Acid-Catalyzed Rearrangement of Certain 2-Amino-1-tetralones[1]

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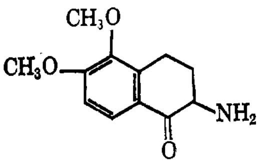
As a part of a continuing study of emetic agents related to apomorphine, it was desired to convert 2-amino-3,4-dihydro-5,6-dimethoxy-1(2H)-naphthalenone (1) to 2-amino-1,2,3,4-tetrahydro-5,6-dimethoxynaphthalene (2). When the hydrochloride of 1 was subjected to conditions of the Clemmensen reduction, a complex mixture of substances resulted, from which two products were isolated in low yields: 1,2,3,4-tetrahydro-5,6-dimethoxynaphthalene (3) and a second compound which contained nitrogen and whose infrared spectrum indicated the presence of a primary amine and the absence of carbonyl. A nuclear magnetic resonance spectrum of this product precluded the possibility that it was 2. Elemental analytical data were consistent with the suggested structure of a dimethoxynaphthylamine system, $C_{12}H_{13}NO_2$. It was apparent, however, that the compound was not 2-amino-5,6-dimethoxynaphthalene (4), since its physical and spectral properties did not agree with those which had been found for 4 which had been prepared by an unequivocal route.[3]



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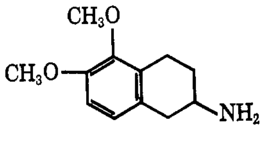

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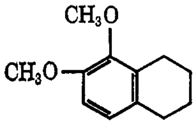

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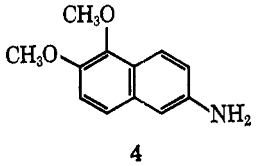

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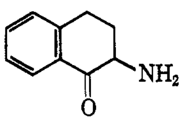

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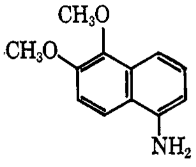

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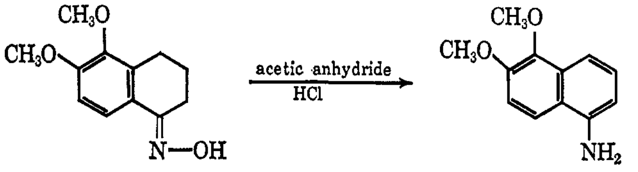
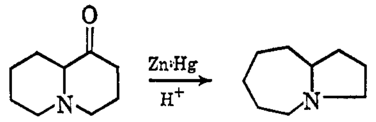
A simpler system, 2-amino-3,4-dihydro-1(2H)-naphthalenone (5), when subjected to Clemmensen conditions identical with those employed for 1, gave rise to low yields of 1,2,3,4-tetrahydronaphthalene and 1-naphthylamine. This result strongly suggested that the amine isolated from Clemmensen treatment of 1 was 5,6-dimethoxy-1-naphthylamine (6). That this was indeed the case was confirmed by synthesis of 6 by a Semmler–Wolff reaction on 7. An infrared spectrum of the Semmler–Wolff product was superimposable upon a similar spectrum of the amino product of the Clemmensen reduction of 1.



7 **6**

Compound 5 was refluxed in ethanol containing hydrochloric acid; the resulting reaction mixture afforded 1-naphthylamine, but no identifiable tetralone derivative could be isolated. In the Clemmensen reduction of 2-amino-1-tetralones, two reaction paths are involved: reduction of the carbonyl function with accompanying loss of the amino group; and a sequence in which the amino function migrates from the 2 position to the 1 position with concomitant aromatization of the ring. No studies have been conducted to elucidate the mechanism(s) of these transformations. Rearrangement of α-amino ketones under conditions of the Clemmensen reaction has been extensively studied by Clemo and co-workers[4] and by Leonard and co-workers;[5] however, these investigations have been limited to ketones having tertiary amino groups α to the carbonyl, as typified by the conversion of 8 to 9. No compounds bearing *primary* amino groups α to the ketonic function were reported. Although this rearrangement of the nitrogen to the carbon bearing the carbonyl group is similar to that observed in the present study, subsequent aromatization or introduction of other unsaturation was not observed. Vorozhtsov and Koptiug[6] and Bhatt[7] have found that oximes of 1-tetralone derivatives undergo the Semmler–Wolff aromatization under acidic conditions, to give aromatic systems having an amino group on the carbon which originally bore the ketonic group.



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It would appear that the amino group migration–aromatization reported herein represents a novel rearrangement without precedent in the literature.

Experimental Section[8]

Attempted Clemmensen Reduction of 2-Amino-3,4-dihydro-5,6-dimethoxy-1(2H)-naphthalenone Hydrochloride (1).—Amal-

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(1) This investigation was supported in part by a grant (NB-04349), National Institute of Neurological Diseases and Blindness and in part by National Institutes of Health Predoctoral Fellowship GM-19445 (W. K. S.). Abstracted in part from a portion of a thesis submitted by W. K. S. in partial fulfillment of the requirements for the degree of Doctor of Philosophy, University of Iowa, 1966.

(2) To whom all correspondence should be addressed.

(3) W. K. Sprenger and J. G. Cannon, unpublished data.

(4) G. R. Clemo, R. Raper, and H. J. Vipond, *J. Chem. Soc.*, 2095 (1949), and preceeding papers in the series.

(5) (a) N. J. Leonard and W. C. Wildman, *J. Am. Chem. Soc.*, **71**, 3089 (1949); (b) N. J. Leonard, J. W. Curry, and J. J. Sagura, *ibid.*, **75**, 6249 (1953), and preceeding papers in the series.

(6) N. N. Vorozhtsov and V. A. Koptiug, *J. Gen. Chem. USSR*, **28**, 1697 (1958).

(7) M. V. Bhatt, *Experientia*, **13**, 70 (1957).

(8) All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus, and are corrected. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Nuclear magnetic resonance spectra were recorded with a Varian A-60 spectrometer at 60 Mc relative to an internal standard of tetramethylsilane. Infrared spectra were obtained with a Beckman IR 5A spectrophotometer. Vapor phase chromatographic analyses were performed on a F and M Model 500 programmed gas chromatograph apparatus using a silicone gum rubber column and a flame ionization detector.

gamated zinc[9] (15.0 g), 3.0 g (0.012 mole) of **1**,[3] 50 ml of ethanol, and 25 ml of concentrated HCl were refluxed for 6 hr, an additional 20 ml of concentrated HCl being added after 3 hr. The reaction mixture was decanted from the remaining zinc amalgam, diluted with 100 ml of water, made strongly alkaline with 20% NaOH, and extracted with four 100-ml portions of ether. The combined ether extracts were washed once with water, dried ($MgSO_4$), filtered, and concentrated to give a dark red liquid (1.5 g) which was dissolved in benzene and was chromatographed on neutral alumina (Merck No. 71707) wet with benzene. The column was eluted with benzene, benzene–ether, and ether–methanol. The eluate fractions yielded 0.28 g of a colorless liquid, 1,2,3,4-tetrahydro-5,6-dimethoxynaphthalene, the infrared spectrum of which was identical with that of an authentic sample; 0.26 g of a yellow liquid, 5,6-dimethoxy-1-naphthylamine **6**, which crystallized on standing; and 0.5 g of a highly impure dark oil which showed bands in the N—H stretching region of its infrared spectrum. Recrystallization of **6** from ethanol gave small, colorless prisms, mp 97.5–98°. An infrared spectrum of **6** ($CHCl_3$) showed a doublet at 2.90 and 2.97 μ (NH_2 stretching) and a strong band at 6.20 μ (NH_2 deformation). A nmr spectrum of **6** ($CDCl_3$) showed a pair of singlets at δ 3.90 and 3.95, superimposed upon a broad band between δ 3.7 and 4.3 (eight protons), and a series of broad, overlapping signals between δ 6.4 and 7.8 (five protons).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 71.10; H, 6.49; N, 7.11.

A hydrochloride salt of **6** was prepared in ether and was recrystallized from ethanol, mp 254–255° dec.

Anal. Calcd for $C_{12}H_{14}ClNO_2$: C, 60.13; H, 5.89; Cl, 14.79; N, 5.84. Found: C, 60.40; H, 5.95; Cl, 15.31; N, 5.93.

1,2,3,4-Tetrahydro-5,6-dimethoxynaphthalene (3).—This compound was obtained by a modification of the method employed by Stork[10] to prepare 1,2,3,4-tetrahydro-6-methoxynaphthalene. A mixture of 117.4 g (0.625 mole) of 1,2-dimethoxynaphthalene,[11] 2 ml of glacial acetic acid, and 20 ml of Raney nickel catalyst W-2[12] in 400 ml of anhydrous ethanol was hydrogenated in a Parr shaker apparatus at a maximum pressure of 45 psig. Approximately 4 days was required for completion of the hydrogenation. The product was isolated by filtration from the catalyst, concentration of the filtrate under reduced pressure, and distillation, to give 115.5 g (96%) of a colorless liquid, bp 81–83° (0.45 mm), $n^{25}D$ 1.5379, d^{20} 1.060. Schroeter and co-workers[13] reported synthesis of this compound by another route, bp 137–138° (12 mm). Vapor phase chromatographic analysis indicated 96% of the product to be a single component. A nmr spectrum (CCl_4) showed a multiplet centered at δ 1.70 (four protons), a multiplet centered at δ 2.65 (four protons), a pair of singlets at δ 3.70 and 3.73 (six protons), and a series of bands between δ 6.5 and 7.2 (two protons).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 75.20; H, 8.29.

Attempted Clemmensen Reduction of 2-Amino-3,4-dihydro-1(2H)-naphthalenone Hydrochloride (5).—Amalgamated zinc (50 g), 10.0 g (0.051 mole) of **5**,[14] 150 ml of ethanol, and 50 ml of concentrated HCl were refluxed 6 hr, an additional 25 ml of concentrated HCl being added after 3 hr. The reaction mixture was decanted from the remaining amalgam, diluted with 250 ml of water, made strongly alkaline with 20% NaOH, and extracted with four 250-ml portions of ether. The combined ether extracts were washed once with water, then were dried ($MgSO_4$). Filtration and concentration of the filtrate under reduced pressure gave 5.1 g of a dark red liquid which was dissolved in benzene and chromatographed as previously described for the Clemmensen reaction mixture of **1**. The eluate fractions yielded 1.7 g (25%) of 1,2,3,4-tetrahydronaphthalene and 1.5 g (21%) of 1-naphthylamine (identified by comparing their infrared spectra with those of authentic samples) and 0.9 g of a highly impure, dark green liquid, which showed weak bands in the N—H stretching region of its infrared spectrum. The alkaline aqueous solution from which 1,2,3,4-tetrahydronaphthalene and 1-naphthylamine had been extracted was made strongly acidic with concentrated HCl, but extraction of this solution with ether failed to provide any identifiable product.

Rearrangement of 2-Amino-3,4-dihydro-1(2H)-naphthalenone Hydrochloride (5) in Ethanol–Hydrochloric Acid.—A solution of 2.0 g (0.01 mole) of **5** in 100 ml of ethanol and 20 ml of concentrated HCl was refluxed for 6 hr. The reaction mixture was cooled, then was made strongly alkaline with 20% NaOH, and was extracted with three 100-ml portions of ether. The combined ether extracts were swirled with $MgSO_4$ for 10 min, then were filtered and concentrated under reduced pressure to give 0.95 g of a yellow-brown liquid which was dissolved in benzene and immediately chromatographed as previously described. The eluate fractions yielded 0.17 g (12%) of 1-naphthylamine (the infrared spectrum of which was superimposable upon that of an authentic sample), and a variety of unidentifiable substances, all of which showed similar infrared spectra: multiple absorption bands in the 2.7–3.1-μ region (N—H and/or O—H stretching) and a broad band in the 5.8–6.2-μ region (C=N and/or C=O stretching).

5,6-Dimethoxy-1-naphthylamine (6).—A modification of the method of Bauer and Hewitson[15] was employed. 3,4-Dihydro-5,6-dimethoxy-1(2H)-naphthaleneone oxime (**7**,[3] 5.0 g, 0.023 mole) was heated in a mixture of 2.5 ml of acetic anhydride and 20 ml of glacial acetic acid for 10 min at 110°, then anhydrous HCl was passed through the solution for 30 min, while maintaining the temperature at 100°. The reaction mixture was cooled overnight in a refrigerator and the gray crystals which separated were collected on a filter. These were washed twice with 10-ml portions of anhydrous ethanol and were air dried to yield 0.6 g (13%) of 5,6-dimethoxy-1-naphthylamine hydrochloride, mp 253–255° dec. An infrared spectrum (Nujol) was superimposable upon a similar spectrum of the hydrochloride salt of the product of the attempted Clemmensen reduction of **1**. The hydrochloride salt obtained above was warmed gently in 5% Na_2SO_3, and the resulting solution was extracted with chloroform, dried ($MgSO_4$), and filtered. The solvent was removed from the filtrate under reduced pressure and the residue was recrystallized repeatedly from ethanol (charcoal), to afford white crystals of 5,6-dimethoxy-1-naphthylamine (**6**), mp 97–98°. An infrared spectrum ($CHCl_3$) of this product was superimposable upon a similar spectrum of the free base form of the amino product isolated from the attempted Clemmensen reduction of **1**.

Acknowledgment.—We acknowledge with thanks the helpful discussions with Professor Ludwig Bauer, University of Illinois, regarding the Semmler–Wolff reaction.

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[9] Prepared by shaking 15 g of clean mossy zinc with a solution of 1.5 g of mercuric chloride in 15 ml of water and 15 ml of 5% HCl, followed by thorough washing with water.

[10] G. Stork, *J. Am. Chem. Soc.*, **69**, 576 (1947).

[11] A. Bezdzik and P. Friedlaender, *Monatsh. Chem.*, **30**, 271 (1909).

[12] Prepared according to the method of R. Mozingo in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N.Y., 1955, p 181.

[13] G. Schroeter, K. Erzberger, and L. Passavant, *Chem. Ber.*, **71**, 1040 (1938).

[14] P. W. Neber, A. Burgard, and W. Thier, *Ann. Chem.*, **526**, 277 (1936). These workers reported mp 117°. H. E. Baumgarten and J. M. Petersen [*J. Am. Chem. Soc.*, **82**, 459 (1960)] reported mp 201–202°. The compound prepared in the present study showed mp 202–203.5° dec.

[15] L. Bauer and R. E. Hewitson, *J. Org. Chem.*, **27**, 3982 (1962).

The Conformational Inversion of D-Mannopyranosides Caused by Certain Aglycons

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D-Mannopyranose is found in nature as a constituent of certain polysaccharides, of nucleotides, and of certain glycoproteins. The elucidation of the conformation of D-mannopyranose moiety in these molecules will be very important in studying their structures, biosyntheses, and biological functions. Both α- and β-D-mannopyranoses are believed to have C1 conforma-