[Contribution from the Bound Brook Laboratories, Research Division, American Cyanamid Co.]

Ethyl 6-Oxo-8-alkoxyoctanoates[1]

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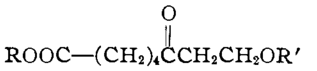
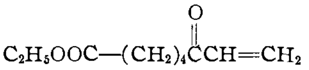
A number of ethyl 6-oxo-8-alkoxyoctanoates have been synthesized by three different procedures. One member of the series was reduced to the corresponding 6-hydroxy compound.

6-Oxo-8-alkoxyoctanoates (I) constitute a hitherto undescribed group of compounds. During the course of work on a proposed synthesis of 6-thioctic acid (protogen, α-lipoic acid) it became desirable to prepare several members of this series. Three methods of synthesis were developed.



$$ROOC{-}(CH_2)_4\overset{\overset{\displaystyle O}{\|}}{C}CH_2CH_2OR'$$

I



$$C_2H_5OOC{-}(CH_2)_4\overset{\overset{\displaystyle O}{\|}}{C}CH{=}CH_2$$

II

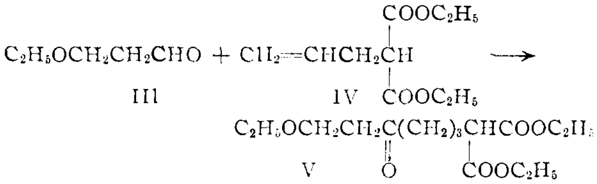
The first procedure (method A) involved the addition of alcohols to ethyl 6-oxo-7-octenoate (II). This approach was convenient and was applicable to a number of different alcohols.

The addition of alcohols to vinyl ketones has been reported[2] several times in the preparation of 4-alkoxybutanones from methyl vinyl ketone and an alcohol. This reaction is usually promoted by the presence of an acid catalyst, the most common one being a mixture of boron trifluoride, mercuric oxide and an alcohol. In the steroid field, alcohols have been added to vinyl ketone structures in base-catalyzed procedures.[3]

The addition of alcohols to other vinyl ketones apparently has not been reported previously.

In the present work methanol, ethanol, *n*-butyl alcohol and benzyl alcohol were added to ethyl 6-oxo-7-octenoate. The reactions were catalyzed by a boron trifluoride etherate–mercuric oxide–methanol mixture, and in one instance by *p*-toluenesulfonic acid. Ethyl 6-oxo-8-alkoxyoctanoates (I) were obtained in yields varying from 5–62%. These yields are not necessarily optimum and represent the amount of analytically pure material obtained. In an attempt to prepare the phenoxy analog (I, R = C_2H_5, R′ = C_6H_5), an exothermic reaction took place but the crude product could not be purified.

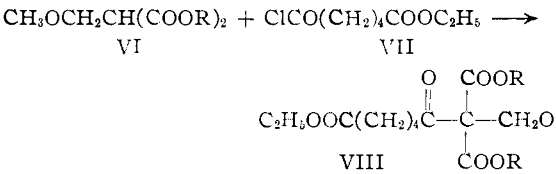
The second procedure (method B) utilized the reaction between an aldehyde and an olefin in the presence of benzoyl peroxide, to yield a ketone.[4] In the present investigation the reaction of a β-alkoxyaldehyde (III) and a substituted malonic ester derivative (IV) bearing an unsaturated bond was used. When III and IV were β-ethoxypropionaldehyde and diethyl allylmalonate, respectively, the product obtained was 2-carbethoxy-6-oxo-8-ethoxyoctanoate (V).



$$\underset{\text{III}}{C_2H_5OCH_2CH_2CHO} + \underset{\text{IV}}{CH_2{=}CHCH_2\overset{\overset{\displaystyle COOC_2H_5}{|}}{\underset{\underset{\displaystyle COOC_2H_5}{|}}{CH}}} \longrightarrow$$

$$\text{V}\quad C_2H_5OCH_2CH_2\underset{\underset{\displaystyle O}{\|}}{C}(CH_2)_3\underset{\underset{\displaystyle COOC_2H_5}{|}}{C}HCOOC_2H_5$$

The third procedure (method C) proved to be the longest and least rewarding of those attempted. In this series of reactions, the acyl malonic ester VIII (R = C_2H_5), was prepared from diethyl methoxymethylmalonate (VI, R = C_2H_5) and ethyl adipoyl chloride (VII).



$$\underset{\text{VI}}{CH_3OCH_2CH(COOR)_2} + \underset{\text{VII}}{ClCO(CH_2)_4COOC_2H_5} \longrightarrow$$

$$\underset{\text{VIII}}{C_2H_5OOC(CH_2)_4\overset{\overset{\displaystyle O}{\|}}{C}}{-}\overset{\overset{\displaystyle COOR}{|}}{\underset{\underset{\displaystyle COOR}{|}}{C}}{-}CH_2OCH_3$$

Attempts were then made to hydrolyze and decarboxylate VIII (R = C_2H_5) to the oxo acid I (R = H, R′ = CH_3). Excessive decomposition resulted and none of the desired product could be isolated. This probably was due[5] to cleavage of the bond between the carbonyl carbon and the carbon bearing the two carbethoxy groups.

The formation of VIII (R = C_2H_5) *via* the sodium salt of VI proceeded smoothly, although the initial formation of the sodium salt was slow. An attempt also was made to carry out the reaction by use of the corresponding magnesium[6] salt, but met with no success.

It later was established[7,8] that the desired oxo acid could be obtained if VIII (R = C_2H_5) were replaced by VIII (R = $CH_2C_6H_5$). This benzyl ester was obtained by transesterifying VI (R = C_2H_5) with benzyl alcohol. The resultant dibenzyl methoxymethylmalonate was then treated, as the sodium salt, with ethyl adipoyl chloride and presumably yielded VIII (R = $CH_2C_6H_5$). When this crude ester without purification was treated with hydrogen over palladium-charcoal catalyst, debenzylation occurred, and the product thus obtained lost two moles of carbon dioxide on refluxing in ethanol. The crude decarboxylation product gave both bicarbonate-soluble and bicarbonate-insoluble

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[1] Presented before the Division of Medicinal Chemistry, 126th Meeting, American Chemical Society, New York, N. Y., September 15, 1954.

[2] D. B. Killian, G. F. Hennion and J. A. Nieuwland, This Journal, **58**, 892 (1936); N. A. Milas, E. Sakal, J. T. Plati, J. T. Rivers, J. K. Gladding, F. X. Grossi, Z. Weiss, M. A. Campbell and H. F. Wright, *ibid.*, **70**, 1597 (1948); W. Oroshnik and A. D. Mebane, *ibid.*, **71**, 2062 (1949).

[3] D. K. Fukushima and T. F. Gallagher, *ibid.*, **73**, 196 (1951); H. Hirschmann, F. B. Hirschmann and M. A. Daus, *ibid.*, **74**, 539 (1952).

[4] M. S. Kharasch, W. H. Urry and B. M. Kuderna, *J. Org. Chem.*, **14**, 248 (1949); E. C. Ladd, U. S. Patent 2,577,133, Dec. 4, 1951; Ng. Ph. Buu-Hoi, *Rec. trav. chim.*, **72**, 84 (1953).

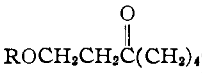
[5] R. E. Bowman, *Nature*, **162**, 111 (1948).

[6] B. Riegel and W. M. Lilienfeld, This Journal, **67**, 1273 (1945).

[7] R. E. Bowman, *J. Chem. Soc.*, 322 (1950).

[8] R. E. Bowman, *ibid.*, 325 (1950).

TABLE I

PROPERTIES OF ETHYL 6-OXO-8-ALKOXYOCTANOATES 

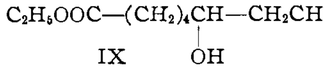
$ROCH_2CH_2\overset{\overset{O}{\|}}{C}(CH_2)_4COOC_2H_5$

R	Yield, %	B.p. °C.	B.p. Mm.	n^tD	t, °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	62 (44)[a]	103–108	2	1.4400	25	61.2	61.2	9.31	9.19
C_2H_5	55	108	0.45	1.4370	26	62.7	62.7	9.64	9.59
n-C_4H_9	39	135–136	.55	1.4390	31	65.1	65.1	10.1	9.98
$C_6H_5CH_2$	5	146–147	.60	1.4940	25	69.8	69.6	8.27	8.32

[a] Catalyst was *p*-toluenesulfonic acid.

fractions. The former was identified as 6-oxo-8-methoxyoctanoic acid (I, R = H, R′ = CH_3), while the latter appeared to be the corresponding ethyl ester, but was not characterized definitely as such.

Treatment of I (R = C_2H_5, R′ = CH_3) with sodium borohydride resulted in the reduction of the oxo group and yielded the corresponding 6-hydroxy compound IX.



$C_2H_5OOC{-}(CH_2)_4\underset{\underset{OH}{|}}{CH}{-}CH_2CH_2OCH_3$

IX

Acknowledgments.—The authors wish to thank Mr. O. E. Sundberg and his group for the microanalytical determinations. We are indebted to Mr. P. Drenchko and to Mr. W. B. Neier and his group for the preparation of several intermediates.

Experimental

Ethyl 6-Oxo-7-octenoate (II).—This compound[9] was prepared by the addition of ethylene to ethyl adipoyl chloride in the presence of aluminum chloride.

Ethyl 6-Oxo-8-alkoxyoctanoates (I). Method A.—A catalyst mixture was prepared by heating and shaking 0.25 g. of red mercuric oxide, 0.25 ml. of boron trifluoride etherate and 2 ml. of dry methanol in a 50-ml. flask for five minutes. The alcohol (10 ml.) was added to the cooled flask and was followed by a solution of 25 g. (0.135 mole) of ethyl 6-oxo-7-octenoate (II) in 30 ml. of the alcohol. The reaction was usually mildly exothermic. When the temperature of the mixture began to drop, the flask was heated on the steam-bath for 30 minutes to 3 hours and then allowed to stand at room temperature for as long as 11 days. The contents of the flask were neutralized with anhydrous potassium carbonate or alcoholic sodium methoxide, filtered and the excess alcohol removed. The residue was then fractionally distilled. The properties of the products thus obtained are listed in Table I.

Ethyl 2-Carbethoxy-6-oxo-8-ethoxyoctanoate (V) Method B.—A vigorously stirred mixture of 51 g. (0.5 mole) of β-ethoxypropionaldehyde[10] and 0.5 g. of benzoyl peroxide was heated at 80–85°, while 20 g. (0.1 mole) of diethyl allylmalonate[11] was slowly added (about two hours). Two additional 0.5-g. portions of benzoyl peroxide were added two and four hours after the malonate addition had been completed. Heating and stirring were continued for a total of 26 hours. The solution was then cooled to room temperature and washed with 50 ml. of water followed by two 50-ml. portions of 5% sodium bicarbonate solution and another 50-ml. portion of water. The oil was then taken up in ether and dried over sodium sulfate. The ether was removed by distillation and the residue was fractionally distilled. The two main fractions, b.p. 90–93° (12 mm.) and 120–124° (14 mm.) were combined and redistilled through a Vigreux column to yield 4.3 g. (14%) of V, b.p. 127–132° (13–14 mm.), n^{26}D 1.4468.

Anal. Calcd. for $C_{15}H_{26}O_6$: C, 59.6; H, 8.69. Found: C, 59.4; H, 8.76.

Method C. Ethyl 6-Oxo-7,7-dicarbethoxy-8-methoxyoctanoate (VIII, R = C_2H_5).—A slurry of 4.25 g. (0.18 g. atom) of sodium sand in 370 ml. of anhydrous ether was prepared and to it was added slowly 37.5 g. (0.18 mole) of diethyl β-methoxymethylmalonate.[12] The mixture was stirred overnight and then refluxed for four hours. It was cooled to room temperature and 35.3 g. (0.18 mole) of ethyl adipoyl chloride was added over a period of 25 minutes. When heat evolution had ceased, the mixture was stirred at room temperature for 2.5 hours. The solids were then dissolved by the cautious addition of 150 ml. of water. The two resultant layers were separated and the aqueous portion was extracted with three 100-ml. portions of ether. The extracts were combined with the organic phase and dried over sodium sulfate. The ether was removed and the residual oil was distilled over a free flame to give 34 g. of product, b.p. 146° (0.15 mm.). Redistillation of a fraction boiling at 140.5–146° (0.15 mm.) gave an additional 8 g. of the product, b.p. 144–148° (0.15 mm.). The combined yield was 42 g. (63%), n^{25}D 1.4457.

Anal. Calcd. for $C_{17}H_{28}O_8$: C, 56.6; H, 7.83. Found: C, 56.4; H, 7.67.

Attempted Hydrolysis and Decarboxylation of VIII (R = C_2H_5).—Small samples of VIII (R = C_2H_5) were treated with various strengths of sulfuric acid at temperatures up to 160–165°. In no case was the theoretical amount of carbon dioxide evolved. When 10 *N* sulfuric acid was used, about 70% of the expected amount of carbon dioxide was obtained, but extensive decomposition also took place.

6-Oxo-8-methoxyoctanoic Acid (I, R = H, R′ = CH_3).—A slurry of 2.3 g. (0.1 g. atom) of sodium sand in 100 ml. of dry benzene was prepared and to it was added a solution of 20.4 g. (0.1 mole) of diethyl β-methoxymethylmalonate in 60 ml. of dry benzene. The mixture was stirred overnight. A white slurry resulted and to it was added 21.6 g. (0.2 mole) of benzyl alcohol (purified by heating with Raney nickel[8]). The mixture was distilled at atmospheric pressure, through a one-foot column packed with helices, at a reflux ratio of 5:1. When the temperature reached 78.8°, the reaction was considered complete. The residue was cooled and to it was slowly added 18.8 g. (0.097 mole) of ethyl adipoyl chloride in 50 ml. of dry ether. The mixture was refluxed for 30 minutes, cooled and poured into ice and water containing a trace of sulfuric acid. The benzene layer was separated and, together with four 200-ml. benzene extracts of the aqueous phase, dried over sodium sulfate. The benzene was removed under reduced pressure and the residue was heated at 80° (0.23 mm.) for 90 minutes.

The crude VIII (R = $C_6H_5CH_2$) (41.9 g.) was dissolved in 150 ml. of absolute ethanol and stirred for one hour with 4 g. of Raney nickel. The solution was filtered and hydrogenated over 1 g. of 10% palladium-on-charcoal catalyst at a temperature under 30°. The catalyst was readily poisoned and two additional 1-g. portions were added. A total of 3.35 l. (76%) of hydrogen was absorbed. After the catalyst was removed, the alcoholic solution was refluxed and a small amount of carbon dioxide was evolved. The solvent was then removed by distillation, some additional gas evolution being noted. The residue (26 g.) was dissolved in ether and extracted with saturated aqueous sodium bicarbonate. The ether layer was then washed and dried, and the solvent removed to give 11.8 g. of material which decomposed on distillation.

The bicarbonate extracts were acidified to *ca.* *p*H 2–3 with dil. hydrochloric acid, and the precipitated oil was extracted with ether. The extracts were combined, washed with water and dried over sodium sulfate. Removal of the solvent left 11.6 g. of material which evolved *ca.* 400 ml. of carbon dioxide when heated to 200°. The residue was dis-

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[9] M. W. Bullock, *et al.*, THIS JOURNAL, **74**, 3455 (1952).

[10] Obtained from Matheson, Coleman and Bell, Inc., and redistilled before use.

[11] R. T. Arnold, M. de M. Campos and K. L. Lindsay, THIS JOURNAL, **75**, 1044 (1953).

[12] J. L. Simonsen, *J. Chem. Soc.*, **93**, 1780 (1908).

tilled. The forerun and residue were discarded, and the center fractions combined and redistilled to give 2.2 g. of 6-oxo-8-methoxyoctanoic acid, b.p. 125–129.5° (1.3 mm.).

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.4; H, 8.57. Found: C, 57.4; H, 8.49.

Ethyl 6-Hydroxy-8-methoxyoctanoate (IX).—Solid sodium borohydride (0.4 g., 0.011 mole) was added in several portions to a solution of 5 g. (0.023 mole) of ethyl 6-oxo-8-methoxyoctanoate in 25 ml. of dry methanol. Heat was generated and the temperature rose to about 50°. The mixture was refluxed for 30 minutes, after which the methanol was removed by evaporation. Water (20 ml.) was added to the residue, and the mixture was heated for 30 minutes, and allowed to stand overnight. The organic layer was withdrawn and combined with three 10-ml. chloroform extracts of the aqueous phase. The organic solution was washed with 10 ml. of dilute sulfuric acid and two 10-ml. portions of water and dried over a mixture of sodium sulfate and sodium bicarbonate. The dried solution was filtered, and the chloroform evaporated to leave 5.1 g. of a yellow liquid which was fractionally distilled to give 2.1 g. (42%) of ethyl 6-hydroxy-8-methoxyoctanoate, b.p. 153–160° (13 mm.), $n^{25}D$ 1.4435.

Anal. Calcd. for $C_{11}H_{22}O_4$: C, 60.6; H, 10.1. Found: C, 60.6; H, 10.1.

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Organic Peroxides. XX. Peroxides from the Ozonization of Olefins in the Presence of Carbonium Ions

BY NICHOLAS A. MILAS, PAULS DAVIS[1] AND JOHN T. NOLAN, JR.

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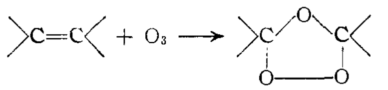
A countercurrent method for the efficient ozonization of olefins has been developed. Several olefins have been ozonized in *t*-butyl alcohol containing *t*-butylcarbonium ions. In several cases, especially with unsymmetrical olefins, two isomeric peroxides containing *t*-butoxy groups were identified from their decomposition products. Some of these products were identified as hydroperoxides containing *t*-butoxy groups. The simplest of these was *t*-butoxymethyl hydroperoxide which also was synthesized by an independent method. A mechanism has been proposed to account for the formation of the initial peroxides as well as those produced as their decomposition products. Since alkylidene peroxides were not isolated from the ozonization products of olefins in the presence of *t*-butylcarbonium ions, the zwitterions responsible for their formation were not produced during the ozonization. Several olefins were also ozonized in non-aqueous solvents and, with the exception of tetraphenylethylene, the yields of alkylidene peroxides were low indicating that the main products were the ozonides.

Introduction

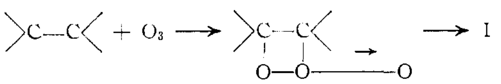
The direct attack of double bonds by ozone has been known for a long time, but in spite of the immense knowledge in this field only recently has the mechanism being elucidated. It is now known with certainty that ozone cleaves double bonds and through the researches of Rieche, *et al.*,[2] the structure of ozonides has been clarified. The simplest explanation of the ozonization of a double bond is illustrated by equation 1.



(1)

I-ozonide

However, it is very difficult to visualize under the extremely mild conditions of ozonization, how the double bond is completely cleaved and the above ozonide formed in one step. Staudinger[3] was the first to suggest that an unstable "molozonide" II is initially formed which rearranges to the more stable ozonide (I).

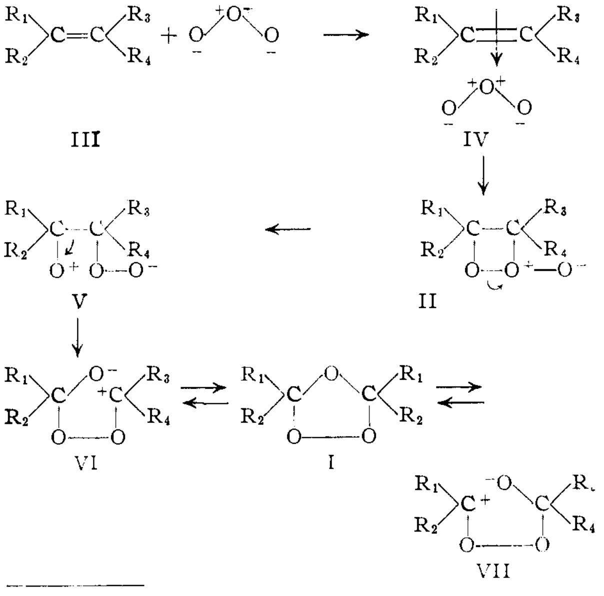


(2)

II

To explain this rearrangement Criegee[4] proposed that the molozonide undergoes an intramolecular change with the momentary formation of a positively polarized oxygen atom which abstracts the remaining two electrons from the carbon–carbon bond and rearranges into the neutral ozonide. The whole process of ozonization therefore may be viewed as an ionic reaction in which the ozonide acts as an electrophilic reagent.

The polar nature of ozone has been established by Lewis and Smyth[5] who proposed that the middle oxygen atom is positively polarized, thus the structure most generally accepted for ozone is the obtuse-angled structure with the oxygen at the apex being positive. Under the influence of the polar ozone molecule a double bond is also polarized in such a manner that the π-electrons attach themselves to the positive oxygen atom of the ozone molecule. The mechanism of such a reaction may be illustrated as



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(1) Lucidol Research Associate 1952–1953.

(2) A. Rieche, R. Meister and H. Sauthoff, *Ann.*, **553**, 187 (1942).

(3) H. Staudinger, *Ber.*, **58**, 1088 (1925).

(4) R. Criegee, *Ann.*, **560**, 127 (1948); *cf.* J. E. Leffler, *Chem. Revs.*, **45**, 385 (1949).

(5) G. L. Lewis and C. P. Smyth, THIS JOURNAL, **60**, 1455 (1938); *cf.* M. J. S. Dewar, *J. Chem. Soc.*, 1299 (1948).