mp 170–171°; $[\alpha]^{26}D$ +6.4° (*c*, 1 CH_3OH); $\bar{\nu}_{max}$ 1645 (sh), 1660, 1730 cm^{-1}; λ_{max} 229 mμ (ε 12,000).

Anal. Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50; O, 24.86. Found: C, 66.45; H, 8.75; O, 24.78.

B. From 3,5,11-Triacetyl-6,7-anhydroerythronolide B (15).—A 1.0-g amount of **15** was dissolved in 25 ml of ethanol and 25 ml of 5% sodium carbonate solution was added. The cloudy solution was heated to reflux for 45 min then stirred at room temperature for 3 hr. Concentration of the solution gave a solid which was collected and recrystallized yielding 0.35 g, mp 168–170°. Material from a second recrystallization had mp 170–171°. This compound was shown to be identical with **14** obtained in procedure A by a mixture melting point determination, infrared spectrum, and thin layer chromatographic comparison (carbon tetrachloride–ether–ethyl acetate, 8:1:1).

3,5,11-Triacetyl-6,7-anhydroerythronolide B (15).—A solution of 3,5,11-triacetylerythronolide B (**7**, 5.0 g) in 50 ml of anhydrous pyridine was stirred at 0° while a solution of 5 ml of thionyl chloride in 25 ml of pyridine was added dropwise. When the addition was complete, the reaction was stirred at 0° for 1 hr then poured onto cracked ice. The mixture was allowed to stand overnight in the cold, and the fluffy solid obtained was collected and washed with water to give 4.3 g (89%), mp 147–148.5°. A recrystallization from ethanol–water gave long needles: mp 148–149°; $[\alpha]^{23}D$ −69° (*c* 1, CH_3OH); $\bar{\nu}_{max}$ 1710, 1735 cm^{-1}; λ_{max} 286 mμ (ε 92).

Anal. Calcd for $C_{27}H_{42}O_9$: C, 63.51; H, 8.29; O, 28.20. Found: C, 63.77; H, 8.18; O, 28.02.

3,5-Diacetyl-6-deoxy-6-demethyl-6-methylene-10,11-anhydro-8-*epi*-erythronolide B (16).—A solution of 3,5-diacetyl-10,11-anhydro-8-*epi*-erythronolide B (**13**, 0.4 g) in 10 ml of anhydrous pyridine was stirred at 0° while a solution of 0.5 ml of thionyl chloride in 5 ml of pyridine was added dropwise. Stirring was continued for 50 min; then the solution was poured onto cracked ice. The mixture was allowed to stand in the cold overnight, and the crystalline solid (0.25 g) which formed was collected, washed with water, and recrystallized from ethanol–water to give tabular crystals: mp 133–134°; $[\alpha]^{26}D$ +66° (*c* 0.7, CH_3OH); $\bar{\nu}_{max}$ 1640, 1670, 1740, 3080 cm^{-1}; λ_{max} 231 mμ (ε 13,500).

Anal. Calcd for $C_{25}H_{38}O_7$: C, 66.64; H, 8.50; O, 24.86. Found: C, 66.72; H, 8.71; O, 24.96.

Registry No.—**1**, 3225-82-9; **7**, 13143-78-7; **9**, 13135-38-1; **10**, 13118-61-1; **11**, 13143-79-8; **12**, 13118-62-2; **13**, 13143-80-1; **14**, 13118-63-3; **15**, 13118-64-4; **16**, 13118-65-5.

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The Absolute Configuration of Sarkomycin[1]

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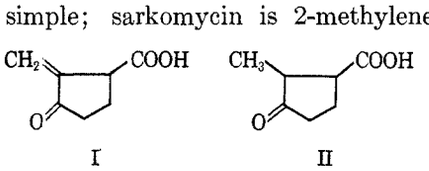
Analysis of the mixture resulting from Mannich condensation on ethyl 3-ketocyclopentanecarboxylate shows that reaction occurs at both positions α to the ketone. As a result, a published assignment of absolute configuration of the antitumor antibiotic sarkomycin, based on the assumption that the Mannich reaction occurs specifically at C-2, is shown to be invalid. Unambiguous proof of configuration is provided by relating (+)-dihydrosarkomycin to standards of absolute configuration in two independent ways. In the first, dihydrosarkomycin is converted to (1*R*;2*R*)-1,2-dimethylcyclopentane, which is in turn prepared from (*R*)-(+)-pulegone. In the second, the Wolff–Kishner reduction product of dihydrosarkomycin is related to (*R*)-(+)-3-methylcyclohexanone. These results establish the (*R*) configuration for sarkomycin, in contrast to the previous assignment.

In 1953 Umezawa, *et al.*,[2] discovered that *Streptomyces erythrochromogenes*, a soil microorganism found in Japan, produces an antibiotic, sarkomycin, which possesses a powerful inhibitory effect on Ehrlich ascites tumors in mice. Subsequent pharmacological studies[3] revealed that sarkomycin caused specific destruction of tumor cells, and a preparation of this substance is now marketed[4] in Japan as a prescription drug against cancer. Sarkomycin selectively inhibits DNA synthesis; it has been suggested that the site of inhibition is DNA polymerase, probably at the sulfhydryl group.[3b]

Hooper and co-workers[5] at the Bristol Laboratories showed that the structure of this antibiotic was surprisingly simple; sarkomycin is 2-methylene-3-ketocyclopentanecarboxylic acid (I). Synthetic support was provided by showing that dihydrosarkomycin was identical[5–7] with the known[8,9] 2-methyl-3-ketocyclopentanecarboxylic acid (II), and several syntheses of sarkomycin itself have subsequently been reported.[10–12]



I II

Sarkomycin possesses a single asymmetric center and is levorotatory.[5,13] Because of the influence of optical configuration on biological activity, it was clearly of interest to determine the absolute configuration of

(1) This investigation was supported by a research grant (RG-6568) from the U. S. Public Health Service, to whom the authors express their gratitude.

(2) H. Umezawa, T. Takeuchi, K. Nitta, T. Yamamoto, and S. Yamaoka, *J. Antibiotics* (Tokyo), **A6**, 101 (1953); H. Umezawa, T. Yamamoto, T. Takeuchi, T. Osato, Y. Okami, S. Yamaoka, T. Okuda, K. Nitta, K. Yagishita, R. Utahara, and S. Umezawa, *Antibiot. Chemotherapy*, **4**, 514 (1954).

(3) (a) S. Oboshi and K. Aoki, *Chemotherapy* (Tokyo), **4**, 91 (1956); *Chem. Abstr.*, **50**, 15939 (1956); (b) S. C. Sung and J. H. Quastel, *Cancer Res.*, **23**, 1549 (1963).

(4) Banyu Pharmaceutical Co., Ltd., Tokyo.

(5) I. R. Hooper, L. C. Cheney, M. J. Cron, O. B. Fardig, D. A. Johnson, D. L. Johnson, F. M. Palermiti, H. Schmitz, and W. B. Wheatley, *Antibiot. Chemotherapy*, **5**, 585 (1955).

(6) M. M. Shemyakin, L. A. Shchukina, E. I. Vinogradova, M. N. Kolosov, R. G. Vdovina, M. G. Karapetyan, V. Ya. Rodionov, G. A. Ravdel, Yu. B. Shvetsov, E. M. Bamdas, E. S. Chaman, K. M. Ermolaev, and E. P. Semkin, *Zh. Obshch. Khim.*, **27**, 742 (1957); *Chem. Abstr.*, **51**, 16313 (1957).

(7) A. P. Arendaruk, E. I. Budovskii, B. P. Gottikh, M. Ya. Karpeiskii, L. I. Kudrvashov, A. P. Skoldinov, N. V. Smirnova, A. Ya. Khorlin, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **27**, 1312 (1957); *Chem. Abstr.*, **52**, 4508 (1958).

(8) (a) W. N. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, **93**, 582 (1908); (b) M. S. Newman and J. L. McPherson, *J. Org. Chem.*, **19**, 1717 (1954).

(9) R. Giuliano, M. Di Fonzo, and M. Artico, *Ann. Chim.* (Rome), **50**, 750 (1960).

(10) K. Toki, *Bull. Chem. Soc. Japan*, **30**, 450 (1957).

(11) K. Toki, *ibid.*, **31**, 333 (1958).

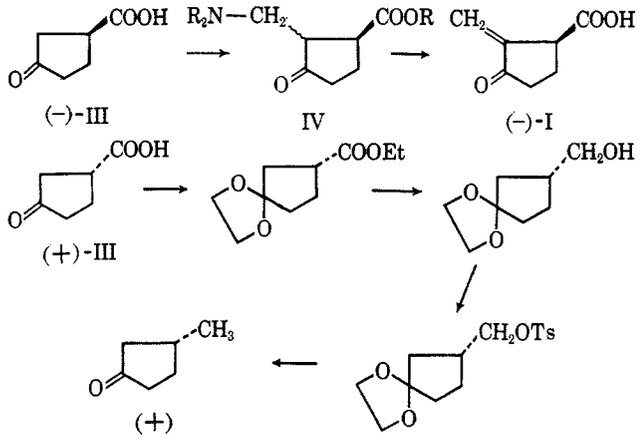
(12) M. M. Shemyakin, G. A. Ravdel, Y. S. Chaman, Y. B. Shvetsov. and Y. I. Vinogradova, *Chem. Ind.* (London), 1320 (1957); M. M. Shemyakin, G. A. Ravdel, E. S. Chaman, Yu. B. Shvetsov, and E. I. Vinogradova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 2188 (1959); *Chem. Abstr.*, **54**, 10886 (1960).

(13) S. Tatsuoka, A. Miyake, M. Inoue, S. Wada, H. Iwasaki, and K. Ogata, *J. Antiobiotics* (Tokyo), **9B**, 157 (1956); *Chem. Abstr.*, **54**, 9784 (1960).

sarkomycin. In 1963, Sato, *et al.*,[14] determined the absolute configuration of (−)-3-ketocyclopentanecarboxylic acid (III), the starting material for Toki's synthesis of natural (−)-sarkomycin,[11] and consequently assigned the (*S*) configuration to sarkomycin. The sequence of reactions used by the Japanese workers to relate sarkomycin to 3-methylcyclopentanone is shown in Scheme I.

SCHEME I

CORRELATION OF SARKOMYCIN WITH 3-METHYLCYCLOPENTANONE[a]

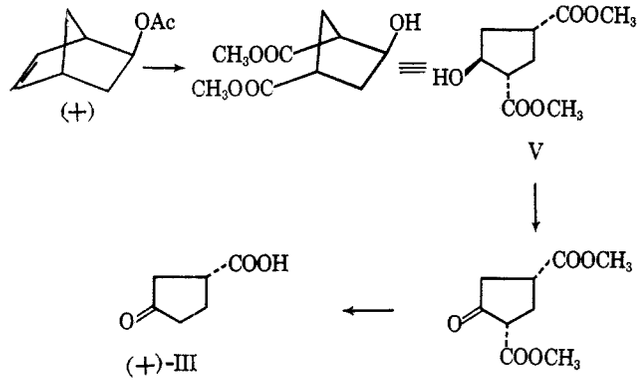


[a] See ref 11 and 14.

The correlation of (+)-3-ketocyclopentanecarboxylic acid (III) with (+)-3-methylcyclopentanone is straightforward,[14] and, since the absolute configuration of 3-methylcyclopentanone is established unambiguously,[15] there seems no doubt that the configuration of III is correctly assigned. As an independent confirmation of this assignment, we have prepared (+)-III from (+)-norbornenyl acetate of known configuration by the sequence of reactions shown in Scheme II. (+)-

SCHEME II

CORRELATION OF 3-KETOCYCLOPENTANECARBOXYLIC ACID WITH NORBORNENYL ACETATE

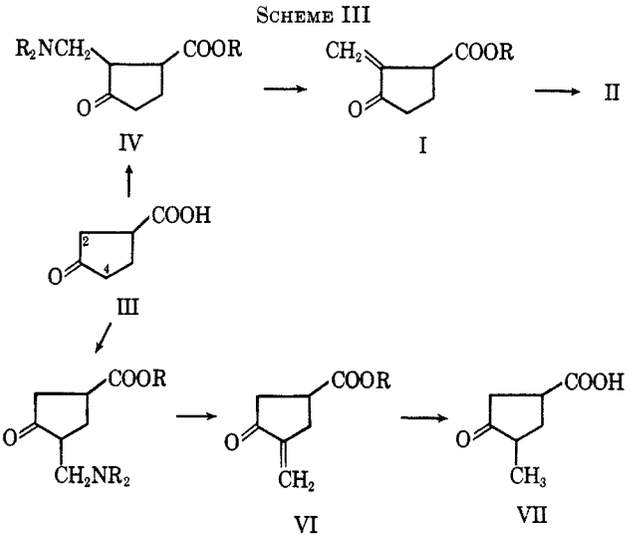


Norbornenyl acetate, prepared by hydroboration of norbornadiene with diisopinocampheylborane[16] followed by acetylation, was ozonized and the product was isolated as the dimethyl ester (V). Oxidation of V with Jones reagent, followed by acid hydrolysis, gave (+)-III. Since (+)-norbornenyl acetate has the (1*R*;2*S*;4*R*) configuration shown,[16,17] (+)-III prepared from it must have the (R) configuration, in agreement with the conclusions of Sato, *et al.*[14]

The reported synthesis[11] of (−)-sarkomycin from (−)-III is, on the other hand, open to serious doubt. Toki reported[10,11] that the Mannich reaction on the ethyl ester of III gave only the stereoisomeric products resulting from reaction at the 2 position. This seems intrinsically unlikely; both of the α positions, C-2 and C-4, are activated by the keto group and would be expected to take part in the reaction. The 4 position might even be preferred because of less steric hindrance.

Other workers[18−20] investigating the Mannich condensation of III and its esters reported only products derived from reaction at the 4 position. In these latter cases the Mannich base, on distillation of the hydrochloride or base-catalyzed elimination of amine from the methiodide, gave a methylene ketone (VI) which was hydrogenated and hydrolyzed to 4-methyl-3-ketocyclopentanecarboxylic acid (VII), identical with a synthetic sample. The Mannich base from the methyl ester of III could be hydrogenated directly to the methyl ester of VII[18] (Scheme III).

SCHEME III



These conflicting reports would be understandable if Mannich condensation of III occurred at both α positions yielding, after pyrolysis, a mixture of I and VI further hydrogenated to a mixture of II and VII, and that from this mixture some workers isolated only II, others only VII. Sarkomycin is a very unstable oil, which makes comparison of synthetic and natural materials tenuous. Toki based his identification of synthetic sarkomycin on comparison of infrared spectra,[10] but the published spectra of sarkomycin[5] and the isomeric 4-methylene-3-ketocyclopentanecarboxylic acid[18] (VI, R = H) are practically indistinguishable. Toki's isolation of II after hydrogenation of his synthetic product showed that some sarkomycin was present, but, since the yield was not reported, the degree of possible contamination with VI cannot be

(14) Y. Sato, S. Nishioka, O. Yonemitsu, and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **11**, 829 (1963).

(15) E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).

(16) K. Mislow and J. Berger, *ibid.*, **84**, 1956 (1962).

(17) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *ibid.*, **83**, 3986 (1961).

(18) S. Umezawa and M. Kinoshita, *J. Antiobiotics* (Tokyo), **9A**, 194 (1956); *Bull. Chem. Soc. Japan*, **30**, 267 (1957).

(19) M. Kinoshita and S. Umezawa, *ibid.*, **32**, 223 (1959).

(20) M. M. Shemyakin, M. N. Kolosov, M. G. Karapetyan, and V. Ya. Rodionov, *Zh. Obshch. Khim.*, **28**, 2068 (1958); *Chem. Abstr.*, **53**, 2228 (1959).

estimated. A recent Japanese patent[21] has confirmed that Mannich condensation of III occurs at both α positions.

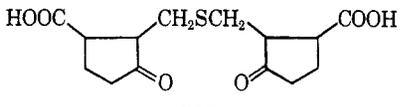
To settle this question unambiguously and rule out the slight possibility that Toki's use of the ethyl ester of III rather than the free acid might have caused some unusual specificity in the Mannich reaction, we have repeated his synthesis and analyzed the products by vapor phase chromatography. Following his procedure exactly, the ethyl ester of III was treated with formalin and piperidine hydrochloride, and the waxy mixture of Mannich base hydrochlorides decomposed thermally *in vacuo*. The mixture of unsaturated ketones had ultraviolet absorption at 231 mμ and infrared bands at 5.78 and 6.05 μ, as expected for I or VI. Vpc analysis showed two major peaks in a 2:1 ratio. The nmr spectrum of the mixture also showed the presence of two components: two separate methyl triplets, two separate methylene quartets, and two sets of *exo*-methylene doublets, each further split, could be distinguished, also in an approximately 2:1 ratio. Making the reasonable assumption that the *exo*-methylene doublet further downfield is that of the ethyl ester of I, the nmr spectrum indicates that VI is the major component. This conclusion was verified by hydrogenating the mixture of I and VI to the ethyl esters of II and VII and again analyzing by vpc, using authentic samples for comparison. To avoid stereochemical complications, both the hydrogenated mixture and the synthetic samples were equilibrated with sodium ethoxide before analysis. On three different columns the major component of the hydrogenated mixture had the same retention time as the ethyl ester of VII, while the minor component had the same retention time as the ethyl ester of II.

These results show clearly that Mannich condensation of III gives a mixture of positional isomers, predominantly the 4-, not the 2-substituted product, and that consequently Toki's synthetic sarkomycin was badly impure. The rotation of the mixture of isomers obtained in his synthesis is of doubtful value in attempting to relate absolute configurations, and the published assignment of configuration to sarkomycin has no sound basis.

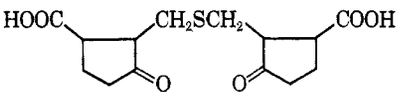
As a result of these findings, we undertook an unambiguous proof of absolute configuration of sarkomycin. We now wish to report that the published assignment is incorrect, and that two independent correlations of configuration of dihydrosarkomycin lead to the (*R*) configuration for natural sarkomycin.

Results

The instability of sarkomycin, characteristic of α-methylene cyclopentanones,[22] coupled with the nonspecificity of Mannich reaction on 3-substituted cyclopentanones, led us to carry out configurational correlations on the stable dihydro derivative, 2-methyl-3-ketocyclopentanecarboxylic acid (II). Natural (−)-sarkomycin has geen hydrogenated[5,13] to II, $[\alpha]_D$ +66.7°. The same dextrorotatory dihydrosarkomycin is obtained by Raney nickel reduction[23] of the two naturally occurring,[24] sulfur-containing relatives of sarkomycin, VIII and IX. The dihydrosarkomycin obtained by reduction is evidently optically pure, since the same rotation has been reported for material obtained by



VIII



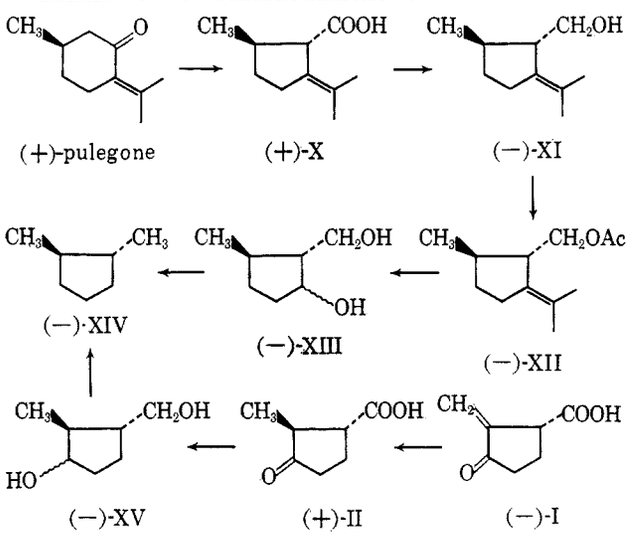
IX

resolution of *dl*-II with either brucine[6] or quinine.[7] Compound II must be the *trans* isomer, since all syntheses of the racemic acid involve strongly equilibrating conditions which should lead to the thermodynamically more stable *trans* compound. Our studies described below provide proof that the substituents in II are *trans*.

From among the limited number of cyclopentane derivatives of known configuration to which dihydrosarkomycin might be related, we chose *trans*-pulegenic acid (X). This acid can be prepared in optically active form by Favorsky rearrangement of pulegone dibromide. Since the absolute configuration of pulegone is known,[15] pulegenic acid serves as an unambiguous standard for configurational correlations. We have therefore converted both (+)-pulegenic acid and (+)-dihydrosarkomycin to a common degradation product, (−)-*trans*-1,2-dimethylcyclopentane, by the reactions shown in Scheme IV.

SCHEME IV

CORRELATION OF DIHYDROSARKOMYCIN WITH PULEGONE



Lithium aluminum hydride reduction of pulegenic acid gave the alcohol (XI), which was acetylated and then ozonized to remove the isopropylidene group. The ozonide was directly reduced to the diol (XIII). The configuration at the cyclopentanol carbon is not known, and undoubtedly a mixture of both epimers is

(21) Y. Toki and Y. Suzuki, *Chem. Abstr.*, **55**, 582 (1961).

(22) (a) M. Mühlstädt, L. Zach, and H. Becwar-Reinhardt, *J. Prakt. Chem.*, **29**, 158 (1965); (b) H. J. Roth, Ch. Schwenke, and G. Dvorak, *Arch. Pharm.*, **298**, 326 (1965); (c) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

(23) S. Tatsuoka, A. Miyake, S. Wada, H. Iwasaki, and K. Ogata, *J. Antibiotics* (Tokyo), **9B**, 153 (1956); *Chem. Abstr.*, **54**, 9784 (1960).

(24) S. Tatsuoka, A. Miyake, S. Wada, and H. Iwasaki, *J. Antibiotics* (Tokyo), **11B**, 275 (1958); *Chem. Abstr.*, **54**, 9785 (1960).

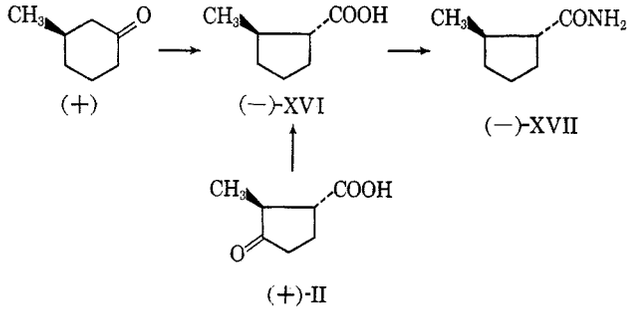
present. Removal of the hydroxyl groups by conversion to the ditosylate and a final reduction with lithium aluminum hydride afforded (−)-1,2-dimethylcyclopentane (XIV). It was carefully purified by preparative vpc and showed infrared, nmr, and mass spectra identical with those of authentic racemic XIV.

(+)-Dihydrosarkomycin (II) was then converted to (−)-XIV by a similar reduction, tosylation, reduction sequence. The isolation of optically active XIV is proof of the *trans* configuration of dihydrosarkomycin.

These correlations demonstrate that (−)-1,2-dimethylcyclopentane derived from pulegenic acid has the (1*R*;2*R*) configuration shown, and that (+)-dihydrosarkomycin has the (1*R*;2*S*) configuration. Natural (−)-sarkomycin consequently has the (*R*) configuration, in contrast to the earlier published conclusion.

To corroborate this result, we carried out an additional, independent proof of configuration of dihydrosarkomycin. Hooper and co-workers[5] reported the Wolff–Kishner reduction of dihydrosarkomycin to an optically active *trans*-2-methylcyclopentanecarboxylic acid (XVI), characterized as its crystalline levorotatory amide (XVII). The identity of the product was confirmed later by repeating the reactions on racemic dihydrosarkomycin.[7] We were able to prove the absolute configuration of this amide by preparing it from (*R*)-(+)-3-methylcyclohexanone. Oxidation of this ketone with selenium dioxide and hydrogen peroxide, in the method developed by Payne,[25] gave a mixture of ring-contracted acids, stereoisomers of 2- and 3-methylcyclopentanecarboxylic acids. The mixture was methylated, equilibrated with sodium methoxide to convert the 2-methyl esters largely to the *trans* isomer, and separated by preparative vpc. The pure *trans*-2-methyl ester was converted to the amide, (−)-XVII (Scheme V). Its structure was proved by infrared and especially nmr comparison with an authentic sample of the racemic amide. The lower rotation of the amide prepared by Wolff–Kishner reduction compared with that from 3-methylcyclohexanone, in which there is no opportunity for racemization, shows, not surprisingly, that a good deal of racemization occurred in the Wolff–Kishner reduction.

SCHEME V



Both of these correlations with compounds of known absolute configuration agree in assigning the (1*R*;2*S*) configuration to dihydrosarkomycin, and thus establish unambiguously the (*R*) configuration of sarkomycin.

(25) G. Payne and C. Smith, *J. Org. Chem.*, **22**, 1680 (1957).

Experimental Section

Conversion of (+)-Norbornenyl Acetate to (+)-3-Ketocyclopentanecarboxylic Acid. Ozonolysis of (+)-Norbornenyl Acetate.—A stream of ozone (2–4%) in oxygen was bubbled through a solution of 10 g of norbornenyl acetate,[16] $\alpha^{26}D$ +15.1° (neat, 1 dm), in 100 ml of methanol at −70° for 6 hr. The solution was allowed to come to room temperature, kept overnight, and concentrated *in vacuo* at room temperature. The oily ozonide was taken up in 100 ml of 90% formic acid and warmed with 28 g of 30% hydrogen peroxide until spontaneous reaction occurred. After the reaction subsided (45 min) the solution was heated at 100° for 1 hr and concentrated under reduced pressure. The residue was taken up in ether, dried over magnesium sulfate, and concentrated.

The residual yellow oil was taken up in 250 ml of methanol containing 5 ml of concentrated sulfuric acid and refluxed for 3 days. The solution was concentrated and distributed between ether and water, the aqueous layer was extracted three times with ether, and the combined ether extracts were dried and distilled. The yield of **dimethyl 4-hydroxycyclopentane-1,3-dicarboxylate** (V), bp 110–115° (1.4 mm), was 5.5 g: $[\alpha]^{26}D$ +14.5° (*c* 0.1, carbon tetrachloride).

The ***p*-nitrobenzoate**, recrystallized from ethanol for analysis, melted at 75–76°.

Anal. Calcd for $C_{16}H_{17}NO_8$: C, 54.70; H, 4.88; N, 3.99. Found: C, 55.05; H, 5.11; N, 4.03.

Oxidation of V to 3-Ketocyclopentanecarboxylic Acid.—A solution of 900 mg of (+)-V in 20 ml of acetone was titrated with standard chromic acid solution (Jones reagent), keeping the temperature at 25–30°. When the solution turned red-brown addition was stopped and the mixture was stirred for 5 min, then poured into 40 ml of water and extracted with ether. The ether extracts were concentrated and the oily residue was heated with 15 ml of 10% sulfuric acid for 14 hr at 100°. The solution was cooled, saturated with ammonium sulfate, and extracted with ether. Concentration of the dried extracts left 210 mg of yellow oil, which was distilled *in vacuo*. The crystalline material in the distillate was dried on porous plate, affording 65 mg of **3-ketocyclopentanecarboxylic acid** (III): mp 60–61°, $[\alpha]^{26}D$ +4.6° (*c* 0.1, methanol). The infrared spectrum was superimposable with that of the racemic compound, mp 65–66°. The 2,4-dinitrophenylhydrazone melted at 148–149°, and had the same infrared spectrum as that of the dinitrophenylhydrazone of *dl*-III, mp 149–150°.

Based on the maximum rotation reported[16] for norbornenyl acetate, the starting material used here was 31.7% optically pure; from the maximum rotation (22°) reported[11,14] for III, the sample obtained by degradation above is 20.8% optically pure. It is apparent that some racemization occurred, most likely in the final hydrolysis leading to III.

Conversion of Ethyl 3-Ketocyclopentanecarboxylate to 2- and 4-Methyl Derivatives.—Ethyl 3-ketocyclopentanecarboxylate was subjected to the Mannich condensation with formalin and piperidine hydrochloride using the method of Toki,[10] affording a waxy hydrochloride. Drying on porous plate gave colorless crystals, decomposing gradually between 150 and 220°. The total hydrochloride was heated in a short-path still at 130° (0.25 mm), taking care not to allow the distillate to run back into the heated chamber. The distillate showed infrared bands at 5.78 (carbonyl), 6.05 (conjugated double bond), and 8.2 μ (ester), as well as ultraviolet absorption at 231 mμ. The nmr spectrum showed two slightly separated methyl triplets at 1.3 (J = 7 cps) and two methylene quartets centered at 4.1 ppm (J = 7 cps) due to the two different ethyl ester groups, complex splitting between 1.9 and 3.2 (5 H), and two pairs of multiplets in the vinyl region, one at 5.3 and 5.9, the other at 5.5 and 6.0 ppm, integration totalling 2 H. Vpc analysis[26] showed two main components in a 2:1 ratio.

Hydrogenation.—A solution of 1.0 g of the above mixture of unsaturated ketones was hydrogenated at atmospheric pressure over 10% palladium–charcoal. After removal of the catalyst and solvent, the residue (1.0 g) was twice heated with sodium ethoxide (1% in ethanol) at 65° for 1.5 hr to equilibrate *cis* and *trans* isomers and reisolated. Vpc comparison with authentic

(26) Using a 6-ft column packed with S.E. 30 on Chromosorb W, column temperature 160°, helium flow rate of 100 ml/min, the major component had a retention time of 2.0 min; the minor component had a retention time of 1.7 min.

samples was carried out on three different columns. (a) On a 10-ft S.E. 30 on Chromosorb W column at 145° and a helium flow rate of 100 ml/min, II ethyl ester had a retention time of 5.3 min with a small second peak at 5.9 min, VII ethyl ester had a retention time of 5.8 min, and the hydrogenated mixture showed two peaks at 5.3 and 5.8 min in an approximately 1:2 ratio.

(b) On a 10-ft SDC 710 on Chromosorb W column at 185° and a helium flow rate of 100 ml/min, II ethyl ester had a retention time of 2.9 min with a very small, second peak at 3.2 min, VII ethyl ester had a retention time of 3.1 min, and the hydrogenated mixture showed two peaks at 2.9 and 3.1 min in an approximately 1:2 ratio.

(c) On a 10-ft Carbowax 20 M on Chromosorb W column at 185° and a helium flow rate of 100 ml/min, II ethyl ester showed a retention time of 7.8 min (with tailing), VII ethyl ester showed a retention time of 9.5 min with a shoulder at 8.8 min, and the hydrogenated mixture showed two peaks in an approximately 1:2 ratio, at 7.8 and 9.5 min (shoulder at 8.8 min).

2-Methyl-3-ketocyclopentanecarboxylic acid (II) was prepared by the method of Newman and McPherson,[8b] mp 90–91° (lit.[8b] mp 94°). The ethyl ester was prepared in the usual way with ethanol and sulfuric acid and distilled before use in the above vpc analysis.

4-Methyl-3-ketocyclopentanecarboxylic acid (VII) was prepared by the method of Hope and Perkin.[27] The ethyl ester was prepared with ethanol and sulfuric acid, and had bp 68° (0.2 mm) [lit.[27] bp 115–117° (14 mm)]. The ethyl ester semicarbazone melted at 137–139° (lit.[27] mp 138–140°).

Conversion of Pulegone to (−)-1,2-Dimethylcyclopentane.—*trans*-**Pulegenic acid** (X)[28] was prepared from pulegone, $[\alpha]^{25}D$ 31.6° (*c* 0.1, chloroform), by the procedure of Wolinsky and Chan.[28b] The distilled acid had bp 102–105° (0.2 mm), $[\alpha]^{22}D$ 34.0° (*c* 0.1, chloroform).

2-Hydroxymethyl-3-methyl-1-isopropylidenecyclopentane (XI) was prepared by reduction of pulegenic acid with lithium aluminum hydride according to the procedure of Kimel, *et al.*[29] After distillation at 78–80° (1.5 mm) [lit.[29] bp 76–77° (0.9 mm)], the alcohol had $[\alpha]^{25}D$ −17.5° (*c* 0.1, chloroform) and was homogeneous by vpc. The ***p*-nitrobenzoate**, recrystallized three times from ethanol, melted at 89–90° (lit.[29] mp 90°).

Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.02; H, 6.87; N, 4.76.

The **acetate** (XII)[30] was prepared by heating the alcohol (35 g) in pyridine (35 ml) with acetic anhydride (59 ml) for 3 hr, then keeping overnight at room temperature. The reaction mixture was poured into water (550 ml) and extracted three times with ether. After washing the extracts with cold 1:1 hydrochloric acid and water, the ether solution was dried over sodium carbonate and magnesium sulfate and distilled, yielding 34 g (75%) of XII: bp 72–76° (0.6 mm), $[\alpha]^{25}D$ −4.6° (*c* 0.1, chloroform).

2-Hydroxymethyl-3-methylcyclopentan-1-ol (XIII).—A solution of acetate XII (11.0 g) in 150 ml of methylene chloride was ozonized at −70° for 6 hr, then allowed to warm to room temperature and the solvent was removed in a stream of dry nitrogen. The ozonide was taken up in 80 ml of ether and added dropwise to a stirred suspension of 5.9 g of lithium aluminum hydride in 80 ml of ether. The mixture was refluxed overnight, cooled, treated with saturated aqueous sodium sulfate, and filtered. The solid salts were dissolved in 1:1 hydrochloric acid and extracted with ether. The combined ether solutions were dried over sodium sulfate and distilled, yielding 6.0 g (82%) of diol XIII: bp 130–140° (2.5 mm), $[\alpha]^{24}D$ −39° (*c* 0.6, chloroform). The **bis-*p*-nitrobenzoate** was prepared in the usual way and recrystallized from ethanol, mp 124–125°.

Anal. Calcd for $C_{21}H_{20}N_2O_8$: C, 58.87; H, 4.71; N, 6.54. Found: C, 58.79; H, 4.85; N, 6.32.

(−)-*trans*-1,2-Dimethylcyclopentane (XIV).—To a solution of 5.0 g of diol XIII in 60 ml of pyridine cooled to 0° was added 21.0 g of *p*-toluenesulfonyl chloride and the mixture was kept in the refrigerator for 48 hr. The mixture was partitioned between ice water and ether, and the aqueous layer was extracted with ether. The combined extracts were washed with cold 1:1 hydrochloric acid, then with water, dried over potassium carbonate, and concentrated at reduced pressure.

The residual ditosylate (13 g) was taken up in 30 ml of ether and reduced with 2.7 g of lithium aluminum hydride in 25 ml of ether, refluxing for 20 hr. The excess hydride was destroyed by the cautious addition of water, the salts were dissolved with dilute hydrochloric acid, and the aqueous solution was extracted with ether. The combined ether extracts were dried over magnesium sulfate and the ether was carefully removed through an 18-in. spinning-band column. On cooling the residue to −70°, it separated into two layers. The lower layer showed strong O–H absorption in the infrared and is probably alcohol derived from cleavage of the S–O bond in the reduction. The upper layer was purified by preparative gas chromatography, using a 20-ft Carbowax column at 100°, to give pure *trans*-1,2-dimethylcyclopentane: 0.47 g, $[\alpha]^{25}D$ −35.2° (*c* 0.2, chloroform).

The mass spectrum[31] (parent peak, 98.10989; calcd 98.10954) had a fragmentation pattern identical with the published spectrum.[32] The infrared spectrum was identical with the published spectrum of *trans*-1,2-dimethylcyclopentane.[33] The nmr spectrum was identical with the published spectrum[34] and is distinctive among the dimethylcyclopentanes in having a single methyl peak.

Conversion of Dihydrosarkomycin to *trans*-1,2-Dimethylcyclopentane. Reduction of Dihydrosarkomycin.—Racemic dihydrosarkomycin (II) was resolved with brucine according to the procedure of Shemyakin, *et al.*[6] A solution of 11.0 g of II, $[\alpha]^{24}D$ +39.4° (*c* 0.1, chloroform), in 125 ml of ether was added dropwise to a slurry of 7.3 g of lithium aluminum hydride in 125 ml of ether and the mixture was stirred under reflux for 48 hr. After cooling, 4 *N* sodium hydroxide was added dropwise until the precipitate of salts was pure white. The mixture was filtered and the filtrate was dried over magnesium sulfate and concentrated, leaving 7.8 g (78%) of **3-hydroxymethyl-2-methylcyclopentan-1-ol** (XV), $[\alpha]^{24}D$ −10.0° (*c* 0.1, chloroform). The **bis-*p*-nitrobenzoate** melted at 135–140°.

Anal. Calcd for $C_{21}H_{20}N_2O_8$: C, 58.87; H, 4.71; N, 6.54. Found: C, 59.07; H, 4.76; N, 6.43.

Conversion of XV to (−)-*trans*-1,2-Dimethylcyclopentane.—A solution of 7.5 g of (−)-XV in 125 ml of pyridine was cooled to 0°, treated with 45 g of *p*-toluenesulfonyl chloride, and kept in the refrigerator for 48 hr. Work-up was carried out as described for the ditosylate of XIII.

A solution of the crude oily ditosylate (22.2 g) in 30 ml of ether was reduced with 3.7 g of lithium aluminum hydride in 50 ml of ether as described for the ditosylate of XIII. Work-up in the same manner yielded 3.0 g of 1,2-dimethylcyclopentane (XIV), $[\alpha]^{24}D$ −26.5° (*c* 0.1, chloroform), homogeneous by vpc. The infrared, nmr, and mass spectra[35] were identical with those of the sample prepared from XIV.

Repetition of this sequence with the (−)-antipode of dihydrosarkomycin yielded (+)-1,2-dimethylcyclopentane, with infrared and nmr spectra identical with those of the (−) enantiomer.

Preparation of *trans*-2-Methylcyclopentanecarboxamide (XVII).—A solution of 4.7 g of selenium dioxide in 150 ml of 30% hydrogen peroxide was refluxed for 1.5 hr. After cooling, 150 ml of 30% hydrogen peroxide containing 5 ml of pyridine was added, followed by a solution of 74 g of 3-methylcyclohexanone, $[\alpha]^{25}D$ +9.6° (*c* 1.0, methanol), in 100 ml of *t*-butyl alcohol. The two-phase mixture was vigorously stirred under reflux for 20 hr, then cooled, made basic with sodium bicarbonate, and washed with ether. The alkaline solution was acidified, saturated with ammonium sulfate, and extracted with ether. The extracts were dried over magnesium sulfate and concentrated, leaving 79 g of crude acidic product. Distillation through a spinning-band column gave 34.1 g of mixed acids, bp 80–115° (13 mm); the tarry residue was not investigated further.

The acid mixture was esterified by refluxing overnight with 350 ml of methanol and 4 ml of sulfuric acid. The reaction mixture was diluted with 300 ml of water, saturated with ammonium sulfate, and extracted with ether. The dried extracts were distilled through a Vigreux column, then redistilled through an

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(28) (a) H. von Rupe and K. Schäfer, *Helv. Chim. Acta*, **11**, 463 (1928); (b) J. Wolinsky and D. Chan, *J. Org. Chem.*, **30**, 41 (1965); (c) D. Varech, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. France*, 1662 (1965).

(29) W. Kimel, N. Sax, S. Kaiser, G. Eichmann, G. Chase, and A. Ofner, *J. Org. Chem.*, **23**, 153 (1958); see also G. Ohloff, G. Uhde, A. F. Thomas, and E. Sz. Kovats, *Tetrahedron*, **22**, 309 (1966).

(30) J. Wolinsky, T. Gibson, D. Chan, and H. Wolf, *ibid.*, **21**, 1247 (1965).

(31) We are grateful to Dr. Henry M. Fales, National Heart Institute, for obtaining the mass spectrum.

(32) American Petroleum Institute Mass Spectral Data, Research Project 44, Serial No. 187.

(33) P. Natalis, *Bull. Soc. Chim. Belges*, **72**, 178 (1963).

(34) American Petroleum Institute Nuclear Magnetic Resonance Spectral Data, Research Project 44, Serial No. 538.

(35) We thank Mr. E. B. Miller for obtaining the mass spectrum.

18-in. spinning-band column, collecting the fraction (9.5 g) of bp 140–170°. Vpc analysis (on a column of DC 710 supported on Chromosorb W, 20 mesh, at 165° with a helium flow rate of 75 ml/min) showed two peaks with retention times of 29 and 32 min, in the ratio 2:5. Samples of both substances were collected by repeated injection on the same column.

The faster moving component was identified as **methyl-*trans*-2-methylcyclopentanecarboxylate**, $[\alpha]^{25}D$ −57.5° (*c* 0.2, carbon tetrachloride). It was converted to the amide by bubbling dry ammonia through a solution of the ester (120 mg) in 5 ml of methanol for 30 min, then keeping the solution sealed at room temperature for 3 days. The solvent was removed in a stream of dry nitrogen and the residue was crystallized from benzene–petroleum ether (bp 30–60°). The amide (XVII) had mp 149.0–149.5°, $[\alpha]^{26}D$ −40.2° (*c* 0.0076, water).[36] Hooper, *et al.*,[5] reported mp 152–153.5°, $[\alpha]^{20}D$ −13.7° (c 1, water), for the amide prepared from dihydrosarkomycin. The infrared and nmr spectra of XVII were identical with those of an authentic sample of the racemic amide,[37] mp 149–150°.

The second substance eluted from the vpc column was an isomeric ester [mol wt 142 (mass spectrum), $[\alpha]^{25}D$ −6.8° (*c* 0.2, carbon tetrachloride)] which was converted in the same manner to the amide [mp 148.5–149.5°, $[\alpha]^{25}D$ −32.2° (*c* 0.01, water)].[36] This is tentatively regarded as one of the stereoisomers of 3-methylcyclopentanecarboxamide; the racemic amide (configuration unknown) melted[37a] at 147–148°.

Registry No.—(−)-I, 13012-37-8; (+)-III, 13012-38-9; (+)-III 2,4-dinitrophenylhydrazone, 13012-39-0; V, 13052-48-7; V *p*-nitrobenzoate, 13012-40-3; (+)-X, 7712-68-7; (−)-XI, 13012-42-5; (−)-XII, 13012-43-6; (−)-XIII, 13012-44-7; (−)-XIII bis-*p*-nitrobenzoate, 13012-45-8; (−)-XIV, 13012-46-9; (−)-XV, 13012-47-0; (−)-XV bis-*p*-nitrobenzoate, 13012-48-1; (−)-XVII, 13012-49-2; methyl *trans*-2-methylcyclopentanecarboxylate, 13012-50-5; 3-methylcyclopentanecarboxamide, 13012-51-6.

Acknowledgment.—The authors express their thanks to Mr. Norman Gilman for obtaining the nmr spectra.

(36) This rotation was measured on a Cary spectropolarimeter; we thank Mr. Grant Krow for the measurement.

(37) (a) W. O. Ney, W. W. Crouch, C. E. Rannefeld, and H. L. Lochte, *J. Am. Chem. Soc.*, **65**, 770 (1943); (b) H. Pines and N. E. Hoffman, *ibid.*, **76**, 4417 (1954); (c) M. Julia and F. Le Goffic, *Bull. Soc. Chim. France*, 1550 (1965). We are grateful to Professor M. Julia and Mr. M. Maumy for sending us a sample of racemic *trans*-2-methylcyclopentanecarboxylic acid.

Synthetic Experiments in the Eudalene Group of Bicyclic Sesquiterpenes. III.[1] Total Synthesis of (+)-α- and (+)-β-Eudesmols

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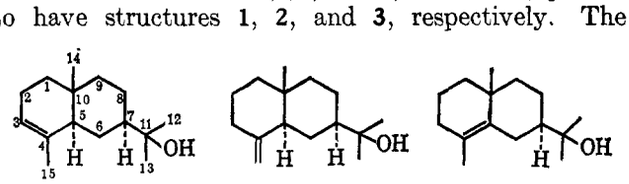
The total syntheses of (+)-α-eudesmol and (+)-β-eudesmol are described.

The natural product known as eudesmol has been recognized for many years to be a mixture of two and sometimes three isomeric alcohols, depending upon the source of the material.[6] These alcohols are the double-bond isomers α-, β-, and γ-eudesmols, proved to have structures **1**, **2**, and **3**, respectively. The



1 **2** **3**

constitution **3** assigned to γ-eudesmol is based on its chemical transformations,[7] and it has been confirmed by total synthesis[8] that **3** represents the structure and absolute configuration of (+)-γ-eudesmol. The structure **2** for the β isomer is also based on its chemical behavior,[6] and stereochemical studies[9] have shown that **2** represents (+)-β-eudesmol; a recent stereoselective total synthesis of (±)-β-eudesmol has provided confirmation.[10] The structure of α-eudesmol (**1**) is based on its chemical transformations.[6] In this paper we describe stereoselective total syntheses of (+)-α-eudesmol and (+)-β-eudesmol, which confirm structures and absolute configurations **1** and **2**, respectively, for these alcohols.[11]

Synthesis of (+)-β-Eudesmol

The starting point in our first approach to (+)-β-eudesmol was (+)-15-nor-α-cyperone[12] (**4**) obtainable by a Robinson–Mannich annelation reaction between (+)-dihydrocarvone and 1-diethylaminobutan-3-one methiodide.[1] Compound **4** was a minor product of the annelation reaction; it was isolated through its semicarbazone by a rather tedious procedure, and in very poor yield.[1] Nevertheless, sufficient material was obtained to make a synthetic sequence starting from it possible. The absolute configuration of **4** was settled by the observation that its ORD curve is almost superimposable on that of (+)-α-cyperone, of proven absolute configuration (**5**).[13] Treatment of **4**

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(2) Abstracted in part from theses presented by D. C. H. and R. A. W. in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Wales.

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(11) For preliminary accounts, see (a) R. P. Houghton, D. C. Humber, and A. R. Pinder, *Tetrahedron Letters*, 353 (1966); (b) D. C. Humber and A. R. Pinder, *ibid.*, 4985 (1966).

(12) We are using the numbering for the eudesmane ring system proposed by W. Cocker and T. B. H. McMurry, *Tetrahedron*, **8**, 181 (1960), as depicted in formula **1**. In our earlier paper[1] we have described compound **4** as (+)-4-nor-α-cyperone; we now feel it is better designated (+)-15-nor-α-cyperone.

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