The Reaction of ε-Caprolactone with Inorganic Cyanide

B. E. Burgert[1] and J. E. Krueger

Physical Research Laboratory, The Dow Chemical Company, Midland, Michigan

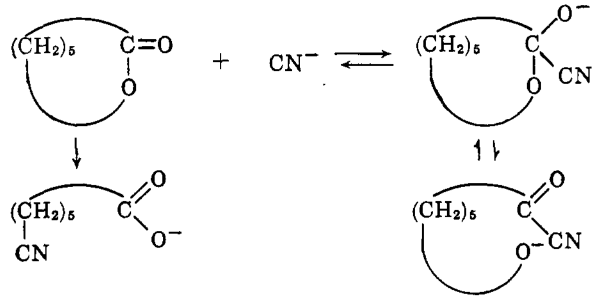
Received January 10, 1963

The reaction of γ-lactones with inorganic cyanides to give cyano acids apparently was first studied by Wislicenus[2,3] and Blaise,[4] and Blanc[5] applied the reaction in structure determinations. More recently a patent[6a] and publication[6b] described improvements in the reaction as applied to γ-butyrolactone and Price[7] has used it in a synthetic sequence. Reppe[8] found that the reaction could be extended to δ-valerolactone to give 5-cyanovaleric acid. It was of interest to see if the reaction might be extended to the next higher homolog, the seven-membered ring lactone, ε-caprolactone.

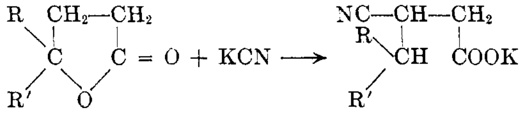
When the reaction of dry powdered potassium cyanide with ε-caprolactone was carried out at a temperature of 240–280°, a 95% yield of poly-ε-caprolactone was obtained and 95% of the potassium cyanide was recovered. However at 300° a rapid exothermic reaction, accompanied by decomposition, gave potassium 6-cyanohexanoate, isolated as its ethyl ester. The proof of structure was based on the hydrolysis of the cyano acid ester to pimelic acid, which was identical with an authentic sample. The yield in the ε-caprolactone–potassium cyanide reaction varied from 49–71% depending on the maximum temperature reached and the time the mixture was heated after the reaction began.[9]

Since the possibility existed that the reaction was taking place between the inorganic cyanide and the linear (or macrocyclic) polyester, the reaction was investigated with an aliphatic ester. Indeed when the reaction of potassium cyanide and *n*-butyl stearate (used because of its high boiling point) was carried out at 350°, valeronitrile was obtained, identical with an authentic sample. It seems unusual that no reaction was observed with potassium cyanide and benzyl benzoate under the same conditions in view of the results of Wislicenus[3] with phthalide. However, Koelsch[10] previously had observed that γ-phenyl-γ-butyrolactone did not react at 250°.

The reaction is possibly best explained in terms of a competition between a reversible reaction of the cyanide ion at the carbonyl group and an irreversible, probably much slower, nucleophilic attack of cyanide on the alkyl carbon of the ester.[11]



It is worth remarking that γ,γ-dimethyl-γ-butyrolactone (I)[4] and γ-*p*-anisyl-γ-butyrolactone (II)[7] give rearranged β-cyano acids.



I, $R = R' = CH_3$
II, $R = p\text{-}CH_3OC_6H_4$; $R' = H$

Presumably β,γ-unsaturated acids are formed by pyrolysis of these tertiary and benzylic esters and undergo rearrangement to α,β-unsaturated acids to which the cyanide then adds. There was, however, no evidence of the formation of other isomeric cyanohexanoic acids of unsaturated acids from ε-caprolactone.

Experimental[12]

Ethyl 6-Cyanohexanoate.—A mixture of 5.7 g. (0.05 mole) of ε-caprolactone and 3.26 g. (0.05 mole) of dry, powdered potassium cyanide was heated in a test tube in a nitrogen atmosphere initially at 210°. During a period of 22 min. the temperature was raised to 287°. The lactone refluxed for a short period at 258° and then the mixture became quite viscous. A plot of pot temperature *vs.* bath temperature showed little deviation from a constant difference. After cooling the reaction mixture was treated with 50 ml. of acetone and the insoluble salt removed by filtration. The salt was shown to be potassium cyanide by formation of a white precipitate with silver nitrate and by giving a potassium color in the flame test. The isolation of 3.01 g. represented a recovery of 95.3%. The acetone filtrate was evaporated and heated at 80° at 3-mm. pressure for 3 hr. to give 5.17 g. of a brittle yellow-tan solid, m.p. *ca.* 60°. This poly-ε-caprolactone sample gave an infrared spectrum identical with an authentic sample of the polyester prepared by the thermal polymerization of ε-caprolactone.

When the reaction of ε-caprolactone (0.30 mole) and potassium cyanide (0.3 mole) was repeated at an even higher temperature, an exothermic reaction set in at 296° which continued for 4 min. The total heating time was 41 min. and the final temperature of reaction mixture 314°. The cooled residue was treated with 20 ml. of concentrated sulfuric acid in 200 ml. of absolute ethanol and the precipitated potassium sulfate removed by filtration. An additional 200 ml. of absolute ethanol and 200 ml. of benzene were added to the filtrate and the resulting solution was refluxed for 10 hr. The reaction mixture was treated with potassium bicarbonate to neutralize the sulfuric acid and filtered to remove the solid potassium sulfate. The filtrate was stripped of solvent

---

(1) To whom inquiries should be addressed.

(2) W. Wislicenus, *Ber.*, **18**, 172 (1885).

(3) W. Wislicenus, *Ann.*, **233**, 101 (1886).

(4) E. Blaise, *Compt. rend.*, **124**, 89 (1897); *Bull. soc. chim. France*, (3) **29**, 335 (1903).

(5) G. Blanc, *ibid.*, (3) **33**, 886, 904 (1905).

(6a) German Patent 707,853 (1941); (b) J. W. Reppe, *Ann.*, **596**, 158 (1955).

(7) C. C. Price and W. Kaplan, *J. Am. Chem. Soc.*, **66**, 477 (1944).

(8) J. W. Reppe, *Ann.*, **596**, 80 (1955).

(9) These conditions are probably not yet optimal because the high temperature accentuates their importance. The use of a suitable solvent offers an attractive possibility of improving the yield. Reaction conditions are somewhat milder for γ-butyrolactone and δ-valerolactone, which react at about 200°[6b] and 230°[8], respectively.

(10) C. F. Koelsch, *J. Am. Chem. Soc.*, **65**, 2093 (1943).

(11) A similar mechanistic path is probably involved in the reaction of methoxide ion with methyl benzoate [J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1950)] to give dimethyl ether in 74% yield. Here the fast reversible reaction regenerates the starting materials, hence the only product possible is that derived from the slower irreversible reaction. This paper discusses additional reactions of this type. In the case of caprolactone it is possible that the reaction could proceed through the monomeric lactone, despite the fact that polymerization precedes the reaction which would form the cyano acid. A small amount of the monomeric lactone in reversible equilibrium with the polymer could give rise to the observed result.

(12) All melting points and boiling points are uncorrected.

and flash distilled to give 37.17 g. of crude product, b.p. 82–103° at 0.8–1.7 mm. Distillation through a Podbielniak column with 13 in. of "Heli-pak" packing gave 3.73 g. of pure ethyl 6-cyanohexanoate, b.p. 99–100° at 1.3 mm., n^{35}_{D} 1.4292. The column holdup, 4.57 g., was 98% pure cyano ester and these two fractions represent a 16% yield. Other fractions contained considerable amounts of the cyano ester.

Anal. Calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.13; H, 8.54; N, 8.26.

A more effective method of separating the hydroxy ester from the cyano ester was found to be chromatography on alumina. Thirty grams of a mixture of the hydroxy ester and cyano ester (64% cyano ester by infrared analysis[13]) in 100 ml. of benzene was passed over a 1 × 12 in. column of wet packed chromatographic alumina (Fisher 80–200 mesh) and eluted with benzene. Five 200-ml. fractions were collected. The first fraction gave 16.9 g. of ethyl 6-cyanohexanoate after evaporation of the benzene. Infrared analysis of the material showed it to be 90% pure cyano ester with trace impurities of benzene and the hydroxy ester. The other four fractions from the elution with benzene gave a total of 7.55 g. of residues which were mixtures of the hydroxy ester and the cyano ester. Elution of the column with 200 ml. of formula 30 ethanol gave an additional 6 g. of material, which by infrared analysis was shown to contain a maximum of 9% of the cyano ester and was predominately the hydroxy ester (some ethanol was present in the sample).

One gram (5.96 mmoles) of ethyl 6-cyanohexanoate was refluxed with 3 g. (54 mmoles) of potassium hydroxide in 15 ml. of water for 4.25 hr. The cooled hydrolysate was neutralized to pH 2 with concentrated hydrochloric acid and saturated with salt. The white solid which separated was filtered and the aqueous solution was extracted with three 30-ml. portions of ether. The residue from the evaporation of the ether was combined with the solid and recrystallized from benzene to give 0.3 g. of pimelic acid, m.p. 104.5–106.5°. A mixture melting point with authentic sample of pimelic acid, m.p. 105–106°, gave no depression.

Valeronitrile.—A mixture of 6.51 g. (0.1 mole) of dry, powdered potassium cyanide and 34.1 g. (0.1 mole) of *n*-butyl stearate in a 250-ml. reaction flask equipped with a stirrer, thermometer, nitrogen inlet, and side arm for distillation was heated by means of a Woods metal bath (at 260° initially) to 350° during 40 min. During the next 8 min. a liquid distilled from the reaction flask. Thirty-four minutes additional heating up to 397° yielded little more distillate. Infrared analysis showed the nitrile to be contaminated with alcohol. Redistillation of the distillate, 6.2 g., yielded 1.63 g. (19.7%) of valeronitrile, b.p. 139.8–140°, n^{35}_{D} 1.3908. The infrared spectrum of the product was identical with an authentic sample of valeronitrile (Eastman Kodak White Label).

---

[13] Infrared analyses were performed by H. J. Sloane and R. A. Nyquist.

Steroids. LXX.[1,2] The Preparation of Some Pentacyclic Steroid Derivatives

Samuel G. Levine, Monroe E. Wall, and Nancy H. Eudy

Natural Products Laboratory, Research Triangle Institute,
Durham, North Carolina

Received January 4, 1963

A recent report[1b] from this laboratory describes the base-catalyzed condensation of acetone with steroidal Δ^{16}-20-ketones to produce pentacyclic products containing a 16,17-butanoandrostane ring system. We describe here an alternate approach to this class of compounds employing a Diels–Alder reaction[3] for the ring forming step.

3β,20-Diacetoxy-pregna-5,16,20-triene (I),[4] prepared by enol acetylation of 16-dehydropregnenolone acetate, reacted readily with dimethyl acetylene dicarboxylate to yield a mixture of epimeric (at C-16) adducts from which the major component, m.p. 197–198°, could be isolated by crystallization in 40–50% yield. The infrared spectrum of this compound contained bands at 1760 (enol acetate), 1730–1740 (esters), and 1640 cm.$^{-1}$ (olefin). These results as well as the elemental analysis, n.m.r. spectrum (see Experimental), and mode of formation are in agreement with structure II for the adduct; the 16β-H configuration proposed for the ring juncture is based solely on the known preference for 16α- attack shown by other addition reactions[5] of 16-dehydro steroids.

Dehydrogenation of the new cyclohexadiene ring of the adduct II was accomplished in 69% yield[6] by treatment with chloranil[7] in refluxing chlorobenzene or simply by boiling in nitrobenzene.[7] The aromatic product III could be crystallized from hexane, cyclohexane, or isopropyl alcohol. In each case, the product melted with evolution of gas within the range 120–130°. The crystals from isopropyl alcohol showed weak hydroxyl absorption in the infrared at 3600 cm.$^{-1}$ and gave an elemental analysis which checked well for one-half molecule of isopropyl alcohol of crystallization. Similarly, a n.m.r. spectrum[8] of the product from cyclohexane crystallization included a sharp singlet at 8.57 (6H) indicating a half mole of solvent of crystallization. Another noteworthy feature of this spectrum was evident in the high field methyl resonance region where two sharp singlets (3H each) were found at 8.91 and 8.98, respectively. The latter absorption peak, present also in the spectrum of the adduct II, may be assigned to the C-19 angular methyl group.[9] The C-18 methyl resonance which in most steroids appears at *higher* field[9] must, in this case, be identified with the *lower* field resonance line. This extreme deshielding of the C-18 methyl resonance is presumably caused by the magnetic anisotropy effect of the nearby aromatic ring.[10]

---

[1] (a) Presented in part at the American Chemical Society Southwest-Southeast Regional Meeting, December 7-9, 1961; (b) Paper LXIX, M. E. Wall, S. Serota, H. Kenney, and G. S. Abernethy, in press.

[2] This work was carried out under contract SA-43-ph-4351 of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health.

[3] Maleic anhydride has already been reported to undergo diene addition reactions with 20-methylene-Δ^{16}-pregnenes and with 20-acetoxy-$\Delta^{16,20}$-pregnadiene derivatives; see F. Sondheimer and R. Mechoulam, *J. Org. Chem.*, **24**, 106 (1959), and references therein cited.

[4] R. B. Moffett and D. I. Weisblat, *J. Am. Chem. Soc.*, **74**, 2183 (1952).

[5] (a) D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951); (b) J. Romo, M. Romero, C. Djerassi, and G. Rosenberg, *ibid.*, **73**, 1528 (1951); (c) H. Hirschmann, E. B. Hirschmann, and M. A. Daus, *ibid.*, **74**, 539 (1952); (d) D. Gould, F. Gruen, and E. B. Hershberg, *ibid.*, **75**, 2510 (1953); (e) G. P. Mueller and B. Riegel, *ibid.*, **76**, 3686 (1954); (f) D. Gould, E. L. Shapiro, L. E. Finckenor, F. Gruen, and E. B. Hershberg, *ibid.*, **78**, 3158 (1956); (g) J. Romo, *Tetrahedron*, **3**, 37 (1958); (h) R. H. Mazur and J. H. Cella, *ibid.*, **7**, 130 (1959); (i) P. F. Beal and J. E. Pike, *J. Org. Chem.*, **26**, 3887 (1961).

[6] A reasonable yield of dehydrogenation product was also obtained from the amorphous epimer mixture remaining after crystallization of the adduct II (see Experimental).

[7] L. M. Jackman in "Advances in Organic Chemistry," Vol. II, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1960.

[8] The n.m.r. spectra were taken in methylene chloride solution on a Varian Associates HR-60 spectrometer using tetramethylsilane as an internal standard (τ = 10.0). We thank Wallace Lawrence of the Chemstrand Research Laboratories for running these spectra.

[9] J. N. Shoolery and M. T. Rogers, *J. Am. Chem. Soc.*, **80**, 5121 (1958).

[10] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, Chap. 7.