STUDIES ON THE SYNTHESES OF AZONIA-AZULENES AND RELATED COMPOUNDS

by

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SUMMARY

Some substituted azonia-azulenes have been prepared for the first time. The synthetic route involves the double elimination of hydrogen bromide from the appropriate α,α-dibromoketone using lithium chloride in dimethylformamide. Attempts have been made to synthesise the unsubstituted azonia-azulenes from the intermediate azepinones but these were not successful.

A brief review is given of the uses of lithium halides in dimethylformamide as reagents for elimination.

The double dehydrobromination reaction has been extended to give a new synthesis of benzo[2,3]tropones and related systems. Investigations into the mechanism of elimination have been carried out and a possible reaction pathway proposed.

ACKNOWLEDGMENTS

I am indebted to Dr. G. Jones for his guidance and encouragement during this work.

I would like to thank Professor H.D. Springall and the University of Keele for the provision of laboratory facilities and the Science Research Council for financial support.

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I would also like to thank Mrs P. Bebb for the typing of this thesis.

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PART I

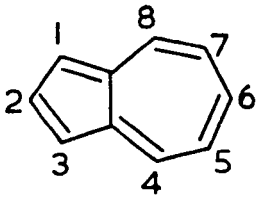
INTRODUCTION

Nomenclature

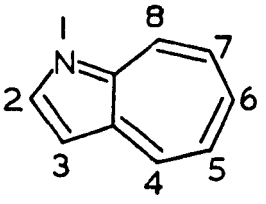
Since the fifteenth century certain essential oils were found to develop blue colours on treatment with acids or oxidising agents. In 1864[1] the name 'azulenes' was first used to describe these blue oils, and when the chemical structure of azulenes was elucidated the parent hydrocarbon (1) was given the name 'azulene'.[2]

Compounds derived by the introduction of a single nitrogen atom into any position in the azulene ring other than the bridgehead have been termed aza-azulenes (2).

The term 'azonia' has been used to describe an aromatic compound derived from another by the replacement of a bridgehead carbon atom by a quaternary nitrogen.[3] Thus in the azulene series a quaternary nitrogen atom at the bridgehead becomes an azonia-azulene (3). The systematic names given to the azonia-azulenes (3) and (4) are pyrrolo[1,2-a]azepinium and azepino[1,2-a]indolium salts respectively.



(1)



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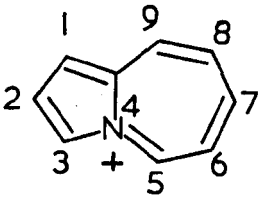

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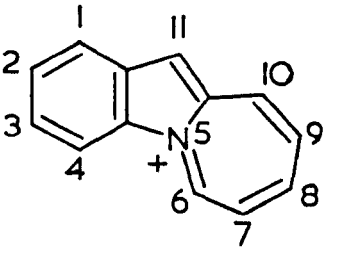
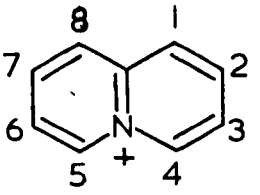


(4)

The numbering system of the azulene ring (1) has also been employed to describe the aza-azulenes. In the azonia-azulenes the bridgehead nitrogen atom is included in the numbering system as shown in the salts (3) and (4).

Historical Review.

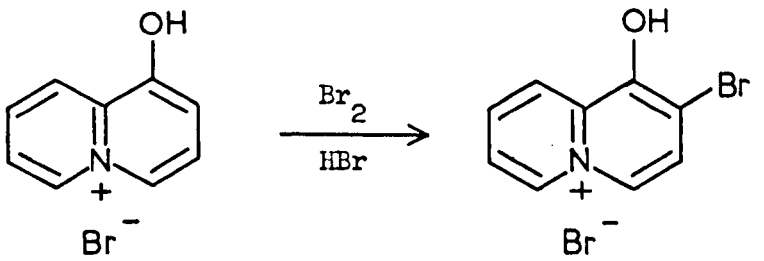
Salts of the parent quinolizinium cation (5) were first prepared by Beaman and Woodward[4] although the first published synthesis was that due to Boekelheide and Gall[5] in an overall yield of 10%. Since then other synthetic methods have been developed and probably the best available for the synthesis of the parent quinolizinium ion is that due to Glover and Jones.[6]



(5)

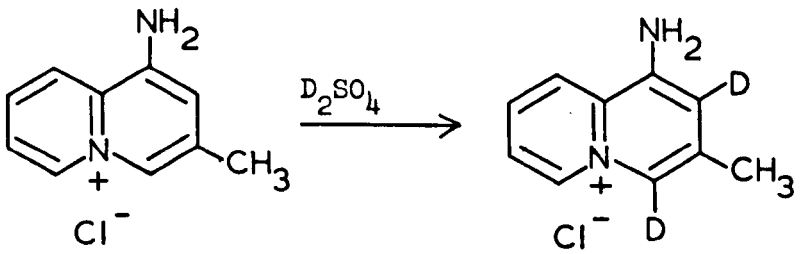
The synthesis of the quinolizinium cation has shown the basic stability of this particular system. As a π-electron deficient species carrying a delocalised positive charge susceptibility to nucleophilic attack was expected. Calculations of electron densities[7] predicted nucleophilic attack at positions 2 and 4 and to some extent this has been confirmed by the work of Miyadera[8] on the reaction of Grignard reagents with quinolizinium bromide. The nucleophilic species attacks the 4-position with ring opening to give pyridylbutadienes. Similar results[9,10] were obtained from reactions between unsubstituted and substituted quinolizinium salts and lithium aluminium hydride.

On account of the delocalised positive charge carried by the quinolizinium cation electrophilic attack was expected to be more difficult than in pyridine or quinoline. The introduction of a powerful electron-donating group, however, modified the resistance of the quinolizinium system sufficiently to allow electrophilic substitution to occur. This was illustrated[11] by the ready bromination of 1-hydroxy quinolizinium bromide (6) to the 2-bromo derivative (7) in 80% yield.



(6) (7)

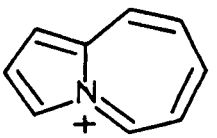
More recently[12] it has been shown that hydrogen-deuterium exchange takes place at the 2 and 4 positions of 1-amino-3-methyl quinolizinium chloride (8) in deuterosulphuric acid to give the 2,4-dideuteroderivative (9).



(8) (9)

The stability of the quinolizinium ion suggested the possible existence of other iso π-electronic heterobicyclic aromatic analogues. Several of the possible 6,5-bicyclic ring systems, formed by the replacement of two adjacent CH units in the quinolizinium ring by a secondary heteroatom, have been prepared.

In turn, this has led to an interest in the possibility of synthesising the 5,7-bicyclic azonia analogue of azulene, notably the pyrrolo[1,2-a]azepinium system (10).



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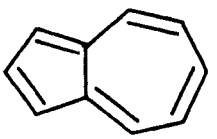
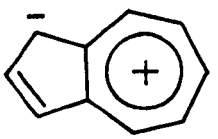
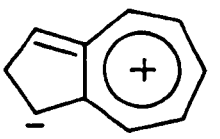


(1)

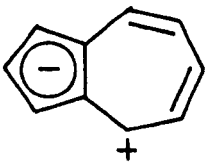
Azulene (1) itself has a conjugated system involving 10 π-electrons and shows many properties typical of an aromatic compound. Apart from the two Kekulé representations it is possible to write several dipolar structures (11a) to (11e) which have been used to explain the nucleophilic and electrophilic character of the five and seven membered rings respectively.



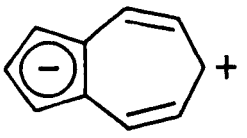
(11a)



(11b)



(11c)



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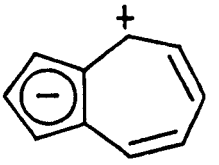
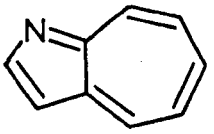


(11e)

Furthermore, it could be anticipated that in the azonia-azulene (10) the seven membered ring would also be susceptible to nucleophilic attack. Electrophilic attack might be expected to occur in the five membered ring but due to the positive charge carried by the azonia-azulene (10) this would probably be more difficult than in azulene (1).

When work began on a possible synthesis of the pyrrolo[1,2-a] azepinium system (10) there were no examples of any azonia-azulene salts reported in the literature. The most closely related aromatic systems known at the time were the aza-azulenes (2) and (12).



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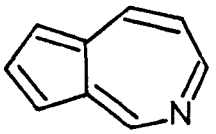
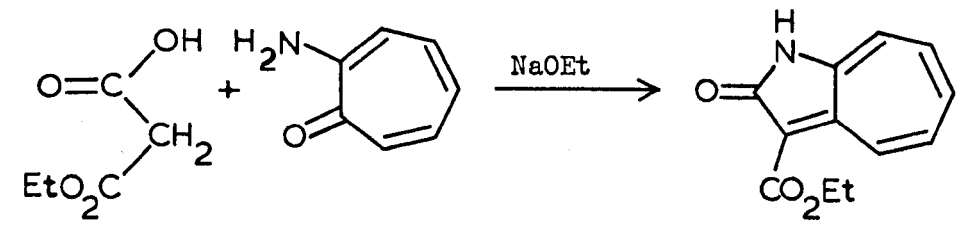


(12)

Nozoe et al.[13] condensed 2-aminotropone with ethyl malonate in the presence of sodium ethoxide to give the carbethoxy aza-azulanone (13). This was hydrolysed and decarboxylated with hydrobromic acid at 120-130°, and the product (14) on treatment with phosphorus oxychloride reacted in the tautomeric form (15) to give the 2-chloro-1-aza-azulene (16). Heating the 2-chloro derivative (16) with hydrazine hydrate gave the 2-hydrazino compound (17) which on treatment with dilute acetic acid in the presence of a cupric salt gave a 67% yield of the 1-aza-azulene (2) as a red oil. Absorptions in the ultra-violet occurred at 263, 316, 330 and 460 nm.

SCHEME I



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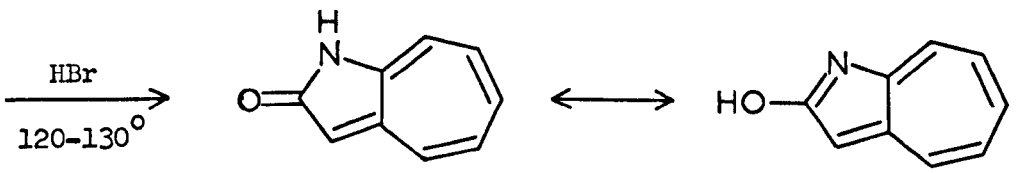

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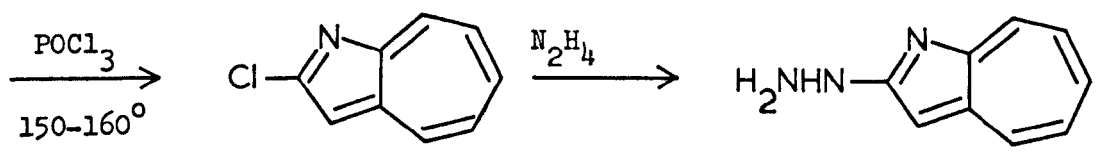

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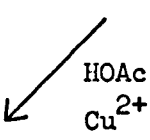
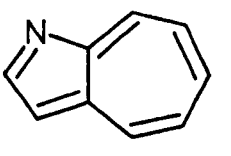


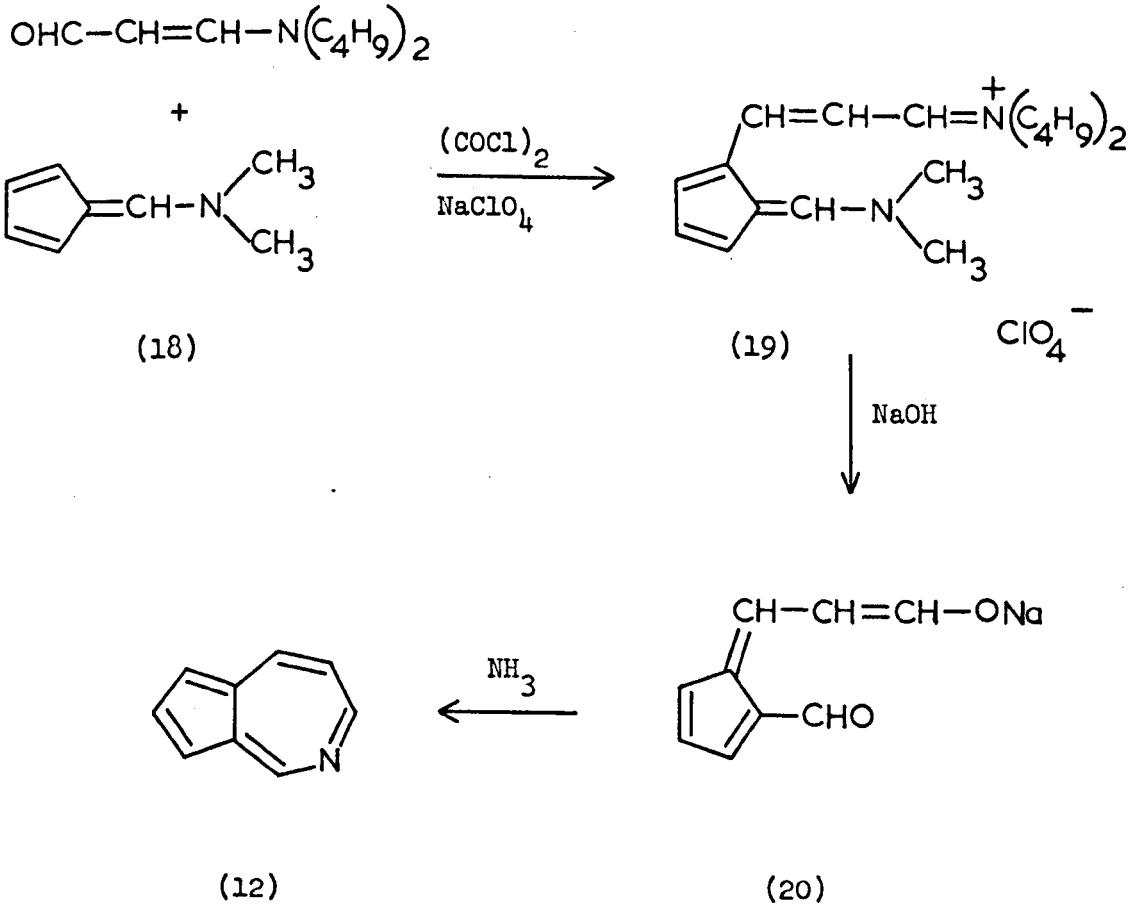
(17)



(2)

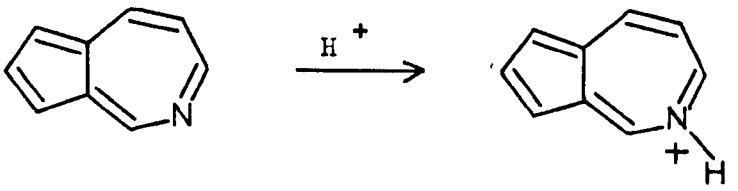
The synthesis of the 5-aza-azulene (12) was first reported by Hafner and Kreuder[14] in 1961. 6-Dimethylaminofulvene (18) reacted with N.N-dibutylaminoacrolein under the influence of oxalyl chloride and sodium perchlorate to give the perchlorate salt (19). Alkaline hydrolysis of the salt (19) gave the aldehyde (20) which cyclised to the aza-azulene (12) on boiling in aqueous ammonia.

SCHEME II



(18) (19) (20) (12)

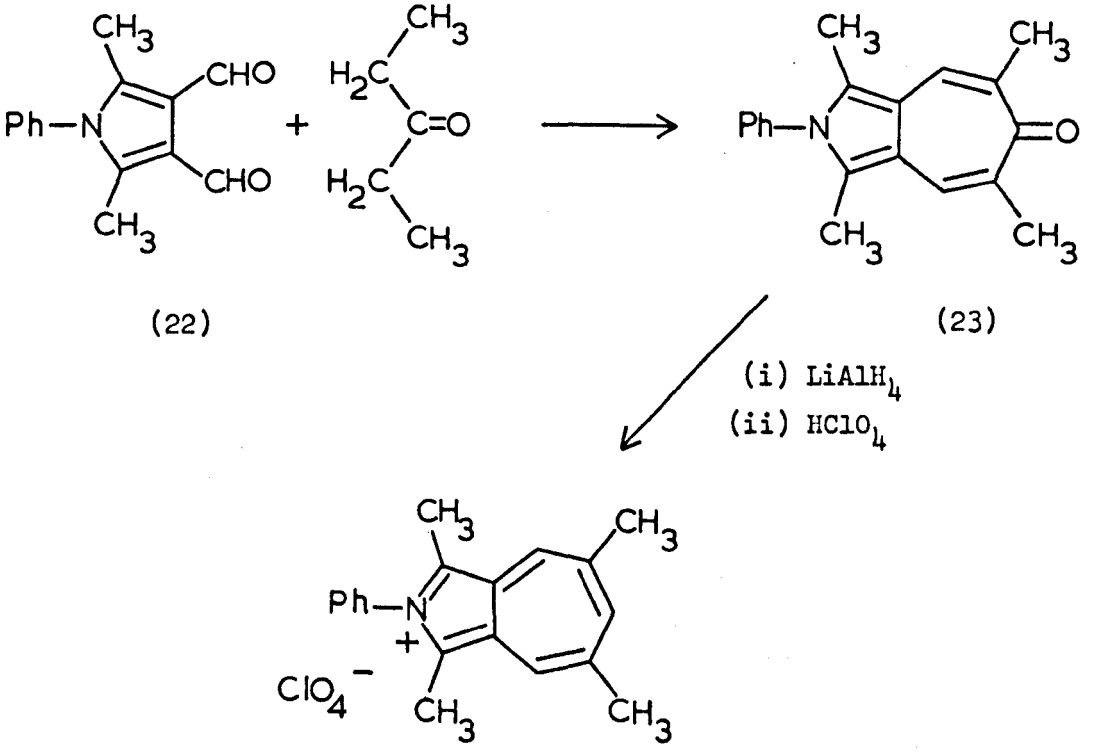
The aza-azulene (12) was obtained as violet plates, the longer wavelength absorption in the ultra-violet occurring at 652 nm. It was also reported[15] that protonation occurred on the nitrogen to give the aza-azulenium salt (21).



(12) (21)

In 1968 El'tsov, Ginesina and Kivokurtseva[16] reported the synthesis of a highly substituted 2-aza-azulenium salt (24). Condensation of the 3,4-diformyl-2,5-dimethylpyrrole (22) with diethyl ketone gave the tropone (23). This was readily reduced with lithium aluminium hydride to the carbinol which on treatment with perchloric acid gave the substituted 2-aza-azulenium perchlorate (24).

SCHEME III



(22) (23)

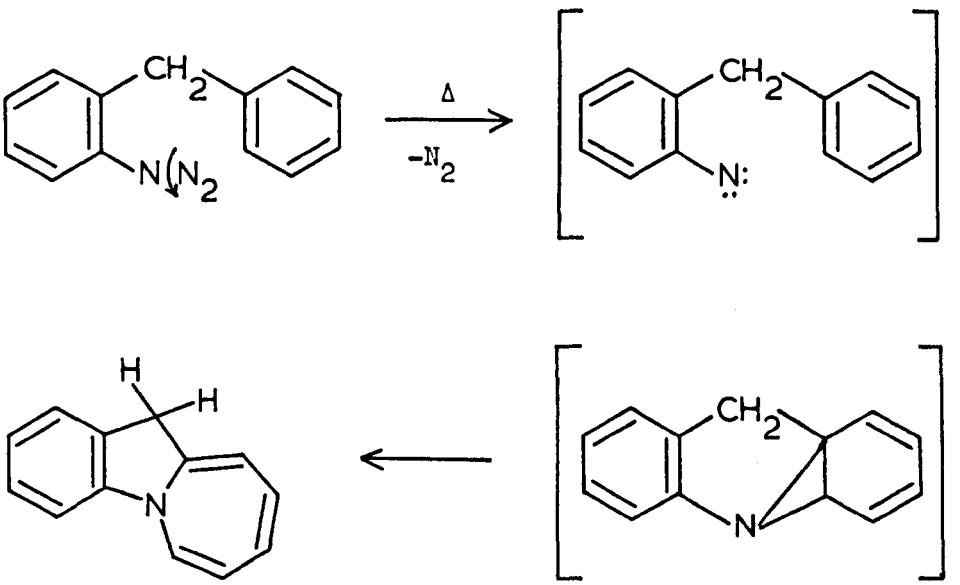
(24)

The salt (24) was deep blue having the longwave band between 660-710 nm. in the electronic spectrum.

Corresponding sulphur analogues were also prepared and from molecular orbital calculations carried out on the thio-derivative it appeared that the electron density at positions 1 and 3 of the ion were relatively increased, and positions 4 (8) and 6 were most electrophilic.

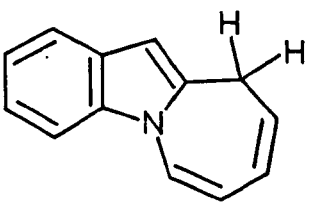
More recently, Krbechek and Takimoto,[17] studying the thermal decomposition of ortho-substituted phenyl azides found that ring expansion occurred when o-azidodiphenylmethane was heated in 1,2,4-trichlorobenzene at 160°. The product was formulated as the azepino[1,2-a]-11H-indole (25) produced as shown in Scheme IV.

SCHEME IV



(25)

However, in the light of further evidence obtained this structure has been revised and now shown[18] to be the azepino[1,2-a]-10H-indole (26).



(26)

DISCUSSION

The review has shown that several aza-azulenes have been prepared. The only reported synthesis to date of any azonia-azulene salts is that due to Collington and Jones[19,20] and is described later in this discussion.

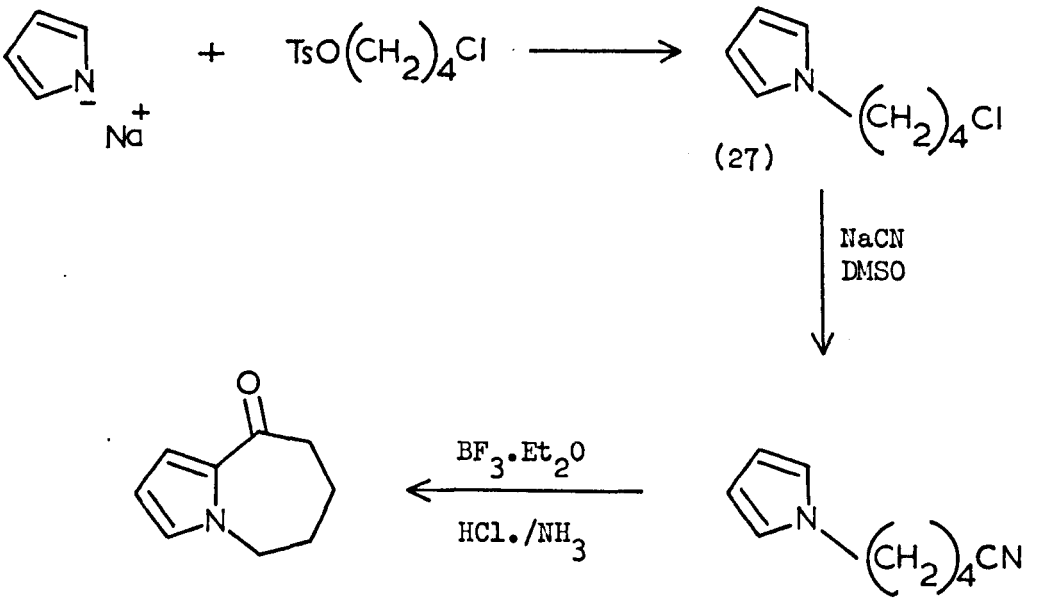
Synthesis and bromination studies on 6,7,8,9-tetrahydro-5H-pyrrolo [1,2-a]azepin-9-one (29)

The route envisaged for the preparation of a bicyclic azonia-azulene entailed a bromination and dehydrobromination sequence from the already known 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (29).[21]

The procedure described for the preparation of N-(4-chlorobutyl)-pyrrole (27) was modified by employing an inverse addition technique of the sodium pyrrolide to 4-chlorobutyl p-toluenesulphonate improving the yield from 32 to 51%. Treatment of the chlorobutylpyrrole (27) with sodium cyanide in dimethyl sulphoxide gave the N-(4-cyanobutyl)pyrrole (28). Cyclisation of the nitrile (28) was effected using hydrogen chloride and boron trifluoride etherate catalyst and the intermediate imine formed was hydrolysed to the bicyclic ketone (29) by boiling in aqueous ammonia. The periodic addition of more ammonia during hydrolysis was found to improve the reported yield by 17%. The n.m.r. spectrum of the bicyclic ketone (29) showed both methylene absorptions adjacent to the nitrogen

and the carbonyl function as triplets centred at 5.66 and 7.2τ respectively.

SCHEME V



A preliminary bromination was carried out at room temperature on a carbon tetrachloride solution of the bicyclic ketone (29) using three molar equivalents of bromine. The reaction product, a dark oil, was shown from its n.m.r. spectrum to be a mixture of brominated materials. The disappearance of the triplet centred at 7.2τ and the formation of a one proton triplet centred at 5.1τ suggested that a bromine atom occupied an α-position to the carbonyl group. The decreased

intensity of the pyrrole ring protons also suggested a certain amount of nuclear bromination. Several unsuccessful attempts were made to separate the components of the mixture by column chromatography. Over several days the brominated mixture was observed to change into a black intractable tar.

Marquet and co-workers[22] have successfully used phenyltrimethylammonium tribromide for the selective α-bromination of a ketone in the presence of a double bond, and it was hoped that the use of the reagent on the bicyclic ketone (29) would avoid the possibility of bromination on the pyrrole ring.

However, treatment of the bicyclic ketone (29) in dry tetrahydrofuran with an equimolar amount of phenyltrimethylammonium tribromide was again found to give a mixture of brominated materials in which a certain amount of nuclear bromination had also occurred.

Since no success at separation of the brominated mixture had been obtained previously it was thought that if dehydrobromination of the mixture could be readily effected to give the respective unsaturated ketones, then these might prove more easily separable by chromatography.

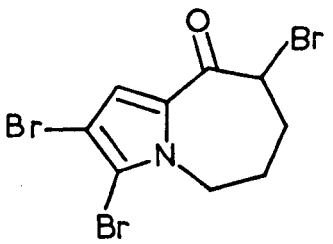
A freshly prepared sample of the brominated mixture was heated with excess 2,6-lutidine for 1hr. Working up gave a brown liquid which had fairly strong absorption at 1640 and 1600 cm^{-1} (α,β-unsaturated carbonyl) in the infrared, and a bathochromic shift of 33 nm in the ultra-violet. Examination of the liquid by thin layer chromatography (t.l.c.) using benzene - 10% ethyl acetate showed four components. A

sample of the liquid was chromatographed on a column of silica-gel. The first eluting solvent used, benzene, failed to elute anything from the column, but benzene containing up to 10% ethyl acetate eluted a large proportion of the unsaturated ketone mixture. The remaining material on the column was eluted with benzene - 20% ethyl acetate and two fractions from this later elution were found to give single peaks on the Vapour Phase Chromatogram (V.P.C.). However, when attempts were made to remove the eluting solvent mixture the contents rapidly turned purple and investigation of the residue formed suggested polymerisation had occurred.

Since it is generally known that conditions used for the halogenation of pyrroles must be mild or decomposition occurs, it was felt that removal of the hydrogen bromide formed during the initial experiments on bromination might enable a cleaner product to be isolated and a possible separation obtained.

The bicyclic ketone (29) in carbon tetrachloride, containing suspended calcium carbonate, was treated dropwise with an equimolar amount of bromine in the same solvent. After stirring for 2hr. at room temperature the solvent was removed to give a light brown oil. V.P.C. analysis showed two products in addition to a small amount of starting material. The mixture was chromatographed on a column of activity III alumina and eluted with benzene-petroleum ether (b.p. 40-60^{o}). Although V.P.C. examination of the fractions collected showed that a complete separation had not been achieved, a white solid slowly crystallised from

an ether solution of one of the fractions. The n.m.r. spectrum of this solid showed a one-proton singlet in the aromatic region at 2.8τ which suggested two bromine atoms were present in the pyrrole ring. A one-proton triplet centred at 5.1τ also suggested that a bromine atom occupied an α-position to the carbonyl function. The analysis figures obtained were consistent with those of a tribromoketone and this information led to the tentative assignment of structure (30) for this compound.



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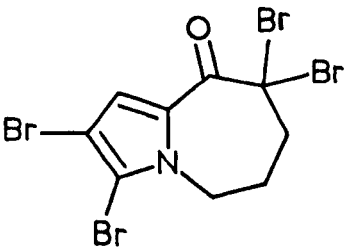


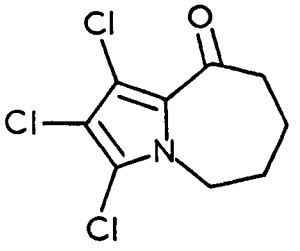
(31)

In order to acquire more of the tribromoketone (30), the bicyclic ketone (29) was treated with three molar equivalents of bromine under the same conditions as those described above. The n.m.r. spectrum of the residue showed it to contain some of the tribromoketone (30) together with what appeared to be a tetrabromoketone indicated by the presence of a methylene triplet centred at 7.0τ. On trituration of the residue with dry ether pale yellow crystals were deposited. These

were subsequently shown to be the tetrabromoketone, which was tentatively assigned structure (31). Again a definite assignment of the position of the two bromine atoms on the pyrrole ring could not be made.

Bromination of the bicyclic ketone (29) with four molar equivalents of bromine proceded smoothly to give the tetrabromoketone (31) in 75% yield.

Finally, an attempt was made to chlorinate the bicyclic ketone (29) with a chlorine saturated solution of carbon tetrachloride. The product isolated was identified as the trichloroketone (32). The n.m.r. spectrum did not possess any absorption below the N-methylene multiplet centred at 5.65τ.



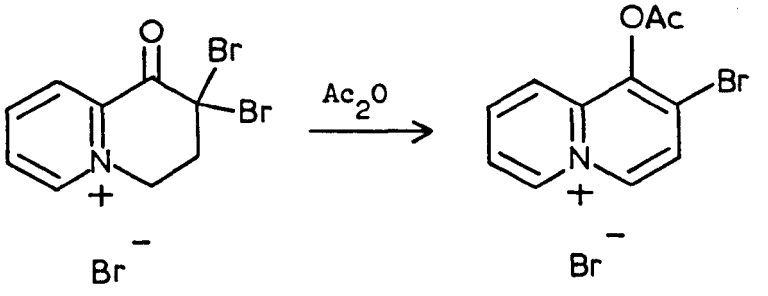
(32)

Attempted introduction of unsaturation into the aza-cycloheptanone ring.

Since the tetrabromoketone (31) was fairly readily available, initial attempts at introducing unsaturation into the seven membered ring

centred on a possible dehydrobromination.

Fozard and Jones[11] have shown that boiling acetic anhydride can be used to convert 2,2-dibromo-1-oxo-1,2,3,4-tetrahydroquinolizinium bromide (33) to the 1-acetoxy-2-bromoquinolizinium bromide (34) in 86% yield.



(33) (34)

However, when the tetrabromoketone (31) was heated under reflux with acetic anhydride only starting material was recovered.

Another attempt to dehydrobrominate the tetrabromoketone (31) was made using an equimolar amount of 2,6-lutidine in boiling chloroform. Again, removal of the solvent showed that no reaction had occurred.

The severity of the conditions were increased by heating the tetrabromoketone (31) with excess pyridine for 1hr. After working up a dark solid remained which had a m.p. >350°. Both the n.m.r. and infrared spectra were so confused that any interpretation proved impossible.

Heating a methanolic solution of the tetrabromoketone (31) with Amberlite IR 45 (OH) again failed to produce any reaction.

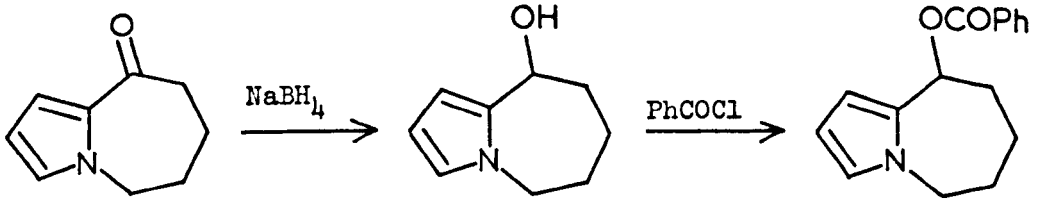
As a further attempt at dehydrobromination freshly prepared sodium ethoxide was added to the tetrabromoketone (31) in hot xylene and the mixture boiled for 1hr. Working up gave a black tar, the infrared spectrum of which indicated it to be mainly unchanged tetrabromoketone (31); there was no evidence of any absorption due to α,β-unsaturation.

A second approach to the introduction of unsaturation into the seven membered ring involved the reduction of the bicyclic ketone (29) with sodium borohydride. The formation of the alcohol (35) was monitored by the disappearance of the λ_{max} 294 nm absorption in the ultra-violet. In the n.m.r. spectrum the C-9 proton absorption appeared as a multiplet centred at 5.05τ.

Since p-toluenesulphonyl is recognised as a relatively good leaving group an attempt was made to prepare the tosyl derivative of the alcohol (35). An acetone solution of p-toluenesulphonyl chloride was added to the alcohol (35) in sodium hydroxide solution and the mixture shaken for half an hour. Only starting material was recovered. An attempt was made to prepare the tosylate in pyridine at 0° but the solution gradually turned red and the solid isolated could not be characterised. Although the attempts made to prepare a tosyl derivative were unsuccessful, treatment of a pyridine solution of the alcohol (35) at 0° with benzoyl chloride gave a benzoate (36) as a yellow oil, which

did not solidify. The infrared spectrum showed the ester carbonyl absorption at 1715 cm^{-1}.

SCHEME VI



(29) (35) (36)

When a sample of the benzoate (36) was heated gently to 50° under reduced pressure white crystals of benzoic acid sublimed. The residue remaining was, however, very charred and was insoluble in all the usual polar solvents.

Clearly some stabilisation of the pyrrole ring was necessary to try and prevent polymerisation occurring after elimination. It was felt the introduction of one or more electron withdrawing groups might provide the required stability.

The alcohol (35) was treated with three molar equivalents of bromine under the usual conditions to give a green solid which had no significant n.m.r. or infrared spectrum. Attempted bromination with dioxan dibromide also gave a solid which could not be characterised.

It has been reported[23] that pyrrole can be acetylated at C-2 by employing a mixture of dimethylacetamide and phosphorus oxychloride in ethylene dichloride. In another attempt at increasing the stability,

the alcohol (35) was subjected to the above conditions. The result was a solid product which again could not be characterised. This approach was then discontinued.

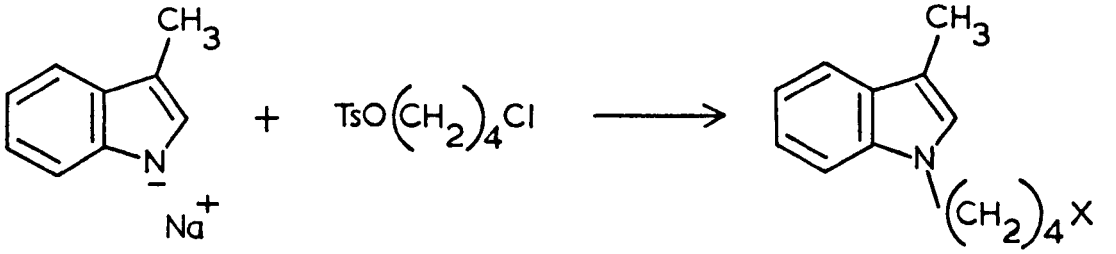
Synthesis of 10-hydroxy-11-methylazepino[1,2-a]indolium and 1,2,3-tribromo-9-hydroxypyrrolo[1,2-a]azepinium bromides.

Since mixtures were obtained from the brominations of the bicyclic ketone (29) it was decided to try and simplify these experiments by working with a pyrrole with no free nuclear positions. Because it was readily available, 3-methylindole was thought to be a suitable derivative.

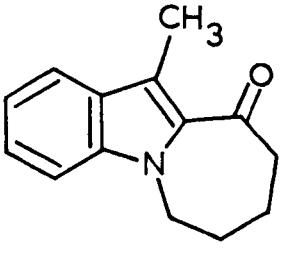
Treatment of 4-chlorobutyl p-toluenesulphonate at room temperature with the 3-methylindolide ion (prepared from sodium hydride on 3-methylindole) gave a 76% yield of the chlorobutylindole (37). The n.m.r. spectrum showed the indole 2-proton as a singlet at 3.2τ. The triplets centred at 6.0 and 6.6τ were assigned to the N-methylene and chloromethylene proton absorptions respectively by comparison with the spectrum of the previously prepared pyrrole compound. Sodium cyanide in dimethyl sulphoxide readily converted the chlorobutylindole (37) to the corresponding nitrile (38). Attempts to cyclise the nitrile (38) using boron trifluoride etherate and hydrogen chloride were unsuccessful, starting material being recovered. The action of polyphosphoric acid at 140° on the nitrile (38) was found to give the amide (39). Previous

workers have also reported[24] that amides resulted from attempted cyclisation of nitriles with polyphosphoric acid. Hydrolysis of the nitrile (38) with boiling aqueous alcoholic sodium hydroxide gave a 94% yield of the acid (40). The n.m.r. spectrum showed the indole 2-proton absorption as a singlet at 3.1τ, and the acid proton absorption as a broad peak between 0 and -0.3τ which disappeared on shaking with D_2O. The infrared spectrum showed a carbonyl stretching frequency at 1713 cm^{-1}. Cyclisation of the acid (40) to the tricyclic ketone (41) was effected using polyphosphoric acid. The conditions of the cyclisation were varied with temperatures ranging from 90-120° for reaction periods from 10 minutes to 1hr., until the optimum yield of 50% of tricyclic ketone (41) was obtained from a temperature of 95° for 15 minutes. The disappearance of the indole 2-proton singlet in the n.m.r. spectrum of the tricyclic ketone (41) confirmed the cyclisation at position 2 on the indole ring, rather than at position 7 to give the isomer (42).

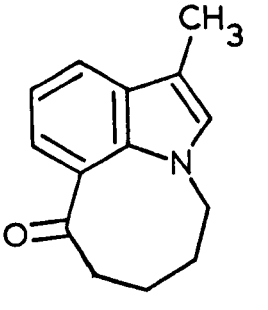
SCHEME VII



(37) X = Cl
(38) X = CN
(39) X = $CONH_2$
(40) X = CO_2H



(41)



(42)

An attempt to prepare the tricyclic ketone (41) using the Friedel Crafts cyclisation reaction was unsuccessful because of failure to prepare the acid chloride of the acid (40) on treatment with thionyl chloride. Copious evolution of hydrogen chloride was accompanied by the formation of a purple intractable tar.

An initial experiment on the bromination of the tricyclic ketone (41) with one molar equivalent of bromine was again found to give a mixture of mono- and dibromoketones. However, by using two molar equivalents of phenyltrimethylammonium tribromide in tetrahydrofuran a high yield of the crystalline dibromoketone (43) was obtained. The n.m.r. spectrum showed the C-8 methylene absorption as a triplet centred at 7.0τ.

There are numerous reports in the literature[25] on the use of lithium chloride in dimethylformamide as a relatively mild dehydrobrominating agent. The dibromoketone (43) was heated with excess lithium chloride in dimethylformamide at 150° for 1.5hr. Working up gave an orange solid which exhibited carbonyl stretching in the infrared at 1656, 1603 and 1570 cm^{-1}, in contrast to 1668 cm^{-1} in the starting dibromoketone (43). The analysis figures were consistent with the formula $C_{14}H_{11}NO$ in which two molecules of hydrogen bromide had been eliminated. The n.m.r. spectrum in deuterochloroform, shown in Figure 1, was in accord with the formulation 11-methylazepino[1,2-a]indol-10-one (44).

N.m.r. spectrum of 11-methylazepino[1,2-a]indol-10-one in $CDCl_3$

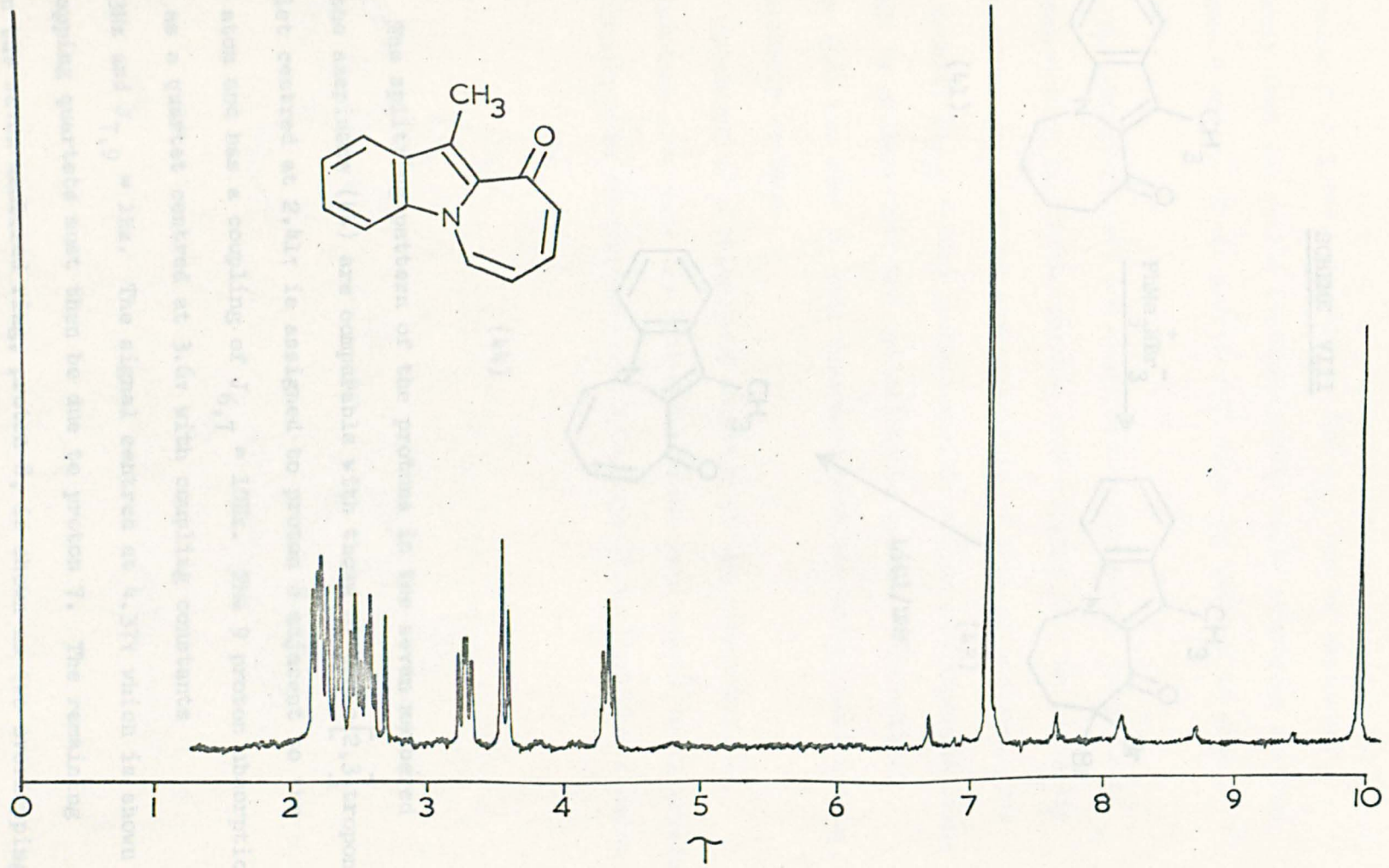
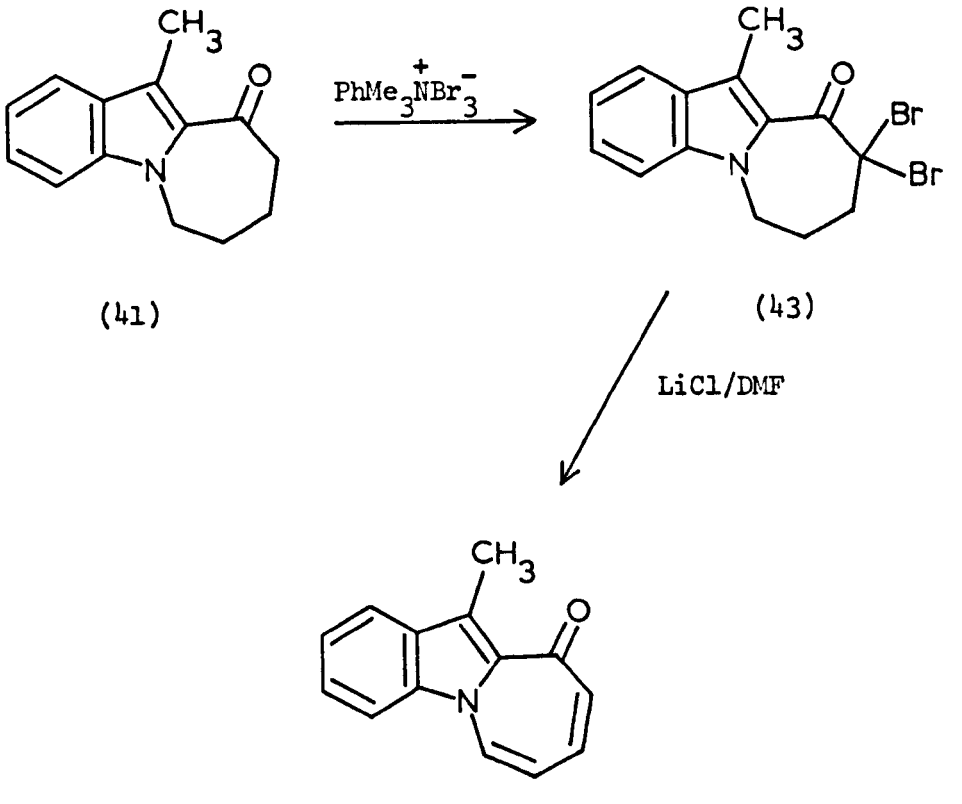


Figure 1

SCHEME VIII



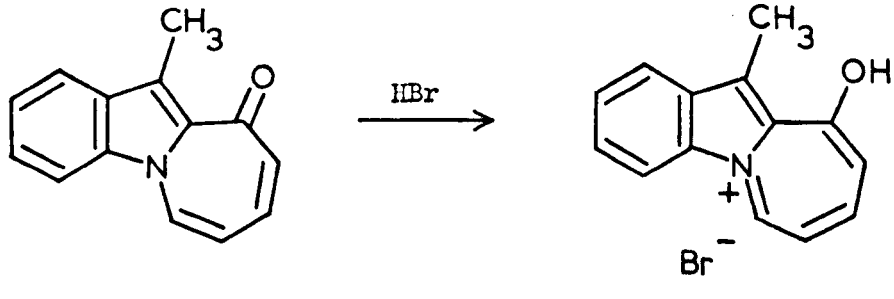
(41) (43) (44)

The splitting pattern of the protons in the seven membered ring of the azepinone (44) are comparable with those of benzo[2,3]tropone.[26] The doublet centred at 2.41τ is assigned to proton 6 adjacent to the nitrogen atom and has a coupling of $J_{6,7}$ = 10Hz. The 9 proton absorption is shown as a quartet centred at 3.6τ with coupling constants $J_{8,9}$ = 13Hz and $J_{7,9}$ = 1Hz. The signal centred at 4.37τ which is shown as overlapping quartets must then be due to proton 7. The remaining proton in the seven membered ring, proton 8, is shown as two overlapping

doublets centred at 3.34τ. Two values for $J_{7,8}$ can be estimated independently from the easily distinguishable major couplings derived from protons 6 and 9. These agreed well with one another to give a value of 8Hz.

The structure (44) was confirmed by the n.m.r. spectrum of the protonated form in trifluoroacetic acid (Figure 2). An intensely deep blue colour was produced characteristic of that of azulene. The 6 proton doublet ($J_{6,7}$ = 9Hz) centred at 1.0τ showed the expected downfield shift by analogy with the quinolizinium system. The methyl singlet at 6.8τ was also in good agreement with the methyl position in other quaternary systems.

Treatment of a chloroform solution of the recrystallised azepino-indolone (44) with dry hydrogen bromide gave almost black crystals of analytically pure 10-hydroxy-11-methylazepino[1,2-a]indolium bromide (45).



(44) (45)

N.m.r. spectrum of 11-methylazepino[1,2-a]indol-10-one in CF_3CO_2H

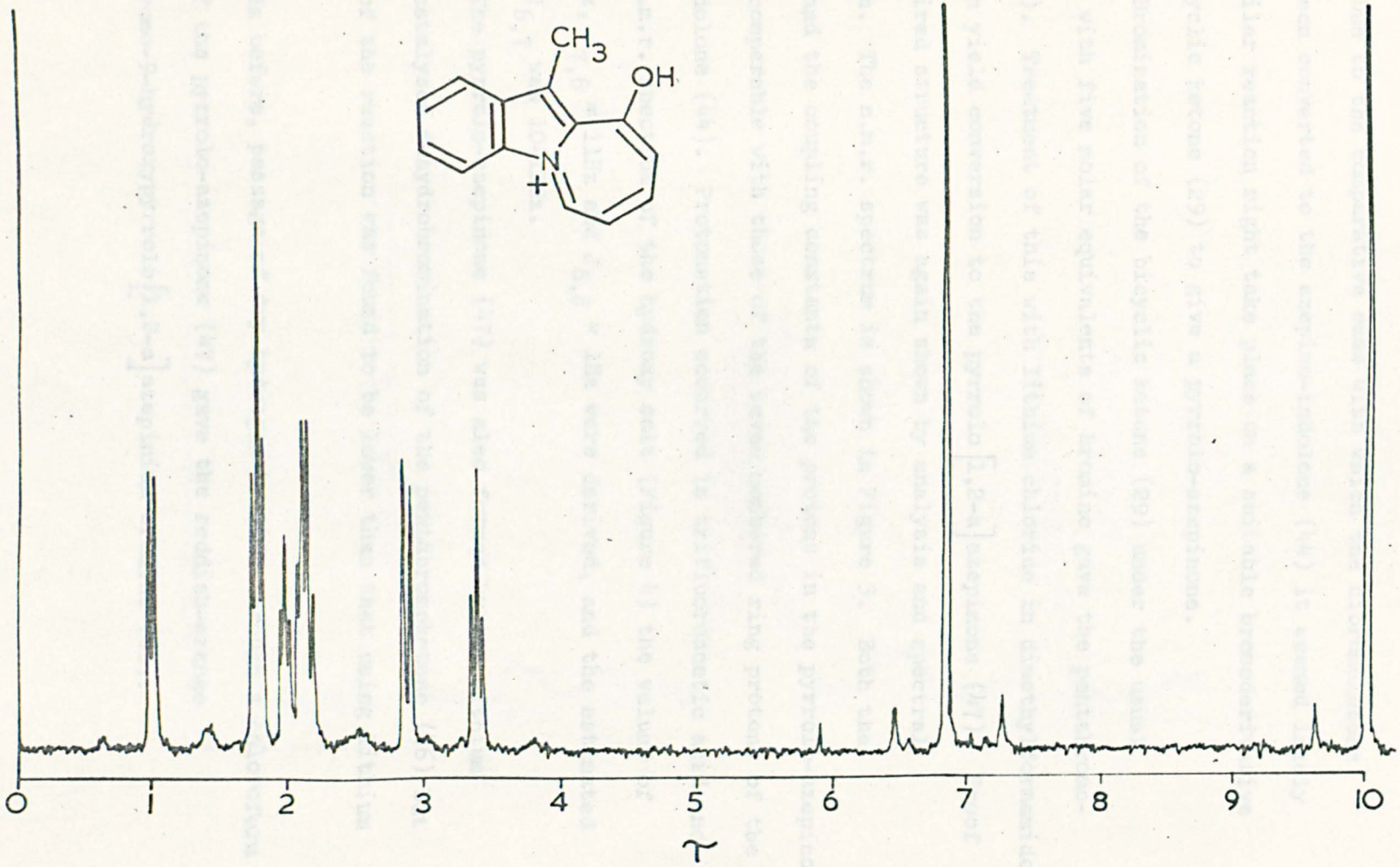


Figure 2

Due to the comparative ease with which the dibromoketone (43) had been converted to the azepino-indolone (44) it seemed likely that a similar reaction might take place on a suitable bromoderivative of the bicyclic ketone (29) to give a pyrrolo-azepinone.

Bromination of the bicyclic ketone (29) under the usual conditions with five molar equivalents of bromine gave the pentabromoketone (46). Treatment of this with lithium chloride in dimethylformamide gave a high yield conversion to the pyrrolo[1,2-a]azepinone (47). Proof of the desired structure was again shown by analysis and spectral examination. The n.m.r. spectrum is shown in Figure 3. Both the positions and the coupling constants of the protons in the pyrrolo-azepinone (47) were comparable with those of the seven membered ring protons of the azepino-indolone (44). Protonation occurred in trifluoroacetic acid and from the n.m.r. spectrum of the hydroxy salt (Figure 4) the values of $J_{5,6}$ = 10Hz, $J_{7,8}$ = 11Hz and $J_{6,8}$ = 1Hz were derived, and the estimated value for $J_{6,7}$ was 10-11Hz.

The pyrrolo-azepinone (47) was also formed by the lithium carbonate catalysed dehydrobromination of the pentabromoketone (46) but the yield of the reaction was found to be lower than that using lithium chloride.

As before, passage of dry hydrogen bromide through a chloroform solution of the pyrrolo-azepinone (47) gave the reddish-orange 1,2,3-tribromo-9-hydroxypyrrolo[1,2-a]azepinium bromide (48).

N.m.r. spectrum of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one in $CDCl_3$

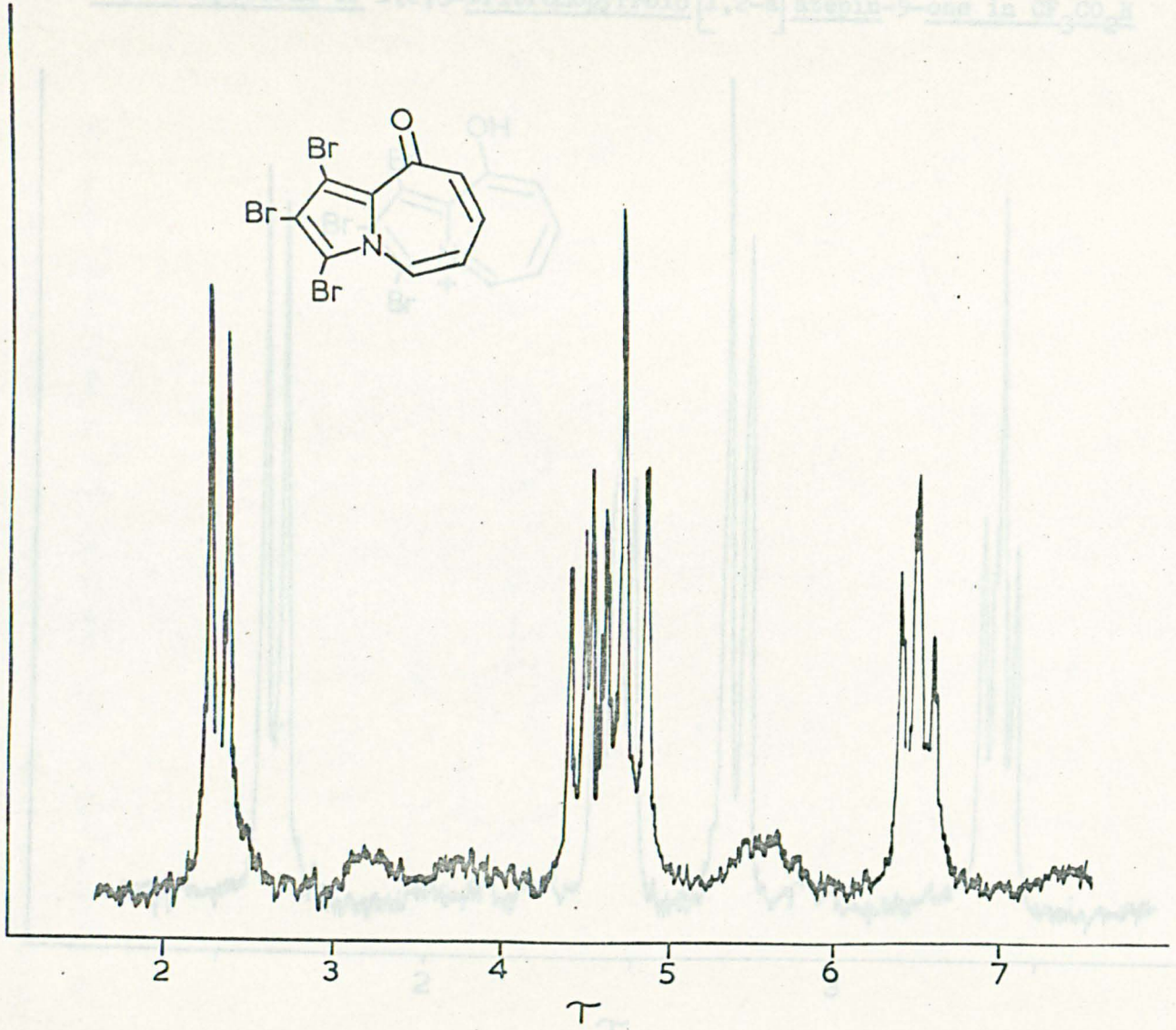


Figure 3

N.m.r. spectrum of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one in CF_3CO_2H

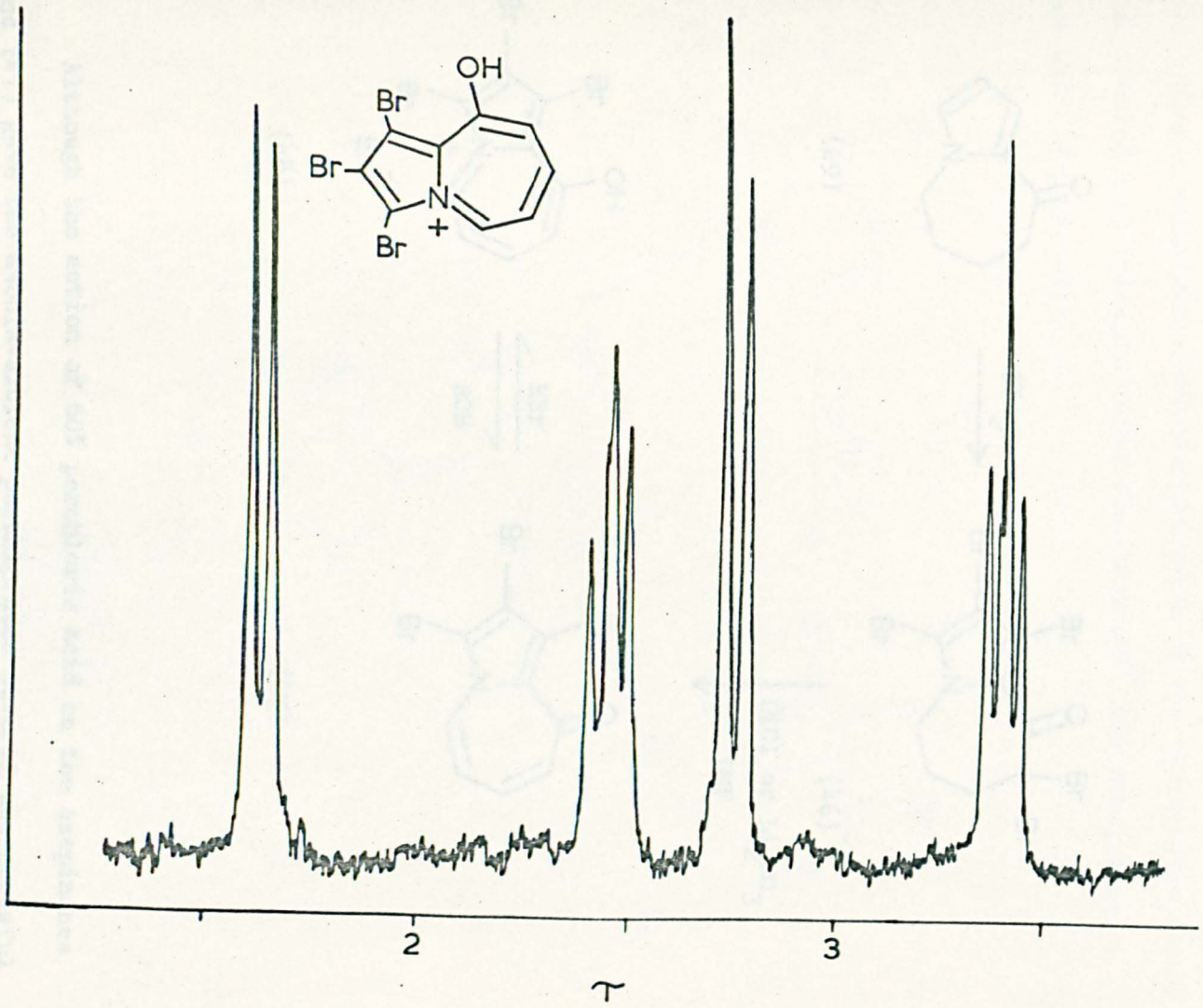
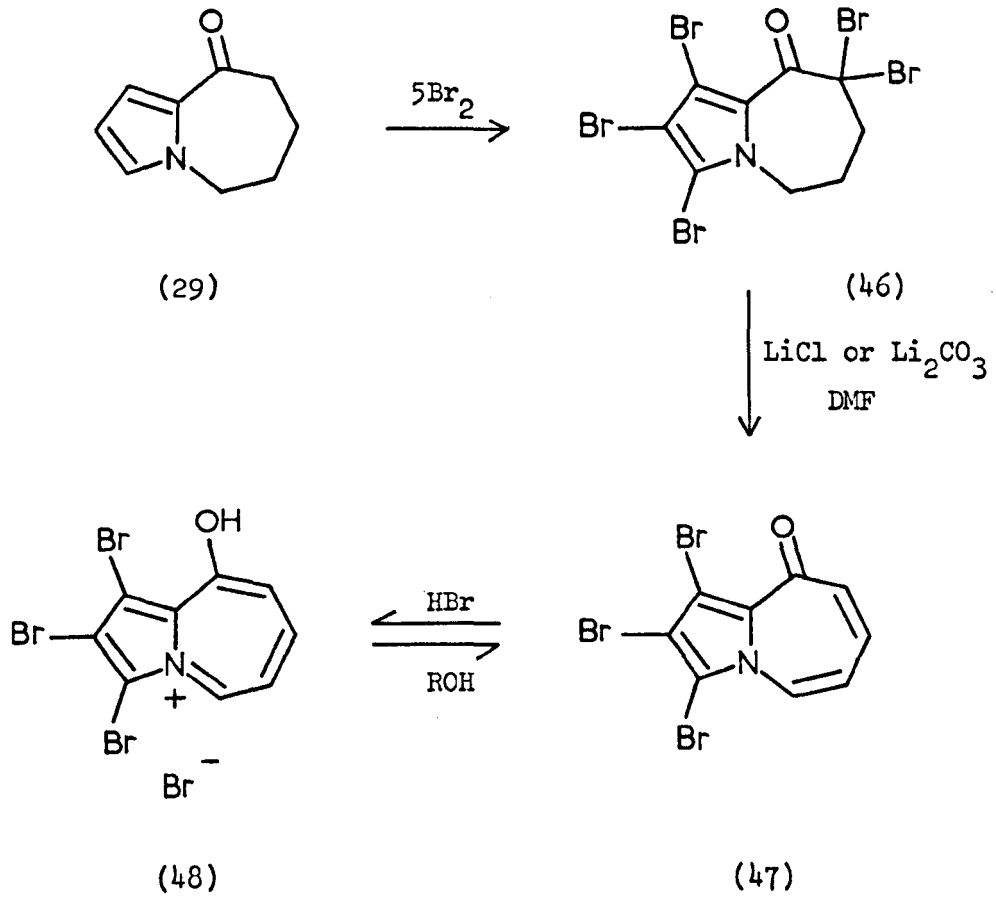


Figure 4

SCHEME IX

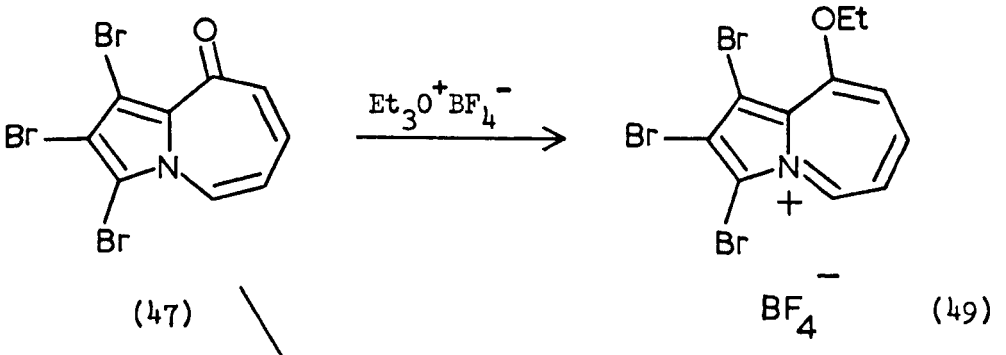


Although the action of 60% perchloric acid on the azepinones (44) and (47) gave the azonia-azulene perchlorates several unsuccessful attempts were made to obtain satisfactory analyses.

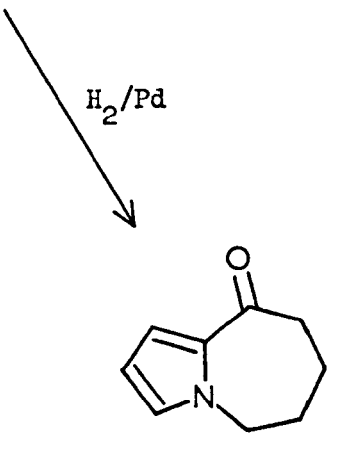
The hydroxy azonia-azulene salts (45) and (48) were found to be very unstable to hydroxylic solvents and were easily reconverted to

the corresponding azepinones on dilution with alcohol.

When a methylene dichloride solution of the pyrrolo-azepinone (47) was boiled with triethyloxonium fluoroborate[27] the ethoxyazonia-azulene salt (49) was obtained.



(47) (49)



(29)

To confirm the retention of the original 5:7 bicyclic skeleton in the pyrrolo-azepinone (47), catalytic reduction with 10% palladium charcoal led to the uptake of five molar equivalents of hydrogen to

give the bicyclic ketone (29), which indicated that no ring contraction or expansion had taken place.

The use of lithium chloride in dimethylformamide as a dehydrobrominating agent has been extended to the production of benztropones. An account of these syntheses and investigations carried out to establish the mechanism of double elimination will be discussed later in Part II of this thesis.

Studies on the synthesis of the parent azonia-azulenes from the intermediate azepinones.

After the successful syntheses of the substituted azonia-azulenes attention was directed towards removal of the substituents in an attempt to prepare the parent salts.

The instability of the azonia-azulene salts (45) and (48) to hydroxylic solvents was thought to be due to the presence of the ring hydroxyl group allowing the immediate reconversion to the more stable azepinones. Consequently, initial experiments were concerned with the removal of the carbonyl group in the intermediate azepinones.

Unlike tropones, the pyrrolo-azepinone (47) and the azepino-indolone (44) do not form 2,4-dinitrophenylhydrazones under normal conditions. An attempt to reduce the azepino-indolone (44) in ether solution at room temperature with lithium aluminium hydride gave the product as a gum which solidified with difficulty on scratching in

light petroleum. The solid was very unstable and all efforts to recrystallise it were unsuccessful. The n.m.r. spectrum on the crude material showed rather ill-defined peaks between 2.1-4.5τ. A doublet (J = 6Hz) centred at 5.35τ integrated for less than one proton. The position of the methyl singlet at 7.64τ showed an upfield shift consistent with reduction of the carbonyl group. However, no exchange occurred on shaking with D_2O. The appearance of a multiplet between 7.7-8.1τ might have arisen by the β-addition of hydride. The reduction of the azepino-indolone (44) was repeated using lithium aluminium deuteride. This time the n.m.r. spectrum did not show a doublet around 5.3τ but the methyl singlet had again moved upfield to 7.64τ. On shaking with D_2O an HDO peak was produced although this was not accompanied by any noticeable difference in the spectrum. The infrared spectra of both crude reduction products showed stretching bands at 1649, 1612 and 1583 cm^{-1}. Further reference to this reaction is made later in this thesis (see page 42).

Reaction of the azepino-indolone (44) with sodium borohydride in ethanol at room temperature was found to be extremely slow. After stirring for 72hr. the product isolated exhibited an n.m.r. spectrum very similar to the product obtained from the lithium aluminium hydride reduction.

In contrast, reaction of the pyrrolo-azepinone (47) with sodium borohydride was completed in 1hr. and after working up an unstable solid was again produced. The n.m.r. spectrum of this solid showed an

extremely complex pattern between 2.5-6.2τ and no interpretation was made.

Another plausible method for the removal of the carbonyl group in the azepino-indolone (44) was thought to be via the hydrazone with subsequent Wolff-Kishner reduction to give a methylene group. When the azepino-indolone (44) in ethanol was boiled with 100% hydrazine hydrate a red-brown solid was produced. Micro-analysis agreed with a formula $C_{14}H_{15}N_3O$. The n.m.r. spectrum in deuterochloroform (Figure 5) suggested the structure to be the substituted pyrazoline (50). The doublet centred at 6.9τ which integrated for two protons was assigned to the methylene group adjacent to the carbonyl function, and has a coupling of J = 6Hz. The multiplet between 7.0-7.8τ which also integrated for two protons was considered to be due to the non-equivalent geminal protons H_A and H_B. The one proton multiplet centred at 5.86τ must be assigned to proton H_M, and the rather broad one proton singlet at 3.22τ to proton H_X. Exchange of the NH protons occurred on shaking with D_2O. Further proof of the structure (50) was obtained from double irradiation experiments. Irradiation of the proton H_M at 5.86τ caused the doublet at 6.9τ to collapse to a singlet and also eliminated a major coupling from the multiplet between 7.0-7.8τ. On irradiation at 3.22τ the only change was the removal of the minor coupling from the 7.0-7.8τ multiplet. On protonation the n.m.r. spectrum (Figure 6) showed the downfield shift of the H_X proton absorption to 2.0τ indicating protonation on the adjacent nitrogen atom. It was now possible to estimate the coupling constants of

all the protons on the pyrazoline ring and the values derived were J_{AB} = 16Hz, $J_{AM} = J_{BM}$ = 10Hz, and $J_{AX} = J_{BX}$ = 2Hz. These are in good agreement with literature quoted values for Δ^2-pyrazolines.[28,29,30] The infrared carbonyl stretching frequency at 1646 cm^{-1} and the ultraviolet spectrum are also in accordance with the above formulation. A suggested mechanism which explains the formation of the pyrazoline (50) is outlined in Scheme X.

N.m.r. spectrum of 3-methyl-2-(2-pyrazolin-5ylacetyl) indole in $CDCl_3$

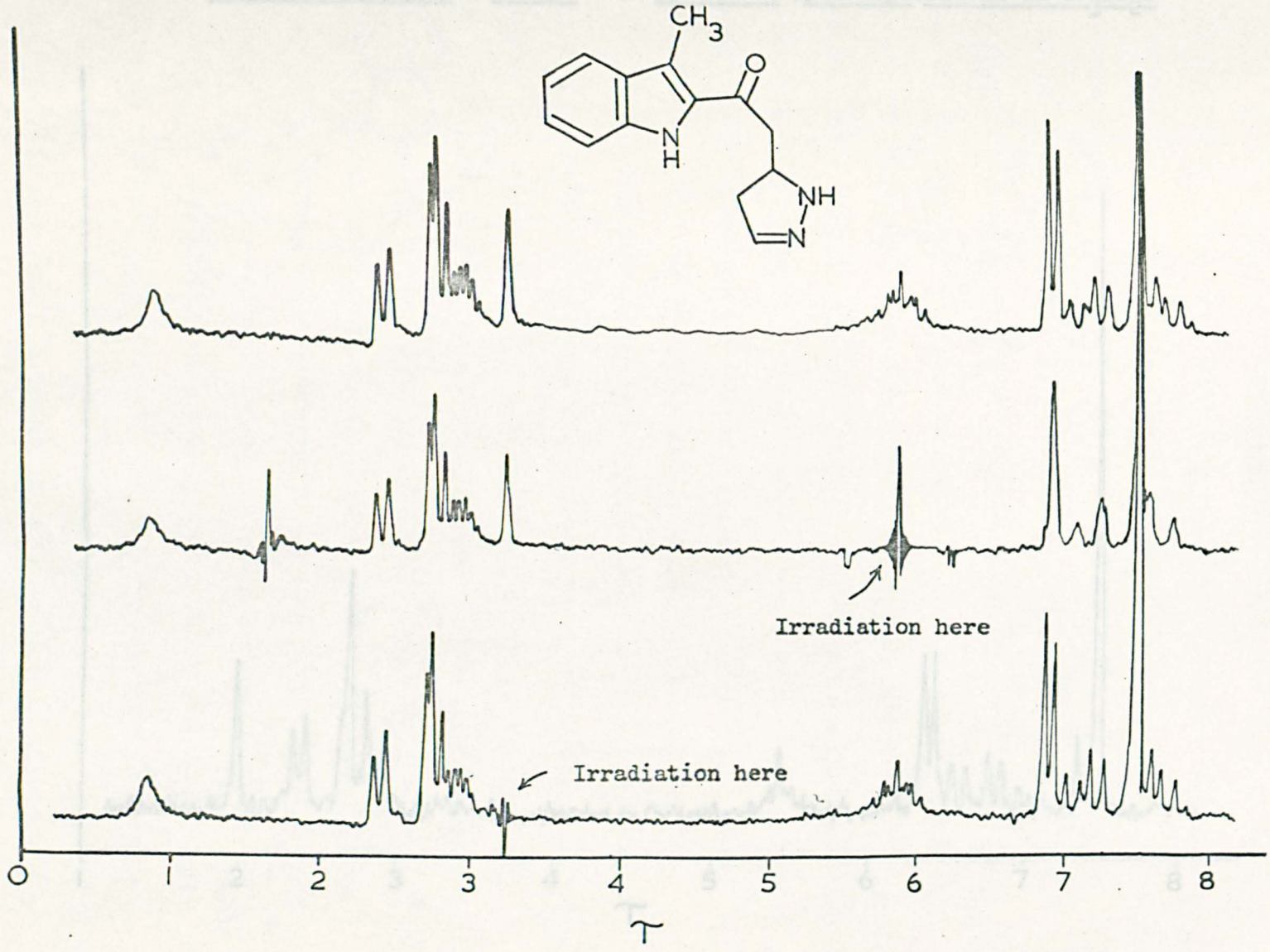


Figure 5

N.m.r. spectrum of 3-methyl-2-(2-pyrazolin-5ylacetyl)indole in CF_3CO_2H

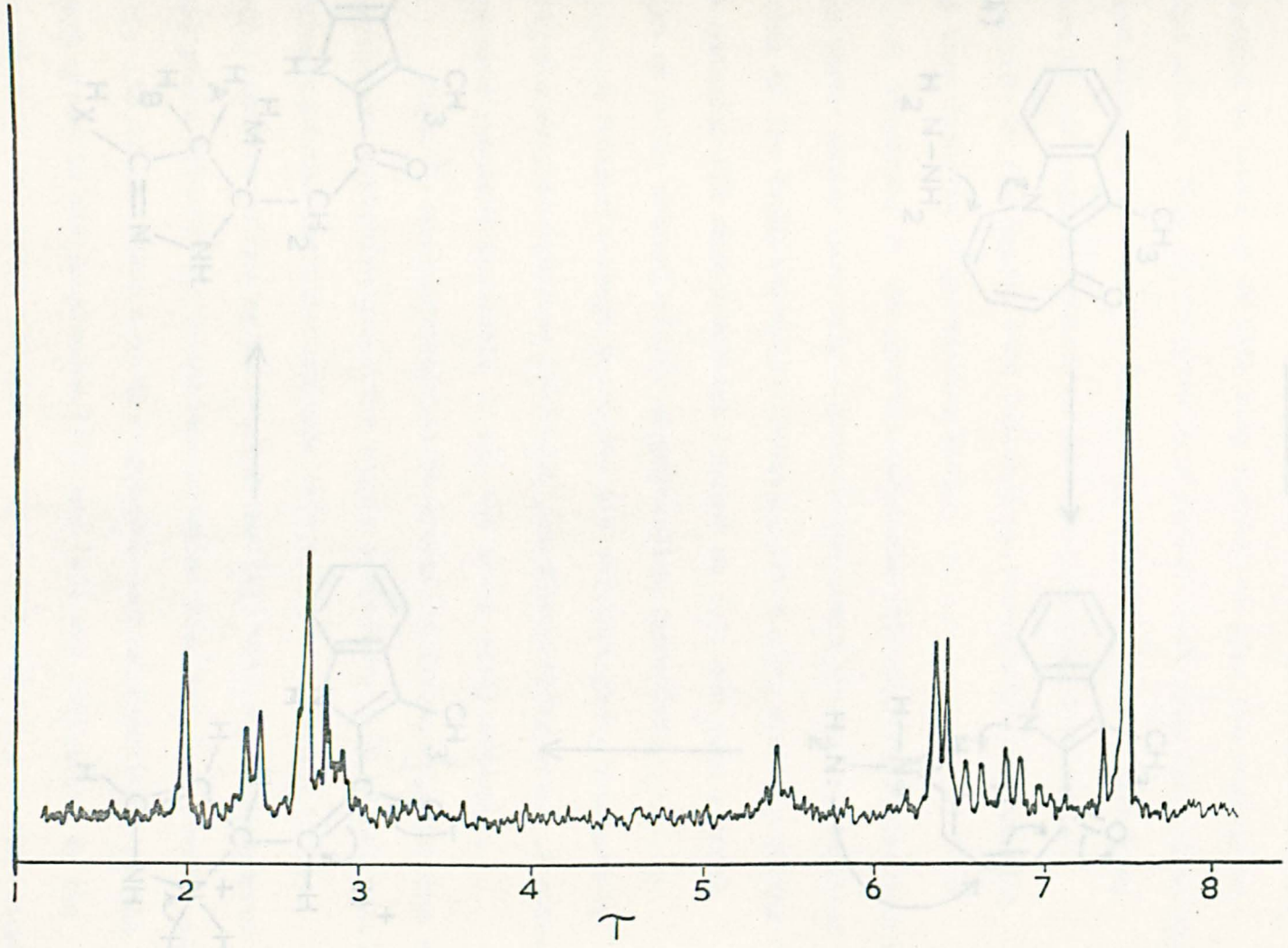
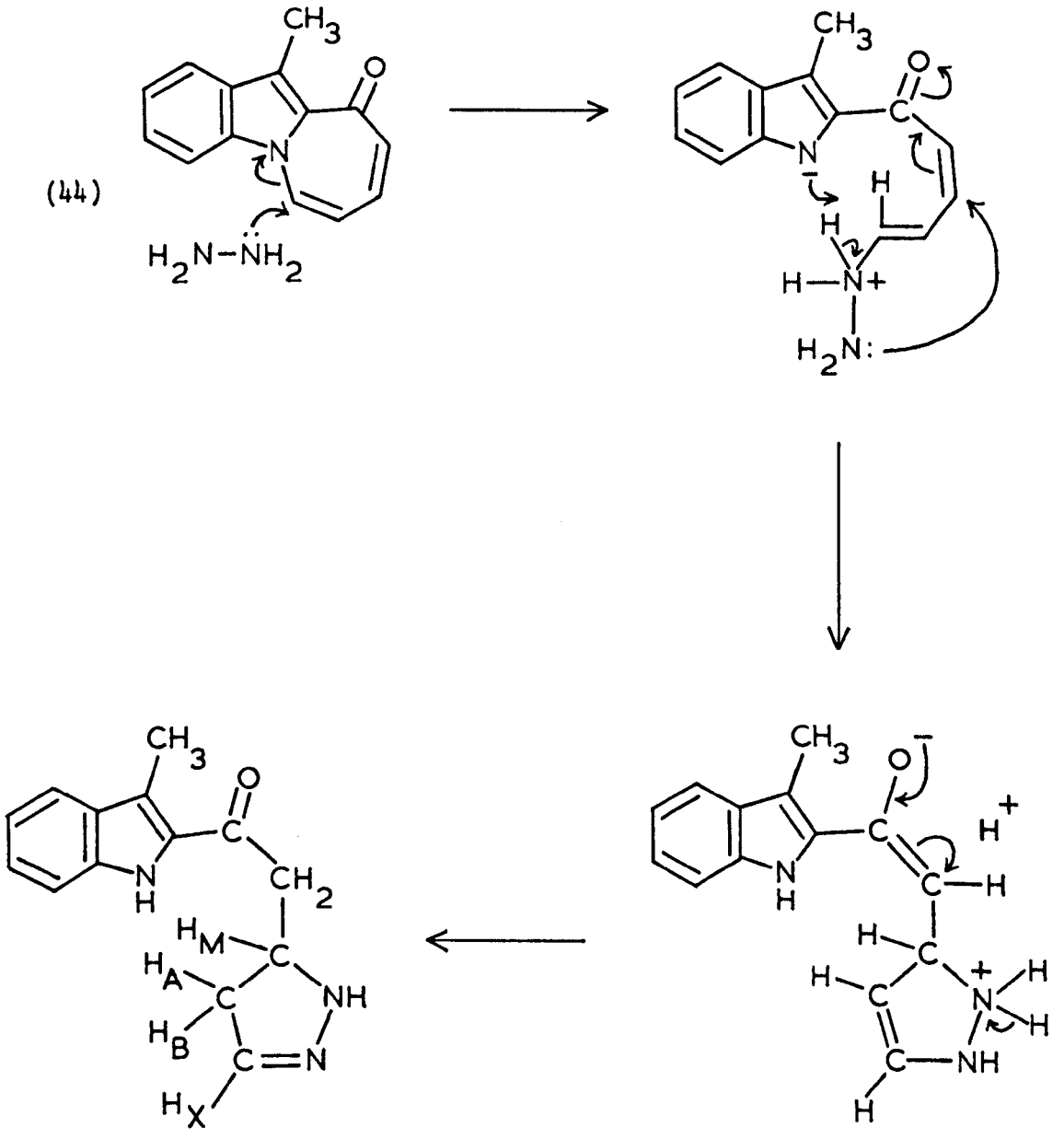


Figure 6

SCHEME X



(44)

(50)

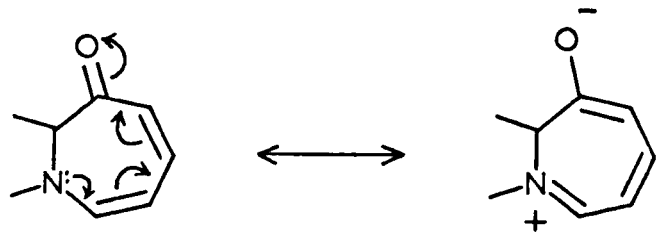
Nucleophilic attack of hydrazine onto the azepino-indolone (44) is assumed to occur at C6 with ring opening to give the stabilised indolyl anion. This is followed by a proton shift from the positively charged nitrogen atom to the indolyl nitrogen with subsequent ring closure by nucleophilic attack at C8. De-protonation again, and protonation on the oxygen atom followed by tautomeric isomerisation would then form the Δ^2-pyrazoline (50).

Treatment of the pyrrolo-azepinone (47) with hydrazine hydrate in the above manner gave only a glass which could not be crystallised from any of the usual solvents. However, the n.m.r. spectrum on the crude material did show a doublet centred at 6.7τ and also a broad singlet at 2.95τ characteristic of pyrazoline formation.

A further attempt to remove the carbonyl group was made by heating the azepino-indolone (44) with phosphorus tribromide. A carbonaceous mass remained insoluble in all the usual polar solvents.

Mayer[31] has reported that treatment of dibenzo[b,f]tropone with phosphorus pentasulphide gives the thione derivative. It seemed possible therefore that the pyrrolo-azepinone (47) might also form a thione. However, reaction of the pyrrolo-azepinone (47) with solid phosphorus pentasulphide directly or in benzene solution resulted in a charred solid.

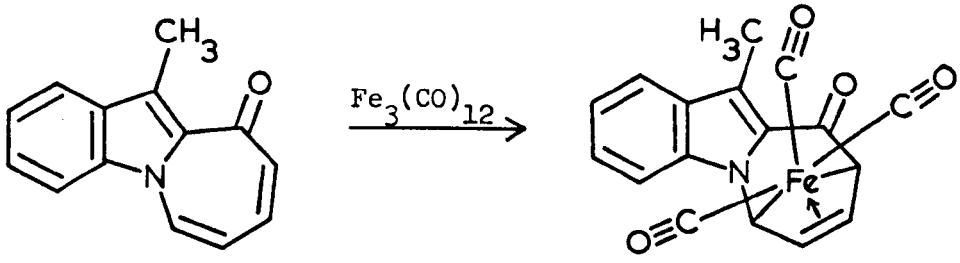
It would appear that the apparent lack of reactivity of the carbonyl group in the azepinones (44) and (47) was influenced by the conjugation of this group through the seven membered ring to the bridgehead nitrogen atom, which would enable amide type resonance to exist.



It seemed probable that if the 'diene' part of the seven membered ring could be fixed then normal carbonyl reactions might take place. Accordingly, the pyrrolo-azepinone (47) was treated with dimethylacetylene dicarboxylate, but even under severe conditions starting material was recovered.

Birch and Lewis[32] have reported the preparation of iron tricarbonyl complexes of some cyclohexa- and cycloheptadienes. The reactions were usually carried out with pentacarbonyliron or dodecacarbonyltri-iron.

When the azepino-indolone (44) was reacted with dodecacarbonyltri-iron in boiling benzene solution under nitrogen a 60% yield of the iron tricarbonyl complex (51) was obtained. In its infrared spectrum, the complex (51) showed sharp metal carbonyl bands at 2072 and 2016 cm^{-1} and also a broad band at 1616 cm^{-1} due to the ketonic carbonyl. The n.m.r. spectrum showed a doublet ($J_{8,9}$ = 8Hz) centred at 6.22τ assigned to the proton at C-9.



(44) (51)

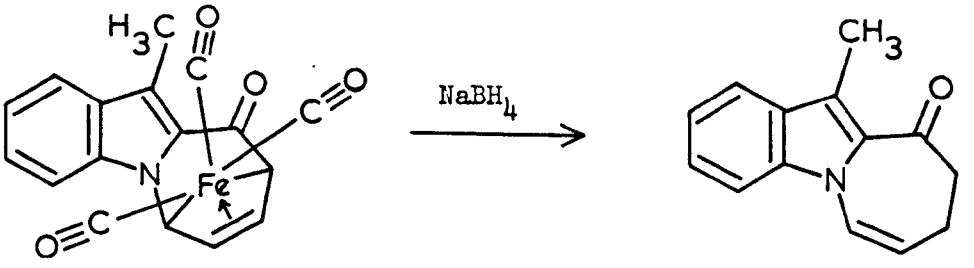
The formulae of the iron tricarbonyl complexes have been drawn in several ways.[33] The above representation uses an arrow to denote donation of two electrons by the double bond to give the metal atom an inert gas configuration.

Reaction of the iron tricarbonyl complex (51) with sodium borohydride gave a brown oil, which showed three spots on a thin layer chromatogram. The components were separated by Preparative Layer Chromatography (P.L.C.) using 20% ether-toluene as eluent. The material extracted from the upper band (I) showed a broad ketonic carbonyl stretching frequency at 1660 cm^{-1} in the infrared, but no absorptions were visible between 2000 - 2100 cm^{-1} characteristic of metal carbonyl bands. The n.m.r. spectrum showed a one proton multiplet centred at 4.45τ and two methylene multiplets between 6.8-7.7τ. From micro-analysis and the above spectral data the structure of the product

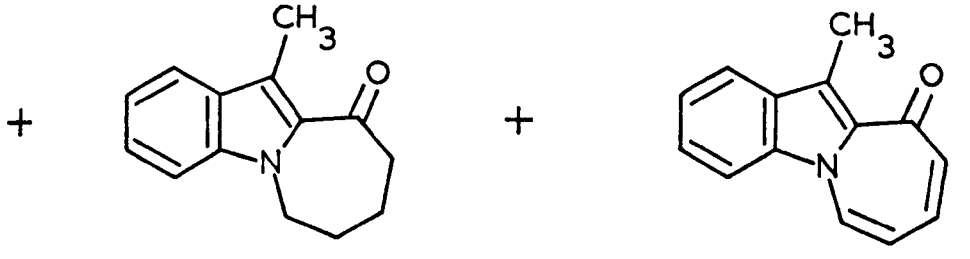
was concluded to be 8,9-dihydro-11-methylazepino[1,2-a]indol-10-one (52).

The centre band (II) exhibited an n.m.r. spectrum consistent with that of a mixture of the complex (51), the azepino-indolone (44), and the tricyclic ketone (41).

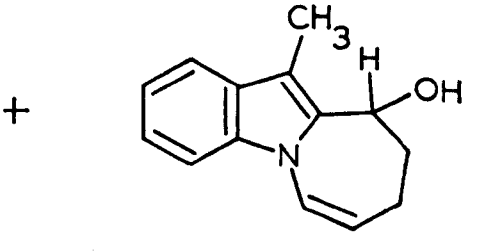
The content of the lower band (III) showed a poorly resolved n.m.r. spectrum, but a multiplet centred at 5.8τ suggested the product might be the alcohol (53).



(51) (52)



(41) (44)

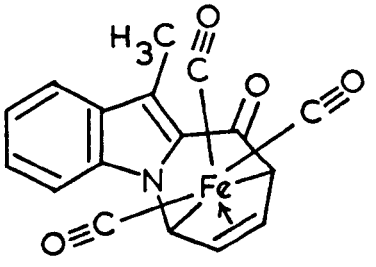


(53)

It appeared that the iron tricarbonyl complex (52) had decomposed to the azepino-indolone (44) on reaction with sodium borohydride. Subsequent β-addition of hydride ion onto the azepino-indolone (44) would then give the 8,9-dihydroketone (52), and further reduction of this would account for the presence of the tricyclic ketone (41) and the suspected alcohol (53).

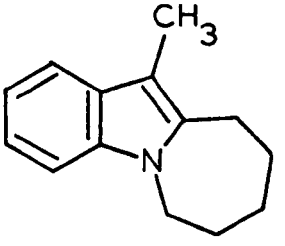
Support for the above hypothesis was provided by the stability of the complex (51) to chromatography, since on elution on a preparative plate with 20% ether-toluene it was recovered unchanged, indicating the formation of the azepino-indolone (44) during the borohydride reaction.

This instability of the complex (51) to hydride reduction was also apparent when the complex reacted with lithium aluminium hydride. A mixture of products were again obtained and after separation by P.L.C. they were identified as 7,8,9,10-tetrahydro-11-methyl-6H-azepino[1,2-a]indole (54), the 8,9-dihydroketone (52), the tetrahydroketone (41), and the alcohol (55) together with a small amount of unchanged complex (51).



(51)

$LiAlH_4$



(54)

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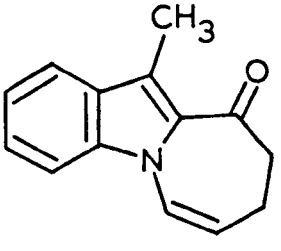

(52)

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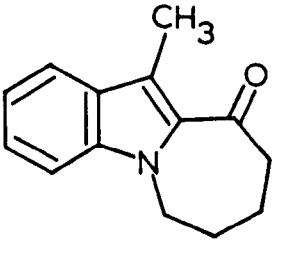

(41)

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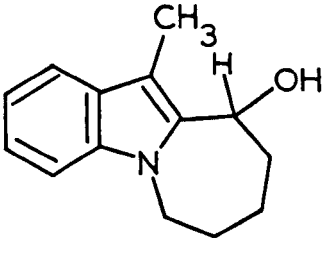
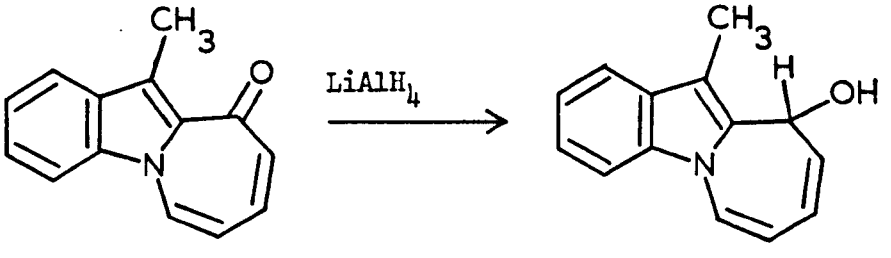


(55)

Clearly reduction was more drastic with lithium aluminium hydride than with sodium borohydride. Identification of the alcohol (55) and the indole (54) was made by a comparison of their spectra with those of authentic samples prepared by borohydride and Wolff-Kishner reduction

respectively of the tricyclic ketone (41).

In the light of evidence obtained from hydride reduction of the complex (51) it was clear that the product obtained from the previously mentioned lithium aluminium hydride reduction of the azepino-indolone (44) was not the 8,9-dihydroketone (52). On repeating this reduction it was surprisingly found that the product readily solidified, and, in contrast to the earlier experiment some purification could be achieved by precipitation from warm carbon tetrachloride. The n.m.r. spectrum of this material showed a five proton aromatic absorption between 2.0-2.7τ, and two complex multiplets centred at 3.6 and 4.2τ which both integrated for two protons. The methyl singlet appeared at 7.64τ together with a slight bulge between 7.8-8.1τ which integrated for one proton. On the basis of the n.m.r. spectra of the known azepino-indoles it was probable that the above product was the desired alcohol (56).



(44) (56)

Further indication was obtained from the mass spectrum which showed a strong peak at $^{m}/e$ 194. Although the molecular weight of the alcohol (56) would be 211, it is known that the molecular ion peak of alcohols is often very small and sometimes not even recognisable. The loss of an OH radical from the molecular ion of the alcohol (56) might be expected since this would result in the formation of the aromatic azonia-azulene radical ion of $^{m}/e$ 194.

An attempt to prepare the azonia-azulene salt by passage of dry hydrogen bromide into a chloroform solution of the alcohol (56) failed, and gave only a black intractable tar.

As part of the study to prepare the parent azonia-azulene further attempts were concentrated on the removal of the bromine substituents in the pyrrolo-azepinone (47).

The pyrrolo-azepinone (47) was dissolved in concentrated sulphuric acid and the solution was allowed to stand at room temperature for 48hr. Examination of the n.m.r. spectrum indicated that no substitution had taken place; even after 1.5hr. at 140° in concentrated sulphuric acid the pyrrolo-azepinone (47) was regenerated on dilution of the acid solution with water.

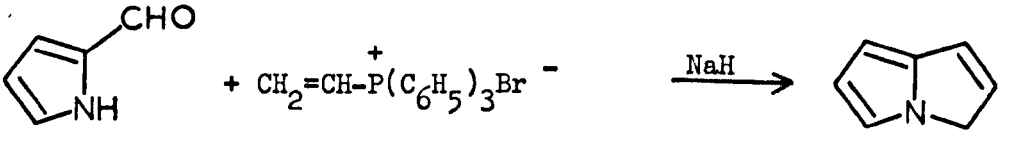
Although the hydroxyazonia-azulenes are unstable towards hydroxylic solvents, reconversion to the azepinones was found to be much slower in glacial acetic acid. As a result an attempt was made to reduce the pyrrolo[1,2-a]azepinium bromide (48) using hydrogen and Adams catalyst in glacial acetic acid. However, this again proved unsuccessful

since reduction was apparent in the seven membered ring.

Bryce-Smith and Wakefield[34] have reported the reduction of numerous organic halides using magnesium and a secondary or tertiary alcohol in a hydrocarbon solvent. The addition of a solution of the pyrrolo-azepinone (47) and isopropanol in decahydronaphthalene to a boiling suspension of magnesium in the same solvent, failed to give any reaction. Several attempts to form a Grignard reagent of the pyrrolo-azepinone (47) were not successful.

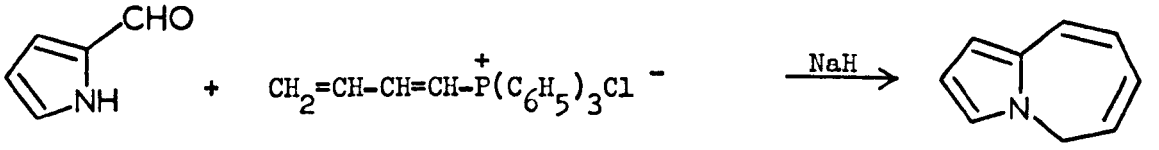
Attempted synthesis of 5H-pyrrolo[1,2-a]azepine (60).

Schweizer and Light[35] have prepared 3H-pyrrolizine (58) by reacting pyrrole-2-aldehyde with the vinylphosphonium salt (57) in the presence of sodium hydride.



(57) (58)

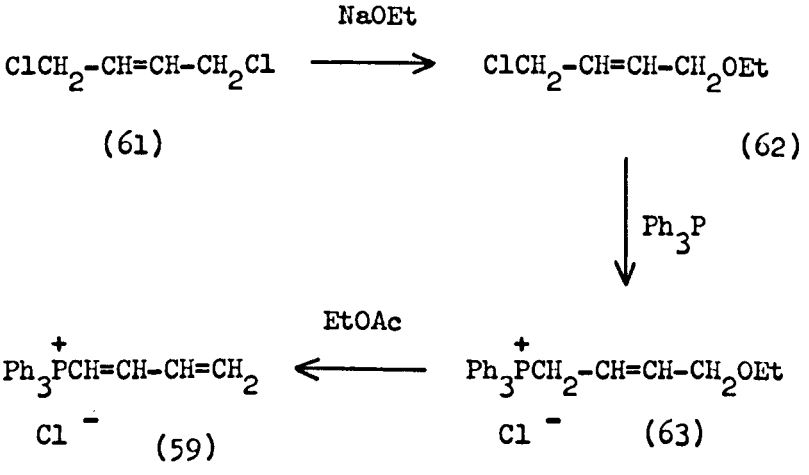
It was thought that the application of the same reaction using the buta-1,3-dienylphosphonium salt (59) might afford some of the 5H-pyrrolo[1,2-a]azepine (60).



(59) (60)

The preparation of the buta-1,3-dienylphosphonium salt (59) was attempted via an analogous route to that used by Schweizer[36] for the vinyl salt (57). 1-Ethoxy-4-chlorobut-2-ene (62)[37] was prepared in 62% yield by treatment of 1,4-dichlorobut-2-ene (61) with sodium ethoxide. Heating the ethoxybutene (62) with triphenylphosphine in ethanol gave the phosphonium salt (63). The attempted elimination of ethanol from the phosphonium salt (63) was carried out in boiling ethyl acetate. The n.m.r. spectrum of the crude reaction product was so confused that little interpretation could be made. When the product was recrystallised from ethanol or tetrahydrofuran the n.m.r. spectrum was again poorly resolved but showed peaks attributable to the recrystallising solvent which could not be removed even after drying for several hours. No conclusion could be drawn on whether or not elimination had occurred.

SCHEME XI



Although this reaction was not pursued further it could be that the final elimination step might occur more cleanly if the corresponding phenoxy derivatives were used.

EXPERIMENTAL

Preliminary Notes

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infrared absorption spectra were measured on a Perkin Elmer 257 spectrophotometer. The spectra of solids were determined in solution (e.g. $CHCl_3$) or as Nujol mulls, indicated by (Nujol). The spectra of liquids were determined as liquid films (Film).

Electronic absorption spectra were recorded on a Unicam SP 800 instrument.

Nuclear magnetic resonance (n.m.r.) spectra, unless stated otherwise, were recorded on a Perkin Elmer R10 60 MHz instrument and are quoted as 'tau' (τ) values from an internal tetramethylsilane standard (10.0τ). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quadruplet, and m = multiplet.

Microanalyses were carried out on an F & M carbon/hydrogen/nitrogen analyser at the University of Keele, and by Drs. G. Weiler and F.B. Strauss of Oxford.

Mass spectra were determined on an Hitachi-Perkin Elmer RMU-6 instrument.

Analytical vapour phase chromatography (V.P.C.) was performed on a Pye series 104 instrument using a 5' spiral column packed with Chromosorb G coated with Apiezon L.

Woelm alumina deactivated by the addition of water was used in column chromatography.

Thin layer chromatography (t.l.c.) was carried out on 7.5 x 2.5 cm. microscope slides coated with Kieselgel PF_{254} (Merck). The components were visualised under ultraviolet light.

Preparative layer chromatography (P.L.C.) was carried out on 40 x 20 cm. glass plates coated with a 1.5 mm. layer of Kieselgel PF_{254}. The separated components, visualised under ultraviolet light, were isolated by scraping off the silica and extracting several times with hot methanol. The filtered methanolic solution was evaporated to leave a residue which contained some silica. The residue was then dissolved in chloroform, filtered and evaporated.

The distance moved from the base line to the centre of a component band on a preparative plate is given by the 'R' value in cm.

Unless otherwise indicated, light petroleum refers to the fraction of b.p. 40-60°.

4-Chlorobutyl p-toluenesulphonate.

Prepared as described by Field and Holsten.[38] Yield 60%; B.p. 157-8°/0.1 mm. (lit.,[38] 46%, b.p. 164-5°/0.1 mm.).

N-(4-chlorobutyl)pyrrole (27).

Pyrrole (33.5g.) was added dropwise at room temperature to a suspension of sodium hydride (24g., 50% dispersion in oil) in previously dried 1,2-dimethoxyethane (350 ml.) under nitrogen. The mixture was then heated under reflux for 1hr. The resultant suspension was then blown over with nitrogen into a dropping funnel and added dropwise to a stirred, boiling solution of 4-chlorobutyl p-toluenesulphonate (135g.) in 1,2-dimethoxyethane (50 ml.). Boiling was continued for 0.5hr. and the solution was then stirred for 12hr. at room temperature. The solvent was evaporated off and the residue taken up in water and extracted with ether. The ethereal extract was dried (Na_2SO_4), filtered, and evaporated. Distillation gave the N-(4-chlorobutyl)pyrrole (41g., 50.6%) as a colourless liquid, b.p. 64-6°/0.05 mm. (lit.,[21] b.p. 95°/12 mm.).

N-(4-cyanobutyl)pyrrole (28).

Prepared as described by Patterson, Brasch and Drenko.[21] Yield 54%; b.p. 89-90°/0.02 mm. (lit.,[21] b.p. 119-120°/3 mm.).

6,7,8,9-Tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (29).

Prepared as described by Patterson, Brasch and Drenko,[21] except that during the 18hr. hydrolysis of the intermediate imine, additional portions of aqueous ammonia were added at intervals. Extraction of the aqueous ammoniacal mixture with chloroform, drying of the chloroform solution ($CaCl_2$) and distillation gave the bicyclic ketone (29) (49%), b.p. 96-8°/0.05 mm., m.p. 31-2° (lit.,[21] m.p. 32.5-34.5°; yield 31%).

n.m.r. ($CDCl_3$): τ 2.7-2.9 (1H, q, J = 4.5Hz, J = 2.5Hz, H3), 2.9-3.1 (1H, q, H2), 3.6-3.8 (1H, q, J = 4.5Hz, H1), 5.5-5.8 (2H, t, $CH_2.N$), 7.0-7.3 (2H, t, CH_2CO), and 7.7-8.3 (4H, m, H7 and H8).

2,4-Dinitrophenylhydrazone, red needles from benzene, m.p. 222-5°.

Found: C, 55.0; H, 4.43; N, 20.9%

$C_{15}H_{15}N_5O_4$ requires: C, 54.7; H, 4.59; N, 21.2%

Bromination of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (29).

Bromine (4.8g.) in carbon tetrachloride (10 ml.) was added to a stirred solution of the bicyclic ketone (29) (1.49g.) in carbon tetrachloride (10 ml.). Hydrogen bromide was evolved. After the addition, stirring was continued for a further 15 minutes when the carbon tetrachloride and excess bromine were removed under reduced pressure.

The resulting oil was dissolved in chloroform and washed with sodium bicarbonate solution, dried (Na_2SO_4), and evaporated. The spectra of the product indicated that it was a mixture of brominated products in which bromination had occurred both on the pyrrole nucleus and α to the ketonic carbonyl. The crude mixture (2.8g.) was dissolved in dry benzene and chromatographed on a column of activated alumina (Woelm, grade IV, 100g.). The column was eluted with benzene and the following (100 ml.) fractions were collected.

Fraction	Weight in grams
1	0.1057
2	0.9106
3	0.8423
4	0.4538
5	0.0189
Total	2.3313

Recovery = ca. 83%

Fractions 2 and 3 contained about 60% of the total amount of material applied to the column and nuclear magnetic resonance spectra indicated that elution had been too rapid for separation to occur.

The brominated mixture (2.3g.) was rechromatographed using a 50:50 mixture of benzene and light petroleum on grade III alumina (100g.). N.m.r. spectra again indicated that no separation had occurred. No

further investigation was pursued.

Phenyltrimethylammonium tribromide.

Prepared from dimethylaniline as described by Marquet et al.[22]

Bromination of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (29) with phenyltrimethylammonium tribromide.

Phenyltrimethylammonium tribromide (2.5g.) was added to a solution of the bicyclic ketone (29) (1g.) in anhydrous tetrahydrofuran (10 ml.) at room temperature and the mixture was set aside with occasional shaking for 2hr. It was then filtered, the insoluble quaternary salt was washed with a little tetrahydrofuran and the combined filtrates evaporated in vacuo to give a brown oil (2.13g.). The n.m.r. spectrum again indicated a mixture of brominated products.

Attempted dehydrobromination of the crude brominated mixture.

A solution of freshly prepared brominated mixture (4g.) in 2,6-lutidine (20 ml.) was boiled under reflux for 1hr. The reaction mixture was cooled and excess lutidine removed under reduced pressure. Water was added, and the aqueous solution extracted with ether. The ethereal extracts were dried (Na_2SO_4) and evaporated to give a light brown

liquid. T.l.c., eluting with benzene - 10% ethyl acetate showed the presence of four components. The mixture (1g.) was dissolved in dry benzene and run onto a column of silica gel. The column was eluted successively with benzene and benzene-ethyl acetate mixtures. The following fractions (100 ml.) were obtained:-

Fraction	Solvent	Weight in grams
1	benzene	nil
2-6	10% ethyl acetate-benzene	0.4510
7-10	20% ethyl acetate-benzene	0.2749
11-15	30%, 40%, and 50% ethyl acetate-benzene	nil

V.P.C. analysis showed single peaks for fractions 9 and 10 only. However, on removal of the solvent the material rapidly turned purple. The residue was examined by n.m.r. and a confused spectrum resulted which suggested polymerisation had occurred.

Bromination of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (29) with one molar equivalent of bromine.

Bromine (1.6g.) in carbon tetrachloride (5 ml.) was added to a stirred solution of the bicyclic ketone (29) (1.49g.) in carbon tetrachloride (30 ml.) containing a few gm. of calcium carbonate. After the addition stirring was continued for a further 2hr., the calcium bromide

was filtered and washed well with carbon tetrachloride. The combined solutions were washed with sodium bicarbonate, dried and evaporated to small volume giving the crude product as a light brown oil (1.67g.). V.P.C. analysis showed at least two products.

The mixture (1.6g.) was dissolved in benzene-light petroleum and run onto a column of activated alumina (Woelm, grade III, 100g.). The column was eluted with benzene-light petroleum and the following (100 ml.) fractions collected.

Fraction	Weight in grams.
1	nil
2	0.5512
3	0.2417
4	0.1137

V.P.C. analysis showed no separation had occurred but on standing a solid (0.28g.) crystallised from fraction 2. Recrystallisation from ether gave colourless needles, m.p. 102-3°. N.m.r. and infrared spectra indicated that it was the tribromoketone (30).

Found: C, 27.5; H, 1.93; N, 3.5%

$C_9H_8Br_3NO$ requires: C, 28.0; H, 2.08; N, 3.6%

$\nu_{max.}$ ($CHCl_3$) 1653 cm^{-1} (CO)

n.m.r. ($CDCl_3$): τ 2.8 (s, pyrrole H), 5.0-5.2 (1H, t, CHBr), 5.5-5.8 (2H, m, $CH_2.N$), 7.4-7.9 (4H, m, $-CH_2.CH_2-$).

Bromination of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (29) with three molar equivalents of bromine.

The procedure used was as described above. From 1.49g. of bicyclic ketone (29) and 4.8g. of bromine in 40 ml. of carbon tetrachloride a yield of 3.76g. of a brown oil was obtained. The n.m.r. spectrum showed the product to be a mixture of tribromo- and tetrabromoketones. Trituration with ether gave 0.64g. of the tetrabromoketone (31) as pale yellow crystals, recrystallised from ether, m.p. 129-132°.

Found: C, 23.0; H, 1.27; N, 2.8%

$C_9H_7Br_4NO$ requires: C, 23.2; H, 1.52; N, 3.0%

$\nu_{max.}$ ($CHCl_3$) 1663 cm^{-1} (CO)

n.m.r. ($CDCl_3$): τ 2.8 (s, pyrrole H), 5.5-5.8 (2H, m, $CH_2.N$), 6.8-7.2 (2H, m, $CH_2.CBr_2$), and 7.5-8.0 (2H, m).

2,3,8,8-Tetrabromo-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (31).

The tetrabromoketone (31) was prepared as above in 75% yield by the bromination of the bicyclic ketone (29) with four molar equivalents of bromine.

Attempted chlorination of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (29).

An excess of a saturated solution of chlorine in carbon tetrachloride was added slowly at room temperature to a stirred solution of the bicyclic ketone (29) (1g.) in carbon tetrachloride (10 ml.) with suspended calcium carbonate. After stirring for 12hr. and working up in the usual way a light green solid (1.49g.) was obtained. Recrystallisation from ether afforded 1,2,3-trichloro-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (32) as colourless needles, m.p. 127-130°.

Found: C, 42.6; H, 2.87; N, 5.4%

$C_9H_8Cl_3NO$ requires: C, 42.8; H, 3.19; N, 5.5%

$\nu_{max.}$ (Nujol) 1650 cm^{-1} (CO)

n.m.r. ($CDCl_3$): τ 5.5-5.8 (2H, m, $CH_2.N$), 7.0-7.4 (2H, m, $CH_2.CO$), and 7.8-8.3 (4H, m, $-CH_2.CH_2-$).

Attempted dehydrobromination of 2,3,8,8-tetrabromo-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (31).

The following reagents and reaction conditions were tried.

a) The tetrabromoketone (31) (0.5g.) was boiled under reflux with acetic anhydride (10 ml.) for 1hr. and the acetic anhydride distilled off under reduced pressure. Infrared analysis of the residue indicated that it was unchanged starting material.

b) 2,6-Lutidine (0.113 ml.) was added to a solution of the tetrabromoketone (0.465g.) in chloroform (10 ml.) and the mixture boiled under reflux for 1hr. After cooling, water was added and the layers separated. Only starting material was recovered.

c) The tetrabromoketone (0.25g.) was dissolved in pyridine (3 ml.) and the solution heated under reflux for 1hr. After cooling and adding dilute hydrochloric acid a dark solid precipitated which could not be characterised.

d) The tetrabromoketone (0.5g.) was boiled under reflux in methanol for 1hr. with IR 45 (OH) ion exchange resin (5g.). The resin was filtered off and the methanol evaporated under reduced pressure. Spectral analysis of the residue indicated that it was starting material.

e) A suspension of sodium ethoxide (0.136g.) in xylene was prepared according to the procedure described in Vogel.[39] The resultant suspension was added dropwise to a solution of the tetrabromoketone (0.93g.) in hot xylene (20 ml.) and the mixture boiled under reflux for 1hr. After cooling and pouring onto ice water the organic layer was extracted with ether. The ethereal extracts were dried (Na_2SO_4) and evaporated. The xylene was removed under reduced pressure yielding a black tar (0.83g.). The infrared spectrum was somewhat confused but indicated only starting material.

6,7,8,9-Tetrahydro-5H-pyrrolo[1,2-a]azepin-9-ol (35).

A solution of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (29) (1.49g.) in absolute ethanol (20 ml.) was treated dropwise with stirring with a solution of sodium borohydride (0.25g.) in 2N-sodium hydroxide (0.2 ml.) diluted with water (3 ml.). Stirring was continued at room temperature and the reaction was monitored by the disappearance of the $\lambda_{max.}$ (95% EtOH) 294 nm. ultraviolet absorption. After 2.5hr. the ethanol was removed under reduced pressure and the residue was diluted with water (10 ml.) and extracted with ether (30 ml.). The extract was dried ($MgSO_4$), filtered, and evaporated to leave a pale yellow oil (1.36g., 90%), which gradually solidified. Crystallisation from light petroleum gave the alcohol (35) as colourless rods, m.p. 72-4°.

Found: C, 71.6; H, 8.76; N, 9.4%

$C_9H_{13}NO$ requires: C, 71.5; H, 8.67; N, 9.3%

$\nu_{max.}$ (Nujol) 3260 cm^{-1} (OH)

$\lambda_{max.}$ (95% EtOH) 220 n.m. ($\log_{10}\varepsilon$, 3.83)

n.m.r. (CCl_4): τ 3.4-3.6 (pyrrole α-H), 3.9-4.2 (2H, pyrrole β-position), 4.9-5.2 (1H, m, CH.O), 5.7-6.0 (2H, m, CH_2.N) and 7.6-8.6 (6H, m).

Attempted preparation of a tosylate of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-ol (35).

a) P-toluenesulphonyl chloride (0.5g.) dissolved in the minimum

amount of acetone was added to a solution of the alcohol (35) (0.25g.) in 10% sodium hydroxide solution (3 ml.), and the mixture shaken for 20-30 minutes. Water (12.5 ml.) was added but no precipitate was formed. The mixture was extracted with ether, dried over Na_2SO_4, and evaporated to give starting material.

b) The alcohol (35) (0.5g.) was dissolved in pyridine (5 ml.) at 0° and p-toluenesulphonyl chloride (0.5g.) was added. The solution was kept at 0° for 12hr. when it gradually turned red. After working up in the usual way a red solid was obtained which could not be characterised.

Preparation of a benzoate of the alcohol (35).

A solution of the alcohol (35) (0.5g.) in pyridine (3 ml.) and benzoyl chloride (0.5g.) was kept at 0° for 18hr. Working up in the usual way gave a yellow oil (0.75g., 88%) which could not be induced to crystallise.

$\nu_{max.}$ (Film) 1715 cm^{-1} (ester CO)

n.m.r. ($CDCl_3$): τ 1.7-2.1 (2H, m) and 2.2-2.8 (3H, m, C_6H_5CO),
3.4-4.1 (4H, pyrrole ring and CH.O.Bz),
5.7-6.0 (2H, m, CH_2N), and 7.6-8.4 (6H, m).

Bulb tube distillation (50°, 5.9×10^{-4} mm.) of the benzoate (36) gave only crystals of benzoic acid. A black polymeric residue remained in the distillation tube.

Attempted bromination of 6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-ol (35).

a) A solution of the alcohol (35) (0.5g.) in carbon tetrachloride (20 ml.) containing calcium carbonate was treated with bromine (1.7g.) and the mixture stirred for 1hr. The initial colourless solution turned purple. After working up in the usual way a green polymeric solid was obtained.

b) A solution of dioxan dibromide in dioxan (prepared by adding bromine (1.1g.) to dry dioxan (5 ml.)) was added dropwise with stirring to a solution of the alcohol (0.5g.) in dioxan (5 ml.) containing suspended calcium carbonate. Filtration gave a red-brown liquid which on dilution with 10% NaOH solution gave a fawn solid which melted above 350°.

Attempted C-acetylation of the alcohol (35).

The method of Ghigi and Drusiani[23] for the preparation of 2-acetylpyrrole was employed.

A mixture of dimethylacetamide (0.6g.) and phosphorus oxychloride (1.1g.) was kept at 10-20° for 0.25hr. Ethylene dichloride (3 ml.) was added and the temperature lowered to 5°. The solution was then added dropwise over a period of 1hr. to the alcohol (35) (0.5g.) in ethylene dichloride (3 ml.). After the addition the mixture was boiled

under reflux for 0.25hr., cooled, and sodium acetate (4.75g.) in water (75 ml.) added and the solution boiled for a further 0.25hr. After cooling the aqeuous layer was extracted several times with ether. The combined extracts were washed with sodium carbonate, dried and evaporated to give a green solid which could not be characterised.

1-(4-Chlorobutyl)-3-methylindole (37).

The procedure used was as described for compound (27) except that the sodium salt suspension was added to the toluene sulphonate solution at room temperature. From 3-methylindole (9.4g.), sodium hydride (50% dispersion; 3.4g.) and 4-chlorobutyl p-toluenesulphonate (18.9g.) the yield of 1-(4-chlorobutyl)-3-methylindole (37) was 12.1g. (76%), b.p. 129-131°/0.25 mm.

Found: C, 70.6; H, 7.35; N, 5.8%

$C_{13}H_{16}ClN$ requires: C, 70.4; H, 7.3; N, 6.3%

n.m.r. (CCl_4): τ 2.3-3.0 (4H, m, aromatic), 3.2 br (s, indole 2-proton), 5.8-6.1 (2H, t, $CH_2.N$), 6.4-6.7 (2H, t, CH_2Cl), 7.7 (3H, s, CH_3), and 7.9-8.5 (4H, m)

1-(4-Cyanobutyl)-3-methylindole (38).

Prepared by an adaptation of Smiley and Arnold's method[40] as described for compound (28). From the chloro-compound (37) (10.0g.) and sodium cyanide (2.21g.) in dimethyl sulphoxide (25 ml.), 1-(4-cyanobutyl)-3-methylindole (38), b.p. 148-150°/0.1 mm. was obtained (4.71g., 49%).

Found: C, 79.0; H, 7.45; N, 13.1%

$C_{14}H_{16}N_2$ requires: C, 79.1; H, 7.6; N, 13.2%

$\nu_{max.}$ (Film) 2235 cm^{-1} (CN)

n.m.r. ($CDCl_3$): τ 2.2-3.0 (4H, m, aromatic), 3.12 (s, indole 2-proton), 5.8-6.1 (2H, t, $CH_2.N$), 7.65 (3H, s, CH_3), 7.7-8.0 (2H, t, CH_2CN), and 8.0-8.6 (4H, m).

The picrate, red needles from ether, had m.p. 91-93°.

Found: C, 54.3; H, 4.45; N, 15.7%

$C_{20}H_{19}N_5O_7$ requires: C, 54.4; H, 4.35; N, 15.85%

Attempted cyclisation of the Nitrile (38).

a) Using the procedure described by Patterson, Brasch, and Drenko,[21] the nitrile (38) was recovered unchanged.

b) A mixture of the nitrile (38) (2.12g.) and polyphosphoric acid (20g.) was slowly heated to 110°, when a red-brown colour developed,

then to 140°. The mixture was kept at 140° for 1hr., cooled to 60-70°, and poured onto ice-water (500 ml.). The mixture was extracted with ether and the extracts were washed with 5% sodium hydroxide solution, dried, and evaporated to leave a brown oil (0.51g.). A sample was distilled (bulb tube) to give the amide (39), b.p. 200-210°/0.15 mm.

$\nu_{max.}$ (Film) 3450, 3350, 3195, and 1662 cm^{-1}

n.m.r. ($CDCl_3$): τ 2.2-3.0 (4H, m, aromatic), 3.1 br. (s, indole 2-proton), 4.2-4.7 br. (2H, NH_2), 5.7-6.1 (2H, t, CH_2N), 7.65 (3H, s, CH_3), and 7.5-8.7 (6H, m).

The picrate, red needles from ether, had m.p. 78-79°.

	Found:	C, 52.4;	H, 5.0;	N, 14.95%
$C_{20}H_{21}N_5O_8$	requires:	C, 52.3;	H, 4.6;	N, 15.25%

5-(3-Methylindol-1-yl)pentanoic acid (40).

A solution of the nitrile (38) (2g.) in ethanol (15 ml.) with aqueous sodium hydroxide (20%; 30 ml.) was boiled for 8hr. The ethanol was distilled off and the aqueous residue was acidified (2N. HCl) and extracted with ether. The extracts were washed with water, dried (Na_2SO_4), and evaporated, leaving an oil which slowly crystallised (2.05g., 94%). The solid was sufficiently pure to be used in the cyclisation, but a sample was crystallised from light petroleum to give the colourless acid (40), m.p. 76-77°.

Found: C, 72.6; H, 7.3; N, 6.2%

$C_{14}H_{17}NO_2$ requires: C, 72.7; H, 7.4; N, 6.1%

$\nu_{max.}$ ($CHCl_3$) 1713 cm^{-1} (acid CO)

n.m.r. ($CDCl_3$): τ -0.25 (CO_2H), 2.2-3.0 (4H, m, aromatic), 3.05 (indole 2-proton), 5.8-6.1 (2H, t, $CH_2.N$), 7.5-7.9 (5H, Me overlapping CH_2CO_2H), and 7.9-8.4 (4H, m)

7,8,9,10-Tetrahydro-11-methyl-6H-azepino[1,2-a]indol-10-one (41).

A mixture of the acid (40) (2.5g.) and polyphosphoric acid (20g.) was heated at 95° for 15 minutes. Working up as described for compound (39), method (b), gave, after distillation, a colourless oil (1.15g., 50%), which slowly crystallised. The ketone (41) had m.p. 70-71° (from light petroleum).

Found: C, 78.5; H, 6.8; N, 6.6%

$C_{14}H_{15}NO$ requires: C, 78.5; H, 7.1; N, 6.6%

$\nu_{max.}$ ($CHCl_3$) 1655 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 214, 242, and 313 nm. ($\log_{10}\varepsilon$, 4.16, 4.22, and 4.26)

n.m.r. (CCl_4): τ 2.2-3.0 (4H, m, aromatic), 5.6-5.9 (2H, t, CH_2N), 7.1-7.4 (2H, t, $CH_2.CO$), 7.51 (3H, s, CH_3), and 7.8-8.2 (4H, m)

Attempted cyclisation of the acid (40) using the Friedel Crafts reaction.

Purified thionyl chloride (0.435 ml.) was slowly added to the acid (40) (1g.) at room temperature. Rapid evolution of hydrogen chloride occurred accompanied by the formation of a purple residue. After evolution had ceased (20 min.) the excess thionyl chloride was removed under reduced pressure yielding a purple tar. The n.m.r. spectrum indicated that decomposition had occurred.

9,9-Dibromo-7,8,9,10-tetrahydro-11-methyl-6H-azepino[1,2-a]indol-10-one (43).

Phenyltrimethylammonium tribromide (3.76g., 0.01 mole) was added to a solution of the tricyclic ketone (41) (1.07g., 0.005 mole) in anhydrous tetrahydrofuran (15 ml.) at room temperature and the mixture was set aside with occasional shaking for 5hr. The solution was filtered, the insoluble quaternary salt was washed with a little tetrahydrofuran and the combined filtrates evaporated in vacuo to give the dibromoketone (43) (1.49g., 80%). Recrystallisation from methanol gave yellow prisms, m.p. 118-119°.

Found: C, 45.6; H, 3.6; N, 3.8%

$C_{14}H_{13}Br_2NO$ requires: C, 45.3; H, 3.55; N, 3.8%

$\nu_{max.}$ ($CHCl_3$) 1668 cm^{-1} (CO)

n.m.r. ($CDCl_3$): τ 2.1-2.9 (4H, m, aromatic), 5.6-5.9 (2H, t, $CH_2.N$), 6.8-7.2 (2H, t, $CH_2.CBr_2$), 7.5 (3H, s, CH_3), and 7.5-8.0 (2H, m)

11-Methylazepino[1,2-a]indol-10-one (44).

A mixture of the dibromoketone (43) (4.45g., 0.012 mole), anhydrous lithium chloride (1.5g., 0.036 mole) and dry dimethylformamide (DMF) (300 ml.) was boiled and stirred under nitrogen for 1.5hr. The reaction mixture was cooled, and the DMF was removed under reduced pressure. Water was added, and the aqueous solution was extracted with ether. The ethereal extracts were dried (Na_2SO_4), and evaporated, giving the azepino-indolone (44) (2.1g., 83%) as an orange solid, recrystallised from methanol, m.p. 124-125°.

Found: C, 80.1; H, 5.15; N, 6.8%

$C_{14}H_{11}NO$ requires: C, 80.35; H, 5.3; N, 6.7%

$\nu_{max.}$ ($CHCl_3$) 1656, 1603, and 1570 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 208, 226, 292, and 329 nm.

($\log_{10}\varepsilon$, 4.14, 4.28, 4.55, and 3.99)

$\lambda_{max.}$ (100% H_2SO_4) 233, 272, 327 (s), 336, 550 (s), and 611 nm. ($\log_{10}\varepsilon$, 4.04, 4.06, -, 4.64, -, and 3.04)

The 220 MHz n.m.r. spectrum is shown in Figure 1 in $CDCl_3$, and in Figure 2 in CF_3CO_2H.

10-Hydroxy-11-methylazepino[1,2-a]indolium bromide (45).

Treatment of a solution of the azepino-indolone (44) (0.6g.) in chloroform with dry hydrogen bromide gave almost black crystals of the bromide (45) (quantitative), m.p. >115° (decomp.)

Found: C, 57.5; H, 4.0; N, 4.7%

$C_{14}H_{12}BrNO$ requires: C, 57.9; H, 4.15; N, 4.8%

1,2,3,8,8-Pentabromo-6,7,8,9-tetrahydro-5H-pyrrolo[1,2-a]azepin-9-one (46).

A solution of bromine (8.0g.) in carbon tetrachloride (40 ml.) was added slowly at room temperature to a stirred solution of the bicyclic ketone (29) (1.49g.) in carbon tetrachloride (10 ml.) with suspended calcium carbonate (ca. 3g.). The stirring was continued for 5hr. after addition of bromine was complete. Working up in the usual way gave a yellow solid (5.07g., 93%) which on recrystallisation from methanol gave the pentabromoketone (46), m.p. 151-155°.

Found: C, 19.5; H, 1.1; N, 2.6%

$C_9H_6Br_5NO$ requires: C, 19.9; H, 1.1; N, 2.6%

$\nu_{max.}$ ($CHCl_3$) 1680 cm^{-1} (CO)

n.m.r. ($CDCl_3$): τ 5.5-5.8 (2H, t, CH_2N), 6.9-7.1 (2H, t, $CH_2.CBr_2$), and 7.5-8.0 (2H, m)

1,2,3-Tribromopyrrolo[1,2-a]azepin-9-one (47).

The procedure was as described for the preparation of the azepino-indolone (44). From the pentabromoketone (46) (5.44g., 0.01 mole), lithium chloride (1.27g., 0.03 mole) and dry DMF (200 ml.) the pyrrolo-azepinone (47) (3.02g., 79%) was obtained as yellow needles, m.p. 187-189°

(from methanol).

Found: C, 27.9; H, 1.03; N, 3.8%

$C_9H_4Br_3NO$ requires: C, 28.3; H, 1.05; N, 3.6%

$\nu_{max.}$ ($CHCl_3$) 1662 and 1612 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 208, 244 (s), 255 (s), and 279 n.m.

($\log_{10}\varepsilon$, 4.09, -, -, and 4.40)

$\lambda_{max.}$ (100% H_2SO_4) 239, 269, 297, 378, and 477 n.m.

($\log_{10}\varepsilon$, 4.22, 4.27, 4.59, 3.87, and 3.2)

The 220 MHz n.m.r. spectrum is shown in Figure 3 in $CDCl_3$, and in Figure 4 in CF_3CO_2H.

Dehydrobromination of 1,2,3,8,8-pentabromo-6,7,8,9-tetrahydro-5H-pyrrolo [1,2-a] azepin-9-one (46) with lithium carbonate in dimethylformamide.

A solution of the pentabromoketone (46) (2.72g.) and lithium carbonate (3.7g.) in DMF (150 ml.) was boiled under nitrogen for 1.5hr., then cooled and the DMF removed under reduced pressure. Water was added, and the aqueous solution was extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give the pyrrolo-azepinone (47) (0.9g., 47%).

1,2,3-Tribromo-9-hydroxypyrrolo [1,2-a] azepinium bromide (48).

Treatment of a solution of pure azepinone (47) in chloroform with dry hydrogen bromide gave reddish-orange crystals of the azepinium

bromide (48), m.p. >125° (decomp.).

Found: C, 23.0; H, 1.0; N, 3.0%

$C_9H_5Br_4NO$ requires: C, 23.3; H, 1.1%; N, 3.0%

1,2,3-Tribromo-9-ethoxypyrrolo[1,2-a]azepinium fluoroborate (49).

A solution of the azepinone (47) with excess triethyloxonium fluoroborate[27] in methylene chloride was boiled (0.5hr.) and cooled to give red crystals of the ethoxyazepinium fluoroborate (49), m.p. >155° (decomp.).

Found: N, 2.85%

$C_4H_9BBr_3F_4NO$ requires: N, 2.8%

$\nu_{max.}$ (KBr) 1120 - 1020 cm^{-1}

Reduction of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one (47).

A solution of the azepinone (47) (0.76g.) in 95% ethanol (300 ml.) was hydrogenated to completion at atmospheric temperature and pressure over 10% palladium-charcoal (0.25g.). The uptake was five molar equivalents. The filtered solution was evaporated to give a brown gum. Dilution with water, and extraction with ether gave, after drying the ethereal extracts and evaporation an almost colourless oil (0.14g.) which solidified to a white solid, identical in m.p. and n.m.r. spectrum with the ketone (29).

Treatment of 11-methylazepino[1,2-a]indol-10-one (44) with lithium aluminium hydride.

The azepino-indolone (44) (0.5g.) was dissolved in dry ether (50 ml.) and the solution added dropwise to a stirred suspension of lithium aluminium hydride (0.1g.) in dry ether (15 ml.) under an atmosphere of nitrogen. The solution was stirred for 3hr. and then water (0.1 ml.) was added to destroy the excess lithium aluminium hydride. The solution was filtered and the residue was extracted with ether. The combined ether extracts were dried (Na_2SO_4) and evaporated to yield a pale orange gum (0.35g.) which solidified with difficulty on scratching in light petroleum. All attempts to recrystallise the crude product were unsuccessful and only green intractable oils were obtained. An n.m.r. spectrum was obtained on the crude solid.

n.m.r. ($CDCl_3$): τ 2.2-3.0 (m), 3.5-4.6 (m), 5.2-5.5 (d), 7.64 (s), 7.7-8.1 (m)

When this experiment was repeated later under identical conditions to those described above the reaction residue appeared to be more stable and readily solidified. Some purification proved possible by precipitation from warm carbon tetrachloride and a fawn coloured solid was obtained which showed the following spectral details.

$\nu_{max.}$ ($CHCl_3$) 1651, 1645 (s), 1616 cm^{-1}

Mass spectrum, $^m/e$ 195, 194, 180, 74, 59

n.m.r. ($CDCl_3$): τ 2.0-2.7 (5H, m), 3.5-3.8 (2H, m), 4.0-4.4

(2H, m), 7.64 (3H, s, CH_3), and 7.8-8.1 (1H, m)

Passage of dry hydrogen bromide through a solution of the reduction product in chloroform gave a black intractable tar.

Treatment of the azepino-indolone (44) with lithium aluminium deuteride.

The azepino-indolone (44) (0.21g.) in dry ether (25 ml.) was reduced with lithium aluminium deuteride (0.05g.) in ether (10 ml.) as described above. Working up gave a yellow gum (0.15g.) which showed an infrared and n.m.r. spectra very similar to those of the crude product obtained using lithium aluminium hydride.

Attempted reduction of the azepino-indolone (44) with sodium borohydride.

A solution of the azepino-indolone (44) (0.75g.) in absolute ethanol (25 ml.) was treated dropwise with stirring with a solution of sodium borohydride (0.2g.) in 2N sodium hydroxide (0.15 ml.) diluted with water (2 ml.). The solution was stirred at room temperature for 72hr. The solvent was evaporated off and the residue taken up in water (15 ml.) and extracted with ether. The ethereal extract was dried (Na_2SO_4), filtered, and evaporated to leave an orange gum (0.63g.). The n.m.r. spectrum was very similar to the product obtained using lithium aluminium hydride.

Attempted reduction of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one (47) with sodium borohydride.

The procedure was as described above. From the pyrrolo-azepinone (47) (0.382g.), sodium borohydride (0.05g.) in ethanol (120 ml.) stirred for 1hr. was obtained a fawn coloured solid (0.35g.). The residue was examined by n.m.r. when an extremely complex spectrum resulted which showed peaks between 2.5-6.2τ.

$\nu_{max.}$ ($CHCl_3$) 3390, 1626, 1607 (s) cm^{-1}

3-Methyl-2-(2-pyrazolin-5ylacetyl)indole (50).

11-Methylazepino[1,2-a]indol-10-one (44) (0.63g.) and 100% hydrazine hydrate (0.16g.) were boiled under reflux in absolute ethanol (25 ml.) for 2hr. The solution was cooled and the ethanol was evaporated to leave the pyrazoline (50) (0.69g., 95%) as a brown solid, recrystallised from benzene as fawn coloured needles, m.p. 166-7°.

Found: C, 69.6; H, 6.04; N, 17.4%

$C_{14}H_{15}N_3O$ requires: C, 69.7; H, 6.25; N, 17.4%

$\nu_{max.}$ ($CHCl_3$) 3455, 1646 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 208, 236, and 308 nm. ($\log_{10}\varepsilon$, 4.28, 4.23, and 4.30)

The 100 MHz n.m.r. spectrum is shown in Figure 5 in $CDCl_3$, and in Figure 6 in CF_3CO_2H.

Treatment of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one (47) with hydrazine hydrate.

The pyrrolo-azepinone (47) (0.5g.) in absolute ethanol (40 ml.) was treated with hydrazine hydrate (0.06g.) as described for the azepino-indolone (44). The product was obtained as a yellow glass (0.53g.) which would not crystallise.

$\nu_{max.}$ ($CHCl_3$) 3390, 1702, 1644.

The n.m.r. spectrum was rather ill-defined but showed a broad peak at 2.95τ and a doublet centred at 6.7τ which suggested pyrazoline formation.

Reaction of 11-methylazepino[1,2-a]indol-10-one (44) with phosphorus tribromide.

Freshly distilled phosphorus tribromide (2 ml.) and the azepino-indolone (44) (0.25g.) were boiled under reflux for 2hr. After cooling the excess phosphorus tribromide was decanted to leave a black intractable solid.

Treatment of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one (47) with phosphorus pentasulphide.

a) A mixture of the pyrrolo-azepinone (47) (1g.) and phosphorus

pentasulphide (4g.) was slowly heated to 150°, when the colour became darker, then to 170°. The mixture was kept at 170° for 5 minutes and then cooled to give a black solid which could not be purified, and which was not soluble in the normal polar solvents.

b) Phosphorus pentasulphide (2g.) was added to a solution of the pyrrolo-azepinone (47) (0.5g.) in benzene (50 ml.) and the mixture boiled for 1hr. The black solid which precipitated was filtered but could not be purified or characterised.

Attempted reaction of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one (47) with dimethylacetylene dicarboxylate.

The pyrrolo-azepinone (47) (0.1g.) was dissolved in dimethylacetylene dicarboxylate (2 ml.) and the solution heated at 160° for 1hr. Evaporation of the ester under reduced pressure gave only starting material.

(6,7,8,9-Tetrahapto-11-methylazepino[1,2-a]indol-10-one)iron tricarbonyl (51).[41]

A mixture of the azepino-indolone (44) (0.36g.), dodecacarbonyltri-iron (0.36g.) and dry benzene (50 ml.) was boiled under nitrogen for 24hr. The solution was cooled and filtered through Hyflo Supercel to remove particles of iron. Evaporation of the solvent yielded a brown glass which on trituration with methanol gave the iron tricarbonyl complex (51) as a

brown solid (0.36g., 60%). Crystallisation from methanol gave red-brown prisms, m.p. >196° (decomp.).

Found: C, 58.6; H, 3.06; N, 4.0%

$C_{17}H_{11}FeNO_4$ requires: C, 58.5; H, 3.17; N, 4.0%

$\nu_{max.}$ ($CHCl_3$) 2072, 2016, and 1616 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 224, 265 (s), and 334 nm. ($\log_{10}\varepsilon$, 4.50, -, and 4.24)

n.m.r. ($CDCl_3$): τ 2.0-2.9 (4H, m, aromatic), 3.6-3.9 (1H, m, H7), 4.1-4.6 (2H, m, H6 and H8), 6.05-6.35 (1H, d, J = 8Hz, H9), and 7.46 (3H, s, CH_3)

Reduction of the iron tricarbonyl complex (51).

a) Sodium borohydride (0.1g.) was added directly to a stirred solution of the complex (51) (0.05g.) in absolute ethanol (80 ml.) and stirring continued for 5hr. Working up in the usual way gave a dark brown oil (0.32g.) which on examination by t.l.c. showed three spots. Separation was by P.L.C. employing toluene - 20% ether as eluent. Band I (48 mg., R = 16.5) was isolated as a brown solid, recrystallised from methanol as yellow needles, m.p. 98-9°. The spectra were consistent with those expected for 8,9-dihydro-11-methylazepino[1,2-a]indol-10-one (52).

Found: C, 79.4; H, 5.93; N, 6.8%

$C_{14}H_{13}NO$ requires: C, 79.6; H, 6.2; N, 6.63.

$\nu_{max.}$ ($CHCl_3$) 1660 (broad) cm^{-1}

$\lambda_{max.}$ (95% EtOH) 221 (s), 244, 313, and 353 (s) nm.
($\log_{10}\varepsilon$, -, 4.13, 4.19, -.)
n.m.r. ($CDCl_3$): τ 2.0-3.0 (5H, m, aromatic and H6),
4.2-4.6 (1H, m, H7), 6.8-7.15 (2H, m, H9),
7.2-7.7 (5H, m, CH_3 and H8)

Band II (43 mg., R = 14.8) was shown from its n.m.r spectrum to be a mixture, consisting of approximately 24% of the azepino-indolone (44), 57% of the tricyclic ketone (41), and 19% of the starting complex (51).
Band III (50 mg., R = 11.4) showed a rather ill-defined n.m.r. spectrum but a multiplet between 5.6-6.0τ and the methyl singlet at 7.65τ suggested that the product might be 8,9-dihydro-11-methylazepino[1,2-a] indol-10-ol (53).

b) The iron tricarbonyl complex (51) (0.5g.) in dry tetrahydrofuran (50 ml.) was reduced with lithium aluminium hydride (0.06g.) in tetrahydrofuran (10 ml.) in the usual way. The solution was stirred under nitrogen for 3hr. Water (0.06 ml.) was then added to decompose the excess lithium aluminium hydride and the solution was filtered and the residue extracted with tetrahydrofuran. The extracts were combined and dried over Na_2SO_4, filtered, and evaporated to give a brown oil (0.23g.) separated by P.L.C., eluting with toluene-15% ether, into the following components.
Band I (19 mg., R = 15) was shown to be 7,8,9,10-tetrahydro-11-methyl-6H-azepino[1,2-a]indole (54) by comparison of its spectra with those of an authentic sample prepared by Wolff-Kishner reduction of 7,8,9,10-tetrahydro-11-methylazepino[1,2-a]indol-10-one (41) described below.

Band II (6 mg., R = 8.7) was shown from its n.m.r. spectrum to be 8,9-dihydro-11-methylazepino[1,2-a]indol-10-one (52).

Band III (22 mg., R = 6.2), isolated as a yellow oil, showed an n.m.r. spectrum identical with that of the tricyclic ketone (41). The infrared spectrum showed low intensity bands at 2072 and 2016 cm^{-1} indicative of a small amount of the starting complex (51) as contaminant.

Band IV (49 mg., R = 4) was 7,8,9,10-tetrahydro-11-methyl-6H-azepino[1,2-a]indol-10-ol (55) identified by a comparison with an authentic sample prepared by borohydride reduction of the tricyclic ketone (41) described below.

7,8,9,10-Tetrahydro-11-methyl-6H-azepino[1,2-a]indole (54).

A mixture of the tricyclic ketone (41) (2.5g.), potassium hydroxide (4g.), 85% hydrazine hydrate (3 ml.), and diethylene glycol (30 ml.) was heated under reflux for 5hr. After cooling the solution was diluted with water (30 ml.), made acidic with 6N hydrochloric acid (18 ml.) and extracted several times with ether. The combined extracts were washed with water, dried (Na_2SO_4), and concentrated to give a quantitative yield of the azepino-indole (54) (2.3g.). Recrystallisation three times from light petroleum afforded colourless needles, m.p. 94-5°.

Found: C, 84.3; H, 8.6; N, 7.2%

$C_{14}H_{17}N$ requires: C, 84.4; H, 8.6; N, 7.03%

$\lambda_{max.}$ (95% EtOH) 230 and 287 nm. ($\log_{10}\varepsilon$, 4.27 and 3.85)

n.m.r. (CCl_4): τ 2.3-3.1 (4H, m, aromatic), 5.7-6.1 (2H, m, CH_2.N), 7.0-7.4 (2H, m, HlO), 7.73 (3H, s, CH_3), and 8.0-8.6 (6H, m)

7,8,9,10-Tetrahydro-11-methyl-6H-azepino[1,2-a]indol-10-ol (55).

The procedure was as described for the bicyclic alcohol (35). From the tricyclic ketone (41) (2.13g.), sodium borohydride (0.25g.) and absolute ethanol (25 ml.) was obtained the alcohol (55) (2.1g., 98%), crystallised from light petroleum as colourless cubes, m.p. 67-75°.

Found: C, 78.5; H, 8.2; N, 6.3%

$C_{14}H_{17}NO$ requires: C, 78.1; H, 8.0; N, 6.5%

$\nu_{max.}$ (Nujol) 3220 (broad) cm^{-1} (OH)

$\lambda_{max.}$ (95% EtOH) 230 and 285 nm.

n.m.r. ($CDCl_3$): τ 2.2-3.0 (4H, m, aromatic), 4.5-4.7 (1H, m, CH.O), 5.6-6.0 (2H, m, CH_2.N), 7.7 (3H, s, CH_3), and 7.7-8.6 (6H, m)

Treatment of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one (47) with concentrated sulphuric acid.

The pyrrolo-azepinone (47) (0.04g.) was dissolved in concentrated sulphuric acid (1 ml.) and the solution heated at 140° for 1.5hr. The

solution darkened, but the starting material was recovered on addition of water.

Attempted reduction of 1,2,3-tribromo-9-hydroxypyrrolo[1,2-a]azepinium bromide (48).

A solution of the bromide (48) (0.5g.) in purified glacial acetic acid (150 ml.) was reduced with Adams catalyst (0.03g.) at room temperature and atmospheric pressure. The reduction was stopped after the uptake of three molar equivalents of hydrogen. Filtration and evaporation gave an oily residue which would not crystallise. The n.m.r. spectrum of the oil showed that reduction had occurred in the seven membered ring.

Treatment of 1,2,3-tribromopyrrolo[1,2-a]azepin-9-one (47) with magnesium and iso-propanol.

The method of Bryce-Smith and Wakefield[34] was employed.

A solution of the pyrrolo-azepinone (47) (1.53g.) and iso-propanol (0.36g.) in decahydronaphthalene (100 ml.) was added dropwise to a boiling suspension of magnesium (0.24g.) in decahydronaphthalene (5 ml.) containing a crystal of iodine under a nitrogen atmosphere. There was no visible sign of reaction. After the addition the mixture was heated under reflux for 1hr., cooled, and treated with 6N hydrochloric acid until no solid remained. The organic layer was separated, washed

with water and dried over calcium chloride. Dilution of the organic solution with light petroleum gave only starting material.

1-Ethoxy-4-chlorobut-2-ene (62).[37]

A solution of sodium ethoxide (prepared by dissolving sodium (2.3g.) in 'super dry' ethanol (150 ml.)) was added slowly over 30 minutes to a solution of 1,4-dichlorobut-2-ene (125g.) in dry ethanol (500 ml.). The mixture was boiled for 3hr. and stirred at room temperature for a further 12 hr., cooled, and the sodium chloride filtered off. Evaporation of the ethanol and distillation of the residue gave the 1-ethoxy-4-chlorobut-2-ene (62) (83g., 62%) as a colourless liquid, b.p. 62°/14 mm. (lit.,[42] b.p. 61-4°/14 mm.).

4-Ethoxybut-2-enyltriphenylphosphonium chloride (63).

Prepared by an adaptation of Schweizer and Bach's method.[36]

1-Ethoxy-4-chlorobut-2-ene (62) (75g.) and pure triphenylphosphine (146g.) were boiled in dry ethanol (900 ml.) for 46hr. The ethanol was evaporated until the volume of the reaction mixture had decreased to about 200 ml., when the remaining solution was stirred into anhydrous ether (5l.) and agitated until white crystals appeared. The mixture was filtered, and the solid thoroughly washed with dry ether. Drying in vacuo gave an essentially quantitative yield of the ethoxy salt

(63) (215g.) as colourless needles, m.p. 148-150°.

Found: C, 72.6; H, 6.8%

$C_{24}H_{26}ClOP$ requires: C, 72.6; H, 6.6%

n.m.r. (D_2O): τ 1.9-2.6 (15H, m, aromatic), 4.0-4.3 (2H, m, -CH=CH-), 5.4-6.2 (4H, m), 6.4-6.9 (2H, q, OCH_2CH_3), and 8.7-9.0 (3H, t, CH_3)

Attempted preparation of buta-1,3-dienyltriphenylphosphonium chloride (59).

4-Ethoxybut-2-enyltriphenylphosphonium chloride (63) (45g.) in dry ethyl acetate (450 ml.) was boiled and stirred for 36hr. The mixture was cooled, poured into dry ether (2 l.) and shaken until solid. The solid was filtered, dried and examined by n.m.r. but the spectrum was ill-defined and little could be gained from it. Crystallisation of the solid from ethanol-ethyl acetate gave colourless rhombs., m.p. 238° (decomp.).

Found: C, 71.1; H, 6.0%

The n.m.r. spectrum on the crystallised material was again poorly resolved.

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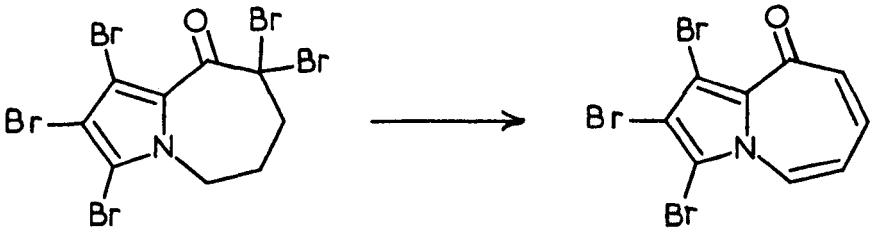
PART II

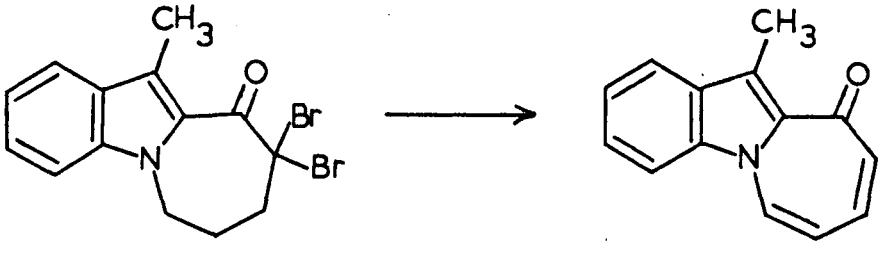
INTRODUCTION

A brief historical account is given of the uses of lithium halides in dimethylformamide as reagents for elimination.

It has been described in Part I of this thesis how the pyrrolo-azepinone (1) and the azepino-indolone (2) can be prepared in high yield by the one step double dehydrobromination of the corresponding α,α-dibromoketones using lithium chloride in boiling dimethylformamide.



(1)



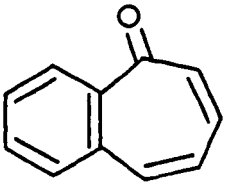
(2)

It will be shown that this double dehydrobromination reaction can be applied to the synthesis of benztropone and its derivatives.

The mechanism of elimination has been investigated. Attempts to isolate possible intermediates have centred on the examination of two reaction pathways.

NOMENCLATURE

In 1957 Eschenmoser et al.[1] reported the preparation of the bicyclic ketone (3). Since then three systems of numbering (4, 5 and 6) have been employed giving rise to the names benz[2,3]tropone, 1,2-benzocyclohepta-1,4,6-trien-3-one, and 5H-benzocyclohepten-5-one respectively.



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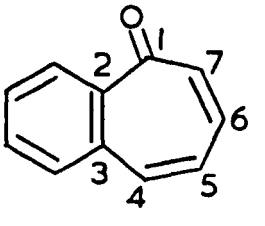

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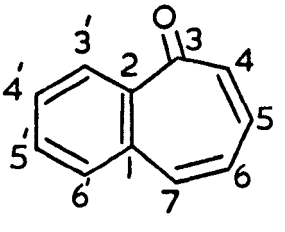

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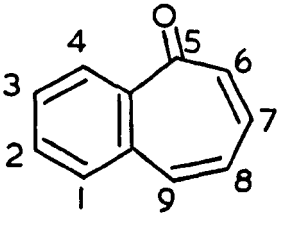
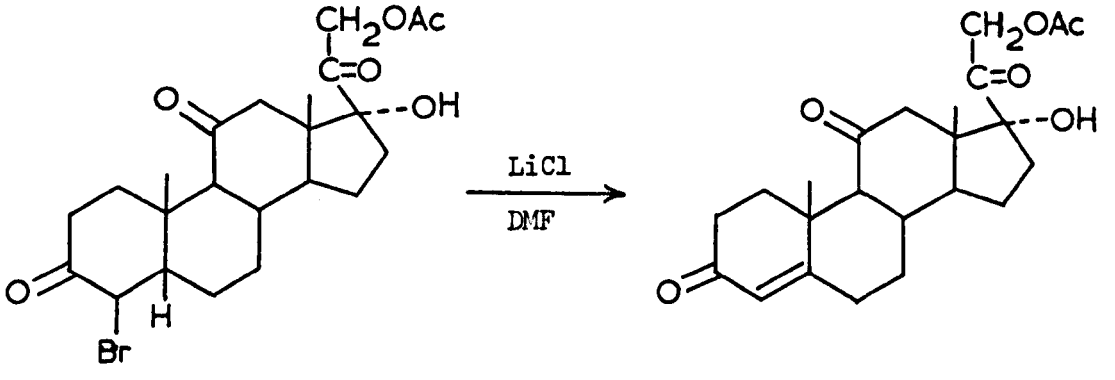


(6)

The latter name has now been adopted by "Chemical Abstracts", and will be used in the experimental section of this part of the thesis. However, for simplicity the name benztropone will be used during discussion to describe compounds of the above type.

ELIMINATION USING LITHIUM HALIDE IN DIMETHYLFORMAMIDE

In the search for improved conditions in the synthesis of cortisone, Holysz[2] in 1953 experimented with certain metallic halides in amide solvents as possible reagents for the dehydrobromination of 4-halo-3-ketosteroids to the corresponding Δ^4-3-ketones. In particular he found that lithium chloride in dimethylformamide was most effective, and that on treating the 4-bromoketosteroid (7) with three equivalents of anhydrous lithium chloride in dimethylformamide at 100° under nitrogen an 80% yield of cortisone acetate (8) was obtained.



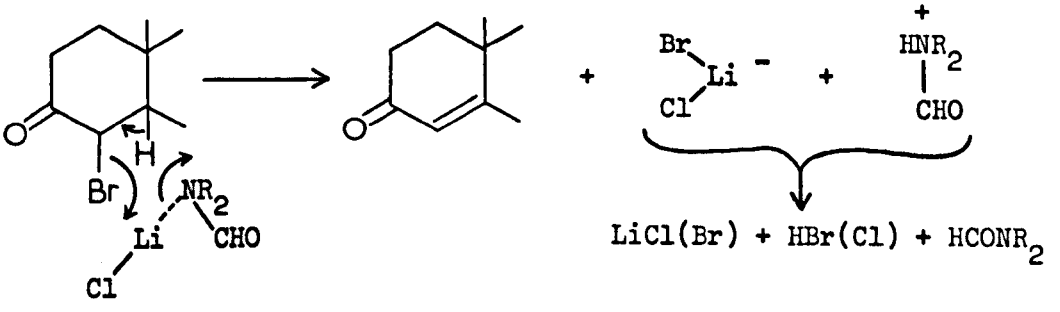
(7) (8)

Holysz found that in dimethylformamide, chlorides containing cations of similar size to lithium i.e. magnesium, beryllium and aluminium also dehydrobrominated the bromoketone (7) to the enone (8)

almost as well as lithium chloride, whereas sodium, ammonium or calcium chlorides in formamide-dimethylformamide led to no appreciable amounts of Δ^4-3-ketone.

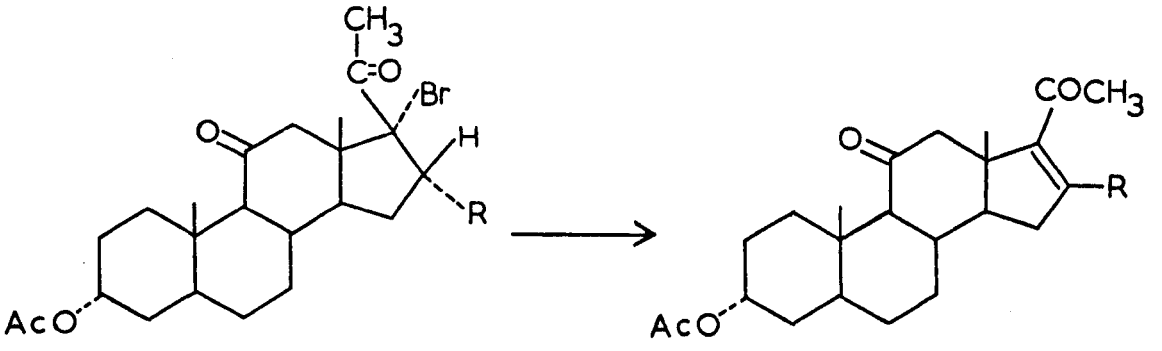
As a possible mechanism, outlined in Scheme I, Holysz proposed a transition state involving the halo-ketosteroid, lithium chloride and dimethylformamide in a six membered ring orientation with simultaneous bond formation and bond cleavage to give the olefinic product.

SCHEME I



Experimental observations suggested that a cis configuration between the C-4 bromine and C-5 hydrogen would be the most favourable for the above mechanism.

Wendler, Taub and Kuo[3] found that in the dehydrobromination of the 16α-deuterio-17α-bromoketone (9) with lithium chloride in dimethylformamide, that 98% of the deuterium was retained giving the 3α-acetoxy-16-deuterio-Δ^{16}-pregnene-11,20-dione (11).



(9) R = D

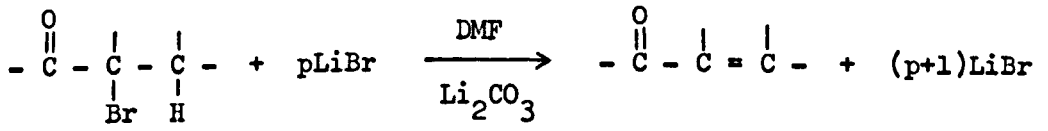
(10) R = H

(11) R = D

(12) R = H

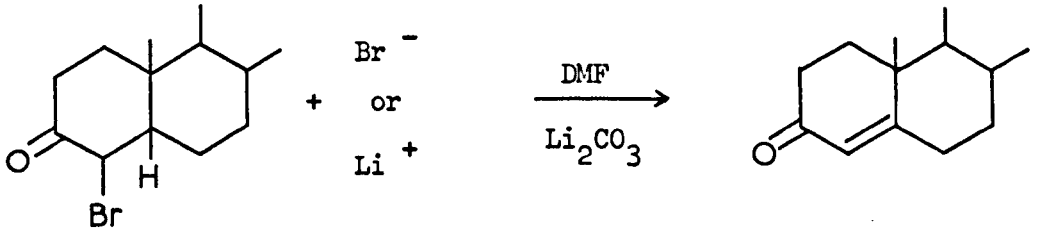
Examination of the nuclear magnetic resonance spectrum of the dione (11) indicated 15-20% of hydrogen at C-16, from which it was concluded that a corresponding amount of randomly distributed deuterium was present in the bromoketone (9). Since the orientation of the deuterium and the bromine atoms in the ketone (9) are well established[4,5] it became evident that the dehydrobromination was essentially an E2 trans elimination process.

Further study on the dehydrobromination of α-monobromoketosteroids has been carried out by Delaroff et al.[6] The overall reaction for the dehydrobromination of the 4-bromoketosteroid (7) to cortisone acetate (8) and the bromoketone (10) to the pregnene dione (12) was represented by



where the speed of the reaction was first order with respect to the bromosteroid and of order p with respect to lithium bromide. Lithium carbonate did not interfere in the reaction other than by neutralisation of the hydrogen bromide. From the value of p obtained Delaroff concluded that the dehydrobromination of the 3-keto-4-bromosteroid (7) was in accord with the following Scheme II.

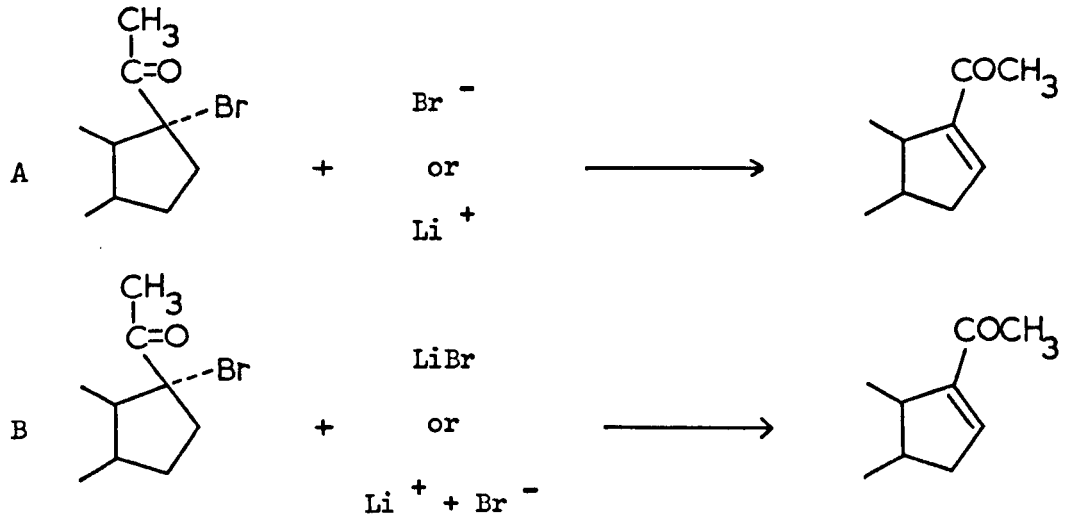
SCHEME II



(7) (8)

By varying the nature of the cations and anions present in the reaction he found that initial attack was by abstraction of a proton by the halide anion which in dimethylformamide is a strong nucleophilic base. For the formation of the Δ^{16}-pregnenedione (12) the value of p suggested the existence of two reactions running concurrently (Scheme III) involving either undissociated lithium bromide (or simultaneously the ions Li^+ and Br^-) or one ion as in the case of Scheme II.

SCHEME III



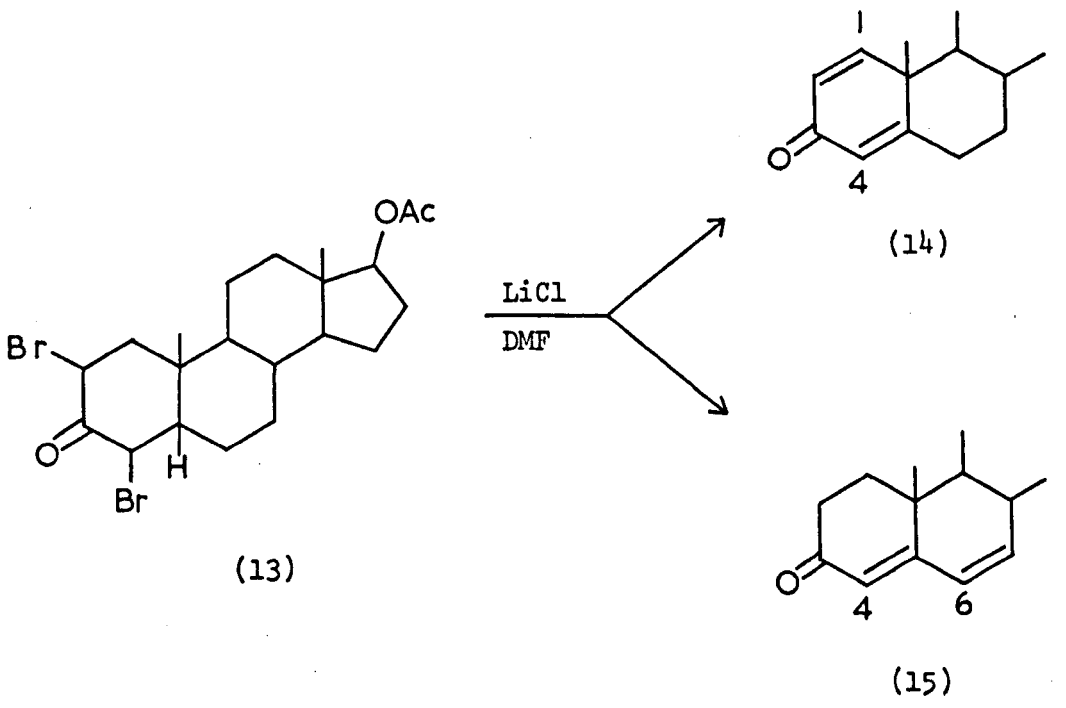
A rise in temperature was found to favour path A at the expense of path B.

In effect these results agreed with those obtained by Wendler, Taub and Kuo[3] but comparative examination of the amounts of deuterium in both the final product and the precursors did not permit the entire exclusion of the formation of small amounts of non-deuterated Δ^{16}-pregnenedione (12) by path A. Delaroff summarised his observations by concluding that the general mode of reaction was attack by the halide anion, and that in cases where stereochemical orientation was favourable there was a concurrent attack by undissociated LiX or by the two ions Li^+ and X^-.

The use of lithium halide in dimethylformamide for dehydrohalogenation has been found to give rise to rearranged products in addition to the normally expected ones. Joly and his co-workers[7]

investigating the dehydrobromination of 2β,4β-dibromo-17β-acetoxyetiocholane (13) under the same conditions as those employed by Holysz[2] found that a mixture of the 1,4-dienone (14) and the 4,6-dienone (15) was obtained.

SCHEME IV

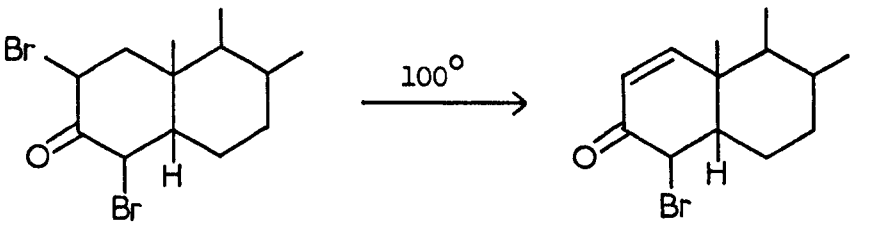


(13)

(14)

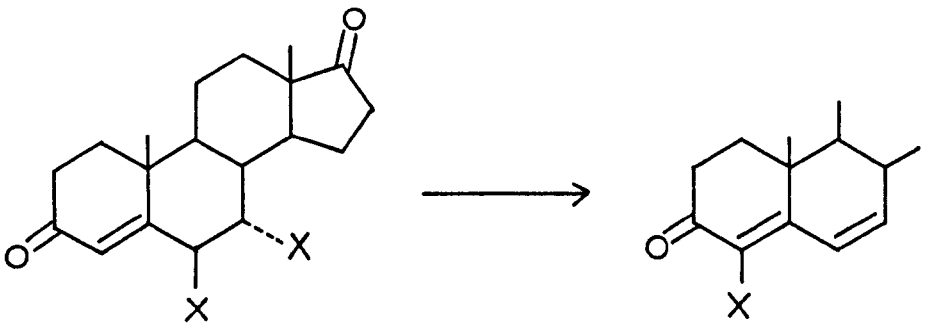
(15)

The 1,4-dienone (14) was isolated pure in high yield by the introduction of lithium carbonate into the reaction medium. By moderating the conditions Joly[8] was able to isolate the intermediate 4β-bromo-Δ^1-ene-3-one (16).



(13) (16)

Dehydrohalogenation with migration of a halogen atom has been observed by Brückner, Hampel and Johnsen[9] when 6β,7α-dibromo (17) or 6β,7α-dichloro-Δ^4-androstene-3,17-dione (18) were treated with lithium chloride in dimethylformamide. The products were the 4-halo-$\Delta^{4,6}$-androstadiene-3,17-diones (19A,B).

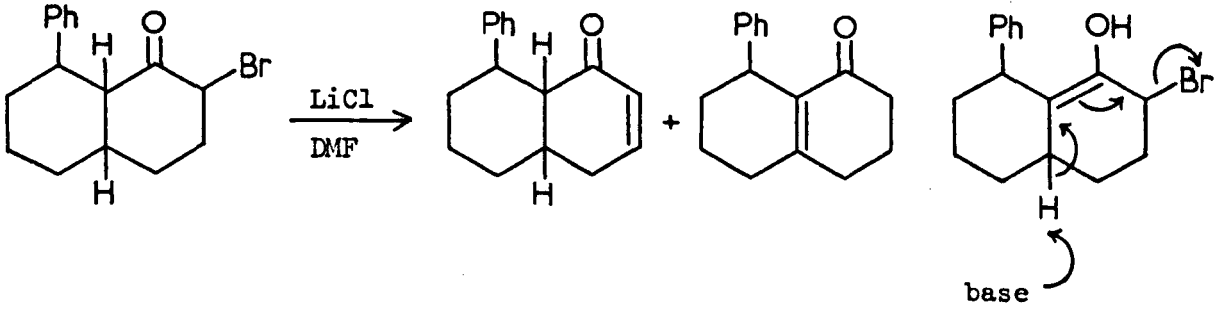


(17) X = Br (19A) X = Br

(18) X = Cl (19B) X = Cl

House and Bashe[10] were able to effect dehydrobromination of the bromoketone (20) to the unrearranged ketone (21) using lithium carbonate in dimethylformamide. However, use of the less basic lithium

chloride led to mixtures of the unrearranged ketone (21) and the rearranged ketone (22). Treatment of ketone (21) with hydrogen bromide in acetic acid caused slow isomerisation to ketone (22). It was suggested that dehydrobromination of the bromoketone (20) to the rearranged ketone (22) involved conjugate elimination of the enol (23).



(20) (21) (22) (23)

Hauptschein and Oesterling[11] studied the reaction of various nucleophilic reagents on telomer iodides of 1,1-difluoroethylene (e.g. 24). They reported the preferential β-elimination of hydrogen iodide by reaction with lithium chloride in dimethylformamide.

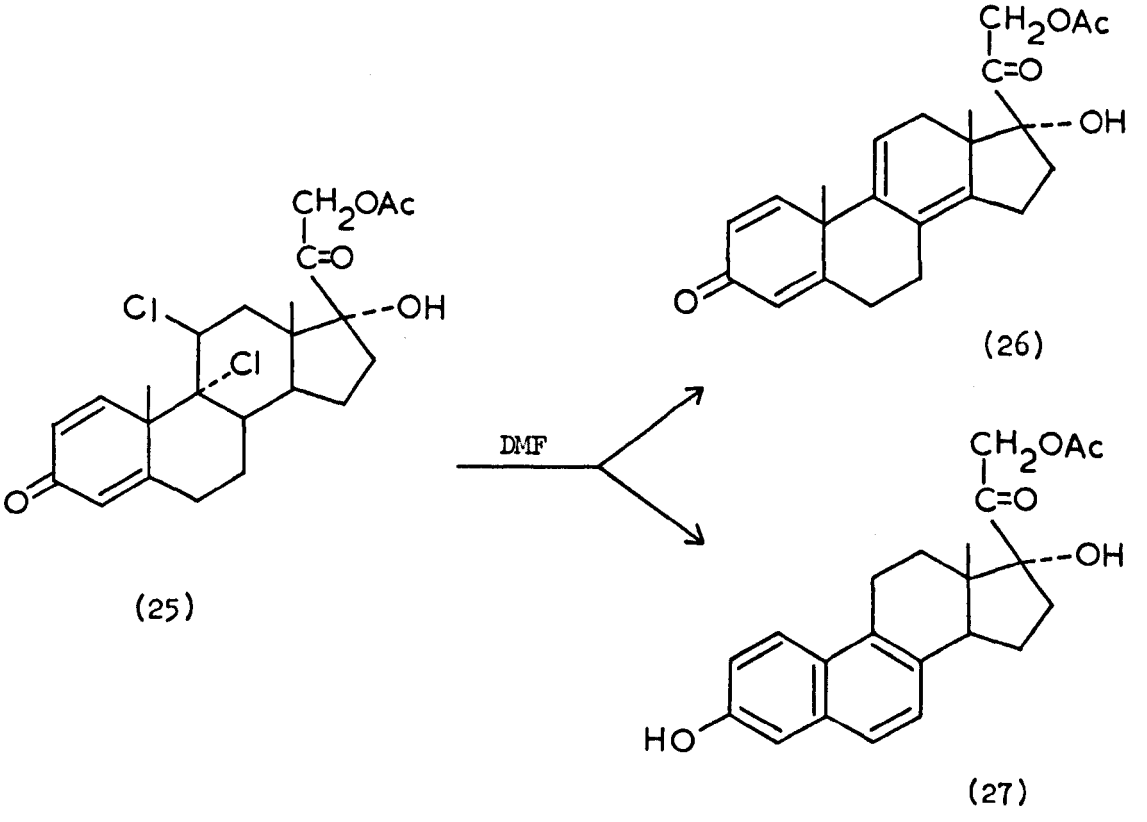
$$CF_3CH_2CF_2I + LiCl \xrightarrow{DMF} CF_3CH = CF_2 + HCl + LiI$$

(24)

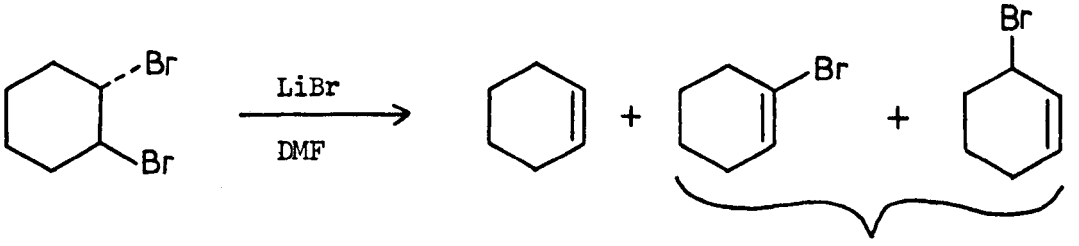
Ring AB aromatic steroids have been prepared from non-aromatic

intermediates by elimination of the C-19 methyl group using dimethylformamide alone. Heller, Lenhard and Bernstein[12] found that when the 9α,11β-dichloro-1,4-diene (25) was treated with boiling dimethylformamide two products resulted each in 20-25% yield. These were identified as the tetraene (26) and the ring AB aromatic product (27). The C-19 methyl group was cleaved as methyl chloride during aromatisation. A reaction mechanism was suggested which involved attack by the halide ion (generated by elimination of the 9α-chlorine) on the C-19 methyl group facilitated by protonation of the C-3 oxygen.

SCHEME V



The elimination of bromine catalysed by bromide ion has also been reported. Badea and his co-workers[13] treated several vicinal dibromides with lithium bromide in dimethylformamide at 100° and obtained products resulting from trans elimination of bromine. The trans 1,2-dibromocyclohexane (28) gave 30% of cyclohexene in addition to products obtained by cis and trans elimination of hydrogen bromide.



(28) 30% 17%

Kinetic experiments indicated that direct action of the bromide ion on the organically linked bromine atom was the rate determining step.

Dimethylformamide, because of its high dielectric constant (37.6), has been described[14] as a 'dipolar aprotic' solvent. Unlike 'protic' solvents, which are hydrogen donors, 'dipolar aprotic' solvents are unable to donate suitably labile hydrogen atoms and consequently cannot form strong hydrogen bonds with an appropriate species.

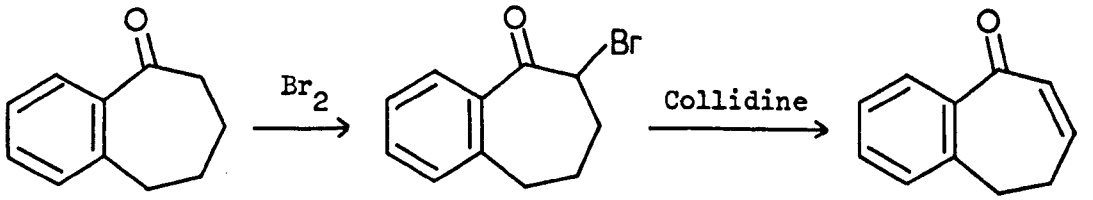
The good dehydrohalogenating properties of halide ions in dimethylformamide are due not only to the fact that halide anions are strong bases and powerful nucleophiles in dimethylformamide, but also to the ability of dimethylformamide to efficiently solvate cations and readily act as a hydrogen acceptor.

DISCUSSION

Syntheses of 5H-benzocyclohepten-5-ones using lithium chloride in dimethylformamide and analogous reagents.

The most convenient syntheses of 5H-benzocyclohepten-5-ones have proceeded from the bicyclic ketone (29) by bromination and dehydrobromination sequences. Buchanan and Lockhart[15] prepared the unsaturated ketone (31) by bromination of the ketone (29) with bromine, followed by dehydrobromination using collidine. They found it very unstable and were unable to use it for further work.

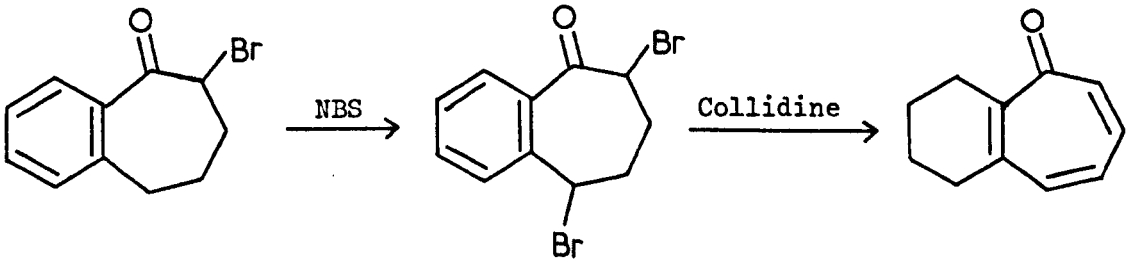
SCHEME VI



(29) (30) (31)

The same authors independently employing the route used by Elad and Ginsberg[16] for the synthesis of a related tropone, further brominated the bromoketone (30) with N-bromosuccinimide to give the dibromoderivative (32), which when heated in collidine afforded the benztropone (33). The overall yield was 65%.

SCHEME VII

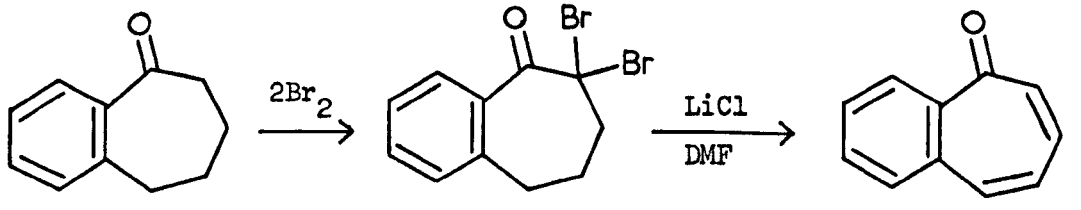


(30) (32) (33)

5H-Benzocyclohepten-5-one (33)

The 6,6-dibromoketone (34) was prepared in almost quantitative yield by brominating a carbon tetrachloride solution of the parent ketone (29) with two molar equivalents of bromine. The position of the bromine atoms was confirmed by the n.m.r. spectrum which showed the 7 and 9 methylene groups as broadened triplets between 7.0-7.4τ. Heating the dibromoketone (34) with an excess of lithium chloride in dimethylformamide at 150° for 1hr. gave the benztropone (33). The yield was 92%.

SCHEME VIII



(29) (34) (33)

N.m.r. spectrum of 5H-benzocyclohepten-5-one in $CDCl_3$

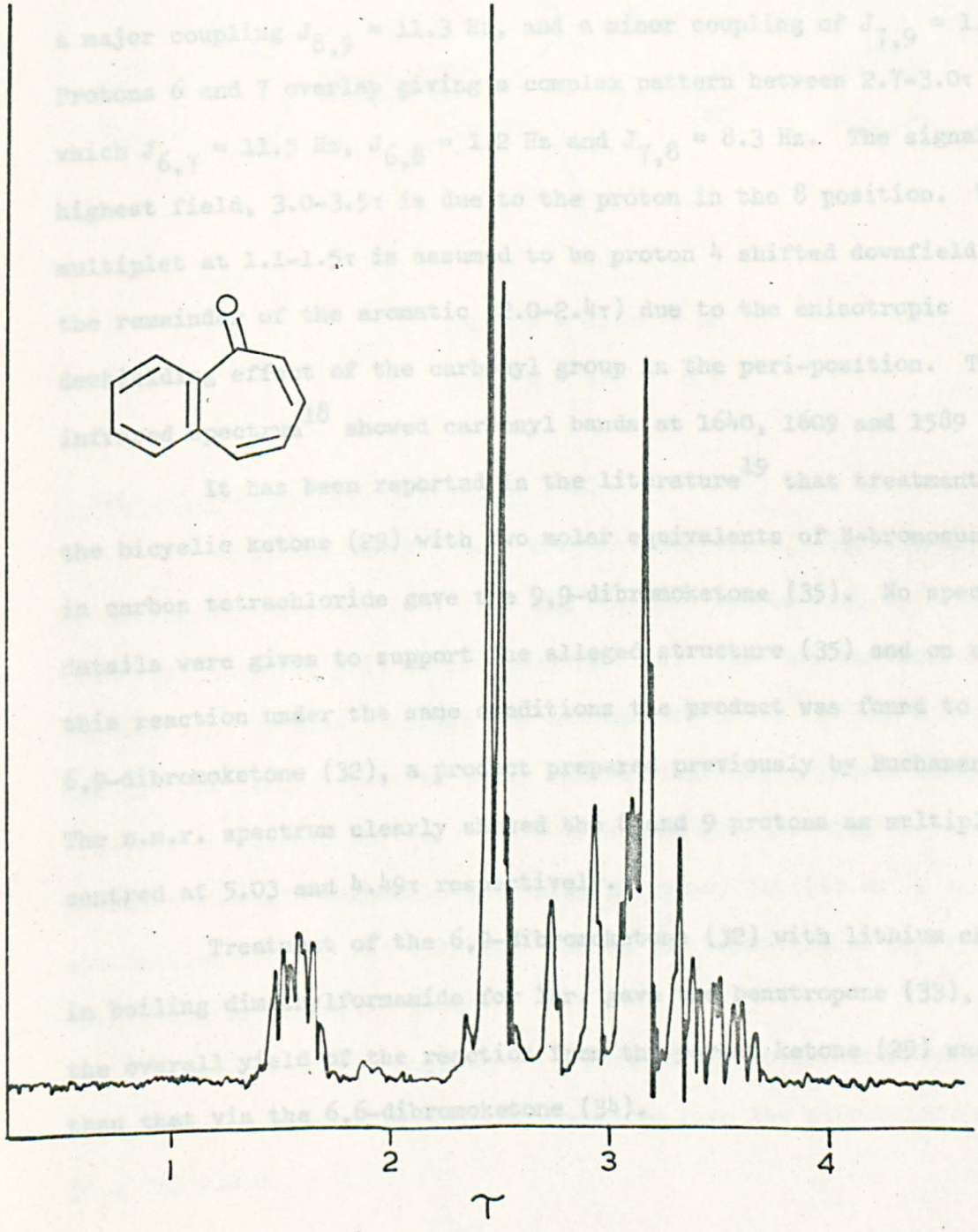


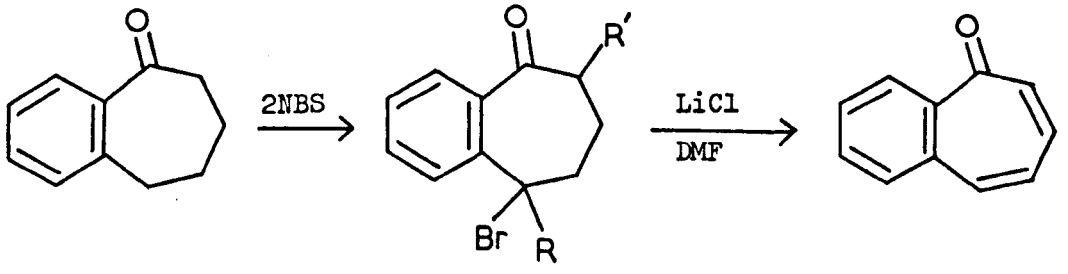
Figure 1

The n.m.r. spectrum of the tropone (33), shown in Figure 1, has been analysed by Bertelli, Gerig and Herbelin.[17] The quartet centred at 2.55τ is due to the proton in the 9 position which has a major coupling $J_{8,9}$ = 11.3 Hz, and a minor coupling of $J_{7,9}$ = 1.2 Hz. Protons 6 and 7 overlap giving a complex pattern between 2.7-3.0τ from which $J_{6,7}$ = 11.5 Hz, $J_{6,8}$ = 1.2 Hz and $J_{7,8}$ = 8.3 Hz. The signal at highest field, 3.0-3.5τ is due to the proton in the 8 position. The multiplet at 1.1-1.5τ is assumed to be proton 4 shifted downfield from the remainder of the aromatic (2.0-2.4τ) due to the anisotropic deshielding effect of the carbonyl group in the peri-position. The infrared spectrum[18] showed carbonyl bands at 1640, 1609 and 1589 cm^{-1}.

It has been reported in the literature[19] that treatment of the bicyclic ketone (29) with two molar equivalents of N-bromosuccinimide in carbon tetrachloride gave the 9,9-dibromoketone (35). No spectral details were given to support the alleged structure (35) and on repeating this reaction under the same conditions the product was found to be the 6,9-dibromoketone (32), a product prepared previously by Buchanan.[15] The n.m.r. spectrum clearly showed the 6 and 9 protons as multiplets centred at 5.03 and 4.49τ respectively.

Treatment of the 6,9-dibromoketone (32) with lithium chloride in boiling dimethylformamide for 1hr. gave the benztropone (33), although the overall yield of the reaction from the parent ketone (29) was lower than that via the 6,6-dibromoketone (34).

SCHEME IX



(29) (32) R = H, R' = Br (33)

(35) R = Br, R' = H

3-Nitro-5H-benzocyclohepten-5-one (38)

Smith and Berry[20] have prepared 3-nitro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (36) from the bicyclic ketone (29) by nitration with fuming nitric acid at low temperatures. This was successfully treated with bromine to yield the dibromoderivative (37) as a colourless solid. The n.m.r. spectrum again showed broadened triplets between 6.8-7.3τ attributed to the 7 and 9 methylene groups. The infrared spectrum showed a carbonyl stretching frequency at 1710 cm^{-1}, and strong absorptions at 1610 and 1342 cm^{-1} due to the asymmetrical and symmetrical stretching of the nitro group.

The nitrodibromoketone (37) was dehydrobrominated by lithium chloride in refluxing dimethylformamide to give the nitrobenztropone (38) in a 76% yield.

N.m.r. spectrum of 3-nitro-5H-benzocyclohepten-5-one in $CDCl_3$

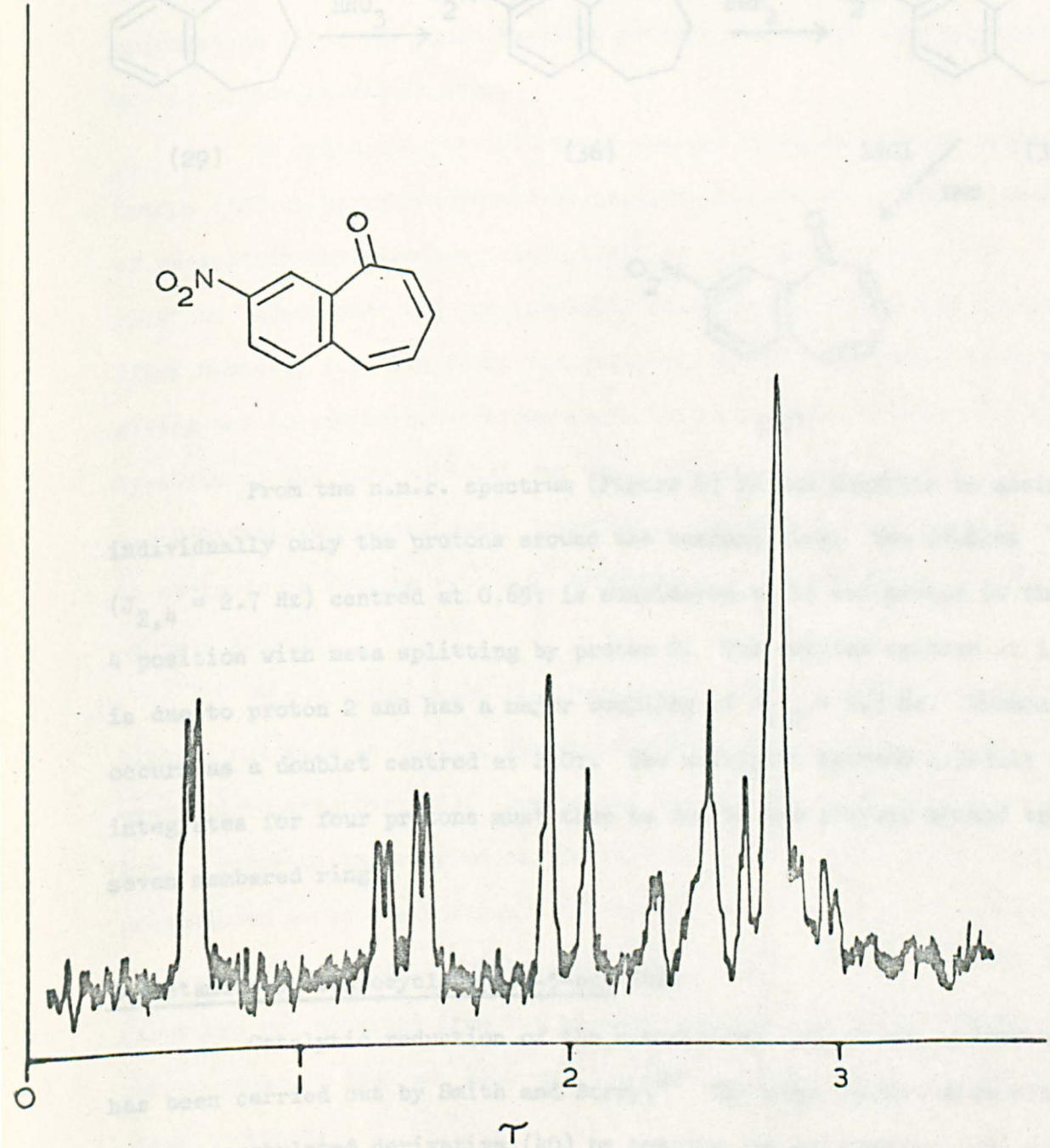
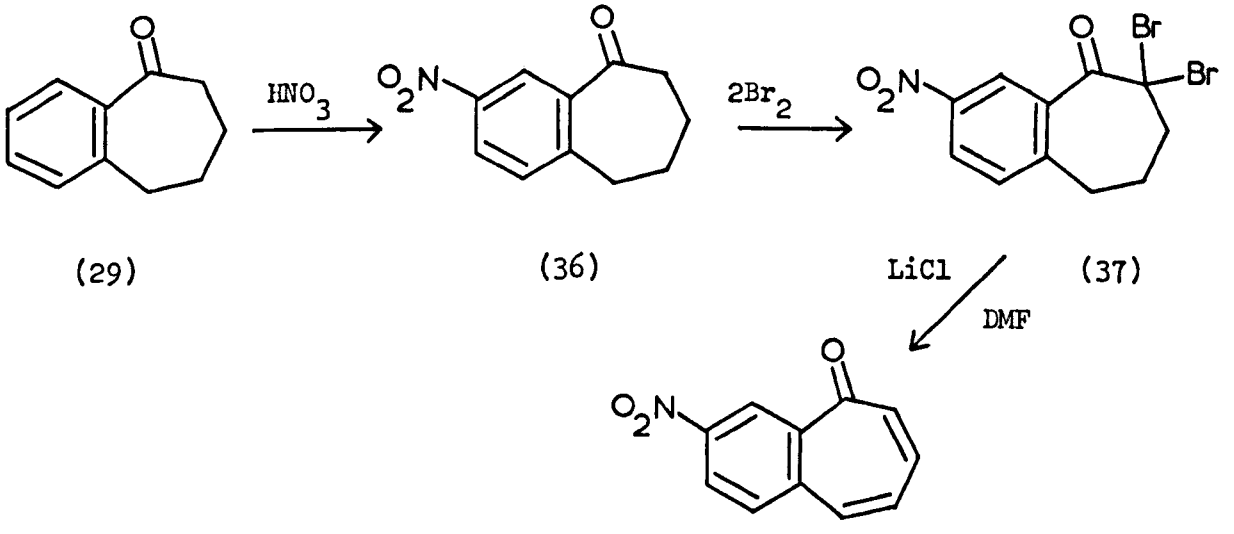


Figure 2

SCHEME X



(29) (36) (37) (38)

From the n.m.r. spectrum (Figure 2) it was possible to assign individually only the protons around the benzene ring. The doublet ($J_{2,4}$ = 2.7 Hz) centred at 0.65τ is considered to be the proton in the 4 position with meta splitting by proton 2. The quartet centred at 1.35τ is due to proton 2 and has a major coupling of $J_{1,2}$ = 9.3 Hz. Proton 1 occurs as a doublet centred at 2.0τ. The multiplet between 2.3-3.1τ which integrates for four protons must then be due to the protons around the seven membered ring.

3-Acetamido-5H-benzocyclohepten-5-one (42)

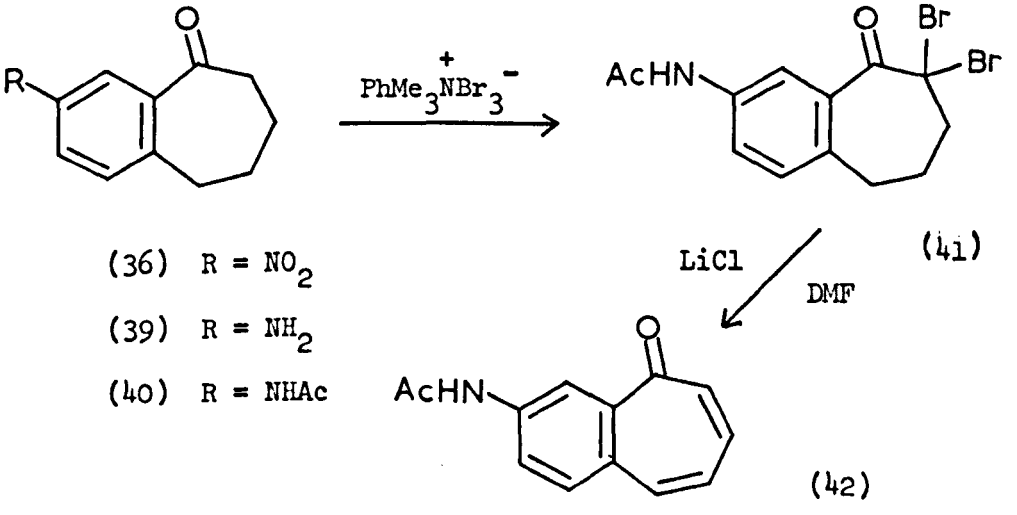
Catalytic reduction of the nitroketone (36) to the aminoketone (39) has been carried out by Smith and Berry.[20] The same authors also obtained the monoacetylated derivative (40) by heating the aminoketone (39) with an

acetic anhydride-acetic acid mixture on a steam bath for half an hour. On repeating these reactions it was found that a higher yield of acetamidoketone (40) could be obtained if instead of isolating the aminoketone (39), the crude reaction product was heated directly with acetic anhydride-acetic acid.

To avoid the possibility of nuclear bromination the acetamidoketone (40) in tetrahydrofuran was treated with two molar equivalents of phenyltrimethylammonium tribromide[21] at room temperature. The solution became warm and the insoluble monobromide salt slowly precipitated. After standing for five hours the solution was filtered and evaporated giving the acetamido-6,6-dibromoketone (41) as a brown solid. The n.m.r. spectrum of the pure material was comparable with those of the other α,α-dibromoketones previously described. The NH proton, which was shown to exchange on shaking with D_2O, appeared as a rather broad singlet centred at 1.5τ.

The dibromoketone (41) was equally easily dehydrobrominated with lithium chloride in boiling dimethylformamide to give a 95% yield of acetamidobenztropone (42). Due to its low solubility in chloroform the n.m.r. spectrum was carried out in trifluoroacetic acid. However, protonation caused many signals to overlap and a definite assignment of the individual aromatic protons was not possible. Proof of the desired structure was obtained from the analysis and the infrared spectrum which showed peaks at 1640 and 1612 cm^{-1} comparable with those obtained in the other tropones.

SCHEME XI



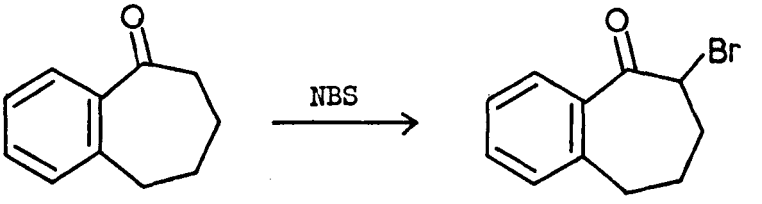
6-Bromo-5H-benzocyclohepten-5-one (45)

In an attempt to prepare a bromobenztropone it was decided to try and synthesise 6,6,9-tribromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (43), which could then be doubly dehydrobrominated with lithium chloride in dimethylformamide to give a monobromobenztropone.

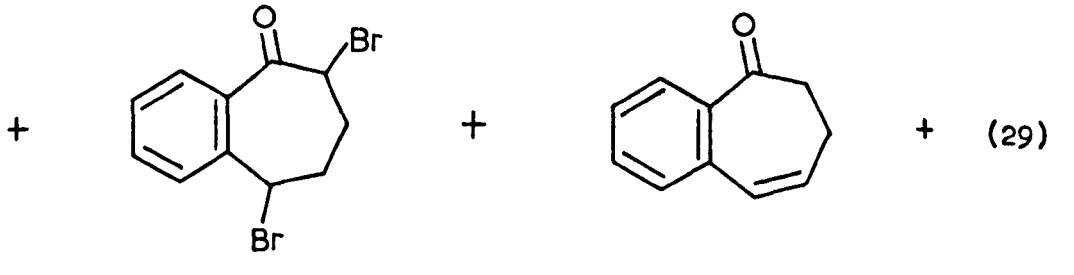
As an initial approach the possible introduction of a bromine atom into position 9 of the parent ketone (29) was investigated. If the 9-bromoketone resulted subsequent dibromination in the α-position to the carbonyl would give the desired 6,6,9-tribromoderivative (43).

However, treatment of the parent ketone (29) with a one molar equivalent of N-bromosuccinimide gave unexpectedly a mixture of four components. These were separated by preparative layer chromatography (P.L.C.) and identified as the parent ketone (29), the 6-bromo (30) and 6,9-dibromo (32) derivatives, and a crude product which from spectral

evidence was concluded to be 6,7-dihydro-5H-benzocyclohepten-5-one (44). Although inconsistent analyses were obtained the mass spectrum showed a molecular ion peak at 158 with loss of 28 as the initial breakdown. The infrared spectrum showed a carbonyl stretching frequency at 1680 cm^{-1} [cf. 1680 cm^{-1} for 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29)] indicating non-conjugation of the double bond with the ketone group. The n.m.r. spectrum (Figure 3) showed the four benzene aromatic protons between 1.8-2.8τ; a doublet ($J_{8,9}$ = 13 Hz) centred at 3.39τ attributed to the proton in the 9 position; two triplets centred at 3.64 and 3.84τ with a minor coupling $J_{7,8}$ = 4.7 Hz due to proton 8, and the 6 and 7 methylene groups at 7.05 and 7.5τ respectively. The formation of this product had presumably occurred by initial bromination in the 9 position with subsequent dehydrobromination.



(29) (30)



(32) (44)

N.m.r. spectrum of 6,7-dihydro-5H-benzocyclohepten-5-one in CCl_4

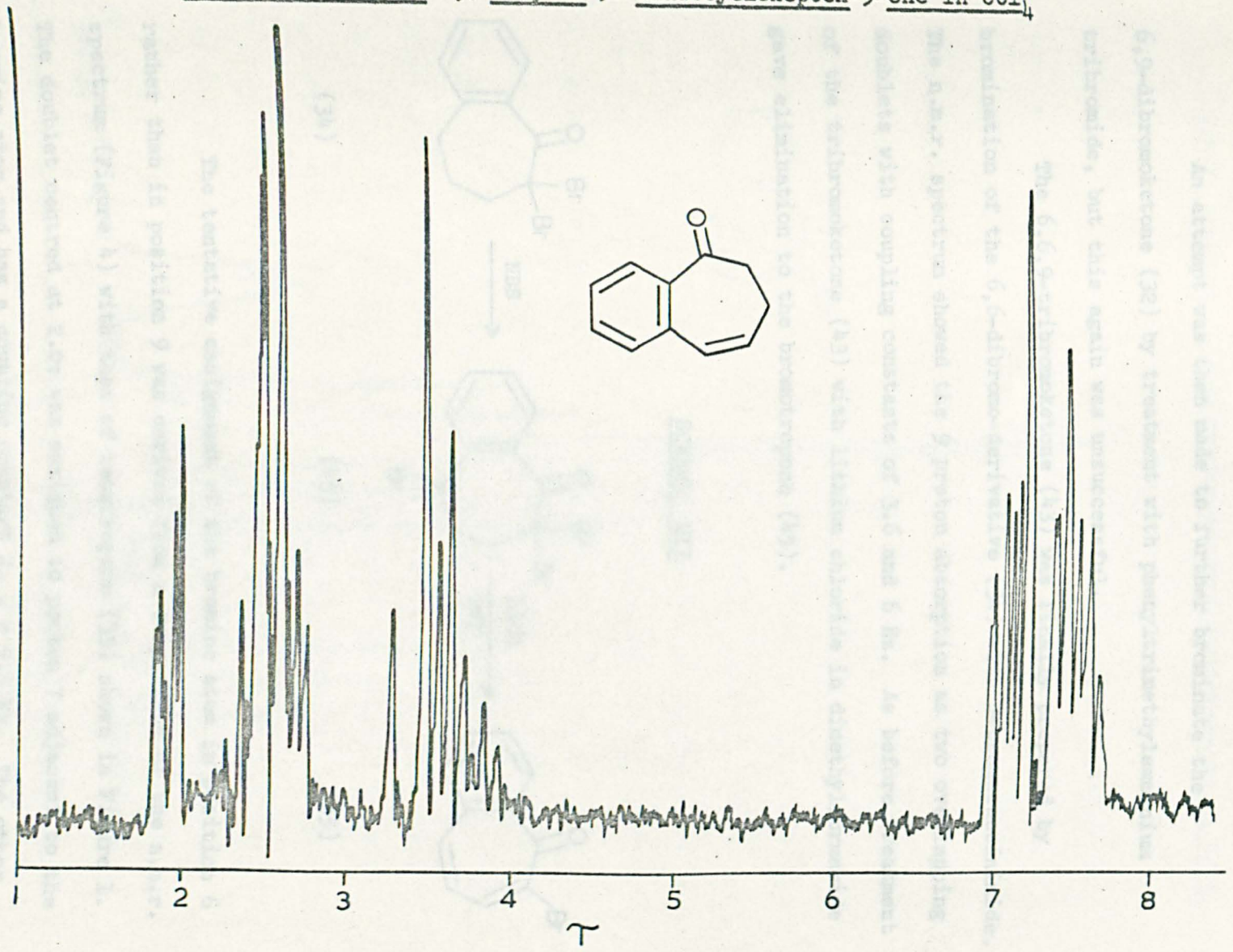
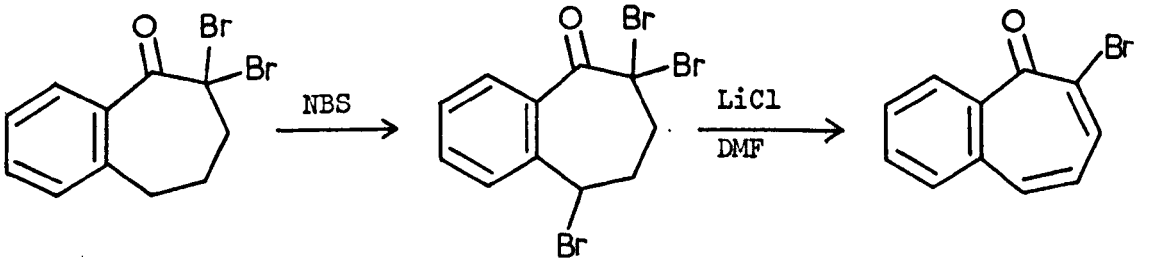


Figure 3

An attempt was then made to further brominate the 6,9-dibromoketone (32) by treatment with phenyltrimethylammonium tribromide, but this again was unsuccessful.

The 6,6,9-tribromoketone (43) was finally prepared by bromination of the 6,6-dibromo-derivative (34) with N-bromosuccinimide. The n.m.r. spectrum showed the 9 proton absorption as two overlapping doublets with coupling constants of 3.6 and 6 Hz. As before treatment of the tribromoketone (43) with lithium chloride in dimethylformamide gave elimination to the bromotropone (45).

SCHEME XII



(34) (43) (45)

The tentative assignment of the bromine atom in position 6 rather than in position 9 was derived from a comparison of the n.m.r. spectrum (Figure 4) with that of benztropone (33) shown in Figure 1. The doublet centred at 2.0τ was assigned to proton 7 adjacent to the bromine atom and has a coupling constant $J_{7,8}$ = 9.3 Hz. The other doublet centred at 2.52τ ($J_{8,9}$ = 11.3 Hz) was assigned to the proton in

N.m.r. spectrum of 6-bromo-5H-benzocyclohepten-5-one in $CDCl_3$

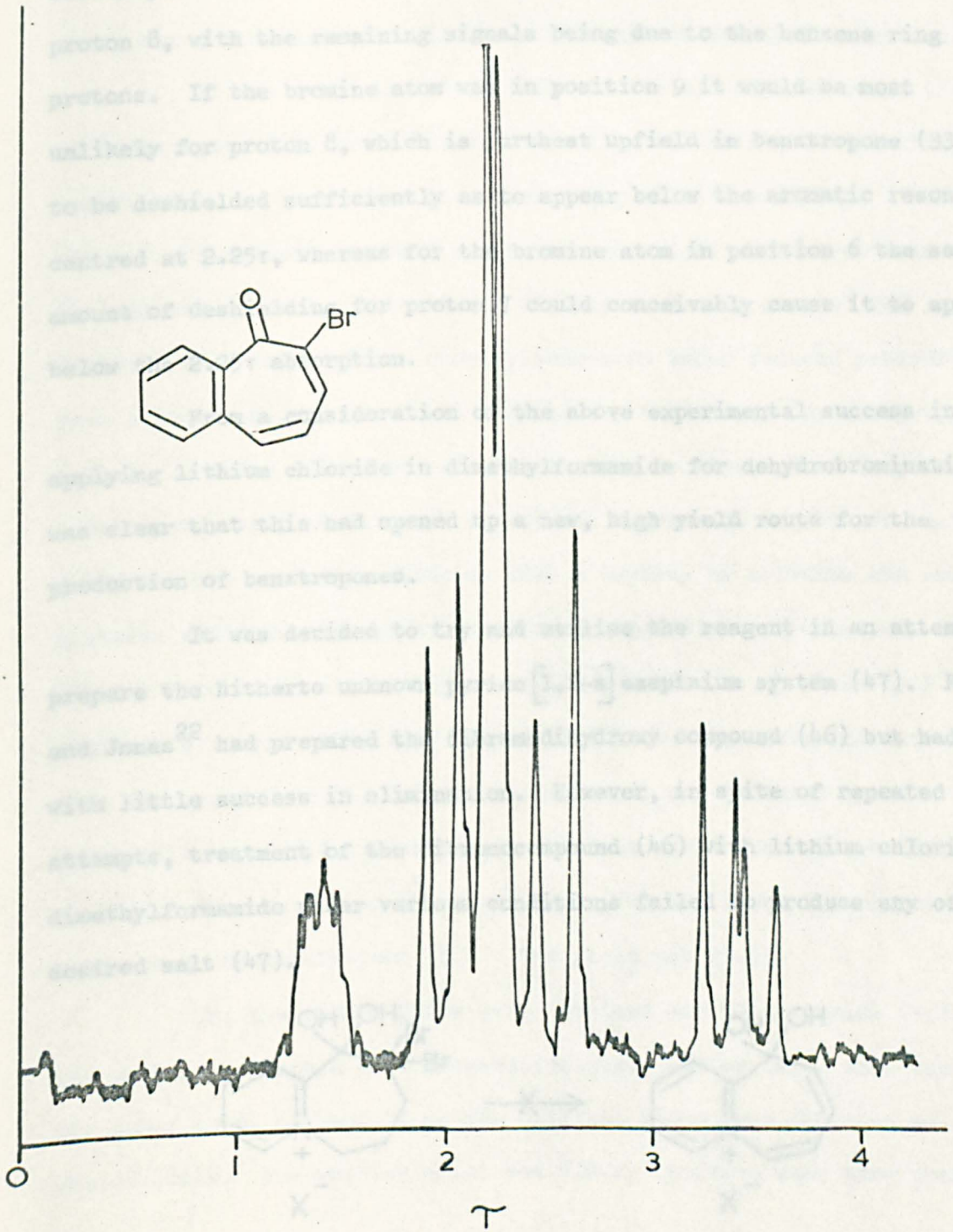
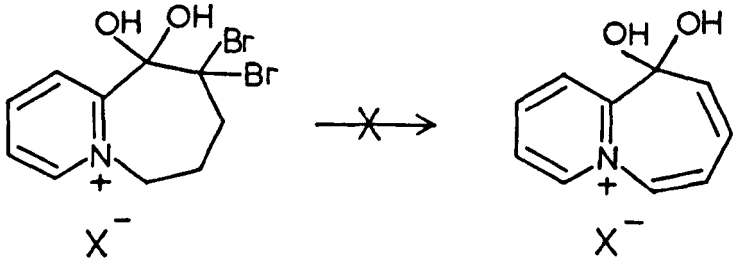


Figure 4

position 9 by direct comparison with the position of the 9-proton in benztropone (33). The quartet between 3.2-3.6τ was then assigned to proton 8, with the remaining signals being due to the benzene ring protons. If the bromine atom was in position 9 it would be most unlikely for proton 8, which is furthest upfield in benztropone (33), to be deshielded sufficiently as to appear below the aromatic resonance centred at 2.25τ, whereas for the bromine atom in position 6 the same amount of deshielding for proton 7 could conceivably cause it to appear below the 2.25τ absorption.

From a consideration of the above experimental success in applying lithium chloride in dimethylformamide for dehydrobromination it was clear that this had opened up a new, high yield route for the production of benztropones.

It was decided to try and utilise the reagent in an attempt to prepare the hitherto unknown pyrido[1,2-a]azepinium system (47). Fozard and Jones[22] had prepared the dibromodihydroxy compound (46) but had met with little success in elimination. However, in spite of repeated attempts, treatment of the dibromocompound (46) with lithium chloride in dimethylformamide under various conditions failed to produce any of the desired salt (47).



(46) (47)

As part of an investigation into the high yield elimination of α,α-dibromoketones catalysed by lithium chloride it was decided to carry out a few variations in the conditions of dehydrobromination.

It was found that conversion of the 6,6-dibromoketone (34) to benztropone (33) could be achieved using collidine, but the reaction was found to be less clean than that using lithium chloride.

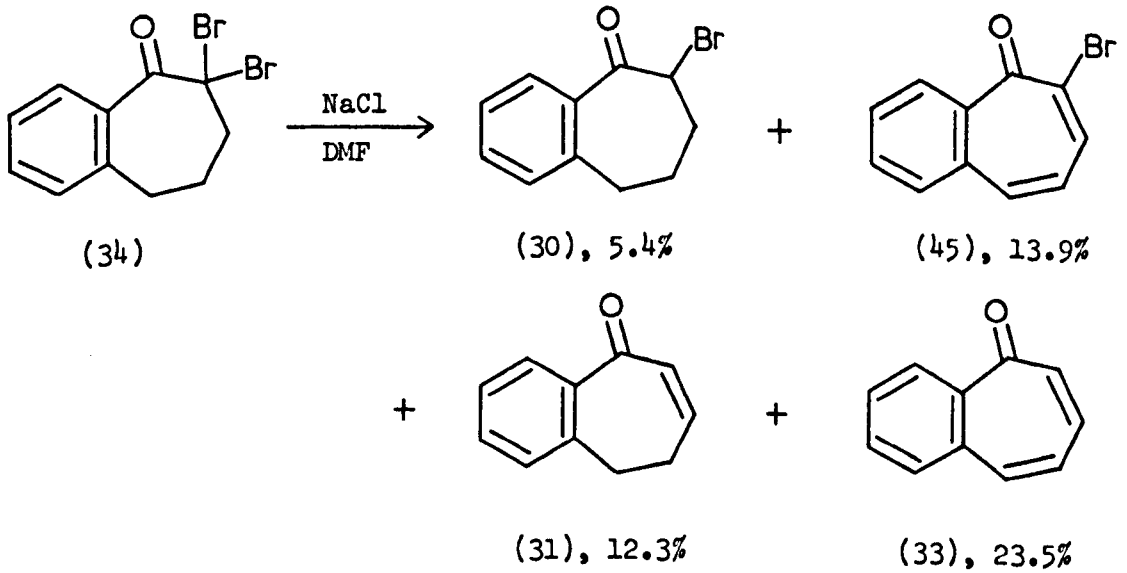
Treatment of the 6,6-dibromoketone (34) with three molar equivalents of sodium chloride in dimethylformamide at 150° for 1hr. followed by removal of the dimethylformamide under reduced pressure gave a brown residue which was examined by thin layer chromatography (t.l.c.). Using 10% light petroleum-xylene as eluent four components were clearly visible although a complete separation of the two centre bands was not achieved. Elution with a variety of solvents and solvent mixtures was investigated but no better separation was achieved. An initial separation of the upper and lower bands was obtained by P.L.C. eluting twice with 10% light petroleum-xylene. The material extracted from the upper band (I) had identical n.m.r. and infrared spectra to those of 6-bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (30).

The content of the lower band (IV) was shown from spectral evidence to be benztropone (33). The yield was 23.5%.

The two centre bands were combined and the material isolated was rechromatographed on a preparative plate eluted twice with toluene. The upper band, or band II on the original plate, was obtained as a yellow solid. The melting point and n.m.r. spectrum were identical with

those of the product obtained from the treatment of 6,6,9-tribromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (43) with lithium chloride, and concluded to be the 6-bromo-5H-benzocyclohepten-5-one (45).

The material in the lower band (III) was shown to be 8,9-dihydro-5H-benzocyclohepten-5-one (31) by a comparison of its n.m.r. spectrum (Figure 5) with that of a sample prepared by the method of Buchanan and Lockhart.[15] The two triplets centred at 3.05 and 3.25τ were assigned to proton 7, with a major coupling $J_{6,7}$ = 12 Hz and a minor coupling $J_{7,8}$ = 4.7 Hz. The proton in position 6 also appeared as two triplets centred at 3.58 and 3.78τ with a minor coupling of 1 Hz with the C-8 methylene protons. The C-8 and C-9 methylene protons appeared as multiplets centred at 7.4 and 6.9τ respectively. The aromatic signals between 1.9-2.8τ were similar to those of the other benztropone derivatives already described. Examination of the infrared spectrum of the dihydro-ketone (31) showed peaks at 1645, 1625 and 1600 cm^{-1} indicative of the presence of an α,β-unsaturated carbonyl group.



(34) (30), 5.4% (45), 13.9%

(31), 12.3% (33), 23.5%

N.m.r. spectrum of 8,9-dihydro-5H-benzocyclohepten-5-one in CCl_4

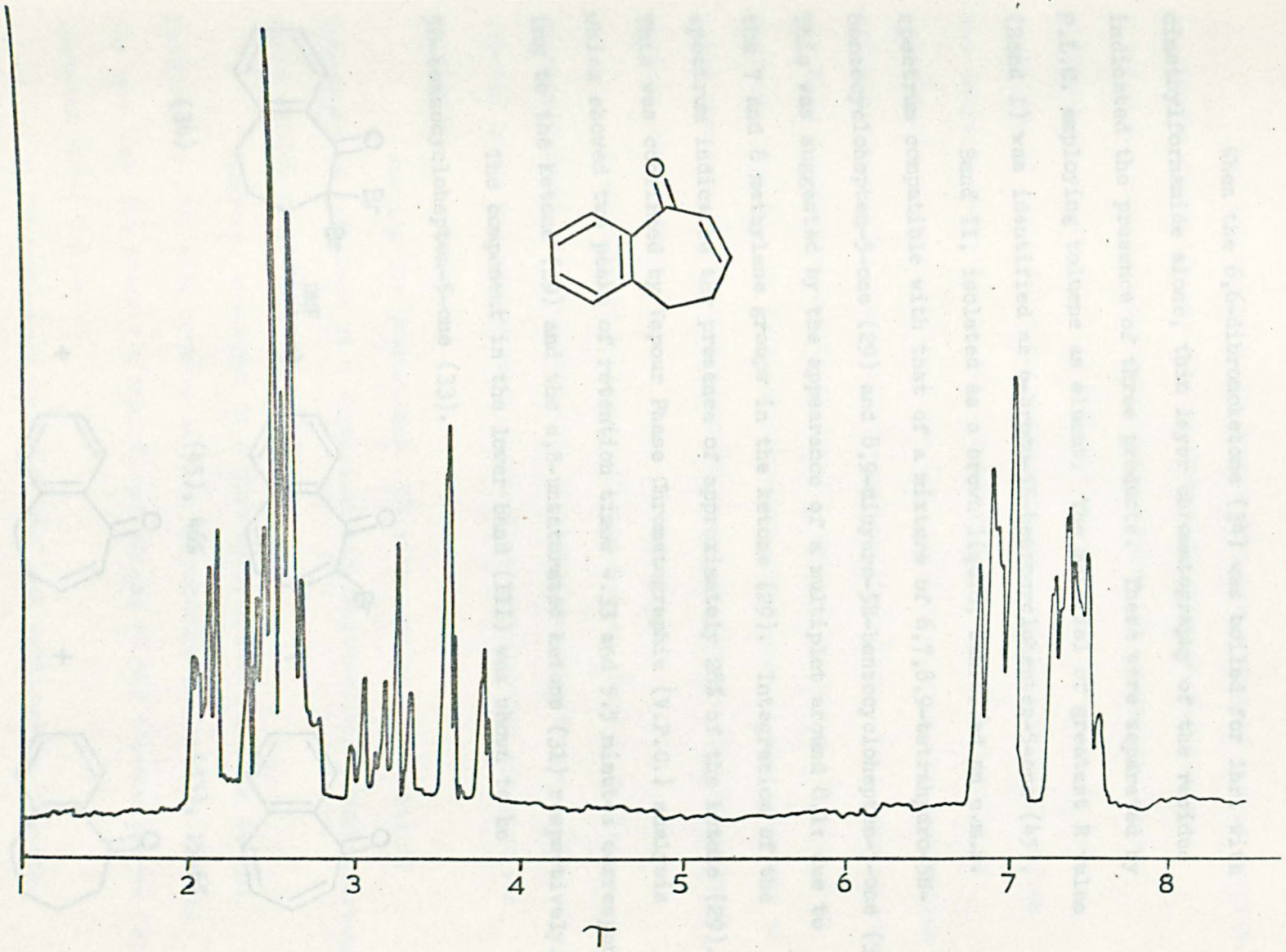
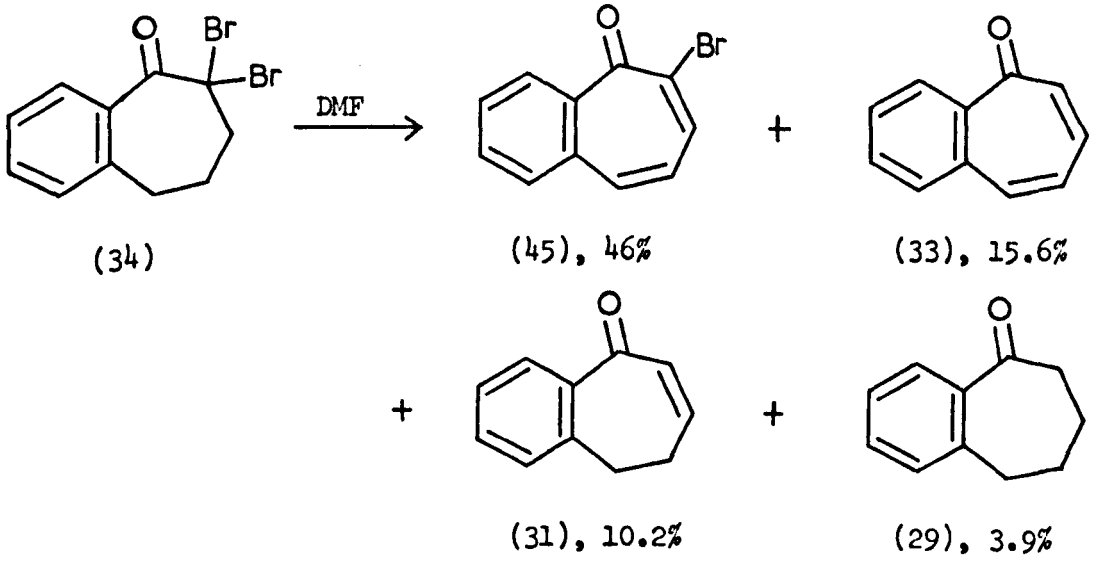


Figure 5

When the 6,6-dibromoketone (34) was boiled for 1hr. with dimethylformamide alone, thin layer chromatography of the residue indicated the presence of three products. These were separated by P.L.C. employing toluene as eluent. The material of greatest R value (Band I) was identified as 6-bromo-5H-benzocyclohepten-5-one (45).

Band II, isolated as a brown liquid, exhibited an n.m.r. spectrum compatible with that of a mixture of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) and 8,9-dihydro-5H-benzocyclohepten-5-one (31). This was suggested by the appearance of a multiplet around 8.1τ due to the 7 and 8 methylene groups in the ketone (29). Integration of the spectrum indicated the presence of approximately 28% of the ketone (29). This was confirmed by Vapour Phase Chromatographic (V.P.C.) analysis which showed two peaks of retention times 4.33 and 5.5 minutes corresponding to the ketone (29) and the α,β-unsaturated ketone (31) respectively.

The component in the lower band (III) was shown to be 5H-benzocyclohepten-5-one (33).



(34) (45), 46% (33), 15.6%

(31), 10.2% (29), 3.9%

The various products formed from the action of sodium chloride in dimethylformamide and dimethylformamide alone on 6,6-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (34) suggested that elimination was competitive with reduction. The formation in both reactions of the 8,9-dihydrobenztropone (31) presumably resulted from the dehydrobromination of the 6-bromoketone (30). The presence of 6-bromo-5H-benzocyclohepten-5-one (45) could have arisen by bromination of benztropone (33) previously formed by elimination. This bromination may have occurred with bromine itself, the α-bromoketone (30), or even hydrogen bromide. To substantiate these hypotheses it was necessary to carry out some bromination experiments on benztropone (33) under these various conditions.

A solution of 5H-benzocyclohepten-5-one (33) in boiling dimethylformamide was treated with dry hydrogen bromide gas. Even after several hours boiling no reaction resulted and starting material was recovered.

Boiling the benztropone (33) with a molar equivalent of bromoacetone (selected as a convenient α-bromoketone) in dimethylformamide again failed to produce any reaction.

However, treatment of a dimethylformamide solution of the benztropone (33) with bromine at room temperature followed by boiling for one hour did produce a significant amount of the 6-bromotropone (45) isolated after P.L.C.

It thus appeared that with the less efficient elimination catalysts that reduction was occurring concurrently with double

dehydrobromination, and it was felt, that since benztropone (33) was unreactive towards hydrogen bromide and bromoacetone that bromination of benztropone (33) with bromine itself led to the formation of the 6-bromoderivative (45). The isolation of a larger percentage of 6-bromotropone (45) by the action of dimethylformamide alone suggested that reduction was more prominent in dimethylformamide alone than with sodium chloride in dimethylformamide.

The small amount of mechanistic work that has been reported on lithium halide catalysed elimination has been mentioned in the introduction.

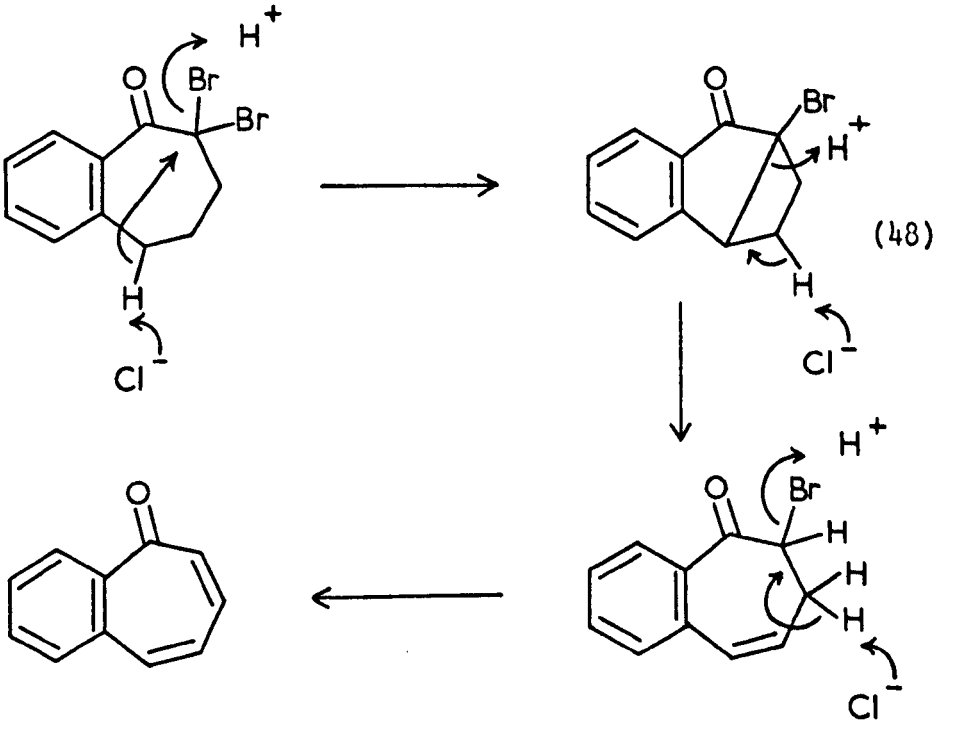
It has been reported[23] that halide anions in dimethylformamide are virtually unsolvated and that this accounts for their ability to act as efficient bases and nucleophiles. It is also conceivable, in view of the above results using sodium chloride, that because of its small size, very strong solvation of the lithium ion prevents its participation in the reaction.

Although several mechanisms were suggested for the double dehydrobromination of the α,α-dibromoketones the main point was considered to be the elimination of the second bromine atom. With this in mind investigations were concentrated on two proposed pathways.

Synthesis of the 3,4-benzobicyclo[3,2,0]heptan-2-one system.

As a result of helpful discussion with Professor T.S. Stevens a pathway for double elimination, outlined in Scheme XIII, was proposed. This has been suggested in a preliminary communication.[24]

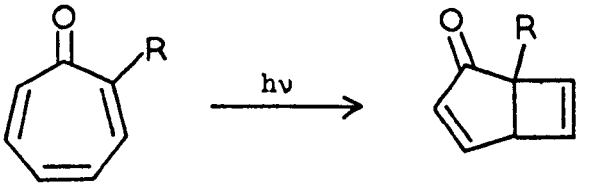
SCHEME XIII



It was proposed that chloride ion would abstract the relatively acidic proton from position 9 with subsequent ring closure and loss of bromide ion to give the tricyclic intermediate (48). Chloride ion initiated ring opening would then give the ethylenic bond in the 8,9-position

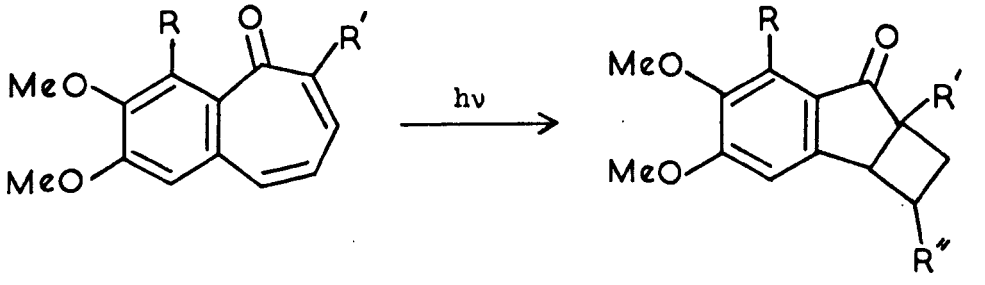
leaving the straightforward elimination of hydrogen bromide from adjacent positions for the formation of the benztropone.

It has been reported[25] that in solution, many tropone derivatives (49) upon irradiation afford their valence isomer (50).



(49) (50)

Although up to 1966 this isomerisation had not been reported for benztropone derivatives, Forbes and Griffiths[26] found that irradiation of an ethanolic solution of the benztropone (51) gave a complex mixture of products, from which was isolated the photoisomer (53).



(51) R = H, R' = OMe

(52) R = R' = OMe

(53) R = R'' = H, R' = OMe

(54) R = R'' = OMe, R' = H

Later work[27] showed that irradiation of the tetra-O-methylpurpurogallin (52) in benzene or cyclohexane gave the rearranged photoproduct (54).

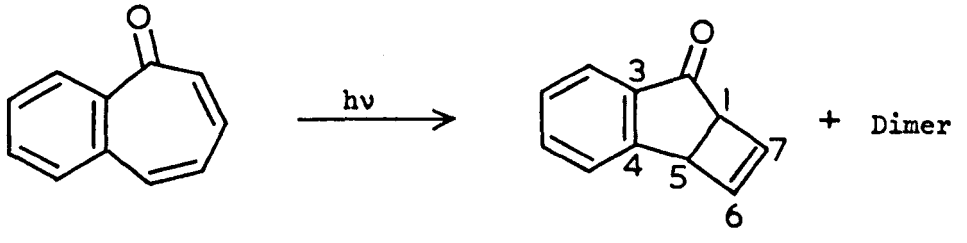
In spite of irradiation experiments carried out on benztropone derivatives no record could be found in the literature of the irradiation of benztropone (33) itself. It was thought that the photolysis of benztropone (33) might provide a convenient route to the 3,4-benzobicyclo[3,2,0]heptan-2-one system.

A methanolic solution of benztropone (33) was irradiated using a Hanovia medium pressure mercury lamp and the course of the photolysis monitored by t.l.c. After 18hr. irradiation t.l.c. revealed the presence of one photo-product in addition to unchanged benztropone (33) and polymeric material. Evaporation of the methanol gave the mixture as a tarry residue. When the material was eluted on preparative plates it was found that in addition to the large amount of polymeric material left on the base line that coloured impurity ran with the required components and a complete separation of the mixture proved extremely difficult.

Extraction of the band (I) of largest R value gave a brown liquid, which when dissolved in a small volume of ether left behind a few mgm. of a white solid which was filtered off. The n.m.r. spectrum of this solid was rather complex but the integration suggested a dimeric structure. A multiplet and a doublet centred at 5.55 and 6.15τ respectively both integrated for one proton. A broad singlet at 6.87τ which integrated for two protons was considered to be a methylene group

adjacent to either a benzene ring or a carbonyl group. The rest of the absorption occurred in the aromatic region between 1.7-3.8τ and integrated for twelve protons. The ultraviolet spectrum was similar to that of benztropone (33).

The ether filtrate of band I was evaporated and the crude residue distilled from a bulb tube to give a colourless liquid. The n.m.r. spectrum (Figure 6) indicated the product to be the desired photoisomer 3,4-benzobicyclo[3,2,0]hept-6-ene-2-one (55).



(33) (55)

By analogy with similar structures[26,28] the quartet at highest field was assigned to proton 1 adjacent to the carbonyl group with coupling constants $J_{1,5}$ = 3 Hz and $J_{1,7}$ = 1.3 Hz. The doublet centred at 5.75τ was assigned to the benzylic proton, 5, no further coupling being discernable. The quartet centred at 3.77τ and the doublet centred at 3.5τ must then be due to protons 7 and 6 respectively. The remaining resonance between 2.3-3.0τ was due to the four benzene ring protons. The infrared spectrum of the photoisomer (55) showed a carbonyl stretching frequency at 1704 cm^{-1} which could be compared with that of 1-indanone[29] at 1710 cm^{-1}.

N.m.r. spectrum of 3,4-benzobicyclo[3,2,0]hept-6-ene-2-one in CCl_4

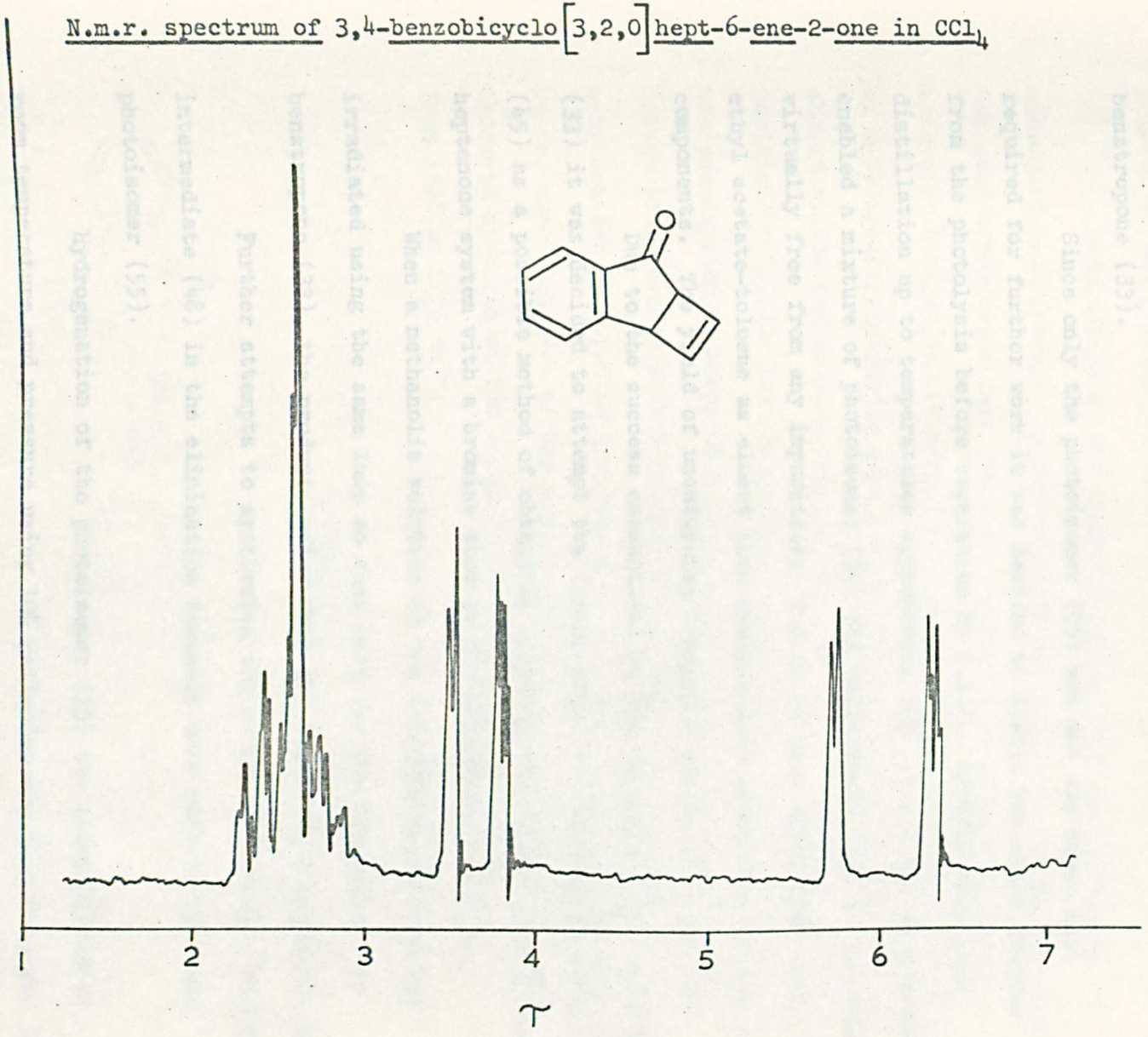


Figure 6

The material isolated from band II was shown to be unchanged benztropone (33).

Since only the photoisomer (55) and not the dimer was required for further work it was decided to distil the crude residue from the photolysis before separation by P.L.C. Careful bulb tube distillation up to temperatures approaching 160° at 0.1 mm. Hg pressure enabled a mixture of photoisomer (55) and benztropone (33) to be isolated virtually free from any impurities. P.L.C. of this distillate using 5% ethyl acetate-toluene as eluent then enabled easy separation of the two components. The yield of unsaturated tricyclic ketone (55) was 13%.

Due to the success encountered in the photolysis of benztropone (33) it was decided to attempt the irradiation of the 6-bromoderivative (45) as a possible method of obtaining directly the benzobicyclo[3,2,0] heptenone system with a bromine atom in the bridgehead position.

When a methanolic solution of the 6-bromotropone (45) was irradiated using the same lamp as that used for the irradiation of benztropone (33), the product, after work up, showed only polymeric material.

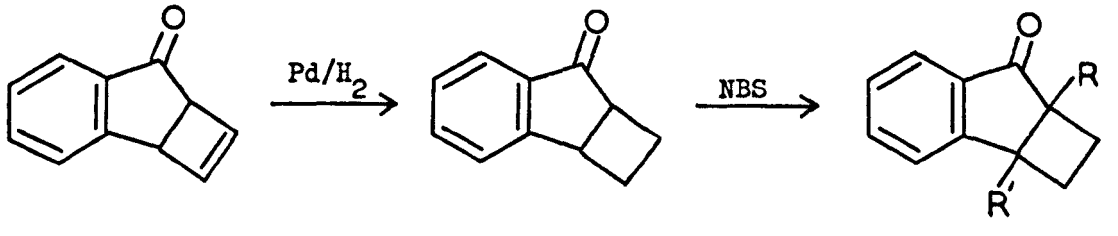
Further attempts to synthesise the proposed tricyclic bromoketone intermediate (48) in the elimination sequence were pursued from the photoisomer (55).

Hydrogenation of the photoisomer (55) was accomplished at room temperature and pressure using 10% palladium-charcoal catalyst in absolute methanol, to give the tricyclic ketone (56). The apparent simplicity of the n.m.r. spectrum of the photo-product (55) was lost on reduction to the ketone (56) due to the introduction of two pairs of

non-equivalent geminal protons.

Bromination of the tricyclic ketone (56) was initially attempted using phenyltrimethylammonium tribromide in tetrahydrofuran, but even after seven days there was no reaction. Treatment of the tricyclic ketone (56) in carbon tetrachloride with one molar equivalent of N-bromosuccinimide did give a reaction and monitoring by t.l.c. showed mainly one product after heating for 24hr. The product was purified by P.L.C. Its n.m.r. spectrum was still fairly complex but two overlapping doublets (J = 10 Hz and J = 6 Hz) centred at 6.38τ integrating for one proton indicated that the bromine atom had entered a bridgehead position to give one of the isomers (57). No conclusion on the exact position of the bromine atom could be drawn from the infrared spectrum as the carbonyl stretching frequency had only shifted from 1708 to 1716 cm^{-1}.

SCHEME XIV

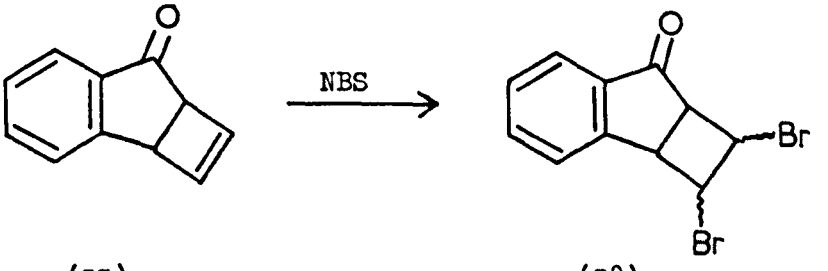


(55) (56) (57A) R = Br, R' = H

(57B) R = H, R' = Br

It was thought that if an analogous brominated product of the photoisomer (55) could be made its n.m.r. spectrum would be much simpler and might lead to a more definite assignment of the position of the bromine atom.

The photoisomer (55) was treated with N-bromosuccinimide under the same conditions as those employed for the tricyclic ketone (56) and the reaction again monitored by t.l.c. When all the N-bromosuccinimide had disappeared t.l.c. showed the residue to be a mixture of three components, the one of lowest R value being unreacted photoisomer (55). The two products of the reaction were separated by P.L.C. Their spectral characteristics indicated them to be two of the isomers (58) in which bromine had added to the double bond.



(55) (58)

In spite of an inability to characterise completely the product from the bromination of the tricyclic ketone (56) it was thought that either isomer (57A) or (57B) would provide a reasonable model for the ring opening reaction since both possessed hydrogen atoms sufficiently

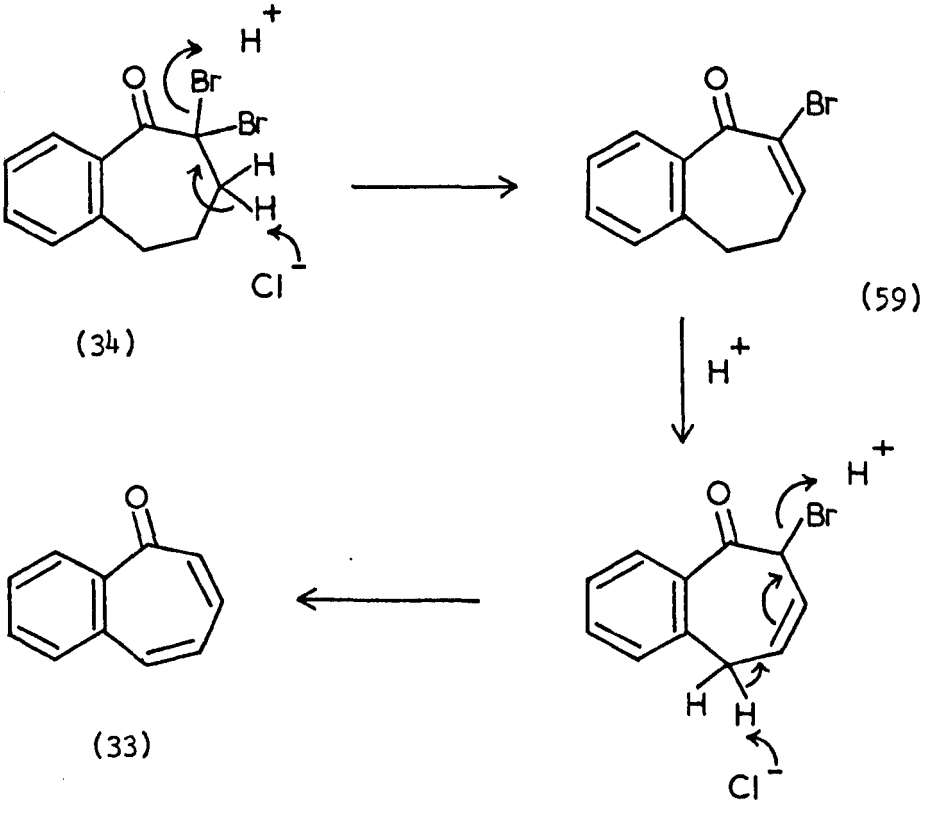
acidic to react with chloride ion. However, treatment of the bromoketone (57) with lithium chloride in dimethylformamide gave no reaction and the starting material was recovered.

Clearly the above evidence indicated that the mechanism outlined in Scheme XIII was not that by which the double dehydrobromination had occurred.

Synthetic approaches to 6-bromo-8,9-dihydro-5H-benzocyclohepten-5-one (59)

An alternative approach to the mechanism of elimination was concerned with the synthesis of the unsaturated bromoketone (59) as a possible intermediate. The proposed pathway is outlined in Scheme XV.

SCHEME XV

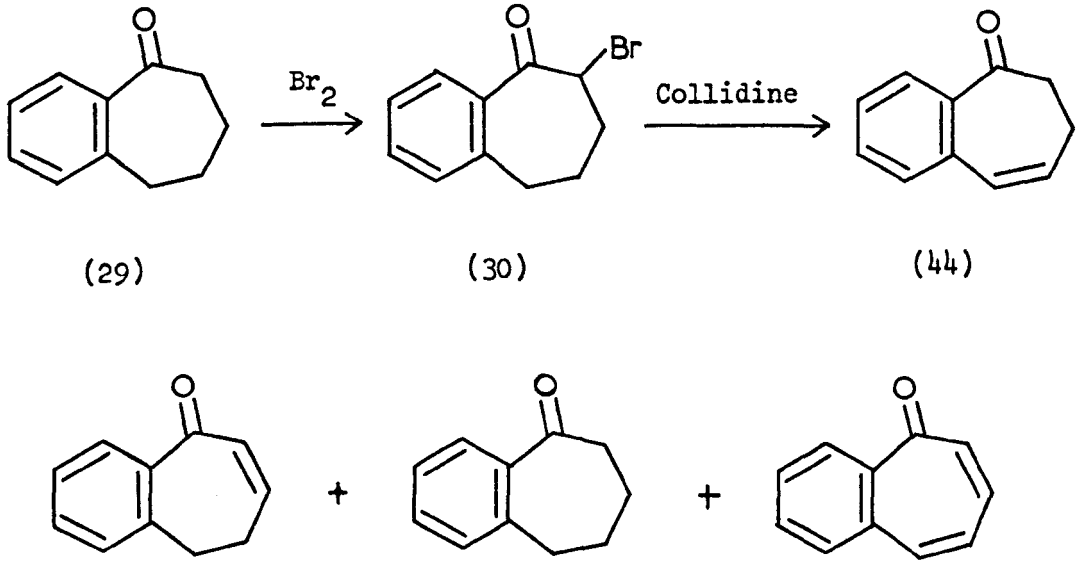


Chloride ion initiated elimination of hydrogen bromide from the dibromoketone (34) would give the α,β-unsaturated bromoketone (59). Acid catalysed isomerisation of the double bond would then give rise to a system ideally set up for further elimination to the benztropone (33).

The most logical approach to the unsaturated bromoketone intermediate (59) appeared to be via the α,β-unsaturated ketone (31). As mentioned previously, Buchanan and Lockhart[15] have prepared the ketone (31) but found it very unstable and unsuitable for further work. However, it was decided to repeat this work in the hope that further reaction on it would be possible.

Treatment of the saturated ketone (29) in ether at 0^{o} with bromine gave the 6-bromoderivative (30).[30] The n.m.r. spectrum showed the 6-proton absorption as a quartet centred at 5.03τ with a splitting of 7 Hz and 5 Hz with the non-equivalent protons of the 7-methylene group. Boiling the bromoketone (30) with collidine[15] for 1hr. gave a brown, oily residue which was found to give three spots on a thin layer chromatogram. The components were separated by P.L.C. and identified as benztropone (33), the 6,7-dihydrobenztropone (44), and a mixture which contained approximately 80% of the 8,9-dihydrobenztropone (31) and 20% of the saturated ketone (29).

SCHEME XVI



(29) (30) (44)

+ (31) + (29) + (33)

The formation of the 6,7-dihydrobenztropone (44) had presumably occurred by acid catalysed isomerisation of the first formed 8,9-dihydrobenztropone (31). Reductive debromination of the bromoketone (30) would give the saturated ketone (29), and addition of the bromine formed across the double bond of the 8,9-dihydroketone (31) followed by double dehydrobromination of the product, would account for the presence of benztropone (33).

Treatment of the bromoketone (30) with lithium chloride in boiling dimethylformamide for 1hr. was also found to give a mixture of products. These were again separated by P.L.C. and identified as unchanged

starting material (30) together with a mixture which consisted of about 80% of the 8,9-dihydroketone (31) and 20% of the saturated ketone (29).

On closer examination of a mixture of the α,β-unsaturated ketone (31) and the saturated ketone (29) on both thin layer and preparative plates, it was observed that there was no significant difference in R values and that a complete separation of the two by such methods was virtually impossible. It has already been stated that these two ketones have a difference in retention times of approximately 1.17 minutes on the analytical V.P.C. at a column temperature of 189°. Several variations in the operating conditions of the V.P.C. instrument were carried out in the hope that this difference could be increased. However, the difference in retention times could only be extended to 1.5 minutes on the analytical instrument and this was found to be insufficient time for a separation on the preparative scale.

It will have been noticed from the preceding account, in contrast to the statement made by Buchanan,[15] that the 6,7-dihydroketone (44) was sufficiently stable to be isolated from P.L.C. (see experimental section for conditions of work up) and could even be recovered unchanged after short periods above 150°. It appeared that the chances of resinification were slight especially if reactions were carried out at low temperatures.

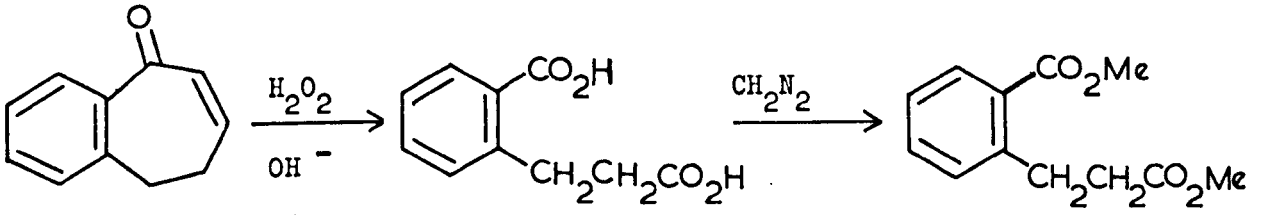
Since a separation of the α,β-unsaturated ketone (31) and the saturated ketone (29) could not be achieved prior to reaction it was decided to carry out reactions on the mixture.

Previous work[31,32] has shown that epoxides formed from α,β-unsaturated ketones readily undergo ring opening and elimination on treatment with hydrogen bromide in acetic acid to give the corresponding α-halo unsaturated ketone. It was thought that application of a parallel route to the unsaturated ketone (31) might lead to the desired intermediate ketone (59).

A methanolic solution of the mixed ketones (31) and (29) was treated with alkaline hydrogen peroxide at room temperature and then allowed to stand at -10° for 72hr. The white solid which had precipitated was found to be inorganic and not the desired epoxide. The methanol was evaporated and the residue extracted with ether to give the saturated ketone (29). The aqueous solution was acidified with dilute hydrochloric acid and again extracted with ether. The n.m.r. spectrum of the resulting oil indicated it to be a ring opened product. A di-carboxylic acid was suggested since a broad signal between 0.8-1.4τ, which integrated for two protons, was shown to disappear on shaking with D_2O. The infrared spectrum showed a broad carbonyl stretching frequency around 1705 cm^{-1} which also suggested the product to be an acid. Purification proved difficult and the acid was characterised as its dimethyl ester formed by treatment with diazomethane at 0°. From the analysis figures and the n.m.r. spectrum of the ester, which showed two

triplets centred at 6.7 and 7.4τ each integrating for two protons, the structure (60) was established.

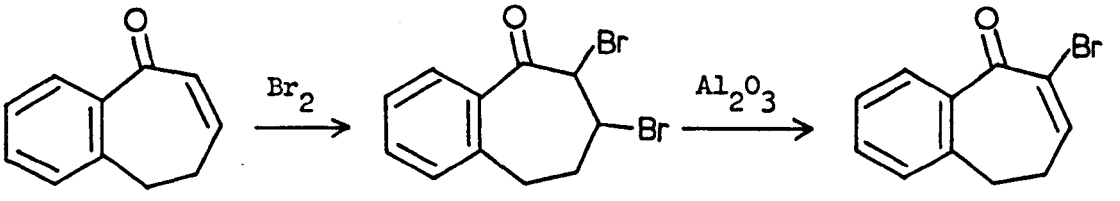
SCHEME XVII



(31) (60)

Another approach to obtaining the unsaturated bromoketone intermediate (59) was from the 8,9-dihydroketone (31) by bromination and selective dehydrobromination. Treatment of an ether solution of the mixed ketones (29) and (31) at 0° with bromine gave the expected mixture of the 6-bromoketone (30) and the 6,7-dibromoketone (61). These two ketones were easily separated by P.L.C. The n.m.r. spectrum of the 6,7-dibromoketone (61) showed the C-6 proton absorption as a doublet ($J_{6,7}$ = 5 Hz) centred at 4.92τ, and the C-7 proton absorption as a multiplet centred at 5.15τ. Shoppee, Roy and Goodrich[33] reported the selective dehydrobromination of 2,3-dibromo-5α-cholestan-1-one to the 2-bromo-2-enone derivative by percolation through a column of aluminium oxide. Subsequent investigation showed that the 6,7-dibromoketone (61) could readily be dehydrobrominated selectively and in high yield to the required intermediate (59) by stirring an ether solution with Spence alumina for 30 minutes.

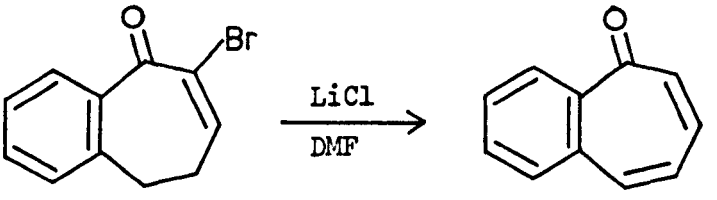
SCHEME XVIII



(31) (61) (59)

In the aliphatic region the n.m.r. spectrum of the bromoketone (59) was similar to that of the 8,9-dihydroketone (31). Due to the deshielding from the neighbouring bromine atom, the C-7 olefinic proton was found to overlap with the four benzene aromatic protons.

Treatment of the bromoketone (59) with lithium chloride in dimethylformamide at 150° for 1hr. did in fact give benztropone (33).



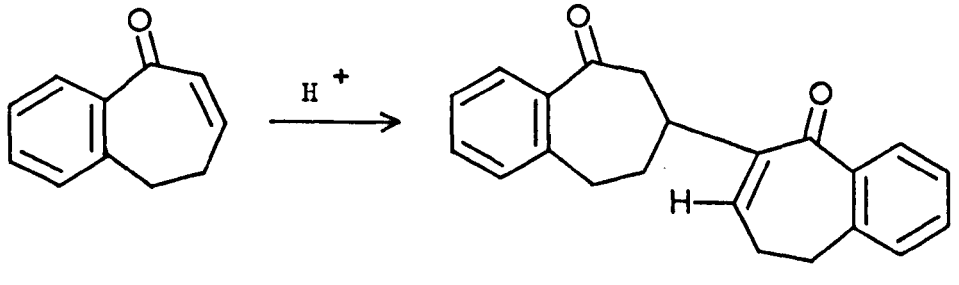
(59) (33)

Although it seemed probable that the formation of benztropone (33) from the 6,6-dibromoketone (34) had occurred via the intermediate bromoketone (59), it was felt that some evidence of double bond migration was necessary to further support this elimination mechanism.

Attempted isomerisation of 8,9-dihydro-5H-benzocyclohepten-5-ones.

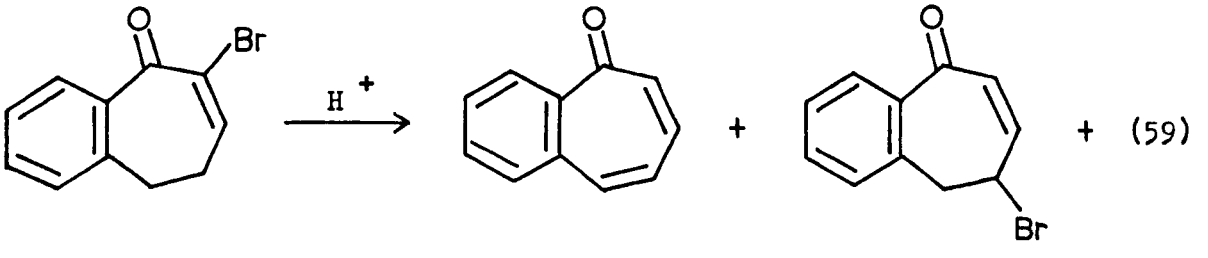
A search of the literature has shown that in cycloheptenone systems α,β- to β,γ-ethylenic isomerisation is well established. Braude and Evans[34] found that dehydrobromination of 2-bromocycloheptanone with collidine gave a mixture of cyclohept-2- and -3-enone. Furthermore, Heap and Whitham[35] have shown that the acid catalysed interconversion between cyclohept-2- and -3-enone rests at an equilibrium composition of 73:27.

An initial experiment was directed towards a possible acid catalysed isomerisation of 8,9-dihydro-5H-benzocyclohepten-5-one (31). The mixture of the 8,9-dihydroketone (31) and the saturated ketone (29) was heated with a 1.5% solution of p-toluenesulphonic acid in benzene and the reaction monitored by t.l.c. After boiling for 1hr. t.l.c. indicated a new product in addition to the presence of the unchanged ketone (29). This product, isolated by P.L.C. as a colourless solid, exhibited an n.m.r. spectrum consistent with that of a dimer. A single ethylenic proton as a triplet centred at 3.3τ was in agreement with the expected structure (62).



(31) (62)

Although the above attempt at interconversion proved unsuccessful it was thought there was a greater probability that the bromoketone (59) would isomerise since the bromine atom at C-6 would sterically prevent dimerisation. Treatment of the 6-bromoketone (59) with a catalytic amount of p-toluenesulphonic acid in benzene gave three components. These were separated by P.L.C. and identified as the unchanged bromoketone (59), benztropone (33), and a product whose spectra indicated it to be 8-bromo-8,9-dihydro-5H-benzocyclo-hepten-5-one (63). The n.m.r. spectrum of the 8-bromoketone (63) is shown in Figure 7. From a comparison with the n.m.r. spectrum of the 8,9-dihydro-ketone (31) shown in Figure 5, the doublet centred at 3.71τ ($J_{6,7}$ = 13 Hz) was assigned to the proton at C-6, and the two overlapping doublets ($J_{7,8}$ = 5 Hz) centred at 3.1τ to the proton at C-7. The multiplet between 4.7-5.0τ integrating for one proton must then be due to that proton attached to the bromine carrying carbon atom.



(59) (33) (63)

The formation of the 8-bromoketone (63) was assumed to have arisen by isomerisation of the double bond in the 6-bromoketone (59) followed by an allylic shift of the bromine atom. As mentioned

N.m.r. spectrum of 8-bromo-8,9-dihydro-5H-benzocyclohepten-5-one in CCl_4

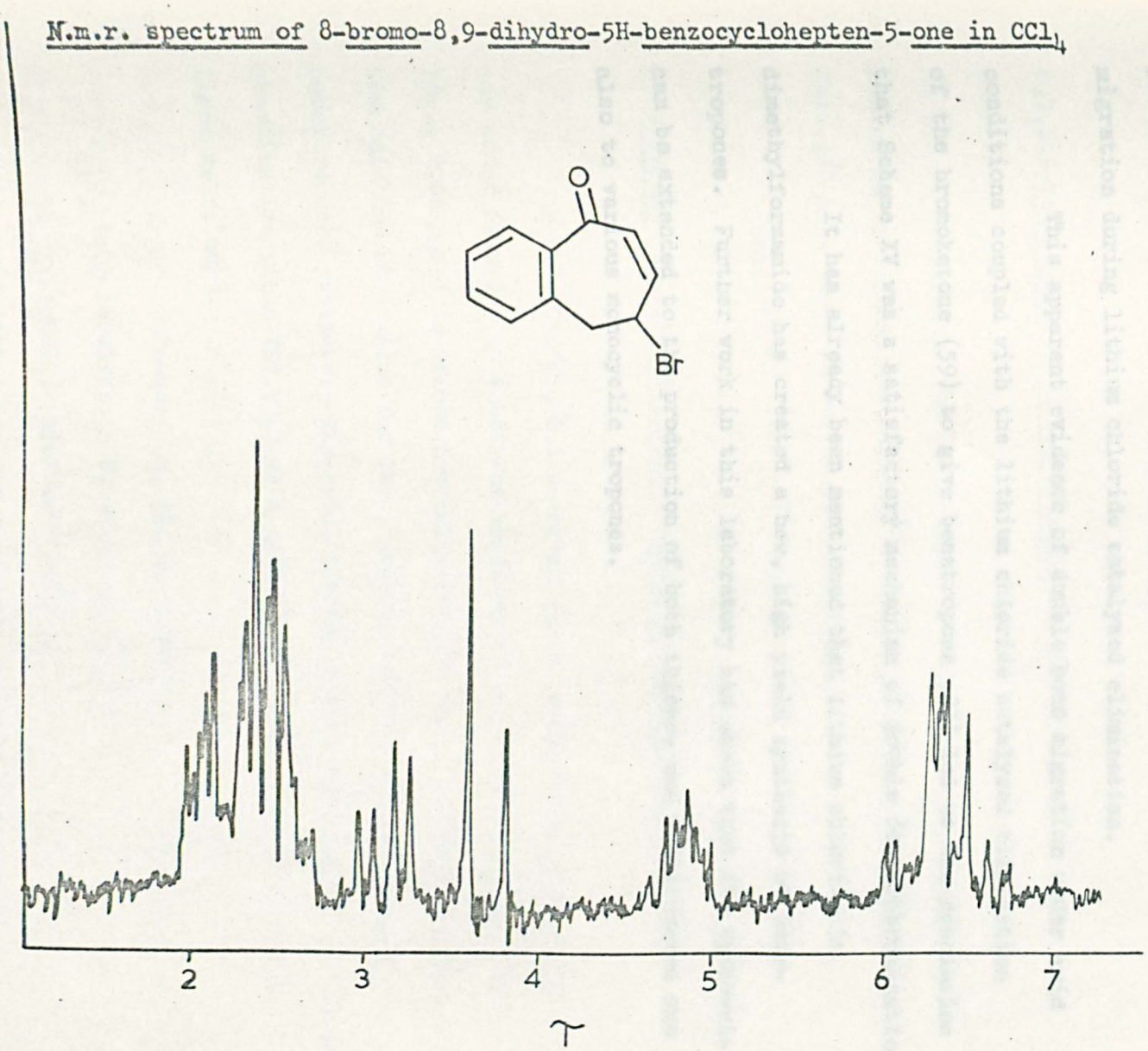


Figure 7

previously in the introduction there are analogies for such bromine migration during lithium chloride catalysed elimination.

This apparent evidence of double bond migration under acid conditions coupled with the lithium chloride catalysed elimination of the bromoketone (59) to give benztropone (33) led to the conclusion that Scheme XV was a satisfactory mechanism of double dehydrobromination.

It has already been mentioned that lithium chloride in dimethylformamide has created a new, high yield synthesis of benztropones. Further work in this laboratory has shown that the synthesis can be extended to the production of both thieno- and furotropones and also to various monocyclic tropones.

EXPERIMENTAL

6,7,8,9-Tetrahydro-5H-benzocyclohepten-5-one (29).

Prepared by the cyclisation of 5-phenyl valeric acid as described by Gilmore and Horton.[36] Yield 79%, b.p. 77°/0.1 mm., (lit.,[36] b.p. 90-93°/1 mm., - yield 83.5%).

$\nu_{max.}$ (Film) 1680 cm^{-1} (CO)

6,6-Dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (34).

Bromine (16g., 0.1 mole) in carbon tetrachloride (15 ml.) was added dropwise to a stirred solution of the bicyclic ketone (29) (8g., 0.05 mole) in carbon tetrachloride (50 ml.). After the addition the solution was boiled for 1hr., cooled, and the solvent removed under reduced pressure. The crude dibromide (34) was obtained in almost quantitative yield (15.9g.) as a colourless solid, m.p. 42-4° (from light petroleum).

Found: C, 41.9; H, 2.92%

$C_{11}H_{10}Br_2O$ requires: C, 41.5; H, 3.16%

$\nu_{max.}$ ($CHCl_3$) 1705 cm^{-1} (CO)

n.m.r. (CCl_4): τ 2.2-2.9 (4H, aromatic), 7.0-7.4 (4H, m, CH_2CBr_2 and CH_2Ar), 7.7-8.3 (2H, m, H8)

5H-Benzocyclohepten-5-one (33).

A mixture of the dibromoketone (34) (12g., 0.038 mole), anhydrous lithium chloride (4.8g., 0.114 mole) and dry dimethylformamide (DMF) (350 ml.) was boiled and stirred under a nitrogen atmosphere for 1hr. The mixture was cooled, and the DMF removed under reduced pressure. Water was added, and the aqueous solution extracted with ether. The combined ethereal extracts were dried (Na_2SO_4) and distilled to give the tropone (33) (5.4g., 92%) b.p. 106°/0.04 mm. (lit.,[1] b.p. 111°/0.2 mm.).

$\nu_{max.}$ (Film) 1640, 1609, and 1589 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 229, 260 (s), 307 (s), 320 and 343 (s) nm.

($\log_{10}\varepsilon$, 4.33, -, -, 3.81, -.)

The n.m.r. spectrum is shown in Figure 1.

6,9-Dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (32).

N-bromosuccinimide (4.5g., 0.025 mole) and benzoyl peroxide (two crystals) were added to 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) (2g., 0.0125 mole) in dry carbon tetrachloride (30 ml.), and the mixture was boiled under reflux (200-w lamp) for 6hr. After cooling, the solution was filtered and the solvent evaporated in vacuo giving an oil (3.9g., 98.5%) which slowly crystallised. Recrystallisation from

light petroleum gave colourless rods, m.p. 83°, (lit.,[15] m.p. 80°).

Found: C, 41.1; H, 3.6%

Calculated for $C_{11}H_{10}Br_2O$: C, 41.5; H, 3.2%

$\nu_{max.}$ ($CHCl_3$) 1687 cm^{-1} (CO)

n.m.r. (CCl_4): τ 2.3-2.7 (4H, m, aromatic), 4.34-4.64 (1H, m, CHBrAr), 4.9-5.15 (1H, m, CHBrCO), 6.6-8.0 (4H, m)

Dehydrobromination of 6,9-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (32).

Performed as described for the 6,6-dibromoketone (34) to give 5H-benzocyclohepten-5-one (33) in 81% yield.

3-Nitro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (36).

Prepared as described by Smith and Berry.[20] From 9g. of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) and 39.1g. of fuming nitric acid a yield of 10.4g. (90%) of a nearly white solid was obtained (lit.,[20] 82.5%).

6,6-Dibromo-3-nitro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (37).

A stirred solution of the nitroketone (36) (5.13g.) in carbon tetrachloride (400 ml.) was treated dropwise over 30 minutes with a

solution of bromine (8.8g.) in carbon tetrachloride (15 ml.). After the addition stirring was continued for a further 12hr. Evaporation under reduced pressure and crystallisation of the residue from 95% ethanol gave the dibromonitroketone (37) (8.6g., 94.5%) as a colourless solid, m.p. 86° which resolidified then remelted at 110°.

Found: C, 36.6; H, 2.32; N, 4.1%

$C_{11}H_9Br_2NO_3$ requires: C, 36.4; H, 2.49; N, 3.9%

$\nu_{max.}$ ($CHCl_3$) 1710 (CO), 1610, and 1342 cm^{-1}

n.m.r. ($CDCl_3$): τ 1.3-1.6 (1H, m, H4), 2.3-2.6 (2H, m, H1 and H2), 6.8-7.3 (4H, m, $CH_2.CBr_2$ and CH_2Ar), 7.6-8.1 (2H, m)

3-Nitro-5H-benzocyclohepten-5-one (38).

Prepared as described for 5H-benzocyclohepten-5-one (33). From the dibromonitroketone (37) (3.63g., 0.01 mole), lithium chloride (1.27g., 0.03 mole), and dry DMF (175 ml.) the nitrobenztropone (38) (1.53g., 76%) was obtained as pale yellow needles, m.p. 169-172° (from methanol).

Found: C, 65.3; H, 3.36; N, 6.8%

$C_{11}H_7NO_3$ requires: C, 65.7; H, 3.51; N, 6.96%

$\nu_{max.}$ ($CHCl_3$) 1641, 1602, and 1584 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 219, 253, and 346 nm. ($\log_{10}\epsilon$, 4.31, 4.3, and 4.02)

The n.m.r. spectrum is shown in Figure 2.

3-Amino-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (39).

Prepared by the reduction of 3-nitro-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (36) as described by Smith and Berry.[20]

Light yellow crystals, m.p. 103-4° (lit.,[20] m.p. 104-5°)

n.m.r. ($CDCl_3$): τ 2.7-3.3 (3H, m, aromatic), 6.5 (2H, broad singlet, NH_2), 7.0-7.4 (4H, m, CH_2CO and CH_2Ar), and 8.0-8.4 (4H, m)

The acetyl derivative (40),[20] prepared in the usual way, formed colourless plates, m.p. 103-4° (lit.,[20] 103-4°).

$\nu_{max.}$ ($CHCl_3$) 3416, 3320, and 1675 (broad) cm^{-1}

3-Acetamido-6,6-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (41).

A solution of the acetamidoketone (40) (2.1g.) in anhydrous tetrahydrofuran (40 ml.) was treated with phenyltrimethylammonium tribromide (7.28g.) and the mixture was set aside with occasional shaking at room temperature for 5hr. The solution was filtered, the insoluble quaternary salt was washed with a little tetrahydrofuran and the combined filtrates evaporated in vacuo to give a light brown oil which solidified (3.07g., 87%) on trituration with light petroleum. Recrystallisation from aqueous ethanol afforded colourless plates, m.p. 136-8°.

Found: C, 44.2; H, 3.47; N, 4.0%

$C_{13}H_{13}Br_2NO_2$ requires: C, 44.8; H, 3.47; N, 3.7%

$\nu_{max.}$ ($CHCl_3$) 3416, 3320, and 1690 cm^{-1}

n.m.r. ($CDCl_3$): τ 1.5 (1H, s, NH), 1.7-2.9 (3H, m, aromatic), 7.0-7.5 (4H, m, CH_2CBr_2 and CH_2Ar), 7.72 (3H, s, CH_3), and 7.6-8.2 (2H, m)

3-Acetamido-5H-benzocyclohepten-5-one (42).

The acetamidodibromoketone (41) (2.18g.) was dehydrobrominated with lithium chloride (0.742g.) in boiling DMF (125 ml.) in the usual way giving the acetamidobenztropone (42) as yellow needles (1.18g., 95%) m.p. 213-215° (from methanol).

Found: C, 73.3; H, 5.15; N, 6.6%

$C_{13}H_{11}NO_2$ requires: C, 73.2; H, 5.20; N, 6.6%

$\nu_{max.}$ ($CHCl_3$) 3416, 3310, 1690, 1640, and 1612 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 207, 242, 330, and 375 nm. ($\log_{10}\varepsilon$, 4.04, 4.42, 3.99, and 3.72)

n.m.r. (CF_3CO_2H): τ 0.1-0.4 (2H, m), 0.8-2.0 (5H, m), 7.4 (3H, s, CH_3)

Attempted monobromination of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) with N-bromosuccinimide.

A mixture of the bicyclic ketone (29) (4g.), N-bromosuccinimide

(4.5g., one molar equivalent), and benzoyl peroxide (a trace) in dry carbon tetrachloride (50 ml.) was boiled over a 200-w lamp for 6hr. Working up in the usual way gave a brown oil. T.l.c. eluting with toluene showed four components: 0.57g. of the mixture were separated by P.L.C. (three multiple runs eluting with toluene) and the following bands obtained.

Band I (64 mg., R = 13.1) was obtained as a colourless solid, m.p. 83°. N.m.r. and infrared spectra indicated it to be 6,9-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (32).

Band II (120 mg., R = 11.0), a colourless oil, bulb tube distilled b.p. 98-104°/0.04 mm. The n.m.r. spectrum was identical with that of 6-bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (30) prepared by the bromination of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) as described later.

Band III (71 mg., R = 7.6), a pale yellow oil identified by n.m.r. and infrared spectra as 6,7-dihydro-5H-benzocyclohepten-5-one (44), although inconsistent analyses were obtained.

$\nu_{max.}$ (Film) 1680 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 235, 266, and 320 nm. ($\log_{10}\varepsilon$, 4.33, 3.72, and 3.45)

Mass spectrum $^{m}/e$ 158 (M^{+}), 130, 129, 115, 102.

The n.m.r. spectrum is shown in Figure 3.

Band IV (48 mg., R = 5.1), a colourless liquid shown from spectral examination to be unchanged 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29).

Attempted bromination of 6,9-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (32).

Phenyltrimethylammonium tribromide (1.13g.) was added to a solution of the 6,9-dibromoketone (32) (0.95g.) in dry tetrahydrofuran (20 ml.) and the mixture allowed to stand at room temperature with occasional shaking for 24hr. Working up in the usual way gave starting material.

6,6,9-Tribromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (43).

A mixture of 6,6-dibromoketone (34) (1.59g.), N-bromosuccinimide (0.9g.) and benzoyl peroxide (two crystals) in dry carbon tetrachloride (30 ml.) gave after boiling under reflux for 4.5hr. the tribromoketone (43) (1.8g., 91%) as a white solid. Recrystallisation from light petroleum gave colourless plates, m.p. 89-91°.

Found: C, 33.2; H, 2.19%

$C_{11}H_9Br_3O$ requires: C, 33.2; H, 2.28%

$\nu_{max.}$ ($CHCl_3$) 1704 cm^{-1} (CO)

n.m.r. ($CDCl_3$): τ 2.2-2.7 (4H, m, aromatic), 4.3-4.6 (1H, m, CHBr), 6.4-7.9 (4H, m, $-CH_2.CH_2-$)

6-Bromo-5H-benzocyclohepten-5-one (45).

The dehydrobromination was carried out in the usual way. From the tribromoketone (43) (1.24g.) and lithium chloride (0.4g.) in DMF (50 ml.) was obtained the 6-bromotropone (45) (0.66g., 90%) as pale yellow prisms from light petroleum, m.p. 78-81°.

Found: C, 56.2; H, 2.7%

$C_{11}H_7BrO$ requires: C, 56.2; H, 3.0%

$\nu_{max.}$ ($CHCl_3$) 1630 (s), 1619 and 1596 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 210, 239, 262 (s), 270 (s), 332, and 360 nm. ($\log_{10}\varepsilon$, 4.07, 4.37, -, -, 3.94, and 3.85)

Mass spectrum $^m/e$ 236/234 (M^+), 208/206, 156, 128, 127

The n.m.r. spectrum is shown in Figure 4.

9,9-Dibromo-10,10-dihydroxy-7,8,9,10-tetrahydro-6H-pyrido[1,2-a]azepinium bromide (46).

Prepared by the method of Fozard and Jones.[22]

$\nu_{max.}$ (Nujol) 3080 cm^{-1} (OH)

Attempted dehydrobromination of 9,9-dibromo-10,10-dihydroxy-7,8,9,10-tetrahydro-6H-pyrido[1,2-a]azepinium bromide (46).

A mixture of the dibromocompound (46) (0.84g.), lithium chloride (0.25g.) and DMF (100 ml.) was boiled and stirred under nitrogen for 1hr. The DMF was removed under reduced pressure and the residue extracted with water. The aqueous solution was filtered and an excess of a saturated aqueous solution of sodium picrate was added. A dark brown solid was precipitated which could not be characterised.

Treatment of 6,6-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (34) with collidine.

The dibromoketone (34) (3.5g.) was boiled under reflux in 2,4,6-collidine (30 ml.) for 1hr. The initially colourless solution turned dark brown. After cooling and treating with 50% HCl (100 ml.) the aqueous solution was thoroughly extracted with ether. The ethereal extracts were washed with water, dried, and concentrated. The resulting liquid (0.9g.) was shown to be mainly 5H-benzocyclohepten-5-one (33).

Treatment of 6,6-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (34) with sodium chloride in dimethylformamide.

The dibromoketone (34) (1.91g., 0.006 mole) was boiled and stirred under nitrogen in dry DMF (40 ml.) with anhydrous sodium chloride (1.05g., 0.018 mole) for 1hr. Working up in the usual way gave a brown liquid (0.85g.). T.l.c. of the product eluting with 10% light petroleum-xylene, showed four components. The mixture (0.6g.) was applied to two preparative plates and eluted twice with 10% light petroleum-xylene. The following bands were obtained:-

Band I (41 mg., R = 10.2). N.m.r. and infrared spectra were identical with those of 6-bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (30).

Band IV (116 mg., R = 3.4), a yellow liquid shown to be 5H-benzocyclohepten-5-one (33).

Bands II and III (280 mg., R = 7.5) were rather ill-defined and consequently were combined and rechromatographed eluting twice with toluene.

Band II (104 mg., R = 10.0) isolated as a yellow solid and shown from spectral evidence to be 6-bromo-5H-benzocyclohepten-5-one (45).

Band III (62 mg., R = 7.3) showed n.m.r. and infrared spectra consistent with those of 8,9-dihydro-5H-benzocyclohepten-5-one (31).

$\nu_{max.}$ (Film) 1645, 1625, and 1600 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 212, 230, 240 (s), and 262 (s) nm.

($\log_{10}\varepsilon$, 4.04, 4.11, -, -.)

The n.m.r. spectrum is shown in Figure 5.

Treatment of 6,6-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (34) with dimethylformamide alone.

The dibromoketone (34) (0.94g.) was boiled under nitrogen in dry DMF (30 ml.) for 1hr. After working up in the usual way a brown liquid (0.48g.) was obtained which on examination by t.l.c. showed three spots. The mixture (0.32g.) was separated by P.L.C. eluting with toluene.

Band I (101 mg., R = 9.8), a yellow solid shown from spectral examination to be 6-bromo-5H-benzocyclohepten-5-one (45).

Band II (44 mg., R = 7.5). The n.m.r. spectrum was consistent with that of a mixture of 8,9-dihydro-5H-benzocyclohepten-5-one (31) and 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29). V.P.C. analysis (column temperature 189°) confirmed this showing two peaks of retention times 4.33 and 5.5 minutes corresponding to the ketones (29) and (31) respectively.

Band III (48 mg., R = 4.5). The n.m.r. spectrum was identical with that of 5H-benzocyclohepten-5-one (33).

Attempted bromination of 5H-benzocyclohepten-5-one (33).

a) Dry hydrogen bromide was bubbled into a boiling solution of 5H-benzocyclohepten-5-one (33) (0.47g.) in DMF (50 ml.) under nitrogen. Samples of the mixture were withdrawn periodically and investigated by t.l.c. No reaction resulted.

b) The benztropone (33) (0.234g.) in DMF (30 ml.) was heated under reflux in a nitrogen atmosphere for 1hr. with bromoacetone (0.206g.). After working up in the usual way only starting material was recovered and no reaction had occurred.

c) A solution of the benztropone (33) (0.59g.) in DMF (25 ml.) was treated dropwise at room temperature with one molar equivalent of bromine (0.6g.) in DMF (5 ml.). The solution was stirred for 0.5hr. and then boiled under reflux for 1hr. Working up in the usual way gave a brown residue which on examination by t.l.c. showed two components. Separation was by P.L.C. using toluene as eluent.

Band I (82 mg., R = 7.4) isolated as a yellow solid had m.p. and spectral evidence consistent with those of 6-bromo-5H-benzocyclohepten-5-one (45).

Band II (185 mg., R = 3.7), a pale yellow liquid shown from its n.m.r. spectrum to be 5H-benzocyclohepten-5-one (33).

Irradiation of 5H-benzocyclohepten-5-one (33).

A solution of 5H-benzocyclohepten-5-one (33) (0.826g.) in absolute methanol (800 ml.) contained in a 1 l. Pyrex flask was flushed with nitrogen. The solution was exposed to radiation from a mercury lamp (Hanovia, medium pressure) and the irradiation monitored by thin layer chromatography. After 18hr. exposure, t.l.c. showed an additional component to the tropone (33). Removal of the solvent under reduced pressure gave a brown gum (0.8g.) which was chromatographed on three

P.L.C. plates using toluene-5% ethyl acetate as eluent.

Band I (105 mg., R = 7.1) isolated as a brown liquid which on trituration with ether and filtration gave 6 mg. of a white solid. The accumulated solids from several experiments were crystallised from absolute ethanol to give a dimer as colourless rhombs., m.p. 206-10°.

Found: C, 84.0; H, 4.89%

$C_{22}H_{16}O_2$ requires: C, 84.5; H, 5.16%

$\nu_{max.}$ ($CHCl_3$) 1671 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 234, 259, and 305 nm. ($\log_{10}\varepsilon$, 4.62, 4.14, and 3.62

n.m.r. ($CDCl_3$): τ 1.7-3.8 (12H, m, aromatic), 5.4-5.7 (1H, m), 6.0-6.3 (1H, d, J = 7Hz), 6.7-6.9 (2H, broad s)

Evaporation of the ether gave a residue which still contained a small amount of the above solid. The major component was purified by bulb tube distillation giving a colourless liquid, b.p. 80-83°/0.02 mm. The n.m.r. spectrum indicated the product to be the photochemical isomer, 3,4-benzobicyclo[3,2,0]hept-6-ene-2-one (55) (95 mg., 12%).

Found: C, 84.6; H, 5.15%

$C_{11}H_8O$ requires: C, 84.5; H, 5.16%

$\nu_{max.}$ ($CHCl_3$) 1704 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 215, 248, and 295 nm. ($\log_{10}\varepsilon$, 4.17, 3.98, and 3.37)

The n.m.r. spectrum is shown in Figure 6.

Band II (113 mg., R = 5.6) was shown to be unchanged 5H-benzocyclohepten-5-one (33).

A large amount of material assumed to be polymeric, remained on the base line of the preparative plates.

For the isolation of the tricyclic ketone (55) required for future experiments the above work up was slightly modified. The crude residue from the photolysis was distilled under reduced pressure and the resulting distillate then separated by P.L.C. The result was a cleaner and easier separation since most of the polymeric material had been removed in the initial distillation. No significant change in yield (13%) was observed.

Irradiation of 6-bromo-5H-benzocyclohepten-5-one (45).

The bromotropone (45) (0.83g.) was irradiated in dry methanol (800 ml.) by the procedure described above. Monitoring of the photolysis by t.l.c. showed decreasing amounts of starting material with the formation of only polymeric material, until finally after 72hr. irradiation only the latter remained.

3,4-Benzobicyclo[3,2,0]heptan-2-one (56).

A solution of the tricyclic ketone (55) (0.125g.) in dry methanol (20 ml.) was hydrogenated at atmospheric temperature and

pressure with a 10% palladium-charcoal catalyst (0.05g.). After the absorption of one molar equivalent of hydrogen (~10 minutes) the solution was filtered and evaporated to give 3,4-benzobicyclo [3,2,0]heptan-2-one (56) (0.125g., 99%) as a colourless liquid. Purification was by bulb tube distillation, b.p. 85-90°/0.1 mm.

Found: C, 83.2; H, 6.2%

$C_{11}H_{10}O$ requires: C, 83.5; H, 6.4%

$\nu_{max.}$ (Film) 1708 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 213, 246, and 292 nm. ($\log_{10}\varepsilon$, 4.02, 4.03, and 3.39)

Mass spectrum, $^{m}/e$ 158 (M^{+}), 130, 102, 77

n.m.r. (CCl_4): τ 2.2-3.0 (4H, m, aromatic), 6.2-6.6 (1H, m), 6.8-7.3 (1H, m), 7.3-8.0 (2H, m), and 8.3-8.7 (2H, m)

Attempted bromination of 3,4-benzobicyclo[3,2,0]heptan-2-one (56).

a) The tricyclic ketone (56) (0.153g.) was subjected to brominating conditions in the usual way using phenyltrimethylammonium tribromide (0.364g.) in dry tetrahydrofuran (10 ml.). The solution was allowed to stand at room temperature with occasional shaking for seven days. After working up only starting material was recovered.

b) The tricyclic ketone (56) (0.107g.), N-bromosuccinimide (0.12g.) and benzoyl peroxide (a trace) were boiled under reflux (200-w lamp) in carbon tetrachloride (5 ml.). The reaction was monitored by t.l.c. and

after 24hr. nearly all trace of starting material had disappeared. The solution was filtered and the solvent evaporated to yield a brown liquid (0.15g.). Purification of the crude residue by P.L.C. gave 0.048 g. of product (57).

$\nu_{max.}$ (Film) 1716 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 216, 245, 290 nm.

Mass spectrum, $^{m}/e$ 238/236, 210, 208, 157, 129, 101.

($C_{11}H_9BrO$ requires M^+ 238/236)

n.m.r. (100 MHz) ($CDCl_3$): τ 2.1-2.7 (4H, m, aromatic), 6.2-6.6 (1H, 2d, J = 10 Hz, J = 6Hz, CHBr), 6.6-7.6 (3H, m), and 8.0-8.4 (1H, m)

Reaction between 3,4-benzobicyclo[3,2,0]hept-6-ene-3-one (55) and N-bromosuccinimide.

The photoisomer (55) (0.125g.) was treated with N-bromosuccinimide (0.142g.) in the usual way. After boiling for 24hr. examination of the residue by t.l.c. showed three components. These were separated by P.L.C. (toluene) into the following bands:-

Band I (8 mg., R = 11.7), a colourless solid, m.p. 153-5°.

$\nu_{max.}$ ($CHCl_3$) 1719 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 215, 249, and 288 nm.

Mass spectrum, $^{m}/e$ 318, 316, 314, 237, 235, 156, 128, 102. ($C_{11}H_8Br_2O$ requires 318/316/314)

n.m.r. (CCl_4): τ 2.2-3.0 (4H, m, aromatic), 5.0-5.5 (1H, m), 5.8-6.3 (2H, m), and 6.4-6.9 (1H, m)

Band II (27 mg., R = 10.2) was isolated as an oil which slowly solidified.

$\nu_{max.}$ ($CHCl_3$) 1716 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 214, 249, and 290 nm.

Mass spectrum, $^m/e$ 318, 316, 314, 237, 235, 156, 128, 102

n.m.r. (CCl_4): τ 2.1-2.8 (4H, m, aromatic), 5.0-5.4 (1H, m), and 5.7-6.8 (3H, m)

Band III (7 mg., R = 6.6) was unchanged photoisomer (55).

Treatment of the bromo-3,4-benzobicyclo[3,2,0]heptan-2-one (57) with lithium chloride in dimethylformamide.

The bromoketone (57) (0.05g.) was treated with lithium chloride (0.03g.) in DMF (10 ml.) in the usual way. After boiling under nitrogen for 1hr. only starting material was recovered.

6-Bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (30).

Prepared by the method of Ramirez and Kirby.[30]

A stirred solution of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) (4.8g.) in ether (35 ml.) at 0° was treated dropwise with bromine (4.8g.) in chloroform (15 ml.). The solvent was removed and

distillation of the residue gave the bromoketone (30) (6.74g.), 94%), b.p. 110-112°/0.12 mm. (lit.,[30] b.p. 139-141°/1 mm.).

Found: C, 55.7; H, 4.4%

Calculated for $C_{11}H_{11}BrO$: C, 55.3; H, 4.6%

$\nu_{max.}$ (Film) 1685 cm^{-1} (CO)

n.m.r. ($CDCl_3$): τ 2.1-2.8 (4H, m, aromatic), 4.9-5.2 (1H, q, J = 7Hz., J = 5Hz., H6), 6.8-7.2 (2H, m, CH_2Ar), and 7.4-8.3 (4H, m)

Treatment of 6-bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (30) with collidine.

The method of Buchanan and Lockhart[15] was employed.

The bromoketone (30) (2.4g.) was boiled under reflux with 2,4,6-collidine (15 ml.) for 1hr. Working up in the usual way gave a brown oil (1g.) which on examination by t.l.c. showed the presence of three spots. Separation of the mixture by P.L.C. (four multiple runs in toluene) gave the following bands:-

Band I (52 mg., R = 10.7) was shown from its n.m.r. spectrum to be 6,7-dihydro-5H-benzocyclohepten-5-one (44).

Band II (376 mg., R = 9.6) was shown from its n.m.r. spectrum to be a mixture, consisting of approximately 80% of 8,9-dihydro-5H-benzocyclohepten-5-one (31) and 20% of 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29).

Band III (65 mg., R = 3.3) exhibited spectra identical with those of 5H-benzocyclohepten-5-one (33).

Treatment of 6-bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (30) with lithium chloride in dimethylformamide.

The usual procedure was employed. From the bromoketone (30) (3.6g.), anhydrous lithium chloride (1.91g.) in DMF (150 ml.) boiled for 1hr. was obtained a brown liquid (2.1g.). Examination of the residue by t.l.c. showed two spots.

The crude mixture (1.07g.) was separated on three preparative plates eluted with toluene (three multiple runs) and the following bands were obtained:-

Band I (26 mg., R = 17.4) was shown from spectral evidence to be unchanged bromoketone (30).

Band II (349 mg., R = 13.2) was shown from its n.m.r. spectrum to be a mixture of 8,9-dihydro-5H-benzocyclohepten-5-one (31) (ca. 80%) and 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) (ca. 20%).

Attempted separation of 8,9-dihydro-5H-benzocyclohepten-5-one (31) from 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) by preparative V.P.C.

An analytical run of the mixture on the preparative instrument at varying temperatures between 150-200° did not give a peak separation

greater than 1.5 minutes. The preparative separation was carried out isothermally at 170° with a nitrogen flow rate of about 200 ml. $min.^{-1}$. The sample (0.2 ml.) was injected automatically and the fractions collected in spiral traps cooled in an acetone-dry ice bath. In this trial preparative run only 0.026g. of material were recovered which was shown by n.m.r. to be still a mixture of the starting materials. Since the recovery from the column was only about 12% it was decided that it was not economical to pursue further a separation by preparative V.P.C.

Oxidation of 8,9-dihydro-5H-benzocyclohepten-5-one (31).

An analytical run on the V.P.C. showed the mixture of the ketones (31) and (29) to be in the ratio 81:19.

Aqueous 30% hydrogen peroxide solution (6 ml.) and 4N. sodium hydroxide (6 ml.) were added simultaneously, dropwise with stirring, to a solution of the mixture (1.28g.) in methanol (120 ml.). The solution became bright red. The solution was allowed to stand at -10° for 72hr. when a white solid which had separated (0.68g.) was filtered off. Subsequent investigation of this solid showed it not to be the desired epoxide and it was discarded. Concentration of the filtrate gave an aqueous basic mixture which was extracted with ether. The ethereal extracts were dried and evaporated to give 6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (29) (0.234g.). The aqueous layer was acidified

with dilute hydrochloric acid and extracted several times with ether. After drying (Na_2SO_4), the solvent was removed giving a colourless oil (1.07g.) which partially crystallised.

$\nu_{max.}$ ($CHCl_3$) 1705 cm^{-1} broad (CO)

n.m.r. ($CDCl_3$): τ 0.8-1.4 (2H, disappeared on shaking with D_2O), 1.6-2.7 (4H, m, aromatic), 6.3-7.3 (4H, m)

The spectra indicated that ring opening had occurred to give a di-carboxylic acid.

Esterification of the acid.

An ether solution of the acid (0.63g.) was treated with a slight excess of diazomethane (generated from N-nitrosomethylurea) in ether at 0°. The pale yellow solution was then allowed to stand at room temperature until the colour had discharged (1.25hr.), when removal of the solvent gave the dimethylester (0.65g.) as a colourless liquid. A sample was purified by bulb tube distillation, b.p. 104-6°/0.2 mm. The analysis and n.m.r. spectrum indicated the product to be methyl 2-2'-methoxycarbonylethyl benzoate (60), (lit.,[37] b.p. 124°/2.5 mm.).

Found: C, 65.1; H, 6.25%

Calculated for $C_{12}H_{14}O_4$: C, 64.9; H, 6.35%

$\nu_{max.}$ (Film) 1736 (s), 1726 cm^{-1} (CO)

$\lambda_{max.}$ (95% EtOH) 208, 231, and 278 nm. ($\log_{10}\varepsilon$, 3.77, 3.91, and 3.13)

n.m.r. (CCl_4): τ 1.8-2.8 (4H, m, aromatic), 6.06 (3H, s, OCH_3), 6.31 (3H, s, OCH_3), 6.5-6.9 (2H, m), and 7.2-7.6 (2H, m)

6,7-Dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (61).

V.P.C. analysis showed the mixture of ketones (31) and (29) in the ratio 76:24.

A solution of the mixed ketones (0.63g.) in ether (20 ml.) containing suspended calcium carbonate was treated, dropwise with stirring, with bromine (0.63g.) in chloroform (10 ml.) at 0°. During further stirring (1hr.) the mixture was allowed to reach room temperature, then filtered and the solid washed well with ether. The combined organic filtrates were evaporated to give a brown oil (1.16g.) showed by t.l.c. to consist of two products.

The crude oil (1.16g.) was chromatographed on three P.L.C. plates eluting with a 50% light petroleum-50% toluene solvent mixture. Band I (591 mg., R = 8.0), isolated as a colourless oil, solidified on trituration with light petroleum. Recrystallisation from light petroleum gave 6,7-dibromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (61) as colourless rods, m.p. 65-6°.

Found: C, 41.5; H, 3.05%

$C_{11}H_{10}Br_2O$ requires: C, 41.5; H, 3.16%

$\nu_{max.}$ ($CHCl_3$) 1686 cm^{-1} (CO)

n.m.r. (CCl_4): τ 2.1-2.8 (4H, m, aromatic), 4.92 (1H, d, J = 5Hz., COCHBr), 5.0-5.3 (1H, m, H7), and 6.0-7.7 (4H, m, H8 and H9)

Band II (87 mg., R = 4.5) was shown from n.m.r. and infrared spectra to be the expected 6-bromo-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-one (30).

6-Bromo-8,9-dihydro-5H-benzocyclohepten-5-one (59).

A solution of the 6,7-dibromoketone (61) (0.124g.) in dry ether (20 ml.) was vigorously stirred at room temperature with Spence alumina (Type H., 5g.). The reaction was monitored by t.l.c. After 30 minutes the alumina was filtered off and washed well with ether. The combined solutions were evaporated to yield 6-bromo-8,9-dihydro-5H-benzocyclohepten-5-one (59) (0.85g., 92%) as a pale yellow oil. A sample for analysis was purified by P.L.C.

Found: C, 55.5; H, 3.92%

$C_{11}H_9BrO$ requires: C, 55.7; H, 3.82%

$\nu_{max.}$ (Film) 1660 (s), 1655, 1615, and 1601 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 209, 261, 280 (s) nm. ($\log_{10}\varepsilon$, 3.86, 3.81, -.)

n.m.r. (CCl_4): τ 2.0-2.9 (5H, m, aromatic + CH=CBr), 6.7-7.1 (2H, m), and 7.1-7.6 (2H, m)

Treatment of 6-bromo-8,9-dihydro-5H-benzocyclohepten-5-one (59) with lithium chloride in dimethylformamide.

The unsaturated bromoketone (59) (0.16g.) was boiled and stirred under nitrogen in dry DMF (30 ml.) with lithium chloride (0.086g.) for 1hr. Working up in the usual way gave a brown liquid (0.09g.) whose n.m.r. spectrum confirmed that it was 5H-benzocyclohepten-5-one (33).

Attempted acid catalysed isomerisation of 8,9-dihydro-5H-benzocyclohepten-5-one (31).

A sample of the mixed ketones (31) and (29) was analysed by V.P.C. and shown to contain 3.3% of the saturated ketone (29).

The p-toluenesulphonic acid was dried by azeotroping with benzene for 2hr. using a Dean and Stark apparatus, followed by evaporation of the benzene.

A solution of the ketone (31) (0.227g.) in dry benzene (10 ml.) containing p-toluenesulphonic acid (0.15g.) was boiled under reflux for 1hr. The solution was cooled, poured into aqueous sodium carbonate, and the benzene layer was separated and dried. Evaporation of the solvent gave a brown oil (0.22g.) which on examination by t.l.c. showed one product in addition to the known impurity ketone (29). The crude mixture (0.22g.) was separated by P.L.C. eluting with benzene (four multiple runs)

and the following bands obtained:-

Band I (4 mg., R = 9.8) was shown to be unchanged ketone (29).

Band II (150 mg., R = 4.9), isolated as a viscous oil, crystallised on trituration with light petroleum. Recrystallisation from 95% ethanol afforded the dimer (62) as colourless prisms, m.p. 103-4°.

Found: C, 83.5; H, 6.36%

$C_{22}H_{20}O_2$ requires: C, 83.5; H, 6.37%

$\nu_{max.}$ ($CHCl_3$) 1670, 1642, and 1600 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 211, 248, and 274 (s) nm. ($\log_{10}\varepsilon$, 4.26, 4.22, -.)

Mass spectrum, $^m/e$ 316 (M^+), 160, 157, 132, 131, 115, 105, 103, 90, 77

n.m.r. (CCl_4): τ 1.9-2.9 (8H, m, aromatic), 3.1-3.4 (1H, t, CH=C), 6.6-7.6 (9H, m), and 7.7-8.4 (2H, m)

Isomerisation of 6-bromo-8,9-dihydro-5H-benzocyclohepten-5-one (59).

A solution of the 6-bromoketone (59) (0.308g.) in dry benzene (15 ml.) containing p-toluenesulphonic acid (0.225g.) was boiled under reflux for 1.75hr. Working up as described above gave a brown liquid (0.283g.) which on examination by t.l.c. showed it to contain three components. Separation by P.L.C. eluting with toluene gave the following bands:-

Band I (87 mg., R = 6.9) was shown by n.m.r. and infrared spectra to be unchanged bromoketone (59).

Band II (26 mg., R = 4.2), a pale yellow oil, exhibited spectra which were consistent with 8-bromo-8,9-dihydro-5H-benzocyclohepten-5-one (63).

Found: C, 55.0; H, 4.14%

$C_{11}H_9BrO$ requires: C, 55.7; H, 3.82%

$\nu_{max.}$ (Film) 1650, 1628, and 1602 cm^{-1}

$\lambda_{max.}$ (95% EtOH) 217 and 236 nm. ($\log_{10}\varepsilon$, 3.93 and 3.94)

The n.m.r. spectrum is shown in Figure 7.

Band III (15 mg., R = 1.4) was shown to be 5H-benzocyclohepten-5-one (33).

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