107. *New Therapeutic Agents of the Quinoline Series. Part II. Dipyridylquinolines.*

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α-4-Aminophenylpyridine has been converted into 8-nitro-6-α-pyridylquinoline and thence into 6-α-pyridyl-8-pyridylquinoline. 6 : 8-Dipyridylquinoline has also been prepared by stepwise introduction of pyridyl groups to yield 1 : 3-dipyridylbenzene, introduction into this of an amino-group, and submission of the product to the Skraup reaction. Similarly, pyridyl groups were introduced stepwise in 1 : 4-positions into the benzene nucleus, and the resulting dipyridylbenzene eventually converted into 5 : 8-dipyridylbenzene.

The compounds described below represent attempts to increase the spasmolytic activity of pyridylquinolines by the introduction of a second pyridyl group.

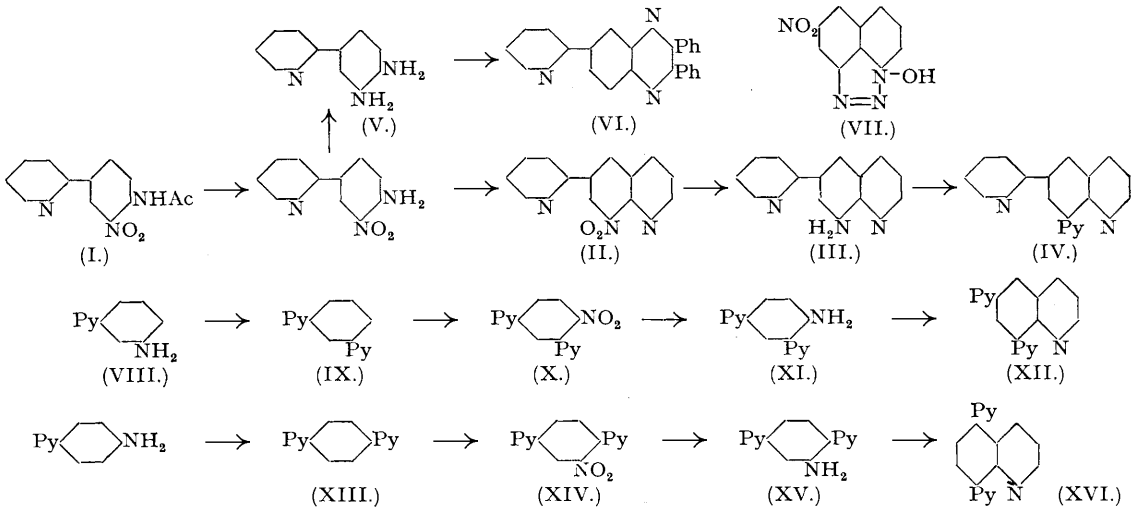
On nitration α-4-acetamidophenylpyridine (Heilbron, Hey, and Lambert, J., 1940, 1281) gave α-3-*nitro*-4-*acetamidophenylpyridine* (I), which was hydrolysed to α-3-*nitro*-4-*aminophenylpyridine*. The application of the Skraup reaction to the latter gave 8-*nitro*-6-α-*pyridylquinoline* (II), which was reduced to 8-*amino*-6-α-*pyridylquinoline* (III). By diazotisation of this amine and subsequent reaction with pyridine, a mixture of 6-α-*pyridyl*-8-α (β and γ)-*pyridylquinoline* (IV) was obtained. The constitution of α-3-nitro-4-aminophenylpyridine was confirmed by its reduction to α-3 : 4-*diaminophenylpyridine* (V) and conversion of this into 2 : 3-*diphenyl*-6-α-*pyridylquinoxaline* (VI).

Alternative methods for the preparation of dipyridylquinolines were then investigated. No success attended attempts to tetrazotise 6 : 8-diaminoquinoline, so the direct simultaneous introduction of two pyridyl groups appeared impracticable. 6-Nitro-8-aminoquinoline reacted with nitrous acid; the product, however, was not a diazonium salt but resembled those obtained from other diazotised 8-aminoquinolines when deficiency of acid is used (D.R.-P. 576,119). It is provisionally regarded as the cyclised triazen (VII).

Mixed 3-nitrophenylpyridines, prepared by the reaction between diazotised *m*-nitroaniline and pyridine (Haworth, Heilbron, and Hey, J., 1940, 349), were reduced to the corresponding amino-compounds (VIII) (cf. Heilbron, Hey, and Lambert, *loc. cit.*), which on diazotisation and subsequent reaction with pyridine gave a mixture of 1 : 3-*dipyridylbenzenes* (IX) in 50% yield. The latter was very resistant to nitration, but a single nitro-group was finally introduced by heating the mixed *dinitrates* with concentrated sulphuric acid. The product, regarded as a mixture of 4-*nitro*-1 : 3-*dipyridylbenzenes* (X) (compare the nitration of *m*-terphenyl; France, Heilbron, and Hey, J., 1939, 1288), was reduced to a mixture of the corresponding amines (XI), which was converted into a mixture of 6 : 8-*dipyridylquinolines* (XII) by means of the Skraup reaction. This mixture had a higher melting point than that of 6-α-pyridyl-8-α(β and γ)-pyridylquinolines and the difference is attributed to the presence of a greater proportion of higher-melting isomerides.

p-Nitroaniline was converted into *p*-nitrophenylpyridines and thence by reduction into a mixture of *p*-aminophenylpyridines. Diazotisation of this mixture and reaction of the aqueous diazonium salt with pyridine gave a considerable yield of p-*dipyridylbenzene* (XIII). The material so obtained probably consists of six isomerides,

the separation and identification of which have not been attempted. Since the final quinoline was required only for comparative physiological tests, the dipyridylbenzene was converted into its nitrate mixture and thence into a *mononitrodipyridylbenzene* (XIV) mixture by heating with sulphuric acid. Each of the unsymmetrical *p*-dipyridylbenzenes may yield two mononitro-derivatives and the total number of nitro-compounds in the mononitration product may be as high as nine; it was not surprising, then, that the nitrodipyridyl-



benzene mixture was an oil. It was converted into 2 : 5-*dipyridylaniline* (XV), a yellow glass, in the usual manner and this into 5 : 8-*dipyridylquinoline* (XVI) by a Skraup reaction using dilute sulphuric acid in presence of vanadium pentoxide (cf. B.P. 394,416). A product of high quality was obtained in good yield; again nine isomerides are theoretically possible, but the quinoline readily solidified and repeated crystallisation afforded a substance of sharp melting point which was probably a single isomeride.

Experimental.

α-3-*Nitro*-4-*acetamidophenylpyridine*.—α-4-Acetamidophenylpyridine (49 g.) (Heilbron, Hey, and Lambert, J., 1940, 1282) was stirred in small portions into nitric acid (*d* 1·5; 200 c.c.) at 0°; after ½ hour, the solution was poured on ice, and the excess of acid neutralised with caustic soda solution. Crystallisation of the pale yellow precipitate from alcohol gave α-3-*nitro*-4-*acetamidophenylpyridine* (45 g.) in silky needles, m. p. 142—143° (Found: C, 60·8; H, 4·6. $C_{13}H_{11}O_3N_3$ requires C, 60·7; H, 4·3%).

The preceding compound (45 g.) was refluxed with a solution of caustic soda (60 g.) in water (300 c.c.) for 20 minutes. Crystallisation of the resulting solid from benzene gave α-3-*nitro*-4-*aminophenylpyridine* in red needles, m. p. 148—149° (Found: C, 61·5; H, 4·2. $C_{11}H_9O_2N_3$ requires C, 61·4; H, 4·2%).

8-*Nitro*-6-α-*pyridylquinoline*.—This was prepared from α-3-nitro-4-aminophenylpyridine (17 g.) as described under 6-α-pyridylquinoline (preceding paper). After removal of solvents the residue was crystallised from alcohol (charcoal), giving 8-*nitro*-6-α-*pyridylquinoline* (6·3 g.) in pale yellow needles, m. p. 123—124° (Found: C, 66·8; H, 3·6. $C_{14}H_9O_2N_3$ requires C, 66·9; H, 3·6%).

8-*Amino*-6-α-*pyridylquinoline*.—A solution of 8-nitro-6-α-pyridylquinoline (9 g.) in alcohol (160 c.c.), water (2 c.c.), and hydrochloric acid (0·7 c.c.) was stirred with iron filings (11 g.) under reflux on the steam-bath for 24 hours. After being made alkaline with caustic soda solution, the liquid was filtered, the sludge extracted with alcohol, and the combined extracts and filtrate evaporated to dryness. Crystallisation of the residue from benzene (charcoal) gave 8-*amino*-6-α-*pyridylquinoline* (6·7 g.) in reddish-yellow plates, m. p. 125—126° (Found: C, 75·9; H, 5·3. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0%).

6-α-*Pyridyl*-8-α(β and γ)-*pyridylquinoline*.—8-Amino-6-α-pyridylquinoline (3 g.), dissolved in concentrated hydrochloric acid (15 c.c.) and water (5 c.c.), was diazotised at 5—10° with sodium nitrite (0·96 g.) in water. After 10 minutes, the liquid was filtered and stirred into pyridine (100 c.c.) at 45—50°. Stirring was continued for 2 hours at 50°, excess of a concentrated solution of caustic soda then added, the pyridine layer separated, and excess of pyridine removed in steam. When cool, the aqueous layer was decanted, and the tarry residue extracted with benzene. After removal of the benzene, distillation at 90—130° in a high vacuum gave a pale yellow, viscous oil which formed a hard glass on cooling. Crystallisation from benzene–light petroleum (b. p. 40—60°) yielded 6-α-*pyridyl*-8-α(β and γ)-*pyridylquinoline* (0·9 g.) in small colourless needles, m. p. 118—121° (Found: C, 80·8; H, 4·4. $C_{19}H_{13}N_3$ requires C, 80·6; H, 4·6%).

α-3 : 4-*Diaminophenylpyridine*.—α-3-Nitro-4-aminophenylpyridine (0·8 g.) in alcohol (100 c.c.) was reduced with stannous chloride (5 g.) and concentrated hydrochloric acid (6 c.c.) in the normal manner. After the addition of a large excess of concentrated caustic soda solution, the base was extracted in ether and crystallised from benzene–light petroleum (b. p. 60—80°), α-3 : 4-*diaminophenylpyridine* being obtained in almost colourless needles, m. p. 126—126·5° (Found: C, 71·4; H, 6·0. $C_{11}H_{11}N_3$ requires C, 71·3; H, 5·9%). A solution of α-3 : 4-diaminophenylpyridine (0·1 g.) and benzil (0·13 g.) in alcohol was refluxed for ½ hour. 2 : 3-*Diphenyl*-6-α-*pyridylquinoxaline* separated on cooling in pale yellow prisms, m. p. 198—199° (Found: C, 83·7; H, 4·8. $C_{25}H_{17}N_3$ requires C, 83·5; H, 4·7%).

Reaction of Diazotised 3-*Aminophenylpyridine with Pyridine*.—A mixture of 3-nitrophenylpyridines prepared as described by Haworth, Heilbron, and Hey (J., 1940, 349) was reduced with stannous chloride and hydrochloric acid. The resulting amino-compounds distilled at 176—181°/1 mm. as a colourless oil which partially solidified on cooling. The solid material crystallised from moist alcohol in plates, m. p. 102—104°. This corresponds to the monohydrate of α-3-aminophenylpyridine described by Forsyth and Pyman (J., 1926, 2912). The mixture of bases was diazotised, and the red diazonium solution added with stirring during 1½ hours to excess of pyridine at 20—22°. After standing

overnight, the mixture was rendered alkaline with 30% aqueous caustic soda, the pyridine layer removed, and the excess of pyridine distilled in steam. The residue was extracted with benzene and after the removal of the solvent, distillation at 195—218°/1 mm. gave a mixture of 1 : 3-dipyridylbenzenes as a yellow oil in 50% yield. The *dinitrate*, crystallised from alcohol, had m. p. 110—120° (Found : C, 53·6; H, 4·1. $C_{16}H_{12}N_2,2HNO_3$ requires C, 53·6; H, 3·9%).

4-*Nitro*-1 : 3-*dipyridylbenzenes*.—Mixed 1 : 3-dipyridylbenzene dinitrates (14 g.) were dissolved in concentrated sulphuric acid and heated on the steam-bath for 1 hour. The solution was then cooled, diluted with water, and made alkaline with caustic soda solution. A mixture of 4-*nitro*-1 : 3-*dipyridylbenzenes* was obtained as a pale yellow oil (10·5 g.), which crystallised from dilute alcohol in almost colourless needles, m. p. 137—140° (Found : C, 69·1; H, 4·2. $C_{16}H_{11}O_2N_3$ requires C, 69·3; H, 4·0%).

The mixture of 4-nitro-1 : 3-dipyridylbenzenes (10 g.) in alcohol (100 c.c.) was reduced with stannous chloride (60 g.) and concentrated hydrochloric acid (60 c.c.), excess of a concentrated solution of caustic soda added, and the liberated base extracted with benzene. After removal of the benene, distillation at 210—225°/0·004 mm. gave a mixture of 4-amino-1 : 3-dipyridylbenzenes (7·5 g.) as a pale yellow oil, which formed a hard glass on cooling.

6 : 8-*Dipyridylquinolines*.—A solution of mixed 4-amino-1 : 3-dipyridylbenzenes (7 g.), sodium *m*-nitrobenzenesulphonate (14 g.), and glycerol (15 g.) in sulphuric acid (66%, 80 c.c.) was refluxed with stirring for 6 hours, cooled, diluted with water to 400 c.c., and made alkaline with caustic soda solution. The material extracted after 12 hours from the tarry precipitate with benzene was crystallised from benzene–light petroleum (b. p. 60—80°), giving a mixture of 6 : 8-*dipyridylquinolines* (3·2 g.) in needles, m. p. 152—156° (Found : C, 80·9; H, 4·6. $C_{19}H_{13}N_3$ requires C, 80·6; H, 4·6%).

p-*Dipyridylbenzene*.—*p*-Aminophenylpyridine (b. p. 160—180°/0·5 mm., 62·5 g.) in 5N-hydrochloric acid (300 c.c.) was diazotised with sodium nitrite (26 g. in 50 c.c. of water), and the solution cooled and added during 30 mins. to pyridine (800 c.c.) at −10°; the temperature rose to about 40°. The dark solution was stirred overnight at room temperature, sodium hydroxide (200 g.) added, and the pyridine removed in steam. The residue was extracted repeatedly with benzene. Removal of solvent, followed by distillation, gave dipyridylbenzene (b. p. 210—230°/0·002 mm., 36 g.) as a yellow oil which rapidly solidified. Solution in ethanol, followed by cautious addition of concentrated nitric acid, gave the insoluble mixed nitrates. The nitrate mixture in concentrated sulphuric acid (65 c.c.) was heated on the steam-bath for 90 minutes, cooled, and poured on ice. Ammonia was added, the separated oil extracted with benzene, and the combined extracts boiled with charcoal. Removal of solvent gave a brown oil which could not be crystallised. Preparation of the nitrate and three crystallisations of the latter from 2N-nitric acid gave a product which, although crystalline, gave an oily base on regeneration. Repeated nitration effected no improvement and the free base was therefore converted directly into the corresponding amine. 2 : 5-Dipyridylnitrobenzene (25 g.) was treated in ethanol (300 c.c.) with stannous chloride (200 g.) in concentrated hydrochloric acid (200 c.c.), and the solution heated on the steam-bath overnight. After removal of ethanol, the residue was treated rapidly with 30% sodium hydroxide solution (1200 c.c.), and the clear aqueous layer extracted with benzene. Removal of benzene, followed by distillation, gave 2 : 5-dipyridylaniline (b. p. 210—230°/0·1 mm.) as a yellow glass (14·5 g.). This base (13 g.), sulphuric acid (60%, 180 c.c.), glycerol (28 g.), arsenic acid (36 g.), and vanadium pentoxide (0·55 g.) were refluxed for 6 hours at 160—170°. The solution was cooled, diluted with water, filtered after a few hours, and made alkaline with sodium hydroxide. After 24 hours the precipitate was collected and extracted with boiling benzene; the combined extracts were refluxed with charcoal, filtered, and evaporated to *ca.* 50 c.c. The product after filtration and drying was a white powder (9 g.), m. p. 140—154°. Two crystallisations from benzene–light petroleum (b. p. 80—100°) gave a fraction (3·5 g.) crystallising in colourless needles, m. p. 157—163°. Further crystallisation of a portion of this fraction gave long colourless needles, m. p. 167° (Found : C, 80·8; H, 4·5. $C_{19}H_{13}N_3$ requires C, 80·6; H, 4·6%). From the mother-liquors concentration gave a fraction (4·5 g.), m. p. 138—149°, crystallising in micro-needles (Found : C, 80·8; H, 4·8%).

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