NOTES

The Synthesis of Ethyl 4-Carbethoxy-3-keto-2-tetrahydrothiophenevalerate, the Synthetic Intermediate of Biotin

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Biotin has previously been synthesized by Cheney and his co-workers through the diethylester of 4-carboxy-3-keto-2-tetrahydrothiophenevaleric acid[1] and by Baker and his coworkers through the corresponding dimethylester.[2] Although these synthetic intermediates were prepared by the same investigators, many steps were involved in their methods, and hence the yields were poor.

This paper will describe an improved method of synthesizing ethyl 4-carbethoxy-3-keto-2-tetrahydrothiophenevalerate, a method in which five steps are involved, as is shown in Fig. 1.

The starting compound, cyclohexanone, was first converted to 2-carbethoxycyclohexanone (II) and then to 6-bromo-2-carbethoxycyclohexanone (III) by Brenner's method.[3] Compound III condensed readily with ethyl β-mercaptopropionate in the presence of sodium ethoxide to produce 2-carbethoxy-6-(β-carbethoxyethylthio)cyclohexanone (IV), which gave an intense purple color with ferric chloride in ethanol.

The treatment of IV with a strong alkali gave a ring-opening product, 2-carboxyethyl 1,5-dicarboxyamyl sulfide (V), along with a by-product, 2-(β-carboxyethylthio)cyclohexanone (IX). The isolation and purification of V and IX were not attempted in this step, since their boiling points were too high for them to be distilled, even under reduced pressure. The esterification of a mixture of V and IX gave the corresponding esters, 2-carbethoxyethyl 1,5-dicarbethoxyamyl sulfide (VI) and 2-(β-carbethoxyethylthio)cyclohexanone (X). The by-product, X, was identified by means of a comparison of its infrared spectrum and the melting point of its 2,4-dinitrophenyhydrazone with those of an authentic sample prepared from 2-chlorocyclohexanone (VIII) and ethyl β-mercaptopropionate, as is shown in Fig. 2.

The yields of VI and X varied to some

1) L. C. Cheney et al., *J. Am. Chem. Soc.*, **66**, 1040 (1944); **67**, 729 731, 2213, 2252 (1945).
2) B. R. Baker et al., *J. Org. Chem.*, **12**, 138, 155, 160, 167, 174, 186, 322, 328, 475, 483 (1947); **13**, 123 (1948).
3) J. E. Brenner, ibid., **26**, 22 (1961).

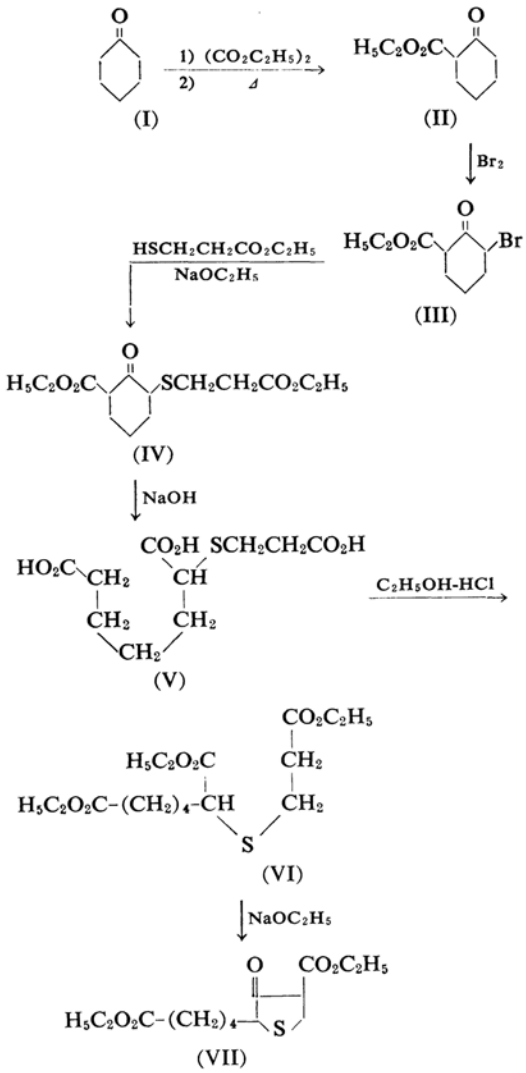

Fig. 1.

extent in each experiment. Compound VI was obtained in a 64% yield based on IV under the reaction conditions described in the "Experimental" section.

The Dieckmann cyclization of VI was performed by Cheney's method to produce VII. The melting point of its copper chelate compound agreed satisfactorily with the literature value.[1]

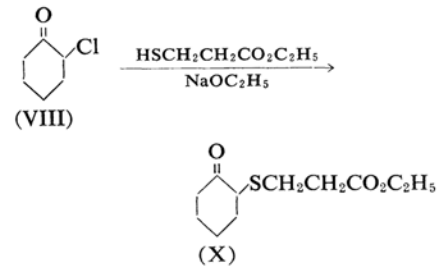

Fig. 2.

Experimental*

2-Carbethoxy-6-(β-carbethoxyethylthio)-cyclohexanone (IV). — To a solution of sodium ethoxide (4.6 g. of sodium and of 70 ml. absolute ethyl alcohol), a solution of 27 g. of ethyl β-mercaptopropionate in 10 ml. of absolute ethyl alcohol was added. After this mixture had been cooled in a dry ice-acetone bath to −20°C, a solution of 50 g. of 6-bromo-2-carbethoxycyclohexanone in 20 ml. of ethyl alcohol was stirred drop by drop into the mixture under nitrogen. After the addition had been completed, stirring was continued for two hours at room temperature. During this period sodium bromide precipitated. After it had stood for fifteen hours at room temperature, the mixture was concentrated under reduced pressure to about 70 ml. The residue was poured into water, and the oily layer obtained was separated. The aqueous layer was then extracted three times with ether. The oily compound and the extracts were combined, washed with sodium bicarbonate solution, and dried over sodium sulfate. The ether was removed, and the residue was distilled to give 51 g. (84%) of IV as a colorless oil; b. p. 141—142°C/0.1 mmHg.

Found: C, 55.67; H, 7.42. Calcd. for $C_{14}H_{22}O_5S$: C, 55.61; H, 7.33%.

2-Carbethoxyethyl 1,5-Dicarbethoxyamyl Sulfide (VI).—In a 300 ml. three-necked flask equipped with a stirrer, a dropping funnel, a reflux condenser, a gas inlet tube and a thermometer were placed 50 g. of sodium hydroxide, 40 g. of water and 110 g. of ethyl alcohol. The stirred mixture was then heated for half an hour in a water bath at 50°C under nitrogen. A solution of 20 g. of 2-carbethoxy-6-(β-carbethoxyethylthio)cyclohexanone in 40 ml. of ethyl alcohol was then added to the mixture over a period of twenty minutes. The resulting mixture was heated further for five hours at 50°C. After this mixture had been diluted with 100 ml. of water, ethyl alcohol was removed under reduced pressure. The residue was washed with 50 ml. of ether, and the aqueous layer was made acidic to Congo red with concentrated hydrochloric acid. The mixture was continuously extracted with ether for forty hours, and the extract was dried over sodium sulfate. The ether was removed, and the residual, thick, oily compound was dissolved in 150 ml. of absolute ethyl alcohol. The solution was cooled in an ice-bath, saturated with dry hydrogen chloride, and refluxed for half an hour. Ethyl alcohol was then evaporated to about 50 ml. The residue was diluted with 200 ml. of water, and the oily compound obtained was separated. The aqueous layer was extracted with ether. The oily compound and the extracts were combined and washed with a sodium bicarbonate solution and then with water.

After the ether had been removed, the VI, distilling at 178.5—180°C/0.25 mmHg., weighed 14.8 g. (64%). The redistillation of the lower boiling

* All boiling and melting points are uncorrected.

distillate gave 1.9 g. (13%) of 2-(β-carbethoxyethylthio)cyclohexanone, b. p. 149—151°C/1 mmHg.

2-(β-Carbethoxyethylthio)cyclohexanone (X). — To a solution of 3.5 g. of sodium in 80 ml. of absolute ethyl alcohol, 20 g. of ethyl β-mercapto-propionate in 10 ml. of ethyl alcohol was added. To the stirred solution 20 g. of 2-chlorocyclohexanone in 40 ml. of ethyl alcohol was then added over a period of half an hour while the temperature was maintained at −20°C. After it had stood for fifteen hours at room temperature the mixture was diluted with 300 ml. of water and extracted three times with ether. The combined extract was then washed successively with aqueous sodium bicarbonate and dilute hydrochloric acid. After the ether had been removed, 31 g. (89%) of an oil was obtained; b. p. 151—152°C/1 mmHg.

Found: C, 57.48; H, 8.02. Calcd. for $C_{11}H_{18}O_3S$: C, 57.36; H, 7.88%.

The 2,4-dinitrophenylhydrazone prepared in the usual manner was separated as orange-yellow crystals from ethyl alcohol; m. p. 103—104°C.

Ethyl 4-Carbethoxy-3-keto-2-tetrahydrothiophenevalerate (VII). — According to the method of Cheney,[3] 3 g. of 2-carbethoxyethyl-1,5-dicarbethoxyamylsulfide (VI) in dry benzene was treated with sodium ethoxide at room temperature. The light-brown oil thus obtained gave a deep-red color when treated with ferric chloride in an alcoholic solution. The oil was converted into a copper chelate compound by treating it with a saturated cupric acetate solution. The recrystallization of the chelate compound from ether-petroleum ether yielded 2.6 g. (90.5%) of fine, light-green crystals, m. p. 120—121°C.

Found: C, 50.60; H, 6.55. Calcd. for $(C_{14}H_{22}O_4S)_2$-Cu: C, 50.32; H, 6.63%.

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