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Synthesis of Isomeric Hexahydro- and Perhydroisoindol-1-ones

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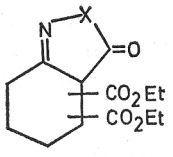
Catalytic hydrogenation of triethyl 2-cyanocyclohex-1-(XIV) and -2(XV)-ene-1,5,5-tricarboxylates yielded the corresponding 2--cyanocyclohexane (XVII) and diethyl perhydroisoindol-1-one-6,6--dicarboxylate (V), the latter being formed through spontaneous intramolecular cyclisation of triethyl 2-aminomethylcyclohexane--1,5,5-tricarboxylate (XXI). Regiospecific reductions and isomerisations of cyanocyclohexenes (XIV) and (XV), and their conversion into corresponding hexahydroisoindol-1-ones (IV) and (III) were shown to depend on the hydrogenating conditions and catalysts.

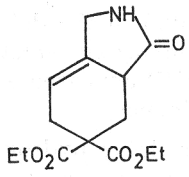
INTRODUCTION

Continuing our efforts toward azabicyclo [4.3.0]-nonane systems already studied in tetrahydro-indazolone[1–3] (I) and hexahydrobenzisoxazolone[4,5] (II) series led us to examine the synthesis and some stereochemical features of analogous diethyl 2,3,5,6,7,7a-(III) and 2,3,4,5,6,7-hexahydro-(IV), and perhydro-(V) isoindol-1-one-6,6-dicarboxylates. The bicyclic skeleton of isoindolones (IV) and (V) attracted also our interest due to structural relationship with sesquiterpenoid confertifolin and its dihydro derivative[6].

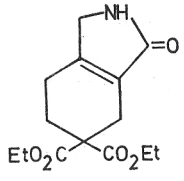


(I) X = NH

(II) X = O



(III)

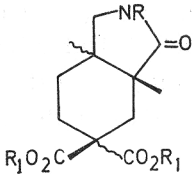


(IV)

(V) R = H, R_1 = Et

(XIX) R = Bz, R_1 = Et

(XX) R = R_1 = H



Among the methods used to obtain azabicyclo [4.3.0]-nonane-(V) and -nonene derivatives (III) and (IV) the one involving the cyclisation of 2-aminomethyl-1--carbethoxy-cyclohexanes and -cyclohex-1(2)-ene derivatives promised to be generally applicable. For such a purpose the triethyl 2-cyano-2-hydroxycyclohexane-1,5,5-tricarboxylate (VI) was prepared as starting material by cyanohydration[7] of the corresponding cyclohexanone derivative[8].

The cyanohydration of ethyl cyclohexanone carboxylates bearing keto group in β-position to carboxylate may bring about major effects on the yields and stabilities of thus obtained cyanohydrins. Namely, whereas diethyl 4-oxocyclohexane-1,1-dicarboxylate[9] afforded diethyl 4-cyano-4-hydroxycyclohexane-1,1-dicarboxylate[10] (VII) in more than 90% yields, the cyanohydrin (VI) as well as the diethyl 2-cyano-2-hydroxycyclohexane-1,3-dicarboxylate (VIII) and diethyl 2-cyano-2-hydroxycyclohexane-1,6-dicarboxylate (IX) were isolated in lower yields due to partial hydrolysis of their 1-carbethoxy group. Thus, the preparations of compounds (VI) and (VIII) were accompanied by the formation of ethyl 2-cyano-2-hydroxy-5-(X) and -3-(XI) carbethoxy-1-cyclohexanecarboxylic acids, respectively, the latter being converted spontaneously into 2-carboxamido--2-hydroxycyclohexane derivative (XII). While the structure of cyanohydrin--carboxylic acid (XI) was proved by an esterification into ester (VIII) and diethyl-2-carboxamido-2-hydroxycyclohexane-1,3-dicarboxylate (XIII), the most unstable cyanohydrin-carboxylic acid (X) was examined by mass 296 (M^+ —17) and NMR spectra showing a broad singlet at τ 2.0 due to OH and —COOH protons (disappearing in D_2O).

The dehydration of freshly prepared cyanohydrin (VI), using thionyl chloride in pyridine[11] yielded triethyl 2-cyanocyclohex-1-ene-(XIV) and 2-cyanocyclohex-2-ene-1,5,5-tricarboxylate (XV), separated (ratios 5.7 : 4.3) by careful silica gel chromatography, showing marked differences in NMR spectra. Thus, while the cyclohex-2-ene (XV) exhibited an unresolved multiplet at τ 3.12—3.33 due to the vinylic C-3 proton, the cyclohex-1-ene (XIV) showed methylene multiplets only in the τ 6.91—7.98 region. Under above mentioned conditions cyanohydrin (IX) was also dehydrated into a mixture of diethyl 2-cyanocyclohex-1(2)-ene-1,6-dicarboxylate (XVI) in which cyclohex-2-ene was the predominant one.

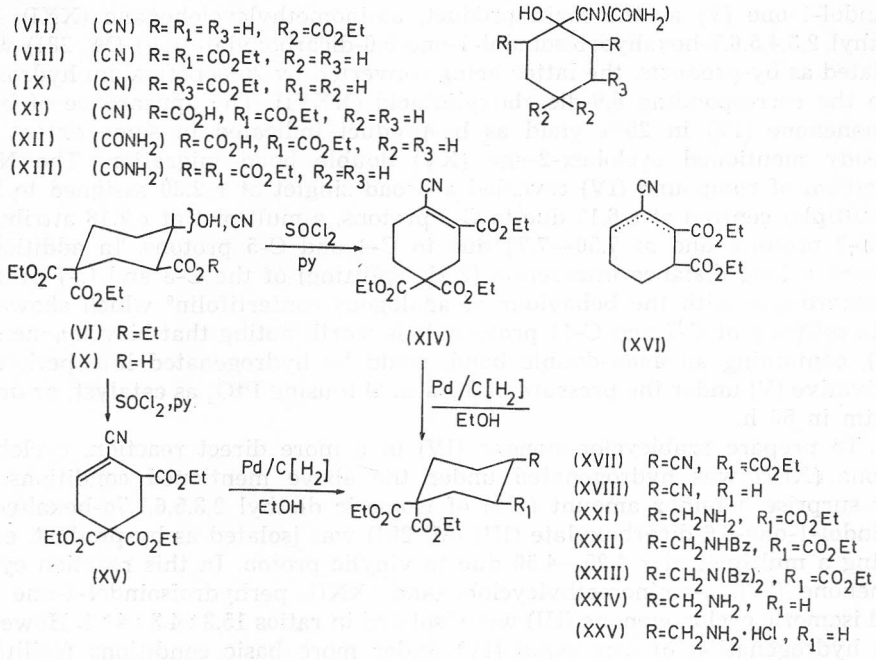
A similar duality, earlier found in the dehydration products of a mixture of *cis*- and *trans*- (Me : CN) 1-hydroxy-2-methylcyclohexane-1-carbonitrile[12], indicated that the cyanohydrins (VI) appeared as a pair of diastereoisomers, one of them being in slight predominancy.

The regioselective and controllable hydrogenation of cyanocyclohex-2-ene (XV) at 1 atm*, using 10% paladium on carbon as catalyst, afforded a mixture of epimeric triethyl 2-cyanocyclohexane-1,5,5-tricarboxylate (XVII), showing in the IR spectrum absorption at ν_{max} 2245 cm^{-1} for the C≡N group and all expected cyclohexane protons in the NMR spectrum. The hydrogenation of carefully purified isomer (XV), in a shorter interval of time, yielded minor amounts of cyclohex-1-ene (XIV) as a product of double bond migration.

The low hydrogenating susceptibility of the fully substituted ethylenic bond in cyclohex-1-ene (XIV), in comparison with those in cyclohex-2-ene (XV) and

* 1 atm = 101 325 Pa.

diethyl 4-cyanocyclohex-3-ene-1,1-dicarboxylate[10] the latter being smoothly converted into diethyl 4-cyanocyclohexane-1,1-dicarboxylate (XVIII) — was in good accordance with earlier reported results[13].



The cyanocyclohexane (XVII) was also evidenced by gas chromatography (on silicone column) as an expected[14] mixture of two diastereoisomers (ratios 3 : 2), in which the more energetically favourable *trans*- conformer was possibly the predominant one. Tedious separation of this mixture by chromatography on a thermostated silica gel column forced us to hydrogenate the unresolved sample of cyanocyclohexane (XVII) by a modified method of T. Naito et al[15]. This reduction conducted in methanol-aqueous ammonia solution and in the presence of Raney nickel as catalyst led us to 69% yield of the crystalline diethyl perhydroisoindol-1-one-6,6-dicarboxylate (V) (M^+ 283) which on benzoylation[16] yielded *N*-benzoyl derivative (XIX) (M^+ 383), and on hydrolysis (in 20% methanolic potassium hydroxide) the corresponding 6,6-dicarboxylic acid (XX). The intermediary triethyl 2-aminomethylcyclohexane-1,5,5-tricarboxylate (XXI), which spontaneously cyclised into perhydroisoindol-1-one (V), was characterized as *N*-benzoyl-(XXII) and *N,N'*-dibenzoyl derivative (XXIII).

At this point it is worth noting that *trans*-4-aminomethylcyclohexane--1-carboxylic acid[17] and analogous derivatives of benzoic acid[18], bicycloalkane-[19] and naphtalene-[20] carboxylic acids were evaluated as the most active antiplasmin agents. Therefore cyanocyclohexane (XVIII) was also converted into diethyl 4-aminomethylcyclohexane-1,1-dicarboxylate (XXIV) and its hydrochloride (XXV).

The NMR spectrum of perhydroisoindol-1-one (V) showed predominantly a broad band envelope consistent with a *trans*-fused ring system, very similar

to earlier reported *trans*-fused 1-amino-8-azabicyclo[4.3.0]nonan-7-one[21] obtained from ethyl *cis*-2-amino-*trans*-2-aminomethylcyclohexane-1-carboxylate.

While the hydrogenation of 2-cyanocyclohex-2-one (XV) in ammoniacal solution (4 h), using deactivated Raney nickel as catalyst[15], afforded perhydroisoindol-1-one (V) as the main product, aminomethylcyclohexane (XXI), and diethyl 2,3,4,5,6,7-hexahydroisoindol-1-one-6,6-dicarboxylate (IV) (M^+ 281) were isolated as by-products, the latter being converted by 20% potassium hydroxide into the corresponding 6,6-dicarboxylic acid (XXVI). The appearance of bicyclononenone (IV) in 25% yield as by-product indicated in some extent the already mentioned cyclohex-2-ene (XV) double bond migration. The NMR spectrum of compound (IV) revealed a broad singlet at τ 2.30 assigned to NH, a multiplet centred at τ 6.12 due to C-3 protons, a multiplet at τ 7.18 attributed to C-7 protons, and at 7.50—7.77 due to C-4 and C-5 protons. In addition it showed a long distance interaction (2 Hz splitting) of the C-3 and C-7 protons in accordance with the behaviour of analogous confertifolin[6] which showed a 5 Hz splitting of C-7 and C-11 protons. It is worth noting that bicyclononenone (IV), containing an *endo*-double bond, could be hydrogenated into perhydroderivative (V) under the pressure of 3.5 atm (4 h using PtO_2 as catalyst) or under 1 atm in 50 h.

To prepare azabicyclononenone (IV) in a more direct reaction, cyclohex-1-one (XIV) was hydrogenated under the above mentioned conditions. To our surprise a minor amount (4%) of isomeric diethyl 2,3,5,6,7,7*a*-hexahydroisoindol-1-one-6,6-dicarboxylate (III) (M^+ 281) was isolated as by-product, exhibiting a multiplet at τ 4.25—4.50 due to vinylic proton. In this reaction cyclononenone (IV), 2-aminomethylcyclohexane (XXI), perhydroisoindol-1-one (V), and isomeric cyclononenone (III) were isolated in ratios 15.3 : 4.3 : 4 : 1. However, the hydrogenation of compound (IV) under more basic conditions facilitated the migration of double bond generating a 3.5 : 1 : 1 : 2.3 ratios of the above listed compounds.

EXPERIMENTAL

The same techniques and apparatus were used as described previously[10]. In addition neutralisation equivalents were determined by potentiometric microtitration in dioxan — water (1 : 1) with an 0.1 mol dm^{-3} solution of sodium hydroxide. Gas chromatography was performed on a Hewlett Packard, type 700, apparatus, with thermal detector.

Diethyl 2-Cyano-2-hydroxycyclohexane-1,3-dicarboxylate (VIII)

(*a*) A cooled solution of diethyl 2-oxocyclohexane-1,3-dicarboxylate[8] (727 mg, 3 mmol) in ethanol (7.5 ml) and water (11 ml) was treated portionwise with potassium cyanide (273 mg, 4.2 mmol) dissolved in water (1.5 ml) during a period of 30 min. The mixture was then stirred at 0 °C for 17 h and then acidified with 2.5 mol dm^{-3} sulphuric acid and extracted with ether. From the ethereal extract, which was washed with 5% sodium carbonate solution and water, the oily product separated (705 mg, 63%), b. p. 113—119 °C at 5.10^{-4} mm Hg.*

Anal. $C_{13}H_{19}NO_5$ (269.29) calc'd.: C 57.98; H 7.11; N 5.20%
found: C 58.24; H 7.34; N 5.27%

IR spectrum: ν_{max} 3356, 3195, 2890, and 1724 cm^{-1}.

From acidified sodium carbonate washings, ether extracted a crystalline product (196 mg, 27%) identified as 2-cyano-2-hydroxy-3-carbethoxy-1-cyclohexanecarboxylic acid (XI), m. p 142—143 °C (from methylene chloride-*n*-hexane).

* 1 mm Hg = 133.322 Pa.

Anal. $C_{11}H_{15}NO_5$ (241.24) calc'd.: C 54.76; H 6.27; N 5.81%
found: C 54.77; H 6.50; N 5.82%

IR spectrum: ν_{max} 3356, 2882 br, and 1706 cm^{-1}

A crude sample, kept aside for 30 days, afforded a crystalline product identified as 2-carboxamido-2-hydroxy-3-carbethoxy-1-cyclohexanecarboxylic acid (XII), m. p. 246—248 °C (from methanol).

Anal. $C_{11}H_{17}NO_6$ (259.25) calc'd.: C 50.96; H 6.61; N 5.40%
found: C 50.74; H 6.86; N 5.29%

IR spectrum: ν_{max} 3413, 3236, 2941, 2421br, 1908br, 1730, 1686, and 1640sh cm^{-1}. NMR spectrum (in CD_3SOCD_3): τ 2.80 (2H, s, $CONH_2$), 6.01 (2H, q, $O \cdot CH_2$), 8.83 (3H, t, CH_3).

(*b*) A solution of 2-cyano-2-hydroxy-3-carbethoxy-1-cyclohexanecarboxylic acid (XI) (330 mg, 1.37 mmol) in 3% ethanolic hydrochloric acid (33 ml) was heated under reflux for 10 h and then evaporated under reduced pressure to a volume of 10 ml. This solution was diluted with water and extracted with ether. From organic layer an oil separated (240 mg), which triturated with cooled ether, afforded an crystalline fraction and the oily product (138 mg, 37%), b. p. 110—116 °C at $5 \cdot 10^{-4}$ mm Hg, identical (IR spectrum) with that described under (*a*).

The crystalline fraction (49 mg, 12.5%) was purified on silica gel (1 g) column as diethyl 2-carboxamido-2-hydroxycyclohexane-1,3-dicarboxylate (XIII), m. p. 128—129 °C (from ether).

Anal. $C_{13}H_{21}NO_6$ (287.31) calc'd.: C 54.34; H 7.37; N 4.88%
found: C 54.58; H 7.36; N 4.59%

IR spectrum: ν_{max} 3413, 3322, 3049br, 2882, 1736, 1715, 1698, and 1672 cm^{-1}.

Triethyl 2-Cyano-2-hydroxycyclohexane-1,5,5-tricarboxylate (VI)

The treatment of 2-oxocyclohexane-1,5,5-tricarboxylate[8] (6.6 g, 21.1 mmol) with potassium cyanide as described for cyanohydrin (VIII) yielded the oily product (2.93 g, 40.8%), and an acidic fraction (3.92 g, 59.2%) identified as 2-cyano-2-hydroxy-5,5-dicarbethoxy-1-cyclohexanecarboxylic acid (X).

MS (*m/e*): 296 (M^+—OH) and 268 (M^+—CO_2H). NMR spectrum: τ 1.70—2.31 (1H, br, OH; disappearing in D_2O), 5.80 (4H, q, $2 \times OCH_2$, J_{CH_2, CH_3} 7.0 Hz), 8.72 and 8.76 (each 3H, 2t, $2 \times CH_3$, J_{CH_3, CH_2} 7.0 Hz).

Diethyl 2-Cyano-2-hydroxycyclohexane-1,6-dicarboxylate (IX)

Following the above described procedure diethyl 2-oxocyclohexane-1,6-dicarboxylate[22] (484 mg, 2 mmol) gave the product (403 mg, 75%), b. p. 95—100 °C at $5 \cdot 10^{-4}$ mm Hg.

Anal. $C_{13}H_{19}NO_5$ (269.29) calc'd.: C 57.98; H 7.11; N 5.20%
found: C 57.87; H 7.43; N 4.83%

IR spectrum: ν_{max} 3378, 2882, 2227, and 1721br cm^{-1}.

Triethyl 2-Cyanocyclohex-1-(XIV) and -2(XV)-ene-1,5,5-tricarboxylates

Freshly prepared triethyl 2-cyano-2-hydroxycyclohexane-1,5,5-tricarboxylate (VI) (2.93 mg, 8.6 mmol) was dissolved in anhydrous pyridine at 0 °C and treated with thionyl chloride dropwise during a period of 10 min. It was heated at 90 °C for additional 2 h. This mixture was diluted with cooled water and extracted with ether. The organic layer was washed with 5% solution of sodium carbonate and water to separate an oily product (2.64 g, 95%) consisting of two similar components (by TLC in methylene chloride). These products were then separated on thermostated silica gel (200 g) column (detected by UV recorder). Methylene chloride eluted an oily product identified as 2-cyanocyclohex-1-ene (XIV) (1.27 g, 57%) which on rechromatography afforded the analytical sample.

Anal. $C_{16}H_{21}NO_6$ (323.34) calc'd.: C 59.43; H 6.55; N 4.33%
found: C 59.60; H 6.64; N 4.39%

UV spectrum: λ_{max} 229 nm (log ε 3.93). IR spectrum: ν_{max} 3021, 2976sh, 2242, 1730br, and 1634 cm^{-1}. NMR spectrum: τ 5.65 and 5.76 (6H, 2q, 3 × OCH_2, J_{CH_2, CH_3} 7.0 Hz), 6.91—7.08 (2H, m, 6-H_2), 7.40 (1H, t, 3-H_a), 7.56 (1H, t, 3-H_b), 7.71 and 7.81 (each 1H, 2s, 2 × 4-H), 8.62 and 8.73 (9H, 2t, 3 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

Further elution with methylene chloride yielded 2-cyanocyclohex-2-ene (XV) (954 mg, 43%) which was also purified by rechromatography.

Anal. $C_{16}H_{21}NO_6$ (323.34) calc'd.: C 59.43; H 6.55; N 4.33%
found: C 59.66; H 6.69; N 4.12%

UV spectrum: λ_{max} 245sh nm (log ε 2.81). IR spectrum: ν_{max} 3030, 2950sh, 2247, 1742br, and 1642 cm^{-1}. NMR spectrum: τ 3.12—3.33 (1H, m, 3-H), 5.74, 5.76, and 5.78 (each 2H, 3q, 3 × OCH_2, $J_{CH_2CH_3}$ 7.0 Hz), 6.37—6.79 (1 H, m, 1-H), 7.07—7.42 (2H, m, 4-H), 7.42—7.87 (2H, m, 6-H_2), 8.69 and 8.75 (9H, 2t, 3 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

Diethyl 2-Cyanocyclohex-1(2)-ene-1,6-dicarboxylate (XVI)

Following the above described procedure a crude sample of diethyl 2-cyano-2-hydroxycyclohexane-1,6-dicarboxylate (IX) (1.15 g, 4.25 mmol) was dehydrated into the product (806 mg, 74%), b. p. 115—120 °C at $5 \cdot 10^{-4}$ mm Hg.

Anal. $C_{13}H_{17}NO_4$ (251.27) calc'd.: C 62.15; H 6.82; N 5.57%
found: C 61.85; H 6.72; N 5.68%

IR spectrum: ν_{max} 2924, 2212, 1724, and 1631 cm^{-1}. NMR spectrum of cyclohex-2-ene (in predominancy): τ 3.19 (1H, t, with secondary splitting, 3-H), 5.72 and 5.8 (each 2H, 2q, 2 × OCH_2), 6.18—6.41 (1H, m, 1-H), 6.68—7.01 (1H, m, 6-H), 8.69 and 8.73 (each 3H, 2t, 2 × CH_3).

Triethyl 2-Cyanocyclohexane-1,5,5-tricarboxylate (XVII)

(*a*) 2-Cyanocyclohex-2-ene (XV) (322 mg, 1 mmol) in ethanol (42 ml) containing 10% Pd/C (960 mg) was stirred in hydrogen athmosphere under 1.01 atm for 5 h. The catalyst was filtered off and the filtrate evaporated to a homogeneous oil (325 mg, 100%) (TLC in methylene chloride), which chromatographed on silica gel column afforded the analytical sample.

Anal. $C_{16}H_{23}NO_6$ (325.35) calc'd.: C 59.06; H 7.13; N 4.31%
found: C 59.29; H 7.32; N 4.33%

IR spectrum: ν_{max} 3040br, 2268, and 1742br cm^{-1}. NMR spectrum: τ 5.72, 5.77, 5.79, and 5.81 (6H, 4q, 3 × OCH_2, J_{CH_2, CH_3} 7.0 Hz), 6.40—6.76 (1H, m, 2-H), 8.70 and 8.74 (9H, 2t, 3 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

(*b*) 2-Cyanocyclohex-1-ene (XIV) (323 mg, 1 mmol) in ethanol (42 ml) was hydrogenated at 1 atm over 10% Pd/C (960 mg) for 17 h. Work up as already described gave a mixture (323 mg) which chromatographed on silica gel (18 g) column in methylene chloride separated the starting material (114 mg), R_F ca. 0.55 (in methylene chloride). Methylene chloride—methanol (97 : 3) then eluted the product (85 mg, 26%), R_F ca. 0.5 identical (TLC, gas chromatography, IR, and NMR spectra) with that obtained under (*a*). Basic fractions (75 mg) were comparable with aminomethylcyclohexane derivatives.

Diethyl 4-Cyanocyclohexane-1,1-dicarboxylate (XVIII)

Following the above described hydrogenation, 4-cyanocyclohex-3-ene-1,1-dicarboxylate[10,23] (93 mg, 0.37 mmol) was converted after 4 h into the product (80 mg) which chromatographed on silica gel (5 g) column separated as pure sample (70 mg, 75%), b. p. 95—100 °C at $5 \cdot 10^{-3}$ mm Hg.

Anal. $C_{13}H_{19}NO_4$ (253.29) calc'd.: C 61.64; H 7.56; N 5.53%
found: C 61.49; H 7.50; N 5.30%

IR spectrum: ν_{max} 2994, 2252, and 1724br cm^{-1}.

Diethyl Perhydroisoindol-1-one-6,6-dicarboxylate (V)

(*a*) To a solution of triethyl 2-cyanocyclohexane-1,5,5-tricarboxylate (XVII) (325 mg, 1 mmol) in methanol (10 ml) and aqueous ammonia (0.4 ml) prehydrogenated suspension of Raney nickel (1.2 ml) in methanol (12 ml) was added and then stirred in an athmosphere of hydrogen at room temperature for 6 h. The catalyst was filtered off, the filtrate evaporated to an oil (290 mg) and chromatographed on a silica gel (8 g) column. Methylene chloride—methanol (98 : 2) eluted the product (195 mg, 69%), R_F ca. 0.5 [in methylene chloride—methanol (10 : 1)], m. p. 125—126 °C (from chloroform—ether.

Anal. $C_{14}H_{21}NO_5$ (283.32) calc'd.: C 59.35; H 7.47; N 4.94%
found: C 59.35; H 7.63; N 4.77%

IR spectrum: ν_{max} 3425, 3012, 2941, 1739, 1712, and 1681 cm^{-1}. MS (*m/e*): 283 (M^+), 256 (M^+—27), 239 (M^+—44), 209 (M^+—CO_2Et). NMR spectrum: τ 3.01—3.30 (1H, m, NH, disappearing in D_2O), 5.78 and 5.82 (each 2H, 2q, 2 × OCH_2, J_{CH_2, CH_3} 7.0 Hz), 8.75, 8,76, and 8.81 (6H, 3 t, 2 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

Methylene chloride—methanol (95 : 5) then eluted the oily triethyl 2-aminomethylcyclohexane-1,5,5-tricarboxylate (XXI) (70 mg, 21%) characterized (vide infra) as *N*-benzoyl (XXII) and *N,N'*-dibenzoyl derivative (XXIII).

(*b*) Cyanocyclohex-2-ene (XV) (387 mg, 1.2 mmol) was hydrogenated under the above described conditions into an oily mixture (336 mg). The chromatography on silica gel (15 g) column and methylene chloride as eluant separated the product (169 mg, 49.2%) identical (mixed m. p., IR, NMR, and mass spectra) to that described under (*a*) and a fraction (84 mg, 25%), R_F ca. 0.48, identified as diethyl 2,3,4,5,6,7-hexahydroisoindol-1-one-6,6-dicarboxylate, m. p. 148—149 °C (from chloroform—ether).

Anal. $C_{14}H_{19}NO_5$ (281.30) calc'd.: C 59.77; H 6.81; N 4.98%
found: C 59.49; H 7.17; N 5.14%

IR spectrum: ν_{max} 3521br, 3257, 3125, 3030, 1742, 1681sh, and 1672 cm^{-1}. MS (*m/e*): 281 (M^+), 237 (M^+—44).

NMR spectrum: τ 2.18—2.41 (1H, m, NH), 2.37—2.60 (1H, br, NH, disappearing in D_2O), 5.80 (4H, q, 2 × OCH_2, J_{CH_2, CH_3} 7.0 Hz), 6.06—6.22 (2H, m, 3-H), 7.05—7.30 (2H, m, 7-H). 7.50—7.77 (4H, m, 4- and 5-H_2), 8.77 (6H, t, 2 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

Methylene chloride—methanol (95 : 5) then eluted the oily triethyl 2-aminomethylcyclohexane-1,5,5-tricarboxylate (XXI) (84 mg, 21.6%).

(*c*) From 2-cyanocyclohex-1-ene (XIV) (502 mg, 1.55 mmol) under the above described hydrogenating conditions an oily mixture (430 mg) was obtained which chromatographed on silica gel (17 g) column and eluted with methylene chloride—methanol (98 : 2) afforded a fraction (18 mg, 4.0%), R_F ca. 0.52, identified as diethyl 2,3,5,6,7,7a-hekahydroisoindol-1-one-6,6-dicarboxylate (III), m. p. 137—138 °C (from chloroform—ether).

IR spectrum: ν_{max} 3472br, 3226, 3106, 2994, 1727, and 1669 cm^{-1}. MS (*m/e*): 281 (M^+), 237 (M^+—44). NMR spectrum: τ 2.94—3.16 (1H, br, NH), 4.26—4.53 (1H, br, 4-H), 5.81 and 5.83 (each 2H, 2q, 2 × OCH_2, J_{CH_2, CH_3} 7.0 Hz), 6.03—6.20 (2H, m, 3-H), 8.77 (6H, t, 2 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

Further elution with methylene chloride—methanol (98 : 2) afforded perhydroisoindol-1-one (V) (70 mg, 16%), R_F ca. 0.50, identical (mixed m. p. IR, NMR, and mass spectra) to that described under (*a*), and then diethyl 2,3,4,5,6,7-hexahydroisoindol-1--one (IV) (268 mg, 64%), R_F ca. 0.48, identical (mixed m. p., IR, and NMR spectra) to the by-product described under (*b*).

Methylene chloride—methanol (95 : 5) then eluted the oily triethyl 2-aminomethylcyclohexane-1,5,5-tricarboxylate (XXI) (75 mg, 15%).

(*d*) A solution of 2,3,4,5,6,7-hexahydroisoindol-1-one (IV) (200 mg, 0.71 mmol) in ethanol (5 ml) was hydrogenated in the presence of pre-hydrogenated PtO_2 (37 mg) in ethanol (11 ml), in an athmosphere of hydrogen at room temperature for 50 h. A crystalline product separated (200 mg, 99%) identical (mixed m. p., IR, NMR, and mass spectra) to the perhydroisoindol-1-one (V) described under (*a*).

(*e*) A solution of 2,3,5,6,7,7a-hexahydroisoindol-1-one (III) (51 mg, 0.18 mmol) in ethanol (2 ml) was hydrogenated for 4 h in the presence of PtO_2 (19 mg) in ethanol (3 ml), as already described. A crystalline product separated (52 mg, 100%) identical (mixed m. p., IR, NMR, and mass spectra) to the already described product under (*a*).

Diethyl N-Benzoyl-perhydroisoindol-1-one-6,6-dicarboxylate (XIX)

A solution of perhydroisoindol-1-one (V) (133 mg, 0.47 mmol) in methylene chloride (1.3 ml) and pyridine (0.5 ml) was treated with benzoyl chloride (0.1 ml) and stirred at room temperature for 9 days and then two h at 90 °C. This mixture was cooled and diluted with water to be partitioned with methylene chloride. From the organic layer, washed with 2 M hydrochloric acid, 5% solution of sodium carbonate, and water, an oily mixture was obtained, which chromatographed on silica gel (9 g) column and eluted with methylene chloride—methanol (97 : 3) afforded the oily product (90 mg, 50.5%), R_F ca. 0.5.

Anal. $C_{21}H_{25}NO_6$ (387.42) calc'd.: C 65.10; H 6.50; N 3.62%
found: C 65.15; H 6.77; N 3.41%

UV spectrum: λ_{max} 231 nm (log ε 3.88). IR spectrum: ν_{max} 3012br, 1748sh, 1733, and 1672 cm^{-1}. MS (*m/e*): 387 (M^+), 309 (M^+-Ph). NMR spectrum: τ 2.24—2.65 (5H, m, aromatic), 5.80, 5.82, and 5.85 (4H, 3q, 2 × OCH_2, J_{CH_2, CH_3} 7.0 Hz), 8.76 and 8.78 (6H, 2t, 2 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

Perhydroisoindol-1-one-6,6-dicarboxylic acid (XX)

Diester (V) (248 mg, 0.88 mmol) was dissolved in 20% methanolic potassium hydroxide (3.4 ml), heated under reflux for 4 h, evaporated to a solid, and diluted with water (3.4 ml). By adding 10% hydrochloric acid a crystalline product separated (140 mg, 70%), m. p. 172—173 °C (from ethanol—ether—*n*-hexane).

Anal. $C_{10}H_{13}NO_5$ (227.21) calc'd.: C 52.86; H 5.77; N 6.17%
found: C 52.92; H 5.81; N 6.22%

Found: equiv. wts. 228.64 and 113.10. Required: 227.21 and 113.61; pK_1 5.10, pK_2 7.84 [c (1.66×10^{-3} mol dm^{-3})]. IR spectrum: ν_{max} 3460, 2976br, 2899, 2577br, 1727, and 1637 cm^{-1}.

2,3,4,5,6,7-Hexahydroisoindol-1-one-6,6-dicarboxylic acid (XXVI)

Diester (IV) (264 mg, 0.94 mmol) was treated with 20% methanolic potassium hydroxide (3.5 ml) and worked up as described for dicarboxylic acid (XX). It gave the product (170 mg, 75%), m. p. 271—273 °C (from ethanol—ether).

Anal. $C_{10}H_{11}NO_5 \cdot H_2O$ (243.21) cacl'd.: C 49.38; H 5.39; N 5.76%
found: C 49.11; H 5.40; N 5.59%

Found: equiv. wts. 239.00 and 121.63. Required: 243.21 and 121.61; pK_1 3.45, pK_2 5.56 [c (1.5×10^{-3} mol dm^{-3}) in H_2O]. IR spectrum: ν_{max} 3623, 3509, 3413, 2500br, 1946br, 1689br, and 1603 cm^{-1}.

Triethyl N-Benzoyl-2-aminomethylcyclohexane-1,5,5-tricarboxylate (XXII)

To a solution of 2-aminomethylcyclohexane-1,5,5-tricarboxylate (XXI) (96 mg, 0.3 mmol) in methylene chloride (0.8 ml) and pyridine (0.2 ml), benzoyl chloride (0.1 ml) was added. The mixture was stirred at room temperature for 48 h and then 2 h at 90 °C to be worked up as described for compound (XIX). The chromatography

of the crude material (100 mg) on silica gel (5 g) column gave an oily product (80 mg, 61.5%) which on rechromatography yielded analytical sample.

Anal. $C_{23}H_{31}NO_7$ (433.49) calc'd.: C 63.72; H 7.21; N 3.23%
found: C 63.33; H 7.48; N 3.20%

UV spectrum: λ_{max} 231 and 248sh nm (log ε 3.88 and 3.75), λ_{min} 216 nm (log ε 3.76). IR spectrum: ν_{max} 3378, 2967, 1724, 1661, 1639, 712 and 692 cm^{-1}. MS (*m/e*): 433 (M^+). NMR spectrum: τ [2.12—2.40 (2H, m) and 2.46—2.67 (3H, m), aromatic], 3.36—3.80 (1H, s, NH), 5.69—6.12 (6H, m, 3 × OCH_2), 6.36—6.84 (1H, m, 2-H), 8.77 and 8.79 (9H, 2t, 3 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

Triethyl N,N'-*Dibenzoyl-2-aminomethylcyclohexane-1,5,5-tricarboxylate (XXIII)*

2-Aminomethylcyclohexane-1,5,5-tricarboxylate (XXI) (170 mg, 0.5 mmol) in methylene chloride (1.4 ml) and pyridine (0.4 ml) was treated with benzoyl chloride (0.2 ml) and set aside at room temperature for 9 days and then 2 h at 90 °C. Work up as for compound (XIX). The thus obtained oily mixture (250 mg) was chromatographed on silica gel (13 g) column and eluted with methylene chloride—ether (99 : 1—97 : 3). It separaeed *N*-benzoyl derivative (XXII) (35 mg, 8.1%), R_F ca. 0.3, and the product (180 mg, 64.5%), R_F ca. 0.6, which on rechromatography yielded analytical sample.

Anal. $C_{30}H_{35}NO_8$ (537.59) calc'd.: C 67.02; H 6.56; N 2.61%
found: C 67.27; H 6.81; N 2.40%

UV spectrum: λ_{max} 225 and 250 nm (log ε 4.15 and 4.07), λ_{min} 219 and 243.5 nm (log ε 4.14 and 4.06). IR spectrum: ν_{max} 2994br, 1721br, 1689, 1658, 720, and 694 cm^{-1}. NMR spectrum: τ [2.50—3.02 (10 H, m, aromatic)], 5.60—6.04 (6H, m, 3 × OCH_2, J_{CH_2, CH_3} 7.0 Hz), 8.69, 8.77, and 8.79 (each 3H, 3t, 3 × CH_3, J_{CH_3, CH_2} 7.0 Hz).

Diethyl 4-Aminomethylcyclohexane-1,1-dicarboxylate (XXIV)

A solution of 4-cyanocyclohexane-1,1-dicarboxylate[23] (XVIII) (196 mg, 0.77 mmol) in methanol (12.3 ml) and aqueous ammonia (0.22 ml) was hydrogenated in the presence of Raney nickel (0.7 ml) during a period of 4.30 h as described for compound (V). An oily product separated (176 mg, 83%), b. p. 85—90 °C at 10^{-3} mm Hg; n_D^{22} 1.4760.

Anal. $C_{13}H_{23}NO_4$ (257.32) calc'd.: C 60.68; H 9.01; N 5.44%
found: C 60.53; H 8.97; N 5.22%

IR spectrum: ν_{max} 3401, 2933, 2857, and 1721 cm^{-1}.

Hydrochloride of diethyl 4-aminomethylcyclohexane-1,1-dicarboxylate (XXV) was obtained quantitatively in a solution of ethanolic hydrochloric acid, m. p. 63—64 °C (from chloroform—ether- *n*-hexane).

Anal. $C_{13}H_{24}ClNO_4$ (293.79) calc'd.: C 53.14; H 8.24; N 4.77; Cl 12.07%
found: C 52.86; H 8.43; N 4.56; Cl 11.97%

IR spectrum: ν_{max} 3534, 3125, 2941br, and 1637 cm^{-1}.

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SAŽETAK

Sinteza izomernih heksahidro- i perhidroizoindol-1-ona

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Katalitičko hidriranje trietil-2-cijanocikloheks-1-(XIV) i -2(XV)-en-1,5,5-trikarboksilata daje odgovarajući 2-cijanocikloheksan (XVII) i dietil perhidroizoindol-1-on-6,6-dikarboksilat (V). Perhidroizoindol-1-on (V) pri tom nastaje spontanom intramolekularnom ciklizacijom trietil-2-aminometilcikloheksan-1,5,5-trikarboksilata (XXI). Regiospecifične redukcije i izomerizacije cikloheksena (XIV) i (XV), kao i njihovo prevođenje u odgovarajuće heksahidroizoindol-1-one (IV) i (III) ovise o uvjetima hidriranja i o katalizatorima.

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