

168. Attempts to find New Antimalarials. Part XXII.

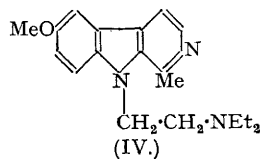
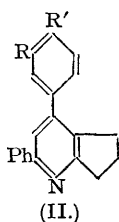
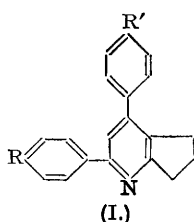
By M. J. S. DEWAR.

In continuation of the programme outlined in Part XXI, attention has been directed to the diphenyl-azahydrindene series of compounds, the synthetic procedure of Stobbe and Volhard (*Ber.*, 1902, **35**, 3973) being used. In this connexion a new method of diethylaminoethylation of amines has been devised by using the Eisleb reaction; this has also been applied to harmine. Finally, unsuccessful attempts to prepare the quinazoline analogue of plasmoquine and sulphanilamido-derivatives of quinazoline are described, and also some new methods for synthesising quinazolines.

STOBBE and VOLHARD (*loc. cit.*) describe a synthesis of 5:7-diphenyl-4-azahydrindene derivatives by Michael addition of cyclopentanone to the double bond of chalcones, followed by ring closure of the diketone with hydroxylamine hydrochloride. This method has been used to make the *methiodides*, (I; R, R' = H) and (I; R = H, R' = OMe), respectively, also (I; R = H; R' = NMe₂), (I; R = NHAc, R' = NMe₂), and (II; R = NO₂, R' = H) and (II; R = H, R' = NO₂), respectively. Catalytic reduction of the nitro-compounds over Raney nickel gave the corresponding *amines*, which were converted in the usual manner by way of their *p*-acetamidobenzenesulphonyl derivatives into the *sulphanilamide* derivatives (II; R = *p*-NH₂·C₆H₄·SO₂·NH, R' = H and *vice versa*). In the syntheses the yields were extremely good with the nitrochalcones, moderate with chalcone itself, and poor with the other chalcones. The intermediate diketones were not as a rule isolated, as they could not be crystallised. In the preparation of (I; R = H, R' = OMe) much gum was formed and the yield of quaternary salt was poor; perhaps demethylation took place, as with 4-methoxyppyridine.

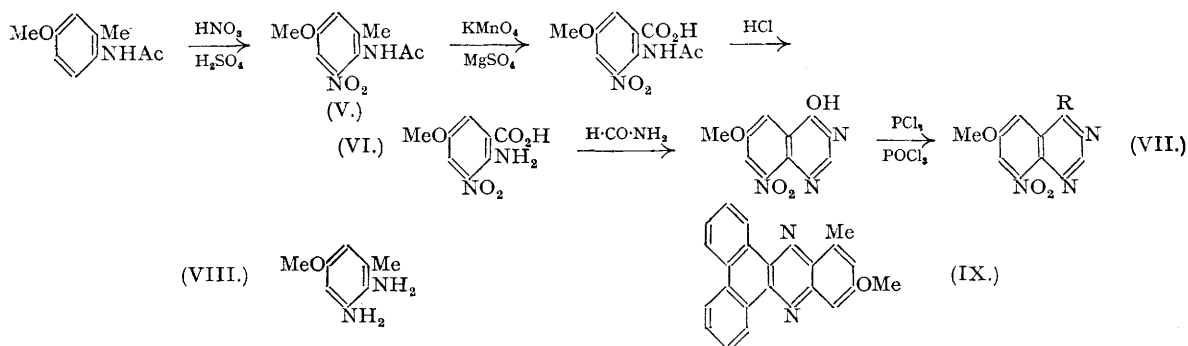
The next objective was the aminoalkylation of the amines (II; R = NH₂, R' = H) and (II; R = H, R' = NH₂). The conventional method, by heating the free amine with a chloroalkylamine hydrochloride, was not attractive, because the high molecular weight of these products would make the usual purification by distillation impossible. Eisleb has described a method of diethylaminoethylating active methylene groups (*Ber.*, 1941, **74**, 1433) by means of sodamide and chloroethyldiethylamine in boiling toluene; under these conditions the chloride is, surprisingly enough, not attacked by sodamide and good yields of the desired products are obtained. Eisleb also used the same process successfully to *N*-alkylate diphenylamine, carbazole, 2-methylindole, and acridone, but did not extend it to simpler amines. When aniline and methylaniline were treated with sodamide and chloroethyldiethylamine in toluene, excellent yields of diethylaminoethylaniline (III;

R = H) and diethylaminoethylmethylaniline (III; R = Me) were obtained; crystalline derivatives of these compounds were prepared for the first time.



The same process applied to harmine gave 9-diethylaminoethylharmine (IV), whereas the two amines of type (II) were smoothly converted into the corresponding 5-phenyl-7-(β-diethylaminoethylaminophenyl)-4-azahydroindenes (II; R = NH₂·CH₂·CH₂·NEt₂, R' = H, and vice versa), in 74% and 86% yields respectively. In the former case the chloride hydrochloride method was actually tried and by it a 20% yield of an impure oxalate of (II; R = NH·CH₂·CH₂·NEt₂, R' = H) was obtained. In these cases, N-alkylation would be expected to occur much more readily than C-alkylation of the methylene groups attached to the α-position of the pyridine ring. There is little doubt that the formulation of the products is correct. Moreover, neither of the alkylated pyridine derivatives could be diazotised, in contrast to their parent amines.

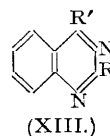
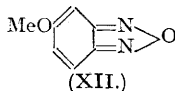
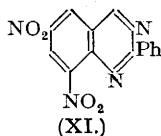
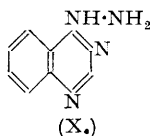
In an unsuccessful attempt to synthesise the quinazoline analogue of plasmoquine, 4-chloro-8-nitro-6-methoxyquinazoline (VII; R = Cl) was prepared by the following reactions :



The orientation of (V) was established by hydrolysis to 3-nitro-5-methoxy-*o*-toluidine, followed by reduction to the diamine (VIII) and condensation with phenanthraquinone to 10-methyl-12-methoxyphenanthrazine (IX). Solutions of (IX) in benzene showed a typical though weak fluorescence, and with sulphuric acid it gave an intense violet colour. The deep colour of (VI) and 3-nitro-5-methoxy-*o*-toluidine, in contrast to their pale acetyl derivatives, confirmed the *o*-nitroaniline structure.

Another possible route to (VI), by nitration of acetyl-5-methoxyanthranilic acid, was abandoned when the methylation of 4-hydroxyazobenzene-2-carboxylic acid proved unexpectedly difficult, although some 4-methoxyazobenzene-2-carboxylic acid was eventually obtained. It was, moreover, realised from analogy with aceto-2-nitroanisidine (which is nitrated ortho to the nitro-group) that nitration of the acetylanthranilic acid might occur in the 6-position.

As a model for the reduction of (VII; R = Cl), 4-chloroquinazoline was investigated. Catalytic reduction over palladised charcoal gave exclusively dihydroquinazoline; chemical reduction or reduction in hydroxylic solvents gave only 4-quinazalone or its derivatives. With hydrazine in alcohol chloroquinazoline gave 4-quinazolylhydrazine (X); unlike true hydrazines, this did not reduce copper salts in acetic acid, but was oxidised by Fehling's solution to quinazoline. These methods constitute two new syntheses of quinazoline, since dihydroquinazoline can be oxidised to quinazoline with ferricyanide (Gabriel, *Ber.*, 1903, 36, 808). The latter method appeared more promising in view of the known sensitivity of 8-amino-6-methoxyquinoline to oxidation; (VII; R = Cl) was therefore converted by means of hydrazine in alcohol into 8-nitro-6-methoxy-4-quinazolylhydrazine (VII; R = NH·NH₂) which, however, resisted oxidation by Fehling's solution or ferricyanide. With toluenesulphonyl chloride the toluenesulphonyl derivative was obtained, and by heating this with potassium carbonate in water (cf. McFadyen and Stevens, *J.*, 1936, 584), a little 8-nitro-6-methoxyquinazoline (VII; R = H) was obtained; unfortunately, all attempts to raise the yield failed. It is likely that 4-quinazolylhydrazines react mainly in the tautomeric hydrazone form and therefore show abnormal reactions.



At this point circumstances required this line of work to be abandoned, but two other routes to (VII; R = H) have been explored. The condensation of 3 : 5-dinitro-2-methoxybenzaldehyde with benzamidine gave 6 : 8-dinitro-2-phenylquinazoline (XI), but this new quinazoline synthesis, based on Hill and Robinson's dinitrostrychol synthesis (J., 1933, 487), failed with acetamidine. An attempt was also made to condense 2-nitroacetanilide with urethane in presence of phosphoric anhydride, following Sen and Rây (J., 1926, 646), but the only product isolated appeared to be 5-methoxybenzofurazan (XII). Its volatility and analysis indicated the simple formula $C_7H_6O_2N_2$, including one methoxyl; it was neutral and stable to acids and alkalis, and in general had the properties expected for such a structure.

Finally, attempts were made to prepare quinazoline analogues of sulphadiazine, which is known to have antimalarial action. 4-Chloroquinazoline reacted easily with ammonia in alcohol to give 4-aminoquinazoline (XIII; R = H, R' = NH_2), but this very sparingly soluble substance was almost non-basic and was unchanged by acid halides even in boiling pyridine; probably it exists as an iminodihydroquinazoline, because the properties of the 4-quinazolylhydrazines and the ready reduction of the quinazoline ring suggest a peculiar stability of the 3 : 4-dihydro-form. Attempts were also made to condense acetylsulphanilamide or its sodium salt with 4-chloroquinazoline but under a variety of conditions none of the desired sulphonamide was obtained.

In contrast to 4-aminoquinazoline, the 2-amino-isomer (XIII; R = NH_2 , R' = H), prepared from 2-chloroquinazoline and ammonia, seemed quite normal in its properties and reacted readily with acetamidobenzene-sulphonyl chloride and pyridine; unfortunately, the product was mostly alkali-insoluble, and probably nuclear acylation predominated. A small alkali-soluble fraction was obtained which appeared to be the required 2-(p-acetamidobenzene-sulphonamido)quinazoline (XIII; R = $NHAc \cdot C_6H_4 \cdot SO_2 \cdot NH$, R' = H), but the yield was extremely poor, and could not be improved.

EXPERIMENTAL.

(All salts were dried for analysis in a high vacuum at 60°.)

5 : 7-Diphenyl-4-azahydrindene Methiodide (as I; R, R' = H).—A solution of diphenylazahydrindene (2 g.) (Stobbe and Volhard, *Ber.*, 1902, 35, 3973) and methyl iodide (2 g.) in methanol (10 c.c.) was heated for 10 hours at 130° in a Carius tube. When cold, the methiodide was collected, and crystallised from water in superb golden needles with an adamantine lustre, m.p. 240° (decomp.) (Found: C, 60.8; H, 5.0; I, 30.8. $C_{21}H_{20}NI$ requires C, 61.0; H, 4.8; N, 30.8%).

5-Phenyl-7-(p-anisyl)-4-azahydrindene Methiodide (as I; R = H, R' = OMe).—Prepared similarly, this methiodide was contaminated with much gummy water-insoluble material; it was purified by crystallisation from water, forming small, orange polyhedra, m. p. 250° (decomp.) (Found: C, 59.4; H, 4.9; I, 28.4. $C_{22}H_{22}ONI$ requires C, 59.6; H, 5.0; I, 28.6%).

5-Phenyl-7-(p-dimethylaminophenyl)-4-azahydrindene (I; R = H, R' = NMe_2).—Prepared by the method of Stobbe and Volhard (*loc. cit.*) from p-dimethylaminobenzylideneacetophenone (13 g.), the base crystallised from alcohol in ochre bipyramids (8.2 g., 50%) containing a little recalcitrant impurity. The extremely deliquescent hydrochloride crystallised from ethyl acetate containing a little alcohol in orange prisms, m. p. 135° with gas-evolution (Found: C, 68.6; H, 6.7; N, 7.1. $C_{22}H_{22}N_2 \cdot HCl \cdot 2H_2O$ requires C, 68.3; H, 7.0; N, 7.2%). From the hydrochloride the pure base was regenerated, and crystallised from alcohol in long, flat, pale yellow, rhombic needles, m. p. 155° (Found: C, 84.0; H, 7.2; N, 8.8. $C_{22}H_{22}N_2$ requires C, 84.1; H, 7.0; N, 8.9%).

5-Phenyl-7-(m-nitrophenyl)-4-azahydrindene (II; R = NO_2 , R' = H).—Prepared similarly from m-nitrobenzylideneacetophenone (5 g.), the azahydrindene crystallised from aqueous alcohol in short, pale yellow prisms (5.1 g., 82%), m. p. 119—120° (Found: C, 74.4; H, 4.8; N, 8.8. $C_{20}H_{14}O_2N_2 \cdot \frac{1}{2}H_2O$ requires C, 74.5; H, 5.2; N, 8.7%).

5-Phenyl-7-(m-aminophenyl)-4-azahydrindene.—The nitro-compound (43.2 g.) was reduced in alcohol over Raney nickel with hydrogen at 100°/90 atm., and the amine distilled at 220—225°/0.1 mm. as a clear glass (23.1 g., 59%), which crystallised on fusion and slow cooling, m. p. 136—137° (Found: C, 83.6; H, 6.4; N, 9.8. $C_{20}H_{18}N_2$ requires C, 83.9; H, 6.3; N, 9.8%).

5-Phenyl-7-[m-(p-acetamidobenzene-sulphonamido)phenyl]-4-azahydrindene.—p-Acetamidobenzene-sulphonyl chloride (1.25 g.) was added to a solution of the amine (1.27 g.) in dry acetone (10 c.c.) and pyridine (0.7 c.c.). Next day, water was added, and the acetylsulphonamide collected; it crystallised from acetic acid in colourless, microscopic needles (1.45 g., 72%), m. p. 212° (decomp.) (Found, in material dried for 5 hours at 100°/20 mm.: C, 66.1; H, 5.3; N, 7.8. $C_{28}H_{25}O_3N_3S \cdot C_2H_4O_2$ requires C, 66.3; H, 5.3; N, 7.7%).

5-Phenyl-7-[m-(p-aminobenzene-sulphonamido)phenyl]-4-azahydrindene.—The crude acetylsulphonamide from the amine (3 g.) was dissolved in n-sodium hydroxide solution (100 c.c.) and boiled for 1 hour under reflux with charcoal (1 g.), filtered, and the aminosulphonamide precipitated with acetic acid and crystallised from aqueous alcohol, forming small colourless rhombohedra, m. p. 175° (Found, in material dried at 100°/20 mm.: C, 68.9; H, 5.2; S, 6.8. $C_{26}H_{22}O_2N_3S \cdot \frac{3}{2}H_2O$ requires C, 68.9; H, 5.4; S, 7.1%). Diazotisation and coupling with β -naphthol gave an orange colour.

5-Phenyl-7-(p-nitrophenyl)-4-azahydrindene.—Prepared similarly from p-nitrobenzylideneacetophenone (46.8 g.), the azahydrindene crystallised from alcohol (charcoal) in colourless rosettes (54 g., 92%), m. p. 146—150°, raised by recrystallisation to 154—155° (Found: C, 74.5; H, 5.2; N, 8.4. $C_{20}H_{16}O_2N_2 \cdot \frac{1}{2}H_2O$ requires C, 74.5; H, 5.2; N, 8.7%). Found, in material dried at 100°/0.01 mm.: C, 74.8; H, 5.1. $C_{20}H_{16}O_2N_2 \cdot \frac{1}{2}H_2O$ requires C, 74.9; H, 5.1%).

5-Phenyl-7-(p-aminophenyl)-4-azahydrindene.—The nitro-compound (20 g.) was reduced as before to the amine, which distilled at 225—230°/0.1 mm. as a clear glass (14.1 g., 78%), and this crystallised from alcohol in long, pale yellow needles, m. p. 169° (Found, in material dried at 100°/20 mm.: C, 84.0; H, 6.4; N, 9.9. $C_{20}H_{18}N_2$ requires C, 83.9; H, 6.3; N, 9.8%).

5-Phenyl-7-[p-(p-acetamidobenzene-sulphonamido)phenyl]-4-azahydrindene.—Prepared in the same way as its isomer, this acetylsulphonamide crystallised from 50% alcohol in pale yellow, hexagonal plates, m. p. 155° with sintering (Found: C, 67.8; H, 5.6; S, 5.8. $C_{28}H_{25}O_3N_3S \cdot C_2H_4O_2$ requires C, 68.1; H, 5.8; S, 6.0%).

5-Phenyl-7-[p-(p-aminobenzene-sulphonamido)phenyl]-4-azahydrindene.—Prepared by alkali hydrolysis, the aminosulphonamide contained some of its sodium salt and was purified by solution in acetic acid and precipitation with ammonia; it then crystallised from aqueous alcohol in colourless rosettes, m. p. 132° (Found, in material dried at 100°/12 mm.: C, 68.3; H, 5.7; S, 7.0. $C_{26}H_{23}O_2N_3S \cdot H_2O$ requires C, 68.0; H, 5.4; S, 7.0%). The amorphous sodium salt was almost insoluble in water, and the azo-dye with β -naphthol was orange.

4-Dimethylamino-4'-acetamidochalkone.—Sodium hydroxide solution (20 c.c. of 20%) was added to *p*-acetamidoacetophenone (20.6 g.) and *p*-dimethylaminobenzaldehyde (17.5 g.) in alcohol (200 c.c.). Next day, water was added, and the chalkone collected; it crystallised from alcohol in orange prisms (16.5 g., 39%), m. p. 197—202°, raised by recrystallisation to 205° (Found: N, 9.3. $C_{19}H_{20}O_2N_2$ requires N, 9.1%).

4-Acetamidophenacyl-4'-dimethylaminophenyl-2''-ketocyclopentylmethane.—A mixture of the chalkone (9.6 g.), cyclopentanone (6 g.), and piperidine (1 c.c.) was heated for 1 hour on a steam-bath. Crystallisation from alcohol (90%) gave bright yellow needles of the diketone (11.0 g., 90%), m. p. 125—128°, raised by recrystallisation to 130° (Found, in material dried at 100°/20 mm.: C, 71.6; H, 7.3; N, 7.2. $C_{24}H_{28}O_3N_2 \cdot \frac{1}{2}H_2O$ requires C, 71.8; H, 7.2; N, 7.0%).

5-(*p*-Acetamidophenyl)-7-(*p*-dimethylaminophenyl)-4-azahydrindene.—A mixture of the diketone (4.2 g.), hydroxylamine hydrochloride (5 g.), alcohol (70 c.c.), and hydrochloric acid (1 c.c., 35%) was boiled for 6 hours under reflux, and the base then precipitated with ammonia; since it gave a positive diazo-reaction, it was reacylated with acetic anhydride on a steam-bath, and the resulting azahydrindene crystallised from aqueous alcohol in almost colourless needles, m. p. 123—124° with gas-evolution (Found, in material dried at 100°/0.01 mm.: C, 76.6; H, 6.8; N, 10.9. $C_{24}H_{25}ON_3 \cdot \frac{1}{2}H_2O$ requires C, 76.7; H, 6.8; N, 11.2%).

β -Diethylaminoethylamine (III; R = H).—Powdered sodamide (2.3 g.) was added to a solution of aniline (6.3 g.) and β -chloroethyldiethylamine (9.15 g.) in toluene (25 c.c.), and the mixture heated in an oil-bath to 70° whereupon vigorous evolution of ammonia began. After $\frac{1}{2}$ hour at 70° the bath temperature was raised during another $\frac{1}{2}$ hour to 115°, and the solution then refluxed for 2½ hours. When it was cold, water was added, and the toluene layer separated and extracted with dilute acetic acid; from the acid layer the bases were isolated with alkali and ether and fractionated. β -Diethylaminoethylamine was collected at 162—164°/25 mm. as a colourless liquid (8.4 g., 66%; 79% allowing for recovered aniline), n_D^{20} 1.5217 (Found: C, 74.7; H, 10.6. Calc. for $C_{12}H_{20}N_2$: C, 75.0; H, 10.4%). No crystalline derivative of this amine had been reported. The monopicronolate crystallised from acetone in large rectangular orange tablets, m. p. 146—147° (Found: C, 58.2; H, 6.4; N, 17.4. $C_{12}H_{20}N_2 \cdot C_{10}H_8O_5N_4 \cdot \frac{1}{2}C_2H_6O$ requires C, 58.1; H, 6.4; N, 17.3%). The dipicronolate crystallised from acetone containing picronic acid in lemon-yellow, pointed prisms, m. p. 160—162° (Found: C, 53.3; H, 5.3. $C_{12}H_{20}N_2 \cdot 2C_{10}H_8O_5N_4$ requires C, 53.3; H, 5.0%). The dipicrate crystallised after 2 months from acetone and alcohol containing picric acid in short, orange prisms, m. p. 95—97° (Found: C, 44.3; H, 4.6. $C_{12}H_{20}N_2 \cdot 2C_6H_3O_7N_3 \cdot \frac{1}{2}C_2H_6O$ requires C, 44.5; H, 4.3%). The monopicronolate is the best derivative for characterisation.

β -Diethylaminoethylmethylamine (III; R = Me).—Prepared similarly from methylamine (35 g.), β -chloroethyldiethylamine (48.7 g.), sodamide (15.3 g.), and toluene (120 c.c.), the amine was collected at 165—170°/20 mm. as a colourless oil (56.4 g., 84%; 100% allowing for recovery), n_D^{20} 1.5243 (Found: C, 75.8; H, 10.7. Calc. for $C_{13}H_{22}N_2$: C, 75.7; H, 10.7%). No derivative had been reported; the dipicrate crystallised from alcohol-acetone containing picric acid in bright yellow, dendritic prisms, m. p. 153—155° (Found: C, 45.1; H, 4.7. $C_{13}H_{22}N_2 \cdot 2C_6H_3O_7N_3 \cdot \frac{1}{2}C_2H_6O$ requires C, 45.3; H, 4.5%).

5-Phenyl-7-(*m*- β -diethylaminoethylaminophenyl)-4-azahydrindene.—Prepared in the same way as above from the amine (14.3 g.), chloroethyldiethylamine (7.5 g.), sodamide (2.2 g.), and toluene (30 c.c.), this base was converted into its oxalate, which crystallised from alcohol in bright yellow rhombs (15.7 g., 74%), m. p. 98—100° with gas-evolution (Found: C, 62.4; H, 6.5; N, 7.7. $C_{26}H_{31}N_3 \cdot 2C_2H_2O_4 \cdot \frac{1}{2}H_2O$ requires C, 62.7; H, 6.3; N, 7.3%). The hydrochloride, prepared in ether, was a deliquescent, cream-coloured powder (Found: C, 63.1; H, 7.4; N, 8.7. $C_{26}H_{31}N_3 \cdot 2HCl \cdot 2H_2O$ requires C, 63.2; H, 7.5; N, 8.5%). Recrystallisation was effected with difficulty by gradual addition of ether to a solution in acetone and alcohol, almost colourless needles, m. p. 138—140°, of a monohydrate separating (Found: C, 65.5; H, 7.2. $C_{26}H_{31}N_3 \cdot 2HCl \cdot H_2O$ requires C, 65.5; H, 7.3%).

5-Phenyl-7-(*p*- β -diethylaminoethylaminophenyl)-4-azahydrindene.—Prepared in the same way from the amine (6.45 g.), chloroethyldiethylamine (3.38 g.), sodamide (0.99 g.), and toluene (30 c.c.), the azahydrindene derivative was converted into its oxalate, which crystallised from alcohol in deliquescent, saffron-coloured needles (8.25 g., 86%), m. p. 141—142° with gas-evolution (Found: C, 61.4; H, 6.3; N, 7.3. $C_{26}H_{31}N_3 \cdot 2C_2H_2O_4 \cdot H_2O$ requires C, 61.7; H, 6.3; N, 7.2%). The hydrochloride, prepared in ether, was an extremely deliquescent, orange powder, m. p. 75° with gas-evolution (Found: C, 64.7; H, 8.2; N, 7.4. $C_{26}H_{31}N_3 \cdot 2HCl \cdot 2\frac{1}{2}C_2H_6O$ requires C, 64.9; H, 8.4; N, 7.3%).

9- β -Diethylaminoethylharmine (IV).—A mixture of powdered harmine (12 g.), chloroethyldiethylamine (9.5 g.), powdered sodamide (3 g.), and toluene (30 c.c.) was boiled for 3 hours under reflux, and the base isolated in the usual way, dissolved in light petroleum and filtered from some unchanged harmine, and then distilled; it (5.75 g., 33%) was collected at 205°/0.15 mm. as a viscous yellow syrup, n_D^{20} 1.5902 (Found: C, 73.7; H, 8.0; N, 13.1. $C_{19}H_{25}ON_3$ requires C, 73.3; H, 8.0; N, 13.5%). The hydrochloride, solutions of which had a superb blue-violet fluorescence, crystallised from 90% alcohol in colourless needles, m. p. 275° (decomp.) (Found: C, 56.9; H, 7.3; N, 10.8. $C_{19}H_{25}ON_3 \cdot 2HCl \cdot H_2O$ requires C, 56.7; H, 7.2; N, 10.5%).

Harmine Methobromide.—When methylsopharmine and γ -phenoxypropyl bromide were heated together in alcohol under pressure, the only product was harmine methobromide, which crystallised from aqueous alcohol in colourless needles, m. p. 280° (decomp.) (Found: C, 54.8; H, 5.0; N, 9.2; Br, 26.6. $C_{14}H_{15}ON_2Br$ requires C, 54.7; H, 4.9; N, 9.1; Br, 26.0%).

3-Nitro-2-acetamido-5-methoxytoluene.—To a solution of acetic acid (80 c.c.) in nitric acid (140 c.c., *d* 1.5), stirred mechanically and kept below 0°, was added in portions 2-acetamido-5-methoxytoluene (67 g.). After 3 hours the solution was poured on ice, and the nitro-compound collected; it crystallised from alcohol in very pale yellow needles (60 g., 70%), m. p. 173—176°, raised by repeated recrystallisation from alcohol and then ethyl acetate to 187° (Found: C, 53.5; H, 5.5; N, 12.5. $C_{10}H_{12}O_4N_2$ requires C, 53.6; H, 5.3; N, 12.5%).

3-Nitro-5-methoxy-*o*-toluidine.—Hydrolysis of the acetyl derivative with hydrochloric acid gave the free amine, which crystallised from ethyl acetate in large, ruby prisms, m. p. 134° (Found: C, 53.0; H, 5.6; N, 15.4. $C_8H_{10}O_3N_2$ requires C, 52.7; H, 5.5; N, 15.4%).

12-Methoxy-10-methylphenanthrazine (IX).—Prepared by reduction of the nitromethoxytoluidine with zinc dust and alcoholic hydrochloric acid, followed by condensation with phenanthraquinone, the phenanthrazine crystallised from acetic acid in silvery fawn plates, m. p. 217—218° (Found: C, 80.2; H, 5.4. Found, in material dried at 120°/0.01 mm.: C, 80.3; H, 4.9. $C_{22}H_{16}ON_2 \cdot \frac{1}{2}C_2H_4O_2$ requires C, 80.0; H, 5.2%). The compound gave a violet coloration with sulphuric acid, and its yellow solution in benzene had a faint violet fluorescence.

3-Nitro-*N*-acetyl-5-methoxyanthranilic Acid.—To a suspension of powdered nitroacetamidomethoxytoluene (44 g.) in a solution of magnesium sulphate (60.3 g. of heptahydrate) in water (3 l.), stirred mechanically at 75—80°, was added powdered potassium permanganate (85.5 g.). After 3 hours, the acetylanthranilic acid (39.0 g.) was isolated in the usual way; it crystallised from acetic acid in small, chrome-yellow needles, m. p. 250° (decomp.) (Found: C, 47.3; H, 4.0; Ac, 17.5. $C_{10}H_{10}O_6N_2$ requires C, 47.2; H, 3.9; Ac, 16.9%).

3-Nitro-5-methoxyanthranilic Acid.—The acetyl derivative (8.2 g.) was heated for 5 hours on a steam-bath with hydrochloric acid (40 c.c. of 25%). On cooling, a yellow hydrochloride separated, which was collected and decomposed by crystallisation from water (500 c.c.) to give red-black prisms (6.02 g., 88%) of the free anthranilic acid; at 185° this was

converted into a red form with partial fusion and resolidification, and then melted at 225–226° (rapid heating) to a red liquid (Found: C, 45.4; H, 3.9; N, 13.2. $C_9H_8O_3N_2$ requires C, 45.3; H, 3.8; N, 13.2%).

8-Nitro-6-methoxy-4-quinazolone.—Prepared by heating a mixture of the anthranilic acid (11.5 g.) and formamide (11.5 g.) for 3 hours at 165°, the *quinazolone* crystallised from aqueous pyridine in pale yellow needles (10.9 g., 91%), m. p. 270° (decomp.) (Found: C, 49.1; H, 3.4; N, 18.7. $C_9H_7O_3N_3$ requires C, 48.9; H, 3.2; N, 19.0%).

4-Chloro-8-nitro-6-methoxyquinazoline (VII; R = Cl).—After a mixture of the *quinazolone* (5.7 g.), phosphorus pentachloride (10 g.), and phosphorus oxychloride (60 c.c.) had been boiled under reflux till solution was complete, and then evaporated to dryness under reduced pressure, the residue was extracted in a Soxhlet with light petroleum (b. p. 60–80°) to give orange rhombs of the *chloro*-compound (4.65 g., 75%), m. p. 144–147°, raised by recrystallisation to 149° (Found: N, 17.5; Cl, 14.9. $C_9H_6O_3N_3Cl$ requires N, 17.5; Cl, 14.8%).

8-Nitro-6-methoxy-4-quinazolylylhydrazine (VII; R = NH·NH₂).—The *chloro*-compound (3.55 g.) was added to a solution of hydrazine hydrate (12 g.) in alcohol (50 c.c.), and after 1½ hours the *hydrazine* (2.86 g., 87%) was collected; it crystallised from butanol in orange-brown, microscopic needles, m. p. 202° (decomp.) (Found: C, 45.9; H, 4.0; N, 29.8. $C_9H_9O_3N_5$ requires C, 45.9; H, 3.8; N, 29.8%). Attempts to oxidise the hydrazine with copper salts or ferricyanide gave no new compound.

8-Nitro-6-methoxy-4-quinazolylyl-p-toluenesulphonylhydrazine.—Prepared in pyridine from the hydrazine (2.13 g.), the *toluenesulphonyl* derivative was insoluble in all solvents except formic acid, from which it was precipitated by addition of water in microscopic, orange needles (3.32 g., 94%), m. p. 225° (decomp.) (Found: C, 49.3; H, 4.0; N, 18.3; S, 7.7. $C_{16}H_{15}O_5N_5S$ requires C, 49.3; H, 3.9; N, 18.0; S, 8.2%).

8-Nitro-6-methoxyquinazoline (VII; R = H).—A mixture of the *toluenesulphonyl* derivative (500 mg.), potassium carbonate (500 mg.), and water (5 c.c.) was boiled for 30 minutes under reflux. When cold, the solid was collected and extracted with boiling water (10 c.c.), from which, after charcoal treatment, the *quinazoline* separated on cooling as a brown powder (22 mg.), m. p. 168–170°. Recrystallisation gave saffron-coloured needles, m. p. 170° (Found: C, 51.1; H, 3.8; N, 19.6. $C_9H_8O_3N_3$ requires C, 51.2; H, 3.7; N, 19.9%). The yield could not be improved.

Attempts to reduce 4-Chloroquinazoline.—Reduction in boiling xylene over palladised charcoal gave almost quantitatively dihydroquinazoline, characterised as its picrate, feathery, saffron-coloured needles from alcohol, m. p. 220–222° (lit. 215°) (Found: C, 46.2; H, 3.1; N, 19.5. Calc. for $C_8H_8N_3$, $C_8H_8O_3N_3$: C, 46.5; H, 3.0; N, 19.4%). Chemical reducing agents or the use of hydroxylic solvents led only to 4-substituted quinazolines. **4-Ethoxyquinazoline picrate** crystallised from toluene in long, yellow needles, m. p. 178° (Found: C, 47.7; H, 3.2. $C_{10}H_{10}ON_2$, $C_8H_8O_7N_3$ requires C, 47.6; H, 3.2%).

4-Quinazolylylhydrazine (X).—Prepared from the *chloroquinazoline* and hydrazine hydrate in alcohol, the *hydrazine* crystallised from pyridine in pale yellow needles, m. p. 186° (decomp.) (rapid heating) (Found: C, 59.7; H, 4.6. $C_8H_8N_4$ requires C, 60.0; H, 5.0%). The compound did not reduce acid or neutral copper solutions, but with Fehling's solution or ferricyanide some *quinazoline* was produced, isolated as its picrate, long, saffron-coloured prisms from water, m. p. 185–186° (lit. 188–190°) (Found, in material dried at 80°/0.01 mm.: C, 44.3; H, 2.9; N, 18.7. Calc. for $C_8H_8N_3$, $C_8H_8O_7N_3$, H_2O : C, 44.6; H, 2.9; N, 18.6%).

6:8-Dinitro-2-phenylquinazoline.—To a solution of benzamide in chloroform, prepared from the hydrochloride (7 g.) and dried over potash, was added 3:5-dinitro-2-methoxybenzaldehyde (6 g.) (Hill and Robinson, J., 1933, 487), and the whole was boiled for 4 hours under reflux. After evaporation to dryness and extraction with hot alcohol (500 c.c.), the residue crystallised from amyl alcohol in pale yellow needles of the *quinazoline*, m. p. 231–233° (Found: C, 57.0; H, 3.0; N, 18.8; OMe, 0.0. $C_{14}H_8O_4N_4$ requires C, 56.7; H, 2.7; N, 18.9%). The reaction failed with acetamide.

5-Methoxybenzofurazan (XII).—To a solution of 2-nitro-4-methoxyacetanilide (12 g.) and urethane (8 g.) in xylene (30 c.c.) boiling gently under reflux, phosphoric oxide (35 g.) was gradually added, and boiling continued for a further 2 hours. When the mixture was cold, water and excess of sodium hydroxide were added, and the contents of the flask steam-distilled. After the xylene had been rejected, a yellow solid collected, which crystallised from light petroleum in beautiful, colourless needles, m. p. 97–98°, with the characteristic smell of benzofurazan, apparently *5-methoxybenzofurazan* (Found: C, 56.1, 56.0; H, 4.0, 3.9; N, 18.5, 18.4; OMe, 20.2. $C_9H_8O_2N_2$ requires C, 56.0; H, 4.0; N, 18.7; OMe, 20.7%). The compound was slightly soluble in boiling water, crystallising on cooling, very soluble in organic solvents except light petroleum and unaffected by boiling acid or alkali.

4-Aminoquinazoline.—4-Chloroquinazoline (4 g.) was dissolved in alcohol saturated with ammonia at 0° (20 c.c.), and the solution heated for 3 hours at 100° in a sealed tube. When cold, the solid separating was washed with dilute alkali and crystallised from pyridine, giving colourless plates of the *aminoquinazoline* (3 g., 85%), m. p. 259–260° (Found: C, 66.2; H, 4.7. $C_8H_7N_3$ requires C, 66.2; H, 4.8%). The compound was practically non-basic and under a variety of conditions failed to react with acid chlorides.

2-Aminoquinazoline.—Crude 2-chloroquinazoline (9 g.) was heated for 3 hours at 160° in an autoclave with alcoholic ammonia (75 c.c.), then evaporated to dryness, and the residue washed with dilute alkali. The residue was sublimed at 220°/20 mm., and then crystallised from alcohol to give arborescent, citron prisms of *2-aminoquinazoline* (4.3 g.), m. p. 198° (Found: C, 66.3; H, 5.1. $C_8H_7N_3$ requires C, 66.2; H, 4.8%). The same compound was formed in poor yield by heating *o*-aminobenzaldehyde with guanidine carbonate or cyanamide, or with methylisothiourea in amyl alcohol.

2-(p-Acetamidobenzenesulphonamido)quinazoline.—p-Acetamidobenzenesulphonyl chloride (0.40 g.) was added to a solution of the amine (0.24 g.) in dioxan (3 c.c.) and pyridine (0.2 g.) at 45°. Next day, water was added and a little *sulphonamide* extracted with alkali from the major non-acidic product; it was precipitated with acid and crystallised from alcohol in microscopic, colourless needles, m. p. 270° (Found, in material dried at 100°/0.01 mm.: N, 16.5. $C_{16}H_{14}O_3N_4S$ requires N, 16.4%).

4-Methoxyazobenzene-3-carboxylic Acid.—The hydroxy-acid was methylated with a large excess of methyl sulphate and sodium methoxide in methanol, and the resulting ester hydrolysed to the *methoxy-acid*, which crystallised from alcohol in bright orange needles, m. p. 142–144° (Found: C, 65.6; H, 4.9; N, 10.9. $C_{14}H_{12}O_3N_2$ requires C, 65.6; H, 4.7; N, 10.9%).

The author thanks Professor Sir Robert Robinson, F.R.S., for his interest and encouragement in this work, and also Imperial Chemical Industries Limited, Dyestuffs Division, for facilities.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

[Received August 5th, 1944.]