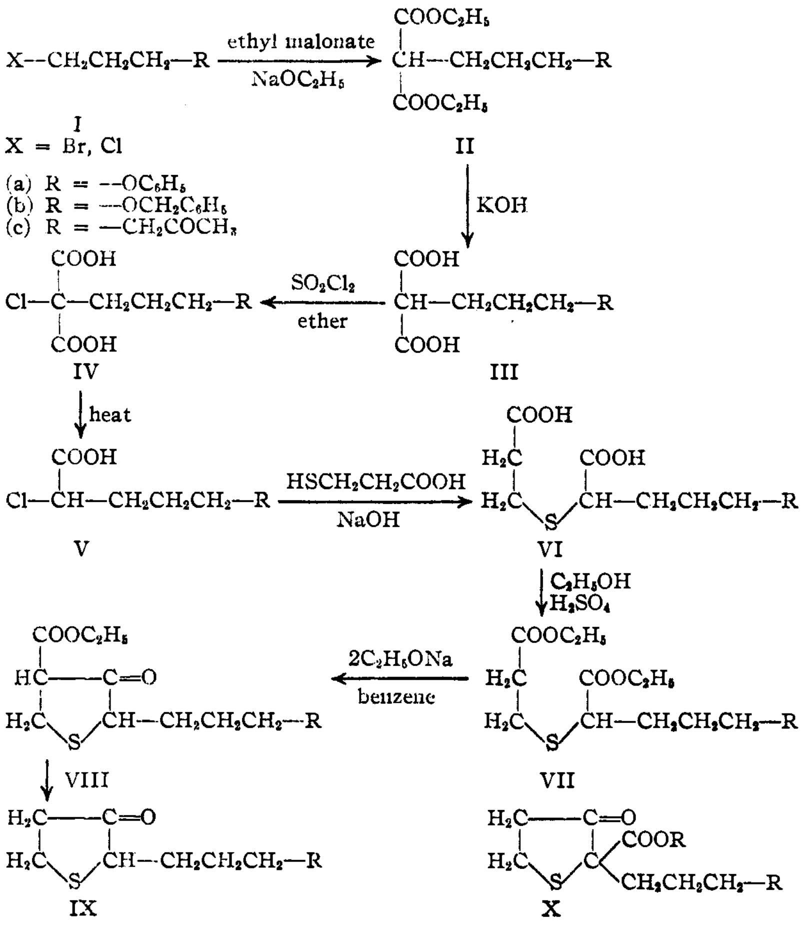
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

Some Tetrahydrothiophene β-Keto Ester Derivatives

BY LEE C. CHENEY AND J. ROBERT PIENING

In a recent report[1] the aromatization of the oximes of certain 4-carbethoxy-3-keto-2-(-ω-R-alkyl)-tetrahydrothiophenes was described. The sequence of reactions utilized for the synthesis of the parent keto esters may be presented schematically as follows



A similar series of reactions provided ethyl 4-carbethoxy-3-keto-2-tetrahydrothiophenevalerate, a key intermediate in the synthesis of 2,3,4,5-tetradehydrobiotin.[2]

The favorable over-all yields realized in the preparation of ethyl 3-keto-2-γ-phenoxypropyl-4-tetrahydrothiophenecarboxylate (VIIIa) rendered this compound particularly useful as a model for further experimentation directed toward the synthesis of biotin and related compounds.

The photobromination of γ-phenoxypropylmalonic acid (IIIa) under conditions approximating those employed by Fischer and Blumenthal[3] for the bromination of the homologous β-phenoxyethylmalonic acid led to an impure oily product attributed to appreciable nuclear halogenation. In contrast, the use of sulfuryl chloride afforded pure γ-phenoxypropylchloromalonic acid in yields of 85–90%.

Difficulties encountered in the cleavage of the phenyl ether in certain derivatives of VIIIa prompted the preparation of the corresponding benzyl ether by the sequence of reactions shown. To the more soluble, less stable intermediates in this series the lower yields may be ascribed.

In view of the fact that 5-hydroxy-2-pentanone can be chlorinated with sulfuryl chloride at 0°,[4] it was not surprising that the chlorination of IIIc failed to yield pure δ-acetylbutylchloromalonic acid (IVc). The crude reaction product, however, was carried through the sequence to obtain a small yield of VIIIc.

The Dieckmann cyclization of the diester sulfides (VII) could conceivably cause the formation of compounds corresponding to the alternate formula X. For the reasons that all of the keto esters develop an intense coloration with ferric chloride, form a characteristic green copper chelate compound with cupric acetate and undergo typical hydrolysis with dilute sulfuric acid to yield the corresponding ketones (IX), the assigned structure (VIII) is definitely established.

Since the completion of this work several research groups have disclosed the independent syntheses of various β-keto esters of tetrahydrothiophene by procedures comparable to the ones herein described.[5]

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(1) Cheney and Piening, THIS JOURNAL, **67**, 729 (1945).

(2) Cheney and Piening, *ibid.*, **67**, 731 (1945).

(3) Fisher and Blumenthal, *Ber.*, **40**, 107 (1907).

(4) Buchman, U. S. Patent 2,218,349 (1940); Perrine, *ibid.*, 2,216,574 (1940).

(5) Buchman and Cohen, THIS JOURNAL, **66**, 847 (1944); Woodward and Eastman, *ibid.*, **66**, 849 (1944); Karrer and Schmid, *Helv. Chim. Acta*, **27**, 116, 124, 1280 (1944); Schmid, *ibid.*, **27**, 127 (1944); Karrer and Kehrer, *ibid.*, **27**, 142 (1944); Karrer, Keller and Usteri, *ibid.*, **27**, 237 (1944); Bergel, Haworth and Avison, Roche Products Ltd., British Patents 562,313 and 562,314 (1944); Harris, Wolf, Mozingo, Anderson, Arth, Easton, Heyl, Wilson and Folkers, THIS JOURNAL, **66**, 1756 (1944); Harris, Easton, Heyl, Wilson and Folkers, *ibid.*, **66**, 1757 (1944); Surrey, Hammer and Suter, *ibid.*, **66**, 1933 (1944); Avison, Bergel, Cohen and Haworth, *Nature*, **154**, 459 (1944)

Experimental[6]

Ethyl γ-Phenoxypropylmalonate.[7]—Ethyl malonate was alkylated with γ-phenoxypropyl bromide[8] by the procedure of Merchant, Wickert and Marvel.[7a]

γ-Phenoxypropylmalonic Acid (IIIa).—To a cold, stirred mixture of 505 g. (1.71 moles) of IIa, b. p. 176–180° at 1–2 mm., $n^{20}\text{D}$ 1.4892, and 45 ml. of alcohol was slowly added a solution of 344 g. of potassium hydroxide in 550 ml. of water. The mixture was stirred for sixteen hours at room temperature. While being cooled in an ice–salt-bath the resulting clear pale-yellow solution was acidified by the introduction of a solution of 437 ml. of concentrated hydrochloric acid in 700 ml. of water at such a rate that the temperature was maintained below 20°. The product was extracted with ether and the washed extracts were dried over calcium chloride. Ether was removed in a current of air, care being taken to maintain the temperature below 50°. The oil was stirred with 1 liter of petroleum ether (b. p. 35–60°) to obtain 395.4 g. (97% yield) of colorless crystals, m. p. 115–116° (dec.).[9]

Anal. Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.40; H, 5.96.

γ-Phenoxypropylchloromalonic Acid (IVa).—Into a stirred solution of 540 g. (2.26 moles) of IIIa in 1950 ml. of anhydrous ether protected by a calcium chloride tube was added dropwise 309 g. (2.22 moles) of freshly distilled sulfuryl chloride (an excess should be avoided) over a period of three hours. After being stirred for ten hours at room temperature, the pale-yellow solution was refluxed for two hours. Most of the ether was removed by distillation. The remainder was evaporated in a jet of air while holding the temperature below 50°. The resulting oil was mixed with 2.7 liters of petroleum ether (b. p. 60–90°) and the cooled suspension was stirred until crystallization had taken place. The product was collected, washed with petroleum ether and air dried to produce 543 g. (88% yield) of the white crystalline chloro acid; m. p. 117–118° (dec.).

Anal. Calcd. for $C_{12}H_{13}O_5Cl$: C, 52.85; H, 4.80. Found: C, 53.01; H, 4.70.

α-Chloro-δ-phenoxyvaleric Acid (Va).—Three hundred and twenty grams (1.17 moles) of IVa was heated in a wax-bath to a temperature of 140–145°. When the evolution of carbon dioxide had ceased, the product was cooled and allowed to crystallize. The yield was quantitative (268 g.); m. p. 72–74°. Recrystallization of a sample from carbon tetrachloride produced white crystals, m. p. 74–75°.

Anal. Calcd. for $C_{11}H_{13}O_3Cl$: C, 57.77; H, 5.74. Found: C, 57.48; H, 5.59.

2-Carboxyethyl 1-Carboxy-4-phenoxybutyl Sulfide (VIa).—To a stirred solution of 156 g. (3.9 moles) of sodium hydroxide in 725 ml. of water was added 138 g. (1.3 moles) of β-mercaptopropionic acid[2] and 100 ml. of water used as a rinse. A solution of 291 g. (1.27 moles) of Va in 300 ml. of alcohol was then added dropwise. Following the removal of the alcohol by distillation, the clear solution was refluxed for two hours, chilled and acidified to congo red with concentrated hydrochloric acid. The white precipitate was extracted with ether and the washed extracts were dried over sodium sulfate. Removal of solvent left a quantitative yield (379 g.) of amber sirup which crystallized; m. p. 84–86°. A sample was recrystallized twice from benzene to produce small white crystals, m. p. 89.5–90.5°.

Anal. Calcd. for $C_{14}H_{18}O_5S$: C, 56.36; H, 6.08. Found: C, 56.37; H, 6.01.

2-Carbethoxyethyl 1-Carbethoxy-4-phenoxybutyl Sulfide (VIIa).—A mixture of 141.4 g. (0.47 mole) of the aforementioned acid (VIa), 1440 ml. of absolute alcohol and 14.5 ml. of concentrated sulfuric acid was refluxed on the steam-bath for 2.5 hours, whereupon 1 liter of alcohol was rapidly distilled through a nine-inch Vigreux column by means of an oil-bath maintained at 135–140°. The hot solution was poured on crushed ice and extracted with ether. Ether extracts were washed with sodium bicarbonate solution and dried over sodium sulfate. Distillation from a Claisen flask provided 147.1 g. (88% yield) of the ester as a pale-yellow oil, b. p. 200–205° at 3 mm.; $n^{20}\text{D}$ 1.5120.

Anal. Calcd. for $C_{18}H_{26}O_5$: C, 60.99; H, 7.40. Found: C, 60.99; H, 7.21.

Simplified Procedure.—A mixture of 168 g. (1.1 moles) of β-bromopropionic acid (Dow), 83.6 g. (1.1 moles) of thiourea and 1 liter of alcohol was refluxed for four hours. Most of the alcohol was distilled and the residue was refluxed for one hour with a solution of 140 g. (3.5 moles) of sodium hydroxide in 700 ml. of water. Into the resulting stirred mixture was introduced a solution of 42 g. of sodium hydroxide in 200 ml. of water, followed by the dropwise addition of an alcoholic solution of 228 g. (1.0 mole) of Va. The alcohol was then slowly distilled from the dark solution. The chilled solution was acidified to congo red and the product was extracted with ether. Removal of solvent from the dried ether solution afforded the crude acid (VIa) which was esterified as described above, but distillation of the ester was found unnecessary for the Dieckmann reaction. Moisture and low-boiling impurities were removed by dissolving the crude product in benzene, distilling the solvent and finally raising the bath temperature to 200° under reduced pressure (6 mm.). The crude, yellow ester, $n^{20}\text{D}$ 1.5108, weighed 322 g. (91% yield).

Ethyl 3-Keto-2-γ-phenoxypropyl-4-tetrahydrothiophenecarboxylate (VIIIa).—Thoroughly dried sodium ethoxide (wax-bath at 190–200° for several hours *in vacuo*) from 51.1 g. (2.22 moles) of clean sodium and 1 liter of absolute alcohol was cooled and suspended in 1800 ml. of sodium-dried benzene in an atmosphere of nitrogen. The suspension was swirled and cooled while 395.5 g. (1.11 moles) of undistilled ester (VIIa) in 400 ml. of dry benzene was added in several portions. The stoppered flask was shaken until practically all of the sodium ethoxide had dissolved. After standing overnight at room temperature the orange solution was refluxed under nitrogen for two hours, then cooled and acidified with a cold solution of 220 ml. of glacial acetic acid in 1800 ml. of water. The layers were separated and the aqueous layer was treated with 10 ml. of concentrated hydrochloric acid and extracted with 500 ml. of benzene. Combined benzene extracts were washed twice with sodium bicarbonate solution and water and dried over sodium sulfate. Solvents and low-boiling impurities were removed *in vacuo* up to a bath temperature of 190° to obtain the crude keto ester weighing 292 g. (85% yield).

Purification was effected through its copper chelate derivative. The crude keto ester dissolved in 250 ml. of ether was added portionwise to an excess of a saturated aqueous solution of cupric acetate and after shaking vigorously and allowing to stand several hours in the cold the pea-green granules were collected by suction and washed with water, alcohol and petroleum ether. A sample was digested with alcohol and recrystallized from benzene four times to obtain light-green microcrystals, m. p. 149–150° (dec.).

Anal. Calcd. for $C_{32}H_{38}O_8S_2Cu$: C, 56.65; H, 5.65; Cu, 9.39. Found: C, 56.65; H, 5.91; Cu, 9.30.

The keto ester was regenerated by shaking the chelate derivative with an excess of 15% sulfuric acid and 1 liter of ether. The layers were separated and the acid layer extracted with 1 liter of ether in two portions. Combined extracts were washed with sodium bicarbonate solution and water and dried over sodium sulfate. Removal of solvent and desiccation *in vacuo* gave 264 g. (77% yield) of a light-brown oil; $n^{20}\text{D}$ 1.5481.

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[6] All melting points are corrected.

[7] (a) Merchant, Wickert and Marvel, THIS JOURNAL, **49**, 1828 (1927), who cite prior work; (b) Prelog, Heimbach and Seiwerth, *Ber.*, **72**, 1319 (1939).

[8] Marvel and Tanenbaum, "Organic Syntheses," Coll. Vol. I, 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 435.

[9] Gabriel, *Ber.*, **25**, 418 (1892), has described the crude acid, m. p. 75–95°, which apparently suffered partial decarboxylation during recrystallization from water.

Anal. Calcd. for $C_{16}H_{20}O_4S$: C, 62.31; H, 6.53. Found: C, 62.19; H, 6.58.

In alcohol the compound develops an intense red-violet coloration with ferric chloride solution. It reacts with concentrated ammonium hydroxide to form a white crystalline compound which is unstable in the air,[10] owing to loss of ammonia. A semicarbazone was not obtained by the procedure which gave excellent results for the corresponding ketone (IXa).

A mixture of 15 g. (0.049 mole) of the keto ester (VIIIa), 6.8 g. (0.056 mole) of α-methyl-α-phenylhydrazine and two drops of glacial acetic acid was heated under an atmosphere of nitrogen in an oil-bath at 110–115° for three hours. The oily product was dissolved in 300 ml. of ether, washed with 100 ml. of 2% hydrochloric acid solution in three portions followed by three washings with water, and dried over sodium sulfate. Removal of solvent and desiccation *in vacuo* afforded 19.4 g. (94% yield) of the **α-methyl-α-phenylhydrazone,** a viscous orange oil which exhibited no tendency to crystallize.

Anal. Calcd. for $C_{23}H_{28}O_3N_2S$: N, 6.79. Found: N, 6.88.

3-Keto-2-γ-phenoxypropyltetrahydrothiophene (IXa).—A stirred suspension of 61.7 g. (0.2 mole) of VIIIa in 200 g. of 10% sulfuric acid was refluxed for fourteen hours. Cooling caused the dark bottom layer to crystallize in the form of a hard mass which was collected by filtration and crystallized from alcohol subsequent to treatment with Darco; weight, 26 g. (54.5% yield); m. p. 42–43°. Recrystallization of a sample from alcohol did not alter the melting point of the platelets.

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.06; H, 6.82. Found: C, 65.88; H, 6.74.

A sample of the aforementioned ketone was dissolved in dilute alcohol and warmed with an excess of semicarbazide hydrochloride and sodium acetate. Recrystallization of the **semicarbazone** from methyl isobutyl ketone gave colorless crystals, m. p. 192–193°.

Anal. Calcd. for $C_{14}H_{19}O_2N_3S$: N, 14.32. Found: N, 14.12.

Ethyl γ-Benzyloxypropylmalonate (IIb).—A solution of 68 g. (2.96 g. atoms) of sodium in 1250 ml. of absolute alcohol was made in a five-liter three-necked flask. The solution was cooled and treated with 675 g. (4.23 moles) of ethyl malonate. The suspension was refluxed and stirred while 520 g. (2.82 moles) of γ-benzyloxypropyl chloride[11] was added over a period of three hours, and then the stirring and refluxing were continued for twenty-one hours. Most of the alcohol was removed by distillation, the residue cooled, and water added to dissolve inorganic salt. The layers were acidified with glacial acetic acid and separated. The water layer was extracted three times with ether. Oil and extracts were combined, washed once with water, twice with 10% sodium bicarbonate, once with saturated sodium chloride solution and finally dried over sodium sulfate. The product distilling at 193–200° at 4 mm. weighed 606.7 g. (77% yield); $n^{20}\text{D}$ 1.4836. About 50 g. of γ-benzyloxypropyl chloride was recovered.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 65.89; H, 8.04.

γ-Benzyloxypropylmalonic Acid (IIIb).—To a cold, well-stirred solution of 405 g. of potassium hydroxide in 648 ml. of water and 50 ml. of alcohol was added 606.7 g. (1.96 moles) of IIb over a period of two hours. The resulting solution was stirred for six hours in an ice-bath and then was allowed to stand overnight. After extracting the yellow solution twice with 500-ml. portions of ether, it was cooled in an ice-bath, diluted with 800 ml. of water, covered with 1 liter of ether, and made acid to congo red with concentrated hydrochloric acid. The layers were separated and the acid layer extracted three times with 500-ml. portions of ether. Extracts were combined, washed twice with water, once with saturated sodium chloride solution, and dried over sodium sulfate. After filtration about two-thirds of the ether was removed by distillation. The residue was transferred to a large evaporating dish and the residual ether removed on the steam-bath in a stream of air. When crystals began to form, 500 ml. of petroleum ether (30–60°) was added. The crystallization was aided by stirring. The white crystals were collected on a Büchner funnel, washed with petroleum ether and dried. The yield was 470.7 g. (95%); m. p. 89–90°. When the compound was recrystallized from ether by adding petroleum ether until a turbidity remained, the melting point was 91°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.19; H, 6.58.

γ-Benzyloxypropylchloromalonic Acid (IVb).—A solution of 470 g. (1.86 moles) of IIIb in 1500 ml. of dry ether was placed in a three-liter three-necked flask fitted with a mercury-sealed stirrer, condenser and dropping funnel, both protected by calcium chloride tubes. To the stirred solution was added 150 ml. (251 g., 1.86 moles) of redistilled sulfuryl chloride over a period of 1.5 hours. When addition was completed the stirred solution was refluxed for two hours. Most of the ether was removed by distillation. The residue was poured into an evaporating dish and the excess ether removed by warming and blowing with a jet of air. When the product began to crystallize 500 ml. of petroleum ether was stirred into the product until crystallization was completed. The crystals were washed by decantation with petroleum ether, then collected and dried *in vacuo*. The yield was 508.2 g. (95.5%); m. p. 120°. Recrystallization of a sample from ether-petroleum ether gave white crystals which melted at 123–124° with gas evolution.

Anal. Calcd. for $C_{13}H_{15}O_5Cl$: C, 54.45; H, 5.27. Found: C, 54.61; H, 5.41.

δ-Benzyloxy-α-chlorovaleric Acid (Vb).—Portions of about 100 g. each of IVb were decarboxylated in a wax-bath maintained at 120–125°. The internal temperature never rose above 123° at any time. In all, 494.7 g. of the substituted malonic acid were decarboxylated, yielding the theoretical amount (419 g.) of product which remained as a thick oil.

Anal. Calcd. for $C_{12}H_{15}O_3Cl$: C, 59.40; H, 6.23. Found: C, 59.74; H, 6.43.

Ethyl 2-γ-Benzyloxypropyl-3-keto-4-tetrahydrothiophenecarboxylate (VIIIb).—β-Mercaptopropionic acid was prepared from 264 g. (1.73 moles) of β-bromopropionic acid according to the simplified procedure given for the preparation of 2-carbethoxyethyl 1-carbethoxy-4-phenoxybutyl sulfide (VIIa).

A solution of 112.4 g. (2.73 moles) of sodium hydroxide in 600 ml. of water was added to the reaction mixture and the whole warmed to 60°. An alcoholic solution of 419 g. (1.73 moles) of Vb was added over a period of one and a half hours. The suspension was heated for two hours while alcohol was being removed by distillation, cooled and extracted twice with ether. The basic solution was cooled, made acid to congo red with concentrated hydrochloric acid, and extracted thrice with 500-ml. portions of ether. The extracts were washed thrice with water, once with saturated sodium chloride solution and dried over sodium sulfate; solvent was removed and chloroform added and distilled to remove residual water. All attempts to crystallize the acid (VIb) failed, so the crude oil weighing 440 g. (82% yield) was esterified as such.

A mixture of 440 g. (1.41 moles) of VIb, 700 ml. of absolute alcohol, 480 ml. of toluene and 2.5 ml. of concentrated sulfuric acid was heated in a two-liter flask connected to a downward condenser. The azeotropic mixture of alcohol, toluene and water distilled at 75°. Heating was continued until the temperature rose to 78° (oil-bath temperature during this time was 115°). The distillate was collected in a flask containing 212 g. of anhydrous potassium carbonate and the flask was stoppered and shaken vigorously. After filtering the distillate through a

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(10) For comparable compounds see Dieckmann, *Ann.*, **317**, 37, 58, 100 (1901).

(11) Bennett and Hock, *J. Chem. Soc.*, **128**, 472 (1927).

Büchner funnel it was returned to the original flask. Heating was begun again and continued until the temperature of the vapor reached 80°. The flask was cooled and the residue diluted with water and ether. The ether layer was shaken with 10% sodium bicarbonate solution until free of acid, then washed with water and saturated sodium chloride solution and dried over sodium sulfate. Solvents were removed and the residue was placed in a modified Claisen flask and heated to 195° at 4 mm. This treatment removed all lower boiling impurities and the residue (378.3 g., 73% yield) was essentially the desired ester.

A portion of the ester (VIIb) distilled at 210–216° at 2 mm., but distillation was not necessary to obtain a product sufficiently pure for the Dieckmann reaction.

Dry sodium ethoxide was prepared from 4.35 g. (0.189 mole) of sodium and 70 ml. of absolute alcohol and suspended in 100 ml. of dry benzene. To this suspension was added 34.8 g. (0.0945 mole) of 2-carbethoxyethyl 1-carbethoxy-4-benzyloxybutyl sulfide (VIIb), b. p. 210–216° at 2 mm., dissolved in 50 ml. of dry benzene. The whole was shaken thoroughly and cooled when the flask became warm. The dark-brown solution was allowed to stand overnight, then was cooled in an ice-bath and acidified with a solution of 20 ml. of glacial acetic acid in 160 ml. of water. The layers were separated and the water layer was extracted twice with benzene. Benzene fractions were washed with water, sodium bicarbonate solution and clarified with saturated sodium chloride solution. Benzene was removed by distillation and the residue, weighing 26.44 g., was shaken with a saturated solution of cupric acetate. The green chelate compound was taken up in ether and the ether solution evaporated to a small volume and treated with petroleum ether. Scratching the sides of the flask initiated crystallization. The light-green product was collected on a Büchner funnel, washed with water until free of acetic acid and dried. The yield of product was 23.5 g. A portion was recrystallized from alcohol to a constant m. p. of 107–108°.

Anal. Calcd. for $C_{34}H_{44}O_8S_2Cu$: C, 57.64; H, 6.26; Cu, 8.97. Found: C, 57.55; H, 6.04; Cu, 9.10.

The keto ester was regenerated by shaking an ether solution of the copper compound with 10% sulfuric acid. The ether layer was washed with water, 10% sodium bicarbonate solution and dried over sodium sulfate. After the solvent was removed, the residue weighed 20.4 g. (69% yield).

Anal. Calcd. for $C_{17}H_{22}O_4S$: C, 63.32; H, 6.87. Found: C, 63.41; H, 6.61.

Ethyl δ-Acetylbutylmalonate (IIc).—Into the cooled, stirred solution of sodium ethoxide prepared from 22.2 g. (0.965 mole) of sodium in 335 ml. of absolute alcohol was slowly introduced 310 g. (1.93 moles) of ethyl malonate. The resulting mixture was refluxed during the dropwise addition of 173 g. (0.965 mole) of 6-bromo-2-hexanone,[12] b. p. 93–96.5° at 10 mm., and the refluxing was continued for sixteen hours. Following distillation of the alcohol the salt was dissolved in a minimum of cold water and the mixture was acidified with acetic acid. The ester was extracted with ether and the solution was washed successively with sodium bicarbonate solution, saturated sodium chloride solution and dried over sodium sulfate. Distillation from a modified Claisen flask produced 185 g. (74% yield) of the colorless ester, b. p. 154–157° at 3 mm.

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.62; H, 8.37.

δ-Acetylbutylmalonic Acid (IIIc).—To a stirred solution of 212 g. of potassium hydroxide in 340 ml. of water and 40 ml. of alcohol cooled to 10° was added dropwise 272 g. (1.05 moles) of IIc. The mixture was stirred overnight while the ice melted without replacement. Following extraction with ether the stirred yellow alkaline solution was cooled and then acidified by the gradual introduction of 275 ml. of concentrated hydrochloric acid while maintaining the internal temperature below 10°. After enough water had been added to dissolve the potassium chloride, the mixture was extracted five times with ether. Combined ether extracts were washed with a saturated solution of sodium chloride and dried over sodium sulfate. Removal of ether in a current of air at a temperature below 35° left an oil which crystallized in a vacuum desiccator; m. p. 79–82° (dec.) with previous softening; weight, 181.9 g. (85% yield).

Anal. Calcd. for $C_9H_{14}O_5$: C, 53.46; H, 6.98. Found: C, 53.43; H, 6.96.

Ethyl 2-δ-Acetylbutyl-3-keto-4-tetrahydrothiophenecarboxylate (VIIIc).—To a stirred suspension of 138.2 g. (0.68 mole) of δ-acetylbutylmalonic acid in 1200 ml. of dry ether was added dropwise 55.3 ml. (0.68 mole) of freshly distilled sulfuryl chloride over a period of one and a half hours. The resulting solution was stirred for five hours and allowed to stand overnight. After most of the ether had been distilled the residual solvent was removed in a current of air. The oily product (IVc) failed to crystallize during desiccation *in vacuo* for four days. Consequently, the oil was decarboxylated in a wax-bath at 150° to obtain 128.5 g. (a 98% yield based on IIIc) of crude α-chloro-ζ-ketooctanoic acid (Vc) as a dark-brown oil which could not be crystallized.

Under an atmosphere of nitrogen a solution a 67.1 g. (0.253 mole) of the chloro acid (Vc) was added dropwise to a cold, stirred solution prepared from 200 ml. of water, 42 g. of sodium hydroxide and 37.2 g. (0.35 mole) of β-mercaptopropionic acid. When addition was completed the mixture was refluxed for two hours. Most of the alcohol was then distilled and the well-cooled mixture was rendered acid to congo red with hydrochloric acid. The brown oil which precipitated was extracted with ether and dried over sodium sulfate. Following removal of solvent the brown oily crude acid (VIc), which weighed 96.6 g., was refluxed for two hours with 1100 ml. of absolute alcohol and 11 ml. of concentrated sulfuric acid. The ester (VIIc) was isolated as described for VIIa. Considerable decomposition attended the distillation from a modified Claisen flask. The fraction boiling over the range 174–195° at 1–2.5 mm. weighed 42.7 g. Dieckmann cyclization of 40.9 g. (0.13 mole) of this product in accordance with the method employed for the preparation of VIIIa yielded 22.8 g. of orange-brown oil from which 11.7 g. of the yellow-green copper chelate derivative, m. p. 105–106.5°, was obtained. Decomposition of the latter with 15% sulfuric acid afforded 7.2 g. of the purified keto ester (VIIIc) as an orange-red oil. When dissolved in alcohol it was colored cherry red by ferric chloride solution.

Anal. Calcd. for $C_{12}H_{20}O_4S$: C, 57.33; H, 7.40. Found: C, 57.07; H, 7.07.

Acknowledgment.—The authors wish to thank Mr. A. W. Spang for the microanalyses.

Summary

The syntheses of ethyl 3-keto-2-γ-phenoxypropyl-4-tetrahydrothiophenecarboxylate (VIIIa), ethyl 2-γ-benzyloxypropyl-3-keto-4-tetrahydrothiophenecarboxylate (VIIIb) and ethyl 2-δ-acetylbutyl-3-keto-4-tetrahydrothiophenecarboxylate (VIIIc) are described.

DETROIT, MICHIGAN RECEIVED JULY 27, 1945

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[12] (a) Kipping and Perkin, Jr., *J. Chem. Soc.*, **55**, 331 (1889); (b) Lipp, *Ann.*, **289**, 182 (1896).