32. *Attempts to find New Antimalarials. Part XXVII. Derivatives of Various Benzacridines and Pyridoacridines.*

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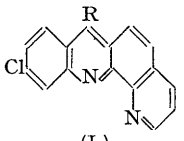
In view of the pronounced antimalarial activity of derivatives of 3 : 4 : 2′ : 3′-pyridoacridine containing a chlorine atom in position 8 and a basic side chain in position 5 of the acridine nucleus, analogous derivatives have been prepared of 3 : 4-benzacridine and 3 : 4 : 3′ : 2′-pyridoacridine. The benzacridine derivative was active whilst the new pyridoacridine was only doubtfully so. Corresponding derivatives of 1 : 2-benzacridine and of 1 : 2 : 3′ : 2′-pyridoacridine have also been prepared, but these like the already known 1 : 2 : 2′ : 3′ pyridoacridine derivatives were without significant antimalarial activity.

In a previous paper (Dobson and Kermack, *J.*, 1946, 150) an account has been given of the preparation of derivatives of 1 : 2 : 2′ : 3′-pyridoacridine and 3 : 4 : 2′ : 3′-pyridoacridine carrying in position 5 of the acridine nucleus a basic side chain of the type present in mepacrine. It was reported that tests in chicks infected with *P. gallinaceum* had demonstrated that certain derivatives of 3 : 4 : 2′ : 3′-pyridoacridine such as 8-chloro-5-(γ-diethylaminopropylamino)-3 : 4 : 2′ : 3′-pyridoacridine (II, R = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$) evinced considerable antimalarial activity in this test, but that the corresponding 1 : 2 : 2′ : 3′-pyridoacridine (I, R = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$) was inactive. Evidently the position of the additional pyridine ring has a great effect on the antimalarial activity.

It seemed desirable in the light of these results to prepare the corresponding benzacridines. When this work was begun, no compounds of the type envisaged appeared to have been made,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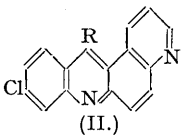
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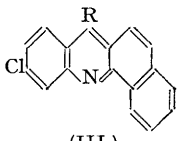
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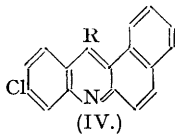
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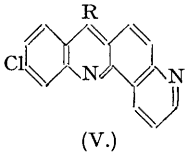
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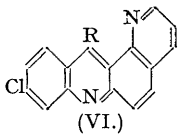
(VI.)

but since its completion a paper has appeared by Bachman and Picha (*J. Amer. Chem. Soc.*, 1946, **68**, 1599) describing the synthesis of various benzacridines from α- and β-naphthylamine. Only three of our compounds happen to have been prepared by the American workers; these are derived from α-naphthylamine and 2 : 4-dichlorobenzoic acid. None of the bases prepared by Bachman and Picha possessed antimalarial activity.

As the chlorine atom in position 8 of the acridine nucleus appeared important, 2 : 4-dichlorobenzoic acid rather than *o*-chlorobenzoic acid was employed in our work. This acid was condensed with α-naphthylamine to yield 4-chloro-2-α-naphthylaminobenzoic acid which readily cyclised on boiling with phosphoryl chloride to 5 : 8-dichloro-1 : 2-benzacridine (III, R = Cl) (cf. Bachman and Picha, *loc. cit.*). A similar series of reactions starting from β-naphthylamine and 2 : 4-dichlorobenzoic acid gave 4-*chloro*-2-β-*naphthylaminobenzoic acid* and 5 : 8-*dichloro*-3 : 4-*benzacridine* (IV, R = Cl). The condensation of the two dichlorobenzacridines with diethylaminoalkylamines was carried out in phenol solution, and in this way the two bases, 8-*chloro*-5-(γ-*diethylaminopropylamino*)-1 : 2-*benzacridine* (III, R = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$) and 8-*chloro*-5-(δ-*diethylamino*-α-*methylbutylamino*)-3 : 4-*benzacridine* (IV, R = $NH{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$) were obtained.

As shown in the table of biological results given below, the 3 : 4-benzacridine derivative was active, whilst the representative of the 1 : 2-benzacridine series was without antimalarial activity. This latter result agrees with that reported by Bachman and Picha (*loc. cit.*). It appeared that the position in which the extra ring was fused on was of greater importance than the nature of the ring whether pyridine or benzene.

It seemed that further useful information on the relation between structure and chemotherapeutic action in this group of compounds might be obtained by the preparation and biological testing of suitable derivatives of 1 : 2 : 3′ : 2′-pyridoacridine and 3 : 4 : 3′ : 2′-pyridoacridine. The simplest route for synthesising these appeared to be from 5- and 7-aminoquinoline respectively. The synthesis of 8-*chloro*-5-(γ-*diethylaminopropylamino*)-1 : 2 : 3′ : 2′-*pyridoacridine* (V, R = $NH{\cdot}[CH_2]_3{\cdot}NEt_2$) from 5-aminoquinoline and 2 : 4-dichlorobenzoic acid went smoothly through 4-*chloro*-5′-*quinolylanthranilic acid* and 5 : 8-*dichloro*-1 : 2 : 3′ : 2′-*pyridoacridine* (V, R = Cl), the condensation of the latter compound with γ-diethylaminopropylamine yielding the crystalline base. From 7-aminoquinoline and 2 : 4-dichlorobenzoic acid, 4-chloro-7′-quinolylanthranilic acid, purified as its *ethyl* ester, was obtained, and cyclised with phosphoryl chloride containing phosphorus pentachloride to 5 : 8-dichloro-3 : 4 : 3′ : 2′-pyridoacridine. The product, which after repeated crystallisations contained some admixed 8-chloro-3 : 4 : 3′ : 2′-pyridoacridone, was condensed with γ-diethylaminopropylamine to yield a product which separated from ligroin as an apparently homogeneous crystalline base, m. p. 99—100°, but was shown on analysis to possess the composition $3C_{23}H_{25}N_4Cl,C_{16}H_9ON_2Cl,3H_2O$.

This product lost water on drying over anhydrone under reduced pressure at room temperature. When the dried product was recrystallised several times from dry heptane, a crystalline *base*, m. p. 69—70°, was obtained, which analysed in accordance with the formula $C_{23}H_{25}N_4Cl,H_2O$. It must be assumed that this compound has a high affinity for 1 molecule of water which was not lost on drying over anhydrone under reduced pressure.

The two benzacridine bases fluoresced green in both alcohol and ether; the new pyridoacridine bases, green in alcohol but blue in ether, the fluorescence of 8-chloro-5-(γ-diethylaminopropylamino)-1 : 2 : 3′ : 2′-pyridoacridine in ether being a particularly vivid light blue.

Antimalarial tests were carried out on *P. gallinaceum* infections of chicks in the Biological Laboratories of Imperial Chemical Industries Ltd. Full details will be published elsewhere. The activities of the compounds prepared are shown in the Table, the activity of various doses being indicated as nil (—), doubtful (±), slight (+), or marked (++). For comparison the activities of the corresponding derivatives of 1 : 2 : 2′ : 3′-pyridoacridine and of 3 : 4 : 2′ : 3′-pyridoacridine prepared by Dobson and Kermack (*loc. cit.*) are also shown.

Ref. No.	Base.	Dose, mg./kg.	Activity.
4574	(III) R = NH·[CH_2]$_3$·NEt_2	320	Toxic
		160	—
4377	(IV) R = NH·CHMe·[CH_2]$_3$·NEt_2	120	++
		40	—
5941	(V) R = NH·[CH_2]$_3$·NEt_2	160	Toxic
		80	± (Toxic)
6443	(VI) R = NH·[CH_2]$_3$·NEt_2	160	± (Toxic)
		80	—
3476	(I) R = NH·[CH_2]$_3$·NEt_2	125	—
3652	(II) R = NH·[CH_2]$_3$·NEt	120	++
		80	+
		40	—
—	Mepacrine	40	++
		20	+

Of the two benzacridines and four pyridoacridines listed the most active base is that derived from 3 : 4 : 2′ : 3′-pyridoacridine. The analogous 3 : 4-benzacridine has also considerable activity, but the base derived from 3 : 4 : 3′ : 2′-pyridoacridine (in non-lethal doses) has only doubtful activity. The only 3 : 4-benzacridine base available contained the 5-diethylamino-α-methylbutylamino-side chain, but analogous results in the pyridoacridine series suggest that there would be little difference between this and the compound with the γ-diethylaminopropylamino-side chain. The benzacridine and the two pyridoacridines in which the extra ring is fused on to the 1 : 2 position of the acridine nucleus are all devoid of significant antimalarial activity. Compound No. 6443 [8-chloro-5-(γ-diethylaminopropylamino)-3 : 4 : 3′ : 2′-pyridoacridine] was tested in the form of the hydrated crystals, m. p. 99—100°, which contained about 25% of 8-chloro-3 : 4 : 3′ : 2′-pyridoacridone; the failure of the 3 : 4 : 3′ : 2′-pyridoacridine base to be significantly active shows that the geometrical form of the heterocyclic nucleus, though evidently important, is only one factor out of several which determine the chemotherapeutic activity. All the compounds shown in the Table contain a chlorine atom in position 8 of the acridine nucleus; without this substituent even the 3 : 4 : 2′ : 3′-pyridoacridine base has only slight activity.

Experimental.

5 : 8-*Dichloro*-1 : 2-*benzacridine*.—Potassium 2 : 4-dichlorobenzoate (45·8 g.), α-naphthylamine (28·6 g.), amyl alcohol (50 c.c.), and copper bronze (0·3 g.) were refluxed at 150° for 6 hours. After cooling, the violet solid was filtered off, washed with acetone and dissolved in hot dilute ammonia, the solution filtered, and the filtrate made acid with acetic acid; 4-chloro-2-α-naphthylaminobenzoic acid was then precipitated. Yield, 48·3 g. Pale violet needles from alcohol, m. p. 232°. (Bachman and Picha, *loc. cit.*, give m. p. 236—237·5°.) This acid (24 g.) and phosphoryl chloride (100 c.c.) were refluxed at 150° for 4 hours. The excess of phosphoryl chloride was removed under reduced pressure, and the residue triturated with 2N-sodium hydroxide and ice. The solid residue was separated, dried in a desiccator, and crystallised from dry benzene. Yield, 18 g.; m. p. 192—193°. Further recrystallisation from dry benzene raised the m. p. to 201°. Bachman and Picha (*loc. cit.*) give m. p. 201—202° (Found C, 68·5; H, 2·85; N, 4·7. Calc. for $C_{17}H_9NCl_2$: C, 68·45; H, 3·0; N, 4·7%).

8-*Chloro*-5-(γ-*diethylaminopropylamino*)-1 : 2-*benzacridine*.—This was prepared from 5 : 8-dichloro-1 : 2-benzacridine (6 g.) and γ-diethylaminopropylamine (3·5 g.) in dry phenol (50 g.) at 100° for 2 hours. The base was isolated by pouring the phenol mixture into 2N-sodium hydroxide (300 c.c.), extracting the oily solid with ether, shaking the ethereal extract with 5% acetic acid, and reprecipitating with ammonia. The *base* was finally extracted with ether, the ether extract dried (K_2CO_3), and the ether removed by distillation. The residual oily solid was boiled with dry ligroin and separated as a yellow crystalline solid on cooling. It was further purified from dry ligroin, and the yellow needles melted at 113° (Found :

C, 73·8; H, 6·4; N, 10·6. $C_{24}H_{26}N_3Cl$ requires C, 73·6; H, 6·6; N, 10·7%). Bachman and Picha (*loc. cit.*) describe the dihydrochloride, m. p. 253—255°.

4-*Chloro*-2-*β*-*naphthylaminobenzoic Acid.*—This was prepared from potassium 2 : 4-dichlorobenzoate (45·8 g.) and β-naphthylamine (28·6 g.) in amyl alcohol (50 c.c.) with copper bronze (0·3 g.) at 150° for 6 hours. The *acid* was isolated as described for the α-acid. Yield, 45·4 g. Pale violet needles from alcohol, m. p. 272° (Found : C, 68·2; H, 4·3; N, 4·8. $C_{17}H_{12}O_2NCl$ requires C, 68·6; H, 4·0; N, 4·7%).

5 : 8-*Dichloro*-3 : 4-*benzacridine.*—This was prepared from 4-chloro-2-β-naphthylaminobenzoic acid (16 g.) and phosphoryl chloride (60 c.c.) at 150° for 4 hours. The product was isolated as described for 5 : 8-dichloro-1 : 2-benzacridine. Yield, 11·6 g. 5 : 8-*Dichloro*-3 : 4-*benzacridine* recrystallised from dry benzene to yield pale orange-yellow needles, m. p. 175—176° (Found : C, 68·9; H, 2·9; N, 4·9%).

8 - *Chloro*-5 - (*δ* - *diethylamino* - *α* - *methylbutylamino*) - 3 : 4-*benzacridine.*—This was prepared from 5 : 8-dichloro-3 : 4-benzacridine (5 g.) and δ-diethylamino-α-methylbutylamine (3·5 g.) in dry phenol (50 g.) at 100° for 2 hours. The base, an oil, was isolated as described above, and yielded a crystalline *picrate* which recrystallised from ethyl alcohol in canary-yellow needles, m. p. 176° (Found : C, 51·8; H, 4·1; N, 14·65. $C_{26}H_{30}N_3Cl,2C_6H_3O_7N_3$ requires C, 52·0; H, 4·1; N, 14·4%).

4-*Chloro*-5′-*quinolylanthranilic Acid.*—5-Aminoquinoline (7·4 g.) and potassium 2 : 4-dichlorobenzoate (11·4 g.) were condensed in amyl alcohol (10 c.c.) in the presence of copper bronze (0·1 g.) as described for 4-chloro-2-α-naphthylaminobenzoic acid. The product after removal of the amyl alcohol by steam distillation was filtered off, extracted with 2N-potassium hydroxide on the boiling water-bath, filtered, and the filtrate made acid with acetic acid. The precipitate after being filtered off and dried crystallised from alcohol as yellow-brown needles, m. p. 244°. Yield, 8·2 g. (Found : C, 61·4; H, 3·8; N, 9·25. $C_{16}H_{11}O_2N_2Cl,\frac{3}{4}H_2O$ requires C, 61·5; H, 4·0; N, 9·0%).

5 : 8-*Dichloro*-1 : 2 : 3′ : 2′-*pyridoacridine.*—4-Chloro-5′-quinolylanthranilic acid (5 g.) was refluxed with phosphoryl chloride (30 c.c.) containing phosphorus pentachloride (0·5 g.) for 6 hours in an oil-bath at 150°. The product was worked up as described for 5 : 8-dichloro-1 : 2-benzacridine, except that during crystallisation from dry benzene a pellet of potassium hydroxide was added to prevent hydrolysis to 8-chloro-1 : 2 : 3′ : 2′-pyridoacridone. 5 : 8-*Dichloro*-1 : 2 : 3′ : 2′-*pyridoacridine* formed buff-coloured needles, m. p. 244°. Yield, 3·7 g. (Found : C, 63·9; H, 2·85; Cl, 24·0. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; Cl, 23·7%).

8-*Chloro* - 5 - (*γ* - *diethylaminopropylamino*) - 1 : 2 : 3′ : 2′ - *pyridoacridine.*—5 : 8 - Dichloro-1 : 2 : 3′ : 2′-pyridoacridine (1 g.) and γ-diethylaminopropylamine (1 g.) were condensed in dry molten phenol at 100° as described for 8-chloro-5-(γ-diethylaminopropylamino)-1 : 2-benzacridine. 8-*Chloro*-5-(*γ*-*diethylaminopropylamino*)-1 : 2 : 3′ : 2′-*pyridoacridine* forms bright yellow needles from ligroin, m. p. 98—99° (Found : C, 70·5; H, 6·35; N, 14·1; Cl, 9·15. $C_{23}H_{25}N_4Cl$ requires C, 70·3; H, 6·4; N, 14·3; Cl, 9·0%).

4-*Chloro*-7′-*quinolylanthranilic Acid.*—7-Aminoquinoline (14·8 g.) and potassium 2 : 4-dichlorobenzoate (22·8 g.) were condensed in amyl alcohol (20 c.c.) in the presence of copper bronze as described for 4-chloro-5′-quinolylanthranilic acid. The product proved very difficult to crystallise, but a brown compound, m. p. 289°, was obtained from a fairly concentrated alcoholic solution. This material (0·5 g.) was refluxed gently for 1 hour with ethanol (10 c.c.) and concentrated sulphuric acid (4 c.c.). The mixture was allowed to cool, poured on ice, left for ½ hour, and made alkaline with ammonia. The resulting precipitate crystallised from alcohol as brownish needles of *ethyl* 4-*chloro*-7′-*quinolylanthranilate*, m. p. 76—77° (Found : C, 66·6; H, 4·8; N, 8·35. $C_{18}H_{15}O_2N_2Cl$ requires C, 66·2; H, 4·6; N, 8·6%).

5 : 8-*Dichloro*-3 : 4 : 3′ : 2′-*pyridoacridine.*—4-Chloro-7′-quinolylanthranilic acid (15 g.) was refluxed with phosphoryl chloride (90 c.c.) containing phosphorus pentachloride (1·5 g.) for 6 hours at 150° as described for 5 : 8-dichloro-1 : 2 : 3′ : 2′-pyridoacridine. The product consisted of light brown needles, m. p. 209°. Repeated recrystallisations failed to alter the m. p., but the compound on analysis proved to contain 8-chloro-1 : 2 : 3′ : 2′-pyridoacridone possibly as a molecular complex (Found : C, 65·2; H, 2·95; N, 9·2; Cl, 21·2. $C_{16}H_8N_2Cl_2$ requires C, 64·2; H, 2·7; N, 9·4; Cl, 23·7. $3C_{16}H_8N_2Cl_2,C_{16}H_9ON_2Cl$ requires C, 65·2; H, 2·8; N, 9·5; Cl, 21·1%).

8-*Chloro* - 5 - (*γ* - *diethylaminopropylamino*) - 3 : 4 : 3′ : 2′ - *pyridoacridine.*—6 : 8 - Dichloro - 3 : 4 : 3′ : 2′ - pyridoacridine (1 g.) (containing some 8-chloro-3 : 4 : 3′ : 2′-pyridoacridone as the analytical results showed) and γ-diethylaminopropylamine (1 g.) were condensed in dry molten phenol at 100° for 2 hours as described for 8-chloro-5-(γ-diethylaminopropylamino)-1 : 2-benzacridine. The product (0·8 g.) consisted of orange-yellow needles, m. p. 99—100°. Further recrystallisation from dry ligroin left this m. p. unchanged. The analytical figures were consistent with the presence of some pyridoacridone and water (Found C, 67·8; H, 6·0; N, 12·5; Cl, 9·55. $C_{23}H_{25}N_4Cl$ requires C, 70·3; H, 6·4; N, 14·3; Cl, 9·0. $3C_{23}H_{25}N_4Cl,C_{16}H_9ON_2Cl,3H_2O$ requires C, 67·5; H, 5·9; N, 13·0; Cl, 9·4%). Some of this material was dried over anhydrone under reduced pressure at room temperature; it was then found to have lost 4·2% by weight (loss of $3H_2O$ requires 3·6%). Some of this dried material was recrystallised from specially dried heptane yielding a *base*, m. p. 69—70°, which seemed free from pyridoacridine but still contained one molecule of water of crystallisation (Found : C, 66·7; H, 6·55; N, 14·0. $C_{23}H_{25}N_4Cl,H_2O$ requires C, 67·2; H, 6·6; N, 13·6%).

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