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

Syntheses of 6-Ethyl-8-mercaptooctanoic Acid and its Homologs[1]

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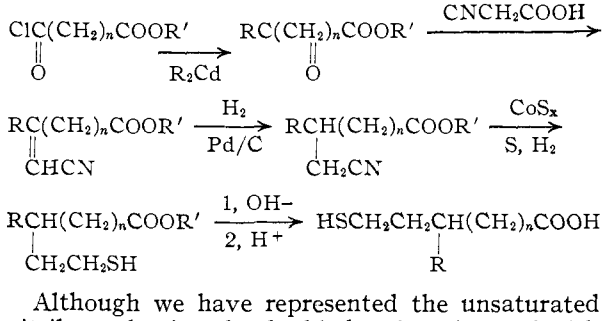
6-Ethyl-8-mercaptooctanoic acid was synthesized through the sequence methyl 5-chloroformylvalerate to methyl 6-oxoöctanoate to methyl 7-cyano-6-ethyl-6-heptenoate to methyl 6-cyanomethyloctanoate to methyl 6-ethyl-8-mercaptooctanoate to free acid. Homologs were synthesized by analogous sequences.

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[3] 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-chloroformylhexanoate[7] 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 acid[8] 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-oxoöctanoate,[10] 81.8% yield, b.p. 125–131° at 14 mm., n^{20}D 1.4337 to 1.4342; methyl 5-oxoheptanoate,[5] 84.2%, b.p. 108–119° at 12.3 mm., n^{20}D 1.4308 to 1.4327; ethyl 7-oxononanoate,[7] 52.7%, b.p. 145–161° at 15 mm., n^{20}D 1.4352 to 1.4377; ethyl 8-oxodecanoate,[6] 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 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-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-

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TABLE I

OXO-ESTERS, $RC(=O)(CH_2)_nCOOR'$

R	R′	n	Yield, %	B.p. °C.	B.p. Mm.	$n^{20}D$	d_{20}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	CH_3	4	79.1	120	14.2	1.4312	1.006	$C_8H_{14}O_3$	60.74	60.58	8.92	9.08
n-C_3H_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	9.41
n-C_4H_9	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
i-C_4H_9	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
C_2H_5	CH_3	2	35.0	123	51	1.4247	1.027	$C_7H_{12}O_3$	58.31	58.02	8.39	8.60

TABLE II

CYANO-ALKENOATES, $NCCH{=}C(R)(CH_2)_nCOOR'$

R	R′	n	Yield, %	B.p. °C.	B.p. Mm.	$n^{20}D$	d_{20}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % 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_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-C_4H_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-C_4H_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

CYANO-ALKANOATES, $NCCH_2CH(R)(CH_2)_nCOOR'$

R	R′	n	Yield, %	B.p. °C.	B.p. Mm.	$n^{20}D$	d_{20}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % 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_3H_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-C_4H_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_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	20.3	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

MERCAPTO-ALKANOATES, $HSCH_2CH_2CH(R)(CH_2)_nCOOR'$

R	R′	n	Yield, %	B.p. °C.	B.p. Mm.	$n^{20}D$	d_{20}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % 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	10.5	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-C_4H_9	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	1.4551–1.4648		$C_9H_{18}O_2S$						
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	1.4651–1.4617		$C_{12}H_{24}O_2S$						
C_2H_5	C_2H_5	6	43.0	176–181	10.5	1.4628–1.4658		$C_{13}H_{26}O_2S$						

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 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 $n^{20}D$ 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 *p*H 7.5 to 8.0 and extracted with ether to remove neutral impurities. The aqueous phase was then

TABLE V

R

MERCAPTO-ACIDS, $HSCH_2CH_2CH(CH_2)_nCOOH$

R	n	Yield, %	B.p. °C.	B.p. Mm.	$n^{20}D$	d_{20}	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % 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	15.70	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-C_4H_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	$C_8H_{16}O_2S$	54.51	54.78	9.15	9.05	18.19	17.66
C_2H_5	3	74.6	148	.85	1.4842	1.031	$C_9H_{18}O_2S$	56.80	57.00	9.53	9.53	16.85	17.22
C_2H_5	5	54.8	142	.05	1.4823	1.004	$C_{11}H_{22}O_2S$	60.50	60.20	10.16	10.02	14.69	14.81
C_2H_5	6	37.2	145	.04	1.4812	0.993	$C_{12}H_{24}O_2S$	62.02	61.64	10.41	10.09	13.80	14.05

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.

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PEARL RIVER, NEW YORK

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

Synthesis of Steroidal Methylene Compounds by the Wittig Reaction[1]

BY FRANZ SONDHEIMER AND RAPHAEL MECHOULAM

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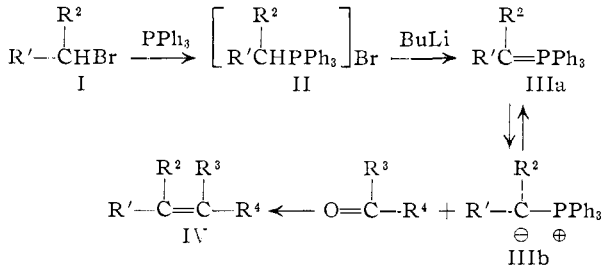
Different types of saturated and α,β-unsaturated steroidal ketones have been converted to the corresponding methylene compounds through reaction with triphenylphosphine-methylene. Such methylene compounds thereby became readily available. Steroidal hydroxy-ketones may be subjected to the reaction either 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



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 way[2] 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 American 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.