42. *Attempts to find New Antimalarials. Part XXIII. Derivatives of 3 : 4 : 2′ : 3′-Pyridoacridine and 1 : 2 : 2′ : 3′-Pyridoacridine.*

By James Dobson and William O. Kermack.

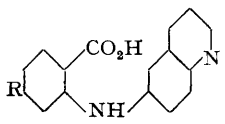
(6′-Quinolyl)anthranilic acid and 4-chloro-(6′-quinolyl)anthranilic acid (from 6-aminoquinoline and *o*-chlorobenzoic acid or 2 : 4-dichlorobenzoic acid) have been cyclised to yield 5-*chloro*-3 : 4 : 2′ : 3′-*pyridoacridine* and 5 : 8-*dichloro*-3 : 4 : 2′ : 3′-*pyridoacridine* respectively. By condensing these compounds with the appropriate dialkylaminoalkylamine, a series of derivatives of 3 : 4 : 2′ : 3′-pyridoacridine has been obtained carrying a basic side-chain in the 5-position. These all show a definite antimalarial activity when tested on *P. gallinaceum* infections of chicks, and this action is particularly marked when a chlorine atom is present in the 8-position of the acridine nucleus. From 8-aminoquinoline or 8-amino-6-methoxyquinoline on the one hand and *o*-chlorobenzoic acid or 2 : 4-dichlorobenzoic acid on the other, 5-*chloro*-1 : 2 : 2′ : 3′-*pyridoacridine* and its 8-*chloro*-, 4-*methoxy*-, and 8-*chloro*-4-*methoxy*-derivatives have been synthesised. The chlorine atom in position 5 in these four compounds has been replaced by diethylaminoethylamino and diethylamino*iso*amylamino groups, but none of the bases of this series, tested biologically, showed antimalarial activity.

The chief synthetic antimalarial compounds, plasmoquin (pamaquin) and atebrin (mepacrine hydrochloride), are derivatives of quinoline and acridine respectively, and both carry the same basic side-chain, namely, diethylamino*iso*amylamino. Extensive investigations have shown that antiplasmodial activity is retained when the structure of the side-chain is varied over wide limits. In the quinoline series, the side-chain need not be in the 8-position as in plasmoquin, for compounds with the side-chain in position 4 or 6 are also stated to be active to some extent. So far, however, attempts to obtain active compounds of the same general type as atebrin and plasmoquin, but based on some other heterocyclic nucleus have not been very successful. For example, various phenanthridine derivatives have been prepared by Walls (*J.*, 1934, 104; 1935, 1405), but these were without antimalarial activity, and derivatives of *p*- and *m*-phenanthroline have been prepared by Kermack and Weatherhead (*J.*, 1940, 1164) and Kermack and Webster (*J.*, 1942, 213) but none of those tested showed unambiguous activity. Certain compounds of the same general class derived from benzoquinoline and *p*- and *m*-phenanthroline are described in the patent literature (B.P. 451,932, 454,525, 481,874; G.P. 668,968) and in one or two instances claims of action on blood parasites are made.

The object of the work now described was to prepare a series of pyridoacridine derivatives carrying a basic side-chain in the 5-position of the acridine nucleus, the position corresponding with that which it occupies in atebrin. 6-Aminoquinoline was condensed in amyl alcohol solution with potassium 2 : 4-dichlorobenzoate (1 mol.) in presence of a trace of copper bronze. When the resulting 4-chloro-(6′-quinolyl)anthranilic acid (I; R = Cl) was refluxed with phosphorus oxychloride it was cyclised and converted into 5 : 8-*dichloro*-3 : 4 : 2′ : 3′-*pyridoacridine* (II; R = Cl, R′ = Cl). The latter was somewhat difficult to purify because of the ease with which the 5-chlorine atom was hydrolysed with the formation of the 8-*chloro*-5-*hydroxypyridoacridine* (II; R = Cl, R′ = OH), or in the alternative isomeric form, 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone (III; R = Cl). For example, when refluxed in ethyl alcohol containing less than one per cent. of water, it dissolved, but on cooling a crystalline material separated, shown to be 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone hydrochloride, and partial hydrolysis occurred even on refluxing with ordinary benzene. The chloropyridoacridone was rapidly formed from the dichloropyridoacridine when it was boiled with dilute mineral acid; but the dichloro-pyridoacridine is very stable in the presence of dilute sodium hydroxide. In keeping with this stability to alkali, the 5-chloro-pyridoacridines reacted very slowly when heated or refluxed with bases such as diethylaminoethylamine, but the reaction proceeded satisfactorily in phenol solution, as with 5-chloroacridine and its derivatives (cf. B.P. 363,392). In this way, 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine was condensed with the following bases: diethylaminoethylamine, diethylaminopropylamine, 2-amino-5-diethylaminopentane, dimethylaminopropylamine, butylaminopropylamine and diethylaminobutylamine. Of the resulting compounds 8-*chloro*-5-(β-*diethylaminoethyl*)*amino*-, 8-*chloro*-5-(γ-*diethylaminopropyl*)*amino*-, 8-*chloro*-5-(γ-*dimethylaminopropyl*)*amino*-, and 8-*chloro*-5-(γ-*butylaminopropyl*)*amino*-3 : 4 : 2′ : 3′-*pyridoacridine* were isolated as crystalline solids; the others were obtained as thick oils which were purified through their *picrates* or *dinitrobenzoates*, from which the bases could be readily recovered on decomposing with sodium hydroxide and extracting with ether.

These bases resemble atebrin in containing a chlorine atom in the 8-position of the acridine nucleus: it was of interest to prepare compounds analogous to the above but without the chlorine atom. 6-Aminoquinoline was condensed with *o*-chlorobenzoic acid and the resulting (6′-quinolyl)anthranilic acid (I; R = H) cyclised with phosphorus oxychloride to yield 5-*chloro*-3 : 4 : 2′ : 3′-*pyridoacridine* (II; R = H, R′ = Cl), a compound which was readily hydrolysed in presence of dilute mineral acid to give 3 : 4 : 2′ : 3′-*pyridoacridone*,

but which was very stable to alkali. This acridone was also prepared directly from (6′-quinolyl)-anthranilic acid by treatment with concentrated sulphuric acid at 100°. 5-Chloropyridoacridine was readily condensed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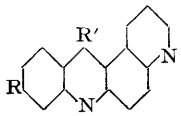
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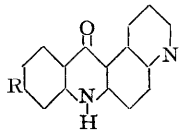
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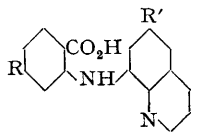
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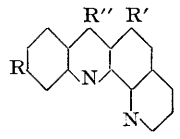
(V.)

in phenol solution with diethylaminoethylamine and 2-amino-5-diethylaminopentane with the formation of the corresponding *bases* (II; R = H, R′ = NH·[CH_2]$_2$·NEt_2, NH·CHMe·[CH_2]$_3$·NEt_2) of which the former was obtained as a crystalline solid, whilst the latter was isolated as the *picrate*.

In addition to the bases containing the 3 : 4 : 2′ : 3′-pyridoacridine nucleus, some derivatives have also been prepared of the isomeric 1 : 2 : 2′ : 3′-pyridoacridine. 8-Aminoquinoline was condensed with *o*-chlorobenzoic acid and with 2 : 4-dichlorobenzoic acid to yield (8′-quinolyl)anthranilic acid (IV; R = H, R′ = H) and 4-chloro-(8′-quinolyl)anthranilic acid (IV; R = Cl, R′ = H) respectively. These acids are readily cyclised with phosphorus oxychloride to form *5-chloro-* (V; R = H, R′ = H, R″ = Cl) and *5 : 8-dichloro-*1 : 2 : 2′ : 3′-*pyridoacridine* (V; R = Cl, R′ = H, R″ = Cl). Like the 5-chloropyridoacridines of the previous series, these compounds undergo hydrolysis of the 5-chlorine atom very readily, 1 : 2 : 2′ : 3′-*pyridoacridone*, and its 8-*chloro*-derivative being formed on heating to 100° with mineral acid, and even on refluxing for 1—2 hrs. with alcohol. 1 : 2 : 2′ : 3′-Pyridoacridone is also formed on heating the (8′-quinolyl)-anthranilic acid with sulphuric acid on the boiling water bath.

An analogous series of compounds was obtained when 8-aminoquinoline was replaced by 8-amino-6-methoxyquinoline. In this way there were prepared (6′-methoxy-8′-quinolyl)anthranilic acid (IV; R = H, R′ = OMe) and 4-chloro-(6′-methoxy-8′-quinolyl)anthranilic acid (IV; R = Cl, R′ = OMe) which yielded *5-chloro-4-methoxy-*1 : 2 : 2′ : 3′-*pyridoacridine* (V; R = H, R′ = OMe, R″ = Cl) and *5 : 8-dichloro-4-methoxy-*1 : 2 : 2′ : 3′-*pyridoacridine* (V; R = Cl, R′ = OMe, R″ = Cl) respectively, and also the corresponding *4-methoxy-*1 : 2 : 2′ : 3′-*pyridoacridone* and *8-chloro-4-methoxy-*1 : 2 : 2′ : 3′-*pyridoacridone*. In general, these resembled in appearance and properties the analogous compounds without the methoxy group.

5-Chloro-1 : 2 : 2′ : 3′-pyridoacridine and its 8-chloro-, 4-methoxy-, and 8-chloro-4-methoxy-derivatives have been condensed with β-diethylaminoethylamine and 2-amino-5-diethylaminopentane. Thus the following eight bases have been synthesised: 5-(β-diethylaminoethyl)amino-1 : 2 : 2′ : 3′-pyridoacridine, 5-(δ-diethylamino-α-methylbutyl)amino-1 : 2 : 2′ : 3′-pyridoacridine, 8-*chloro*-5-(β-*diethylaminoethyl*)*amino*-1 : 2 : 2′ : 3′-*pyridoacridine*, 8-*chloro*-5-(δ-*diethylamino*-α-*methylbutyl*)*amino*-1 : 2 : 2′ : 3′-*pyridoacridine*, 5-(β-diethylaminoethyl)-amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine, 5-(δ-diethylamino-α-methylbutyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine, 8-*chloro*-5-(β-*diethylaminoethyl*)*amino*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* and 8-chloro-5-(δ-diethylamino-α-methylbutyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine. These were analysed either as free bases or as *picrates*.

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 some of the compounds are shown in the Table, the activity at various doses being indicated as negative (−), slight (+) or marked (++).

Reference No.	Formula of base.	Dose, mg./kg.	Activity.
M.3574	V; R = R′ = H, R″ = NH·CHMe·[CH_2]$_3$·NEt_2	125	−
M.3476	V; R = Cl, R′ = H, R″ = NH·[CH_2]$_2$·NEt_2	125	−
M.3303	V; R = Cl, R′ = H, R″ = NH·CHMe·[CH_2]$_3$·NEt_2	125	−
M.3599	V; R = H, R′ = OMe, R″ = NH·CHMe·[CH_2]$_3$·NEt_2	125	−
M.3477	V; R = Cl, R′ = OMe, R″ = NH·[CH_2]$_2$·NEt_2	125	−
M.3533	V; R = Cl, R′ = OMe, R″ = NH·CHMe·[CH_2]$_3$·NEt_2	200	−
		125	±
M.3302	II; R = H, R′ = NH·[CH_2]$_2$·NEt_2	125	+
M.3561	II; R = H, R′ = NH·CHMe·[CH_2]$_3$·NEt_2	125	+
		80	+
M.4582	II; R = Cl, R′ = NH·[CH_2]$_4$·NEt_2	120	+
		80	+
		40	−
M.3652	II; R = Cl, R′ = NH·[CH_2]$_3$·NEt_2	120	++
		80	+
		40	−
M.3902	II; R = Cl, R′ = NH·[CH_2]$_3$·NMe_2	120	++
		40	+
M.3304	II; R = Cl, R′ = NH·[CH_2]$_2$·NEt_2	125	++
M.3555	II; R = Cl, R′ = NH·CHMe·[CH_2]$_3$·NEt_2	125	++
		80	++
		40	+
M.4344	II; R = Cl, R′ = NH·[CH_2]$_3$·NHBu	120	++
		40	+
		20	±

It will be seen that the derivatives of 1 : 2 : 2′ : 3′-pyridoacridine are inactive, and that all the bases containing the 3 : 4 : 2′ : 3′-pyridoacridine nucleus exhibit antimalarial activity. This is relatively feeble in the absence of a chlorine atom in the 8-position but, when this chlorine atom is present, all the bases tested are relatively potent.

Experimental.

4-Chloro-(6′-quinolyl)anthranilic Acid.—Potassium 2 : 4-dichlorobenzoate (45·8 g.), 6-aminoquinoline (28·8 g.), amyl alcohol (50 c.c.) and copper bronze (0·3 g.) were refluxed in an oil bath at 150° for 6 hours. The brown residue was separated and washed with acetone. The solid material was dissolved in a large volume of hot dilute ammonia solution and, after filtering, the filtrate was acidified with acetic acid giving a brown–yellow precipitate of 4-chloro-(6′-quinolyl)-anthranilic acid in relatively small yield. A further quantity was obtained by treating the residue with hot 2N-HCl and filtering the hot solution. The orange hydrochloride of 4-chloro-(6′-quinolyl)anthranilic acid separated, and, after filtration, was suspended in water and carefully neutralised with ammonia. The acid (42·3 g.) was crystallised from ethyl alcohol in yellow needles, m. p. 266°. 4-Chloro-(6′-quinolyl)anthranilic acid was soluble in cold dilute alkali and in hot alcohol and benzene. It gave sodium or potassium salts, separating from concentrated sodium or potassium hydroxide solutions.

The ethyl ester was prepared by refluxing the acid (3 g.) with ethyl alcohol (20 c.c.) and concentrated sulphuric acid (10 c.c.) for 4 hours. The cooled solution was poured into ice-water, filtered and made alkaline with ammonia. A dark red oily substance separated which solidified (2·3 g.) on treatment with dilute sodium bicarbonate solution. *Ethyl 4-chloro-(6′-quinolyl)anthranilate*, crystallised twice from ethyl alcohol, had m. p. 108° (Found: C, 65·9; H, 4·45; N, 8·6; Cl, 11·15. $C_{18}H_{15}O_2N_2Cl$ requires C, 66·2; H, 4·6; N, 8·6; Cl, 10·9%). This ester was also prepared through the acid chloride by dissolving the acid in dry chloroform, adding a slight excess of thionyl chloride, allowing to stand for 4 hours and then refluxing for one hour. On removing the chloroform a crystalline product, evidently the hydrochloride of the acid chloride remained, which, on treatment with warm ethyl alcohol, was immediately converted into the ethyl ester identical with that obtained by direct esterification. The ester was soluble in dilute acid and insoluble in dilute alkali.

5 : 8-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine.—4-Chloro-(6′-quinolyl)anthranilic acid (7 g.) was refluxed with phosphoryl chloride (30 c.c.) in an oil bath at 150° for 4 hours. The excess phosphoryl chloride was distilled away under reduced pressure and the brown residue, after trituration with cold 20% sodium hydroxide, yielded *5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine* as a pale brown crystalline solid. It was important to add the powdered residue in small quantities to the sodium hydroxide solution in such a way that neutralisation of any acid took place immediately and without local heating; otherwise a considerable proportion of the dichloro-compound might be hydrolysed to the acridone. The dichloropyridoacridine was separated, washed till neutral and dried (4·9 g.). Three crystallisations from dry benzene yielded pale yellow needles, m. p. 219° (Found: C, 64·1; H, 2·8; N, 9·5; Cl, 23·8. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; N, 9·4; Cl, 23·75%). 5 : 8-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine exhibited a green fluorescence in alcohol and benzene solutions; it was soluble in dilute acid and insoluble in alkali. When heated at 100° for 2 hours with 2N-NaOH it was unchanged. It was very readily converted on treatment with hot dilute acid into 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone and even prolonged boiling with neutral solvents such as alcohol and benzene containing traces of water caused hydrolysis of the 5-chlorine atom. For this reason the benzene used for recrystallisation of this and analogous 5-chloropyridoacridines described below had to be carefully dried and, even with such precautions, it was difficult to obtain these chloropyridoacridines pure enough for analysis.

8-Chloro-3 : 4 : 2′ : 3′-pyridoacridone.—5 : 8-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) was heated at 100° with N-HCl (10 c.c.) for 2 hours, a yellow crystalline compound, m. p. 386—387°, separating. It was the hydrochloride of 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone since, when treated with dilute alkali, a pale brown solid, m. p. 295—296°, was produced. When crystallised from ethyl alcohol, *8-chloro-3 : 4 : 2′ : 3′-pyridoacridone* separated in fine needles, m. p. 298° (Found: N, 9·6. $C_{16}H_9ON_2Cl$ requires N, 10·0%). The chloropyridoacridone hydrochloride was also obtained by refluxing 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine with ethyl alcohol for one hour. The yellow crystalline solid, treated with dilute alkali, yielded 8-chloro-3 : 4 : 2′ : 3′-pyridoacridone, m. p. 296°. 8-Chloro-3 : 4 : 2′ : 3′-pyridoacridone was very soluble in concentrated sulphuric acid in which it exhibited a marked green fluorescence. The solution in alcohol had a slight green fluorescence. The compound was only very slightly soluble in dilute mineral acid and was insoluble in dilute acetic acid and dilute alkali.

8-Chloro-5-phenoxy-3 : 4 : 2′ : 3′-pyridoacridine.—Carefully dried 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (6 g.) was added to freshly distilled molten phenol (24 g.), previously heated under reduced pressure for an hour at 100°, and the solution heated at 160° for 4 hours. The phenol mixture was poured into 2N-NaOH (150 c.c.) and the brown solid separated. After drying, this was treated with hot dry ligroin which left a small quantity of chloropyridoacridone undissolved. On cooling the *8-chloro-5-phenoxy-3 : 4 : 2′ : 3′-pyridoacridine* separated in pale orange needles, m. p. 218° (Found: C, 74·0; H, 3·55; N, 8·05. $C_{22}H_{13}ON_2Cl$ requires C, 74·1; H, 3·65; N, 7·9%). Its solutions in organic solvents and in dilute acid exhibited green fluorescence. When heated at 100° for 2 hours with dilute sodium hydroxide it remained unchanged. Like the dichloro-pyridoacridine, it was hydrolysed to the acridone when heated with dilute acid.

8-Chloro-5-(β-diethylaminoethyl)amino-3 : 4 : 2′ : 3′-pyridoacridine.—To redistilled phenol (4 g., dried in a vacuum at 100° for 2 hours) β-diethylaminoethylamine (0·3 g.) was added, and the mixture dried as before for another hour. If these precautions to remove traces of water were not taken a large proportion of the dichloropyridoacridine was converted to the chloropyridoacridone and the yield of the desired base correspondingly reduced. 5 : 8-Dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g., dried in the desiccator) was introduced and the dark red-brown mixture heated at 100° under reflux for 2 hours; it then showed the presence of chlorine ions. The cooled phenol mixture was poured into 2N-NaOH (30 c.c.) and the brown precipitate extracted with ether. The base was purified from admixed chloropyridoacridone by shaking the ethereal solution with 5% acetic acid, reprecipitating with ammonia and re-extracting with ether. This ethereal extract was dried with potassium carbonate and, after removing the ether by distillation, the residual red-brown oily solid was heated at 100° under reduced pressure to remove excess ethylamine base. The residual *8-chloro-5-(β-diethylaminoethyl)amino-3 : 4 : 2′ : 3′-pyridoacridine* was dissolved in hot dry ligroin and, on cooling, separated in pale yellow micro-needles. These were crystallised twice from dry ligroin and had m. p. 127° (Found: C, 68·6; H, 6·05; Cl, 9·15. $C_{22}H_{23}N_4Cl,\frac{1}{4}H_2O$ requires C, 68·9; H, 6·1; Cl, 9·3%). The base exhibited a marked green fluorescence in alcohol and in ether. It was soluble in dilute acids with the formation of the corresponding salts which exhibited a green fluorescence in solution. Unless otherwise stated all the succeeding bases had similar properties.

8-Chloro-5-(γ-diethylaminopropyl)amino-3 : 4 : 2′ : 3′-pyridoacridine was prepared from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and γ-diethylaminopropylamine (0·3 g.) in phenol (4 g.) as described above. The base (0·4 g.) separated from hot ligroin in yellow needles, m. p. 119·5—120° (Found: N, 13·8. $C_{23}H_{25}N_4Cl,H_2O$ requires N, 13·65%). The base exhibited a faint blue fluorescence in very dilute alcoholic, ethereal and acid solutions.

8-Chloro-5-(δ-diethylamino-α-methylbutyl)amino-3 : 4 : 2′ : 3′-pyridoacridine was prepared from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and 2-amino-5-diethylaminopentane (0·35 g.) in phenol (4 g.) under anhydrous conditions. This base (0·47 g.) could not be obtained crystalline; it yielded a solid acetate, m. p. 76—78°. The *picrate*, obtained by adding an ethereal solution of picric acid to a solution of the base in ether, crystallised from ethyl alcohol in yellow needles, m, p. 216° (Found : C, 46·3; H, 3·75; N, 16·35; Cl, 3·85. $C_{25}H_{29}N_4Cl,3C_6H_3O_7N_3$ requires C, 46·6; H, 3·4; N, 16·4; Cl, 3·2%).

8-*Chloro*-5-(γ-*dimethylaminopropyl*)*amino*-3 : 4 : 2′ : 3′-*pyridoacridine*, from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and γ-dimethylaminopropylamine (0·25 g.) in phenol (4 g.), crystallised from ligroin in yellow needles (0·4 g.), m. p. 127° (Found : C, 68·95; H, 6·0; N, 15·05. $C_{21}H_{21}N_4Cl$ requires C, 69·1; H, 5·8; N, 15·4%).

8-*Chloro*-5-(γ-*butylaminopropyl*)*amino*-3 : 4 : 2′ : 3′-*pyridoacridine*, from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and γ-butylaminopropylamine (0·3 g.) in phenol (4 g.), crystallised from ligroin in yellow needles (0·43 g.), m. p. 78° (Found : C, 67·0; H, 6·1; N, 13·3. $C_{23}H_{25}N_4Cl,H_2O$ requires C, 67·2; H, 6·6; N, 13·65%).

8-Chloro-5-(δ-diethylaminobutyl)amino-3 : 4 : 2′ : 3′-pyridoacridine, from 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine (0·6 g.) and δ-diethylaminobutylamine (0·35 g.) in phenol (4 g.). The base (0·45 g.) was not obtained crystalline, but yielded a *picrate*, which crystallised from ethyl alcohol in small yellow needles, m. p. 168° (Found : C, 45·05; H, 4·05; N, 16·15. $C_{24}H_{27}N_4Cl,3C_6H_3O_7N_3,H_2O$ requires C, 45·3; H, 3·4; N, 16·4%). The base yielded a 3 : 5-*dinitrobenzoate* which crystallised from ethanol in small pale yellow needles, m. p. 233° (Found : C, 53·8; H, 4·2; N, 13·6. $C_{24}H_{27}N_4Cl.2C_7H_4O_6N_2,H_2O$ requires C, 53·8; H, 4·4; N, 13·2%). This dinitrobenzoate was conveniently used for purifying the base.

(6′-*Quinolyl*)*anthranilic Acid*.—Potassium *o*-chlorobenzoate (19·5 g.), 6-aminoquinoline (14·4 g.), amyl alcohol (30 c.c.) and copper bronze (0·1 g.) were refluxed at 150° for 6 hours. The brown solid was separated, washed with cold acetone and dissolved in a large volume of hot dilute ammonia. When the hot filtered solution was carefully acidified with acetic acid the (6′-quinolyl)anthranilic acid (16·2 g.) separated as a yellow solid. The acid crystallised from ethyl alcohol in pale yellow needles, m. p. 246—247°, and closely resembled 4-chloro-(6′-quinolyl)anthranilic acid in general properties. The ethyl ester was prepared by refluxing the acid (3 g.) with a mixture of ethanol (20 c.c.) and concentrated sulphuric acid (10 c.c.). The alcoholic solution was poured into ice-water, the orange solution filtered and the filtrate basified with ammonia; the ester separated as a pale yellow crystalline solid (2·2 g.). *Ethyl* (6′-*quinolyl*)*anthranilate* crystallised from ethanol in pale yellow needles, m. p. 92·5° (Found : C, 73·5; H, 5·2; N, 9·75. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). The ester was soluble in dilute acid and insoluble in dilute alkali.

5-*Chloro*-3 : 4 : 2′ : 3′-*pyridoacridine*.—(6′-Quinolyl)anthranilic acid (6 g.) was refluxed with phosphoryl chloride (30 c.c.) at 150° for 4 hours. The excess phosphoryl chloride was distilled under reduced pressure from the dark brown solution and the brown residue triturated with cold 20% sodium hydroxide. The same precautions to prevent hydrolysis to the acridone were observed as for 5 : 8-dichloro-3 : 4 : 2′ : 3′-pyridoacridine. The 5-*chloro*-3 : 4 : 2′ : 3′-*pyridoacridine* (4·6 g.) was separated, washed until neutral and recrystallised from dry benzene in pale brown-yellow needles, m. p. 181·5—182° (Found : C, 70·9; H, 3·5; N, 10·5; Cl, 13·4. $C_{16}H_9N_2Cl,\frac{1}{4}H_2O$ requires C, 71·4; H, 3·5; N, 10·4; Cl, 13·2%). 5-Chloro-3 : 4 : 2′ : 3′-pyridoacridine is soluble in alcohol, benzene and cold dilute acid. When heated at 100° for 2 hours with 2N-NaOH it did not dissolve and remained unchanged. It was very unstable to hot acids or even neutral solvents containing water, the acridone being formed.

3 : 4 : 2′ : 3′-*Pyridoacridone*.—When 5-chloro-3 : 4 : 2′ : 3′-pyridoacridine (1 g.) was heated at 100° with N-HCl (10 c.c.) for 2 hours a pale yellow crystalline compound separated which did not melt below 360°. It was evidently a hydrochloride for when treated with dilute alkali a light brown solid (0·84 g.), free from chlorine, was obtained which melted at 357°. The 3 : 4 : 2′ : 3′-*pyridoacridone*, crystallised from ethanol, had m. p. 360° (Found : N, 10·5. $C_{16}H_{10}ON_2,H_2O$ requires N, 10·6%). This compound was also obtained directly by heating (6′-quinolyl)-anthranilic acid (2 g.) with concentrated sulphuric acid (10 c.c.) at 100° for 4 hours. The acid solution, having a marked green fluorescence, was cooled and poured into ice-water. When the filtered dark orange solution was made alkaline with sodium hydroxide 3 : 4 : 2′ : 3′-pyridoacridone, m. p. 358°, separated. 3 : 4 : 2′ : 3′-Pyridoacridone is highly soluble in conc. sulphuric acid, sparingly soluble in dilute acid and insoluble in dilute alkali.

5-(β-*Diethylaminoethyl*)*amino*-3 : 4 : 2′ : 3′-*pyridoacridine* was prepared by condensing 5-chloro-3 : 4 : 2′ : 3′-pyridoacridine (0·5 g.) with β-diethylaminoethylamine (0·3 g.) in dry phenol (4 g.) at 100°, the usual care being taken to remove water. The product was isolated as in previous cases. The base (0·41 g.) crystallised from ligroin in pale yellow needles, m. p. 92° (Found : C, 76·45; H, 7·4; N, 16·1. $C_{22}H_{24}N_4$ requires C, 76·7; H, 7·0; N, 16·3%).

5-(δ-Diethylamino-α-methylbutyl)amino-3 : 4 : 2′ : 3′-pyridoacridine, prepared from 5-chloro-3 : 4 : 2′ : 3′-pyridoacridine (0·5 g.) and 2-amino-5-diethylaminopentane (0·35 g,) in dry phenol (4 g.), was isolated as usual. The non-crystalline base (0·46 g.) formed a *picrate* which crystallised from ethanol in bright yellow needles, m. p. 121° (Found : C, 48·5; H, 4·4; N, 15·9. $C_{25}H_{30}N_4,2C_6H_3O_7N_3,3H_2O$ requires C, 49·5; H, 4·7; N, 15·6%).

(8′-*Quinolyl*)*anthranilic Acid*.—Potassium *o*-chlorobenzoate (9·7 g.) 8-aminoquinoline (7·2 g.), amyl alcohol (15 c.c.) and copper bronze (0·1 g.) were refluxed together in an oil bath at 150° for 6 hours. The dark brown solid was separated, washed with cold acetone and dissolved in a large volume of hot dilute ammonia. The solution was filtered and the yellow filtrate acidified with acetic acid. (8′-Quinolyl)anthranilic acid separated as a yellow precipitate (8·8 g.). It crystallised from ethanol in pale yellow needles, m. p. 243—244°. (8′-Quinolyl)anthranilic acid is soluble in pyridine and dilute alkali. From more concentrated alkali, a relatively insoluble sodium or potassium salt tends to separate. It is insoluble in dilute acid. The *methyl ester* was prepared by refluxing the acid (3 g.) with methanol (20 c.c.) and concentrated sulphuric acid (8 c.c.) for 2 hours. The solution was poured into ice-water, the orange solution filtered, the filtrate basified with ammonia and the pale yellow solid (2·7 g.) collected. The ester, crystallised from ethyl alcohol, had m. p. 142—143° (Found : C, 74·1; H, 4·8; N, 10·1. $C_{17}H_{14}O_2N_2$ requires C, 73·4; H, 5·0; N, 10·1%). The ester is soluble in dilute acid and insoluble in dilute alkali.

5-*Chloro*-1 : 2 : 2′ : 3′-*pyridoacridine*.—(8′-Quinolyl)anthranilic acid (6 g.) and phosphoryl chloride (30 c.c.) were refluxed at 140° for 4 hours. The phosphoryl chloride was removed by distillation under reduced pressure and the solid residue triturated with cold 20% sodium hydroxide solution, the usual precautions being taken to avoid hydrolysis to the acridone. The brown-yellow solid (4·4 g.) was filtered off, washed until neutral and crystallised from dry benzene. 5-*Chloro*-1 : 2 : 2′ : 3′-*pyridoacridine* separated in small pale yellow needles, m. p. 165° (Found : C, 68·0; H, 3·7; Cl, 12·3. $C_{16}H_9N_2Cl,H_2O$ requires C, 68·0; H, 3·9; Cl, 12·6%). It is soluble in cold dilute acid and insoluble in dilute alkali. When heated at 100° with 2N-NaOH for 2 hours it remained unaltered. Like the chloropyridoacridines of the previous series, it is very unstable when heated with acids or even neutral solvents containing moisture, the acridone being produced.

1 : 2 : 2′ : 3′-*Pyridoacridone*.—When 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine (0·5 g.) was heated with N-HCl (8 c.c.) for 2 hours an orange yellow solid (0·4 g.), m. p. 273°, separated. This was the base 1 : 2 : 2′ : 3′-*pyridoacridone* and not the hydrochloride, as might have been expected. Crystallised from ethanol, it had m. p. 275—276° (Found : C, 77·8; H, 4·4; N, 11·0. $C_{16}H_{10}ON_2$ requires C, 78·0; H, 4·1; N, 11·4%). 1 : 2 : 2′ : 3′-Pyridoacridone was also prepared by heating (8′-quinolyl)anthranilic acid (2 g.) with concentrated sulphuric acid (8 c.c.) for 4 hours at 100°

The solution was poured into ice-water, the filtered solution made alkaline with sodium hydroxide and the greenish-yellow solid (1·2 g.), m. p. 273°, separated. It did not depress the m. p. of the 1 : 2 : 2′ : 3′-pyridoacridone from the previous experiment. 1 : 2 : 2′ : 3′-Pyridoacridone is very soluble in conc. sulphuric acid in which it exhibits a marked green fluorescence, sparingly soluble in dilute acid and insoluble in dilute alkali.

4-Chloro-(8′-quinolyl)anthranilic acid, prepared from 8-aminoquinoline (28·8 g.), potassium 2 : 4-dichlorobenzoate (45·8 g.), amyl alcohol (60 c.c.) and copper bronze (0·5 g.) refluxed at 150° for 6 hours, was isolated in the usual way. Crystallised from ethyl alcohol, it was obtained as small pale yellow needles, m. p. 239—240°. It closely resembled (8′-quinolyl)anthranilic acid in general properties. The *ethyl ester* was prepared by refluxing the acid (5 g.) with ethanol (25 c.c.) and concentrated sulphuric acid (10 c.c.); it was isolated in the usual manner as a yellow oil which was extracted with ether. After drying the extract, the ether was removed by distillation; the oily residue solidified when gently warmed with sodium bicarbonate solution. Crystallised from ethanol, the ester formed pale yellow monoclinic crystals, m. p. 103° (Found: C, 66·1; H, 4·7; N, 8·65; Cl, 11·5. $C_{18}H_{15}O_2N_2Cl$ requires C, 66·2; H, 4·6; N, 8·6; Cl, 10·9%). It is soluble in conc. mineral acid, slightly soluble in dilute acid, and insoluble in dilute alkali.

5 : 8-*Dichloro*-1 : 2 : 2′ : 3′-*pyridoacridine*, prepared by refluxing 4-chloro-(8′-quinolyl)anthranilic acid (8 g.) with phosphoryl chloride (30 c.c.) at 150° for 4 hours, was isolated as described for the monochloropyridoacridine. Crystallised from dry benzene it had m. p. 238° (Found: C, 63·5; H, 2·9; N, 9·2; Cl, 23·7. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; N, 9·4; Cl, 23·75%). The properties of this compound closely resembled those of 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine.

8-*Chloro*-1 : 2 : 2′ : 3′-*pyridoacridone*, prepared by heating 5 : 8-dichloro-1 : 2 : 2′ : 3′-pyridoacridine (1 g.) with N-HCl (10 c.c.) at 100° for 2 hours, crystallised from ethanol in small yellow needles, m. p. 311° (Found: C, 67·35; H, 3·4; N, 10·15; Cl, 12·65. $C_{16}H_9ON_2Cl$ requires C, 68·4; H, 3·2; N, 10·0; Cl, 12·65%). It closely resembled 1 : 2 : 2′ : 3′-pyridoacridone in general properties.

(6′-Methoxy-8′-quinolyl)anthranilic acid, prepared from 8-amino-6-methoxyquinoline (17·4 g.), potassium *o*-chlorobenzoate (19·5 g.), amyl alcohol (30 c.c.) and copper bronze (0·2 g.) refluxed at 150° for 4 hours, was isolated as described for (8′-quinolyl)-anthranilic acid. Crystallised from ethanol, the acid (18·8 g.) separated in yellow needles, m. p. 201°. It closely resembled (8′-quinolyl)anthranilic acid in general properties. The *ethyl ester* was prepared by refluxing the acid (5 g.) with ethyl alcohol (25 c.c.) and sulphuric acid (10 c.c.) and pouring into ice-water. The yellow crystalline ester was crystallised from ethanol; it had m. p. 91° (Found: C, 70·6; H, 5·95; N, 8·85. $C_{19}H_{18}O_3N_2$ requires C, 70·8; H, 5·6; N, 8·7%). Its properties resembled those of ethyl (8′-quinolyl)anthranilate.

5-*Chloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine*, prepared from (6′-methoxy-8′-quinolyl)anthranilic acid (6 g.) and phosphoryl chloride (30 c.c.) refluxed at 150° for 4 hours, was isolated as described for 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine. It crystallised from dry benzene in pale yellow needles (4·8 g.), m. p. 169° (Found: C, 67·7; H, 4·2; N, 9·85; Cl, 11·9. $C_{17}H_{11}ON_2Cl,\frac{1}{2}H_2O$ requires C, 67·2; H, 3·95; N, 9·2; Cl, 11·7%). It closely resembled 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine in general properties.

4-*Methoxy*-1 : 2 : 2′ : 3′-*pyridoacridone*.—When 5-chloro-4-methoxy-1 : 2 : 2′ : 3-pyridoacridine (1 g.) and N-HCl (10 c.c.) were heated at 100° for 2 hours the orange hydrochloride (m. p. 298—299°) separated; on making the mixture alkaline the *acridone* was obtained. After crystallisation from ethanol the canary yellow needles had m. p. 245·5° (Found: C, 72·9; H, 4·6; N, 10·3. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·35; N, 10·15%). The properties of this compound closely resembled those of 1 : 2 : 2′ : 3′-pyridoacridone.

4-Chloro-(6′-methoxy-8′-quinolyl)anthranilic acid was prepared by refluxing potassium 2 : 4-dichlorobenzoate (22·9 g.), 8-amino-6-methoxyquinoline (17·4 g.), amyl alcohol (30 c.c.) and copper bronze (0·2 g.) at 150° for 4 hours. The purification of this acid was carried out similarly to that of (8′-quinolyl)-anthranilic acid. It crystallised from ethanol in small yellow needles (18·8 g.), m. p. 258—259°. It resembled (8′-quinolyl)anthranilic acid in general properties. The *ethyl ester* was produced by refluxing the acid (5 g.) with ethyl alcohol (25 c.c.) and sulphuric acid (10 c.c.) and isolated in the usual manner. The yellow solid (4·1 g.) was crystallised from ethanol and obtained in pale yellow needles, m. p. 111° (Found: C, 63·35; H, 4·85; N, 8·1; Cl, 10·0. $C_{19}H_{17}O_3N_2Cl$ requires C, 63·95; H, 4·8; N, 7·85; Cl, 9·95%). The ester closely resembled ethyl (8′-quinolyl)anthranilate in general properties.

5 : 8-*Dichloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyrodoacridine* was obtained by refluxing 4-chloro-(6′-methoxy-8′-quinolyl)-anthranilic acid (6 g.) and phosphoryl chloride (30 c.c.) at 150° for 4 hours and isolated as described for 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine. It crystallised from dry benzene in pale brown-yellow needles (4·5 g.), m. p. 196—197° (Found: N, 8·8. $C_{17}H_{10}ON_2Cl_2$ requires N, 8·5%). The properties of this compound closely resembled those of 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine.

8-*Chloro*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridone*, obtained from 5 : 8-dichloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (1 g.) and N-HCl (10 c.c.) at 100°, separated as the hydrochloride (m. p. 310—312°) for, when treated with alkali, the acridone was obtained. The acridone crystallised from alcohol in yellow needles, m. p. 257—258° (Found: C, 64·3; H, 3·55; N, 9·25; Cl, 11·65. $C_{17}H_{11}O_2N_2Cl,\frac{1}{4}H_2O$ requires C, 64·8; H, 3·65; N, 8·9; Cl, 11·3%). It resembled 1 : 2 : 2′ : 3′-pyridoacridone in general properties.

The following bases were prepared by heating the appropriate 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine and diethylaminoalkylamine in dry phenol for 2 hours at 100° with the same precautions as described for the preparation of 8-chloro-5-(β-diethylaminoethyl)amino-3 : 4 : 2′ : 3′-pyridoacridine (p. 152). The bases were separated from admixed pyridoacridone by extracting the ethereal solution with dilute acetic acid. The base precipitated from the acid solution by the addition of ammonia was extracted with ether and, after drying, the ether was removed by distillation.

5-(β-Diethylaminoethyl)amino-1 : 2 : 2′ : 3′-pyridoacridine was prepared from 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine (0·5 g.) and β-diethylaminoethylamine (0·3 g.) in phenol (4 g.). The non-crystalline base yielded a crystalline *picrate* which crystallised from ethanol in small bright yellow needles, m. p. 196° (Found: C, 49·8; H, 4·15; N, 17·4. $C_{22}H_{24}N_4,2C_6H_3O_7N_3,H_2O$ requires C, 49·8; H, 3·9; N, 17·1%).

5-(δ-Diethylamino-α-methylbutyl)amino-1 : 2 : 2′ : 3′-pyridoacridine was obtained from 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine (0·5 g.) and 2-amino-5-diethylaminopentane (0·4 g.) in dry phenol (4 g.). The non-crystalline base (0·45 g.) yielded a *picrate* which crystallised from ethanol in bright yellow needles, m. p. 198° (Found: C, 52·35; H, 4·35; N, 16·7. $C_{25}H_{30}N_4,2C_6H_3O_7N_3$ requires C, 52·6; H, 4·3; N, 16·6%).

8-*Chloro*-5-(β-*diethylaminoethyl*)*amino*-1 : 2 : 2′ : 3′-*pyridoacridine* was prepared from 5 : 8-dichloro-1 : 2 : 2′ : 3′-pyridoacridine (0·6 g.) and β-diethylaminoethylamine (0·3 g.) in phenol (4 g.). The base (0·42 g.) crystallised from ligroin in small pale yellow needles, m. p. 131° (Found: C, 69·8; H, 6·15. $C_{22}H_{23}N_4Cl$ requires C, 69·75; H, 6·1%). It exhibited a marked blue fluorescence, persisting to high dilutions, in alcoholic and ethereal solutions. Its solution in dilute acids exhibited only a very faint blue fluorescence.

8-*Chloro*-5-(δ-*diethylamino*-α-*methylbutyl*)*amino*-1 : 2 : 2′ : 3′-*pyridoacridine* (0·48 g.), obtained from 5 : 8-dichloro-1 : 2 : 2′ : 3′-pyridoacridine (0·6 g.) and 2-amino-5-diethylaminopentane (0·4 g.) in phenol (4 g.), crystallised from dry ligroin in pale yellow needles, m. p. 118° (Found: C, 71·8; H, 6·85; Cl, 8·0. $C_{25}H_{29}N_4Cl$ requires C, 71·35; H, 6·9; Cl, 8·4%). The base yielded a crystalline *hydrobromide*, m. p. 282° (Found: C, 42·85; H, 5·3; N, 7·6; Ag halides from 1 mg. of compound, 0·999 mg. $C_{25}H_{29}N_4Cl,3HBr,2H_2O$ requires C, 42·9; H, 5·2; N, 8·0%; Ag halides, 1·012 mg.). This hydrobromide was very soluble in water and exhibited a marked green fluorescence even at high dilution.

5-(β-Diethylaminoethyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine was obtained from 5-chloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·6 g.) and β-diethylaminoethylamine (0·3 g.) in dry phenol (4 g.). The non-crystalline base (0·46 g.) yielded a *picrate* which crystallised from alcohol and had m. p. 118° (Found: C, 47·25; H, 4·45. $C_{23}H_{26}ON_4,2C_6H_3O_7N_3,3H_2O$ requires C, 47·4; H, 4·3%).

5-(δ-Diethylamino-α-methylbutyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine, obtained from 5-chloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·6 g.) and 2-amino-5-diethylaminopentane (0·4 g.) in phenol (4 g.), did not crystallise but yielded a crystalline *picrate* which crystallised from alcohol in small bright yellow needles, m. p. 201° (Found : C, 52·2; H, 4·4; N, 16·15. $C_{26}H_{32}ON_4,2C_6H_3O_7N_3$ requires C, 52·2; H, 4·35; N, 16·0%).

8-*Chloro*-5-(β-*diethylaminoethyl*)*amino*-4-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* (0·42 g.), obtained from 5 : 8-dichloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·65 g.) and β-diethylaminoethylamine (0·3 g.) in phenol (4 g.), crystallised from dry ligroin in small pale yellow needles, m. p. 152° (Found : C, 68·2; H, 6·15; Cl, 8·75. $C_{23}H_{25}ON_4Cl$ requires C, 67·6; H, 6·1; Cl, 8·7%). In alcohol and in ether it exhibited a marked blue fluorescence persisting at high dilution. The fluorescence almost entirely disappeared when the solutions were made acid.

8-Chloro-5-(δ-diethylamino-α-methylbutyl)amino-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine, obtained from 5 : 8-dichloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·65 g.) and 2-amino-5-diethylaminopentane (0·4 g.) in phenol (4 g.), did not crystallise from ligroin but yielded a crystalline *picrate* which crystallised from alcohol in orange-yellow needles (1·1 g.), m. p. 158—159° (Found : C, 50·4; H, 4·3; N, 15·35; Cl, 4·3. $C_{26}H_{31}ON_4Cl,2C_6H_3O_7N_3$ requires C, 50·2; H, 4·1; N, 15·4; Cl, 3·9%).

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