; 90 ml) was added to a stirred mixture of lithium (treated as above; 3.0 g) and tetrahydrofuran (purified and dried as above; 90 ml) at a rate such that the solvent boiled gently under reflux. The solution was then cooled to -25° and, after 1 h, furan (purified as above; 13.6 g) was added. Stirring was continued for 4 h at -15° , isopropyl chloride (14.8 g) in tetrahydrofuran (purified and dried as above; 15 ml) was then added, and, after stirring for a further 1 h at -15° , the mixture was left at 25° for 12 h. Work-up as before [ice, ether extraction (2×100 ml), washing, drying, and removal of solvent at 50°] gave a yellow liquid which did not contain any furan material (n.m.r.).

A solution of n-butyl lithium in ether was prepared by Gilman's method⁶⁵ using conditions similar to those described above except that (i) after the initial addition of n-butyl bromide (40 drops), the mixture was cooled to -10° and the remainder of the bromide in ether was added at -10° during 0.5 h, and (ii) after addition was complete, the mixture was allowed to warm to 10° during 2 h. From this, a solution of 2-furyl lithium in ether was then prepared by the method of Ramanathan and Levine⁶⁶ using conditions similar to those described above except that the initial addition of furan to the solution of n-butyl lithium in ether was made at -20° . The resulting solution of 2-furyl lithium in ether was poured on to a slurry of solid carbon dioxide and ether and, after 0.5 h, enough water was added to dissolve the solid material. Acidification of the aqueous layer with 2N-hydrochloric acid, continuous extraction with ether for 24 h, drying of the

extracts over anhydrous magnesium sulphate, and removal of solvent gave a white solid which, after recrystallisation from ethanol/water, was identified by melting point and mixed melting point as furan-2-carboxylic acid, obtained in good yield.

Purification of boron trifluoride-etherate.⁶⁷ - Peroxide-free diethyl ether (dried over sodium; 10 ml) was added to boron trifluoride-etherate (500 ml) and the mixture was distilled from calcium hydride (2 g) at 46°/10 mm yielding peroxide-free boron trifluoride-etherate as a colourless liquid.

2-Furyl methyl ketone (XIII).⁶⁸ - Furan (purified by passing through an alumina column; 17.0 g) was added to a mixture (31.0 g) of 95% acetic anhydride (freshly distilled) and 5% acetic acid (v/v), and the resulting solution was cooled to 0° in ice/salt. Peroxide-free boron trifluoride-etherate (4.0 g) was quickly added, with vigorous stirring, whereupon the solution went black. After stirring for 1 h, water (200 ml) was added, the aqueous layer was extracted with chloroform (3 x 200 ml) and the combined extracts were dried over anhydrous magnesium sulphate. After removal of solvent, the black residue was distilled in vacuo through a Vigreux column, the fraction boiling at 63.5°/20 mm being collected as 2-furyl methyl ketone (17.0 g) which solidified, on standing, to give colourless crystals, m.p. 30-31° (lit.,⁶⁹ 33°, 29°), pure by g.l.c. (column at 100°); n_D^{20} 1.5016 (lit., 1.5017); $\lambda_{\text{max.}}$ 269 nm (ϵ 13,430); $\nu_{\text{max.}}$ 1688, 1470, and 1278 cm^{-1} ; τ 2.46 (quartet, J 0.8 and 1.8 Hz; 5-H), 2.88 (quartet, J 0.8 and 3.5 Hz; 3-H), 3.50 (quartet, J 1.8 and 3.5 Hz; 4-H), and 7.57 (singlet, COCH_3).

2-(2-Furyl)propan-2-ol (XIV).⁶⁴ - Methyl iodide (27.8 g) was added to magnesium turnings (4.7 g) in ether (dried over sodium; 200 ml), under dry nitrogen, at a rate such that the ether boiled gently under reflux. After 0.5 h,

the mixture was filtered through a canula, plugged with glass wool, into a dropping funnel, and was added slowly to a solution of 2-furyl methyl ketone (freshly distilled in vacuo; 20.0 g) in ether (dried over sodium; 50 ml), cooled in ice/salt. After standing for 12 h at 25°, the slurry was poured on to ice (200 g), potassium carbonate was added, and the mixture was distilled in steam for 3 h. Extraction of the distillate with ether (3 x 200 ml) and removal of solvent gave an oil which was treated with an ethanolic solution of semicarbazide hydrochloride (5.0 g) and crystalline sodium acetate (7.5 g) for 1 h. Potassium carbonate and water were added and the mixture was extracted with ether (3 x 200 ml). Drying of the extracts over anhydrous potassium carbonate and removal of solvent by distillation gave a yellow oil. Distillation in vacuo gave 2-(2-furyl)propan-2-ol as a colourless liquid, b.p. 65°/15 mm (lit.,⁶⁴ 62°/11 mm); $\nu_{\text{max.}}$ 2980, 3480, and 3620 cm^{-1} ; τ 2.80 (quartet, $\underline{J}$ 1.0 and 2.0 Hz; 5-H), 3.85 (quartet, $\underline{J}$ 2.0 and 3.5 Hz; 4-H), 3.95 (quartet, $\underline{J}$ 1.0 and 3.5 Hz; 3-H), 7.04 (singlet; $\underline{\text{OH}}$), and 8.55 (singlet; $\underline{\text{CH}_3}$).

2-Isopropylfuran (XII). Attempted preparation. - 2-(2-Furyl)propan-2-ol (3.0 g) in dichloromethane (50 ml) was mixed with ether which had previously been shaken with concentrated hydrochloric acid (5 drops) and Adams' catalyst (0.5 g), and the mixture was hydrogenated at 760 mm until 600 ml of hydrogen had been absorbed (0.5 h). Drying over anhydrous potassium carbonate and removal of catalyst and solvent gave material which consisted mainly of non-aromatic material: the preparation was thus abandoned.

2-Isopropylfuran (XII).⁶² - 2-(2-Furyl)propan-2-ol (5.0 g) was boiled under reflux with acetic anhydride (freshly distilled; 4.5 g) for 0.5 h. The mixture was neutralised with saturated aqueous potassium carbonate solution, and

distilled until the distilling liquid ceased to contain oily drops. After extraction of the distillate with ether (2 x 75 ml) and drying of the extracts over anhydrous potassium carbonate, the ethereal solution was mixed with Adams' catalyst (0.5 g) and hydrogenated at 760 mm until about 600 ml of hydrogen had been absorbed. Removal of catalyst and solvent gave a colourless liquid (2 ml) which was identified by n.m.r. as crude 2-isopropylfuran; τ 2.83 (complex; 5-H), 3.86 (complex; 3-H), 4.16 (complex; 4-H), 6.98 (complex; $\text{CH}(\text{CH}_3)_2$), and 8.80 (doublet, J 7.0 Hz; $\text{CH}(\text{CH}_3)_2$). M.s. of the residue indicated the presence of dimers, trimers, and tetramers of 2-(2-furyl)propene.

5-Isopropylfuran-2-carbaldehyde (XVII). Attempted preparation. -

Furan-2-carbaldehyde (freshly distilled in vacuo; 19.2 g), benzene (dried over sodium; 200 ml), and isopropyl chloride (15.8 g) were cooled to 0° in ice/salt, and tin(IV) chloride (78.3 g) was added, with stirring, during 30 min. The mixture was heated to 60° and then stirred at 25° for 8 h, during which time no evolution of hydrogen chloride was detected. Benzene was removed, nitrobenzene (150 ml) and isopropyl chloride (15.8 g) were added and the mixture was heated to 150°. No evolution of hydrogen chloride occurred, and the mixture polymerised: the preparation was thus abandoned.

5-Isopropylfuran-2-carbaldehyde (XVII). - The method used was similar to that described for 4,5-diisopropylfuran-2-carbaldehyde. A mixture of phosphoryl chloride (3.2 g) and dimethylformamide (1.5 g) was cooled to 0° in ice/salt and crude 2-isopropylfuran was added during 0.5 h. After stirring at 0° for 1 h and warming to 25° during 0.5 h, the mixture was worked up as before. P.t.l.c. (8 x 5% acetone in light petroleum) gave ten bands, the major being identified by n.m.r. as 5-isopropylfuran-2-carbaldehyde. This was purified further by

p.t.l.c. (10 x 5% acetone in light petroleum) to give the aldehyde as a colourless oil, pure by g.l.c. (column at 75°C); $\nu_{\max}$. 1688, 2980, and 1518 cm^{-1} ; τ 0.47 (singlet; CHO), 2.98 (doublet, $\underline{\text{J}}$ 3.8 Hz; 3-H), 3.85 (doublet, $\underline{\text{J}}$ 3.8 Hz; 4-H), 6.97 (septet, $\underline{\text{J}}$ 7.0 Hz; $\text{CH}(\text{CH}_3)_2$), and 8.68 (doublet, $\underline{\text{J}}$ 7.0 Hz; $\text{CH}(\text{CH}_3)_2$).

Ethyl 2-(3-methyl)furyl ketone (XX).⁷⁰ - The method used was similar to that described for 2-furyl methyl ketone. Boron trifluoride-etherate (purified as before; 0.2 ml), propionic anhydride (1.3 g) and 3-methylfuran (0.5 g) gave, after work-up as before, a black tar (0.8 g) which was adsorbed on to a silica column (100 ml). Elution with 20% acetone in light petroleum gave a yellow oil (250 mg), t.l.c. of which indicated the presence of two components, R_F 's 0.50 (major) and 0.42. Further purification by p.t.l.c. (4 x 5% acetone in light petroleum) gave ethyl 2-(3-methyl)furyl ketone as a yellow oil (230 mg), pure by g.l.c. (column at 75°C); $\lambda_{\max}$. 263 nm (ϵ 15,300); $\nu_{\max}$. 1678, 1484, 1410, and 880 cm^{-1} ; τ 2.70 (complex doublet, $\underline{\text{J}}$ 1.6 Hz; 5-H), 3.70 (complex doublet, $\underline{\text{J}}$ 1.6 Hz; 4-H), 7.21 (quartet, $\underline{\text{J}}$ 7.8 Hz; CH_3CH_2), 7.62 (complex; 3- CH_3), and 8.85 (triplet, $\underline{\text{J}}$ 7.8 Hz; CH_3CH_2).

2-Phenylfuran (XX).⁷¹ - Sodium nitrite (7.6 g) in water (25 ml) was added to aniline (freshly distilled in vacuo; 9.3 g) in concentrated hydrochloric acid (24.5 ml) and water (24.5 ml), cooled to 5°C in ice, at a rate such that the temperature of the mixture did not rise above 10°C. The resulting solution was filtered into furan (purified as before; 150 ml) and 5N-aqueous sodium hydroxide solution (60 ml) was added, with vigorous stirring, at 5-10°C, during 1 h. Stirring was continued for 5 h at 5°C, and for 43 h at 25°C. T.l.c. of the organic layer [after washing (water) and drying (anhydrous sodium sulphate)] demonstrated the

presence of seven components; g.l.c. of the mixture (column at 125°) indicated that all but one of the components were present in very small amounts. Removal of excess of furan gave a black liquid (7.5 g), distillation of which (15 mm/100°) gave a golden oil (1.5 g) and an intractable residue.

The preparation was repeated under similar conditions except that purification was achieved by column chromatography on alumina (250 g). Elution with 5% acetone in light petroleum gave 2-phenylfuran (3.0 g) as a golden oil; $\lambda_{\text{max.}}$ 280 nm (ϵ 14,325) and 219 nm (ϵ 7539); $\nu_{\text{max.}}$ 1158, 1478, and 2980 cm^{-1} ; τ 2.65 (complex; phenyl-H and 5-H), 3.48 (quartet, J 0.8 and 3.2 Hz; 3-H), and 3.69 (quartet, J 1.9 and 3.2 Hz; 4-H).

5-Phenylfuran-2-carbaldehyde (XXI).⁷² - The method used was similar to that described for 4,5-diisopropylfuran-2-carbaldehyde. A mixture of phosphoryl chloride (3.7 g) and dimethylformamide (1.8 g) was allowed to stand at 25° for 0.5 h, cooled to 0° in ice/salt, and 2-phenylfuran (3.0 g) was added. The mixture was heated on a steam bath for 1 h and worked up as before. T.l.c. (10% acetone in light petroleum) demonstrated the presence of one major component R_F 0.22. Removal of solvent gave a red oil (3.2 g) which was adsorbed on to a silica column (250 ml). After 12 h, light petroleum-acetone mixtures failed to elute any aromatic material.

The preparation was repeated under similar conditions except that purification of a small sample was achieved by p.t.l.c. (2 x 10% acetone in light petroleum). This gave 5-phenylfuran-2-carbaldehyde as a golden oil, pure by g.l.c. (column at 150°); $\lambda_{\text{max.}}$ 310 nm (ϵ 28,667) and 221 nm (ϵ 12,110); $\nu_{\text{max.}}$ 1682, 1450, and 1025 cm^{-1} ; τ 0.43 (singlet; $\underline{\text{CHO}}$), 2.50 (complex; phenyl-H), 2.84 (doublet, J 3.8 Hz; 3-H), and 3.27 (doublet, J 3.8 Hz; 4-H).

2-(4-Chlorophenyl)furan (XXII).⁷³ - 4-Chloroaniline (25.6 g) in concentrated hydrochloric acid (50 ml) and water (300 ml) was diazotised as described in the preparation of 2-phenylfuran using sodium nitrite (13.8 g) in water (20 ml). After 0.5 h, zinc chloride (27.2 g) in water (100 ml) was added, the solution was cooled to 0° and saturated with salt. The diazonium salt was filtered at the pump, dried by suction for 2 h, and suspended in furan (300 ml). Powdered sodium hydroxide (2.0 g) and sodium acetate (freshly roasted; 20.0 g) were added, with vigorous stirring, and the reaction mixture was maintained at 25°, with stirring, for 24 h. Distillation in steam and extraction of the distillate with ether (6 x 200 ml) gave, after drying (anhydrous magnesium sulphate) and removal of solvent, a yellow solid (10.0 g), t.l.c. of which (10% acetone in light petroleum) demonstrated the presence of two components R_F 's 0.49 (major) and 0.09. Recrystallisation of a portion from methanol/water gave 2-(4-chlorophenyl)furan as white plates, pure by i.l.c., m.p. 66-66.5° (lit.,⁷³ 66°); λ_{max} : 284 nm (ϵ 14,538); ν_{max} : 1100, 1163, and 1480 cm^{-1} ; τ 2.60 (complex; phenyl-H and 5-H), 3.46 (quartet, J 0.8 and 3.2 Hz; 3-H), and 3.63 (quartet, J 1.8 and 3.2 Hz; 4-H).

5-(4-Chlorophenyl)furan-2-carbaldehyde (XXIII).- The method used was similar to that described for 5-phenylfuran-carbaldehyde. 2-(4-Chlorophenyl)furan (3.0 g) in dimethylformamide (10 ml) was added to a mixture of phosphoryl chloride (3.6 g) and dimethylformamide (1.8 g). The mixture was heated on a steam bath for 1 h and worked up as before. Removal of solvent gave a red oil (2.8 g) which crystallised on standing. A small portion was recrystallised from acetone and then sublimed in vacuo to give 5-(4-chlorophenyl)furan-2-carbaldehyde as white needles, m.p. 128.5-129° (Found: C, 63.73; H, 3.73; Cl, 16.9.

$C_{11}H_7ClO_2$ requires: C, 63.9; H, 3.4; Cl, 17.2%); $\lambda_{\max}$. 315 nm (ϵ 30,000) and 223 nm (ϵ 13,300); $\nu_{\max}$. 1686, 1474, and 1096 cm^{-1} ; τ (acetone) 0.39 (singlet; $\underline{CHO}$), 2.40 (complex; phenyl-H), 2.68 (doublet, $\underline{J}$ 3.8 Hz; 3-H), 3.06 (doublet, $\underline{J}$ 3.8 Hz; 4-H); m.s. peaks at m/e 206 (M, 100), 149 (40), 58 (21), 151 (14), 114 (13), and 178 (9).

2-(4-Bromophenyl)furan (XXIV).- The method used was similar to that described for 2-(4-chlorophenyl)furan. 4-Bromoaniline (34.2 g) in concentrated hydrochloric acid (50 ml) and water (300 ml) was diazotised using sodium nitrite (13.8 g) in water (20 ml). The zinc salt [isolated by the addition of zinc chloride (27.2 g) in water (100 ml), as before] was suspended in furan (300 ml) with powdered sodium hydroxide (2.0 g) and anhydrous sodium acetate (20.0 g). After stirring the mixture at 25° for 24 h, distillation in steam for 7 h and extraction of the distillate with ether (5 x 200 ml) gave, after drying (anhydrous magnesium sulphate) and removal of solvent, a yellow solid (12.0 g), t.l.c. of which (20% acetone in light petroleum) demonstrated the presence of three components R_F 's 0.54 (major), 0.24 and 0.12. Sublimation in vacuo of a portion gave 2-(4-bromophenyl)furan as a white solid, pure by t.l.c., m.p. 80-83° (lit.,⁷¹ 85°); $\lambda_{\max}$. 287 nm (ϵ 23,744), 227 nm (ϵ 7196), and 221 nm (ϵ 7972); $\nu_{\max}$. 1396, 1158, 1075, and 904 cm^{-1} ; τ 2.53 (complex; phenyl-H and 5-H), 3.41 (quartet, $\underline{J}$ 0.8 and 3.3 Hz; 3-H), and 3.57 (quartet, $\underline{J}$ 1.8 and 3.3 Hz; 4-H).

5-(4-Bromophenyl)furan-2-carbaldehyde (XXV).- The method used was similar to that described for 5-phenylfuran-2-carbaldehyde. 2-(4-Bromophenyl)furan (3.7 g) in dimethylformamide (10 ml) was added to a mixture of phosphoryl chloride (3.6 g) and dimethylformamide (1.8 g). The mixture was heated on a steam bath for 1 h and worked up as before. Removal of solvent gave a yellow

solid (5.0 g). A small portion was sublimed in vacuo to give 5-(4-bromophenyl)-furan-2-carbaldehyde as white needles, m.p. 151-153° (Found: C, 53.01; H, 3.01; Br, 31.41. $C_{11}H_7BrO_2$ requires C, 52.60; H, 2.81; Br, 31.8%); $\lambda_{\max}$. 242 nm (ϵ 9214); $\nu_{\max}$. 1684, 1468, and 1023 cm^{-1} ; τ (deuteriochloroform) 0.21 (singlet; $\underline{CHO}$), 2.27 (complex; phenyl-H), 2.60 (doublet, $\underline{J}$ 3.8 Hz; 3-H), and 3.06 (doublet, $\underline{J}$ 3.8 Hz; 4-H); m.s. peaks at m/e 250 (M, 100), 252 (98), 193 (30), 195 (28), 249 (25), and 114 (25).

2-(1-Naphthyl)furan (XXVI).⁷¹ - The method used was similar to that described for 2-(4-chlorophenyl)furan. 1-Naphthylamine (14.3 g) in concentrated hydrochloric acid (25 ml) and water (150 ml) was diazotised using sodium nitrite (6.9 g) in water (10 ml). The zinc salt [isolated by the addition of zinc chloride (13.6 g) in water (50 ml), as before] was suspended in furan (150 ml) with powdered sodium hydroxide (1.0 g) and anhydrous sodium acetate (10.0 g). After stirring the mixture at 25° for 24 h, distillation in steam for 10 h and extraction of the distillate with ether (6 x 200 ml) gave, after drying (anhydrous magnesium sulphate) and removal of solvent, a red oil (4.5 g). Distillation in vacuo gave 2-(1-naphthyl)furan, b.p. 160° (bath)/1 mm (lit.,⁷¹ 90.91°/0.02 mm), as a yellow liquid, pure by t.l.c.; $\lambda_{\max}$. 318 nm (ϵ 8050), 227 nm (ϵ 26,564), and 222 nm (ϵ 26,564); $\nu_{\max}$. 904, 1157, 1390, and 3060 cm^{-1} ; τ 1.68 and 2.53 (complex; naphthyl-H and 5-H), 3.42 (quartet, $\underline{J}$ 0.8 and 3.3 Hz; 3-H), and 3.59 (quartet, $\underline{J}$ 1.8 and 3.3 Hz; 4-H).

5-(1-Naphthyl)furan-2-carbaldehyde (XXVII). - The method used was similar to that described for 5-phenylfuran-2-carbaldehyde. 2-(1-Naphthyl)furan (1.6 g) in dimethylformamide (5 ml) was added to a mixture of phosphoryl chloride (1.8 g) and dimethylformamide (0.9 g). After heating the mixture on a steam bath

for 1 h, work-up and removal of solvent gave a golden oil (1.5 g), a portion of which was purified by p.t.l.c. (8 x 5% acetone in light petroleum) to give 5-(1-naphthyl)furan-2-carbaldehyde as a yellow oil, pure by t.l.c. (Found: C, 80.95; H, 4.66. $C_{15}H_{10}O_2$ requires: C, 81.06; H, 4.54%); λ_{max} . 337 nm (ϵ 9903), 277 nm (ϵ 4539), and 222 nm (ϵ 20,137); ν_{max} . 1687, 1386, and 1020 cm^{-1} ; τ 0.25 (singlet; CHO), 1.62 and 2.39 (complex; naphthyl-H), 2.70 (doublet, J 3.8 Hz; 3-H), and 3.19 (doublet, J 3.8 Hz; 4-H).

2-(2-Naphthyl)furan (XXVIII).—The method used was similar to that described for 2-(4-chlorophenyl)furan. 2-Naphthylamine (14.3 g) in concentrated hydrochloric acid (25 ml) and water (150 ml) was diazotised using sodium nitrite (6.9 g) in water (10 ml). The zinc salt [isolated by the addition of zinc chloride (13.6 g) in water (50 ml), as before] was suspended in furan (150 ml) with powdered sodium hydroxide (1.0 g) and anhydrous sodium acetate (10.0 g). After stirring the mixture at 25° for 24 h, distillation in steam for 9 h and extraction of the distillate with ether (6 x 200 ml) gave, after drying (anhydrous magnesium sulphate) and removal of solvent, a red solid (3.5 g). P.t.l.c. (3 x 2% acetone in light petroleum) and recrystallisation from methanol gave 2-(2-naphthyl)furan as colourless plates, m.p. $70-72^\circ$ (Found: C, 86.27; H, 5.36. $C_{14}H_{10}O$ requires: C, 86.57; H, 5.19%); λ_{max} . 314 nm (ϵ 19,233), 301 nm (ϵ 17,560), 269 nm (ϵ 29,769), 261 nm (ϵ 27,093), and 212 nm (ϵ 22,912); ν_{max} . 1158, 1631, and 3060 cm^{-1} ; τ 2.40 (complex; naphthyl-H and 5-H), 3.43 (quartet, J 0.8 and 3.2 Hz; 3-H), and 3.67 (quartet, J 1.8 and 3.2 Hz; 4-H); m.s. peaks at m/e 194 (M, 85), 165 (100), 166 (35), 164 (23), 163 (22), and 139 (14).

5-(2-Naphthyl)furan-2-carbaldehyde (XXX). Attempted preparation.⁷⁴ — 2-Naphthylamine (9.3 g) in concentrated hydrochloric acid (16.5 ml) and water

(200 ml) was diazotised using sodium nitrite (4.9 g) in water (15 ml). After addition of furan-2-carbaldehyde (freshly distilled in vacuo; 8.0 g) and water (50 ml), copper(II) chloride (3.0 g) in water (15 ml) was added dropwise at 20°. After stirring at 20° for 12 h, the solution was distilled in steam for 4 h and the residue extracted with ether (3 x 150 ml) and chloroform (100 ml). T.l.c. (50% acetone in light petroleum) of the extracts [after washing (saturated, aqueous sodium bicarbonate solution, brine) and drying (anhydrous magnesium sulphate)] showed at least three components R_F 's 0.68 (major), 0.59, and 0.49 (cf. furan-2-carbaldehyde R_F 0.59 and 2-naphthylamine R_F 0.52). The crude material could not be induced to crystallise nor was its colour removed on treatment with animal charcoal. A portion (1 g) was adsorbed on to a silica column (250 ml), elution of which with ether/light petroleum mixtures gave two, major (brilliant red) components, neither of which was the required product: the preparation was thus abandoned.

5-(2-Naphthyl)furan-2-carbaldehyde (XXX). - The method used was similar to that described for 5-phenylfuran-2-carbaldehyde. 2-(2-Naphthyl)furan (1.0 g) in dimethylformamide (3.5 ml) was added to a mixture of phosphoryl chloride (1.1 g) and dimethylformamide (0.6 g). After heating the mixture on a steam bath for 1 h and work-up as before, removal of solvent gave a red, crystalline solid (1.0 g) which was adsorbed on to a silica column (150 ml). Elution with 20% acetone in light petroleum gave an orange solid (pure by t.l.c.) which was recrystallised from methanol to give 5-(2-naphthyl)furan-2-carbaldehyde as pale yellow plates, m.p. 106-107° (Found: C, 81.04; H, 4.48. $C_{15}H_{10}O_2$ requires: C, 81.06; H, 4.54%); $\lambda_{max.}$ 347 nm (ϵ 26,217), 330 nm (ϵ 35,309), 286 nm (ϵ 22,623), 273 nm (ϵ 17,929), and 226 nm (ϵ 34,251); $\nu_{max.}$ 1684,

1026, and 1496 cm^{-1} ; τ 0.29 (singlet; CHO), 2.17 (complex; naphthyl-H), 2.76 (doublet, $\underline{J}$ 3.8 Hz; 3-H), and 3.13 (doublet, $\underline{J}$ 3.8 Hz; 4-H); m.s. peaks at m/e 222 (M, 100), 165 (52), 164 (12), 166 (12), 194 (12), and 221 (11).

Furan-2-carboxylic acid (XXXI).⁷⁵ - Potassium permanganate (110 g) in water (2 l) was added during 1 h to a stirred mixture of calcium hydroxide (150 g), water (500 ml) and furan-2-carbaldehyde (freshly distilled in vacuo; 100 g); ice was added from time to time to keep the temperature of the mixture below 20° . After heating on a steam bath for 0.5 h, the hot liquid was filtered at the pump and the filtrate acidified to pH 1 with 50% aqueous hydrochloric acid. Concentration of the filtrate, extraction with ether (6 x 100 ml) and drying (anhydrous magnesium sulphate) gave, after removal of solvent, a yellow solid (50 g), a portion of which was purified by recrystallisation from water and sublimation in vacuo to give furan-2-carboxylic acid, m.p. $129-130^{\circ}$ (lit.,⁶⁹ $129-130^{\circ}$); $\nu_{\text{max.}}$ 1700, 1476, 1018, and 3040 cm^{-1} ; τ (deuteriochloroform) -1.96 (singlet; OH), 2.30 (quartet, $\underline{J}$ 0.8 and 1.8 Hz; 5-H), 2.62 (quartet, $\underline{J}$ 0.8 and 3.2 Hz; 3-H), and 3.40 (quartet, $\underline{J}$ 1.8 and 3.2 Hz; 4-H).

Furan-2-carbonyl chloride (XXXII) (a).⁷⁶ - Furan-2-carboxylic acid (4.4 g) and oxalyl chloride (10.0 g) were boiled under reflux for 3 h. Removal of excess of oxalyl chloride by distillation gave a black liquid which was distilled in vacuo to give furan-2-carbonyl chloride (3.0 g) as a colourless liquid; $\lambda_{\text{max.}}$ 273 nm (ϵ 8110); $\nu_{\text{max.}}$ 1786, 1760 and 1462 cm^{-1} ; τ 2.26 (quartet, $\underline{J}$ 0.9 and 1.7 Hz; 5-H), 2.55 (quartet, $\underline{J}$ 0.9 and 3.6 Hz; 3-H), and 3.38 (quartet, $\underline{J}$ 1.7 and 3.6 Hz; 4-H).

(b)⁷⁷ - Furan-2-carboxylic acid (112 g) and thionyl chloride (freshly distilled; 250 g) were boiled under reflux for 0.5 h. Distillation and fractionation of the

residue at $176^{\circ}/760$ mm gave furan-2-carbonyl chloride (90 g) (lit., ⁷⁸ b.p. $173^{\circ}/760$ mm) identical (i.r., u.v., etc.) with the product obtained previously.

Furan-2-carbonyl bromide (XXXIII). ⁷⁹ - Furan-2-carboxylic acid (10.0 g) and phosphorus tribromide (15.0 g) were boiled under reflux for 1 h. Extraction of the charred residue with light petroleum, washing (saturated aqueous sodium bicarbonate solution, water, and brine), and drying (anhydrous magnesium sulphate) gave, after removal of solvent, a yellow residue which, on distillation in vacuo ($100^{\circ}/35$ mm), afforded furan-2-carbonyl bromide (3.0 g) as a colourless liquid; $\nu_{\text{max.}}$ 1770 and 1781 cm^{-1} ; τ 2.16 (quartet, J 0.8 and 1.8 Hz; 5-H), 2.51 (quartet, J 0.8 and 3.1 Hz; 3-H), and 3.39 (quartet, J 1.8 and 3.1 Hz; 4-H).

Furan-2-carbonyl fluoride (XXIV). Attempted preparation. - Furan-2-carbonyl chloride (13.0 g) and anhydrous zinc fluoride (5.0 g) were heated to 90° whereupon the mixture polymerised. Extraction of the residue with benzene (dried over sodium; 50 ml) gave, after removal of solvent, a green semi-solid mass which i.r. indicated was mainly furan-2-carboxylic acid.

The preparation was repeated with the alteration that zinc fluoride was added in small portions at 60° . After half of the fluoride had been added, the mixture had become semi-solid. An aliquot was removed, the i.r. spectrum of which indicated the presence of acid, acid chloride and acid fluoride in approximately equal amounts. After the remainder of the zinc fluoride had been added, distillation of the residue was attempted but was unsuccessful owing to charring.

The preparation was repeated under dry nitrogen using zinc fluoride which had been roasted at 150° for 0.5 h prior to use. After all of the zinc fluoride had been added, distillation in vacuo of the residue was attempted:

a few drops, only, of colourless liquid were obtained before the mixture carbonised.

The preparation was repeated with the alteration that the acid chloride was added in light petroleum (b.p. 60-80°, distilled from phosphorus pentoxide on to anhydrous potassium carbonate; 20 ml) during 1 h to a slurry of anhydrous zinc fluoride in light petroleum (25 ml), maintained at 80°. Distillation of the residue and i.r. of the fractions indicated that no appreciable reaction had occurred. The route was thus abandoned.

Furan-2-carbonyl fluoride (XXXIV).- Furan-2-carbonyl chloride (10.0 g) and potassium hydrogen fluoride (6.0 g) were heated, under dry nitrogen, at 90°. After 2 d, an aliquot was removed, i.r. of which indicated that some of the required product had been formed. After 2 d at 120°, the mixture was extracted with chloroform. I.r. of this solution indicated that the required product was present along with furan-2-carboxylic acid. The experiment was then repeated under altered conditions.

Furan-2-carbonyl chloride (10.0 g) and potassium hydrogen fluoride (12.0 g) were heated to 160°, under dry nitrogen, whereupon a vigorous reaction occurred. After 45 min, the apparatus was fitted for distillation and a vacuum applied whereupon a colourless liquid (5 ml) distilled. Redistillation in vacuo [70° (bath)/15 mm] gave furan-2-carbonyl fluoride as a colourless, fuming liquid, pure by g.l.c. (column at 50°) (Found: C, 52.9; H, 3.0; F, 17.1. C₅H₃FO₂ requires: C, 52.6; H, 2.6; F, 16.7%); $\lambda_{\text{max.}}$ 253 nm (ϵ 10,869); $\nu_{\text{max.}}$ 1816 and 1827 cm⁻¹; τ 2.26 (octet, J 0.8, 1.6 and 2.5 Hz; 5-H), 2.62 (octet, J 3.6, 0.8, and 0.6 Hz; 3-H), and 3.39 (octet, J 0.8, 1.6, and 3.6 Hz; 4-H); m.s. peaks at m/e 114 (M, 100), 86 (47), 58 (37), 57 (24), 95 (16), and 43 (13).

Thiophen-2-carbonyl chloride (XXXV).⁸⁰ - Thiophen-2-carboxylic acid

(13.0 g) and thionyl chloride (freshly distilled; 25.0 g) were boiled under reflux for 15 min. Distillation and fractionation of the residue at $98^{\circ}/50$ mm gave thiophen-2-carbonyl chloride (8.2 g) as a colourless liquid; $\nu_{\text{max.}}$ 1755, 1410, and 1193 cm^{-1} ; τ 2.10 (quartet, J 1.2 and 4.0 Hz; 3-H), 2.23 (quartet, J 1.2 and 5.0 Hz; 5-H), and 2.85 (quartet, J 4.0 and 5.0 Hz; 4-H).

Thiophen-2-carbonyl fluoride (XXXVIII). - Thiophen-2-carbonyl chloride (5.1 g) and potassium hydrogen fluoride (6.0 g) were heated to 160° , under dry nitrogen, whereupon a vigorous reaction occurred. I.r. examination of the solid residue indicated that it consisted mainly of thiophen-2-carboxylic acid with only a little of the expected product.

The reaction was repeated with several modifications: (i) the apparatus was so arranged that volatile products could be removed by distillation during the course of the reaction; (ii) all apparatus was baked at 250° for 24 h prior to use; (iii) after introduction of the reactants, the apparatus was repeatedly swept with dry nitrogen and then evacuated, and (iv) a partial vacuum of 30 cm was maintained throughout the reaction. The distilled product was sublimed in vacuo on to a finger cooled with acetone/solid carbon dioxide, thiophen-2-carbonyl fluoride being collected as white needles which melted on warming to 25° ; high resolution m.s. found M^{+} , 129.989273 (C_5H_3FOS requires M^{+} , 129.989863); $\nu_{\text{max.}}$ 1811 and 1414 cm^{-1} ; τ 2.10 and 2.23 (complex; 3-H and 5-H), and 2.80 (octet, J 2.2, 4.0, and 5.0 Hz; 4-H); m.s. peaks at m/e 130 (M, 58), 111 (100), 102 (72), 59 (40), 45 (30), and 57 (28).

5-Chloromercurithiophen-2-carboxylic acid (XXXVII)⁸¹; 5-Deuteriothiophen-2-carboxylic acid (XXXIX). - A mixture of thiophen-2-carboxylic acid (1.5 g) in ethanol (12 ml), saturated aqueous mercury(II) chloride solution (80 ml), and

33% aqueous sodium acetate trihydrate (18.0 g) was left at 25° for 10 d. The resulting white precipitate (1.8 g) was dissolved in 2N-aqueous ammonia solution; acidification with 2N-hydrochloric acid gave the required product as a white solid (Found: C, 16.9; H, 0.5; Cl, 8.5; S, 8.1. Calc. for $C_5H_3ClHgO_2S$: C, 16.5; H, 0.1; Cl, 9.8; S, 8.8%).

5-Chloromercurithiophen-2-carboxylic acid (1.8 g) was boiled with 20% aqueous hydrochloric acid for 10 min. Extraction of the residue with ether and washing of the extract with brine gave, after drying (anhydrous sodium sulphate) and removal of solvent, a white solid (0.6 g) shown, by melting point and mixed melting point, to be thiophen-2-carboxylic acid.

The preparation was repeated with the alteration that the chloromercuri-acid was heated with 20% deuterium chloride in deuterium oxide. Work-up as before gave 5-deuteriothiophen-2-carboxylic acid* (0.6 g) as a white solid, m.p. 129-130° (Found: C, 46.3; $[H_2O + D_2O]$, 28.8; S, 24.9. $C_5H_3DO_2S$ requires: C, 46.5; $[H_2O + D_2O]$, 28.7; S, 24.8%); ν_{max} . 1682, 1421, and 1296 cm^{-1} ; τ (deuteriochloroform) -0.2 (singlet; $\underline{OH}$), 2.15 (doublet, $\underline{J}$ 4.0 Hz; 3-H), and 2.89 (doublet, $\underline{J}$ 4.0 Hz; 4-H); m.s. peaks at m/e 129 (M, 74), 112 (100), 44 (23), 84 (15), 57 (14), and 45 (13).

Reduction of Thiophen-2-carbonyl chloride.⁸² - Thiophen-2-carbonyl chloride (0.6 g) in diglyme (2 ml) was cooled, under dry nitrogen, in acetone/solid carbon dioxide, to -78°, and lithium aluminium tri-*t*-butoxyhydride (1.1 g) in diglyme (4 ml) was added with stirring at a rate such that no rise in temperature

* In this and subsequent mono-deuteriated compounds, the deuterium level, estimated by n.m.r. and m.s., was greater than 95%.

was observed. After warming to 25°, the mixture was poured on to ice. Work-up (extraction with ether, washing with water and brine, and drying over anhydrous magnesium sulphate) gave, after removal of solvent, a colourless oil (350 mg), t.l.c. of which (20% acetone in light petroleum) showed two components R_F 's 0.33 and 0.23 (cf. thiophen-2-carbaldehyde R_F 0.33). Purification by p.t.l.c. (3 x 10% acetone in light petroleum) gave thiophen-2-carbaldehyde (60 mg) as a colourless liquid identical (i.r., u.v., etc.) with authentic material.

5-Deuteriothiophen-2-carbaldehyde (XL). - 5-Deuteriothiophen-2-carboxylic acid (0.6 g) was boiled under reflux with thionyl chloride (freshly distilled; 1.2 g) for 6 h. After removal of excess of thionyl chloride by distillation, the residue was dissolved in diglyme (2 ml) and reduced with lithium aluminium tri-*t*-butoxyhydride (1.1 g) in diglyme (4 ml) as described for thiophen-2-carbonyl chloride. Work-up as before gave a yellow oil (0.3 g) which was purified by p.t.l.c. (6 x 10% acetone in light petroleum) to give 5-deuteriothiophen-2-carbaldehyde (50 mg) as a colourless liquid (Found: C, 53.2; $[H_2O + D_2O]$, 32.5; S, 28.6. $C_5H_3D_2OS$ requires: C, 53.1; $[H_2O + D_2O]$, 32.7; S, 28.3%); λ_{max} . 259 nm (ϵ 10,000); ν_{max} . 1688, 1412, 1205, and 663 cm^{-1} ; τ 0.10 (singlet; $\underline{CHO}$), 2.30 (doublet, $\underline{J}$ 4.0 Hz; 3-H), and 2.84 (broad doublet, $\underline{J}$ 4.0 Hz; 4-H); m.s. peaks at m/e 113 (M, 86), 112 (100), 43 (100), 58 (31), 57 (15), and 46 (14).

Furan tetrakismercuriacetate (XLI).⁷⁸ - Furan (2.6 g) was shaken with mercury(II) acetate (50.0 g) in water (200 ml) for 6 h and the mixture left standing at 25° for 12 h. The mercuriacetate derivative was filtered at the pump and dried by suction.

Furan tetrakismercurichloride (XLII).⁷⁸ - The mercuriacetate from above

was digested for 0.5 h on a steam bath with 4% aqueous sodium chloride solution (250 ml). The mercurichloride derivative was filtered at the pump and dried in vacuo over concentrated sulphuric acid (Found: C, 5.3; H, 0.17; Cl, 8.2. Calc. for $C_4Cl_4Hg_4O$: C, 4.8; Cl, 14.0%). The compound was heated on a steam bath with 20% aqueous hydrochloric acid (20 g) whereupon furan (0.7 g) distilled.

The experiment was repeated with the alteration that the mercurichloride derivative was heated with 20% deuterium chloride in deuterium oxide (20.0 g). N.m.r. and i.r. of the furan so formed indicated a 55% deuteration level, with more deuterium at the 2- than at the 3-positions.

5-Bromofuran-2-carbaldehyde (XLIII).⁸³ - Bromine (57.6 g) was added to a mixture of furan-2-carbaldehyde (freshly distilled in vacuo; 28.8 g), sulphur (5 mg), hydroquinone (5 mg), and 1,2-dichloroethane (120 ml), boiling under reflux, at such a rate that the bromine was immediately consumed. After boiling under reflux for 3 h, the residue was distilled in steam for 2 h. Extraction of the residue with ether, drying (anhydrous magnesium sulphate), and removal of solvent gave a yellow solid (27.0 g). Recrystallisation of a portion from ethanol/water and sublimation in vacuo gave 5-bromofuran-2-carbaldehyde as white needles, m.p. 81-82° (lit.,⁸³ 82°); λ_{max} 283 nm (ϵ 13,750); ν_{max} 1719, 1696, and 1455 cm^{-1} ; τ 0.38 (doublet, J 0.5 Hz; CHO), 2.86 (doublet, J 4.5 Hz; 3-H), and 3.46 (quartet, J 0.5 and 4.5 Hz; 4-H).

5-Bromofuran-2-carboxylic acid (XLIV).(a). - The method used was similar to that described for 4-isopropylfuran-2-carboxylic acid. 5-Bromofuran-2-carbaldehyde (3.0 g) was stirred with an ammoniacal silver nitrate solution [from silver nitrate (2.3 g), sodium hydroxide (2.3 g), water (26 ml), and aqueous

ammonia solution] at 35°, for 4 h. Work-up [filtration, acidification (30% aqueous sulphuric acid), extraction with ether (2 x 100 ml), and drying (anhydrous magnesium sulphate)] gave, after removal of solvent, a yellow solid (2.4 g).

Recrystallisation from water gave 5-bromofuran-2-carboxylic acid as white needles, m.p. 190-191° (lit.,⁷⁸ 185°, 190°); $\lambda_{\text{max.}}$ 259 (ϵ 11,984); $\nu_{\text{max.}}$ 1708, 1468, and 1017 cm^{-1} ; τ (acetone) 0.21 (singlet; OH), 2.80 (doublet, J 3.8 Hz; 3-H), and 3.35 (doublet, J 3.8 Hz; 4-H).

(b).⁸⁴ - Finely-powdered potassium permanganate (48.5 g) was added to a mixture of 5-bromofuran-2-carbaldehyde (27.0 g), dioxan (150 ml), anhydrous sodium carbonate (19.7 g), and water (230 ml), at such a rate that the temperature of the mixture did not exceed 60°. After stirring the mixture for 8 h, work-up [filtration, acidification (30% aqueous sulphuric acid), continuous ether extraction (24 h), and treatment of the extracts with animal charcoal] gave, after removal of solvent, a black residue which could not be induced to crystallise. Unreacted aldehyde was removed by distillation in steam for 2 h. The crystalline residue was recrystallised from methanol/water to give 5-bromofuran-2-carboxylic acid (12.0 g) as a white solid identical (i.r., u.v., etc.) with previously-synthesised material.

(c).⁸⁵ - Furan-2-carboxylic acid (30.0 g), bromine (71.5 g) and chloroform (150 ml) were boiled under reflux for 3 h. Removal of solvent and recrystallisation of the solid residue from water (after treatment with animal charcoal) gave the bromo-acid (11.0 g) as a white solid identical (i.r., u.v., etc.) with previously-synthesised material.

5-Bromofuran-2-mercurichloride (XLV)⁸⁶ and 2-Bromo-5-deuteriofuran (XLVI).-

5-Bromofuran-2-carboxylic acid (6.6 g) and sodium hydroxide (1.3 g) in water

(20 ml) were mixed with mercury(II) chloride (20.0 g) in water (200 ml). After 1 h at 25°, the filtered solution was boiled until evolution of carbon dioxide had ceased. Cooling and filtration gave 5-bromofuran-2-mercurichloride (11.6 g) as a pale yellow solid, m.p. 174-176° (lit.,⁸⁶ 175-176°); τ (acetone) 3.44 (complex; 3-H and 4-H).

The mercurichloride was boiled with excess of 20% deuterium chloride in deuterium oxide whereupon 2-bromo-5-deuteriofuran (3 ml) distilled as a colourless liquid, pure by g.l.c. (column at 50°); $\nu_{\text{max.}}$ 1442, 1130, 1333, and 1047 cm^{-1} ; τ 3.72 (complex; 3-H and 4-H); m.s. peaks at m/e 147 (M, 100), 149 (100), 117 (30), 119 (30), 148 (19), and 146 (12).

5-Deuteriofuran-2-carboxylic acid (XLVII) (a). - To a solution of n-butyl-lithium in ether [prepared as described for the attempted synthesis of 2-isopropyl-furan, using lithium wire (0.45 g) and n-butyl bromide (dried over molecular sieve; 4.5 g)] at -30° was added 2-bromo-5-deuteriofuran (2.7 g) in ether (dried over sodium; 15 ml). The mixture was stirred at -30° for 1.5 h, warmed to 10°, and poured on to a slurry of solid carbon dioxide and ether. After 0.5 h, water was added and the aqueous layer, after separation, was acidified to pH 1 with 50% aqueous hydrochloric acid. Ether extraction, washing (brine), drying (anhydrous sodium sulphate), and removal of solvent gave a pale yellow, crystalline solid (2.0 g). Sublimation of a portion in vacuo gave 5-deuteriofuran-2-carboxylic acid as white needles, m.p. 129-130° (Found: C, 53.0; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 32.6. $\text{C}_5\text{H}_3\text{DO}_3$ requires: C, 53.1; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 32.7%); $\nu_{\text{max.}}$ 1700, 1446, 1019, and 1292 cm^{-1} ; τ (deuteriochloroform) 1.32 (singlet; OH), 2.66 (doublet, J 3.4 Hz; 3-H), and 3.45 (doublet, J 3.4 Hz; 4-H); m.s. peaks at m/e 113 (M, 100), 96 (80), 112 (8), 68 (8), 85 (7), and 95 (6).

(b). - 5-Deuteriofuran-2-carbaldehyde (for preparation see later; 10.0 g) was stirred with an ammoniacal silver nitrate solution [prepared as in the preparation of 4-isopropylfuran-2-carboxylic acid using silver nitrate (35.0 g), sodium hydroxide (35.0 g), water (450 ml), and aqueous ammonia solution] at 35° for 2 h. Work-up [filtration, acidification (30% aqueous sulphuric acid), continuous extraction with ether (12 h), and drying (anhydrous magnesium sulphate)] gave, after removal of solvent, 5-deuteriofuran-2-carboxylic acid (7.5 g) identical (i.r., u.v., etc.) with material synthesised previously.

5-Deuteriofuran-2-carbonyl chloride (XLVIII). - 5-Deuteriofuran-2-carboxylic acid (5.4 g) and thionyl chloride (freshly distilled; 11.0 g) were boiled under reflux for 0.5 h. Distillation and fractionation of the residue gave 5-deuteriofuran-2-carbonyl chloride (4.5 g) as a colourless liquid (Found: C, 45.3; [H₂O + D₂O], 21.5; Cl, 27.2. C₅H₂ClDO₂ requires: C, 45.6; [H₂O + D₂O], 21.3; Cl, 27.0%); ν_{max} . 1770, 1423, 1364, and 1026 cm⁻¹; τ 2.59 (doublet, J 3.8 Hz; 3-H) and 3.41 (doublet, J 3.8 Hz; 4-H); m.s. peaks at m/e 131 (M, 28), 43 (100), 96 (98), 58 (42), 68 (20), and 42 (13).

5-Deuteriofuran-2-carbaldehyde (XLIX). Attempted preparation. (a). - The method used was similar to that described for 5-deuteriothiophen-2-carbaldehyde. 5-Deuteriofuran-2-carbonyl chloride (1.0 g) was dissolved in diglyme (2 ml) and reduced with lithium aluminium tri-*t*-butoxyhydride (2.0 g) in diglyme (4 ml) as before. Work-up as before gave a red oil (230 mg) which was purified by p.t.l.c. (11 x 5% acetone in light petroleum). No aldehydic material was detected (n.m.r. and i.r.) and the preparation was thus abandoned.

(b). - Furan-2-carbaldehyde (freshly distilled in vacuo; 9.6 g) in ethanol (40 ml) was added to a mixture of mercury(II) chloride (27.0 g) and sodium acetate trihydrate

(54.4 g) in water (600 ml). The mixture was allowed to stand at 25° for 3 d, boiled under reflux for 2 h, and allowed to stand for a further 2 d at 25°.

Filtration gave a yellow powder (5 g) (Found: C, 3.45; H, 0.41. Calc. for monomercuriation: C, 18.1; dimercuriation: C, 10.6; trimercuriation: C, 7.5%). The preparation was thus abandoned.

(c). - Furan-2-carbaldehyde (freshly distilled in vacuo; 32.0 g) was added, with stirring during 10 min, to acetic anhydride (freshly distilled; 34.0 g) and concentrated sulphuric acid (0.04 ml) at 0°C. After 0.5 h, anhydrous sodium acetate (0.13 g) was added, and the mixture distilled and fractionated in vacuo (140°/20 mm) to give furan-2-carbaldehyde diacetate (30.0 g), m.p. 51-52° (lit.,⁸⁷ 52-53°); λ_{max} . 272 nm; ν_{max} . 1760, 1378 and 1200 cm^{-1} ; τ 2.43 (broad singlet; $\text{CH}(\text{OAc})_2$), 2.58 (quartet, J 0.5 and 1.8 Hz; 5-H), 3.64 (complex; 3-H and 4-H), and 7.93 (singlet, OCOCH_3).

A mixture of furan-2-carbaldehyde diacetate (10.0 g) in ethanol (100 ml), and mercury(II) chloride (13.7 g) and sodium acetate trihydrate (27.4 g) in water (300 ml) was boiled under reflux for 0.5 h. After the mixture had been standing for 30 d at 25°, no product was detected. The experiment was repeated using mercury(II) acetate instead of the chloride, but no product was detected. The route was thus abandoned.

(d). - Dimethylformamide (2.0 g) in ether (dried over sodium; 5 ml) was added to a solution of 5-deuterio-2-furyl lithium in ether, prepared under dry nitrogen, as described in the preparation of 5-deuteriofuran-2-carboxylic acid, from lithium wire (0.45 g), n.butylbromide (dried over molecular sieve; 4.5 g) and 2-bromo-5-deuteriofuran (prepared as before; 2.7 g), at -60°. After standing at 25° for 2 h and boiling under reflux for 0.5 h, the mixture was poured on to ice. Work-up

[acidification (50% aqueous hydrochloric acid), extraction (ether), washing of the extracts (water and brine), and drying (anhydrous magnesium sulphate)] gave, after removal of solvent, a red oil (1.0 g) t.l.c. of which (20% acetone in light petroleum) indicated the presence of the required product, R_F 0.32. Preliminary purification using a silica column gave material n.m.r. of which indicated the presence of the required product along with much aliphatic material. Purification by p.t.l.c. (6 x 2% acetone in light petroleum) failed to give the required product, and the preparation was thus abandoned.

5-Bromofuran-2-carbaldehyde diethyl acetal (L). Attempted preparation. -

A mixture of 5-bromofuran-2-carbaldehyde (18.0 g), ethyl orthoformate (dried over molecular sieve; 20.0 g), ethanol saturated with dry hydrogen chloride (0.6 ml), and ethanol (dried by distillation from magnesium; 120 ml) was boiled under reflux for 4 h. T.l.c. (20% acetone in light petroleum) showed two components R_F 's 0.34 (major) and 0.59; cf. starting material R_F 0.34. After the mixture had been boiled under reflux for 24 h, t.l.c. still showed two components, the relative proportions of which were not affected by addition of more ethanol saturated with hydrogen chloride (0.5 ml) or of hydrochloric acid (0.5 ml). Neutralisation (sodium carbonate), dilution with water, extraction with ether (3 x 100 ml), washing of the extracts with 20% aqueous sodium sulphite solution (250 ml), and drying (anhydrous magnesium sulphate), gave, after removal of solvent, a red oil n.m.r. of which indicated an approximately 1:1 mixture of aldehyde and acetal. Purification by distillation was unsuccessful and the preparation was abandoned.

Furan-2-carbaldehyde diethyl acetal (LI).⁸⁸ - A mixture of furan-2-carbaldehyde (freshly distilled in vacuo; 60.0 g), ethanol (dried by distillation

over calcium oxide; 400 ml), and ethanol saturated with dry hydrogen chloride (0.5 ml) was allowed to stand for 3 d at 25°. Work-up as described in the attempted preparation of 5-bromofuran-2-carbaldehyde diethyl acetal gave a red oil (60 g). Distillation in vacuo (81°/15 mm) gave furan-2-carbaldehyde diethyl acetal as a colourless liquid; $\nu_{\text{max.}}$ 1056, 1151, 2883, and 2980 cm^{-1} ; τ 2.70 (quartet, J 0.8 and 1.8 Hz; 5-H), 3.73 (complex; 3-H and 4-H), 4.57 (singlet; $\text{CH}(\text{OC}_2\text{H}_5)_2$), 6.51 (quartet, J 7 Hz; $-\text{CH}_2\text{CH}_3$), and 8.84 (triplet, J 7 Hz; $-\text{CH}_2\text{CH}_3$).

5-Deuteriofuran-2-carbaldehyde diethyl acetal (LII). - Furan-2-carbaldehyde diethyl acetal (60.0 g) was added at -20° during 10 min to a solution of n-butyl-lithium in ether prepared as described for the attempted synthesis of 2-isopropylfuran, using lithium wire (8.6 g), n-butyl bromide (dried over molecular sieve; 68.5 g), and ether (dried over sodium; 300 ml). Removal of coolant was accompanied by a rapid rise in temperature. The mixture was boiled under reflux for 3 h and stirred with deuterium oxide (10 ml) at 25° for 12 h. Washing (water and brine), drying (anhydrous magnesium sulphate), and removal of solvent gave a red oil. Distillation in vacuo (79°/20 mm) gave 5-deuteriofuran-2-carbaldehyde diethyl acetal (40.0 g) as a colourless liquid (Found: C, 63.0; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 74.0. $\text{C}_9\text{H}_{13}\text{DO}_3$ requires: C, 63.1; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 74.3%); $\nu_{\text{max.}}$ 1056, 1116, 2980, and 2885 cm^{-1} ; τ 3.77 (complex; 3-H and 4-H), 4.59 (singlet; $\text{CH}(\text{OC}_2\text{H}_5)_2$), 6.53 (quartet, J 7 Hz; $-\text{CH}_2\text{CH}_3$), and 8.86 (triplet, J 7 Hz; $-\text{CH}_2\text{CH}_3$); m.s. peaks at m/e 171 (M, 10), 98 (100), 126 (90), 43 (23), 97 (19), and 42 (14).

The preparation was repeated with the alteration that twice the amount of n-butyl lithium required for mono-lithiation was used. Work-up as before gave

5-deuteriofuran-2-carbaldehyde diethyl acetal identical (i.r., n.m.r.) with the product obtained above.

5-Deuteriofuran-2-carbaldehyde (XLIX). - 5-Deuteriofuran-2-carbaldehyde diethyl acetal (32.0 g) in ether (250 ml) was stirred with 5N-aqueous hydrochloric acid (140 ml) for 2 h at 25°. The ether layer was washed (saturated aqueous sodium bicarbonate solution and brine) and dried over anhydrous magnesium sulphate. Removal of solvent and distillation in vacuo (58°/15 mm) gave 5-deuteriofuran-2-carbaldehyde (17.0 g) as a colourless liquid (Found: C, 61.9; [H₂O + D₂O], 38.3. C₅H₃D₂O₂ requires: C, 61.9; [H₂O + D₂O], 38.2%); $\nu_{\text{max.}}$ 1693, 1426, 1018, and 1568 cm⁻¹; τ 0.37 (broad singlet; CHO), 2.77 (doublet, J 3.8 Hz; 3-H), and 3.43 (doublet, J 3.8 Hz; 4-H); m.s. peaks at m/e 97 (M, 94), 96 (100), 44 (19), 68 (12), 95 (12), and 42 (8); cf. furan-2-carbaldehyde, m.s. peaks at m/e 96 (M, 100), 95 (90), 43 (26), 67 (17), 50 (16), and 42 (15).

Methyl 4,5-dibromofuran-2-carboxylate (LIV).⁸⁹ - Bromine (210 ml) was added with stirring during 3 h to a slurry of anhydrous aluminium chloride (550 g) and methyl furan-2-carboxylate (252 g). The mixture was allowed to stand for 20 h at 25°, and water was then added during 2 h until evolution of gas had ceased. Work-up [extraction with ether (3 l), washing (saturated aqueous sodium bicarbonate solution and brine), drying (anhydrous magnesium sulphate) and removal of solvent] gave a red oil (430 g). Distillation and fractionation in vacuo (105°/1 mm) gave methyl 4,5-dibromofuran-2-carboxylate as a white solid (205 g), m.p. 55-56°, pure by g.l.c. (column at 150°); $\lambda_{\text{max.}}$ 270 nm (ϵ 8150); $\nu_{\text{max.}}$ 1730, 1746, 1295, and 1155 cm⁻¹; τ 2.88 (singlet; 3-H) and 6.14 (singlet; CH₃).

4,5-Dibromofuran-2-carboxylic acid (LV).⁹⁰ - Methyl 4,5-dibromofuran-2-carboxylate (200 g) was boiled under reflux with 20% aqueous sodium hydroxide solution (3.5 l) for 5 h. Acidification (50% aqueous hydrochloric acid), extraction (ethyl acetate), washing (brine), drying (anhydrous magnesium sulphate), and removal of solvent gave a white solid (120 g). Sublimation of a portion in vacuo gave 4,5-dibromofuran-2-carboxylic acid, m.p. 168-169°; λ_{max} 278 nm (ϵ 11,536); ν_{max} 1700, 1475, 1188, and 1286 cm^{-1} ; τ (deuteriochloroform) -0.48 (singlet; OH) and 2.69 (singlet; 3-H).

2,3-Dibromofuran (LVI).⁸⁶ - A mixture of 4,5-dibromofuran-2-carboxylic acid (120 g), mercury(II) chloride (120 g) and water (2.5 l) was distilled in steam for 4 h. Extraction of the distillate (ether), washing (brine), drying (anhydrous magnesium sulphate), and removal of solvent gave, after distillation, 2,3-dibromofuran (40 g) as a colourless liquid, b.p. 55-56° (lit.,⁸⁹ 58°); ν_{max} 1158, 1042, 959, and 882 cm^{-1} ; τ 2.63 (doublet, J 1.8 Hz; 5-H) and 3.58 (doublet, J 1.8 Hz; 4-H).

3-Bromofuran-2-carbaldehyde (LVII).⁸⁴ - 2,3-Dibromofuran (40.0 g) in an equal volume of ether (dried over sodium) was added at -60° to a solution of n-butyl-lithium in ether [prepared as before from lithium wire (3.13 g), n-butyl bromide (dried over molecular sieve; 25.0 g), and ether (dried over sodium; 105 ml)]. After 30 min, dimethylformamide (18.8 g) in an equal volume of ether (dried over sodium) was added, and the mixture was allowed to warm to room temperature during 2 h. After boiling under reflux for 0.5 h, the mixture was hydrolysed and extracted with ether, and the extracts were washed (water and brine) and dried (anhydrous magnesium sulphate). Removal of solvent gave a red oil (27 g), distillation of which (94°/15 mm) gave 3-bromofuran-2-carbaldehyde

(10.0 g), m.p. 31-32° (lit.,⁸⁹ 32°); $\nu_{\text{max.}}$ 1691 cm^{-1} ; τ 0.31 (doublet, $\underline{J}$ 0.8 Hz; $\underline{\text{CHO}}$), 2.32 (quartet, $\underline{J}$ 0.8 and 1.8 Hz; 5-H), and 3.35 (doublet, $\underline{J}$ 1.8 Hz; 4-H).

3-Bromofuran-2-carbaldehyde diethyl acetal (LVIII).⁸⁹ - Preparation was attempted using a method similar to that described for furan-2-carbaldehyde diethyl acetal. 3-Bromofuran-2-carbaldehyde (6.0 g), ethanol (dried by distillation over calcium oxide; 100 ml), and ethanol saturated with dry I_2 , drogen chloride (1 ml) were allowed to stand at 25° for 3 d. Work-up as before gave material which n.m.r. indicated to be only 70% converted to the acetal.

The preparation was repeated using 3-bromofuran-2-carbaldehyde (6.0 g), ethanol (dried as before; 50 ml), ethyl orthoformate (4.0 g) and hydrochloric acid (0.3 ml). After boiling under reflux for 2 h and standing at 0° for 2 d, the mixture was worked up as before. Distillation in vacuo (75°/1 mm) gave 3-bromofuran-2-carbaldehyde diethyl acetal (6.0 g) as a colourless liquid (lit.,⁸⁹ b.p. 88°/4 mm); $\nu_{\text{max.}}$ 1058, 1147, and 2968 cm^{-1} ; τ 2.70 (doublet, $\underline{J}$ 1.8 Hz; 5-H), 3.67 (doublet, $\underline{J}$ 1.8 Hz; 4-H), 4.56 (singlet; $\underline{\text{CH}}(\text{OC}_2\text{H}_5)_2$), 6.45 (quartet, $\underline{J}$ 7 Hz; $-\underline{\text{CH}}_2\text{CH}_3$), and 8.84 (triplet, $\underline{J}$ 7 Hz; $-\text{CH}_2\underline{\text{CH}}_3$).

3-Deuteriofuran-2-carbaldehyde (LIX). Attempted preparation. - 3-Bromofuran-2-carbaldehyde diethyl acetal (6.0 g) was added at -60° to a solution of n-butyl-lithium in ether [prepared as before from lithium wire (0.3 g) and n-butyl bromide (dried over molecular sieve; 2.8 g)]. The mixture was allowed to warm to 0° and deuterium oxide (2 ml) was added. After stirring at 25° for 1 h, the mixture was diluted with water and extracted with ether; the extracts were washed (water and brine) and dried. Removal of solvent gave a red oil which was hydrolysed with 5N-aqueous hydrochloric acid as described in the preparation of

5-deuteriofuran-2-carbaldehyde. Work-up as before gave, after distillation in vacuo, an intractable residue and an oil (0.5 g), n.m.r. of which indicated the presence of starting material (50%). P.t.l.c. (1 x 20% acetone in light petroleum) gave furan-2-carbaldehyde deuterated at position 3 to the extent of only 50%

The experiment was repeated with similar results and the preparation was thus abandoned.

4, 5-Dibromofuran-2-carbaldehyde (LX).⁹¹ - Furan-2-carbaldehyde (freshly distilled in vacuo; 288 g) was added during 1 h to finely-powdered, anhydrous aluminium chloride (876 g), cooled in ice. Bromine (960 g) was added during 1 h and the mixture left at 25° for 3 d. Water and anhydrous sodium carbonate were added, and the mixture was distilled in steam for 12 h. Extraction of the distillate with ether, drying (anhydrous magnesium sulphate) and removal of solvent gave a yellow oil (400 g) g.l.c. of which (column at 150°) showed three components. Distillation and fractionation in vacuo (130°/0.1 mm) gave 4, 5-dibromofuran-2-carbaldehyde (160 g) as a white solid, m.p. 35-36° (lit.,⁹¹ 36-37°); λ_{max} 288 nm (ϵ 14,660); ν_{max} 1690, 1456, 1331, and 1102 cm⁻¹; τ 0.49 (singlet; CHO) and 2.82 (singlet; 3-H).

De-halogenation of 5-Bromofuran-2-carbaldehyde. - Powdered zinc (60 mesh; 1.7 g) was mixed with 5-bromofuran-2-carbaldehyde (3.1 g), glacial acetic acid (1.5 g), and water (4.0 g). After 10 min, the mixture was extracted with ether and the extracts were washed (saturated aqueous sodium bicarbonate solution and brine) and dried (anhydrous magnesium sulphate). Removal of solvent gave material consisting largely (70%) of furan-2-carbaldehyde (n.m.r.).

4-Bromofuran-2-carbaldehyde (LXI). - Powdered zinc (60 mesh; 0.4 g) was mixed with 4, 5-dibromofuran-2-carbaldehyde (1.0 g), glacial acetic acid

(0.33 g), and water (0.9 g). Work-up as in the de-halogenation of 5-bromofuran-2-carbaldehyde gave a red oil (0.7 g) consisting of the required product (50%) and material containing hydroxyl groups (n.m.r.). Distillation in vacuo gave an intractable residue and 4-bromofuran-2-carbaldehyde (200 mg) as white cubes, m.p. 52-53° (lit.,⁸⁹ 52°), pure by g.l.c. (column at 125°); $\lambda_{\text{max.}}$ 277 nm (ϵ 10,671) and 232 nm (ϵ 4766); $\nu_{\text{max.}}$ 1690, 1704, 925, and 1472 cm^{-1} ; τ 0.44 (doublet, J 0.6 Hz; CHO), 2.34 (broad doublet, J 0.9 Hz; 5-H), and 2.80 (doublet, J 0.9 Hz; 3-H).

Attempted de-halogenation of 4-Bromofuran-2-carbaldehyde (LXII). - Powdered zinc (60 mesh; 0.4 g) was mixed with 4-bromofuran-2-carbaldehyde (0.7 g), glacial acetic acid (0.33 g), and water (0.9 g). After boiling the mixture under reflux for 0.5 h, work-up as in the de-halogenation of 5-bromofuran-2-carbaldehyde gave a red oil which did not contain aldehydic material (n.m.r.); the preparation was thus abandoned.

4,5-Dibromofuran-2-carbaldehyde diethyl acetal (LXIII). - The method used was similar to that described for 3-bromofuran-2-carbaldehyde diethyl acetal. A mixture of 4,5-dibromofuran-2-carbaldehyde (38.5 g), ethanol (dried by distillation over calcium oxide; 150 ml), ethyl orthoformate (dried over molecular sieve; 30.0 g) and hydrochloric acid (0.5 ml) was boiled under reflux for 2 h and allowed to stand at 0° for 3 d. Work-up as before gave 4,5-dibromofuran-2-carbaldehyde diethyl acetal (44.0 g) as a golden oil; $\lambda_{\text{max.}}$ 288 nm (ϵ 13,273) and 228 nm (ϵ 4748); $\nu_{\text{max.}}$ 1058, 1124, 1160, and 2980 cm^{-1} ; τ 3.58 (singlet; 3-H), 4.64 (singlet; $\text{CH}(\text{OC}_2\text{H}_5)_2$), 6.51 (quartet, J 7 Hz; CH_2CH_3), and 8.81 (triplet, J 7 Hz; CH_2CH_3).

4-Bromofuran-2-carbaldehyde diethyl acetal (LXIV). - 4,5-Dibromofuran-

2-carbaldehyde diethyl acetal (44.0 g) in an equal volume of ether (dried over sodium) was added at -60° during 15 min to a solution of n-butyl-lithium in ether [prepared as before from lithium wire (2.3 g) and n-butyl bromide (dried over molecular sieve; 18.5 g)]. The mixture was warmed to 25° during $1\frac{1}{2}$ h, boiled under reflux for $1\frac{1}{2}$ h, and cooled to -5° ; water (30 ml) was added during 15 min and the mixture stirred at 25° for 4 h. Work-up (dilution with water, extraction with ether, drying over anhydrous magnesium sulphate and removal of solvent) gave a black oil. Distillation in vacuo ($102^{\circ}/1.5$ mm) gave 4-bromofuran-2-carbaldehyde diethyl acetal (23.5 g) as a colourless liquid; $\lambda_{\text{max.}}$ 280 nm (ϵ 4796) and 224 nm (ϵ 4796); $\nu_{\text{max.}}$ 1060, 1132, 927, and 2988 cm^{-1} ; τ 2.67 (doublet, J 0.8 Hz; 5-H), 3.60 (doublet, J 0.8 Hz; 3-H), 4.61 (singlet; $\text{CH}(\text{OC}_2\text{H}_5)_2$), 6.50 (quartet, J 7 Hz; CH_2CH_3), and 8.83 (triplet, J 7 Hz; CH_2CH_3).

4-Deuteriofuran-2-carbaldehyde (LXV). Attempted preparation. -

4-Bromofuran-2-carbaldehyde diethyl acetal (23.5 g) in an equal volume of ether (dried over sodium) was added at -60° during 15 min to a solution of n-butyl-lithium in ether [prepared as before from lithium wire (1.64 g) and n-butyl bromide (dried over molecular sieve; 16.4 g)]. The mixture was warmed to 25° during $1\frac{1}{2}$ h, boiled under reflux for 2 h, and cooled to -5° ; deuterium oxide (10 ml) was added and the mixture stirred at 25° for 5 h. Work-up as in the preparation of 4-bromofuran-2-carbaldehyde diethyl acetal gave a red oil (17.5 g). Distillation in vacuo gave non-brominated material (4 g), starting material (4 g), and an intractable residue. The non-brominated material was hydrolysed with 5N-aqueous hydrochloric acid as described in the preparation of 5-deuteriofuran-2-carbaldehyde. Work-up as before gave furan-2-carbaldehyde deuterated to the extent of only 10% at

position 4 (n.m.r.).

The preparation was repeated with the alteration that deuterium oxide was added in tetrahydrofuran at -50° . Work-up as before gave furan-2-carbaldehyde (1.5 g) deuterated to the extent of 40% at position 4 (n.m.r.) along with much unreacted material and polymer.

The preparation was repeated with the alterations that (i) prior to the addition of deuterium oxide, the solution was kept at -30° for 3 h, warmed to 0° during 2 h, and then cooled again to -40° , and (ii) a larger excess (20 ml) of deuterium oxide in tetrahydrofuran was added. Work-up as before gave partially-deuterated furan-2-carbaldehyde diethyl acetal, unreacted 4-bromofuran-2-carbaldehyde diethyl acetal, and much polymer. The preparation was thus abandoned.

4-Bromo-5-deuteriofuran-2-carbaldehyde diethyl acetal (LXVI). - 4,5-Dibromofuran-2-carbaldehyde diethyl acetal (38.0 g) in an equal volume of ether (dried over sodium) was added at -60° during 15 min to a solution of n-butyl-lithium in ether [prepared as before from lithium wire (2.0 g) and n-butyl bromide (dried over molecular sieve; 16.0 g)]. The mixture was warmed to 25° during $1\frac{1}{2}$ h, boiled under reflux for $1\frac{1}{2}$ h, and cooled to -5° ; deuterium oxide (10 ml) was added and the mixture stirred at 25° for 4 h. Work-up as before gave 4-bromo-5-deuteriofuran-2-carbaldehyde diethyl acetal (20.0 g) as a colourless liquid; $\lambda_{\text{max.}}$ 276 nm (ϵ 9792); $\nu_{\text{max.}}$ 1061, 917, 1148, and 2988 cm^{-1} ; τ 3.64 (singlet; 3-H), 4.65 (singlet; $\text{CH}(\text{OC}_2\text{H}_5)_2$), 6.53 (quartet, J 7 Hz; CH_2CH_3), and 8.86 (triplet, J 7 Hz; CH_2CH_3); m.s. peaks at m/e 249 (M, 17), 204 (100), 206 (99), 176 (80), 103 (34), and 75 (19).

4-Bromo-5-deuteriofuran-2-carbaldehyde (LXVII). - 4-Bromo-5-deuteriofuran-2-carbaldehyde diethyl acetal (2.5 g) was hydrolysed with 5N-aqueous hydrochloric acid as described in the preparation of 5-deuteriofuran-2-carbaldehyde. Work-up as before gave 4-bromo-5-deuteriofuran-2-carbaldehyde (1.5 g) as a white solid, m.p. 52-53° (Found: C, 34.0; [H₂O + D₂O], 15.3; Br, 45.8. C₅H₂BrD₂O₂ requires: C, 34.1; [H₂O + D₂O], 15.9; Br, 45.4%); λ_{max.} 276 nm (ε 10,620) and 232 nm (ε 4670); ν_{max.} 1700, 1443, 1168, and 919 cm⁻¹; τ 0.39 (singlet; CHO) and 2.83 (singlet; 3-H); m.s. peaks at m/e 175 (M, 100), 174 (84), 118 (22), 67 (15), 117 (11), and 146 (7).

3,4,5-Trideuteriofuran-2-carboxylic acid (LXVIII). - Furan-2-carboxylic acid (30.0 g) was heated at 140° with 30% (w/w) sodium deuterioxide in deuterium oxide (100 ml). At 2 d intervals, aliquots were acidified (concentrated hydrochloric acid) and extracted with ethyl acetate: n.m.r. was then used to monitor the deuteration level. After 5 d, the mixture was acidified (concentrated hydrochloric acid) and extracted with ethyl acetate, and the extracts were dried over anhydrous magnesium sulphate. Removal of solvent gave 3,4,5-trideuteriofuran-2-carboxylic acid* (29.0 g), m.p. 129-130° (Found: C, 52.6; [H₂O + D₂O], 33.4. C₅HD₃O₃ requires: C, 52.2; [H₂O + D₂O], 33.9%); λ_{max.} 255 nm (ε 13,500); ν_{max.} 1702, 1190, 1432, and 1290 cm⁻¹; m.s. peaks at m/e 115 (M, 98), 98 (100), and 42 (28).

3,4,5-Trideuteriofuran-2-mercurichloride (LXIX) and 2,3,4,5-Tetra-deuteriofuran (LXX). - 3,4,5-Trideuteriofuran-2-carboxylic acid (5.0 g) and

* In this compound, and in derivatives derived from this compound, the average deuterium level, estimated by n.m.r. and m.s., was about 85%.

sodium hydroxide (1.75 g) in water (20 ml) were mixed with mercury(II) chloride (27.0 g) in water (270 ml), and the mixture was boiled for 0.5 h. Cooling and filtration gave 3,4,5-trideuteriofuran-2-mercurichloride (10.0 g), m.p. 151–152°.

The mercurichloride was boiled with excess of 20% deuterium chloride in deuterium oxide, whereupon 2,3,4,5-tetradeuteriofuran (1.0 g) distilled as a colourless liquid.

3,4,5-Trideuteriofuran-2-carbaldehyde (LXXI). - The method used was similar to that described for 4,5-diisopropylfuran-2-carbaldehyde. Phosphoryl chloride (2.2 g) was added at 0° during 15 min to tetradeuteriofuran (0.7 g) in dimethylformamide (1.0 g). The mixture was allowed to warm to 25° during 3½ h. Work-up as before gave 3,4,5-trideuteriofuran-2-carbaldehyde (0.6 g), pure by t.l.c. and g.l.c. (column at 75°) (Found: C, 60.6; [H₂O + D₂O], 38.0. C₅HD₃O₂ requires: C, 60.6; [H₂O + D₂O], 39.4%); $\nu_{\max}$. 1692, 1412, and 870 cm⁻¹; τ 0.39 (singlet; CHO); m.s. peaks at m/e 99 (M, 100), 98 (99), 42 (60), 41 (59), 70 (30), and 51 (15).

Ethyl 3,4,5-trideuteriofuran-2-carboxylate (LXXII). - A mixture of 3,4,5-trideuteriofuran-2-carboxylic acid (20.0 g), ethanol (dried by distillation over calcium oxide; 280 ml), and concentrated sulphuric acid (20 ml) was boiled under reflux for 4 h. After most of the ethanol had been removed, the mixture was neutralised (anhydrous sodium carbonate) and extracted (ether), and the extracts were washed (brine) and dried (anhydrous magnesium sulphate). Removal of solvent and distillation in vacuo gave ethyl 3,4,5-trideuteriofuran-2-carboxylate (21.6 g) as a white solid, m.p. 32–33°, pure by g.l.c. (column at 125°) (Found: C, 58.7; [H₂O + D₂O], 52.8. C₇H₅D₃O₃ requires: C, 58.7; [H₂O + D₂O], 52.4%); $\nu_{\max}$. 1724, 1740, 1180, and 1289 cm⁻¹;

τ 5.74 (quartet, J 7 Hz; CH_2CH_3) and 8.65 (triplet, J 7 Hz; CH_2CH_3); m.s. peaks at m/e 143 (M, 15), 98 (100), 115 (37), 78 (26), 60 (15), and 85 (14).

Ethyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (LXXIII). - Bromine (25.0 g) in 1,2-dichloroethane (10 ml) was added during 1 h to ethyl 3,4,5-trideuteriofuran-2-carboxylate (20.0 g) in 1,2-dichloroethane (80 ml) boiling under reflux. The solution was boiled under reflux for a further 4 h. Removal of solvent and distillation of the residue in vacuo ($70^\circ/0.05$ mm) gave ethyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (24.2 g) as a yellow oil, pure by g.l.c. (column at 125°) (Found: C, 38.3; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 28.4; Br, 36.6. $\text{C}_7\text{H}_5\text{BrD}_2\text{O}_3$ requires: C, 38.0; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 29.4; Br, 36.2%); ν_{max} . 1720, 1737, 1294, and 1452 cm^{-1} ; τ 5.74 (quartet, J 7 Hz; CH_2CH_3) and 8.65 (triplet, J 7 Hz; CH_2CH_3); m.s. peaks at m/e 220 (M, 35), 175 (100), 192 (75), 97 (45), 148 (35), and 119 (35).

3,4-Dideuteriofuran-2-carboxylic acid (LXXIV). - A mixture of ethyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (19.2 g), glacial acetic acid (7.2 g), powdered zinc (60 mesh; 8.3 g), and water (19.2 g) was stirred at 110° for 3 d. After washing with ether, the mixture was acidified (concentrated hydrochloric acid) and extracted (ethyl acetate), and the extracts were dried (anhydrous magnesium sulphate). Removal of solvent and recrystallisation from water gave 3,4-dideuteriofuran-2-carboxylic acid (9.0 g) as a white solid, m.p. $129-130^\circ$ (Found: C, 52.7; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 32.9. $\text{C}_5\text{H}_2\text{D}_2\text{O}_3$ requires: C, 52.6; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 33.4%); ν_{max} . 1701, 1293, 1189, and 1463 cm^{-1} ; τ (deuteriochloroform) -1.71 (singlet; OH) and 2.38 (singlet; 5-H); m.s. peaks at m/e 114 (M, 100), 97 (80), 69 (8), and 86 (6).

3,4-Dideuteriofuran (LXXV) and 3,4-Dideuteriofuran-2-carbaldehyde (LXXVI).— The methods used were similar to those described for 3-isopropyl furan and 4,5-diisopropylfuran-2-carbaldehyde. 3,4-Dideuteriofuran-2-carboxylic acid (6.0 g) was heated with quinoline (20.0 g) and copper bronze (2.0 g) at 250° for 3 h during which time 3,4-dideuteriofuran distilled.

Phosphoryl chloride (10.0 g) was added at 0° during 15 min to 3,4-dideuteriofuran (1.8 g) in dimethylformamide (5 ml). The mixture was allowed to warm to 25° during 2½ h. Work-up as before and purification by preparative g.l.c. gave 3,4-dideuteriofuran-2-carbaldehyde (Found: C, 61.3; [H₂O + D₂O], 38.6. C₅H₂D₂O₂ requires: C, 61.3; [H₂O + D₂O], 38.8%); $\nu_{\max}$. 1689, 1465, 1448, and 834 cm⁻¹; τ 0.38 (doublet, J 0.7 Hz; $\underline{\text{CHO}}$) and 2.28 (broad singlet; 5-H); m.s. peaks at m/e 98 ($\underline{M}$, 60), 97 (100), and 96 (70).

Methyl 5-deuteriofuran-2-carboxylate (LXXVII).— Methyl 5-bromofuran-2-carboxylate (preparation, see later) (7.2 g) was heated at 110° with acetic anhydride (freshly distilled; 3.0 g), deuterium oxide (1.5 ml), and powdered zinc (60 mesh; 3.5 g) for 10 h. Ether extraction, drying (anhydrous magnesium sulphate), removal of solvent and purification by p.t.l.c. (10 x 2% acetone in light petroleum) gave methyl 5-deuteriofuran-2-carboxylate, pure by g.l.c. (column at 100°) (Found: C, 56.8; [H₂O + D₂O], 43.4. C₆H₅DO₃ requires: C, 56.7; [H₂O + D₂O], 43.3%); $\nu_{\max}$. 1728, 1742, 1302, and 1450 cm⁻¹; τ 2.90 (doublet, J 3.8 Hz; 3-H), 3.53 (doublet, J 3.8 Hz; 4-H), and 6.16 (singlet; $\underline{\text{CH}}_3$); m.s. peaks at m/e 127 ($\underline{M}$, 35) and 96 (100).

Ethyl 5-deuteriofuran-2-carboxylate (LXXVIII).— The preparation was carried out as for the methyl ester using ethyl 5-bromofuran-2-carboxylate (preparation, see later) (0.77 g), acetic anhydride (0.3 g), powdered zinc

(0.35 g), and deuterium oxide (0.2 ml). Work-up and purification as in the preparation of the methyl ester gave ethyl 5-deuteriofuran-2-carboxylate, m.p. 34-35° (Found: C, 59.6; [H₂O + D₂O], 51.4. C₇H₇DO₃ requires: C, 59.6; [H₂O + D₂O], 51.8%); $\nu_{\max}$. 1723, 1739, 1296, and 1137 cm⁻¹; τ 2.93 (doublet, J 3.8 Hz; 3-H), 3.57 (doublet, J 3.8 Hz; 4-H), 5.72 (quartet, J 7 Hz; CH₃CH₂), and 8.66 (triplet, J 7 Hz; CH₃CH₂); m.s. peaks at m/e 141 (M, 17), 96 (100), 113 (45), 97 (18), 141 (17), and 43 (17).

t-Butyl 5-deuteriofuran-2-carboxylate (LXXIX).- Isobutene (condensed from a cylinder; 30 ml), 5-deuteriofuran-2-carboxylic acid (3.0 g), ether (dried over sodium; 80 ml), and sulphuric acid (1.5 ml) were mixed in a thick-walled vessel, cooled in acetone/solid carbon dioxide. The vessel was stoppered and wired and the contents stirred for 3 d at 25°. The vessel was then cooled in acetone/solid carbon dioxide and the mixture was poured into potassium hydroxide (10 g) in water (200 ml). The ether layer was washed with water and brine and dried over anhydrous magnesium sulphate. Removal of solvent and distillation in vacuo (83°/20 mm) gave t-butyl 5-deuteriofuran-2-carboxylate (3.7 g) as a colourless liquid, pure by g.l.c. (column at 100°) (Found: C, 63.7; [H₂O + D₂O], 64.8. C₉H₁₁DO₃ requires: C, 63.9; [H₂O + D₂O], 64.5%); $\nu_{\max}$. 1137, 1308, 1711, and 1729 cm⁻¹; τ 3.03 (doublet, J 3.8 Hz; 3-H), 3.62 (doublet, J 3.8 Hz; 4-H), and 8.48 (singlet; t-C₄H₉); m.s. peaks at m/e 169 (M, 12), 96 (100), 113 (72), 114 (60), 56 (52), and 41 (44).

2-(5-Deuteriofuryl) phenyl ketone (LXXX).- 5-Deuteriofuran-2-carbonyl chloride (1.5 g) in benzene (dried over sodium; 1.0 ml) was added dropwise to anhydrous aluminium chloride (1.7 g) in benzene (2.3 ml). After boiling under reflux for 0.5 h, the solution was poured on to ice and the mixture extracted

with benzene. Work-up [washing (saturated aqueous sodium bicarbonate solution and brine), drying (anhydrous magnesium sulphate), and removal of solvent] gave, after distillation in vacuo ($156^{\circ}/20$ mm), 2-(5-deuteriofuryl) phenyl ketone (1.5 g), pure by g.l.c. (column at 150°); $\nu_{\text{max.}}$ 1651, 1429, 1282, and 900 cm^{-1} ; τ 2.09 and 2.64 (complex; phenyl-H), 2.88 (doublet, J 3.6 Hz; 3-H), and 3.56 (doublet, J 3.6 Hz; 4-H); m.s. peaks at m/e 173 (M, 59), 43 (100), 105 (67), 145 (15), 117 (12), and 172 (11).

5-Deuteriofuran-2-carbonyl fluoride (LXXXI).- The method used was similar to that described for furan-2-carbonyl fluoride. 5-Deuteriofuran-2-carbonyl chloride (1.0 g) was heated to 160° with potassium hydrogen fluoride (1.2 g). Distillation gave 5-deuteriofuran-2-carbonyl fluoride, pure by g.l.c. (column at 50°); $\nu_{\text{max.}}$ 1827, 1816, 1287, and 1066 cm^{-1} ; τ 2.65 (broad doublet, J 3.8 Hz; 3-H) and 3.41 (broad doublet, J 3.8 Hz; 4-H).

Methyl 5-bromofuran-2-carboxylate (LXXXII).- The method used was similar to that described for ethyl 3,4,5-trideuteriofuran-2-carboxylate. A mixture of 5-bromofuran-2-carboxylic acid (4.0 g), methanol (dried by distillation over calcium oxide; 25 ml), and sulphuric acid (1.5 ml) was boiled under reflux for 4 h. Work-up as before gave methyl 5-bromofuran-2-carboxylate (4.0 g) as a white solid, m.p. $64-65^{\circ}$ (lit., ⁷⁸ 59°), pure by g.l.c. (column at 125° ; $\lambda_{\text{max.}}$ 261 nm (ϵ 11,370); $\nu_{\text{max.}}$ 1468, 1299, 1732, and 1113 cm^{-1} ; τ 2.99 (doublet, J 3.6 Hz; 3-H), 3.64 (doublet, J 3.6 Hz; 4-H), and 6.19 (singlet; CH_3).

Ethyl 5-bromofuran-2-carboxylate (LXXXIII).- The method used was similar to that described for ethyl 3,4,5-trideuteriofuran-2-carboxylate. A mixture of 5-bromofuran-2-carboxylic acid (5.0 g), ethanol (dried as before; 25 ml), and

sulphuric acid (0.5 ml) was boiled under reflux for 3 h. Work-up as before gave ethyl 5-bromofuran-2-carboxylate (5.1 g) as a colourless oil, b.p. 135° (bath)/15 mm (lit.,⁷⁸ $133-134^{\circ}$ /31 mm), pure by g.l.c. (column at 125°); $\lambda_{\text{max.}}$ 261 nm (ϵ 14,979); $\nu_{\text{max.}}$ 1718, 1733, 1467, and 1291 cm^{-1} ; τ 2.97 (doublet, J 3.6 Hz; 3-H), 3.61 (doublet, J 3.6 Hz; 4-H), 5.72 (quartet, J 7 Hz; CH_3CH_2), and 8.63 (triplet, J 7 Hz; CH_3CH_2).

t-Butyl 5-bromofuran-2-carboxylate (LXXXIV).—The method used was similar to that described for t-butyl 5-deuteriofuran-2-carboxylate. Isobutene (25 ml), 5-bromofuran-2-carboxylic acid (5.0 g), ether (dried over sodium; 75 ml), and sulphuric acid (2 ml) gave, after work-up as before and distillation in vacuo, t-butyl 5-bromofuran-2-carboxylate (6.0 g) as a colourless liquid, pure by g.l.c. (column at 125°); $\lambda_{\text{max.}}$ 259 nm (ϵ 13,873); $\nu_{\text{max.}}$ 1713, 1731, 1468, and 1311 cm^{-1} ; τ 3.06 (doublet, J 3.6 Hz; 3-H), 3.63 (doublet, J 3.6 Hz; 4-H), and 8.47 (singlet; $t\text{-C}_4\text{H}_9$).

5-Bromofuran-2-carbonyl chloride (LXXXV).—The method used was similar to that described for furan-2-carbonyl chloride. 5-Bromofuran-2-carboxylic acid (8.0 g) and thionyl chloride (freshly distilled; 16.0 g) gave, after work-up as before, 5-bromofuran-2-carbonyl chloride (8.1 g) as a white solid, m.p. $54-55^{\circ}$ (lit.,⁷⁸ $54-56^{\circ}$); $\lambda_{\text{max.}}$ 281 nm (ϵ 7322); $\nu_{\text{max.}}$ 1758, 1452, 1350, and 1020 cm^{-1} ; τ 2.66 (doublet, J 3.8 Hz; 3-H) and 3.46 (doublet, J 3.8 Hz; 4-H).

Methyl 4-bromofuran-2-carboxylate (LXXXVI).—The method used was similar to that described for 4-bromofuran-2-carbaldehyde. Powdered zinc (60 mesh; 3.3 g), methyl 4,5-dibromofuran-2-carboxylate (10.0 g), glacial acetic acid (2.9 g), and water (7.7 g) were heated at 100° for $2\frac{1}{2}$ h. Work-up as before gave a golden oil (6.0 g), t.l.c. of which (10% acetone in light

petroleum) showed the presence of two components, R_F 's 0.40 (major) and 0.42 (minor), cf. starting material R_F 0.42. P.t.l.c. (5 x 2% acetone in light petroleum) of a portion gave methyl 4-bromofuran-2-carboxylate as a white solid, m.p. 44-46° (Found: C, 35.4; H, 2.2; Br, 38.7. $C_6H_5BrO_3$ requires: C, 35.1; H, 2.5; Br, 39.0%); $\lambda_{\max.}$ 255 nm (ϵ 7923) and 220 nm (ϵ 5348); $\nu_{\max.}$ 1300, 1727, 1744, and 1196 cm^{-1} ; τ 2.49 (doublet, J 0.9 Hz; 5-H), 2.92 (doublet, J 0.9 Hz; 3-H), and 6.17 (singlet; CH_3); m.s. peaks at m/e 204 (M , 39), 173 (100), 149 (35), 58 (28), 117 (25), and 66 (25).

4-Bromofuran-2-carboxylic acid (LXXXVII).⁷⁸ The method used was similar to that described for 4,5-dibromofuran-2-carboxylic acid. Methyl 4-bromofuran-2-carboxylate (9.0 g) was boiled under reflux with 20% aqueous sodium hydroxide solution (100 ml) for 3 h. Work-up as before gave a white solid (7.0 g). Sublimation of a portion in vacuo gave 4-bromofuran-2-carboxylic acid, m.p. 127-128° (lit.,⁷⁸ 128-129°); $\lambda_{\max.}$ 255 nm (ϵ 6708) and 218 (ϵ 4845); $\nu_{\max.}$ 1710, 929, 1487, and 1422 cm^{-1} ; τ (deuteriochloroform) -1.84 (OH), 2.39 (doublet, J 0.7 Hz; 5-H), and 2.70 (doublet, J 0.7 Hz; 3-H).

Attempted de-halogenation of Methyl 4-bromofuran-2-carboxylate (LXXXVI). -

The method used was similar to that described for the attempted de-halogenation of 4-bromofuran-2-carbaldehyde. A mixture of powdered zinc (60 mesh; 3.0 g), methyl 4-bromofuran-2-carboxylate (1.0 g), glacial acetic acid (1.5 g), and water (4.0 g) was heated at 110° for 12 h. Work-up as before gave an ethereal solution which did not contain any aromatic material (n.m.r.). The aqueous layer was acidified (5N-aqueous hydrochloric acid) and extracted with ether (3 x 50 ml), and the extracts were washed (brine) and dried (anhydrous magnesium sulphate). Removal of solvent gave a white solid demonstrated by n.m.r. to be

4-bromofuran-2-carboxylic acid. The preparation was thus abandoned.

Ethyl 4-bromofuran-2-carboxylate (LXXXVIII)⁷⁸ - The method used was similar to that described for ethyl 3,4,5-trideuteriofuran-2-carboxylate. 4-Bromofuran-2-carboxylic acid (1.0 g), ethanol (dried as before; 7 ml), and sulphuric acid (0.5 ml) gave, after boiling under reflux and work-up as before, a golden oil (1.0 g). A portion was purified by p.t.l.c. (4 x 2% acetone in light petroleum) to give ethyl 4-bromofuran-2-carboxylate as a white solid, m.p. 28-29° (lit.,⁷⁸ 28-29°); λ_{max} 254 nm (ϵ 8840) and 218 nm (ϵ 6429); ν_{max} 1296, 1185, 1728, and 1742 cm^{-1} ; τ 2.44 (doublet, J 0.7 Hz; 5-H), 2.91 (doublet, J 0.7 Hz; 3-H), 5.70 (quartet, J 7 Hz; CH_2CH_3), and 8.64 (triplet, J 7 Hz; CH_2CH_3).

t-Butyl 4-bromofuran-2-carboxylate (LXXXIX). - The method used was similar to that described for t-butyl 5-deuteriofuran-2-carboxylate. Isobutene (20 ml), 4-bromofuran-2-carboxylic acid (1.0 g), ether (dried over sodium; 25 ml), and sulphuric acid (3 ml) gave, after work-up as before, a colourless oil (4 ml) which contained the required product along with polymerised isobutene (n.m.r.). The mixture was adsorbed on to a silica column and the required material eluted by 10% acetone in light petroleum. A portion was further purified by p.t.l.c. (4 x 2% acetone in light petroleum) to give t-butyl 4-bromofuran-2-carboxylate as a colourless liquid (Found: C, 44.2; H, 4.4; Br, 32.0. $\text{C}_9\text{H}_{11}\text{BrO}_3$ requires: C, 43.7; H, 4.5; Br, 32.4%); ν_{max} 1720, 1736, 1307, and 1160 cm^{-1} ; τ 2.49 (doublet, J 0.8 Hz; 5-H), 2.97 (doublet, J 0.8 Hz; 3-H), and 8.46 (singlet; $\text{t-C}_4\text{H}_9$); m.s. peaks at m/e 246 (M , 17), 190 (100), 56 (93), 173 (60), and 117 (16).

4-Bromofuran-2-carbonyl chloride (XC). - The method used was similar to that described for furan-2-carbonyl chloride. 4-Bromofuran-2-carboxylic acid (purified by sublimation in vacuo; 0.5 g) and thionyl chloride (freshly distilled; 3.0 g) gave, after work-up as before, 4-bromofuran-2-carbonyl chloride (0.5 g) as a colourless liquid, b.p. 70° (bath)/0.05 mm (Found: C, 28.9; H, 1.0; Br, 38.4; Cl, 17.2. C₅H₂BrClO₂ requires: C, 28.7; H, 1.0; Br, 38.2; Cl, 17.0%); λ_{max} . 278 nm (ϵ 8610) and 253 nm (ϵ 4650); ν_{max} . 1766, 1749, 931, and 953 cm⁻¹; τ 2.25 (doublet, J 0.9 Hz; 5-H) and 2.54 (doublet, J 0.9 Hz; 3-H); m.s. peaks at m/e 208 (M , 36), 172 (100), 117 (50), 66 (35), 58 (30), and 145 (15).

3-Bromofuran-2-carboxylic acid (XCI).⁸⁴ - 2,3-Dibromofuran (20.0 g) in an equal volume of ether (dried over sodium) was added at -60° to a solution of n-butyl-lithium in ether [prepared as before from lithium wire (1.6 g) and n-butyl bromide (dried over molecular sieve; 16.4 g)]. The mixture was stirred at -30°C for 3 h and then poured on to a slurry of solid carbon dioxide in ether. After 1 h, the mixture was extracted with water and the extracts were washed with ether. Acidification (5N-aqueous hydrochloric acid), extraction (ethyl acetate), washing and drying of the extracts and removal of solvent gave a cream solid (12.0 g). Sublimation in vacuo gave 3-bromofuran-2-carboxylic acid as a white solid, m.p. 153-155°; λ_{max} . 249 nm (ϵ 11,193); ν_{max} . 1705, 1572, 1486, and 991 cm⁻¹; τ (deuteriochloroform) -1.06 (singlet; OH), 2.46 (doublet, J 1.9 Hz; 5-H), and 3.38 (doublet, J 1.9 Hz; 4-H).

Methyl 3-bromofuran-2-carboxylate (XCII). - The method used was similar to that described for ethyl 3,4,5-trideuteriofuran-2-carboxylate. A mixture of 3-bromofuran-2-carboxylic acid (6.0 g), methanol (dried as before;

150 ml) and concentrated sulphuric acid (10 ml) was boiled under reflux for 4 h. Work-up as before gave a red solid (7.5 g). Distillation in vacuo [100° (bath)/0.2 mm] and purification of a portion by p.t.l.c. (5 x 2% acetone in light petroleum) gave methyl 3-bromofuran-2-carboxylate as a white solid, m.p. 52.5-53.5° (Found: C, 34.9; H, 2.3; Br, 38.5. $C_6H_5BrO_3$ requires: C, 35.1; H, 2.5; Br, 39.0%); $\lambda_{\max}$. 248 nm (ϵ 12,608); $\nu_{\max}$. 1735, 1286, 1124, and 1387 cm^{-1} ; τ 2.55 (doublet, J 1.9 Hz; 5-H), 3.48 (doublet, J 1.9 Hz; 4-H), and 6.15 (singlet; CH_3); m.s. peaks at m/e 204 (M, 52), 173 (100), 117 (20), 66 (14), 146 (11), and 161 (5).

Ethyl 3-bromofuran-2-carboxylate (XCIII).⁸⁹ - The method used was similar to that described for ethyl 3,4,5-trideuteriofuran-2-carboxylate. A mixture of 3-bromofuran-2-carboxylic acid (1.0 g), ethanol (dried as before; 50 ml), and sulphuric acid (3 ml) was boiled under reflux for 3 h. Work-up as before gave a yellow solid (0.9 g). A portion was purified by p.t.l.c. (4 x 2% acetone in light petroleum) to give ethyl 3-bromofuran-2-carboxylate as a white solid, m.p. 55-56° (lit.,⁸⁹ 57°); $\lambda_{\max}$. 248 nm (ϵ 9341); $\nu_{\max}$. 1730, 1282, 1124, and 1178 cm^{-1} ; τ 2.53 (doublet, J 1.9 Hz; 5-H), 3.48 (doublet, J 1.9 Hz; 4-H), 5.66 (quartet, J 7 Hz; CH_2CH_3), and 8.62 (triplet, J 7 Hz; CH_2CH_3).

t-Butyl 3-bromofuran-2-carboxylate (XCIV). - The method used was similar to that described for t-butyl 5-deuteriofuran-2-carboxylate. Isobutene (25 ml), 3-bromofuran-2-carboxylic acid (0.5 g), ether (dried over sodium; 20 ml), and sulphuric acid (3 ml) gave, after work-up as before, a golden oil (0.6 g). A portion was purified by p.t.l.c. (5 x 2% acetone in light petroleum) to give t-butyl 3-bromofuran-2-carboxylate as a colourless liquid (Found: C, 43.7; H, 4.6; Br, 32.1. $C_9H_{11}BrO_3$ requires: C, 43.7; H, 4.5; Br, 32.4%);

$\nu_{\max}$. 1723 cm^{-1} ; τ 2.56 (doublet, J 1.9 Hz; 5-H), 3.51 (doublet, J 1.9 Hz; 4-H), and 8.42 (singlet; $t\text{-C}_4\text{H}_9$); m.s. peaks at m/e 246 (M , 16), 58 (100), 190 (90), 56 (82), 173 (80), and 117 (32).

3-Bromofuran-2-carbonyl chloride (XCV). - The method used was similar to that described for furan-2-carbonyl chloride. 3-Bromofuran-2-carboxylic acid (0.7 g) and thionyl chloride (freshly distilled; 5 ml) gave, after work-up as before, 3-bromofuran-2-carbonyl chloride (0.7 g) as a white solid, m.p. 38-40° (Found: C, 28.9; H, 1.1; Br, 38.4; Cl, 17.6. $\text{C}_5\text{H}_2\text{BrClO}_2$ requires: C, 28.7; H, 1.0; Br, 38.2; Cl, 17.0%); $\lambda_{\max}$. 278 (ϵ 14,810) and 268 nm (ϵ 15,010); $\nu_{\max}$. 1757, 1466, 1384, and 1158 cm^{-1} ; τ 2.36 (doublet, J 1.9 Hz; 5-H) and 3.28 (doublet, J 1.9 Hz; 4-H); m.s. peaks at m/e 208 (M , 15), 173 (100), 117 (25), 66 (14), 65 (8), and 145 (7).

5-Bromo-3,4-dideuteriofuran-2-carboxylic acid (XCVI). - The method used was similar to that described for 4,5-dibromofuran-2-carboxylic acid. Ethyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (5.0 g) was boiled under reflux with a 20% solution of sodium deuterioxide in deuterium oxide (20 ml) for 24 h. Work-up as before gave a cream solid (3.0 g). Sublimation of a portion in vacuo gave 5-bromo-3,4-dideuteriofuran-2-carboxylic acid as white needles, m.p. 189-190° (Found: C, 31.4; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 14.2; Br, 41.5. $\text{C}_5\text{HBrD}_2\text{O}_3$ requires: C, 31.1; $[\text{H}_2\text{O} + \text{D}_2\text{O}]$, 15.0; Br, 41.5%); $\lambda_{\max}$. 262 nm (ϵ 10,203); $\nu_{\max}$. 1710, 1459, 936, and 1170 cm^{-1} ; m.s. peaks at m/e 192 (M , 100), 191 (68), 174 (53), 119 (52), 118 (33), and 173 (32).

Methyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (XCVII). - A mixture of 40% aqueous potassium hydroxide solution (15 ml) and ether (50 ml) was cooled to 0°, with stirring, and finely powdered nitrosomethylurea (5.0 g) was added

during 1 min. The ethereal solution of diazomethane so prepared was decanted, after 1 h, into a solution of 5-bromo-3,4-dideuteriofuran-2-carboxylic acid (1.0 g) in ether (50 ml) at 0°. After warming the solution to 25° during 12 h and drying it over anhydrous magnesium sulphate, removal of solvent gave a white solid (1.1 g). A portion was sublimed in vacuo to give methyl 5-bromo-3,4-dideuteriofuran-2-carboxylate as white needles, m.p. 63-64° (Found: C, 35.1; [H₂O + D₂O], 23.0; Br, 38.7. C₆H₃BrD₂O₃ requires: C, 34.8; [H₂O + D₂O], 22.7; Br, 38.7%); λ_{max.} 261 nm (ε 14,634); ν_{max.} 1729, 1748, 1456, and 1300 cm⁻¹; τ 6.18 (singlet; CH₃); m.s. peaks at m/e 206 (M, 43), 176 (100), 175 (65), 205 (25), 150 (15), and 149 (10).

t-Butyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (XCVIII).- The method used was similar to that described for t-butyl 5-deuteriofuran-2-carboxylate. Isobutene (10 ml), 5-bromo-3,4-dideuteriofuran-2-carboxylic acid (0.5 g), ether (dried over sodium; 30 ml), and sulphuric acid (1.0 ml) gave, after work-up as before, t-butyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (0.6 g) as a colourless liquid, pure by g.l.c. (column at 125°) (Found: C, 43.0; [H₂O + D₂O], 41.0; Br, 32.0. C₉H₉BrD₂O₃ requires: C, 43.4; [H₂O + D₂O], 40.6; Br, 32.2%); λ_{max.} 260 nm (ε 14,300); ν_{max.} 1142, 1714, 1733, and 1310 cm⁻¹; τ 8.47 (singlet; t-C₄H₉); m.s. peaks at m/e 248 (M, 14), 192 (100), 191 (59), 175 (44), 174 (26), and 247 (10).

5-Bromo-3,4-dideuteriofuran-2-carbonyl chloride (XCIX). - The method used was similar to that described for furan-2-carbonyl chloride. 5-Bromo-3,4-dideuteriofuran-2-carboxylic acid (0.5 g) and thionyl chloride (freshly distilled; 5 ml) gave, after work-up as before, 5-bromo-3,4-dideuteriofuran-2-carbonyl chloride (0.5 g) as a white solid, m.p. 55-56°; λ_{max.} 281 nm (ε 13,890);

$\nu_{\text{max.}}$ 1762, 1447, 1301, and 938 cm^{-1} ; m.s. peaks at m/e 210 ($\underline{M}$, 19), 175 (100), 174 (55), 119 (35), 118 (21), and 209 (11).

N-Methylpyrrole-2-carbaldehyde (C). - The method used was similar to that described for 4,5-diisopropylfuran-2-carbaldehyde. Phosphoryl chloride (107.0 g) was added at 0° during $\frac{1}{2}$ h to N-methyl pyrrole (freshly distilled; 42.3 g) in dimethylformamide (51.0 g). The mixture was heated at 60° for 2 h and then worked up as before. Distillation in vacuo ($86^\circ/15\text{ mm}$) gave N-methylpyrrole-2-carbaldehyde (30.0 g) as a colourless oil (lit.,⁹³ b.p. $72-75^\circ/11\text{ mm}$); $\lambda_{\text{max.}}$ 288 nm (ϵ 17,000); $\nu_{\text{max.}}$ 1672, 1410, and 1308 cm^{-1} ; τ 0.47 (doublet, $\underline{J}$ 1.0 Hz; $\underline{\text{CHO}}$), 3.23 (complex; 5-H and 3-H), 3.89 (complex; 4-H) and 6.04 (singlet; $\underline{\text{CH}_3}$).

N-Methylpyrrole-2-carboxylic acid (CI). - The method used was similar to that described for 5-bromofuran-2-carboxylic acid (b). Finely-powdered potassium permanganate (72.5 g) was added to a mixture of N-methylpyrrole-2-carbaldehyde (24.6 g), dioxan (150 ml), anhydrous sodium carbonate (29.4 g), and water (300 ml), at such a rate that the temperature of the mixture did not exceed 60° . After stirring the mixture for 12 h, work-up as before gave a brown solid (30.0 g). Recrystallisation from water and sublimation of a portion in vacuo gave N-methylpyrrole-2-carboxylic acid as white needles, m.p. $134-135.5^\circ$ (lit.,⁹² $135-136^\circ$); $\lambda_{\text{max.}}$ 264 nm (ϵ 12,326); $\nu_{\text{max.}}$ 1670, 1428, 1262, and 1122 cm^{-1} ; τ (deuteriochloroform) -2.21 (singlet; $\underline{\text{OH}}$), 2.92 (quartet, $\underline{J}$ 1.8 and 4.0 Hz; 3-H), 3.19 (overlapped quartet, $\underline{J}$ 1.8 and 2.6 Hz; 5-H), 3.84 (quartet, $\underline{J}$ 2.6 and 4.0 Hz; 4-H), and 6.08 (singlet; $\underline{\text{CH}_3}$).

Methyl N-methylpyrrole-2-carboxylate (CII). - The method used was similar to that described for methyl 5-bromo-3,4-dideuteriofuran-2-carboxylate.

A solution of diazomethane in ether [prepared from 40% aqueous potassium hydroxide solution (15 ml), nitrosomethylurea (5.0 g), and ether (50 ml)] was mixed at 0° with N-methylpyrrole-2-carboxylic acid (1.0 g) in ether (100 ml). Work-up as before gave a red oil (1.0 g). Distillation in vacuo gave methyl N-methylpyrrole-2-carboxylate as a colourless liquid, b.p. 95° (bath)/15 mm (lit.,⁹² 95-98°/28 mm); $\lambda_{\text{max.}}$ 261 nm (ϵ 14,000); $\nu_{\text{max.}}$ 1709, 1436, and 1112 cm^{-1} ; τ 3.25 (quartet, J 1.8 and 4.0 Hz; 3-H), 3.35 (overlapped quartet, J 1.8 and 2.6 Hz; 5-H), 4.05 (quartet, J 2.6 and 4.0 Hz; 4-H), 6.14 (singlet; N-CH₃), and 6.28 (singlet; CH₃).

t-Butyl N-methylpyrrole-2-carboxylate (CIII). - The method used was similar to that described for t-butyl 5-deuteriofuran-2-carboxylate. Isobutene (20 ml), N-methylpyrrole-2-carboxylic acid (1.0 g), ether (dried over sodium; 30 ml), and sulphuric acid (1 ml) gave, after work-up as before, a red oil (1.0 g). A portion was purified by p.t.l.c. (2 x light petroleum) and distilled in vacuo to give t-butyl N-methylpyrrole-2-carboxylate as a colourless liquid (Found: C, 65.9; H, 8.1; N, 7.5. C₁₀H₁₅NO₂ requires: C, 66.3; H, 8.3; N, 7.7%); $\lambda_{\text{max.}}$ 262 nm (ϵ 12,549); $\nu_{\text{max.}}$ 1702, 1113, 1413, and 1326 cm^{-1} ; τ 3.32 (quartet, J 1.8 and 4.0 Hz; 3-H), 3.42 (overlapped quartet, J 1.8 and 2.6 Hz; 5-H), 4.08 (quartet, J 2.6 and 4.0 Hz; 4-H), 6.13 (singlet; CH₃), and 8.47 (singlet; t-C₄H₉); m.s. peaks at m/e 181 (M , 19), 125 (100), 108 (46), 43 (27), 106 (22), and 80 (19).

DISCUSSION - SPECTROSCOPIC

A. Infra Red Investigations

The order of discussion of the results and the numbering of experiments in this section correspond directly to the order and numbering used in the "Experimental-Spectroscopic" section. Similar conventions are also used; thus, "A" represents the area of an i.r. band, "D" represents the optical density of a band, "T" represents the absolute temperature, and the subscripts "l" and "h" refer to the lower- and higher-frequency bands in a rotamer carbonyl doublet.

Furan-2-carbaldehyde C=O band assignment

Experiments 2, 3, 4, 5, and 6. As noted previously (vide "Introduction"), it is generally accepted that furan-2-carbaldehyde, as a dilute solution in a non-polar solvent, exists as a mixture of anti (IIa) and syn (IIb) forms, but there is disagreement about the relative stabilities of these rotational isomers. By a comparison of the i.r. spectra of 3-, 4-, and 5-isopropylfuran-2-carbaldehydes with the spectra of furan-2-carbaldehyde and related aldehydes and ketones, it was hoped to resolve the controversy.

For furan-2-carbaldehyde, the very small variation of carbonyl band intensities with concentration of the aldehyde (Table 4) implies that intermolecular association is not responsible for the carbonyl band doubling. Also, if a "hot transition" (a transition from the first excited vibrational level) were involved, then this would correspond to the less intense component of the carbonyl doublet at 1681 cm^{-1} , the area of which relative to that of the band at higher wave-number should then increase with increase in temperature (assuming a similar

temperature dependence of the absorption coefficients for the two bands): the reverse of this is observed. Furthermore, a hot transition would not be expected to display the considerable dependence on solvent dielectric constant which is observed for the furan-2-carbaldehyde carbonyl bands. The possible involvement of Fermi-resonance was discounted by the present author²¹ and others^{32,33} principally because band multiplicity is also observed in the i.r. C-H bending and stretching regions. The case for rotational isomerism being the correct explanation for the observed carbonyl band doubling appeared particularly strong when it was found that the variable-temperature data (Table 5) could be analysed to give a not unreasonable ΔH° value for the (supposed) equilibrium of $3200 \pm 300 \text{ J mol}^{-1}$.²¹ It was felt that by the substitution of an alkyl group for hydrogen at the 3-position in furan-2-carbaldehyde, a predictable steric effect on the rotameric equilibrium would be achieved, which could be used to assign the twin carbonyl bands to particular rotamers.

The 3-, 4- and 5-isopropyl-, and the 4,5-diisopropyl-furan-2-carbaldehydes all show single i.r. carbonyl absorptions, at about 1686 cm^{-1} in carbon tetrachloride at 30°C . Similarly, in chloroform solutions, the 4- and 5-isopropyl-, and the 4,5-diisopropyl-furan-2-carbaldehydes show single carbonyl absorptions at a frequency lower by the expected figure of ca. 12 cm^{-1} . However, 3-isopropyl-furan-2-carbaldehyde exhibits a carbonyl doublet in chloroform at 1678 (D 0.37) and 1667 cm^{-1} (D 0.44). A comparison with the 4- and 5-isopropyl aldehydes indicates that the new band in chloroform is the band at 1667 cm^{-1} . If this band is a consequence of rotational isomerism, that is if its appearance corresponds to the emergence of a new rotamer in solution, then it must be associated with the rotamer which is favoured by an increase in steric hindrance at the 3-position and

by an increase in solvent polarity. Although it seems reasonably clear that the syn rotamer would be favoured compared with the anti rotamer by an increase in steric hindrance at the 3-position, the question of the effect of solvent polarity is less easily answered. Despite complications in the literature³⁶ concerning the direction of the dipole moment in furan, it appears likely that the balance of inductive and mesomeric moments is a moment directed towards the hetero atom: this moment (0.7 D) is smaller than that of tetrahydrofuran but is in the same sense. On this basis, the syn rotamer is the more polar and would thus be favoured compared with the anti rotamer by an increase in solvent polarity. On two counts, therefore, the new band at 1667 cm^{-1} may be assigned to the syn rotamer. Since the positions of the carbonyl bands (in carbon tetrachloride) of the three mono-isopropylated aldehydes are very similar, it seems unlikely that the special effects observed with the 3-isomer (in chloroform) are inductive in origin. As noted earlier, these arguments assume that the appearance of a second band in chloroform for the 3-isopropyl aldehyde is a consequence of rotational isomerism. Alternative explanations are, however, available, the most likely being Fermi resonance. Two observations suggested that Fermi resonance may not be involved: firstly, 3-methylfuran-2-carbaldehyde⁷⁰ shows the same solvent effects as the isopropyl compound, and secondly, Fermi resonance is not observed in the i.r. carbonyl bands of 3-bromofuran-2-carbaldehyde (see later) and 3-iodofuran-2-carbaldehyde.⁹⁰

The results with the 2-ketones (Experiment 6) support the above reasoning. The extinction coefficients of the u.v. absorptions (Table 7) indicate that non-planar conformations make little contribution. If the single carbonyl absorptions (Table 6) corresponded to syn forms, then severe steric hindrance would be expected in the ethyl 2-(3-methyl)furyl ketone case. The relative positions of the i.r.

carbonyl bands for the ketones suggest that all the ketones are in the same conformation, and combined with the u.v. evidence, imply that this conformation is anti (a similar conformational assignment has been made previously by the author²¹ for substituted 2-benzoyl furans). It is not surprising that second carbonyl bands are not observed for the 2-ketones in chloroform solutions, for the replacement of an aldehydic hydrogen by a methyl or an ethyl group means that there is now less to be gained (in stability terms) by the change anti to syn than was the case for 3-isopropylfuran-2-carbaldehyde. Since, if the twin bands of furan-2-carbaldehyde (ν_{max} 1700 and 1681 cm^{-1}) are a consequence of rotational isomerism, one band of the aldehyde must correspond to the anti form of 2-furyl methyl ketone (XIII) (ν_{max} 1683.5 cm^{-1}), and since it would be unprecedented for the conversion -CHO to -CO.CH₃ to increase the C=O frequency, then the aldehyde band assignments become apparent.

Several features, however, are difficult to accommodate on this basis.

(i) it is not obvious why the alkylfuran-2-carbaldehydes and the unhindered 2-ketones should show such a marked preference for the anti form; (ii) it is not possible to reconcile the i.r. assignments with those from n.m.r. studies (vide "Introduction"); (iii) it is not possible (without the inclusion of a further hypothesis) to explain the occurrence of three bands in the carbonyl overtone region of furan-2-carbaldehyde or the occurrence of three carbonyl bands at temperatures below 0°C for the aldehyde in carbon disulphide solution; (iv) the synthesis of a range of furan-2- and thiophen-2-carbaldehydes shows that carbonyl doublets occur only rarely with these compounds, and (v) the observation (Experiment 9) that furan-2-carbonyl chloride (XXXII) in carbon tetrachloride solution has four i.r. carbonyl bands establishes that rotational isomerism alone cannot be the general explanation

of multiple absorptions in heterocyclic compounds having carbonyl groups at the 2-position. It was therefore decided to re-examine this problem using the approaches described as "Solid State Studies" and "Fermi Resonance Studies".

Solid State Studies

Experiments 7, 8, and (in part) 16. As an alternative approach to the problem of structure assignments, it was intended to use X-ray diffraction analysis. This requires that a rigorous correlation can be made between solid- and solution-phase i.r. spectra and that the compound chosen for analysis must preferably exist almost entirely in one form in the solid phase.

The exploratory work of Experiment 7 demonstrates that while various 2-oxo-furans show single carbonyl bands in carbon tetrachloride solution, the situation becomes more complex in the solid state. This is particularly apparent for 5-bromo- and 5-chloro-furan-2-carbaldehydes [(XLIII) and (XVI)] which have single carbonyl bands in carbon tetrachloride solution (because of their positions and the observations below, the minor bands at 1713.5 and 1718 cm^{-1} cannot be considered as comprising parts of rotamer carbonyl doublets) whereas in the solid state twin carbonyl bands are observed (along with minor bands to higher wave-number as in the solution cases). It seems reasonable to suppose that the twin bands correspond to syn and anti forms of the aldehydes both of which must therefore exist in the solid state. The question then arises as to why twin carbonyl bands occur in the solid state for these compounds but not in solution. One explanation is that for 2-oxo-furans in solution, the carbonyl bands of the syn and anti forms occur at identical frequencies; another explanation is that in solution the differing polarities of the forms produce differing degrees of solvent ordering this leading to

an entropy difference which causes one form to be preferred compared with the other: in the solid state this effect would not be found.

In Experiment 8, attempts were made to synthesise 2-oxo-furans the rotamers of which, because of bulky substituents, would not be able equally to occupy the same crystal sites. Table 9 demonstrates that even when the furan nucleus is substituted at an α -position with the bulky 2-naphthyl group, a single carbonyl band is not observed in the solid state. Comparing Tables 8 and 9, the 5-halo- and 5-aryl-furan-2-carbaldehydes in carbon tetrachloride solutions all show single carbonyl bands which, from their positions, would seem to correspond to the same rotamers (assuming that syn and anti forms are not absorbing at the same frequencies); in the solid state the situation becomes much more confused partly, perhaps, because of the uncertainty in the positions of the band maxima arising out of a general lack of symmetry of the bands. The shifts (in wavenumbers) corresponding to the change solution to solid, for the compounds listed in Tables 8 and 9 are summarised in Table 39 using the conventions of Table 8.

Compound	Shift (cm^{-1})
(XVI)	<u>13</u> ; <u>22</u> ; (5.5)
(XLIII)	<u>14.5</u> ; <u>25.5</u> ; (6)
(XXX)	<u>29.5</u>
(XXXV)	<u>17</u> ; (4)
(XVIII)	<u>20</u> ; (4)
(XXIII)	<u>4</u> ; (24)
(XXV)	<u>5.5</u> ; (14); (26.5)
(XXIX)	<u>14</u> ; <u>18</u>

Table 39

It is clear that no generalisations can be made about these results, for even within a group of compounds of similar structure [e.g., the 5-arylfuran-2-carbaldehydes, (XXIII), (XXV), and (XXIX)] a regular pattern cannot be detected.

With the publication by other workers⁴⁵ of an X-ray structure for 4-bromofuran-2-carbaldehyde (vide "Introduction") proposing that the compound exists, in the solid state, in the syn conformation, the synthesis of this molecule was undertaken with a view to comparing the solid and solution phase i.r. spectra (Experiment 16). Whereas, in the solid state, a broad band centred at 1675 cm^{-1} with a shoulder at 1700 cm^{-1} was observed, in carbon tetrachloride solution two bands in the carbonyl region were observed at 1705.5 and 1690.5 cm^{-1} . Since these observations are the reverse of the trends noted in Tables 8 and 9, it is apparent that not all of the results can be explained by the one hypothesis of rotational isomerism. This conclusion led to the experiments described under the general heading of "Fermi Resonance Studies".

Fermi Resonance Studies

Experiments 9 to 16. Since furan-2-carbonyl chloride (XXXII) in carbon tetrachloride solution, exhibits four i.r. bands in the carbonyl region (Figure 5), it was decided that this compound should serve as a starting point for studies on Fermi resonance because the complex band envelope cannot be explained in terms of rotational isomerism alone. Several features, in addition to the complexity of the band envelope, point to the involvement of Fermi resonance (Experiment 9): (i) there are dramatic temperature effects; (ii) there is little concentration dependence; (iii) dramatic changes in the appearance of the band envelope occur

when chloroform or bromoform replace carbon tetrachloride as the solvent; (iv) in the carbonyl overtone region, three distinct maxima are observed, and (v) in the vapour phase, a band envelope of extraordinary complexity is obtained in the carbonyl region. Furthermore, the acid fluoride (XXXIV) and acid bromide (XXXIII) exhibit essentially doublet absorptions in the carbonyl region (Experiment 10), and thiophen-2-carbonyl fluoride (XXXVII) and chloride (XXXVI) essentially singlet carbonyl absorptions (Experiment 11).

In order to test whether or not Fermi resonance is involved in the i.r. spectrum of furan-2-carbonyl chloride, 5-deuteriofuran-2-carbonyl chloride (XLVIII) and the fluoride (LXXXI) were prepared (Experiment 12). Comparing the acid fluoride with its non-deuterated analogue, there is little difference in the carbonyl absorptions, whereas for the acid chloride, on deuteration, the four component absorption is replaced by a doublet which no longer has the dramatic temperature dependence of the non-deuterated analogue (Experiment 12). Furthermore, in the carbonyl overtone region, 5-deuteriofuran-2-carbonyl chloride shows only two main absorptions (at 3516 and 3472 cm^{-1} in carbon tetrachloride solution) whose intensities parallel those of the fundamentals (cf. the non-deuterated analogue discussed previously).

Thus, the conclusion arising from these experiments is that Fermi resonance is partly responsible for the complex appearance of the carbonyl envelope of furan-2-carbonyl chloride.

The carbonyl band positions and intensities (quoted as relative optical densities) of the deuterated acid chloride (XLVIII) are compared, in Table 40, with those of the deuterated and non-deuterated acid fluorides [(LXXXI) and (XXXIV)] and of the non-deuterated acid bromide (XXXIII).

Compound	Bands at (cm^{-1})	$\Delta\nu$ (cm^{-1})
(XLVIII)	1767 (1.6), 1756 (1)	11
(LXXXI)	1828.5 (1.6), 1816 (1)	12.5
(XXXIV)	1828.5 (1.7), 1816 (1)	12.5
(XXXIII)	1780 (1.5), 1769 (1)	11

Table 40

The band relative intensities and separations are all very similar and the band positions may easily be explained by considering the balance between negative inductive and positive mesomeric effects. It is probable, therefore, that the carbonyl doublets of the compounds listed in Table 40 are a consequence of rotational isomerism. This conclusion could not have been reached merely by comparing deuterated and non-deuterated furan-2-carbonyl chlorides for, although deuteration produces obvious simplifications and shifts many of the i.r. vibrations, there is nothing to show that some residual Fermi resonance is not still involved. However, as soon as the comparison of Table 40 is made, it becomes clear that the simplification which occurs on deuteration of the acid chloride produces a spectrum which, in the carbonyl region, is comparable with the spectra of the non-deuterated acid fluoride and acid bromide: since it is extremely unlikely that Fermi resonance would occur to the same extent in all of the compounds listed in Table 40, then the conclusion stated previously becomes very likely. It is interesting (and fortunate for the present study) that isotopic substitution at only one position in furan-2-carbonyl chloride should produce a total collapse of Fermi resonance; since the bands at 1461, 1388, 1165, and 950 cm^{-1} in the non-

deuterated material all diminish greatly on deuteration, it is possible that the resonance is caused by a combination band arising from one of these bands and a band at lower wavenumber.

Having established that isotopic substitution using deuterium provides a method for distinguishing between Fermi resonance and rotational isomerism, it was decided to apply the method to a system where a controversy existed concerning the origin of the observed carbonyl band multiplicity. Such a system is provided by thiophen-2-carbaldehyde (vide "Introduction") where the observation (Experiment 13) of three maxima in the carbonyl region (at 1687.5, 1677, and 1659.5 cm^{-1}) and also of dramatic solvent effects on the intensities of the maxima suggest that rotational isomerism alone cannot be the explanation for the carbonyl band multiplicity. In support of this conclusion, previous work by the author²¹ has shown that an unexpectedly high enthalpy difference between the supposed rotamers is obtained if the carbonyl band area data is processed in the usual way.

The synthesis of 5-deuteriothiophen-2-carbaldehyde (XL) was therefore undertaken with a view to comparing its i.r. spectrum with that of the non-deuterated material (Experiment 14). As is the case with furan-2-carbonyl chloride, dramatic simplifications in the appearance of the carbonyl bands occur on deuteration. Thus, the band at 1659.5 cm^{-1} disappears and the band at 1677 cm^{-1} is replaced by a much weaker band at 1672 cm^{-1} ; the band at 1687.5 cm^{-1} remains virtually unchanged in position. Thus, Fermi resonance is partly responsible for the complex appearance of the carbonyl envelope of thiophen-2-carbaldehyde. Since the band at 1687.5 cm^{-1} in the non-deuterated material is virtually unaffected by deuterium substitution, it would appear that the "true" carbonyl band envelope would consist of a major component at

1687.5 cm^{-1} with a minor component to lower wavenumber, the intensity of which is exaggerated, and the position of which is displaced to higher wavenumber by Fermi resonance which also causes the emergence of a new band at lower wavenumber. Other workers³⁸ have shown that in thiophen-2-deuterio-carbaldehyde, three carbonyl bands are still observed [at 1686, 1672 (strongest) and 1658 cm^{-1}], whereas when the carbonyl oxygen of the non-deuterated aldehyde is enriched with ^{18}O two additional carbonyl bands [at 1659 (D 1.43) and $1645.5\text{ (D 1.0) cm}^{-1}$] are observed. Comparing these results with those from the 5-deuterio compound, it seems that some Fermi resonance is still to be found in both the $-\text{CDO}$ and the $-\text{CH}^{18}\text{O}$ compounds, since in both cases the carbonyl bands are more complex than is the case for the 5-deuterio compound.

Because of the successes achieved by deuterium labelling in the furan-2-carbonyl chloride and thiophen-2-carbaldehyde cases, it was then resolved to apply this method to the problem of the doublet carbonyl absorption of furan-2-carbaldehyde, the origin of which was still in doubt despite the studies described earlier in this section. The syntheses of 5-deuteriofuran-2-carbaldehyde (XLIX), 3,4,5-trideuteriofuran-2-carbaldehyde (LXXI), and 3,4-dideuteriofuran-2-carbaldehyde (LXXVI) were therefore undertaken and their i.r. spectra were recorded (Experiment 15). In the mono- and tri-deuterio compounds, singlet carbonyl absorptions only occur (at 1694 cm^{-1}) whereas in the 3,4-dideuterio compound a carbonyl doublet, with components (at 1696 and 1690 cm^{-1}) of approximately equal intensities, is observed [cf. the non-deuterated aldehyde (Experiment 2) which has bands in the carbonyl region at 1700 (D 3.0) and $1681\text{ (D 1.0) cm}^{-1}$]. The doublet carbonyl absorption of furan-2-carbaldehyde is thus a consequence of Fermi resonance and not of rotational isomerism. As in the

cases considered previously, it is deuteration at the 5-position which leads to maximal simplification of the carbonyl band, for in the 3,4-dideuterio aldehyde although the spectrum is very different from that of the non-deuterated compound it is, if anything, more complex.

For the mono- and tri-deuterio compounds, an increase in polarity of the solvent does not cause the appearance of a second carbonyl band, in the carbonyl overtone region, single bands are still observed (at 3370 cm^{-1}) and in carbon disulphide, at low temperatures, only single bands occur. The gas phase spectra are complex, but different from the spectrum of the non-deuterated compound.

In the C-H stretching and bending regions, all of the deuterated aldehydes show absorptions which are as complex as those of the non-deuterated compound. It is clear, therefore, that the observation of complexity of absorptions in these regions does not necessarily lend weight to any assignment of observed complexity in the carbonyl region.

Finally, it was noted earlier (under "Solid State Studies") that whereas most furan-2-carbaldehyde derivatives show singlet carbonyl absorptions in carbon tetrachloride solution and more complex absorptions in the solid state, 4-bromofuran-2-carbaldehyde (LXI) shows doublet carbonyl absorptions in solution but a broad singlet in the solid state. To clarify this problem, the syntheses of 3-bromofuran-2-carbaldehyde (LVII) and 4-bromo-5-deuteriofuran-2-carbaldehyde (LXVII) were undertaken and a comparison was then made between the spectra of these compounds and of 4-bromofuran-2-carbaldehyde (Experiment 16). Once again, a dramatic simplification occurs on deuteration in that the doublet carbonyl absorption of the 4-bromo compound (1705.5 and 1690.5 cm^{-1} in carbon tetra-

chloride) collapses to a singlet (at 1697 cm^{-1}); little difference can be detected between the solid-phase carbonyl absorptions of the deuterated and non-deuterated compounds. Thus Fermi resonance is responsible for the doubling of the carbonyl absorption of 4-bromofuran-2-carbaldehyde.

In comparing the relative positions of the carbonyl absorptions of the 3-bromo- and 4-bromo-5-deuterio aldehydes, it is significant that the 3-bromo compound absorbs at lower wavenumber (1691 cm^{-1} in carbon tetrachloride), partly because the negative inductive effect of a 3-halogen should be more important than that of a 4-halogen substituent, and partly because it has been shown⁹⁴ that a halogen atom adjacent to a carbonyl group raises the group's absorption frequency by a dipolar field effect. The answer to this problem is to be found in a comparison of the positions of the carbonyl absorptions of the above two compounds with that of the carbonyl band of 5-bromofuran-2-carbaldehyde (Table 41).

Compound	C=O band at (cm^{-1} in CCl_4 at 303°K)
5-Bromofuran-2-carbaldehyde	1689
4-Bromo-5-deuteriofuran-2-carbaldehyde	1697
3-Bromofuran-2-carbaldehyde	1691

Table 41

In the 4-bromo compound, mesomerism must necessarily be less significant than in the 3- and 5-bromo compounds, and so the inductive effect becomes relatively more important leading to a carbonyl band at a position several wavenumbers

higher than the carbonyl band of 5-deuteriofuran-2-carbaldehyde (1694 cm^{-1}).

In the 3- and 5-bromo-2-carbaldehydes, the halogen atom is in direct conjugation with the carbonyl group and the frequency of the latter is lowered. That the 3-aldehyde absorbs at a slightly higher frequency than the 5-aldehyde may be a consequence either of a dipolar field effect or of a greater negative inductive effect when the halogen is close to the carbonyl group.

In conclusion, the problem, which was originally to assign the twin carbonyl absorptions of furan-2-carbaldehyde to particular rotational isomers, no longer exists because the work discussed above demonstrates that Fermi resonance is responsible for the band doubling. Another problem then emerges, however, which is to decide whether or not the singlet carbonyl absorptions observed in solution (either before or after deuterium substitution) for furan aldehydes and ketones imply that one conformation only is adopted in solution. Several factors oppose this view: firstly, it is intrinsically unlikely that such a wide range of compounds would all adopt one conformation to the total exclusion of the other; secondly, it is equally unlikely that if such a single conformation were adopted, it would be retained when the polarity of the solvent is increased (unless the highly favoured conformation were always the more polar), and thirdly, there is a wealth of evidence from other physical techniques, especially n.m.r.^{40, 42, 95} (vide "Introduction" and later in this section), in favour of a rotameric equilibrium in furan-2-carbaldehyde which is highly solvent-dependent, the energy between the rotamers being about zero in a solvent of dielectric constant of about 5.

The author therefore concludes that the single carbonyl absorptions do not imply the presence of single conformations, and that it is thus not meaningful to use the carbonyl band positions as indicating the adoption of a particular

conformation. In general it would seem that the stretching frequencies of aldehyde and ketone functions are not sensitive to the steric and electronic differences between the syn and anti rotameric forms of substituted furans, whereas if the carbonyl group is directly bonded to a polar atom or group (as in acid halides and esters) then the sensitivity of the carbonyl group to its environment is increased (see later).

Digital Computer Studies

Experiments 17 to 24. Since one of the aims of this work was to set up a facility for the digital recording of i.r. intensity data and then to use this data for computed curve resolutions, Experiments 17 to 22 are concerned with the preparation and testing of a computer program for the resolution of overlapped i.r. bands. The program was at first used with an English Electric KDF-9 computer and then modified for use with an ICL 1906A machine. Since no facility within the program was provided for the integration of bands, a program was written for a Hewlett-Packard programmable calculator for the evaluation of the Voigt product convolution (given output indices from the computer resolution program, x_1 to x_4) and for its subsequent integration by Simpson's rule (Experiment 18). The integration function is:

$$\int_{x_0}^{x_2} f(X) dX = \frac{h}{3} (Y_0 + 4Y_1 + Y_2) - \frac{1}{90} h^5 f^{(4)}(\epsilon)$$

"h" being the distance between successive abscissal integration points. The second term on the right hand side of the equation (the error term) can be ignored if h is sufficiently small. Doubling the value of h was found to produce no change in the

value of the integral (to four decimal places) this indicating that the value of h chosen was below the threshold required for ignoring the error. Because the time taken for integrations was comparatively long, the program was re-written for the 1906A computer (Experiment 23) and finally included as a subroutine in the main curve resolution program. Since it was thought desirable to have pictorial representations of the computed curve resolutions in order that the closeness of fit could be assessed by eye (in addition to the mathematical assessments made by the computer), a program was written for the 1906A plotting subroutines in order to obtain graphical records of the curve resolutions. Many examples of the use of this program are to be found in the "Experimental-Spectroscopic" section.

Because the data-logging equipment used in this work is time-based rather than frequency-based, it is essential to know that the spectrophotometer scan rate is linear: that this is so is demonstrated by Experiment 22. It should be noted that because of this time base, the band positions generated by the curve resolution program are dummy positions; where necessary for presentation, they have been converted to real positions; this does not, of course, have any effect upon band area ratios measured consecutively (Experiment 21).

Having established a tested method for data logging and for the integration of band envelopes, it was then possible to examine the problem of "natural decrease". This was referred to under "Theoretical Considerations" in connection with the thermodynamic treatment of i.r. data using Equations (XV), (XVI) and (XVIII)(which are re-written below for convenience).

$$\log_{10} \frac{A_l}{A_h} = \frac{-\Delta H^\circ}{2.303R} \cdot \frac{1}{T} + \frac{\Delta S^\circ}{2.303R} + \log_{10} \frac{a_l}{a_h} \quad (XV)$$

$$\Delta \underline{G}^{\circ} = -RT \ln \left[\frac{A_{\underline{l}}}{A_{\underline{h}}} \cdot \frac{\alpha_{\underline{h}}}{\alpha_{\underline{l}}} \right] \quad (\text{XVI})$$

$$A_{\underline{h}} = -(\alpha_{\underline{h}}/\alpha_{\underline{l}})A_{\underline{l}} + \alpha_{\underline{h}}p_c \quad (\text{XVIII})$$

$\Delta \underline{H}^{\circ}$ can be calculated if the ratio $\alpha_{\underline{l}}/\alpha_{\underline{h}}$ is independent of temperature [by plotting $\log_{10}(A_{\underline{l}}/A_{\underline{h}})$ against $1/T$] whereas measurement of $\Delta \underline{G}^{\circ}$ (and hence $\Delta \underline{S}^{\circ}$) requires that the α -ratio be known. This ratio can be evaluated from Equation (XVIII) (by plotting $A_{\underline{h}}$ against $A_{\underline{l}}$), but only if each of the α -values is independent of temperature.

To test the temperature-dependence of α , three compounds, methyl m-chlorobenzoate (CIV), methyl 3-methyl-2-furyl ketone (CV), and 5 α -androstan-17-one-3 β -yl thiophen-2'-carboxylate (CVI), the first two of which have symmetrical singlet carbonyl absorptions the third having two symmetrical absorptions (corresponding to the two carbonyl functions) which are slightly overlapped, were examined as carbon tetrachloride solutions in the temperature range -15° to 75°C with digital data logging (Experiment 23). Three sets of areas were measured: (i) the band envelopes were integrated without curve fitting; (ii) Voigt (digital-generated) curves were used to fit the envelopes [single curves for compounds (CIV) and (CV), two curves for (CVI)] and were then integrated, and (iii) analogue-generated curves were used to fit the envelopes and were then integrated. Tables 42, 43, and 44 summarise the results noted in detail in Tables 12 to 18 and also include the decrease in apparent optical densities of the bands observed with increase in temperature and the decrease that would be expected from concentration changes arising from expansion of carbon tetrachloride

according to the equation:⁹⁶

$$V_t = V_0(1 + 1.18384 \cdot 10^{-3}t + 0.8988 \cdot 10^{-6}t^2 + 1.35135 \cdot 10^{-8}t^3)$$

where "t" is the temperature in °C, and V_t and V_0 are volumes at $t^{\circ}\text{C}$ and 0°C , respectively. [Previous work by the author²¹ (based upon the measurement of interference fringes from an empty i.r. cell as a function of temperature) demonstrates that expansion of the cell in a direction parallel to the radiation beam is negligible.]

Methyl m-chlorobenzoate

t (°C)	A _{envelope}	A _{dig.}	A _{ana.}	D	A _{CCl₄ exp.}
-15	100.0%	100.0%	100.0%	100.0%	100.0%
0	90.3	96.0	96.5	97.1	98.2
15	92.7	93.7	91.0	94.5	96.5
30	92.7	92.0	89.0	96.7	94.8
45	86.4	87.9	85.0	93.1	93.0
60	85.9	85.9	81.0	93.1	91.2
75	80.8	83.4	78.5	90.5	89.3

Table 42

Methyl 3-methyl-2-furyl ketone

t (°C)	A _{envelope}	A _{dig.}	A _{ana.}	D	A _{CCl₄ exp.}
-15	100.0%	100.0%	100.0%	100.0%	100.0%
0	97.6	97.2	95.0	97.3	98.2
15	102.1	96.3	92.0	97.8	96.5
30	96.4	92.3	89.0	95.0	94.3
45	98.8	90.5	85.0	95.5	93.0
60	95.5	90.0	81.5	93.3	91.2
75	90.8	88.7	76.5	88.5	89.3

Table 43

5α-Androstan-17-one-3β-yl thiophen-2'-carboxylate

t (°C)	A _{envelope}	A _{dig.}		A _{ana.}		D		A _{CCl₄ exp.}
		<u>h</u>	<u>l</u>	<u>h</u>	<u>l</u>	<u>h</u>	<u>l</u>	
-15	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
0	95.0	97.6	97.0	95.5	95.5	96.3	96.4	98.2
15	92.5	94.0	95.2	92.5	92.0	94.3	95.0	96.5
30	90.0	93.9	92.9	89.0	89.0	92.9	93.3	94.8
45	85.5	89.5	88.8	86.5	85.0	89.9	89.4	93.0
60	82.6	85.9	86.6	81.5	82.0	87.4	88.3	91.2
75	78.2	83.6	83.5	78.5	79.0	84.4	85.0	89.3

Table 44

Comparing the results tabulated above, the natural decrease of α with increase of temperature is a real phenomenon although the extent of the decrease varies from

compound to compound. The decrease cannot, in general, be explained solely by solvent expansion nor is the change in optical density a particularly good guide to the extent of area change. It is revealing that the variations between the area and optical density changes of the two carbonyl bands of the steroidal compound, by any particular method of estimation, are much less than the variations observed when the actual molecule is changed, implying that the extent of natural decrease is structure- rather than group-dependent. The estimated extent of natural decrease is also dependent upon the method of observation, the digital method proving very marginally superior to the analogue (taking the "A_{envelope}" values as being the true values). The "A_{envelope}" and "D" values fluctuate more widely than the analogue- and digital-derived areas because the former are taken directly from raw experimental data whereas in estimating the latter, a smoothing effect necessarily occurs.

What is clear is that Equations (XVI) and (XVIII) cannot be used to supply free energy and hence entropy estimates unless the band areas are in some way "corrected" for the natural decrease. The following treatment is proposed: assuming that all carbonyl bands show the same fractional natural decrease in area with increase in temperature, "x", then, comparing the areas of the two bands of a rotamer carbonyl doublet at a temperature T and at a higher temperature T':

$$A_{\underline{h}} = \alpha_{\underline{h}} c_{\underline{h}} p$$

$$A_{\underline{l}} = \alpha_{\underline{l}} c_{\underline{l}} p$$

$$A'_{\underline{h}} = \alpha_{\underline{h}} (1 - x)(c_{\underline{h}} + k)p$$

$$A'_{\underline{l}} = \alpha_{\underline{l}} (1 - x)(c_{\underline{l}} - k)p$$

where "k" is the change in rotamer population with temperature. The value of "x" may be obtained either from another isolated, symmetrical carbonyl band in the same molecule or, more usually, from the carbonyl band of another molecule. For such an isolated carbonyl band:

$$A_{\underline{i}} = \alpha_{\underline{i}} c_{\underline{i}} p_{\underline{i}}$$

$$A'_{\underline{i}} = \alpha_{\underline{i}} (1 - x) c_{\underline{i}} p_{\underline{i}}$$

and so:

$$\frac{A'_{\underline{i}}}{A_{\underline{i}}} = (1 - x)$$

This ratio may then be used to correct $A'_{\underline{h}}$ and $A'_{\underline{l}}$ for the temperature dependence of α :

$$A_{\underline{h}}^c = A'_{\underline{h}} \times \frac{A_{\underline{i}}}{A'_{\underline{i}}} = \alpha_{\underline{h}} (c_{\underline{h}} + k) p_{\underline{h}}$$

$$A_{\underline{l}}^c = A'_{\underline{l}} \times \frac{A_{\underline{i}}}{A'_{\underline{i}}} = \alpha_{\underline{l}} (c_{\underline{l}} - k) p_{\underline{l}}$$

The $A_{\underline{h}}^c$ and $A_{\underline{l}}^c$ values now measure only the variations in rotamer concentration with temperature and a plot of $A_{\underline{h}}^c$ against $A_{\underline{l}}^c$ should give the true α -ratio.

It must be stressed that this method is only very approximate since it assumes an equal natural decrease for all carbonyl bands. Also, different values of "x" must be applied depending upon whether the data is derived from the analogue or the digital method. The general validity of the approach may be seen later in this section when the positive (i.e., physically untenable) slopes of some $A_{\underline{h}}$ against $A_{\underline{l}}$ plots become negative on application of the correction.

That all carbonyl bands do not show the same natural decrease is very serious since it allows the possibility that the bands of syn and anti forms of a molecule may each have a different temperature dependence, making even enthalpy values suspect. The results obtained with the thiophen steroidal ester suggest, however, that within a particular molecule, the assumption of equal temperature dependence of carbonyl bands may be valid. The proposed natural decrease correction was therefore applied to three steroidal furan esters, all of which contain a ketone function at the 17-position [5 α -androstan-17-one-3 β -yl 5'-bromo-2'-furoate (CVII), the 5'-chloro compound (CVIII), and the 5'-phenyl compound (CIX), (Experiment 24)]. All the esters show a doublet carbonyl absorption which may be ascribed to rotational isomerism of the ester function (see later for a general discussion of ester conformations) and a further carbonyl band, to higher wavenumber, corresponding to the isolated keto-group. The natural decrease of this isolated group was then used to correct the doublet ester absorption in each particular case. Because the extent of overlap between the three carbonyl groups is considerable in all cases (vide Figures 10, 11, and 12), although the curve resolutions are mathematically valid, their physical validity is more open to question than would be the case for a simple, well-separated, carbonyl doublet. The results for the three compounds [calculated using the "all-purpose" computer program (Experiment 33)] are presented in Table 45, in which the conventions used are those of the Analysis of Variance Table constructed in the "Theoretical Considerations" section. The symbol "c" implies that a correction has been applied for the natural decrease and "m" indicates that a slope has been estimated by the method of means. Plots of the relevant graphs are included as Figures 23 to 25.

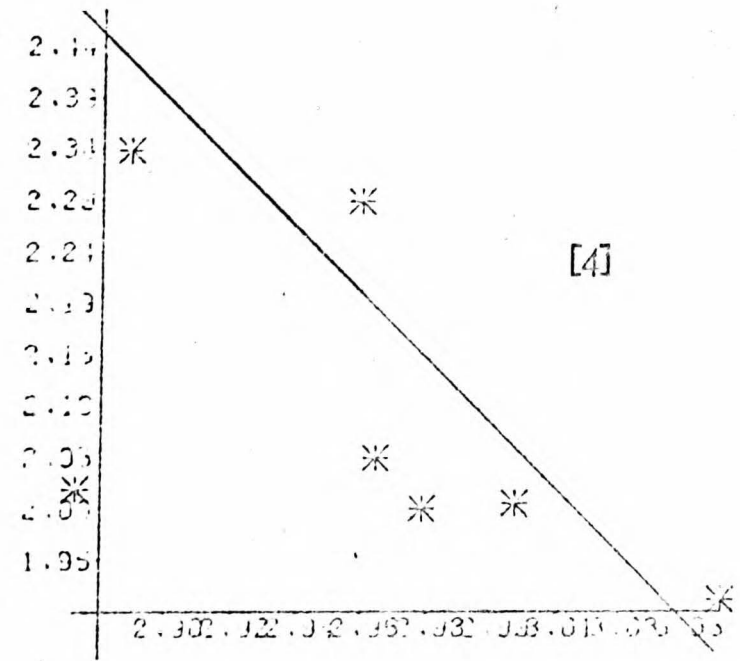
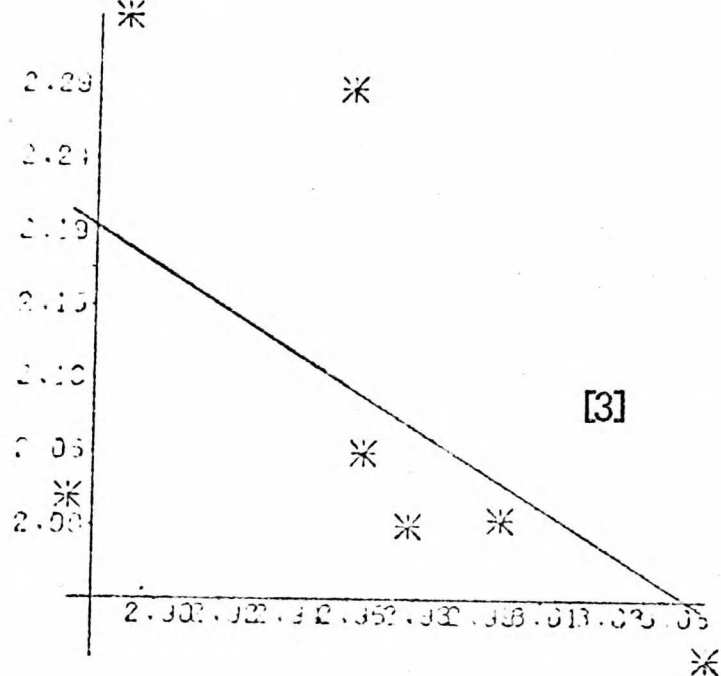
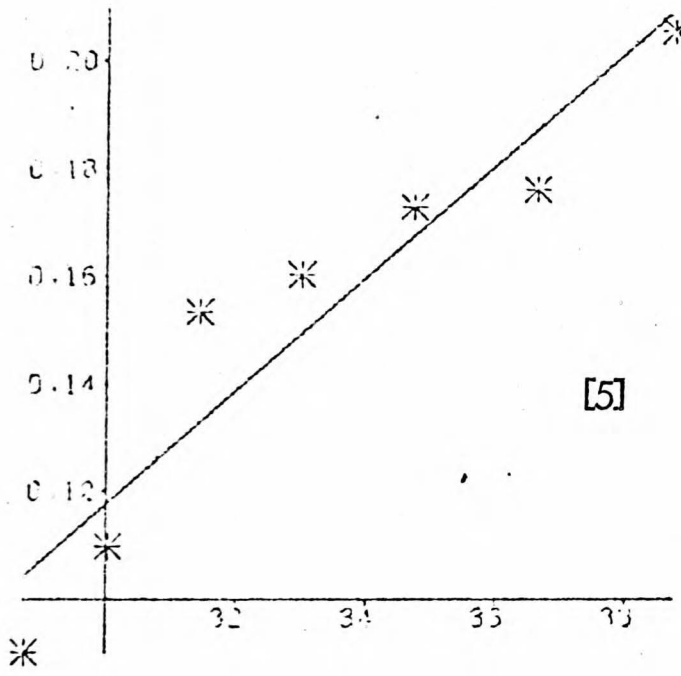
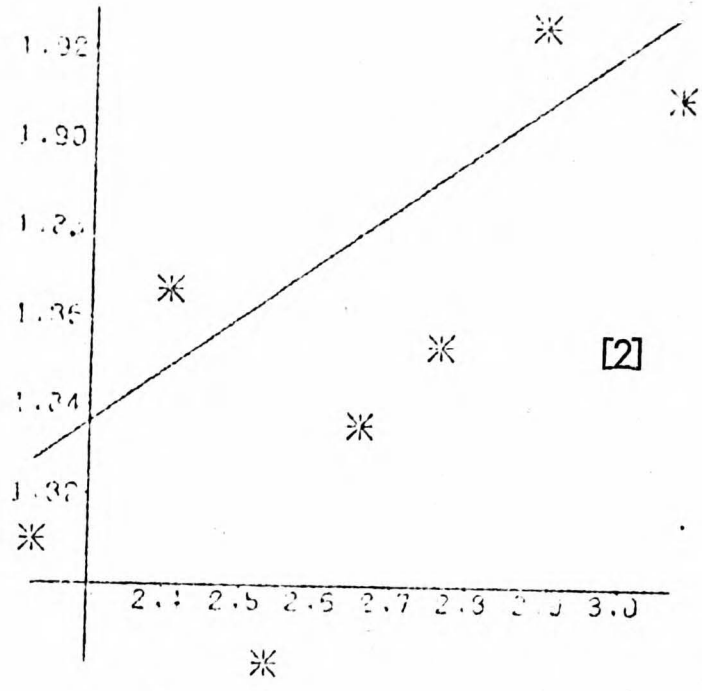
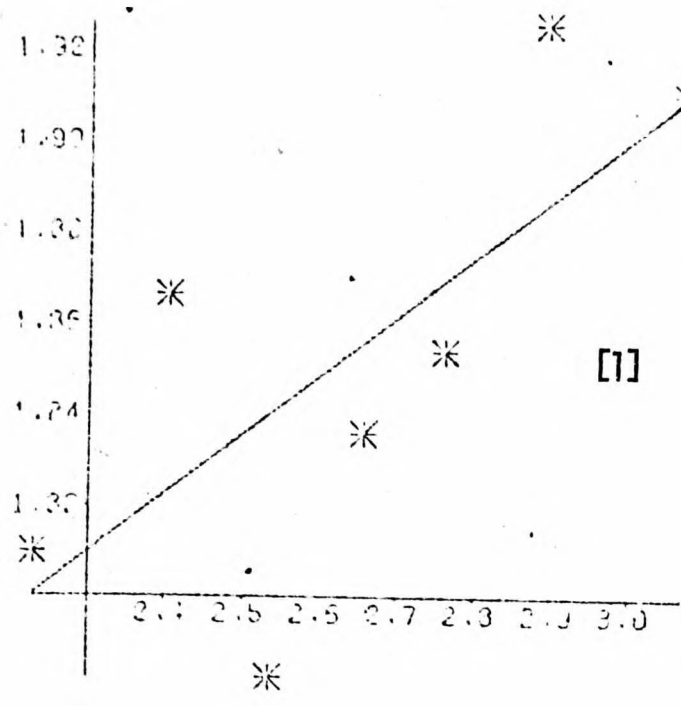


Figure 23

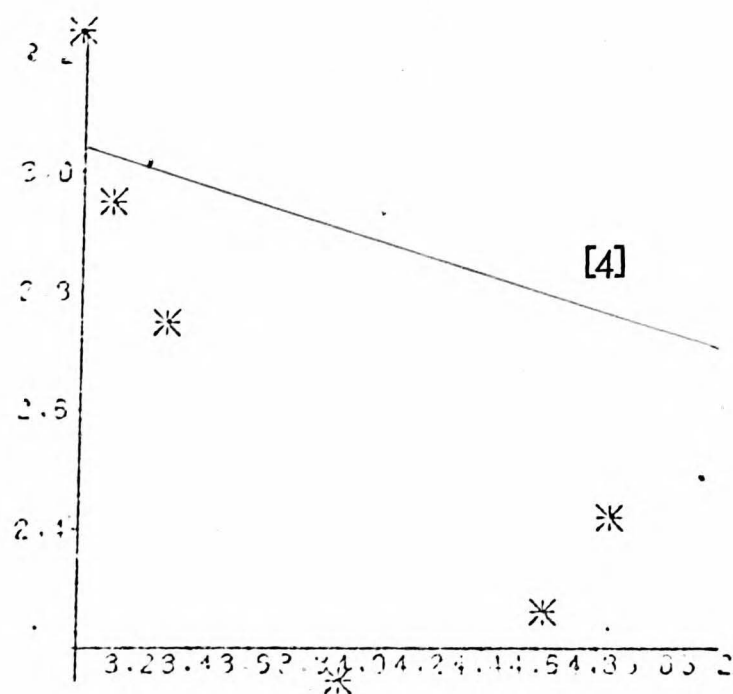
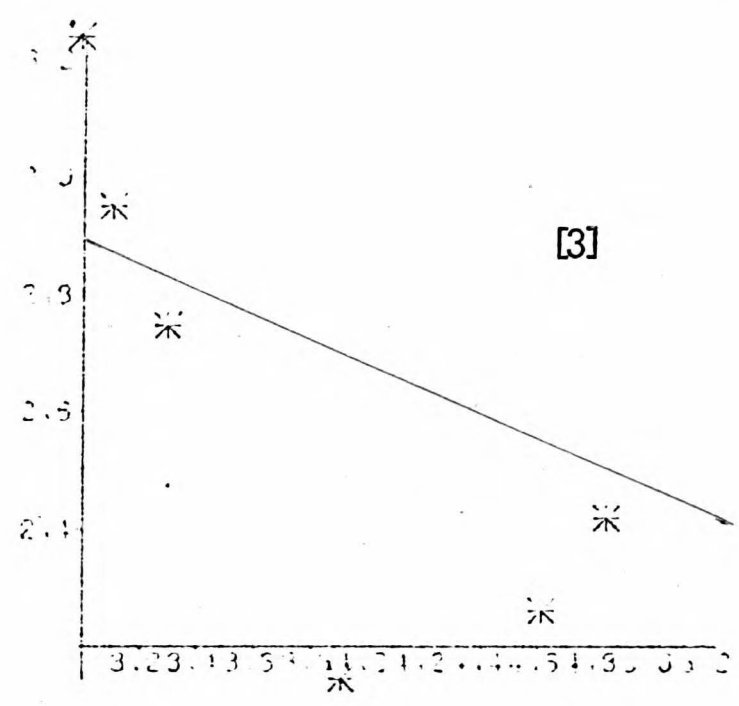
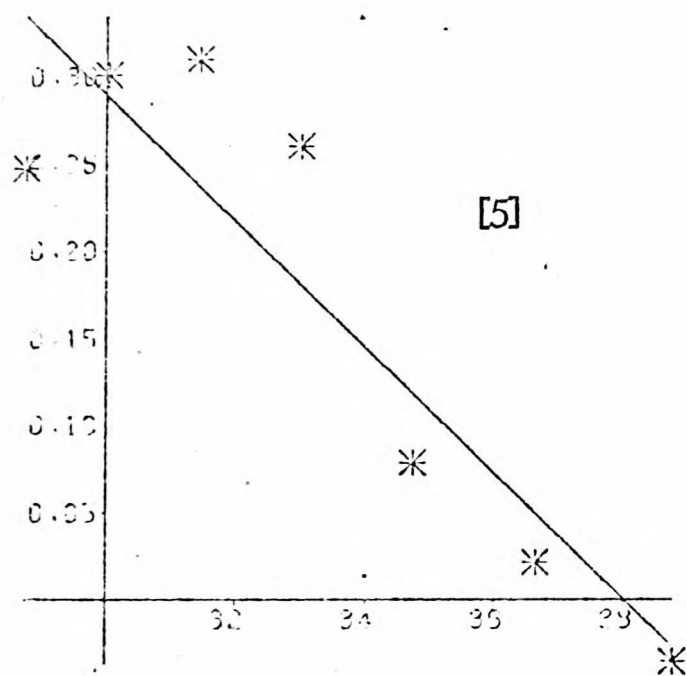
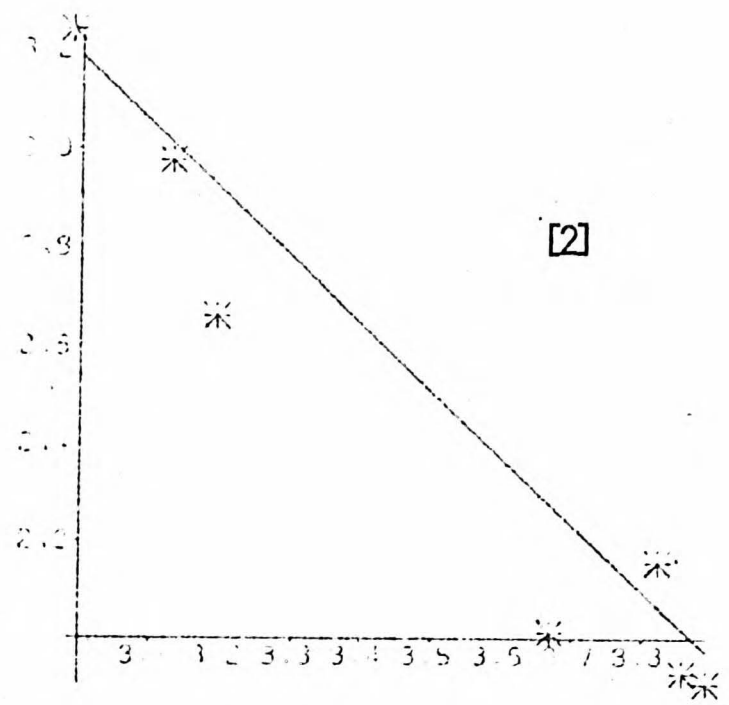
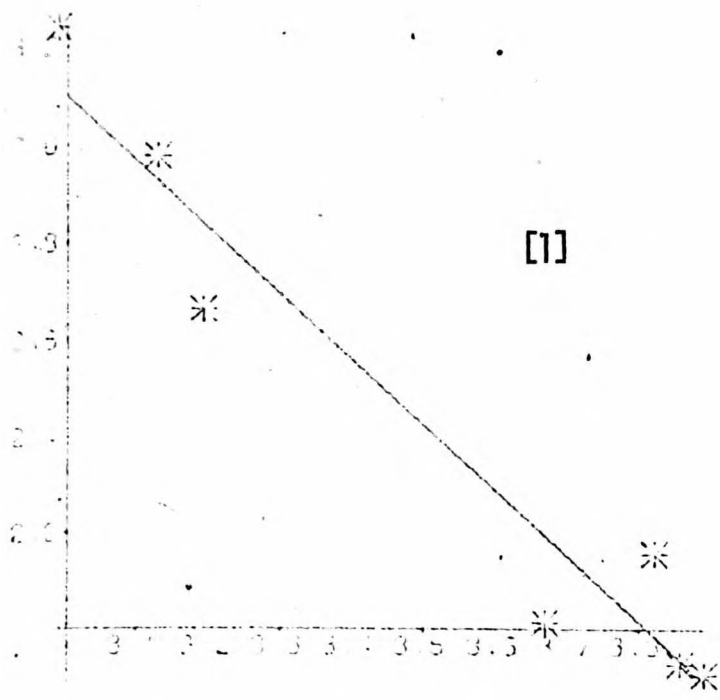


Figure 24

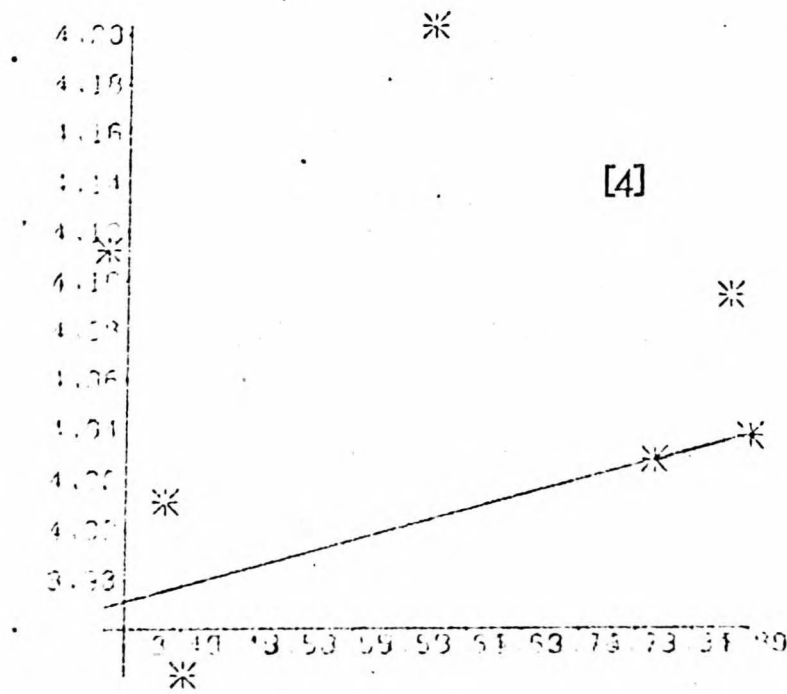
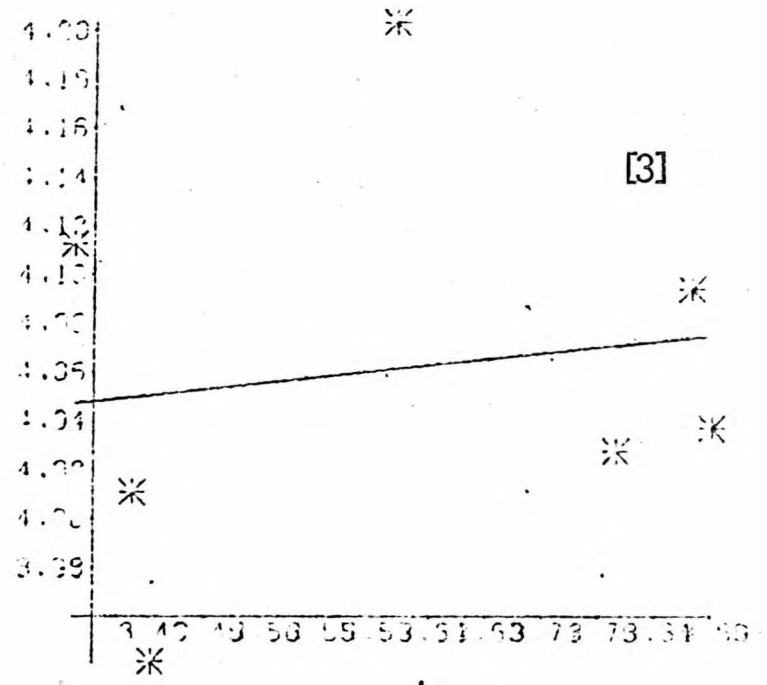
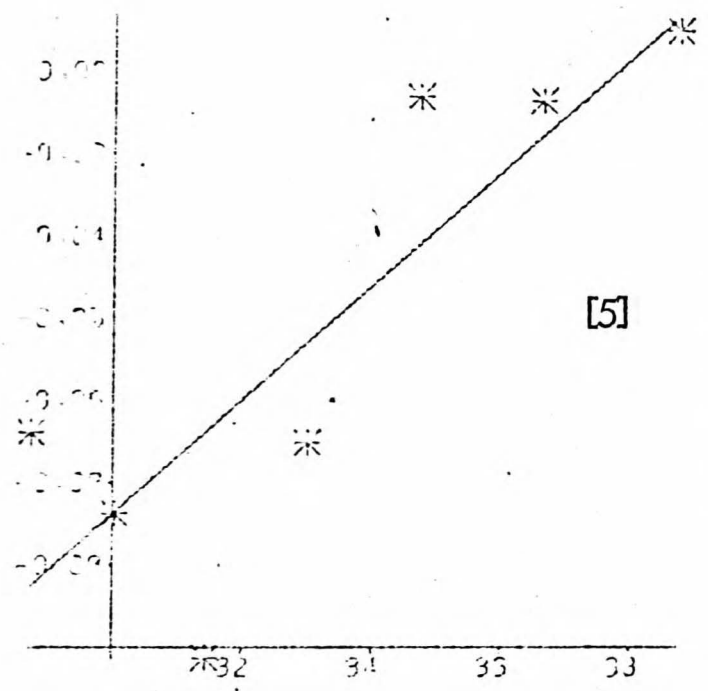
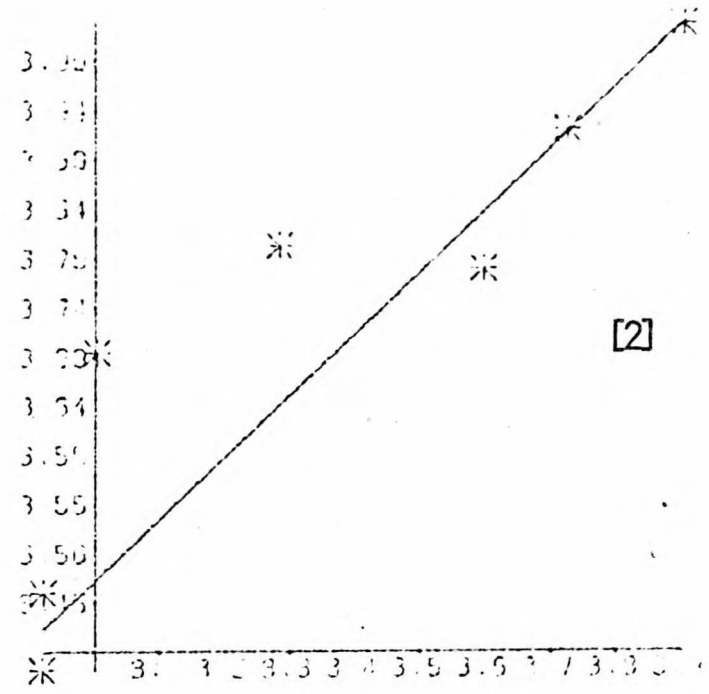
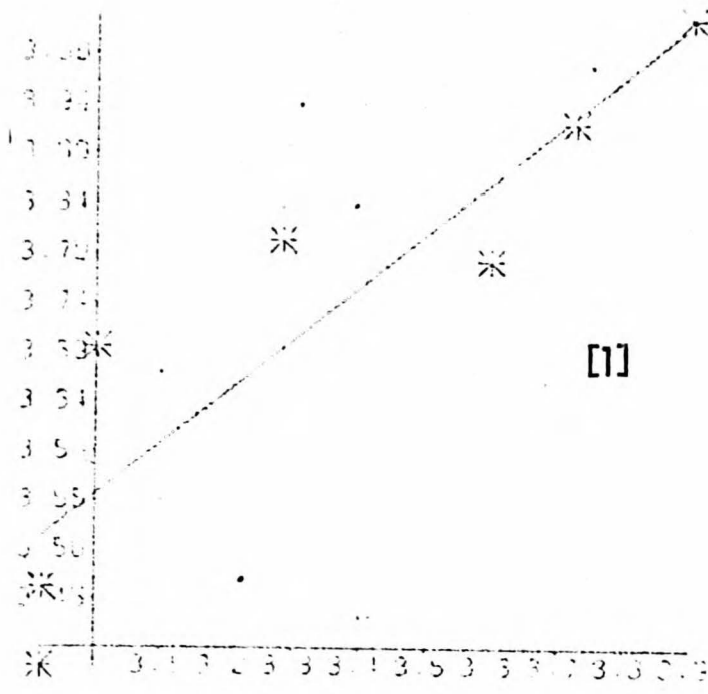


Figure 25

Compound		Slope	A = M ₀	M ₁
(CVII)	$A_{\underline{h}} \underline{\text{vs.}} A_{\underline{l}} \text{ [1]}$	0.129	0.008	0.002
	$A_{\underline{h}} \underline{\text{vs.}} A_{\underline{l}} \text{ (m) [2]}$	0.120	0.008	0.002
	$A_{\underline{h}}^{\underline{c}} \underline{\text{vs.}} A_{\underline{l}}^{\underline{c}} \text{ [3]}$	-1.376	0.052	0.022
	$A_{\underline{h}}^{\underline{c}} \underline{\text{vs.}} A_{\underline{l}}^{\underline{c}} \text{ (m) [4]}$	-3.176	0.121	0.057
	$\log_{10}(A_{\underline{l}}/A_{\underline{h}}) \underline{\text{vs.}} 1/T \text{ [5]}$	105.4	0.009	0.000
(CVIII)	[1]	-1.353	1.664	0.022
	[2]	-1.361	1.674	0.032
	[3]	-0.193	0.183	0.162
	[4]	-0.206	0.196	0.234
	[5]	-360.9	0.102	0.004
(CIX)	[1]	0.529	0.279	0.012
	[2]	0.630	0.333	0.017
	[3]	0.049	0.001	0.008
	[4]	0.121	0.002	0.013
	[5]	69.325	0.004	0.000

Table 45

The thermodynamic parameters calculated for the compounds are listed in Table 46. Values of $\Delta \underline{G}^{\circ}$ and $\Delta \underline{S}^{\circ}$ derived from area ratios which have been corrected neither for the α -ratio nor for the natural decrease are not included: the two values of these parameters quoted for each compound arise from the two methods of estimating the best straight line for the $A_{\underline{h}} \underline{\text{vs.}} A_{\underline{l}}$ plots. The units of $\Delta \underline{H}^{\circ}$ and $\Delta \underline{G}^{\circ}$ are J mole^{-1} and of $\Delta \underline{S}^{\circ}$ are $\text{J}^{\circ} \text{K}^{-1} \text{mole}^{-1}$.

Compound	ΔH°	ΔG°_{303}	$\Delta G^\circ_{303} \text{ (m)}$	ΔS°	$\Delta S^\circ \text{ (m)}$
(CVII)	-2019 ± 942	-1735 ± 252	-3842 ± 252	-1.2 ± 3.9	-5.8 ± 3.9
(CVIII)	6911 ± 942	2634 ± 252	2471 ± 252	14.1 ± 3.9	13.1 ± 3.9
(CIX)	-1327 ± 942	-	-	-	-

Table 46

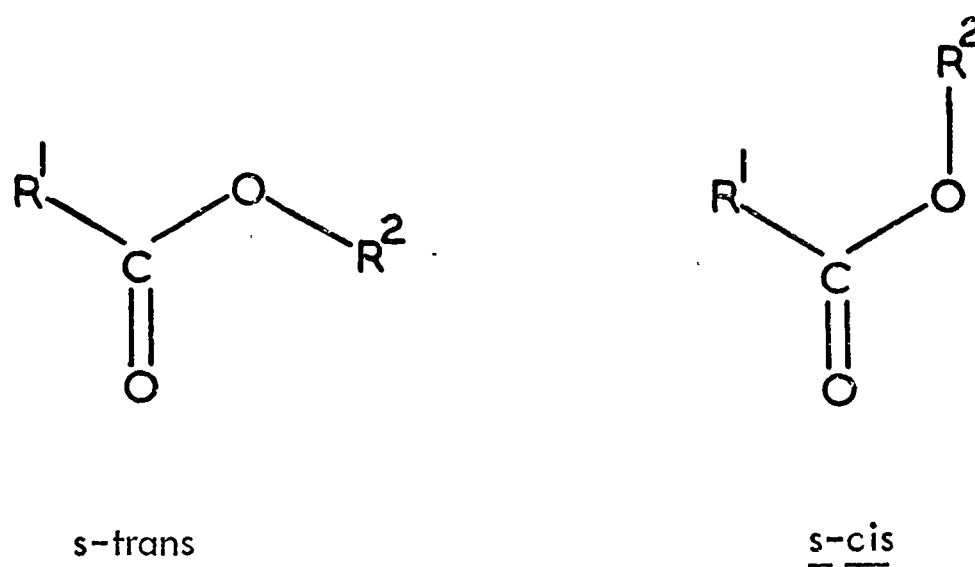
The values of the parameters will be discussed later, when the conformations of esters are considered. It should, however, be noted that the inclusion of the natural decrease correction causes the slopes of the A_h vs. A_l plots to change sign in one case (in another case, the slope is already negative and remains so on correction). The differences between the parameters derived from the means and least squares methods emphasise the difficulty in estimating the best straight line between variables when both variables are subject to large errors.

Conformations of Esters: Analogue and Digital Resolutions.

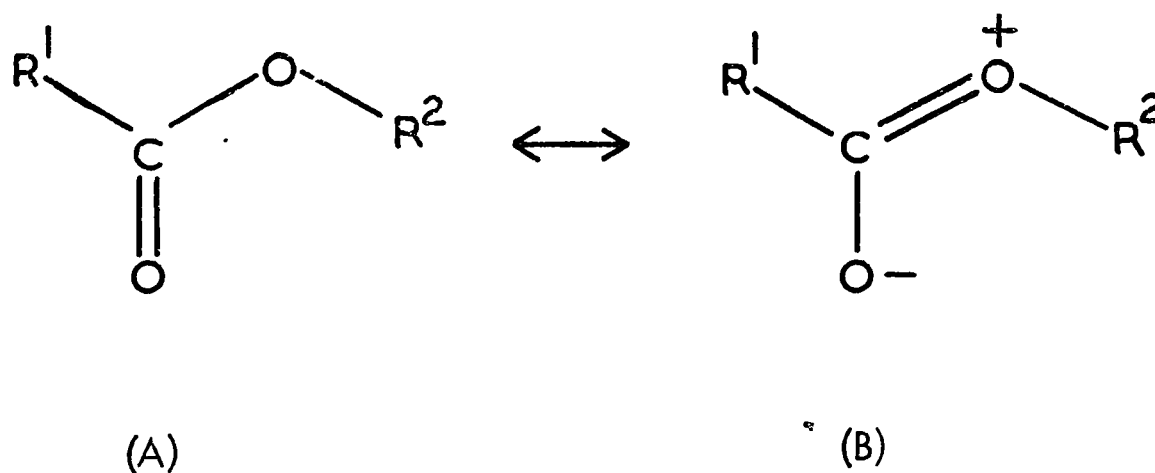
Experiments 25 to 32 and (in part) 24. With a reliable approach (based upon a combination of deuterium labelling, solvent, temperature, concentration, and overtone studies) for distinguishing between Fermi resonance and rotational isomerism as the most likely causes of carbonyl doubling established, and a viable data-processing approach devised, the time was deemed opportune to apply these approaches to a large group of compounds all of which exhibit carbonyl band doubling. Experiments 25 to 32 are therefore concerned with a study of the methyl, ethyl, and t-butyl esters of furan-2-carboxylic acid and of the esters of the 3-, 4-, and 5-bromofuran-2-carboxylic acids. These compounds provide an opportunity of

comparing the analogue and digital methods of curve resolution in rather more detail than is possible from Experiment 19 (since actual thermodynamic parameters calculated using the two methods can now be compared), and also of examining the effect of position of substitution in the furan ring upon a rotameric equilibrium. The bromo acid chlorides and two N-methylpyrrole-2-carboxylates are included for comparison as also are the 5-deuterio- and 5-bromo-3,4-dideuterio-furan-2-carboxylates. The conformations of the esters will firstly be discussed, and a comparison of the thermodynamic parameters will then be made.

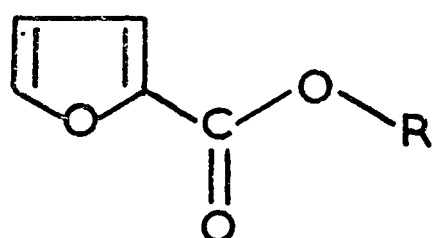
The conformations of simple aliphatic esters are normally considered⁹⁷ in terms of an equilibrium between two planar rotational isomers, s-cis and s-trans:



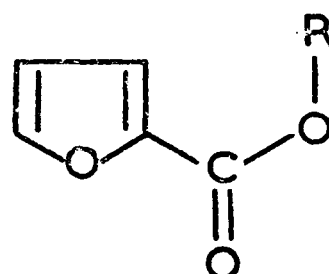
the assumption of planarity relying upon the partial double bond character of the C-O bond arising from mesomerism:



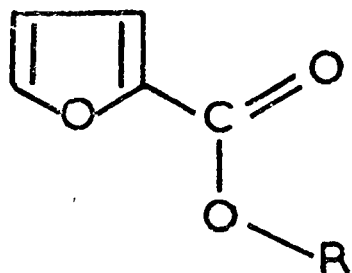
The observed planarity (or deviation therefrom) is a compromise between an increase in stabilisation owing to contributions from canonical (B), and a decrease owing to steric repulsions between R^2 and the carbonyl oxygen or R^1 . There is much experimental evidence (e.g., dipole moment studies,^{98,99} microwave spectroscopy studies,¹⁰⁰ and electron diffraction studies¹⁰¹) in support of the assumption of planar conformations with the s-trans conformation predominating. In this form, the dipoles of the carbonyl and alkyl-oxygen bonds are roughly antiparallel (which situation would be favoured by a solvent of low polarity) and repulsions between the lone-pair electrons of the oxygen atoms and between the alkyl groups are minimised. The s-cis conformation is only rarely observed, e.g., in t-butyl formate⁹⁷ where R^1 is small and R^2 is bulky. There are thus four possible planar conformations for an ester of furan-2-carboxylic acid [(C) to (F)]:



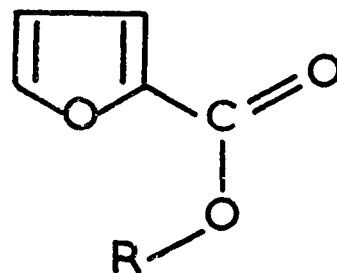
(C) syn-s-trans



(D) syn-s-cis



(E) anti-s-trans



(F) anti-s-cis

In the compounds studied here it is considered that the observed carbonyl band

doubling arises from rotational isomerism between the syn-s-trans and the anti-s-trans forms because the frequency separations of the doublets (15 to 20 cm^{-1}) are larger than would be expected for cis-trans isomerism⁹⁷ and because the esters do not have any of the special structural features which lead to the adoption of s-cis forms. Several observations demonstrate that Fermi resonance is not the general explanation of the band doubling: (i) of the eighteen furan-2-carboxylates listed here, fourteen show well separated carbonyl doublets the relative positions of which are entirely logical; (ii) replacement of hydrogen by deuterium at the 3-, 4-, and 5-positions causes no change in the appearance of the carbonyl absorptions except for methyl 5-bromofuran-2-carboxylate (LXXXII) where the 4-component absorption collapses to a doublet; (iii) dramatic solvent and temperature effects are observed only for one compound [(LXXXII), the compound having a 4-component carbonyl absorption]; (iv) where doublets are observed in the carbonyl fundamentals, they are also observed in the first overtone region where the relative intensities parallel those of the fundamentals, and (v) the introduction of a bromine atom at the 3-position has a logical effect upon the carbonyl doublets. The positions (at 303°K) of the fundamental carbonyl absorptions of all of the furan esters studied here are compared in Table 47 where relative optical densities are given in brackets and "s" implies a shoulder on the main absorption.

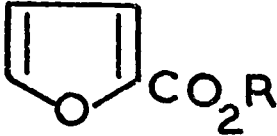
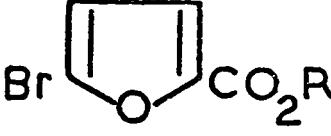
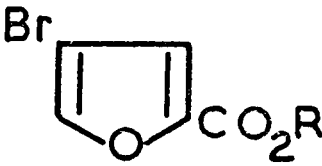
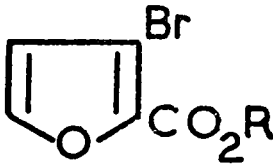
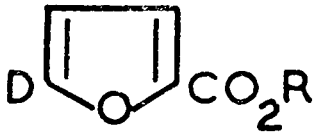
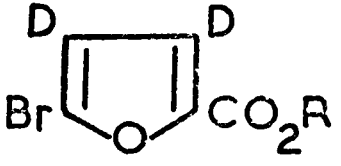
Compound	R =	Bands at (cm ⁻¹)	
		CCl ₄	CH ₃ CN
	CH ₃	1740 (1.1); 1725 (1)	1733 (1.3); 1725 (1)
	C ₂ H ₅	1734 (1); 1718 (1.1)	1726.5 (1.2); 1717 (1)
	^t C ₄ H ₉	1729 (1); 1711 (1.1)	1719 (1.2); 1710 (1)
	CH ₃	1748 (1); 1738.5 (1.6) 1731.5 (1.7); 1720 (1.5)	1731.5 (1.5); 1719.5 (1)
	C ₂ H ₅	1735 (1); 1719 (1.5)	1726.5 (1.2); 1716 (1)
	^t C ₄ H ₉	1731 (1); 1712.5 (1.5)	1721.5 (1.1); 1710.5 (1)
	CH ₃	1746 (1); 1728.5 (1)	1738 (1); 1727.5 (1.2)
	C ₂ H ₅	1739.5 (1); 1724 (1.1)	1730 (1.2); 1722 (1)
	^t C ₄ H ₉	1734 (1.1); 1718 (1)	1724 (1.3); 1717 (1)
	CH ₃	1733; 1712 _S	1727.5; 1720 _S
	C ₂ H ₅	1727.5	1721
	^t C ₄ H ₉	1723.5	1713.5
	CH ₃	1740.5 (1.1); 1725.5 (1)	
	C ₂ H ₅	1734 (1); 1718 (1.1)	
	^t C ₄ H ₉	1729 (1); 1711 (1)	
	CH ₃	1743 (1); 1729.5 (1.3)	1731
	C ₂ H ₅	1736 (1); 1719 (1.6)	1727 (1.2); 1716.5 (1)
	^t C ₄ H ₉	1731 (1); 1712.5 (1.5)	1721 (1); 1711 (1)

Table 47

In carbon tetrachloride solutions, with the exception of methyl 5-bromofuran-2-carboxylate, in which the quartet carbonyl absorption is clearly a consequence of Fermi resonance (cf. methyl 5-bromo-3,4-dideuteriofuran-2-carboxylate which has only a doublet carbonyl absorption), all of the esters show very similar separations between the components of the carbonyl doublets (the separation with the t-butyl esters being a little greater than with the methyl and ethyl esters), all show similar changes in band positions with change of alkyl group (the positions of the bands at lower wavenumber in a carbonyl doublet being slightly more sensitive to change than the positions of the higher wavenumber bands), and all show similar changes in band positions with change in the position of halogen substituent (the sensitivity of bands at higher and lower wavenumber being similar in this respect). When the polarity of the solvent is increased, the positions of the bands at higher wavenumber are much more sensitive to the change than are the positions of the lower wavenumber bands; related to this is the observation that the intensities of the bands at higher wavenumber relative to those of the lower wavenumber bands increase with increase in solvent polarity: both observations suggest that in all of the esters, the rotamers responsible for the higher wavenumber bands are more polar than those responsible for the lower wavenumber bands.

The gross trends observed when hydrogen is replaced by bromine are similar to those observed for the corresponding aldehydes (or deuterioaldehydes when Fermi resonance was present in the non-deuterated compounds). Thus, the introduction of a bromine atom at the 4-position raises the positions of the carbonyl absorptions considerably (because mesomerism must necessarily be less important than in the 3- and 5-bromo compounds, the inductive effect then becoming relatively more important), introduction of bromine at the 5-position raises the

carbonyl band positions slightly (reflecting the balance between induction and mesomerism), and introduction of bromine at the 3-position lowers the carbonyl band positions and causes the disappearance of one of the components of the carbonyl doublets. Considering the positions of, and the solvent effects upon, the remaining bands in the 3-bromo esters, it is clear that these bands correspond to the higher wavenumber components of the doublet absorptions of the 4- and 5-bromo esters.

A tentative assignment of the syn conformation to the higher frequency components of the doublet carbonyl absorptions can now be made, since the syn conformations of simple furan-2-carboxylates will almost certainly have larger dipole moments than the anti conformations. Two factors strongly support this assignment: (i) a syn rotamer would be expected to have a higher carbonyl stretching frequency than an anti rotamer, because the dipolar canonical $\overset{+}{\text{C}}-\overset{-}{\text{O}}$ should be disfavoured in the syn rotamer owing to electrostatic repulsion between the negatively charged carbonyl oxygen atom and the ring oxygen atom, and (ii) if the higher frequency components correspond to anti rotamers, then in the 3-bromo esters only the anti rotamers are observed and, because of the proximity of the carbonyl and carbon-bromine dipoles, a dramatic lowering of the carbonyl frequency compared with the non-brominated compound would not be expected: this is the reverse of what is observed. The observation that the 3-bromo esters have carbonyl bands at much lower frequencies than the 5-bromo esters lends support to the syn assignment since dipolar field effects between the negatively-polarised carbon-bromine bond and the alkoxy oxygen should favour π -electron donation into the carbonyl group.

An interesting comparison may be made between the carbonyl absorptions

of the furan esters considered above and simple esters of the 2-acids of thiophen¹⁰² and N-methylpyrrole, for in the latter compounds single carbonyl bands only are observed for carbon tetrachloride solutions. There are two possible explanations for the single bands: (i) the syn and anti forms are both absorbing at the same carbonyl frequencies, or (ii) one form is grossly destabilised compared with the other. The first explanation is the less likely because it does not explain why thiophen-2-esters which are substituted at the 3- and 4-positions show carbonyl band doubling¹⁰² and because it is unlikely that the balance of inductive, mesomeric, and field effects would be identical in pyrroles and thiophens but not in furans. It is, perhaps, a little surprising that such a strong preference for one conformation should exist in pyrrole and thiophen: the origin of this preference, which cannot be steric alone, is not understood.

Finally, it is clear from the results of Experiment 32 that in the bromo furan-2-carbonyl chlorides the situation is complicated (as it is in furan-2-carbonyl chloride) by the occurrence of Fermi resonance. The general trends (e.g., the occurrence of only one carbonyl band for the 3-bromo compound; changes in band positions with change in substituent position and solvent, and greater sensitivity of the positions of higher wavenumber components of carbonyl envelopes to solvent change compared with the lower wavenumber components), however, seem to parallel those observed with the bromo-esters.

The results for the esters [calculated using the "all-purpose" computer program (Experiment 33)] are presented in Table 48, in which the conventions used are those of Table 45; these are summarised below, along with the compound numbers:

Alkyl furan-2-carboxylates; alkyl = methyl : (CX)
 alkyl = ethyl : (CXI)
 alkyl = t-butyl: (CXII)

Alkyl 5-bromofuran-2-carboxylates; alkyl = ethyl : (LXXXIII)
 alkyl = t-butyl: (LXXXIV)

Alkyl 4-bromofuran-2-carboxylates; alkyl = methyl : (LXXXVI)
 alkyl = ethyl : (LXXXVIII)
 alkyl = t-butyl: (LXXXIX)

Graph of: A_h vs. A_l : [1]
 : A_h vs. A_l (m) : [2]
 : A_h^c vs. A_l^c : [3]
 : A_h^c vs. A_l^c (m) : [4]
 : $\log_{10}(A_l/A_h)$ vs. $1/T$: [5]

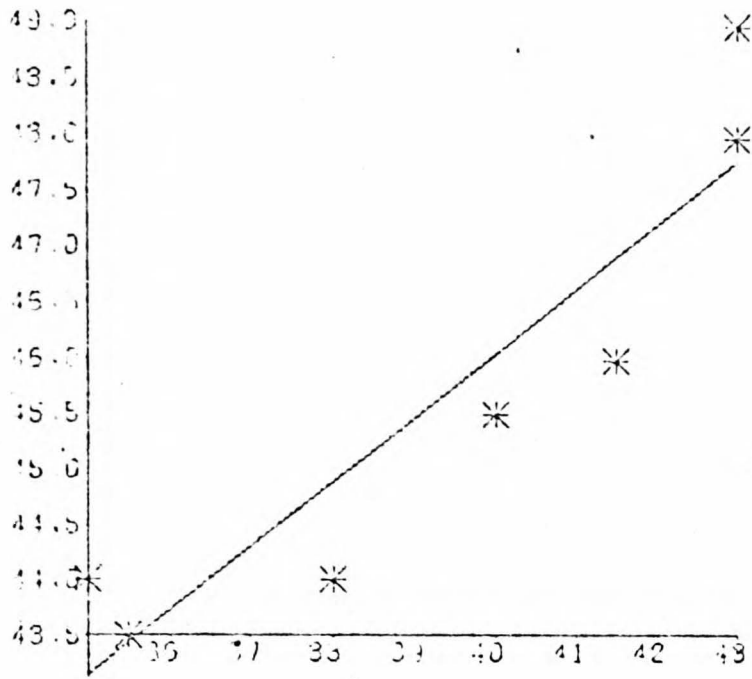
$A = M_0$ = Mean Square of variation due to regression.

M_1 = Mean Square of residual regression.

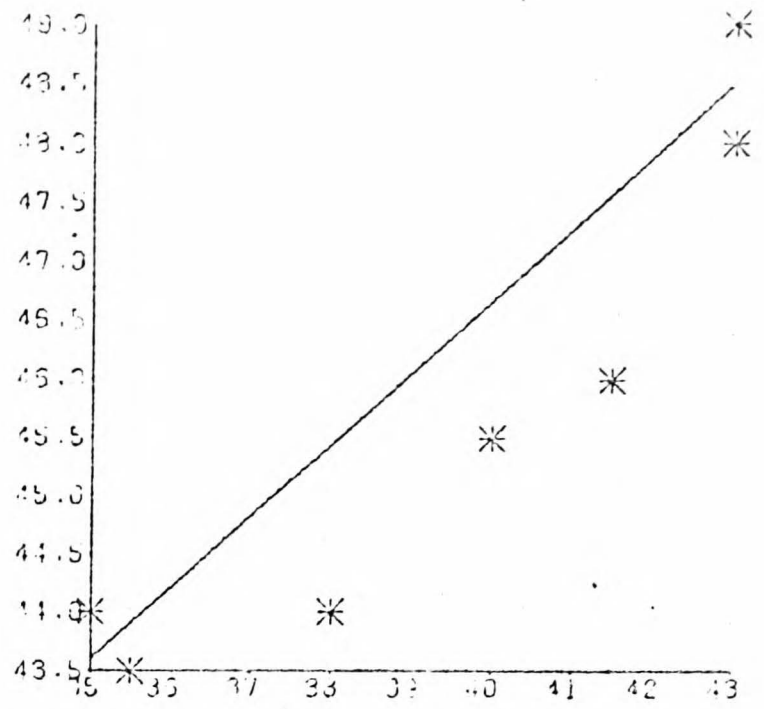
c = natural decrease corrected.

m = slope from method of means.

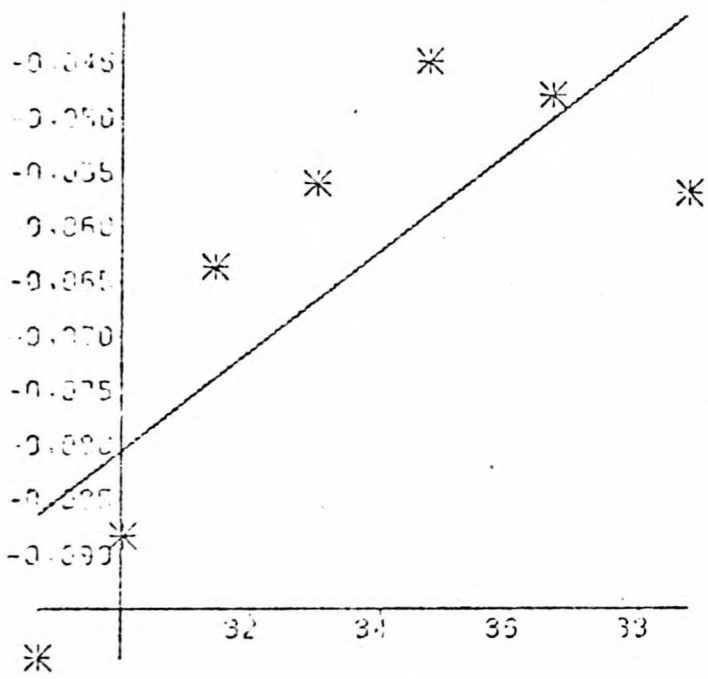
For three compounds [(CX), (CXI), and (CXII)] the data from both analogue and digital resolutions has been analysed; for the remaining compounds, only digital data was used. The natural decrease correction used was an average of the data in Tables 15 to 17 (digital) and Table 18 (analogue). Plots of the graphs are included as Figures 26 to 36.



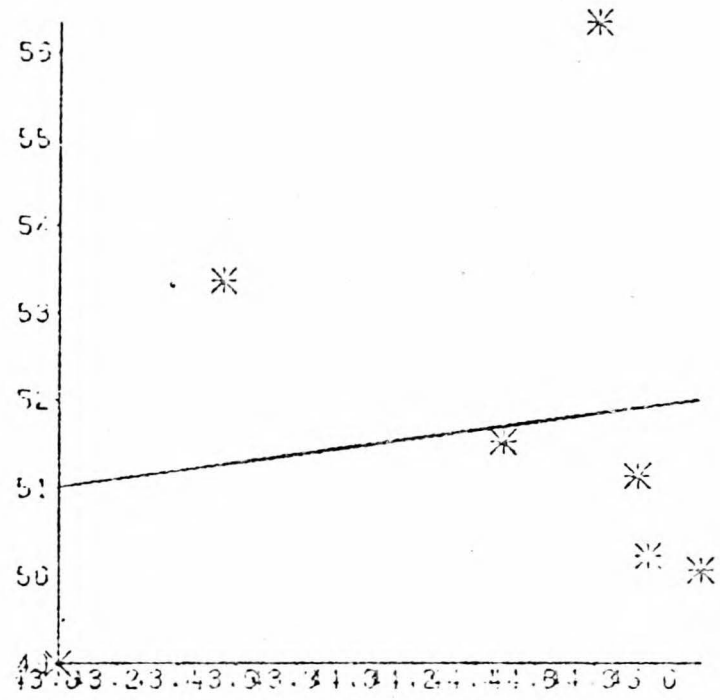
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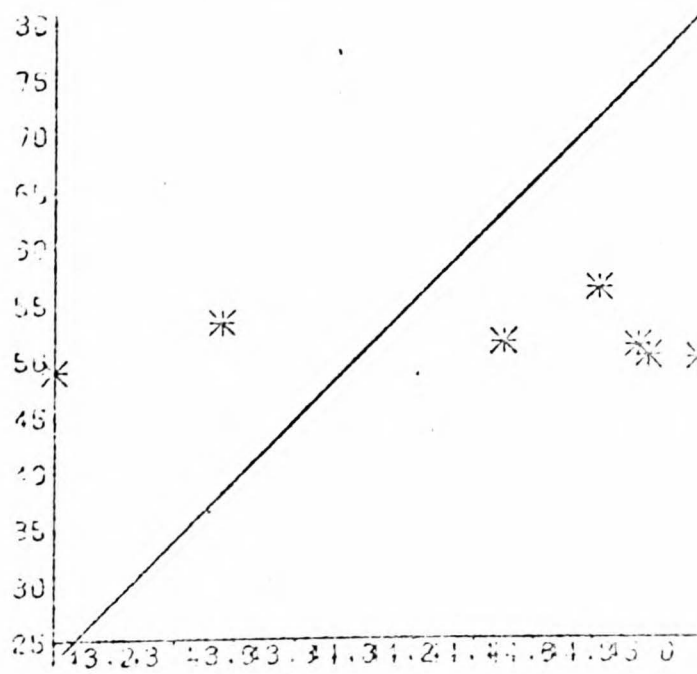
[2]



[5]



[3]



[4]

Figure 26

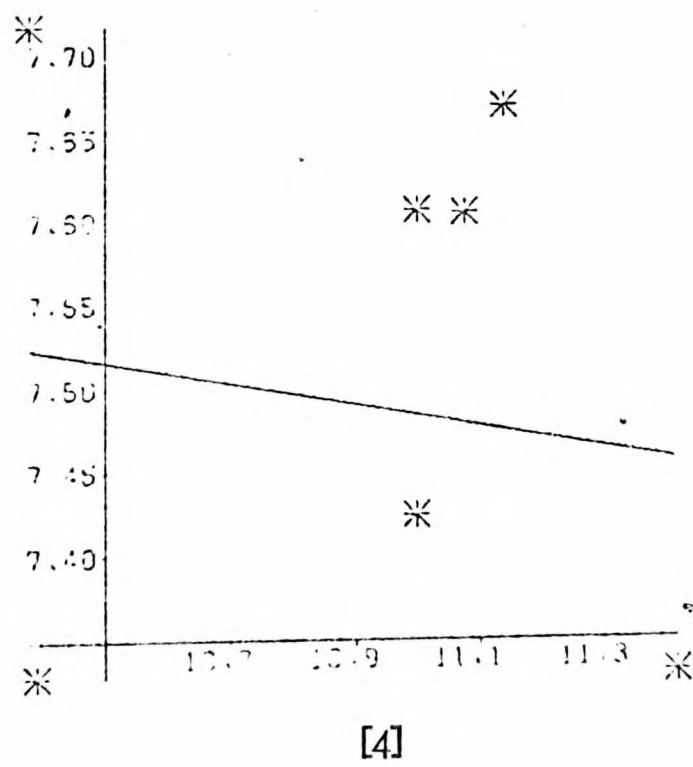
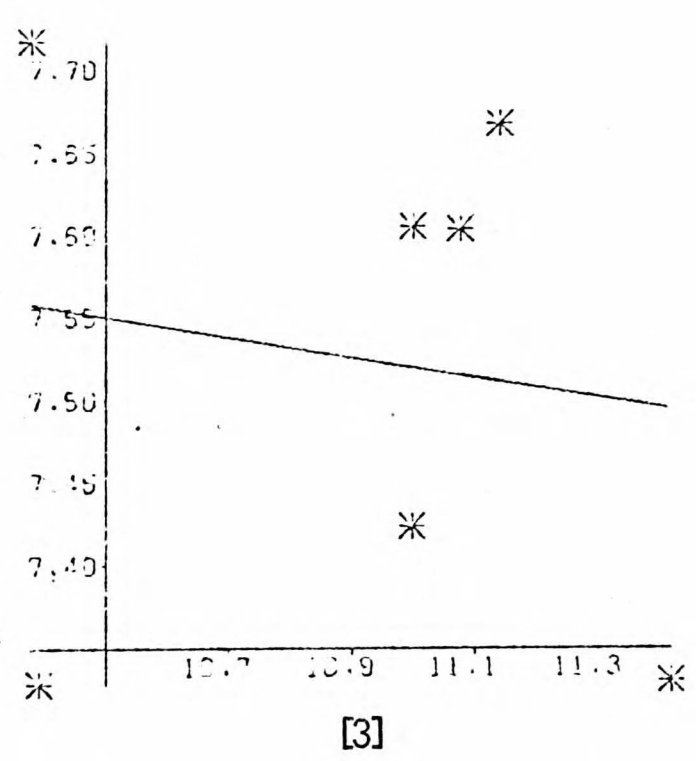
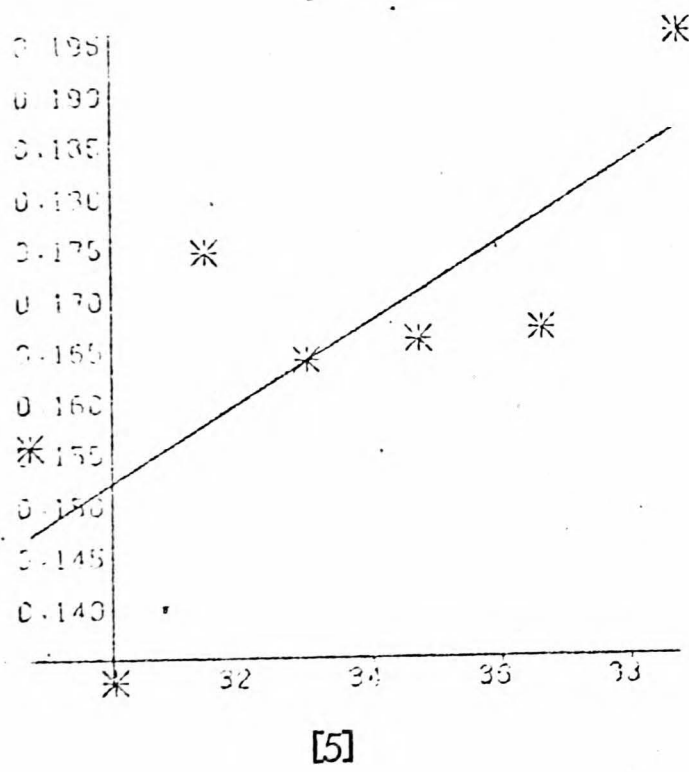
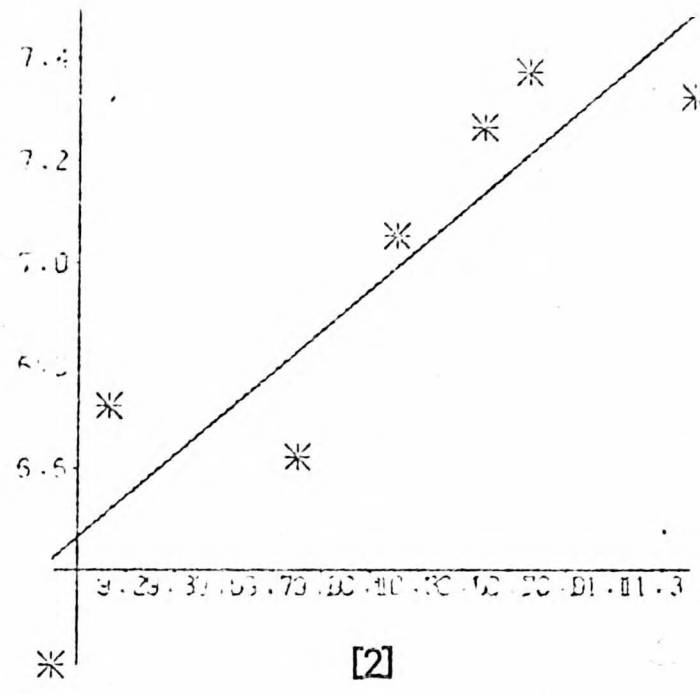
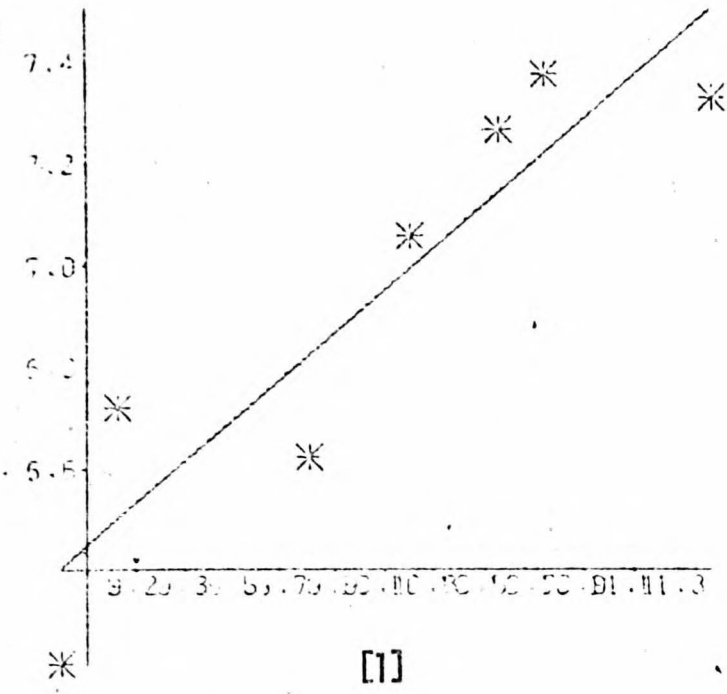
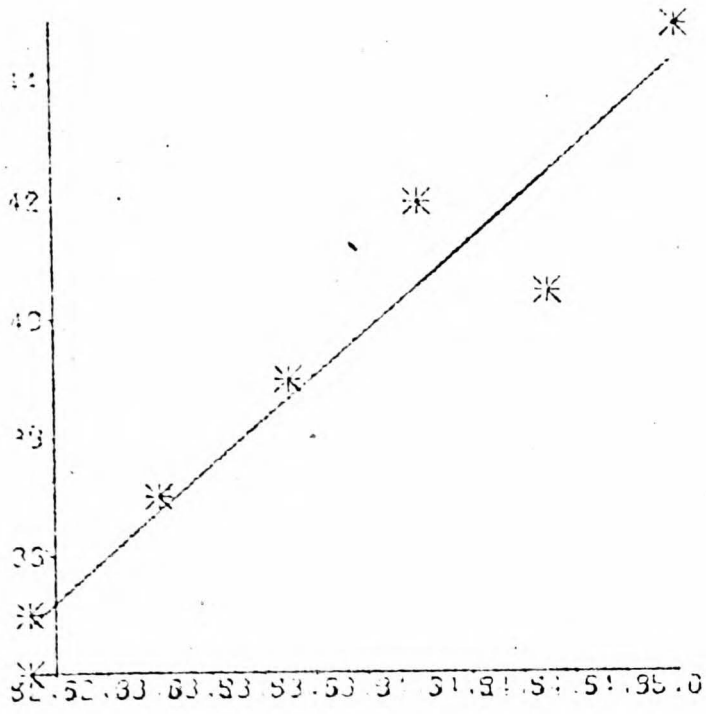
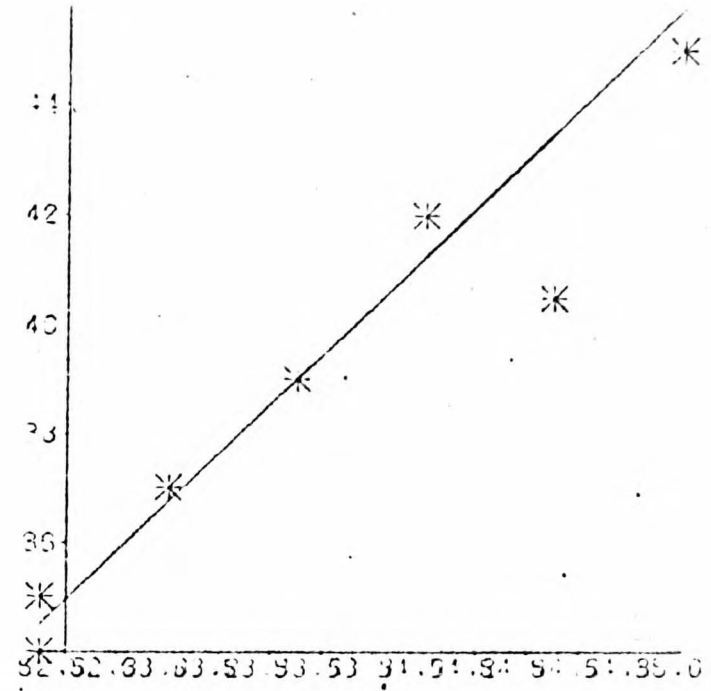


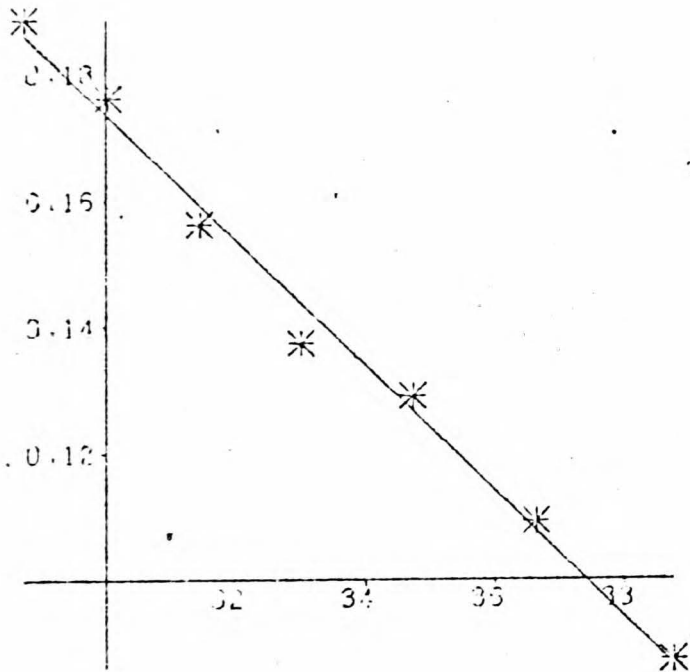
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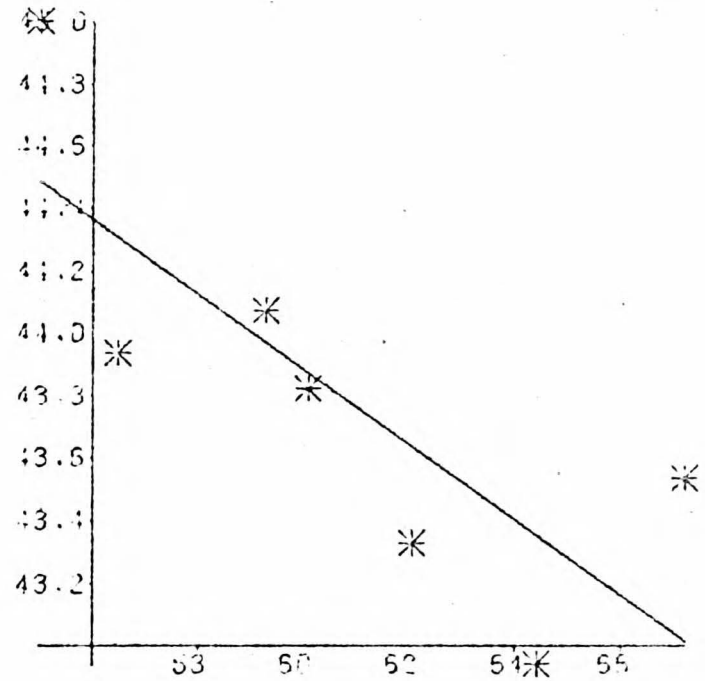
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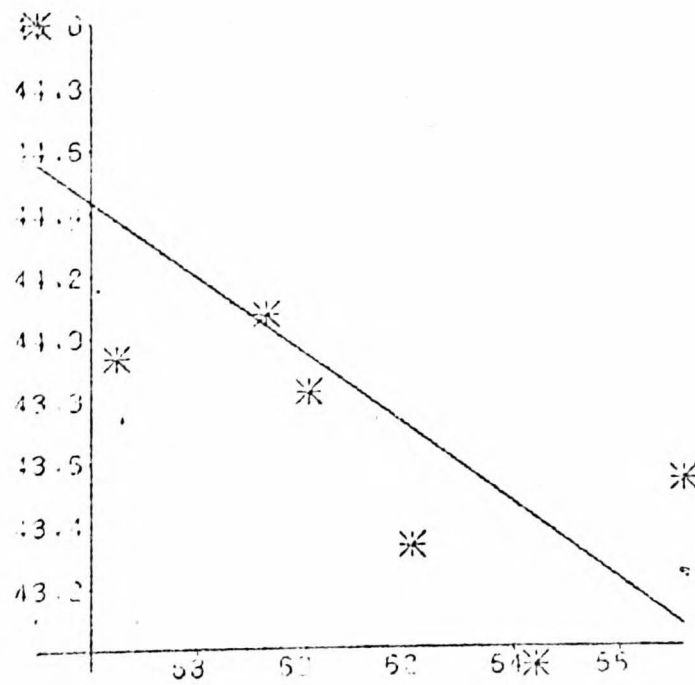
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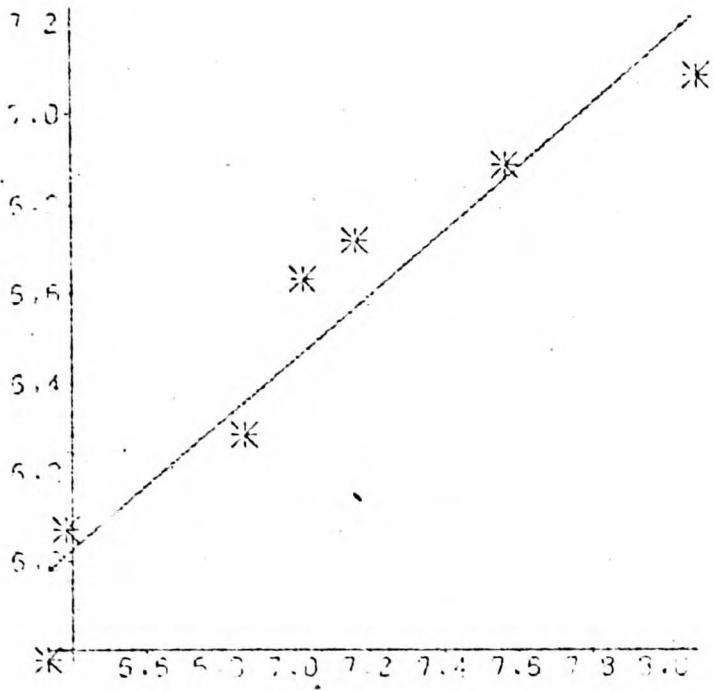


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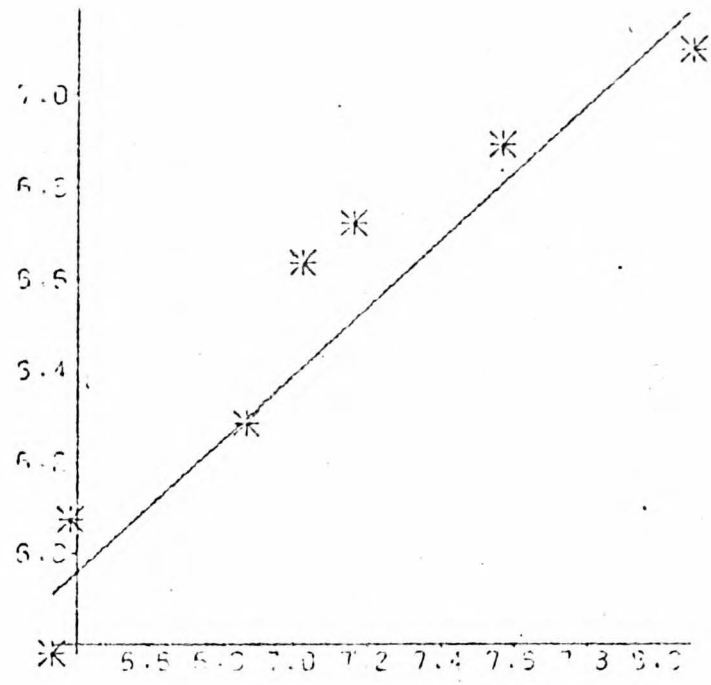


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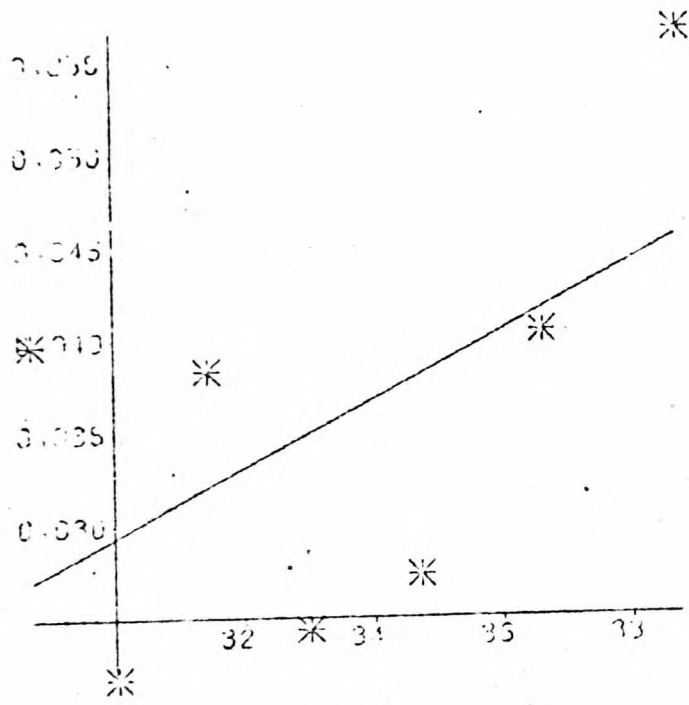
Figure 28



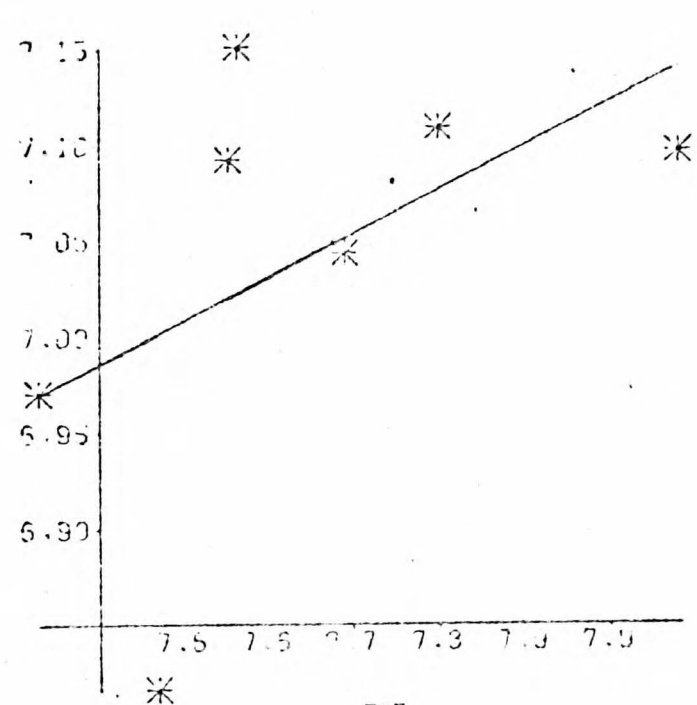
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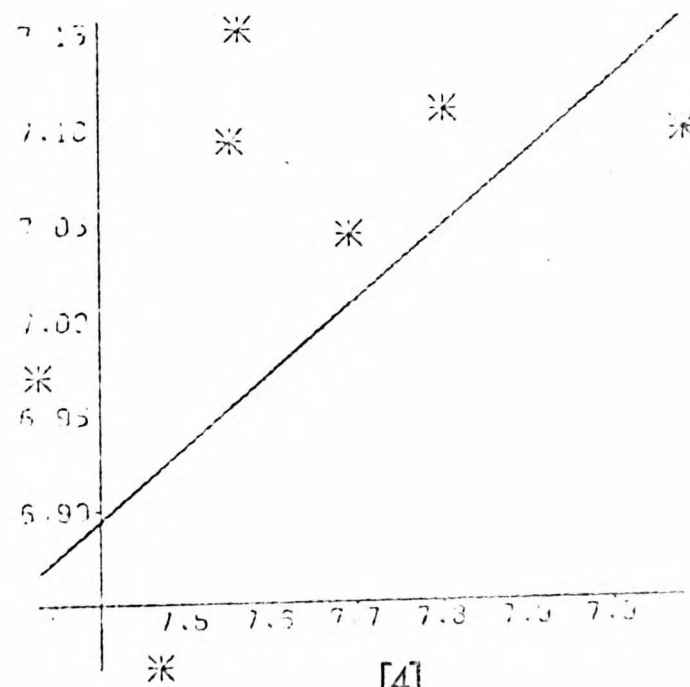
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[3]



[4]

Figure 29

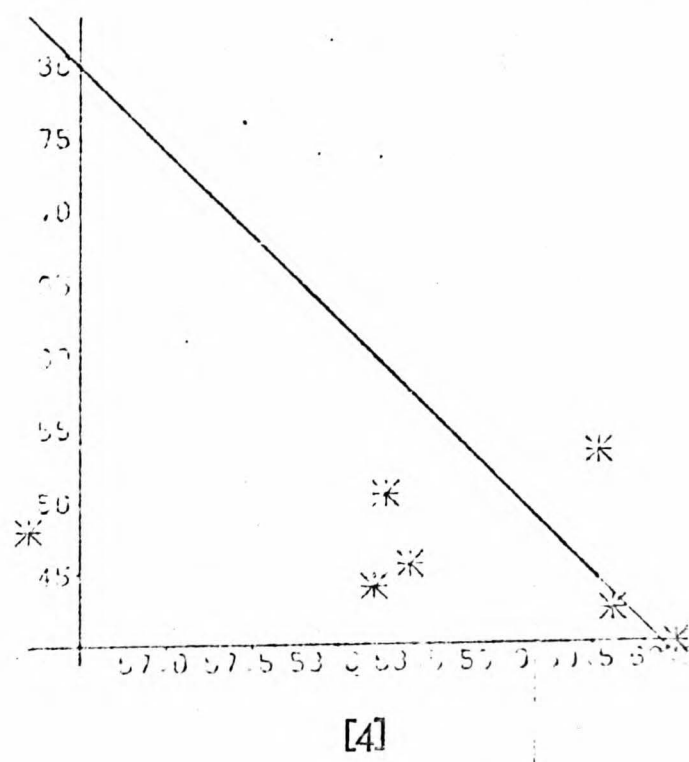
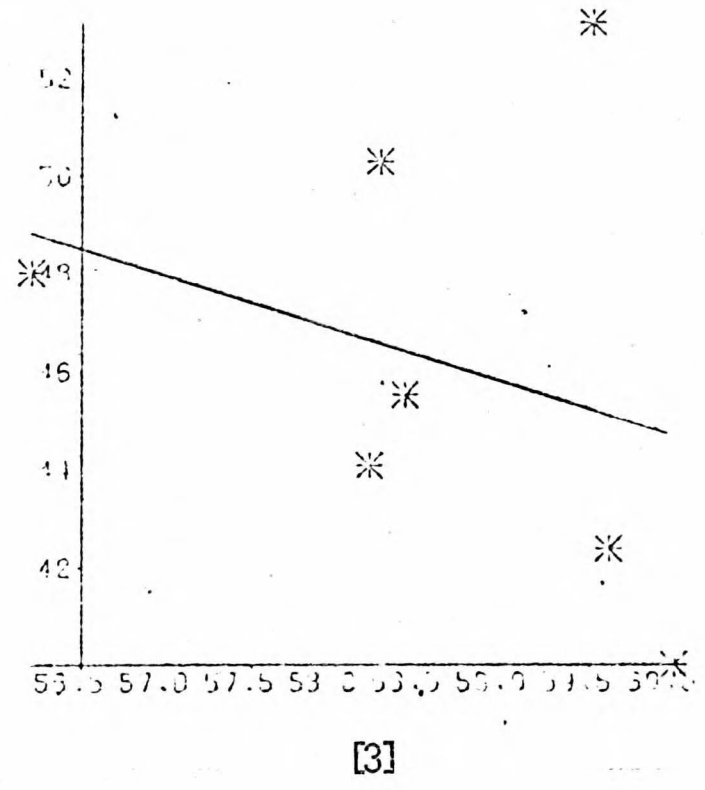
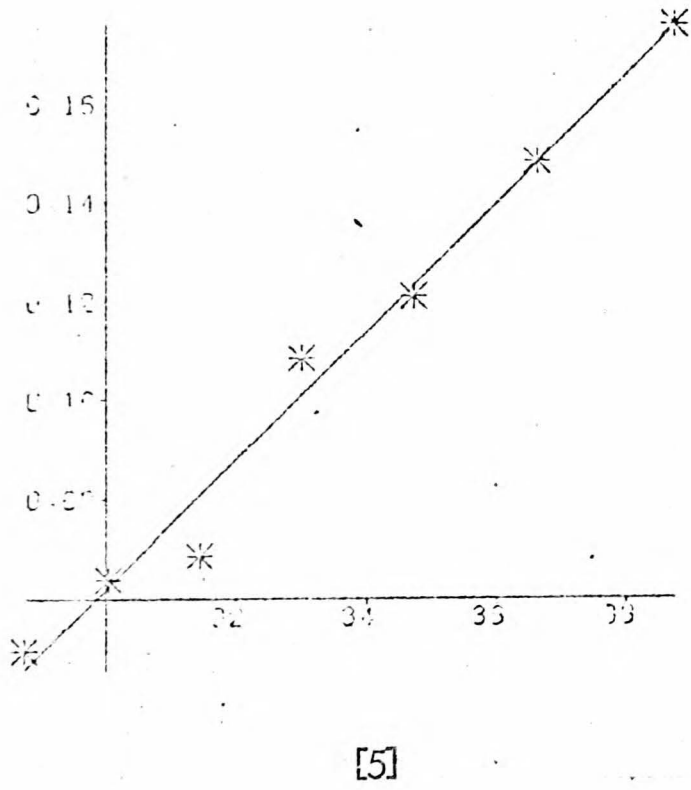
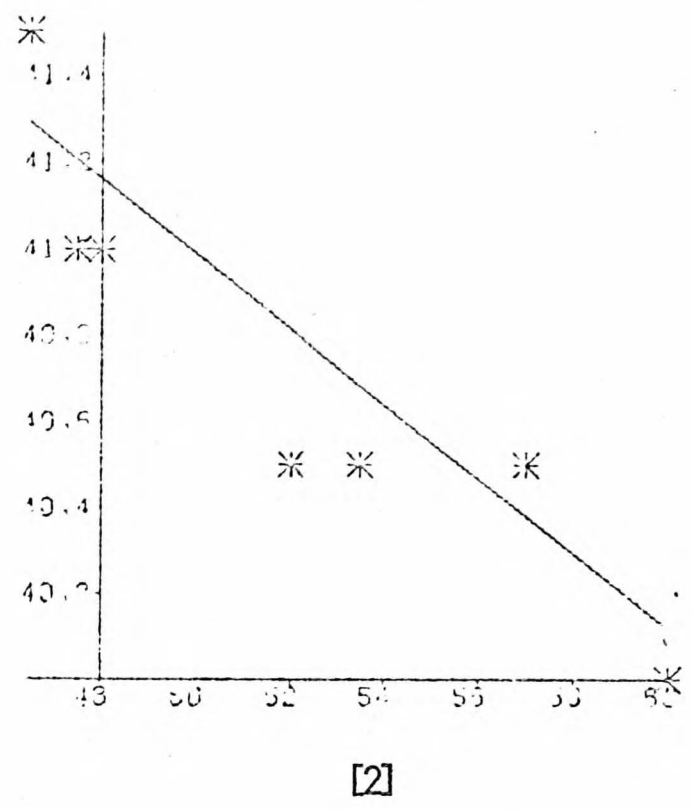
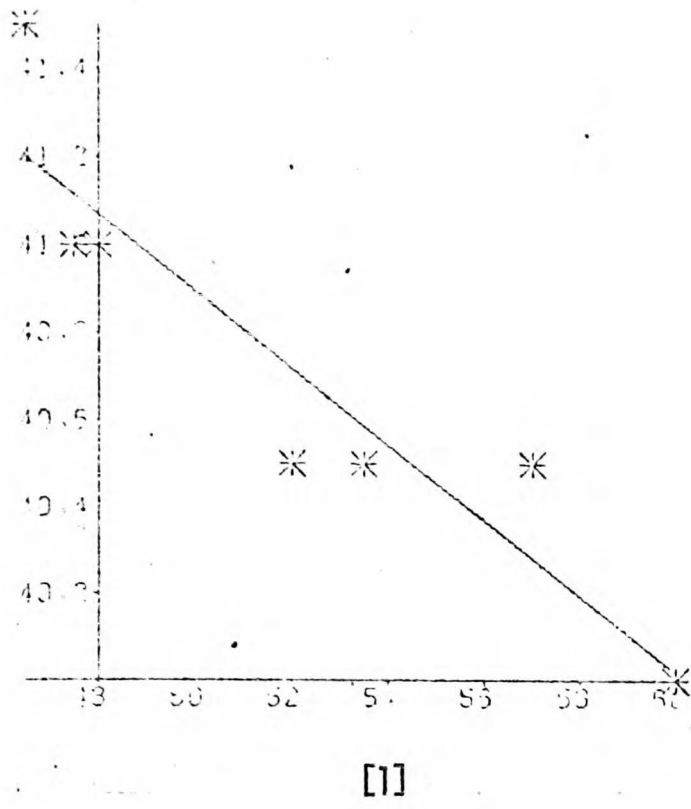
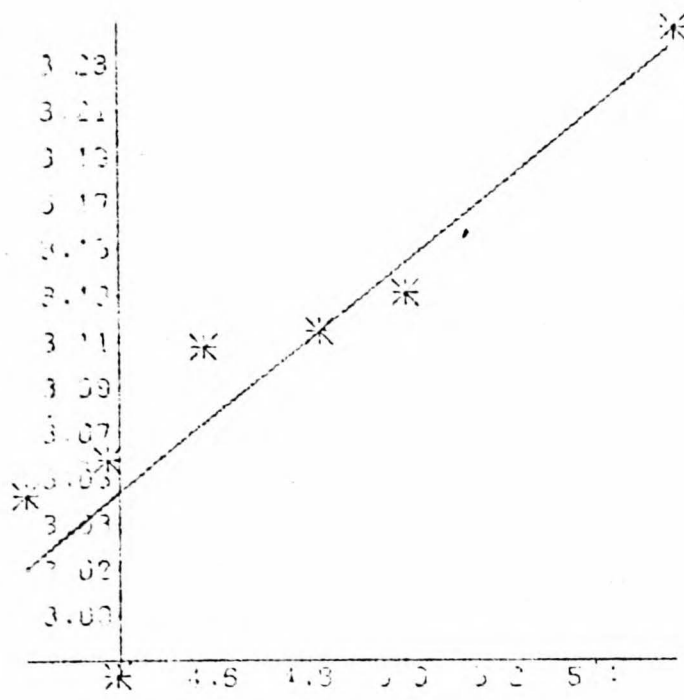
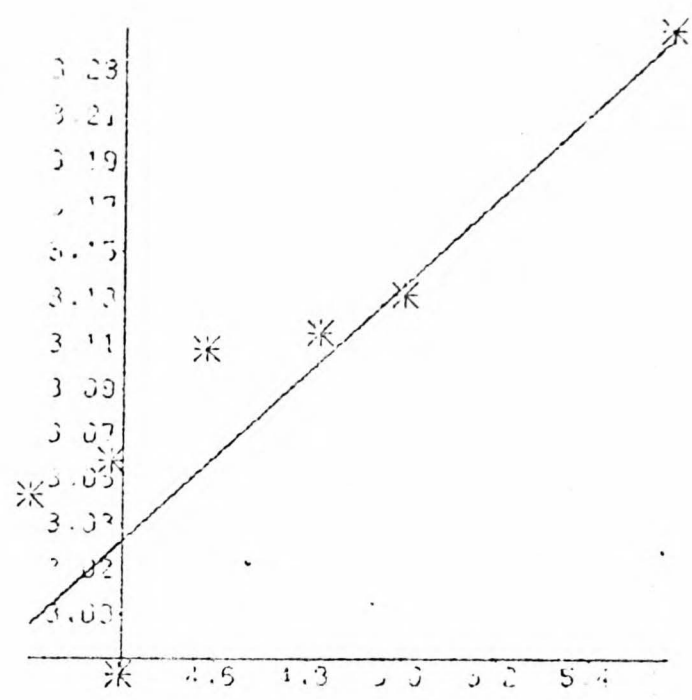


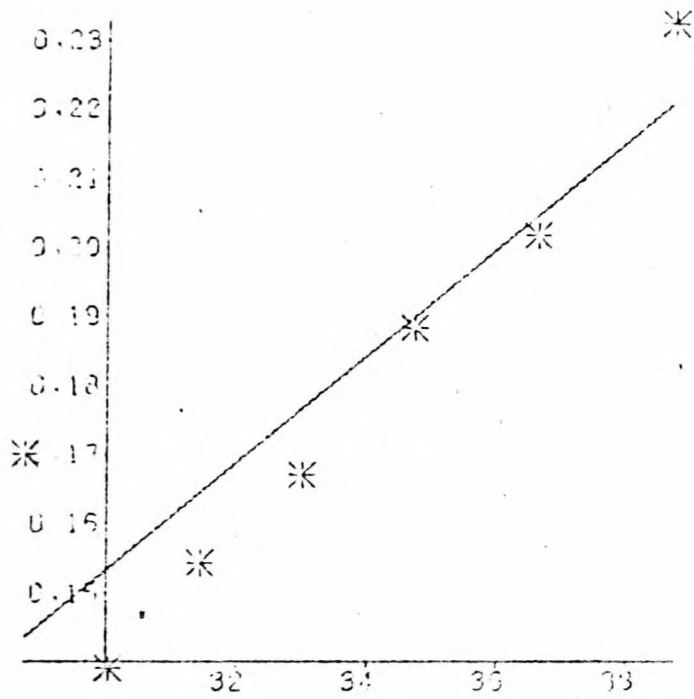
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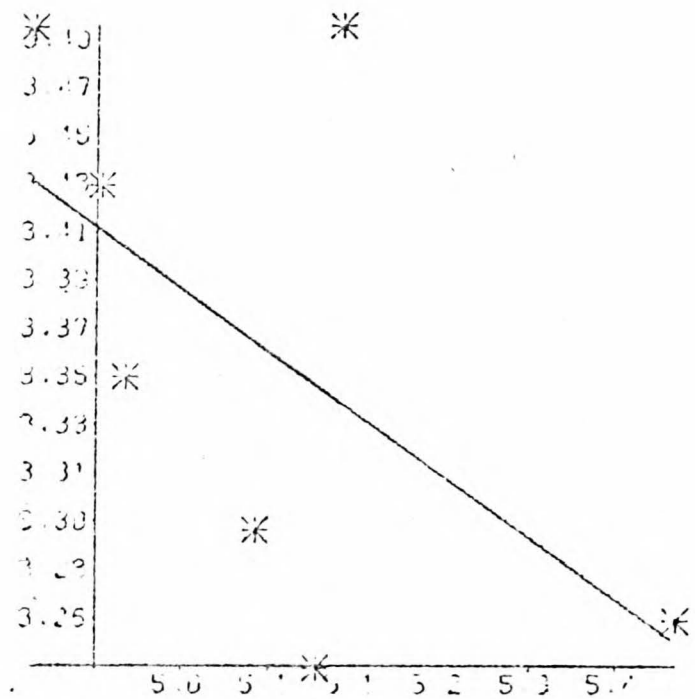
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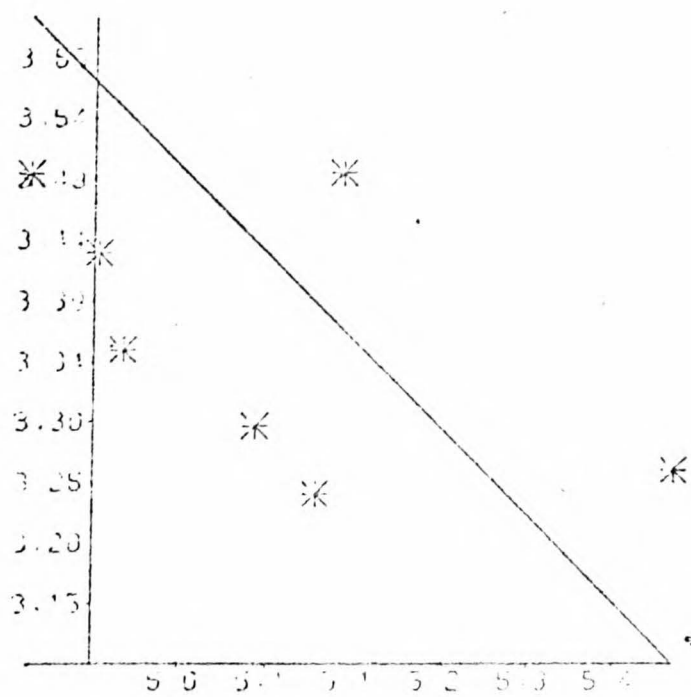
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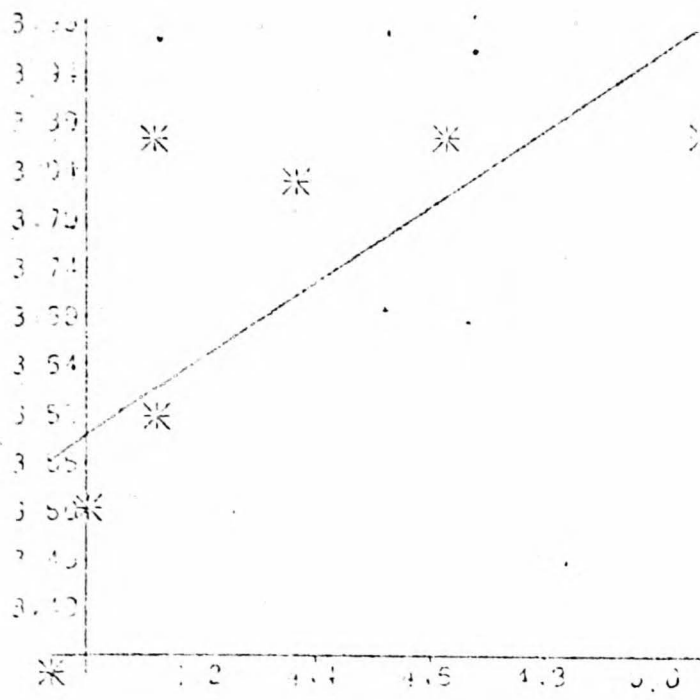


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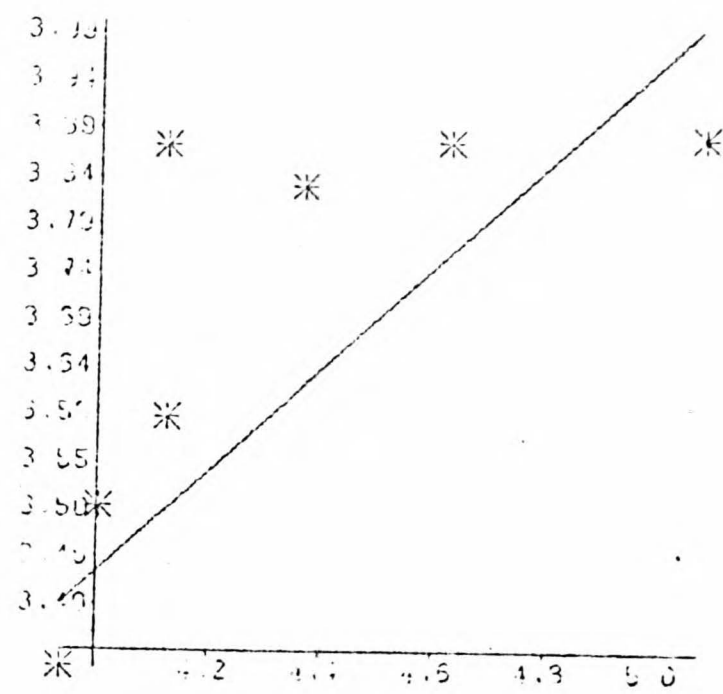


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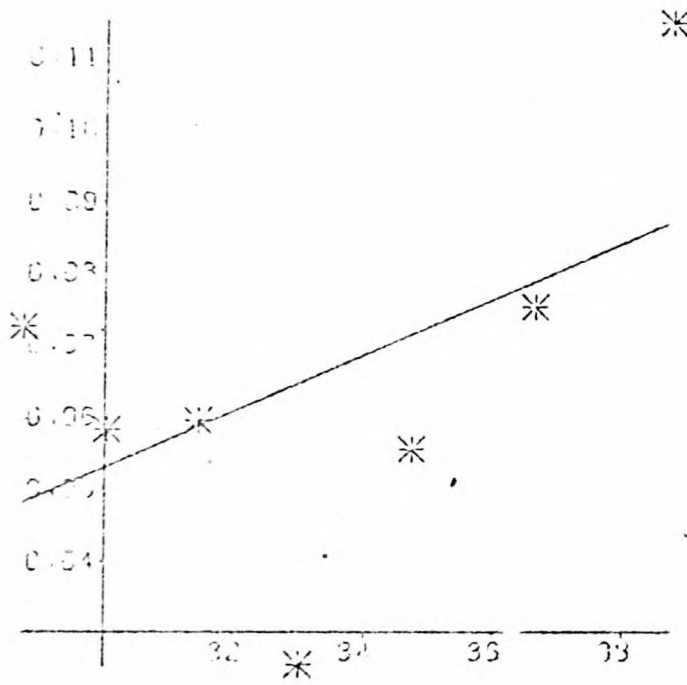
Figure 31



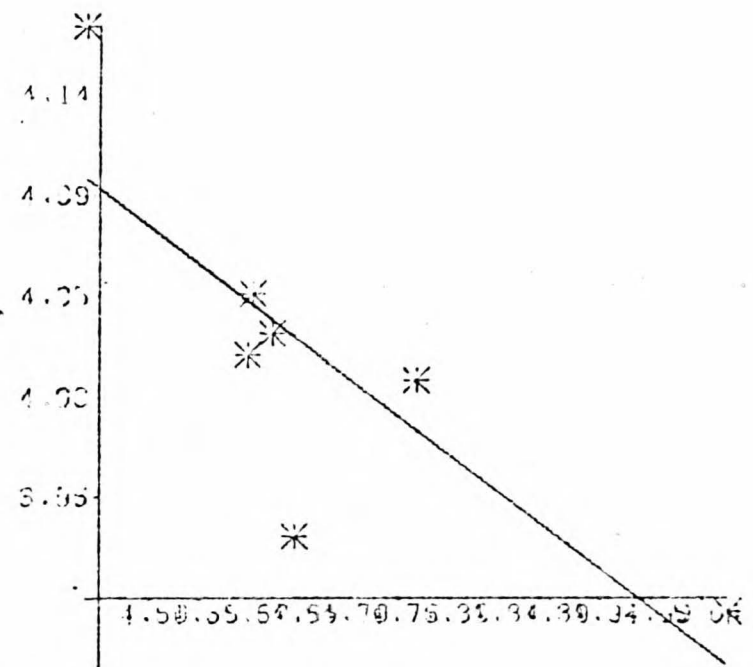
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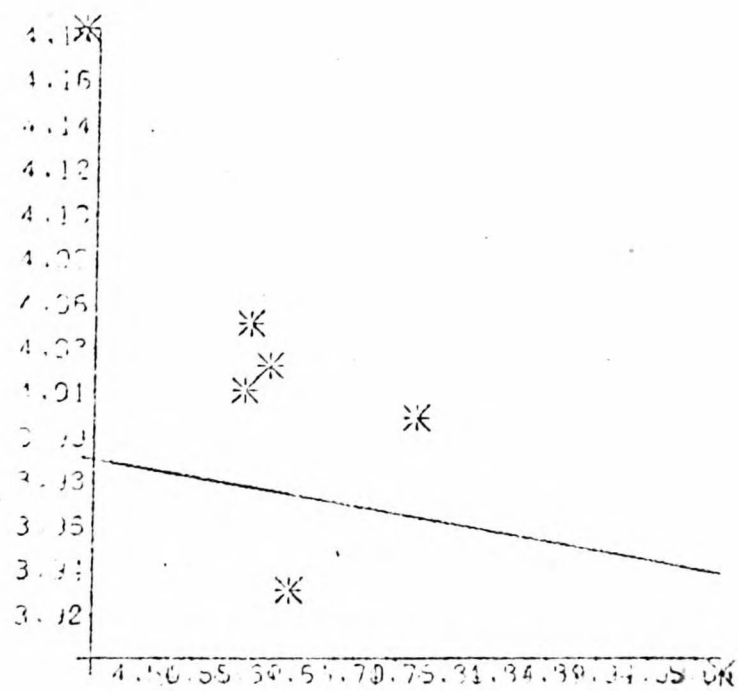
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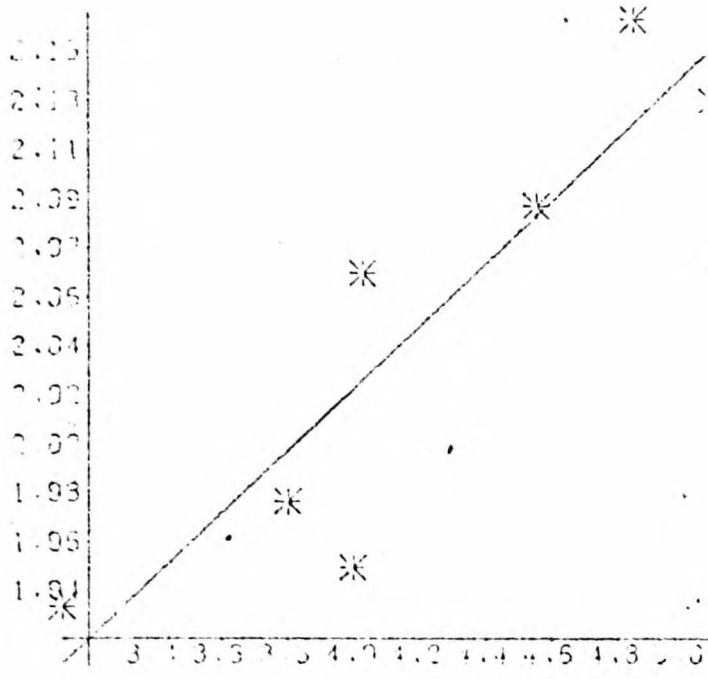


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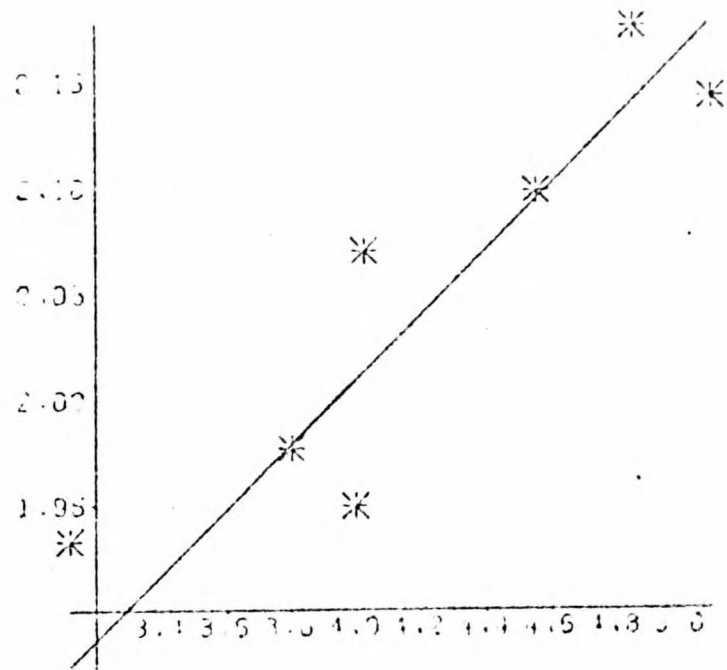


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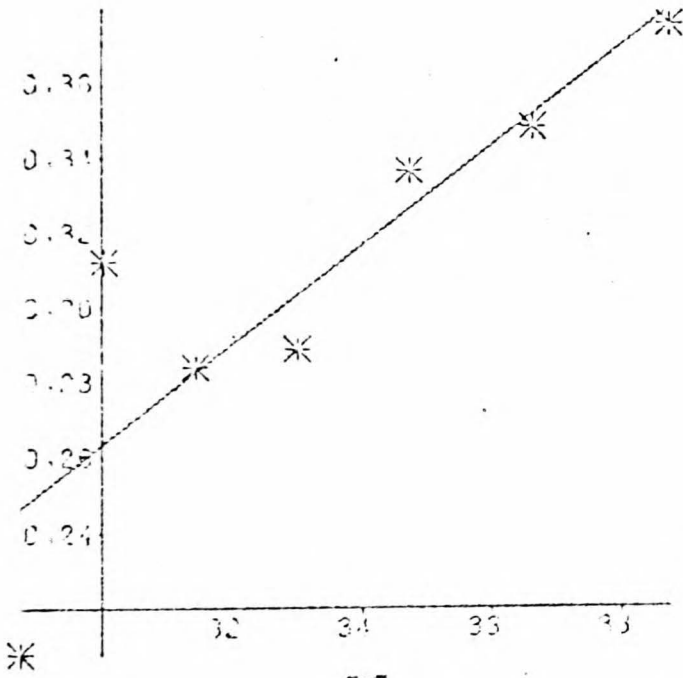
Figure 32



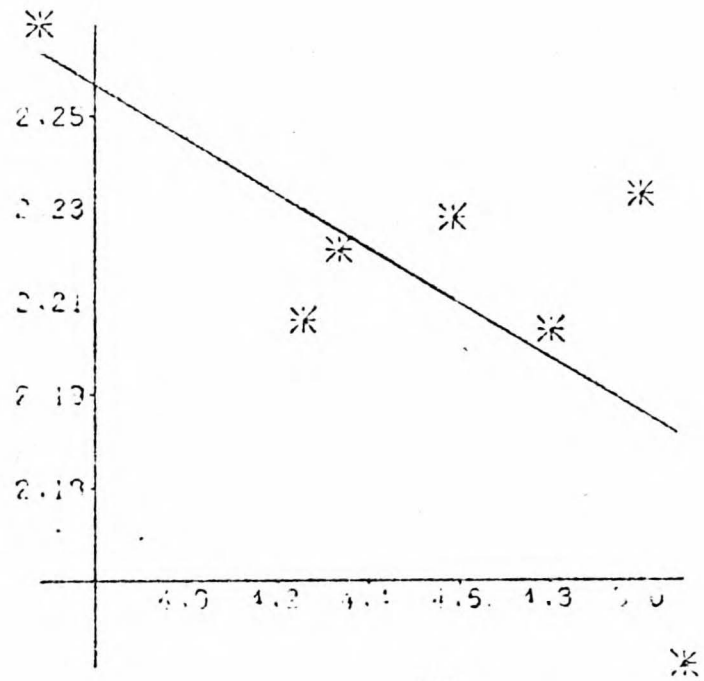
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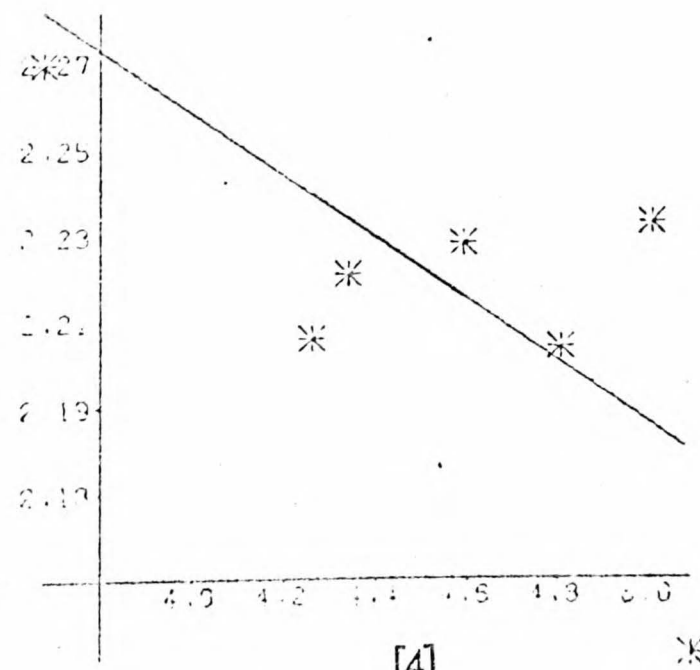
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Figure 33

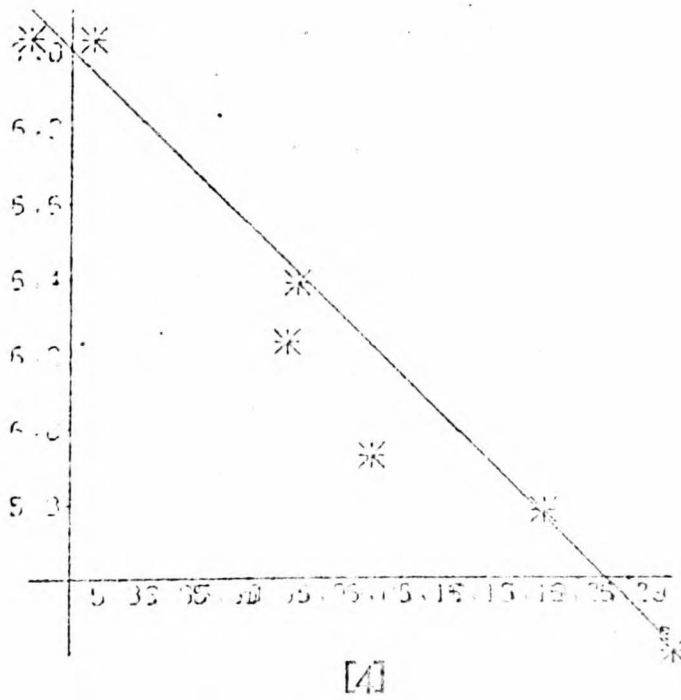
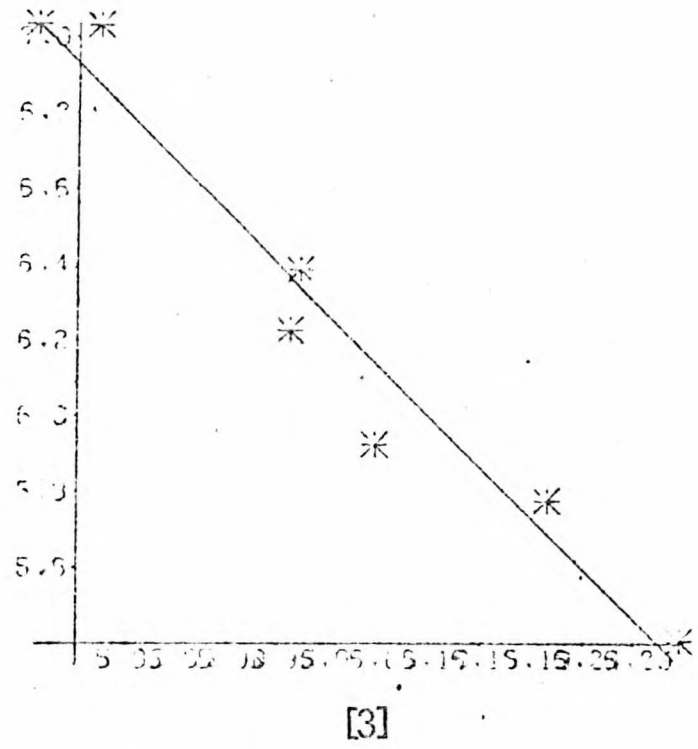
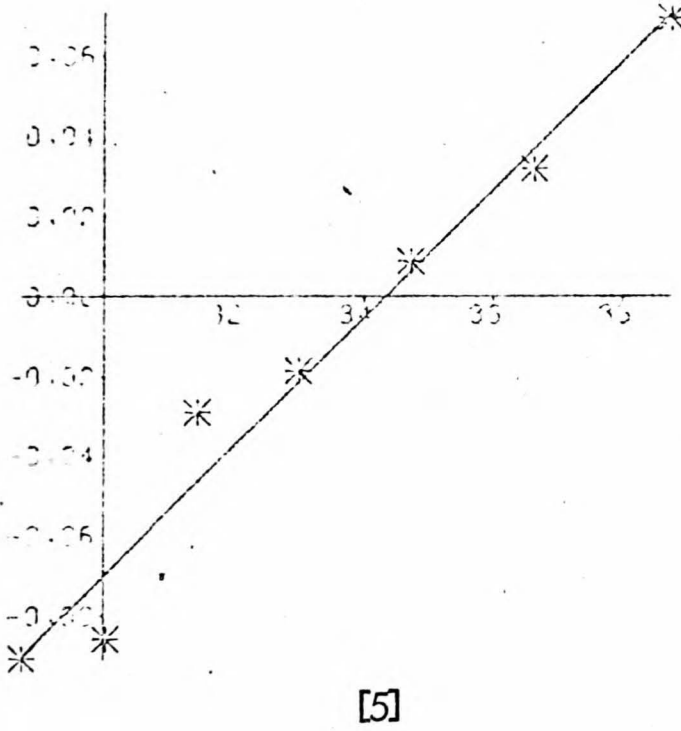
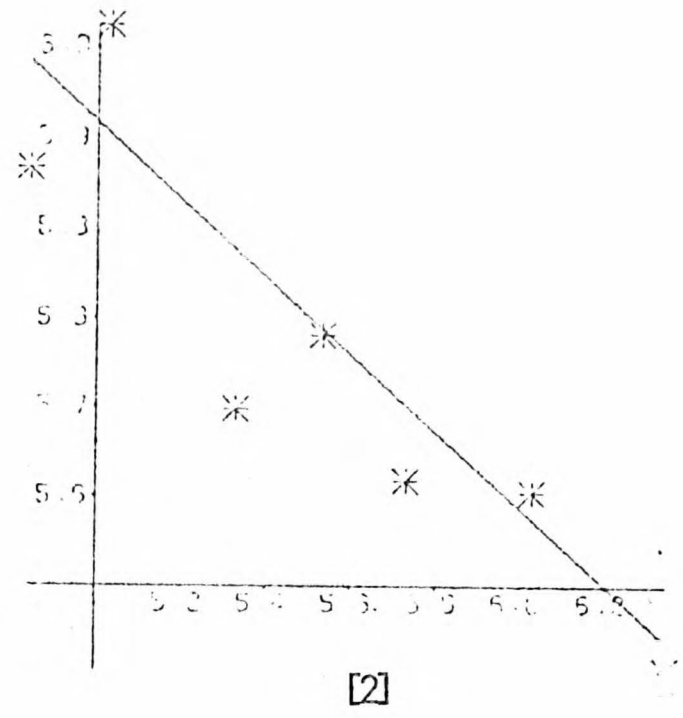
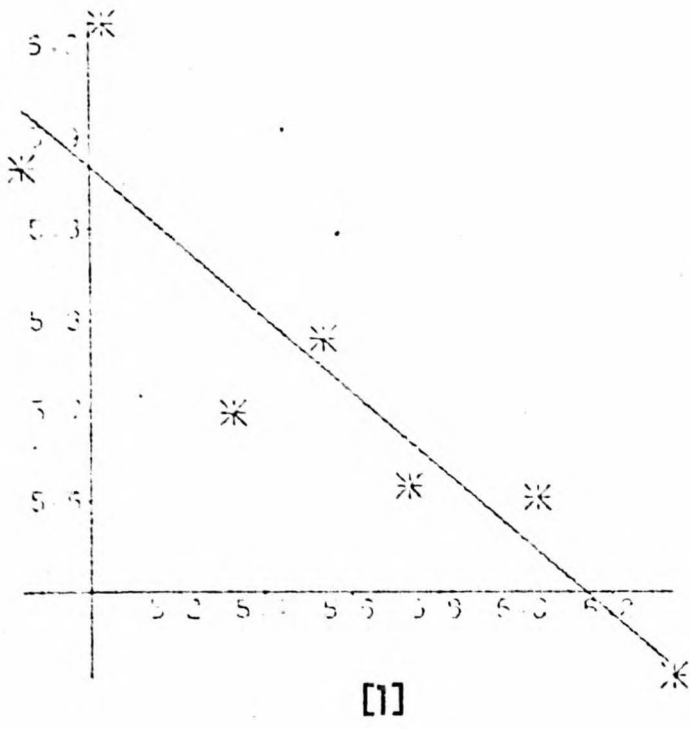
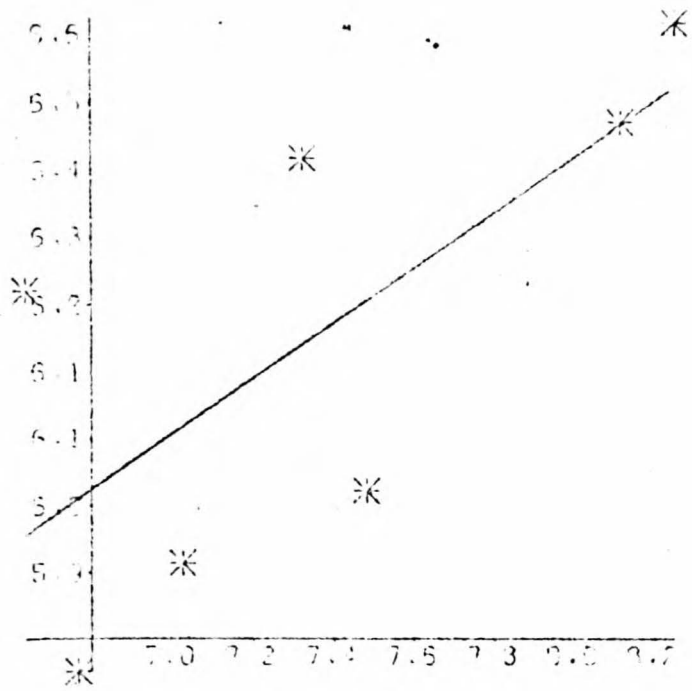
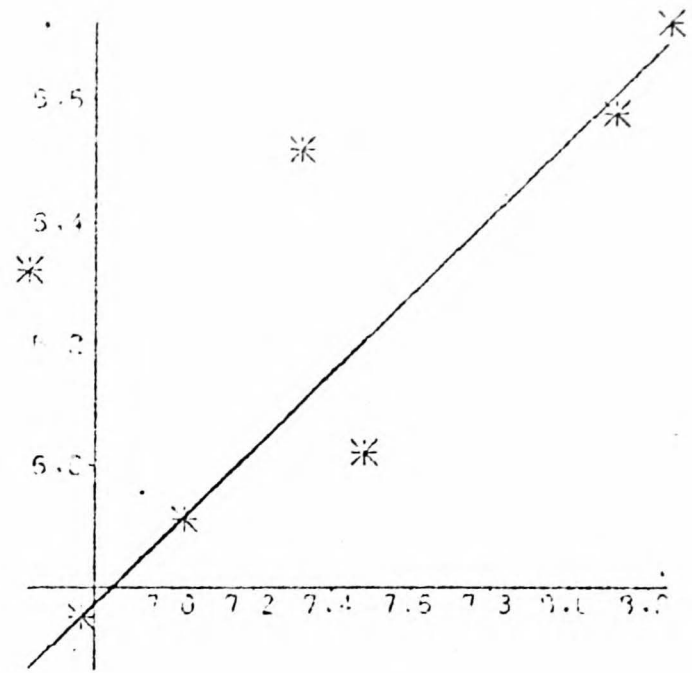


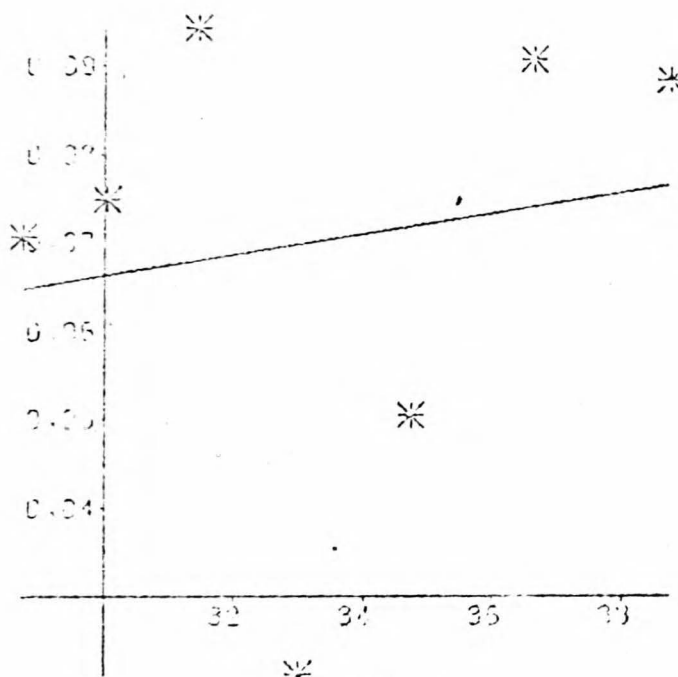
Figure 34



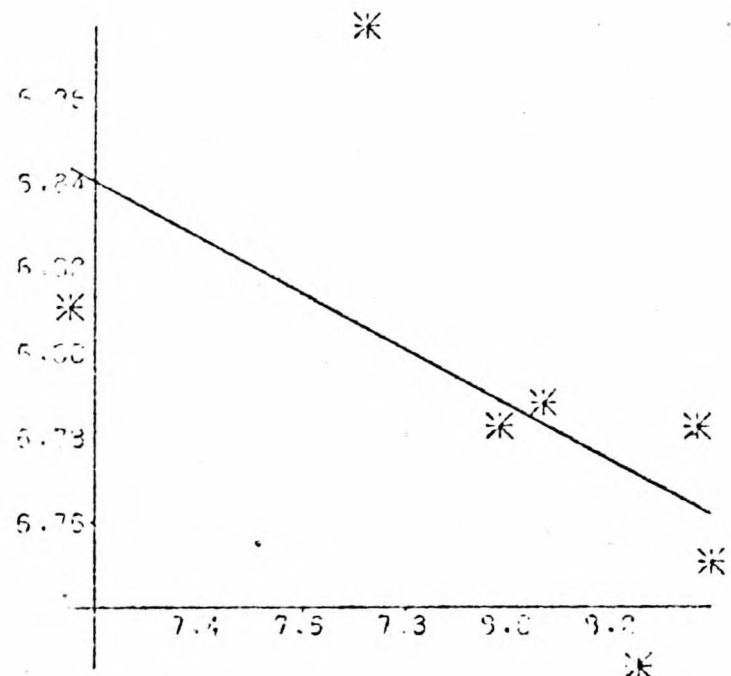
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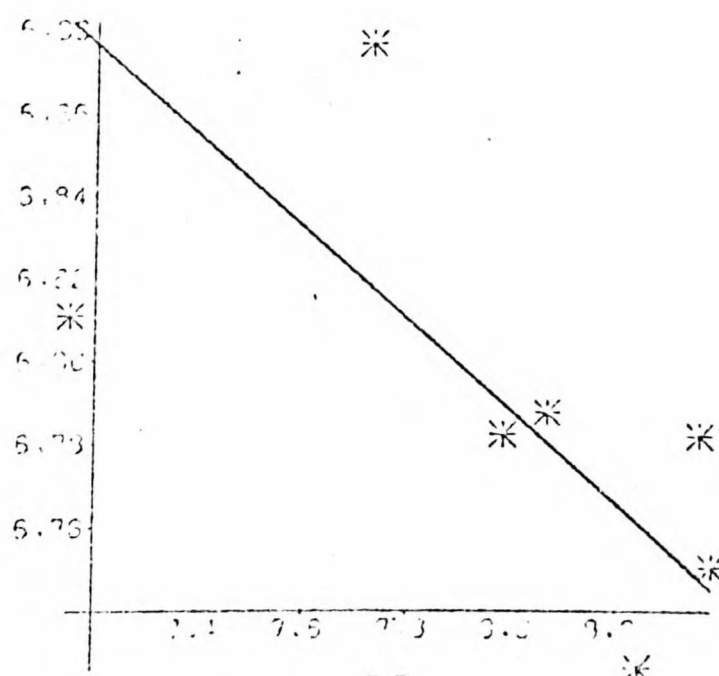
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[3]



[4]

Figure 35

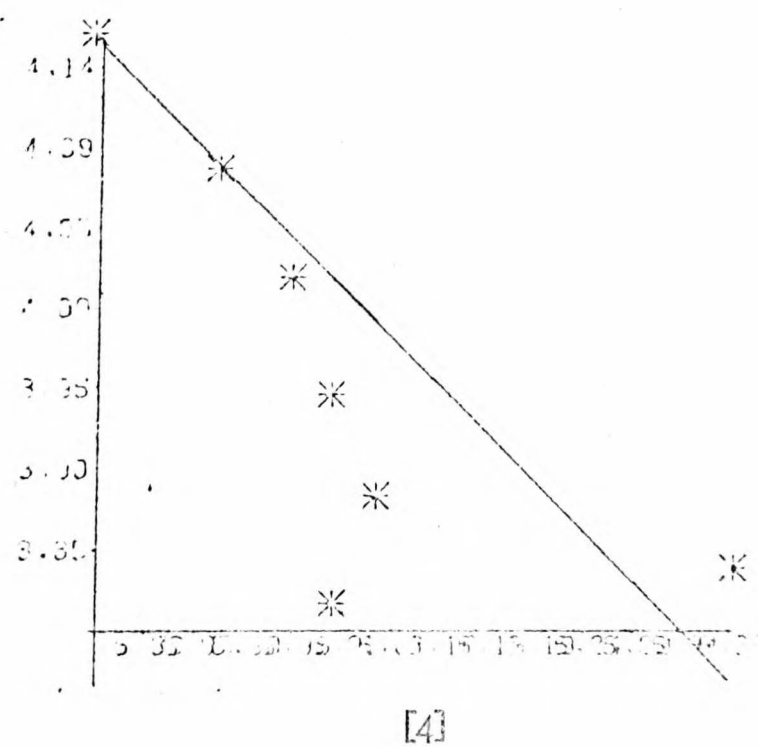
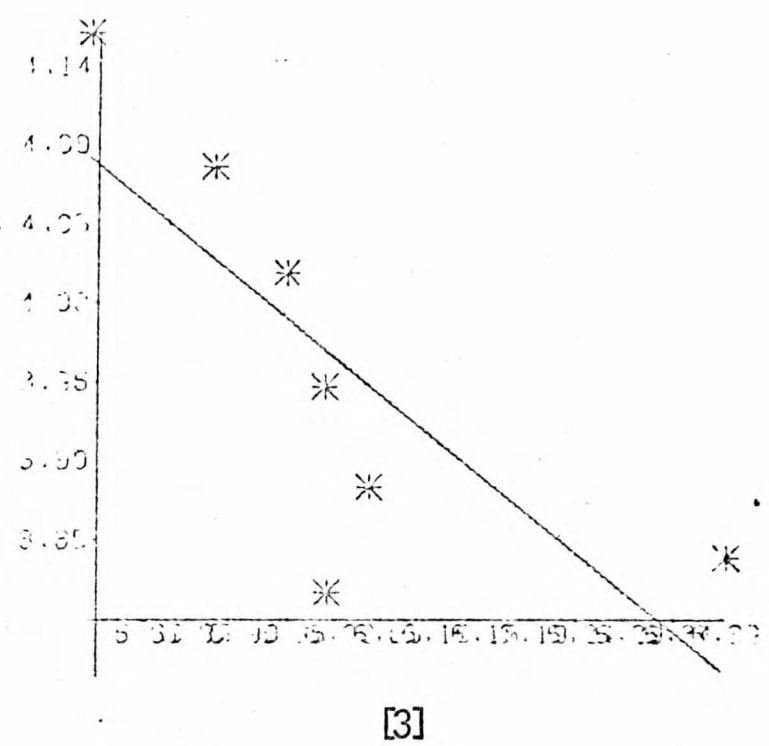
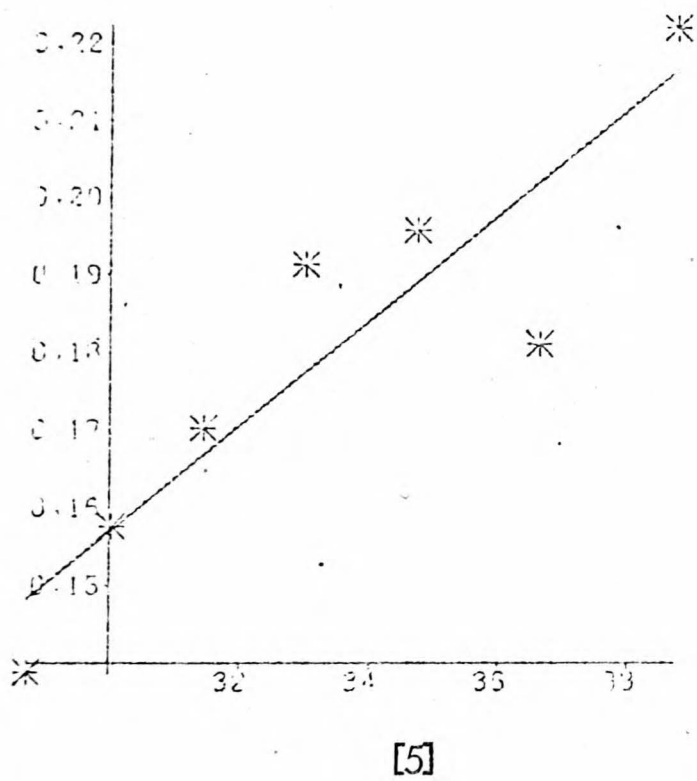
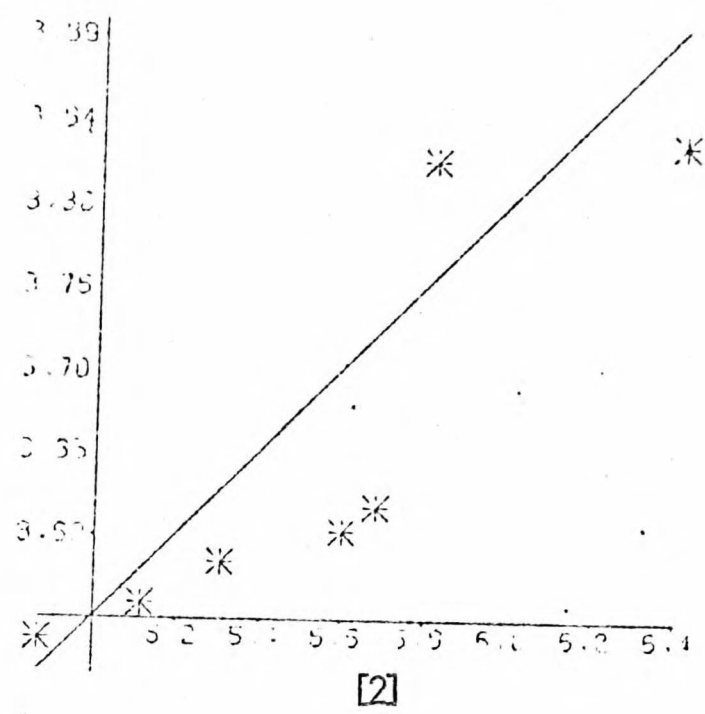
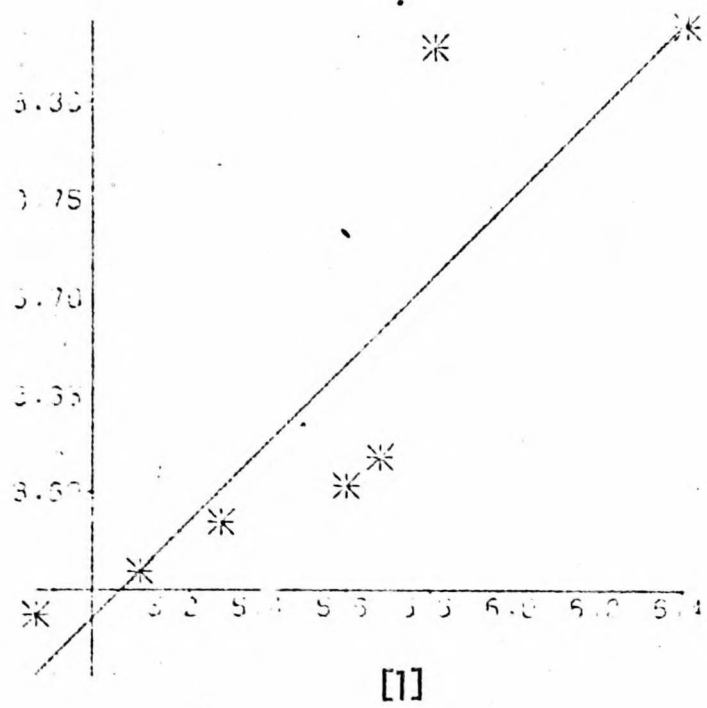


Figure 36

Compound	Graph	Slope	$A = M_0$	M_1
(CX) Analogue	[1]	0.582	22.754	0.835
	[2]	0.613	23.969	1.347
	[3]	0.458	0.852	7.207
	[4]	26.688	49.575	690.266
	[5]	46.085	0.002	0.000
(CX) Digital	[1]	0.421	0.938	0.040
	[2]	0.408	0.910	0.040
	[3]	-0.061	0.003	0.031
	[4]	-0.065	0.004	0.033
	[5]	39.592	0.001	0.000
(CXI) Analogue	[1]	3.856	84.975	1.448
	[2]	4.500	99.161	2.138
	[3]	-0.121	1.609	0.190
	[4]	-0.122	1.626	0.196
	[5]	-99.578	0.008	0.000
(CXI) Digital	[1]	0.719	1.210	0.024
	[2]	0.730	1.228	0.029
	[3]	0.227	0.019	0.012
	[4]	0.385	0.032	0.018
	[5]	18.385	0.000	0.000
(CXII) Analogue	[1]	-0.088	1.218	0.042
	[2]	-0.087	1.205	0.055
	[3]	-1.090	11.760	22.935
	[4]	-11.697	126.194	359.057
	[5]	129.564	0.013	0.000

-183-				
(CXII) Digital	[1]	0.170	0.038	0.002
	[2]	0.191	0.043	0.002
	[3]	-0.257	0.024	0.010
	[4]	-0.720	0.069	0.033
	[5]	77.471	0.005	0.000
(LXXXIII)	[1]	0.399	0.158	0.030
	[2]	0.538	0.213	0.048
	[3]	-0.378	0.034	0.004
	[4]	-0.084	0.008	0.011
	[5]	39.122	0.001	0.001
(LXXXIV)	[1]	0.129	0.046	0.002
	[2]	0.154	0.055	0.003
	[3]	-0.059	0.005	0.001
	[4]	-0.073	0.006	0.001
	[5]	133.204	0.014	0.001
(LXXXVI)	[1]	-0.409	0.287	0.012
	[2]	-0.430	0.302	0.014
	[3]	-2.670	2.177	0.021
	[4]	-2.671	2.178	0.029
	[5]	160.857	0.020	0.000
(LXXXVIII)	[1]	0.420	0.415	0.082
	[2]	0.640	0.632	0.127
	[3]	-0.066	0.005	0.002
	[4]	-0.111	0.008	0.002
	[5]	11.976	0.000	0.001
(LXXXIX)	[1]	0.218	0.073	0.005
	[2]	0.256	0.085	0.007
	[3]	-0.493	0.061	0.009
	[4]	-0.601	0.075	0.013
	[5]	68.498	0.004	0.000

Table 48

The thermodynamic parameters calculated for the compounds are listed in Table 49. Values of ΔG° and ΔS° derived from area ratios which have been corrected neither for the α -ratio nor for the natural decrease are not included: no ΔG° and ΔS° values are therefore included for (CX) analogue or for (CXI) digital. The units, conventions and statistical errors are those of Table 46.

Compound	ΔH°	ΔG°_{303}	$\Delta G^\circ_{303}(m)$	ΔS°	$\Delta S^\circ(m)$
(CX) Analogue	-882	-	-	-	-
(CX) Digital	-758	6104	5928	-22.7	-22.1
(CXI) Analogue	1907	4535	4509	-8.5	-8.5
(CXI) Digital	-352	-	-	-	-
(CXII) Analogue	-2481	-847	-6826	-5.5	14.2
(CXII) Digital	-1483	2452	-142	-12.8	-4.2
(LXXXIII)	-749	2301	6104	-9.3	-21.9
(LXXXIV)	-2551	5458	4924	-26.2	-24.4
(LXXXVI)	-3080	-2364	-2366	-2.4	-2.4
(LXXXVIII)	-229	6711	5418	-22.9	-17.7
(LXXXIX)	-1312	671	153	-6.8	-5.1

Table 49

With very few exceptions, the following general conclusions apply: (i) the conformers responsible for the lower frequency components of carbonyl band doublets are thermochemically more stable but thermodynamically less stable than the conformers responsible for the higher frequency components; (ii) the conformers responsible for the lower frequency components have lower entropies in solution than the higher frequency conformers, and (iii) the introduction of the natural

decrease correction causes a distinct improvement in the slopes of the A_h vs. A_l plots. The extra thermochemical stability of what is presumed to be the anti conformation may be a consequence of increased conjugation in this form, although since all the enthalpy values are small and many are smaller than the assumed error too much significance should not be given to the actual values. The negative values for ΔS° are surprising since it seems likely that the higher entropies of the syn forms are a result of reduced solvent ordering, yet it is thought (see previously) that the syn forms are more polar than the anti forms. It may be that it is naïve to assume that there is a direct correlation between molecular dipole moment and degree of solvation, since molecular polarisability must also be involved. As was noted in Table 46, the differences between the parameters derived from the means and least squares methods once again emphasise the difficulty in estimating the best straight line between variables when both variables are subject to large errors. The differences between the analogue- and digital-derived results (which are often greater than the assumed experimental errors), and the poor correlation between the data from the steroidal esters (which required three-band resolutions) and the data from the simple esters emphasise the general problems associated with all methods of curve resolution. It may well be that these problems provide an insuperable stumbling block to the use of i.r. curve areas for the evaluation of accurate thermodynamic parameters. The boldness of this statement is justified by the results of Experiment 34.

Methods of Curve Resolution: A Comparison

Experiment 34. Since the analogue and digital methods of curve resolution gave appreciably different answers for the thermodynamic parameters for furan-2-

carboxylates, it was decided that an experiment should be devised which would provide an accurate assessment of the relative merits not only of the analogue and digital methods, but also of the various so-called graphical methods. The experiment carried out (Experiment 34) involves the artificial overlap by computer of two single i.r. carbonyl bands, the degree of overlap being controlled by the programmer. The extent of overlap was varied from maximal, where the second band was only detectable as an inflection on the shoulder of the first, to minimal, where two virtually independent bands were obtained.

The results (which are presented in Table 38) show that at minimal overlap, all methods of curve area estimation give more or less the same result. However, as the degree of overlap increases, the accuracy of the methods varies considerably. At large overlap, both the analogue and the digital methods tend to equalise the component band areas hence producing inaccurate, although mathematically acceptable, solutions. Thus for an overlap as great as or greater than 3 (vide Table 38 and Figure 22) the digital method can lead to considerable errors, whereas the analogue method can lead to errors even at the extent of overlap labelled 4. Of the "graphical" methods, the method of outer halves yields unpredictable results and the method of the minimum tends to equalise areas at large overlap; the method of the mid-point however gives consistently good estimates even at large overlap. The method using optical densities also provides a good estimate of the areas, even at large overlap, although there appears to be a consistent tendency towards under-estimation.

At the risk of being accused of arguing from the particular to the general, the author therefore concludes that if area ratios of overlapped doublet carbonyl absorptions are required then the method of the mid-point (using computer

integration) should always be used, and that for an overlap as great as 1 (Figure 22) there is no method which can be relied upon to produce the true answer. If the shapes of the component curves are required, then, of course, analogue and digital curve resolutions must be attempted. In the cases considered previously, the degree of overlap is probably in the region of 4 and the errors involved are not then too great; it should, however, be borne in mind that to use computed resolutions for overlaps greater than 4 courts disaster.

B. Nuclear Magnetic Resonance Investigations

Experiments 35 and 36. Because furan-2-carbaldehyde, in its proton n.m.r. spectrum, shows a coalescence phenomenon at about -90°C (vide "Introduction"), which is a consequence of stereospecific long-range spin-coupling between the aldehydic hydrogen atom and the ring hydrogen atoms at positions 4 and 5, it was thought desirable to examine the proton n.m.r. spectrum, at low temperatures, of furan-2-carbonyl fluoride (Experiment 35). In this compound, all of the ring protons show long-range coupling to fluorine, which is in accordance with a recent re-examination of the furan-2-carbaldehyde n.m.r. spectrum⁹⁵ which demonstrates the existence of a previously unobserved, small coupling to the hydrogen at position 3. Although a coalescence phenomenon was not observed at temperatures down to -70°C , a gradual disappearance of one of the couplings (presumed to be the H-F coupling) for the hydrogen atom at position 4 but not at position 5 was noted as the temperature was lowered. This may be a consequence of stereospecific hydrogen to fluorine coupling, the molecule preferentially adopting one conformation, as the temperature is lowered, in which there is very little long-range coupling to the hydrogen atom at position 4.

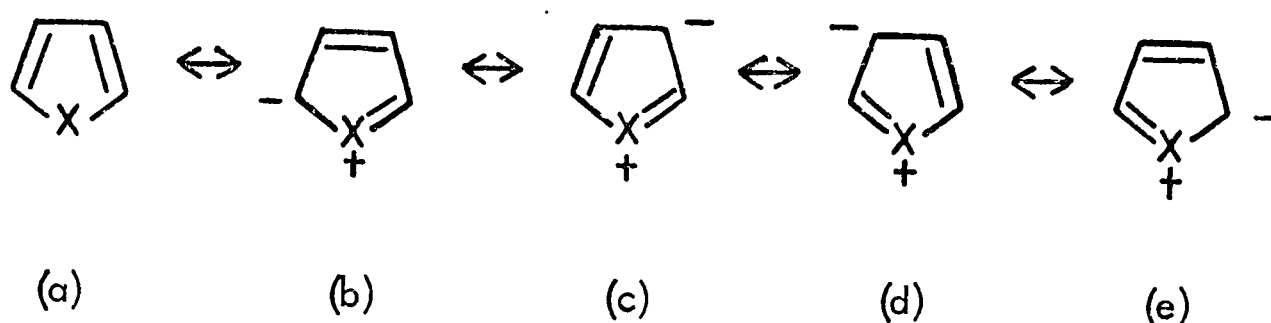
A similar lack of a "coalescence" phenomenon is to be found in the carbon-13 spectrum of methyl furan-2-carboxylate (Experiment 36), whereas for furan-2-carbaldehyde, at about -45°C , collapse and broadening of the C-13 signals assigned to the carbonyl carbon atom and to the carbon atom at the 3-position is observed (these carbon atoms are the ones that are most likely to be affected by hindered rotation about the ring-carbonyl carbon bond). It seems that the barrier to internal rotation about the ring-carbonyl carbon bond is lower in esters and acid halides than in aldehydes. This may be a consequence of reduced π -electron donation from the ring when an atom or group with a positive mesomeric effect is attached to the carbonyl carbon atom.

DISCUSSION - PREPARATIVE

In order to achieve the aims outlined previously, it was necessary, in the preparative phase of the work, to synthesise a wide range of substituted furans, and to devise and investigate routes to specifically deuterated derivatives of furan and thiophen.

The five-membered aromatic heterocyclic compounds furan, thiophen, and pyrrole are described as consisting of planar arrays of atoms in which the sp^2 -hybridised carbon atoms each has one electron in a p_z -orbital and the hetero-atoms two such electrons; overlap between the p_z -orbitals produces "aromatic sextets". The experimental evidence upon which this description is based is plentiful: i.r., Raman, and microwave spectra indicate that the rings are planar;^{103,104} bond lengths are intermediate between those characteristic of pure single bonds and pure double bonds;¹⁰⁵ the molecular diamagnetic susceptibilities are greater than would be predicted from Pascal's constants;¹⁰⁶ the rings are able to sustain an induced ring current as evinced by the deshielding of the ring protons in n.m.r.,¹⁰⁷ and the compounds display, to varying degrees, a tendency to undergo substitution, rather than addition, reactions.

Compared with benzene, these compounds are highly reactive towards¹⁰⁸ electrophiles, this being a consequence of the unsymmetrical charge distributions whereby the carbon atoms possess a greater electron density than the carbon atoms of benzene. The Hammond postulate predicts that for such reactive substrates, the position at which electrophilic substitution preferentially occurs will be governed by the electron distribution in the ground-state molecules. Using the valence-bond treatment, the five most important ground-state canonicals are:

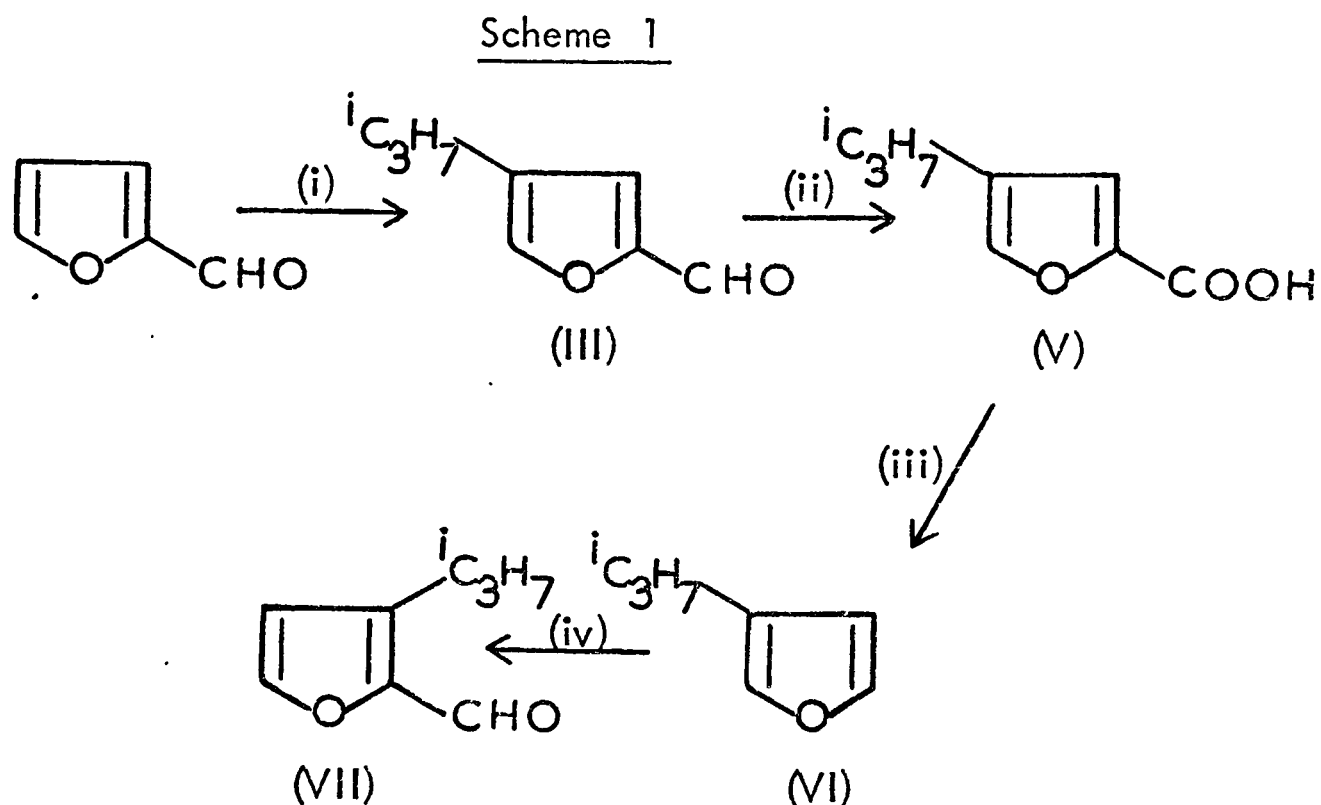


(a) is of greatest importance since no charge separation is involved, and (b) and (e) are thought to be more important than (c) and (d) since there is greater charge separation in the latter and conjugation is through the hetero-atoms. Thus, electrophilic substitution is predicted to occur preferentially at the 2- and 5- (α -) positions, a conclusion which would also have been reached had the stabilities of the reaction intermediates been considered. This α -preference is especially marked in furans where, even when an electron-withdrawing group is present at position 2, further substitution is almost always at position 5. Possibly the only exception to this rule is that furan-2-carbaldehyde is alkylated with isopropyl chloride and anhydrous aluminium chloride at position 4 to give 4-isopropylfuran-2-carbaldehyde (vide infra).

The preparative work, which is discussed below, is grouped under headings which allow cross reference between this section and the spectroscopic sections.

Furan-2-carbaldehyde C=O band assignment. The approach adopted to this problem required the syntheses of 3-, 4-, and 5-isopropylfuran-2-carbaldehydes, the isopropyl group being chosen because of the ready synthesis of 4-isopropyl-

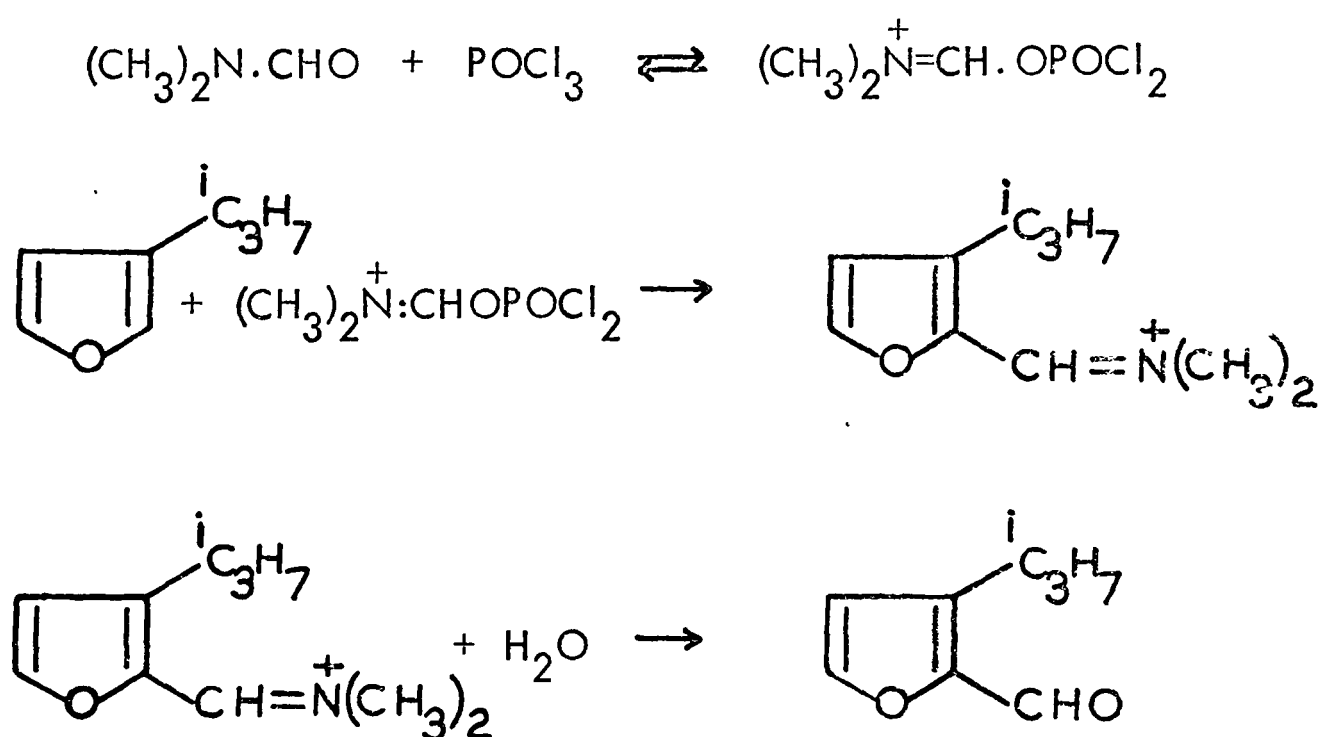
furan-2-carbaldehyde (III). . Scheme 1 shows the route adopted to 3-isopropylfuran-2-carbaldehyde (VII).



Reagents: (i) $\text{AlCl}_3\text{-}i\text{-C}_3\text{H}_7\text{Cl-CS}_2$; (ii) $\text{Ag}_2\text{O-NH}_3\text{-H}_2\text{O}$; (iii) Cu-bronze-quinoline, and (iv) $\text{POCl}_3\text{-(CH}_3)_2\text{N.CHO}$.

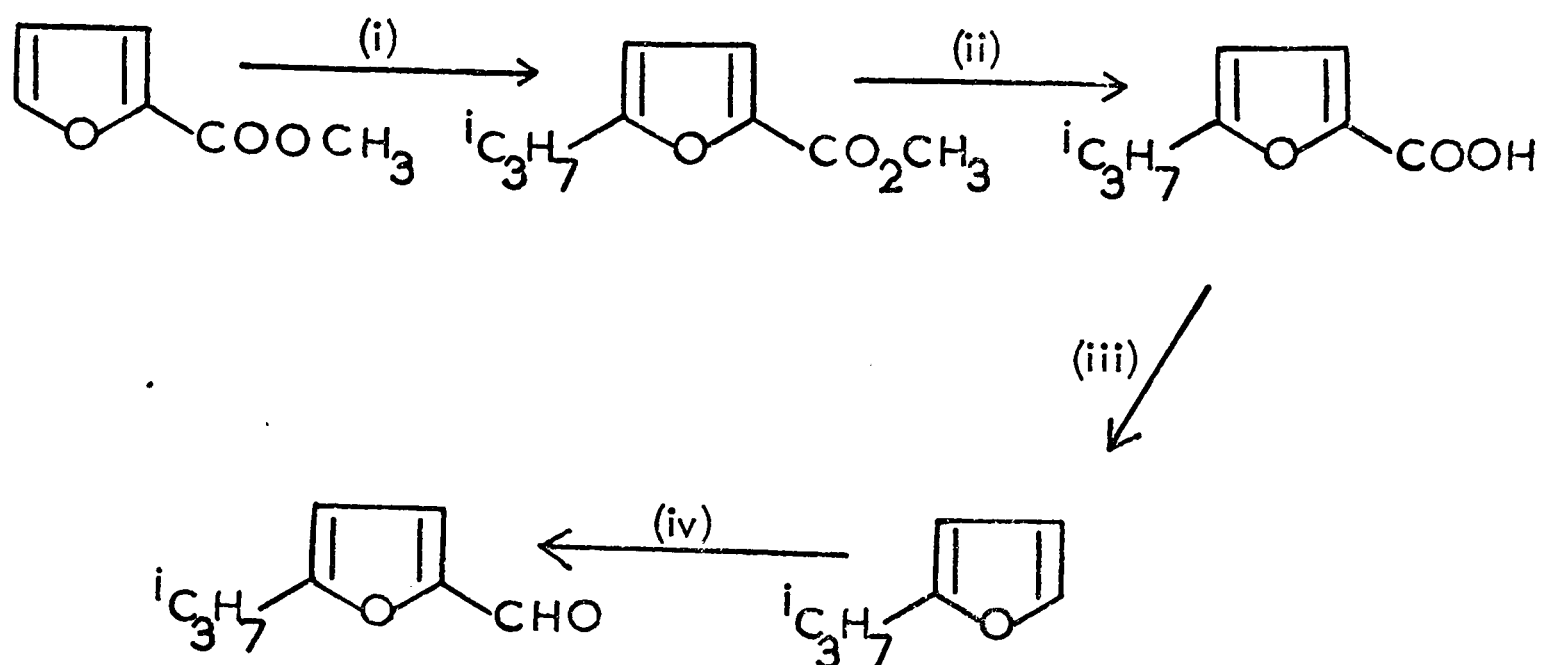
The initial isopropylation was also investigated using dichloromethane as solvent but surprisingly little product was obtained. As would be expected, the alkylation is not specific in that small amounts of the 3- and 5-alkyl compounds were detected. Furthermore, a considerable amount of 4,5-diisopropylfuran-2-carbaldehyde was formed. The yield is low partly because of polymerisation of the substrate during reaction and partly because of incomplete reaction. It was thought that the substitution of tin(IV) chloride for aluminium chloride might alter the orientation of alkylation and thus provide a route to the 5-isomer. No reaction could be detected, however, even at 150° . The oxidation step was also

investigated using a less-expensive silver oxide/copper oxide reagent but, because the latter gave unpredictable results, Tollen's reagent was preferred in this, and subsequent, Schemes. The Wilsmeier reaction [POCl_3 and $(\text{CH}_3)_2\text{N} \cdot \text{CHO}$] although giving mainly the 2,3-product also gives some 4-isopropylfuran-2-carbaldehyde: separation was achieved by multiple-elution p.t.l.c. The preference for the 2,3-product is comparable with the preference of cumene to undergo electrophilic substitution ortho and para rather than meta, since this reaction involves electrophilic attack:



An apparently straightforward route to the 5-isomer was devised (Scheme 2), the route being adopted because previous workers had claimed⁶² that the initial alkylation was satisfactory.

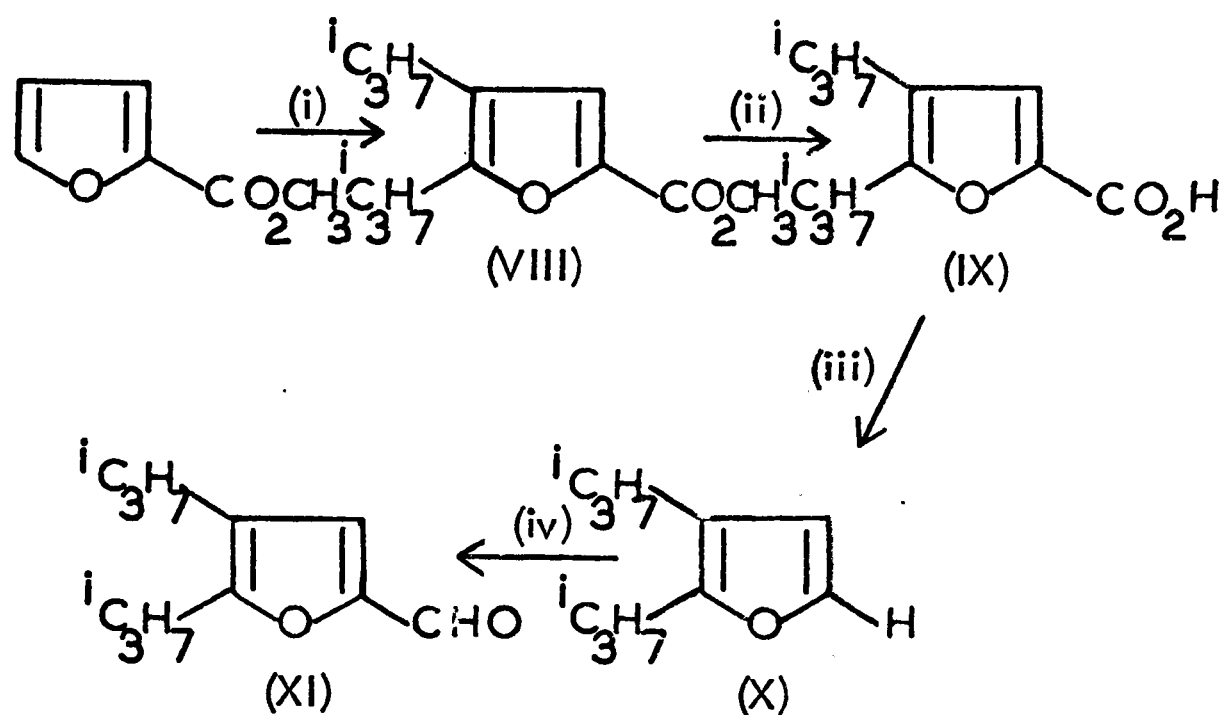
Scheme 2



Reagents: (i) AlCl₃-i-C₃H₇Cl-CS₂; (ii) NaOH-H₂O, then HCl-H₂O;
(iii) Cu-bronze-quinoline, and (iv) POCl₃-(CH₃)₂N·CHO.

However, even when only half of the quantity of halide required for mono-alkylation was used, the main product was shown to be 4,5-diisopropyl methyl-2-furoate (VIII), very little mono-isopropylated material being detected. This tendency towards polyalkylation is well known in benzenoid Friedel-Crafts alkylations, and reflects the increased reactivity of a substrate to electrophilic attack when mono-substituted with an electron-donating alkyl group. That the problem here is more acute with an ester than with an aldehyde must in part arise from the greater electron-withdrawing effect of the aldehyde function: since the 4-position is meta to an electron-withdrawing group in both aldehyde and ester, it is not surprising that the 4,5- rather than the 3,5-isomers are formed. Scheme 3 shows the reactions carried out with 4,5-diisopropyl methyl-2-furoate.

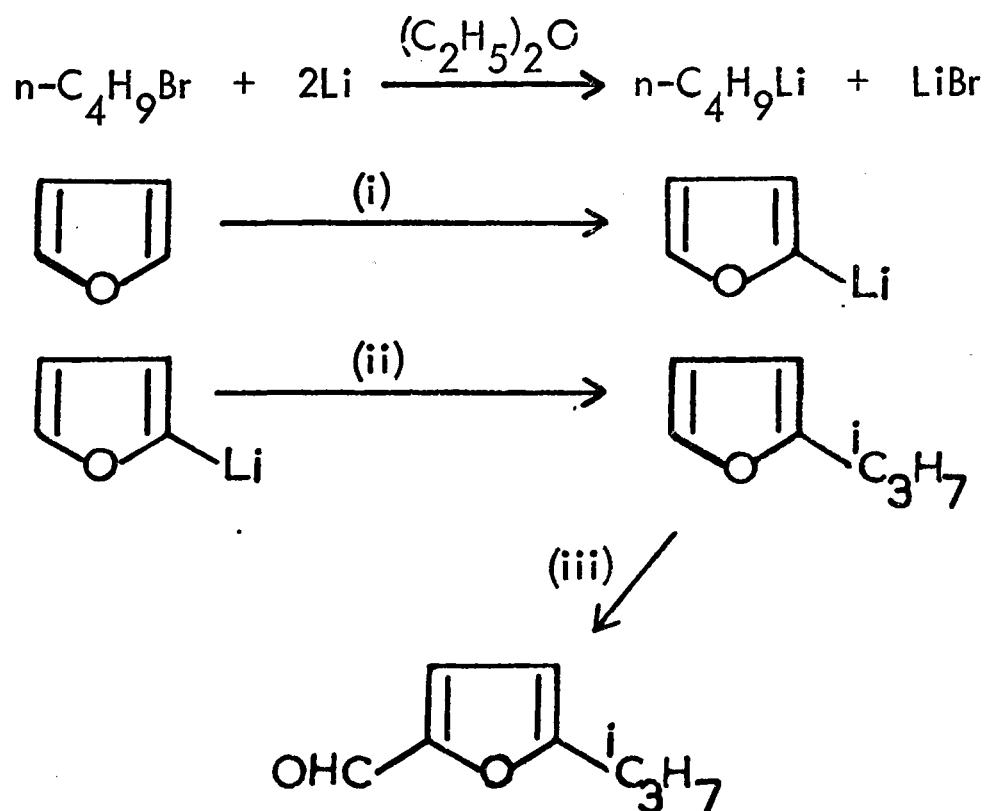
Scheme 3



Reagents: (i) $\text{AlCl}_3\text{-i-C}_3\text{H}_7\text{Cl-CS}_2$; (ii) $\text{NaOH-H}_2\text{O}$, then $\text{HCl-H}_2\text{O}$; (iii) $\text{Cu-bronze-quinoline}$, and (iv) $\text{POCl}_3\text{-(CH}_3)_2\text{N.CHO}$.

An alternative route to 5-isopropylfuran-2-carbaldehyde was devised (Scheme 4) but no 2-isopropylfuran was detected.

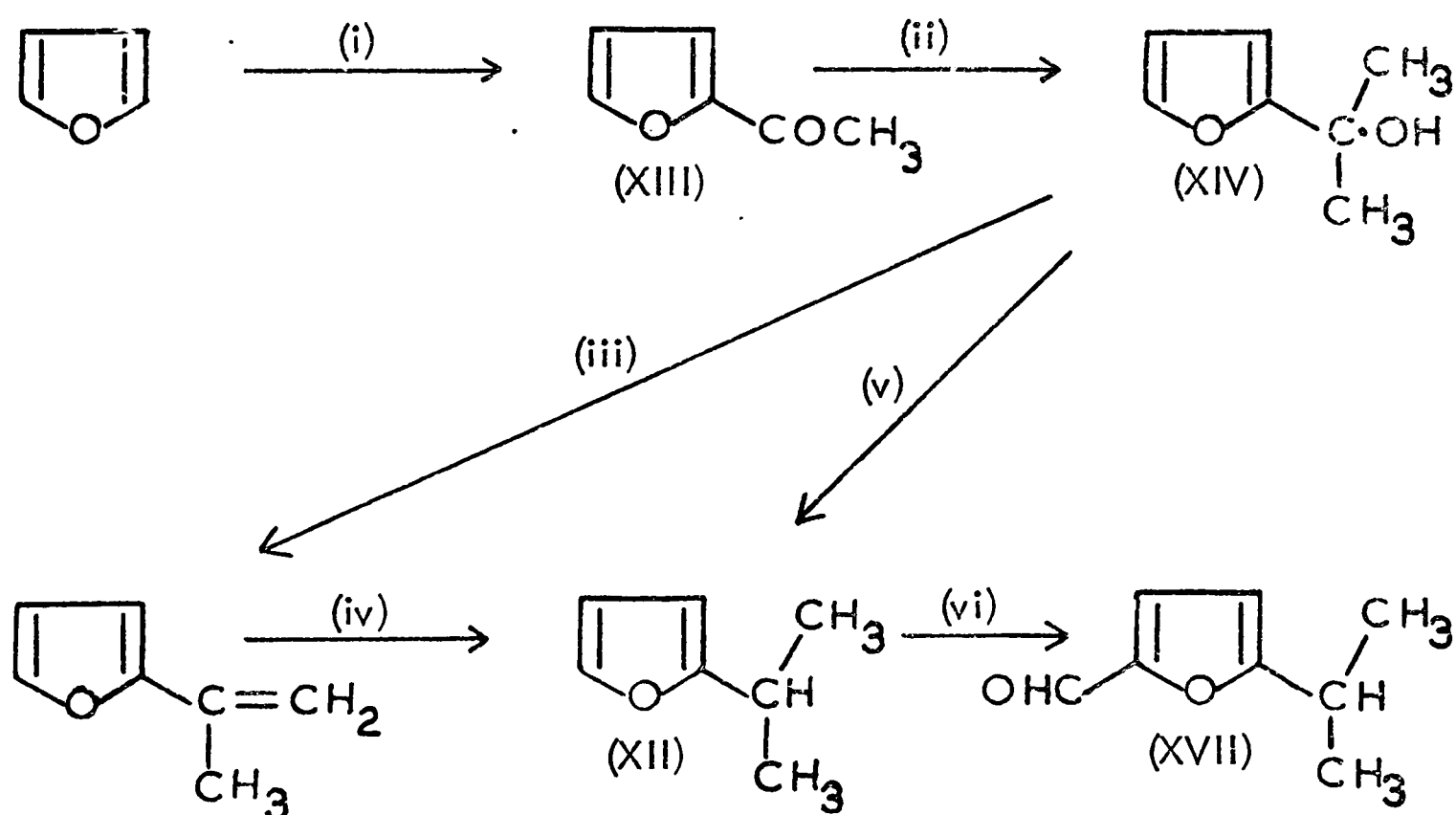
Scheme 4



Reagents: (i) $\text{n-C}_4\text{H}_9\text{Li-(C}_2\text{H}_5)_2\text{O}$; (ii) $\text{i-C}_3\text{H}_7\text{Cl-(C}_2\text{H}_5)_2\text{O}$, and (iii) $\text{POCl}_3\text{-(CH}_3)_2\text{N.CHO}$.

Since 2-furyl-lithium is said to react with n-butyl chloride in tetrahydrofuran (t.h.f.) but not in ether,⁶⁶ the reactions of Scheme 4 were repeated using t.h.f. as solvent: again, no 2-isopropylfuran was detected. In order to demonstrate that the 2-furyl-lithium was being formed, the preparation was repeated with the alteration that the solution of 2-furyl-lithium was poured on to a slurry of solid carbon dioxide and ether: the isolation of furan-2-carboxylic acid in good yield indicates that it is the failure of the substitution reaction of 2-furyl-lithium on the alkyl halide which is responsible for the failure of the Scheme. This must reflect the reduced tendency of a secondary alkyl halide to react by an S_N2 mechanism compared with a primary halide. A further route to 5-isopropylfuran-2-carbaldehyde was therefore devised (Scheme 5).

Scheme 5

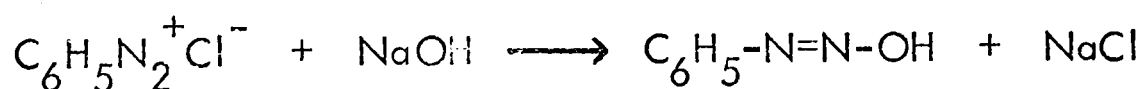


Reagents: (i) $(CH_3CO)_2O \cdot BF_3 \cdot (C_2H_5)_2O$; (ii) $CH_3MgI \cdot (C_2H_5)_2O$; (iii) $(CH_3CO)_2O$ -boil; (iv) $H_2 \cdot PtO_2$; (v) $PtO \cdot (C_2H_5)_2O \cdot HCl$, and (vi) $POCl_3 \cdot (CH_3)_2N \cdot CHO$.

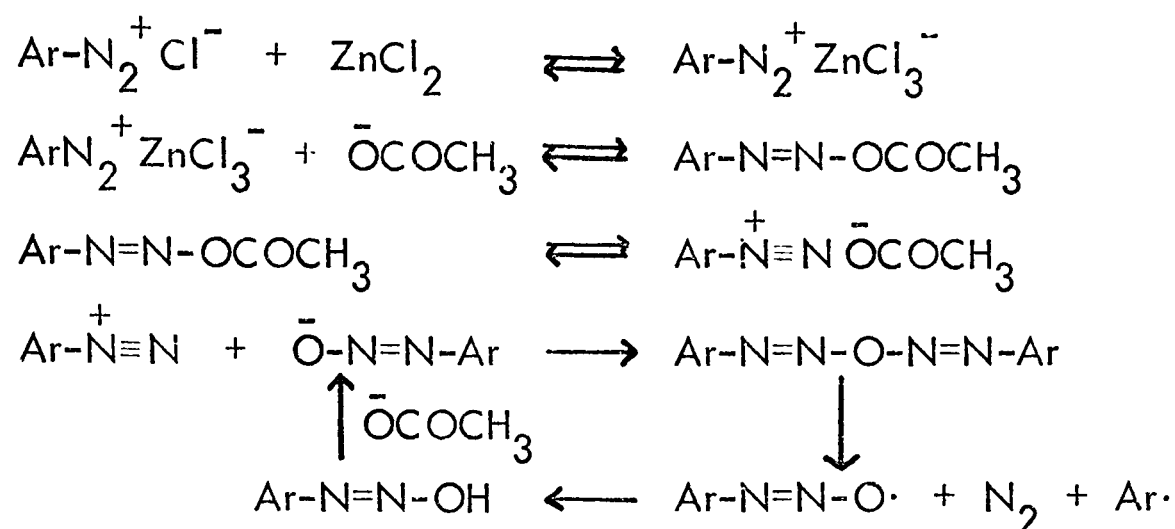
In the route initially adopted, the isolation of 2-(2-furyl)propene was avoided by attempting to dehydrate and to hydrogenate in the same step. Although hydrogen was taken up rapidly, the resulting product was shown to consist mainly of ring-reduced material. The successful approach involved the isolation of 2-(2-furyl)-propene which was subsequently hydrogenated. Yields are poor owing to extensive polymerisation of the olefin.

Solid-state studies. It was originally intended to synthesise a substituted furan which in the solid state would exist as one rotational isomer only and to determine the structure by X-ray crystallography. It was then hoped to correlate solid state with solution i.r. spectra and hence determine structures of substituted furans in solution. Theoretical considerations suggested that 5-substituted furan-2-carbaldehydes would be suitable, and a selection of 5-arylfuran-2-carbaldehydes was therefore synthesised using a modified Gomberg procedure. In all cases, a large excess of furan was used since this improves yields, possibly by reducing the tendency of aryl radicals to polymerise.

For 2-phenylfuran (XX), Johnson's procedure⁷¹ (in which an aqueous benzenediazonium chloride solution is stirred vigorously with furan and an aqueous sodium hydroxide solution for two days) was adopted. A covalent diazohydroxide (which acts as a source of phenyl radicals) is formed:

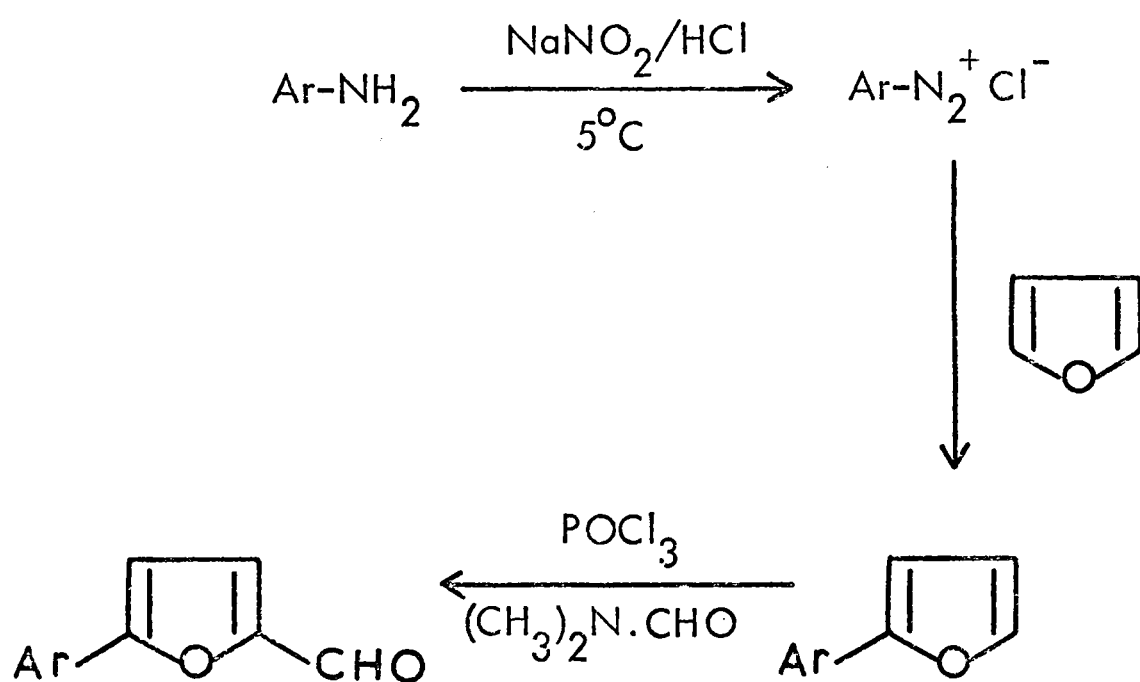


Further aryl furans were synthesised using a modification of this procedure in which the stabilised zinc diazonium salt is suspended along with powdered sodium hydroxide and sodium acetate in a large excess of furan. The reaction probably proceeds via a diazoacetate which decomposes to aryl radicals:



Yields can be improved considerably by using this modification since the rate of generation of radicals and hence their tendency to polymerise is reduced. The syntheses which were carried out are summarised in Scheme 6.

Scheme 6



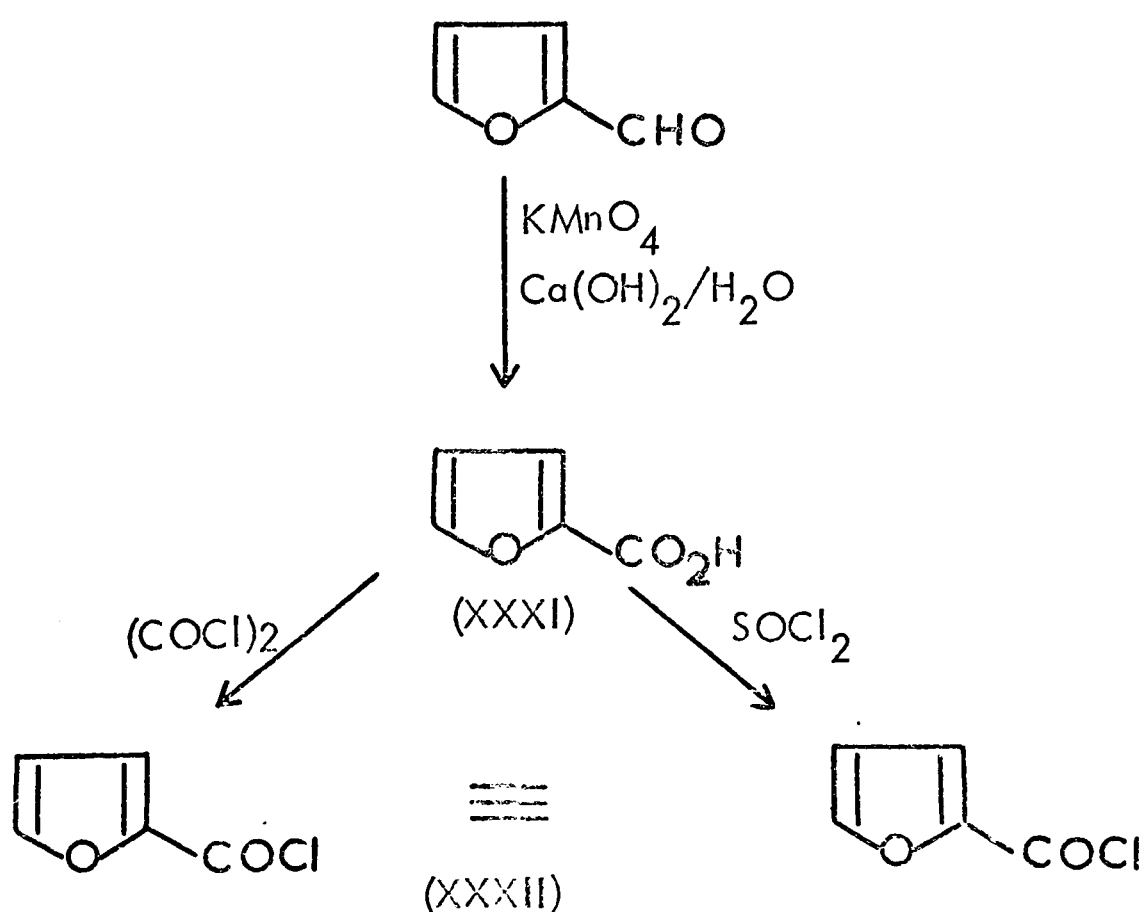
Ar : C₆H₅; p-Cl-C₆H₄; p-Br-C₆H₄; α-Naphthyl; β-Naphthyl

Ar-furan : (XX) (XXII) (XXIV) (XXVI) (XXVIII)

Ar-furan-CHO : (XXI) (XXIII) (XXV) (XXVII) (XXIX)

Owing to the reduced reactivity of aryl-furans towards electrophilic attack compared with isopropyl-furans, somewhat more vigorous conditions were used for the Wilsmeier reactions in that the reaction mixtures were heated at 100°C for one hour prior to work up. For one compound [5-(2-naphthyl)furan-2-carbaldehyde, (XXIX)], preparation was also attempted using the Gomberg reaction on furan-2-carbaldehyde. Recognisable products were not obtained, and the reaction was not pursued further.

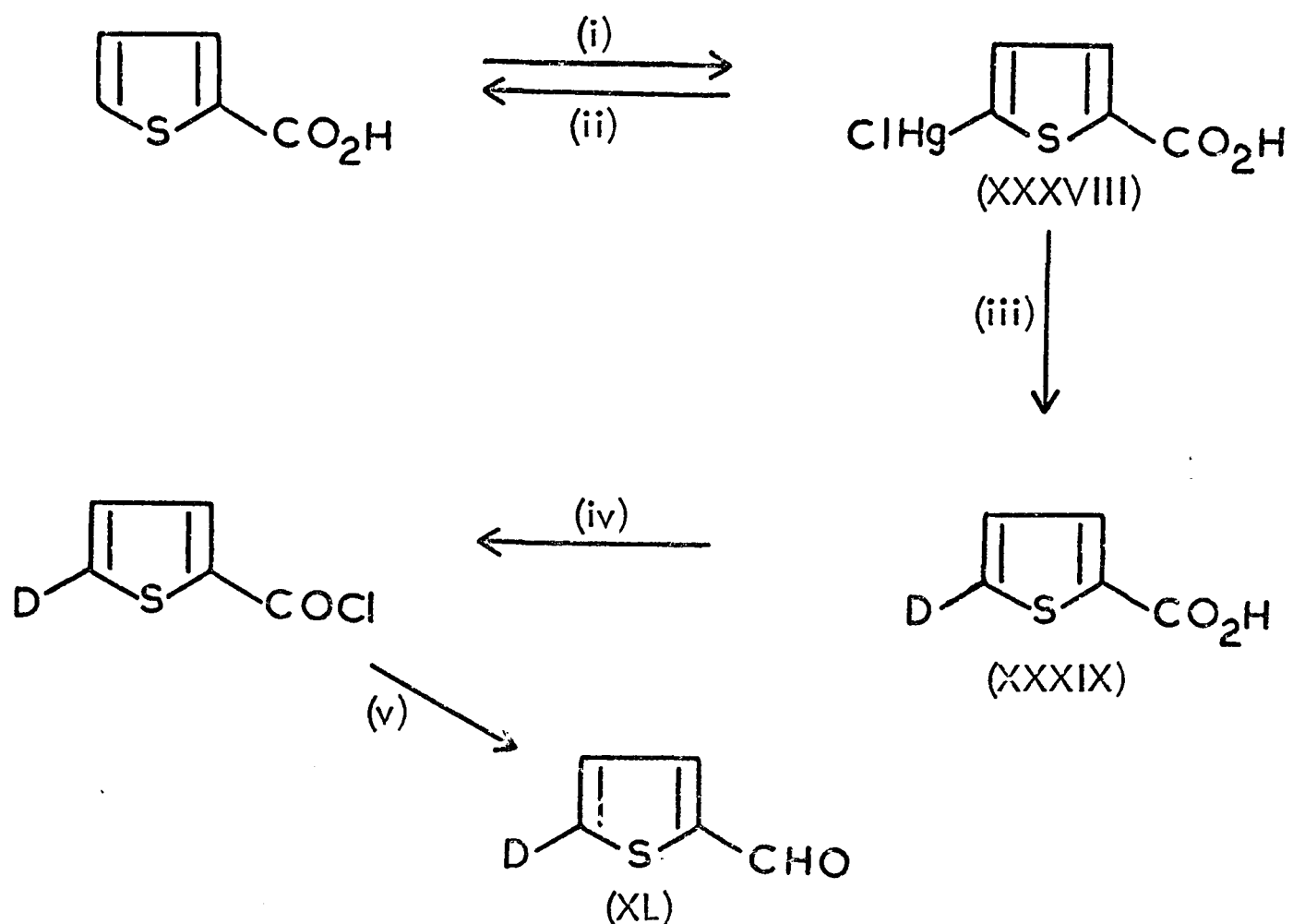
Fermi resonance studies: routes to deuterated heterocyclic compounds. Previous work by the author²¹ had demonstrated that furan-2-carbonyl chloride (XXXII) had four i.r. bands in the carbonyl region, and it was felt that this complexity might be a consequence of Fermi resonance. In order to exclude the possibility that the band complexity is due to an impurity of the 3-isomer, the acid chloride was synthesised from furan-2-carbaldehyde known, from g.l.c. and comparison of physical constants with well-documented literature values, to be pure:



For comparison purposes, the acid bromide (XXXIII) and fluoride (XXXIV) were required. Synthesis of the former (phosphorus tribromide on the acid) was straightforward, but the latter compound was unknown. The route attempted originally (heating the acid chloride with anhydrous zinc fluoride) has been used in aliphatic chemistry. The reaction was repeated several times with slight variations including the use of a solvent (light petroleum): in the absence of a solvent, polymerisation always occurred whereas in the presence of a solvent, no reaction could be detected. The polymerisation may be a consequence of successive Friedel-Crafts reactions, catalysed by the zinc chloride formed in the reaction. The compound was finally prepared successfully using potassium hydrogen fluoride, a similar method being used for the thiophen analogue (XXXVII). Both acid fluorides were observed to be much more prone to hydrolysis than the chlorides, this reflecting the greater electronegativity of fluorine over chlorine. Furthermore, the thiophen halides are more easily hydrolysed than the furan analogues which implies greater π -electron donation by the furan ring than by thiophen. This may be a result of poorer orbital overlap between sulphur and carbon than between oxygen and carbon.

As observed previously (vide "Introduction"), the most reliable method for diagnosing Fermi resonance, in a particular case, involves the synthesis of functional and isotopic analogues. Routes to deuterated furans and thiophens were therefore devised. Scheme 7 summarises the successful approach used for the synthesis of 5-deuteriothiophen-2-carbaldehyde.

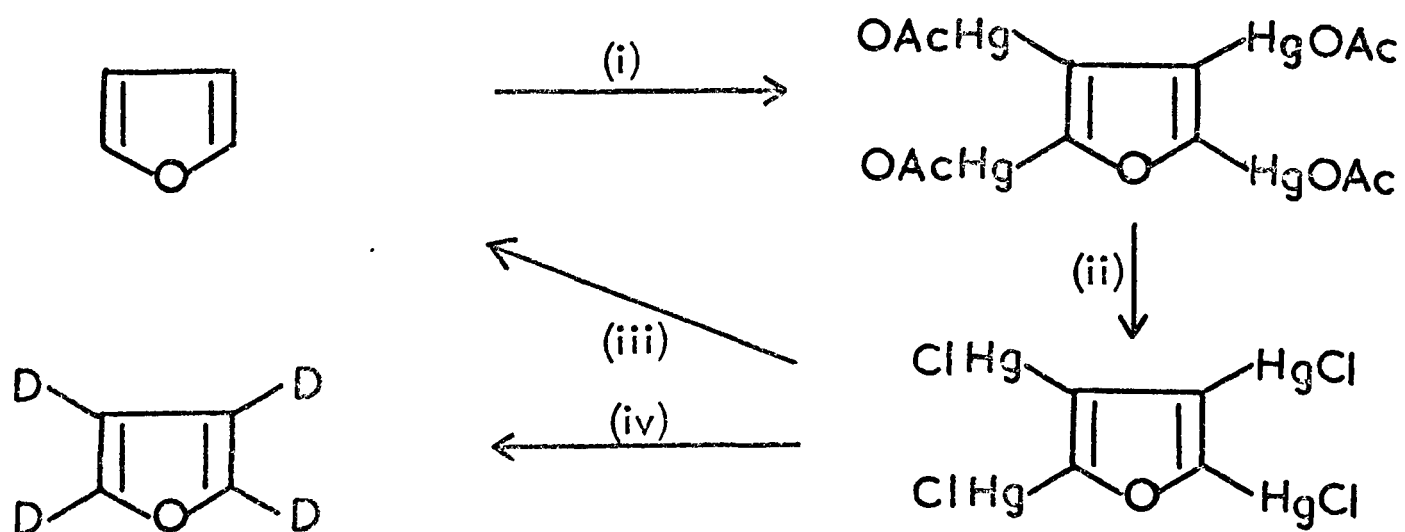
Scheme 7



Reagents: (i) $\text{HgCl}_2\text{-NaOCOCH}_3\cdot 3\text{H}_2\text{O}$ -10 d; (ii) 20% HCl in H_2O -10 min; (iii) 20% DCl in D_2O -10 min; (iv) SOCl_2 , and (v) $\text{LiAl}(\text{O}^+\text{Bu})_3\text{H}$ -diglyme.

The first approach attempted for the synthesis of deuterated furans is shown in Scheme 8.

Scheme 8

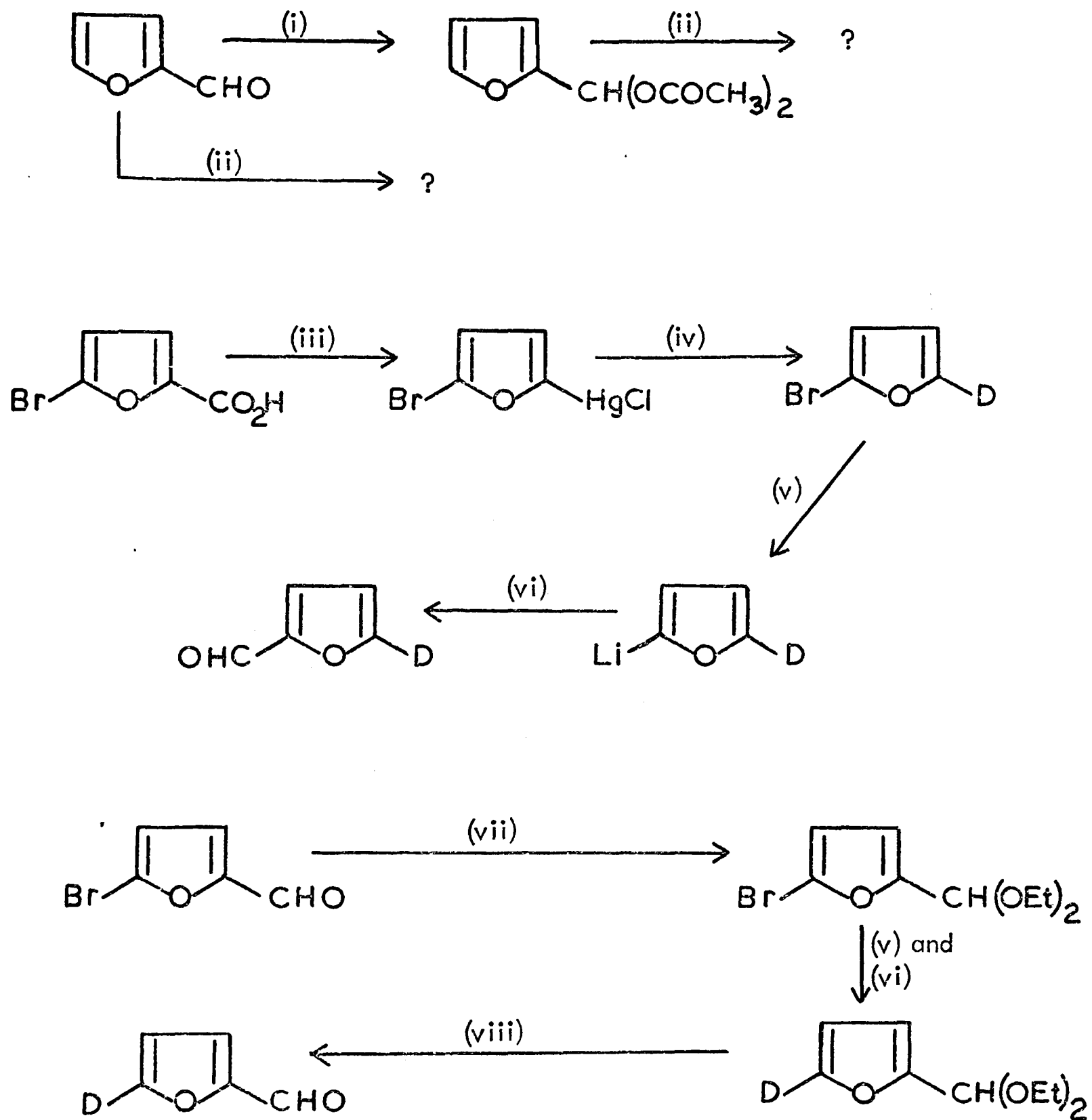


Reagents: (i) $\text{Hg}(\text{OCOCH}_3)_2\text{-H}_2\text{O}$ -12 h; (ii) $\text{NaCl-H}_2\text{O}$; (iii) 20% $\text{HCl-H}_2\text{O}$, and (iv) 20% $\text{DCl-D}_2\text{O}$.

Reagents: (i) $\text{Br}_2\text{-Cl(CH}_2)_2\text{Cl}$; (ii) $\text{Br}_2\text{-CHCl}_3$; (iii) $\text{KMnO}_4\text{-dioxan-H}_2\text{O-Na}_2\text{CO}_3$; (iv) $\text{Ag}_2\text{O-NH}_3$; (v) Na-salt-HgCl_2 ; (vi) 20% $\text{DCl-D}_2\text{O}$; (vii) $\text{n-C}_4\text{H}_9\text{Li-(C}_2\text{H}_5)_2\text{O}$, then $\text{CO}_2\text{-(C}_2\text{H}_5)_2\text{O}$; (viii) SOCl_2 ; (ix) KHF_2 ; (x) $\text{C}_6\text{H}_6\text{-AlCl}_3$, and (xi) $\text{isobutene-(C}_2\text{H}_5)_2\text{O-H}_2\text{SO}_4$.

It was hoped that it would be possible to prepare 5-deuteriofuran-2-carbaldehyde (XLIX) from the acid chloride [using lithium aluminium tri-*t*-butoxyhydride in diglyme (by analogy with the method used for the thiophen derivative)]. In the furan case, a complex mixture was obtained from the reaction, and after prolonged chromatography no recognisable material was isolated. It is probable that the reaction does produce some of the required material, but because of the need for extensive purification, a more satisfactory route was sought. Various, unsatisfactory approaches which were attempted are summarised in Scheme 10.

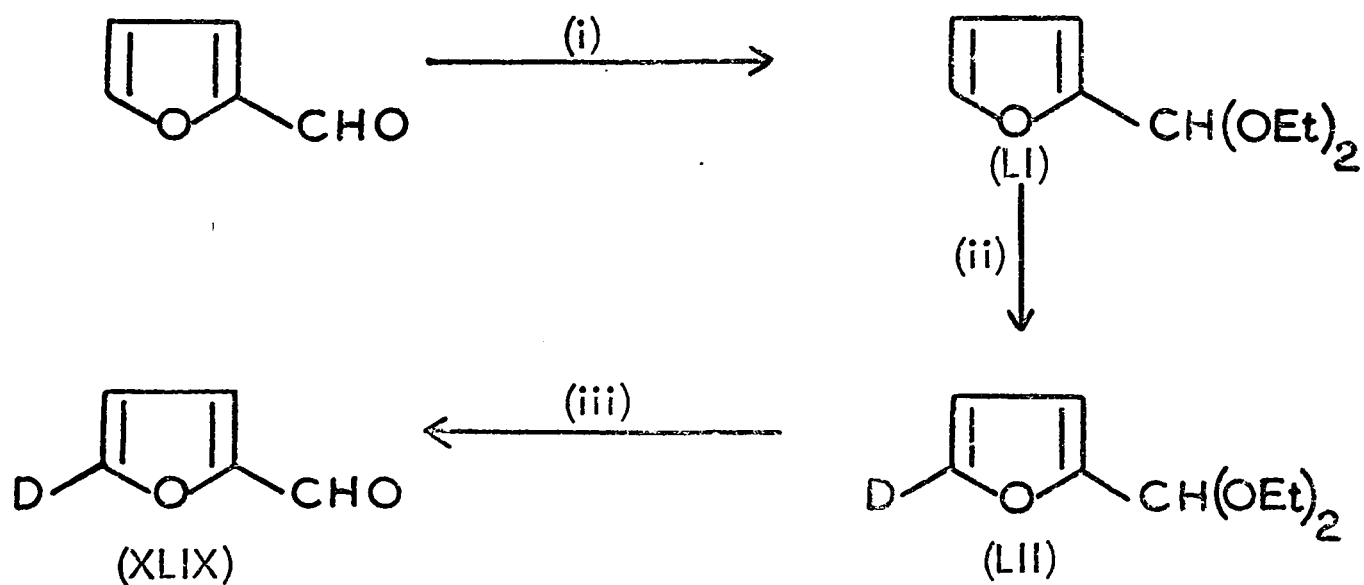
Scheme 10



Reagents: (i) $(\text{CH}_3\text{CO})_2\text{O}-\text{H}_2\text{SO}_4$; (ii) $\text{C}_2\text{H}_5\text{OH}-\text{HgCl}_2-\text{NaOCOCH}_3 \cdot 3\text{H}_2\text{O}$;
 (iii) $\text{Na-salt}-\text{HgCl}_2$; (iv) 20% $\text{DCl}-\text{D}_2\text{O}$; (v) $n\text{-C}_4\text{H}_9\text{Li}-(\text{C}_2\text{H}_5)_2\text{O}$;
 (vi) $(\text{CH}_3)_2\text{N} \cdot \text{CHO}$ then H_2O ; (vii) $(\text{C}_2\text{H}_5\text{O})_3\text{CH}-\text{C}_2\text{H}_5\text{OH}-\text{HCl}$, and
 (viii) $\text{HCl}-\text{H}_2\text{O}$.

The failure of furan-2-carbaldehyde and of its diacetate to mercuriate is a consequence of the reduced π -electron availability in these compounds compared with furan. The reaction of dimethylformamide with 5-deuterio-2-furyl-lithium is, in principle, a satisfactory route, and further investigation of this reaction by co-workers^{90,109} has shown that the yields, though variable, are much improved if the reaction is carried out below -30°C : this presumably reduces the tendency for ring-opening side-reactions to occur. The final sequence of reactions shown in Scheme 10 (which has since been used, in outline, by co-workers¹⁰⁹ as an alternative route to 5-deuteriothiophen-2-carbaldehyde) was abandoned partly because of the apparently unfavourable position of the acetal-formation equilibrium, and partly because an alternative (successful) route was being investigated concurrently. This is shown in Scheme 11.

Scheme 11

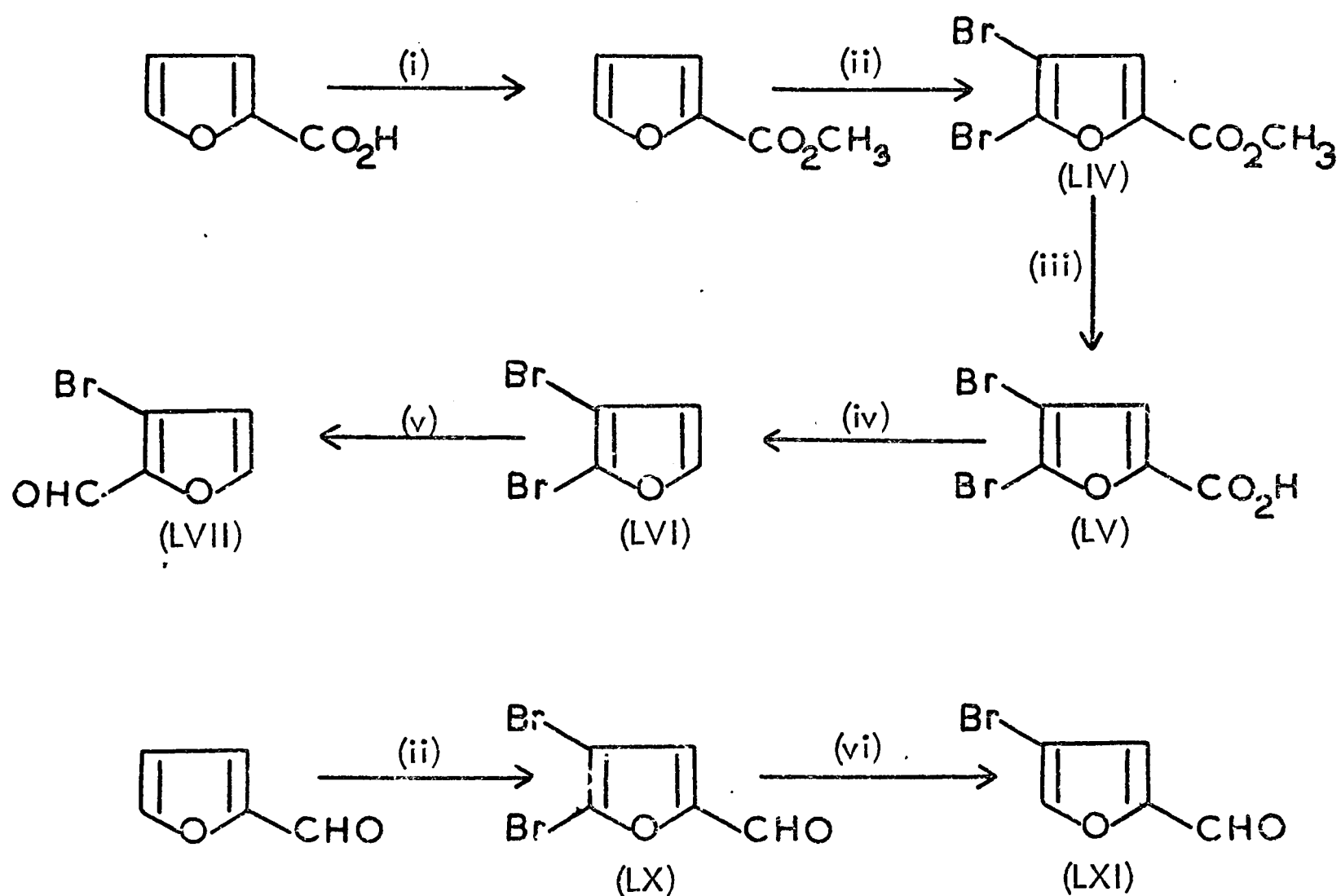


Reagents: (i) $\text{C}_2\text{H}_5\text{OH-HCl}$; (ii) $n\text{-C}_4\text{H}_9\text{Li-(C}_2\text{H}_5)_2\text{O}$ then D_2O , and (iii) $\text{HCl-H}_2\text{O}$.

Since aliphatic thio-acetals react with *n*-butyl-lithium with loss of the acetal hydrogen, it was not certain that Scheme 11 would be successful: 5-deuterio-furan-2-carbaldehyde was, however, obtained in good yield.

Routes to 3- and 4-bromofuran-2-carbaldehydes were successfully explored (Scheme 12).

Scheme 12

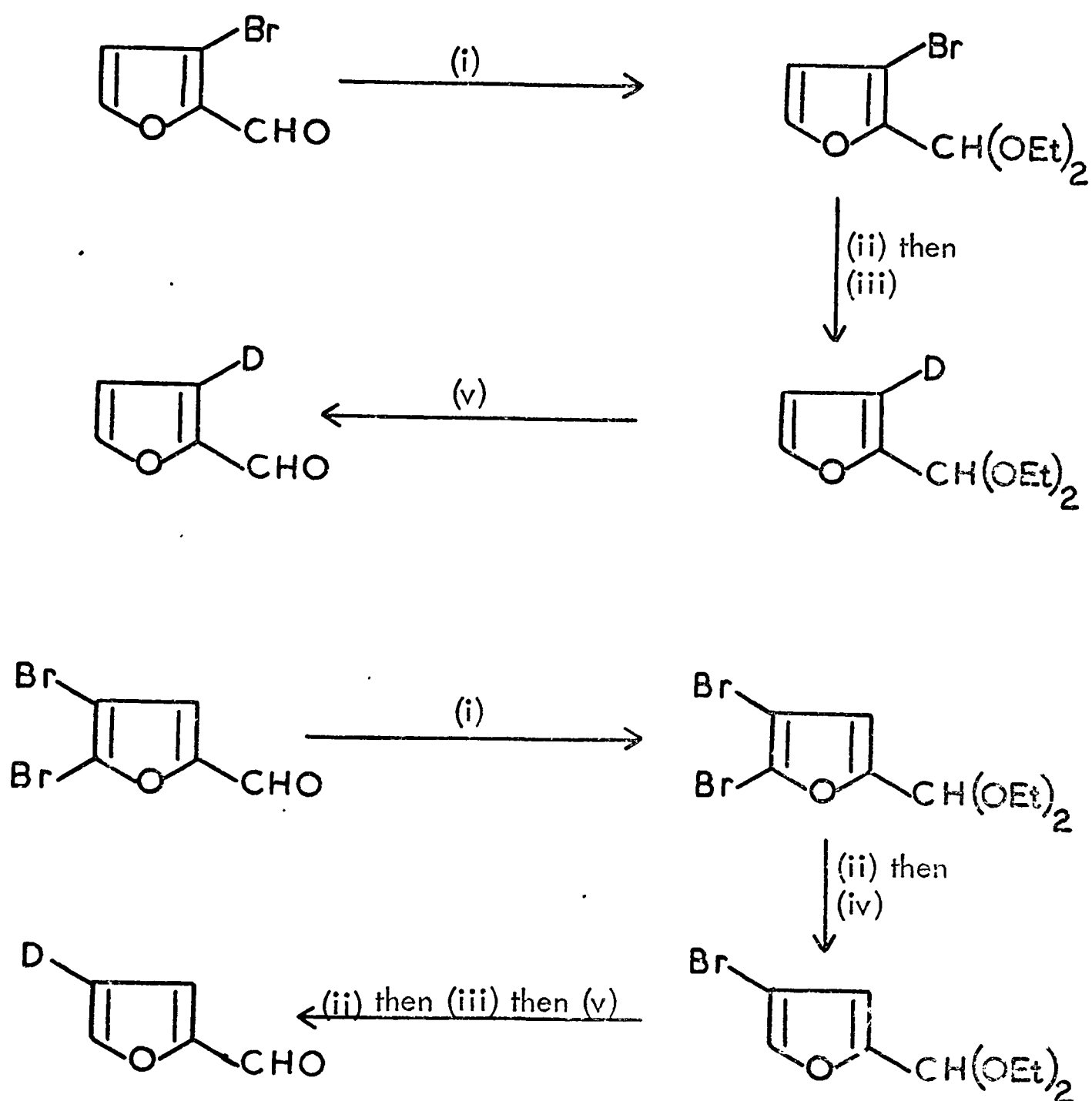


Reagents: (i) $\text{CH}_3\text{OH}-\text{H}_2\text{SO}_4$; (ii) $\text{Br}_2-\text{AlCl}_3$; (iii) $\text{NaOH}-\text{H}_2\text{O}$, then $\text{HCl}-\text{H}_2\text{O}$; (iv) $\text{HgCl}_2-\text{H}_2\text{O}$; (v) $n\text{-C}_4\text{H}_9\text{Li}-(\text{C}_2\text{H}_5)_2\text{O}$, then $(\text{CH}_3)_2\text{N}\cdot\text{CHO}$ and H_2O , and (vi) $\text{Zn}-\text{CH}_3\text{CO}_2\text{H}-\text{H}_2\text{O}$.

The key step in both routes is the di-bromination of a substituted furan using bromine and anhydrous aluminium chloride. This reaction has been studied in detail by co-workers⁹⁰ who have found that (i) a Lewis-acid catalyst is essential for the introduction of a second bromine atom, and (ii) 4-bromo-5-chloro-compounds [the amounts (which can be large) depending critically on reaction conditions] are formed as by-products. The usefulness of zinc for the removal of an α -bromine atom from a 2,5-disubstituted or a 2,4,5-trisubstituted furan depends largely upon the nature of other groups present in the molecule. Prior to using this reagent for the preparation of 4-bromofuran-2-carbaldehyde (Scheme 12), the reaction between zinc and acetic acid and 5-bromofuran-2-carbaldehyde was studied. In both the 4,5-dibromo- and 5-bromo-aldehydes, the use of short reaction times gave reasonable yields of the required materials, but prolonged times led to considerable reduction of the aldehyde groups. A more reliable method for the removal of α -bromine atoms from bromofuran-2-carbaldehydes is to proceed via *n*-butyl-lithium on the diethylacetal: this approach is adopted in later Schemes. However, the use of zinc for the removal of α -bromine atoms from bromofuran esters is far more satisfactory since the ester functions are not reduced by zinc under the conditions employed: this reaction is used extensively in later Schemes. Under no circumstances was any evidence found for β -bromine atoms being removed by zinc.

Routes to 3- and 4-deuteriofuran-2-carbaldehydes were subsequently investigated (Scheme 13).

Scheme 13

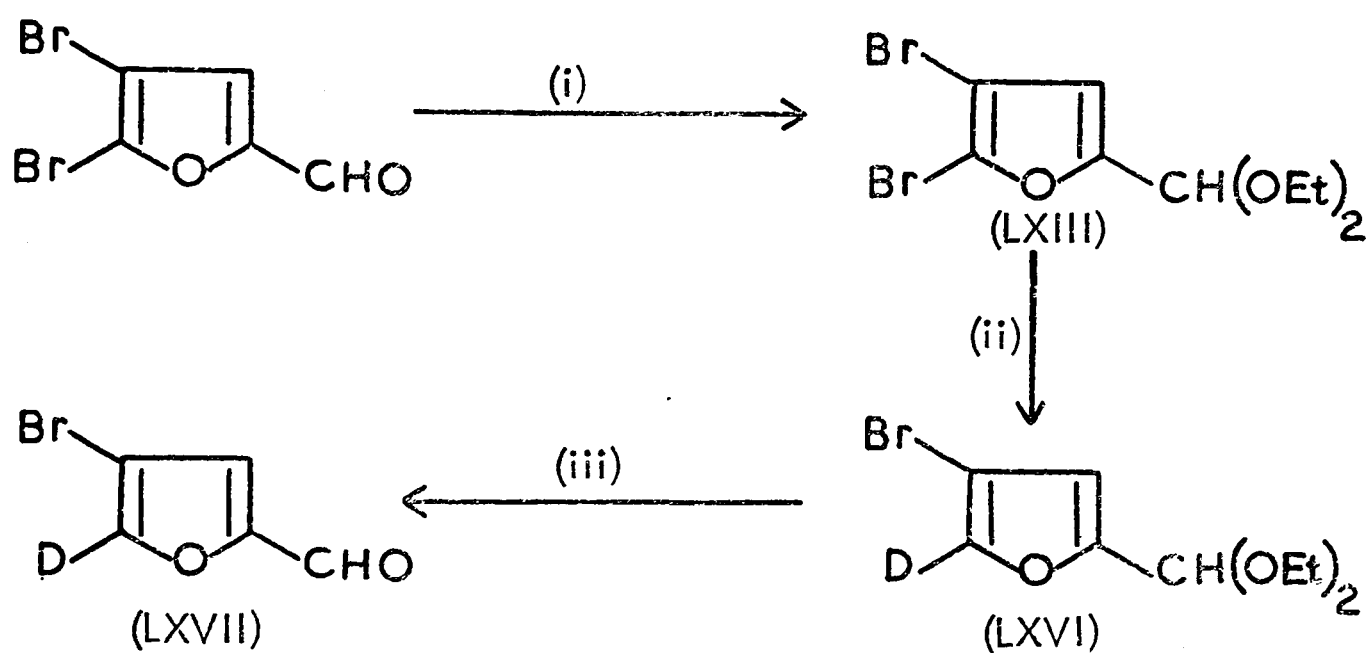


Reagents: (i) $(C_2H_5O)_3CH-C_2H_5OH-HCl$; (ii) $n-C_4H_9Li-(C_2H_5)_2O$; (iii) D_2O ; (iv) H_2O , and (v) $HCl-H_2O$.

A significant amount of protonated, along with some deuterated, product was obtained in both cases. The route to 3-deuteriofuran-2-carbaldehyde has been reinvestigated by co-workers⁹⁰ who conclude that the deuteration level of the product is improved markedly by keeping the β -furyl-lithium solution always below $-60^\circ C$, and that yields are better if the deuterio-acetal is hydrolysed in situ

rather than isolated. These conclusions suggest that β -furyl-lithium is much more unstable than the α -isomer (the former decomposing significantly above -60°C ; the latter withstanding boiling in ether) and that the ring-opened products contain labile hydrogen atoms. For comparison purposes, 4-bromo-5-deuteriofuran-2-carbaldehyde was synthesised (Scheme 14).

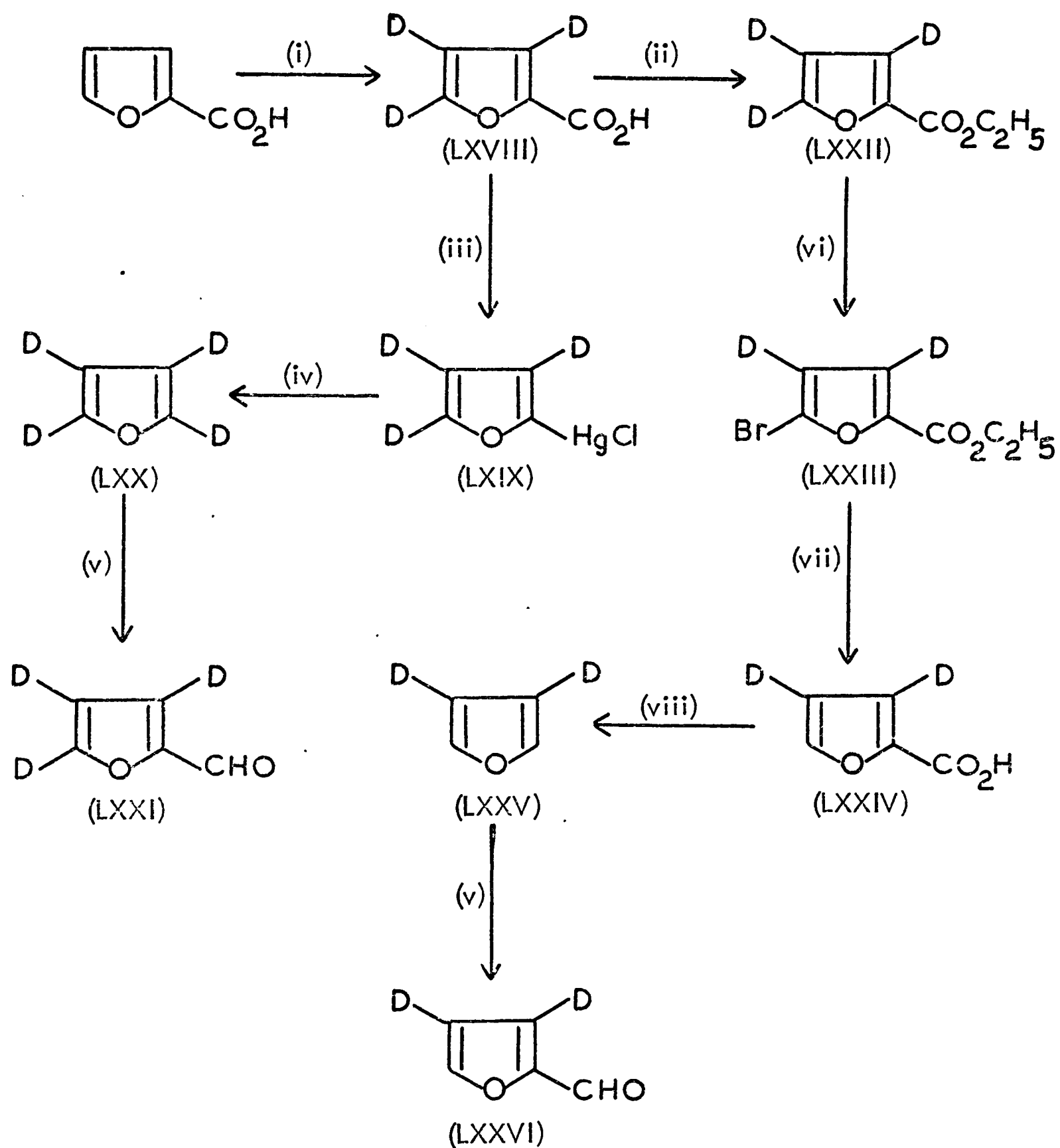
Scheme 14



Reagents: (i) $(\text{C}_2\text{H}_5\text{O})_3\text{CH-C}_2\text{H}_5\text{OH-HCl}$; (ii) $n\text{-C}_4\text{H}_9\text{Li}$, then D_2O , and (iii) $\text{HCl-H}_2\text{O}$.

The routes to the β -mono-deuterated furans were not pursued further since a successful preparation of 3,4-di-deuteriofurans had been devised (Scheme 15). This also provides a route to tri-deuteriofurans and to tetra-deuteriofuran (LXX).

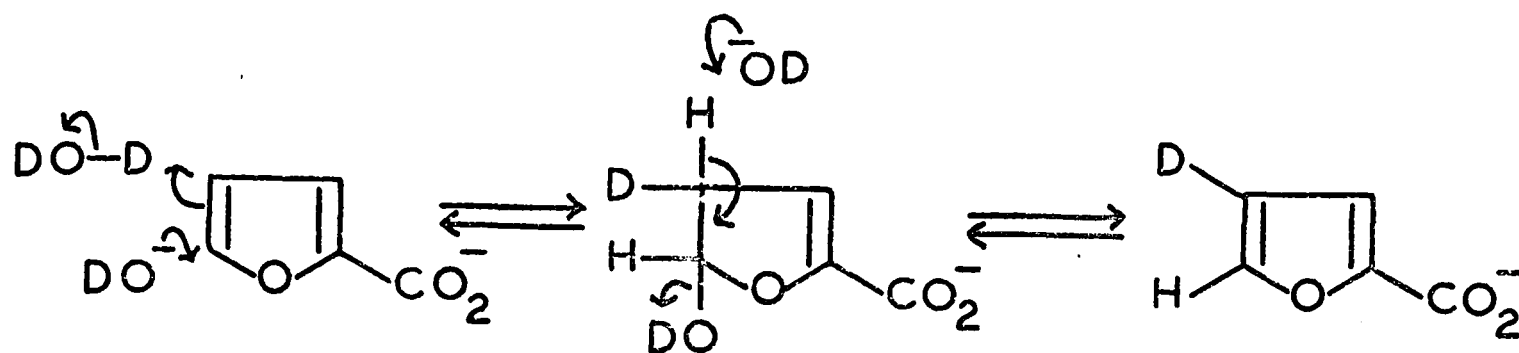
Scheme 15



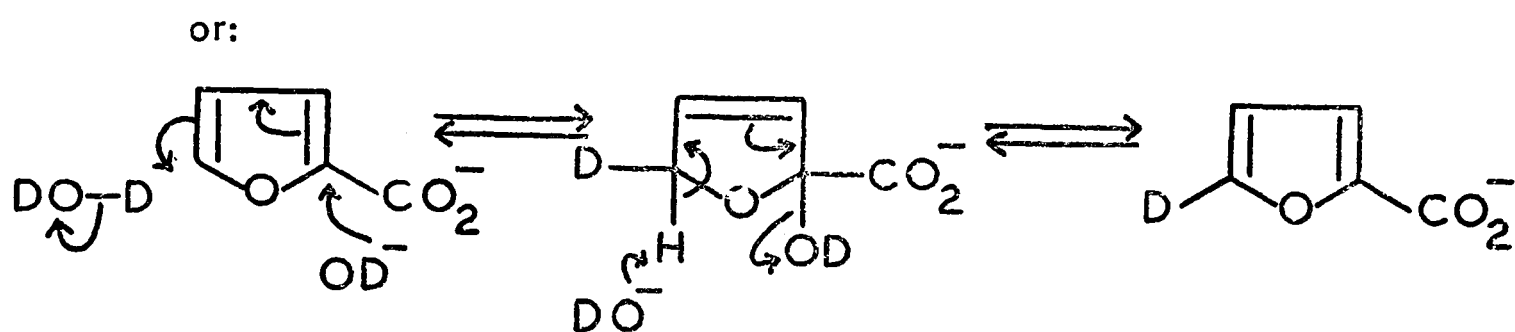
Reagents: (i) 30% NaOD-D₂O; (ii) C₂H₅OH-H₂SO₄; (iii) Na-salt-HgCl₂-H₂O; (iv) 20% DCl-D₂O; (v) POCl₃-(CH₃)₂N·CHO; (vi) Br₂-Cl(CH₂)₂Cl; (vii) Zn-CH₃CO₂H-H₂O, and (viii) Cu-bronze-quinoline.

The hydrogen-deuterium exchange is reversible and approximately first-order in deuterioxide. Also, deuteration is more rapid at the α - than at the β -positions.

The mechanism may involve direct proton abstraction, or addition and elimination:



similarly for α

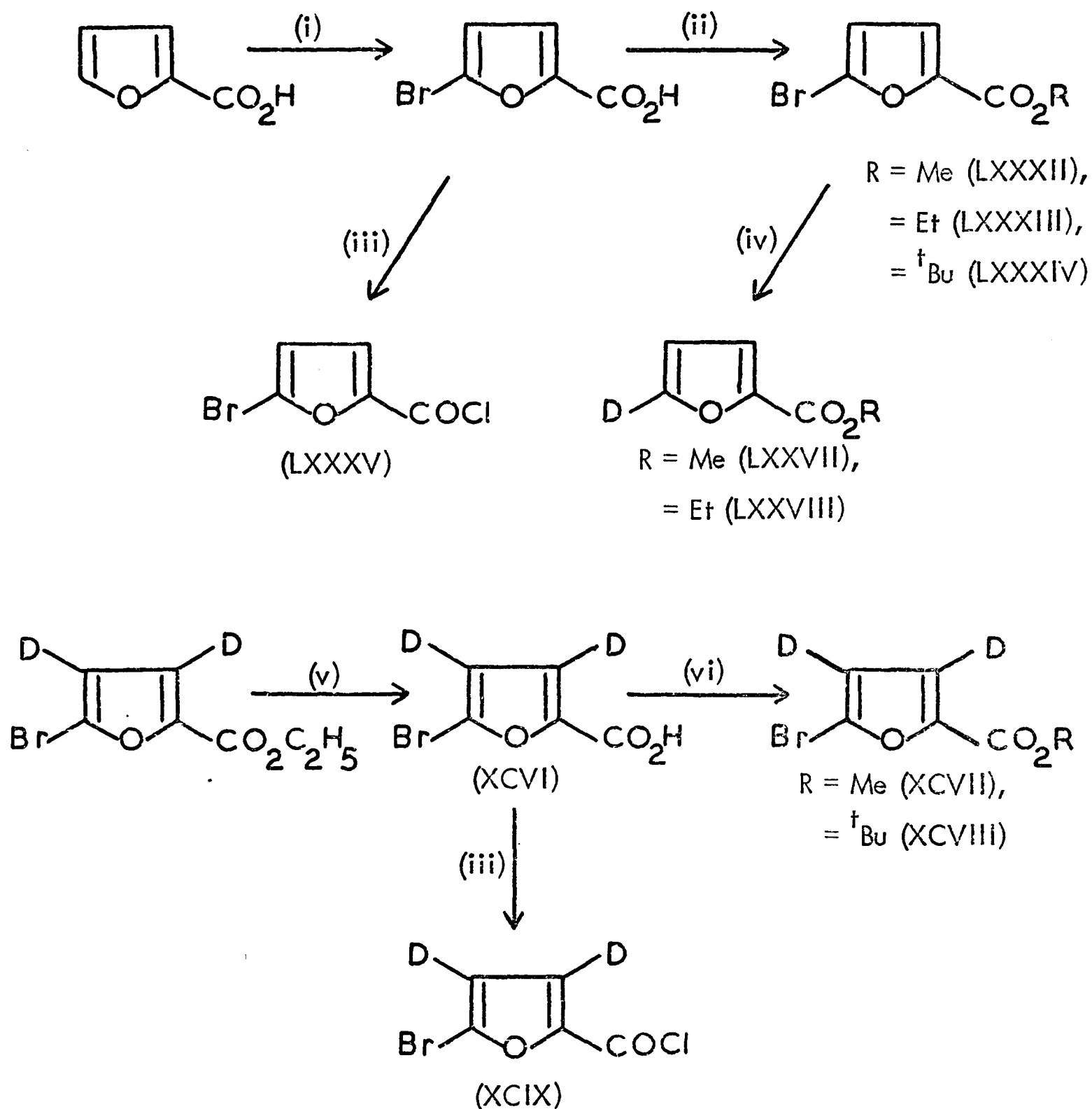


Because of the reversibility of deuteration, it is not possible to saponify (with aqueous sodium hydroxide solution) a deuterated furan ester without reducing the level of deuterium substitution. To circumvent this problem, the conversion of ethyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (LXXIII) to 3,4-dideuteriofuran-2-carboxylic acid (LXXIV) (Scheme 15) was carried out directly using zinc and acetic acid [which has the effect of removing the bromine atom and (in time) the ester group without affecting the deuterium content appreciably].

Substituent effects on i.r. carbonyl vibrations; conformations of esters. The

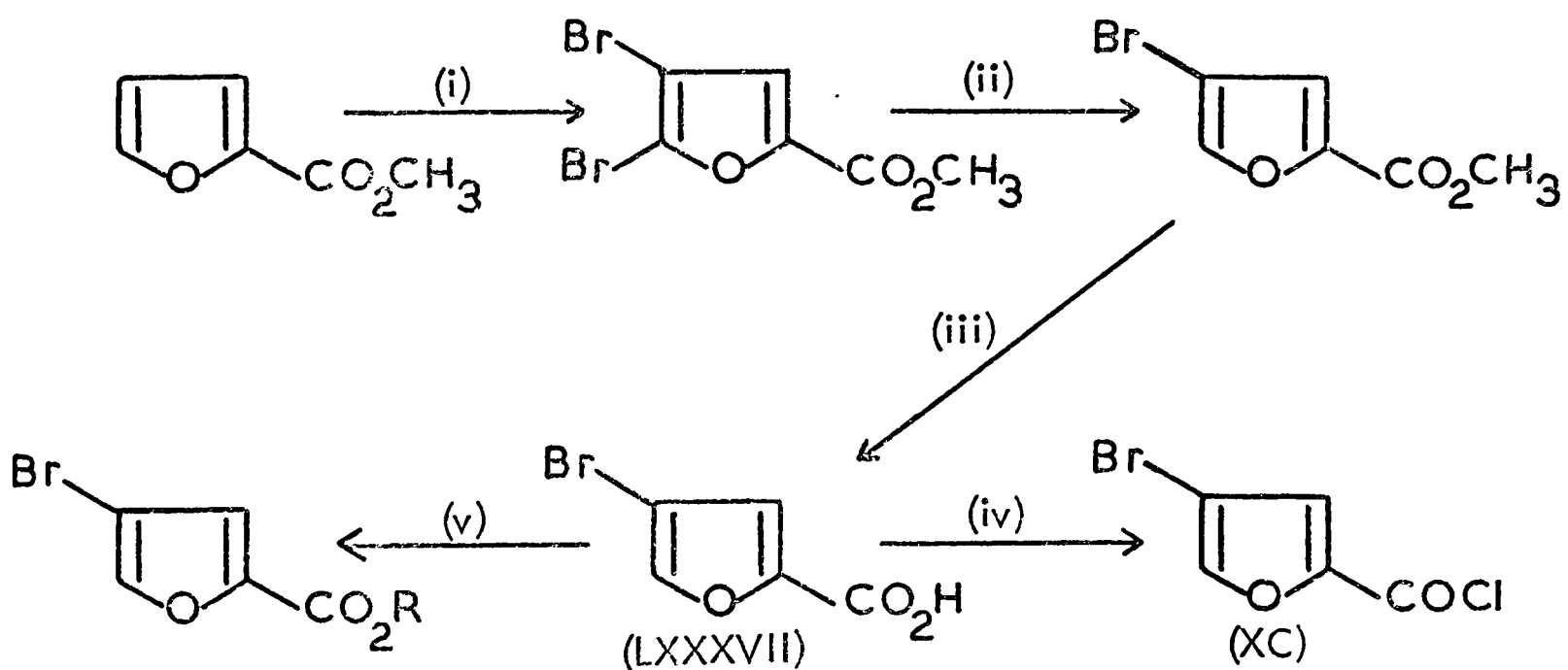
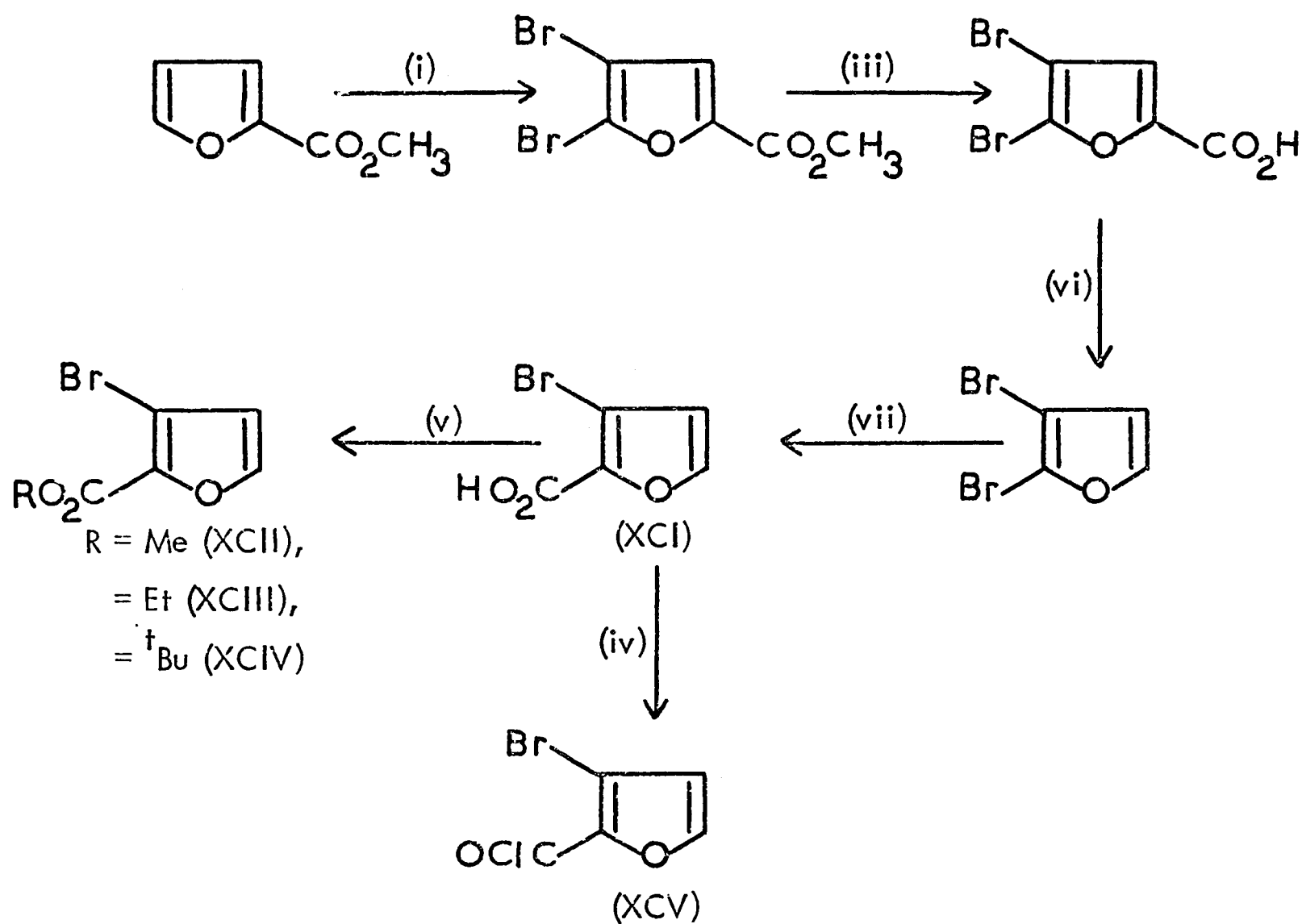
remaining synthetic work involved the preparation of 3-, 4-, and 5-mono-brominated furan esters and acid chlorides, of selected deuterated furan esters, and of two pyrrole esters. The reactions are summarised in Schemes 16, 17, and 18.

Scheme 16



Reagents: (i) $\text{Br}_2\text{-CHCl}_3$; (ii) CH_3OH ($\text{R} = \text{CH}_3$), $\text{C}_2\text{H}_5\text{OH}$ ($\text{R} = \text{C}_2\text{H}_5$), isobutene ($\text{R} = \text{t-C}_4\text{H}_9$), and H_2SO_4 ; (iii) SOCl_2 ; (iv) $\text{Zn-(CH}_3\text{CO)}_2\text{O-D}_2\text{O}$; (v) 20% $\text{NaOD-D}_2\text{O}$, and (vi) $\text{CH}_2\text{N}_2\text{-(C}_2\text{H}_5)_2\text{O}$.

Scheme 17

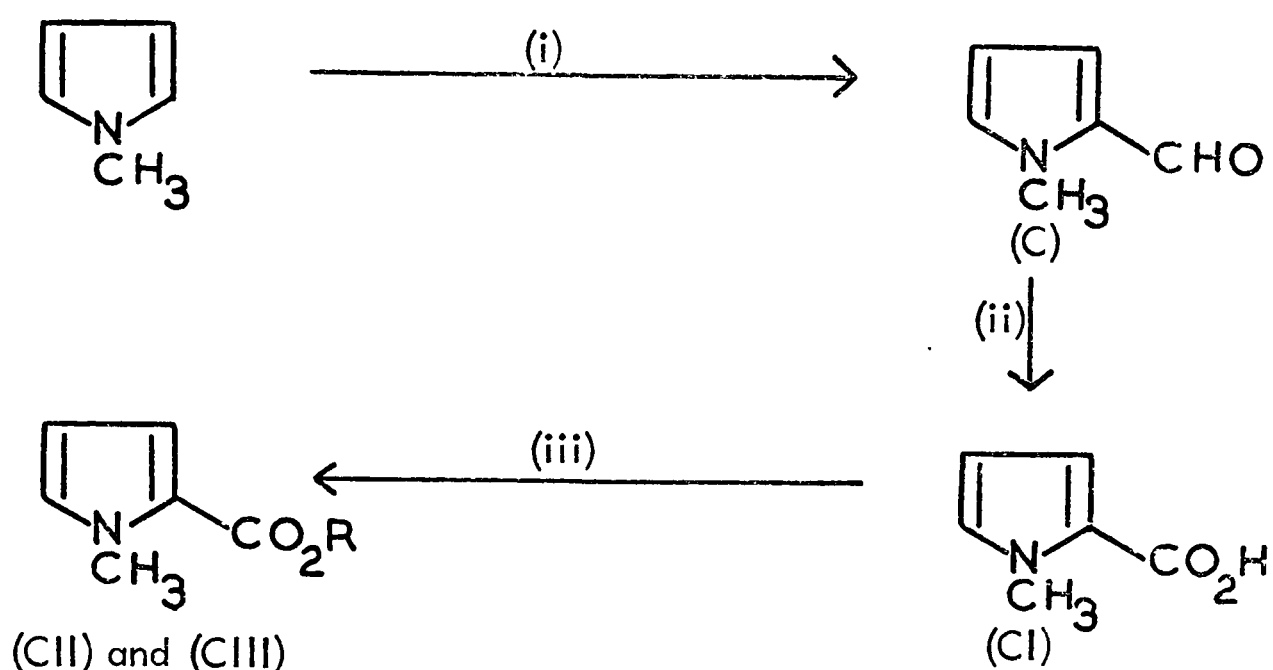


Reagents: (i) $\text{Br}_2\text{-AlCl}_3$; (ii) $\text{Zn-CH}_3\text{CO}_2\text{H-H}_2\text{O}$; (iii) 20% $\text{NaOH-H}_2\text{O}$;

(iv) SOCl_2 ; (v) CH_3OH (R = CH_3), $\text{C}_2\text{H}_5\text{OH}$ (R = C_2H_5), isobutene (R = $t\text{-C}_4\text{H}_9$),

and H_2SO_4 ; (vi) $\text{HgCl}_2\text{-H}_2\text{O}$, and (vii) $n\text{-C}_4\text{H}_9\text{Li}$, then $\text{CO}_2\text{-(C}_2\text{H}_5)_2\text{O}$.

Scheme 18



Reagents: (i) POCl_3 -(CH_3)₂N-CHO; (ii) KMnO_4 -dioxan- H_2O - Na_2CO_3 ; (iii) CH_2N_2 -(C_2H_5)₂O (R = CH_3), isobutene (R = t-C₄H₉)- H_2SO_4 .

Because of the sensitivity of pyrrole derivatives towards mineral acids, methyl N-methylpyrrole-2-carboxylate (CII) was prepared by using diazomethane on the carboxylic acid (Scheme 18), a similar reaction being used for methyl 5-bromo-3,4-dideuteriofuran-2-carboxylate (XCVII). The 5-deuteriofuran esters [(LXXVII) and (LXXVIII)] were prepared using zinc, acetic anhydride, and deuterium oxide, which is a simple modification of the zinc-acetic acid dehalogenation discussed earlier.

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Appendix A

```

0005 MASTER IAD
0006 DIMENSION YI(2000),HEAD1(20),HEAD2(20)
0007 9 CONTINUE
0008 WRITE(6,99)
0009 READ(7,100)(HEAD1(I),I=1,10)
0010 READ(7,100)(HEAD2(I),I=1,10)
0011 WRITE(6,100)(HEAD1(I),I=1,10)
0012 WRITE(6,100)(HEAD2(I),I=1,10)
0013 READ(7,101)NP,NPDATA
0014 READ(7,112)SHIFT
0015 READ(7,102)WB,WI
0016 WRITE(6,103)NP
0017 WRITE(6,113)SHIFT
0018 WRITE(6,104)WB
0019 WRITE(6,105)WI
0020 WRITE(6,111)
0021 READ(7,106)(YI(I),I=1,NP)
0022 WRITE(6,108)(YI(I),I=1,NP)
0023 NR=NP+1
0024 NK=NP+2
0025 YI(NR)=100,00000
0026 YI(NK)=100,00000
0027 FINT=0,0
0028 I=1
0029 1 CONTINUE
0030 J=I+2
0031 K=I+1
0032 IF(YI(J),EQ,100,00000)GO TO 8
0033 FINT=FINT+((YI(I)+4,0*YI(K)+YI(J))*WI/3,0)
0034 I=I+2
0035 GO TO 1
0036 8 CONTINUE
0037 WRITE(6,110)FINT
0038 IF(NPDATA,EQ,2)GO TO 9
0039 CALL EXIT
0040 99 FORMAT(//,54H CURVE AREAS BY SIMPSON'S 1/3 RULE)
0041 100 FORMAT(10A8)
0042 101 FORMAT(2I5)
0043 102 FORMAT(2F15,5)
0044 103 FORMAT(30H THE NUMBER OF DATA POINTS IS:,I5)
0045 104 FORMAT(//,48H THE STARTING WAVENUMBER IS:,F15,5)

```

0044	105	FORMAT(//,55H THE INTEGRATION INTERVAL(CM-1) IS:,F15.5)
0047	106	FORMAT(15X,F15.5)
0048	107	FORMAT(//,53H THE DATA IN ABSORBANCE UNITS IS:,//)
0049	108	FORMAT(5F15.5)
0050	109	FORMAT(//,50H THE VALUE OF THE INTEGRAL IS:,F15.5)
0051	111	FORMAT(//,57H THE DATA IN ABSORBANCE IS:,//)
0052	112	FORMAT(5F15.5)
0053	113	FORMAT(//,43H THE BASELINE SHIFT IS:,F15.5)
0054		STOP
0055		END

END OF SEGMENT, LENGTH 216, NAME IAD

Appendix B

```

0007 MASTER CURVE
0008 DIMENSION XV(3000),YV(3000),ZV(3000),IV(3000),HEAD1(20),HEAD2(20),
0009 IX(1000)
0010 READ(8,100)(HEAD1(I),I=1,10)
0011 READ(8,100)(HEAD2(I),I=1,10)
0012 WRITE(6,100)(HEAD1(I),I=1,10)
0013 WRITE(6,100)(HEAD2(I),I=1,10)
0014 READ(8,101)VI
0015 READ(8,101)SPACE
0016 READ(8,102)N,NP
0017 VL=VI-(NP-1)*SPACE
0018 CALL LIMITS(3,0,6,5,3,0,6,5)
0019 VVL=VL-4,0
0020 VVI=VI+4,0
0021 CALL REGION(VVL,VVI,-0,1,1,0)
0022 CALL AXES
0023 DO 1 N=1,NP
0024 ZV(N)=0
0025 1 CONTINUE
0026 WRITE(6,105)VI
0027 WRITE(6,106)M
0028 WRITE(6,107)NP
0029 READ(8,101)A
0030 WRITE(6,114)A
0031 TEST=0,0
0032 DO 2 I=1,M
0033 J=I+M
0034 K=J+M
0035 L=K+M
0036 READ(8,103)X(I),X(J),X(K),X(L)
0037 WRITE(6,104)
0038 WRITE(6,108)
0039 WRITE(6,109)X(I),X(J),X(K),X(L)
0040 Z=0,0
0041 XI=VI
0042 DO 3 N=1,NP
0043 IF(TEST.EQ,1,0)GO TO 6
0044 XV(N)=XI-Z
0045 XI=XV(N)
0046 6 YV(N)=X(I)*((1+X(K)**2*((XV(N)-X(J))**2))**(-1))*(EXP((-X(L)**2)*

```

```

0047      1(XV(N)-X(J))*+2)))
0048      ZV(N)=ZV(N)+YV(N)
0049      Z=SPACE
0050      3 CONTINUE
0051      TEST=1,0
0052      DO 7 N=1,NP
0053      YV(N)=YV(N)+A
0054      7 CONTINUE
0055      WRITE(6,111)
0056      WRITE(6,110)(YV(N),XV(N),N=1,NP)
0057      CALL GRAPHN(XV,YV,1,NP)
0058      2 CONTINUE
0059      DO 5 N=1,NP
0060      ZV(N)=ZV(N)+A
0061      3 CONTINUE
0062      WRITE (6,111)
0063      WRITE(6,110)(ZV(N),XV(N),N=1,NP)
0064      CALL GRAPHN(XV,ZV,1,NP)
0065      CALL PROKEN(0,5)
0066      READ(6,112)(IY(I),I=1,NP)
0067      DO 4 N=1,NP
0068      4 ZV(N)=0.4543*(ALOG(1/(0.001*IY(N))))
0069      WRITE(6,115)
0070      WRITE(6,110)(ZV(N),XV(N),N=1,NP)
0071      CALL GRAPHN(XV,ZV,1,NP)
0072      CALL GREN
0073      CALL EXIT
0074      100 FORMAT(10A8)
0075      101 FORMAT(F15,5)
0076      102 FORMAT(2I5)
0077      103 FORMAT(4F15,5)
0078      104 FORMAT(//,18H INPUT PARAMETERS:)
0079      105 FORMAT(//,28H THE STARTING WAVENUMBER IS:,F15,5)
0080      106 FORMAT(//,34H THE NUMBER OF COMPONENT BANDS IS:,I5)
0081      107 FORMAT(//,36H THE NUMBER OF POINTS CALCULATED IS:,I5)
0082      108 FORMAT(//,15X,5H X(1),17X,5H X(2),17X,5H X(3),17X,5H X(4))
0083      109 FORMAT(1X,4(6X,F15,5))
0084      110 FORMAT(4(F10,5,2X,F10,5,4X))
0085      111 FORMAT(//,32H THE CALCULATED DATA POINTS ARE:)
0086      112 FORMAT((8(1X,I5,2X)),1X,I5,1X)
0087      113 FORMAT(//,34H THE EXPERIMENTAL DATA POINTS ARE:)
0088      114 FORMAT(//,26H THE BASELINE CONSTANT IS:,F15,5)
0089      STOP
0090      END

```

END OF SEGMENT, LENGTH 662, NAME CURVE

Appendix C

```

0005 MASTER DOITALL
0006 DIMENSION HEAD1(20),HEAD2(20),AH(100),AL(100),T(100),XH(100),XL(10
0007 0)
0008 READ(5,100)(HEAD1(I),I=1,10)
0009 READ(5,100)(HEAD2(I),I=1,10)
0010 READ(5,101)NP,ICORRECT
0011 WRITE(6,100)(HEAD1(I),I=1,10)
0012 WRITE(6,100)(HEAD2(I),I=1,10)
0013 WRITE(6,102)
0014 READ(5,103)(AH(I),AL(I),I=1,NP)
0015 READ(5,104)(T(I),I=1,NP)
0016 WRITE(6,105)NP
0017 JUMPOUT=2
0018 8 WRITE(6,106)
0019 WRITE(6,107)(AH(I),AL(I),T(I),I=1,NP)
0020 DO 1 I=1,NP
0021 XH(I)=AH(I)
0022 XL(I)=AL(I)
0023 1 CONTINUE
0024 ALPHA=1.0
0025 A=0.0
0026 CALL LEASTSQ(XH,XL,NP,ALPHA,A)
0027 CALL PLOTITOUT(XH,XL,ALPHA,NP,A,JUMPOUT)
0028 IF(ALPHA.GT.0.0000)GO TO 2
0029 GO TO 4
0030 2 WRITE(6,108)
0031 CALL MEANS(AH,AL,NP,ALPHA,A)
0032 CALL PLOTITOUT(XH,XL,ALPHA,NP,A,JUMPOUT)
0033 IF(ALPHA.GT.0.0000)WRITE(6,108)
0034 IF(ALPHA.LT.0.0000)GO TO 12
0035 10 CONTINUE
0036 WRITE(6,113)
0037 DO 3 I=1,NP
0038 XH(I)=ALOG10(AL(I)/AH(I))
0039 XL(I)=1.0/T(I)
0040 3 CONTINUE
0041 WRITE(6,114)(XH(I),XL(I),I=1,NP)
0042 CALL LEASTSQ(XH,XL,NP,ALPHA,A)
0043 CALL DELTAH(XH,XL,T,NP,ALPHA)
0044 IF(JUMPOUT.EQ.1)JUMPOUT=3
0045 CALL PLOTITOUT(XH,XL,ALPHA,NP,A,JUMPOUT)

```

```

0046      IF(JUMPOUT.EQ.3)JUMPOUT=1
0047      GO TO 6
0048  4 CONTINUE
0049      WRITE(6,109)
0050      WRITE(6,113)
0051      DO 5 I=1,NP
0052      XH(I)=ALOG10(-ALPHA*AL(I)/AH(I))
0053      XL(I)=1.0/T(I)
0054  5 CONTINUE
0055      WRITE(6,114)(XH(I),XL(I),I=1,NP)
0056      CALL LEASTSQ(XH,XL,NP,ALPHA,A)
0057      CALL DELTAH(XH,XL,T,NP,ALPHA)
0058      CALL MEANS(AH,AL,NP,ALPHA,A)
0059      CALL PLOTITOUT(AH,AL,ALPHA,NP,A,JUMPOUT)
0060      IF(ALPHA.GT.0.0000)WRITE(6,108)
0061      IF(ALPHA.GT.0.0000)WRITE(6,115)
0062      IF(ALPHA.GT.0.0000)GO TO 10
0063  12 CONTINUE
0064      DO 11 I=1,NP
0065      XH(I)=ALOG10(-ALPHA*AL(I)/AH(I))
0066      XL(I)=1.0/T(I)
0067  11 CONTINUE
0068      WRITE(6,113)
0069      WRITE(6,114)(XH(I),XL(I),I=1,NP)
0070      CALL LEASTSQ(XH,XL,NP,ALPHA,A)
0071      CALL DELTAH(XH,XL,T,NP,ALPHA)
0072      WRITE(6,115)
0073      GO TO 10
0074  6 CONTINUE
0075      IF(JUMPOUT.EQ.1)GO TO 7
0076      WRITE(6,110)
0077      IF(ICORRECT.EQ.1)GO TO 13
0078      AH(2)=AH(2)+100.0/95.6
0079      AH(3)=AH(3)+100.0/91.9
0080      AH(4)=AH(4)+100.0/89.0
0081      AH(5)=AH(5)+100.0/85.4
0082      AH(6)=AH(6)+100.0/81.5
0083      AH(7)=AH(7)+100.0/78.1
0084      AL(2)=AL(2)+100.0/95.6
0085      AL(3)=AL(3)+100.0/91.9
0086      AL(4)=AL(4)+100.0/89.0
0087      AL(5)=AL(5)+100.0/85.4
0088      AL(6)=AL(6)+100.0/81.5
0089      AL(7)=AL(7)+100.0/78.1

```

```

0090      IF(ICORRECT.EQ.2)GO TO 14
0091 13 CONTINUE
0092      AH(2)=AH(2)*100.0/97.0
0093      AH(3)=AH(3)*100.0/94.8
0094      AH(4)=AH(4)*100.0/92.8
0095      AH(5)=AH(5)*100.0/89.2
0096      AH(6)=AH(6)*100.0/87.1
0097      AH(7)=AH(7)*100.0/84.8
0098      AL(2)=AL(2)*100.0/97.0
0099      AL(3)=AL(3)*100.0/94.8
0100      AL(4)=AL(4)*100.0/92.8
0101      AL(5)=AL(5)*100.0/89.2
0102      AL(6)=AL(6)*100.0/87.1
0103      AL(7)=AL(7)*100.0/84.8
0104 14 CONTINUE
0105      JUMPOUT=1
0106      GO TO 8
0107 7 WRITE(6,111)
0108      TT1=0.0
0109      TT2=0.0
0110      DO 9 I=1,NP
0111      TT1=TT1+(1.0/(T(I)**2))
0112      TT2=TT2+(1.0/T(I))
0113 9 CONTINUE
0114      TT2=TT2**2
0115      BP=NP
0116      TT=SQRT(1.0/(TT1-(1.0/BP)*TT2))
0117      WRITE(6,112)TT
0118      TTH=8.31432*TT*0.1
0119      TTG=8.31432*303.0*0.1
0120      TTS=8.31432*0.1*((TT/303.0)+1.0)
0121      WRITE(6,116)
0122      WRITE(6,117)TTH
0123      WRITE(6,118)TTG
0124      WRITE(6,119)TTS
0125      CALL EXIT
0126 100 FORMAT(10A8)
0127 101 FORMAT(2I5)
0128 102 FORMAT(//,36H THIS PROGRAM WILL DO ALL YOUR WORK.)
0129 103 FORMAT(2F15.5)
0130 104 FORMAT(F15.5)
0131 105 FORMAT(//,30H THE NUMBER OF DATA POINTS IS:,I5)
0132 106 FORMAT(//,25X,5H A(H),11X,5H A(L),11X,2H T)
0133 107 FORMAT(//,17X,F15.5,1X,F15.5,1X,F15.5)

```

0134	108	FORMAT(//,56H THE ALPHA-CORRECTION CANNOT BE MADE WITH THE ABOVE D
0135		ATA)
0136	109	FORMAT(//,38H THE ALPHA CORRECTION WILL NOW BE MADE)
0137	110	FORMAT(//,40H THE NATURAL-DECREASE CORRECTION WILL NOW BE MADE,/,1
0138		19H VALUES ARE EX DJC.,/,74H IF THE NUMBER OF DATA POINTS IS NOT EQ
0139		2UAL TO 7,THIS CORRECTION IS INVALID)
0140	111	FORMAT(//,46H THE T-ERROR TERM(EX LF)WILL NOW BE CALCULATED)
0141	112	FORMAT(//,15H THE T-TERM IS:,F15.5)
0142	113	FORMAT(//,32X,17H LOG10(A(L)/A(H)),3X,4H 1/T)
0143	114	FORMAT(/,22X,F15.5,F15.5)
0144	115	FORMAT(//,45H THE ALPHA-UNCORRECTED VALUES ARE AS FOLLOWS:)
0145	116	FORMAT(//,25H ASSUMING 10P ERROR IN K,)
0146	117	FORMAT(/,19H THE ERROR IN H IS:,F15.5)
0147	118	FORMAT(/,27H THE ERROR IN G AT 303K IS:,F15.5)
0148	119	FORMAT(/,27H THE ERROR IN S AT 303K IS:,F15.5)
0149		END

END OF SEGMENT, LENGTH 747, NAME DOITALL

```

0150      SUBROUTINE PLOTITOUT(XH,XL,ALPHA,NP,A,JUMPOUT)
0151      DIMENSION XV(100),YV(100),XH(100),XL(100)
0152      CALL LIMITS(4.0,6.5,4.0,6.5)
0153      XHMAX=-100.0
0154      XLMAX=-100.0
0155      XHMIN=100.0
0156      XLMIN=100.0
0157      NNP=NP-1
0158      DO 3 I=1,NNP
0159      J=I+1
0160      XHMIN=AMIN1(XH(I),XH(J),XHMIN)
0161      XLMIN=AMIN1(XL(I),XL(J),XLMIN)
0162      XHMAX=AMAX1(XH(I),XH(J),XHMAX)
0163      XLMAX=AMAX1(XL(I),XL(J),XLMAX)
0164      3 CONTINUE
0165      DO 2 I=1,NP
0166      XV(I)=XL(I)
0167      YV(I)=ALPHA*XL(I)*A
0168      2 CONTINUE
0169      DO 4 I=1,NNP
0170      J=I+1
0171      XHMIN=AMIN1(YV(I),YV(J),XHMIN)
0172      XHMAX=AMAX1(YV(I),YV(J),XHMAX)
0173      4 CONTINUE
0174      CALL REGION(XLMIN,XLMAX,XHMIN,XHMAX)
0175      CALL AXESSI(0.0,0.0)
0176      CALL CRSIZE(0.1)
0177      DO 1 I=1,NP
0178      CALL PLOTNC(XL(I),XH(I),-13)
0179      1 CONTINUE
0180      CALL PTPLOT(XV,YV,1,NP,-1)
0181      IF(JUMPOUT.EQ.3)CALL GREND
0182      CALL FRAME
0183      RETURN
0184      END

```

END OF SEGMENT, LENGTH 230, NAME PLOTITOUT

```

0185      SUBROUTINE DELTAH(XH,XL,T,NP,ALPHA)
0186      DIMENSION XH(100),XL(100),T(100),G(100),S(100)
0187      H=-2.303*8.31432*ALPHA
0188      WRITE(6,300)H
0189      WRITE(6,301)
0190      SAV=0.0
0191      DO 1 I=1,NP
0192      G(I)=-8.31432*2.303*T(I)*XH(I)
0193      S(I)=(H-G(I))/T(I)
0194      SAV=SAV+S(I)
0195 1 CONTINUE
0196      SAV=SAV/NP
0197      WRITE(6,302)(T(I),G(I),S(I),I=1,NP)
0198      WRITE(6,304)
0199      WRITE(6,303)SAV
0200      RETURN
0201 300 FORMAT(//,28H THE CALCULATED ENTHALPY IS:,F15.5)
0202 301 FORMAT(//,25X,2H T,25X,2H G,25X,2H S)
0203 302 FORMAT(//,15X,F15.5,12X,F15.5,12X,F15.5)
0204 303 FORMAT(//,24H THE AVERAGE ENTROPY IS:,F15.5)
0205 304 FORMAT(1H1)
0206      END

```

END OF SEGMENT, LENGTH 131, NAME- DELTAH

```

0207 SUBROUTINE LEASTSQ(XH,XL,NP,ALPHA,A)
0208 DIMENSION XH(100),XL(100)
0209 VH=0.0
0210 VL=0.0
0211 T1=0.0
0212 T2=0.0
0213 T3=0.0
0214 DO 1 I=1,NP
0215 VH=VH+XH(I)
0216 VL=VL+XL(I)
0217 1 CONTINUE
0218 VHM=VH/NP
0219 VLM=VL/NP
0220 DO 3 I=1,NP
0221 T1=T1+((XH(I)-VHM)*(XL(I)-VLM))
0222 T3=T3+((XH(I)-VHM)**2)
0223 T2=T2+((XL(I)-VLM)**2)
0224 3 CONTINUE
0225 R=T1/(SQRT(T2*T3))
0226 B=T1/T2
0227 A=(VH/NP)-(B*VL/NP)
0228 WRITE(6,200)B
0229 WRITE(6,201)R
0230 WRITE(6,202)A
0231 WRITE(6,203)
0232 WRITE(6,204)
0233 WRITE(6,203)
0234 AA=0.0
0235 DO 2 I=1,NP
0236 AA=AA+(XH(I)-VHM)**2
0237 2 CONTINUE
0238 BB=(1.0-(R**2))*AA
0239 CC=AA
0240 AA=(R**2)*AA
0241 WRITE(6,205)AA,AA
0242 WRITE(6,203)
0243 IDOF=NP-2
0244 XM1=BB/IDOF
0245 WRITE(6,206)IDOF,BB,XM1
0246 WRITE(6,203)
0247 IDOF=NP-1

```

```

0248      WRITE(6,207) IDOF,CC
0249      WRITE(6,203)
0250      S1=SQRT(XM1)
0251      WRITE(6,208) S1
0252      WRITE(6,209)
0253      ALPHA=B
0254      RETURN
0255 200  FORMAT(//,40H A PLOT OF THE 1ST COL VS 2ND HAS SLOPE:,F15.5)
0256 201  FORMAT(//,32H THE CORRELATION COEFFICIENT IS:,F15.5)
0257 202  FORMAT(//,18H THE INTERCEPT IS:,F15.5)
0258 203  FORMAT(//,20H -----
0259      1-----)
0260 204  FORMAT(//,20H SOURCE OF VARIATION,13X,7H D.O.F.,13X,15H SUM OF SQU
0261      ARES,13X,12H MEAN SQUARE)
0262 205  FORMAT(//,18H DUE TO REGRESSION,16X,2H 1,18X,F15.5,11X,F15.5)
0263 206  FORMAT(//,28H ABOUT REGRESSION (RESIDUAL),6X,15,14X,F15.5,11X,F15.
0264      15)
0265 207  FORMAT(//,6H TOTAL,28X,15,14X,F15.5)
0266 208  FORMAT(//,36H THE RESIDUAL STANDARD DEVIATION IS:,F15.5)
0267 209  FORMAT(1H1)
0268      END

```

END OF SEGMENT, LENGTH 256, NAME LEASTSQ

```

0269      SUBROUTINE MEANS(AH,AL,NP,ALPHA,A)
0270      DIMENSION AH(100),AL(100)
0271      WRITE(6,400)
0272      Y3=(AH(7)+AH(6))/2.0
0273      Y1=(AH(1)+AH(2))/2.0
0274      X3=(AL(7)+AL(6))/2.0
0275      X1=(AL(1)+AL(2))/2.0
0276      ALPHA=(Y3-Y1)/(X3-X1)
0277      WRITE(6,401)ALPHA
0278      A=((Y3*X1)-(X3*Y1))/(X1-X3)
0279      WRITE(6,402)A
0280      X=0.0
0281      Y=0.0
0282      DO 1 I=1,NP
0283      X=X+AL(I)
0284      Y=Y+AH(I)
0285 1      CONTINUE
0286      X=X/NP
0287      Y=Y/NP
0288      AA=0.0
0289      DO 2 I=1,NP
0290      AA=AA+(AH(I)-Y)*(AL(I)-X)
0291 2      CONTINUE
0292      AA=ALPHA*AA
0293      WRITE(6,403)AA
0294      BB=0.0
0295      DO 3 I=1,NP
0296      BB=BB+(AH(I)-A-(ALPHA*AL(I)))**2
0297 3      CONTINUE
0298      BB=BB/(NP-2)
0299      WRITE(6,404)BB
0300      RETURN
0301 400  FORMAT(/,30H THE PLOT IS BEING REPEATED USING MEANS)
0302 401  FORMAT(/,14H THE SLOPE IS:,F15.5)
0303 402  FORMAT(/,18H THE INTERCEPT IS:,F15.5)
0304 403  FORMAT(/,22H M.SQUARE DUE TO REG.:,F15.5)
0305 404  FORMAT(/,21H M.SQUARE ABOUT REG.:,F15.5)
0306      END

```

Appendix D

```

0007      MASTER CURVETEST
0008 C THIS PROGRAM IS DESIGNED TO FUSE TOGETHER 2 SINGLE I.R. BANDS WHOSE
0009 C PROFILES ARE PROVIDED ON PAPER TAPE IN THE FORM OF TRANSMITTANCE DATA.
0010 C THE CURVES ARE OVERLAPPED TO / DIFFERING EXTENTS, STARTING WITH AN
0011 C OVERLAP OF 400 DATA POINTS, AND THEN DECREASING IN UNITS OF 25.
0012 C TWO PLOTS ARE PRODUCED FOR EACH OVERLAP, ONE IS LARGE IN ORDER TO TEST
0013 C GRAPHICAL METHODS OF CURVE RESOLUTION, AND ONE IS SMALL FOR THESIS
0014 C PURPOSES. A PUNCHED TAPE RECORD OF THE COMBINED PROFILES IS ALSO PRODUCED
0015 C AND THIS IS STORED IN A STATED FILE. THE PUNCHED OUTPUT IS IN ABSORBANCE
0016 C AND WAVENUMBER AND CAN THEN BE USED (AFTER CONVERSION) FOR CURVE RESOLUTION.
0017      DIMENSION HEAD1(20), HEAD2(20), IX1(2000), IX2(2000), XV(4000), XI1(200
0018      10), XI2(2000), XIX(4000)
0019      READ(5,100)(HEAD1(I), I=1,10)
0020      READ(5,100)(HEAD2(I), I=1,10)
0021      WRITE(6,100)(HEAD1(I), I=1,10)
0022      WRITE(6,100)(HEAD2(I), I=1,10)
0023      READ(5,101)WB,WI
0024      READ(5,102)NP1,NP2
0025      READ(5,108)ALPHA1,ALPHA2
0026      WRITE(6,109)ALPHA1
0027      WRITE(6,110)ALPHA2
0028      WRITE(6,103)WB
0029      WRITE(6,104)WI
0030      WRITE(6,105)NP1
0031      WRITE(6,106)NP2
0032      READ(5,107)(IX1(I), I=1,NP1)
0033      WRITE(6,107)(IX1(I), I=1,NP1)
0034      READ(5,107)(IX2(I), I=1,NP2)
0035      WRITE(6,107)(IX2(I), I=1,NP2)
0036      L=400
0037      DO 4 I=1,NP1
0038      XI1(I)=0.4343*(ALOG(1.0/(0.001*IX1(I))))
0039      4 XI1(I)=XI1(I)-ALPHA1
0040      WRITE(6,111)(XI1(I), I=1,NP1)
0041      DO 5 I=1,NP2
0042      XI2(I)=0.4343*(ALOG(1.0/(0.001*IX2(I))))
0043      5 XI2(I)=XI2(I)-ALPHA2
0044      WRITE(6,111)(XI2(I), I=1,NP2)
0045      DO 99 N=1,7
0046      DO 1 I=1,L
0047      XIX(NP1-L+I)=XI1(NP1-L+I)+XI2(I)

```

```

0048      1 CONTINUE
0049      J=NP1-L
0050      DO 2 I=1,J
0051      XIX(I)=X11(I)
0052      2 CONTINUE
0053      J=L+1
0054      DO 3 I=J,NP2
0055      XIX(NP1-L+I)=X12(I)
0056      3 CONTINUE
0057      K=NP1+NP2-L
0058      WRITE(6,111)(XIX(I),I=1,K)
0059      CALL LIMITS(1,0,8,0,1,0,8,0)
0060      PK=K-1
0061      WL=UB-PK*WI
0062      CALL REGION(WL,WB,-0.1,1,0)
0063      CALL AXES
0064      Q=0,0
0065      XB=WB
0066      DO 6 I=1,K
0067      XV(I)=XB-Q
0068      XB=XV(I)
0069      6 Q=WI
0070      CALL GRAPHN(XV,XIX,1,K)
0071      CALL FRAME
0072      CALL LIMITS(3,0,6.5,3.0,6,5)
0073      CALL REGION(WL,WB,-0.1,1,0)
0074      CALL AXES
0075      CALL GRAPHN(XV,XIX,1,K)
0076      CALL FRAME
0077      WRITE(7,108)(XV(I),XIX(I),I=1,K)
0078      CALL RUNOUT(7)
0079      L=L-25
0080      99 CONTINUE
0081      CALL GREND
0082      CALL EXIT
0083      100 FORMAT(10A8)
0084      101 FORMAT(2F15,5)
0085      102 FORMAT(2I5)
0086      103 FORMAT(//,28H THE STARTING WAVENUMBER IS:,F15,5)
0087      104 FORMAT(//,28H THE WAVENUMBER INTERVAL IS:,F15,5)
0088      105 FORMAT(//,31H THE 1ST.SET OF POINTS NUMBERS:,I5)
0089      106 FORMAT(//,31H THE 2ND.SET OF POINTS NUMBERS:,I5)
0090      107 FORMAT((8(1X,I3,2X)),1X,I3,1X)
0091      108 FORMAT(F15,5,F15,5)

```

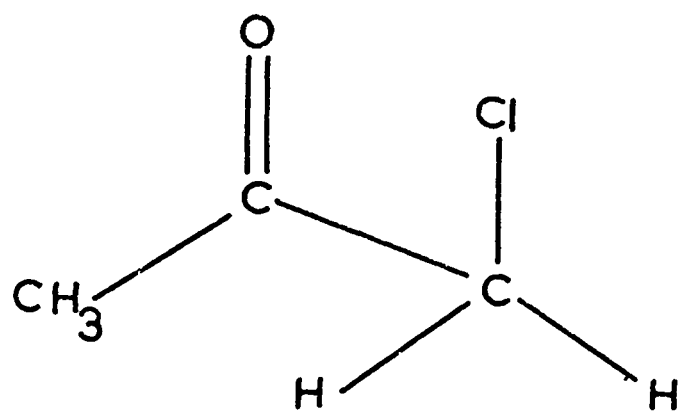
```
0092      109 FORMAT(//,27H THE 1ST,BASELINE SHIFT IS:,F15.5)
0093      110 FORMAT(//,27H THE 2ND,BASELINE SHIFT IS:,F15.5)
0094      111 FORMAT(6(F15.5,3X))
0095          STOP
0096          END
```

END OF SEGMENT, LENGTH 456, NAME CURVETEST

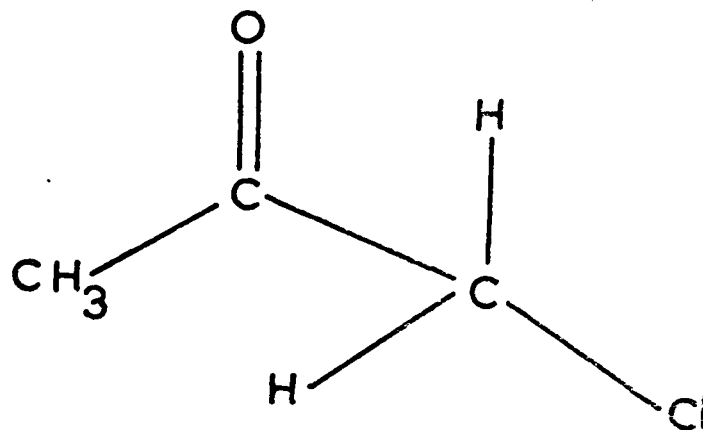
SUMMARY

Because the measured thermodynamic properties of ethane did not agree with those calculated from statistical mechanics, Pitzer¹ proposed the existence of energy barriers hindering internal rotation about single bonds. A consequence of hindered rotation is that molecules may exist in more than one stable conformation: these conformations are referred to as "rotational isomers". Depending on the magnitude of the energy barrier relative to thermal energy, the conformers (or rotamers) may be individually isolable (as in ortho-substituted biphenyls²) or in dynamic equilibrium (as in halogeno-ethanes). There is no simple explanation for the magnitudes of energy barriers: the various theories which have been proposed are reviewed by Dale³ and Lowe.⁴

Irrespective of the barrier height, the infra red spectrum of a mixture of two rotamers often shows doubling of characteristic group bands. Thus chloroacetone (I), in carbon tetrachloride solution, has two carbonyl bands^{5,6} which may be assigned to rotamers (Ia) and (Ib).



(Ia)



(Ib)

Similar band doubling is found in, inter alia, α -haloesters,⁷ α -hydroxyesters,⁸ and α -haloamides.⁵ There are, however, many cases of carbonyl band doubling which either cannot, or can only in part, be a consequence of rotational isomerism; examples are legion and include cyclopentanone,⁹ benzoyl chloride,¹⁰ and p-benzoquinone.¹⁰ Often, in a particular case, the origin of observed carbonyl band doubling may not be obvious, possible additional sources of band complexity being dimer or complex formation, Fermi resonance, and the fortuitous occurrence of hot bands, combination bands, and overtones in the carbonyl region.

The nuclear magnetic resonance spectrum of a molecule may be affected by rotational isomerism. When the energy barrier between rotamers is small compared with thermal energy, a single time-averaged parameter (chemical shift or coupling constant) is observed. In favourable cases, the parameters of individual isomers may be measured from low-temperature spectra where the rotameric equilibrium is "frozen".

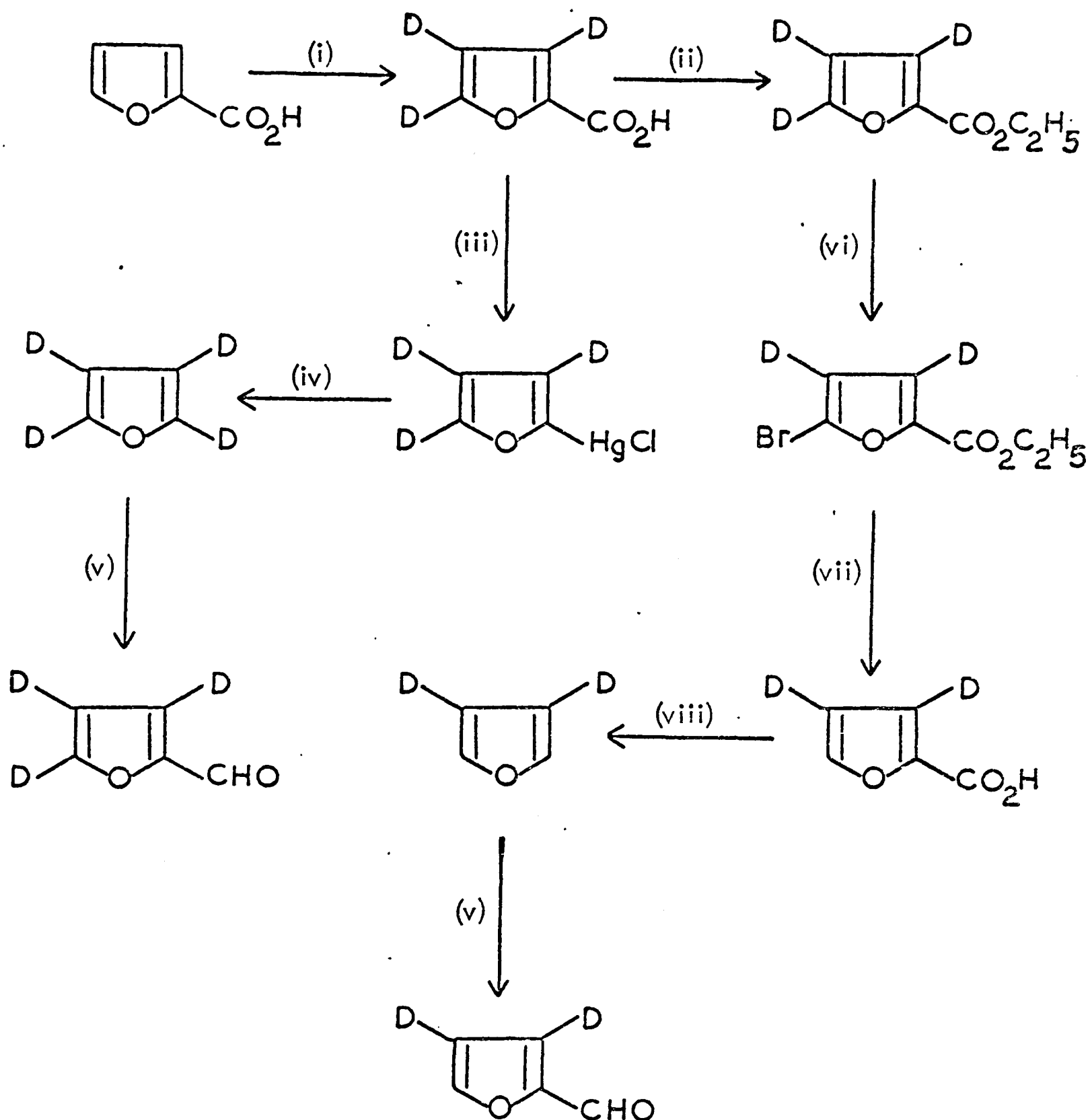
The present work is concerned with: (i) an investigation into the origins of the i.r. carbonyl band complexities of furan-2-carbaldehyde, thiophen-2-carbaldehyde, and furan-2-carbonyl chloride; (ii) an investigation, generally, into the occurrence of rotational isomerism and Fermi resonance in 2-oxo-furans, which provided reliable criteria for distinguishing between the two phenomena and reconciled the results of n.m.r., i.r., and X-ray studies; (iii) the devising of synthetic routes to specifically deuterated furans and thiophenes with a view to topics (i) and (ii); (iv) the assigning of particular conformations to particular components of the i.r. carbonyl doublets in simple esters of furan-2-carboxylic acid and of the 4- and 5-bromofuran-2-acids, where rotational isomerism is demonstrated to be responsible for the band doubling; (v) the setting up and

modifying of computer programs for the digital resolution of overlapping i.r. curves, which allowed a comparison to be made between analogue, digital, and graphical methods; (vi) an examination of the theoretical basis of the i.r. method for the determination of the energy and entropy differences between rotamers, and (vii) the devising of computer programs for data processing based upon the results from topics (v) and (vi).

Topics (i), (ii) and (iii) involved the synthesis and examination (by high resolution i.r. spectrometry, over a temperature range of at least 100°C, in a variety of solvents, and at different concentrations) of some 35 derivatives of furan and thiophen including 5-deuterio-, 3,4-dideuterio-, and 3,4,5-trideuterio-furan-2-carbaldehydes, 5-deuteriofuran-2-carbonyl chloride, and 5-deuterio-thiophen-2-carbaldehyde. The synthesis of deuterated heterocyclic compounds is not straightforward, multi-stage syntheses often being required. The routes to some of the key compounds are shown in Schemes 1 and 2.

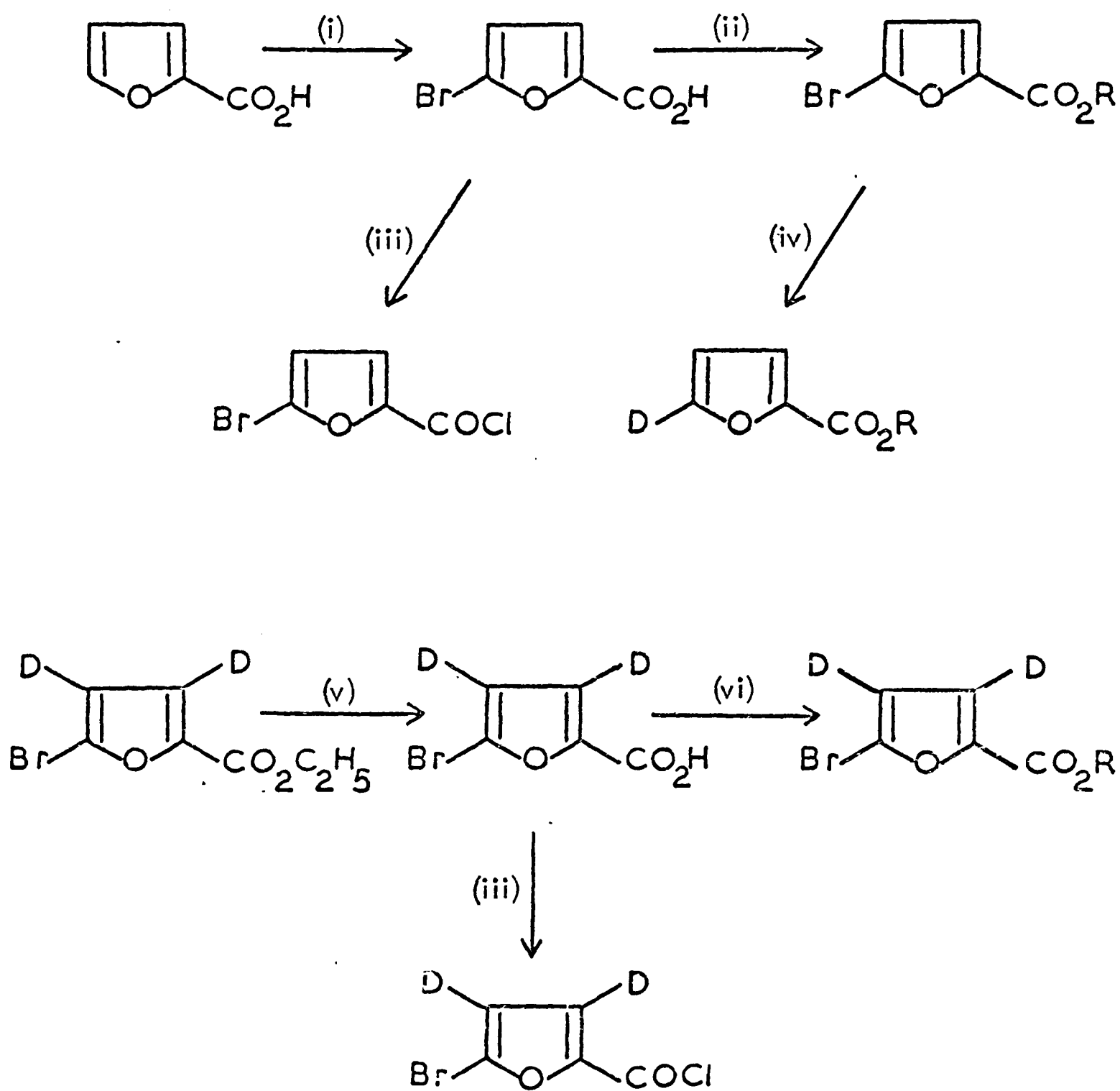
In the i.r. carbonyl region, furan-2-carbaldehyde has two bands (at 1700 and 1681 cm^{-1} in carbon tetrachloride at 30°C), of which neither the temperature dependence, nor the concentration dependence, nor the solvent dependence suggest that anything other than rotational isomerism is responsible; thiophen-2-carbaldehyde, however, has three bands in the carbonyl region (at 1688, 1677, and 1659 cm^{-1} in carbon tetrachloride at 30°C) which show a dramatic solvent and temperature dependence, and furan-2-carbonyl chloride has four such bands. When the hydrogen atom at the 5-position in each of these compounds is replaced by deuterium, dramatic changes in the carbonyl band envelopes occur in all cases: thus, (a) in furan-2-carbaldehyde, the doublet is replaced by a singlet (at 1693 cm^{-1}); (b) in thiophen-2-carbaldehyde, the bands at

Scheme 1



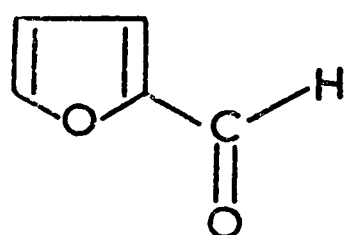
Reagents: (i) 30% NaOD-D₂O; (ii) C₂H₅OH-H₂SO₄; (iii) Na-salt-HgCl₂-H₂O; (iv) 20% DCl-D₂O; (v) POCl₃-(CH₃)₂N·CHO; (vi) Br₂-Cl(CH₂)₂Cl; (vii) Zn-CH₃CO₂H-H₂O, and (viii) Cu-bronze-quinoline.

Scheme 2

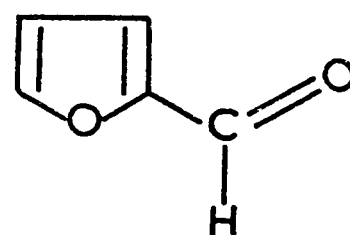
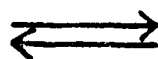


Reagents: (i) $\text{Br}_2\text{-CHCl}_3$; (ii) CH_3OH ($\text{R} = \text{CH}_3$), $\text{C}_2\text{H}_5\text{OH}$ ($\text{R} = \text{C}_2\text{H}_5$), isobutene ($\text{R} = \text{t-C}_4\text{H}_9$), and H_2SO_4 ; (iii) SOCl_2 ; (iv) $\text{Zn-(CH}_3\text{CO)}_2\text{O-D}_2\text{O}$; (v) 20% $\text{NaOD-D}_2\text{O}$, and (vi) $\text{CH}_2\text{N}_2\text{-(C}_2\text{H}_5)_2\text{O}$.

1659 and 1677 cm^{-1} disappear and a new, weak band at 1672 cm^{-1} emerges, and (c) the four component absorption of furan-2-carbonyl chloride is replaced by a doublet. The observed multiple absorptions are therefore caused completely or mainly by Fermi resonance in the aldehydes, and (very probably) by a combination of Fermi resonance and rotational isomerism in furan-2-carbonyl chloride. Thus, although it is a simple matter to distinguish between many of the possible causes of i.r. carbonyl band doubling, to distinguish between rotational isomerism and Fermi resonance in a particular case requires: (a) the synthesis of specifically deuterated analogues; (b) the synthesis of structural analogues; (c) a detailed examination of solvent, temperature, and concentration dependence of carbonyl bands, and (d) a detailed examination of the carbonyl overtone and other i.r. spectral regions. Results of studies of types (c) and (d) are not conclusive without those of types (a) and (b), for, in the furan-2-carbaldehyde example, studies of type (c) reveal no anomalies, and band doubling is observed in the carbonyl overtone and other spectral regions. Since there is a wealth of evidence^{11,12,13,14} from other physical techniques in favour of furan-2-carbaldehyde and related compounds existing in solution, as equilibrium mixtures of syn and anti rotamers [(IIa) and (IIb)]:



(IIa)

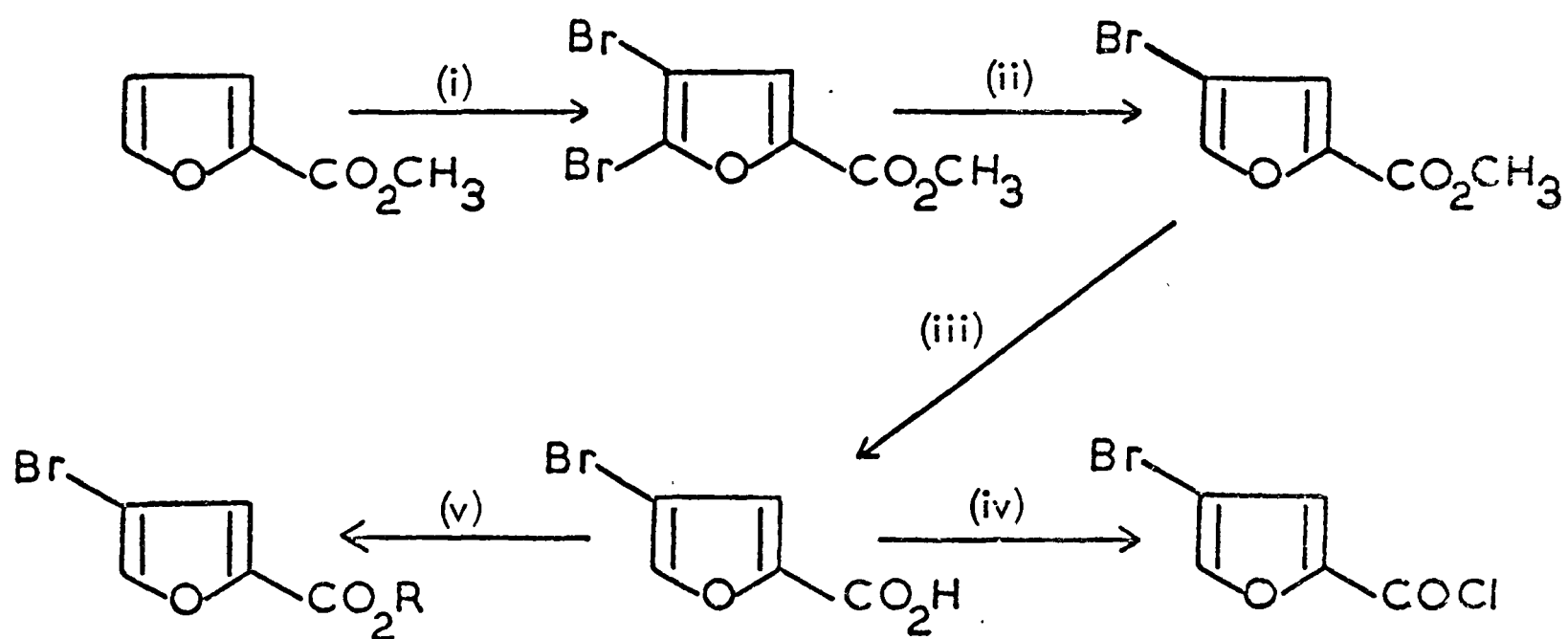
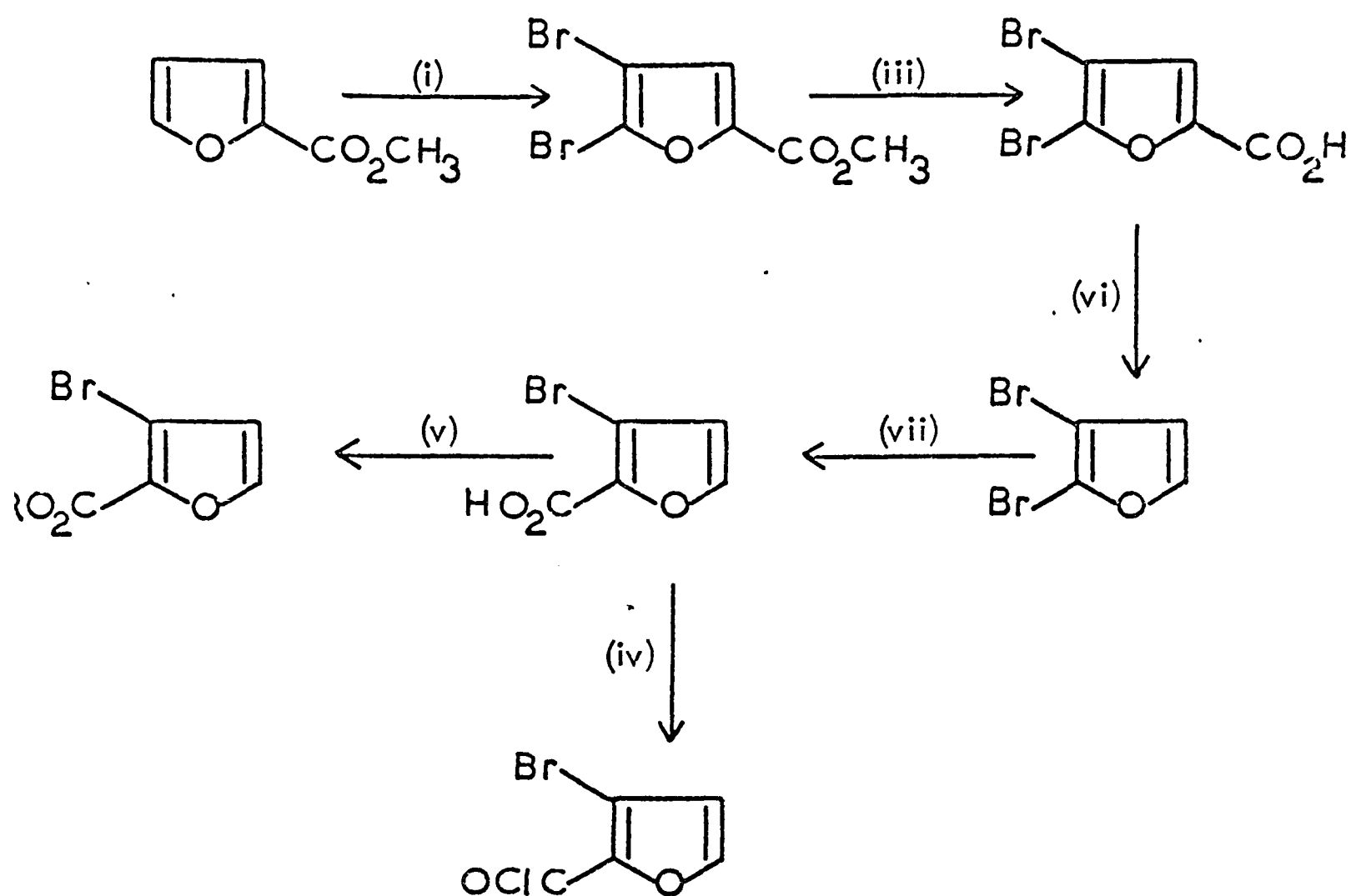


(IIb)

and since carbonyl band doubling is only rarely observed in substituted furan-2-aldehydes and -ketones, it must be concluded that the i.r. carbonyl absorptions of syn and anti forms occur at very similar frequencies in these compounds.

The problem of assigning particular conformations to individual components of i.r. carbonyl doublets [Topic (iv)] was approached by the synthesis and examination of 3-, 4-, and 5-bromofuran-2-carboxylates and of related non-brominated and deuterated esters. Some of the compounds are shown in Schemes 2 and 3; in all, some 30 compounds were examined. The general conclusion is that simple esters of furan-2-carboxylic acid, and of 4- and 5-bromofuran-2-carboxylic acids, exhibit rotational isomerism in dilute carbon tetrachloride solutions at room temperature, a consequence being the occurrence of doublet carbonyl bands separated by 15 to 20 cm^{-1} . This conclusion is supported by the results of deuteration experiments (all of the deuterated esters have carbonyl absorptions very similar to those of the protio analogues except in the case of methyl 5-bromofuran-2-carboxylate where the four-component carbonyl absorption collapses, on deuteration at the 3- and 4-positions, to a doublet), and by examinations of the carbonyl overtone region and of the solvent, temperature, and concentration dependence of the carbonyl bands. Because, in all cases, the position of the band at higher wavenumber in an i.r. carbonyl band doublet is more sensitive to change in solvent polarity than the position of the lower wavenumber band, and because the intensities of the higher wavenumber bands increase relative to those of the lower wavenumber bands as the solvent polarity is increased, it is deduced that the rotamer of greater polarity is responsible for the higher wavenumber carbonyl band. A consideration of the relative positions of the carbonyl bands of the various bromo-esters, and the observation that only one carbonyl band is found for the

Scheme 3

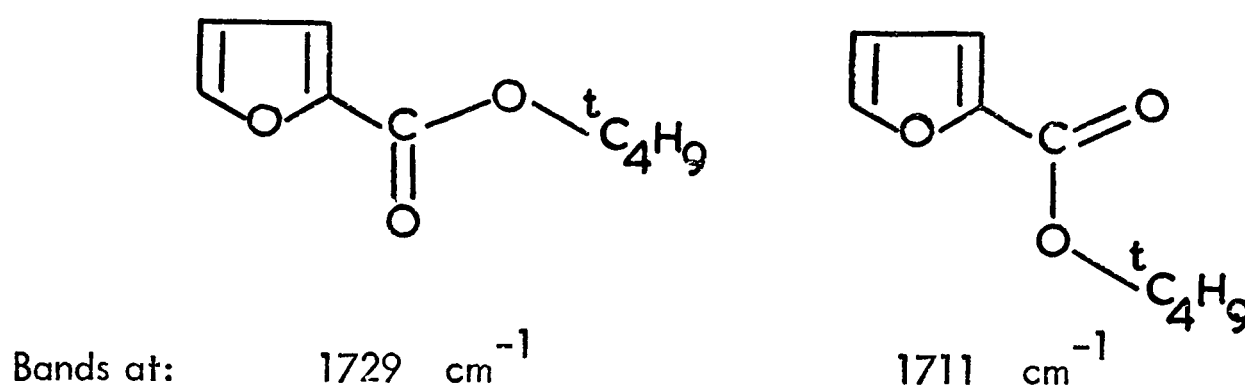


Reagents: (i) $\text{Br}_2\text{-AlCl}_3$; (ii) $\text{Zn-CH}_3\text{CO}_2\text{H-H}_2\text{O}$; (iii) 20% $\text{NaOH-H}_2\text{O}$;

(iv) SOCl_2 ; (v) CH_3OH ($\text{R} = \text{CH}_3$), $\text{C}_2\text{H}_5\text{OH}$ ($\text{R} = \text{C}_2\text{H}_5$), isobutene ($\text{R} = \text{t-C}_4\text{H}_9$),

and H_2SO_4 ; (vi) $\text{HgCl}_2\text{-H}_2\text{O}$, and (vii) $\text{n-C}_4\text{H}_9\text{Li}$, then $\text{CO}_2\text{-(C}_2\text{H}_5)_2\text{O}$.

3-bromo-esters, lead to the conclusion that the syn forms of the esters have carbonyl bands at higher wavenumber than the anti forms: the assignment for t-butyl furan-2-carboxylate is shown below, as an example.



Since the carbonyl bands of rotamers are usually overlapped, it is essential, for accurate quantitative work, to decompose such bands into the component curves. Analogue and digital computer methods were compared using some of the esters discussed previously as model systems [Topic (v)]. Agreement was not good, and the methods were therefore compared with several graphical methods and with a method which takes apparent optical densities as being proportional to component band areas. The comparison was achieved by overlapping artificially (using a computer) two single carbonyl bands of known areas to seven differing extents, and then measuring the areas of the component bands by the various methods. The conclusions from this experiment are that the graphical method of the "mid-point" (which involves dividing the distance between the maxima and integrating from this mid-point) is superior to all other methods, and that the computer resolution methods become inaccurate at close overlap.

The use of i.r. band areas over a range of temperatures, as being proportional to concentrations of species responsible for the bands, to determine

energy and entropy differences between rotamers, assumes that the integrated absorption coefficients of the component bands of a carbonyl doublet are temperature independent. This assumption was tested [Topic (vi)] and found to be invalid, since, whichever method is used to estimate band areas, the areas of carbonyl bands are observed to decrease by about 25% over a 100°C range. A "first-order" correction was therefore devised, which assumes that the absorption coefficients of rotamer doublet carbonyl bands have a similar temperature dependence, which is in turn similar to that observed for arbitrarily selected singlet carbonyl bands. A computer program was then written to apply this correction to data from the esters discussed previously. If the area of one of the component bands of a rotamer carbonyl doublet is plotted against the area of the other, at different temperatures, then the slope of the graph should be negative and equal to the ratio of the absorption coefficients, but only if the absorption coefficients are independent of temperature. In the majority of cases, area plots for the esters give positive (i.e., physically untenable slopes). However, after application of the correction (which has the effect of removing the temperature dependence of the absorption coefficients) these slopes become negative. Because this correction is large, it should be borne in mind that the significance of thermodynamic parameters determined by the i.r. method is open to question.

Finally, since below -90°C the aldehydic proton resonance in the n.m.r. spectrum of furan-2-carbaldehyde appears as two doublets of intensity ratio 8:1, these being assigned¹¹ to individual rotational isomers, the experiment was repeated using C-13 Fourier-transform n.m.r. spectroscopy. At about -45°C , collapse and broadening of the signals assigned to the carbonyl carbon atom and to the carbon atom at the 3-position was observed. A similar variable temperature experiment

with methyl furan-2-carboxylate showed no such "coalescence" phenomenon nor was the phenomenon observed in a variable temperature proton n.m.r. experiment with furan-2-carbonyl fluoride. The barrier to internal rotation about the ring-carbonyl carbon bond in esters and acid halides would therefore seem to be lower than in aldehydes.

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