yield to 1.5 g. (62%). The analytical sample (from aqueous dioxane melted at 207–209°.

Anal. Calcd. for $C_{10}H_8N_2O_4S$: C, 47.61; H, 3.20; N, 11.11; S, 12.71. Found: C, 47.83; H, 3.08; N, 10.96; S, 12.75.

Diethyl 4-Alkylthiopyridine-2,6-dicarboxylate.—A slight excess of alkyl halide (or dimethyl sulfate) was added to a warm solution of ammonium 2,6-dicarbethoxypyridine-4-thiolate in a fivefold amount of dimethylformamide. The mixture, filtered when necessary, was diluted with water. The solid thioethers were filtered, washed and dried, while liquid ones were taken up with ether; the ether solutions were washed with water and sodium carbonate solution, dried, the solvent removed, and the residue distilled *in vacuo*. Additional preparative information, physical constants, and analytical data are summarized in Table II.

Oxidation of Thioethers with Hydrogen Peroxide.—The sample of thioether was dissolved in a fivefold amount of acetic acid and an equal volume of hydrogen peroxide (30%) was added. The mixture then was allowed to stand for several days. In some cases starting material was precipitated upon addition of the oxidizing agent, but dissolved slowly on standing, and, upon further standing, a new solid was formed. In other cases a clear solution was obtained and the sulfone was precipitated by addition of water. The crude products were filtered and recrystallized. Further experimental information, physical constants, and analytical data are summarized in Table III.

Diethyl 4-Ethylsulfonylpyridine-2,6-dicarboxylate.—A solution of 3.0 g. of diethyl 4-ethylthiopyridine-2,6-dicarboxylate in 15 ml. of acetic acid was oxidized by gradual addition of 4.0 g. of chromium trioxide. The dark reaction mixture was poured into water and 1.4 g. (42%) of the crystalline sulfone was filtered and recrystallized from water containing a little ethanol. It had m.p. 131–132° and no depression was observed when a sample was mixed with material obtained by oxidation of the same thioether with hydrogen peroxide.

Dimethyl 4-Phenylsulfonylpyridine-2,6-dicarboxylate.—This compound was obtained similarly in a yield of 36%. A sample recrystallized from methanol melted at 202–202.5°.

Anal. Calcd. for $C_{15}H_{13}NO_6S$: C, 53.78; H, 3.91; N, 4.18; S, 9.56. Found: C, 53.67; H, 3.88; N, 4.46; S, 9.66.

Diethyl 4-phenylsulfonylpyridine-2,6-dicarboxylate was isolated in 2.3% yield when diethyl 4-phenylthiopyridine-2,6-dicarboxylate was oxidized with chromium trioxate, m.p. 155–157°; there was no depression when mixed with a sample obtained by oxidation with hydrogen peroxide.

Acknowledgment.—The author wishes to thank the National Science Foundation for financial support of this investigation.

Syntheses of Reduced Lipoic Acid and Analogs of Lipoic Acid

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Received January 28, 1963

Methyl 8-chloro-6-keto-7-octenoate has been prepared by condensation of methyl δ-chloroformylvalerate with acetylene. This β-chlorovinyl ketone has been converted to reduced lipoic acid by various routes. It also has served as an intermediate to the lipoic acid analogs 3-pyrazolevaleric acid and 5-isoxazolevaleric acid.

Lipoic acid, 1,2-dithiolane-3-valeric acid, has been the subject of many investigations directed to the clarification of its role in biological processes.[1] It has been reported to be useful in the treatment of various disorders,[2,3] although, a recent indication of liver cell damage following intraperitoneal administration has been reported.[4] This interest has led to much research[5] to make lipoic acid and related compounds available for experimental purposes.

In the course of our studies on lipoic acid, we investigated the utility of appropriately substituted chlorovinyl ketones[6] as intermediates for synthesis of lipoic acid and its analogs. Condensation of methyl δ-chloroformylvalerate with acetylene in tetrachloroethane solution gave methyl 8-chloro-6-keto-7-octenoate (I) in high yields.

$$CH_3O_2C(CH_2)_4COCl \xrightarrow[AlCl_3]{CH\equiv CH} CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH{=}CHCl$$

I

This β-chlorovinyl ketone is a skin irritant; extreme care must be exercised to prevent exposure. The material can be readily distilled under reduced pressure and is conveniently recrystallized from heptane. The pure compound, m.p. 51–52°, can be stored indefinitely at −80° but decomposes in a few days to a red oil if allowed to stand at room temperature.

Methyl 8-chloro-6-keto-7-octenoate possesses, and is readily transformed into other structures which possess, the proper functionality for conversion into lipoic acid type compounds. Reduction of this chlorovinyl ketone

$$I + NaBH_4 \longrightarrow CH_3O_2C(CH_2)_4\underset{\underset{OH}{|}}{CH}{-}CH{=}CHCl$$

II

$$I + CH_3\overset{\overset{O}{\|}}{C}SH \longrightarrow CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH_2CH(S\overset{\overset{O}{\|}}{C}CH_3)_2$$

III

$$I + C_2H_5SH \longrightarrow CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH{=}CHSC_2H_5$$

IV

$$I + NaOCH_3 \longrightarrow CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH_2CH(OCH_3)_2 + CH_3O_2C(CH_2)_4\overset{\overset{O}{\|}}{C}CH{=}CHOCH_3$$

V VI

with sodium borohydride gave the chlorovinyl alcohol II. Reaction of I with thiolacetic acid in the presence of pyridine gave methyl 8,8-bis(acetylthio)-6-ketooctanoate (III) in very good yields. With ethyl mercaptan, the only product isolated was methyl 8-ethylthio-6-keto-7-octenoate (IV). When chlorovinyl ketone I reacted with sodium methoxide, both the ketoacetal V

(1) For a review of the early work with lipoic acid, see L. J. Reed, *Advan. Enzymol.*, **18**, 319 (1957).

(2) F. Rausch, *Arzneimittel-Forsch.*, **5**, 32 (1955).

(3) A. Segre, *Nature*, **177**, 75 (1956).

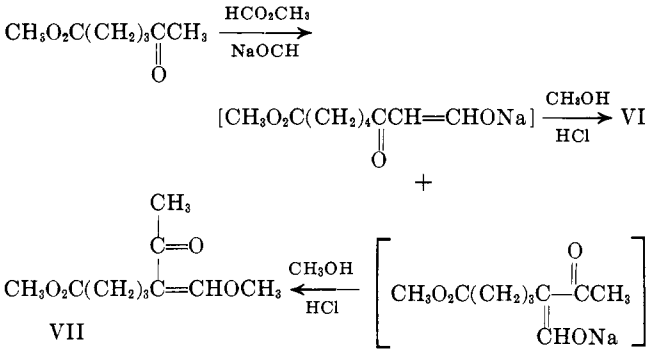
(4) Z. T. Wirtschafter and F. W. Smith, *J. Lab. Clin. Med.*, **60**, 649 (1962).

(5) For a list of references to prior synthetic work, see D. S. Acker and W. J. Wayne, *J. Am. Chem. Soc.*, **79**, 6483 (1957).

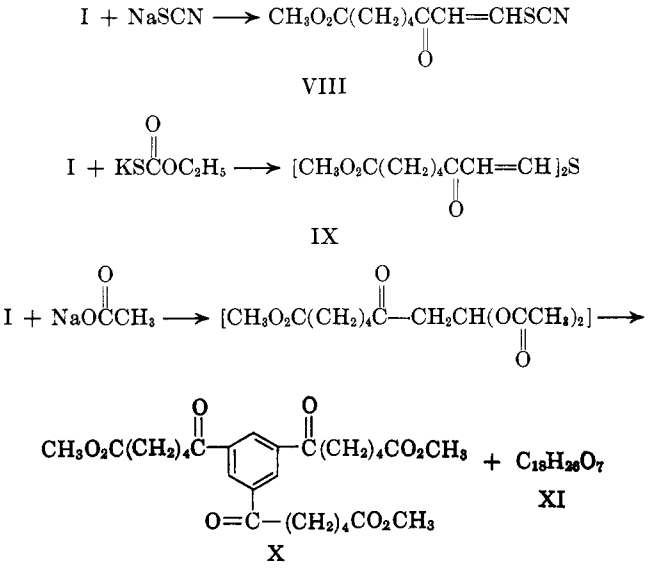
(6) For a review of the synthesis and chemistry of chlorovinyl ketones, see N. K. Kochetkov, *Usp. Khim.*, **24**, 32 (1955).

and methyl 8-methoxy-6-keto-7-octenoate (VI) could be isolated. By slight modification of the reaction conditions, a 60% yield of the unsaturated VI could be obtained.

The latter product also was obtained, although in low yield, by condensation of methyl formate with methyl 6-ketoheptanoate and subsequent treatment with methanolic hydrogen chloride. Also formed was a second product, tentatively assigned the structure VII, which would result from initial formylation of the methylene group adjacent to the ketone carbonyl.



Reaction of the chlorovinyl ketone I with sodium thiocyanate led to the expected methyl 8-thiocyano-6-keto-7-octenoate (VIII) in 83% yield. However, a simi-



lar reaction with potassium ethyl xanthate gave a mixture of products from which only the unsaturated sulfide IX was isolated. When chlorovinyl ketone I reacted with sodium acetate, only further reaction products of the expected 8,8-diacetyl-6-ketooctanoate were isolated. The product XI, the less soluble in ether, appears to be formed by elimination of water from two molecules of methyl 7-formyl-6-ketoheptanoate. A more soluble material was identified by chemical analysis and infrared examination as 1,3,5-tris(4-methoxycarbonylvaleroyl)benzene (X), which would be expected from aldol condensation of three molecules of the keto-aldehyde.

Conversion of many of these products to 6,8-dimercaptooctanoic acid, reduced lipoic acid, by reductive thiolation techniques[7] was possible. In several cases, the products were not isolated, but the lipoic acid activity of the crude reaction mixture was determined by microbiological assay.[8] The results of these reductive thiolations are summarized in Table I.

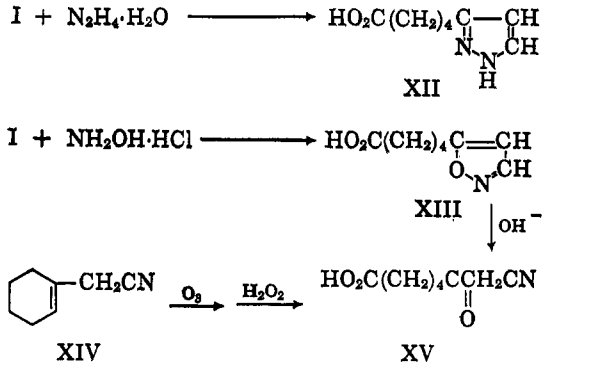
Table I

REDUCTIVE THIOLATIONS

Compound reduced	Solvent used	Lipoic acid, % yield
Methyl 8-chloro-6-keto-7-octenoate (I)	Acetic anhydride[a]	20.5[b]
Methyl 8,8-bis(acetylthio)-6-ketooctanoate (III)	Methanol	60.5
Methyl 8,8-dimethoxy-6-ketooctanoate (V)	Acetic acid	4
Methyl 8-methoxy-6-keto-7-octenoate (VI)	Acetic anhydride	19.5[b]
Methyl 8-thiocyano-6-keto-7-octenoate (VII)	Acetic acid	30[a]

[a] An equivalent of fused sodium acetate also was present. [b] Yield determined by microbiological assay. Other yields are on isolated material.

β-Chlorovinyl ketones are known to be versatile intermediates for the synthesis of various heterocyclic systems.[6] It was of interest to synthesize, from methyl 8-chloro-6-keto-7-octenoate, structures that resemble lipoic acid that are unable to participate in its biological functions. Reaction of the chlorovinyl ketone (I) with hydrazine hydrate led to the isolation of 3-pyrazolevaleric acid (XII) in high yield. With hydroxylamine, 5-isoxazolevaleric acid (XIII) was prepared. Neither compound interfered with the action of lipoic acid in the microbiological assay.



The structure of the isoxazole XIII was proved by conversion to 7-cyano-6-ketoheptanoic acid (XV) by treatment with alkali. This acid XV has previously been prepared by ozonolysis of 1-cyclohexenylacetonitrile.[9] It also can serve as an intermediate to lipoic acid *via* reductive thiolation.

Experimental

Methyl 8-Chloro-6-keto-7-octenoate (I).—This compound is a skin irritant capable of raising uncomfortable blisters. Due caution should be exercised throughout this preparation. A suspension of 453.6 g. (1 lb., 3.4 moles) of powdered anhydrous aluminum chloride in 2000 g. of tetrachloroethane was stirred at

(7) M. W. Farlow, W. A. Lazier, and F. K. Signaigo, *Ind. Eng. Chem.*, **42**, 2547 (1950).

(8) I. C. Gunsalus, M. I. Dolin, and L. Struglia, *J. Biol. Chem.*, **194**, 849 (1952).

(9) D. S. Acker, U.S. Patent 2,752,375 (1956).

5–15°, while 285.5 g. (1.6 moles) of methyl δ-chloroformylvalerate was added rapidly. After the addition was complete, the temperature was lowered to 10° and acetylene, bubbled through concentrated sulfuric acid, was passed in at slightly greater than the saturation rate for 2 hr. The reaction mixture was gradually allowed to warm to room temperature, and the passage of acetylene was continued for another 2 hr. At this time, there was no detectable absorption of acetylene. The product was thoroughly mixed with 2000 g. of ice and 200 ml. of concentrated hydrochloric acid. The organic phase was separated and dried over anhydrous sodium sulfate. The solvents were removed at reduced pressure, and the residue distilled through a 6-in. Vigreux column. Methyl 8-chloro-6-keto-7-octenoate, 250–275 g. (73–84% yield), distilled at 111–112° (0.5 mm.) and solidified in the receiver. It can be recrystallized from heptane (1 g./6 ml.) with 80–90% recovery. The pure solid melts at 51–52°. It decomposes to a red oil in a few days if left at room temperature, but appears to be stable if stored at −80°.

Anal. Calcd. for $C_9H_{13}ClO_3$: C, 52.9; H, 6.4; Cl, 17.3. Found: C, 53.0; H, 6.5; Cl, 17.3.

The infrared spectrum of this compound shows ester C=O at 1740 cm.$^{-1}$; ketone C=O at 1695 cm.$^{-1}$; and conjugated C=C at 1575 cm.$^{-1}$, a high position which is attributed to the chlorine substituent.

Methyl 8-Chloro-6-hydroxy-7-octenoate (II).—Methyl δ-chloroformylvalerate (0.8 mole) was combined with acetylene using the previous procedure. The organic layer from the decomposition of the aluminum chloride complex was washed twice with water and then with 200 ml. of a 5% sodium bicarbonate solution. A solution of 10 g. of sodium borohydride in 300 ml. of 95% ethanol was added over a 30-min. period while stirring the reaction mixture at 10°. The stirring was continued overnight. The reaction mixture was decomposed with 20 ml. of concentrated hydrochloric acid, washed with water, and then dried over a mixture of sodium bicarbonate and magnesium sulfate. Distillation yielded 108.6 g. (64.6%) of methyl 8-chloro-6-hydroxy-7-octenoate, b.p. 137° (0.5 mm.). A portion was redistilled to give an analytical sample, b.p. 111° (0.18 mm.), $n^{25}D$ 1.4735.

Anal. Calcd. for $C_9H_{15}ClO_3$: C, 52.3; H, 7.3; Cl, 17.2. Found: C, 51.4; H, 7.3; Cl, 17.8.

The infrared spectrum is consistent with proposed structure showing OH at 3390 cm.$^{-1}$, ester C=O at 1735 cm.$^{-1}$, and C=C at 1625 cm.$^{-1}$.

Methyl 8,8-Bis(acetylthio)-6-ketooctanoate (III). Method A.—A suspension of 205 g. (1.0 mole) of methyl 8-chloro-6-keto-7-octenoate in 300 ml. of ether was stirred at 5–15°, while 200 g. (2.6 moles) of thiolacetic acid and then 160 ml. of pyridine were added. After stirring at room temperature overnight, the resulting suspension was cooled to −15° and stirred rapidly while a solution of 100 ml. of hydrochloric acid in 200 ml. of water was added. The oil was separated and washed with 100 ml. of water. After drying over anhydrous sodium sulfate, volatile material was removed at the water pump and then at 0.05 mm. while heating at 50°. The light yellow residue of methyl 8,8-bis(acetylthio)-6-ketooctanoate weighed 282.9 g. (88%); $n^{32}D$ 1.5092.

Anal. Calcd. for $C_{13}H_{20}O_5S_2$: C, 48.7; H, 6.3; S, 20.0. Found: C, 48.3; H, 6.5; S, 20.7.

Method B.—In order to minimize the hazards of handling, a preparation of methyl 8,8-bis(acetylthio)-6-ketooctanoate was carried through without isolating the intermediate β-chlorovinyl ketone. Methyl α-chloroformylvalerate (1.6 moles) was combined with acetylene using the procedure previously described. The organic layer from the decomposition of the aluminum chloride complex was concentrated under reduced pressure on a steam bath. The residue was stirred at 5–15° while 300 g. (3.95 moles) of thiolacetic acid and then 240 ml. of pyridine were added. After stirring overnight, the product was isolated as indicated in method A. The yield of dark green oil suitable for reductive thiolation was 462.7 g. (90%).

Methyl 8-Ethylthio-6-keto-7-octenoate (IV).—A suspension of 110 g. (0.538 mole) of methyl 8-chloro-6-keto-7-octenoate in 300 ml. of ether was stirred at 5–15° while 100 g. (1.16 moles) of ethyl mercaptan and then 80 ml. of pyridine were added. After stirring at room temperature overnight, the resulting suspension was cooled to −15° and stirred rapidly while a solution of 50 ml. of hydrochloric acid in 100 ml. of water was added. The oil was separated and washed with two 100-ml. portions of water. After drying over anhydrous sodium sulfate, volatile material was removed at the water pump while heating at 50°. The dark green residue (97.3 g.) had the sulfur content calculated for methyl 8-ethylthio-6-keto-7-octenoate (found, 13.8; calcd., 13.9). A 33-g. portion of this oil was distilled to give 17.6 g. (42%) of product, b.p. 144° (0.6–0.7 mm.); $n^{30}D$ 1.5158–1.5162.

Anal. Calcd. for $C_{11}H_{18}O_3S$: C, 57.4; H, 7.9; S, 13.9. Found: C, 56.3; H, 7.7; S, 14.6.

Methyl 8,8-Dimethoxy-6-ketooctanoate (V) and Methyl 8-Methoxy-6-keto-7-octanoate (VI).—A solution of 150 g. (0.73 mole) of methyl 8-chloro-6-keto-7-octenoate in 200 ml. of methanol was stirred at −10° while a solution of 30 g. (0.75 mole) of sodium hydroxide in 350 ml. of methanol was added. The addition was spaced over 2 hr., and then the reaction mixture was stirred for another hour at −8°. At the end of this time, the mixture was poured into 1 kg. of saturated sodium chloride solution and extracted with 400 ml. of benzene in four equal portions. The organic extracts were dried over anhydrous potassium carbonate and then distilled through a 6-in. Vigreux column with added potassium carbonate. After removal of the benzene, there was collected 20.5 g. (12%) of methyl 8,8-dimethoxy-6-ketooctanoate, b.p. 125–128.5° (0.5 mm.); $n^{25}D$ 1.4454–1.4458.

Anal. Calcd. for $C_{11}H_{20}O_5$: C, 56.9; H, 8.7. Found: C, 57.4; H, 8.7.

The still residue was recrystallized from heptane to give 49 g. (33%) of methyl 8-methoxy-6-keto-7-octenoate, m.p. 54–55°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 60.0; H, 8.0. Found: C, 60.0; H, 8.1.

The infrared spectrum of this compound shows an ester C=O at 1740 cm.$^{-1}$, conjugated ketone C=O at 1658 cm.$^{-1}$, and conjugated C=C at 1625 cm.$^{-1}$.

Another preparation carried out at 5°, in which the sodium chloride was removed by filtration, and then the mother liquor distilled, gave a 60% yield of methyl 8-methoxy-6-keto-7-octenoate, b.p. 126–127° (0.3 mm.). The solid was stored at −15° to retard decomposition.

Formylation of Methyl 6-Ketoheptanoate and Subsequent Reaction with Methanol.—Thirty grams (0.5 mole) of methyl formate (freshly distilled from phosphorus pentoxide) was added to a stirred suspension of 54 g. (1 mole) of sodium methoxide in 500 ml. of dry ether and was followed by a mixture of 90 g. (1.5 moles) of methyl formate and 158 g. (1 mole) of methyl 6-ketoheptanoate. The mixture was stirred for 2.5 hr. after the addition was complete, and then the ether was removed at the water pump. The residue was suspended in 6 moles of methanol and treated with a solution of 2 moles of hydrogen chloride in 4 moles of methanol while stirring at 15–20°. After stirring at room temperature for 16 hr., the suspension was made alkaline to litmus with a saturated solution of potassium hydroxide in methanol. The salts were removed by filtration, and the residue distilled to give 88.6 g. (56%) of recovered starting ester and 32 g. of higher boiling material. This was separated by distillation and recrystallization into 8 g. of an unidentified, unsaturated oil, b.p. 120–127° (0.2 mm.), $n^{21}D$ 1.4770 (probably methyl 6-methoxy-5-acetyl-5-hexenoate (VII), resulting from initial formylation on the methylene side of the ketone carbonyl), and 10 g. (5%) of the desired methyl 8-methoxy-6-keto-7-octenoate (VI), m.p. 54–55°.

Methyl 8-Thiocyano-6-keto-7-octenoate (VIII).—A solution of 60 g. (0.62 mole) of potassium thiocyanate in 60 ml. of water was added to a stirred solution of 79.9 g. (0.39 mole) of methyl 8-chloro-6-keto-7-octenoate in 400 ml. of acetone. The resulting solution was stirred at room temperature for 20 hr. and then for 3 hr. on a steam bath. After filtering to remove potassium chloride, the solution was cooled to 0°. Methyl 8-thiocyano-6-keto-7-octenoate (56.6 g.) crystallized in white flakes, m.p. 96–98°. Addition of water to the mother liquor and recrystallization of the precipitate gave an additional 15 g. of product, m.p. 95.5–97.5°, to make the total yield 71.6 g. (82%). Recrystallization from methanol gave the pure product, m.p. 98–99°.

Anal. Calcd. for $C_{10}H_{13}NO_3S$: C, 52.8; H, 5.8; N, 6.2; S, 14.1. Found: C, 52.8; H, 5.8; N, 6.2; S, 14.3.

Reaction of Potassium Ethylxanthate with Methyl 8-Chloro-6-keto-7-octenoate.—A solution of 20 g. (0.125 mole) of potassium ethylxanthate in 25 ml. of water was added to a stirred solution of 20.5 g. (0.1 mole) of methyl 8-chloro-6-keto-7-octenoate in 100 ml. of acetone. The resulting solution was stirred at room temperature for 20 hr. and then for 1 hr. on a steam bath. Addition of water precipitated 15.5 g. of solid melting at 85–95°. This was recrystallized from methanol to give material melting at 95–100° (39% recovery). Further recrystallization from

methanol gave a constant melting point of 97–99°. This product is not the expected xanthate derivative but $[CH_3O_2C(CH_2)_4CCH{=}CH]_2S$.

Anal. Calcd. for $C_{18}H_{26}O_6S$: C, 58.3; H, 7.1; S, 8.7; mol. wt., 370. Found: C, 58.0; H, 7.1; S, 8.8; mol. wt., 428.

The infrared spectrum of this product shows unsaturated CH absorption at 3030 cm.$^{-1}$, saturated CH at 2940 cm.$^{-1}$, ester C=O at 1740 cm.$^{-1}$, α,β-unsaturated C=O at 1680 cm.$^{-1}$, and absorption at 1540 cm.$^{-1}$ which can be attributed to sulfur attached to a double bond.

Reaction of Sodium Acetate with Methyl 8-Chloro-6-keto-7-octenoate.—A mixture of 34.9 g. (0.17 mole) of methyl 8-chloro-6-keto-7-octenoate and 14.0 g. (0.17 mole) of fused sodium acetate in 150 ml. of glacial acetic acid was stirred at room temperature for 72 hr. and then on a steam bath for 1 hr. After cooling the reaction mixture to room temperature, the insoluble material was removed by filtration, and the acetic acid was removed at reduced pressure. The residue was extracted with benzene, and these extracts were concentrated at 0.22 mm. while warming on a steam bath. There remained 32.6 g. of dark brown oil. A 28.6-g. portion of this oil was distilled to give 6.5 g. of liquid boiling over the range 110–140° (0.1–0.5 mm.). The liquid solidified upon cooling and was crystallized from ether to give 2.1 g. of white crystals, m.p. 35–37°. Extraction of the still residue with hot ether yielded another 4.0 g. of solid, m.p. 34–35°. By repeated recrystallization from ether, two compounds were isolated. The more insoluble compound, m.p. 101.5–102°, apparently was formed by condensation of two molecules of methyl 7-formyl-6-ketooctanoate with the elimination of one molecule of water.

Anal. Calcd. for $C_{18}H_{26}O_7$: C, 61.0; H, 7.4; mol. wt., 354. Found: C, 61.1; H, 7.4; mol. wt., 363.

This material exhibits bands at 1575, 1655, 1710, and 1740 cm.$^{-1}$ in the C=O and C=C region of the infrared. These absorptions can be used to rationalize various pyrone or cyclohexanone structures.

The mother liquor yielded a second compound, m.p. 36–37°. The analyses and infrared spectrum indicate that it is 1,3,5-tris-(4-methoxycarbonylvaleroyl)benzene (X), which would be expected from aldol condensation of three molecules of methyl 7-formyl-6-ketoheptanoate.

Anal. Calcd. for $C_{27}H_{36}O_9$: C, 64.3; H, 7.2; mol. wt., 505. Found: C, 64.4; H, 7.1; mol. wt., 535.

The infrared spectrum showed ester C=O at 1740 cm.$^{-1}$, ketone C=O at 1695 cm.$^{-1}$, and aromatic C=C at 1600 cm.$^{-1}$.

Reductive Thiolations.—In a typical reductive thiolation experiment, 1.0 mole of the compound to be reduced was charged into a stainless steel hydrogenation autoclave together with 3 moles of sulfur, 20 g. of cobalt polysulfide paste[7] and 200 ml. of appropriate solvent. The autoclave was filled with hydrogen to an initial pressure of 1500 p.s.i. and agitated and heated at 150° with frequent addition of hydrogen as needed to maintain the total pressure in the range of 1000–2500 p.s.i. As the rate of hydrogen absorption decreased, the temperature was gradually increased to a maximum of 200° and maintained at that level until all absorption ceased. The total reaction time was about 4 hr. The contents of the autoclave were filtered to remove the catalyst, and the solvents were removed under reduced pressure. This crude product was then tested for lipoic acid activity in the microbiological assay.[8] Fractionation gave methyl 6,8-dimercaptooctanoate and some of the free acid. In some cases, the crude product was not processed further. A summary of the reductive thiolations is given in Table I.

3-Pyrazolevaleric Acid (XII).—A solution of 99 g. (0.48 mole) of methyl 8-chloro-6-keto-7-octenoate in 250 ml. of ether was stirred in an icewater bath while 50 g. (1.0 mole) of hydrazine hydrate was added. The reaction mixture was stirred at room temperature overnight, heated under reflux for 2 hr., and then cooled in an ice bath. Two hundred milliliters of 45% potassium hydroxide was added with efficient stirring. The ether layer was separated and discarded, and the aqueous solution was neutralized with concentrated hydrochloric acid to precipitate 40.0 g. of 3-pyrazolevaleric acid, m.p. 134–136°. Evaporation of the mother liquor and extraction of the residue with alcohol gave another 34 g. of slightly less pure product to make the total yield 84 g. (92%). An analytical sample was prepared by recrystallization from water to constant melting point of 136–138°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.1; H, 7.2; N, 16.7. Found: C, 57.1; H, 7.4; N, 16.9.

5-Isoxazolevaleric Acid (XIII).—A mixture of 20.5 g. (0.1 mole) of methyl 8-chloro-6-keto-7-octenoate and 7.0 g. of hydroxylamine hydrochloride in 200 ml. of methanol was heated under reflux for 3 hr. Fifty grams (0.22 mole) of $CdCl_2 \cdot 2.5H_2O$ was added and refluxing was continued for another hour. The reaction mixture was allowed to stand at room temperature overnight, and then the crystalline complex was collected and decomposed by refluxing in water for 2 hr. Extraction with three 100-ml. portions of ether, removal of the ether, and recrystallization from benzene–cyclohexane gave 4.6 g. (27%) of 5-isoxazolevaleric acid, m.p. 82–84°. An analytical sample, m.p. 84–85°, was prepared by recrystallization from carbon tetrachloride.

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.8; H, 6.5; N, 8.3. Found: C, 56.9; H, 6.6; N, 8.0. The structure of this isoxazole was determined by conversion to 7-cyano-6-ketoheptanoic acid[9] in 65% yield by treatment with 10% sodium hydroxide. (If the side chain were in the 3-position, the compound would be stable to treatment with alkali.)

7-Cyano-6-ketoheptanoic Acid (XV). Method A. Ozonization of 1-Cyclohexenylacetonitrile.—A solution of 30 g. of 1-cyclohexenylacetonitrile in 500 ml. of methylene chloride was treated with 4.2% ozone for 3 hr. at −80°. An insoluble polymeric ozonide was formed. The methylene chloride was replaced with 500 ml. of glacial acetic acid and the resulting suspension added dropwise to a stirred solution of 17.1 g. of 30% hydrogen peroxide in 200 ml. of acetic acid held at 50–60° by a hot water bath. The resulting solution was heated to 90° for 4 hr. and the excess peroxide was decomposed with ferrous sulfate. The acetic acid and water were removed under reduced pressure, and the residue was extracted with ether to give 15.2 g. (36%) of material which was recrystallized several times from chloroform to give 7-cyano-6-ketoheptanoic acid, m.p. 99–99.5°.

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.8; H, 6.6; N, 8.3. Found: C, 56.6; H, 6.8; N, 8.0.

The infrared spectrum of this product shows C≡N absorption at 2250 cm.$^{-1}$, fine structure in the 2700–2500-cm.$^{-1}$ region for $-CO_2H$, and strong carboxy C=O at 1720 cm.$^{-1}$ with 1695-cm.$^{-1}$ shoulder for ketone C=O.

Method B. *Via* **5-Isoxazolevaleric Acid.**—A mixture of 41 g. (0.2 mole) of methyl 8-chloro-6-keto-7-octenoate and 15 g. of hydroxylamine hydrochloride in 400 ml. of methanol was heated under reflux for 3 hr. After standing at room temperature for 20 hr., the methanol was removed by distillation from the steam bath. The residue of 5-isoxazolevaleric acid was heated on a steam bath with a solution of 20 g. of sodium hydroxide in 300 ml. of water for 3 hr. Acidification with hydrochloric acid precipitated 20 g. (59%) of crude 7-cyano-6-ketoheptanoic acid. Recrystallization from ether gave material with a melting point of 96–98°. The infrared absorption of this material was identical in all respects to that of an authentic sample.

Acknowledgment.—The microbiological assays were carried out by Dr. C. W. deFiebre.