75. *Arylpyridines. Part III. Anisyl- and Nitroanisyl-pyridines.*

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Further examples of the preparation of arylpyridines by the action of aqueous diazonium solutions on pyridine are described. The action of diazotised *o*-, *m*-, and *p*-anisidine on pyridine gives mixtures of the 2-, 3-, and 4-methoxyphenylpyridines respectively. In the case of *o*-anisidine all three isomerides (α-, β-, and γ-2-methoxyphenylpyridine) are isolated, but with *m*- and *p*-anisidine only two isomerides are isolated in each case. The constitutions of the products are proved by their conversion into or synthesis from known compounds by unambiguous methods; *e.g.*, α-2-methoxyphenylpyridine is oxidised to picolinic acid, and α-3-, α-4-, and β-2-methoxyphenylpyridine are prepared from the appropriate known nitrophenylpyridines by reduction and replacement of the amino-group by methoxyl. Nitration of both α-2- and α-4-methoxyphenylpyridine yields a single nitromethoxyphenylpyridine, the constitution of which is established by its synthesis by the action of the appropriate diazotised nitroanisidine on pyridine. The reactions described supply additional evidence for the general nature of this method for the preparation of arylpyridines.

The new method for the preparation of arylpyridines described in Part I (this vol., p. 349) is now applied to the preparation of a series of anisyl- and nitroanisyl-pyridines, thus supplying additional evidence of the general nature of the reaction.

The action of diazotised *o*-anisidine on pyridine gave a mixture of 2-methoxyphenylpyridines in 50% yield. Fractional crystallisation of the picrates gave three isomeric products melting at 155—156°, 182°, and 205°. The *picrate*, m. p. 155—156°, which constitutes the major product of the reaction, gave, on treatment with alkali, α-2-methoxyphenylpyridine, the constitution of which was proved by oxidation with acid permanganate to give picolinic acid. The *picrate*, m. p. 182°, was shown to be that of β-2-methoxyphenylpyridine, which was prepared from β-2-nitrophenylpyridine, by reduction to the amine, subsequent diazotisation, and reaction with methyl alcohol. This reaction is in sharp contrast to the action of methyl alcohol on diazotised α-2-aminophenylpyridine, which gave α-phenylpyridine and not α-2-methoxyphenylpyridine (see Part I). By elimination the third *picrate*, m. p. 205°, must be that of γ-2-methoxyphenylpyridine. Nitration of α-2-methoxyphenylpyridine gave a single product, shown to be α-5-*nitro*-2-*methoxyphenylpyridine*, since the same compound was isolated from the product obtained from the action of diazotised 5-nitro-2-methoxyaniline on pyridine. The action of diazotised 4-nitro-2-methoxyaniline on pyridine gave a mixture of 4-nitro-2-methoxyphenylpyridines in 21% yield, from which two isomerides were isolated. These are regarded as α- and γ-4-*nitro*-2-*methoxyphenylpyridine*.

The action of diazotised *p*-anisidine on pyridine gave, in like manner, a mixture of 4-methoxyphenylpyridines in 54% yield. Fractional crystallisation of the picrates gave two *isomerides*, m. p. 191—192° and 205—206°, which on treatment with alkali liberated two *bases*, m. p. 49—50° and 95° respectively. The former, which predominates, was shown to be α-4-*methoxyphenylpyridine* by its synthesis from α-4-nitrophenylpyridine by successive reduction, diazotisation, and treatment with methyl alcohol. By analogy with previous results the base, m. p. 95°, is regarded as γ-4-*methoxyphenylpyridine*. Nitration of α-4-methoxyphenylpyridine gave a single product, shown to be α-3-*nitro*-4-*methoxyphenylpyridine*, since the same compound was isolated from the product obtained from the action of diazotised 3-nitro-4-methoxyaniline on pyridine.

The action of diazotised *m*-anisidine on pyridine gave a mixture of 3-methoxyphenylpyridines in 30% yield, from which two isomerides were isolated as *picrates*, m. p. 154—155° and 203—204°. The former, which is the major product, was shown to be α-3-methoxyphenylpyridine picrate by its identity with the picrate obtained from the compound prepared from α-3-nitrophenylpyridine by reduction to the amine, subsequent diazotisation, and treatment with methyl alcohol. The second isomeride is regarded as γ-3-methoxyphenylpyridine picrate.

It is highly probable that in all three reactions between the diazotised anisidines and pyridine, as in the corresponding reactions between the diazotised nitroanilines and pyridine (Part I, *loc. cit.*), three isomeric anisylpyridines are formed in each case, although only in the case of *o*-anisidine was it possible to isolate all three products. In the nitration of both α-2-methoxyphenylpyridine and α-4-methoxyphenylpyridine it is, as expected, the powerful *op*-directing influence of the methoxyl group which determines the position taken up by the entering group.

Experimental.

Action of Diazotised o-*Anisidine on Pyridine.*—A solution of *o*-anisidine (31 g.) in a mixture of concentrated hydrochloric acid (90 c.c.) and water (60 c.c.) was diazotised at 0—5° with a concentrated aqueous solution of sodium nitrite (17·5 g.). The resulting diazonium solution was dropped during 2 hours into pyridine (250 c.c.) stirred at 70—80°. The mixture was heated for a further hour at 80°, ammonia added, and the excess of pyridine removed with steam. When cold, the separated oil was extracted with benzene. Removal of the benzene from the dried extract left a residue, which on distillation at 160—180°/0·5 mm. yielded a mixture of *o*-anisylpyridines (23 g.) as a yellow liquid. A hot solution of picric acid (27 g.) in alcohol (300 c.c.) was added to a concentrated alcoholic solution of the *o*-anisylpyridines, and the resulting mixture of picrates, which separated on cooling, was subjected to systematic fractional crystallisation from acetone. Three products were isolated as follows: (a) α-2-*methoxyphenylpyridine picrate* in hard golden-yellow needles, m. p. 155—156° (Found: C, 52·3; H, 3·4. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%); (b) β-2-*methoxyphenylpyridine picrate* in yellow needles, m. p. 182° (Found: C, 52·5; H, 3·4%); and (c) γ-2-*methoxyphenylpyridine picrate* in silky yellow needles, m. p. 205° (Found: C, 52·5; H, 3·4%). The major product of the reaction was the α-isomeride. The free bases, obtained from the picrates by warming with 5% aqueous sodium hydroxide, were yellow oils readily soluble in organic solvents but sparingly soluble in water.

Oxidation of α-2-*Methoxyphenylpyridine.*—To a solution of α-2-methoxyphenylpyridine (1 g.), liberated from the picrate as outlined above, in 25% sulphuric acid (50 c.c.) at 90—100° was added dropwise a solution of potassium permanganate (5·5 g.) in warm water (55 c.c.) with frequent shaking during 4 hours (cf. Tschitschibabin, *Ber.*, 1904, **37**, 1373). A few drops of alcohol were then added and the solution was made slightly alkaline with aqueous potassium hydroxide. The precipitated manganese hydroxide was washed with hot water and the combined filtrate and washings were evaporated to small bulk, neutralised with dilute sulphuric acid, and evaporated to dryness. The residue was extracted several times with boiling alcohol; evaporation of the extract left a residue of potassium picolinate, which was dissolved in a small quantity of water and treated with a saturated aqueous solution of copper acetate at 60°. The copper salt of picolinic acid which separated was collected, dissolved in water, and treated with hydrogen sulphide. After filtration and evaporation the picolinic acid was sublimed and obtained in colourless needles, m. p. 135—136°, both alone and on admixture with an authentic specimen.

Synthesis of β-2-*Methoxyphenylpyridine.*—A solution of β-2-aminophenylpyridine (0·5 g.), obtained by reduction of β-2-nitrophenylpyridine as described in Part I (this vol., p. 354), in concentrated hydrochloric acid (3 c.c.) was diazotised at 5—10° with an aqueous solution of sodium nitrite (0·2 g.). Methyl alcohol (50 c.c.) was added, and the mixture boiled under reflux for 2 hours. It was then evaporated to small bulk, poured into excess of dilute aqueous sodium hydroxide, and extracted with ether. Evaporation of the ether from the dried extract left a yellow oil, which was treated with alcoholic picric acid. Crystallisation of the resulting picrate from acetone gave β-2-methoxyphenylpyridine picrate in yellow needles, m. p. 180—181°, both alone and on admixture with the picrate, m. p. 182°, isolated from the reaction between diazotised *o*-anisidine and pyridine.

Nitration of α-2-*Methoxyphenylpyridine.*—Fuming nitric acid (*d* 1·5, 4 c.c.) was added in

successive portions of 1 c.c. during ½ hour to a solution of α-2-methoxyphenylpyridine (2 g.), liberated from the picrate as outlined above, in glacial acetic acid (10 c.c.). The mixture was then boiled under reflux for ½ hour and finally poured into an excess of dilute aqueous sodium hydroxide. The nitration product, which separated as an almost white solid (2·1 g., m. p. 122—125°), was crystallised from alcohol, α-5-*nitro*-2-*methoxyphenylpyridine* separating in fine lustrous needles, m. p. 126—127° (Found: C, 62·8; H, 4·4. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·35%).

Synthesis of α-5-*Nitro*-2-*methoxyphenylpyridine.*—A suspension of 5-nitro-2-methoxyaniline (28 g.) in a mixture of hydrochloric acid (60 c.c.) and water (40 c.c.) was diazotised at 5—10° with a solution of sodium nitrite (12 g.) in water (30 c.c.), and the resulting diazonium solution was dropped during 2 hours into pyridine (200 c.c.) stirred at 30—40°. After ½ hour's heating on the steam-bath, ammonia was added, and the excess of pyridine removed with steam. The viscous oil which separated was extracted with benzene, the benzene evaporated, and the residue distilled under reduced pressure. The fraction (7·5 g.) collected at 200—220°/0·2 mm., which solidified, was crystallised four times from alcohol, from which pure α-5-nitro-2-methoxyphenylpyridine separated in very pale yellow needles, m. p. 124—126°. The m. p. was raised to 125—126° on admixture with the product obtained above from the nitration of α-2-methoxyphenylpyridine. The alcoholic mother-liquors containing the isomeric 5-nitro-2-methoxyphenylpyridines were not further investigated.

Synthesis of α-4-*Nitro*-2-*methoxyphenylpyridines.*—4-Nitro-2-methoxyaniline (28 g.) was diazotised, as described above for 5-nitro-2-methoxyaniline, and added to pyridine. The product (8 g.), worked up as described in the preceding example, was collected at 190—210°/0·4 mm., and crystallised from alcohol, from which the main constituent, regarded as α-4-*nitro*-2-*methoxyphenylpyridine*, separated in pale yellow needles, m. p. 132—133° (Found: C, 62·5; H, 4·2. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·35%); the *picrate*, formed in the usual manner, separated from acetone in yellow needles, m. p. 163—164° (Found: C, 47·1; H, 2·6. $C_{12}H_{10}O_3N_2,C_6H_3O_7N_3$ requires C, 47·1; H, 2·8%). Treatment of the original alcoholic mother-liquors with alcoholic picric acid and crystallisation of the resulting picrates from acetone yielded a second isomeric *picrate*, m. p. 215—216° (Found: C, 47·3; H, 2·9%), from which aqueous sodium hydroxide liberated a second isomeric *base*, m. p. 115° after crystallisation from alcohol (Found: C, 62·3; H, 4·5%), which is regarded as γ-4-*nitro*-2-*methoxyphenylpyridine*. Admixture of α-4-nitro-2-methoxyphenylpyridine (m. p. 132—133°) with the nitration product of α-2-methoxyphenylpyridine (m. p. 126—127°) resulted in a marked depression in m. p.

Action of Diazotised p-*Anisidine on Pyridine.*—This reaction was carried out exactly as described above for the corresponding reaction with *o*-anisidine. The crude product, consisting of a mixture of *p*-anisylpyridines, was collected at 160—190°/0·1 mm., and solidified on cooling to a pinkish white solid (25 g.). As before, the product was treated with alcoholic picric acid, and the resulting picrates subjected to fractional crystallisation from acetone. The main product, which separated first in sparingly soluble, silky needles, m. p. 191—192°, consisted of α-4-*methoxyphenylpyridine picrate* (Found: C, 52·5; H, 3·5. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%), from which 5% aqueous sodium hydroxide liberated α-4-*methoxyphenylpyridine*, which crystallised from light petroleum (b. p. 40—60°) in small white plates, m. p. 49—50° (Found: C, 77·9; H, 5·9. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9%). Concentration of the acetone mother-liquors gave a second isomeric *picrate*, regarded as that of γ-4-*methoxyphenylpyridine*, in orange needles, m. p. 205—206° (Found: C, 52·4; H, 3·3%), from which 5% aqueous sodium hydroxide liberated the free γ-4-methoxyphenylpyridine, which crystallised from light petroleum (b. p. 40—60°) in white needles, m. p. 95° (Found: C, 77·9; H, 6·0%). The two picrates, on admixture, showed a pronounced depression in m. p., but the free bases obtained from them did not show a depression in m. p. on admixture.

Synthesis of α-4-*Methoxyphenylpyridine.*—Methyl alcohol (50 c.c.) was added to a solution of diazotised α-4-aminophenylpyridine (2 g.), prepared by reduction of α-4-nitrophenylpyridine as described by Forsyth and Pyman (J., 1926, 2917) and subsequent treatment with nitrous acid, and the mixture heated under reflux for 2 hours. The whole was evaporated to small bulk, added to excess of dilute aqueous sodium hydroxide, and extracted with ether. The residue obtained on evaporation of the ether from the dried extract was purified by distillation in a vacuum and treated with alcoholic picric acid. Crystallisation of the resulting picrate from acetone gave α-4-methoxyphenylpyridine picrate in yellow silky needles, m. p. 191—192°, both alone and on admixture with the picrate of the same m. p. isolated from the reaction between diazotised *p*-anisidine and pyridine. As before, treatment of the picrate with 5% aqueous sodium hydroxide gave α-4-methoxyphenylpyridine, m. p. 49—50° after crystallisation from light petroleum (b. p. 40—60°).

Nitration of α-4-*Methoxyphenylpyridine.*—Fuming nitric acid (*d* 1·5, 4 c.c.) was added to a solution of α-4-methoxyphenylpyridine (2 g.) in glacial acetic acid (10 c.c.). The mixture was boiled under reflux for ½ hour and then poured into dilute aqueous sodium hydroxide. The precipitated nitration product (2·2 g., m. p. 79—81°) gave α-3-*nitro*-4-*methoxyphenylpyridine*, which crystallised from alcohol in colourless needles, m. p. 85—86° (Found: C, 62·7; H, 4·2. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·3%).

Synthesis of α-3-*Nitro*-4-*methoxyphenylpyridine.*—3-Nitro-4-methoxyaniline (5·6 g.) was diazotised as described above for 5-nitro-2-methoxyaniline and added dropwise with stirring to pyridine (100 c.c.) at 30—35°. The mixture was heated on the steam-bath for ½ hour, ammonia added, and the excess of pyridine removed with steam. The oily residue was extracted with benzene and, after removal of the benzene from the dried extract, the residue was distilled under reduced pressure. The resulting viscous oil (2 g.) was dissolved in alcohol. On standing, a yellow solid was deposited. Further recrystallisation from alcohol yielded α-3-nitro-4-methoxyphenylpyridine in pale yellow needles, m. p. 85—86°, both alone and on admixture with the product obtained from the nitration of α-4-methoxyphenylpyridine. The isomeric 3-nitro-4-methoxyphenylpyridines present in the alcoholic mother-liquors were not investigated

Action of Diazotised m-*Anisidine on Pyridine.*—This reaction was carried out exactly as described above for the corresponding reaction with *o*-anisidine, except that the addition to the pyridine was effected at 40°. The crude product (14 g.), collected at 165—185°/<1 mm., was treated with hot alcoholic picric acid and the resulting mixture of picrates was submitted to systematic fractional crystallisation from acetone. The predominant isomeride, α-3-*methoxyphenylpyridine picrate*, separated in yellow plates, m. p. 154—155° (Found: C, 52·2; H, 3·4. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4%). A second isomeric *picrate*, isolated from the mother-liquors in yellow prisms, m. p. 203—204° (Found: C, 52·0; H, 3·5%), is regarded as that of γ-3-methoxyphenylpyridine. The free bases, regenerated from the picrates by means of 5% aqueous sodium hydroxide, were obtained as yellow oils.

Synthesis of α-3-*Methoxyphenylpyridine.*—This was carried out from α-3-aminophenylpyridine, obtained by the reduction of α-3-nitrophenylpyridine (cf. Part I, *loc. cit.*), by diazotisation and reaction with methyl alcohol exactly as previously described for the synthesis of β-2-methoxyphenylpyridine from β-2-nitrophenylpyridine. The α-3-methoxyphenylpyridine was obtained as a brown oil, which was treated with alcoholic picric acid. Crystallisation of the picrate from acetone gave α-3-methoxyphenylpyridine picrate in yellow plates, m. p. 154—155°, both alone and on admixture with the product of similar m. p. obtained above from the reaction between diazotised *m*-anisidine and pyridine.

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