# **446.** *A Non-catalytic Alcoholysis of Nitriles.*

By B. Robinson.

The scope and mechanism of a reaction involving the formation of hydroxyalkyl esters by thermal interaction between nitriles and diols have been investigated.

In an attempt to prepare 2-cyanoindole from *cis*-pyruvonitrile phenylhydrazone[1] in refluxing ethane-1,2-diol,[2] the only product isolated was 2-hydroxyethyl indole-2-carboxylate, the nitrile group having undergone an unexpected alcoholysis, normally acid-catalysed.[3] The structure was supported by analytical and spectral data and by reduction to 2-hydroxymethylindole[4] by lithium aluminium hydride.

The reaction has been found to be generally applicable to nitriles, for benzonitrile, several substituted benzonitriles, and aliphatic nitriles (see Table) similarly gave 2-hydroxyethyl esters.

Restrictions in the alcoholic reactant have, however, been found. 3-Hydroxypropyl benzoate was obtained from propane-1,3-diol; however, with benzonitrile and butane-1,4-diol, the reflux temperature, initially 196°, dropped in 1 hr. to a constant value of 144° owing to formation of tetrahydrofuran (both this and water were detected by infrared spectroscopy) and no ester could be detected, presumably owing to the lowering of the

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[1] Thesing and Witzel, *Chem. Ber.*, 1955, **88**, 117.

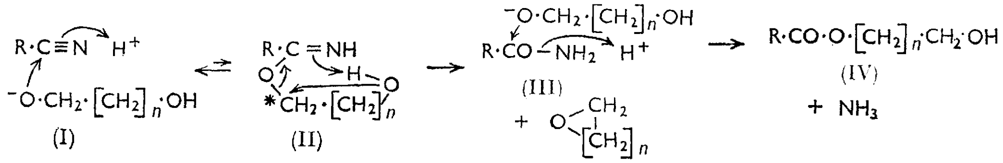
[2] FitzPatrick and Hiser, *J. Org. Chem.*, 1957, **22**, 1703.

[3] " Chemistry of Carbon Compounds," ed. Rodd, Elsevier Publ. Co., Amsterdam, 1951, Vol. 1A, p. 607; Cram and Hammond, " Organic Chemistry," McGraw-Hill, New York, Toronto, London, 1959, p. 277.

[4] Taylor, *Helv. Chim. Acta*, 1950, **33**, 164.

reflux temperature. Similarly, even prolonged refluxing of benzonitrile in pentane-1,5-diol or hexane-1,6-diol gave the ester only very slowly. Monohydric alcohols of boiling points close to that of ethane-1,2-diol (2-phenylethanol, octan-1-ol, and decan-1-ol), and 2-ethoxyethanol gave no ester. It seems that the reaction requires the presence of at least two hydroxyl groups in the solvent-reactant, with an optimum rate for vicinal diols, and a temperature in the region of 200° (nitriles can be prepared from alkyl halides and potassium cyanide in ethane-1,2-diol at temperatures ranging from 50° to 150° [5]).

The possibility that the corresponding amide is an intermediate was supported by the observation that on treatment of benzamide in refluxing ethane-1,2-diol ammonia was evolved and after 3 days' refluxing a good yield of 2-hydroxyethyl benzoate was obtained. That it was the formation of the amide rather than the conversion of this into the ester which required the presence of the two hydroxyl groups in the alcohol above was verified when benzamide was refluxed in decan-1-ol or octan-1-ol; ammonia was evolved in both cases, and after 4 and 8 days' refluxing, respectively, the amide C=O stretching band at 1670 ± 5m cm.$^{-1}$ had been replaced by an ester C=O stretching band at 1720 ± 10s cm.$^{-1}$.



The annexed mechanism is postulated for this non-catalytic nitrile alcoholysis. Partial heterolysis of one hydroxyl group of the diol in the presence of the nitrile at the high reaction temperature leads to the establishment of the equilibrium (I) $\rightleftharpoons$ (II). This is then irreversibly broken in favour of the imidate (II) by a concerted electron movement involving the second hydroxyl group of the initial diol, the rate of breaking of this equilibrium depending on the spatial proximity of this second hydroxyl group to the nitrogen and the C* atom in (II). This leads to the intermediate amide (III) which can then react with a second diol molecule, partially heterolysed as before under the reaction conditions, to give the ester (IV). Instead of involving these partial heterolyses, the formation of the imidate (II) and ester (IV) could proceed directly by nucleophilic attack by the oxygen *p*-electron pair, followed by proton transfer.

The following further support for this mechanism has been obtained by reaction of benzonitrile with ethane-1,2-diol. At least a 2-molar excess of diol to nitrile is needed for the complete alcoholysis of the nitrile; and the gaseous product consists of a mixture of ethylene oxide and ammonia.

When benzonitrile was heated with ethane-1,2-diol in a sealed tube for 6 days at 220°, no ester formation occurred, the nitrile being converted into the di-imidate $[Ph\cdot C(:NH)\cdot O\cdot CH_2]_2$, presumably by attack of the hydroxyl group in the intermediate imidate (II) on a further nitrile molecule.

## EXPERIMENTAL

*2'-Hydroxyethyl Indole-2-carboxylate.*—*cis*-Pyruvonitrile phenylhydrazone [1] (2·50 g.) and redistilled ethane-1,2-diol (80 c.c.) (protected from moisture; NaOH) were refluxed until evolution of ammonia ceased (2 days), and then cooled. Water (500 c.c.) was added and the liberated oil extracted with ether (3 × 40 c.c.). After drying and removal of the solvent the ether extracts afforded a dark-brown gum (2·49 g.) which partially crystallised on trituration with ether. Removal and washing of the solid with a little ether gave tan crystals (1·025 g., 32%), which after one recrystallisation from ether–carbon tetrachloride gave white needles, m. p. 130° (832 mg.). A second crop, m. p. 128—130° (137 mg.), of the *indole* was obtained

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[5] Lewis and Susi, *J. Amer. Chem. Soc.*, 1952, **74**, 840.

by concentration of the mother-liquors (Found: C, 64·6; H, 5·4; N, 6·7. $C_{11}H_{11}NO_3$ requires C, 64·4; H, 5·4; N, 6·8%). It had $\nu_{max.}$ (in Nujol) 3431m (OH), 3218m (NH), and 1691s cm.$^{-1}$ (C=O), $\lambda_{max.}$ 293 mμ (ε 20,500 in EtOH) [cf. ethyl indole-2-carboxylate,[4] $\lambda_{max.}$ 293 mμ (ε 22,000 in EtOH)]. The filtrate from the original crystals afforded a red-brown oil (1·32 g.), whose infrared spectrum (liquid film) showed absorption due to C=O and NH and/or OH but none due to C≡N.

This hydroxyethyl ester (146 mg.) was refluxed in dry ether (25 c.c.) for 24 hr. with an excess of lithium aluminium hydride. After decomposition by water, the product was extracted with ether (3 × 25 c.c.) which afforded 2-hydroxymethylindole (102·6 mg., 98%), prisms (from water), m. p. 75—76° (lit.,[4] 75°) (Found: C, 73·4; H, 5·9. Calc. for $C_9H_9NO$: C, 73·5; H, 6·2%), $\lambda_{max.}$ 270 and 280 mμ (ε 8090 and 7060, respectively, in ethanol).

*Alcoholyses of the Nitriles.*—These reactions were effected by refluxing the nitrile (1 mol) and diol (5 mol.) (redistilled or recrystallised before use and protected from moisture as above) for 2—7 days (see Table). Completion of the reaction was indicated by the cessation of evolution of ammonia, the complete disappearance of the C≡N band between 2200 and 2300 cm.$^{-1}$, and appearance of the strong ester C=O stretching band between 1690 and 1740 cm.$^{-1}$ (liquid film). Details are tabulated. The esters showed ester C=O (s) and OH (m) stretching bands (liquid films; solids in Nujol).

Esters $R\cdot CO\cdot O\cdot[CH_2]_2\cdot OH$ formed by alcoholysis of the nitriles.

| R | Reaction time (days) | Yields (%) | B. p./mm. or m. p. | Found (%) C | H | N | Formula | Required (%) C | H | N | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ph ........... | 3 | 74 | 160—162°/14 | 64·5 | 6·05 | | $C_9H_{10}O_3$ | 65·05 | 6·1 | | *a* |
| $CH_2Ph$ ...... | 7 | 66 | 171—172°/13 | 66·25 | 6·7 | | $C_{10}H_{12}O_3$ | 66·65 | 6·7 | | *a* |
| n-$C_7H_{15}$ ...... | 7 | 58 | 146—149°/12 | 63·8 | 10·5 | | $C_{10}H_{20}O_3$ | 63·8 | 10·7 | | *a* |
| *o*-Tolyl ...... | 6 | 61 | 168—170°/12 | 65·7 | 6·3 | | $C_{10}H_{12}O_3$ | 66·6 | 6·7 | | *a* |
| *m*-Tolyl ...... | 4 | 65 | 172—175°/11 | 66·0 | 6·45 | | $C_{10}H_{12}O_3$ | 66·7 | 6·7 | | *a* |
| *p*-Tolyl ...... | 4 | 68 | 180—183°/11 | 65·8 | 6·9 | | — | — | — | | *a, b* |
| *m*-$NO_2\cdot C_6H_4$ | 2 | 41 | 53—55° | 51·3 | 4·5 | 6·9 | $C_9H_9NO_5$ | 51·2 | 4·3 | 6·65 | *c, d* |
| *p*-$NO_2\cdot C_6H_4$ | 2 | 12 | 77—78° | 51·5 | 4·3 | 6·65 | $C_9H_9NO_5$ | 51·2 | 4·3 | 6·65 | *c, e* |
| *p*-$MeO\cdot C_6H_4$ | 3 | 59 | 164—166°/12 | 62·0 | 6·3 | | $C_{10}H_{12}O_4$ | 61·2 | 6·15 | | *a* |

(*a*) Isolated by addition of water, extraction with ether, washing, and distillation. (*b*) Analysis indicates 10% of diol in the product. (*c*) Decomp. during reaction. (*d*) Pale yellow needles from ether. (*e*) Isolated by addition of water, removal of the dark brown ppt., collection of the product from the filtrate after 3 days at 5°, and recrystallisation from aqueous ethanol (needles).

During the reaction between benzonitrile and ethane-1,2-diol, the gaseous products were condensed [solid carbon dioxide and light petroleum], gas–liquid chromatography [performed by Mr. J. Read, using 1 : 2 polyethylene glycol–dinonyl phthalate (total 15%) on Celite at room temperature] showing them to be ammonia and ethylene oxide. Although ethylene oxide and ammonia at room temperature give mono-, di-, and tri-ethanolamine, it appears that in this case the low temperature of the condensate prevents or retards this reaction and allows isolation of the two components. No ethylene oxide was formed on refluxing pure ethane-1,2-diol for 3 days.

Propane-1,3-diol and benzonitrile gave, in 4 days, the impure monobenzoate (24%), b. p. 175—195°/13 mm. (Found: C, 65·9; H, 6·95%).

*Interaction of Benzonitrile and Ethane-*1,2-*diol in a Sealed Tube.*—Redistilled benzonitrile (5 g.) was heated with redistilled ethane-1,2-diol (20 c.c.) in a sealed tube at 220° for 6 days. The resulting brown oil partly crystallised after 48 hr. at room temperature. The crystals were removed and washed with water and ether. Recrystallisation from ethanol afforded *ethylene dibenzimidate* as needles, m. p. 250—251° (2·9 g., 45%) (Found: C, 71·3; H, 6·0; N, 9·85. $C_{16}H_{16}N_2O_2$ requires C, 71·6; H, 6·0; N, 10·45%), $\nu_{max.}$ (in Nujol) 3290 ± 10m (NH) and 1635 ± 10ms cm.$^{-1}$ (C=N). The brown oil remaining showed no infrared band (liquid film) due to a C≡N group and only very weak bands due to C=O and C=N groups.

This work was carried out during the tenure of an Imperial Chemical Industries Post-doctoral Research Fellowship.

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[*Received, November 7th,* 1962.]