CROATICA CHEMICA ACTA CCACAA 47 (2) 145—152 (1975)

CCA-865

YU ISSN 0011-1643
547.595
Original Scientific Paper

Synthesis and Properties of the Stereoisomeric Triethyl 2-Aminocyclohexane-1,5,5-tricarboxylates

V. Škarić, B. Djuras, and Đ. Škarić

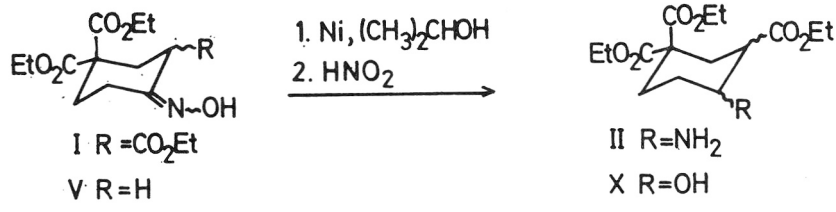
Laboratory of Stereochemistry and Natural Products, Institute »Ruđer Bošković«, 41000 Zagreb, Croatia, Yugoslavia

Received February 17, 1975

Hydrogenation of triethyl 2-oxyiminocyclohexane-1,5,5-tricarboxylate (I) over Raney nickel in isopropanol afforded the two stereoisomeric triethyl 2-aminocyclohexane-1,5,5-tricarboxylates (II). The conformationally controlled deamination of *cis*-(IIa) and *trans*-(IIb) isomer yielded the corresponding cyclohexanes (VIII) and (IX) and 2-hydroxy-1,5,5-tricarboxylates (X).

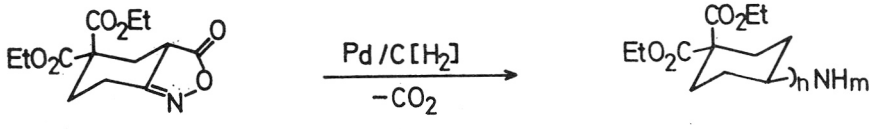
The preparation of oxyiminotricarboxylate I in acidic media yielded diethyl 4,5,6,7-tetrahydro-3-oxo(2,1)benzisoxazole-5,5-dicarboxylate (III).

We have already reported the stereochemical characteristics of the reductive cleavage of diethyl 4,5,6,7-tetrahydro-3-oxoindazole-5,5-dicarboxylate in isopropanol using Raney nickel as catalyst[1,2]. Hydrogenation of triethyl 2-oxyiminocyclohexane-1,5,5-tri-carboxylate (I) proceeds selectively to triethyl 2--aminocyclohexane-1,5,5-tricarboxylates (II), with predominant formation of the *cis* isomer.



I R = CO_2Et
V R = H

II R = NH_2
X R = OH



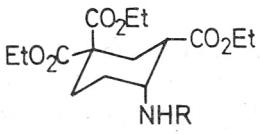
III

IV n=1, m=2
VI n=2, m=1

The oxime I was prepared from the corresponding triethyl cyclohexanone tricarboxylate[3]. Prolonged oximation with an excess of hydroxylamine hydrochloride in acidic medium afforded diethyl 4,5,6,7-tetrahydro-3-oxo(2,1)benzisoxazole-5,5-dicarboxylate (III) in 95% yield. Hydrogenation of isoxazolone III over 10% palladium on carbon yielded diethyl 4-aminocyclohexane-1,1-dicarboxylate (IV) which was also obtained from diethyl 4-oxyiminocyclohexane-1,1--dicarboxylate[4] (V).

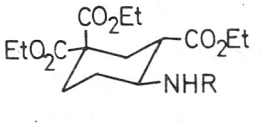
It should also be noted that hydrogenation of oxime V over palladium in ethanol gave the amine IV (53%) and bis(diethyl cyclohex-4-yl-1,1-dicarboxylate)-amine (VI) (47%). When glacial acetic acid was used as a solvent, the primary amine IV was predominantly obtained as the hydroacetate (90%). In contrast, due to competing reactions, hydrogenation of 2-oxyiminocyclohexane tricarboxylate, I, in glacial acetic acid yielded only 10% of aminotricarboxylate II as the hydroacetate. The stereoisomeric *cis*- and *trans*-2-aminocyclohexane tricarboxylates, II (ratio 83 : 17) were isolated in highest yield (75%) when oxime I was hydrogenated over Raney nickel in isopropanol. The addition of conc. ammonia in ethanol decreased the amount of amines to 39.4%.

The n. m. r. spectrum of II (see Table II) indicated that the major product was triethyl *c*-2-aminocyclohexane-*r*-1,*c*-5, t-5-tricarboxylate (IIa). Thus, the cis-2-aminotricarboxylate (IIa) with an axial amino group showed an unresolved multiplet (width 9.5 Hz) centred at $\tau = 6.49$ due to the equatorial C-2 proton. The axial benzamido group of VIIa caused a wider downfield multiplet



IIa R=H

VIIa R=Bz



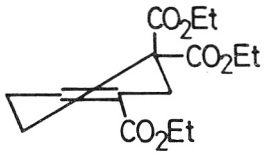
IIb R=H

VIIb R=Bz

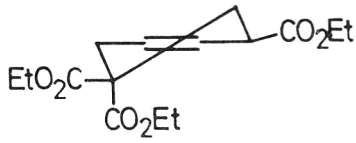
due to the α-proton centred at $\tau \approx 5.51$ (width 19 Hz). The trans-2-amino isomer (IIb), obtained in lower yield, showed the expected octet centred at $\tau = 7.28$ for the axial C-2 proton. The ease of its benzoylation to the *N*-benzoyl derivative VIIb and concomitant downfield shift of the 2-proton signal (at $\tau \approx 5.80$) supports the stereochemical assignment of the equatorial 2-benzamido group.

The predominant formation of *cis*-2-aminotricarboxylate IIa shows that the hydrogenation proceeded selectively. The specific adsorption of the 1,5,5--trisubstituted cyclohexanone oxime on the surface of Raney nickel catalyst with its d-bond vacancy and affinity for the π electrons of C=N linkage, may be the product determining step. Thus, the distribution of the stereoisomeric amines most probably depends on the structure of the substrate. Namely, the hydrogenation of disubstituted 2-oxyminocyclohexanes[6] over Raney nickel proceeds preferably to *trans*-2-aminodicarboxylate.

The conformationally controlled deamination of the axial amine IIa by nitrous acid yielded cyclohexenes VIII and IX, and cyclohexanols X. The triethyl cyclohex-1-ene-1,5-tricarboxylate (VIII) as the main product showed a triplet centred at $\tau = 3.26$ due to the C-2 proton. The cyclohex-2-ene with the



VIII



IX

isolated double bond caused a broad signal at $\tau = 4.64 - 5.08$ due to the C-2 and C-3 protons.

The equatorial amine IIb, however, yielded two cyclohexenes VIII and IX (ratio 1 : 3) in lower yield (32.8%) than cyclohexanols X (53%). The ratio of VIII and IX was determined from the signal intensities of C-2 and C-2,3 protons in the n. m. r. spectrum.

EXPERIMENTAL

General comments and reaction conditions for the benzoylation and deaminations have been reported[5]. The R_f values are for methylene chloride — methanol (9 : 1) (unless otherwise stated). Spots were located by exposure of t. l. c. plates to iodine vapour or by u. v. illumination.

Triethyl 2-oxyiminocyclohexane-1,5,5-tricarboxylate (I) (Table I)

A solution of triethyl 2-oxocyclohexane-1,5,5-tricarboxylate[3] (1.89 g, 6 mmol) in ethanol (4 ml) was treated with hydroxylamine hydrochloride (522 mg, 7.6 mmol) in water (1.5 ml), and then portionwise with sodium carbonate (428 mg, 6.2 mmol) in water (1.5 ml) during a time interval of 15 minutes. To this mixture, which was stirred for additional 45 minutes, water (8 ml) and ether was added. The organic layer yielded an oil (1.7 g) which crystallized on standing. Chromatography on a silica gel (30 g) column and elution with methylene chloride — methanol (99 : 1 to 97 : 3) yielded the crystalline oxime (1.37 g, 81%, $R_f \approx 0.6$) and a fraction (320 mg, 19%) which was identified as benzisoxazole-5,5-dicarboxylate III.

Diethyl 4,5,6,7-tetrahydro-3-oxo(2,1)benzisoxazole-5,5-dicarboxylate (III)

To a solution of cyclohexanone tricarboxylate[3] (815 mg, 2.6 mmol) in ethanol (4 ml) hydroxylamine hydrochloride (314 mg, 4.53 mmol) in water (1.5 ml) and sodium carbonate (244 mg, 2.3 mmol) in water (2.5 ml) were added. The mixture was stirred for 8 h at 40 °C, acidified with 12 M HCl (0.32 ml), and then stirred for additional 2 hrs at 40 °C. Extraction with ether and purification on a silica gel column yielded a crystalline product (698 mg, 95%), $R_f \approx 0.38$, m. p. 81—82 °C (from ether-hexane).

Anal. $C_{13}H_{17}NO_6$ (283.3) calc'd.: C 55.12; H 6.06; N 4.95%
found: C 54.94; H 5.85; N 5.15%

I. r. spectrum: ν_{max} 3420, 3090, 2985, 2830, 1740, 1705, and 1660 cm^{-1}. U. v. spectrum: λ_{max} 262 nm ($\log \varepsilon = 3.97$). Mass spectrum: calc'd.: 283.3; found: 283.0.

Diethyl 4-oxyiminocyclohexane-1,1-dicarboxylate (V) (Table I)

Diethyl 4-oxocyclohexane-1,1-dicarboxylate[3] (242 mg. 1 mmol) was oximated as already described (4 h). From the ether extract a crystalline product separated (244 mg, 95%), $R_f \approx 0.54$.

TABLE I

2-Oxyimino-, amino-, hydroxy- and benzamido carboxylates

Compound	M. p./°C [B. p./°C; mmHg]	% Yield	Calc'd. % / Found % C	H	N	Found *M*	Formula	Mol. wt.	ν_{max}/cm^{-1}
(I)	80—81[a]	84	54.70 54.84	7.04 7.03	4.25 4.39		$C_{15}H_{23}NO_7$	329.3	3460, 2990, 1725, 1650
(IIa)	[120; 0.05]	83[b]	57.13 56.74	7.99 8.07	4.44 4.42	315	$C_{15}H_{25}NO_6$	315.4	3460, 3000, 1725 (broad), 1590
(IIb)	[120—-122; 0.05]	17[b]	57.13 57.00	7.99 8.24	4.44 4.30	315	$C_{15}H_{25}NO_6$	315.4	3430, 2980, 1725, 1585
N-Bz (VIIa)[c]	[140; 0.05]	72	62.99 63.04	6.97 6.83	3.34 3.53	419	$C_{22}H_{29}NO_7$	419.5	3350, 2980, 1725, 1670 (sh), 1640, 1610(sh), 1580, 695
N-Bz (VIIb)[c]	95—97	90	62.99 63.30	6.97 6.94	3.34 3.46	419	$C_{22}H_{29}NO_7$	419.5	3300, 2980, 1715(sh), 1630 1580(sh), 1550, 701
(V)	61—63[d] (Lit.[4] 62—63)	95	56.02 55.98	7.44 7.77	5.44 5.58	257	$C_{12}H_{19}NO_4$	257.3	3220, 2920, 1749, 1725, 1660
(IV)	[80; 0.01]	53	57.12 56.99	8.79 8.97	5.59 5.64	252[e]	$C_{12}H_{21} \cdot 1/2\ H_2O$	252.3[d]	3310, 2900, 1725, 1580
(IV) · HCl	190—194[d] (Lit.[4] 187—188)	79	51.51 51.67	7.93 8.02	5.00 4.81		$C_{12}H_{22}ClNO_4$[f]	279.8	3390, 2900, 1725
(IV) · HBr	180—182[d]	37	44.45 44.53	6.83 6.53	4.32 4.24		$C_{12}H_{22}BrNO_4$	324.2	3490, 2970 (broad), 1725, 1600

[a] From *n*-hexane. [b] Based on total amount of isolated stereoisomers. [c] λ_{max} = 224 nm (log ε = 3.33). [d] $CHCl_3$-ether-*n*-hexane. [e] Equiv. wt. [f] Found: Cl 12.44; calc'd.: Cl 12.67%.

Hydrogenation of 4-oxyiminocyclohexane-1,1-dicarboxylate (V)

(a) A solution of 4-oxyiminodicarboxylate[4] V (514 mg, 2 mmol) in anhydrous ethanol (5 ml), containing 10% palladium on carbon (514 mg) was hydrogenated under ambient conditions until 2 mol of hydrogen had been adsorbed (ca. 7 h). The solution was filtered, evaporated to dryness and chromatographed on a silica gel (10 g) column. Methylene chloride — methanol (100 : 1 to 100 : 6) eluted diethyl 4-aminocyclohexane dicarboxylate (IV) (265 mg, 53%), $R_f \approx 0.4$ (see Table I) and a fraction identified as bis(diethylcyclohex-4-yl-1,1-dicarboxylate)amine (VI) (220 mg, 47%), $R_f \approx 0.6$, m. p. 48—50 °C (from *n*-hexane).

Anal. $C_{24}H_{35}NO_8$ (469.5) calc'd.: C 61.39; H 8.37; N 2.98%
found: C 61.33; H 8.72; N 2.61%

I. r. spectrum: ν_{max} 3390, 2890, and 1735 cm^{-1}.

4-Aminodicarboxylate IV (622 mg, 2.6 mmol) refluxed for 1 hr in 6 M HCl (66 ml), yielded the hydrochloride, m. p. 254—258 °C (dec.) (from water-ethanol-ether) which, passed through a column of ion exchange resin [IR-4B(OH)] (50 ml), afforded 4-aminocyclohexane-1,1-dicarboxylic acid (380 mg, 90%), m. p. 230—235 °C (from water--ethanol-ether).

Anal. $C_8H_{13}NO_4 \cdot 1/2\ H_2O$ (196.2) calc'd.: C 48.97; H 7.19%
found: C 49.20; H 6.87%

I. r. spectrum: ν_{max} 3450, 2960 (broad), 1680 (broad), and 1610 cm^{-1}.

(b) A solution of 4-oxyiminocyclohexane[4] V (1.4 g, 5.45 mmol) in glacial acetic acid (30 ml) was hydrogenated over 10% palladium on carbon (2.8 g) for 5 h and then evaporated to yield an oil. Separation on a silica gel column yielded the hydroacetate of amine IV (1.37 g, 90%), $R_f \approx 0.39$, m. p. 130—135 °C (from chloroform-ether-

Anal. $C_{14}H_{25}NO_6$ (303.35) calc'd.: C 55.43; H 8.31; N 4.62%
found: C 55.19; H 8.35; N 4.67%

I. r. spectrum: ν_{max} 3400, 2900 (broad), 1745, 1725, and 1660 cm^{-1}.

The second eluted fraction yielded the hydroacetate of the secondary amine VI (142 mg, 10%), R_f 0.56, m. p. 110—115 °C (from ether-hexane).

Anal. $C_{26}H_{43}NO_{10}$ (529.6) calc'd.: C 58.96; H 8.18; N 2.62%
found: C 58.48; H 8.35; N 2.41%

I. r. spectrum: ν_{max} 3350, 2895, 1725 (sh), 1715, and 1620 cm^{-1}.

(c) Tetrahydrobenzisoxazole, III, in glacial acetic acid was hydrogenated as described in (b) and then chromatographed. The hydroacetate of IV (66%) and VI (13.5%) were isolated.

Stereoisomeric triethyl 2-aminocyclohexane-1,5,5,-tricarboxylate (II)

(a) A solution of triethyl 2-oxyiminocyclohexane-1,5,5-tricarboxylate (I) (990 mg, 3 mmol) in isopropanol (30 ml) was treated with Raney nickel (about 1.5 g), stirred, refluxed for 2 h and then filtered. The filtrate yielded an oil (910 mg) which was chromatographed on a silica gel (20 g) column. Methylene chloride eluted an unidentified product (129 mg) and methylene chloride — methanol (100 : 0.5) an oily triethyl 2-isopropylaminocyclohexane-1,5,5-tricarboxylate derivative (98 mg), $R_f \approx 0.33$ (intensive violet spot by ninhydrine spraying). m. p. 48—50 °C (from n-hexane).

Anal. $C_{18}H_{33}NO_6$ (359.45) calc'd.: N 3.90%
found: N 3.58%

TABLE II

N. m. r. spectra[a,b] *(τ values)*

Compound	H-1,3,4,6[c]	H-2 [W][d]	NH_2[NHCO]	OCH_2 (q)[e]	CH_3 (t)[e]
IIa	7.06—8.50	6.49(m) [9.5]	8.35(s)	5.79	8.76
IIb	7.48—8.50	7.28(o) [3.0]	8.42(s)	5.74	8.74
		$J_{2ax,1ax}$ / $J_{2ax,3ax}$ 16.0 + 10.5		5.83	8.78
		($J_{2ax,3eq} = 3.5$)			
VIIa	6.90—8.58	5.51(m)[f] [19.0]	*ca.* [3.32(d)]	5.88	8.76
				5.93	8.78
				5.99	8.80
VIIb	7.22—8.56	5.80(m)[f]	[3.64(d)]	5.77	8.76
				5.81	8.78
				5.88	

[a] introduction to Experimental section. [b] Aromatic proton signals of VIIa and VIIb are not recorded. [c] Unresolved multiplet. [d] Band width (W) and coupling constants in Hz. [e] $J_{Et} = 7$ Hz. [f] Estimated positions when resonance is obscured by those of other protons.

I. r. spectrum: ν_{max} 3480, 3370, 2990, and 1725 cm^{-1}.

Methylene chloride-methanol (100 : 5) then eluted the stereoisomeric cyclohexylamine II (683 mg, 75%).

The repeated chromatography of the cyclohexylamine II (230 mg) on a silica gel (12 g) column (50 × 0.5 cm) and elution with methylene chloride — methanol (100 : 0.1—1) afforded triethyl c-2-aminocyclohexane-r-1,5,5-tricarboxylate (IIa) (190 mg, 83%) and the t-2-amino isomer (IIb) (40 mg, 17%). For analytical and spectroscopic data for the isolated isomers and their benzamido derivatives VIIa and VIIb see Tables I and II.

(b) The solution of oxime I (347 mg, 1.05 mmol) in ethanol (10 ml) and conc. NH_4OH (0.36 ml) was treated with Raney nickel (about 0.5 g) and stirred under H_2 atmosphere at room temperature. The solution was filtered, evaporated to dryness and worked up as described in (a). Yield 130 mg (39.4%).

(c) The solution of 2-oxyiminotricarboxylate I (329 mg, 1 mmol) in glacial acetic acid (5 ml) was hydrogenated over palladium on carbon (660 mg) for 6 h and worked up as described under IV (b). The hydroacetate of II was isolated in 10% yield eluted with methylene chloride — methanol (100 : 6), m. p. 125—130 °C (from chloroform--ether-hexane).

Anal. $C_{17}H_{29}NO_8$ (375.4) calc'd.: C 54.39; H 7.79; N 3.73%
found: C 53,98; H 8.19; N 4.16%

I. r. spectrum: ν_{max} 3350, 2900 (broad), 1725, 1710 (sh), and 1640 cm^{-1}.

Deamination of triethyl 2-aminocyclohexane-1,5,5-tricarboxylate (II) with nitrous acid

From the deaminated cis-amine isomer IIa (286 mg) two cyclohexenes (150 mg, 60%), $R_f \approx 0.42$ (detected by iodine reagent) were eluted with methylene chloride on a silica gel (8 g) column. From this mixture triethyl cyclohex-1-ene-1,5,5-tricarboxylate (VIII) (62%), b. p. 75 °C at 0.01 mmHg was isolated by preparative t. l. c.

Anal. $C_{15}H_{22}O_6$ (298.3) calc'd.: C 60.39; H 7.43%
found: C 60.39; H 7.69%

I. r. spectrum: ν_{max} 3505, 2990, 1725 (broad), and 1660 cm^{-1}. U. v. spectrum: λ_{max} 223 nm ($\log \varepsilon = 3.97$). Mass spectrum: calc'd.: 298.3; found: 298.

Further elution with methylene chloride — methanol (9 : 1) yielded triethyl 2--hydroxycyclohexane-1,5,5-tricarboxylates (X) (89 mg, 35.5%), $R_f \approx 0.12$ and 0.17 (developed five times in methylene chloride), b. p. 110 °C at 0.005 mmHg.

Anal. $C_{15}H_{24}O_7$ (316.3) calc'd.: C 56.95; H 7.65%
found: C 56.71; H 7.59%

I. r. spectrum: ν_{max} 3550, 2980, and 1725 cm^{-1}. Mass spectrum: calc'd.: 316.3; found: 316.

The deamination of the trans-amine isomer IIb (60 mg) yielded two cyclohexenes VIII and IX (18 mg, 32.8%), and cyclohexanols X (53%), the isomer with $R_f = 0.12$ of which was predominant.

Acknowledgement. We thank Mrs. A. Poturić for experimental assistance and Mrs. M. Tonković and Mrs. Lj. Babić for microanalyses.

REFERENCES

1. Đ. Škarić, V. Škarić, and V. Turjak-Zebić, *Croat. Chem. Acta* **35** (1963) 263.
2. V. Škarić, L. Stuhne, Đ. Škarić, and V. Turjak-Zebić, *J. Chem. Soc.* C (1969) 2783.
3. L. Hardegger, P. A. Plattner, and F. Blanck, *Helv. Chim. Acta* **27** (1944) 793.

4. M. Fetizon and S. Nanthavong, *Bull. Soc. Chim. Fr.* (1969) 194.
5. V. Škarić, V. Turjak-Zebić, and Đ. Škarić, *J. C. S. Perkin Trans.* (1974) 1406.
6. V. Škarić, B. Djuras, and V. Turjak-Zebić, in preparation.

SAŽETAK

Svojstva i sinteza stereoisomernih trietil-2-aminocikloheksan-1,5,5-trikarboksilata

V. Škarić, B. Djuras i Đ. Škarić

Hidriranje trietil 2-oksiminocikloheksan-1,5,5-trikarboksilata (I) refluksiranjem u izopropanolu i uz Raney-nikal kao katalizator daje dva stereoizomerna trietil 2-aminocikloheksan-1,5,5-trikarboksilata (II). Konformacijski kontrolirane deaminacije *cis*-(IIa) i *trans*-(IIb) izomera daju odgovarajuće cikloheksene (VIII) i (IX), te hidroksi-1,5,5-trikarboksilate (X).

Priprava 2-oksiminotrikarboksilata (I) u kiselom mediju daje dietil-4,5,6,7-tetrahidro-3-okso(2,1)benzizoksazol-5,5-dikarboksilat (III).

LABORATORIJ ZA STEREOKEMIJU I PRIRODNE SPOJEVE
INSTITUT »RUĐER BOŠKOVIĆ«
41001 ZAGREB

Prispjelo 17. veljače 1975