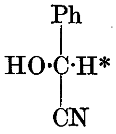
IV.—*The Influence of Substituents on the Benzoin Reaction.*

By Herbert Henry Hodgson and Wolf Rosenberg.

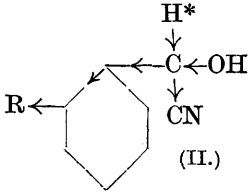
The present investigation in conjunction with the results of Ekecrantz and Ahlqvist (*Arkiv Kemi Min. Geol.*, 1908, **3**, No. 13) shows that substituents inhibit the benzoin reaction in varying degrees according to their electronic character. On Lapworth's theory (J., 1903, **84**, 1004) that the possibility of the benzoin condensation depends on the mobility of the hydrogen atom * in the initially formed mandelonitrile (I), (a) *a meta-directing group* (R) will activate this hydrogen * (II) but deactivate the carbonyl group of the second molecule of the reacting benzaldehyde (III), and (b) *when* R *is* op-*directing*, H* (IV) is deactivated but CO (V) is activated. In case (a) the benzoin condensation of (II) and (III) would appear to depend on the relative activation and deactivation : *e.g.*, when R is NO_2 (strong), it over-activates H* but renders the CO (III) much less capable of forming the initial cyanohydrin, hence excessive production of nitrobenzoic acid occurs (compare Lapworth and Manske, J., 1928, 2533); when R is Cl (weak), only 5% of *o*-chlorobenzoic acid can be isolated, and benzoin formation ensues. In case (b), although cyanohydrin formation may readily occur, the subsequent benzoin condensation of (IV) and (V) may be inhibited because of the deactivated hydrogen * : *e.g.*, (1) attempts to produce a benzoin from any monohydroxybenzaldehyde have all failed owing to the presence of anionoid oxygen ($R = \overset{\ominus}{O}$), and (2) although the alkyloxybenzaldehydes all give benzoins, the introduction of a second group as in *p*-benzyloxy-*m*-methoxybenzaldehyde brings about the necessary deactivation and no benzoin is formed.

On the above theory, 2-chloro-3-methoxybenzaldehyde produces a benzoin more readily than does 3-methoxybenzaldehyde owing to a reduction by chlorine of the hydrogen deactivation produced by the methoxyl group (VI). 3-Chloro-2-hydroxybenzaldehyde (80%) and 3-chloro-4-hydroxybenzaldehyde (25%), however, appear to react only as far as the cyanohydrin stage, and Ekecrantz and Ahlqvist (*loc. cit.*) found that *p*-hydroxybenzaldehyde and vanillin were unreactive towards alcoholic potassium cyanide, the complete internal satisfaction of the electronic demands of the carbonyl group thus being exhibited.

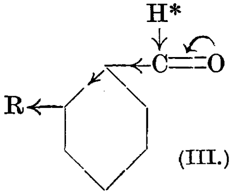


$$\mathrm{HO{\cdot}\overset{Ph}{\underset{CN}{C}}{\cdot}H^*}$$

(I.)



(II.)



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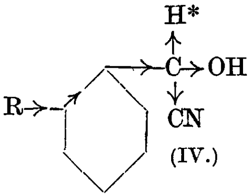
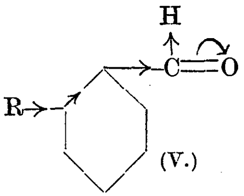
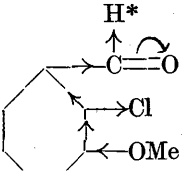


(IV.)

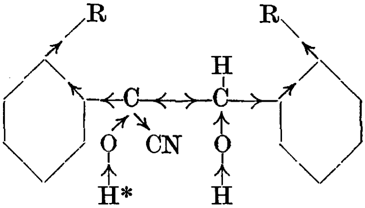


(V.)

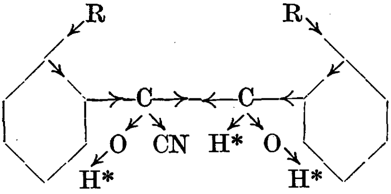


(VI.)

The possibility of the benzoin reaction taking place might also be considered from the standpoint of the influence of groups on the stabilities of the respective hypothetical intermediate benzoin cyanohydrins (VII and VIII) (Lapworth, *loc. cit.*) :

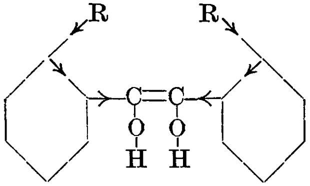


(VII.)

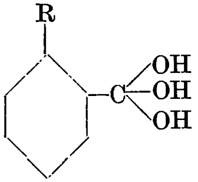


(VIII.)

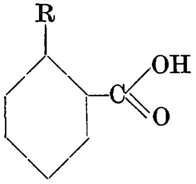
(a) *When* R *is meta-directing* (VII), the H* tends to be ionised, formation of hydrogen cyanide thereby being promoted, so that, when R is sufficiently strong (*e.g.*, NO_2), the initial formation of mandelonitrile is prevented and no benzoin reaction can occur. (b) *When* R *is* op-*directing* (VIII), the hydrogens * are deactivated and CN is activated. Subsequent reaction can and, so far as the end-products are evidence, does occur in two ways : (1) the formation of a benzoin, and (2) the intermediate formation of the isomeride (IX) of this benzoin, which is hydrolysed, giving a benzyl alcohol and an unstable phenylorthoformic acid (X), the latter changing to a stable benzoic acid (XI) ; *e.g.*, from *o*- and *p*-anisaldehydes, considerable quantities of *o*- and *p*-anisic acids are produced together with the *o*- and *p*-anisoins.



(IX.)



(X.)



(XI.)

EXPERIMENTAL.

2 : 2′-*Dichlorobenzoin*.—Solutions of *o*-chlorobenzaldehyde (5 g.) in alcohol (10 c.c.) and of potassium cyanide (1 g.) in water (4 c.c.) were heated together under reflux on the water-bath for 1 hour and poured into aqueous sodium bicarbonate, which dissolved the *o*-chlorobenzoic acid formed (5%); after 1 hour, the whole was extracted with ether, and the extract shaken with aqueous sodium bisulphite to remove unchanged *o*-chlorobenzaldehyde. (Benzoins and benzils do not easily form hydrazones or sodium bisulphite addition compounds, a fact which has been utilised for the removal of unchanged initial material in the various reactions studied.) The 2 : 2′-*dichlorobenzoin* (40% yield) was obtained by removal of the ether and extraction of the residue with acetic acid or alcohol, from which it separated in white prisms, m. p. 56—57° (Found : Cl, 25·0. $C_{14}H_{10}O_2Cl_2$ requires Cl, 25·2%). The final resinous residue (40%) contained nitrogen, presumably as cyanohydrin, but no alcohol corresponding to *o*-chlorobenzoic acid was isolated (compare Ekecrantz and Ahlqvist, *loc. cit.*). The acid may have been formed partly by air oxidation, since the amount increased when the reaction mixture was kept for several days.

An alcoholic solution of 2 : 2′-dichlorobenzoin when treated with aqueous-alcoholic sodium hydroxide gives a brownish-red colour, deeper than that given by unsubstituted benzoin, which deepens on boiling but disappears on shaking (compare Hantzsch and Glover, *Ber.*, 1907, **40**, 1520), returns on keeping but disappears again on shaking, and so on.

2 : 2′-*Dichlorobenzil* was prepared by the usual nitric acid method, but better results were obtained when 2 : 2′-dichlorobenzoin (1 g.), dissolved in glacial acetic acid (10 c.c.), was heated with a slight excess of chromium trioxide on the water-bath for 1 hour. After dilution with water and extraction with ether, the benzil crystallised from benzene in pale yellowish-green prisms, m. p. 128° (Found :

Cl, 25·2. $C_{14}H_8O_2Cl_2$ requires Cl, 25·4%), which were sparingly soluble in boiling alcohol, ether, and glacial acetic acid.

3 : 3′-*Dimethoxybenzoin* (m-*Anisoin*).—Powdered potassium cyanide (1 g.) was added to a boiling solution of *m*-methoxybenzaldehyde (10 g.) in 50% aqueous alcohol (30 g.). After boiling for 2 hours, the mixture was kept over-night in a freezing mixture, and the oily yellowish-brown solid obtained was removed, freed from oil, and washed with ether; the residue crystallised from alcohol in micro-prisms (2 g.), m. p. 41—42° (Found: C, 70·8; H, 5·7. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

2 : 2′-*Dichloro*-3 : 3′-*dimethoxybenzoin*, readily obtained by the ordinary method, crystallised from alcohol in prisms, m. p. 133—134° (Found: Cl, 20·6. $C_{16}H_{14}O_4Cl_2$ requires Cl, 20·8%). The p-*nitrophenylhydrazone* crystallised from glacial acetic acid in yellow needles, m. p. 129° (Found: N, 9·0; Cl, 14·8. $C_{22}H_{19}O_5N_3Cl_2$ requires N, 8·8; Cl, 14·9%), which gave a reddish-violet colour with aqueous-alcoholic sodium hydroxide.

2 : 2′-*Dichloro*-3 : 3′-*dimethoxybenzil*, prepared in the same way as 2 : 2′-dichlorobenzil, crystallised from benzene in very pale greenish-yellow prisms, m. p. 200° (Found: Cl, 20·8. $C_{16}H_{12}O_4Cl_2$ requires Cl, 20·9%).

2 : 2′-*Dichloro*-3 : 3′-*dimethoxybenzilic acid*, formed by boiling 2 : 2′-dichloro-3 : 3′-dimethoxybenzil (5·5 g.), dissolved in alcohol (11 g.), with a mixture of potassium hydroxide (5·5 g.) and water (11 g.) for 10 minutes, crystallised from water in colourless needles, decomp. 182—185° (Found: Cl, 20·0. $C_{16}H_{14}O_5Cl_2$ requires Cl, 19·9%).

2-*Chloro*-3-*methoxybenzoic acid* was prepared by gradually adding a saturated aqueous solution of potassium permanganate to a boiling aqueous suspension of 2-chloro-3-methoxybenzaldehyde until it was no longer decolorised and the aldehydic odour had disappeared. The excess of permanganate was destroyed by sulphur dioxide; the solution on cooling deposited colourless needles, m. p. 161·5° after recrystallisation from water (Found: Cl, 19·1. $C_8H_7O_3Cl$ requires Cl, 19·0%).

Approximate Determination of the Reactivities of Various Aldehydes from the Quantities of Resinous Products formed.—These experiments were undertaken to investigate the combined influence of two groups of opposed electronic effects. In each case the benzoin reaction mixture was poured into water and acidified with acetic acid, the precipitate dissolved in ether, and the solution washed with aqueous sodium bisulphite to remove unchanged initial material, and dried; the ether was then removed, and the residue weighed.

Benzaldehyde.	Unchanged material (g.).	Reaction product (g.).
3-Hydroxy-	4·0	9·5
3-Chloro-2-hydroxy-	0·4	2·9
3-Chloro-4-hydroxy-	4·5	1·5

From the resinous products, and from the corresponding synthetic cyanohydrins, nothing could be obtained crystalline.

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