Studies on Sarkomycin—Preparation of Optically Active 2-Methylenecyclopentanone-3-carboxylic Acids

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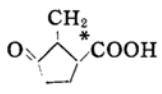
Hooper et al.[1] reported in 1955 that the effective ingredient of the natural sarkomycin is 2-methylenecyclopentanone-3-carboxylic acid. Afterwards, the present author[2] synthesized *dl*-2-methylenecyclopentanone-3-carboxylic acid (I), starting from alkyl cyclopentanone-3-carboxylate. Tatsuoka et al.[3] showed that the naturally occurring sarkomycin is in the levoform.



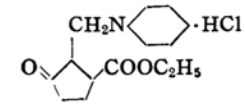
I

In the present paper, the preparation of optically active 2-methylenecyclopentanone-3-carboxylic acids is described.

Since 2-methylenecyclopentanone-3-carboxylic acid is a very unstable compound, and, moreover, is an α,β-unsaturated ketone liable to react with active amines, a direct resolution may be very difficult. As 2-methylenecyclopentanone-3-carboxylic acid has only one asymmetric carbon, preparation from an active intermediate is likely more convenient to obtain it in the optically active form. The use of active cyclopentanone-3-carboxylic acid being suggested, the present author resolved *dl*-cyclopentanone-3-carboxylic acid with brucine which was the best suited for this purpose.

When brucine was combined with *dl*-cyclopentanone-carboxylic acid in aqueous solution, 80% of the expected amount of brucine *d*-cyclopentanone-3-carboxylate was deposited, and the mother liquor gave the nearly pure brucine *l*-cyclopentanone-3-carboxylate on evaporation. Pure salts were obtained in theoretical yields by repeated recystallization from hot water. The active acid and the alkaloid were easily recovered by adding aqueous ammonia or a mineral acid.

When cinchonine was employed, separation of cinchonine *d*- and *l*-cyclopentanone-3-carboxylates required laborious recrystallization. The two optically active 2-methylenecyclopentanone-3-carboxylic acids were synthesized starting from the active cyclopeotanone-3-carboxylic acids by a four-stage process in the same manner as described for the racemic acid. Though ethyl 2-(piperidinomethyl)-cyclopentanone-3-carboxylate (II) from each active cyclopentanone-3-carboxylic acid, the final intermediate prepared by the Mannich reaction, was a mixture of two diastereoisomers, it was used without separation, because separation at this stage was unnecessary for the preparation of active 2-methylenecyclopentanone-3-carboxylic acid.



II

The infrared spectra of the synthetic optically active 2-methylene-cyclopentanone-3-carboxylic acids and natural sarkomycin Hooper[1] were essentially identical and exhibited a characteristic peak at 6.1 μ.

Details of the biological studies on the synthetic optically active 2-methylenecyclopentanone-3-carboxylic acid will be published elsewhere.

Experimental

Resolution of Cyclopentanone-3-carboxylic acid with Brucine.—A mixture of 112 g. (0.88 mol.) of racemic cyclopentanone-3-carboxylic acid and 400 g. of brucine-$4H_2O$ was warmed with 2000 ml. of water with stirring to a clear solution. When the solution was allowed to stand overnight in a refrigerator, 580 g. (wet) of silky needles of brucine *d*-cyclopentanone-3-carboxylate, m.p. 110~113°, precipitated. The crude product was recrystallized from hot water several times, m.p. 115~117°, $[\alpha]_D^{25}$ −28.4 (chloroform, C=1.6). Yield 205 g. Further 50 g. of the same substance was obtained on evaporation of the mother liquor and recrystallization. Total yield 255 g.

The combined mother liquor was evaporated to dryness and the residue was recrystallized

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1) I. R. Hooper et al., *Antibio. & Chem.*, 5, 588 (1955).
2) K. Toki, This Bulletin, **30**, 450 (1957).
3) S. Tatsuoka et al., *J. Antibio., Ser.* B, **IX** 157 (1956).

from hot water several times to yield 250 g. of brucine *l*-cyclopentanone-3-carboxylate, m.p. 103 ~105°, $[\alpha]_D^{25}$ −38.5 (chloroform, C=1.3).

Brucine *d*-cyclopentanone-3-carboxylate (235 g.) was dissolved in 400 ml. of hot water and then an excess of concentrated aqueous ammonia was added to the solution.

After being cooled overnight in a refrigerator, 200 g. of silky needles of brucine was recovered by filtration. The filtrate was concentrated and acidified with hydrochloric acid. The condensed filtrate was saturated with ammonium sulfate, and extracted with ether. After removal of ether, *d*-cyclopentanone-3-carboxylic acid was distilled at 138~140°/0.2 mm. Yield 55 g. (98.2%), m.p. 66~67°, $[\alpha]_D^{21}$+22.1 (methanol, C=1.9).

Anal. Found: C, 56.20; H, 6.08. Calcd. for $C_6H_8O_3$: C, 56.25; H, 6.25%.

l-Cyclopentanone-3-carboxylate was obtained in the same manner as described above. Yield 53 g. (94.6%) from 250 g. of the brucine salt. b.p. 138~140°/0.2mm., m.p. 65~66°, $[\alpha]_D^{21}$−22.2 (methanol, C=2.0).

Anal. Found: C, 56.23; H, 6.21. Calcd. for $C_6H_8O_3$: C, 56.25; H, 6.25%.

Esterification of *d*- and *l*-Cyclopentanone-3-carboxylic Acids.—A mixture of 55 g. (0.43 mol.) of *d*-cyclopentanone-3-carboxylic acid, 50 g. of absolute ethanol, 80 g. of absolute benzene, and a small amout of *p*-toluenesulfonic acid, was heated on a water bath using a water separater for about eight hours. The reaction mixture was concentrated, poured into ice and aqueous sodium bicarbonate and extracted with ether. After drying over anhydrous sodium sulfate and evaporation, ethyl *d*-cyclopentanone-3-carboxylate was separated by fractional distillation. Yield 55.5 g. (83.7%), b.p. 116~118°/16 mm., n_D^{21} 1.4523, $[\alpha]_D^{21}$+20.0 (methanol, C=1.5).

Anal. Found: C, 61.73; H, 7.66. Calcd. for $C_8H_{12}O_3$: C, 61.54; H, 7.69%.

The 2,4-dinitrophenylhydrazone melted at 172 ~173°.

Anal. Found: C, 49.80; H, 4.93; N, 16.72. Calcd. for $C_{14}H_{16}O_6N_4$: C, 60.00; H, 4.76; N, 16.67%.

Unchanged *d*-cyclopentanone-3-carboxylic acid (6.4 g.) was recovered from the alkaline solution.

A mixture of 53 g. (0.41 mol.) of *l*-cyclopentanone-3-carboxylic acid, 50 g. of absolute ethyl alcohol, 80 g. of absolute benzene, and a small amount of *p*-toluenesulfonic acid, was treated similarly to obtain ethyl *l*-cyclopentanone-3-carboxylate. Yield 56.2 g. (87.80%), b.p. 117°/16 mm, n_D^{24} 1.4510, $[\alpha]_D^{21}$−21.9 (methanol, C=1.6).

Anal. Found: C, 61.49; H, 7.68. Calcd. for $C_8H_{12}O_3$; C, 61.54; H, 7.69%.

The 2,4-dinitrophenylhydrazone melted at 172 −173°.

Anal. Found: C, 49.89; H, 4.98; N, 16.62. Calcd. for $C_{14}H_{16}O_6N_4$: C, 50.00; H, 4.76; N, 16.67%.

Unchanged *l*-cyclopentanone-3-carboxylic acid (4.0 g.) was recovered from the alkaline solution.

Ethyl *d*- and *l*-2-Methylenecyclopentanone-3-carboxylates.—(*a*) *Ethyl d-2-methylenecyclopentanone-3-carboxylate.* A mixture of 10 g. (0.06 mol.) of ethyl *d*-cyclopentanone-3-carboxylate, 7.2 g. (0.06 mol.) of piperidine hydrochloride, and 4.3 g. of 37% formaline, was heated on a water bath at 75~80° with stirring for thirty minutes. After extracting the unchanged ethyl *d*-cyclopentanone-3-carboxylate with ether, the aqueous layer was concentrated to dryness under a reduced pressre. Ethyl 2-(piperidinomethyl)-*d*-cyclopentanone-3-carboxylate hydrochloride was produced in a semi-solid mass. The hydrochloride was purified by recrystallization from methanol for analysis. Yield 9.7 g., m.p. 156°(sinter), $[\alpha]_D^{25}$+37.5 (methanol C=1.6).

Anal. Found: C, 57.86; H, 8.22; N, 4.82. Calcd. for $C_{14}H_{24}O_3NCl$: C, 58.13; H, 8.30; N, 4.84%.

The 2,4-dinitrophenylhdrazone melted at 128 ~130°.

The residual oil separated from the crystals was considered to be a diastereo-isomer of ethyl 2-(piperidinomethyl)-*d*-cyclopentanone-3-carboxylate hydrochloride and could be also used for successing reaction.

The crystalline hydrochloride was disssolved in a amount of water and pH was adjusted to 9~10 with aqueous sodium bicarbonate. The mixture was extracted with ether and the ethereal solution was dried over anhydrous sodium sulfate and evaporated. The residue was distilled under a reduce pressure (90~100°/0.1 mm.).

The distillate was dissolved in ether and the solution was washed with diluted hydrochloric acid to remove piperidine. Thus ethyl *d*-2-methylenecyclopentanone-3-carboxylate was obtained. Yield 1.11 g. (11.0% from ethyl *d*-cyclopentanone-3-carboxylate), $[\alpha]_D^{26}$+15.8 (methanol, C=3.4).

The 2,4-dinitrophenylhydrazone melted at 179 ~180°

Anal. Found: C, 51.70; H, 4.52; N, 16.00. Calcd. for $C_{15}H_{16}O_6N_4$: C, 51.72; H, 4.60; N, 16.09%.

(*b*) *Ethyl l-2-methylenecyclopentanone-3-carboxylate.* A mixture of 10 g. (0.06 mol.) of ethyl *l*-cyclopentanone-3-carboxylate, 7.2 g. (0.06 mol.) of piperidine hydrochloride, and 4.3 g. of 37% formaline, was treated in the same manner as mentioned above. Ethyl 2-(piperidinomethyl)-*l*-cyclopentanone-3-carboxylate hydrochloride was obtained in this way. Yield 9.3 g., m.p. 155° (sinter), $[\alpha]_D^{23}$−37.3 (methanol, C=1.6).

The residual oil separated from the crystals was considered a diastereo-isomer of ethyl 2-(piperidinomethyl)-*l*-cyclopentanone-3-carboxylate hydrochloride and could be used for next reaction.

Anal. Found: C, 57.89; H, 8.19; N, 4.80. Calcd. for $C_{14}H_{24}O_3NCl$: C, 58.13; H, 8.30; N, 4.84%.

The 2,4-dinitrophenylhydrazone melted at 129 ~131°.

Ethyl *l*-2-methylenecyclopentanone-3-carboxylate was obtained by heat decomposition. Yield 0.89 g. (8.8% from ethyl *l*-cyclopentanone-3-carboxylate), $[\alpha]_D^{23}$−15.4 (methanol, C=1.3).

The 2,4-dinitrophenylhydrazone melted at 179 ~180°.

Anal. Found: C, 51.70; H, 4.48; N, 16.07. Calcd. for $C_{15}H_{16}O_6N_4$: C, 51.72; H, 4.60; N, 16.09%.

***d*- and *l*-2-Methylenecyclopentanone-3-carboxylic Acids.**—(*a*) *d-2-Methylenecyclopentanone-*

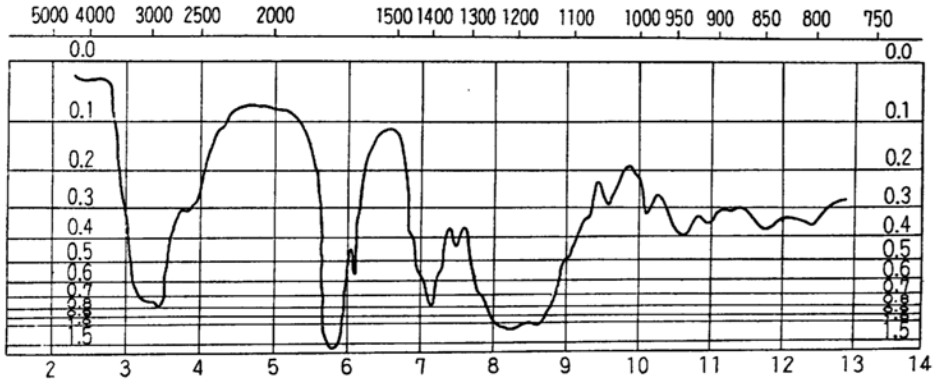

Fig. 1. Infrared spectrum of *d*-2-methylenecyclopentanone-3-carboxylic acid.

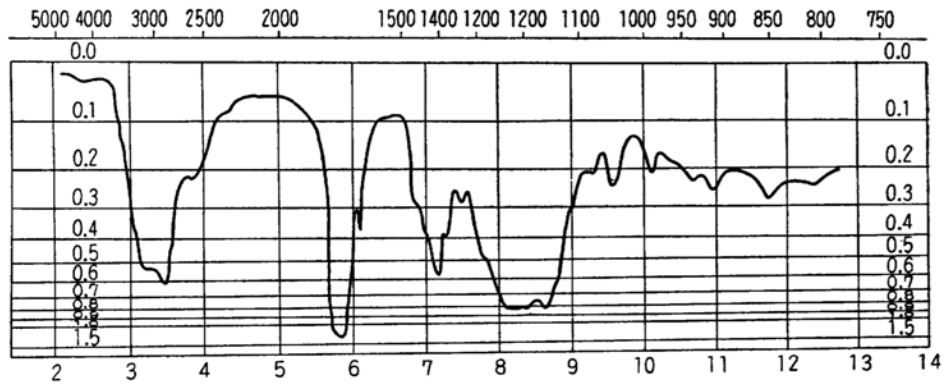

Fig. 2. Infrared spectrum of *l*-2-methylenecyclopentanone-3-carboxylic acid.

3-carboxylic acid. A mixture of 3.5 g. of ethyl *d*-2-methlenecyclopentanone-3-carboxylate and 35 ml. of a 5% acetone solution of the hydrochloride was allowed to stand at 20° for ten hours, and then an equivalent amount of aqueous sodium dicarbonate was added to the mixture with cooling. After removal of acetone under a reduced pressure, the aqueous layer was shaken with ether to recover the unchanged ester. The aqueous layer was then acidified with dilute hydrochloric acid with cooling, saturated with ammonium sulfate, and extracted with ethyl acetate. The ethyl acetate solution was concentrated under a reduced pressure. *d*-2-Methylenecyclentanone - 3 - carboxylic acid was obtained in a pale yellow oil in a yield of 0.85 g. (29.0%), $[\alpha]_D^{23}+28.9$ ** (ethylacetate, C=1.6). The infrared spectrum is shown in Fig. 1.

Anal. Found: C, 59.81; H, 5.43. Calcd. for $C_7H_8O_3$: C, 60.00; H, 5·71%.

(*b*) *l-2-Methylenecyclopentanone - 3 - carboxylic acid.*—*l*-2-Methylenecyclopentanone - 3 - carboxylic acid (2.2 g.) was obtained in the same manner as mentioned above. Yield 0.39 g. (21.5% from 2.2 g. of the corresponding ethyl ester), $[\alpha]_D^{23}-28.4$ **(ethyl acetate, C=1.6). Fig. 2. shows the infrared spectrum of the substance.

Anal. Found: C, 59.62; H, 5.31. Calcd. for $C_7H_8O_3$: C, 60.00; H, 5.71%.

** The values will be flexible becouse of the unstability of 2-methylenecyclopentanone-3-carboxylic acid.

Both *d*- and *l*-2-methylenecyclopentanone-3-carboxylic acid showed essentially identical infrared absorption as natural sarkomycin (Hooper[1]).

Summary

d- and *l*-2-Methylenecyclopentanone-3-carboxylic acid were synthesized starting from optically active cyclopentanone-3-carboxylic acid obtained by resolution of the racemic acid with brucine, and both *d*- and *l*-isomer, thus obtained, showed the same infrared absorption as natural sarkomycin (Hooper).

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