CLXXXVI.—*Some Reactions of Ortho-derivatives of Aldehydes and Ketones.*

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The description "ortho-derivatives" in the title is here intended to include all compounds in which the oxygen atom of the carbonyl group $>C=O$ of an aldehyde or ketone is replaced by two like or unlike unicovalent radicals such as OH, OAlk, $NAlk_2$, CN, and Cl which, with their bonding electrons, have appreciable anionic stability, as shown, for example, by the readiness with which sodium and potassium expel hydrogen from the hydrides, H·OH, H·OAlk, $H \cdot NAlk_2$, etc.

Such ortho-derivatives frequently display great facility in the anionic elimination or exchange of the radicals as above defined, and the generalisations now available as to the conditions which favour such changes in different cases furnish a basis for testing the plausibility of ideas on reaction mechanism which have been advanced at various times.

A. *Some Reactions in Alkaline Solution.*—The ready conversion of chloral by means of potassium cyanide into the potassium salt of dichloroacetic acid is but one example of a mode of reaction apparently common to α-chloro-aldehydes. The explanation which appears to receive most support from analogies is that associated with the names of Pinner (*Ber.*, 1877, **10**, 1065; 1884, **17**, 1999; 1885, **18**, 753, 2852) and more especially Kötz (*J. pr. Chem.*, 1913, **88**, 531). This explanation assumes that (in the particular case mentioned) the formation of chloral cyanohydrin is an essential stage in the reaction, but in a more generalised form may be expressed by the following series of equations representing successive changes :

$$(1)\ \mathrm{{>}CCl{\cdot}CH{:}O + KCN + H{\cdot}OX \longleftrightarrow \underset{(a)}{{>}CCl{\cdot}CH(OH){\cdot}CN} + K{\cdot}OX}$$

where H·OX = H·OH, H·OEt, etc.

$$(2)\ \mathrm{\underset{(a)}{{>}CCl{\cdot}CH(OH){\cdot}CN} \longrightarrow \underset{(b)}{{>}C{:}C(OH){\cdot}CN} + ClH}$$

$$(3)\ \mathrm{\underset{(b)}{{>}C{:}C(OH){\cdot}CN} \longrightarrow \underset{(c)}{{>}CH{\cdot}CO{\cdot}CN}}$$

$$(4)\ \mathrm{\underset{(c)}{{>}CH{\cdot}CO{\cdot}CN} + 2KOH \longrightarrow \underset{(d)}{{>}CH{\cdot}CO{\cdot}OK} + KCN}$$

or, when H·OX = H·OEt, for example,

$$(4')\ \mathrm{\underset{(c)}{{>}CH{\cdot}CO{\cdot}CN} + KOX \longrightarrow \underset{(d')}{{>}CH{\cdot}CO{\cdot}OX} + KCN}$$

In association with stage (2) there must be introduced :

$$(1')\ \mathrm{KCN + HCl \longrightarrow HCN + KCl}$$

As cyanohydrins are much more powerfully acidic than simple alcohols, bearing comparison in this respect with phenols (compare J., 1904, **85**, 1207 *et seq.*), stage (1) must be considered as always associated with the reversible reaction :

$$(1'')\ \mathrm{{>}CCl{\cdot}CH(OH){\cdot}CN + K{\cdot}OX \longleftrightarrow {>}CCl{\cdot}CH(OK){\cdot}CN + H{\cdot}OX}$$

Stage (2) is entirely consistent with the ready escape of halogen by hydride from the analogous β-halogenated ketones and β-carboxylic esters consequent on the lability conferred on the α-hydrogen atom by the carbonyl group. The present authors have prepared 2-chloro-1-cyano*cyclo*hexane and found that it breaks down with great readiness in the sense indicated (p. 1383). In absence of any further evidence than this, it would not be unreasonable to maintain that ·OH, attached to the same carbon atom as ·H and ·CN, might, in virtue of its powerful electron-releasing primary effect (compare Cocker, Lapworth, and Walton, J., 1930, 446, lines 13 to 20), suppress the usual influence of ·CN on the hydrogen atom in the system, $\mathrm{H}\cdot\overset{\cdot}{\underset{\cdot}{\mathrm{C}}}\cdot\mathrm{CN}$. This may hold true for the static or average molecule of an aldehyde cyanohydrin; but the study of the benzoin and related reactions (compare J., 1907, **91**, 697; Greene and Robinson, J., 1922, **121**, 2182) has made it evident that ·OH (and even $\cdot\mathrm{NH}\cdot\mathrm{C_6H_5}$) in this position does not prevent some of the molecules present at any moment from displaying the properties normally associated with the system in question, and, in particular, the characteristic lability of the α-hydrogen atom. (For cases of instability of analogous β-chloro-ketones, compare, for example, *Annalen*, 1895, **284**, 7; *Ber.*, 1895, **28**, 960; J., 1904, **85**, 1355.)

Stage (3), or ketonisation of an enol, offers no theoretical difficulties, while stage (4) represents a well-established reaction of acyl cyanides. In order still more fully to justify (4′), the present authors prepared benzoyl cyanide, allowed it to react with alcoholic sodium ethoxide in the cold, and had no difficulty in isolating the expected product, ethyl benzoate (d′; p. 1383), b. p. 212° (Found: C, 72·3; H, 6·95. Calc.: C, 72·0; H, 6·7%), the change being: $\mathrm{C_6H_5\cdot CO\cdot CN + NaOEt = C_6H_5\cdot CO\cdot OEt + NaCN}$, corresponding to (4′), p. 1383.

Thus Wallach's observation that chloral in alcoholic solution yields ethyl dichloroacetate is accounted for on the generalised Pinner–Kötz theory without assuming, as some have thought it necessary to do, that dichloroacetic acid or its potassium salt is produced at any intermediate stage (compare V. Meyer, *Ber.*, 1877, **10**, 1740; Wallach, *ibid.*, p. 2124. Chattaway and Irving, J., 1929, 1039, do not accept Meyer's suggestion).

For much other experimental evidence in support of the theory, reference to the original papers of Pinner, Kötz (*locc. cit.*) and others should be made.

Recently Chattaway and Irving (J., 1929, 1038 *et seq.*) have mentioned a number of facts which, according to them, " seem to indicate that the formation of a cyanohydrin is not a necessary step " in the chloral–potassium cyanide reaction (*loc. cit.*, p. 1040). One of the facts supposed to point in that direction is that the action of potassium cyanide upon an alcoholic solution of " chloral alcoholate " is as violent as, or even more violent than, its action on a similar solution of chloral cyanohydrin. But, by operating on preformed cyanohydrin, the total heat, Q_1, evolved in the formation of any given product (say ethyl dichloroacetate) is connected with the heat, Q_2, which is evolved when starting from alcoholate by the relation

$$Q_2 - Q_1 = Q_3$$

where Q_3 is the heat evolved in the reaction

$$CCl_3\cdot CH(OH)\cdot OEt + HCN = CCl_3\cdot CH(OH)\cdot CN + HOEt.$$

The argument used by Chattaway and Irving could carry weight *either* if Q_3 were negative, *or* if conversion of alcoholate into cyanohydrin (or its potassium derivative) by the action of potassium cyanide were very slow. No evidence in favour of either of these requirements was furnished, and all the evidence within the knowledge of the present authors indicates that neither requirement is fulfilled. If cold alcoholic solutions of chloral alcoholate and hydrogen cyanide, each containing a drop or two of tripropylamine to facilitate cyanohydrin formation, are mixed, a rise (about 20°) of temperature occurs, often reaching its maximum in two minutes or less. Subsequent addition of more catalyst produces no further appreciable rise of temperature, cyanohydrin formation having been almost completed. On removal of the solvent at the ordinary temperature in a vacuum, a crystalline mass of chloral cyanohydrin, contaminated with very little oil (no doubt mainly catalyst and traces of alcohol), remains. Analysis of this crude product (compare J., 1930, 453) gave CN, 14·5, while $CCl_3\cdot CH(OH)\cdot CN$ requires CN, 14·9%. Good yields of the pure cyanohydrin (m. p. 58—59°) and of trichlorolactic acid were obtained from similar products by recrystallisation and by acid hydrolysis respectively.

These observations also indicate that the formation of the cyanohydrin is rapid even in presence of so small a quantity of comparatively feeble catalyst. The observed behaviour of chloral alcoholate is here precisely like that of all aldehydes in alcoholic solution examined in these laboratories during a number of years, and there can be no reasonable doubt that the heat evolution noticed is that associated with cyanohydrin formation. Moreover the speed of cyanohydrin formation is always very much greater when potassium cyanide is used instead of free hydrogen cyanide and small amounts of tertiary base. The comparatively poor yields of free cyanohydrin obtained when free hydrogen cyanide is not present is due, not to a slow speed of formation, but to the nature of the resulting system,

$$R_2CO + KCN + HOH \text{ (or HOEt)} \longleftrightarrow R_2C(OH)\cdot CN + KOH$$

(or KOEt), in which equilibrium is attained, often in a few seconds, and from which the potassium hydroxide (or ethoxide) formed must be removed (as, for example, by gradual addition of an acid) if the maximum yield of cyanohydrin is desired.

Measurements of the temperature coefficients of dissociation constants of a number of aldehyde cyanohydrins in these laboratories have all given direct evidence of considerable positive heat-toning associated with cyanohydrin formation.

Chattaway and Irving state that " all conditions which favour the formation of cyanohydrin in the reaction hinder rather than promote the formation of an alkyl dichloroacetate," and, as an example of such conditions, those authors specify " the slow addition of the cyanide to the solution of the alcoholate at low temperatures " (*loc. cit.*, p. 1042). Low temperatures, however, cannot favour the actual speed of formation of cyanohydrin, but on the contrary; moreover, such conditions would favour the stability of the compound when formed.

Chattaway and Irving obtained dichloroacetamide by the action of potassium cyanide upon chloral-ammonia, dissolved in alcohol saturated with ammonia, and remark that cyanohydrin formation in these circumstances is " unlikely " (p. 1040) without explaining why they hold this opinion, which the present authors do not share. It may be pointed out (1) that aldehyde-ammonias readily revert to aldehydes and ammonia and (2) that even free potassium hydroxide in 10% concentration does not prevent *cyclo*hexanone from combining within less than 30 seconds with potassium cyanide in cold aqueous solution (Lapworth, Manske, and Robinson, J., 1927, 2054), forming the potassium salt of the weakly acidic cyanohydrin. But salts of weak acids in solution are in constant equilibrium with quantities of the free acids produced by ordinary salt hydrolysis (compare equation 1″, p. 1383) and the production in this way of free mandelonitrile from benzaldehyde and potassium cyanide in alkaline aqueous solution was demonstrated many years ago (J., 1903, **83**, 1003).

Whilst a just appreciation of the merits of the Pinner–Kötz theory in any of its applications is impossible without clear recognition of the fact that an organic compound (such as an aldehyde or ketone) can withdraw the elements of hydrogen cyanide from an aqueous or alcoholic solution of potassium cyanide even in strongly alkaline solution, it is no less necessary to realise that even the equations on p. 1383 of the present paper do not present the theory in its most generalised form. Thus, if instead of (a), there were written the expression $>CCl\cdot CH(NH_2)\cdot CN$, then, instead of (b),(c), and (d), there would appear the expressions $>C{:}C(NH_2)\cdot CN$,

$>CH\cdot C(:NH)\cdot CN$ and $>CH\cdot C(:NH)\cdot OK$ respectively, and the last of these represents the unstable potassium salt of a weakly acidic *iso*amide, from which, by interaction with water, alcohol and other proton-donating compounds present in the system, the normal amide $>CH\cdot C(NH_2):O$ would certainly be formed by salt hydrolysis and isomerisation of the resulting free *iso*amide.

Some erroneous ideas connected with the present subject have found their way even into text-books, and it is necessary to emphasise the point that, although amino-nitriles can in practice be obtained by the action of ammonia or amines on the corresponding cyanohydrins (hydroxy-nitriles), this fact is the sole basis for the belief that cyanohydrins are precursors of amino-nitriles. Consideration of the known effects of the substituents leads inevitably to the conclusion that in such a conversion the cyanohydrin must first be broken down by detachment of the cyano-group in the normal manner, and the amino-nitrile molecule then built up from the products together with ammonia or amine.

It has been shown elsewhere (Cocker, Lapworth, and Walton, J., 1930, 449) that the groups $\cdot NAlk_2$ (including also NH_2 and $NHAlk$) and OH (usually, in alkaline solution, operating in the ionised form $O\ominus$) when occupying position Y in $Y\cdot\dot{C}\cdot R$ facilitate to a remarkable degree the capacity of a radical R to separate from the carbon atom as a negative ion or to undergo replacement by other unicovalent radicals such as CN, OH, OAlk, $NAlk_2$. The groups OH and $NAlk_2$ (where Alk includes H) can thus function in two different ways, namely (*a*) as activators in position Y, promoting the latent anionic properties of R, and (*b*) as radicals with latent anionic properties in position R. The group CN on the other hand shows properties of type (*b*) only; or rather, in virtue of its powerful electron-restraining primary effect on attached carbon, CN, when in position Y, must exercise on C and R an effect of the opposite character from that produced by OH or $NAlk_2$. It follows that exchange of OH in the case of $CN\cdot\overset{\bullet}{\underset{\bullet}{C}}\cdot OH$ for groups such as $NAlk_2$ or CN should occur much less readily than in the case of the simple alcohol $H\cdot\overset{\bullet}{\underset{\bullet}{C}}\cdot OH$. Consistently with this it is found that in no circumstances can $CN\cdot\overset{\bullet}{\underset{\bullet}{C}}\cdot OH$ be transformed into $CN\cdot\overset{\bullet}{\underset{\bullet}{C}}\cdot CN$ by the action of hydrogen cyanide or cyanidion, and $CN\cdot\overset{\bullet}{\underset{\bullet}{C}}\cdot CN$ shows no tendency whatever to exchange CN for OH, OAlk, or $NAlk_2$. The possibility that $CN\cdot\overset{\bullet}{\underset{\bullet}{C}}\cdot OH$ might exchange OH for NH_2, NHAlk or $NAlk_2$ is therefore extremely remote; on the other hand it is certain that ammonia or amine facilitates partial conversion of $CN\cdot\overset{\bullet}{\underset{\bullet}{C}}\cdot OH$

into HCN and $\dot{C}{=}O$, from which, *via* the compound $NAlk_2{\cdot}\dot{C}{\cdot}OH$, amino-nitrile is readily formed.

If, then, as above suggested, the amino-nitrile is the true precursor of dichloroacetamide in the reaction between chloral, cyanide, and ammonia, it is justifiable to reject, as Chattaway and Irving do, the idea that the cyanohydrin represents an intermediate stage in the reaction, though, contrary to the opinion expressed by these workers, the conditions are quite favourable to the production (reversibly) of cyanohydrin by an independent path.

In order to avoid misunderstanding, it may be pointed out that the conversion of $HO{\cdot}CH_2{\cdot}CN$ into $CH_3O{\cdot}CH_2{\cdot}CN$ by alkali and methyl sulphate is a replacement of H by CH_3 and not of OH by $O{\cdot}CH_3$.

Experiments described in the present paper prove that *cyclo*hexanone is in part converted into the corresponding amino-nitrile on treatment with potassium cyanide and excess of ammonia, and that acetaldehyde reacts in quite analogous manner with potassium cyanide and excess of aqueous diethylamine.

Chattaway and Irving mention 6-nitro-2 : 4-bis(trichloromethyl)-1 : 3-benzdioxin as the case of a compound from which potassium cyanide is effective in causing elimination of the elements of hydrogen chloride, using this observation to support their suggestion that cyanide might operate similarly on the hydrates, alcoholates or ammonia addition products of α-chloro-aldehydes. The present authors, however, have found that in this case the cyanide is not specific, as the dioxin is also acted on readily by sodium hydroxide and the product contains the same compound as was isolated by Chattaway and Irving when using potassium cyanide as agent (direct comparison of specimens and mixed melting points obtained by both methods. Found: Cl, 46·4. Theory requires Cl, 46·7%).

In the reactions of α-chloro-aldehydes at present under discussion no known agent gives results in the least like those obtained when metallic cyanide is used, and cold dilute alkalis, acting on chloral or its hydrate or alcoholate, liberate no detectable traces either of dichloroacetate or of chloridion, which are the products characteristic of the action of aqueous potassium cyanide on this compound. The theory of Pinner and Kötz, logically extended, embodies an explanation of the specificity of the agent and demands no assumption for which some good reason or close analogy cannot be found in experimental facts quite outside the range of phenomena which it was specially devised to account for. The explanation offered by Chattaway and Irving is defective in both these respects.

B. *Reactions in Acid Solutions.*—The type $>C(OAlk)_2$ is readily formed in a reversible manner in acid but not in alkaline solution, as shown by the conditions of reversible formation and decomposition of acetals. This is readily understood on the basis of the well-known theory first proposed by Kastle (*Amer. Chem. J.*, 1898, **19**, 894) in connexion with the catalytic action of acids on many of the reactions of carbonyl compounds. His theory postulates the formation of highly sensitive oxonium salts of the carbonyl compounds and their derivatives, and there is no difficulty in perceiving that the union of the group OH or OAlk with proton will increase the restraint exercised by the electrons of the oxygen atom, so that the activation energy required for the separation of neutral HOH or HOEt would be smaller than for separation of $OH^{\ominus}$ and $OAlk^{\ominus}$ respectively. No such elementary theoretical consideration can be used to explain why, if Kastle's theory is correct, the methyl ether–proton complex $H{\cdot}CH_2{\cdot}O(CH_3)H^{\oplus}$ is so extremely insensitive as compared with the complex $CH_3O{\cdot}CH_2{\cdot}O(CH_3)H^{\oplus}$, and here the numerous data which support the idea of association of a powerful electron-releasing primary effect with AlkO indicate how this hiatus in Kastle's theory may be filled.

Assuming the correctness of the theory in question, it is now clear that the primary effect of AlkO on the carbon atom in the complex $\mathrm{AlkO}{\cdot}\overset{\bullet}{\underset{\bullet}{\mathrm{C}}}{\cdot}\mathrm{R}$ is normally sufficient to permit of ready elimination or exchange, at the ordinary temperature, of R, together with its bonding electrons, when R = Cl, $OH_2{}^{\oplus}$, $OAlk{\cdot}H^{\oplus}$, but not when R = OAlk or CN.

The type $\mathrm{Cl}{\cdot}\overset{\bullet}{\underset{\bullet}{\mathrm{C}}}{\cdot}\mathrm{Cl}$ in some respects resembles $\mathrm{AlkO}{\cdot}\overset{\bullet}{\underset{\bullet}{\mathrm{C}}}{\cdot}\mathrm{OAlk}$, and its hydrolysis to carbonyl is greatly accelerated by mineral acids. There would seem to be no sufficient reason to assume the mechanism of acid hydrolysis to be different with the two types. Supporters of Kastle's theory will therefore hope for more direct evidence that unicovalent chlorine can act as proton-acceptor.

The inertness of the type $\mathrm{CN}{\cdot}\overset{\bullet}{\underset{\bullet}{\mathrm{C}}}{\cdot}\mathrm{CN}$ (even in acid solution) has been mentioned elsewhere (p. 1387).

EXPERIMENTAL.

This section gives further details of some of the newer experiments on which statements in Section A are based.

2-*Chloro*-1-*cyano*cyclo*hexane*.—*cyclo*Hexanone was converted into its cyanohydrin (b. p. 140°/15 mm.), which was boiled with excess of thionyl chloride for 3 hours, the whole being then cooled and poured into water, and the product fractionated. The resulting 1-cyano-*cyclo*hexene (b. p. 86°/15 mm.; yield, 77% of the theoretical), dissolved in ice-cold ether, absorbed hydrogen chloride, and after

3 hours' continuous passage of the gas and subsequent fractionation gave *2-chloro-1-cyano*cyclo*hexane* as a colourless, faintly opalescent, somewhat unstable liquid, b. p. 138°/15 mm. (Found: Cl, 24·2. $C_7H_{10}NCl$ requires Cl, 24·7%).

The odour of the chloro-nitrile was pungent and in no way reminiscent of that of the cyano*cyclo*hexene, which is very characteristic. The odour of the unsaturated nitrile is very quickly developed, however, if the chloro-nitrile is warmed with dilute sodium hydroxide solution or even with water, hydrogen chloride being eliminated; moreover, the volatile product formed has the boiling point and other properties of cyano*cyclo*hexene.

Formation of Amino-nitriles by the Action of Potassium Cyanide and Excess of Ammonia on (i) cyclo*Hexanone and* (ii) *Acetaldehyde.*—(i) *cyclo*Hexanone (12·25 g.) (chosen because the derived amino-nitrile is soluble in petroleum) was dissolved in light petroleum (50 c.c.) and continuously shaken with a cold solution of potassium cyanide (8·1 g.) in aqueous ammonia (*d* 0·880, 21 c.c.) for 12 hours. The petroleum was then separated, and the aqueous layer extracted with fresh petroleum (50 c.c.). The combined petroleum extracts were dried over anhydrous sodium sulphate and filtered, and a stream of dry hydrogen chloride passed through them; a copious white precipitate was then formed. This was separated by filtration, thoroughly washed with ether, drained, and finally extracted with absolute alcohol. Little or no residue was left, and the alcohol on evaporation deposited large square plates (2·5 g.) of the *hydrochloride* of 1-aminocyano*cyclo*hexane, m. p. 233° (decomp.) (Found: Cl, 24·3, 23·9. $C_7H_{12}N_2,HCl$ requires Cl, 22·1%). This salt dissolved readily in water and when boiled with dilute alkali regenerated ammonia, cyanide, and *cyclo*hexanone. The last was identified by means of its 2 : 4-dinitrophenylhydrazone (m. p. 153°. A specimen of the hydrazone made from highly purified *cyclo*hexanone had m. p. 156·5—157°).

Another specimen of the hydrochloride in question (yield, 4·5 g. from 50 g. of *cyclo*hexanone after 2 days' contact with aqueous potassium cyanide and excess of ammonia) was isolated as above, and 4·3 g. of this were heated with dilute sulphuric acid for 3 hours at 115—120°. After removal of the free sulphuric acid by means of barium carbonate, the clear filtrate yielded 1·9 g. of 1-*amino*cyclo*hexanecarboxylic acid*, which separated from water in large plates, m. p. (closed tube) 350° (decomp.) (Found: N, 10·3. $C_7H_{13}O_2N$ requires N, 9·8%). The identity of the acid was established by comparison of the acid and derivatives with specimens prepared from *cyclo*hexanone by orthodox methods (compare *Ber.*, 1906, **39**, 1727; 1908, **41**, 2063).

(ii) Acetaldehyde (11 g.) was shaken with aqueous potassium cyanide and excess of diethylamine for 4 hours. The ethereal layer, together with ether used in a subsequent continuous extraction of the aqueous layer, was dried, and the ether cautiously evaporated. A liquid was left from which there were readily obtained 11 g. of the picrate of α-diethylaminopropionitrile, which had the melting point (103—104°) and all the other properties of authentic specimens of this salt (J., 1930, 454).

Summary.

It is pointed out that consideration of the conditions under which R and R′ in the complex $>CRR'$ can be anionically exchanged for other radicals or introduced in place of oxygen in the complex $>C{=}O$, affects materially the plausibility of some theories of reaction mechanism.

Special reference is made (1) to the action of potassium cyanide on chloral and its alcoholate in various circumstances, (ii) to the supposed direct conversion of cyanohydrins of aldehydes and ketones into amino-nitriles, and (iii) to the reversible formation of acetals from aldehydes and ketones under the influence of acid catalysts.

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