72. *A Study of the Properties of Fluorine-substituted* 5-*Aminoacridines and Related Compounds. Part III. Some* 5-*Amino*-1 : 2 : 2′ : 3′-*Pyridoacridines.*

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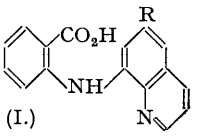
The preparation of 5-*amino*-1 : 2 : 2′ : 3′-*pyridoacridine* and its 4-*fluoro*- and 4-*methoxy*-derivatives from the corresponding 6-substituted 8-aminoquinolines is described. The three compounds have been examined for antibacterial and trypanocidal activity.

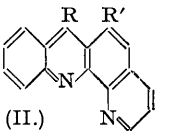
In furtherance of our plan to study fluorine-substituted 5-aminoacridines, we now report the preparation of 4-*fluoro*-5-*amino*-1 : 2 : 2′ : 3′-*pyridoacridine* (II, R = NH_2, R′ = F) which has

been submitted for antibacterial and trypanocidal tests. *5-Amino-1 : 2 : 2′ : 3′-pyridoacridine* (II, R = NH_2; R′ = H) and its 4-*methoxy*-derivative (II, R = NH_2; R′ = OMe) have been prepared for comparison. While this work was in progress, Dobson and Kermack (*J.*, 1946, 150) described the preparation of a number of substituted 5-amino-1 : 2 : 2′ : 3′-pyridoacridines which were examined as potential antimalarials.

The new compounds were prepared by the same route as that used by Dobson and Kermack, namely, by cyclisation of the corresponding *N*-(8′-quinolyl)anthranilic acid, which was obtained by Ullmann condensation of the appropriate 8-aminoquinoline with *o*-halogeno-benzoic acids.



(I.)



(II.)

Since Swarts (*Rec. Trav. chim.*, 1915—1916, **35**, 139) has drawn attention to the poor yield obtained on nitration of *p*-fluoroacetanilide with acetyl nitrate in acetic anhydride, we decided to use ethyl nitrate as nitrating agent in a sulphuric acid medium. A yield of 85% of pure 4-fluoro-2-nitroacetanilide was obtained. Hydrolysis with 8N-hydrochloric acid gave the corresponding nitroaniline which was converted into 6-*fluoro*-8-*nitroquinoline* by the Skraup method, as modified by Richter and Smith (*J. Amer. Chem. Soc.*, 1944, **66**, 396). Reduction to 6-*fluoro*-8-*aminoquinoline* was effected by refluxing with reduced iron and alcohol. The product was condensed with *o*-chlorobenzoic acid to give N-(6′-*fluoro*-8′-*quinolyl*)*anthranilic acid* (I, R = F). In view of the low yield of *N*-(6′-chloro-8′-quinolyl)anthranilic acid (I; R = Cl) obtained when 6-chloro-8-aminoquinoline was used, we did not consider it worth while proceeding with the preparation of 4-chloro-5-amino-1 : 2 : 2′ : 3′-pyridoacridine at present, unless the biological results on other compounds of this type indicated high activity. *N*-(8′-Quinolyl)-anthranilic acid (I, R = H) and its 6′-methoxy-derivative (I, R = OMe) were prepared by Dobson and Kermack (*loc. cit.*) in 66% and 64% yields respectively, and our results in these preparations substantially confirmed their yields.

Ring closure with phosphorus oxychloride gave *5-chloro-4-fluoro-1 : 2 : 2′ : 3′-pyridoacridine* (II, R = Cl, R′ = F) and its analogues, and these were converted into the corresponding 5-amino-compounds by treatment with ammonium carbonate in phenol. The monohydrochlorides of the 5-amino-derivatives were also obtained by treatment of the appropriate 5-methoxy-compounds with ammonium chloride (Barber, Wilkinson, and Edwards, *J. Soc. Chem. Ind.*, 1947, **66**, 411).

The bases were orange-yellow substances which resembled 5-aminoacridine in their general properties. 4-Fluoro-5-amino-1 : 2 : 2′ : 3′-pyridoacridine (II, R = NH_2, R′ = F) proved to be markedly less soluble in organic solvents than the 4-methoxy- and non-halogenated derivatives. Its mono- and di-hydrochlorides were similarly less soluble in water. In contrast with most 5-aminoacridine hydrochlorides, the hydrochlorides of all three bases exhibited little or no fluorescence in dilute solution by daylight. All three bases readily gave diacetyl derivatives when refluxed with acetic anhydride. These crystallised well and closely resembled 5-diacetylaminoacridine (Wilkinson and Finar, *J.*, 1946, 115).

5-Amino-1 : 2 : 2′ : 3′-pyridoacridine and its 4-fluoro- and 4-methoxy-derivatives showed no trypanocidal activity against *T. equiperdum*, and, although bactericidally active, were not sufficiently so to render them of any practical importance.

Experimental.

(M. ps. are corrected.)

4-Fluoro-2-nitroaniline.—*p*-Fluoroacetanilide (25 g.) was dissolved in sulphuric acid (75 c.c.) and the solution cooled to 0°. Ethyl nitrate (13·75 c.c., 5% excess) was added over a period of 45 minutes at 0—2° with mechanical stirring, after which the mixture was kept at 0° for a further 15 minutes. 4-Fluoro-2-nitroacetanilide (27·3 g., 85%) was isolated by pouring the mixture on crushed ice (400 g.); m. p. 71° (Swarts, *loc. cit.*, gives m. p. 71·5°). The anilide (10 g.) was hydrolysed by refluxing it with 8N-hydrochloric acid (25 c.c.) for 15 minutes, cooling, and making the mixture alkaline with sodium hydroxide (10 c.c., 50%). The product separated as a red oil which hardened on standing to an orange-red solid (7·69 g., 96%); m. p. 93—94° (Swarts, *loc. cit.*, gives m. p. 92·5°).

6-Fluoro-8-nitroquinoline.—4-Fluoro-2-nitroaniline (3 g.) was dissolved in anhydrous glycerol (7·2 g.); arsenic pentoxide (3·3 g.) was added and the mixture treated with sulphuric acid (4 g.) at such a rate that the temperature did not exceed 130°. The mixture was heated at 130—135° for 4 hours, then at 160° for 30 minutes. The cooled solution was treated with water (50 c.c.) and then with ammonia to precipitate the product which was collected and dried. Extraction (Soxhlet) with benzene gave pure

6-*fluoro*-8-*nitroquinoline* (2·31 g., 61·5%) as buff-coloured silky needles, m. p. 121° (Found: C, 56·5; H, 2·8; N, 14·6. $C_9H_5O_2N_2F$ requires C, 56·4; H, 2·6; N, 14·6%).

6-*Fluoro*-8-*aminoquinoline*.—A solution of the fluoronitroquinoline (3 g.) in 70% alcohol (50 c.c.) was refluxed with reduced iron (9 g.) and calcium chloride (0·6 g.) for 5 hours. The mixture was filtered and the bulk of the alcohol was removed from the filtrate. The residue was diluted with water, and the product extracted with ether and distilled. 6-*Fluoro*-8-*aminoquinoline* was obtained as a pale yellow oil (2·03 g., 79%), b. p. 110°/0·15 mm., which solidified on standing to a colourless waxy solid, m. p. 49° (Found: N, 17·2. $C_9H_7N_2F$ requires N, 17·3%).

N-(6′-*Fluoro*-8′-*quinolyl*)*anthranilic Acid*.—*o*-Chlorobenzoic acid (2·22 g.) was dissolved in amyl alcohol (10 c.c.) and the solution treated with anhydrous potassium carbonate (4 g.). 6-Fluoro-8-aminoquinoline (2·3 g.) and copper-bronze catalyst (0·1 g.) were added; the mixture was refluxed for 5 hours, after which the solvent was removed by steam distillation. The residue was filtered and the filtrate acidified with 2N-acetic acid. The product was dissolved in hot 4N-hydrochloric acid, and the solution filtered (charcoal). The purified product (1·5 g., 36%) was isolated by precipitation with aqueous sodium acetate solution. N-(6′-*Fluoro*-8′-*quinolyl*)*anthranilic acid* crystallised from benzene in pale yellow needles, m. p. 234° (decomp.) (Found: C, 67·9; H, 4·05; N, 9·7. $C_{16}H_{11}O_2N_2F$ requires C, 68·1; H, 3·9; N, 9·9%).

5-*Chloro*-4-*fluoro*-1 : 2 : 2′ : 3′-*pyridoacridine*.—*N*-(6′-Fluoro-8′-quinolyl)anthranilic acid (1·4 g.) was refluxed with phosphorus oxychloride (5 c.c.) for 30 minutes, after which the excess of oxychloride was removed by distillation. The residue was dissolved in chloroform (30 c.c.) and poured into ammonia (*d* 0·88, 50 c.c.) cooled with ice. The chloroform layer was separated and the solvent removed, finally under reduced pressure. The residue (1·22 g., 87%) afforded pure 5-*chloro*-4-*fluoro*-1 : 2 : 2′ : 3′-*pyridoacridine* on crystallisation from benzene. It was obtained in small pale yellow prisms, readily soluble in alcohol; m. p. 207—208° (Found: N, 9·7. $C_{16}H_8N_2ClF$ requires N, 9·9%).

4-*Fluoro*-5-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine*.—5-Chloro-4-fluoro-1 : 2 : 2′ : 3′-pyridoacridine (1·7 g.) was refluxed with a solution of sodium methoxide prepared from sodium (0·15 g.) and methanol (20 c.c.) for 30 minutes. Benzene (50 c.c.) was added to the cooled solution which was then treated with water (100 c.c.). The benzene layer was separated and dried (K_2CO_3). The solvent was removed by distillation, and the residue (1·4 g., 84%) crystallised from benzene. 4-*Fluoro*-5-*methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* was obtained in pale yellow needles, m. p. 184°, readily soluble in alcohol, benzene, and aqueous acetic acid (Found: N, 9·8. $C_{17}H_{11}ON_2F$ requires N, 10·1%).

4-*Fluoro*-5-*amino*-1 : 2 : 2′ : 3′-*pyridoacridine*.—4-Fluoro-5-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (0·5 g.) and ammonium chloride (0·12 g.) were dissolved in 85% methanol (5 c.c.). The solution was maintained at 60° for 6 hours, after which the solvent was removed. The residue was dissolved in hot water and filtered from a little unreacted methoxy-compound. The filtrate was made alkaline with 2N-sodium hydroxide. The product was collected, washed free from alkali, and dried at 100° (0·41 g., 87%). 4-*Fluoro*-5-*amino*-1 : 2 : 2′ : 3′-*pyridoacridine* crystallised from pyridine in short yellow hexagonal prisms, m. p. 297—298°. It was sparingly soluble in alcohol, benzene, and xylene (Found: C, 72·8; H, 3·9; N, 15·9. $C_{16}H_{10}N_3F$ requires C, 73·0; H, 3·85; N, 15·97%). The same product was also obtained by heating a mixture of 5-chloro-4-fluoro-1 : 2 : 2′ : 3′-pyridoacridine (1·25 g.), phenol (3 g.), and ammonium carbonate (0·31 g., 20% excess) at 120° for 1 hour. Acetone (25 c.c.) was added to precipitate the hydrochloride of the 5-amino-compound which was converted into the base (36 g., 74%) as described above. The monohydrochloride was obtained as a pale yellow powder, soluble in water and alcohol to give solutions which exhibited a faint blue fluorescence on dilution. When the base (0·1 g.) was refluxed with acetic anhydride (0·5 c.c.) for 5 minutes and the mixture treated with water (5 c.c.), the *diacetyl* derivative (0·11 g.) was obtained. This crystallised from 60% alcohol in pale yellow rhombic plates, m. p. 227—228° (decomp., charring *ca.* 220°). It was soluble in alcohol, but sparingly soluble in benzene. In ultra-violet light an alcoholic solution exhibited a blue fluorescence which became more intense on the addition of alkali (Found: N, 12·05. $C_{20}H_{14}O_2N_3F$ requires N, 12·1%).

N-(8′-*Quinolyl*)*anthranilic Acid*.—*o*-Iodobenzoic acid (6·2 g.) was dissolved in amyl alcohol (25 c.c.) and treated with anhydrous potassium carbonate (3·5 g.). 8-Aminoquinoline (3·6 g.) and copper bronze catalyst (0·5 g.) were added and the mixture was refluxed for 4 hours, after which the amyl alcohol was removed by steam distillation. The residue was extracted with boiling water (250 c.c.) and ammonium chloride (50 g.) was added to the filtered extract to precipitate the ammonium salt of the product. The latter was dissolved in dilute alkali and the free acid (4·86 g., 74%) isolated by precipitation with acetic acid. Crystallisation from 70% alcohol gave golden-yellow hexagonal plates, m. p. 247° (Dobson and Kermack, *loc. cit.*, give m. p. 243—244°) (Found: C, 72·8; H, 4·65; N, 10·4. Calc. for $C_{16}H_{12}O_2N_2$: C, 72·7; H, 4·55; N, 10·6%).

5-*Chloro*-1 : 2 : 2′ : 3′-*pyridoacridine*.—*N*-(8′-Quinolyl)anthranilic acid (3 g.) and phosphorus oxychloride (15 c.c.) were refluxed for 1 hour. The excess of oxychloride was removed under reduced pressure, and the residue dissolved in chloroform (100 c.c.). The product was isolated as described for the 4-fluoro-derivative and crystallised from 70% alcoholic ammonia (N/30). 5-Chloro-1 : 2 : 2′ : 3′-pyridoacridine monohydrate (2·2 g., 73%) was obtained in pale yellow, almost colourless, needles, m. p. 164° (Dobson and Kermack, *loc. cit.*, give m. p. 165°) (Found: N, 9·8. Calc. for $C_{16}H_9N_2Cl,H_2O$: N, 9·9%). The *anhydrous* form was obtained by drying at 100°. The m. p. (164°) was unchanged on subsequent crystallisation from dry benzene (Found: N, 10·7. $C_{16}H_9N_2Cl$ requires N, 10·6%).

5-*Methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine*.—5-Chloro-1 : 2 : 2′ : 3′-pyridoacridine (2·92 g.) was refluxed for 30 minutes with sodium methoxide (0·65 g., 10% excess) in methanol (30 c.c.). The 5-methoxy-derivative separated as an oil on the addition of water (100 c.c.) to the cooled solution. It was extracted with benzene, and the extract was concentrated to about 10 c.c. An equal volume of light petroleum (b. p. 80—100°) was added. 5-*Methoxy*-1 : 2 : 2′ : 3′-*pyridoacridine* crystallised in buff-coloured needles (2·28 g., 79%), m. p. 167—168°, readily soluble in benzene and alcohol but sparingly soluble in ether (Found: N, 10·9. $C_{17}H_{12}ON_2$ requires N, 10·75%).

5-*Amino*-1 : 2 : 2′ : 3′-*pyridoacridine*.—5-Methoxy-1 : 2 : 2′ : 3′-pyridoacridine (2·2 g.) and ammonium

chloride (0·55 g., 20% excess) were dissolved in 90% alcohol (30 c.c.) and the solution maintained at 60° for 14 hours. The mixture was evaporated to about 10 c.c. and the hydrochloride of the product collected by filtration. After being washed with acetone and dried at 100°, it was dissolved in boiling water (70 c.c.) and filtered from the small amount of 1 : 2 : 2′ : 3′-pyridoacridone, m. p. 275°. The filtrate was treated with alkali to precipitate the product (2·2 g., 82%). *5-Amino-*1 : 2 : 2′ : 3′*-pyridoacridine* crystallised from 70% alcohol in orange-yellow triangular prisms, m. p. 252° with preliminary softening (Found : C, 76·2; H, 5·2; N, 15·55. $C_{16}H_{11}N_3,\frac{1}{2}C_2H_5OH$ requires C, 76·1; H, 5·2; N, 15·7%) When dried at 130°/12 mm., the alcohol of crystallisation was removed (loss : 8·2; calc. : 8·6%), and the *base* was obtained in orange prisms, highly soluble in most organic solvents (Found : C, 78·5; H, 4·6; N, 16·9. $C_{16}H_{11}N_3$ requires C, 78·4; H, 4·5; N, 17·1%). The hydrochloride was a light yellow powder, readily soluble in water and alcohol; the solutions showed a faint blue fluorescence on dilution. The *diacetyl* derivative crystallised from benzene in colourless prisms, m. p. 191—192°. It was highly soluble in alcohol giving a solution which exhibited a violet fluorescence in ultra-violet light (Found : N, 12·5. $C_{20}H_{15}O_2N_3$ requires N, 12·75%).

N-(6′-Methoxy-8′-quinolyl)anthranilic acid (16·5 g., 56%) was prepared from *o*-iodobenzoic acid (24·9 g.), 6-methoxy-8-aminoquinoline (19·1 g., 10% excess), potassium carbonate (14 g.), copper-bronze catalyst (0·5 g.), and water (100 c.c.), substantially as described for *N*-(8′-quinolyl)anthranilic acid. The product crystallised from alcohol in pale yellow prisms, m. p. 207° (Dobson and Kermack, *loc. cit.*, report m. p. 201°) (Found : N, 9·5. Calc. for $C_{17}H_{14}O_3N_2$: N, 9·5%).

*5-Chloro-4-methoxy-*1 : 2 : 2′ : 3′*-pyridoacridine.*—*N*-(6′-Methoxy-8′-quinolyl)anthranilic acid (10 g.) was refluxed with phosphorus oxychloride (20 c.c.) for 2 hours, after which the phosphorus oxychloride was removed by distillation. The product (10 g., quantitative) was isolated as described for 5-chloro-1 : 2 : 2′ : 3′-pyridoacridine. It crystallised from 90% alcoholic ammonia (N/30) in golden yellow needles, m. p. 105—106°, which appeared to be hydrated since when heated at 78°/18 mm. water was lost and the m. p. rose to *ca.* 170° (Dobson and Kermack, *loc. cit.*, give m. p. 169°) (Found : N, 9·3. Calc. for $C_{17}H_{11}ON_2Cl$: N, 9·5%).

4 : 5-*Dimethoxy-*1 : 2 : 2′ : 3′*-pyridoacridine* was prepared by refluxing 5-chloro-4-methoxy-1 : 2 : 2′ : 3′-pyridoacridine (3·12 g.) with a solution of sodium methoxide prepared from sodium (0·3 g.) and anhydrous methanol (20 c.c.) for 30 minutes. It was isolated as described for the other 5-methoxy-derivatives; it crystallised from 50% methanol in pale buff-coloured rhombs, m. p. 205° (Found : N, 9·75. $C_{18}H_{14}O_2N_2$ requires N, 9·65%).

*5-Amino-4-methoxy-*1 : 2 : 2′ : 3′*-pyridoacridine.*—A solution of 4 : 5-dimethoxy-1 : 2 : 2′ : 3′-pyridoacridine (3·6 g.) and ammonium chloride (0·83 g., 20% excess) in 90% alcohol (25 c.c.) was heated at 60° for 8 hours, after which the alcohol was evaporated and the hydrochloride of the product (3·14 g., 81%) collected by filtration. This was dissolved in water (30 c.c.) and treated with sodium hydroxide to precipitate the *base* (2·43 g.), which crystallised from 40% alcohol in yellowish-brown prisms, highly soluble in most organic solvents, m. p. 220° (Found : C, 68·6; H, 5·2; N, 14·4. $C_{17}H_{13}ON_3,H_2O$ requires C, 69·6; H, 5·2; N, 14·35%). The dihydrochloride crystallised from water in orange-yellow prisms, soluble in about 2 parts of water, highly soluble in alcohol. A dilute solution was not fluorescent by daylight but exhibited a faint green fluorescence in ultra-violet light. When dried at 130°/10 mm., water and hydrogen chloride were lost and the residue consisted of the *monohydrochloride.* This was obtained in orange prisms, m. p. *ca.* 360° (Found : N, 13·25; Cl, 11·5. $C_{17}H_{13}ON_3,HCl$ requires N, 13·5; Cl, 11·4%). The *diacetyl* derivative crystallised from alcohol in pale yellow highly refractive plates, sparingly soluble in alcohol, m. p. 255—256° (decomp.) (Found : N, 11·3. $C_{21}H_{17}O_3N_3$ requires N, 11·7%).

N-(6′-Chloro-8′-quinolyl)anthranilic acid was prepared by refluxing a mixture of 6-chloro-8-aminoquinoline (4·46 g.), *o*-chlorobenzoic acid (3·91 g.), potassium carbonate (3·5 g.), and copper–bronze catalyst (0·1 g.) in amyl alcohol (15 c.c.) for 8 hours, after which the solvent was removed by steam distillation. The residue was extracted with hot water and the product (0·82 g.) isolated by acidification of the filtered extract with acetic acid. It was a pale yellow powder, sparingly soluble in most organic solvents, but readily soluble in mineral acids and alkalis, m. p. 206—209°. Since crystallisation proved impracticable, the *methyl* ester was prepared by refluxing the acid (0·8 g.) with methanol (4 c.c.) and sulphuric acid (2 c.c.) for 2 hours. The mixture was poured into water (20 c.c.) and the sparingly soluble sulphate of the ester was precipitated. Trituration with ammonia gave the free ester (0·75 g.) which was washed free from non-esterified acid with ammonia solution followed by water. It crystallised from methanol in bright yellow needles, m. p. 132° (Found : C, 65·3; H, 4·3; N, 8·9. $C_{17}H_{13}O_2N_2Cl$ requires C, 65·3; H, 4·15; N, 8·9%).

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