The Syntheses of Trimethyl *dl*-3-(Methoxycarbonylmethyl)-1,2,4-cyclopentanetricarboxylates[1]

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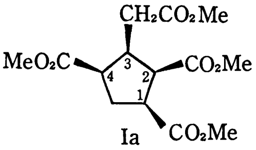
(Received August 21, 1972)

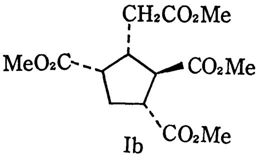
The five trimethyl *dl*-3-methoxycarbonylmethyl-1,2,4-cyclopentanetricarboxylates have been synthesized and their configurations determined. A comparison of their spectral properties with those of the corresponding ester obtained from ikarugamycin indicates that the latter has a *cis*, *trans*, *trans* configuration.

In the course of structural studies of a new antibiotic, ikarugamycin, a monocyclic tetramethyl ester, I ($C_{14}H_{20}O_8$) was obtained as one of the chromic acid oxidation products of ikarugamycin and has played an important role in the determination of the structure and the stereochemistry of ikarugamycin.[2]

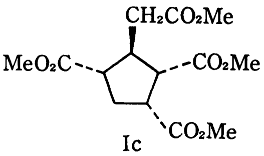
The structure of I was assumed to be trimethyl 3-methoxycarbonylmethyl-1,2,4-cyclopentanetricarboxylate on the basis of the concomitant formations of tetramethyl 1,2,3,4-butanetetracarboxylate and tetramethyl 1,2,3,4-cyclopentanetetracarboxylate[2a] and of the following spectral data: δ 2.1—3.4 (8H, m), 3.58 (3H, s), 3.60 (6H, s), 3.63 (3H, s); *m/e* 316.1160. In order to determine the structure and stereochemistry of I, five stereoisomers of trimethyl *dl*-3-methoxycarbonylmethyl-1,2,4-cyclopentanetricarboxylates (Ia—Ie) were synthesized and their stereochemistry was unambiguously established.



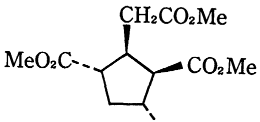
Ia



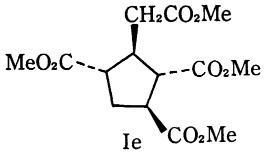
Ib



Ic

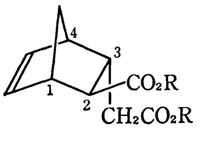


Id

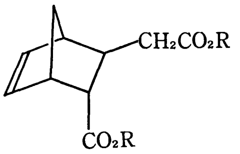


Ie

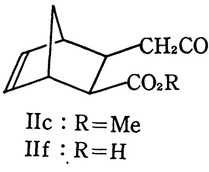
The syntheses of two the stereoisomers, Ia[3] and Id,[4] had already been reported. The *cis*, *cis*, *cis*-isomer (Ia) had been prepared by the oxidation of *endo*-dicyclopentadiene with ozone and then with performic acid. Three stereoisomers (the *trans*, *trans*, *cis*-isomer (Ib), the *cis*, *trans*, *trans*-isomer (Ic), and the *trans*, *cis*, *trans*-isomer (Id)) were obtained by the oxidative fission of the double bond of each of three stereoisomeric 2-methoxycarbonyl-3-methoxycarbonylmethylbicyclo[2.2.1]hept-5-enes (IIa, IIb, and IIc respectively). The two *trans*-dimethyl esters (IIa and IIb) were prepared by the Diels-Alder reaction of cyclopentadiene with dimethyl *trans*-glutaconate and were separated by preparative glc. The stereochemistry of those stereoisomers was determined as follows. The dimethyl ester (IIb) was hydrolysed to the corresponding dicarboxylic acid (IIe), which was then easily converted into an iodolactone, IIIa, when treated with iodine and potassium iodide in the presence of sodium bicarbonate.[5] The IR spectrum of IIIa shows two absorption bands for a γ-lactone (1805 cm^{-1}) and a carboxylic acid (1739 cm^{-1}). The NMR spectrum of IIIa exhibits close similarities with that of IIIb[6] with respect to the chemical shifts and the coupling constants of three protons (H-1, 5-*endo*, and 6-*exo*). In addition, the iodolactone (IIIa) was reconverted into the carboxylic acid (IIe) when treated with zinc in acetic acid.[5] The above facts indicate that the iodolactone has the structure IIIa. Accordingly, the configuration of IIb was established. The *exo*, *cis*-dimethyl ester (IIc) was prepared, although in a low yield, by the Arndt-Eistert reaction of the half methyl ester derived from *exo*, *cis*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride.[7] By heating under reflux with methanolic sodium methoxide, the dimethyl ester, Ia, was completely isomerized to the fifth isomer (Ie) as the main product, together with Ic as a minor product.



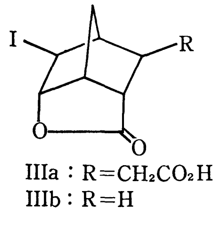
IIa : R=Me
IId : R=H



IIb : R=Me
IIe : R=H



IIc : R=Me
IIf : R=H



IIIa : R=CH₂CO₂H
IIIb : R=H

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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.*, 2557 (1972).

[3] M. I. Fremery and E. K. Frieds, *J. Org. Chem.*, **28**, 2537 (1963).

[4] R. H. Sullivan, Ger. 1078120 (1960).

[5] For example, J. Meinwald, S. S. Labana, and M. S. Chadha, *J. Amer. Chem. Soc.*, **85**, 582 (1963).

[6] R. M. Moriarty, H. Gopal, H. G. Walsh, K. C. Ramey, and D. C. Lini, *Tetrahedron Lett.*, **1966**, 4555.

[7] D. Craig, *J. Amer. Chem. Soc.*, **73**, 4889 (1951).

The IR and NMR spectra and the behavior upon glc of the naturally derived ester (I) were identical with those of the synthetic *cis, trans, trans*-ester (Ic). On the other hand, the other isomers (Ia, Ib, Id, and Ie) were different from I in many respects.

Experimental

All melting points were uncorrected. The IR spectra were recorded on a JASCO IR-S spectrometer. The NMR spectra were recorded on a Nihondenshi JNM-C60H spectrometer, using CCl_4 as the solvent, unless otherwise stated. The chemical shifts are given in ppm relative to the internal TMS, and the coupling constants are given in Hz. The mass spectra were obtained on a Hitachi RMU-6D mass spectrometer operating with an ionization energy of 70 eV. The glc were carried out on a Varian Aerograph 1828-4 instrument. All the microanalytical samples of oily materials were obtained by the preparative glc.

Trimethyl cis, cis, cis-*3-Methoxycarbonylmethyl-1,2,4-cyclopentanetricarboxylate (Ia).* A solution of *endo*-dicyclopentadiene (300 mg) in methanol (60 ml) was ozonized at -70°C until the solution turned blue. The excess ozone was removed with a nitrogen stream, and then the solvent was evaporated under reduced pressure. After adding 98% formic acid (30 ml) and 53% hydrogen peroxide (4.5 ml), the mixture was stirred at 0°C for 1 hr and then at room temperature overnight. After the excess oxidizing reagents had been destroyed with sodium bisulfite, the mixture was concentrated under reduced pressure. The residue was digested in methanol and then filtered. The filtrates were concentrated under reduced pressure. The treatment of the residue with diazomethane gave a crude methyl ester (910 mg), which was chromatographed on silica gel (15 g) and eluted with *n*-hexane–ether (2: 1) to give 210 mg (29%) of Ia as a colorless oil; δ 2.0—3.3 (8H, m), 3.60 (6H, s), 3.62 (6H, s); *m/e* 316 (M^+). Found: C, 52.77; H, 6.85%. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37%.

trans-*2-Methoxycarbonyl-3-methoxycarbonylmethylbicyclo[2.2.1]-hept-5-enes (IIa and IIb).* A solution of dimethyl *trans*-glutaconate (2.88 g) and cyclopentadiene (6.6 g) in toluene (10 ml) was heated at 150°C for 22 hr. The subsequent distilation of the mixture gave 2.05 g (61%) of a mixture of IIa and IIb (bp 143—152°C/18 mmHg), which was then chromatographed on silica gel (70 g) and eluted with *n*-hexane–ether (6: 1) to give the following three fractions: Fraction 1 (1.20 g); IIa: IIb=4: 1, Fraction 2 (0.27 g); IIa: IIb=1: 1, and Fraction 3 (0.45 g); IIa: IIb=1: 19. The pure samples of IIa and IIb were obtained by preparative glc (5% OV-17 column at 200°C) from Fractions 1 and 3 respectively. 2-*exo*-3-*endo*-isomer (IIa): δ 3.57 (3H, s), 3.62 (3H, s), 6.15 (2H, m); *m/e* 224 (M^+), 164, 159, 151, 66. 2-*endo*-3-*exo*-isomer (IIb): δ 3.55 (3H, s), 3.59 (3H, s), 5.96 (1H, dd, 5.6, 3.0), 6.19 (1H, dd, 5.6, 3.0); *m/e* 224 (M^+), 164, 159, 151, 66.

exo,cis-*2-Methoxycarbonyl-3-methoxycarbonylmethylbicyclo[2.2.1]-hept-5-ene (IIc).* A solution of *exo,cis*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride[7] (2.5 g) in methanol (25 ml) was refluxed for 2 hr. The subsequent removal of the solvent under reduced pressure gave a half methyl ester ($\nu_{max}^{CHCl_3}$ 1741, 1711 cm^{-1}), which was then dissolved in benzene (20 ml). To the stirred solution, oxalyl chloride (4 ml) was added at 0°C; the mixture was kept at 0°C for 0.5 hr and then at room temperature for 2 hr. The solvent and the excess reagent were removed under reduced pressure to afford a crude acid chloride, which was then dissolved in benzene (10 ml). To a stirred, ethereal diazomethane (120 ml), the benzene solution was added, drop by drop at -10—-5°C over a period of 0.5 hr; the mixture was then stirred at 0°C for 0.5 hr and subsequently at room temperature overnight. The removal of the solvent gave a crude diazoketone ($\nu_{max}^{CHCl_3}$ 2150, 1746, 1643 cm^{-1}), which was then dissolved in methanol (100 ml). A mixture of the methanol solution and silver oxide (freshly prepared from 1 g of silver nitrate) was refluxed for 2 hr with stirring. The mixture was then treated with charcoal, filtered through celite, and washed methanol. The filtrates were concentrated under reduced pressure to give a reddish oil (3.1 g), which was chromatographed on silica gel (35 g). Elution with *n*-hexane–ether (2: 1) afforded a mixture (0.63 g) containing IIc, which was purified by preparative glc (5% SE-30 column at 230°C) to give 0.21 g (7%) of IIc as a colorless oil; δ 3.64 (6H, s), 6.20 (2H, m); *m/e* 224 (M^+), 164, 159, 151, 66.

Alkaline Hydrolyses of IIa, IIb, and IIc. (a) 2-*endo*-3-*exo*-dicarboxylic acid (IIe): A solution of IIb (255 mg) in methanol (3 ml) and 10% aqueous potassium hydroxide (3 ml) was heated at 50°C for 2 hr. Working-up usual gave 155 mg (70%) of IIe as plates; mp 158—159°C (from chloroform). Found: C, 61.19; H, 6.08%. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%. (b) 2-*exo*-3-*endo*-dicarboxylic acid (IId): The hydrolysis of IIa (21 mg) as described in (a) afforded 10 mg (55%) of IId as plates; mp 115—117°C (from benzene-*n*-hexane). Found: C, 61.29; H, 6.21%. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%. (c) *exo,cis*-dicarboxylic acid (IIf): The hydrolysis of IIc (43 mg) as described in (a) afforded 32 mg (85%) of IIf as plates; mp 144—146°C (from benzene-*n*-hexane). Found: C, 61.63; H, 6.12%. Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17%.

Trimethyl trans, trans, cis-*3-Methoxycarbonylmethyl-1,2,4-cyclopentanetricarboxylate (Ib).* Into a solution of IIa (102 mg) in methanol (20 ml), ozone was passed at -70°C until the solution turned blue. The excess ozone was removed with a nitrogen stream, and then the solvent was evaporated under reduced pressure. To the residue, 98% formic acid (10 ml) and 35% hydrogen peroxide (1 ml) were added; the solution was subsequently stirred at 0°C for 3 hr, and then at room temperature overnight. After destroying the excess oxidizing reagents with sodium bisulfite, the mixture was concentrated under reduced pressure to leave a residue, which was digested in methanol and then filtered. The filtrates were concentrated under reduced pressure to leave an oily residue. Further treatment with diazomethane gave a crude methyl ester, which was purified by preparative tlc with *n*-hexane–ether (1:1) as a mobile phase to give 104 mg (73%) of Ib as a colorless oil; δ 2.1—3.4 (8H, m), 3.62 (6H, s), 3.68 (6H, s): *m/e* 316 (M^+). Found: C, 53.90; H, 6.67%. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37%.

Trimethyl cis, trans, trans-*3-Methoxycarbonylmethyl-1,2,4-cyclopentanetricarboxylate (Ic).* The dimethyl ester, IIb (101 mg), was oxidized as in the case of IIa to give 91 mg (64%) of Ic as a colorless oil; δ 2.1—3.5 (8H, m), 3.58 (3H, s), 3.60 (6H, s), 3.64 (3H, s); *m/e* 316 (M^+). Found: C, 53.36; H, 6.76%. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37%.

Trimethyl trans, cis, trans-*3-Methoxycarbonylmethyl-1,2,4-cyclopentanetricarboxylate (Id).* The dimethyl ester, IIc (32 mg), was oxidized as in the case of IIa to give 45 mg (100%) of Id as a colorless oil; δ 2.0—3.5 (8H, m), 3.61 (3H, s), 3.63 (3H, s), 3.67 (3H, s); *m/e* 316 (M^+). Found: C, 52.64; H, 6.46%. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37%.

Base-catalysed Equilibration of Ia: The Formation of Trimethyl trans, trans, trans-*3-Methoxycarbonylmethyl-1,2,4-cyclopentanetricarboxylate (Ie).* A solution of Ia (540 mg) and sodium methoxide in methanol (prepared from 200 mg of sodium and 10 ml of methanol) was refluxed for 1 hr. After having been acidified with diluted hydrochloric acid, the reaction a mixture was concentrated under reduced pressure and then extracted with ether. The ethereal extracts were washed with water and a saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. The subsequent removal of the solvent gave a brown residue, which was chromatographed on silica gel (10 g) and eluted with *n*-hexane-ether (2:1) to give 345 mg (64%) of pure Ie as a colorless oil. Further elution with *n*-hexane-ether (1:1) gave a mixture (70 mg) of Ie and Ic. The latter was purified by preparative glc to give 15 mg of pure Ic. Ie: δ 1.9—3.5 (8H, m), 3.60 (3H, s), 3.64 (3H, s), 3.66 (6H, s); *m/e* 316 (M^+). Found: C, 52.90; H, 6.39%. Calcd for $C_{14}H_{20}O_8$: C, 53.16; H, 6.37%.

The Formation of Iodolactone IIIa. To a solution of the dicarboxylic acid, IIb (98 mg), and sodium bicarbonate (168 mg) in water (30 ml), a solution of iodine (254 mg) and potassium iodide (0.5 g) in water (1.5 ml) was added; the mixture was then stirred at room temperature for 20 hr in the dark. After extraction with ether, the aqueous layer was acidified with 6N hydrochloric acid, treated with sodium bisulfite until it became a clear, colorless solution, and then extracted with ether. The ethereal extracts were succesively washed with water and a saturated sodium chloride solution, and then dried over anhydrous magnesium sulfate. The evaporation of the solvent afforded crude crystals, which were recrystallized from chloroform to give 124 mg (76%) of IIIa as plates; mp 138—141°C; $\nu_{\max}^{\mathrm{CHCl_3}}$ 1800, 1786, 1725 (shoulder), 1716 cm^{-1}; $\nu_{\max}^{\mathrm{THF}}$ 1805, 1739 cm^{-1}; $\delta^{\mathrm{CDCl_3}}$ 1.7—2.7 (7H, m), 3.18 (1H, m, H-1), 3.91 (1H, broad d, 2.4, H-5-*endo*), 5.11 (1H, broad d, 5.1, H-6-*exo*), 9.3 (1H, broad s, disappeared on addition of D_2O). Found: C, 37.29; H, 3.43%. Calcd for $C_{10}H_{11}O_4I$: C, 37.29; H, 3.44%.

Conversion of IIIa into IIb. A mixture of IIIa (31 mg) and zinc powder (100 mg) in acetic acid (10 ml) was stirred at room temperature for 0.5 hr, and then filtered through celite. The filtrate was concentrated to leave a residue, which was subsequently dissolved in diluted hydrochloric acid and extracted with ether. The extracts were washed with water and dried over anhydrous magnesium sulfate. The evaporation of the solvent afforded an oil, which was crystallized from chloroform to give 8 mg of plates; mp 155—157°C. The IR spectrum (KBr) of this material was completely identical with that of IIb.