Resolution of ($\pm$)-2,2'-Spirobi[indan]-1,1'-dione

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Optically active 2,2'-spirobi[indan]-1,1'-dione has been prepared in good yield and high optical purity by a procedure including the following four steps: 1. stereoselective reduction of ($\pm$)-2,2'-spirobi[indan]-1,1'-dione to ($\pm$)-1'-hydroxy-2,2'-spirobi[indan]-1-one; 2. acylation of this compound with (–)-*o*-camphanic acid chloride to give two diastereomeric camphanic esters; 3. reduction of the higher melting diastereomer to optically active 2,2'-spirobi[indan]-1,1'-diol, and 4. oxidation of the latter compound to (+)-2,2'-spirobi[indan]-1,1'-dione. The optical purity of this compound was higher than 95 %, according to differential thermal analysis.

In continuing the studies of some aromatic spiro-compounds, *e.g.* ($\pm$)-2,2'-spirobi[indan]-1,1'-dione,¹ I, we have also recently resolved I. Two recent publications,^{2,3} prompt us to publish our results at the present stage of studies.

The primary aim was to elaborate a resolution, which could yield the optically active compound I in quantity and in high optical purity. Two methods were examined, resolution by chromatography and *via* diastereomer formation. No resolution was, however, obtained by chromatography of racemic I on partially acetylated cellulose with benzene as eluent.

The method applying diastereomer formation involves reduction of the racemic ketone to the corresponding diastereomeric secondary alcohols followed by resolution of one of these and finally reoxidation of the enantiomeric alcohols to the enantiomeric ketones.

Reduction of I with excess of lithium aluminium hydride in tetrahydrofuran gave predominantly one of the three possible diastereomeric dihydroxy derivatives. The yield of this isomer (III, Scheme 1) was 65 %.

The NMR spectrum of III in DMSO-*d*₆

demonstrates, that the secondary alcohol groups at the 1 and 1' positions have opposite configurations, and that the methylene groups at the 3 and 3' positions are not equivalent. It is thus concluded that III is identical with ($\pm$)-2,2'-spirobi[indan]-(1*R*,1'*S*)-diol.

The monoreduction of I could be achieved by using lithium tri-*t*-butoxyaluminium hydride as reducing agent in tetrahydrofuran. The reduction shows high stereoselectivity since the isomer (IIa, Scheme 1) could be isolated in a yield higher than 70 %.

Scheme 1.

Chemical reactions (Scheme 1) and spectroscopic properties (NMR, IR) of the monoreduction product are consistent with structure IIa.

Experiments to resolve III were not successful. Resolution of IIa according to Scheme 1 did, however, succeed. This method follows the reaction sequence used in resolution of spiro[4.5] decan-1,6-dione⁴ (Scheme 1).

Acylation of ($\pm$)-IIa with (–)-*o*-camphanic acid chloride in pyridine afforded the camphanic ester IIb, (–)-IIb + (+)-IIb, in about 95 % yield. The separation of the two diastereomers (–)-IIb and (+)-IIb, respectively, could be achieved by fractional crystallization from

benzene or acetone. This separation gave the higher melting diastereomer (-)-IIb in almost pure form in 25–30 % yield.

The NMR spectra of the two diastereomers (+)-IIb and (-)-IIb are identical except for the camphanic acid residues, whose proton signals appear at higher field than those of the rest of the molecule. The signals from the three methyl groups in (-)-IIb and (+)-IIb, respectively, appear as three singlets. The separation of the methyl signals of the two diastereomers allows evaluation of the ratio between (-)-IIb and (+)-IIb.

Reduction of (-)-IIb or (+)-IIb, respectively, with excess of lithium aluminium hydride in tetrahydrofuran afforded a mixture of the two possible epimeric dihydroxy derivatives (III+III'), which was optically active.

In the dihydroxy derivative III', the configuration at C₁ and C₁' must be the same; this is proved by NMR, which shows only one AB system for the secondary alcohol groups at C₁ and C₁' and only one AB system for the two methylene groups at the 3 and 3' positions.

An alternative route to that outlined in Scheme 1 for conversion of IIb to I is hydrolysis of the camphanic ester (IIb) to give IIa, followed by oxidation of IIa to I.

Hydrolysis of (-)-IIb in alkaline solution gave a nearly quantitative yield of IIa, but the product was optically inactive; it is concluded that this racemization must involve cleavage of one of the bonds to the spiro atom C₂.

Oxidation of optically active 2,2'-spirobi[indan]-1,1'-diol (III+III') with Jones reagent gave (+)-I or (-)-I, respectively, according to the correlation outlined in Scheme 1. The yield of optically active 2,2'-spirobi[indan]-1,1'-dione was about 70 %.

Differential thermal analysis performed on (+)-I indicated that the optical purity was high, since the corresponding thermogram showed only one sharp endotherm on heating; (+)-I thus gives a thermogram typical for a pure compound.

Differential thermal analysis performed on a mixture of (±)-I and (+)-I, prepared with an optical purity of 93 %, displayed a thermogram on which an endotherm corresponding to (±)-I easily could be detected; from the peak height of the endotherm it is judged that

the optical purity of (+)-I is higher than 95 %. If one accepts the melting point curve in Ref. 3 (Fig. 3), then the optical purity of our product would be ~90 %.

The CD spectrum of (+)-I in methanol shows two positive and two negative absorption maxima in the $n-\pi^*$ range at 354, 340, 329, and 318 nm, respectively, while two positive and one negative CD maxima are observed in the $\pi-\pi^*$ range at 297, 244, and 230 nm.

The CD spectrum of (+)-I is thus in gross accordance with that recently published.²

The ORD spectrum of (+)-I in methanol shows three cotton effects in the wavelength range 250–400 nm, positive cotton effects at 355 and 295 nm, respectively, and a negative one at 331 nm.

The ORD spectrum of (+)-I could thus be correlated to the CD spectrum in the $n-\pi^*$ and the first $\pi-\pi^*$ band.

EXPERIMENTAL

NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer, using TMS as internal standard. The chemical shifts are expressed in τ values and the coupling constants numerically in Hz. IR spectra were recorded on a Perkin-Elmer model 521 spectrophotometer. The mass spectra were determined on a CEC 21/104 instrument. Optical rotations were measured with a Zeiss polarimeter, using a 2 dm cell to determine specific rotations, c being expressed as g/100 ml of solution. The circular dichroism was measured on a Roussel-Jouan Dichrographe. The ORD spectrum was performed on a F.J.C.A. spectropol instrument. Differential thermal analyses were performed with a Du Pont 900 Differential Thermal Analyser Instrument. Elemental analyses were determined in the laboratories of Dornis und Kolbe, Mülheim.

(±)-2,2'-Spirobi[indan]-1,1'-dione (I) was prepared by cyclization of (±)-2-benzyl-3-(*o*-carboxyphenyl)propionic acid.¹ Instead of purification by sublimation, the dried raw product was recrystallized directly (without pretreatment with Na₂CO₃) from benzene (charcoal). The yield was 75 %.

(±)-2,2'-Spirobi[indan]-(1R,1'S)-diol (III). To a stirred mixture of LiAlH₄ (1.52 g, 0.04 mol) and tetrahydrofuran (35 ml), distilled over LiAlH₄, was added a solution of (±)-2,2'-spirobi[indan]-1,1'-dione (I) (2.48 g, 0.01 mol) in tetrahydrofuran (100 ml) at 20 °C. The temperature of the mixture rose to 36 °C. Stirring was continued at 30 °C for 1 h. The reaction mixture was decomposed by successive addition of ethyl acetate (20 ml) and H₂O (80 ml). The inor-

ganic precipitate was filtered with suction and washed with warm CHCl_3 . The CHCl_3 phase in the filtrate was separated and washed with H_2O and saturated NaCl solution. After drying (CaSO_4), the filtered solution was evaporated, and the crystalline residue (2.19 g) recrystallized from benzene (30 ml) to give III (1.61 g, 64 %), m.p. 155–157.5°C. (Found: C 80.44; H 6.29. Calc. for $\text{C}_{17}\text{H}_{16}\text{O}_2$; C 80.92; H 6.39). MS (70 eV): m/e 234 ($\text{M}^+ - \text{H}_2\text{O}$, 100 %), 118 (64 %), 91 (79 %), 69 (67 %). NMR [$(\text{CD}_3)_2\text{SO}$]: τ 2.63–2.86 (m, 8 H, arom. protons), 4.72 (d, 1 H, $J = 6.5$ Hz), 5.40 (d, 1 H, $\text{HO}-\text{C}-\text{H}$), 4.87 (d, 1 H, $J = 6.5$ Hz), 5.21 (d, 1 H, $\text{HO}-\text{C}-\text{H}$), 6.54 (d, 1 H, $J = 15.5$ Hz), 7.45 (d, 1 H, CH_2), 7.20–7.26 (m, 2 H, CH_2).

(±)-1'-Hydroxy-2,2'-spirobi[indan]-1-one (IIa). To a stirred mixture of $\text{LiAlH}_4(\text{OC}_2\text{H}_5)_3$ (3.81 g) (≥ 90 %, Fluka) and tetrahydrofuran (50 ml), distilled over LiAlH_4 , was added a solution of (±)-2,2'-spirobi[indan]-1,1'-dione (I) (2.48 g, 0.01 mol) in tetrahydrofuran (100 ml) at room temperature. The mixture was refluxed with stirring for 2 h. To the warm reaction mixture was added ethyl acetate (5 ml). After the exothermic reaction had subsided, the mixture was cooled and H_2O (10 ml) added; stirring was continued for further 15 min. The reaction mixture was filtered with suction, and the inorganic precipitate washed with warm CHCl_3 . The combined filtrate was evaporated to dryness and the residue recrystallized from benzene (140 ml) to give IIa (1.81 g, 72 %), m.p. 198.5–199.5°C. (Found: C 81.28; H 5.99. Calc. for $\text{C}_{17}\text{H}_{14}\text{O}_2$; C 81.58; H 5.64). MS (70 eV): m/e 250 (M^+ , 24 %), 232 ($\text{M}^+ - \text{H}_2\text{O}$, 100 %), 131 (68 %). $\nu_{\text{max}}(\text{CHCl}_3)$: 1719 cm^{-1} ($\text{C}=\text{O}$). NMR [$(\text{CD}_3)_2\text{SO}$]: τ 2.17–2.78 (m, 8 H, arom. protons), 4.21 (d, 1 H, $J = 6.2$ Hz), 4.65 (d, 1 H, $\text{HO}-\text{C}-\text{H}$), 6.31 (d, 1 H, $J = 17.5$ Hz), 7.23 (d, 1 H, CH_2), 6.78 (d, 1 H, $J = 15.5$ Hz), 7.11 (d, 1 H, CH_2).

(-)- ω -Camphanic acid was prepared by hydrolysis of (-)- α -bromocamphoric anhydride as previously described.^{5,6}

Acylation of (±)-IIa with (-)- ω -camphanic acid chloride. The sodium salt of camphanic acid was prepared from camphanic acid (2.97 g, 0.015 mol), NaHCO_3 (1.32 g, 0.016 mol) and H_2O (10 ml). The resulting solution was evaporated. Benzene (5 ml), was added to the residue, and the mixture was again evaporated; this operation was repeated twice followed by drying at 50–60°C. Benzene (10 ml) and pyridine (0.2 ml) were added to the dry sodium salt. The mixture was cooled in ice and a solution of oxalyl chloride (6.43 ml, 0.075 mol) in benzene (10 ml) was added during 5–10 min, while the reaction flask was shaken. After cooling for further 10 min the mixture was placed at room temperature for 19 h. After evaporation *in vacuo*, benzene (5 ml) was added to the residue followed by evaporation *in vacuo*, this operation was repeated twice. To the flask with the prepared camphanic acid

chloride was added (±)-1'-hydroxy-2,2'-spirobi[indan]-1-one (IIa) (3.0 g, 0.012 mol). The reaction flask was cooled in ice and pyridine (20 ml) added. After cooling for 0.5 h the reaction flask was placed at room temperature for 92 h. To the mixture was added CHCl_3 (30 ml). The CHCl_3 solution was washed successively with H_2O , HCl (2 N) and Na_2CO_3 (5 %). After drying (CaSO_4) the CHCl_3 solution was evaporated *in vacuo* to give crystalline IIb (4.85 g, 94 %). One recrystallization of the camphanic ester (IIb) from acetone (40 ml) gave (-)-IIb (1.52 g, 29.4 %), m.p. 198–200°C. (Found: C 75.23; H 6.24. Calc. for $\text{C}_{25}\text{H}_{20}\text{O}_5$; C 75.33; H 6.09). MS (70 eV): m/e 249 ($\text{M}^+ - 181$, 24 %), 232 ($\text{M}^+ - 198$, 100 %). $\nu_{\text{max}}(\text{CHCl}_3)$: 1734, 1758, 1808 cm^{-1} ($\text{C}=\text{O}$). NMR (CDCl_3): τ 2.12–2.72 (m, 8 H, arom. protons), 3.44 (s, 1 H, $\text{H}-\text{C}-\text{OR}$), 6.22–7.22 (m, 4 H, $\text{CH}_2-\text{C}-\text{CH}_2$), 7.60–8.40 (m, 4 H, CH_2-CH_2), 8.97 (9.12, 9.41, 3 s, 3 CH_2). $[\alpha]_D^{25} - 89.75^\circ$ (c 2.0, CHCl_3). Evaporation of the filtrate from the isolation of (-)-IIb afforded a mixture of (+)-IIb and (-)-IIb (2.96 g, 57.3 %). NMR (CDCl_3): τ 2.12–2.72 (m, 8 H, arom. protons), 3.44 (s, 1 H, $\text{H}-\text{C}-\text{OR}$), 6.20–7.20 (m, 4 H, $\text{CH}_2-\text{C}-\text{CH}_2$), 7.5–8.6 (m, 4 H, CH_2-CH_2), 8.97 (9.12, 9.41, 3 s, 3 CH_2), 8.95 (9.12, 9.17, 3 s, 3 CH_2). The ratio between (-)-IIb and (+)-IIb in the two isolated fractions were 97:3 and 30:70, respectively, as determined from the NMR spectra.

2,2'-Spirobi[indan]-1,1'-diol (III + III'). To a stirred mixture of LiAlH_4 (1.73 g, 45.5 mmol) in tetrahydrofuran (12 ml), distilled over LiAlH_4 , was added a solution of the camphanic ester (-)-IIb (1.31 g, 3.03 mmol) in tetrahydrofuran (30 ml) at room temperature. The mixture was refluxed with stirring for 5 h. Excess LiAlH_4 was destroyed by dropwise addition of ethyl acetate (10 ml). After the exothermic reaction had subsided, the reaction mixture was cooled and H_2O (40 ml) added dropwise. After work up as described above for III, the CHCl_3 solution was evaporated and the crystalline residue treated with warm benzene (5 ml) to give preferentially III (0.51 g). $[\alpha]_D^{25} + 10.9^\circ$ (c 4.0, tetrahydrofuran). The filtrate from the isolation of III was evaporated, and the residue (0.25 g) subjected to further reduction with LiAlH_4 (0.33 g) in tetrahydrofuran (10 ml). The mixture was stirred and refluxed for 2 h. After work up as described for the isolation of III, 0.1 g crystalline dihydroxy derivative (III + III') was isolated. NMR (of III') [$(\text{CD}_3)_2\text{SO}$]: τ 2.63–2.85 (m, 8 H, arom. protons), 4.52 (d, 2 H, $J = 6.4$ Hz), 4.99 (d, 2 H, $\text{HO}-\text{C}-\text{H}$), 7.03 (d, 2 H, $J = 15.5$ Hz), 7.35 (d, 2 H, CH_2). The total yield of dihydroxy derivative was 80 %. From the integrated intensities of the ($\text{HO}-\text{C}-\text{H}$) signals in the two isolated fractions, the ratio of III to III' was evaluated to be 9:1 and 4:6, respectively.

Alkaline hydrolysis of (-)-IIb. A mixture of (-)-IIb (0.22 g, 0.5 mmol), ethanol (5 ml, 96 %),

H₂O (3 ml) and aqueous KOH (2.0 ml, 0.5 N) was refluxed for 8 min. After cooling in ice-water the reaction mixture was extracted with CHCl₃. The CHCl₃ phase was extracted successively with H₂O and saturated NaCl solution. After drying (CaSO₄), the CHCl₃ solution was evaporated *in vacuo* to give crystalline IIa (0.12 g, 96 %). The product, which was optically inactive could be oxidized to (±)-I by means of Jones reagent.

(+)-2,2'-Spiro[indan]-1,1'-dione [(+)-I]. To a mixture of III + III' (0.32 g, 1.27 mmol), prepared by reduction of (-)-IIb, and acetone (10 ml), distilled from KMnO₄, was added rapidly at room temperature with stirring 0.80 ml of 8 N CrO₃ reagent (10 ml, 8 N reagent was prepared from CrO₃ (2.67 g), conc. H₂SO₄ (2.3 ml) and H₂O). After addition of CrO₃ reagent the temperature in the reaction mixture rose to 39 °C. The reaction flask was placed in a water-bath of room temperature and stirring was continued for further 20 min. To the reaction mixture, which contained a dark coloured precipitate, was added H₂O (10–15 ml). The dark coloured precipitate disappeared, and a white precipitate was formed. After filtration and drying the product (0.26 g) was recrystallized from ethanol (18 ml, 96 %) to give (+)-I (0.215 g, 68.3 %) m.p. 210.5–212.5 °C. $[\alpha]_D^{24.5} +151.86^\circ$ (c 3.22, CHCl₃). The NMR spectrum was identical with that of (±)-I previously reported.¹ $\nu_{\max}(\text{KBr})$: 1705, 1735 cm⁻¹ (C=O). CD spectrum (methanol), ($\nu_{\max}$ nm, $\Delta \epsilon$): 354 (+0.34), 340 (+0.27), 329 (−0.58), 318 (−1.1), 297 (+10), 244 (+5.2), 230 (−8.5).

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