Synthesis and Properties of the Stereoisomeric Diethyl 6-Aminocyclohexane-1,3-dicarboxylates

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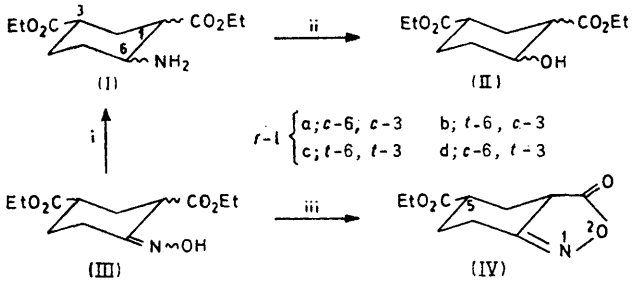
Hydrogenation of diethyl 6-hydroxyiminocyclohexane-1,3-dicarboxylate (III) yielded the four stereoisomeric diethyl 6-aminocyclohexane-1,3-dicarboxylates (I), deamination of which afforded the corresponding 6-hydroxy-derivatives (II) along with cyclohexenes. The amines (I) and the alcohols (II) were characterised as their *N*- and *O*-benzoyl derivatives, respectively. Attempted preparation of the oxime (III) in acidic media yielded mainly ethyl 3,3a,4,5,6,7-hexahydro-3-oxo-2,1-benzisoxazole-5-carboxylate (IV).

WE have already described the synthesis and properties of the stereoisomeric diethyl 2-aminocyclohexane-1,4-dicarboxylates,[1] and now report the preparation of the stereoisomeric diethyl 6-amino- (I) and 6-hydroxy-cyclohexane-1,3-dicarboxylates (II). The reductive cleavage [2] of diethyl 3,3a,4,5,6,7-hexahydro-3-oxo-2*H*-indazole-5,5-dicarboxylate [2] in propan-2-ol with Raney nickel as catalyst was applied to the hydrogenation of diethyl 6-hydroxyiminocyclohexane-1,3-dicarboxylate (III), giving the isomeric amines (I).

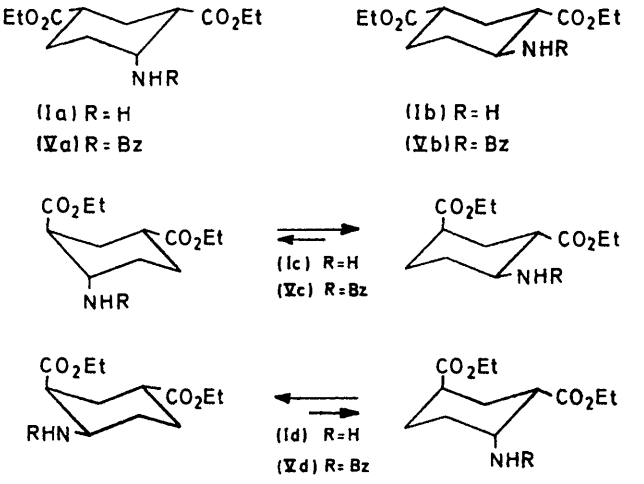
The oxime (III) was prepared from the corresponding cyclohexanone [3,4] by the usual method.[5] Acidic media [6] promoted intramolecular cyclisation of the *Z-eq*-isomer of (III) to the benzisoxazole (IV), which, under the



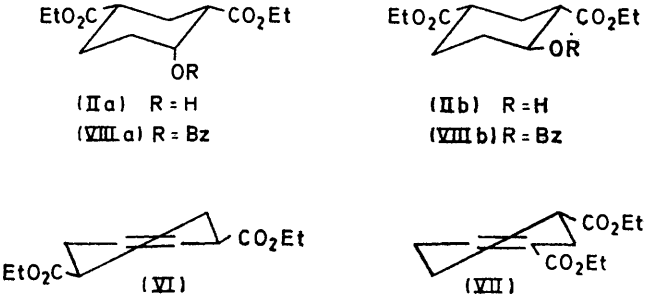
Reagents: i, Pr^{i}OH–Raney Ni; ii, $NaNO_2$–10% HOAc; iii, 3% HCl–EtOH

above mentioned reductive conditions, underwent decarboxylation to give ethyl 4-aminocyclohexane-1-carboxylate.

The amines (Ia—d) were separated (ratio 13 : 54 : 10 : 23) by silica gel chromatography, characterized as *N*-benzoyl derivatives (Va—d) (see Table 1), and identified from their n.m.r. spectra (see Supplementary Publication) on the basis of arguments similar to those given previously.[1] The *c*-6-amino-*c*-3-carboxylate (Ia), with an axial amino-group gave an unresolved multiplet (*W* 9.5 Hz) centred at τ 6.40 due to the equatorial C-6 proton. The axial C-6 proton resonances of the tri-equatorial *t*-6-amino-isomer (Ib) and of the isomer (Ic) which prefers the 1,6-diequatorial conformation, showed the expected similarities [τ 7.23 (*W* 26 Hz) and *ca.* 7.10 (25 Hz) respectively]. The unresolved C-6 proton multiplet of (Id) centred at τ *ca.* 6.95 (*W* 25 Hz) also indicated its axial orientation.



Treatment of the triequatorial stereoisomer (Ib) with nitrous acid afforded the diethyl *cis*- and *trans*-6-hydroxydicarboxylates (IIa and b) (see Table 2), the cyclohex-5-ene-*cis*-1,3-diester (VI), and diethyl cyclohex-3-ene-1,3-dicarboxylate (VII). In contrast, deamination of the axial cyclohexylamine (Ia) yielded larger amounts of cyclohexenes (VI) and (VII) than of cyclohexanols (IIa and b).



Deamination of the *c*-6-aminocarboxylate (Id) yielded the cyclohexanols (IIc and d) (see Table 2) and diethyl cyclohex-5-ene-*trans*-1,3-dicarboxylate (IX). The n.m.r. spectral data of the cyclohexanols (IIa—d) and

[1] V. Škarić, V. Turjak-Zebić, and D. Skarić, *J.C.S. Perkin I*, 1974, 1406.
[2] V. Škarić, L. Stuhne, D. Škaric, and V. Turjak-Zebić, *J. Chem. Soc.* (*C*), 1969, 2783, and references cited therein.
[3] E. Hardegger, P. A. Plattner, and F. Blanck, *Helv. Chim. Acta*, 1944, **27**, 793.
[4] T. Kutsuma and S. Sugasawa, *Tetrahedron*, 1958, **3**, 175.
[5] E. W. Bousquet, *Org. Synth.*, Coll. Vol. II, 1943, p. 913.
[6] A. R. Katritzky, S. Øksne, and A. J. Boulton, *Tetrahedron*, 1962, **18**, 777.

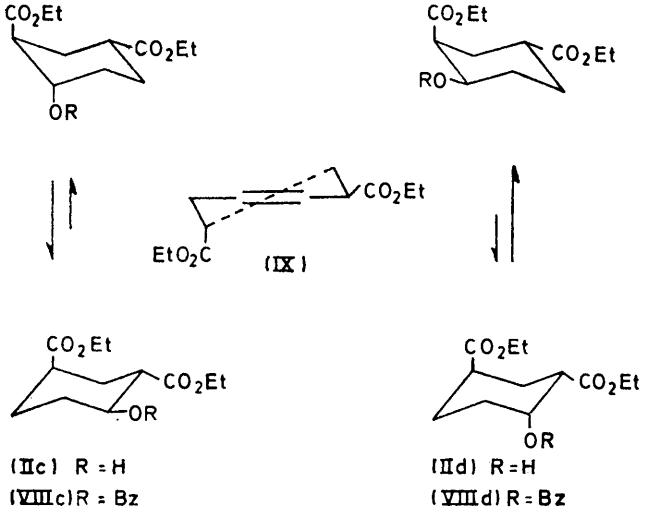
their *O*-benzoyl derivatives (VIIIa—d) (see Supplementary Publication) indicate conformational isomerism and equilibria analogous to those described for the 2-hydroxy-1,4-diesters.[1]

The chemical shifts of the C-5 and C-6 protons of the *cis*- and *trans*-cyclohexene diesters (VI) and (IX) [τ 4.34 (4.23) and 4.37 (4.29)] indicated the presence of the isolated double bond. The vinylic C-4 proton signal of the conjugated cyclohexene (VII) appeared at τ 2.88.

EXPERIMENTAL

General comments and reaction conditions for benzoylations and deaminations have been reported.[1] Analytical and spectroscopic data are available as Supplementary Publication No. SUP 21460 (5 pp.).*

Diethyl 6-Hydroxyiminocyclohexane-1,3-dicarboxylate (III).—To a solution of diethyl 6-oxocyclohexane-1,3-dicarboxylate (2.42 g, 10 mmol) in ethanol (7 ml), hydroxylamine



hydrochloride (1.0 g, 14.4 mmol) in water (2 ml) was added. The mixture was then treated with sodium carbonate (0.77 g, 7.2 mmol) in water (3 ml) for 15 min, stirred for an additional 30 min, and diluted with water. An ethereal extract was evaporated to dryness and the residue chromatographed on a silica gel (70 g) column. Methylene chloride eluted an oily component (1.25 g, 55%), R_F *ca.* 0.49 [t.l.c. in methylene chloride–methanol (30 : 2.5), detected by iodine reagent and u.v. illumination], which crystallized from n-hexane as *needles*, m.p. 64—65° (Found: C, 55.95; H, 7.4; N, 5.3. $C_{12}H_{19}NO_5$ requires C, 56.0; H, 7.45; N, 5.45%), M^+ 257, $\nu_{max.}$ 3 460, 2 970, 1 725, and 1 670 cm^{-1}, τ 8.76 (6 H, t, 2 × Me), 6.43—8.51 (8 H, m, ring protons), and 5.83 and 5.57 (4 H, q, 2 × O·CH_2).

Ethyl 3,3a,4,5,6,7-Hexahydro-3-oxo-2,1-benzisoxazole-5-carboxylate (IV).—The above described separation of (III) afforded a fraction (1.05 g, 45%), R_F *ca.* 0.32, which was also obtained in 60% yield when the oxime (III) was treated with 3% hydrochloric acid (pH *ca.* 4) for 4 h at 10—15 °C. An ethereal extract was worked up as for compound (III). Elution with methylene chloride yielded a crystalline product as *prisms*, m.p. 55—57° (from n-hexane) (Found: C, 57.0; H, 6.5; N, 6.65. $C_{10}H_{13}NO_4$ requires C, 56.85; H, 6.2; N, 6.65%), M^+ 211, $\lambda_{max.}$ 262 nm (log ε 3.75), $\nu_{max.}$ 3 490, 3 000, 1 810, 1 730b, and 1 630 cm^{-1}, τ 8.73 (3 H, t, Me), 6.50—8.51 (7 H, m, ring protons), 5.83 (2 H, q, O·CH_2), and 2.61 (1 H, s, OH).

Stereoisomeric Diethyl 6-Aminocyclohexane-1,3-dicarboxylates (Ia—d).—To a solution of the oxime (III) (1.0 g, 4.13 mmol) in propan-2-ol (50 ml), Raney nickel (*ca.* 2 g) was added and the mixture was refluxed with swirling for 90 min. The catalyst was filtered off and the filtrate evaporated to an oil (0.95 g), which was chromatographed on a silica gel (20 g) column. Methylene chloride eluted an oil (285 mg, 30%), R_F *ca.* 0.8 [t.l.c. in methylene chloride–methanol (9 : 1), detected by iodine vapour and ninhydrin spraying], identified as diethyl 6-oxocyclohexane-1,3-dicarboxylate, and a secondary cyclohexylamine (95 mg, 10%), R_F *ca.* 0.57, identified as diethyl 6-isopropylaminocyclohexane-1,3-dicarboxylate. Methylene chloride–methanol (100 : 5) then eluted the cyclohexylamines (Ia—d) (570 mg, 60%).

The rechromatography of the mixture of amines (Ia—d) (0.9 g) on a silica gel (45 g) column (110 × 2.5 cm) and elution with a linear gradient of 0.1—4.0% methanol in methylene choride during 160 h yielded (i) the *amino-dicarboxylate* (Ia), R_F *ca.* 0.38 [t.l.c. in methylene chloride–methanol (30 : 4), detected by ninhydrin spraying], (ii) the *isomer* (Ib) (R_F *ca.* 0.33), (iii) an unidentified product (30 mg), (iv) the *isomer* (Ic) (R_F *ca.* 0.19), and (v) the *isomer* (Id) (R_F ca. 0.15). For details see Table 1.

TABLE 1

Diethyl 6-aminocyclohexane-1,3-dicarboxylates and their *N*-benzoyl derivatives

Compd.	M.p. (°C) [B.p. (°C); mmHg]	Yield (%)	Compd.	M.p. (°C) [B.p. (°C); mmHg]	Yield (%)
(Ia)	[70—75; 0.05]	13 [a]	(Ic)	[65—75; 0.01]	10 [a]
(Va)	115—117 [b]	65	(Vc)	128—130 [b]	83
(Ib)	[75—80; 0.05]	53.5 [a]	(Id)	[75—80; 0.01]	23.5 [a]
(Vb)	140—143 [b]	90	(Vd)	138—140 [b]	85

[a] Based on total isolated stereoisomers. [b] From ether–hexane.

Deamination[1] of *Diethyl 6-Aminocyclohexane-1,3-dicarboxylates* (I) *with Nitrous Acid*.—From the products of deamination of the stereoisomer (Ia) (66 mg), methylene chloride eluted (silica gel column; 4 g) two cyclohexenes

TABLE 2

Diethyl 6-hydroxycyclohexane-1,3-dicarboxylates and their *O*-benzoyl derivatives

Compd.	M.p. (°C) [B.p. (°C); mmHg]	Yield (%)	Compd.	M.p. (°C) [B.p. (°C); mmHg]	Yield (%)
(IIa)	[85—85; 0.001]	10 [a]	(IIc)	[90—95; 0.005]	23 [b]
(VIIIa)	[124—127; 0.01]	50	(VIIIc)	[120—125; 0.005]	92
(IIb)	55—57 [c]	35 [a]	(IId)	[83—88; 0.001]	31 [b]
(VIIIb)	[120—125; 0.005]	80	(VIIId)	[120—125; 0.01]	81

[a] Based on the amino-diester (Ib). [b] Based on the amino-diester (Id). [c] From ether–hexane.

(32 mg, 50%) identified as diethyl cyclohex-5-ene-*cis*-1,3-dicarboxylate (VI) ($\nu_{max.}$ 2 990, 1 725, and 1 550 cm^{-1}) and diethyl cyclohex-3-ene-1,3-dicarboxylate (VII), $\nu_{max.}$

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1974, Index issue.

2 940, 1 725br, and 1 645 cm^{-1}. Methylene chloride–methanol (99 : 1) eluted two cyclohexanols (24 mg, 37.5%), identified as *diethyl* c-6-*hydroxyclohexane*-r-1,c-3-*dicarboxylate* (IIa) and *diethyl* t-6-*hydroxycyclohexane*-r-1,c-3-*dicarboxylate* (IIb). Deamination of the isomer (Ib) (455 mg) and separation on a silica gel column (25 g) yielded the cyclohex-5-ene diester (VI) (50 mg, 12.5%), the cyclohex-3-ene diester (VII) (16 mg, 4%), an unidentified product (134 mg), and the *cyclohexanols* (IIa) (40 mg, 10%) and (IIb) (140 mg, 35%)(see Table 2).

Deamination of the stereoisomer (Id) (70 mg) yielded an unstable oil identified as diethyl cyclohex-5-ene-*trans*-1,3-dicarboxylate (IX) (12 mg, 18%), $\nu_{max.}$ 2 930, 1 725br, and 1 540 cm^{-1}, an unidentified product (23 mg), and the *cyclohexanols* (IIc) (15 mg, 23%) and (IId) (20 mg, 31%) (see Table 2).

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