SYNTHESIS OF QUINOLINE BASES OF POSSIBLE ANTIMALARIAL ACTIVITY: SYNTHESIS OF DERIVATIVES OF 8-METHYLQUINOLINE AND 8-AMINOCARBOSTYRIL

by

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THESIS

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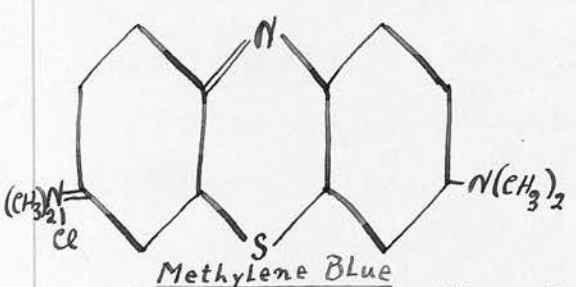
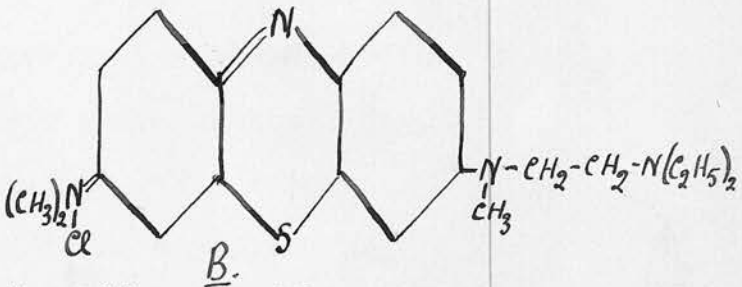
Contents

INTRODUCTION

The first definite advance in the preparation of synthetic antimalarials dates from the discovery that methylene blue had some effect on the quartan parasite. About ten years ago, it was found by Schulemann (Proc. Roy. Soc. Med., 25, 897) that the compound B showed an increase in anti-malarial



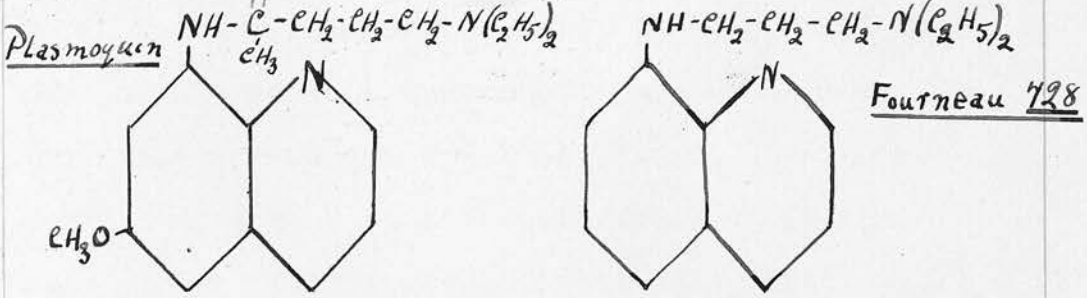
Methylene Blue



B.

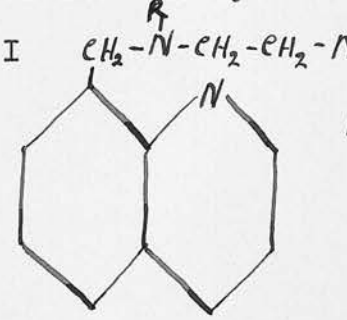
activity compared with methylene blue itself. By following up the evidence obtained above and employing the technique elaborated by Roehl, in which canaries are used as test animals, it was found that, when 8-aminoquinoline was subjected to a similar modification, compounds of marked antimalarial activity were produced. The best known compound of this type is plasmoquin or 8-[δ-diethylamino-α-methyl-butylamino]-6-methoxyquinoline, but other compounds of similar type but varying somewhat in detail are now being employed for the treatment of human malaria. These include plasmocide or Fourneau 728 which is

8-[γ-diethylaminopropylamino]-quinoline.



Fourneau 498

Compounds of the plasmocide group are essentially quinoline derivatives with a basic side chain containing two nitrogen atoms through one of which the side chain is attached to the nucleus in the 8-position. It appeared to be of considerable interest to find out if antimalarial activity would result when one of the nitrogen atoms of the side chain was not directly attached to the nucleus. When it is remembered that the side chain, in the case of quinine, is attached to the nucleus through a CHOH group, there seems to be no a priori reason for thinking that the linkage through nitrogen is essential. It was therefore decided in the first place to examine methods for the synthesis of compounds of the type I



R = H, Me etc.

I

The results of this work are described in Section I

of this thesis. Tests carried out by Dr Keilin under the auspices of the Chemo-therapy Committee showed that none of the compounds synthesised exhibited any antimalarial activity. At the same time, they are of considerable interest in that they possess fairly marked local anaesthetic activity. They have been tested in this respect by Professor Clark and Dr Sinha of the Pharmacological Department of Edinburgh University and the following table gives a brief summary of some typical results.

Novocaine = Cocaine in human wheal

Name of Compound	Toxicity Cocaine=1	Activity Cocaine=1
Di-[quinolyl-8-methyl-]-piperazine.	·75	7
Di-[quinolyl-8-methyl-]-aminoethyldiethylamine	2·5 - 3	12
8-[β-diethylaminoethyl-alkylamino(methyl)-]-quinoline.		
When alkyl group= CH_3	1	3
= C_2H_5	1	4
= C_3H_7	1	5
=iso-C_4H_9	1	8 - 9 (irritant)

N.B. A similar series of results were obtained from the corresponding 8-[β-piperidinoethylalkyl-aminomethyl-]-quinolines.

The above results were obtained by the method employing a rabbit's cornea. Since novocaine cannot be tested by this method, a comparison by the method of the human wheal ~~method~~ is quoted.

It is of interest to note that Bovet has shown that compounds of the plasmoquin type, especially those with a methoxy or ethoxy group in position 6 and a branched side_chain in position 8, also demonstrated considerable local anaesthetic activity.

In this work various efforts to synthesise compounds bearing a methoxy group in position 6 proved unsuccessful, whilst the side chain has been limited to two nitrogen atoms separated by a straight chain of two carbon atoms. Nevertheless, as will be seen from the above table, some of the compounds possess quite high activity. It would appear that the local anaesthetic action is a much more general and less highly specific property in relation to chemical constitution than is antimalarial action.

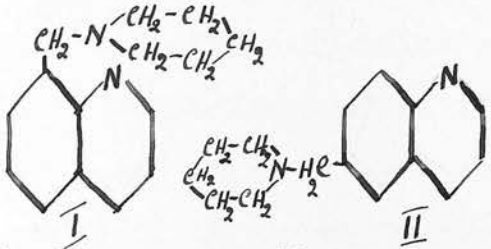
In Section II various experiments are described which were carried out with the object of preparing compounds of the plasmoquin type but derived from 8-aminocarbostyril instead of 8-aminoquinoline. For reasons described in detail later this object was not attained, but the various observations of chemical interest, which were made in the process of the work, are presented.

In the course of the attempts to synthesise the

methoxy derivatives of the compounds described in Section I a bromo derivative of 6-methoxy-8-methyl-quinoline was isolated and elucidation of the exact constitution of this compound necessitated the carrying out of a series of experiments which are described in Section III.

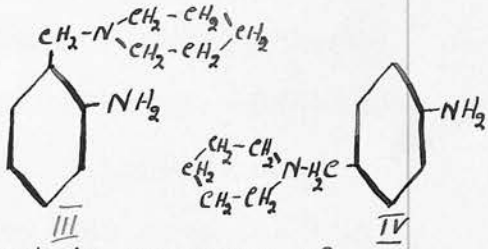
THE SYNTHESIS OF ω-SUBSTITUTED DERIVATIVES OF 8-METHYL QUINOLINE

By means of the Skraup Reaction, Kermack and Muir (unpublished) had already obtained 8-[piperidinomethyl-]-quinoline (I) and 6-[piperidinomethyl-]-quinoline (II) from o- and p-amino-[piperidinomethyl-]-benzenes (III and IV) respectively.



I

II

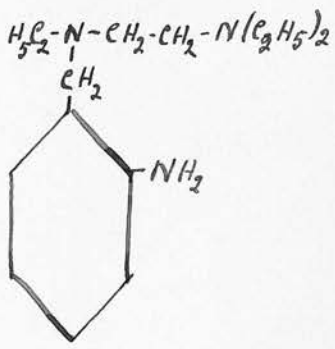


III

IV

The Skraup reaction was carried out in presence of ferrous sulphate and boric acid which decreased the vigour of the reaction sufficiently to prevent any extensive decomposition.

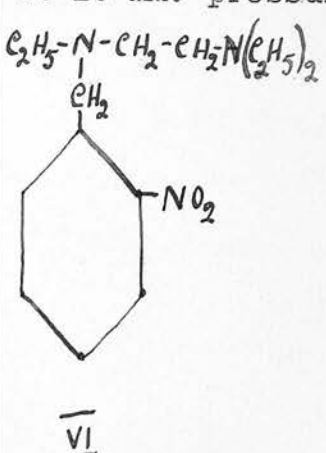
An attempt was now made to extend this synthesis to include the preparation of bases having two or more nitrogen atoms in the side chain. The first method proposed was to prepare o-amino-[β-diethyl-aminoethylethylaminomethyl-]-benzene (V) and subject it to the Skraup Reaction.



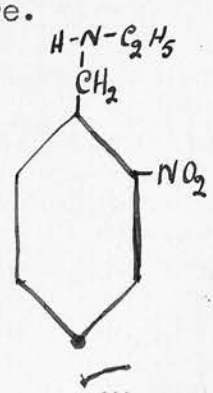
V

The starting materials were o-nitrobenzyl chloride and β-diethylaminoethanol. In the first place, the latter was converted into β-diethylaminoethyl chloride hydrochloride by means of thionyl chloride (Gough and King, J.C.S. 1928, 2436).

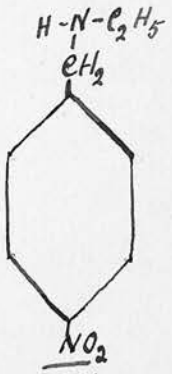
In order to obtain the desired intermediate compound o-nitro-[β-diethylaminoethylethylaminomethyl]-benzene (VI), ethylamine was condensed with o-nitrobenzyl chloride (c.f. C.Wolff Ber.1892, 25, 3038) in sufficient alcohol to dissolve the nitro-compound readily. After refluxing in presence of potassium carbonate, the o-nitrobenzylethylamine (VII) was separated from unchanged o-nitrobenzyl chloride by extraction with acid. The acid extract, on basifying and extracting with ether, yielded a brown coloured oil, b.p.149° at 15 mm. pressure. p-Nitrobenzyl chloride (c.f. Paul and Springer, Ber., 1897, 30, 63), on similar treatment, yielded p-nitrobenzylethylamine (VIII) as a viscous light brown oil, b.p. 160° at 16 mm. pressure.



VI



VII

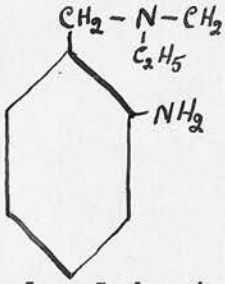


VIII

o-Nitrobenzylethylamine also condensed readily with β-diethylaminoethyl chloride, in benzene solution, in presence of a little copper bronze and potassium carbonate; when a higher boiling solvent was employed, extensive tarring took place. Any excess of o-nitrobenzylethylamine could readily be recovered from the reaction mixture by taking advantage of the insolubility of its hydrochloride in acetone. The acetone-soluble hydrochlorides were converted into picrates by adding an alcoholic solution of picric acid to the free bases in alcohol. After extraction of the brownish yellow oily picrates with hot alcohol, a residue was obtained which proved to be the dipicrate of the desired compound. It was isolated as light yellow needles, m.p.167°-168° on recrystallising the residue from a large volume of water. The base was obtained by decomposing the picrate with dilute alkali and extracting with ether. No appreciable change in the yield or purity of the product could be obtained by varying the proportions of the two reactants, for example, by using two molecules of o-nitrobenzylethylamine to one molecule of β-diethylaminoethyl chloride.

Reduction was carried out by West's method

(c.f. J.C.S. 1925, 494). The product was obtained as a light yellowish brown coloured oil which contained an amino group, as shown by the diazo reaction, but which did not appear to be pure, as it yielded a picrate which failed to melt sharply. The impurity was probably unchanged nitro compound, but this was no disadvantage as, in the Skraup synthesis, the corresponding nitro compound may be employed as oxidising agent; for example, in the synthesis of (I) Kermack and Muir (loc. cit.) used a mixture of o-amino and o-nitrobenzylpiperidines. The impure o-amino-[β-diethylaminoethylethylaminomethyl-]-benzene (IX) was boiled



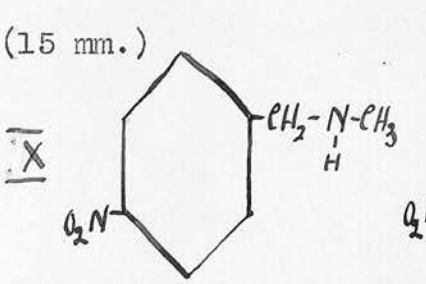
IX

up with arsinic and sulphuric acids in presence of ferrous sulphate. When the reaction mixture was worked up, a basic oil was obtained from which, however, no crystalline picrate or other salt could be separated.

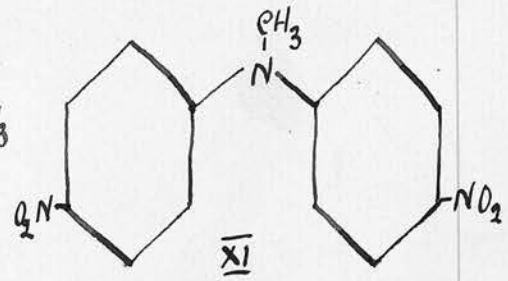
In addition to o-nitro-[β-diethylaminoethylethylaminomethyl-]-benzene, attempts were made to prepare

the corresponding p-compound but all attempts to cause β-diethylaminoethyl chloride to react with p-nitrobenzylethylamine failed to yield a definite product.

The next scheme of synthesis involved the preparation of p-nitrobenzylmethylamine (X) (c.f. Paul and Springer, Ber., 1898, 30, 62). The latter proved rather difficult to obtain in large quantities owing to the tendency of the p-nitrobenzyl chloride to react with two rather than with one molecule of methylamine. The base was finally obtained in about 30 per cent yield by heating the chloride with an excess of methylamine in a sealed tube at 60°-70° for about two hours. Di-[p-nitrobenzyl-]-methylamine (XI) formed as a by-product separated out as orange crystals which were filtered off. On working up the filtrate the base remained as a brown oil b.p. 156° (15 mm.)



X

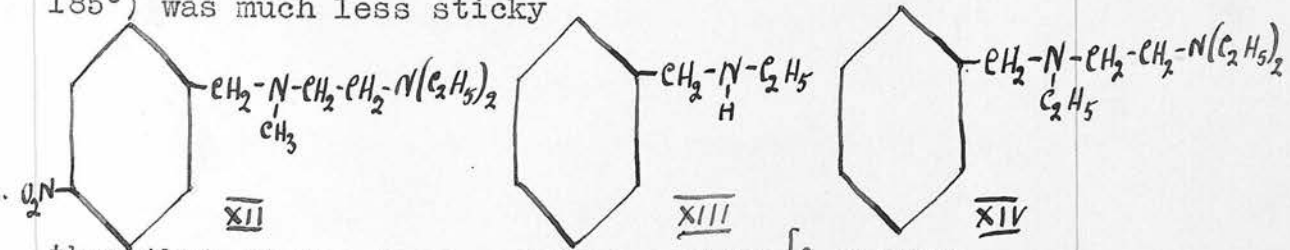


XI

In contrast to the behaviour of p-nitrobenzylethylamine it was found that this condensed readily in benzene solution with β-diethylaminoethyl chloride. When hydrogen chloride was passed into the resulting

yellowish-brown solution, an amorphous white salt was precipitated. This salt was dissolved in hot acetone and filtered from a small quantity of insoluble residue. P-Nitro-[β-diethylaminoethylmethylaminomethyl-]-benzene (XII) recovered from the acetone, formed a picrate which recrystallised from alcohol as minute plates (m.p.195°-197°). The yields in the above stages were, however, not very satisfactory and so this line of investigation has not been further pursued.

Finally, an attempt was made to obtain o- and p-nitro-[βdiethylaminoethylethylaminomethyl-]-benzenes in the following manner. Benzyl chloride was condensed with ethylamine to produce benzyl ethylamine (XIII) (c.f. Kraft, Ber., 1890, 23, 2781) in about fifty per cent yield. This compound readily condensed, in benzene solution, with β-diethylaminoethyl chloride to yield β-diethylaminoethylethylaminomethylbenzene (XIV). The hydrochloride (m.p.183°-185°) which was much less sticky



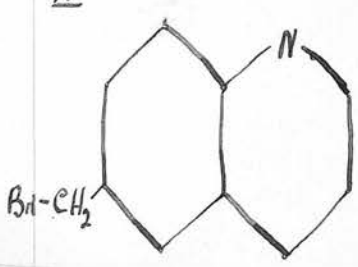
XII XIII XIV

than that of the corresponding o-nitro-[β-diethylaminoethylethylaminomethyl-]-benzene was recrystallised from acetone, decomposed and converted into a picrate

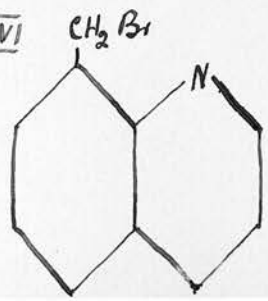
which, after recrystallisation, melted at 151°-152°. The base was nitrated in a mixture of concentrated sulphuric acid and glacial acetic acid at 0°-5°. The resultant nitro compounds were separated by pouring into water and making alkaline when the base was extracted with ether and distilled in vacuo. Three fractions were obtained which distilled at 156°-160° (19 mm.), 165°-175° (18 mm) and 200°-210° (16 mm). Many attempts to recrystallise the picrates from these three fractions failed to yield any pure product as they invariably separated in an oily or sticky condition and were obviously impure. The failure to obtain crystalline picrates demonstrated fairly definitely that the fractions were not pure, but probably consisted of mixtures of the o, m and p derivatives with one preponderating in each fraction.

On account of these difficulties it was decided to explore a somewhat different line of approach and to attempt to obtain the desired bases by condensation of 6 or 8-ω-bromomethylquinoline (XV and XVI) with the appropriate aliphatic amines. For this purpose, p- and o-toluidines were readily converted into the corresponding quinolines by the Skraup Synthesis (c.f.

XV

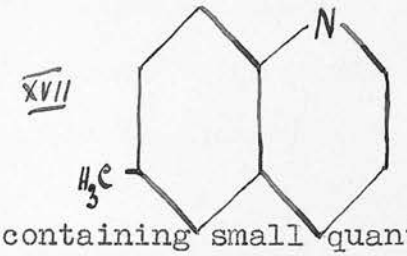


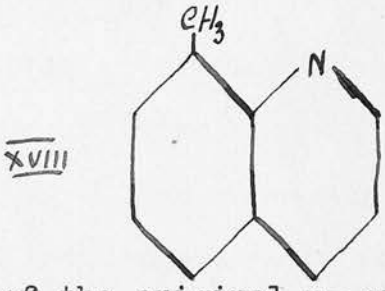
XVI



Meyer and Jacobson, Vol II, part 3, pp.938-940).

A 60 per cent yield was obtained in both cases when the reaction was carried out with ferrous sulphate, glycerol, arsinic acid as oxidising agent, and 96 per cent sulphuric acid. The reaction mixture was made alkaline and, on steam distillation, a light yellow oil was obtained which was the desired 6- or 8-methyl-quinoline (XVII and XVIII)





containing small quantities of the original p- and o-toluidines respectively. The latter were readily converted into the corresponding cresols through their respective diazo compounds. The relatively pure 6- and 8-methylquinolines were now obtained by steam-distilling the alkaline liquid and extracting the distillate with ether.

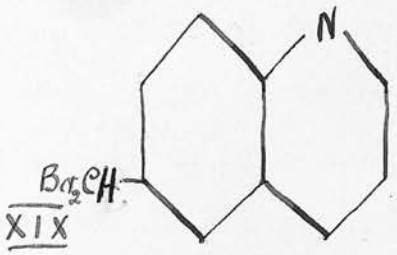
The bromination of 6- and 8-methylquinolines had already been studied by Müller and Lang (Inaug. Dissert. Univ. Freiburg, 1897). Howitz and Philipp (Ann., 1912, 396, 33) obtained a dibromo addition product of the hydrobromide of 6-methyl-quinoline in the following way. Dry hydrogen bromide was

passed into a solution of the methylquinoline in two to three times its volume of chloroform until the former was all converted into the hydrobromide. The bromo-addition product was readily formed when one molecule of bromine was added drop by drop with cooling and separated out on standing as a fine, reddish, crystalline deposit. It was found that the same method could be applied to prepare the bromo-addition product of 8-methylquinoline, but in order to increase the yields of 8-ω-brommethyl-quinoline a modification was introduced. In the original method considerable quantities of tar were formed at a later point in the preparation. This appeared to be related to the fact that it was difficult to prevent the hydrobromide of the 8-methyl-quinoline separating out from the chloroform. On addition of bromine the latter was quickly covered with a layer of insoluble dibromo-addition product with the result that the final product contained a large proportion of unchanged 8-methylquinoline hydrobromide. It was considered probable that the tar was due to the bromo_addition product tending to condense with the excess 8-methylquinoline

leading to the formation of a quaternary salt. This difficulty was overcome by using larger volumes of chloroform so that no separation of the hydrobromide occurred. Furthermore, it appeared advantageous to avoid clumping by stirring continuously during the addition of the bromine. When these modifications were employed, the product came down as a fine reddish orange crystalline deposit which was separated and dried.

The bromo addition products of 6- and 8-methylquinoline reacted differently on heating. In the case of the former, Howitz and Philipp found that, after heating for two hours at 170°-180°, in spite of a large evolution of hydrogen bromide, no bromo compound could be separated from the sticky reaction product. However, in other experiments, the reaction mixture, after heating for one and a half hours at 170° was allowed to cool to 140° and a second molecule of bromine added. When the reaction was completed by further heating for an hour and a half at 170°, a red-coloured, glassy mass remained which was extracted with hot water. The 6-ω-dibrommethylquinoline (XIX), which precipitated on adding alkali, recrystallised from alcohol as rose-coloured

needles (m.p.159°-160°).



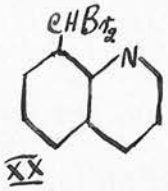
XIX

With the dibromo addition product of 8-methylquinoline, somewhat different results were obtained. Howitz and Nöther (Ber., 1906, 39, 2709) described an efficient method of working up the reaction product although they referred to the original authors, namely, Müller and Lang, for the details of the actual reaction. The bromo addition product, on heating, first melted at 120° and then gave off hydrogen bromide steadily until, after about two hours heating at 140°, it solidified into a yellowish, crystalline mass. This was extracted with a mixture of equal volumes of concentrated sulphuric acid and water when a small quantity of tar separated out. If the addition product was prepared by the modified method described above, the quantity of tar formed was quite small, especially if the heating was carried out at 160° for two to three hours, instead of at 140° for four hours. The solution obtained above was now poured into a large amount of water when 8-ω-dibrommethylquinoline, (XX) m.p.140°, which is insoluble

in dilute acids, separated out. After standing a short time (it is essential that the solution should not stand too long as the 8-ω-monobrommethylquinoline slowly crystallises out), the solution was filtered and the filtrate basified with sodium hydroxide and filtered. The 8-ω-monobrommethylquinoline after drying recrystallised from petrol-ether as needles (m.p. 84°). This compound had a highly irritant action on the skin and eyes as well as on the mucous membrane of the nose. The highest yield of 8-ω-monobrommethylquinoline obtained from 100 gm. of 8-methylquinoline was 45 gm. Usually about 30 to 40 gm. of unchanged 8-methylquinoline, contaminated with 8-ω-monobrommethylquinoline, were recovered, whilst the average yield of 8-ω-dibrommethylquinoline was approximately 10 gm. but varied considerably in different experiments.

The 8-ω-brommethylquinoline, obtained in this way, reacted readily with primary and secondary amines. With aniline a vigorous reaction took place in the cold, giving orange-coloured crystals. After completing the reaction on the water bath, making alkaline, and steam distilling the excess aniline off,

8-anilinomethylquinoline (XXI) separated as a dark



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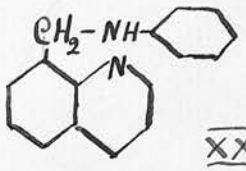
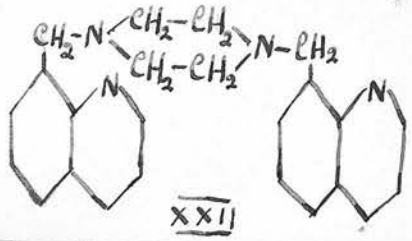


XXI

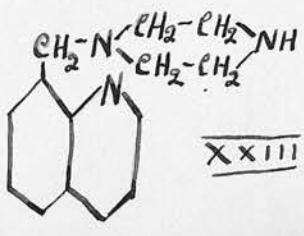
brown amorphous solid which recrystallised from alcohol and water as light brown plates, m.p.71°-73°. The salts were insoluble in water and the base was therefore unsuitable for testing therapeutically.

8-ω-Brommethylquinoline also reacted readily with piperidine in benzene solution to form the hydrobromide of a base which was extracted with dilute hydrochloric acid. After basifying the extract, the oil which separated was taken up in ether from which it was recovered. The resultant light brown oil yielded a monopicrate when a saturated alcoholic solution of picric acid was added gradually to its alcoholic solution. The melting point of this picrate after recrystallisation from alcohol was 183°, whilst the melting point of the corresponding picrate prepared by the method of Kermack and Muir (c.f.page 9.) was 179°. A mixture of the two melted at 180°. Though the picrate of the base prepared from the Skraup reaction is somewhat more orange in colour than that obtained by the method described above, it seems highly probable that this and the

slightly lower melting point are both due to small quantities of tarry material which are difficult to remove entirely. For the preparation of derivatives of 8-methylquinoline of this type the new method is superior to the method employed by Kermack and Muir (loc.cit.) both in the yield and in the quality of the product. One molecule of piperazine condensed with two molecules of 8-ω-brommethylquinoline to yield di-[quinolyl-8-methyl-]-1,4-piperazine (XXII). This compound was obtained as a light brown oil which solidified on standing. Recrystallisation from an alcohol-water mixture produced small plates, m.p.153°-154°. Like many derivatives of piperazine, this compound gave up its water of crystallisation only with difficulty and analysis showed that it still retained a half molecule of water after one hour's heating at 100°. The bromine content of the tetra-hydrobromide was slightly below that which was calculated for the above. This may be due to its containing alcohol (or water) of crystallisation or to its containing some tri- or dihydrobromide as impurity. In any case, the the only other possibility, namely, that it is the mono derivative of piperazine (8-ω-piperazinomethylquinoline XXIII) is excluded



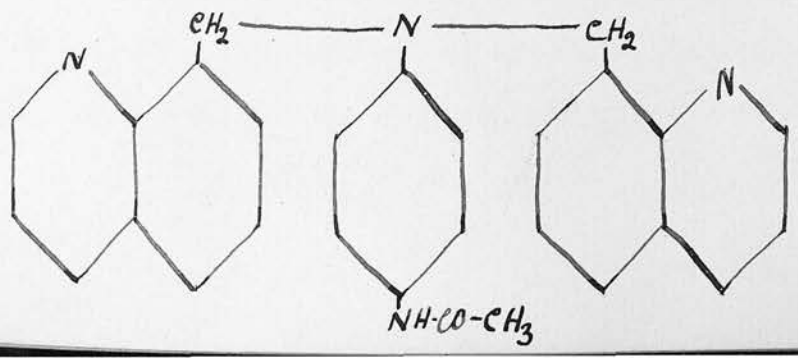
XXII



XXIII

by the analytical results. It is to be noted that no monoquinolyl derivative of piperazine could be obtained even when considerable excess of piperazine was employed. This observation is in accordance with the well-known difficulty of obtaining mono-derivatives of this (c.f. Moore, Boyle and Thorn, J.C.S. 1929, 39). For chemo-therapeutic purposes a tartrate was also prepared by adding an alcoholic solution of tartaric acid to the base in alcohol. The light buff coloured precipitate obtained dissolved in hot alcohol and separated, ~~from~~ on cooling, as plates, m.p.185°-186°.

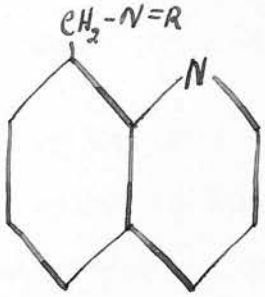
P-Aminoacetanilide condensed readily with 8-ω-brommethylquinoline in alcoholic solution. The light yellow coloured hydrobromide which separated from the dark coloured liquid was filtered and the base recovered by heating with dilute alkali. The red coloured, amorphous base dissolved readily in alcohol from which it separated as ruby coloured plates, m.p.237°. This, on analysis, proved to be di-[quinolyl-8-methyl]- p-amino acetanilide (XXIV).



XXIV

Owing to the insolubility of the base in dilute acids it was impossible to test its chemo-therapeutic activity.

In order to prepare bases of the type (XXV) it



XXV

was necessary to condense 8-ω-brommethylquinoline with polybasic amines containing at least one primary or secondary nitrogen atom. For this purpose, a very suitable starting-out material is β-diethylaminoethanol which can be purchased commercially and the conversion of which into the corresponding chloride has already been mentioned. The general method was to condense this with primary bases of the type NH_2R, where R is an alkyl group according to the equation

$$NH_2R + (C_2H_5)_2N \cdot CH_2 \cdot CH_2 \cdot Cl \rightleftharpoons H \cdot \underset{\dot{R}}{N} \cdot CH_2 \cdot CH_2 \cdot N(C_2H_5)_2 + HCl \text{ -----1.}$$

β-Diethylaminoethyl chloride hydrochloride was added to an excess of ammonia, methylamine, ethylamine, butylamine or iso-butylamine to which sufficient alcohol had been added to keep the former in solution.

The excess of amine serves to neutralise the hydrogen chloride formed during the reaction. The excess is also desirable for the further reason that it is likely to decrease the yield of tertiary amine formed according to the following equation:

$$2(C_2H_5)_2N\cdot CH_2\cdot CH_2\cdot Cl + H_2N\cdot R = \underset{2HCl}{\left[(C_2H_5)_2\cdot N\cdot CH_2\cdot CH_2\right]_2:N\cdot R} \quad \ldots\ldots\ldots\ldots \underline{2}.$$

The tendency for the reaction to yield a tertiary amine according to the above equation appeared to be very great, especially with the lower homologues. In the cases of methylamine, ethylamine, propylamine, butylamine and <u>iso</u>-butylamine, the yields of the desired secondary amines which were obtained were respectively 40 per cent, 50 percent, 60 per cent, 70 per cent and 70 per cent of the theoretical. With ammonia the yield was 30 per cent of the theoretical. It will be seen with ammonia and methylamine that the yields were smaller in spite of the fact that a very large excess of five to ten molecules of the base was employed, whilst in the case of the higher homologues the yields rose gradually with increase in the length of R. The product obtained was made alkaline, the base extracted with ether and recovered by distillation at ordinary pressures. In all the experiments, in

addition to the desired amines which boiled in the neighbourhood of 150°-200° according to the particular homologue in question (cf. table Page 30), a second fraction remained which boiled about 100° higher. This was apparently obtained by the condensation of one molecule of amine with two molecules of β-diethylaminoethyl chloride according to equation (2).

The corresponding bases of the piperidine series, with the exception of β-piperidinoethylamine were similarly prepared from β-piperidinoethyl chloride hydrochloride (m.p.208°, c.f. Knorr, Horlein and Roth, Ber., 1905, 38, 3138) which in its turn had been prepared from β-piperidinoethylalcohol (b.p.199° at 760 mm., cf. Ladenburg Ber., 1881, 14, 1877) by the thionyl chloride method already mentioned. β-Piperidinoethylalcohol itself is readily obtained in quantity by heating one molecule of ethylene chlorohydrin on the water bath with one molecule of piperidine when the hydrochloride of β-piperidinoethylalcohol is formed. The latter is dissolved in hot water rendered alkaline and extracted with ether. After drying and evaporation of the ether extract, the residue is distilled under ordinary pressure when β-piperidinoethylalcohol distils at 190° -200°.

β-Piperidinoethylamine was prepared from β-bromethylphthalimide and piperidine by the method of Kermack and Smith (J.C.S. 1931, 3098). The resultant β-piperidinoethylphthalimide was hydrolysed by hydrazine hydrate (cf.Ing. and Manske, J.C.S.1926, 2348) to yield the desired β-piperidinoethylamine. The bases α,γ-di-(diethylamino-)-iso-propylamine, α,γ-di-(diethylamino-)-iso-propylmethylamine and α,γ-di-(dimethylamino-)-iso-propylmethylamine (cf. table page 30, nos.13, 14 and 15 respectively) proved more difficult to synthesise. In order to prepare numbers (13) and (14) epichlorhydrin was refluxed in alcoholic solution with two molecules of diethylamine in presence of potassium carbonate. The α,γ--di(diethylamino-)-iso-propyl alcohol (XXVI) (cf.B.P. 363, 392) was extracted with ether, the ether extract dried, evaporated down and the residue distilled when the alcohol distils at 220°-230° at 760 mm. This was converted into the corresponding α,γdi-(diethylamino-)-iso-propyl chloride (XXVII) (cf.B.P. 363, 392) by the method of Gough and King (loc.cit.).

$$(C_2H_5)_2N-CH_2-\underset{\underset{OH}{|}}{CH}-CH_2-N(C_2H_5)_2$$

XXVI

$$(C_2H_5)_2N-CH_2-\underset{\underset{Cl}{|}}{CH}-CH_2-N(C_2H_5)_2$$

XXVII

After the completion of the reaction, the base was extracted from the chloroform with dilute acid since evaporation of the chloroform and excess thionyl chloride causes tarring. The base was liberated by addition of caustic soda, extracted with ether in the usual way and purified by distillation under a partial vacuum (b.p. 190° under 400 mm. pressure). α,γ-Di-(diethylamino)-iso-propyl chloride readily condensed with ammonia or methylamine to yield the bases (13) and (14) (cf. Table p.30) respectively. These were purified by distillation under a partial vacuum _ usually about 200 mm pressure and distilled at 170°-180° and 180°-190° respectively. Both amines formed well defined picrates which recrystallised from acetone-alcohol mixtures in the form of plates, m.p. 161° and 162°, respectively.

For the preparation of α,γ-di-(dimethylamino)-iso-propylmethylamine, dimethylamine and epichlorhydrin were refluxed in presence of three equivalents of potassium carbonate when α,γ-di-(dimethylamino)-iso-propyl alcohol (XXVIII) was extracted in similar manner to its diethyl homologue. The preparation of the chloro compound (XXVIX) and the condensation

with methylamine were carried out as in the case of

$$(CH_3)_2N-CH_2-\underset{\underset{OH}{|}}{CH}-CH_2-N(CH_3)_2$$

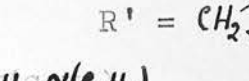
XXVIII

$$(CH_3)_2N-CH_2-\underset{\underset{Cl}{|}}{CH}-CH_2-N(CH_3)_2$$

XXIX

the diethyl homologue, the only difficulty arising being that of extracting sufficient base owing to its great solubility in water. α,γ-Di-(dimethylamino)-iso-propylmethylamine formed a well-defined picrate which recrystallised from alcohol acetone mixtures in the form of plates, m.p.187°. The various aliphatic bases which have been prepared are tabulated in the following table which gives the boiling points of the bases as well as the melting points of their picrates.

	Name of compound	b.p.	m.p. of dipicrate		Reference
1.	$R-NH_2$	145°	-		Ristenpart Ber.,1896, 29, 2526.
2.	$R-NH-CH_3$	157°	-		B.P.269,615
3.	$R-NH-C_2H_5$	165°	mono-,139°-140°. di-, 151°		B.P.310,074
4.	$R-NHC_3H_7$	185°	mono-,133°-135°.		-
5.	$R-NH-CH_2CH_2CH_2CH_3$	210°	234°		-
6.	$R-NH-CH_2CH(CH_3)_2$	197°	141°		-
7.	R^1NH_2	-	mom,225°		Kermack and Smith, J.C.S.1931, 3098.
8.	$R'-NHCH_3$	190°-200°	174°		-
9.	$R'-NH-C_2H_5$	200°-210°	154°		-
10.	$R'-NH-C_3H_7$	220°-230°	169°		-
11.	$R'-NH-CH_2CH_2CH_2CH_3$	230- 240°	191-2°		-
12.	$R'-NH-CH_2CH(CH_3)_2$	230°-240°	167-8°		-
13.	$R''-NH_2$	170°-180° (200mm)	160-1°		B.P.363,392
14.	$R''-NH-CH_3$	180°-190° (200mm)	161-2°		-
15.	$R'''-NH-CH_3$	180-5° (200mm)	185-7°		-

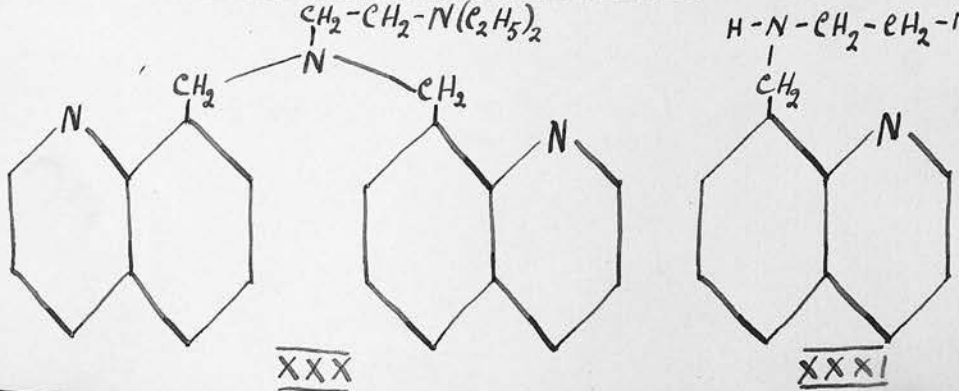
$R = (C_2H_5)_2N-CH_2CH_2-$ $R' =$ 

$R'' = (C_2H_5)_2N-CH-\underset{|}{CH}-CH_2-N(C_2H_5)_2$

$R''' = (CH_3)_2N-CH_2-\underset{|}{CH}-CH_2-N-(CH_3)_2$

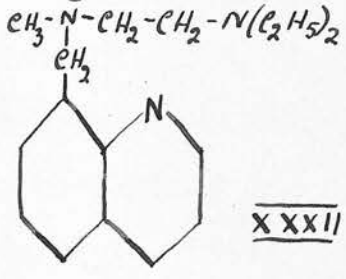
The following was found to be the best method of condensing these amines with 8-ω-brommethylquinoline. The base was dissolved in benzene and the 8-ω-brommethylquinoline added gradually. The homogeneous solution obtained in this way was refluxed in presence of dry potassium carbonate and the 8-[polyaminomethyl-]-quinoline extracted with acid. The base was separated by liberating with alkali and extracting with ether. A small quantity of oil sometimes observed may be quaternary base.

When β-diethylaminoethylamine was treated in this way, two compounds were obtained. After extracting with ether and evaporating, the residue set, on cooling, to an oily white solid. This was readily soluble in hot petrol ether and from this solution di-[quinolyl-8-methyl-]-aminoethyldiethylamine (XXX) separated as long rectangular plates, m.p.98°. The mother liquor, on evaporation, gave a light yellow oil which was dissolved in alcohol and converted into its hydrobromide, m.p.225°. This proved on analysis to be the hydrobromide of 8-[β-diethylaminoethylaminomethyl-]-quinoline (XXXI).

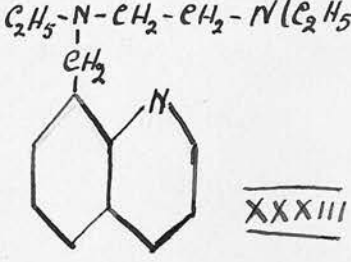


8-[β-Diethylaminoethylmethylaminomethyl-]-quinoline (XXXII) was a light brown coloured oil which was readily precipitated as its trihydrobromide, m.p. 215°-216°, when alcoholic hyrdobromic acid was added to its solution in alcohol.

8-[β-Diethylaminoethylethylaminomethyl-]-quinoline (XXXIII) was similarly separated in the form of its hydrobromide, m.p. 218°-219°. Both these salts were moderately soluble in hot alcohol and separated on cooling in the form of minute plates.

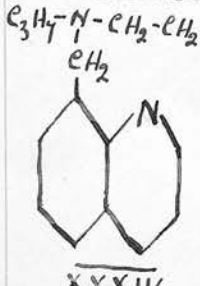


XXXII

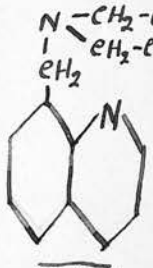


XXXIII

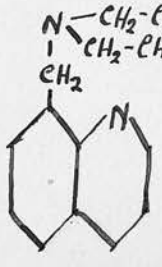
The higher homologues did not form crystalline hydrobromides on treatment with alcoholic ~~by~~ hydrobromic acid and, accordingly, had to be worked up in the form of their picrates. 8-[β-Diethylaminoethylpropylaminomethyl-]-quinoline (XXXIV) formed mono and dipicrates, whilst 8-[β-diethylaminoethyl-n-butylaminomethyl-]-quinoline (XXXV) and 8-[β-diethylaminoethyl-iso-butylaminomethyl-]-quinoline (XXXVI) both formed dipicrates only. On addition of the



XXXIV



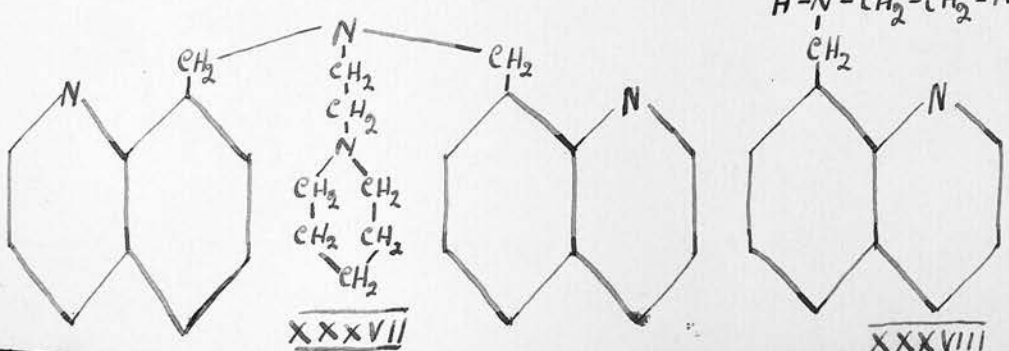
XXXV



XXXVI

base in alcohol to alcoholic picric acid, the first-named formed a mixture of mono (m.p.113°-115°) and di (m.p.163°-164°) picrates which were readily separated owing to the latter being practically insoluble in alcohol. The dipicrates, although insoluble in alcohol, were readily soluble in alcohol-acetone mixtures from which they were deposited on cooling in the form of small plates, melting respectively at 183°-185° and 170°-171°.

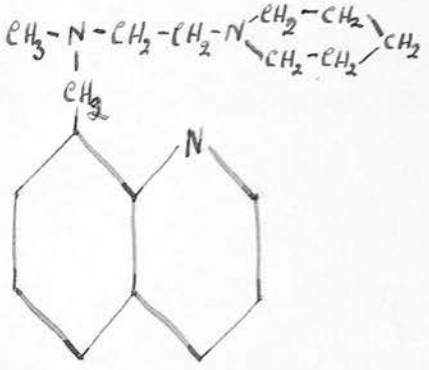
When 8-ω-brommethylquinoline was heated in alcoholic solution with β-piperidinoethylamine, only one product could be isolated. This proved, on analysis, to be di-[quinolyl-8-methyl]-aminoethyl-piperidine (XXXVII) m.p.97°-98° and, as the crude product was sticky and obviously impure, it is probable that 8-[β-piperidinoethylaminomethyl]-quinoline (XXXVIII) is also formed in the reaction, but attempts to isolate the latter from the mother liquor from the crystallisation proved unsuccessful. When this mother liquor was evaporated to dryness, attempts to purify the residue through the hydrobromide or picrate did not yield a pure product.



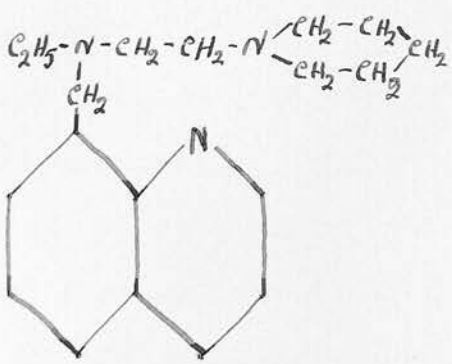
XXXVII

XXXVIII

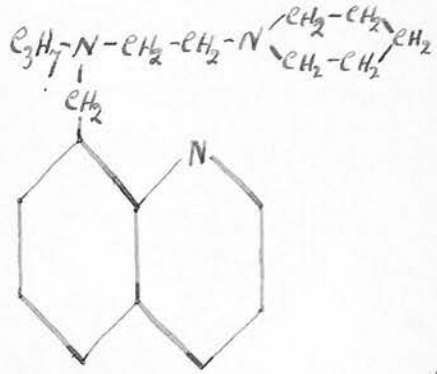
The higher homologues of the piperidinoseries readily condensed with 8-ω-brommethylquinoline in the manner already described for the corresponding homologues of the diethylamino series. The brown coloured oils resulting were all dissolved in alcohol. 8-[β-Piperidinoethylmethylaminomethyl]-quinoline (XXXIX), 8-[β-piperidinoethylethylamino-methyl]-quinoline, (XL), 8-[β-piperidinoethylpropyl-aminomethyl]-quinoline (XLI) and 8-[β-piperidino-ethyl-n-butylaminomethyl-]-quinoline (XLII) formed crystalline hydrobromides on the addition of alcoholic hydrobromic acid.



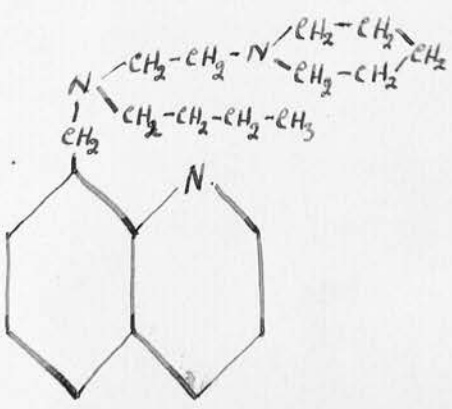
XXXIX



XL



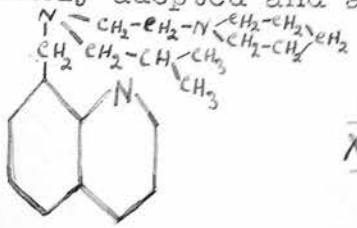
XLI



XLII

These were found to be readily recrystallisable from alcohol from which they were deposited in the form of plates, melting respectively at 217°-218°; 222°, 210° and 211°. With the exception of the hydrobromide of XXXIX, these analysed correctly. 8-[β-Piperidino-ethylmethylaminomethyl-]-quinoline, however, formed a picrate, m.p. 205°-206°, on addition of alcoholic picric acid which was readily crystallisable from an alcohol acetone mixture and which analysed correctly. It is probable that the low result in the case of the hydrobromide is due to its being a mixture of the di and trihydrobromides. 8-[β-Piperidinoethyl-iso-butylaminomethyl-]-quinoline (XLIII) did not form a crystalline hydrobromide when treated with alcoholic hydrobromic acid but on treatment with picric acid, dissolved in alcohol, formed a picrate, m.p. 210°-211°, which recrystallised from an alcohol acetone mixture.

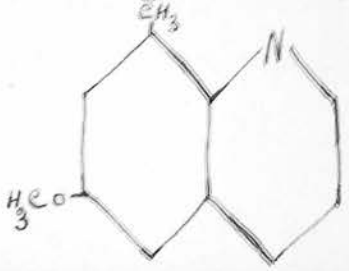
The attempts to condense the bases α,γ-di-(diethylamino)-iso-propylamine, α,γ-di-(diethylamino)-iso-propylmethylamine and α,γ-di-(dimethylamino)-iso-propylmethylamine (cf. table page 30) with 8-ω-brom-methylquinoline did not meet with success. In each case, the general proceedure was the same as that previously adopted and a yellowish-brown oil which



XLIII

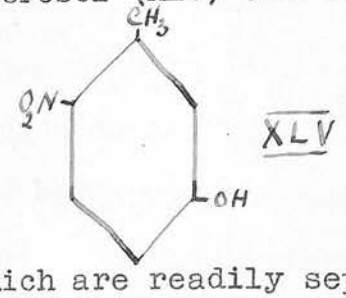
contained no bromine was obtained. This, however, yielded no crystalline hydrobromide on addition of alcoholic hydrobromic acid. In the case of (13), the first fraction obtained by adding alcoholic picric acid to the base in alcohol was very sticky and obviously impure, but on adding more picric acid a small quantity of less sticky material separated which, after several recrystallisations, proved, on analysis, to be the picrate, m.p.161°, of the unchanged α,γ-di-(diethylamino)-iso-propylamine. The product from (14)(loc.cit) behaved similarly and the small quantity of picrate, m.p.158°, isolated, on analysis, proved to be the picrate of α,γ-di-(diethylamino)-iso-propylmethylamine. In the case of (15, loc.cit), a similar experience was met with, the greater part of the picrate being precipitated in an oily impure condition.

The next line to be investigated was the possibility of obtaining compounds with a methoxyl or other group in position 6. In the first place, 6-methoxy-8-methylquinoline (XLIV) was prepared by the following stages. *m*-Cresol was nitrated (cf. Lapworth and Haworth, J.C.S. 1923, 123, 2984) by fuming nitric acid in the presence of glacial acetic acid at -5°.

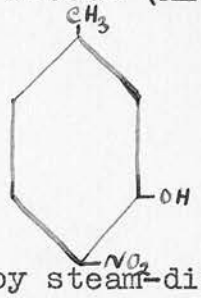


XLIV

Under those conditions two isomers, namely, 6-nitro-m-cresol (XLV) and 4-nitro-m-cresol (XLVI), are formed



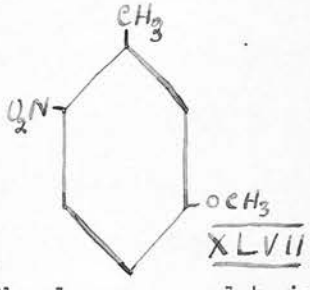
XLV



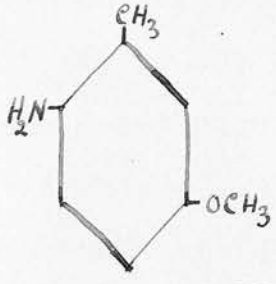
XLVI

which are readily separated by steam-distillation. The latter was obtained in a comparatively pure condition from the distillate, whilst the former remained as a black sticky residue which, after treatment, with animal charcoal in hot benzene, separated as brown coloured needles, m.p.126°, which were sufficiently pure to proceed to the next stage. If, during the nitration, the temperature rises above -5° more than one nitro group tends to be introduced and the yield of the mono-nitro derivative may be very poor. The methylation of 6-nitro-m-cresol was carried out by the method of Dapworth and Haworth (loc.cit.). The cresol was refluxed overnight with a mixture of xylene and dimethyl sulphate in presence of anhydrous potassium carbonate. After removal of the xylene by steam distillation, the residue was extracted with ether. 6-Nitro-3-methoxytoluene (XLVII) was obtained pure by distillation in vacuo when it came over as a pale yellow oil at 160°-180° under 10-15 mm. This oil quickly solidified, on cooling, to a pale yellow

crystalline solid, m.p.50°. The reduction was carried out according to the method recommended by the same authors (loc.cit.). The nitro compound was added to a solution containing the theoretical amount of stannous chloride dissolved in dilute hydrochloric acid. This, after heating for some time, was neutralised and the crude 6-amino-3-methoxytoluene (XLVIII) liberated, distilled in steam.



XLVII

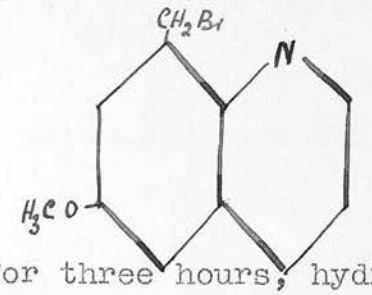


XLVIII

The base so obtained was fairly soluble in water, but was readily extracted with chloroform. The latter was removed and the residue distilled in vacuo when the fraction, b.p.180° (20 mm. pressure) was retained. This formed an acetyl derivative, m.p.131°-132°, which is identical with the melting point given by Lapworth and Haworth (loc.cit.). It was found that 6-amino-3-methoxytoluene could be readily converted into the corresponding quinoline by the Skraup synthesis. This was carried out by boiling the base for about four hours with a mixture of ferrous sulphate, glycerol, arsinic and sulphuric acids. 6-Methoxy-8-methylquinoline was separated by making alkaline and steam-distilling when it was obtained in the

form of a light brown coloured oil which was extracted with ether. The base formed a light yellow coloured hydrobromide which crystallised from alcohol as plates, m.p.268°. It also formed a picrate which crystallised from alcohol as plates, m.p.233°-234°.

6-Methoxy-8-methyłquinoline formed a dibromo addition product when bromine was dropped into a solution of the hydrobromide in chloroform. This compound was reddish-orange in colour and closely resembled that prepared from 8-methylquinoline. It was hoped that, by similar treatment to that described on page 19, it could by converted into 6-methoxy-8-ω-brommethylquinoline (XLIX). When it was heated at



XLIX

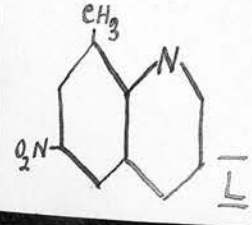
160°-170° for three hours, hydrogen bromide was given off without fusion and after one and a half hours the evolution of hydrogen bromide almost ceased and the product assumed a grey colour. This colour was in marked contrast to the results obtained with 8-methylquinoline, the dibromo addition product of which solidified to a light yellowish crystalline mass.

The product of the reaction was extracted in the usual way with 50 per cent sulphuric acid. The greyish-white compound, precipitated on making alkaline, recrystallised from petrol ether as needles, m.p.116°-117°, and its bromine content showed it to be a mono-bromo derivative of 6-methoxy-8-methylquinoline. It soon became clear, however, that it was not the desired 6-methoxy-8-ω-brommethylquinoline. Unlike 8-ω-brommethylquinoline it failed to react with piperazine, piperidine and alcoholic caustic potash, no bromine ions being liberated even after prolonged boiling with these reagents. It was therefore concluded that the bromine atom had not entered the methyl group in position 8, but had entered the quinoline nucleus probably in position 3, 5 or 7. This question is discussed more fully in section III of the present work. The fact that the compound, m.p. 116°-117°, had not a bromine atom in the methyl group in position 8 made it impossible to carry out the original plan of condensing the compound with the various bases of the type described on page. 30.

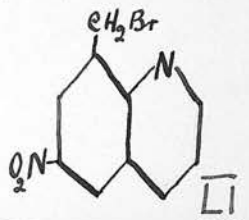
In view of the great desirability of obtaining a derivative of 8-ω-brommethylquinoline with a methoxyl group in position 6, experiments were made to

ascertain whether the compound, m.p. 116°-117°, could be further brominated in the hope that the second bromine atom would enter the methyl group. Exactly similar conditions were employed to obtain a dibromo-addition product which was heated up and extracted as before. The resulting bromo compound, however, proved to consist of the unchanged mono-bromo-6-meth-oxy-8-methylquinoline.

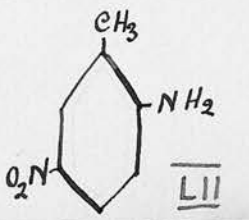
It was next thought desirable to study the bromination of 6-nitro-8-methylquinoline (L), partly to ascertain the effect of the nitro group on the bromination and partly in the hope of preparing 6-nitro-8-ω-brommethylquinoline (LI) which could be used to prepare bases desired for chemo-therapeutic purposes. Accordingly 6-nitro-8-methylquinoline was synthesised by a Skraup synthesis from 5-nitro-o-toluidine (LII)(cf. Lellmann and Ziemassen, Ber., 1891, 24, 2116). The last-named compound was heated up for four hours with glycerol, ferrous sulphate, arsinic and sulphuric acids. The resultant quinoline was separated by making alkaline, filtering and extracting with alcohol. The alcoholic solution was concentrated by evaporation and the base (L) deposited on cooling as needles m.p.129°. When 6-nitro-8-methylquinoline was dissolved in chloroform



L



LI



LII

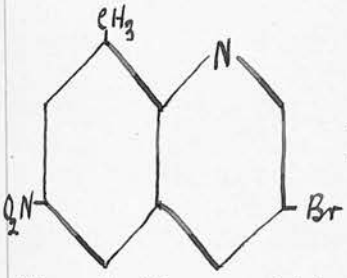
and dry hydrogen bromide passed through the solution, a light yellow precipitate of the hydrobromide was formed. Bromine was added to the chloroform suspension and the whole kept agitated to give the greatest possible opportunity for the formation of the dibromo-addition product. Owing to the insolubility of the hydrobromide in chloroform, it was not found possible to keep it in solution as in the case of 8-methylquinoline itself. The colour of the suspension changed from light yellow to reddish-brown, due presumably to the formation of the dibromo-addition product. The latter was filtered off, dried and heated for two hours at 150°-160°. The resulting greyish-coloured material was worked up in the usual way, the only product obtained being 6-nitro-8-methylquinoline. An attempt to brominate the latter by heating the compound on the water bath for two hours with a solution of bromine in chloroform also proved unsuccessful. Finally, the compound was refluxed for two hours with one molecule of bromine in glacial acetic acid solution, when a mixture of reddish-orange crystals and a greyish-white substance was formed with evolution of hydrogen bromide. The resulting mass was diluted with water,

filtered and the residue extracted with hot dilute hydrochloric acid. On cooling, a light yellow crystalline deposit was obtained which was filtered and again extracted with acid. This was filtered off, dried and recrystallised from petrol ether when a mono-brom-derivative, m.p.188°-189°, was obtained. It was found in a second experiment that, when monochloracetic acid was employed as solvent, a larger yield of the product was obtained while a shorter time (15 minutes) was necessary to complete the reaction

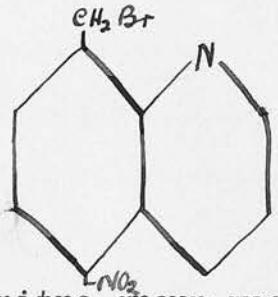
When this mono-brom-6-nitro-8-methylquinoline was refluxed with piperidine, alcoholic caustic potash or piperazine, no bromine ions appeared even after prolonged heating. On account of this it seemed very unlikely that bromine had entered the methyl group. Similarly, positions 5 and 7 are also unlikely because it is to be expected that the nitro group in the o-position would cause the bromine atom to react to some extent at least with one or other of the above reagents. Positions 2 and 4 are also excluded as a halogen atom in these positions in the quinoline nucleus usually reacts with piperidine and the other reagents mentioned with relative ease. It therefore appears highly probable that the bromine

atom has entered position 3, so that the compound is probably 3-bromo-6-nitro-8-methylquinoline (LIII).

In view of the difficulty in brominating the methyl group of 6-nitro-8-methylquinoline, an attempt was made to nitrate 8-ω-brommethylquinoline. This was carried out by a nitration mixture of concentrated nitric and sulphuric acids at 0°. On pouring the reaction mixture into water, a light yellow-coloured mononitro derivative (LIV) separated. When recrystallised from ligroin this melted at 119°.



LIII

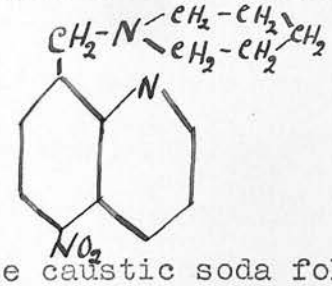


LIV

Though the position of the nitro group was not definitely established, it is probable that it is in position 5. This conclusion is based on the facts (a) that benzyl bromide nitrates in the o- and p-positions (b) that quinoline itself nitrates in the 5- and 8- positions.

When 5-nitro-8-ω-brommethylquinoline was heated on the steam bath with excess piperidine, a dirty brown product was obtained, accompanied by the liberation of bromine ions. When the condensation was carried out in ethereal solution, a purer product was obtained. 5-Nitro-8- piperidinomethyl-quinoline

(LV) was separated by washing the ethereal solution



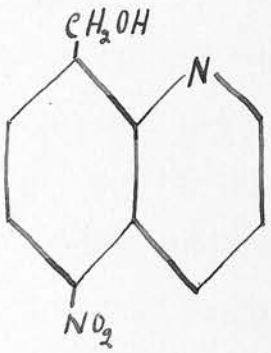
LV

with dilute caustic soda followed by water, the ether finally being distilled off after drying over anhydrous potassium carbonate. It is essential that the ethereal solution should be well washed with water, so as to remove all free alkali and piperidine, otherwise the residue which remains after evaporation is tarry and difficult to convert into a crystalline salt. The light yellow oil obtained above dissolved readily in alcohol and yielded light, brown-coloured plates of the mono-hydrobromide, m.p. 249°, on treatment with alcoholic hydrobromic acid.

The reduction of 5-nitro-8- piperidinomethyl - quinoline was unsuccessfully attempted by two different methods, namely, by stannous chloride and hydrochloric acid, and by West's method (loc.cit.)

When 5-nitro-8-ω-brommethylquinoline was heated with piperazine hexahydrate at 140° a tar resulted within a few minutes; at a lower temperature and in presence of a solvent, the reaction proceeded less vigorously. After several experiments, the following were found to be the best conditions. The nitro compound was dissolved in hot toluene, the piperazine

added and the mixture heated on the water bath for one hour. On cooling, a light brown-coloured precipitate was obtained which was filtered off. This proved to be a hydrobromide from which a base was readily obtained by treatment with dilute ammonia. After recrystallisation from chloroform, the compound melted at 261° with decomposition and the analytical figures suggested that it was 5-nitroquinolyl-8-methylalcohol (LVI). Presumably the



LVI

water in the piperazine hexahydrate was responsible for the replacement of Br by OH.

The condensation of 5-nitro-8-ω-brommethylquinoline and β-diethylaminoethylethylamine was attempted but in every case the product was tarry and crystalline salts could not be prepared.

PRACTICAL I

β-Diethylaminoethyl chloride hydrochloride.

β-Diethylaminoethanol (59 gm) dissolved in chloroform (100c.c.) was added slowly with stirring to a mixture of thionyl chloride (12 gm) and chloroform (500 c.c.) cooled to -5° - the temperature during the addition should never exceed 0°. After standing for an hour at room temperature, most of the chloroform was removed on the water bath and the last traces of thionyl chloride eliminated by twice evaporating the residue under reduced pressure with alcohol (100 c.c.). The white crystalline mass, which remained, was dissolved in the minimum quantity of hot alcohol (about 50 c.c.). On cooling β-diethylaminoethyl chloride hydrochloride separated as colourless needles m.p.209°-210°. A further quantity was obtained by adding ether to the mother liquor and filtering. The combined yields usually amounted to about 80 gm.

o-Nitrobenzylethylamine.

o-Nitrobenzyl chloride (20 gm) was added gradually, with shaking, to a solution of monoethylamine (35 c.c.) in absolute alcohol (70 c.c.). A small amount (about 5 gm.) of potassium carbonate was added and the solution finally refluxed for one hour. During the reaction the colour changed from dark green to a deep brown colour. The resultant solution was acidified and the unchanged o-nitrobenzyl chloride removed by filtration. The filtrate was then made strongly alkaline when o-nitrobenzylethylamine separated as a dark brown oil. This was extracted with ether, the extract dried over anhydrous K_2CO_3 and evaporated to dryness on the water bath. The residue was distilled in vacuo when the fraction b.p.145°-155° (16 mm) was retained, yield 15 gm.

The picrate, formed by the addition of a solution of picric acid in alcohol to the base dissolved in alcohol, melted at 123°. The hydrochloride (cf.Wolff, Ber., 1892, 25, 3038) melted at 186°.

p-Nitrobenzylethylamine

p-Nitrobenzyl chloride (20 gm) was added slowly, with shaking, to a solution of 33% monoethylamine (34cc) in alcohol (70 c.c.). After refluxing for one hour in presence of 5 gm. of K_2CO_3, the solution was acidified, the unchanged p-nitrobenzyl chloride filtered off and the filtrate made strongly alkaline with caustic soda. The p-nitrobenzylethylamine which separated was extracted with ether, the extract dried over anhydrous K_2CO_3 and evaporated down on the water bath. The residue was distilled in vacuo when the fraction b.p.155°-165° (16 mm) was retained, yield 15 gm.

The picrate formed by adding alcoholic picric acid to the base in alcohol melted at 179°. The hydrochloride melted at 226° (cf. Paal and Springer, Ber., 1897, 30, 63).

o-Nitro-[β-diethylaminoethylethylaminomethyl-]-benzene.

o-Nitrobenzylethylamine (15gm) was dissolved in dry benzene (50 c.c.) and β-diethylaminoethyl chloride hydrochloride (15 gm.) added. Anhydrous K_2CO_3 (15 gm.) and a trace of copper bronze were added and the mixture refluxed for four hours. The resultant

dark brown solution was filtered and the residue well washed with small quantities of hot dry benzene. The filtrate and washings were then saturated with dry hydrogen chloride when a sticky mass separated. The supernatant liquid was decanted off and the mixture of hydrochlorides boiled up with acetone (200 c.c.) filtered and the insoluble o-nitrobenzylethylamine hydrochloride washed with a small quantity of hot acetone. The filtrate and washings were then evaporated to dryness and the residue treated with dilute alkali when the crude o-nitro-[β-diethylaminoethylethylaminomethyl-]-benzene separated as a dark brown oil. This was extracted with ether, the extract dried over anhydrous K_2CO_3 and evaporated to dryness on the water bath. The residue was dissolved in a small quantity of alcohol and added to a saturated solution of picric acid in alcohol. The sticky dirty yellow picrate which separated was twice boiled with alcohol (100 c.c.) and filtered hot. The yellowish-brown coloured residue recrystallised from a large volume of hot water as light yellow needles m.p.167°-168°, yield 15gm. Found N=17·2%, $C_{27}H_{31}O_{16}N_9$ requires N=17·1%.

The base, recovered by heating the picrate

with dilute alkali and extracting with ether, is a brown-coloured oil which is very soluble in alcohol acetone, chloroform, benzene and ether. Yield about 6·5 gm.

o-Amino-[β-diethylaminoethylethylaminomethyl-]-benzene.

o-Nitro-[β-diethylaminoethylethylaminomethyl-]-benzene (6 gm.) was dissolved in methylated spirits (20 c.c.) and concentrated HCl (6 c.c.) added. The solution was kept boiling vigorously and iron filings (4 gm) added in 1 gm portions over a period of fifteen minutes. After refluxing for two hours, the solution was neutralised by adding alcoholic caustic soda and the precipitated ferric hydroxide filtered off. The filtrate was then evaporated down, when the residue was treated with dilute alkali and extracted with ether. After drying over anhydrous K_2CO_3, the extract was evaporated to dryness leaving the crude o-amino-[β-diethylaminoethylethylaminomethyl-]-benzene as a brown-coloured oil, yield about 90% of the theoretical. This was contaminated with the original nitro compound, but, as this was no disadvantage, in the Skraup Synthesis, the crude product was utilised for this purpose.

The monopicrate was prepared by gradually adding alcoholic picric acid to the base dissolved in alcohol. It came down very sticky at first, but on standing small plates separated from the mother liquor. These were filtered off and, after several recrystallisations, separated as light yellow plates melting at 134°. Found C=52·2%, H=7·45%, $C_{27}H_{33}O_{14}N_9$ requires C=52·7%, H=7·3%.

The base is very soluble in dilute mineral acids, alcohol, acetone, chloroform, ether and benzene.

Attempt to prepare 8-[β-diethylaminoethylethylaminomethyl-]-quinoline.

$FeSO_4$ (·1 gm.), glycerol (6 gm), o-amino-[β-diethylaminoethylethylaminomethyl-]-benzene (6 gm), arsinic acid (2·5 gm) and concentrated H_2SO_4 (5·5 gm) were mixed in the above order and kept refluxing gently for three to four hours. The resultant dark brown sticky solution was poured into water, allowed to stand overnight and filtered. The filtrate was made strongly alkaline with caustic soda and the precipitated ferric hydroxide filtered off. The latter was then extracted two or three times with hot alcohol and the alcohol removed by distillation.

The light brownish-yellow oil remaining was dissolved in alcohol and an alcoholic solution of picric acid added. The resultant picrate proved to be very impure even after several recrystallisations from acetone alcohol mixtures. The hydrochloride and oxalate were precipitated on addition of alcoholic hydrochloric acid and alcoholic oxalic acid, but these salts both proved equally difficult to purify.

p-Nitrobenzylmethylamine

p-Nitrobenzyl chloride (12 gm) was heated with 33% methylamine (26 gm) in alcohol in a sealed tube for two hours at 60°-70°. The mixture, on cooling, deposited yellow crystals which were filtered off and washed with a little alcohol. The filtrate was evaporated down, treated with dilute HCl and filtered. The filtrate was then made alkaline and the crude p-nitro-benzylmethylamine extracted with ether. After drying over anhydrous K_2CO_3, the extract was evaporated to dryness and the residue distilled in vacuo. The fraction distilling at 155°-160° under 20 mm pressure contained practically pure p-nitrobenzylmethylamine, yield 4 gm.

p-Nitro-{β-diethylaminoethylmethylaminomethyl}-benzene.

p-Nitrobenzylmethylamine (4 gm) was heated in benzene (15 c.c.) for four hours with β-diethylaminoethyl chloride (3·4 gm), anhydrous K_2CO_3 (2·5 gm) and a trace of copper bronze. The resulting brown solution was filtered and the residue well washed with hot, dry benzene. The filtrate was then saturated with dry hydrogen chloride and the hydrochloride which separated boiled up with acetone (100 c.c.) and again filtered. This filtrate contained the desired p-nitro-{β-diethylaminoethylmethylaminomethyl}-benzene, which separated as its hydrochloride on evaporation of the solution to dryness. The base which was liberated by the addition of dilute alkali was extracted with ether and the ether evaporated off. The resulting yellowish-brown oil was dissolved in alcohol and converted into the dipicrate by adding this solution slowly to a saturated solution of picric acid in alcohol. Recrystallisation from alcohol yielded small yellow plates m.p.195°-197°.

Found N=17·3%, $C_{26}H_{29}O_{16}N_9$ requires N=17·4%.

The base is readily soluble in mineral acids, alcohol, acetone, chloroform, benzene and ether.

Benzylethylamine

Benzyl chloride (15 gm) was added slowly to a solution of 33% ethylamine (36c.c.) in alcohol (40 cc.) containing K_2CO_3 (7gm). The resulting clear coloured solution was refluxed for over an hour, diluted with water and acidified with dilute hydrochloric acid. The unchanged benzyl chloride was extracted with ether and the aqueous layer containing the desired benzyl-ethylamine made alkaline with dilute caustic soda. The oil separating was extracted with ether, the extract dried over anhydrous K_2CO_3 and evaporated to dryness. The residue was then distilled in vacuo when the fraction distilling at 130°-140° at 14 mm. pressure was retained, yield 8 gm.

This yielded a picrate when its alcoholic solution was added to alcoholic picric acid. This after recrystallisation from alcohol was obtained as yellow plates m.p.118°-120°.

β-Diethylaminoethylethylaminomethylbenzene

Benzylethylamine (15 gm) and β-diethylaminoethyl chloride (15 gm) were dissolved in benzene (50 c.c.) and refluxed for four hours in presence of anhydrous

K_2CO_3 (15 gm). The resulting light brown solution was filtered and well washed with hot dry benzene. The filtrate and washings were saturated with dry hydrogen chloride and a white precipitate was obtained. This was filtered off and recrystallised from acetone as colourless fethery plates m.p.180°-185°, yield 25 gm. The analysis indicated a percentage of chlorine intermediate between those required of the mono- and di-hydrochlorides. A portion was therefore dissolved in water and made alkaline with dilute caustic soda. The oil separating was extracted with ether, the extract dried over K_2CO_3 and the ether evaporated off. The light yellow coloured oil was dissolved in alcohol and added to alcoholic picric acid when the dipicrate separated out. This crystallised from alcohol in the form of small yellow plates m.p.150°-152°. Found N=16·1%, $C_{27}H_{32}O_8N_{14}$ requires N=16·2%.

The base dissolved readily in dilute mineral acids, alcohol, acetone, chloroform, benzene and ether.

Nitration of β-diethylaminoethylethylaminomethylbenzene.

Conc. H_2SO_4 (200 gm), β-diethylaminoethylethylaminomethylbenzene (20 gm.) and glacial acetic acid (100 gm) were mixed together and cooled to -5°. A mixture of concentrated H_2SO_4 (5 c.c.) and conc. HNO_3 (2·5 c.c. of d.=1·414) was then added slowly, with stirring. After standing overnight the resultant solution was poured over ice (1500 gm) and the solution neutralised with caustic soda. The precipitated nitro-compounds were extracted with ether, the extract dried over K_2CO_3 and evaporated to dryness. The brown oil which remained was distilled in vacuo when the following fractions were collected:

At 19 mm.	pressure	156°-160°	6·5 gm
At 18 "	"	165°-175°	3·7 gm
At 16 "	"	200°-210°	3·2 gm.

All three fractions were light yellow coloured oils which did not form crystalline picrates. An analysis carried out on the distilled but unfractionated reaction product yielded N=14·8%, a mononitro compound, namely, $C_{15}H_{25}O_2N_3$ requires N=15·0%. This indicated that nitration had taken place, but, in view of the difficulty in obtaining pure products, this line was discontinued.

6-Methylquinoline

Ferrous sulphate (12 gm), glycerine (304 gm), p-toluidine (110 gm), arsinic acid (146 gm) and conc. H_2SO_4 (280 gm) were mixed together in a 2-litre flask and gently boiled under reflux for four hours. The resultant dark liquid was diluted with water, made alkaline and steam-distilled. The crude 6-methylquinoline was extracted with ether, dissolved in dil. H_2SO_4 (1000 c.c. of about 4N) and cooled to 0°. A saturated solution of sodium nitrite was added slowly with stirring until a distinct excess was shown by starch iodide paper. The solution was then made alkaline and again steam-distilled when 6-methylquinoline came over as a light yellow oil. This was extracted with ether, the extract dried over anhydrous K_2CO_3 and evaporated to dryness.

8-Methylquinoline was prepared in exactly the same way from o-toluidine. In both cases, the yields vary, but, as a rule, the yield obtained was about 60 per cent of the theoretical.

Dibromo addition product of 8-methylquinoline hydrobromide.

8-Methylquinoline (100 gm) was dissolved in chloroform (900 c.c.) and dry hydrogen bromide passed through the solution until it was no longer absorbed/

It is desirable to shake frequently and it is important, as already explained, that no separation of hydrobromide should be allowed to occur. When saturation was reached, the solution was cooled to 0° and bromine (40 c.c.) added drop by drop with vigorous stirring. The dibromo addition product immediately separated out and the reaction was completed by allowing the solution to stand overnight. The reddish-orange crystalline deposit was then filtered off, well washed with dry chloroform and dried on a porous plate, yield 270 gm.

8-ω-Dibrommethylquinoline and 8-ω-brommethylquinoline.

The product obtained above was divided into 40 gm. batches and heated on an oil-bath. As the temperature rose from 100°-120°, traces of hydrogen bromide were given off and the compound began to melt. At 140°, it had melted completely, while large volumes of hydrogen bromide mixed with a trace of bromine were evolved. The heating was continued at 160° for two hours when the molten mass solidifed in the form of an apparently crystalline, light orange-yellow mass. After further heating for an hour, when the evolution of hydrogen bromide had almost ceased, the flask was removed and allowed to

cool. The crystalline mass was now dissolved by heating with a mixture of equal volumes of conc. H_2SO_4 and water. The solution was poured into a large volume of water and allowed to stand for one hour. 8-ω-Dibrommethylquinoline which separated as a light yellow flocculent precipitate was filtered off and dried on a porous plate, m.p.137°, yield 10 gm. The filtrate was now made alkaline with caustic soda, the temperature being kept down by the addition of crushed ice. The greyish-white precipitate which separated was filtered, well washed with water and dried on a porous tile. 8-ω-Brommethylquinoline was recrystallised from petrol ether (60°-80°), when long colourless needles m.p.84° separated, yield 45 gm. (N.B.) A large quantity (30-40 gm) of unchanged 8-methylquinoline was obtained from the filtrate and washings by extraction with ether.

8-Piperidinomethylquinoline

8-ω-Brommethylquinoline (1 gm) was added to a solution of piperidine (1 gm) in benzene (6 c.c.) and the whole refluxed for one hour. The resultant solution, from which needles of piperidine hydrobromide had separated, was extracted with dilute

HCl and the extract rendered alkaline with dilute caustic soda. The oil separating was extracted with ether, the extract well washed with water and dried over anhydrous K_2CO_3. The ether was removed by evaporation and the light brown oil remaining dissolved in alcohol and converted into a monopicrate by adding a saturated alcoholic solution of picric acid gradually. The picrate separated as a light yellow precipitate which recrystallised from alcohol as light yellow needles m.p.183°. Found C=55%, H=4·6%, $C_{21}H_{21}O_7N_5$ requires C=55·4%, H=4·6%.

o-Aminobenzylpiperidine was subjected to the Skraup Reaction in the following way. Boric acid (4 gm) dissolved in glycerol (25 gm) was thoroughly mixed with o-nitropiperidinomethylbenzene (9 gm) and ferrous sulphate (2·3 gm) added. Sulphuric acid (12 c.c. of 96%) were then carefully added and the whole brought to the boil and allowed to simmer gently for twenty hours. The dark solution was steam-distilled, made alkaline, and again steam-distilled to remove any unchanged volatile products. The residue was then extracted with ether several times and the ether extract washed with water to remove alkali, dried over anhydrous K_2CO_3 and taken

to dryness. 8-Piperidinomethylquinoline was left behind as a dark brown oil which yielded a dirty yellow picrate when alcoholic picric acid was slowly added to its solution in alcohol. This, after several recrystallisations from alcohol, separated as deep yellow needles m.p.179°. Found C=55·2%, H=4·7%, N=15·6%, $C_{21}H_{21}O_7N_5$ requires C=55·4%, H=4·6%, N=15·4%. A mixture of this picrate and that prepared by the preceding method melted at 180°.

The base is very soluble in alcohol, acetone, ether, benzene, chloroform and dilute acids. A solution in dilute HCl gives a reddish-brown precipitate with dilute iodine and a reddish-brown precipitate with gold chloride.

8-ω-Anilinomethylquinoline

8-ω-Brommethylquinoline (2 gm) was added gradually to aniline (2 gm). The mixture immediately deposited reddish-orange crystals which had formed a solid cake by the time the addition was complete. After heating for one hour on the steam bath, the cake was dissolved in a little water, made alkaline with dilute Na_2CO_3 and steam-distilled. The dark brown oily/

brown oily residue which solidified on standing overnight was dissolved in the minimum of hot alcohol and came down on cooling as light brown plates, m.p. 71°-73°, yield 1·2 gm. Found N=11·7%, $C_{16}H_{14}N_2$ requires N=12·0%.

The base is not very soluble in dilute mineral acids, but is very soluble in acetone, benzene, alcohol, chloroform and ether.

A white crystalline precipitate of the hydrobromide was obtained by adding alcoholic hydrobromic acid to the base in alcohol. A dilute aqueous solution of this gave a reddish-brown precipitate with dilute iodine, a light yellow precipitate with $K_3FeC_6N_6$, a lemon yellow flocculent precipitate with phosphomolybdic acid and a reddish-brown precipitate with gold chloride.

Di-{quinolyl-8-methyl-}-1,4-piperazine

8-ω-Brommethylquinoline (2 gm) and piperazine hexahydrate (2 gm) were refluxed at 130°-140° for two hours. The resultant brown mass was extracted with hot dilute HCl and the extract made faintly alkaline with Na_2CO_3. The oil, first formed, gradually solidified on standing and recrystallised from the minimum quantity of hot alcohol in the form of light

brown plates m.p.153°-154°. Found C=76·6%, H=6·4%, N=14·6%, $C_{24}H_{24}N_4\frac{1}{2}H_2O$ requires C=76·4%, H=6·6%, N=14/9%.

The base is soluble in dilute mineral acids and deposits a white crystalline hydrobromide (m.p.265°-267°) from its alcoholic solution on addition of alcoholic hydrobromic acid. It is soluble in benzene, ether, chloroform and alcohol. A dilute solution of the hydrobromide in water yields a light yellow flocculent precipitate with gold chloride and phospomolybdic acid, a reddish-brown precipitate with dilute iodine and a white flocculent precipitate with silicotungstic acid.

Di-{quinolyl-8-methyl-}-p-aminoacetanilide

8-ω-Brommethylquinoline (2·2 gm) was added to a solution of p-aminoacetanilide (1·5 gm) in alcohol and the whole refluxed for one and a half hours. At the end of this time the light yellow crystalline precipitate which had separated was filtered off after allowing the liquid to cool. The hydrobromide was dissolved by heating the salt with dilute HCl when a red-coloured solution resulted. On making this solution alkaline, the base was deposited as a rose-

coloured amorphous precipitate which separated from alcohol in the form of ruby-coloured plates m.p.236°-237°. Found N=13·0%, $C_{28}H_{24}ON_4$ requires N=13·0%.

The base is sparingly soluble in dilute mineral acids, acetone, alcohol and chloroform, but is insoluble in benzene and ether. A solution in dilute HCl gives faint yellow precipitates with phosphomolybdic acid and gold chloride, a reddish-brown precipitate with dilute iodine and a white flocculent precipitate with silico-tungstic acid.

β-Diethylaminoethylamine.

β-Diethylaminoethyl chloride hydrochloride (8 gm) was slowly added with shaking to a mixture of ammonia (25c.c. of S.G. ·880) and alcohol (25 c.c.) and the mixture gently heated under reflux for two hours. The alcohol was distilled off on the water bath, the residue made strongly alkaline with caustic soda and the β-diethylaminoethylamine separated by several extractions with ether. The ether extract was dried over anhydrous K_2CO_3 and evaporated to dryness. The residue was then distilled under ordinary pressure when the fraction distilling at 145°-155° was retained, yield 2·2 gm.

β-Diethylaminoethylmethylamine

β-Diethylaminoethyl chloride hydrochloride (6·8 gm) was added slowly with shaking to 33 % methylamine in alcohol (15 gm). The mixture was then refluxed for one hour in presence of K_2CO_3 (3·4gm). The resultant solution was diluted with 200 c.c. of water and rendered strongly alkaline with caustic soda. The β-diethylaminoethylmethylamine which separated was extracted with ether, the extract dried over anhydrous K_2CO_3 and evaporated to dryness. The residue was distilled at ordinary pressures when the fraction b.p.157°-160° was retained, yield 1·8 gm.

β-Diethylaminoethylethylamine

β-Diethylaminoethyl chloride hydrochloride (6 gm) was added slowly with shaking to 33% monoethylamine (14 c.c.) and alcohol (15c.c.). The mixture was then refluxed for two hours in presence of 3-4 gm of K_2CO_3. The resultant solution was diluted with water and rendered strongly alkaline with caustic soda. The oil separating out was extracted with ether, the extract dried over anhydrous K_2CO_3 and the ether distilled off. The residue was distilled under ordinary pressure and the fraction b.p.165°-170° retained, yield 2·1 gm. A mixture of two picrates was obtained by adding

alcoholic picric acid to the base dissolved in alcohol. These were separated by fractional crystallisation, the more soluble monopicrate, separated as light yellow needles, melting at 139°-140°; whilst the dipicrate, separated as yellow plates, melting at 150°-151°.

β-Diethylaminoethylpropylamine.

n-Propylamine (8 gm) was dissolved in alcohol (24 c.c.) and β-diethylaminoethyl chloride hydrochloride (8 gm) added slowly with shaking. Anhydrous K_2CO_3 (3-4 gm) was added and the whole refluxed gently for two hours. The resultant solution was diluted with water and rendered strongly alkaline with caustic soda. The oil separating out was extracted with ether, the extract dried over anhydrous K_2CO_3 and the ether distilled off. The residue was distilled under ordinary pressure when the fraction b.p.184°-200° was retained, yield 4 gm.

A picrate, obtained by adding alcoholic picric acid to the base in alcohol, recrystallised from alcohol in the form of yellow rectangular plates m.p.133°-135°. Found N=18·2%, $C_{15}H_{25}O_7N_5$ requires N=18·1%.

β-Diethylaminoethyl -n-butylamine

n-Butylamine (8 gm) was dissolved in alcohol (24 c.c.) and β-diethylaminoethyl chloride hydrochloride (8 gm) added gradually with shaking. Anhydrous K_2CO_3 (4 gm) were added and the liquid refluxed for two hours. Water was added to dissolve the potassium salts and the resulting solution made strongly alkaline with caustic soda and extracted with ether. The ether extract was dried over K_2CO_3 and evaporated to dryness. The brown oil remaining was distilled at ordinary pressures when β-diethylaminoethyl-n-butylamine distilled as a colourless oil at 207°-212°. The dipicrate formed by adding alcoholic picric acid to the base in alcohol crystallised from acetone-alcohol mixtures as yellow plates m.p.234°.
Found C=42·0%, H=4·8%, $C_{22}H_{30}O_{14}N_8$ requires C=41·9%, H=4·8%.

β-Diethylaminoethyl-iso-butylamine.

iso-Butylamine (8 gm) and β-diethylaminoethyl chloride hydrochloride (8 gm) were condensed in alcohol (24 c.c.) in similar manner to that described above. The resulting β-diethylaminoethyl-iso-butylamine distilled at 194°-200°. The dipicrate which separated on the addition of alcoholic picric acid to the base in alcohol crystallised from alcohol

acetone mixtures as yellow rods m.p.141°.
Found C=42·2%, H=4·8%, $C_{22}H_{30}O_{14}N_8$ requires C=41·9%, H=4·8%.

β-Piperidinoethylamine

A solution of piperidine (6·8 gm) and phthalo-β-bromoethylimide (10 gm) in dry toluene (15 c.c.) was refluxed in presence of anhydrous K_2CO_3 (11 gm) for four hours. The yellow solution was filtered hot and the residue of potassium bromide washed with hot toluene. The filtrate after concentration deposited large, pale yellow prisms of phthalo-β-piperidino-ethylimide, yield 70%, m.p.91° after recrystallisation from alcohol.

Phthalo-β-piperidinoethylimide (7·7 gm) was hydrolysed with hydrazine hydrate (3 gm of a 50% solution). The white precipitate obtained by heating the resultant solution with excess hydrochloric acid (about 50c.c. of 5N) on the water bath was filtered off. The filtrate was diluted with water and the alcohol distilled off. The solution was made strongly alkaline with caustic soda and the oily base which separated was extracted with ethylacetate. After removal of this solvent by distillation, a viscous brown oil remained which decomposed when heated in a vacuum. The picrate recrystallised

from hot water as yellow prisms m.p.225°.

β-Piperidinoethyl alcohol

Ethylene chlorhydrin (20 gm) and piperidine (21 gm) were mixed and heated on the water bath for one hour. The resultant brownish crystalline mass was dissolved in water, made strongly alkaline with caustic soda and the oil which separated taken up with ether. The ether, after drying over anhydrous K_2CO_3, was distilled off and the residue distilled at ordinary pressures. The fraction b.p.190° was retained, yield 26 gm.

β-Piperidinoethyl chloride hydrochloride

β-Piperidinoethyl alcohol (26 gm) was dissolved in chloroform (26 c.c.) and added gradually with stirring to a solution of thionyl chloride (46 gm) in chloroform (100 c.c.) previously cooled to -5°. After the addition was complete, the stirring was continued for one hour at the ordinary temperature. The chloroform was distilled off and the residue twice dissolved in alcohol and evaporated to dryness under reduced pressure. The white crystalline mass remaining was dissolved in the minimum amount of alcohol (about 50 c.c.) from which colourless needles m.p.228°-230° deposited on cooling, yield 32gm.

The following secondary amines were prepared in exactly similar manner from β-piperidinoethyl chloride hydrochloride as were the corresponding amines of the diethylamino series (described above) from β-diethylaminoethyl chloridehydrochloride.

β-Piperidinoethylmethylamine distilled at 190°-200° at ordinary pressures, yield 3·7 gm from 8·7 gm of β-piperidinoethyl chloride hydrochloride.

β-Piperidinoethylmethylamine, on addition of alcoholic picric acid to the base in alcohol, yielded a dipicrate which separated from acetone alcohol mixtures as yellow plates, m.p.174°. Found C=40·2%, H=4·0%, $C_{20}H_{24}O_{14}N_8$ requires C=40·0%, H=4·0%.

β-Piperidinoethylethylamine distilled at 200°-210° at ordinary pressures, yield 4·5 gm from 8 gm of the β-piperidinoethyl chloride hydrochloride.

β-Piperidinoethylethylamine also formed a dipicrate by the method described above which separated from acetone alcohol mixtures as yellow plates, m.p.154°. Found C=41·2%, H=4·4%, $C_{21}H_{26}O_{14}N_8$ requires C=41·0%, H=4·2%.

β-Piperidinoethylpropylamine distilled at 220°-230° at ordinary pressures, yield 5·7 gm from 8 gm of β-piperidinoethyl chloride hydrochloride

The dipicrate formed in the manner described above separated from acetone alcohol mixture as yellow plates, m.p.169°. Found C=42·3%, H=4·5%, $C_{22}H_{28}O_{14}N_8$ requires C=42·0%, H=4·5%.

β-Piperidinoethyl -n-butylamine distilled at 230°-240° at ordinary pressures, yield 5·9 gm from 8 gm of β-piperidinoethyl chloride hydrochloride. The dipicrate formed in the manner described above separated from acetone alcohol mixtures as yellow plates m.p.191-192°. Found N=43·1%, H=4·8%, $C_{23}H_{30}O_{14}N_8$ requires C=43·0% H=4·7%.

β-Piperidinoethyl-iso-butylamine distilled at 230°-240° at ordinary pressures, yield 5·9 gm from 8 gm of β-piperidinoethyl chloride hydrochloride. The dipicrate, formed in the manner described above, separated from acetone alcohol mixtures in the form of yellow plates m.p.167°-168°. Found C=43·3%, H=4·8%, $C_{23}H_{30}O_{14}N_8$ requires C=43·0%, H=4·7%.

The amines of the β-diethylamine series, namely β-diethylaminoethylamine, β-diethylaminoethylmethylamine, β-diethylaminoethylethylamine, β-diethylaminoethylpropylamine, β-diethylaminoethyl-n-butylamine and β-diethylaminoethyl-iso-butylamine show a marked resemblance in properties to those described above.

Each one is very soluble in alcohol, ether, benzene chloroform, acetone and dilute mineral acids. They are all soluble in water, but this property decreases proportionately with the size of the group R in the formulae

(a) $(C_2H_5)_2N-CH_2-CH_2-NHR$; (b) $CH_2<^{CH_2-CH_2}_{CH_2-CH_2}>N-CH_2-CH_2-NHR$

α,γDi-(diethylamino)-iso-propyl alcohol

Epichlorhydrin (18·5 gm) was refluxed with diethylamine (29·2 gm) in presence of anhydrous K_2CO_3 (13·8 gm) for one hour. The resultant brown solution was diluted with water and basified with caustic soda. The oil separating was extracted with ether and the ether extract dried over anhydrous K_2CO_3. The ether was distilled off and the residue distilled at ordinary pressures when the fraction, boiling at 220°-240°, was retained, yield 30 gm.

α,γ-Di-(diethylamino)-iso-propyl chloride

α,γ-Di-(diethylamino)-iso-propyl alcohol (30 gm) in chloroform (30 c.c.) was added gradually, with stirring, to thionyl chloride (35 gm) in chloroform (100 c.c.) cooled to -5°. The light brown solution was stirred for a further half-hour at room temperature and finally extracted with dilute HCl. The acid extract was basified and the oil separating extracted

with ether. The ether extract was dried over anhydrous K_2CO_3 and the ether distilled off. The residue was distilled at about 400 mm. pressure when the fraction b.p.185°-195° was retained, yield 24 gm.

α,γ-Di-(diethylamino)-iso-propylamine

α,γ-Di-(diethylamino)-iso-propyl chloride (12 gm) was added gradually with shaking to ammonia (30 c.c. of S.G. ·880) in alcohol (30 c.c.). Anhydrous K_2CO_3 (3-4 gm) was added and the whole refluxed gently for two hours. The alcohol was distilled off on the water bath and the residue rendered strongly alkaline with caustic soda. The base separating was extracted with ether, the extract dried over anhydrous K_2CO_3 and evaporated to dryness. The residue was distilled at 200 mm. pressure when the fraction boiling at 180°-190° was retained, yield 6 gm.

The dipicrate formed by the addition of alcoholic picric acid to the base in alcohol separated in the form of yellow plates m.p.160°-161° from acetone-alcohol mixtures. Found C=41·5%, H=4·8%, $C_{23}H_{33}O_{14}N_9$ requires C=41·2%, H=5·0%.

The base is very soluble in water, alcohol, ether, benzene, chloroform, acetone and dilute mineral acids.

α,γ-Di-(diethylamino)-iso-propylmethylamine

α,γ-Di-(diethylamino)-iso-propyl chloride (12 gm) was added slowly with shaking to a solution of 21 per cent methylamine (30 gm) in alcohol (30 c.c.). The solution was refluxed in presence of anhydrous K_2CO_3 (3-4 gm) and worked up in similar manner to the previous experiment. The residue obtained after distilling off the ether was distilled at 200 mm. pressure when the fraction b.p.180°-190° was retained, yield 7 gm.

The dipicrate formed by the addition of alcoholic picric acid to the base in alcohol separated from acetone alcohol mixtures as yellow plates m.p.161°-162° Found C=42·6%, H=4·9%, $C_{24}H_{35}O_{14}N_9$ requires C=42·7%, H=5·2%.

The base is very soluble in water, acetone, alcohol, chloroform, benzene and mineral acids.

α,γ-Di-(dimethylamino)-iso-propyl alcohol

Epichlorhydrin (13·8 gm) and dimethylamine hydrochloride (26 gm) were refluxed in alcohol (50 cc.) for four hours in presence of anhydrous K_2CO_3 (28 gm). The solution was filtered and the alcohol distilled off on the water bath. The residue was dissolved in ether and washed well with dilute alkali.

The ethereal solution was dried over anhydrous K_2CO_3 and evaporated to dryness and the residue distilled at 400 mm. pressure, the fraction b.p.178°-182° being retained, yield 15 gm.

α,γ-Di-(dimethylamino)-iso-propyl chloride

The chlorination was carried out in similar manner to that described for α,γ-di-(diethylamino)-iso-propyl chloride by adding slowly, with stirring, α,γ-di-(dimethylamino)-iso-propyl alcohol (15 gm) in chloroform (15 c.c.) to a solution of thionyl chloride (17 gm) in chloroform (50 c.c.) cooled to -5°. After similar treatment to that already described, a yellow oil was obtained which was distilled at 400 mm. pressure. The fraction coming over at 180°-185° was retained, yield 5 gm. The low yield is probably due to the great solubility of the base in water.

α,γ-Di-(dimethylamino)-iso-propylmethylamine

α,γ-Di-(dimethylamino)-iso-propyl chloride (5 gm) was added gradually with shaking to a solution of 21 per cent methylamine (15 gm) in alcohol (15 cc). After refluxing for one hour in presence of anhydrous K_2CO_3 (3 gm), the alcohol was distilled off on the water bath and the residue made strongly alkaline

with caustic soda. The clear solution was extracted with ether and the ether extract, after drying over anhydrous K_2CO_3, evaporated to dryness. The residue was distilled at 400 mm. pressure when the fraction coming over at 180°-185° was retained, yield 2 gm.

The dipicrate which was formed by adding alcoholic picric acid to the base in alcohol, separated from an acetone-alcohol mixture as yellow plates m.p.185°-187°. Found C=38·9%, H=4·2%, $C_{20}H_{27}O_{14}N_9$ requires C=38·9%, H=4·4%.

The base is very soluble in water, dilute acids, acetone, ether, benzene, chloroform and alcohol.

Di-{quinolyl-8-methyl-}-aminoethyldiethylamine

β-Diethylaminoethylamine (3 gm) was dissolved in benzene (10 c.c.) and 8-ω-brommethylquinoline (3 gm) added slowly with shaking. Anhydrous K_2CO_3 (3 gm) was added, the mixture refluxed for two hours and extracted with dilute HCl. The acid extract was basified and the oil separating taken up in ether. The ether extract was well washed with water, dried over anhydrous K_2CO_3 and evaporated to dryness. The light brown oil, on cooling, quickly solidified to an oily cake which was dissolved up in the minimum quantity (about 5 c.c.) of petrol ether (60°-80°). On cooling, long colourless rectangular

needles, m.p. 97°-98°, of di-{quinolyl-8-methyl}-aminoethyldiethylamine separated. These were filtered off, dried and recrystallised from petrol ether, yield 1 gm. Found C=77·9%, H=7·5%, $C_{26}H_{30}N_4$ requires C=78·4%, H=7·5%.

A picrate was obtained by adding alcoholic picric acid slowly with shaking to the base in alcohol. This recrystallised from alcohol as yellow plates, m.p. 191°.

The base is very soluble in alcohol, acetone, benzene, ether and mineral acids, but is insoluble in water.

8-{β-Diethylaminoethylaminomethyl}-quinoline

The mother liquor from the first treatment with petrol ether in the above experiment was evaporated to dryness when a light brown oil was obtained. This was dissolved in alcohol and alcoholic hydrobromic acid added. The salt which separated out was filtered off and recrystallised from alcohol in the form of colourless long prisms m.p. 223°-224°. Analysis of the bromine content of this salt proved it to be the trihydrobromide of 8-{β-diethylaminoethylaminomethyl}-quinoline. Found Br=47·9%, $C_{16}H_{26}N_3Br_3$ requires Br=48·0%.

8-{β-Diethylaminoethylmethylaminomethyl}-quinoline

β-Diethylaminoethylmethylamine (1·3 gm) and

8-ω-brommethylquinoline (2 gm) were refluxed in benzene (10 c.c.) in presence of anhydrous K_2CO_3 (2 gm) for two hours. The resultant light brown solution was extracted with dilute HCl. The acid extract was basified with caustic soda and the oil separating extracted with ether. The ether extract was well washed with water and finally dried and separated from any insoluble oil by drying over anhydrous K_2CO_3. The ether was distilled off on the water bath and the light brown oil remaining dissolved in alcohol and converted into a hydrobromide by adding alcoholic hydrobromic acid. T he white precipitate forming was boiled up and, on cooling, deposited in a more compact, less sticky condition. This was filtered off and recrystallised from alcohol in the form of small colourless plates, m.p.215°-216°, yield 2 gm. Found Br=46·3%, $C_{17}H_{28}N_3Br_3$ requires Br=46·7%.

8-{β-Diethylaminoethylethylaminomethyl}-quinoline.

β-Diethylaminoethylethylamine (1·5 gm) and 8-ω-brommethylquinoline (2 gm) were condensed in similar manner to that described above. The light brown oil resulting was converted into the hydrobromide in similar manner. The trihydrobromide of 8-{β-diethylaminoethylethylaminomethyl}-quinoline

prepared in this way separated from alcohol as colourless plates, m.p.218°-219°, yield 2 gm. Found Br=45·6% $C_{18}H_{30}N_3Br_3$ requires Br=45·4%.

The mono-picrate was also formed by slowly adding alcoholic picric acid to the base dissolved in alcohol. This recrystallised from alcohol as yellow plates m.p.131°-132°. Found N=15·9% $C_{24}H_{30}O_7N_6$ requires N=16·3%.

8-[β-Diethylaminoethylpropylaminomethyl-]-quinoline

β-Diethylaminoethylpropylamine (2 gm) and 8-ω-brommethylquinoline (2 gm) were condensed in similar manner to the foregoing. T he light brown oil obtained was dissolved in alcohol and alcoholic picric acid added slowly with shaking. The yellow precipitate separating was extracted twice with boiling alcohol (50-100 c.c.). On cooling, the alcohol deposited light yellow plates of the mono-picrate which, after two crystallisations from alcohol, melted at 113°-115°. Found C=56·8%, H=6·1%, $C_{25}H_{32}O_7N_6$ requires C=56·8%, H=6·1%. The insoluble residue dissolved readily in acetone alcohol mixtures from which it deposited, on cooling, as deep yellow plates, m.p.163°-164°. Found C=49·0%, H=4·5%, $C_{31}H_{35}O_{14}N_9$ requires C=49·1%, H=4·6%.

8-{β-Diethylaminoethyl-n-butylaminomethyl-}-quinoline.

β-Diethylaminoethyl-n-butylamine (2 gm) and 8-ω-brommethylquinoline (2 gm) were condensed in similar manner to the foregoing. The resultant light brown oil was dissolved in alcohol and alcoholic picric acid added slowly, with shaking. The resultant picrate was almost insoluble in hot alcohol, but dissolved readily in hot acetone alcohol mixtures from which it deposited on cooling as deep yellow rectangular prisms, m.p.178°-180°. Found C=50·1%, H=4·9%, $C_{32}H_{37}O_{14}N_9$ requires C=49·9%, H=4·8%.

8-{β-Diethylaminoethyl-iso-butylaminomethyl-}-quinoline.

β-Diethylaminoethyl-iso-butylamine (2 gm) and 8-ω-brommethylquinoline (2 gm) were condensed in similar manner to the foregoing. The light brown oil obtained was dissolved in alcohol and alcoholic picric acid added slowly, with shaking. The light yellow picrate proved to be insoluble in hot alcohol, but recrystallised from alcohol acetone mixtures in the form of deep yellow rectangular prisms, m.p.169°-171°. Found C=50·0%, H=4·8%, $C_{32}H_{37}O_{14}N_9$ requires C=49·9%, H=4·8%.

The picrates obtained from the three bases described above were readily decomposed by heating on the water bath with dilute alkali. After cooling

the free base was extracted with ether and the ether well washed with water. After drying over anhydrous K_2CO_3, the ether was distilled off, leaving the base as a light brown oil.

The bases 8-[β-diethylaminoethylalkylaminomethyl-]-quinoline (alkyl=H, CH_3, C_2H_5, C_3H_7, n-C_4H_9 or iso-C_4H_9) are all very soluble in alcohol, acetone, benzene, ether, and dilute mineral acids. The lower members of the series are sparingly soluble in water, but the solubility decreases proportionately with increase in the size of the alkyl group with the result that the last two members are practically insoluble in water; in all cases, particularly in the cases of the lower members, addition of caustic soda decreases greatly their solubility.

Di-[quinolyl-8-methyl-]-aminoethylpiperidine.

β-Piperidinoethylamine (2 gm) was dissolved in alcohol (6 c.c.) and 8-ω-brommethylquinoline (2 gm) added slowly with shaking. The solution was then refluxed for two hours. The resultant brown liquid was diluted with water, made alkaline with ammonia and allowed to stand overnight. The sticky brown solid which separated was filtered and recrystallised from a water-alcohol mixture.

Di-[quinolyl-8-methyl-]-aminoethylpiperidine separated

as colourless rhombic prisms, m.p.97°-98°. Found C=78·9%, H=7·3%, $C_{27}H_{30}N_4$ requires C=79%, H=7·3%.

The picrate was formed by adding alcoholic picric acid to the base in alcohol. The pale yellow picrate obtained was almost insoluble in alcohol, but separated from a large volume as pale yellow needles m.p.228°-229°.

The base is very soluble in alcohol, ether, acetone, benzene and dilute mineral acids, but is insoluble in water.

8-[β-Piperidinoethylmethylaminomethyl-]-quinoline

β-Piperidinoethylmethylamine (2·2 gm) was dissolved in benzene (10 c.c.) and 8-ω-brommethyl-quinoline (3 gm) added slowly, with shaking. Anhydrous K_2CO_3 (3 gm) was added and the whole refluxed for two hours. The resultant light brown solution was extracted with dilute HCl and the acid extract basified with dilute caustic soda. The oil separating out was taken up in ether, the ether extract well washed with water and dried over anhydrous K_2CO_3. The ether was distilled off and the light brown oil remaining dissolved in alcohol. Alcoholic hydrobromic acid was added and the solution heated on the water bath. On cooling and scratching, white crystals

separated which were filtered off and recrystallised from alcohol as colourless plates m.p.217°-218°, yield 3 gm. Found Br=41·8%, $C_{18}H_{28}N_3Br_3$ requires Br=45·4%.

The picrate was formed by adding alcoholic picric acid slowly, with shaking, to the base in alcohol. The light yellow picrate which separated recrystallised from an acetone-alcohol mixture in the form of yellow plates, m.p.205°-206°. Found C=48·8%, H=4·2%, $C_{30}H_{31}O_{14}N_9$ requires C=48·6%, H=4·2%.

8-[β-Piperidinoethylethylaminomethyl-]-quinoline

β-Piperidinoethylethylamine (2·2 gm) and 8-ω-brommethylquinoline (3 gm) were condensed in exactly similar manner to the foregoing. The light brown oil resulting was dissolved in alcohol and alcoholic hydrobromic acid added. The solution was heated up on the water bath and, on cooling, a salt which separated out slowly, rapidly deposited on rubbing the side of the beaker with a glass rod. This salt recrystallised from alcohol in the form of small colourless plates, m.p.222°, yield 3 gm. Found Br=44·3%, $C_{19}H_{30}N_3Br_3$ requires Br=44·4%.

8-[β-Piperidinoethylpropylaminomethyl-]-quinoline

β-Piperidinoethylpropylamine (2·5 gm) and 8-ω-brommethylquinoline (3 gm) were condensed in

similar manner to the foregoing. The light brown oil obtained was dissolved in alcohol and converted into a hydrobromide in similar manner to that described above. The salt recrystallised from alcohol in the form of colourless small plates m.p.210°. Found Br=43·1%, $C_{20}H_{32}N_3Br_3$ requires Br=43·3%.

8-{β-Piperidinoethyl-n-butylaminomethyl-}-quinoline.

β-Piperidinoethyl-n-butylamine (2 gm) and 8-ω-brommethylquinoline (2·5 gm) were condensed in similar manner to the foregoing. The light brown oil obtained was dissolved in alcohol and converted into a hydrobromide in similar manner to that described above. The salt obtained recrystallised from alcohol in the form of small colourless plates m.p.211°-212°, yield 3 gm. Found Br=42·2%, $C_{21}H_{34}N_3Br_3$ requires Br=42·3%.

8-{β-Piperidinoethyl-iso-butylaminomethyl-}-quinoline

β-Piperidinoethyl-iso-butylamine (2 gm) and 8-ω-brommethylquinoline (2·5 gm) were condensed in similar manner to the foregoing. The light brown oil obtained was dissolved in alcohol and alcoholic picric acid added slowly with shaking. The light yellow picrate which separated was filtered off and recrystallised from an acetone-alcohol mixture as small yellow plates m.p.210°-211°, yield 3 gm.

Found C=50·8%, H=4·7%, $C_{33}H_{37}O_{14}N_9$ requires C=50·6% H=4·7%.

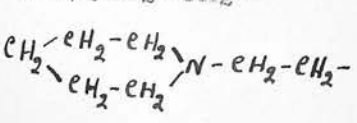
The base was easily obtained by decomposing the picrate with dilute caustic soda on the water bath. On cooling, 8-[β-piperidinoethyl-iso-butylaminomethyl-]-quinoline was extracted with ether. The ether extract was well washed with water, dried over anhydrous K_2CO_3 and the ether distilled off, leaving a light brown oil.

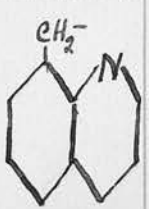
The bases 8-[β-piperidinoethylalkylaminomethyl]-quinoline (where alkyl = CH_3, C_2H_5, C_3H_7, n-C_4H_9 or iso-C_4H_9) are all very soluble in acetone, benzene, alcohol, chloroform, ether and dilute mineral acids. The solubility in water decreases proportionately with increase in the size of the alkyl group; for example, 8-[β-piperidinoethylmethylaminomethyl-]-quinoline is slightly soluble in water, whilst 8-[β-piperidinoethyl-iso-butylaminomethyl-]-quinoline is insoluble in water.

The following table gives a brief resume of the action of the various alkaloidal reagents:-

Name of Compound	Reagent employed: Dilute Iodine	Phospho-Molybdic acid	Silico-tungstic acid	Gold Chloride	Potassium Ferricyanide
(R'-NH)-R	Reddish-brown ppt.	Light yellow ppt.	White floc. ppt.	Light yellow ppt.	No ppt.
(R'-NCH_3)-R	"	"	"	"	"
(R'-NC_2H_5)R	"	"	"	Orange yellow ppt.	"
(R'-NC_3H_7)-R	"	"	"	Light yellow ppt.	"
(R'-N-n-C_4H_9)-R	"	"	"	"	Light yellow ppt.
(R'-N-iso-C_4H_9)-R	"	"	"	"	"
(R''-NCH_3)-R	"	"	"	Orange yellow ppt.	No ppt.
(R''-NC_2H_5)-R	"	"	"	"	"
(R''-NC_3H_7)-R	"	"	"	"	Light yellow ppt.
(R''-N-n-C_4H_9)-R.	"	"	"	"	"
(R''-N-iso-C_4H_9)-R	"	"	"	Light yellow ppt.	"
(R_2-N-R'	"	"	"	"	No ppt.
R_2-N-R''	"	"	"	"	"

R'=$(C_2H_5)_2CH_2-CH_2-$

R'' = 

R = 

6-Nitro-m-cresol and 4-nitro-m-cresol

m-Cresol (140 gm) was mixed with glacial acetic acid (140 gm) and added drop by drop with stirring to a solution of fuming HNO_3 (200 gm of S.G.1·5) in glacial acetic acid (400 gm). It is essential that the temperature should never rise above -5° during the addition. After the addition, the stirring was continued for one and a half hours and the reddish-brown liquid poured on to ice (3000 gm). After standing overnight, the yellow precipitate was filtered off and the filtrate extracted with ether. The yellow precipitate along with the reddish-brown oil recovered from the ether were steam-distilled. 4-Nitro-m-cresol came over as a light yellow oil which rapidly solidified to a light yellow solid m.p.50°, yield 44 gm. After all the 4-nitro-m-cresol had been removed, a black sticky residue remained in the flask. The water was decanted off and the residue dissolved in benzene, any water remaining being readily removed by drying over anhydrous Na_2SO_4. The dry benzene solution was boiled for ten minutes with a small quantity of animal charcoal, filtered and concentrated on the water bath. After cooling, 6-nitro-m-cresol

deposited as light brown needles, m.p.126°, yield 60 gm.

6-nitro-3-methoxytoluene

6-Nitro-m-cresol (50 gm) xylene (200 c.c.) and anhydrous K_2CO_3 (74 gm) were refluxed and dimethyl sulphate (80 gm) slowly added; after eighteen to twenty hours, the yellow colour of the solution had disappeared. The whole was then cooled, mixed with water (100 c.c. containing 2-3 gm of sodium hydroxide) and steam-distilled, the break in the speed of distillation indicating the point when all the xylene had passed over. The residue was dissolved in ether, dried over anhydrous K_2CO_3 and the ether distilled off. The residue was distilled in vacuo when the fraction b.p.160°-180° at 10-15 mm. was retained. The yellow oil quickly solidified to a pale yellow solid m.p.50°, yield 50 gm.

6-Amino-3-methoxytoluene

6-Nitro-3-methoxytoluene (60 gm) was heated on the steam bath with stannous chloride (270 gm), dissolved in conc. HCl (350 c.c.) and diluted with water. After three hours, the clear solution was rendered strongly alkaline with sodium hydroxide and distilled with steam. The clear brown distillate

was extracted with chloroform and dried over anhydrous Na_2SO_4. The chloroform was distilled off, leaving a dark brown oil which was distilled in vacuo, the fraction b.p.185°-190° (25 mm.) being retained, yield 38 gm. The acetyl derivative prepared by treating the base with acetic anhydride dissolved in glacial acetic acid for an hour in presence of fused sodium acetate separated from alcohol as colourless needles, m.p.132°.

6-Methoxy-8-methylquinoline

Ferrous sulphate (2 gm), glycerol (38 gm), 6-amino-3-methoxytoluene (16·5 gm) arsinic acid (17 gm) and conc. H_2SO_4 were boiled gently under reflux for four hours. After allowing to cool, the black sticky residue was diluted with water, made strongly alkaline and steam-distilled. 6-Methoxy-8-methylquinoline was extracted from the distillate with ether. The ether, after drying over anhydrous K_2CO_3, was distilled off, leaving a light brown oil, yield 9 gm.

The picrate was readily formed by slowly adding alcoholic picric acid to the base in alcohol. It separated as a light yellow precipitate which recrystallised from alcohol in the form of yellow plates m.p.232°-233°.

The hydrobromide prepared by adding alcoholic hydrobromic acid to the base in alcohol separated as light yellow plates, m.p.268°, from alcohol. Found Br=31·5%, $C_{11}H_{12}ONBr$ requires Br=31·5%.

The base is very soluble in acetone, alcohol, benzene, chloroform and ether. The hydrobromide dissolves readily in water to yield a solution with a faint blue fluorescence.

5-Bromo-6-methoxy-8-methylquinoline

6-Methoxy-8-methylquinoline (9 gm) was dissolved in chloroform (30 c.c.) and dry hydrogen bromide passed through the solution until no more was absorbed. Bromine (3 c.c.) was now added drop by drop with stirring and cooling. The resultant solution was allowed to stand overnight when a reddish-brown crystalline deposit was obtained. This was filtered off, well washed with dry chloroform and dried. This was heated in an oil bath at 160°-170° for three hours. During this period, there was a continuous evolution of hydrogen bromide while the colour of the residue changed gradually from reddish-brown to light grey. The residue was allowed to cool and extracted with hot 50 per cent H_2SO_4 (40 c.c.) poured into water (400 c.c.) and filtered. The filtrate was made alkaline and the greyish-white precipitate which

separated filtered off and dried. After recrystallisation from petrol ether (60°-80°), colourless rectangular plates m.p.116°-117° were obtained, yield 6·2 gm. Found Br=31·9%, $C_{11}H_{10}ONBr$ requires Br=31·8%.

The base is very soluble in ether, benzene, alcohol and mineral acids (yielding a solution with a faint blue fluorescence), but is only moderately soluble in petrol ether and ligroin.

The hydrobromide, light yellow plates m.p.230°, was obtained by adding alcoholic hydrobromic acid to the base in acetone and evaporating to dryness.

6-Nitro-8-methylquinoline

Ferrous sulphate (2 gm), glycerol (38 gm), 5-nitro-o-toluidine (18 gm), arsinic acid (17 gm) and conc. H_2SO_4 (33 gm) were mixed together and refluxed gently for four hours. The resultant sticky black liquid was diluted with water and made alkaline with caustic soda. The precipitated 6-nitro-8-methylquinoline was filtered off and freed from ferric hydroxide by extracting twice with hot alcohol. After concentrating the alcoholic extract, the base separated as light grey needles, m.p.129°, yield 12 gm.

3-Bromo-6-nitro-8-methylquinoline

6-Nitro-8-methylquinoline (5 gm) and monochloracetic acid (40 gm) were mixed and heated until a

homogeneous solution was obtained. Bromine (2·5 cc) was added slowly, with shaking and the whole refluxed gently for fifteen minutes. By this time, the solution had deposited a greyish-white crust on the flask and all traces of bromine had vanished from the vapour entering the condenser. During the course of the reaction, large volumes of hydrogen bromide were evolved. The residue was diluted with HCl (200 c.c. of about 2N), boiled for a few minutes and filtered. On cooling, a light yellow crystalline deposit was obtained which was filtered off. This treatment with dilute acid was repeated until only a small quantity of insoluble residue remained, but, as a rule, two extractions in all were necessary. The compound obtained above contained bromine and was found to separate from benzene as light yellow needles, m.p.188°- 189°, yield 4 gm. Found Br=30·2%, $C_{10}H_7O_2N_2Br$ requires Br=30·0%. A small quantity of unchanged 6-nitro-8-methylquinoline was obtained by basifying the acid filtrates obtained above.

3-Bromo-6-nitro-8-methylquinoline is slightly soluble in petrol ether, ether, alcohol and ligroin, soluble in acetone and benzene, but is insoluble in water and dilute mineral acids.

5-Nitro-8-ω-brommethylquinoline

8-ω-Brommethylquinoline (20 gm) was dissolved in H_2SO_4 (100 c.c. of 96%) and cooled to 0°. A nitrating mixture of HNO_3 (6 c.c. of S.G.1·412) and H_2SO_4 (6 c.c. of 96%) was added drop by drop with stirring, the temperature never being allowed to rise above 5°. The solution turned a deep yellow and traces of nitrous fumes developed. After standing overnight at room temperature, the solution was poured slowly, with stirring, into a large volume of water. The light yellow precipitate was filtered, well washed with water and dried at 100°, yield 20 gm. Recrystallisation from ligroin yielded long, fine, faint yellow needles, m.p.118°-119°. Found Br=29·9%, $C_{10}H_7O_2N_2Br$ requires Br=30·0%.

5-Nitro-8-ω-brommethylquinoline is very soluble in acetone, ether, chloroform and benzene, sparingly soluble in alcohol, petrol ether and ligroin, but is insoluble in dilute mineral acids.

5-Nitro-8-piperidinomethylquinoline

5-Nitro-8-ω-brommethylquinoline (2 gm) was added slowly, with shaking to piperidine (1·6 gm) in ether (50 c.c.). The yellow solution was refluxed for three hours, allowed to cool and well washed with dilute sodium carbonate solution and finally with water. After drying over anhydrous K_2CO_3, the ether was distilled off on the water bath and the

light yellow oil remaining dissolved in alcohol. When this solution was heated with excess alcoholic hydrobromic acid, light brown rectangular plates, m.p.248°-249°, of the monohydromide were deposited on cooling. After recrystallisation from alcohol, found Br=22·8%, $C_{15}H_{18}O_2N_3Br$ requires Br=22·7%.

The base is a light yellow oil very soluble in alcohol, acetone, chloroform, benzene, ether and dilute mineral acids.

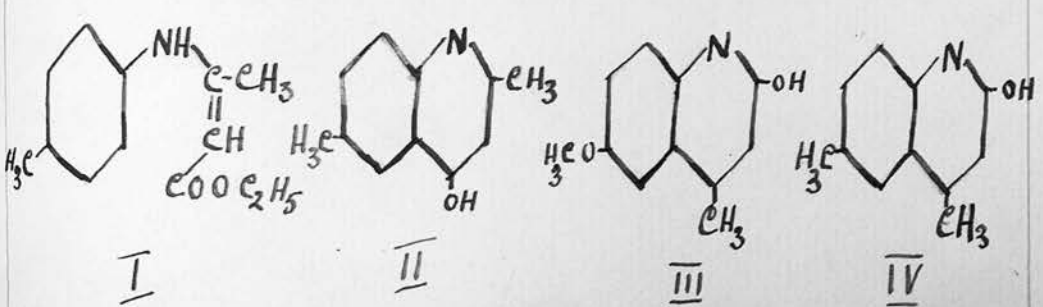
[5-Nitroquinolyl-]-8-methyl alcohol

5-Nitro-8-ω-brommethylquinoline (5 gm) was dissolved in toluene (40 c.c.) and piperazine (3·7 gm) added. The whole was heated on the water bath for one hour, cooled and the light brown precipitate, which had formed, filtered off. The residue was then boiled with dilute ammonia, cooled and filtered, yield 3·5 gm.

[5-Nitroquinolyl-]-8-methyl alcohol is very insoluble in alcohol, acetone, ether, benzene, toluene, ligroin and petrol ether, but is sparingly soluble in chloroform from which it separates as light brown needles, m.p.261° (decomp.). Found N=13·7%, $C_{10}H_8O_3N_2$ requires N=13·7%.

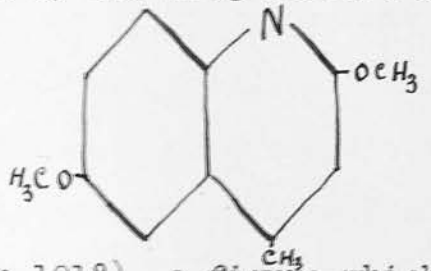
DERIVATIVES OF CARBOSTYRIL

The condensation of aceto-acetic ester with p-toluidine or p-anisidine gave rise to several interesting products. This condensation may proceed in either of two ways. In the first case, equimolecular quantities are mixed together and kept for 12 hours at 37°C when ethyl-β-p-totylaminocrotonate (I) is produced. This on heating for one hour at 250° is converted into 2-methyl-4-hydroxy-6-methylquinoline (II) (cf. Conrad and Limpach, Ber., 1887, 20, 947). If, on the other hand, four molecules of ester are mixed with one molecule of amine and the mixture heated to 155°-160° for four hours, an acetoacetanilide (cf. Ewins and King, J.C.S.1913, 103, 104) results which may be cyclised by heating with 96% sulphuric acid at 100°C. In this way, 4-methyl- 6-methoxycarbostyril (III) and 4,6-dimethylcarbostyril (IV) were prepared from p-anisidine and p-toluidine respectively.



I II III IV

A curious discrepancy in the melting points of samples of 4-methyl-6-methoxy-carbostyril prepared in different ways had already been observed by Kermack and Muir (J.C.S.1933, 84, 300). They found that 4-methyl-2,6-dimethoxyquinoline (V), on partial hydrolysis, yielded a carbostyril, m.p.271°-272°, (picrate m.p.165°-166°) while the same compound, prepared by the ring closure method melted at 255°

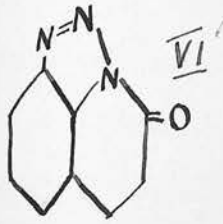


V

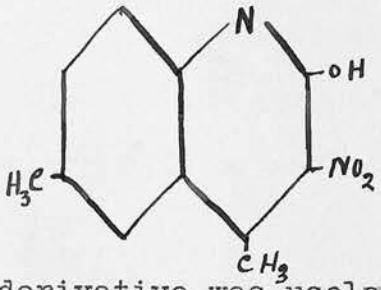
(picrate 191°), a figure which remained constant after several recrystallisation. In the present work, it was found that the compound described above melted after several recrystallisations at 267°-268° (picrate m.p.194°). This compound was found to be similar to the compound prepared by Backeberg (m.p.271°; picrate m.p.196°) (J.C.S.1933, 84, 1031) from aceto-acet-p-anisidide by ring closure with 96 per cent sulphuric acid. It must be noted that slight preliminary decomposition takes place in each case with the result that the melting points are not very sharp.

4-Methyl-6-methoxycarbostyril (III) and 4,6-dimethylcarbostyril (IV)(cf. Balaban, J.C.S.1930, 2346) nitrated readily on treatment with concentrated nitric and concentrated sulphuric acids. On pouring the reaction mixtures into water, the mononitro derivatives separated out as yellow solids, which,although insoluble in the common organic solvents, dissolved readily in hot glacial acetic acid and, on cooling, separated as light orange and light yellow-coloured needles respectively. It was found, however, that these compounds were reduced with difficulty by concentrated hydrochloric acid and stannous chloride and that the resultant impure amino compounds on diazotisation coupled with β-naphthol. It is to be expected that, if the amino group were in position 8 (cf. Balaban J.C.S.1930, 81, 2346), these compounds, when treated with nitrous acid, would form a triazole ring (for example, compound VI) and not a diazonium salt, capable of coupling with β-naphthol. This evidence excludes position 8. Positions 4 and 6 are already occupied and in view of the results of Kaufmann and Petherd (Ber., 1917, 50, 336) who showed that carbostyril, when fully nitrated, formed 3:6:8-trinitrocarbostyril, Balaban concluded that, in the case of 4,6-dimethyl carbostyril, the nitro group entered

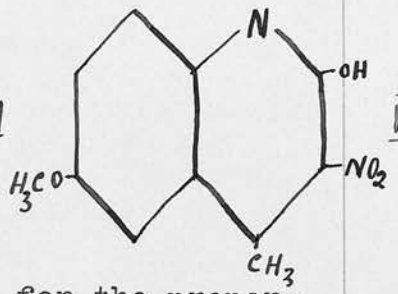
position 3 yielding 3-nitro-4,6-diemethylcarbostyril (VII). On similar grounds, it is probable that the mononitro derivative derived from 6-methoxy-4-methyl-carbostyril is 3-nitro-4-methyl-6-methoxycarbostyril (VIII).



VI

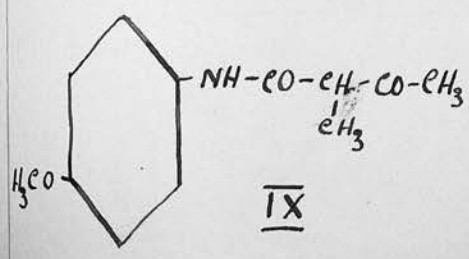


VII

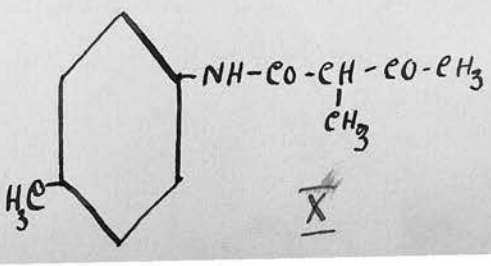


VIII

As this amino derivative was useless for the preparation of 8-aminocarbostyrils, a fresh start was made with p-anisidine (or p-toluidine) and ethylmethylacetoacetate. It was found that the desired anilides could be obtained by employing the same method as was successful in the preparation of the simpler acetoacetanilides. In spite of the greater insolubility of the esters in ligroin,- a point which rendered the separation more difficult,- β-methylacetoacet-p-anisidide (IX) and β-methylacetoacet-p-toluidide (X) were obtained as white crystalline products which, after recrystallisation from alcohol-water mixtures, melted at 105°-106° and 84°-85° respectively.



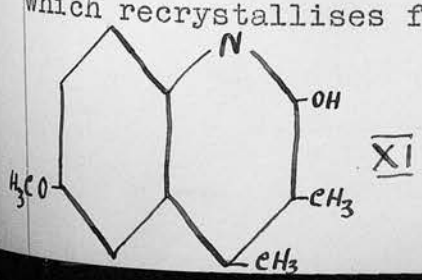
IX



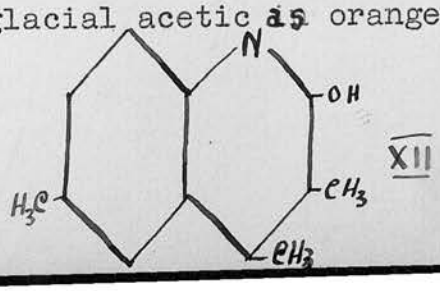
X

In order to obtain the corresponding carbostyrils, the anilides were heated on the water bath with 96 per cent sulphuric acid and on pouring into water 3,4-dimethyl-6-methoxycarbostyril (XI) and 3,4,6-trimethylcarbostyril (XII) were precipitated as white solids. Both recrystallised in the form of fine white needles from alcohol-water mixtures and melted at 279° and 269° respectively.

3,4-Dimethyl-6-methoxycarbostyril nitrated readily when a mixture of concentrated nitric and sulphuric acids were added to its solution in sulphuric acid. The resultant nitro compound was separated by pouring the acid on to ice when a mono-nitro derivative was obtained as an orange-yellow coloured precipitate. This dissolved readily in glacial adetic acid from which it separated, on cooling, as orange-yellow plates, m.p. 299°. This nitrogroup is presumably in position 8 as the other reactive positions namely, 3 and 6 are already occupied. The compound is therefore probably 8-nitro-3,4-dimethyl-6-methoxycarbostyril (XIII). 3-4-6-trimethylcarbostyril (XII) nitrates similarly to form a mononitro derivative, presumably 8-nitro-3,4,6-trimethylcarbostyril (XIV) which recrystallises from glacial acetic as orange-

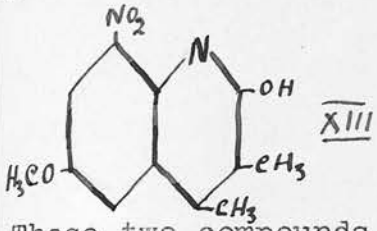


XI

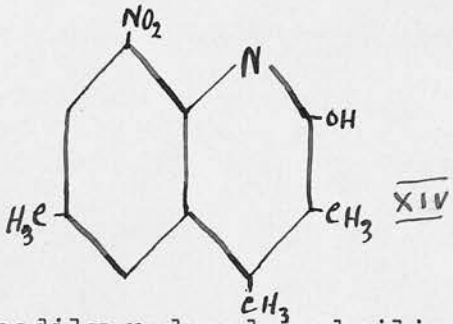


XII

yellow plates(m.p.278°).



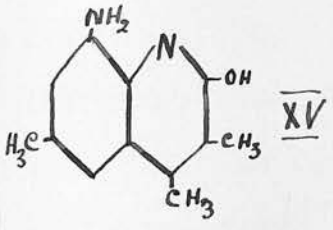
XIII



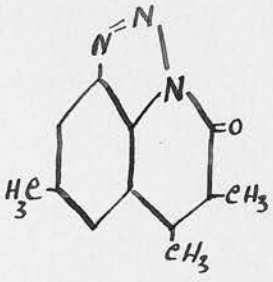
XIV

These two compounds were readily reduced in boiling acetic acid solution with zinc dust. The resultant bases were separated by pouring into a large amount of water and filtering off the precipitated amino-compounds. These were almost insoluble in most organic solvents, but dissolved readily in hot glacial acetic acid and separated from acetic acid-water mixtures as light brown-coloured plates, ~~m.p.313°~~. Only 8-amino-3,4,6-trimethylcarbostyril, m.p.312°(XV) was obtained analytically pure. Neither of these two amino compounds when treated with nitrous acid and β-naphthol gave an azo-dye stuff, thus supporting the view that the amino group is in position 8, and so confirming the formula assigned to the two nitro compounds. In the case of 8-amino-3,4,6-trimethyl-carbostyril, the triazole derivative(XVI)was prepared by adding sodium nitrite to the base dissolved in strong acetic acid. On neutralisation, the brown precipitate which separated was filtered off. This dissolved in a large quantity of hot dilute acetic acid from which the desired compound separated, on

cooling, as an amorphous, brown-coloured precipitate which gradually turned crystalline on standing. The compound was slightly soluble in dilute caustic soda, insoluble in dilute hydrochloric acid and did not melt below 320°.



XV



XVI

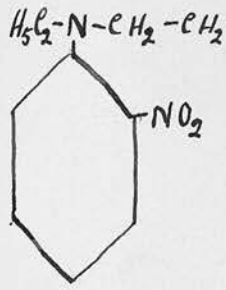
The acetyl derivative of 8-amino-3,4,6-trimethyl-carbostyril ~~(XVI)~~ obtained by boiling the base with acetic anhydride separated, after pouring into water as a light pink-coloured precipitate, m.p. 262°.

Attempts made to condense 8-amino-3,4,6-trimethyl-carbostyril with β-diethylaminoethyl chloride proved unsuccessful. In the first instance, equimolecular quantities of each base were heated together at 120° for three hours and the resultant dark brown-coloured mass extracted with moderately concentrated hydrochloric acid. The extract, on dilution, deposited a large quantity of unchanged amine, but no trace of the desired compound could be isolated. This experiment was repeated with the following modifications, (a) the temperature was kept at 150° instead of 120° and (b) the two compounds were dissolved in tetralene and refluxed (at 200°) in presence of

copper bronze. In both cases, 8-amino-3,4,6-trimethylcarbostyril was recovered unchanged. A compound separating on neutralisation of the filtrate, obtained after removal of the unchanged carbostyril, was found on analysis to consist of unchanged 8-amino-3,4,6-trimethylcarbostyril. It is probable therefore that an 8-amino group, present in carbostyril, is less reactive than in the corresponding quinoline group.

In order to obtain a carbostyril derivative with a basic side chain in the 8 position, an attempt was next made by a method in which the side chain was built up before closing the ring. For this purpose, o-chloro-nitrobenzene was condensed with β-diethylaminoethylethylamine. This reaction does not proceed very readily and several experiments had to be carried out before a method, giving a good yield, was obtained. In the first place, the condensation of o-bromonitrobenzene and β-diethylaminoethylethylamine was attempted in benzene solution, in presence of anhydrous potassium carbonate and a trace of copper bronze. Although producing bromine ions, the amount of unconverted o-bromonitrobenzene showed that the reaction was

very incomplete, even after prolonged boiling. To remedy this, the condensation was attempted (a) in toluene, (b) without a solvent and increasing yields resulted. As the yield was still low, it was decided to use the less expensive o-chloronitrobenzene, in large excess, in place of the equimolecular amounts of o-bromonitrobenzene employed above. Using three molecules of o-chloronitrobenzene to one molecule of amine at 150° for one hour in presence of copper bronze, a dark brown coloured product resulted, which was extracted with moderately concentrated hydrochloric acid, the unchanged nitro compound and any tar present being extracted with ether. The solution was then basified, the base extracted with ether and distilled in vacuo when o-[β-diethylaminoethylethylamino]-nitrobenzene (XVII) was obtained as a light brown-coloured oil, b.p. 180°-190° at 20 mm. pressure. This compound did not readily form salts, but a crystalline picrate (m.p. 85°-87°) was ultimately obtained by adding aqueous picric acid to a solution of the hydrochloride in water and recrystallising the precipitated picrate several times from hot water.



XVII

The base was reduced by adding the calculated amount (3 mols) of stannous chloride to its solution in concentrated hydrochloric acid, the reaction being complete after heating for an hour on the water bath. The solution was now saturated with hydrogen sulphide, the precipitated sulphide filtered off, and the filtrate basified. The oil which separated was extracted with ether and finally distilled in vacuo. The temperature did not remain steady but rose gradually from 175° to 200° at 15 mm. pressure. This would appear to indicate a mixture, a point confirmed by the failure of the base to form a crystalline salt. Attempts to produce a picrate and an acetyl derivative gave, in both cases, a sticky oil which did not crystallise on standing.

PRACTICAL II

Acetoacet-p-anisidide.

One molecule of p-anisidine (25 gm) was heated with four molecules (100 gm.) of ethylacetoacetate in an oil-bath at 155° for four hours. The excess ethyl-acetoacetate was distilled off in vacuo, care being taken to keep the temperature below 120° and the residue poured out and left to crystallise overnight. The sticky solid which separated was washed with hot ligroin until the last traces of ester had been removed; the acetoacet-p-anisidide remaining recryst-allised from alcohol and water as colourless needles m.p.113°, yield 7 gm.

Acetoacet-p-toluidide.

Four molecules (100 gm,) of ethylacetoacetate and one molecule (25 gm) of p-toluidine on similar treatment yielded acetoacet-p-toluidide which separated from alcohol-water mixture as colourless needles m.p.91°, yield 6 gm.

6-Methoxy-4-methylcarbostyril.

Acetoacet-p-anisidide (7 gm) was dissolved in 96% H_2SO_4 (15cc) and the resultant solution heated on the water bath for one hour. After cooling, the dark-coloured liquid was poured slowly, with stirring, into water when a white solid separated out. This was filtered off and separated from a water-alcohol mixture as colourless needles m.p.267°-268°, yield 4·5 gm.

4-6-Dimethylcarbostyril

Acetoacet-p-toluidide (6 gm), similarly treated with 96% H_2SO_4 (13cc), yielded a white precipitate on pouring into water which dissolved in hot alcohol-water mixtures and separated, on cooling, as colourless needles m.p.251°, yield 4·8 gm.

3-Nitro-4-methyl-6-methoxycarbostyril.

A nitrating mixture of HNO_3 (2c.c. of d. 1·41) and 96% H_2SO_4 (4 c.c.) was added slowly, with stirring, to a solution of 6-methoxy-4-methylcarbostyril (4 gm) in 96% H_2SO_4 (20 c.c.), cooled to 5°. After allowing to stand at room temperature for several hours, the liquid was poured on to ice when 3-nitro-4-methyl-6-methoxycarbostyril separated out as an orange-yellow precipitate. This, after filtering and

washing with water and dilute sodium carbonate solution, recrystallised from the minimum amount of glacial acetic acid in the form of orange-coloured needles m.p.280°, yield 2·8 gm.. Found N=12·3%, $C_{11}H_{10}O_4N_2$ requires N=12·0%.

3-Nitro-4,6-dimethylcarbostyril.

4-6-Dimethylcarbostyril (2 gm.) dissolved in 96% H_2SO_9 (10c.c.) was similarly nitrated by the addition of a mixture of HNO_3 (1 c.c. of d.1·41) and 96% H_2SO_4 (2 c.c.) to give a canary-yellow coloured solid which recrystallised from the minimum amount of acetic acid as light yellow needles m.p. 284°, yield 1 gm..

β-Methylacetoacet-p-anisidide

p-Anisidine (10 gm.) and ethylmethylaceto-acetate (40 gm.) were heated together on the oil bath at 155° for 4 hours. The excess ethylmethyl-acetoacetate was distilled off in vacuo below 130° and the dark reddish-brown coloured residue left to crystallise overnight. The resulting sticky mass was well pressed in a Buchner funnel and the remaining liquid removed by recrystallisation from a large volume of ligroin when β-methylacetoacet-

-p-anisidide separated as colourless needles which were recrystallised from alcohol and water m.p.117°, yield 5·5 gm.. Found N=6·5%, $C_{12}H_{15}O_3N$ requires N=6·3%.

β-Methylacetoacet-p-toluidide

p-Toluidine (10 gm.) and ethylmethylacetoacetate (40 gm.) on similar treatment yielded colourless needles of β-methylacetoacet-p-toluidide after recrystallisation from alcohol and water m.p.85°, yield 5·5 gm. Found N=7·0%, $C_{12}H_{15}O_2N$ requires N=6·9%.

Both these compounds are relatively insoluble in ligroin, benzene and petrol ether, but are very soluble in alcohol and acetone.

6-Methoxy-3,4-dimethylcarbostyril.

The ring closure was effected by heating a solution of β-methylacetoacet-p-anisidide (4 gm.) in 96% H_2SO_4 (10c.c.) on the water bath for one hour. 6-Methoxy-3-4-dimethylcarbostyril which separated on pouring into water, recrystallised from alcohol as colourless needles m.p.279°, yield 2·5 gm. Found N=6·9%, $C_{12}H_{13}O_2N$ requires N=6·9%.

3,4,6-Trimethylcarbostyril.

β-Methylacetoacet-p-toluidide (4 gm.) was in similar manner converted into 3,4,6-trimethylcarbostyril. The latter recrystallised from alcohol in colourless needles m.p.269°, yield 3·2 gm. Found N=7·4%, $C_{12}H_{13}ON$ requires N=7·5%.

Both these carbostyrils are insoluble in benzene, ligroin and petrol ether, but are sparingly soluble in alcohol.

8-Nitro-6-methoxy-3,4-dimethylcarbostyril

6-Methoxy-3,4-dimethylcarbostyril (2 gm.) was dissolved in 96% H_2SO_4 (10c.c.) and cooled to 0°C. A nitrating mixture of HNO_3 (1 c.c. of d.1·41) and 96 per cent H_2SO_4 (2 c.c.) was added slowly, with stirring, and the resultant solution allowed to stand at room temperature for two hours. The dark brown solution was then poured into water and the yellowish-brown precipitate filtered off and recrystallised from glacial acetic acid as orange-yellow plates m.p.299°, yield 1·5 gm. Found N=11·4%, $C_{12}H_{12}O_4N_2$ requires N=11·3%.

8-Nitro-3,4,6-trimethylcarbostyril.

3,4,6-Trimethylcarbostyril (6 gm.) was dissolved in 96 per cent H_2SO_4 (30 c.c.) and nitrated similarly to the above by a nitrating mixture of HNO_3 (2·5 c.c.

of d.1·41) and 96 per cent H_2SO_4 (5 c.c.). The resultant solution yielded, on pouring onto ice, 8-nitro-3,4,6-trimethylcarbostyril as an orange - yellow precipitate which crystallised from a small quantity of glacial acetic acid as orange-yellow plates m.p.278°, yield 6 gm. Found N=11·9%, $C_{12}H_{12}O_3N_2$ requires N=12·0%.

The two nitrocarbostyrils mentioned above are insoluble in alcohol, acetone, benzene, ligroin and petrol ether, but are both very soluble in glacial acetic acid.

8-Amino-3,4,6-trimethylcarbostyril

8-Nitro-3,4,6-trimethylcarbostyril (5 gm.) was dissolved in 90% acetic acid (50 c.c.) and heated till boiling. Zinc dust (6 gm) was then added in small portions and the mixture finally refluxed for one hour. The resultant yellowish-brown solution was filtered off and poured into a large volume of water and the 8-amino-3,4,6-trimethylcarbostyril which precipitated out was filtered off. The light-brown coloured amorphous solid recrystallised from an acetic acid-water mixture as light-brown plates m.p.312°. Found N=13·5%, C=70·8%, H=6·9%, $C_{12}H_{14}ON_2$ requires N=13·9%, C=71·2%, H=6·9%.

The base is insoluble in all the common organic

solvents and in dilute mineral acids, but is soluble in concentrated hydrochloric acid and very soluble in glacial acetic acid.

When it was boiled up with an excess of acetic anhydride for 10 minutes, a colourless solution resulted from which 8-acetylamino-3,4,6-trimethyl-carbostyril m.p.261° was precipitated, on pouring into water, as a light pink coloured precipitate.

The base was treated with sodium nitrite in acetic acid solution. After neutralisation with sodium hydroxide, a brown solid, which separated out, was filtered off and recrystallised from dilute acetic acid. This was ~~slightly~~ insoluble in dilute Na_2CO_3, slightly soluble in dilute NaOH, but insoluble in dilute HCl. It also proved to be very infusible as its melting point was above 320°. In addition, it failed to couple with β-naphthol and was probably the triazole derivative of 8-amino-3,4,6-trimethylcarbostyril.

Attempts to prepare 8-β-diethylaminoethylamino - 3,4,6-trimethylcarbostyril.

(a) 8-Amino-3,4,6-trimethylcarbostyril (2 gm.) was heated with β-diethylaminoethylchloride (1·5 gm.) and a trace of copper bronze for three hours at 120° and the resultant greyish-brown coloured mass

extracted with hot, moderately concentrated hydrochloric acid. The dark-brown solution was diluted with five to six times its volume of water when the unchanged 8-amino-3,4,6-trimethylcarbostyril was precipitated and filtered off. The filtrate on neutralisation gave a small dark brown precipitate which, after filtering and drying, melted at 305° (mixed with 8-amino-3,4,6-trimethylcarbostyril, m.p.309°)

(b) The above experiment was repeated at 15 0°, but a similar result was obtained.

(c) The experiment was carried out in presence of tetralene (20 c.c.) which enabled the temperature of the reaction to reach 200°. Although the heating was continued for eight hours, the same result was obtained as before.

o--[β-Diethylaminoethylethylamino-]-nitrobenzene.

β-Diethylaminoethylethylamine (6 gm.), o-chloronitrobenzene (18 gm) and a trace of copper bronze were heated at 160° for one hour. The resultant mixture was extracted with moderately concentrated hydrochloric acid and filtered, the filtrate being freed from tar by two extractions with ether. The dark-brown solution was then made alkaline and the

oil which separated extracted with ether. The ether extract was washed with water, dried over K_2CO_3 and evaporated down on the water bath. The dark brown-coloured oil remaining was distilled in vacuo, when the fraction distilling at 180°-190° under 20 mm. pressure was retained, yield 5 gm. This fraction containing practically pure o-[β-diethylaminoethylethylamino]-nitrobenzene was a light yellow coloured oil which was soluble in dilute mineral acids, alcohol, ether, acetone, benzene and chloroform.

The monopicrate was formed by adding a saturated aqueous solution of picric acid to a solution of the base in dilute HCl. The precipitate obtained recrystallised from hot water as short yellow prisms m.p.85°-87°. Found C=48·4%, H=5·3%, $C_{20}H_{26}O_9N_6$ requires C=48·6%, H=5·3%.

Attempt to reduce o-[β-diethylaminoethylethylamino]-nitrobenzene.

o-[β-Diethylaminoethylethylamino]-nitrobenzene (13·5 gm) was dissolved in concentrated HCl (65c.c.) and stannous chloride (29gm.) added. A slight cloudiness appeared at first, but this rapidly disappeared on heating on the water bath.

After heating for one hour, the solution was diluted to 600 c.c. and hydrogen sulphide passed through until all the tin had been precipitated as sulphide. The latter was filtered off and discarded. The filtrate and washings were then made alkaline with caustic soda and the oil separating extracted with ether. The ether extract was dried over anhydrous K_2CO_3 and evaporated down to dryness. The brown-coloured oil remaining was distilled in vacuo, when the fraction distilling at 180°-200° under 30 mm. pressure was retained.

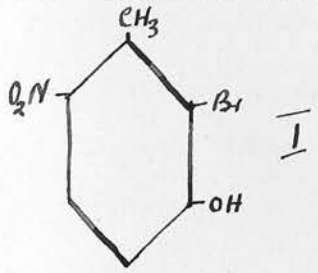
The picrate which was formed by the addition of alcoholic picric acid to the base in alcohol proved to be difficult to crystallise and, in every case, only a sticky oil remained.

DERIVATIVES OF m-CRESOL

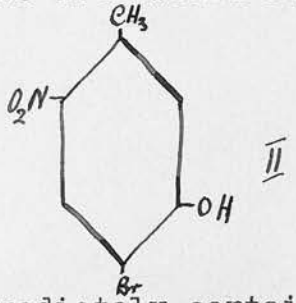
It has already been shown in Section I that 6-methoxy-8-methylquinoline is brominated by the method of Müller and Lang (loc.cit.) and that the monobromo derivative which is formed does not have the bromine atom in the ω-position, but that instead it has entered the nucleus. The following experiments show that, in all probability, it enters position 5, so that the compound, m.p. 116°-117°, is 6-methoxy-5-bromo-8-methylquinoline.

When 6-nitro-m-cresol (cf. Section I) was heated with bromine in chloroform solution at 35°-50° for three hours, a mixture of isomeric monobromo-6-nitro-m-cresols was obtained. As these proved impossible to separate by recrystallisation from benzene or ligroin, the mixture was dissolved in hot 10 per cent caustic soda. On cooling, a yellow precipitate of the sodium salts was obtained, but the cresol, regenerated from this by treatment with acid, though melting more sharply than the original product, was obviously still a mixture. Accordingly, the above

procedure was repeated several times and ultimately a crystalline product was obtained, which, after recrystallisation from benzene, melted sharply at 95°-97° (A). The combined mother-liquors produced on acidification a compound which was treated with 12 per cent caustic soda in the same manner as above. The resulting insoluble sodium salt was converted into a bromo-6-nitro-m-cresol which melted at 85°-110°. This was recrystallised from a fairly large amount of benzene, when the first batch of crystals, m.p.141°-144°, separating wœs retained and after further recrystallisation meltedat 145-146° (B). The compounds A and B are probably 2-bromo-6-nitro-m-cresol (I) and 4-bromo-6-nitro-m-cresol (II) as it is very unlikely that the bromine atom would enter



I



II

position 5, but it is not immediately certain which isomer is (A) and which is (B).

In order to determine the position of the bromine atom in the compounds A and B, an attempt was made

to convert them into the corresponding dibromo-6-nitrotoluenes which could be identified (cf. Cohen and Dutt J.C.S.1914, 105, 502; 3,4-dibromo-6-nitrotoluene). The bromonitrocresols were heated up with phosphorous pentabromide in chloroform, but, after refluxing for an hour, the only product obtained was unchanged bromo-6-nitro-m-cresol. When phosphorous pentabromide and the latter were heated alone on the water bath only a tar resulted.

In view of the failure of this method of establishing the identity of the compounds A and B, an alternative procedure was adopted, namely, methylation of the hydroxyl group, reduction of the nitro group and replacement of the amino group by bromine. The resultant dibromo-m-tolyl methyl ether was then synthesised by an alternative method, the identity of the two compounds leaving no doubt as to their orientation.

The two compounds (A and B) were therefore methylated by a modification of the method of Lapworth and Haworth (cf. Section I). The bromo-6-nitro-m-cresol was refluxed in benzene solution with dimethyl sulphate in presence of anhydrous potassium carbonate for eighteen hours. After filtering and

distilling off the benzene, an oil remained which was treated with dilute caustic soda to remove any unmethylated cresol. It then slowly solidified and the resulting colourless solid recrystallised from petrol ether, that derived from (A) in the form of rectangular plates, m.p.63°-65°, and that derived from (B) as needles, m.p.110°-111°, respectively.

The reduction of the compounds, m.p.63°-65°, and 110°-111°, was carried out by West's method (loc.cit.). The solution, obtained after filtering off the ferric hydroxide was evaporated to small volume and dilute hydrochloric acid added; any unchanged nitro-compound or tar present was then extracted with ether. The amino compound was separated by making alkaline and extracting with ether. After drying and evaporating the ether extract, a brown sticky oil remained which quickly solidified. On recrystallisation from petrol ether, purple (m.p.52°-54°) and brown (m.p.79°-80°) needles were obtained from the nitro compounds, m.p.63°-65° (from A), and m.p.110°-111° (from B) respectively. The compound, m.p.52°-54°, was obtained in very good yield along with very little tar. The compound, m.p.79°-80°, on the other hand, was obtained in relatively poor yield along with appreciable amounts of tar and a little unchanged nitro compound.

The compound, m.p. 52°-54°, formed an acetyl derivative when heated with acetic anhydride at 100°. This recrystallised from hot water in the form of pink needles, m.p. 150°-154°.

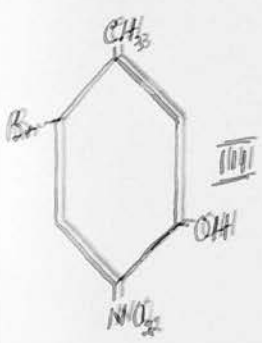
The base, m.p. 52°-54°, was converted into the corresponding dibromo derivative by means of a Sandmeyer Reaction in the usual way. After treatment of the diazo solution with cuprous bromide, a dark-coloured puffy mass resulted which, on treatment with water, yielded a dark brown oil which was extracted with ether and finally steam distilled. The distillate tended to be oily but, on standing overnight, it partly solidified to a white crystalline solid. This crystallised from petrol ether in the form of rectangular plates, m.p. 73°-74°.

This dibromo-m-tolylmethylether was then synthesised by a second method. 4-Nitro-6-bromo-m-cresol (III) had already been prepared (cf. Gibbs and Robertson J.C.S. 1914, 105, 1890). In the present work, bromination of 4-nitro-m-cresol was carried out under similar conditions to those described above with the exception that chloroform was used instead of acetic acid. The residue obtained after distilling off the chloroform was in this case homogeneous and, after one recrystallisation, 6-bromo-4-nitro-m-cresol was obtained in the form of light yellow

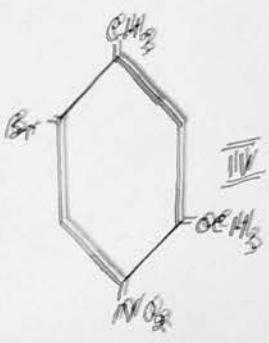
m-cresol was obtained in the form of light yellow rectangular plates, m.p.124°-126°. It is of interest to note that the sodium and potassium salts of this compound are a bright orange-red colour and are relatively insoluble in water. The corresponding salts of 6-nitro-m-cresol, its two bromo derivatives and 4-nitro-m-cresol are yellow and soluble in water.

The methylation was carried out in a similar manner to that already described for the two bromo-6-nitro-m-cresols. In this case, a solid was obtained after evaporation of the benzene. Since the sodium salt of 6-bromo-4-nitro-m-cresol is insoluble in water, the light red solid obtained by grinding the reaction product with dilute alkali was extracted with hot ligroin from which 6-bromo-4-nitro-5-methoxytoluene (IV) separated in the form of light pink needles, m.p.113°-115°.

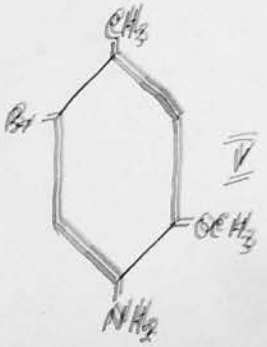
The reduction was carried out by West's Method (loc.cit.) and the reaction product worked up in the manner described above. 6-Bromo-5-methoxy-p-toluidine (V) so obtained recrystallised from



III



IV

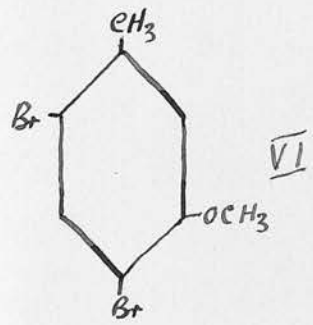


V

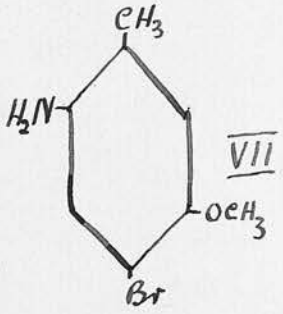
petrol ether in fern-shaped masses of needle-like rods, m.p. 71°-73°. In this reduction very little tar was produced and the yields amounted to 80-90 per cent of the theoretical. The acetyl derivative prepared by heating the base at 100° with acetic anhydride, recrystallised in the form of colourless needles, m.p. 130°-133°, from hot water.

6-Bromo-3-methoxy-p-toluidine was subjected to the Sandmeyer Reaction in similar manner to the base, m.p. 52°-54°. In this case, a reddish-brown cuprous diazo salt separated which had to be decomposed by heating on the water bath for a few minutes. The product was purified by steam distillation, the oil in this case crystallising rather more rapidly and completely than in the previously described experiment. The product, on recrystallisation, melted, as before, at 73°-74° and mixtures of the two gave no depression of the melting point and, in all other respects, were identical. Since the only dibromo product obtainable from 6-bromo-3-methoxy-p-toluidine by the Sandmeyer Reaction is 3-methoxy-4,6-dibromo-toluene (cf. Lapworth and Haworth J.C.S. 1923, 123, 2995) (VI), the compound, m.p. 73°-74°, must have this constitution. It therefore follows that the constitution of the base, m.p. 52°-54°, is 4-bromo-5-

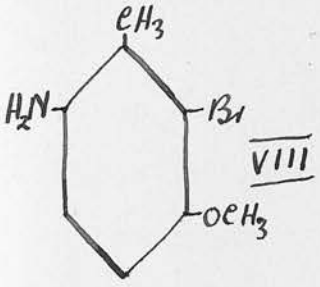
methoxy-o-toluidine (VII). The constitution of the compound, m.p. 79°-80°, is probably 6-bromo-5-methoxy-o-toluidine (VIII), the compounds A and B, 4-bromo-6-nitro-m-cresol (IX) and 2-bromo-6-nitro-m-cresol (X) respectively and the compounds, m.p. 63°-65°, and, m.p. 110°-111°, 4-bromo-6-nitro-3-methoxytoluene (XI) and 2-bromo-6-nitro-3-methoxytoluene (XII) respectively.



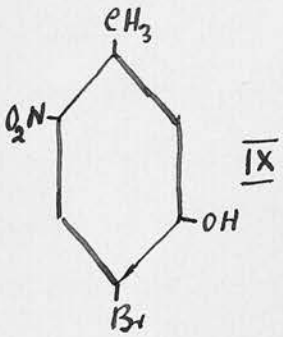
VI



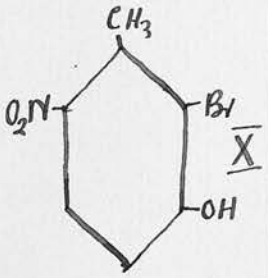
VII



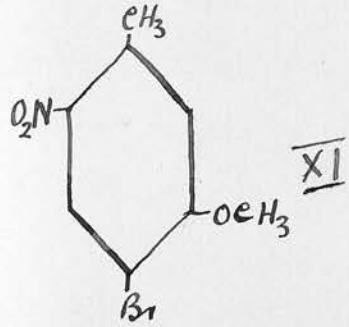
VIII



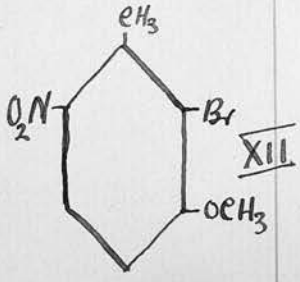
IX



X



XI



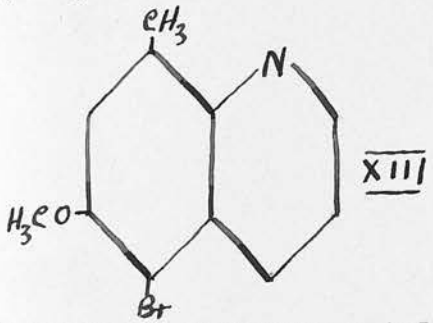
XII

4-Bromo-5-methoxy-o-toluidine was submitted to the Skraup Synthesis in the usual way. The dark brown reaction product obtained after four hours' heating with ferrous sulphate, glycerine, arsinic acid, and sulphuric acid was dissolved in water, made alkaline and filtered. The resulting mixture was freed from ferric hydroxide by extraction with alcohol. The base, recovered from the alcohol, was freed from any inorganic material by extraction with ether. The product obtained was impure and melted indefinitely about 100° after several recrystallisations. After several unsuccessful attempts to purify the product by recrystallisation from various solvents, it was found that the mixture could be separated into two hydrobromides. The base was dissolved in acetone and alcoholic hydrobromic acid added when a small quantity of an insoluble hydrobromide was obtained and filtered off. The filtrate on evaporation yielded a light yellow crystalline salt which readily dissolved in water and yielded a base, m.p.108°-110°, on making alkaline. The above treatment was repeated when a further small quantity of insoluble hydrobromide was obtained. The base, regenerated from its salt, now melted at 112° and, after recrystallisation from petrol ether,

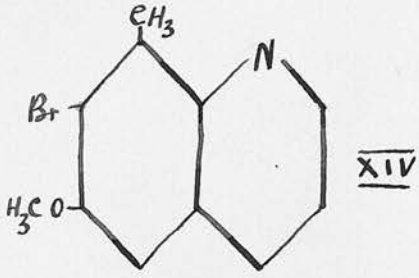
melted at 116°. This base constituted the main product of the reaction. A mixed melting point determination with the compound, m.p.116°-117°, obtained by bromination of 6-methoxy-8-methylquinoline, showed them to be identical. The insoluble hydrobromide, which constituted only a small fraction of the total yield of crude product was insoluble in water, but was, however, readily converted into a base by boiling with dilute alkali when a colourless compound melting about 120° was obtained. This, after several recrystallisations from petrol ether, finally melted sharply at 134°-135°. Analysis proved that this compound was also a monobromo derivative of 6-methoxy-8-methylquinoline.

The unexpected occurrence of the second monobromo-6-methoxy-8-methylquinoline is difficult to explain. It does not seem possible that the Skraup Reaction, applied to 4-bromo-5-methoxy-o-toluidine, could yield any product of this empirical constitution other than 5-bromo-6-methoxy-8-methylquinoline (XIII). The possibility must therefore be considered that the 4-bromo-5-methoxy-o-toluidine employed was contaminated with a small quantity of an isomer. Although the compounds 4-bromo-6-nitro-m-cresol, m.p.

95°-97°, 4-bromo-6-nitro-3-methoxytoluene, m.p.63°-65°, and 4-bromo-5-methoxy-o-toluidine, m.p.52°-54°, gave no indication of being other than pure substances, it was realised that they showed a certain lack of sharpness in their melting points. This was particularly marked in the case of the acetyl derivative of 4-bromo-5-methoxy-o-toluidine. Various attempts to effect further purification of these compounds have, however, been without success. Nevertheless, it seems that this explanation is most probably the true one and that the quinoline compound, m.p.134°-135°, is 7-bromo-6-methoxy-8-methylquinoline (XIV) formed from a small admixture of



XIII



XIV

6-bromo-5-methoxy-o-toluidine in the 4-bromo-5-methoxy-o-toluidine employed. It is realised that this conclusion introduces a small element of doubt into the conclusions arrived at above regarding the orientation of these bromo derivatives, as it is always possible that the dibromo-m-tolylmethyl ether, isolated in the Sandmeyer Reaction, applied to the 4-bromo-5-methoxy-o-toluidine, may have originated

~~4-brome-5-methoxy-o-toluidine, may have originated~~ from the impurity present. Consideration of the yields obtained, however, seems to render this possibility extremely unlikely. It is hoped that further work will result in excluding it completely, but, at present, it is necessary to note that the orientations of the compounds established in this section, though extremely probable, must be regarded as provisional.

PRACTICAL III

4-Bromo-6-nitro-m-cresol and 2-bromo-6-nitro-m-cresol.

6-Nitro-m-cresol (40 gm) was dissolved in chloroform (140 c.c.) at 35° and bromine (13·6 c.c.) in chloroform (14 c.c.) added. The mixture was heated at 40° for three hours when hydrogen bromide was steadily evolved. After standing overnight, the chloroform was distilled off, leaving a light yellow crystalline residue. This was dissolved by heating with caustic soda (200 c.c. of 10%). After cooling, a yellow crystalline salt separated which was filtered off and recrystallised several times from 10% caustic soda. The salt was then decomposed by dilute acid and the crude 4-bromo-6-nitro-m-cresol obtained recrystallised several times from benzene. This compound was finally obtained as colourless needles m.p.95°-97°, yield 24 gm. Found C=36·4%, H=2·7%, $C_7H_6O_3NBr$ requires C=36·2%, H=2·6%.

The combined filtrates from the sodium salt were made acid and the cresol which separated was heated with stronger caustic soda solution (12%).

The sodium salt which crystallised out on cooling was filtered off, decomposed by acid and dissolved in hot benzene. After concentrating and cooling, the first batch of crystals which separated was filtered off and light brown needles, m.p.145°-146°, of 2-bromo-6-nitro-m-cresol were obtained pure after one recrystallisation from benzene, yield 3 gm. Found C=36·3%, H=2·6%, $C_7H_6O_3NBr$ requires C=36·2%, H=2·6%.

Both 2-bromo- and 4-bromo-6-nitro-m-cresols are sparingly soluble in hot ligroin, moderately soluble in hot benzene and very soluble in cold acetone, ether, chloroform, alcohol, dilute caustic soda and dilute caustic potash.

6-Bromo-4-nitro-m-cresol was prepared from 4-nitro-m-cresol in exactly similar manner as described above for 2-bromo-and 4-bromo-6-nitro-m-cresols. The crystalline mass obtained after distilling off the chloroform proved in this case to be homogeneous and on recrystallisation from benzene, light yellow rectangular plates, m.p.124°-126°, of 6-bromo-4-nitro-m-cresol were obtained.

This compound differs from the two preceding in that it forms red insoluble sodium and potassium salts with dilute caustic soda and dilute caustic potash respectively.

4-Bromo-6-nitro-3-methoxytoluene

4-Bromo-6-nitro-m-cresol (18·4 gm), benzene (120 c.c.) and dimethylsulphate (12 c.c.) were refluxed in presence of anhydrous K_2CO_3 (12·4 gm) for eighteen hours. The K_2CO_3 and K_2SO_4 were separated by filtering the hot liquid, the benzene removed by distillation and the residue treated with dilute caustic soda when the insoluble oil gradually solidified. The product was filtered, washed with water, dried in vacuo and recrystallised from petrol ether as colourless rectangular plates, m.p.63°-65°, yield 70%. Found Br=32·6%, $C_8H_8O_3NBr$ requires Br=32·6%.

2-Bromo-6-nitro-3-methoxytoluene

2-Bromo-6-nitro-m-cresol (3gm), benzene (20c.c.), dimethylsulphate (2 c.c.) and anhydrous K_2CO_2 (2 gm) were similarly treated. 2-Bromo-6-nitro-3-methoxy-toluene recrystallised from petrol ether in the form of colourless needles, m.p.110°-111°, yield 2 gm. Found Br=31·6% and 31·4%, $C_8H_8O_3NBr$ requires Br=32·6%.

6-Bromo-4-nitro-3-methoxytoluene

6-Bromo-4-nitro-m-cresol was prepared in similar manner with the exception that it was necessary to extract the 6-bromo-4-nitro-3-methoxytoluene with hot ligroin after treatment with dilute caustic soda. After concentration the compound separated as light pink needles, m.p.113°-115°, yield 90 per cent.

Found C=38·8%, H=3·3%, $C_8H_8O_3NBr$ requires C=39·0%; H=3·4%.

These three isomers are alike in their general properties; that is, they are all very soluble in acetone and chloroform, soluble in ether, benzene and alcohol. 6-Bromo-4-nitro-3-methoxytoluene, however, is only slightly soluble in hot ligroin and petrol ether, whilst the other two are moderately soluble in these reagents.

4-Bromo-5-methoxy-o-toluidine

4-Bromo-6-nitro-3-methoxytoluene (5 gm) was dissolved in methylated spirits (25 c.c.) containing conc. HCl (2 c.c.). Iron filings (3·5 gm) were added in four batches at five minute intervals to the boiling solution and the whole kept boiling vigorously for a further two hours. The hot solution was neutralised with hot alcoholic caustic potash, filtered and washed well with hot alcohol. The alcohol was removed by distillation and the oily residue treated with dilute acid and extracted with ether. The acid extract was made alkaline and again extracted with ether. The ether extract was dried over anhydrous K_2CO_3 and evaporated to dryness when a brown oil, which solidified on standing, was obtained. This recrystallised from petrol ether as

purple needles, m.p.52°-54°, yield 80% - 90% of the theoretical. Found Br=37·3%, $C_8H_{10}ONBr$ requires Br=37·0%.

This base yielded a hydrochloride sparingly soluble in dilute HCl.

The acetyl derivative which was prepared by heating the base with excess acetic anhydride on the water bath, separated on pouring into water as a light pink precipitate, which recrystallised from hot water as pink needles m.p.150°-154°. Found C=46·5%, H=4·7%, $C_{10}H_{12}O_2NBr$ requires C=46·5%, H=4·6%.

6-Bromo-5-methoxy-o-toluidine

2-Bromo-6-nitro-3-methoxytoluene (2 gm) was similarly treated in methylated spirit (10 c.c.) and conc. HCl (1 c.c.) with iron filings (1·4 gm). In this case, a large amount of the crude product remained insoluble in dilute HCl and was extracted with ether. The oil obtained from the second ether extraction solidified quickly and dissolved readily in hot petrol ether, depositing light brown needles, m.p.79°-80°, on cooling, yield very small. Found Br=36·9%, $C_8H_{10}ONBr$ requires Br=37·0%.

6-Bromo-3-methoxy-p-toluidine

6-Bromo-4-nitro-3-methoxytoluene (5 gm) was treated similarly to the above with methylated spirit (25 c.c.), conc. HCl (2 c.c.) and iron filings (3·5 gm).

The crude product was practically entirely soluble in dilute HCl and a brown oil which quickly solidified was finally obtained. This dissolved readily in hot petrol ether and separated, on cooling, as fern-shaped masses of needle-like rods m.p.71°-73°. Found Br=37·3%, $C_8H_{10}ONBr$ requires Br=37·0%.

The acetyl derivative which was prepared by heating the base with excess acetic anhydride on the water bath, separated as a white precipitate on pouring into water. This recrystallised from hot water as colourless needles, m.p.130°-133°. Found C=46·2%, H=4·7%, $C_{10}H_{12}O_2NBr$ requires C=46·5%, H=4·6%.

The three bases described above are all very soluble in ether, alcohol, acetone, chloroform and benzene, soluble in petrol ether and moderately soluble in dilute mineral acids.

3-Methoxy-4,6-dibromotoluene

(a) From 6-Bromo-3-methoxy-p-toluidine

6-Bromo-3-methoxy-p-toluidine (2 gm) was ground up with conc. HCl (2 c.c.) and water (1·2 cc.) in order to obtain a fine suspension of the hydrochloride. This was cooled to 0° and solid sodium nitrite (·8 gm) added slowly with shaking. The clear brown solution obtained in this way was now

added slowly with stirring to a solution of cuprous bromide (3-4 c.c.) obtained in the following way. Cupric sulphate (18 gm) in water (60 c.c.) and potassium bromide (9 gm) in water (20 c.c.) were mixed and reduced by sulphur dioxide. The white precipitate obtained was filtered, washed with water and dissolved in hydrobromic acid (30 c.c.) of S.G.1·49). The nitrogen was immediately evolved and a reddish-brown precipitate formed which was decomposed by heating on the steam bath with further evolution of nitrogen. The liquid was now steam-distilled when an oil came over which partially crystallised to a colourless solid. This was filtered off, dried on a porous tile and recrystallised from petrol ether as colourless rectangular plates m.p.73°-74°.
Found Br=57·3%, $C_8H_8OBr_2$ requires Br=57·5%.

(b) From 4-Bromo-5-methoxy-o-toluidine.

4-Bromo-5-methoxy-o-toluidine (2 gm) was submitted to the Sandmeyer Reaction in exactly similar manner to that described above, but in this case no reddish-brown precipitate was obtained. The product on steam distillation, crystallised less completely than in the previous experiment. The colourless crystals obtained separated from petrol ether as colourless rectangular plates, m.p.73°-74°.
A mixture of this product with the above gave no

depression in the melting point and, in all other respects, the two products were identical.

5-Bromo-6-methoxy-8-methylquinoline and 7-bromo-6-methoxy-8-methylquinoline.

Ferrous sulphate (·4 gm), glycerol (8·4 gm), 4-bromo-5-methoxy-o-toluidine (6 gm), arsinic acid (4 gm) and sulphuric acid (8 gm. of 96%) were thoroughly mixed and gently refluxed for four hours. The resultant dark brown sticky liquid was poured into water (500 c.c.) and allowed to stand overnight. Any tar which had separated was filtered off and the filtrate made strongly alkaline and again filtered. The residue was extracted three times with boiling alcohol and the extract evaporated to dryness. A small quantity of water was added and the whole extracted with ether. The ether extract was washed with water, dried over anhydrous K_2CO_3 and evaporated to dryness. The red-coloured residue which quickly solidified was dissolved in acetone and an equal quantity of alcoholic hydrobromic acid added. A small quantity of a white precipitate was filtered off and the filtrate evaporated to dryness. The light yellow salt remaining was converted into the base and again treated in similar fashion employing smaller quantities of the reagents, when a further small quantity of a white insoluble salt was obtained.

The filtrate on evaporation yielded a pale yellow crystalline hydrobromide from which 5-bromo-6-methoxy-8-methylquinoline was obtained on treatment with alkali. The base recrystallised from petrol ether as colourless rectangular plates, m.p.116°, and was found to be identical to the product obtained in section I of the present work. (N.B.A hydrobromide obtained in the manner indiciated above melted at 230° and was identical in every respect to the corresponding hydrobromide described in section I).

The insoluble hydrobromide obtained above proved to be insoluble in water, but, after boiling with dilute caustic soda, cooling and filtering, a small quantity of what is probably 7-bromo-6-methoxy-8-methylquinoline was obtained. This after several recrystallisations from petrol ether was obtained as colourless rectangular prisms, m.p.134°-135°. Found C=52·6%, H=4·2%, N=5·4%, Br=31·6%, $C_{11}H_{10}ONBr$ requires C=52·4%, H=4·0%, N=5·4% and Br 31·7%.

7-Bromo-6-methoxy-8-methylquinoline is soluble in alcohol, acetone, chloroform, ether and dilute H_2SO_4, moderately soluble in petrol ether, but is insoluble in dilute HCl and HBr.

SUMMARY

II. Various attempts to synthesise derivatives of 6- and 8-methylquinoline are described. The synthesis of di-[quinolyl-8-methyl-]-1,4-piperazine, di-[quinolyl-8-methyl-]-aminoethyldiethylamine, di-[quinolyl-8-methyl-]-aminoethylpiperidine, 8-[β-diethylaminoethylaminomethyl-]-quinoline and 8-[β-piperidinoethylmethylaminomethyl-]-quinoline, 5-bromo-6-methoxy-8-methylquinoline, 3-bromo-6-nitro-8-methylquinoline and the syntheses of a number of related compounds are described.

III. The synthesis of a number of carbostyril derivatives of which 8-amino-3,4,6-trimethylcarbostyril is the most important, is described.

IV. The synthesis of 5-bromo-6-methoxy-8-methylquinoline from m-cresol, in addition to the bromination of m-cresol, the methylation, reduction and ultimate orientation of the two isomers formed, is described.