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SYNTHESIS IN DIHALOGENATED 5-AMINOACRIDINE SERIES

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5 *N*-substituted amino-2 :3-dichloro-7-methoxy- and the corresponding demethoxy-acridine derivatives have been described.

Atabrine, the well-known antimalarial, is 2-chloro-7-methoxy-5-(4-diethylamino-1-methylbutyl)amino-acridine dihydrochloride. It has been established that chlorine is more effective in endowing antimalarial properties in acridine derivatives than the methoxy group. Moreover, 1-chloro-, 2-chloro- and 3-chloro-5-(4-diethylamino-1-methylbutyl)amino-acridines were reported as active with quinine equivalent as 0.8, 4.0 and 0.6 respectively (Wiselogle, "Survey of Antimalarial Drugs", 1941-45, Vol. II, Part II, pp. 1930-31).

With a view to studying the effect of an additional chlorine atom on the antimalarial properties of atabrine, dialkylamino-alkylamino derivatives of 2 : 3-dichloro-7-methoxy-acridine and the corresponding demethoxy-acridine diervatives have been synthesised.

3′ : 4′-Dichloro- and 3′ : 4′-dichloro-4-methoxy-diphenylamine-2-carboxylic acids, required for the synthesis of 2 : 3-dichloro- and 2 : 3-dichloro-7-methoxy-5-(4-diethylamino-1-methylbutyl)aminoacridines, were obtained by Ullmann's condensation (*Ber.*, 1905, **38**, 2156) of 3 : 4-dichloroaniline with *o*-chlorobenzoic acid and 6-bromo-3-methoxybenzoic acid respectively. The above-mentioned acids on cyclisation with an excess of phosphorus oxychloride afforded the mixture of two isomeric 5-chloroacridines, viz., 2 : 3 : 5-trichloro- and 3 : 4 : 5-trichloro-7-methoxyacridines which were separated by repeated fractional crystallisation from toluene, followed by acetone.

Usually it is found that 5-chloroacridine, obtained by *para*-closure, has a higher melting point than the 5 chloroacridine obtained by *ortho*-closure (Albert and Linnell, *J. Chem. Soc.*, 1936, 88 ; Lehmstedt and Schrader, *Ber.*, 1937, **70**, 838). Therefore the product having higher m.p. (192-93°) may be 2 : 3 : 5-trichloro-7-methoxyacridine, while one having lower m.p. (179°) may be 3 : 4 : 5-trichloro-7-methoxyacridine. 2 : 3 : 5-Trichloro-7-methoxyacridine was prepared by Feldman and Kopeliowitsch (*Arch. Pharm.*, 1935, **273**, 488) by an unambiguous synthesis. They obtained it as an oily product on cyclising 4 : 5-dichloro-4′-methoxydiphenylamine-2-carboxylic acid and recorded its m.p. as 192-93°. This supports the conclusion which has been drawn above.

The yields of the above-mentioned 5-chloroacridines were very small ; and in the case of 3′:4′-dichlorodiphenylamine-2-carboxylic acid, 2 : 3-dichloroacridone was obtained instead of the expected 5-chloroacridine derivative ; the alternative method of preparing substituted 5-aminoacridines through acid chloride was adopted.

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EXPERIMENTAL

3′:4′-Dichloro-4-methoxydiphenylamine-2-carboxylic acid was prepared by refluxing the mixture of 6-bromo-3-methoxybenzoic acid (9 g.), fused potassium carbonate (6 g.), *iso*amyl alcohol (30 c.c.), 3:4-dichloroaniline (7 g.) and copper powder (0.3 g.) for 4 hours at 140°. After removal of amyl alcohol by steam-distillation, the residual liquid was treated with animal charcoal and filtered hot. The solid separating on acidification was crystallised from acetic acid in small green needles, m.p. 187°, yield 6 g. (Found: Cl, 22.9; equiv., 312.0. $C_{14}H_{11}O_3NCl_2$ requires Cl, 22.8%; equiv., 312.0). The *acid chloride* was obtained by refluxing a mixture of the above acid (1 g.), thionyl chloride (3 c.c.) and benzene (10 c.c.) and crystallised from benzene, m.p. 117°. (Found: Cl, 32.6. $C_{14}H_{10}O_2NCl_3$ requires Cl, 32.2%).

2:3:5-Trichloro- and 3:4:5-trichloro-7-methoxyacridines were obtained in the form of a mixture by treating the preceding acid (5 g.) with $POCl_3$ (30 c.c.) at 110-15° for 3 hours. After removing the excess of $POCl_3$ by petrol-ether, the residual insoluble, dark red, sticky liquid was treated with chloroform. The chloroform-extract, after treating it with ice and ammonia, was dried and the chloroform removed by distillation. A green solid was obtained which melted between 157° and 200°. Two isomers were separated by fractional crystallisation from toluene. The first fraction crystallised as a fine yellow solid, m.p. 192°. (Found: Cl, 34.4. $C_{14}H_{18}ONCl_3$ requires Cl, 34.1%). The second fraction was obtained in a pure state after repeated crystallisations from acetone, m.p. 179°. (Found: Cl, 34.3. $C_{14}H_{18}ONCl_3$ requires Cl, 34.1%).

2:3-Dichloro-5-phenoxy-7-methoxyacridine was prepared by refluxing the mixture of 2:3:5-trichloro-7-methoxyacridine (1 g.) and freshly distilled phenol (5 g.) for 3 hours at 120°. When the reaction mixture, after cooling, was poured into 2N NaOH solution (30 c.c.), a yellow solid separated which crystallised from acetic acid, m.p. 180°. (Found: Cl, 18.3. $C_{21}H_{14}O_2NCl_2$ requires Cl, 18.1%).

3:4-Dichloro-5-phenoxy-7-methoxyacridine was obtained by refluxing 3:4:5-trichloro-7-methoxyacridine (1 g.) with phenol (5 g.), as mentioned above, m.p. 153°. (Found: Cl, 18.4. $C_{21}H_{14}O_2NCl_2$ requires Cl, 18.1%).

7-Methoxy-2:3-dichloro-5-(4-diethylamino-1-methylbutyl)amino-acridine dihydrochloride was prepared by heating the mixture of the acid chloride of 3′:4′-dichloro-4-methoxydiphenylamine-2-carboxylic acid (1 g.), dry benzene (30 c.c.) and 4-diethylamino-1-methylbutylamine (0.5 g.) for half an hour. $POCl_3$ (3 c.c.) was then added to the reaction mixture and refluxed for 6 hours. After removing benzene, the residue was twice washed with petroleum ether to remove excess of $POCl_3$. The dark red residue was extracted with absolute alcohol, from which a yellow solid separated on adding acetone. It was then purified by redissolving it in absolute alcohol and reprecipitating by acetone. The dried product melted at 237°. (Found: N, 8.0; Cl, 28.2. $C_{23}H_{31}ON_3Cl_4$ requires N, 8.2; Cl, 28.0%).

Other 5-*N*-substituted aminoacridine derivatives have been obtained by following the method described above and they are summarised in Table I.

TABLE I

[AD stands for aminoacridine dihydrochloride]

S. No.	Product.	M.P.	Mol. formula.	% Chlorine. Found.	Calc.
1.	7-Methoxy-2 :3-dichloro-5-(γ-piperidinopropyl)-AD	158°	$C_{21}H_{23}O_2N_3Cl_2$	16.6	16.5
2.	7-Methoxy-2 :3-dichloro-5-(γ-morpholinopropyl)-AD	238°	$C_{22}H_{27}ON_3Cl_4$	29.2	28.9
3.	2 :3-Dichloro-5-(γ-piperidinopropyl)-AD	254°	$C_{21}H_{25}N_3Cl_4$	31.0	30.9
4.	2 :3-Dichloro-5 (4-diethylamino-1-methylbutyl)-AD	248°	$C_{22}H_{29}N_3Cl_4$	29.9 8.73*	29.9 8.8*

* Refers to nitrogen value.

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