Characterisation of *threo*- and *erythro*-2-Benzyl-3-phenylsuccinic Acids

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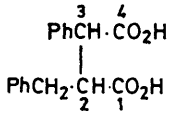
Chemical and n.m.r. spectroscopic evidence indicates that the higher and lower melting forms of 2-benzyl-3-phenylsuccinic acid (1) are the *erythro* and *threo* diastereoisomers, respectively. The n.m.r. spectra of the dimethyl esters reflect the conformational preferences of these derivatives in solution.

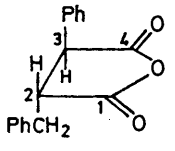
ALTHOUGH a 2-benzyl-3-phenylsuccinic acid (1) was isolated over sixty years ago [1] and several subsequent studies [2-5] have produced one or both diastereoisomeric forms of the acid and its derivatives, no identification of the *threo* and *erythro* forms has been made. We report here evidence which identifies these acids and indicates the preferred conformations of their dimethyl esters in solution.

Methyl phenylpyruvate was converted into a dimethyl 2-benzyl-3-phenylsuccinate (m.p. 86—88°), diester (A), and its higher melting isomer (m.p. 122—123°), diester (B), in high overall yield, when heated with sodium methoxide in dioxan. In methanol quantities of 4-benzyl-2-hydroxy-4-methoxycarbonyl-3-phenylbut-2-en-4-olide were also formed (*cf.* ref. 4). Alkaline hydrolysis of each diester gave an acidic fraction which could be separated chromatographically into two isomers. One of these (A) [m.p. 165° (decomp.)] was converted by treatment with diazomethane into the diester (A) and the other (B) [m.p. 184° (decomp.)] into the diester (B). We presume that partial inversion at C-3 accompanied the hydrolysis. The figures for the m.p.s refer to slow heating (<0·5 deg min^{-1}). With more rapid heating, isomer (A) melts sharply at 184° and isomer (B) less sharply at 208°, which probably accounts for ambiguities in the early literature.

Both acids could be readily converted into a common anhydride which is expected to have the *threo* structure (II) on steric grounds. The n.m.r. spectrum of the anhydride confirms this assignment. The aliphatic protons gave rise to an ABMX spectrum which was analysed to reveal chemical shifts which are in good



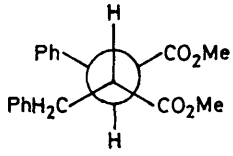
(I)



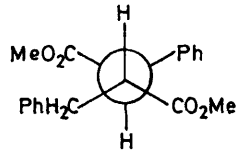
(II)

agreement with those found for related succinic anhydrides in which phenyl and benzyl groups are *trans* disposed.[6] The high value found for $J_{2,3}$ (8·0 Hz) further illustrates the marked sensitivity to substitution of the vicinal coupling within this class of compound.[7] Hydrolysis of the anhydride under mild conditions led to isomer (A), clearly establishing that this compound is *threo*-2-benzyl-3-phenylsuccinic acid.

The n.m.r. spectra of the dimethyl esters showed strong coupling between H-2 and H-3; J 11·7 and 11·4 Hz for the *threo*-ester and the *erythro*-ester, respectively. The contribution to these average values from the staggered conformations (III) and (IV) is therefore high. Con-



(III)



(IV)

sideration of the chemical shifts also leads to this conclusion. In conformation (III) shielding of the methylene portion of the benzylic group at C-2 by the phenyl group at C-3 is expected, and the spectrum of the *threo*-ester shows an average shift of 20 Hz to higher field for these protons relative to the corresponding protons in the *erythro*-ester. Perturbation and a shift to higher field of the signals from one phenyl ring is also apparent. This is probably the benzyl phenyl ring, which is forced to lie very close to the C-3 ester carbonyl in conformation (III). Marked shielding of the C-1 methoxy-group by both the phenyl rings is anticipated if the *erythro*-ester is in conformation (IV) and a shift to higher field of 44 Hz is observed for one methoxy-group signal relative to the corresponding signal in the *threo*-ester. We therefore conclude that the predominant conformations in the *threo*-ester and the *erythro*-ester are (III) and (IV), respectively, and that in the former compound the dipole repulsion between the two ester groups in conformation (III) is small relative to the increase in the steric repulsion in other conformations.

EXPERIMENTAL

U.v. spectra were measured with a Hilger Ultrascan H 999 Mark II recording spectrophotometer, and i.r. spectra were determined with a Perkin-Elmer recording spectrophotometer, model 21. N.m.r. spectra were recorded at 100 MHz with a JEOL MH-100 instrument.

Methyl Phenylpyruvate.—A mixture of the enol and keto forms of methyl phenylpyruvate was obtained as an oil (10 g) (b.p. 105—107° at 2·5 mmHg) when phenylpyruvic acid (13·9 g) was heated under reflux for 18 h with dry methanol (25 cm^3) in ethylene dichloride (95 cm^3). Crystallisation (n-hexane) of the oil gave methyl phenylpyruvate (enolic form) (3·0 g) as needles, m.p. 58—60° (Found: C,

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67·2; H, 5·7. Calc. for $C_{10}H_{10}O_3$: C, 67·4; H, 5·7%); $\lambda_{max.}$ (n-hexane) 282, 293, and 307 nm (log ε 4·36, 4·48, and 4·38); $\lambda_{max.}$ [MeOH + 0·1N-NaOH(trace)] 335 nm (log ε 4·31); $\nu_{max.}$ (KBr) 3400 (OH str.) and 1700 cm^{-1} (unsat. CO str.); τ ($CDCl_3$) 2·20—2·90 (5H, m, aryl H), 3·55 (exchangeable) (1H, s, OH), 3·55 (1H, s, ·CH:), and 6·15 (3H, s, OMe).

threo- *and* erythro-*Methyl 2-Benzyl-3-phenylsuccinate*.—A neutral product (0·72 g) was obtained when methyl phenylpyruvate (1·1 g) in dioxan (10 cm^3) was heated under reflux for 17 h with sodium methoxide [from sodium (0·13 g) and anhydrous methanol (30 cm^3)]. The neutral material was chromatographed on silica gel in benzene–chloroform (95 : 5) to give two products. *erythro*-Dimethyl 2-benzyl-3-phenylsuccinate (0·26 g) was obtained as needles (from light petroleum), m.p. 122—123° (Found: C, 73·1; H, 6·5. Calc. for $C_{19}H_{20}O_4$: C, 73·1; H, 6·45%); $\lambda_{max.}$ (MeOH) 223 and 260 nm (log ε 3·81 and 2·60); $\nu_{max.}$ (KBr) 1728 cm^{-1} (ester C:O str.); τ ($CDCl_3$) 2·71 (5H, s, aryl H), 2·79 (5H, s, aryl H), 6·15 * (1H, d, $J_{2.3}$ 11·4 Hz, 3-H), 6·35 (3H, s, OMe), 6·52 * (1H, m, $J_{2.3}$ 11·4, $J_{2.H_a}$ 10·9, $J_{2.H_b}$ 3·7 Hz, 2-H), 6·85 (3H, s, OMe), 7·04 * (1H, m, $J_{2.H_a}$ 10·9, $J_{H_aH_b}$ 13·2 Hz, H_a–C–H_b), and 7·11 * (1H, m, $J_{2.H_b}$ 3·7, $J_{H_aH_b}$ 13·2 Hz, H_a–C–H_b). *threo*-Dimethyl 2-benzyl-3-phenylsuccinate (0·3 g) was obtained as needles (light petroleum), m.p. 86—88° (Found: C, 72·9; H, 6·4. Calc. for $C_{19}H_{20}O_4$: C, 73·1; H, 6·45%); $\lambda_{max.}$ (MeOH) 223 and 260 nm (log ε 4·74 and 3·66); $\nu_{max.}$ (KBr) 1740 and 1738 cm^{-1} (ester C:O str.); τ ($CDCl_3$) 2·55 (5H, s, aryl H), 2·71 (3H, m, *m*- and *p*-aryl H), 2·95 (2H, m, *o*-aryl H), 6·07 * (1H, d, $J_{2.3}$ 11·7 Hz, 3-H), 6·37 (3H, s, OMe), 6·41 (3H, s, OMe), 6·52 (1H, m, $J_{2.3}$ 11·7, $J_{2.H_a}$ 10·1, $J_{2.H_b}$ 6·1 Hz, 2-H), 7·11 * (1H, m, $J_{2.H_a}$ 10·1 Hz, $J_{H_aH_b}$ 12·9 Hz, H_a–C–H_b), and 7·43 (1H, m, $J_{2.H_b}$ 6·1, $J_{H_aH_b}$ 12·9 Hz, H_a–C–H_b).

erythro- *and* threo-2-*Benzyl-3-phenylsuccinic Acids*.—The *erythro*-dimethyl ester (0·26 g) was hydrolysed by heating with 2M-potassium hydroxide solution (30 cm^3) in ethanol (20 cm^3) for 3 h. The acidic fraction was isolated and chromatographed on a silicic acid column (gradient elution with chloroform–ethyl acetate) to give two products. *erythro*-2-Benzyl-3-phenylsuccinic acid (0·1 g) was obtained as prisms (H_2O–AcOH), m.p. 184° (decomp.) (Found: C, 72·3; H, 6·0. Calc. for $C_{17}H_{16}O_4$: C, 71·8; H, 5·7%); $\nu_{max.}$ (KBr) 3640—2230 (carboxy OH str.) and 1695 cm^{-1} (carboxy C=O str.); τ [$(CD_3)_2SO$] 2·60 (5H, s, aryl H), 2·67 (5H, s, aryl H), 6·10—7·20 (4H, complex, CH_2·CH·CH); R_F (Kieselgel GF_{254}; $CHCl_3$–MeOH–AcOH, 95 : 20 : 4) 0·72. Methylation with diazomethane gave a quantitative yield of the *erythro*-dimethyl ester, m.p. 122—123°. *threo*-2-Benzyl-3-phenylsuccinic acid (0·08 g) was obtained as prisms (H_2O–AcOH), m.p. 165° (decomp.) (Found: C, 72·2; H, 5·8. Calc. for $C_{17}H_{16}O$: C, 71·8; H, 5·7%); $\nu_{max.}$ (KBr) 3680—2240 (carboxy OH str.) and 1700 cm^{-1} (carboxy C=O str.); τ [$(CD_3)_2SO$] 2·57 (5H, s, aryl H), 2·65—3·15 (5H, m, aryl H), and 6·20—7·62 (4H, complex, CH_2·CH·CH); R_F (same system) 0·65. The acid was cleanly converted into the *threo*-dimethyl ester, m.p. 86—87°, on treatment with diazomethane.

The two acids were also obtained from the *threo*-dimethyl ester by an identical procedure.

threo-2-*Benzyl-3-phenylsuccinic Anhydride*.—*threo*-2-Benzyl-3-phenylsuccinic acid (32 mg) was converted into the *anhydride* by treatment with acetic anhydride (2 cm^3) at room temperature for 2 days. The distilled anhydride [b.p. 150—158° (bath) at 0·02 mmHg slowly solidified; m.p. 53—55° (Found: C, 76·7; H, 5·4. $C_{17}H_{14}O_3$ requires C, 76·7; H, 5·3%); $\nu_{max.}$ (KBr) 1865 and 1790 cm^{-1} (anhydride C=O str.); τ ($CDCl_3$) 2·65 (5H, m, aryl H), 2·85 (5H, m, aryl H), 6·05 * (1H, d, $J_{2.3}$ 8·0 Hz, 3-H), 6·48 * (1H, m, $J_{2.H_a} = J_{2.H_b}$ 6·2 Hz, 2-H), 6·83 * (1H, m, $J_{2.H_a}$ 6·2, $J_{H_aH_b}$ 14·4 Hz, H_a–C–H_b), and 6·90 * (1H, m, $J_{2.H_b}$ 6·2, $J_{H_aH_b}$ 14·4 Hz, H_a–C–H_b).

Material with the same m.p. and i.r. and n.m.r. spectra as the above compound was isolated when (i) the *threo*-acid was heated at its m.p. for 10 min, (ii) the *erythro*-acid was treated with acetic anhydride for 2 days at room temperature, and (iii) the *erythro*-acid was heated at its m.p. for 10 min.

Hydrolysis of threo-2-*Benzyl-3-phenylsuccinic Anhydride*.—The oily product obtained when *threo*-2-benzyl-3-phenylsuccinic anhydride (0·14 g) was kept in ethanol (10 cm^3) and 0·2M-sodium hydroxide solution (10 cm^3) at room temperature for 18 h, was chromatographed on a silica gel column ($CHCl_3$ and $CHCl_3$–EtOAc) to give two major components. The more polar product (60 mg) was identified as *threo*-2-benzyl-3-phenylsuccinic acid, m.p. 165° (decomp.), by direct comparison with authentic material (i.r., n.m.r., t.l.c.) and by conversion into the dimethyl ester, m.p. 85—87°. The less polar product (40 mg), a mixture of ethyl half esters (n.m.r.), was further hydrolysed in M-potassium hydroxide solution at room temp. for 2 days to give *threo*-2-benzyl-3-phenylsuccinic acid (30 mg) and a trace of the *erythro*-acid (t.l.c.).

Hydrolysis of the anhydride in neutral and acidic aqueous ethanolic solutions, at room temperature, also gave the *threo*-acid and its ethyl half esters as the two major products.

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* Treated as part of an ABMX spectrum.

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