CCLXIX.—*Formation and Decomposition of Ketone Cyanohydrins, with Special Reference to some Compounds recently classified as such.*

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IN a recent paper (*Ber.*, 1927, **60**, 586) Houben and Pfankuch described some new nitriles two of which were considered to be the stereoisomeric cyanohydrins of camphor. These workers commented on the remarkable stability of these nitriles, which did not show any tendency to dissociate into hydrogen cyanide and ketone; but having also found that the direct union of hydrogen cyanide and camphor cannot be effected, they concluded that these observations illustrate the rule that " ein Korper, der schwer entsteht, meistens schwer wieder zerfällt " (*loc. cit.*, p. 587).

Houben and Pfankuch described another new nitrile which they regarded as " menthon-cyanohydrin " (*loc. cit.*, p. 599). They did not state specifically that this compound has the same remarkable stability as the supposed camphor cyanohydrins, but, as they were able to purify it (apparently without adopting any special precautions) from boiling ligroin and to hydrolyse it with methyl-alcoholic potassium hydroxide, there can be no doubt that the compound was much more stable than most of the known cyanohydrins of other simple ketones.

Passerini, in a still more recent paper (*Ber.*, 1927, **60**, 1201, 1202), accepts the views of Houben and Pfankuch, but finds that the supposed " menthon-cyanohydrin " described by these authors is converted on hydrolysis with acids into a lactone, and infers that here " das Hydroxyl des Menthon-cyanohydrin in den Menthan-Ring wandert." Such a migration in a saturated compound has no parallel within the knowledge of the present authors.

A long series of measurements of equilibria in systems containing cyanohydrin, hydrogen cyanide and ketone (or aldehyde) in aqueous alcohol has been made in these laboratories during the last 3 years and among the cases studied were those comprising camphor and menthone respectively. It was found that, out of some 60 ketones and aromatic aldehydes examined, only 2, benzophenone and camphor, gave no detectable amounts of cyanohydrin by direct combination with hydrogen cyanide. With the others, a sensibly constant equilibrium condition was attained within 24 to 36 hours at most in aqueous alcohol, if a very small proportion of tripropylamine was present as catalyst. The dissociation constants of the cyanohydrins varied very widely, ratios of extremes observed being at least 1 : 25,000, and the failure of camphor and benzophenone to yield measurable quantities of cyanohydrin is doubtless to be ascribed to the exceptionally high dissociation constants of the cyanohydrins rather than to catastrophic disappearance of reaction velocity.

It is quite otherwise in the case of menthone, the cyanohydrin * of which is formed quite readily in the cold, the time required in the above conditions to attain a concentration practically identical with the equilibrium value not exceeding 24 hours.

Experiment A illustrates some of these statements : Menthone (11·38 g.), 2 c.c. of ethyl alcohol containing 0·24 g. of tripropylamine, and 5 c.c. of anhydrous hydrogen cyanide dissolved in cold dry methyl alcohol (about 30 c.c.) were mixed and left over-night in a stoppered flask, previous experience having shown that further contraction (initially attendant on combination) is inappreciable after such a period. The vessel was then opened, the contents made up to 50 c.c. with more dried methyl alcohol, and the flask again closed with a waxed stopper and allowed to remain in an ice-chest for 60 hours, a period considerably exceeding that (24—36 hours) which previous experiments, under not wholly dissimilar conditions, had shown to be amply sufficient for the attainment of a practically steady state.† The solution was then analysed by a method based on that of Ultée (*Rec. trav. chim.*, 1909, **28**, 248), which depends on the fact that in presence of mineral acid, silver nitrate in the cold precipitates only cyanidion which is not in combination with the aldehyde or ketone. An aliquot portion of the solution was removed and at once added to excess of standard silver nitrate solution acidified with nitric acid, the whole being shaken, and the silver cyanide removed by filtration. The excess of silver in the filtrate was determined by titration with standard thiocyanate in the usual way. The free hydrogen cyanide present in the original 50 c.c. of solution was thus found to be 1·95 g.

Another portion of the solution was removed and allowed to remain in the cold with five times its bulk of *N*-sodium hydroxide for 45 minutes. The whole was acidified with nitric acid and mixed with excess of standard silver nitrate and the excess of silver was determined as before. The total hydrogen cyanide found in this way was 3·49 g. (comparing favourably with 3·53 g. found in the

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* Strictly speaking, as menthone itself is a mixture of two dynamic isomerides, each of which can theoretically give rise to two stereoisomeric addition compounds with hydrogen cyanide, the cyanohydrin formed as above must be a mixture of four isomerides.

† A blank experiment in which the menthone was omitted showed that the total amount of hydrogen cyanide remaining after these manipulations would be approximately 3·53 g. if no combination had taken place.

blank experiment above mentioned). It is probable that a minute but hardly measurable quantity of the sodium derivative of the cyanohydrin remains in equilibrium with menthone and cyanidion in presence of sodium hydroxide :

$$C_{10}H_{18}O + CN' \rightleftharpoons C_{10}H_{18}(CN){\cdot}O'.$$

From the titres, it may be deduced (1) that at equilibrium under the conditions specified above, 1 mol. of menthone is converted to the extent of about 0·8 mol. into cyanohydrin, in equilibrium with which 0·2 mol. of unchanged menthone remains with about 1 mol. of uncombined hydrogen cyanide, (2) that menthone cyanohydrin is almost completely converted into menthone and sodium cyanide by cold *N*-sodium hydroxide in not more than 45 minutes, the rapid acidification preventing appreciable recombination.

While the equilibrium may be effectively " frozen " by excess of mineral acid in aqueous or dilute alcoholic solution (as is shown by the failure of silver nitrate to decompose the cyanohydrin in these circumstances), it has not been found possible to separate the cyanohydrin from unchanged menthone owing to the instability of the former. It is quite easy to convert menthone to the extent of 90% into mixed cyanohydrins with excess of anhydrous hydrogen cyanide in presence of a trace of tripropylamine ; but when attempts were made to remove hydrogen cyanide at the ordinary temperature by the use of a vacuum, even after adding some excess of hydrogen chloride in ether in the endeavour to stabilise the cyanohydrin, the latter underwent considerable decomposition and in the end constituted only about 30% of the residual oil.

On subjecting the equilibrium mixtures to hydrolytic action of mineral acids, including sulphuric acid, concentrated or dilute, in the cold, no evidence was obtained of the formation of any acid amide or carboxylic acid, and Pinner's method for the conversion of nitriles into imino-ethers in ethereal solution also gave negative results ; the nitrile group is, in fact, extremely resistant to cold acid hydrolysts. If the temperature be raised, thermal dissociation occurs and hydrogen cyanide is lost, again before any effective hydrolysis has taken place. With alkalis, as has been demonstrated, the cyanohydrin is almost quantitatively decomposed even in the cold in a short time—probably within a few seconds. The great speed at which equilibrium is reached from either side in systems comprising ketone and cyanohydrin in presence of considerable concentrations of hydroxylion or cyanidion or both is perhaps not generally realised. *Experiment B* is described to illustrate the last point.

B. Cold saturated aqueous potassium cyanide (1 c.c.) at about

20° is shaken in a test-tube with 0·2 c.c. of *cyclo*hexanone which has been purified through the bisulphite compound. The ketone, at first immiscible, very quickly disappears, if the temperature is initially about 15°, a clear solution being formed with rise of temperature; then, as a rule, crystals of the potassium derivative of the cyanohydrin almost at once begin to appear and the whole sets, within about 30 seconds from the beginning of the experiment, to a semi-solid mass.

How little the concentration of *free* hydrogen cyanide affects the addition process may also be observed by repeating the experiment with the previous addition of 0·5 c.c. of 30% aqueous potassium hydroxide to the potassium cyanide. Although the concentration of free hydrogen cyanide due to salt hydrolysis must be reduced thereby many thousand-fold, the same phenomena are observed, while the time taken for setting is not more than doubled. The apparent decrease in speed is doubtless due in the main to the salting-out action of the potassium hydroxide reducing the already small solubility of the *cyclo*hexanone in the aqueous phase.

Observations already mentioned show that menthone cyanohydrin is readily formed and decomposed even in the cold in alkaline media and therefore, if the phenomena just described are not reproduced when menthone is used instead of *cyclo*hexanone, it is not because reaction is indefinitely delayed, but because the dissociation constants of menthone cyanohydrin and of its potassium derivative are much higher than those of *cyclo*hexanone cyanohydrin and of its potassium derivative respectively.* If, therefore, the compound described by Houben and Pfankuch were, in fact, menthone cyanohydrin, then at a very early stage in the alkaline hydrolysis which they carried out (*loc. cit.*, p. 600) equilibrium must have been attained, and this equilibrium should be reached no less rapidly by simply boiling menthone with potassium cyanide and potassium hydroxide in methyl-alcoholic solution, and with similar results on allowing hydrolysis to proceed. *Experiment C* was therefore carried out.

C. Menthone (10 g.) with potassium cyanide (10 g., or 2·5 mols.) and methyl alcohol (100 c.c.) was heated on the steam-bath for 48 hours. (A small portion of the product was removed at this point and worked up for carboxylic acid, but none could be detected.) Potassium hydroxide (25 g.) was next added and the heating was continued for a further 70 hours. On working up the whole for carboxylic acid, 1·9 g. of oily product, sparingly soluble in water but

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* The dissociation constants of the two cyanohydrins in aqueous alcoholic solution at the ordinary temperature have been measured by one of us (R. H. F. M.) and found to be roughly in the ratio 72 : 1.

readily soluble in aqueous sodium carbonate, were isolated. Doubtless Houben and Pfankuch would have commented on such a poor yield after so prolonged a period of heating, but they do not mention either. It may be added that on attempting to convert the acid material into amide by the method used by Houben and Pfankuch only a small proportion of the product was soluble in hot ligroin, and even that portion failed to yield any crystalline solid.

Conclusions.—True menthone cyanohydrin, *i.e.*, the mixture of cyanohydrins produced by addition of hydrogen cyanide to ordinary menthone, is readily formed and decomposed reversibly in solutions which are at all alkaline and its properties indicate that Houben and Pfankuch were dealing with quite another compound. The characters ascribed by these workers to the compounds which they describe as camphor cyanohydrins are also at variance with those of all known ketone cyanohydrins.

It is suggested that a transformation of the Wagner type occurs when the nitrogen atom is separated from carbon in the experiments described by Houben and Pfankuch.

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