

gion of the double bond stretching vibration. These absorption spectra confirm the chemical evidence for the presence of a double bond in these compounds. In the triethers, the strong absorption at

3.47–3.57 μ is characteristic of the C–H stretching vibration in the alkyl groups and the double bond stretching vibration bands at 6.13–6.18 μ .

BOULDER, COLORADO

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[CONTRIBUTION FROM RESEARCH CENTER, B. F. GOODRICH COMPANY]

β -Propiolactone. X.¹ Reactions with Compounds Containing Active Methylene Hydrogen

BY T. L. GRESHAM, J. E. JANSEN, F. W. SHAVER, M. R. FREDERICK AND W. L. BEBARS

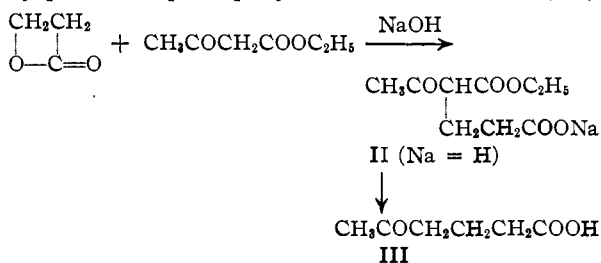
Reactions of β -propiolactone in water or alcohol with ethyl acetoacetate, acetylacetone, benzoylacetone, cyanoacetamide and diethyl malonate are described. The products isolated in all cases were the result of C-alkylation. Some evidence was obtained for the presence of unstable O-alkylates in certain cases.

The reactions of β -propiolactone (I) with salts of inorganic and organic acids are described in previous papers.^{2,3} It was of interest to investigate the reactions of I with the sodio derivatives of compounds containing active methylene hydrogen. In general these reactions were found to be rapid and could be conducted either in water or alcohol. The only products isolated and identified were those resulting from carbon alkylation.

Since the O-alkylated derivatives would be expected to pyrolyze readily and the formation of acrylic acid and the original active methylene compound during redistillation of the crude products was evidence for their presence, none was isolated.

Competing reactions were the hydrolysis of I and the reaction of I at the carboxylate ion in the primary product. No appreciable improvement in the yields of C-alkylation products, which were usually in the range of 40%, was obtained by variation of the reaction conditions. The reactions are unique, however, in that they provide a direct synthesis of the free β -carboxyethyl alkylates. Some of these compounds have not been prepared previously or are difficult to prepare by other means.

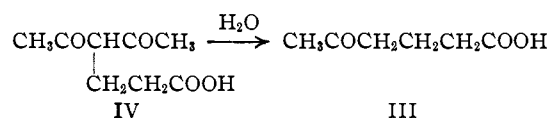
The salt of 4-carbomethoxy-5-oxohexanoic acid (II) is formed rapidly from ethyl acetoacetate and I in aqueous or alcoholic sodium hydroxide. It was difficult to obtain the pure product by distillation because it was contaminated with certain by-products, principally 5-oxohexanoic acid (III)



and in the case of the alcohol reactions, the ester of II. Slow decomposition to acrylic acid and ethyl acetoacetate was observed during the distillation but pure II was stable. This mixture

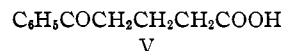
was extracted with two portions of water and redistilled after each washing. Since the compound still was not pure attempts were made to crystallize it at sub-zero temperatures. No crystallization occurred except at the surfaces where the material was exposed to atmospheric moisture. This was shown to be the hydrate and the whole product was recrystallized as the hydrate. Dehydration yielded pure 4-carbomethoxy-5-oxohexanoic acid. The product was readily hydrolyzed to III with dilute base or acid.

Acetylacetone and I in aqueous or alcoholic sodium hydroxide give the salt of 4-acetyl-5-oxohexanoic acid (IV). Slow decomposition to acrylic acid and acetylacetone occurred during distillation, again indicating the presence of unstable O-alkylate in the crude product. Hy-



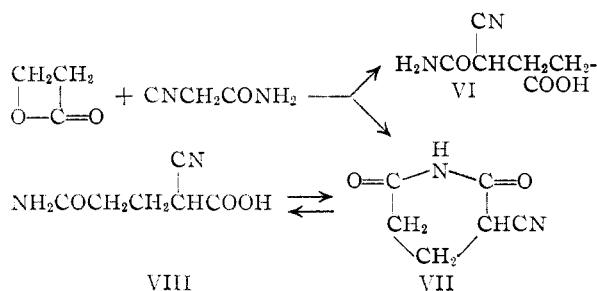
drolysis of IV with base gave III. The competing hydrolysis of I and reaction with the carboxylate ion of II and of IV probably obscured any difference in yield of C-alkylate which might have been expected from the great difference in enol content of ethyl acetoacetate and acetylacetone.

With benzoylacetone the C-alkylate was more readily hydrolyzed with base and thus the only product isolated from the basic reaction solution was γ -benzoylbutyric acid (V).



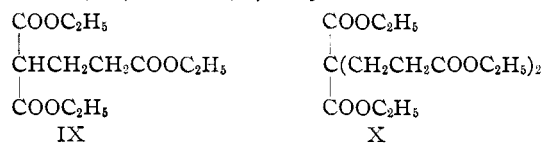
Cyanoacetamide and I in aqueous sodium hydroxide gave the salt of 4-cyanoglutaramic acid (VI), a new compound. In absolute alcohol with sodium ethylate the product was a mixture of VI and 3-cyanoglutarimide⁴ (VII) which was readily separated by crystallization from alcohol. It was not possible to form VII from VI under the conditions of the reaction, or with other dehydrating methods, thus it is not likely that VI is the intermediate in the formation of the cyclic imide, VII. Strong hydrolysis of VII with acid gave glutaric acid. With milder conditions and base the hydrolysis of VII gave a new compound which is

(1) For Paper IX of this series see *THIS JOURNAL*, **72**, 4867 (1950).(2) Gresham, Jansen, Shaver and Gregory, *ibid.*, **70**, 999 (1948).(3) Gresham, Jansen and Shaver, *ibid.*, **70**, 1003 (1948).(4) C. Barat, *J. Indian Chem. Soc.*, **8**, 37–44 (1931).

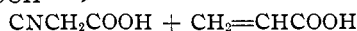


almost certainly the 2-cyanoglutaramic acid (VIII) resulting from cleavage of the amide linkage closest to the cyano group. Cleavage of the other amide linkage would have given VI. The new compound VIII regenerated VII when it was heated above its melting point.

Diethyl malonate does not react readily with aqueous sodium hydroxide and little or no product was obtained by the addition of I. In alcohol and sodium ethylate, however, a mixture of the esters of mono-(IX) and di-(X) alkylate⁵ was obtained.



Cyanoacetic ester was so rapidly hydrolyzed in water and alkali that the addition of I gave only β -(cyanoacetoxy)-propionic acid (XI) by reaction at the carboxyl ion. Attempts to distil this product resulted in rapid pyrolysis to cyanoacetic and acrylic acids. With nitroalkanes in water and $\text{CNCH}_2\text{COOCH}_2\text{CH}_2\text{COOH} \longrightarrow$



sodium hydroxide the addition of I gave ether-soluble oils which readily decomposed to acrylic acid on attempted vacuum distillation. Nitroalkanes generally give O-alkylates with halides.⁶ It is quite likely that the products obtained with I are the unstable O-alkylates.

Experimental

4-Carboethoxy-5-oxohexanoic Acid (II): (a) In Water.—Ethyl acetoacetate (2 moles, 260 g.) was added with vigorous stirring to a cooled solution of 80 g. (2 moles) of sodium hydroxide in 800 ml. of water. The temperature was held below 30° with external cooling and the final mixture was a thick slurry of white solid sodio derivative. β -Propiolactone (144 g., 2 moles) was then added slowly (15 min.) with continued stirring and cooling to maintain the temperature below 30°. After an additional hour the clear solution was acidified with 180 ml. of concentrated hydrochloric acid and the upper organic layer removed by extraction with three 400-ml. portions of ether. The combined extracts were freed of ether by boiling at reduced pressure. The residue was distilled at 1 mm. and after removal of the unreacted ethyl acetoacetate (76 g.), the product was collected at 92–132°, 138 g. (34% yield). On redistillation at 1 mm., acrylic acid and ethyl acetoacetate were collected in the Dry Ice trap. Analysis of the product was unsatisfactory due to contamination with 5-oxohexanoic acid. This mixture was extracted with two 100-ml. portions of water and redistilled after each washing. The hydrate of the final product was crystallized, and recrystallized from alcohol. Since the hydrate could not be dried to a constant weight it was dehydrated in a vacuum oven and distilled, b.p. 121–122° (0.2 mm.); n_D^{25} 1.4500.

(5) Ruzicka, Almeida and Brack, *Helv. Chim. Acta*, **17**, 183 (1934).

(6) Hass and Bender, *This Journal*, **71**, 1767 (1949).

Anal. Calcd. for $\text{C}_9\text{H}_{14}\text{O}_6$: C, 53.42; H, 6.94; neut. equiv., 202; sapon. equiv., 101. Found: C, 53.43; H, 7.12; neut. equiv., 203; sapon. equiv., 100.

A similar mixture also was hydrolyzed at 40–50° in a solution of 80 g. (2 moles) of sodium hydroxide in 250 ml. of water. After standing for one hour the solution was acidified with concentrated hydrochloric acid and the organic layer separated by extracting four times with 300-ml. portions of ether. Distillation of the residue, after removal of ether from the combined extracts, gave 75 g. (29%) of 5-oxohexanoic acid (III); b.p. 140–144° (9 mm.); hydrate, m.p. 35–36°; semicarbazone, m.p. 165–166°.

Anal. Calcd. for $\text{C}_6\text{H}_{10}\text{O}_3$: neut. equiv., 130. Found: neut. equiv., 131.

(b) **In Ethanol.**—Ethyl acetoacetate (292.5 g., 2.5 moles) was added to a solution of 46 g. of sodium in 1200 ml. of absolute alcohol with stirring and cooling at 25°. Two moles (144 g.) of β -propiolactone was added dropwise to this solution maintained at 25° with cooling and vigorous stirring over a period of one hour. After an additional hour the solution was acidified with 180 ml. of concentrated hydrochloric acid, filtered from salt, and the alcohol and water removed by distillation under vacuum. The residue was distilled at 0.7 mm. to give a fraction of crude product; b.p. 54–118°. Redistillation at 0.1 mm. gave 162 g. (35%) of a mixture of products; b.p. 80–112° similar to that obtained in (a) above. Ethyl acrylate and ethyl acetoacetate collected in the Dry Ice trap during redistillation. Saponification of the crude product with sodium hydroxide as in (a) above gave 5-oxohexanoic acid, b.p. 140–144° (9 mm.); semicarbazone, m.p. 165–166°.

4-Acetyl-5-oxohexanoic Acid (IV) (a) In Water.—Acetylacetone (300 g., 3 moles) was added with stirring and cooling at 25° to a solution of 100 g. (2.5 moles) of sodium hydroxide in 800 ml. of water. β -Propiolactone (144 g., 2 moles) was added to this solution at 25° with stirring and cooling over a period of one hour. After an additional hour the solution was acidified with 215 ml. of concentrated hydrochloric acid and the organic layer was extracted three times with 300 ml. of ether. The ether was removed from the combined extracts at reduced pressure and the residue distilled; unreacted acetylacetone (98 g.); b.p. 40–90° (10 mm.) was collected first and crude 4-acetyl-5-oxohexanoic acid was collected as the main fraction; b.p. 124–142° (1 mm.); wt. 142 g. (41.5%). The product slowly crystallized and after recrystallization from benzene-hexane it melted at 73–76°.

Anal. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_4$: C, 55.81; H, 6.98; neut. equiv., 172. Found: C, 55.91; H, 7.12; neut. equiv., 170.

γ -Benzoylbutyric Acid (V).—Operating in a manner similar to that for acetylacetone, 72 g. (1 mole) of β -propiolactone was added to the suspension of 100 g. (0.61 mole) of benzoylacetone in a solution of 40 g. of sodium hydroxide in 500 ml. of water. The unreacted benzoylacetone was removed by filtration. After acidification the filtrate was extracted with ether. The product was removed from the ether with aqueous sodium bicarbonate leaving a residue of benzoylacetone (total recovery 81 g.). Acidification of the bicarbonate solutions, ether extraction, and evaporation gave solid γ -benzoylbutyric acid which was recrystallized from benzene-hexane, m.p. 126°, wt. 9 g. (29%).

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 68.75; H, 6.25; neut. equiv., 192. Found: C, 68.56; H, 6.18; neut. equiv., 194.

4-Cyanoglutaramic Acid (VI).—A suspension of 168 g. (2 moles) of cyanoacetamide in a solution of 80 g. (2 moles) of sodium hydroxide in 600 ml. of water was prepared at 15°. After stirring five minutes the suspension was cooled to 5° and 144 g. (2 moles) of β -propiolactone added rapidly with good stirring. The temperature rose to 72° in three minutes and the resulting solution was red. After 30 minutes the solution was cooled to 20° and acidified with 113 g. of concd. sulfuric acid. Filtration gave 4-cyanoglutaramic acid which, after recrystallization from alcohol-water, melted at 169–170° (with decomposition), wt. 50 g. (16%).

Anal. Calcd. for $\text{C}_6\text{H}_9\text{O}_3\text{N}_2$: C, 46.15; H, 5.13; N, 17.95; neut. equiv., 156. Found: C, 46.06; H, 5.35; N, 17.74; neut. equiv., 158.

(7) Tatevosyan, Melikyan and Tuteryan, *Bull. armenian Branch, Acad. Sci. U. S. S. R.*, No. 516, 37 (1944); *C. A.*, **40**, 3398 (1946).

(8) Ali, Desai, Hunter and Muhammad, *J. Chem. Soc.*, 1013 (1937).

3-Cyanoglutarimide (VII).—Cyanacetamide (189 g., 2.25 moles) was added to a solution of 46 g. of sodium in 1200 ml. of absolute alcohol at 35° and the suspension was stirred until it was well dispersed. β -Propiolactone was added slowly (30 min.) with good stirring and external cooling while keeping the temperature below 50°. After two additional hours the solution was acidified with 113 g. of concentrated sulfuric acid and filtered to remove the crystalline solid. The solid was washed with water and recrystallized from two liters of hot water to give 34 g. (12.3%) of 3-cyanoglutarimide, m.p. 207–208°.⁴

Anal. Calcd. for C₆H₆O₂N₂: N, 20.3. Found: N, 20.4.

The filtrate was concentrated at 15 mm. and the solid which deposited on cooling was filtered, recrystallized from alcohol–water to give 13 g. (4.1%) of 4-cyanoglutaramic acid, m.p. 169–170°. The melting point of a mixture with the 4-cyanoglutaramic acid obtained previously was not depressed.

Attempts to cyclize 4-cyanoglutaramic acid to 3-cyanoglutarimide (VII) by acidifying an alcoholic solution of its sodium salt, by treatment with acetic anhydride containing sulfuric acid or by heating with acids in alcohol gave none of the desired product.

2-Cyanoglutaramic Acid (VIII).—Some of the 3-cyanoglutarimide (6.9 g., 0.05 mole) was dissolved in 50 ml. of water containing 2 g. (0.05 mole) of sodium hydroxide. The solution was heated at 50° for one hour, cooled to 25° and acidified. After standing overnight a crystalline product had separated. This was removed by filtration, the filtrate was evaporated one-half and cooled, a second crop of crystals was obtained. The yield was 4.6 g., 59% of 2-cyanoglutaramic acid, m.p. 142–143° (with gas evolution) after recrystallization from alcohol–water.

Anal. Calcd. for C₆H₈O₅N₂: C, 46.15; H, 5.13; N, 17.95; neut. equiv., 156. Found: C, 46.17; H, 5.16; N, 17.97; neut. equiv., 155.

On continued heating of the melted compound it resolidified and then finally remelted at 208–210°, the melting point for 3-cyanoglutarimide, which it was proved to be by the mixture-melting point method.

Diethyl 2-Carboxyglutarate (IX) and Diethyl 4,4-Bis-carboxypimelate (X).—Diethyl malonate (680 g., 4.25

moles) was added rapidly to a solution of sodium ethylate in alcohol (prepared from 92 g. of sodium and 3 liters of absolute alcohol) with vigorous stirring and the temperature maintained below 40° with external cooling. β -Propiolactone (288 g., 4 moles) was added to this yellow solution over a period of 30 minutes with stirring and controlling of the temperature at 30–35° by use of an ice-bath. After two additional hours during which time some heat was evolved the solution was acidified with 400 ml. of concentrated hydrochloric acid, filtered from salt and the salt washed with alcohol. The combined filtrate and washes were distilled to remove alcohol, some ethyl acrylate and other by-products, until the temperature rose to 100°. The residue was filtered from salt and distilled at 0.5 mm. to give 244 g. (36%) of diethyl malonate, b.p. 48–75°, 588 g. of product, b.p. 75–190° at 0.5 to 2 mm., and 25 g. of tarry residue.

The product fraction was dissolved in an equal volume of ether. The ether solution was washed twice with 800-ml. portions of saturated sodium bicarbonate solutions, twice with 400-ml. portions of water, dried over calcium chloride and distilled at reduced pressure to remove the ether. Distillation of the residue gave two main fractions—(a) diethyl 2-carboxyglutarate,⁵ b.p. 99–108° (0.5 mm.); 233 g. (21.4%); n_D^{20} 1.4319; d_4^{20} 1.0778.

Anal. Calcd. for C₁₂H₂₀O₆: C, 55.5; H, 7.7; sapn. equiv., 87; *MR*_D 62.58. Found: C, 55.3; H, 7.8; sapn. equiv., 85; *MR*_D 62.59.

(b) Diethyl 4,4-bis-carboxypimelate,⁹ b.p. 138–149° (0.3 mm.); n_D^{20} 1.444; d_4^{20} 1.0983

Anal. Calcd. for C₁₇H₂₈O₈: *MR*_D 87.32. Found: *MR*_D, 87.21.

A sample of diethyl 4,4-bis-carboxypimelate was saponified with alcoholic potassium hydroxide to give, after acidification and decarboxylation, 4-carboxypimelic acid,⁹ m.p. 115–116°.

Acknowledgment.—The authors are indebted to J. R. Kubik for microanalyses and to W. P. Tyler and A. K. Kuder for the other analyses.

(9) Bottomley and Perkins, *J. Chem. Soc.*, **77**, 299 (1900).

BRECKSVILLE, OHIO

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[CONTRIBUTION NO. 92 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Action of Formaldehyde on *m*-Hydroxybenzoic Acid. III. Stepwise Degradation of the Lactone of 6-Hydroxymethyl-1,3-benzodioxan-5-carboxylic Acid

By C. A. BUEHLER, ARCHIE V. SLACK, D. A. SHIRLEY, PHILIP A. SANGUINETTI AND SHELDON H. FREY

The lactone of 6-hydroxymethyl-1,3-benzodioxan-5-carboxylic acid has been degraded stepwise by two routes to 4-hydroxybenzene-1,2,3-tricarboxylic acid or a simple derivative of this acid. The results confirm the structure originally assigned to the lactone.

In a previous article¹ the structure of 6-hydroxymethyl-1,3-benzodioxan-5-carboxylic acid lactone was established by its synthesis and the conversion of its permanganate oxidation product into 4-hydroxyphthalide-7-carboxylic acid. Original attempts at structural proof through oxidation in one operation to the hydroxytricarboxylic acid were unsuccessful. However, degradation stepwise by two routes which involved the cleavage of the two non-benzenoid rings in opposite order and which led to 4-hydroxybenzene-1,2,3-tricarboxylic acid or suitable derivatives of this acid were successful. These results, which support the structure originally assigned, are reported in the present paper.

The dioxanyl phthalide I was oxidized with

(1) C. A. Buehler, J. O. Harris, C. Shacklett and B. P. Block, *This Journal*, **68**, 574 (1946).

chromium trioxide in acetic acid² to give the dioxanone II, which on hydrolysis produced the hydroxycarboxylic acid III. Methylation of the latter gave the methoxy acid IV which on oxidation with permanganate yielded the known 4-methoxybenzene-1,2,3-tricarboxylic acid (V). Methylation of the latter produced the known trimethyl-4-methoxybenzene-1,2,3-tricarboxylate (VI).

The oxidation of I to the dicarboxylic acid VII was accomplished with alkaline permanganate followed by careful acidification.¹ To protect the two ortho carboxyl groups in VII, the compound was converted first into the anhydride VIII and then into the imide IX. Oxidation of the latter with chromium trioxide in acetic acid gave the dioxanone X which was converted first into the known 4-hydroxybenzene-1,2,3-tricarboxylic acid

(2) Borsche and Berkhout, *Ann.*, **330**, 92 (1904).