82. *Preparation of Some Aminopyridoquinolines and their Quaternary Salts.*

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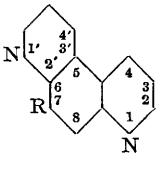
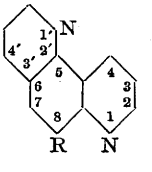
The preparations of the 1- or 1′-metho-salts of 7-amino-6 : 5 : 2′ : 3′-pyridoquinoline (I; R = NH_2) and 8-amino-5 : 6 : 2′ : 3′-pyridoquinoline (II; R = NH_2) are described.

The object of the present investigation was the preparation of the 1′- or 1-metho-salts of 7-amino-6 : 5 : 2′ : 3′-pyridoquinoline (I; R = NH_2) and 8-amino-5 : 6 : 2′ : 3′-pyridoquinoline (II; R = NH_2) respectively for test as trypanocidal agents. These structures were selected, first, because of the observation (Browning *et al.*, *J. Path. Bact.*, 1938, **46**, 203; 1940, **50**, 371) that complex heterocyclic compounds, *e.g.*, 7-amino-9-(*p*-aminophenyl)-10-methylphenanthridinium chloride, are active agents against *Tr. Congolense*, and secondly, because they show a structural relationship to the quaternary salt present in acriflavine.

(I.) 

 (II.)

The preparation of the isomeric 7-amino-5 : 6 : 2′ : 3′-pyridoquinoline by stannous chloride reduction of the corresponding 7-nitro-compound, obtained by a double Skraup reaction on 5-nitro-*m*-phenylenediamine (Korczynski and Brydowna, *Bull. Soc. chim.*, 1925, **37**, 1483), is described in E.P. 454,525. This patent also describes the preparation of (II; R = NH_2) and a number of derivatives, but a variety of new methods for the preparation of aminopyridoquinolines have now been examined.

Attempts to nitrate either 5 : 6 : 2′ : 3′- (II; R = H) or 6 : 5 : 2′ : 3′-pyridoquinoline (I; R = H), obtained by double Skraup reactions on *m*- and *p*-phenylenediamine, respectively (Smith, *J. Amer. Chem. Soc.*, 1930, **52**, 397), were unsuccessful; the pyridoquinolines were recovered after treatment with concentrated or fuming nitric acid in the presence of concentrated sulphuric acid at 20° or 100°. The required nitropyridoquinolines (I and II; R = NO_2) could not be prepared by double Skraup reactions on 2-nitro-*m*-phenylenediamine (Bulow and Mann, *Ber.*, 1897, **30**, 979) and 4-nitro-*m*-phenylenediamine (Morgan and Wootton, J., 1905, **107**, 941; Gordonov, *Anilinokras. Prom.*, 1934, **4**, 277), respectively. The attractive approach from 2 : 5-diaminobenzenesulphonic acid, which is readily obtained from *p*-phenylenediamine (Friedländer, III, 40), was abandoned because conditions could not be found for the conversion of the sulphonic acid into the pyridoquinolinesulphonic acid (I; R = SO_3H) (contrast E.P. 451,932).

As the literature (E.PP. 394,416, 454,525, 454,526) indicated that the aminopyridoquinolines could be

obtained by amination of the corresponding bromo-derivatives, the preparation of the bromo-bases (I and II; R = Br) has been examined. The last patent describes the preparation of (I; R = Br) from 2-bromo-*p*-phenylenediamine, but we were unable to prepare the latter by the bromination of *p*-phenylenediamine either directly in hydrobromic acid solution or by way of the diformyl or diacetyl derivative. A successful synthesis from *p*-nitroaniline has, however, been developed. 2-Bromo-*p*-nitroaniline, prepared by the method of Nicolet and Ray (*J. Amer. Chem. Soc.*, 1927, **49**, 1803) gave a 60% yield of 8-bromo-6-nitroquinoline by a Skraup reaction using arsenic acid. Reduction with stannous chloride gave 8-*bromo*-6-*aminoquinoline*, m. p. 148°, in 60% yield, which was converted into 7-bromo-6 : 5 : 2′ : 3′-pyridoquinoline (I; R = Br) in 60% yield by a Skraup reaction using *m*-nitrobenzenesulphonic acid.

The preparation of 4-bromo-*m*-phenylenediamine by bromination of diacetyl-*p*-phenylenediamine in acetic acid is described in E.P. 454,526; a more convenient preparation from diformyl-*m*-phenylenediamine, giving 80% yields, has now been developed. 4-Bromo-*m*-phenylenediamine was converted into 8-bromo-5 : 6 : 2′ : 3′-pyridoquinoline (II; R = Br) in yields varying from 10 to 30% by a double Skraup reaction using either arsenic acid or *m*-nitrobenzenesulphonic acid.

The bromopyridoquinolines (I and II; R = Br) were not aminated by heating with dry ammonia in phenolic solution either alone or in presence of formamide or acetamide (Jacini, *Gazzetta*, **1940**, **70**, 621). The best conditions for the amination consisted of heating the bromo-bases with phenol and concentrated aqueous ammonia at 180° for 3 days in the presence of small amounts of copper sulphate; in this way 8-amino-5 : 6 : 2′ : 3′-pyridoquinoline (II; R = NH_2), m. p. 139—141° (E.P. 454,525 gives m. p. 143°), and 7-*amino*-6 : 5 : 2′ : 3′-*pyridoquinoline* (I; R = NH_2), m. p. 213—215°, were obtained each in 45% yields.

In view of the small yield of 8-bromo-5 : 6 : 2′ : 3′-pyridoquinoline (II; R = Br) produced in the double Skraup reaction discussed above, other routes to this base have been examined. 8-Hydroxyquinoline was converted in good yield by the method of Fischer and Renouf (*Ber.*, 1884, **17**, 1643) into 5-amino-8-hydroxyquinoline sulphate, and the latter, subjected to a Skraup reaction with *m*-nitrobenzenesulphonic acid, yielded 8-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline (II; R = OH), m. p. 158—159° (Matsumura, *J. Amer. Chem. Soc.*, **1930**, **52**, 3974, gives m. p. 157—158°), in 60% yield. This hydroxy-base, heated with ammonia for 15 hours at 210—220°, gave 8-amino-5 : 6 : 2′ : 3′-pyridoquinoline (II; R = NH_2) in 90% yields.

In order to convert one of the tertiary nitrogen atoms of the aminopyridoquinolines into the quaternary salt, the primary amino-group was protected as in the acriflavine preparation (Grandmougin and Smirous, *Ber.*, 1913, **46**, 3431). The *acetyl* derivatives of the bases (I and II; R = NHAc), m. p. 188° and 198°, respectively (E.P. 454,525 gives 201° for the latter), were easily obtained in high yield by warming with acetic anhydride, but they showed a remarkable difference in reactivity towards methyl iodide. 7-Acetamido 5 : 6 : 2′ : 3′-pyridoquinoline was readily converted into the *monomethiodide* by heating with excess methyl iodide at 100°; and on warming with methyl-alcoholic hydrogen chloride and silver chloride, deacetylation and conversion into 7-*amino*-6 : 5 : 2′ : 3′-*pyridoquinoline methochloride* was effected. Attempts to methylate 8-acetamido-5 : 6 : 2′ : 3′-pyridoquinoline by methyl sulphate or iodide each under a wide variety of conditions yielded the unchanged tertiary base, tars, or the hydriodide or methyl hydrogen sulphate of the tertiary base (compare Kermack and Webster, J., 1942, 213). The methylation was eventually accomplished by heating with excess of methyl *p*-toluenesulphonate at 120—130°, but the quaternary salt was not obtained in the presence of solvents, *e.g.*, xylene. Deacetylation and conversion of the resulting quaternary compound into 8-*amino*-5 : 6 : 2′ : 3′-*pyridoquinoline methochloride* was accomplished by refluxing with 20% aqueous hydrochloric acid.

Conclusive proof of the positions of the methochloride groups has not been obtained, but positions 1 (I; R = NH_2) and 1′ (II; R = NH_2) are considered probable.

Experimental.

8-*Bromo*-6-*nitroquinoline*.—A mixture of 2-bromo-4-nitroaniline (78·5 g., m. p. 98—102°, obtained in 80% yield by the method of Nicolet and Ray, *loc. cit.*), water (210 c.c.), concentrated sulphuric acid (270 c.c.), glycerol (100 c.c.), and arsenic acid (120 c.c., *d*, 1·8) was refluxed for 3—4 hours. The cooled solution was diluted to 2—3 l., filtered from a small amount of tar, and sodium hydroxide (450 g.) in water was added with cooling to the filtrate. The crude base was collected, dried (80 g.), and crystallised from benzene (charcoal); yellow-brown prisms (70 g.), m. p. 162—164°, were obtained (Claus and Hartman, *J. pr. Chem.*, 1896, **53**, 207, give m. p. 164°). Unsatisfactory results were obtained when the arsenic acid was replaced by *m*-nitrobenzenesulphonic acid.

8-*Bromo*-6-*aminoquinoline*.—A solution of stannous chloride dihydrate (60 g.) in concentrated hydrochloric acid (25 c.c.) was gradually added with stirring to a solution of 8-bromo-6-nitroquinoline (20 g.) in warm concentrated hydrochloric acid (60 c.c.). When the vigorous reaction had subsided, the mixture was heated for 10 minutes on the steam-bath, cooled, filtered, and the residual stannichloride was suspended in hot water, and decomposed with hydrogen sulphide. The hot filtrate on cooling deposited 8-*bromo*-6-*aminoquinoline hydrochloride* in yellow, felted needles, containing water of crystallisation, which was completely lost after ½ hr.'s heating at 96° (Found: loss, 12·2. $C_9H_7N_2Br,HCl,2H_2O$ requires loss, 12·2%. Found, on dried material: Cl, 13·8. $C_9H_7N_2Br,HCl$ requires Cl, 13·7%). The hydrochloride, which does not melt at 275°, was dissolved in hot water (400 c.c.), and the solution made slightly alkaline by addition of sodium hydroxide solution. 8-*Bromo*-6-*aminoquinoline* (14 g.) was collected, and crystallised from benzene as clusters of pale yellow squat needles giving the appearance of plates in bulk, m. p. 148° (Found: Br, 35·4. $C_9H_7N_2Br$ requires Br, 35·8%). The *acetyl* derivative, prepared by warming the base with acetic anhydride on the water-bath for a few minutes and basifying the diluted mixture with sodium hydroxide solution, crystallised from dilute acetic acid in minute, plume-like clusters of threads, forming a white felted mass, m. p. 199° (Found: Br, 30·4. $C_{11}H_9ON_2Br$ requires Br, 30·2%), on collection.

7-*Bromo*-6 : 5 : 2′ : 3′-*pyridoquinoline* (I; R = Br).—Nitrobenzene (17 c.c.) was sulphonated by heating with 65%

fuming sulphuric acid (10 c.c.) on the steam-bath until a test portion was completely soluble in water. 8-Bromo-6-aminoquinoline (20 g.), concentrated sulphuric acid (40 c.c.), water (50 c.c.), and glycerol (25 c.c.) were added, and the mixture was refluxed for 4 hours, cooled, diluted, and filtered. The filtrate, basified with sodium hydroxide solution, deposited an oil which was taken up in benzene. The extract was dried, the solvent removed, and the residue distilled at 0·01 mm. The bromo-base (I; R = Br) was obtained as a pale yellow distillate (20 g.), which solidified on cooling, and crystallised from alcohol or benzene in colourless needles, m. p. 147—149° (E.P. 454,526 gives m. p. 150°). The *hydrochloride*, prepared by mixing a warm methyl-alcoholic solution of the base with hydrochloric acid, was obtained as small bunches of colourless needles which darkened but did not melt at 325° (Found: Cl, 11·9. $C_{12}H_7N_2Br,HCl$ requires Cl, 12·0%). The *monomethiodide*, prepared by heating the base with excess of methyl iodide at 100° for 30 minutes, crystallised from hot water in orange prisms, m. p. 305° (decomp.) with previous darkening and softening (Found: I, 31·2. $C_{12}H_7N_2Br,CH_3I$ requires I, 31·6%).

7-*Amino*-6 : 5 : 2′ : 3′-*pyridoquinoline* (I; R = NH_2).—7-Bromo-6 : 5 : 2′ : 3′-pyridoquinoline (I; R = Br) (3 g.), phenol (3 g.), concentrated ammonium hydroxide (10 c.c.), and crystalline copper sulphate (0·3 g.) were heated for 3 days in a sealed tube at 180—200°. The product, which solidified on cooling, was collected, taken up in dilute hydrochloric acid, and filtered. Traces of phenol were removed in benzene, and on basification of the acid layer, 7-*amino*-6 : 5 : 2′ : 3′-*pyridoquinoline* (I; R = NH_2) separated as an oil which gradually solidified; the yellow-brown product was collected, dried, and distilled at 0·01 mm.; the distillate (1·3 g.) separated from methylated spirits in yellow needles, m. p. 213—215° (Found: C, 74·2; H, 4·9. $C_{12}H_9N_3$ requires C, 73·9; H, 4·6%). The *acetyl* derivative, prepared by heating with acetic anhydride, diluting with water and basifying, crystallised from benzene in colourless needles, m. p. 188° (Found: C, 70·5; H, 5·1. $C_{14}H_{11}ON_3$ requires C, 70·8; H, 4·6%).

7-*Acetamido*-6 : 5 : 2′ : 3′-*pyridoquinoline methiodide*, obtained in quantitative yield by the action of methyl iodide at 100°, separated from hot water in monohydrated, pale yellow needles, m. p. 283° (decomp.) (Found, for material air-dried at 96°: I, 31·7. $C_{14}H_{11}ON_3,CH_3I,H_2O$ requires I, 32·0%. Found: loss on drying in a vacuum over P_2O_5 at 95°, 4·2. $C_{14}H_{11}ON_3,CH_3I,H_2O$ requires H_2O, 4·5%. Found for anhydrous material: I, 33·6. $C_{14}H_{11}ON_3,CH_3I$ requires I, 33·5%).

7-*Amino*-6 : 5 : 2′ : 3′-*pyridoquinoline methochloride* was prepared by refluxing the above 7-acetamido-methiodide with an equal weight of freshly prepared silver chloride in methyl-alcoholic hydrogen chloride for 12 hours. The filtered solution was treated with ether, and the precipitated methochloride crystallised as a *monohydrate* from alcohol; yellow-orange needles, m. p. 272° (decomp.), were obtained (Found, for air-dried substance: Cl, 13·3. $C_{12}H_9N_3,CH_3Cl,H_2O$ requires Cl, 13·5%. Found: loss on drying in a vacuum over P_2O_5 at 95°, 6·3. $C_{12}H_9N_3,CH_3Cl,H_2O$ requires H_2O, 6·8%. Found, for anhydrous material: Cl, 14·8. $C_{12}H_9N_3,CH_3Cl$ requires Cl, 14·5%).

4-*Bromo*-m-*phenylenediamine*.—A solution of bromine (8 c.c.) in 90% formic acid (75 c.c.) was gradually added with stirring to a solution of diformyl-*m*-phenylenediamine, m. p. 155° (20 g., prepared in 95% yield by the method of Tobias, *Ber.*, 1882, **15**, 2447), and sodium formate (14 g.) in 90% formic acid (75 c.c.). The temperature rose about 7° during the addition (larger preparations require water cooling). After dilution with warm water (800 c.c. at 40°), the diformyl derivative which separated on standing was collected, washed with sodium hydrogen carbonate solution and water, and dried. The product (25 g.), m. p. 175—176°, was purified by addition of water to a concentrated formic acid solution; a white powder, m. p. 179—180°, was obtained (Found: Br, 32·8. $C_8H_7O_2N_2Br$ requires Br, 32·7%). The *diformyl* derivative (24 g.) was boiled for 5 minutes with hydrochloric acid (100 c.c., 18%), water (400 c.c.) added, and the solution neutralised with concentrated ammonia. The 4-bromo-1 : 3-diaminobenzene was collected, dried in a desiccator (18 g., m. p. *ca.* 100°), and crystallised from benzene; white prisms, m. p. 109—111°, were obtained, which darkened on exposure to the air (Morgan, J., 1900, **77**, 1205, gives m. p. 111—112°).

8-*Bromo*-5 : 6 : 2′ : 3′-*pyridoquinoline* (II; R = Br), m. p. 109—110°, was prepared in yields varying from 10 to 30% by the method described in E.P. 454,526 or as follows: 4-Bromodiformyl-*m*-phenylenediamine (20 g.) was boiled for 5—10 minutes with a mixture of concentrated sulphuric acid (80 c.c.) and water (80 c.c.). Glycerol (40 c.c.) and sodium *m*-nitrobenzenesulphonate (40 g.) were then added, and the mixture heated under reflux for 4 hours. The solution was cooled, diluted, filtered from hydroxymetanilic acid, and made alkaline with sodium hydroxide. The syrup which separated was taken up in hot benzene and combined with a hot benzene extract of the alkaline liquor, dried, and the solvent removed. The residue distilled at 0·01 mm., yielding an orange, viscous distillate from which the bromopyridoquinoline (II; R = Br) (5 g., m. p. 105—109°) was obtained by crystallisation from hot methyl alcohol (*ca.* 20 c.c.); a second crystallisation gave colourless needles, m. p. 109—110°. The *monohydrochloride*, m. p. 268—274°, with previous softening, was prepared as small clusters of white needles by mixing a solution of the base in hot alcohol with alcoholic hydrogen chloride (Found: Cl, 11·8. $C_{12}H_7N_2Br,HCl$ requires Cl, 11·8%). The picrate, prepared in alcoholic solution, crystallised from alcohol in yellow prisms, m. p. 229—230°. The chromate separated as minute yellow needles, m. p. 181° (decomp.), on addition of potassium chromate to an aqueous solution of the base sulphate.

8-*Hydroxy*-5 : 6 : 2′ : 3′-*pyridoquinoline* (R = OH).—5-Amino-8-hydroxyquinoline sulphate (20 g., prepared by the method of Fischer and Renouf, *loc. cit.*), sodium *m*-nitrobenzenesulphonate (40 g.), concentrated sulphuric acid (50 c.c.), water (60 c.c.), and glycerol (25 c.c.) were heated under reflux for 4 hours. The diluted and cooled solution was filtered, and the filtrate neutralised by addition of dilute ammonium hydroxide. The crude hydroxy-base was collected, dried (50 g.), and distilled at 0·01 mm. The product (10 g., m. p. 155°) separated from benzene in colourless slender prisms, m. p. 158—159° (Matsumura, *loc. cit.*, gives m. p. 158—159°). The *dihydrochloride*, m. p. 315° (decomp.), separated from concentrated hydrochloric acid in pale yellow, slender prisms (Found: Cl, 26·5. $C_{12}H_8ON_2,2HCl$ requires Cl, 26·4%). The picrate crystallised from alcohol in clusters of yellow needles, m. p. 243° (decomp.) (Matsumura, *loc. cit.*, gives m. p. 237°, decomp.).

8-*Amino*-5 : 6 : 2′ : 3′-*pyridoquinoline* (II; R = NH_2).—(a) The bromo-base (II; R = Br), aminated as described in the preparation of (I; R = NH_2), gave 45% yields of the amino-base (II; R = NH_2). (b) The hydroxy-base (II; R = OH), aminated as described in E.P. 451,932, gave the amino-base (II; R = NH_2) in 90% yield.

The *hydrochloride*, obtained by passing dry hydrogen chloride into a dry ethereal solution of the base, crystallised from methyl alcohol in small yellow needles, m. p. 295° (decomp.) (Found: Cl, 15·3. $C_{12}H_9N_3,HCl$ requires Cl, 15·3%). The picrate crystallised from water in small yellow needles, m. p. 235° (decomp.) with previous darkening. The amino-base (II; R = NH_2), which crystallised from benzene in yellow needles, m. p. 139—141° (E.P. 454,525 gives m. p. 143°), was converted into 8-acetamido-5 : 6 : 2′ : 3′-pyridoquinoline (II; R = NHAc), m. p. 197—198° (E.P. 454,525 gives m. p. 201°). The picrate crystallised from water in small yellow needles, m. p. 237° (decomp.) with previous darkening and softening.

8-*Amino*-5 : 6 : 2′ : 3′-*pyridoquinoline Methochloride*.—8-Acetamido-5 : 6 : 2′ : 3′-pyridoquinoline (2 g.) and methyl *p*-toluenesulphonate (8 g.) were heated for 2 hours at 120—130°. Addition of ether precipitated the quaternary salt as a deliquescent solid, which was collected, washed with ether, and heated under reflux for 3 hours with 20% hydrochloric acid (30 c.c.). Acetone added to the cooled solution precipitated the *methochloride* (2 g.), which was collected, washed with acetone and ether, and crystallised from alcohol–ether; orange needles, m. p. 280° (decomp.), were obtained (Found: Cl, 23·8. $C_{12}H_9N_3,CH_3Cl,HCl,H_2O$ requires Cl, 23·7%). The analytical figures suggest that the orange

needles, m. p. 280°, are the monohydrate of the methochloride hydrochloride, and this is supported by the strongly acid nature of an aqueous solution of the salt.

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