

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

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

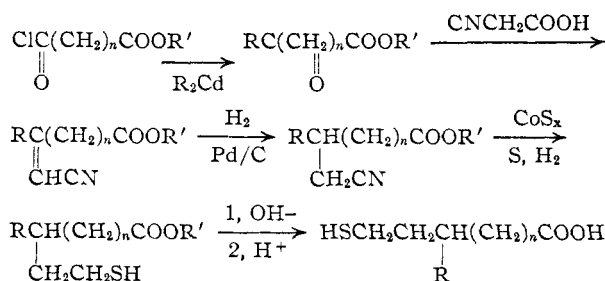
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RECEIVED APRIL 8, 1957

6-Ethyl-8-mercaptooctanoic acid was synthesized through the sequence methyl 5-chloroformylvalerate to methyl 6-oxooctanoate 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-dimercaptooctanoic 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 reported³ for these analogs.

The syntheses were carried out according to the scheme



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 4.52 μ 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,⁴ methyl 4-chloroformyl butyrate,⁵ methyl chloroformylvalerate,⁶ ethyl 6-chloro-

formylhexanoate⁷ and ethyl 7-chloroformylheptanoate,⁷ were prepared by treating the corresponding half-ester-half-acids with thionyl chloride.

Oxo-esters.—Methyl 6-oxoheptanoate was prepared by refluxing for 10 hr. 5.37 moles of 6-oxoheptanoic acid⁸ in 2.2 l. 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 previously reported compounds were also prepared: methyl 6-oxooctanoate,¹⁰ 81.8% yield, b.p. 125–131° at 14 mm., n_D^{20} 1.4337 to 1.4342; methyl 5-oxoheptanoate,⁵ 84.2%, b.p. 108–119° at 12.3 mm., n_D^{20} 1.4308 to 1.4327; ethyl 7-oxononanoate,⁷ 52.7%, b.p. 145–161° at 15 mm., n_D^{20} 1.4352 to 1.4377; ethyl 8-oxodecanoate,⁸ 37.8%, b.p. 159 to 169° at 13 to 15 mm., n_D^{20} 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 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.¹² 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 *N* hydrochloric acid, 0.25 *M* potassium permanganate, decolorized 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-mercaptooctanoate 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-

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TABLE I

OXO-ESTERS, $\text{RC}(\text{CH}_2)_n\text{COOR}'$											
R	R'	n	Yield, %	°C.	B.p. Mm.	n_D^{20}	d_{20}	Formula	Carbon, %		Hydrogen, %
									Calcd.	Found	Calcd.
CH ₃	CH ₃	4	79.1	120	14.2	1.4312	1.006	C ₈ H ₁₄ O ₃	60.74	60.58	8.92
<i>n</i> -C ₃ H ₇	CH ₃	4	90.2	137	14.8	1.4350	0.976	C ₁₀ H ₁₈ O ₃	64.49	64.49	9.74
<i>n</i> -C ₄ H ₉	CH ₃	4	84.9	149	13.5	1.4377	.960	C ₁₁ H ₂₀ O ₃	65.97	66.01	10.07
<i>i</i> -C ₄ H ₉	CH ₃	4	31.5	140	13.7	1.4343	.962	C ₁₁ H ₂₀ O ₃	65.97	65.91	10.07
C ₂ H ₅	CH ₃	2	35.0	123	51	1.4247	1.027	C ₇ H ₁₂ O ₃	58.31	58.02	8.39

TABLE II

CYANO-ALKENOATES, $\text{NCCH}=\text{C}(\text{CH}_2)_n\text{COOR}'$														
R	R'	n	Yield, %	°C.	B.p. Mm.	n_D^{20}	d_{20}	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
									Calcd.	Found	Calcd.	Found	Calcd.	Found
CH ₃	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 ₂ H 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
<i>n</i> -C ₃ H 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
<i>n</i> -C ₄ H ₉	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>i</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 ₂ H ₅	CH ₃	2	34.9	130	5.9	1.4600	1.019	C ₉ H ₁₃ NO ₂	64.65	64.61	7.84	8.24	8.38	8.41
C ₂ H 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 ₂ H ₅	C ₂ H 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 ₂ H ₅	C ₂ H 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

CYANO-ALKANOATES, $\text{NCCH}_2\text{CH}(\text{CH}_2)_n\text{COOR}'$														
R	R'	n	Yield, %	°C.	B.p. Mm.	n_D^{20}	d_{20}	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
									Calcd.	Found	Calcd.	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 ₂ H 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
<i>n</i> -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
<i>n</i> -C ₄ H 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>i</i> -C ₄ H ₉	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 ₂ H ₅	CH ₃	2	44.0	145	15.4	1.4422	.994	C ₉ H ₁₅ NO ₂	63.88	63.84	8.94	9.49	8.28	8.44
C ₂ H ₅	CH ₃	3	70.5	164	20.3	1.4437	.979	C ₁₀ H ₁₇ NO ₂	65.54	65.78	9.35	9.43	7.64	7.62
C ₂ H ₅	C ₂ H 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 ₂ H ₅	C ₂ H 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

MERCAPTO-ALKANOATES, $\text{HSCH}_2\text{CH}_2\text{CH}(\text{CH}_2)_n\text{COOR}'$														
R	R'	n	Yield, %	°C.	B.p. Mm.	n_D^{20}	d_{20}	Formula	Carbon, %		Hydrogen, %		Sulfur, %	
									Calcd.	Found	Calcd.	Found	Calcd.	Found
CH ₃	CH ₃	4	56.2	155	20	1.4663	0.976	C ₁₀ H ₂₀ O ₂ S	58.78	59.02	9.87	9.82	15.70	15.36
C ₂ H ₅	CH ₃	4	63.4	148	10	1.4697	.975	C ₁₁ H ₂₂ O ₂ S	60.50	60.83	10.16	10.05	14.69	15.03
<i>n</i> -C ₃ H ₇	CH ₃	4	63.0	160	10.5	1.4678	.966	C ₁₂ H ₂₄ O ₂ S	62.02	62.11	10.41	10.06	13.80	13.86
<i>n</i> -C ₄ H ₉	CH ₃	4	64.5	163	7.7	1.4690	.958	C ₁₃ H ₂₆ O ₂ S	63.36	63.26	10.64	10.84	13.01	12.66
<i>i</i> -C ₄ H ₉	CH ₃	4	16.0	170	16	1.4673	.959	C ₁₃ H ₂₆ O ₂ S	63.36	63.13	10.64	10.39	13.01	12.67
C ₂ H ₅	CH ₃	2	32.2	138-141	21	1.4551- 1.4648		C ₉ H ₁₈ O ₂ S						
C ₂ H ₅	CH ₃	3	57.5	147	15.5	1.4699	0.992	C ₁₀ H ₂₀ O ₂ S	58.78	58.80	9.87	9.56	15.70	15.38
C ₂ H ₅	C ₂ H ₅	5	50.0	163-164	7.5	1.4651- 1.4617		C ₁₂ H ₂₂ O ₂ S						
C ₂ H ₅	C ₂ H ₅	6	43.0	176-181	10.5	1.4628- 1.4658		C ₁₃ H ₂₆ O ₂ S						

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. 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 ether, washed with aqueous potassium carbonate, water and dried over sodium sulfate. Removal of the solvent and dis-

tillation 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 n_D^{20} 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

