339. *Attempts to find New Antimalarials. Part XV. The Synthesis of Acridine Compounds related to Atebrin.*

By Robert R. Goodall and William O. Kermack.

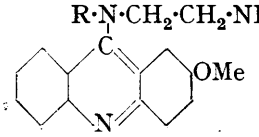
Atebrin and achrichin, the two best-known antimalarials of the acridine series, are 8-chloro-5-(δ-diethylamino-α-methylbutylamino)- and 8-chloro-5-(γ-diethylamino-*n*-propylamino)-3-methoxyacridine respectively. The objects of the present investigation were to synthesise acridine compounds, (*a*) with a side chain in the 5-position of the acridine nucleus, containing two tertiary nitrogen atoms, instead of one tertiary and one secondary as in atebrin; (*b*) containing different nuclear substituents.

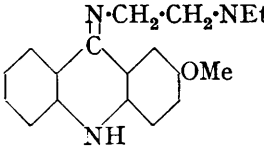
(*a*) Unsuccessful attempts were made to condense amines of the type

$$NEt_2 \cdot CH_2 \cdot CH_2 \cdot NHAlk$$

with 5-chloro-3-methoxyacridine by heating them together, or in presence of solvents (with or without a trace of copper-bronze or cuprous chloride). 5-*Phenoxy*-3-*methoxyacridine* was therefore prepared by heating 5-chloro-3-methoxyacridine in phenol containing 1 mol. of potassium hydroxide. When this phenoxy-derivative was refluxed with β-diethylaminoethylalkylamine, the reaction proceeded slowly with the formation of the

desired compound. The yield of the butyl compound was very poor. The shorter the alkyl group, the more easily the reaction proceeded, but, even with β-diethylaminoethylmethylamine, the reaction was slower and the yield much poorer than in the case of the primary amines β-diethylaminoethylamine and γ-diethylamino-*n*-propylamine. The new compounds of the structure (I; R = Pr or Me) differ from the homologous secondary base (I; R = H) in that they dissolve in dilute mineral acids to yield solutions, which exhibit no fluorescence (in contrast to the striking green fluorescence of the secondary base) and, even at room temperature, undergo decomposition with the separation of 3-methoxyacridone (cf. Magidson and Grigorowski, *Ber.*, 1936, **69**, 400).

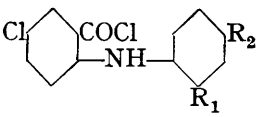
(I.) 



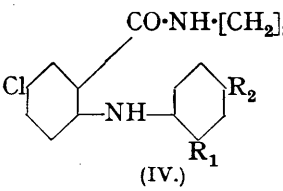
(II.)

The tertiary bases (I; R = Alk) are therefore much more easily hydrolysed in neutral or slightly acid solution than is 5-(β-diethylaminoethylamino)-3-methoxyacridine. These differences suggest that the latter may predominantly exist in the form (II).

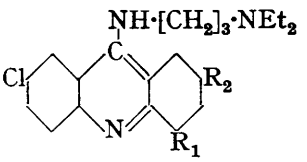
(*b*) The choice of substituents introduced into the acridine nucleus was determined by the availability of the intermediate compounds. 1 : 3 : 5-*Trichloro-* and 5-*chloro*-1-*bromo*-3-*methyl-acridine* were readily obtained by the action of phosphorus oxychloride on 2 : 4-dichloro- and 2-bromo-4-methyl-diphenylamine-2′-carboxylic acids (cf. this vol., p. 1163) respectively. Treatment with sodium phenoxide in phenol yielded the corresponding 5-*phenoxy*-derivatives, which were then condensed with β-diethylaminoethylamine or γ-diethylamino-*n*-propylamine, to yield 1 : 3-*dichloro-* and 1-*bromo*-3-*methyl*-5-(β-*diethylaminoethylamino*)*acridine* or the corresponding γ-diethylamino-*n*-propylamino-compounds.



(III.)



(IV.)



(V.)

2 : 4 : 4′-Trichlorodiphenylamine-2′-carboxylic acid chloride (III; R_1 and R_2 = Cl) (*loc. cit.*) condensed immediately in benzene, at room temperature, with γ-diethylamino-*n*-propylamine to yield the corresponding amide (IV; R_1 and R_2 = Cl), and this, when refluxed in excess of phosphorus oxychloride, cyclised, with the formation of 1 : 3 : 7-*trichloro*-5-(γ-*diethylamino*-n-*propylamino*)*acridine* (V; R_1 and R_2 = Cl). Similarly, the condensation of 4′-chloro-2-bromo-4-methyldiphenylamine-2′-carboxylic acid chloride (III; R_1 = Br, R_2 = Me) with γ-diethylamino-*n*-propylamine, followed by cyclisation of the intermediate amide (IV; R_1 = Br, R_2 = Me), yielded 7-*chloro*-1-*bromo*-5-(γ-*diethylamino*-n-*propylamino*)-3-*methylacridine* (V; R_1 = Br, R_2 = Me), and 2 : 5-dichlorodiphenylamine-2′-carboxylic acid chloride (*loc. cit.*) yielded 1 : 4-dichloro-5-(γ-diethylamino-*n*-propylamino)acridine. This route to compounds of the atebrin type, through the diphenylamine-*o*-carboxylic acid amides (cf. E.P., 363,392), is an extremely convenient one, the reactions proceeding very smoothly and in good yield.

Experimental.

5-*Phenoxy*-3-*methoxyacridine*.—Finely powdered potassium hydroxide (2·6 g.) was dissolved in melted phenol (30 g.), and 5-chloro-3-methoxyacridine (8 g.) added with stirring. After 1 hour at 100° the hot melt was poured into 10% sodium hydroxide solution (200 c.c.), stirred well, and kept overnight. The supernatant liquid was decanted, and the residue ground with 5% sodium hydroxide solution (about 50 c.c.). The product was filtered off, washed free from alkali, and dried. Yield, 8·4 g. White needles, m. p. 146—147°, were obtained from alcohol (Found: C, 79·9; H, 5·0. $C_{20}H_{15}O_2N$ requires C, 79·7; H, 5·0%). The *base* is soluble in benzene,

alcohol, chloroform, and ligroin. It is moderately soluble in dilute hydrochloric acid, and is hydrolysed, on boiling, to 3-methoxyacridone, identified by its m. p. (270°) and by its marked violet fluorescence in alcoholic solution.

5-(β-*Diethylaminoethylmethylamino*)-3-*methoxyacridine* (I; R = Me).—5-Phenoxy-3-methoxyacridine (3 g.), β-diethylaminoethylmethylamine (Kermack and Wight, J., 1935, 1425) (2·4 g.), and a trace of copper powder were refluxed together at 150—160° for 20 hours. The dark brown oil was poured into 50 c.c. of 5% sodium hydroxide solution, and the latter, as well as the semi-solid residue, thoroughly extracted with ether. The combined extracts were shaken five times with 33% acetic acid and the cooled acetic acid solution was basified with ammonia. A dark oil separated; this was extracted thrice with ether, and the extract dried over potassium carbonate. Evaporation left an oily base, which was converted into the dihydrobromide with concentrated alcoholic hydrogen bromide. After a few hours the precipitate was filtered off, washed with a little alcoholic hydrogen bromide, and then with ether. The dry product, 5-(β-*diethylaminoethylmethylamino*)-3-*methoxyacridine dihydrobromide*, was an orange powder (2·8 g.), which, recrystallised from ethyl alcohol, formed micro-needles, m. p. 239—240° (Found: C, 50·2; H, 5·8; Br, 31·4. $C_{21}H_{27}ON_3$,2HBr requires C, 50·5; H, 5·8; Br, 32·0%). It is readily soluble in water and methyl alcohol, forming non-fluorescent orange solutions. After standing overnight at room temperature in aqueous solution, it is hydrolysed with the separation of 3-methoxyacridone.

5-(β-*Diethylaminoethyl*-n-*propylamino*)-3-*methoxyacridine*.—5-Phenoxy-3-methoxyacridine (2·5 g.) and β-diethylaminoethyl-*n*-propylamine (2·5 g.) (*loc. cit.*) were refluxed together at 180° for 19 hours. The product was worked up as above. When the small amount of base obtained after purification was treated with alcoholic hydrogen bromide, only 0·06 g. of 5-(β-*diethylaminoethyl*-n-*propylamino*)-3-*methoxyacridine dihydrobromide* was precipitated, as a red amorphous powder, m. p. 142—143°. The filtrate was diluted to five times its original volume with ether; a further 0·23 g., m. p. 142—143°, was then obtained. This was washed with ether till free from acid, recrystallised from alcohol, and dried in a vacuum to constant weight (Found: C, 49·8, 49·7; H, 6·4, 6·5. $C_{23}H_{31}ON_3$,2HBr requires C, 52·4; H, 6·3%. $C_{23}H_{31}ON_3$,2HBr,$2H_2O$ requires C, 49·0; H, 6·6%). As the compound was recrystallised from ethyl alcohol, the presence of water of crystallisation is somewhat unexpected, but there does not seem to be any other simple explanation of the analytical results; lack of material prevented a more complete investigation of the anomaly. In aqueous solution after a few hours at room temperature, the dihydrobromide is hydrolysed to 3-methoxyacridone.

5-(β-*Diethylaminoethylamino*)-3-*methoxyacridine* (II).—5-Phenoxy-3-methoxyacridine (3 g.), β-diethylaminoethylamine (2 g.) (*loc. cit.*), and a trace of copper-bronze were heated under reflux at 150° for 4 hours. The product was poured into 50 c.c. of 2% sodium hydroxide solution and worked up as above. The new base was isolated as its *dihydrobromide* (yield, 3·4 g.) which, recrystallised from methyl alcohol, formed yellow micro-needles; these were dried to constant weight in a vacuum (Found: C, 47·9; H, 5·5; Br, 32·3. $C_{21}H_{25}ON_3$,2HBr,H_2O requires C, 47·7; H, 5·8; Br, 31·8%). This dihydrobromide, like all the other dihydrobromides described below, is readily soluble in water and alcohol, forming yellow solutions with an intense green fluorescence, persisting even in high dilution. They are insoluble in benzene, ligroin, chloroform, acetone, and ether. The aqueous solutions remain stable at room temperature for 2—3 weeks, but small quantities of the corresponding acridone may slowly separate, apparently as the result of the hydrolytic removal of the side chain.

5-(γ-*Diethylamino*-n-*propylamino*)-3-*methoxyacridine dihydrobromide* (cf. Magidson and Grigorowski, *loc. cit.*, p. 406) was similarly prepared from 5-phenoxy-3-methoxyacridine (2 g.) and γ-diethylamino-*n*-propylamine (1 g.) (yield, 2·3 g.). Recrystallised from methyl alcohol, it formed yellow micro-needles, m. p. 242—245°, which were dried to constant weight in a vacuum (Found: C, 50·0, 49·8; H, 5·5, 5·6. $C_{21}H_{27}ON_3$,2HBr requires C, 50·5; H, 5·8%).

1 : 3 : 5-*Trichloroacridine*.—2 : 4-Dichlorodiphenylamine-2′-carboxylic acid (Ullmann, *Annalen*, 1909, **355**, 340) (12 g.) and phosphorus oxychloride (25 c.c.) were refluxed at 120°. After 1 hour, the phosphorus oxychloride was distilled under reduced pressure. The residue was dissolved in acetone (100 c.c.), and the solution basified carefully with acetone containing about 30% of concentrated aqueous ammonia. The yellow precipitate was filtered off, washed with acetone, and dried. The *trichloroacridine* was separated from inorganic salts by repeated extraction with benzene, from which it crystallised in fine yellow needles, m. p. 175° (Found: C, 55·0; H, 2·3. $C_{13}H_6NCl_3$ requires C, 55·2; H, 2·1%). This base, like the corresponding 5-chloro-1-bromo-3-methylacridine (see below), is soluble in alcohol and benzene and sparingly soluble in acetone, chloroform, and ether. Both compounds are sparingly soluble in dilute

hydrochloric acid, but, when boiled, the solutions are decomposed, with the separation of the corresponding acridone. The same compound was obtained by treatment of 1 : 3-dichloroacridone (Ullmann, *loc. cit.*) with a mixture of phosphorus oxychloride and phosphorus pentachloride at 120° for 1 hour. Ullmann gives the m. p. of 1 : 3-dichloroacridone as over 360°, but our compound, which was apparently homogeneous, melted sharply at 305° when purified by sublimation.

1 : 3-*Dichloro*-5-*phenoxyacridine*.—1 : 3 : 5-Trichloroacridine (4 g.) was added with stirring to phenol (10 g.), containing potassium hydroxide (1·5 g.), and the green mixture heated at 100° for 2 hours. The product was worked up as in the case of 5-phenoxy-3-methoxyacridine. Yield, 4·5 g. Recrystallisation from ligroin gave rhombic prisms, m. p. 171° (Found : C, 66·8; H, 3·6. $C_{19}H_{11}ONCl_2$ requires C, 66·9; H, 3·5%). This *base*, like the corresponding 1-bromo-5-phenoxy-3-methylacridine, is soluble in alcohol and benzene and slightly soluble in ligroin, acetone, and ether. Both phenoxy-compounds are somewhat more soluble in dilute hydrochloric acid than the 5-chloro-compounds, but, like the latter, readily decompose on boiling, with the separation of the corresponding acridones.

1 : 3-*Dichloro*-5-(β-*diethylaminoethylamino*)*acridine*.—1 : 3-Dichloro-5-phenoxyacridine (1·2 g.), phenol (0·5 g.), and β-diethylaminoethylamine (0·46 g.) were heated together at 120° for 2 hours. The product was worked up in the manner already described for the analogous bases, except that the *base* was more conveniently extracted with benzene, rather than ether (in which it was but sparingly soluble), and it was not isolated as the hydrobromide, since the free base separated as a solid, crystallising from ligroin in orange needles, m. p. 121—122° (Found : C, 63·1; H, 6·0. $C_{19}H_{21}N_3Cl_2$ requires C, 63·0; H, 5·8%). The base is very soluble in alcohol, acetone, and benzene and slightly soluble in ligroin and chloroform. It is insoluble in water, but dissolves readily in dilute mineral acids. It forms a hydrobromide decomposing at about 200°.

1 : 3-*Dichloro*-5-(γ-*diethylamino*-n-*propylamino*)*acridine*.—1 : 3-Dichloro-5-phenoxyacridine (1·2 g.), phenol (1·5 g.), and γ-diethylamino-*n*-propylamine (0·6 g.) were heated together at 120—140° for 2 hours. The product was worked up in the usual way, and isolated as the *dihydrobromide*. Yield, 0·57 g. This, recrystallised from ethyl alcohol, formed yellow micro-needles, decomposing at about 200° (Found : C, 44·8; H, 5·0. $C_{20}H_{23}N_3Cl_2,2HBr$ requires C, 44·6; H, 4·8%).

5-*Chloro*-1-*bromo*-3-*methylacridine*.—2-Bromo-4-methyldiphenylamine-2′-carboxylic acid (19 g.) (Goodall and Kermack, this vol., p. 1163) and phosphorus oxychloride (50 c.c.) were refluxed at 120°, and the product worked up as in the case of 1 : 3 : 5-trichloroacridine. 5-*Chloro*-1-*bromo*-3-*methylacridine* crystallised from ligroin in sparkling yellow needles (11 g.), m. p. 159—161° (Found : C, 54·7; H, 3·2. $C_{14}H_9NClBr$ requires C, 54·9; H, 2·9%).

The same compound was obtained by cyclising 2-bromo-4-methyldiphenylamine-2′-carboxylic acid (15 g.) with sulphuric acid (150 c.c.) at 100° for 4 hours and treating the resulting 1-bromo-3-methylacridone (yield, 10·4 g.; m. p. 255°) with a mixture of phosphorus oxychloride (20 c.c.) and phosphorus pentachloride (10 g.).

1-*Bromo*-5-*phenoxy*-3-*methylacridine*.—Potassium hydroxide (2 g.) was dissolved in phenol (20 g.), and 5-chloro-1-bromo-3-methylacridine (6 g.) added with stirring. After 2 hours' heating at 100°, the product was worked up as in the case of 5-phenoxyacridine. 1-*Bromo*-5-*phenoxy*-3-*methylacridine* formed yellow needles, m. p. 145°, from ligroin (Found : C, 65·9; H, 3·9. $C_{20}H_{14}ONBr$ requires C, 65·7; H, 3·8%).

1-*Bromo*-5-(β-*diethylaminoethylamino*)-3-*methylacridine*.—1-Bromo-5-phenoxy-3-methylacridine (1 g.), phenol (2 g.), and diethylaminoethylamine (0·4 g.) were heated together at 120° for 2 hours. The product was worked up as in the case of 1 : 3-dichloro-5-(β-diethylaminoethylamino)acridine. 1-*Bromo*-5-(β-*diethylaminoethylamino*)-3-*methylacridine* formed orange plates, m. p. 114°, from ligroin (Found : C, 62·2; H, 6·2. $C_{20}H_{24}N_3Br$ requires C, 62·3; H, 6·4%). This base is very similar in properties to 1 : 3-dichloro-5-(β-diethylaminoethylamino)acridine.

1-Bromo-5-(γ-diethylamino-*n*-propylamino)-3-methylacridine, obtained from the 5-phenoxy-compound (1 g.), phenol (2 g.), and γ-diethylamino-*n*-propylamine (0·5 g.) by heating at 120° for 2 hours, did not readily crystallise; it was therefore converted into the *dihydrobromide*, which separated slowly from alcohol in yellow micro-needles (0·5 g.), decomp. about 230° (Found : C, 44·8; H, 5·2. $C_{21}H_{26}N_3Br,2HBr$ requires C, 44·9; H, 5·0%).

1 : 3 : 7-*Trichloro*-5-(γ-*diethylamino*-n-*propylamino*)*acridine*.—γ-Diethylamino-*n*-propylamine (0·3 g.) was added slowly, with stirring, to a mixture of 2 : 4 : 4′-trichlorodiphenylamine-2′-carboxylic acid chloride (III; R_1 and R_2 = Cl) (0·5 g.) in benzene (5 c.c.). The canary-yellow mixture was immediately transformed into a colourless syrup, from which the benzene was

removed in a vacuum. The residual oily amide (IV; R_1 and R_2 = Cl) was refluxed with phosphorus oxychloride (1 c.c.) for 1 hour, and the excess of the latter was removed under reduced pressure. The product, after dilution with ice-water, was basified slowly with ammonia whilst cooling in a freezing mixture. 1 : 3 : 7-*Trichloro*-5-(*γ-diethylamino*-n-*propylamino*)-*acridine* (V; R_1 and R_2 = Cl) was precipitated as an orange powder, which was filtered off, washed with water, and recrystallised from ligroin, yielding micro-needles, m. p. 155° (Found: C, 58·4; H, 5·5. $C_{20}H_{22}N_3Cl_3$ requires C, 58·5; H, 5·4%). This base, like the three following, is moderately easily soluble in alcohol, ether, and benzene and sparingly soluble in ligroin. The hydrobromide decomposes at 240—250°.

7-*Chloro*-1-*bromo*-5-(*γ-diethylamino*-n-*propylamino*)-3-*methylacridine*.—4′-Chloro-2-bromo-4-methyldiphenylamine-2′-carboxylic acid chloride (III; R_1 = Br, R_2 = Me) (1 g.) was condensed in benzene (10 c.c.) with γ-diethylamino-*n*-propylamine (0·6 g.), and the product (IV; R_1 = Br, R_2 = Me) cyclised with phosphorus oxychloride (1·5 c.c.) as in the last example. Yield, 1 g. The *base* (V; R_1 = Br, R_2 = Me), recrystallised from ligroin, formed yellow micro-needles, m. p. 130—131° (Found: C, 58·1; H, 5·7. $C_{21}H_{25}N_3ClBr$ requires C, 58·0; H, 5·8%). The hydrobromide decomposed from 252—254°.

1 : 4-*Dichloro*-5-(*γ-diethylamino*-n-*propylamino*)*acridine Dihydrobromide*.—2 : 4-Dichlorodiphenylamine-2′-carboxylic acid chloride (1 g.) was condensed in benzene (5 c.c.) with γ-diethylamino-*n*-propylamine (0·6 g.), and the sticky product cyclised with phosphorus oxychloride (1·5 c.c.) as above. The resulting oily base was converted into the *dihydrobromide*, which formed yellow micro-needles from alcohol, decomposing about 225—230° (Found: C, 44·8; H, 4·9. $C_{20}H_{23}N_3Cl_2,2HBr$ requires C, 44·6; H, 4·8%).

We thank the Department of Scientific and Industrial Research for a grant to one of us (R. R. G.), and Imperial Chemical Industries, Ltd., for financial and other help.

RESEARCH LABORATORY, ROYAL COLLEGE OF PHYSICIANS,
EDINBURGH. [*Received, August 15th*, 1936.]