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4,5,6,7-Tetrahydroindazol-3-one Carboxylic Acids. II. Reductive Cleavage to Ring Substituted 2-Carboxamide Cyclohexylamine

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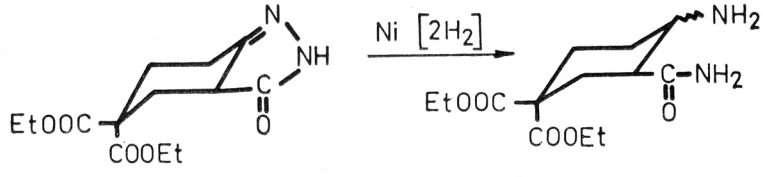
The synthesis of diethyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate (I) and its reductive cleavage into 2-carboxamide-4,4-dicarbethoxy-cyclohexylamine (II) using Raney nickel-catalyst in *iso*-propanol and methanol were described.

The reductive opening of I in ethanol favored the formation of Schiff base, 2-carboxamide - 4,4 - dicarbethoxy - *N* - ethylidene-cyclohexylamine (III).

The synthesis and the properties of 2-phenyl-4,5,6,7-tetrahydroindazol--3-one carboxylic acids were recently reported[1]. We turned now to related de-phenyl derivatives to demonstrate their suitability for the synthesis of very attractive ring substituted 2-carboxamide-cyclohexylamines. In this way diethyl - 4,5,6,7 - tetrahydroindazol - 3 - one-5,5-dicarboxylate (I) was reductively cleaved into 2-carboxamide-4,4-dicarbethoxy-cyclohexylamine (II) using Raney nickel-catalyst in *iso*-propanol or methanol. The method of synthesis is in effect an extension of the method used for the preparation of 2-aminopyrazine-3-carboxamide[2] with the reductive opening of pyrazolo-ring. In addition to the reductive opening of the heterocyclic ring of indazolone (I) the preparation of alicyclic compound II includes also another reductive step over the most probable intermediary ketimine.



I II

The hydrogenolysis in *iso*-propanol and methanol of I yielded one of the two possible diastereoisomeric amines in crystalline form, m.p. 137°, characterized as hydrochloride and acetate. However, as it was expected[3], the attempt to reduce indazol-3-one I in ethanol favored the formation of Schiff base. The isolation of 2 - carboxamide - 4,4 - dicarbethoxy - *N* - ethylidenecyclohexylamine (Schiff base) III, m.p. 115° besides compound IV, m.p. 142°, as well as the conversion of crystalline amine II into stereoisomeric Schiff base

III by a direct treatment with acetaldehyde[4] contributes towards the conformational analysis of the obtained stereoisomeric products and to the clarification of stereochemical criterions for a reductive cleavage of 4,5,6,7,--tetrahydroindazol-3-ones.

Ring substituted cyclohexylamine II has a twofold significance as an amide of β-alanine and an ester of δ-aminovaleric acid. It adds to our searching of metal sequestering reagents and at the same time serves for the syntheses of the stereoisomeric *N,N*-diacetic acid-cyclohexylamines.

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. UV spectra were measured in 95% ethanol on a Perkin-Elmer model 137-UV spectrophotometer with automatic gain control. The IR-absorption bands were recorded in potassium bromide plates on a Perkin-Elmer infracord model 137 and reported in wavelength followed by relative intensities in brackets: strong (*s*), medium (*m*), weak (*w*) and very weak (*vw*).

Diethyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate (I)

To a solution of triethyl cyclohexanone-2,4,4-tricarboxylate[5] (3.5 g., 11.2 mmole) in 50% ethanol (26 ml.) excess of hydrazine hydrate (0.7 g., 15 mmole) was added. It was refluxed for 15 hours and then cooled in ice overnight. After water has been added, the crystalline product was separated, filtered off and washed with water. Yield 3 g. (94%). Crystallization from ethylacetate-hexane gave analytical sample as colorless microcrystals, m.p. 164—165°.

Anal. $C_{13}H_{18}N_2O_5$ (282.29) calc'd C 55.31; H 6.43; N 9.92%
found: C 55.24; H 6.42; N 10.21%

The potentiometric titration was performed in dioxane-water (1 : 3). Ten ml. of 0.0025 *M* indazolone was titrated with 0.10117 *N* solution of sodium hydroxide. Neutral equivalent calc'd.: 282.3; found: 279.4.

UV-spectrum: $\lambda\lambda_{max}$ 204.5 mμ, log ε 3.639; 251 mμ, log ε 3.669 and shoulder λ 232 mμ, log ε 3.532; λ_{min} 219 mμ, log ε 3.474. IR-spectrum: 278 (*m*), 3.23 (*m*), 5.85 (*s*), 6.33 (*s*), 6.49 (*m*), 6.62 (*m*), 7.74 (*s*), 8.00 (*s*), 8.55 (*s*), 8.63 (*s*), 9.16 (*m*), 9.63 (*m*), 11.7 (*w*), 12.2 (*w*), 12.7 (*m*), 13.1 (*m*), 14.1 (*w*) μ.

2-Carboxamide-4,4-dicarbethoxy-cyclohexylamine (II)

a) Hydrogenolysis in *iso-propanol.* — A mixture of diethyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate (0.5 g., 1.77 mmole), *iso*-propanol (50 ml.) and moist Raney nickel[6] (about 2.5 g.) was refluxed with swirling for two and a half hours. The hot solution was filtered and filtrate evaporated at the water pump. The remaining oil (0.42 g.) crystallized on standing, m.p. 137° (extended). Crystallization from chloroform-ether-hexane gave 0.33 g. (65%) of colorless plates. The analytical sample melted at 136—138°.

Anal. $C_{13}H_{22}N_2O_5$ (286.32) calc'd.: C 54.53; H 7.75; N 9.78%
found: C 54.28; H 7.39; N 9.72%
Sublimed at 140° and $5 \cdot 10^{-2}$ mm Hg:
found: C 54.30; H 7.51%

UV-spectrum: λ_{max} 203 mμ, log ε 2.915 and shoulder λ 213.5 mμ, log ε 2.654. IR-spectrum: 3.03 (*m*), 5.58 (*s*), 6.02 (*s*), 6.33 (*w*), 6.95 (*m*), 7.35 (*w*), 8.13 (*s*), 8.93 (*m*), 9.80 (*m*), 10.8 (*w*), 11.0 (*w*), 11.6 (*w*) μ.

b) Hydrogenolysis in methanol. — Diethyl-4,5,6,7-tetrahydroindazol-3-one-5,5--dicarboxylate (0.5 g., 1.77 mmole) in methanol was treated with Raney nickel following the procedure described above. A semicrystalline product separated (0.34 g.). It crystallized from chloroform-ether-hexane to give 0.18 g. (35.5%) of colorless plates with m.p. undepressed on admixture with the sample obtained from hydrogenolysis in *iso*-propanol. IR-spectra of both samples were superimposable.

Hydrochloride. — 2-Carboxamide-4,4-dicarbethoxy-cyclohexylamine in ethanolic hydrochloric acid afforded the crystalline hydrochloride in quantitative yield. For analysis it was recrystallized from methanol-ether-hexane as colorless prisms, m.p. 243—245°.

Anal. $C_{13}H_{13}ClN_2O_5$ (322.78) calc'd.: C 48.37; H 7.18; N 8.68%
found: C 48.44; H 6.79; N 8.55%

IR-spectrum: 2.88 (*m*), 3.56 (*m*), 4.00 (*w*), 4.97 (*vw*), 5.85 (*s*), 6.02 (*s*), 6.25 (*m*), 6.33 (*m*), 6.71 (*m*), 8.03 (*s*), 8.77 (*s*), 9.52 (*m*), 11.6 (*vw*), 11.7 (*vw*), 11.9 (*vw*) μ.

Hydroacetate. — 2-Carboxamide-4,4-dicarbethoxy-cyclohexylamine was dissolved in 10% acetic acid and then evaporated to dryness under reduced pressure. The yield was quantitative. For analysis it was recrystallized from chloroform-ether-hexane as colorless plates, m.p. 113.5—115°.

Anal. $C_{15}H_{26}N_2O_7$ (346.38) calc'd.: C 52.01; H 7.57; N 8.09%
found: C 52.06; H 7.19; N 8.09%

IR-spectrum: 2.91 (*m*), 3.39 (*m*), 3.91 (*m*), 4.59 (*w*), 5.78 (*s*), 5.95 (*s*), 6.02 (*s*), 6.15 (*s*), 6.41 (*s*), 7.14 (*s*), 8.00 (*s*), 10.9 (*w*), 11.6 (*w*) μ.

2-Carboxamide-4,4-dicarbethoxy-N-ethylidenecyclohexylamine (III)

A mixture of diethyl-4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate (2 g., 7.06 mmole), ethanol (20 ml.) and moist Raney nickel (about 20 g.) was refluxed and stirred for three hours. The oil (1.8 g.) was isolated exactly as described above. It was dissolved in benzene and chromatographed on neutral alumina (activity III according to Brockmann) and eluted with benzene. The eluate on evaporation yielded 0.97 g. (43.8%) of crystalline isomer III. Further elution with chloroform and chloroform-methanol gave 0.406 g. of compound IV. For analysis isomer III was recrystallized from benzene-hexane as colorless plates, m.p. 114—115°.

Anal. $C_{15}H_{24}N_2O_5$ (312.36) calc'd.: C 57.67; H 7.74; N 8.97%
found: C 57.80; H 7.65; N 9.19%

UV-spectrum: λ_{max} 207.5 mμ, log ε 3.517. IR-spectrum: 3.1 (*w*), 3.39 (*w*), shoulder 5.78 (*s*), 5.81 (*s*), 6.04 (*s*), 6.71 (*w*), 6.92 (*w*), 8.03 (*s*), 8.44 (*m*), 8.60 (*m*), 9.15 (*m*), 9.76 (*w*), 11.6 (*w*) μ.

Compound IV was recrystallized from benzene-ether-hexane as colorless prisms, m.p. 140—142°.

UV-spectrum: λ_{max} 203.5 mμ, log ε 3.031 and shoulder λ 217 mμ, log ε 2.708. IR-spectrum: 2.97 (*m*), 3.39 (*w*), 3.55 (*w*), 5.75 (*s*), 5.85 (*s*), 5.99 (*s*), 6.90 (*w*), 7.95 (*s*), 8.26 (*s*), 9.05 (*m*), 9.76 (*m*), 11.7 (*w*), 12.6 (*w*) μ. It corresponds to *N*-ethyl cyclohexylamine.[3]

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IZVOD

4,5,6,7-Tetrahidroindazol-3-on karbonske kiseline. II. Reduktivno cijepanje do 2-karboksamid cikloheksilamina supstituiranih u prstenu

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Opisana je sinteza dietil-4,5,6,7-tetrahidroindazol-3-on-5,5-dikarboksilata (I) kao i njegovo reduktivno cijepanje u 2-karboksamid-4,4-dikarbetoksi-cikloheksilamin (II). Tvar je karakterizirana kao hidroklorid i acetat. Hidrogenoliza -N-N- veza dietil--4,5,6,7-tetrahidroindazol-3-on dikarboksilata kao i daljnja redukcija najvjerojatnijeg intermedijarnoga ketimina posebna je značajka ove sinteze u *izo*-propanolu ili metanolu pored Raney nikla kao katalizatora. Redukcija u etanolu daje 2-karboksamid--4,4-dikarbetoksi-N-etilidencikloheksilamin (Schiffovu bazu) (III).

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