

Synthesis and Proton Nuclear Magnetic Resonance Spectra of Diastereoisomeric Ethyl 3-Hydroxy-2-methyl-3-(*p*-substituted phenyl)butyrates

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A series of *erythro*- and *threo*-ethyl 3-hydroxy-2-methyl-3-(*p*-substituted phenyl)butyrates has been prepared. The ^1H n.m.r. spectra of these compounds and their use in assigning diastereoisomeric configurations are discussed.

IN connection with a programme for the synthesis of compounds of pharmacological interest,¹ it was necessary to prepare a series of ethyl 3-hydroxy-2-methyl-3-(*p*-substituted phenyl)butyrates [(III) and (IV)]. Pure *erythro*- (III) and *threo*-diastereoisomers (IV) were also needed² (Table 1). Mixtures of (III) and (IV) were obtained from the Reformatsky reaction of acetophenones (I) with ethyl α -bromopropionate (II). The diastereoisomeric composition of these mixtures changes

¹ A. Balsamo, P. L. Barili, P. Crotti, B. Macchia, F. Macchia, A. Pecchia, A. Cuttica, and N. Passerini, submitted for publication in *J. Medicin. Chem.*

² A. Balsamo, P. L. Barili, P. Crotti, M. Ferretti, B. Macchia, and F. Macchia, *Tetrahedron Letters*, 1974, 1005.

with the reaction time, owing to a slower equilibration of (III) and (IV) in the reaction medium.² The compositions of the crude reaction mixtures after 2 h reaction are shown in Table 2; the *erythro*- β -hydroxyesters (III) predominate² in each case, in agreement with the results of the analogous reaction of unsubstituted acetophenone (I; R = H).^{3,4} The isomers (III) and (IV) were separated by preparative g.l.c. and t.l.c. Conformational analysis of these esters through their n.m.r. spectra can

³ J. Canceill, J.-J. Basselier, and J. Jacques, *Bull. Soc. chim. France*, 1967, 1024.

⁴ Y. Beziat and M. Mousseron-Canet, *Bull. Soc. chim. France*, 1968, 1187.

be used to assign the relative configurations to these compounds.

By calculating the non-bonding *gauche* interactions and possible attractive interactions (such as intramolecular hydrogen bonding) between groups in the three

diastereoisomers (IVb and c). Therefore, the populations of these conformers should be favoured⁸ with respect to those of conformers (IIIb) and (IVa), respectively. Of conformers (IIIa) and (IIIc), (IIIa) should be favoured because of the strong Ar-Me interaction

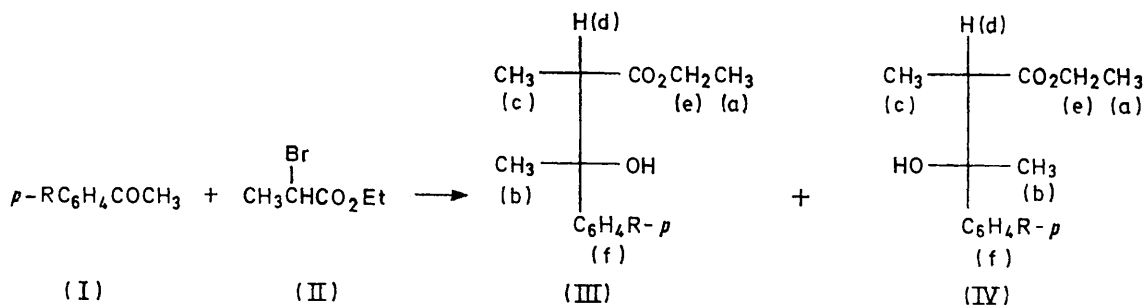


TABLE I
erythro-(III) and *threo*-Ethyl 3-hydroxy-2-methyl-3-(*p*-substituted phenyl)butyrates

Compound	n_D^{20}	Found (%)		Formula	Required (%)		¹ H N.m.r. spectra (δ values, J in Hz)							
		C	H		C	H	CH ₃ (a)	CH ₃ (b)	CH ₃ (c)	H(d)	CH ₂ (e)	<i>p</i> -C ₆ H ₄ R(f)	J_{ae}	J_{cd}
(III; R = MeO)	1.5066	66.55	8.0	C ₁₄ H ₂₀ O ₄	66.65	8.0	1.00	1.45	1.32	3.00	4.00	7.34	7.12	7.10
(III; R = Me)	1.4981	70.95	8.5	C ₁₄ H ₂₀ O ₃	71.15	8.55	0.98	1.43	1.30	2.97	3.92	7.15	7.08	7.12
(III; R = H)	1.4977			C ₁₃ H ₁₈ O ₃			0.95	1.44	1.31	2.97	3.91	7.32	7.11	7.12
							0.90 ^d	1.30 ^d	1.23 ^d	2.85 ^d	3.78 ^d			
							0.90 ^e	1.33 ^e	1.27 ^e	2.89 ^e	3.80 ^e			
(III; R = F)	1.4840	64.95	7.2	C ₁₃ H ₁₇ FO ₃	65.0	7.15	0.99	1.43	1.31	2.97	3.93	7.17	7.14	7.05
(III; R = Cl)	1.5114	61.05	6.7	C ₁₃ H ₁₇ ClO ₃	60.8	6.65	0.99	1.41	1.30	2.92	3.92	7.35	7.10	7.14
(III; R = Br)	1.5267	51.8	5.7	C ₁₃ H ₁₇ BrO ₃	51.85	5.7	1.00	1.41	1.31	2.96	3.93	7.35	7.10	7.13
(IV; R = MeO)	<i>a</i>	66.8	8.05	C ₁₄ H ₂₀ O ₄	66.65	8.0	1.30	1.57	0.98	2.84	4.31	7.26	7.16	7.19
(IV; R = Me)	1.4992	71.3	8.55	C ₁₄ H ₂₀ O ₃	71.15	8.55	1.30	1.56	0.96	2.81	4.22	7.22	7.10	7.12
(IV; R = H)	1.4984			C ₁₃ H ₁₈ O ₃			1.29	1.56	0.95	2.81	4.22	7.37	7.10	7.12
							1.22 ^d	1.42 ^d	0.85 ^d	2.80 ^d	4.10 ^d			
							1.23 ^e	1.46 ^e	0.89 ^e	2.72 ^e	4.15 ^e			
(IV; R = F)	<i>b</i>	65.05	6.9	C ₁₃ H ₁₇ FO ₃	65.0	7.15	1.29	1.55	0.95	2.80	4.22	7.21	7.11	7.15
(IV; R = Cl)	<i>c</i>	60.95	6.5	C ₁₃ H ₁₇ ClO ₃	60.8	6.65	1.29	1.54	0.95	2.80	4.23	7.37	7.11	7.12
(IV; R = Br)	1.5261	52.0	5.7	C ₁₃ H ₁₇ BrO ₃	51.85	5.7	1.29	1.55	0.95	2.80	4.24	7.37	7.08	7.10

^a M.p. 31—31.5° (from light petroleum). ^b M.p. 55—57° (from light petroleum). ^c M.p. 55—56° (from light petroleum). ^d For CS₂ solution. ^e For CCl₄ solution.

staggered rotamers of (III) and (IV),⁵ we can predict which conformation will be preferred for each isomer; these conformations would be expected to lead to significant differences in the n.m.r. spectra of the two diastereoisomers. On the basis of the value of their conformational free energy differences,^{6,7} the groups attached to the

present in (IIIc). This unfavourable interaction is present in both conformers (IVb) and (IVc), but conformer (IVb) should be preferred, since the Me-Me interaction present in (IVc) is missing.

The n.m.r. spectra of (III) and (IV) should reflect the relative populations of rotamers present at equilibrium and, therefore, should be in agreement with a time-averaged predominance of conformations (IIIa) and (IVb), respectively.

Table I summarizes the n.m.r. parameters of the β -hydroxyesters (III) and (IV). From an examination of these data, it is evident that the spectra agree with the conformational hypothesis. The signals of CH₃(a), CH₃(b), and CH₂(e) are at higher fields for the *erythro*- than for the *threo*-compounds. On the other hand, the signals of H(d) and CH₃(c) of the *erythro*-esters are at a lower field than the same protons of the *threo*-series. The centre of the phenyl resonance is at practically the same field or does not alter appreciably in the

R	Composition (%)		B.p. (°C) [mmHg]	Yield (%)
	(III)	(IV)		
MeO	74	26	145—150 [4.5]	60
Me	73	27	138—142 [4]	64
H*	71	29	108—111 [0.8]	70
F	68	32	155—160 [6]	86
Cl	69	31	150—155 [6]	85
Br	64	36	150—156 [3.5]	92

* Lit. (J. Canceill, J. Gabard, and J. Jacques, *Bull. Soc. chim. France*, 1966, 2653), b.p. 109—110 °C at 3 mmHg; yield 87%.

asymmetric carbon atoms in (III) and (IV) can be arranged; aryl > Me > CO₂Et > OH > H. Moreover, hydrogen bonding between OH and CO₂Et groups is possible^{3,4} in two of the three rotamers of both the *erythro*- β -hydroxyesters (IIIa and c) and of the *threo*-

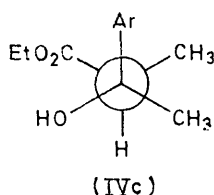
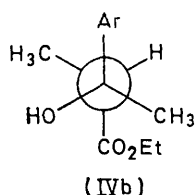
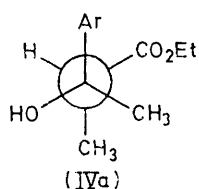
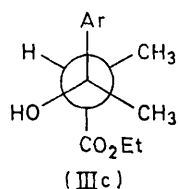
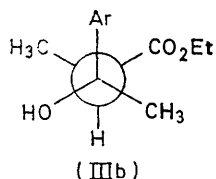
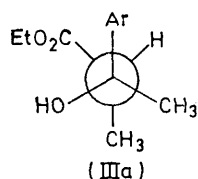
⁵ E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, p. 137, *et seq.*

⁶ E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, 'Conformational Analysis,' Interscience, New York, 1965, p. 44, *et seq.*

⁷ J. A. Hirsch, *Topics Stereochem.*, 1967, **1**, 199.

⁸ C. A. Kingsbury, *J. Org. Chem.*, 1970, **35**, 1319.

two series; evidently, the diamagnetic anisotropy of the phenyl group, as well as the deshielding effect of the carbonyl group, are the main causes of the shifts observed. By examining molecular models of the expected most stable conformers (IIIa) and (IVb), we can observe that CH₂(e) and CH₃(a) in the *erythro*-diastereoisomers,



and CH₃(c) in the *threo*-compounds, are located in the shielding region of the phenyl group. In the *threo*-diastereoisomers, CH₃(b) is situated in the deshielding region of the carbonyl group.⁹

It might seem that the chemical shift of H(d) should not change on passing from one diastereoisomer to another, because its position relative to the aryl group is the same in both the preferred rotamers (IIIa) and (IVb); however, the shift towards higher fields observed on passing from the *erythro* to the *threo*-series may be attributed to a different rotameric position of the phenyl group in the two conformers (IIIa) and (IVb), owing to its different relative position with respect to the ethoxy-carbonyl group. The values of the shifts due to the diamagnetic anisotropy of the phenyl group are not affected by the substituent on the phenyl group; this shows that the different electronic density on the phenyl group, depending on the different substituent, does not

significantly influence the shielding effect of the aromatic group.

Assignment of the signals was based on the agreement of the measured chemical shifts with those expected, and on the basis of the multiplicity and the integration of the signals.

EXPERIMENTAL

N.m.r. spectra were determined for *ca.* 10% solutions in CDCl₃ with a JEOL C-60 HL spectrometer using tetramethylsilane as internal standard. Chemical shifts and coupling constants were measured directly from the spectra determined at a sweep width of 540 Hz. G.l.c. analyses were run on a Carlo Erba Fractovap GV apparatus with a flame ionization detector using a dual column system with glass columns (2.5 mm × 2 m) packed with 1% neopentylglycol succinate on 80–100 mesh silanized Chromosorb W; the order of retention times was (III) < (IV).

Reformatsky Reaction of Acetophenones (I) with Ethyl α-Bromopropionate (II).—A portion (8 ml) of a solution of the acetophenone (I) (0.09 mol) and (II) (18.1 g, 0.1 mol) in anhydrous benzene (25 ml) was added to zinc powder (7.20 g, 0.1 mol) and the flask was warmed gently until the reaction started. Stirring was then started and the remainder of the solution was added at such a rate that a gentle reflux was maintained. The addition was complete in 10 min. The mixture was then refluxed for 2 h, cooled at 0°, and hydrolysed by addition of ice-cold 20% sulphuric acid (35 ml). The organic layer was washed with 10% sodium carbonate (20 ml) and with water (40 ml), filtered, and evaporated to dryness. The crude residue was examined by g.l.c. (Table 2) and distilled to give the mixture of (III) and (IV).

Separation of (III) and (IV).—Portions of distilled mixtures of (III) and (IV) were subjected to preparative g.l.c. when R = F, Cl, or Br, and to preparative t.l.c. when R = MeO, Me, or H.

Preparative g.l.c. was carried out on a Perkin-Elmer model F-21 gas chromatograph, using a stainless steel column (8 mm × 2 m) packed with 5% Carbowax 20M on 60–80 mesh silanized Chromosorb G.

Preparative t.l.c. was carried out on silica gel plates (Merck F₂₅₄), with light petroleum-ether (90 : 10) as eluant; elution was repeated 4 times and the esters were located with u.v. light (245 nm); *threo*-diastereoisomers were extracted from the faster-moving band.

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* G. J. Karabatsos, G. C. Sonnichsen, H. Nsi, and D. J. Fenoglio, *J. Amer. Chem. Soc.*, 1967, **89**, 5067.