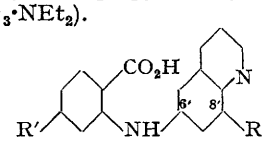
130. *Attempts to find New Antimalarials. Part XXV. Some Derivatives of 3 : 4 : 2′ : 3′-Pyridoacridine substituted in the 2-Position.*

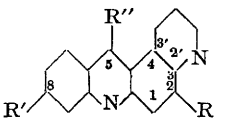
By William C. Hutchison and William O. Kermack.

A number of derivatives of 3 : 4 : 2′ : 3′-pyridoacridine have been prepared containing a chlorine atom in position 2, with and without a chlorine atom simultaneously present in position 8. A further series of derivatives contain a methyl group in position 2 and a chlorine atom in position 8. Of the compounds containing a γ-diethylaminopropylamino-side chain in position 5, the 2-chloro-derivative possessed considerable antimalarial activity, whilst the 2 : 8-dichloro-derivative was markedly active.

The preparation of certain 3 : 4 : 2′ : 3′-pyridoacridine derivatives possessing activity against *P. gallinaceum* in chicks has been described (Dobson and Kermack, *J.*, 1946, 150), and the chemotherapeutic effect was found to be intensified by a chlorine atom in position 8 of the acridine nucleus. It appeared of interest to ascertain the effect of a chlorine atom at position 2, which in the unsubstituted acridine nucleus is equivalent to position 8. To this end 8-*chloro*-6-*amino*-*quinoline* was condensed with *o*-chlorobenzoic acid to yield 8′-chloro-6′-quinolylanthranilic acid (I, R = Cl; R′ = H), purified as its *ethyl* ester. This acid was cyclised by treatment with phosphoryl chloride to 2 : 5-*dichloro*-3 : 4 : 2′ : 3′-*pyridoacridine* (II, R = R″ = Cl; R′ = H) from which 2-*chloro*-3 : 4 : 2′ : 3′-*pyridoacridone* (II, R = Cl; R′ = H; R″ = OH) was prepared by heating with dilute hydrochloric acid. The 2 : 5-dichloro-3 : 4 : 2′ : 3′-pyridoacridine on treatment with γ-diethylaminopropylamine in dry phenol at 100° yielded 2-*chloro*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine* (II, R = Cl; R′ = H; R″ = NH·[CH$_2$]$_3$·NEt$_2$).

(I.)

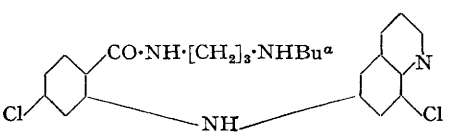




(II.)

The effect of a second chlorine atom in this base was investigated by carrying out a similar series of reactions in which the *o*-chlorobenzoic acid was replaced by 2 : 4-dichlorobenzoic acid. This yielded successively 4 : 8′-*dichloro*-6′-*quinolylanthranilic acid* (I, R = R′ = Cl), 2 : 5 : 8-trichloro-3 : 4 : 2′ : 3′-pyridoacridine (II, R = R′ = R″ = Cl), and 2 : 8-*dichloro*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine* (II, R = R′ = Cl; R″ = NH·[CH$_2$]$_3$·NEt$_2$). 2 : 8-*Dichloro*-5-(γ-*butylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine* (II, R = R′ = Cl; R″ = NH·[CH$_2$]$_3$·NHBu) was obtained from 2 : 5 : 8-trichloro-3 : 4 : 2′ : 3′-pyridoacridine and γ-butylaminopropylamine.

2 : 8-Dichloro-5-(γ-butylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine was also prepared in poor yield by refluxing 4 : 8′-dichloro-6′-quinolylanthranil-(γ-butylaminopropyl)amide (III) (from 4 : 8′-dichloro-6′-quinolylanthranilic acid chloride and γ-butylaminopropylamine)



(III.)

with phosphoryl chloride. This method has previously been used by Drosdov (*J. Gen. Chem. Russia*, 1938, **8**, 1192) in preparing compounds of the mepacrine type.

When 6-amino-8-methylquinoline was condensed with 2 : 4-dichlorobenzoic acid, 4-chloro-(8′-methyl-6′-quinolyl)anthranilic acid (I, R = Me; R′ = Cl) was obtained and purified as its *ethyl* ester, but all attempts to convert this acid directly with phosphoryl chloride into 5 : 8-*dichloro*-2-*methyl*-3 : 4 : 2′ : 3′-*pyridoacridine* (II, R = Me; R′ = R″ = Cl) failed to give a satisfactory product. Most of the material obtained after treatment with dilute sodium hydroxide solution was insoluble in benzene, and the small quantity which did crystallise from benzene gave unsatisfactory analytical results. A two-stage process, however, was successful; the acid was cyclised to 8-*chloro*-2-*methyl*-3 : 4 : 2′ : 3′-*pyridoacridone* (II, R = Me; R′ = Cl; R″ = OH) with warm concentrated sulphuric acid, and, when this pyridoacridone was refluxed with phosphoryl chloride containing phosphorus pentachloride, 5 : 8-dichloro-2-methyl-3 : 4 : 2′ : 3′-pyridoacridine was obtained. Condensation of this compound with γ-diethylamino-propylamine in phenol yielded the expected 8-*chloro*-2-*methyl*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine* (II, R = Me; R′ = Cl; R″ = NH·[CH_2]$_3$·NEt_2).

Antimalarial tests were carried out on *P. gallinaceum* infections of chicks in the Biological Laboratories of Imperial Chemical Industries Ltd. Full details of the biological tests will be published elsewhere. The activities of the compounds prepared are shown in the Table, the activity at various doses being indicated as negative (−), slight (+), or marked (++). For comparison the activities of mepacrine and of 8-chloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine (3652) prepared by Dobson and Kermack (*loc. cit.*) are also shown.

Reference No.	Formula of base.	Dose, mg./kg.	Activity.
—	Mepacrine	40	++
		20	+
3652	II, R = H; R′ = Cl; R″ = NH·[CH_2]$_3$·NEt_2	120	++
		80	+
		40	−
4774	II, R = Cl; R′ = H; R″ = NH·[CH_2]$_3$·NEt_2	120	++
		80	++
		40	−
4602	II, R = R′ = Cl; R″ = NH·[CH_2]$_3$·NEt_2	120	++
		80	++
		40	++
		20	+
5070	II, R = R′ = Cl; R″ = NH·[CH_2]$_3$·NHBu	160	++
		120	++
		80	++
		40	±
5754	II, R = Me; R′ = Cl; R″ = NH·[CH_2]$_3$·NEt_2	80	++
		40	+

It will be seen that the 2-chloro-compound (4774) is at least as active as, if not slightly more active than, the 8-chloro-isomer (3652), and that the 2 : 8-dichloro-compound (4602) is more potent than either of these monochloro-derivatives. The γ-butylaminopropylamino-side chain, which was better than γ-diethylaminopropylamino- in the 8-chloro-series, did not show a corresponding superiority in the 2 : 8-dichloro-series. The methyl group in position 2 appears to increase slightly the antimalarial activity of the 8-chloro-compound, but the toxicity seems also to be considerably raised.

Experimental.

8′-*Chloro*-6′-*quinolylanthranilic Acid*.—8-Chloro-6-aminoquinoline * (21·5 g., m. p. 154°, obtained by reduction of 8-chloro-6-nitroquinoline by West's method (*J.*, 1925, **127**, 494)), potassium *o*-chlorobenzoate (24·5 g.), copper bronze (0·1 g.), and amyl alcohol (40 c.c.) were refluxed for 6 hours in an oil-bath at 150°. The amyl alcohol was removed by filtration, and the residue well washed with acetone and extracted with a large volume of hot dilute ammonia; the filtrate yielded, on acidification with acetic acid, a brown-yellow precipitate of 8′-chloro-6′-quinolylanthranilic acid in relatively small yield. A further quantity was obtained by extracting the residue with 2N-hydrochloric acid on the boiling water-bath and filtering hot. The hydrochloride of the acid separated on cooling; it was suspended in water and made alkaline with ammonia. The yellow residue insoluble in dilute hydrochloric acid evidently consisted of the relatively insoluble hydrochloride of the acid, for on treatment with ammonia it yielded crude 8′-chloro-6′-quinolylanthranilic acid. 8′-Chloro-6′-quinolylanthranilic acid crystallised from alcohol as grey-brown needles, m. p. 256°. Yield, 20·5 g.

For analysis, the ethyl ester was prepared by refluxing the acid (1 g.) with ethyl alcohol (10 c.c.) and

* This *compound* had previously been prepared by Dr. F. H. S. Curd (private communication) who recrystallised it from ethyl acetate–light petroleum (charcoal); it then had m. p. 156—157° (Found : C, 60·55; H, 4·15; Cl, 20·15. $C_9H_7N_2Cl$ requires C, 60·5; H, 3·9; Cl, 19·9%).

concentrated sulphuric acid (3 c.c.) for 2 hours. The cooled solution was poured into ice–water, filtered, the filtrate made alkaline with ammonia, and the yellow oily precipitate extracted with ether. The residue after removal of the ether solidified on treatment with warm dilute aqueous sodium hydrogen carbonate and cooling. *Ethyl 8′-chloro-6′-quinolylanthranilate* crystallised from alcohol as white needles, m. p. 118° (Found: C, 66·25; H, 4·5; N, 8·6. $C_{18}H_{15}O_2N_2Cl$ requires C, 66·2; H, 4·6; N, 8·6%).

2 : 5-*Dichloro*-3 : 4 : 2′ : 3′-*pyridoacridine*.—8′-Chloro-6′-quinolylanthranilic acid (6 g.) and phosphoryl chloride (30 c.c.) were refluxed for 6 hours in an oil-bath at 150°. The excess of phosphoryl chloride was removed by distillation under reduced pressure, and the residue triturated with 2N-sodium hydroxide and ice. The washed residue was dried in a desiccator and extracted in the presence of a pellet of potassium hydroxide with benzene which had been dried over sodium. The *pyridoacridine* crystallised easily from dry benzene as yellow needles, m. p. 208°. Yield, 4·7 g. (Found: C, 64·75; H, 2·6; N, 9·6; Cl, 23·5. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; N, 9·4; Cl, 23·7%).

2-*Chloro*-3 : 4 : 2′ : 3′-*pyridoacridone*.—2 : 5-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine was heated for 2 hours at 100° with N-hydrochloric acid. The bright yellow compound formed, evidently the hydrochloride (m. p. >400°), changed to light yellowish-brown on treatment with ammonia, and the filtrate gave a reaction for chloride ions. The *pyridoacridone* crystallised from alcohol as yellow needles, m. p. over 400° (Found: C, 67·4; H, 3·6; N, 9·9. $C_{16}H_9ON_2Cl,\frac{1}{4}H_2O$ requires C, 67·4; H, 3·3; N, 9·8%).

2-Chloro-3 : 4 : 2′ : 3′-pyridoacridone was also produced by refluxing 2 : 5-dichloro-3 : 4 : 2′ : 3′-pyridoacridine with ethyl alcohol, even though the latter contained less than 1% of water (cf. Dobson and Kermack, *loc. cit.*).

2-*Chloro*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*.—2 : 5-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) and γ-diethylaminopropylamine (1 g.) were heated in dry molten phenol at 100° for 2 hours (cf. Dobson and Kermack, *loc. cit.*). The cooled phenol mixture was poured into 2N-sodium hydroxide and the yellow oily precipitate extracted with ether. The base was purified by shaking the ethereal extract with 5% acetic acid, reprecipitating with ammonia, and re-extracting with ether. This ethereal extract was dried (K_2CO_3) and the ether distilled off. The residual brownish-red oily solid was heated at 100° in a vacuum to remove excess of γ-diethylaminopropylamine and the sticky solid which remained dissolved in hot dry ligroin. 2-*Chloro*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*, which separated from the filtered solution on cooling, crystallised after 2 days at room temperature. Yield, 0·7 g., m. p. 109°. Twice recrystallised from dry ligroin, it had m. p. 115° (Found: C, 69·9; H, 6·4; N, 13·95. $C_{23}H_{25}N_4Cl$ requires C, 70·3; H, 6·4; N, 14·3%).

4 : 8′-*Dichloro*-6′-*quinolylanthranilic Acid*.—8-Chloro-6-aminoquinoline (12 g.), potassium 2 : 4-dichlorobenzoate (15·3 g.), amyl alcohol (16·7 c.c.), and copper bronze (0·1 g.) were heated under reflux for 6 hours in an oil-bath at 150°. The product was worked up exactly as described for 8′-chloro-6′-quinolylanthranilic acid. Yield, 12·3 g. The *acid* crystallised from alcohol as white needles, m. p. 300°. This acid like the other quinolylanthranilic acids was difficult to purify, and even a sample recrystallised several times showed a trace of ash [Found: C, 56·6; H, 3·35; N, 8·65; ash, 0·5 (approx.). $C_{16}H_{10}O_2N_2Cl_2,\frac{1}{2}H_2O$ requires C, 56·1; H, 3·2; N, 8·2%].

2 : 5 : 8-*Trichloro*-3 : 4 : 2′ : 3′-*pyridoacridine*.—4 : 8′-Dichloro-6′-quinolylanthranilic acid (6 g.) was refluxed with phosphoryl chloride (30 c.c.) as described above for 8′-chloro-6′-quinolylanthranilic acid. Yield, 3 g. The product even after repeated recrystallisations from dry benzene (brown-yellow needles, m. p. 286°) was not analytically pure, but was used for condensation with γ-diethylaminopropylamine and γ-butylaminopropylamine. This failure to obtain 2 : 5 : 8-trichloro-3 : 4 : 2′ : 3′-pyridoacridine pure was an example in an acute form of the general difficulty of purification encountered with almost all 5-chloropyridoacridines.

The residue insoluble in benzene appeared to consist largely of 2 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridone, for when 5 g. of it were refluxed with phosphoryl chloride (25 c.c.) containing phosphorus pentachloride (3·3 g.) for 6 hours in an oil-bath at 150° and the product worked up as described above, some 2 : 5 : 8-trichloro-3 : 4 : 2′ : 3′-pyridoacridine was obtained. Yield, 1 g.; m. p. 268—269°.

2 : 8-*Dichloro*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*.—2 : 5 : 8-Trichloro-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) and γ-diethylaminopropylamine (1 g.) were heated in dry molten phenol (10 g.) for 2 hours at 100°. The cooled phenol mixture was poured into 2N-sodium hydroxide (30 c.c.) and the brown precipitate filtered off, washed, extracted with 5% acetic acid, filtered, and the filtrate basified with ammonia to give a yellow precipitate which was filtered off, washed, and dried in a desiccator. The dry material was crystallised from dry ligroin yielding the *pyridoacridine* as yellow needles, m. p. 144°. Yield, 0·6 g. (Found: C, 64·45; H, 5·7; N, 13·1. $C_{23}H_{24}N_4Cl_2$ requires C, 64·6; H, 5·6; N, 13·1%).

2 : 8-*Dichloro*-5-(γ-*butylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*. (*a*) 2 : 5 : 8-Trichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·5 g.) was condensed with γ-butylaminopropylamine (0·25 g.) in dry molten phenol as described for 2 : 8-dichloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine. The *pyridoacridine* crystallised from dry ligroin as yellow needles, m. p. 131°. Yield, 0·2 g. (Found: C, 64·55; H, 5·7; N, 13·05. $C_{23}H_{24}N_4Cl_2$ requires C, 64·6; H, 5·6; N, 13·1%).

(*b*) Thionyl chloride (2·4 g.) was dissolved in chloroform (10 c.c.) which had been dried over phosphoric oxide, and the solution added to a suspension of 4 : 8′-dichloro-6′-quinolylanthranilic acid (6 g.) in dry chloroform (80 c.c.). The mixture was maintained at room temperature for 3½ hours and then boiled under reflux for a further hour. The chloroform and excess of thionyl chloride were then removed by distillation and the bright yellow residue, presumably 4 : 8′-dichloro-6′-quinolylanthranilic acid chloride, was dissolved in dry chloroform (34 c.c.). A solution of γ-butylaminopropylamine (2·6 g.) in dry chloroform (10 c.c.) was added and the mixture heated under reflux for 1 hour. A small amount of white sublimate formed in the condenser melted at 325° but was not identified. The chloroform solution was filtered and the chloroform removed from the filtrate leaving a dark reddish-brown oil, probably 4 : 8′-dichloro-6′-quinolylanthranil-(γ-butylaminopropyl)amide hydrochloride. This was refluxed with phosphoryl chloride (20 c.c.) for 2 hours in an oil-bath at 150°; hydrogen chloride was evolved. The excess of phosphoryl chloride was removed under reduced pressure and the thick dark red oil remaining was dissolved in ice–water. The brown solution so obtained was filtered and the filtrate made alkaline

with ammonia; crude 2 : 8-dichloro-5-(γ-monobutylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine was thus obtained as a yellowish solid in poor yield and was crystallised from ligroin, m. p. 130°. A mixed melting point with a sample prepared by method (*a*) was not depressed.

6-*Nitro*-8-*methylquinoline*.—Concentrated sulphuric acid (440 c.c.) was added to water (343 c.c.) and to this diluted acid were added 5-nitro-*o*-toluidine (100 g.), glycerol (176 c.c.), and arsenic acid (194·5 c.c of 65% As_2O_5 solution). The mixture was brought slowly to the boil and refluxed gently for 8 hours at the end of which no unchanged amine could be detected by the diazo-test. After cooling it was diluted with its own volume of water and basified with 10N-sodium hydroxide. The precipitate of 6-nitro-8-methylquinoline was filtered off, dried at 70° (yield, 97 g.), and crystallised from alcohol and then from benzene as whitish needles, m. p. 130° (Found : C, 63·75; H, 4·25. Calc. for $C_{10}H_8O_2N_2$: C, 63·8; H, 4·3%).

6-*Amino*-8-*methylquinoline*.—6-Nitro-8-methylquinoline (30·4 g.) was dissolved in boiling methylated spirit (100 c.c.) containing concentrated hydrochloric acid (5 c.c.), and iron filings (34 g.) were added in four portions at five-minute intervals. The mixture was kept boiling vigorously for two hours, the acid neutralised with 10N-sodium hydroxide solution, and the mixture then filtered hot and the residue well washed with hot spirit. The alcohol was distilled off on the water-bath and the residue crystallised from benzene to yield 6-amino-8-methylquinoline as buff-coloured needles, m. p. 129°. Yield, 20 g. Alternatively, the final crystallisation may be made from alcohol.

For analysis 6-*acetamido*-8-*methylquinoline* was prepared by heating 6-amino-8-methylquinoline (1 g.) with acetic anhydride (10 c.c.) under an air condenser for 2 hours in the water-bath. The mixture was poured into cold water, and a blue fluorescence then appeared. Addition of ammonia gave a cream precipitate which was filtered off, washed, and dried at 70°. The compound recrystallised from hot water in glistening white plates, m. p. 174—174·5° (Found : C, 71·95; H, 5·75. $C_{12}H_{12}ON_2$ requires C, 72·0; H, 6·0%).

4-*Chloro*-(8′-*methyl*-6′-*quinolyl*)*anthranilic Acid*.—6-Amino-8-methylquinoline (31·8 g.), potassium 2 : 4-dichlorobenzoate (46·2 g.), copper bronze (0·1 g.), and amyl alcohol (60 c.c.) were heated under reflux in an oil-bath at 150° for 6 hours. The amyl alcohol was removed by filtration, and the residue well washed with acetone and extracted with a large volume of hot dilute ammonia. Alternatively, the amyl alcohol can be removed by distillation in steam and the residue filtered off and extracted with ammonia as before. Acidification of the ammoniacal extract with acetic acid yielded a small amount of the required acid (8%). A further yield was obtained from the residue insoluble in ammonia, which was found to be completely soluble in hot 2N-hydrochloric acid. On cooling, the hydrochloride of the acid separated, was filtered off and dissolved in hot 2N-hydrochloric acid, and ammonia added to precipitate the acid (72%) as a pale yellow compound which crystallised from alcohol as buff-coloured needles, m. p. 275°. Total yield, 48 g.

The *ethyl* ester was prepared by refluxing the acid (0·5 g.), ethyl alcohol (10 c.c.), and concentrated sulphuric acid (4 c.c.) for 1 hour. The mixture was allowed to cool, poured on ice, and, after ½ hour, made alkaline with ammonia. The grey precipitate so produced recrystallised from alcohol in light brown needles, m. p. 74° (Found : C, 66·8; H, 5·1; N, 8·1. $C_{19}H_{17}O_2N_2Cl$ requires C, 67·0; H, 5·0; N, 8·2%).

8-*Chloro*-2-*methyl*-3 : 4 : 2′ : 3′-*pyridoacridone*.—4-Chloro-(8′-methyl-6′-quinolyl)anthranilic acid (5 g.) and concentrated sulphuric acid (50 c.c.) were mixed in a round-bottomed flask, maintained at 100° for 4 hours, allowed to cool, and poured on ice. The yellow-brown precipitate, presumably the sulphate of the *pyridoacridone*, was filtered off, suspended in water, and excess of ammonia added. The flocculent precipitate was separated, washed, dried, and crystallised from alcohol as yellow needles, m. p. 383° (decomp.) (Found : C, 67·6; H, 3·9; N, 9·65. $C_{17}H_{11}ON_2Cl,\frac{1}{2}H_2O$ requires C, 67·2; H, 4·0; N, 9·2%).

5 : 8-*Dichloro*-2-*methyl*-3 : 4 : 2′ : 3′-*pyridoacridine*.—8-Chloro-2-methyl-3 : 4 : 2′ : 3′-pyridoacridone (10 g.), phosphorus pentachloride (4 g.), and phosphoryl chloride (60 c.c.) were refluxed for 6 hours in an oil-bath at 150°. The product was worked up as described for 2 : 5-dichloro-3 : 4 : 2′ : 3′-pyridoacridine. The crude product (10 g., m. p. 217—218°), crystallised from dry benzene, gave yellow needles of the *pyridoacridine*, m. p. 232°. Yield, 6 g. (Found : C, 65·75; H, 3·5; N, 8·7; Cl, 21·5. $C_{17}H_{10}N_2Cl_2$ requires C, 65·2; H, 3·2; N, 8·95; Cl, 22·7%).

8-*Chloro*-2-*methyl*-5-(γ-*diethylaminopropylamino*)-3 : 4 : 2′ : 3′-*pyridoacridine*.—This *compound* was prepared from 5 : 8-dichloro-2-methyl-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) and γ-diethylaminopropylamine (0·5 g.) in dry phenol (10 g.) as described under the preparation of 2 : 8-dichloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine. Yield, 0·4 g.; m. p. 110° (Found : C, 70·3; H, 6·45; N, 13·9. $C_{24}H_{27}N_4Cl$ requires C, 70·9; H, 6·6; N, 13·8%).

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