Chemical Research Department, Hoffmann-La Roche Inc.

1-(2-Pyridyl)-3,4-dihydro-6,7-dimethoxyisoquinoline and Some of Its Hydrogenated and *N*-Substituted Derivatives

Wilhelm Wenner and Mychajlo Stefaniw

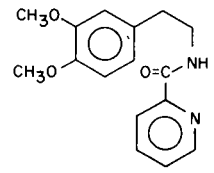
The preparation of 1-(2-pyridyl)- and 1-(2-piperidyl)-substituted, partly hydrogenated derivatives of 6,7-dimethoxyisoquinoline is described.

In the literature (1) several isoquinoline derivatives were described which carry a pyridyl group in position 1 of the isoquinoline system. We have now investigated the preparation and some of the reactions of the hitherto unknown 1-(2-pyridyl)-3,4-dihydro-6,7-dimethoxyisoquinoline (II), which was obtained by a Bischler-Napieralski ring closure from *N*-(3,4-dimethoxyphenethyl)picolinamide (I). The cyclization of the free amide was not satisfactory, but ring closure proceeded smoothly in yields of 60% or more with the hydrochloride of the amide. The dihydroisoquinoline derivative (II) possessed a strong tendency to form metal complexes. With ferrous sulfate, for example, it united to a deep blue complex which was very similar in its properties to the complex formed by the fully aromatic compounds 2,2′-bipyridyl (V) (2) and 1-(2-pyridyl)isoquinoline (VI) (3). The complex formation of these two pyridine derivitives was utilized for the colorimetric determination of iron (3). The base (II) was converted into the blue iron complex with a stoichiometric amount of ferrous chloride in aqueous solution. Its ultraviolet spectrum proved to be quite similar to that shown by Cagle and Smith (3a) for their complex with 2,2′-bipyridyl.

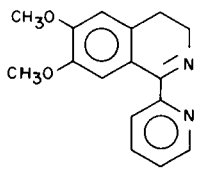
The dihydro compound (II) was reduced catalytically or with sodium borohydride to the tetrahydro derivative (III). The use of sodium borohydride is preferred, because the tendency of II to form metal complexes slows down catalytic hydrogenations. The tetrahydro derivative (III) does not give a blue color when treated with ferrous chloride. The color reaction is therefore a convenient test for complete reduction of the dihydro compound.

Previous investigators made only picrates and chloroplatinates of their compounds containing the 2,2′-bipyridyl system. We found that II and III form only monohydrochlorides. Obviously the proximity of the two nitrogen atoms in both compounds influences the basic properties in the same manner as in the numerous examples of similar situations described in detail by Mann and Watson (4).

We prepared three derivatives of the racemic tetrahydro derivative (III) by substitution of the H of the NH group: The *N*-acetyl derivative (VII), the *N*-carbomethoxy derivative (VIII), and the *N*-carbethoxymethyl derivative (IX). All three racemic compounds were then hydrogenated in dilute acetic acid over rhodium on charcoal at moderate temperatures, below 50°, and at pressures of 600-700 lbs., resulting in the formation of the corresponding piperidyl derivatives X, XI, and XII. All three were racemic compounds. The unsubstituted tetrahydro derivative (III), upon hydrogenation in dilute hydrochloric acid over platinum oxide, yielded the dibasic 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-piperidyl)isoquinoline (IV). No attempts



I



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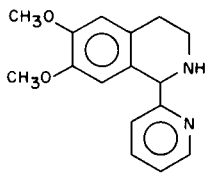
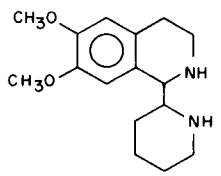


III



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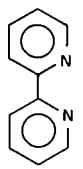

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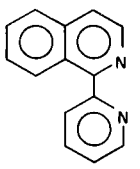
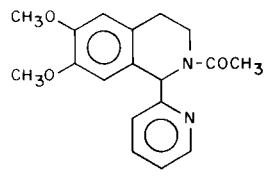


VI



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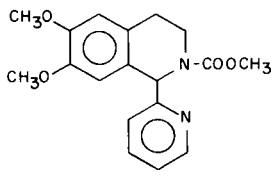
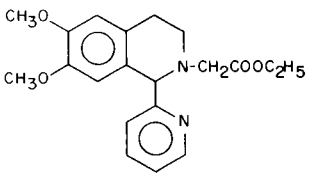
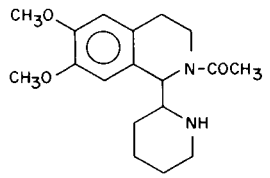


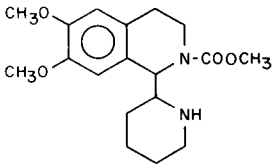
VIII



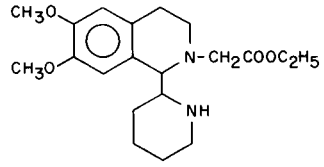
IX



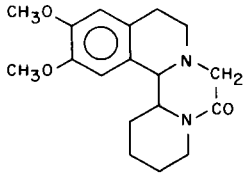
X



XI



XII



XIII

at optical resolution of the piperidyl derivatives, which contain two asymmetric carbon atoms, were made.

Mono substitution of the base (IV) could give two isomeric compounds, carrying the substituent either in the tetrahydroisoquinoline or in the piperidine moiety. Treatment of IV with one mole of acetic anhydride, or with one mole of methyl chloroformate gave yields of more than 50% of the racemic mono acetyl derivative (X) and of the racemic mono carbomethoxy derivative (XI), which were identical with the compounds obtained by catalytic hydrogenation of the pyridyl groups of the compounds VII and VIII. This proves that mono substitution of the base (IV) occurred primarily in the tetrahydroisoquinoline moiety.

The dihydrobromide of XII, when treated with dilute alkali, did not yield the corresponding free base. The only compound isolated from this reaction was racemic 5,6,11, 12,13,14,14a,14b-octahydro-2,3-dimethoxypyrido[2′,1′: 3,4]pyrazino[2,1-*a*]isoquinoline-9(8*H*)-one (XIII). Even under the mildest conditions the free ester therefore cyclizes to a compound with an amide linkage. The infrared spectra confirm this cyclization: The dihydrobromide of XII shows absorption at 1737 cm^{-1}, in the region characteristic of acetate groups. The free base (XIII), however, absorbs in the 1639 cm^{-1} region, which is characteristic of 6 membered lactams.

EXPERIMENTAL (5)

N-(3,4-Dimethoxyphenethyl)picolinamide (I).

A. Free Base.

Homoveratrylamine (36 g.) and methyl picolinate (29 g.) were mixed and heated on a steam bath for 12 hours. After cooling to room temperature 150 ml. of ether was added. On standing for several hours with occasional shaking the amide crystallized. Recrystallization from ethyl acetate yielded 35 g. of pure amide, m.p. 60-62°.

Anal. Calcd. for $C_{16}H_{18}N_2O_3$: C, 67.13; H, 6.34; N, 9.78. Found: C, 67.44; H, 6.46; N, 9.54.

B. Hydrochloride.

A solution of 6 g. of the free base (I) in ethanol was neutralized with an excess of 2-propanolic hydrogen chloride. The hydrochloride precipitated immediately. After recrystallization from ethanol the pure hydrochloride (6 g.) melted at 130-132°. It contained solvent of crystallization. The analysis was carried out with a sample dried for several hours *in vacuo* over phosphorus pentoxide.

Anal. Calcd. for $C_{16}H_{18}N_2O_3 \cdot HCl$: C, 59.51; H, 5.91; Cl, 10.99. Found: C, 59.79; H, 5.86; Cl, 10.82.

3,4-Dihydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline (II).

A. Free Base.

N-(3,4-Dimethoxyphenethyl)picolinamide hydrochloride (20 g.) was added cautiously with ice cooling to 150 ml. of phosphorus oxychloride. The mixture was refluxed with stirring in an oil bath for about 1.5 hours. The excess phosphorus oxychloride was then distilled *in vacuo* and the dark residue was poured into excess ice-water. After standing overnight at room temperature, the solution was filtered with charcoal and made alkaline with dilute sodium hydroxide solution. The liberated base was extracted with benzene. The extract was washed with water and allowed to stand. The base crystallized (14 g.). After washing with water, which removed most of the colored by-products, the base was recrystallized from 2-propanol. The pure base melted at 114-115°; yield 10 g.

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.57. Found: C, 71.93; H, 5.97; N, 10.57.

B. Hydrochloride.

The free base (II) (4 g.) was dissolved in 2-propanol and 2-propanolic hydrogen chloride added in excess. The pale yellow hydrochloride (4.5 g.) separated immediately. It was washed with acetone and dried at 80° *in vacuo* over phosphorus pentoxide to remove the solvent of crystallization. The dried salt melted at 202-204°.

Anal. Calcd. for $C_{16}H_{16}N_2O_2 \cdot HCl$: C, 63.07; H, 5.62; Cl, 11.63. Found: 63.14; H, 5.70; Cl, 11.69.

C. Ferrous Complex.

The free base (II) (1 g.) was dissolved in 100 ml. of water at 50-60°. To the solution was added a solution of 0.345 g. of ferrous sulfate heptahydrate in 300 ml. of water. The mixture turned deep blue. It was adjusted to an exact volume of 500 ml. The absorption and molecular extinction are shown in Table I. The

TABLE I

U.V. Spectrum of Ferrous Sulfate Complex of II
2.3774 g. of Complex in 1000 ml. of water

Own *p*H		*p*H = 4		*p*H = 8	
(mμ)	max	(mμ)	max	(mμ)	max
254	34,300	255	34,300	–	–
277/9	38,900	276/7	39,150	279	45,900
360/4	18,940	360/6	19,200	360/3	22,600
595/600	16,200	596/9	16,420	596/600	19,000

complex has the formula $Fe(C_{16}H_{16}N_2O_3)_3^{++}SO_4^{--}$, M. W. 956.8. It is stable at *p*H 4 and at *p*H 8 and was not destroyed by light.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline (III).

A. Free Base by Catalytic Hydrogenation of II.

3,4-Dihydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline hydrochloride (II) (43 g.) was dissolved in 1000 ml. of water. The filtered solution was hydrogenated at about 20 lbs. pressure and 20-25° over 400 mg. of platinum oxide. The mixture turned quite dark (6) during the hydrogenation. After about 8 hours the calculated amount of hydrogen was absorbed. The solution was filtered and made alkaline with dilute sodium hydroxide solution. The liberated base was extracted with benzene and the extract was evaporated to yield 36 g. of the crude tetrahydro base as a yellow oil which slowly solidified. Recrystallization from ethyl acetate gave the pure base (28 g.), m.p. 81-82°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.21; H, 7.02; N, 10.25.

B. Free Base by Reduction of II with Sodium Borohydride.

3,4-Dihydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline (II) (5.3 g.) was dissolved in 50 ml. of dry methanol. The solution was stirred at room temperature; over a period of 2 hours sodium borohydride (2.3 g.) was added in small portions. After complete addition, stirring was continued for 1 hour and then 300 ml. of ice water was slowly added. The free base was extracted with chloroform. The dried extract was evaporated, leaving 5 g. of crude oily base which solidified on standing. After washing with a little ether it melted at 80-82°

C. Monohydrochloride.

Four grams of free base (III) from B was dissolved in one equivalent of 1 *N* hydrochloric acid (14 ml.). The solution was filtered and distilled to dryness *in vacuo*. The residue crystallized and was triturated with dry acetone leaving 4 g. of the compound. Recrystallization from water methanol (1:4) did not change the melting point, 252-253°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2 \cdot HCl$: C, 62.63; H, 6.24; Cl, 11.56. Found: C, 62.62; H, 5.91; Cl, 11.56, 11.76.

D. Monohydrobromide.

A sample of free base from B (*ca.* 200 mg.) was dissolved in ether and neutralized with ethanolic hydrogen bromide. The monohydrobromide crystallized at once. Recrystallization from methanol gave the pure compound, m.p. 249-250°.

Anal. Calcd. for $C_{16}H_{18}N_2O_2 \cdot HBr$: C, 54.71; H, 5.46; Br, 22.75; N, 7.97. Found: C, 54.95; H, 5.44; Br, 22.53; N, 7.86.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-piperidyl)isoquinoline (IV).

A. By Hydrogenation of 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline (III).

Compound III (134 g.) was dissolved in 1000 ml. of 3 *N* hydrochloric acid. The solution was treated with charcoal, filtered and was then hydrogenated over *ca.* 1 g. of platinum oxide at 95-100° and 1000 lbs. pressure until absorption of hydrogen stopped. The catalyst was filtered, and the filtrate was made alkaline with excess dilute ammonia. The liberated base was extracted with chloroform. The chloroform was distilled and the oily residue was covered with ether. The base soon crystallized. It was filtered and washed with cold ether. The yield was 120 g. of m.p. 94-97°. It was pure enough for further reactions. For analysis a sample was crystallized from ethyl acetate and dried *in vacuo* over phosphorus pentoxide. It melted at 98-99°.

Anal. Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.55; H, 8.74; N, 10.13. Found: C, 69.15, 69.21; H, 8.65, 8.77; N, 9.92.

Addition of excess 2-propanolic hydrochloric acid to a solution of the base (1 g.) in ether precipitated the dihydrochloride. After recrystallization from ethanol and drying at 80° at about 1 mm pressure, it melted at 257-259°; yield 1 g.

Anal. Calcd. for $C_{16}H_{24}N_2O_2 \cdot 2HCl$: C, 55.06; H, 7.50; N, 8.01; Cl, 20.28. Found: C, 55.24; H, 7.48; N, 7.76; Cl, 20.17.

B. By Hydrogenation of 3,4-Dihydro-6,7-dimethoxy-1-(2-pyridyl)-isoquinoline (II).

The free base of II (86 g.) was dissolved in 600 ml. of 3 *N* hydrochloric acid. The solution was filtered through charcoal and was hydrogenated over 1 g. of platinum oxide at 80-100° and *ca.* 1000 lbs. pressure. After absorption of hydrogen had stopped the catalyst was filtered, and the filtrate was made alkaline with dilute sodium hydroxide. The liberated base was extracted with benzene. The benzene was distilled leaving 65 g. of a viscous oil. When stirred with ether it solidified. The base was dried in a desiccator and recrystallized from ethyl acetate, yielding 50 g. of the pure base, m.p. 97-99°, identical with material from A.

2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline (VII).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline (III) (7 g.) was dissolved in 50 ml. of dry dioxane. The solution was stirred and cooled with ice water, and a solution of 5.5 g. of acetic anhydride in 20 ml. of dry dioxane was slowly added. After complete addition the mixture was warmed for about 15 minutes on the water bath and then evaporated to dryness *in vacuo*. The residue was dissolved in 60 ml. of cold water, dilute sodium hydroxide was added and the liberated base was extracted with chloroform. The dried chloroform extract was evaporated, leaving 7 g. of crude VII. Recrystallization from ethanol gave 6 g. of the pure compound of m.p. 150-151°.

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.28; H, 6.27; N, 9.15.

Methyl 3,4-Dihydro-6,7-dimethoxy-1-(2-pyridyl)-2(1*H*)isoquinoline-carboxylate (VIII).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline (III) (13 g.) was dissolved in 300 ml. of dry ether. The solution was cooled with ice water and was stirred. First, 5.5 g. of triethylamine was added in one portion, and then the methyl chloroformate (4.8 g.), dissolved in 50 ml. of dry ether, was slowly dropped into the stirred solution. After standing for a few hours at room temperature the solid was filtered. It weighed 16 g. and melted unsharply. Trituration with 50 ml. of water followed by recrystallization from ethyl acetate gave 10 g. of the pure compound of m.p. 110-112°.

The base contained one-half mole of water of crystallization.

Anal. Calcd. for $C_{18}H_{20}N_2O_4 \cdot \frac{1}{2}H_2O$: C, 64.21; H, 6.25; N, 8.32. Found: C, 64.42, 64.62; H, 6.09, 5.94; N, 8.90.

Ethyl 3,4-Dihydro-6,7-dimethoxy-1-(2-pyridyl)-2(1*H*)isoquinolineacetate (IX).

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-pyridyl)isoquinoline (III) (20 g.) was dissolved in 200 ml. of dry ether. After addition of 7.5 g. of triethylamine the mixture was cooled with ice water and a solution of 12.4 g. of ethyl bromoacetate in 50 ml. of ether was slowly added. After standing overnight at room temperature the crystals of triethylamine hydrobromide were filtered. The filtrate was shaken first with sodium bicarbonate solution and then with water. The ether layer was dried over potassium carbonate and distilled to dryness, leaving a yellowish, viscous residue, which was dissolved in ethanol and neutralized with ethanolic hydrogen bromide. Ether was then added, precipitating the crystalline dihydrobromide (23 g.) which was recrystallized from ethanol yielding 18 g. of pure material. The salt contained one mole of water of crystallization and melted at 155-157°.

Anal. Calcd. for $C_{20}H_{24}N_2O_4 \cdot 2HBr \cdot H_2O$: C, 44.79; H, 5.26. N, 5.23. Found: C, 44.74; H, 5.42; N, 5.23.

2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-piperidyl)isoquinoline (X).

A. From 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-piperidyl)isoquinoline (IV) with Acetic Anhydride.

The free base of IV (2 g.) was dissolved in about 100 ml. of dry ether. With ice cooling 0.74 g. of acetic anhydride, dissolved in 50 ml. of dry ether, was slowly added. After standing at room temperature for one day the ether was distilled. The residue was treated with water and dilute sodium hydroxide, and the mixture was extracted repeatedly with benzene. The benzene was distilled and the residue was shaken with a small amount of ether. The acetyl derivative crystallized. It was recrystallized from ether-ligroin and melted at 141-142°, yield 2 g.

Anal. Calcd. for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.59; H, 8.31; N, 8.57.

B. From 2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-pyridyl)-isoquinoline (VII).

The acetyl derivative VII (5.6 g.) was dissolved in 200 ml. of acetic acid. The solution was hydrogenated over 10% rhodium on charcoal at 20° and 600-700 lbs. pressure. The catalyst was filtered and the filtrate was distilled to dryness *in vacuo*. The residue was stirred with dilute sodium hydroxide and the liberated base was extracted with chloroform. The filtered chloroform solution was distilled to dryness, leaving a viscous residue which crystallized on standing. The crude compound (5 g.) melted at 138-140°. Recrystallization from ethyl acetate yielded 4.5 g. of the pure compound of m.p. 141-142°. The mixture melting point with material prepared according to A showed no depression.

Anal. Calcd. for $C_{18}H_{26}N_2O_3$: C, 67.90; H, 8.23; N, 8.80. Found: C, 67.88; H, 7.90; N, 9.01.

Methyl 3,4-Dihydro-6,7-dimethoxy-1-(2-piperidyl)-2(1*H*)isoquinolinecarboxylate (XI).

A. From 1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-piperidyl)isoquinoline (IV) with Methyl Chloroformate.

Compound IV (11 g.) was dissolved in 200 ml. of ether. A solution of 3.8 g. of methyl chloroformate in 25 ml. of ether was slowly added with ice cooling and stirring. After standing for several hours at room temperature crystals separated. The crude material (13 g.) was recrystallized from 120 ml. of ethanol, yielding 10 g. of the pure monohydrochloride, m.p. 245-247°.

Anal. Calcd. for $C_{18}H_{26}N_2O_4 \cdot HCl$: C, 58.29; H, 7.35; Cl, 9.56; N, 7.55. Found: C, 58.03; H, 7.42; Cl, 9.79; N, 7.73.

B. From Methyl 3,4-Dihydro-6,7-dimethoxy-1-(2-pyridyl)-2(1*H*)-isoquinolinecarboxylate (VIII).

The free base of VIII (8 g.) was dissolved cautiously in 200 ml. of acetic acid. The solution was hydrogenated over 300 mg. of 10% rhodium on charcoal at 20-25° and 600-700 lbs. pressure. The solution was filtered and the clear filtrate was concentrated *in vacuo* to a small volume. Water and chloroform were added, and the cooled and stirred mixture was cautiously neutralized with dilute ammonia, so that the liberated base was immediately taken up into the chloroform. The chloroform layer was separated at once from the aqueous phase. It was dried over sodium sulfate and evaporated *in vacuo* at a temperature not exceeding 15°.

The residue was dissolved in ether. With ice cooling 2-propanolic hydrochloric acid was slowly added. The hydrochloride separated immediately and was filtered and washed with hot absolute ethanol. The yield was 5 g., m.p. 246-247°. The mixture melting point with the material from A showed no depression.

Anal. Calcd. for $C_{18}H_{26}N_2O_4 \cdot HCl$: C, 58.29; H, 7.35; N, 7.55. Found: C, 58.33; H, 7.17; N, 7.62.

Ethyl 3,4-Dihydro-6,7-dimethoxy-1-(2-piperidyl)-2(1*H*)isoquinolineacetate (XII).

Ethyl 3,4-dihydro-6,7-dimethoxy-1-(2-pyridyl)-2(1*H*)isoquinolineacetate (IX) (10 g.) was dissolved in 200 ml. of acetic acid. The solution was hydrogenated over 10% rhodium on charcoal at 20-25° and a pressure of 600-700 lbs. The catalyst was filtered, and the filtrate was cautiously acidified with an excess of ethanolic hydrogen bromide. The solution was frozen in a dry ice-acetone mixture and was evaporated at room temperature at very low pressure. The solid residue was dissolved at room temperature in absolute ethanol. The filtered solution was diluted with dry ether until it was slightly turbid. On standing the salt crystallized. It was washed with dry ether and with dry acetone. Recrystallization from 2-propanol-ethanol (3:2) yielded 7 g. of the pure dihydrobromide, m.p. 218-220°.

Anal. Calcd. for $C_{20}H_{30}N_2O_4 \cdot 2HBr$: C, 45.82; H, 6.15; N, 5.34. Found: C, 45.37; H, 6.11; N, 5.30.

5,6,11,12,13,14,14a,14b-Octahydro-2,3-dimethoxypyrido[2′,1′:3,4]pyrazino[2,1-*a*]isoquinoline-9(8*H*)-one (XIII).

A. Free Base.

The dihydrobromide of ethyl 3,4-dihydro-6,7-dimethoxy-1-(2-piperidyl)-2(1*H*)isoquinolineacetate (XII) (1 g.) was dissolved in 30 ml. of water. Dilute sodium hydroxide solution was added until the solution was alkaline to phenolphthalein. The liberated base was extracted with benzene. The benzene was distilled leaving 0.6 g. of the crude base, which was recrystallized from ethyl acetate. The pure material melted at 145-147°, yield 0.4 g.

Anal. Calcd. for $C_{18}H_{24}N_2O_3$: C, 68.33; H, 7.65; N, 8.85; Found: C, 68.39; H, 7.71; N, 8.76.

B. Hydrobromide.

Ethyl 3,4-dihydro-6,7-dimethoxy-1-(2-piperidyl)-2(1*H*)isoquinolineacetate dihydrobromide (XII) (1 g.) was dissolved in water and the solution was made alkaline with dilute sodium hydroxide.

The liberated base was extracted with benzene. Evaporation of the solution left 0.6 g. of the free base, which was dissolved in ether and neutralized with ethanolic hydrogen bromide. The hydrobromide was precipitated by adding more ether. It was recrystallized from ethanol and dried over phosphorus pentoxide at 80° *in vacuo*

for 3 hours. It melted at 258-260°, yield 0.7 g.

Anal. Calcd. for $C_{18}H_{24}N_2O_3 \cdot HBr$: C, 54.41; H, 6.34; N, 7.06. Found: C, 54.55; H, 6.64; N, 6.93, 6.84.

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(5) Melting points were determined by the capillary tube method using the Thomas-Hoover apparatus. They are uncorrected. The infrared spectra were taken on a Beckman IR5 spectrophotometer and the ultraviolet spectra were taken on a Carey Model 14 spectrophotometer.

(6) It appears that a complex with platinum was formed, analogous to the ferrous complex mentioned earlier. This complex formation slows down the hydrogenation.

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