Synthesis of Sarkomycin. II.[1] *A New Synthesis of the Alkyl Cyclopentanone-3-carboxylate*

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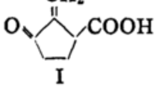
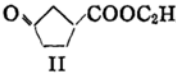
In the previous report[1], the present author described the synthesis of *dl*-sarkomycin (2-methylenecyclopentanone-3-carboxylic acid) (I) starting from ethyl cyclopentane-3-carboxylate[2] (II).



I



II

Though the alkyl cyclopentanone-3-carboxylate (II) is a key substance for the preparation of *dl*-sarkomycin, the hitherto published methods are so complicated for the commercial preparation of alkyl cyclopentanone-3-carboxylate (II) that the present author has studied the synthesis of this intermediate by means of a new convenient route.

It was found that the cyclopentanone-3-carboxylate (II) can be readily obtained by the thermal decomposition of monoester of 1, 2, 4-butanetricarboxylic acid (3-alkoxycarbonyladipic acid) (VI) which was prepared from butadiene (III) and alkyl acrylate (IV) according to the following new scheme. (See Fig. 1).

Cyclohexene-4-carboxylate[3] (V) was prepared in a good yield (71.4%) by heating butadiene (III) with alkyl acrylate (IV) in an autoclave at 170∼180° in the presence of polymerization inhibitors such as hydroquinone.

Monoester of 1, 2, 4-butanetricarboxylic acid (VI) was obtained by the oxidation[4] of V with potassium permanganate in a 67.2% yield. While cyclopentanone-3-carboxylic acid (X) could be prepared from the triester VII according to Kay's precedure[2], the cyclopentanone-3-carboxylate (II) was formed directly when monoester VI was heated at 200∼300° at atmospheric pressure and then distilled under a reduced pressure. The cyclopentanone-3-carboxylate (II), thus obtained, was identical with the specimen prepared by Kay's method[2].

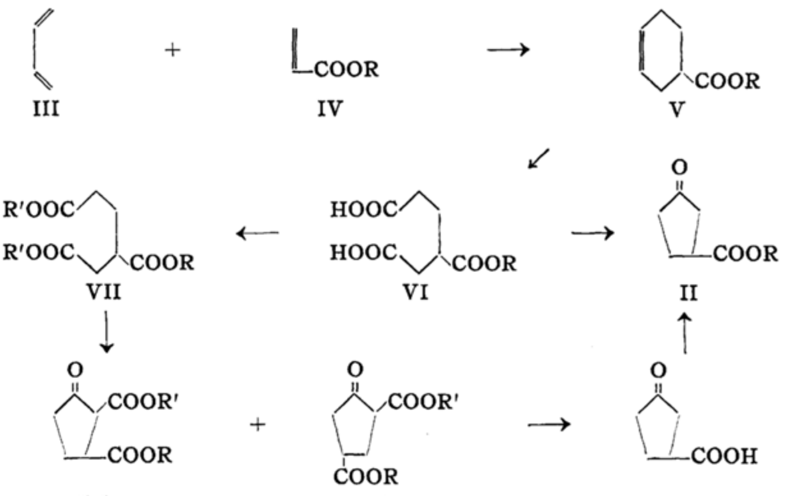


Fig. 1. The new route for the synthesis of alkyl cyclopentanone-3-carboxylate.

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[1] I. Synthesis. of *dl*-sarkomycin (2-methylenecyclopentane-3-carboxylic acid). K. Toki, This Bulletin, **30**, 450 (1957).

[2] F. W. Kay et al., *J. Chem. Soc.*, **89**, 1640 (1906).

[3] Ger., Pat., 857, 637, Dec. 1, (1952).

[4] Brit. Pat., 688, 344, Mar. 4, (1953).

Experimental

Methyl cyclohexene-4-carboxylate (V, R=CH_3).—A mixture of 86 g. (1 mole) of methyl acrylate (IV, R=CH_3), 108 g. (2 moles) of butadiene[5] (III) and 1 g. of hydroquinone was heated in an autoclave at 170° for twenty hours. The reaction mixture was distilled in vacuo to remove the polymeric materials and the distillate was fractionated through a Widmer-column. The fraction boiling at 182~185° (99~107°/100 mm.), n_D^{31} 1.4574, was collected. The yield was 90 g. (64.3%).

Anal. Found: C, 68.56; H, 8.58. Calcd. for $C_8H_{12}O_2$: C, 68.57; H, 8.57%.

Ethyl cyclohexene-4-carboxylate (V, R=C_2H_5).—A mixture of 100 g. (1 mole) of ethyl acrylate (IV, R=C_2H_5), 108 g. (2 moles) of butadiene and 1 g. of hydroquinone was treated in the same manner as above. The yield of V (R=C_2H_5), b.p. 105~110°/100 mm., was 110g. (71.4%).

Anal. Found: C, 70.03; H, 8.88. Calcd. for $C_9H_{14}O_2$: C, 70.13, H, 9.09%.

Monoester of 1,2,4-butanetricarboxylic acid (3-Alkoxycarbonyladipic acid (VI)).—*a*) *Methylester.*—Finely powdered potassium permanganate (461 g.) was added in small portions to a mixture of 140 g. (1 mole) of V and 2000 ml. of water with vigorous stirring over a period of five hours at temperatures below 50°. Manganese dioxide was filtered off and the filtrate was acidified with diluted hydrochloric acid and extracted with ether in a large continuous extracter for five days. The ether layer was dried over anhydrous sodium sulfate, the ether was removed and the residue was then distilled in vacuo. The yield of VI, (R=CH_3) b.p. 209~213°/0.4 mm., was 137.1 g. (67.2%). It was recrystallized from a mixture of ethyl acetate and petroleum ether, m.p. 95~97°.

Anal. Found: C, 47.05; H, 5.79. Calcd. for $C_8H_{12}O_6$: C, 47.06; H, 5.88%.

b) *Ethylester.*—A suspension of 154 g. (1.0 mole) of V (R=C_2H_5) in 2000 ml. of water was oxidized with 461 g. of potassium permanganate in the same manner as described above. The yield of VI (R=C_2H_5), b.p. 217~220°/0.5 mm., was 140 g. (64.2%).

Anal. Found: C, 49.48; H, 6.37. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.42%.

Diethyl methyl 1,2,4-butanetricarboxylate (VII, R=CH_3, R′=C_2H_5).—A mixture of 102 g. (0.5 mole) of VI (R=CH_3), 1000 ml. of absolute ethanol and 10 g. of concentrated sulfuric acid was refluxed on a water bath for eight hours. After concentration of the reaction mixture, the residue was poured into ice and water. The oily layer was extracted with ether, washed with 5% aqueous sodium bicarbonate solution and dried over anhydrous sodium sulfate. The ether was removed and the residue was distilled under a reduced pressure. The yield of VII, b.p. 185~190°/28 mm., n_D^{24} 1.4412, was 80 g. (61.5%).

Anal. Found: C, 55.34; H, 7.53. Calcd. for $C_{12}H_{20}O_6$: C, 55.38; H, 7.69%.

Triethyl 1,2,4-butanetricarboxylate (VII, R=R′=C_2H_5).—A mixture of 109 g. (0.5 mole) of VI (R=C_2H_5), 1000 ml. of absolute ethanol and 10 g. of concentrated sulfuric acid was refluxed on a water bath for eight hours. The reaction mixture was warked up in the same manner as above. The final product, b.p. 190~202°/24 mm., weighed 73 g. (53.3%).

Anal. Found: C, 57.00; H, 8.00. Calcd. for $C_{13}H_{22}O_6$: C, 56.93; H, 8.03%.

Methyl cyclopentanone-3-carboxylate (II, R=CH_3).—After heating 51 g. (0.25 mole) of VI (R=CH_3) with 1 g. of barium oxide at 250~300° for 10~30 minutes, the mixture was distilled under a reduced pressure. The product came over at 122~125°/18 mm. and weighed 10.2 g. (28.7%).

Anal. Found: C, 59.18; H, 7.00. Calcd. for $C_7H_{10}O_3$: C, 59.15; H, 7.04%.

The 2,4-dinitrophenylhydrazone melted at 182~184° (recrystallized from a mixture of ethyl acetate and petroleum ether).

Ethyl cyclopentanone-3-carboxylate (II, R=C_2H_5) from VII (R=R′=C_2H_5).—To a suspension of 13 g. of sodium-sand in 300 ml. of benzene was added 137 g. (0.5 mole) of triethyl 1,2,4-butanetricarboxylate (VII, R=R′=C_2H_5). When the vigorous reaction subsided, the reaction mixture was heated for two hours with stirring and acidified with diluted hydrochloric acid.

The whole mixture was extracted with ether and the ether layer was washed with 5% aqueous solution of sodium bicarbonate and then with water. The ether solution was dried over anhydrous calcium chloride, the ether was removed and the residue was distilled. The yield of diethyl cyclopentanone-2,3- and -2,4-carboxylates, b.p. 131~137°/0.6 mm., was 96 g. (84%).

A solution of 96 g. (0.42 mole) of diethyl cyclopentanone-2,3- and -2,4-carboxylates in 1. of 8% sulfuric acid was boiled for three hours. Cyclopentanone-3-carboxylic acid (X) was extracted from the reaction mixture with ether, the ether layer was dried over anhydrous calcium chloride and the ether was distilled off. The residue was distilled at 138~145°/0.3 mm., m.p. 64~65°, and weighed 45 g. (83%).

A mixture of 45 g. (0.35 mole) of X, 180 ml. of benzene, 75 ml. of 99% alcohol and 4 g. of *p*-phenolsulfonic acid was refluxed for two days, a water separator being used. The ethyl ester (II) was obtained in a yield of 51 g. (93%): b.p. 127~128°/20 mm.

Anal. Found: C, 61.48 H, 7.63. Calcd. for $C_8H_{12}O_3$: C, 61.54; H, 7.69%.

The 2,4-dinitrophenylhydrazone melted at 153~154°.

Anal. Found: C, 49.77; H, 4.65; N, 16.93. Calcd. for $C_{14}H_{16}O_6N_4$: C, 50.00; H, 4.76; N, 16.67%.

Summary

Cyclopentanone-3-carboxylate which is the starting material for the synthesis of *dl*-sarkomycin (2-methylenecyclopentanone-3-carboxylic acid) was obtained by a new

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[5] Butadiene was prepared by the procedure described in "Organic Syntheses", Coll. Vol. II, John Wiley and Sons, Inc., New York (1943), p. 102.

route from butadiene and alkyl acrylate through alkyl cyclohexene-4-carbonylate and thence 3-alkoxycarbonyl adipic acid.

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