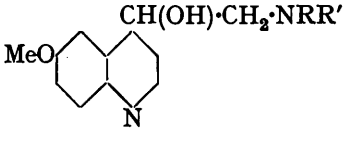
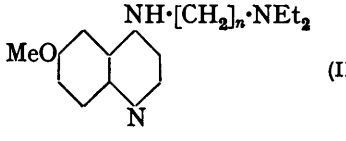
249. *Antiplasmodial Action and Chemical Constitution. Part IV. The Synthesis of some Complex Carbinolamines and Polyamines.*

By Thomas S. Work.

It has already been shown (King and Work, preceding paper) that antimalarial activity is not completely dependent on the nature of the " quinuclidine half " of compounds related to quinine. A wide variety of carbinolamines and polyamines without a quinoline nucleus have now been prepared in an attempt to assess the importance of the " quinoline half." None of the compounds prepared showed any antiplasmodial activity when tested on *Plasmodium relictum* in canaries. These results bring out the importance of the quinoline nucleus.

In Part III (*loc. cit.*) it was shown that compounds of the type (I) possessed weak antiplasmodial properties when R = R′ = butyl, amyl, or hexyl. Magidson and Rubtzow (*J. Gen. Chem., U.S.S.R.*, 1937, **17**, 1896) have also shown that weak antiplasmodial activity was shown by substances of the type (II). It is perhaps significant that bases

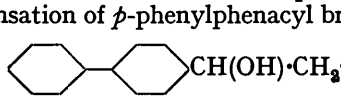
(I.) 

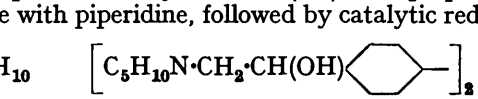


(II.)

showing antiplasmodial action, such as the cinchona alkaloids, the synthetic drugs plasmochin, atebrin, and numerous allied bases (Fourneau, *Ann. Inst. Pasteur*, 1933, **50**, 731; Magidson, *Arch. Pharm.*, 1934, **272**, 74), and substances such as (I) and (II), all have molecular weights between 300 and 400 and that structural specificity is not great, provided the molecular weight is above a certain limiting value. The aim of the present investigation was, therefore, to see whether the methoxyquinoline portion of the molecule of substances of types (I) and (II) could be replaced by other aromatic nuclei or by aliphatic chains of sufficient length to bring the molecular weight of the final base within the optimal zone.

With this aim in view 4-diphenylylpiperidinomethylcarbinol (III) was prepared by condensation of *p*-phenylphenacyl bromide with piperidine, followed by catalytic reduction

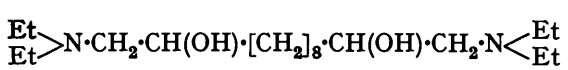
(III.) 



(IV.)

of the resulting ketone. The doubly substituted 4 : 4′-bis(β-*piperidino*-α-*hydroxyethyl*)-*diphenyl* (IV) was obtained similarly from 4 : 4′-*bis*-ω-*chloroacetyldiphenyl*. The inter-

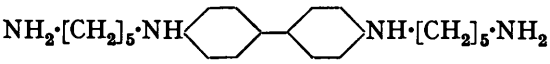
mediate substance, diphenyl-4 : 4′-dicarboxylic acid, had a high melting point and was extremely sparingly soluble, so that to prepare its di-acid chloride it was necessary to use phosphorus pentachloride in molten diphenyl. The bis-ω-chloroacetyldiphenyl was then obtained from it through the bis-diazo-ketone. In this way also the corresponding *dichloro-ketones* were prepared from sebacic acid and from decanedicarboxylic acid. Both of these dichloro-ketones condensed readily with piperidine and with diethylamine, but the conversion of the resultant keto-amines into the corresponding carbinols could only be accomplished by prolonged reduction, a large excess of fresh platinum oxide being used. In this way 1 : 12-dipiperidino- and 1 : 12-bisdiethylamino-2 : 11-dihydroxydodecane (V) were obtained. Reduction by aluminium amalgam in neutral solution led to fission of the amino-ketone at the C–N linkage without reduction of the keto-group. The Ponndorf method also was impracticable. These results seem to suggest that α-keto-amines are more readily reduced to carbinols when the ketone group is conjugated with an aromatic system. The difficulty was avoided in the case of the tetradecane derivatives by the preparation of the ditertiary carbinol, 1 : 14-*dipiperidino*-2 : 13-*dihydroxy*-2 : 13-*dipropyltetradecane* (VI) by the action of propylmagnesium iodide.



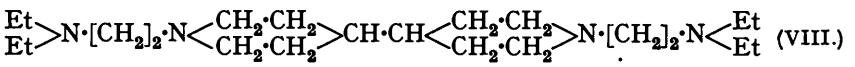
(V.)

(VI.)

As no antiplasmodial activity was shown by any of these carbinols based on the type (I), attention was directed to the preparation of substances based on (II). Benzidine di-*p*-toluenesulphonate was successfully condensed in the presence of two molecular proportions of sodium hydroxide with γ-diethylaminopropyl chloride and with 1-chloro-5-benzamidopentane. On removal of the toluenesulphonate radicals, *NN*′-bis-(γ-diethylaminopropyl)benzidine and *NN*′-bis-(5″-aminoamyl)benzidine (VII) were obtained.

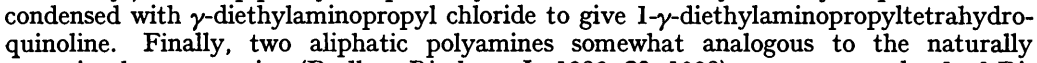


(VII.)



(VIII.)

Benzidine is a weak base of comparable strength with the aminoquinolines. As no antiplasmodial activity was found in these basic derivatives, attention was directed to the two very strong bases 4 : 4′-dipiperidyl and 2 : 4′-dipiperidyl, which are now available commercially. Each of these condensed readily with β-diethylaminoethyl chloride to give 1 : 1′-bis-(β-diethylaminoethyl)-4 : 4′-dipiperidyl (VIII) and 1 : 1′-bis-(β-diethylaminoethyl)-2 : 4′-dipiperidyl respectively. In a similar way tetrahydroquinoline was condensed with γ-diethylaminopropyl chloride to give 1-γ-diethylaminopropyltetrahydroquinoline. Finally, two aliphatic polyamines somewhat analogous to the naturally occurring base, spermine (Dudley, *Biochem. J.*, 1926, **20**, 1082), were prepared. 1 : 6-Diaminohexane and 1 : 10-diaminodecane were converted into their di-*p*-toluenesulphonyl derivatives, and these were alkylated with γ-diethylaminopropyl chloride. On removal of the toluenesulphonyl groups 1 : 6-bis-(γ-diethylaminopropylamino)hexane and 1 : 10-*bis*(γ-*diethylaminopropylamino*)*decane* (IX) were isolated. For comparison with these a base of somewhat simpler structure, 1 : 10-bis*iso*amylaminodecane (X) was prepared.



(IX.) (X.)

As none of the basic substances of moderately high molecular weight described in this communication have exhibited antiplasmodial activity, it must be concluded that the quinoline nucleus of the cinchona alkaloids and of synthetic antimalarials is a potent factor in the production of antiplasmodial activity. The recent surprising results of Fulton (*Ann. Trop. Med. Parasit.*, 1940, **34**, 53) on the antiplasmodial activity of such a simple base as 1-diethylamino-4-aminopentane are contrary to this conclusion, but attempts to confirm his results have been unsuccessful.

Experimental.

4-Diphenylylpiperidinomethylcarbinol (III).—*p*-Phenylphenacyl bromide (4·0 g.) (Drake and Bronitsky, *J. Amer. Chem. Soc.*, 1930, **52**, 3716), dissolved in acetone, was added slowly with shaking to piperidine (2·5 g.) and after 1 hour the product was diluted with ether, and the precipitated piperidine hydrobromide collected. The filtrate was evaporated in a vacuum at room temperature, and the free base crystallised from ether; m. p. 86°. The *picrate*, crystallised from methanol–acetone, had m. p. 188° (Found: C, 59·5; H, 4·8; N, 11·4. $C_{19}H_{21}ON,C_6H_3O_7N_3$ requires C, 59·1; H, 4·7; N, 11·0%). The yield was almost quantitative. The free base was dissolved in ethanol, made just acid to Congo by addition of concentrated hydrochloric acid, and reduced, Adams's catalyst being used. Complete reduction was troublesome and the final product still contained some amino-ketone, which was removed most conveniently by recrystallisation of the free base from methanol. The pure hydroxyamine melted at 120° and gave a *methiodide*, m. p. 205° (Found: C, 56·7; H, 6·3. $C_{19}H_{23}ON,CH_3I$ requires C, 56·4; H, 6·1%). The hydrochloride melted at 243° (decomp.).

Diphenyl-4 : 4′-dicarboxylic Acid.—Benzidine (37 g.) was dissolved in concentrated hydrochloric acid (100 c.c.), and ice (400 g.) added. Sodium nitrite (about 90 c.c. of 30%) was added slowly until some free nitrous acid was present; the diazonium chloride solution was then neutralised by addition of saturated aqueous sodium carbonate. This mixture was added slowly with stirring to a solution of cuprous cyanide at 90° (from 171·6 g. of potassium cyanide and 159·8 g. of copper sulphate in 1060 c.c. of water). After cooling and standing overnight, the solid product was collected, dried, and extracted with alcohol (Soxhlet). The alcohol-soluble material (2·7 g.), m. p. 230—233°, was diphenyldinitrile and the alcohol-insoluble material (32·7 g.) appeared to be a copper complex, which was decomposed by warming on the water-bath for ½ hour with excess of concentrated hydrochloric acid. The acid was diluted, and the solid material filtered off, washed free from acid, and extracted with acetone (Soxhlet). The acetone-soluble extract crystallised readily, m. p. 230—233°, and was identical with the previous crop of diphenyldinitrile; total yield, 45%. The dinitrile (10·0 g.) was mixed with 70% sulphuric acid (90 c.c.) and refluxed for 45 minutes. The product when cold was poured into water, and the diphenyldicarboxylic acid filtered off, washed, and dried. The yield was 95%, and the product was sufficiently pure for conversion into the acid chloride.

Diphenyl-4 : 4′-dicarboxylic Acid Chloride.—Diphenyldicarboxylic acid (12·5 g.) was powdered, mixed with diphenyl (50 g.), heated under a reflux condenser to 150°, and powdered phosphorus pentachloride (21 g.) added slowly. After removal of the phosphorus oxychloride the diphenyl di-acid chloride, which was soluble in hot diphenyl, was purified by distilling off most of the diphenyl in a vacuum and pouring the residue into hot benzene. The acid chloride crystallised in long white needles sparingly soluble in cold benzene, m. p. 184° (yield, 80%). Purification was also attempted by distillation in a high vacuum, but resulted in considerable decomposition. Attempts to use thionyl chloride in place of phosphorus pentachloride were unsuccessful.

4 : 4′-Di-ω-chloroacetyldiphenyl.—Diphenyl di-acid chloride (8·0 g.) in solution in warm benzene (300 c.c.) was added slowly to a solution of diazomethane (from 20 g. of nitrosomethylurea) in ether. When the vigorous reaction had ceased, the precipitated diazo-ketone, m. p. 165° (decomp.), was collected and used immediately for the next stage without further purification. The diazo-ketone was suspended in benzene (250 c.c.), warmed to 40°, and a rapid stream of dry hydrogen chloride passed into the solution until no more nitrogen was evolved. The pale yellow, crystalline product was filtered off and recrystallised from dioxan; m. p. 226—227°, yield 5·2 g. (Found: C, 62·6; H, 3·9. $C_{16}H_{12}O_2Cl_2$ requires C, 62·5; H, 3·9%).

4 : 4′-Bis-(β-piperidino-α-hydroxyethyl)diphenyl (IV).—The dichloro-ketone (4·0 g.) from the previous preparation was finely powdered, suspended in chloroform (25 c.c.), heated to the b. p., and added all at once to a hot solution of piperidine (4·55 g.) in chloroform (25 c.c.). After heating in a water-bath at 50° for ½ hour, the chloroform was concentrated to 25 c.c., and ether (100 c.c.) added. The precipitated piperidine hydrochloride (2·8 g.) was removed, the filtrate evaporated in a vacuum, and the solid residue recrystallised from ethanol; m. p. 140° (Found: C, 77·0; H, 7·7. $C_{26}H_{32}O_2N_2$ requires C, 77·2; H, 7·9%). The *amino-ketone* was dissolved in ethanol, made just acid to Congo by addition of hydrochloric acid, and reduced, Adams's catalyst being used (630 c.c. of hydrogen). 4 : 4′-Bis-(β-piperidino-α-hydroxyethyl)-diphenyl dihydrochloride, sparingly soluble in hot absolute alcohol, was readily isolated from the solution after removal of the catalyst and from it was obtained the free *base* (3·7 g.), m. p. 158° after recrystallisation from methanol (Found: C, 76·4; H, 8·5. $C_{26}H_{36}O_2N_2$ requires C, 76·5; H, 8·8%).

1 : 12-*Dichloro*-2 : 11-*diketododecane*.—Sebacic acid (20 g.) was converted into the acid chloride by treatment with phosphorus pentachloride (2 mols.), and the acid chloride purified by distillation, b. p. 140—143°/2 mm. The yield was almost quantitative. The acid chloride was dissolved in dry ether and run slowly into an ethereal solution of excess of diazomethane (from 50 g. of nitrosomethylurea), and the mixture kept overnight. The ether and diazomethane were removed by gentle warming in a vacuum and the *diazo-ketone*, which crystallised, was collected, m. p. 91° after recrystallisation from benzene; it was sparingly soluble in ether. Yield, 19·3 g. (Found: N, 22·4. $C_{12}H_{18}O_2N_4$ requires N, 22·7%). The diazo-ketone was dissolved in the minimum quantity of benzene, and dry hydrogen chloride passed in rapidly until no more nitrogen was evolved. The white crystalline product, sparingly soluble in cold benzene, melted at 92° after recrystallisation; yield, 19·5 g. (Found: C, 53·9; H, 7·5; Cl, 27·0. $C_{12}H_{20}O_2Cl_2$ requires C, 53·9; H, 7·5; N, 26·6%).

1 : 12-*Dipiperidino*-2 : 11-*dihydroxydodecane*.—To a solution of piperidine (2·55 g.) in acetone (10 c.c.) was added, slowly, powdered dichlorodiketododecane (2·0 g.). The mixture was kept for 1 hour at 35°, then diluted with ether, and the precipitated piperidine hydrochloride (1·7 g.) collected. The filtrate was evaporated in a vacuum, and the low-melting solid residue dissolved immediately in ethanol, made just acid to Congo with hydrochloric acid, and reduced, Adams's platinum catalyst being used. Reduction was troublesome and could not be completed. The desired amino-alcohol was isolated by fractional crystallisation from light petroleum, in which it was much less soluble than the amino-ketone. The amino-alcohol melted at 78° and gave a *dipicrate*, m. p. 152° (Found: C, 49·6; H, 5·8; N, 13·4. $C_{22}H_{44}O_2N_2,2C_6H_3O_7N_3$ requires C, 49·4; H, 6·0; N, 13·5%). The recovered unreduced ketone melted at 43°.

1 : 12-*Diethylamino*-2 : 11-*dihydroxydodecane*.—The method of condensation of the chloro-ketone (2·0 g.) and diethylamine was as in the previous experiment. Reduction with Adams's catalyst was again troublesome. In order to separate the ketone from the alcohol the product of the reduction was treated with Girard's " reagent P " and separated into water-soluble and ether-soluble fractions. From the ether-soluble fraction an oil was obtained (1·1 g.) giving a crystalline *dipicrate*, m. p. 121°, from alcohol (Found: N, 14·0. $C_{20}H_{44}O_2N_2,2C_6H_3O_7N_3$ requires N, 13·9%).

1 : 14-*Dichloro*-2 : 13-*diketotetradecane*.—The method was the same as that used in the preparation of dichlorodiketododecane. *n*-Decanedicarboxylic acid was converted into the acid chloride and treated with diazomethane. The *diazo-ketone* after crystallisation from benzene melted at 96° (Found: C, 60·5; H, 7·9. $C_{14}H_{22}O_2N_4$ requires C, 60·4; H, 7·9%). The diazo-ketone, treated with hydrochloric acid, gave the *chloro-ketone*, m. p. 97° (Found: C, 57·2; H, 8·4. $C_{14}H_{24}O_2Cl_2$ requires C, 56·9; H, 8·2%). The yield was 17·0 g. from 20·0 g. of decanedicarboxylic acid.

1 : 14-*Dipiperidino*-2 : 13-*diketotetradecane*.—The chloro-ketone (2·9 g.), condensed with piperidine (3·2 g.) in the same way as in the case of the lower homologue, gave crystalline dipiperidinodiketotetradecane (2·9 g.), but reduction of this compound could not be carried out satisfactorily either with Adams's catalyst or with palladised charcoal. An attempt was made to carry out the reduction with neutral aluminium amalgam. The base (m. p. 48°) was exactly neutralised with hydrochloric acid and kept for 3 hours in aqueous solution over a large excess of aluminium amalgam which had been prepared by treating clean aluminium turnings with a saturated ethereal solution of mercuric chloride for a few seconds and then washing thoroughly with ether (cf. Weitz, Kõnig, and Wistinghausen, *Ber.*, 1924, **57**, 167). The residual aluminium amalgam was removed and washed with alcohol and ether, and the filtrate and washings acidified slightly and extracted with ether. The extract gave a white solid, which was crystallised from light petroleum; m. p. 75° (yield, 150 mg.) (Found: C, 73·9; H, 11·5. $C_{14}H_{26}O_2$ requires C, 74·3; H, 11·5%). The compound gave a precipitate with 2 : 4-dinitrophenylhydrazine and was apparently 2 : 13-*diketotetradecane*. The aqueous fraction was made alkaline and extracted with ether. From the ether a base (160 mg.) was obtained from which no crystalline derivative could be prepared.

1 : 14-*Dipiperidino*-2 : 13-*dihydroxy*-2 : 13-*dipropyltetradecane* (VI).—Dipiperidinodiketotetradecane (2·7 g.) in ether (25 c.c.), prepared as described above, was added slowly to a Grignard reagent, prepared from magnesium (0·33 g.) and propyl bromide (1·7 g.) in ether (25 c.c.), with vigorous stirring. After ½ hour, cold 3N-hydrochloric acid was added and the resulting solution, after being washed with ether, was made alkaline with ammonia and extracted with ether. The extract gave 2·6 g. of a colourless oil. This product could not be purified as a crystalline derivative and was therefore distilled, b. p. 230—240°/0·3 mm. The substance

was not dehydrated by this process and analysis showed that it was mainly the desired *dicarbinol* (Found : C, 74·5; H, 12·4; N, 6·4. $C_{30}H_{60}O_2N_2$ requires C, 75·3; H, 12·1; N, 5·9%). No crystalline derivative was obtained.

*Benzidine Di-*p*-toluenesulphonate.*—The preparation was carried out as described by Willstätter and Kalb (*Ber.*, 1904, **37**, 3772), but the method of purification of the crude amide was modified. The crude product from the Schotten–Baumann reaction was dried and extracted continuously with alcohol (Soxhlet) until the m. p. of the material dissolving in the alcohol was about 140°. The solid remaining in the thimble was crystallised from acetone (charcoal); m. p. 241—243°, yield 70%.

NN'-Bis-(γ-diethylaminopropyl)benzidine.—Benzidine ditoluenesulphonate (6·56 g.), γ-diethylaminopropyl chloride (4·0 g.), sodium hydroxide (1·06 g.), and 75% alcohol (200 c.c.) were heated in a sealed bottle for 24 hours in a boiling water-bath. The solvent was removed from the product, which was then shaken with water, and the water decanted and evaporated (1·34 g. of sodium chloride). The water-insoluble gum was heated in a sealed tube for 4 hours at 180° with glacial acetic acid (10 c.c.) and concentrated hydrochloric acid (25 c.c.). The product was evaporated to dryness, dissolved in water, filtered from insoluble residue, made alkaline, and extracted repeatedly with benzene. The benzene-soluble oil distilled at 230—250°/0·9 mm. The distillate (2·2 g.) gave a crystalline *tetrahydrobromide*, m. p. 260° (decomp.), from methanol (Found : C, 42·3; H, 6·4; N, 7·8. $C_{26}H_{40}N_4,4HBr$ requires C, 42·6; H, 6·1; N, 7·7%).

NN'-Bis-(5''-aminoamyl)benzidine (VII).—Benzidine ditoluenesulphonate (6·56 g.), sodium hydroxide (1·06 g.), 1-chloro-5-benzamidopentane (Ainley and King, *Proc. Roy. Soc.*, 1938, **125**, 68), and 50% aqueous acetone (50 c.c.) were mixed thoroughly and heated in a sealed tube at 150—160° for 3 hours. When cold the aqueous acetone was decanted from the heavy oily product, which was washed with water. NN'-*Bis-(5''-benzamidoamyl)benzidine di-*p*-toluenesulphonate* crystallised on trituration with acetone and on recrystallisation from the same solvent had m. p. 192°; yield, 6·5 g. (Found : C, 68·8; H, 6·0. $C_{50}H_{54}O_6N_4S_2$ requires C, 69·1; H, 6·0%). This product (4·25 g.) was suspended in glacial acetic acid (25 c.c.), and hydrogen chloride passed into the mixture until the solid dissolved. The solution was heated with concentrated hydrochloric acid (10 c.c.) in a Carius tube at 180—190° for 3½ hours. The liquid was evaporated to dryness, the residue dissolved in water, and benzoic acid (0·86 g.) extracted with ether. The aqueous layer was filtered and evaporated to dryness. The resultant yellow gum crystallised when triturated with absolute alcohol, and was recrystallised from methanol; m. p. 270° (decomp.), yield 1·8 g. The *tetrahydrochloride* was hygroscopic (Found : C, 52·4; H, 6·8; N, 11·3. $C_{22}H_{34}N_4,4HCl$ requires C, 52·8; H, 7·4; N, 11·2%).

1 : 1'-*Bis-*(β-*diethylaminoethyl*)4 : 4'-*dipiperidyl* (VIII).—Dipiperidyl (4·2 g.), β-diethylaminoethyl chloride (6·8 g.), and alcohol (25 c.c.) were heated in a sealed tube at 100° for 18 hours. The alcohol was removed, and the product dissolved in water, made alkaline, and extracted with chloroform. The oil remaining on evaporation of the extract was distilled at 0·3 mm. and the portion boiling between 200° and 230° (3·04 g.) was further fractionated by the method of differing basicities (King, J., 1919, **117**, 991). The three main portions (2·12 g.) were identical and gave a *tetrapicrate* very sparingly soluble in acetone, m. p. 250° (decomp.) (Found : C, 43·5; H, 4·7. $C_{22}H_{46}N_2,4C_6H_3O_7N_3$ requires C, 43·1; H, 4·5%).

1 : 1'-*Bis-*(β-*diethylaminoethyl*)-2 : 4'-*dipiperidyl.*—A mixture of 2 : 4'-dipiperidyl (4·2 g.), β-diethylaminoethyl chloride, and alcohol (25 c.c.) was treated as described above (14 hours' heating). The oil obtained from the chloroform extract gave on distillation two fractions, b. p. 150—160°/0·5 mm., and 200—210°/0·5 mm. The latter, b. p. 205—210°/0·5 mm. on redistillation, gave a crystalline *tetrapicrate* (3·5 g.) moderately easily soluble in acetone, m. p. 170° (Found : C, 43·2; H, 4·5; N, 17·3. $C_{22}H_{46}N_4,4C_6H_3O_7N_3$ requires C, 43·1; H, 4·5; N, 17·6%).

1-*γ-Diethylaminopropyltetrahydroquinoline.*—Tetrahydroquinoline (8·0 g.) and γ-diethylaminopropyl chloride (4·0 g.) were heated together at 100° without solvent for 10 hours, aqueous alkali added, and the base extracted with ether. The oil obtained gave a main fraction, b. p. 190—192°/11·0 mm., 192°/10·0 mm. on redistillation (yield, 6·2 g.), which gave a crystalline *dipicrate* from ethanol, m. p. 147° (Found : C, 47·9; H, 4·5; N, 16·4. $C_{16}H_{28}N_2,2C_6H_3O_7N_3$ requires C, 47·9; H, 4·2; N, 16·0%).

1 : 6-*Bis-*p-*toluenesulphonylaminohexane.*—1 : 6-Diaminohexane (4·0 g.) was added to *p*-toluenesulphonyl chloride (13·5 g.) previously covered with a little water, and aqueous sodium hydroxide (3·0 g. in 15 c.c.) added. The mixture was heated on the water-bath for 1 hour and then cooled rapidly and shaken vigorously. The white solid was recrystallised from alcohol; m. p. 152°, yield 13·9 g. (Found : C, 56·7; H, 6·7. $C_{20}H_{28}O_4N_2S_2$ requires C, 56·6; H, 6·7%).

1 : 6 - *Bis* - (*γ* - *diethylaminopropylamino*)*hexane*.—1 : 6 - Bis-*p*-toluenesulphonylaminohexane (13·0 g.) was dissolved in alcohol (200 c.c. of 70%) containing sodium hydroxide (2·45 g.; 2 mols.), and to this was added *γ*-diethylaminopropyl chloride (9·17 g.; 2 mols.). The mixture was heated in a sealed bottle at 100° for 16 hours, then evaporated to dryness, the residue dissolved in absolute alcohol, and the precipitated sodium chloride (2·55 g.) filtered off. On evaporation of the alcohol a colourless syrup was obtained, which was heated with glacial acetic acid (20 c.c.) and concentrated hydrochloride acid (4·5 c.c.) in a sealed tube at 180° for 2 hours. After cooling, the toluene formed was removed, and the acid solution evaporated. The brown gum was dissolved in water (20 c.c.), made alkaline with 50% potassium hydroxide solution, and shaken with ether. Three layers formed, the bottom one being aqueous alkali. This was run off, and water added to the two remaining layers in sufficient quantity to dissolve the oily layer; the aqueous and the ethereal layer were then worked up separately. The latter gave an uncrystallisable oil (3·5 g.). The aqueous solution was extracted continuously with chloroform for 12 hours, and the chloroform dried and evaporated, giving 4·7 g. of a base, which on fractional distillation at 0·5 mm. gave 0·4 g. up to 135°, 2·7 g. at 135—140°, and 1·0 g. at 160—220°. The middle fraction gave a hygroscopic crystalline *hydrobromide*, m. p. 64°, which was purified with difficulty by crystallisation from alcohol–acetone (Found: C, 34·1; H, 7·8; N, 8·6. $C_{20}H_{46}N_4$,4HBr requires C, 35·8; H, 7·6; N, 8·4%).

1 : 10-*Bis*-p-*toluenesulphonylaminodecane*.—Sebaconitrile was reduced by sodium and alcohol to 1 : 10-diaminodecane in 85% yield (Phookan and Krafft, *Ber.*, 1892, **25**, 2253). The diaminodecane (11·2 g.) was treated with *p*-toluenesulphonyl chloride (24·1 g.) and sodium hydroxide (5·1 g.) as described for the preparation of the lower homologue, and the *product* crystallised from alcohol; m. p. 129°, yield 28·2 g. (Found: C, 60·3; H, 7·6. $C_{24}H_{36}O_4N_2S_2$ requires C, 60·0; H, 7·5%).

1 : 10-*Bis*-(*γ*-*diethylaminopropylamino*)*decane* (IX).—1 : 10-Bis-*p*-toluenesulphonylaminodecane (6·24 g.), *γ*-diethylaminopropyl chloride (3·9 g.), sodium hydroxide (1·05 g.), and 70% alcohol (100 c.c.) were heated in a sealed bottle for 16 hours. The product was evaporated to dryness, the residue dissolved in absolute alcohol, the sodium chloride (1·4 g.) removed, and the filtrate evaporated to a clear gum. This was heated with glacial acetic acid (10 c.c.) and concentrated hydrochloric acid (25 c.c.) in a sealed tube at 180—190° for 4 hours. The product was evaporated to dryness, and the residue dissolved in water, made strongly alkaline with sodium hydroxide, cooled in ice, and extracted rapidly several times with ethyl acetate. The ethyl acetate was evaporated, and the residue dissolved in benzene and filtered while hot. The filtrate was evaporated to a brown oil, which was distilled at 1·5 mm. and separated into two fractions, b. p. up to 150° and b. p. 178—184°. The former (0·67 g.) was recovered diaminodecane; the higher-boiling fraction, after redistillation, gave a very hygroscopic hydrobromide, m. p. 142—143° (crude), which could not be readily purified. The free *base* was preferred for analysis (Found: C, 73·0; H, 13·7; N, 13·7. $C_{24}H_{54}N_4$ requires C, 72·7; H, 13·7; N, 14·0%).

1 : 10-*Bis*iso*amylaminodecane* (X).—1 : 10-Bis-*p*-toluenesulphonylaminodecane (6·24 g.), *iso*amyl bromide (4·0 g.), sodium hydroxide (1·05 g.), and 70% alcohol (100 c.c.) were heated together as in the previous experiment, and sodium bromide (2·2 g.) removed from the product. Hydrolysis of the alcohol-soluble gum was carried out as in the previous experiment and the product, which was tarry, was poured into hot water; the liquid was boiled for several minutes and filtered hot. The white crystalline precipitate which formed on cooling was 1 : 10-*bis*-iso*amylaminodecane dihydrochloride* (1·5 g.), m. p. 318° (Found: C, 62·3; H, 11·1. $C_{20}H_{44}N_2$,2HCl requires C, 62·3; H, 12·0%). From the aqueous mother-liquor, 1·1 g. of diaminodecane hydrochloride were recovered.

γ-Diethylaminopropyl Chloride.—The method of Magidson (*Arch. Pharm.*, 1933, **271**, 569) was successfully employed, but the yields in the first stages were not as good as reported, being only about 50% in the condensation of diethylamine and trimethylene chloroacetate with hydrolysis to diethylaminopropanol. The b. p. of *γ*-diethylaminopropyl chloride was found to be 75—76°/29 mm. and not 85°/28 mm. as recorded by Magidson.

I desire to express my thanks to Miss Ann Bishop, D.Sc., working in the laboratory of Prof. D. Keilin, F.R.S., at the Molteno Institute, Cambridge, for carrying out the biological tests. I am also indebted to Mr. N. Schunmann for technical assistance.

National Institute for Medical Research, London, N.W. 3. [*Received, July 30th*, 1940.]