CCXLVII.—*Substituted Aromatic Aldehydes in Hantzsch's Pyridine Condensation. Part II. Methyl- and Nitro-benzaldehydes.*

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THE general effect of substituents in carbonyl compounds and the direct dependence of the activity of the carbonyl group on the electronic character of the substituent have been elucidated mainly by Robinson and Lapworth and their co-workers. The failure of the ester and amide groups to exhibit normal carbonyl activity has been explained by Rây and Robinson (J., 1925, **127**, 1618; compare also Allan, Oxford, Robinson, and Smith, J., 1926, 404, Case 4) as being due to the combination of the carbonyl group with the strongly electron-donating group, OEt or NH_2, which causes the kationoid character of the carbon atom (compare Lapworth, *Nature*, 1926, **115**, 625) to diminish to a minimum. This conception has been extended by Lapworth and Manske (J., 1928, 2538) to the general case, $A_0CR{=}X$, in which, as A_0 is replaced successively by NMe_2, OMe, CH_3, H, COR, and NO_2, the compound becomes more kationoid. The sequence thus obtained corresponds with that previously deduced by Ingold, Shoppee, and Thorpe (J., 1926, 1482) for the enhancement of three-carbon prototropic mobility.

This view of the activity of substituted carbonyl compounds also affords an adequate explanation of the results of Stewart (J., 1905, **87**, 185, 410) on the formation of bisulphite compounds. The gradation in properties of $C_6H_5{\cdot}CHO$, $CH_3{\cdot}CHO$, and $H{\cdot}CHO$ can similarly be correlated with the order, $C_6H_5 > CH_3 > H$, established by Burton and Ingold (J., 1928, 909) for the facilitation of three-carbon anionotropy.

The influence of the substituent on the behaviour of a substituted benzaldehyde has been discussed for the benzoin reaction by Hodgson and Rosenberg (J., 1930, 14), who consider that the presence of a *meta-directing* group will deactivate and that of an *ortho-para-directing* group will activate the carbonyl group of the molecule of aldehyde reacting with the initially formed cyanohydrin. Since in this reaction the possibility of condensation is regarded (Lapworth, J., 1903, **83**, 1004) as dependent on the mobility of the hydrogen atom of the cyanohydrin, these conclusions can only be applied to such a reaction, in which there is proton addition to the carbonyl group, the facility of internal ionisation of the carbonyl group being therefore the primary factor. In the case of anion addition, the general considerations outlined above must be applied, and since the primary reaction with aromatic aldehydes consists normally of anion addition to the side-chain kationoid carbonyl carbon atom, this class of reaction comes within the scope of the classification proposed by Ingold and Rothstein (J., 1928, 1217, Type B_2) and a substituent which supplies electrons will tend to inhibit the reaction and one which withdraws electrons to facilitate it. The effect of substituent groups cannot, however, be directly inferred from their orienting effects in benzene substitution. Shoppee has shown (J., 1930, 969) that the facilitation of prototropy does not run parallel with retardation of benzene hydrogen-substitution, due to different demands for electron transference in the two cases. With aromatic aldehydes, the " tautomeric effect " of a substituent can only have a second-order effect on the carbonyl carbon, since a free path for electron transference is not present when the substituent is in the meta-position, and when it is in the ortho- or para-position it forms a " continuous system " with the carbonyl group, the polarisation of which is enhanced or depressed with but little effect on the kationoid character of the carbon atom.

In Part I (J., 1929, 750), the effects of three substituents, Cl, OMe, and OH, on the behaviour of benzaldehyde in the Hantzsch pyridine condensation were described, but as all three substituents are of a mixed electronic type ($-I + T$; compare Ingold and Shaw, J., 1927, 2918) it became necessary to study the effects of substituent groups of less complex types, and the methyl ($+I$) and nitro- ($-I-T$) groups were chosen as the most suitable.

With the methyl group, the permanent electron repulsion will depress the kationoid character of the carbonyl carbon atom. According to Ingold and Shaw (*loc. cit.*) the coefficients of activation for the three nuclear positions in toluene for nitration are in the ratio $o : m : p :: 27{\cdot}6 : 2{\cdot}1 : 34{\cdot}6$, with benzene as unity, so that the order of kationoid activity in the tolualdehydes can be taken as *o*- and *p*- <*m*-, and with the operation of any *ortho effect*, the anticipated order of yield of product in the Hantzsch condensation should be *o*- <*p*-<*m*-<benzaldehyde, and this theoretical order has now been established experimentally.

In the case of the nitro-group, the permanent electron affinity of the group will lead to enhancement of kationoid character, which will, however, be modified in the case of the *o*- and *p*-compounds owing to conjugation and the operation of the " Thiele factor " (Lapworth and Manske, *loc. cit.*). The order of kationoid activity should thus be: *m*->unsubstituted, and *m*->*o*- and *p*-. The behaviour of the nitrobenzaldehydes in the Hantzsch condensation has previously been studied by Lepetit (*Ber.*, 1887, **20**, 1338), who states that while the *m*-compound gives a 65% yield of the dihydropyridine derivative, the *p*- gives a poor yield and the *o*- gives a mixture of the corresponding pyridine derivative with a compound, the constitution of which he did not determine. The experimental conditions described for each aldehyde vary, notably so with the *o*-nitro-compound, with which equimolecular proportions of nitro-aldehyde and ethyl acetoacetate were employed, instead of the usual ratio of 1 : 2 mols. respectively. Employing the conditions described in the experimental portion, we find that all three nitro-aldehydes yield over 60% of dihydropyridine derivative, the order agreeing with the above theoretical order. With both *o*- and *p*-nitrobenzaldehydes, about 1% of a "second compound" was isolated and under suitably modified conditions all three nitro-aldehydes can be made to yield the corresponding "second compound," the nature of which is under investigation.

In these Hantzsch condensations, it has been found that the yields of dihydropyridine derivative vary considerably with the experimental conditions and that in order to obtain reproducible quantitative results it is necessary to adhere strictly to uniform conditions. The conditions finally adopted as standard are described in the experimental portion and, for comparison, the condensations previously studied in Part I have been repeated under these conditions. The results obtained with the five substituents are embodied in the following table.

TABLE I.

Percentage yields of dihydropyridine derivative.

Substituent.	*o.*	*m.*	*p.*
Nitro	62	88	64
Chloro	62	76	73
Hydroxy	—	67	68
Methoxy	57	75	64
Methyl	9	57	37
Unsubstituted		74	

From a consideration of these results several general conclusions can be drawn, apart from the agreement, already noted, between the experimental results and the anticipated orders of yields with the methyl and nitro-aldehydes.

With each substituent, the yield is lowest for the *o*-compound and, while the anomalous effect of the *o*-hydroxyl group may be attributed to chelation (compare Sidgwick and Callow, J., 1924, **125**, 527) and the difference between the *o*- and *p*-nitro-compounds is small, there is definite evidence of the operation of a *steric* or *ortho*-effect. This observation is not incompatible with that made by Lapworth and Manske (*loc. cit.*), that an *o*-substituent increases the stability of the benzaldehydecyanohydrin, as similar phenomena have been observed with benzoic acid derivatives, an *o*-substituent retarding both the esterification of benzoic acid and the hydrolysis of the pre-formed benzoic ester (compare, *inter alia*, Meyer, *Ber.*, 1895, **28**, 1255; Kellas, *Z. physikal. Chem.*, 1897, **24**, 221).

The sequence of yields obtained with the *m*-compounds : NO_2, Cl, OMe, (H), OH, Me, corresponds, with the exception of hydroxyl, to the inductive polar sequence of the groups and is also in substantial agreement with the sequence obtained by Tasman (*Rec. trav. chim.*, 1927, **46**, 653, 922) for 5-substituted phthalides in his experiments on the velocity of opening of the phthalide ring. The initial stage in the latter reaction must be regarded (Ingold, *Ann. Reports*, 1927, **24**, 157) as consisting in the addition of hydroxide ions at the carbonyl carbon atom. The position of hydroxyl in our sequence of yields may be attributable to ionisation (compare Ingold, *ibid.*, 1928, **25**, 148, footnote), but, on the other hand, a similar displacement does not occur with the *p*-compounds, the three substituents of similar electronic type, Cl, OH, OMe, being placed in their normal polar sequence.

Except for the hydroxyl group, with which the *m*- and *p*- yields are almost identical, the yield is highest with the *m*-compound and this must correspond to the possible operation of the *tautomeric* effect of the substituent from the *o*- and *p*-positions, giving secondary effects, but not from the *m*-position.

In addition to the above monosubstituted aldehydes, six aldehydes containing more than one methyl or nitro-group have been examined, the results being collected in Table II.

TABLE II.

Benzaldehyde.	% Pyridine derivative.
3 : 4-Dimethyl-	35
2 : 4-Dimethyl-	33
2 : 5-Dimethyl-	44
2 : 4 : 6-Trimethyl-	0
3 : 5-Dinitro-4-methyl-	68
3 : 5-Dinitro-2 : 4 : 6-trimethyl-	<1

The three dimethyl compounds give yields lying between the extreme values for the tolualdehydes and although two contain an ortho-substituent, the yields are appreciably greater than that with *o*-tolualdehyde, indicating that the retarding influences due to each methyl group do not act independently, but that some neutralisation must occur. It would be expected that this interference would be at a maximum when the methyl groups are para to one another, and this is shown by the 2 : 5-compound giving the highest yield. The lowest yield is given by the 2 : 4-compound, with methyl groups *o*- and *p*- to the aldehyde group. With the introduction of a further *o*-group, as in 2 : 4 : 6-trimethylbenzaldehyde, the condensation fails.

Since the nitro-group acts oppositely to the methyl group in its effect on the carbonyl group, and the introduction of a *m*-nitro-group into benzaldehyde causes the largest increase in yield, the introduction of *m*-nitro-groups into *p*-tolualdehyde should cause a marked increase in yield. With 3 : 5-dinitro-4-methylbenzaldehyde the yield is nearly doubled and the increase in yield is approximately double the increase caused by one *m*-nitro-group in benzaldehyde. The total inhibition of the condensation with 2 : 4 : 6-trimethylbenzaldehyde is emphasised by the almost complete inaction found with its dinitro-derivative, the presence of the two *m*-nitro-groups failing to cause any real condensation.

EXPERIMENTAL.

Standard Method of Condensation.—The requisite aldehyde (0·05 g.-mol.) was mixed with ethyl acetoacetate (13·5 g.; in slight excess of 0·1 g.-mol.), and ammonia (0·85 g.; 0·05 g.-mol.) in alcohol (26 c.c.) added. The mixture was kept overnight in a screw-stoppered pressure bottle of 300 c.c. capacity and then heated for 7 hours in a steam-bath. When cold, the contents of the bottle, which in some cases partly separated as a solid, were transferred to a glass basin and stirred until crystallisation started. (In those cases where the yield of dihydropyridine compound was small and separation of the solid did not occur on stirring, the liquid was evaporated to a small bulk and small quantities of methyl alcohol were added from time to time, with stirring, until separation began.) The crystals deposited were drained by suction and washed free from sticky material with small quantities of methyl alcohol; the washings were added to the filtrate and allowed to evaporate in the air, with occasional stirring, any solid which separated being treated as before. The process of evaporation after addition of methyl alcohol to the filtrate was continued until no more solid was obtainable. The melting point of each solid portion was determined in order to ascertain that the last portions did not consist of any secondary product, and only with *o*- and *p*-nitrobenzaldehydes was there any indication of such a product.

In all cases the condensations were carried out in duplicate, the mean of the two yields being the value given in the tables. In the condensations where low yields were obtained, good agreement between the duplicate experiments was not always obtained, owing to the difficulty of isolating the product free from sticky material without loss. This difficulty was most marked with the dimethylbenzaldehydes and to a lesser extent with the tolualdehydes, all of which, except *m*-tolualdehyde, give less than a 50% yield.

Condensations with o-, m-, *and* p-*Tolualdehydes.—Ethyl* 4-o-*tolyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in small colourless plates, m. p. 114° (Found : C, 69·5; H, 7·3. $C_{20}H_{25}O_4N$ requires C, 70·0; H, 7·3%). Yields : 1·6 and 1·35 g., 9·3 and 7·9%.

Ethyl 4-m-*tolyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in colourless needles, m. p. 138° (Found : C, 70·2 ; H, 7·3%). Yields : 9·4 and 10·0 g., 54·8 and 58·3%.

Ethyl 4-p-*tolyl*-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in colourless sword-shaped needles, m. p. 140° (Found : C, 70·0; H, 7·4%). Yields : 6·1 and 6·5 g., 35·6 and 37·9%.

Condensations with o-, m-, *and* p-*Nitrobenzaldehydes.*—Ethyl 4-*o*-nitrophenyl-2 : 6-dimethyl-1 : 4-dihydropyridine-3 : 5-dicarboxylate crystallised from alcohol in yellow plates, m. p. 125° (Lepetit, *loc. cit.*, records m. p. 119—120°), which were phototropic, rapidly turning brown in sunlight (Found : C, 60·7; H, 5·8. Calc. : C, 61·0; H, 5·9%). Yields : 11·5 and 11·6 g., 61·5 and 62·0%. Evaporation of the final residue to a very small bulk yielded 0·3 g. of a more soluble compound, m. p. 171°. This compound is being investigated.

Ethyl 4-o-*Nitrophenyl*-2 : 6-*dimethylpyridine*-3 : 5-*dicarboxylate.*—The above dihydro-ester (1 g.) was heated under reflux with *N*-nitric acid (50 c.c.) until solution was effected. The cooled and filtered solution was neutralised with sodium carbonate; the light brown solid which separated crystallised from alcohol in colourless needles, m. p. 75° (Found : C, 61·3; H, 5·6. $C_{19}H_{20}O_6N_2$ requires C, 61·3; H, 5·4%).

Ethyl 4-*m*-nitrophenyl-2 : 6-dimethyl-1 : 4-dihydropyridine-3 : 5-dicarboxylate was almost entirely deposited immediately on stirring and crystallised from alcohol in thick, pale yellow prisms, m. p. 164° (Lepetit records m. p. 161°) (Found : C, 60·6; H, 6·2; N, 7·2. Calc. : N, 7·5%). Yields : 16·6 and 16·2 g., 88·8 and 86·6%.

Ethyl 4-*p*-nitrophenyl-2 : 6-dimethyl-1 : 4-dihydropyridine-3 : 5-dicarboxylate crystallised from aqueous alcohol in light yellow plates, m. p. 136° (Lepetit records m. p. 118—122°) (Found : C, 60·5; H, 5·9%. Lepetit gives only N, 7·9%). Yields : 12·0 and 11·8 g., 64·2 and 63·1%. As in the case of *o*-nitrobenzaldehyde, about 0·3 g. of a more soluble compound, m. p. 140°, was isolated from the concentrated residue.

Condensations with Chloro-, Methoxy-, and Hydroxy-benzaldehydes.—The corresponding dihydropyridine esters having already been described in Part I (*loc. cit.*), only the yields under the present standard conditions are therefore given :

o-Chloro-, 11·1 and 11·3 g., 61·1 and 62·2%.
m-Chloro-, 13·8 and 13·7 g., 75·9 and 75·4%.
p-Chloro-, 13·2 and 13·2 g., 72·6%.
o-Methoxy-, 10·4 and 10·2 g., 57·9 and 56·8%.
m-Methoxy-, 13·5 and 13·5 g., 75·2%.
p-Methoxy-, 11·3 and 11·6 g., 63·0 and 64·6%.
m-Hydroxy-, 11·5 and 11·5 g., 66·7%.
p-Hydroxy-, 11·6 and 11·7 g., 67·3 and 67·8%.

The *o*-hydroxy-aldehyde gradually yields only small quantities of a mixture of compounds, in which it has not yet been possible to identify the Hantzsch derivative and which is being further investigated.

Condensation with Benzaldehyde.—Yields : 12·1 and 12·3 g., 73·6 and 74·8%.

Condensations with Dimethylbenzaldehydes.—*Ethyl* 4-(3′ : 4′-*dimethylphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in light yellow needles, m. p. 114° (Found : C, 70·3; H, 7·7. $C_{21}H_{27}O_4N$ requires C, 70·6; H, 7·6%). Yields : 6·2 and 6·15 g., 34·7 and 34·5%.

Ethyl 4-(2′ : 4′-*dimethylphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in small colourless prisms, m. p. 157° (Found : C, 70·4; H, 7·8%). Yields : 6·4 and 5·4 g., 35·9 and 30·3%.

Ethyl 4-(2′ : 5′-*dimethylphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in small colourless needles, m. p. 140° (Found : C, 70·0; H, 7·7%). Yields : 7·4 and 8·15 g., 41·5 and 45·7%.

Condensation with Dinitro-p-*tolualdehyde.*—*Ethyl* 4-(3′ : 5′-*dinitro*-4′-*methylphenyl*)-2 : 6-*dimethyl*-1 : 4-*dihydropyridine*-3 : 5-*dicarboxylate* crystallised from aqueous alcohol in yellow needles, m. p. 166° (Found : C, 54·9; H, 5·2. $C_{20}H_{23}O_8N_3$ requires C, 55·4; H, 5·3%). Yields : 14·4 and 15·0 g., 66·5 and 69·3%.

Condensations with 2 : 4 : 6-*Trimethyl- and* 3 : 5-*Dinitro*-2 : 4 : 6-*Trimethyl-benzaldehydes.*—Even after prolonged treatment no separation of solid occurred in the case of the trimethyl-aldehyde. With the dinitro-trimethylaldehyde (Hinkel, Ayling, and Morgan, this vol., p. 1170), a solid, m. p. 273°, separated after some days, the yield (0·17 g.; $<1\%$) being too small to allow of further purification and examination.

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