183. *Structure and Antimalarial Activity. Part I. Some Acridine Derivatives.*

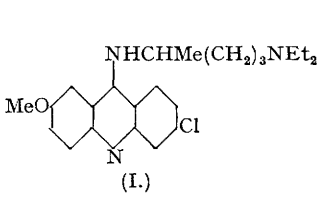
By D. Muriel Hall and E. E. Turner.

Compounds (II) and (III), in which cyclic systems partly take the place of the carbon chain in atebrine (I), have been synthesised and found to be active against avian malaria. 1-*Chloro*-5-δ-*diethylamino*-α-*methylbutylamino*-9-*methylacridine* was also prepared and appears to be the first 1 : 9-disubstituted 5-diethylaminoalkylaminoacridine to show antimalarial activity. 1-*Chloro*-5-δ-*diethylamino*-α-*methylamino*-8-*methylacridine* also showed slight activity.

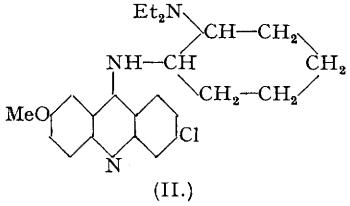
Most of the compounds possessing antimalarial activity contain not less than two basic centres; it is probable that there is some stereospecificity in the action of these compounds on living material and therefore their configuration, whether fixed or " preferred," and in particular the distance apart of the two basic centres, may be of considerable importance.

Some evidence on this point seemed to be obtainable from a comparison of atebrine (I) with a compound in which part of the carbon chain in the ·NH·CHMe·$(CH_2)_3$·NEt_2 radical (R) is made part of an alicyclic ring, thus fixing the relative positions in space of the two nitrogen atoms in the radical.

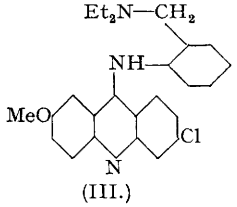
We have therefore prepared 2-*chloro*-5-(2′-*diethylamino*cyclo*hexylamino*)-7-*methoxyacridine* (II), in which, as can be seen by an inspection of a model (of either the *cis* or *trans* form), the NH and NEt_2 groups are separated in space by approximately the same distance as these groups are in a possible preferred configuration of the radical in atebrine. The hydrochloride of (II) was in fact active against *Plasmodium relictum*.



(I.)



(II.)

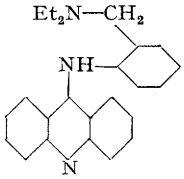


(III.)

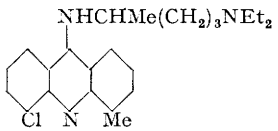
It then became of interest to discover the effect of replacing two of the aliphatic chain carbon atoms by two carbon atoms forming part of a benzene nucleus. We therefore prepared 2-*chloro*-5-ω-*diethylamino*-o-*toluidino*-7-*methoxyacridine* (III) by condensing 2 : 5-dichloro-7-methoxyacridine with *o*-aminobenzyldiethylamine. This compound showed definite antimalarial activity, but the subsequently synthesised compound (IV), in which the chlorine atom and the methoxyl group are absent, was inactive, as perhaps was to be anticipated.

Magidson and Grigorovski (*Ber.*, 1936, **69**, 396) stated that, in their experience, activity with the atebrine type of molecule was not shown by compounds unsubstituted in either the 2 or the 3 position. With the development of the Jamison and Turner method of preparing acridones (*J.*, 1937, 1954), it became possible to synthesise the otherwise rather inaccessible compound, 1 : 5-*dichloro*-9-*methylacridine*, and thence 1-*chloro*-5-δ-*diethylamino*-α-*methylbutylamino*-9-*methylacridine* (V), which showed definite activity and appears to be the first known example of a 1 : 9-disubstituted-5-diethylaminoalkylaminoacridine to do so. On the other

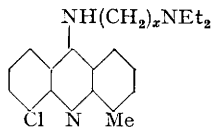
hand, (VI; $x = 2$ or 3) was inactive. Similarly, (VII), in which the aromatic group replaces the aliphatic group, was devoid of activity.



(IV.)

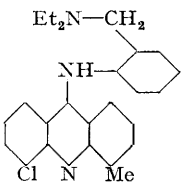


(V.)

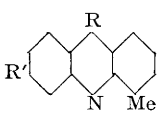


(VI.)

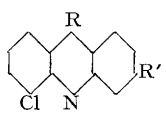
Rather strikingly, variation of the position of the chlorine atom in (V), or removal of chlorine atom or the methyl group, was accompanied by total disappearance of activity (compounds VIII; R′ = Cl or H, R = $NHCHMe(CH_2)_3NEt_2$ and IX; R′ = H; R = $NHCHMe(CH_2)_3NEt_2$). On the other hand, compound (IX), where R = $NHCHMe(CH_2)_3NEt_2$ and R′ = CH_3, in which the 9-position of the methyl group has been altered to the 8-position, showed slight activity against *P. gallinaceum* but was inactive against *P. relictum*.



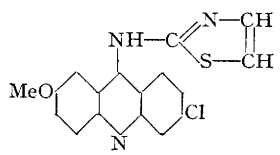
(VII.)



(VIII.)



(IX.)



(X.)

Substitution of the aliphatic chain in atebrine by the 2-thiazolyl group gave a compound (X) which was very sparingly soluble in hydrochloric acid, and a suspension of the " base " in aqueous gelatin was inactive.

For the synthesis of compound (II) 2-diethylamino*cyclo*hexylamine was required. Various methods were tried for the synthesis of this base. The successful one was the interaction of 2-*chloro*cyclo*hexyldiethylamine* with ammonia over a long period. The chloro-compound was obtained by treating the corresponding hydroxy-compound with thionyl chloride although Osterberg and Kendall (*J. Amer. Chem. Soc.*, 1920, **42**, 2616) found 2-amino*cyclo*hexanol to be unaffected by this reagent. The configuration of the 2-diethylamino*cyclo*hexylamine isolated is not certain, and similar uncertainty attaches to the configuration of 2-diethylamino*cyclo*hexanol (cf. Osterberg and Kendall, *ibid.*, 1921, **43**, 1370; Heckel and Adams, *ibid.*, 1927, **49**, 1303). Condensation of 2-diethylamino*cyclo*hexylamine with 2 : 5-dichloro-7-methoxyacridine in phenol gave (II), together with 2-chloro-5-phenoxy-7-methoxyacridine and a little 2-chloro-7-methoxyacridone.

In connection with the Jamison–Turner synthesis of acridones, it was found that satisfactory yields of *o*-chlorophenylbenzimino-6′-carbomethoxy-2′-methylphenyl ether were obtained using a smaller proportion, *viz.*, only one molecule of methyl *o*-cresotate to one molecule of benz-*o*-chloroanilideiminochloride. The hydrolysis of methyl 2-chloro-*N*-benzoyl-2′-methyldiphenylamine-6′-carboxylate, obtained from the above imino ether, could be carried out using excess of caustic soda without the benzoyl group being attacked. Removal of the latter could only be achieved by using a large excess of strong alkali. This is evidently a steric effect of the kind noticed by Chapman (*J.*, 1929, 569).

The standard method for the preparation of *N*-substituted 5-aminoacridines is the condensation of the appropriate substituted amine with 5-chloroacridine in the presence of phenol (Magidson and Grigorovski, *loc. cit.*). These authors found the presence of phenol to be essential for condensations with aliphatic amines, and concluded that the formation of 5-phenoxyacridine is an intermediate stage in the reaction, since 5-phenoxyacridines react readily with amines. In the present work the Magidson–Grigorovski method was successful with the aliphatic bases but failed entirely with the aromatic base, *o*-aminobenzyldiethylamine. For this and similar bases, a new method was developed in which the reactants were heated together in toluene solution. Unchanged 5-chloroacridine was readily removed by treatment with hydrochloric acid, since the hydrochlorides of 5-chloroacridines are very much less water-soluble than those of the condensation products.

The condensation of β-diethylaminoethylamine with 1 : 5-dichloro-9-methylacridine could be carried out by both methods but that with toluene gave a better yield. This was the only case in which a condensation with an aliphatic base was actually effected in toluene. In an attempt to prepare atebrine in toluene, 75% of the 2 : 5-dichloro-7-methoxyacridine used was recovered unchanged.

When the condensation producing (III) was attempted in phenol 2-*chloro*-7-*methoxy*-5 : 10-*dihydroacridine* was obtained as a by-product.

The acridines, except (X), were tested as the water-soluble hydrochlorides, which in most cases were not analysed.

The pharmacological tests were done by Dr. Ann Bishop of the Molteno Institute on *Plasmodium relictum* and by Imperial Chemical Industries, Ltd., and Miss I. Tonkin of the National Institute for Medical Research on *P. gallinaceum*.

Experimental.

The method for preparing *o*-nitrobenzyldiethylamine of Noelting and Kregczy (*Bull. Soc. chim.*, 1916, (4), **19**, 335) was modified as follows: a mixture of diethylamine (60 g.; 2·5 mols.), alcohol (44 c.c.) and *o*-nitrobenzyl chloride (57 g.; 1 mol.) was boiled under reflux for 1 hour; most of the solvent was distilled off, water and then alkali added and the *o*-nitrobenzyldiethylamine extracted with ether. *o*-Nitrobenzyldiethylamine (63·5 g., 91% yield) having b. p. 163—164°/28 mm., 158°/20 mm., 143—144°/11 mm., was obtained. The picrate (Found: N, 16·1. Calc.: N, 16·0%), made in alcoholic solution, had m. p. 123—124°; Noelting and Kregczy (*loc. cit.*) give m. p. 117°.

o-Aminobenzyldiethylamine, obtained by reducing the nitro compound in alcoholic solution with hydrogen in the presence of Raney nickel, had b. p. 152°/40 mm. *o-Acetamidobenzyldiethylamine* crystallised from alcohol in prisms, m. p. 89—90° (Found: N, 12·9. $C_{13}H_{20}ON_2$ requires N, 12·7%).

p-Aminobenzyldiethylamine.—Catalytic reduction of *p*-nitrobenzyldiethylamine gave *p*-aminobenzyldiethylamine, b. p. 145°/12 mm., which subsequently solidified and then crystallised from ligroin (b. p. 60—80°) in prisms, m. p. 46—47° (Found: N, 15·8. Calc.: N, 15·7%). The dipicrate had m. p. 135°. (Noelting and Kregczy, *loc. cit.*, give m. p. 130° and describe the amino-compound as a liquid.)

Diethylaminoacetonitrile was obtained in 96% yield by Luten's method (*J. Org. Chem.*, 1939, **3**, 588). The *picrate* crystallised from alcohol in yellow needles, m. p. 155° (Found: N, 20·7. $C_{12}H_{15}O_7N_5$ requires N, 20·5%). β-Diethylaminoethylamine was obtained by reducing the nitrile (30 g.) in absolute alcoholic solution (525 c.c.) by means of sodium (50 g.). The mixture, after acidification with hydrochloric acid, was evaporated to dryness and the alcoholic extract of the residue evaporated. The hydrochloride was treated with concentrated potassium hydroxide solution and the mixture extracted with benzene. Distillation gave the base in 33% yield, b. p. 149°/764 mm. The dipicrate had m. p. 209° (decomp.). Ristenpart (*Ber.*, 1896, **29**, 2526) gave m. p. 211° (decomp.) and was unable to obtain a *monopicrate*, but we obtained this as yellow plates from alcohol, m. p. 115° (Found: N, 20·6. $C_{12}H_{19}O_7N_5$ requires N, 20·3%). The *dioxalate* crystallised from aqueous oxalic acid in needles, m. p. 178° (decomp.) (Found: N, 9·3. $C_{10}H_{20}O_8N_2$ requires N, 9·45%).

2-Diethylamino*cyclo*hexanol, prepared by the method of Brunel (*Ann. Chim.*, 1905, (8), **6**, 200), gave a *picrate* which crystallised from benzene in yellow rhombic prisms, m. p. 94—95° (Found: N, 14·4. $C_{16}H_{24}O_8N_4$ requires N, 14·0%).

2-Diethylamino*cyclo*hexanol (20 g., 1 mol.) was added gradually to thionyl chloride (28 g., 2 mols.) with cooling. The initially vigorous reaction was completed by heating at about 90°. Excess of thionyl chloride was boiled off and water added, followed by solid sodium carbonate. Extraction with ether, etc., gave 2-chloro*cyclo*hexyldiethylamine (13·5 g., 61%) as a colourless liquid, b. p. 108°/13 mm. The *picrate* was precipitated from alcoholic solution by ligroin (b. p. 40—60°); it crystallised from 30% alcohol in yellow rhombic prisms, m. p. 121° (Found: N, 13·45. $C_{16}H_{23}O_7N_4Cl$ requires N, 13·4%). A mixture of 2-chloro*cyclo*hexyldiethylamine (12 g.) and ammonia (*d* 0·88, 100 c.c.) was kept for several months. The mixture was extracted with ether, the extract dried over potassium carbonate and distilled under diminished pressure. The crude 2-diethylamino*cyclo*hexylamine (4 g., 37%) had b. p. 102°/13 mm.—103°/12 mm. The *dipicrate* was precipitated from alcoholic solution with ligroin (b. p. 40—60°) and crystallised from water in small yellow prisms, m. p. 192—193° (Found: C, 42·4; H, 4·3; N, 17·8. $C_{22}H_{28}O_{14}N_8$ requires C, 42·0; H, 4·5; N, 17·8%).

Under the conditions given by Weissenberger (*Monatsh.*, 1912, **33**, 821) for the condensation of diethylamine and *o*-chloronitrobenzene almost all the latter was unchanged, but by heating *o*-chloronitrobenzene with excess of diethylamine (2·2 mols.) in the presence of a catalytic quantity of copper bronze and omitting a solvent (22 hours at 103—105°) a 68% yield of *o*-nitrodiethylaniline was obtained. The base was purified by distillation in superheated steam or through the picrate (m. p. 123—124°; Weissenberger, *loc. cit.*, gives m. p. 119—120°). Some specimens of the base decomposed violently on attempted distillation under diminished pressure.

NN-Diethyl-*o*-phenylenediamine, b. p. 127°/25 mm., was obtained in 77% yield by the reduction of *o*-nitrodiethylaniline with iron, water and acetic acid. The *monopicrate* crystallised from alcohol in orange prisms, m. p. 162° (Found: C, 49·0; H, 5·0; N, 17·4. $C_{16}H_{19}O_7N_5$ requires C, 48·85; H, 4·9; N, 17·8%. The dipicrate, $C_{22}H_{22}O_{14}N_8$, requires C, 42·45; H, 3·6; N, 18·0%). Weissenberger (*loc. cit.*) described a picrate, m. p. 236° (Found: N, 17·96%) to which he gave the formula $C_{10}H_{16}N_2,C_6H_3O_7N_3$. Presumably his compound was the dipicrate. *o*-(*p-Toluenesulphonamido*)-*diethylaniline* crystallised from aqueous alcohol in prisms, m. p. 64—65° (Found: C, 64·4; H, 7·25. $C_{17}H_{22}O_2N_2S$ requires C, 64·1; H, 7·0%).

The hydrochloride of *NN*-diethyl-*o*-phenylenediamine was prepared by passing hydrogen chloride into a solution of the base in ligroin (b. p. 60—80°) and reduced in 50% alcoholic solution with hydrogen in the presence of Adams' platinum oxide–platinum black catalyst (compare Hiers and Adams, *Ber.*, 1926, **59**, 162). The product, apart from some unchanged *NN*-diethyl-*o*-phenylenediamine, consisted entirely of *cyclo*hexylamine, which was identified as the picrate, m. p. 157—158°, the acetyl derivative, m. p. 106°, and the benzoyl derivative, m. p. 148—149°; the p-*toluenesulphonyl* derivative, m. p. 86—87°, crystallised from aqueous alcohol in needles (Found: C, 61·1; H, 7·4; N, 5·5. $C_{13}H_{19}O_2NS$ requires C, 61·6; H, 7·6; N, 5·5%). No 2-diethylamino*cyclo*hexylamine could be detected. (Compare Greenstein and Wyman, *J. Amer. Chem. Soc.*, 1938, **60**, 2341, who found that, while *m*- and *p*-aminobenzoic acids were readily hydrogenated using Adams' platinum oxide–platinum black catalyst, anthranilic acid gave hexahydrobenzoic acid.)

The chlorination of toluene by the method of Silberrad (*J.*, 1925, 2677) gave a mixture of mono-, di- and trichlorotoluenes, which were separated by fractional distillation with an 8″ Young pear column. 2 : 4-Dichlorotoluene, b. p. 197—201°, was obtained in 28% yield. The oxidation of 2 : 4-dichlorotoluene with dilute permanganate (Bornwater and Holleman, *Rec. trav. chim.*, 1912, **31**, 221) or chromic acid gave very low yields of 2 : 4-dichlorobenzoic acid. The acid was best obtained by the hydrolysis in 85% yield of 2 : 4-dichlorobenzonitrile with 80% sulphuric acid. The nitrile was prepared from 2 : 4-dichloroaniline (Gomberg and Cone, *Annalen*, 1909, **370**, 142). 3-Chloro-4′-methoxydiphenylamine-6-carboxylic acid was obtained in 77% yield by usual methods. The sparingly soluble potassium salt crystallised in fine needles.

5-Chloroacridines were prepared from the corresponding diphenylamine-2-carboxylic acids by adding the acid gradually to an excess of phosphoryl chloride (2—3 mols.) and heating the mixture at 140° for 1 hour. The product was treated with ice-water, ground with ammonia and the chloroacridine dried and crystallised.

Condensations of bases with 5-chloroacridines in phenol solution were carried out as follows: The chloroacridine was dissolved in an excess of warm phenol (6 mols.) and the base (1·3 mols.) added. The mixture was heated at 100° for 2 hours, poured into boiling 10% sodium hydroxide solution and the substance separating (usually a gum) washed with alkali and water. It was usually purified through the hydrochloride and, if still not crystalline, converted into the picrate.

Condensations in toluene solution were carried out by boiling a mixture of the chloroacridine, toluene and the base (2·5 mols.) for 2 hours. The mixture was washed with alkali and water; the solvent and excess of base were removed by distillation under diminished pressure. The residue was purified, usually through the hydrochloride, and crystallised.

2 : 5-Dichloro-7-methoxyacridine was obtained from 3-chloro-4′-methoxydiphenylamine-6-carboxylic acid in 87% yield. It crystallised from light petroleum (b. p. 80—100°) in yellow needles, m. p. 164° (Magidson and Grigorovski, *loc. cit.*, and Mauss, D.R.P. 565,411, give m. p. 160—161°).

2-*Chloro*-5-(2′-*diethylamino*cyclo*hexylamino*)-7-*methoxyacridine* (II).—2 : 5-Dichloro-7-methoxyacridine (4·2 g.) was condensed with 2-diethylamino*cyclo*hexylamine in phenol solution. The yellow gum obtained rapidly went solid and was separated into three substances by repeated fractional crystallisation from alcohol, (*a*) a small amount of 2-chloro-7-methoxyacridone, m. p. >280°, (*b*) 2-chloro-5-phenoxy-7-methoxyacridine, m. p. and mixed m. p. with authentic specimen, 156° (Mietzsch and Mauss, D.R.-P. 553,072 give m. p. 152—153°), (*c*) a solid, crystallising from alcohol in yellow flat needles, m. p. 180—181°, from which 2-*chloro*-5-(2′-*diethylamino*cyclo*hexylamino*)-7-*methoxyacridine* was isolated as the *hydrochloride*, which crystallised from water in yellow microscopic plates, m. p. 223° (Found : C, 54·6; H, 7·4; N, 7·5. $C_{24}H_{30}ON_3Cl,2HCl,2H_2O$ requires C, 55·3; H, 7·0; N, 8·1%).

2-*Chloro*-5-ω-*diethylamino*-o-*toluidino*-7-*methoxyacridine* (III).—(1) Condensation of 2 : 5-dichloro-7-methoxyacridine with *o*-aminobenzyldiethylamine in phenol solution gave none of the required compound but a considerable amount of 2-*chloro*-5 : 10-*dihydroxy*-7-*methoxyacridine* was obtained. It crystallised from benzene in light yellow needles, m. p. 187—188° (Found : N, 5·75. $C_{14}H_{12}ONCl$ requires N, 5·7%). (2) Condensation in toluene solution (1·6 g. of chloroacridine) gave a dark red residue which was extracted with hydrochloric acid and the solution treated with potassium iodide; the sparingly soluble hydriodide was filtered off, dissolved in a large volume of water and the solution treated with ammonia. 2-*Chloro*-5-ω-*diethylamino*-o-*toluidino*-7-*methoxyacridine* was precipitated as a yellow solid, which gave orange crystals, m. p. 113—114°, from ligroin (b. p. 80—100°) (Found : C, 71·2; H, 6·1. $C_{25}H_{26}ON_3Cl$ requires C, 71·5; H, 6·2%). Once the base had been obtained crystalline purification through the hydriodide was unnecessary (yield 20%).

The preparation of *N*-phenylbenzimino-*o*-carbomethoxyphenyl ether was carried out with three variations. (1) Sodium (2·35 g., 1 atom) was dissolved in alcohol (150 c.c.) and methyl salicylate (15·5 g., 1 mol.) added, immediately followed by a solution of benzanilideiminochloride (22 g., 1 mol.) in 200 c.c. of dry ether. The mixture was kept overnight, made just acid with dilute hydrochloric acid and the solution buffered with sodium acetate. Unchanged methyl salicylate was removed in steam. The yield of imino-ether was 18·5 g. (54%). (2) Using sodium (2·9 g., 1·25 atoms) and methyl salicylate (19·4 g., 1·25 mols.) the yield was 21 g. (62%). (3) Using sodium (3·5 g., 1·5 atoms) and methyl salicylate (23·25 g., 1·5 mols.) the yield was 21 g. (62%).

Methyl *N*-benzoyl-*N*-phenylanthranilate, obtained by heating the imino-ether, was hydrolysed with excess of boiling aqueous alcoholic alkali. The *N*-phenylanthranilic acid was obtained in 78% yield, m. p. 184—186°. 5-Chloroacridine was obtained from *N*-phenylanthranilic acid in 60% yield and crystallised from ligroin (b. p. 80—100°) (Soxhlet) in yellow needles, m. p. 119—120°, which turned brown after keeping for some time. The method of Drozdov (*J. Gen. Chem. Russia*, 1934, **4**, 117) proved unsatisfactory.

5-ω-*Diethylamino*-o-*toluidinoacridine* (IV) was obtained by the condensation of 5-chloroacridine (3·3 g.) with *o*-aminobenzyldiethylamine in toluene solution. The product was dissolved in dry benzene (1 l.) and passed through a short column (6″) of Birlec alumina. The filtrate and washings were evaporated to dryness, the residue converted into the hydrochloride and the base reprecipitated with ammonia. 5-ω-Diethylamino-*o*-toluidinoacridine separated as a gum which slowly solidified. It crystallised from alcohol in yellow prisms, m. p. 137—138° (Found : C, 80·7; H, 6·9. $C_{24}H_{25}N_3$ requires C, 81·1; H, 7·1%). Condensations in phenol solution gave a mixture from which only 5 : 10-dihydroacridine could be isolated (Found : C, 85·4; H, 6·2; N, 8·1. Calc., C, 86·2; H, 6·1; N, 7·7%).

Attempts to esterify *o*-cresotic acid in the presence of dry hydrogen chloride were unsuccessful. The acid chloride was prepared by adding *o*-cresotic acid (152 g.) to thionyl chloride (149 g.) in benzene (90 c.c.) heated under reflux. When the reaction was complete, excess of thionyl chloride was removed and methanol (100 c.c.) added. The methyl *o*-cresotate (142 g., 86%) was washed with water, dried over sodium sulphate and distilled under diminished pressure, b. p. 120°/20 mm. Sodium (9·7 g., 1 atom) was dissolved in alcohol (525 c.c.), the solution cooled to 25° and methyl *o*-cresotate (70 g.) added, followed immediately by benz-*o*-chloroanilideiminochloride (105 g.) dissolved in dry ether. The mixture was kept for 2 hours and most of the alcohol distilled off. The product was poured into water and the *o*-chlorophenylbenzimino-6′-carbomethoxy-2′-methylphenyl ether crystallised from methyl alcohol (yield, 115·5 g., 72%), m. p. 85°.

A solution of methyl 2-chloro-*N*-benzoyl-2′-methyldiphenylamine-6′-carboxylic acid (obtained by heating the above imino-ether, 40 g.) in alcohol (300 c.c.) was heated under reflux at 100° with caustic soda (10·5 g., 2 mols.) in water (20 c.c.) for 1½ hours. The alcohol was distilled off, water added, and the acid precipitated with hydrochloric acid. 2-Chloro-*N*-benzoyl-2′-methyldiphenylamine-6′-carboxylic acid (35·5 g., 92%) crystallised from acetone–ligroin (b. p. 40—60°) in needles and prisms, m. p. 198—199°. The *sodium* salt crystallised from water in hexagonal plates, m. p. 73°, decomposing at 106° (Found : H_2O, 24·5. $C_{21}H_{15}O_3NClNa,7H_2O$ requires H_2O, 24·5%). The salt was soluble in benzene, alcohol, acetone and chloroform and insoluble in ether and ligroin. It lost water of crystallisation at 100° and the anhydrous salt was insoluble in benzene. A solution of the benzoyl compound (10 g.) in a mixture of alcohol (50 c.c.), caustic soda (85 g.) and water (100 c.c.) was boiled under a reflux for 2 hours and the alcohol then evaporated; heating was continued for another 4 hours. The product was dissolved in water, hydrochloric acid added and the precipitate extracted with hot water to remove benzoic acid. Unhydrolysed benzoyl compound was removed by repeated crystallisation from first benzene and then glacial acetic acid, and pure 2-*chloro*-2′-*methyldiphenylamine*-6′-*carboxylic acid*, m. p. 181—182°, obtained (Found : N, 5·2. $C_{14}H_{12}O_2NCl$ requires N, 5·35%).

1-*Chloro*-9-*methylacridone*.—2-Chloro-*N*-benzoyl-2′-methyldiphenylamine-6′-carboxylic acid (20 g.) was heated at 240°; the reaction was strongly exothermic, the temperature rising to 275°. After 10 mins. the liquid was allowed to cool and the resulting solid extracted 3 times with hot water to remove benzoic acid. The 1-*chloro*-9-*methylacridone* (11·5 g., 86%) crystallised from alcohol in glistening, light yellow-brown needles, m. p. 197—198° (Found : N, 5·65. $C_{14}H_{10}ONCl$ requires N, 5·75%). 1 : 5-*Dichloro*-9-*methylacridine* was obtained in 89% yield from 1-chloro-9-methylacridone (5 g.) by the method used for the preparation of 5-chloroacridines from diphenylamine-2-carboxylic acids. It crystallised from ligroin (b. p. 60—80°), using a Soxhlet extractor, in pale yellow needles, m. p. 169—170° (Found : N, 5·3. $C_{14}H_9NCl_2$ requires N, 5·3%). The hydrochloride was brick-red in the presence of concentrated hydrochloric acid but almost colourless in the presence of dilute acid.

1-*Chloro*-5-δ-*diethylamino*-α-*methylbutylamino*-9-*methylacridine* (V).—1 : 5-Dichloro-9-methylacridine (2·6 g.) was condensed with 2-amino-5-diethylaminopentane in phenol solution. Neither the acridine, the hydrochloride nor the hydriodide would crystallise, even after passing a benzene solution of the acridine through a column of Birlec alumina. It was therefore purified by conversion into 1-*chloro*-5-δ-*diethylamino*-α-*methylbutylamino*-9-*methylacridine dipicrate*, which crystallised from acetone in yellow prisms, m. p. 183° (α-form) (Found : C, 50·55; H, 4·6; N, 14·8. $C_{35}H_{36}O_{14}N_9Cl,C_3H_6O$ requires C, 50·7; H, 4·7; N, 14·0%). A subsequent preparation of the dipicrate gave a product with m. p. 153° (β-form) (Found : C, 50·9; H, 4·9; N, 14·6%). It was then found that the α-form had gradually changed into the β-form and melted at 154°. The melt of the β-form solidified to the α-form, which again showed the m. p. of 183°.

1-*Chloro*-5-*β*-*diethylaminoethylamino*-9-*methylacridine* (VI; $x = 2$).—(1) 1 : 5-Dichloro-9-methylacridine (2·1 g.) condensed with *β*-diethylaminoethylamine (2 mols.) in phenol solution to give a product, which, after extraction with chloroform and removal of the solvent, gave a solid residue; fractional crystallisation of the latter from ligroin (b. p. 60—80°) gave a yellow substance, *A*, m. p. 170—172°, some 1-chloro-9-methylacridone, m. p. 193—194°, and yellow prismatic needles (0·35 g., 11%), m. p. 89—90°, of 1-*chloro*-5-*β*-*diethylaminoethylamino*-9-*methylacridine* (Found: C, 70·35; H, 7·25; N, 12·3. $C_{26}H_{24}N_3Cl$ requires C, 70·3; H, 7·1; N, 12·3%). (2) The condensation in toluene solution gave a product which was fractionally crystallised from ligroin (b. p. 60—80°) into unchanged 1 : 5-dichloro-9-methylacridine and 1-chloro-5-*β*-diethylaminoethylamino-9-methylacridine; the latter, after being purified through the hydrochloride and crystallised from ligroin (b. p. 60—80°), had m. p. 89—90°. Yield 32%.

1-*Chloro*-5-*γ*-*diethylaminopropylamino*-9-*methylacridine* (VI; $x = 3$).—Condensation of 1 : 5-dichloro-9-methylacridine (5·2 g.) with 3-diethylaminopropylamine in phenol solution gave a yellow oil. On treatment with dilute hydrochloric acid, part dissolved and part separated as an orange solid; the latter on treatment with ammonia gave 1-chloro-9-methylacridone (1·5 g.). Addition of ammonia to the filtrate precipitated 1-*chloro*-5-*γ*-*diethylaminopropylamino*-9-*methylacridine* as a yellow solid which crystallised from alcohol (charcoal) in yellow hexagonal plates (1·5 g., 21%), m. p. 94° (Found: C, 70·1; H, 7·5. $C_{21}H_{26}N_3Cl$ requires C, 70·9; H, 7·4%). The hydrochloride was prepared by adding concentrated hydrochloric acid to a solution of the base in acetone.

1-*Chloro*-5-*ω*-*diethylamino*-o-*toluidino*-9-*methylacridine* (VII).—A mixture of 1 : 5-dichloro-9-methylacridine (12 g.), toluene, *o*-aminobenzyldiethylamine and a little copper bronze was boiled for 20 hours. The 1-*chloro*-5-*ω*-*diethylamino*-o-*toluidino*-9-*methylacridine* was separated from unchanged 1 : 5-dichloro-9-methylacridine through the hydrochloride. It crystallised from ligroin (b. p. 80—100°) in orange-yellow pointed prisms (3·5 g., 19%), m. p. 165—166° (Found: C, 74·4; H, 6·8; N, 10·3. $C_{25}H_{26}N_3Cl$ requires C, 74·3; H, 6·5; N, 10·4%).

5-*Chloro*-2′-*methyldiphenylamine*-2-*carboxylic Acid*.—A mixture of potassium 2 : 4-dichlorobenzoate (23 g.), *o*-toluidine (64 g.), potassium carbonate (10 g.), copper bronze (1 g.) and amyl alcohol (60 c.c.) was boiled for 6 hours. Sodium hydroxide was added and, after steam distillation, the acid was precipitated with hydrochloric acid. It was dissolved in sodium carbonate solution, reprecipitated and crystallised from alcohol (charcoal). Yield, 15·5 g. (60%). 5-*Chloro*-2′-*methyldiphenylamine*-2-*carboxylic acid* forms rectangular needles, m. p. 216—217° (decomp.) (Found: N, 5·3. $C_{14}H_{12}O_2NCl$ requires N, 5·4%). 2 : 5-*Dichloro*-9-*methylacridine* was prepared from 5-chloro-2′-methyldiphenylamine-2-carboxylic acid (14 g.) and crystallised from light petroleum (b. p. 80—100°) in pale yellow needles (13 g., 93%), m. p. 149° (Found: Cl, 26·6. $C_{14}H_9NCl_2$ requires Cl, 27·0%).

2-*Chloro*-5-*δ*-*diethylamino*-*α*-*methylbutylamino*-9-*methylacridine* (VIII; R = $NHCHMe(CH_2)_3NEt_2$; R′ = Cl).—2 : 5-Dichloro-9-methylacridine (5·0 g.) was condensed with 2-amino-5-diethylaminopentane in phenol solution. The product was taken through the hydrochloride and then converted into the picrate in alcoholic solution. 2-*Chloro*-5-*δ*-*diethylamino*-*α*-*methylbutylamino*-9-*methylacridine dipicrate* crystallised (12 g., 75%) from acetone in yellow plates, m. p. 189—190° (Found: C, 49·4; H, 4·4; N, 15·3. $C_{35}H_{36}O_{16}N_9Cl$ requires C, 49·9; H, 4·3; N, 15·0%).

2′-Methyldiphenylamine-2-carboxylic acid was obtained in 73% yield, m. p. 190—191° (Ullmann, *Annalen*, 1907, **355**, 312, gives m. p. 185°; Lehmstedt, Bruns and Klee, *Ber.*, 1936, **69**, 2399, give m. p. 189°). The acid was converted into 5-chloro-1-methylacridine (yield, 76%), m. p. 94°, by the method of Gleu and Nitzsche (*J. prakt. Chem.*, 1939, **153**, 200).

5-*δ*-*Diethylamino*-*α*-*methylbutylamino*-1-*methylacridine* (VIII; R = $NHCHMe(CH_2)_3NEt_2$; R′ = H).—5-Chloro-1-methylacridine (5 g.) was condensed with 2-amino-5-diethylaminopentane in phenol solution. The yellow gum obtained was extracted with chloroform and filtered from a small amount of sparingly soluble material. The solvent was removed and the residue converted into the picrate in alcohol. 5-*δ*-*Diethylamino*-*α*-*methylbutylamino*-1-*methylacridine dipicrate* (11 g., 62%) crystallised from methyl alcohol in yellow irregular prisms, m. p. 153—154° (Found: C, 51·7; H, 4·8; N, 16·4. $C_{35}H_{37}O_{14}N_9$ requires C, 52·0; H, 4·6; N, 15·6%).

2′-Chlorodiphenylamine-2-carboxylic acid was obtained in 65% yield, m. p. 195—196°, by the method of Ullmann (*loc. cit.*), who gave m. p. 192°. This acid (10 g.) was treated with phosphoryl chloride in the usual way. Crystallisation of the product from benzene, chloroform or acetone gave mainly 1-chloroacridone, which crystallised from chlorobenzene in pale yellow needles, m. p. >250° (Found: Cl, 16·0. Calc. for $C_{13}H_8ONCl$: Cl, 15·4%). This was heated for 3 hours with phosphoryl chloride and the crude 1 : 5-dichloroacridine obtained used for condensations with bases without further purification.

1-*Chloro*-5-*δ*-*diethylamino*-*α*-*methylbutylaminoacridine* (IX; R = $NHCHMe(CH_2)_3NEt_2$; R′ = H).—Crude 1 : 5-dichloroacridine (5 g.) was condensed with 2-amino-5-diethylaminopentane in phenol solution. The yellow gum obtained was extracted with chloroform and filtered from the insoluble solid residue (1·3 g.). After removal of the solvent, the gum was taken through the hydrochloride and reprecipitated with ammonia. It was then extracted with benzene and converted into the picrate in benzene solution. 1-*Chloro*-5-*δ*-*diethylamino*-*α*-*methylbutylaminoacridine dipicrate* crystallised (4·9 g., 30%) from acetone–alcohol (1 : 1), m. p. 163—164° (Found: C, 49·4; H, 4·3; N, 15·4. $C_{34}H_{34}O_{14}N_9Cl$ requires C, 49·3; H, 4·1; N, 15·2%).

m-Bromo-*p*-toluidine hydrochloride was converted into the nitrile in 30% yield by diazotisation and treatment with cuprous cyanide (Claus and Kunath, *J. prakt. Chem.*, 1889, **39**, 485). The nitrile was hydrolysed to the acid in over 90% yield when boiled for 8 hours with 20% sodium hydroxide solution. Hydrolysis with alcoholic potash or 70% sulphuric acid gave lower yields. A mixture of potassium *m*-bromo-*p*-toluate (20 g.), *o*-chloroaniline (30 g.), potassium carbonate (5·5 g.), copper bronze (1 g.) and amyl alcohol (50 c.c.) was boiled for 6 hours. After steam distillation the solution was filtered hot and the acid precipitated with hydrochloric acid and crystallised (12 g., 60%) from benzene or alcohol (charcoal). 2′-*Chloro*-5-*methyldiphenylamine*-2-*carboxylic acid* crystallised from benzene in rectangular plates, m. p. 217° (decomp.) (Found: N, 5·4. $C_{14}H_{12}O_2NCl$ requires N, 5·4%). 1 : 5-*Dichloro*-8-*methylacridine* was prepared from 2′-chloro-5-methyldiphenylamine-2-carboxylic acid (11 g.) but the reaction mixture was heated at 115° instead of 140° as higher temperatures gave lower yields. The crude acridine was extracted with light petroleum (b. p. 60—80°) in a Soxhlet extractor. Concentration of the solution gave impure 1 : 5-*dichloro*-8-*methylacridine*; crystallisation from benzene gave light brown needles (4·4 g.; 40%), m. p. 152° (Found: Cl, 26·7. $C_{14}H_9NCl_2$ requires Cl, 27·0%).

1-*Chloro*-5-*δ*-*diethylamino*-*α*-*methylbutylamino*-8-*methylacridine* (IX; R = $NHCHMe(CH_2)_3NEt_2$; R′ = CH_3).—The method of Burckhalter, Jones, Holcomb and Sweet (*J. Amer. Chem. Soc.*, 1943, **65**, 2012) was adapted. 1 : 5-Dichloro-8-methylacridine (7 g.) was heated with phenol (30 g.) for 15 mins. and potassium carbonate (1·8 g.) and 2-amino-5-diethylaminopentane (4·2 g.) added. Heating was continued for 4 hours and the hot product poured into ether (250 c.c.). After washing with 10% sodium hydroxide solution and water, the ethereal solution was filtered and dried over potassium carbonate. A little was taken down to dryness and the residue converted into the picrate in alcoholic solution. This proved to be unsuitable as a means of purification, since repeated crystallisations did not give a substance of sharp melting point. The rest of the ethereal solution was treated with hydrogen chloride and the flocculent precipitate of 1-*chloro*-5-*δ*-*diethylamino*-*α*-*methylbutylamino*-8-*methylacridine hydrochloride* filtered rapidly, dissolved in a little water, filtered and the filtrate evaporated to dryness in vacuum over sodium hydroxide. It crystallised from alcohol–ether as a yellow microcrystalline powder (Found, on material dried at 30° in vacuum: C, 59·1; H, 7·45; N, 8·8. $C_{23}H_{32}N_3Cl_3,\frac{1}{2}H_2O$ requires C, 59·3; H, 7·1; N, 9·0%).

2-*Chloro*-5-(2′-*thiazolylamino*)-7-*methoxyacridine* (X.)—2 : 5-Dichloro-7-methoxyacridine (5·6 g.) was condensed with 2-aminothiazole in phenol solution at 110° for 3 hours. Crystallisation of the product from *cyclo*hexanol–alcohol gave 2-*chloro*-5-(2′-*thiazolylamino*)-7-*methoxyacridine* (4·5 g., 66%) as a red microcrystalline powder, m. p. 246° (Found : C, 60·2; H, 3·9; N, 12·2. $C_{17}H_{12}ON_3ClS$ requires C, 59·7; H, 3·5; N, 12·3%).

The 5-aminoacridine hydrochlorides were prepared, except where otherwise stated, by dissolving the free base in dilute hydrochloric acid and evaporating to dryness in vacuum over sodium hydroxide.

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