CCA-313

547.779:542.941.7:541.63

Original Scientific Paper

4,5,6,7-Tetrahydroindazol-3-one Carboxylic Acids. III. Reductive Cleavage Related to Conformational Analysis of 2-Carboxamide-4,4-dicarbethoxy-cyclohexylamine

Đ. Škarić, V. Škarić, and V. Turjak-Zebić

Institute »Ruđer Bošković«, Zagreb, Croatia, Yugoslavia

Received November 1, 1963

2-Carboxamide-4,4-dicarbethoxy-cyclohexylamine (II) with axial amino group satisfied the necessary geometrical requirement of coplanarity in an elimination reaction with nitrous acid yielding mostly cyclohexene derivatives.

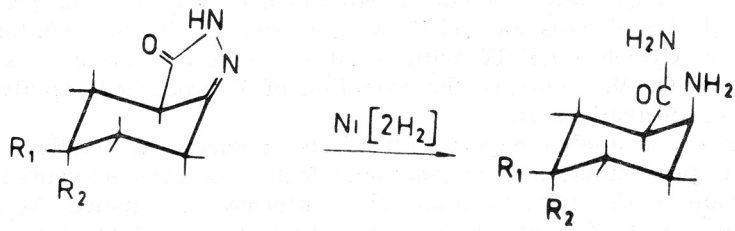
The conformational analysis of cyclohexylamine II provided the evidence for the stereoselectivity of the Raney nickel-catalyst as well as for stereospecific reductive opening of diethyl 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate (I).

The reductive cleavage of I using Raney nickel-catalyst in ethanol yielded the Schiff base VI besides 2-carboxamide-4,4-dicarbethoxy-N-ethylcyclohexylamine (VII). The conformations of VI and VII were interrelated to that of cyclohexylamine II.

The properties and synthesis of 4,5,6,7-tetrahydroindazol-3-one-5-carboxylic acid (IX) and its ethylester VIII are described.

The potentiometric titrations, UV and IR absoption spectra were recorded.

It has been shown recently (*vide* part II)[1] that reductive cleavage of diethyl 4,5,6,7-tetrahydroindazol-3-one-5,5-dicarboxylate using Raney nickel-catalyst in *iso*-propanol or methanol produced 2-carboxamide-4,4-dicarbethoxy-cyclohexylamine (II). The present investigation was concerned, *inter alia*, with the conformation of cyclohexylamine II and its relationship to the steric course of reductive opening.



I. $R_1 = R_2 = COOEt$

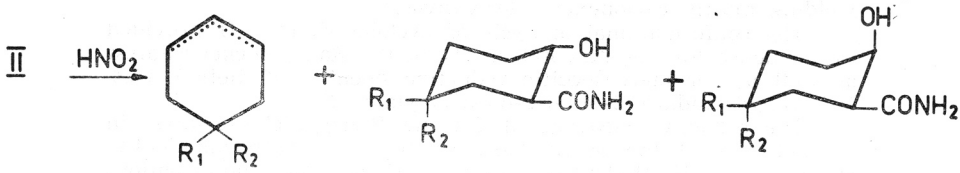
II. $R_1 = R_2 = COOEt$

VIII. $R_1 = COOEt$, $R_2 = H$

IX. $R_1 = COOH$, $R_2 = H$

The conversions of equatorial and axial alicyclic amines by nitrous acid into cyclohexanols and cyclohexenes, respectively, demonstrated by Mills[2], Dauben[3,4] and Barton[5] are conformationally controled. Namely, equatorial amines were converted into alcohols with retention of configuration in ~ 100% yield, while axial amines yielded mostly olefins (~ 50—70%) aside with a mixture of alcohols in which the less hindered, equatorial, isomer predominated. Although these facts were observed on more rigid bicyclic sistems we found the same conformational pathway on monocyclohexylamine II. The stereospecificity was preserved because the bulky functional groups forced the cyclohexane ring into one selected conformation.

The treatment of cyclohexylamine II with nitrous acid afforded three products: a) cyclohexenes III (an oil, pressumably composed from 3-carboxamide-5,5-dicarbethoxycyclohexene and 2-carboxamide-4,4-dicarbethoxycyclohexene) in 50% over-all yield, b) 2-carboxamide-4,4-dicarbethoxy-cyclohexanol IV (m. p. 156°) in 30% yield and c) isomeric cyclohexanol V (m. p. 120°) in the poorest (20%) yield.



III IV V

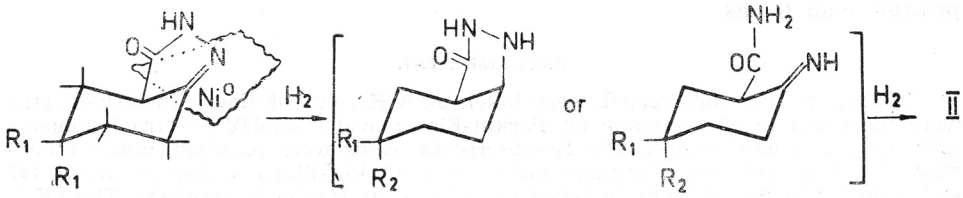
$R_1 = R_2 = COOEt$

The main product III, most probably a mixture of carboxamidocyclohexenes, showed in UV a broad band with λ_{max} at 211 mμ ($\log \varepsilon$ 3.487). The stereoisomers IV and V were closely similar in IR, except in the 5.78—6.32 μ region and near to 10.0 μ. The preponderanting *trans*-[(*e*)-OH, (*e*)-$COHN_2$]--stereoisomer IV revealed the band-splittings in those regions. The *cis*-isomer V had an additional band at 6.32 μ, pressumably due to a free -$COHN_2$ group. As it was expected the UV spectra of IV (λ_{max} 202.5 m μ, $\log \varepsilon$ 2.903; shoulder λ 212 m μ, $\log \varepsilon$ 2.721) and V (λ_{max} 202 m μ, $\log \varepsilon$ 2.944; shoulder λ 213.5, $\log \varepsilon$ 2.632) resembled to the UV spectrum of cyclohexylamine II (λ_{max} 203 m μ, $\log \varepsilon$ 2.915; shoulder λ 213.5 m μ, $\log \varepsilon$ 2.654). The pK_a's values for *trans*- (11.4) and *cis*-isomer (11.17) were consistent with their conformational relationship. Cyclohexanol IV with equatorial hydroxyl group was resistent to oxidation. On the contrary the oxidation of V proceeded rapidly yielding cyclohexene derivatives III.

Using the available experimental facts it was then relatively easy to deduce the predominating conformational feature of cyclohexylamine II with amino group in the axial position. The conformation satisfied the criterions for deamination having planar four-centered transition states. The equatorial carboxamido group of II resulted from the sequence of the reductive opening assuming the more stable chair conformation for the cyclohexane ring.

The reductive cleavage of indazolone I, yielding 65% of cyclohexylamine II indicated that the hydrogenolysis had proceeded stereospecifically. The

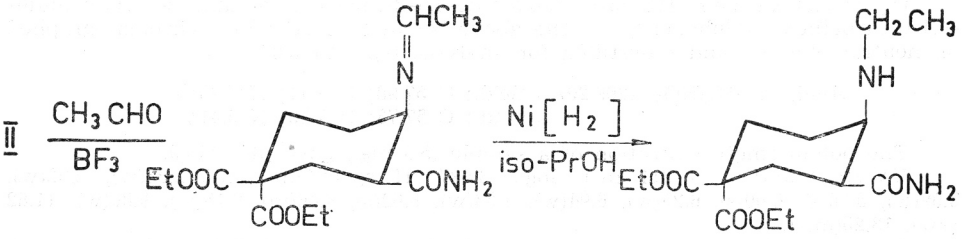
surface of the Raney nickel-catalyst with its *d*-bond vacancy has the affinity for negative elements and π-electrons of unsaturated linkage[6,7]. Thus, the consequent adsorption of the catalyst to the less hindered side, as illustrated in the conformational drawing, permitted the formation of intermediary bicyclic *cis*-fused system A as well as monocyclic ketimine B. However, in case B the hydrogenation would follow the analogous stereospecific pathway after the cleavage of -*N*-*N*- bond had occured. In spite of a hydrogenolysis--cleavage competition the over-all product seemed to be the same. We hope to ascertain this intermediary peculiarities in a forthcomming investigation.



I A B

$R_1 = R_2 = COOEt$

In an earlier paper[1] from this laboratory the reductive opening of indazolone I in ethanol was reported. Besides 2-carboxamide-4,4-dicarbethoxy-*N*--ethylidenecyclohexylamine (Schiff base) VI a by-product, m. p. 142°, was isolated. The same compound was obtained from catalytic hydrogenation of Schiff base VI in *iso*-propanol. It indicated clearly the presence of 2-carboxamide-4,4-dicarbethoxy-*N*-ethylcyclohexylamine (VII) in the products of reductive cleavage in ethanol. The conformation of Schiff base VI was that observed for cyclohexylamine II. Namely, the same base VI was smoothly prepared from II in reaction with acetaldehyde using boron fluoride-etherate as catalyst[8].



VI VII

In connection with our investigations and interest for indazolone-type compounds[9] as sequestering agents the synthesis and properties of ethyl 4,5,6,7-tetrahydroindazol-3-one-5-carboxylate (VIII) from diethyl cyclohexanone-2,4-dicarboxylate and hydrazine-hydrate was described. The hydrolysis of monoester VIII in 10% hydrochloric acid gave rise to 4,5,6,7-tetrahydroindazol-3-one-5-carboxylic acid (IX) with, as expected, the equatorial carboxy group in predominance. An interesting feature of diester I was the direct iso-

lation of monocarboxylic acid IX after I had been treated with hydrochloric acid only. This behaviour of I was in discrepancy with the results reported for the hydrolysis of analogous diethyl 2-phenyl-4,5,6,7-tetrahydroindazol-3--one-5,5-dicarboxylate[9] where the dicarboxylic acid under the same conditions separated in good yield. Such immediate decarboxylation of I followed the same steric pathway as described for the phenyl-derivative yielding a monocarboxylic acid identical to compound IX.

In comparison with phenyl derivatives[9] the curves of potentiometric titrations for indazolone I, VIII and IX showed more extended inflexions if enolization had taken place. This is in agreement with the existence of two possible enol forms.

EXPERIMENTAL

Melting points, uncorrected, were taken on a Kofler hot stage. The UV-spectra were measured in 95% ethanol on Perkin-Elmer model 137-UV spectrophotometer with automatic gain control. The IR-absorption bands were recorded, unless otherwise stated, in potassium bromide plates on a Perkin-Elmer Infracord model 137 and reported in wavelengths followed by relative intensities in brackets. The pK_a's values were determined by potentiometric micro-titrations in dioxane-water (1 : 3), with 0.10155 *N* solution of sodium hydroxide. The *p*H values were not corrected.

Reaction of 2-Carboxamide-4,4-dicarbethoxy-cyclohexylamine with Nitrous Acid

To a solution of 2-carboxamide-4,4-dicarbethoxy-cyclohexylamine hydroacetate (0.27 g., 0.8 mmole) in 10% acetic acid (0.7 ml.) sodium nitrite (0.08 g., 1.17 mmole) dissolved in water (0.5 ml.) was added. The mixture was left for 15 minutes at room temperature. It was warmed on the water bath for an additional 90 minutes, cooled, evaporated at the water pump to a syrup, diluted with water and extracted with chloroform. The chloroform extract was washed, dried and evaporated to an oil. It crystallized when ether was added as isomer IV (*vide, infra*), m.p. 152—156°, yield 60 mg. (30%). The mother liquor was evaporated to dryness. The residue (140 mg.) was redissolved in benzene, chromatographed on neutral alumina (activity III, according to Brockmann) and eluted with benzene-chloroform (1 : 1). The eluate on evaporation yielded 100 mg. (50%) of oily cyclohexenes III (*vide infra*). Further elution with chloroform gave 40 mg. (20%) of crystalline isomer V, m. p. 114—116°. (The percentages were based upon the sum of products).

Cyclohexenes III (3-carboxamide-5,5-dicarbethoxy- and 2-carboxamide--4,4-dicarbethoxycyclohexene). — The above isolated oil III was rechromatographed on neutral alumina and redestilled for analysis, b.p. 145°/0.05 mm.

Anal. $C_{13}H_{19}NO_5$ (269.29) calc'd.: C 57.98; H 7.11; N 5.20%
found : C 57.73; H 7.29; N 5.41%

The potentiometric titration of a sample (5.8 mg.) gave pK_a 11.39.

UV-spectrum: λ_{max} 211 mμ, log ε 3.487. IR-spectrum (oil): 2.83(w), 2.92(w), 3.09(w), 5.80(s), 6.00(s), 6.25(w), 6.94(w), 7.33(w), 8.02(s), 8.46(m), 9.15(w), 9.80(w), 11.62 (vw), 13.25(m) μ.

A careful chromatography on neutral alumina separated two oily fractions, roughly in same quantities, with UV and IR-spectra practically superimposable.

trans-2-Carboxamide-(4,4-dicarbethoxy)-cyclohexanol (IV) — The first crystalline component, m. p. 154—156°, separated in the reaction with nitrous acid, recrystallized from chloroform-ether-hexane as the analytical sample, m. p. 156—157° (colorless prisms).

Anal. $C_{13}H_{21}NO_6$ (287.31) calc'd.: C 54.34; H 7.37; N 4.88%
found : C 54.08; H 7.24; N 4.88%

The potentiometric titration of a sample (4.7 mg.) gave pK_a 11.42.

UV-spectrum: λ_{max} 202.5 mμ, log ε 2.903 and shoulder λ 212 mμ, log ε 2.721.

IR-spectrum: 2.93(s), 3.10(s), 3.39(w), 5.78(s), 5.85(s), 6.00(s), 6.19(s), 6.97(s), 7.24(m), 7.44(m), 7.62(w), 7.75(m), 7.87(s), 8.08(s), 8.17(s), 8.48(s), 8.55(s), 8.91(s), 9.27(s), 9.41(m), 9.88(s), 10.64(vw), 10.89(w), 11.58(w), 11.67(w) μ.

When a sample (20 mg.) was treated with chromic acid-pyridine complex (*Sarett's* method) or with chromic acid (10 mg.) in acetic acid (1 ml.) crystals separated with m. p. undepressed on admixture with starting material. Their IR-spectra were superimposable.

Another sample (30 mg.) in ethanol (10 ml.) was subjected to hydrogenation in the presence of platinum oxide under pressure of 60 *psi* for 3 hours. The starting material was reisolated quantitatively.

cis-2-Carboxamide-(4,4-dicarbethoxy)-cyclohexanol (V) — The second crystalline fraction, m. p. 114—116°, from the reaction with nitrous acid, recrystallized from benzene-hexane as the analytical sample, m. p. 120° (colorless prisms).

Anal. $C_{13}H_{21}NO_6$ (287.31) calc'd.: C 54.34; H 7.37; N 4.88%
found : C 54.25; H 7.42; N 5.09%

The potentiometric titration of a sample (4.5 mg.) gave pK_a 11.17.

UV-spectrum: λ_{max} 202 mμ, log ε 2.944 and shoulder λ 213.5 mμ, log ε 2.632. IR-spectrum: 2.92(s), 3.12(m), 3.39(m), 5.83(s), 6.12(s), 6.35(m), 6.95(m), 7.16(s), 7.36(m) 7.47(w), 7.63(m), 7.75(s), 7.88(s), 8.10(s), 8.25(s), 8.53(s), 8.95(s), 9.21(m), 9.41(s), 9.58(m), 9.76(s), 10.07(w), 10.60(w), 10.97(vw), 11.55(m) μ.

A sample (11 mg.) was treated with chromic acid (5 mg.) in acetic acid (0.5 ml.) for 2 hours. An oil separated. Its IR-spectrum was superimposable on that of cyclohexenes III.

cis-2-Carboxamide-(4,4-dicarbethoxy)-N-ethylidenecyclohexylamine (VI)

To a solution of 2-carboxamide-4,4-dicarbethoxy-cyclohexylamine II (0.2 g., 0.7 mmole) in chloroform (5 ml.) acetaldehyde (0.053 g., 1.2 mmole), ethanol (0.2 ml.) and boron fluoride-etherate (0.02 ml.) were added. The mixture was refluxed for 15 minutes and then evaporated at the water pump to an oil. The residue was dissolved in chloroform and washed with 5% sodium carbonate solution and water. Chloroform layer on evaporation yielded 0.2 g. (91.5%) of an oil which crystallized on standing. For analysis it was recrystallized from benzene-hexane as colorless plates, m. p. 113—114°, undepressed on admixture with sample obtained from reductive cleavage of indazolone I in ethanol[1] IR-spectra of both samples were superimposable.

Anal. $C_{15}H_{24}N_2O_5$ (312.36) calc'd.: C 57.67; H 7.74%
found : C 57.93; H 7.47%

cis-2-Carboxamide-(4,4-dicarbethoxy)-N-ethylcyclohexylamine (VII)

A mixture of *cis*-2-carboxamide-(4,4-dicarbethoxy)-N-ethylidenecyclohexylamine (VI) (100 mg., 0.4 mmole), iso-propanol (10 ml.) and moist Raney nickel (~ 0.5 g.) was refluxed and stirred for 5 hours. The hot filtration and filtrate's evaporation at the water pump yielded 70 mg. (69%) of crystals. For analysis it was recrystallized from benzene-hexane, m. p. 138—140°, as colorless prisms, undepressed on admixture with the by-product obtained from reductive cleavage of indazolone I in ethanol[1]. IR-spectra of both samples were superimposable.

Anal. $C_{15}H_{26}N_2O_5$ (314.37) calc'd.: C 57.31; H 8.34%
found : C 57.32; H 8.31%

Ethyl 4,5,6,7-tetrahydroindazol-3-one-5-carboxylate (VIII)

To a solution of diethyl cyclohexanone-2,4-dicarboxylate[10] (2 g., 8.26 mmole) in 50% ethanol (15 ml.) hydrazine-hydrate (0.43 g., 8.5 mmole) was added and refluxed for 18 hours. On cooling crystalline product separated, filtered off and washed with ether. Yield 1.7 g. (97%), m. p. 212—215°. For analysis it was recrystallized from ethanol-water (1 : 2) as plates, m. p. 215—216.5°.

Anal. $C_{10}H_{14}N_2O_3$ (210.23) calc'd.: C 57.13; H 6.71; N 13.33%
found : C 57.16; H 6.36; N 13.34%

Neutralization equivalent in dioxane-water (1 : 1) by potentiometric titration with 0.1012 *N* solution of sodium hydroxide calc'd.: 210.2; found: 212.6.

UV-spectrum: λ_{max} 205 m μ, log ε 3.602; 250.5 m μ, log ε 3.744; λ_{min} 217 m μ, log ε 3.440. IR-spectrum: 2.84(w), 3.38(s), 3.50(s), 3.74(s), 5.81(s), 6.33(s), 6.48(m), 6.64(m), 7.22(s), 7.29(s), 7.79(m), 7.95(m), 8.08(m), 8.49(s), 9.23(s), 9.74(m), 11.10(w), 12.43(s), 12.81(s), 13.96(m) μ.

4,5,6,7-Tetrahydroindazol-3-one-5-carboxylic acid (IX)

a). Hydrolysis of monoester VIII. — A solution of ethyl 4,5,6,7-tetrahydroindazol--3-one-5-carboxylate (0.5 g., 2.38 mmole) in 10% hydrochloric acid (15 ml.) was refluxed for 15 hours. After cooling it was evaporated to dryness at the water pump. The residue, as hydrochloride, was dissolved in redistilled water (250 ml.), passed through a column of Amberlite IR-4B (2.5 g.) and eluted with 0.1 *N* acetic acid (1000 ml.). The eluate collected and evaporated to dryness yielded 418 mg. (96.5%) of 4,5,6,7-tetrahydroindazol-3-one-5-carboxylic acid, m. p. 255—260°. Crystallization from water gave the analytical sample as colorless prisms, m. p. 262—263°.

Anal. $C_8H_{10}N_2O_3$ (182.18) calc'd.: C 52.74; H 5.53; N 15.38%
found : C 52.78; H 5.65; N 15.38%

Neutralization equivalents by potentiometric titration with 0.10117 *N* solution of sodium hydroxide calc'd.: 182.2 and 91.1; found: 180.7 and 90.4.

UV-spectrum: λλ_{max} 206 m μ, log ε 3.566; 251 m μ, log ε 3.744; λ_{min} 217 m μ, log ε 3.433. IR-spectrum: 2.73(w), 2.91(m), 3.50(m), 4.39(w), 5.30(w), 5.97(s), 6.37(s), 6.65(m), 7.06(m), 7.42(w), 7.61(w), 7.75(m), 8.09(s), 8.32(m), 10.22(w), 12.32(m), 13.27(m) μ.

b) Simultaneous hydrolysis and decarboxylation of diester I. — Diethyl 4,5,6, 7-tetrahydroindazol-3-one-5,5-dicarboxylate (3 g., 10.8 mmole) was treated with 10% hydrochloric acid (90 ml.) and refluxed for 15 hours. The product was isolated after had been passed through a column of Amberlite IR-4B (15 g.), as described above. Yield 1.8 g. (86%), m. p. 256—258°. Crystallization from water gave the analytical sample as colorless prisms, m. p. 261—262°, undepressed on admixture with the sample obtained from monoester VIII. IR-spectra of both samples were superimposable.

Anal. $C_8H_{10}N_2O_3$ (182.18) calc'd.: C 52.74; H 5.53; N 15.38%
found : C 52.94; H 5.70; N 15.56%

Acknowledgment. We thank Mrs. J. Zake, Mrs. E. Galogaža, and Mrs. O. Hadžija for the microanalyses and Mrs. A. Poturić for technical assistance.

REFERENCES

1. Đ. Škarić, V. Škarić, and V. Turjak-Zebić, *Croat. Chem. Acta* **35** (1963) 143.
2. J. A. Mills, *J. Chem. Soc* **1953**, 260.
3. W. G. Dauben, R. C. Tweit, and C. H. Mannerskantz, *J. Am. Chem. Soc.* **76** (1954) 4420.
4. W. G. Dauben, R. C. Tweit, and R .L. MacLean, *J. Am. Chem. Soc.* **77** (1955) 48.
5. D. H. R. Barton and R C. Cookson, *Quart. Rev.* **10** (1956) 44.
6. S. Mitsui and S. Imaizumi, *Bull. Chem. Soc. Japan* **34** (1961) 744.
7. S. Mitsui, Y. Senda, and K. Konno, *Chem. and Ind.* **32** (1963) 1354.
8. M. E. Taylor and T. L. Fletcher, *J. Org. Chem.* **26** (1961) 940.
9. Đ. Škarić, V. Škarić, V. Turjak-Zebić, and Z. Veksli, *Croat. Chem. Acta* **34** (1962) 75.
10. F. W. Kay and W. H. Perkin, *J. Chem. Soc.* **89** (1906) 1640.

IZVOD

4,5,6,7-Tetrahidroindazol-3-on karbonske kiseline. III. Konformacijska analiza 2-karboksamid-4,4-dikarbetoksi-cikloheksilamina u odnosu sa reduktivnim cijepanjem

Đ. Škarić, V. Škarić i V. Turjak-Zebić

2-Karboksamid-4,4-dikarbetoksi-cikloheksilamin (II), kojem je amino grupa aksialna, zadovoljava uvjete prelaznih stanja sa 4 centra u ravnini. To potvrđuje reakcija eliminacije s dušičnatom kiselinom kao i iz toga izolirani cikloheksen derivati. Diastereoizomerni par odgovarajućih cikloheksanola IV i V, kao produkti supstitucije, nastaju u manjim iskorištenjima.

Konformacijska analiza cikloheksilamina II daje dokaze za stereoselektivnost Raney nikla kao katalizatora, kao i za stereospecifičnost reduktivnoga cijepanja dietil 4,5,6,7-tetrahidroindazol-3-on-5,5-dikarboksilata (I).

Reduktivno cijepanje tvari I u etanolu daje Schiffovu bazu VI pored 2-karboksamid-4,4-dikarbetoksi-N-etilcikloheksilamina (VII). Obrađeni su njihovi konformacijski odnosi sa cikloheksilaminom II.

Opisana su svojstva i sinteze 4,5,6,7-tetrahidroindazol-3-on-5-karbonske kiseline (IX) i njena estera VIII.

Priloženi su podaci o potenciometrijskim titracijama, ultraljubičastim i infracrvenim apsorpcionim spektrima.

INSTITUT »RUĐER BOŠKOVIĆ«
ZAGREB

Primljeno 1. studenoga 1963