[CONTRIBUTION FROM THE NUTRITION AND PHYSIOLOGY SECTION, RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Syntheses of 6-Ethyl-8-mercaptooctanoic Acid and its Homologs¹

By John A. Brockman, Jr., and Paul F. Fabio RECEIVED APRIL 8, 1957

6-Ethyl-8-mercaptooctanoic acid was synthesized through the sequence methyl 5-chloroformylvalerate to methyl 6oxoöctanoate to methyl 7-cyano-6-ethyl-6-heptenoate to methyl 6-cyanomethyloctanoate to methyl 6-ethyl-8-mercaptooctanoate to free acid. Homologs were synthesized by analogous sequences.

The syntheses reported here are part of a program to prepare biologically interesting analogs of thioctic (lipoic) acid (cyclic disulfide of 6,8-dimercaptoöctanoic acid). The similarity of the structures of these analogs to that of 6-acetylthio-8-mercapto-octanoic acid,² one of the important biological forms of thioctic acid, is readily apparent. Inhibitory activity for the growth of certain microorganisms has been reported for these analogs.

The syntheses were carried out according to the scheme

$$\begin{array}{c|c} \text{CIC}(\text{CH}_2)_n \text{COOR}' & \text{RC}(\text{CH}_2)_n \text{COOR}' & \xrightarrow{\text{CNCH}_2\text{COOH}} \\ \hline O & \text{R}_2\text{Cd} & O \\ \hline \\ \text{RC}(\text{CH}_2)_n \text{COOR}' & \xrightarrow{\text{H}_2} & \text{RCH}(\text{CH}_2)_n \text{COOR}' & \xrightarrow{\text{CoS}_x} \\ \hline \\ \text{CHCN} & & \text{CH}_2\text{CN} \\ \hline \\ \text{RCH}(\text{CH}_2)_n \text{COOR}' & \xrightarrow{\text{I}_1 \text{ OH}_2} & \text{HSCH}_2\text{CH}_2\text{CH}(\text{CH}_2)_n \text{COOH} \\ \hline \\ \text{CH}_2\text{CH}_2\text{SH} & & \text{R} \\ \hline \end{array}$$

Although we have represented the unsaturated nitriles as having the double bond conjugated with the nitrile, in actual fact the products obtained were probably mixtures of conjugated and unconjugated compounds. Thus the infrared spectrum of methyl 7-cyano-6-ethylheptenoate showed a doublet with peaks at 4.46 and 4.52μ in the nitrile region. Furthermore, when catalytic reduction was carried out with old, somewhat less active catalyst, a decided decrease in the rate of hydrogen uptake was noted after about half the theoretical amount had been absorbed.

Most of the reactions proceeded nicely and gave products fairly easy to purify. However, the mercapto-esters were difficult to purify and in a few cases could not be obtained in analytically pure form even on careful fractionation through a Podbielniak column. Nevertheless, saponification led readily to the pure acids.

Experimental

Half-ester-half-acid Chlorides.—These compounds, methyl 3-chloroformylpropionate, methyl 4-chloroformylbutyrate, methyl chloroformylvalerate, ethyl 6-chloroformylhexanoate7 and ethyl 7-chloroformylheptanoate,7 were prepared by treating the corresponding half-ester-halfacids with thionyl chloride.

Oxo-esters.—Methyl 6-oxoheptanoate was prepared by refluxing for 10 hr. 5.37 moles of 6-oxoheptanoic acid8 in 2.21. of methanol containing 22 ml. of sulfuric acid. Other oxo-esters were prepared by slight modifications of the method of Cason and Prout.9 Products were distilled through a 35-cm. Vigreux column and collected usually over a 5 or 10° range. Properties and analytical data for new compounds are given in Table I. The following prenew compounds are given in Table I. The following previously reported compounds were also prepared: methyl 6-oxoöctanoate, ¹⁰ 81.8% yield, b.p. 125-131° at 14 mm., n^{20} D 1.4337 to 1.4342; methyl 5-oxoheptanoate, ¹⁰ 84.2%, b.p. 108-119° at 12.3 mm., n^{20} D 1.4308 to 1.4327; ethyl 7-oxononanoate, ¹⁰ 52.7%, b.p. 145-161° at 15 mm., n^{20} D 1.4352 to 1.4377; ethyl 8-oxodecanoate, ¹⁰ 37.8%, b.p. 159 to 169° at 13 to 15 mm., n^{20} D 1.4380 to 1.4387. Cyano-alkenoates were prepared by modification of the method of Cope, et al. ¹¹ The following preparation of methyl 7-cyano-6-methyl-6-heptenoate is typical: 634 g. of methyl 6-oxoheptanoate, 306 g. of cyanoacetic acid, 11.5 g. of ammonium acetate and 300 ml. of benzene were refluxed under a 50-cm. column of glass rings leading to a phase separator

a 50-cm. column of glass rings leading to a phase separator until no further water was collected. About 24 hr. was required. Benzene was removed at atmospheric pressure, and the boiler temperature was allowed to rise until vigorous decarboxylation began (ca. 150 to 175°). After no further carbon dioxide was evolved, the mixture was cooled, taken up in ether, washed with aqueous potassium carbonate and dried over anhydrous sodium sulfate. Removal of the ether and distillation of the residue through a 35-cm. Vigreux column gave the product collected over an 8° range. Properties and analytical data are given in Table II.

Cyano-alkanoates.—A solution of the unsaturated nitrile in 3A alcohol (6 to 7 mole/l.) was shaken with 10% palladium-on-charcoal (5 g./mole) in a Parr low pressure hydrogenation apparatus at a hydrogen pressure of 2 to 3 atm. until the hydrogen uptake was theoretical or somewhat greater. With fresh catalyst 2 to 6 hr. was adequate; with less active catalyst 24 to 48 hr. was required. After the catalyst and solvent were removed, the residual oil was taken up in an equal volume of ether and washed with 1 Nhydrochloric acid, 0.25 M potassium permanganate, de-colorized with sodium bisulfite, washed with dilute ferrous sulfate, water and dried over anhydrous sodium sulfate. The ether was removed and the residual oil was distilled at reduced pressure through a 35-cm. Vigreux column. Properties and analytical data are given in Table III.

Mercapto-alkanoates were prepared by the reduction of

the cyano-alkanoates in hydrogen sulfide by modification of the method of Signaigo.¹³ The following preparation of methyl 6-methyl-8-mercaptoöctanoate is a typical example: cobalt polysulfide paste (prepared from 95.2 g. of cobalt chloride hexahydrate by the method of Bullock, et al.). 14 47.8 g. of sulfur and 135 g. of methyl 7-cyano-6-methyl-

⁽¹⁾ Presented before the 131st American Chemical Society Meeting, Miami, Florida, April, 1957.

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TABLE I Oxo-esters. RC(CH₂)_nCOOR'

R'	72	Yield, %	°C.	3.p. Mm.	120D	d_{20}	Formula	Carbo Calcd.	on, % Found	Hydrogen, Caled.	% Found	
CH_3	4	79.1	12 0	14.2	1.4312	1.006	$C_8H_{14}O_3$	60.74	60.58	8.92	9.08	
CH_3	4	90.2	137	14.8	1.4350	0.976	$C_{10}H_{18}O_3$	64.49	64.49	9.74	9.41	
CH_3	4	84.9	149	13.5	1.4377	.960	$C_{11}H_{20}O_3$	65.97	66.01	10.07	10.35	
CH_3	4	31.5	140	13.7	1.4343	.962	$C_{11}H_{20}O_3$	65.97	65.91	10.07	9.91	
CH_3	2	35.0	123	51	1.4247	1.027	$C_7H_{12}O_3$	58.31	58.02	8.39	8.60	
	CH₃ CH₃ CH₃ CH₃	CH ₃ 4 CH ₃ 4 CH ₃ 4 CH ₃ 4	R' n % CH ₃ 4 79.1 CH ₃ 4 90.2 CH ₃ 4 84.9 CH ₃ 4 31.5	R' n % °C. CH ₃ 4 79.1 120 CH ₃ 4 90.2 137 CH ₃ 4 84.9 149 CH ₃ 4 31.5 140	R' n % °C. Mm. CH ₃ 4 79.1 120 14.2 CH ₃ 4 90.2 137 14.8 CH ₃ 4 84.9 149 13.5 CH ₃ 4 31.5 140 13.7	R' n % °C. Mm. n²⁰b CH3 4 79.1 120 14.2 1.4312 CH3 4 90.2 137 14.8 1.4350 CH3 4 84.9 149 13.5 1.4377 CH3 4 31.5 140 13.7 1.4343	R' n Yield, % °C. B.p. Mm. n²º₀ d₂₀ CH₃ 4 79.1 120 14.2 1.4312 1.006 CH₃ 4 90.2 137 14.8 1.4350 0.976 CH₃ 4 84.9 149 13.5 1.4377 .960 CH₃ 4 31.5 140 13.7 1.4343 .962	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	

TABLE II

	R
CYANO-ALKENOATES,	$NCCH = C(CH_2)_n COOR'$

			Yield, B.p.							Carbon, %		Hydrogen, %		Nitrogen, %	
R	R'	72	%	°C.	Mm.	$n^{20}D$	d_{20}	Formula	Caled.	Found	Caled.	Found	Calcd.	Found	
CH,	CH_3	4	73.3	153	10	1.4604	0.998	$C_{10}H_{15}NO_2$	66.27	66.17	8.34	8.37	7.73	7.52	
C_2H_5	CH_3	4	62.2	102	0.05	1.4612	. 983	$C_{11}H_{17}NO_2$	67.66	67.65	8.78	8.87	7.18	7.43	
$n-C_3H_7$	CH_3	4	70.3	142	3.25	1.4601	.970	$C_{12}H_{19}NO_2$	68.86	68.76	9.15	9.38	6.69	6.52	
n-C₄H∘	CH_3	4	71.5	152	3.2	1.4602	. 959	$C_{13}H_{21}NO_2$	69.92	69.75	9.48	9.19	6.27	6.56	
i-C ₄ H ₉	CH_3	4	22.2	143	2.9	1.4588	. 954	$C_{13}H_{21}NO_2$	69.92	69.78	9.48	9.57	6.27	6.02	
C_2H_5	CH_3	2	34.9	130	5.9	1.4600	1.019	$C_9H_{13}NO_2$	64.65	64.61	7.84	8.24	8.38	8.41	
C_2H_5	CH_3	3	58.9	130	4.4	1.4601	1.006	$C_{10}H_{15}NO_2$	66.27	65.90	8.34	8.52	7.73	7.72	
C_2H_5	C_2H_5	5	60.4	152	3.0	1.4579	0.957	$C_{13}H_{21}NO_2$	69.92	69.54	9.48	9.64	6.27	5.90	
C_2H_5	C_2H_5	6	57.8	157	2.3	1.4582	0.955	$C_{14}H_{23}NO_2$	70.85	70.49	9.77	9.49	5.90	6.19	

TABLE III

R CYANO-ALKANOATES, NCCH₂CH(CH₂)_nCOOR'

		Yield, B.p.							Carbon, %			gen, %	Nitrogen, %	
R	R'	п	%	°C.	Mm.	$n^{20}{ m D}$	d_{20}	Formula	Caled.	Found	Caled.	Found	Calcd.	Found
CH_3	CH_3	4	87.2	152	10.5	1.4410	0.972	$C_{10}H_{17}NO_2$	65.54	65.90	9.35	9.50	7.64	7.35
C_2H_5	CH_3	4	77 .0	141	4.6	1.4458	. 967	$C_{11}H_{19}NO_2$	66.97	66.93	9.71	9.61	7.10	6.90
n-C ₃ H ₇	CH_3	4	69.7	141	3	1.4468	.951	$C_{12}H_{21}NO_2$	68.21	67.89	10.02	9.64	6.63	6.75
$n-C_4H_9$	CH_3	4	64.0	149	2.9	1.4498	.948	$C_{13}H_{23}NO_2$	69.29	69.56	10.29	10.06	6.22	6.10
i-C4H9	CH_3	4	40.0	144	$^{2.8}$	1.4542	. 949	$C_{13}H_{23}NO_2$	69.29	68.99	10.29	9.92	6.22	6.16
C_2H_5	CH_3	2	44.0	145	15.4	1.4422	. 994	$C_9H_{15}NO_2$	63.88	63.84	8.94	9.49	8.28	8.44
C_2H_5	CH_3	3	70.5	164	2 0.3	1.4437	. 979	$C_{10}H_{17}NO_2$	65.54	65.78	9.35	9.43	7.64	7.62
C_2H_5	C_2H_5	5	54.3	152	3.3	1.4470	.947	$C_{13}H_{23}NO_2$	69.29	68.90	10.29	10.07	6.22	6.34
C_2H_5	C_2H_5	6	63.4	153	2.5	1.4499	.944	$C_{14}H_{25}NO_2$	70.25	70.48	10.53	10.30	5.85	5.84

TABLE IV

R MERCAPTO-ALKANOATES, HSCH₂CH₂CH(CH₂), COOR'

			Yield.	B.p						m , C_c		gen, %	Sulfu	
ĸ	R'	12	%	°C. '	Mm.	$H^{20}D$	d_{20}	Formula	Caled.	Found	Caled.	Found	Caled.	Found
CH_3	CH_3	4	56.2	155	20	1.4663	0.976	$C_{10}H_{20}O_2S$	58.78	59.02	9.87	9.82	15.70	15.36
C_2H_5	CH_3	4	63.4	148	10	1.4697	.975	$C_{11}H_{22}O_2S$	60.50	60.83	10.16	10.05	14.69	15.03
n - C_3H_7	CH_3	4	63.0	160	40.5	1.4678	.966	$C_{12}H_{24}O_2S$	62.02	62.11	10.41	10.06	13.80	13.86
$n-C_4H_9$	CH_3	4	64.5	163	7.7	1.4690	.958	$C_{13}H_{26}O_2S$	63.36	63.26	10.64	10.84	13.01	12.66
i-C4H9	CH_3	4	16.0	170	16	1.4673	.959	$C_{13}H_{26}O_2S$	63.36	63.13	10.64	10.39	13.01	12.67
C_2H_5	CH_3	2	32.2	138-141	21	1.4551 -		$C_9H_{18}O_2S$						
						1.4648								
C_2H_5	CH_3	3	57.5	147	15.5	1.4699	0.992	$C_{10}H_{20}O_2S$	58.78	58.80	9.87	9.56	15.70	15.38
C_2H_5	C_2H_5	5	50.0	163-164	7.5	1.4651 -		$C_{12}H_{24}O_2S$						
						1.4617								
C_2H_5	C_2H_5	6	43.0	176-181	10.5	1.4628 -		$C_{13}H_{26}O_2S$						
						1.4658								

heptanoate were hydrogenated in 280 ml. of acetic acid at 1000 to 1500 pounds per square inch. The temperature was raised slowly until at ca. 140° a sudden uptake of hydrogen indicated a reduction of the catalyst and the sulfur. drogen indicated a reduction of the catalyst and the sulfur. After this initial reaction subsided, the temperature was gradually raised to 200° and held there until no further hydrogen uptake was observed, ca. 8 hr. The catalyst was filtered, washed with methanol and the filtrate was freed of solvent. The residue was refluxed with 540 ml. of methanol and 25 ml. of concentrated sulfuric acid for 4.5 hr. and was then poured onto ice. The product was collected in other, washed with aqueous potassium carbonate, water and ether, washed with aqueous potassium carbonate, water and dried over sodium sulfate. Removal of the solvent and distillation of the residual oil gave crude product (boiling point 118 to 136° at 1.8 mm.) which was redistilled through a 20 × 200 mm. column packed with Heli-pak to give 84.8 g. of product boiling at 137 to 142° at 10 mm. and having n²0 p 1.4663 to 1.4687. To obtain analytically pure material, it was necessary to carefully fractionate through a Podbielniak column. Properties and analytical data for those esters which could be obtained pure are given in Table IV.

Mercapto-acids.—The above esters were saponified in 6 to 8 N potassium hydroxide in 10-40% aqueous alcohol by refluxing 2 hr. The solutions were diluted with water, neutralized to pH 7.5 to 8.0 and extracted with ether to remove neutral impurities. The aqueous phase was then

17.22

14.81

14 05

 C_2H_5

 C_2H_5

 C_2H_5

5

54.8

37.2

Table V

R

	Mercapto-acids, $HSCH_2CH_2CH(CH_2)_nCOOH$														
_		Yield,	B.p.					Carbon,_%		Hydrogen, %		Sulfur			
R	72	%	°C.	Mm.	n ²⁰ D	d_{20}	Formula	Calcd.	Found	Caled.	Found	Calcd.	Found		
CH_3	4	81.3	116	0.14	1.4802	1.016	$C_9H_{18}C_2S$	56.80	57.16	9.53	9.83	16.85	16.92		
C_2H_5	4	75.3	133	.09	1.4813	1.013	$C_{10}H_{20}O_2S$	58.78	58.98	9.87	10.21	15. 7 0	15.89		
$n-C_3H_7$	4	54.6	140	.08	1.4809	0.995	$C_{11}H_{22}O_2S$	60.50	60.62	10.16	10.10	14.69	14.68		
n - C_4H_7	4	74.4	141	. 1	1.4810	. 988	$C_{12}H_{24}O_2S$	62.02	62.22	10.41	10.13	13.80	14.10		
<i>i</i> -C₄H ₇	4	60.5	173	1.0	1.4810	. 987	$C_{12}H_{24}O_2S$	62.02	62.40	10.41	10.44	13.80	13.34		
C_2H_5	2	52.2	107	0.05	1.4839	1.044	$C_PH_{16}O_2S$	54.51	54.78	9.15	9.05	18.19	17.66		

 $C_9H_{18}O_2S$

 $C_{11}H_{22}O_2S$

 $C_{12}H_{24}O_2S$

acidified and extracted with ether. After drying and removal of the ether, the residue was distilled at low pressure. Properties and analytical data are given in Table V.

.05

.04

142

145

1.4842

1.4823

1.4812

1.031

1.004

0.993

Acknowledgments.—We are indebted to Mr. L. Brancone and staff for microanalytical determina-

tions, to Mr. W. Fulmor and staff for infrared studies and to Mr. J. Sanjurjo for assistance in the high pressure operations.

9.53

10.16

10.41

10.02

10.09

14.69

13.80

PEARL RIVER, NEW YORK

60.50

62.02

60.20

61 64

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

Synthesis of Steroidal Methylene Compounds by the Wittig Reaction¹

By Franz Sondheimer and Raphael Mechoulam Received March 22, 1957

Different types of saturated and α,β -unsaturated steroidal ketones have been converted to the corresponding methylene compounds through reaction with triphenylphosphine-methylene. Such methylene compounds thereby became readily available. Steroidal hydroxy-ketones may be subjected to the reaction either directly or after protection of the hydroxyl group. Several methylene steroids described previously are shown to have been impure.

The recently discovered reaction between triphenylphosphine-alkylidenes of type III (obtained from the bromides I by the sequence shown) and carbonyl compounds to produce the corresponding ethylenes IV, the so-called Wittig reaction, has become one of wide scope and utility in synthetic chemistry.² We first became interested in the application of this reaction in the steroid field in

$$\begin{array}{c} R^{2} \\ R'-CHBr \xrightarrow{PPh_{3}} \begin{bmatrix} R^{2} \\ R'CHPPh_{3} \end{bmatrix} Br \xrightarrow{BuLi} \begin{array}{c} R^{2} \\ R'C=PPh_{3} \\ III \end{array}$$

$$\begin{array}{c} IIIa \\ \downarrow \uparrow \\ R'-C=C-R^{4} & O=C-R^{4}+R'-C-PPh_{3} \\ IV & \oplus & \oplus \\ IIIb \end{array}$$

connection with a study we undertook to find new methods for constructing compounds containing sterol side chains from 17-keto and 20-keto steroids. This study led us to investigate the interaction between a variety of steroidal ketones with different triphenylphosphine-alkylidenes. It was found that the reaction proceeded most smoothly when triphenylphosphine-methylene (III, $R^1 = R^2 = H$) was employed and the present paper records the use of this reagent for the synthesis of

various methylene-steroids (IV, $R^1 = R^2 = H$) from both saturated and α,β -unsaturated steroidal monoketones. We were not certain how successful the reaction would be with ketones containing other functions (hydroxy and acetoxy groups) which may react with triphenylphosphine-methylene, but in fact it was found that reasonably satisfactory results were obtained also with these polyfunctional substances. The methylene compounds thus obtained are often prepared only with difficulty and in some cases in impure form by other methods. On the other hand, the present route produces the methylene steroids simply and in a high state of purity.

The triphenylphosphine-methylene reagent was prepared in ether solution in the usual way2 by treatment of methyltriphenylphosphonium bromide with butyllithium, and the reactions with the ketones were best carried out in refluxing tetrahydrofuran. The various steroidal ketones investigated are listed in Table I, together with the yields and properties of the products. The structures of the resulting methylene-steroids were confirmed by the elemental analyses, infrared spectra (disappearance of the carbonyl band and appearance of the terminal methylene bands at ca. 890 and 1650 cm. -1)3 and in some cases by comparison of the properties with those reported for the previously described compounds.

Cholestan-3-one (no. 1), a simple monofunctional compound containing the system Va, produced 3-

⁽¹⁾ Presented in part before the Organic Chemistry Division at the 131st Meeting of the America Chemical Society, Miami, Fla., April, 1957.

⁽²⁾ Cf. G. Wittig, Experientia, 12, 41 (1956); Angew. Chem., 68, 505 (1956), and earlier references cited there.

⁽³⁾ Cf. N. Sheppard and D. M. Simpson, Quart. Revs. (London), 6, 1 (1952), Table 7.