rium constant to give a value of the difference in the standard free energy change of combination of the two haptens with antibody. The only assumption underlying our treatment of hapten inhibition data is that inhibition of precipitation is the result of combination of the antibody with molecules of the hapten.

This investigation was carried out with the aid of a grant from The Rockefeller Foundation. Mr. Allan L. Grossberg, Mr. George Cleland, and Mr. Dan Rice aided in the preparation of antigens and haptens and in the analytical work. We are indebted to Professor Dan H. Campbell and Dr. Verner Schomaker for their interest and advice.

Summary

Experiments have been made on the precipitation of antisera homologous to the *o*-, *m*-, and *p*-azophenylarsonic acid groups, prepared by injecting rabbits with sheep serum coupled with diazotized *o*-, *m*-, and *p*-arsanilic acids, with azo-ovalbumins containing these groups, and on the effect of various haptens, mainly substituted phenylarsonic acids, in inhibiting this precipitation.

It has been found that the relative values of the hapten-inhibition constants of the substituted phenylarsonic acids can be in large part accounted for by consideration of the operative intermolecular forces, including electronic van der Waals attraction of the substituent group and the antibody, the formation of hydrogen bonds, and steric hindrance.

PASADENA, CALIFORNIA RECEIVED DECEMBER 26, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

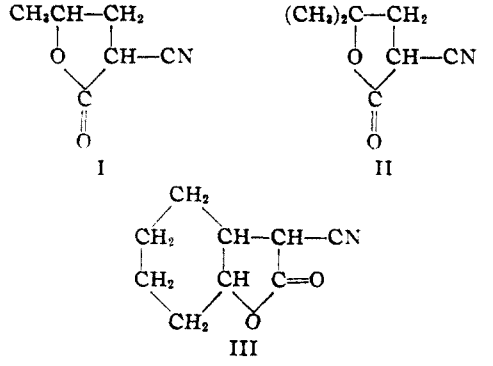
Condensation of Ethyl Cyanoacetate with Alkene Oxides

BY SAMUEL A. GLICKMAN AND ARTHUR C. COPE

The reaction of alkene oxides with the sodium derivatives of ethyl malonate and ethyl acetoacetate has been used as a method for the preparation of α-carbethoxy and α-acetyl-γ-lactones.[1-5] In these condensations, the base (sodium ethoxide) and alkene oxides were used in equivalent amounts. Two instances have been reported in which improved yields were obtained by using two molar equivalents of ethyl malonate.[6,7]

This paper describes the condensation of ethyl cyanoacetate with propylene oxide, isobutylene oxide and cyclohexene oxide, in the presence of one equivalent and one-tenth equivalent of sodium ethoxide, and an investigation of the structures of the reaction products.

Condensation of ethyl cyanoacetate with the three alkene oxides in the presence of one molar equivalent of alcoholic sodium ethoxide proceeded simply to the α-cyano-γ-lactones I, II and III.



I II

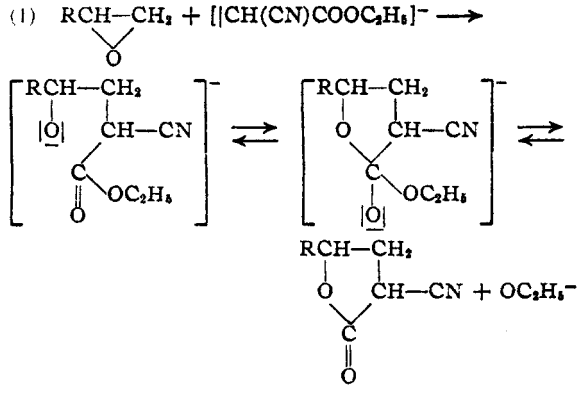
III

The structures of the α-cyanolactones were established by hydrolysis to α-carboxylactones, which were decarboxylated by distillation to known γ-lactones. These γ-lactones were converted to known solid derivatives of the corresponding γ-hydroxy acids by reaction with phenylhydrazine or ammonia. Cleavage of the unsymmetrical alkene oxides by attachment of the enolate anion to the least substituted carbon atom is in agreement with the mode of cleavage observed by Rothstein in reactions with ethyl malonate.[8]

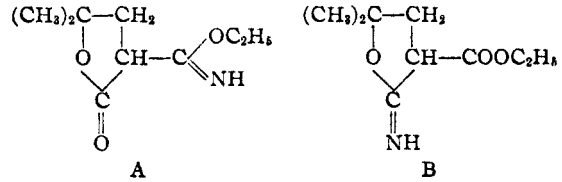
The course of the reaction [7,9-11] is presumed to involve attachment of the enolate anion to the least substituted carbon atom with rupture of the oxide link, lactonization of the resulting anion and elimination of ethoxide ion.

Surprisingly, the expected α-cyanolactone II was not isolated from the condensation of isobutylene oxide with ethyl cyanoacetate in the presence of one-tenth equivalent of sodium ethoxide. Instead, a product IV with the molecular formula $C_9H_{13}NO_3$ (m. p. 64.5–65.5°) was isolated. IV was soluble in dilute hydrochloric acid at room temperature, and hydrolyzed without heating to give α-carbethoxy-γ-isocaprolactone (V). V was identified by hydrolysis to α-

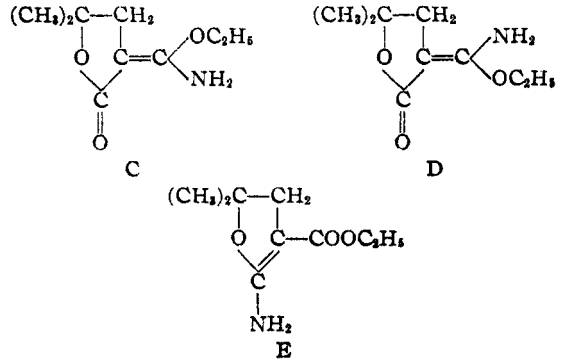
(1) Traube and Lehmann, *Ber.*, **34**, 1971 (1901).
(2) Haller and Blanc, *Comp. rend.*, **143**, 1471 (1906).
(3) Coffey, *Rec. trav. chim.*, **42**, 387 (1923).
(4) Kötz and Hoffman, *J. prakt. Chem.*, **110**, 101 (1925).
(5) Rothstein, *Bull. soc. chim.*, [5] **2**, 80 (1935).
(6) Leuchs, *Ber.*, **44**, 1507 (1911).
(7) Grigsby, Hind, Chanley and Westheimer, THIS JOURNAL, **64**, 2606 (1942).
(8) Rothstein, *Bull. soc. chim.*, [5] **3**, 1936 (1935).
(9) Hudson and Hauser, THIS JOURNAL, **63**, 3162 (1941).
(10) Dubinen and Chelentsev, *J. Gen. Chem.* (U.S.S.R.) **7**, 2368 (1937); *C. A.*, **32**, 2123 (1938).
(11) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 143, 303.



carboxy-γ-isocaprolactone (VI) and decarboxylation to γ-isocaprolactone. These reactions suggest the imino-ester structures A or B, but IV was



found to have an exaltation in molecular refraction (indicating conjugation) which cannot be explained on the basis of these structures, and



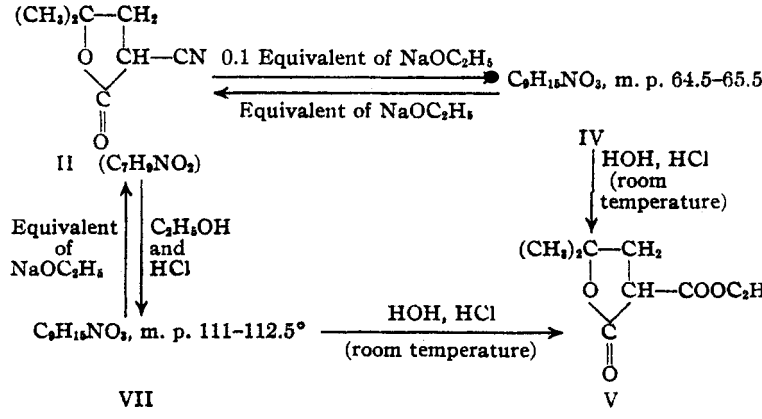
must therefore be one of the tautomeric enamines C, D or E. C and D are geometric isomers. The observed exaltation in refraction (molecular exaltation 2.69, specific exaltation 1.45) is reasonable for C, D or E, and may be compared with the specific exaltations reported for ethyl β-ethoxycrotonate (1.09) and ethyl β-aminocrotonate (2.05).[12] It may be noted that compounds C and E could chelate, with a resulting stabilization. This fact, and the circumstance that *cis–trans* isomers (such as C and D) corresponding to the enolic forms of ethyl acetoacetate and related compounds have not been isolated, combine to make structures C and E more probable than D.

The formation of C or D in the reaction may be explained by addition of alcohol to the nitrile group of II, followed by shift of the hydrogen to the resulting imino group. E could be formed by shift of the α-hydrogen to the imino group in B, the latter arising through internal imino-ester formation from the intermediate acyclic ion in equation (1). In connection with the formation of such structures, it may be noted that the production of imino-esters has been observed to occur in the alkylation of malononitriles,[13,14] and that reversible addition of ethoxide ion to nitriles has been reported.[15]

The α-cyanolactone II has been converted partially to IV by treatment with one-tenth equivalent of sodium ethoxide. This reaction does not exclude formula E, however, because the lactone ring might open and close again through the nitrile group under these conditions. IV was also converted to II by treatment with a molar equivalent of sodium ethoxide.

An independent synthesis of IV was attempted by the reaction of the cyanolactone II with absolute alcohol and dry hydrogen chloride, followed by liberation of the base from the resulting hydrochloride. However, the compound isolated (VII, m. p. 111–112.5°) was isomeric with IV (m. p. 64.5–65.5°). The high melting isomer (VII) was soluble in hydrochloric acid, and was converted to the same series of products (→ V → VI) as the low melting isomer. Treatment with a molar equivalent of alcoholic sodium ethoxide also converted VII into the α-cyanolactone II. These reactions are shown in the equations below.

The presence of closely related conjugated unsaturation in IV and VII is confirmed by their ultraviolet absorption spectra, reported in the following paper. These compounds are believed to correspond to two of the three possible structures C, D and E. The fact that they possess



(12) von Auwers and Susemihl, *Ber.*, **63**, 1072 (1930).

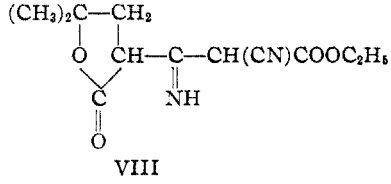
(13) Hesse, *Am. Chem. J.*, **18**, 743 (1896).

(14) Hessler, *ibid.*, **22**, 169 (1899).

(15) Marshall and Acree, *ibid.*, **49**, 127 (1913).

an enamine rather than an imino structure is of considerable interest in connection with the phenomenon of imino-enamine tautomerism and may be compared to the fact that ethyl β-aminocrotonate is an enamine rather than an imino compound.[12]

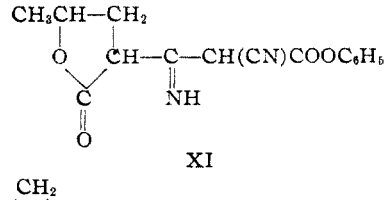
Another product isolated from the condensation of isobutylene oxide with ethyl cyanoacetate in the presence of one-tenth equivalent of sodium ethoxide was VIII. The structure of this compound was established (except for the possibility that it too might be an enamine) by its preparation from isobutylene oxide and ethyl α-cyano-β-iminoglutarate.



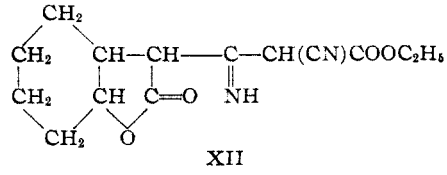
VIII

Condensation of propylene oxide with ethyl cyanoacetate in the presence of one-tenth molar equivalent of sodium ethoxide yielded a homologous enamine, IX, m. p. 39.5–40.5°, with the same exaltation in specific refraction (1.44) as IV. Like the α-cyanolactone II, I was converted to a higher melting isomer of IX (X, m. p. 96–97°) by treatment with absolute alcohol and dry hydrogen chloride. Both isomers were degraded to γ-valerolactone by the method employed for IV and VII. The presence of a similar conjugated system in IX and X is indicated by their absorption spectra, as shown in the following paper, and they are therefore presumed to have the structures of homologs of C, D and E, in which one methyl group is replaced by hydrogen (designated C′, D′ and E′, in the Experimental Part and in the following paper).

A compound XI derived from one mole of propylene oxide and two moles of ethyl cyanoacetate also was isolated from the condensation of these reactants in the presence of one-tenth equivalent of sodium ethoxide. It was proved to have the structure indicated by synthesis from propylene oxide and ethyl α-cyano-β-iminoglutarate.



XI



XII

Condensation of cyclohexene oxide with ethyl cyanoacetate in the presence of one-tenth molar equivalent of sodium ethoxide gave a product XII, corresponding to XI and VIII, whose structure was proved in a similar manner.

Experimental[16]

Ethyl Cyanoacetate–Alkene Oxide Condensations in the Presence of a Molar Equivalent of Sodium Ethoxide.—The following general procedure was used. Sodium (23 g., 1.0 atom) was dissolved in 500 ml. of absolute alcohol in a 1-liter three-necked flask equipped with a mercury-sealed stirrer, reflux condenser, dropping funnel and thermometer. The solution was cooled to 10° and ethyl cyanoacetate (113 g., 1.0 mole) was added. The resulting suspension was stirred for several minutes and one mole of the dry, redistilled alkene oxide was added during five minutes at 10°. The mixture was allowed to come to room temperature during thirty minutes, heated to 50° in the course of thirty minutes and maintained at that temperature until the sodium salt went into solution and an exothermic reaction occurred (after about thirty minutes), which was controlled by cooling. The mixture was then heated at 60° for six hours, after which most of the alcohol was removed by distillation *in vacuo*. Benzene (200 ml.) was added to the red sirupy residue, followed by a mixture of 200 ml. of ice and water and 100 ml. of concd. hydrochloric acid. The benzene layer was separated and the red aqueous layer was extracted with four 100-ml. portions of benzene. The combined benzene solutions were washed successively with water, saturated sodium bicarbonate solution (which removed most of the red color), and water. After preliminary drying over sodium sulfate, the benzene solution was concentrated and the product distilled through a Widmer column *in vacuo*.

α-Cyano-γ-valerolactone (I).—By the above procedure propylene oxide (58 g., 1.0 mole) yielded 86.2 g. of fairly pure I, which on redistillation gave 76.2 g. (61%) of I, b. p. 109° (0.35 mm.); $n^{25}D$ 1.4558; d^{25}_4 1.1555; M_D calcd. 29.19, found 29.42.

Anal. Calcd. for $C_6H_7NO_2$: C, 57.61; H, 5.64; N, 11.20. Found: C, 57.55; H, 5.34; N, 11.30.

I (12.5 g.) was refluxed with 100 ml. of 3 *N* sodium hydroxide for one and one-half hours, at which time evolution of ammonia ceased. The alkaline solution was cooled, treated with a mixture of 50 g. of ice and 30 ml. of concd. hydrochloric acid, and distilled to dryness *in vacuo*. The residual solid cake was refluxed with 100 ml. of alcohol-free ether, and the solution filtered and concentrated. The viscous residue of α-carboxy-γ-valerolactone[17] was decarboxylated by distillation *in vacuo*, yielding 5.4 g. (54%) of γ-valerolactone, b. p. 85° (15 mm.); $n^{25}D$ 1.4310. This lactone was characterized by reaction with phenylhydrazine to give the phenylhydrazide of γ-hydroxyvaleric acid by the procedure described by Wislicenus[18]; m. p. 78–80°.

α-Cyano-γ-isocaprolactone (II).—Isobutylene oxide (72 g., 1.0 mole) by the above procedure yielded 114.4 g. (82%) of II, b. p. 130–131° (1.4 mm.); $n^{25}D$ 1.4515; d^{25}_4 1.1007; M_D calcd. 33.81, found 34.07. II crystallized and was recrystallized from ether and pentane; m. p. 43.0–43.5°.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.40; H, 6.52; N, 10.07; mol. wt., 139.2. Found: C, 60.62; H, 6.72; N, 10.40; mol. wt., 135.4 (b. p. method in chloroform).

II (25 g.) was refluxed for one and one-half hours with a mixture of 50 ml. of concd. hydrochloric acid and 50 ml. of glacial acetic acid. The solution was cooled, filtered from precipitated ammonium chloride, neutralized with sodium carbonate, and extracted with four 50-ml. portions of ether. Distillation of the extracts gave 8.0 g. (40%) of γ-isocaprolactone, b. p. 95° (20 mm.); $n^{25}D$ 1.4312. The lactone was identified by conversion to γ-hydroxyisocaproamide by the procedure described by Strom[19]; m. p. 99°.

(16) Melting and boiling points are uncorrected.

(17) Marburg, *Ann.*, **294**, 122 (1897).

(18) Wislicenus, *Ber.*, **20**, 402 (1887), reports m. p. 76–79°.

(19) Strom, *J. prakt. Chem.*, [2] **48**, 220 (1893), reports m. p. 101°;

α-Cyanohexahydroisocoumaranone (III).—The general procedure was followed with cyclohexene oxide[20] (88.2 g., 0.9 mole), except that quantities were reduced to a 0.9-mole basis. After two fractionations, 25.0 g. (17%) of III was obtained, b. p. 137° (0.35 mm.); $n^{25}D$ 1.4862; d^{25}_4 1.1495; M_D calcd. 41.27, found 40.85.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.48. Found: C, 65.40; H, 6.72; N, 8.33.

III (16.5 g.) was refluxed with 100 ml. of 3 *N* sodium hydroxide until no more ammonia was evolved (four and one-half hours). α-Carboxyhexahydroisocoumaranone[3] was isolated by the procedure described under the hydrolysis of I and decarboxylated by distillation *in vacuo*. Redistillation yielded 9.0 g. (66%) of hexahydroisocoumaranone, b. p. 124–126° (11 mm.); $n^{25}D$ 1.4758. Reaction with phenylhydrazine yielded the corresponding phenylhydrazide,[21] m. p. 167.5–168.5°.

Ethyl Cyanoacetate–Alkene Oxide Condensations in the Presence of One-tenth Molar Equivalent of Sodium Ethoxide

Isobutylene Oxide; Synthesis of IV.—A solution of sodium ethoxide prepared from 1.15 g. (0.05 atom) of sodium and 200 ml. of absolute alcohol was cooled to room temperature and ethyl cyanoacetate (56.5 g., 0.5 mole) and isobutylene oxide (36 g., 0.5 mole) were added. The mixture was heated at 70° for nine hours, after which the red solution was cooled, 16.7 ml. (0.05 mole) of 3 *N* hydrochloric acid was added, and the solution was cooled again. A crystalline product VIII (3.0 g., m. p. 199.5–200.5°) which is described below was separated by filtration. The filtrate was concentrated *in vacuo*, diluted with 150 ml. of water, and extracted with four 100-ml. portions of benzene. The benzene extracts were washed with water and aqueous sodium bicarbonate, dried over sodium sulfate, and distilled *in vacuo*. The yield of crude IV, b. p. 103–110° (0.8–1.2 mm.), was 44.4 g. Continued distillation of the residue resulted in its decomposition. IV could not be purified completely by distillation, but solidified and was purified by recrystallization from 50% ethanol, which yielded 34.0 g. (37%), m. p. 64.5–65.5°, b. p. 135–137° (12 mm.). The supercooled liquid had $n^{25}D$ 1.5032; d^{25}_4 1.0817; M_D calcd. for formulas A and B 46.82, for C, D and E 47.95; found 50.64 (on the basis of formulas C, D and E molecular exaltation 2.69, specific exaltation 1.45).

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.35; H, 8.16; N, 7.57; mol. wt., 185.2. Found: C, 58.60; H, 8.46; N, 7.32; mol. wt., 180.2 (b. p. method in chloroform).

Structure of IV.—IV (12 g.) was dissolved in 75 ml. of 3 *N* hydrochloric acid at room temperature. The solution became warm and an oil separated. After standing for one hour the oil was extracted with benzene and distilled *in vacuo*. α-Carbethoxy-γ-isocaprolactone (V) was obtained, yield 11.2 g. (93%), b. p. 95° (0.5 mm.); $n^{25}D$ 1.4412; d^{25}_4 1.0932; M_D calcd. 44.88; found 45.00.

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.92; H, 7.37.

V (9.3 g.) was refluxed with 60 ml. of 10% sodium hydroxide for one hour. The solution was cooled, 16 ml. of concd. hydrochloric acid was added, and the mixture was distilled to dryness *in vacuo*. The solid residue was boiled with 75 ml. of alcohol-free chloroform for ten minutes. The chloroform solution, after filtration and evaporation, gave a solid residue which was recrystallized from benzene, yielding 7.0 g. of α-carboxy-γ-isocaprolactone (VI) m. p. 98–99°.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.14; H, 6.37. Found: C, 53.02; H, 6.40.

Decarboxylation of VI (5.5 g.) was accomplished by distillation *in vacuo*, which yielded 3 g. (76%) of γ-isocaprolactone, b. p. 95° (20 mm.); $n^{25}D$ 1.4315; d^{25}_4 1.0088; M_D calcd. 29.37, found 29.32. This lactone was identified by conversion to γ-hydroxyisocaproamide, m. p. 98.5–99°.[18]

Interconversion of II and IV.—II (35.5 g.) was added to the sodium ethoxide prepared from 0.5 g. of sodium and 100 ml. of absolute alcohol, and the solution was heated at 60° for twelve hours. After cooling, the solution was acidified with 1.2 g. of glacial acetic acid and the alcohol was removed *in vacuo*. Water (100 ml.) was added to the residue, and the product was extracted with three 75-ml. portions of ether and distilled. The lowest boiling fraction (5.5 g., b. p. 96–99° (0.3 mm.)) was a mixture of IV and II, from which 2.3 g. of pure IV was obtained by crystallization from 50% ethanol; m. p. and mixed m. p. 64.5–65.5°. The highest boiling fraction was recovered II (22.9 g.), b. p. 117–121° (0.7–0.8 mm.); $n^{25}D$ 1.4521.

IV (4.0 g.) was added to the sodium ethoxide prepared from 0.51 g. of sodium and 50 ml. of absolute alcohol, and the solution was heated at 70° for nine hours. After cooling, 25 g. of ice and 7.1 ml. of 3 *N* hydrochloric acid were added. The alcohol was removed *in vacuo* and the residue was diluted with water and extracted with ether. Distillation of the extracts gave 3.3 g. of crude II. On seeding, the distillate crystallized, and after recrystallization from ether and pentane it had m. p. and mixed m. p. with II of 43–43.5°.

Conversion of II to VII.—A solution of II (41.7 g., 0.3 mole) in absolute alcohol (15.5 g., 0.33 mole) and dry ether (40 g.) was cooled in an ice–salt-bath and dry hydrogen chloride was passed through the solution until the increase in weight was 14.5 g. The mixture, which solidified after one hour, was kept in a refrigerator overnight. The solid was filtered rapidly, washed with ether, and added in small portions with vigorous stirring to a mixture of 46 g. of sodium bicarbonate suspended in 500 ml. of water and 250 ml. of ether. The white solid which appeared at the ether–water interface was filtered and dried; yield 46 g. (83%) of VII, m. p. 110–112°. Two crystallizations from 50% ethanol raised the m. p. to 111–112.5°.

Anal. Calcd. for $C_9H_{15}NO_3$: C, 58.35; H, 8.16; N, 7.57. Found: C, 58.28; H, 8.28; N, 7.78.

VII (13.0 g.) was dissolved in 75 ml. of 3 *N* hydrochloric acid. The solution became warm and an oil separated. After one hour it was extracted with benzene and distilled, yielding 11.4 g. (88%) of α-carbethoxy-γ-isocaprolactone (V), b. p. 91° (0.3 mm.); $n^{25}D$ 1.4412. A sample of V from this source (4.7 g.) was identified by saponification in the manner described under structure of IV, which yielded 3.5 g. of α-carboxy-γ-isocaprolactone (VI), m. p. and mixed m. p. with the VI obtained from IV 98–99°.

Conversion of VII to II.—VII (4.0 g.) was treated with a molar equivalent of alcoholic sodium ethoxide under the conditions outlined above for similar treatment of IV. After adding hydrochloric acid, extracting and distilling, 2.0 g. of crude II was obtained, which solidified on seeding, and after recrystallization from ether and pentane was identical in m. p. and mixed m. p. with II.

Structure of VIII.—VIII proved to be identical with the condensation product of isobutylene oxide and ethyl α-cyano-β-iminoglutarate,[22] which was prepared as follows. A solution of sodium ethoxide prepared by dissolving 1.15 g. of sodium in 100 ml. of absolute alcohol was cooled to room temperature and ethyl α-cyano-β-iminoglutarate (11.3 g.) and isobutylene oxide (6.0 g.) were added. The solution was heated at 60° for six hours, cooled, and acidified with 3 g. of glacial acetic acid. The crystalline solid which separated was filtered and recrystallized from alcohol; yield 10.0 g. (80%), m. p. 199.5–200.5° (mixed m. p. with VIII was not depressed).

Anal. Calcd. for $C_{12}H_{16}O_4N_2$: C, 57.12; H, 6.39; N, 11.11. Found: C, 56.82; H, 6.12; N, 11.02.

VIII was also obtained in small yield by adding IV (4.7 g.) to the sodium enolate prepared from ethyl cyanoacetate (2.9 g.) and a solution of 0.12 g. of sodium in 10 ml. of absolute alcohol. The mixture was heated at 60°

(20) "Organic Syntheses," Coll. Vol. I, 2nd edition, John Wiley and Sons, New York, N. Y., 1941, p. 185.

(21) Ref. 3, p. 404 reports m. p. 165.5°.

(22) Baron, Remfry and Thorpe, *J. Chem. Soc.*, **85**, 1736 (1904); Best and Thorpe, *ibid.*, **95**, 1518 (1909).

for five hours, cooled and acidified with 0.3 g. of glacial acetic acid. After refrigerating overnight 0.32 g. of VIII was obtained and identified by m. p. and mixed m. p.

Propylene Oxide; Synthesis of IX.—Propylene oxide (29 g., 0.5 mole) was condensed with 0.5 mole of ethyl cyanoacetate in the presence of 0.05 mole of sodium ethoxide by the procedure described above for isobutylene oxide. Distillation gave 21.6 g. of crude IX, b. p. 103–107° (1.0–1.2 mm.). After purification by crystallization from ether and pentane 13 g. of pure IX was obtained, m. p. 39.5–40.5°. As a supercooled liquid IX had $n^{25}D$ 1.5128; d^{25}_4 1.1233; M_D calcd. for formulas C′, D′ and E′ 43.33; found 45.79 (molecular exaltation 2.46, specific exaltation 1.44).

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.13; H, 7.65; N, 8.18. Found: C, 56.26; H, 7.74; N, 8.31.

Structure of IX.—IX (5.1 g.) was dissolved in 30 ml. of 3 *N* hydrochloric acid at room temperature. After one hour the oil which had separated was extracted with three portions of benzene and distilled. The yield of α-carbethoxy-γ-valerolactone was 4.3 g. (84%), b. p. 108° (1.4 mm.); $n^{25}D$ 1.4418; d^{25}_4 1.1271; M_D calcd. 40.26, found 40.41.

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.81; H, 7.03. Found: C, 56.14; H, 7.26.

A 10.3-g. sample of α-carbethoxy-γ-valerolactone obtained in this manner from IX was refluxed for one hour with 60 ml. of 3 *N* sodium hydroxide. The α-carboxylactone was isolated by the method described under the hydrolysis of I, and decarboxylated by distillation *in vacuo* to γ-valerolactone (4.8 g., 80%), b. p. 94° (19 mm.); $n^{25}D$ 1.4308; d^{25}_4 1.0500; M_D calcd. 24.75; found 24.67. Reaction with phenylhydrazine gave the phenylhydrazide[18] of γ-hydroxyvaleric acid, m. p. 77.5–80°.

Conversion of I to X.—By the procedure which was used to convert II to VII, I (37.5 g., 0.3 mole) yielded 23.5 g. (46%) of X, m. p. 96–97°. This m. p. was not changed by recrystallization from 50% ethanol.

Anal. Calcd. for $C_8H_{13}NO_3$: C, 56.26; H, 7.65; N, 8.18. Found: C, 56.13; H, 7.72; N, 8.13.

X (6.8 g.) was dissolved in 40 ml. of 3 *N* hydrochloric acid. After one hour the oil which separated was extracted with benzene and distilled. α-Carbethoxy-γ-valerolactone was obtained (5.3 g., 78%), b. p. 122° (3 mm.); $n^{25}D$ 1.4419. The α-carbethoxy-γ-valerolactone from this source (5.3 g.) was hydrolyzed to the α-carboxylactone, which on decarboxylation yielded 1.7 g. (55%) of γ-valerolactone, b. p. 80–83° (11 mm.); $n^{25}D$ 1.4307.

Structure of XI.—In a preparation similar to the one described above in which IX was obtained (but conducted on a 1.0-mole scale), the benzene extract containing the crude product was allowed to stand for some time before concentrating. It deposited 26 g. of XI, which after recrystallization from alcohol had m. p 160.5–161°.

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.96. Found: C, 55.45; H, 5.97; N, 11.94.

XI was synthesized as follows. A solution of sodium ethoxide was prepared from 1.15 g. of sodium and 100 ml. of absolute alcohol, and to this was added 11.3 g. of ethyl α-cyano-β-iminoglutarate and 5 g. of propylene oxide. The solution was heated at 60° for four hours, cooled, and acidified with 3.5 g. of glacial acetic acid. XI (8.5 g., 71%) crystallized on standing, identical in m. p. and mixed m. p. with the sample described above.

Cyclohexene Oxide.—Cyclohexene oxide (98 g., 1.0 mole) and ethyl cyanoacetate (113 g., 1.0 mole) were condensed in the presence of 0.1 mole of sodium ethoxide under the conditions described for the isobutylene oxide condensation. The benzene solution of the crude reaction products deposited 18.5 g. of a crystalline solid (XII), m. p. 170.5–171° (raised to 172.5–173° by recrystallization from alcohol).

Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.40; H, 6.52; N, 10.07. Found: C, 60.10; H, 6.49; N, 10.18.

After removal of the benzene from the filtrate, attempted distillation of the residue *in vacuo* resulted in decomposition, and no other pure product was isolated.

The structure of XII was verified by the following synthesis. Ethyl α-cyano-β-iminoglutarate (11.3 g.) was added to 200 ml. of dry benzene and 1.2 g. of powdered sodium. Absolute alcohol (3 ml.) was added, and the mixture was refluxed for three hours. Cyclohexene oxide (10 g.) was then added, and refluxing was continued for fifteen hours. After removing the benzene *in vacuo*, the residue was treated with ice water containing 6 ml. of concd. hydrochloric acid and extracted with ether. Evaporation of the ether and recrystallization of the residue from alcohol gave 0.5 g. of XII, identical in m. p. and mixed m. p. with the product described above.

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Summary

The condensation of propylene oxide, isobutylene oxide and cyclohexene oxide with ethyl cyanoacetate in the presence of one molar equivalent of sodium ethoxide yields the corresponding α-cyano-γ-lactones I, II and III. When one-tenth molar equivalent of sodium ethoxide is employed, isobutylene oxide and propylene oxide give as the principal products crystalline enamines, IV and IX. An enamine VII which is isomeric with IV and an enamine X which is isomeric with IX were obtained by treating the corresponding α-cyanolactones with alcohol and hydrogen chloride and liberating the bases. The possible structures for these pairs of isomers are illustrated in the case of IV and VII by formulas C, D and E.

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