LIV.—*Nitration of Phenyl Substituents of Heterocyclic Nuclei.*

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Nitration of 2-phenylglyoxaline by addition of the nitrate of the base to cold sulphuric acid and heating at 100° gave 2-*p*-, 2-*o*-, and 2-*m*-nitrophenylglyoxalines in yields of 50, 1·5, and 0·2% of the theoretical respectively (Pyman and Stanley, J., 1924, **125**, 2484). In view of the poor total yield, the nitration has now been repeated, the mixture, however, being kept for 60 hours at the ordinary temperature instead of being heated: the result was but little better, 2-*p*-nitrophenylglyoxaline being obtained in a yield of 57% of the theoretical, and oxidation of the by-products gave a mixture of acids from which crude *m*-nitrobenzoic acid was isolated in 5% yield. Attempts to obtain a clearer picture of a similar nitration by employing 2-phenyl-1-methylglyoxaline were unsuccessful, for the only identifiable products in this case were the *p*-nitro-derivative in

39% yield and *p*-nitrobenzoic acid (by oxidation of the by-products) in 4·4% yield.

Whilst the above nitrations yield *p*-nitro-derivatives as main products, the nitration of 2-phenylglyoxaline-4 : 5-dicarboxylic acid (Pyman and Stanley, *loc. cit.*), 2-phenyl-4 : 5-dihydroglyoxaline, and benzamidine (Forsyth, Nimkar, and Pyman, J., 1926, 800) have been shown to yield predominantly *m*-nitro-derivatives. In the hope of throwing light on this difference in substitution, the nitration of a number of allied compounds has been studied, but experimental difficulties prevented anything more than an incomplete picture of the nitration being obtained in each case. 4-Hydroxy-2-phenyl-6-methylpyrimidine gave 50% of the *m*-nitro-compound, and oxidation of the mother-liquor gave a further 7% of *m*-nitrobenzoic acid : it thus resembles benzamidine rather than 2-phenylglyoxaline. The nitration of phenylacetamidine gave 75% of the *p*-nitro-derivative, just as the nitration of β-phenylethylamine gives mainly the *p*-compound, and 1-phenylglyoxaline also gave the *p*-nitro-compound (58%). On nitration, 4-phenylpiperidine gave the *p*-, *o*-, and *m*-nitro-compounds in yields of 52, 8, and 3% respectively : the proportion of *m*-compound is thus considerably less than in the nitration of 4-phenylpyridine, where the *p*-, *o*-, and *m*-compounds were isolated in yields of 38, 13, and 28% respectively.

We regret that in publishing our paper on the nitration of 2-, 3-, and 4-phenylpyridines (J., 1926, 2912) we overlooked the previous publication of Tschitschibabin and Schemjakina (*J. Russ. Phys. Chem. Soc.*, 1921, **53**, 217) owing to the fact that no reference was made to it in our *Abstracts*, although it was abstracted in the *Chem. Zentralblatt*, 1923, ii, 1024. These authors, using different methods from ours, separated from the products of interaction of pyridine with diazotised *p*-nitroaniline two *p*-nitrophenylpyridines, m. p. 131—131·5° and 146—147° respectively. They proved that the first was 2-*p*-nitrophenylpyridine (for which we found m. p. 130·5—131·5°) and assumed that the second was 4-*p*-nitrophenylpyridine. In view of our results, however, it is clear that their second compound was 3-*p*-nitrophenylpyridine, for which we found m. p. 148—149°.

EXPERIMENTAL.

Nitration of 2-Phenyl-1-methylglyoxaline.—*2-Phenyl-1-methylglyoxaline nitrate*, described as needles, m. p. about 100°, but not analysed by Balaban and King (J., 1925, **127**, 2701), crystallises from dry acetone in prismatic needles, m. p. 126—127° (corr.). It is anhydrous, readily soluble in water, and fairly readily soluble in alcohol or acetone (Found : C, 54·2 ; H, 5·3 ; N, 19·1. $C_{10}H_{10}N_2,HNO_3$ requires C, 54·3 ; H, 5·0 ; N, 19·0%).

This salt (5 g.) was added to sulphuric acid (10 c.c.) below 0° and the solution was kept for an hour, heated at 100° for another hour, and diluted with ice-water. The colourless crystals which separated (0·56 g.; m. p. 167—168°) were rejected, as was also an ether-extract of the solution (0·38 g. of gummy crystals). When the aqueous solution was basified with sodium hydroxide, pale yellow crystals separated (2·4 g.; m. p. 90—100°); chloroform extracted from the mother-liquor 1·21 g. of syrupy bases. The precipitated base was converted into nitrate, which was crystallised from alcohol, giving pure 2-*p*-nitrophenyl-1-methylglyoxaline nitrate (2·05 g.; m. p. 184—185° [corr.]; yield, 34·1%); the mother-liquors gave a further 4·8% yield of the same substance rather less pure, and after oxidation with permanganate a 4·4% yield of crude *p*-nitrobenzoic acid.

The above nitrate and the base, m. p. 117—118° (corr.), and picrate, m. p. 214—215° (corr.), prepared from it were shown by the mixed melting-point method to be identical with the base and its salts prepared by the methylation of 2-*p*-nitrophenylglyoxaline, for which Balaban and King (*loc. cit.*) give the m. p.'s (nitrate) 186°, (base) 116·5°, and (picrate) 212° (all corr.).

Phenylacetamidine Nitrate.—Phenylacetiminoethyl ether hydrochloride was prepared by the method of Luckenbach (*Ber.*, 1884, **17**, 1421) in 92% yield; it had m. p. 99—100° (corr.; efferv.) after sintering from 97°. Luckenbach gives m. p. 85° after softening at 60°. This salt was converted into crude phenylacetamidine hydrochloride by means of alcoholic ammonia (Luckenbach, *loc. cit.*) and thence into the nitrate by means of silver nitrate. Phenylacetamidine nitrate was thus obtained in 93% yield. It crystallises from water in large rhombic prisms, m. p. 168—169° (corr.). Bernton (*Arkiv Kemi Min. Geol.*, 1918, **7**, 1) gives m. p. 166—167°, but does not give an analysis of this salt. It is moderately easily soluble in water and sparingly soluble in alcohol (Found: N, 21·6. $C_8H_{10}N_2,HNO_3$ requires N, 21·3%).

Nitration of Phenylacetamidine.—Phenylacetamidine nitrate (5 g.) was added to sulphuric acid (10 c.c.) below 0°. The solution was kept for one hour, heated at 100° for 2 hours, cooled, and diluted with ice-water. On extraction with ether, only a trace of material was removed. The aqueous solution was mixed with sufficient aqueous barium chloride to remove sulphate ions, filtered from barium sulphate, and concentrated to small bulk. Since the hydrochlorides obtained did not crystallise, they were dissolved in water and mixed with the equivalent quantity of silver nitrate. After removal of silver chloride and concentration, crude *p*-nitrophenylacetamidine nitrate separated (5·66 g.; m. p. 150°); the mother-liquor gave on evaporation a sticky residue (0·59 g.; m. p. 100—115°). Crystal-

lisation of the nitrate of higher m. p. from alcohol gave pure *p*-nitrophenylacetamidine nitrate (4·42 g.; m. p. 157° [corr.]; yield, 69·7%), which was identified with the synthetic product described below by the mixed melting-point method. Attempts to fractionate the remaining material by crystallisation as nitrate, or as picrate, or after oxidation as nitrobenzoic acids, were fruitless. Orientation of *p*-nitrophenylacetamidine was effected by its synthesis from *p*-nitrophenylacetonitrile.

Synthesis of p-*Nitrophenylacetamidine.*—A suspension of *p*-nitrophenylacetonitrile (16·2 g.) in dry ether (20 c.c.) and absolute alcohol (4·6 g.) was saturated with dry hydrogen chloride. After 3 days, the p-*nitrophenylacetiminoethyl ether hydrochloride*, which had separated as a colourless crystalline powder, was collected and washed with ether (yield, 21·6 g.; 88%). When heated slowly from the ordinary temperature, it softened at about 188° and melted at 191—192° (corr.; decomp.), but it decomposed when placed in a bath at 150° (Found: Cl, 14·2. $C_{10}H_{12}O_3N_2$,HCl requires Cl; 14·5%). This salt is fairly readily soluble in alcohol, but sparingly soluble in ether; it is decomposed by water.

To *p*-nitrophenylacetiminoethyl ether hydrochloride (10 g.), suspended in absolute alcohol (10 c.c.), absolute alcohol saturated with ammonia at 0° was added gradually until a slight excess of ammonia remained after prolonged shaking. After being kept at 30° for 2 days, the mixture was diluted with water, acidified faintly with hydrochloric acid, concentrated to remove alcohol, and extracted with ether. The aqueous liquor was mixed with sufficient aqueous silver nitrate to remove chlorine ions, filtered from silver chloride, and concentrated. *p*-Nitrophenylacetamidine nitrate [7·6 g.; m. p. 157° (corr.)] then separated, and the mother-liquor on concentration gave a further deposit which, after removal of non-basic material by ether, afforded a further 0·72 g. of the nitrate, m. p. 157° (corr.). Total yield, 81%.

p-*Nitrophenylacetamidine nitrate* crystallises from water or moist alcohol in colourless coarse needles which rapidly become pale yellow in contact with air. It contains $\frac{1}{2}H_2O$, which is lost slowly over sulphuric acid, and the dried salt has m. p. 157° (corr.). It is moderately easily soluble in water or alcohol. Its aqueous solution becomes intensely red on addition of alkali (Found in air-dried salt: loss over H_2SO_4, 3·6. $C_8H_9O_2N_3$,HNO_3,$\frac{1}{2}H_2O$ requires $\frac{1}{2}H_2O$, 3·6%. Found in dried salt: C, 39·8; H, 4·3; N, 22·9. $C_8H_9O_2N_3$,HNO_3 requires C, 39·7; H, 4·1; N, 23·1%). The picrate crystallises from water or alcohol in yellow needles, m. p. 210° (corr.). It is very sparingly soluble in both these solvents, but fairly readily soluble in acetone.

Nitration of 4-Hydroxy-2-phenyl-6-methylpyrimidine.—The pyrimidine (5 g.) was added to sulphuric acid (10 c.c.) below 0°, followed gradually by potassium nitrate (2·7 g.). The mixture was kept for 2 hours at the ordinary temperature, heated for 2 hours at 100°, cooled, and poured into water; crude 4-hydroxy-2-*m*-nitrophenyl-6-methylpyrimidine then separated (4·02 g.; m. p. 245—247°). After prolonged fractional crystallisation, this product gave 3·1 g. (yield, 50%) of the pure base, m. p. 257° (corr.), and small quantities (in all, 7%) of crude *m*-nitrobenzoic acid were obtained by oxidising the bases isolated from the mother-liquors. Orientation of the main product was effected by its oxidation and comparison of the oxidation product with *m*-nitrobenzoic acid, and by its identification with 4-hydroxy-2-*m*-nitrophenyl-6-methylpyrimidine prepared from *m*-nitrobenzamidine and ethyl acetoacetate. The base so prepared by us had m. p. 257° (corr.); Pinner (*Ber.*, 1895, **28**, 485) gives m. p. 254°.

Nitration of 4-Phenylpiperidine.—4-Phenylpiperidine was prepared by the reduction of 4-phenylpyridine with sodium and alcohol after Bailly (*Ber.*, 1887, **20**, 2590), and the base, which distilled mainly at 264—267° (corr.)/756 mm. (Bailly gives b. p. 255—257°/725 mm.), was converted into nitrate, the yield of pure nitrate being 67% of the theoretical calculated on the 4-phenylpyridine employed. *4-Phenylpiperidine nitrate* crystallises readily from water in colourless, diamond-shaped, anhydrous plates, m. p. 139° (corr.) (Found: C, 58·8; H, 7·1. $C_{11}H_{15}N,HNO_3$ requires C, 58·9; H, 7·1%).

4-Phenylpiperidine nitrate (30 g.) was added to concentrated sulphuric acid (60 c.c.) cooled with water, and the solution was heated for ½ hour at 100°. After being basified with sodium hydroxide, the product was collected by ether and mixed with 5*N*-nitric acid (28 c.c.); a crystalline nitrate (24 g.; m. p. 140—145°) then separated. The mother-liquor was evaporated to dryness and the residue was mixed with absolute alcohol and kept; it then deposited an oil which became partly crystalline. This product was separated into crystalline and oily nitrates. All the crystalline nitrates were recrystallised several times from water (3—4 parts) and gave 16·4 g. of pure 4-*p*-nitrophenylpiperidine nitrate. The mother-liquors from this were mixed with sodium iodide and gave a mixture of hydriodides from which 4-*m*-nitrophenylpiperidine hydriodide separated first on crystallisation from water. The hydriodide mother-liquors were basified and extracted with ether and the recovered base was converted into nitrate, a little more of the pure *p*-salt being obtained; the mother-liquors then yielded with sodium iodide a mixture of hydriodides from which more of the *m*-salt was obtained. The oily nitrates mentioned above gave with

sodium iodide in aqueous solution an oily hydriodide, which became partly crystalline, and the crystalline part on recrystallisation from water gave 4-*o*-nitrophenylpiperidine hydriodide. The yields were *p*-nitrate, 19·42 g. pure (52·5%); *m*-hydriodide, 1·17 g. pure + 0·2 g. of m. p. 225° (3·1%); *o*-hydriodide, 3·8 g. pure air-dried (8·1%).

The three bases were precipitated by sodium hydroxide from aqueous solutions of their salts as oils, and when these were collected by ether the *p*- and *m*-bases crystallised, melting without further purification at 95° and 77° respectively, whereas the *o*-base did not crystallise. All three bases readily absorbed carbon dioxide from the air, yielding crystalline carbonates. On oxidation with permanganate the three bases gave the corresponding nitrobenzoic acids, which were identified by the mixed m. p. method.

4-p-*Nitrophenylpiperidine nitrate* crystallises from water in very pale buff plates, m. p. 162—163° (corr.), which are anhydrous and sparingly soluble in cold water (Found: C, 49·1; H, 5·7. $C_{11}H_{14}O_2N_2,HNO_3$ requires C, 49·1; H, 5·6%). The *hydriodide* crystallises from alcohol in deep yellow, anhydrous prisms, m. p. 189—190° (corr.), which are sparingly soluble in cold water or alcohol (Found: C, 39·9; H, 4·5. $C_{11}H_{14}O_2N_2,HI$ requires C, 39·5; H, 4·5%).

4-m-*Nitrophenylpiperidine hydriodide* crystallises from water in flat, pale yellow needles, m. p. 236° (corr.). It is anhydrous and sparingly soluble in cold water (Found: C, 39·6; H, 4·5. $C_{11}H_{14}O_2N_2,HI$ requires C, 39·5; H, 4·5%). The nitrate crystallises from water in cream-coloured prismatic needles, m. p. 205—206° (corr.), which are sparingly soluble in cold water.

4-o-*Nitrophenylpiperidine hydriodide* crystallises from water in almost colourless prismatic needles, containing $1H_2O$, which are sparingly soluble in cold water. After drying at 100°, it melts at 160—161° (corr.) (Found in air-dried salt: loss at 100°, 5·1. $C_{11}H_{14}O_2N_2,HI,H_2O$ requires H_2O, 5·1%. Found in dried salt: C, 39·5; H, 4·5%). The nitrate crystallises from water in almost colourless prisms, m. p. 131—132° (corr.), which are more readily soluble in water than the nitrates of the *p*- and *m*-isomerides.

Nitration of 1-Phenylglyoxaline.—When 1-phenylglyoxaline was dissolved in a slight excess of 5*N*-nitric acid, a solution was obtained which did not crystallise, but after addition of an excess of concentrated nitric acid and concentration of the solution under diminished pressure over sulphuric acid and sodium hydroxide, *1-phenylglyoxaline dinitrate* crystallised in large prisms, m. p. 82—86° (corr.) (Found: C, 40·0; H, 3·7. $C_9H_8N_2,2HNO_3$ requires C, 40·0; H, 3·7%). This salt (3·5 g.) was added gradually to concentrated

sulphuric acid (7 c.c.), cooled with water. The solution was kept for 2 hours, diluted with water (50 c.c.), filtered from a colourless non-basic precipitate (0·12 g.), and basified with aqueous sodium hydroxide; brown crystals (1·85 g.; m. p. 195° after sintering earlier) were then collected. The mother-liquor on extraction with ether gave only 0·1 g. of a brown oil, which became partly crystalline, but was neglected. When the brown crystals were extracted with hot dilute hydrochloric acid, some resin remained undissolved; the solution, after treatment with charcoal, was basified, 1-*p*-nitrophenylglyoxaline (1·6 g.; m. p. 198—200° after previous sintering) being precipitated. After crystallisation from alcohol, this gave 1·42 g. of the pure base (yield, 58%).

1-p-*Nitrophenylglyoxaline* crystallises from alcohol in cream-coloured prismatic needles, m. p. 204—205° (corr.) (Found: C, 56·9; H, 3·9. $C_9H_7O_2N_3$ requires C, 57·1; H, 3·7%). It is insoluble in water and sparingly soluble in cold alcohol. The *hydrochloride* crystallises from dilute hydrochloric acid in almost colourless, elongated, anhydrous prisms, m. p. 293—294° (corr.; decomp.) (Found: Cl, 15·7. $C_9H_7O_2N_3$,HCl requires Cl, 15·7%).

In order to determine the orientation of the nitro-group, the base (0·75 g.) and methyl sulphate (0·75 c.c.) were heated for a few minutes at 100°; a crystalline methosulphate was then formed. This was decomposed by boiling with aqueous sodium hydroxide; the *p*-nitroaniline (0·45 g.; m. p. 132°) that separated gave 0·15 g. of the pure base (m. p. 148°, alone or mixed with pure *p*-nitroaniline) after purification.

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