143. *Substituted Aromatic Aldehydes in Hantzsch's Pyridine Condensation. Part III. Nitromethoxy- and Nitrohydroxy-benzaldehydes.*

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THE influence of some substituents on the behaviour of benzaldehyde in Hantzsch's pyridine condensation has previously been described (J., 1931, 1835), the results obtained, particularly those with the methyl and nitro-groups, being in good agreement with theoretical anticipations. Several aldehydes containing more than one methyl or nitro-group were also examined, the results with three dimethylbenzaldehydes indicating that the retarding influences due to each methyl group do not act independently, and with 3 : 5-dinitro-4-methylbenzaldehyde, the influence of *m*-nitro-groups in increasing the yield of dihydropyridine derivative is most marked. In order further to study the mutual influence of substituents and especially the effect of the introduction of nitro-groups on the behaviour of an aromatic aldehyde in the condensation, a series of ten nitromethoxy- and nitrohydroxy-benzaldehydes has been examined.

The results obtained with the nitromethoxybenzaldehydes (see Table I) indicate that the influence of each substituent is mainly additive. 2- and 4-Methoxybenzaldehydes give yields of 57 and 64% respectively (*loc. cit.*) and the introduction of a *m*-nitro-group into each causes increases in yields of 20 and 13% respectively, comparable with the increase of 14% caused by the introduction of a *m*-nitro-group into benzaldehyde itself (*loc. cit.*). Similarly, with 3-methoxybenzaldehyde a yield of 75% is obtained (*loc. cit.*) and the introduction of a nitro-group in the 4- or 6-position causes a diminution of 6 and 11% respectively, comparable with the respective diminution of 10 and 12% observed when a *p*- or *o*-nitro-group is introduced into benzaldehyde (*loc. cit.*).

TABLE I.

Benzaldehyde.	% Pyridine derivative.	Benzaldehyde.	% Pyridine derivative.
5-Nitro-2-methoxy-	77	6-Nitro-3-methoxy-	64
2-Nitro-3-methoxy-	51	3-Nitro-4-methoxy-	77
4-Nitro-3-methoxy-	69	2 : 6-Dinitro-3-methoxy- ...	0

That the influences are not wholly additive, but depend partly on the relative positions of the substituents, is shown by a comparison of 2-nitro- with 6-nitro-3-methoxybenzaldehyde and of 5-nitro-2-methoxy- with 3-nitro-4-methoxy-benzaldehyde. With the former pair the yield is reduced much more in the case of the *vic.*- than the *as.*-compound, due probably to an enhancement of the *o*-effect of the nitro- by the adjacent methoxy-group, the weak inductive effect of the latter (Type $-I+T$) reinforcing the stronger similar effect of the nitro-group (Type $-I-T$). The similar yields obtained with 5-nitro-2-methoxy- and 3-nitro-4-methoxy-benzaldehydes, contrasting with the difference between *o*- and *p*-methoxybenzaldehydes themselves (yields, 57 and 64% respectively; *loc. cit.*), indicate that the *o*-effect of the methoxy-group must be eliminated by the nitro-group in the *p*-position to it, a similar " continuous system " involving the nitro- and methoxy-groups being possible in both compounds.

With 2 : 6-dinitro-3-methoxybenzaldehyde, the presence of the two *o*-nitro-groups completely inhibits the condensation.

Of the four nitrohydroxybenzaldehydes examined (see Table II), 3-nitro-4-hydroxy- and 6-nitro-3-hydroxy-benzaldehydes yield anomalous results.

TABLE II.

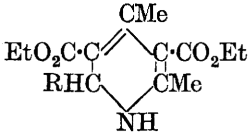
Benzaldehyde.	% Pyridine derivative.	Benzaldehyde.	% Pyridine derivative.
5-Nitro-2-hydroxy-	14	6-Nitro-3-hydroxy-	51
4-Nitro-3-hydroxy-	57	3-Nitro-4-hydroxy-	61

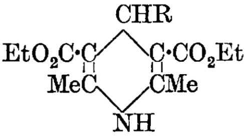
While 2-hydroxybenzaldehyde only yields small quantities of a mixture in the condensation (*loc. cit.*), the influence of the *m*-nitro-group in 5-nitro-2-hydroxybenzaldehyde is shown by this compound yielding 14% of the Hantzsch derivative as the only solid product. Similarly, 3-hydroxybenzaldehyde gives a yield of 67% (*loc. cit.*), and the introduction of the 4-nitro-group leads to a diminution in yield of 10%, similar to the diminution resulting from the introduction of a *p*-nitro-group into benzaldehyde (*loc. cit.*).

The case of 3-nitro-4-hydroxybenzaldehyde is anomalous in that the introduction of a *m*-nitro-group into 4-hydroxybenzaldehyde, with which the yield is 68% (*loc. cit.*), causes a diminution in yield. This may be attributable to an enhancement by the nitro-group of any tendency to ionisation of the hydroxyl group ortho to it. Any tendency for the oxygen to become anionoid would be a retarding influence, since the inductive effect of anionoid oxygen ($+ I + T$) would act analogously to that of the methyl group ($+ I$) (*loc. cit.*). This effect is transmitted to a greater extent from the *p*- than the *m*-position and, if small, might not be observed in the case of a *m*-hydroxy-compound with a nitro-group ortho to the hydroxyl, such as 4-nitro-3-hydroxybenzaldehyde, which, as shown above, behaves normally. A similar retarding influence may also be present in 5-nitro-2-hydroxybenzaldehyde, since an even higher yield might reasonably be expected with this compound.

6-Nitro-3-hydroxybenzaldehyde presents an anomaly of a different type, since while the total yield (51%) is 16% less than with 3-hydroxybenzaldehyde, comparable with the diminution (12%) caused by an *o*-nitro-group in benzaldehyde (*loc. cit.*), the product consists of a mixture of two compounds, m. p. 214° and 205° respectively, both of which give the analytical results required for the dihydropyridine derivative. The first compound yields on methylation a methyl ether, m. p. 170°, identical with the ethyl 4-(6′-nitro-3′-methoxyphenyl)-2 : 6-dimethyl-1 : 4-dihydropyridine-3 : 5-dicarboxylate derived from 6-nitro-3-methoxybenzaldehyde, and is therefore the true Hantzsch derivative. The second compound, m. p. 205°, yields, on methylation, a compound, m. p. 118°, which corresponds, by analysis, to an isomeride of the methoxydihydropyridine above and can be oxidised to a compound which again appears to be isomeric with the normal pyridine derivative, obtained by oxidation of the above nitromethoxyphenyldihydropyridine derivative. From these facts it would appear, unless some new type of stereoisomerism be admitted, that the second compound obtained in the condensation is a substituted 2-phenyldihydropyridine derivative (I; R = $NO_2{\cdot}C_6H_3{\cdot}OMe$) instead of the 4-phenyl derivative (II), which is the normal formulation of the Hantzsch compound and would correspond to the compound, m. p. 214°, obtained in this condensation.

(I.)





(II.)

The formula (I) was suggested by Hantzsch (*Annalen*, 1882, **215**, 1; *Ber.*, 1883, **16**, 1946) for the normal condensation product, which was, however, shown later to have the constitution (II) (Hantzsch, *Ber.*, 1885, **18**, 1744, 2579), the aldehyde radical taking the γ- and not the α-position.

EXPERIMENTAL.

Materials.—The following compounds were prepared in accordance with the authorities quoted: 5-nitro-2-methoxybenzaldehyde (Voswinckel, *Ber.*, 1882, **15**, 2027; Schnell, *ibid.*, 1884, **17**, 1382), 3-nitro-4-hydroxybenzaldehyde (Paal, *ibid.*, 1895, **28**, 2413) and 5-nitro-2-hydroxybenzaldehyde (v. Miller, *ibid.*, 1887, **20**, 1928), although in the last case it was found necessary to crystallise the sodium salt of the nitrohydroxybenzaldehyde five times in order completely to remove the small quantity of 3-nitro-compound also formed.

The nitration of 3-methoxybenzaldehyde with nitric acid alone (compare Tiemann, *ibid.*, 1889, **22**, 2342; Rieche, *ibid.*, p. 2349; Friedländer and Schreiber, *ibid.*, 1895, **28**, 1385) was not satisfactory, owing to the ready occurrence of dinitration, and the reaction proceeded more smoothly with a mixture of nitric and sulphuric acids: 3-Methoxybenzaldehyde (10 g.) was added with constant shaking to a water-cooled mixture of nitric acid (*d* 1·42; 50 c.c.) and concentrated sulphuric acid (20 c.c.), and the whole kept at room temperature for 30 minutes. Pouring into ice-water yielded a light yellow solid (13·3 g., 100%), from which 2-nitro-3-methoxybenzaldehyde was separated by the method of Rieche (*loc. cit.*). It was not found possible to obtain either the 4- or the 6-nitro-derivative from the mixture (compare Tröger and

Fromm, *J. pr. Chem.*, 1925, **111**, 217), although Hodgson and Beard (J., 1927, 2380) have demonstrated that the 6-nitro-derivative is formed.

The nitration of 3-methoxybenzaldehyde (11 g.) in glacial acetic acid (11 c.c.) by addition to a water-cooled mixture of nitric acid (*d* 1·5; 110 c.c.) and glacial acetic acid (55 c.c.) yielded a solid (12 g.), from which was obtained, by one crystallisation from benzene, 2 : 6-dinitro-3-methoxybenzaldehyde, m. p. 156° (compare Hodgson and Beard, *loc. cit.*).

In the preparation of 3-nitro-4-methoxybenzaldehyde, difficulty was experienced in the nitration of anisaldehyde both with a mixture of nitric and sulphuric acids (Einhorn and Grabfeld, *Annalen*, 1888, **243**, 370) and with nitric acid alone (Salway, J., 1909, **95**, 1164) owing to oxidation; better yields were obtained by employing a mixture of fuming nitric and glacial acetic acids: Anisaldehyde (20 g.) in glacial acetic acid (20 c.c.) was added gradually to a water-cooled mixture of nitric acid (*d* 1·5; 200 c.c.) and glacial acetic acid (200 c.c.), and the whole poured into water; the mixture became hot and the product went into solution. On cooling, 3-nitro-4-methoxybenzaldehyde (24 g., 83%) separated, m. p. 84°, after washing with warm light petroleum (b. p. 60—80°).

3-Hydroxybenzaldehyde was nitrated by Pschorr and Seidel's method (*Ber.*, 1901, **34**, 4000): the resulting mixture of isomerides, treated according to Friedländer and Schenck (*ibid.*, 1914, **47**, 3043), yielded 4-nitro- and 6-nitro-3-hydroxybenzaldehydes, but the 2-nitro-compound could not be obtained pure.

Methylation of 6-nitro-3-hydroxybenzaldehyde by means of methyl sulphate and sodium hydroxide solution yielded 6-nitro-3-methoxybenzaldehyde, m. p. 84° (Tiemann and Ludwig, *Ber.*, 1882, **15**, 2055, give m. p. 82—83°).

Treatment of 4-nitro-3-methoxybenzaldehyde with either methyl sulphate and sodium hydroxide solution or with methyl iodide and potassium hydroxide in methyl alcohol (*ibid.*, p. 2054) failed to give a satisfactory yield of the methyl ether, which was finally prepared by the action of methyl sulphate and sodium bicarbonate solution (compare Hodgson and Beard, J., 1926, 153).

Standard Method of Condensation.—The procedure previously described (J., 1931, 1839) was adopted throughout. With each aldehyde, except 4-nitro-3-methoxybenzaldehyde, the condensation was carried out in duplicate, the mean of the two yields being the value given in the tables. With 4-nitro-3-methoxybenzaldehyde, material sufficient for only one condensation was obtainable.

Condensations with Nitromethoxybenzaldehydes.—*Ethyl* 4-(5'-*nitro*-2'-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarb*-

oxylate crystallised from aqueous alcohol in light yellow plates, m. p. 221° (Found: C, 59·2; H, 5·8. $C_{20}H_{24}O_7N_2$ requires C, 59·4; H, 5·9%). Yields: 15·6 and 15·7 g., 77·2 and 77·7%.

Ethyl 4-(2'-*nitro*-3'-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from benzene–light petroleum (b. p. 40—60°) in colourless plates, m. p. 137° (Found: C, 59·5; H, 5·8%). Yields: 10·2 and 10·5 g., 50·5 and 52·0%.

Ethyl 4-(4'-*nitro*-3'-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in light yellow, rectangular crystals, m. p. 134° (Found: C, 58·9; H, 6·0%). Yield: 14·0 g., 69·3%.

Ethyl 4-(6'-*nitro*-3'-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from methyl alcohol in light yellow, rhombic plates, m. p. 170° (Found: C, 59·1; H, 6·2; N, 7·3. $C_{20}H_{24}O_7N_2$ requires N, 6·9%). Yields: 12·6 and 13·1 g., 62·4 and 64·9%.

The dihydro-ester (2 g.) was heated under reflux with *N*-nitric acid (100 c.c.) until solution was effected. The cooled and filtered solution was neutralised with sodium carbonate; the light solid which separated crystallised from aqueous alcohol in colourless square laminæ, m. p. 99°, of *ethyl* 4-(6'-*nitro*-3'-*methoxyphenyl*)-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* (Found: C, 59·1; H, 5·6. $C_{20}H_{22}O_7N_2$ requires C, 59·7; H, 5·5%).

Ethyl 4-(3'-*nitro*-4'-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in colourless prismatic clusters, m. p. 113° (Found: C, 59·2; H, 5·8%). Yields: 15·5 and 15·6 g., 76·7 and 77·2%.

Condensation with 2 : 6-*Dinitro*-3-*methoxybenzaldehyde*.—This was attempted, but even after prolonged treatment no separation of solid product occurred.

Condensations with Nitrohydroxybenzaldehydes.—*Ethyl* 4-(5'-*nitro*-2'-*hydroxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* separated from alcohol as a light yellow, crystalline powder, m. p. 184° (Found: C, 58·4; H, 5·0; N, 7·9. $C_{19}H_{22}O_7N_2$ requires C, 58·5; H, 5·6; N, 7·2%). Yields: 2·5 and 3·1 g., 12·8 and 15·9%.

Ethyl 4-(4'-*nitro*-3'-*hydroxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in light yellow prisms, m. p. 145° (Found: C, 57·9; H, 5·4%). Yields: 11·0 and 11·4 g., 56·4 and 58·5%.

Ethyl 4-(3'-*nitro*-4'-*hydroxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in orange plates, m. p. 161° (Found: C, 57·9; H, 5·6%). Yields: 12·0 and 11·9 g., 61·5 and 61·0%.

Condensation with 6-*Nitro*-3-*hydroxybenzaldehyde.*—Gradual evaporation of the reaction mixture yielded two different crystalline compounds in approximately equal quantities. The *compound* which first separated crystallised from alcohol in dark orange prisms, m. p. 205° (Found : C, 57·9; H, 5·6; N, 7·2%). The more soluble compound, *ethyl* 4-(6′-*nitro*-3′-*hydroxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate*, crystallised from aqueous alcohol in small yellow needles, m. p. 214° (Found : C, 58·2; H, 5·7; N, 7·3%). Total yields : 9·85 and 10·0 g., 50·5 and 51·3%. Methylation of the latter compound by means of methyl sulphate and sodium hydroxide solution yielded the methyl ether, m. p. 170° (Found : C, 59·2; H, 6·1; N, 7·1%), which m. p. was unchanged by admixture with the ethyl 4-(6′-nitro-3′-methoxyphenyl)-2 : 6-dimethyl-1 : 4-dihydropyridine-3 : 5-dicarboxylate described above.

Methylation of the compound, m. p. 205°, in a similar manner yielded the *methyl* derivative, which crystallised from aqueous alcohol in reddish needles, m. p. 118° (Found : C, 59·6; H, 6·0. $C_{20}H_{24}O_7N_2$ requires C, 59·4; H, 5·9%). Oxidation of this methyl derivative, by means of *N*-nitric acid in the manner described above, yielded a *compound*, which crystallised from aqueous methyl alcohol in small colourless needles, m. p. 91·5° (Found : C, 59·7; H, 5·7. $C_{20}H_{22}O_7N_2$ requires C, 59·7; H, 5·5%).

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