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Unusual Transposition of the Carbonyl Group in the Reduction of 2-Amino-1-indanone

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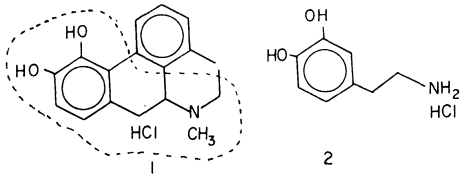
The catalytic reduction procedure of 2-amino-4,5-dimethoxy-1-indanone hydrochloride gave a major reduction product of 2-amino-4,5-dimethoxyindan hydrochloride, along with a small amount of a rearranged 4,5-dimethoxy-2-indanone. The isolated intermediate, 2-amino-4,5-dimethoxy-1-indanol hydrochloride yielded exclusively 4,5-dimethoxy-2-indanone under catalytic reaction conditions (acid treatment). The unusual transformation product was verified on the basis of IR, NMR and the result of elemental analysis. A plausible mechanism for the rearrangement is discussed.

Apomorphine (**1**) which has assumed considerable importance in efforts at understanding the role of dopamine (**2**) in the etiology and therapy of Parkinsonism,[1] has structural similarities (see the dotted line) to dopamine. It is currently believed that apomorphine is a dopaminergic agonist and presumably it is through this mechanism that this agonist is effective clinically. By the Dreiding model inspection of apomorphine and dopamine, the 2-amino-4,5-indandiol hydrochloride (**3**) suggests itself as a candidate for possession of dopaminergic activity. This relationship has been noted by Rekker *et al.*[2] as the rationale for the biologically active pharmacophore of the catechole ring and the amino group of dopamine.



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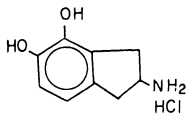
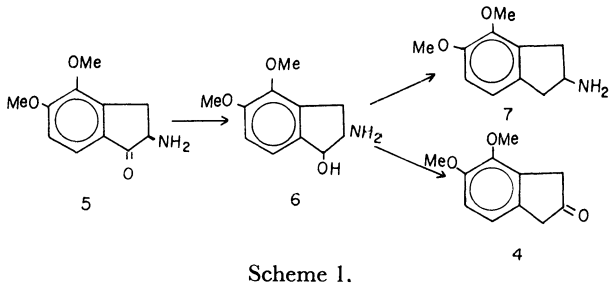


Our prior works have dealt with a synthesis[3] and dopamine-like effects[4] of 2-amino-4,5-indandiol series **3**. The objective of this investigation is to deal with the isolation and identification of an unusual rearranged product, 4,5-dimethoxy-2-indanone (**4**) from the catalytic reduction of 2-amino-4,5-dimethoxy-1-indanone (**5**).

Results and Discussion

Illustrating the previously published results[3] in brief (Scheme 1), the carbonyl group α to the benzene ring of the amino ketone **5** was removed by hydrogenolysis in the presence of palladium on charcoal; the intermediate amino alcohol, 2-amino-4,5-dimethoxy-1-indanol (**6**) was not isolated, but **6** was continuously hydrogenated in the presence of $HClO_4$ to bring about hydrogenolysis of the benzylic hydroxyl group directly to give 2-amino-4,5-dimethoxyindan (**7**). However, the catalytic reduction method of **5** gave exclusively a desired reduction product of **7**, along with a small amount of a white solid, having a higher mobility than that of **7** in thin layer chromatogram. Repeats of the catalytic hydrogenation reactions yielded consistently a small amount of a solid which has much lower melting point (89—90 °C) than those of the compounds **5** (193.5—194.5 °C) and **7** (205—206.5 °C).

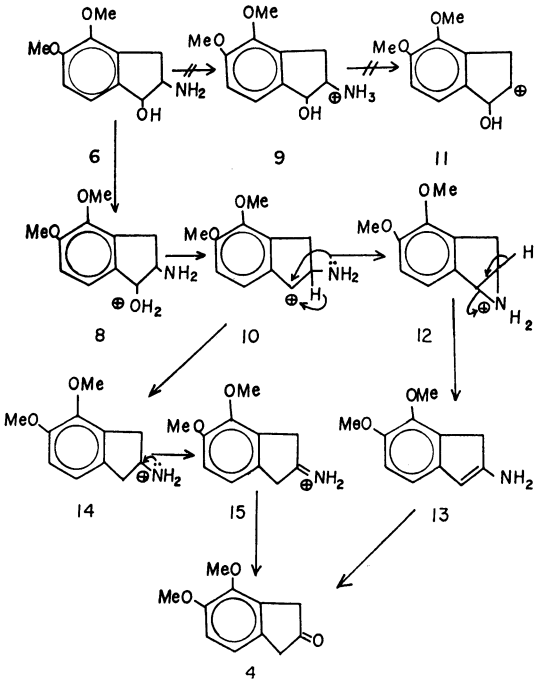


Scheme 1.

The IR spectrum (KBr) of the starting material **5** showed a benzylic carbonyl absorption peak at 1710 cm^{-1}. The unknown white solid showed a new absorption peak at 1740 cm^{-1} which is assumed to be a carbonyl stretching vibration 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 group, the C=O bond length as in **5** increases and the frequency of absorption decreases. An integration of nuclear magnetic resonance spectrum of the unknown compound demonstrated two methoxyl and two aromatic protons plus four aliphatic proton signals. The characteristic proton signal of the four aliphatic C-1 and C-3 protons gave two singlets (δ 2.51 and 2.53), quite different from those of the compounds, **5** and **7** which showed a multiplet.

The white compound is thus believed to be 4,5-dimethoxy-2-indanone **4**, in veiw of the spectral characteristics of the NMR and IR spectra, and the result of the elemental analysis.

In order to further test whether the unknown compound, 4,5-dimethoxy-2-indanone was derived from the intermediate **6**, we isolated the intermediate, 2-amino-4,5-dimethoxy-1-indanol **6**, before the $HClO_4$ treatment in the catalytic hydrogenation process (see Experimental), and treated **6** with a few drops of concentrated HCl. At this stage, a white solid **4** was exclusively obtained as a major product, and the mp and spectroscopic data of the compound was exactly identical with those of the compound obtained from the hydrogenolysis.



Scheme 2.

The following Scheme 2 shows a plausible mechanism for the rearranged product formation of **4** from **6**. A central problem in the fundamental understanding of a plausible mechanism at the amino alcohol intermediate stage, is the question of whether **6** involves either kinetically controlled protonation at the hydroxyl oxygen to form oxonium ion **8**, or thermodynamically controlled protonation at the basic nitrogen atom to form ammonium salt **9** under the acidic conditions of the catalytic hydrogenation step. Since the good leaving groups will be those that can best stabilize an extra pair of electrons, that is a week base,[6] the stronger base, NH_3 is hard to leave as a leaving group[7] as in **9**, and therefore the weaker base, OH_2 will become a better leaving group, thus making **8** the sole reactive intermediate. Secondly, the generated carbonium ion **10** has relatively good deal of influences on the speed of this ionization which partly depends on the stability of the carbonium ions formed. The much more stable, long-lived benzylic carbonium ion **10**, will predominantly favor the mechanistic routes in **8**→**10**→**12**, excluding a route **9**→**11**.

With these two controlling factors, the protonated oxonium ion **8** is preferentially formed and then converted to the enamine **13**,[8] which is hydrolyzed to give the rearranged product **4** eventually. However, the pinacol-pinacolone type rearrangement from the hydride shift of **10** to **14**, followed by the imminium salt **15**, has not been eliminated as a possibility. On the basis of the presently available data, the enamine-favored mechanistic path is more compatible, and it is reasonable to discard a route **9**→**11**.

Experimental

All melting points were determined using a Polytemp (Polyscience Corporation) or Fisher-Johns apparatus, and are uncorrected. The IR spectra were taken in KBr disks with a Shimadzu 400 spectrophotometer. The ^1H NMR spectra were obtained at 60 MHz using a Varian EM-60 spectrometer with TMS as an internal standard.

*2-Amino-4,5-dimethoxyindan Hydrochloride (**7**·**HCl**).* A mixture of 3 g (0.013 mol) of **5** and 0.6 g of 10% Pd/C in 100 ml of glacial AcOH was hydrogenated in a Parr apparatus at 38 °C under maximum pressure of 3.16 kg/cm². Uptake of 1 mol of H_2 was complete in 48 h. The reaction mixture was cooled and 3 ml of $HClO_4$ was added with rinsing with 3 ml of glacial AcOH, and hydrogenation was continued at 70 °C for 18 h employing a maximum pressure of 2.81 kg/cm². The catalyst was removed from the reaction mixture by filtration and the clear filtrate (yellow color) was treated with 6 g of KOAc; $KClO_4$ precipitated immediately and was removed by filtration. The filtrate was taken up to dryness under reduced pressure (steam bath) and 100 ml of aq 5% HCl was added to the residue and the small amounts of the insoluble solids were filtered. The aq solution was extracted with two 50 ml portions of Et_2O which were discarded. The aq phase was made strongly basic with 20% KOH, then was extracted with four 75 ml portions of Et_2O. The combined Et_2O extracts were washed with 75 ml of H_2O, 75 ml of 10% NaCl, and finally with 75 ml of H_2O and then dried ($MgSO_4$) and filtered. The filtrate was treated with ethereal HCl to form 2.13 g (71%) of a white solid. Recyrstallization from MeOH–Et_2O (charcoal) gave 1.92 g (66%) of white crystals, mp 205—206.5 °C. IR (KBr) showed a disappearance of a strong band at 1710 cm^{-1}. NMR (D_2O); δ 2.77—3.88 (m, 5H, Aliphatic H), 3.88 (s, 6H, -OMe), 7.07 (q, 2H, Aromatic H).

Found: C, 57.62; H, 7.13; N, 5.81%. Calcd for $C_{11}H_{16}ClNO_2$: C, 57.49; H, 7.02; N, 6.13%.

Evaporation of the filtrate under reduced pressure gave a yellow oil which was distilled through a "short path column" apparatus, as a clear colorless liquid, bp 115—119 °C (0.25 mmHg) to give the free base **7**.

*Isolation of the Intermediate, 2-Amino-4,5-dimethoxy-1-indanol Hydrochloride (**6**·**HCl**).* At the end of the complete uptake of 1 mol H_2, the catalyst was removed from the reaction mixture by filtration and the filtrate was evaporated under reduced pressure to obtain the oily residues. The residues were taken up into $CHCl_3$–Et_2O (1 : 6) and ethereal HCl was added to precipitate the salt. The amino-indan hydrochloride salt was very hygroscopic and was dried in a vaccum desicator. Recrystallization from EtOH–Et_2O gave a white solid, mp 163—165 °C. IR (KBr): 3327 (OH), 2892 (NH_3^+); NMR (D_2O): δ 3.18 and 3.98 (2s, 6H, OMe), 7.11 and 7.35 (dd, 2H, Aromatic H).

Found: C, 53.76; H, 6.56; N, 5.70; Cl, 14.14%. Calcd for $C_{11}H_{16}NClO_3$: C, 53.49; H, 6.51; N, 5.91%.

*Isolation of 4,5-Dimethoxy-2-indanone (**4**).* The insoluble solids and the "discarded" two 50 ml portions were combined, and evaporated under reduced pressure. The residue obtained, was crystallized from cyclohexane (charcoal) to yield a white solid, mp 89—90 °C. IR (KBr); 1740 cm^{-1}; NMR ($CDCl_3$): δ 2.51 and 2.53 (s, 4H, Aliphatic H), 3.81 and 3.87 (2s, 6H, OMe) and 7.19 (s, 2H, Aromatic H).

Found: C, 58.73; H, 6.29%. Calcd for $C_{11}H_{12}O_3$: C, 58.65; H, 6.21%.

*Reaction of **6**·**HCl** with Hydrochloric Acid (Preparation of 4,5-Dimethoxy-2-indanone).* The amino alcohol intermediate, **6**·**HCl** (1.11 g, 0.0022 mol) was dissolved in 100 ml of $CHCl_3$ and added 7 ml of concd HCl and the reaction mixture was refluxed for 18 h. At the end of the reaction, the reaction mixture was washed with three 30 ml portions of saturated $NaHCO_3$ solution, three 30 ml portions of NaCl solution,

three 30 ml portions of H_2O and the $CHCl_3$ layer was dried over $MgSO_4$. Fitration and evaporation *in vacuo* gave solid residue, which were crystallized from cyclohexane (charcoal) to give 0.39 g (55%) of white solids, mp 89—90 °C. The IR and NMR spectra were identical with that of the previously obtained compound.

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