106. *New Therapeutic Agents of the Quinoline Series. Introduction and Part I. Monopyridylquinolines.*

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Existing spasmolytics are briefly reviewed, and their relation to the present series indicated. The variation of antispasmodic action with changing orientation and substitution among pyridylquinolines and related compounds is described.

By diazotising aminoquinolines and coupling the diazonium salts with pyridine, 3-, 5-, and 8-pyridylquinolines were prepared; in the first case two (a, β) of the three possible isomerides were isolated; only 5-a-pyridylquinoline was obtained by this route, but in the remaining case all three isomerides were obtained. In addition the 5-a-, 6-a-, 6-β-, 6-γ-, 8-a-, and 8-β-representatives as well as 7-a-pyridylquinoline were synthesised from the appropriate aminophenylpyridine by the Skraup reaction.

INTRODUCTION.

The following series of investigations arose out of a comprehensive study of arylpyridines and related compounds, the earlier results of which have already appeared (J., 1940, 349, 355, 358, 1279). It was anticipated that pyridylquinolines would prove of pharmacological interest, and biological examination, carried out in the laboratories of I.C.I. (Dyestuffs) Ltd., revealed that their most notable feature was a pronounced antispasmodic action with the promise of useful additions to the range of drugs suitable for treating asthmatic and other conditions.

Of existing spasmolytics, the best known are adrenaline and ephedrine and the alkaloids papaverine and atropine. Many 1-aryl- and 1-homoaryl-*iso*quinolines resembling papaverine in constitution and pharmacological action have been adopted or suggested for clinical use (*e.g.*, Ellinger, Koschara, and Seerar, *Klin. Woch.*, 1934, **13**, 411; F.P. 760,825; Slotta and Haberland, *Angew. Chem.*, 1933, **46**, 766; Bruckner and Fodor, *Ber.*, 1938, **71**, 541; Werder, *Mercks Jahresber.*, 1936, **50**, 88; B.P. 348,956; F.P. 719,638; G.P. 549,967, 613,005) and here it is particularly interesting to note that 6 : 7-methylenedioxy-1-β-pyridyl-3-methyl*iso*quinoline (G.P. 549,967) can be used in place of papaverine.

In the present studies, a wide variety of pyridylquinolines, dipyridylquinolines, and related compounds has been synthesised. As clinical trials are still in progress and as the pharmacological detail is outside the province of the present papers, only such findings as appear to be of chemical significance are given here.

Of monopyridylquinolines there was a marked dependence of activity on the relative orientation of the pyridyl and quinolyl residues. Thus the 3- and 6-pyridyl compounds were more active than the corresponding 5-, 7-, and 8-isomerides and in general the γ-pyridyl compounds were superior to either the a- or the β-derivatives, having a potency comparable with that of adrenaline. Among the lutidylquinolines the 6-isomeride was again outstanding. The dicarboxylic esters and dihydro-esters from which these bases were derived possessed only feeble antispasmodic activity. Whereas 6-lutidylquinoline was highly active, the isomeric aa'-dimethyl-6-β-pyridylquinoline was much less potent. The replacement of the pyridyl residue by amidino-, pyrryl or thiazyl groups gave disappointing results, only the last showing any promise. Among the pyridylacridines even the γ-pyridyl compounds had only very slight activity.

Schönhöfer ("Medicine in its Chemical Aspects," 1934, II, 229) has shown that the antispasmodic action of alkoxy (chiefly methoxy)-quinolines is enhanced by introducing further similar groups into *m*-positions in the quinoline ring and it was therefore of interest to observe whether a similar enhancement could be brought about in monopyridylquinolines already possessing considerable activity. This would seem to be the case, for 6 : 8-dipyridylquinoline, even as a mixture which must have contained a large proportion of a-pyridyl constituents, was at least as effective as the most active γ-monopyridylquinoline; when the pyridyl residues no longer stood in *m*-relation, as in 5 : 8-dipyridylquinoline, the activity again receded. Similarly 6-methoxy-8-pyridyl- and 8-methoxy-6-pyridyl-quinolines were superior to the simple pyridylquinoline and once again the γ-pyridyl compounds were outstanding.

PART I. MONOPYRIDYLQUINOLINES.

Prior to the present work, the preparation of two pyridylquinolines had already been recorded, but their physiological activity does not appear to have been examined. 7-β(or γ)-Pyridylquinoline (I) was prepared by the distillation of the silver salt of 5 (or 4)-7'-quinolylpyridine-3-carboxylic acid (Fischer and van Loo, *Ber.*,

1886, **19**, 2475), and an excellent yield of 2-α-pyridylquinoline (II) was obtained by the condensation of *o*-aminobenzaldehyde with α-pyridyl methyl ketone in alcoholic potassium hydroxide (Smirnoff, *Helv. Chim. Acta*, 1921, **4**, 806).

Pyridylquinolines have now been obtained (*a*) by diazotising aminoquinolines and allowing the diazonium salts to react with pyridine; and (*b*) from the appropriate nitrophenylpyridines by reduction to the corresponding aminophenylpyridine, followed by the Skraup or Doebner–Miller reaction. Similar reactions have been embodied in B.P. 544,190 (I.C.I. Ltd., Basford and Rose).

2-Aminopyridine can be diazotised only with difficulty by the usual methods, whereas the sodium diazotate is relatively easily obtained by the interaction of the amine, amyl nitrite, and alkali. 2-Aminoquinoline has not hitherto been diazotised and it was concluded that sodium quinoline-2-diazotate offered the better likelihood of directly introducing the pyridyl residue. No difficulty was experienced in preparing the diazotate by the action of amyl nitrite and sodium ethoxide on 2-aminoquinoline, but subsequent reaction with pyridine afforded no evidence of coupling and only a small yield of 2-aminoquinoline was recovered.

4-Aminoquinoline likewise failed to give any 4-pyridylquinoline either by orthodox diazotisation in concentrated sulphuric acid and later reaction with pyridine or by the action of ethereal nitrosyl chloride on a solution of 4-aminoquinoline in excess of pyridine. In view of the abnormal and even amide nature of 2- and 4-aminoquinoline, those failures were not surprising.

3-*Pyridylquinoline.*—3-Aminoquinoline (Renshaw and Friedman, *J. Amer. Chem. Soc.*, 1939, **61**, 3321) diazotised normally and the diazonium salt reacted with pyridine to give a high yield of 3-*pyridylquinolines*. This mixture was fractionated in the form of its picrate, two pure (probably α- and β-) isomerides being isolated. That resulting in preponderating amount was regarded as 3-α-pyridylquinoline (III), the α-compound being the major constituent in all similar reactions.
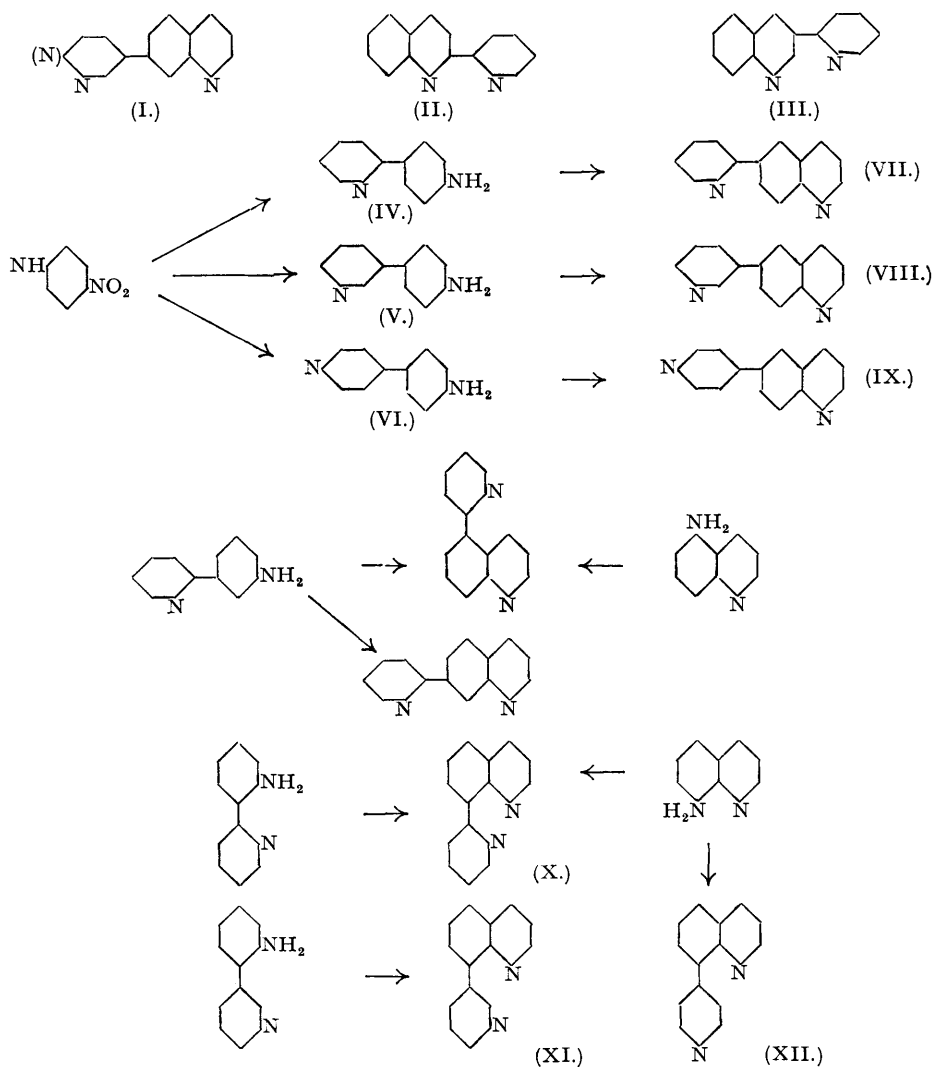
5- and 7-Pyridylquinoline.—3-α-Aminophenylpyridine (Heilbron, Hey, and Lambert, J., 1940, 1281) was converted by means of the Skraup reaction into a mixture of 5-α- and 7-α-*pyridylquinoline*; separation by fractional crystallisation from light petroleum gave the pure components, the separate identities of which were proved by the following unambiguous method. Diazotisation of 5-aminoquinoline and reaction with pyridine in the normal way gave a mixture of 5-pyridylquinolines, from which 5-α-pyridylquinoline was isolated by fractionally crystallising the picrates from acetone.

6-Pyridylquinolines.—α-, β-, and γ-4-Nitrophenylpyridine, isolated from the reaction between diazotised *p*-nitroaniline and pyridine (Haworth, Heilbron, and Hey, J., 1940, 349), were separately reduced to the corresponding α- (IV), β-(V), and γ-4-aminophenylpyridine (VI) (Heilbron, Hey, and Lambert, J., 1940, 1279), which were converted, as indicated above, into the corresponding 6-α-(VII), 6-β-(VIII), and 6-γ-*pyridylquinoline* (IX).

8-Pyridylquinolines.—8-Nitroquinoline was reduced to 8-aminoquinoline; this base was dizaotised and on reacting with pyridine gave a mixture of 8-pyridylquinolines from which three pure compounds were isolated by fractionally crystallising the picrate mixture. One of these was identified as 8-α-pyridylquinoline (X), for it was also obtained by the Skraup reaction on α-2-aminophenylpyridine. β-2-Nitrophenylpyridine gave an *amine* on reduction which afforded 8-β-*pyridylquinoline* (XI) identical with another of the above products, and the structure of 8-γ-*pyridylquinoline* (XII) followed by elimination.

<div align="center">EXPERIMENTAL.</div>

3-Pyridylquinoline.—A solution of 3-aminoquinoline (37 g.) (Renshaw and Friedman, *loc. cit.*) in water (50 c.c.) and concentrated hydrochloric acid (100 c.c.) was cooled to 5°, sodium nitrite (18 g.) in water (50 c.c.) added as quickly as possible below 10°, and the solid diazonium salt dissolved by addition of ice and water (800 g.). The solution was introduced during 2 hours into pyridine (1 l.), which was stirred and maintained at 50°. The reaction solution was made alkaline with ammonia, and pyridine removed in steam. The residual tar was extracted with boiling benzene, and the extract distilled, eventually in a vacuum. The 3-pyridylquinolines were collected at 165—185°/0·2 mm. as a golden-yellow oil (25 g.) which soon solidified. After a single crystallisation from benzene–light petroleum the mixture of isomerides had m. p. 70—80° (Found : N, 14·0. $C_{14}H_{10}N_2$ requires N, 13·6%).

When the picrates were crystallised from *cyclo*hexanone, the α-*isomeride* was readily obtained pure; it had m. p. 227—229° (Found : N, 16·3. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires N, 16·1%). 3-α-*Pyridylquinoline*, liberated by warming the picrate with 10% sodium hydroxide solution, crystallised from benzene–light petroleum in hard white needles, m. p. 101·5° (Found : N, 13·4%). The residual picrate was crystallised from acetone to yield a second *isomeride*, m. p. 196° (decomp.) (Found : N, 16·2%). The free *base*, liberated as in the preceding preparation, separated in white needles, m. p. 123°, from benzene–light petroleum (Found : N, 13·8%).

5- and 7-Pyridylquinoline.—α-3-Aminophenylpyridine (10 g.), anhydrous glycerol (13·5 g.), 98% sulphuric acid (9 c.c.), and anhydrous arsenic acid (8·5 g.) were heated together at 160° for 6 hours. After dilution with water, the solution was made alkaline and extracted with benzene. Distillation of the residue after removal of solvent gave a brown oil (3·7 g.), b. p. 140—155°/0·4 mm., which solidified on standing. Several crystallisations from light petroleum yielded 7-α-*pyridylquinoline* in clusters of needles, m. p. 87—88° (Found : C, 81·9; H, 4·9. $C_{14}H_{10}N_2$ requires C, 81·6; H, 4·9%); the picrate had m. p. 221°. The mother-liquors from the 7-compound gave 5-α-*pyridylquinoline*, which separated from light petroleum in fine colourless needles, m. p. 88—89° (Found : C, 81·8; H, 5·0%). The picrate had m. p. 212°. 5-Nitroquinoline, separated from the mixture of 5- and 8-nitroquinoline obtained by direct nitration of quinoline (Le Fèvre and Le Fèvre, J., 1935, 1472), was reduced with tin and hydrochloric acid to 5-aminoquinoline (Dikshoorn, *Rec. Trav. chim.*, 1929, **48**, 147). To a solution of this base (11 g.) in concentrated hydrochloric acid (64 c.c.) at 90°, water (41 c.c.) was added, and the whole cooled quickly to 0°. The paste of hydrochloride was diazotised at 0° with 5N-sodium nitrite (14 c.c.), and the diazo-solution stirred, during 1 hour, into pyridine (200 c.c.) at 50—60°. After a further hour's stirring at 70—80°, excess of a concentrated solution of caustic soda was added, the pyridine layer separated, and the excess of pyridine removed with steam. The tarry non-volatile layer was extracted with benzene, and the extracts distilled. After removal of solvent 5-pyridylquinolines (4·5 g.) were collected at 152—172°/<0·1 mm. as a red-brown oil. This mixture was treated with alcoholic picric acid, and the mixed picrates fractionally crystallised from acetone. 5-α-Pyridylquinoline picrate separated in fine yellow needles, m. p. 212°, not depressed by the picrate of the base of m. p. 88—89° (above).

6-Pyridylquinolines.—α-4-Aminophenylpyridine (Heilbron, Hey, and Lambert, J., 1940, 1279) (5 g.) was heated with anhydrous glycerol (9 g.), concentrated sulphuric acid (8·5 g.), and anhydrous arsenic acid (4·0 g.) at 160—170° for 6 hours. The mixture was cooled, diluted with 2 vols. of water, kept overnight, and filtered; the filtrate was made just alkaline with dilute caustic soda solution, and the precipitated oily solid extracted with benzene. After removal of benzene, distillation at 70—150° in a high vacuum gave 6-α-*pyridylquinoline* as a pale green solid, which crystallised from light petroleum (b. p. 40—60°) in small colourless needles, m. p. 82—83° (Found : C, 81·6; H, 4·6%). β-4-Amino-phenylpyridine (Heilbron, Hey, and Lambert, *loc. cit.*) (10 g.) was treated as described for the corresponding α-isomeride, and the precipitated oil extracted with benzene. After removal of benzene, distillation at 170—173°/0·1 mm. gave a yellow viscous liquid (7·7 g.) which did not solidify. This product was treated with alcoholic picric acid (2 mols.); the *dipicrate* crystallised from glacial acetic acid in small needles, m. p. 249—250° (Found : N, 16·7. $C_{14}H_{10}N_2,2C_6H_3O_7N_3$ requires N, 16·9%). Heating with 20% caustic soda solution gave a viscous liquid which crystallised slowly. Recrystallisation from light petroleum yielded colourless hygroscopic needles of 6-β-*pyridylquinoline*, m. p. 32—34° (Found : C, 81·3; H, 4·7%). γ-4-Aminophenylpyridine (Heilbron, Hey, and Lambert, *loc. cit.*) (1·5 g.), sodium *m*-nitrobenzene-sulphonate (2·5 g.), and glycerol in sulphuric acid (66% ; 13 g.) were refluxed for 5 hours. The mixture was cooled, diluted with water to 50 c.c., filtered, and made alkaline. After 12 hours, the precipitated base was extracted with benzene. Distillation of the residue, obtained on removal of solvent, at 90—110° in a high vacuum gave 6-γ-*pyridyl-quinoline* (1·5 g.), which separated from light petroleum in small prisms, m. p. 104—105° (Found : C, 82·0 ; H, 4·7%).

8-Pyridylquinolines.—8-Nitroquinoline (Meigen, *J. pr. Chem.*, 1908, **77**, 473) (83 g.) in ethanol (147 c.c.), water (24 c.c.), and concentrated hydrochloric acid (9·6 c.c.) was treated with iron filings (143 g.), and the whole stirred under reflux on the steam-bath for 24 hours. After being made alkaline, the liquid was filtered, the sludge extracted with ethanol, and the combined extracts and filtrate evaporated to dryness. Crystallisation of the residue from benzene–light petroleum yielded 8-aminoquinoline (47 g.) in small plates, m. p. 64°. The amine (47 g.), dissolved in concentrated hydrochloric acid (470 c.c.) and water (180 c.c.), was diazotised at 0° with sodium nitrite (18 g.) in water (60 c.c.), and the filtered diazonium solution added with stirring during 1½ hours to pyridine (400 c.c.) at 60°. After a further hour's stirring at

60°, a concentrated solution of caustic soda was added, and the pyridine layer separated. The excess of pyridine was removed in steam, and the tarry residue extracted with benzene. After removal of solvent, distillation at 120° in a high vacuum gave a viscous liquid (10·2 g.). After chromatography from benzene on alumina the material recovered from the filtrate was converted into a mixture of picrates, which on fractional crystallisation from acetone afforded 8-*α-pyridylquinoline picrate* in fine needles, m. p. 209—210° (Found : N, 16·0. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires N, 16·1%) ; the free base was identical with 8-α-pyridylquinoline obtained by the Skraup reaction (see below) ; the *styphnate* separated from methyl ethyl ketone in yellow needles, m. p. 181·5—182·5° (decomp.) (Found : N, 15·5. $C_{14}H_{10}N_2,C_6H_3O_8N_3$ requires N, 15·5%). Further crystallisation gave 8-β-pyridylquinoline picrate, m. p. 224—225°, both the picrate and the free base being identified with the product of the Skraup reaction (see below). Elution of the alumina with ethanol and crystallisation of the eluate as picrate from the same solvent gave 8-*γ-pyridylquinoline picrate* in yellow needles, m. p. 238—240° (decomp.) (Found : N, 15·8%) ; the free *base* separated from benzene–light petroleum in colourless prisms, m. p. 127° (Found : C, 81·6 ; H, 4·9%).

α-2-Aminophenylpyridine (4·1 g.), sodium *m*-nitrobenzenesulphonate (8·2 g.), glycerol (10 g.), sulphuric acid (d 1·56, 50 c.c.), and vanadium pentoxide (0·1 g.) were refluxed for 5½ hours. After cooling, the mixture was diluted with ice and water, heated to 80°, filtered, and the filtrate made alkaline with ammonia. The solution was cooled at 0° for several hours, the supernatant liquid decanted, and the resultant black tar extracted thoroughly with benzene. The extract was filtered through a short column of alumina, the clear filtrate giving crude 8-*α-pyridylquinoline* (2 g.) on evaporation. Recrystallised from benzene–light petroleum, it gave large prisms, m. p. 74—76°, identical with the product obtained as picrate above (Found : N, 13·5. $C_{14}H_{10}N_2$ requires N, 13·6%). β-2-Nitrophenylpyridine (Haworth, Heilbron, and Hey, J., 1940, 354) (9·5 g.) in ethanol (95 c.c.) was reduced with stannous chloride (51 g.) and concentrated hydrochloric acid. After removal of most of the ethanol, a large excess of concentrated caustic soda solution was added, and the base extracted with ether. Distillation of the residue, obtained on removal of the ether, at 168°/0·06 mm. gave β-2-aminophenylpyridine (4·9 g.) as a viscous liquid, which solidified on cooling to a snow-white mass of needles, m. p. 72°. β-2-Aminophenylpyridine (3·6 g.) was heated with anhydrous glycerol (4·8 g.), anhydrous arsenic acid (3·2 g.), and concentrated sulphuric acid (3·2 c.c.) at 160—170° for 7 hours. The mixture was cooled, diluted with water (2 vols.), and made alkaline. After standing overnight, the tarry precipitate was extracted with benzene. Distillation of the residue, after removal the solvent, at 120° in a high vacuum gave 8-*β-pyridylquinoline*, which separated from benzene–light petroleum in colourless needles, m. p. 111—112° (Found : C, 82·0 ; H, 5·0%). The *picrate* separated from acetone in very fine needles, m. p. 226° (Found : N, 16·0. $C_{14}H_{10}N_2,C_6H_3O_7N_3$ requires N, 16·1%).

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