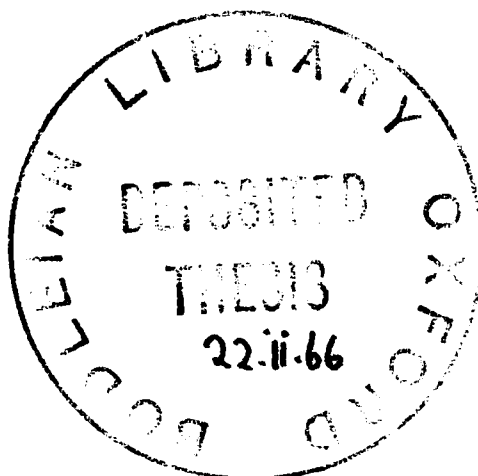


ADDITION REACTIONS OF
SOME UNSATURATED SYSTEMS
POSSESSING ONE OR MORE HETERO ATOMS

A Thesis submitted for the
Degree of Doctor of Philosophy
to the Board of Physical Sciences

by
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PREFACE

The aim of the work described in this thesis was to investigate the reaction of dimethyl acetylenedicarboxylate with as wide a variety of heterocycles as possible, especially those containing two or more nitrogen atoms, in order to determine whether any new types of reactions occurred.

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ABBREVIATIONS

In the structural formulas, α refers to the group $-\text{COOMe}$, except in Chapter Five, where it also refers to the group $-\text{COOEt}$ when indicated by the text.

In tables of infrared absorption spectra, maxima are reported in μ .

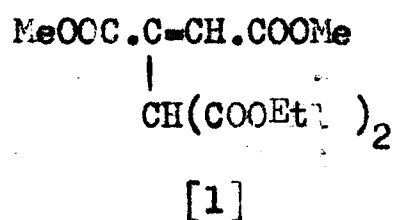
In tables of ultraviolet absorption spectra, maxima are reported in $m\mu$ (10^{-4}s), and the solvents used are methanol (not specified), methanol acidified with one drop of 72% perchloric acid (A), methanol:72% perchloric acid (P), and methanol acidified, then made basic with sodium methoxide (B).

In tables of nuclear magnetic resonance spectra, chemical shifts are reported in τ values, and coupling constants (J) in cycles per second.

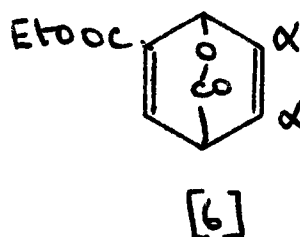
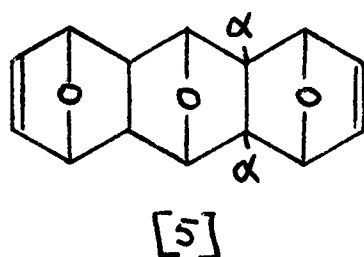
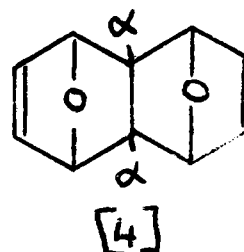
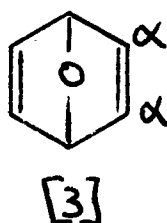
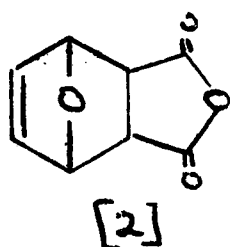
INTRODUCTION

Nucleophilic addition readily occurs to carbon-carbon double bonds conjugated with electron-withdrawing groups; the most important class of these conjugate additions being the well-known Michael reaction.¹ This involves attack by a nucleophile, classically a carbanion, but generally any molecule containing an unshared pair of electrons, on a carbon-carbon multiple bond conjugated with a carbonyl or any other electron withdrawing group.

Dimethyl acetylenedicarboxylate, as well as being attacked by electrophiles, e.g. hydrogen halides and sulphuric acid, readily undergoes the Michael addition. Thus, Michael and Blicher found that sodium ethoxide and the above acetylenic ester gave a mixture of dimethyl diethoxysuccinate, dimethyl ethoxymaleate, and dimethyl ethoxyfumarate,² while the anion of diethyl malonate, followed by protonation gave [1]³



This high reactivity of the triple bond led Diels and Alder to make use of dimethyl acetylenedicarboxylate as one component in investigations of the addition reactions between dienes and dienophiles. They first tried heteroaromatic compounds as potential dienes in 1929, when furan and maleic anhydride were found to react together to give [2]⁴, while dimethyl acetylenedicarboxylate gave [3] which with more furan gave [4] and [5]



α -Pyrones gave similar adducts⁶, e.g. [6], but thiophenes do not react with dienophiles under typical Diels-Alder conditions.⁷ This is in accord with their great resonance stabilisation. Diels and Alder believed that furan was reacting as a conjugated diene (but see later), and in the next decade they investigated the reaction between dimethyl acetylenedicarboxylate and many nitrogenous heterocyclic bases. Except for some unpublished work,⁸ little research was then made in this field until 1954, since when much of Diels' work has been repeated, and many of the structures he proposed for the adducts have been revised, and the adducts found to be Michael-type rather than Diels-Alder type.

The reaction between heterocyclic compounds and dimethyl acetylenedicarboxylate can occur in several ways. However, all the reactions can be explained if the initial step is a Michael addition between one mole of each reactant to give a zwitterion $\text{=}\overset{+}{\text{N}}\text{-C}\alpha\text{=}\bar{\text{C}}\alpha$ which can then

- i) rearrange by a proton shift to form a neutral molecule,
- ii) gain a proton from the solvent,
- iii) cyclise to a "Diels-Alder type" adduct,
- iv) attack a second mole of ester, and then cyclise, or
- v) attack the solvent, then a second mole of ester, and cyclise.

Case (iii) is not easily distinguishable from the true Diels-Alder reaction, both giving the same final product.

In recent years, the kinetics and mechanism of the Diels-Alder reaction have been widely studied. It is generally agreed that the reaction is bimolecular,⁹ but the actual detailed mechanism is still in doubt, the difficulty being that the structure of the transition state can be deduced from kinetic studies alone. Three proposals are current:-

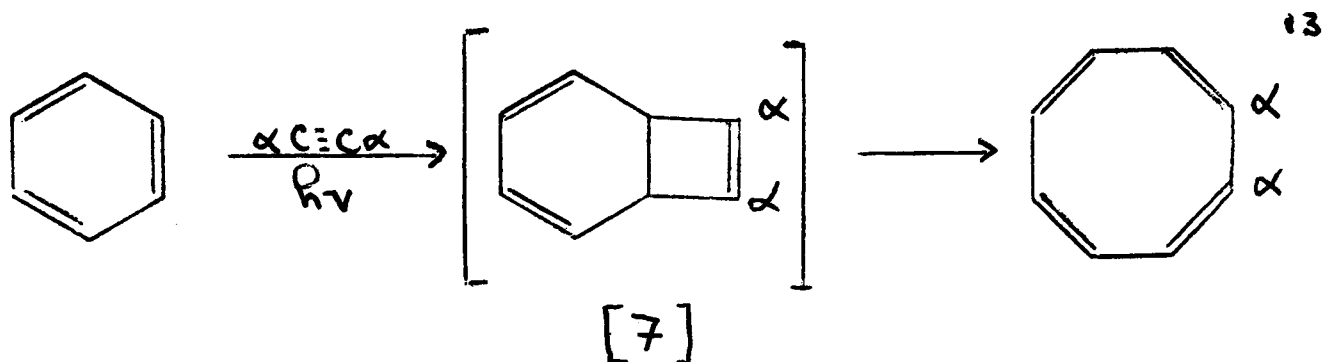
a) The "two-stage" mechanism of Woodward and Katz,¹⁰ in which the transition state contains one of the new bonds, and secondary attractive forces give the intermediate a rigid geometry.

b) The four-centre mechanism¹¹ postulates that the transition state contains the two diene-dienophile bonds, which are partially formed.

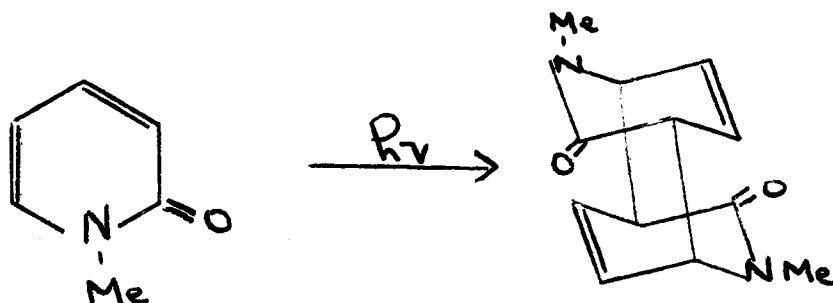
c) The diradical mechanism¹² supports a two-step reaction, the rate-controlling first step of which results in the formation of a diradical, which quickly cyclises to the product.

The differences between (a) and (b) are not great, and possibly some Diels-Alder reaction are of one type, some, of the other. The distinction between them is the nature of the secondary attractive forces.

Mechanism (c) is the most doubtful for normal Diels-Alder conditions, and most of the evidence put forward in support of this theory has been re-evaluated and found to be either ambiguous or supporting either (a) or (b). However, it appears that, activated by ultraviolet light, some additions to dienes occur via a diradical intermediate e.g.



Evidence for [7] being momentarily formed is strengthened by the preparation of the parent hydrocarbon, which rapidly isomerises to cyclooctatetraene at room temperature.¹⁴ The intermediate in the above reaction is a 1,2-diradical, and so this is not a true Diels-Alder addition. However, the photodimerisation of 2-pyridones and 2-aminopyridines presumably proceeds via a 1,4-diradical¹⁵ e.g.

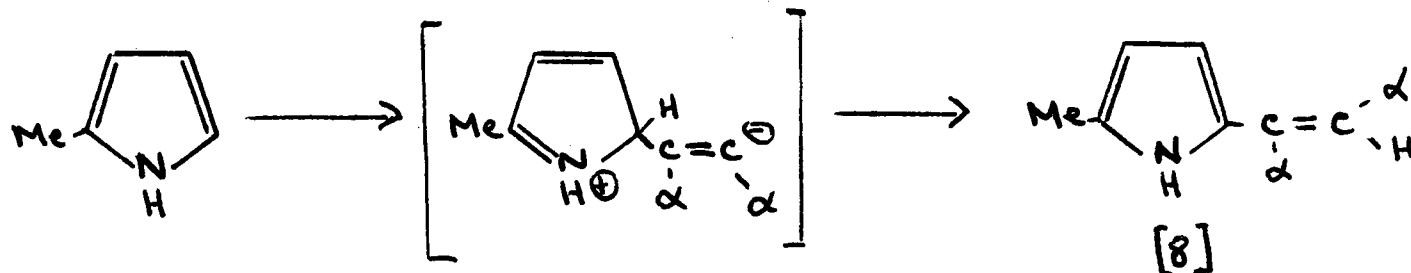


The five reaction types listed on page 2 can be regarded as primary reactions; and the adducts formed by these processes can then undergo secondary transformations such as elimination, rearrangement, or addition of more acetylenic ester in a "true" Diels-Alder fashion.

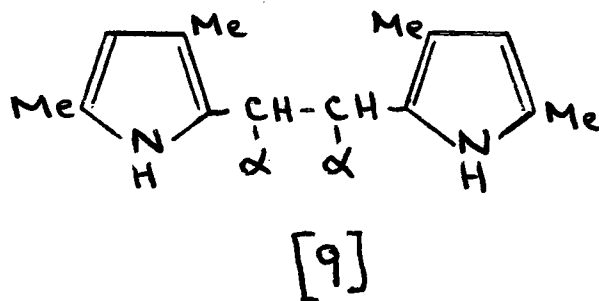
As the possible combinations of these primary and secondary reactions are so numerous, it is best to consider each heterocyclic system separately.

1. Pyrroles unsubstituted on the nitrogen atom react preferentially at the α -position with one mole of dimethyl acetylenedicarboxylate to give a zwitterion which then undergoes proton transfer to give a maleate

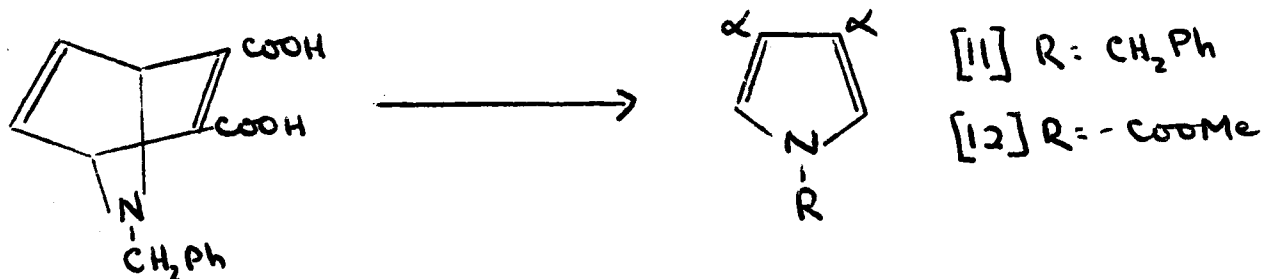
and/or fumarate. Thus, 2-methylpyrrole gives [8]¹⁶ 1,2-Dimethylpyrrole,



2,3-dimethylpyrrole, and 2,3,4-trimethylpyrrole react similarly, but 2,4-dimethylpyrrole give the bis-Michael adduct, [9]¹⁷. If both α -positions are substituted, reaction occurs at a β -position, if one is free.

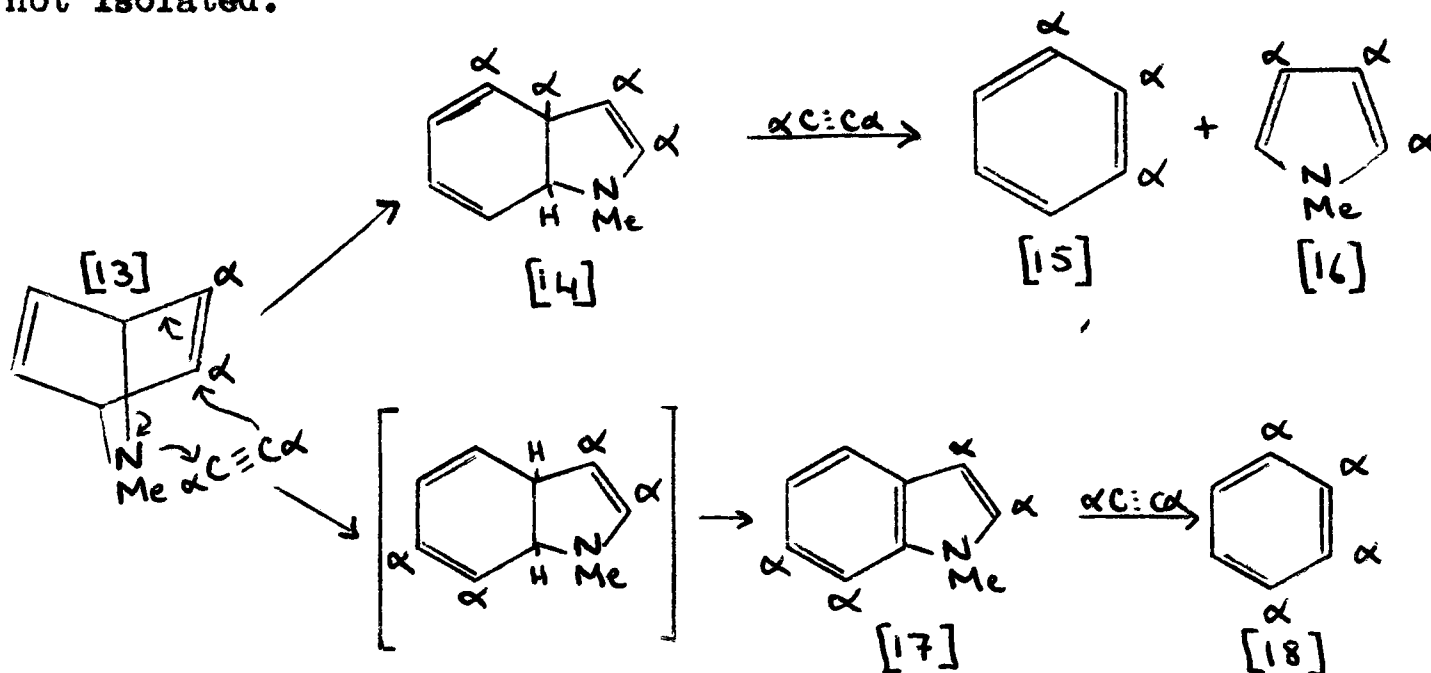


1-Benzylpyrrole and acetylenedicarboxylic acid give a mixture of the 2-pyrrolylfumaric and -maleic acids, plus a small amount of the "Diels-Alder type" adduct [10], which on treatment with diazomethane eliminates acetylene to give [11]¹⁸

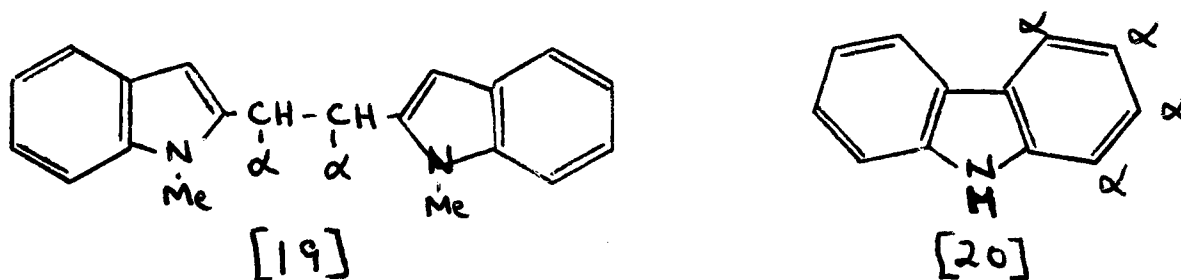


[10] is probably stabilised by formation of a zwitterion. Methyl pyrrole-1-carboxylate and dimethyl acetylenedicarboxylate at 170-200° give [12] and acetylene directly,¹⁹ presumably by way of an intermediate analogous

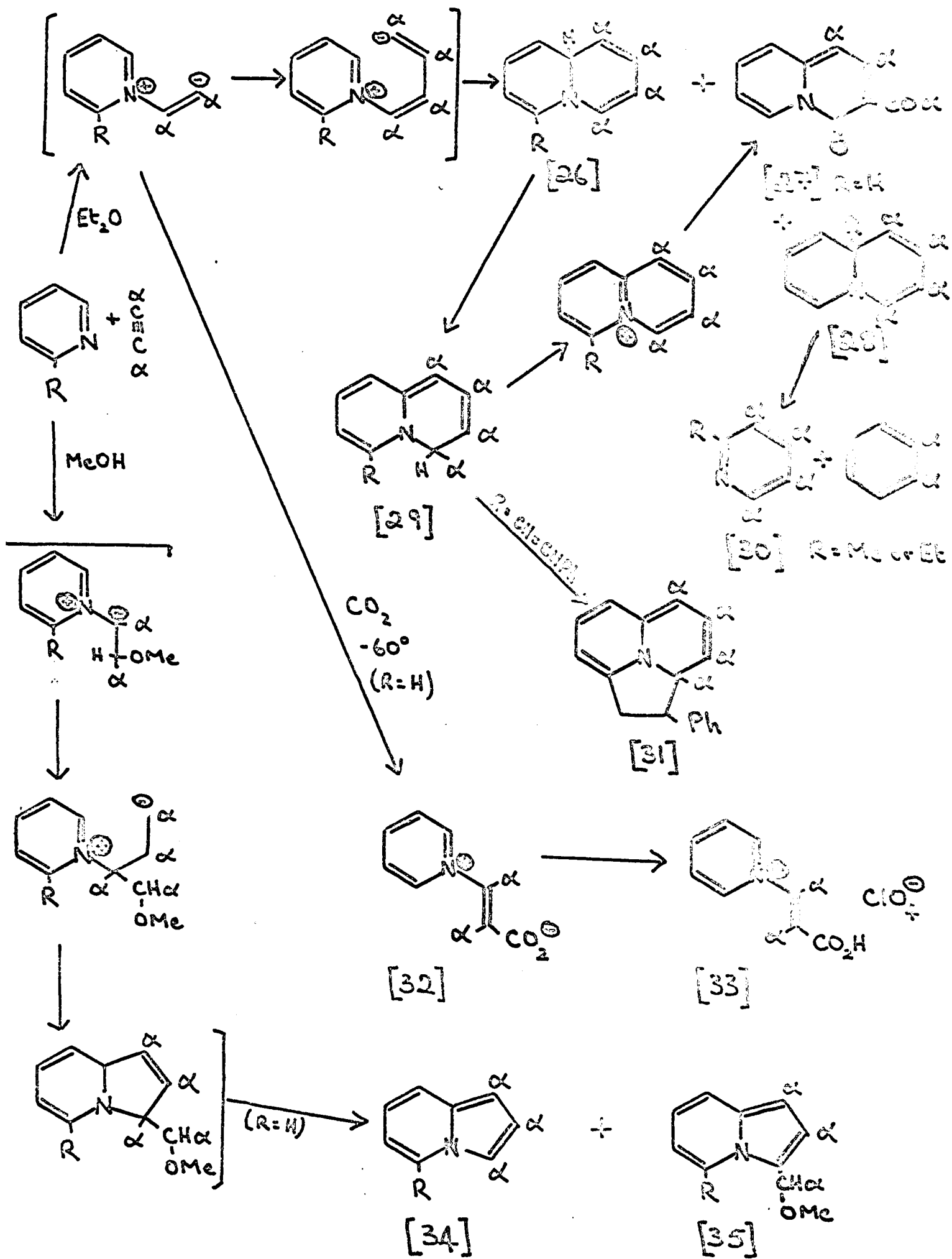
to [10]. 1-Methylpyrrole and the ester react together to give [14]-[18]. The formation of these is due to attack of a second mole of acetylenic ester on the initially-former "Diels-Alder type" adduct [13], itself not isolated.²⁰

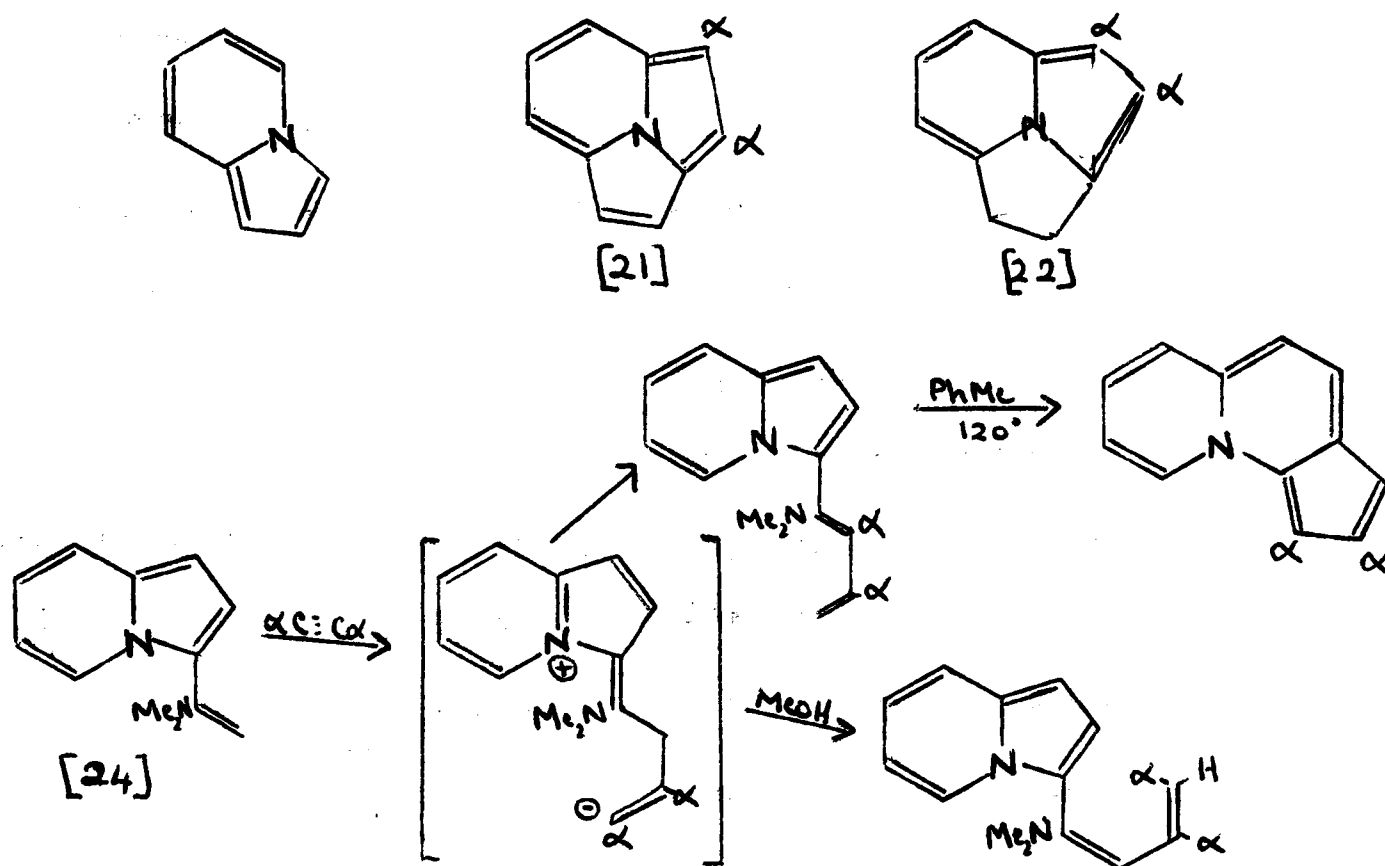


2. Indoles react in a similar manner to pyrroles, but attack occurs at the more reactive 3-position. Thus, 2-methylindole gives a mixture of the indolyl-3-fumarate and -3-maleate.²¹ 1-Methylindole allegedly gives the bis-Michael adduct [19]¹⁶, but the 3,3'-isomer is much more likely, while indole itself gives several adducts with dimethyl acetylenedicarboxylate,²² the major product being the carbazole [20]



3. Indolizine reacts with dimethyl acetylenedicarboxylate under dehydrogenating conditions to give a mixture of [21] and [22],²³ while the enamine [24] undergoes the reactions shown²⁴





4. Pyridines (see flow sheet opposite page 7) The addition of dimethyl acetylenedicarboxylate to pyridine was first studied by Diels and co-workers.²⁵ The major product in ether was the 9aH-quinolizine (the "labile" adduct) which rapidly isomerised to the 4H-quinolizine ("stable" adduct), whose structures were later shown to be [26], (R=H) and [29] (R=H)²⁶ respectively. A minor product, Kashimoto's compound, was shown to have the structure [27]⁸, and can be formed by treatment of the perchlorate of [29] with aqueous sodium bicarbonate.²⁷

With 2-alkylpyridines, the 9aH- and 9a-alkylquinolizines are formed; the former isomerise to the corresponding 4H-quinolizines, but the latter cannot. Instead, they can react with a further mole of acetylenic ester to give [30], ((R=Me or Et)).^{28, 29}

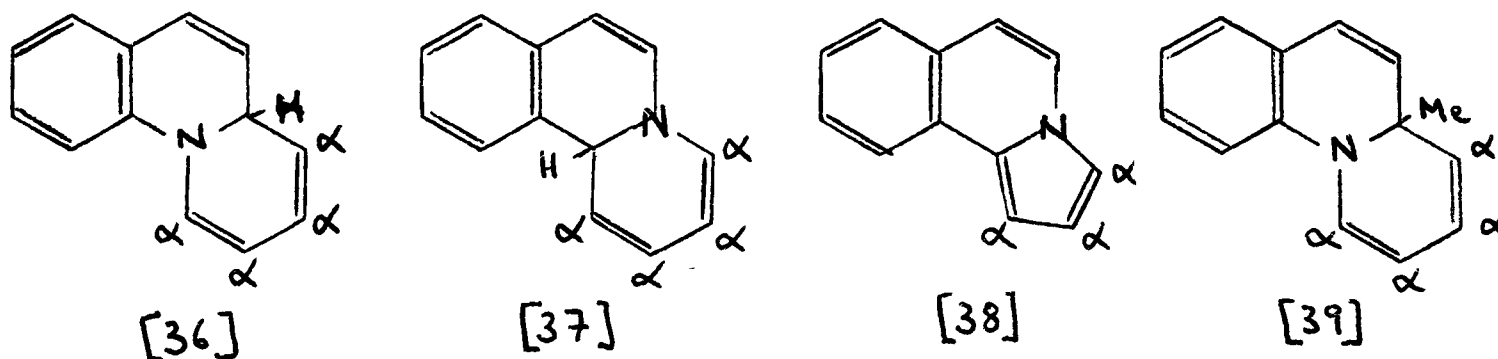
The reaction between pyridine and the ester is probably a two-step Michael reaction. Evidence for this was obtained by Acheson and Plunkett,³⁰

who isolated the betaine [32] by carrying out the reaction at -60° in the presence of carbon dioxide. [32] has been isolated in the cis and trans forms, which both rapidly decompose to starting materials at room temperatures, but form stable perchlorates, [33].

The ease of isomerisation of 9aH-quinolizines to 4H-quinolizines decreases with increase in conjugation or the number of alkyl substituents on the pyridine ring. Thus, the 9aH-quinolizine from pyridine itself is difficult to isolate,^{25, 31, 26} but to isomerise the corresponding compound from phenanthridine (see later) requires heating in quinoline at 140° . A further isomerisation of the 4H-quinolizine from 2-styrylpyridine [29, R=CH=CH-Ph] occurs to give [31].³²

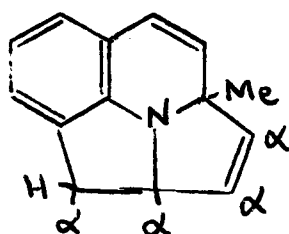
In methanol, pyridine and dimethyl acetylenedicarboxylate give a mixture of [34]³³ and [35]³⁴, probably by the scheme shown.³⁵

5. Quinoline and Isoquinoline. In ether, these react with dimethyl acetylenedicarboxylate to give the benzoquinolizines ([36]³⁶ and [37]³⁷ respectively), which can be isomerised to the 4H-isomers,^{37, 38} while in methanol, isoquinoline gives [38]³⁷

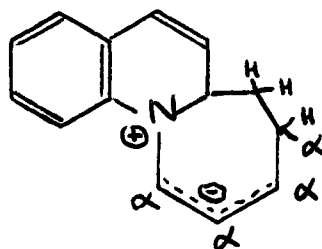


Quinaldine and the ester give some of the adduct [39], but the major product is an isomeric compound, which Diels et al. formulated as [40]³⁸. However, later workers showed by n.m.r. spectroscopy that the

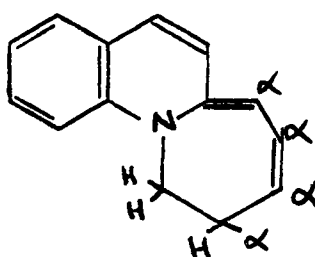
adduct had no C-methyl group, and on little evidence assigned the "ylid" structure [41]³⁹ which would be expected to undergo proton transfer to give an uncharged molecule. More recent work on this compound and analogous adduct from 1-methylisoquinoline and 6-methylphenanthridine has led to the further structure [42] and [43]⁴⁰ being suggested.



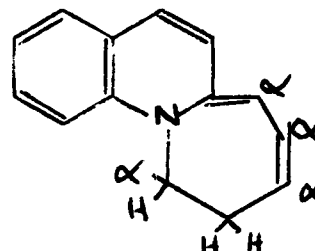
[40]



[41]

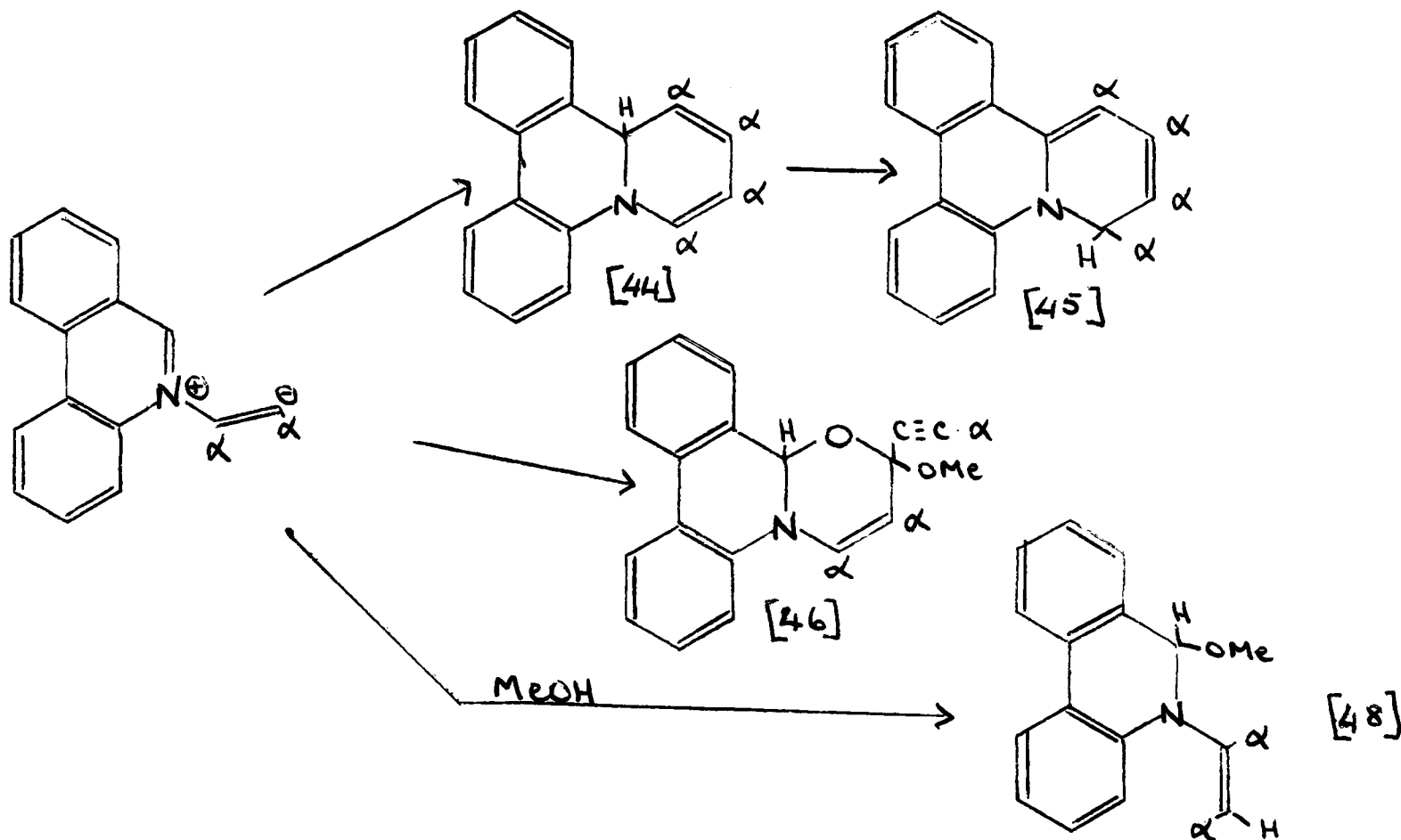


[42]



[43]

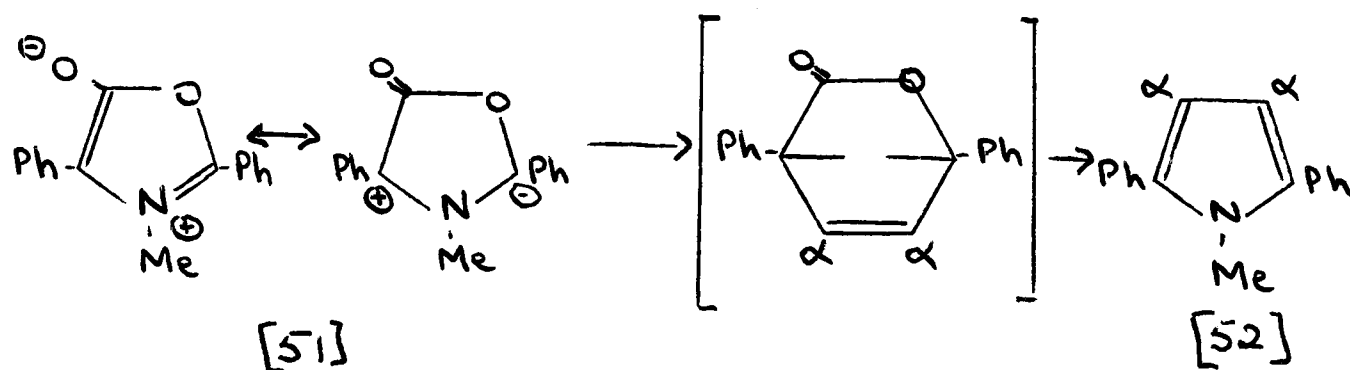
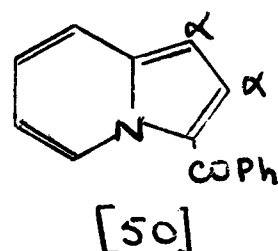
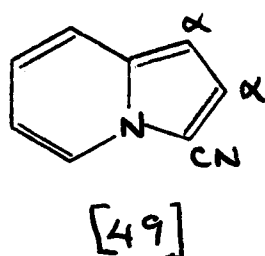
6. Phenanthridine reacts with dimethyl acetylenedicarboxylate in benzene to give [44] as the major product,³⁵ which can be isomerised to the corresponding "stable" isomer [45] by heating in quinoline. A minor product is [46], which results from the initially-formed zwitterion attacking a carbonyl group of the second ester molecule rather than the triple bond. In methanol, the 1:1:1 molar adduct [48] is formed. An



analogous adduct is formed by acridine in methanol.⁴²

The reactions between dimethyl acetylenedicarboxylate and heterocyclic compounds containing two or more hetero atoms have not been widely studied, and those that have will be reviewed in the discussion section.

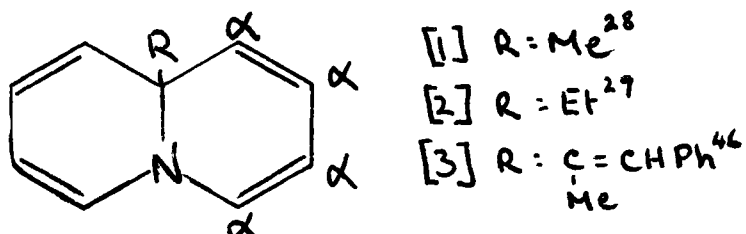
1,3-dipolar additions are closely related to Diels-Alder and the Michael additions above. Examples of this class of reaction are the addition of dimethyl acetylenedicarboxylate to pyridinium-1-dicyanomethylide to give [49]⁴³, to 1-phenylacetylpyridinium bromide to give [50]⁴⁴, and to the azlactone [51] to give [52]⁴⁵.



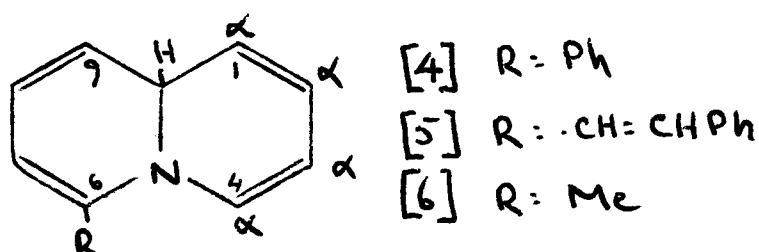
CHAPTER ONE

The Addition of Dimethyl Acetylenedicarboxylate to some 2-Substituted Pyridines

A number of quinolizines of the type [1]-[3] have been prepared, and it was hoped to make such a compound with $R = Ph$.



However, 2-phenylpyridine and dimethyl acetylenedicarboxylate in ether, or better, refluxing acetonitrile, gave a single 1:2 molar adduct, which was shown to be tetramethyl 6-phenyl-9aH-quinolizine-1,2,3,4-tetracarboxylate [4] by comparison of its nuclear magnetic resonance spectrum with those of known compounds (table I). The spectrum



of [4] is closer to that of [5] than of [6], the signals being at lower field due to the deshielding effect of the phenyl ring. The opposite shielding effect of the phenyl group is also shown by the very high field position of the ester signal at 7.00 τ . This must be due to the 4-carbomethoxy group being rigidly held above the benzene ring.

TABLE I

N.m.r. Spectra

<u>4H</u>	<u>6H</u>	<u>7H</u>	<u>8H</u>	<u>9H</u>	<u>9aH</u>	<u>Ester OMe</u>
[4]	2.46-2.72(m) (CH ₅)	3.62	3.92(m)	4.2 — 4.42(m)	4.80 — 4.84(m)	6.08, 6.19, 6.41, 7.00
[5] ⁴⁶			3.8(m)	4.2(m)	4.88(m)	6.08, 6.20, 6.35, 6.57
[6] ²⁹		3.9 —	4.2(m)	4.35(d)	5.03(t)	6.12, 6.16, 6.24, 6.33
[7] 3.68(s)	2.3-2.7(m) (C ₆ H ₅ +8H)	3.20(q) J ₇₈ =7, J ₇₉ =1	2.3-2.7(m)	1.30(q)		6.08, 6.25, 6.29, 6.43
[8] ⁴⁶ 3.32(s)		2.95(d) J ₇₈ =7, J ₇₉ =2	2.48(m)	1.35(d)		6.05 — 6.30
[9] ²⁹ 3.44(s)		3.22(d)	2.56(q)	1.42(d)		6.08, 6.20, 6.27, 6.31
[10]	2.2 — (C ₆ H ₅ + 7H)	2.8(m)	3.4-3.8(m)	4.18(d) J ₃₉ =8	4.64(s)*	6.10, 6.18, 6.33(2) 6.41, 6.82

* this is the proton of the fumarate side chain at the 9a-position

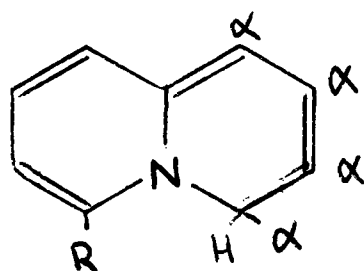
The ultraviolet absorption spectrum of [4], unchanged by acid, is in accord with its structure, being more conjugated than that of [6], but not as conjugated as that of [5] (table II)

TABLE II

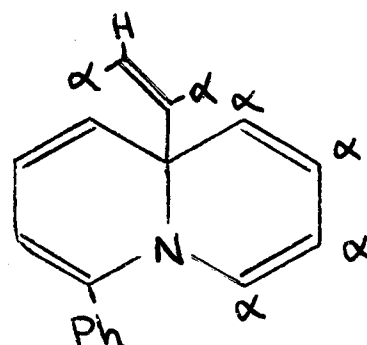
U.V. Spectra

[4]	231*(1.64), 276 (1.71), 318(1.33), 436(0.58)
[5]	231 (1.71), 295* (1.39), 339(2.28), 417(0.46)
[6]	236 (1.61), 294 (1.20) 433(0.52)
[7] M	273.5(1.40), 312(1.56), 356(1.12), 453(1.20)
A	223*(1.58), 260* (0.70), 328(1.15)
[8] M	228 (2.07), 311(2.92), 365(0.99), 465(1.07)
A	226*(1.90) 309(2.04) 390(1.65), 480*(0.36)
[9] M	266 (0.92), 307(1.08), 349(1.14), 443(1.05)
A	321(1.12)
[10]	253 (1.88), 310.5(2.82), 435(1.35)

Heating [4] gives the isomeric tetramethyl 6-phenyl-4H-quinolizine-1,2,3,4-tetracarboxylate [7], as expected by analogy, and shown by comparison of the nuclear magnetic resonance spectrum (table I) and ultraviolet absorption spectrum (table II) of [7] with the spectra of [8] and [9].



[7] R: Ph
[8] R: CH=CHPh
[9] R: Me



[10]

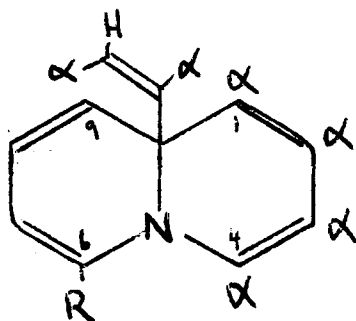
It is noticeable that the nuclear magnetic resonance spectrum of [7] no longer has a very high field methoxyl signal, unlike that of [4], since the 4-carbon has become tetrahedral, and the ester group is no longer held rigidly above the phenyl group.

Heating the quinolizine [4] with excess dimethyl acetylenedicarboxylate gives a 1:1 molar addition compound, whose ultraviolet absorption spectrum resembles that of [4], and is unaffected by acid. The nuclear magnetic resonance spectrum is similar to that of [4], having a very high field methoxyl signal, similar positions of the 7-, 8- and 9-protons, and no low field proton (unlike the spectrum of [7]). Therefore, the compound is assigned structure [10].

Efforts to produce analogous compounds from the 1,2,3,4-tetracarboxy 9aH-quinolizines of pyridine, 3,5-lutidine, quinoline, isoquinoline, and phenanthridine, were unsuccessful.

An attempt was made to synthesise model compounds to compare with [10] by reacting 2-vinylpyridines with the acetylenic ester.

2-Methyl-6-vinylpyridine and dimethyl acetylenedicarboxylate in refluxing acetonitrile give a 1:2 molar adduct, which is formulated as [11] on the basis of its proton resonance spectrum. This has a methyl resonance at 8.07 τ which is the usual position for 6-methyl-9aH-quinolizines. The isomeric 9a-methyl-9aH-quinolizines have a signal at ca. 8.7 τ .²⁹

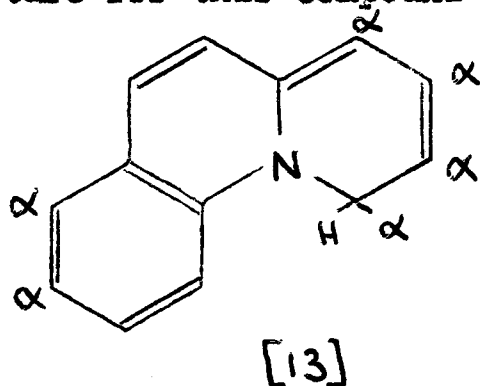


[11] R = Me

[12] R = H

In the corresponding reaction with 2-vinylpyridine, the major product is 9a-vinyl-9aH-quinolizine-1,2,3,4-tetracarboxylate, [12], identified by its nuclear magnetic resonance spectrum, which differs from that of [11] in having no methyl resonance, but has a multiplet at 3.5-3.9 τ assigned to the 6-H atom. Otherwise, the two compounds have a very similar pattern in the region 4-5 τ (7-, 8-, 9-H and vinyl protons), except that additional splitting in the spectrum of [12] occurs because of the additional hydrogen atom. The two spectra have not yet been completely analysed.

A second product was also obtained from this reaction. This was a yellow solid, isolated only once, which rapidly isomerized to an orange compound, even in methanolic solution. Successive attempts to prepare it gave only the orange compound, which is a 1:3 molar adduct, less two hydrogen atoms. The nuclear magnetic resonance spectrum shows the presence of six methoxyl groups and five protons, one of which gives a singlet at 3.08 τ , while the remaining four give four doublets at 1.46 and 2.49 τ ($J = 11\text{c.p.s.}$), and 1.85 and 2.27 τ ($J = 10\text{c.p.s.}$). A possible structure for this compound is [13]



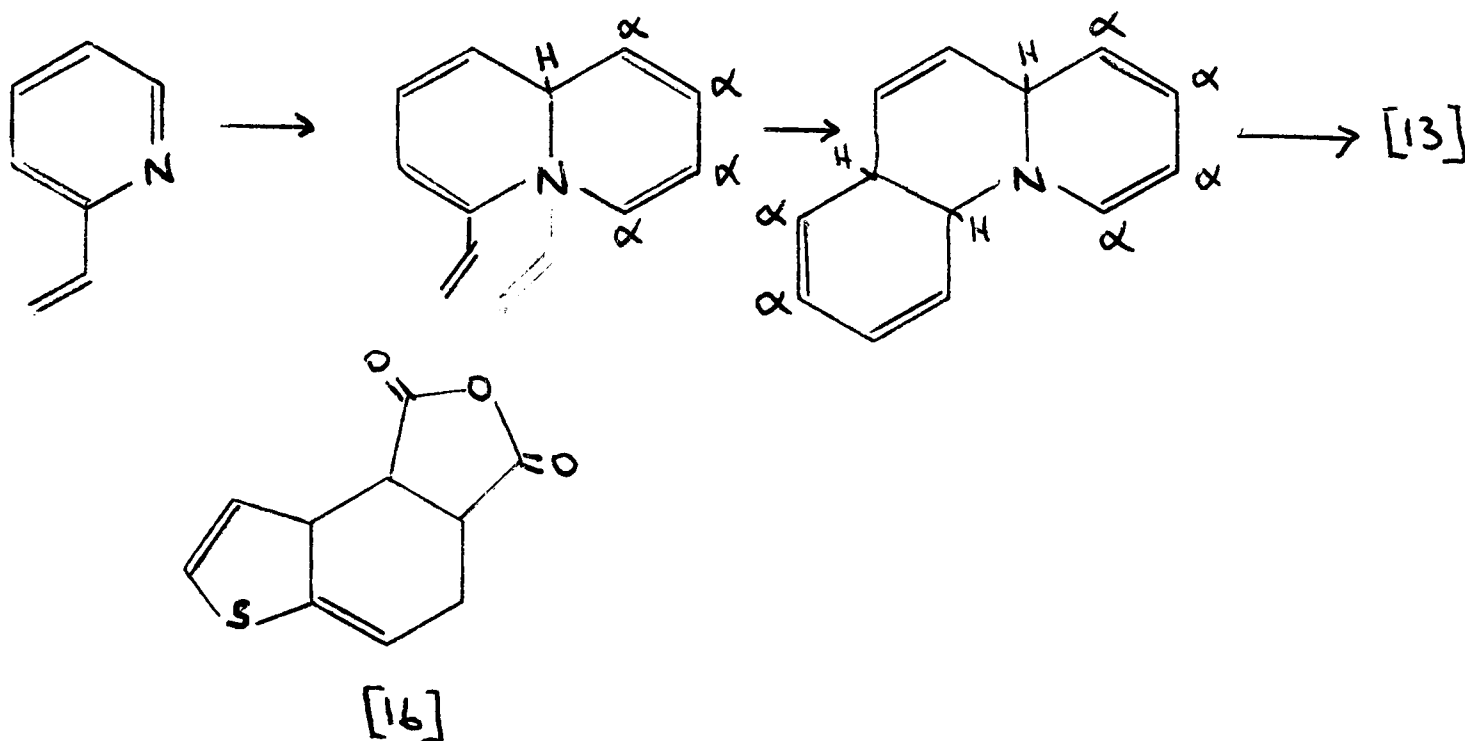
($J_{10,11} = 10$ c.p.s), and the remaining protons give a multiplet at 1.9-2.6 τ .

Unlike the ultraviolet absorption spectrum of [14]³⁸, that of [13] does not change in acid solution. This may be due to the two additional carbomethoxy groups causing a decrease in the basicity. However, in neutral solution the two spectra resemble each other:-

U.V. Spectra

[13]	241*(2.73)	248.5(2.95)	252*(2.94)	280(1.60)	317*(1.05)	356*(0.62)	465(1.67)
[14]		239(2.29)		296(1.51)		330*(0.83)	459(1.33)

A possible mode of formation of [13] is addition of two moles of acetylenic ester to give [15], which then undergoes a Diels-Alder addition across the diene system formed by the vinyl group and one of the double bonds of the ring system (such an addition occurs between 2-vinylthiophene and maleic anhydride to give [16]⁴⁷), followed by aromatisation. The unstable yellow compound may be the dihydro derivative of [13], or the 11a-H isomer of [13]. (The reduction of the acetylenic ester to methyl fumarate in reactions with pyridine has been noted.)

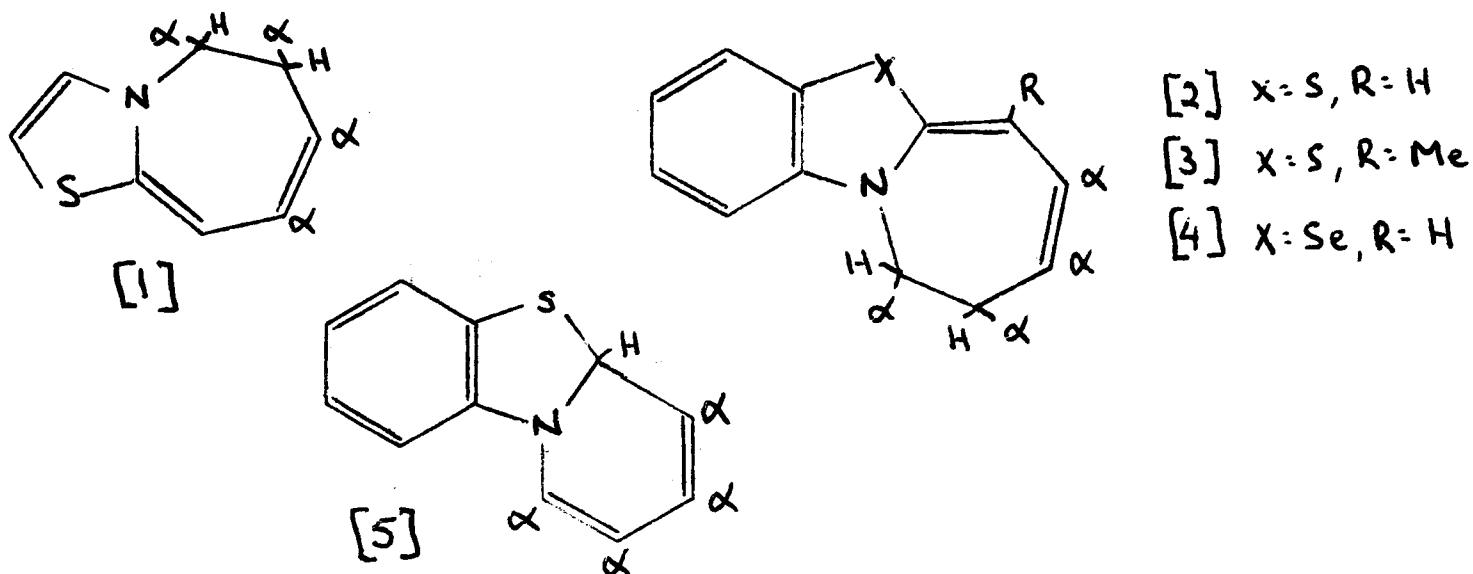


CHAPTER TWO

The Addition of Dimethyl Acetylenedicarboxylate to Azoles

(1) Thiazole, Oxazole, and Isoxazole Adducts.

In an earlier thesis⁴⁸, adducts [1]-[4] from dimethyl acetylenedicarboxylate and 2,4-dimethylthiazole, 2-methyl-, 2-ethylbenzothiazole, and 2-methylbenzoselenazole were described. Benzothiazole



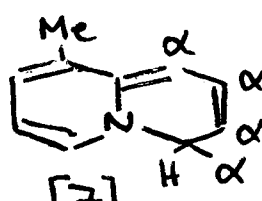
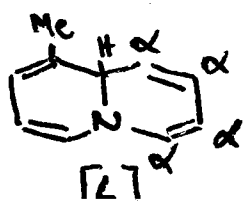
gave the adduct [5], but the structures of the adducts obtained from benzoxazole and thiazole in preliminary experiments were not proved.

It has now been found that thiazole with dimethyl acetylenedicarboxylate in dry ether gives mainly a 1:2 molar adduct, which possesses an infrared absorption spectrum similar to that of tetramethyl 9-methyl-9aH-quinolizine-1,2,3,4-tetracarboxylate²⁶ [6] in the 5-7 μ region, and unlike that of the corresponding 4H-quinolizine [7] (table I).

TABLE I

I.R. Spectra

[8]	5.75, 5.80, 5.84, 5.91, 6.24, 6.68, 6.87, 6.98
[9]	5.75, 5.87, 6.24, 6.63, 6.96
[6]	5.75 5.80 5.89 6.20, 6.64 6.97
[7]	5.75 5.99, 6.17, 6.35, 6.49, 6.83, 6.97



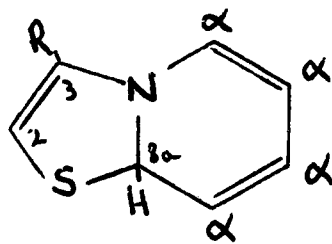
The ultraviolet absorption spectrum also closely resembles those of 9aH-quinolizines, e.g. [6] (table II).

TABLE II

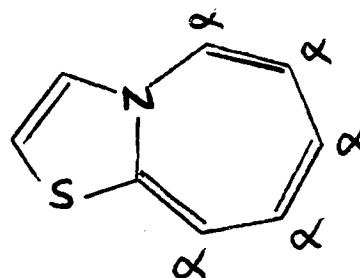
U.V. Spectra

[8]	226.5(1.11)	283(1.84)	435(0.42)	
[9]	227.5(1.43)	287(1.99)	445(0.43)	
[13] ⁴⁹	239 (1.35)	295(1.74)	446(0.52)	
[6]	235 (1.48)	289(1.48)	441(0.46)	
[7]	262(0.74)	311(1.0)	360(1.3)	439(0.97)

Therefore, this adduct is assigned structure [8]. In confirmation of this, the nuclear magnetic resonance spectrum shows a singlet at 1.77 τ (8a-H), and doublets at 3.35 (3H) and 3.94 τ (2H) ($J_{23} = 5$ c.p.s). The angular proton is at an exceptionally low field for a saturated carbon atom. However, the lone proton of benzaldehyde dibenzoate appears at 1.72 τ .¹¹⁰



[8] R=H
[9] R=Me



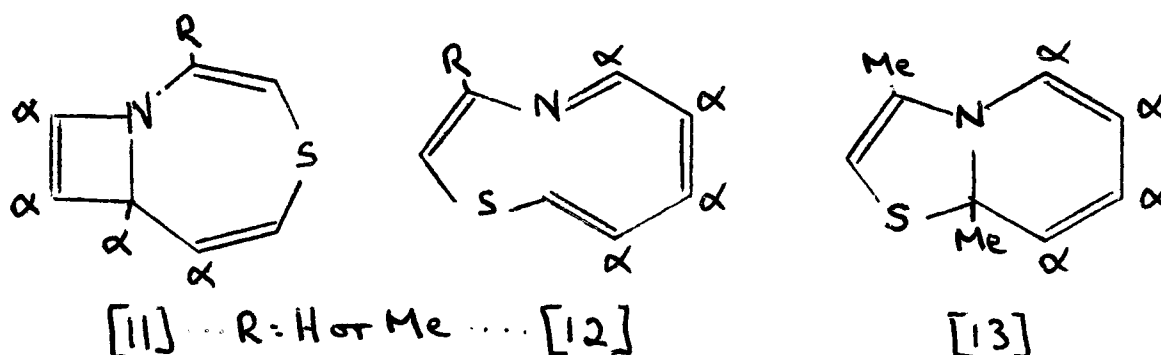
[10]

4-Methylthiazole and the acetylenic ester give the analogous adduct [9]. The proton resonance spectrum shows singlets at 1.88 τ (8aH), 4.22 τ (2H) and 7.86 τ (3-CH₃). The olefinic protons in these adducts are at higher field than in the thiazoles themselves⁶², in accord with the ex-

pected decrease in ring current.

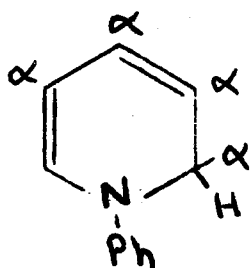
A minor product of the reaction of thiazole and the ester is a yellow compound, analysing for $C_{18}H_{17}NO_{10}S$. Structure [10] is consistent with the nuclear magnetic resonance spectrum of the compound, which shows five ester methyl groups and two olefinic protons at 1.53 (3H) and 2.61 τ (2H) ($J_{23} = 5$ c.p.s). The lower field position of these, compared with those of [8] is due to the greater ring current. The ultraviolet absorption spectrum also shows greater conjugation than that of [8].

Since this work was completed Reid et al⁴⁹ published results corroborating the structures of some of the adducts from 2-methylthiazoles. However, for the adducts from thiazole and 4-methylthiazole, they postulate structure [11] or [12], while 2,4-dimethylthiazole is said to give [13] with the ester in dimethylformamide solution. The ultraviolet absorption

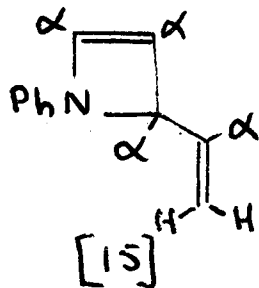


spectra of all three compounds are very similar (table II), and it is difficult to reconcile the different structures for such similar spectra. The similarity in the infrared absorption spectra of the thiazole adduct and the 9 α H-quinolizines, but not the 4H-quinolizines, which have a carbomethoxy group on a saturated carbon atom α to a nitrogen atom, is a specific point against structure [11]. The spectral characteristics of the adduct from benzothiazole indicate that it has a structure analogous to that from thiazole. Desulphurisation of the benzothiazole adduct is

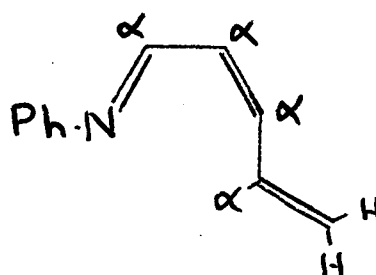
expected to give [14], [15], or [16], depending on whether the structure of the analogous thiazole is [8], [11], or [12] respectively. The nuclear magnetic resonance spectrum of the desulphurised compound⁴⁸ shows two doublets ($J = 1.7$ c.p.s) which rules out the presence of an olefinic methylene group possessed by [15] and [16]. The ultraviolet



[14]



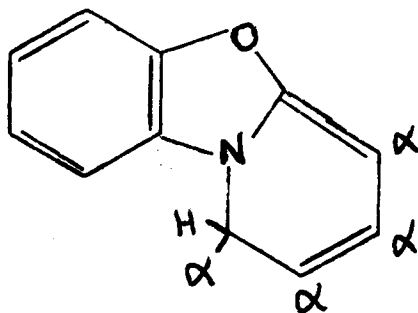
[15]



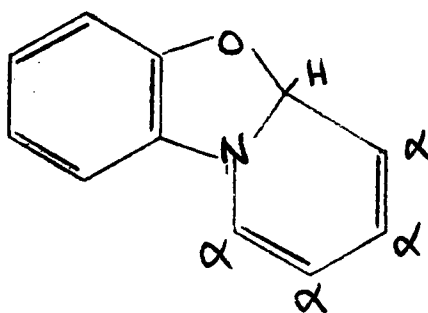
[16]

absorption spectrum of the compound shows more conjugation than would be expected of [15], and is not changed by acid, which would be unexpected of [16].

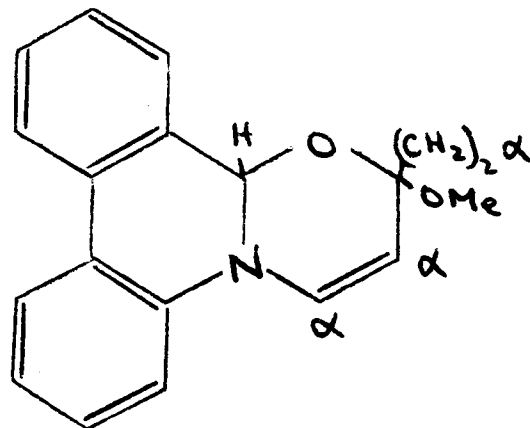
Benzoxazole and the acetylenic ester give a 1:2 molar adduct, whose nuclear magnetic resonance spectrum shows, as well as peaks due to the aromatic and methoxyl protons, a singlet (one proton) at 3.82τ . This is at much higher field than in the benzothiazole adduct (1.50τ), and at a comparable position to the 4-H of 4H-quinolizines.²⁹ A possible structure is therefore [17]. However, the ultraviolet absorption spectrum is unchanged by acid, and so a more likely structure is [18]. Comparison of



[17]



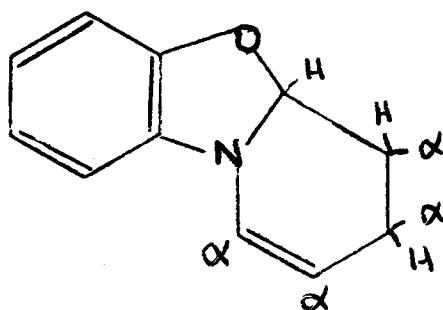
[18]



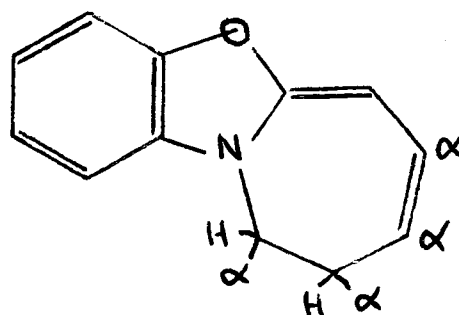
[19]

the proton resonance spectra of model compounds [19]³⁵ and the triacetates of inosine and adenosine⁵⁰ shows that an angular C-H group between nitrogen and oxygen atoms gives a signal at 3.8, 3.83, and 3.80 τ respectively.

Hydrogenation of [18] gives a dihydro compound whose nuclear magnetic resonance spectrum shows the presence of three aliphatic hydrogens on three adjacent carbon atoms. The ultraviolet absorption spectrum of this compound is also unchanged by acid, and consequently the dihydro adduct is assigned structure [20].



[20]



[21]

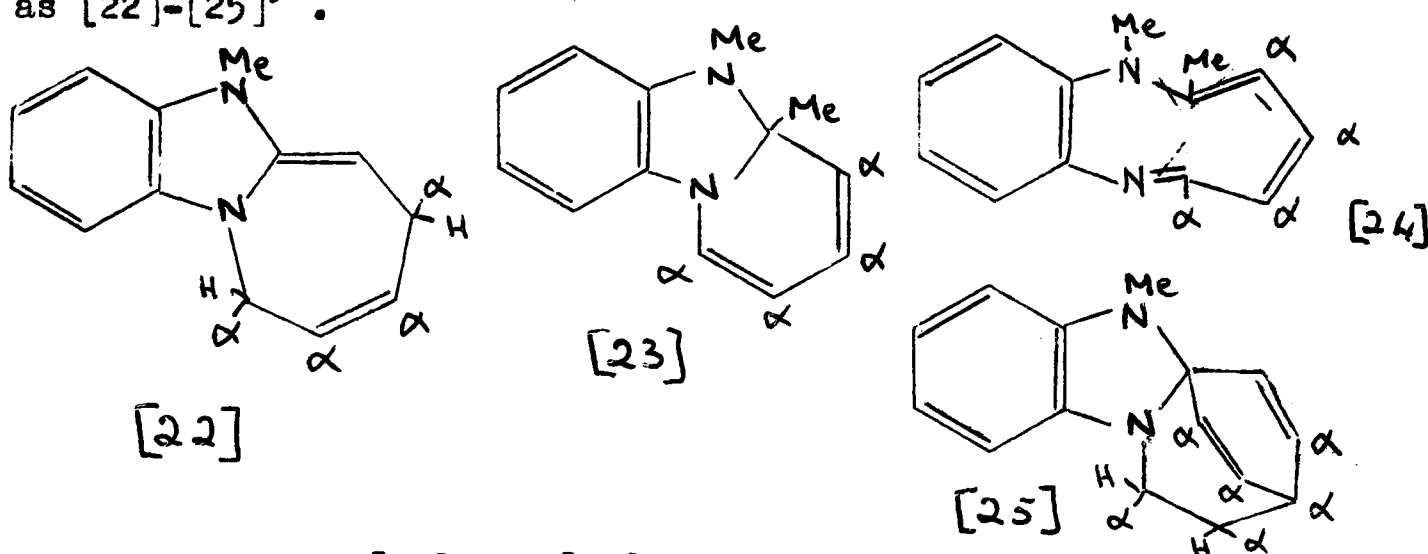
In an earlier thesis⁴⁸, it was stated that no crystalline product could be isolated from the reaction between 2-methylbenzoxazole and dimethyl acetylenedicarboxylate. Repeating this addition in boiling acetonitrile gives a small yield of tetramethyl 9,10-dihydrobenzoxazole-[3,2,a]azepine-7,8,9,10-tetracarboxylate [21], identified by its proton resonance spectrum. This shows a multiplet at 2.7-3.0 τ (4 aromatic protons), doublets at 4.25 (10H) and 4.55 τ (9H) ($J_{9,10} = 5$ c.p.s), and a singlet at 5.03 τ (6H). The 9- and 10- protons have comparable chemical shifts and coupling constants, while the 6-proton is at higher field, to those of the analogous adduct from 2-methylbenzothiazole.⁴⁸ This is expected since the atom in the 5-position will not greatly affect the 9-, and 10- protons, but will

affect the closer 6-proton.

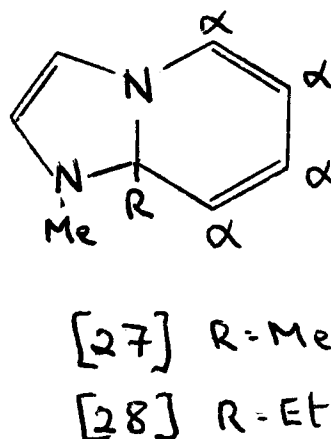
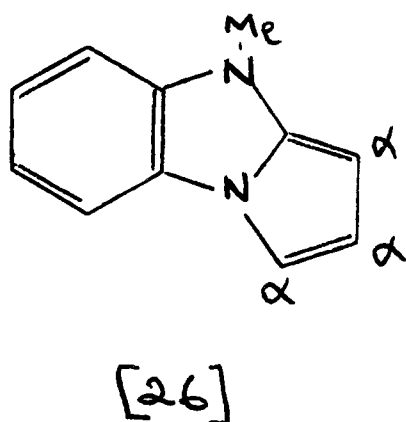
Isoxazole and some derivatives were heated with the ester in the hope of obtaining adducts analogous to that from benzoxazole, but there was no apparent reaction with these compounds, probably due to their low basicity.

Benziminazoles

Mills isolated four adducts from the reaction of 1,2-dimethylbenziminazole with dimethyl acetylenedicarboxylate which he formulated as [22]-[25]⁵¹.



He proposed that [23] and [24] existed as a tautomeric mixture in solution, and obtained similar compounds from 2-ethyl-1-methylbenziminazole, as well as an adduct to which he assigned structure [26]. Other workers had obtained the adducts [27]¹⁶ and [28]⁵² from 2-alkyl-1-methyliminazoles.



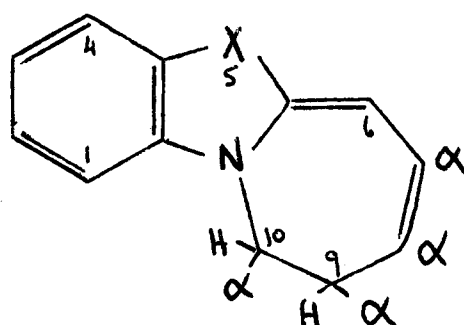
Since the structures proposed by Mills were doubtful, these reactions were reinvestigated. In acetonitrile, 1,2-dimethylbenziminazole and the acetylenic ester gave only one adduct, identical to the "yellow adduct" which Mills formulated as [22]. The ultraviolet absorption spectrum is intermediate between those of the adducts from 2-methylbenzothiazole and 2-methylbenzoxazole, and like them shows a hypsochromic shift in acid solution, reversible on dilution (table III).

TABLE III

U.V. Spectra

[29]	253.5(0.9), 240 (2.39)	296*(0.42) 243(2.4)249(2.29)	431(6.6) 326(3.54)
[30]	253.5(0.82)	295*(0.38) 244(1.14)249(1.13)	431(5.73) 326(2.24)
[21]	249*(0.64) 239*(0.89)	288(0.29) 244(0.92), 249(0.88),	403(3.62) 336(1.86)
[2]	268.5*(0.64)	320*(0.30) 254(1.84)259(1.95),	429(4.11) 344(2.76)

The nuclear magnetic resonance spectrum shows the absence of a C-methyl group, the hydrogen atoms becoming an AB doublet and a singlet. Comparison with the spectra of similar compounds (table IV) indicates that the adduct has the structure [29]. An analogous adduct [30] is obtained from 1-ethyl-2-methylbenziminazole.



- [29] X: -N-Me
 [30] X: N-Et
 [21] X: O
 [2] X: S
 [4] X: Se

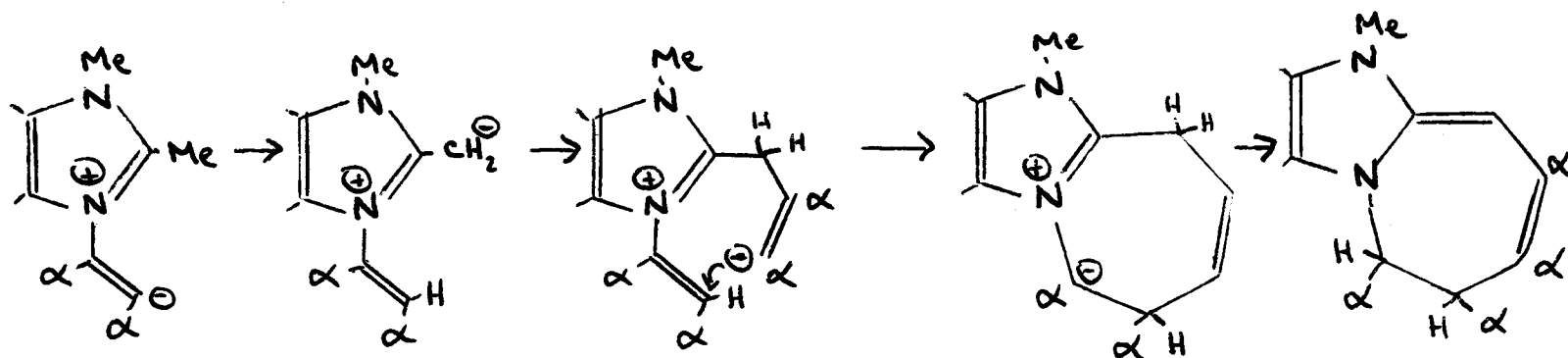
TABLE IV

N.m.r. Spectra

<u>ArH</u>	<u>6H</u>	<u>2H</u>	<u>10H</u>	<u>N-R</u>	<u>OMe</u>
[29] 2.8-2.95	5.55(s)	4.53(d) $J_{9,10} = 6$	4.05(d) $J_{9,10} = 6$	6.59(s)	6.15, 6.26, 6.31, 6.47
[30] 2.8-2.95	5.54(s)	4.55(d) $J_{9,10} = 6$	4.07(d) $J_{9,10} = 6$	8.68(t)* (CH ₃)J=7	6.17, 6.28, 6.32, 6.49
[21] 2.7-3.0	5.03(s)	4.55(d) $J_{9,10} = 5$	4.25(d) $J_{9,10} = 5$		6.19, 6.24, 6.33, 6.44
[2] 2.45-3.0	4.82(s)	4.54(d) $J_{9,10} = 6$	4.01(d) $J_{9,10} = 6$		6.18, 6.22, 6.31, 6.42
[4] 2.45-3.05	4.71(s)	4.55(d) $J_{9,10} = 6$	3.95(d) $J_{9,10} = 6$		6.15, 6.21, 6.30, 6.41

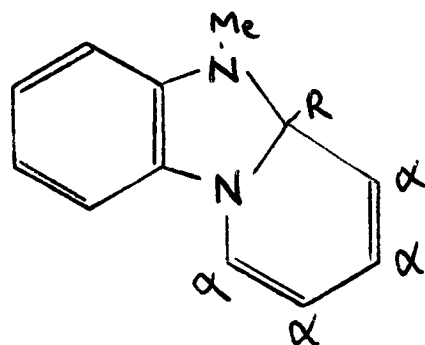
(* CH₂ signal is partly hidden by signals of methoxyl groups)

Mills discounted structure [29] on the grounds that the singlet at 5.55 τ was at too high field for the 6-proton; such a proton would be more deshielded. However, table IV shows the gradation of the positions of the signals due to the 6- and 10-protons, as X goes from the highly deshielding selenium atom to the less deshielding oxygen atom, while N-alkyl groups have an even less deshielding effect. A possible scheme for the formation of these azepines is shown below :-



In tetrahydrofuran, 1,2-dimethylbenzimidazole and the acetylenic ester gave the adduct [29]⁵¹, the orange and pale-yellow adducts, previously reported, and stated to have the structures [24] and [25] respectively, were not isolated.

The nuclear magnetic resonance spectrum of the dark-red adduct (table V) shows a C-methyl signal at 8.56 τ , which is at a similar position to the 9a-methyl group of 9a-methyl-9aH-benzoquinolizines.²⁹ Consequently, this adduct is formulated as [23].



[23] R = Me

[31] R = Et

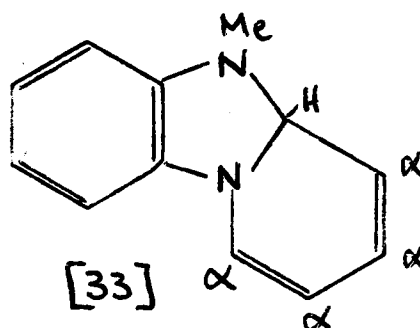
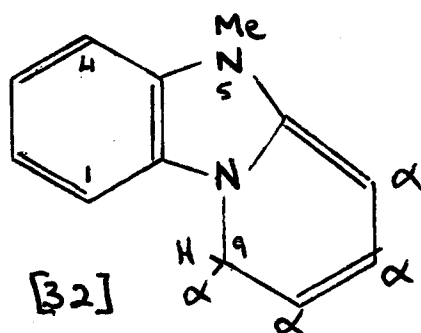
The analogue [31] is obtained as the sole product of the reaction between 2-ethyl-1-methylbenziminazole and dimethyl acetylenedicarboxylate in acetonitrile solutions. It is interesting to note that CH_2 group is not reactive enough to give a seven-membered ring adduct, unlike that of 2-ethylbenzothiazole.

This isolation of pure adducts would seem to invalidate Mills' claim of tautomerism between [23] and [24], but rather support the existence of two separate compounds. As well as the adduct [30], 1-ethyl-2-methylbenziminazole gives a dark red solid, analysing for a 1:2 molar adduct, whose proton resonance spectrum shows a complexity consistent with the presence of two separate compounds. They have not been separated yet.

Earl reported two adducts from the reaction of benziminazole and the acetylenic ester⁵³, one of which he formulated as the 5aH-isomer of [34], on its analytical data and the absence of N-H absorption in the infrared absorption spectrum; while Mills obtained no adducts from the ester and 1-methylbenziminazole.

These reaction were repeated. In acetonitrile, 1-methylbenziminazole and dimethyl acetylenedicarboxylate give, as the major product, a yellow 1:2 molar adduct. The nuclear magnetic resonance spectrum of this compound (table V) shows a single hydrogen atom at 3.74τ , while the N-methyl group is at 6.03τ . The latter has a much lower τ value than the N-methyl group of the adduct [23] (6.91τ) or that of 1,2-dimethylbenziminazole (7.01τ), indicating a greater ring current than that of [23]. The ultra-violet absorption spectrum of the compound (table VI) changes in acid

solution, but is reversed on addition of base to the acid solution. However, addition of base to an acid solution of [23] does not give back the original ultraviolet absorption spectrum. Consequently, the yellow adduct of 1-methylbenziminazole is formulated as [32].



The second product of the 1-methylbenziminazole reaction is an orange adduct, isomeric with [32]. The ultraviolet absorption spectrum of this compound (table VI) is unlike that of [32], and is changed very little on protonation. Addition of base does not give back the original spectrum. The nuclear magnetic resonance spectrum of the compound (table VI) contains a lone proton at 1.74 τ and a N-methyl group at 6.89 τ , which is at a comparable position to the N-methyl group of [23]. The single proton has a slightly greater chemical shift than that of the benzothiazole adduct [5] (1.50 τ) but a much lower one than that of the benzoxazole adduct [18] (3.82 τ), but this may be due to slight differences in the geometry of the molecules, resulting in different deshielding effects. Therefore, the orange adduct of 1-methylbenziminazole is provisionally assigned structure [33].

TABLE V

N.m.r. Spectra

<u>ArH</u>	<u>5aH</u>	<u>9H</u>	<u>5-R</u>	<u>OMe</u>
[23] 2.9 -3.45(m)	8.56(s) (CH ₃)	.	6.91 (CH ₃)	5.96,6.19,6.23,6.26
[31] 2.8 -3.5(m)	9.24(t)J=8 (CH ₃)7.96(q)(CH ₂)		6.83 (CH ₃)	5.92,6.17,6.22(2)
[33] 2.81-3.33(m)	1.74(s)		6.89 (CH ₃)	6.09,6.20(2), 6.28
[32] 2.63(s)		3.74(s)		6.03,6.18,6.23,6.29(2) (1-NMe + 4OMe)
[34] 2.61(t)		3.69(s)	3.37(s) (C=CH)	6.08,6.10,6.20 6.22,6.29,6.33
[35] 2.57-2.74(m)		3.76(s)	4.24(q)(CH) [*] J _{CH} =10, J _{CH} =4	6.06,6.20,6.23 6.30(2),6.50

(* CH₂ signal is hidden by peaks due to methoxyl groups)

TABLE VI

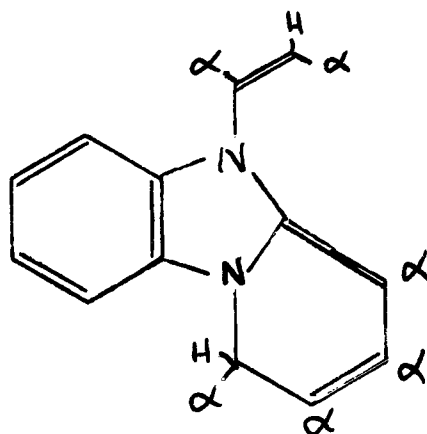
U.V. Spectra

[23]	220 (2.05), 256(1.51) 315(0.76), 441(0.91)
(A)	242.5(1.86), 295(1.04)
(B)	270, 302 408
[33]	236* (1.74)271.5(1.56),301(1.02),437(0.89)
(P)	234.5*(2.73)236.5(2.71),269(1.16)299.5(0.89)345(0.79)436(0.94)
(B)	271 401
[32]	245(1.08) 316.5(2.95)400(1.93)
(P)	268(0.85), 275(0.97), 283(0.86) 333(0.16)
[34]	242*(0.7) 265*(0.50) 309(1.44) 403(1.06)
[35]	250.5*(0.85) 316.5(2.54)397(1.61)
(P)	269* (0.88)276(1.02) 283.5(0.92)

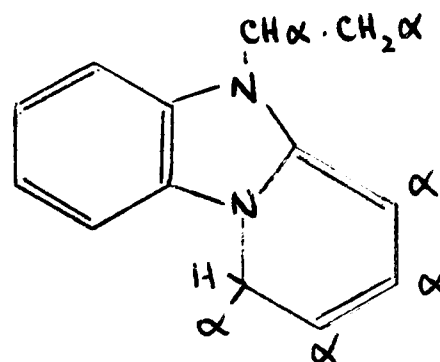
The adduct [33] could not be converted to [32] by heating at 250°, and the action of bromine in acetic acid/perchloric acid did not convert [32] and [33] into the same compound.

The addition of the acetylenic ester to 1-methylbenziminazole was carried out in methanol, in the hope of obtaining the adduct [26], previously obtained from 2-ethyl-1-methylbenziminazole, but no crystalline product was isolated.

Benziminazole and dimethyl acetylenedicarboxylate give two adducts, one of which (the white adduct) is still being investigated. The major product in benzene is a yellow 1:3 molar adduct, and comparison of the nuclear magnetic resonance and ultraviolet absorption spectra (tables V and VI) show it to be analogous to [32] rather than the 5aH-isomer. On this evidence the compound is assigned the structure [34].



[34]



[35]

Catalytic reduction of the adduct [34] gives a dihydro derivative, whose ultraviolet absorption spectrum closely resembles that of the parent compound (table VI). The nuclear magnetic resonance spectrum still contains a single proton at 3.7τ , but the single vinyl proton has been replaced by a quartet, due to one proton, while the signal due to the methylene group is hidden by the methoxyl signals. Therefore, this reduced adduct is formulated as [35].

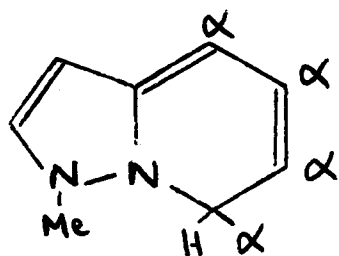
Johnson⁵⁴ reported that 1-methyliminazole gave a 2:1 molar adduct with the acetylenic ester, but such a compound could not be found in the literature. Attempts to prepare such an adduct gave only hexamethyl mellitate.

Pyrazole and Indazole Adducts

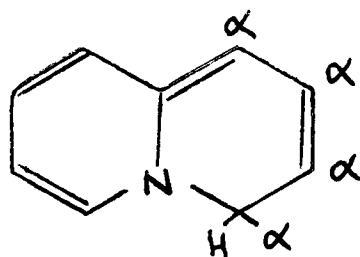
Poulter was unable to obtain any crystalline compounds from the reaction between 1-methylpyrazole and dimethyl acetylenedicarboxylate.⁵⁵

Repeating this reaction in acetonitrile, two adducts are obtained. The major product is a 1:2 molar adduct. The nuclear magnetic resonance spectrum of this compound contains signals due to four methoxyl and one N-methyl groups, a singlet at 4.60τ (one proton) and two doublets at 1.80 and 3.65τ (one proton each, $J = 13$ c.p.s). Such a spectrum is

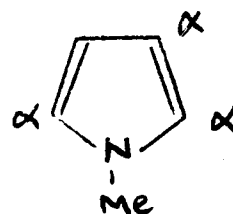
consistent with the structure [36].



[36]



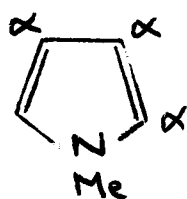
[37]



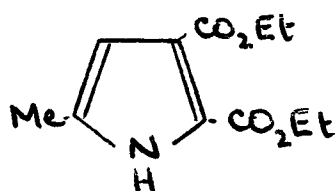
[38]

The ultraviolet absorption spectrum is not as conjugated as that of the 4H-quinolizine [37], as would be expected.

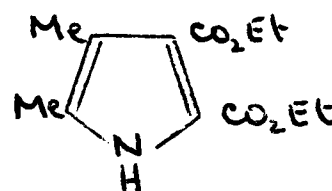
A second product of this reaction is a white compound which analyses for $C_{11}H_{13}NO_6$. This is provisionally formulated as the pyrrole [38] on the basis of its ultraviolet absorption and proton resonance spectra. A comparison of the ultraviolet absorption spectra of [38] and some other pyrrole esters is shown in table VIII.



[39]



[40]



[41]

TABLE VII

U.V. Spectra

[38]	227* (1.16)	254(2.12),	302(0.44)
[39] ²⁰	217.5(2.9)	264(1.2)	
[40] ¹¹⁰		243(0.56)	290(1.06)
[41] ¹¹⁰		250(0.45)	293(1.05)

If [38] is the correct structure, it is difficult to see how it is formed. Vernon isolated [39] from the reaction of 1-methylpyrrole with

the acetylenic ester²⁰ (see Introduction, p. 6), but formation of [38] cannot occur by a similar scheme.

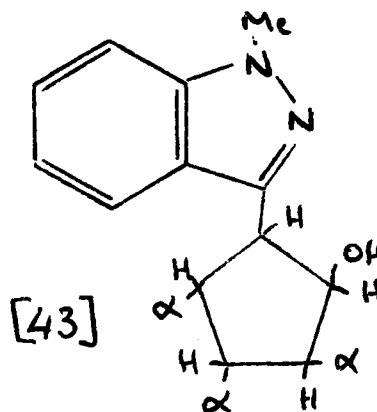
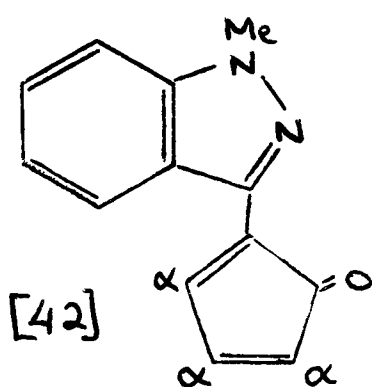
Indazole was methylated with (i) methyl sulphate in aqueous sodium hydroxide solution, (ii) sodium and methyl iodide, and (iii) sodamide in liquid ammonia, and methyl iodide. Only method (iii) gives good yields of 1-methylindazole, and it is also a satisfactory method of converting 3-methylindazole to 1,3-dimethylindazole.

1-methylindazole and dimethyl acetylenedicarboxylate give a compound whose analysis corresponds to $C_{19}H_{16}N_2O_7$, that is, a 1:2 molar adduct less methanol. The infrared absorption spectrum has three carbonyl absorptions in the region 5.5-6 μ , one being at 5.99 μ . The ultra-violet absorption spectrum shows that the adduct is slightly more conjugated than 1-methylindazole. In the nuclear magnetic resonance spectrum, there are three methoxyl and one N-methyl peaks (5.89, 5.93, 6.02, 6.27 τ) and two aromatic multiplets (1.2-1.35 τ , one proton, 2.3-2.85 τ , three protons).

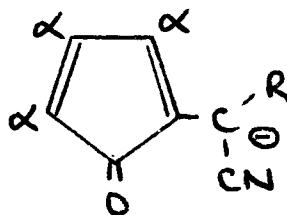
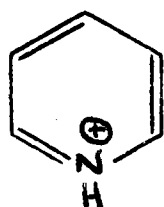
Catalytic reduction of the adduct results in the addition of three moles of hydrogen, the infrared absorption spectrum now showing no long wavelength carbonyl absorption but the presence of an -OH or -NH group in the molecule. The addition of six hydrogen atoms and the presence of one hydrogen atom which exchanges in deuterium oxide is confirmed by the nuclear magnetic resonance spectra which also contain a single aromatic signal (four protons). Five of the added protons have chemical shifts of 5.4-6.7 τ .

Oxidation of the reduced compound gives back the original adduct, which is unaffected by neutral permanganate or chromic acid.

Possible structures for the adduct and its hexahydroderivative are [42] and [43].



Salts [44] and [45] of a similar nature have been described by Le Goff and Lacount⁵⁶ from the condensation of dimethyl acetylenedicarboxylate with malononitrile and ethyl cyanoacetate in the presence of pyridine and acetic acid.



[44] R: CN

[45] R: COOEt

No crystalline product was isolated from the reaction of 1,3-dimethylindazole with the acetylenic ester.

Triazole Adducts

Dimethyl acetylenedicarboxylate was reacted with 1-methyl-1,2,3-triazole in the hope of effecting an addition across the nitrogen-nitrogen double bond, but the only crystalline product isolated was hexamethyl mellitate, formed by trimerisation of the acetylene.

However, two adducts are obtained from 1-methylbenzotriazole and the ester, great difficulty being encountered in separating them. The yield is also very dependent on solvent and concentration, the best yields being

obtained in ether. In more polar solvents, the primary product is hexamethyl mellitate.

The product of the reaction is mainly a 1:2 molar adduct [46], together with a tiny amount of a 1:2 molar compound less CH_2 [47]. These are separated by fractional crystallisation. Further amounts of [47] are produced by dissolving the crude reaction product in mineral acid, and basifying with aqueous ammonia solution. The precipitated solid is then separated (incompletely) by thin layer chromatography, giving [46] and [47] in the ratio of ca 5:1.

The ultraviolet absorption and nuclear magnetic resonance spectra of [46] and [47] are shown in tables IX and X. Although the ultraviolet absorption spectra are different in neutral solution, the two compounds have the same chromophore in acid solution.

The difference in the proton resonance spectra of the two compounds is the presence of high field methoxyl signal in that of [46], being replaced by a single proton peak in the spectrum of [47].

The chemistry of [46] (flow sheet on p.38) is complicated by the ready loss of a methylene group during reactions, and so, often mixtures of compounds are obtained.

Catalytic reduction of [46] gives two products, a white compound [48], $\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_8$, and a yellow one [49], $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_7$, while reduction with stannous chloride and concentrated hydrochloric acid gives a product [50], $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_7$.

TABLE IX U.V. Spectra

[46]	M	221	(1.99)	247*	(1.21)	276	(0.93)	396	(0.66)	
	P	237	(2.52)	273*	(0.95)	358	(1.19)	475	(0.97)	
	B	218, 266, 276, 320, 333, 384								
[47]	M	218	235*	(1.2)	266	(0.79)	275(0.84)	309*(0.75)	319(0.99)	332(0.81) 385(0.46)
	P	237	275*		358		475			
[48]	†	225	(1.41)	267	(0.4)			342	(0.74)	
[49]		219.5(2.74), 270	(0.81)	322	(1.38)			333*(1.14)	402(0.42)	
[50]	M		243.5(3.71)	316	(0.91)			326*(0.84)		
	A		239 (6.87)	316	(0.88)			326 (0.82)		
[51]		226	(2.61)	252*	(1.58)	280*	(0.79)			
[52]	M		243*	(1.61)	275	(1.12)		392	(1.02)	
	P		238*	(3.08)	274*(1.06)			361	(1.13)	477 (1.0)
	B		252, 263, 281, 320*							
[53]		223*	(1.93), 267.5(0.57)	340	(1.14)			245	(1.18)	

(† figures in parentheses for compounds [47] and [48] are optical densities, not extinction coefficients)

TABLE X
N.m.r. Spectra

<u>ArH</u>	<u>OMe</u>	<u>NMe</u>	
[46] 1.90-2.05(1) 2.55-2.75(3)	6.07(9) 6.94(3)	6.51(3)	
[47] 1.8 -2.0(1) 2.6 -2.85(3)	6.03(3) 6.08(3) 6.11(3)	6.44(3)	5.29(s)(1)
[48] 1.9 -2.1(1) 2.6 -2.85(3)	6.06(3) 6.15(3) 6.22(3) 6.90(3)	6.44(3)	5.74(d)(1) 6.73(d)(1) J=13 c.p.s.
[49] 2.04-2.33(1) 2.68-2.93(3)	6.05(3), 6.08(3) 6.25(3)	6.50(3)	5.08(s)(1)
[50] 2.3-2.8(4)	5.88(3) 5.96(3) 6.10(3)	6.36(3)	
[52] 1.93(1) 2.6-3.0(8)	6.07(6) 6.10(3) 6.91(3)		4.44(d) 4.96(d) (CH ₂) J=16
[53] 2.1 -2.3(1) 2.6 -3.1(8)	6.11(3) 6.20(3) 6.35(3)		4.71(d)(CH ₂), 5.4-5.65(m) 5.75-5.85(m) 6.69(d) J=15

(Figures in parentheses refer to the number of protons)

[46] gives crystalline salts with both hydrochloric and perchloric acids, but satisfactory analyses were not obtained for these compounds, while alkaline hydrolysis of [46], followed by acidification, gave a crystalline solid which readily lost carbon dioxide, and could not be crystallised to a constant melting point.

Treatment of [46] with excess methyl magnesium iodide gives a white solid, whose analysis corresponds to $C_{20}H_{23}N_3O_5$ [51]. The infrared absorption spectrum contains peaks due to hydroxyl and carbonyl groups, while the nuclear magnetic resonance spectrum shows the presence of four aromatic protons, one methoxyl group, one N-methyl group, and three or four C-methyl groups. The spectrum could only be measured in acetonitrile, which hid the region 7.5-8.5 τ .

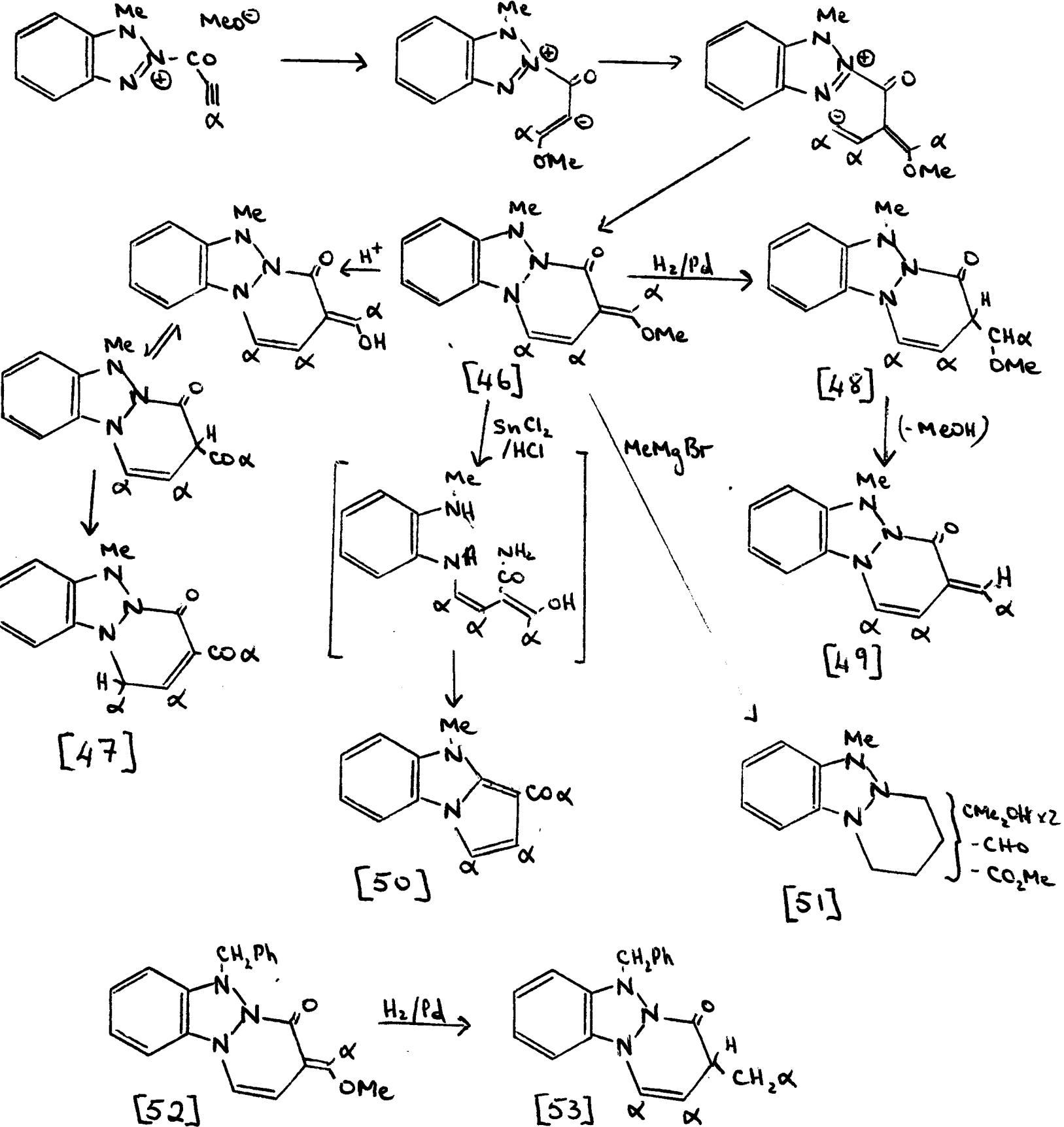
The adduct [46] gave only tars when treated with bromine in methanol and acetic acid, potassium permanganate in acetone, and refluxing hydriodic acid.

1-Benzylbenzotriazole and the ester give a compound [52] whose ultra-violet absorption spectrum shows it to be the benzyl analogue of [46]. The nuclear magnetic resonance spectrum is very similar to that of [46], except the methylene group appears as a quartet, showing the different environment of the two hydrogen atoms.

Catalytic reduction of this adduct gives a compound [53] which analyses for $C_{24}H_{23}N_3O_7$, while treatment of [52] with neutral potassium permanganate, manganese dioxide, bromine, or refluxing pyridine gives 1-benzylbenzotriazole. This indicates that addition of the acetylene is to the nitrogen atoms only, and that the triazole skeleton is still present

jections to a vinyl ether grouping are that [46] is not converted quantitatively to [47], and that [52] does not appear to give an analogue of [47].

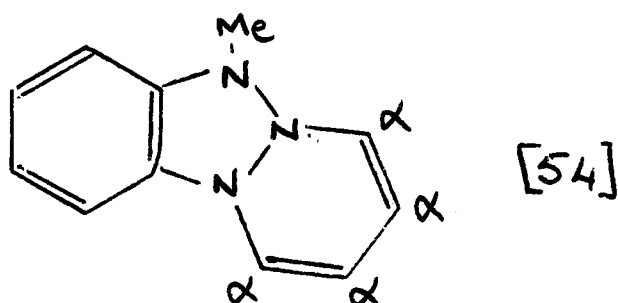
and modes of formation are :-



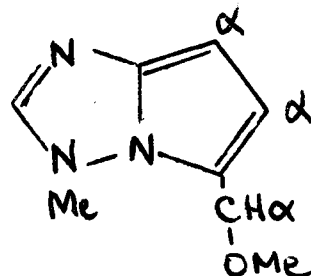
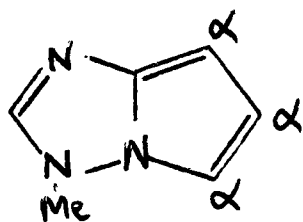
The formation of [53] from [52] could proceed via benzyl analogues of [48] and [49].

The newly formed ring of [46] could also be the other way round, that is, with the carbonyl group adjacent to the 3-nitrogen atom of the triazole.

The reactions of these adducts are not so easy to explain on the basis of structure [54], which might have been expected by analogy with the pyridine adducts.



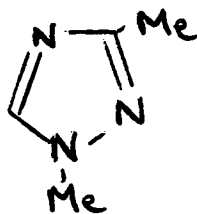
Unlike 1-methyl-1,2,3-triazole, 1-methyl-1,2,4-triazole gives an adduct with dimethyl acetylenedicarboxylate. The compound analyses for $C_{12}H_{13}N_3O_6$ and contains three methoxyl groups, while the nuclear magnetic resonance spectrum has a singlet at 1.26 τ (one proton) and four singlets at 5.61, 5.93, 6.02 and 6.07 τ (three protons each). A structure consistent with this data is [55], while a second adduct isolated only once in very small yield from this reaction, was assigned the structure [56] on its proton resonance spectrum. This possesses two singlets at 2.11 and 3.03 τ (one proton each) as well as signals at 6.08-6.25 τ due to five methyl groups.



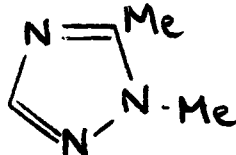
Cyclisation may occur between the 4- and 5- positions. Calculations have shown that in triazole itself,⁵⁴ the position of highest electron density is the 4-nitrogen, but no calculations have been made with the 1-methyl derivative.

Compounds similar to [55] and [56] are formed from pyridine in the presence of traces of alcohols.^{33, 57} Although [55] was prepared under supposedly aprotic conditions, some methanol may have been present, or have been formed in situ.

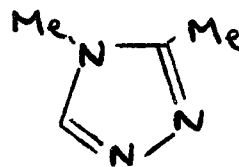
3-Methyl-1,2,4-triazole is methylated with methyl iodide and sodium methoxide, when it is presumed that the triazole anion is attacked, to give a dimethyltriazole. Three isomers are possible [57], [58] and [59]. None of these are described in the literature, but Atkinson and Polya have



[57]



[58]

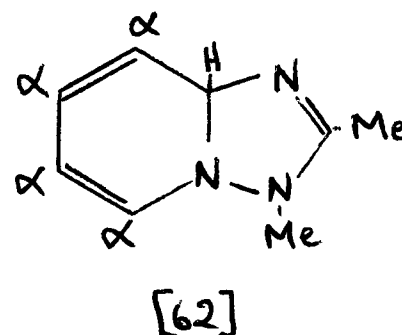
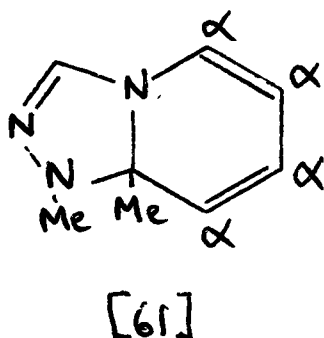
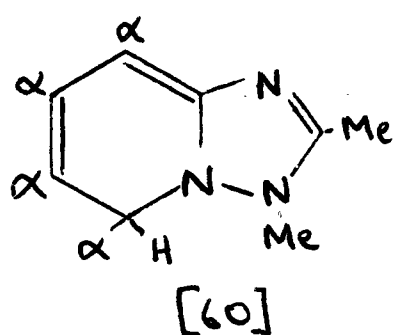


[59]

calculated the π -electron density on each nitrogen atom in both neutral triazole and its anion.⁵⁸ In the anion, the 1- and 2-nitrogen atoms have much higher electron densities than the 4-nitrogen. A methyl group at the 3-position increases the electron density of the nitrogen atoms adjacent to it. Thus 3-methyl-5-phenyltriazole gives a mixture of the 2- and 1-methyl derivatives in the ratio of 3.7:1. Therefore, the most likely isomer formed above is [58] and some of [57], but none of [59].

The dimethyl-1,2,4-triazole and dimethyl acetylenedicarboxylate give

a mixture of three adducts, only one of which so far has been obtained pure. However, all three are 1:2 molar adducts. The pure adduct is pale yellow, and its nuclear magnetic spectrum has peaks at 4.08 τ (one proton) and 7.59 τ (C-methyl group) as well as the peaks due to four methoxyl and one N-methyl group. The ultraviolet absorption spectrum is similar to that of the 1:2 molar adduct of 1-methylpyrazole ([36], p.31) and assuming that the structure of the starting material is [58], a possible structure is [60]. The chemical shift of the C-methyl group is too low for that of a saturated carbon.

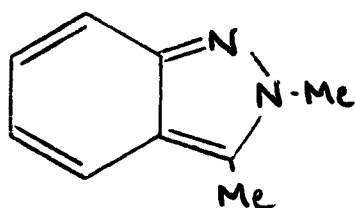


The other material obtained from the reaction is a dark-red solid whose nuclear magnetic resonance spectrum is consistent with the presence of two adducts in almost equal proportions. The spectrum shows two singlets at 2.96 and 5.10 τ (one hydrogen each), two N-methyl peaks at 6.88 and 6.95 τ , and two C-methyl peaks at 7.95 and 8.72 τ . This last peak must be due to a methyl group on a saturated carbon atom, and again assuming the starting material to be [58], a possible structure of one component of the mixture is [61], the lone hydrogen giving the peak at 2.96 τ . This means the third compound could be [62], and this would fit the remainder of the "mixed" proton resonance spectrum.

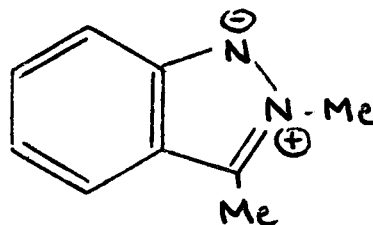
These structures are proposed on the assumption that the dimethyl-

triazole is a single substance, and if it is, only an unambiguous synthesis can prove the correct arrangement of the methyl groups.

Dimethyl acetylenedicarboxylate reacted with 2-methylbenzotriazole, 2-methylindazole, 2,3-dimethylindazole, and anthranil, but no crystalline products were isolated. These heterocycles are characterised by being classically represented as having lost their benzene conjugation e.g. [63], but more recent views regard them as resonance stabilised molecules, with zwitterions such as [64] making a major contribution.



[63]



[64]

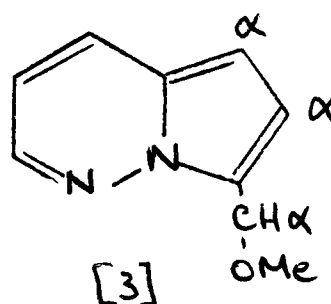
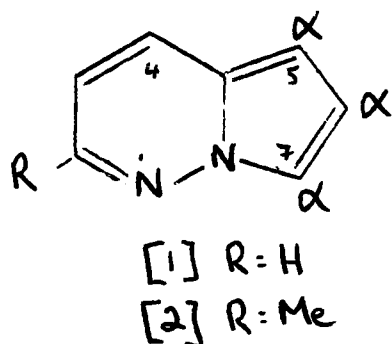
The nuclear magnetic resonance spectra of 1,3-dimethylindazole and its 2,3-isomer show that the aromatic protons have similar chemical shifts, as have the N-methyl groups, but the C-methyl peak of the former is at 7.47 τ , while that of the 1,2-isomer is at 7.61 τ , indicating that 1,3-dimethylindazole has the greater ring current.

CHAPTER THREE

The Addition of Dimethyl Acetylenedicarboxylate to Diazines

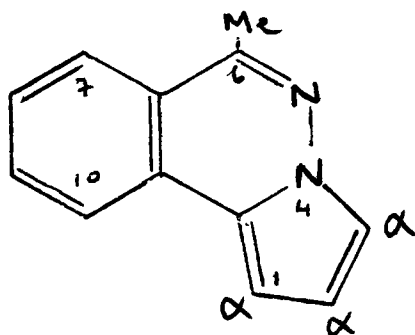
Pyridazines and Pyrazines

A previous investigation⁵⁹ of the reaction between dimethyl acetylenedicarboxylate and pyridazines showed that, in methanol, pyridazine and 3-methylpyridazine gave the pyrrolo-[1,2-b]-pyridazines, [1] and [2]. From pyridazine, a "yellow contaminant" was also isolated, but only the melting point was reported. In ether, no crystalline materials were isolated. 3,6-Dimethylpyridazine failed to give solid products in either solvent.

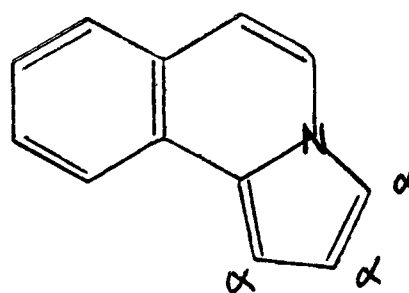


These reactions were repeated in acetonitrile, and several new adducts were obtained. Minor products from pyridazine and 3-methylpyridazine were [1] and [2]. Their nuclear magnetic resonance spectra confirmed their structures (table I). The reaction between pyridazine and the acetylenic ester in methanol was repeated in the hope of isolating Letsinger and Lasco's "yellow contaminant", as we thought this might be the methoxymethylpyrrolo-[1,2-b]-pyridazine, [3]. However, no trace of this was found.

A minor product of the reaction between dimethyl acetylenedicarboxylate and 1-methylphthalazine was shown by analysis and nuclear magnetic resonance spectroscopy to have structure [4]. The ultraviolet absorption spectrum is similar to that of the benzindolizine [5] (table II)⁵⁷.

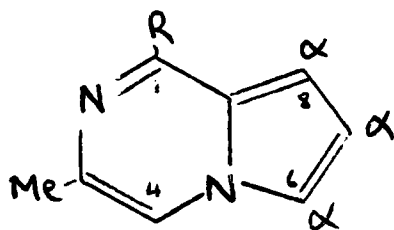


[4]

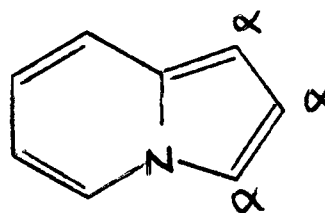


[5]

The only crystalline solids obtained from the reactions of 2-methyl- and 2,6-dimethylpyrazine with the acetylenic ester in aprotic solvents were shown by analysis and spectroscopy to have the structures [6] and [7] respectively. [6] is only one of three possible pyrrolopyrazines



[6] R=H
[7] R=Me



[8]

which might be formed, but the nuclear magnetic resonance spectrum of [6] is very like that of [7]. If the methyl group were in the 1-position, an AB spectrum with a coupling constant of 6-14 c.p.s. would be expected, while if the methyl group were in the 4-position, it would be expected to be at a lower field, due to deshielding by the 6-carbomethoxy group.

The ultraviolet absorption spectra of [6] and [7] are similar to those of [1] and [2], and also [8]⁵⁷ in neutral solution, but unlike them, change on acidification (table II).

From table I, it can be seen that whenever a hydrogen atom is peri to a carbomethoxy group, it is pulled down to very low field. This has also been found for the asterisked hydrogen atom in the 4H-quinolizine

TABLE I

N.m.r. Spectra

	<u>1-H</u>	<u>2-H</u>	<u>3-H</u>	<u>4-H</u>	<u>OMe</u>
[1]		1.28-1.46(m)	2.85(q)	1.28-1.46(m)	5.99, 6.05, 6.09
[2]		7.36(s) (CH ₃)	2.96(d) J ₃₄ =9	1.51(d)	5.98, 6.04, 6.07
[6]	0.46(d) J ₁₄ =1		7.44(s) (CH ₃)	0.90(d)	6.04, 6.09(2)
[7]	7.06(s) (CH ₃)		7.47(s) (CH ₃)	0.94(s)	6.03, 6.07, 6.10
[4]	0.59(q)(10-H), 1.9-2.35(m)(7,8,9-H); 6.0-6.05(3OMe); 7.16(s)(6-CH ₃) J _{9,10} =7, J _{9,11} =2				

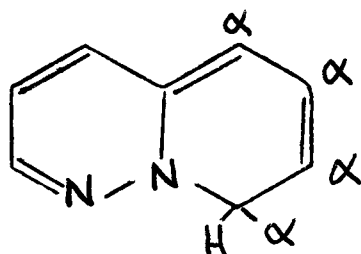
TABLE II
U.V. Spectra

[1]	222(1.86)249(2.67),256*(2.27),263*(1.80),284(0.44),294.5(0.57)305(0.60),307(0.60)343(0.39)
[2]	223(1.17)250(1.51),255*(1.32),265(1.13),285(0.51) 291* (0.59)296(0.65),307(0.68)336(0.48)
[8]	243, 270, 320
[6] M	224(0.93),249.5(1.47),257.5(1.34)265*(0.89),331(0.93)
A	221(1.08),257* (1.58),261(1.64), 330*(0.18),371(0.30)
[7] M	230(1.71),248.5(2.63),251* (2.62)
A	224(1.86),300* (0.21),313 (0.33),328(0.38),363.5(0.63)
[4]	225(2.64),235* (2.34),265.5(4.65),273.5(4.74),282*(2.65),310(1.51)
[5]	240, 269, 337, 354

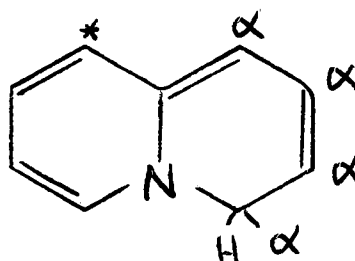
series e.g. in [10]. The presence of an additional nitrogen in the system causes this shift to be even greater.

A possible mode of formation of compounds analogous to the above has been proposed,³⁵ and as this involves methanol, some methanol, or another hydroxylic solvent, must have been present in catalytic amount, despite rigorous attempts to exclude it, or must have been formed in situ in the reacting mixture.

The major product from pyridazine and dimethyl acetylenedicarboxylate in acetonitrile is a 1:2 molar adduct, whose ultraviolet absorption spectrum resembles that of the 4H-quinolizine [10]²⁶ (table III). The nuclear magnetic resonance spectrum also resembles that of [10] (table IV), bearing in mind that the presence of an additional unsaturated nitrogen atom in the system will cause a shift downfield of the chemical shifts of the protons adjacent to the nitrogen. The adduct is, therefore, given structure [9].



[9]



[10]

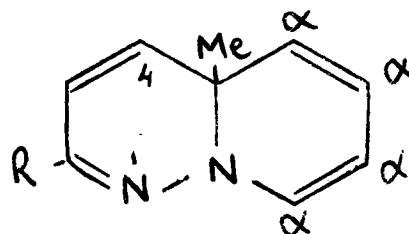
A third adduct from this reaction is obtained in too small a yield for adequate structural investigations.

TABLE III

U.V. Spectra

[9]	219(1.03), 274.5(0.66), 302.5(1.08), 369(0.62), 443(0.52)
[10]	259 (0.98), 306 (1.57), 344.5(1.11), 441(1.11)
[11]	267(1.36) 399 (0.73)
[12]	266(1.38), 351* (0.51), 400 (0.77)

3-Methylpyridazine and the acetylenic ester in acetonitrile give mainly a 1:2 molar adduct. The chemical shift (table IV) of the C-methyl group is too high for the methyl group to be on anything other than a saturated carbon atom, and so by analogy with adducts from 2-alkylpyridines,²⁹ the compound is assigned structure [11]. A similar adduct [12] is obtained in small yield from 3,6-dimethylpyridazine. The assignments of the chemical shifts to each proton of [11] and [12] are made by comparing the two spectra. The low field proton in the spectrum of [11] must be 2-H, (since it is absent in the spectrum of [12]) while the high field quartet must be 3-H, since its coupling constants are the sum of the major coupling constants of the other two protons. Since the positions of the 3- and 4-H are similar in the two spectra, unambiguous assignments can be made to the protons of [12].



[11] R = H

[12] R = Me

TABLE IV

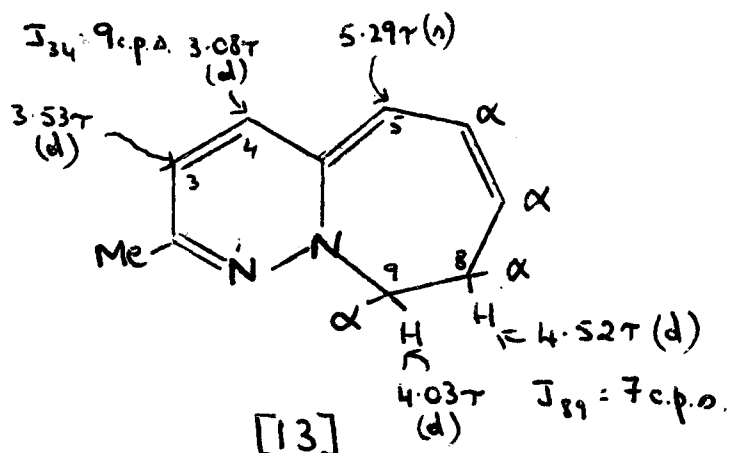
N.m.r. Spectra

	2H	3H	4H	4aH	8H	OMe
[9]	1.67(q) $J_{2,3}=4, J_{2,4}=2$	2.69(m) $J_{23}+J_{24}=14$	0.82(q) $J_{34}=10, J_{24}=2$		3.50(s)	5.99, 6.10, 6.17, 6.20
[10] ²⁹	3.15(t)	2.3-2.6(m)	1.32(q)		3.94(s)	6.07, 6.20, 6.24, 6.28
[11]	2.62(q) $J_{23}=4$	3.82(q)	3.42(q) $J_{34}=10, J_{24}=2$	8.71(s) (CH ₃)		5.98, 6.11, 6.13, 6.18
[12]	7.91(s) (CH ₃)	3.97(d) $J_{34}=10$	3.44(d)	8.76(s) (CH ₃)		6.08, 6.20, 6.24, 6.29

(* The numbering system of this compound has been changed in the table to aid comparison with [9]).

Attempts were made to add another mole of acetylenic ester to [11] and [12], but only starting materials could be isolated, while catalytic reduction of [11] gave an oil which could not be induced to crystallise.

The major product from the reaction of 3,6-dimethylpyridazine and the ester is a 1:2 molar adduct, whose nuclear magnetic resonance spectrum shows the presence of only one C-methyl group, which is attached to an unsaturated carbon atom. The hydrogens of the other methyl group of the original base now appear as an AB doublet at 4.03 and 4.52 τ ($J = 7$), and a singlet at 5.29 τ . This is characteristic of the adducts from 2-methyl-benzoxazole etc. (see table IV, p. 24), and the adduct must have the structure [13]. The ultraviolet absorption spectrum also resembles those



of the adducts described on page 23 in showing a hypsochromic shift of the maxima in strongly acid solution, the process being reversed on dilution.

Catalytic reduction of [13] gives only an oil which could not be crystallised. It was hoped to obtain crystalline reduction products of the seven-membered ring system, since earlier attempts to reduce analogues from the thiazole adducts had been thwarted by poisoning of the catalyst.

As well as the adduct [4], 1-methylphthalazine and dimethyl acetylene-dicarboxylate give a 1:2 molar adduct. By analogy with 3-methylpyridazine,

the more basic 2-nitrogen would be expected to attack the acetylenic bond to give, finally, an adduct possessing a methyl group at the bridgehead. However, the nuclear magnetic resonance spectrum of this compound shows the methyl signal to be at 7.51τ (too low to be on a saturated carbon atom), while the singlet at 4.22τ is at too high field for the system $-CH=N-$. Consequently, attack must occur on the 3-nitrogen to give the adduct [14].

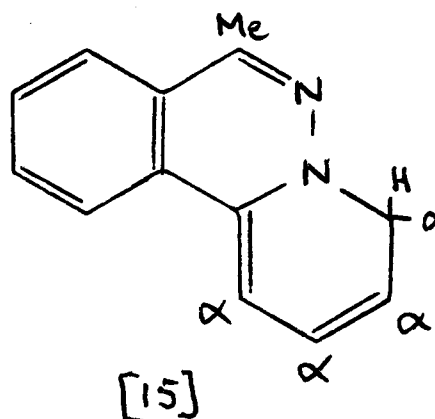
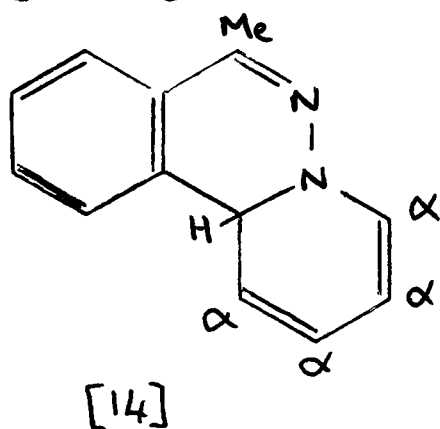


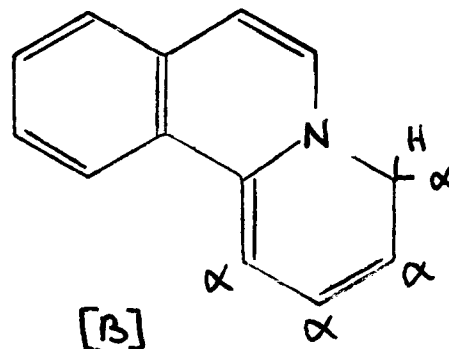
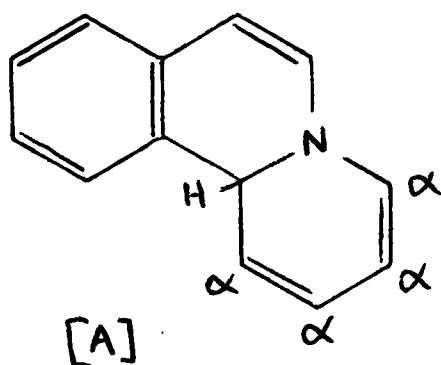
TABLE V

U.V. Spectra

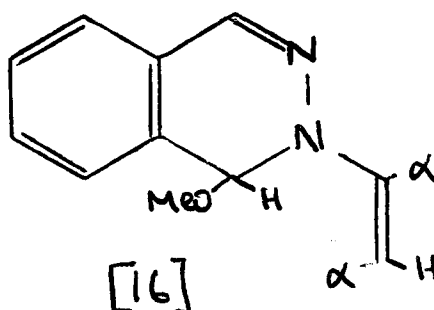
[14]	225 (1.72)	271 (2.08)	335 (0.54)	460 (0.76)
(P)	235* (2.02)	275* (2.12)	280 (2.14)	333 (0.81) 460(0.87)
[A]	238 (1.59)	266* (1.48)	292 (2.01)	300 (1.78) 438(0.59)
[15]	225 (2.78)	255* (0.83)	306.5 (0.9)	327.5 (0.83) 453(1.09)
(P)	218 (1.99)	245.5 (3.23)	283 (0.56)	326 (0.45)
[B]	229 (4.47)	260 (1.12)	322 (1.51)	338* (1.29) 464(1.66)
(P)	242 (3.6)	275 (0.58)	347(0.47)	

Treatment of [14] with acid gives an isomeric compound which by analogy with adducts of the pyridine series, is formulated as [15]. The proton resonance spectrum of [15] shows a single proton at 3.65τ . Comparison of the ultraviolet absorption spectra of [14] and [15] with the corres-

ponding adducts of isoquinoline [A] and [B] is shown in table V.



Phthalazine and dimethyl acetylenedicarboxylate give no crystalline product in aprotic solvents, but in methanol, the adduct [16] is formed, identified by its nuclear magnetic resonance spectrum, and ultraviolet absorption spectrum, which, in strongly acid solution, resembles that of the phthalazinium ion.



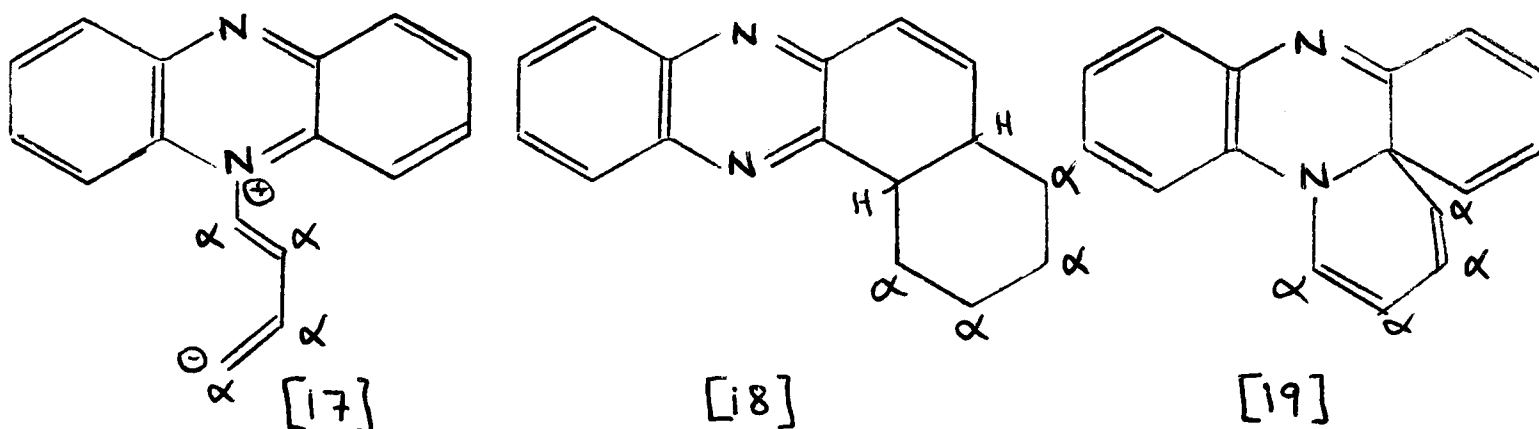
4-Methylcinnoline with both dimethyl and diethyl acetylenedicarboxylate gives crystalline solids, which analyse for 2:3 molar adducts. The two adducts have very similar infrared absorption spectra in the 5-7 μ region, and their nuclear magnetic resonance spectra are comparable. Thus the aromatic signals are virtually the same, both show a singlet at 5.03 τ (one proton) and a methyl resonance at 8.4 τ . In addition, the methyl adduct shows a doublet at 5.54 τ ($J = 13$ c.p.s), (one proton) two ester methyl peaks at 5.9 and 6.1 τ , a multiplet at 6.2-6.45 τ (12-13 protons) and a second C-methyl group at 8.63 τ . In the spectrum of the ethyl adduct, further comparison cannot be made, due to the broad signals of the ethyl

groups. However, the integral indicates a total of 46 protons. The ultra-violet absorption spectrum shows the cinnoline chromophore to be no longer present.

Bromination of the adduct from the methyl ester gave a green solid, which rapidly became an oil, while oxidation and reduction gave solids which could not be recrystallised to constant melting points. Until further chemistry is done on these adducts, no structures can be proposed for them on the above scant evidence.

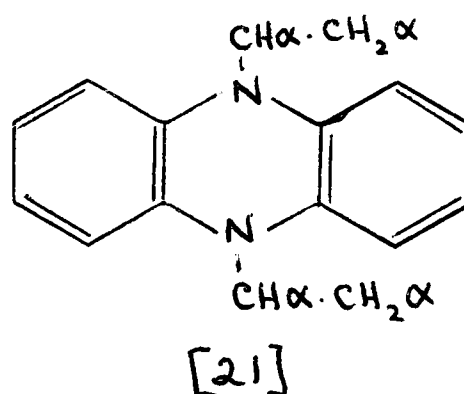
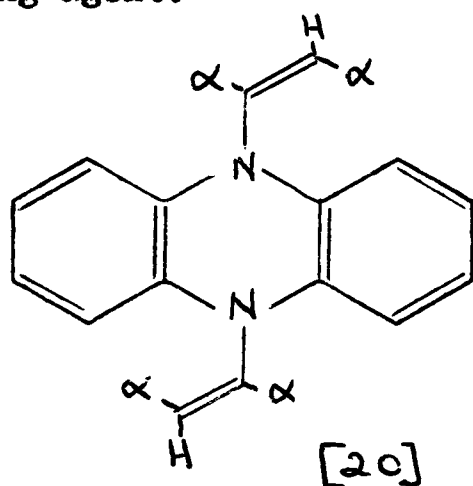
Phenazine

Lora Tamayo and co-workers isolated an adduct from the reaction between phenazine and dimethyl acetylenedicarboxylate in methanol.⁶⁰ They favoured structure [17], but did not exclude structures such as [18] and [19].



This addition was repeated in both acetonitrile and methanol. In the former solvent, only purple tars are formed, but in methanol, the described adduct is obtained. Objections to structure [17] are the ready solubility of the adduct in non-polar solvents such as benzene, and the failure to form salts. The analysis fits a compound of empirical formula $C_{24}H_{22}N_2O_8$, rather than $C_{24}H_{20}N_2O_8$ ([17]), and the nuclear magnetic

resonance spectrum is in accord with the presence of twenty two protons. The spectrum is very symmetrical, showing a singlet at 2.61τ , a multiplet at $3.35-3.6\tau$, a multiplet at $3.8-4.0\tau$, and two singlets at 6.19 and 6.24τ , the area under the peaks being in the ratio $1:2:2:3:3$. The very high field aromatic protons ($3.35-4.0$) indicate that the conjugation has been decreased from that of phenazine (in whose spectrum the aromatic protons give two multiplets at 1.84 and 2.26τ)⁶¹, and that the nitrogen atoms have become saturated. The structure which best fits this data is [20], the two additional protons being donated by the solvent which acts as a reducing agent.



Catalytic reduction of [20] confirms this formulation. Two moles of hydrogen are absorbed, and the nuclear magnetic resonance spectrum of the reduced adduct is consistent with structure [21]. The low field singlet (2.61τ) of [20] has disappeared, being replaced by three quartets, each due to one proton, at 4.82 , 6.53 , and 7.18τ ($J_{\alpha,\alpha'} = \pm 17$, $J_{\alpha\beta} = 8$, $J_{\alpha'\beta} = 6$ c.p.s.).

Bromination of [20] gives mainly a pentabromophenazine

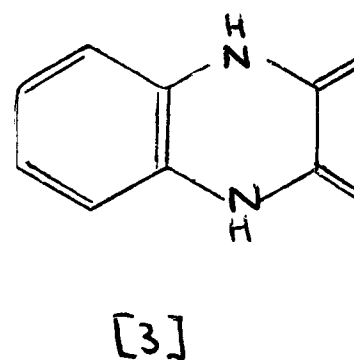
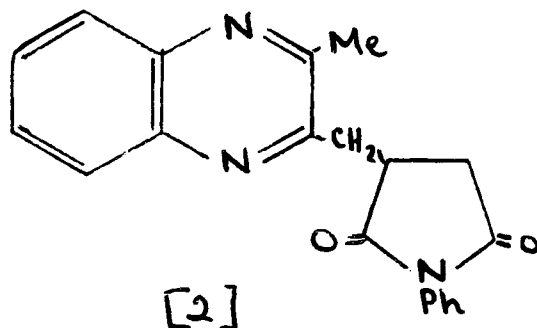
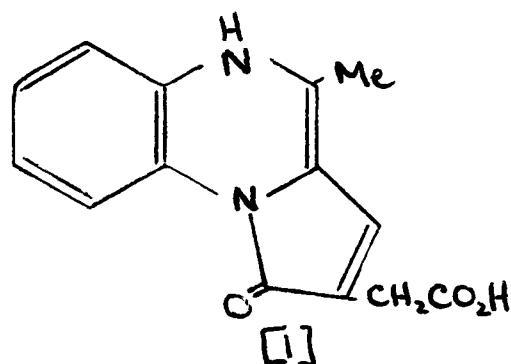
A preliminary examination of a compound obtained from 3,4-benzocinnoline and the acetylenic ester in methanol indicates that it has a

similar structure to that of the phenazine adduct [20], but investigations have been hampered by its low solubility.

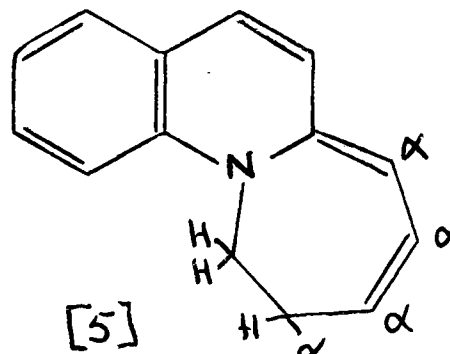
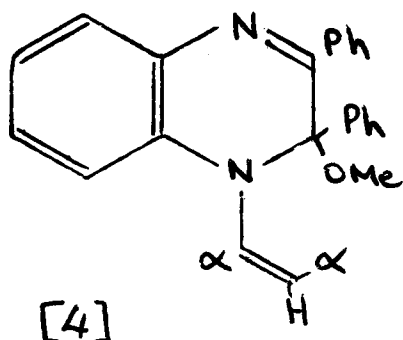
CHAPTER FOUR

The Addition of Acetylenic Esters to 2-Alkylquinoxalines and Related Compounds

2,3-Dimethylquinoxaline has recently been shown to be an addend in Michael additions e.g. maleic anhydride²³ and N-phenylmaleimide⁶⁴ give the adducts [1] and [2] respectively. Earlier workers had believed these compounds were Diels-Alder type adducts, the quinoxaline reacting as the tautomeric diene [3].⁶⁵ The only reported reactions between quinoxalines



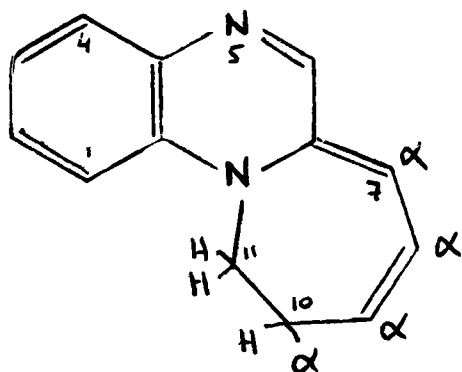
and dimethyl acetylenedicarboxylate have been carried out in methanol, 2,3-diphenylquinoxaline giving the adduct [4]⁶⁶.



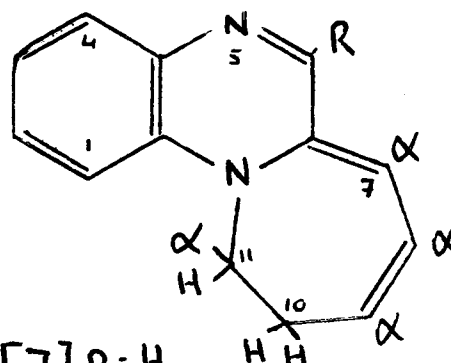
In a recently published thesis,⁴⁰ Gagan proposes the structure [5] for the main product of the reaction between quinaldine and dimethyl acetylenedicarboxylate, on the basis of spectroscopic and chemical evidence.

This investigation is concerned with the addition of acetylenic diesters to alkylquinoxalines and related compounds in aprotic solvents. Thus, 2-methylquinoxaline and dimethyl acetylenedicarboxylate in acetonitrile give a mixture of two 1:2 molar adducts. It will be most convenient if the structures [6] and [7] are proposed for the two adducts, in order to discuss how such formulations fit the chemical and spectroscopic data. These

structures are partly based on analogy with similar adducts from quinaldine and 1-methylisoquinoline e.g. [5].⁴⁰



[6]



[7] R = H
[8] R = Me

The major product of the reaction is [6] and varying amounts of [7] are formed, there being great difficulty in separating the two.

The infrared absorption spectra of the two compounds differ widely in the carbonyl absorption region (5.5 - 6 μ) (table I) but are almost identical in the remainder of the spectrum. The extra complexity shown by [7] may be due to the carbonyl group at the 11-position being subjected to different steric factors.

TABLE I

I.R. Spectra

[6]	5.71,	5.98, 6.18, 6.27, 6.37
[7]	5.68 5.72, 5.80, 5.93,	6.17, 6.25, 6.36
[8]	5.82, 5.93	6.29, 6.48

The ultraviolet absorption spectra of [5] and [6] are identical in both neutral and acid solution, and therefore, the same chromophore must be present in both adducts. In neither neutral nor acid solution do the

NMR Spectrum

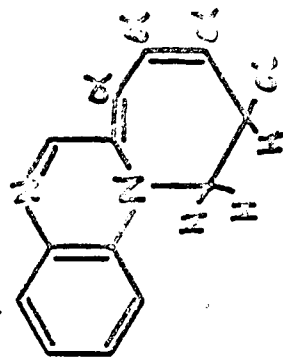
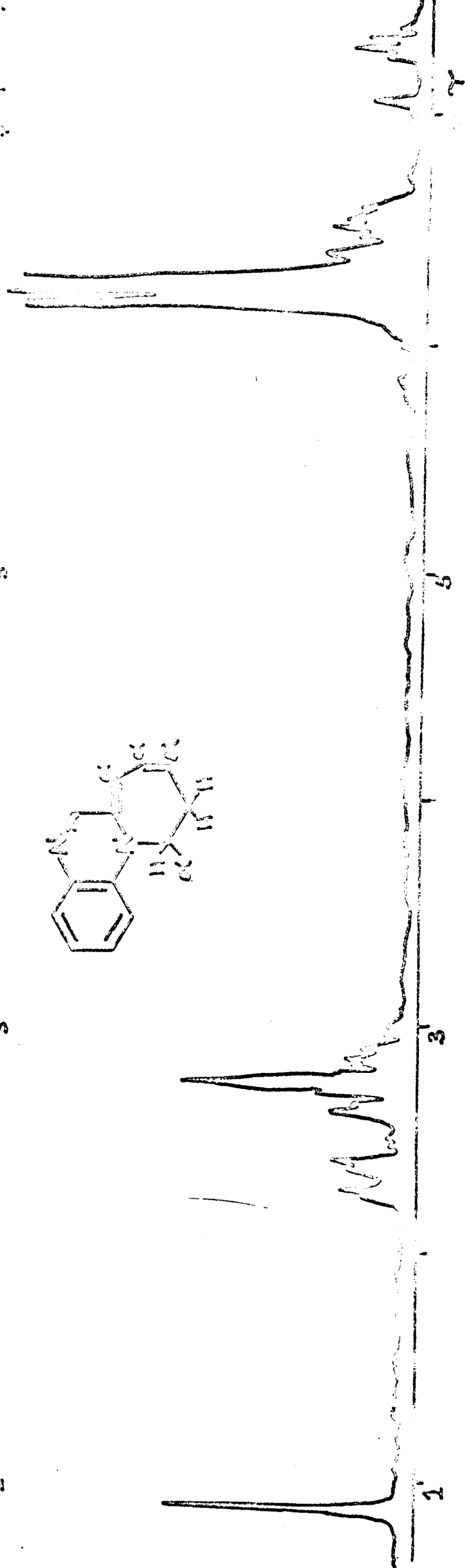
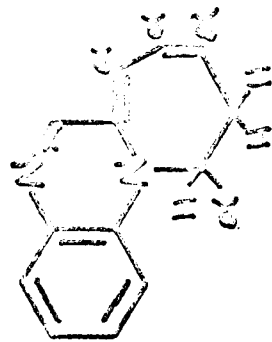
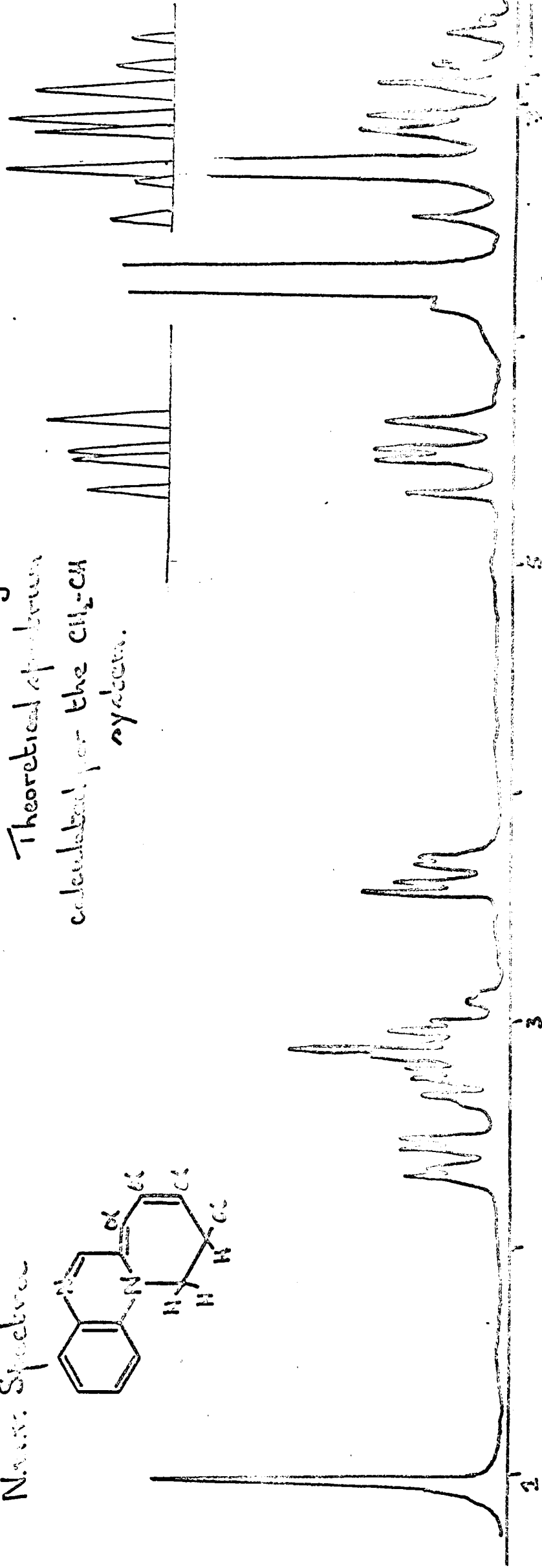
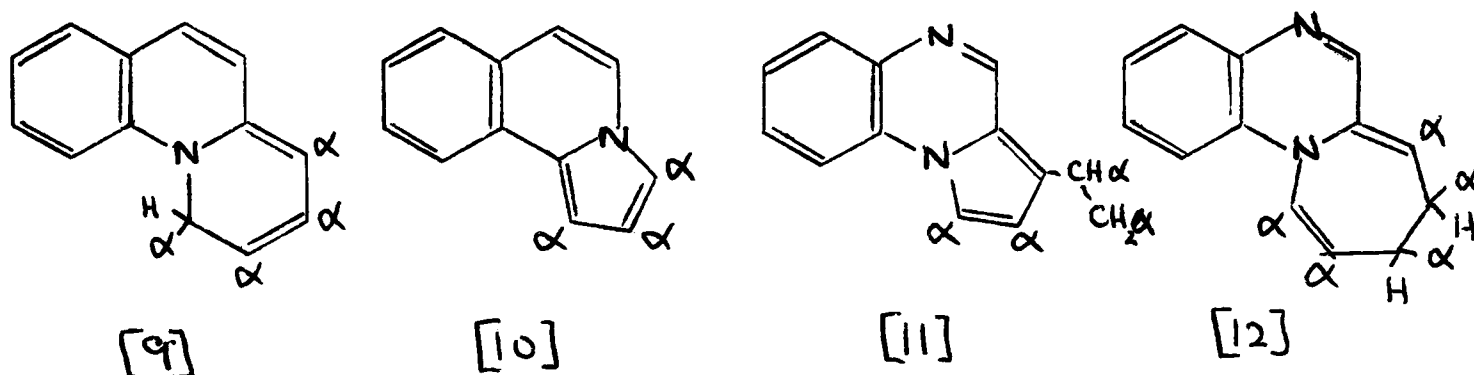


Fig. I
Theoretical spectrum
calculated for the CH₂-CH
system.



spectra resemble those of 2-methylquinoxaline or its protonated form, but show that the adducts are much more conjugated, and resemble the ultraviolet absorption spectra of the quinaldine adduct [5]⁴⁰, and the quinoline adduct [9]³⁸.



Structures such as [11] and [12] can be disregarded, since their ultraviolet absorption spectra would be similar to, or less conjugated than that of the benzindolizine [10]⁵⁷.

The nuclear magnetic resonance spectra of the compounds [5] and [6] are shown in fig. I. It is evident that the compounds contain no C-methyl group, but the single proton in the hetero ring still is present, although pulled slightly down-field (in the spectrum of 2-methylquinoxaline itself it appears at 1.27 τ). Calculations, made by Dr. R.M. Acheson, on the multiplets at 5.45 and 6.5-7.3 τ in the spectrum of compound [6] show that this system must be of the ABX type, and the best agreement between observed and calculated spectra is obtained when the following parameters are used:

$$H_A = 6.70\tau, H_B = 7.06\tau, H_X = 5.48\tau$$

$$J_{AB} = -13.0, J_{AX} = 10.0, J_{BX} = 7.5 \text{ c.p.s.}$$

Such a large, negative coupling constant (J_{AB}) is only found between geminal protons, and so the ABX system must be a $\text{CH}_2\text{-CH-}$ grouping.

TABLE II

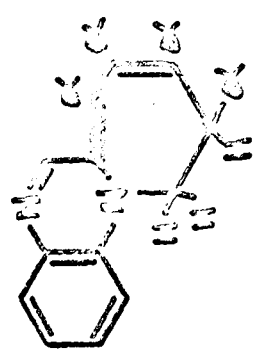
U.V. Spectra

(i) in methanol

[6] (a)†	221 (1.74), 286* (1.84), 304 (2.14), 459(0.93) 480*(0.89)
[6] (b)†	222 (1.81) 286* (1.69), 304 (2.01) 459(0.81) 480*(0.79), 518*(0.36)
[7]	220.5(1.69) 287.5(1.77) 303.5(2.18) 460(0.91),474*(0.89)
[8]	224.5(2.24) 286* (1.37) 308.5(1.78) 451(1.01) 464*(1.0)
[5]	265(1.59), 276(1.85), 296(2.21), 307(2.25), 320(1.60) 400*(0.8), 424(1.22), 448(1.19), 480*(0.57)
[9]	222 (2.34) 239 (2.29) 296 (1.51) 330*(0.83) 459 (1.33)
[10]	240 269 337 354
(ii) in methanol: 72% perchloric acid (2:1 v/v)	
[6] (a)†	218 (1.74) 285* (1.73), 309(2.44) 370*(0.16), 570(0.59)
[6] (b)†	219 (1.52) 286* (1.68), 304(2.26) 370*(0.18), 576(0.54)
[7]	285* (1.55), 308(2.28) 370*(0.27) 572(0.67)
[8]	221 (1.35), 252 (0.69), 286* (1.20), 309(1.90) 349*(0.24) 545(0.53)
[5]	228 (6.07) 242 (425) 322 (1.36)
[9]	265 (1.93) 362 (1.64)

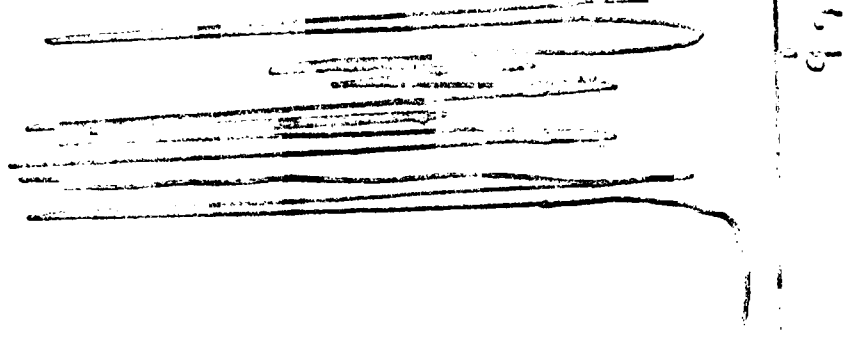
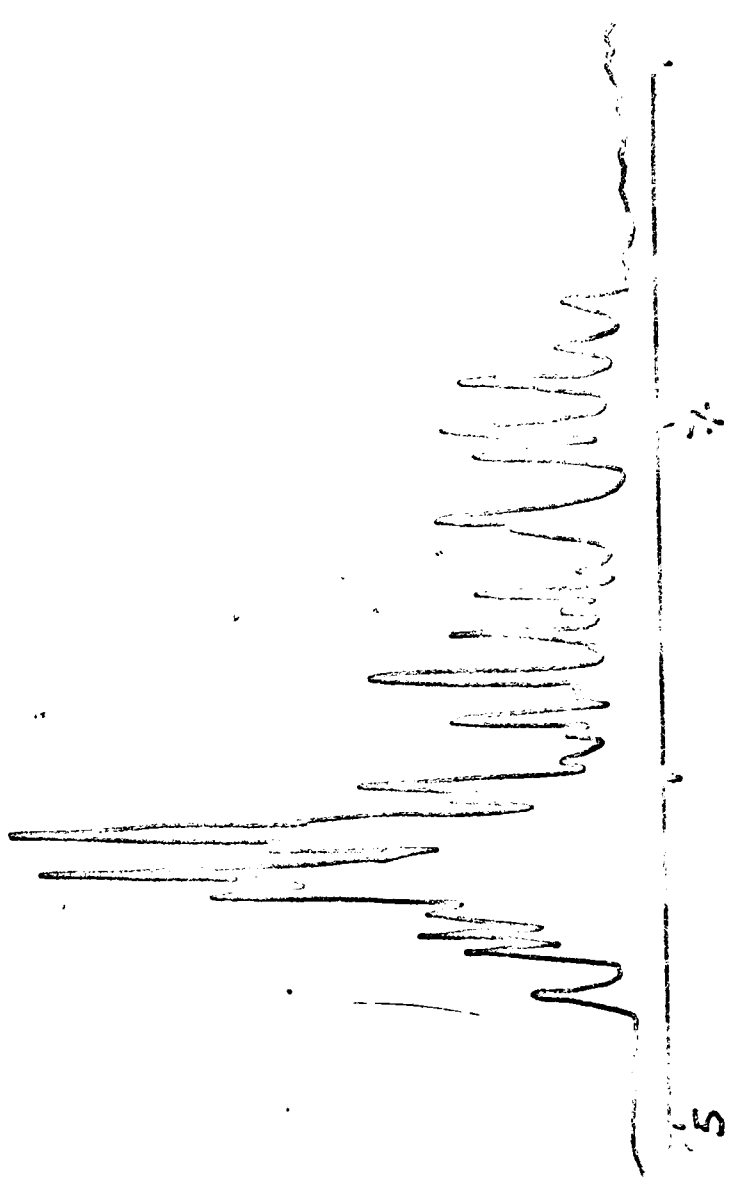
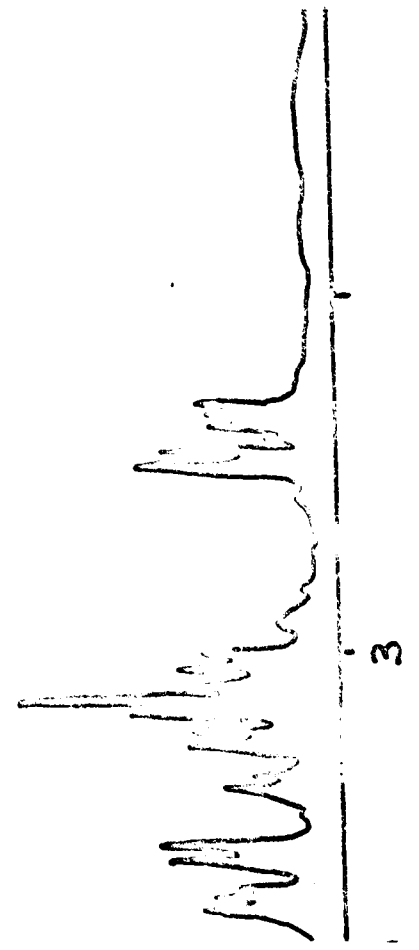
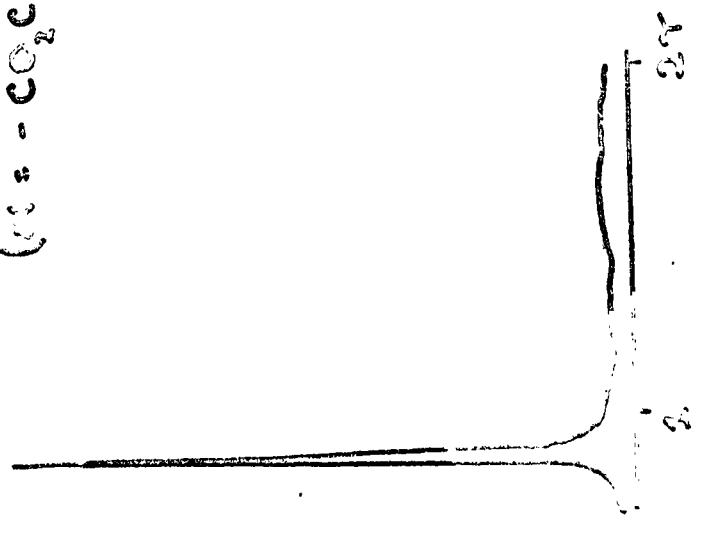
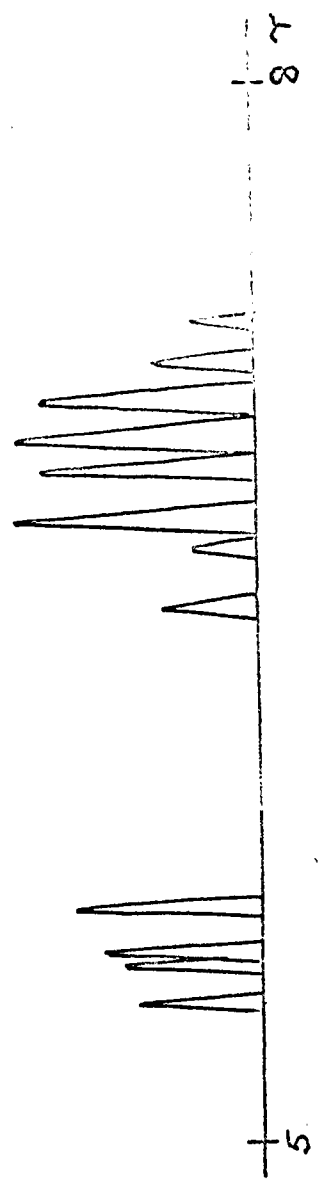
(† (a) and (b) are the methyl and ethyl esters of [6] respectively)

N.m.r. Spectra Fig. II



($\alpha = -\text{CO}_2\text{C}_{11}\text{H}_3$)

Theoretical spectrum,
calculated for the $\alpha\text{H}-\beta\text{H}$ system.



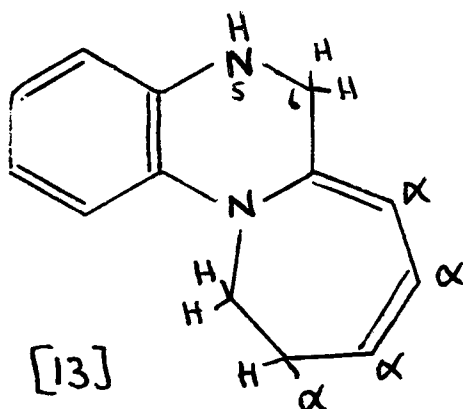
Since the ester methyl signal at high field in the spectrum of [6] partly masks the ABX signal, the corresponding adduct from 2-methyl-quinoxaline and diethyl acetylenedicarboxylate was prepared. The nuclear magnetic resonance spectrum of this compound is shown in fig. II, and now eleven of the twelve predicted absorption lines of the ABX spectrum are clearly visible. Excellent agreement between the observed and calculated spectra again are found, using the parameters :-

$$H_A = 6.71\tau, H_B = 7.10\tau, H_X = 5.52\tau$$

$$J_{AB} = -13.0, J_{AX} = 10.0, J_{BX} = 7.0 \text{ c.p.s.},$$

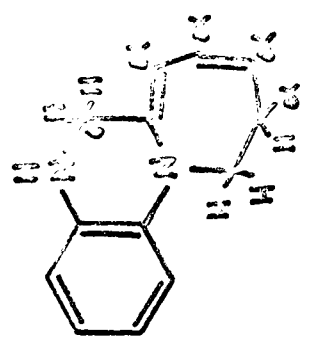
which are almost the same as those of the methyl adduct above.

Catalytic reduction of the compound [6] results in the addition of one mole of hydrogen; and the introduction of an NH group into the molecule (peak in I.R. spectrum at 2.96μ) shows that the 5-6 C=N bond is reduced. The nuclear magnetic resonance spectrum of this dihydro adduct [13] (fig. III) indicates that the low field aromatic proton of the original adduct has moved upfield. Since only the 5-6 bond has been affected by reduction, and, generally, increase in saturation leads to an increase in shielding, in compound [6] the lowest field proton must be the 4-H, and consequently the quartet at 3.6τ must be due to the 1-H, since the coupling constants of this quartet are 7 and 2 c.p.s., characteristic of an aromatic proton with ortho and meta coupling.



Nmr. Spectrum

a) Observed



6-CH₂

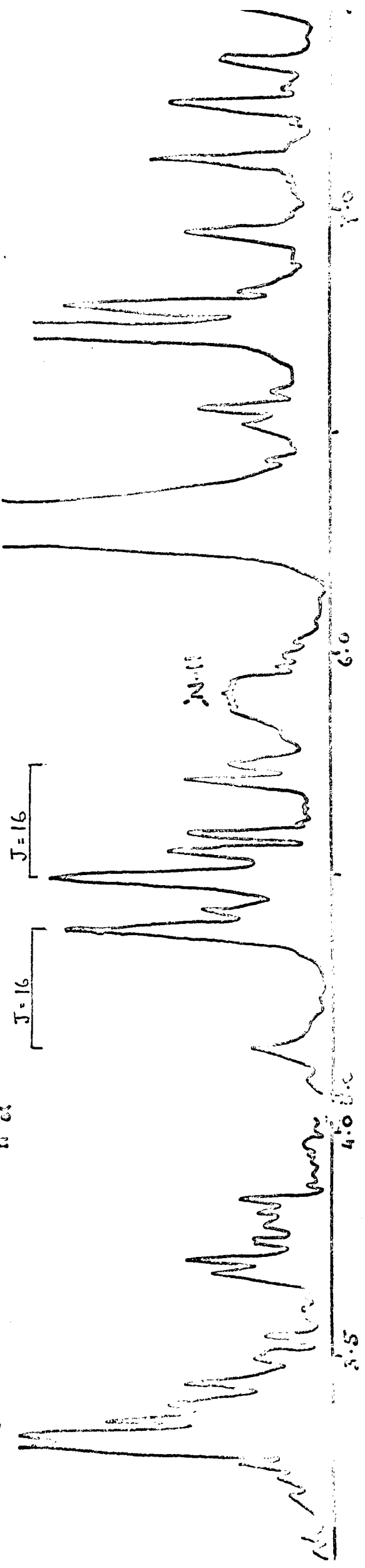
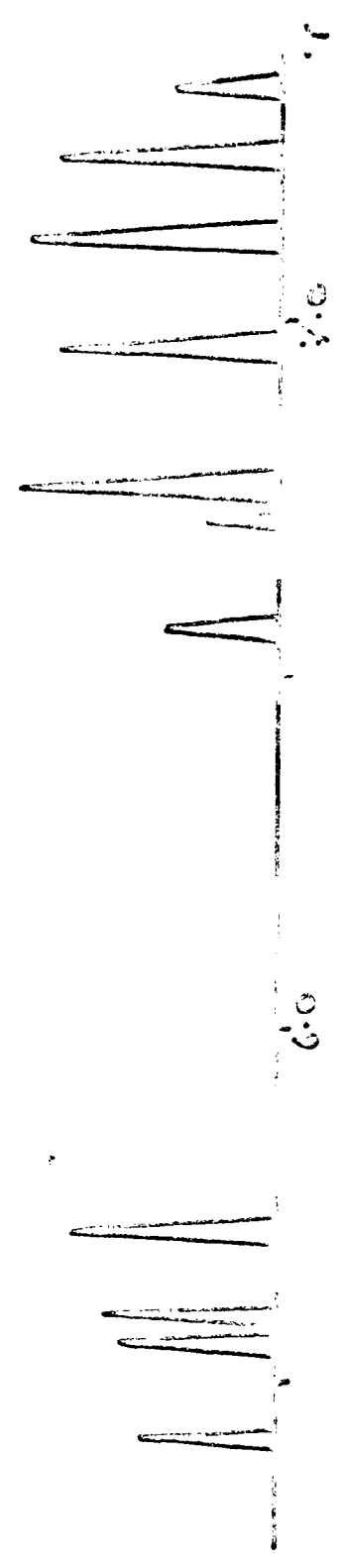


Fig. III

(b) Theoretical spectrum,
calculated for the CH₂-CH system.



Calculations made on the $\text{CH}_2\text{-CH}$ spectrum of [13] again give good agreement between observation and theory (fig. III), and the parameters are approximately the same as those of the starting adduct

$$\text{i.e. } H_A = 6.78\tau, H_B = 7.27\tau, H_X = 5.58\tau$$

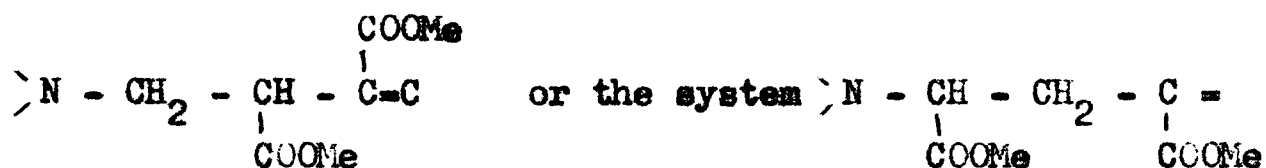
$$J_{AB} = -13.0, J_{AX} = 10.5, J_{BX} = 7.0 \text{ c.p.s.},$$

showing the environment of the ABX system does not change markedly when the adduct is reduced.

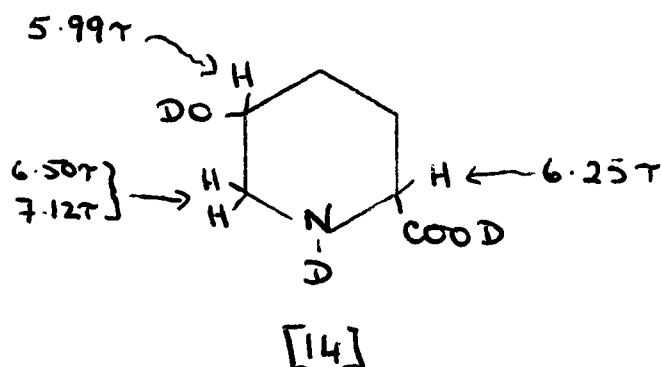
The major product from the reaction between 2,3-dimethylquinoxaline and dimethyl acetylenedicarboxylate is a 1:2 molar adduct, whose infrared and ultraviolet absorption spectra and nuclear magnetic resonance spectrum show it to be the methyl analogue of [7], i.e. compound [8]. In the proton resonance spectra of both these compounds, an ABX system appears to be present, but is partly hidden by the ester methyl signals. Consequently, no calculations could be made, and attempts to obtain the analogous adducts from the ethyl ester were complete failures. However, both contain a low field aromatic proton with a similar chemical shift to that of the 10-H of the adduct [6]. Unlike [6], these compounds have no high field aromatic proton, and the pattern of the ABX spectrum is completely different. A possible explanation is that [7] and [8] have a carbomethoxy group at the 11-position and the CH_2 group at position 10 (these are reversed in [6]). The carbomethoxy group then deshields the 1-proton, so that its chemical shift is similar to the 2- and 3-protons. The chemical shifts of the ABX protons are 7.3 τ (one of the protons at the 10-position), while the other 10-H and the 11-H have similar chemical shifts of ca 6.3 τ .

The chemical shifts of the ABX protons of the quinaldine adduct [5] are 6.3-6.4 (two protons) and 7.37 τ .⁴⁰ These are at higher field than those of [6], but comparable to those of [7]. However, structures [5] and [6] should be analogous. Possibly the presence of the additional nitrogen atom in [6] causes the shift to lower field of these protons, or the CH₂-CH group should be inverted for the quinaldine adduct.

Model compounds containing either the system



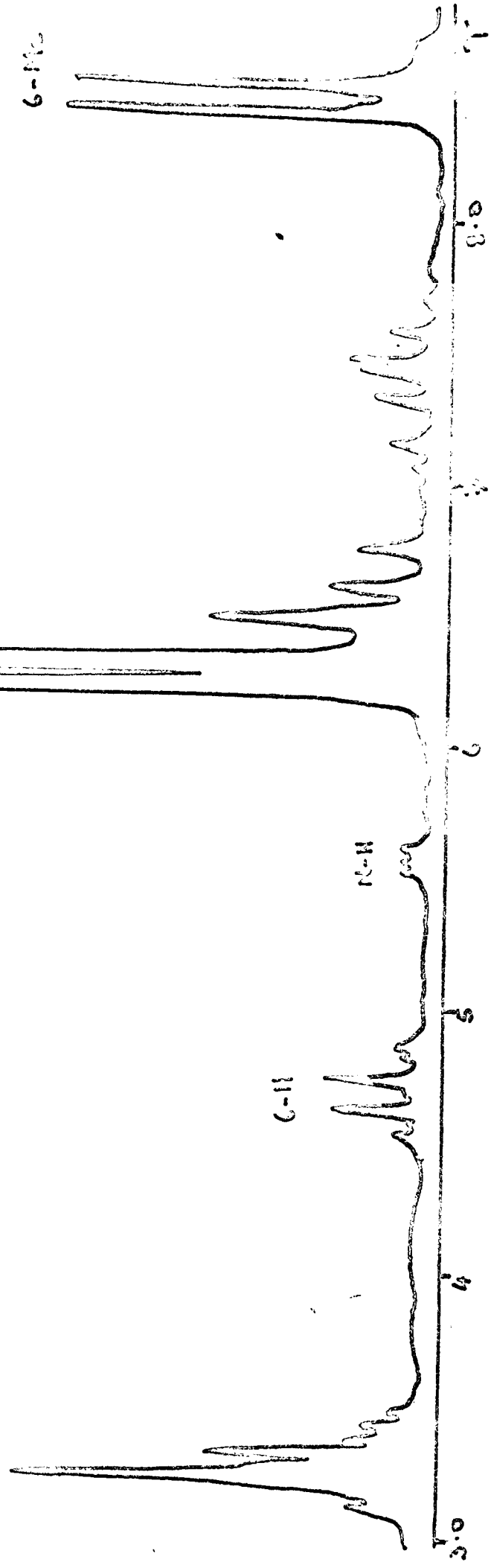
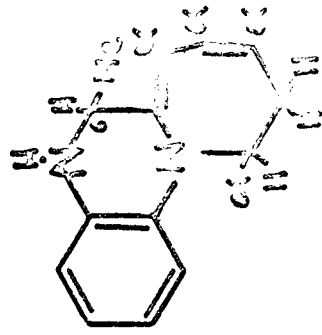
whose proton resonance spectra had been recorded could not be found, the nearest being 5-hydroxypipicollic acid [14],⁵⁰ the chemical shifts of the relevant protons being shown.



The nuclear magnetic resonance spectra of the adducts in trifluoroacetic acid, in which solvent their ultraviolet absorption spectra are very similar to those in 30% methanolic perchloric acid, do not shed much light on the structure of these compounds. The spectrum of [6] changes very little, except that all the peaks are shifted downfield by about 0.2 τ , while that of the 6-H is shifted downfield 0.45 τ , and is slightly split (ca 1 c.p.s.). This indicates protonation has occurred on the nitrogen atom at position 5, and the N⁺-H exchanges with the solvent at almost the

N.M.R. Spectrum.

Fig. IV

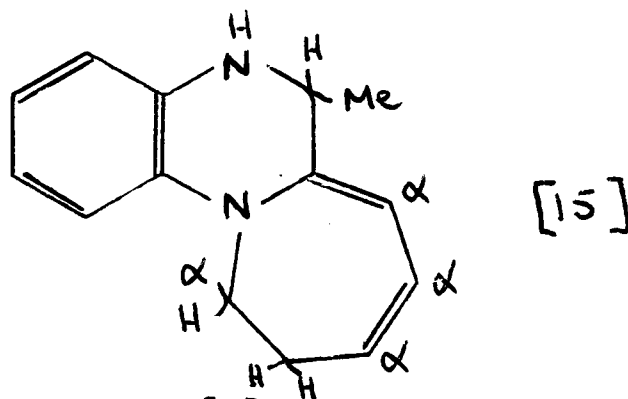


frequency of the instrument. The N^+-H peak is not observed, and is possibly hidden in the solvent peak. The splitting of the 6-H disappears when the spectrum is measured in deuterio-trifluoroacetic acid.

The spectrum of [8] in trifluoroacetic acid shows protonation occurs in two places - two new peaks appear at 4.13 and 4.44 τ in approximately a 2:1 ratio. These disappear in deuterio-trifluoroacetic acid. The position of protonation cannot be determined, but both [6] and [8] have similar ultraviolet absorption spectra in acid solution, and so must contain a similar chromophore.

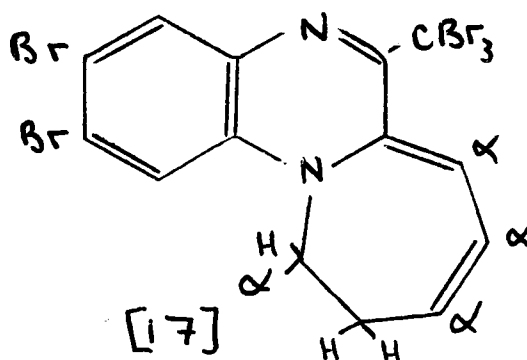
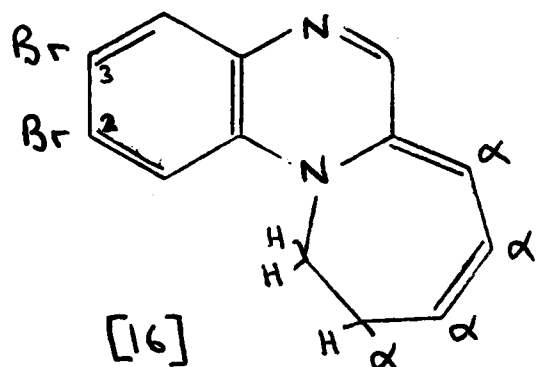
Various chemical reagents were used to try to degrade the adducts [6] and [8], especially with a view to opening the seven-membered ring. Unfortunately, this ring proved exceptionally stable, the majority of products being formed by attack on the rest of the molecule.

Catalytic reduction of [6] has been described (p.60), and a similar dihydro compound [15] is given by [8]. The nuclear magnetic resonance spectrum of [15] is shown in fig.IV, and confirms that the 4-H in the spectrum of [8] gives the low field aromatic signal (see p. 60)



Bromination of the adduct [6] gives a dibromo compound containing no ionic bromine. The nuclear magnetic resonance spectrum shows that both bromine atoms have entered the aromatic ring, and the remaining two

aromatic protons give two sharp singlets. Therefore, the compound must be the 2,3-dibromo derivative [16].



Bromination of the adduct [8] gives a pentabromide, five hydrogen atoms being replaced. The nuclear magnetic resonance spectrum shows two sharp singlets in the aromatic region and no C-methyl group. On this evidence, the pentabromide is formulated as [17]. The use of N-bromosuccinimide prevents aromatic bromination, and a white mono - and dark-red tribromomethyl derivative are obtained, depending on the amount of N-bromosuccinimide used. A second white compound was also obtained whose analysis was not good, but which indicated it was the dibromomethyl derivative.

Attempts to obtain useful derivatives by the oxidation of [6] were unsuccessful. The adduct is recovered in high yield when treated with neutral potassium permanganate, freshly prepared manganese dioxide, or osmium tetroxide. However, with manganese dioxide, the adduct recovered from the reaction mixture had identical analysis, infrared and ultraviolet absorption and nuclear magnetic resonance spectra to the starting material, but the melting point had risen from 155-6° to 170-1°. It is possible, that since [6] and [7] have such similar structures, they form mixed crystals (with [7] present in such small proportion that it is not detectable by

proton resonance spectroscopy), but the traces of [7] are removed by the manganese dioxide (different absorption?). Oxidation of [6] with acid permanganate gives a tar from which no crystalline solid could be isolated.

The adduct [8] was oxidised with peracetic acid to a colourless oil, which would not crystallise, and whose infrared absorption spectrum gave little information. Chromic acid oxidation of [8] gives a small amount of a compound, whose analysis corresponds with $C_{20}H_{24}N_2O_{10}$. The infrared absorption spectrum shows the presence of ester, hydroxyl, and, possibly, amino groups. The ultraviolet absorption spectrum shows the chromophore of the original adduct is no longer present, but, from the proton resonance spectrum, it is evident that the CH_2-CH- group is still present, the low field aromatic proton has moved upfield, and the C-methyl group has disappeared. A broad signal at 1.8τ , which does not exchange with deuterium oxide could be the NH group of an amide. No further work has yet been done on this compound.

The adduct [8] is oxidised with selenium dioxide in tiny yield to a compound, shown by mixed melting point and spectroscopy, to be the adduct [7]. Presumably, the methyl group is oxidised to a carboxylic acid, which then decarboxylates.

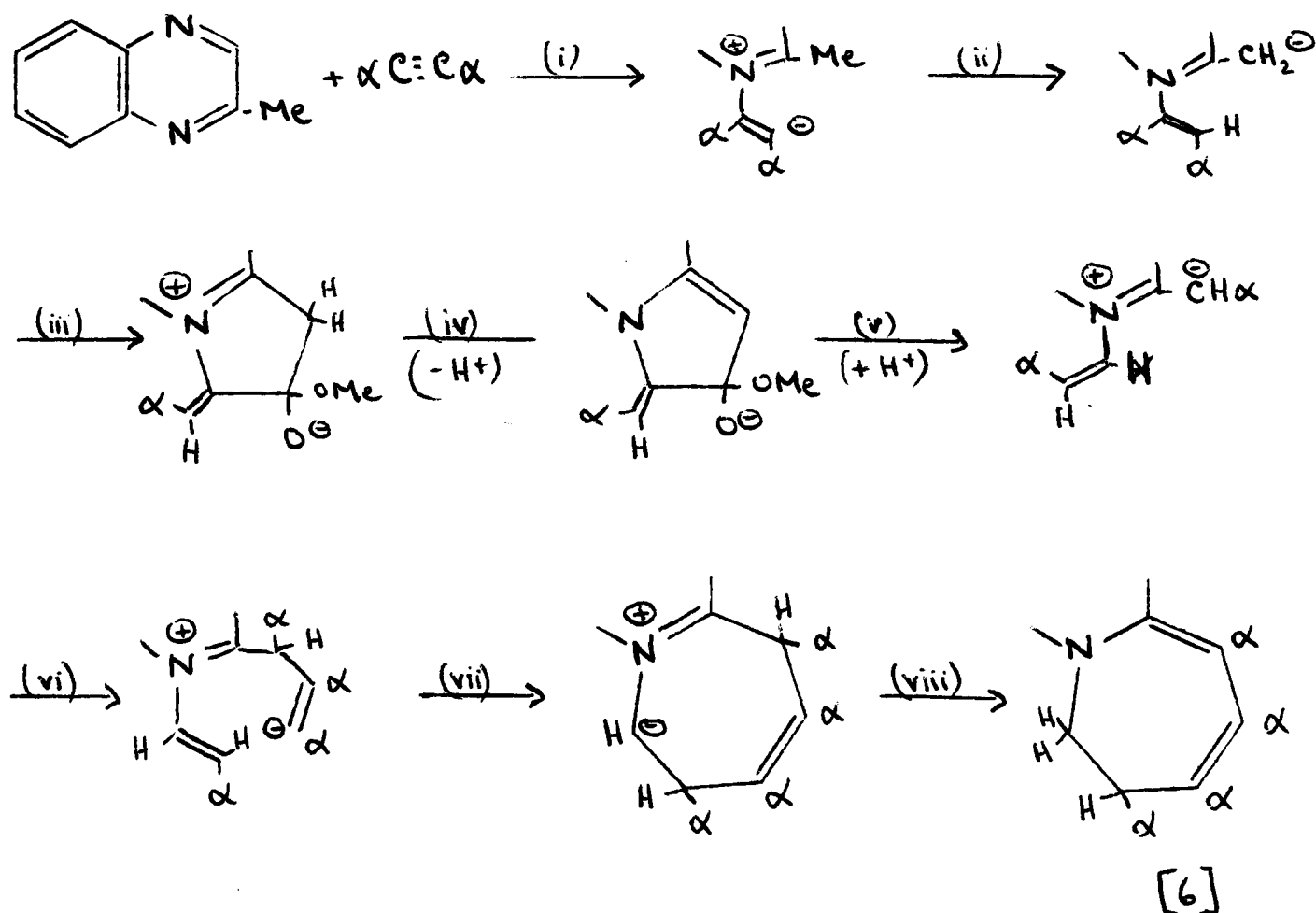
Condensation of [6] with benzaldehyde under basic conditions gives a red oil, from which no crystalline material was obtained, while [8] under similar conditions gave a mixture of a red oil and dark-red crystals of a compound provisionally formulated as the 6-styryl derivative of [8].

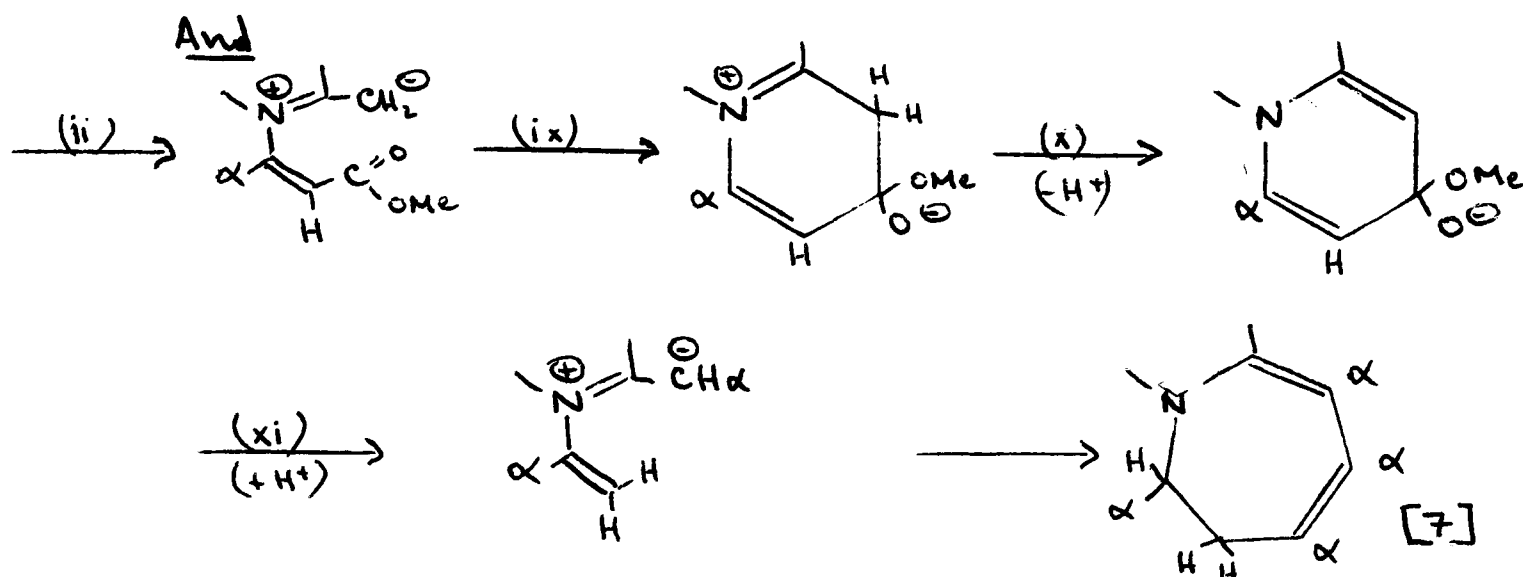
The failure of benzaldehyde to give a crystalline product with [6] is in agreement with a structure which has the CH_2 group adjacent to a saturated nitrogen atom.

Attempts were made to introduce other functional groups into the seven membered ring by reacting the ester groups of [5] with ammonia (no reaction) and methyl magnesium iodide and lithium aluminium hydride. These two reagents gave non-crystallisable tars, as did both alkaline and acid hydrolysis.

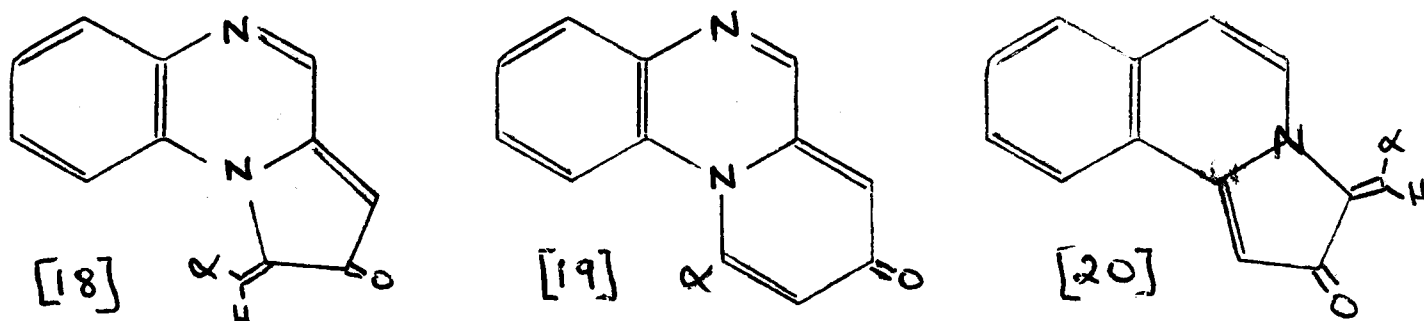
The original heterocyclic ring was then attacked. The dihydro derivatives [13] and [15] were reacted with excess methyl iodide. Although crystalline methiodides were not obtained, the crude mixtures were reacted with silver hydroxide, and the solutions containing the quaternary hydroxide, were hydrogenated. However, no products were isolated.

A possible mode of formation of [6] and [7] is outlined below :-





The weakness of this mechanism is that the intermediates formed by stages (iii) and (ix) could be expected to lose methanol to give [18] or the isomeric [19], both stable moieties. No such compound has been isolated from comparable additions with methyl-substituted heterocycles, but Gagan obtained the compound [20] from the addition of dimethyl-acetylenedicarboxylate to 1-ethylisoquinoline.⁴⁰



An alternative mode of formation of the adducts from 2-methyl-quinoxaline must take into account the following considerations :-

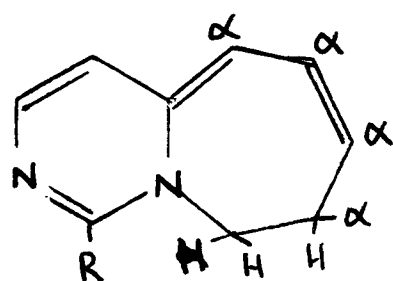
- Two possible isomers possessing the same chromophore can be formed. However, some steric effect may occur, since 2,3-dimethylquinoxaline forms only one of the isomers in isolable yield.
- The methyl group α to the nitrogen is involved in the reaction, the hydrogen atoms becoming a CH_2-CH group.

(c) There can be no hydrogen atom adjacent to the 3H (of the original quinoxaline ring), since, in the nuclear magnetic resonance spectra of the adducts, this hydrogen gives a singlet.

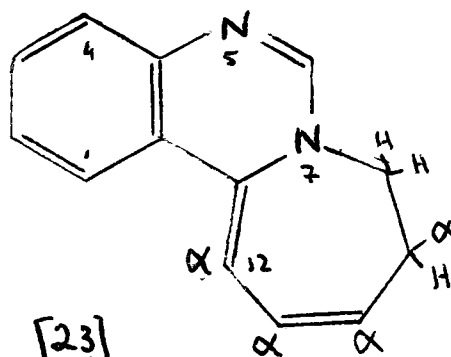
The definite method to solve the structure of these "seven-membered ring" adducts would seem to be a complete X-ray analysis of some bromo-derivative. An attempt has been made using a bromo derivative of the quinaldine adduct [5], but this ended in failure.⁴⁰

Adducts of Methylpyrimidines.

Both 4,6-dimethylpyrimidine and 2,4,6-trimethylpyrimidine give 1:2 molar adducts with dimethyl acetylenedicarboxylate, possessing almost identical ultraviolet absorption spectra and, in their proton resonance spectra, similar but not identical high field ABC spectra. In each adduct one of the C-methyl groups is no longer present. These adducts are formulated as [21] and [22] respectively, by analogy with the quinoxaline adducts, although the positions of the $-\text{CH}_2-$ and $-\text{CH}(\text{COOMe})-$ groups may be reversed. In the adduct [22], the 2-methyl rather than the 4-methyl group of 2,4,6-trimethylpyrimidine may have reacted. However,



[21] R:H
[22] R:Me

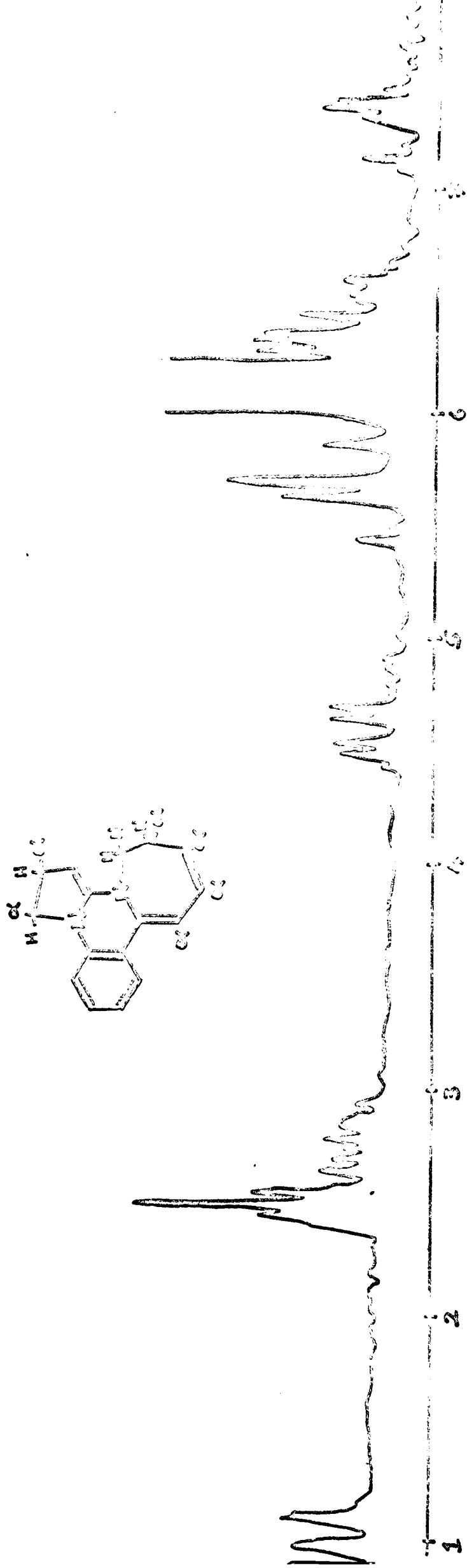
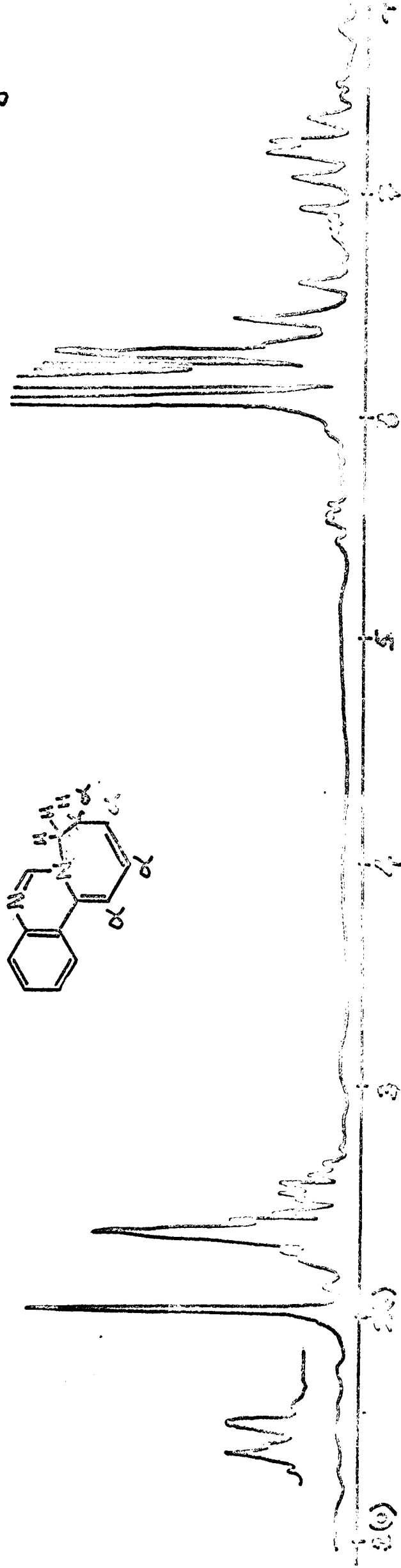


[23]

2-methylquinazoline fails to give a crystalline adduct, while 4-methylquinazoline gives the adduct [23]. The nuclear magnetic resonance spectrum of this compound (fig. V) shows the presence of an extremely low field signal (0.52 τ) due to the $-\bar{\text{p}}\text{roton}$ being highly de-

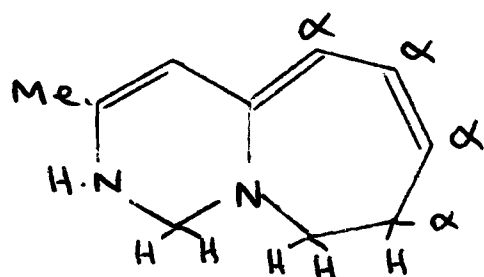
N.m.r. Spectro-

Fig. V

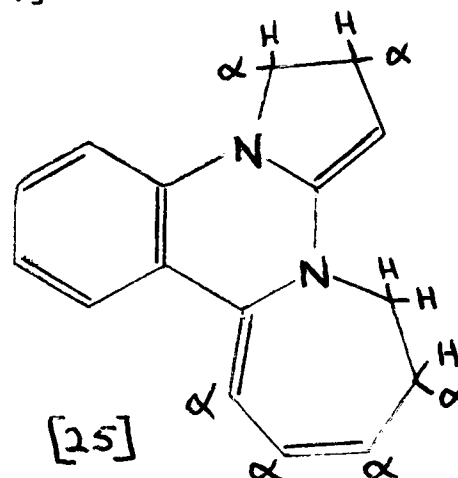


shielded by the carbomethoxy group in the 12 position.

Little chemistry has been done on these compounds, because of the low yields in which they are obtained. However, catalytic reduction of [21] gives a dihydro derivative, whose infrared absorption spectrum possesses an NH absorption. The nuclear magnetic resonance spectrum confirms the presence of an NH signal, which, on addition of deuterium oxide to the sample, disappears, leaving two doublets. Therefore, the reduced adducts must have structure [24].

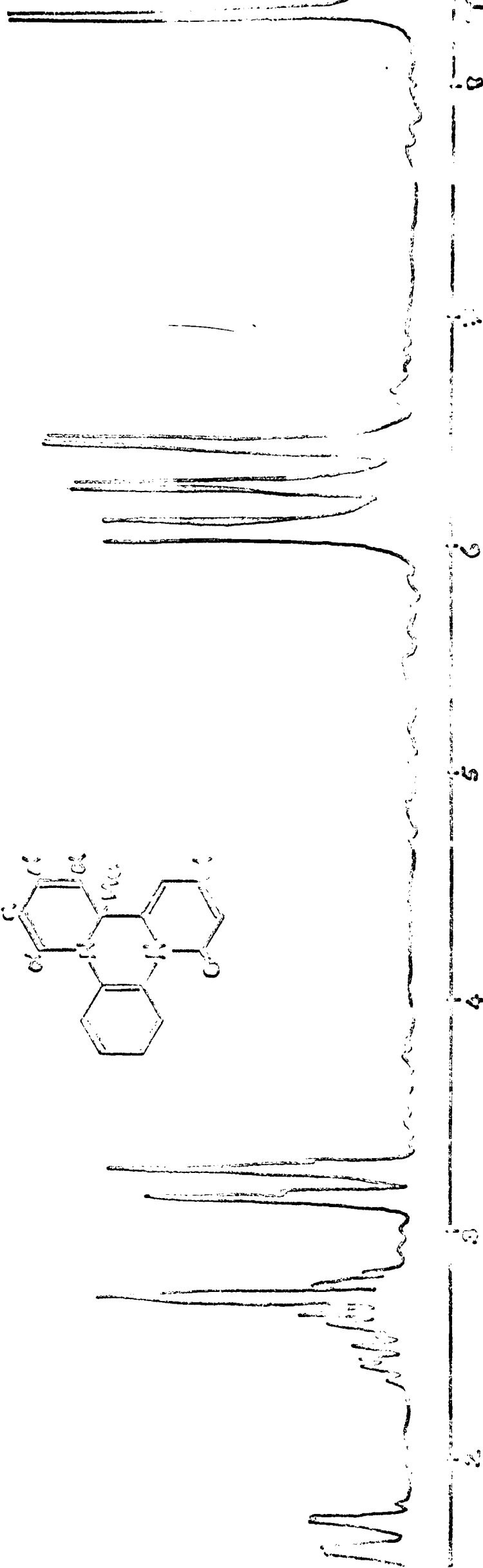
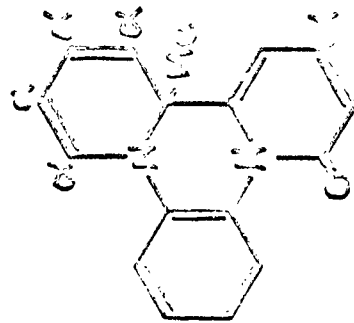
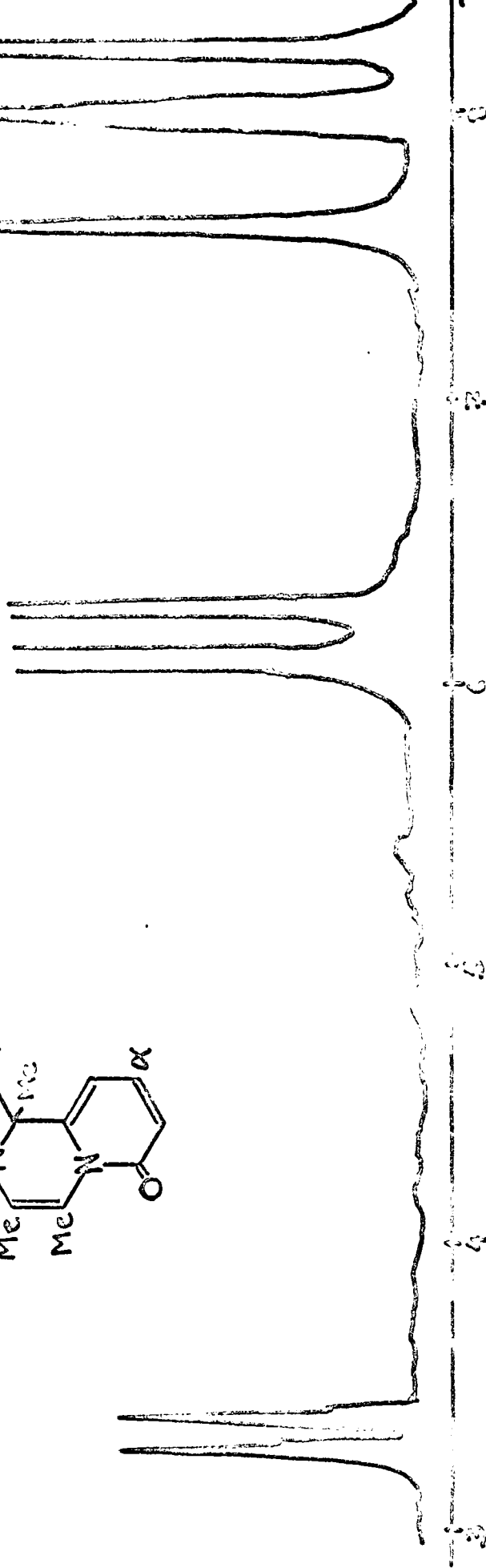
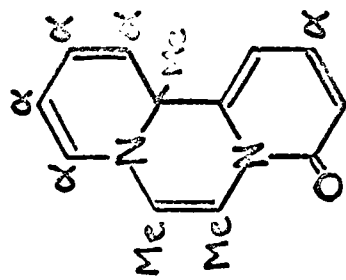


[24]



[25]

2,4-Dimethylquinazoline and dimethylacetylenedicarboxylate give not the methyl analogue of [23] but a 1:3 molar adduct, in which both methyl groups have reacted. A provisional structure [25] is proposed for this compound, on the basis of its very small absorption in the ultraviolet, and its nuclear magnetic resonance spectrum (fig. V). In this the positions of the very low field and other aromatic proton signals have moved upfield as compared with the adduct [23] from 4-methylquinazoline. This is expected since saturation of the 1-nitrogen will lower its deshielding effect and also buckle the whole system, so that the carbomethoxy group in the 14-position will no longer be in the same plane as the 1-H as in [23], and so will not deshield it as much. This buckling



effect has been shown by making Dreiding models of [23] and [25]. The multiplets between 4.7 and 7.5 τ appear to be due to two ABX systems, one of which is comparable to that of the adduct [23]. However, further chemical evidence is necessary, together with the results of decoupling experiments, before a structure can be firmly formulated.

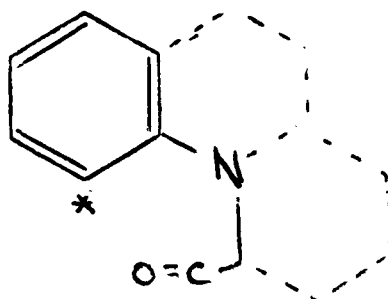
The 2,3,5,6-Tetramethylpyrazine Adduct.

This heterocycle and dimethyl acetylenedicarboxylate give a product of the composition required of $C_{25}H_{26}N_2O_{11}$, that is, a 1:3 molar adduct less methanol. An analogous compound is also formed as the minor product from the reaction of 2,3-dimethylquinoxaline and the ester. The infrared absorption spectra of the two compounds are compared below :-

[27] 5.75, 5.79, 5.87, 6.14, 6.20, 6.29, 6.54

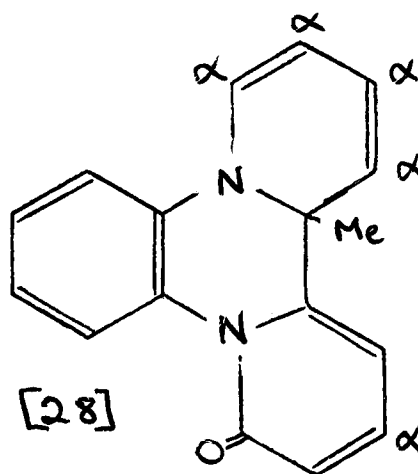
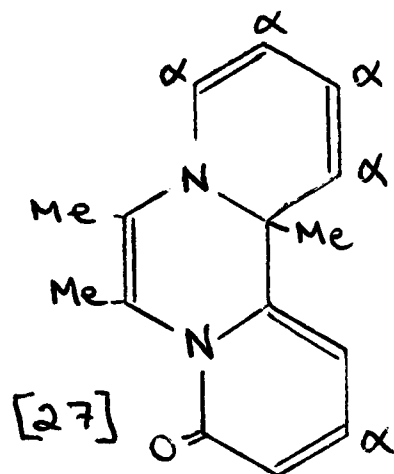
[28] 5.72, 5.80, 5.86, 6.18, 6.25, 6.33, 6.51, 6.71.

The compounds contain five methoxyl groups (shown by analysis) while the proton resonance spectra (fig. VI) of both compounds have signals due to a C-methyl group on a saturated carbon atom, and two doublets (due to two protons) with coupling constants of under one c.p.s. This small coupling constant strongly suggests the protons are not on adjacent carbon atoms. The aromatic proton (asterisked) with a chemical shift of 1.71 τ in the spectrum of the dimethylquinoxaline adduct suggests the system [26].



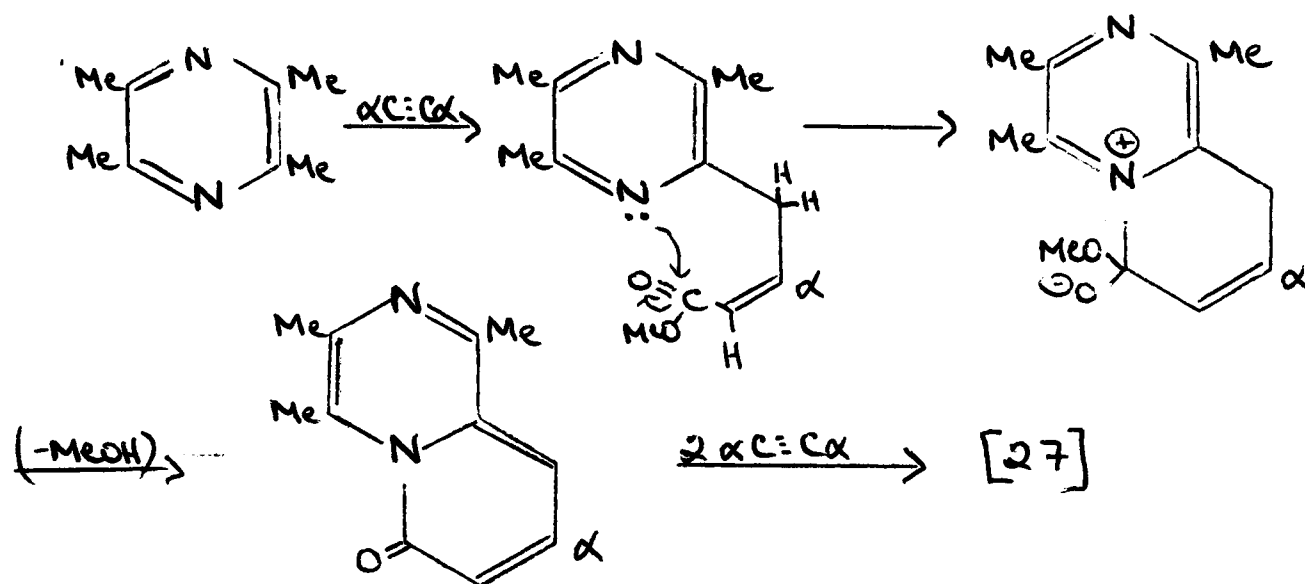
[26]

Possible structures for these adducts are [27] and [28].

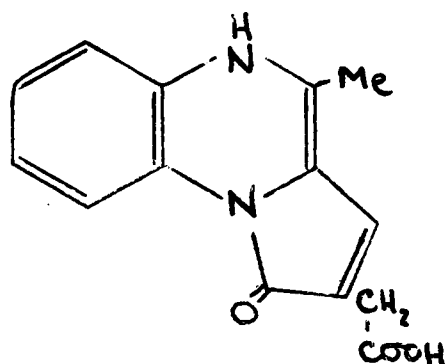


The ultraviolet absorption spectra of such compounds should not be affected by the addition of acid, and this is found to be the case.

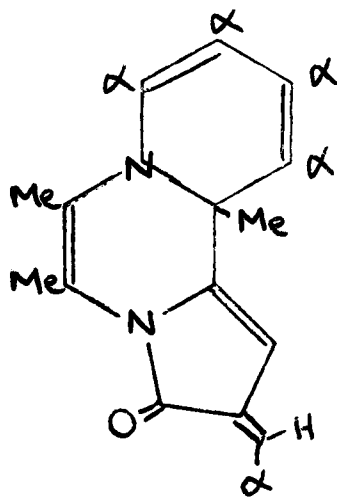
A possible mode of formation is outlined below :-



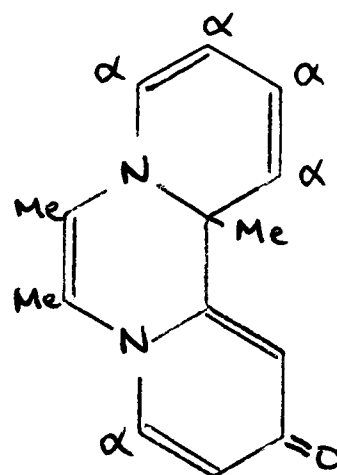
This is a comparable reaction to the formation of [1].⁶³ The remaining methyl groups make the other nitrogen atom basic enough to attack more acetylenic ester in the usual Michael fashion (see introduction, p. 2). Of course, in step (iii) above, the nitrogen could attack the other carbonyl group, to give finally the isomeric [29], while initial attack on the acetylene by the nitrogen atom rather than by the methyl group would give [30].



[1]



[29]



[30]

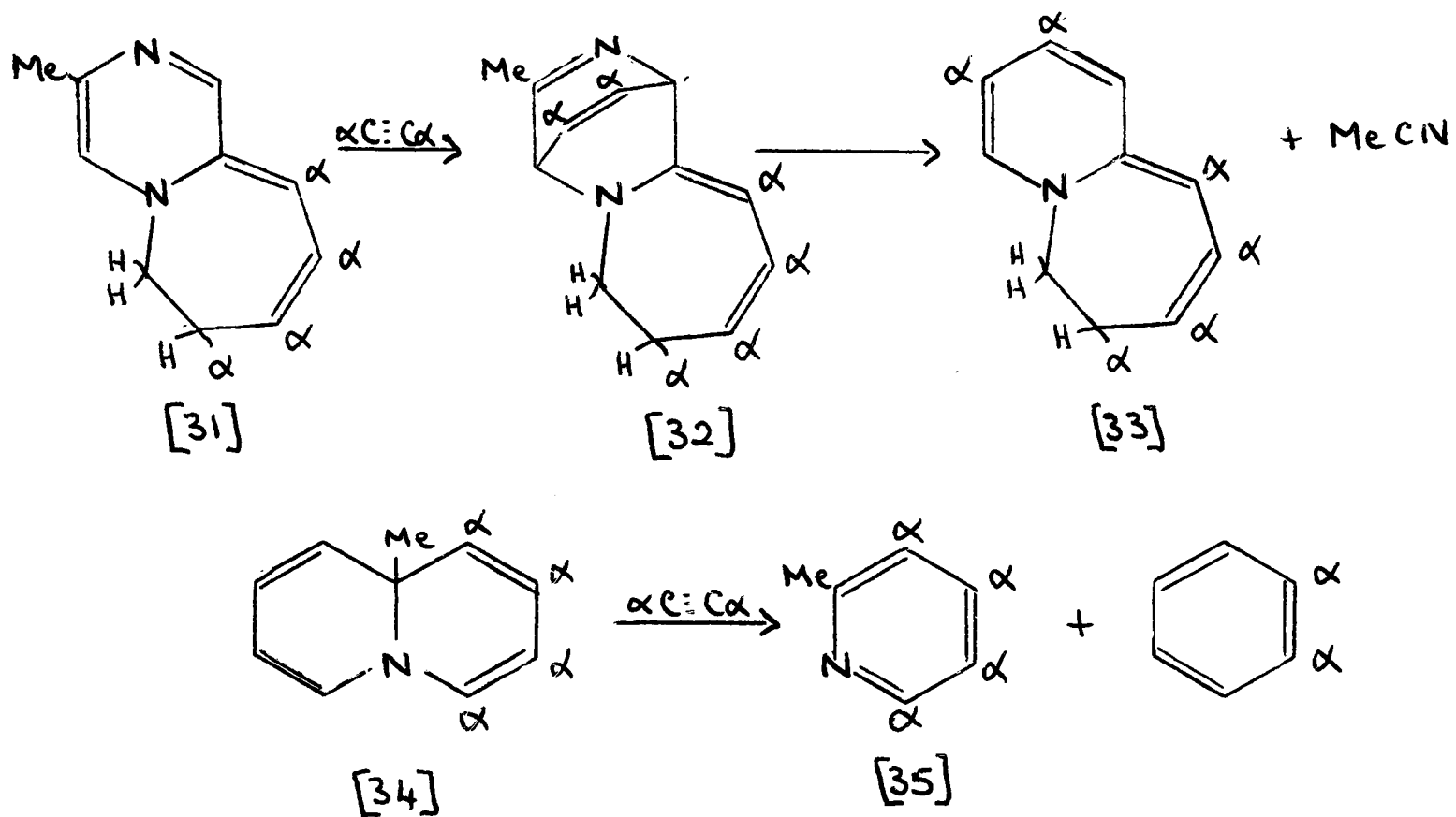
Structure [27] is preferred over [29] since Dreiding models show that, whether the nitrogen atoms be planar or pyramidal, the formation of a five-membered ring would lead to much more strain than a six-membered ring.

Again the chemistry of these compounds will have to be examined before definite structures can be proven.

The 2,5-Dimethylpyrazine Adduct.

The adduct of 2,5-dimethylpyrazine and dimethyl acetylenedicarboxylate analyses for $C_{22}H_{23}NO_{12}$, which corresponds to a 1:3 molar adduct less C_2H_3N . Little information can be gleaned from the infrared and ultra-violet absorption spectra, but the proton resonance spectrum is consistent with the presence of six methoxyl groups, an ABX system (comparable to those of the pyrimidine adducts, fig.V p.68) and two single protons with chemical shifts of 1.93 and 2.62τ. No C-methyl groups are present. Since the compound probably contains a CH_2-CH grouping, the first intermediate formed could be [31], which then undergoes a Diels-Alder addition with a third mole of ester to give [32]. The adduct formulated as [33], is thought to be formed by the elimination of acetonitrile. An analogy is

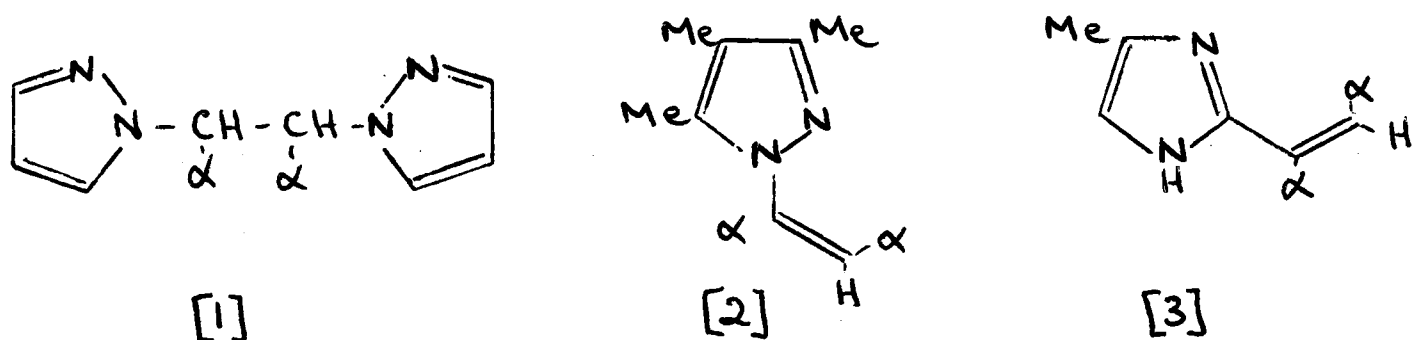
the reaction of [34] to give [35] and dimethyl phthalate.²⁸



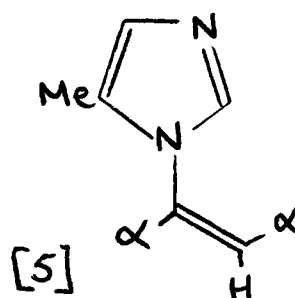
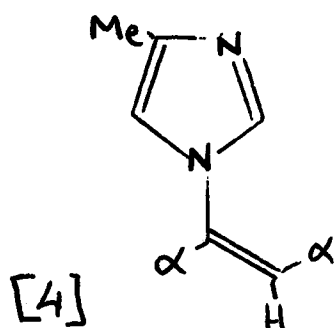
CHAPTER FIVE

The Addition of Dimethyl Acetylenedicarboxylate to Compounds possessing an Amino Group

Except for pyrroles¹⁶ and indoles²¹, which are attacked at the 2- and 3-positions respectively, little work has been published on the reactions of dimethyl acetylenedicarboxylate with heterocyclic compounds possessing free N-H groups. Pyrazoles are known to give 2:1 and 1:1 molar adducts e.g. [1] and [2].⁵⁵ A similar 1:1 molar adduct has also been obtained from 2-methyliminazole,⁵¹ while Diels and Alder reported that 4-methyliminazole gave [3] or the cis isomer.¹⁶

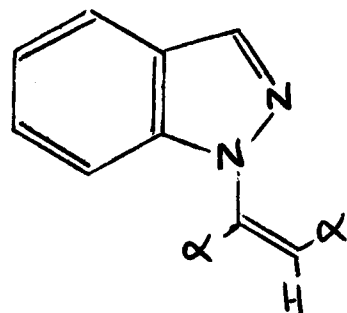


Since 2-methyliminazole is known to react at the 1-position with the acetylenic ester,⁵¹ it seems unlikely that 4-methyliminazole would react at the 2-position. Therefore, the reaction was repeated, giving a 1:1 molar adduct with the same meltingpoint as the compound isolated by Diels. The infrared absorption spectrum shows no NH absorption, and as no change in the nuclear magnetic resonance spectrum is caused by the addition of deuterium oxide, structure [3] is excluded. The most likely structures are [4] or [5]. The trans configuration is preferred, since the adducts of acridine⁴² and phenanthridine⁴¹ with dimethyl acetylenedicarboxylate have been proved to have a trans structure, and, generally, nucleophilic addition to acetylenes gives such a configuration. A choice between [4] and [5] cannot be made with the present data.

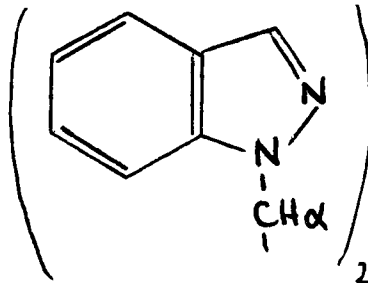


Indazole and dimethyl acetylenedicarboxylate in refluxing acetonitrile, give two products, one of which is a 1:1 molar adduct. The ultraviolet absorption spectrum shows the compound is more conjugated than indazole, while the infrared absorption spectrum contains no NH stretching frequency. Therefore, the most probable structure is [6], given a trans configuration by analogy. The nuclear magnetic resonance spectrum supports this formulation, having peaks due to two ester methyl groups (5.95, 6.20 τ), four aromatic protons, and two single protons (1.86 and 3.17 τ). The most deshielded single proton is probably at the 3-position, as this proton in the spectrum of indazole is at 1.87 τ , while the second proton has the same chemical shift as the vinyl protons of diethyl fumarate, but not diethyl maleate (3.72 τ).

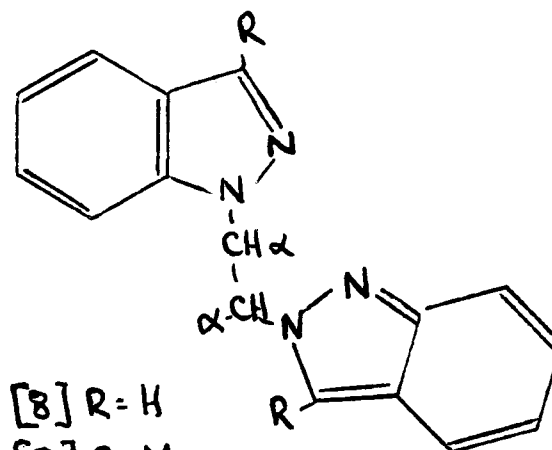
The second adduct of indazole and the acetylenic ester is a 2:1 molar adduct, which shows no NH stretching frequency in the infrared absorption spectrum, and has a similar ultraviolet absorption spectrum to that of indazole. This evidence, plus the analogy with the pyrazole adducts, would suggest the structure [7]. However, the nuclear magnetic resonance spectrum contains two ester methyl signals (6.23, 6.29 τ), a quartet due to the two succinate protons (3.57, 3.77 τ , $J = 11$ c.p.s.) and two singlets



[6]



[7]

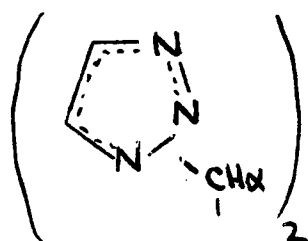


[8] R = H
[9] R = Me

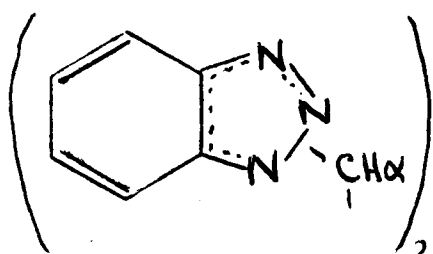
(2.03, 2.36 τ) allocated to the protons at the 3-positions of the indazole rings. This means the molecule is unsymmetrical, and, accordingly is formulated as [8].

3-Methylindazole gives a similar adduct [9], with a proton resonance spectrum in which the succinate protons are at 3.30 and 3.55 τ (J=11 c.p.s.), the two C-methyl groups are at 7.13 and 7.43 τ , and surprisingly, the two methoxyl groups are much more shielded than in [8], and appear as a single peak at 6.60 τ . Comparison with the spectra of 1,3-dimethyl- and 2,3-dimethyl-indazole suggests that the C-methyl group of [9] at higher field is in that indazole molecule in which the side-chain is attached to the nitrogen atom in the 2-position.

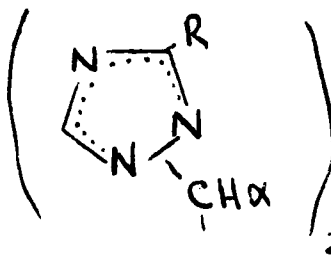
The succinates [10] - [13] are obtained by refluxing the heterocycle with the acetylenic ester in acetonitrile, and the structures were assigned by nuclear magnetic resonance and infrared absorption spectra.



[10]



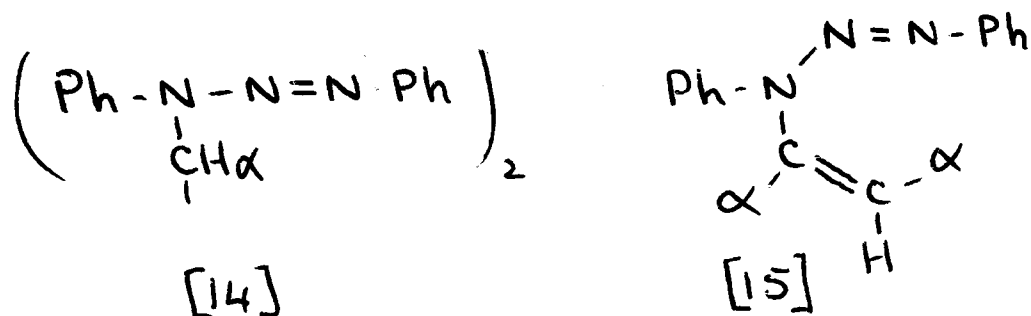
[11]



[12] R = H
[13] R = Me

In the above adducts it has not been established to which nitrogen atom the side chain is attached.

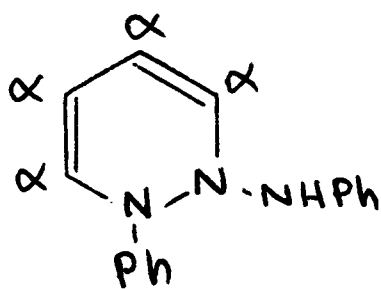
A similar reaction involving the NH group occurs between diazoaminobenzene and dimethyl acetylenedicarboxylate. One of the products is dimethyl α, α' - 1,1' - bis-(1,3-diphenyltriazenyl) succinate [14], whose structure is confirmed by nuclear magnetic resonance spectroscopy. The spectrum is symmetrical, showing ten aromatic protons, a single proton (3.68 τ) and one methoxyl group (6.31 τ).



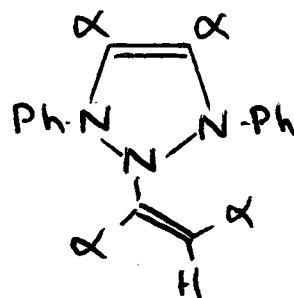
A minor product of the reaction is the 1:1 molar adduct [15], whose proton resonance spectrum shows two aromatic protons (1.7 - 1.9 τ), probably the ortho protons of the 1-phenyl group, seven aromatic protons at 2.53 τ , a single proton at 3.39 τ (the olefinic proton), and two methoxyl groups at 6.15 and 6.67 τ . The high field methoxyl group must be above the 1-phenyl group.

A third product is a 1:2 molar adduct, for which two structures [16] and [17] suggested themselves. The infrared absorption spectrum shows no NH absorption, and none of the peaks in the nuclear magnetic resonance spectrum exchanged with deuterium oxide. The adduct is recovered unchanged from refluxing acetic anhydride. Therefore, structure [16] is

discounted, and structure [17] is proposed for this compound.



[16]



[17]

EXPERIMENTAL

Infrared absorption spectra were measured on a Perkin-Elmer "Infracord" Spectrophotometer in paraffin mulls or in chloroform solution (C). Maxima are recorded in microns for the region 0-7 μ .

Ultraviolet absorption spectra were measured on a Perkin-Elmer "Ultracord 137" Spectrophotometer fitted with a deuterium lamp. The following solvents were used :-

methanol
methanol acidified with one drop of 72% perchloric acid (A)
methanol: 72% perchloric acid (2:1 v/v) (P)
methanol basified with one drop of 5% sodium methoxide solution (B)

The maxima are recorded in m μ , with 10⁻⁴ e in parentheses.

Inflexions are marked with an asterisk.

Nuclear magnetic resonance spectra were obtained on a Perkin-Elmer Spectrometer operating at 60Mc./s. at 34⁰, using tetramethylsilane as internal standard. The solvent used was deuteriochloroform (99.5%) unless otherwise stated. Peaks are reported in τ values, and coupling constants in cycles per second (c.p.s.).

Meltingpoints were measured on a Reichert Microscope "RCH" Kofler Micro Heating Stage, and are reported uncorrected.

Chromatography. For column chromatography, the alumina used was Spence's grade H, 100/200 mesh, deactivated by shaking for 12 hr. with 5% of its weight of 10% aqueous acetic acid. Columns were made up in benzene unless otherwise stated. The mixture to be chromatographed was dissolved in the minimum amount of benzene: chloroform (1:1 v/v) and poured onto the column. The fractions eluted off the column were evaporated to dryness under reduced pressure, and the residue was triturated

with methanol. This method was used always, unless otherwise stated, and will be described in the following pages simply as "chromatography on alumina", followed by a description of the eluent.

For thin-layer chromatography, Merck's silica gel G, was used, in thicknesses of 30 μ .

Microanalyses were carried out by Dr. A. Bernhardt (Mülheim).

Dimethyl Acetylenedicarboxylate⁶⁷ was prepared from the monopotassium salt of acetylenedicarboxylic acid, sulphuric acid, and methanol in 81% yield, and had b.p. 91-4°/16mm., $n_D^{25} = 1.4450$ (lit. b.p. 95-8°/19mm., $n_D^{25} = 1.4444-1.4452$).

Diethyl Acetylenedicarboxylate was prepared similarly in 46% yield, and had b.p. 105 - 9°/16mm., $n_D^{25} 1.4395$ (lit.⁶⁷ b.p. 96 - 8°/8mm., $n_D^{25} 1.4397$).

2-Phenylpyridine, prepared by the literature method⁶⁸ in 39% yield, had b.p. 128-30°/9mm., $n_D^{25} 1.613$ (lit. b.p. 140°/12mm).

Isoxazole, prepared according to Protopopova and Skoldinov,⁶⁹ in 68% yield, had b.p. 93-5° (lit. b.p. 95°)

5-Methylisoxazole, obtained by the method of Claisen,⁷⁰ had b.p. 120-2° (lit. b.p. 122°)

3,5-Dimethylisoxazole,⁷¹ from acetylacetone and hydroxylamine, had b.p. 140-2° (lit. b.p. 140-2°)

Benzisoxazole was prepared by the thermal decomposition of the oxime acetate of o-salicylaldehyde⁷² in 12% yield. It had b.p. 80-2°/12mm. (lit. b.p. 82-3°/14mm.)

1-Ethyl-2-methylbenziminazole:- 2-Methylbenziminazole (13.2g.) was added in small portions to a stirred solution of sodium (2.4g.) and ferric nitrate (0.1g.) in liquid ammonia (150ml.). After stirring for 15 min., ethyl bromide (10.9g.) was added dropwise. The ammonia was allowed to evaporate, water (50 ml .) was added, and the mixture was continuously extracted with ether for 24 hr. The dried (MgSO_4) extract was distilled to give 1-ethyl-2-methyl benziminazole (9.72g., 61%) as a pale yellow oil, b.p. $166-8^\circ/15\text{mm.}$, (lit.⁷³ b.p. $110-2^\circ/0.3-0.4\text{mm.}$)

N-Methylpyrazole. Pyrazole⁷⁴ was obtained from 1,1,3-trimethoxy-3-ethoxypropane and hydrazine hydrochloride in 77% yield, b.p. $83-5^\circ/12\text{mm.}$, m.p. $68-70^\circ$ (lit. b.p. $95-7^\circ/20\text{mm.}$, m.p. 70°). Methylation by the method of Finar and Lord⁷⁵ gave N-methylpyrazole, b.p. $124-6^\circ$ (72%) (lit. b.p. $126-7^\circ$)

Indazole and its Methylation Products. Indazole,⁷⁶ prepared in 53% yield, had m.p. $145-7^\circ$ (lit. m.p. 148°).

Indazole (10g.) was added in small portions to a solution of sodium (1.75g.) and ferric nitrate (0.1g.) in liquid ammonia (200ml.) The mixture was stirred for 15min., then methyl iodide (6 ml.) was added dropwise. The ammonia was allowed to evaporate, water (25ml.) was added, and the mixture was extracted with chloroform (3 x 100ml.). The combined extracts were dried (Mg SO_4), and distillation gave 1-methylindazole (6.5g., 55%), b.p. $108-10^\circ/16\text{mm.}$, m.p. $59-61^\circ$ (lit.⁷⁷ b.p. $109-10^\circ/15\text{mm.}$, m.p. $60-1^\circ$) and 2-methylindazole (2.7g., 14%), b.p. $132-5^\circ/16\text{mm.}$, m.p. $54-6^\circ$ (lit.⁷⁷ b.p. $132-3^\circ/15\text{mm.}$, m.p. 56°).

3-Methylindazole and N-Methylation:- 3-methylindazole, obtained like indazole, but using 2-ethylaniline, had m.p. $111-3^{\circ}$ (46%) (lit.⁷⁷ m.p. 113°).

Methylation as above, using sodamide in liquid ammonia, gave 1,3-dimethylindazole (60.5%), b.p. $126-7^{\circ}/16\text{mm.}$, m.p. $34-6^{\circ}$ (lit.⁷⁷ b.p. 240° , m.p. 36°) and 2,3-dimethylindazole (7%), b.p. $140-5^{\circ}/16\text{mm.}$, m.p. $78-9^{\circ}$ (lit.⁷⁷ b.p. 286° m.p. $79-80^{\circ}$).

1,2,3-Triazole: Propiolic acid⁷⁸ (25g.) was added to a solution of hydrogen azide⁷⁹ (from 65g. sodium azide) in benzene (1 l.) The solution was refluxed 16hr., the solvent evaporated under reduced pressure, and the residue was recrystallised from water to give 1,2,3-triazole-4-carboxylic acid (20g.), m.p. $218-9^{\circ}$ (decomp.). The acid was heated at $220^{\circ}-230^{\circ}$ until effervescence ceased. Distillation of the residue gave 1,2,3-triazole (10g.), b.p. $204-208^{\circ}$ (lit.⁸⁰ $203-4^{\circ}/715\text{ mm.}$)

1-Methyl-1,2,3-triazole - Methyl azide⁸¹ (from 78g. sodium azide, 40g. sodium hydroxide, and 99g. methyl sulphate) was passed into a solution of propiolic acid⁷⁸ (28g.) in dry toluene (200ml.) The mixture was left at room temperature for 24hr., during which time 1-methyl-1,2,3-triazole-4-carboxylic acid (30.3g., 60%) was deposited, and filtered off.

The triazole acid (9g.) was heated at 250° until evolution of carbon dioxide had ceased. The residue was distilled to give 1-methyl-1,2,4-triazole (5g., 87%), b.p. $222-4^{\circ}/756\text{mm}$ (lit.⁸² $228^{\circ}/752^{\circ}$)

Methylation of Benzotriazole⁸³ :- Benzotriazole was methylated with methyl sulphate and sodium hydroxide solution to give 2-methylbenzotriazole (23.5%), b.p. $108-12^{\circ}/22\text{mm.}$ (lit. b.p. $106-7^{\circ}/16\text{mm.}$) and 1-methyl-

benzotriazole (41%), b.p. 154-5°/17mm., m.p. 62-4° (lit. b.p. 152°/14mm., m.p. 63-4°)

1-Benzylbenzotriazole. Benzotriazole was benzylated according to Gibson,⁸⁴ to give 1-benzylbenzotriazole (59%), colourless needles, m.p. 115-6°, from methanol (lit. m.p. 115-6°).

1,2,4-Triazole was prepared by the method of Ainsworth⁸⁵ in 49% yield, m.p. 118-21° (lit. m.p. 119-20°)

1-Methyl-1,2,4-triazole⁸⁶:- 1,2,4-triazole was methylated with sodium and methyl iodide to give 1-methyl-1,2,4-triazole (74%), b.p. 177-8° (lit. b.p. 175-80°)

3-Methyl-1,2,4-triazole, prepared by the method of Jones and Ainsworth⁸⁷ had m.p. 96-9° (lit. m.p. 94°)

3,N-Dimethyl-1,2,4-triazole:- Methyl iodide (23.1g.) was added to 3-methyl-1,2,4-triazole (13.5g.) in methanol (100ml.) containing sodium methoxide (from 4g. sodium), and the solution was heated in an autoclave at 140-50° for 2hr., cooled, and evaporated to dryness. The residue was extracted with boiling benzene (50ml.) and boiling chloroform (3x50ml.). On cooling the combined extracts, unchanged triazole (0.9g.) separated out. The filtrate was evaporated at reduced pressure, and the residue distilled, giving 3,N-dimethyl-1,2,4-triazole (10.2g., 65%), b.p. 75-7°/14mm., $n_D^{20} = 1.4650$.

3-Methylpyridazine was prepared according to Clauson-Kaas and Limborg⁸⁸ in 46% yield, and had b.p. 102-4°/22mm. (lit. b.p. 73-6°/6mm.)

3,6-Dimethylpyridazine⁸⁹:- 2,5-Dimethylfuran was oxidised to 2,5-dimethoxy-2,5-dimethyldihydrofuran, which, on treatment with hydrazine hydrate and dilute acid gave 3,6-dimethylpyridazine (27%), b.p. 68-70°/11mm. (lit. b.p. 55°/1mm.).

4-Methylcinnoline⁹⁰, obtained from methyl anthranilate in three steps in 62% yield, had m.p. 73-4° (lit. 73-74.5°).

1-Methylphthalazine:- 4-chloro-1-methylphthalazine (9.7g.), (prepared according to Stephenson⁹¹), 10% palladised charcoal (2.0g.), 5N aqueous sodium hydroxide (15ml.), and ethanol (200ml.) were shaken together in an atmosphere of hydrogen (4 atmos.) for 4hr. The residue, obtained by filtration and evaporation of the filtrate, in ether was dried (MgSO₄) and distilled, giving 1-methylphthalazine (5.02g., 63% from 2-acetylbenzoic acid), b.p. 182-3°/15mm., m.p. 69-71°, (lit.⁹¹ b.p. 125-35°/0.05mm., m.p. 70.5-71.5°).

3,4-Benzocinnoline was obtained by the reduction of 2,2'-dinitrodiphenyl with lithium aluminium hydride⁹² in 84% yield, yellow rhombs, m.p. 155-6°, from methanol, (lit. m.p. 156°)

2,4,6-Trimethylpyrimidine (12%) was prepared as described,⁹³ and had b.p. 58-60°/13mm. (lit. b.p. 68-72°/11.5mm.)

Quinazoline was prepared by (i) reducing o-nitrobenzaldehyde with zinc dust and acetic acid,⁹⁴ and (ii) chlorinating, then reducing 4-hydroxyquinazoline (from anthranilic acid and formamide).⁹⁵ It had b.p. 108-10°/14mm., m.p. 47-8°, (lit.⁹⁵ b.p. 120-1°/17-18mm., m.p. 48°)

2-Methylquinazoline, obtained by the reduction of o-nitrobenzaldehyde acetamide with zinc dust and acetic acid,⁹⁶ had b.p. 133-5°/16mm.,

m.p. $40-2^{\circ}$ (lit.⁹⁷ b.p. 255° , m.p. 41°)

4-Methylquinazoline :- o-Nitroacetophenone prepared by the literature method⁹⁸ in 84% yield, b.p. $145-8^{\circ}/11\text{mm}$, n_D^{25} 1.547 (lit. b.p. $158-9^{\circ}/16\text{mm}$., n_D^{25} 1.548), was catalytically reduced to give o-aminoacetophenone⁹⁹ (82%), b.p. $120-2^{\circ}/12\text{mm}$. (lit. b.p. $130-1^{\circ}/14\text{mm}$.). This was then converted, via N-formyl-o-aminoacetophenone, to 4-methylquinazoline¹⁰⁰ (77%), b.p. $122-4^{\circ}/14\text{mm}$., m.p. $35-36^{\circ}$, (lit. b.p. $140-2^{\circ}/20\text{mm}$., m.p. $36-7^{\circ}$)

2,4-Dimethylquinazoline,⁹⁷ obtained in 90% yield by heating N-acetyl-o-aminoacetophenone with ammonia in a sealed tube, had b.p. $127-9^{\circ}/13\text{mm}$., (lit. b.p. $257^{\circ}/760\text{mm}$.)

Quinoxaline and Alkylquinoxalines :- Quinoxaline was prepared by the condensation of o-phenylenediamine with glyoxal,¹⁰¹ in 80% yield, b.p. $103-5^{\circ}/10\text{mm}$., m.p. $27-9^{\circ}$ (lit. b.p. $108-11^{\circ}/12\text{mm}$., m.p. $29-30^{\circ}$)

A similar condensation using pyruvaldehyde gave 2-methylquinoxaline in 87.5% yield, b.p. $108-9^{\circ}/10\text{mm}$., (lit.¹⁰² b.p. $125-7^{\circ}/11\text{mm}$.), while diacetyl gave 2,3-dimethylquinoxaline (94%), m.p. $105-6^{\circ}$ (lit.¹⁰³ m.p. $104-6^{\circ}$)

Oxidation of propion¹⁰⁴ with cupric acetate gave hexan-3,5-dione,¹⁰⁵ which, on condensation with o-phenylenediamine, gave 2,3-diethylquinoxaline in 69% yield, m.p. $48-50^{\circ}$ (lit.¹⁰⁶ m.p. $50-5^{\circ}$)

1-Methyl-1,3-diphenyltriazene,¹⁰⁷ prepared from benzenediazonium chloride and N-methylaniline in 74% yield, was purified by chromatography on alumina, using hexane as eluent.

1,1-Dimethyl-3-phenyltriazene¹⁰⁸ was obtained in 64% yield, b.p. $113-6^{\circ}/16\text{mm}$. (lit. b.p. $125-7^{\circ}/19\text{mm}$.)

PART ONE

(Structure numbers [] refer to Chapter One)

Tetramethyl 6-Phenyl-9aH-quinolizine-1,2,3,4-tetracarboxylate [4]:-
2-Phenylpyridine (10g.) and dimethyl acetylenedicarboxylate (18.5g.) in acetonitrile (300ml.) were refluxed 15hr., and the tar, obtained on evaporation, was chromatographed on alumina (800ml.). Elution with benzene (1 l.) gave only a tar, but further elution with benzene (5l.) gave tetramethyl 6-phenyl-9aH-quinolizine-1,2,3,4-tetracarboxylate (2.94g., 16%), recrystallised from methanol as yellow rods, m.p. 176°

Found: C, 63.2; H, 4.9; N, 3.2; OMe, 28.8%
 $C_{23}H_{21}NO_8$ requires C, 62.9; H, 4.8; N, 3.2; 4OMe, 29.0%

5.79, 5.87*, 5.93*, 5.99*, 6.18, 6.42, 6.61, 6.72 μ

231*(1.64), 276(1.71), 318(1.33), 436(0.58) $m\mu$

Tetramethyl 6-Phenyl-4H-quinolizine-1,2,3,4-tetracarboxylate [7]:-
Tetramethyl 6-phenyl-9aH-quinolizine-1,2,3,4-tetracarboxylate (0.5g.) was heated at 190° for 10 min. The dark brown tarry mass was dissolved in boiling methanol, and, on cooling, crystals were deposited. Recrystallisation from methanol gave tetramethyl 6-phenyl-4H-quinolizine-1,2,3,4-tetracarboxylate (0.42g., 84%) as orange rods, m.p. 184-5°.

Found: C, 63.0; H, 4.9; N, 3.3; OMe, 28.9%
 $C_{23}H_{21}NO_8$ requires C, 62.9; H, 4.8; N, 3.2; 4OMe, 28.2%

5.77, 5.89, 6.00, 6.18, 6.39, 6.54, 6.71 μ

273.5(1.40), 312(1.56), 356(1.12), 453(1.20) $m\mu$

(P) 223*(1.58), 260*(0.77), 328(1.15) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to Tetramethyl 6-Phenyl-9aH-quinolizine-1,2,3,4-tetracarboxylate :- The phenylquinolizine (1.0g.) and dimethyl acetylenedicarboxylate (5ml.) were heated together at 100° for 50hr. The mixture rapidly became black. Chromatography using benzene over alumina (50ml.) gave a pale yellow fraction (dimethyl acetylenedicarboxylate), followed by a bright yellow eluate. Evaporation and recrystallisation of the residue gave tetramethyl 9a-transdicarbomethoxyvinyl-6-phenyl-9aH-quinolizine-1,2,3,4-tetracarboxylate [10] as yellow, rectangular plates from methanol, m.p. 240-1°.

Found: C, 59.9; H, 4.8; N, 2.5; OMe, 31.7%
 $C_{29}H_{27}NO_{12}$ requires C, 59.9; H, 4.7; N, 2.4; 6OMe, 32.0%

5.69, 5.73, 5.86, 6.06, 6.28, 6.49 μ

253(1.88), 310.5(2.82), 435(1.35)m μ

This reaction was repeated with the analogous 9aH-quinolizines from 3,5-lutidine, quinoline, isoquinoline, and phenanthridine. Only in the last experiment was any crystalline solid obtained, and this was starting material.

Pyridine (1.0g.) was added in fine drops to cold (-10°), well stirred dimethyl acetylenedicarboxylate (50ml.) in an atmosphere of nitrogen. The excess acetylenic ester was distilled off under reduced pressure, and the residue was triturated with methanol. The solid precipitated was tetramethyl 4H-quinolizine-1,2,3,4-tetracarboxylate, m.p. and mixed m.p. 186-7°.

Addition of Dimethyl Acetylenedicarboxylate to 2-Methyl-6-vinylpyridine:- 2-Methyl-6-vinylpyridine (6g.) and dimethyl acetylenedicarboxylate (14.4g.) in acetonitrile (200ml.) were refluxed for 16hr. After evaporation of the solvent, the residual tar was chromatographed on alumina (600ml.).

Elution with benzene (2 l.) gave a yellow fraction, from which was isolated dimethyl fumarate (0.1g.), identified by m.p. and mixed m.p. (101-2°). Further elution with benzene (1.75 l.) gave an orange fraction, which gave tetramethyl 6-methyl-9a-vinyl-9aH-quinolizine-1,2,3,4-tetracarboxylate, [11], (0.85g., 4.2%), recrystallised from methanol as red cubes, m.p. 112.5-113°.

Found: C, 59.7; H, 5.3; N, 3.7; OMe, 30.7%
 $C_{20}H_{21}NO_8$ requires C, 59.6; H, 5.3; N, 3.5; 4OMe, 30.7%

5.74, 5.84, 6.04, 6.27, 6.60 μ

227(1.28), 295.5(1.14), 445(0.55) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to 2-Vinylpyridine :-

2-Vinylpyridine (10g.) and dimethyl acetylenedicarboxylate (21g.) in acetonitrile (350ml.) were refluxed for 15hr. Evaporation gave a tar which was chromatographed on alumina (1500ml.). Elution with benzene (4.5 l.) gave tetramethyl 9a-Vinyl-9aH-quinolizine-1,2,3,4-tetracarboxylate [12], (6.4g., 21%), yellow needles, m.p. 111-2°, from methanol.

Found: C, 58.5; H, 5.1; N, 3.6; OMe, 31.7%
 $C_{19}H_{19}NO_8$ requires C, 58.6; H, 4.9; N, 3.6; 4OMe, 31.8%

5.73, 5.84, 5.87, 6.04*, 6.19, 6.31, 6.54 μ

224*(1.24), 281(1.29), 332(0.45), 402(0.68) $m\mu$

Further elution with benzene (5 l.) and benzene: chloroform (3:1 v/v, 2.5 l.) gave an orange fraction from which was isolated a yellow solid, which could not be purified, and rapidly was converted to an orange compound. This was hexamethyl 4H - benzo[c]quinolizine-1,2,3,4,7,8-hexacarboxylate, [13], (0.36g., 1.2%), orange microneedles, m.p. 240-2°, from methanol.

Found: C, 56.8; H, 4.5; N, 2.5; OMe, 36.2%
 $C_{25}H_{23}NO_{12}$ requires C, 56.7; H, 4.4; N, 2.6; 6OMe, 35.2%

5.72, 5.79, 5.86, 5.95, 6.17, 6.30, 6.41, 6.63 μ

241*(2.73), 248.5(2.95), 252*(2.94), 280(1.6), 317*(1.05), 356*(0.62), 465(1.67) μ .

PART TWO

(Structure numbers [] refer to Chapter Two)

Addition of Dimethyl Acetylenedicarboxylate to Thiazole: (a preliminary experiment is described in ref.48) Thiazole (10g.) was added to dimethyl acetylenedicarboxylate (36g.) in dry ether (50ml.) at 0°, and the mixture was kept at 0° for one hr., and at room temperature for 72hr. The ether layer was decanted and the residual tar was dissolved in benzene and chromatographed on alumina (600 ml.) with benzene as eluent. The first (colourless) fraction yielded unchanged ester on evaporation. The second (orange) fraction was evaporated under reduced pressure, and the residue was recrystallised from methanol to give tetramethyl 8aH-benzo[b]thiazole-5,6,7,8-tetracarboxylate [8] (3.6g., 8%) as orange plates, m.p. 150°

Found: C, 48.7; H, 4.1; N, 3.7; OMe, 33.5%
 $C_{15}H_{15}NO_8S$ requires C, 48.8; H, 4.1; N, 3.8; 4OMe, 33.6%

(c) 5.75, 5.80, 5.84, 5.91, 6.24, 6.68, 6.87, 6.98 μ

226.5(1.11), 283(1.84), 435(0.42) $m\mu$

The third (yellow) fraction yielded, on evaporation, pentamethyl thiazolo[3,2-a]azepine-5,6,7,8,9-pentacarboxylate [10] (0.2g., 0.4%), yellow needles, m.p. 260°, from methanol.

Found: C, 49.8; H, 3.5; N, 3.0%
 $C_{18}H_{17}NO_{10}S$ requires C, 49.2; H, 3.9; N, 3.2%

(c) 5.63, 5.74, 5.83, 5.90, 5.98, 6.25, 6.41, 6.52, 6.66, 6.86, 6.99 μ

242(1.41), 317*(1.51), 326(1.84), 423(1.94) $m\mu$

Tetramethyl 8aH-benzo[b]thiazole-5,6,7,8,-tetracarboxylate was recovered unchanged after refluxing in benzene for 15hr., and after standing

Tetramethyl 9,10-Dihydrobenzoxazolo [3,2-a]azepine - 7, 8, 9, 10-tetracarboxylate [21]:- 2-Methylbenzoxazole (5 g.), dimethyl acetylenedicarboxylate (7.5 g.) and acetonitrile (150 ml.) were refluxed together 16 hr. Evaporation in vacuo gave a tar which was chromatographed on alumina (450 ml.). Elution with benzene (2 l.) gave unreacted ester, and further elution with benzene (4 l.) gave a yellow fraction, from which, after ten days, was isolated

16hr. in glacial acetic acid - concentrated sulphuric acid (3:2 v/v).

The adduct did not react with dimethyl acetylenedicarboxylate on heating at 100° for 16hr.; addition of a trace of hydrochloric acid did not induce reaction.

Tetramethyl 3-Methyl-8aH-benzo[b]thiazole-5,6,7,8-tetracarboxylate

4-Methylthiazole (5g.) was added to dimethyl acetylenedicarboxylate (16g.) in dry ether (25ml.) at 0°. After two days at room temperature, the precipitated solid was collected, and recrystallised from methanol to give tetramethyl 3-methyl-8aH-benzo[b]thiazole-5,6,7,8-tetracarboxylate [9] (2.8g, 13%) as orange plates, m.p. 226°.

Found: C, 50.2; H, 4.3; N, 3.7; OMe, 32.1%
 $C_{16}H_{17}NO_8$ requires C, 50.1; H, 4.4; N, 3.7; 4OMe, 32.3%

(c) 5.75, 5.87, 6.24, 6.63, 6.96 μ

227.5(1.43), 287(1.99), 445(0.43) μ

Reduction of Tetramethyl 5aH-Dibenzo[bd]oxazole-6,7,8,9-tetracarboxylate:⁴⁸ The oxazole (0.8g.), 10% palladised charcoal (0.4g.), and methanol (300ml.) were shaken together for 4hr. under hydrogen (4 atmos.). Filtration and evaporation of the filtrate under reduced pressure gave tetramethyl 6,7-dihydro-5aH-dibenzo[bd]oxazole-6,7,8,9-tetracarboxylate [20], (0.55g., 70%), colourless rhombs, m.p. 209°, from methanol.

Found: C, 56.3; H, 4.7; N, 3.5; OMe, 30.6%
 $C_{19}H_{19}NO_9$ requires C, 56.3; H, 4.8; N, 3.8; 4OMe, 30.2%

(c) 5.72, 5.77, 5.82, 5.91, 6.11, 6.23, 6.75, 6.87, 6.98 μ

252*(0.52), 268(0.65), 273(0.65), 317(3.91) μ

Tetramethyl 9,10-Dihydrobenzoxazol[o[3,2-a]azepine-7,8,9,10-tetracarboxylate (0.2g., 1.4%), pale yellow cubes, m.p. 167-8°, from methanol.

Insert opp.
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Found: C, 57.5; H, 4.7; N, 3.8; OMe, 29.8%
 $C_{20}H_{19}NO_9$ requires C, 57.6; H, 4.6; N, 3.4; 4OMe, 29.7%

5.78, 5.93, 6.09, 6.21, 6.52, 6.72 μ

249*(0.64), 288(0.29), 403(3.62) $m\mu$
 (P) 239*(0.89), 244(0.92), 249(0.88), 336(1.86) $m\mu$

Attempted Addition of Dimethyl Acetylene dicarboxylate to Isoxazoles:-

Isoxazole (2g), dimethyl acetylenedicarboxylate (8.25g.) and acetonitrile (50 ml.) were refluxed 24hr. Evaporation of the solvent under reduced pressure gave a yellow liquid, which smelt strongly of the starting materials. No crystalline product could be isolated from this liquid after chromatography. Heating isoxazole with the acetylenic ester at 100° for 6hr. caused no visible reaction, and no solid material could be isolated.

No solid products were obtained from the reaction between dimethyl acetylenedicarboxylate and 5-methylisoxazole, 3,5-dimethylisoxazole, benzisoxazole, or anthranil.

Addition of Dimethyl Acetylenedicarboxylate to 1,2-Dimethylbenziminazole:- (i) In tetrahydrofuran. This was carried out as described by Mills⁵¹ to give tetramethyl 9,10-dihydro-5-methylbenziminazolo[3,2-a]azepine-7,8,9,10-tetracarboxylate, [29] (33.5%), yellow plates from methanol, m.p. 206-7°

Found: C, 58.5; H, 5.2; N, 6.7; OMe, 29.3%
 $C_{21}H_{22}N_2O_8$ requires C, 58.6; H, 5.2; N, 6.5; 4OMe, 28.8%

5.72, 5.79, 5.83, 5.94, 6.25, 6.62, 6.72 μ

217(1.87), 253.5(0.9), 296*(0.42), 431(6.6) $m\mu$
 (P) 240(2.39), 243.5(2.4), 249 (2.29), 326(3.54)

and tetramethyl 5,5a-dimethyl-5aH-dibenzo[ad]iminazole-6,7,8,9-tetracarboxylate [23] (2.5%) red plates from methanol, m.p. 138-9°

Found: C, 58.6; H, 5.1; N, 6.4; OMe, 29.0%
 $C_{21}H_{22}N_2O_8$ requires C, 58.6; H, 5.2; N, 6.5; 4OMe, 28.8%

5.79, 5.85, 5.91, 6.25, 6.25, 6.74 μ

220(2.05), 256(1.51), 315(0.76), 441(0.91) $m\mu$
 (A) 242.5(1.86) 295(1.04) $m\mu$

(ii) In acetonitrile. The reaction was repeated in acetonitrile, to give tetramethyl 9,10-dihydro-5-methylbenziminazolo[3,2-a]azepine-7,8,9,10-tetracarboxylate (13%), as the sole product. The adduct had identical m.p. and mixed m.p. (206-7°) with that prepared in (i) above.

Addition of Dimethyl Acetylenedicarboxylate to 2-Ethyl-1-methylbenziminazole :- (An account of this addition in tetrahydrofuran has been reported⁵¹.) 2-Ethyl-1-methylbenziminazole (1.0g.) and dimethyl acetylenedicarboxylate (1.78g.) in acetonitrile (25ml.) were stood together for 4 days. The solvent was removed under reduced pressure, and the residual tar was chromatographed on alumina (100ml.) Elution with benzene (500ml) gave a red fraction, from which was isolated tetramethyl 5a-ethyl-5-methyl-5aH-dibenzo[ad]iminazole-6,7,8,9-tetracarboxylate [31] (0.24g., 9%), dark-red parallelipeds, m.p. 144-6°, from methanol

Found: C, 59.6; H, 5.6; N, 6.4; OMe, 29.7%
 $C_{22}H_{24}N_2O_8$ requires C, 59.5; H, 5.4; N, 6.3; 4OMe, 27.9%

5.79, 5.91, 6.26*, 6.32, 6.71, 6.81 μ

220(1.97), 254(1.47), 332.5(0.68), 457(0.8) $m\mu$
 (A) 253(1.87) 296(1.07) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to 1-Ethyl-2-Methylbenziminazole :- Dimethyl acetylenedicarboxylate (8.9g.) was added to 1-ethyl-2-methylbenziminazole (5g.) in dry tetrahydrofuran (50ml.), and the solution was left at room temperature for 4 days. A yellow solid was

deposited. This was filtered off and recrystallised from methanol as yellow parallelipeds of tetramethyl 5-ethyl-9,10-dihydrobenziminazolo[3,2-a]azepine-7,8,9,10-tetracarboxylate [30], (2.3g.), m.p. 204-5°.

Found: C,59.3; H,5.7; N,6.3; OMe,28.2%
 $C_{22}H_{24}N_2O_8$ requires C,59.5; H,5.4; N,6.3; 4OMe,27.9%

5.70, 5.79, 5.83, 5.94, 6.25, 6.62, 6.73 μ

216.5(1.68), 253.5(0.82), 295*(0.38), 431(5.73) $m\mu$
 244(1.14), 249(1.13) 326(2.24) $m\mu$

The filtrate was evaporated to dryness, and chromatographed on alumina (500ml.). Elution with benzene (2.15 l.) gave a red fraction, from which was isolated a red solid, consisting of two isomeric adducts, which could not be separated, and were recrystallised as a mixture, orange-red plates, m.p. 146-7°, from methanol.

Found: C,59.4; H,5.9; N,6.4; OMe,28.3%
 $C_{22}H_{24}N_2O_8$ requires C,59.5; H,5.4; N,6.3; 4OMe,27.9%

5.73, 5.79, 5.90, 6.27, 6.62 μ

Addition of Dimethyl Acetylenedicarboxylate to Benziminazole :-

(a preliminary experiment has been described⁵³) (i) Benziminazole (1g.) and dimethyl acetylenedicarboxylate (1.2g.) in acetonitrile (25ml.) were refluxed 16hr. There was no visible reaction, but after evaporation of the solvent in vacuo, and trituration of the residue with ether (10ml.), a white solid was deposited on standing the mixture at 0° for 24 hr. This was recrystallised from methanol as colourless microneedles, m.p. 165-6° of the "white adduct" (1.1g., 50%)

Found: C,55.3; H,5.2; N,6.3; OMe,35.7%
 $C_{20}H_{22}N_2O_9$ requires C,55.3; H,5.1; N,6.5; 5OMe,35.7%

5.77, 5.88, 6.21, 6.30, 6.74 μ

250.5(1.38) 284(1.60) 325(2.52) $m\mu$
 (A) 263* (0.79) 271(0.84) 276*(0.81) $m\mu$

(ii) Benziminazole (2g.) and dimethyl acetylenedicarboxylate (7.2g.) in benzene (100 ml.) were refluxed 16hr. The solution was concentrated to ca. 20ml., and chromatographed on alumina(300 ml.). Elution with benzene (700 ml.) gave the white adduct (0.3g., 3.2%), identified by m.p. and mixed m.p. (164-5°). Further elution with benzene (2 l.) and benzene:chloroform (2:1 v/v, 1.3 l.) gave tetramethyl 5-transdicarbomethoxyvinyl-9H-dibenzo[ad] iminazole-6,7,8,9-tetracarboxylate, [32], (1.93g., 21%) as yellow rods, m.p. 191-2°, from methanol.

Found: C, 55.1; H, 4.4; N, 5.3; OMe, 34.2%
 $C_{25}H_{24}N_2O_{12}$ requires C, 55.2; H, 4.4; N, 5.2; 6OMe, 34.2%

5.74, 5.89, 5.95, 6.07, 6.27, 6.65 μ

242*(0.70), 265*(0.50), 309(1.44), 403(1.06) μ

The above yellow adduct [32] (0.88g.), 10% palladised charcoal (0.3g.) and methanol (250ml.) were shaken together under hydrogen (3.5 atmos.) for 17 hr. Filtration, and evaporation of the filtrate to dryness in vacuo gave tetramethyl 5-(1',2'-dicarbomethoxyethyl)-9H-dibenzo[ad]-iminazole-6,7,8,9-tetracarboxylate, [35], (0.46g., 52%) as light green crystals, m.p. 173-4°, from methanol.

Found: C, 55.0; H, 4.8; N, 5.0; OMe, 34.7%
 $C_{25}H_{26}N_2O_{12}$ requires C, 55.0; H, 4.8; N, 5.1; 6OMe, 34.1%

5.74, 5.79, 5.96, 6.28, 6.66 μ

250.5*(0.83), 316.5(2.54), 397(1.61) μ
 (P) 269* (0.9) 276 (1.02), 283.5(0.92) μ

Addition of Dimethyl Acetylenedicarboxylate to 1-Methylbenziminazole :-

A mixture of 1-methylbenziminazole (5g.) and dimethyl acetylenedicarboxylate (10.8g.) in acetonitrile (100 ml.) was refluxed 14hr. The initial reaction

was violent. The solvent was removed in vacuo, and the residual tar was chromatographed on alumina (600 ml.). Elution with benzene (1.5 l.) gave an orange fraction, from which was isolated tetramethyl 5-methyl-5aH-dibenzo[ad]iminazole-6,7,8,9-tetracarboxylate [33], (0.46g., 2.9%), orange-red rectangular plates, m.p. 173-4°, from methanol.

Found: C, 57.7; H, 4.8; N, 6.7; OMe, 29.8%
 $C_{20}H_{20}N_2O_8$ requires C, 57.8; H, 4.9; N, 7.0; 4OMe, 29.5%

5.75, 5.86, 6.27, 6.59, 6.71 μ

236*(1.74), 271.5(1.56), 301(1.02), 437(0.89) $m\mu$
 (P) 234.5(2.73) 236.5(2.71), 269(1.16), 299.5(0.89) 345(0.79), 436(0.94) $m\mu$

Further elution with benzene (1 l.) and benzene: chloroform (1:1 v/v, 1.5 l.) gave a green fraction, from which was obtained tetramethyl 5-methyl-9H-dibenzo[ad]iminazole-6,7,8,9-tetracarboxylate, [32], (3.7g., 23%) yellow rhombs, m.p. 225-6°, from methanol.

Found: C, 57.6; H, 4.8; N, 6.7; OMe, 29.7%
 $C_{20}H_{20}N_2O_8$ requires C, 57.7; H, 4.8; N, 6.7; 4OMe, 29.8%

5.74*, 5.76, 5.99, 6.20, 6.33, 6.60, 6.72 μ

245(1.08), 316.5(2.95), 400(1.93) $m\mu$
 (P) 268*(0.85), 275 (0.97), 283(0.86) 333*(0.16) $m\mu$

Excess bromine was added to a solution of tetramethyl 5-methyl-9H-dibenzo[ad]iminazole-6,7,8,9-tetracarboxylate (0.5g.) in glacial acetic acid (10 ml.), containing 72% perchloric acid (0.5 ml.). The solution was heated at 100° for 30 min., cooled, and ether (10 ml.) added. Crystals were precipitated, collected, and recrystallised from methanol containing a trace of perchloric acid, as pale yellow rods, m.p. 188-9° of 6,7,8,9-tetracarbomethoxy-5-methyldibenzo[ad]iminazolinium perchlorate (0.46 g.)

Found: C, 46.1; H, 3.4; N, 5.6; OMe, 22.2%
 $C_{20}H_{19}N_2ClO_{12}$ requires C, 46.3; H, 3.7; N, 5.4; 4OMe, 23.9%

The reaction was repeated, using the 5aH-isomer [35], (0.18g.), and this gave a monobromo derivative, (0.15g.), yellow ^{plates} from methanol, m.p. 223-4°

Found: C, 46.9; H, 3.6; N, 5.6; Br, 15.8%
 $C_{20}H_{19}N_2O_8Br$ requires C, 48.5; H, 3.8; N, 5.7; Br, 16.2%

Attempted Addition of Dimethyl Acetylenedicarboxylate to 1-Methyl-
iminazole :- Dimethyl acetylenedicarboxylate (6.1g.) was added to 1-methyl-
iminazole (1.8g.) in acetonitrile (30 ml.). A violent reaction occurred, and the solution darkened immediately. After this initial reaction, the solution was refluxed 16hr., evaporated to dryness, and the residue was chromatographed on alumina (300 ml.). Elution with benzene (2.75 l.) gave hexamethyl mellitate (0.2g.), identified by m.p. and mixed m.p. (187-8°). Further elution gave only tars.

Addition of Dimethyl Acetylenedicarboxylate to 1-Methylpyrazole :-

A solution of 1-methylpyrazole (9.2g.) and dimethyl acetylenedicarboxylate (33g.) in acetonitrile (100 ml.) was refluxed 12hr. After removal of the solvent, the residual tar was chromatographed on alumina (1200 ml.). Elution with benzene gave a single yellow fraction, from which was isolated tetramethyl 1-methyl-7H-pyrazolo-[2,3-a]pyridine-4,5,6,7-tetracarboxylate, [36], (0.5g., 1.3%), yellow rods from methanol, m.p. 193°

Found: C, 52.7; H, 4.5; N, 7.6; OMe, 33.9%
 $C_{16}H_{18}N_2O_8$ requires C, 52.5; H, 4.9; N, 7.7; 4OMe, 33.9%

5.76, 5.81, 5.88, 6.09, 6.26, 6.43, 6.50, 6.54* μ

274(1.13), 375.5(5.75) $m\mu$

Concentration of the mother liquor from the first recrystallisation of

the above adduct to one third its volume gave trimethyl 1-methylpyrrole-2,3,5-tricarboxylate [38]. (0.1g., 0.4%), colourless rods from methanol, m.p. 164°

Found: C, 51.8; H, 5.0; N, 5.4; OMe, 36.3%
 $C_{11}H_{13}NO_6$ requires C, 51.8; H, 5.1; N, 5.5; 3OMe, 36.4%

5.73*, 5.77*, 5.81, 6.28, 6.39, 6.55 μ

227*(1.16), 254(2.14), 302(0.44) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to 1-Methylindazole :-

Dimethyl acetylenedicarboxylate (6.6g.), 1-methylindazole (4g.) and acetonitrile (80 ml.) were refluxed together 24 hr. Removal of the solvent under reduced pressure, and trituration of the residual tar with methanol (15 ml.) gave, after four days, 1-methyl-3-(2',3',4'-tricarbomethoxycyclopentadienonyl)indazole, [42], (1.07g., 10%), colourless rods from methanol, m.p. 194-5°

Found: C, 59.4; H, 4.1; N, 7.4; OMe, 24.5%
 $C_{19}H_{16}N_2O_7$ requires C, 59.4; H, 4.2; N, 7.3; 3OMe, 24.2%

5.71, 5.80, 5.99, 6.20, 6.26, 6.40, 6.46* μ

231(3.78), 288(2.0), 352(0.54) $m\mu$

The adduct (0.5g.) was recovered unchanged after refluxing with potassium permanganate (5g.) in acetone (300 ml.) for 5 hr., and after being heated at 100° for 30 min. with chromium trioxide (1.0g.) in 70% acetic acid (25 ml.).

The adduct (1.0g.), 10% palladised charcoal (0.5g.), and methanol (200 ml.) were shaken together under hydrogen (4 atmos.) for 16 hr. Filtration and evaporation of the filtrate in vacuo gave 1-methyl-3-(2',3',4'-tricarbomethoxy-5'-hydroxycyclopentyl)indazole [43], (0.7g., 70%) as

colourless microneedles from ethyl acetate, m.p. 138-40°

Found: C, 58.6; H, 5.7; N, 7.3; OMe, 24.0%
 $C_{19}H_{22}N_2O_7$ requires C, 58.5; H, 5.7; N, 7.2; 3OMe, 23.8

3.02, 5.68, 5.77, 6.14, 6.23, 6.27*, 6.49, 6.55*, 6.72 μ

227 (3.30), 238* (1.89), 307 (0.82), 317 (0.79), 330* (0.49)
225* (1.55) 242.5 (2.65) 309 (0.91) 313 (0.95) 328* (0.78)

The reduced adduct of 1-methylindazole [43] (0.4g.) was refluxed with potassium permanganate (3g.) in acetone (200ml.). After one hour, the purple colour had been discharged, so more permanganate (3g.) was added, and the mixture was refluxed a further 2hr. The acetone was removed under reduced pressure, water (50 ml.) was added to the residue, and sulphur dioxide was passed into the suspension, until the manganese dioxide had dissolved. The white precipitate was filtered off, and recrystallised from methanol to give 1-methyl-3-(2',3',4'-tricarboxymethoxycyclopentadienonyl)-indazole, (0.35g.), identified by its m.p. and mixed m.p. (194-5°)

Attempted Addition of Dimethyl Acetylenedicarboxylate to 1,3-

Dimethylindazole :- 1,3-Dimethylindazole (5g.) and dimethyl acetylenedicarboxylate (10g.) in acetonitrile (80 ml.) were refluxed together for 40hr. The red solution was evaporated to dryness to give a tar, from which, after chromatography on alumina, no crystalline products could be isolated.

Attempted Addition of Dimethyl Acetylenedicarboxylate to 1-Methyl-

1,2,3-triazole:- A solution of 1-methyl-1,2,3-triazole (4g.) and dimethyl acetylenedicarboxylate (15g.) in acetonitrile (50 ml.) was refluxed 16hr. Evaporation under reduced pressure gave a tar, which, after chromatography on alumina, gave only hexamethyl mellitate, identified by its m.p. and mixed m.p. with an authentic sample.

Addition of Dimethyl Acetylenedicarboxylate to 1-Methylbenzotriazole:-

Dimethyl acetylenedicarboxylate (12.9g.) was added to 1-methylbenzotriazole (6.g.) in dry ether (50 ml.) at room temperature. The mixture was stood at room temperature for 4 days, the ether then was allowed to evaporate, and the residue was triturated with methanol (20 ml.). The precipitated solid was collected, and recrystallised from methanol to give dimethyl 6,7,8,11-tetrahydro-5-methyl-8-(carbomethoxy-methoxy-methylene)-7-oxo-benzo[d]pyridazino[1,2-a]triazole-9,10-dicarboxylate, [46], (3.57g., 19%), as yellow rods, m.p. 193-4°

Found: C, 54.7; H, 4.6; N, 10.4; OMe, 29.1%
 $C_{19}H_{19}N_3O_8$ requires C, 54.7; H, 4.6; N, 10.1; 4OMe, 29.7%

5.75, 5.80, 5.96, 6.11, 6.22, 6.27*, 6.58, 6.67 μ

	221(1.99)	247*(1.21),	276(0.93),	396(0.66) $m\mu$
(P)	237(2.52),	273*(0.95),	358(1.19),	475(0.97) $m\mu$
(B)	217,	266	276	320, 333, 384 $m\mu$

Concentration of the mother liquors from the first recrystallisation of the above adduct gave a solid which was purified by thin-layer chromatography, using benzene : ethyl acetate (4:1 v/v) as solvent. The slower-band gave the above adduct [46], while the faster-moving band gave dimethyl 6,7,10,11-tetrahydro-5-methyl-8-carbomethoxyoxomethyl-7-oxo-benzo[d]pyridazino[1,2-a]triazole-9,10-dicarboxylate, [47] (0.12g.) as yellow plates from methanol, m.p. 182-3°.

Found: C, 53.7; H, 4.2; N, 10.6%
 $C_{18}H_{17}N_3O_8$ requires C, 53.6; H, 4.2; N, 10.4%

5.67, 5.78, 5.94, 6.11, 6.21, 6.57, 6.66 μ

	218,	235*,	266,	275,	309*,	319,	332,	385 $m\mu$
(P)	237,			275		358		475 $m\mu$

Reactions of the 1-Methylbenzotriazole Adduct [46]

(i) The adduct [46] (1g.) was dissolved in concentrated hydrochloric acid (5ml.), and the red solution formed was added to excess 0.880 ammonia solution. A yellow solid was precipitated, and extracted with chloroform (2 x 50 ml.). Evaporation of the extracts, and thin-layer chromatography of the residue, using benzene : ethyl acetate (4:1 v/v), gave the above two 1-methylbenzotriazole adducts [46] and [47] in the proportions 10:1.

(ii) The adduct (1.0g.), 10% palladised charcoal (0.5g.) and methanol (200 ml.) were shaken together for 15 hr. under hydrogen (4 atmos.). Filtration, and concentration of the filtrate to ca. 10 ml. gave a white precipitate. This was dimethyl 6,7,8,11-tetrahydro-5-methyl-8-carbomethoxy-methoxymethyl-7-oxo-benzo[d]pyridazino[1,2-a]-1,2,3-triazole-9,10-dicarboxylate [48] (0.51g.), colourless parallelipeds from methanol, m.p. 167°

Found: C, 54.3; H, 5.6; N, 9.6; OMe, 30.0%
 $C_{19}H_{21}N_3O_8$ requires C, 54.4; H, 5.1; N, 10.0; 4OMe, 29.6%

5.75, 5.80, 5.90, 5.97, 6.23, 6.32, 6.66 μ

225, 267, 342 $m\mu$

After the above compound had been filtered off, concentration of the filtrate to ca. 4ml. gave dimethyl 6,7,8,11-tetrahydro-5-methyl-8-carbomethoxymethylene-7-oxo-benzo-[d]pyridazino[1,2-a]-1,2,3-triazole-9,10-dicarboxylate [49] (0.25g.), yellow needles from methanol, m.p. 178-9°

Found: C, 55.8; H, 4.4; OMe, 17.5%
 $C_{18}H_{17}N_3O_7$ requires C, 55.7; H, 4.4; 3OMe, 24.0%

5.83, 5.97, 6.12, 6.22, 6.34, 6.65 μ

219.5(2.74), 270.5(0.81), 322(1.38), 333*(1.14), 402(0.42) $m\mu$

(iii) A suspension of the adduct (0.5g.) and anhydrous stannous chloride (5g.) in ether (100 ml.) saturated with dry hydrogen chloride was stirred 24 hr. at room temperature. The mixture was neutralised with 0.880 ammonia solution, and extracted with chloroform (3 x 100 ml.). The dried (MgSO_4) extracts were evaporated to dryness, and the residue was triturated with methanol (10 ml.) The precipitated solid was dimethyl 4-methyl-3-carbomethoxyoxomethylpyrrolo[1,2-a]benziminazole-1,2-dicarboxylate [50], (0.27g.), colourless needles from methanol, m.p. 167° .

Found: C, 58.0; H, 4.3; N, 7.6; OMe, 25.6%
 $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_7$ requires C, 58.1; H, 4.3; N, 7.5; 3OMe, 25.0%

5.81, 6.02, 6.18, 6.27, 6.40, 6.57 μ

243.5(3.71), 316(0.91), 326*(0.84) $\text{m}\mu$
(A) 239 (6.87), 316(0.88), 326 (0.82) $\text{m}\mu$

(iv) Excess (> 8 equivalents) methyl magnesium iodide in ether was added dropwise with stirring to the adduct (0.5g.) in dry tetrahydrofuran (25 ml.). The solution turned blood-red, then orange, and a pale yellow precipitate was formed. The mixture was stirred one hour, and the precipitate was filtered off. Recrystallisation from methanol gave colourless rods of the methylated derivative, [51], m.p. $233-4^\circ$.

Found: C, 62.3; H, 6.1; N, 10.8; OMe, 7.9%
 $\text{C}_{20}\text{H}_{23}\text{N}_3\text{O}_5$ requires C, 62.3; H, 6.0; N, 10.9; OMe, 8.1%

3.08, 5.75, 5.84, 5.95, 6.09, 6.25, 6.51, 6.64 μ

226(2.61), 252*(1.58), 280*(0.79) $\text{m}\mu$

(v) The adduct (1.0g.), potassium permanganate (10g.) and acetone (350 ml.) were refluxed 5hr. The acetone was evaporated off, and water (25 ml.) added to the residue. Sulphur dioxide was passed into the suspension until the

manganese dioxide had dissolved. Extraction with chloroform gave a brown syrup which could not be crystallised.

(vi) The adduct (0.1g.) was dissolved in warm methanolic potassium hydroxide solution (2N., 10 ml.), and heated at 100° for 10 min. Neutralisation of the solution with 2N hydrochloric acid, and extraction with chloroform (3 x 20 ml.) gave a pale yellow solid, which could not be recrystallised to a constant melting point.

(vii) The adduct (1g.) and concentrated hydrochloric acid (50 ml.) were heated at 100° for one hour. The red solution was evaporated to dryness under reduced pressure, and the red residue was recrystallised, but was too hygroscopic to be analysed. A similar compound from perchloric acid was also hygroscopic, while refluxing the adduct with hydriodic acid gave a black tar.

(viii) The adduct (0.5g.), bromine (1 ml.) and glacial acetic acid were heated together at 100° for 30 min. Evaporation to dryness under reduced pressure gave a red tar which could not be recrystallised.

Attempted Addition of Dimethyl Acetylenedicarboxylate to 2-Methylbenzotriazole:- Refluxing a solution of 2-methylbenzotriazole (1g.) and dimethyl acetylenedicarboxylate (2.2g.) in acetonitrile (20 ml.) for 12hr. gave a red tar from which no crystalline products could be isolated.

Addition of Dimethyl Acetylenedicarboxylate to 1-Benzylbenzotriazole:- 1-Benzylbenzotriazole (15g.), dimethyl acetylenedicarboxylate (20.4g.) and acetonitrile (500 ml.) were refluxed 15 hr. The solvent was removed under reduced pressure, and the residual red oil was chromatographed

on alumina (600 ml.). The single yellow fraction, eluted with benzene (3.5 l.) gave dimethyl 5-benzyl-6,7,8,11-tetrahydro-8-(carbomethoxy-methoxy-methylene)-7-oxo-benzo[d]pyridazino[1,2-a]-1,2,3-triazole-9,10-dicarboxylate, [52], (9.5g., 25%), yellow needles from methanol, m.p. 159-60°

Found: C, 60.6; H, 4.8; N, 8.5; OMe, 25.2%
 $C_{25}H_{23}N_3O_8$ requires C, 60.8; H, 4.7; N, 8.5; 4OMe, 25.1%

5.72*, 5.77, 5.81*, 5.95, 6.04*, 6.14, 6.23, 6.55, 6.67 μ

243*(1.61), 275 (1.12), 392(1.02) $m\mu$
238*(3.08), 274*(1.06), 361(1.13), 477(0.99) $m\mu$

Reduction of the Adduct [52] :- The adduct (1.0g.), 10% palladised charcoal (0.4g.) and methanol (300 ml.) were shaken together for 15 hr. under hydrogen (4 atmos.). Filtration, and concentration of the filtrate to ca. 15 ml. gave a white solid. This was dimethyl 5-benzyl-6,7,8,11-tetrahydro-8-carbomethoxymethyl-7-oxo-benzo[d]pyridazino[1,2-a]-1,2,3-triazole-9,10-dicarboxylate, [53], (0.4g.), colourless rods from methanol, m.p. 164-5°.

Found: C, 61.8; H, 5.0; N, 9.2; OMe, 19.9%
 $C_{24}H_{23}N_3O_7$ requires C, 61.9; H, 5.0; N, 9.0; 3OMe, 20.0%

5.79, 5.90, 6.01, 6.24, 6.66 μ

223*(1.93), 267.5(0.57), 340*(1.14), 345(1.18) $m\mu$

Oxidation of the Adduct [52]

(i) Excess bromine was added to a boiling solution of the adduct (1.0g.) in chloroform (15 ml.). The solution was boiled to dryness, and the residue was triturated with methanol (10 ml.). The solution, on standing 24 hr. at 0°, deposited 1-benzylbenzotriazole (0.37g. 88%), colourless needles from methanol, m.p. and mixed m.p. 114-5°.

(ii) The adduct (2g.), potassium permanganate (20g.) and acetone (400 ml.) were refluxed 4 hr. Removal of the acetone and addition of water

(100 ml.) and excess sulphur dioxide gave a colourless solution. This was boiled to expel excess sulphur dioxide, cooled, and extracted with chloroform (4 x 100 ml.). The dried (MgSO_4) combined extracts were evaporated to dryness and the residue was recrystallised from methanol to give 1-benzylbenzotriazole (0.82g., 97%) m.p. and mixed m.p. 115-6°.

(iii) The adduct (1.0g.) and freshly prepared manganese dioxide¹⁰⁹ (42g.) in chloroform (250 ml.) were stirred at room temperature for 24 hr. Filtration, and evaporation to dryness of the filtrate gave 1-benzylbenzotriazole (0.42g.), m.p. and mixed m.p. 115-6°.

Addition of Dimethyl Acetylenedicarboxylate to 1-Methyl-1,2,4-triazole:-

1-Methyl-1,2,4-triazole (5g.), dimethyl acetylenedicarboxylate (17.1g.) and acetonitrile (50 ml.) were refluxed 16 hr. Evaporation under reduced pressure gave a tar which was chromatographed on alumina (700 ml.). Elution with benzene gave a bright yellow fraction, from which was isolated trimethyl 1-methylpyrrolo[1,2-b]triazole-4,5,6-tricarboxylate [55], (1.89g. 8.6%), yellow rectangular plates from methanol, m.p. 178-9°.

Found: C, 48.9; H, 4.5; N, 14.2; OMe, 30.9%
 $\text{C}_{12}\text{H}_{13}\text{N}_3\text{O}_6$ requires C, 48.8, H, 4.4; N, 14.2; 3OMe, 31.5%

3.21, 5.76, 5.88, 5.98, 6.05*, 6.24, 6.59, 6.64* μ

223(0.73), 260(0.79), 306*(1.61), 312(1.99) μ

Further elution with benzene gave a dark green fraction, from which was isolated once dimethyl 1-methyl-6-(carbomethoxymethoxymethyl)-pyrrolo [1,2-b]triazole-4,5-dicarboxylate, [56] (30mg), colourless rods from methanol, m.p. 182-3°.

Addition of Dimethyl Acetylenedicarboxylate to N,3-Dimethyl-1,2,4-triazole :- N,3-Dimethyl-1,2,4-triazole (5g.), dimethyl acetylenedicarboxylate (14.7g.) and acetonitrile (100 ml.) were refluxed together for 16 hr. The solvent was removed in vacuo, and the resulting tar was chromatographed on alumina (700 ml.). Elution with benzene (2.5 l.) gave an orange solid (2.4g., 16%). This was purified by thin-layer chromatography, using benzene:ethyl acetate (4:1 v/v) as solvent. The faster-moving band was scraped off the plate and extracted with methanol to give a dark-red solid. This was a mixture of two isomers, which could not be separated, [61] and [62], mixed m.p. 127°.

Found: C,50.3; H,5.0; N,11.0; OMe,33.4%
 $C_{16}H_{19}N_3O_8$ requires C,50.4; H,5.0; N,11.0; 4OMe,32.5%

The slower moving band gave the yellow adduct [60], yellow rods from methanol, m.p. 216-8°.

Found: C,50.3; H,5.0; N,10.9; OMe,33.3%
 $C_{16}H_{19}N_3O_8$ requires C,50.4; H,5.0; N,11.0; 4OMe,32.5%

5.77, 5.87, 5.98, 6.04*, 6.26, 6.35, 6.57, 6.60 μ

230.5(0.51), 294(1.36), 380(1.33)m μ
No U.V. absorption in 30% $HClO_4$

The yellow adduct was recovered unchanged after refluxing in glacial acetic acid for 30 min.

PART THREE

(Structure numbers refer to Chapter Three)

Addition of Dimethyl Acetylenedicarboxylate to Pyridazine :-

Dimethyl acetylenedicarboxylate (29.6g.) was added to pyridazine (8.3g.) in acetonitrile (100ml.), the temperature being kept below 10° by external cooling. The solution, which darkened immediately, was left at room temperature for 4 days. Evaporation of the solvent under reduced pressure gave a tar which was chromatographed on alumina (1200 ml.). Elution with benzene (2.5 l.) gave a pale yellow fraction, which smelt strongly of starting materials, and from which no solid product could be isolated. Elution with benzene;chloroform (2:1 v/v, 3.5 l.) gave an orange fraction from which was obtained tetramethyl 8H-pyridino[1,2-b]pyridazine-5,6,7,8-tetracarboxylate, [9], (2.1g., 5.5%), orange plates from methanol, m.p. $189-90^{\circ}$

Found: C, 52.6; H, 4.4; N, 7.8; OMe, 33.7%
 $C_{16}H_{16}N_2O_8$ requires C, 52.7, H, 4.4; N, 7.7; 4OMe, 34.0%

5.71, 5.78, 5.83, 5.92*, 5.98, 6.03*, 6.20, 6.39, 6.53 μ

219(1.03), 274.5(0.66), 302.5(1.08), 369(0.62), 443(0.52) $m\mu$

Concentration of the mother liquors from the recrystallisation of the above adduct gave trimethyl pyrrolo[1,2-b]pyridazine-5,6,7-tricarboxylate, [1] (0.6g., 1.6%), colourless needles from methanol, m.p. $163-4^{\circ}$ (lit.⁵⁹ m.p. $160-1^{\circ}$).

Found: C, 53.4; H, 4.3; N, 9.7%
 Calc. for $C_{13}H_{12}N_2O_6$: C, 53.4; H, 4.1; N, 9.6%

5.74, 5.87, 5.91*, 6.16, 6.47, 6.54, 6.64, 6.63 μ

222(1.86), 249(2.67), 256*(2.27), 263*(1.80), 284*(0.44), 294.5(0.57), 305(0.6),
 307(0.6), 343(0.39). $m\mu$

Further elution with benzene:chloroform (2:1 v/v, 2.5 l.) gave a red fraction from which were isolated pale orange needles (0.1g.), m.p. 252-3° (decomp.)

5.73, 5.84, 5.92*, 6.14, 6.32, 6.50, 6.58, 6.63 μ

294, 331, 442, m_{μ}

Repetition of the above reaction using methanol as solvent, gave only trimethyl pyrrolo[1,2-b]pyridazine-5,6,7-tricarboxylate (28%), m.p. and mixed m.p. with the sample from the preceding reaction, 162-4°.

Addition of Dimethyl Acetylenedicarboxylate to 3-Methylpyridazine:-

A mixture of 3-methylpyridazine (5.1g.), dimethyl acetylenedicarboxylate (15.4g.) and acetonitrile (100 ml.) was kept at 0° for 4 days. The solvent was removed under reduced pressure, and the residual tar was chromatographed on alumina (1200 ml.). Elution with benzene gave a pale yellow fraction, from which was isolated dimethyl fumarate (0.1g.), m.p. and mixed m.p. 101-2°. Further elution with benzene gave a bright yellow fraction. This gave a mixture of yellow and white solids which were separated by thin-layer chromatography, using benzene:ethyl acetate (4:1 v/v) as solvent. The yellow faster moving band was scraped off the plates and washed from the silica with methanol. Evaporation of the methanol and recrystallisation of the residue from methanol gave tetramethyl 4a-methyl-4aH-pyridino[1,2-b]-pyridazine-5,6,7,8-tetracarboxylate, [11], (0.78g., 3.8%), as lemon-yellow cubes, m.p. 160-1°.

Found: C, 54.1; H, 4.8; N, 7.4; OMe, 32.7%
 $C_{17}H_{18}N_2O_8$ requires C, 54.0; H, 4.8; N, 7.4; 4OMe, 32.8%

5.72, 5.81, 5.88, 6.20, 6.53 μ

216(1.27), 267(1.36), 399(0.73) m_{μ}

The slower moving band gave trimethyl 2-methylpyrrolo-[1,2-b]pyridazine-5,6,7-tricarboxylate, [2], (0.22g., 1.1%), colourless needles from methanol, m.p. 166-7° (lit.⁵⁹ m.p. 164.5-5°)

Found: C, 55.2; H, 4.5; N, 9.6; OMe, 30.1%
Calc. for $C_{14}H_{14}N_2O_6$: C, 54.9; H, 4.6; N, 9.2; 3OMe, 30.4%

5.75, 5.86, 5.91*, 6.43, 6.54, 6.71 μ

223(1.17), 250(1.51), 255*(1.32), 265(1.13), 285(0.51), 291*(0.59),
296(0.65), 307(0.68), 336(0.48) $m\mu$.

A mixture of tetramethyl 4a-methyl-4aH-pyridino[1,2-b]pyridazine-5,6,7,8-tetracarboxylate (0.28g.) and dimethyl acetylenedicarboxylate (0.5g.) was heated at 100° for 84 hr. On cooling, the original pyridinopyridazine was deposited and identified by m.p. and mixed m.p. (160°).

Addition of Dimethyl Acetylenedicarboxylate to 3,6-Dimethylpyridazine:-

A mixture of 3,6-dimethylpyridazine (7g.) dimethyl acetylenedicarboxylate (18.6g.) and acetonitrile (150 ml.) was kept at 0° for 4 days, then evaporated to dryness under reduced pressure. The residual tar was chromatographed on alumina (750 ml.). Elution with benzene gave a yellow fraction, from which was isolated tetramethyl 2,4a-dimethyl-4aH-pyridino[1,2-b]pyridazine-5,6,7,8-tetracarboxylate, [12], (1.59g., 5.8%), yellow rods from methanol, m.p. 141-2°.

Found: C, 55.1; H, 5.0; N, 7.1; OMe, 31.5%
 $C_{18}H_{20}N_2O_8$ requires C, 55.1; H, 5.1; N, 7.1; 4OMe, 31.6%

5.70, 5.80, 5.87, 6.19, 6.56, 6.61* μ

215(1.35), 266(1.38), 351*(0.51), 400(0.77) $m\mu$

A red fraction, eluted with more benzene, gave tetramethyl 9,10-dihydro-2-methylazepino[1,2-b]pyridazine-6,7,8,9-tetracarboxylate, [13],

(4.2g., 16%), orange-red rods from methanol, m.p. 197-8°.

Found: C, 54.9; H, 5.2; N, 7.3; OMe, 31.1%
 $\text{CH}_{18}\text{H}_{20}\text{N}_2\text{O}_8$ requires C, 55.1; H, 5.1; N, 7.1; 4OMe, 31.6%

5.77, 5.83*, 5.98, 6.07*, 6.15, 6.51*, 6.66 μ

234(0.86), 318(1.83), 325*(1.72), 393(0.60), 448(0.56) μ
(P) 258*(0.62) 298*(0.32) μ

A mixture of dimethyl acetylenedicarboxylate (0.7g.) and tetramethyl 2,4a-dimethyl-4aH-pyridino[1,2-b]pyridazine-5,6,7,8-tetracarboxylate (0.31g.) was heated at 100° for 66 hr. The resulting black mobile liquid was chromatographed on alumina (50 ml.). Elution with benzene gave the original pyridinopyridazine, identified by m.p. and mixed m.p. (140-2°).

The pyridinopyridazine [12] (0.5g.), 10% palladised charcoal (0.2g.) and methanol were shaken together under hydrogen (4 atmos.) for 16 hr. Filtration, and evaporation to dryness of the filtrate gave a colourless oil, which could not be induced to crystallise.

A similar catalytic reduction of the azepinopyridazine [13] also gave an oil, which did not crystallise.

Addition of Dimethyl Acetylenedicarboxylate to 2-Methylpyrazine :-

2-Methylpyrazine (5g.), dimethyl acetylenedicarboxylate (15.1g.) and acetonitrile (100 ml.) were refluxed 16 hr. Evaporation of the solvent under reduced pressure and chromatography of the residual tar on alumina (600 ml.) gave a pale yellow fraction, eluted with benzene (2.7 l.).

Evaporation of the eluate gave trimethyl 3-methylpyrrolo[1,2-a]pyrazine-6,7,8-tricarboxylate, [6], (0.47g., 2.3%) colourless rods from methanol, m.p. 178-9°

Found: C, 54.8; H, 4.6; N, 9.1; OMe, 30.2%
 $C_{14}H_{14}N_2O_6$ requires C, 54.9; H, 4.6; N, 9.2; 3OMe, 30.3%

5.72, 5.76*, 5.85, 6.18, 6.57 μ

(A) 224(0.93), 249.5(1.47), 257.5(1.34), 265*(0.89), 331(0.93) μ
 221(1.08) 257* (1.58), 261 (1.64), 330*(0.18),
 371(0.3) μ

Further elution with benzene-chloroform (4:1 v/v, 2 l.) gave a dark-red fraction, from which no crystalline product could be obtained.

Addition of Dimethyl Acetylenedicarboxylate to 2,6-Dimethylpyrazine :-
 2,6-Dimethylpyrazine (5g.) and dimethyl acetylenedicarboxylate (13.2g.) in acetonitrile (100 ml.) were refluxed for 16 hr. The acetonitrile was evaporated under reduced pressure, and the residual tar was chromatographed on alumina (600 ml.). Elution with benzene gave a pale yellow fraction, from which was obtained trimethyl 1,3-dimethylpyrrolo[1,2-a]pyrazine-6,7,8-tricarboxylate, [7], (0.66g., 3.6%), colourless microneedles from methanol, m.p. 129-30°.

Found: C, 56.1; H, 5.0; N, 8.6; OMe, 28.8%
 $C_{15}H_{16}N_2O_6$ requires C, 56.3; H, 5.0; N, 8.8; 3OMe, 29.0%

5.71, 5.85, 6.16, 6.56, 6.73 μ

(A) 230(1.71), 248.5(2.63), 251*(2.61), 331(0.87) μ
 224(1.86), 300* (0.21), 313 (0.33), 328(0.38), 363.5(0.63) μ

Further elution with benzene gave an orange fraction from which no crystalline product could be isolated.

Addition of Dimethyl Acetylenedicarboxylate to 1-Methylphthalazine :-
 1-Methylphthalazine (4.69g.) and dimethyl acetylenedicarboxylate (9.25g.) in acetonitrile (100 ml.) were refluxed 15 hr. Evaporation under reduced pressure gave a red tar which was chromatographed on alumina (600 ml.)

Elution with benzene (2.5 l.) gave an orange fraction, from which was obtained trimethyl 6-methylpyrrolo[1,2-a]phthalazine-1,2,3-tricarboxylate, [4], (0.1g.), colourless rods from methanol, m.p. 196-7°.

Found: C, 60.7; H, 4.6; N, 7.9; OMe, 25.9%
 $C_{18}H_{16}N_2O_6$ requires C, 60.7; H, 4.5; N, 7.9; 3OMe, 26.1%

5.80, 5.87, 6.22, 6.45, 6.53, 6.66 μ

225(2.64), 235*(2.33), 265.5(4.73), 273.5(4.83), 282*(2.67), 315(1.51) $m\mu$

Further elution with benzene (2 l.) and evaporation of the eluate gave tetramethyl 5-methyl-11aH-pyridino[2,1-a]phthalazine-8,9,10,11-tetracarboxylate, [14], (1.47 g., 11%), orange rhombs from methanol, m.p. 155-6°

Found: C, 58.8; H, 5.0; N, 6.4; OMe, 29.1%
 $C_{21}H_{20}N_2O_8$ requires C, 58.9; H, 4.7; N, 6.5; 4OMe, 29.0%

5.73, 5.84, 5.88*, 5.99*, 6.21, 6.42, 6.63, 6.73 μ

225(1.72), 271 (2.08), 335(0.54), 460(0.76) $m\mu$
 233*(2.02), 275*(2.12), 280(2.14), 333(0.81), 460(0.87) $m\mu$

The 11aH-pyridino[2,1-a]phthalazine [14], (0.5g.), glacial acetic acid (10 ml.) and concentrated sulphuric acid (5 ml.) were left at room temperature for 48 hr. The acid was neutralised with solid sodium carbonate, and the inorganic salts were dissolved in water. Extraction with chloroform gave tetramethyl 5-methyl-8H-pyridino[2,1-a]phthalazine-8,9,10,11-tetracarboxylate, [15], (0.44g., 88%), orange parallelipipeds from methanol, m.p. 214-5°.

Found: C, 59.2; H, 4.9; N, 6.8; OMe, 29.6%
 $C_{21}H_{20}N_2O_8$ requires C, 58.9; H, 4.7; N, 6.5; 4OMe, 29.0%

5.77, 5.87*, 5.97, 6.33, 6.47, 6.72 μ

225(2.78), 255*(0.83), 306.5(0.9), 327.5(0.83), 453(1.09) $m\mu$
 (P) 218(1.99), 245.5(3.23), 283 (0.56), 326(0.45) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to Phthalazine :-

A solution of phthalazine (1.0g.) and dimethyl acetylenedicarboxylate (2.2g.)

in methanol (40 ml.) was left at 0° for 2 weeks, during which time a pale yellow solid was deposited. This was filtered off and recrystallised from methanol as colourless needles of dimethyl (1,2-dihydro-1-methoxy-phthalaziny) fumarate, [16], (0.9g., 41%), m.p. 136-7°

Found: C, 59.0; H, 5.3; N, 9.0; OMe, 30.8%
 $C_{15}H_{16}N_2O_5$ requires C, 59.2; H, 5.3; N, 9.2; 3OMe, 30.6%

5.75, 5.89, 5.94, 6.24, 5.43, 6.49*, 6.69 μ

233(1.29), 263*(0.5) 328(2.6) 341(2.4) $m\mu$
 (P) 243(3.31) 291*(0.78), 326*(0.6) $m\mu$

Repeating the experiment in benzene or acetonitrile gave tars, from which no crystalline products could be isolated.

Attempted Addition of Dimethyl Acetylenedicarboxylate to Quinazoline and Quinoxaline :- The acetylenic ester and the heterocycle (in 2:1 molar proportions) in acetonitrile were refluxed 15 hr., but, even after chromatography, no crystalline products were isolated in either reaction.

Addition of Dimethyl Acetylenedicarboxylate to 4-Methylcinnoline :- A solution of 4-methylcinnoline (15g.) and dimethyl acetylenedicarboxylate (30g.) in acetonitrile (250 ml.) was left at 0° for 4 days, and then the solvent was evaporated under reduced pressure. Trituration of the residual tar with methanol (100 ml.) gave the adduct (4.9g., 11%), which was recrystallised from methanol:chloroform (10:1 v/v) as yellow rods, m.p. 209-10° (decomp.)

Found: C, 61.3; H, 5.1; N, 7.9; OMe, 26.2%
 $C_{36}H_{34}N_4O_{12}$ requires C, 60.5; H, 4.3; N, 7.8; 6OMe, 26.1%

5.66, 5.74, 5.77*, 5.89, 6.25, 6.34, 6.70 μ

255*(0.31), 345(0.29) $m\mu$
 (figures in parentheses are optical densities)

Addition of Diethyl Acetylenedicarboxylate to 4-Methylcinnoline:-

A solution of diethyl acetylenedicarboxylate (5.5g.) and 4-methylcinnoline (3.0g.) in acetonitrile (50 ml.) was left at 0° for 4 days. The solvent was evaporated in vacuo and the residual tar was chromatographed on alumina (400 ml.). Elution with benzene gave two yellow fractions, the second of which gave the ethyl adduct (1.05g., 12%), yellow parallelepiped from ethanol, m.p. 159-60°.

Found: C, 62.7; H, 6.1; N, 6.4; OEt, 34.8%
 $C_{42}H_{46}N_4O_{12}$ requires C, 63.2; H, 5.8; N, 6.3; 6OEt, 33.8%

5.73, 5.79*, 5.82*, 6.08, 6.23, 6.32, 6.70 μ

258(1.50), 285*(0.50), 349.5(1.48) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to Phenazine :- Phenazine

(10g.) and excess dimethyl acetylenedicarboxylate (24g.) in methanol (250 ml.) were refluxed 16 hr. The solution was concentrated to ca. 50 ml., when a purple solid was deposited. This was filtered off, and recrystallised from methanol as ash-grey needles of 9,10-dihydro-9,10-di(transdicarbomethoxy-vinyl)phenazine, [20], 7.5g. 42%), m.p. 229-30°.

Found: C, 61.7; H, 4.7; N, 6.2; OMe, 26.7%
 $C_{24}H_{22}N_2O_8$ requires C, 61.8; H, 4.8; N, 6.0; 4OMe, 26.6%

5.79, 6.04, 6.22, 6.71 μ

245.5(4.42), 336(0.49), 540(0.1) $m\mu$

Using acetonitrile as solvent gave a purple tar, from which no crystalline products were isolated.

The dihydrodivinylphenazine [20], (1.0g.), 10% palladised charcoal (0.5g.) and methanol (200 ml.) were shaken together under hydrogen (4 atmos.) for

12 hr. Filtration and concentration of the filtrate to ca 10 ml. gave 9,10-dihydro-9,10-di(1',2'-dicarbomethoxyethyl)phenazine, [21] (0.72g.), colourless rhombic plates from methanol, m.p. 129-30°.

Found: C, 61.5; H, 5.3; N, 6.2%
 $C_{24}H_{26}N_2O_8$ requires C, 61.3; H, 5.6; N, 6.0%

5.77, 6.20, 6.57*, 6.72 μ

(P) 222.5*(1.29), 245(4.19), 263* (0.79), 330(0.70) μ
 245(3.65) 256.5*(1.68) 274(0.63) 328(0.58) μ

Excess bromine was added to the dihydrodivinylphenazine [20] (0.5g.) in boiling chloroform. The solution was boiled to dryness, and the residue triturated with methanol (15 ml.). The yellow precipitate was recrystallised from glacial acetic acid to give yellow microneedles of pentabromophenazine (0.2g.) m.p. > 320°.

Found: C, 22.9; H, 0.6; N, 4.7; Br, 0.0%
 $C_{12}H_3N_2Br_5$ requires C, 22.0; H, 0.5; N, 4.3%

Concentration of the filtrate gave a red solid, which, when chromatographed on a thin-layer plate, gave eleven bands. Attempts to separate these were abandoned.

Addition of Dimethyl Acetylenedicarboxylate to 3,4-Benzocinnoline :-

3,4-Benzocinnoline (2.5g.), excess dimethyl acetylenedicarboxylate (5g.) and methanol (75 ml.) were refluxed together for 16 hr., during which time a solid was precipitated. The mixture was cooled, and a red solid was filtered off. This was recrystallised from methanol:chloroform (1:1 v/v) as red plates of 1,2-dihydro-1,2-di(transdicarbomethoxyvinyl)-dibenzo[ce]pyridazine, (1.05g.), m.p. 166-7°

Found: C, 61.6; H, 4.3; N, 5.7; OMe, 24.0%
 $C_{24}H_{22}N_2O_8$ requires C, 61.8; H, 4.8; N, 6.0; 4OMe, 26.6%

5.67, 5.76, 6.19, 6.49, 6.60, 6.67 μ

PART FOUR

(Structure numbers refer to Chapter Four)

Addition of Dimethyl Acetylenedicarboxylate to 2-Methylquinoxaline :-

2-Methylquinoxaline (10g.) dimethyl acetylenedicarboxylate (20g.), and acetonitrile (200 ml.) were refluxed 16 hr. Evaporation of the solvent under reduced pressure gave a tar which was chromatographed on alumina (1200 ml.). Elution with benzene (6 l.) gave a single orange fraction, from which was isolated tetramethyl 10,11-dihydroquinoxalino[1,2-a]azepine-7,8,9,10-tetracarboxylate, [6], (4.7g., 16%), orange-red parallelepiped from methanol, m.p. 157-8°.

Found: C, 58.8; H, 4.7; N, 6.5; OMe, 29.0%
 $C_{21}H_{20}N_2O_8$ requires C, 58.9; H, 4.7; N, 6.5; 4OMe, 29.0%

5.71, 5.98, 6.18, 6.27, 6.37 μ

221(1.74), 286*(1.84), 304(2.14), 368*(0.22), 459(0.93), 480*(0.89) μ
 (P) 218(1.25), 285*(1.73), 309(2.44), 370*(0.16), 570(0.59) μ

Concentration of the mother liquors from the first recrystallisation of the above adduct gave a second adduct, purified by fractional crystallisation from methanol. This was tetramethyl 10,11-dihydroquinoxalino[1,2-a]azepine-7,8,9,11-tetracarboxylate, [7], (0.6g., 2%), orange parallelepiped, from methanol, m.p. 138-9°.

Found: C, 58.6; H, 4.7; N, 6.5; OMe, 28.7%
 $C_{21}H_{20}N_2O_8$ requires C, 58.9; H, 4.7; N, 6.5; 4OMe, 28.9%

5.68, 5.72*, 5.80, 5.93, 5.97, 6.17, 6.25, 6.36 μ

220.5(1.69), 287*(1.77), 303.5(2.18), 460(0.91), 474*(0.89) μ
 (P) 285*(1.55), 308(2.28), 360 (0.27), 572 (0.67) μ

Reactions of Tetramethyl 10,11-dihydroquinoxaline[1,2-a]azepine-7,8,9,10-tetracarboxylate, [6] ("the adduct").

(1) Reduction:- (a) The adduct (1.0g.), 10% palladised charcoal (0.5g.), and methanol (250 ml.) were shaken together under hydrogen (4 atmos.) for 16 hr. Filtration, and evaporation of the filtrate to dryness under reduced pressure gave tetramethyl 5,6,10,11-tetrahydroquinoxaline[1,2-a]azepine-7,8,9,10-tetracarboxylate, [13], (0.73g., 73%), pale yellow rods from methanol, m.p. 220-1°.

Found: C, 58.6; H, 5.2; N, 6.7%
 $C_{21}H_{22}N_2O_8$ requires C, 58.6; H, 5.2; N, 6.5%

296, 5, 5.80, 5.87, 5.97, 6.17, 6.29, 6.60 μ

(P) 218.5(1.87), 272 (1.31), 344(1.34) μ
 218 (0.96), 295*(0.92), 327(2.01) μ

(b) Lithium aluminium hydride (1g.) in dry ether (10 ml.) was added to a solution of the adduct (0.54g.) in dry benzene (50 ml.), and the mixture was refluxed 4 hrs. Water (10 ml.) was cautiously added, and the precipitated lithium salts were dissolved in 10% aqueous acetic acid. The solution was extracted with chloroform (3 x 150 ml.), the extracts were washed with saturated sodium bicarbonate solution, and dried ($MgSO_4$). Evaporation of the chloroform gave a black tar, from which no crystalline matter could be isolated.

(ii) Bromination :- Excess bromine was added to the adduct (0.28g.) in chloroform (10 ml.). The solution was refluxed 10 min., then evaporated to dryness. The residue was recrystallised from methanol to give tetramethyl 2,3-dibromo-10,11-dihydroquinoxalino[1,2-a]azepine-7,8,9,10-

tetracarboxylate, [16], (0.31 g., 93%), crimson rods m.p. 207-9°.

Found: C, 42.9; H, 3.2; N, 4.5; OMe, 21.3; Br, 27.3%
 $C_{21}H_{16}N_2O_8Br_2$ requires C, 43.0; H, 3.1; N, 4.8; 4OMe, 21.2; Br, 27.3%

5.70, 5.74, 5.98, 6.20, 6.31, 6.44, 6.50 μ

228*(2.3, 231.5(2.37)), 286*(2.8), 295(3.02), 310(2.88), 323*(2.02), 457(1.27) μ

(iii) Oxidation :- (a) The adduct (0.8g.), potassium permanganate (10.g), and 2N aqueous sulphuric acid (100 ml.) were heated at 100° for 2 hr., during which time the solution became yellow. The solution was continuously extracted with chloroform for 24 hrs., and the dried (MgSO₄) extract was evaporated to dryness to give a small quantity of brown tar which could not be crystallised. The aqueous fraction from the above extraction was neutralised with ammonia solution and re-extracted with chloroform, but nothing was obtained.

(b) The adduct (1.0g.), potassium permanganate (5.0g.) and acetone (400 ml.) were refluxed one hour. The acetone was evaporated under reduced pressure, water (50 ml.) was added to the residue, and sulphur dioxide was passed into the suspension until the manganese dioxide had dissolved. An orange solid was filtered off, and recrystallised from methanol to give unreacted adduct (0.7g.), identified by its m.p. and mixed m.p. (156-8°).

(c) The adduct (1.0g.), freshly prepared manganese dioxide (50g.), and chloroform (300 ml.) were stirred at room temperature for 24 hr. Filtration, and evaporation to dryness of the filtrate gave an orange solid. This had identical infrared and ultraviolet absorption and nuclear magnetic resonance spectra and analysis to the original adduct, but m.p. was

170-1° (mixed m.p. 163-7°).

(d) The adduct (0.84g.), osmium tetroxide (1.0g.), and freshly distilled, dry dioxan (50 ml.) were stirred at room temperature for 7 days. Water (20 ml.) was added, and sulphur dioxide was passed into the solution.

The precipitated osmium was filtered off, the filtrate evaporated to dryness under reduced pressure, and the residue extracted with boiling chloroform to give back the original adduct, m.p. and mixed m.p. 156-7°.

(iv) Condensation :- The adduct (1.0g.), benzaldehyde (0.5 ml.) pyridine (50 ml.) and piperidine (2 ml.) were refluxed 18 hr. Removal of the solvent under reduced pressure gave a red oil, which was only eluted from an alumina column by boiling methanol. Attempts to obtain crystals from this oil failed.

(v) Action of Methyl Magnesium Iodide :- The adduct (0.5g.) in dry tetrahydrofuran (30 ml.) was added to methyl magnesium iodide (from 0.22g. Mg) in ether (50 ml.). A vigorous reaction ensued. The ether was boiled off, more tetrahydrofuran (25 ml.) was added, and the mixture was refluxed 6 hr. 10% aqueous ammonium chloride (50 ml.) was added to the mixture, which was extracted with chloroform (5 x 100 ml.). The dried (MgSO_4) extracts gave, on evaporation, a tar, from which no crystalline material could be isolated.

(vi) The dihydro adduct [13] (1.0g.), methyl iodide (5 ml.), and methanol (50 ml.) were left at 0° for 4 days. Evaporation of the methanol gave a yellow syrup which could not be induced to crystallise. This crude mixture was shaken with freshly prepared silver hydroxide in water (10 ml.), filtered, and shaken with 10% palladised charcoal (0.4g.) and methanol (100 ml.)

under hydrogen (4 atmos.) for 12 hr. Filtration and evaporation of the solvent under reduced pressure gave a tar from which no crystalline product was isolated.

Addition of Diethyl Acetylenedicarboxylate to 2-Methylquinoxaline:-

2-Methylquinoxaline (5g.), diethyl acetylenedicarboxylate (12.5g.) and acetonitrile (150 ml.) were refluxed 16 hr. Removal of the solvent under reduced pressure gave a tar which was chromatographed on alumina (600 ml.). Elution with benzene (3.5 l.) gave a single orange fraction, from which was isolated tetraethyl 10,11-dihydroquinoxalino[1,2-a]azepine-7,8,9,10-tetracarboxylate [6], (.89g., 5%), crimson parallelipeds, m.p. 127-8°

Found: C,62.0; H,5.8; N,5.8; OEt,36.9%
 $C_{25}H_{28}N_2O_8$ requires C,62.0; H,5.8; N,5.8; 4OEt,37.2%

5.75, 5.95, 6.18, 6.28, 6.36 μ

222(1.81), 286*(1.69), 304(2.01), 459(0.81), 480*(0.79), 518*(0.30) μ
 (P) 219(1.52), 286*(1.68), 304(2.26), 370(0.18), 480*(0.30), 576 (0.54) μ

Addition of Dimethyl Acetylenedicarboxylate to 2,3-Dimethylquinoxaline:-

2,3-Dimethylquinoxaline (6g.), dimethyl acetylenedicarboxylate (10.8g.), and acetonitrile (150 ml.) were refluxed 18 hr. After evaporation of the solvent, the residual tar was chromatographed on alumina (600 ml.). Elution with benzene (2 l.) gave a yellow fraction, from which was obtained pentamethyl 5,9a,13,14-tetrahydro-9a-methyl-13-oxo-dipyridino[1,2-a,2,1-c]quinoxaline-6,7,8,9,11-pentacarboxylate, [28], (0.57g., 3.4%), yellow rods from methanol, m.p. 209-10°.

Found: C,58.6; H,4.5; N,5.6; OMe,27.7%
 $C_{27}H_{24}N_2O_{11}$ requires C,58.7; H,4.4; N,5.1; 5OMe,27.7%

5.72, 5.80, 5.86, 6.18, 6.26, 6.33, 6.51, 6.71 μ

253(2.48), 265*(2.12), 379(0.64) μ

Further elution with benzene (5 l.), and evaporation of the eluate gives tetramethyl 10,11-dihydro-6-methylquinoxalino[1,2-a]azepine-7,8,9,11-tetracarboxylate, [8], (1.45g., 8.7%), orange plates from methanol, m.p. 170-1°.

Found: C, 59.7; H, 5.1; N, 6.3; OMe, 28.6%
 $C_{22}H_{22}N_2O_8$ requires C, 59.7; H, 5.0; N, 6.3; 4OMe, 28.1%

5.82, 5.93, 6.29, 6.48 μ

224.5(2.24) 286*(1.37), 308.5(1.78), 451 (1.01), 464*(1.0) $m\mu$
(P) 221 (1.35) 252(0.69), 286*(1.2), 309 (1.9) 349*(0.24), 545 (0.53) $m\mu$

Reactions of Tetramethyl 10,11-Dihydro-6-methylquinoxalino[1,2-a]-azepine-7,8,9,11-tetracarboxylate [8] (the "adduct")

(i) Reduction:- The adduct (0.92g.), 10% palladised charcoal (0.4g.) and methanol were shaken together under hydrogen (4 atmos.) for 16 hr. Filtration gave a yellow solution, which when evaporated to dryness under reduced pressure gave tetramethyl 5,6,10,11-tetrahydro-6-methylquinoxalino[1,2-a]azepine-7,8,9,11-tetracarboxylate, [15], (0.59g., 64%), pale yellow rods from methanol, m.p. 216-7°.

Found: C, 59.6; H, 5.4; N, 6.4; OMe, 28.4%
 $C_{22}H_{24}N_2O_8$ requires C, 59.5; H, 5.4; N, 6.3; 4OMe, 27.9%

2.96, 5.73, 5.91, 5.97, 6.17, 6.30, 6.60 μ

220(1.84), 266 (1.27), 353 (1.33) $m\mu$
(P) 227(0.70), 245*(0.39), 297*(331(2.06) $m\mu$

(ii) Bromination (a) Excess bromine was added to a boiling solution of the adduct (0.2g.) in methanol (15 ml.). The solution was boiled for 10 min., then cooled, when a precipitate was formed. This was filtered off, and recrystallised from acetonitrile as carmine-red needles of tetramethyl 2,3-dibromo-10,11-dihydro-6-tribromomethylquinoxalino[1,2-a]

azepine-7,8,9,11-tetracarboxylate, [17], (0.34g.), m.p. $> 320^{\circ}$.

Found: C, 32.4; H, 2.2; N, 3.4; OMe, 14.8; Br, 47.2%
 $C_{22}H_{17}N_2O_8Br_5$ requires C, 31.6; H, 2.0; N, 3.4; 4OMe, 14.8; Br, 47.6%

5.72, 5.95, 6.28, 6.41, 6.54 μ

242.5(0.79), 325(0.95), 493(0.24) $m\mu$
(figures in parentheses are optical densities)

(b) The adduct (0.5g.), N-bromosuccinimide (1.0g.), and chloroform; carbon tetrachloride (1:1 v/v, 60 ml.) were refluxed 2 hr., during which time the yellow solution turned deep-red. The solution was concentrated to half its original volume, and more carbon tetrachloride (30 ml.) was added. The precipitated succinimide was filtered off, and the filtrate was evaporated to dryness. Trituration of the residue with methanol (2 ml.) gave tetramethyl 10,11-dihydro-6-tribromomethylquinoxalino[1,2-a]azepine-7,8,9,11-tetracarboxylate, (0.48g.), red-brown rods from methanol, m.p. $182-3^{\circ}$.

Found: C, 39.6; H, 3.0; N, 4.1; OMe, 18.6; Br, 36.0%
 $C_{22}H_{19}N_2O_8Br_3$ requires C, 38.9; H, 2.8; N, 4.1; 4OMe, 18.3; Br, 35.4%

5.70, 5.86, 5.94, 6.67 μ

230(2.22), 286(1.58), 322(2.04), 501(0.72) $m\mu$

(c) Experiment (b) was repeated using the adduct (0.5g.) and N-bromo-succinimide (0.21g.) in 1:1 molar proportions. From the reaction mixture was isolated tetramethyl 10-11-dihydro-6-monobromomethylquinoxalino[1,2-a]azepine-7,8,9,11-tetracarboxylate, (0.4g.), colourless rods from methanol, m.p. $166-8^{\circ}$.

Found: C, 50.5; H, 4.3; N, 5.2; OMe, 23.0; Br, 15.4%
 $C_{22}H_{21}N_2O_8Br$ requires C, 50.7; H, 4.0; N, 5.4; 4OMe, 23.8; Br, 15.4%

5.63, 5.69, 5.99 μ

250(3.65), 321(0.58) $m\mu$

(iii) Oxidation (a) The adduct (0.5g.), 30% (w/v) hydrogen peroxide solution (50 ml.), and glacial acetic acid (100 ml.) were heated at 100° for 15 hr. The deep-red solution gradually turned colourless. Evaporation under reduced pressure gave a trace of a syrup, which could not be induced to crystallise.

(b) Chromium trioxide (1.0g.) in 75% aqueous acetic acid (12 ml.) was added dropwise to a boiling solution of the adduct (1.0g.) in glacial acetic acid. The dark green solution was boiled for a further 10 min, evaporated to dryness, and methanol was added to destroy excess chromic acid. After again evaporating the solution to dryness, water (20 ml.) was added to the residue, and the mixture was extracted with chloroform (3 x 20 ml.). The dried (K_2CO_3) extracts were evaporated to dryness. Recrystallisation of the residue from methanol gave pale yellow rods of the oxidation product, m.p. 131-2°.

Found: C, 52.9; H, 5.3; N, 6.1%
 $C_{20}H_{24}N_2O_{10}$ requires C, 53.1; H, 5.4; N, 6.2%

3.10, 5.68*, 5.72, 5.82, 5.92, 6.19, 6.59 μ

231.5(0.87), 236(0.85), 270*(0.3), 299*(0.49), 306*(0.55), 312(0.6), 322(0.59) $m\mu$

(c) The adduct (0.5g), freshly sublimed selenium dioxide (0.5g.) and 80% aqueous dioxan (50 ml.) were refluxed together 16 hr. The precipitated selenium was filtered off, the filtrate was evaporated to dryness under reduced pressure, and the residue was chromatographed on alumina (100 ml.).

Elution with benzene gave a single yellow fraction, which gave a yellow solid. This was purified by thin-layer chromatography, using benzene: ethylacetate (4:1 v/v) was solvent. The band was scraped off the plate, washed with methanol, filtered, and the filtrate evaporated to dryness. The residue was recrystallised from methanol to give tetramethyl 10,11-dihydroquinoxalino [1,2-a]azepine-7,8,9,11-tetracarboxylate, [7], (27 mg.), orange parallelepiped, m.p. and mixed m.p. 138-9°.

(iv) Hydrolysis (a) The adduct (0.5g.) and 5N aqueous sodium hydroxide solution (25 ml.) were warmed until the mixture was homogenous, then left at room temperature for 14 days. The solution was acidified with 2N hydrochloric acid, and continuously extracted with chloroform for 15 hr. Evaporation of the dried (K_2CO_3) extract gave a black tar, from which no crystalline product could be isolated.

(b) The adduct (0.5g.) and concentrated hydrochloric acid (50 ml.) were refluxed 5 hr. Evaporation to dryness under reduced pressure gave a black tar, from which no crystalline material could be obtained.

(v) Nitration:- A suspension of the adduct (0.5g.) in 2N nitric acid (10 ml.) was heated at 100° for 5 hr. The solid became yellow and gum-like, but, on filtration, gave a white powder. However, attempts to recrystallise this powder gave only syrups.

(vi) Condensation:- The adduct (0.5g.), benzaldehyde (2 ml.), pyridine (50 ml.), and piperidine (5 ml.) were refluxed 12 hr. The solution was evaporated to dryness, and the residual tar was chromatographed on alumina (100 ml.). Elution with benzene gave a dark-red fraction, which, after evaporation of the eluate, gave tetramethyl 10,11-dihydro-6-styryl-

quinoxalino[1,2-a]azepine-7,8,9,11-tetracarboxylate, (58 mg.), m.p. 209-10°, as carmine-red rods.

Found: C, 65.1, H, 4.4; N, 5.4.
 $C_{29}H_{26}N_2O_8$ requires C, 65.7; H, 4.9; N, 5.3%

5.79, 5.96, 6.14, 6.53 μ

(A) 226(0.54), 277(0.84), 336(0.83), 514(0.33) μ
285(0.66), 251(0.45), 303(0.97), 321*(0.84), 430(0.47) μ
(figures in parentheses are optical densities)

(viii) The dihydro adduct, [15], (1.0g.), methyl iodide (5 ml.) and methanol (25 ml.) were left at 0° for 7 days. Evaporation of the solvent gave a yellow oil, which could not be induced to crystallise. However, the crude product was shaken with freshly prepared silver oxide and water (15 ml.) added, filtered, and the filtrate was shaken with 10% palladised charcoal (0.5g.) and methanol (150 ml.) under hydrogen (4 atmos.) for 12 hr. Filtration, and evaporation of the filtrate under reduced pressure gave a tar, from which no crystalline products were obtained.

(vi) The adduct (0.1g.) and dimethyl acetylenedicarboxylate (0.5g.) were heated at 100° for 48 hr. The dark-red oil was chromatographed on alumina (30 ml.) in light petroleum (b.p. 60-80°). Elution with light petroleum (b.p. 60-80°) (200 ml.) removed excess acetylenic ester, while further elution with benzene (400 ml.) gave a red fraction, from which no crystalline product could be isolated.

Attempted Addition of Diethyl Acetylenedicarboxylate to 2,3-

Dimethylquinoxaline :- Refluxing 2,3-dimethylquinoxaline (2g.), diethyl acetylenedicarboxylate (4.3g.) and acetonitrile (50 ml.) for 16 hr., evaporation of the solvent, and chromatography of the resultant tar on

alumina, gave 2,3-dimethylquinoxaline (50 mg.) as the only crystalline material isolated.

Attempted Addition of Dimethyl Acetylenedicarboxylate to 2,3-Diethylquinoxaline :- Refluxing these reagents in acetonitrile, followed by chromatography gave only tars, from which no crystalline product could be obtained.

Addition of Dimethyl Acetylenedicarboxylate to 4,6-Dimethylpyrimidine :- 4,6-Dimethylpyrimidine (5 g.), dimethyl acetylenedicarboxylate (13.2 g.) and acetonitrile (100 ml.) were refluxed 16 hr. The tar, obtained by removal of the solvent under reduced pressure, was chromatographed on alumina (600 ml.), and elution with benzene gave a bright yellow fraction. Evaporation of the eluate gave tetramethyl 8,9-dihydro-3-methylpyrimidino[3,4-a]azepine-5,6,7,8-tetracarboxylate, [21], (1.94g., 11%), yellow rods, from methanol m.p. 201-2°

Found: C, 55.1; H, 5.2; N, 7.2; OMe, 31.8%
 $C_{18}H_{20}N_2O_8$ requires C, 55.1; H, 5.1; N, 7.1; 4OMe, 31.6%

5.66, 5.74, 5.81, 5.97, 6.10, 6.41, 6.60 μ

359.5(2.18), 370(1.85) $m\mu$
(P) 356 (0.55) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to 2,4,6-Trimethylpyrimidine :- 2,4,6-Trimethylpyrimidine (5.6g.), dimethyl acetylenedicarboxylate (13.2g.), and acetonitrile (100 ml.) were refluxed 14 hr. Evaporation of the acetonitrile under reduced pressure gave a tar, which was chromatographed on alumina (600 ml.). Elution with benzene gave a single orange fraction, from which was isolated tetramethyl 8,9-dihydro-1,3-dimethylpyrimidino[3,4-a]azepine-5,6,7,8-tetracarboxylate, [22],

(1.08g., 5.8%), yellow cubes from methanol, m.p. 161-2°

Found: C, 56.0; H, 5.6; N, 7.0; OMe, 30.3%
 $C_{19}H_{22}N_2O_8$ requires C, 56.2; H, 5.5; N, 6.9; 4OMe, 30.5%

5.72, 5.95, 6.18, 6.36, 6.58 μ

(P) 220*(0.65), 310(1.78), 320 (1.72), 383(0.39)
 312(2.07), 323*(1.59)

Addition of Dimethyl Acetylenedicarboxylate to 4-Methylquinazoline :-

4-Methylquinazoline (4.2g.), dimethyl acetylenedicarboxylate (9.1g.) and acetonitrile (100 ml.) were refluxed 16 hr. The solution was evaporated to dryness under reduced pressure, and the residual tar was chromatographed on alumina (500 ml.). Elution with benzene gave a single orange fraction, from which was obtained tetramethyl 8,9-dihydroquinazolino-[3.4-a]azepine-9,10,11,12-tetracarboxylate, [23], (0.3g., 2.3%), pale yellow decahedrons from methanol, m.p. 187-8°.

Found: C, 58.8; H, 4.7; N, 6.7; OMe, 28.6%
 $C_{21}H_{20}N_2O_8$ requires C, 58.9; H, 4.7; N, 6.5; 4OMe, 28.9%

5.69, 5.75, 5.91, 6.18, 6.22, 6.43 μ

(P) 218.5(3.39), 244(0.7), 283*(0.79), 291.5(1.01), 354(0.98), 372(0.96), 409*(0.57)
 218.5(2.61) 283*(1.26) 288 (1.32) 347(1.47)

Attempted Addition of Dimethyl Acetylenedicarboxylate to 2-Methyl-

quinazoline :- After refluxing 2-methylquinazoline (2.4g.) and dimethyl acetylenedicarboxylate (5.2g.) in acetonitrile (75 ml.) for 12 hr., and chromatographing the resulting tar on alumina, no crystalline adducts were isolated.

Addition of Dimethyl Acetylenedicarboxylate to 2,4-Dimethyl-

quinazoline :- 2,4-Dimethylquinazoline (6g.), dimethyl acetylenedicarboxylate (16.2g.), and acetonitrile (150 ml.) were refluxed 16 hr. The

solvent was removed in vacuo, and the resulting tar was chromatographed on alumina (750 ml.). Elution with benzene (4 l.) gave a yellow fraction, from which only tarry material was obtained. Further elution with benzene:chloroform (1:1 v/v, 3 l.) gave a green fraction. Evaporation of the eluate gave hexamethyl 1,2,11,12-tetrahydro-azepino[1,2-c],-pyrrolo[1,2-a]quinazoline-2,3,4,5,11,12-hexacarboxylate, [25] (0.52g., 2.3%), pale yellow rhombic plates from methanol:chloroform (20:1 v/v), m.p. 274-6°.

Found: C, 57.4; H, 4.8; N, 4.8; OMe, 30.4%
 $C_{28}H_{28}N_2O_{12}$ requires C, 57.5; H, 4.8; N, 4.8; 6OMe, 31.8%

5.69, 5.74, 5.90, 6.29, 6.42, 6.76 μ

243(0.77), 278(0.68), 320(2.08), 336*(1.91) $m\mu$
 (P) 223.5(1.35), 282(0.98), 343(0.98) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to 2,3,5,6-Tetramethylpyrazine :- Tetramethylpyrazine (5g.), dimethyl acetylenedicarboxylate (10g.) and acetonitrile (100 ml.) were refluxed 16 hr. Evaporation under reduced pressure gave a tar which was chromatographed on alumina (600 ml.). Elution with benzene (1.5 l.) and benzene:chloroform (1:1 v/v, 500 ml.) gave a single orange fraction, from which was isolated pentamethyl 4a,8,9,12-tetrahydro-4a-methyl-8-oxo-dipyridino[1,2-a,2,1-c]pyrazine-1,2,3,4,6-pentacarboxylate, [27], (0.29g., 2.2%), orange rods from methanol, m.p. 229-31°.

Found: C, 56.6; H, 5.3; N, 5.3; OMe, 29.1%
 $C_{25}H_{26}N_2O_{11}$ requires C, 56.5; H, 4.9; N, 5.3; 5OMe, 29.3%

5.71, 5.78, 5.85, 6.19, 6.27, 6.51 μ

247.5(2.34), 274(1.9), 388(0.61) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to 2,5-Dimethylpyrazine:-

A solution of 2,5-dimethylpyrazine (20 g.) and dimethyl acetylenedicarboxylate (52.8g.) in acetonitrile (250 ml.) was refluxed 16 hr. Evaporation of the solvent under reduced pressure and chromatography of the residual tar on alumina (1200 ml.) gave a single orange fraction, eluted with benzene. From this was obtained hexamethyl 8,9,-dihydropyridino[a]azepine-2,3,5,6,7,8-hexacarboxylate, [33], (5.4g., 7.5%)

Found: C, 53.4; H, 4.7; N, 2.9; OMe, 37.6%
 $C_{22}H_{23}NO_{12}$ requires C, 53.6; H, 4.7; N, 2.8; 6OMe, 37.7%

5.73, 5.88, 5.97, 6.15, 6.62 μ

232*(0.99), 347.5(2.89), 357*(2.65), 441(0.52) $m\mu$

PART FIVE

(Structure Numbers refer to Chapter Five)

Addition of Dimethyl Acetylenedicarboxylate to 4-Methyliminazole:-

Dimethyl acetylenedicarboxylate (4.75g.) was added to 4-methyliminazole (3g.) in acetonitrile (25 ml.). The solution darkened rapidly, and heat was evolved. After the initial violence had ceased, the solution was refluxed 15 hr. Removal of the solvent in vacuo gave a mobile red liquid which was chromatographed on alumina (250 ml.). Elution with benzene (2 l.) gave dimethyl 1-(4(5)-methyliminazolyl)fumarate [4 or 5], (2.27g., 29%), as colourless parallelepipeds, m.p. 103-103.5°, from light petroleum (b.p. 60-80°):methyl acetate (5:1 v/v)

Found: C, 53.8; H, 4.6; N, 12.4; OMe, 27.5%
 $C_{10}H_{10}N_2O_4$ requires C, 54.1; H, 4.5; N, 12.6; 2OMe, 27.9%

5.73, 5.82, 6.07, 6.29, 6.63, 6.74 μ

258 (1.17) $m\mu$

(A) 241*(0.63) $m\mu$

Attempted Addition of Dimethyl Acetylenedicarboxylate to Iminazole:-

Dimethyl acetylenedicarboxylate (1.1g.) was added to a solution of iminazole (1.0g.) in acetonitrile (15 ml.). Heat was evolved, and the solution darkened rapidly. The solution was refluxed 16 hr., evaporated to dryness under reduced pressure, and the resulting tar was triturated with boiling methanol (50 ml.). On cooling, a white solid was deposited. On filtration, this rapidly reverted to a gum, which could not be induced to crystallise.

Attempted Addition of Dimethyl Acetylenedicarboxylate to 2-Methyl-

benziminazole :- 2-Methylbenziminazole (1.86g.) and dimethyl acetylenedicarboxylate (1g.) in acetonitrile (10 ml.) were refluxed 16 hr. Evaporation of the solvent under reduced pressure, and trituration of the residual tar with ether (15 ml.) gave unchanged 2-methylbenziminazole (1.5g., 81%), identified by m.p. and mixed m.p. (177-8°).

Addition of Dimethyl Acetylenedicarboxylate to Indazole :-

A solution of indazole (4.1g.) and dimethyl acetylenedicarboxylate (3.5g.) in acetonitrile (50 ml.) was refluxed 6 hr. The solvent was removed under reduced pressure, and the residue, triturated with ether (5 ml.), was stood at 0° for 24 hr. The precipitate of dimethyl 1-indazolyfumarate [6] (2.65g., 31%) was filtered off, and recrystallised from light petroleum (b.p. 60-80°), containing a little methyl acetate, as colourless, hexagonal plates, m.p. 96°.

Found: C, 60.3; H, 4.7; N, 10.7; OMe, 23.6%
 $C_{13}H_{12}N_2O_4$ requires C, 60.0; H, 4.7; N, 10.8; 2OMe, 23.8%

5.74, 5.83, 6.08, 6.56 μ

246(2.68), 314(3.95) μ

Evaporation of the mother liquors from the above, and trituration with methanol (5 ml.) gave dimethyl α, β -(1,2'-diindazolyl)succinate [8] (1.7g., 22%), colourless rods, m.p. 175-6°, from methanol.

Found: C, 63.6; H, 4.9; N, 15.0; OMe, 16.4%
 $C_{20}H_{18}N_4O_4$ requires C, 63.5; H, 4.8; N, 14.8; 2OMe, 16.4%

5.74, 5.82*, 6.11, 6.17, 6.56, 6.66 μ

252(0.67), 259.5(0.67), 280*(0.73), 285*(0.77), 289(0.84), 295(0.81), 301(0.67),
 314*(0.14) μ

Addition of Dimethyl Acetylenedicarboxylate to 3-Methylindazole:-

Dimethyl acetylenedicarboxylate (2g.) and 3-methylindazole (2g.) in acetonitrile (25 ml.) were refluxed for 6 hr. The solution was evaporated to dryness under reduced pressure, the residue was triturated with ether (10 ml.), and the precipitated solid was recrystallised from methanol as white rods of dimethyl α, β -(1,2'-di-3-methylindazolyl)succinate [9], (1.5g., 37.5%), m.p. 171-171.5°.

Found: C, 65.2; H, 5.6; N, 13.8; OMe, 15.5%
 $C_{22}H_{22}N_4O_4$ requires C, 65.0; H, 5.5; N, 13.8; 2OMe, 15.3%

5.72, 6.11, 6.18, 6.62, 6.72 μ

(P) 219(3.40), 267(0.71), 282.5(0.93), 295(1.18), 300(1.19), 307(1.13), 319(0.38) μ
 256*(1.36), 261.5(1.44), 298.5(1.17), 304(1.17) μ

Addition of Dimethyl Acetylenedicarboxylate to 1,2,3-Triazole :-

A solution of 1,2,3-triazole (1g.) and dimethyl acetylenedicarboxylate (0.95g.) in acetonitrile (10 ml.) was refluxed 12 hr. Evaporation under reduced pressure gave a yellow syrup, which, on trituration with ether (5 ml.), deposited dimethyl α, β -di-1(2)-(1,2,3-triazolyl)succinate [10] (0.4g., 20%) colourless needles, m.p. 125°, from methanol.

Found: C, 42.6; H, 4.8; N, 30.0; OMe, 21.9%
 $C_{10}H_{12}N_6O_4$ requires C, 42.9; H, 4.3; N, 30.0; 2OMe, 22.1%

3.22, 5.75, 5.89(μ) μ

No absorption above 220 $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to Benzotriazole :-

Benzotriazole (1.68g.), dimethyl acetylenedicarboxylate (1.0g.) and acetonitrile (25 ml.) were refluxed 14 hr. Removal of the solvent in vacuo gave a brown oil, from which was isolated, by trituration with ether (10 ml.) dimethyl α -di-1(2)-benzotriazolylsuccinate [11], (1.9g., 71%), colourless rods, m.p. 134°, from methanol.

Found: C, 56.9; H, 4.2; N, 22.3; OMe, 16.3%
 $C_{18}H_{16}N_6O_4$ requires C, 56.8; H, 4.2; N, 22.1; 2OMe, 16.3%

5.67, 5.79, 6.29, 6.68 μ

255(1.02), 275(0.70), 315*(0.10) $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to 1,2,4-Triazole :-

A solution of 1,2,4-triazole (2g.) and dimethyl acetylenedicarboxylate (1.9g.) in acetonitrile (15 ml.) was refluxed 15 hr. Evaporation of the solvent under reduced pressure gave a pale yellow solid, which was recrystallised from methanol as dimethyl α , α -di-1(2)-triazolylsuccinate [12], (0.9g., 23%), colourless rods, m.p. 155°.

Found: C, 42.6; H, 4.5; N, 29.7; OMe, 21.9%
 $C_{10}H_{12}N_6O_4$ requires C, 42.9; H, 4.3; N, 30.0; 2OMe, 22.1%

3.20, 5.70, 6.62 μ

No absorption above 220 $m\mu$

Addition of Dimethyl Acetylenedicarboxylate to 3-Methyl-1,2,4-triazole:-

Dimethyl acetylenedicarboxylate (1.71g.), 3-methyl-1,2,4-triazole (2g.) and

acetonitrile (25 ml.) were refluxed together for 16 hr. Evaporation in vacuo gave a violet oil, which, when dissolved in benzene (10 ml.) and stood at 0° for 3 days, gave dimethyl α,α -di-1(2 or 4)-(3-methyl-1,2,4-triazolyl)succinate [13], (0.75g., 20%) as colourless needles, m.p. 164°, from methanol.

Found: C, 46.9; H, 5.3; N, 27.2; OMe, 19.9%
 $C_{12}H_{16}N_6O_4$ requires C, 46.8; H, 5.2; N, 27.3; 2OMe, 20.1%

3.24, 5.73, 5.82*, 6.58 μ

No absorption above 220 m μ

Addition of Dimethyl Acetylenedicarboxylate to Diazoaminobenzene :-

A mixture of dimethyl acetylenedicarboxylate (14.4g.,) and diazoaminobenzene (10g.) in dry ether (200 ml.) was stood at room temperature for 5 days. Evaporation of the solvent gave a mobile red tar, which was chromatographed on alumina (750 ml.). Elution with benzene (500 ml.) gave a mixture of dimethyl α,α -di-1-(1,3-diphenyltriazenyl)succinate [14], (2.4g., 10%) and dimethyl 2,3-dihydro-1,3-diphenyl-2-transdicarbomethoxy-vinyl-1,2,3-triazole-4,5,-dicarboxylate [17] (0.5g.). These were separated by fractional crystallisation from methanol, the former being the much more soluble. Dimethyl α,α -di-1-(1,3-diphenyltriazenyl)succinate was recrystallised from methanol as pale yellow hexagonal plates, m.p. 170-1° (decomp.)

Found: C, 67.1; H, 5.1; N, 15.7; OMe, 11.8%
 $C_{30}H_{28}N_6O_4$ requires C, 67.2; H, 5.2; N, 15.7; 2OMe, 11.6%

5.74, 5.88*, 6.26, 6.69 μ

232(4.43), 334(4.58)m μ
 (P) 268(2.02)

Further elution with benzene (500 ml.) gave more dimethyl 2,3-dihydro-1,3-diphenyl-2-transdicarbomethoxyvinyl-1,2,3-triazole-4,5,-dicarboxylate (1.2g., total yield 7%), yellow rods, m.p. 188.5-9°, from methanol.

Found: C, 60.1; H, 5.0; N, 8.9; OMe, 26.1%
 $C_{24}H_{23}N_3O_8$ requires C, 59.9; H, 4.8; N, 8.7; 4OMe, 25.0%

5.68, 5.82, 6.23, 6.45, 6.63

238(2.48), 285(0.5), 293*(0.47), 348(1.18) μ

Elution with more benzene (2 l.) gave dimethyl 1-3-diphenyl-triazenyl)fumarate [15], (17mg.), pale yellow rods, m.p. 222-3°, from methanol.

Found: C, 62.5; H, 4.3; N, 11.4%
 $C_{18}H_{17}N_3O_4$ requires C, 63.7; H, 5.1; N, 12.4%

Addition of Dimethyl Acetylenedicarboxylate to 1-Methyl-1,3-diphenyltriazene :- A solution of 1-methyl-1,3-diphenyltriazene (5g.) and dimethyl acetylenedicarboxylate (6.75g.) in acetonitrile (100 ml.) was refluxed for 40 hr. Evaporation of the solvent under reduced pressure gave a mobile brown tar which was chromatographed on alumina (500 ml.). Elution with benzene gave first a pale yellow fraction, which, after evaporation of the eluate, smelt strongly of the starting materials. Further elution with benzene gave a second yellow fraction. The eluate was evaporated, and the residue was dissolved in methanol (10 ml.) and left for 2 weeks. Crystals (29 mg.) were deposited. This solid was recrystallised from methanol m.p. 108-9°, but is, as yet, uncharacterised.

5.75, 8.92, 6.38, 6.67 μ

245(0.91), 300(.1.02) μ

(A) 258.5(0.87) μ

(figures in parentheses are optical densities).

Attempted Addition of Dimethyl Acetylenedicarboxylate to 1,1-

Dimethyl-3-phenyltriazene :- A solution of 1,1-dimethyl-3-phenyltriazene (5g.) and dimethyl acetylenedicarboxylate (9.5g.) in acetonitrile (50 ml.) was refluxed for 16 hr. Evaporation of the solvent under reduced pressure gave a brown oil, smelling strongly of dimethyl acetylenedicarboxylate. Chromatography of this oil on alumina gave no crystalline material.

Attempted Addition of Dimethyl Acetylenedicarboxylate to Azobenzene :-

Azobenzene was recovered quantitatively after refluxing 12 hr. with dimethyl acetylenedicarboxylate in acetonitrile.

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ABSTRACT

The introduction reviews the Michael addition, and shows how the addition of dimethyl acetylenedicarboxylate to heterocycles can be explained if initial attack gives a zwitterion, $\overset{+}{=}\text{N}-\text{C}\overset{-}{=}\text{C}\overset{-}{=}$, which can then react further in several ways. A summary of how the acetylenic ester combines with various heterocycles is given, and brief mention is made of the related Diels-Alder and 1,3-dipolar additions.

Chapter One discusses the reaction of 2-phenylpyridine with dimethyl acetylenedicarboxylate. The initial product has structure [1], which, on heating above its melting point, isomerises to [2], these structures being assigned by consideration of the spectral properties. Heating [1] with excess acetylenic ester gives the 9a-vinyl-9aH-quinolizine, [3], whose spectra resemble those of [1] rather than those of [2]. The 9a-vinyl-9aH-quinolizines, [4] and [5], are obtained from the acetylenic ester and 2-vinyl- and 2-methyl-6-vinylpyridine, respectively. A minor product from 2-vinylpyridine is [6], and a possible mode of formation is proposed.

In Chapter Two, the addition of dimethyl acetylenedicarboxylate to azoles is discussed. Thiazole and 4-methylthiazole give the adducts [7] and [8], while a minor product of the thiazole reaction is [9]. Objections to alternative structures¹ for [7] and some analogues are put forward. Benzoxazole forms the adduct [10] which can be reduced to the dihydro-derivative [11]. 2-Methylbenzoxazole and the acetylenic ester give the compound [12], a possible reaction scheme being postulated, and the similar compounds [13] and [14] are obtained from 1-alkyl-2-methyl-

benziminazoles. The nuclear magnetic resonance spectra of these adducts are discussed, and compared with those of [15] and [16], previously prepared.² 1,2-Dimethylbenziminazole gives a second adduct which has been shown to be [17]. The sole adduct from 2-ethyl-1-methylbenziminazole and the acetylenic ester is the analogous compound [18].

Comparison of the nuclear magnetic resonance and ultraviolet absorption spectra of these compounds with those of a minor product from the reaction of 1-methylbenziminazole and dimethyl acetylenedicarboxylate, indicate⁴ it has the structure [19], but the major product of the reaction is [20]. A similar compound [21] is obtained from benziminazole. Attempts to convert [19] into [20], or both into the same perchlorate, were unsuccessful.

Two adducts [22] and [23] are obtained from 1-methylpyrazole, while 1-methylindazole and the acetylenic ester give [24]. These structures are based mainly on spectral evidence.

1-Methyl- and 1-benzylbenzotriazole react with dimethyl acetylenedicarboxylate to give 1:2 molar adducts, which are formulated as [25] and [26], on the basis of their reduction and oxidation products, and their respective spectra. Structure [25] is preferred to [27], which might be expected by analogy with earlier results, because of its ready loss of CH_2 , characteristic of vinyl ethers. A method of formation of [25] and related compounds is suggested. 1-Methyl-1,2,4-triazole and the acetylenic ester form the compound [28], but the N-methyl derivative of 3-methyl-1,2,4-triazole gives three 1:2 molar adducts, for which no definite structures could be proposed.

The reactions between some diazines and dimethyl acetylenedicarboxylate are considered in Chapter Three. In acetonitrile, the sole products from 2-methyl- and 2,6-dimethylpyrazine and the ester are [29] and [30], while the similar compounds [31], [32], and [33] are minor products when pyridazine, 3-methylpyridazine, and 1-methylphthalazine are used. The structures [31] and [32], previously described³, are confirmed by nuclear magnetic resonance spectroscopy, which was also used to assign structures to the major products of the reactions of the acetylenic ester with pyridazine and its 3-methyl derivative, [34] and [35] respectively. [36], the analogue of [35] is obtained from 3,6-dimethylpyridazine and the ester, but the major product of this reaction is [37], identified by its proton resonance spectrum, which is similar to those of the compounds [12]-[16]. Unlike 3-methylpyridazine, 1-methylphthalazine gives a 1:2 molar adduct with a hydrogen at the bridgehead, [38], and this is isomerised to [39] in acid solution.

In aprotic solvents, phthalazine, quinazoline, and quinoxaline give no crystalline products with dimethyl acetylenedicarboxylate, but, in methanol, phthalazine gives [40]. Phenazine and the acetylenic ester in methanol form the adduct [41], the structure being supported by the proton resonance spectrum, consistent with a symmetrical molecule, and derivatives obtained on reduction and bromination.

Chapter Four is concerned with alkylquinoxalines and methyl-substituted diazines, whose methyl groups take part in the reactions with acetylenic esters. Thus, 2-methylquinoxaline and dimethyl acetylenedicarboxylate give two isomeric 1:2 molar adducts, [42] and [43]. These

structures are based partly on analogy with the "red adduct" from quinaldine⁴, and partly on the chemistry and spectra of the compounds. The nuclear magnetic resonance spectrum of [42] is discussed in detail, and a theoretical spectrum of the $\text{CH}_2\text{-CH}$ system has been calculated⁵, excellent agreement being found between calculated and observed spectra for both methyl and ethyl esters. Reduction of [42] gives [45], and again agreement between observed and calculated proton resonance spectra is found. 2,3-Dimethylquinoxaline forms the methyl analogue of [43], i.e. [44], and the differences in the $\text{CH}_2\text{-CHCOOMe}$ systems of [42] and [44] are used to justify the differences in the respective proton resonance spectra.

Attempts to degrade these adducts were unsuccessful. Reduction of [44] gives the 5,6-dihydro derivative, while bromination of [42] gives the 2,3-dibromo derivative, and bromination of [44] gives bromo-compounds, substituted in the benzene ring and/or the methyl side chain. An interesting reaction is the conversion of [44] to [43] by selenium dioxide. Possible ways in which these adducts could be formed are discussed.

4,6-Dimethyl- and 2,4,6-trimethylpyrimidine and 4-methylquinazoline form 1:2 molar adducts with dimethyl acetylenedicarboxylate, whose nuclear magnetic resonance spectra show the presence of $\text{CH}_2\text{-CH}$ groupings. Structures [46], [47], and [48] are proposed for these compounds, although the $\text{CH}_2\text{-CH}$ systems may be reversed. A 1:3 molar adduct from 2,4-dimethylquinazoline and the acetylenic ester is formulated as [49], on the basis of its nuclear magnetic resonance spectrum.

2,3,5,6-Tetramethylpyrazine and the acetylenic ester give a compound, whose structure is considered to be [50], although alternatives are

discussed. The similar compound [51] is obtained in small yield from 2,3-dimethylquinoxaline, while 2,5-dimethylpyrazine and dimethyl acetylenedicarboxylate give an adduct, whose properties support the structure [52]. A scheme is suggested for the formation of this compound.

In Chapter Five, adducts from the acetylenic ester and some heterocycles containing a free amino group are shown to be one of two types. 4-Methylimidazole and indazole form adducts like [53], while indazole, 3-methylindazole, 1,2,3-triazole, benzotriazole, 1,2,4-triazole, and 3-methyl-1,2,4-triazole give adducts of the type [54]. The position of attachment of the side chain cannot be decided, except in the adducts of indazole and 3-methylindazole, [55] and [56] respectively. Unlike the other succinates, [55] and [56] show two sets of peaks in their nuclear magnetic resonance spectra, indicating the asymmetry of the molecules.

Diazoaminobenzene and dimethyl acetylenedicarboxylate give three adducts, two of which correspond to [53] and [54], while the structure [57] is suggested for the third adduct.

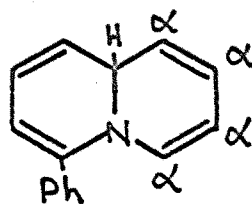
References for Abstract

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5. by Dr. R.M. Acheson, at the University of Oregon.

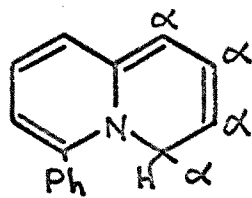
STRUCTURES [1] - [30] for ABSTRACT

STRUCTURES FOR ABSTRACT

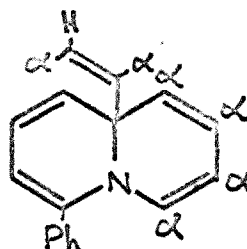
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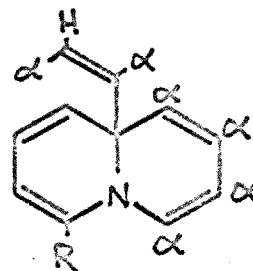
[1]



[2]



[3]

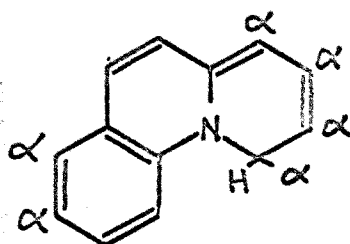


[4]

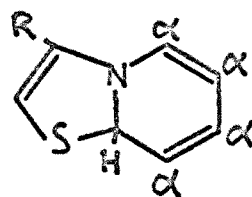
R = H

[5]

R = Me

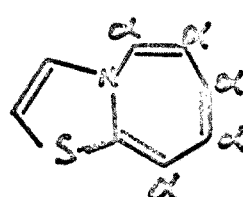


[6]

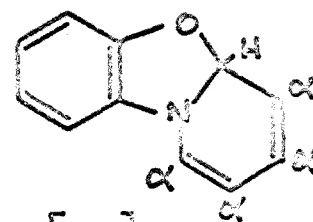


[7] R = H

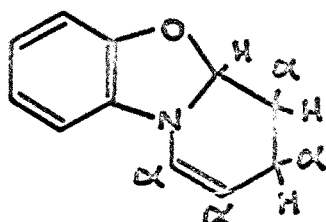
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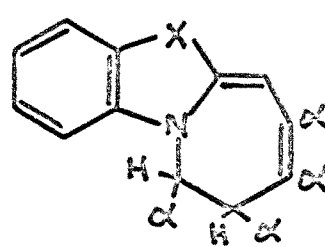
[9]



[10]



[11]



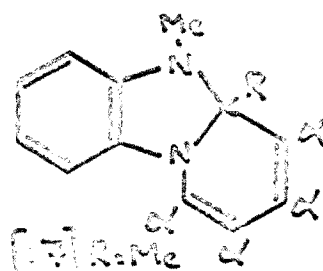
[12] X = O

[13] X = N·Me

[14] X = N·Et

[15] X = S

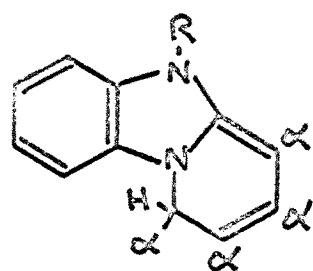
[16] X = Se



[17] R = Me

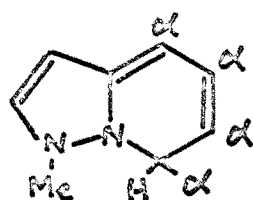
[18] R = Et

[19] R = H



[20] R = Me

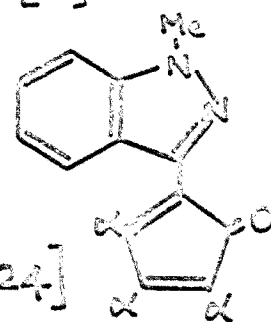
[21] R = CH=CH α



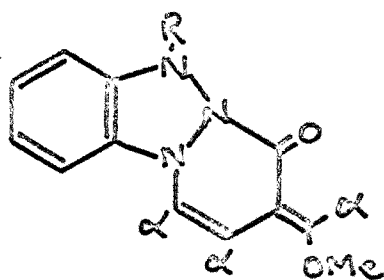
[22]



[23]

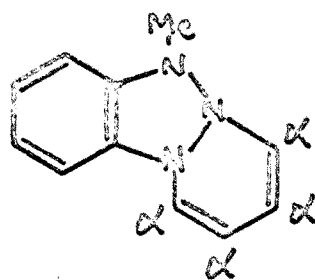


[24]

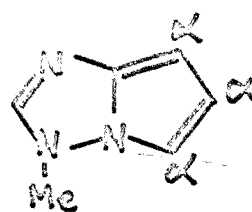


[25] R = Me

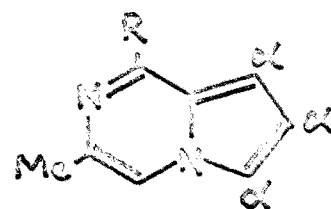
[26] R = CH₂Ph



[27]

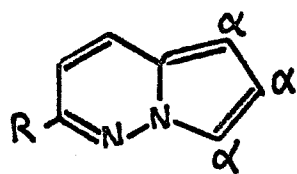


[28]



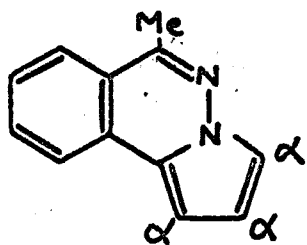
[29] R = H

[30] R = Me

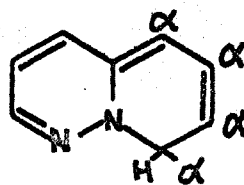


[31] R = H

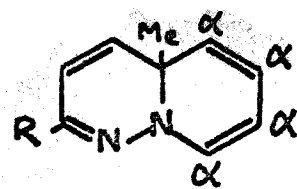
[32] R = Me



[33]

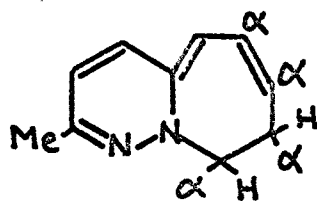


[34]

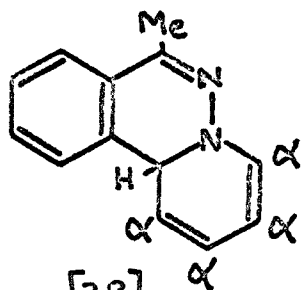


[35] R = H

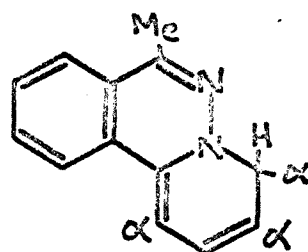
[36] R = Me



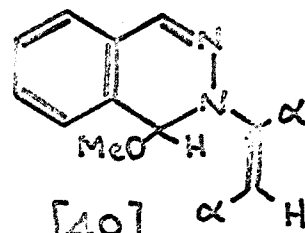
[37]



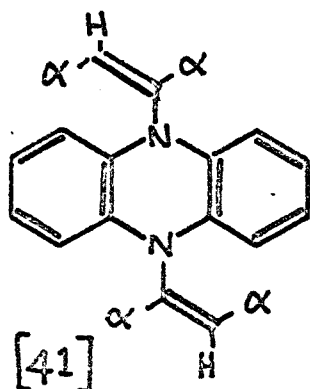
[38]



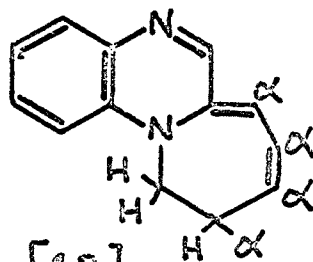
[39]



[40]

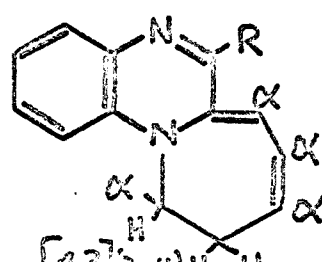


[41]



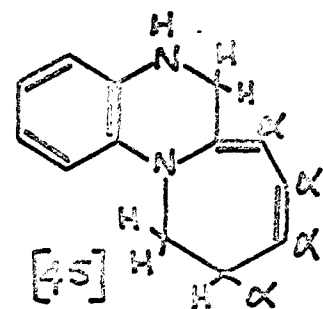
[42]

($\alpha = \text{CO}_2\text{Me}$ or CO_2Et)

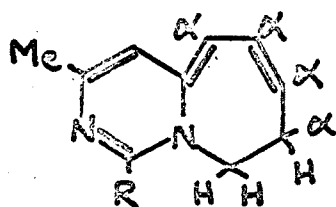


[43] R = H

[44] R = Me

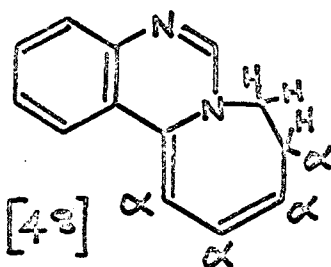


[45]

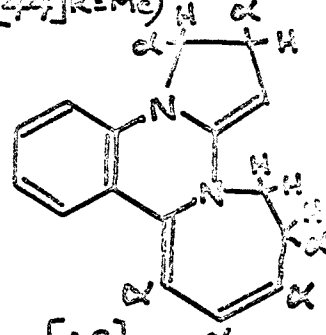


[46] R = H

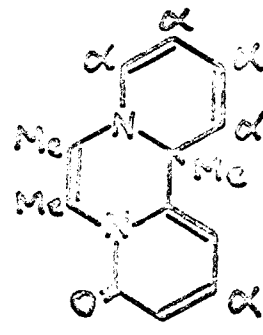
[47] R = Me



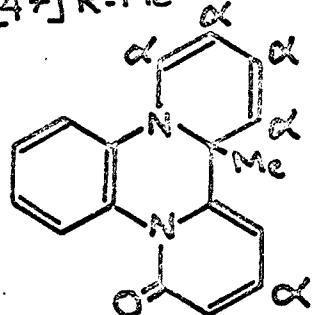
[48]



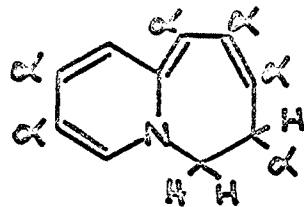
[49]



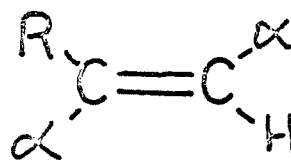
[50]



[51]

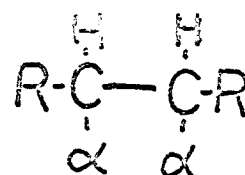


[52]

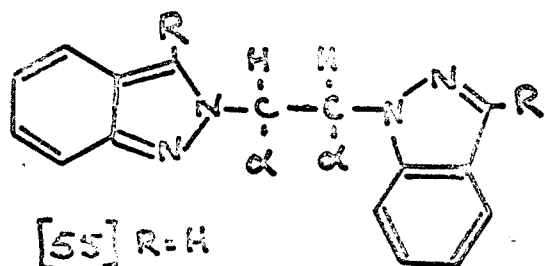


[53]

(R = heterocycle or Ph-N=N-Ph)

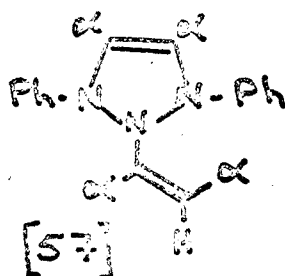


[54]



[55] R = H

[56] R = Me



[57]