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# 2-아미노-5, 6-디메톡시-1, 2, 3, 4-테트라히드로나프탈렌 염화히드로의 합성

金正均 · 李錫琪 · 金昌培* · 韓錫圭** · 崔舜圭 · 李京熙**

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# An Alternate Synthesis of 2-Amino-5, 6-dimethoxy-1, 2, 3, 4-Tetrahydronaphthalene Hydrochloride

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요 약. 2-Amino-5, 6-dimethoxy-1, 2, 3, 4-tetahydronaphthalene hydrochloride를 2-nitro-3, 4-dihydro-5, 6-dimethoxy-(2*H*)-naphthalenone으로부터 합성하여서 Neber rearrangement로부터 얻은 2-amino-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone hydrochloride로 부터 합성한 방법과 수득률 및 실업적인 조작을 비교 설명하였다.

**ABSTRACT.** An alternate synthesis of 2-amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride from 2-nitro-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone, was described and compared the overall yields and experimental procedures with the previous synthetic routes obtained from Neber rearrangement product, 2-amino-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone hydrochloride.

## INTRODUCTION

A number of derivatives, congeners and fragments of Apomorphine (**1**) have been perpared[1,2], and shown to be capable of *anti*-Parkinson effect (and/or dopaminergic effect).[3~5] A general importance of these compounds results from their inter-relationship to dopamine biochemistry[3] and their abilities to act as a dopamine receptor agonist[4], coupled with the emetic activity. The potent biologioal activites exhibited by the 2, 2-dimethylamino-5, 6-dihydroxy-1, 2, 3, 4-tetrahydronaphthalene (**2**)[5], which is closely related structurally to the apomorphine, was evidenced[6] that an *anti* disposition (**3**) of the catechol ring and amino group of dopamine is

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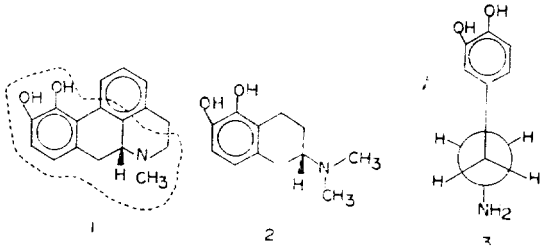
the biologically active form rather the gauche conformation (**4**): the recent conclusion[7] for the emetic pharmacophore of apomorphine neccessarily includes free, unetherified catechol group and the amino function of dopamine.



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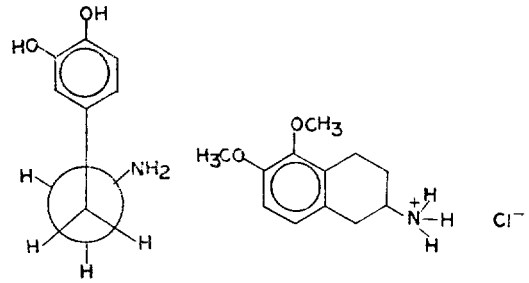

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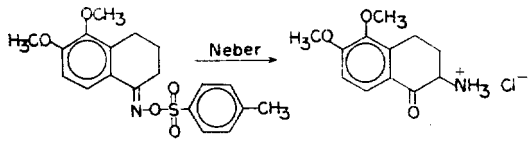
An inspection of Dreiding molecular model of the 2, 2-dimethylamino-5, 6-dihydroxy-1, 2, 3, 4-tetrahydronaphthalene (**2**) suggests itself as a candidate for possession of dopaminergic and *anti*-parkinsonian activity: the tetraline deriva tives, **2** supperimposes (see the dotted lines as indicated) almost perfectly, atom for atom, upon the corresponding portion of the apomorphine molecule, **1**, if it is assumed that there is a pseudo equatorial disposition of the amino group on the tetraline ring. This relationship has been noted by us,[1~5] as the rationale for synthesis of some 2-amino-5, 6-dihydroxy-1, 2, 3, 4-tetrahy dronaphthalene derivatives.

## CHEMISTRY

Thus, the preparation of the critically important intermediate, 2-amino-5, 6-dimethoxy-1, 2 3, 4-tetrahydronaphthalene hydrochloride (**5**), which is a precurser of **2**, was undertaken.

In 1969, Sprenger, *et al*. reported preparation of 3, 4-dihydro-2-amino-5, 6-dimethoxy-1(2*H*) -naphthalenone hydrochloride (**6**) via a Neber rearrangement[9,10] of 3, 4-dihydro-5, 6-dimetho-xy-1 (2*H*)-naphthalenone-*O*-*p*-toluene-sulfonyl oxime (**7**). Sprenger accomplished this transformation by treating an alcoholic suspension of **7** with potassium ethoxide. In the present work, numerous attempts to repeat Sprenger's proceldures failed; there were isolated ony potassium *p*-toluenesulfonate and a high melting (above 300°C) gray solid whose infrared spectrum (no benzylic ketonic a bsorption at 1675 $cm^{-1}$) was not identical with that of an authentic sample of **6**.

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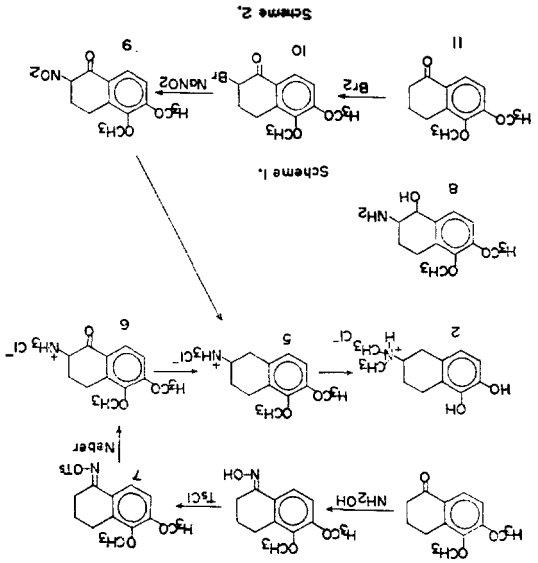
The literature revealed that oxime arylsulfonates can rearrange to a variety of products, depending on the specific reaction conditions. Such substances as *O*-alkyl and *O*-arylimine ethers[11], amidines[12], imidazoles[12], and *O*-imidyl phosphates[13] have been obtained from oxime arylsulfonate rearrangements. Cyclohexanone *O*-*p*-toluene-sulfonyl oxime has been reported to rearrange to a tetra-hydroazepine derivatives.[14] A literature variations[15~17] involving use of an anhydrous benzene as the Neber reaction medium and subsequent hydrolytic treatment performed directly on the benzene solution, permitted a successful Neber rearrangement of the oxime tosylate **7** to afford **6** (*Scheme* 1). Using this anhydrous benzene as a Neber rearrangement medium, repeated experiments gave a consistent reproducibility of the product **6**.



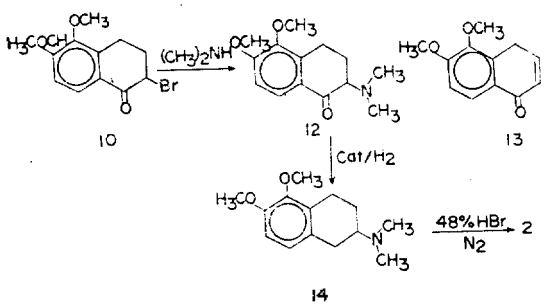
The benzylic carbonyl function of the amino ketone, **6** was removed by hydrogenolysis in the presence of palladium on charcoal; the intermediate amino alcohol (**8**) was not isolated, but were hydrogenated in the presence of perchloric acid to bring about hydrogenolysis of the benzylic alcohol group.[18] to give the desired intermediate, 2-amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphthalene hydrochloride **5**. Eschweiler-Clarke methylation reaction of **5**, followed by the etheral cleavage, would give the candidate compound, 2, 2-dimethylamino-5, 6-dihydroxy-1, 2, 3, 4-tetrahydronaphthalen, **2**.

However, most of the compounds prepared by the *Scheme* 1, gave the tedious, long synthetic procedures, coupled with the poor yield of Neber rearrangement product, and its use of the *Scheme* 1 was further discouraged to obtain a large quantity of **5** for biological evaluations of **2**.

An alternate route (*Scheme* 2) to the 5 is based upon synthetic methods utilized by us;[19] 2-nitro-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone (**9**) was prepared by the treatment of 2-bromo-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone (**10**) by sodium nitrite and phloroglucinol in dimethylsulfoxide. Bromination of 3, 4-dihydro-5, 6-dimethoxy-1(2*H*) naphthalenone (**11**) afforded 2-bromo-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone in excellent yield. The yields for those 2-bromo- and 2-nitro-compounds (**9** and **10**) obtained by the *Schemc* 2, generally were excellent, and as its *Scheme* 2 shows, only three synthetic steps were needed to obtain the final candidate compound **5**, in contrast to the *Scheme* **1** in which the total five synthetic routes were neccessary. In comparisons with the *Scheme* 1 and 2, it is obvious that the *Scheme* 2 is better in overall yields than *Scheme* 1, in all aspects of organic synthetic experimental procedures.

Both synthetic pathways (*Scheme* 1 and 2) involve the catalytic reduction of benzylic ketonic functions of the respective $\alpha$-amino- and $\alpha$-nitro ketones. The $\alpha$-amino-ketone **6** was easily and smoothly reduced by Pd/C, followed by hydro perchloric acid treatment. When the $\alpha$-nitro-ketonic compound **9** was subjected to the above condition, the nitro group was not reduced as indicated by the infrared spectrum (presence of nitro group), and then intractable tars were obtained. Treatment of $\alpha$-nitro ketone by *bis* (2-methoxyethoxy)-aluminium hydride (Red-al; Aldrich) followed by catalytic reduction and $HClO_4$ treatment gave good yields of the **5**; the intermediate, amino alcohol (**8**) was not isolated in the conversion from **9** to **5** but was continously hydrogenated as the same condition of **6** was used.

It should also be noted that a direct nucleophilic displacement reaction (*Scheme* 3) of 2-bromo-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone **10** by dimethylamine as a nucleophile (followed by catalytic reduction would give a precurser of (**2**) would not give an appreciable yield of 2-*N*, *N*-dimethylamino-3, 4-dihydro-5,



*Scheme* 3.

6-dimethoxy-1(2*H*)-naphthalenone (**12**), rather the elimination product (**13**) was observed as a major product on thin layer chromatography and nuclear magentic resonance spectrum. The thin layer chromatography in ethyl acetate-cyclohexene (1:1) showed the product to be a two-component mixture (**12** and **13**) with the elimination product **13**, approximately predominating in the ratio of 10:1. The NMR spetrum reveled that the higher *Rf* material (major elimination product) showed a vinylic protons, a multiplet centered at $\tau$3.85, and the infrared spectrum of **13** corresponded to the presence of $\alpha,\beta$-conjugated ketonic adsorption (1625 and 1679 $cm^{-1}$). To obtain directly a precurser of **14**, through **10** to **12**, this phase of the research was abandoned.

## EXPERIMENTAL

Melting points were determined in open glass capilaries using a Thomas-Hoover Uni-melt apparatus, and are corrected. Elemental analyses were performed by the Division of Medicinal Chemistry and Natural Products, the University of Iowa. Infrared spectra were determined with Beckman IR-5 and IR-10 spectrophotometers. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer at 60 Mc. relative to an internal standard of TMS: *s*, signifies singlet; *d*, doublet; *t*; triplet; *q*, quartet; *m*; multiplet.

**2-Amino-3, 4-dihydro-5, 6-dimethoxy-1-(2*H*)-naphthalenone Hydrochloride 6.** The method used was a modified procedure of Sprenger, *et al.*[8] To a stirred solution of KOEt, freshly prepared by dissolving 7.6 g (0.193 g-atom) of K in 240 m*l* of absolute EtOH was added a suspension of 72g (0.198 mole) of 3,4-dihydro-5,6-dimethoxy-1(2*H*)-naphthalenone-*O*-*p*-toluene-sulfonyl oxime **7**[8] in 440 m*l* of dry $C_6H_6$. The resulting yellow suspension was stirred at 0 °C for 0.25 hour, and left at 4 °C with occasional swiring for 22 hours. The dark greenish viscous mass was filtered through a sintered glass filter, and the solid material which was collected was washed with 440 m*l* of dry benzene. The combined filtrates were extracted with four 440 m*l* portions of 10 % HCl. Evaporation of the aq. phase under reduced pressure at 40 °C gave a brown residue which was crystallized twice from MeOH-$Et_2O$ (charcoal) to give 23.4 g(46 %) of a tan colored solid, m.p 227~229.5 °C(lit[3] m.p 208~210 °C). IR (KBr) 1675 $cm^{-1}$ (C=O). NMR ($D_2O$) $\delta$ 3.84~4.00 (2*s*, 6, $-OCH_3$), and 7.18~7.83 (2*d*, a, 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; C, 13.76; N, 5.54.

**2-Amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphthalene Hydrochloride 5 from Neber Reaction 6.** A mixture of 3 g(0.013 mole) of **6** and 0.6 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 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

6 g of KOAc; $KClO_4$ precipitated immediately and was removed by filtration. The filtrate was taken to dryneess under reduced pressure (steam bath), and 100 m*l* of 5% HCl was added to the residue. ether which were discarded. The aq. phase was made strongly basic with 20 % KOH, then was extracted with four 75 m*l* portions of ether. The combined ether extracts were washed with 76 m*l* of water, 75 m*l* of 10 % NaCl, and finally with 75 m*l* of water, and then dried over $MgSO_4$ and filtered. The filtrate** was treated with ethereal HCl to form 2.13 g(69 %) of a white solid. Recrystallization from MeOH-$Et_2O$ (charcoal) gave 1.67 g (62 %) of white crystals, m. p 285 °dec. (lit[8]. 270~272 °C). IR (KBr) showed disappearance of the strong band at 1675 $cm^{-1}$. NMR ($D_2O$) $\delta$ 1.66~3.87 (*m*, 7, Alphatic-H), and 6.70 (*q*, 3 ArH).

*Anal.* Calcd. for $C_{12}H_{18}ClNO_2$: C, 60.02; H, 5.89; Cl, 14.79; N, 5.84. Found. C, 60.07; H, 5.93, N, 5.81.

**2-Amino-5, 6-dimethoxy-1, 2, 3, 4-tetrahydronaphthalene Hydrochloride 5 from 2-Nitro-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone 9.** A mixture of 1.66 g (6.27 mmole) of 2-nitro-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone[19] and 14.47 g (50.16 mmole) of *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 excess Red-Al was decomposed by slow addition of 150 m*l* of wate. 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 the solvents, the residue was take up into dry chloroform-ether (4:1) and dry HCl added to precipitate the salt. The crude amino alcohol **8**, was not isolated and purified crude weight 1.27 g(64 %); To the crude aminotetralol salt **8** 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 hyrogenated at an initial pressure of 50 psig. Shaking was conitinued for 11 hours at room temperature. 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* of water and basified with 5 % Na OH solution. The basic solution was extracted with with 3 100m*l* of ether, and the combined ether extracts were washed with water until the washings were neutral, and dried over $MgSO_4$, and dried over $MgSO_4$, and filtered. The filtrate** was treatedwith ethereal HCl to give 0.78 g (79 %) of a white solid. Recrystallization from Me-OH-$Et_2O$ (charcoal) afforded 0.65 g(70 %) of white crystals, m. p 285° dec (lit[8] 270~272 °C). (overall yield from **9**, 41 %). The infrareds and nuclear magetic resonance spectra were identical with that of an authentic sample from Neber reaction. Mixed melting points also gave no depression.

**Attempted Preparation of 2-*N*, *N*-Dimethylamino-3, 4-dihydro-5, 6-dimethoxy-1(2*H*)-naphthalenone 12.** To an ice-cooled solution of 5.76 g (0.56mole) of 2-bromo-3, 4-dihydro-5, 6-dimethoxy-1 (2*H*)-naphthalenone,[19] **10** in 350 m*l* of dry benzene was slowly added 6.31 g (0.513 mole) of dimethylamine under nitrogen

**Evaporation of the filtrate under reduced pressure (steam bath) gave a yellow oil which was distilled through a "short path" apparatus, as a clear colorless liquid, b.p 110~119° (0.25 mm) to give the free base of **5**.

atmosphere, and the reaction mixture was refluxed for 15 hours. The mixture was cooled to room temperature and evaporated in vacuo to dryness To the dried residue added 100 m*l* of ethereal HCl and crystallization from MeOH-$Et_2O$ afforded 0.51 g(7.5 %) of **12** which was not enough for the synthetic preparation method, and the crystallization filtrate gave an oily residue after evaporation. The crude weight of the oily residue was 5.12 g(76 %).

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