110. *New Therapeutic Agents of the Quinoline Series. Part V. Pyridylacridines.*

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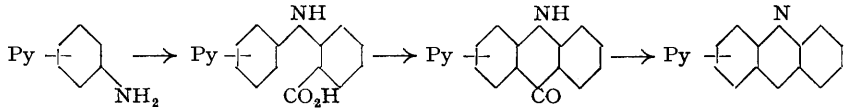
A series of pyridylacridines has been prepared for comparison with pyridylquinolines. Pyridylanilines of known orientation were condensed with *o*-chlorobenzoic acid, the products cyclised, and the resulting pyridylacridones reduced. Additional experiments on pyridyldiphenylamines and the preparation of 5-β-pyridylacridine from diphenylamine and nicotinic acid are also described.

In other papers of this series it has been shown not only that many pyridylquinolines possess spasmolytic activity but also that this property persists when the unsubstituted pyridyl nucleus is replaced by other heterocyclic systems. It was therefore desirable to see whether the quinoline nucleus also could be replaced by other basic groups. In the present work a number of compounds containing linked pyridine and acridine nuclei are described. The bactericidal and therapeutic qualities of acridines made this series of particular interest, but those members which were prepared proved to be much less active than the comparable pyridylquinolines.

The general method of preparation was to cyclise suitable pyridyldiphenylaminecarboxylic acids and reduce the resulting acridones :



Thus α-4-aminophenylpyridine was converted into 4-α-*pyridyldiphenylamine-2'-carboxylic acid* by heating in amyl alcohol with *o*-chlorobenzoic acid and potassium carbonate in presence of copper powder (cf. Tuttle, *J. Amer. Chem. Soc.*, 1923, **45**, 1906). This acid was converted into 3-α-*pyridylacridone* in almost theoretical yield by the action of sulphuric acid at 90°. Attempts to reduce this acridone to the acridine with zinc dust (Graebe and Lagodzinski, *Ber.*, 1892, **25**, 1735) or with potassium cyanide were unsuccessful, only oils being obtained. Sodium amalgam gave an impure product in low yield and the best results, though they were still not completely satisfactory, were obtained with aluminium amalgam in alcoholic solution.

In the course of this work 4-α-pyridyldiphenylamine-2'-carboxylic acid was decarboxylated to 4-α-*pyridyldiphenylamine*. This constitution was confirmed by allowing diazotised 4-aminodiphenylamine to react with pyridine, a good yield of 4-*pyridyldiphenylamines* being obtained; fractionation of the picrate of this material afforded only one of the anticipated three isomerides which proved to be identical with the above product of decarboxylation.

Reaction of β-4-aminophenylpyridine with *o*-chlorobenzoic acid afforded 4-β-*pyridyldiphenylamine-2'-carboxylic acid* and this was cyclised in good yield to the acridone, which was reduced, again best with aluminium

amalgam, to 3-β-*pyridylacridine*. A similar series of reactions was carried out with γ-4-aminophenylpyridine, leading to 3-γ-*pyridylacridine*, though this aniline was much less reactive towards *o*-chlorobenzoic acid and gave only a very poor yield of 4-γ-*pyridyldiphenylamine-2'-carboxylic acid*. In the same manner α-2-aminophenylpyridine was converted into 2-α-*pyridyldiphenylamine-2'-carboxylic acid*, which was smoothly cyclised to 1-α-*pyridylacridone* with hot sulphuric acid; reduction with aluminium amalgam then gave 1-α-*pyridylacridine*.

Finally the interaction of nicotinic acid and diphenylamine in presence of zinc chloride at 260° (cf. Bernthsen, *Annalen*, **1884**, **224**, 1) gave a poor yield of 5-β-*pyridylacridine*. In this synthetic method, the yield of acridine obtainable from a carboxylic acid and diphenylamine is known to vary greatly and it was not surprising to find that picolinic acid failed to give any of the desired 5-α-pyridylacridine.

Representative pyridylanilines were condensed with *o*-chloronitrobenzene to give, for example, 2'-*nitro*-4-α-*pyridyldiphenylamine*; such compounds we hoped to cyclise to pyridylnitroacridines and thence by reduction, diazotisation and reaction with pyridine, to obtain dipyridylacridines. The poor yields in the Bernthsen synthesis and the unfavourable spasmolytic activity of monopyridylacridines already prepared caused this part of the project to be abandoned.

Experimental.

3-α-*Pyridylacridine*.—α-4-Aminophenylpyridine (m. p. 97°, 6 g.), *o*-chlorobenzoic acid (5·5 g.), potassium carbonate (6·5 g.), and copper bronze (0·2 g.) in amyl alcohol (60 c.c.) were refluxed for 3½ hours, the amyl alcohol then removed in steam, and the residual solution heated with charcoal for 1 hour, filtered, and made alkaline with ammonia. The 4-α-*pyridyldiphenylamine-2'-carboxylic acid* obtained crystallised from alcohol in yellow prisms (5·5 g.), m. p. 198° (Found: C, 74·8; H, 5·1. $C_{18}H_{14}O_2N_2$ requires C, 74·5; H, 4·8%). A solution of the acid (5 g.) in concentrated sulphuric acid (50 c.c.) was warmed on the steam-bath for 25 minutes and poured into water, and excess of ammonia added. Filtration gave 3-α-*pyridylacridone* (4·8 g.), which crystallised from alcohol in yellow needles, m. p. 315—317° (Found: C, 79·7; H, 4·5. $C_{18}H_{12}ON_2$ requires C, 79·4; H, 4·4%). Its solution in concentrated sulphuric acid was pale yellow with blue fluorescence, in alcoholic potassium hydroxide pale yellow with green fluorescence.

3-α-Pyridylacridone (3 g.) was dissolved in 95% alcohol (160 c.c.) containing sodium hydroxide (1·7 g.) and precipitated in a finely divided state by neutralisation with 5N-hydrochloric acid, amalgamated aluminium foil (1·25 g.) added during 2 hours with stirring and the whole refluxed until the aluminium had dissolved. The solution was filtered, the residue extracted with alcohol, and the combined liquors evaporated to dryness under reduced pressure. The product was extracted with hot hydrochloric acid (4N), and the extracts heated to boiling and treated with aqueous ferric chloride (10%) until a permanent excess was present. The solution was filtered and made alkaline, and the precipitate extracted with alcohol. After removal of alcohol the dark oil was extracted with benzene, and the solution concentrated to about 100 c.c., filtered, and chromatographed on a column of alumina (28 × 1·3 cm.); the lower pale yellow band was developed with benzene and eluted with benzene containing 10% of ether. Evaporation of the eluate gave 3-α-*pyridylacridine* (0·8 g.), which formed pale yellow needles, m. p. 140°, from benzene–light petroleum (Found: C, 84·2; H, 4·7. $C_{18}H_{12}N_2$ requires C, 84·2; H, 4·7%).

3-β-*Pyridylacridine*.—4-β-*Pyridyldiphenylamine-2'-carboxylic acid* was obtained from β-4-aminophenylpyridine, exactly as described for the α-isomeride, as a powder, which separated from ethanol in brownish needles, m. p. 248—250° (decomp.) (Found: N, 9·6. $C_{18}H_{14}O_2N_2$ requires N, 9·6%). 3-β-*Pyridylacridone*, prepared as above, crystallised from ethanol in yellow micro-needles, m. p. 314—316°. A dilute solution in alcohol had violet fluorescence, and a solution in concentrated sulphuric acid was yellow with blue fluorescence (Found: C, 79·1; H, 4·4%). Reduction of the acridone gave, after chromatography on alumina, the *acridine* (0·8 g.), which formed pale yellow needles, m. p. 132°, from light petroleum (Found: C, 84·3; H, 4·4%).

3-γ-*Pyridylacridine*.—γ-4-Aminophenylpyridine was converted as in the preceding examples into 4-γ-*pyridyldiphenylamine-2'-carboxylic acid*, which crystallised from ethanol in brown needles, m. p. 244° (Found: C, 74·1; H, 5·1%). The crude product was cyclised to give 3-γ-*pyridylacridone*, which separated from aqueous alcohol in pale yellow needles, m. p. 343° (Found: C, 79·4; H, 4·4%). In concentrated sulphuric acid the fluorescence was blue, in alcoholic potassium hydroxide green, and in dilute alcohol violet. The acridone (2 g.) was reduced as already described for the α-isomeride. Chromatography on alumina of the impure product in benzene solution gave 3-γ-*pyridylacridine* (0·25 g.), which crystallised from benzene in yellow leaflets, m. p. 179° (Found: C, 84·0, H, 4·9%).

1-α-*Pyridylacridine*.—From α-2-aminophenylpyridine (8 g.) and *o*-chlorobenzoic acid (7·8 g.), crude 2-α-*pyridyldiphenylamine-2'-carboxylic acid* (12·7 g.) was obtained. Crystallisation from benzene–light petroleum gave pale yellow prisms, m. p. 165—166° (Found: C, 75·1; H, 5·0%). Cyclisation of the acid, followed by crystallisation of the product from dilute ethanol, gave 1-α-*pyridylacridone* (9·5 g.) in yellow needles, m. p. 186—187°. The solution in alcoholic potassium hydroxide showed blue fluorescence (Found: C, 79·6; H, 4·4%). 1-α-Pyridylacridone (8 g.) was reduced overnight in boiling aqueous alcohol (95%, 400 c.c.) with amalgamated aluminium (4·5 g.). Oxidation of the crude product in dilute hydrochloric acid with ferric chloride and chromatography on alumina from benzene solution afforded 1-α-*pyridylacridine* (2 g.), which crystallised from benzene–light petroleum in yellow needles, m. p. 111·5°. Concentrated sulphuric acid gave a yellow solution with bright green fluorescence (Found: C, 84·2; H, 5·0%).

5-β-*Pyridylacridine*.—Nicotinic acid (5 g.), diphenylamine (7 g.), and finely powdered zinc chloride (15 g.) were heated at 260° for 14 hours, the product ground and dissolved in hot alcohol, and the extract evaporated to 100 c.c. and poured into excess of concentrated aqueous ammonia. The black tar was extracted with benzene, and the extracts washed with 2N-hydrochloric acid. Chromatography of the liberated base on alumina from benzene–ether, followed by distillation in a high vacuum at 140°, gave a yellow semi-solid product (*ca.* 1 g.) which on repeated crystallisation from benzene–light petroleum yielded yellow leaflets, m. p. 118° (Found: C, 84·4; H, 4·7%).

4-*Pyridyldiphenylamine*.—The paste obtained by rapidly cooling a solution of 4-aminodiphenylamine (20 g.) in warm 20% sulphuric acid (320 c.c.) to 5° was diazotised with sodium nitrite (7·8 g.). The mixture was kept overnight at 0°, and diphenylamine-4-diazonium sulphate then salted out with ammonium sulphate and added during 1 hour to pyridine (500 c.c.) stirred at room temperature. The solution was kept overnight, made alkaline, pyridine removed in steam, and the residue extracted with hot benzene. Washing, drying, and removal of solvent gave a black viscous oil, which was distilled at low pressure. 4-Pyridyldiphenylamine (7 g.), b. p. 220—235°/<1 mm., was obtained as a dark red oil. Conversion into the picrate and crystallisation from acetone gave a pure *picrate* (3 g.), m. p. 196·5° (Found: N, 14·55. $C_{17}H_{14}N_2,C_6H_3O_7N_3$ requires N, 14·7%). The picrate (2 g.) was heated on the steam-bath for 30 minutes with aqueous sodium hydroxide (5%, 100 c.c.), and the precipitated 4-pyridyldiphenylamine (*ca.* 1 g.) collected. Chromatographed in benzene solution on alumina, it formed a well-defined, narrow, yellow band below other coloured zones. Elution, with benzene containing 10% of ether gave a pure compound, regarded as 4-α-*pyridyldiphenylamine* (0·8 g.), m. p. 133°

which, recrystallised from benzene–light petroleum, formed pale yellow sheaves of needles, m. p. 133° (Found : C, 83·0; H, 5·8. $C_{17}H_{14}N_2$ requires C, 82·9; H, 5·7%).

4-α-Pyridyldiphenylamine-2′-carboxylic acid (5 g.) was heated with copper powder (0·3 g.) at 240° for 30 minutes. The product was extracted with hot benzene, and the extracts filtered, evaporated to small volume, and chromatographed on alumina. The lower, pale yellow band was developed with benzene and washed through the tower with benzene containing 10% of ether. 4-α-Pyridyldiphenylamine (4 g.) was recovered and recrystallised from benzene–light petroleum to yield 3·3 g., m. p. 134°; it gave no depression with the product previously described, m. p. 133°.

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