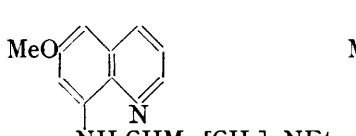
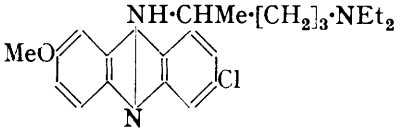
136. *The Synthesis of Substituted Acridines as Possible Antimalarials.*

By G. R. CLEMO and W. HOOK.

DURING recent years the magnitude and complexity of the malaria problem has been realised and in consequence a considerable amount of work has been done on the synthesis of possible antimalarial compounds. The best known and most valuable of such compounds are the I.G. products plasmoquin (I) and atebrin (II).



(I.)



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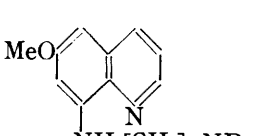


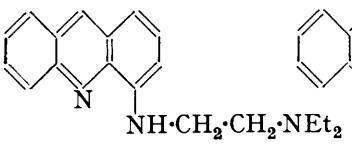
(III.)

Robinson and Baldwin (J., 1929, 2959; 1934, 1264) have prepared compounds related to plasmoquin, and Robinson and Meisel (J., 1934, 1267) showed that the most effective compound of this type was 8-(δ-aminobutylamino)-6-methoxyquinoline (III; R = H). Meanwhile Strukow and Magidson (*Arch. Pharm.*, 1933, **271**, 569) had prepared similar compounds with R = ethyl. Magidson and Grigorowsky (*Ber.*, 1936, **69**, 396) have also prepared compounds related to atebrin.

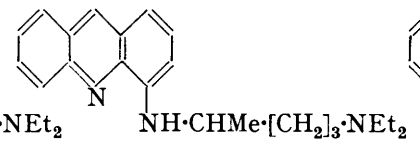
In consequence of the well-known antiseptic action of certain acridine derivatives and the fact that atebrin is an acridine derivative of which, at that time, the constitution was generally unknown, it was thought desirable to synthesise compounds of acridine containing the characteristic basic centres and alkylamino-side chain of plasmoquin.

Compounds of 1-aminoacridine were decided upon, as the alkylamino-side chains would then be in the same relative position to the heterocyclic nitrogen atom as in plasmoquin and related effective compounds. 1-(β-*Diethylaminoethylamino*)*acridine* (IV) has been prepared by direct condensation of 1-aminoacridine and β-chloroethyldiethylamine, and also by condensing β-chloroethyldiethylamine with the *p*-toluenesulphonamide of 1-amino-5 : 10-dihydroacridine and subsequent hydrolysis of the resulting *p*-toluenesulphonamide.

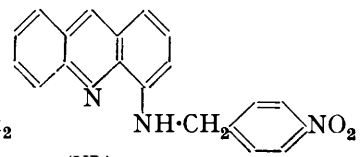
All attempts to prepare 1-(δ-diethylamino-α-methylbutylamino)acridine (V) in a similar manner have failed because of the ease with which δ-chloro-α-diethylaminopentane, $CH_3·CHCl·[CH_2]_3·NEt_2$, loses the elements of hydrogen chloride in the presence of strong bases. δ-Chloro-α-diethylaminopentane could not be isolated in the free state, as it isomerised to give the ethochloride of 2-methyl-1-ethylpyrrolidine, isolated as the ethopicrate; nor did it yield a crystalline hydrochloride, but a crystalline *methiodide* was obtained and used in some of the condensation attempts.



(IV.)



(V.)



(VI.)

Attempted condensation of 1-chloroacridine and δ-amino-α-diethylaminopentane also failed to produce (V). 1-Aminoacridine has also been condensed with *p*-nitrobenzyl bromide to yield 1-(p-*nitrobenzyl*)*aminoacridine* (VI), and this has been reduced to the *amino*-compound, which gives a crystalline water-soluble dihydrochloride.

EXPERIMENTAL.

p-*Toluenesulphonamide of* 1-*Methylamino*-5 : 10-*dihydroacridine*.—The *p*-toluenesulphonamide of 1-amino-5 : 10-dihydroacridine (Clemo, Perkin, and Robinson, J., 1924, **125**, 179) (1 g.) was dissolved in 10 c.c. of 5% methyl-alcoholic potash and 5 c.c. of water, and 3 c.c. of

methyl sulphate added; a solid began to separate almost immediately. This (0·9 g.) crystallised from alcohol in stout yellow prisms, m. p. 170° (Found: C, 68·8; H, 5·7. $C_{21}H_{20}O_2N_2S$ requires C, 69·2; H, 5·5%).

1-*Methylaminoacridine*.—The above amide (2 g.) was dissolved in sulphuric acid (15 c.c.) and gave a cinnamon-coloured solution with an intense green fluorescence. After standing for 3 hours and heating on the water-bath for 1 hour, it was poured on ice, giving a red solution. On addition of excess of sodium carbonate, a yellow oil separated. This was taken up in ether, the ether removed, and the residue crystallised from light petroleum (b. p. 40—60°), giving fine orange prisms, m. p. 75° (Found: C, 80·6; H, 5·9. $C_{14}H_{12}N_2$ requires C, 80·8; H, 5·8%). The product was 1-*methylaminoacridine*, showing that during hydrolysis and subsequent working up, the 5:10-dihydro-compound had been oxidised to the acridine. These preparations were carried out as preliminaries to the following,

1-(β-*Diethylaminoethyl*)*aminoacridine* (IV).—1-Aminoacridine (4 g.), β-chloroethyldiethylamine hydrochloride (4 g.), and fused sodium acetate (2 g.) in alcohol (20 c.c.) were refluxed for 15 hours. The product was poured into water, excess of sodium carbonate added, and the oil which separated extracted with ether. Fractionation gave (IV) (6·4 g.) as a viscous, dark red oil, b. p. 180°/1 mm. (Found: C, 78·1; H, 7·9. $C_{19}H_{23}N_3$ requires C, 77·8; H, 7·85%). (IV) gives a *dipicrate*, dark red needles, m. p. 192° (Found: C, 49·5; H, 4·3. $C_{19}H_{23}N_3,2C_6H_3O_7N_3$ requires C, 49·5; H, 3·9%), and a *monopicrate*, scarlet prisms, m. p. 151° (Found: C, 57·5; H, 5·3. $C_{19}H_{23}N_3,C_6H_3O_7N_3$ requires C, 57·5; H, 5·0%). 1-Aminoacridine forms only a *monopicrate*, purplish-black plates, m. p. 220° (Found: C, 53·9; H 3·2. $C_{13}H_{10}N_2,C_6H_3O_7N_3$ requires C, 53·9; H, 3·1%).

The *dihydrochloride* of (IV) crystallised from moist acetone–methyl alcohol in dark red prisms, m. p. 104°, containing two molecules of water (Found: N, 10·5; Cl, 17·7. $C_{19}H_{23}N_3,2HCl,2H_2O$ requires N, 10·45; Cl, 17·65%). It was extremely soluble in water and alcohol. (IV) was also prepared by hydrolysing the *p*-toluenesulphonamide of 1-(β-*diethylaminoethyl*)*amino*-5:10-*dihydroacridine* prepared in the usual manner; m. p. 88° (Found: C, 70·0; H, 7·2. $C_{26}H_{31}O_2N_3S$ requires C, 69·6; H, 6·9%).

δ-*Chloro*-α-*diethylaminopentane*.—α-Diethylamino-δ-hydroxypentane (0·5 g.) in chloroform (1 c.c.) was added slowly to 2 c.c. of thionyl chloride in chloroform (2 c.c.). After 2 hours the chloroform and the excess of thionyl chloride were removed in a vacuum at 30°. Excess of 10% sodium hydroxide solution was added, and the base extracted immediately with ether. On removal of the ether at room temperature, the chloro-base was obtained as a yellow oil. This formed a *methiodide*, which crystallised from acetone–ether in white prisms, m. p. 116° (Found: C, 36·9; H, 7·1; N, 4·7. $C_{10}H_{23}NClI$ requires, C, 37·5; H, 7·2; N, 4·4%). The alcohol does not give a crystalline methiodide.

The chloro-base slowly isomerised to give a deliquescent solid, which gave a *picrate*, yellow needles, m. p. 270° (decomp.) (Found: C, 47·9; H, 5·9. $C_9H_{20}N,C_6H_2O_7N_3$ requires C, 48·5; H, 5·9%).

1-(p-*Nitrobenzyl*)*aminoacridine* (VI).—1-Aminoacridine (1·9 g.), *p*-nitrobenzyl bromide (2·1 g.), and sodium acetate (0·8 g.) in alcohol (30 c.c.) were heated on the water-bath for 30 hours. After cooling, the *solid* was collected, washed with water and alcohol, and crystallised from a large volume of dilute alcohol, giving dark red needles (2·6 g.), m. p. 170° (Found: C, 72·4; H, 4·8; N, 12·7. $C_{20}H_{15}O_2N_3$ requires C, 72·9; H, 4·6; N, 12·8%).

1-(p-*Aminobenzyl*)*aminoacridine*.—The nitro-compound (0·2 g.) was reduced by tin and hydrochloric acid, and the amino-compound obtained as the *dihydrochloride*, which formed purple needles, m. p. 168°, from alcohol–ether (Found: C, 61·9; H, 5·8. $C_{20}H_{17}N_3,2HCl,H_2O$ requires C, 61·5; H, 5·4%). The *dipicrate* formed red needles, m. p. 178° (decomp.), from alcohol (Found: C, 51·0; H, 3·85. $C_{20}H_{17}N_3,2C_6H_3O_7N_3$ requires C, 50·7; H, 3·4%).

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