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The Absolute Configulation of Dimethyl (−)-*erythro*-2-Ethyl-3-methylglutarate

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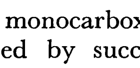
In the course of the structure elucidation of a new antibiotic, ikarugamycin, dimethyl (−)-2-ethyl-3-methylglutarate, $[\alpha]_D^{25}$ −8.6° (*c* 0.64, $CHCl_3$), was obtained as an oxidation product of ikarugamycin.[2]

The two diastereomeric forms of 2-ethyl-3-methylglutaric acid (IIa and IIIa) have been prepared by Michael and Moss,[3] but their stereochemistry has yet been determined distinctly. On the other hand, the absolute configuration of 2-ethyl-3-methylsuccinic acid has recently been determined by Brockmann and Müller-Enoch.[4] Therefore, (+)-*erythro*-2-ethyl-3-methylsuccinic acid (Ia), whose absolute configuration had been proved to be 2*R*, 3*S*,[4] was converted into optically-active dimethyl *erythro*-2-ethyl-3-methylglutarate (IIb) and dimethyl *erythro*-3-ethyl-2-methylglutarate (IV) as follows:

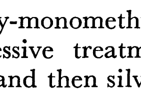
The *cis*-anhydride derived from Ia by the known method[5] was heated with methanol to give a mixture of monocarboxy-monomethyl esters. It was homologized by successive treatment with oxalyl chloride, diazomethane, and then silver oxide in methanol. The resulting mixture consisted of three esters, Ib, IIb, and IV, which could be separated by preparative glc.

The structures of (−)-IIb, $[\alpha]_D^{25}$ −14.9°, and IV, $[\alpha]_D^{25}$ +46.3°, were determined on the basis of the following NMR and mass spectral evidence: The NMR spectrum of IIb shows two C-methyl signals in a relatively high field (δ 0.89 and 0.93), and its mass spectrum exhibits a peak due to McLafferty rearrangement at *m*/*e* 102. These facts indicate the presence of the $CH_3-CH_2-\overset{|}{C}H-COOMe$ group. On the other hand, the presence of the $CH_3-\overset{|}{C}H-COOMe$ group in IV is confirmed by the appearance of a C-methyl doublet at δ 1.07 and a peak due to McLafferty rearrangement at *m*/*e* 88.

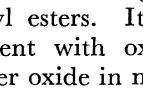
The optically-active dicarboxylic acid IIa could not be crystallized, but it formed a crystalline dicyclohexylamine salt. To obtain further proofs for the IIb structure, racemic IIb and IIIb were prepared as authentic samples. A mixture of synthetic IIa and IIIa was converted into a mixture of anhydrides, which could be separated by preparative glc. The hydrolysis of the anhydrides gave (±)-IIa, mp 97—98°C, and (±)-IIIa, mp 99—100°C, respectively. The latter could also be obtained by repeated recrystallizations of the crude mixture of dicarboxylic acids.



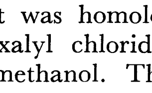
Ia: R=H
Ib: R=Me



IIa: R=H
IIb: R=Me



IIIa: R=H
IIIb: R=Me



IV

The IR spectra of the naturally-derived ester, the optically-active synthetic ester ((−)-IIb), and the racemic ester ((±)-IIb) were superimposable on one another. Thus, the absolute configuration of dimethyl (−)-*erythro*-2-ethyl-3-methylglutarate ((−)-IIb) was determined to be 2*R*, 3*R*.

Experimental

All the melting points are uncorrected. The IR spectra were recorded on a JASCO IR-S spectrometer. The NMR spectra were recorded on a Nihondenshi JNM-C60H spectrometer, using TMS as the internal reference. The mass spectra were measured on a Hitachi RMU-6D mass spectrometer operating with an ionization energy of 70 eV. The optical rotations were measured on a JASCO ORD/UV-5 spectrometer and a JASCO DIP-SL spectrometer. The glc were carred out on a Varian Aerograph 1828-4 instrument.

Syntheses of Dimethyl (−)-erythro-*2-ethyl-3-methylglutarate (IIb) and Dimethyl (+)*-erythro-*3-ethyl-2-methylglutarate (IV).* (+)-*erythro*-2-Ethyl-3-methylsuccinic acid (Ia)[6] (290 mg) was converted into the *cis*-anhydride (255 mg) by the known method.[5] A solution of the anhydride in methanol (5 ml) was refluxed for 4 hr, and then concentrated to give a mixture of half methyl esters ($\nu_{max}^{CCl_4}$ 1748, 1711 cm^{-1}); the NMR spectrum of this mixture showed it to consist of two isomers in the ratio of *ca.* 2: 1. Into a solution of the half methyl esters in benzene (2 ml), oxalyl chloride (2 ml) was stirred in one portion at 0°C; the mixture was then stirred at the same temperature for 1 hr and at room temperature for 5 hr. The subsequent concentration of the mixture under reduced pressure gave crude acid chlorides (330 mg), which were then dissolved in benzene (5 ml). Into an ethereal diazomethane (30 ml), the solution was vigorously stirred, drop by drop, at −10°C over a period of 0.5 hr; the mixture was then stirred at −10—0°C for 0.5 hr and at room temperature for 5 hr. The excess diazomethane and the solvent were removed under reduced pressure to give crude diazoketones ($\nu_{max}^{CCl_4}$ 2130, 1742, 1649 cm^{-1}). A mixture of the diazoketones and silver oxide (freshly-prepared from 0.2 g of silver nitrate) in methanol (30 ml) was refluxed for 2 hr with stirring. The mixture was then treated with charcoal, filtered through celite, and washed with methanol. The filtrates were concentrated under reduced pressure to give a mixture (215 mg) of dimethyl esters, which was roughly separated by column chromatography on silica gel (10 g) with

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[1] A part of this work was preliminarily reported in Ref. 2b.

[2] a) S. Ito and Y. Hirata, *Tetrahedron Lett.*, **1972**, 1185. b) S. Ito and Y. Hirata, *ibid.*, **1972**, 2557.

[3] A. Michael and J. Moss, *J. Amer. Chem. Soc.*, **53**, 1150 (1931).

[4] H. Brockmann, Jr. and D. Müller-Enoch, *Chem. Ber.*, **104**, 3704 (1971).

[5] J. H. Golden and R. P. Linstead, *J. Chem. Soc.*, **1958**, 1732.

[6] $[\alpha]_D^{25}$ +8.6° (*c* 2.5, EtOH); mp 179°C (lit,[4] $[\alpha]_D^{20}$ +8.6° (*c* 2.5, EtOH); mp 180°C).

n-hexane–ether (9: 1) as the eluent. Further purification by repeated preparative glc (10% OV-17 column at 160°C) gave pure (+)-Ib (12 mg), (−)-IIb (35 mg), and (+)-IV (17 mg) as colorless oils. (+)-Ib: $[\alpha]_D^{25}$ +9.7° (*c* 1.0, $CHCl_3$). (−)-IIb: $[\alpha]_D^{25}$ −14.9° (*c* 1.13, $CHCl_3$); δ^{CCl_4} 0.89 (3H, d, *J*=6.8), 0.93 (3H, d, 6.3), 1.1—2.7 (6H, m), 3.61 (3H, s), 3.62 (3H, s); *m/e* 171 (M^+–OMe), 142, 129, 102, 101 (base peak), 87, 74. (+)-IV: $[\alpha]_D^{25}$ +46.3° (*c* 0.81, $CHCl_3$); δ^{CCl_4} 0.92 (3H, t, *J*=6.5), 1.07 (3H, d, 7.2), 1.1—1.6 (3H, m), 1.9—2.8 (3H, m), 3.61 (3H, s), 3.62 (3H, s); *m/e* 171 (M^+–OMe), 142, 129, 115, 88 (base peak), 73.

Dicyclohexylamine Salt of (−)-IIa. A solution of (−)-IIb (17 mg) in methanol (0.3 ml) was treated with 10% aqueous potassium hydroxide (0.3 ml) at 50°C for 2 hr. Working up as usual afforded 13 mg of (−)-IIa as an oil which could not be crystallized. Crude crystals of dicyclohexylamine salt of (−)-IIa were recrystallized from ethyl acetate–*n*-hexane to give 13 mg of needles; $[\alpha]_D^{25}$ −16.7° (*c* 0.72, MeOH). It showed no distinct melting point; mp *ca.* 103—108°C. Found: C, 67.59; H, 10.80; N, 3.94%. Calcd for $C_8H_{14}O_4 \cdot C_{12}H_{23}N$: C, 67.57; H, 10.49; N, 3.94%.

*Preparation of (±)-*erythro*-(IIa) and (±)-*threo*-2-ethyl-3-methylglutaric acid (IIIa).* A mixture of (±)-IIa and (±)-IIIa was prepared according to the procedure of Snyder and Putnan.[7] A mixture of the acids (100 mg) and acetic anhydride (2 ml) was refluxed for 4 hr, and then concentrated under reduced pressure to give 80 mg of a mixture of *trans*- and *cis*-anhydrides. Separation with preparative glc (5% OV-17 column at 160°C) afforded 42 mg of *trans*-anhydride (93% pure) as an earlier fraction and 20 mg of *cis*-anhydride (80% pure) as a later fraction.

trans-Anhydride: $\nu_{max}^{CCl_4}$ 1821, 1772 cm^{-1}; δ^{CCl_4} 0.98 (3H, t, *J*=7.2), 1.13 (3H, d, 6.0).

cis-Anhydride: $\nu_{max}^{CCl_4}$ 1821, 1773 cm^{-1}; δ^{CCl_4} 0.98 (3H, d, *J*=6.0), 1.04 (3H, t, 6.6).

Each anhydride was hydrolysed by refluxing it in tetrahydrofuran–water (2: 1) for 2 hr; this gave crude acids. Several recrystallizations from ether–*n*-hexane gave pure (±)-IIIa (37 mg) and (±)-IIa (10 mg) as prisms respectively. The pure (±)-IIIa was also obtained by repeated recrystallization of a mixture of (±)-IIa and IIIa from ether–*n*-hexane.

(±)-IIIa: mp 99—100°C (lit, mp 100—101°C[3]). The dimethyl ester ((±)-IIIb): δ^{CCl_4} 0.89 (3H, t, *J*=6.8), 0.95 (3H, d, 6.8), 1.1—2.6 (6H, m), 3.62 (3H, s), 3.64 (3H, s).

(±)-IIa: mp 97—98°C (lit, 88°C[3]). The NMR and IR spectra of its dimethyl ester ((±)-IIb) were identical with those of the natural and synthetic (−)-IIb.

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[7] H. R. Snyder and R. E. Putnan, *J. Amer. Chem. Soc.*, **76**, 33 (1954).