379. *Some Reactions of Substituted 2-Bromopyridines.*

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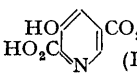
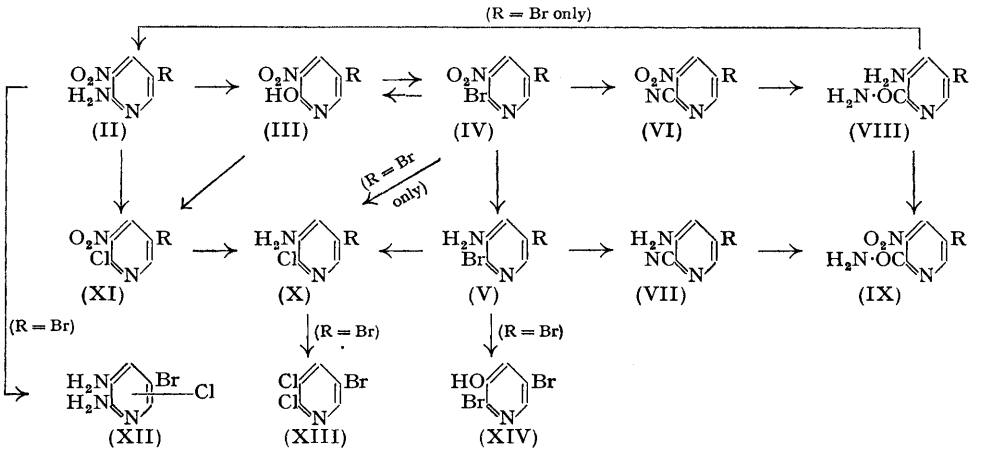
A synthesis of 3-amino-5-bromopicolinamide is described, during which the reactions of 3-nitro- and 3-amino-2-bromopyridines and the corresponding 5-chloro- and 5-bromo-derivatives with cuprous cyanide and with hydrochloric acid have been studied. Such substitution at the 3- or the 3- and 5-positions in 2-bromopyridine does not influence the reaction with cuprous cyanide (replacement of $-Br$ by $-CN$). The reaction with hydrochloric acid, however, is controlled by the nature of the 3-substituent, a 2-bromo-3-nitropyridine being converted into the corresponding pyridone whilst a 3-amino-2-bromopyridine gives the corresponding 3-amino-2-chloropyridine irrespective of the nature of the 5-substituent.

The experiments described in this paper have as their ultimate objective the preparation of 3-hydroxy*iso*cinchomeronic acid (I) which is required for synthesis of lysergic acid; a synthesis of 3-amino-5-bromopicolinamide (IX; R = Br) is now described.



(I)

2-Amino-3-nitropyridine (II; R = H) (Tschitschibabin and Kirssanow, *Ber.*, 1927, **60**, 766) is converted into 2-hydroxy-3-nitropyridine (III; R = H) by treatment with nitrous acid (Tschitschibabin and Bylinkin, *J. Russ. Phys. Chem. Soc.*, 1920, **50**, 471), and reaction of this compound with phosphorus tribromide–phosphorus pentabromide gives 2-bromo-3-nitropyridine (IV; R = H) which can be reduced to 3-amino-2-bromopyridine (V; R = H). The reactions of (IV; R = H) and (V; R = H) with cuprous



cyanide give, respectively, 3-nitro- (VI; R = H) and 3-amino-picolinonitrile (VII; R = H) which have been characterised by hydrolysis to 3-nitro- (VIII; R = H) and 3-amino-picolinamide (IX; R = H), respectively. The relation between the last two compounds is confirmed by reduction of the former to the latter.

When 2-bromo-3-nitropyridine (IV; R = H) is treated with concentrated hydrochloric acid it is converted into the 2-hydroxy-compound (III; R = H), whereas similar treatment of 3-amino-2-bromopyridine (V; R = H) with hydrochloric acid gives 3-amino-2-chloropyridine (X; R = H), which has been obtained by Schickh, Binz, and Schulz (*Ber.*, 1935, **68**, 2593) from both 3-aminopyridine and 2-chloro-3-nitropyridine (XI; R = H). The last compound was obtained by Tschitschibabin and Bylinkin (*loc. cit.*) by treatment of (II; R = H) with nitrous and hydrochloric acid, and we find that it is also obtained in good yield by treatment of (III; R = H) with phosphoryl chloride–phosphorus pentachloride.

Similar transformations have been effected in the series of 5-chloro-compounds (R = Cl), starting from 2-amino-5-chloro-3-nitropyridine (II; R = Cl) (Tschitschibabin and Jegorow,

J. Russ. Phys. Chem. Soc., 1928, **60**, 683; Tschitschibabin and Kirssanow, *loc. cit.*), and in the 5-bromo-series (R = Br), starting from 2-amino-5-bromo-3-nitropyridine (II; R = Br) (Caldwell, Tyson, and Lauer, *J. Amer. Chem. Soc.*, 1944, **66**, 1479; Petrow and Saper, *J.*, 1948, 1389). Additional proof of the structure of (II; R = Br) was obtained by its reduction to 2 : 3-diamino-5-bromo-4(6)-chloropyridine (XII), which forms a quinoxaline derivative with phenanthraquinone.

In addition to the method used in the series R = H and R = Cl, 3-amino-5-bromo-2-chloropyridine (X; R = Br) has been obtained by treatment of 2 : 5-dibromo-3-nitropyridine (IV; R = Br) with tin and hydrochloric acid. The position of the entering nitrile group in the picolinonitriles (VI and VII; R = Br) is confirmed by the conversion by hypohalite of 5-bromo-3-nitropicolinamide (VIII; R = Br) into 2-amino-5-bromo-3-nitropyridine. 3-Amino-2 : 5-dibromopyridine (V; R = Br) has been characterised by conversion into 2 : 5-dibromo-3-hydroxypyridine (XIV), and 3-amino-5-bromo-2-chloropyridine (X; R = Br) by diazotisation in hydrochloric acid followed by treatment with copper powder to give 5-bromo-2 : 3-dichloropyridine (XIII).

Experimental

2-Bromo-3-nitropyridine.—2-Hydroxy-3-nitropyridine (14 g.) was added to a mixture of phosphorus tribromide (50 g.) and bromine (16 g.) and heated at 100° for 5 hours. The cooled mixture was treated dropwise with methanol (100 c.c.) and then with water (300 c.c.), and the precipitated solid was collected, dried, and extracted with boiling benzene (2 × 200 c.c.). The solid obtained on evaporation of the solvent was extracted with light petroleum (b. p. 60—80°; 2 × 150 c.c.) and crystallised from aqueous ethanol (charcoal), giving *2-bromo-3-nitropyridine* (10 g.) as prisms, m. p. 125° (Found: C, 30·0; H, 1·7. $C_5H_3O_2N_2Br$ requires C, 29·6; H, 1·5%).

2-Bromo-5-chloro-3-nitropyridine was obtained in 59% yield from 5-chloro-2-hydroxy-3-nitropyridine by the method described above; it separated from aqueous ethanol (charcoal) as prisms, m. p. 75° (Found: C, 25·8; H, 0·8; N, 11·4. $C_5H_2O_2N_2ClBr$ requires C, 25·3; H, 0·8; N, 11·8%). *2 : 5-Dibromo-3-nitropyridine*, obtained in 80% yield by similar treatment of 5-bromo-2-hydroxy-3-nitropyridine, separated from light petroleum (b. p. 60—80°) as stout needles, m. p. 93° (Found: C, 21·4; H, 1·0. $C_5H_2O_2N_2Br_2$ requires C, 21·3; H, 0·7%).

2-Hydroxy-3-nitropyridine.—A solution of 2-bromo-3-nitropyridine (1·0 g.) and concentrated hydrochloric acid (10 c.c.) in glacial acetic acid (10 c.c.) was refluxed for 3 hours and evaporated. Crystallisation of the residue from methanol gave 2-hydroxy-3-nitropyridine (0·5 g.) as pale yellow needles, m. p. 224° undepressed by a specimen, m. p. 224°, prepared by Tschitschibabin and Bylinkin's method (*loc. cit.*). 5-Chloro-2-hydroxy-3-nitropyridine, obtained in 54% yield by similar treatment of 2-bromo-5-chloro-3-nitropyridine, separated from ethanol as yellow prisms, m. p. 235° alone or mixed with a specimen (m. p. 235°) prepared by Berrie, Newbold, and Spring's method (*loc. cit.*).

5-Bromo-2-hydroxy-3-nitropyridine.—(*a*) Treatment of 2 : 5-dibromo-3-nitropyridine with hydrochloric and acetic acid as described above gave *5-bromo-2-hydroxy-3-nitropyridine* (yield 64%) which separated from ethyl acetate as pale yellow needles, m. p. 242° (decomp.) (Found: C, 27·7; H, 1·0. $C_5H_3O_3N_2Br$ requires C, 27·4; H, 1·4%).

(*b*) A solution of 2-amino-5-bromo-3-nitropyridine (10·0 g.) in sulphuric acid (25 c.c.; *d* 1·84) was treated at 0° with a solution of sodium nitrite (6·0 g.) in water (15 c.c.), and kept at this temperature for 30 minutes. Water (150 c.c.) was added and the orange precipitate collected, dried, and crystallised from ethanol, giving 5-bromo-2-hydroxy-3-nitropyridine (6·05 g.) as pale yellow needles, m. p. 240—241° (decomp.) alone or when mixed with a specimen prepared by method (*a*) (Found: C, 27·6; H, 1·2%).

2-Chloro-3-nitropyridine.—A mixture of 2-hydroxy-3-nitropyridine (0·7 g.), phosphorus pentachloride (2·0 g.), and phosphoryl chloride (1·5 c.c.) was heated at 100° for 2 hours; methanol (10 c.c.) was added and the mixture evaporated to dryness under reduced pressure. The residue was shaken with water (10 c.c.), and the solid collected and crystallised from aqueous ethanol (charcoal), giving 2-chloro-3-nitropyridine (0·2 g.) as prisms, m. p. 101° alone or when mixed with a specimen, m. p. 101°, prepared by the action of nitrous and hydrochloric acids on 2-amino-3-nitropyridine (Tschitschibabin and Bylinkin, *loc. cit.*).

2 : 5-Dichloro-3-nitropyridine.—(*a*) This *compound* was obtained in 52% yield from 5-chloro-2-hydroxy-3-nitropyridine by using the method described above; it separated from aqueous ethanol as prisms, m. p. 43° (Found: N, 14·6. $C_5H_2O_2N_2Cl_2$ requires N, 14·5%).

(*b*) 2-Amino-5-chloro-3-nitropyridine (1·74 g.) was shaken with hydrochloric acid (20 c.c.; *d* 1·19) at −10° and the mixture treated with a solution of sodium nitrite (1·5 g.) in water (4 c.c.), added dropwise. After being shaken for a further hour below 0° the solution was nearly neutralised by the addition of 30% sodium hydroxide solution with cooling. The solid was collected and crystallised from aqueous ethanol (charcoal), giving 2 : 5-dichloro-3-nitropyridine (1·3 g.) as prisms, m. p. 43° alone or mixed with a specimen prepared by method (*a*).

5-*Bromo*-2-*chloro*-3-*nitropyridine* was obtained in 45% yield by treatment of 5-bromo-2-hydroxy-3-nitropyridine with phosphorus pentachloride and phosphoryl chloride by using the method described above; it separated from aqueous ethanol as prisms, m. p. 68° alone or when mixed with a specimen, m. p. 68°, prepared in 51% yield from 2-amino-5-bromo-3-nitropyridine by the method (*b*) described for 2 : 5-dichloro-3-nitropyridine [Found: (*a*) C, 25·7; H, 0·7. (*b*) C, 25·6; H, 1·0. $C_5H_2O_2N_2ClBr$ requires C, 25·3; H, 0·8%].

3-*Nitropicolinonitrile*.—A mixture of 2-bromo-3-nitropyridine (0·75 g.) and cuprous cyanide (0·7 g.), in a flask fitted with a vertical condenser loosely plugged with cotton wool, was gradually heated to 150°, whereupon a vigorous reaction occurred. The pressure was immediately reduced to 1 mm. and the heat source removed after 15 seconds. When cold, the reaction mass, together with the sublimed solid held by the cotton wool, was extracted with hot acetone. Evaporation of the solvent and crystallisation of the residue from benzene–light petroleum (b. p. 60—80°) gave 3-*nitropicolinonitrile* (0·3 g.) as prisms, m. p. 78° (Found: C, 47·9; H, 2·3. $C_6H_3O_2N_3$ requires C, 48·3; H, 2·0%).

5-*Chloro*-3-*nitropicolinonitrile* was obtained from 2-bromo-5-chloro-3-nitropyridine by using the method described above (yield 30%); it separated from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 98° (Found: C, 39·6; H, 0·9; N, 23·0. $C_6H_2O_2N_3Cl$ requires C, 39·3; H, 1·1; N, 22·9%).

5-*Bromo*-3-*nitropicolinonitrile* was obtained in 66% yield from 2 : 5-dibromo-3-nitropyridine; it separated from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 102° (Found: C, 31·5; H, 1·2; N, 18·3. $C_6H_2O_2N_3Br$ requires C, 31·6; H, 0·9; N, 18·4%). 3-*Amino-picolononitrile*, obtained in 32% yield from 3-amino-2-bromopyridine, separated from benzene as needles, m. p. 149° (Found: C, 60·4; H, 4·5. $C_6H_5N_3$ requires C, 60·5; H, 4·2%). 3-*Amino*-5-*chloropicolinonitrile*, obtained in 20% yield from 3-amino-2-bromo-5-chloropyridine, separated from benzene as needles, m. p. 175° (Found: C, 47·0; H, 2·4. $C_6H_4N_3Cl$ requires C, 46·9; H, 2·6%). 3-*Amino*-5-*bromopicolinonitrile*, obtained in 25% yield from 3-amino-2 : 5-dibromopyridine, separated from benzene as needles, m. p. 175° (Found: N, 21·3. $C_6H_4N_3Br$ requires N, 21·2%).

3-*Nitropicolinamide*.—A mixture of 3-nitropicolinonitrile (100 mg.) and sulphuric acid (0·2 c.c.; *d* 1·84) was kept at 100° for 2 hours. Water (2 c.c.) was added with cooling and the precipitate collected. Crystallisation from aqueous acetone gave 3-*nitropicolinamide* (50 mg.) as needles, m. p. 211° (Found: C, 43·5; H, 3·0. $C_6H_5O_3N_3$ requires C, 43·1; H, 3·0%). The amide sublimes readily at $100°/10^{-5}$ mm. 5-*Chloro*-3-*nitropicolinamide* was obtained in 55% yield from 5-chloro-3-nitropicolinonitrile by using the method described above; it separated from aqueous acetone as needles, m. p. 230° (Found: C, 35·5; H, 2·0; N, 20·7. $C_6H_4O_3N_3Cl$ requires C, 35·7; H, 2·0; N, 20·8%). 5-*Bromo*-3-*nitropicolinamide*, obtained in 56% yield from 5-bromo-3-nitropicolinonitrile, separated from water as needles, m. p. 232—233° (decomp.) (Found: C, 29·1; H, 2·0; N, 17·1. $C_6H_4O_3N_3Br$ requires C, 29·3; H, 1·6; N, 17·1%).

3-*Amino*-2-*bromopyridine*,—A mixture of 2-bromo-3-nitropyridine (1·45 g.), glacial acetic acid (12 c.c.), and iron filings (2·0 g.) was heated at 100° for 2 hours, diluted with water (15 c.c.), and basified by the addition of 30% sodium hydroxide solution with cooling. The mixture was shaken with chloroform (50 c.c.) and filtered, and the chloroform layer separated and evaporated. Crystallisation of the residue from aqueous methanol (charcoal) gave 3-*amino*-2-*bromopyridine* (0·8 g.) as needles, m. p. 79° (Found: C, 34·9; H, 3·0. $C_5H_5N_2Br$ requires C, 34·7; H, 2·9%).

3-*Amino*-2-*chloropyridine*.—(*a*) Reduction of 2-chloro-3-nitropyridine (1·1 g.) by the method described above gave 3-amino-2-chloropyridine (0·1 g.), which separated from aqueous acetone (charcoal) as plates, m. p. 79—80° (Schickh, Binz, and Schulz, *loc. cit.*, give m. p. 80°).

(*b*) A solution of 3-amino-2-bromopyridine (1·0 g.) in hydrochloric acid (10 c.c.; *d* 1·19) was refluxed for 3 hours, and the solution then evaporated to dryness. A solution of the residue in the minimum quantity of water was cooled and basified by the addition of 30% sodium hydroxide solution. Crystallisation of the precipitated solid from aqueous acetone (charcoal) gave 3-amino-2-chloropyridine (0·5 g.) as plates, m. p. 78° alone or mixed with a specimen prepared by method (*a*).

3-*Aminopicolinamide*.—(*a*) A mixture of 3-nitropicolinamide (20 mg.), glacial acetic acid

(0·12 c.c.), and iron filings (20 mg.) was kept at 100° for 2 hours. The cooled mixture was treated with water (0·15 c.c.) and partially neutralised by the addition of sodium hydroxide (40 mg.) in water (0·1 c.c.). The solid was collected, dried, and extracted with hot acetone (20 c.c.). Evaporation of the acetone followed by crystallisation of the residue from water gave 3-*aminopicolinamide* (10 mg.) as needles, m. p. 175—177°, which readily sublimed at 100°/10^{-5} mm. (Found: C, 52·0; H, 5·0. $C_6H_7ON_3$ requires C, 52·5; H, 5·1%).

(*b*) A solution of 3-aminopicolinonitrile (120 mg.) in sulphuric acid (0·24 c.c.; *d* 1·84) was heated at 100° for 2 hours. Water (1 c.c.) was added and the mixture basified by the addition of 30% sodium hydroxide solution with cooling. The precipitate was extracted with acetone, the filtered extract evaporated, and the solid residue crystallised from water, giving 3-aminopicolinamide (10 mg.) as needles, m. p. 175° alone or mixed with the specimen described in (*a*).

3-*Amino-5-chloropicolinamide.*—Reduction of 5-chloro-3-nitropicolinamide by using iron filings and glacial acetic acid as described above gave 3-*amino-5-chloropicolinamide* (yield 67%) which crystallised from aqueous acetone as needles, m. p. 168° (Found: C, 41·8; H, 3·5; N, 24·4. $C_6H_6ON_3Cl$ requires C, 42·0; H. 3·5; N, 24·5%).

3-Amino-5-chloropicolinamide was also obtained in 11% yield from 3-amino-5-chloropicolinonitrile by using the method (*b*) described above. It separated from water as needles, m. p. 168° undepressed by the specimen obtained by method (*a*). 3-*Amino-5-bromopicolinamide* was obtained in 72% yield from 5-bromo-3-nitropicolinamide and in 18% yield from 3-amino-5-bromopicolinonitrile by using the methods (*a*) and (*b*) described for the preparation of 3-aminopicolinamide. It separated from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 168° (Found: N, 19·0. $C_6H_6ON_3Br$ requires N, 19·4%).

3-*Amino-2-bromo-5-chloropyridine*, obtained in 81% yield from 2-bromo-5-chloro-3-nitropyridine, separated from aqueous acetone (charcoal) as needles, m. p. 142° (Found: C, 28·6; H, 1·8. $C_5H_4N_2ClBr$ requires C, 28·9; H, 1·9%). Light absorption in ethanol: Max. at 2520 (ε = 11,500) and 3140 Å (ε = 5700).

3-*Amino*-2 : 5-*dibromopyridine* was obtained from 2 : 5-dibromo-3-nitropyridine in 84% yield; it separated from aqueous acetone (charcoal) as needles, m. p. 153° (Found: C, 24·2; H, 1·3. $C_5H_4N_2Br_2$ requires C, 23·8; H, 1·6%).

3-*Amino*-2 : 5-*dichloropyridine.*—(*a*) Reduction of 2 : 5-dichloro-3-nitropyridine with iron filings and acetic acid gave 3-*amino*-2 : 5-*dichloropyridine* in 87% yield; it separated from aqueous acetone as needles, m. p. 129° (Found: N, 17·0. $C_5H_4N_2Cl_2$ requires N, 17·2%).

(*b*) A solution of 3-amino-2-bromo-5-chloropyridine (0·5 g.) in hydrochloric acid (10 c.c.; *d* 1·19) was refluxed for 2 hours. The residue obtained on evaporation was crystallised from aqueous acetone, giving 3-amino-2 : 5-dichloropyridine (0·2 g.) as long needles, m. p. 129° alone or mixed with a specimen prepared by method (*a*).

3-*Amino-5-bromo-2-chloropyridine.*—(*a*) Reduction of 5-bromo-2-chloro-3-nitropyridine with iron filings and acetic acid gave 3-*amino-5-bromo-2-chloropyridine* (yield 85%) which crystallised from aqueous acetone as needles, m. p. 131° (Found: C, 29·1; H, 2·1; N, 13·8. $C_5H_4N_2ClBr$ requires C, 28·9; H, 1·9; N, 13·5%). Light absorption in ethanol: Max. at 2510 (ε = 7200) and 3140 Å (ε = 4700).

(*b*) 3-Amino-2 : 5-dibromopyridine (1 part) was refluxed with hydrochloric acid (20 parts; *d* 1·19) for 2 hours. Crystallisation of the product from water (charcoal) gave 3-amino-5-bromo-2-chloropyridine (yield 35%) as needles, m. p. 131° undepressed by the specimen prepared by method (*a*). Light absorption in ethanol: Max. at 2510 (ε= 7200) and 3120 Å (ε = 4900).

(*c*) A mixture of 2 : 5-dibromo-3-nitropyridine (2·82 g.), hydrochloric acid (30 c.c.; *d* 1·19), and granulated tin (7 g.) was refluxed until solution was complete. The solution was evaporated to dryness, and the residue dissolved in hot water (15 c.c.), and the solution filtered. The cold solution was basified by the addition of sodium hydroxide solution (30 c.c.; 50%), and the precipitate was collected, dried, and extracted with boiling benzene (3 × 100 c.c.). Evaporation of the solvent and crystallisation of the residue from water (charcoal) gave 3-amino-5-bromo-2-chloropyridine (0·2 g.) as needles, m. p. 131° alone or mixed with a specimen (*a*) (Found: C, 28·9; H, 1·6%).

2 : 3-*Diamino-5-bromo*-4(6)-*chloropyridine.*—This was obtained in 21% yield from 2-amino-5-bromo-3-nitropyridine by using the method (*c*) described above; it separated from water as long needles, m. p. 164° (Found: N. 18·7. $C_5H_5N_3ClBr$ requires N, 18·9%).

Quinoxaline derivative. A filtered solution of 2 : 3-diamino-5-bromo-4(6)-chloropyridine (100 mg.) in glacial acetic acid (5 c.c.) was added to a hot filtered solution of phenanthraquinone (120 mg.) in glacial acetic acid (15 c.c.), and the mixture heated at 100° for 15 minutes. The crystalline solid (orange needles) which separated was collected, washed with glacial acetic acid,

and dried; the *derivative* (70 mg.) had m. p. 270—272° (Found: N, 11·0. $C_{19}H_9N_3ClBr$ requires N, 10·6%).

5-Bromo-2 : 3-dichloropyridine.—A solution of 3-amino-5-bromo-2-chloropyridine (0·3 g.) in hydrochloric acid (10 c.c.; *d* 1·19) was treated at 0° with one of sodium nitrite (0·55 g.) in water (1·5 c.c.), added dropwise with shaking. Copper powder (1·1 g.) was added, and the mixture was shaken for 1 hour and then almost neutralised by the addition of 30% sodium hydroxide solution with cooling. The precipitate was separated, dried, and extracted with hot acetone, the acetone extract evaporated, and the residue stirred with light petroleum (b. p. 40—60°; 5 c.c.). The filtered petroleum extract was evaporated and the residue crystallised from aqueous acetone, giving *5-bromo-2 : 3-dichloropyridine* (100 mg.) as needles, m. p. 30—31° (Found: Cl + Br, 66·0. $C_5H_2NCl_2Br$ requires Cl + Br, 66·5%).

2 : 5-Dibromo-3-hydroxypyridine.—A solution of 3-amino-2 : 5-dibromopyridine (1·26 g.) in one of sodium nitrite (0·35 g.) in sulphuric acid (8 c.c.; *d* 1·84) at 20° was shaken for 30 minutes and then diluted with water (25 c.c.) with cooling. The solution was heated gradually to 100° and kept at this temperature until no more gas was evolved; after cooling a solution of sodium hydroxide (11·0 g.) in water (20 c.c.) was added and the precipitate collected, dried, and extracted with hot acetone. Evaporation of the solvent and crystallisation of the residue from aqueous methanol (charcoal) gave *2 : 5-dibromo-3-hydroxypyridine* (0·6 g.) as needles, m. p. 195—197° (Found: C, 24·1; H, 1·2. $C_5H_3ONBr_2$ requires C, 23·7; H, 1·2%).

2-Amino-5-bromo-3-nitropyridine.—5-Bromo-3-nitropicolinamide (12·1 g.) was added to a solution of potassium hypobromite, prepared at 0° from bromine (9·0 g.) and potassium hydroxide (35 g.) in water (500 c.c.). After being shaken vigorously for 3 hours at room temperature the mixture was kept at 70° for 30 minutes and then at 0° for 16 hours. The precipitate was collected and crystallised from ethyl acetate, giving 2-amino-5-bromo-3-nitropyridine (7·0 g.) as yellow needles, m. p. 205° not depressed when the specimen was mixed with one of m. p. 105°, prepared by Tschitschibabin and Tjashelowa's method (*J. Russ. Phys. Chem. Soc.*, 1920, **50**, 483).

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