DAEHAN HWAHAK HWOEJEE
(*Journal of the Korean Chemical Society*)
Vol. 23, No. 2, 1979
Printed in Republic of Korea

2-Amino-와 2-Nitro-3, 4-dihydro-5, 6-dimethoxy-1(2H)-naphthalenone의 촉매수소화에서 5, 6-Dimethoxy-1, 2, 3, 4-tetrahydro-2(1H)-naphthalenone의 분리 및 구조결정

金 正 均

부산대학교 문리과대학 화학과

(1978. 9. 25 접수)

Isolation and Characterization of 5, 6-Dimethoxy-1, 2, 3, 4-tetrahydro-2(1H)-naphthalenone from the Catalytic Reductions of the Respective 2-Amino-, and 2-Nitro-3, 4-dihydro-5, 6-dimethoxy-1(2H)-naphthalenone

Jack C. Kim

Department of Chemistry, Busan National University, Busan 607, Korea

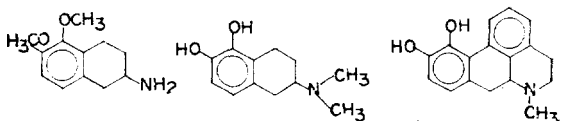
(Received Sept. 25, 1978)

요 약. 2-Amino-와 2-nitro-3, 4-dihydro-5, 6-dimethoxy-1(2H)-naphthalenone의 촉매수소화에서 주생성물인 2-amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphthalene을 얻었고 동시에 극소량의 5, 6-dimethoxy-1, 2, 3, 4-tetrahydro-2(1H)-naphthalenone을 얻었다. 이 전이된 생성물의 구조결정은 ir와 nmr, 그리고 원소분석으로 확인하였고 전이메카니즘을 제시하였다.

ABSTRACT. From the catalytic reductions of the respective 2-amino-, and 2-nitro-3, 4-dihydro-5, 6-dimethoxy-1(2H)-naphthalenone, a major reduction product of 2-amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydro-naphthalene was obtained, along with a minute amount of rearranged product, 5, 6-dimethoxy-1, 2, 3, 4-tetrahydro-2(1H)-naphthalenone. he unusual formation of 5, 6-dimethoxy-1, 2, 3, 4-tetrahydro-2(1H)-naphthalenone was verified on the basis of ir, and nmr spectra, and elemental analysis. A plausible mechanism for the rearrangement is proposed.

INTRODUCTION

In previous work from this laboratory we have shown two synthetic methods of 2-amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydro-naphalene (**1**),[1~3] and reported dramatically high order and wide spectrum of biological effects of 2-N, N-dimethylamino-5, 6-dihydroxy-1, 2, 3, 4-tetraydronaphthalene (**2**),[4,5] as compared with those of apomorphine (**3**). Our prior works have dealt with a number of derivatives, congeners and fragments of apomorphine.[7] In view



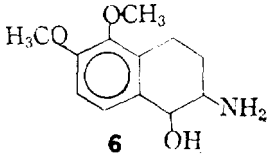
1 2 3

of the significant increase in biological activity on N, N-dimethylation of the 2-amino-5, 6-dihydroxy-1, 2, 3, 4-tetrahydronaphthalene system **2**, we have investigated an alternate, better synthetic procedures of the amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphthalene **I**, which is a precurser of the **2**.

The following *Schemes* 1 and 2 which we have been previously described,[1~3] show the two synthetic routes to prepare an important intermediate **I**.

RESULTS AND DISCUSSION

In the *Scheme* 1, the carbonyl group α to the benzene ring of the coupound **4**, obtained from the Neber rearrangement of the 3, 4-dihydro-5, 6-dimethoxy 1(2H)-naphthalenone-***O***-*p*-tolunesulfonyl oxime (**5**), was removed by hydrogenolysis in the presence of palladium on charcoal; the intermediate aminoalcohol, 2-amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphhtalen-1-ol (**6**) was not isolated, but were continously hydrogenated in the presence of hydroperchloric acid to bring about hydrogenolysis of the benzylic hydroxyl group **6** directly to give **1**.

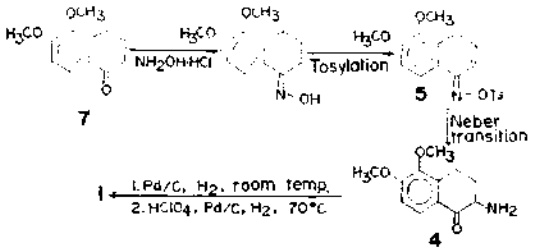


6

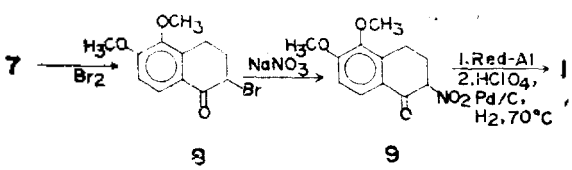
In the *Scheme* 2, bromination of 3, 4-dihydro-5, 6-dimethoxy-1(2H)-naphthalenone (**7**), followed by the nitration of the bromo-product **8** afforded a 2-nitro-3, 4-dihydro-5, 6-dimethoxy-1(2H)-naphthalenone (**9**). This α-nitroketone **9** was placed on the reductive conditions with sodium *bis*(2-methoxyethoxy) aluminium hydride (Red-Al), followed by palladium on charcoal in the presence of hydroperchloric acid to yield the compound **1**. No intermediate **6** was attempted to isolate.

In either cases (See *Schemes* 1 and 2), the catalytic reduction methods of the respective **4** and **9** gave exclusively a major reduction product of **1**, along with a minute amount of a crystalline compound, having a higher mobility than that of a **1** in thin layer chromatography. Repeats of the catalytic hydrogenolysis reactions yielded consistently a small amount of a crystalline solid which has much lower melting point than those of the compounds **1**, **4**, and **9**, respectively.

The ir spectra of **4** and **9** showed a benzylic carbonyl absorption peak at 1675 and 1679 cm^{-1}, respectively, and that of an unknown crystalline solid exhibited an absorption at 1700 cm^{-1}. The new infrared absorption peak at 1700 cm^{-1} is assumed to be a carbonyl stretching absorption of an isolated ketonic group. As the conjugation of the carbonyl group with the benzene ring results in delocalization of the π electrons from the carbonyl groups as in both **4** and **9**, the C=O bond length increases and



Scheme 1.



Scheme 2.

then the frequency of absorption decreases.

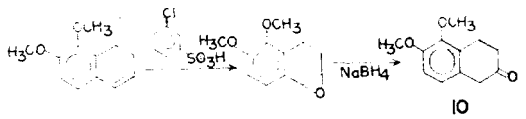
A nuclear magnetic resonance spectrum of the unknown compound demonstrated six aliphatic protons plus two methoxy protons and two aromatic protons.

The crystalline solid is thus believed to be a 1, 2, 3, 4-tetrahydro-5, 6-dinethoxy-2(1H)-naphthalenone (**10**) in view of the spectroscopic data and the result of the elemental analysis.

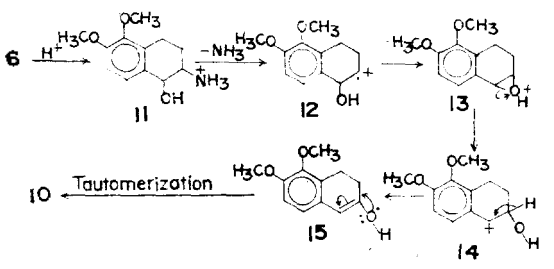
In order to test further whether the compound **10** was 1, 2, 3, 4-tetrahydro-5, 6-dimethoxy-2 (1H)-naphthalenone, we isolated an intermediate amino-alcohol **6**, before the perchloric acid treatment in the catalytic hydrogenation operations (See Experimental Sections), and treated the **6** with a few drops of conc. HCl (or $HClO_4$). At this condition, a crystalline solid, m. p 64~65 °C was obtained as a major product, and the spectroscopic datas of the compound are identical with those of the compound obtained from the hydrogenolysis reaction, as well as a literature value. The unequivocal synthesis of **10** is shown in *Scheme* 3.

The following *Scheme* 4. shows a plausible mechanism for the transformation of **10** from the intermediate **6**.

In the acidic medium, the catalytic hydrogenation intermediate **6** will be protonated at the basic nitrogen atom to give the positive species of **11** which will give rise to the carbonium ion **12**. The generated carbonium ions, **12** and **14** have relatively good deal of influence on the proposed mechanism in the *Scheme* 4; the speed of this ionization partly depends upon the stability of the carbonium ions formed. The more stable (long-lived) benzylic carbonium ion **14**, will be predominantly favored through the epoxide formation **13**. The benzylic carbonium ion **14** is much more stable than the carbonium ion **12**.



Scheme 3.



Scheme 4.

The stable, long-lived benzylic carbonium ion **14** will drive to form the enol **15** initially. Analogous to the keto-enol system,[10] the enol **15**rapidly tauto-merizes into the more stable keto form; Then equilibrium favors the formation of **10**.

On the basis of the proposed mechanism, along with the spectral and elemental analysis data, we thus firmly believe that the "unknown crystalline compound, m. p 64~65 °C is a transformation product of 5, 6-dimethoxy-1, 2, 3, 4-tetrahydro-2(1H)-naphthalenone **10** from 2-amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphthalen-1-ol, **6**.

EXPERIMENTAL

Catalytic Reduction of 2-Amino-3, 4-dihydro-5, 6-dimethoxy-1(2H)-naphthalenone(4), and Isolation of 1, 2, 3, 4-tatrahydro-5, 6-dimethoxy-2(1H)-naphthalenone(10). A mixture of 3g(0. 013mole) of 2-amino-3, 4-dihydro-5, 6-dimethoxy-1(2H)-naphthalenone[8] and 0. 06 g of 10 % Pd/C in 100 m*l* of glacial AcOH was hydrogenated in a Parr apparatus at 38 °C and a maximum pressure of 3. 16 kg/cm^2. Uptake of 1 mole of H_2 was complete in 48 hours. The reaction vessel was cooled (At this stage, the amino-alcohol was isolated; After

complete evapoaration *in vaccuo*, the oily residue was dissolved and dry HCl gas bubbled through, and obtained a solid from the crystallization ($EtOH/Et_2O$) and 3 m*l* of $HClO_4$ was added with rinsing with 3 m*l* of glacial AcOH, and hydrogenation was continued at 70 °C for 18 hours, employing a maximum pressure of 2.81 kg/cm^2.

The catalyst was removed from the reaction mixture by filtration and the clear yellow filtrate was treated with 6g of KOAc; $KClO_4$ precipitated immediately and was removed by filtration. The filtrate was taken up to dryness under reduced pressure* and 100 m*l* of 5 % HCl was added to the residue. This aq. solution was extracted with two 50 m*l* portions of Et_2O which were discarded. The aq. phase was made strongly basic with 20 % KOH, then was extracted with four 75 m*l* portions of Et_2O. The combined Et_2O extracts were washed with 75 m*l* of H_2O, 75 m*l* of 10 % NaCl, and finally with 75 m*l* of H_2O, and then dried ($MgSO_4$) and filtered. The filtrate was treated with etheral HCl to form 2.13 g (71 %) of a white solid. Recrystallization from MeOH-Et_2O (charcoal) gave 1.92 g (66 %) of white crystals, m.p 285 dec. (*lit.*[8] m.p 270~272). Ir (KBr) 1675 cm^{-1} (C=O), nmr (D_2O) τ 6.13~6.00 (2*s*, 6, -OMe), and 2.82~2.1 (2*d*, 2, ArH).

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: C, 55.92; H, 6.26; Cl, 13.76; N, 5.43. Found: C, 55.79; H, 6.20; Cl, 13.76; N, 5.54.

*When the filtrate was taken up to the dryness under reduced pressure, a few semi-solids were appeared to the whole residue. Repetion of crystallization from cyclohexane (charcoal) gave 0.09 g of white crystals (10). m.p 63~65 °C (*lit.*[9] 64~65). Ir (KBr) 1700 cm^{-1} (C=O), nmr ($CDCl_3$) τ 7.55, 6.85 (*t*, 4H, $-CH_2-$), 6.45 (*s*, 2H, $-CH_2-$), 6.20, 6.16 (*s*, 6H, -OMe) and 3.15 (*s*, 2H, Ar-H).

Anal. Calecd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84, Found: C, 69.79, H, 6.91.

Catalytic Reduction of 2-Nitro-3,4-dihydro-5,6-dimethoxy-1(2H)-naphthalenone (9) and Isolation of 1,2,3,4-tetrahydro-5,6-dimethoxy-2(1H)-naphthaleone**. A mixture of 1.66 g (6.27 mmole) of 2-nitro-3,4-dihydro-5,6-dimethoxy-1(2H)-naphthalenone[1] and 14.47 g (50.16 mmole) of sodium *bis*(2-methoxyethoxy) aluminium hydride (Red-Al, Aldrich Chemical) in 200 m*l* of dry benzene was carefully heated to reflux with stirring for 6 hours and then continously stirred at room temperature for additional 5 hours, and then cooled and the excess Red-Al was decomposed by slow addition of 150 m*l* of water. The benzene layer was separated and the water phase filtered to remove alumina salts and then extracted with 3 × 150 m*l* of chloroform. The combined chloroform and benzene solutions were dried over $MgSO_4$. After filtering and removing and removing the solvents, the residue was taken up into dry chloroform-ether (4:1) and dry HCl gas added to precipitate the salt. The crude aminoalcohol **6**, was isolated for the conversion into **10**.

To the crude aminotetralol salts, **6** was added 25 m*l* of glacial AcOH, 0.9 m*l* of 70 % $HClO_4$, and 0.65 g of 10 % Pd/C and the mixture was placed in a Parr hydrogenation apparatus and hydrogenated at 2.81 kg/cm^2 pressure.

Shaking was continued for 11 hours at 70 °C at which time hydrogen uptake was complete. The catalyst was removed by filtration and 2.00 g of KOAc was added to the filtrate; after removing the immediately formed $KClO_4$, the filtrate** was concentrated under reduced pressure and the residual oil taken up into 100 m*l*

When the filtrate was evaporated, a few semi-solid appeared in the residual oil, was crystallized from cyclohexane (charcoal) to give a white needle, m.p 63~65 °C which was identical with that of the previously obtained compound, **10.

of wat er and basified with 5 % NaOH solution. The basic solution was extracted with 3×100 m*l*, and the combined ether extracts were washed with water until the washings were neutral, and dried over $MgSO_4$, and filtered. The filtrate was treated with etheral HCl to give 0.78 g (79 %) of white solid. Recrystallization from MeOH-Et_2O (charcoal) afforded 0.65 g (70 %) of white crystals, m. p 285° dec. (*lit.*[8] m. p 270~272 °C). The infrared and nuclear magn etic resonance spectra were identical with that of an authentic sample.

Preparation of 1, 2, 3, 4-Tetrahydro-5, 6-dimethoxy-2(1H)-naphthalenone (10) from the Isolated 2-Amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydro-naphthalen-1-ol (6). From the catalytic-reaction mixtures (see both *Schemes* 1 and 2), the 2-amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphthalen-1-ol (**6**) was isolated as shown in the experimentals; the aminoalcohol, **6** (0.08 g, 0.0004 mole) was dissolved in 25 m*l* of chloroform and added a few drops of conc. HCl (or $HClO_4$), and the reaction mixture was refluxed overnight (18 hours). After evaporation *in vaccuo*, the light yellow semi-solid residues were crystallized from cyclohexane (charcoal) to give 0.063 g (76 %) of white crystals, m. p 63~65 °C (*lit.*[9] m. p 64~65 °C). Ir (KBr) 1700 cm^{-1}. Nmr ($CDCl_3$) was identical with that of the previously obtained compound **10**.

REFERENCES

1. J. C. Kim, S. K. Han S. K. Choi, *J. Kor. Chem. Soc.*, **20**, 91 1976.
2. J. C. Kim, *J. Kor. Chem. Soc.*, **21**, 187 1977.
3. J. G. Cannon and J. C. Kim, *J. Med. Chem.*, **15**, 348 1972.
4. J. C. Kim, J. G. Cannon, J. P. Long and S. Heintz, *ASPET MEETING, East Lansing, Mich.*, 1973, *Abstract* 129.
5. J. P. Long, S. Heintz, J. G. Cannon and J. C. Kim *J. Pharmacol. Exp. Ther.*, **192**, 336 1975.
6. J. G. Cannon and J. C. Kim, *U. S. Patent*, **374**, **170** (June 27, 1974).
7. J. G. Cannon, J. C. Kim and A. M. Aleem, *J. Heterocycl. Chem.*, **9**, 731 1972.
8. W. K. Sprenger, *et al.*, *J. Med. Chem.*, **12**, 487 1969.
9. J. G. Cannon, J. P. O'Donnell, J. P. Rosazza and C. R. Hoppin, *J. Med. Chem.*, **17**, 565 1974.
10. R. L. Hinman, *Tetrahdron*, **24**, **185** 1968. J. Ficini and A. Krief, *Tetrahedron Letters*, No. **17**, 1397 1970. P. Y. Sollenberger and R. B. Martin, *J. Amer. Chem. Soc.*, **92**, 4291 1970.