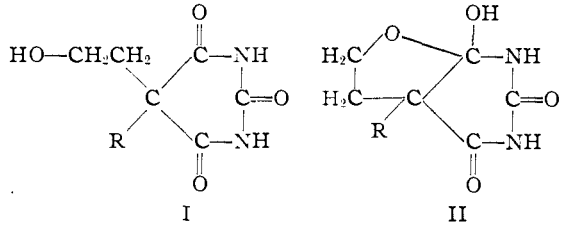
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF DELAWARE]

α-Carboxethyllactones and Related Barbituric Acid Derivatives

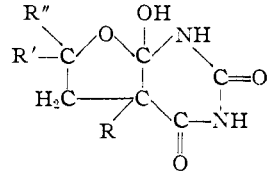
BY GLENN S. SKINNER AND RICHARD DEV. HUBER

A method for the practical synthesis of secondary and tertiary α-carboxethyllactones from unsaturated acid esters using one hundred per cent. sulfuric acid is described. The acidic by-products are the corresponding lactone acids. Both the secondary and the tertiary lactone esters were converted to the 5-ethyl-5-hydroxyalkylbarbituric acids. The fact that the tertiary chloroalkylethylbarbituric acid gives by alkaline hydrolysis the original hydroxy acid with no evidence for the unsaturated compound suggests the possibility of a hemiketal structure. The infrared absorption data, however, indicate the presence of three carbonyl groups and the absorption band for hydroxyl disappears when the hydroxyl is replaced by chlorine. The *cis*- and *trans*-5-ethyl-5-(1-chloro-3-propenyl)-barbituric acids are among the unsaturated compounds that are reported.

Previously the product of the condensation of an α-carboxethyl-γ-butyrolactone with urea has been formulated[1] as an alcohol (I). It can be shown, however, with the Fisher–Hirschfelder models that two isomeric hemiketal structures[2] (II) are possible. Since all of these lactones are derivable from primary alcohols, it was deemed desirable to condense lactone esters (Table II) related to secondary (III) and tertiary (IV) hydroxyalkylbarbituric acids with the object of observing any differences in behavior.



I II



III R′ = CH_3, R″ = H
IV R′ = CH_3, R″ = CH_3

A number of alkenanyl[3] ethylmalonic esters (Table I) have been prepared and used in the preparation of the corresponding barbituric acids (Table III). The lactonization studies were confined to the known ethyl-(3-propenyl)- and ethyl-(2-methyl-3-propenyl)-malonic esters.

The saponification of these malonates to the acid esters caused no difficulty but the procedures in the literature[4] for the formation of lactones from simple unsaturated acids by the use of 50–70% sulfuric acid were unsuccessful. We, therefore, devised a method which, at its best, involves dissolution of the unsaturated acid ester in 100% sulfuric acid at −25°. Sulfuric acid (1.84) can be used also, but the yield of the lactone ester is lowered and the yield of the lactone acid is increased. These lactones are assigned the gamma rather than the delta ring structure on account of the known difficulty[5] of forming delta lactones of this type and the fact also that lactonization is easier at a tertiary or a secondary rather than a primary carbon atom. The assignment of the gamma lactone structure is further supported by the similarity of the infrared spectrograms (Fig. 1-A,B,C) to that of the primary lactone ester which cannot exist as a delta lactone. All measurements were made with the pure liquids. The per cent. transmission in the area 9.4–10.0 microns decreases as the lactone ring varies from primary to tertiary. This may be interpreted as corresponding to an increase in the strength of the bond of this carbon to the oxygen in the lactone ring. The per cent. transmission at 9.0 microns attributable to the bond between the carbonyl carbon and the oxygen of the lactone ring remains at the same level.

It was possible to obtain the customary precipitate of sodium salt from the condensation of the secondary lactone ester with urea (III) but it was not obtained analytically pure. No precipitate of the sodium salt of a product (IV) was obtained from the tertiary lactone ester, but an acid analyzing correctly for 5-ethyl-5-(2-hydroxy-2-methylpropyl)-barbituric acid was obtained in 75% yield. If the lactone ring is opened the compound should behave as a tertiary alcohol. When vigorously

TABLE I

UNSATURATED MALONIC ESTER DERIVATIVES, $C_2H_5RC(CO_2C_2H_5)_2$

R—	B.p., °C. (4.5 mm.)	$MR^{25°}$ Calcd.	$MR^{25°}$ Found	Chlorine, % Calcd.	Chlorine, % Found	$\eta^{25°}$	$\gamma^{25°}$	$d^{25°}_4$
cis-ClHC=CH—CH_2—	116–121	65.32	65.32	13.48	13.33	0.0762	29.6	1.091
trans-ClHC=CH—CH_2—	120–125	65.32	65.18	13.48	13.26	.1092	31.0	1.089
H_2C=CCl—CH_2—	109–111[a]	65.32	64.95	13.48	13.61	.1025	31.4	1.0895
CH_3CCl=CH—CH_2—[b]	109–110[c]	69.90	70.09	12.81	12.65	.0985	30.48[e]	1.0692
CH_2=CH—CH_2—	93–95[a]	60.44	60.31	[g]		.03916	28.8	0.9845
CH_2=CCH_3—CH_2—	100–104[d]	65.0	65.1	[g]		.0553	28.4[f]	0.9828[f]

[a] 2 mm.. [b] Preparation and analysis by George Limperos. [c] 5 mm. [d] 6 mm. [e] 27.5°. [f] 26°. [g] H. A. Shonle, U. S. Patent 2,237,265; *C. A.*, **35**,[2] 4392 (1941).

(1) E. F. Rosenberg, R. F. Kneeland and G. S. Skinner, THIS JOURNAL, **56**, 1339 (1934).

(2) G. S. Skinner, A. E. Stokes and G. S. Spiller, *ibid.*, **69**, 3083 (1947).

(3) Alkenanyl as compared to alkenenyl indicates that the unsaturated radical is linked through a saturated rather than an unsaturated carbon.

(4) R. P. Linstead and H. N. Rydon, *J. Chem. Soc.*, 583 (1933).

(5) A. Michael and N. Weiner, THIS JOURNAL, **58**, 1001 (1936).

TABLE II

LACTONE ESTERS

	α-Carboxethyl-α-ethyl-γ-*n*-valerolactone	α-Carboxethyl-α-ethyl-γ-isocaprolactone
B.p., °C.	113–115 (3 mm.)	127–133 (6 mm.)
d	1.069 (27°)	1.050 (25°)
γ	31.8 (26°)	32.8 (25°)
M.p. (calcd.)	449.5	489
M.p. (obs.)	445 (26°)	487 (25°)
n_D	1.4418 (27°)	1.4432 (25°)
MR_D (calcd.)	49.5	54.1
MR_D (obsd.)	49.4 (27°)	54.0 (25°)
η	0.0785 (27°)	0.1095 (25°)

shaken with fuming hydrochloric acid at room temperature it gave the expected chloroalkyl acid. Aside from the tertiary character of this alcohol the ease with which the reaction proceeds should still be expected since the corresponding primary hydroxy compounds also react with hydrochloric acid to give the chloro derivatives.[6] Alkaline hydrolysis of the tertiary chloride in alcohol, however, gave no trace of unsaturated acid, but instead the original

TABLE III

BARBITURIC ACIDS, $C_2H_5RC(CONH)_2CO$

R—	M.p., °C.	Yield, %	Nitrogen, % Calcd.	Found
cis-ClHC=CH—CH_2—	141–142	74	Cl, 15.38	15.34
trans-ClHC=CH—CH_2—	152–153	65	Cl, 15.38	15.46
HC_2=CCl—CH_2—	188–190	90	Cl, 15.38	15.12
H_3C—CCl=CH—CH_2—	152	63	11.45	11.46
$CH_3CHOHCH_2$—	178–180	81	13.10	13.30
$(CH_3)_2COH$—CH_2—	194	75	12.28	12.35
$(CH_3)_2CCl$—CH_2—	181	55	11.4	11.1

(6) G. S. Skinner, THIS JOURNAL, **59**, 322 (1937).

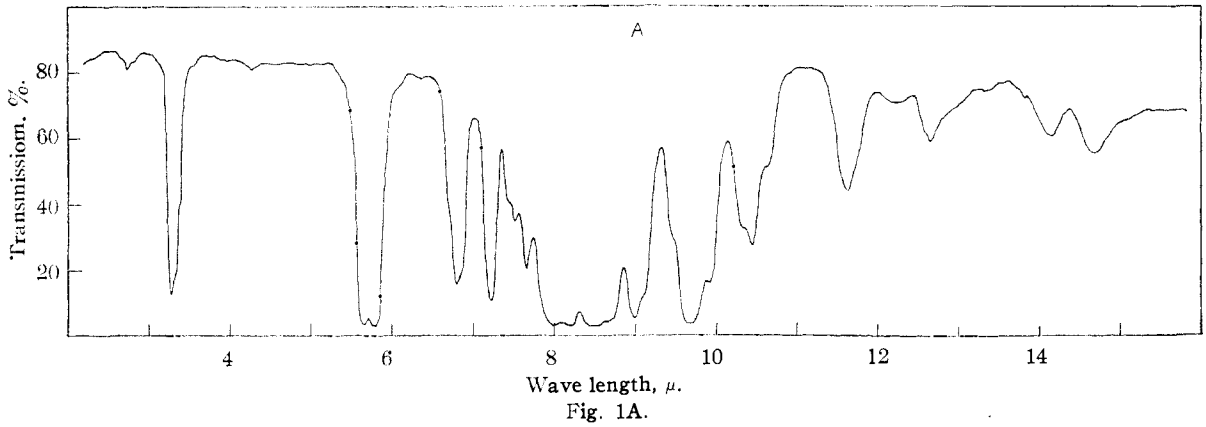


Fig. 1A.

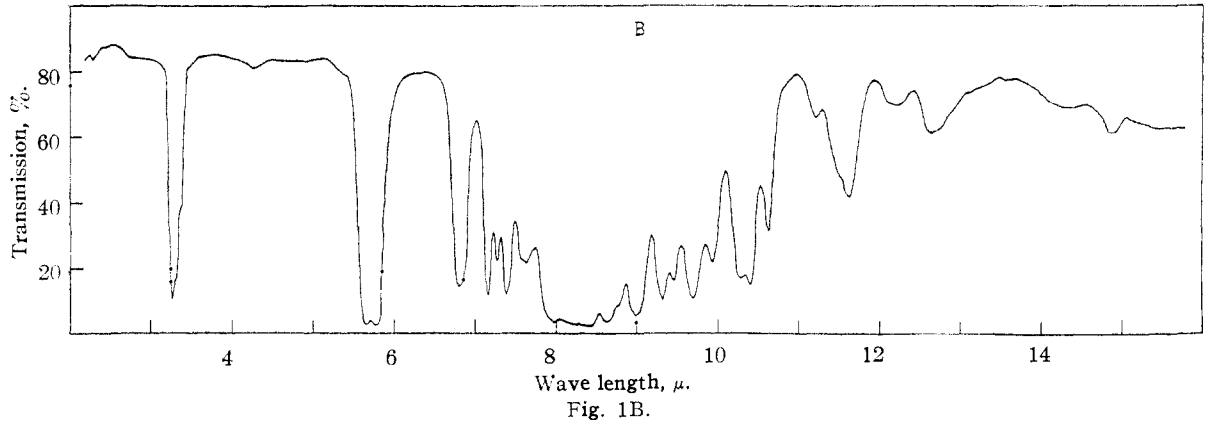


Fig. 1B.

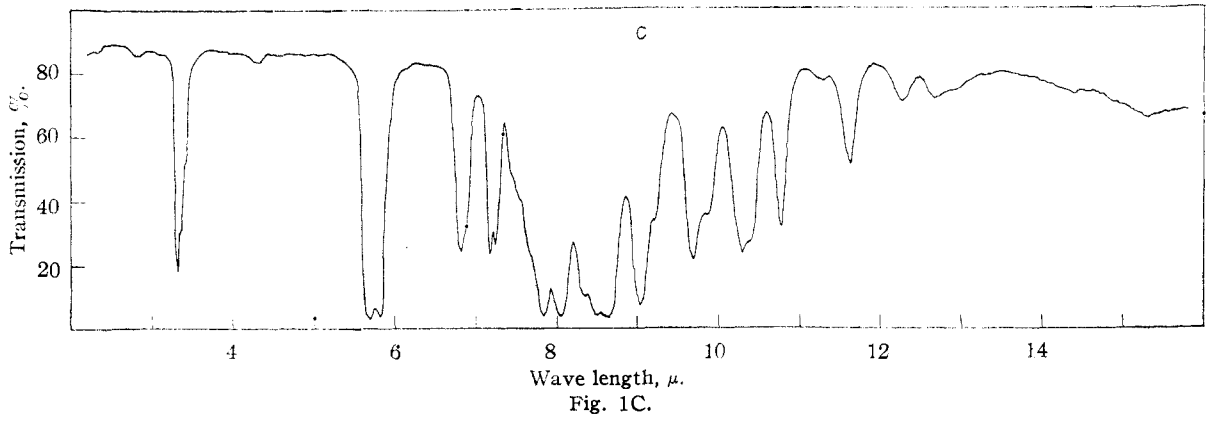


Fig. 1C.

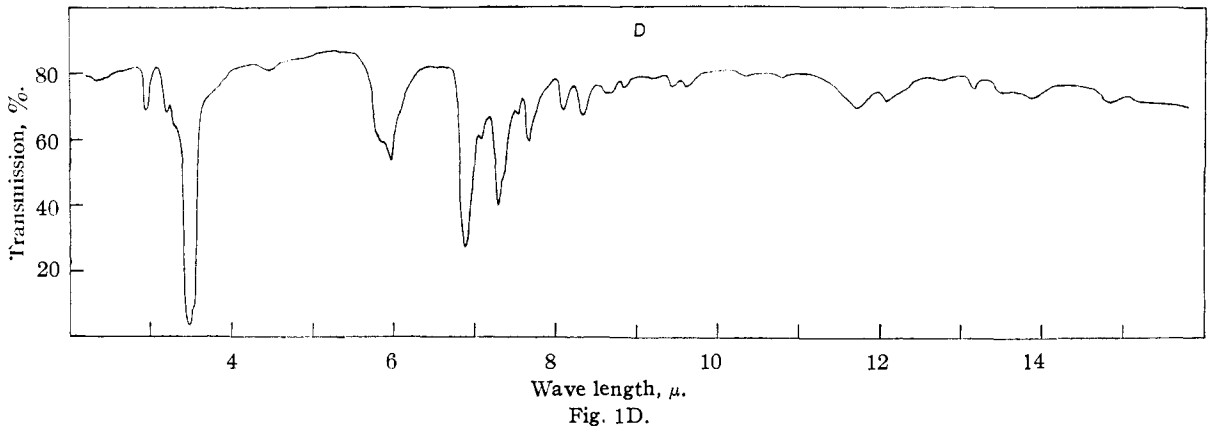


Fig. 1D.

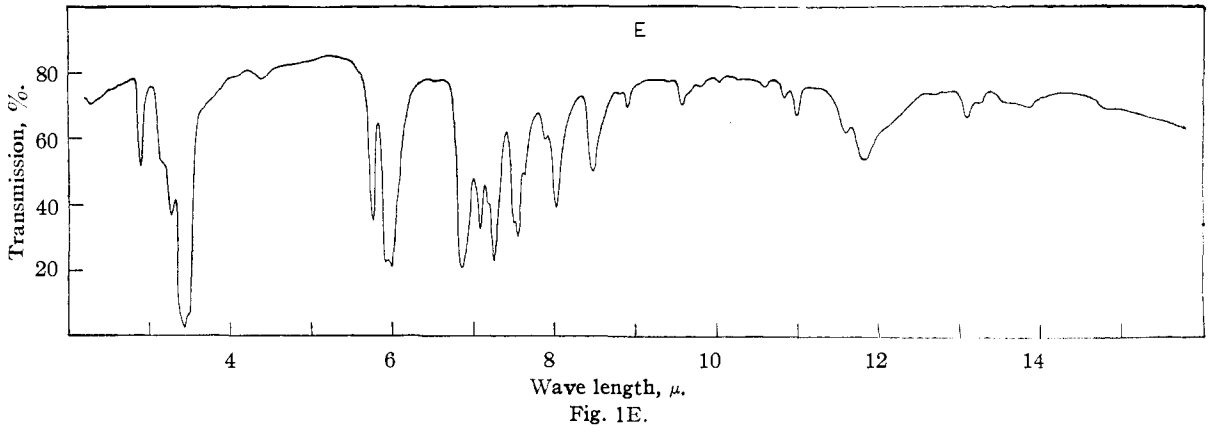


Fig. 1E.

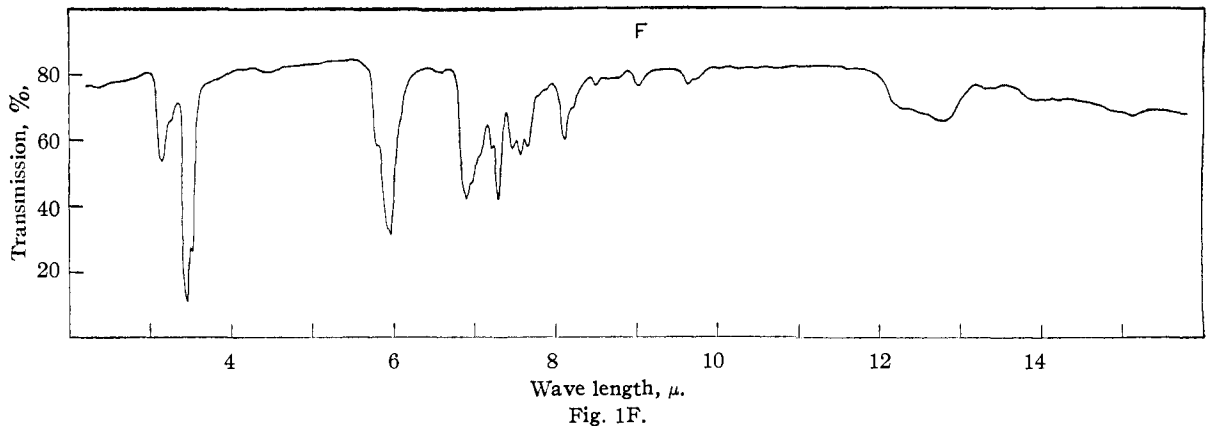


Fig. 1F.

Fig. 1—Infrared absorption spectra. Measurements by R. de V. Huber, Janet Hucks and Mrs. M. P. Kraus under instruction of Dr. Harold C. Beachell. Lactone esters as pure liquids. Barbituric acid derivatives as suspensions in Nujol. A. α-Carboxethyl-α-ethyl-γ-butyrolactone. B. α-Carboxethyl-α-ethyl-γ-*n*-valerolactone. C. α-Carboxethyl-α-ethyl-γ-isocaprolactone. D. 5-Ethyl-5-(β-hydroxypropyl)barbituric acid. E. 5-Ethyl-5-(β-hydroxyisobutyl)barbituric acid. F. 5-Ethyl-5-(β-chloroisobutyl)barbituric acid.

hydroxy acid in a higher state of purity. This recalls our previous observation[2] that the diazotization of a 5-alkyl-5-(β-aminoethyl)-barbituric acid gives no unsaturate but a quantitative yield of the hydroxy acid. The non-formation of unsaturation from the tertiary compound is surprising if, indeed, it possesses the open-chain structure. If the lactone ring remains intact the formation of unsaturated compounds should not be expected. The possibility of the formation of an isomeric chloro compound from the hemiketal is therefore not eliminated by the chemical behavior.

For the lactone esters the absorption in the region 5.6–6.0 μ attributable to the carbonyl of the lactone ring very nearly coincides with that of the carbonyl of the ester group. The same effect holds also for the hydroxyalkylbarbituric acids (D,E) and for the chloroalkylbarbituric acid (F), all of which give indication for three carbonyl groups, although the break for the third carbonyl is scarcely distinguishable in the case of the secondary compound (D). This would appear to deny the existence of the hemiketal structure since it is obvious that the chloro derivative of such a structure could not con-

tain three carbonyl groups. The expected absorption at 2.9 μ for hydroxyl disappears in case of the chloro compound (F) and a distinctive band assignable to the C–Cl bond appears at 12.8 μ.

Experimental

Halides.—The unsaturated halides were redistilled in apparatus with glass joints. The *cis-trans* isomers were fractionated through a column equivalent to fifteen equilibrizations. 2,3-Dichloro-1-propene, b.p. 92–94° (762 mm.); *cis*-1,3-dichloro-1-propene, b.p. 102–104.5° (765 mm.); *trans*-1,3-dichloro-1-propene, b.p. 110–112.5° (765 mm.); 1,3-dichloro-2-butene,[7] b.p. 43° (27 mm.).

Alkenanylethylmalonic Esters.—These esters (Table I) were prepared in the usual way from ethylmalonic ester and the appropriate halide using alcohol as the medium. The yields were 70–80% of the theoretical.

Lactones.—The following procedure for the preparation of the acid esters gave the best results. To a stirred solution of 91.2 g. (0.40 mole) of diethyl ethyl-(3-propenyl)-malonate in 200 cc. of absolute alcohol at 75° there was added during ten hours 22.5 cc. of an aqueous solution containing 16.2 g. of sodium hydroxide. To accomplish this slow addition the dropping funnel was equipped with a suitable capillary tip. After standing overnight the alcohol was removed under diminished pressure from a bath at 50°. The residue by the addition of cold water and extraction with ether gave 16 g. of unreacted ester. The acid ester obtained from the water layer by acidification and extraction was dried *in vacuo* at room temperature with the aid of a capillary, yield 65.0 g. (81.3%); neut. eq. 199, calcd. for $C_{10}H_{16}O_4$, 200.

The acid ester, dissolved in sodium bicarbonate solution, quickly reduced alkaline permanganate and decolorized bromine in carbon tetrachloride. When heated to 160° it evolved carbon dioxide. A single distillation of 71 g. of the acid ester under diminished pressure gave, in addition to unchanged acid ester, 17.3 g. of bicarbonate insoluble material, b.p. 65–70 (20 mm.). After redistillation it gave the usual tests for unsaturation. Calcd. for ethyl ethyl-(3-propenyl)-acetate, $C_9H_{16}O_2$; neut. equiv., 156. Found: neut. equiv., 154. No lactone ester was found.

Attempts to obtain the desired lactone ester by usual procedures[3] for lactones resulting from monobasic unsaturated acids using 50–70% sulfuric acid also gave negative results. The use of enough alcohol to secure a homogeneous mixture increased the formation of the neutral ester but gave no lactone ester.

Precooled 95% sulfuric acid (16.5 cc.) was poured slowly with stirring upon 16.5 g. (0.0825 mole) of ice-cold acid ester. After standing at room temperature for 72 hours the reddish-yellow solution was poured upon 33 g. of finely divided ice. The mixture was saturated with ammonium sulfate and extracted with ether. The ether solution was washed with sodium bicarbonate solution. From the ether solution there was obtained 7.0 g. (42.4%) of the lactone ester and from the bicarbonate layer 6.0 g. (42.4%) of the acidic by-product. When 100% sulfuric acid was used under the same conditions the yield of the lactone ester increased to 47.0% and the yield of the acidic by-product decreased to 34.8%. A solution of the acid ester (0.100 mole) in 20 cc. of 100% sulfuric acid at −25° when allowed to stand four hours at this temperature gave 11.0 g. (55%) of lactone ester and 4 g. (23%) of the acidic by-product.

The purified lactone ester (Table II) did not decolorize alkaline permanganate or a solution of bromine in carbon tetrachloride. *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.1; sapn. eq., 100. Found: C, 59.7; H, 8.5; sapn. eq., 99.3.

The acidic by-product was stable toward bromine and only slowly reduced alkaline permanganate. It gave no test for an alcohol group with ceric nitrate. It was soluble in water and unstable toward heat. Most of the distillate, after heating 20 minutes at 150°, came over at 85–88° (7 mm.). However, the crude products gave a neut. eq. of 190 and a sap. eq. of 90.6. Calcd. for $C_8H_{12}O_4$, 172 and 86. The product reacted with thionyl chloride and then with aniline in benzene. The anilide after recrystallization from alcohol melted at 83–84°. *Anal.* Calcd. for $C_{14}H_{17}O_3N$: N, 5.7. Found: N, 6.1. The by-product is, therefore, the lactone acid.

(7) Crude product furnished by Jackson Laboratory of the du Pont Company.

The acid ester was similarly obtained by partial saponification of diethyl ethyl-(2-methyl-3-propenyl)-malonate. The yield of crude product was 67%. Calcd. for $C_{11}H_{18}O_4$: neut. eq., 214. Found: 193. It lost carbon dioxide when heated for five minutes at 150–170°. The residue did not dissolve in sodium bicarbonate solution. It also rapidly decolorized alkaline permanganate and bromine in carbon tetrachloride. The acid ester (50 g.) when dissolved in 100% sulfuric acid (50 cc.) at −25° and allowed to stand four hours gave 39.0 g. (78%) of lactone ester and 6.5 g. (15% calculated as lactone acid) of the acidic by-product. Both products slowly decolorized permanganate but neither decolorized bromine in carbon tetrachloride. Distillation of the crude lactone ester gave 2.5 g. (b.p. 100–125°, 6 mm.), 31.5 g. of the desired substance (b.p. 127–133°, 6 mm.) and 2.5 g. of residue which solidified upon cooling to room temperature. *Anal.* Calcd. for $C_{11}H_{18}O_4$: C, 61.6; H, 8.5; sap. eq., 107. Found: C, 60.9; H, 8.2; sap. eq., 109.

Attempts to prepare a crystalline anilide of this acidic by-product were unsuccessful. It gave no test for unsaturation. The test with ceric nitrate for an alcohol group was likewise negative. *Anal.* Calcd. for $C_9H_{14}O_4$: neut. eq., 186; sapn. eq., 93. Found: neut. eq., 195; sapn. eq., 94. It is therefore the corresponding lactone acid.

Barbituric Acids.—The higher boiling isomer of diethyl-(1-chloro-3-propenyl)-ethylmalonate (18.4 g.) and 8.4 g. of urea were dissolved in a solution of sodium ethoxide prepared from 4.8 g. of sodium and 90 cc. of alcohol. The mixture was heated to 60° in the course of an hour and then held at that temperature for twenty-four hours. The product obtained in the usual manner weighed 10.5 g., m.p. 140–146°. The pure product (8.8 g.) m.p. 152–153° was obtained by dissolving in 5% NaOH and precipitating with carbon dioxide. This acid (1.2 g.) gave 0.87 g. of ethyl-*n*-propylbarbituric acid, m.p. 146–147°, when hydrogenated with the aid of platinum oxide. From the lower boiling isomer there was obtained 12.0 g. crude product, m.p. 108–115°. This acid was precipitated by carbon dioxide from alkaline solution in poor yield, m.p. 135–140°. It could not be recrystallized from 50% alcohol but could be recrystallized from water, m.p. 141–142°. The mixture of equal quantities of the higher and lower melting isomers melted at 115–118°.

The lactone ester (13.3 g.) from diethyl ethyl-(3-propenyl)-malonate gave according to the previously described procedure[2] 11.3 g. of crude sodium salt. Attempts to purify this for analysis have been unsuccessful. It gave the expected ethyl-(hydroxypropyl)-barbituric acid which after crystallization from alcohol melted at 178–180°. The lactone ester from diethyl ethyl-(2-methyl-3-propenyl)-malonate (14.3 g.) when similarly reacted gave no precipitate of a salt. However, the reaction product when worked up in the usual way gave 11.4 g. of the crude barbituric acid, m.p. 148–156°. This was crystallized four times by dissolving in a minimum of hot dioxane, cooling somewhat and adding twice the volume of petroleum ether, 7.74 g., m.p. 190°.

5-Ethyl-5-(2-hydroxy-2-methylpropyl)-barbituric Acid.—The acid derivative (1.0 g.) was shaken vigorously with 25 cc. of hydrochloric acid (1.19) until dissolved. Most of the reaction product had separated after a half-hour, 0.60 g., m.p. 181° (Table III). Mixed with the hydroxy acid (m.p. 194°) the m.p. was 168–175°. This chloride (3.0 g.) was allowed to stand 24 hours at 25° in a sodium ethoxide solution prepared from 0.60 g. of sodium and 35 cc. of absolute alcohol. After precipitation of the sodium with the aid of dry hydrogen chloride and removal of the alcohol a pasty product remained which was washed on a suction funnel with ice-cold water and petroleum ether, yield of dry product 2.0 g., m.p. 180–190°. After two recrystallizations from alcohol it melted sharply at 194°. Mixed with the previous preparation (m.p. 190°) it melted at 192–193°. This purified sample, like the starting material, did not dissolve in sodium bicarbonate and did not react with permanganate or bromine. Two grams of the hydroxy acid, when heated in an oven at 150° for four hours, melted completely and solidified to a glass after cooling to room temperature. Three crystallizations from dioxane and petroleum ether gave 1.0 g. of material melting definitely at 144°. It gave negative tests for unsaturation and was insoluble in sodium bicarbonate solution. *Anal.* Calcd. for $C_{16}H_{16}O_4N_2 \cdot H_2O$: N, 11.4. Found: N, 11.2. The identity of this substance has not been established.

NEWARK, DELAWARE RECEIVED DECEMBER 6, 1950