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

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Received May 10, 1963 

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-aminopyra-
zine-3-carboxamide\(^2\) with the reductive opening of pyrazolo-ring. In addition 
to the reductive opening of the heterocyclic ring of indazolone (I) the pre-
paration of alicyclic compound II includes also another reductive step over 
the most probable intermediary ketimine.

The hydrogenolysis in iso-propanol and methanol of I yielded one of 
the two possible diastereoisomeric amines in crystalline form, m.p. 137\(^0\), cha-
recterized 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-\(N\)-ethylidene
cyclohexylamine (Schiff base) III, m.p. 115\(^0\) besides compound IV, m.p. 142\(^0\), as 
well as the conversion of crystalline amine II into stereoisomeric Schiff base
III by a direct treatment with acetaldehyde 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 \(\beta\)-alanine and an ester of \(\beta\)-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 (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°.

**Analytical**

C13H18N2O5 (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:** \(\lambda_{\text{max}} 204.5 \, \text{m}\mu, \log \varepsilon 3.639; 251 \, \text{m}\mu, \log \varepsilon 3.669\) and shoulder \(\lambda 232 \, \text{m}\mu, \log \varepsilon 3.532; \lambda_{\text{min}} 219 \, \text{m}\mu, \log \varepsilon 3.474.\) 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 (about 2.5 g.) was refluxed with swirling for two and a half hours. The 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°.

**Analytical**

C13H22N2O5 (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 5·10⁻² mm Hg:

found: C 54.30; H 7.51\%.

**UV-spectrum:** \(\lambda_{\text{max}} 203 \, \text{m}\mu, \log \varepsilon 2.915 \) and shoulder \(\lambda 213.5 \, \text{m}\mu, \log \varepsilon 2.654.\) IR-spectrum: 3.03 (m), 5.58 (s), 6.02 (s), 6.33 (w), 6.95 (m), 7.85 (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 (0.54 g.). It crystallized from chloroform-ether-hexane to give 0.18 g. (35.5\%) of colorless plates with m.p. underpressed 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_{12}ClN_{2}O_{5} (322.78) calc'd.: C 48.37; H 7.18; N 8.68°/o
found: C 48.44; H 6.79; N 8.55°/o

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 (w), 11.7 (w), 11.9 (vw)µ.

Hydroacetate. — 2-Carboxamide-4,4-dicarbethoxy-cyclohexylamine was dissolved in 100/o 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_{2}O_{7} (346.38) calc'd.: C 52.01; H 7.57; N 8.09°/o
found: C 52.06; H 7.19; N 8.09°/o

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°/o) 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_{2}O_{5} (312.36) calc'd.: C 57.67; H 7.74; N 8.97°/o
found: C 57.80; H 7.65; N 9.19°/o

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

Acknowledgment. We acknowledge with thanks our indebtedness to Mrs. J. Zake, Mrs. E. Galogaza and Mrs. O. Hadžija for the microanalyses and to Mrs. A. Poturic for technical assistance.

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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 intermediarnoga 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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