607. *Reactions of Ethylene Oxides. Part V. The Interaction of Alkali Cyanides with Epichlorohydrin.*

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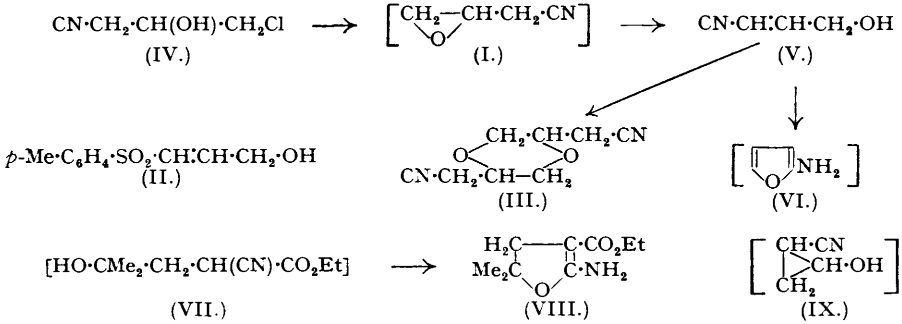
In the above reaction a 65% yield of γ-chloro-β-hydroxybutyronitrile (IV) is rapidly produced when the alkali formed is continuously neutralised. The main products in the absence of neutralisation are 2 : 5-dicyanomethyl-1 : 4-dioxan (III), and impure γ-hydroxycrotononitrile (V), which readily cyclises with alkali to give unstable unisolable 2-aminofuran.

Pazschke (*J. pr. Chem.*, 1870, [ii], **1**, 97) and Hartenstein (*ibid.*, 1873, [ii], **7**, 297) condensed potassium cyanide and epichlorohydrin to produce " epicyanohydrin " (βγ-epoxybutyronitrile) (I), m. p. 162—163°, hydrolysable by hot mineral acid or alkali to form the corresponding " 2 : 3-epoxybutyric acid " (βγ-epoxybutyric acid), m. p. 225°. The stability of the acid and the high melting points of both products make the above formulæ unlikely, though their Raman spectra have nevertheless been measured in good faith by Ballaus and Wagner (*Z. physikal. Chem.*, 1940, **45**, *B*, 272). It is to be expected that the reaction of epichlorohydrin with potassium cyanide will be analogous to that with sodium toluene-*p*-sulphinate (Culvenor, Davies, and Savige, *J.*, 1949, 2198) of which the first product is the chlorohydrin, 1-chloro-3-*p*-tolylsulphonylpropan-2-ol. However, if the alkali produced in the reaction is not continuously neutralised, the unsaturated alcohol 3-*p*-tolylsulphonylprop-2-en-1-ol (II) is rapidly formed in the cold, and this is dimerised by further alkali treatment to give 2 : 5-di-(*p*-tolylsulphonylmethyl)dioxan.



Experiment has largely justified this analogy between the reactions of potassium cyanide and sodium toluene-*p*-sulphinate. A molecular-weight determination has shown that the " epicyanohydrin " is 2 : 5-biscyanomethyl-1 : 4-dioxan (III), hydrolysable to the corresponding diacetic acid. The correct structure of these compounds has also been shown by van Dormael (*Bull. Acad. roy. Belg., Cl. Sci.*, 1942, [v], **28**, 501; see also Legrand, *Bull. Soc. chim. Belg.*, 1944, **53**, 166), these war-time publications not yet being available in Australia. The chlorohydrin, γ-chloro-β-hydroxybutyronitrile (IV) is the first product, and this has previously been prepared (van Dormael, *loc. cit.*) by interaction of epichlorohydrin and hydrogen cyanide (Hormann, *Ber.*, 1879, **12**, 23; Lespieau, *Bull. Soc. chim.*, 1905, [iii], **33**, 466), preferably with the addition of potassium cyanide crystals as catalyst (Rambaud, *ibid.*, 1936, [v], **3**, 138). These prolonged processes involving the use of anhydrous hydrogen cyanide are much less practical than the present method of using alkali cyanide in neutral aqueous solution, whereby a 65% yield of (IV) is rapidly formed. This easy preparation of (IV) makes its reactions and derivatives of importance from the synthetic point of view. On the one hand, dehydration with phosphoric oxide (cf. Lespieau, *loc. cit.*) yields γ-chlorocrotononitrile, itself a valuable synthetic reagent (cf. Jones, O'Sullivan, and Whiting, *J.*, 1949, 1415). On the other hand, (IV) is converted by alkali into the unsaturated alcohol, γ-hydroxycrotononitrile (V), which is remarkably reactive and unstable.

The present work confirms the difficulty encountered by van Dormael (*loc. cit.*) in preparing a pure specimen of (V). He succeeded in obtaining a satisfactory (still rather low) analytical value for nitrogen only after fourteen distillations and six crystallisations, and attributed this low value to the tendency of the compound to hydrate during the manipulations. The explanation is now advanced that the instability is due to cyclisation to the notoriously unstable, still unisolated 2-aminofuran (VI), which readily evolves ammonia. This change is facilitated by the sodium hydroxide. The presence of a primary amine in a freshly prepared specimen of (VI) [made *via* (V) from (IV) and alkali] is shown by the carbylamine reaction, and its aromatic nature is proved by diazotisation and coupling reactions. This conclusion, though not supported by the isolation of pure derivatives of (VI), is in agreement with the properties of the few known aminofurans (*Ann. Reports*, 1939, **36**, 311; Marquis, *Ann. Chim.*, 1905, [viii], **4**, 231; Singleton and Edwards, *J. Amer. Chem. Soc.*, 1938, **60**, 540; Stevenson and Johnson, *ibid.*, 1937, **59**, 2525).

Perhaps the closest recorded analogy to this cyclisation is the production of (VIII) from (VII) (not isolated), which is formed from the interaction of *iso*butylene oxide and ethyl cyanoacetate (Glickman and Cope, *ibid.*, 1945, **67**, 1012). The sulphur analogue of (VIII) is similarly formed from *iso*butylene sulphide (Snyder and Alexander, *ibid.*, 1948, **70**, 217), but in the present work failure met attempts to prepare the unstable 2-aminothiophen (the analogue of VI) by starting with chloropropylene sulphide instead of with epichlorohydrin.

With regard to the conversion of (IV) into (V) by means of alkali, van Dormael postulates the intermediate formation of 2-cyano*cyclo*propan-1-ol (IX). A probable intermediate, however, is the ethylene oxide (I), where a hydrogen atom on the carbon α- to the cyano-group would be expected to be active enough to react intramolecularly in the same sense that ethyl cyanoacetate reacts intermolecularly with ethylene oxides. This view is supported by the dearth, in the literature, of authentic ethylene oxides containing a strong electrophilic group on the carbon atom attached to an ethylene oxide ring (as I), and oxides of this type containing a sulphone group which have been prepared in this Department (unpublished work) are characterised by extreme instability and easy conversion into the unsaturated alcohol.

EXPERIMENTAL.

Interaction of Epichlorohydrin and Alkali Cyanides.—(a) *In non-neutralised solution.* A solution of epichlorohydrin (48 g.) and sodium potassium cyanide double salt (30 g.) in water (120 c.c.) was stirred at ordinary temperatures, and the reaction which slowly developed controlled by cooling. After 3 hours, the dark red, strongly alkaline solution was filtered, and the white 2 : 5-biscyanomethyl-1 : 4-dioxan (III) (1·1 g.) collected and crystallised from alcohol in lustrous plates, m. p. 166—167° [Found : C, 57·8; H, 6·0; N, 16·9; *M* (Rast), 148, 178. Calc. for $C_8H_{10}O_2N_2$: C, 57·5; H, 6·0; N, 16·5%; *M*, 166]. It (1·0 g.) was refluxed (30 minutes) with concentrated hydrochloric acid (6 c.c.) and yielded brilliant needles (0·6 g.), m. p. 228° (Found : C, 47·0; H, 5·5. Calc. for $C_8H_{12}O_6$: C, 47·1; H, 5·9%). The m. p. agrees with that (225°) recorded by Hartenstein (*loc. cit.*) for "2 : 3-epoxybutyric acid."

The aqueous alkaline filtrate from 2 : 5-biscyanomethyl-1 : 4-dioxan gave, after continuous extraction with ether, a water-soluble oil containing a small amount of γ-chloro-β-hydroxybutyronitrile (IV), b. p. 134—136°/13 mm., but consisting essentially of impure γ-hydroxycrotononitrile (V), b. p. 119—120°/13 mm., 103°/1 mm. (Found, on day of distillation : N, 12·1; after six weeks in a well-stoppered glass bottle : N, 10·6. Calc. for C_4H_5ON : N, 16·9%).

(b) *In neutral solution.* To a continuously stirred solution of epichlorohydrin (30 g., 0·31 mol.) in alcohol (65 c.c.) containing a few drops of thymol-blue, sodium potassium cyanide double salt (19 g., 0·33 mol.) in water (75 c.c.) was gradually added, with cooling, during 30 minutes. Neutrality was maintained throughout by the dropwise addition of standard dilute acetic acid and for an additional 30 minutes after all the cyanide had been added. The solution was set aside for an hour, neutralised again if necessary, and continuously extracted with ether or ethyl acetate. The ethereal solution was washed with water, dried (Na_2SO_4), and yielded 25·4 g. (65·5%) of γ-chloro-β-hydroxybutyronitrile (IV),

b. p. 136—145°/15 mm., redistilled 134—136°/13 mm. (Found: N, 11·7. Calc. for C_4H_6ONCl: N, 11·3%). Braun (*J. Amer. Chem. Soc.*, 1930, **52**, 3167) recorded b. p. 138—142°/14 mm. In the preparation, the amount of acetic acid neutralised corresponded to the production of 0·99 mol. of alkali.

The characteristic property of (IV) was instability to alkali, and the Schotten–Baumann reaction accordingly failed under ordinary conditions. But *γ-chloro-β-benzoyloxybutyronitrile*, needles m. p. 44°, from ether–light petroleum, was obtained when (IV) (0·1 g.) in dioxan (1 c.c.) was shaken with benzoyl chloride (0·2 g.) and powdered potassium hydroxide (0·2 g.) at ordinary temperatures; it was also formed by the use of dry pyridine and benzoyl chloride (Found: N, 6·1. $C_{11}H_{10}O_2NCl$ requires N, 6·3%). (IV) was converted into (III) by the action of aquous alkali at room temperture in poor yield, 15% with 1 mole of sodium hydroxide, and 35% when added to 10 moles of potassium hydroxide. These poor yields, which were in contrast to the almost complete dimerisation (Culvenor, Davies, and Savige, *loc. cit.*) of (II) derived from 1-chloro-3-*p*-tolylsulphonylpropan-2-ol by the action of alkali, were due to reactions other than dimerisation.

Crude γ-hydroxycrotononitrile, best prepared by the cautious addition of less than one mole of sodium hydroxide to (IV), was colourless when freshly distilled, but rapidly darkened and slowly deposited crystals of the dimer (III). The production of this dimer by interaction of sodium hydroxide and (IV) as above was preceded by immediate coloration and evolution of ammonia, and the orange-coloured liquid reduced ammoniacal silver nitrate, and hot Benedict's solution. This reducing property is not typical of ethylene oxides, because epichlorohydrin, *cyclo*hexene oxide, and ethyl phenylglycidate are inert to Benedict's solution. When potassium hydroxide was added to chlorohydrin (IV) dissolved in chloroform and alcohol, the carbylamine odour was immediately evident and persisted for a few hours. A red azo-dye mixed with the colourless dimer was precipitated when (IV) was treated with cold 10% sodium hydroxide for 4—5 minutes, diazotised, and coupled with β-naphthol. (The optimum time of alkali treatment for maximum dye-formation was about 5 minutes, though some colour was formed after alkali treatment for a few seconds and also for 10 minutes). Similarly intense colours were formed from α-naphthol and acetylacetone. A red colour was also formed when an alkaline solution of the chlorohydrin was added, at varied short time intervals, to an acid solution of benzenediazonium chloride. However, no derivative of 2-aminofuran was obtained by condensation of an alkaline solution of (IV) with chloro-2 : 4-dinitrobenzene, fluoro-2 : 4-dinitrobenzene, toluene-*p*- or *p*-nitrobenzene-sulphonyl chloride.

Chloropropylene sulphide and aqueous alcoholic potassium cyanide gave viscous material, which was also formed by the slow interaction of chloropropylene sulphide and excess of dry hydrogen cyanide in the presence of potassium cyanide crystals for six months in a sealed tube at room temperature. Apart from some darkening when the tube was opened, there was no evidence of formation of the extremely unstable 2-aminothiophen (Steinkopf, " Die Chemie des Thiophens," 1941, p. 59).

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