

CIV.—*The Mechanism of Reactions induced by Hydrogen Chloride between Aromatic Aldehydes and Aldehydecyanohydrins in Solution.*

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THE object of this research was to elucidate the mechanism of the formation of oxazoles and other substances by the action of hydrogen

chloride upon ethereal solutions of aromatic aldehydes and aldehydecyanohydrins. Fischer (*Ber.*, 1896, **29**, 205) first employed this method to prepare 2 : 5-diphenyloxazole, the constitution of which he established by an alternative synthesis and by degradation, but he made no suggestion as to the mode of formation of the final products.

The action of hydrogen chloride upon ethereal solutions (both dry and moist) of aldehydecyanohydrins, alone and also in the presence of aldehydes, has now been investigated, and, besides oxazoles, mandelamide derivatives and 3-keto-2 : 5-diaryl-3 : 4-dihydro-1 : 4-diazines have been obtained. The example studied in greatest detail was that of benzaldehyde and benzaldehydecyanohydrin (mandelonitrile), and the most salient observations made in connexion with this aldehyde and its derivatives may be summarised as follows :

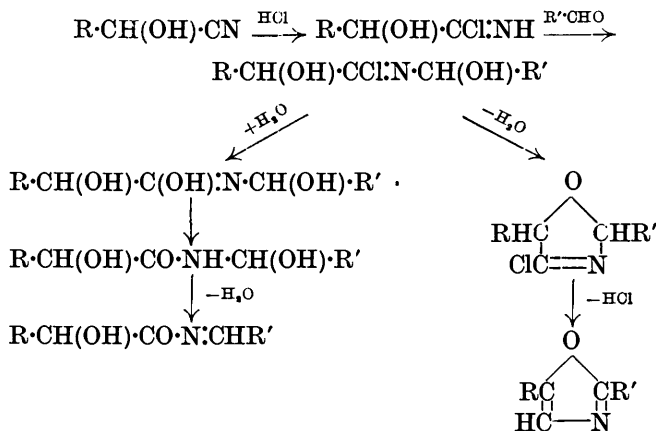
(1) Exclusion of moisture favoured oxazole formation and inhibited the production of mandeloarylideneamides, and *vice versa*.

(2) The "blocking" of the hydroxyl group of the cyanohydrin (*e.g.*, by benzylation or by substitution of chlorine) precluded oxazole formation.

(3) Imino-chlorides were produced as intermediates.

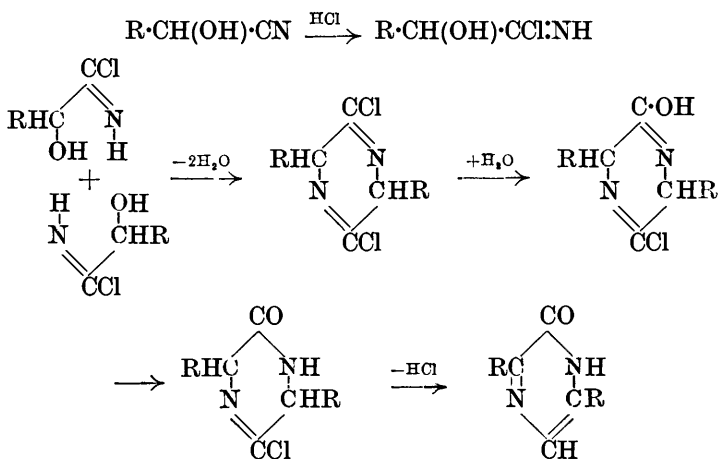
(4) The proportion of diazine derivative produced was greater in the absence than in the presence of free aldehyde.

The observations support the following mechanism for the production of oxazoles and mandeloarylideneamides from aldehydes and aldehydecyanohydrins :

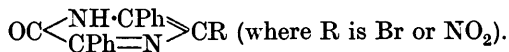


The diazine obtainable from benzaldehydecyanohydrin was first prepared from that substance by Minovici (*Ber.*, 1899, **32**,

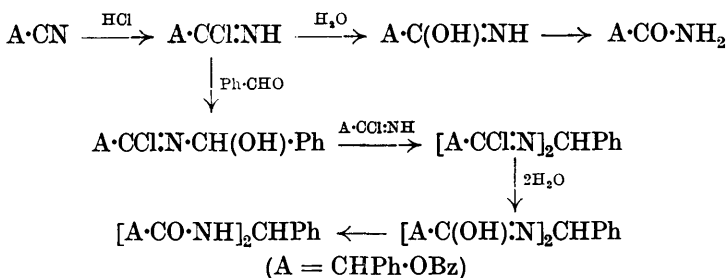
2206), who, however, assigned to it an extremely improbable structure. Later, Japp and Knox (J., 1905, 87, 701) determined its constitution, but not its mode of formation. In this connexion, the generalisations (3) and (4) given above, and the statement of Japp and Knox (*loc. cit.*) that “. . . attempts to obtain the condensation product by acting on mandelonitrile with other dehydrating agents did not give the desired result . . .” are highly significant; they seem, however, to have been overlooked by previous workers. These observations support the following mechanism for the production of 3-keto-2:5-diaryl-3:4-dihydro-1:4-diazines from aromatic aldehydecyanohydrins :



Minovici also prepared a monobromo- and a mononitro-derivative of the diazine obtainable from benzaldehydecyanohydrin, and their formation is quite consistent with the structure assigned by Japp and Knox to this diazine if they are formulated thus :



The condensation of benzoylmandelonitrile with benzaldehyde in ethereal solution in presence of hydrogen chloride gave no oxazole, but two isomeric forms of benzylidenebisbenzoylmandelamide. In the absence of benzaldehyde and moisture, the iminochloride of benzoylmandelonitrile was obtained, whilst if a trace of moisture was present benzoylmandelamide was produced. For similar reasons to those given for the production of oxazoles, the mechanism of the reactions would appear to be as follows :



EXPERIMENTAL.

General.—Hydrogen cyanide was prepared by Wade and Panting's method (J., 1898, 73, 255), and redistilled over phosphorus pentoxide (except in experiments 1 and 2 of the benzaldehydecyanohydrin series). It was condensed with the aldehyde by being kept for at least 20 hours with this in ethereal (or ether-benzene) solution in the presence (except in the experiments 1 and 2 mentioned above) of tripropylamine as a basic catalyst (Ultée, *Rec. trav. chim.*, 1909, 28, 718). The solvents required were dried with sodium and redistilled over phosphorus pentoxide, and the hydrogen chloride was dried with sulphuric acid and calcium chloride. The liquid aldehydes were redistilled several times in a vacuum, and the solid aldehydes (B.D.H.) were dried in a vacuum over concentrated sulphuric acid.

Condensation of Benzaldehydecyanohydrin and Benzaldehyde (compare Fischer, *loc. cit.*).—In each experiment benzaldehydecyanohydrin (12.5 g.; 1 mol.) and benzaldehyde (10 g.; 1 mol.) in 60 c.c. of dry ether were employed. After cyanohydrin formation had taken place (as described above), the solution, protected from moisture, was saturated at 0° with hydrogen chloride. The oxazole and mandelamide thus produced were separated by fractional crystallisation from alcohol and ligroin.

An ethereal solution of α -chlorophenylacetoneitrile (see below) was saturated with hydrogen chloride, 1 mol. of benzaldehyde then added, and the passage of hydrogen chloride continued. An unidentified substance was obtained, but no 2:5-diphenyloxazole or mandelobenzylideneamide was detected in the product.

α -Chlorophenylacetoneitrile was prepared by the action of thionyl chloride upon benzaldehydecyanohydrin in ethereal solution and obtained as a greenish-yellow, pungent liquid, b. p. 170°/ about 120 mm. It has an irritant action on the skin, and its vapour is a strong lachrymatory (compare Michaël and Jeanprêtre, *Ber.*, 1892, 25, 1679).

Expt.	Special conditions of experiment.	Yields.			
		2 : 5-Diphenyl-oxazole hydrochloride.		Mandelo-benzylidene-amide.	
		Grams.	%.	Grams.	%.
1	As in (3), but without a solvent, with a drop of aqueous KOH as catalyst, and without exclusion of moisture.....	nil		nearly theoretical	
2	As in (3), but with 200 c.c. of solvent, and with catalyst as in (1)	trace		nearly theoretical.	
3	As outlined in the general description ...	14	58	7	31
4	As in (3); the cyanohydrin, however, was frozen in solid CO ₂ , and the highest-melting fraction (m. p. about 15°) employed *	10.5	43	8	36
5	As in (3), with addition of 7 g. of anhydrous zinc chloride	nil	—	15	67
6	As in (3), with addition of 15 g. of thionyl chloride immediately before passage of hydrogen chloride	9	37	nil ‡	—
7	As in (6), but with more rapid passage of hydrogen chloride.†	14	58	nil ‡	—

* Ultée (*loc. cit.*) gives the m. p. of pure benzaldehydecyanohydrin as 21.5—22°.

The relatively larger proportion of mandelobenzylideneamide obtained in this than in the previous experiment is explained by the assumption that the cyanohydrin absorbed a little atmospheric moisture during the process of freezing.

† The larger yield of oxazole hydrochloride in this case than in the previous one is in accordance with theoretical considerations—the condensation taking place more rapidly, the thionyl chloride would have less time in which to “block” the hydroxyl group of the cyanohydrin and thus prevent oxazole formation.

‡ A considerable quantity of *o*-chlorophenylacetonitrile was formed in each case.

Condensation of Benzoylmandelonitrile and Benzaldehyde.—By the action of hydrogen chloride upon an ethereal solution of benzoylmandelonitrile (Francis and Davis, J., 1909, **95**, 1403) and benzaldehyde in molecular proportion, a white solid was produced, which was separated into two portions by extraction with alcohol for several hours. The residue, which was insoluble in acetone, acetic acid, and benzene, melted at 250—251° (Found: C, 74.0; H, 5.3; N, 5.1. C₃₇H₃₀O₆N₂ requires C, 74.2; H, 5.0; N, 4.7%); the sparingly soluble portion was an isomeride and crystallised from alcohol in microscopic needles, m. p. 223—224° (Found: C, 74.2; H, 5.5; N, 5.1%). 2 : 5-Diphenyloxazole could not be detected in the original alcoholic mother-liquor, even after concentration, by means of picric acid.

The two isomerides were readily debenzoylated by alcoholic

potash, giving a substance which crystallised from alcohol in colourless, microscopic needles, m. p. 216—217° (Found: C, 70·4; H, 6·0; N, 7·7. $C_{23}H_{22}O_4N_2$ requires C, 70·8; H, 5·6; N, 7·2%). The isomerides were not affected by boiling dilute sulphuric acid, but when a solution of either in concentrated sulphuric acid was kept for $\frac{1}{2}$ hour and poured into water, benzoic and mandelic acid, benzaldehyde and ammonia were formed. This reaction, in conjunction with the action of alcoholic potash upon the isomerides of m. p.'s 250—251° and 223—224°, shows that these substances are isomeric forms of *benzylidenebisbenzoylmandelamide*,
 $(OBz \cdot CHPh \cdot CO \cdot NH)_2CHPh$.

This structure was confirmed by the isolation of a small quantity of the higher-melting isomeride (identity determined by the mixed melting-point method) from the product of the fusion of benzoylmandelamide (excess) and benzaldehyde at 140—160° for 2 hours.

The production of similar substances has been recorded—ethylidenedibenzamide (Hepp and Spiess, *Ber.*, 1876, 9, 1425); benzylidenebisacetylmandelamide (Japp and Knox, *loc. cit.*).

Action of Hydrogen Chloride upon Benzoylmandelonitrile.—Hydrogen chloride, dried by sulphuric acid, was passed for about 20 hours through a dry, cooled, ethereal solution of benzoylmandelonitrile, protected from atmospheric moisture. On removal of the ether, a clear, viscous, amber-coloured oil remained which would not solidify, and gave benzoylmandelamide when boiled with 10% aqueous alcohol for 2 hours.

When moisture was not excluded during the reaction, much benzoylmandelamide was produced. After several crystallisations from alcohol, it was obtained as a colourless, microcrystalline mass, m. p. 160—161° (Found: C, 70·4; H, 5·8. Calc. for $C_{15}H_{13}O_3N$: C, 70·6; H, 5·1%) (compare Orton, J., 1901, 79, 1354).

Condensation of Acetaldehydecyanohydrin and Benzaldehyde.—When these substances were condensed by hydrogen chloride in ethereal solution, lactobenzylideneamide, m. p. 132° (Found: C, 67·5; H, 6·5. Calc. for $C_{10}H_{11}O_2N$: C, 67·8; H, 6·2%), was formed, but no 2-phenyl-5-methyloxazole could be detected (compare Fischer, *loc. cit.*).

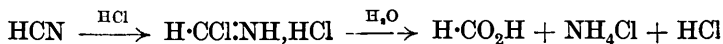
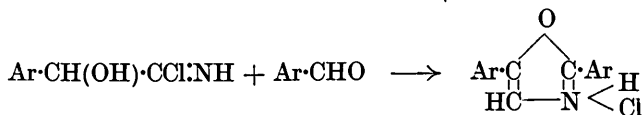
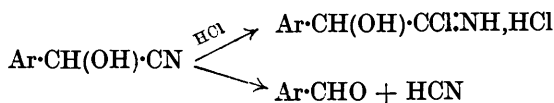
Condensation of Anisaldehydecyanohydrin and Anisaldehyde.—Minovici studied the action of hydrogen chloride upon anisaldehydecyanohydrin in ethereal solution alone (*Ber.*, 1899, 32, 2206) and in the presence of anisaldehyde (*Ber.*, 1896, 29, 2097) and obtained in each case a white, crystalline substance, $C_{17}H_{15}O_3N$, m. p. 145°. In the latter case he described it as 2:5-dianisylloxazole, but in the former he assigned to it the constitution $OMe \cdot C_6H_4 \cdot CH(CN) \cdot CO \cdot C_6H_4 \cdot OMe$

without giving any evidence for his conclusion. When his experiments were repeated, 2 : 5-dianisylloxazole, m. p. 143—144°, was isolated in each case (Found : C, 72.8; H, 5.6. Calc. : C, 72.6; H, 5.3%). The picrate was obtained in yellow needles, m. p. 214—216°, after one crystallisation from acetone.

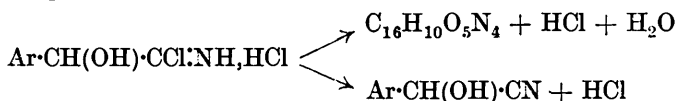
Condensation of m-Nitrobenzaldehydecyanohydrin and m-Nitrobenzaldehyde.—This condensation was performed similarly to the preceding ones; it was necessary, however, to add some benzene to the ether to bring the aldehyde into solution. (Such addition was necessary in the succeeding condensations also.) The yellow reaction product was extracted for several hours with alcohol. The sparingly soluble substance (*A*) that separated from the extract was obtained as a canary-yellow, microcrystalline mass, m. p. 277—278°, after recrystallisation from glacial acetic acid (Found : C, 56.8; H, 3.5, 3.6%). The residue from the extraction was separated by fractional crystallisation from acetic acid into a less soluble substance, m. p. 238° (Found : C, 57.9; H, 2.9. $C_{15}H_9O_5N_3$ requires C, 57.9; H, 2.9%), and a more soluble one, m. p. 225—227° (Found : C, 57.8; H, 3.2%). Since the latter remained unchanged in melting point after recrystallisation from acetic acid and from nitrobenzene, these two substances are regarded as isomeric forms of 2 : 5-di-*m*-nitrophenyloxazole.

Condensation of m-Nitrobenzaldehydecyanohydrin and Benzaldehyde.—The crude product contained a substance which, after four crystallisations from alcohol, was obtained in cream-coloured needles, m. p. 156—157°, and is probably 2-phenyl-5-*m*-nitrophenyloxazole (Found : C, 67.2; H, 3.9. $C_{15}H_{10}O_3N_2$ requires C, 67.7; H, 3.7%). A considerable quantity of the substance (*A*), m. p. 277—278° (see preceding experiment), was isolated from the crude product. That it is produced from the *m*-nitrobenzaldehydecyanohydrin only was proved by the following experiment.

Action of Hydrogen Chloride upon m-Nitrobenzaldehydecyanohydrin.—The action of hydrogen chloride upon an ether-benzene solution of this cyanohydrin produced a pale yellow substance which, when dried over paraffin wax and solid sodium hydroxide, contained ionic chlorine and melted at 95—99° (decomp.). When a methyl- or ethyl-alcoholic solution of it was kept or boiled, a precipitate formed rapidly. This precipitate, on purification, yielded a substance, m. p. 277—278°, identical with the substance (*A*), and much ammonium chloride and 2 : 5-di-*m*-nitrophenyloxazole were found in the mother-liquor. It seems probable, therefore, that the following reactions took place during the passage of hydrogen chloride into the cyanohydrin solution ($Ar = NO_2 \cdot C_6H_4$),



and that on boiling the crude product with alcohol (or water) the following reactions occurred :



The similarity in the methods of preparation and in properties of the substance (*A*) and the compound obtained by Japp and Knox and by Minovici from benzaldehydecyanohydrin, makes it highly probable that they have similar structures. The substance (*A*) (Found : C, 56.8; H, 3.5. $\text{C}_{16}\text{H}_{10}\text{O}_5\text{N}_4$ requires C, 56.8; H, 3.0%) is therefore considered to be *3-keto-2:5-di-m-nitrophenyl-3:4-dihydro-1:4-diazine*. Its colour is slowly changed from canary-yellow to moderately deep brown by light. When the diazine was treated with chromic and acetic acids, 80% of it was recovered unchanged and no trace of the remainder could be found.

Condensation of p-Nitrobenzaldehydecyanohydrin and p-Nitrobenzaldehyde.—This condensation was performed similarly to that of the *m*-isomeride, and *3-keto-2:5-di-p-nitrophenyl-3:4-dihydro-1:4-diazine* was obtained as a canary-yellow, microcrystalline mass, m. p. 332—334° (Found : C, 56.9; H, 3.3. $\text{C}_{16}\text{H}_{10}\text{O}_5\text{N}_4$ requires C, 56.8; H, 3.0%), by extraction of the crude product twice with alcohol and crystallisation of the residue twice from acetic acid and once from nitrobenzene.

All the various residues were mixed together and, after removal of the solvents, the product was extracted several times with alcohol and finally crystallised from alcohol and from acetone, golden-yellow, microscopic needles of *2:5-di-p-nitrophenyloxazole*, m. p. 228—232°, being obtained (Found : C, 58.4; H, 3.3. $\text{C}_{15}\text{H}_9\text{O}_5\text{N}_3$ requires C, 57.9; H, 2.9%).

Attempted Hydrolysis of "Minovici's Compound."—The compound was heated with concentrated hydrochloric acid (20 parts) in a sealed tube at 200° for 21 hours, and was converted thereby merely into its hydrochloride.

The author is indebted to Dr. H. Stephen for suggesting the subject of the research, and for valuable advice connected therewith, and also to the Chemical Society for a grant towards its cost.

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[*Received, January 20th, 1927.*]
