185. *Substituted Aromatic Aldehydes in Hantzsch's Pyridine Condensation. Part IV. Derivatives of* 3 : 4-*Dihydroxybenzaldehyde.*

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In order to extend the study of the effect of the nitro-group on the behaviour of aromatic aldehydes in Hantzsch's pyridine synthesis, the condensation of the methyl ethers of 3 : 4-dihydroxybenzaldehyde, namely, vanillin, *iso*vanillin, and veratraldehyde, and of six of their nitro-derivatives has been investigated.

Vanillin, *iso*vanillin, and veratraldehyde exhibit very little difference in behaviour, the yields, 74, 73, and 76% respectively, approximating to those given by benzaldehyde and *m*-methoxybenzaldehyde (74 and 75% respectively; see Part II, J., 1931, 1835).

The effect of a nitro-group in these methyl ethers is markedly less than has been observed in previous cases, but the nitro-groups in 5-nitro*iso*vanillin (76% yield) and 6-nitro-veratraldehyde (68%) tend to influence the condensation in the normal manner, the *m*- and *o*-nitro-groups having an effect analogous to, but less than, that of these groups in similar positions in benzaldehyde (*loc. cit.*). As previously observed with 2 : 6-dinitro-3-methoxybenzaldehyde (Part III, J., 1932, 1112), the presence of two *o*-nitro-groups in 2 : 6-dinitro-*iso*vanillin inhibits the condensation. An unexpected result with this compound was the formation of its ammonium salt, which also failed to react in the condensation.

With three substituents present, the likelihood for anomalies, due to the mutual influence of substituents, is increased and the nitro-groups in 5-nitro- and 2-nitro-veratraldehyde and 2-nitrovanillin yield anomalous results, the *m*-nitro-group in the first causing a diminution in yield (76 to 70%) and the *o*-nitro-group in the second having no appreciable effect. With 2-nitrovanillin, consistent yields could not be obtained, but the highest recorded (72%) indicates that the *o*-nitro-group is having only a slight influence.

Four other derivatives of 3 : 4-dihydroxybenzaldehyde examined were the methylene ether, piperonal, and its 6-bromo-, 6-chloro-, and 6-nitro-derivatives, which give yields of 72, 70, 67, and 61% respectively. Piperonal thus compares with the above methyl ethers, the *o*-substituent decreasing the yield in each case.

The diminutions with the chloro- and nitro-compounds (5 and 11%) compare with those caused by chlorine and the nitro-group in the *o*-position in benzaldehyde (12%, Part II). The order of influence on the yield is: Br<Cl<NO_2, which corresponds to the normal sequence of increase of general inductive effect with these three substituents, thus indicating that the ortho-effect of the substituent is polar rather than steric. In the latter event, the substituents would be placed in the order: Cl<NO_2<Br, taking, as a measure of the spatial effect, the "internuclear distances" calculated by Stanley and Adams (*J. Amer. Chem. Soc.*, 1930, **52**, 1200; compare Adams and Yuan, *Chemical Reviews*, 1933, **12**, 284) for determining the possible interference of groups in the 2 : 2′ : 6 : 6′-positions in diphenyl.

Shaw and Wagstaffe (J., 1933, 77) consider that the influence of a nitro-group on the behaviour of an aromatic aldehyde should only be an enhancing one, giving the order: 2 : 4-dinitro>mononitro>unsubstituted, in accordance with their observations on the condensation of aromatic aldehydes with 2-picoline and with those of Bennett and Willis (J., 1928, 1960) on condensations with 2-methylquinoxaline. We have examined, in all, the behaviour of seventeen mono- and four di-nitro-aldehydes in the Hantzsch condensation, and in only seven cases is the yield with the nitro-aldehyde greater than with the corresponding unsubstituted aldehyde; these seven nitro-aldehydes all contain *m*-nitro- or *mm*′-dinitro-groups. With each of the seven *o*-nitro- and three *p*-nitro-aldehydes studied, the yield is never greater than with the corresponding unsubstituted aldehyde, the diminutions in yield generally approximating to those observed with benzaldehyde itself, and *oo*′-dinitro-groups appear completely to inhibit the condensation. Where comparisons are possible, the relations originally derived for the enhancing influence of a nitro-group, *viz.*, *m*>unsubstituted and *m*->*o*- and *p*- (compare Part II), are usually confirmed.

EXPERIMENTAL.

Materials.—The substituted aldehydes employed were prepared in accordance with the authorities cited: veratraldehyde (Perkin and Robinson, J., 1907, **91**, 1079), 2-nitrovanillin, 2-nitro- and 6-nitro-veratraldehydes (Pschorr and Sumuleanu, *Ber.*, 1899, **32**, 3407; compare Pisovschi, *Ber.*, 1910, **43**, 2139), 5-nitro*iso*vanillin, 5-nitroveratraldehyde, and 2 : 6-dinitro*iso*vanillin (Pschorr and Stöhrer, *Ber.*, 1902, **35**, 4393); 6-nitro- (Parijs, *Rec. trav. chim.*, 1930, **49**, 18; compare Wilkendorf, *Ber.*, 1919, **52**, 606), 6-chloro- and 6-bromo-piperonal (Parijs, *loc. cit.*; Orr, Robinson, and Williams, J., 1917, **111**, 947). The 5-nitro*iso*vanillin obtained melted at 121° (recorded m. p. 113°) (Found: C, 48·8; H, 3·7. Calc.: C, 48·7; H, 3·6%).

Standard Method of Condensation.—The procedure previously described (J., 1931, 1839) was adopted throughout. With each aldehyde the condensation was carried out in duplicate, the mean of the two yields being the value recorded in the introductory portion.

Condensations with Vanillin and 2-Nitrovanillin.—*Ethyl* 4-(4′-*hydroxy*-3′-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in colourless needles, m. p. 164° (Found: C, 64·4; H, 6·8. $C_{20}H_{25}O_6N$ requires C, 64·0; H, 6·7%). Yields: 13·9 and 13·9 g., 74·1%. Methylation of this compound with methyl sulphate and sodium hydroxide yielded the dimethoxy-derivative, m. p. 144°, identical with the dihydropyridine derivative obtained from veratraldehyde (see below).

Ethyl 4-(2′-*nitro*-4′-*hydroxy*-3′-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from ethyl acetate in light yellow plates, m. p. 118° (Found: C, 56·7; H, 5·8. $C_{20}H_{24}O_8N_2$ requires C, 57·1; H, 5·7%). It was not possible to obtain consistent yields in the condensation, owing to the difficulty of isolating the product free from sticky material without loss. The compound was best isolated by complete evaporation of the alcohol from the reaction mixture, dissolution of the sticky residue in ether, and washing of the ethereal solution with dilute sulphuric acid. The product obtained on removal of ether from the dried ethereal solution was recrystallised as above. Examples of yields: 15·1 and 12·1 g., 71·9 and 57·6%.

Condensations with iso*Vanillin* and 5-*Nitro*iso*vanillin*.—*Ethyl* 4-(3′-*hydroxy*-4′-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in light yellow needles, m. p. 165° (Found: C, 64·4; H, 6·8. $C_{20}H_{25}O_6N$ requires C, 64·0; H, 6·7%). Yields: 13·9 and 13·65 g., 74·1 and 72·8%. Methylation of the compound, as above, yielded the dimethoxy-derivative, identical with the dihydropyridine derivative obtained from veratraldehyde (see below).

Ethyl 4-(5'-*nitro*-3'-*hydroxy*-4'-*methoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in orange-yellow prismatic needles, m. p. 185°, containing alcohol of crystallisation (Found : C, 56·2; H, 6·3; $C_2H_5\cdot OH$, 9·9. $C_{20}H_{24}O_8N_2,C_2H_5\cdot OH$ requires C, 56·7; H, 6·4; $C_2H_5\cdot OH$, 9·9%), which, on being heated at 110—120° for 2 hours, yielded the alcohol-free *compound* as a light yellow powder, m. p. 185° (Found : C, 57·1; H, 5·2; N, 7·1. $C_{20}H_{24}O_8N_2$ requires C, 57·1; H, 5·7; N, 6·7%). Yields (of alcohol-free product) : 15·9 and 15·9 g., 75·7%.

Condensations with Veratraldehyde and its Nitro-derivatives.—*Ethyl* 4-(3' : 4'-*dimethoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in colourless prisms, m. p. 144° (Found : C, 64·7; H, 7·0. $C_{21}H_{27}O_6N$ requires C, 64·8; H, 6·9%). Yields : 14·8 and 14·9 g., 76·1 and 76·6%.

Ethyl 4-(2'-*nitro*-3' : 4'-*dimethoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in colourless plates, m. p. 141·5° (Found : C, 57·6; H, 6·1; N, 6·8. $C_{21}H_{26}O_8N_2$ requires C, 58·1; H, 6·0; N, 6·5%). Yields : 16·1 and 16·7 g., 74·2 and 77·0%.

Ethyl 4-(5'-*nitro*-3' : 4'-*dimethoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in light yellow needles, m. p. 154° (Found : C, 57·6; H, 6·1%). Yields : 15·05 and 15·5 g., 69·3 and 71·4%.

Ethyl 4-(6'-*nitro*-3' : 4'-*dimethoxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in yellow prisms, m. p. 229° (Found : C, 58·3; H, 6·1%). Yields : 14·9 and 14·6 g., 68·7 and 67·3%.

Condensations with 2 : 6-*Dinitro*isovanillin *and its Ammonium Salt.*—Condensation of 2 : 6-dinitro*iso*vanillin yielded only the *ammonium* salt of the nitro-aldehyde, which crystallised from methyl alcohol–acetone in fine reddish needles, m. p. 190° (decomp.) (Found : C, 36·7; H, 3·6. $C_8H_9O_7N_3$ requires C, 37·1; H, 3·5%). The salt, when shaken with warm dilute hydrochloric acid, regenerated the original nitroaldehyde. Condensation of the ammonium salt was attempted, but it was recovered unchanged.

Condensations with Piperonal and its Derivatives.—*Ethyl* 4-(3' : 4'-*methylenedioxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from methyl alcohol in pale yellow prisms, m. p. 132° (Found : C, 64·2; H, 6·4. $C_{20}H_{23}O_6N$ requires C, 64·3; H, 6·2%). Yields : 13·4 and 13·3 g., 71·9 and 71·3%.

Ethyl 4-(6'-*chloro*-3' : 4'-*methylenedioxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from methyl alcohol in pale yellow prisms, m. p. 139° (Found : Cl, 8·3. $C_{20}H_{22}O_6NCl$ requires Cl, 8·7%). Yields : 13·6 and 13·7 g., 66·7 and 67·2%.

Ethyl 4-(6'-*bromo*-3' : 4'-*methylenedioxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* separated from methyl alcohol as a yellow crystalline mass, m. p. 169° (Found: Br, 17·8. $C_{20}H_{22}O_6NBr$ requires Br, 17·7%). Yields : 15·8 and 15·7 g., 69·9 and 69·5%.

Ethyl 4-(6'-*nitro*-3' : 4'-*methylenedioxyphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from glacial acetic acid in yellow plates, containing solvent of crystallisation, m. p. 144° (Found : C, 55·7; H, 5·0; N, 6·1. $C_{20}H_{22}O_8N_2,C_2H_4O_2$ requires C, 55·2; H, 5·4; N, 5·9%), and from alcohol in pale yellow plates, with solvent of crystallisation, m. p. 101° (decomp.) (Found : C, 56·4; H, 6·1. $C_{20}H_{22}O_8N_2,C_2H_6O$ requires C, 56·9; H, 6·0%). Yields (as solvent-free material) : 12·45 and 12·85 g., 59·6 and 61·5%.

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