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143. Yasuhiko Sato, Shiro Nishioka, Osamu Yonemitsu, and Yoshio Ban : The Absolute Configuration of Sarkomycin.[*1]

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Sarkomycin, an antibiotic with inhibitory effect on the Ehrlich ascites tumor in mice, was first isolated and named by Umezawa, *et al.* in 1953,[1] who discovered that this antibiotic is produced by *Streptomyces erythrochromogenes* (Strain No. W-115-C), which was obtained from soil found at Kamakura, Japan. In 1955, Hooper, *et al.*[2] reported that the effective component of sarkomycin is 2-methylene-3-oxocyclopentanecarboxylic acid (II), containing only one asymmetric carbon. On the other hand, it was shown by Tatsuoka, *et al.*[3] that the natural sarkomycin is in the *levo*-form ($[\alpha]_D^{15}$ $-32.5°$ (c=1, MeOH)). The synthesis of *rac*-sarkomycin was first achieved by Toki,[4] who obtained the ultimate product by a four step process starting from 3-oxocyclopentanecarboxylic acid (I).[5] Thereafter, Shemyakin[6] also succeeded in the synthesis of *rac*-sarkomycin, and either of these syntheses confirms that the effective ingredient of sarkomycin should be represented by the plane formula (II). Moreover, Toki applied his synthetic method of *rac*-sarkomycin (II) to the optical active series, thus obtaining (−)-sarkomycin ($[\alpha]_D^{23}$ $-28.9°$ (ethyl acetate)) from (−)-3-oxocyclopentanecarboxylic acid ($[\alpha]_D^{21}$ $-22.2°$ (MeOH)).[7] Accordingly, the absolute configuration of the natural sarkomycin should be elucidated if that of one of the two optical isomers of 3-oxocyclopentanecarboxylic acid (I) is established.

In the present paper, we wish to report that (+)-3-oxocyclopentanecarboxylic acid ((+)-isomer of I) was chemically correlated with (+)-3-carboxyadipic acid (VI)[8] and also with (+)-3-methylcyclopentanone (XXIII)[9]; both of the latters are of known absolute configurations.[8,9]

[*1] A preliminary communication of this paper has appeared in Chem. & Ind. (London), **1963**, 490.

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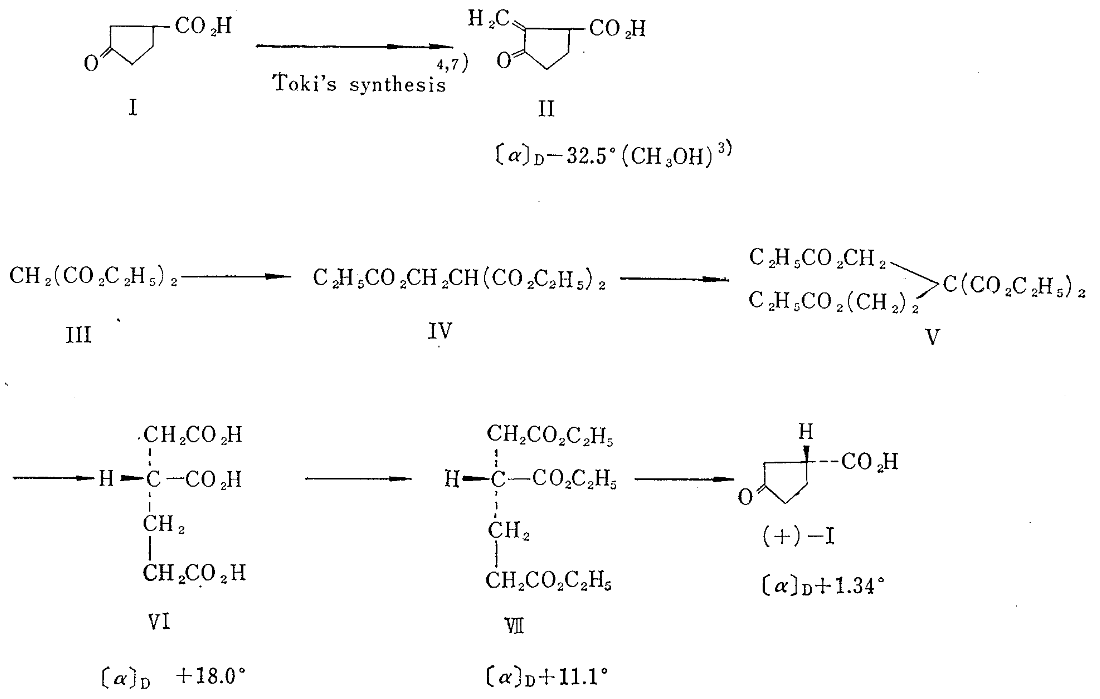

Chart 1.

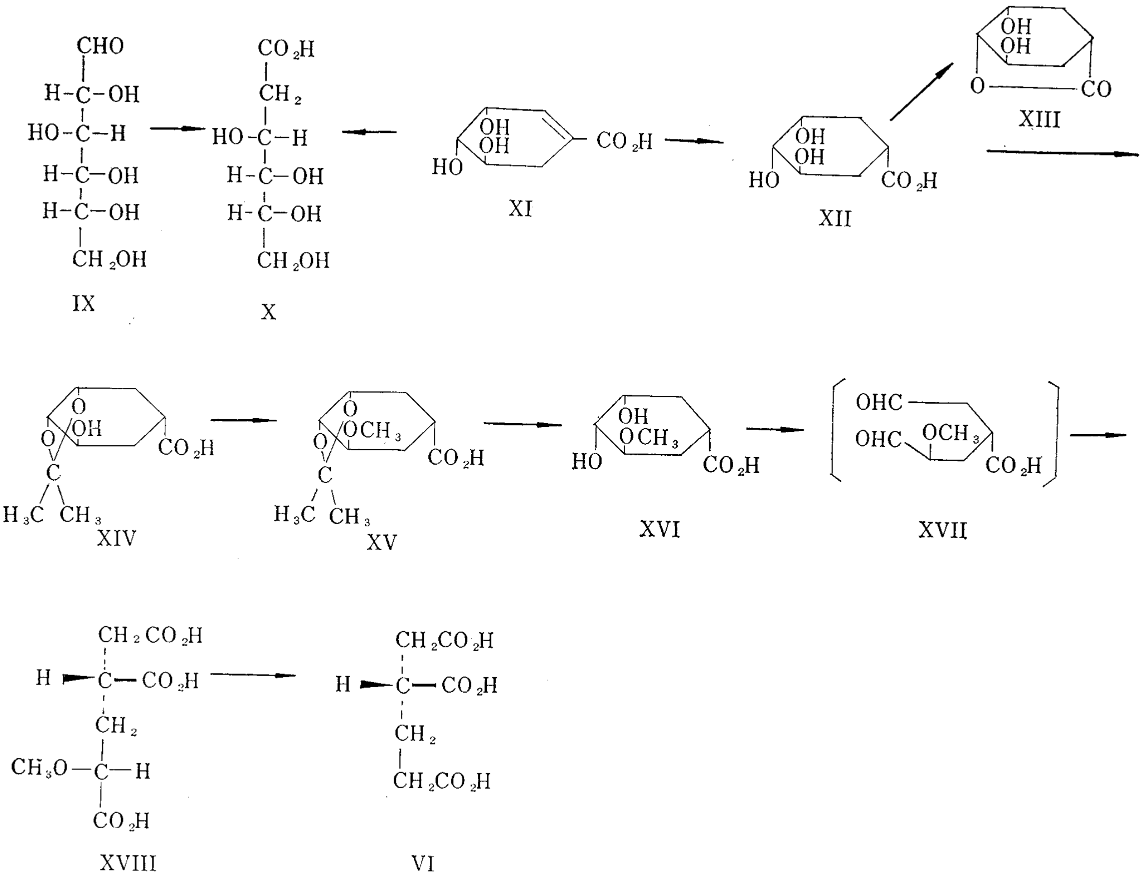

Chart 2.

As is shown in the correlation map of Chart 2, (+)-3-carboxyadipic acid (VI) is derived from 3-carboxy-5-methoxyadipic acid (XVIII), which is correlated with (−)-shikimic acid (XI) *via* XII, XIV, XV, XVI, and XVII. The stereochemistry of (−)-dihydroshikimic acid (XII) is confirmed by formation of the lactone (XIII) and (−)-shikimic acid (XI) is further correlated with (+)-glucose (IX) *via* X.[8] Thus, (+)-3-carboxyadipic acid is represented by the formula (VI) in terms of absolute configuration. In order to correlate (+)-3-oxocyclopentanecarboxylic acid ((+)-I) with one of the two optical isomers (VI and its mirror image form) of 3-carboxyadipic acid, diethyl malonate (III) was reacted with ethyl bromoacetate to afford diethyl ethoxycarbonylsuccinate (IV), according to the Kay's method,[5] which was further condensed with ethyl 3-bromopropionate to give diethyl 3,3-bis-(ethoxycarbonyl)adipate (V). This tetraester was hydrolyzed and decarboxylated with concentrated hydrochloric acid to afford 3-carboxyadipic acid (*rac*-VI), which was optically resolved with (−)-ephedrin by the Freudenberg's procedure.[8a] (−)-Ephedrin-(+)-3-carboxyadipic acid salt was recrystallized many times from acetone and was liberated to give (+)-3-carboxyadipic acid (VI), m.p. 101∼103°, $[\alpha]_D^{19}$ +15.3° (c=3.0, Me_2CO) recrystallized from ethyl acetate. This acid was esterified to afford the corresponding ester (VII), b.p$_{18}$ 180°, $[\alpha]_D^{17}$ +11.1° (c=3.0, MeOH) which was subjected to the Dieckmann condensation, followed by hydrolysis and decarboxylation to yield a preponderance of (+)-3-oxocyclopentanecarboxylic acid, m.p. 60∼62° (b.p$_7$ 138∼141°), $[\alpha]_D^{19.5}$ +1.34° (c=15, MeOH). Although the magnitude of rotation of this acid is extremely low compared with that of the optically pure compound, $[\alpha]_D^{21}$ +22.1° (c=1.9, MeOH),[7] this correlation essentially suggested that the configuration of (+)-3-oxocyclopentanecarboxylic acid is represented by the formula ((+)-I, C−1 is *R*), which is the same as that of (+)-3-carboxyadipic acid (VI) of known absolute stereochemistry. For confirmation of this result, *rac*-3-oxocyclopentanecarboxylic acid was synthesized and optically resolved with brucine by the Toki's procedure,[7] thus obtaining (+)-3-oxocyclopentanecarboxylic acid ((+)-I), m.p. 65∼67°, $[\alpha]_D^{23}$ +22.0° (c=1.5, MeOH), which was derived to ethyl ester (VIII), b.p$_{10}$ 90∼91°, $[\alpha]_D^{21}$ +20.8° (c=2.5, MeOH), IR ν_{max} cm^{-1} : 1740 (five membered ring ketone), 1725 (ester).

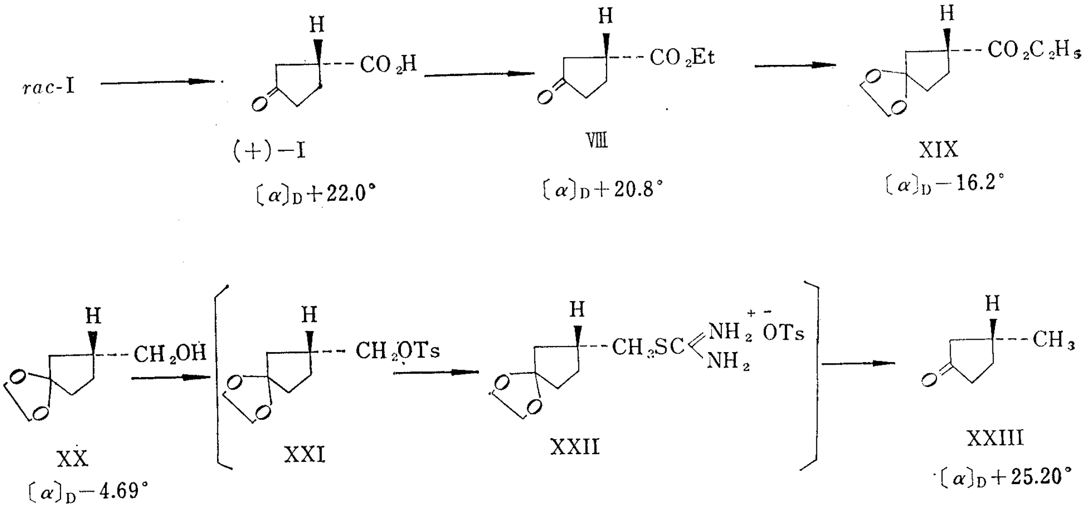

Chart 3.

On treating the ester with ethylene glycol in the usual manner, there was obtained the corresponding ketal-ester (XIX), b.p$_{16}$ 125∼129°, $[\alpha]_D^{21}$ −16.2° (c=2, MeOH), in 81.5% yield, which was confirmed by disappearance of IR band at 1740 cm^{-1}. This ketal-ester (XIX) was subjected to the reduction with lithium aluminum hydride to yield the corresponding alcohol (XX), b.p$_{26}$ 122∼125°, $[\alpha]_D^{20}$ −4.69° (c=5.15, pyridine) in 93.6% yield, the structure of which was also supported by disappearance of ester band at 1725 cm^{-1}. This alcohol was tosylated to XXI, followed by treatment with thiourea to give the thiouronium salt (XXII), which in turn, was reduced with rather inactive Raney nickel and then hydrolyzed with 10% HCl to afford (+)-3-methylcyclopentanone (XXIII), b.p. 138~140°, $[\alpha]_D^{21}$ +25.20° (c=5, $CHCl_3$) which gives 2,4-dinitrophenylhydrazone, m.p. 122°, of the satisfactory analytical data. The magnitude of the rotation indicates that the partial racemization occurred during the above reaction sequence, as compared with $[\alpha]_D^{25}$ +154.8° ($CHCl_3$) of the optically pure material (XXIII).⁹⁾ But, optical rotatory dispersion curves of these compounds in Fig. 1, clearly indicate that the optically active component of the present conversion product is (+)-3-methylcyclopentanone.¹⁰⁾ Consequently, this result is enough to conclude that the configuration of the carbon atom carrying carboxyl group of (+)-3-oxocyclopentanecarboxylic acid ((+)-I) is the same as that of (+)-3-methylcyclopentanone (XXIII).

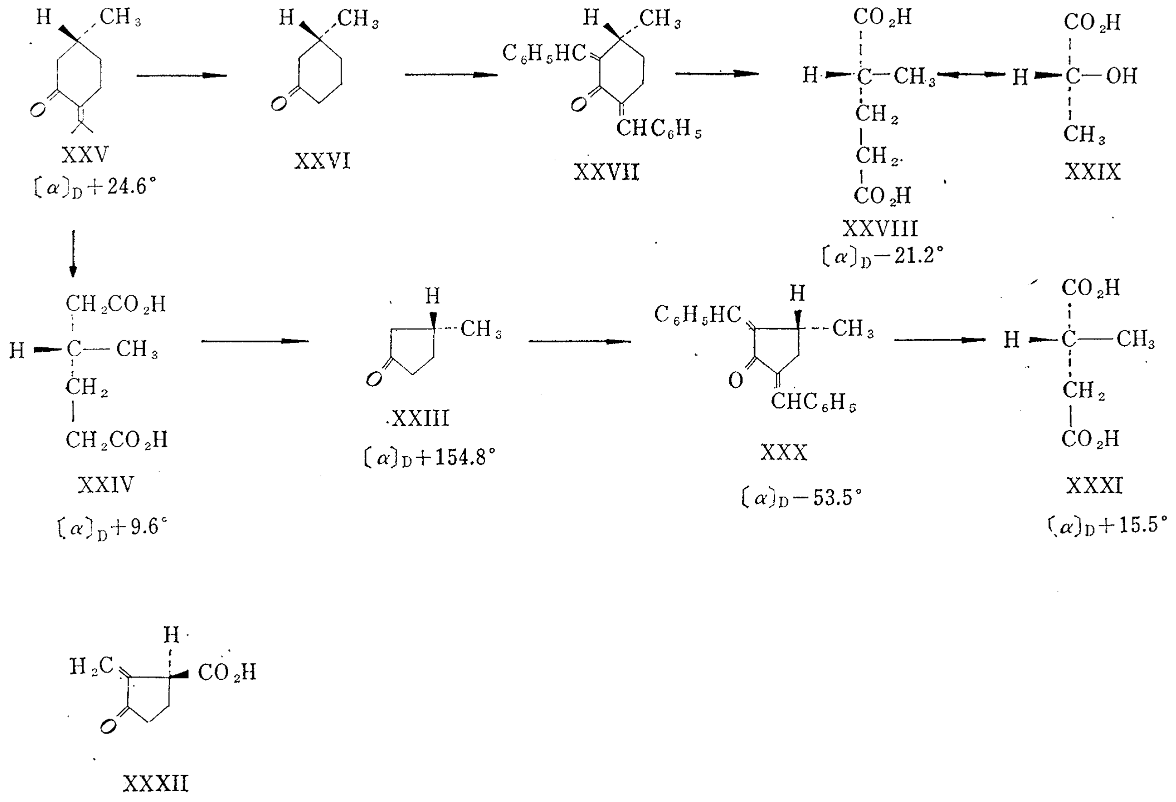

Chart 4.

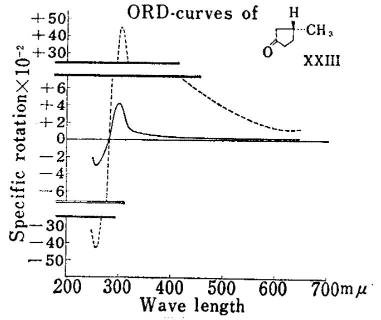

Fig. 1.

------ optically pure material¹⁰⁾
—— the present conversion product

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The configuration of (+)-3-methylcyclopentanone has already been established as *R* by Eisenbraun and McElvain,[9] who correlated this compound with (−)-2-methylglutaric acid (XXVIII) *via* (+)-pulegon (XXV), XXVI and XXVII as are shown in Chart 4; the configuration of XXVIII had been established by Fredga[11] by his method of quasi-racemates, compared with (−)-lactic acid (XXIX). Furthermore, they converted (+)-3-methylcyclopentanone (XXIII) to (+)-2-methylsuccinic acid (XXXI) *via* XXX, which is also in accord with Fredga's conclusion.[11] Thus, the above correlation of (+)-3-oxocyclopentanecarboxylic acid with (+)-3-methylcyclopentanone (XXIII) establishes the configuration of the former acid as *R* being represented by (+)-I.

According to the present correlation, (−)-3-oxocyclopentanecarboxylic acid has been established to be the mirror image form of (+)-I, and since it was derived to (−)-2-methylene-3-oxocyclopentanecarboxylic acid by the Toki's synthesis,[7] the absolute configuration of the natural (−)-sarkomycin is represented by XXXII, of which the asymmetric carbon (C-1) is designated as the *S*-configuration.

Experimental[*3]

Diethyl (+)-3-Ethoxycarbonyladipate (VII)——The synthetic method of the *rac*-product[5] was followed. To a solution of 6.3 g. of (+)-3-carboxyadipic acid (VI) (m.p. 101°, $[\alpha]_D^{19}$ +15.3° (c=3.0, Me_2CO), (lit.[8a] m.p. 106°, $[\alpha]_D^{20}$ +16.39°)) in 32 ml. of absolute ethanol was added 3.2 g. of conc. H_2SO_4 and the resulting solution was refluxed in an oil-bath kept at 110° for 20 hr. After cooling, the reaction mixture was basified with saturated Na_2CO_3 solution, extracted with Et_2O, and the dried over anhyd. Na_2SO_4. Evaporation of the Et_2O and distillation of the residue gave 6.085 g. (Yield, 60.0%) of the corresponding ester, colorless liquid, b.p$_{18}$ 180°, $[\alpha]_D^{17}$ +11.1° (c=3, MeOH). *Anal.* Calcd. for $C_{13}H_{22}O_6$: C, 56.91; H, 8.08. Found: C, 56.66; H, 8.13.

(+)-3-Oxocyclopentanecarboxylic Acid ((+)-I)——The method was followed according to the Kay's procedure for the *rac*-product.[5] To a suspension of 1.02 g. of Na dust in 30 ml. of absolute toluene, was added 6.085 g. of the foregoing diethyl (+)-3-ethaxycarbonyladipate, and the whole mixture was warmed at 80~90° for 2 hr. The reaction mixture was cooled by ice, acidified with 10% HCl and extracted with Et_2O. The Et_2O was removed to give a crude oil, to which without further purification, was added 70 ml. of 8% H_2SO_4. The mixture was heated in an oil bath kept at 110° for 3 hr. to effect the decarboxylation. After the completion of evolution of carbon dioxide, the mixture was concentrated, saturated with $(NH_4)_2SO_4$, and extracted thoroughly with Et_2O ten times. The Et_2O extract was dried over anhyd. Na_2SO_4, the Et_2O was removed and the residual oil was distilled to yield 1.386 g. (53.6%) of (+)-3-oxocyclopentanecarboxylic acid, white crystals, m.p. 60~62° (from benzene), b.p$_7$ 138~141°. $[\alpha]_D^{19.5}$ +1.34° (c=15, MeOH). *Anal.* Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.22. Found: C, 56.15; H, 6.19.

Optical Resolution of 3-Oxocyclopentanecarboxylic Acid——Optical resolution of 3-oxocyclopentanecarboxylic acid by brucine was crried out according to the Toki's procedure[7] to give (+)-acid, m.p. 65~67°, recrystallized from benzene, b.p$_4$ 138~141°, $[\alpha]_D^{23}$ +22.0° (c=1.5, MeOH). *Anal.* Calcd. for $C_6H_8O_3$: C, 56.24; H, 6.22. Found: C, 56.51; H, 6.52.

Ethyl 3-Oxocyclopentanecarboxylate——Esterification of the foregoing (+)-acid was also carried out by the Toki's procedure[7] to give ethyl (+)-3-oxocyclopentanecarboxylate, b.p$_{10}$ 90~91° $[\alpha]_D^{21}$ +20.8° (c =2.5, MeOH), (lit.[7] b.p$_{16}$ 116~118°. $[\alpha]_D^{21}$ +20.0° (MeOH)). *Anal.* Calcd. for $C_8H_{12}O_3$: C, 61.52; H, 7.72. Found: C, 61.45; H, 7.79. 2,4-Dinitrophenylhydrazone: Yellow needles, m.p. 149~150° (Toki reported m.p. 172~173°). *Anal.* Calcd. for $C_{14}H_{16}O_6N_4$: C, 49.99; H, 4.79; N, 16.67. Found: C, 49.62; H, 5.14; N, 16.61.

Ethyl (−)-3-Oxocyclopentanecarboxylate Cyclic Ethylene Acetal (XIX)——A solution of 4.136 g. (0.0265 mol.) of ethyl (+)-3-oxocyclopentanecarboxylate, 1.92 g. (0.031 mol.) of ethylene glycol, 20 mg. of *p*-toluenesulfonic acid in 40 ml. of absolute benzene was heated under reflux in an oil bath kept at 110~120° for 7 hr. The mixture was concentrated to about a half volume, and Et_2O was added. The solution was washed with saturated $NaHCO_3$ solution and then with saturated NaCl solution. After drying over anhyd. Na_2SO_4, the solvent was removed to give a residual oil, which was distilled to yield 4.321 g. (81.5%) of colorless transparent oil, b.p$_{16}$ 125~129°, $[\alpha]_D^{21}$ −16.2° (c=2, MeOH). *Anal.* Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.56; H, 8.09.

[*3] All melting points are not corrected.

11) A. Fredga: Arkiv. Kemi. Mineral. Geol., **24A**, No. 32 (1947).

(−)-**3-Hydroxymethylcyclopentanone Cyclic Ethylene Acetal** (XX)——To a solution of 880 mg. of $LiAlH_4$ in 50 ml. of absolute Et_2O was added a solution of 3.046 g. of ethyl 3-oxocyclopentanecarboxylate cyclic ethylene acetal (XIX) in 20 ml. of Et_2O over a period of 30 min. under stirring and ice-cooling. After the addition, the reaction mixture was refluxed for 3.5 hr., cooled to room temperature and the excess of $LiAlH_4$ was decomposed with H_2O The inorganic substance was filtered off, and the Et_2O solution was dried over anhyd. Na_2SO_4. Evaporation of the Et_2O and the distillation of the residue gave colorless transparent oil, b.p$_{26}$ 122∼125°, 2.226 g. (93.6%), $[\alpha]^{20}_{D}$ −4.69° (c=5.15, pyridine). *Anal.* Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found : C, 61.04; H, 8.96.

(+)-**3-Methylcyclopentanone** (**XXIII**)——To a solution of 2.103 g. (0.0133 mol.) of 3-hydroxymethylcyclopentanone cyclic ethylene acetal in 5 ml. of pyridine was added 3.049 g. of *p*-toluenesulfonyl chloride in 15 ml. of pyridine under ice-cooling. The whole solution was allowed to stand at room temperature for 2 days, to which was added under ice-cooling saturated sodium bicarbonate solution. The mixture was allowed to stand at room temperature for 4 hr., with occasional shaking. After extracting with $CHCl_3$, the extract was dried over anhyd. Na_2SO_4, the solvent was removed *in vacuo* at room temperature to leave 4.160 g. of the residual oil (XXI) which without further purification was subjected to the following reaction.

To a solution of 1.110 g. (0.0146 mol.) of thiourea in 40 ml. of ethanol was added 4.160 g. of the foregoing tosylate (XXI) in 20 ml. of ethanol, which was refluxed with stirring in an oil bath maintained at 100° for 4.5 hr. The EtOH was removed *in vacuo* to leave 5.260 g. of the viscous oil, which was subjected to the following reduction.

In an autoclave fitted with magnetic stirrer, was placed 2.510 g. of the foregoing thiouronium tosylate (XXII), 30 g. of Raney-Ni(W-2) and 50 ml. of MeOH, which mixture was heated to 100∼110° with stirring for 8 hr. After standing overnight, the autoclave was opened and Raney-Ni was filtered off, the filtrate was concentrated to leave the residual oil, to which was added 3 ml. of 10% HCl. The mixture was warmed in a water-bath for 30 min., and after cooling, was extracted with Et_2O. The Et_2O extract was washed with saturated $NaHCO_3$ solution, followed by water, and with concentrated $CaCl_2$ solution five times. After the extract was dried over anhyd. Na_2SO_4 for 2 days, the Et_2O was removed to leave the oil, which was distilled to give 132 mg. (20.8%) of colorless oil, b.p. 138∼140°, $[\alpha]^{21}_{D}$ +25.20° (c=5, $CHCl_3$). This oil contained neither N nor S. 2,4-Dinitrophenylhydrazone : Orange yellow needles, m.p. 122°. *Anal.* Calcd. for $C_{12}H_{14}O_4N_4$: C, 51.79; H, 5.07; N, 20.13. Found : C, 51.76; H, 5.08; N, 20.08. The optical rotatory dispersion curve of this ketone (XXIII) is shown in Fig. 1.

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Summary

(+)-3-Oxocyclopentanecarboxylic acid was chemically correlated with (+)-3-carboxyadipic acid and with (+)-3-methylcyclopentanone, both of which are of known absolute configurations. This correlation established that the natural sarkomycin, (−)-2-methylene-3-oxocyclopentanecarboxylic acid, is represented by the formula (XXXII), of which C-1 is *S*.

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