BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 45, 1167—1169 (1972)

Stereochemical Studies and Synthetic Applications of Bis-β-keto Sulfoxides

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(Received September 23, 1971)

Bis-β-keto sulfoxides of the $MeSOCH_2CO(CH_2)_nCOCH_2SOMe$ ($n=7$, 8, or 10) type are prepared. The *dl* and *meso* isomers are isolated, and the stereochemistry of bis-β-keto sulfoxides ($n=8$) is established by means of the asymmetric synthesis of the resolvable isomer from an optically-active ester, (−)-menthyl-O-CO$(CH_2)_8$-CO-O-(−)-menthyl, and methylsulfinylcarbanion. It is concluded that the higher-melting one is the meso isomer and that the lower-melting one is racemic. The condensation of bis-β-keto sulfoxides, $MeSOCH_2CO(CH_2)_8COCH_2SOMe$, and allyl bromide in the presence of a base and the subsequent desulfurization give the olefinic ketone, $(CH_2{=}CHCH_2CH_2CO(CH_2)_4)_2$. Optically active sulfoxide, $MeSOCH_2COPh$, is obtained from (−)-menthyl benzoate and methylsulfinylcarbanion.

Sulfoxides (R_1R_2SO) are chiral and are configurationally stable enough under ordinary conditions to be resolvable into enatiomeric forms.[1] Hence, bis-β-keto sulfoxide, $MeSOCH_2CO$-X-$COCH_2SOMe$,[2] may be expected to exist in *dl* and *meso* forms. Though Corey and his co-workers have obtained bis-β-keto sulfoxide from dimethyl azelate and methylsulfinylcarbanion ($DMSO^-$), they have described nothing about the separation of diastereomers.[2a] The present paper will report that the bis-β-keto sulfoxides are separable into two isomers, whose stereochemistry is established by means of asymmetric synthesis.

Dimethyl sebacate was treated with a carbanion solution obtained from sodium hydride and dimethyl sulfoxide (DMSO) at room temperature. A subsequent work-up gave bis-β-keto sulfoxide I (X= $(CH_2)_8$) in a 55% yield. The recrystallization of I from chloroform gave crystals which melted at 145.5—147°C (Ia), whereas the treatment of the mother liquor with ether, followed by purification, gave crystals melting at 131—132°C (Ib). As a mixture of Ia and Ib showed a mp of 125—142°C, the two are different from each other. The IR spectra are shown in Fig. 1, in which the points of clear difference are enlarged.

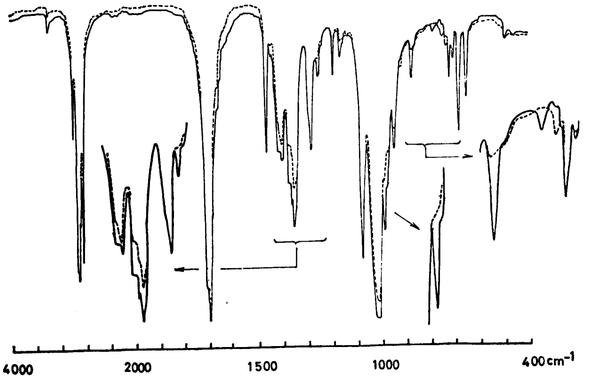

Fig. 1. IR spectra of bis-β-keto sulfoxides, Ia (——) and Ib (----) (KBr).

The higher homolog, II (X=$(CH_2)_{10}$), was similarly prepared (76%) and separated into isomers melting at 145—147°C (IIa) and at 125—127°C (IIb). A mixed-melting-point depression and IR differences were observed as in I. Bis-β-keto sulfoxides (III, X=$(CH_2)_7$) (19%) obtained from dimethyl azelate were also separated into two isomers, melting at 138—140°C and at 116—118°C (IIIb).

The independent reduction of each isomer (Ia or Ib) by means of an aluminum amalgam[2a,3,4] in aqous THF gave the same, single diketone, dode-

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[1] a) M. Axelrod, P. Bickart, J. Jacobus, M. M. Green, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4835 (1968) and Refs. cited; b) K. K. Anderson, *Tetrahedron Lett.*, **1962**, 93; c) A. C. Cope and E. A. Caress, *J. Amer. Chem. Soc.*, **88**, 1711 (1966).

[2] a) E. J. Corey and M. Chaykovsky, *ibid.*, **87**, 1345 (1965) and Refs. cited. For β-keto sulfoxides see: b) H.-D. Becker, G. J. Mikol, and G. A. Russell, *ibid.*, **85**, 3410 (1963); c) G. A. Russell and L. A. Ochrymowycz, *J. Org. Chem.*, **34**, 3618 (1969).

[3] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964).

[4] G. A. Russell and G. J. Mikol, *ibid.*, **88**, 5498 (1966).

cane-2,11-dione. Both sulfoxides, IIa and IIb, similarly yielded a single diketone, tetradecane-2,13-dione.

On the basis of these results, it may be concluded that the separated bis-β-keto sulfoxides, Ia and Ib or IIa and IIb, are diastereoisomers.

The Ia-Ib pair of diastereomers showed no perceptible difference in NMR spectra (Fig. 2) even in the presence of shift reagents such as tris(dipivalomethanato)Eu(III) (Eu(DPM)$_3$).[5]

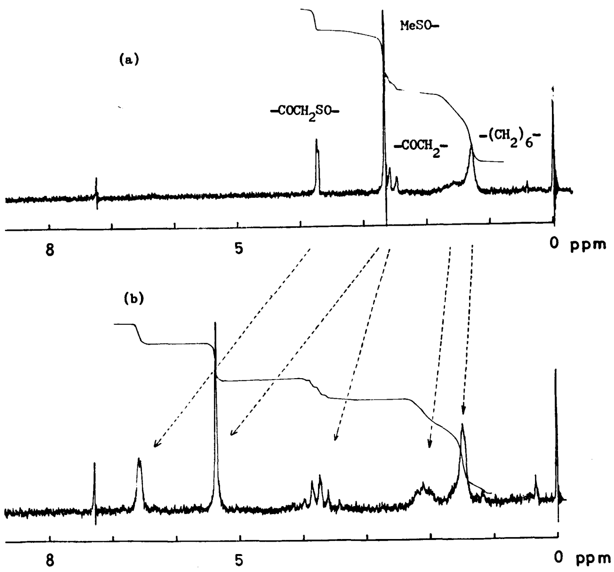

Fig. 2. NMR spectra of (a) sulfoxide Ia and (b) Ia (32 mg, 0.1 mmol) in CDCl$_3$ (0.75 m*l*) containing Eu(DPM)$_3$ (48 mg, 0.068 mmol),

The stereochemical assignment was finally established by means of an asymmetric synthesis of the resolvable isomers. Di-(−)-menthyl sebacate (IV), prepared from sebacoyl chloride and (−)-methnol, was treated with lithium methylsulfinylcarbanion in THF-hexane.[6] The resulting products were separated into two isomers by the method described above.

The sulfoxide melting at 141—143°C was optically inactive, $[\alpha]_D$ 0.0° (*c* 3.98, CHCl$_3$), whereas the other one, melting at 120—122°C, showed a specific rotation of $[\alpha]_D$ +1.22° (*c* 6.08, CHCl$_3$). Obviously, the higher-melting Ia is the *meso* isomer, while the lower-melting Ib is the *dl* isomer. Incidentally, the reaction of (−)-menthyl benzoate (V)[7] gave optically active methyl phenacyl sulfoxide (VI) $[\alpha]_D$ −1.68° (*c* 8.00, CHCl$_3$), of an unknown optical purity.

The condensation of I with allyl bromide in the presence of sodium hydride yielded an intractable oil. The subsequent desulfurization of this oil by means of an aluminum amalgam gave olefinic ketone (CH$_2$=CHCH$_2$CH$_2$CO(CH$_2$)$_4$-)$_2$ (21%). The bis-β-keto sulfoxides, such as I and II, are apparently useful in preparing long, straight chain compounds.

Experimental

All the mps are uncorrected. The microanalyses were performed by Mrs. K. Fujimoto of this department. The NMR spectra were obtained on a 60 MHz instrument (JEOL C-60H spectrometer) in deuteriochloroform, with tetramethylsilane as the internal standard. The mass spectra were taken on a Hitachi RMU-6L spectrometer.

The Reaction of Dimethyl Sebacate with DMSO⁻. A carbanion solution was obtained from sodium hydride (4.8 g, 0.20 mol) and DMSO (80 m*l*) under N$_2$. This was diluted with THF (50 m*l*), and then a solution of dimethyl sebacate (11.5 g, 0.05 mol) in THF (30 m*l*) was added, drop by drop in the course of 30 min under stirring and cooling in an ice bath. The ice bath was then removed, and stirring was continued at room temperature for 3 hr. The reaction mixture was then poured into water, acidified with diluted hydrochloric acid to a pH of about 5—6 (pH paper), and extracted with chloroform. The subsequent evaporation of chloroform *in vacuo* yielded I (8.95 g, 55%). The recrystallization of this product from chloroform gave the sulfoxide Ia (1.31 g, 8%); mp 145.5—147°C. The treatment of the mother liquor with ether and recrystallization from chloroform-ether (trace) gave the sulfoxide Ib (0.15 g, 1%); mp 131—132°C.

The Reaction of Dimethyl Dodecanedioate with DMSO⁻. The treatment of the ester (12.9 g, 0.05 mol) with a carbanion prepared from sodium hydride (4.8 g, 0.20 mol) and DMSO (80 m*l*) in THF (80 m*l*) at room temperature for 4 hr gave bis-β-keto sulfoxide II (13.3 g, 76%). This sulfoxide was separated into two isomers, IIa (1.24 g, 7%), mp 145—147°C, and IIb (0.68 g, 4%), mp 125—127°C.

Dimethyl azelate gave bis-β-keto sulfoxides (III) (19%), which were also separated into two isomers, IIIa (1%), mp 138—140°C, and IIIb (2%), mp 116—118°C. A mixed-melting-point depression and IR differences were observed as in I and II.

The Reduction of Ia with an Aluminum Amalgam. Bis-β-keto sulfoxide Ia (1.61 g, 0.005 mol) was dissolved in THF (40 m*l*) and water (30 m*l*), and then HgCl$_2$-pretreated aluminum foil (2.7 g) was stirred into the solution at room temperature. Stirring was continued at 60—70°C for 5 hr, during which time an additional amount of a mixed solvent (THF : water = 1 : 1) was added in order to overcome the difficulty in stirring due to the formation of aluminum hydroxide. The reaction mixture was then filtered with suction, and the residual solids were washed with chloroform. The combined organic solutions were washed with water and dried (Na$_2$SO$_4$). Upon the evaporation of the solvent, we obtained dodecane-2,11-dione (0.89 g, 90%), mp 68—69°C(lit,[8] 68—68.5°C). IR (Nujol): 1705 cm^{-1} (C=O). MS: 198 (M$^+$). NMR (CDCl$_3$): δ 1.00—1.90 (m, 12H, -(CH$_2$)$_6$-), 2.13 (s, 6H, COMe) and 2.42 (t (J=7 Hz), 4 H, -CH$_2$CO).

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[5] a) K. J. Eisentraut and R. E. Sievers, *J. Amer. Chem. Soc.*, **87**, 5254. (1965); b) J. K. M. Sanders and D. E. Williams, *Chem. Commun.*, **1970**, 422; c) R. R. Fraser and Y. Y. Wigfield, *ibid.*, **1970**, 1471; d) K. K. Anderson and J. J. Uebel, *Tetrahedron Lett.*, **1970**, 5253; e) G. M. Whitesides and D. W. Lewis, *J. Amer. Chem. Soc.*, **92**, 6979 (1970).

[6] For a recent review in asymmetric synthesis, see: a) T. D. Inch, *Synthesis*, **1970**, 466; b) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice, Inc., Englewood Cliffs, New Jersey (1971).

[7] R. W. Taft, Jr., M. S. Newman, and F. H. Verhoek, *J. Amer. Chem. Soc.*, **72**, 4511 (1950).

[8] Y. L. Goldfarb, M. A. Kalik, and M. L. Kirmalova, *Zhur. Obsch. Khim.*, **29**, 2034 (1959); *Chem. Abstr.*, **54**, 8776 (1961).

The sulfoxide Ib yielded the same diketone (97%).

The reduction of II under conditions similar to those used for I gave tetradecane-2,13-dione (90%), mp 72.5—74.5°C (lit,[9] 76—77°C). IR (Nujol): 1705 cm^{-1} (C=O). MS: 226 (M$^+$). NMR ($CDCl_3$): δ 1.00—1.90 (m, 16 H, $-(CH_2)_8-$), 2.14 (s, 6 H, -COMe), and 2.43 (t(J=7 Hz), 4 H, $-CH_2CO-$).

The Reaction of Di-(—)-menthyl Sebacate (IV) with Lithium Methylsulfinylcarbanion. Lithium methylsulfinylcarbanion was prepared by adding a hexane solution of *n*-butyllithium (1.50 N, 107 m*l*, 0.16 mol) to a stirred mixture of DMSO (12.8 g, 0.16 mol) in THF (70 m*l*) under ice cooling. The lithium salt separated as fine white precipitates. To this suspension, a solution of the ester IV (9.40 g, 0.02 mol) in THF (20 m*l*) was added at -30°C over a period of 30 min, after which the reaction mixture was stirred at -30——15°C for 2 hr. A work-up followed by the separation of the isomers gave sulfoxides Ia and Ib. The sulfoxide Ia, mp 141—143°C, showed $[\alpha]_D$ 0.0° (c 3.98, $CHCl_3$), and Ib, mp 120—122°C, showed $[\alpha]_D$ $+1.22$° (c 6.08, $CHCl_3$).

The Reaction of (—)-Methyl Benzoate (V) with Lithium Methylsulfinylcarbonion. The treatment of (—)-menthyl benzoate (2.7 g, 0.01 mol) with lithium methylsulfinylcarbanion prepared from a hexane solution of *n*-butyllithium (1.15 N, 35 m*l*, 0.04 mol) and DMSO (3.2 g, 0.04 mol) in THF (20 m*l*) gave methyl phenacyl sulfoxide VI (0.74 g, 41%). The sulfoxide VI showed a mp of 85—88°C (lit,[2a]) 86—86.5°C); $[\alpha]_D$ -1.68° (c 8.00, $CHCl_3$).

The Condensation of I and Allyl Bromide in the Presence of Sodium Hydride. The treatment of I (3.23 g, 0.01 mol) with sodium hydride (0.48 g, 0.02 mol) in DMSO (15 m*l*) at 40°C for 1 hr gave a brown solution. To this, allyl bromide (2.42 g, 0.02 mol) in DMSO (15 m*l*) was added, after which the reaction mixture was stirred at 60°C for 3 hr. A work-up gave an intractable oil. This oil was dissolved in THF (40 m*l*) and water (30 m*l*), and this solution was treated with Hg_2Cl_2-pretreated aluminum foil (5.4 g) at 60—70°C for 3 hr. Subsequent distillation and chromatography on a Silicagel column gave octadeca-1,17-diene-5,14-dione (0.59 g, 21%), mp 68—71°C. IR (Nujol): 1710 cm^{-1} (C=O) and 1640, 995 and 915 cm^{-1} ($-CH=CH_2$). NMR ($CDCl_3$): δ 0.80—1.85 (m, 12 H, $-(CH_2)_6-$), 1.85—2.80 (m, 12 H, $-CHCH_2CH_2COCH_2-$), 4.80—5.25 (m, 4 H CH_2-) 1.85—2.80 (m, 12 H, $=CHC\underline{H}_2C\underline{H}_2COC\underline{H}_2-$), 4.80—5.25 (m, 4H, $CH_2=$) and 5.50—6.20 (m, 2 H, $=CH-$).

Found: C, 77.9; H, 10.8%. Calcd for $C_{18}H_{30}O_2$: C, 77.7; H, 10.9%.

The authors are grateful to Professor K. Sisido for his generous help. The financial support from the Ministry of Education, the Japanese Government, and from the Toray Science Foundation is also acknowledged with pleasure.

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[9] E. G. Hawkins and D. P. Young, *J. Chem. Soc.*, **1950**, 2804.