CV.—*Substituted Aromatic Aldehydes in Hantzsch's Pyridine Condensation. Part I. Methoxy-, Chloro-, and Hydroxy-benzaldehydes.*

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It has already been shown (Hinkel and Cremer, J., 1920, **117**, 137) that in Hantzsch's pyridine synthesis the introduction of a *p*-dimethylamino-group into benzaldehyde has a marked inhibitory effect upon the condensation. As no systematic study has hitherto been made involving both the nature and the position of the substituent groups in the aldehydes, condensations have been carried out under similar experimental conditions with *o*-, *m*-, *p*-methoxy-, -chloro-, and -hydroxy-benzaldehydes. Since the three substituting groups are electronegative in character, although of varying intensity, it might be expected that the results obtained with the groups in the *o*-, *m*-, or *p*-position would to some extent be comparable and that similar gradations in the yields of condensation product would be shown. From the theory of alternate polarities (Lapworth and Shoesmith, J., 1922, **121**, 1391) negative groups in the *o*- and *p*-positions should augment the activity of the aldehyde oxygen, and a negative group in the *m*-position diminish it. In all cases (Table I), however, the presence of the substituent lowers the yield of the product as compared with that from benzaldehyde, which gives a 90% yield (compare Hinkel and Cremer, *loc. cit.*).

TABLE I.

Percentage yields of dihydropyridine derivative.

Substituent.	*o*.	*m*.	*p*.
Methoxy	48	33	65
Chloro	38	78	69
Hydroxy	0	36	49

These results, apart from the general depressant effect noted above, are not in agreement with the theory of alternate polarities (Table II), but appear to be in general agreement with the depressant effects of substituents on the affinity of benzaldehyde for hydrogen cyanide as recently recorded by Lapworth and Manske (J., 1928, 2533). It would appear that the factors influencing the ionisation constants of substituted benzoic acids (Flürscheim, J., 1909, **95**, 726) affect similarly the reactivity of the aldehyde group. Since, in the above cases, the yields of dihydropyridine derivatives are smaller than the yield from benzaldehyde, the general " electropolar " factor of each of the three substituents is more pronounced than the " quantitative " factor. The quantitative factor is least pronounced in the case of chlorine, since the *m*- and *p*-chloro-deriv-

TABLE II.

Substituent.	Comparison.	Agreement (+) or reverse (−) with deduction from polarity standpoint.
Methoxy	*m* and *o*	+
	m ,, *p*	+
Hydroxy	*m* ,, *o*	−
	m ,, *p*	+
Chloro	*m* ,, *o*	−
	m ,, *p*	−

atives show the least difference in yield. Further, the quantitative factor for chlorine is unexpectedly exerted in the opposite sense to those for the methoxy- and the hydroxy-group, since with these the yield of the *m*-derivative is less than that of the *p*-derivative, which is the reverse of that found with chlorine. The influence of the steric factor is seen in the decreased yields of *o*-chloro- and *o*-methoxy-derivatives as compared with the corresponding *p*-derivatives. The abnormal behaviour of *o*-hydroxybenzaldehyde would be expected from the conclusions of Sidgwick and Callow (J., 1924, **125**, 527), that co-ordination occurs between the hydroxy- and the aldehyde group, the typical properties of each group being diminished.

With the exception of the derivatives of the hydroxy-aldehydes, the oxidation of the dihydropyridine compounds proceeded normally and in no case was there any apparent tendency for the elimination of the phenyl group. The dihydropyridine derivatives from the hydroxy-aldehydes, owing to their phenolic character and tendency to form nitroso-compounds, do not lend themselves to the normal oxidation by means of nitrous fumes.

EXPERIMENTAL.

Ethyl 4-p-*Methoxyphenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate*.—A mixture of 10 g. (1 mol.) of *p*-methoxybenzaldehyde, 19·2 g. (2 mols.) of ethyl acetoacetate, and 20 c.c. of alcohol was saturated with ammonia gas and, after remaining at the ordinary temperature for an hour, heated on a water-bath for several hours. (This procedure was adopted in all subsequent condensations, in which, therefore, only the treatment of the product will be described.) The yellow solid obtained on cooling crystallised from alcohol in almost colourless tetrahedra (17 g.), m. p. 159° (Found: C, 66·3; H, 7·1; N, 4·0. $C_{20}H_{25}O_5N$ requires C, 66·8; H, 7·0; N, 3·9%).

Ethyl 4-p-*Methoxyphenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate*.—The dihydro-ester was made into a thin paste with alcohol and nitrous fumes were led into the mixture until a clear solution was obtained. The greater portion of the alcohol was removed by evaporation and the residue was neutralised with sodium carbonate solution and extracted with ether (this procedure was adopted in all subsequent oxidations). The solid obtained after removal of the ether slowly crystallised from light petroleum (b. p. 40—60°) in colourless rhombohedra, m.p. 50° (Found: C, 66·6; H, 6·5. $C_{20}H_{23}O_5N$ requires C, 67·2; H, 6·4%).

Ethyl 4-o-*Methoxyphenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate*.—The condensation product from 10 g. of *o*-methoxybenzaldehyde was concentrated on a water-bath. The solid obtained on cooling and stirring, after being washed with benzene, crystallised from alcohol in small yellow needles (12 g.), m. p. 151° (Found : C, 68·8 ; H, 7·1 ; N, 4·2%).

Ethyl 4-o-*methoxyphenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* crystallised from alcohol in colourless stout needles, m. p. 65° (Found : C, 66·7 ; H, 6·6%).

Ethyl 4-m-*Methoxyphenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate*.—The viscous product obtained from the condensation of 10 g. of *m*-methoxybenzaldehyde became semi-solid on standing. It was stirred with a small quantity of benzene, collected, and washed with light petroleum (b. p. 40—60°) ; when these washings were added to the benzene filtrate, more of the solid was obtained. It crystallised from aqueous alcohol in clusters of very small, colourless needles (9·2 g.), m. p. 120° (Found : C, 66·9 ; H, 7·3%).

Ethyl 4-m-*methoxyphenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in colourless mica-like plates, m. p. 82° (Found : C, 67·3 ; H, 6·7%).

Ethyl 4-p-*Chlorophenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate*.—The crude product obtained from 14 g. of *p*-chlorobenzaldehyde deposited crystals on cooling which separated from alcohol in almost colourless, flat tetrahedra (25 g.), m. p. 149° (Found : Cl, 9·3. $C_{19}H_{22}O_4NCl$ requires Cl, 9·75%).

Ethyl 4-p-*chlorophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* crystallised from light petroleum (b. p. 60—80°) in colourless thick prisms, m. p. 68° (Found : Cl, 9·4. $C_{19}H_{20}O_4NCl$ requires Cl, 9·8%).

Ethyl 4-o-*Chlorophenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate*.—The viscous mass obtained from 14 g. of *o*-chlorobenzaldehyde was stirred with a small quantity of benzene. The fine solid which separated was removed, and a further yield obtained by the gradual addition of light petroleum (b. p. 40—60°) to the filtrate. The solid crystallised from aqueous methyl alcohol in cubes (12·6 g.), m. p. 132° (Found : Cl, 9·5%).

Ethyl 4-o-*chlorophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* crystallised from light petroleum (b. p. 40—60°) in colourless rhombohedra, m. p. 62° (Found : Cl, 9·8%).

Ethyl 4-m-*Chlorophenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate*.—The product obtained from the condensation of 14 g. of *m*-chlorobenzaldehyde solidified completely on cooling. It crystallised from aqueous methyl alcohol in stellate clusters of needles (32 g.), m. p. 142° (Found : Cl, 9·4%).

Ethyl 4-m-*chlorophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate* crystallised from methyl alcohol in colourless tetrahedra, m. p. 53° (Found : Cl, 9·5%).

Ethyl 4-p-*Hydroxyphenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate.*—The viscous condensation product obtained from 10 g. of *p*-hydroxybenzaldehyde slowly set to a semi-solid mass. This was slightly diluted with aqueous alcohol, and the solid removed; more was obtained from the concentrated filtrate on treatment with aqueous alcohol. The solid crystallised from alcohol in clusters of fine prisms (13·3 g.), m. p. 227° (Found: C, 65·8; H, 6·8. $C_{19}H_{23}O_5N$ requires C, 66·1; H, 6·7%).

Ethyl 4-m-*Hydroxyphenyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate.*—The product from 10 g. of *m*-hydroxybenzaldehyde solidified almost completely on being cooled and stirred and was then treated with aqueous alcohol as described above. The solid obtained crystallised from alcohol in small thick prisms (10·2 g.), m. p. 202° (Found: C, 66·0; H, 6·6%).

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