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THE PREPARATION AND CYCLISATION

OF SOME

N-(3-BROMOPROPYL) ARYLAMINE HYDROHALIDES

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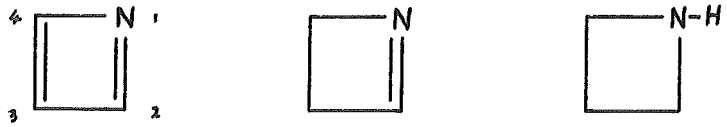
ABSTRACT

A number of N-(3-bromopropyl) arylamine hydrohalides have been prepared. Their behaviour with various bases has been investigated and it has been shown that, under certain conditions, these starting materials may be cyclised to N-arylazetidines. A brief study has also been made of the possibility of forming 1,4-dihydro-4-oxocyclohexa-2,5-dienespiro-2'-pyrrolidine from N-(3-bromopropyl)-p-hydroxyaniline hydrobromide.

I.

INTRODUCTION

One small class of the large family of heterocyclic compounds is the four membered ring system containing one nitrogen atom. The unsubstituted members of this class are azete (I), azetine (II), and azetidine (III); of these,



(I) (II) (III)

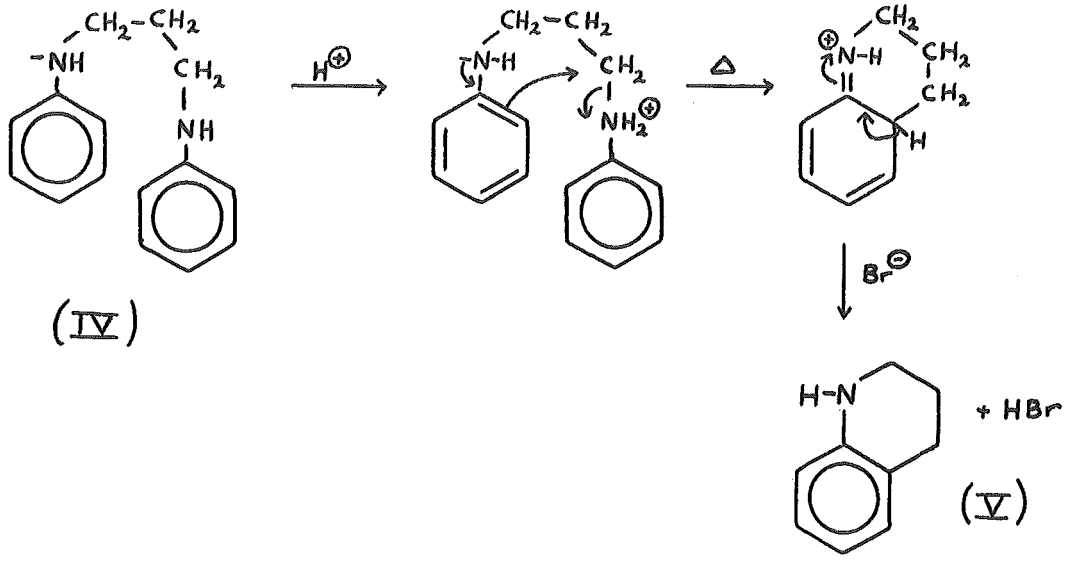
the saturated member, azetidine, is the only one to have been isolated.

This ring system is rather difficult to prepare by the cyclisation of straight chain intermediates. The ring is a strained one and, furthermore, of the conformations available to the intermediates, few are favourable for ring formation. Thus it is only when the cyclising atoms are suitably oriented and the appropriate stimulus is applied that the ring can form. Consequently, due to these preparative difficulties, relatively little work on azetidines has been carried out.

Azetidine itself was first prepared in 1888[1] but was not isolated in pure form until 1899[2]. Some 2-, 3-, and 4- substituted azetidines, together with various N-alkylazetidines have also been prepared. However, N-arylazetidines are unknown and it was the aim of the present work to investigate the possible syntheses of these compounds.

In 1899, Scholtz[3] did claim to have prepared N-phenylazetidine from the interaction of 1,3 - dibromopropane and aniline. This was obtained as a low boiling fraction when the main reaction product N,N' - diphenyltrimethylenediamine (IV) was distilled. Veer[4] later carried out the same preparation and found that his first distillation fraction contained only aniline.

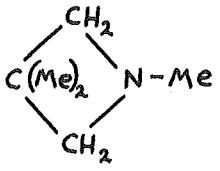
Fischer, Topsom, and Vaughan[5] found, in repeating Scholtz's preparation, that the low-boiling fraction contained aniline and a compound answering to Scholtz's description of N-phenylazetidine. However, this description also fitted 1,2,3, 4 - tetrahydroquinoline (V), with which the compound was readily identified. It was suggested that this reaction could be represented mechanistically as a normal Hofmann - Martius reaction.



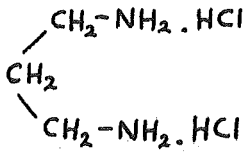
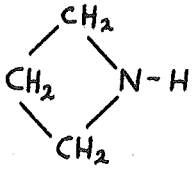
(IV) (V)

Before considering possible syntheses of N-arylazetidines, it is necessary to review methods which have been used in the preparation of other azetidines. The methods of preparing these compounds may conveniently be classified into four main groups[6]:-

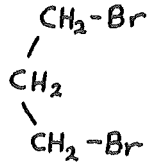
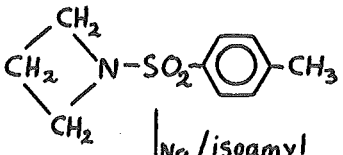
(1) The dehydrohalogenation of 3 - haloalkylamines:-

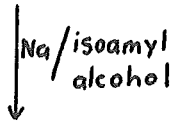
e.g.[7] $NHMe\text{-}CH_2\text{-}C(Me)_2\text{-}CH_2\text{-}Br.HBr \xrightarrow[KOH]{50\%}$ 

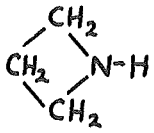
(2) The pyrolysis of diamines and related compounds:-

e.g.[8]  $\xrightarrow[distillation]{Dry}$  (Low yield and impure)

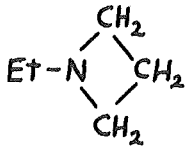
(3) The reaction of a dihalide with an amide or amine:-

e.g.[9,10]  $H_2NSO_2\text{-}C_6H_4\text{-}CH_3 \longrightarrow$ 



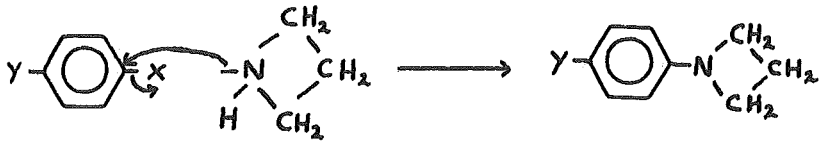


(4) The reaction of 3 - aminoalkyl hydrogen sulphates with a base:-

e.g.[11] $Et\text{-}NH\text{-}(CH_2)_3\text{-}OH \xrightarrow[(ii)\ OH^{\ominus}]{(i)\ ClSO_3H}$ 

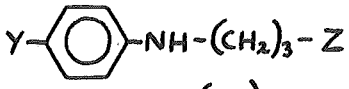
In searching for a preparative method for N - arylazetidines, there are two possible approaches. The azetidine ring may be formed either before or after the aryl group becomes attached to the nitrogen atom. If ring formation is to precede attachment of the aryl group, then formation of an N - arylazetidine will

involve nucleophilic substitution by azetidine on a suitably substituted benzene ring.



If azetidine were available in sufficient quantity and if it were a sufficiently strong nucleophile, the above reaction should provide a useful preparative route, especially where the group Y is activating towards nucleophilic attack. G.J. Leary (in this department) has, concurrently with this thesis, investigated this possibility and has indeed prepared, among others, N -(p-nitrophenyl) azetidine from p-bromonitrobenzene and azetidine.

The other possibility, viz. the azetidine ring formed subsequent to N-aryl substitution, would involve cyclisation of an intermediate of the type:-



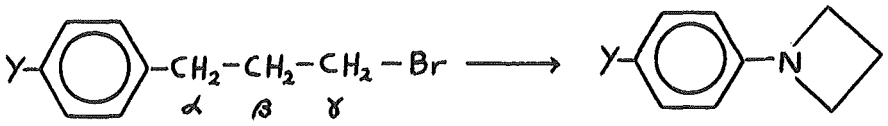
(VI)

(cf. reactions (1) and (4) p. 3)

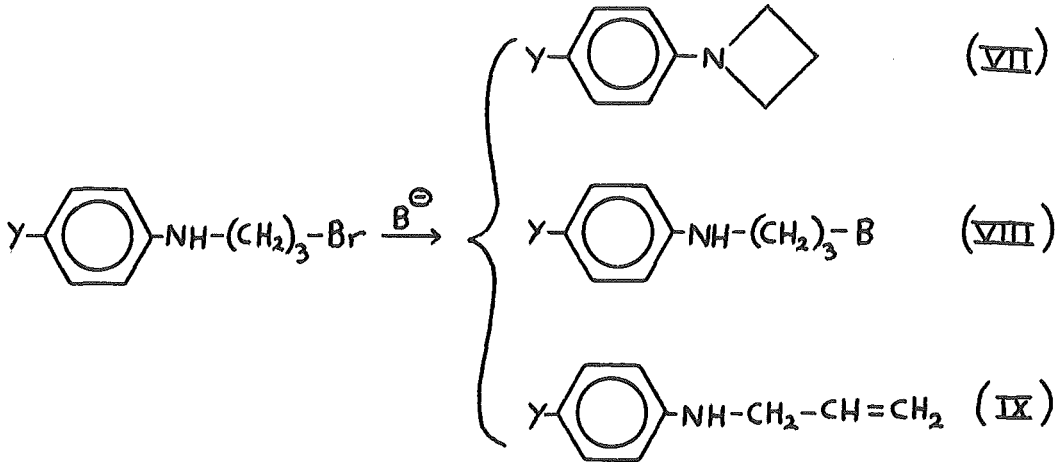
and the present work consists of an investigation of this possible reaction course.

In all reactions studied, bromine was used as group Z (cf. reaction (1) p. 3) although the reaction using chlorsulphonic acid and base where Z= $-OSO_3H$ would seem to be equally feasible (cf. reaction (4) p. 3). However, Leary has examined this possibility for the case in which Y=CH_3, but has found no evidence for N-(p-tolyl) azetidine formation.

Cyclisation to form the azetidine ring involves attack by the nitrogen lone pair of electrons on the γ-carbon atom, and the elimination of hydrogen bromide.



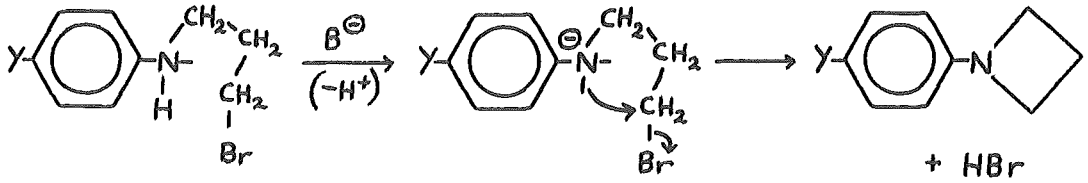
Under the influence of a base, $B^{\ominus}$, a compound of type (VI) could also undergo two other important reactions. The first of these is the standard nucleophilic substitution by $B^{\ominus}$ on the γ-carbon atom to form (VIII) and the second is the removal of bromine from the γ-carbon together with a hydrogen atom from a neighbouring carbon, i.e. an elimination reaction with the formation of an N-allylarylamine (IX).



Clearly, the nature of $B^{\ominus}$ and the solvent may have a marked effect on the course of the reaction and by varying the conditions, the ratio of products should also vary. It is common for elimination and substitution reactions to occur together, but

the stronger the nucleophilicity of $B^{\ominus}$, the greater will be the tendency for elimination to take place[12]. Hence, in this case, increasing the strength of $B^{\ominus}$ as a nucleophile (e.g. from hydroxide to t-butoxide) should result in an increased yield of (IX) with respect to (VIII).

It is not possible, from these considerations, to deduce the probable effect of the nature of $B^{\ominus}$ on the yield of (VII). It is clear, however, that some basic conditions are required to ensure that the nitrogen lone pair is free to attack the γ-carbon atom.



In order to obtain the optimum conditions for the formation of N-arylazetidines, this reaction was therefore studied under a variety of basic conditions.

Besides the reaction conditions, the other factor which may influence the course of the reaction is the nature of the substituent group Y. This effect should be negligible in reactions involving only the γ-carbon atom, i.e. formation of (VIII) and (IX); on the other hand, the substituent Y is likely to have a marked influence on the ease of azetidine ring formation.

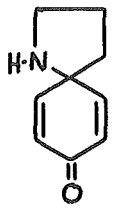
It can be seen that the greater the electron density around the nitrogen, the more readily should ring closure take place.

Thus, electron donor groups in the para position of the benzene ring would be expected to facilitate the formation of the azetidine ring while electron-withdrawing para substituents should retard the reaction.

In order that this effect might be examined, it was proposed that a number of intermediates should be prepared, with the group Y varying in its electronic effect. The proposed substituents were Y=H, CH_3-, Cl-, CH_3O-, and HO-.

If the above deduction is correct, then the yield of N-arylazetidine should increase in the order Y=Cl < H < CH_3 < HO < CH_3O.

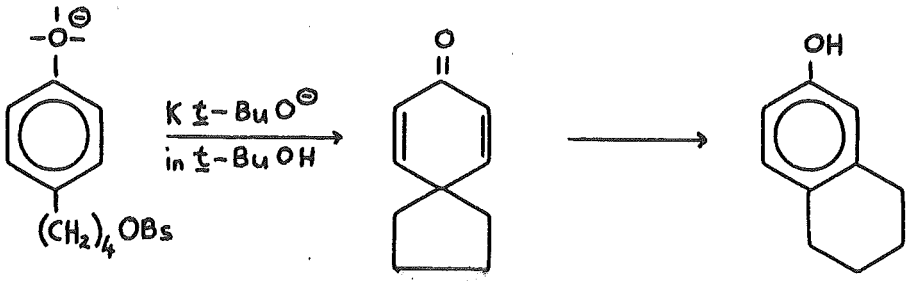
The case of Y=HO- is unique among these compounds in that, under basic conditions, there is also the possibility of formation of 1,4-dihydro-4-oxocyclohexa-2,5-dienespiro-2'-pyrrolidine (X).



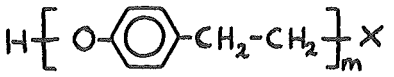
(X)

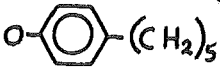
It was proposed, if time allowed, to examine this possibility in detail.

Analogous homocyclic spiro compounds have been isolated. Winstein and Baird[13] reported isolation of spiro -[4:5] - deca - 1,4-dien-3-one (XI) by the treatment of 4-p-hydroxyphenyl - 1 - butyl p-bromobenzenesulphonate with a slight excess of potassium t-butoxide in anhydrous t-butanol. This compound was found to rearrange quantitatively to 5,6,7,8 - tetrahydro-2-naphthol (XII) in a special case of the dienone - phenol rearrangement[14].



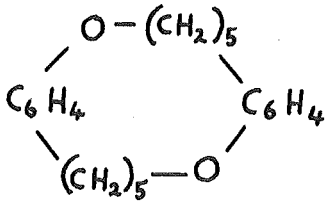
(XI) (XII)

The same workers[15] also prepared spiro-[2:5] -octa - 1,4-dien-3-one,  =O, (XIII) by passing an ethereal solution of 2-p-hydroxyphenyl -1- ethyl bromide through a column of basic alumina. By using dry, neutral glassware, it was possible to isolate the product by evaporating off the ether. While an ether solution of the dienone, at a concentration of 5×10^{-3}M, could be kept for about a week, the solid was not stable for more than 20-30 minutes due to the formation of the polymeric ether  (XIV). Solvolytic opening of the three-membered ring was found to occur readily under basic, neutral, or acid conditions; for example, the half-life of the dienone at 25° in 10^{-5}M methanolic perchloric acid proved to be less than ten seconds.

Dreiding[16] reported the preparation of spiro-[5:5]- undeca-1,4 - dien -3-one,  =O, (XV) by heating a 0.00156M solution of  in t-butanol in a sealed tube at 170°. Besides formation of the dienone, concurrent intermolecular O-alkylation occurred.

i.e.  etc. (XVI)

As the concentration of the reaction mixture was increased, it was found spectroscopically that the yield of spiro compound decreased, while that of the ether (XVI) increased. In 0.0068M solution, besides the dienone, a small amount of a further neutral substance was formed and it was suggested that this was the cyclic ether (XVII).



(XVII)

From this short review it is clear that these spiro compounds are difficult to prepare and that they are unstable, ring-opening occurring readily under a variety of conditions.
Preferential formation of polymeric ethers, e.g. (XIV), (XVI), and (XVII), which reduce the dienone yield still further, make the preparation more difficult.

A priori, there appeared to be no reason why a preparation of 1,4-dihydro-4-oxocyclohexa-2,5-dienespiro-2^1-pyrrolidine(X), by a procedure somewhat analagous to that used for spiro-[4:5]-deca-1,4-dien-3-one (XI), should not be feasible. Models of (X) and (XI) indicated that neither ring was particularly strained sterically, and that the amount of strain was approximately the same in both cases. On steric grounds then, the ease of preparation of (X) should be comparable with that of (XI).

Electronically, however, there is one difference between the two. With N-(3-bromopropyl)-p-hydroxyaniline, some conjugation between the nitrogen and the ring must occur, which

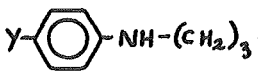
would give partial double bond character to the bond. The atomic arrangement favourable to such conjugation is unfavourable to spiro formation. This should not be a major barrier to the formation of the hetero-spiro ring however, because, in the aminophenol, cross conjugation involving the phenolic hydroxyl is present, and the energy lost in attaining a conformation more favourable to spiro formation should be quite small.

Experimentally, the difficulties associated with aminophenols would also be expected to make preparation of (X) a greater problem. The presence of the basic amino and acidic phenol groups in the one compound would increase the difficulties accompanying separation and extraction procedures. As with the homocyclic spiro compound (XI), the presence of the phenoxide ion in alkaline solution would enhance the possibility of polymer formation (see XVI).

It was hoped, however, to obtain at least some positive evidence if the compound did indeed exist, even if isolation proved impracticable.

The programme of work to be attempted was then as follows:-

(1) The preparation of intermediates of the type

 where Y=H, CH_3, Cl, CH_3O, HO.

(2) An investigation of their decomposition under various basic conditions in an attempt to prepare N-arylazetidines.

(3) For the case in which Y=HO, an investigation into the possibility of forming 1,4-dihydro-4-oxocyclohexa-2,5-dienespiro-2'-pyrrolidine (X).

II.

EXPERIMENTAL

(1) GENERAL ACCOUNT

Four N-arylazetidines were successfully synthesised. These were N-phenylazetidine, N-(p-tolyl) azetidine, N-(p-chlorophenyl) azetidine, and N-(p-methoxyphenyl) azetidine.
All were prepared by a method which is considered to be of general application; it involves the cyclisation of the appropriate para - substituted N-(3-bromopropyl) aniline hydrohalide under basic conditions.

In the preparation of these straight-chain intermediate compounds, a "general" method was again used, except in the cases of N-(3-bromopropyl) - p - anisidine hydrochloride and N-(3-bromopropyl) -p-hydroxyaniline hydrobromide which are mentioned below.

Rindfusz and Harnack[17] prepared N-(3-hydroxypropyl) aniline by refluxing a mixture of aniline, 3-chloropropan-1-ol, and anhydrous sodium carbonate. After filtering and washing the residue with ether, the product was collected by distillation.

The method adopted in the present work utilised 3-bromopropan-1-ol, which had the advantage of reacting more rapidly than 3-chloropropan-1-ol. The bromopropanol was prepared by the method of Bogert and Slocum[18]. This consisted of passing dry hydrogen bromide gas into trimethylene glycol at a low temperature and distilling the resultant mixture. This reaction was repeated several times to obtain a quantity of bromopropanol adequate for subsequent preparations. It was found more convenient to use

100 ml. portions of the glycol, rather than to carry out the reaction on a much larger scale, because of the length of time required to form a reasonable amount of product.

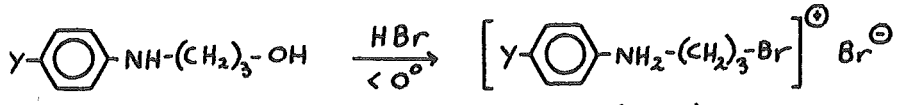
In the preparation of the intermediates, this bromopropanol was condensed with an excess of the arylamine. The result was the elimination of hydrogen bromide and the formation of an alcohol (XVIII). The method of Rindfusz and Harnack was altered here in that sodium carbonate was not included in the reaction except in the case of p-hydroxyaniline. Rather, the reaction mixture was made alkaline and the product (XVIII) extracted with ether.

(XVIII)

y = H, CH_3, Cl, CH_3O, HO.

This method of extraction could not be used when Y=HO because the product, being a phenol, would have been soluble in the alkaline layer; in this case, therefore, the hydrogen bromide formed was removed by shaking the solution with the appropriate amount of sodium carbonate (cf. Rindfusz and Harnack above). This resulted in evolution of carbon dioxide and precipitation of sodium bromide.

The alcohol formed in this preparation was subsequently treated with cold concentrated hydrobromic acid. This replaced the alcoholic hydroxyl group by bromine and resulted in the formation of the hydrobromide salt (XIX).



(XIX)

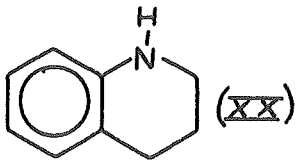
In the first preparation of N-(3-bromopropyl) aniline hydrobromide (XIX ; Y=H), the N-(3-hydroxypropyl) aniline (XVIII) was isolated and purified by distillation before treatment with hydrobromic acid. However, in a subsequent preparation, this was not done. The entire material remaining after the ether and excess aniline were removed was cooled and treated with concentrated hydrobromic acid. This was time-conserving and it resulted in an increased yield of product. This modified method was then used in the preparation of the other intermediates.

This conversion of alcohol to hydrobromide salt could not be used in the case formwhich Y=CH_3O, because concentrated hydrobromic acid reacts with ethers of the type Ar-O-R to form phenols, Ar-O-H. The procedure was therefore modified, and, in this case, bromination was carried out with phosphorus tribromide. Because of the ease of purification, it was decided to make a salt of the product rather than attempt to isolate the neutral compound. As hydrogen chloride does not readily convert aryl-alkyl ethers into phenols, the hydrochloride salt was made so that the final compound was N-(3-bromopropyl) - p-anisidine hydrochloride. The action of hydrobromic acid on N-(3-hydroxypropyl) -p-anisidine was made the basis for an alternative preparation of N-(3-bromopropyl) -p-hydroxyaniline hydrobromide.

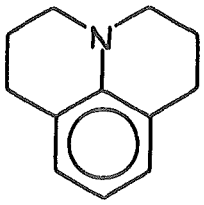
After the intermediates were prepared, the reaction of the unsubstituted compound, i.e. Y=H, under different basic conditions

was studied in order to obtain the optimum conditions for formation of the azetidine ring.

The reaction was first carried out in hot (100°) 50% sodium hydroxide solution (cf. reaction (1) p. 3). Under these conditions the main reaction was expected to be formation of the substitution product, N-(3-hydroxypropyl) aniline, together with a small amount of the elimination product, N-allylaniline, and possibly some N-phenylazetidine. However, solubility difficulties were encountered here and the reaction mixture became very viscous. After extraction with ether, distillation yielded 1,2,3,4-tetrahydroquinoline (XX) and julolidine (XXI) only.



(XX)



(XXI)

These two products were also found when N-(3-bromopropyl) aniline hydrobromide was dry distilled, the inference being that the hydroxide had not in fact reacted with the N-(3-bromopropyl) aniline.

The nucleophilicity of the cyclising agent was then markedly increased in an effort to obtain some N-phenylazetidine. The reaction was carried out in t-butanol as solvent using potassium t-butoxide as cyclising agent. It was expected that under these conditions there would be a decrease in the amount of substitution product with a corresponding increase in the yield of elimination product and, as postulated, the main product was N-allylaniline. However, no evidence for the presence of any N-phenylazetidine was obtained, i.e., the elimination reaction proceeded to the virtual

exclusion of the cyclisation product.

When this experiment was first carried out, the ether, N-(3-ethoxypropyl) aniline, was isolated. Its formation was traced to the presence of ethanol in the t-butanol used and the lower alcohol would of course have reacted preferentially with the added potassium to form potassium ethoxide. Before repeating the experiment, the t-butanol was treated with neutral potassium dichromate, which oxidised the ethanol, and the pure t-butanol was collected after fractionation.

As neither hydroxide nor the much stronger nucleophile t-butoxide had resulted in the formation of N-phenylazetidine, it was then decided to use intermediate conditions. The actual method followed here was analogous to that used by Heine, Kapur, and Mitch[19] for the preparation of the closely related N-phenylethylenimine from N-(2-bromoethyl) aniline hydrobromide and involved the use of a sodium hydroxide / water / ethanol mixture.

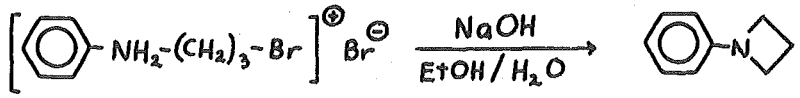
This alcoholic sodium hydroxide solution would contain free ethoxide ions, which are intermediate in nucleophilic character between hydroxide and t-butoxide. Under these conditions, both the unsaturated elimination product, N-allylaniline, and the substitution product, N-(3-ethoxypropyl) aniline, would be expected as major products, together with an unpredictable amount of N-phenylazetidine.

It was experimentally found that the low boiling fraction of the final distillation contained a very small amount of material which, on isolation, proved to be N-phenylazetidine. The major reaction product was N-(3-ethoxypropyl) aniline as expected. Apart from high boiling material, assumed to be polymeric products, the other isolated

reaction product was N-allylaniline which was present in even smaller quantity than the azetidine.

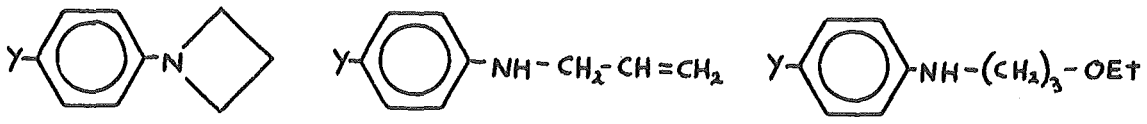
It was found that halving the amount of ethanol in the reaction mixture had no apparent effect on the course of the reaction. The main product was still the ether and the yield of N-phenylazetidine was not increased.

From these experiments, it was concluded that the best conditions for N-phenylazetidine formation were provided by the reaction using the sodium hydroxide / water / ethanol conditions.



Cyclisation of the other intermediates under these conditions was then attempted. With the exception of the <u>para</u> - hydroxy compound, i.e. Y=OH, which behaved anomalously and will be dealt with later, all were successful in varying degrees.

With one exception, all gave the same isolated products:-



(XXII) (XXIII) (XXIV)

For Y=CH_3O, however, the major product was not the ether (XXIV) but the alcohol, N-(3-hydroxypropyl)-<u>p</u>-anisidine, and indeed no definite ether fraction was obtained. The relative amounts of (XXII) and (XXIII) were found to depend on the nature of Y, and the ratio of N-arylazetidine to N-allylarylamine increased in the order Y=Cl < H < CH_3 < CH_3O.

The chief experimental difficulty encountered in all cases was in

the separation of the elimination product from the N-arylazetidine. The situation when Y=H may be taken as typical. In the distillation of the final residue, the first fraction collected gave the analytical figures expected for N-phenylazetidine, viz:-

	C	H	N
% Found	80.5	8.34	10.62
% Calculated	81.20	8.27	10.53

However, the infrared spectrum of the crude fraction showed the presence of an N-H fundamental stretching vibration at 2.95 μ which indicated that something other than the N-phenylazetidine was present. This led to the conclusion that the fraction consisted of a mixture of N-phenylazetidine and N-allylaniline, both of which have the same molecular formula. Separation of the two was finally effected by gas chromatography and the pure compounds were isolated. The machine used for this purpose was a Beckman Megachrom Preparative Gas Chromatograph. The N-allylaniline was characterised by comparison of the infrared spectrum with that of an authentic sample.

This chromatographic procedure was used in all other preparations and in each case the elimination product passed through the column first, closely followed by the N-arylazetidine. The azetidines were identified by the absence of an N-H peak, and presence of a tertiary aromatic amine C-N peak in their infrared spectra (p.20). With N-phenylazetidine and N-(p-tolyl) azetidine, the picrates also were prepared. From the peak areas of the Megachrom recorder graph, the relative amounts of (XXI) and (XXIII) could be obtained.

Only very small quantities of all products were obtained from the Megachrom. The collection efficiency of the column traps is extremely

high for a component volume in excess of 2ml.. Below this, however, the efficiency declines markedly due to the decreased surface area available for condensation of the component. As the total volume of the sample injected into the Megachrom was generally less than 2ml., some material was not trapped; as a result, only small samples of the pure compounds were obtained. In the cases of N-(p-chlorophenyl) azetidine and N-(p-methoxyphenyl) azetidine, amounts of product sufficient only for an infrared spectrum were obtained.

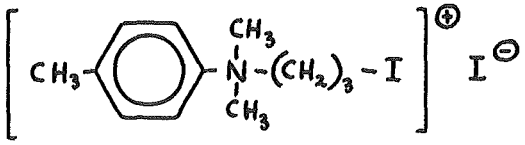
An attempt was made to prepare the hydrobromide salt of N-phenylazetidine. It was found that on treatment with cold, concentrated hydrobromic acid, the azetidine ring opened and the straight-chain compound, N-(3-bromopropyl) aniline hydrobromide, was formed. This was shown to be so by a mixed melting point with an authentic sample of the compound. It is interesting to note that N-allylaniline, when treated under the same conditions, yielded a salt which analysed to $C_9 H_{12} Br$, i.e., $\left[C_6H_5\text{-}NH_2\text{-}CH_2\text{-}CH{=}CH_2\right]^{\oplus} Br^{\ominus}$. The hydrobromic acid did not add across the double bond under these conditions.

Hydrogen bromide gas was produced in a bromine - tetralin generator and, after drying over calcium chloride and phosphorus pentoxide, was bubbled through a solution of N-phenylazetidine in sodium-dried ether. As with the aqueous hydrobromic acid, the ring opened and the straight chain hydrobromide was formed.

When this experiment was repeated using an ethereal solution of N-(p-tolyl) azetidine, the result was again cleavage of the ring and the formation of N-(3-bromopropyl)-p-toluidine hydrobromide.

These experiments indicated that N-arylazetidines are unstable under acid conditions. This was to be expected by analogy with the behaviour of azetidine itself with acid[20].

An attempt was also made to prepare the methiodide of N-(p-tolyl) azetidine. Once again, however, the ring was cleaved under these conditions with the formation of a compound which analysed to N-methyl-N-(3-iodopropyl)-p-toluidine methiodide.

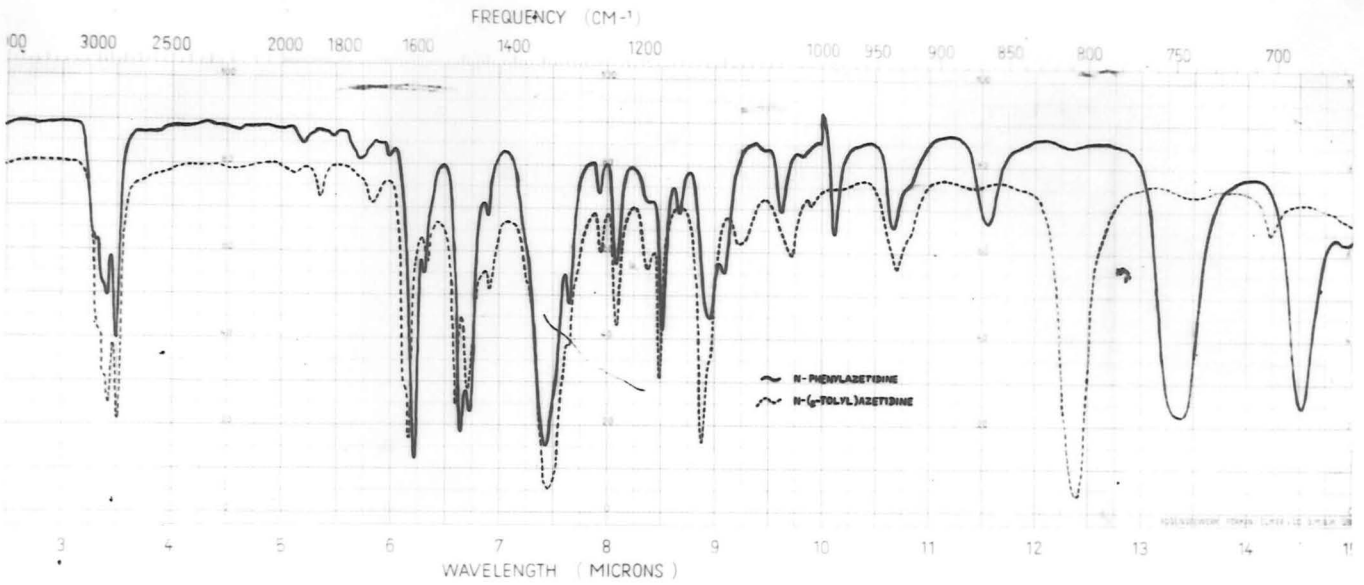


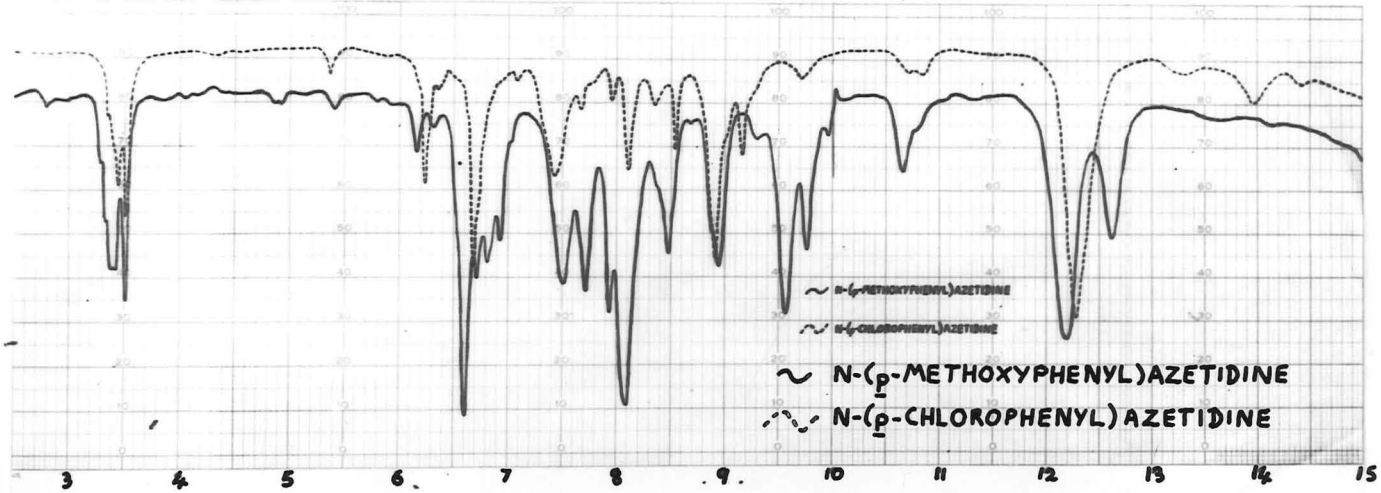
The infrared spectra of the N-arylazetidines (p20) proved to be most helpful in their identification. Two features in particular were very useful. First, all N-arylazetidines exhibited an aromatic tertiary amine C-N fundamental stretching frequency in their spectra at 7.4-7.5μ. On the other hand, the spectra of all elimination products, e.g. N-allylaniline, showed an aromatic secondary amine C-N stretching frequency at 7.6μ . This shift, though small, was quite clear and unmistakable in all cases.

The second major characteristic of the N-arylazetidine spectra was the absence of an N-H fundamental stretching vibration at 2.95μ. This very sharp clear peak was present in all spectra of the elimination and substitution products as expected.

As the N-arylazetidines were the only tertiary amines possible in the experiments carried out, these spectral peaks were a valuable aid in their identification.

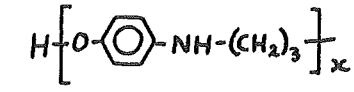
For N-(3-bromopropyl)-p-hydroxyaniline hydrobromide, the possibility of forming both N-(p-hydroxyphenyl) azetidine and 1,4-


FREQUENCY (CM⁻¹)
3000
2500
2000
1800
1600
1400
1200
1000
950
900
850
800
750
700
N-PHENYLAZETIDINE
N-(p-TOLYL)AZETIDINE
3
4
5
6
7
8
9
10
11
12
13
14
WAVELENGTH (MICRONS)


N-(p-METHOXYPHENYL)AZETIDINE
N-(p-CHLOROPHENYL)AZETIDINE
3
4
5
6
7
8
9
10
11
12
13
14
15

dihydro-4-oxocyclohexa-2,5-dienespiro-2'-pyrrolidine required investigation. However, no experimental evidence for either was found in preliminary work carried out in the time available.

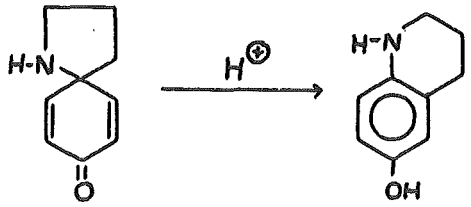
From other N-arylazetidine preparations, the best conditions for the formation of N-(p-hydroxyphenyl) azetidine were expected to be those involving the sodium hydroxide / water / ethanol mixture. However, the reaction of N-(3-bromopropyl) -p-hydroxyaniline hydrobromide under these azetidine-forming conditions differed from that of the other intermediates.

After completion of the reaction, the reaction mixture was extracted with ether and the aqueous layer treated to yield a phenolic precipitate. Attempts at isolating components of this material by recrystallisation, chromatography, and acetylation were unsuccessful. The ether extract, on evaporation, yielded a brown powder which, from its low solubility in common organic solvents and its high molecular weight, was taken to consist of polymeric substances, probably of the type  .

In the attempted preparation of 1,4-dihydro-4-oxocyclohexa-2,5-dienespiro-2'pyrrolidine, a dilute solution of potassium t-butoxide in t-butanol was used as the cyclising agent, as in the preparation of analogous compounds mentioned earlier (pp7-8). Chromatography, with both activated and deactivated alumina, was used in an attempt to isolate the product after the reaction. However, the solutions emerging from the column, on evaporation, invariably gave intractable tars or brown powders which were insoluble in most solvents. None of these was successfully recrystallised and all charred and shrank

before melting at high temperatures.

After numerous unsuccessful attempts at isolating the components of the reaction mixture, a different reaction scheme was followed in an attempt to gain some evidence for the presence of the dienone. Any spiro compound present in the reaction mixture was separated from the phenolic material and was treated with concentrated acid to convert it into 1,2,3,4-tetrahydro-6-quinolinol by the dienone-phenol rearrangement.



By analogy with the instability of spiro- [4:5] - deca - 1,4 - dien - 3 - one (see p.8), this reaction should proceed rapidly. However, no evidence for the presence of any quinolinol was subsequently obtained.

(2) EXPERIMENTAL DETAILS

General: (1) Melting points are uncorrected.

(2) All analyses were carried out in the Microanalytical Laboratory at the University of Otago.

(A) Preparation of intermediates :-

3-Bromopropan-1-ol: Redistilled trimethylene glycol (100 ml., 157g.; b.p. 126°/21mm.) was placed in a 250 ml. flask on an ice-salt bath. Dry hydrogen bromide gas, produced from a tetralin-bromine generator, was bubbled through the glycol for 5 hours. A white complex gradually formed. This dissolved on warming and on distilling at 20mm., 1,3-dibromopropane passed over at 68°. The crude 3-bromopropan-1-ol was collected at 80-110°. This was fractionated at 24mm. and the 3-bromopropan-1-ol (73g., 25.6%) collected at 88-90°.

N-(3-Hydroxypropyl)aniline: Redistilled aniline (103g.; b.p. 182-185°) was placed in a 250 ml. flask fitted with dropping funnel, stirrer, and condenser. To this was added, dropwise and with stirring, 3-bromopropan-1-ol (25g.) and the temperature was maintained at 55° by means of a water bath. After completion of the addition, the reactants were heated together at 55° for a further 1½ hours and then left to cool. During the reaction, the solution gradually turned dark red and crystals of aniline hydrobromide were formed.

The contents of the flask were transferred to a separating funnel, ether (300 ml.) was added, and the solution was made slightly alkaline with dilute sodium hydroxide solution. The red ether layer was

separated, washed three times with water, and dried over magnesium sulphate.

After removing the ether by distillation at atmospheric pressure, excess aniline was distilled off under reduced pressure (b.p. 72°/ 10mm.) and the residue was distilled at 11mm.. N-(3-Hydroxypropyl) aniline (24g., 88.5%) was collected at 172-179°. (b.p. 173-180°/10mm - Beilstein 12,II,190)

N-(3-Bromopropyl) aniline hydrobromide:

(a) N-(3-Hydroxypropyl) aniline (20g.) was cooled below 0° and hydrobromic acid (60 ml., S.G. 1.48), precooled below 0°, was added slowly, with shaking. After standing for 1½ hours, the mixture was fractionated until constant - boiling hydrobromic acid passed over (124°) and then left for 2 hours.
The product crystallised out. One recrystallisation from absolute ethanol, followed by one from 20% ethanol / 80% benzene, yielded N-(3-bromopropyl) aniline hydrobromide (25g., 64%), m.p. 131-132°.

Analysis:-	C	H	N
% Found	36.82	4.63	4.75
% Calculated	36.61	4.41	4.75

The compound was further characterised by neutralising a small sample with dilute sodium hydroxide solution and extracting with ether. The ether was evaporated off, leaving N-(3-bromopropyl) aniline.

Analysis:-	Br
% Found	37.10
% Calculated	37.38

(b) In a further preparation, using 500g. of aniline and 140g. of 3-bromopropan-1-ol, the N-(3-hydroxypropyl) aniline was not purified by distillation, but the entire material remaining after excess aniline had been removed was cooled below 0°. On treatment with cold, concentrated hydrobromic acid as before, the dark tar which formed on cooling dissolved, and the solution turned dark blue. After fractionation and crystallisation, the final yield of product (m.p. 132°) was 177g. (60%) after two recrystallisations. The overall yield in method (a) was 56.5%.

N-(3-Bromopropyl)-p-toluidine hydrobromide: The method followed was analogous to that used in the preparation of N-(3-bromopropyl) aniline hydrobromide by method (b) p. 25. From 3-bromopropan-1-ol (70g.) and redistilled p-toluidine (180g.; b.p. 84°/10mm.) was obtained N-(3-bromopropyl)-p-toluidine hydrobromide. This had m.p. 151° (55g., 33%) after three recrystallisations from absolute ethanol.

Analysis:-	C	H	Br
% Found	38.63	4.65	51.80
% Calculated	38.83	4.85	51.78

N-(3-Bromopropyl)-p-chloroaniline hydrobromide:

3-Bromopropan-1-ol (75g.) was added, dropwise and with stirring, to redistilled p-chloroaniline (125g.;b.p. 120°/13mm.). For this reaction the temperature was maintained at 80° to avoid solidification of the solvent (m.p. 71°). The remainder of the preparation was analogous to that used in preparing N-(3-bromopropyl) aniline hydrobromide by method (b) p.25 . After two recrystallisations

from absolute ethanol, N-(3-bromopropyl) -p- chloroaniline hydrobromide, (110g, 62%) m.p. 175-176°, was obtained.

Analysis:-	C	H	N	Halogen
% Found	33.17	3.63	3.96	59.2
% Calculated	32.78	3.64	4.25	59.33

N-(3-Hydroxypropyl) -p- anisidine: Redistilled p-anisidine (115g.; b.p. 128°/15mm.), dissolved in absolute ethanol (100ml.), was placed in a 500ml. flask fitted with stirrer, condenser, and dropping funnel. To this was added, dropwise and with stirring, 3-bromopropan-1-ol (75g.), and the temperature was maintained at 70° by means of a water bath. The reactants were heated together at 70° for a further 1½ hours after the addition was complete.

Water (100ml.) was added and the ethanol (70ml.) was distilled off. The remaining solution was cooled, ether (750ml.) was added, and the solution was made slightly alkaline with dilute sodium hydroxide solution. The red ether layer was separated, washed three times with water, and dried over magnesium sulphate.

After removing the ether at atmospheric pressure, excess p-anisidine was distilled off under reduced pressure, and the residue was distilled at 1mm. N-(3-Hydroxypropyl) -p-anisidine (31g., 32%) was collected at 153-160°; n_D^{23} 1.5560.

Analysis:-	C	H	N
% Found	66.45	8.76	7.50
% Calculated	66.30	8.29	7.73

N-(3-Bromopropyl) -p- anisidine hydrochloride:

N-(3-Hydroxypropyl) -p- anisidine (30g.), in benzene (300ml.), was placed in a 500ml. flask fitted with stirrer, condenser, and dropping funnel. Phosphorus tribromide (15g.), in benzene (100ml.), was added dropwise, and with stirring, and the temperature was maintained at about 5° by means of an ice bath. Stirring was continued at 5° for 30 minutes after completion of the addition, and then for 30 minutes at room temperature. A cream tar formed in the bottom of the flask. The mixture was then heated at 60-70° on a water bath for 5 hours.

Water was added and the tar dissolved to give an acid solution. This was made slightly alkaline with dilute sodium hydroxide solution and the layers were separated. The aqueous layer was extracted with ether and the combined benzene and ether extracts were washed thoroughly with water and dried over magnesium sulphate.

Dry hydrogen chloride gas (produced by dropping concentrated sulphuric acid on ammonium chloride and dried over concentrated sulphuric acid and phosphorus pentoxide) was bubbled through the light yellow solution. The white crystals of N-(3-bromopropyl) -p-anisidine hydrochloride which formed were filtered off and washed with ether. After recrystallisation from 20% ethanol / 80% benzene, the product (23g., 40%) had m.p. 139-141°.

Analysis:-	C	H	Halogen
% Found	42.77	5.54	40.49
% Calculated	42.78	5.35	41.18

N-(3-Bromopropyl) -p- hydroxyaniline hydrobromide:

(a) From p-hydroxyaniline:- A mixture of 3-bromopropan-1-ol (150g.) and absolute ethanol (400ml.) was placed in a 1 litre flask fitted with condenser, stirrer, and wide-mouthed funnel. The temperature was maintained at 50° on a water bath. To this was added, slowly and with stirring, recrystallised p-hydroxyaniline (118g.). After completion of the addition, the solution was refluxed until all p-hydroxyaniline had disappeared and was then left for 1 hour.

Sodium carbonate (57g.) was added and the flask shaken until carbon dioxide evolution ceased. Sodium bromide was precipitated. This was filtered off and washed with ethanol. Almost all the ethanol was removed from the filtrate under reduced pressure. As the volume of the solution was decreased, a small amount of sodium bromide precipitated out and this was filtered off. On standing, the residue turned to a dark tar.

This residue was cooled below 0° and shaken with precooled hydrobromic acid (500ml., S.G.1.7). The tar dissolved and the solution turned dark blue. This was allowed to stand for 2 hours and was then fractionated until constant boiling hydrobromic acid passed over (124°). The residue was placed in a vacuum desiccator and the N-(3-bromopropyl)-p-hydroxyaniline hydrobromide crystallised out. After two recrystallisations from absolute ethanol, the yield was 130g. (38.7%) and had m.p. 170-171°.

Analysis:-	C	H	Br
% Found	34.54	4.41	50.78
% Calculated	34.73	4.18	51.45

(b) From p-anisidine:- 3-Bromopropan-1-ol (100g.) and redistilled p-anisidine (230g.; b.p. 128°/ 15mm.) were used and the method was analogous to that adopted for the preparation of N-(3-bromopropyl) aniline hydrobromide, except that the temperature was maintained at 70° on a water bath to avoid solidification of the p-anisidine (m.p. 59°). Method (b) p. 25 was then followed through and yielded N-(3-bromopropyl)-p-hydroxyaniline hydrobromide. After recrystallisation twice from absolute ethanol and twice from 20% ethanol / 80% benzene, 52.5g. (25%) of product, m.p. 170-171°, was obtained.

Analysis:-	C	H	Br
% Found	34.35	4.09	51.69
% Calculated	34.73	4.18	51.45

(B) The reaction of N-(3-bromopropyl) aniline hydrobromide under various basic conditions:-

(i) Sodium hydroxide: N-(3-Bromopropyl) aniline hydrobromide (25g.) was added to a solution of sodium hydroxide (12.5g.) in water (25ml.), and the resultant solution was heated to 100°. A red oil formed in the bottom of the flask and after 10 minutes rose to the surface of the liquid. A continuous increase in viscosity was noted as the reaction proceeded.

After 45 minutes, ethanol (25ml.) was added and the mixture again heated for 30 minutes but the viscous red oil did not dissolve. The ethanol was distilled off under reduced pressure and the residue was extracted with ether (100ml). The ether layer was separated, washed with water, and dried over potassium carbonate.

Distillation at atmospheric pressure removed the ether, and the red, oily residue was distilled at 23mm. Decomposition took place

and hydrogen bromide fumes were evolved, which indicated that the alkali had not removed all bromine from the starting material. 1,2,3,4-Tetrahydroquinoline and julolidine were obtained. The former was identified by its boiling point, comparison of the infrared spectrum with that of an authentic sample, and refractive index, n_D^{25} 1.5929. [Handbook of Chemistry and Physics - $n_D^{23.9}$ 1.5933]. Julolidine was identified by a mixed melting point of the hydrobromide salt with that of an authentic sample.

(ii) Potassium t-butoxide: t-Butanol was treated with neutral potassium dichromate, to oxidise the ethanol impurity, and was then fractionated. Potassium (6.63g.) was dissolved in this ethanol - free t-butanol (250ml.) in a 500 ml. flask fitted with stirrer, condenser, and wide-mouthed funnel. N-(3-Bromopropyl) aniline hydrobromide (24g.) was added, slowly and with stirring, and the temperature was maintained at 50-55° by means of a water bath. Potassium bromide was precipitated and the solution became orange in colour. After completion of the addition, the temperature of the water bath was raised to 85-90° for 1 hour. The solution was then left to stand for 2 hours.

Potassium bromide was filtered off and washed with ether. The ether and t-butanol were removed from the filtrate under reduced pressure. The residue was distilled through a Vigreux column at 1mm. and two main fractions were obtained.

	Temperature	Weight	Appearance
(1)	72-78°	3.8g.	Yellow liquid
(2)	125-145°	3.2g.	Colourless liquid which turned orange on standing.

Fraction (1) was redistilled through a Vigreux column at 1mm. and the fraction with b.p. 72-74° (n_D^{20} 1.5645) was collected. The boiling point and infrared spectrum indicated that the product was N-allylaniline and this was confirmed by analysis.

Analysis:-	C	H
% Found	81.01	8.51
% Calculated	81.20	8.27

Fraction (2) above was expected to be N-(3-t-butoxypropyl) aniline. However, on redistillation no definite fraction was obtained, there being continuous distillation from 50-140°/1mm. A sample, b.p. 134-138°/1mm., on analysis gave figures incompatible with those for any expected compound.

When this experiment was first carried out, using untreated t-butanol, a fraction b.p. 158-162°/24mm. (n_D^{27} 1.5320) was obtained. The infrared spectrum showed an acyclic ether peak at 9μ. The boiling point, refractive index, and spectrum indicated that this was the ethyl ether, N-(3-ethoxypropyl) aniline. Analysis of a redistilled sample (b.p. 154-156°/22mm.) was in accord with this identification.

Analysis:-	C	H	N
% Found	74.11	9.70	7.72
% Calculated	73.74	9.50	7.82

(iii) Sodium hydroxide / water / ethanol: Preparation of N-phenylazetidine: N-(3-Bromopropyl) aniline hydrobromide (24g.) was dissolved in water (35ml.) and 96% ethanol (40ml.). This solution was added, dropwise and with stirring, to a mixture of sodium hydroxide solution (32ml., 6N) and 96% ethanol (80ml.) in a 250ml. flask fitted with stirrer, condenser and dropping funnel.

During the addition, the temperature was maintained at 50° by means of a water bath. After completion of the addition, the temperature was raised to 85° for 1 hour.

Ethanol (90ml.) was distilled off, at which point the flask contents separated into two layers. The residue was cooled to room temperature and extracted with three 100 ml. portions of ether. The combined ether extracts were washed with water. This water was then added to the aqueous layer which was subsequently extracted with a further 100ml. of ether. The total ether extract was dried over magnesium sulphate and then distilled to remove the ether and remaining ethanol.

The residue was distilled through a Vigreux column at 11mm. and two main fractions were obtained.

	Temperature		Weight	Appearance
(1)	104-112°		1.1g.	Colourless liquid
		$n_D^{15.5}$	1.5658	
(2)	130-150°		3.7g.	Colourless liquid

Fraction (1): The components of this fraction were separated by gas chromatography and samples of N-phenylazetidine and N-allylaniline were obtained. The former was a colourless liquid, $n_D^{23.5}$ 1.5695, whose identity was confirmed by the infrared spectrum (p. 20) and analysis.

Analysis:-	C	H	N
% Found	80.93	8.35	10.80
% Calculated	81.20	8.27	10.53

The N-allylaniline was identified by a comparison of the boiling

point and infrared spectrum with those of the N-allylaniline obtained in the previous experiment.

From the peak areas on the Megachrom recorder graph it was deduced that the ratio of N-phenylazetidine to N-allylaniline was approximately 2:1.

The picrate of N-phenylazetidine formed in ethanol. This was recrystallised from ethanol to give yellow needles, mp. 110°.

Analysis:-	C	H	N
% Found	49.83	4.26	15.40
% Calculated	49.72	3.87	15.47

Fraction (2): This was redistilled through a Vigreux column at 10mm. and N-(3-ethoxypropyl) aniline ($n_D^{22.5}$ 1.5338) was collected at 142-144°. Its identity was confirmed by the characteristic acyclic ether peak in the infrared spectrum at 9μ and by analysis.

Analysis:-	C	H	N
% Found	73.69	9.01	8.09
% Calculated	73.74	9.50	7.82

(C) Preparation of other N-arylazetidines:-

(i) N-(p-Tolyl) azetidine: N-(3-Bromopropyl) -p- toluidine hydrobromide (25g.), dissolved in water (35ml.), and 96% ethanol (40ml.) was allowed to react with a mixture of sodium hydroxide solution (32ml., 6N) and 96% ethanol (80ml.). The procedure was analogous to that followed in the preparation of N-phenylazetidine.

The final residue was distilled through a Vigreux column at 9mm. to yield two main fractions.

	Temperature	Weight	Appearance
(1)	112-116°	1.0g.	Light yellow liquid
(2)	148-154°	1.1g.	Colourless liquid $n_D^{12.5}$ 1.5358

Fraction (1): The components of this fraction were separated by gas chromatography and samples of N-(p-tolyl) azetidine and another component were obtained. The former was a white solid (m.p. 34°) and the latter a yellow oil which, by analogy with the preparation of N-phenylazetidine, was taken to be the elimination product, N-allyl-p-toluidine.

In a subsequent preparation, using 50g. of N-(3-bromopropyl)-p-toluidine hydrobromide, the fraction distilling at 112-118°/9mm. solidified in the collecting flask. This was recrystallised from absolute ethanol and yielded N-(p-tolyl) azetidine (0.9g.), m.p. 37° .

That this was indeed the required product was shown by the infrared spectrum (p. 20) and an analysis.

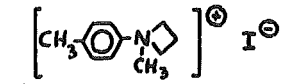
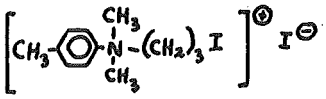
Analysis:-	C	H	N
% Found	81.2	8.85	9.84
% Calculated	81.63	8.84	9.52

The picrate formed in ethanol. This was recrystallised from ethanol, washed with ether, and had m.p. 122-123°.

Analysis:-	C	H	N
% Found	51.49	4.56	14.50
% Calculated	51.06	4.26	14.89

A small amount of N-(p-tolyl) azetidine was dissolved in excess methyl iodide. The solution was warmed for 5 minutes and then cooled on an ice-salt bath. A methiodide was precipitated. This

was recrystallised from ethanol to yield a light-yellow powder, m.p. 136°.

Analysis:	C	H	N
% Found	33.45	4.67	2.70
% Calculated for 	45.67	5.54	4.84
% Calculated for 	33.41	4.41	3.25

This indicates that the azetidine ring is cleaved by methyl iodide under the conditions used.

Fraction (2): The infrared spectrum of the crude fraction showed the characteristic acyclic ether peak at 9μ and by analogy with the preparation of N-phenylazetidine, this was taken to be N-(3-ethoxypropyl)-p-toluidine.

(ii) N-(p-Chlorophenyl) azetidine: A slurry of N-(3-bromopropyl)-p-chloroaniline hydrobromide (27g.) in 96% ethanol (40ml.) and water (35ml.) was added to 96% ethanol (80ml.) and sodium hydroxide solution (32ml., 6N) under the same conditions as in the preparation of N-phenylazetidine.

The final residue was distilled through a Vigreux column at 1mm. and yielded two main fractions.

	Temperature	Weight	Appearance
(1)	94-102°	1.0g.	Yellow liquid n_D^{16} 1.5800
(2)	120-130°	4.1g.	Colourless liquid n_D^{16} 1.5500

Fraction (1): The components of this fraction were separated by gas chromatography and samples of N-allyl-p-chloroaniline and N-(p-chlorophenyl) azetidine were obtained. The former appeared as

a yellow oil and was identified by a comparison of its infrared spectrum with that of N-allylaniline. The azetidine appeared as a light-yellow solid, m.p. 34-37°, but was obtained in insufficient quantity for further purification and analysis. The infrared spectrum (p.20) was, however, compatible with this identification.

From the peak areas on the Megachrom recorder graph, it was deduced that the ratio of N-(p-chlorophenyl) azetidine to N-allyl-p-chloroaniline was approximately 1:10.

Fraction (2): This was redistilled through a Vigreux column at 1mm. and the N-(3-ethoxypropyl)-p-chloroaniline (n_D^{19} 1.5472) was collected at 128-130°.

Analysis:-	C	H	N
% Found	62.26	7.63	6.55
% Calculated	61.83	7.49	6.56

The infrared spectrum showed a characteristic acyclic ether peak at 9 μ.

(iii) N-(p-Methoxyphenyl) azetidine: N-(3-Bromopropyl)-p-anisidine hydrochloride (22g.), dissolved in 96% ethanol (40ml.) and water (35ml.), was added to a mixture of absolute ethanol (80ml.) and sodium hydroxide solution (28ml., 6N) under the same conditions as in the preparation of N-phenylazetidine.

The final residue was distilled through a Vigreux column at 1mm. and yielded two main fractions.

	Temperature	Appearance
(1)	98-110°	Light-yellow liquid
(2)	152-166°	Colourless liquid

The components of fraction (1) were separated by gas

chromatography. By analogy with the preparation of N-phenylazetidine, the first compound to pass through the column was taken to be N-allyl-p-anisidine. This was closely followed by N-(p-methoxyphenyl) azetidine in quantity sufficient only for an infrared spectrum (p. 20) which was consistent with this identification. From the peak areas on the Megachrom recorder graph, it was deduced that the ratio of N-(p-methoxyphenyl) azetidine to N-allyl-p-anisidine was approximately 7.5:1.

Fraction (2) above was redistilled through a Vigreux column at 1mm. and the fraction b.p. 158-160° (n_D^{22} 1.5562) was collected. The refractive index, boiling point, and infrared spectrum indicated that this was N-(3-hydroxypropyl)-p-anisidine and not N-(3-ethoxypropyl) -p-anisidine. The analytical figures were in accord with this identification.

Analysis:-	C	H	N
% Found	66.38	8.61	7.43
% Calculated	66.30	8.29	7.73

(D) Other reactions:

(i) The action of an ethanol / sodium hydroxide / water mixture on N-(3-bromopropyl)-p-hydroxyaniline hydrobromide:- A mixture of sodium hydroxide solution (40ml., 6N) and 96% ethanol (100ml.) was placed in a 250ml. flask fitted with stirrer, wide-mouthed funnel, and condenser. A slurry of N-(3-bromopropyl)-p-hydroxyaniline hydrobromide (30g.) in water (40ml.) and 96% ethanol (50ml.) was added, slowly and with stirring, and the temperature of the reaction was maintained at 50° by means of a water bath. After the addition was complete, the temperature of the water bath was raised to 85° for 1 hour.

The colour of the solution changed from light green to dark brown as the reaction proceeded.

Ethanol (120ml.) was distilled off. The residue was cooled and extracted with three 70ml. portions of ether. The aqueous layer, which was dark coloured and alkaline, was made acid with dilute hydrobromic acid. A brown precipitate formed. This was filtered off to yield 12g. of material (m.p. ca.100° after charring) which could not be successfully recrystallised. Lassaigne's sodium fusion test gave a positive test for nitrogen but negative for bromine, and the material also gave positive phenol tests, e.g., a white precipitate with bromine water and a dark coloration with ferric chloride. Attempts at isolation of components of this mixture by chromatography and acetylation were unsuccessful.

The ether extract above was washed with water, dried over magnesium sulphate, and evaporated to dryness. An orange-red powder (5g.;m.p. 90-96°), largely insoluble in ethanol and acetone, was left . A sodium fusion test showed that the powder contained nitrogen but no bromine and an isopiestic molecular weight determination indicated that the molecular weight of the material was 500. The conclusion was thus reached that this material was polymeric in nature.

(ii) The action of potassium t-butoxide on N-(3-bromopropyl) -p-hydroxyaniline hydrobromide:- Potassium (3.8g.) was dissolved in t-butanol (1250ml.) in a 3 litre flask on a water bath at 50-55°. N-(3-Bromopropyl)-p-hydroxyaniline hydrobromide (15g.) was added slowly and with shaking. The solution immediately turned green. After completion of the addition, the temperature was raised to 85° for 1 hour. Potassium bromide was precipitated and the solution gradually changed

colour to orange-brown.

The potassium bromide was filtered off and washed with ether. Ether (1000ml.), water (550ml.), and a small quantity of 10% sodium hydroxide solution were added to the filtrate.

The sodium hydroxide would cause separation of phenolic material (soluble in alkali) from any 1,4-dihydro-4-oxocyclohexa-2,5-dienespiro-2'-pyrrolidine which would be soluble in ether. The yellow ether layer was washed with 1% sodium hydroxide solution until the aqueous layer was colourless, and then washed three times with water.

Hydrochloric acid (100ml., 5N) was added to the ethereal solution and the mixture was stirred vigorously for 1½ hours, the purpose being to convert any dienone into 1,2,3,4- tetrahydro-6-quinolinol (see P 22.). The acid layer after this treatment was slightly yellow in colour.

The solution was then made alkaline to extract any quinolinol from the ether layer. After separation and washing with ether, the alkaline layer was neutralised with dilute hydrochloric acid and evaporated to dryness. Sodium chloride, together with some material sufficient only to impart a yellow colour to the sodium chloride, was left. This was refluxed for a short while with absolute ethanol, undissolved sodium chloride was filtered off and the filtrate was evaporated to dryness. This extraction was repeated several times, but the total product, merely a yellow smear on the bottom of the flask, was insufficient to test for the presence of any quinolinol.

III.

DISCUSSION

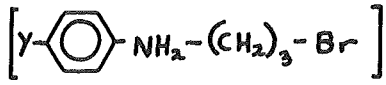
In the syntheses of N-arylazetidines (described in the previous section) the yield, irrespective of the nature of the para- substituent, was never high. This may be ascribed to the inherent difficulty of forming the strained four-membered ring and the relative ease with which other, more stable products could be formed under the reaction conditions. Gabriel and Weiner[1] originally produced azetidine from 3-bromopropylamine hydrobromide and alkali. Schaeffer[21] repeated this preparation and obtained a variable yield of organic base (6-26%). No attempt was made to establish how much of this base was azetidine itself, but the yield clearly was not very great. As Schaeffer stated, "it is apparent that azetidine formation was only a minor side-reaction accompanying condensation reactions".

In the present work, the amounts of each azetidine formed were not sufficient for a satisfactory comparison of percentage yields, However, as stated earlier, the Megachrom recorder graph offered a means of estimating the relative amounts of cyclisation and elimination which took place. The experimentally observed trend in the ratio of N-arylazetidine to N-allylarylamine, viz, that the proportion of azetidine increased as the electron-donating power of the para-substituent increased, was to be expected from the theoretical considerations mentioned in the introduction (p. 6).

The essential condition for the formation of N-arylazetidines, by the dehydrobromination of N-(3-bromopropyl) arylamines, is that the nitrogen electron lone pair is available to attack the γ-carbon atom.

To ensure that this condition is fulfilled, it is necessary that the para-substituent should be electron-donating or only weakly electron-withdrawing. The very small amount of N-(p-chlorophenyl) azetidine obtained would seen to indicate that the chloro substituent represents the deactivation limit compatible with practicable N-arylazetidine formation.

There appears to be no reason why ortho- and meta- substituted N-arylazetidines could not be prepared in the same manner. As deactivating substituents in general have their greatest electron-withdrawing effect on the ortho and para positions, then it may be possible to prepare meta-substituted N-arylazetidines in which the substituent has a greater withdrawing power than chlorine. For example, while the p-nitro substituent would be too deactivating, N-(m-nitrophenyl) azetidine could perhaps be produced and the yield of N-(m-chlorophenyl) azetidine would certainly be expected to be greater than that of N-(p-chlorophenyl) azetidine. For o-substituted N-arylazetidines, steric factors would need to be considered. A bulky o-substituent could hinder the approach of the γ-carbon atom, and subsequent ring formation, thus further complicating the preparation.

It is of interest that in the preparation of the straight-chain intermediates,  , the yield varied with the electronic effect of Y. However, in this case, the trend was in the opposite direction to that noted in N-arylazetidine formation, i.e., the yield of intermediate increased in the order $Y=CH_3O- < HO- < CH_3- < H < Cl$. This order was unexpected as, in the initial condensation of bromopropanol with the arylamine, it was assumed that

para electron-donating substituents in the benzene ring, which would make the nitrogen more nucleophilic, would aid the reaction. The reason for the observed trend is not clear but it may in part be due to a concurrent elimination reaction taking place with the formation of allyl alcohol from the bromopropanol.

The tendency for this reaction to take place would increase as the nucleophilicity of the arylamine increased.

One further feature of the present work requires comment. This was the failure to obtain evidence for the existence of any 1,4-dihydro-4-oxocyclohexa-2,5-dienespiro-2'-pyrrolidine. It is possible that only a minute quantity of the dienone may have been formed and could readily have been missed. On the other hand, if a reasonable quantity had been formed, it must have been very unstable under the alkaline conditions (cf. spiro-[2:5]-octa-1,4-dien-3-one p. 8) and hence have broken down rapidly to phenolic material, i.e., it had only a transient existence.

Furthermore, a noticeable feature of the reported preparations of analogous homocyclic spiro compounds[13,15,16] was the very dilute reaction conditions used in each case, e.g., Dreiding[16], in his work, used 0.00156M solution. Bearing in mind the difficulties accompanying separation and isolation of the product from such dilute solutions, it had been decided that in the preliminary investigations undertaken in the present work, more concentrated solutions (ca. 0.04M) would be used to facilitate handling of the product. In the above preparations,

polymeric products were common. Clearly, the more concentrated the solution, the greater would be the probability of polymer formation. The presence of the electron-donating amino group in N-(3-bromopropyl)-p-hydroxyaniline would make any phenoxide ion present in alkaline solution more nucleophilic than in the case of 4-(p-hydroxyphenyl)-1-bromobutane. This would make polymer formation even more probable. Thus the necessity for working with very dilute solutions is greater with the aminophenol. It is therefore possible that further experiments, which involve more dilute solutions, may prove successful in providing evidence for the formation of the spiro compound.

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