Reactions of Alicyclic Aminonitrile

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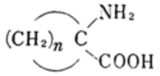
α-Aminonitriles are generally unstable and directly hydrolyzed to the corresponding amino acids commonly without their isolation in Strecker's synthesis.



I: $n=5$
I': $n=4$

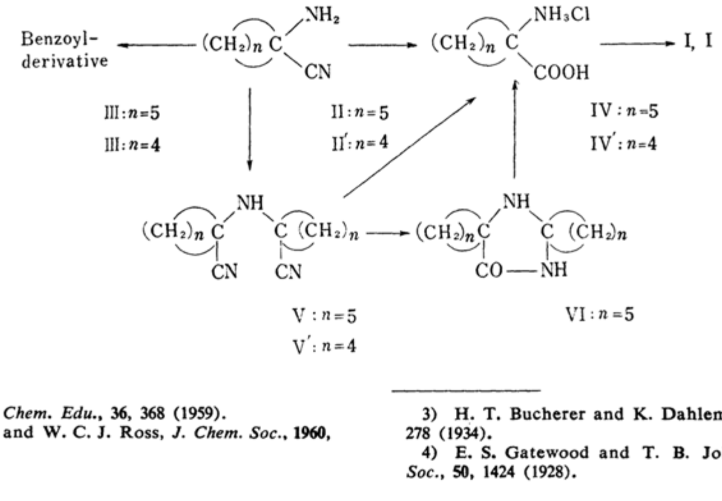
In an attempted synthesis of alicyclic amino acids I, I', some of which have been known as physiologically interesting substances[1,2], the authors found some characteristic reactions of alicyclic aminonitriles.

1-Aminocyclohexylonitrile (II) could be isolated only as an oily product by ether extraction from the reaction mixture of cyclohexanone, potassium cyanide and ammonium chloride, and this aminonitrile was characterized by the quantitative conversion into its benzoyl-derivative III and by hydrolysis to 1-aminocyclohexanecarboxylic acid (I).

This oily 1-aminocyclohexylonitrile (II) was, however, solidified after being kept at room temperature for a few weeks or heating under reduced pressure for a few hours giving a crystalline substance (m. p. 138°C). This substance was confirmed by elemental analysis and infrared spectrum to be 1, 1'-imino-dicyclohexylonitrile (V) and seemed to be identical with the compound, which Bucherer[3] isolated as a by-products in a rather low yield from the reaction mixture of aminonitrile and carbon dioxide. V was also hydrolyzed with concentrated hydrochloric acid giving I.

While, II was softly hydrolyzed in the presence of sodium hydroxide in the ethanol solution to give the compound of formula $C_{13}H_{22}ON_2$, which melted at 213°C. This compound was confirmed to be 2, 4-dicyclohexyliminazolidone-(5) (VI) by elemental analysis and infrared spectrum, which showed strong absorption bands at 3280 cm^{-1} (–NH–) and at 1710 cm^{-1} (ring forming amide), and then no band at 1500~1600 cm^{-1} region (free amide). Analogous to 2, 4-dicyclohexyl-5-thiaiminazolidone which was prepared by Gatewood[4] from α-aminonitrile and hydrogen sulfide, formation of VI was thought to proceed through the intermediate of V by the fact that V was similarly treated giving the same product VI. In addition, the structure VI may be explained by the following equation, because VI gave equimolecular I and ammonium chloride on heating with concentrated hydrochloric acid.

Moreover, V was allowed to stand with concentrated sulfuric acid at room temperature giving 1, 1'-iminodicyclohexanecarboximide sulfate (VII), which was neutralized yielding 1, 1'-iminodicyclohexanecarboximide (VIII). VIII was heated in 10% sodium hydroxide solution to give mono-amide IX, which was cyclized again to imide salt with



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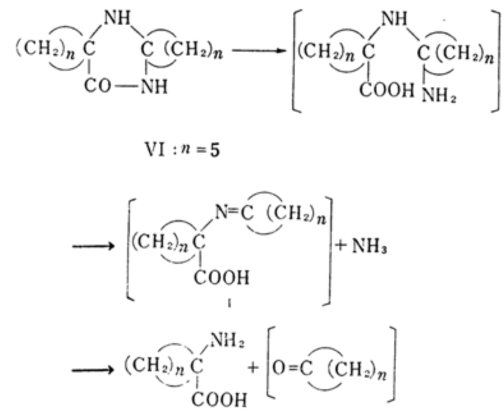
[1] R. B. Ross, *J. Chem. Edu.*, 36, 368 (1959).

[2] T. A. Connors and W. C. J. Ross, *J. Chem. Soc.*, **1960**, 2119.

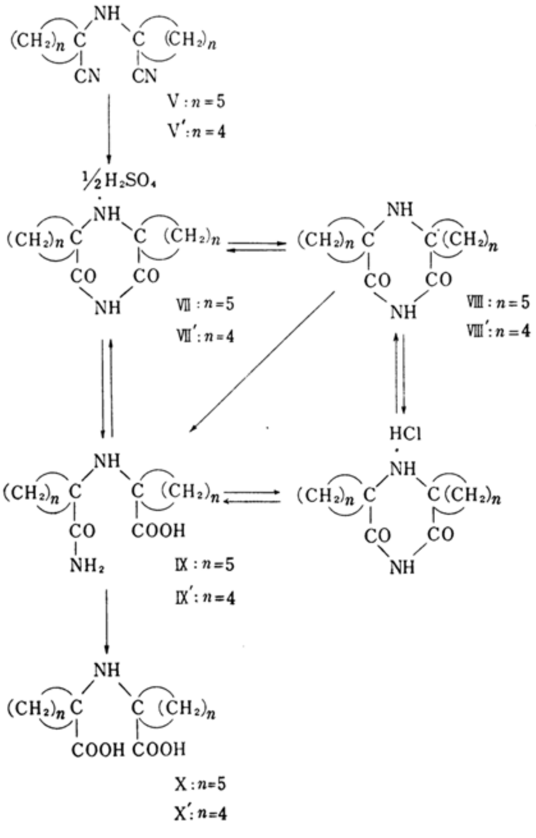
[3] H. T. Bucherer and K. Dahlem, *J. prakt. Chem.*, **140**, 278 (1934).

[4] E. S. Gatewood and T. B. Johnson, *J. Am. Chem. Soc.*, **50**, 1424 (1928).


VI : $n=5$

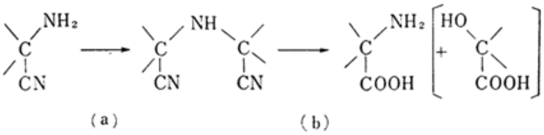
mineral acid, but was heated for a long time (16 hr.), giving 1, 1′-iminodicyclohexanecarboxylic acid (X).

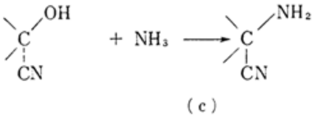
This synthetic schema was also repeated beginning with cyclopentane derivatives, which involved physiologically interesting compounds²⁾, 1-aminocyclopentanecarboxylic acid (I′) and 1, 1′-iminodicyclopentanecarboxylic acid (X′). 1, 1′-Iminodicyclopentylonitrile (V′) was similarly prepared from 1-aminocyclopentylonitrile (II′) but in a rather low yield.

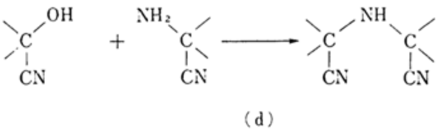


V : $n=5$
V′ : $n=4$
VII : $n=5$
VII′ : $n=4$
VIII : $n=5$
VIII′ : $n=4$
IX : $n=5$
IX′ : $n=4$
X : $n=5$
X′ : $n=4$

In view of above results, it is very interesting that imino-dinitrile was synthesized easily from aminonitrile and was hydrolyzed to amino acid as following equations a and b. In addition, aminonitrile can be prepared from hydroxynitrile (Eq. c)⁵⁾ and imino-dinitrile from hydroxynitrile and aminonitrile (Eq. d)⁶⁾.

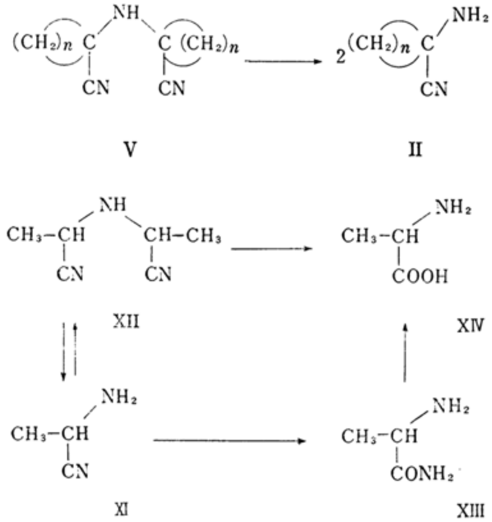

(a) (b)


(c)


(d)

In this consideration, it was desirable to investigate the behavior of ammonolysis of iminodinitrile. In fact, it was discovered that 1, 1′-iminodicyclohexylonitrile (V) was heated with aqueous ammonia in a sealed tube giving 2 mol. of 1-aminocyclohexylonitrile (II), which was confirmed by conversion into its benzoyl-derivative.

Further experiments were tried in order to acertain that aliphatic iminodinitrile could be converted into α-aminonitrile. α, α'-Iminodipropionitrile (XII) was similarly treated


V II
XII XIV
XI XIII

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5) H. T. Bucherer and H. Barsch, *J. prakt. Chem.*, **140**, 79 (1934).

6) J. V. Dubsky, *Ber.*, **49**, 1045 (1916).

TABLE I

Substance	Amino-nitrile yield %	Hydro-chloride m. p. °C	Benzoyl-deriv. M. p. °C	Benzoyl-deriv. Yield %	Amino-acid hydrochloride M. p. °C	Amino-acid hydrochloride Yield %	Amino acid M. p. °C	Amino acid Yield %
Cyclohexane	80~90	190[a]	139[b]	95	298[c] decomp.	75	320[d] decomp.	65
Cyclopentane	70	174	129[e]	90	274[f] decomp.	72	330[g] subli.	60

a) Found: N, 17.34. Calcd. for $C_7H_{13}N_2Cl$: N, 17.40.
b) Found: N, 12.55. Calcd. for $C_{14}H_{16}ON_2$: N, 12.27.
c) Found: N, 7.78. Calcd. for $C_7H_{14}O_2NCl$: N, 7.82.
d) Found: N, 9.66. Calcd. for $C_7H_{13}O_2N$: N, 9.78.
e) Found: N, 13.13. Calcd. for $C_{13}H_{14}ON_2$: N, 13.08.
f) Found: N, 8.34. Calcd. for $C_6H_{12}O_2NCl$: N, 8.47.
g) Found: C, 49.24; H, 8.77; N, 9.79. Calcd. for $C_6H_{11}O_2N \cdot H_2O$: C, 48.96; H, 8.90; N, 9.59.

TABLE II

Substance	Iminodinitrile M. p. °C	Iminodinitrile Yield %	C Found	C Calcd.	H Found	H Calcd.	N Found	N Calcd.
Cyclohexane	138	80	72.60	72.68	9.28	9.15	18.12	18.17
Cyclopentane	52~53	25	71.05	70.90	8.52	8.43	20.66	20.67

(Analysis of iminodinitrile: C, H, N)

with aqueous ammonia giving 2 mol. of α-aminopropionitrile (XI), which was confirmed conversion into benzoyl derivative. In this case, the benzoyl derivative isolated was α-benzaminopropionic amide (XIII) which was hydrolyzed to DL-alanine (XIV) in good yield. XIII was also hydrolyzed with hydrochloric acid giving 1 mol. of XIV (90%) and was treated after ammonolysis giving 2 mol. of XIV (60%).

Experimental

Alicyclic Aminonitrile II, II′′. — Aminonitriles were prepared by Strecker's method[7] and extracted with ether. The ether solutions were dried with anhydrous sodium sulfate and gave a syrupy residue after removal of the solvent. These syrups were confirmed to be aminonitrile by conversion into benzoyl derivatives and α-amino acids. Benzoyl derivatives III, III′ were prepared by Schotten-Baumann's method. Aminonitriles were suspended in sodium bicarbonate solution and benzoyl chloride added under stirring. Precipitates were filtered off and recrystallized from ethanol-water giving prisms.

Alicyclic Amino Acid I, I′.—Aminonitriles were heated in ten times the volume of concentrated hydrochloric acid for 4 hr. The reaction mixtures were concentrated to half the volume and allowed to stand overnight. The precipitates of their hydrochloride IV, IV′ were collected and gave prisms by recrystallization (from water). These hydrochlorides were dissolved in a little water and neutralized with sodium bicarbonate. The precipitates were collected and recrystallized from ethanol-water. Colorless crystals were obtained. These data are summarized in Table I.

Alicyclic 1, 1′-Iminodinitriles (V), (V′).—Syrup of II or II′ was warmed for 5~6 hr. under reduced pressure and allowed to stand overnight at room temperature. Solidified compounds were collected and recrystallized from ethanol giving prisms. The infrared spectrum of V showed -C≡N band at 2260 cm^{-1} and -NH- band at 3380 cm^{-1}. These data were summarized in Table II.

Hydrolysis of V.—A solution of V (5 g.) in 50 ml. of concentrated hydrochloric acid was heated for 4 hr. The reaction mixture was concentrated to 10 ml. volume and allowed to stand at room temperature. Two grams of precipitates was collected. This product was identical to IV.

2, 4-Dicyclohexyliminazolidon-(5) (VI). — To a solution of II (2 g.) in 10 ml. of ethanol was added 2 ml. of 10% sodium hydroxide solution. The mixture was refluxed on a water-bath for 6 hr. and allowed to stand overnight at room temperature. The precipitates were collected and recrystallized from ethanol giving 1 g. of colorless prisms, melted at 213°C.

Found: C, 70.27; H, 10.11; N, 12.51. Calcd. for $C_{13}H_{22}ON_2$: C, 70.23; H, 9.97; N, 12.60%.

Infrared spectrum of VI showed strong bands at 1710 cm^{-1} (-CONH-) and at 3280 cm^{-1} (-NH-). V was similarly treated to give the same product VI.

1, 1′ - Imino - dicyclohexanecarboximide Sulfate (VII).—V (5 g.) was dissolved in 30 ml. of concentrated sulfuric acid under cooling and allowed to stand overnight at room temperature. The mixture was added in ice-water and then gave precipitates. This product was collected and recrystallized from water giving 4 g. of crystals, melted at 273~274°C (decomp.).

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7) V. Zelinsky and G. Stadnikoff, ibid., 39, 1728 (1906).

Found: N, 9.40. Calcd. for $C_{14}H_{22}O_2N_2 \cdot 1/2 \cdot H_2SO_4$: N, 9.36%.

1,1'-Iminodicyclohexanecarboximide (VIII).—VII (2 g.) was dissolved in small water and neutralized with a solution of sodium bicarbonate. The precipitated product was collected and recrystallized from ethanol giving 1 g. of colorless crystals, melted at 164°C.

Found: C, 67.52; H, 8.71; N, 11.30. Calcd. for $C_{14}H_{22}O_2N_2$: C, 67.17; H, 8.86; N, 11.19%.

Hydrochloride of VIII.—A solution of VIII in hydrochloric acid was concentrated to give precipitates. The product was collected and recrystallized from ethanol-water giving colorless crystals, melted at 268°C (decomp.).

Found: N, 9.63. Calcd. for $C_{14}H_{22}O_2N_2 \cdot HCl$: N, 9.67%.

In a similar manner, a solution of VIII in sulfuric acid gave VII.

Mono-amide of 1,1'-Iminodicyclohexanecarboxylic Acid (IX).—Two grams of VIII was heated for 30 min. in 20 ml. of 10% sodium hydroxide solution. The mixture acidified with acetic acid to give precipitates. The product was collected and recrystallized from ethanol, giving 1.8 g. of colorless crystals, melted at 204°C (decomp.).

Found: C, 62.48; H, 8.84; N, 10.42. Calcd. for $C_{14}H_{24}O_3N_2$: C, 62.66; H, 9.02; N, 10.44%.

1,1'-Iminodicyclohexanecarboxylic Acid (X).—One gram of IX was heated with 10ml. of 10% sodium hydroxide solution for 10 hr. After cooling, the mixture was acidified with acetic acid to give precipitates. This product was collected and recrystallized from ethanol-water giving 0.4 g. of crystals, melted at 134°C. (decomp.).

Found: C, 62.31; H, 8.63; N, 5.50. Calcd. for $C_{14}H_{23}O_4N$: C, 62.43; H, 8.61; N, 5.20%.

1,1'-Iminodicyclopentanecarboximide Sulfate (VII').—Four grams of this sulfate from 5 g. of V' was obtained in a manner similar to VII and melted at 274∼275°C (decomp.)

Found: N, 10.78. Calcd. for $C_{12}H_{18}O_{12}N_2 \cdot 1/2H_2 \cdot SO_4$: N, 10.33%.

1,1'-Iminodicyclopentanecarboximide (VIII').—In a manner similar to VIII, 1.3 g. of this imide was obtained from 2 g. of VII' and melted at 146°C.

Found: C, 64.57; H, 8.05; N, 12.49. Calcd. for $C_{12}H_{18}O_2N_2$: C, 64.84; H, 8.39; N, 12.66%.

Mono-amide of 1,1'-Iminodicyclopentanecarboxylic Acid (IX).—In a manner similar to IX, 1.5 g. of IX' was obtained from 2 g. of VIII' and melted at 188∼181°C (decomp.).

Found: N, 11.25. Calcd. for $C_{12}H_{20}O_3N_2$: N, 11.66%.

1,1'-Iminodicyclopentanecarboxylic Acid (X).—IX' (1 g.) was heated in 10 ml. of 10% sodium hydroxide solution for 16 hr. The mixture was treated in a manner similar to X giving crystals (0.4 g.), which did not show clear melting point and sublimed at high temperature (above 200°C).

Found: C, 60.41; H, 8.36; N, 5.73. Calcd. for $C_{12}H_{19}O_4N$: C, 59.73; H, 7.94; N, 5.81%.

Ammonolysis of 1,1'-Iminodicyclophexylonitrile.—V (1 g.) was heated with 30 ml. of 28% aqueous ammonia in a sealed tube for 6 hr. The reaction mixture was extracted with ether. The ether solution was dried with anhydrous sodium sulfate and afforded syrupy residue after removal of the solvent and the syrup was confirmed by conversion into benzoyl derivative in a manner similar to III. 1.8 g. of crystals was obtained, (m. p. 138°C) and was identical to III. The melting point did not depress by mixing III.

α,α'-Iminodipropionitrile (XII).—This iminodinitrile was prepared from acetaldehyde by Dubsky's method[6], m. p. 66.5°C (reported m. p. 68°C).

Ammonolysis of α,α-Imino-dipropionitrile.—XII (6 g.) was treated with 28% aqeous ammonia in a manner described above. Oily syrup (crude 7 g.) was obtained. This syrup (1 g.) was converted into benzoylderivative (2 g.), which melted at 230∼231°C and was confirmed to be α-benzaminopropionic amide (XIII) by elemental analysis.

Found: C, 62.36; H, 6.36; N, 14.42. Calcd. for $C_{10}H_{12}O_2N_2$: C, 62.48; H, 6.29; N, 14.58%.

This amide (4 g.) was heated in 40 ml. of hydrochloric acid. The reaction mixture was concentrated to dryness. After removal of ammonium chloride, the ethanol solution was neutralized with aniline giving crystalline (3 g., m. p. 260°C (decomp.)), which was identical to DL-alanine (XIV).

Hydrolysis of XII with Hydrochloric Acid.—a) XII (5 g.) was heated in 50 ml. hydrochloric acid and treated in a manner described above giving crystals of XIV (3 g., 90% to 1 mol.).

b) XII (5 g.) was treated similarly after ammonolysis giving 4.2 g. of XIV (60% to 2 mol.).

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