CROATICA CHEMICA ACTA CCACAA 48 (3) 341—349 (1976)

CCA-941

YU ISSN 0011-1643
547.595
Original Scientific Paper

Synthesis and Properties of the Stereoisomeric Diethyl 2-Aminocyclohexane-1,6-dicarboxylates

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Received December 8, 1975

The stereoisomeric diethyl 2-aminocyclohexane-1,6-dicarboxylates (Ia-d) have been synthesised from diethyl 2-hydroxyiminocyclohexane-1,6-dicarboxylate (III) and deaminated to corresponding 2-hydroxy derivatives (IIa-d) along with cyclohexenes. The amines I and the alcohols II were characterized as their *N*- and *O*-benzoyl derivatives, respectively. While the oxime III undergoes intramolecular cyclisation to give ethyl 3,3*a*,4,5,6,7-hexahydro-3-oxo--(2,1)-benzisoxazole-4-carboxylate (IV), spontaneous cyclisation of c-2-aminocyclohexane-*r*-1,*c*-6-dicarboxylate (Id) afforded ethyl 7--oxo-6-azabicyclo[3.2.1] octane-8-carboxylate (VI).

We have already reported the synthesis and properties of the stereoisomeric diethyl 2-aminocyclohexane-1,4-dicarboxylates[1] and diethyl 6-aminocyclohexane-1,3-dicarboxylates[2]*. This paper described the synthesis of the previously unreported stereisomeric diethyl 2-amino- (I) and 2-hydroxy- (II) cyclohexane-1,6-dicarboxylates. The hydrogenation of diethyl 2-hydroxyiminocyclohexane-1,6-dicarboxylate (III) in propan-2-ol and Raney nickel as catalyst[3] yielded all four stereoisomeric amines (Ia—d), separated (ratio 22:58:8:12) by silica gel chromatography, characterized as *N*-benzoyl derivatives (Va—d) (see Table I).

The oxime III was obtained from the corresponding cyclohexanone[4] in good yield by the usual method[5]. It should be noted that prolonged oximation proceeded to the benzisoxazole IV due to the intramolecular cyclisation of Z-eq-isomer of III.

The NMR spectra supported the conformational assignement of the isolated amines Ia—d and their benzamido derivatives Va—d (see Table II). Thus, the differences in chemical shifts and coupling constants for the C-2-proton multiplets of the *c*-2-amino-isomer Ia centred at τ 6.42 (W 9.0 Hz) and for the *t*-2-aminocarboxylates Ib and c centred at τ 7.13 (W 24 Hz) and 6.90 (W 25 Hz) are clearly discernible to characterize their conformational orientations. The equatorial configuration of the amino groups of Ib—d were also

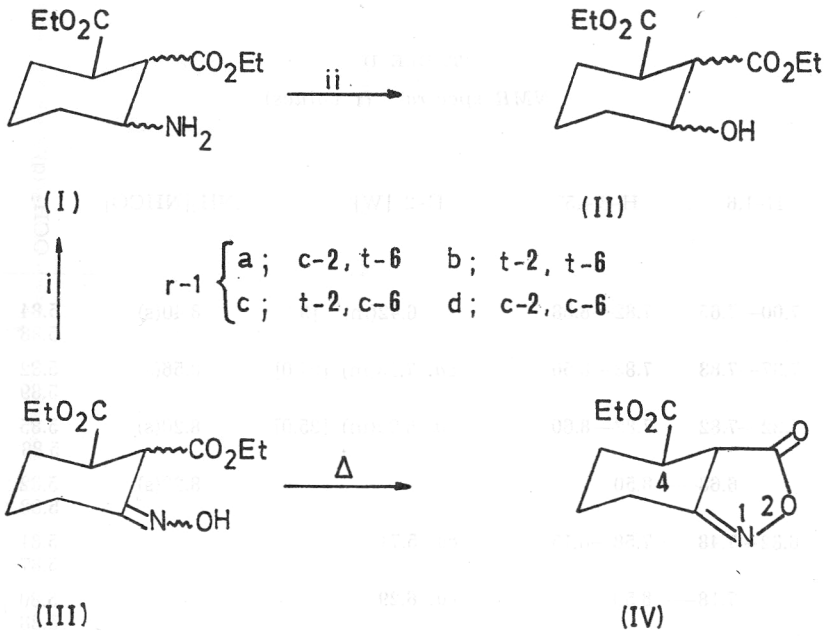
* The more correlative name for this isomer is diethyl 2-amino-1,5-dicarboxylate.

TABLE I

Stereoisomeric diethyl 2-aminocyclohexane-1,6-dicarboxylates and their N-benzoyl derivatives

Isomers	M. p./°C[a] [B. p./°C; mmHg]	Yield/%	Found/%			Formula	Required/%			$\lambda_{max.}$/nm (log ε)	$\nu_{max.}$/cm^{-1}
			C	H	N		C	H	N		
(Ia)	[70—75; 0.05]	22[b]	59.08	8.63	6.07	$C_{12}H_{21}NO_4$	59.25	8.70	5.75		3390, 2915, 1721[c]
N-Bz (Va)	119—121	68	65.94	7.55	4.06	$C_{19}H_{25}NO_5$	65.70	7.25	4.05	228 (4.07)	3378, 2976, 1733, 1639, 1580, 1536, 693
(Ib)	[75—80; 0.05]	58[b]	58.97	8.51	5.80	$C_{12}H_{21}NO_4$	59.25	8.70	5.75		3436, 2950, 1730
N-Bz (Vb)	165—167	91	65.70	7.51	4.11	$C_{19}H_{25}NO_5$	65.70	7.25	4.05	228 (4.10)	3333, 2874, 1730, 1634, 1582, 1550, 696
(Ic)	[75—77; 0.05]	8[b]	59.23	8.89	5.83	$C_{12}H_{21}NO_4$	59.25	8.70	5.75		3425, 2941, 1730
N-Bz (Vc)	130—135	85	65.45	7.13	4.18	$C_{19}H_{25}NO_5$	65.70	7.25	4.05	228 (4.06)	3401, 2959, 1742, 1642, 1587, 1538, 695
(Id)		12[b]									3367, 2924, 1718
N-Bz (Vd)	96—98	88	65.85	7.34	4.13	$C_{19}H_{25}NO_5$	65.70	7.25	4.05	228 (4.08)	3356, 2967, 1724, 1637, 1575, 1531, 694

[a] From ether — *n*-hexane. [b] Based on total amount of isolated stereoisomers. [c] Bands. splitting.



Reagents: *i*, Pr^{i}OH—Raney Ni; *ii*, $NaNO_2$—10% HOAc

confirmed by ease of the benzoylation and concomitant shifts of the C-2 protons resonances of *N*-benzoyl derivatives Vb—d to lower fields (τ 5.81—5.90).

The slow formation of ethyl 7-oxo-6-azabicyclo-[3.2.1]octane-8-carboxylate (VI) allow us to conclude the intramolecular elimination from the thermodynamically less stable 2,6-diaxial conformation of the c-2-amino-c-6-carboxylate Id.

From the conformationally controlled deamination of the triequatorial dietyl *trans*-2-aminodicarboxylate Ib with nitrous acid larger amounts of the *trans*-IIb than of *cis*-2-hydroxy diester IIa were isolated (see Table III) and only 6% of diethyl cyclohex-1-ene-1,6-dicarboxylate (VII). The same treatment of the *cis*-2-aminocarboxylate Id afforded the cyclohexanols IIc and d (see Table III) and diethyl cyclohex-2-ene-*cis*-1,6-dicarboxylate (VIII). The NMR spectra confirmed conformational isomerisation and equilibria of the cyclohexanols IIa—d and their *O*-benzoyl derivatives IXa—d (see Table II) on the basis of arguments similar to those given previously[1].

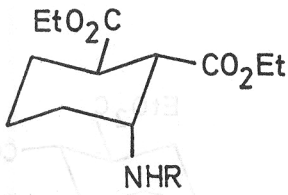
The chemical shifts of the vinylic C-2-proton of the conjugated cyclohexene VII appeared at τ 2.87 (t) while the resonances at τ 4.22 (s) and 4.30 (s) for C-2 and C-3 protons of cyclohexene VIII indicated the presence of the isolated double bond.

TABLE II

NMR spectra[a,b] *(τ values)*

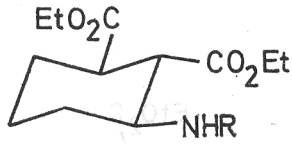
Compound	H-1,6[c]	H-3,4,5[c]	H-2 [W][d]	NH_2[NHCO]	OCH_2 (q)[e]	CH_3 (t)[e]
(Ia)	7.00—7.65	7.82—8.58	6.42(m)[f] [9.0]	8.40(s)	5.84 5.88	8.78
(Ib)	7.37—7.83	7.83—8.50	*ca.* 7.13(m) [24.0]	8.56(s)	5.82 5.89	8.74 8.78
(Ic)	7.32—7.82	7.82—8.60	*ca.* 6.90(m) [25.0]	8.20(s)	5.85 5.88	8.78
(Id)	6.68——8.50			8.20(s)	5.82 5.88	8.73 8.78
(IIa)	6.82—7.48	7.58—8.15	*ca.* 5.71		5.81 5.87	8.74
(IIb)	7.18——8.50		*ca.* 6.29		5.80 5.88	8.73 8.77
(IIc)	6.82—7.32	7.32—8.55	[obscured by OCH_2]		5.82 5.88	8.74 8.78
(IId)	6.82——8.51		6.51(m) [21.0]		5.80 5.89	8.77 8.79
(Va)	6.72—7.12	7.63—8.52	5.11—5.48(m) [20.0]	[3.41](d)	5.83 5.87	8.74 8.79
(Vb)	7.00—7.41	7.41—8.50	*ca.* 5.81(m)	[3.34](d)	5.88 5.91	8.79 8.89
(Vc)	7.00—7.41	7.41—8.50	*ca.* 5.81	[3.49](d)	5.88 5.91	8.77 8.87
(Vd)	6.82—7.50	7.50—8.50	*ca.* 5.90(m)	[obscured]	5.80 5.87	8.73 8.76
(IXa)	6.72—7.24	7.56—8.56	4.25(m) [9.5]		5.80 5.94	8.72 8.91
(IXb)	7.40——8.50		4.89(m) [22.0]		5.78 5.80	8.72
(IXc)	6.82——8.50		*ca.* 4.52—5.01(m) [28.0]		5.83 5.88	8.73 8.78
(IXd)	6.82——8.60		4.88(m)		5.88 5.96	8.79 8.93

[a] See introduction to experimental section (ref. 1). [b] Aromatic proton signals of (Va-d) and (IXa-d) are not recorded. [c] Unresolved multiplet. [d] Band width (W). [e] J_{Et} 7 Hz. [f] Unresolved multiplet (m). *ca.* refers to estimated positions when resonance is obscured by those of other protons.



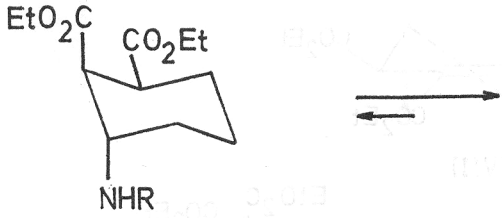
(Ia) R=H

(Va) R=Bz



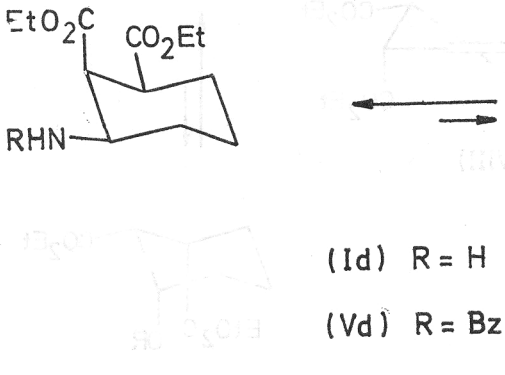
(Ib) R=H

(Vb) R=Bz



(Ic) R=H

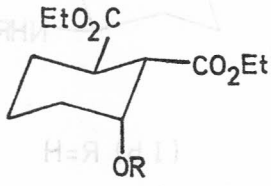
(Vc) R=Bz



(Id) R=H

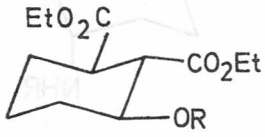
(Vd) R=Bz

(VI) R=H



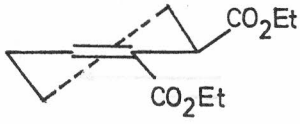
(II a) R=H

(IX a) R=Bz

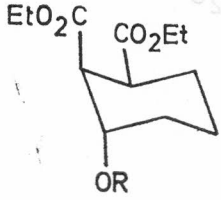


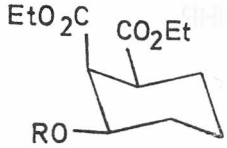
(II b) R=H

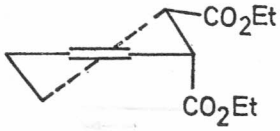
(IX b) R=Bz



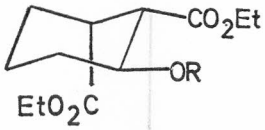
(VII)





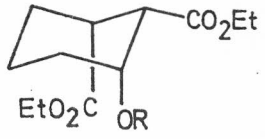


(VIII)



(II c) R=H

(IX c) R=Bz



(II d) R=H

(IX d) R=Bz

TABLE III

Stereoisomeric diethyl 2-hydroxycyclohexane-1,6-dicarboxylates and their O-benzoyl derivatives

Isomers	B.p./°C; mmHg [M.p./°C]	Yield/%	Found/%		Formula	Required/%		$\lambda_{max.}$/nm (log ε)	$\nu_{max.}$/cm^{-1}
			C	H		C	H		
(IIa)	80—85; 0.01	14[a]	59.29	8.15	$C_{12}H_{20}O_5$	59.00	8.25		3413, 2933, 1718
O-Bz (IXa)	130—134; 0.005	55	65.78	6.87	$C_{19}H_{24}O_6$	65.50	6.95	232 (4.07)	2941, 1724, 1597, 1445, 713
(IIb)	[58—60[b]]	42[a]	59.21	8.40	$C_{12}H_{20}O_5$	59.00	8.25		3356, 2959, 2882, 1748
O-Bz (IXb)	128—130; 0.005	95	65.22	6.96	$C_{19}H_{24}O_6$	65.50	6.95	232 (4.09)	2959, 1727, 1629, 1582, 714
(IIc)	78—80; 0.005	21[c]	58.77	8.22	$C_{12}H_{20}O_5$	59.00	8.25		3356, 2959, 2882, 1748
O-Bz (IXc)	125—130; 0.001	83	65.35	6.85	$C_{19}H_{24}O_6$	65.50	6.95	232 (4.06)	2985, 1730, 1605, 1587, 714
(IId)	80—82; 0.005	46[c]	58.85	8.16	$C_{12}H_{20}O_5$	59.00	8.25		3509, 2941, 1724
O-Bz (IXd)	135—138; 0.01	85	65.42	6.96	$C_{19}H_{24}O_6$	65.50	6.95	232 (4.07)	2959, 1724, 1600, 1580, 713

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

EXPERIMENTAL

General comments, reaction conditions for benzoylations, and deaminations have been reported[1].

Diethyl 2-Hydroxyiminocyclohexane-1,6-dicarboxylate (III)

To a solution of diethyl 2-oxocyclohexane-1,6-dicarboxylate[4] (1.21 g, 5 mmol) in ethanol (4 ml) hydroxylamine hydrochloride (560 mg, 8 mmol) in water (1 ml) was added. The mixture was treated portionwise with sodium carbonate (424 mg, 4 mmol) in water (1 ml) during a time interval of 30 minutes at 10—15 °C, stirred for an additional 5.5 hr, and diluted with water (5 ml). The ether extract was evaporated to an oily product (1.18 g) which was chromatographed in methylene chloride on a silica gel (24 g) column. Methylene chloride—methanol (100 : 0.5 and 100 : 1) eluted a fraction (0.9 g, 70%) which on standing in ice crystallized, $R_f \approx 0.65$ [TLC in methylene chloride — methanol (9 : 1], m. p. 88—90 °C (*n*-hexane).

Anal. $C_{12}H_{19}NO_5$ (257.28) calc'd.: C 56.00; H 7.45; N 5.75%
found: C 55.85; H 7.35; N 5.60%

Ir spectrum: ν_{max} 3215, 2882, 1724, 1650 cm^{-1}.

Ethyl 3,3a,4,5,6,7-Hexahydro-3-oxo-(2,1)-benzisoxazole-4-carboxylate (IV)

The above described oximation of cyclohexanone dicarboxylate (1.21 g, 5 mmol) with hydroxylamine hydrochloride (438 mg, 6.3 mmol) and sodium carbonate (332 mg, 3.13 mmol) at room temperature for 24 hr gave an oil which by chromatography on silica gel (22 g) column and elution with methylene chloride—methanol (100 : 0.5 to 100 : 2) yielded a crystalline product (0.63 g, 60%), $R_f \approx 0.24$ [TLC in methylene chloride—methanol (9 : 1)], m. p. 66—67 °C (ether-*n*-hexane).

Anal. $C_{10}H_{13}NO_4$ (211.2) calc'd.: C 56.86; H 6.20; N 6.63%
found: C 56.70; H 6.40; N 6.65%

Ir spectrum: ν_{max} 3378, 2907, 2809, 1715, 1689, 1656, and 1575 cm^{-1}. Uv spectrum: λ_{max} 260 nm (log ε 4.04).

Stereoisomeric Diethyl 2-Aminocyclohexane-1,6-dicarboxylates (Ia—d)

The solution of diethyl 2-hydroxyiminocyclohexane-1,6-dicarboxylate (III) (1.29 g, 5 mmol) in propan-2-ol (50 ml) was treated with Raney nickel (about 2 g) and the oily product (1.1 g) was chromatographed on a silica gel (25 g) column as already described[1,2]. Methylene chloride eluted unreacted starting material, methylene chloride—methanol (100 : 0.5) an oil (154 mg, 14%), $R_f \approx 0.43$ [TLC in methylene chloride—methanol (30 : 4)], identified as diethyl 2-*N*-*iso*propylaminocyclohexane-1,6-dicarboxylate; ir spectrum: ν_{max} 3520, 3380, 2990, 1740 cm^{-1}; NMR spectrum: τ 9.07 (3H, s, C · CH_3), 9.00 (3H, s, C · CH_3), 8.79 (3H, t, Me), 8.74 (3H, t, Me), 6.96—8.52 (9H, m,ring protons), 5.90 (2H, q, O · CH_2) 5.85 (2H, q, O · CH_2). Methylene chloride—methanol (100 : 6) eluted a mixture of stereoisomeric cyclohexylamines Ia-d (680 mg, 62%), $R_f \approx 0.39$, 0.34, 0.20 and 0.16.

The mixture of cyclohexylamines Ia-d was rechromatographed on a silica gel (40 g) column (110 × 2.5 cm) and fractionated by elution with methylene chloride—methanol (100 : 1—4) during a time interval of 125 hr. For details on isolated stereoisomers see Table I.

Deamination of Diethyl 2-Aminocyclohexane-1,6-dicarboxylates (I) with Nitrous Acid

Following earlier reported procedure[1] from the deaminated stereoisomer Ib (390 mg) methylene chloride eluted (silica gel column, 20 g) the oily diethyl cyclohex--1-ene-1,2-dicarboxylate (VII) (20 mg, 6%), $R_f \approx 0.52$ (TLC in methylene chloride); ir spectrum: ν_{max} 2976, 1736, 1645 cm^{-1}; NMR spectrum: τ 8.79 (3H, t, Me), 8.76 (3H, t, Me), 6.39—8.50 (7H, m, ring protons), 5.87 (2H, q, O · CH_2), 5.81 (2H, q, O · CH_2), 2.87 (1H, t, 2-H). Methylene chloride—methanol (100 : 0.1) then eluted diethyl *c*-2-hydroxycyclohexane-*r*-1,*t*-6-dicarboxylate (IIa) (54 mg, 14%) and methylene chloride—

methanol (100 : 1) diethyl *t*-2-hydroxycyclohexane-*r*-1,*t*-6-dicarboxylate (IIb) (151 mg, 42%) (see Table III).

From the deaminated stereoisomer Id (140 mg) methylene chloride eluted (silica gel column, 7 g) the oily diethyl cyclohex-2-ene-*cis*-1,6-dicarboxylate (VIII) (15 mg, 14%); ir spectrum: ν_{max} 2976, 1724, 1629, 1550 cm^{-1}; NMR spectrum: τ 8.77 (3H, t, Me), 8.72 (3H, t, Me), 7.68—8.52 (4H, m, 4-, 5-H), 6.60—7.32 (2H, m, 1-, 6-H), 5.89 (2H, q, O · CH_2), 5.83 (2H, q, O · CH_2), 4.30 (1H, s, 3-H), 4.22 (1H, s, 2-H). Methylene chloride—methanol (100 : 0.1) separated diethyl *t*-2-hydroxycyclohexane-*r*-1,*c*-6-dicarboxylate (IIc) (23 mg, 21%) and methylene chloride—methanol (100 : 0.5) diethyl *c*-2-hydroxycyclohexane-*r*-1,*c*-6-dicarboxylate (IId) (51 mg, 46%) (see Table III).

Ethyl 7-Oxo-6-azabicyclo[3.2.1]octane-8-carboxylate (VI)

Diethyl *c*-2-aminocyclohexane-*r*-1,*c*-6-dicarboxylate (Id) (60 mg, 0.25 mmol) partly cyclized at room temperature for 48 hr and separated on silica gel (3 g) column by elution with methylene chloride—methanol (100 : 1—3) in 30% yield (15 mg), $R_f \approx 0.2$ [TLC in methylene chloride—methanol (30 : 4), detected by iodine vapour].

The same cyclic compound was obtained when Id (40 mg, 0.165 mmol) was heated at 240 °C for 7 minutes under nitrogen atmosphere. Preparative TLC (silica gel) [developed in methylene chloride—methanol (100 : 3)] and elution with methylene chloride gave a crystalline product (23 mg, 74%), m. p. 115—117 °C (from ether — *n*-hexane).

Anal. $C_{10}H_{15}NO_3$ (197.2) calc'd.: C 60.89; H 7.67; N 7.10%
found: C 60.85; H 7.90; N 6.80%

Ir spectrum: ν_{max} 3367, 2976, 1739, 1675 cm^{-1}. NMR spectrum: τ 8.76 (3H, t, Me), 7.75—8.50 (6H, m, 2—3—4-H), 7.42 (1H, s, 8-H), 7.19 (1H, m, 1-H), ca. 5.89 (1H, m, 5-H), 5.82 (2H, q, O · CH_2), and 4.08 br (1H, s, NH).

Acknowledgement. We are grateful to Mrs. A. Poturić for experimental assistance and Mrs. M. Tonković for microanalyses.

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SAŽETAK

Sinteza i svojstva stereoizomernih dietil 2-aminocikloheksan-1,6-dikarboksilata

V. Škarić, B. Djuras i V. Turjak-Zebić

Stereoizomerni dietil 2-aminocikloheksan-1,6-dikarboksilati (Ia—d) sintetizirani su iz dietil 2-oksiminocikloheksan-1,6-dikarboksilata (III) da bi deaminiranjem dali odgovarajuće hidroksi derivate (IIa—d) i cikloheksene. Amini I i alkoholi II karakterizirani su kao *N*- odnosno *O*-benzoil derivati. Dok oksim III intramolekularnom ciklizacijom prelazi u 3,3*a*,4,5,6,7-heksahidro-3-okso-(2,1)-benzizoksazol-4-karboksilat (IV), spontana ciklizacija dietil *c*-6-aminocikloheksan-*r*-1,*c*-2-dikarboksilata (Id) daje etil 7-okso-6-azabiciklo[3.2.1]-oktan-8-karboksilat (VI).

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Prispjelo 8 prosinca 1975.