74. *Arylpyridines. Part II. Some Substituted Phenylpyridines.*

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By means of the method described in Part I a number of substituted arylpyridines have been prepared from the reactions between diazotised substituted anilines and pyridine. This may be regarded as a general characteristic reaction of aqueous diazonium salts. *p*-Chloroaniline, *p*-bromoaniline, *p*-phenetidine, and *p*-aminobenzoic acid were used and in each case two of the three possible isomeric products were shown to be formed. α-4-*Chloro-* and α-4-*bromo-phenylpyridine* were identified by comparison with the corresponding products obtained from α-4-aminophenylpyridine by means of the Sandmeyer reaction. α-4-Aminophenylpyridine has also been converted into α-4-hydroxyphenylpyridine, α-4-*iodophenylpyridine* and α-4-*cyanophenylpyridine*. Hydrolysis of the last gave α-*phenylpyridine*-4-*carboxylic acid*, identical with one of the products obtained from the reaction between diazotised *p*-aminobenzoic acid and pyridine.

The reaction described in Part I (preceding paper) is now shown to be of general applicability by its employment with a number of simple substituted anilines. In every case a mixture of isomerides is formed, from which, in general, the pure constituents can be isolated readily by fractional crystallisation of the picrates from acetone. Although it is held that, as with diazotised aniline and the nitroanilines (cf. Part I, *loc. cit.*), all three isomeric arylpyridines are doubtless formed, in the experimental work now described only two isomerides have actually been isolated in each case, the major product being the α-isomeride. In the absence of evidence to the contrary the second constituent is tentatively regarded as the γ-isomeride, which, as indicated in Part I (*loc. cit.*), is likely to be less soluble than the β-isomeride, which would remain in the final mother-liquors. The failure to isolate the third isomeride is attributed solely to practical difficulties and working with insufficient quantities.

The action of aqueous solutions of diazotised *p*-chloro- and *p*-bromo-aniline on pyridine gave a mixture of two isomeric 4-chloro- and 4-bromo-phenylpyridines respectively. Both α-4-*chlorophenylpyridine* and α-4-*bromophenylpyridine* were characterised by their identity with the corresponding compounds prepared from α-4-aminophenylpyridine by means of the Sandmeyer reaction. Diazotised *p*-phenetidine and pyridine gave, in like manner, a mixture from which two isomerides were isolated, one of which was obviously identical with the α-4-ethoxyphenylpyridine prepared by Forsyth and Pyman (J., 1926, 2912) from diazotised α-4-aminophenylpyridine and ethyl alcohol. α-4-Aminophenylpyridine has also been converted by means of the Sandmeyer reaction into α-4-hydroxyphenylpyridine, α-4-*iodophenylpyridine*, and α-4-*cyanophenylpyridine*. Hydrolysis of the last gave α-*phenylpyridine*-4-*carboxylic acid*, which was converted into its *methyl* ester. The α-phenyl-

pyridine-4-carboxylic acid was identical with one of the products isolated from the action of diazotised *p*-aminobenzoic acid on pyridine. The latter reaction was also shown to give rise to the formation of some γ-phenylpyridine-4-carboxylic acid, since decarboxylation of the crude product gave both α- and γ-phenylpyridine.

Experimental.

Action of Diazotised p-*Chloroaniline on Pyridine.*—An aqueous solution of *p*-chlorobenzenediazonium chloride (from *p*-chloroaniline, 22 g.) was added slowly to pyridine (250 c.c.) with stirring at room temperature. After standing overnight, aqueous sodium hydroxide was added, and the excess of pyridine rapidly removed with steam. Steam-distillation was then continued for several hours, and the distillate extracted with ether and dried. After removal of solvent the residue, distilled under reduced pressure, gave a mixture of 4-chlorophenylpyridines (12 g., b. p. 170—210°/14 mm.) as an oil, which partly solidified. The product was treated with alcoholic picric acid, and the resulting picrates fractionally crystallised from acetone. The less soluble *picrate*, m. p. 225—227° (Found: C, 48·9; H, 2·7. $C_{11}H_8NCl,C_6H_3O_7N_3$ requires C, 48·8; H, 2·6%), yielded with aqueous alkali a compound regarded as γ-4-*chlorophenylpyridine*, which crystallised from light petroleum (b. p. 40—60°) in white needles, m. p. 70—71° (Found: C, 69·9; H, 4·1. $C_{11}H_8NCl$ requires C, 69·7; H, 4·2%). The more soluble isomeride, α-4-chlorophenylpyridine picrate, separated in yellow needles, m. p. 169—170° both alone and on admixture with the chlorophenylpyridine picrate prepared below from α-4-aminophenylpyridine. Treatment with aqueous alkali gave α-4-chlorophenylpyridine, which crystallised from light petroleum (b. p. 40—60°) in white needles, m. p. and mixed m. p. 52—53°.

Action of Diazotised p-*Bromoaniline on Pyridine.*—An aqueous solution of *p*-bromobenzenediazonium chloride (from *p*-bromoaniline, 43 g.) was added gradually with stirring to pyridine (250 c.c.) at room temperature. After standing overnight, the excess of pyridine was removed with steam and the residue, made strongly alkaline with aqueous sodium hydroxide, was extracted with ether and dried. After removal of solvents at ordinary pressure further distillation under reduced pressure yielded an oil (10 g.), b. p. 200—230°/28 mm. Treatment with alcoholic picric acid, followed by fractional crystallisation of the picrates from acetone, gave a less soluble *picrate*, m. p. 213—214° (Found: C, 44·2; H, 2·2. $C_{11}H_8NBr,C_6H_3O_7N_3$ requires C, 44·0; H, 2·4%), from which aqueous alkali liberated a compound regarded as γ-4-*bromophenylpyridine*, m. p. 129—131° after crystallisation from light petroleum (b. p. 40—60°) (Found: C, 56·8; H, 3·6. $C_{11}H_8NBr$ requires C, 56·5; H, 3·4%). Concentration of the acetone mother-liquors gave α-4-bromophenylpyridine picrate in yellow needles, m. p. 168°, both alone and on admixture with the picrate of the bromophenylpyridine prepared below from α-4-aminophenylpyridine. The free base, liberated by treatment with alkali, separated from light petroleum (b. p. 40—60°) in white needles, m. p. and mixed m. p. 62°.

Action of Diazotised p-*Phenetidine on Pyridine.*—An aqueous solution of *p*-ethoxybenzenediazonium chloride (from *p*-phenetidine, 34 g.) was added to pyridine (250 c.c.), and the product treated as described above for the corresponding reaction with *p*-chloroaniline. Steam-distillation gave an oil which solidified. The solid distillate (20 g.), dissolved in alcohol, was treated with an equivalent of picric acid dissolved in hot alcohol and the mixture of picrates thus obtained was submitted to fractional crystallisation from acetone. α-4-Ethoxyphenylpyridine picrate separated first in yellow needles, m. p. 169—170° (cf. Forsyth and Pyman, *loc. cit.*), and concentration of the mother-liquors yielded a second isomeric *picrate*, m. p. 199—200° (Found: C, 53·4; H, 3·8. $C_{13}H_{13}ON,C_6H_3O_7N_3$ requires C, 53·3; H, 3·7%). Treatment of the former picrate with 5% aqueous sodium hydroxide liberated α-4-ethoxyphenylpyridine, which separated from light petroleum (b. p. 40—60°) in white needles, m. p. 75°. Treatment of the latter picrate in similar manner gave an isomeride, regarded as γ-4-*ethoxyphenylpyridine*, which separated from light petroleum (b. p. 40—60°) in white needles, m. p. 100—101° (Found: C, 78·2; H, 6·6. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·5%).

Action of Diazotised p-*Aminobenzoic Acid on Pyridine.*—The diazonium solution prepared from a suspension of *p*-aminobenzoic acid (34 g.) in a mixture of concentrated hydrochloric acid (90 c.c.) and water (100 c.c.) by addition of aqueous sodium nitrite (17·5 g. in 40 c.c.) at 5—10° was dropped during 2 hours into pyridine (300 c.c.) stirred at 30—40°. The reaction mixture was then warmed on the steam-bath for ½ hour, and the pyridine subsequently removed with steam. The brown solid (31 g.) which separated on cooling was filtered off, washed, and dried, and a further quantity (11 g.) was precipitated on neutralisation of the filtrate with aqueous sodium hydroxide. Purification was effected by sublimation in a vacuum, followed by repeated

crystallisation from alcohol, in which the phenylpyridinecarboxylic acid was sparingly soluble. Pure α-phenylpyridine-4-carboxylic acid was obtained, m. p. 228—229° both alone and on admixture with the acid prepared below from the hydrolysis of α-4-cyanophenylpyridine (Found : C, 72·6; H, 4·6. Calc. for $C_{12}H_9O_2N$: C, 72·4; H, 4·5%). Decarboxylation of the crude product (10 g.) by distillation with soda-lime (25 g.) yielded a mixture of phenylpyridines, the picrates of which were fractionally crystallised from acetone. Both α-phenylpyridine picrate (m. p. and mixed m. p. 173—174°) and γ-phenylpyridine picrate (m. p. and mixed m. p. 193—194°) were isolated. A portion of the crude product (8 g.) was boiled under reflux for 3 hours with methyl alcohol (100 c.c.) saturated with dry hydrogen chloride. After removal of the greater portion of the alcohol by distillation, the residue was diluted, made slightly alkaline, and extracted with ether. The residue (6 g.) obtained on evaporation of the ether was purified by sublimation in a vacuum, followed by crystallisation from light petroleum (b. p. 40—60°), which gave *methyl α-phenylpyridine-4-carboxylate* in white plates, m. p. 90° (Found : C, 73·3; H, 4·9. $C_{13}H_{11}O_2N$ requires C, 73·2; H, 5·2%). A sample of the pure acid (m. p. 228—229°) esterified in similar manner gave an identical product.

Reactions with α-4-Aminophenylpyridine.—α-4-Nitrophenylpyridine (m. p. 130—131°), prepared from diazotised *p*-nitroaniline and pyridine as described in Part I (preceding paper), was reduced to α-4-aminophenylpyridine, m. p. 96° (Found : C, 77·9; H, 5·6. Calc. for $C_{11}H_{10}N_2$: C, 77·7; H, 5·85%), as described by Forsyth and Pyman (*loc. cit.*). Solutions of α-4-aminophenylpyridine (4 g.) in a mixture of concentrated hydrochloric acid (10 c.c.) and water (15 c.c.) were diazotised at 10° with a solution of sodium nitrite (3·5 g.) in water (20 c.c.) and the following reactions were carried out : (a) The diazonium solution was diluted with water (80 c.c.) and heated gradually to about 90°. When evolution of nitrogen had ceased, ammonia was added until the solution was just alkaline ; the excess of ammonia was then removed by heating. The solid which separated from the resulting neutral solution was filtered off, washed, and dried. Crystallisation from light petroleum (b. p. 80—100°) gave α-4-hydroxyphenylpyridine in white needles, m. p. 159—160° (Found : C, 77·2; H, 5·1. Calc. for $C_{11}H_9ON$: C, 77·2; H, 5·3%) (Tschitschibabin and Schemyakina, *Chem. Zentr.*, 1923, III, 1024, recorded m. p. 160°). (b) The diazonium solution was added in portions with stirring to a solution of cuprous chloride [prepared by passing sulphur dioxide into a mixture of copper sulphate (6 g.) and sodium chloride (3 g.) in water (20 c.c.) at 60—70° and subsequent filtration and washing] in concentrated hydrochloric acid (5 c.c.). After the reaction mixture had been heated on the steam-bath, it was made alkaline with aqueous sodium hydroxide and steam-distilled. The cooled steam-distillate deposited *α-4-chlorophenylpyridine*, which separated from light petroleum (b. p. 40—60°) in white needles, m. p. 52—53° (Found : C, 69·7; H, 4·2. $C_{11}H_8NCl$ requires C, 69·7; H, 4·2%). The *picrate*, prepared in alcoholic solution in the usual way, separated from acetone in yellow needles, m. p. 169—170° (Found : C, 49·0; H, 3·0. $C_{11}H_8NCl,C_6H_3O_7N_3$ requires C, 48·8; H, 2·6%). (c) The diazonium solution was added in portions with stirring to a solution of cuprous bromide [prepared by passing sulphur dioxide into a mixture of copper sulphate (3 g.) and potassium bromide (1·5 g.) in water (25 c.c.) and subsequent filtration and washing] in hydrobromic acid (*d* 1·49, 5 c.c.) cooled in ice. When evolution of nitrogen had slackened, the mixture was heated on the steam-bath for 1 hour. The cooled mixture was made alkaline with aqueous sodium hydroxide, and the bromo-compound filtered off. Crystallisation from light petroleum (b. p. 40—60°) gave *α-4-bromophenylpyridine* in white needles, m. p. 62° (Found : C, 56·8; H, 3·2. $C_{11}H_8NBr$ requires C, 56·5; H, 3·4%). The *picrate*, prepared in the usual manner, crystallised from alcohol in yellow needles, m. p. 168° (Found : C, 43·7; H, 2·3. $C_{11}H_8NBr,C_6H_3O_7N_3$ requires C, 44·0; H, 2·4%). (d) To the cold diazonium solution, a solution of potassium iodide (3 g.) in water (5 c.c.) was added gradually with stirring. After 3 hours the mixture was heated gently until evolution of nitrogen had ceased. Addition of aqueous sodium hydroxide to the cooled reaction mixture precipitated *α-4-iodophenylpyridine*, which separated from light petroleum (b. p. 40—60°) in white needles, m. p. 85—86° (Found : C, 47·0; H, 3·1. $C_{11}H_8NI$ requires C, 47·0; H, 2·85%). (e) The diazonium solution was added in 5 c.c. portions and with frequent shaking to a warm solution of cuprous cyanide, prepared by adding aqueous potassium cyanide (3·5 g. in 10 c.c.) to warm aqueous copper sulphate (3 g. in 12·5 c.c.). Rapid evolution of nitrogen occurred and when addition of the diazonium solution was complete the mixture was warmed on the steam-bath. The mixture, rendered slightly alkaline with ammonia, was subjected to distillation with steam. When cold, the aqueous distillate deposited *α-4-cyanophenylpyridine*, which crystallised from light petroleum (b. p. 40—60°) in white needles, m. p. 97—98° (Found : C, 79·7; H, 4·2. $C_{12}H_8N_2$ requires C, 80·0; H, 4·4%). A portion of the nitrile (1 g.) was hydrolysed by boiling under reflux with 10% aqueous sodium hydroxide

(25 c.c.). To the cold solution, dilute hydrochloric acid was cautiously added until precipitation of the carboxylic acid was complete. The acid was filtered off, dried, and sublimed in a vacuum. α-*Phenylpyridine-4-carboxylic acid* was obtained as a white microcrystalline powder, m. p. 232° (Found : C, 72·4; H, 4·5. $C_{12}H_9O_2N$ requires C, 72·4; H, 4·5%).

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