Investigations Toward the Total Syntheses of Proaporphine and Homoproaporphine Alkaloids (1)

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The reaction of 1,2,3,5-tetrahydro-6-methoxy-1-[2-(4-methoxy-1,4-cyclohexadien-1-yl)ethyl]-1-methyl-7-isoquinolinol (**12**) with hot phosphoric acid afforded (±)-tetrahydro-homoglaziovine (**14**) in good yield. Similar treatment of 1,2,3,4-tetrahydro-6-methoxy-1-[2-(4-methoxy-1,4-cyclohexadien-1-yl)methyl]-2-methyl-7-isoquinolinol (**13**) did not produce the desired (±)-tetrahydroglaziovine (**18**) but rather a mixture of diastereomeric 4,5,6,6aϵ,7,7aϵ,8,9,11,11aϵ-decahydro-1-hydroxy-2-methoxy-6-methyl-10*H*-dibenzo[*de*,*g*]quinolin-1-ones (**16** and **17**) was obtained.

The proaporaphine alkaloids are a recently discovered group of alkaloids that are the precursors of some aporphine type alkaloids (2). These alkaloids were predicted by Barton and Cohen some six years before they were actually isolated from natural sources (3). More recently members of the homoproaporphine series have been isolated (4). This report describes a synthetic approach to these systems. The essential feature being the preparation and ring-closure of an appropriately substituted enol ether. The rationale for this synthesis comes from the Grewe synthesis of the morphinan ring system (5,6).

Several total syntheses of proaporphines have been reported (7). Other syntheses of pro- and homoproaporphine ring systems involving phenolic oxidative coupling of the requisite isoquinoline derivates have also appeared (*vide infra*).

The synthesis of the enol-ether derivative **5** was accomplished in a straightforward manner as shown on Chart I. Reaction of 3-methoxy-4-benzyloxyphenylethylamine (8) with 3-(*p*-methoxyphenyl)-propionic acid by the mixed anhydride procedure afforded amide **1** which was readily cyclized to the desired isoquinoline **3** using standard Bischler-Napieralski reaction conditions. The enol ether **5** was obtained by employing the Dryden modification (9) of the Birch reduction on the dihydroisoquinoline **3**. This procedure utilizes tetrahydrofuran and *t*-butyl alcohol as co-solvents with liquid ammonia. The compound was not obtained in the form of an analytically pure crystalline solid but its ir and nmr spectra were consonant with structure **5**. Mild acid treatment (saturated aqueous potassium bisulfate solution) gave a mixture from which two compounds were isolated after partition chromatography. These compounds are presumably a pair of diastereoisomers (**9a** + **b**). Both compounds exhibited, (a) carbonyl bands at 1715 cm^{-1} indicative of a six-membered ring ketone, (b) two aromatic protons and no vinyl type protons in the nmr, and (c) very similar mass spectral fragmentation patterns with the molecular ion at m/e 301. Treatment of enol ether **5** with other Lewis acids gave similar results and none of the desired homoproaporphine analog was obtained.

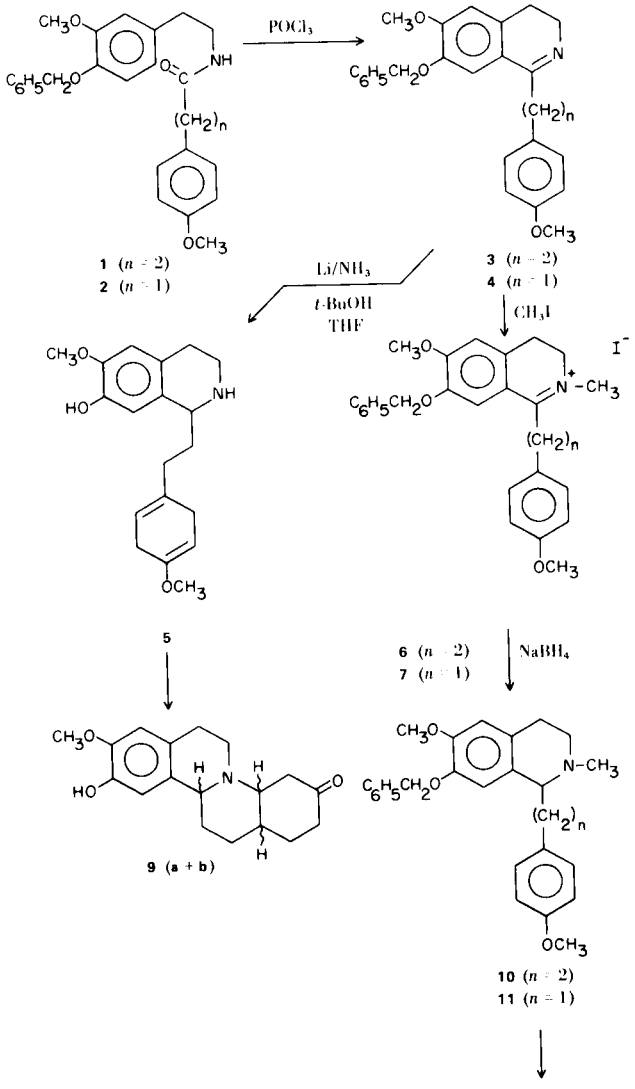
In order to avoid cyclization on nitrogen the synthesis of *N*-methyl derivative **6** was carried out by methylation of compound **3** (Chart I). Birch reduction, using the Dryden procedure (9), of methiodide **6** afforded only a low yield of a compound presumed to be the enol ether **12**. The tetrahydroisoquinoline **10** was then prepared by sodium borohydride reduction of **6**. Treatment of compound **10** with lithium in a mixture of liquid ammonia, *t*-butyl alcohol and tetrahydrofuran afforded a good yield of enol ether **12** as a white crystalline solid, identified by elemental analyses, infrared and nmr spectra. When the enol ether **12** was heated in phosphoric acid, cyclization occurred giving the desired (±)-tetrahydrohomoproaporphine **14**. The structure of this product was unequivocally established by the synthesis of the (±)-homoglaziovine **15** *via* oxidative coupling as described by Kametani, *et al.* (10,11,12) followed by treatment with hydrogen over palladium on carbon. The compound so obtained was identical to **14**, derived from the acid-catalyzed cyclization of enol ether **12** as shown by infrared spectroscopy and thin-layer chromatography.

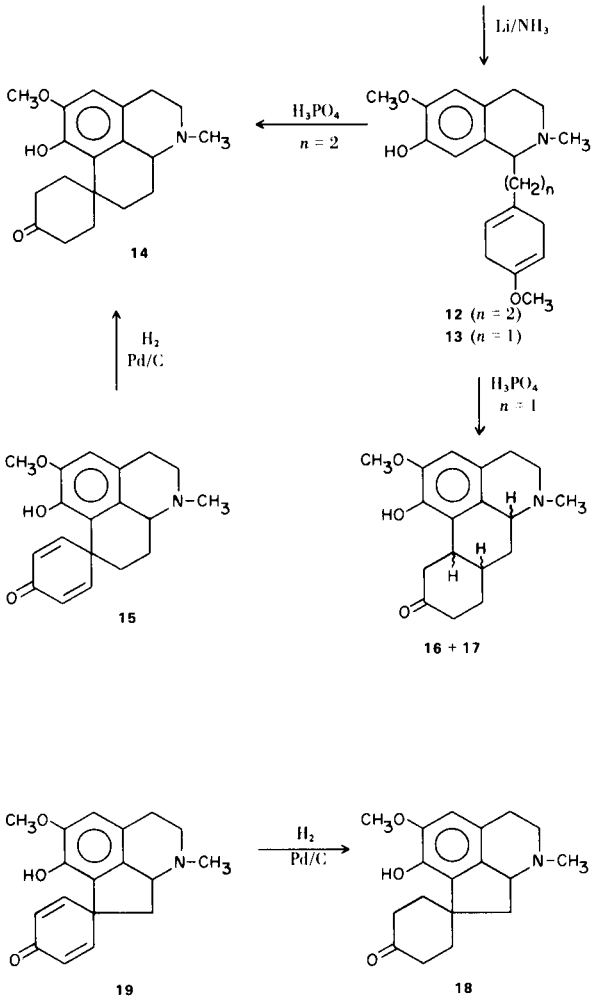
The success encountered in the above-described synthesis prompted us to investigate extension to the pro-

aporphine series. The synthesis of the requisite enol ether **13** was accomplished in a manner similar to that described for the homo analog **12**. Thus, amide **2** was cyclized using the Bischler-Napieralski method to afford dihydroisoquinoline **4** (Chart I). Methylation of compound **4** gave **7** and sodium borohydride reduction produced the tetrahydroisoquinoline **11** which was also formed by methylation of the compound obtained from borohydride reduction of **4** under Eschweiler-Clarke conditions. Compound **11** was readily converted to the crystalline enol ether **13** with the expected spectral properties, by the usual Dryden modification (9) of the Birch reduction.

When enol ether **13** was treated with hot phosphoric acid, two crystalline products were isolated after partition chromatography. Neither of these compounds was the

Chart I





desired (±)-tetrahydroglaziovine **18** as shown by comparison of their infrared spectra and thin-layer chromatographic behavior with an authentic specimen of **18** which was synthesized from (±)-glaziovine **19** [prepared in 1% yield as described by Kametani and Yagi (13)] by catalytic hydrogenation.

The two compounds (a major and minor isomer) obtained from acid treatment of enol ether **13** have been assigned structures **16** and **17**, but the available information does not allow differentiation between the two nor any stereochemical assignment. Both compounds exhibit only one unsplit aromatic proton proving that a Friedel-Crafts type cyclization has taken place. Mild acid treatment (saturated aqueous potassium bisulfate) of enol ether **13** gave a mixture whose infrared spectrum was indicative of α,β- and β,γ-unsaturated ketones derived from **13** with the latter predominating. Attempted ring-closure of this mixture using several different types of milder conditions gave back the mixture of ketones. More vigorous aqueous treatment (hot 6*N* hydrochloric acid) of this mixture afforded the same mixture of products as described

previously.

It is perhaps not surprising to find that the more stable six-membered ring compounds (**14** and **16** + **17**) were formed in the cyclization of both enol ethers **12** and **13** (14). Nor is it surprising that **12** readily cyclizes to spiro compound **14**, **13** containing one less carbon atom, does not cyclize to the spiro analog **18**. Similar arguments have been put forth by Kametani, *et al.*, (10) to explain the low yields of (±)-glaziovine (**19**) obtained by phenol oxidation reactions as compared to (±)-homoglaziovine (**15**).

EXPERIMENTAL

N-[4-(Benzyloxy)-3-methoxyphenethyl]-*p*-methoxyhydrocinnamamide (**1**).

p-Methoxyphenylpropionic acid (9.4 g., 0.0366 mole) was dissolved in 100 ml. of tetrahydrofuran and chilled in an ice-bath. To the stirred solution was added 8.7 ml. (0.0366 mole) of tri-*n*-butylamine followed in 5 minutes by 4.8 ml. (0.0366 mole) of isobutyl chloroformate. After an additional 10 minutes a cold solution of 9.4 g. (0.0366 mole) of 4-benzyloxy-3-methoxyphenethylamine (8) in 100 ml. of tetrahydrofuran was added to the mixture. The reaction mixture was stirred in the cold for 10 minutes at room temperature for 15 minutes, heated to boiling, cooled and poured into 200 ml. of water to afford a white crystalline product. The mixture was extracted with three 100-ml. portions of chloroform and then was washed with saturated sodium bicarbonate solution, 10% hydrochloric acid and saturated salt solution and then was dried (magnesium sulfate). Removal of the chloroform at reduced pressure gave a white crystalline solid which was recrystallized from chloroform:hexane, yield 10.1 g. (66%), m.p. 139-141° (lit. (15) 135-136°).

Anal. Calcd. for $C_{26}H_{29}NO_4$: C, 74.4; H, 6.97; N, 3.34. Found: C, 74.5; H, 7.08; N, 3.34.

7-(Benzyloxy)-6-methoxy-1-(*p*-methoxyphenethyl)-3,4-dihydroisoquinoline (**3**).

Compound **1** (10.0 g., 0.0238 mole) was added to 200 ml. of benzene containing 25 ml. of phosphorus oxychloride and refluxed for 1.5 hours. The solvent was removed at reduced pressure and the resulting crystalline solid was dissolved in 150 ml. of chloroform. The chloroform solution was shaken thoroughly with 150 ml. of 10% aqueous ammonium hydroxide, then 100 ml. of water followed by 100 ml. of saturated salt solution and dried (magnesium sulfate). Removal of the chloroform at reduced pressure gave an oil which was crystallized from ethyl acetate:hexane to give 6.6 g. of **3** as light yellow crystals; m.p. 87-90°. An additional 2.0 g., m.p. 84-94° (90% total yield) was obtained by concentrating the filtrate.

Anal. Calcd. for $C_{26}H_{27}NO_3$: C, 77.8; H, 6.78; N, 3.49. Found: C, 77.4; H, 6.80; N, 3.40.

1,2,3,4-Tetrahydro-6-methoxy-1-[2-(4-methoxy-1,4-cyclohexadien-1-yl)ethyl]-7-isoquinolinol (**5**).

A solution of compound **3** (17.7 g., 0.044 mole) in 150 ml. of tetrahydrofuran containing 150 ml. of *t*-butyl alcohol was added to 350 ml. of liquid ammonia in a dry ice/methanol bath over 0.5 hour with stirring. Lithium wire (10.5 g., 1.52 g.-atoms) was added over 10 minutes and the mixture was stirred in the dry ice bath for 5.0 hours. Ethanol (50 ml.) and then methanol (100 ml.) were added over a 1.5 hour period to decompose the excess lithium, followed by evaporation of the liquid ammonia. A solution of 350 ml. of saturated aqueous ammonium chloride was added and the mixture was extracted with two 250 ml. portions of chloroform. The combined chloroform extracts were washed with 250 ml. of saturated salt solution and then dried over magnesium sulfate. Evaporation of the chloroform left an oil which was crystallized from chloroform:hexane to afford 5.5 g. of **5** as white crystals; ir (chloroform) 1670 and 1695 cm^{-1} (enol ether bands); nmr (deuteriochloroform) δ 3.55 (s, 3, enol OCH_3), 3.84 (s, 3, aromatic OCH_3), 4.62 (m, 1, olefinic H), 5.44 (m, 1, olefinic H), 6.55 (s, 1, aromatic H), 6.67 (s, 1, aromatic H).

An additional 6.0 g. of **5** was obtained from the filtrate. The ir and nmr spectra were similar to that given by the first crop. No analytically pure sample could be obtained.

1,2,4,4a,6,7,11bβ-12,13,13a-Decahydro-10-hydroxy-9-methoxy-3*H*-dibenzo[*a*,*f*]quinolizin-3-ones (**9a** + **b**).

Enol ether **5** (1.0 g., 3.18 mmoles) was added to 10 ml. of saturated aqueous potassium bisulfate solution and stirred at room temperature for 0.5 hour. Water (10 ml.) was added to the reaction mixture and, after an additional 5.0 minutes, 2.5 ml. of concentrated ammonium hydroxide was added. The resulting gummy precipitate was extracted into chloroform and the chloroform solution was washed with saturated salt solution and dried (magnesium sulfate). Removal of the solvent at reduced pressure gave an oily residue which was chromatographed on 660 g. of Celite 545 using heptane:ethyl acetate:methanol:water (60:40:15:6) as the solvent system. Two major compounds were obtained in yields of 81 and 178 mg., respectively. Both products show ir (potassium bromide pellet) 1715 cm^{-1} (C=O) and nmr (deuteriochloroform) δ 3.82 (3H, s, OCH_3), 6.50 (1H, s, aromatic H), 6.72 (1H, s, aromatic H); calculated for $C_{18}H_{23}O_3N$, M.W. 301.4; found for both isomers, m/e 301. The fragmentation patterns of both compounds were very similar and did not allow any definite conclusions regarding exact structural assignments of **9a** + **b**.

7-(Benzyloxy)-3,4-dihydro-6-methoxy-1-(*p*-methoxyphenethyl)-2-methylisoquinolinium Iodide (**6**).

A solution of 12.4 g. (0.031 mole) of isoquinoline **3** was dissolved in 150 ml. of ethanol containing 15 ml. of methyl iodide and was refluxed for 2.5 hours. Removal of the solvents at reduced pressure afforded an oil which was crystallized from ethanol to yield 12.3 g. (73%) of **6** as yellow crystals, m.p. 141-143° (Lit. (15) m.p. 126-127°).

Anal. Calcd. for $C_{27}H_{30}NO_3I$: C, 59.7; H, 5.57; N, 2.58; I, 23.4. Found: C, 59.4; H, 5.41; N, 2.46; I, 23.5.

7-(Benzyloxy)-1,2,3,4-tetrahydro-6-methoxy-1-(*p*-methoxyphenethyl)-2-methylisoquinoline (**10**) Hydrochloride.

To a stirred mixture of methiodide **6** (25.2 g., 0.0465 mole) in 350 ml. of methanol containing 5 ml. of water was added 2.0 g. (0.053 mole) of sodium borohydride. Three more 2.0 g. portions of sodium borohydride were added after 10, 20 and 30 minutes and then the reaction mixture was refluxed for 1.0 hour. Evaporation under reduced pressure gave an oil which was slurried in 300 ml. of water and then extracted with three 100-ml. portions of chloroform. The combined chloroform extracts were washed with water and saturated salt solution and dried (magnesium sulfate). Evaporation of the solvent gave an oil which was dissolved in 300 ml. of absolute ethanol containing 8.0 ml. of concentrated hydrochloric acid. Removal of the solvents at

reduced pressure afforded an oil which was crystallized from ethanol-ether to yield 17.6 g. (84%) of **10**·HCl as white crystals, m.p. 149-151.5° (16).

Anal. Calcd. for $C_{27}H_{31}NO_3$·HCl: C, 71.4; H, 7.10; N, 3.09; Cl, 7.80. Found: C, 71.4; H, 7.15; N, 2.94; Cl, 7.82.

1,2,3,4-Tetrahydro-6-methoxy-1-[2-(4-methoxy-1,4-cyclohexadien-1-yl)ethyl]-2-methyl-7-isoquinolinol (**12**).

Compound **10** hydrochloride (9.5 g., 0.021 mole) was added to a solution of 100 ml. of liquid ammonia containing 50 ml. of tetrahydrofuran and 50 ml. of *t*-butyl alcohol in a dry ice and methanol bath. The mixture was stirred and lithium wire (2.5 g., 0.36 atom) was added, in small pieces, over 10 minutes. The stirring was continued for 4.5 hours in the cold bath followed by slow addition of 25 ml. of methanol to destroy the excess lithium. The ammonia was allowed to evaporate and then 200 ml. of saturated aqueous ammonium chloride solution was added. The aqueous solution was extracted with three 100-ml. portions of chloroform and the combined extracts were washed with saturated salt solution and then dried over magnesium sulfate. Removal of the chloroform at reduced pressure gave an oil which was crystallized from ether to yield 4.7 g. (68%) of **12** as white crystals, m.p. 111-113.5°; ir (chloroform): 3540 (OH), 1670 and 1695 cm^{-1} (enol ether bands); nmr (deuteriochloroform): δ 2.43 (s, 3, NCH_3), 3.55 (s, 3, enol OCH_3), 3.85 (s, 3, aromatic OCH_3), 4.62 (m, 1, olefinic NCH_3), 6.54 (s, 1, aromatic H), 6.67 (s, 1, aromatic H).

Anal. Calcd. for $C_{20}H_{27}NO_3$: C, 72.9; H, 8.26; N, 4.25. Found: C, 73.3; H, 8.18; N, 4.22.

(±)-Tetrahydrohomoglaziovine (**14**).

Method A.

A solution of enol ether **12** (3.2 g., 9.4 mmoles) in 60 ml. of 85% phosphoric acid was heated on a steam-bath for 4.0 hours, cooled and poured onto ice. The aqueous portion was brought to *p*H 8-9 by careful addition of 150 ml. of concentrated ammonium hydroxide solution and then extracted with five 100 ml. portions of chloroform. The combined chloroform extracts were washed with saturated salt solution and dried (magnesium sulfate). Evaporation of the solution at reduced pressure left a glass which was triturated with ether to give 1.7 g. (57%) of **14** as a white crystalline solid, m.p. 190-200°; tlc indicates a few minor impurities. Recrystallization from ethanol gave white crystals, m.p. 206-211° dec.; ir (potassium bromide pellet): 1710 (C=O); nmr (deuteriochloroform) δ 2.43 (3H, s, NCH_3), 3.84 (3H, s, OCH_3), 6.50 (1H, s, aromatic H).

Anal. Calcd. for $C_{19}H_{25}NO_3$: C, 72.4; H, 7.99; N, 4.44. Found: C, 72.4; H, 8.43; N, 4.27.

Method B.

(±)-Homoglaziovine (**15**) (10) (32 mg.) was dissolved in 5 ml. of ethanol containing 30 mg. of palladium on carbon and hydrogenated at atmospheric pressure for 1.0 hours. The catalyst was removed by filtration and the filtrate was evaporated to dryness at reduced pressure. The residue was purified by preparative thin layer chromatography using silica gel and acetonitrile, concentrated ammonium hydroxide (9:1) as solvent. The ir spectrum and tlc behavior of this product were identical with material prepared by Method A.

N-[4-(Benzyloxy)-3-methoxyphenyl]-2-(*p*-methoxyphenyl)acetamide (**2**).

Isobutyl chloroformate (24.0 g., 0.175 mole) was added to a stirred tetrahydrofuran solution of 29.0 g. (0.175 mole) of *p*-methoxyphenylacetic acid and 17.7 g. (0.175 mole) of *N*-methylmorpholine in an ice-methanol bath. After 5 minutes, a cold solution of 45.0 g. (0.175 mole) of 4-benzyloxy-3-methoxyphenethylamine was added and the mixture was stirred in the cold for 15 minutes and then at room temperature for 1.0 hour. The solvent was removed at reduced pressure and the residue was taken up in 500 ml. of chloroform and washed with saturated sodium bicarbonate, 5% hydrochloric acid and saturated salt solution and dried (magnesium sulfate). Removal of the chloroform gave an oil which was dissolved in hot ethyl acetate (200 ml.) and treated with Norit. Hexane was added to induce crystallization, yield 48.6 g. (69%) of amide **2** as a white crystalline solid, m.p. 109.5-112.5°. Recrystallization from ethyl alcohol gave white crystals, m.p. 110.5-113° (Lit. (17) m.p. 117°).

Anal. Calcd. for $C_{25}H_{27}NO_4$: C, 74.1; H, 6.71; N, 3.45. Found: C, 73.9; H, 6.73; N, 3.38.

7-(Benzyloxy)-6-methoxy-1-(*p*-methoxybenzyl)-3,4-dihydroisoquinoline (**4**) Hydrochloride.

A solution of amide **2** in 400 ml. of benzene containing 60 ml. of phosphorus oxychloride was refluxed for 3.0 hours and then evaporated under reduced pressure. The residual red-brown syrup was slurried in 400 ml. of toluene and again evaporated to dryness and then dissolved in 150 ml. of ethanol and chilled to give 16.6 g. (89%) of cream-colored crystals of **4** hydrochloride, m.p. 214-217° dec. (18).

Anal. Calcd. for $C_{25}H_{25}NO_3$·HCl: C, 70.8; H, 6.18; N, 3.31; Cl, 8.38. Found: C, 71.0; H, 6.26; N, 3.26; Cl, 8.47.

7-(Benzyloxy)-3,4-dihydro-6-methoxy-1-(*p*-methoxybenzyl)-2-methylisoquinolinium Iodide (**7**).

Compound **4**·HCl (8.5 g., 0.02 mole) in 130 ml. of ethanol was treated with sodium ethoxide and methyl iodide under nitrogen to give 5.5 g. (52%) of yellow crystals of **7**, m.p. 172-175° (Lit. (17) m.p. 167-168°).

Anal. Calcd. for $C_{26}H_{28}NO_3I$: C, 59.0; H, 5.34; N, 2.65; I, 24.0. Found: C, 58.8; H, 5.34; N, 2.34; I, 24.2.

7-(Benzyloxy)-1,2,3,4-tetrahydro-6-methoxy-1-(*p*-methoxybenzyl)-isoquinoline.

Compound **4**·HCl (20.3 g., 0.048 mole) was dissolved in 300 ml. of methanol containing 5.0 ml. of water. The solution was stirred and 2.0 g. of sodium borohydride was carefully added. Four more 2.0 g. portions of sodium borohydride were added at 10 minute intervals after which the mixture was refluxed for 1.0 hour. The solvent was removed at reduced pressure and 300 ml. of water was added. The mixture was extracted with three 100-ml. portions of chloroform and the combined extracts were washed with 100 ml. of saturated salt solution. The solution was dried over magnesium sulfate and evaporated to give an oil which was used for the preparation of **11**.

7-(Benzyloxy)-1,2,3,4-tetrahydro-6-methoxy-1-(*p*-methoxybenzyl)-2-methylisoquinoline (**11**) Hydrochloride.

Method A.

The above crude (from 0.048 mole of **4**·HCl) was dissolved in a mixture of 50 ml. of formaldehyde and 35 ml. of formic acid and refluxed for 3.0 hours and then evaporated under reduced pressure. The residual oil was slurried in 200 ml. of water, basified with 35 ml. of 5*N* sodium hydroxide and extracted with chloroform. The chloroform extract was washed with saturated salt solution, dried (magnesium sulfate) and evaporated to give 16.7 g. (86%) of **11** as an oil. A small portion was converted to the white crystalline hydrochloride salt, m.p. 141-143° (19).

Anal. Calcd. for $C_{26}H_{29}NO_3 \cdot HCl \cdot \frac{1}{2}H_2O$: C, 69.5; H, 6.98; N, 3.12; Cl, 7.93; H_2O, 2.0. Found: C, 68.9; H, 6.73; N, 3.06; Cl, 7.96; H_2O (K.F.), 2.5.

Method B.

A mixture of methiodide **7** (10.0 g., 0.019 mole) and 150 ml. of ethanol containing 5.0 ml. of water was treated with sodium borohydride (4.0 g., 0.015 mole) as described for compound **10** to give 7.5 g. (86%) of **11**·HCl as white crystals, m.p. 142-144°.

1,2,3,4-Tetrahydro-6-methoxy-1-[2-(4-methoxy-1,4-cyclohexadien-1-yl)methyl]-2-methyl-7-isoquinolinol (**13**).

Compound **11**·HCl (27.0 g., 0.060 mole) was added to a solution of 300 ml. of liquid ammonia containing 150 ml. of *t*-butyl alcohol and 150 ml. of tetrahydrofuran in a dry ice/methanol bath. Lithium wire (7.0 g., 1.01 atoms) was added over 15 minutes and the resulting mixture was stirred for 4.0 hours. This reaction was worked-up in a manner similar to that described for compound **12** to give 14.7 g. (78%) of the enol ether **13** as an oil; ν cm^{-1} (chloroform): 1660 and 1690; tlc indicated some minor impurities. Crystallization from ether gave **13** as white crystals, m.p. 78-80°; ir (chloroform): 1660 and 1690 cm^{-1} (enol ether bands); nmr (deuteriochloroform): δ 2.44 (3H, s, NCH_3), 3.54 (3H, s, enol OCH_3), 3.84 (3H, s, aromatic OCH_3), 4.63 (1H, m, =C-*H*), 5.41 (1H, m, =C-*H*), 6.55 (1H, s, aromatic *H*), 6.64 (1H, s, aromatic *H*).

Anal. Calcd. for $C_{19}H_{25}NO_3$: C, 72.4; H, 7.99; N, 4.44. Found: C, 72.0; H, 8.07; N, 4.09.

4,5,6,6aϵ,7,7aϵ,8,9,11,11aϵ-Decahydro-1-hydroxy-2-methoxy-6-methyl-10*H*-dibenzo[*de*,*g*]quinolin-10-ones (**16** +**17**).

Crude enol ether **13** (9.2 g., 0.029 mole) was dissolved in 160 ml. of 85% phosphoric acid and heated on a steam-bath for 3.0 hours, cooled, poured onto ice and brought to *p*H 8-9 by carefully adding 400 ml. of concentrated ammonium hydroxide. The mixture was extracted with three 250 ml. portions of chloroform and the combined extracts were washed with saturated salt solution and dried (magnesium sulfate). Removal of the solvent at reduced pressure gave an oil which was crystallized from acetonitrile using Norit to give 3.6 g. (41%) of product. Recrystallization from acetonitrile afforded two different types of tan crystals (yield 2.6 g.).

One g. of the above mixture was chromatographed on 675 g. of Celite 545 using heptane:ethyl acetate:diethylamine:water (75:25:15:6) as the solvent system. The two main fractions were evaporated to give 0.206 g. (6%) of fraction A and 0.645 g. (19%) of fraction B. Fraction B was crystallized from ethanol using Norit to give 0.33 g. of off-white crystals, m.p. 161-163°, of the major isomer; uv max (chloroform): 288 mμ (ϵ, 3,600); ir (chloroform): 3660 (OH), 1710 (C=O), 1630 cm^{-1}; nmr (deuteriochloroform): δ 2.47 (s, 3H, N-CH_3), 3.82 (s, 3H, O-CH_3), 6.50 (s, 1H, aromatic); mass spectrum m/e 301 (parent peak). Fraction A was combined with 0.184 g. obtained from a similar run and crystallized from ether and then recrystallized from chloroform:hexane to afford 0.109 g. of off-white crystals, m.p. 176-178°, of the minor isomer; uv max (chloroform): 288 mμ (ϵ, 3,600); ir (chloroform): 3660 (OH), 1710 (C=O), 1625 cm^{-1}; nmr (deuteriochloroform): δ 2.54 (s, 3H, N-CH_3), 3.84 (s, 3H, O-CH_3), 6.52 (s, 1H, aromatic); mass spectrum m/e 301 (parent peak).

(±)-Tetrahydroglaziovine (**18**).

A solution of (±)-glaziovine (**19**) (13) (24 mg.) in 5.0 ml. of ethanol was hydrogenated at atmospheric pressure over 10% palladium on carbon for 30 minutes. The product **18** was isolated as a light yellow oil by preparative thin-layer chromatography; ir 1710 cm^{-1} (C=O).

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(14) For a similar type cyclization involving a carbonium ion rearrangement see F. Schneider and K. Bernauer, *Helv. Chim. Acta*, **53**, 938 (1970).

(15) T. Kametani, S. Takano, and T. Kobari, *J. Chem. Soc.* (C), 2770 (1969).

(16) Reference 15 reports the isolation of the free base of this compound as a yellow syrup.

(17) T. Kametani, S. Takano, H. Iida, and M. Shinbo, *J. Chem. Soc.* (C), 298 (1969).

(18) Reference 17 reports the isolation of the free base as a yellow syrup.

(19) Reference 17 reports this compound as the picrate salt.