79. *Antiplasmodial Action and Chemical Constitution. Part VI. Compounds related to Lepidylamine.*

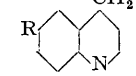
By Thomas S. Work.

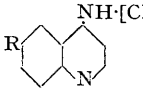
The aim of this investigation was the preparation of polyamines containing the lepidylamine nucleus for test as antimalarials. Polyamines have been synthesised containing the diethylamino*iso*amyl side chain of plasmochin attached to the lepidylamine nucleus and to 6-chloro- and 6-methoxy-lepidylamine. Reduction of amidodichlorides by stannous chloride in ethereal hydrogen chloride (Work, following paper) is a valuable preparative method for the syntheses of substituted lepidylamines from cinchoninamides.

Sulphanilyl derivatives of the afore-mentioned lepidylamines have also been prepared.

In Part IV (Work, J., 1940, 1315) the conclusion was reached that, for the exhibition of antiplasmodial action in polyamines, the presence of the quinoline nucleus was of major importance. A series of bases of the

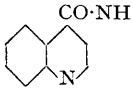
type (I) has therefore been prepared, allied to compounds of type (II) reported by Magidson and Rubtzow (*J. Gen. Chem., U.S.S.R.*, 1937, **17**, 1896) to be active.

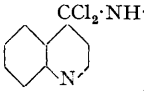
(I.) 

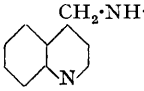
(II.) 

α-Diethylamino-δ-aminopentane, present in plasmochin and atebrin and reported by Fulton (*Ann. Trop. Med. Parasit.*, 1940, **34**, 53) to have slight antiplasmodial activity, was considered the most desirable type of side chain to introduce into bases of type (I).

α-Diethylamino-δ-aminopentane was condensed with benzaldehyde, salicylaldehyde, anisaldehyde and *m*-nitrobenzaldehyde; the azomethine, obtained in good yield, was readily reduced to the desired amine with either palladium–charcoal or palladised strontium carbonate catalyst. In the case of the nitro-compound simultaneous reduction to the amino-group took place. Similarly quinoline-4-aldehyde (kindly supplied by Prof. Clemo) condensed with α-diethylamino-δ-aminopentane at room temperature to give an oily azomethine which was readily reduced to α-diethylamino-δ-amyl-lepidylamine (V). Quinoline-4-aldehyde is not, however, very readily prepared (Clemo and Hoggarth, J., 1939, 1242; cf. Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2654) and substituted quinoline-4-aldehydes are unknown, so an easier route to the desired quinolinepolyamines was sought, and found in the reduction of the cinchoninamide of α-diethylamino-δ-aminopentane (III) to the base (V) by the action of stannous chloride on the amidodichloride (IV), a new type of reaction which is discussed elsewhere (Work, *loc. cit.*).

(III.) 

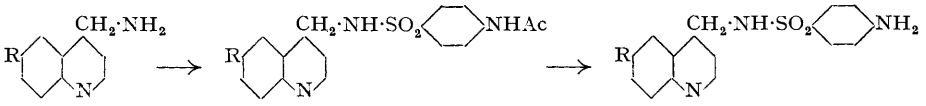
(IV.) 

(V.) 

This reaction provided an easy route for the subsequent analogous syntheses of α-diethylamino-δ-amyl-6-methoxylepidylamine and α-*diethylamino-δ-amyl-6-chlorolepidylamine*. 6-Chlorolepidylamine was synthesised from 5-chloroisatin, which was converted into 6-*chlorocinchoninic acid* by condensation with pyruvic acid, followed by partial decarboxylation of the resulting 6-*chloroquinoline*-2 : 4-*dicarboxylic acid* (cf. Renshaw and Friedman, *J. Amer. Chem. Soc.*, 1939, **61**, 3320). 6-Chlorocinchoninic acid was converted into the *amide*, which was readily dehydrated in 77% yield by boiling with phosphoric oxide in nitrobenzene, a procedure found to be much more satisfactory in this case and also in the preparation of 4-cyanoquinoline and 6-methoxy-4-cyanoquinoline, than the thionyl chloride method described by Wojahn (*Arch. Pharm.*, 1936, **274**, 83).

Attempts to prepare dialkylaminoalkylaminolepidines by the condensation of *diethylamino-ω-chlorohexane* with lepidylamine were unsuccessful.

The observation that derivatives of sulphanilamide or diaminodiphenylsulphone have some action on experimental malaria (Coggeshall, *J. Exp. Med.*, 1940, **71**, 13) and on human malaria (Coggeshall, Maier, and Best, *J. Amer. Med. Assoc.*, 1941, **117**, 1077) suggested the preparation of sulphonamide derivatives of lepidylamine for trial on bird malaria. Condensation of acetylsulphanilyl chloride with lepidylamine and its 6-chloro- and 6-methoxy-derivatives proceeded without difficulty and the N^4-acetylsulphonamides were hydrolysed by alkali to the corresponding aminosulphonamides.



None of the polyamines containing the quinoline nucleus and none of the sulphonamides showed any activity against *Plasmodium relictum* in canaries. The sulphonamides were highly toxic and are being tested against other organisms.

Experimental.

α-Diethylamino-δ-amylbenzylamine.—When the initial reaction between benzaldehyde (2·1 g.) and diethyl-δ-aminoamylamine (3·1 g.) had subsided, the product was heated for 2 minutes on the steam-bath, dissolved in absolute alcohol (50 c.c.), and reduced with a palladium–charcoal catalyst. Alcohol was removed, and the product distilled; the fraction (3·06 g.), b. p. 184—188°/25 mm., had b. p. 187—189°/25 mm. on redistillation (Found : C, 76·6; H, 11·2; N, 11·9. $C_{16}H_{28}N_2$ requires C, 77·4; H, 11·3; N, 11·9%).

*α-Diethylamino-δ-amyl-*p*-methoxybenzylamine*, obtained from anisaldehyde (2·72 g.) and diethyl-δ-aminoamylamine (3·16 g.) by the above procedure, had b. p. 218°/17 mm. (4·73 g.) (Found : C, 73·0; H, 10·6. $C_{17}H_{30}ON_2$ requires C, 73·4; H, 10·8%).

*α-Diethylamino-δ-amyl-*m*-aminobenzylamine* (2·5 g.), similarly obtained (*m*-nitrobenzaldehyde, 3·02 g.; diethyl-δ-aminoamylamine, 3·16 g.; hydrogen consumed, 1910 c.c.), had b. p. 184—186°/25 mm. (Found : C, 72·8; H, 10·8. $C_{16}H_{29}O_3$ requires C, 73·0; H, 11·0%).

α-Diethylamino-δ-amyl-lepidylamine.—Quinoline-4-aldehyde (0·43 g.) was added to diethyl-δ-aminoamylamine (0·43 g.), and the mixture warmed to complete the reaction. The azomethine was reduced in the usual way, and the oily product purified as the *dipicrate*, which crystallised from alcohol in needles, m. p. 147—148° (Found : C, 49·0; H, 5·0; N, 17·0. $C_{19}H_{29}N_3,2C_6H_3O_7N_3$ requires C, 49·2; H, 4·7; N, 16·7%).

Method II. Cinchoninic acid (2 g.) was converted by thionyl chloride into the acid chloride hydrochloride, which was powdered and added slowly to a solution of diethyl-δ-aminoamylamine (6·0 g.) in chloroform (100 c.c.). The

solution was warmed for a few minutes on the water-bath, washed with water, and dried, and the chloroform and the excess of diethyl-δ-aminoamylamine removed, the latter in a vacuum. The residual viscous amide was dissolved in dry chloroform (25 c.c.), and phosphorus pentachloride (5 g.) added. Chloroform and phosphorus oxychloride were removed and the solid residue was powdered and added to a solution prepared by passing dry hydrogen chloride into a suspension of anhydrous stannous chloride (10 g.) in ether (100 c.c.) until the chloride dissolved and formed a clear lower layer. After 24 hours' shaking, the ether was decanted, and the semi-crystalline sludge dissolved in water, washed with ether, and mixed with a considerable excess of 50% sodium hydroxide solution. Ether then extracted an oil (2·73 g.), which was distilled, giving (1) 1·3 g., b.p. 180—200°/1 mm., and (2) 0·8 g., b. p. 200—220°/1 mm. Fraction (1) gave a dipicrate, m. p. 145—146°, identical with that described above.

Cinchoninonitrile.—Phosphoric oxide (2·0 g.) was added to a boiling solution of cinchoninamide (2·0 g.) in nitrobenzene (15 c.c.). After refluxing for 5 minutes, the solution was poured into water, the residual gum dissolved in hot water and added to the main bulk, sodium hydroxide added in excess, and the nitrobenzene separated and washed. The alkaline solution was extracted with chloroform, the extract added to the nitrobenzene, the chloroform evaporated, and the nitrobenzene diluted with petrol and extracted with 2N-hydrochloric acid. The acid solution was washed with petrol, made alkaline, and extracted with chloroform, which removed almost pure cinchoninonitrile; after crystallisation from petrol the yield was 78%.

Lepidylamine.—This was obtained in almost quantitative yield by reducing 4-cyanoquinoline (2·0 g.) in a mixture of methanol (60 c.c.), N-hydrochloric acid (60 c.c.), and platinic oxide (0·05 g.) (cf. Rabe, *Ber.*, 1913, **46**, 1025).

N^1-*Lepidylsulphanilamide.*—Acetylsulphanilyl chloride (2·2 g.) was added to hot acetone–water (1 : 1; 50 c.c.) containing lepidylamine (1·58 g.) and sodium bicarbonate (0·9 g.), maintained at 68° for ½ hour, and cooled. The crystalline product (2·45 g.), recrystallised from alcohol–water, formed long needles, m. p. 134—136°, and 185—190° after drying at 120°. N^4-Acetyl-N^1-lepidylsulphanilamide (1·0 g.) was refluxed in 10% sodium hydroxide solution (10 c.c.) for 1 hour, and N^1-*lepidylsulphanilamide* (0·68 g.) isolated from the acidified solution by means of sodium bicarbonate; crystallised from methanol, it melted at 194° (Found: C, 61·4; H, 4·7; N, 13·4. $C_{16}H_{15}O_2N_3S$ requires C, 61·4; H, 4·8; N, 13·4%).

Quininamide.—A solution of methyl quininate (45 g., prepared by the same procedure as methyl 6-chlorocinchoninate; see below) in methyl alcohol (280 c.c.) saturated with ammonia was kept for 48 hours at 37° and then concentrated. The quininamide (35 g.) obtained crystallised from ethyl acetate in small hard prisms and from alcohol–water in long needles, both m. p. 210—212° (Found: C, 65·5; H, 4·8. Calc. for $C_{11}H_{10}O_2N_2$: C, 65·3; H, 4·9%). Hirsch (*Monatsh.*, 1896, **17**, 331) gives m. p. 197° (from ethyl acetate).

Quininonitrile.—Quininamide (5 g.) in boiling nitrobenzene (50 c.c.) was treated with phosphoric oxide (7·5 g.), added during 5 mins. After 15 mins.' boiling, the nitrile was isolated (see cinchoninonitrile) and crystallised from alcohol–water; m. p. 155°. Kaufmann and Peyer (*Ber.*, 1912, **45**, 1807) give m. p. 157°.

6-*Methoxylepidylamine.*—A solution of quininonitrile (4·0 g.) in absolute alcohol (700 c.c.) and *N*-hydrochloric acid (120 c.c.) was readily reduced with platinic oxide as catalyst. The catalyst was removed, and the solution of dihydrochloride concentrated to a gum, which crystallised on trituration with alcohol. The product, recrystallised from alcohol–water, had m. p. 255—256° (cf. D.R.-P. 279,193); yield, almost quantitative. The base, obtained from the dihydrochloride by continuous extraction with ether from sodium carbonate solution, was a colourless oil turning violet in air.

N^4-*Acetyl*-N^1-(6-*methoxylepidyl*)*sulphanilamide* (2·2 g.), obtained from acetylsulphanilyl chloride (2·2 g.) and 6-methoxylepidylamine (1·88 g.) by the procedure already described and recrystallised from acetone, had m. p. 215° (Found: C, 59·0; H, 4·7; N, 10·5. $C_{19}H_{19}O_4N_3S$ requires C, 59·2; H, 4·9; N, 10·9%).

N^1-(6-*Methoxylepidyl*)*sulphanilamide*, prepared by refluxing the preceding acetyl derivative with 2N-sodium hydroxide for 45 minutes, and isolated by adding sodium bicarbonate to the acidified solution, was crystallised from acetone; m. p. 194° (Found: C, 59·4; H, 4·9. $C_{17}H_{17}O_3N_3S$ requires C, 59·5; H, 4·9%).

α-*Diethylamino*-δ-*amyl*-6-*methoxylepidylamine.*—Quininic acid (2 g.) was converted by thionyl chloride into the acid chloride hydrochloride. The subsequent procedure was that described for the preparation of α-diethylamino-δ-amyl-lepidylamine (quantities used: diethyl-δ-aminoamylamine, 6 g., in chloroform, 100 c.c.; resulting gum, 3·7 g., in chloroform, 25 c.c.; phosphorus pentachloride, 4·4 g.; anhydrous stannous chloride, 10 g., in ethereal hydrogen chloride, 100 c.c.; 48 hours' shaking with glass beads). The gum obtained from the sludge was distilled at 1·0 mm., fraction (1), b. p. 200—210°, and (2) b. p. 210—212°. Fraction (2) gave a *tripicrate*, m. p. 87—88°, from alcohol (1·36 g.). Fraction (1) gave, after some manipulation, a less pure sample (0·85 g.) of the same picrate (Found: C, 44·0; H, 4·4; N, 15·6. $C_{20}H_{31}ON_3,3C_6H_3O_7N_3$ requires C, 44·8; H, 4·0; N, 16·3%).

6-*Diethylaminohexanol.*—Hexamethylene chlorohydrin (64 g.) (Bennett and Turner, J., 1938, 814) and diethylamine (140 g.) were heated in a sealed bottle at 100° for 16 hours. The excess of diethylamine was recovered, the residue diluted with ether, diethylamine hydrochloride collected, and the ether removed. The resulting oil, distilled at 2 mm., was separated into three fractions boiling at (*a*) 83° (2·5 g.), (*b*) 83—93° (5·0 g.), and (*c*) 93—100° (52·4 g.). Fraction (*c*) redistilled at 2 mm. mainly at 96—99° (47·4 g.) (Found: C, 69·2; H, 13·2. $C_{10}H_{23}ON$ requires C, 69·4; H, 13·3%).

Diethylamino-ω-*chlorohexane.*—Diethylaminohexanol (10·5 g.) in dry chloroform (50 c.c.) was run slowly into thionyl chloride (45 g.) in chloroform (50 c.c.) at 0°. After 1½ hours chloroform and the excess of thionyl chloride were removed under reduced pressure, and alcohol (5 c.c.) added. The product was diluted with ether, washed with sodium carbonate and water, and distilled, giving a fraction (5·76 g.), b. p. 118—120°/19 mm. (Found: C, 62·3; H, 11·6. $C_{10}H_{22}NCl$ requires C, 62·6; H, 11·5%).

5-*Chloroisatin.*—This was prepared from *p*-chloroaniline by a process similar to that described in *Organic Syntheses* (Coll. Vol. I, 321; cf. Sandmeyer, *Helv. Chim. Acta*, 1919, **2**, 238) for the preparation of isatin. A large excess of sodium sulphate in the initial condensation between *p*-chloroaniline, chloral hydrate, and hydroxylamine was essential. The resulting *p*-chloro*iso*nitrosoacetanilide was converted into the isatin by addition to concentrated sulphuric acid at 90—95°, and the temperature was raised to 105° for 10 minutes to complete the reaction (yield, 55 g. from 64 g. of *p*-chloroaniline).

6-*Chloroquinoline*-2 : 4-*dicarboxylic Acid.*—5-Chloroisatin (134 g.) was dissolved in hot 33% aqueous potassium hydroxide (1085 c.c.), and pyruvic acid (114 g.) added (cooling in tap-water). After 48 hours at 37° the mixture was cooled, and the potassium salt collected, washed with a little ice-cold 33% potassium hydroxide solution and with absolute alcohol, and dissolved in water. The 6-*chloroquinoline*-2 : 4-*dicarboxylic acid* was precipitated with hydrochloric acid, redissolved in bicarbonate, and reprecipitated by acid; m. p. about 250° (decomp.) (Found: C, 49·3; H, 3·0; N, 4·9. $C_{11}H_6O_2NCl,H_2O$ requires C, 49·0; H, 3·0; N, 5·2%).

6-*Chlorocinchoninic Acid.*—A suspension of 6-chloroquinoline-2 : 4-dicarboxylic acid (15·5 g.) in dry nitrobenzene (100 c.c.) was boiled for 20 minutes and cooled. The crystalline product (12·25 g.) was very slightly soluble in all organic solvents, but could be recrystallised from nitrobenzene; m. p. 302° (Found: C, 57·9; H, 3·1. $C_{10}H_6O_2NCl$ requires C, 57·9; H, 3·1%).

Methyl ester. The acid (30 g.) was refluxed in dry chloroform (50 c.c.) with thionyl chloride (50 c.c.) for ½ hour,

the excess of chloride removed on the water-bath, methyl alcohol added to the residue, and the ester hydrochloride diluted with water and made alkaline. The *methyl* ester, extracted with chloroform, crystallised from ligroin–benzene in needles (26·0 g.), m. p. 79·5° (Found : C, 59·8; H, 3·6. $C_{11}H_8O_2NCl$ requires C, 59·6; H, 3·6%).

6-*Chlorocinchoninamide*.—The methyl ester was dissolved in excess of methyl alcohol saturated with ammonia and left for 3 days at 37°; the solution was concentrated on the water-bath. The crystalline *amide* (20·85 g.) had m. p. 244° (Found : C, 57·7; H, 3·5. $C_{10}H_7ON_2Cl$ requires C, 58·1; H, 3·4%).

6-*Chlorocinchoninonitrile*.—To a boiling solution of 6-chlorocinchoninamide (7·7 g.) in nitrobenzene (50 c.c.), phosphoric oxide (8·0 g.) was added in several small lots. After 4 mins.' boiling, the hot product was poured into water, and the residual gum dissolved in boiling water and added to the main bulk of solution, which was then made alkaline and diluted with chloroform. The chloroform–nitrobenzene was separated and dried, chloroform removed, and as much as possible of the nitrobenzene distilled under reduced pressure. The residue was triturated with petrol, and the crystalline product (5·53 g.), m. p. 164°, collected. 6-*Chlorocinchoninonitrile* crystallised in long needles, m. p. 164°, from ethyl acetate (Found : C, 63·8; H, 2·9. $C_{10}H_5N_2Cl$ requires C, 63·7; H, 2·7%).

6-*Chloro*-4-*aminomethylquinoline*.—To a solution of the preceding nitrile (4 g.) in absolute alcohol (700 c.c.), N-hydrochloric acid (120 c.c.) and platinic oxide (0·2 g.) were added. The solution, shaken at normal pressure, absorbed 1400 c.c. of hydrogen in 8 hours. On concentration 6-*chloro*-4-*aminomethylquinoline dihydrochloride* (32 g.) separated in rhombs, m. p. about 250° (decomp.), sparingly soluble in alcohol (Found : C, 45·6; H, 4·3; N, 10·5. $C_{10}H_9N_2Cl,2HCl$ requires C, 45·2; H, 4·14; N, 10·5%). The base, obtained from the dihydrochloride and sodium carbonate solution by continuous extraction with ether, was moderately easily soluble in water; it crystallised from ether in colourless needles, m. p. 90°, which turned bright violet on exposure to air.

N^4-*Acetyl*-N^1-(6-*chlorolepidyl*)*sulphanilamide*—6-Chlorolepidylamine (1·93 g.) was dissolved in aqueous acetone (50 c.c.) containing sodium bicarbonate (0·9 g.) and treated with acetylsulphanilyl chloride (2·2 g.) by the same procedure as used previously. The product (2·85 g.) crystallised from acetone in needles (2·75 g.), m. p. 194° (Found : C, 55·4; H, 4·2. $C_{18}H_{16}O_3N_3ClS$ requires C, 55·4; H, 4·2%).

N^1-(6-*Chlorolepidyl*)*sulphanilamide*.—The acetyl derivative (1·73 g.) was refluxed in 2N-sodium hydroxide (15 c.c.) for 1 hour. The product was isolated in the usual way (1·43 g.) and crystallised from methanol; yield 1·05 g., m. p. 200° (Found : C, 55·0; H, 4·1; N, 11·6. $C_{16}H_{14}O_2N_3ClS$ requires C, 55·2; H, 4·0; N, 12·1%).

6-*Chlorocinchoninamide* of *Diethyl*-δ-*aminoamylamine*.—6-Chlorocinchoninic acid (2·0 g) was converted by thionyl chloride into the acid chloride hydrochloride, which was powdered and added to a solution of diethyl-δ-aminoamylamine (6·0 g.) in chloroform (100 c.c.). After ½ hour the chloroform solution was washed with water, dried, and evaporated. The residual brown oil crystallised on prolonged standing and was recrystallised from ligroin (2·65 g.). The *amide*, even when pure, m. p. 99°, could only be crystallised with difficulty, as, when dissolved in hot ligroin, it separated as a stiff gel which only crystallised very slowly (Found : C, 65·5; H, 7·4; N, 11·7. $C_{19}H_{26}ON_3Cl$ requires C, 65·6; H, 7·5; N, 12·1%).

α-*Diethylamino*-δ-*amyl*-6-*chlorolepidylamine*.—The preceding amide (2·4 g.) was dissolved in dry chloroform (20 c.c.) and treated with phosphorus pentachloride (2·9 g.). Chloroform was distilled off on the steam-bath, and the residue heated at 100° for ½ hour. A solution of stannous chloride (10 g.) in ethereal hydrogen chloride (100 c.c.) was added to the cooled residue, which was then shaken for 48 hours with glass beads. The polyamine (2·14 g.) was isolated by the usual procedure as a brown oil and converted into a picrate (tripicrate?), m. p. 97—99°, which crystallised readily from acetone–alcohol. The picrate was reconverted into the base, which was distilled in a high vacuum before analysis (Found : C, 67·8; H, 8·6; N, 13·1; Cl, 10·8. $C_{19}H_{28}N_3Cl$ requires C, 68·3; H, 8·5; N, 12·6; Cl, 10·6%).

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