CROATICA CHEMICA ACTA CCACAA **55** (4) 457—465 (1982)

YU ISSN 0011—1643
CCA-1349 UDC 547.466
Original Scientific Paper

Geometrical Isomers in the 2-Amino-(2-Hydroxy-)cyclohexane--1,3-, -1,4-, -1,5-, and -1,6-dicarboxylic Acids Series

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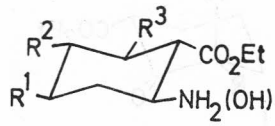
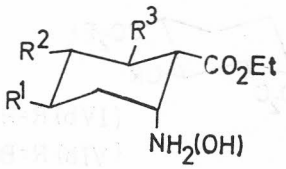
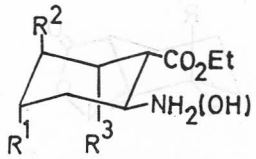
Received May 10, 1982

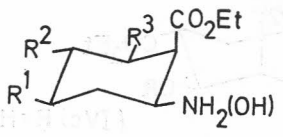
The synthesis of previously inaccessible cis-cis-(a) trans--cis-(b), and trans-trans-(c) stereoisomers in the diethyl 2-hydroxy-(IV) and 2-amino-(VII)-cyclohexane-1,3-dicarboxylates series is described. The geometries of these isomers and their O- (VI) and N- (X) benzoyl derivatives are established by NMR spectroscopy in relation to deshielding effects on the geminal C-2 protons.

In previous publications[1–3] we described the syntheses, separations, and properties of the stereoisomeric diethyl 2-amino-(2-hydroxy-)cyclohexane-1,4- (I), -1,5- (II), and -1,6- (III) dicarboxylates, each of them revealing four different geometrical forms. As part of our continuing interest in the conformational characteristics of aminocyclohexane dicarboxylic acids and their intramolecular cyclisations[4] into physiologically attractive azabicycloalkanones, the









(I) $R^1 = CO_2Et$

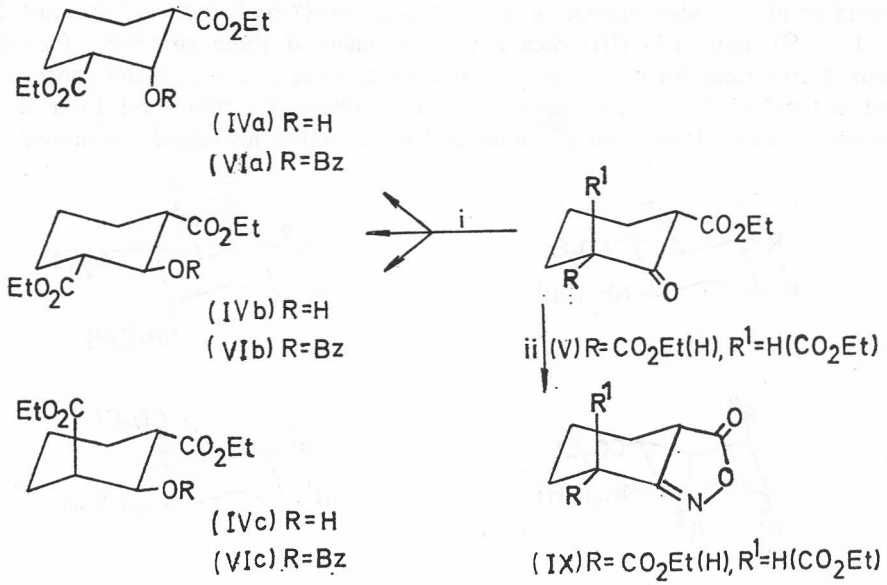
(II) $R^2 = CO_2Et$

(III) $R^3 = CO_2Et$

R^1, R^2, R^3 = H unless CO_2Et denoted

synthesis of all possible positional isomers in this series seemed necessary. Moreover, these stereoisomers could lead to geometrically controlled preparation of the unusual, hitherto unknown, aminocyclohexane carboxylic acid peptides[4,5] and to the evaluation of their structure-activity relationship.

In order to complete the title series, the present paper deals with the synthesis and properties of the stereoisomeric diethyl 2-hydroxycyclohexane--1,3-dicarboxylates (IV). It has already been shown that reduction of the homologous dimethyl 2-oxocyclohexane-1,3-dicarboxylate with sodium borohydride[6] gave rise to two of the three possible isomers. Only one isomer was obtained when the hydrogenation was carried out over Adam's (PtO_2) catalyst.[6,7] It is worth noting that in the middle 30th the diethyl 2-hydroxycyclohexane diester (IV) was described as a stereochemically undefined product.[8] Our approach to the synthesis of all possible geometrical isomers was accomplished by the hydrogenation of a mixture of the two stereoisomeric diethyl 2-oxocyclohexane-1,3-dicarboxylates (V)[9] over PtO_2 in anhydrous ethanol, followed by careful silica gel — celite chromatography. The thus separated products, in a ratio of *ca.* 10 : 1 : 10, were identified as diethyl c-2-hydroxycyclohexane-r-1,c-3-dicarboxylate (IVa), diethyl t-2-hydroxycyclohexane-r-1,c-3-dicarboxylate (IVb), and diethyl t-2-hydroxycyclohexane-r-1,t-3-dicarboxylate (IVc), respectively.

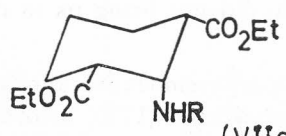


Reagents: i, EtOH—PtO_2; ii, EtOH—$HONH_2 \cdot HCl$—Na_2CO_3

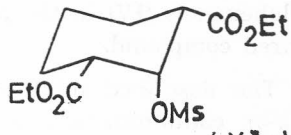
The NMR spectra of cyclohexanols (IVa-c) and the corresponding 2-benzoxy derivatives (VIa-c) clearly indicated their geometries in relation to deshielding effects on the geminal C-2 protons. Thus, the cis-cis isomer (IVa)

with the axial hydroxyl group gave a double-triplet centred at τ 5.37 (W 7.3 Hz) due to the equatorial C-2 proton. The corresponding 2-benzoxy compound (VIa) showed the equatorial C-2 proton as the downfield triplet centred at τ 3.89 (W 4.0 Hz). The axial C-2 proton resonances of the trans-cis isomer (IVb) and trans-trans isomer (IVc) were obscured by those of OCH_2 in the regions centred at τ ca. 6.0 and 5.85, respectively. Their benzoylated products (VIb) and (VIc) showed parallel shifts for the C-2 proton resonances exhibiting a triplet at τ 4.45 (W 21.0 Hz) and double-doublet at τ 4.35 (W 10.0 Hz), respectively. In addition the NMR spectra of the cis-cis (IVa) and trans-cis (IVb) hydroxy compounds as well as the corresponding benzoxy derivatives (VIa) and (VIb) demonstrated their symmetric configurations by sharp quartets and triplets atributed to the 1- and 3-ethoxycarbonyl groups. On the other hand the trans-trans geometry of compounds (IVc) and (VIc) revealed two quartets and two triplets for conformationally different C-1 and C-3 ethoxycarbonyl groups.

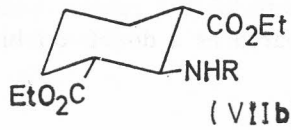
The successful separations of the 2-hydroxycyclohexane dicarboxylates (IVa-c) encouraged us to attempt the preparation of the geometrically defined diethyl 2-aminocyclohexane-1,3-dicarboxylates (VII). For this purpose the nucleophilic addition of ammonia to diethyl cyclohex-1-ene-1,3-dicarboxylate (VIII) appeared to offer the most accessible route.[1] All attempts to hydrogenate diethyl 2-oxyiminocyclohexane-1,3-dicarboxylate into a mixture of stereoisomeric aminocyclohexane diesters (VII) failed. Namely, during the oximation of cyclohexanone (V) a spontaneous intramolecular cyclisation of the intermediary oxyimino derivative generated ethyl 4,5,6,7-tetrahydro-3-oxo(2,1)benzisoxazole-7-carboxylate (IX) in high yield.



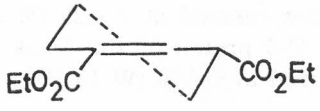
(VIIa) R=H
(Xa) R=Bz



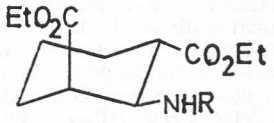
(XIa)



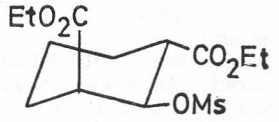
(VIIb) R=H
(Xb) R=Bz



(VIII)



(VIIc) R=H
(Xc) R=Bz



(XIc)

The stereoisomeric aminocyclohexane diesters (VII) were isolated by silica gel — celite chromatography as diethyl c-2-aminocyclohexane-r-1,c-3-dicarboxylate (VIIa), diethyl t-2-aminocyclohexane-r-1,c-3-dicarboxylate (VIIb), and diethyl t-2-aminocyclohexane-r-1,t-3-dicarboxylate (VIIc) in a ratio of 1 : 2.5 : : 1.5 and characterized as the respective N-benzoyl derivatives (X a-c).

The NMR spectral data of the aminocyclohexane diesters (VIIa-c) and their N-benzoyl derivatives (Xa-c) exhibited chemical shifts for C-2, C-3, and ethoxycarbonyl protons parallel to those described for the corresponding protons of the hydroxycyclohexane carboxylates (IVa-c) and their benzoxy derivatives (VIa-c). Thus, the cis-cis isomer (VIIa) gave a triplet at τ 6.15 (W 6 Hz) due to the equatorial C-2 proton, while the trans-cis (VIIb) and trans-trans (VIIc) isomer gave a wide triplet at τ 6.81 (W 20 Hz) and at τ 6.85—7.33 (obscured by that of C-3 proton), respectively, due to the C-2 axial protons. The benzamido derivatives (Xa-c) showed signals for C-2 protons as a downfield double-triplet centred at τ 4.83 (W 17.5 Hz) (appearing as a triplet (W 8 Hz) when treaaed with deuteriumoxide), a multiplet at τ ca. 5.85 (obscured by those of OCH_2) and a triplet of doublets at τ 5.46 (W 24.9 Hz), respectively.

The cyclohexene (VIII), used for the above described amination was conveniently prepared by an elimination reaction of a stereoisomeric mixture of diethyl c-(t)-2-methylsulphonylcyclohexane-r-1,c(t)-3-dicarboxylates (XIa) (XIc) using potassium phthalimide in dioxan as the agent. The elimination reaction of the cis-cis isomer (XIa), in which the 2-mesyloxy group, as well as the C-1 and C-3 protons are axially situated, proceeded much faster to cyclohexene (VIII) than did the reaction of the corresponding trans-trans isomer (XIc). It is worth noting that attempts to repeat the earlier reported[8] dehydration of cyclohexanols (IV) in the presence of thionyl chloride did not bring us to the desired compound.

The described mixture of stereoisomeric 2-hydroxycyclohexane diesters (IVa-c), containing a minor amount of the trans-cis isomer (IVb), afforded a mixture of 2-mesyloxycyclohexane diesters (XI) from which the cis-cis (XIa) and trans-trans (XIc) isomers could be isolated in 41.9% and 43.2% yields, respectively. The cis-cis isomer (XIa), with an axial mesyloxy group, gave a triplet centred at τ 4.20 (W 4.0 Hz) due to the equatorial C-2 proton, while the C-2 proton of the trans-trans isomer (XIc) appeared as a double-doublet centred at τ 4.70 (W 10 Hz).

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. IR spectra were obtained for potassium bromide pellets or liquid films using a Perkin-Elmer 297, UV spectra for solutions in 95% ethanol with a Beckman DU-2 spectrophotometer and NMR spectra for solutions in deuteriochloroform with a JEOL JNM-FX 100 spectrometer with tetramethylsilane as the internal standard. Mass spectra were measured with a Varian MAT CH7 spectrometer. Column chromatography was performed over a mixture of silica gel (Merck; less than 0.063 mm) and celite (Carl Roth, J. M. Celite 535) in methylene chloride. The silica gel (Merck, HF_{254}, type 60) which was used for preparative layer chromatography (20 cm plates) was activated at 110 °C for 60 min. TLC was performed on Merck silica gel 60 F_{254} plates (5 × 10 cm). The products were rendered visible by treatment with iodine vapour, by UV illumination, and by use of a ninhydrine spray.

Stereoisomeric Diethyl 2-Hydroxycyclohexane-1,3-dicarboxylates (IV)

To a solution of diethyl 2-oxocyclohexane-1,3-dicarboxylate (V)[9] (670 mg, 2.75 mmol) in anhydrous ethanol (19 ml) PtO_2 was added (134 mg). The mixture was shaken in an atmospehere of hydrogen (at 0.34 mPa) for 48 h. The catalyst was filtered off and the filtrate evaporated to dryness (627 mg, 92.8%). The filtrate was then chromatographed on a silica gel column preformed with celite (ratio 1 : 60 : 50). Methylene chloride — methanol (99 : 1) eluted diethyl c-2-hydroxycyclohexane-r-1,c--3-dicarboxylate (IVa) (R_F ca. 0.35), diethyl t-2-hydroxycyclohexane-r-1,t-3-dicarboxylate (IVc) (R_F ca. 0.30), and then diethyl t-2-hydroxycyclohexane-r-1,c-3-dicarboxylate (IVb) (R_F ca. 0.13) in 48.8%, 46.1% and 5.1% yields, respectively.

Diethyl c-2-hydroxycyclohexane-r-1,c-3-dicarboxylate (IVa) was distilled, b. p. 58—60 °C at 2.7 Pa, and then crystallized, m. p. 44—45 °C.

Anal. $C_{12}H_{20}O_5$ (244.28) calc'd.: C 59.00; H 8.25%
found: C 58.99; H 8.20%

IR spectrum: ν_{max} 3519, 3001, 2965, 2948, 2913 sh, 1728, and 1719 sh cm^{-1}. NMR spectrum: τ 5.37 (1H, dxt, $J_{2eq,1ax}$ 2.7 Hz, $J_{2eq,3ax}$ 2.7 Hz, $J_{2eq,OH}$ 1.95 Hz, 2-H), 5.82 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 6.80 (1H, d, $J_{OH,H}$ 1.95 Hz, exchanging in D_2O, OH), 7.48—7.85 (2H, m, 1- and 3-H), 7.95—8.48 (6H, m, 4-, 5-, and 6-H_2), 8.73 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl t-2-hydroxycyclohexane-r-1,c-3-dicarboxylate (IVb) separated as an oil. IR spectrum: ν_{max} 3497, 2976, 2933, 2865, 1742 sh, 1730, and 1715 sh cm^{-1}. NMR spectrum: τ 5.85 (4H, q, J_{Et} 7.0 Hz, 2 × $0CH_2$), ca. 6.0 (1H, m, 2-H, obscured by those of OCH_2), 6.83 (1H, d, $J_{OH,H}$ 3.0 Hz, OH), 7.37—8.53 (8H, m, 1- and 3-H, 4-, 5-, and 6-H_2), 8.72 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl t-2-hydroxycyclohexane-r-1,t-3-dicarboxylate (IVc) was distilled, b. p. 75—80 °C at 1.3 Pa.

Anal. $C_{12}H_{20}O_5$ (244.28) calc'd.: C 59.00; H 8.25%
found: C 58.95; H 8.45%

IR spectrum: ν_{max} 3521, 2994, 2950, 2874, and 1730 br cm^{-1}. NMR spectrum: τ 5.81 and 5.83 (each 2H, 2xq, J_{Et} 7.0 Hz, 2 × OCH_2), ca. 5.85 (1H, m, 2-H, obscured by those of OCH_2), 6.47 (1H, d, $J_{OH,2ax}$ 6.35 Hz, OH), 6.24—6.97 (2H, m, 1- and 3-H), 7.80—8.60 (6H, m, 4-, 5-, and 6-H_2), 8.72 and 8.73 (each 3H, 2xt, J_{Et} 7.0 Hz, 2 × Me).

Stereoisomeric Diethyl 2-Benzoxycyclohexane-1,3-dicarboxylates (VI)

Each stereoisomeric hydroxycyclohexane diester (IV) (0.07—0.22 mmol) dissolved in methylene chloride (0.1 ml) and anhydrous pyridine (0.5—1.7 ml) was treated with an equimolar amount of benzoyl chloride. The mixture was stirred at room temperature for 13 days, poured into chilled water and then extracted with methylene chloride. The organic layer was washed successively with 5% hydrochloric acid, 5% sodium hydrogen carbonate, and water, and then dried over sodium sulphate and evaporated to an oil. Preparative TLC (silica gel, 2 developments) and elution in/with methylene chloride afforded the purified product.

Diethyl c-2-benzoxycyclohexane-r-1,c-3-dicarboxylate (VIa), yield 75.3%, R_F ca. 0.44 (in methylene chloride), b. p. 118—120 °C at 2.7 Pa.

Anal. $C_{19}H_{24}O_6$ (348.38) calc'd.: C 65.50; H 6.94%
found: C 65.45; H 6.94%

UV spectrum: λ_{max} 230 nm (log ε 4.14), λ_{min} 210 nm (log ε 3.59). IR spectrum: ν_{max} 2985, 2950, 2899 sh, 2874, 1739 sh, 1733 br, 1600, 1585, and 709 cm^{-1}. NMR spectrum: τ 1.92—2.22 and 2.42—2.68 (2H and 3H, 2 × m, ArH), 3.89 (1H, t, $J_{2eq,1ax}$ 2.0 Hz, $J_{2eq,3ax}$ 2.0 Hz, 2-H), 5.97 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 7.18—7.75 (2H, m, 1-H and 3-H), 7.75—8.35 (6H, m, 4-, 5-, and 6-H_2), 8.86 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl t-2-benzoxycyclohexane-r-1,c-3-dicarboxylate (VIb), yield 90.8%, R_F ca. 0.41 (in methylene chloride), m. p. 62—63 °C (from n-hexane).

Anal. $C_{19}H_{24}O_6$ (348.38) calc'd.: C 65.50; H 6.94%
found: C 65.28; H 6.71%

UV spectrum: λ_{max} 230 nm (log ε 4.14), λ_{min} 210 nm. (log ε 3.52). IR spectrum: ν_{max} 2983, 2965, 2913, 2872, 1740 sh, 1734 sh, 1722 sh, 1603, 1583, and 710 cm^{-1}. NMR spectrum: τ 1.83—2.12 and 2.33—2.63 (2H and 3H, 2 × m, ArH), 4.45 (1H, t, $J_{2ax,1ax}$ 10.5 Hz, $J_{2ax,3ax}$ 10.5 Hz, 2-H), 5.96 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 7.08—7.60 (2H, m, 1- and 3-H), 7.74—8.67 (6H, m, 4-, 5-, and 6-H_2), 8.95 (6H, t, J_{Et} 7.0 Hz ,2 × Me).

Diethyl t-2-benzoxycyclohexane-r-1,t-3-carboxylate (VIc), yield 84.9%, R_F ca. 0.48 (in methylene chloride), b. p. 110—125 °C at 5.3 Pa.

Anal. $C_{19}H_{24}O_6$ (348.38) calc'd.: C 65.50; H 6.94%
found: C 65.20; H 6.93%

UV spectrum: λ_{max} 230 nm (logε 4.14), λ_{min} 210 nm (log ε 3.60). IR spectrum: ν_{max} (net) 2985, 2933, 2907 sh, 2865, 1736 sh, 1724 br, 1600, 1582, and 709 cm^{-1}. NMR spectrum: τ 1.87—2.17 and 2.38—2.70 (2H and 3H, 2 × m, ArH), 4.35 (1H, d × d, $J_{2ax,1ax}$ 6.0 Hz, $J_{2ax,3eq}$ 4.0 Hz, 2-H), 5.88 and 5.98 (each 2H, 2q, J_{Et} 7.0 Hz, 2 × OCH_2), 6.62—7.02 (2H, m, 1- and 3-H), 7.82—8.52 (6H, m, 4-, 5-, and 6-H_2), 8.78 and 8.91 (each 3H, 2 × t, J_{Et} 7.0 Hz, 2 × Me).

Stereoisomeric Diethyl 2-Aminocyclohexane-1,3-dicarboxylates (VII)

A solution of diethyl cyclohex-1-ene-1,3-dicarboxylate (VIII) (805 mg, 3.56 mmol) in aqueous 25% ammonia (6.3 ml) was heated in a sealed tube at 150 °C for 60 h. The mixture was then evaporated to an oily product (640 mg), dissolved in ethanolic 3% hydrochloric acid (64 ml) and heated under reflux for 17 h. This mixture was evaporated to dryness, neutralized with aqueous ammonia, and extracted with methylene chloride. From the organic layer was separated a basic product (616 mg) which was chromatographed on a silica gel (30.8 g) column performed with celite (28.4 g). Methylene chloride eluted starting cyclohexene (280 mg). Methylene chloride-methanol (99.5 : 0.5) eluted diethyl c-2-aminocyclohexane-r,-1-c-3-dicarboxylate (VIIa) (36.6 mg, 20.1%), F_F ca. 0.73 (in methylene chloride—methanol, 9 : 1), diethyl t-2-aminocyclohexane-r-1,c-3-dicarboxylate (VIIb) (92.4 mg, 50.6%), R_F ca. 0.69, and diethyl t-2-aminocyclohexane-r-1,t-3-dicarboxylate (VIIc) (53.5 mg, 29.3%), R_F ca. 0.56.

Diethyl c-2-aminocyclohexane-r-1,c-3-dicarboxylate (VIIa) was distilled, b. p. 90—97 °C at 2.7 Pa. Mass spectrum calc'd.: (M^+) 243.3; found: 243. IR spectrum: ν_{max} 3444 sh, 3409, 3352 sh, 2981, 2937, 2870, 1735 sh, 1729, and 1717 sh cm^{-1}. NMR spectrum: τ 5.85 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 6.15 (1H, t, $J_{2eq,1ax}$ 3.0 Hz, $J_{2eq,3ax}$ 3.0 Hz, 2-H), 7.30—7.83 (2H, m, 1- and 3-H), ca. 7.83—8.37 (6H, m, 4-, 5-, and 6-H_2), 8.52 (2H, s, NH_2), 8.70 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl t-2-aminocyclohexane-r-1,c-3-dicarboxylate (VIIb) was distilled, b. p. 80—82°C at 1.3 Pa.

Anal. $C_{12}H_{21}NO_4$ (243.30) calc'd.: C 59.24; H 8.70; N 5.76%
found: C 59.03; H 8.58; N 5.96%

IR spectrum: ν_{max} 3445, 3398, 3319, 2991, 2947, 2871, 1745 sh, 1739 sh, and 1718 sh cm^{-1}. NMR spectrum: τ 5.83 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 6.81 (1H, t, $J_{2ax,1ax}$ 10.0 Hz, $J_{2ax,3ax}$ 10.0 Hz, 2-H), ca. 7.51—8.30 (8H, m, 1-, 3-H, and 4-, 5-, and 6-H_2), 8.36 (2H, s, NH_2), 8.71 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl t-2-aminocyclohexane-r-1,t-3-dicarboxylate (VIIc) was distilled, b. p. 70—75 °C at 0.7 Pa.

Anal. $C_{12}H_{21}NO_4$ (243.30) calc'd.: C 59.24; H 8.70; N 5.76%
found: C 59.03; H 8.59; N 5.57%

IR Spectrum: ν_{max} 3432 sh, 3397, 3329 sh, 2937, 1738 sh, and 1726 br cm^{-1}. NMR spectrum: τ 5.92 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 6.85—7.33 (2H, m, 2- and 3-H), ca. 7.75—8.49 (7H, m, 1-H and 4-, 5-, and 6-H_2), 8.53 (2H, s, NH_2), 8.74 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Ethyl 4,5,6,7-Tetrahydro-3-oxo(2,1)benzisoxazole-7-carboxylates (IX)

To a solution of the 2-oxocyclohexane dicarboxylate (V) (528 mg, 2.18 mmol) in ethanol (2.5 ml) hydroxylamine hydrochloride (186.5 mg, 2.68 mmol) in water (0.54 ml),

and then sodium carbonate (152.6 mg, 1.44 mmol) in water (0.54 ml) were added. The mixture was stirred at room temperature for 16 h, diluted with water (3.5 ml) and extracted with ether. From the organic layer the oily product separated in 85.4% yield (393 mg), precipitated from ether—n-hexane, R_F ca. 0.66 (methylene chloride—methanol, 9.5 : 0.5).

Anal. $C_{10}H_{13}NO_4$ (211.2) calc'd.: C 56.86; H 6.20; N 6.63%
found: C 56.67; H 6.45; N 6.92%

UV spectrum: λ_{max} 263 nm (log ε 3.84). IR spectrum: ν_{max} 3433 sh, 3233 br, 2947, 2871, 1805, 1730 br, and 1628 cm^{-1}. NMR spectrum: τ 5.84 (2H, q, J_{Et} 7.0 Hz, OCH_2), 6.13—6.70 (2H, m, 3a-H and 7-H), 7.30—8.47 (6H, m, 4-, 5-, and 6-H_2), 8.70 (3H, t, J_{Et} 7.0 Hz, Me).

Stereoisomeric Diethyl 2-Benzamidocyclohexane-1,3-dicarboxylates (X)

Each stereoisomeric aminocyclohexane diester (VII) (0.045—0.20 mmol) was dissolved in methylene chloride (0.01—0.05 ml) and pyridine (0.5—1.5 ml) and then treated with an equimolar amount of benzoyl chloride. The mixture was worked up as described for the preparation of the benzoxycyclohexane diesters (VI). Preparative TLC (developments and elution in/with methylene chloride) afforded the purified product.

Diethyl c-2-benzamidocyclohexane-r-1,c-3-dicarboxylate (Xa), yield 79.6%, R_F ca. 0.44 (in methylene chloride—ether, 9 : 1), m. p. 148—149.5 °C (from methylene chloride-ether-n-hexane).

Anal. $C_{19}H_{25}NO_5$ (347.40) calc'd.: C 65.69; H 7.25%
found: C 66.07; H 7.74%

UV spectrum: λ_{max} 224 nm (log ε 4.06), λ_{min} 212 nm (log ε 3.94). IR spectrum: ν_{max} 3365, 2983, 2957, 2897, 1734, 1716, 1673, 1603, 1580, 1520, and 697 cm^{-1}. NMR spectrum: τ 2.11—2.30 and 2.36—2.54 (2H and 3H, 2 × m, ArH), 3.26 (1H, d, $J_{NH,2eq}$ 9.5 Hz, exchanging in D_2O, NHCO), 4.83 (1H, d × t, $J_{2eq,1ax}$ 4.0 Hz, $J_{2eq,3ax}$ 4.0 Hz, $J_{2eq,NH}$ 9.5 Hz, 2-H), 5.88 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 8.0—8.37 (6H, m, 4-, 5-, and 6-H_2), 8.78 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl t-2-benzamidocyclohexane-r-1,c-3-dicarboxylate (Xb), yield 88.2%, R_F ca. 0.34 (in methylene chloride—ether, 9 : 1), m. p. 166.5—168 °C (from methylene chloride-ether-n-hexane).

Anal. $C_{19}H_{25}NO_5$ (347.40) calc'd.: C 65.69; H 7.25; N 4.03%
found: C 65.90; H 6.91; N 4.30%

UV spectrum: λ_{max} 225 nm (log ε 4.05), λ_{min} 212 nm (log ε 3.87). IR spectrum: ν_{max} 3298, 2965, 2939, 1728 br, 1640, 1603, 1578, 1541 br, and 699 cm^{-1}. NMR spectrum: τ 2.28—2.72 (5H, m, ArH), 3.70 (1H, d, NHCO), ca. 5.85 (1H, m, obscured by those of OCH_2, 2-H), 5.92 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 7.08 (2H, m, 1- and 3-H), 7.80—8.68 (6H, m, 4-, 5-, and 6-H_2), 8.86 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl t-2-benzamidocyclohexane-r-1,t-3-dicarboxylate (Xc), yield 86.7%, R_F ca. 0.48 (in methylene chloride-ether, 9 : 1), m. p. 74—74.5 °C (from ether-n-hexane).

Anal $C_{19}H_{25}NO_5$ (347.40) calc'd.: C 65.69; H 7.25; N 4.03%
found: C 65.99; H 7.56; N 4.16%

UV spectrum: λ_{max} 226.5 nm (log ε 4.03), λ_{min} 212 nm (log ε 3.85). IR spectrum: ν_{max} 3299, 2940, 2873, 1738 ,1723, 1714, 1644, 1630, 1604, 1581, 1535, and 693 cm^{-1}. NMR spectrum: τ 2.18—2.39 and 2.48—2.68 (2H and 3H, 2 × m, ArH), 2.92 (1H, d, $J_{NH,2ax}$ 9.3 Hz, NHCO), 5.46 (1H, d × d × d, $J_{2ax,3eq}$ 4.6 Hz, $J_{2ax,NH}$ 9.3 Hz, $J_{2ax,1ax}$ 11.0 Hz, 2-H), 5.82 and 5.93 (4H, 2xq, J_{Et} 7.0 Hz, 2 × OCH_2), 6.77—7.17 (2H, m, 1- and 3-H), 7.63—8.52 (6H, m, 4-, 5-, and 6-H_2), 8.34 and 8.86 (each 3H, 2 × t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl Cyclohex-1-ene-1,3-dicarboxylate (VIII)

To a mixture of stereoisomeric diethyl 2-methylsulphonylcyclohexane-1,3-dicarboxylate (XI) (595 mg, 1.85 mmol) dissolved in anhydrous dioxan (93 ml) potassium phthalimide (376.3 mg, 2.04 mmol) was added and the mixture was heated

under reflux for 48 h. A precipitate was then filtered off, the filtrate evaporated to dryness, washed with ether, and the residue chromatographed on a silica gel (19 g) column preformed with celite (14.6 g). Methylene chloride eluted the product (331 mg, 79.3%), R_F ca. 0.48 (in methylene chloride), b. p. 75—80 °C at 2.7 Pa.

Anal. $C_{12}H_{18}O_4$ (226.26) calc'd.: C 63.70; H 8.02%
found: C 63.74; H 7.72%

UV spectrum: λ_{max} 216 nm (log ε 3.93). IR spectrum: ν_{max} 2981, 2937, 2911 sh, 2871 br, 1732, 1711, and 1664 cm^{-1}. NMR spectrum: τ 2.95 (1H, m, 2-H), 5.78 and 5.81 (each 2H, 2 × q, J_{Et} 7.0 Hz, 2 × OCH_2), 6.57—6.99 (1H, m, 3-H), 7.54—7.90 (2H, m, 6-H_2) 7.90—8.59 (4H, m, 4- and 5-H_2), 8.71 and 8.73 (each 3H, 2 × t, J_{Et} 7.0 Hz, 2 × Me).

The elimination reaction of the cis-cis (XIa) and the trans-trans (XIc) isomers under the above described conditions but heated under reflux for 16 h, afforded the product (VIII) in 58.3% and in 43.5% yields, respectively.

Stereoisomeric Diethyl 2-Methylsulphonylcyclohexane-1,3-dicarboxylates (XI)

To a solution of stereoisomeric diethyl 2-hydroxycyclohexane-1,3-dicarboxylates (IV) (672 mg, 2.75 mmol) in anhydrous pyridine (5.6 ml), cooled to —10 °C, was added methylsulphonylchloride (0.445 ml, 5.87 mmol). The mixture was stirred at 0°C for 16 h and then the solvent removed under reduced pressure. The residue was partitioned between water and methylene chloride. The organic layer was washed with 5% hydrochloric acid and then with 5% sodium hydrogen carbonate and water, dried over Na_2SO_4, and evaporated to an oil (958 mg), which was chromatographed on a short silica gel (2 g) column. Methylene chloride eluted a mixture of stereoisomeric products (870 mg, 98.1%), which on rechromatography in methylene chloride afforded diethyl t-2-methylsulphonylcyclohexane-r-1,t-3-dicarboxylate (XIc), (383.3 mg, 43.2%), R_F ca 0.44; diethyl c-2-methylsulphonylcyclohexane-r-1,c-3-dicarboxylate (XIa), (362 mg, 41.9%), R_F ca. 0.30; diethyl cyclohex-1-ene-1,3-dicarboxylate (VIII), (35.75 mg, 5.7%), and some minor unidentified by-products.

Diethyl c-2-methylsuphonylcyclohexane-r-1,c-3-dicarboxylate (XIa) was recrystallized from ethanol, m. p. 105 °C.

Anal. $C_{13}H_{22}O_7S$ (322.37) calc'd.: C 48.43; H 6.88; N 9.95%
found: C 48.62; H 7.10; N 10.16%

IR spectrum: ν_{max} 2985, 2959, 2879 sh, 1736, 1727 sh, 1475, 1447, 1333, 1166, and 1131 cm^{-1}. NMR spectrum: τ 4.20 (1H, d × d, $J_{2eq,1ax}$ 2.0 Hz, $J_{2eq,3ax}$ 2.0 Hz, 2-H), 5.80 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), 7.01 (3H, s, MsMe), 7.27—7.71 (2H, m, 1- and 3-H), 7.91—8.48 (6H, m, 4-, 5-, and 6-H_2), 8.71 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Diethyl t-2-methylsulphonylcyclohexane-r-1,t-3-dicarboxylate (XIc) was distilled, b. p. 133—135 °C at 6.7 Pa.

Anal. $C_{13}H_{22}O_7S$ (322.37) calc'd.: C 48.43; H 6.88; N 9.95%
found: C 48.69; H 7.14; N 9.75%

IR spectrum: ν_{max} 2994, 2941, 2915 sh, 2874, 1733 br, 1449, 1361 br, and 1179 cm^{-1}. NMR spectrum: τ 4.70 (1H, d × d, $J_{2ax,1ax}$ 6.5 Hz, $J_{2ax,3eq}$ 3.5 Hz, 2-H), 5.80 (4H, q, J_{Et} 7.0 Hz, 2 × OCH_2), ca. 6.48—6.93 (2H, m, 1- and 3-H), 6.98 (3H, s, MsMe), 7.90—8.52 (6H, m, 4-, 5-, and 6-H_2), 8.73 (6H, t, J_{Et} 7.0 Hz, 2 × Me).

Acknowledgement. — The authors thank Mrs. A. Poturić for technical assistance.

REFERENCES

1. V. Škarić, V. Turjak-Zebić, and D. Škarić, *J. Chem. Soc. Perkin I* (1974), 1406.
2. V. Škarić, B. Djuras, and V. Turjak-Zebić, *J. Chem. Soc. Perkin I* (1975), 1959.
3. V. Škarić, B. Djuras, and V. Turjak-Zebić, *Croat. Chem. Acta* **48** (1976) 341.
4. V. Škarić, M. Sedjak, V. Turjak-Zebić, and D. Škarić, *Can. J. Chem.* **58** (1980) 1860.

5. V. Škarić, M. Kovačević, and D. Škarić, *J. Chem. Soc. Perkin I* (1976), 1199.
6. S. N. Balasubrahmanyam, M. Balasubramanian, and K. R. Nagaraja Rao, *Indian J. Chem.* **11** (1973) 449.
7. F. F. Blicke and F. J. McCarty, *J. Org. Chem.* **24** (1959) 1069.
8. G. A. R. Kon and B. L. Nandi, *J. Chem. Soc.* (1933), 1628.
9. N. S. Vul'fson and V. I. Zaretskii, *Zhur. Obschei Khim.* **28** (1958) 1909.

SAŽETAK

Geometrijski izomeri u serijama 2-amino-(2-hidroksi)-cikloheksan-1,3, -1,4-, -1,5- i -1,6-dikarboksilnih kiselina

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Opisane su sinteze dosad nepripravljenih cis-cis(a), trans-cis-(b) i trans-trans-(c) stereoizomera u seriji dietil 2-hidroksi-(IV) i 2-amino-(VII) cikloheksan-1,3-dikarboksilata. Geometrije ovih izomera i njihovih O-(VI) i N-(X) benzoil derivata su utvrđene pomoću NMR spektroskopije, posebno u odnosu na efekte otkrivanja kod geminalnih C-2 protona.