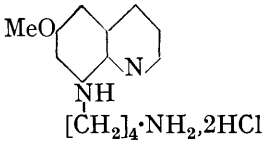
330. *Attempts to find New Antimalarials. Part XII. Further Variations in the Group of the Quinolines with Basic Side Chains.*

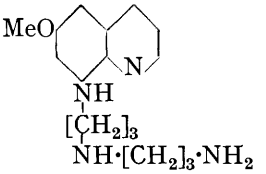
By ROBERT ROBINSON and (Miss) M. L. TOMLINSON.

THE general underlying idea of this series of investigations has been sufficiently explained in earlier parts; in extending the work we have been guided by biological reports and by the desire to exploit all the more readily accessible forms of side-chain basic groups. In addition we wished to prepare plasmoquine analogues in the carbazole and acridine groups, but have not yet completed the latter projects.

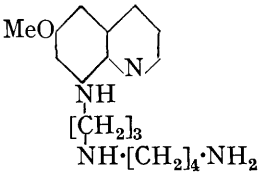
The following is a summary of the experimental section. (1) 8-Amino-6-methoxyquinoline and phthalo-δ-bromobutylimide were condensed and the product was hydrolysed to give 8-δ-*aminobutylamino*-6-*methoxyquinoline dihydrochloride* (I).



(I.)



(II.)

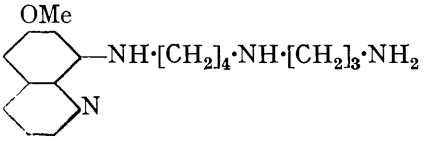


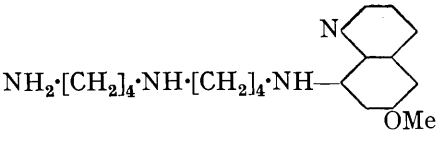
(III.)

(2) 8-γ-Aminopropylamino-6-methoxyquinoline has been condensed with phthalo-γ-bromopropylimide and with phthalo-δ-bromobutylimide and the products have been hydrolysed to give the hydrochlorides of 8-γ′-aminopropyl-γ-aminopropylamino-6-methoxyquinoline (II) and 8-δ′-aminobutyl-γ-aminopropylamino-6-methoxyquinoline (III) respectively.

8-δ-Aminobutylamino-6-methoxyquinoline has been condensed with phthalo-γ-bromopropylimide and with phthalo-δ-bromobutylimide and the products have been hydrolysed to give the hydrochlorides of (IV) and (V) respectively. These four substances have not been obtained in a demonstrably pure condition, but the specimens have a powerful antimalarial action.

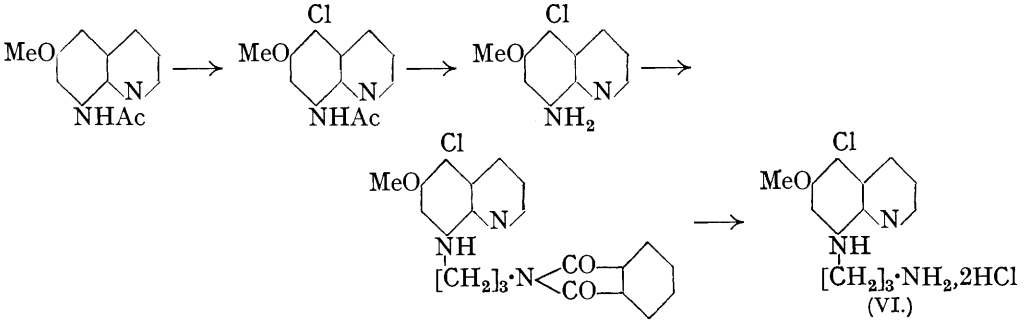
(IV.)





(V.)

(3) 5-*Chloro*-8-γ-*aminopropylamino*-6-*methoxyquinoline dihydrochloride* (VI) has been prepared :

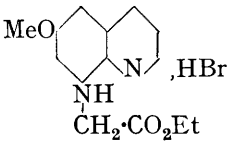


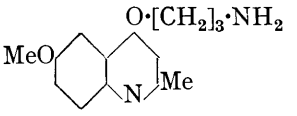
(VI.)

(4) 8-Amino-6-methoxyquinoline has been condensed with ethyl bromoacetate with formation of (VII).

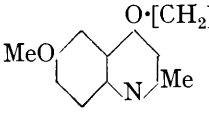
(5) 4-Hydroxy-6-methoxyquinaldine (Slater, J., 1931, 109) has been condensed with

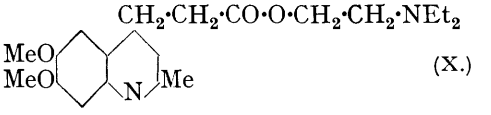
phthalo-γ-bromopropylimide, and the product hydrolysed to 4-*γ-aminopropoxy*-6-*methoxyquinaldine* (VIII).

(VII.) 


(VIII.)

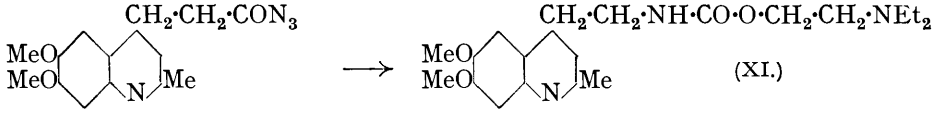
(6) 4-γ-Aminopropoxy-6-methoxyquinaldine has been condensed with phthalo-γ-bromopropylimide, and the product hydrolysed to give the *trihydrochloride* of 4-γ′-aminopropyl-γ-aminopropoxy-6-methoxyquinoline (IX).

(IX.) 

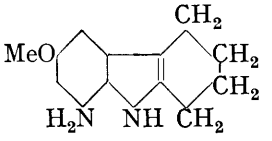

(X.)

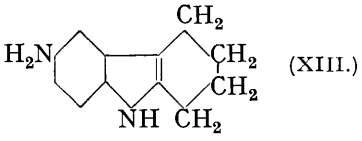
(7) Methyl 6 : 7-dimethoxyquinaldine-4-propionate (Miki and Robinson, J., 1933, 1467) has been converted into the diethylaminoethyl ester (X).

(8) The azide of 6 : 7-dimethoxyquinaldine-4-propionic acid has been decomposed in diethylaminoethanol solution, yielding the corresponding urethane (XI).


(XI.)

(9) 8-Amino-6-methoxytetrahydrocarbazole (XII) was prepared, but could not be condensed with phthalo-γ-bromopropylimide. Neither could 6-aminotetrahydrocarbazole

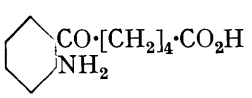
(XII.) 

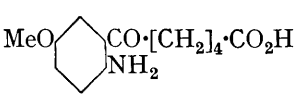

(XIII.)

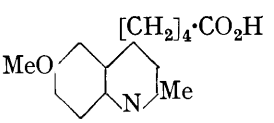
(XIII) (Perkin and Plant, J., 1921, **119**, 1833) be condensed with phthalo-γ-bromopropylimide to a crystalline product. Furthermore, 9-acylation did not improve the position and even 3 : 6-diaminocarbazole (Ziersch, *Ber.*, 1909, **42**, 3799) failed to yield a crystalline product on reaction with phthalo-γ-bromopropylimide.

(10) Perkin and Plant (J., 1923, **123**, 676) found that when 9-benzoyltetrahydrocarbazole was nitrated, 11-nitro-9-benzoyl-10-hydroxyhexahydrocarbazole was obtained, and on hydrolysis with potassium hydroxide this substance yielded δ-*o*-aminobenzoylvaleric acid (XIV).

It was thought that it might be possible to prepare δ-5-methoxy-2-aminobenzoylvaleric acid (XV) in a similar way from 6-methoxytetrahydrocarbazole (Borsche, Witte, and Bothe, *Annalen*, 1908, **359**, 64), which was accordingly benzoylated and nitrated, but the only product isolated was a nitro-substitution product, probably 5(or 7)-*nitro*-6-*methoxy*-9-*benzoyltetrahydrocarbazole*. The project for the synthesis of 6-methoxyquinaldine-4-valeric acid (XVI) from δ-5-methoxy-2-aminobenzoylvaleric acid by condensation with acetone was perforce abandoned (compare the method of Miki and Robinson, *loc. cit.*).

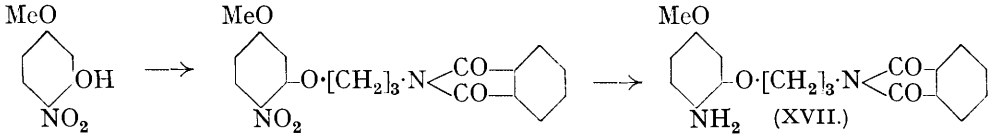

(XIV.)


(XV.)

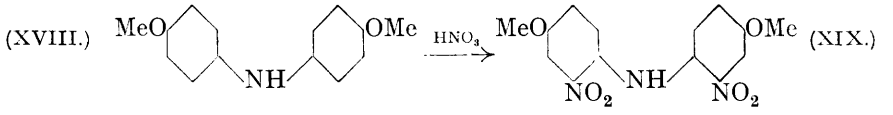

(XVI.)

(11) 2-Nitro-5-methoxyphenol (Hodgson and Clay, J., 1929, 2795) has been condensed with phthalo-γ-bromopropylimide and the nitro-group reduced to give 2-*amino-γ-phthal-*

imidopropoxy-5-methoxybenzene (XVII). This amine could not, however, be converted into either quinoline or tetrahydrocarbazole derivatives.

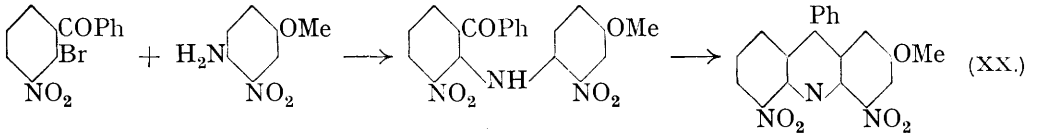


(12) 4-Iodo-3-nitroanisole (Reverdin, *Ber.*, 1896, **29**, 2595) was condensed with 3-nitro-*p*-anisidine with formation of 2 : 2′-dinitro-4 : 4′-dimethoxydiphenylamine (XIX), which has also been prepared by nitration of 4 : 4′-dimethoxydiphenylamine (XVIII) (Wieland, *Ber.*, 1908, **41**, 3493). All attempts to convert this compound or its acetyl derivative into acridines have failed.



By treating this diphenylamine with formaldehyde in sulphuric acid solution, an unidentified red substance, $C_{16}H_{13}O_8N_3$, has, however, been obtained and this may be related to the acridine series.

2-Bromo-3-nitrobenzophenone (Plant and Tomlinson, J., 1932, 2191) condensed with 3-nitro-*p*-anisidine to give 1 : 9-*dinitro-3-methoxy-5-phenylacridine* (XX), which has been reduced and the crude product acetylated to produce 1 : 9-*diacetamido-3-methoxy-5-phenylacridine*; this on hydrolysis affords a sparingly soluble hydrochloride.



Experimental.

8-δ-*Phthalimidobutylamino-6-methoxyquinoline Hydrobromide.*—8-Amino-6-methoxyquinoline (2 g.) and phthalo-δ-bromobutylimide (3 g.) were heated together at 130° for 6 hours. The product, recrystallised from alcohol, formed yellow prisms, m. p. 196—198° (decomp.) (Found : N, 9·5; Br, 17·5. $C_{22}H_{21}O_3N_3$,HBr requires N, 9·2; Br, 17·5%). The *hydrobromide* was decomposed by trituration with caustic soda and the base was isolated by means of ether.

8-δ-*Aminobutylamino-6-methoxyquinoline Dihydrochloride.*—An alcoholic solution of the above base along with hydrazine (1 equiv.) was boiled for 1½ hours and then concentrated, and the residue heated with dilute hydrochloric acid for 15 minutes. Phthalhydrazide was removed by filtration and the solution was rendered alkaline and the base extracted with ether, the ethereal solution dried with potassium carbonate, and the *hydrochloride* precipitated by passage of hydrogen chloride. The product crystallised from alcohol in orange-yellow needles, m. p. 208° (decomp.) (Found : C, 51·4; H, 6·8; N, 12·3; Cl, 21·3. $C_{14}H_{19}ON_3$,2HCl,0·5H_2O requires C, 51·4; H, 6·7; N, 12·8; Cl, 21·7%) (R.72).

8-γ′-*Aminopropyl-γ-aminopropylamino-6-methoxyquinoline Hydrochloride* (R.63).—8-γ-Aminopropylamino-6-methoxyquinoline was heated at 115° with an equivalent of phthalo-γ-bromopropylimide for 7 hours. The product was hydrolysed by hydrazine, followed by dilute hydrochloric acid, and the base isolated and converted into an extremely deliquescent hydrochloride. It was found impossible to crystallise either this salt or the picrate.

Butylation of the above base (2·2 g.) was effected by boiling it with *n*-butyl iodide (4 g.) in sodium carbonate solution (40 c.c. of 10%) for 6 hours, and a hydrochloride (R.64) was obtained in the usual way.

8-γ′-*Octylaminopropyl-β-aminoethylamino-6-methoxyquinoline Hydrochloride* (R.66).—8-β-Aminoethylamino-6-methoxyquinoline was condensed with phthalo-γ-bromopropylimide in the usual way and the base obtained by hydrolysis with hydrazine was boiled for 6 hours with *n*-octyl bromide (2·5 mols.) in sodium carbonate solution. The product was isolated as the deliquescent hydrochloride.

In a similar manner 8-γ-aminopropylamino-6-methoxyquinoline has been condensed with

phthalo-δ-bromobutylimide to give 8-δ′-aminobutyl-γ-aminopropylamino-6-methoxyquinoline (R.76), and 8-δ-aminobutylamino-6-methoxyquinoline has been condensed with both phthalo-γ-bromopropylimide and phthalo-δ-bromobutylimide to give 8-γ′-aminopropylamino-δ-butylamino-6-methoxyquinoline (R.74) and 8-δ′-aminobutylamino-δ-butylamino-6-methoxyquinoline (R.75) respectively. The hydrochlorides of all these products were extremely soluble, deliquescent substances and in no case was it possible to obtain pure crystalline compounds. They have been examined in this state for antimalarial activity and are only mentioned here because preliminary reports on the specimens show that their therapeutic indices in bird malaria are unusually high.

8-*Acetamido*-6-*methoxyquinoline*.—8-Amino-6-methoxyquinoline was gently heated with acetic anhydride for a few minutes, and the mixture poured into water. The product crystallised from alcohol in colourless needles, m. p. 126° (Found : N, 12·7. $C_{12}H_{12}O_2N_2$ requires N, 13·0%).

5-*Chloro*-8-*acetamido*-6-*methoxyquinoline*.—A saturated solution of chlorine in acetic acid (7 c.c.) was added to a solution of the above acetamido-compound in a little acetic acid; a solid hydrochloride then separated. This was triturated with ammonia; the *base* crystallised from alcohol in colourless plates, m. p. 169° (Found : C, 57·5; H, 4·3. $C_{12}H_{11}O_2N_2Cl$ requires C, 57·6; H, 4·4%).

5-*Chloro*-8-*amino*-6-*methoxyquinoline*.—The acetyl derivative was boiled with hydrochloric acid for a few minutes. The *hydrochloride* obtained crystallised from alcohol in shining red needles, m. p. 264° (decomp.) (Found : N, 11·6; Cl, 28·8. $C_{10}H_9ON_2Cl,HCl$ requires N, 11·4; Cl, 29·0%). The related *base* crystallised from methyl alcohol in prisms, m. p. 150—152° (Found: C, 57·8; H, 4·5. $C_{10}H_9ON_2Cl$ requires C, 57·7; H, 4·3%).

5-*Chloro*-8-γ-*phthalimidopropylamino*-6-*methoxyquinoline*.—Equivalent quantities of 5-chloro-8-amino-6-methoxyquinoline and phthalo-γ-bromopropylimide were heated together at 100° for 8 hours. The product was rubbed with alcohol and the crystalline hydrobromide obtained was triturated with aqueous caustic soda; the *base* crystallised from alcohol in yellow needles, m. p. 153—154° (Found : C, 63·9; H, 4·7. $C_{21}H_{18}O_3N_3Cl$ requires C, 63·9; H, 4·6%).

5-*Chloro*-8-γ-*aminopropylamino*-6-*methoxyquinoline Dihydrochloride*.—The phthalimido-compound (2 g.) was refluxed for 5 hours with alcohol (200 c.c.) and hydrazine hydrate (0·4 g.), the solution evaporated to dryness, and the residue heated with dilute hydrochloric acid for 15 minutes. The deep red, filtered solution was basified and extracted with ether, the extract dried, and hydrogen chloride passed, giving a *dihydrochloride*, which separated from alcohol in red prisms, m. p. 235° (decomp.) and earlier darkening (Found : C, 43·9; H, 5·6; N, 11·6; Cl, 29·6. $C_{13}H_{16}ON_3Cl,2HCl,H_2O$ requires C, 43·8; H, 5·6; N, 11·8; Cl, 29·8%) (R.77).

Ethyl 6-*Methoxyquinolyl*-8-*aminoacetate*.—8-Amino-6-methoxyquinoline was heated on a steam-bath with an excess of ethyl bromoacetate; 8-amino-6-methoxyquinoline hydrobromide quickly separated. This was removed by filtration and washed with ether; hydrogen chloride was then passed into the filtrate and a yellow hydrochloride was precipitated. A solution of this salt was basified, and an ester extracted and distilled; the fraction, b. p. 115—130°/13 mm., was collected. It crystallised and was converted into a *hydrobromide*, which separated from alcohol in yellow needles, m. p. 203° (decomp.) with previous blackening (Found : C, 49·5; H, 4·9; Br, 23·6. $C_{14}H_{16}O_3N_2,HBr$ requires C, 49·3; H, 5·0; Br, 23·5%) (R.73).

Condensation of 8-*Amino*-6-*methoxyquinoline with Ethylene Chlorohydrin*.—A solution of 8-amino-6-methoxyquinoline in ethylene chlorohydrin was refluxed for ½ hour and then washed with ether, leaving a reddish-brown residue. This was freely soluble in water but could not be purified (Found : N, 8·4. $C_{14}H_{20}O_3N_2Cl_2$ requires N, 8·4%). The nitrogen content indicates an average introduction of two hydroxyethyl groups.

4-γ-*Phthalimidopropoxy*-6-*methoxyquinaldine*.—4-Hydroxy-6-methoxyquinaldine (8 g.), phthalo-γ-bromopropylimide (10 g.), and potassium carbonate (4 g.) were heated together at 140° for ½ hour. The mass fused and solidified again to a purple solid, which was washed with water and recrystallised from alcohol, forming fine colourless needles, m. p. 197° (Found : C, 70·2; H, 5·5. $C_{22}H_{20}O_4N_2$ requires C, 70·2; H, 5·3%).

4-γ-*Aminopropoxy*-6-*methoxyquinaldine*.—The above phthalimido-compound (1 g.) was hydrolysed in the usual way with hydrazine and later with dilute hydrochloric acid. The resulting *base* crystallised from ethyl acetate in needles, m. p. 170° (Found : C, 68·5; H, 7·7; N, 11·4. $C_{14}H_{18}O_2N_2$ requires C, 68·3; H, 7·3; N, 11·4%).

The hydrochloride, prepared in alcoholic solution, was obtained as pale yellow prisms, m. p. 215° (decomp.) (R.69).

4-γ′-*Phthalimidopropyl*-γ-*aminopropoxy*-6-*methoxyquinaldine Hydrobromide*.—4-γ-Aminopropoxy-6-methoxyquinaldine (1·0 g.) and phthalo-γ-bromopropylimide (0·8 g.) were heated together for 5 hours at 120° and the glassy product was twice crystallised from alcohol, forming

small colourless prisms, m. p. 200—202°, of the *hydrobromide* (Found : C, 56·6; H, 5·4. $C_{25}H_{27}O_4N_3,HBr,H_2O$ requires C, 56·4; H, 5·3%).

4-*γ'-Aminopropyl-γ-aminopropoxy-6-methoxyquinaldine Hydrochloride.*—The above hydrobromide was hydrolysed by means of hydrazine and dilute hydrochloric acid as usual. After removal of the phthalhydrazide the solution was evaporated to dryness and the *trihydrochloride* obtained was twice crystallised from alcohol, forming pale yellow needles, m. p. 145° (decomp.) (Found : N, 9·3; Cl, 23·6. $C_{17}H_{25}O_2N_3,3HCl,2H_2O$ requires N, 9·2; Cl, 23·7%) (R.70).

Hydrochloride of β-Diethylaminoethyl 6 : 7-Dimethoxyquinaldine-4-propionate.—Methyl 6 : 7-dimethoxyquinaldine-4-propionate was refluxed for 8 hours with an excess of β-diethylaminoethanol and the excess of the alcohol was then removed by distillation under diminished pressure. The product was taken up in dry ether, and hydrogen chloride passed into the solution, precipitating a *hydrochloride*, which absorbed water to form a solid hydrate (Found : N, 6·0; Cl, 16·2. $C_{21}H_{30}O_4N_2,2HCl$ requires N, 6·3; Cl, 15·9%) (R.71).

The *picrate* crystallised from alcohol and then from acetone in yellow needles, m. p. 186° after sintering at 175° (Found : C, 47·8; H, 4·4. $C_{21}H_{30}O_4N_2,2C_6H_3O_7N_3$ requires C, 47·6; H, 4·3%).

Hydrochloride of β-Diethylaminoethyl β-6 : 7-Dimethoxyquinaldyl(4)ethylcarbamate.—The azide of 6 : 7-dimethoxyquinaldine-4-propionic acid was warmed with β-diethylaminoethanol until the evolution of nitrogen ceased. The excess of the alcohol was removed by distillation under reduced pressure and the residue was dissolved in a little hydrochloric acid and converted into a *picrate*, which crystallised from alcohol in yellow needles, m. p. 187° (Found : C, 47·1; H, 4·6. $C_{33}H_{37}O_{18}N_9$ requires C, 46·8; H, 4·3%). The picrate was dissolved in concentrated hydrochloric acid and picric acid was extracted with ether. The solution was then rendered alkaline, and the base isolated by means of ether and converted into an extremely deliquescent colourless hydrochloride (R.78).

β-Diethylaminoethyl p-Anisylcarbamate.—Anishydrazide (2 g.) was dissolved in acetic acid (10 c.c.) and sodium nitrite (1 g.) in a little water was added slowly. The azide, which separated in colourless plates, was washed well with water and dried in a vacuum desiccator; m. p. 68°. It was then covered with β-diethylaminoethanol, and the mixture heated on a steam-bath until evolution of nitrogen ceased. The excess of the alcohol was removed in a vacuum and the resulting oil was washed with a very little ether and then dissolved in hydrochloric acid and converted into a *picrate*, which crystallised from alcohol in yellow needles, m. p. 150—152° (Found : C, 48·7; N, 5·1. $C_{14}H_{22}O_3N_2,C_6H_3O_7N_3$ requires C, 48·5; H, 5·1%). A hydrochloride was prepared from the picrate for trial of its antimalarial properties, if any (R.79).

9-*Benzoyl-6-methoxytetrahydrocarbazole.*—Magnesium (3·6 g.) was added to an ethereal solution of ethyl bromide (17·3 g.); when solution was complete, 6-methoxytetrahydrocarbazole (30 g.) was added slowly, followed by benzoyl chloride (21·4 g.). The mixture was then decomposed by the addition of dilute hydrochloric acid and the product was isolated by means of ether and distilled in a high vacuum. It crystallised from alcohol in yellow prisms, m. p. 134° (Found : N, 4·7. $C_{20}H_{19}O_2N$ requires N, 4·6%).

Nitration of 9-Benzoyl-6-methoxytetrahydrocarbazole.—Nitric acid (10·8 g. of *d* 1·4) in a little acetic acid was added gradually to a solution of the above compound (2 g.) in acetic acid (15 c.c.). On standing, yellow needles of a *mononitro*-derivative, m. p. 150°, separated (Found : C, 68·1; H, 5·4. $C_{20}H_{18}O_4N_2$ requires C, 68·5; H, 5·1%). No compound in which hydroxyl and nitroxyl had been added to the double bond was obtained (compare Perkin and Plant, *loc. cit.*).

2-*Nitro-4-methoxyphenylhydrazine.*—A solution of 2-nitro-4-methoxyaniline (10 g.) in hydrochloric acid (25 c.c.) and water (25 c.c.) was diazotised below 0° with sodium nitrite (4·4 g.) dissolved in a little water. The cold diazo-solution was added to crystallised stannous chloride (35 g.) dissolved in hydrochloric acid (35 c.c.). When precipitation was complete, the solid was collected, dissolved in water, and on addition of sodium acetate the *hydrazine* separated. Crystallisation from light petroleum (b. p. 60—80°) afforded red shining plates, m. p. 127° (Found : N, 22·2. $C_7H_9O_3N_3$ requires N, 23·0%).

8-*Nitro-6-methoxytetrahydrocarbazole.*—A mixture of the hydrazine with one half of its weight of *cyclo*hexanone was heated on a steam-bath for 10 minutes; on cooling, the mass solidified; the *hydrazone* crystallised from alcohol in red needles, m. p. 69°. The hydrazone was heated on a steam-bath with dilute sulphuric acid (18%) for ½ hour, the mixture cooled, and the solid collected and extracted repeatedly with hot carbon tetrachloride; on cooling, red needles, m. p. 136°, separated. Recrystallisation from alcohol gave a mixture of polymorphous forms, needles and prisms, and on standing the labile form (needles) disappeared, leaving red prisms (Found : N, 11·6. $C_{13}H_{14}O_3N_2$ requires N, 11·4%).

8-*Amino*-6-*methoxytetrahydrocarbazole*.—Excess of sodium hydrosulphite was added gradually to a hot alcoholic solution of 8-nitro-6-methoxytetrahydrocarbazole which had been rendered alkaline with sodium hydroxide. Water was added to the decolorised solution, and the precipitated *amine* was dried in a vacuum desiccator. It crystallised from light petroleum in almost colourless needles, m. p. 149° (Found : N, 12·8. $C_{13}H_{16}ON_2$ requires N, 13·0%).

Various attempts have been made to condense 8-amino-6-methoxytetrahydrocarbazole with phthalo-γ-bromopropylimide but all without success. Experiments were carried out by heating together equivalent quantities of the two substances on a steam-bath in air or in carbon dioxide, for periods varying between 1 and 24 hours, both with and without the addition of potassium carbonate. The condensation was also tried in the presence of solvents such as benzene, nitrobenzene, and ether. In all cases the product was a black or dark brown mass from which no crystalline material could be isolated.

Attempts have also been made to condense 6-aminotetrahydrocarbazole, 6-amino-9-acetyltetrahydrocarbazole, 3 : 6-diaminocarbazole, and 6-amino-9-methyltetrahydrocarbazole with phthalo-γ-bromopropylimide under various conditions but in no case was a homogeneous product obtained.

6-*Amino*-9-*acetyltetrahydrocarbazole*.—6-Nitro-9-acetyltetrahydrocarbazole was mixed with an excess of iron filings and heated on a steam-bath for several hours with alcohol containing a little hydrochloric acid with frequent shaking. The filtered solution, on cooling, deposited the *amine*, which crystallised from light petroleum (b. p. 60—80°) in long needles, m. p. 140° (Found : N, 12·6. $C_{14}H_{16}ON_2$ requires N, 12·3%).

Coupling of Diazotised 6-*Amino*-9-*acetyltetrahydrocarbazole with* m-*Phenylenediamine*.—A solution of the amine (1 g.) in *N*/10-sulphuric acid (88 c.c.) was diazotised by means of sodium nitrite (0·3 g.) with the usual precautions. The diazo-solution was added to one of *m*-phenylenediamine (0·8 g.) in a little water. The product crystallised from alcohol in dark orange needles, m. p. 195° (Found : N, 20·8. $C_{19}H_{21}ON_5$ requires N, 20·9%). The *azo*-derivative was dissolved in dry ether and hydrogen chloride was passed, giving glistening black needles of the hydrochloride, which was tested by Professor C. H. Browning for antiseptic properties with negative results.

Attempts were made to condense 6-chloro-7-nitrotetrahydrocarbazole and 6-chloro-5-nitrotetrahydrocarbazole with methylamine, phthalimide and *p*-toluidine, but without success.

2-*Nitro*-5-*methoxy*-γ-*phthalimidopropoxybenzene*.—2-Nitro-4-methoxyphenol (2 g.), phthalo-γ-bromopropylimide (3·2 g.), and potassium carbonate (1 g.) were heated together at 145° for 2 hours. The product was ground with hot water and crystallised from acetic acid, forming colourless needles, m. p. 178° (Found : C, 60·4; H, 4·6. $C_{18}H_{16}O_6N_2$ requires C, 60·7; H, 4·5%).

2-*Amino*-5-*methoxy*-γ-*phthalimidopropoxybenzene*.—The above nitro-compound was reduced by boiling it for 4 hours in alcoholic solution with iron powder and a little hydrochloric acid. The solution was filtered hot and the product was precipitated with water; it crystallised from alcohol in brown needles, m. p. 94—96°. On drying there was a loss of 3·5%, which corresponds exactly to the loss of $\frac{1}{4}C_2H_5{\cdot}OH$ (Found after drying : C, 66·0; H, 5·4. $C_{18}H_{18}O_4N_2$ requires C, 66·3; H, 5·5%). The same product could be obtained by catalytic reduction of the nitro-compound in acetic acid solution with a palladised charcoal catalyst.

When the reduction of this nitro-compound was carried out by the action of zinc dust on its solution in acetic acid, a different product was obtained. It separated from alcohol in almost colourless needles, m. p. 162—164° (Found : C, 65·6; H, 6·3; N, 8·7. $C_{18}H_{20}O_4N_2$ requires C, 65·9; H, 6·1; N, 8·5%). This substance, like the first-mentioned, is a primary amine and it seems that the phthalimido-group must have suffered reduction. Fruitless attempts were made to effect a Skraup synthesis with 2-amino-4-methoxy-γ-phthalimidopropoxybenzene. An unsuccessful attempt was also made to prepare a quinoline from this amine by the action of benzaldehyde and pyruvic acid, as also to prepare the corresponding hydrazine and to convert it into a tetrahydrocarbazole.

2 : 2′-*Dinitro*-4 : 4′-*dimethoxydiphenylamine*.—A mixture of 4-iodo-2-nitroanisole (10 g.), nitroanisidine (5 g.), potassium carbonate (2 g.), and copper powder (2 g.) was heated at 110° for ½ hour. The product crystallised from pyridine in deep red needles, m. p. 218° (Found : C, 52·6; H, 4·0. $C_{14}H_{13}O_6N_3$ requires C, 52·7; H, 4·0%). [From the pyridine mother-liquors a *compound* $Cu_2I_2,C_5H_5N,3H_2O$, which crystallised from xylene in colourless needles, was isolated (Found : C, 11·8; H, 2·0; Cu, 23·5; I, 50·4. $Cu_2I_2,C_5H_5N,3H_2O$ requires C, 11·2; H, 2·1; Cu, 23·9; I, 47·5%). A similar compound was obtained by crystallising moist cuprous iodide from xylene containing some pyridine.]

Nitration of 4 : 4′-dimethoxydiphenylamine in acetic acid solution with an equivalent

quantity of fuming nitric acid dissolved in acetic acid yielded 2 : 2′-dinitro-4 : 4′-dimethoxydiphenylamine identical with the above.

N-*Acetyl*-2 : 2′-*dinitro*-4 : 4′-*dimethoxydiphenylamine*.—The dinitrodimethoxydiphenylamine was refluxed with acetic anhydride containing a trace of sulphuric acid for 2 hours. The product crystallised from alcohol in yellow prisms, m. p. 134—135° (Found : C, 53·5; H, 4·2; N, 11·8. $C_{16}H_{15}O_7N_3$ requires C, 53·2; H, 4·1; N, 11·6%). Attempts were made to convert 2 : 2′-dinitro-4 : 4′-dimethoxydiphenylamine into the corresponding acridine.

(1) The diphenylamine (1 part), zinc chloride (1 part), chloroform (1 part), and zinc oxide (½ part) were heated in a sealed tube for 7 hours at 200°. The product was completely charred.

(2) A formic acid solution of the diphenylamine was refluxed with 4 times its weight of zinc chloride for 5 hours. It was unchanged.

(3) Boiling with acetic anhydride in the presence of some sulphuric acid for 6 hours yielded a charred mass.

(4) The diphenylamine was dissolved in nitrobenzene and treated with an equivalent of aluminium chloride and methylene iodide. The mixture was kept over-night and was then heated on a steam-bath; the diphenylamine derivative was recovered unchanged.

Attempts were also made to ring-close the *N*-acetyl derivative to give a methylacridine : it was unchanged after it had been (1) refluxed with acetic anhydride, acetic acid, and twice its weight of zinc chloride for 10 hours; (2) fused with zinc chloride at 170° for 10 hours; (3) boiled with alcoholic hydrogen chloride for 5 hours. It was also refluxed with acetic anhydride and sulphuric acid for 5 hours, but no crystalline product could be isolated.

The most promising line was the following :—

2 : 2′-Dinitro-4 : 4′-dimethoxydiphenylamine dissolved in a little concentrated sulphuric acid to a deep mauve solution. On the addition of a few drops of formalin a deep blue colour was produced, which changed to brownish-green on gentle warming or after a little time. The solution was poured on ice and a scarlet precipitate separated, which crystallised from pyridine and subsequently from alcohol in orange-scarlet needles, m. p. 223—224° (Found : C, 51·1; H, 3·8; N, 11·2; MeO, 0·0. $C_{16}H_{13}O_8N_3$ requires C, 51·1; H, 3·5; N, 11·2%. $C_{16}H_{15}O_8N_3$ requires C, 50·9; H, 4·0; N, 11·1%). On boiling for 2 hours with acetic anhydride containing a drop of sulphuric acid, a substance was obtained which crystallised from alcohol and then from acetone in small yellow prisms, m. p. 219—221° (Found : C, 52·1; H, 3·8; N, 9·6. $C_{18}H_{15}O_9N_3$ requires C, 51·8; H, 3·6; N, 10·0. $C_{20}H_{17}O_{10}N_3$ requires C, 52·2; H, 3·7; N, 9·1%). It was very difficult to obtain these substances in adequate amount and their nature has not yet been precisely ascertained.

2 : 2′-*Dinitro*-4-*methoxy*-6′-*benzoyldiphenylamine*.—2-Bromo-3-nitrobenzophenone (1 g.), *m*-nitro-*p*-anisidine (0·5 g.), potassium carbonate (0·4 g.), and copper powder (0·2 g.) were mixed and heated at 150° for 1 hour. The product was crystallised from alcohol and recrystallisation from acetic acid yielded orange-brown prisms, m. p. 175° (Found : C, 61·4; H, 3·8. $C_{20}H_{15}O_6N_3$ requires C, 61·1; H, 3·8%).

1 : 9-*Dinitro*-3-*methoxy*-5-*phenylacridine*.—The above diphenylamine was refluxed for 4 hours with acetic acid containing twice its weight of zinc chloride. The mixture was then poured into water and the precipitate crystallised from acetic acid; the *acridine* separated in yellow needles, m. p. 272° (Found : C, 64·0; H, 3·8. $C_{20}H_{13}O_5N_3$ requires C, 64·0; H, 3·5%).

1 : 9-*Diacetamido*-3-*methoxy*-5-*phenylacridine*.—The dinitroacridine was suspended in aqueous ammonia and an excess of sodium hydrosulphite was added with shaking and gentle heating; an oily substance was formed and solidified on cooling. It could not be crystallised and was therefore acetylated by means of acetic anhydride. The derivative crystallised from alcohol in yellow prisms, m. p. 258° (Found : C, 72·7; H, 5·6; N, 10·1. $C_{24}H_{21}O_3N_3$ requires C, 72·2; H, 5·3; N, 10·5%). The alcoholic solution exhibited a green fluorescence.

1 : 9-*Diamino*-3-*methoxy*-5-*phenylacridine Hydrochloride*.—The acetyl derivative was hydrolysed by means of boiling concentrated hydrochloric acid in a few minutes and a *hydrochloride* separated. This crystallised from alcohol in brown needles, m. p. 245° (decomp.) (Found : C, 67·8; H, 5·2; Cl, 10·1. $C_{20}H_{19}ON_3,HCl$ requires C, 68·4; H, 5·1; Cl, 10·0%). Trituration of the salt with caustic soda and acetylation with acetic anhydride yielded the initial acetyl derivative, m. p. 258°. This hydrochloride, m. p. 245°, was almost insoluble in water.

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THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, July 19th,* 1934.]