[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation and Some Reactions of Ethyl α-Acetamidoacetoacetate

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During the course of our investigations on useful intermediates for amino acid synthesis, we had occasion to prepare and study ethyl α-acetamidoacetoacetate, II. This compound was prepared in quantitative yield by reduction of ethyl α-oximinoacetoacetate, I, in acetic acid–acetic anhydride solution in the presence of a palladium–charcoal catalyst. Zinc dust reduction of I in the same solvent gave 79% of the theoretical yield of II, m. p. 47°.

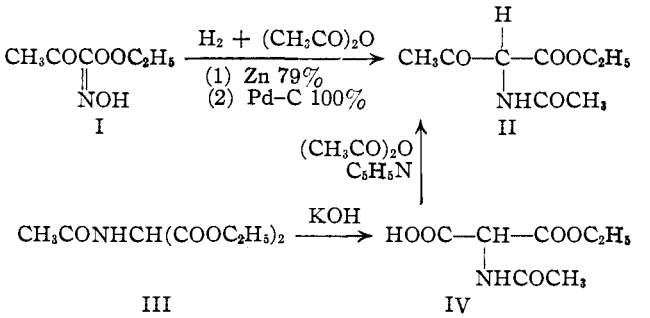
Cerchez and Colesiu[2] reported the preparation of II, m. p. 141°, by reduction of the acetate of I with aluminum amalgam. In view of the discrepancy in melting points we attempted to repeat this work, but were unable to obtain a substance whose properties corresponded with those of the one described. Aluminum amalgam reduction of acetyloximinoacetoacetic ester in the presence of moist ether gave 2,5-dimethyl-3,6-dicarbethoxypyrazine when the suggested method[3] of Cerchez and Colesiu[2] was followed. However, simultaneous addition of acetic anhydride and water to the reaction mixture gave II.[4]

Convincing proof that this low-melting solid, II, was indeed ethyl α-acetamidoacetoacetate was furnished by a fourth method of synthesis. Ethyl acetamidomalonate (III) was saponified to its half-ester with one equivalent of potassium hydroxide. The ester, IV, was then treated with acetic anhydride in the presence of pyridine according to the method of Dakin[5] for converting amino acids to acetamido ketones. The desired compound was obtained as a crystalline solid identical in all respects with the compound obtained in the other preparations. The reactions involved are given in the scheme.

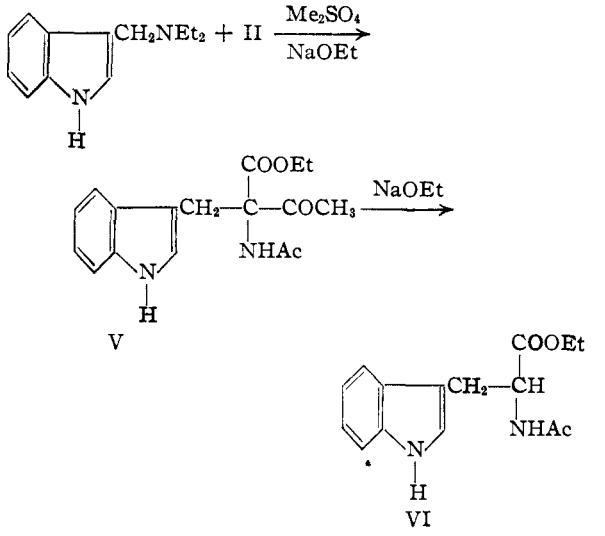
For the preparation of larger quantities of the ester, II, a method was employed whereby the isolation of the oximino-ester, I, was avoided. Aside from possessing the obvious advantage of eliminating several manipulations, the procedure is safer since it obviates the necessity of isolating the oxime. In one experiment the oxime, I, decomposed with explosive violence while being heated on the steam-bath to remove the last traces of solvent. It was possible to obtain II in 70% of the theoretical yield based on ethyl acetoacetate by following the zinc dust reduction procedure described in the experimental part.

The zinc dust method of reduction was also applied to the preparation of α-propionamidoacetoacetic ester.

When the acetamido ester, II was alkylated



with diethylaminomethylindole methosulfate under conditions similar to those used with ethyl acetamidomalonate and gramine[6] the alkylation product, V, was isolated in 83% yield. However,



when there was a delay in adding the dimethyl sulfate to the reaction mixture, no ester, V, could be obtained. When α-acetamidoacetoacetate was warmed with an alcoholic solution of sodium ethylate it cleaved into ethyl acetate and aceturic ester. It was found that V also underwent the same type of cleavage to give N-acetyl tryptophan ethyl ester, VI. This compound was also prepared from ethyl (3-indolylmethyl)-acetamidomalonate for purposes of comparison. Attempts to alkylate

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(2) Cerchez and Colesiu, *Compt. rend.*, **194**, 1954 (1932).

(3) No experimental details were given, but previous publications by these authors give details for aluminum amalgam reduction. However, the authors point out[2] that conditions must be determined for each preparation.

(4) After the cessation of hostilities in Europe one of us (B. F. T.) was able to communicate with Dr. Cerchez at the University of Bucharest. He stated that the m. p. in the literature was a misprint and that the results which he and Colesiu obtained were in agreement with ours.

(5) Dakin, *J. Biol. Chem.*, **78**, 91 (1928).

(6) Albertson, Archer and Suter, THIS JOURNAL, **67**, 36 (1945).

II with benzyl chloride resulted only in cleavage to aceturic ester even when the sodium ethylate was added to the other reactants. Similar cleavage reactions have been observed with other substituted keto-esters.[7]

The behavior of ethyl α-acetamidoacetoacetate on catalytic reduction was examined, since Adkins and Reeve[8] reported that on reduction and subsequent hydrolysis ethyl O-ethyloximinoacetoacetate yielded a mixture of *dl*-threonine and *dl-allo*-threonine which was separated into its diastreomeric components by fractional crystallization from water and ethanol.

It was possible to reduce II in the presence of either Raney nickel or Adams catalyst so that hydrolysis of the intermediate hydroxy-ester led to a mixture of amino acids of approximately the same proportions of threonine and *allo*-threonine in each case. The fractional crystallization method of Adkins was used to separate the mixture into a more soluble fraction, m. p. 225–228°, and a less soluble fraction, m. p. 245–246°. The latter was largely *dl-allo*-threonine, since on benzoylation it gave a monobenzoyl derivative identical with that reported by Carter.[9] Some threonine could be separated from the soluble fraction by benzoylating and using β-phenethylamine according to the procedure of Carter,[10] but more than 75% of the crude hydrolysis mixture was recovered as substantially pure *dl-allo*-threonine. This method is a convenient one for preparing *dl-allo*-threonine since it is possible to obtain over-all yields of 43% based on ethyl acetoacetate via the catalytic reduction route and 41% by the somewhat shorter chemical reduction method.

Experimental[11]

Ethyl α-Oximinoacetoacetate (I).—The procedure of Adkins and Reeve[6] gave 75% yield when petroleum ether (b. p. 60–90°) was added to the toluene to decrease the solubility of the product.

Ethyl α-Acetamidoacetoacetate (II). **A. Catalytic Reduction of Ethyl α-Oximinoacetoacetate.**—One-tenth mole of ethyl α-oximinoacetoacetate was dissolved in a mixture of 50 ml. of acetic anhydride and 150 ml. of acetic acid, 1 g. of 5% palladium–charcoal catalyst[12] added and the mixture subjected to hydrogenation at 50 lb. pressure. After ninety minutes at room temperature the theoretical amount of hydrogen was absorbed. The catalyst and solvent were removed and the residual oil was triturated with petroleum ether (b. p. 60–90°). The crystalline solid thus obtained weighed 18.7 g. (yield quantitative). On crystallization from toluene at −15° it melted at 41–42°.

Anal. Calcd. for $C_8H_{13}NO_4$: N, 7.48. Found: N, 7.35.

When treated with 2,4-dinitrophenylhydrazine the ester yielded a yellow crystalline solid which melted at 199–200° after crystallization from ethanol. Analysis indicated that the derivative was a pyrazolone.

Anal. Calcd. for $C_{12}H_{11}N_5O_6$: N_{total}, 21.80: N_{NO_2}, 8.72. Found: N_{total}, 22.06; N_{NO_2}, 8.96 (by $TiCl_3$ reduction).

B. Reduction of Ethyl α-Oximinoacetoacetate with Zinc Dust.—To a cooled, well-stirred solution of 159 g. of ethyl α-oximinoacetoacetate in 250 ml. of acetic anhydride and 750 ml. of acetic acid, 275 g. of zinc dust was added portionwise during the course of thirty minutes. The temperature was kept at 40° by the addition of the metal. The suspension was stirred for an additional ten minutes and then 750 ml. of water was added at such a rate that the temperature remained at 40°. After stirring for an additional two hours the mixture was filtered and the filter cake washed with two 250-ml. portions of water. The filtrate was extracted with five 250-ml. portions of chloroform and the organic layer then washed with two 200-ml. portions of water. The chloroform was removed by distillation at 30 mm. pressure and the residue triturated with petroleum ether (b. p. 60–90°). The oil crystallized on cooling. The crystals were filtered and air dried, yield, 148 g., 79%, m. p. 47–49°. The dinitrophenylhydrazine derivative melted at 196–197°, undepressed on admixture with the sample prepared above.

C. From Ethyl Acetoacetate Directly.—The oximation of 64 ml. (0.5 mole) of ethyl acetoacetate was carried out according to the method of Adkins and Reeve[8] except that the mixture was not diluted with water. Instead 125 g. of ice and 100 ml. of acetic anhydride were added and the mixture was cooled in an ice-bath. During the course of one hour 125 g. of ice, 50 ml. of acetic anhydride and 65 g. of zinc dust were added to the stirred mixture, while the temperature was maintained below 20°. The product was isolated as in the previous experiment. The yield was 54–59% of the theoretical. When the amount of zinc was increased to 150 g., the yield increased to 71%. The product when recrystallized from acetone or ether melted at 47–49° and was identical with the compounds prepared by methods A or B.

D. From Ethyl Acetamidomalonate.—The ester, IV, was prepared by allowing a solution of 0.1 mole of ethylacetamidomalonate, 0.1 mole of potassium hydroxide in 50 ml. of water and 125 ml. of alcohol to stand for two days. The solvent was then removed, the residue partitioned between 50 ml. of chloroform and 20 ml. of water and the aqueous phase acidified with hydrochloric acid. The solid was collected on a filter, washed with ice water and air dried, m. p. 126–128° (d.).

Anal. Calcd. for $C_7H_{11}O_5N$: N, 7.40. Found: N, 7.15.

Nine and one-half grams of the above acid ester, IV, were slowly added to a mixture of 25 ml. of pyridine and 37 ml. of acetic anhydride with swirling. There was a yellow color produced immediately and carbon dioxide was evolved. The solution was allowed to stand overnight at room temperature and was then diluted with ice. The solvents were removed *in vacuo* to leave 9.2 g. of oil. This was distilled giving 6 g. of product boiling at 93–98° at approximately 1 mm. This product, m. p. 47°, was identical with the samples previously prepared.

When the pyridine and acetic anhydride were distilled from the reaction mixture without prior addition of ice the N-diacetylated compound was obtained as an oil. This gave the same derivative with 2,4-dinitrophenylhydrazine as the monoacetylated compound and could be converted to the monoacetylated compound by warming with sodium bicarbonate.

E. By Aluminum Amalgam Reduction.—Ten and three-tenths grams of Baker aluminum foil was amalgamated by the method of Vogel[13] and covered with 350 ml. of ether. A solution of 34.2 g. of acetyloximinoacetoacetic ester[2] and 35 ml. of acetic anhydride in 50 ml. of ether was dropped in over a ten minute period with simultaneous addition of 6 ml. of water. Two hours later an additional 10 ml. of water was added and the reaction allowed to

(7) Adams, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 269.

(8) Adkins and Reeve, THIS JOURNAL, **60**, 1328 (1938).

(9) Carter, *et al.*, *J. Biol. Chem.*, **129**, 363 (1939).

(10) Carter and Risser, *ibid.*, **139**, 255 (1941).

(11) All m. p.'s are uncorrected.

(12) Mozingo, "Organic Syntheses," vol. 26, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 78D.

(13) Vogel, *J. Chem. Soc.*, 597 (1927).

stand overnight. It was then filtered and the insoluble material washed with ether. When several milliliters of the ether solution were shaken with an aqueous solution of ferric chloride the aqueous layer was colored a deep reddish purple color similar to that obtained with acetamidoacetoacetic ester prepared by the preceding methods.

The ether layer was dried and concentrated to give 17.7 g. of light orange oil. This gave a derivative with 2,4-dinitrophenylhydrazine melting at 201–202.5° and not depressed when mixed with the pyrazolone obtained from acetamidoacetoacetic ester. Nearly all of the oil distilled at 103–106° at 1 mm. and readily crystallized on cooling. It did not depress the m. p. of acetamidoacetoacetic ester prepared by other methods.

When the acetic anhydride was omitted in the above reaction no color with ferric chloride could be obtained and the only product which could be isolated was 2,5-dimethyl-3,6-dicarbethoxypyrazine. When five times as much aluminum was used and no acetic anhydride added, a small amount of *allo*-threonine (m. p. 249° after two recrystallizations from aqueous acetone) separated from the ether solution.

Ethyl α-Propionamidoacetoacetate.—Zinc dust reduction of α-oximinoacetoacetate in the presence of propionic acid and propionic anhydride gave α-propionamidoacetoacetate, m. p. 57° from acetone; b. p. 101–103° at slightly less than 1 mm.

Anal. Calcd. for $C_9H_{15}NO_4$: N, 6.96. Found: N, 7.14.

Ethyl α-Acetamido-α-(3-indolylmethyl)-acetoacetate (V).—To a solution of 0.58 g. of sodium in 50 ml. of absolute alcohol there were added in the order indicated 4.7 g. of ethyl α-acetamidoacetoacetate, 5.1 g. of diethylaminomethylindole and 4.7 ml. of methyl sulfate. The clear solution was warmed on a steam-bath and allowed to stand overnight. It was poured onto dilute acetic acid and the separated solid collected and air-dried, yield, 6.5 g. (83%), m. p. 152–154.5°. Crystallization from dilute ethanol raised the m. p. to 156–159°.

Anal. Calcd. for $C_{17}H_{10}O_4N_2$: N, 8.86. Found: N, 9.06.

Ethyl Aceturate.—To a solution of 1.6 g. of sodium in 40 ml. of ethanol was added 12.5 g. of acetamidoacetoacetic ester. The solution was warmed on a steam-bath. A precipitate started to form within several minutes and the solution darkened in color. After one hour the solution (strong odor of ethyl acetate) was poured onto crushed ice containing some acetic acid and the resulting solution extracted with chloroform. The product was distilled at 92–95° at about 0.5–1 mm. It melted at 44.5–47.5° (lit.[14] b. p. (2 mm.) 106°, m. p. 48°).

N-Acetyl-*dl*-tryptophan Ethyl Ester. (VI). A. From Ethyl Acetamido-(3-indolylmethyl)-malonate.—A mixture of 19.6 g. of ethyl acetamido-3-indolylmethylmalonate, 60 ml. of ethanol, 60 ml. of water and 3.2 g. of potassium hydroxide was allowed to stand at room temperature for two days. It was then concentrated *in vacuo* and partitioned between water (50 ml.) and chloroform. The water layer was acidified with 5 ml. of concentrated hydrochloric acid and the malonic acid collected and washed with water. It was decarboxylated at 160° and the residue taken up in chloroform and washed with 10% sodium carbonate solution and water. Removal of the chloroform gave crystals melting at 128–130°. Recrystallization from aqueous ethanol raised the m. p. to 133.5–135.5°.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: N, 10.21. Found: N, 10.20.

B. From Ethyl α-Acetamido-α-(3-indolylmethyl)-acetoacetate.—This reaction was similar to the preparation of aceturic ester except that the reaction mixture was refluxed for six hours and the product isolated by pouring onto ice and acetic acid and filtering. It proved to be identical with product "A" above.

(14) Cherbuliez and Plattner, *Helv. chim. acta*, **12**, 320 (1929).

***dl-allo*-Threonine. A. Reduction with Raney Nickel Catalyst.**—A quantity of 319 g. of ethyl α-acetamidoacetoacetate in 500 ml. of alcohol was reduced at 1000 lb. pressure in the presence of approximately 10 g. of Raney nickel catalyst. The temperature rose to 68° in the course of the reaction, which was complete in ninety minutes. The catalyst was filtered off (filter-cel) and the solvent removed by distillation at 30 mm. pressure. There remained 315 g. of a colorless, viscous oil, $n^{25}D$ 1.4625. Concentrated hydrochloric acid (800 ml.) was added to this hydroxy ester and the mixture was heated under reflux for three and one-half hours before being concentrated to dryness *in vacuo*. One hundred milliliters of water was added and the mixture taken to dryness again. The crude mixture of hydrochlorides was dissolved in 300 ml. of water in which 70 g. of sodium hydroxide had been dissolved. The solution was made faintly acid to litmus with acetic acid, cooled to 10° and then filtered to yield 85 g. of crude *dl-allo*-threonine, m. p. 245–246°. The mother liquor was diluted with 500 ml. of alcohol and then set in ice for several hours. The crystals that separated were collected on a filter and dried, wt. 70 g., m. p. 225–228°.

The more soluble fraction was then taken up in 150 ml. of hot water, filtered (charcoal) and diluted with 200 ml. of alcohol. On cooling 14 g. more of the *allo* isomer, m. p. 245–248°, separated. The filtrate from this crop was concentrated to dryness and the crystallization repeated several times more. In this way it was possible to obtain a total of 40 g. of the higher-melting compound from the original, more soluble fraction. The crude crops were combined and recrystallized from aqueous ethanol to yield 117 g. of *dl-allo*-threonine, m. p. 251–252° (yield, 58%).

No *dl*-threonine could be isolated directly from the low-melting residue.

In another experiment the low-melting solid from the initial separation was benzoylated according to Carter's method.[9] The crude monobenzoate, m. p. 159–165°, was crystallized several times to raise the m. p. to 172–174°. The substance did not depress the m. p. of an authentic specimen of monobenzoyl-*dl-allo*-threonine. A sample of *dl*-threonine gave a monobenzoate, m. p. 147°, in agreement with the value reported by Carter.

B. Reduction with Adams Catalyst.—When 18.7 g. of ethyl α-acetamidoacetoacetate in 100 ml. of acetic acid was reduced in the presence of 0.3 g. of Adams catalyst, the theoretical amount of hydrogen was absorbed in six hours at room temperature. Removal of the catalyst and evaporation of the solvent left 18.9 g. of the hydroxy ester, $n^{25}D$ 1.4625. Hydrolysis and crystallization by the procedure described above gave 6.9 g. (55%) of pure *dl-allo*-threonine, m. p. 251–252°.

Summary

1. Ethyl α-acetamidoacetoacetate was prepared from ethyl α-oximinoacetoacetate by (a) reduction with hydrogen in the presence of palladium on charcoal in acetic acid–acetic anhydride solution, (b) reduction with zinc dust in acetic acid–acetic anhydride solution, and (c) reduction with aluminum amalgam in the presence of acetic anhydride. In addition it was prepared directly from acetoacetic ester and also from ethyl hydrogen acetamidomalonate by reaction with pyridine and acetic anhydride.

2. Alkylation of ethyl α-acetamidoacetoacetate with diethylaminomethylindole methosulfate gave ethyl α-acetamido-α-(3-indolylmethyl)-acetoacetate. Attempted alkylation with benzyl chloride resulted only in the formation of aceturic ester which was also produced when ethyl α-acetamidoacetoacetate was treated with sodium ethylate.

3. Reduction of ethyl α-acetamidoacetoacetate with either Raney nickel or Adams catalyst afforded, after hydrolysis, *dl-allo*-threonine in 55–58% yield. No *dl*-threonine could be isolated directly.

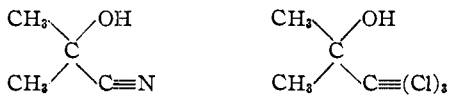
RENSSELAER, NEW YORK RECEIVED SEPTEMBER 16, 1947

[CONTRIBUTION FROM THE GROSVENOR LABORATORY]

The Synthesis of α-Alkoxyisobutyric Acids and Alkyl Methacrylates from Acetonechloroform

BY CH. WEIZMANN, M. SULZBACHER AND E. BERGMANN

From the similarity of acetonecyanohydrin and acetonechloroform the latter appears a possible



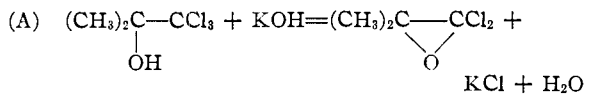
starting material for the preparation of α-hydroxy-isobutyric and methacrylic acid. Equally, its analogs and homologs could be used for the synthesis of the analogs and homologs of these acids.

Literature data regarding the hydrolysis of acetonechloroform and similar compounds are scanty and contradictory: the formation of α-hydroxy-,[1] α-chloro-isobutyric acid and methacrylic acid,[2] *e. g.*, has been observed from acetonechloroform,[3,4] but most of the latter suffers undefined decomposition to acetone, carbon monoxide, phosgene and formic acid.[5]

When acetonechloroform is treated with a solution of four moles of potassium hydroxide or sodium butoxide in *butyl alcohol* at 0°, a vigorous reaction takes place; the alkaline reaction disappears, potassium (or sodium) chloride precipitates in the expected quantity, and the salt of a monobasic acid $C_8H_{16}O_3$ is formed which was identified as *α-butoxy-isobutyric acid.* Every alcohol investigated has given the same reaction which can be formulated as

$$(CH_3)_2C(OH)CCl_3 + 4KOH + ROH = (CH_3)_2C(OR)COOK + 3KCl + 3H_2O$$

As it is surprising that under these conditions a tertiary alcoholic hydroxyl group should be alkylated, the following mechanism is suggested



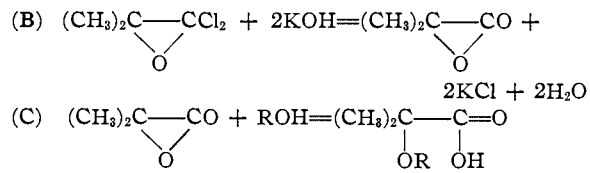
(1) Willgerodt and Schiff, *J. prakt. Chem.*, [2] **41**, 519 (1890).

(2) Ostropjatow, *Ber.*, **29**, Ref. 908 (1896).

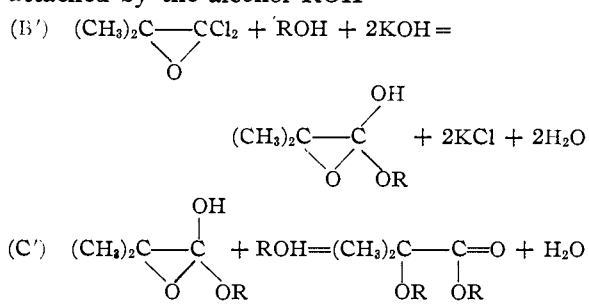
(3) The observations of Thomas and Oxley (British Patent 505,103 (1937) *C. A.* **33**, 7821 (1939)) could not be confirmed; they are theoretically most unlikely.

(4) Trichloromethyl-phenylcarbinol: Jozicz, *Chem. Zentrl.*, **68**, I, 1013 (1897). Rapson, Saunder and Stewart, *J. Chem. Soc.*, **74** (1944). It is doubtful whether the trichloromethylisopropylcarbinol studied by Jozicz actually had that structure; see Howard, THIS JOURNAL, **49**, 1068 (1927).

(5) Compare Bressanin and Segre, *Gazz. chim. ital.*, **41**, I, 671 (1911). See also Peser, *C. A.*, **42**, 514 (1948).



Analogously, the product of step (A) can be attacked by the alcohol ROH



Such esters, indeed, in which the alkyl radicals of the ester and of the ether group are identical, have been observed as by-products.[6]

The intermediary formation of an ethylene oxide from such trichlorinated alcohols and alkaline reagents has already been assumed by Jozicz[4] in order to explain the formation of α-chloroacids in the hydrolysis; this would be due to a pinacolonic re-arrangement, *e. g.*

One might be tempted to assume that the α-alkoxy acids in the above synthesis are formed through the intermediate of these α-chloroacids; however, the high yields obtained would imply that the rearrangement proceeds almost quantitatively, which is unlikely. Moreover, one would rather expect α-chloroacids of such structure to give the corresponding unsaturated acids, upon treatment with alcoholic potassium hydroxide. Methyl methacrylate does not add alcohols under the experimental conditions employed here.

That the acids obtained are actually the α- and not the isomeric β-alkoxy-compounds, can be

(6) The opening of lactone rings by alcohols to form alkoxy acids is not without analogies. See F. E. Küng, U. S. Patent 2,352,641 (*C. A.*, **38**, 5500 (1944)). We owe this observation to one of the Referees. Compare also Aston and Greesburg, THIS JOURNAL, **62**, 2590 (1940).