STUDIES OF ALICYCLIC COMPOUNDS

by

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INTRODUCTION

During the last decade, the synthesis and spectroscopic properties of nitro-compounds have aroused much interest. New synthetic methods have been developed, and the excellence of the nitro group as a chromophore in spectroscopy has been demonstrated.

Nitro-compounds have been prepared in four ways. These are briefly summarised below and will be discussed in more detail in later sections.

(i) Substitution reactions: substitution of alkyl halides by sodium or silver nitrite producing primary, secondary and tertiary nitro-compounds and nitrite esters, of active methylene groups by alkyl nitrates under basic conditions producing nitroketones, nitronitriles and aryl nitro acetic esters, and of aromatic nuclei by the nitronium ion; (ii) Oxidative methods: peracid treatment of amines and oximes to form primary, secondary, and tertiary nitro compounds, N-bromo-succinimide treatment of oximes giving bromonitro-compounds which are readily reduced to primary and secondary nitro-compounds; (iii) Addition reactions: addition of nitrogen oxides, nitrogen oxyhalides and acetyl nitrate to olefines producing a wide variety of compounds; (iv) Direct nitration: vapour or liquid phase nitration of paraffins and olefins.[1] This method is of no relevance to the present work and is not discussed further.

In most branches of spectroscopy, the absorptions associated with the nitro group are of great interest. Compounds containing the nitro group give infrared spectra with characteristic bands in two regions, 1500-1650 and 1250-1350 cm.$^{-1}$, due, respectively, to the antisymmetric and symmetric

stretching modes of the NO bonds,[2] the former mode giving rise to an intense absorption. Deformation and further stretching modes of vibration involving the nitro group occur below 1000 cm.$^{-1}$.[3,4] There is much empirical data on the absorption regions of antisymmetric and symmetric stretching frequencies for various types of nitro compound. Table I shows some frequency ranges for the vibrational modes in certain classes of compound relevant to the present work.

TABLE I

Compound Type	Frequency Ranges (cm.$^{-1}$)		Ref.
	Asym. NO_2	Sym. NO_2	
R_2CHNO_2	1545-1565	1360-1385	3,5,6
$R_2C(NO_2)_2$	1563-1578	1300-1330	1,3,6
$R_2C(Hal.)NO_2$	1553-1565	1342-1348	3,6
Non-enolic cyclic nitroketones	1540-1570	1370-1380	7
Enolic cyclic nitroketones	1558-1565 1515-1521	1340-1375	6,7
αβ unsaturated nitro compounds	1510-1520	1335-1355	3,6
(Furoxans	1410-1475		3,8,9)

The nitro group in saturated aliphatic[10,11,12] systems gives rise to weak ultraviolet absorption in the region of 280 mμ ($\epsilon < 30$), together with strong end absorption,[11] while simple α-unsaturated nitro-compounds[13]

exhibit more intense bands ($\varepsilon > 2000$) at shorter wavelengths (ca. 260 mμ). The 280 mμ absorption is generally ascribed[14,15] to an $n-\pi^*$ transition, but the lack of solvent dependence of this band,[11] and the discovery of a weak band ($\varepsilon < 20$) at 350 mμ[16] has caused some uncertainty as to its origin.

Nitro groups in disymmetric surroundings give rise to Cotton Effects in optical rotatory dispersion and circular dichroism.[17,18] Bull et al.[6,19] qualitatively related the main Cotton Effect to the degree of environmental asymmetry in nitrosteroids by means of a "reversed Octant Rule". In axial nitro-compounds, with greater non-bonded interactions with neighbouring positions than those of equatorial nitro groups, large Cotton Effects are observed. The magnitude of these can be related to the preferred conformation of the nitro group, which changes with temperature in some cases.[20]

The nuclear magnetic resonance spectra of compounds containing the nitro group show a downfield signal between 5 and 6τ due to the α-methine or α-methylene protons. Usually,[21] but not always,[6] axial proton signals occur at higher field than those due to equatorial protons in axial nitro-compounds. Magnetic anisotropy in the nitro group has been invoked to explain the selective deshielding of protons adjacent to, or further afield from a nitro group.[6,21,22]

Previous work in this Department[6,19,20,23] has been concerned with the synthesis and spectroscopic properties of secondary nitrosteroids and related compounds. In the present work, it was intended to extend this investigation to nitro-compounds in the bornane series and to α-nitroketones. As the work on the latter progressed, it became clear that an investigation

of compounds related to α-nitroketones - their oximes, the corresponding furazans, furoxans and vicinal dinitro-compounds - would be of interest. Many steroid oximes and ketones were handled as starting materials, and other ketosteroids were available from microbiological studies. These provided a wide coverage of the positions on the steroid nucleus and it was decided to investigate the solvent shifts of angular methyl groups in the n.m.r. spectra of steroid ketones, and the low field protons and shifts of angular methyl groups in the n.m.r. spectra of steroid and other cyclic oximes.

Accordingly, this thesis is divided into four sections, viz., Section I, 'Nitro-compounds in the bornane series'; Section II, 'α-Nitroketo-steroids and related compounds'; Section III, 'Solvent shifts of angular methyl groups in the n.m.r. spectra of keto-steroids'; Section IV, 'The n.m.r. spectra of some cyclic oximes'. The relevant literature is discussed and the experimental details described in each section. General experimental directions will be found at the beginning of the experimental part of Section I.

Section I

NITRO-COMPOUNDS IN THE BORNANE SERIES

Part (i)

General methods for the preparation of primary, secondary and tertiary nitro-compounds

The great interest which has been aroused in the preparation of nitro-compounds since the first useful synthesis was reported by Meyer and Stuber in 1872,[24] is reflected in the increasingly comprehensive reviews[25-28] and conference reports[29,30] published in the last thirty years. The following summary refers to some of the general aspects of the preparative work in relation to primary, secondary and tertiary nitro-compounds in the aliphatic and alicyclic series. The preparative methods available for the synthesis of α-nitroketones and related compounds are summarised at the beginning of Section II.

The most common types of reaction are substitution and oxidation: this discussion is subdivided accordingly.

Substitution Reactions

(a) Substitution of alkyl halides: By refluxing amyl iodide with silver nitrite, Meyer and Stuber[24] obtained a readily separable mixture of the nitroparaffin and amyl nitrite. Almost simultaneously, Kolbe[31] showed that nitromethane could be prepared by the action of sodium nitrite on the sodium salt of chloroacetic acid. This reaction is limited to a few simple homologues of nitromethane,[32] leaving the Meyer reaction, with its far greater applicability,[33] as the method of choice.

Since 1947, Kornblum and co-workers at Purdue University have systematically investigated substitution reactions of this type, and have greatly increased the understanding of the processes involved. Under high temperature conditions (80-110°), secondary aliphatic bromides[34] and iodides[35] react with silver nitrite to give complex mixtures of products - nitro-compounds, nitrites, nitrates, alcohols, ketones and other products. The sometimes considerable[36] formation of nitrite esters, under these conditions, was attributed[34] to substitution by silver nitrate, formed by thermal decomposition of silver nitrite. The use of low temperature conditions[36] suppressed this side reaction.

The relative proportions of nitro-compound to nitrite ester formed were shown to be highly dependent on the nature of α-substitution of the substrate. The increase in nitrite ester yields on going from primary to tertiary alkyl halides were interpreted[5,37] as indicative of an increasing contribution of S_N1 kinetics in this reaction. The preferential nitrite formation results from attack (on the carbonium ion) by the more electronegative atomic species, oxygen, of the nitrite ion.

By using sodium nitrite in DMF or DMSO, Kornblum et al.,[38] obtained, from primary and secondary aliphatic, cyclopentyl and cyclohexyl halides, a consistently greater amount of nitro-compound than of nitrite ester. The substitution-independence of this reaction contrasts with the highly substitution-dependent reaction using silver nitrite. The difference is interpreted as arising from the greater ability of the silver ions to polarise the C-Hal. bond in the substrate. Thus S_N2 kinetics should always predominate over S_N1 when sodium nitrite is used.

The mechanism of the silver nitrite and silver nitrate reactions have recently been studied by Kornblum et al.,[39] using optically active 2-halo-octanes and α-phenyl ethyl chloride as substrates in different solvents. They showed that the same mechanism prevailed in each reaction. The mechanism is best considered as a concerted process in which the 'pull' of the silver and the 'push' of the anion play a role, the relative importance of the S_N1 and S_N2 character of the transition state varying with the structure of the halide, and with the ability of the solvent to stabilise, by solvation, any carbonium ion character in the transition state.

Application of this type of reaction to the preparation of 3-nitro-steroids by Bull[6,23] was unsuccessful, just as similar attempts in the monocyclic series[40] had been.

(b) Aromatic Nitration: The nitration of aromatic nuclei is a well known reaction and has been extensively reviewed in the literature.[41] Recognition of the nitronium ion (NO_2^+) as the attacking species is supported by much physico-chemical evidence, and has led to a generally accepted mechanism. This form of substitution is not discussed further as it is not relevant to the present work.

Oxidation Reactions

(a) Oxidation of amines: The direct oxidation of amines has been shown to provide a useful route to tertiary nitroparaffins, which are not readily accessible by other methods. Kornblum et al.,[42] obtained good yields (60-83%) of these compounds by potassium permanganate oxidation of

some aliphatic and alicyclic tertiary amines.

Peracetic acid (rather than trifluoroperacetic acid[43] which forms salts) has been successfully used to oxidise some aliphatic,[43] alicyclic[43] and aromatic[43,44] amines to their nitro-compounds. Nitrocyclohexane was prepared in 70% yield by this method.[43] In the steroid field, the 17β-amines of 5α-, and 5β-androstan-3β-yl acetates have been oxidised to their respective 17β-nitro-compounds in 50% yield with perbenzoic acid.[45] The oxidation of amines at the 3α-, 3β-, 20α- and 20β-positions, with m-chloroperbenzoic acid in chloroform, proceeded with >95% retention of configuration in 45, 28, 58 and 79% yields respectively.[46]

(b) Oxidation of oximes: A direct route to primary and secondary nitro-compounds by the oxidation of their corresponding oximes with trifluoroperacetic acid in buffered acetonitrile was established by Emmons and Pagano.[47] The function of the acetonitrile was to catalyse, by its basic properties, the prototropic conversion of the initially formed aci-nitro-compound to the stable end product. This method has been used by Nielsen[40] in oxidising the dioximes of cyclohexa-1,3-, and cyclohexa-1,4-diones to epimeric mixtures of their corresponding nitro-compounds.

$$R_2C = NOH \longrightarrow R_2C = NOOH \longrightarrow R_2CHNO_2$$

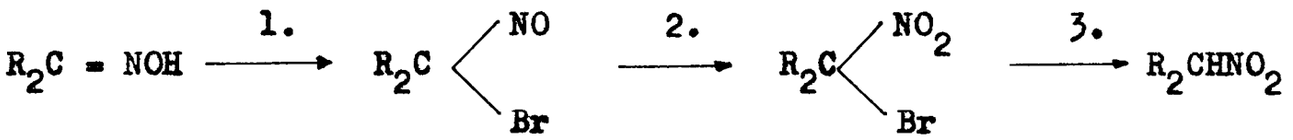
Bull[6,23] found that comparable reactions on 3-hydroxyimino-5α-cholestane involving the use of peracetic acid in chlorinated solvents led to chloro-nitro products in low yield. The main product in this and similar reactions in acetic acid was the lactone derived by Baeyer-Villiger

oxidation from the 3-ketone. When buffered acetonitrile and peracetic acid were used, the main product was the 3-ketone.

In contrast to these results, recent work in this Department,[48] using the conditions of Emmons and Pagano, has shown that 3-oximes of 5α-, and 5β-cholestane may be oxidised to epimeric mixtures of their corresponding nitro-compounds in 25 and 50% yields respectively.

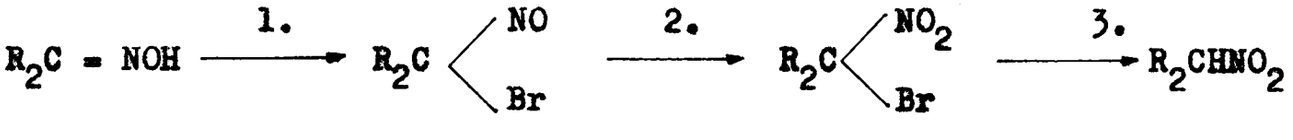
An indirect method for preparing nitro-compounds has been developed by Iffland et al.[49,50] They reinvestigated the old-established bromination of ketoximes, and prepared a variety of nitro-compounds (Sequence A).[49] When certain modifications were introduced (Sequence B),[50] products were obtained in considerably higher yields.

Sequence A



1. Br_2-KOH 2. O_2 3. KOH-EtOH

Sequence B



1. NBS 2. H_2O_2-HNO_3 3. $NaBH_4$

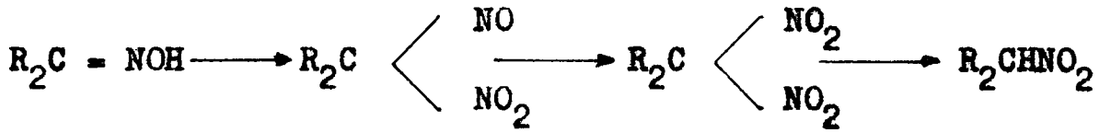
It was shown that this method is useful for preparing simple aliphatic and alicyclic nitro-compounds, and is especially valuable for the oxidation of

hindered ketoximes.[50]

Using a slightly modified procedure, Patchett et al.[51] obtained 17β-nitroandrost-5-en-3β-yl acetate from the corresponding 17-oxime in 55% yield. However, Bull[6,23] found that similar treatment of 3-hydroxyimino-5α-cholestane, even after considerable experimentation, afforded the 3-bromonitro-compound in only 8% yield, accompanied by 4% of the bromonitroso-compound, the main product being the 3-ketone. Similar lack of success was encountered in the NBS oxidation of 3α-acetoxy-5β-pregnan-20-one oxime.[46]

Being unsuccessful with the NBS route, Bull[6,23] evolved a new method for preparing secondary nitrosteroids (Sequence C). Nitration of oximes, by means of fuming nitric acid, produced a blue solution of the pseudo-nitrole, whose oxidation to the dinitro compound was expedited by hydrogen peroxide. Controlled catalytic hydrogenation of the dinitrocompound with the uptake of 4 mols. of hydrogen afforded the nitrosteroid in overall yields varying from 28 to 45%.

Sequence C



Pseudonitrole

Section I

Part (ii)

The preparation of 2-, and 3-nitrobornane

As part of the present study it was decided to prepare nitro-compounds in the bornane series in order to re-examine their properties and to compare aspects of their chemistry with those of the nitrosteroids prepared by Bull.[6,23] (Little work has been done on these bornane compounds since they were first made fifty years ago.*) In this Part, previous work on nitrobornanes and on the conversion of camphor into bornan-3-one is discussed and compared with the present results. The determination of the configurations of 2-, and 3-nitrobornane and the n.m.r. spectra of bornane compounds prepared in the present work, will be described in Part (iii) after discussing the published data on the n.m.r. spectra of bornane compounds.

2-Nitrobornane (4) was first prepared (in 79% yield) by Forster,[52] in 1900, by the action of alcoholic KOH on 2-bromo-2-nitrobornane (3), the latter being formed[53] by hypobromite treatment of camphor oxime (1). Reduction of the bromonitro-compound (3) with phenylhydrazine[54] was less satisfactory, but afforded a purer product. The preparation of 2-bromo-2-nitrobornane (3) was modified by Ginnings and Noyes,[55] and subsequent

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* The literature on bornane compounds up to 1941 is comprehensively abstracted in Elsevier's, "Dictionary of Organic Compounds", Amsterdam, 1948, Vol. 12A. Literature up to 1947 is reviewed in J.L. Simonsen's "The Terpenes", 2nd edn., Vol. II, Cambridge, 1949.

workers[56-58] used this modified method. The only yield quoted for this reaction was 38%.

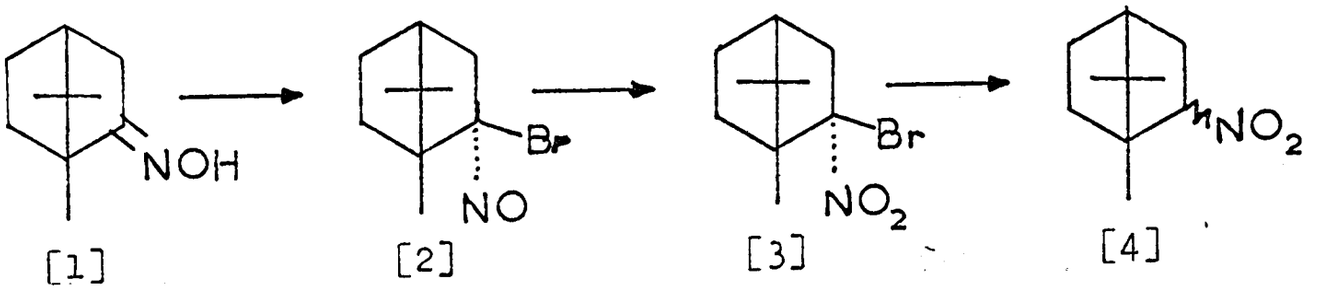
3-Bromo-3-nitrobornane (7) and 3-nitrobornane (8) are not described in the literature.

Iffland et al.[49,50] substituted NBS and $NaHCO_3$ for hypobromite, and $NaBH_4$ for alcoholic KOH, and increased the overall yields of alicyclic nitro-compounds by three to ten-fold (see sequences A and B, previous Part). The intermediate bromonitroso-compound was oxidised to the bromonitro-compound by treatment with nitric acid. This step was eliminated by Patchett[51] who merely lengthened the reaction time with NBS to three days and achieved an overall yield of 50-60% in the case of 17β-nitroandrost-5-en-3β-yl acetate from the corresponding oxime.

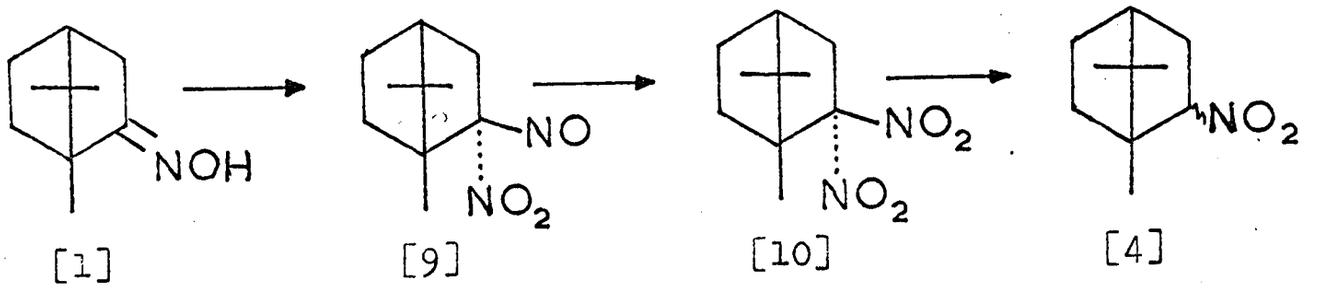
Despite Bull's[6,23] lack of success with 3-hydroxyimino-steroids, this sequence was investigated first in the present study. Camphor oxime (1) (prepared from (+)-camphor), and 3-hydroxyiminobornane (5) (for the conversion of camphor into bornan-3-one, see below) in dioxan-water were vigorously stirred with $NaHCO_3$. Solid NBS was added in portions and the resulting blue solution [bromonitroso-compounds (2,6)] stirred until colourless. The bromonitro compounds (3,7), isolated after chromatography, were reduced with $NaBH_4$ at 20° to the nitro-compounds (4,8).

A second route to 2-nitrobornane (4) was also studied. Bull showed that geminal dinitro compounds, formed by nitric acid and hydrogen peroxide treatment of oximes, are smoothly reduced to secondary nitro-compounds (sequence C, previous Part). Accordingly, camphor oxime (1) in acetic acid

COMPOUNDS 1-17.



[1] [2] [3] [4]



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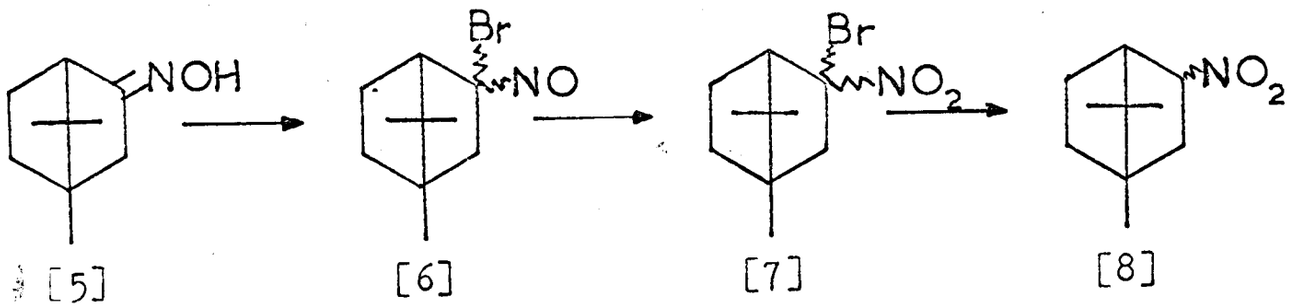
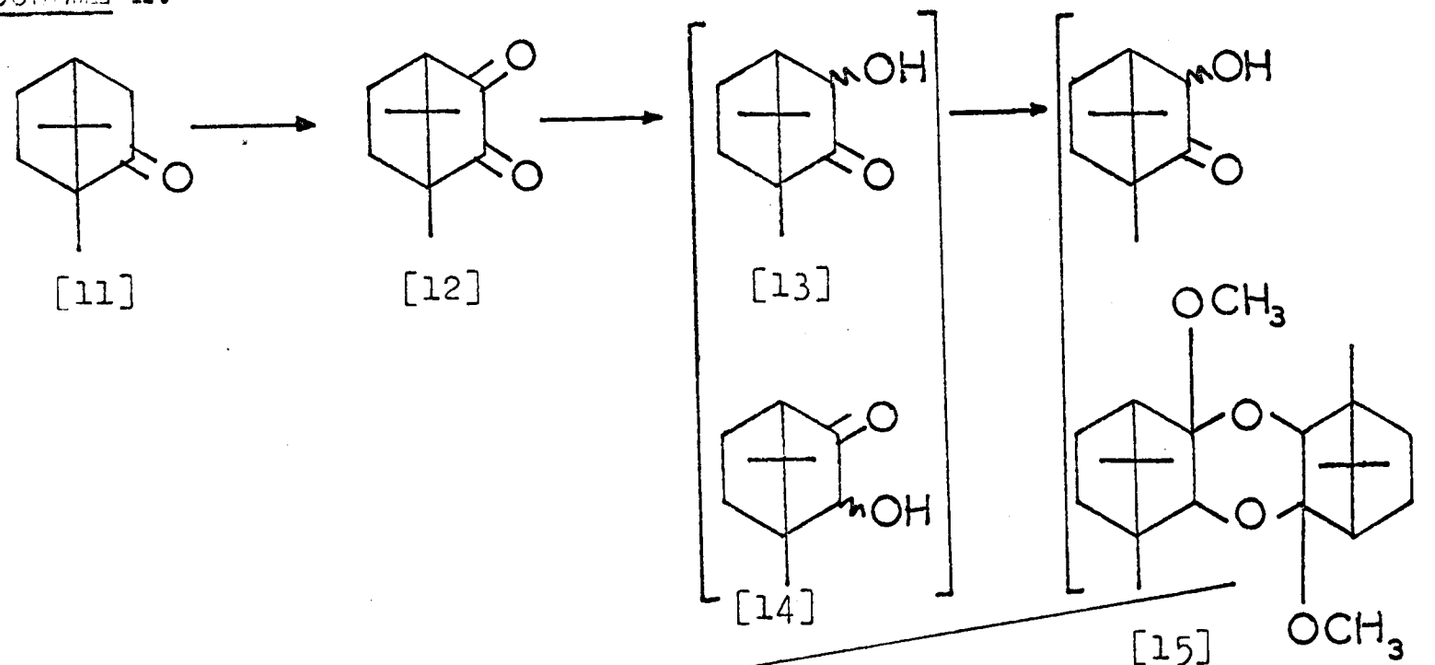
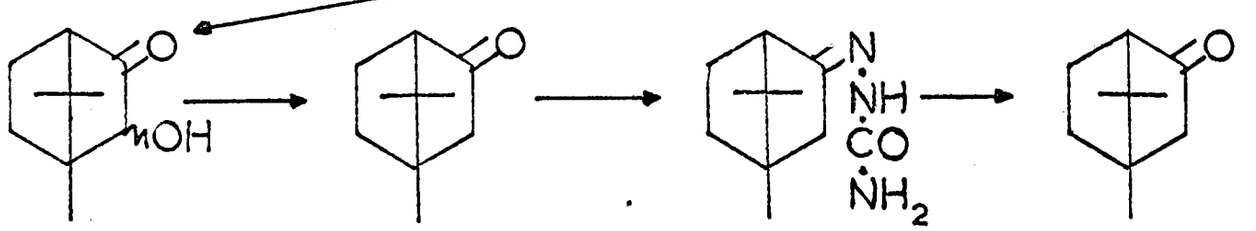


[5] [6] [7] [8]

SCHEME A:



[11] [12] [13] [14] [15]



[14] [16] [17] [16]

was nitrated with pure fuming nitric acid at 20°. The blue intermediate pseudonitrole[59] (9) was not isolated but immediately oxidised by the addition of hydrogen peroxide. Chromatography afforded 2,2-dinitrobornane (10). Hydrogenation of this compound was rapid, and when 4 mds. of hydrogen had been absorbed, the reaction was stopped. The product so obtained was identical with that prepared by the NBS route. The yields for the 2-, and 3- series using the two routes are shown in Table II.

TABLE II

Series	Yield of intermediate from oxime	Yield for reduction stage	Overall yield
2-	$BrNO_2$ - 68%	77%	52%
	NO_2NO_2 - 57%	90%	51%
3-	$BrNO_2$ - 82%	99%	81%

The lower yields in the 2- series can probably be ascribed to greater steric hindrance in the 2- position.

Bornan-3-one [Epicamphor (16)] has been prepared from camphor in two ways. The first route (Scheme A) involves sodium amalgam reduction of 2-hydroxybornan-3-one[60] (14), and the second (Scheme B) the Wolff-Kishner reduction of 3-hydroxyimino camphor hydrazone[61] (19) giving 3-hydroxyimino bornane (5).

Scheme A is the classical route which has been improved recently.[60] This route was closely followed in the present work. The oxidation of camphor with selenium dioxide[62] affords bornan-2,3-dione [Camphorquinone

(12)] in high yield. The observation[60] that it is essential to remove all traces of selenium in order to avoid inactivation of the zinc used in the next stage was substantiated. However, the formation of colloidal selenium, which is not easily removed by crystallisation, may be prevented by keeping the temperature of the reaction mixture below 150°.

Huckel and Fechtig[60] found that the zinc-acetic acid reduction of bornan-2,3-dione (12) proceeded in highest yield (90-95%) at 90-100°. It was found difficult to reproduce this yield. At the working temperature involved, the product, 2-hydroxybornan-3-one (14), and the substrate, steam distil out of the reaction mixture very rapidly. In the experimental conditions finally evolved, therefore, a nearly boiling solution of bornan-2,3-dione (12) in acetic acid was added rapidly, with vigorous stirring, to water boiling under reflux. This produced the fine suspension essential to the reaction. Zinc dust was then added, as a slurry in water, through a dropping funnel and the reaction allowed to proceed in the usual way. In this manner, yields of 99% were consistently achieved.

The third stage,[63-65] the separation of the ketols (13,14), is the least efficient part of the synthesis. Methylation of the ketol mixutre with dry methanolic HCl at 20° afforded 2-hydroxybornan-3-one methyl ether dimer [28% (15)] which crystallised from the solution, and unchanged 3-hydroxybornan-2-one [32% (13)] which was recovered easily from the mother liquors. Yields were low, compared with those previously quoted[60] (40 and 36% respectively). Hydrolysis of the dimeric ether with 35% HCl regenerated the ketol (14) in 76% yield. Huckel and Fechtig[60] obtained this compound in

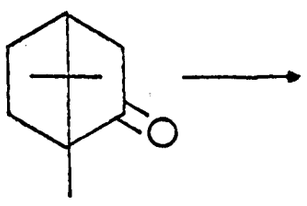
98% yield and reported a melting point of 221°, 9° higher than previous workers had observed. The material prepared in the present work melted (in a sealed tube) at 212°, with concomitant sublimation. The sublimed material melted at 221°.

The sodium amalgam reduction of the ketol (14) (the most effective procedure found by Heckel and Fechtig[60]) proceeded in 99% yield. The product contained >95% bornan-3-one (16), as shown by g.l.c., compared with the reported[60] 75% yield of product containing only 85% bornan-3-one. To remove the camphor from this mixture, advantage is taken of the greater reactivity of the ketone group in the 3-position. Treatment of the mixture with 5% less semicarbazide hydrochloride than was required to react with the bornan-3-one in the mixture, yielded the pure 3-semicarbazone in 60% yield. This was hydrolysed by steam distillation in the presence of oxalic acid, affording bornan-3-one in 80% yield. G.l.c. showed that the product contained <0.5% camphor. The overall yield of bornan-3-one from camphor in this seven stage synthesis was 10% in the present work, compared with Huckel and Fechtig's 14%.[60]

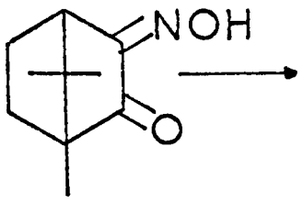
The possibility of a second route to bornan-3-one was indicated in a report by Rapoport and Nilsson[61] of the reduction of α-hydroxyimino-hydrazones under Huang-Minlon conditions. They prepared 3-hydroxyimino camphor hydrazone (19) by treating 3-hydroxyimino camphor (18) with hydrazine hydrate in refluxing ethanol. Reduction of the hydrazone afforded a mixture of 3-hydroxyiminobornane (5) and bornano-[2,3,ν]-triazole (20) in 58 and 32% yields, respectively. The formation of the

COMPOUNDS 18-28.

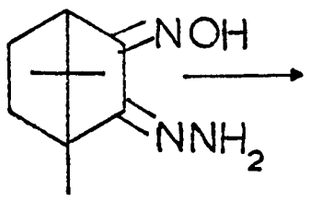
SCHEME B:



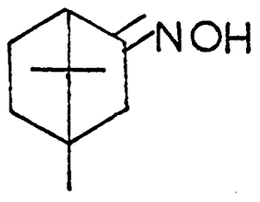
[11]



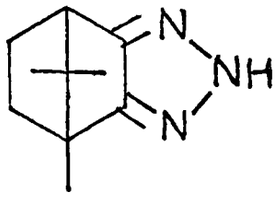
[18]



[19]



[5]



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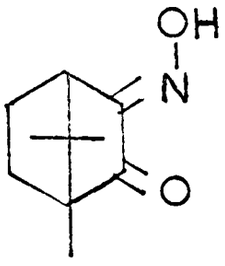

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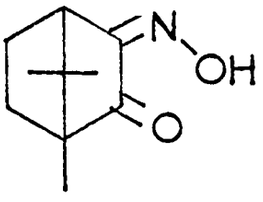

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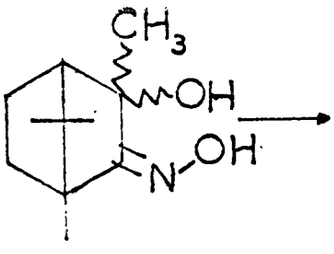

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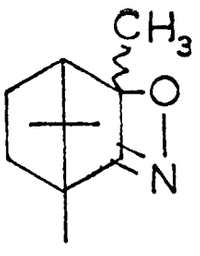

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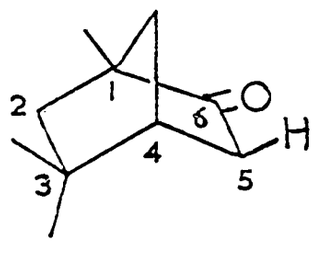

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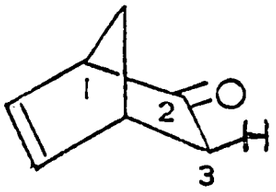

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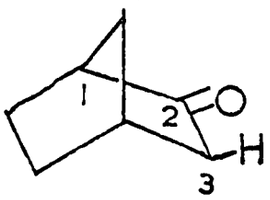

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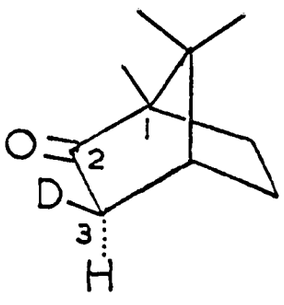


[28]

hydrazone was surprising since Forster and Kuhn[66] (in a paper not mentioned by Rapoport and Nilsson) reported that 'stable' 3-hydroxyimino camphor (m.p. 152°) when heated with hydrazine hydrate under ordinary conditions yields the "hydrazone of bornan-2,3-dione". Forster[67] also showed that the 'stable' 3-hydroxyimino camphor does not react with phenyl hydrazine, although a mixture of the two forms does give a phenyl hydrazone, indicating that it is the unstable form (m.p. 114°) which is reacting. These reports are typical of the confused state of knowledge concerning 3-hydroxyiminocamphor.

The configurations of the 3-hydroxyiminocamphors were first assigned by Forster[68] on the basis of their similarity to the γ- and δ-dioximes of bornan-2,3-dione. The stable form, m.p. 152°, was assigned the syn-, and the unstable form, m.p. 114°, the anti-configuration. Further evidence to support this came from the action of methyl magnesium iodide; only the tertiary alcohol (23) derived from the stable form yielded an anhydride (24). However, Meisenheimer[69] showed that a reversed assignment of configuration (m.p. 152°, anti; m.p. 114°, syn) fitted the published evidence better. Moreover, it was shown that the anhydrides from the methyl magnesium iodide adducts were not of the type (24) and, thus, could not prove configuration. Beckmann rearrangement[69-71] of the two forms was not a reliable guide as both gave the same products, indicating that the syn-form changed into the anti-form under these conditions. Rapoport and Nilsson[61] report that the material first precipitated by acid from an alkaline solution of the mixture of isomers (a method which is reported[68] to produce the lower melting

isomer) had a melting point of 154° and an ir spectrum, in 1% and 10% chloroform solutions, showing intramolecular hydrogen bonding characteristic of the syn-isomer.

3-Hydroxyiminocamphor, when prepared by the action of amyl nitrite and sodium or camphor,[72] contains a mixture of approximately equal amounts of each isomer.[68] The separation of these isomers is complicated by the ease with which the unstable form changes into the stable form, but is reported to have been achieved in several ways. Fractional crystallisation afforded only the higher melting isomer.[67,71] This may also be obtained by treatment of the mixture with ethereal ferric chloride[67] or by heating the mixture at 150°.[68,69] The unstable form is less easy to obtain: benzoylation of the mixture and fractional crystallisation to separate the two isomeric derivatives followed by their individual hydrolysis, afforded the unstable form in 50% yield.[67] Sublimation of the mixture *in vacuo* gave this isomer[69] which may also be prepared by fractional precipitation by acid from an alkaline solution of the mixture.[68,73]

In the present work, all attempts to isolate the unstable form from the mixture of isomers, prepared by Claisen and Manasse's method,[72] failed. Sublimation of this material at 55°/0.1mm. produced a mixture of the isomers slightly richer in the syn-form (the composition of the mixture was determined from its ir spectrum: the anti-form absorbing at 1747 and 1647, and the syn-form at 1712 and 1602 cm^{-1}). Fractional precipitation afforded some enrichment in syn-content, but, in no case, could the pure syn-isomer be obtained. It was shown, however, that when the pure anti-isomer was treated under the same conditions, no isomerisation occurred.

The anti-form, m.p. 152-154°, ν_{max} 1765 and 1660 cm^{-1}, was obtained from the mixture by fractional crystallisation, or by heating the mixture at 150°, alone, or in diethylene glycol. Hydrazine hydrate in refluxing ethanol had a similar effect. The ir spectra of this form, and of the mixture, under conditions where camphor oxime showed no band due to intermolecular hydrogen bonding (0.15 mg./ml.), were very similar. In CCl_4 solution between 3000 and 3600 cm^{-1}, the stable form exhibited a symmetrical band at 3582 cm^{-1}, and a very broad weak band centred on 3280 cm^{-1}; the mixture showed a symmetrical band at 3581 cm^{-1}, and a very broad weak band centred on 3260cm^{-1}. No explanation for these spectra can be put forward at present.

In the 1600-1800 cm^{-1} region, the mixture exhibits bands (1747 and 1647 cm^{-1}) attributable to the stable form which do not correspond to those in the pure compound (1765, 1660), perhaps indicating intermolecular association between the two forms, as postulated by Forster.[74]

The configurations of α-hydroxyimino-ketones has been determined by uv spectroscopy.[75] It is reported that anti-hydroxyimino-ketones exhibit a bathochromic shift (52 mμ), in the uv spectra, on the addition of alkali. No such shift was found in the case of the syn-isomers which showed an absorption maxima in neutral medium 30 mμ to longer wavelength than that of the anti-isomer. In the present work, the stable form (m.p. 152°) of 3-hydroxyiminocamphor exhibits λ_{max}^{EtOH} 240 mμ (ε 8200), $\lambda_{max}^{KOH-EtOH}$ 290 mμ (ε 13400) in accord with an anti-configuration. The uv spectrum of the mixture, is, however, very similar - λ_{max}^{EtOH} 243 mμ (ε 5830), $\lambda_{max}^{EtOH-KOH}$

296 mμ (ε 13500). The n.m.r. spectra of the mixture and of the stable form are discussed in Section IV.

Treatment of the isomeric mixture of 3-hydroxyiminocamphor (21,22) with hydrazine hydrate (either 1 mol. or 40 mols.) in diethylene glycol at 150° for 3 hr., or in refluxing ethanol for 100 hr., yielded the same product as judged by ir examination. This showed the disappearance of the ketone bands at 1747 and 1712, and the appearance of a band at 1120 cm^{-1}. The product was an oil which could not be crystallised. T.l.c. on silica gel or alumina gave no indication of purity, as bornane compounds tail badly on these adsorbents. Despite doubts as to the compound's identity and purity, 19g. were reduced under Huang-Minlon conditions.[61] The extract from the alkaline aqueous layer (8g.) showed no signs of the expected 3-hydroxyiminobornane (5), but 11g. of an acidic compound were obtained. After crystallisation and sublimation, this compound had a melting point of 95-140°, λ_{max} 228 mμ (ε 7720). Despite the similarity of these constants with those of the reported[61] bornano-[2,3,ν]-triazole (20)[m.p. 124-137°, λ_{max} 228 (3300)], analysis showed that this compound contained oxygen.

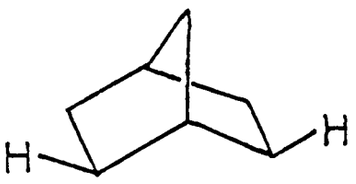
Deuterated compounds were prepared in order to assist in the assignment of signals in n.m.r. spectra. In each case, the parent ketones (11, 16) were deuterated under basic conditions with deuterium oxide. Several workers have demonstrated the remarkable specificity of deuteration under these conditions (one exchange) in isofenchone[76] (25)-97% 5-exo-deuterio, camphor[76] (11)-85% 3-exo-deuterio, and 5,6-dehydronorcamphor[76] (26)-95%

3-exo-deuterio. Norcamphor[76,77] was less specific, one exchange producing 60% d_1 and 34% d_2. This phenomenon has been explained[77] in terms of relief of the 3_N-5_N proton interaction on removal of the C-3-exo-proton. (The abbreviations N and X are used to denote endo- and exo-configuration, respectively.) Another treatment[78] predicts endo-deuteration and speculates on the possibility of bridged structures[79] in enolate intermediates.

In the present work, camphor was deuterated according to the method of Thomas and Willhalm[76] for five days. Mass spectrometry established that deuterium incorporation was 76% d_1, 10% d_2 and 14% d_0. N.m.r. showed that the d_1 compound was 3-exo-deuteriocamphor (28). Comparable deuteration of bornan-3-one produced a surprising amount of incorporation - 65% d_1, 28% d_2 and 7% d_0. After ten days incorporation was 6% d_1 and 94% d_2. The specificity in the deuteration of this ketone would be expected to be similar to that in camphor, but clearly the deuteration is influenced by the presence of the C-10 methyl group close to the α-methylene protons involved. Derivatives were prepared from these deuterated ketones in the normal way. No deuterium exchange occurred during these operations. (It was realised that enolisation during these preparations would lead to exchange of the incorporated deuterium. Model experiments with 4-t-butylcyclohexanone were carried out at an early stage in the present work. It was found that four deuterium atoms (at C-2 and C-6) could be incorporated into this ketone by four exchanges with dioxan-deuterium oxide in the presence of base. The oximation of the d_4-compound occurred without loss of deuterium. Since enolisation would be expected to be easier in this

system than in the bornane series, little exchange of deuterium during the preparation of the nitrobornanes was envisaged.)

COMPOUNDS 29-31.



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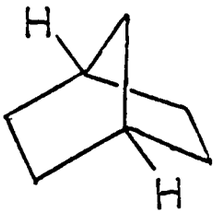

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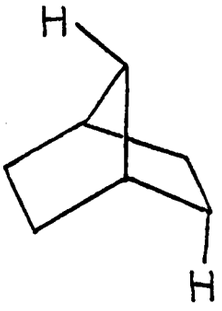

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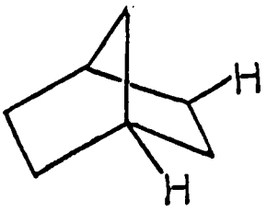

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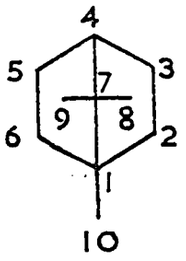

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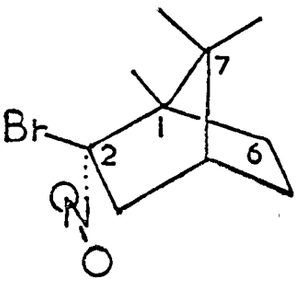

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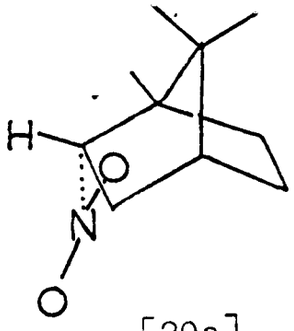

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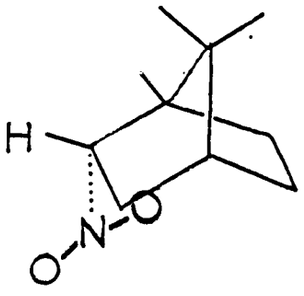

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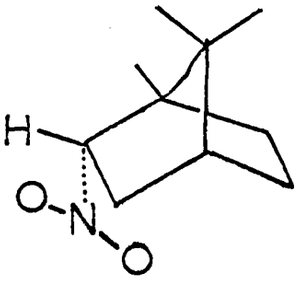

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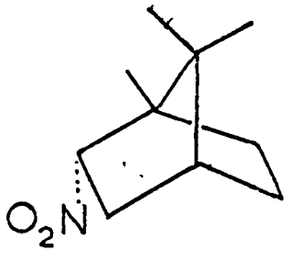

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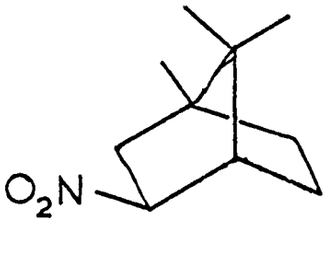

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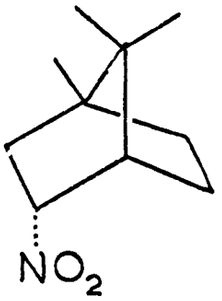

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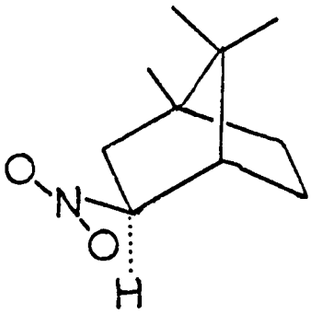

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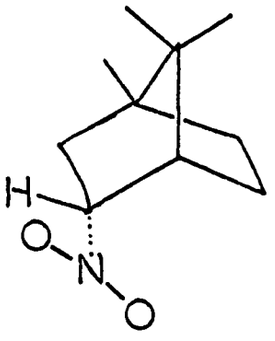

[31a]

Section I

Part (iii)

The n.m.r. spectra of bornane compounds

The study of nuclear magnetic resonance chemical shifts and coupling constants is facilitated by the use of rigid molecules of known geometry. For this reason, the bicyclo [2,2,1] heptane (norbornane) system has attracted much attention. Investigations[80-105] have assigned certain chemical shifts and have established the applicability of the well known Karplus relationships between vicinal coupling constants and dihedral angles (φ)[106] to this system. A linear variation of the magnitudes of vicinal coupling constants and chemical shifts with substituent electronegativity has been reported.[97,99]

Three unusual features are found in the n.m.r. spectra of norbornane derivatives:[101,107] (a) relatively large long range coupling constants (^4J);[109] (b) unequal endo-endo, and exo-exo coupling constants (J_{NN}, J_{XX}) despite equal dihedral angles ($\varphi = 0^o$); and (c) unusual magnetic shieldings. The spectra are further complicated by virtual coupling,[108] whereby the spectrum of a proton in certain spin systems may be complicated by other protons to which it has a zero coupling constant. This second order effect prevents the direct evaluation of coupling constants from an ordinary spectrum. Thus a proton, H_A, strongly coupled to another proton H_B is virtually coupled to a third proton, H_C, through the strong coupling of H_A and H_B, when the difference in chemical shift of protons B and C is equal to or less than the coupling constants between A and B, or B and C.

However, the use of different solvents,[81,99] ^{13}C spectra[99] and spin decoupling,[96,101] have enabled some coupling constants to be evaluated in many cases. In a few cases, a total analysis of the spectrum has been carried out.[99-101]

Long range coupling over four sigma bonds is found to be appreciable only when the four bonds are in an approximately planar 'W' relationship.[109-112] Such a configuration can exist between four pairs of protons on the norbornane nucleus (A, B, C and D). Addition of methyl groups at C-1 and C-7, forming the bornane nucleus removes types B and C, leaving A as the major type of long range coupling (only one example of type D has been found).[112] Values of 0.6-3.0 c.p.s. for this coupling are reported in the literature.[80-112] This long range coupling, together with the inequality of J_{NN} and J_{XX} leads to a characteristic splitting of exo-protons.

endo-Protons are usually,[87,99,101,107] but not always[90,101] shielded by 5-30 c.p.s. relative to exo-protons, analogous to the well known upfield shift of axial protons relative to equatorial protons in cyclohexane systems.[113] The assignment of signals to the three methyl groups in substituted bornanes is a more difficult problem, Kumler et al.[80] made assignments in 3-halogeno-camphors on the basis of the magnetic anisotropy of the carbonyl and halogen groups, and the effect of rotational freedom of the methyl groups which is reflected in the sharpness (or the amplitude) of their signals. The known shielding or deshielding effects of various substituents in different positions on the angular methyl signals in steroids was applied by Kawazoe et al.[114] to bornane derivatives. Flaut and Erman[87] described the large downfield shift of one methyl signal due to

exo-substituents. That the situation was uncertain is shown clearly by the inconsistencies in papers by Tori.[95] Assignment of methyl signals in bornane derivatives was made on the assumptions that (a) the least hindered methyl group (giving the most intense signal) was C-10, and (b) the broader methyl signal at relatively lower field in exo-bornanes was due to C-8. In the case of camphor derivatives, however, the sharpest signal was assigned to C-9. Later, Connolly and McCrindle[115] showed, by deuterium labelling, that the C-10 protons gave rise to the most intense signal. Nevertheless, the work of Tori et al.[95] established that a self-consistent picture of substituent effects on the chemical shifts of the methyl groups could be drawn, provided that the substituents, especially exo-substituents, did not involve a group possessing a powerful diamagnetic anisotropy.

The ranges of the different types of coupling constants found in bicyclo [2,2,1] heptanes are summarised in Table III.

TABLE III

Type	Range (c.p.s.)
$J_{gem.}$	11.5 - 13.3
J_{XX}	7.4 - 11.5
J_{NN}	4.5 - 8.9
J_{XN}	2.0 - 6.0
$J_{3X,4}$, $J_{2X,1}$	3.0 - 5.0
$J_{2X,6X}$, $J_{3X,5X}$	0.6 - 3.0
$J_{3N,4}$ $J_{2N,1}$	~ 0.0

These coupling constants are considered to be linearly dependent on the electronegativity of the substituent.[97,99] In contrast to these results, however, it is to be noted that Huitric et al.[116] found that no simple relation existed for substituent electronegativities and coupling constants in deuterated cyclohexanes. More recently,[117] it has been shown that this effect displays a stereochemical dependency, a trans-coplanar relationship producing the largest effect in cyclohexane systems.

The difference in J_{NN} and J_{XX} cannot be attributed to differences in dihedral angle. The undistorted molecule shows similar dihedral angles ($\varphi = 0^{o}$), and the reported distortions[118] are not large enough[101] to account for the change according to the Karplus equation.[106] Substituted bornanes exhibit the same ranges of coupling constants as norbornanes, indicating that the presence of methyl groups does not increase distortions to an appreciable extent, despite the interference with the free rotation of the methyl groups.[95] Although changes of electronegativity of substituents have been shown to affect coupling constants, this does not seem to be the cause of this difference because an identical difference is observed with the same substituent both endo and exo, and J_{XN} remains about the same in endo-exo pairs showing different vicinal coupling constants.[101] Changes in carbon atom hybridisation (known to affect coupling constants)[99,119] appear to be ruled out in the same manner. It seems more likely that long range contributions from the rest of the molecule to the couplings produce this effect.[107]

Under ideal conditions, therefore, an endo-substituent at C-2 should give rise to a low field n.m.r. signal (due to the α-methine proton) in the

FIGURE 1.

form of a quartet, with each line split further, or broadened, by long range coupling with the C-6_X proton. exo-Substitution should give rise to a triplet, or, at best a quartet with the innermost lines very close together. At the 3-position, the endo-proton will show a similar pattern to that of the C-2_N proton, but the exo-proton will be further split by coupling to the C-4 proton, giving rise to a quintet. To achieve complete resolution of these signals, it may be necessary to modify conditions. Erman[87] showed that, in several cases, the splitting pattern was indeterminate in CCl_4, but in pyridine or benzene, the signal closely approached the expected pattern. These workers attributed this effect to the change in relative chemical shift of the protons concerned, induced by the change in solvent. The "smeared" multiplet, often observed in CCl_4, may be due to virtual coupling,[108] which is destroyed by changing solvent, and hence altering relative chemical shifts. Also the change in coupling constants, observed in different solvents for aliphatic molecules,[120] may play a part. Figure I shows typical examples of the splitting patterns of protons at C-2 and C-3 from the published n.m.r. spectra of bicyclo [2,2,1] heptanes.

The configuration of 2-, and 3-nitrobornane

The assignment of configuration in any system is facitated by the availability of both epimers. In the present work, g.l.c. showed that 2-nitrobornane [see Part (iii)] was a single compound, consistent with its sharp melting point, (154-158°).* Attempts to epimerise this compound

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* Most bicyclic monoterpenes are 'plastic crystals', which are characterised by their diffuse melting points (P. Smith, Physics and Chem. Solids, 1961, 1, 18.)

using Bull's conditions[6,23] - thermodynamic equilibration by refluxing with alcoholic KOH and subsequent acidification at 0° - afforded starting material. These results indicate that the nitro group is already in its most stable configuration, which is also the geometry produced by formation of the compound under kinetic control. The more stable configuration at C-2 in the bornane molecule would be expected to be endo, since a bulky exo-substituent would suffer severe interactions with the C-8 and C-10 methyl groups. The existence of such interactions was demonstrated by Robertson et al.[118] in their determination of the crystal structures of (-)-2-exo-bromo-2-endo-nitrobornane (a compound identical with the intermediate (3) used to prepare 2-nitrobornane in the present work)[121] and (+)-10-bromo-2-exo-chloro-2-endo-nitrosobornane. The distortion caused the angle C-2-C-1-C-7 to be 3-5° larger than the equivalent angle C-6-C-1-C-7. The conformation of the nitro group was shown to be as in (3a), an N-O bond eclipsing the C-2-C-3 bond.

Both 3-bromo-3-nitrobornane (7) and 3-nitrobornane (8) melted at low temperatures over a range (43-50° and 80-95°, respectively) compared to the 2-derivatives. G.l.c. showed that 3-nitrobornane was a 50-50 epimeric mixture (retention times, 9.8 and 10 min.). Equilibration experiments failed to change the composition of this mixture. In the absence of a methyl group in a similar position to that encountered by 2-substituents (C-10), a 3-exo-nitro group suffers less interaction than in the corresponding 2-exo-position. Less steric crowding in the 3-position is also indicated by the greater rates of formation of bornan-3-one hydrazones and oximes compared to the corresponding camphor derivatives,[60,122] and the

presence of both epimers of 3-nitrocamphor in a solution of the 3-endo-epimer [see Part (iv)].

Assignment of configuration by n.m.r. spectroscopy can be accomplished in two ways - (a) by the chemical shift of α-methine protons, and (b) by the magnitudes and number of coupling constants (chemical shift data for methyl signals are not sufficiently well documented to permit assignment on this basis).

Examination of the published chemical shift data for α-methine protons shows that, in all cases where saturated bicyclo[2,2,1]heptane systems were studied, endo-protons absorb at higher field than exo-protons. Ranges of 5.08-5.98 and 5.31-6.39τ for exo-, and endo-protons α- to -OH, -OAC and -Cl, respectively, and 5.1-6.1 and 5.7-6.1τ for exo- and endo-protons in bornan-2,3-diols are recorded. Indications are that, mutatis mutandis, α-methine protons at C-3 are deshielded relative to those at C-2 by about 0.4-1.0τ. Because of the greater electronegativity of the nitro group, it might be expected that the α-methine protons in nitrobornanes would be more deshielded than in the compounds mentioned above. The only published data on a bicyclo[2,2,1]heptane nitro-compound refers to 5-endo-nitronorbornane which exhibits a quintet at 5.27τ (see Figure I).

The n.m.r. spectra of the nitro compounds prepared in the present work confirm that 2-nitrobornane is a single compound and that 3-nitrobornane is a 50-50 epimeric mixture. The spectrum of 2-nitrobornane (see Figure II) shows one low field signal, equivalent to one proton, as an unsymmetrical triplet at 5.39τ - an acceptable chemical shift for an exo-proton.

FIGURES 11 and 111.

Figure 11 : N.m.r. Spectra of 2- and 3-nitrobornane.

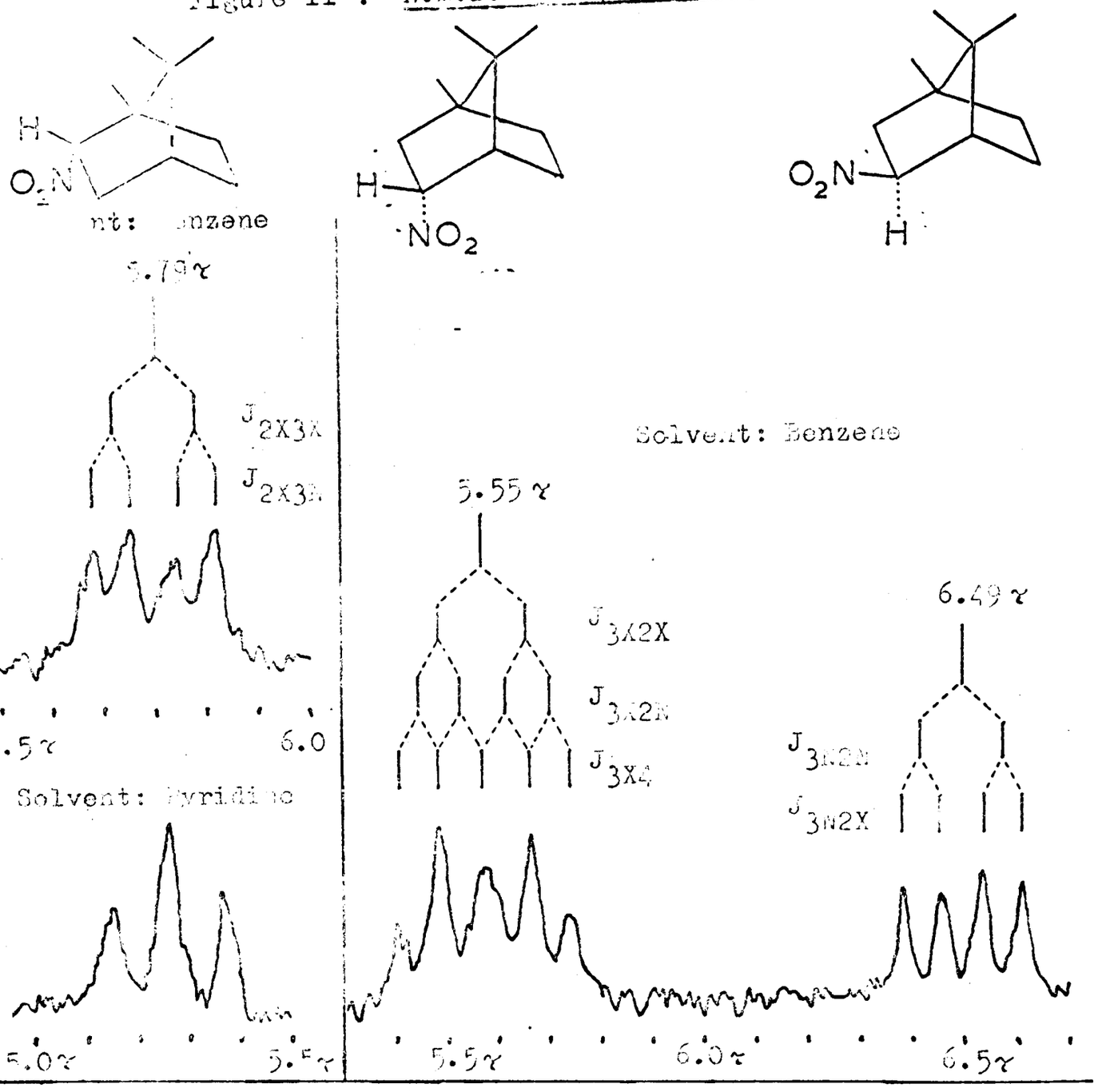


Figure 111

Magnetic anisotropy of carbonyl and nitro groups.



TABLE IV

Compound	Solvent	α-methine proton
2-<u>endo</u>-nitrobornane (28)	CCl_4	5.39 - ut, 7.2
	C_5H_5N	5.20 - ut, 6.9
	C_6H_6	5.79 - q, $J_{2X,3X}$ 9.3, $J_{2X,3N}$ 4.5
3-<u>exo</u>-, and 3-<u>endo</u>-nitrobornane (29, 30)	CCl_4	5.13 - m
		5.95 - q $J_{3N,2N}$ 9.0, $J_{3N,2X}$ 4.6
	C_5H_5N	4.85 - qu $J_{3X,2X}$ 10.2, $J_{3X,2X} = J_{3X,4}$ 5.1
		5.61 - q $J_{3N,2N}$ 9.4, $J_{3N,2X}$ 4.7
	C_6H_6	5.55 - s $J_{3X,2X}$ 10.7, $J_{3X,2X} = J_{3X,4}$ 5.1
		6.49 - q $J_{3N,2N}$ 9.4, $J_{3N,2X}$ 4.7

Chemical shifts in τ values. Coupling constant in c.p.s.

t = triplet, q = quartet, qu = quintet, s = sextet, u = unsymmetrical.

In benzene, this triplet becomes a quartet, whose major coupling constant (9.3 c.p.s.) would be large for an <u>endo</u>-<u>endo</u>-coupling constant (see Table IV). Each part of the quartet is broadened indicating long range coupling - an effect only possible with C-2-H <u>exo</u>. This assignment of configuration [2-<u>endo</u>-nitro (29)] is substantiated by the spectrum of the epimeric 3-nitrobornane mixture: in CCl_4, a multiplet at 5.13τ and a quartet at 5.95τ become, in benzene, a sextet at 5.55 and a quartet at 6.49τ, which can

be ascribed to C-3-H-exo and C-3-H endo (30, 31), respectively. The coupling constants for these signals provide conclusive evidence for these configurational assignments. The additional coupling in the sextet structure (10.7, 5.1 and 5.1 c.p.s.) of the lower field signal is due to coupling with C-4-H, a coupling which is known to take place only with C-3-H-exo. Furthermore, each line in this signal is broadened (relative to the other signal) indicating long range coupling (compatible only with a C-3-H-exo configuration). Finally, the general features of this multiplet are very similar to those in the spectrum of 5-endo-nitronorbornane (Figure I).

It is interesting to note that an assignment of configuration to 2-nitrobornane, after the event, on the basis of coupling constants alone, could be in error since $J_{3N,2N}$ (in 3-exo-nitrobornane) is, unusually, of the same order as $J_{2X,3X}$. However, C-2-H (5.39τ) is, as would be expected from previous results, slightly shielded relative to C-3-H-exo, but not so much as C-3-H-endo (the epimeric difference in chemical shift at C-3 (0.8 p.p.m.) is one of the largest known).

The change in α-methine proton chemical shift on changing the solvent from CCl_4 to benzene (solvent shifts are discussed in Section III) provides further evidence for the postulated configurations. If a benzene molecule and the compound orient themselves in some stable manner, as is the case with ketones in benzene, and as is indicated in the present case by the selective shifts of methyl groups in 2-nitrobornane (see below), then it might be expected that endo-nitro groups at C-2 and C-3, enjoying roughly the same stereochemical environment, would 'complex' with benzene in the same way. Thus their respective α-methine protons would suffer approximately

the same solvent shift on passing from CCl_4 to benzene. Table IV shows that the α-methine proton in 2-nitrobornane and 3-exo-nitrobornane undergo approximately the same solvent shift (0.40, 0.42 p.p.m.), whilst 3-endo-nitrobornane suffers a larger shift (0.54).

The methyl signals in these compounds may be assigned, tentatively, on the basis of (a), the relative sharpness of the signals, (b) the magnetic anisotropy of the nitro group, and (c) the known conformational preferences of nitro groups.

There is much evidence that the C-10 methyl group gives rise to the sharpest signal in both endo- and exo-substituted bornanes.[95,115] It seems likely that this is due less to steric hindrance (which would not operate in the case of endo-substituents), impeding free rotation of the C-8 methyl group, than to a greater intrinsic sharpness in the C-10 methyl group signal, which may arise as follows: long range coupling has been reported (see Section III) between freely rotating methyl groups and fixed protons. The protons of the C-10 methyl group cannot couple with any other protons in a planar "W" arrangement, and any ^4J couplings of this group must be very small. The protons of the C-8 and C-10 methyl groups, however, can couple with themselves and should, therefore, be intrinsically broader than the C-10 signal. The three methyl signals in the spectrum of bornane in CCl_4 are coincident. In benzene, however, two signals appear, one due to 3 protons (C-10) and the other due to 6 protons (C-8 and C-9). The C-10 signal appears to be the sharper of the two signals ($\omega\frac{h}{2}$ = 1.14 and 1.29 c.p.s., respectively), but this result must be viewed with caution since the difference between these measurements (0.15 c.p.s.) is at the limit of the

instrument's resolving power.

The magnetic anisotropy of the nitro group has been shown to be similar, qualitatively, to that of the carbonyl group[123] (Figure III), with cones of shielding of somewhat smaller conical angle.[6]

The presence of a 2-exo-bromine atom in 2-bromo-2-nitrobornane (3a) causes significant distortions of the ring system.[118] The nitro group lies parallel to the C-2-C-3 bond. The removal of the bromine atom would allow the nitro group in 2-endo-nitrobornane (29) to adopt its most stable conformation - which would relieve interactions with C-3-H-endo- by rotating such that its conformation is as in (29a). Further rotation towards C-1 or C-5 would increase interactions with C-6-H-endo and C-5-H-endo, respectively (29b, 29c). The CD and ORD of this compound lend weight to this assumption. A similar preferred conformation would be expected for the 3-endo-nitro compound.(31a). Examination of models shows that a 3-exo-nitro group would adopt a conformation (30a) very similar to that of an endo-nitro compound, the main interaction being with the C-8-methyl group. Accordingly, signals are assigned to the methyl groups as shown in Table V. In pyridine and benzene, attempted assignments of signals to the 3-nitro-bornane mixture were unsuccessful, despite possible analogies to the 2-series.

TABLE V

Compound	Solvent	NO_2	C-8	C-9	C-10
2-endo-nitro-bornane (29)	CCl_4	endo	9.04	9.04	8.93
	C_5H_5N	endo	9.24	9.24	9.01
	C_6H_6	endo	(9.43)	(9.53)	9.10*
3-exo-, and 3-endo-nitro-bornane (30,31)	CCl_4	endo	9.04	9.04	(9.04)
		exo	(9.27)	(9.10)	(9.11)
	C_5H_5N	endo	9.21(6H), 9.26(6H),		
		exo	9.29(3H), 9.34(3H).		
	C_6H_6	endo	9.36(3H), 9.42 + 9.45 (12H),		
		exo	9.51 (3H).		

Chemical shifts in τ values. * denotes sharpest signal.

Figures in parentheses indicate uncertain assignment.

The n.m.r. spectral data of bornane compounds studied in the present work are recorded in Table VI. The spectra were analysed by first order treatment. In general, the features of proton coupling constants are in accord with those reported by other workers.[80-105] Often, however, the expected long range splitting of exo-protons produced only a broadening of the signal, i.e. $^4J < 0.5$ c.p.s., a smaller value than that predicted from previous results. The $J_{4,5N}$ coupling in bornan-2,3-dione (12) and

TABLE Vl.

TABLE VI

N.m.r. data for bornane compounds.

Chemical shifts and coupling constants are expressed in τ values and c.p.s., respectively. Solvents are denoted by numerals in column 3: 1, CCl_4; 2, $CDCl_3$; 3, C_5H_5N; 4, C_6H_6. ^{x} denotes the most intense methyl signal in the spectrum. The following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; u, unsymmetrical. x and n, in abbreviated compound names, and the subscripts X and N, in coupling constants, refer to the exo- and endo-configurations respectively. Uncertain assignments are given in parentheses.

Compound	No.		C-8	C-9	C-10	Other signals
Bornane		1	9.16	9.16	9.16	
		3	9.21	9.21	9.21	
		4	9.16	9.16	9.14^x	
2CO	11	1	9.17	9.04	9.15^x	
		2	9.16	9.04	9.09^x	
		3	[9.16][9.27]		9.12^x	7.67 bd. $J_{3X,3N}$ 18.0
						8.28 d. $J_{3N,3X}$ 18.0
		4	9.39	9.33	9.12^x	7.84 dq. $J_{3X,3N}$ 18.4
						$J_{3X,4}$ 4.2, $J_{3X,5X}$ 3.0
						8.45 d. $J_{3N,3X}$ 18.0
2NOH	1	1	9.07	9.17	9.01^x	7.45 dt. $J_{3X,3N}$ 18.0
						$J_{3X,4}$, $J_{3X,5X}$ 3.0
						0.72 s. NO.H
2xBr-2nNO$_2$	3	1	8.74	9.02	8.66^x	6.63 d. $J_{3N,3X}$ 16.2
						7.24 dt. $J_{3X,3N}$ 16.2
						$J_{3X,4}$, $J_{3X,5X}$ 2.4

TABLE V1 [continued]

Compound	No.		C-8	C-9	C-10	Other signals
$2NO_2$-$2NO_2$	10	1	9.08	8.98	8.53[x]	6.87 d. $J_{3N,3X}$ 16.2
						7.28 dbt. $J_{3X,3N}$ 16.2
3xd$_1$-2CO	28	4	9.39	9.33	9.12[x]	No signals below 8.3.
3xd$_1$-2NOH	117	1	9.07	9.17	9.01[x]	0.80 bs. NO.H
3xd$_1$-2Br-$2NO_2$	3'	1	8.73	9.02	8.65[x]	6.67 bt. $J_{3N,3X-d}$ 3.0
2OH-3CO	14	1	[9.16]	[9.12]	8.96[x]	6.22 s. C-2-H
						6.3 bs. O.H
3OH-2CO	13	1	[8.95]	[9.06]	[9.06]	5.83 d. $J_{3X,4}$ 4.8
						5.9 bs. O.H
Dimeric ether	15	1	[8.96]	[9.13]	[9.13]	6.71 bs. C-2-H
						6.85 s. O.Me
3CO	16	1	8.98	9.06	9.06	
		3	[9.21]	[9.24]	9.16[x]	
		4	9.27	9.27	9.37	
3NOH	5	1	[9.04]	[9.13]	9.10[x]	7.0 d. $J_{4,5X}$ 3.0
						0.42 s. O.H
3Br-$3NO_2$	7	1	[9.30]	[9.01]	9.06[x]	7.37 d. $J_{4,5X}$ 3.0
						6.90 m. 2 protons [C-2]
2CO-3CO	12	1	[8.93]	[8.93]	[9.08]	7.95 bd. $J_{4,5X}$ 3.9
anti-3NOH-2CO	21	1	[9.00]	[9.00]	[9.11]	6.72 bd. $J_{4,5X}$ 3.0
2nOAc		1	9.08	9.13	9.19[x]	5.18 dq. $J_{2X,3X}$ 9.6
						$J_{2X,3N}$ 3.6
						$J_{2X,6X}$ 2.0
						8.02 s. OAc

TABLE V1 [continued]

Compound	No.		C-8	C-9	C-10	Other signals
2xOAc		1	9.02	9.18	9.18	8.06 OAc
						5.36 ut. C-2-H-endo
		3	[9.01]	[9.23]	9.16[x]	8.03 OAc
						5.21 ut. C-2-H-endo
		4	[9.02]	[9.29]	9.17[x]	8.31 OAc
						5.25 t. $J_{2N,3X}$, $J_{2N,3N}$ 6.0
3nBr-2CO	32	1	8.90	9.04	9.06[x]	5.43 q. $J_{3X,4}$ 4.9
						$J_{3X,5X}$ 0.9
		3	[9.10]	[9.11]	[9.20]	5.25 s. C-3-H-endo[trace]
						5.03 q. $J_{3X,4}$ 4.8
						$J_{3X,5X}$ 1.2
		4	[9.33]	[9.48]	9.20[x]	5.61 q. $J_{3X,4}$ 4.5
						$J_{3X,5X}$ 1.3
3Br-3NO_2-2CO	33	1	8.80	8.90	8.96[x]	7.16 bd. $J_{4,5X}$ 3.0
		4	[9.18]	[9.55]	9.29[x]	7.70 bd. $J_{4,5X}$ 3.4
3nNO_2-2CO	34	1	8.91	9.07	9.03[x]	7.29 bm. C-4-H
						5.55 bs. C-3-H-endo
						5.02 bd. $J_{3X,4}$ 4.8
		4	[9.71]	[9.56]	9.29[x]	7.90 bd. $J_{4,5X}$ 5.4
						6.14 bs. C-3-H-endo
						5.32 bd. $J_{3X,4}$ 5.4

3-hydroxyiminocamphor (21) reported by Tori[95] is illusory. The two compounds show broad C-4 doublets. In the case of bornan-2,3-dione (12), the C-4 resonance (7.95τ) is very close to the methylene envelope, and the broadening may, therefore, be due to second order effects. The spectrum of 3-hydroxyiminocamphor will be discussed in Section IV. In compounds (3) and (10) the usual chemical shift relationship between endo- and exo-protons is reversed, the exo-proton absorbing at higher field. This seems to be a consequence of the anisotropic deshielding of the nitro group.

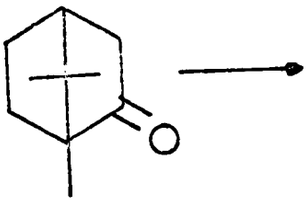
Assignment of the C-3 proton signals in camphor, 2-hydroxyiminobornane (1) and 2-bromo-2-nitrobornane (3a) was made possible by the use of the 3-exo-deuterio analogues. The exo-3-proton, in the case of camphor, is resolved in benzene (7.84, doublet of quartets) and disappears on the introduction of the 3-exo-deuterium atom. At the same time, a sharp singlet, attributable to the endo-3-proton appears in the methylene envelope. A similar deshielding of α-methylene protons is not observed in bornan-3-one (16).

Methyl signals in camphor are assigned according to Connolly and McCrindle.[115] The resonances of C-8 and C-9 occur at similar chemical shifts in CCl_4 and $CDCl_3$. The deshielding of C-10 on passing from CCl_4 to $CDCl_3$ is unusually large. The C-10 signals may be assigned reliably on the basis of their sharpness. The methyl signals at 9.16 and 9.04 ($CDCl_3$), 9.39 and 9.33τ (C_6H_6) have been ascribed to C-8 and C-9, respectively.[87,115] In the absence of deuterium labelling, however, these assignments are open to criticism, since the greater proximity of C-8 to the carbonyl function should lead to a deshielding relative to C-9. The use of solvent shifts

(see Section III) does not provide any useful information, as it is difficult to predict the size of the solvent shift for each of the methyl groups in camphor. Similar difficulties are encountered in bornan-3-one (16). Here assignments are recorded, made on the basis that, in CCl_4, C-8 should be deshielded relative to the C-9 and C-10 methyl groups. These latter should have similar chemical shifts and, while the solvent shifts of C-8 and C-9 should be the same as in camphor, that of C-10 should be markedly different. In pyridine, the methyl signals of camphor and bornan-3-one cannot be assigned.

No self consistent pattern of substituent effects on the methyl signals can be seen in the spectra of the compounds studied: thus most assignments are tentative. The anisotropy of the groups present - carbonyl, oxime and nitro - produce uncharacteristic shifts in this system and make assignments difficult. In this respect, therefore, the present work substantiates the difficulties of working with anisotropic groups, as mentioned by Tori et al.[95]

COMPOUNDS 32-41.



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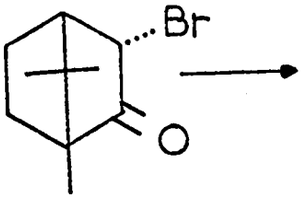

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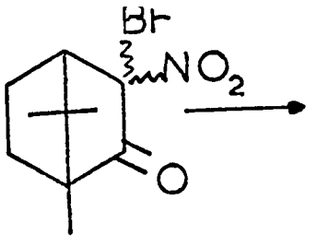

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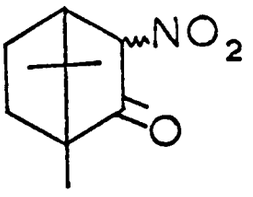

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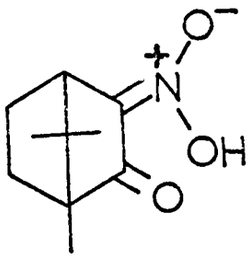

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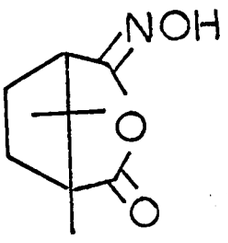

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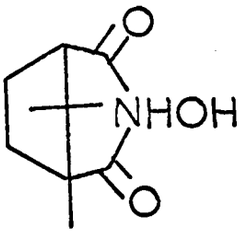

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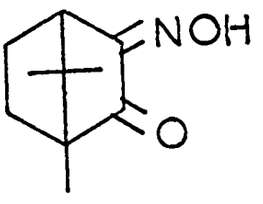

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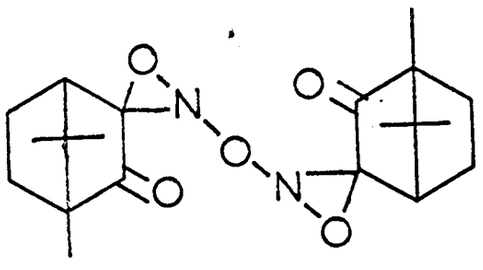

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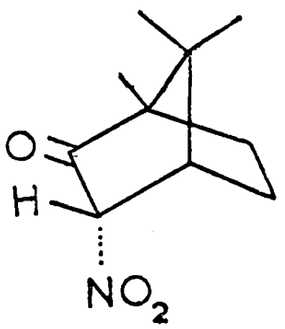

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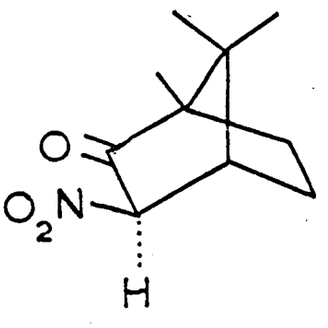

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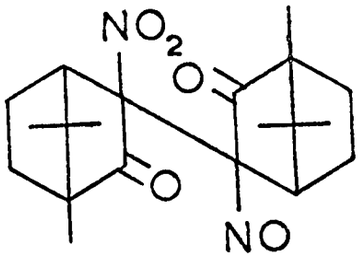


[39]

Section I

Part (iv)

3-Nitrocamphor

As a parallel investigation to the study of α-nitroketo-steroids, it was decided to prepare 3-nitrocamphor (34), a typical non-enolic nitroketone. This would provide an opportunity to re-examine the chemistry of this and related compounds, in the light of modern techniques. These compounds were first prepared over sixty years ago and have attracted scant attention in the intervening years.

3-Nitrocamphor (34) (designated the α form) was first prepared in an impure form by Schiff[124] by reducing 3-bromo-3-nitrocamphor (33) with alcoholic KOH. 3-Bromo-3-nitrocamphor was obtained on nitric acid treatment of 3-bromocamphor (32), the latter being formed by heating camphor and bromine at 100° for 20 hr. Later, he reported preparations involving reduction of 3-bromo-3-nitrocamphor and 3-chloro-3-nitrocamphor with a zinc-copper couple. These results were substantiated by Cazeneuve,[125] who also claimed to have obtained a second nitrocamphor (α') from the mother liquors in the preparation of α-nitrocamphor. In 1898, Lowry[126] established that α' compound was an impure form of α-nitrocamphor. He modified the preparation by treating 3-bromo-3-nitrocamphor (33) with aqueous ethanolic KOH and obtained 3-nitrocamphor from camphor in an overall yield of 13%.

Forster[54] showed that phenyl hydrazine was a better reducing agent than KOH; a further modification of the reduction stage was made by

Lowry and Steele[127] who used sodium methoxide and raised the overall yield from camphor to 50%. They also noted that 3-nitrocamphor could be prepared in quantitative yield by oxidising 3-hydroxyiminocamphor (18) with potassium permanganate, a preparation similar to Forster's earlier potassium ferricyanide oxidation of the same compound.[128] Bell,[129] however, reported low yields (40%), and indicated that this preparation was suitable only on a small scale.

The main features of interest in the chemistry of 3-nitrocamphor have been (a) the phenomenon of mutarotation, and (b) the rearrangements and condensation reactions which 3-nitrocamphor undergoes. Freshly prepared solutions of 3-nitrocamphor suffer a change of rotation upon standing. This is the phenomenon of mutarotation. Lowry[126, 127, 130] showed that the change was dependent of concentration and solvent, and was catalysed by acids and bases. His interpretation of these results - that mutarotation was due to a partial conversion of 3-nitrocamphor into its aci-form (35) - was shown by Bell[129] to be in conflict with the published evidence. A study of the kinetics of mutarotation led Bell to postulate that the change was due to the interconversion of two stereoisomers.

3-nitrocamphor undergoes a modified Nef reaction in the presence of acid. The product was formulated as an oximino compound (36) by Lowry.[126] Larson and Watt[131] established, by unambiguous synthesis, that the product was, in fact, N-hydroxycamphor imide (37). This unusual Nef rearrangement occurred in high yield under acidic or basic conditions. The formation of anhydrides of the structure (38) from 3-nitrocamphor upon heating,

alone or in DMF, was reported by Lowry.[126,127] Larson et al.[132] showed that a more probable structure was (39).

Attempts were made in the present study to brominate camphor under less vigorous conditions than those reported.[127] However, treatment of camphor with bromine in refluxing ether, or in acetic acid containing HBr at 20° afforded starting material only. The nitration of camphor with ethyl nitrate under basic conditions at 20°, as described in Section II, was attempted but no reaction ensued. The two stage synthesis of 3-nitrocamphor by oxidation of 3-hydroxyiminocamphor (18) with permanganate appeared to be a convenient method, but this route was not at all satisfactory. 3-Hydroxyiminocamphor was prepared in 38% yield from camphor by Claisen and Manasse's method.[72] The oxidation of this compound in acetone-water with the theoretical amount of potassium permanganate was not successful. In every case, the product exhibited an ir spectrum very similar to that of 3-nitrocamphor, but no crystalline material could be isolated. In view of these results, 3-nitrocamphor was prepared according to Lowry's method.[127]

The product was a sharp melting compound (102-103°), consistent with its formulation as a single stereoisomer,[127] and exhibited mutarotation. In benzene, at 20°, the specific rotation fell from -116° to 92° over four days. In deuteriochloroform, at 34°, the mutarotation of a 10% solution was slower, falling from -25° to -8° over a week. Both these observations are in good agreement with Lowry's results.[130] The n.m.r. spectrum of 3-nitrocamphor, when first dissolved in deuteriochloroform, shows a doublet at 4.89τ. The intensity of this signal fell slowly over a week. The n.m.r.

spectrum of 3-nitrocamphor in CCl_4 and benzene shows two low field signals immediately (Table VI, this Section): the predominant signal was a doublet (J = 4.8 and 5.4 c.p.s. in CCl_4 and benzene, respectively). The second signal, 0.53 and 0.82τ respectively, upfield from the first signal was a broad singlet. At mutarotation equilibrium, as judged by the specific rotation, these signals appear in the ratio 4:1 (doublet to singlet). By assuming that the specific rotation of the form into which 3-nitrocamphor mutarotated was +180°, Lowry[130] calculated that equilibrium rotation was consistent with a mixture containing 93% of the original form and 7% of the form into which it mutarotated. It seems likely that the two low field signals in the n.m.r. spectrum of 3-nitrocamphor arise from its two possible epimers, and hence provide confirmation of Bell's postulate[129] that mutarotation is due to the interconversion of stereoisomers. The doublet can be ascribed to 3-endo-nitrocamphor (40), since only an exo-proton at C-3 can couple with the proton at C-4. The singlet at higher field is assigned to the endo-proton of 3-exo-nitrocamphor (41) - being unable to couple with the C-4 proton. The configuration of the nitro group in the isolable nitrocamphor is thus endo.

A study of the literature reveals many unsuccessful attempts to isolate the second epimer (3-exo-nitrocamphor) by fractional crystallisation. In view of the incidence of mutarotation, this is hardly surprising. Furthermore, the identification of this compound would be complicated by mutarotation which is known to be catalysed by trace amounts of acids and alkalis, and which may thus convert the compound rapidly into the equilibrium mixture.

Section I

Part (v)

Experimental

Melting points were determined on a hot stage and are uncorrected. Sealed tubes were used in the determination of the melting points of most bornane compounds. Rotations were measured by a Perkin-Elmer 141 photoelectric polarimeter in chloroform solutions, unless otherwise stated. Ultraviolet spectra were recorded for ethanol solutions, unless otherwise stated, with a Cary 14M spectrometer, and infrared spectra for CCl_4 solutions with Perkin-Elmer model 237 or 521 grating spectrometers. N.m.r. spectra were recorded by a Perkin-Elmer R.10 60 Mc/s instrument; the solvents which were used are described in the discussion sections. G.l.c. was carried out, in the case of bornan-3-one, on a DE 208 column (polypropylene glycol on Chromosorb w) at 100° in a Perkin-Elmer F11 gas chromatograph, and, in the case of the nitrobornanes, on a 15% carbowax column at 120° on a gas chromatograph made in this Department.

Neutral alumina was prepared by stirring P. Spence material (Grade H) with an excess of ethyl acetate for 2 days, filtration, washing thoroughly with water, and heating at 250° for 2 days. Deactivated alumina was prepared by treating neutral alumina with the requisite amount of water, and shaking for 24 hr. The silica gel used was Chromedia SG31, unless otherwise stated. This adsorbent was activated, before use, by storage at 110°. Deactivated silica gel was prepared by treating the activated material with the requisite percentage of water (w/w). Light petroleum refers to the

fraction boiling between 60 and 80°.

Dioxan was purified by reflux for 12 hr. with 10-N-HCl (1.5% v/v.) in a stream of nitrogen. Solid KOH was added and the aqueous layer removed. The liquid was stood over KOH for 24 hr., decanted, and refluxed for 12 hr. with sodium and distilled. THF was purified by reflux over sodium, a trace of benzophenone was added, and when the solution developed a blue colour, it was distilled, the fraction boiling between 65 and 67° being collected. This solvent was stored in sealed ampoules in a desiccator, and is extremely hygroscopic. Diethylene glycol was purified by standing over KOH at 100° for 24 hr. and distillation, the fraction boiling at 126°/10 mm. being collected. Acetic acid was purified by two refluxions and distillations from chromium trioxide (10% w/w.). Bu^tOK was sublimed before use at 190°/0.1 mm. Mercury was purified by shaking, successively, with ether, water, dilute nitric acid and water until the aqueous layer was neutral.

2-Hydroxyiminobornane (1): (+) - Camphor (10 g.), hydroxylamine hydrochloride (12 g.) and sodium acetate (20 g.) in ethanol-water (200 ml., 9:1) were refluxed for 1.5 hr. The product was poured into water, collected at the pump and recrystallised from light petroleum to give 2-hydroxyiminebornane, m.p. 116-117° [lit.,[133] m.p. 116-117°].

2-Bromo-2-nitrobornane (3): N-Bromosuccinimide (785 mg.) was added, slowly, in portions, to a stirred mixture of 2-hydroxyiminobornane (412 mg.) and $KHCO_3$ (2 g.) in dioxan-water (24 ml., 1:1) at 20°. The blue solution was stirred until colourless (20 hr.), poured into water and extracted with ether. After drying and evaporation, the product was adsorbed on to

alumina (10 g., 5% deactivated) from light petroleum. Elution with light petroleum (25 ml.) afforded 2-bromo-2-nitrobornane (435 mg.), m.p. 215-218°, $[\alpha]_D$ - 59° (C. 1.0), ν_{max} 1552 cm.$^{-1}$ [lit.,[53] m.p. 220° $[\alpha]_D$ - 55° (EtOH)].

2-Nitrobornane (4): 2-Bromo-2-nitrobornane (1 g.) in ethanol-water (30 ml., 2:1) was treated with sodium borohydride (1 g.) at 20°. After 2 hr., excess reagent was destroyed with hydroxylamine hydrochloride, and the solution poured into water. The crude product was collected at the pump and sublimed at 100°/5 mm. to give 2-nitrobornane (540 mg.), m.p. 154-158°, $[\alpha]_D$ + 10° (C. 0.8) ($CHCl_3$) and + 9° (C. 1.0) (EtOH), ν_{max} 1554 cm.$^{-1}$ [lit.,[54] m.p. 157°, $[\alpha]_D$ + 7.4° (EtOH)].

2,2-Dinitrobornane (9): Fuming nitric acid (20 ml., freshly distilled and treated with urea) was added over 1 min. to 2-hydroxyiminobornane (20 g.) in acetic acid (200 ml.) at 20°. After 15 min. shaking, an intense blue colour had developed and hydrogen peroxide (10 ml., 100 vol.) was added and the mixture shaken until colourless water was added and the product extracted into ether. The extract was washed with aqueous $NaHCO_3$ and water, dried and the solvent removed *in vacuo* at 20°. The product was absorbed on to alumina (400 g., H). Light petroleum-benzene (1 l., 20:1) eluted 2,2-dinitrobornane (15.4 g.), m.p. 108-112°, $[\alpha]_D$ - 120° (C. 1.0), ν_{max} 1547 cm.$^{-1}$ [lit.,[59] m.p. 107-109°].

Hydrogenolysis of 2,2-dinitrobornane (9): 2,2-Dinitrobornane (0.5 g.) in ethyl acetate (30 ml.) was hydrogenated with prereduced Adams catalyst (100 mg.). After the absorption of *ca.* 4 mols. of hydrogen, the reaction was stopped and the filtered solution evaporated. The crude product was

sublimed at 100°/5 mm. to give 2-nitrobornane (362 mg.); m.p. 154-158°, $[\alpha]_D$ + 10° (C. 0.9).

3-exo-deuteriocamphor (28): (+) - Camphor (5 g.) in dioxan-deuterium oxide (32 ml., 1:1) containing sodium (300 mg.) was stirred for 5 days at 20°. Ether was added, and the ether layer separated, dried and evaporated, affording 3-exo-deuteriocamphor (4.55 g.). Mass spectrometry showed that the product contained 76% d_1, 10% d_2, and 14% d_o [lit.,[76] 86% d_1].

2-Hydroxyimino-, 2-bromo-2-nitro-, and 2-nitro-3-exo-deuteriobornane were prepared in the same manner as the undeuterated compounds. Mass spectrometry showed that no exchange of deuterium occurred during this sequence of reactions. 2-Nitro-3-exo-deuteriobornane was shown to contain 75% d_1.

Attempted equilibrations of 2-nitrobornane (4): A 2-Nitrobornane (50 mg.) was refluxed in ethanol-water (5 ml., 9:1) saturated with $NaHCO_3$ for 8 hr. The cooled solution was poured into water and extracted into ether. After drying and evaporation, the product was sublimed at 100°/5 mm. to give 2-nitrobornane, m.p. 156-157°, showing a single peak on g.l.c. (Retention time 9 min.), identical with the starting material.

B 2-Nitrobornane (50 mg.) was refluxed with 0.5% ethanolic KOH (10 ml.) for 18 hr. The solution was cooled to 0° and carefully acidified with acetic acid. After working up in the usual manner, the product was shown to be identical with starting material (m.p. 156-157°, single peak on g.l.c., retention time 9 min.).

Bornan-2,3-dione (12): (+) - Camphor (100 g.) was treated with selenium dioxide (120 g.) according to the method of Simonsen et al.[62]

The product was crystallised from light petroleum to give bornan-2,3-dione (98 g.), m.p. 198-199°, ν_{max} 1777 and 1759 cm.$^{-1}$ [lit.,[62] m.p. 198°].

The ketol mixture (13, 14): Bornan-2,3-dione (33.5 g.) in boiling acetic acid (67 ml.) was added rapidly, with vigorous stirring, to boiling water (600 ml.), producing a fine suspension. Zinc dust (33.5 g.), as a slurry in water (100 ml.) was added to the refluxing suspension which was then boiled for 1.5 hr. After cooling and filtration, 10N-KOH was added until the initial precipitate had redissolved, and the solution extracted with ether. After drying, evaporation afforded the crude ketol mixture (33.6 g.), m.p. 205-207° [lit.,[64] m.p. 203-205°].

Methylation of the ketol mixture: The ketol mixture (15.3 g.) was dissolved in dry methanol (10 ml.) and dry HCl gas passed into the solution for 10 min. After 2 days, the crystalline product (5.0 g.) was filtered off and recrystallised from methanol affording the dimeric methyl ether (15), m.p. 150-151°, ν_{max} 1115, 1050 and 1000 cm.$^{-1}$ [lit.,[60] m.p. 150°].

The reaction mixture mother liquors were evaporated, and the oily residue crystallised from light petroleum yielding 3-hydroxybornan-2-one (13) (4.8 g.), m.p. 197-199°, $[\alpha]_D$ - 12° (C. 1.2), ν_{max} 3585 and 1752 cm.$^{-1}$ [lit.,[60] m.p. 198°].

2-Hydroxybornan-3-one (14): The dimeric methyl ether (15) (7.3 g.) was stirred with 10N-HCl (18.6 ml.) for 5 hr., water (100 ml.) was added. The solution neutralised with Na_2CO_3 and saturated with NaCl. The product was collected at the pump and recrystallised from light petroleum to give 2-hydroxybornan-3-one (4.7 g.), m.p. 219-220°, $[\alpha]_D$ 0° (C. 0.9) ν_{max} 3585 and 1752 cm.$^{-1}$ [lit.,[60] m.p. 221°].

Reduction of 2-hydroxybornan-3-one: A solution of 2-hydroxybornan-3-one (4.4 g.) in water (200 ml.) was added, dropwise in 40 ml. portions, over a total of 45 min. to a vigorously shaken mixture of water (50 ml.) and sodium amalgam (100 g., 5%). After the addition of each portion of ketol solution, a further portion (125 g.) of the sodium amalgam was added. The solution was shaken for a further 4 hr. and the grey product filtered off. This was dissolved in ether, dried, filtered and the solution evaporated affording crude bornan-3-one (4.05 g.) (shown by g.l.c. to contain ca 5% camphor).

Bornan-3-one semicarbazone (17): Bornan-3-one (3.25 g., obtained from the previous experiment) in ethanol (6 ml.) was added to a solution of semicarbazide hydrochloride (1.85 g.) and sodium acetate (2.2 g.) in water (5 ml.). After 12 hr., the precipitate was collected and dried. Recrystallisation from ethanol gave bornan-3-one semicarbazone (2.7 g.), m.p. 240° [lit.,[60] m.p. 240°].

Bornan-3-one (16): Bornan-3-one semicarbazone (2.7 g.) and oxalic acid (2.7 g.) in water (250 ml.) were steam distilled for 2 hr. After ether extraction and drying, evaporation yielded bornan-3-one (1.5 g.) m.p. 178-179°, [lit.,[60] m.p. 186-187°]. G.l.c. showed that < 0.5% camphor was present.

3-Hydroxyiminocamphor (18): (+) - Camphor (102 g.) was hydroxyiminated according to the method of Claisen and Manasse.[72] The product [38.2 g., λ_{max} 243 mμ (ε 5830), $\lambda_{max}^{2N\text{-KOH}}$ 296 mμ (ε 13500)] was shown by its m.p. [some fusion, 110-115°; resolidification, 120°; complete fusion, 149-150°] and its ir spectrum - ν_{max} 1747, 1712, 1647 and 1602 $cm.^{-1}$ to be a mixture

of the syn- and anti-forms. Fractional crystallisation from benzene-light petroleum afforded anti-3-hydroxyiminocamphor, m.p. 149-150°, ν_{max} 1765 and 1660 cm.$^{-1}$, λ_{max} 206 mμ (ε 2440), 240 mμ (ε 8200), $\lambda_{max}^{KOH-EtOH}$ 290 mμ (ε 13400).

Attempted separations of syn- and anti-3-hydroxyiminocamphor (22, 21): (a) 1 g. of the isomeric mixture was dissolved in 10% aqueous NaOH (10 ml.) and cooled to 0°. 20% aqueous acetic acid was added, dropwise, with vigorous stirring for 2 min. after each addition (1 drop). When precipitation began (after the addition of ca. 1 ml.), the solution was filtered after the addition of each drop of acid, the precipitate dried and evaluated by ir. The parent mixture contained approximately equal amounts of each isomer, as indicated by the equal intensity of 1760 and 1720 cm.$^{-1}$ bands. Early fractions showed 10-20% enrichment of the syn- isomer, but despite many variations in the conditions of the experiment - different concentrations of acid, alkali and compound and the use of mineral acid - the pure syn- isomer could not be obtained. An alkaline solution of the anti-isomer, under identical conditions afforded unchanged anti-form on acidification.

(b) Sublimation at 55°/0.1 mm. for 2 hr. afforded 100 mg. of the isomeric mixture, slightly richer in the syn- isomer than that obtained in (a).

(c) The isomeric mixture (10 mg.) was heated at 150° on a Kofler block for 10 min. Almost complete conversion to the anti-form was indicated by allowing part of the melt to cool to 100°, and redetermining its m.p. - 150°-152°. The ir spectrum of the remainder showed the presence of < 5%

of the syn-form.

(d) The isomeric mixture was also converted to the anti-form on heating a solution in diethylene glycol at 150° for 2 hr., and by refluxing an ethanolic solution in the presence of hydrazine hydrate (ca. 40 mols.) for 18 hr.

3-Hydroxyiminobornane (5), 3-bromo-3-nitrobornane (7), and the 3-nitrobornane mixture (29, 30) were prepared in an analogous manner to the corresponding 2-substituted bornanes. The physical constants and yield of each compound are reported below.

3-Hydroxyiminobornane (5): 99%; m.p. 104-105°; $[\alpha]_D$ + 94° (C. 1.0); ν_{max} 1690 cm.$^{-1}$ [lit.,[61] m.p. 104-105°, $[\alpha]_D$ + 99° (C. 4.0) (benzene)].

3-Bromo-3-nitrobornane (7): 82%; m.p. 43-53°; $[\alpha]_D$ + 90° (C. 1.0). ν_{max} 1556 cm.$^{-1}$ (Found: C, 46.2; H, 6.1; N, 6.4. $C_{10}H_{16}BrNO_2$ requires C, 45.8; H, 6.1; N, 5.4%).

The 3-nitrobornane mixture (29, 30): 99%; m.p. 80-95°; $[\alpha]_D$ + 54° (C. 1.0); ν_{max} 1548 cm.$^{-1}$ (Found: C, 65.6; H, 9.2; N, 7.6. $C_{10}H_{17}NO_2$ requires C, 65.6; H, 9.3; N, 7.6%).

Deuterated bornan-3-one: Bornan-3-one was deuterated by the same procedure as camphor. After 5 days, mass spectrometry showed that deuterium incorporation was 65% d_1, 28% d_2, 7% d_o. After 10 days incorporation was 6% d_1, 94% d_2.

Attempted equilibrations of the 3-nitrobornane mixture: The mixture (50 mg.) was refluxed with ethanol-water (20 ml., 9:1) saturated with $NaHCO_3$ for 18 hr. After working up in the usual manner, the product was shown by g.l.c. (two peaks, retention times 9.8 and 10 min.) and n.m.r. to

be identical in composition to the starting material.

The mixture (50 mg.) was refluxed with 0.5% ethanolic KOH (20 ml.) for 20 hr., cooled to 0° and acidified with acetic acid. After the usual working up procedure, the product was shown by g.l.c. and n.m.r. to be identical in composition to the starting material.

3-endo-Bromocamphor (32): Bromine (40 g.) was added over 2 hr. to (+) - Camphor (40 g.) on a steam bath. After a further 5 hr., the product was poured into a saturated solution of sodium sulphite, filtered and crystallised three times from methanol to give 3-endo-bromocamphor (32) (29 g.) as rods, m.p. 74-76°, $[\alpha]_D$ + 134° (C. 1.1), ν_{max} 1762 cm.$^{-1}$ [lit.,[134] m.p. 74°, $[\alpha]_D$ + 169° (EtOH)].

3-Bromo-3-nitrocamphor (33): 3-endo-Bromocamphor (20 g.) was added to nitric acid (200 ml., d. 1.4) and the mixture refluxed for 20 hr., then poured into water and neutralised. After filtration the product was crystallised twice from methanol to give 3-bromo-3-nitrocamphor as needles, m.p. 108-109°, $[\alpha]_D$ - 27° (C. 0.9), ν_{max} 1774 and 1545 cm.$^{-1}$ [lit.,[134] m.p. 104°, $[\alpha]_D$ - 27° (EtOH)].

3-Nitrocamphor (34): 3-Bromo-3-nitrocamphor (12 g.) was dissolved in ethanol (10 ml.) and added to a sodium methoxide solution [sodium (1 g.) in methanol (25 ml.)] at 100°. The bright yellow product was collected and treated at 0° with 2N-HCl. After dilution with water and filtration, the product was crystallised from light petroleum (30-40°) affording 3-nitrocamphor (7.4 g.) as needles, m.p. 102-103°, $[\alpha]_D$ - 29° (C. 1.0), λ_{max} 279 mμ (ε 170), λ_{max}^{KOH} 317 mμ (ε 13600), ν_{max} 1770 and 1554 cm.$^{-1}$ [lit.,[54] m.p. 102-103°, $[\alpha]_D$ - 29°].

Bornane: A solution of (+) - Camphor (5 g.) and hydrazine hydrate (8 ml.) in diethylene glycol (200 ml.) was heated at 150° for 3 hr. After carefully allowing water vapour to escape, the solution was cooled, KOH (5 g.) added and the solution refluxed for 6 hr. The product (3.6 g.) which sublimed out of the reaction mixture during this period, was collected from the upper regions of the condenser, and resublimed (60°/760 mm.) to give bornane, m.p. 158-159° (Found: C, 86.9; H, 12.9. Calculated for $C_{10}H_{18}$: C, 86.9; H, 13.0%) [lit.,[135] 149-151°].

1-Hydroxyimino-2,6-d_4-4-t-butylcyclohexane: 4-t-butylcyclohexanone[136] (5 g.) was heated under nitrogen at 100° for 1 hr. with a solution (50 ml.) prepared by dissolving sodium (300 mg.) in dioxan (185 ml.) and deuterium oxide (16 ml.). The solution was then evaporated on a rotatory evaporator at 20°/0.1 mm. The ketone was treated in a similar manner with three more portions (50 ml.) of the deuterating solution. After evaporation of solvent, ether was added, and the ether layer separated and dried. Evaporation and crystallisation from acetone afforded a product (4.46 g.), m.p. 48-49°, which was shown by mass spectrometry to contain 4 deuterium atoms per molecule.

The ketone (4.4 g.), hydroxylamine hydrochloride (6 g.) and sodium acetate (10 g.) in ethanol-water (220 ml., 10:1) was refluxed for 15 min. The solution was poured into water and the product, collected at the pump and dried, had m.p. 135-136°.[137] Mass spectrometry showed that no exchange of deuterium had occurred.

Similar treatment of 4-methylcyclohexanone afforded, after distillation at 100°/0.1 mm., 2,6-d_4-4-methylcyclohexanone oxime, m.p. 35-36°.[137]

Section II

α-NITROKETO-STEROIDS AND RELATED COMPOUNDS

Part (i)

General preparative methods

The preparation of steroidal α-nitroketones was the original object of the work to be described in this Section. However, as the work progressed, it became clear that an investigation of compounds related to α-nitroketones would be of interest - with a view to the possible synthesis of vicinal-dinitro compounds. Projected work on the latter aspect was restricted to compounds derived from the 3-ketone. Previous work on these types of compound is summarised in this Part; the present work is described in Part (ii).

Preparative methods available for the synthesis of these types of compound can be conveniently divided into two parts - substitution of active methylene groups - involving the formation of α-nitro-, and α-hydroxyiminoketones - and addition to olefinic double bonds - where compounds containing two vicinal nitrogen substituents are described.

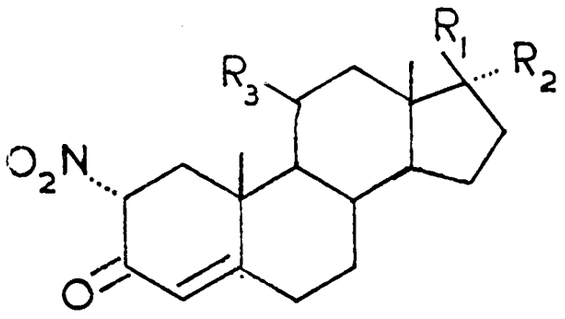
(a) Substitution of active methylene groups: Early work in this field was carried out by Wislicenus et al.[138] who showed that condensation with ethyl nitrate and alkali metal ethoxides of fluorene, arylacetonitriles and arylacetic esters afforded high yields of the corresponding aci-nitro salts.[139] More recently, reactions of this type have been extended to cyclic ketones,[140] aliphatic nitriles, ketones and dinitriles.[141]

The reaction is extremely sensitive to a number of factors. In order to achieve consistently high yields considerable experimentation is necessary. Fuer and co-workers[140,141] established optimum conditions for the nitration of monocyclic ketones. Working at -30°, and adding the ketone to base, minimised self-condensation, which became important only when ketone and base were in contact for over 30 minutes. Carefully purified Bu^tOK, rather than Bu^tONa, was used as the base, because of its greater ability to remove the alcohol, formed in the reaction, by strong hydrogen bonding. The inherent instability of the aci-nitro salts formed demands careful treatment of the products to avoid Nef rearrangements. Initially, this was overcome by bromination of the intermediates,[142] but it was later shown that careful protonation of the bis-condensation products of some cyclic ketones afforded α,ω-dinitroalkanes.[143]

In the steroid field, a 1:1 mixture of 16α-, and 16β- nitroandrost-5-en-3β-ol-17-one was formed in unspecified yield from the parent ketone by means of base catalysed nitration by Hassner et al.[144] These workers also prepared the analogous 5,6-dihydro compound and 2-nitro-5α-cholestan-3-one (42), m.p. 135-136°.

Schaub, Fulmer and Weiss[145] prepared certain α-nitroketones for biological evaluation, using Fuer's method.[140,141] From Δ^4-3-ketones, they prepared the 2α-nitro derivatives of progesterone (43), deoxycorticosterone (44), hydrocortisone (45), testosterone (46), and 17α-methyl testosterone (47) in 70,18,5,40 and 9% yields, respectively. It was inferred that a free hydroxyl group interfered with the reaction as the

TABLE V11.

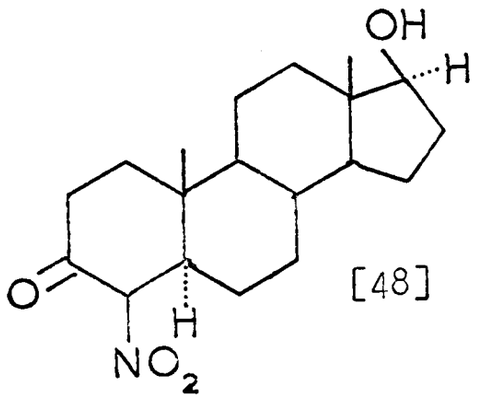


[43] R_1 -OC.CH_3; R_2,R_3 -H.
[44] R_1 -OC.CH_2.OH; R_2,R_3 -H.
[45] R_1 -OC.CH_2.OH; R_2,R_3 -OH.
[46] R_1 -OH; R_2,R_3 -OH.
[47] R_1 -OH; R_2 ~~-H~~ -H. R_3 -Me.

$\lambda_{max.}^{neut.}$ 243 mμ [13000]

$\lambda_{max.}^{0.1\underline{N}HCl}$ 252 mμ [15000]

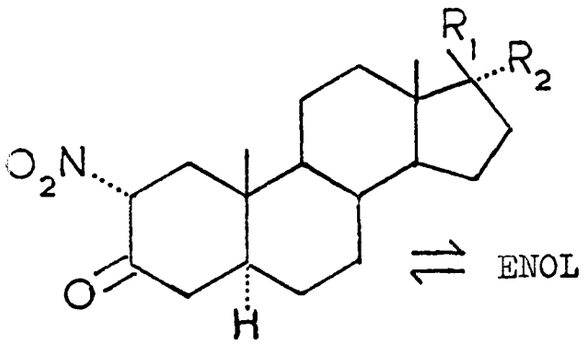
$\lambda_{max.}^{0.1\underline{N}NaOH}$ 244 mμ [8000],
267 mμ [7000],
354 mμ [12000].



[48]

No uv absorption in neutral or acidic media.

$\lambda_{max.}^{0.1\underline{N}NaOH}$ 232 mμ [10000].



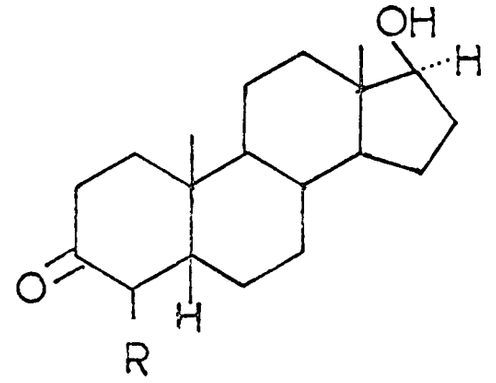
[49] R_1 -OH; R_2 -CH_3.
[50] R_1 -C_5H_8O; R_2 -H.

$\lambda_{max.}^{neut.}$ 330 mμ.

$\lambda_{max.}^{0.1\underline{N}HCl}$ 338 mμ [7000].

$\lambda_{max.}^{0.1\underline{N}NaOH}$ 230 mμ [5000],
340 mμ [11000].

6.45 τ quartet, C-2-H
-4.2 τ singlet, -O.H.



[51] R -H.
[52] R -NO_2.

$\lambda_{max.}^{0.1\underline{N}NaOH}$ 235 mμ [12000],
338 mμ [503].

$\lambda_{max.}^{0.1\underline{N}Bu^tOK}$ 348 mμ [6030].

9.22 τ, [C-18]; 8.83 τ, [C-19];
4.25 τ, [C-4-H].

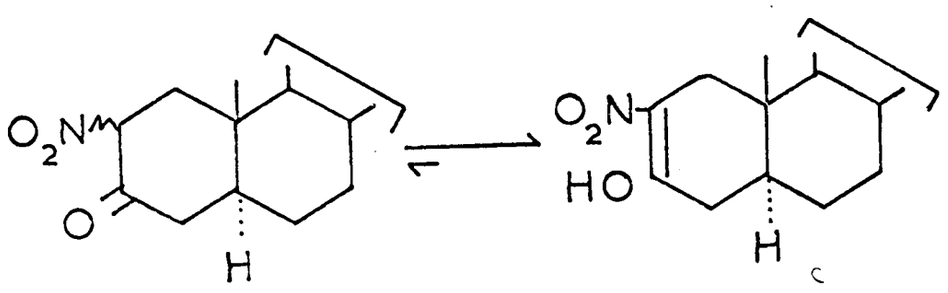
17β-tetrahydropyranyloxy-derivative of (46) reacted to give 42% of the nitro compound. The 20-ketone group, where present, was protected as its ethylene ketal. The nitro group was shown, spectroscopically, to be inserted in the 2α-position. (The spectral data for the nitroketones prepared by these workers are shown in Tables I and VII.)

Testosterone (46) was supposedly nitrated in the 4-position by the use of lithium in liquid ammonia and amyl nitrate.[145] This compound (48) was not fully characterised, but its entirely ketonic nature would preclude 2-substitution (see below). The lack of absorption in the uv spectrum in non-alkaline media indicated the absence of unsaturation.

Nitration of the saturated 3-ketones, 17β-hydroxy-17α-methyl-, and 17β-tetrahydropyranyloxy-5α-androstan-3-one, under Fuer conditions, afforded mixtures of the corresponding 2α-nitroketones (49,50) and their enols in 51 and 52% yield, respectively.[145] Enolisation was indicated, in the ir spectrum, by the appearance of a strong C=C absorption at 1620-1630 cm^{-1}, and a nitro band at 1515-1520 cm^{-1}, and the uv spectrum, by a major absorption at 330 mμ in neutral medium, the intensity of which varied with solvent.

In the 5β-series, the saturated 3-ketone (51) afforded the corresponding 4β-nitro compound (52) in 32% yield. That this compound had the stated configuration was shown from the n.m.r. spectrum, which exhibited a low field doublet, $J_{4\alpha,5\beta}$ = 13 c.p.s. This nitroketone was shown to be non-enolic, and to explain its unusual behaviour in basic media, as indicated by its uv spectrum, it was postulated that small anions (^{-}OH and ^{-}OMe)

COMPOUNDS 42, 53-62.



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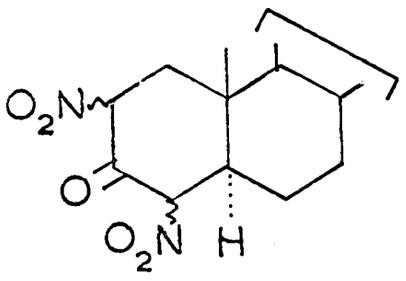

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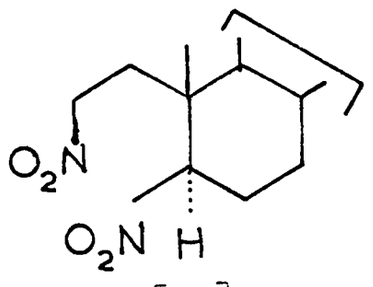

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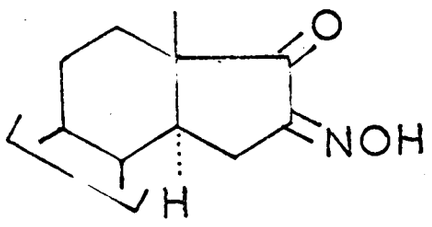

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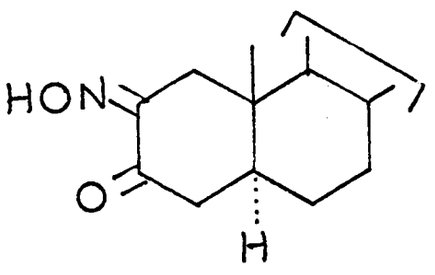
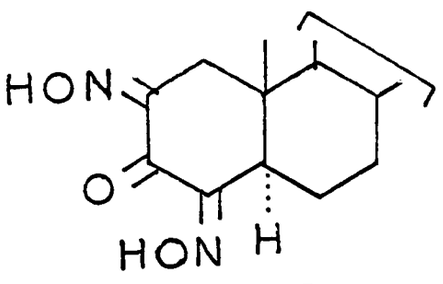


[56]



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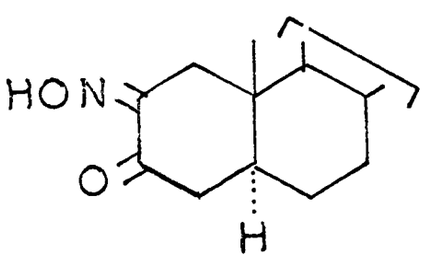

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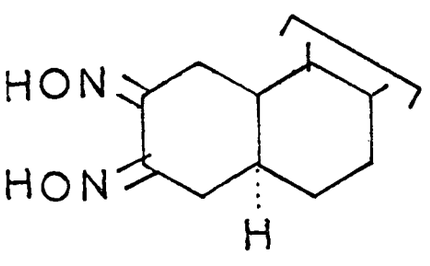
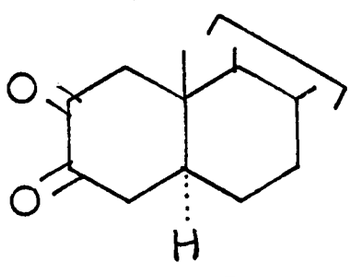


[59]



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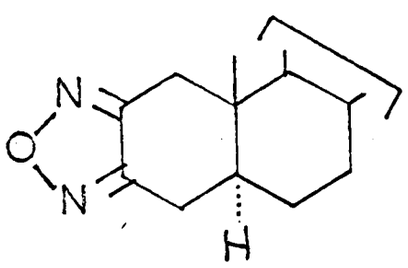

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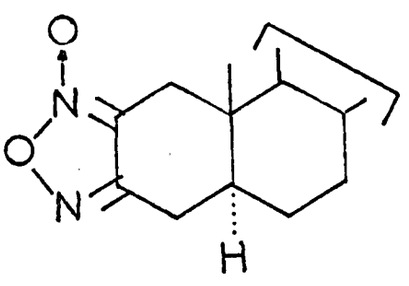

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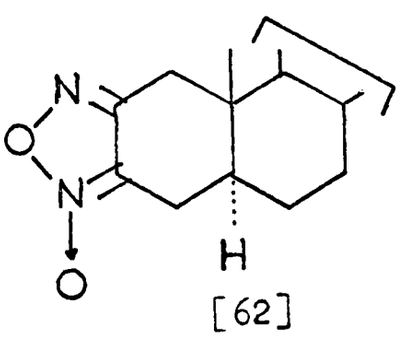


[62]

caused ring opening between C-3 and C-4, and that the larger butoxide ion merely abstracted a proton.

16-Nitro-17-ketones were prepared in 60 and 70% yields from 3-ethylenedioxyandrost-5-en-17-one and oestrone methyl ether.[145] Enolisation was negligible in chloroform, but considerable in more polar solvents. Reduction with $LiBH_4$ afforded the corresponding 17β-hydroxy-nitro compounds in 15% yield.

Bull[6] modified Fuer's conditions[140,141] and, working at 20°, obtained 2-nitro-5α-cholestan-3-one (42) in 30% yield. He showed that this nitro-ketone was almost completely enolic and identified a by-product as 2,4-seco-2,4-dinitro-5α-cholestane (53) - formed by decomposition of the bis-condensation product - 2,4-dinitro-5α-cholestan-3-one (54).

Base catalysed condensation of camphor (11) with amyl nitrite and sodium in ether was used by Claisen and Manasse[72] to prepare 3-hydroxyimino camphor (18). Other ketones react under milder conditions and potassium t-butoxide in t-butanol can be used. Acid catalysed hydroxyimination is also effective.[146]

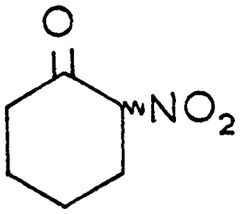
Application of this type of reaction in the steroid field was pioneered by Robinson and Litvan,[147] who found that oestrone methyl ether, when treated with an excess of Bu^tOK and amyl nitrite in t-butanol, yielded 16-hydroxyimino-oestrone methyl ether (55) in >90% yield. The reaction has been applied mainly to 1- and 17-ketones.[148] Three instances of its use with 3-keto-steroids are reported. Sheehan and Erman,[149] using Robinson's conditions, with 1 mol. of base and 1 mol. of nitrite, obtained 2-hydroxy-

imino-5α-cholestan-3-one (56), m.p. 203-205°, in 80% yield. Cava[150] reported the 2-oximation of 4,4-dimethylcholest-5-en-3-one in 90% yield under more vigorous conditions than those of Sheehan and Erman.[149] After the completion of the present work, Weintraub[151] reported that an excess of reagents produced the bis-hydroxyiminoketone (57) in the case of 5α-cholestan-3-one. In a study of steroidal furazans and furoxans, Ohta and collaborators,[152] working with 17- substituted androstan-3-ones, repeated Sheehan and Erman's method and obtained the 2-hydroxyimino derivatives (58) in ca 50% yield. The use of acidic conditions was found to be more satisfactory, the conventional conditions[153] being less effective than a two phase system of substrate and nitrite in benzene and 35% aqueous hydrochloric acid.

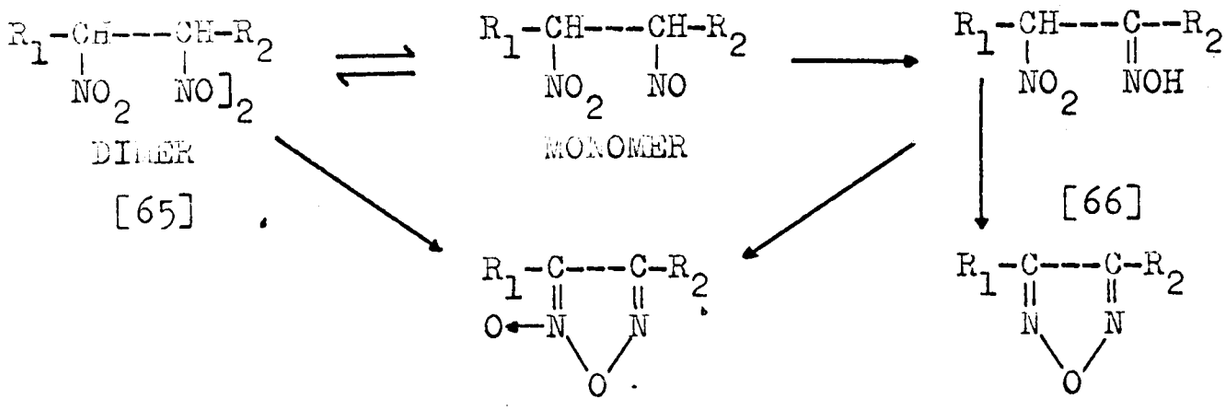
Oximation of the 2-hydroxyimino-3-ketones afforded the 2,3-dioximes (59).[152] Some of these compounds were also prepared by alkaline oxygenation[154] of the parent ketone and oximation of the 2,3-diketone (60) formed. The dioximes were converted to the furazans[155] (61) by treatment with KOH in diethylene glycol at 180°, or by treatment with thionylchloride in liquid sulphur dioxide, or by fusion with succinic anhydride. Oxidation of the dioximes with aqueous alcoholic sodium hypochlorite, or lead tetraacetate, produced the corresponding furoxans[156] (62 or 63), which could be deoxygenated to the furazans by triethyl phospite treatment.

(b) Addition to olefinic double bonds: The ability of nitric oxide,[157,158] dinitrogen tetroxide,[159,160] dinitrogen pentoxide,[161] nitrogen trioxide,[162] nitrylchloride,[163] nitrosylchloride,[164] and acetyl nitrate[160,165] to add

COMPOUNDS 64-68.



[64]



[65] [66] [67] [68]

to olefinic double bonds is well known. Work in this field is complicated by impurities in the reagents which initiate the production of, or themselves form, many products. Of particular interest to the present studies are the reported synthesis of α-nitrocyclohexanone[160] (64), and the properties of some of the products formed by treating olefines with a nitric oxide - air mixture.[158]

The synthesis of α-nitrocyclohexanone (64) was investigated by Griswold and Starcher.[160] Two routes to this compound (the oxidation of the α-nitroalcohol produced by the reaction of dinitrogen tetroxide on cyclohexene, and the ester exchange of the α-nitro-nitrate and α-nitro-acetate formed by treatment of cyclohexene with acetyl nitrate) were found to be inconvenient and inefficient. The favoured route involved addition of acetylnitrate to cyclohexene-1-ol acetate. Direct working up afforded α-nitrocyclohexanone in 40% yield.

Klamann et al.[158] prepared a series of pseudo-nitrosites (65) by passing a stream of nitric oxide and air through solutions of the corresponding olefines. The dimeric pseudo nitrosites were heated in DMF or DMSO and become monomeric at about 100°. Above 115°, these compounds rearranged to the isomeric nitrooximes (66) which could be isolated on cooling the solution. Treatment of the nitrooximes or pseudo-nitrosites with acid at 110° afforded the corresponding furoxans (67). Thionyl-chloride in liquid sulphur dioxide converted the nitrooximes into furazans (68).

Section II

Part (ii)

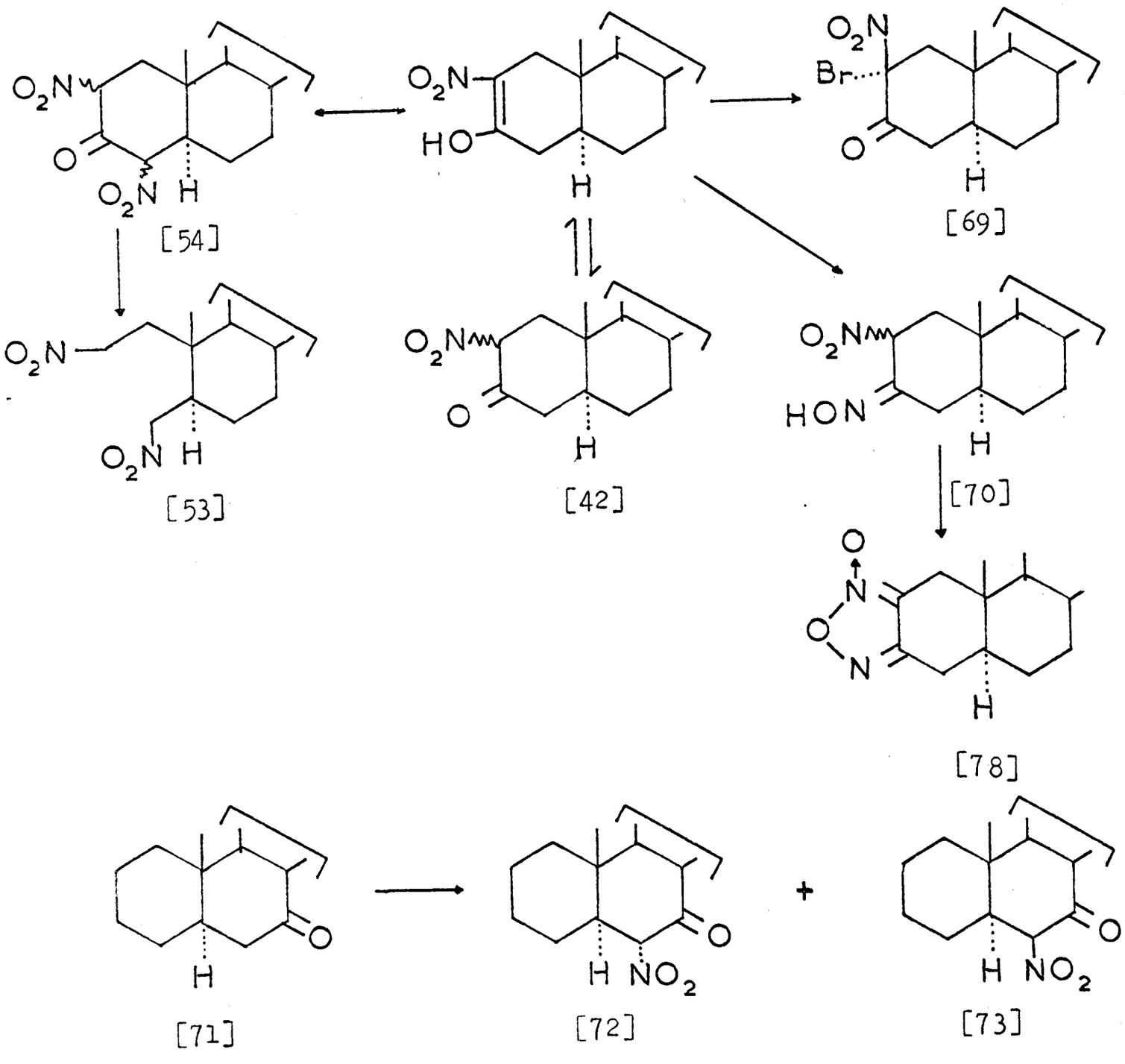
The preparation of α-nitro-ketones and related compounds

The aim of the work to be described in this Part was to prepare steroidal α-nitroketones in order to compare their spectroscopic properties with those of the nitrosteroids prepared by Bull.[6] Evidence in the literature suggested that nitroketones should also possess interesting chemical properties. The direct route to nitroketones - the alkyl nitrate treatment of ketones under strongly basic conditions - was found to be satisfactory. This aspect of the present investigation is described first. Another possible route to α-nitroketones - the alkyl nitrite treatment of ketones leading to α-hydroxyiminoketones, with subsequent oxidation of the oxime group - was not, in fact, carried to its conclusion, but led, instead, to a study of compounds containing two vicinal nitrogen substituents. The work concerned with this aspect is described next. The preparation of the starting materials used in this Section, 5α-cholestan-3-,6- and 7-ketones is to be found in Part (iii) of this Section.

The alkyl nitrate route to α-nitroketones, established by Fuer et al.[143] was modified by Bull.[6] Working with 5α-cholestan-3-one, he carried out the reaction at 20°, and found that the nitroketone (30%, 42) was accompanied by a by-product (19%) - the decomposition product (53) of the bis-nitroketone (54). A study of this reaction formed the starting point for the present work. In the present study, preliminary experiments were carried out on 5α-cholestan-3-one.

On repeating Bull's experiment, it became clear that when the reaction was carried out at 20°, the yield of nitroketone varied from experiment to experiment in an unpredictable manner. Three main factors appeared to influence the success of the reaction (a) the strength of the base present, (b) self-condensation of the ketone, and (c) the formation of the disubstituted ketone. The strength of the base depends on the degree to which the system is anhydrous. No reaction, except self-condensation of the ketone, occurred unless the system was completely dry. Accordingly, the reaction vessels, ketone and solvent were rigorously dried, and Bu^tOK freshly sublimed before use. To avoid appreciable self-condensation the ketone had to be left in contact with the base for only as long as was necessary to reach the equilibrium concentration of the ketone carbanion. The time (30 min.) suggested by Fuer et al.,[143] in their study of monocyclic ketones, before which little self-condensation occurs at -30° appears to be optimistic for 3-keto-steroids. Slow addition of the ketone to base at -30° over a period not exceeding 20 minutes, minimised self-condensation. The formation of the dinitroketone, as indicated by the isolation of the dinitro compound (69), occurred at 20° even when only 1 mol. of base and nitrate were used. This may indicate that the anion of the mononitroketone is more reactive to the alkyl nitrate that the ketone carbanion is. The proportion of the dinitro compound to nitroketone at 20° (1:1.5) was, however, reduced to 1:4, by working at -30°. The final experimental procedure was as follows: A solution of ketone in dry THF was added over 20 minutes to 1.5 mols. freshly sublimed Bu^tOK in dry THF at -30°. Ethyl

COMPOUNDS 42, 53-54, 69-73.


[54]
[53]
[42]
[69]
[70]
[78]
[71]
[72]
[73]

nitrate (1.5 mols.) was added over 10 minutes to this solution which was then allowed to stand at -30° for one hour. The mixture was acidified by dilute hydrochloric acid and worked up in the usual manner.

Bull reported that 2-nitro-5α-cholestan-3-one (42) could be separated from the dinitro compound (53) by chromatography on silica type Sorbsil. This material is no longer available and chromatography on Crosfield or B.D.H. silica gel afforded no separation. However, the mixture of compounds eluted from the column could be separated easily by crystallisation from ethyl acetate. Working at -30°, yields of nitroketone and dinitro compound were 52% and 14% respectively.

The nitroketone (42) exhibited uv maxima of 228 and 327 mμ in ethanol, 228 and 318 mμ in hexane and 235 and 345 mμ in ethanolic KOH. The presence of a band (327 mμ) in ethanol whose intensity (8420) changes on altering the solvent to hexane (318 mμ, ε 8130), and which suffers a bathochromic shift upon the addition of alkali, is characteristic of an enolic nitroketone. Further evidence is given by the ir spectrum which shows only a trace of the normal nitro and ketone bands (1565 and 1740 cm^{-1}), the major bands being due to the C=C and unsaturated nitro groups (1630 and 1515 cm^{-1} respectively). The n.m.r. spectrum shows no α-methine proton at the expected position[145] (5-6τ). No signal attributable to the enolic hydroxyl proton could be found. The hydroxyl band in the ir spectrum is unusually broad (2000-3500 cm^{-1}).

The nitroketone was smoothly brominated at 20° in the presence of 1 mol. of bromine in acetic acid. A similar reaction in CCl_4 failed. The

product (m.p. 150-155°), purified by chromatography and crystallisation, was stable except in the presence of acetone and light, when it rapidly decomposed to give the parent nitroketone in 75% yield. The configuration of the bromine atom and the nitro group were determined from a study of the angular methyl signals in its n.m.r. spectrum.

	C - 18	C - 19
5α-Cholestan-3-one	9.33τ	8.99τ
2α-Bromo-5α-cholestan-3-one	9.31τ	8.92τ
2β-Bromo-5α-cholestan-3-one	9.32τ	8.79τ[200]
2α-Bromo-2β-nitro-5α-cholestan-3-one (69)	9.34τ	9.18τ

The presence of a 2β-bromine atom and a 2α-nitro group (by analogy with Bull's[6] work at C-4) would both be expected to deshield the C-19 protons. In a reversed configuration, the deshielding of the bromine would be expected to be smaller, and the nitro group should shield the C-19 protons strongly. The C-19 protons in the bromonitroketone (69) are shielded by 0.19 ppp.m. relative to 5α-cholestan-3-one, and the configuration of the compound is, therefore, 2α-bromo-2β-nitro-5α-cholestan-3-one (69), in accord with the usual mechanism for the bromination of steroid ketones (attack on the least hindered, α-, face of the molecule).

The nitroketone (42) formed an oxime (70) upon treatment with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol, the optimum reaction time appearing to be 6 hours. The compound melted over a range (70-75°) and could not be crystallised. It was used without further purification to prepared the furoxan (78, see below). The chemical shift

of the C-19 protons in the n.m.r. spectra of the nitro-oxime (70) provide tentative evidence for the configuration of the nitro group. In the 3-oxime (see Section IV), the C-19 protons give rise to a signal at 9.11τ. By analogy with the shifts of the C-19 protons induced by nitro groups at the 4-position,[6] the deshielding of the C-19 protons (0.03 p.p.m.) relative to the 3-oxime, may be interpreted as indicative of a 2α-configuration for the nitro group, but the situation is complicated by the possibility of hydrogen-bonding.

5α-Cholestan-7-one (71) was nitrated under the same conditions as the 3-ketone, and afforded, after chromatography, a mixture of nitroketones in 44% yield. The ir spectrum of the product exhibited a split carbonyl band (1730,1700 cm^{-1}) and a strong nitro band (1560 cm^{-1}). The 1730 cm^{-1} band was approximately twice as intense as the 1700 cm^{-1} band. Crystallisation from light petroleum gave material, m.p. 137-139°, νmax 1735 and 1565 cm^{-1}, which analysed for $C_{27}H_{45}NO_3$. No further pure material could be obtained from the mother liquors, although these showed enrichment in a second nitroketone, νmax 1700 and 1565 cm^{-1}.

Nitration at C-8 was deemed unlikely, and Bull's[6] work on epimeric nitro compounds at the 6-position provided evidence for the compound's identity. He found that a 6 α-nitro group deshielded C-19 by 0.07 p.p.m., and C-18 protons by 0.01 p.p.m. A 6β-nitro group shielded C-19 by 0.01 and deshielded C-18 protons by 0.10 p.p.m. In the compound under consideration, the C-19 and C-18 protons are both deshielded, by 0.09 and 0.04 p.p.m. respectively, relative to the corresponding methyl groups' signals in 5α-cholestan-7-one. The compound may, therefore, be tentatively assigned the

6α-nitro configuration (72). The n.m.r. spectrum also showed a low field doublet at 5.00τ (one proton), whose coupling constant, 12.6 c.p.s., is of the expected order for a diaxial coupling between the 6β-and 5α-protons.

An epimerisation under kinetic control was attempted in the hope of producing the 6β-nitroketone. Treatment of the 6α-nitroketone with refluxing aqueous ethanol saturated with $NaHCO_3$, and acidification, afforded a product which showed a strong nitro band (1560 cm^{-1}) and two carbonyl bands (1730 and 1700 cm^{-1}), the lower frequency carbonyl band being approximately three times as intense as the 1730 cm^{-1} band. Crystallisation afforded a compound, ν_{max} 1695 and 1550 cm^{-1}. This compound melted over a range (155-170°). Further crystallisation did not raise its melting point: Ir examination of the melt revealed that partial epimerisation to the 6α-nitroketone had taken place. The wide melting range is not, therefore, indicative of impurity.

The instability of this compound, m.p. 155-170°, would indicate a 6β-nitro configuration (73) since here the axial nitro group would suffer interactions with C-19. The n.m.r. spectrum gave further evidence for this configuration. The C-18 and C-19 proton signals occur at 9.31 and 9.13τ, the former being deshielded by 0.02 p.p.m. and the latter shielded by 0.14 p.p.m. relative to the 7-ketone. On the basis of the shifts induced by epimeric 6-nitro groups (see above), this compound may be formulated 6β-nitro-5α-cholestan-7-one (73). The spectrum also showed a multiplet (equivalent to two protons) at 5.75τ - presumably the 6α-proton and the 5α-proton (deshielded by lying in the plane of the nitro group).

Further equilibrations were carried out on the 6α- and 6β-nitroketones (72,73). Refluxion with aqueous ethanol saturated with a trace of $NaHCO_3$, without acidification in the working up afforded the same product (similar treatment of the 6β-nitroketone in the absence of $NaHCO_3$ afforded only starting material). Ir examination showed the presence of the 6α-nitroketone and another compound. Preparative t.l.c. separated this second compound (62%) from the nitroketone (38%). It showed bands at 1152 and 1180 in addition to bands at 1736 and 1559 cm^{-1}, and no appreciable absorption in its uv spectrum either in neutral or alkaline media. The n.m.r. spectrum of this compound showed the C-19 protons to be strongly shielded (9.23τ), and exhibited a multiplet (5.9τ) equivalent to three protons. This product could not be crystallised and was not investigated further.

6α-Nitro-5α-cholestan-7-one (72) did not react with bromine, in the presence of hydrogen bromide, in CCl_4 or acetic acid, even after a reaction time of three months.

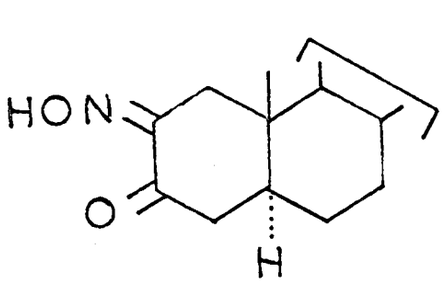
Nitration of 5α-cholestan-6-one (74, containing ca 15% of 5β-cholestan-6-one see Part (iii) of this Section), under the same conditions as those used for the 3- and 7- ketones, gave only a relatively small amount of nitrated material, as judged by ir examination of the product. The carbanion of the ketone was generated satisfactorily in this reaction, since, in cases where the addition of the ketone to the base was carried out at higher temperatures and for longer periods than usual (-30° to -17°, 1 hour) before the addition of nitrate, the proportion of nitrated material was not increased, and the major product consisted of condensed

ketonic material. By lengthening the duration of the nitration stage to two hours, a slight improvement in the amount of nitration was achieved. However, ir examination of the product showed that a band at 1620 cm^{-1} was present, in addition to the expected nitroketone band at 1560cm^{-1}, the former band being about twice as intense as the latter. After extensive chromatography, a compound was isolated which showed bands in its ir spectrum at 1730, 1630 and 1300 cm^{-1}, and a second compound, contaminated with the parent ketone, showing bands at 1720 and 1570 cm^{-1}. Neither of these compounds were obtained in sufficient amounts to allow full characterisation (yields ranged from 2-5% in each case), but the latter compound (ν_{max} 1720 and 1570 cm^{-1}) would appear to be a nitroketone. The lack of success of the nitration reaction encountered with this ketone may be attributed, in part, to steric hindrance by the C-15 protons, impeding attack at C-7.

The preparation of α-hydroxyiminoketones by treatment of the parent ketone with base and amyl nitrite has usually been carried out with ketones possessing only one adjacent nethylene group.[147,148] In ketones possessing two adjacent methylene groups, such as 5α-cholestan-3-one, disubstitution is to be expected.

In the present work, the hydroxyimination of 5α-cholestan-3-one under basic conditions at 20° was found to be capricious. In the presence of 1 mol. of amyl nitrite and Bu^tOK in Bu^tOH, substantial amounts of the disubstituted derivative were formed, and the yield of the 2-hydroxyimino-3-ketone (56) was low (34%). When 2 mols. of nitrite were used, the

COMPOUNDS 56-57,75-79.



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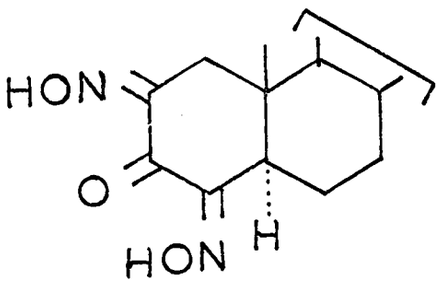
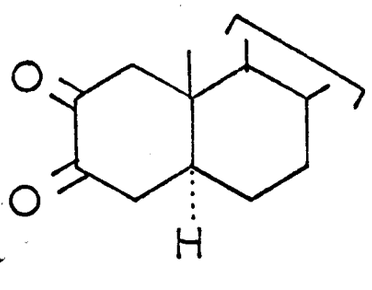


[57]



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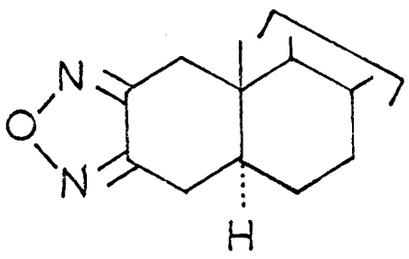
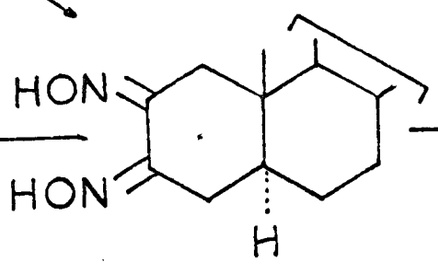


[77].



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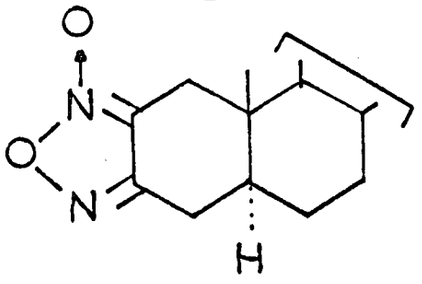
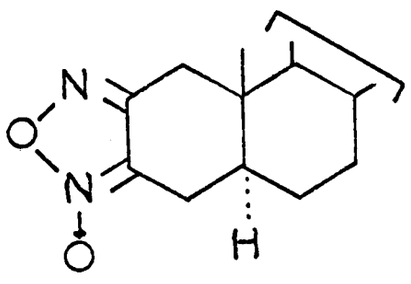


[78]



[79]

dihydroxyiminoketone (57) was the sole product (22%). Both these compounds were very insoluble and their separation and purification were difficult. Despite extensive experimentation, yields could not be improved.

The work of Ohta *et al.*[152] suggested that the acid-catalysed route might be more effective. Accordingly, a solution of the 3-ketone in ether (this solvent was used in preference to the benzene-methanol mixture used by Ohta[152] because of the different solubility of the product in the cholestane series) was vigorously stirred with 12-N-HCl, and 1 mol. of amyl nitrite in ether slowly added. The product, 2-hydroxyimino-5α-cholestan-3-one (56) separated from the reaction mixture in 70% yield in a state of high purity. The *anti*-configuration of this material was demonstrated in two ways: A solution of the compound gave a reddish brown precipitate with nickel sulphate - complexation being characteristic of an *anti*-configuration. The absorption maximum of the compound in ethanol (243 mμ) was shifted to 300 mμ on the addition of alkali in accord with Barton's postulate[75] that the absorption maxima of *anti*-hydroxyiminoketones suffer a bathochromic shift on the addition of alkali, whilst those of *syn*-hydroxyiminoketones remain unchanged. On treatment with hydroxylamine hydrochloride in pyridine, this compound was converted to the 2,3-dioxime (75).

Another route to this dioxime was studied. The 3-ketone was oxygenated under Barton's conditions[201] to give the 2,3-dione - diosphenol mixture (76) in 86% yield. This was oximated under standard conditions

affording the dioxime (75) in 95% yield. A solution of the dioxime (75) in THF gave a pink precipitate with nickel sulphate. Its absorption maximum in ethanol (238 mμ) suffered a bathochromic shift of 41 mμ on the addition of alkali. Both these properties are in accord with an anti-configuration.[152,201]

The dioxime (75) was dehydrated at 180°, in the presence of succinic anhydride, to give the [2,3,c]-furazan (77). This compound exhibited absorption maxima at 215 mμ, and 1500, 1405, 1226, 1010 and 880 cm^{-1}, similar to those of the androstano-[2,3,c]-furazans prepared by Ohta.[152] Oxidation of dioxime (79) with sodium hypochlorite produce the corresponding [2,3,c]-furoxan (78,79). The furoxan structure was confirmed by the absorption bands of the product at 267 mμ, 1620 and 1485 cm^{-1}, which agree well with those of the corresponding androstane derivatives.[152] The n.m.r. spectrum of this compound was identical with that of the furoxan prepared in low yield from the 2-nitro-3-oxime (70) by treatment with phosphoric acid. The most likely structure for this latter furoxan is (78). If the anisotropy of the furoxan ring is such that there is a significant difference in the shielding of the C-19 methyl group between structures (78 and 79), then the compound prepared by oxidation of the dioxime (75) has the former structure (78).

The dioxime was oxidised with buffered trifluoroperacetic acid under conditions where steroid mono-oximes give good yields of the corresponding secondary nitro compounds[48] - slow addition of a solution of trifluoro peracetic acid to a gently refluxing slurry of the dioxime and anhydrous disodium hydrogen phosphate in acetonitrile. After extensive chromatography,

a compound was isolated, in 18% yield, whose ir, uv and n.m.r. spectra were identical to those of the furoxans prepared by sodium hypochlorite oxidation of the dioxime (75) and ring closure of the 2-nitro-3-oxime (70). This compound, therefore, has structure (78). Only a small amount (6%) of impure material was isolated which showed strong absorption associated with a nitro group at 1540 cm^{-1}. The ir spectrum showed no evidence for the presence of other groups, and it may be concluded tentatively that this compound is the desired vicinal dinitro compound.

Section II

Part (iii)

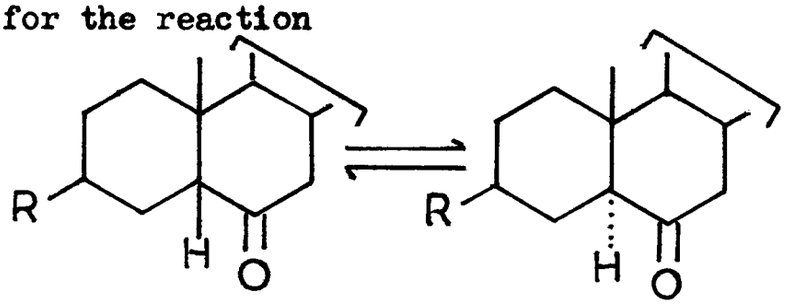
The preparation of starting materials

5α-Cholestan-3-one was prepared in the usual manner by hydrogenating cholesterol in the presence of perchloric acid, and oxidising the resulting alcohol with Jones reagent.

The preparation of 5α-cholestan-6-one, as recorded in the literature,[6,166] appears to be straightforward. However, during the course of the present work, it became apparent that the reactions available were not stereospecific: in the cholestane[167] and androstane[168] series, the two routes from the 5-olefin (hydroboration[166] and nitration[169]) produce a mixture of the 5α- and 5β-ketones. In the androstane series[168] equilibration with 5% methanolic KOH gives a product containing > 99% of the 5α-ketone. In the cholestane series, such an equilibration (see below) affords a mixture containing 10-15% of the 5β-6-ketone, which is not changed by fractional crystallisation. However, in one instance, a melting point some 6° higher than the literature value (97°) was found.[170] In the 3β-acetoxycholestane series[167] both the hydroboration and nitration methods produce a mixture from which the 5α-6-ketone could be separated easily.

A recent paper[171] has done much to clarify the issue. Equilibrations of 5α- and 5β-cholestan-6-ones and a series of their 3-substituted derivatives were carried out by heating the compounds at 230° for five hours, or by refluxing in 25% aqueous ethanol containing 3M-hydrochloric acid, or in 0.5M-hydrochloric acid in glacial acetic acid at 100°. The proportions of

5α- and 5β-compounds present were determined by examining the molar rotations, the α-methine proton signal in the n.m.r. spectra of the mixture, and by separating the components by t.l.c. The mean equilibrium constants for the reaction



were found to be 2.9, in the case of the 6-ketones, 4.6, where R = OH and 6.3 where R = OAc. These workers found, moreover, that 3β-substituted-5β-6-ketones were generally much more soluble than their 5α-analogues and an easy separation by crystallisation was possible. The hydroboration of cholest-5-ene was carried out and an analysis of the products by multi-run t.l.c. showed that the product contained ca 30% 5β-cholestan-6β-ol. This reaction is thus not so stereospecific as had been thought previously.

In the present work the 6-oxo-cholestanes were prepared according to the hydroboration methods of Bull[6] and Djerassi.[172] The former method involves the usual addition of lithium aluminium hydride to olefin, and the latter, used for the preparation of androstan-6-one, uses the 'reversed' addition with direct oxidation of the hydroboration adduct with Jones reagent. In both cases, the product (ca 80% yield) after crystallisation, both before and after the attempted equilibration had a melting point of 95-99°, showed two spots on multi-run t.l.c., a rotation of 0° (5α-cholestan-6-one has $[\alpha]_D$ - 7° and 5β-cholestan-6-one - 42°) but analysed for $C_{27}H_{46}O$. Fractional crystallisation of the mixture failed to raise this melting point.

The mixture was oximated under the usual conditions and after one crystallisation from ethyl acetate, pure 6-hydroxyimino-5α-cholestane was obtained in 71% yield. This was hydrolysed with pyruvic acid and acetic acid at 100° for 90 minutes. The product melted between 90 and 95°, indicating that epimerisation had occurred. In view of the fact that the 6-ketone was to be used under conditions where epimerisation would almost certainly occur (in potassium t-butoxide), the mixture of 5α- and 5β-6-ketones were used without further purification.

5α-Cholestan-7-one was prepared according to the method of Bull[6] - oxidation of cholesteryl acetate with sodium dichromate, treatment of the product, 3β-acetoxycholest-5-ene-7-one with methanolic KOH and hydrogenation of the $\Delta^{3,5}$-7-ketone.

Section II

Part (iv)

Experimental

5α-Cholestan-3-one: This compound was prepared in the usual manner from cholesterol and crystallised from acetone as needles, m.p. 129-130°, $[\alpha]_D$ + 40° (C. 1.1) (lit.,[173] m.p. 127-128°, $[\alpha]_D$ + 42°).

Cholest-5-ene: Cholesterol (25 g.) was treated with thionyl chloride (50 ml.) according to the method of Baker and Squire.[174] The product was filtered through neutral alumina (200 g.) with light petroleum (1 l.) to give cholesteryl chloride (23.7 g.), m.p. 96-97°, $[\alpha]_D$ - 27° (C. 0.5) (lit., m.p. 94-95°, $[\alpha]_D$ - 27°). This product (20 g.) in dry ether (400 ml.) and liquid ammonia (400 ml.) was treated with sodium (6 g.) in small pieces and stirred for 1 hr. Ethanol (ca 100 ml.) was cautiously added and the ammonia evaporated. After washing and drying the ether solution, the solvent was evaporated, giving cholest-5-ene (17.1 g.), m.p. 93-95°, $[\alpha]_D$ - 52° (C. 1.0) (lit.,[175] m.p. 92.5-94°, $[\alpha]_D$ - 56°).

5α-&5β-Cholestan-6-one: $LiAlH_4$ (5.1 g.) in dry ether (250 ml.) was added over 20 min. to a solution of cholest-5-ene (17 g.) and boron trifluoride-ethereate (23 ml.) in dry ether (300 ml.) at 20°, the mixture being stirred in an atmosphere of nitrogen. After standing for 1 hr., wet ether was cautiously added, followed by a saturated solution of sodium sulphate (200 ml.). The ether layer was separated and solvent removed. The residue in T.H.F. (100 ml.) was treated with 4N-sodium hydroxide (100 ml.) and hydrogen peroxide (100 ml., 100 vol.) and the mixture vigorously stirred at

20° for 2 hr. Water was added and the product isolated by ether extraction, dissolved in acetone and treated with 8N-chromic acid (10 ml.). After the usual work up procedure, the residue was chromatographed on neutral alumina (350 g.). Elution with light petroleum (400 ml.) gave cholest-5-ene (2.05 g.), m.p. 90-93°. Benzene (850 ml.) eluted the mixture of 6-ketones (13.1 g.), m.p. 95-99° (lit.,[176] m.p. 98°). This material was refluxed with 5% methanolic KOH (400 ml.) for 6 hr. under nitrogen. The product was poured into water, isolated in the usual way and recrystallised from ethyl acetate, m.p. 95-99°.

Attempted purification by oxime formation: The above mixture (0.5 g.), hydroxylamine hydrochloride (0.3 g.) and sodium acetate (0.6 g.) in ethanol-water (40 ml., 20:1) was refluxed for 1 hr. The product was poured into water, and isolated in the usual way. Crystallisation from ethyl acetate afforded needles (370 mg.), m.p. 193-195°, $[\alpha]_D$ - 9.6° (C. 1.0) (lit.,[6,177] m.p. 204-206°, $[\alpha]_D$ - 11°). The oxime (100 mg.) and pyruvic acid (210 mg.) were heated at 100° in 30% aqueous acetic acid (3.5 ml.). Water was added and the product extracted into chloroform which was then washed with water. After drying and evaporation of solvent, the material was filtered through neutral alumina (10 g.) with benzene (100 ml.). Recrystallisation from ethyl acetate afforded 5α- and 5β-cholestan-6-one, m.p. 95-99°.

5α-Cholestan-7-one: Cholesteryl acetate (200 g.) was oxidised with sodium dichromate (200 g.) according to Ellington's method,[178] to give 3β-acetoxycholest-5-en-7-one (153 g.), m.p. 140-150°. This material was refluxed with 4% methanolic KOH (2.5 l.) for 4 hr., water was added and, after

ether extraction and filtration through 5% deactivated alumina (1.25 Kg.) with benzene (4 l.), cholesta-3,5-dien-7-one (60 g.), m.p. 113-115° was obtained.

A solution of cholesta-3,5-dien-7-one (20 g.) in ether-glacial acetic acid (250 ml., 1:1) was hydrogenated with Adams catalyst for 8 hr. The filtered solution was washed with aqueous $NaHCO_3$ and water, and dried. The solvent was evaporated and the residue in acetone (500 ml.) was oxidised with Jones reagent (6 ml.). The product was isolated in the usual way and chromatographed on neutral alumina (400 g.). Elution with light petroleum (250 ml.) gave 5α-cholestane (2.25 g.) m.p. 80-81°, identified by its i.r. and n.m.r. spectra. Elution with benzene (1 l.) gave 5α-cholestan-7-one (14.3 g.), m.p. 114-115°, $[\alpha]_D$ - 49° (C. 1.1) (lit.,[179] m.p. 114-115°).

2-Nitro-5α-cholestan-3-one (42): A solution of 5α-cholestan-3-one (9.363 g.) in THF (150 ml.) was added over 30 min. to a stirred solution of Bu^tOK (4.14 g., 1.5 mol.) in THF (140 ml.) at -40°. Ethyl nitrate (3.3 ml., 1.5 mol.) was then added over 5 min., and the stirred mixture was allowed to warm up slowly, until after 45 min. (Temperature = 0°) it was acidified with acetic acid. The product was poured into water and extracted in ether. After drying and evaporation the material (10.74 g.) was chromatographed on silica gel (300 g., 20% deactivated). Elution with benzene-light petroleum (1.5 l., 1:9) afforded a mixture (6.93 g.) of the nitroketone and dinitrocompound. Crystallisation from ethyl acetate afforded 2-nitro-5α-cholestan-3-one (5.35 g.), m.p. 133-134°, $[\alpha]_D$ + 108° (C. 0.6), λ_{max}^{Hexane} 228 mμ (ε 2560), 318 mμ (ε 8130), λ_{max} 228 mμ (ε 2890), 327 mμ (ε 8420), $\lambda_{max}^{KOH-EtOH}$ 235 mμ (ε4080) 345 mμ (ε 16300) (lit.,[6,144]

m.p. 135-136°). Evaporation of the mother liquors afforded 2,4-seco-2,4-dinitro-5α-cholestane (1.5 g.) m.p. 166-170° (lit.,[6] m.p. 168-173°).

2α-Bromo-2β-nitro-5α-cholestan-3-one (69): 2-Nitro-5α-cholestan-3-one (157 mg.) was dissolved in acetic acid (100 ml.) at 20° over four days. A solution of bromine in acetic acid (1.9 ml. of a solution containing 1.545 g. bromine in 50ml. acetic acid) was added and the mixture allowed to stand in the dark for 5 hr. After pouring into water and extraction into ether, the ether layer was washed with water three times, dried and evaporated. The product was chromatographed on silica gel (SG 31, 10 g.). Elution with benzene-light petroleum (100 ml., 1:4) afforded 2α-bromo-2β-nitro-5α-cholestan-3-one, m.p. 150-155° (prisms from hexane), $[\alpha]_D$ + 57° (C. 1.0), ν_{max} 1745 and 1570 cm.$^{-1}$ (Found: C, 63.5; H, 8.7; N, 2.45; $C_{27}H_{44}BrNO_3$ requires C, 63.5; H, 8.6; N, 2.75%).

Decomposition of 2α-bromo-2β-nitro-5α-cholestan-3-one: The bromo-nitroketone (64 mg.) was dissolved in the minimum amount of acetone and allowed to stand in sunlight. After a few hours bromine could be detected and in 24 hours precipitation of crystals was complete. These were filtered off and recrystallised from ethyl acetate affording 2-nitro-5α-cholestan-3-one (40 mg.), m.p. 132-133° identical with the material prepared above.

2-Nitro-3-hydroxyimino-5α-cholestane (70): 2-Nitro-5α-cholestan-3-one (500 mg.), hydroxylamine hydrochloride (250 mg.) and pyridine (2.5 ml.) in ethanol-water (200 ml., 40:1) were refluxed for 6 hr. The product was poured into water and worked up in the usual manner to give 2-nitro-3-hydroxyimino-5α-cholestane (70), m.p. 70-75°, ν_{max} 3580, 3240, 1620 and 1550 cm.$^{-1}$, which could not be crystallised. It was used without further

purification for the preparation of the corresponding furoxan (see below).

6α- and 6β-Nitro-5α-cholestan-7-one (72, 73): A solution of 5α-cholestan-7-one (2.09 g.) in THF (30 ml.) was added over 30 min. to a stirred solution of Bu^tOK (1.00 g.) in THF (30 ml.) at - 37°. Ethyl nitrate (1.2 ml.) was added over 5 min. and the solution stirred for 75 min. Acetic acid was added (T = -25°) and the mixture worked up as usual. Chromatography on silica gel (B.D.H., 200 g.) afforded a mixture of the nitroketones (1.02 g.) by elution with benzene-light petroleum (1.8 l., 2:3). Crystallisation from light petroleum gave 6α-nitro-5α-cholestan-7-one (730 mg.), m.p. 137-139°, $[\alpha]_D$ + 2.7° (C. 1.0), λ_{max}^{EtOH} 240 mμ (ε 1610), $\lambda_{max}^{EtOH-KOH}$ 233 mμ (ε 10260), ν_{max} 1735 and 1565 cm.$^{-1}$ (Found: C, 75.0; H, 10.4; N, 2.9. $C_{27}H_{45}NO_3$ requires: C, 75.1; H, 10.5; N, 3.25%).

6β-Nitro-5α-cholestan-7-one (73): 6α-nitro-5α-cholestan-7-one (226 mg.) was refluxed with 10% aqueous ethanol saturated with $NaHCO_3$ (Reagent A, 200 ml.) for 2 hr. Solvent was evaporated off and the residue treated with ether and water. After drying the ether layer, evaporation afforded oily material (210 mg.) which was crystallised from ethyl acetate. The product, 6β-nitro-5α-cholestan-7-one, had m.p. 155-170°, $[\alpha]_D$ + 2.2° (C. 1.0), $\lambda_{max}^{EtOH-KOH}$ 238 mμ (ε 7780) and 300 mμ (ε 557), ν_{max} 1695 and 1550 cm.$^{-1}$ (Found: C, 75.2; H, 10.6; N, 3.0. $C_{27}H_{46}NO_3$ requires: C, 75.1; H, 10.5; N, 3.25%).

Equilibration experiments: The 6α- and 6β-nitroketones (5 mg.) were refluxed with Reagent A (0.1 ml.) and ethanol (10 ml.) for 17 hr. Solvent was evaporated off and CCl_4 added. In both cases, the i.r. spectrum and

t.l.c. showed the presence of the 6α-nitroketone and another compound. The experiment was repeated on a layer scale (61 mg.) and product separated by t.l.c. (Keiselgel H, benzene, 1 run). This gave 6α-nitroketone (15 mg.) and the new compound (46 mg.), ν_{max} 1736, 1559, 1180 and 1152 cm.$^{-1}$, which was not investigated further.

Nitration of 5α-cholestan-6-one: A solution of 5α-cholestan-6-one (74) (2.62 g.) in THF (60 ml.) was added over 20 min. to a solution of Bu^tOK (1.16 g.) in THF (60 ml.) at - 35°. Ethyl nitrate (0.87 ml.) was added and the solution was stood at - 30° for 1 hr., and then allowed to warm up, over 1 hr., to - 14°, at which temperature it was acidified with dil. HCl. After the usual working up procedure, the product was adsorbed onto silica gel (200 g.). Elution with benzene-light petroleum (1:1, 250 ml.) afforded material (48 mg.), ν_{max} 1730, 1630 and 1300 cm.$^{-1}$. Benzene-light petroleum (4:1, 1.2 l.) eluted a mixture (150 mg.) of the parent ketone (identified by t.l.c.) and a second compound, ν_{max} 1720 and 1570 cm.$^{-1}$.

2-Hydroxyimino-5α-cholestan-3-one (56): Method (a): 5α-cholestan-3-one (10 g.) was hydroxyiminated according to the method of Sheehan and Erman[149] and afforded, after crystallisation from ethanol, 2-hydroxyimino-5α-cholestan-3-one (3.6 g.), m.p. 240-241° (d.), $[\alpha]_D$ + 42° (C. 1.0, pyridine), λ_{max} 243 mμ (ε 7209), $\lambda_{max}^{EtOH-NaOH}$ 300 mμ (ε 12730), ν_{max} 3300, 3150, 1730, 975, 955 cm.$^{-1}$ (Found: C, 78.6; H, 11.1; N, 3.3. Calculated for $C_{27}H_{45}NO_2$: C, 78.1; H, 10.7; N, 3.4%) (lit.,[149] m.p. 203-205°).

Method (b): 5α-cholestan-3-one (1 g.) was dissolved in ether (30 ml.) and mixed with 12N-HCl

(6.5 ml.), methanol (4 ml.) and water (1 ml.). The mixture was vigorously stirred and amylnitrite (0.35 ml., 1 mol.) in ether (20 ml.) added over 20 min. The suspension of crystals was stirred for a further 15 min. and filtered. The product was washed with ether, and water and dried, affording 2-hydroxyimino-5α-cholestan-3-one (0.75 g.) m.p. 240-241 (d.), identical with the material above.

2,4-Dihydroxyimino-5α-cholestan-3-one (57): 5α-cholestan-3-one (1 g.) was hydroxyiminated according to Sheehan and Erman's method, using 2 mol. (0.71 ml.) amylnitrite. The product was recrystallised from ethanol to give 2,4-dihydroxyimino-5α-cholestan-3-one (57) (250 mg.), m.p. 218-221° (d), $[\alpha]_D$ + 34° (c. 1.0, pyridine), λ_{max} 260 mμ (ε 8050), $\lambda_{max}^{EtOH-KOH}$ 350 mμ (ε 14600), ν_{max} 3120, 1720, 1615, 1550, 975, 950 cm.$^{-1}$ (Found: C, 73.3; H, 9.9; N, 5.30. $C_{27}H_{44}N_2O_3$ requires C, 72.8; H, 9.9; N, 6.3%).

5α-Cholesta-2,3-dione (76): 5α-cholestan-3-one (5.25 g.) was dissolved in Bu^{t}OH (400 ml.) containing potassium (20 g.) and oxygenated according to Barton's procedure.[201] After the evaporation of Bu^{t}OH, the product was extracted into ether. The ether layer was treated with 20% aqueous KOH (3 x 100 ml.), the precipitate in the aqueous layer was separated, treated with Celite 545, and collected at the pump. After washing with ether and 6N-HCl, the product was dissolved in ethanol, filtered, and crystallised to give 5α-cholesta-2,3-dione (4.82 g.), m.p. 117-134°, λ_{max} 272 mμ (ε 5360), ν_{max} 3440, 1680, 1665 cm.$^{-1}$ [lit.,[180] m.p. 132-134°, λ_{max} 270 (3700)].

2,3-Dihydroxyimino-5α-cholestane (75): A. 5α-cholesta-2,3-dione (4.12 g.), hydroxylamine hydrochloride (2.6 g.) and sodium acetate (6.0 g.)

in ethanol-water (100 ml., 9:1) were refluxed for 1 hr. The solution was allowed to cool, and the precipitate, collected at the pump, was washed with water and dried. Recrystallisation from ethanol afforded 2,3-dihydroxyimino-5α-cholestane, m.p. 218-220°, $[\alpha]_D$ + 71° (c. 1.0, pyridine), λ_{max} 238 mμ (ε 6620), $\lambda_{max}^{EtOH-KOH}$ 279 mμ (ε 6500), ν_{max} 3390, 3160, 1620, 950 cm.$^{-1}$ (Found: C, 74.5; H, 10.5; N, 6.9. $C_{27}H_{46}N_2O_2$ requires C, 75.2; H, 10.7; N, 6.5%).

B: 2-Hydroxyimino-5α-cholestan-3-one (56), (100 mg.), hydroxylamine hydrochloride (30 mg.) and in pyridine (20 ml.) were heated at 100° for 1 hr. The solution was poured into water and the precipitate, collected at the pump, washed with water and dried. Crystallisation from ethanol afforded material, m.p. 218-220°, λ_{max} 239 mμ (ε 5740), $\lambda_{max}^{KOH-EtOH}$ 280 mμ (ε 8770), identical to that provided by method A.

5α-Cholestano-[2,3,c]-furazan (77): 2,3-Dihydroxyimino-5α-cholestane (0.5 g.) and succinic anhydride (0.5 g.) were heated at 180° for 8 min. The melt was allowed to cool and water and chloroform added. The extract was washed with water, dried and evaporated. The product (414 mg.) was chromatographed on silica gel (SG 31, 15 g.). Elution with benzene (160 ml.) afforded, after crystallisation from ethanol, 5α-cholestano-[2,3,c]-furazan (158 mg.), m.p. 103-105°, $[\alpha]_D$ + 50.2 (C. 1.0), λ_{max} 215 mμ (ε 4150), 253 (284), ν_{max} 1405, 1226, 1010, 880 cm.$^{-1}$ (Found: C, 78.4; H, 10.6; N, 6.6. $C_{27}H_{44}N_2O$ requires C, 78.9; H, 10.7; N, 6.8%).

5α-Cholestano-[2,3,c]-furoxan (78): A. 2,3-Dihydroxyimino-5α-cholestane (1 g.) and sodium hydroxide (3 g.) were suspended in methanol-

water (120 ml., 3:1) at 0°. Sodium hypochlorite solution (20 ml., prepared by saturating 20% aqueous NaOH with chlorine) was added over 20 min. The solution was filtered and the product washed with water and dried. Recrystallisation from benzene-methanol afforded 5α-cholestano-[2,3,c]-furoxan (312 mg.), m.p. 202-203°, $[\alpha]_D$ + 62.5 (C. 1.0), λ_{max}^{Ether} 267 mμ (ε 8030), ν_{max} 1630, 1475 cm.$^{-1}$ (Found: C, 75.0; H, 10.4; N, 6.8. $C_{27}H_{44}N_2O_2$ requires C, 75.7; H, 10.3; N, 6.6%).

B. 2-Nitro-3-hydroxyimino-5α-cholestane (70) (103 mg.) and ortho-phosphoric acid (1 ml.) was heated at 115° for 1 hr. under nitrogen. The product was poured into water, extracted into ether, and the ether layer washed with water until neutral. After drying and evaporation, the product was filtered through silica gel (SG 31, 10 g.) with benzene (100 ml.) affording 5α-cholestano-[2,3,c]-furoxan (18 mg.), m.p. 202-203°, ν_{max} 1630, 1475 cm.$^{-1}$, shown to be identical with the furoxan produced by method A.

Oxidation of the dioxime (79) by trifluoroperacetic acid: A solution of 87% hydrogen peroxide (0.3 ml.) and trifluoroacetic anhydride (1.75 ml.) in acetonitrile (5 ml.) was added, over 45 min., to a gently refluxing slurry of 2,3-dihydroxyimino-5α-cholestane (1 g.), disodium hydrogen phosphate (4 g.) and urea (0.2 g.) in acetonitrile (100 ml.). The slurry was refluxed for a further hour, poured into water, and extracted with ether. After washing with water, 10% aqueous $NaHCO_3$, 10% aqueous sodium iodide, and 10% aqueous sodium thiosulphate (to remove any peroxides present), and drying, the ether extract was evaporated, and the residue (909 mg.) adsorbed onto silica gel (SG 31, 100 g.). Elution with benzene-

light petroleum (1:4, 400 ml.) afforded material (61 mg.), ν_{max} 1540 and 1580 cm.$^{-1}$, which was shown by t.l.c. to be impure. Elution with benzene-light petroleum (4:1, 500 ml.) gave pale yellow crystals (175 mg.) m.p. 180-185°, λ_{max} 262 mμ, ν_{max} 1630, 1475 cm.$^{-1}$, whose spectral properties were identical to those of the furoxan (78) prepared above.

Section III

SOLVENT SHIFTS OF ANGULAR METHYL GROUPS IN THE N.M.R. SPECTRA OF STEROID KETONES[181]

Many steroid ketones were handled as starting materials in the present work; other keto-steroids were available from microbiological studies, and from previous work in the Department. These ketones provided a wide coverage of the positions on the steroid nucleus, and it was decided to investigate the solvent shifts of angular methyl groups in these compounds.

The position of a ketonic group in the steroid nucleus strongly influences the chemical shifts of the angular methyl groups' resonances. Zurcher's study,[182] in which steroids were examined as solutions in deuterochloroform, was later extended by using different solvents (notably benzene, carbontetrachloride and pyridine).

Much research[115,183-190] into the nature of the interactions between benzene and solute molecules has been stimulated by Bhacca and Williams' generalisations[191-193] relating the solvent shift (i.e., the shift of a methyl group's signal caused by changing the solvent from $CDCl_3$ to benzene) to the relative dispositions of the methyl and ketonic groups. Initially,[191] they suggested that these shifts were due to a collision complex in which the steroid ketone associated with the benzene in a planar manner (Figure IV). Methyl groups lying in front of a plane drawn through the carbon of the carbonyl group and at right angles to the carbon-oxygen bond were deshielded, those lying close to the plane suffered only

FIGURES 1V - V11.

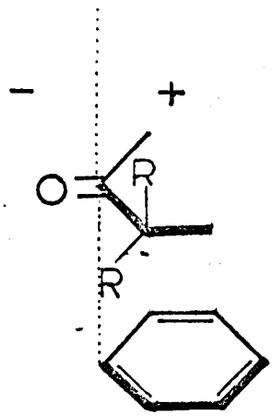


Figure IV

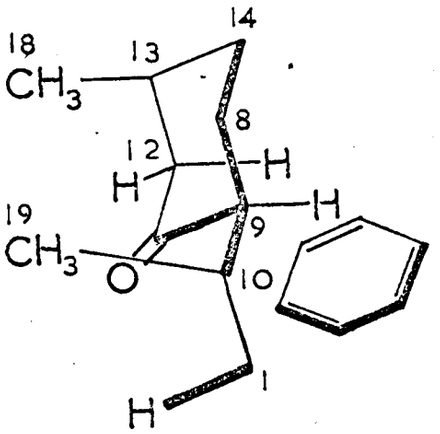


Figure V

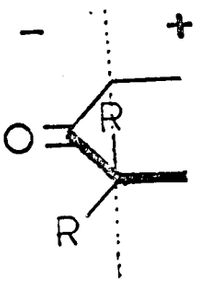


Figure VI

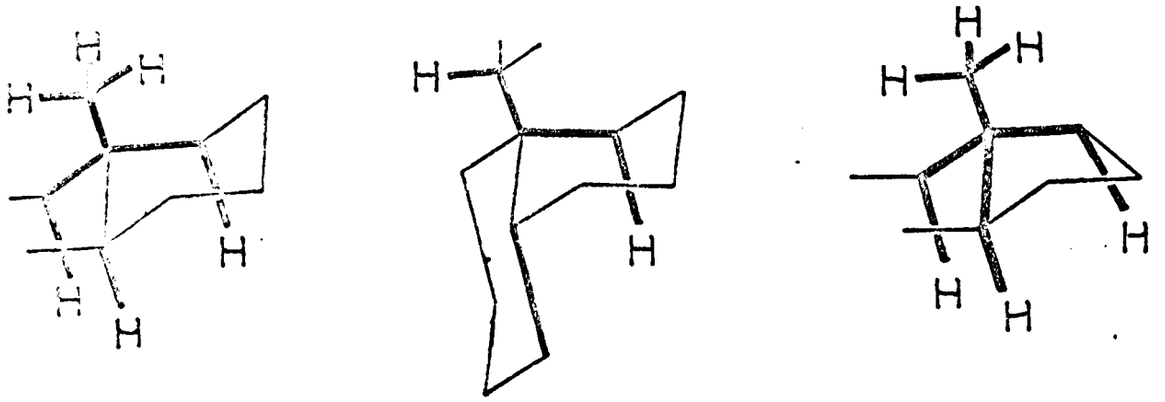


Figure VII

small shifts and those behind the plane were shielded. It was later shown,[115] however, that this generalisation was still valid in cases where the formation of a planar complex was unlikely because of steric factors. A modified model was proposed,[185] in the case of 5α-androstan-11-one, where the angle between the benzene molecule and the steroid was approximately 90°, the benzene molecule now being parallel to the plane formed by carbon atoms 9, 11 and 12 (Figure V).

The nature of the complex has been determined by concentration[183,184,186-188] and variable temperature[190] techniques. These showed that an equilibrium

$$\text{ketone} + \text{solvent} \rightleftharpoons \text{complex}$$

existed at room temperature. An increase in solute concentration or a decrease in temperature drove the equilibrium to the right (with a corresponding increase in solvent shifts) in such a manner that a 1:1 complex was indicated.

The concepts outlined above have been shown to be applicable also to acetates[185,191] lactones and anhydrides[194] and acids.[195] The solvent shifts arising from the use of pyridine have been studied less extensively. In a study of the shifts induced by twenty aromatic solvents on the methyl signal of acetonitrile, Ledaal[186] showed that the solvent shift decreased with increasing polarity of the solvent, and that the solvent shift due to pyridine was thus very small. Williams[196] formulated a generalisation for the prediction of solvent shifts of steroid ketones in pyridine similar to that for ketones in benzene except that the reference plane passed through the carbon atoms α- to the carbonyl group (Figure VI).

TABLE V111.

TABLE VIII

Chemical shifts [τ-values] and solvent shifts [Δ-values] for resonances of C-19, C-18 and side-chain methyl protons in mono-ketones.

Solvents: 1, CCl_4; 2, $CDCl_3$; 3, C_6H_6; 4, C_5H_5N.

$\Delta_1^2 = \tau_{CDCl_3} - \tau_{CCl_4}$ for a particular signal, and the other Δ symbols represent corresponding differences [e.g., $\Delta_2^4 = \tau_{C_5H_5N} - \tau_{CDCl_3}$].

With signals marked * the assignments are not unambiguous, but are considered more probable than the alternatives. Underlined figures are from the publications cited: many of these figures refer to the ketonic type rather than the particular ketones listed.

Compound	No.		τ_1	τ_2		τ_3	τ_4
5α-Cholestan-1-one	80	19	8.89	8.85	<u>8.852</u>[a]	9.11	8.92
		18	9.35	9.34	<u>9.345</u>[a]	9.32	9.33
		C_8H_{17}	9.08	9.07		9.02	9.06
			9.18	9.17		9.11	9.15
5α-Cholestan-2-one	81	19	9.27	9.26	<u>9.242</u>[a]	9.42	9.30
		18	9.36	9.36	<u>9.343</u>[a]	9.42	9.38
		C_8H_{17}	9.09	9.10		9.04	9.07
			9.18	9.20		9.13	9.16
5α-Cholestan-3-one	82	19	8.99	8.98	<u>8.983</u>[b]	9.31	9.08
		18	9.33	9.31	<u>9.316</u>[b]	9.35	9.32
		C_8H_{17}	9.08	9.07		9.02	9.05
			9.17	9.17		9.12	9.14

TABLE V111

Compound	No.		Δ_1^2	Δ_1^3	Δ_1^4	Δ_2^3	Δ_2^4
5α-Cholestan-1-one	80	19	-0.04	+0.22	+0.03	+0.30[c]	
		18	-0.01	-0.03	-0.02	0.00[c]	
		C_8H_{17}	-0.01	-0.06	-0.02		
			-0.01	-0.07	-0.03		
5α-Cholestan-2-one	81	19	-0.01	+0.15	+0.03	+0.16[c]	+0.05[e]
		18	0.00	+0.06	+0.02	+0.06[c]	+0.07[e]
		C_8H_{17}	+0.01	-0.05	-0.02		
			+0.02	-0.05	-0.02		
5α-Cholestan-3-one	82	19	-0.01	+0.32	+0.09	+0.37[c]	+0.11[e]
					+0.13[d]		
		18	-0.02	+0.02	-0.01	+0.10[c]	+0.03[e]
					+0.06[d]		
		C_8H_{17}	-0.01	-0.06	-0.03		
			0.00	-0.05	-0.03		

TABLE V111 [continued]

Compound	No.		ν_1	ν_2		ν_3	ν_4
5β-Cholestan-3-one	83	19	8.99	8.98	8.977[a]	9.23	9.07
		18	9.33	9.32	9.313[a]	9.37	9.33
		C_8H_{17}	9.09	9.09		9.02	9.04
			9.18	9.18		9.11	9.14
5α-Cholestan-4-one	84	19	9.28	9.26	9.255[a]	9.38	9.29
		18	9.35	9.34	9.342[a]	9.38	9.35
		C_8H_{17}	9.08	9.08		9.02	9.05
			9.18	9.17		9.11	9.14
5α-Cholestan-6-one	85	19	9.30	9.27	9.275[b]	9.36*	9.27*
		18	9.35	9.34	9.341[b]	9.46*	9.38*
		C_8H_{17}	9.08	9.08		9.02	9.04
			9.17	9.17		9.11	9.14
5α-Androstan-6-one	86	19	9.29	9.26	9.25[c]	9.38*	9.30*
					9.258[b]	9.37[c]	
		18	9.29	9.29	9.38[c]	9.45*	9.38*
					9.291[b]	9.44[c]	
5β-Cholestan-6-one	87	19	9.17	9.16	9.142[b]	9.23*	9.18*
		18	9.34	9.34	9.341[b]	9.47*	9.39*
		C_8H_{17}	9.08	9.08		9.01	9.05
			9.17	9.17		9.10	9.15
5α-Cholestan-7-one	88	19	8.96	8.94	8.950[b]	9.22	9.01
		18	9.37	9.34	9.350[b]	9.38	9.33
		C_8H_{17}	9.08	9.08		9.02	9.05
			9.18	9.18		9.11	9.14

Compound	No.		Δ_1^2	Δ_1^3	Δ_1^4	Δ_2^3	Δ_2^4
5β-Cholestan-3-one	83	19	-0.01	+0.24	+0.02		
		18	-0.01	+0.04	0.00		
		C_8H_{17}	0.00	-0.07	-0.05		
			0.00	-0.07	-0.04		
5α-Cholestan-4-one	84	19	-0.02	+0.10	+0.01		
		18	-0.01	+0.03	0.00		
		C_8H_{17}	0.00	-0.06	-0.03		
			-0.01	-0.07	-0.04		
5α-Cholestan-6-one	85	19	-0.03	+0.06	-0.03		
		18	-0.01	+0.11	+0.03		
		C_8H_{17}	0.00	-0.06	-0.04		
			0.00	-0.06	-0.03		
5α-Androstan-6-one	86	19	-0.03	+0.09	+0.01	+0.12[c]	-0.04[e]
		18	0.00	+0.16	+0.09	+0.06[c]	+0.03[e]
5β-Cholestan-6-one	87	19	-0.01	+0.06	+0.01		
		18	0.00	+0.13	+0.05		
		C_8H_{17}	0.00	-0.07	-0.03		
			0.00	-0.07	-0.02		
5α-Cholestan-7-one	88	19	-0.02	+0.26	+0.05	+0.32[c]	+0.04[e]
		18	-0.03	+0.01	-0.04	+0.08[c]	-0.02[e]
		C_8H_{17}	0.00	-0.06	-0.03		
			0.00	-0.07	-0.04		

TABLE V111 [continued]

Compound	No.		ν_1	ν_2		ν_3	ν_4
5α-Androstan-11-one	89	19	9.01	9.00	8.991[b]	8.84	8.88
			9.01[f]				
		18	9.34	9.34	9.341[b]	9.44	9.39
			9.34[f]				
5α-Androstan-17-one	90	19	9.19	9.18	9.183[a]	9.31	9.25
					9.19[c]	9.31[c]	
		18	9.19	9.14	9.137[a]	9.37	9.22
					9.14[c]	9.36[c]	
5β-Androstan-17-one	91	19	9.03	9.04	9.058[b]	9.15	9.10
		18	9.17	9.16	9.141[b]	9.38	9.21
3α,5-Cyclo-5α-	92	19	9.15	9.11		9.12	9.19
androstan-17-one		18	9.08	9.07		9.34	9.08

[a] and [b], values observed[a] by Zurcher, or calculated[b] from Zurcher's tables [reference 182].

[c] and [d], values for oxo-5α-androstanes reference 193[c] and 196[d].

[e], general values for Δ_2^4 calculated from reference 199

[f], values for 5α-androstan-11-one recorded in reference 185.

Compound	No.		Δ_1^2	Δ_1^3	Δ_1^4	Δ_2^3	Δ_2^4
5α-Androstan-11-one	89	19	-0.01	-0.17	-0.13		-0.16
			-0.03[f]	-0.15[f]	-0.11[f]		
		18	0.00	+0.10	+0.05		-0.02
			-0.01[f]	+0.10[f]	+0.04[f]		
5α-Androstan-17-one	90	19	-0.01	+0.12	+0.06		+0.13
					+0.06[d]	+0.12[c]	
		18	-0.05	+0.18	+0.03		+0.07
					+0.04[d]	+0.22[c]	
5β-Androstan-17-one	91	19	+0.01	+0.12	+0.07		
		18	-0.01	+0.21	+0.04		
3α,5-Cyclo-5α-	92	19	-0.04	-0.03	+0.04		
androstan-17-one		18	-0.01	+0.26	0.00		

TABLE 1X.

TABLE IX

Chemical shifts and solvent shifts for C-19 and C-18 protons in dioxo- and trioxo-5α-androstanes.

The column headings and abbreviations have the same meanings as in Table VIII; Signals marked ± show a noticeable degree of splitting.

Compound	No.		τ_1	τ_2		τ_3	τ_4
5α-Androstane-1,6-dione	93	19	8.89	8.88	8.883[b]	9.21	8.92
		18	9.27	9.27	9.274[b]	9.46	9.38
5α-Androstane-3,6-dione	94	19	9.05	9.03	9.016[b]	9.50	9.12
		18	9.25	9.25	9.249[b]	9.50	9.36
5α-Androstane-3,17-dione	95	19	8.96	8.96	8.947[a]	9.41	9.11
					8.94[c]	9.43[c]	
		18	9.16	9.11	9.102[a]	9.39	9.21
					9.11[c]	9.40[c]	
5α-Androstane-6,11-dione	96	19	9.08	9.04	9.041[b]	8.96	8.93
		18	9.32	9.32	9.324[b]	9.59	9.42
5α-Androstane-6,17-dione	97	19	9.26	9.24	9.241[b]	9.45	9.31
		18	9.17	9.12	9.124[b]	9.51	9.25
3α,5-Cyclo-5α-androstane-6,17-dione	98	19	9.11	9.05		9.23	9.04
		18	8.96	8.94		9.45	9.19
5α-Androstane-11,17-dione	99	19	9.00	8.97	8.974[b]	8.91	8.90
		18	9.22	9.18	9.170[b]	9.50±	9.24

TABLE 1X

Chemical shifts and solvent shifts for C-19 and C-18 protons in dioxo- and trioxo-5α-androstanes.

Compound	No.		Δ^2_1	$\Delta^3_{1[found]}$	$\Delta^3_{1[calc.]}$	Δ^4_1
5α-Androstane-1,6-dione	93	19	-0.01	+0.32	+0.31	+0.03
		18	0.00	+0.19	+0.13	+0.11
5α-Androstane-3,6-dione	94	19	-0.02	+0.45	+0.41	+0.07
		18	0.00	+0.25	+0.18	+0.11
5α-Androstan-3,17-dione	95	19	0.00	+0.45	+0.44	+0.15
		18	-0.05	+0.23	+0.20	+0.05
5α-Androstan-6,11-dione	96	19	-0.04	-0.12	-0.11	-0.15
		18	0.00	+0.27	+0.21	+0.10
5α-Androstane-6,17-dione	97	19	-0.02	+0.19	+0.21	+0.05
		18	-0.05	+0.34	+0.34	+0.08
3α,5-Cyclo-5α-androstane-6,17-dione	98	19	-0.06	+0.12	+0.06	-0.07
		18	-0.02	+0.49	+0.42	+0.23
5α-Androstane-11,17-dione	99	19	-0.03	-0.09	-0.05	-0.10
		18	-0.04	+0.28	+0.28	+0.02

TABLE 1X [continued]

TABLE IX [continued]

Chemical shifts and solvent shifts for C-19 and C-18 protons in dioxo- and trioxo-5α-androstanes.

Compound	No.		τ_1	τ_2		τ_3	τ_4
5α-Androstane-1,6,11-trione	100	19	8.73	8.68	8.666[b]	8.81	8.60
		18	9.33	9.33	9.307[b]	9.61	9.42
5α-Androstane-1,6,17-trione	101	19	8.89	8.84	8.866[b]	9.29	8.92
		18	9.15	9.13	9.107[b]	9.53	9.24
5β-Androstane-1,6,17-trione	102	19	9.01	8.95	8.891[b]	9.04	8.89
		18	9.17	9.13	9.124[b]	9.63	9.27
5α-Androstane-3,11,17-trione	103	19	8.79	8.73	8.732[b]	9.03	8.76
		18	9.19	9.13	9.132[b]	9.53±	9.22
5α-Androstane-3,12,15-trione	104	19	8.90	8.86	8.858[b]	9.59	9.05
		18	8.90	8.82	8.816[b]	9.38	8.97
5α-Androstane-6,11,17-trione	105	19	9.05	9.01	9.024[b]	9.03	8.94
		18	9.18	9.15	9.157[b]	9.63±	9.24

TABLE IX [continued]

Chemical shifts and solvent shifts for C-19 and C-18 protons in dioxo- and trioxo-5α-androstanes.

Compound	No.		Δ^2_1	$\Delta^3_{1[found]}$	$\Delta^3_{1[calc.]}$	Δ^4_1
5α-Androstane-1,6,11-trione	100	19	-0.05	+0.08	+0.14	-0.13
		18	0.00	+0.28	+0.23	+0.09
5α-Androstane-1,6,17-trione	101	19	-0.05	+0.40	+0.43	+0.03
		18	-0.02	+0.38	+0.31	+0.09
5β-Androstane-1,6,17-trione	102	19	-0.06	+0.03	+0.40	-0.12
		18	-0.04	+0.46	+0.31	+0.10
5α-Androstane-3,11,17-trione	103	19	-0.06	+0.24	+0.27	-0.03
		18	-0.06	+0.34	+0.30	+0.03
5α-Androstane-3,12,15-trione	104	19	-0.04	+0.69	+0.62	+0.15
		18	-0.08	+0.48	+0.46	+0.07
5α-Androstane-6,11,17-trione	105	19	-0.04	-0.02	+0.04	-0.11
		18	-0.03	+0.45	+0.44	+0.06

EXPERIMENTAL

The spectra were measured in duplicate at a probe temperature of 34° on a Perkin-Elmer R.10 spectrometer (60 Mc./sec.) using an expanded scale (1 cycle/unit). Errors in the τ values are estimated to be less than ± 0.015. Solvents, except $CDCl_3$, were purified: the solutions (0.4 ml.) contained the oxo-steroid (25 mg.) and a little tetramethylsilane.

RESULTS AND DISCUSSION

Tables VIII and IX show the τ values of the methyl groups' signals and the shifts (Δ values) which occur when the reference solvent (carbon tetrachloride) is replaced by deuterochloroform, benzene and pyridine. Assignment of the signals of the deuterochloroform solutions to the C-18 or C-19 protons is made easily by referring to Zürcher's comprehensive study,[182] in which the same solvent was used. With all but two of the oxo-steroids (nos. 92 and 98) the τ values of the methyl groups can be compared with those found in Zürcher's work (nos. 80, 81, 84 and 90) or predicted from it (the remaining twenty compounds). In 46 comparisons (see Tables) the greatest discrepancy (with one exception, no. 102, see below) is less than 0.025 p.p.m., thus confirming the assignments made here and showing that Zürcher's predicted values are remarkably accurate, even with triketones. Using carbon tetrachloride as solvent rather than deuterochloroform causes small shifts of the methyl resonances. The Δ_1^2 values (as defined in Table VIII) range from +0.02 to -0.08 p.p.m., many being close to -0.02,[197] and allocation of the signals is again clear-cut.

With some steroid monoketones the methyl groups' resonances are

shifted markedly in benzene, generally,[192,193] but not invariably,[185] towards higher field. Assignments of the benzene spectra's signals can be based on:- (i) the expected dependence of the shift value (here Δ_1^3) on the geometrical relationship of the methyl and ketonic groups[193] (i.e., the distance between the groups and their relative orientations), (ii) the relative half-height widths of the resonances, and (iii) the requirement that the shift values so obtained should be reasonably additive (see later).

Variations in the extent of the coupling of the methyl protons, and, therefore, in the widths of the signals, with change of the ketonic site arise mainly from the operation or removal of W interactions.[109-112] In general, it is found[198] that angular methyl groups situated at cis-ring junctions give rise to signals which are sharper than those at trans-ring junctions, because they suffer fewer W interactions (see Figure VII). However, the relative widths of the two methyl signals, each appearing as an unresolved resonance, should not be influenced by changing the solvent unless the signals are shifted significantly away from or further into the background methylene envelope.

With the monoketones in Table VIII approaches (i) and (ii) lead to the same assignments with all but the 6-oxo-steroids (nos. 85, 86 and 87). Williams and Bhacca[193] allocated the higher field resonance of 5α-androstant-6-one (no. 86) in benzene to the C-18 protons, and that at lower field to the C-19 protons: comparison with the deuterochloroform values showed a bigger shift (Δ_2^3 = + 0.12) for the C-19 than for the C-18 protons

(+ 0.06 p.p.m.), as expected from approach (i). However, the value (9.38 τ) for the 18-protons' signal in deuterochloroform[193] is incorrect,* and when the present value (9.29 τ) is used the C-18 resonance is seen to shift more than does that of C-19 when the solvent is changed from carbon tetrachloride or deuterochloroform to benzene. To harmonise with the expectations of approach (i) the assignments in benzene should be reversed, but the lower field signal is the narrower in both deuterochloroform and benzene. Support for the original signal allocation,[193] which accords with the line-width approach (ii), is provided by the 5β-6-ketone (no. 87) where the preferred assignments (Table VIII) lead to Δ_1^3 values of + 0.06 (C-19) and + 0.13 p.p.m. (C-18). Reversed attribution of the resonances of the benzene solution gives values of + 0.30 (C-19) and -0.11 p.p.m. (C-18): a negative value for the latter is very unlikely.[115-193] Thus it appears that the signal of the methyl group more remote from the oxo-function experiences the larger shift in the 5β-6-ketone, thereby reducing the force of the objection to the corresponding assignments for the 5α-6-ketones.

From Table VIII the shifts (Δ_1^3) of the angular methyl groups in 17-ketones (nos. 90 and 91) are seen to be little affected by the 5-configureation. Surprisingly, those of the 6-ketones are similarly insensitive to inversion at position 5 (cf. nos. 85, 86 and 87). This is difficult to rationalise on either the earlier[192] or the modified[185] model requiring directionally specific ketone-benzene association, thus

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* Dr. D.H. Williams has kindly informed me that re-examination of 5α-androstan-6-one in deuterochloroform at 100 Mc/sec. shows the signal to be at 9.29 τ.

raising doubts (already expressed[115]) as to whether there is a preferred orientation for solute-solvent interaction.

Values of Δ_2^3 shifts are available[193] for the ketonic types (the 12-, 15-, and 16-oxo-compounds) not included in Table VIII. Assuming (see above) that Δ_1^2 is -0.02 p.p.m., the benzene-carbon tetrachloride shifts can be combined with the present results to give the Δ_1^3 values shown. As expected,

Δ_1^3 values (p.p.m.) for 5α-steroids

Oxo group										
C-19 protons	+0.22	+0.15	+0.32	+0.10	+0.09	+0.26	-0.17	+0.22	+0.08	+0.13	+0.12
C-18 protons	-0.03	+0.06	+0.02	+0.03	+0.16	+0.01	+0.10	+0.24	+0.20	+0.30	+0.18

most of these figures are fairly close to the benzene-deuterochloroform (Δ_2^3) shifts recorded and discussed by Williams and his co-workers.[185,192,193] The pyridine-carbon tetrachloride (Δ_1^4) shifts exemplify a wider range of structure than examined hitherto[185,196,199] they follow the trends which can be predicted empirically,[196] but are generally smaller than the benzene-induced shifts and of consequentially diminished diagnostic significance.

The solvent shifts for the methyl signals of dioxo- and trioxo-5α-androstanes are shown in Table IX. While the Δ_1^2 and Δ_1^4 values are small (only one exceeding 0.15 p.p.m.), large shifts (up to 0.69 p.p.m.) are found with benzene (Δ_1^3). The main point to emerge is that the Δ_1^3 values

are roughly additive, as shown previously for the Δ_2^3 shifts of four dioxo-5α-androstanes.[193] There is no ambiguity in assigning the signals of the benzene spectra, even with the compounds containing 6-oxo-group. [For example, reversing the assignments of 5α-androstane-6,11-dione (no. 96) would lead to unacceptable Δ_1^3 values. Further, in the benzene spectrum of the 11, 17-diketone (no. 99) there is, as expected,[198] a noticeable splitting of the C-18 protons' signal: with the 6,11,17-triketone (no. 105) the 9.63 τ resonance, which is similarly split, must arise from the 18-protons.] The two possible sets of Δ_1^3 figures for 5α-androstan-6-one (no. 86) can then be used to see which gives the better additivity with the di- and tri-ketones. In each of six cases (nos. 96, 97, 98, 100 and 101) the preferred set (that in Table VIII) leads to a closer fit with the observed Δ_1^3 values in Table IX. With 5β-androstane-1,6,17-trione (102), the value for the C-19 protons' resonance in deuterochloroform, calculated from the scanty information in the literature,[182,202] differs from the observed value by a considerable amount (0.06 p.p.m.) compared with the other oxo-steroids studied in this work. This difference may be ascribed to the lack of data on 5β-1-ketones. The 5β-1,6,17-trione also fails to show addivity in its Δ_1^3 values, showing that 1-ketones, unlike 6- and 17-ketones are not insensitive to inversion at C-5.

Examination of 5α-androstane in different solvents confirmed the findings of Williams and Wilson,[185] that the methyl resonances were shifted only very slightly. Likewise, 5β-cholestane behaved in the expected manner. However, the methyl signals of the 5α-cholestane are modified dramatically

FIGURE V111.

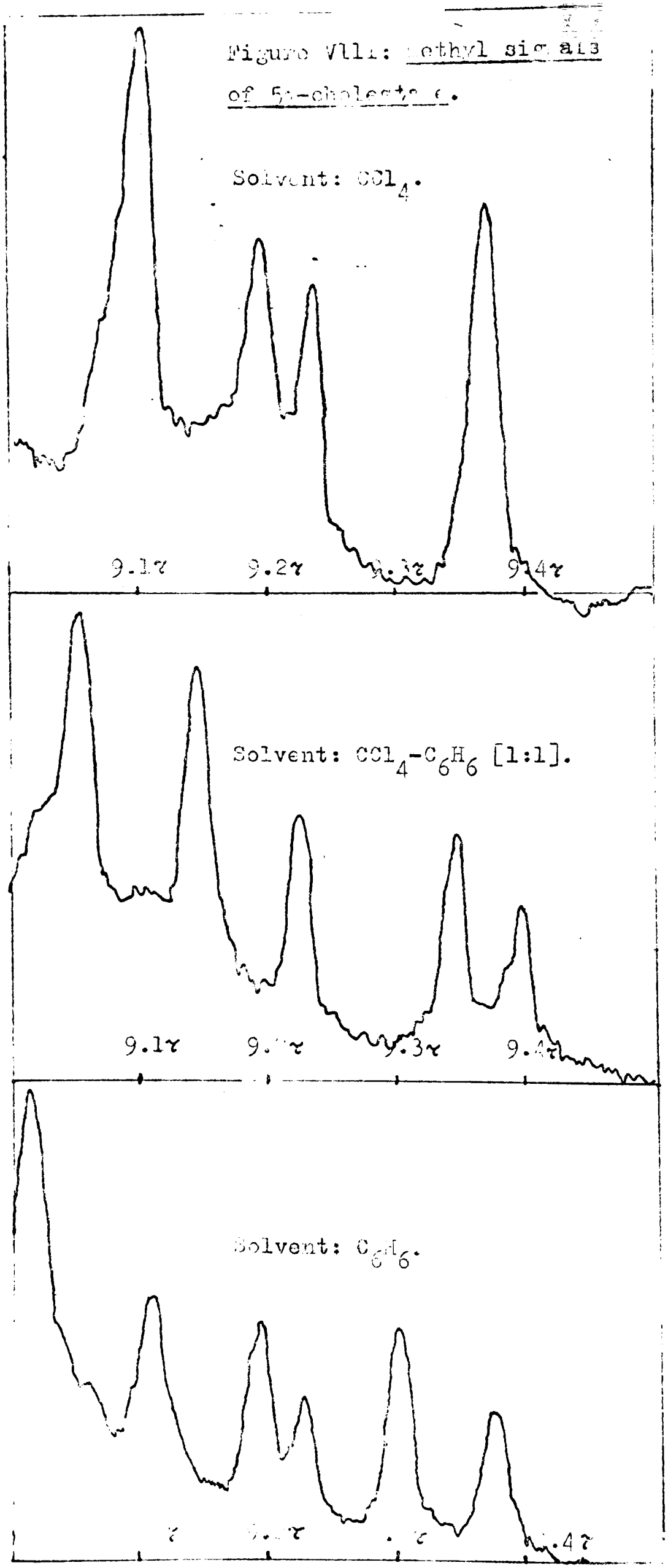
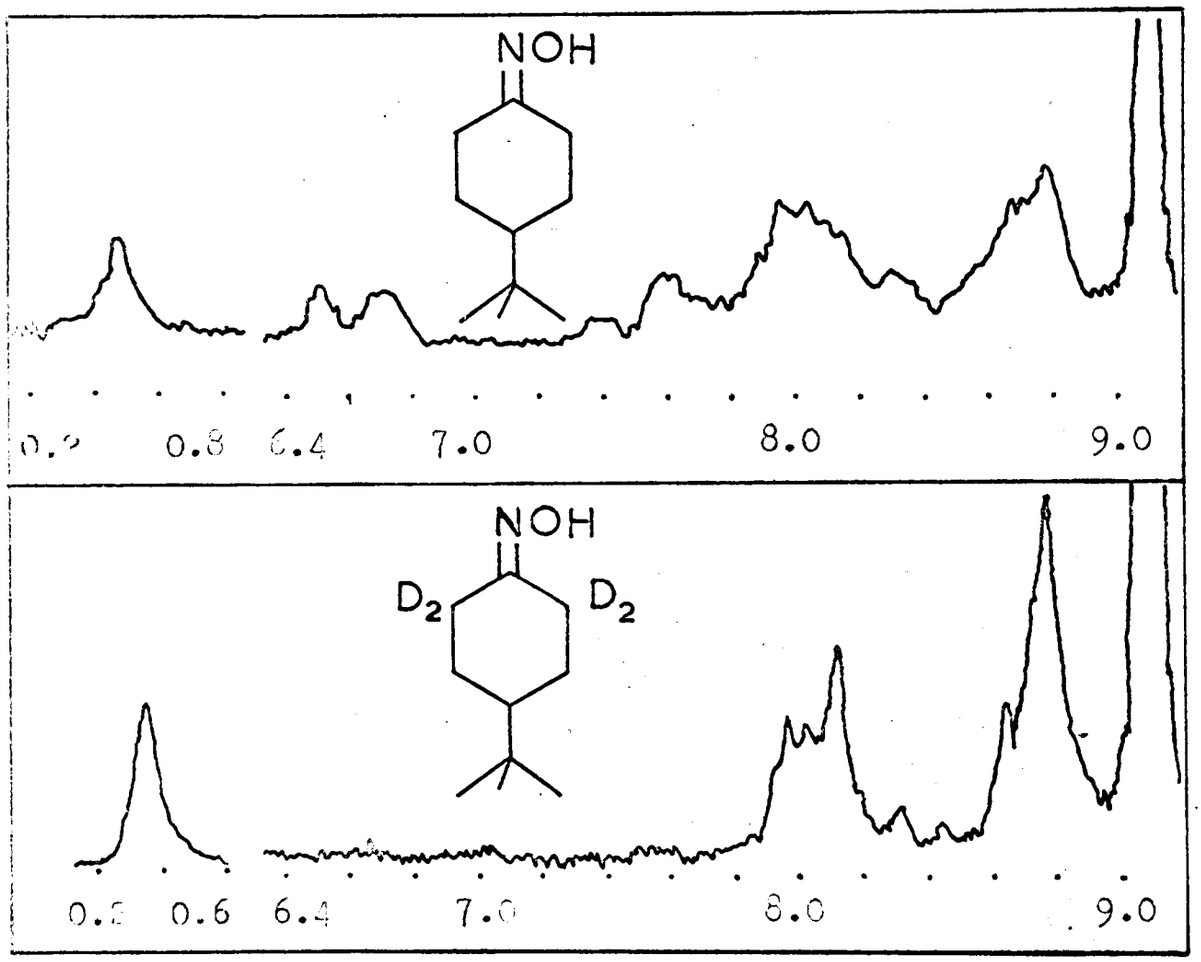


Figure VIIa: Methyl signals of 5α-cholestan-6-one.

on changing from carbon tetrachloride to benzene, and the spectrum obtained using a 1:1 mixture of the solvents does not correspond to combination of those recorded with the individual solvents. These results, illustrated in Figure VIII, could not be rationalised by assuming that only the side-chain methyl groups' signals are being influenced. It appears that the resonances of the angular methyls are also affected by the presence of benzene. The origin of this effect is, at present, unclear.

FIGURE 1X.

Figure 1X



Section IV

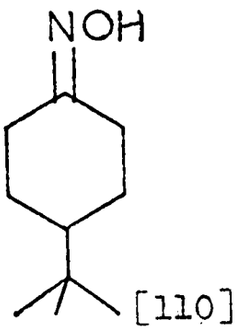
THE N.M.R. SPECTRA OF SOME CYCLIC OXIMES

During the preparation of 2,2,6,6-d_4-4-substituted cyclohexanone oximes in the present work, characteristic differences were observed between the n.m.r. spectra of the parent oximes and those of their deuterated analogues; in particular, low field signals of uncertain origin. Similar low field signals could be seen in the n.m.r. spectra of steroid oximes used in the present, and past work,[6,48] in this Department. It was decided, therefore, to examine the spectra of a series of cyclic oximes in the hope that such a study might throw light on the nature of the protons responsible for the low field signals. With steroid oximes, it was also of interest to compare the shifts of the angular methyl signals with those in the corresponding ketones.

Huitric and Trager[203] have recently analysed the spectra of 4-t-butylcyclohexanone oxime (110) and 4-t-butylcyclohexane-3(axial),5,5-d_3 oxime. (110a) On the basis that the low field signal in the spectrum of the former (see Figure IX) remained unchanged in the spectrum of the latter both at 60 and 100 Mc/s., they ascribed this signal to one of the equatorial protons adjacent to C-1 (the present work verified that the signal was due to a proton at C-1, since this signal was absent in the spectrum of the 2,2,6,6-d_4 oxime). The second equatorial proton adjacent to C-1 gave rise to a signal at 7.52τ, and the axial protons at 7.95 and 8.29τ, respectively.

The deshielding of one of the equatorial protons ~ to C-1, relative

COMPOUNDS 1,5,21,106-118.



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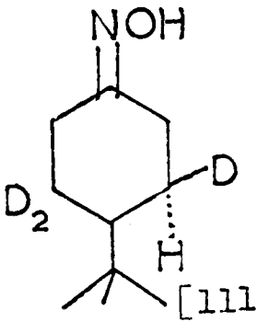
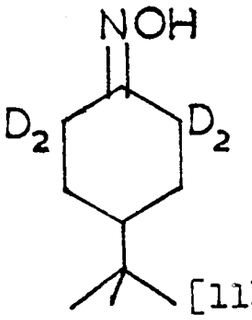
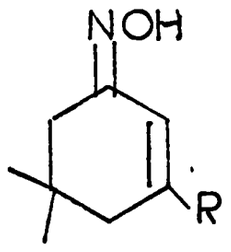


[111a]



[111]



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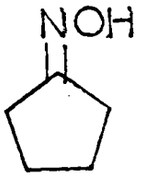

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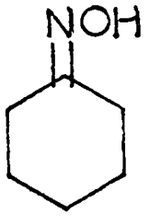

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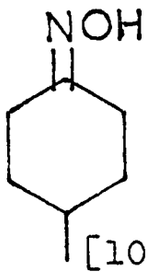

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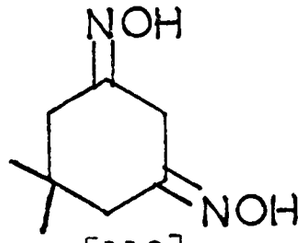

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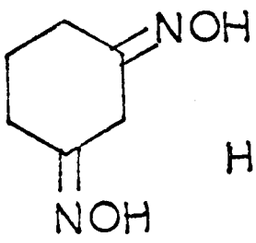

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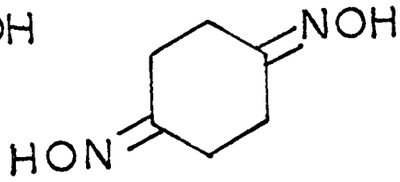

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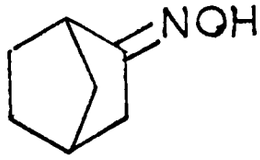

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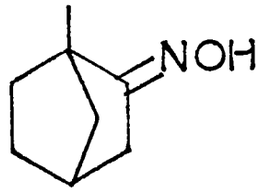

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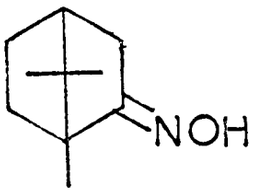

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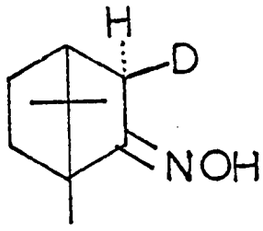

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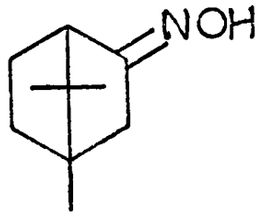

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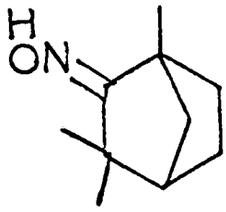

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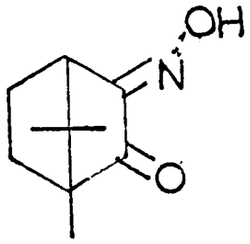

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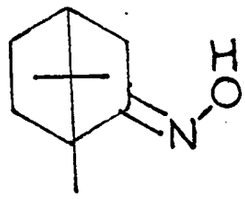


[1a]

to its axial counterpart is ascribed to the magnetic anisotropy of the oxime group.[203] The geometry of this is not known with certainty. Saito and co-workers[204] studied the n.m.r. spectra of several cyclic oximes and their hydrochlorides, and found that the difference in chemical shift between the two equatorial protons adjacent to C-1 in the spectra of the oximes, became zero in the hydrochlorides. Thus, they attributed the greatest deshielding effect to the proximity of the unshared pair of electrons on the nitrogen atom. However, other workers[205-209] have indicated that the largest deshielding effect is caused by the proximity of the hydroxyl group. In particular, Benson and Pohland[209] found that in 3-substituted isophorone oximes (106), the C-2 proton was deshielded by about 0.7 p.p.m. in the syn-isomer relative to the anti-isomer. The syn- and anti- configurations of these compounds were deduced from Mazur's determination[208] of the structures of the isophorone oximes by Beckmann rearrangement.

Three groups of oximes were examined in the present work: monocyclic mono- and dioximes, some bicyclic monoterpene oximes and steroid oximes at positions 1, 2, 3, 4, 6 and 17. In the monocyclic series, the oximes studied (see Table X) - cyclopentanone oxime (107), cyclohexanone oxime (108), 4-methylcyclohexanone oxime (109), 4-t-butylcyclohexanone oxime (110) and its 2,2,6,6-d_4 analogue (111), dimedone dioxime (112), cyclohexa-1,3-dione dioxime (113) and cyclohexa-1,4-dione dioxime showed the features already reported.[203,204]

Features of note in the bicyclic monoterpenes studied - norcamphor oxime (115), 1-methylnorcamphor oxime (116), camphor oxime (1), 3-exo-

TABLE X.

TABLE X

N.m.r. data for monocyclic oximes.

Chemical shifts and coupling constants are expressed in τ values and c.p.s., respectively. Figures in parentheses denote the number of protons in each signal, as estimated by integration. For abbreviations see Table VI.

Compound	No.		Signals
Cyclopentanone oxime	107	1	8.26 m.[4]; 7.6 m.[4]. 0.22 s.[1] =NO.H.
Cyclohexanone oxime	108	2	8.37 m.[6]; 7.76 bs.[2]; 7.46 m.[2].
4-Methylcyclohexanone oxime	109	1	9.05 d.[3]; 6.7 bd. J,12 [1]. 0.9 bs.[1] =NO.H.
4-t-Butylcyclohexanone oxime	110	1	9.10 s.[9]; 6.6 bd. J,12 [1]. 0.48 bs.[1] =NO.H.
2,2,6,6-d_4-4-t-butylcyclohexanone oxime	111	1	9.10 s.[9]; 8.8 m.[3]; 8.05.m.[2]; 0.34 bs.[1] =NO.H.
Dimedone dioxime	112	3	9.04 s.[6]; 7.59 s.[4]; 5.79 s.[2].
Cyclohexa-1,3-dione dioxime	113	3	8.3 m.[4]; 7.3 m.[4]; 5.75 s.[2] =NO.H.
Cyclohexa-1,4-dione dioxime	114	3	7.22 6-line m.[8]; 4.93 s.[2] =NO.H.

TABLE Xl.

TABLE XI

N.m.r. data for terpene oximes.

Compound	No.		Signals
Norcamphor oxime	115	1	8.5 bm.[6]; 7.85 t.[2]; 7.55 s.[1]; 7.15 s.[1]; 1.0 bs.[80 c.p.s.] =NO.H.
1-Methylnorcamphor oxime	116	1	8.70 s.[3] C-10; 8.6 m.[6]; 7.7 m.[3]; 0.80 s.[1] =NO.H.
Camphor oxime[x]	1	1	7.45 dt. J,18.4,3.0; 0.72 s.[1] =NO.H.
3-exo-d_1-camphor oxime[x]	117	1	0.80 s.[1] =NO.H.
Bornan-3-one oxime[x]	5	1	7.0 d.[1] C-4-H; 0.42 s.[1] =NO.H.
Fenchone oxime	118	2	9.27 s.[3]; 9.19 s.[3]; 9.17 s.[3]; 1.6 s.[1] =NO.H.
anti-3-Hydroxyimino-camphor[x]	21	1	6.72 bd.[1] C-4-H; 0.0 bs.[1] =NO.H.
Mixture of syn- and anti-3-hydroxyimino-camphor	21,22	1	7.3 bd. C-4-H [syn]; 6.72 bd. C-4-H [anti].

[x] chemical shifts for these compounds are recorded in Table VI.

deuteriocamphor oxime (117), bornan-2-one oxime (5), fenchone oxime (118) and 3-hydroxyimino camphor (21) - were that the hydroxyl resonance of the oxime function was sharp in compounds 116, 1, 117 and 5 relative to the broad signals (60 c.p.s) in compounds 115 and 117 (see Table XI). The C-10 protons' signal was shielded by 0.31 p.p.m. on passing from compound 116 to camphor oxime (1). In this latter compound (1), the isomer (1a) should be preferred over the isomer in which the oxime group is syn- to C-10, because of interactions with that methyl group. The C-3-exo-proton is deshielded sufficiently to be visible and exhibits the expected splitting pattern (doublet of triplets). No deshielding of the equivalent methylene protons at C-2 in bornan-2-one oxime (5) is observed, but, as is the case with most 3-substituted bornanes, the C-4 proton is deshielded sufficiently to lie outside the methylene envelope. This proton is clearly observed in anti-3-hydroxyimino camphor (21) at 6.73τ. In the spectrum of the mixture of the syn- and anti- isomers, the C-4 signal attributable to the syn- isomer occurs at 7.30τ - a clear indication that the deshielding is due to the close approach of the hydroxyl group.

The spectra of the steroid oximes (Table XII) at the 1, 2, 3, 4, 6 and 7 (5α-configuration) and 3(5β-configuration) positions (nos. 119, 120, 122, 123, 124, 125 and 121) show a low field signal equivalent to one proton. In these compounds, except nos. 121 and 122, the signal takes the form of a broad doublet, indicating that the deshielded proton is equatorial, since axial protons would be expected to appear as a broad triplet because of the large diaxial coupling they would experience in addition to geminal coupling. In the 6- and 7- oximes (124, 125), the

TABLE XII.

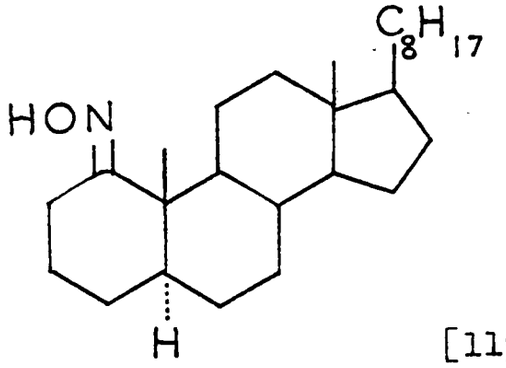
TABLE XII

N.m.r. data for steroid oximes.

w = width of low field signals [c.p.s.]. Ch = cholestane, And = androstane. Other abbreviations, see Table VI.

Compound	No.		C-18	C-19	C_8H_{17}		Other signals
5α-Ch-1=NOH	119	2	9.32	8.93	9.08	9.18	6.65 d.[1] J,9; 2.8 s. w= 24.
5α-Ch-2=NOH	120	2	9.34	9.27	9.08	9.18	6.61 m.[1] w = 24; 2.4 bs. w = 24
5α-Ch-3=NOH	121	2	9.33	9.11	9.09	9.18	6.9 bt.[1] J,12; 1.2 bs. w = 40.
5β-Ch-3=NOH	122	2	9.33	9.02	9.07	9.16	7.1 m.[2] w = 39; 0.18 bs. w = 30.
5α-Ch-4=NOH	123	2	9.34	9.23	9.08	9.18	6.6 m.[1] w = 24; 0.49 s. w = 6.
5α-Ch-6=NOH	124	2	9.34	9.25	9.09	9.18	6.66 d.[1] J,11; 0.22 s. w = 6.
5α-Ch-7=NOH	125	2	9.33	9.06	9.10	9.19	6.83 d.[1] J,10; 1.42 s. w = 6.
5α-And-17=NOH	126	2	9.10	9.20	--	--	7.5 m.[2] w = 18; 0.95 s. w = 12.

COMPOUNDS 119,123-125.



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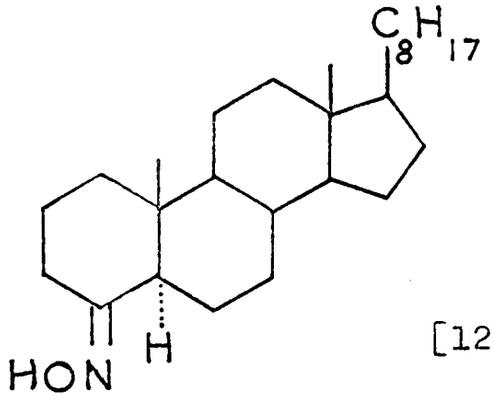

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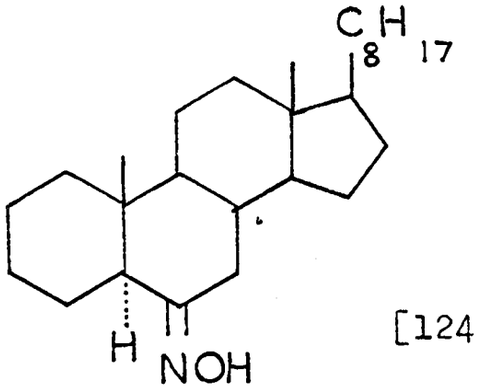

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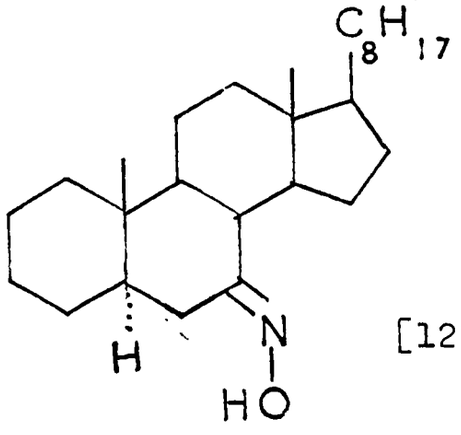

[125]

equatorial nature of the deshielded proton is clearly indicated: the signals are relatively sharp doublets and the large coupling, which would be experienced by axial protons, to the 5α- and 8β-protons is absent. In the 17-oxime a low field signal equivalent to two protons is observed - both protons at C-16 being deshielded. Models indicate that in 6-membered rings, the hydroxyl group of the oxime function approaches equatorial protons more closely than axial protons, and that in the 1-, 4-, 6- and 7-oximes, isomers (119, 123, 124 and 125) are preferred over the alternatives because of strong interactions with the C-11, C-6, C-4 and C-15 methylene groups. In the case of the 2-, 5α- and 5β-3-, and 17-oximes, models show that the compounds, as usually prepared, should contain approximately equal amounts of both isomers. However, t.l.c. examination revealed no separation of the isomers, if present.

The shifts of the angular methyl groups in the oximes studied, relative to the parent hydrocarbons are shown in Table XII. Comparison of the shifts induced by the oxime group with the corresponding data for ketones[182,202] shows that the general effect of the oxime function is

Oxime group	5α-1	5α-2	5α-3	5β-3	5α-4	5α-6	5α-7	5α-17
C-18	-0.03	-0.01	-0.02	-0.02	-0.01	-0.01	-0.02	-0.21
C-19	-0.29	+0.05	-0.11	-0.06	+0.01	+0.03	-0.16	-0.01

Ketone group	5α-1	5α-2	5α-3	5β-3	5α-4	5α-6	5α-7	5α-17
C-18	-0.02	-0.01	-0.04	-0.04	-0.02	-0.02	-0.01	-0.17
C-19	-0.38	+0.02	-0.24	-0.12	+0.03	+0.05	-0.28	-0.02

similar to that of the carbonyl group. It may be tentatively concluded

that the overall anisotropy of the oxime function is similar to that of the carbonyl group.

EXPERIMENTAL

The spectra were measured at a probe temperature of 34° on a Perkin-Elmer R.10 spectrometer (60 Mc/s). The monocyclic and terpene oximes were examined in CCl_4 or pyridine solution at a concentration of approximately 25 mg./0.4 ml, the steroid oximes in $CDCl_3$ at 40 mg./0.4 ml. The angular methyl signals of the steroid oximes were recorded in duplicate on expanded state (1 cycle/unit) and errors in τ values are estimated to be less than $\pm$ 0.02.

The monocyclic oximes were prepared from the commercially available ketones (107, 108, 109, 112, 113, 114) or alcohols (110) by standard methods. 2,2,6,6-d_4-4-t-butylcyclohexanone oxime (111) was prepared as described in Section I, as were the terpene oximes, except norcamphor and 10-methylnorcamphor oximes which are commercially available. Of the steroid oximes, all, except the 1- and 2-oximes, were available from past work in the Department.[6,48] The 1- and 2-oximes were prepared from the available alcohols by standard procedures, the 1-ketone requiring prolonged treatment (24 hours at 78°) for complete oxime formation, and melted 150-151° and 199-200°, respectively (lit.,[210,211] m.p. 151-153°, 200° respectively).

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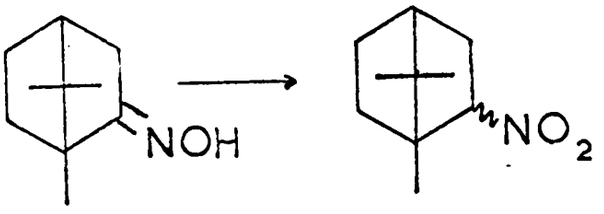
ABSTRACT

During the last decade the synthesis and spectroscopic characteristics of nitro compounds have aroused much interest. New synthetic methods have been developed, and the excellence of the nitro group as a chromophore in spectroscopy has been demonstrated. Previous work in this Department[1] has been concerned with the synthesis and spectroscopic properties of secondary nitrosteroids and related compounds. In the present work, this investigation was extended to nitro compounds in the bornane series, and to α-nitroketosteroids and related compounds. Many oximes and ketones were handled as starting materials, and other ketosteroids were available from microbiological studies. These provided a sufficiently wide coverage of the positions on the steroid nucleus to enable studies to be made of the solvent shifts of angular methyl groups in the n.m.r. spectra of the ketones, and of the low field signals and chemical shifts of the angular methyl groups in the n.m.r. spectra of the oximes. Accordingly, the present investigation is divided into four sections.

In the first Section, general methods for the preparation of secondary nitro compounds are reviewed, and the preparation, and elucidation of the structures of the 2- and 3-nitrobornanes (1, 2) are described. 3-Nitrocamphor (3) was prepared and its behaviour as a non-enolic nitroketone studied. Preparation of the 3-nitrobornanes involved the conversion of camphor (4) into bornan-3-one (5). Both the methods available for this conversion, the classical route[2] *via* the sodium amalgam reduction of the ketol (6), prepared from bornan-2,3-dione (7), and the reported sequence[3]

COMPOUNDS 1-15.



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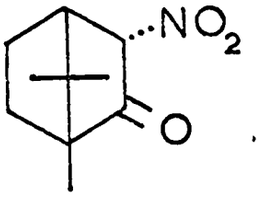

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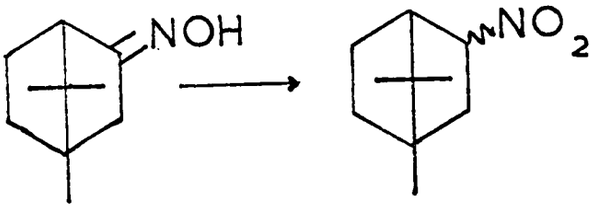

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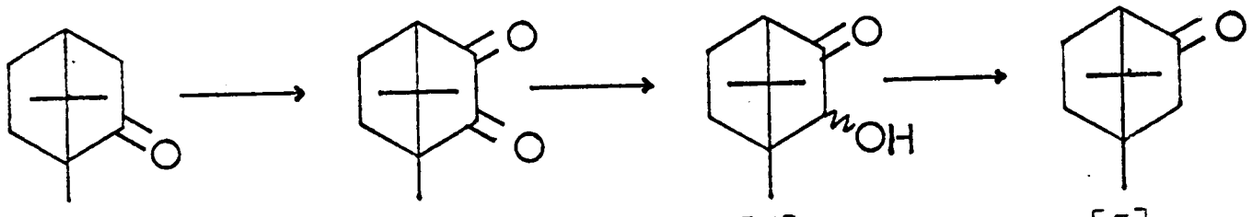
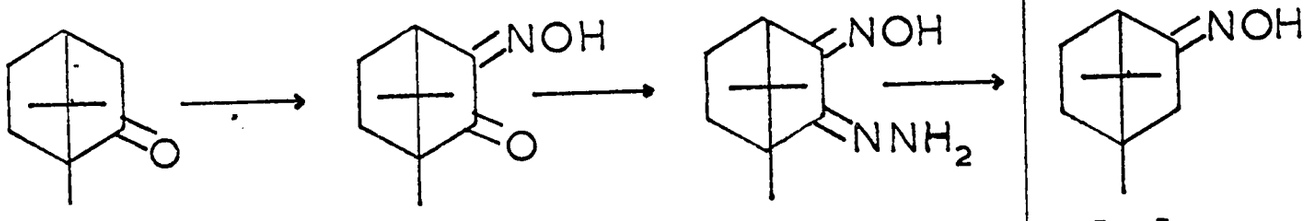
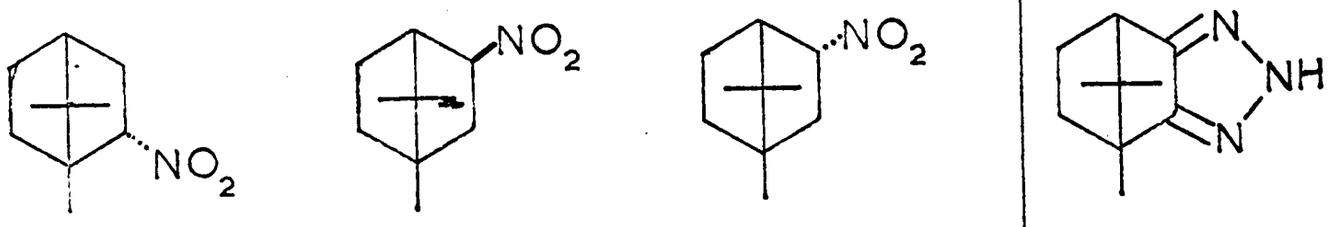


[4] [7] [6] [5]



[4] [9] [8] [10]



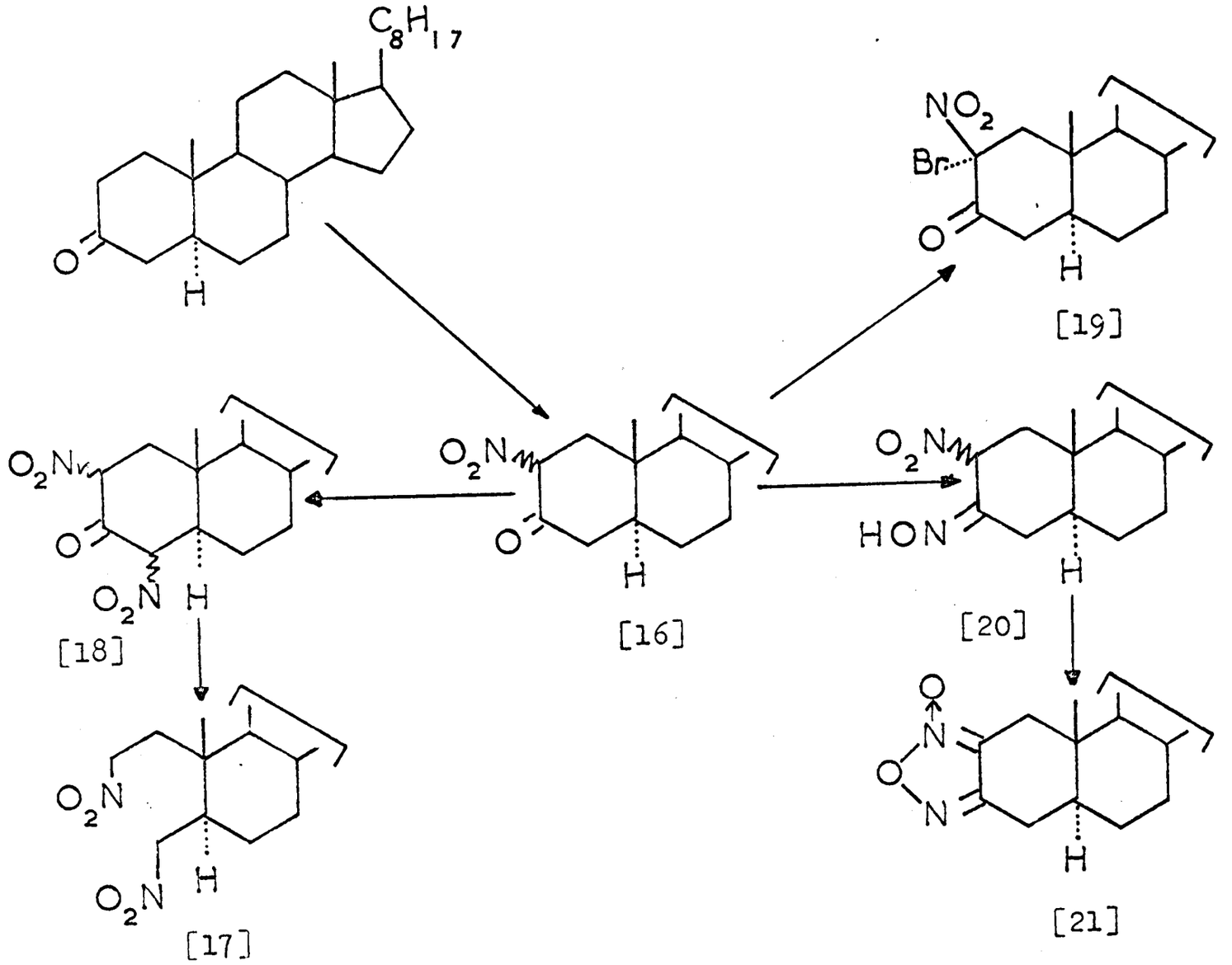
[13] [14] [15] [11]

involving Huang-Minlon reduction of 3-hydroxyiminocamphor hydrazone (8), were studied. The former route was found to be satisfactory and bornan-3-one (5) was prepared from camphor in an overall yield of 10%. The latter route was not satisfactory: attempts to prepare 3-hydroxyiminocamphor hydrazone (8) failed, and reduction of the reaction product from treatment of the isomeric mixture of syn- and anti-3-hydroxyiminocamphor (9) with hydrazine hydrate, under a variety of conditions, did not yield either of the reported products,[3] 3-hydroxyiminobornane (10) and bornano-[2,3,ν]-triazole (11). 2-Nitrobornane (1) was prepared both by N-bromosuccinimide, and nitric acid treatment of camphor oxime (12), with reduction of the bromo-nitro-, and gem-dinitro-intermediates. 3-Nitrobornane (2) was prepared by the N-bromosuccinimide route.

2-Nitrobornane (1) was shown to be a single compound, and 3-nitrobornane (2) to be a 50:50 epimeric mixture. The literature on the n.m.r. spectra of the bicyclo-[2,2,1]-heptane system was summarised, and the structures of these compounds were deduced by n.m.r. examination to be 2-endo-nitrobornane (13), and 3-exo-, and 3-endo-nitrobornane (14, 15). A study of these spectra, those of their respective intermediates and, in some cases, of their deuterated analogues, confirmed previously reported features and revealed some unexpected differences between 2- and 3-substituted bornanes.

3-Nitrocamphor (3) was prepared from camphor by the classical route,[4] reactions involving less vigorous conditions, and base catalysed nitration with ethyl nitrate having failed. The mutarotation[5] of this compound was studied by n.m.r. spectroscopy and polarimetry. The configuration of the

COMPOUNDS 16-23.


[16]
[17]
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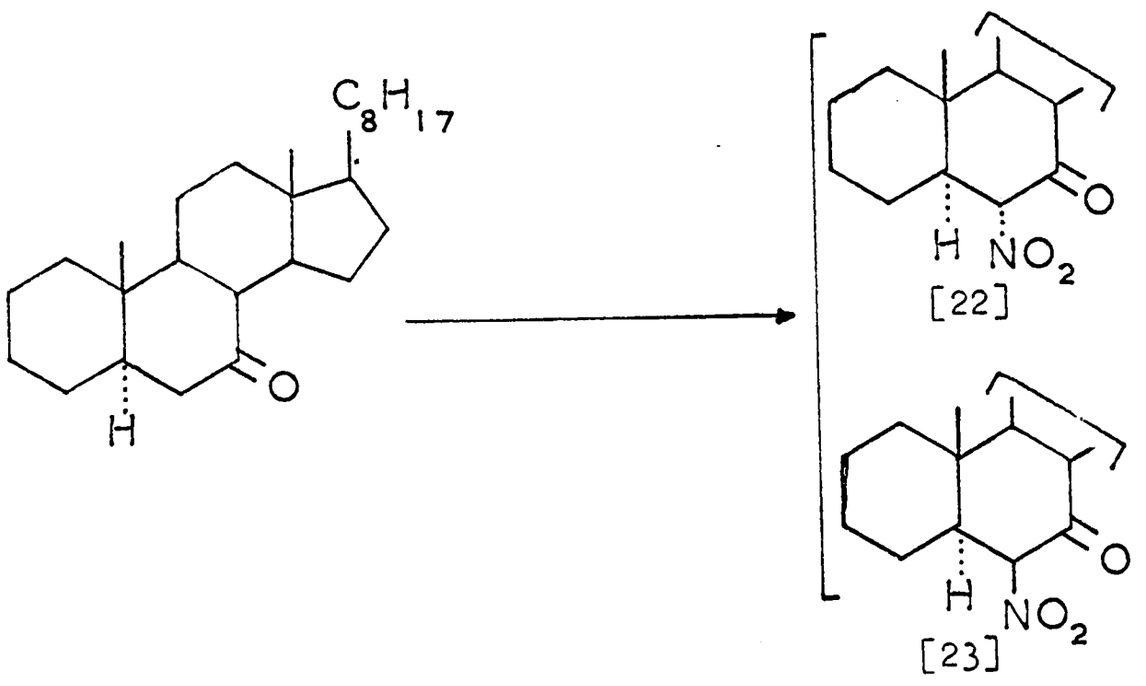
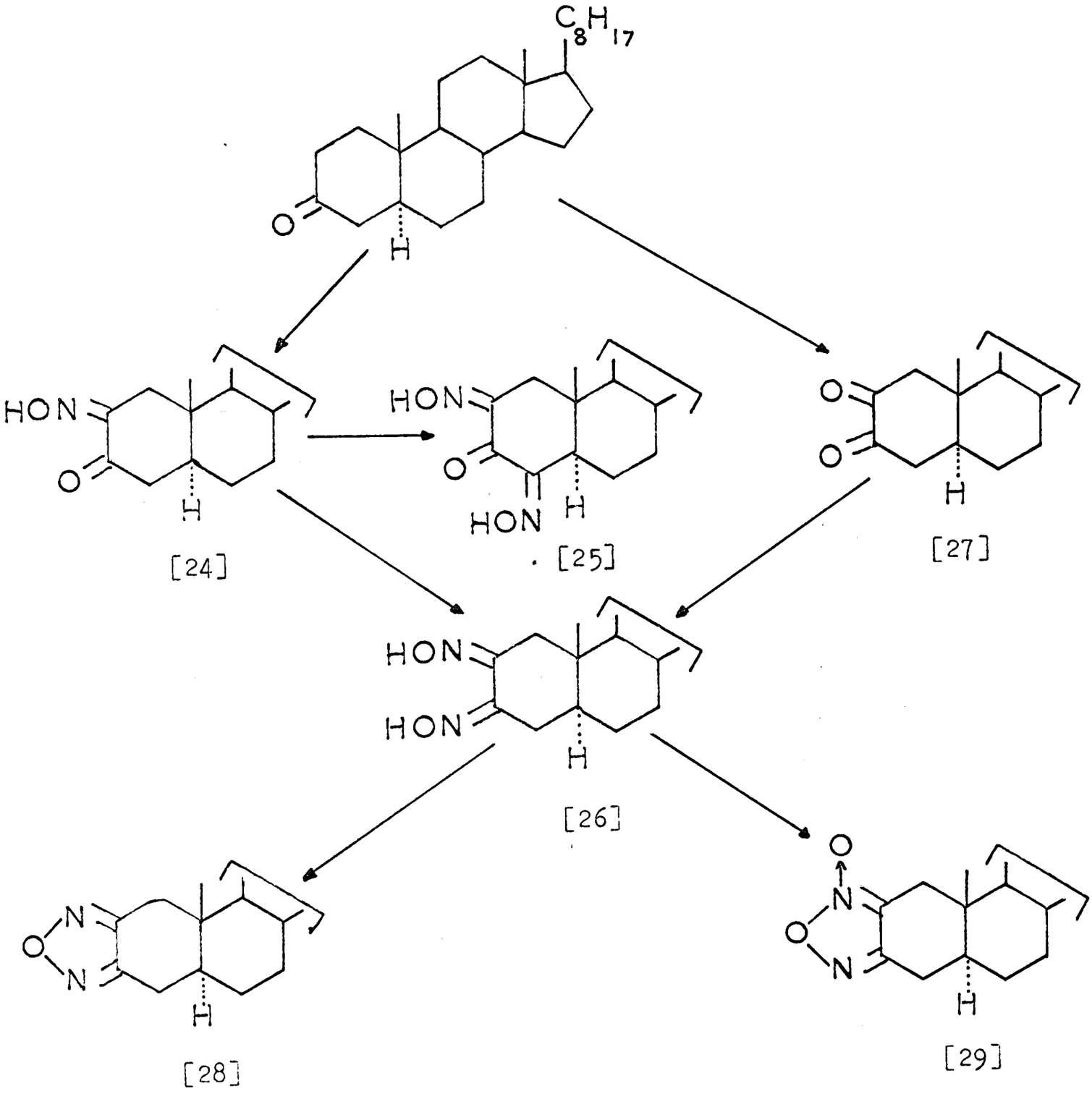

[22]
[23]

nitro group in the only isolable nitrocamphor was shown to be endo-, and Bell's postulate[6] that mutarotation involved the interconversion of stereoisomers was confirmed.

In Section II methods for preparing α-nitroketones and related compounds are described. Base catalysed nitration of 5α-cholestan-3-one, 5α-cholestan-6-one and 5α-cholestan-7-one was carried out. The conditions for this reaction, originally used for the nitration of monocyclic[7] and steroid[8] ketones, and modified by Bull,[1] were studied in detail. The experimental conditions finally evolved afforded 2-nitro-5α-cholestan-3-one (16) in reproducible yields of 52%. The proportion of byproduct, 2,4-seco-2,4-dinitro-5α-cholestane (17) formed from the bis-condensation product (18), was substantially reduced by working at - 30°. The nitroketone (16) was shown, spectroscopically, to be almost totally enolic, and was smoothly brominated to give 2α-bromo-2β-nitro-5α-cholestan-3-one (19), which could be decomposed to give the parent nitroketone (16) in 75% yield. The nitroketone formed an oxime (20) which was used to prepare the furoxan (21).

5α-Cholestan-7-one was nitrated under the same conditions as the 3-ketone and afforded a mixture of nitroketones (44%). Crystallisation of the mixture gave 6α-nitro-5α-cholestan-7-one (22), and equilibration of the mixture by treatment with $NaHCO_3$ and acidification yielded 6β-nitro-5α-cholestan-7-one (23). The structures of these compounds were determined by n.m.r. spectroscopy, and were confirmed by the instability of the 6β-nitroketone (23) due to interaction with C-19. Both nitroketones, on treatment with a trace of $NaHCO_3$, without acidification in the working up,

COMPOUNDS 24-30.


C8H17
O
H
HON
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O
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H
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O
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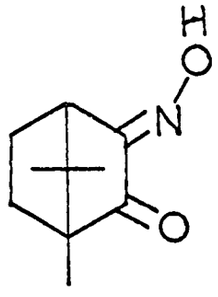
H
O
N
O

[30]

afforded the 6α-nitroketone (22), and a second compound which was not investigated further. Nitration of 5α-cholestan-6-one occurred only in low yield (<5%), the major product being unchanged ketone. This is attributed to hindrance of approach to C-7 by the C-15 methylene group.

A second route to steroid nitroketones was investigated, but not carried to its conclusion. This route led, instead, to a study of compounds containing vicinal nitrogen substituents. 5α-Cholestan-3-one was hydroxyiminated[9] under basic conditions: with one mol. of amyl nitrite, 2-hydroxyimino-5α-cholestan-3-one (24) was obtained in 34% yield. With 2 mols. of nitrite, the 2,4-disubstituted ketone (25) was obtained (22%). Under acid catalysed conditions,[10] the hydroxyiminoketone (24) was obtained in 70% yield, and was converted to the 2,3-dioxime (26) in 99% yield. This dioxime was also prepared by oxygenating 5α-cholestan-3-one under Barton's conditions,[11] and oximating the resulting dionediosphenol mixture (27). This dioxime was dehydrated to the furazan (28), and oxidised with sodium hypochlorite to the furoxan (29). The properties of these compounds were in agreement with analogous compounds previously reported.[10] The furoxan (29) was shown to have the structure (29) by comparison with the furoxan (21) prepared from the 2-nitro-3-oxime (20). The dioxime was oxidised under conditions (buffered peracid) where steroid monoximes give good yields of secondary nitro-compounds,[1] but the only identifiable product (18%) was a furoxan whose properties were similar to those of the product prepared above. A small amount of material (6%) was isolated which exhibited strong nitro absorption in its i.r. spectrum (1540, 1580 $cm.^{-1}$).

During the preparation of the starting materials used in this section,

it was found that the hydroboration of cholest-5-ene in the preparation of the 6-ketone, was not as stereospecific as had been reported.[12] The mixture of 5α- and 5β-6-ketones produced was subjected to an alkaline epimerisation without any change in composition. In view of the fact that the ketone would be used under equilibrating conditions, the material prepared, containing approximately 15% of 5β-cholestan-6-one, was used without further purification.

The signals of the angular methyl groups in twenty-six mono-, di- and tri-oxo-steroids, free from other substituents were examined in carbon tetrachloride, deuterochloroform, benzene and pyridine (Section III). Benzene was found, as expected,[13] to give rise to the largest shifts, and the Δ_1^3 values ($\tau_{C_6H_6} - \tau_{CCl_4}$) of the methyl groups varied characteristically with the position of the ketonic groups. With the 6-ketones, the Δ_1^3 value appeared to be greater for the C-18 than for the C-19 protons: unexpectedly, changes in stereochemistry at C-5 had little effect on the shifts in the 6- and 17-ketones. The methyl resonances of deuterochloroform solutions of di- and tri-oxo-5α-androstanes showed remarkably good agreement with the figures predicted from Zürcher's survey,[14] and the observed Δ_1^3 values were close to those calculated from the shifts of the corresponding monoketones.

In Section IV, a study of the n.m.r. spectra of eight monocyclic mono- and dioximes, eight bicyclic monoterpene oximes and steroid monoximes at the 1, 2, 3, 4, 6, 7 and 17 positions is described. The features of the spectra of the monocyclic oximes were found to be in agreement with those previously reported.[15] In the spectra of the isomeric mixture of <u>syn</u>- and <u>anti</u>-3-hydroxyimino camphor (9) and of pure <u>anti</u>-3-hydroxyimino camphor (30), a

clear indication of the deshielding effect of the hydroxyl group of the oxime function on the C-4 proton was observed. The low field signals in the spectra of the steroid oximes were shown to be equatorial in nature because of their appearance as doublets. Comparison of the shifts of the C-18 and C-19 protons' signals in these compounds, relative to the parent hydrocarbons, with those of compounds with ketone groups in the same positions indicated that the general effect of the oxime function is similar to that of the carbonyl group, since the observed shifts were of the same magnitude and sign.

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