149. *Attempts to find New Antimalarials. Part XX.*

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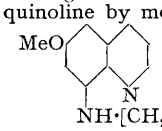
Up to the present the basic side-chain in antimalarials of the plasmoquin (pamaquin) type has terminated with a primary or tertiary amine group. The present investigation was undertaken with the object of including *sec.*-amine end-groups in the series.

A general method has been devised for this purpose which consists in alkylation of 8-amino-6-methoxyquinoline by means of a chlorohydrin, replacement of the hydroxyl group in the product by chlorine, and reaction of the chloroalkylamino-compound with primary bases. The method can naturally also be used for *tert.*-bases by employing *sec.*-bases at the last stage.

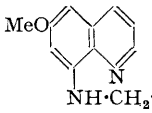


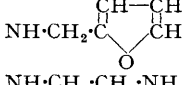
The general formula of bases allied to plasmoquin that can be conveniently prepared in this way is annexed and in the present communication we explore the series where $x = 3$.

Condensation of 8-amino-6-methoxyquinoline and trimethylenechlorohydrin affords 8-*γ-hydroxypropylamino-6-methoxyquinoline*, $MeO{\cdot}C_9H_5N{\cdot}NH{\cdot}[CH_2]_3{\cdot}OH$ (I), which is converted by thionyl chloride into the corresponding *chloride*, $MeO{\cdot}C_9H_5N{\cdot}NH{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2Cl$ (II). A red by-product is always produced and this becomes the sole product if the reaction with thionyl chloride is at all prolonged, for example, to ½ hour; the substance is very probably the *hydrochloride* of *bis-(8-γ-chloropropylamino-6-methoxy-5-quinolyl) sulphide*; the free base is crystalline. Reaction with diethylamine gives a thio-bis-rhodoquin, $S(MeO{\cdot}C_9H_4N{\cdot}NH{\cdot}[CH_2]_3{\cdot}NEt_2)_2$ (III), the first member of a group capable of considerable extension.

Reaction of (II) with various primary and secondary bases has given a series of antimalarials showing interesting variations of activity.

The following results of tests on bird malaria due to *Plasmodium relictum* in canaries of some of the compounds described in this paper have been received from Professor D. Keilin, F.R.S., and Dr. Ann Bishop, of the Molteno Institute, Cambridge. In each case the dose was given on six successive days.



Number in R series.	X.	Max. tolerated dose in mg. per 20 g. of body weight.	Min. effective dose in mg. per 20 g. of body weight.	Therapeutic index.
105	NHMe	2·56	0·32	1/8
106	NHEt	0·16	0·04	1/4
119	NHPr$^{\alpha}$	0·64	0·04	1/16
108	NHPr$^{\beta}$	0·32	0·02	1/16
107	NH-*n*-C_4H_9	0·32	0·04	1/8
110	NH-*iso*-C_4H_9	0·16	0·02	1/8
109	NH-*tert.*-C_4H_9	0·32	0·01	1/32
114	NH-*n*-C_7H_{15}	0·64	0·16	1/4
117	NH·CH_2Ph	0·32	0·08	1/4
111	NH·CHMe·CH_2Ph	0·32	0·16—0·08	1/2—1/4
112		0·32	0·02	1/16
115	NH·CH_2·CH_2·NH_2	5·12	2·56	1/2
116	NEt_2	0·32	0·02	1/16
120	NH·$[CH_2]_3$·NH_2		(Inactive)	

The new synthesis of 8-γ′-aminopropyl-γ-aminopropyl-6-methoxyquinoline,

$$MeO{\cdot}C_9H_5N{\cdot}NH{\cdot}[CH_2]_3{\cdot}NH{\cdot}[CH_2]_3{\cdot}NH_2$$

from (II) and trimethylenediamine confirms that of Part XVIII. The substance is reported as devoid of antimalarial properties and it is now certain that R. 63 owes its activity to some other constituent.

Experimental.

8-Amino-6-methoxyquinoline.—8-Nitro-6-methoxyquinoline (102 g.) was hydrogenated in methyl alcohol (200 c.c.) for 1 hour at 60°/80 atm. in presence of a Raney nickel catalyst. The product, b. p. 162°/0·2 mm., crystallised in almost colourless prisms, m. p. 41° (83 g., 95%).

8-γ-Hydroxypropylamino-6-methoxyquinoline (I).—A mixture of 8-amino-6-methoxyquinoline (58 g.), trimethylenechlorohydrin (32 g.), finely powdered potassium carbonate (25 g.), and octyl alcohol (about 3 c.c.) was refluxed (bath, 125—130°) for 10 hours and then added to water and extracted with chloroform. On distillation a small amount of

unchanged material was recovered. The *product* (59 g., 76%) was a pale yellow oil, b. p. 200°/0·1 mm.; it crystallised, on keeping, in yellow prisms, m. p. 53° (Found : C, 67·1; H, 7·0. $C_{13}H_{16}O_2N_2$ requires C, 67·2; H, 6·9%).

The picrate crystallised from benzene in orange needles, m. p. 128°; the hydrogen oxalate crystallised from alcohol–ethyl acetate, containing oxalic acid, in yellow needles, m. p. 109°; the hydrochloride separated from alcohol as deliquescent orange needles, m. p. 178°.

8-γ-*Chloropropylamino*-6-*methoxyquinoline* (II).—Thionyl chloride (15 g., 3 mols.) was added to 8-γ-hydroxypropylamino-6-methoxyquinoline (10 g.) in chloroform (30 c.c.) at − 5°, and the mixture distilled from the steam-bath as rapidly as convenient. When the evolution of gases became less vigorous (3—5 minutes), saturated alcoholic hydrogen chloride (30 c.c.) was added, and the hot solution filtered from a red by-product, traces of which were always formed in the reaction. On cooling, the hydrochloride crystallised from the filtrate in brown needles. A further crop was obtained by washing the by-product with boiling alcohol and by evaporating the combined mother-liquors. After boiling with charcoal in alcoholic solution and several recrystallisations from alcohol–ethyl acetate the hydrochloride was obtained as orange needles, m. p. 180° (7·4 g., 60%). It was converted into the free *base*, which distilled as a yellow oil, bath at 115°/0·0001 mm. (Found : C, 62·1; H, 5·8. $C_{13}H_{15}ON_2Cl$ requires C, 62·3; H, 6·0%). Even under these conditions a considerable amount of decomposition occurred and the more satisfactory means of purification was recrystallisation of the hydrochloride and passage of a solution of the free base in chloroform through an alumina column.

The picrate separated from benzene in orange needles, m. p. 128°.

Bis-(8-γ-*chloropropylamino*-6-*methoxy*-5-*quinolyl*) *Sulphide*.—The red by-product, mentioned above was formed in amounts varying with the conditions under which the reaction was carried out. If the reactants were refluxed together for ½ hour or more, it was obtained in practically theoretical yield. Since it was extremely sparingly soluble in all solvents, it could not be purified directly, but was converted into the free *base* by means of aqueous ammonia. This crystallised from alcohol–benzene in fine, yellow needles, m. p. 144°, readily soluble in benzene, sparingly soluble in alcohol, ether and ethyl acetate, and almost insoluble in water and light petroleum (Found : C, 58·9; H, 5·1; N, 10·6; Cl, 13·1; S, 6·3; active H, 0·38. $C_{26}H_{28}O_2N_4Cl_2S$ requires C, 58·8; H, 5·3; N, 10·6; Cl, 13·4; S, 6·0; 2H, 0·38%). On heating with camphor, decomposition occurred so that a Rast determination of the molecular weight could not be carried out. Attempted benzoylation and acetylation did not give crystalline derivatives.

Hydrochloride. The free base, dissolved in benzene, was mixed with an excess of ethereal hydrogen chloride; the finely divided, deliquescent, red precipitate was separated centrifugally, washed with ethyl acetate, and again centrifuged, and the process repeated until the washings were no longer acid; it was then dried in a desiccator; m. p. 200—201° (Found : C, 47·6; H, 5·6; Cl, 21·3. $C_{26}H_{28}O_2N_4Cl_2S,2HCl,3H_2O$ requires C, 47·4; H, 5·5; Cl, 21·5%). Attempts to crystallise the salt were unsuccessful, as on boiling with water or alcohol hydrolysis occurred and the free base was formed.

Bis-(8-γ-*diethylaminopropylamino*-6-*methoxy*-5-*quinolyl*) *Sulphide* (III) (R. 118, index 1 : 7—1 : 8).—Bis-(8-γ-chloropropylamino-6-methoxy-5-quinolyl) sulphide (10 g.) was heated with a large excess of diethylamine (10 g.) in a sealed tube at 120—125° for 12 hours. The product was treated with aqueous sodium carbonate, and the excess of diethylamine removed by distillation. The *product* (9·1 g., 80%) crystallised from benzene–light petroleum in stout yellow needles, m. p. 85° (Found : C, 67·2; H, 8·0; N, 14·0; OMe, 9·8. $C_{34}H_{48}O_2N_6S$ requires C, 67·2; H, 7·9; N, 13·9; 2OMe, 10·2%). The meconate separated from alcohol–ethyl acetate in yellow polyhedra, m. p. 140° (decomp.); the picrate crystallised from alcohol in yellow prisms, m. p. 173° (decomp.) (evacuated capillary).

The *hydrochloride* was a deliquescent, orange, micro-crystalline powder, m. p. 150° (decomp.) (Found : C, 53·1; H, 7·3; N, 10·7; Cl, 18·3. $C_{34}H_{48}O_2N_6S,4HCl,H_2O$ requires C, 53·1; H, 7·3; N, 10·7; Cl, 18·5%). It crystallised from alcohol–ethyl acetate but owing to its deliquescent nature and fine state of division it was necessary to remove the mother-liquor and to wash the solid by centrifuging and decantation. An attempt to remove the water of crystallisation by heating at 100° in a vacuum over phosphoric oxide resulted in decomposition.

Condensation of 8-γ-*Chloropropylamino*-6-*methoxyquinoline with Primary and Secondary Amines*.—The chloro-compound was heated with a large excess of the amine in sealed tubes at 125—135° for 7—12 hours.

8-γ-*Methylaminopropylamino*-6-*methoxyquinoline* (R. 105). The reaction product was treated with dilute aqueous sodium carbonate and extracted with ether. The ether and excess of methylamine were evaporated; the residual oil had b. p. 166°/0·5 mm. (Found : C, 68·6; H, 7·9. $C_{14}H_{19}ON_3$ requires C, 68·6; H, 7·8%). Some decomposition occurred on distillation, and crystallisation of the *hydrogen oxalate* was found to be a better method of purification. This derivative separated from ethyl acetate–alcohol, containing oxalic acid, in yellow prisms, m. p. 188° (Found : C, 50·7; H, 5·5. $C_{14}H_{19}ON_3,2C_2H_2O_4$ requires C, 50·8; H, 5·4%).

The *hydrochloride* was prepared in ethereal solution and washed with ether. It crystallised from alcohol in deliquescent, orange needles, m. p. 218° (Found : C, 52·5; H, 6·9; N, 12·9. $C_{14}H_{19}ON_3,2HCl$ requires C, 52·8; H, 6·6; N, 13·2%).

8-γ-*Ethylaminopropylamino*-6-*methoxyquinoline* (R. 106). As in the last case, the excess of amine was removed by distillation with ether. The *hydrogen oxalate*, purified by several crystallisations from alcohol–ethyl acetate mixtures containing oxalic acid, formed yellow prisms, m. p. 139° (Found : C, 51·5; H, 5·8. $C_{15}H_{21}ON_3,2C_2H_2O_4$ requires C, 51·9; H, 5·7%). The free base was obtained from the pure oxalate by the action of aqueous sodium carbonate; its solution in chloroform was passed through an alumina column and evaporated. The *hydrochloride*, prepared by means of ethereal hydrogen chloride, crystallised from alcohol–ethyl acetate in deliquescent, orange needles, m. p. 206° (Found : C, 51·8; H, 7·0. $C_{15}H_{21}ON_3,2HCl,H_2O$ requires C, 51·5; H, 7·1%).

n-*Propylamine*. Propionitrile (55 g.) was hydrogenated in alcoholic ammonia (200 c.c., saturated at 0°) for 4 hours at 100—150°/100 atm., a Raney nickel catalyst being used. The product was worked up through the hydrochloride, and the free bases fractionated, b. p. 49—52°/748 mm. (45 g., 75%). *n*-Propylamine picrate formed yellow needles from alcohol, m. p. 132—134° (lit. 135°).

8-γ-*Propylaminopropylamino*-6-*methoxyquinoline* (R. 119). The excess of propylamine was removed by distillation in a stream of chloroform, and the *hydrogen oxalate* prepared and purified by several crystallisations from alcohol containing oxalic acid. It formed golden-yellow plates, m. p. 173° (Found : C, 52·7; H, 6·1. $C_{16}H_{23}ON_3,2C_2H_2O_4$ requires C, 53·0; H, 6·0%). A solution of the free base in chloroform was passed through an alumina column. The *hydrochloride* crystallised from alcohol in deliquescent, golden-orange plates, m. p. 162° (Found : C, 55·3; H, 7·3. $C_{16}H_{23}ON_3,2HCl$ requires C, 55·5; H, 7·2%).

iso*Propylamine*. Acetoxime (73 g.) was hydrogenated for 3 hours in alcoholic ammonia (100 c.c., saturated at 0°) at 90—130°/60 atm., a Raney nickel catalyst being used. *iso*Propylamine (30 g., 50%), b. p. 32°, was obtained by way of the mixture of hydrochlorides; the benzenesulphonamide had m. p. 98° (lit. 99°).

8-γ-iso*Propylaminopropylamino*-6-*methoxyquinoline* (R. 108). The excess of *iso*propylamine was removed by distillation with chloroform, and the *hydrogen oxalate* prepared and purified by several crystallisations from aqueous alcohol containing oxalic acid. It formed golden plates, m. p. 136° (Found : C, 53·0; H, 6·0. $C_{16}H_{23}ON_3,2C_2H_2O_4$ requires C, 53·0; H, 6·0%). The meconate crystallised from aqueous alcohol in golden plates, m. p. 195°. The *hydrochloride* crystallised from alcohol in well-formed yellow needles, m. p. 210° (Found : C, 55·8; H, 7·1. $C_{16}H_{23}ON_3,2HCl$ requires C, 55·5; H, 7·2%).

8-γ-n-*Butylaminopropylamino*-6-*methoxyquinoline* (R. 107). After removal of the excess of *n*-butylamine by distillation with chloroform the *hydrogen oxalate* was prepared. It crystallised from alcohol, containing oxalic acid, in small, yellow needles, m. p. 141° (Found : C, 52·3; H, 6·2; N, 8·3. $C_{17}H_{25}ON_3,2C_2H_2O_4,H_2O$ requires C, 52·0; H, 6·4; N, 8·7%). The *picrate* crystallised from much alcoholic picric acid as a pale yellow, microcrystalline powder, m. p. 178° (Found : N, 17·1. $C_{17}H_{25}ON_3,2C_6H_3O_7N_3$ requires N, 16·9%). The *hydrochloride* crystallised from alcohol–ethyl acetate in deliquescent orange needles, m. p. 180° (Found : C, 54·2; H, 7·5. $C_{17}H_{25}ON_3,2HCl,H_2O$ requires C, 53·9; H, 7·7%). The anhydrous salt, obtained by heating the monohydrate at 60° in a vacuum over phosphoric oxide for 12 hours, crystallised from alcohol as a microcrystalline, buff-coloured powder, m. p. 79° (evacuated capillary). It rapidly took up moisture from the atmosphere, becoming orange.

8-γ-iso*Butylaminopropylamino*-6-*methoxyquinoline* (R. 110). The excess of *iso*butylamine was removed by evaporation with benzene. The *hydrogen oxalate* crystallised from aqueous alcohol in lustrous buff-coloured plates, m. p. 218° (Found : C, 58·6; H, 6·9; N, 10·6. $C_{17}H_{25}ON_3,C_2H_2O_4,H_2O$ requires C, 58·9; H, 7·1; N, 10·3%). The *hydrochloride* was precipitated as an oil but crystallised, on keeping, in orange needles, m. p. 192—195°. On heating at 60° in a vacuum over phosphoric oxide for several days, the anhydrous form was obtained, m. p. 178° after crystallisation from alcohol–ethyl acetate (Found : C, 56·4; H, 7·6; N, 11·7. $C_{17}H_{25}ON_3,2HCl$ requires C, 56·7; H, 7·5; N, 11·7%).

8-γ-tert.-*Butylaminopropylamino*-6-*methoxyquinoline* (R. 109). The excess of *tert.*-butylamine was removed by distillation with chloroform. The *meconate*, crystallised from aqueous alcoholic meconic acid, formed yellow prisms, m. p. 188° (Found : C, 54·1; H, 5·0. $C_{17}H_{25}ON_3,2C_7H_4O_7$ requires C, 54·1; H, 4·8%). The hydrogen oxalate crystallised from alcohol in orange needles, m. p. 184°. The *hydrochloride* crystallised from alcohol in pinkish-orange needles, m. p. 174° (Found : C, 57·0; H, 7·7; N, 12·1. $C_{17}H_{25}ON_3,2HCl$ requires C, 56·7; H, 7·5; N, 11·7%).

n-*Heptylamine*. *n*-Heptaldehyde (57 g.) was mixed with alcoholic ammonia (300 c.c., saturated at 0°), considerable heat being evolved. The mixture was hydrogenated for 3 hours at 90—130°/60 atm., a Raney nickel catalyst being used. *n*-Heptylamine was obtained as a colourless liquid, b. p. 153°/756 mm. (34 g., 60%); the picrate formed yellow needles from alcohol, m. p. 121° (lit. 120—122°).

8-γ-n-*Heptylaminopropylamino*-6-*methoxyquinoline* (R. 114). The excess of *n*-heptylamine was removed by steam distillation in a vacuum. A solution of the free base in chloroform was passed through an alumina column and evaporated, and the *hydrogen oxalate* prepared. It crystallised from alcohol in lustrous yellow needles, m. p. 181° (Found : C, 56·7; H, 7·2. $C_{20}H_{31}ON_3,2C_2H_2O_4$ requires C, 56·6; H, 6·9%). The free base was again purified by means of an alumina column, and the *hydrochloride* precipitated in ethereal solution. It crystallised, on standing, in deliquescent orange needles which darkened in the air, m. p. 110—112° (Found in material dried at 60° in a high vacuum : C, 59·7; H, 8·3; N, 10·4. $C_{20}H_{31}ON_3,2HCl$ requires C, 60·0; H, 8·4; N, 10·5%).

8-γ-*Benzylaminopropylamino*-6-*methoxyquinoline* (R. 117). The excess of benzylamine was removed by steam distillation in a vacuum, a chloroform solution of the free base passed through an alumina column and evaporated and the *hydrogen oxalate* prepared. It crystallised from aqueous alcoholic oxalic acid in golden plates, m. p. 230° (Found : C, 62·8; H, 6·2; N, 9·3; OMe, 7·0. $C_{20}H_{23}ON_3,C_2H_2O_4,C_2H_6O$ requires C, 63·0; H, 6·8; N, 9·2; 1OMe, 6·8%). The *hydrochloride* crystallised from alcohol in fine, yellow needles, m. p. 204° (Found : C, 59·7; H, 6·7; Cl, 17·3. $C_{20}H_{23}ON_3,2HCl,\frac{1}{2}H_2O$ requires C, 59·6; H, 6·5; Cl, 17·6%).

8-β′-*Phenyliso*propyl-γ-*aminopropylamino*-6-*methoxyquinoline* (R. 111). The excess of β-phenyl*iso*propylamine was removed by steam distillation in a vacuum. A solution of the free base in chloroform was passed through an alumina column and evaporated, and the *hydrogen oxalate* prepared. It crystallised from aqueous alcoholic oxalic acid in fine, buff-coloured needles, m. p. 128° (Found : C, 63·2; H, 6·4; N, 9·3. $C_{22}H_{27}ON_3,C_2H_2O_4,H_2O$ requires C, 63·2; H, 6·4; N, 9·2%). The *hydrochloride* crystallised from alcohol–ethyl acetate in deliquescent, yellow needles, m. p. 127° (Found : C, 62·4; H, 7·1. $C_{22}H_{27}ON_3,2HCl$ requires C, 62·6; H, 6·9%).

cyclo*Hexylamine*. *cyclo*Hexanoneoxime (56·5 g.) was hydrogenated for 3 hours in alcoholic ammonia (200 c.c., saturated at 0°) at 90—130°/80 atm., a Raney nickel catalyst being used. *cyclo*Hexylamine, b. p. 134°/762 mm. (56 g., 56%), was obtained on fractionation of the bases obtained by way of the hydrochlorides; hexahydrobenzanilide formed colourless needles from alcohol, m. p. 147° (*lit.* 147°).

8-γ-cyclo*Hexylaminopropylamino*-6-*methoxyquinoline*. The excess of *cyclo*hexylamine was removed by steam distillation in a vacuum. A solution of the free base in chloroform was passed through an alumina column and evaporated, and the *hydrogen oxalate* prepared. It crystallised from alcoholic oxalic acid in buff-coloured prisms, m. p. 215° (Found : C, 62·6; H, 7·2; N, 10·0. $C_{19}H_{27}ON_3,C_2H_2O_4$ requires C, 62·5; H, 7·1; N, 10·4%). The yield in this case was very poor and the hydrochloride has not, as yet, been prepared.

8-γ-*Furfurylaminopropylamino*-6-*methoxyquinoline* (R. 112). The *hydrogen oxalate* was prepared like previous examples and purified by several crystallisations from aqueous alcoholic oxalic acid. It formed buff-coloured prisms, m. p. 209° (Found in material dried at 80° in a high vacuum : C, 58·6; H, 5·9. $C_{18}H_{21}O_2N_3,C_2H_2O_4,H_2O$ requires C, 58·5; H, 5·6%). The *hydrochloride* crystallised from alcohol–ethyl acetate in fine, deliquescent, yellow needles, m. p. 203° (Found : C, 55·6; H, 6·7; N, 9·9. $C_{18}H_{21}O_2N_3,2HCl,C_2H_6O$ requires C, 55·8; H, 6·7; N, 9·8%). There was no loss in weight on heating at 80° over phosphoric oxide in a high vacuum for several days.

8-β′-*Aminoethyl*-γ-*aminopropylamino*-6-*methoxyquinoline* (R. 115). The excess of ethylenediamine was removed by steam distillation in a vacuum. The alkaline solution was then continuously extracted with chloroform for 3 hours, and the chloroform solution passed through an alumina column. After evaporation the *hydrogen oxalate* was prepared. It crystallised from aqueous oxalic acid in yellow prisms, m. p. 221° (Found : C, 43·9; H, 4·8; N, 8·9. $C_{15}H_{22}ON_4,4C_2H_2O_4$ requires C, 43·5; H, 4·7; N, 8·8%). The *meconate* crystallised from aqueous alcoholic meconic acid in light orange prisms, m. p. 186° (decomp.) (Found : C, 48·3; H, 5·6; N, 7·7. $C_{15}H_{22}ON_4,3C_7H_4O_7,3H_2O$ requires C, 48·5; H, 5·0; N, 7·7%). An attempt to obtain the anhydrous form by heating at 100° in a high vacuum over phosphoric oxide resulted in decomposition. The *hydrochloride* crystallised from aqueous alcohol in deliquescent, orange needles, m. p. 244° (Found : C, 46·5; H, 6·5; N, 14·7. $C_{15}H_{22}ON_4,3HCl$ requires C, 46·9; H, 6·5; N, 14·6%).

Trimethylenediamine. The methods available for the preparation of this base have been compared and the best is probably the application of the Hofmann reaction to glutardiamide.

(*a*) Hydrolysis of 1 : 3-diphthalimidopropane by means of hydrazine hydrate gave a product contaminated with hydrazine, from which it was not possible to separate it by distillation.

(*b*) By the method of Gabriel and Weiner (*Ber.*, 1888, **21**, 2670) diphthalimidopropane (56 g.) gave 6 g. (58%), b. p. 135°, of the anhydrous base; dipicrate, yellow needles, m. p. 248° (decomp.) (lit. 250°).

(*c*) An attempt was made to hydrogenate malononitrile in alcoholic ammonia with a Raney nickel catalyst at 90—130°/80 atm., but before the theoretical volume of hydrogen had been absorbed large quantities of solid separated which prevented further stirring and it was obvious that the nitrile had polymerised.

(*d*) (cf. Galat and Elion, *J. Amer. Chem. Soc.*, 1939, **61**, 3585). Condensation of hexamine with trimethylene dibromide in aqueous alcoholic solution in presence of sodium iodide gave sticky resin. The method did not appear to be promising.

(*e*) (cf. Aspinall, *J. Amer. Chem. Soc.*, 1941, **63**, 2843). After trial of other methods, glutardiamide was prepared as follows. Glutaryl dichloride was added gradually, with good stirring, to a mixture of ether (500 c.c.) and aqueous

ammonia (500 c.c., *d* 0·880) cooled to 0°. The solution was evaporated to dryness under reduced pressure and the mixture of ammonium chloride and glutardiamide was extracted several times with boiling amyl alcohol. On cooling, the glutardiamide separated as a buff-coloured, micro-crystalline powder, m. p. 168° (26 g., 61%). After several crystallisations (charcoal) from boiling amyl alcohol it formed colourless plates, m. p. 176° with evolution of gas (lit. 176°) (22 g., 50%). Bromine (160 g.) was gradually added to a solution of potassium hydroxide (280 g.) in water (750 c.c.) at 0°. Glutardiamide (65 g.) was introduced, and the temperature allowed to rise, and kept at 60° for 2 hours. The mixture was then steam-distilled, and the base in the distillate estimated by the gradual addition of hydrochloric acid (methyl-orange) (base, 29 g., 78%). The neutralised distillate was evaporated to dryness, the residue treated with excess of saturated aqueous potassium hydroxide, and aqueous trimethylenediamine distilled; it was dried over potassium hydroxide, and later sodium, and distilled (20 g. of anhydrous base, 54%).

(*f*) Sodium azide (3·2 g.) was mixed with warm water (4 c.c.) and chloroform (10 c.c.), then cooled to 0°, and concentrated sulphuric acid (2·5 g.) added gradually with good stirring below 5°. The organic layer was decanted and dried over sodium sulphate. This solution was added gradually to one of glutaric acid (2·64 g.) in concentrated sulphuric acid (5 c.c.) and chloroform (5 c.c.) at 43—45° with good stirring until carbon dioxide and nitrogen were no longer evolved. The mixture was then added to ice and neutralised, and the trimethylenediamine isolated as the dipicrate, m. p. 250° (9·6 g. of dipicrate or 0·96 g. of base, 65%). When an attempt was made to carry out the reaction on a larger scale (0·5 g.-mol.), the yield was very much diminished.

8-*γ'-Aminopropyl-γ-aminopropylamino*-6-*methoxyquinoline* (R. 120). The excess of trimethylenediamine was removed by steam distillation in a vacuum. The alkaline solution was extracted continuously with chloroform for a considerable time, the free base being readily soluble in water, and the extract was passed through an alumina column, the solvent evaporated, and the *hydrogen oxalate* prepared. It crystallised from aqueous alcoholic oxalic acid in tiny, pale yellow needles, m. p. 221° (Found: C, 50·8; H, 6·0; N, 11·8; OMe, 6·5. $C_{16}H_{24}ON_4,2C_2H_2O_4$ requires C, 51·2; H, 6·0; N, 11·9; 1OMe, 6·6%). The oxalate was decomposed with aqueous sodium carbonate, and the base again extracted continuously with chloroform. The solution was passed through an alumina column, the chloroform distilled, and the basic oil mixed with ethereal hydrogen chloride. Two hydrochlorides were formed and separated by fractional crystallisation from aqueous alcohol. The main product was the *hydrochloride* of 8-*γ'-aminopropyl-γ-aminopropylamino*-6-*methoxyquinoline*; it crystallised in deliquescent, yellow needles, m. p. 225° (decomp.) (Found: C, 47·7; H, 6·8; N, 14·2; Cl, 25·7. $C_{16}H_{24}ON_4,3HCl,\frac{1}{2}H_2O$ requires C, 47·2; H, 6·9; N, 13·7; Cl, 26·2%). The second hydrochloride, which was formed in small relative amount, crystallised from alcohol in deliquescent, colourless needles, m. p. 173°. Analysis indicated that the alkylamino-side chain had been eliminated, but the substance has not yet been identified (Found: Cl, 18·1%).

8-*δ'-Amino*-n-*butyl-γ-aminopropylamino*-6-*methoxyquinoline* (R. 121). Tetramethylenediamine was prepared from adipic acid both by the Schmidt reaction (yield, 65%) and by the Hofmann reaction (yield, 72%). The methods used were those described above in the case of trimethylenediamine (cf. von Braun and Lemke, *Ber.*, 1922, **55**, 3526; 1934, **67**, 1059; Oesterlin, *Z. angew. Chem.*, 1932, **45**, 536; Adamson and Kenner, J., 1934, 842; Adamson, J., 1939, 1564); dipicrate, pale yellow prisms from water; on heating it turned brown at 250°, and decomposed at 250—255° (lit. 250—255°). The condensation and purification followed those of the lower homologue. The *hydrogen oxalate* crystallised from aqueous alcoholic oxalic acid in tiny, yellow prisms, m. p. 183—185° (Found: C, 50·3; H, 6·5. $C_{17}H_{26}ON_4,2C_2H_2O_4,H_2O$ requires C, 50·4; H, 6·4%). The picrate crystallised from aqueous picric acid in yellow plates, decomp. 194° (evacuated capillary). The *hydrochloride* crystallised from alcohol–ethyl acetate in deliquescent orange-yellow prisms, which on heating underwent some change, probably dehydration, at 125—132°, m. p. 210° (Found: C, 47·7; H, 6·9. $C_{17}H_{26}ON_4,3HCl,H_2O$ requires C, 47·5; H, 7·2%).

Pentamethylenediamine. Glutardinitrile (31 g.) was hydrogenated in alcoholic ammonia (300 c.c., saturated at 0°) for 8 hours at 110—150°/80 atms. with a Raney nickel catalyst. The base was distilled, dried over potassium hydroxide, and redistilled, b. p. 178—180°/750 mm. (24 g., 70%); dibenzoylcadaverine had m. p. 135° (lit. 135°).

8-*ε-Amino*-n-*amyl-γ-aminopropylamino*-6-*methoxyquinoline* (R. 122). The excess of cadaverine was removed by steam distillation in a vacuum and the alkaline solution was extracted six times with chloroform; the base appeared to be considerably less readily soluble in water than the lower homologues. The chloroform solution was passed through an alumina column, the chloroform removed, and the *hydrogen oxalate* prepared. It crystallised from aqueous alcoholic oxalic acid in small yellow prisms, m. p. 162° (Found: C, 49·4; H, 6·2. $C_{18}H_{28}ON_4,3C_2H_2O_4$ requires C, 49·1; H, 5·8%). The *hydrochloride* crystallised from alcohol in deliquescent, yellow needles, m. p. 196° (Found: C, 50·4; H, 7·4. $C_{18}H_{28}ON_4,3HCl$ requires C, 50·8; H, 7·3%).

8-*β-Hydroxyethyl-γ-aminopropylamino*-6-*methoxyquinoline.* Ethanolamine was removed by steam distillation in a vacuum, and the free base extracted continuously with chloroform for several hours. The chloroform solution was passed through an alumina column, then evaporated, and the *picrate* prepared. It crystallised from aqueous alcoholic picric acid in yellow needles, m. p. 159° (decomp.) (evacuated capillary) (Found: C, 44·2; H, 3·7; N, 17·1. $C_{15}H_{21}O_2N_3,2C_6H_3O_7N_3$ requires C, 44·2; H, 3·7; N, 17·2%). The picrolonate, m. p. 216° (decomp.) (evacuated capillary), and the styphnate, m. p. 172° (decomp.) (evacuated capillary), both crystallised in yellow needles from aqueous alcohol. The hydrogen oxalate, m. p. 72°, and meconate, m. p. 204°, did not crystallise well from any solvent and were unsuitable for purification purposes. Difficulty was experienced in the decomposition of the picrate because the free base was oxidised by the action of sodium picrate in alkaline solution. The deliquescent *hydrochloride* crystallised from alcohol–ethyl acetate in small, orange rhombs which on heating melted at 98°, resolidified, and melted finally at 154° (Found in material dried at 80° in a high vacuum: C, 51·6; H, 6·8; N, 11·9; Cl, 26·9. $C_{15}H_{21}O_2N_3,2HCl$ requires C, 51·7; H, 6·6; N, 12·1; Cl, 26·8%).

8-*γ-Diethylaminopropylamino*-6-*methoxyquinoline* (Rhodoquin, R. 116). The free base was distilled, b. p. 198°/1 mm. (Magidson and Strukow, *Arch. Pharm.*, 1933, **271**, 572). The picrate crystallised from alcohol in orange needles, m. p. 186° (lit. 190°). When crystallised from pure alcohol, the monomeconate, yellow needles, m. p. 133—134° (lit. 133—134°), was obtained; when crystallised from alcoholic meconic acid, the *dimeconate*, yellow needles, m. p. 178°, was isolated (Found: C, 54·2; H, 5·1; N, 6·2. $C_{17}H_{25}ON_3,2C_7H_4O_7$ requires C, 54·1; H, 4·8; N, 6·1%). The *hydrochloride* crystallised from alcohol in deliquescent yellow needles, m. p. 208° (Found: C, 56·4; H, 7·6; N, 11·7; Cl, 19·2. $C_{17}H_{25}ON_3,2HCl$ requires C, 56·7; H, 7·5; N, 11·7; Cl, 19·3%).

Methyl-*n*-propylamine was prepared by the action of formaldehyde on *n*-propylamine and reduction of the tripropyltrimethylenetriamine so formed with zinc and hydrochloric acid (Graymore, J., 1931, 1492). The method is said to give an almost quantitative yield of methylpropylamine; propylamine (8%) was, however, obtained as a by-product. The b. p. of tripropyltrimethylenetriamine, which is not recorded, is 170°/752 mm.

8-*γ-Methylpropylaminopropylamino*-6-*methoxyquinoline* (R. 123). The free base was distilled (bath at 115—120°/0·015—0·02 mm.) as a clear yellow oil. The *meconate* crystallised from alcoholic meconic acid in yellow needles, m. p. 168° (Found: C, 53·2; H, 4·7; N, 6·2. $C_{17}H_{25}ON_3,2C_7H_4O_7,H_2O$ requires C, 52·8; H, 4·9; N, 6·0%). The *picrate* separated from acetone–benzene as an orange, microcrystalline powder, m. p. 152—154° (decomp.) (evacuated capillary) (Found: C, 46·9; H, 4·1; N, 16·8. $C_{17}H_{25}ON_3,2C_6H_3O_7N_3$ requires C, 46·7; H, 4·2; N, 16·9%). The picrolonate separated from alcohol as a yellow microcrystalline powder, m. p. 128°. The *hydrochloride* crystallised from

aqueous alcohol in fine, orange needles, m. p. 180—184° (Found : C, 52·7; H, 7·5; N, 10·5. $C_{17}H_{25}ON_3,2HCl,1\frac{1}{2}H_2O$ requires C, 52·7; H, 7·8; N, 10·9%).

8-*β-Hydroxyethylmethyl-γ-aminopropylamino*-6-*methoxyquinoline* (R. 124). After steam distillation in a vacuum the base was extracted six times with chloroform. The *meconate* crystallised from aqueous alcoholic meconic acid in yellow needles, m. p. 128° (decomp.) (Found : C, 54·8; H, 5·9; N, 8·3. $C_{16}H_{23}O_2N_3,C_7H_4O_7,H_2O$ requires C, 54·4; H, 5·9; N, 8·0%). The *hydrochloride* crystallised from alcohol in fine, deliquescent, deep yellow needles, m. p. 212° (Found : C, 53·0; H, 6·8; N, 11·5; Cl, 19·8. $C_{16}H_{23}O_2N_3,2HCl$ requires C, 53·0; H, 6·9; N, 11·6; Cl, 19·6%).

*Methyl*iso*propylamine*. A mixture of acetone (58 g.) and aqueous methylamine (200 c.c. of 33% w/v) was hydrogenated for 14 hours at 140—160°/60 atms. with a Raney nickel catalyst. The filtered solution was acidified with hydrogen chloride and evaporated to dryness. The mixture of hydrochlorides was then extracted several times with boiling chloroform, and the extracts evaporated. Methyl*iso*propylamine hydrochloride crystallised in colourless deliquescent needles, m. p. 71—74° (lit. 77°). Saturated potassium hydroxide solution was added, and the amine distilled, dried over potassium hydroxide, and redistilled, b. p. 50° (47 g., 65%); *N'*-phenyl-*N*-methyl-*N-iso*propylurea formed colourless needles from aqueous alcohol, m. p. 131°.

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