# Electrolytic Decarboxylation of Quinuclidine-2-carboxylic Acid

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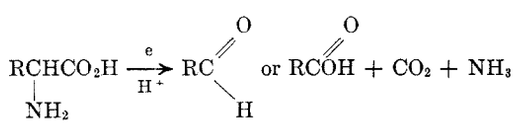
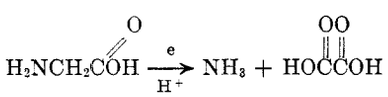
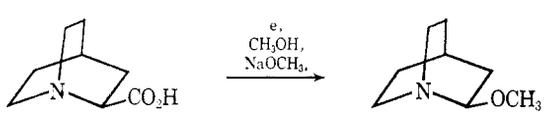
Although numerous examples of electrolytic decarboxylation have been reported for $\alpha$-amino acids,[2,3] practically all of these studies have been carried out in either sulfuric or nitric acid. All of these examples follow the same reaction pattern in that the amino acids lose carbon dioxide and ammonia and yield either aldehydes or acids as the remaining fragment.



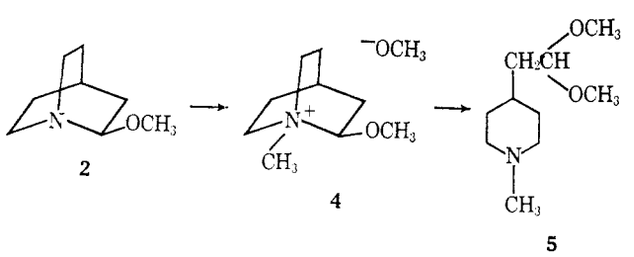
In the case of certain, simple amino acids, oxalic acid was also often isolated. In general, the yields in these reactions were very low.



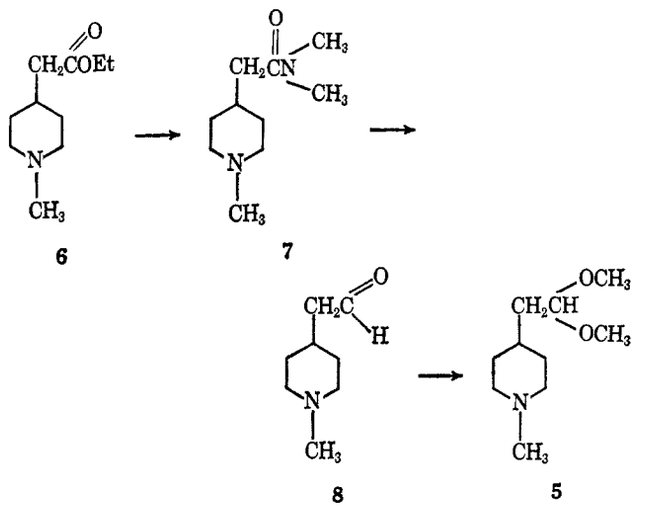
We wish to report the electrolysis of an amino acid under basic conditions. When 1-azabicyclo[2.2.2]-octane-2-carboxylic acid (**1**) was electrolyzed in basic solution, 2-methoxy-1-azabicyclo[2.2.2]octane (**2**) was obtained in 43% yield.



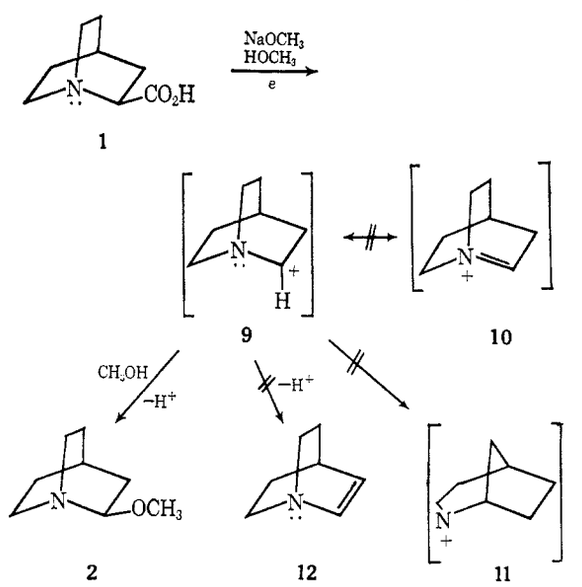
The structure of **2** was proven by Hofmann degradation coupled with synthesis of the degradation product. Conversion of **2** into the methiodide (**3**), followed by passage of a methanolic solution of **3** through Amberlite IR-A 400 ion-exchange resin, gave the syrupy quaternary methoxide (**4**). Pyrolysis of **4** gave a 92% yield of clear, colorless liquid which consisted of 85% of the acetal (**5**).



The degradation product (**5**) was synthesized from ethyl 2-(1-methyl-4-piperidyl)acetate (**6**) *via* conversion of **6** to the N,N-dimethylamide (**7**) followed by reduction of **7** to the aldehyde, **8**. The acid-catalyzed conversion of **8** to the acetal (**5**) with trimethyl orthoformate gave a sample of **5** which was identical in all respects with the acetal obtained from the pyrolysis of **4**.



The replacement of the carboxyl group by a methoxyl group has ample precedent in carbocyclic systems where this reaction most likely occurs *via* a carbonium ion process.[4] A similar reaction path for **1** would yield the carbonium ion, **9**. Owing to the bicyclic nature



of **9**, formation of **10** would not be expected to occur since Bredt's rule predicts that such a bridgehead double bond could not be formed. An alternate mode of reaction for **9** would be alkyl migration from nitrogen to carbon. Although alkyl migration from carbon to electron-deficient nitrogen is well documented,[5] alkyl migration from nitrogen to electron-deficient

(1) Esso Fellow, summer 1964; American Cyanamid Fellow, 1964–1965; Goodyear Foundation Fellow, 1965–1966.

(2) For references prior to 1910, see C. Neuberg, *Biochim. Z.*, **17**, 270 (1909); **24**, 152 (1910).

(3) F. Fichter and M. Schmid, *Helv. Chim. Acta*, **3**, 704 (1920); F. Fichter and F. Kuhn, *ibid.*, **7**, 167 (1924); Y. Takayama, *J. Chem. Soc. Japan*, **52**, 155, 188, 544, 765 (1931); **53**, 1197, 1205 (1932); **62**, 31 (1941); Y. Takayama, *Bull. Chem. Soc. Japan*, **8**, 125, 137, 173, 178, 189, 213 (1933); Y. Takayama, H. Matsusaka, and Y. Tsubuku, *ibid.*, **17**, 45 (1942); Y. Takayama, Y. Tsubuku, and T. Matsumato, *ibid.*, **17**, 53 (1942).

(4) For recent references to the generation of carbonium ions *via* electrolytic decarboxylation see (a) E. J. Corey, N. L. Bauld, R. T. LaLonde, J. Casanova, Jr., and E. T. Kaiser, *J. Am. Chem. Soc.*, **82**, 2645 (1960); (b) E. J. Corey and J. Casanova, Jr., *ibid.*, **85**, 165 (1963); (c) W. J. Koehl, Jr., *ibid.*, **86**, 4686 (1964); and (d) P. G. Gassman and F. V. Zalar, *ibid.*, **88**, 2252 (1966).

(5) For a recent example, see P. G. Gassman and B. L. Fox, *Chem. Commun.*, 153 (1966).

carbon would not be expected on the basis of electronegativity arguments.[6] Loss of a proton to yield **12** is another possibility. By comparison with carbocyclic systems, **12** would be expected to be at best a minor product. Indeed, no evidence was found which would indicate the presence of **12**. Thus, the most probable route for **9** to follow would be reaction with solvent to yield **10**.

### Experimental Section

**1-Azabicyclo[2.2.2]octane-2-carboxylic Acid (Quinuclidine-2-carboxylic Acid) (1).**—2-Carbethoxyquinuclidine, prepared by the method of Braschler, Grob, and Kaiser,[7] was refluxed in 6 *N* hydrochloric acid for 8 hr. Evaporation of the solvent yielded the amino acid hydrochloride as a white powder which darkened at 295° but failed to melt at 300° (lit.[8] 292–294°, decomposition). An aqueous solution of 3.0 g of the amino acid hydrochloride was passed through a column of Amberlite IR-4B ion-exchange resin. The eluent was evaporated to dryness on a rotary evaporator and the yellow, crystalline residue was dissolved in absolute ethanol, boiled briefly with charcoal, filtered, and concentrated to dryness. The residual white powder was recrystallized from absolute ethanol–petroleum ether (bp 60–70°) to give 2.26 g (93%) of quinuclidine-2-carboxylic acid as a white, amorphous powder melting at 265–280° dec (lit. mp 276–278° dec,[8a] 280° dec[9]).

**Electrolysis of Quinuclidine-2-carboxylic Acid.**—A 1-l. flask was equipped with a reflux condenser, constant-pressure dropping funnel, gas inlet tube, and smooth, platinum electrodes.[10] Anhydrous methanol (500 ml) was added and the system was flushed continually with a slow stream of nitrogen. A voltage of 90 v was applied across the electrodes, and 4.59 g (29.6 mmoles) of quinuclidine-2-carboxylic acid and 1.60 g (29.6 mmoles) of sodium methoxide in 100 ml of anhydrous methanol were added dropwise with stirring over a period of 1 hr. Stirring and electrolysis was continued for 8 hr. During this time, the current rose to 3.75 amp, sufficient heat being generated to cause the methanol to reflux. The dark solution was concentrated to *ca.* 50 ml on a steam bath and cooled and diethyl ether was added, causing a yellow gum to precipitate. The mixture was boiled briefly and the liquid was decanted and saved. After extracting the gum once more with ether, it was dissolved in 75 ml of water and extracted eight times with 30-ml portions of ether. The combined extracts were dried over anhydrous magnesium sulfate, and the solvent was distilled through a short column packed with glass helices. Distillation of the residue afforded a 0.41-g forecut and a main fraction consisting of 1.78 g (43%) of 2-methoxy-1-azabicyclo[2.2.2]octane (**2**), bp 70–72° (16 mm). This product was shown to be essentially pure by vapor phase chromatography using a 10 ft × 1/8 in. column of 20% (4:1) Apiezon L–KOH on 60–80 firebrick. An analytical sample was prepared by preparative vapor phase chromatography, $n^{27}$D 1.4711.

*Anal.* Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.37; H, 10.86; N, 9.89.

The nmr spectrum was consistent with the proposed structure having the following integrated intensities and multiplicities: $\tau$ 6.13, 1 H (triplet, $J$ = 6.4 cps); 6.77, 3 H (singlet); and two, broad envelopes between 7.2 and 8.9, 11 H.

**Hofmann Degradation of 2-Methoxy-1-azabicyclo[2.2.2]octane (2).**—To 1.0 g (7.09 mmoles) of **2** in 4 ml of ether was added excess methyl iodide. An amber oil separated which was washed with ether and scratched to induce crystallization. This gave 1.65 g (82%) of the methiodide (**3**), mp 171–173°. Passage of a methanolic solution of 1.42 g of the methiodide through Amberlite IR-A 400 ion-exchange resin followed by concentration *in vacuo* at room temperature gave the quaternary ammonium methoxide as a clear oil. Pyrolysis at 80–110° (30 mm) afforded 0.85 g of clear, colorless liquid, which was shown to contain one principal component by vapor phase chromatography on a 10 ft × 1/8 in. column of 20% (4:1) Apiezon L–KOH on 60–80 firebrick at 180°. Distillation at 89–90° (6 mm) afforded pure 1-methyl-4-(2,2-dimethoxyethyl)piperidine (**5**), $n^{26}$D 1.4484.

*Anal.* Calcd for $C_{10}H_{20}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 64.11; H, 11.38; N, 7.45.

The nmr spectrum displayed the following integrated intensities and multiplicities: $\tau$ 5.70, 1 H (triplet, $J$ = 5.2 cps); 6.88, 6 H (singlet); 7.41, 2 H (multiplet); and 7.92, 8 H (center of broad envelope).

**Ethyl 2-(1-Methyl-4-piperidyl)acetate.**—To a solution of 10 g (60.6 mmoles) of ethyl 2-(4-pyridyl)acetate[11] in 50 ml of ether was added with stirring excess methyl iodide. An orange oil separated which solidified after continued stirring of the reaction mixture for 8 hr. Recrystallization from absolute ethanol afforded 12.47 g (67%) of the methiodide as yellow crystals, mp 104–106° (lit. mp 103–104°,[12] 102.5–103.5°[13]). This methiodide was taken up in 200 ml of 95% ethanol and hydrogenated at 3 atm using 0.5 g of Adams catalyst. The catalyst was filtered off and the filtrate was taken to dryness on a rotary evaporator. The residue was dissolved in 30 ml of saturated potassium bicarbonate solution and extracted with six 40-ml portions of chloroform. The extracts were dried over anhydrous magnesium sulfate, the desiccant was removed by filtration, and the solvent was distilled through a short column packed with glass helices. Distillation of the residue gave 3.35 g (44%) of ethyl 2-(1-methyl-4-piperidyl)acetate, bp 98° (8 mm), as a clear, colorless liquid [lit.[14] bp 106–108° (11 mm)].

**N,N-Dimethyl-2-(1-methyl-4-piperidyl)acetamide (7).**—Ethyl 2-(1-methyl-4-piperidyl)acetate (3.06 g, 16.5 mmoles) was taken up in 40 ml of 6 *N* hydrochloric acid and refluxed for 10 hr. The water was removed on a rotary evaporator and the residue was dried by azeotropic distillation with benzene. The amino acid hydrochloride was then refluxed for 1 hr in 25 ml of thionyl chloride. After cooling, the excess thionyl chloride was removed *in vacuo*, the last traces being removed by codistillation with dry benzene to give the amino acid chloride hydrochloride as a light yellow solid. This was suspended in 50 ml of dry benzene, excess dimethylamine was added, and the reaction was stirred for 8 hr at room temperature. The reaction was concentrated on a steam bath, the residue was taken up in saturated potassium bicarbonate solution, and the benzene layer was removed and saved. The aqueous layer was extracted six times with 25-ml portions of chloroform. The benzene and chloroform layers were combined and dried over anhydrous magnesium sulfate, the drying agent was removed by filtration, and the solvent was distilled off. Vacuum distillation of the residue gave 2.42 g (80% over-all from the ester) of the desired amide (**7**), bp 94–98° (0.18 mm), which was pure by vapor phase chromatography on a 5 ft × 1/8 in. column of SE-30 on Fluoropak at 160°. Treatment of a few drops of this amide with a saturated solution of picric acid in 95% ethanol gave the picrate, mp 168–169°.

*Anal.* Calcd for $C_{16}H_{23}N_5O_8$: C, 46.49; H, 5.61; N, 16.94. Found: C, 46.47; H, 5.65; N, 17.02.

**1-Methyl-4-(2,2-dimethoxyethyl)piperidine.**—Lithium triethoxyaluminohydride was prepared by the dropwise addition of 1.32 g (15.1 mmoles) of ethyl acetate to 0.40 g (10.5 mmoles) of lithium aluminum hydride in 10 ml of anhydrous ether, followed by stirring for 0.5 hr. A solution of 1.83 g (9.9 mmoles) of the amide from above in 10 ml of dry ether was then added dropwise with stirring over 20 min while maintaining the temperature at 0–7°. Stirring at ice-bath temperature was continued for 40 min after the addition was complete. The ice bath was removed and stirring continued for 20 min. The reaction was hydrolyzed at ice-bath temperature with 1.60 ml of water and the salts were filtered off. After the ethereal solution was dried over anhydrous magnesium sulfate, the desiccant was filtered off and the filtrate was concentrated by distilling the solvent through a short column packed with glass helices. Distillation of the residue afforded 0.20

(6) For a discussion of the relative ease of formation of nitrenium ions *vs.* carbonium ions see R. F. Tietz and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 4007 (1955).

(7) V. Braschler, C. A. Grob, and A. Kaiser, *Helv. Chim. Acta*, **46**, 2646 (1963).

(8) (a) M. V. Rubstov and M. I. Dorokhova, *Dokl. Akad. Nauk SSSR*, **88**, 843 (1953); *Chem. Abstr.*, **48**, 3975 (1954); (b) M. V. Rubstov, E. S. Nikitskaya, A. D. Yanina, and V. S. Usovskaya, *Khim. Med.*, **15**, 16 (1962); *Chem. Abstr.*, **58**, 4507b (1963).

(9) V. Prelog and E. Cerkovnikov, *Ann.*, **532**, 83 (1937).

(10) The electrodes were hollow cylinders of 45 mesh platinum gauze, the anode being 2.25 × 0.5 in. (diameter), the cathode 2.25 × 1.25 in. (diameter).

(11) J. W. Hey and J. P. Wibaut, *Rec. Trav. Chim.*, **72**, 525 (1953).

(12) D. R. Bragg and D. B. Wibberley, *J. Chem. Soc.*, 5074 (1961).

(13) R. A. Jones and A. R. Katritzky, *Australian J. Chem.*, **17**, 455 (1964).

(14) N. Sperber, M. Shertok, D. Papa, and D. Kender, *J. Am. Chem. Soc.*, **81**, 704 (1959).

g (22% based on unrecovered starting material) of the aldehyde (**8**), bp 85° (6 mm), and 0.66 g of starting material. The aldehyde was immediately dissolved in 4 ml of trimethyl orthoformate, 0.20 g of *p*-toluenesulfonic acid monohydrate was added, and the reaction was stirred for 12 hr at room temperature. The temperature was then held at 65–75° for 12 hr while allowing methyl formate to distill off through a short-path distillation apparatus. After cooling, the reaction mixture was extracted twice with 2-ml portions of cold 4 *N* hydrochloric acid. The acid extracts were immediately made basic with saturated potassium bicarbonate solution and extracted ten times with 10-ml portions of ether. The etheral extracts were dried over anhydrous magnesium sulfate, the desiccant was removed, and the filtrate was concentrated by distillation of the solvent. The residue was shown to have the same vpc retention time as the degradation product from **2** using a 10 ft × $^1/_8$ in. column of SE-30 on Fluoropak at 160°, and also a 10 ft × $^3/_8$ in. column of 20% (4:1) Apiezon L–KOH on 60–80 firebrick at 138°. Preparative vapor phase chromatography using the latter column afforded a pure sample of 1-methyl-4-(2,2-dimethoxyethyl)-piperidine having an infrared spectrum identical with that of the product from degradation of **2**.

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## Nonpolar Solvent Effects. II. Nuclear Magnetic Resonance Evidence for Complex Formation

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We have recently reported[1] significant solvent effects upon the Curtius reaction of 2-naphthoyl azide and *o*-nitrobenzoyl azide in nonpolar solvents. No satisfactory correlation of the reaction rates with bulk solvent properties was found. Consequently, the nature of the solutions of 2-naphthoyl azide in several nonpolar solvents has been investigated by means of nuclear magnetic resonance spectroscopy (nmr), and the results are reported herein.

One spectrum is shown in Figure 1. Data for the spectra are given in Table I. Complete analysis of the 2-naphthoyl azide spectrum is not necessary for the purposes of this study. Partial analysis of nmr spectra of substituted naphthalenes has been made[2] as well as a complete analysis of the spectrum of naphthalene[3] itself. The low-field resonance (A in Figure 1) may be assigned to the $\alpha$ hydrogen *ortho* to the carbonyl group based on the following: $\alpha$ hydrogens appear at lower field than $\beta$ hydrogens;[2,3] aromatic hydrogens are deshielded by *ortho* carbonyl groups;[4] the low-field resonance in the spectrum of 2-acetonaphthone has been assigned to the $\alpha$ hydrogen *ortho* to the carbonyl group;[2] and finally, the integration curve for the spectrum of 2-naphthoyl azide shows

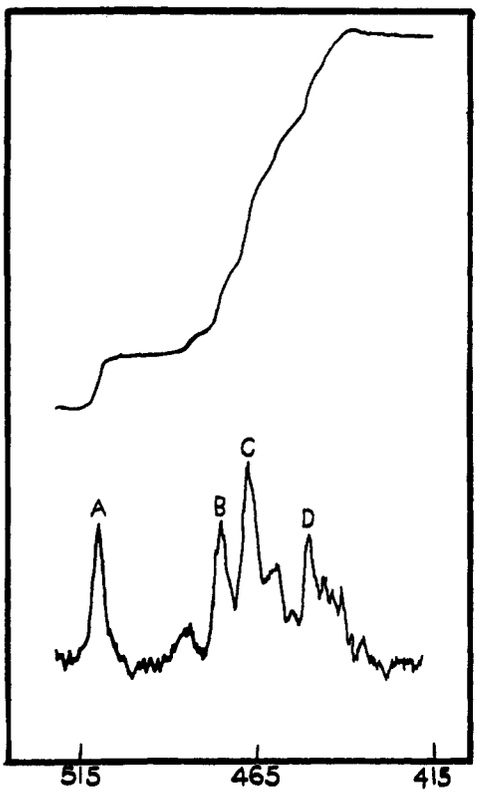


Figure 1.—Nmr spectrum of 2-naphthoyl azide in cyclohexane solution at 47.5°. Details are in the text.

that the low-field resonance is equivalent to one hydrogen.

The chemical shifts of the protons of a solute molecule are affected by the following factors when the solvent is changed:[5–8] hydrogen bonding, van der Waals interactions, bulk magnetic susceptibilities of the solvents, solvent magnetic anisotropies, reaction field effects, specific solute–solvent interactions, and changes in conformational populations.[9] Use of an internal reference eliminates solvent anisotropy effects if no specific solute–solvent interactions are present[7] and also solvent bulk magnetic susceptibility effects in any case.[6] Hydrogen bonding does not occur in the present system. The use of the dilute solutions in this study eliminates solute–solute interactions except for specific solute–solute complexing. Shifts owing to van der Waals interactions should be diminished by use of an internal reference and similar type solvents.[6] The high-temperature spectra obtained in the four hydrocarbon solvents are all the same within experimental error; therefore, at that temperature in these solvents none of the effects contributing to solvent shifts listed above have any significance, *i.e.*, these solutions are purely physical solutions in this temperature range. Table II shows the effect of temperature on the spectra in each solvent. The change in the spectral positions with temperature variation is within experimental error with all solvents except *n*-heptane (and possibly 1-octene). This temperature effect in the *n*-heptane solutions could be

(1) D. C. Berndt, M. Zuika, and M. S. Clark, Jr., *Chem. Ind.* (London), 139 (1965).
(2) G. O. Dudek, *Spectrochim. Acta*, **19**, 691 (1963).
(3) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp 147 ff, 247 ff.
(4) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall Co., Inc., Englewood Cliffs, N. J., 1965, p 79.
(5) A. D. Buckingham, T. Schaefer, and W. G. Schneider, *J. Chem. Phys.*, **32**, 1227 (1960).
(6) J. V. Hatton and W. G. Schneider, *Can. J. Chem.*, **40**, 1285 (1962).
(7) W. G. Schneider, *J. Phys. Chem.*, **66**, 2653 (1962).
(8) A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960).
(9) G. M. Whitesides, J. J. Grocki, D. Holtz, H. Steinberg, and J. D. Roberts, *J. Am. Chem. Soc.*, **87**, 1058 (1965).