Syntheses in the Isoquinoline Series. Selective Demethylation of 6,7- and 7,8-Dimethoxy-2,3-dihydro-4(1H)-isoquinolones

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Treatment of 6,7- and 7,8-dimethoxy-2,3-dihydro-4(1H)-isoquinolones with a 1:1 mixture of 48% aqueous hydrobromic acid and glacial acetic acid at 115° leads to selective ether cleavage of the methoxyl group in position 6 or 8, respectively. The structure of the reaction products was ascertained by chemical transformation to the corresponding 1,2,3,4-tetrahydroisoquinolines and by ultraviolet analysis. This selective demethylation provides an easy route to 6-hydroxy-7-methoxy- or 8-hydroxy-7-methoxyisoquinoline derivatives.

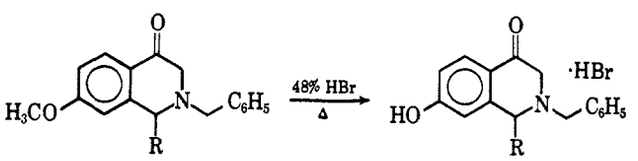
In the course of a synthesis of natural products containing aromatic hydroxyl and methoxyl groups it is often very convenient or necessary to have the hydroxyl groups protected. Usually they are protected as an ether, frequently the benzyl ether. Some serious disadvantages connected with benzyloxy derivatives are their lability and susceptibility to hydrogenolysis; in addition rather vigorous conditions are sometimes required for their preparation. On the other hand, methyl ethers can be prepared conveniently and, in many instances, under very mild and neutral conditions. However, their stability becomes a disadvantage when they have to be demethylated. In connection with our work in the field of isoquinolines we became interested in the potential of partial or selective O-demethylation as a useful synthetic tool for obtaining various hydroxy- and alkoxy-substituted compounds.

Prior to our work, Brossi and coworkers[1-3] reported the preferential cleavage of the 7-methoxyl group in 6,7-dimethoxy-3,4-dihydroisoquinoline and 6,7,8-trimethoxy-3,4-dihydroisoquinoline upon treatment with 63% aqueous hydrobromic acid or concentrated sulfuric acid and 20% hydrochloric acid, respectively. Since 3,4-dihydroisoquinolines can be readily reduced with sodium borohydride to the corresponding 1,2,3,4-tetrahydroisoquinolines, a convenient route to 6-methoxy-7-hydroxy- and 6,8-dimethoxy-7-hydroxyisoquinoline derivatives is available. The selective O-demethylation in these cases is explained by preferential protonization of the methoxyl group with the highest electron density (position 7). The basicity of the methoxyl groups in position 6 or 8 is reduced owing to their conjugation with the protonated imino group.

In order to achieve selective demethylation of the methoxyl groups at C-6 or C-8, it is necessary to have isoquinoline derivatives which have a low electron density at the methoxyl group in position 7. It was anticipated that this effect could be obtained by introducing a carbonyl group in position 4.[4] Therefore we studied the demethylation of 6,7- and 7,8-dimethoxy-2,3-dihydro-4(1H)-isoquinolones, the preparation of which was subject of the preceding papers.[5]

Results and Discussion

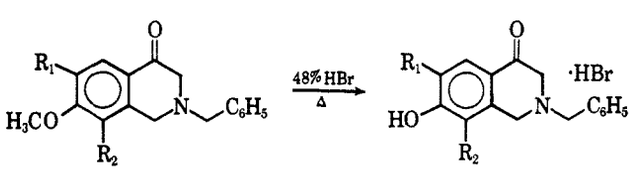
The O-demethylation of monomethoxy derivatives of 2,3-dihydro-4(1H)-isoquinolones is normally carried out by heating the compound with boiling 48% aqueous hydrobromic acid for at least 5 hr; examples are the preparation of **3** and **4** from **1** and **2**, respectively.



1, R = H
2, R = CH_3

3, R = H
4, R = CH_3

Treatment of the dimethoxy derivatives **5** and **7** with 48% aqueous hydrobromic acid under the same conditions gave the completely demethylated products **6** and **8**.

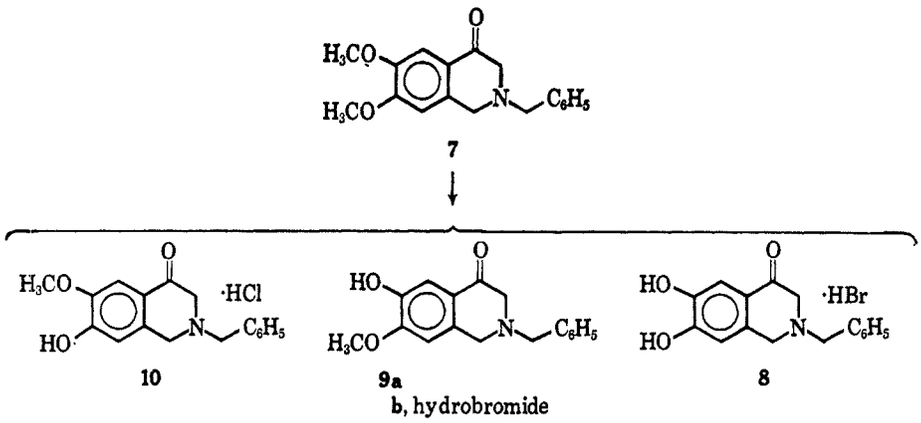


5, R_1 = H; R_2 = OCH_3
7, R_1 = OCH_3; R_2 = H

6, R_1 = H; R_2 = OH
8, R_1 = OH; R_2 = H

The selective O-demethylation of dimethoxy-2,3-dihydro-4(1H)-isoquinolones was first studied with the 6,7-dimethoxy derivative **7**. Optimal reaction conditions with respect to reaction time and temperature were worked out by following the course of the reaction by thin layer chromatography. Heating a solution of **7** in a 1:1 mixture of 48% aqueous hydrobromic acid and glacial acetic acid at 115° for 3 hr gave in 80% yield one major product which was accompanied by three minor components. Two of these were identified as starting material **7** and as the dihydroxy derivative **8**, respectively, by comparison with authentic material. The third minor component which was isolated only in a very small amount is isomeric with the major product. This was proven by elemental analyses and nmr spectra which showed only one methoxyl group. For reasons outlined above, the major product can be expected to have structure **9**; correspondingly, structure **10** would have to be assigned to the minor isomer. These assignments were ascertained by a careful study of the ultraviolet absorption of these compounds.

(1) A. Brossi, M. Baumann, and R. Borer, *Monatsh. Chem.*, **96**, 25 (1965).
(2) A. Brossi and R. Borer, *ibid.*, **96**, 1409 (1965).
(3) H. Bruderer and A. Brossi, *Helv. Chim. Acta*, **48**, 1945 (1965).
(4) After our work was completed, the selective demethylation of 3,4-dimethoxy substituted aromatic aldehydes and ketones was reported by A. Brossi, H. Gurien, A. I. Rachlin, and S. Teitel, *J. Org. Chem.*, **32**, 1269 (1967).
(5) (a) G. Grethe, H. L. Lee, M. Uskoković, and A. Brossi, *ibid.*, **33**, 491 (1968); (b) *ibid.*, **33**, 494 (1968).



In absolute ethanol the absorption spectra of both compounds exhibit a benzenoid band at 235 mμ and two-electron transfer (ET) bands at 279 and 322 mμ for **9b** and 281 and 315 mμ for **10** (Figures 1 and 2). Since it is known that in sodium acetate solution only rather strongly acidic phenolic hydroxyl groups are dissociated,[6] the uv spectra were recorded in absolute ethanol saturated with sodium acetate. As demonstrated in Figure 1 practically no dissociation occurred

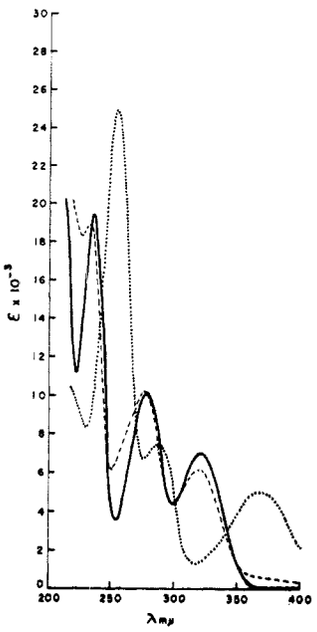


Figure 1.

with **9b**, while **10** exhibited a bathochromic shift of the principal ET band to 352–353 mμ (Figure 2) indicating dissociation of the relatively acidic phenolic hydroxyl group *para* to the carbonyl function. The bathochromic shift seen in the uv spectra of both compounds in 0.002 *M* ethanolic sodium ethoxide is in accord with the fact that all phenolic hydroxyl groups, except those which are sterically hindered, are dissociated under these conditions.[6]

Moreover, the good agreement of the observed and calculated principal ET band[7] of the anions of **9b** and **10** (Table I), the difference in the pK_a values of both compounds (Table I), and the fact that hydrogenation

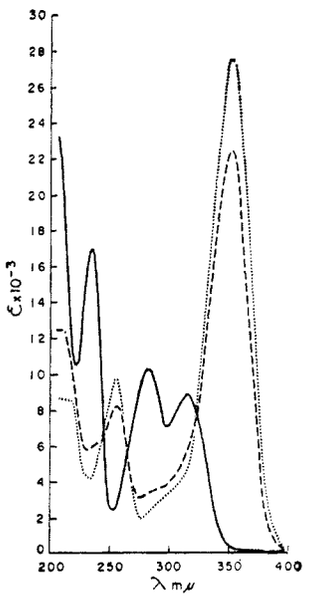


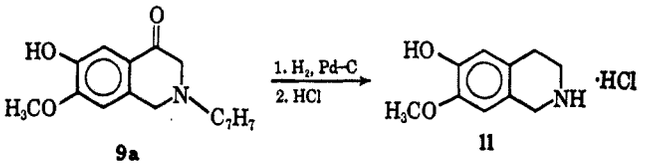
Figure 2.

TABLE I

	Electron transfer bands in 0.002 *M* ethanolic sodium ethoxide, mμ		
	Calcd[a]	Obsd	pK_a
9b	294	288	9.0
10	334	352	7.5
12a	294	297	8.9
15	294	285	9.6
16	334	348	7.8

[a] See ref 7.

of **9a** gave the known 1,2,3,4-tetrahydroisoquinoline **11**[8,9] supported the structural assignments.



In analogy with these results, the corresponding demethylation of 7,8-dimethoxy-2,3-dihydro-4(1H)-isoquinolones would be expected to occur selectively at position 8. This prediction was verified experimentally. Thus, treatment of 2-benzyl-2,3-dihydro-7,8-dimethoxy-4(1H)-isoquinolone (**5**) with a 1:1 mixture of

(6) L. Jurd, *Arch. Biochem. Biophys.*, **66**, 284 (1957).
(7) A. I. Scott, *Experientia*, **17**, 68 (1961).
(8) J. M. Bobbit, J. McNew Kiely, K. L. Khanna, and R. Eberman, *J. Org. Chem.*, **30**, 2247 (1965).
(9) D. Beke and C. Szantay, *Acta Chim. Acad. Sci. Hung.*, **14**, 325 (1958).

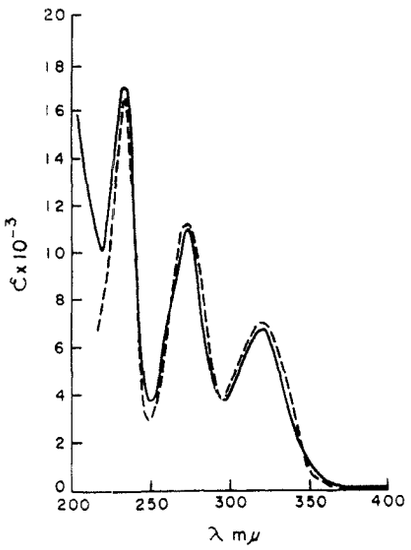


Figure 3.

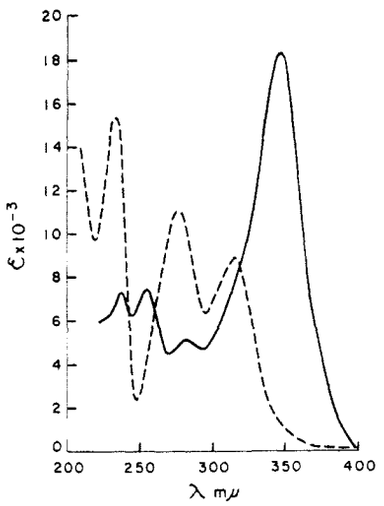
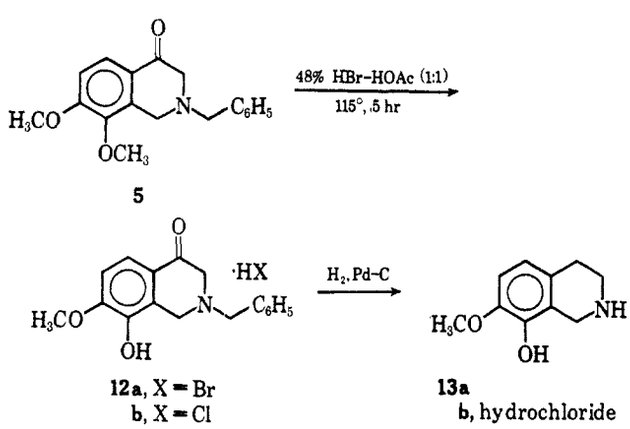


Figure 4.

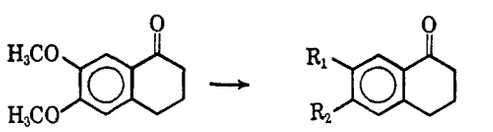
48% aqueous hydrobromic acid and glacial acetic acid at 115° for 5 hr gave the expected compound **12a** in yields exceeding 80%. The structural assignment was ascertained by spectral data, particularly ultraviolet. As in the case of compound **9b**, the spectrum of **12a** when recorded in ethanol saturated with sodium acetate showed no bathochromic shift of the ET band at 284 mμ, *i.e.*, no dissociation of the phenolic hydroxyl group was observed, in agreement with the expectation that this derivative is the less acidic of the two possible monohydroxyl compounds. The fact that hydrogenation of the free base of **12** at high pressure and elevated temperature afforded the known 1,2,3,4-tetrahydroisoquinoline **13**[8] secured the structure of this product.



12a, X = Br
b, X = Cl

13a
b, hydrochloride

In order to appraise the effect of the nitrogen atom, the isostere of **7**, 2,3-dihydro-6,7-dimethoxy-1(4H)-naphthalenone (**14**),[10] was demethylated under identical conditions. The crude reaction mixture contained, in addition to some starting material, three other compounds which could be separated by preparative thin layer chromatography to give compounds **15**, **16**, and **17** in a ratio of 14:2:1. This indicated that preferential demethylation had taken place, as expected, at the methoxyl group in position 7. The dihydroxy derivative **17** was identified by its mass spectrum, which exhibited the molecular ion peak at *m/e* 178; its melting point was identical with that reported in the literature.[11] The assignment of structures **15** and **16** to the isomeric monohydroxy derivatives was again made on the basis of the uv analysis. The spectra of **15** and **16** in ethanol and ethanol saturated with sodium acetate are represented in Figure 3 and Figure 4, respectively.



14

15, R_1 = OH; R_2 = OCH_3
16, R_1 = OCH_3; R_2 = OH
17, R_1 = R_2 = OH

Figure 4 indicates that compound **16** is ionized in ethanolic sodium acetate solution as shown by the bathochromic shift of the principal ET band from 277 to 348 mμ, while the less acidic 7-hydroxy isomer **15** does not exhibit this shift in this medium (Figure 3). The pK_a's of the two compounds, which differ by 1.8 units, are given in Table I. Furthermore, the position of the observed principal ET band of the anions is in good agreement with the calculated value[7] (Table I).

The fact that the course of these selective demethylations is qualitatively the same for the tetralone and isoquinolone series shows that the presence of a nitrogen atom has practically no effect.

The results reported in this paper combined with the findings of Bruderer and Brossi[3] on the selective demethylation of 3,4-dihydroisoquinolines open interesting synthetic possibilities for the preparation of various types of isoquinoline alkaloids which contain aromatic hydroxyl and methoxyl substituents. The scheme is made even more attractive by the fact that 2,3-dihydro-4(1H)-isoquinolones can be converted readily into 3,4-dihydroisoquinolines *via* the corresponding 1,2,3,4-tetrahydroisoquinolines, and, depending at which point the ether cleavage is carried out, differently hydroxymethoxy-substituted isoquinoline derivatives can be obtained from the same starting material.

(10) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 1248 (1958).

(11) T. Monose, H. Oya, Y. Ohkura, and M. Iwasaki, *Chem. Pharm. Bull.* (Tokyo), **2**, 119 (1954).

Experimental Section[12]

2-Benzyl-2,3-dihydro-7-hydroxy-4(1H)-isoquinolone Hydrobromide (3).—A solution of 14 g of **1**[5] in 100 ml of 48% aqueous hydrobromic acid was heated at 120° with stirring for 2 hr. Glacial acetic acid (100 ml) was added, and heating at reflux was continued for another 3 hr. Evaporation of the solvent under reduced pressure gave a solid residue which, after recrystallization from methanol, gave 15.2 g (87%) of **3**, mp 243–244°. Two recrystallizations from methanol gave analytically pure **3**: mp 246–248° dec with sublimation starting at 225°; ν_{max}^{KBr} 3080 (center of multiple bands, *t*-amine salt and OH), 1680 (C=O), 1610 and 1580 (phenyl), and 1295 and 1220 cm^{-1} (OH); λ_{max}^{EtOH} 222 mμ (ε 12,800), 285 (15,050), $\lambda_{max}^{0.1\text{-}N\ KOH\text{-}50\%\ EtOH}$ 247 mμ (ε 7800), 337 (28,800).

Anal. Calcd for $C_{16}H_{15}NO_2 \cdot HBr$ (334.23): C, 57.50; H, 4.83; N, 4.19. Found: C, 57.52; H, 4.99; N, 4.26.

2-Benzyl-2,3-dihydro-7-hydroxy-1-methyl-4(1H)-isoquinolone Hydrobromide (4).—This compound was obtained from **2**[5a] in 92% yield by the same method described for **3**. After recrystallization from methanol, **4** had mp 254–255°; ν_{max}^{KBr} 3110 (broad, OH), 2600 (broad, *t*-amine salt), 1682 (C=O), and 1286 and 1208 cm^{-1} (OH); $\lambda_{max}^{CH_3OH}$ 222 mμ (ε 12,800), 288 (13,100); $\lambda_{max}^{0.1\ N\ KOH}$ 236 mμ (ε 9400), 336 (30,700).

Anal. Calcd for $C_{17}H_{17}NO_2 \cdot HBr$ (348.26): C, 58.63; H, 5.21; N, 4.02. Found: C, 58.97; H, 5.08; N, 3.93.

The hydrochloride had mp 256–258° after recrystallization from methanol.

Anal. Calcd for $C_{17}H_{17}NO_2 \cdot HCl$ (303.80): C, 67.21; H, 5.97; N, 4.61. Found: C, 67.15; H, 6.22; N, 4.56.

2-Benzyl-7,8-dihydroxy-2,3-dihydro-4(1H)-isoquinolone Hydrobromide (6).—A solution of 3 g of **5**[5b] in 100 ml of 48% aqueous hydrobromic acid in an open flask was heated in an oil bath at 150° for 4 hr. The flask was then fitted with a reflux condenser, and the reaction mixture was refluxed for 16 hr. During this time a precipitate formed. The mixture was cooled to room temperature, and the precipitate was collected by filtration. Recrystallization from methanol gave 2.7 g (77%) of **6**, mp 256–257° dec. For analysis a sample was recrystallized twice from methanol and dried at 65° under reduced pressure for 15 hr: mp 250–253° dec; ν_{max}^{KBr} 3285 (OH), 2720 and 2600 (*t*-amine salt), 1690 (C=O), 1605 and 1595 (phenyl), and 1218 and 1258 cm^{-1} (OH); λ_{max}^{MeOH} 237 mμ (ε 15,200), 288 (9500), 314–316 (8000) (unstable in 0.1 *N* KOH); nmr (DMSO-d_6), δ 4.17 (2 H, s, broad CH_2–CO), 4.58 and 4.70 (2 H each, s, CH_2–N–CH_2), 7.05 and 7.45 (2 H, AB pattern, J = 9 cps, C_5–H and C_6–H), 7.56 (5 H, phenyl), *ca.* 10.4 (3 H, b, OH and $^+$NH).

Anal. Calcd for $C_{16}H_{15}NO_3 \cdot HBr$ (350.23): C, 54.87; H, 4.61; N, 4.00. Found: C, 54.58; H, 4.69; N, 4.10.

2-Benzyl-6,7-dihydroxy-2,3-dihydro-4(1H)-isoquinolone Hydrobromide (8).—A stirred solution of 2.6 g of **7**[5] in 80 ml of 48% aqueous hydrobromic acid was heated at 125° for 5 hr. Removal of the solvent under vacuum gave a crystalline residue which was treated with 30 ml of ethanol. The solid material (**8**), collected by filtration, weighed 2.5 g (91%), mp 234–236°. Recrystallization from methanol–ether afforded analytically pure **8**: mp 234–236°; ν_{max}^{KBr} 3280 (center of multiple bands, OH and *t*-amine salt), 1690 (C=O), 1610 (phenyl), and 1300, 1240, and 1200 cm^{-1} (OH); $\lambda_{max}^{isopropyl\ alcohol}$ 239 mμ (ε 16,500), 281–282 (10,000), 323 (8400); $\lambda_{max}^{0.1\ N\ KOH}$ 267–268 mμ (ε 12,100), 328 (8200), 388 (14,200).

Anal. Calcd for $C_{16}H_{15}NO_3 \cdot HBr$ (350.24): C, 54.87; H, 4.61; N, 4.00. Found: C, 54.58; H, 4.59; N, 4.00.

Preferential O-demethylation of 2-benzyl-2,3-dihydro-6,7-dimethoxy-4(1H)isoquinolone (7).—A solution of 4 g of **7**[5] in 160 ml of a 1:1 mixture of glacial acetic acid and 48% aqueous hydrobromic acid was heated at 115° for 4 hr. The solvent was removed under reduced pressure at 40–50°. The residue was dried by repeated addition and removal by distillation under reduced pressure of 50 ml of a 1:1 mixture of ethanol–benzene. The crystalline residue was dissolved in water and the pH was adjusted to 8.5 by the addition of ammonium hydroxide. The mixture was extracted three times with chloroform, and the combined organic solution was washed, dried, and filtered. Evaporation of the filtrate under reduced pressure afforded 3 g of crystalline residue, mp 160–168°. This crude material was dissolved in warm acetonitrile and, on cooling, 1.3 g of crystalline precipitate was obtained. The solid obtained by evaporating the filtrate was dissolved in a minimum amount of a mixture of acetonitrile–ammonium hydroxide (95:5) and chromatographed on 500 g of silica gel (Grace-Davison; i.d. of column = 55 mm) with acetonitrile–ammonium hydroxide (95:5) as the liquid phase.[13] After an initial empty fraction (75 ml) two cuts of 75 ml each were collected, combined, and evaporated under reduced pressure. The solid residue (581 mg) was dissolved in ethanol, and addition of ethanolic hydrogen chloride gave 518 mg (11%) of the hydrochloride of **7**,[5] mp 215–218°. The chromatography was continued by collecting cuts of 100 ml each. Fractions 6 and 7 were combined and, after evaporation of the solvents, 202 mg of solid was obtained. This was combined with the 1.3 g of crystalline material already obtained. A small amount (260 mg) was recrystallized from ethanol to give **2-benzyl-2,3-dihydro-6-hydroxy-7-methoxy-4(1H)-isoquinolone (9a)**: mp 171–174°; $\nu_{max}^{CHCl_3}$ 3550 (OH), 1684 (C=O), 1620 (phenyl), and 1296 cm^{-1} (OCH_3); $\lambda_{max}^{CH_3OH}$ 233 mμ (ε 20,700), 275 (12,050), 318–320 (7800); nmr (DMSO-d_6), δ 3.17 (2 H, s, CH_2–CO), 3.64 and 3.65 (2 H each, s, (CH_2–N–CH_2), 3.78 (3 H, s, OCH_3), 6.81 and 7.21 (1 H each, s, aromatic protons), 7.30 (5 H, s, phenyl), 9.23 (1 H, s, OH).

Anal. Calcd for $C_{17}H_{17}NO_3$ (283.33): C, 72.07; H, 6.05; N, 4.94. Found: C, 72.00; H, 6.19; N, 5.06.

A solution of **9a** (1.24 g) in methanol, on addition of ethanolic hydrogen bromide, gave 1.31 g (27%) of the crystalline hydrobromide **9b**, mp 222–226°. Two recrystallizations from methanol furnished pure **9b**: mp 224–229°, decomposition at >210°; pK_a 9; ν_{max}^{KBr} 3210 (OH), 2705 and 2605 (*t*-amine salt), 1697 (C=O) 1605 (phenyl), 1286 (OCH_3), and 1213 and 1208 cm^{-1} (OH); for uv data, see Figure 1; nmr (DMSO-d_6), δ 3.82 (3 H, s, OCH_3), 4.14 (2 H, b, CH_2–CO), 4.52 and 4.58 (2 H each, s, CH_2–$^+$N–CH_2), 7.06 and 7.29 (1 H each, s, aromatic protons), 7.4–7.7 (5 H, cp, phenyl).

Anal. Calcd for $C_{17}H_{17}NO_3 \cdot HBr$ (364.26): C, 56.06; H, 4.98; N, 3.85; Br, 21.94. Found: C, 56.02; H, 5.05; N, 3.88; Br, 22.24.

After several cuts totalling 800 ml which, after evaporation, contained 112 mg of a mixture of compounds, elution with 800 ml of the solvent mixture gave 481 mg of solid material. This was dissolved in ethanol and, on addition of ethanolic hydrogen chloride, a crystalline precipitate was obtained. Two recrystallizations from methanol gave 30 mg (1%) of **2-benzyl-2,3-dihydro-7-hydroxy-6-methoxy-4(1H)-isoquinolone hydrochloride (10)**: mp 208–218°; ν_{max}^{KBr} 3160 (broad, OH), 2550 (broad, *t*-amine salt), 1680 (C=O), 1610, 1585 (phenyl), 1310 (OCH_3), and 1220 and 1210 cm^{-1} (OH); for uv data, see Figure 2; nmr (DMSO-d_6), δ 3.80 (3 H, s, OCH_3), 3.90 and 3.95 (2 H, AB-pattern, J = 4 cps, CH_2–CO), 4.37 and 4.42 (2 H each, s, CH_2–$^+$N–CH_2), 6.81 and 7.33 (1 H each, s, aromatic protons), 7.3–7.7 (5 H, cp, phenyl); pK_a 7.5.

Anal. Calcd for $C_{17}H_{17}NO_3 \cdot HCl$ (319.80); C, 63.85; H, 5.67; N, 4.38. Found: C, 63.82; H, 5.73; N, 4.43.

The dihydroxy derivative **8** could not be isolated from the reaction mixture, but its presence was indicated by tlc.

2-Benzyl-2,3-dihydro-6-hydroxy-7-methoxy-4(1H)-isoquinolone Hydrobromide (9b).—A solution of 4 g of **7**[5] in 40 ml of 48% aqueous hydrobromic acid was heated at 120° for 1.5 hr. Then 40 ml of glacial acetic acid was added and refluxing was continued for 2.5 hr. The solvent was removed under reduced pressure, and the solid residue was washed with ethanol and subsequently with acetone. Recrystallization from methanol gave 3.8 g (78%) of **9b**, mp 226–228°.

(12) Melting points were taken in capillaries with a Thomas–Hoover melting point apparatus and are uncorrected. Infrared spectra were determined with a Beckman infrared spectrophotometer Model IR-5 or IR-9. The uv spectra were recorded on a Cary Recording spectrophotometer Model 14M. The apparent pK_a's were estimated from spectral data at various pH's. The pH's were measured on a Beckman Research pH-meter Model 1019 using conventional electrodes at room temperature. The ionic strength of the buffers was adjusted to 0.01 between pH 2 and 10. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 or HA-100 spectrophotometer, and chemical shifts are reported in δ using tetramethylsilane as internal reference (δ 0). The following abbreviations are used in connection with the nmr data: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (b) broad featureless peak, (cp) complex band pattern, (m) multiplet. Unless stated otherwise, organic solutions were dried over sodium sulfate.

(13) The progress of the chromatography and the purity of the fractions were monitored by tlc on silica gel F_{254} (Merck) with acetonitrile–ammonium hydroxide (95:5) as the mobile phase. With this system compounds **7**, **9**, and **10** have R_f values of 0.92, 0.6, and 0.2, respectively, while **8** does not move.

1,2,3,4-Tetrahydro-7-methoxy-6-isoquinolinol Hydrochloride (11).—A solution of 256 mg of **9a** in 50 ml of glacial acetic acid was hydrogenated over 10% palladium on charcoal (100 mg) at 88–108° and 65 atm until the hydrogen uptake ceased (2 hr). The catalyst was removed by filtration and washed thoroughly with warm methanol. The combined filtrate and washings were evaporated under reduced pressure, and the residue was dissolved in 5 ml of ethanol. The solution was acidified with isopropanolic hydrogen chloride and, on addition of ether, 89 mg of crystalline precipitate was obtained. Recrystallization from ethanol–ether gave 41 mg (21%) of **11**, mp 255–257°. A second crystalline fraction (32 mg, mp 250–252°) was obtained from the mother liquor. Recrystallization of the first fraction from ethanol afforded 27.6 mg of **11**, mp 256–258.[14] This compound was identical on tlc (silica gel DF-5, Camag; the solvent system was acetonitrile–ammonium hydroxide (9:1)) with material prepared by another route.[15]

2-Benzyl-2,3-dihydro-8-hydroxy-7-methoxy-4(1H)-isoquinolone Hydrobromide (12a).—A suspension of 4.3 g of **5**[5b] in 180 ml of a mixture of 48% hydrobromic acid and glacial acetic acid (1:1) was heated at 115° for 5 hr. The solvent was removed under reduced pressure at 50°, and the solid residue was recrystallized from methanol–ether to give 4.6 g (87%) of **12a**, mp 233–240° dec. An analytical sample was recrystallized from methanol–ether: mp 237–240° dec (vacuum); ν_{max}^{KBr} 3295 (broad, OH), 2560 (broad, *t*-amine salt), 1682 (C=O), 1610 (phenyl), 1295 and 1255 (OCH_3), and 1210 cm^{-1} (OH); λ_{max}^{EtOH} 235 mμ (ε 18,500), 284 (10,000), 316 (6800); λ_{max} (in ethanol saturated with sodium acetate) 234 mμ (ε 17,900), 283 (9800), 311–312 (5800); λ_{max} (in 0.002 *M* sodium ethoxide) 255–256 mμ (ε 24,400), 297 (5350), 367–368 (4800); nmr (DMSO-d_6), δ 3.93 (3 H, s, OCH_3), 4.20 (2 H, broad s, CH_2–CO), 4.60 and 4.70 (2 H each, s, CH_2–$^+$N–CH_2), 7.0–7.8 (C_5–H, C_8–H, and phenyl).

Anal. Calcd for $C_{17}H_{17}NO_3 \cdot HBr$ (364.26): C, 56.06; H, 4.98; N, 3.85. Found: C, 55.90; H, 4.80; N, 3.76.

The hydrobromide **12a** (1 g) was suspended in 25 ml of water, the same volume of chloroform was added, and excess ammonium hydroxide was added to the vigorously stirred mixture. The chloroform layer was separated immediately, and the aqueous solution was extracted twice with chloroform. The combined organic solution was washed with water, dried, and filtered. The filtrate was evaporated under reduced pressure. The residue was dissolved in methanol, excess isopropyl alcoholic hydrogen chloride was added and the crystalline hydrochloride **12b** formed which was recrystallized twice from hot methanol, mp 235–240° dec (vacuum).

Anal. Calcd for $C_{17}H_{17}NO_3 \cdot HCl$ (319.80): C, 63.85; H, 5.67; N, 4.38; Cl, 11.09. Found: C, 64.01; H, 5.67; N, 4.32; Cl, 11.04.

1,2,3,4-Tetrahydro-7-methoxy-8-isoquinolinol Hydrochloride (13b).[8]—A solution of 740 mg of the free base of **12** in 100 ml of glacial acetic acid was hydrogenated over 10% palladium on charcoal at 120° and 80 atm for 2 hr. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure. The residue was dissolved in ethanol and, on addition of isopropyl alcoholic hydrogen chloride, 310 mg (55%) of the crystalline hydrochloride **13b** precipitated, mp 283–284°. A mixture melting point with an analytical sample prepared by an alternative route[8] showed no depression. Compound **13b** and the analytical sample were identical on tlc (silica gel F_{254} Merck; the solvent system was acetonitrile–ammonium hydroxide (9:1)).

A vigorously stirred suspension of **2** g of **13b** in 15 ml of water and 30 ml of chloroform was adjusted to pH 9.5 by the addition of ammonium hydroxide. The chloroform layer was separated, and the aqueous part was extracted immediately with three 30-ml portions of chloroform. The combined organic solution was washed with water (30 ml), dried, and filtered. The filtrate, on evaporation under reduced pressure, gave 1.6 g (96%) of the crystalline free base **13a**. Two recrystallizations from hot ethanol yielded analytically pure **13a** as yellow crystals, mp 178–180°,[16] after drying at 55° for 24 hr under reduced pressure: nmr (DMSO-d_6), δ 2.52 and 2.80 (2 H each, t, J = 5.5 cps, CH_2-3 and CH_2-4), 3.67 (5 H, s, OCH_3 and CH_2-1), *ca.* 5.2 (2 H, b, NH, OH), 6.38 and 6.63 (2 H, AB pattern, J = 8 cps, C_5-H, C_6-H); λ_{max}^{EtOH} 230 mμ (ε 5800) (sh), 280 (2170); $\lambda_{max}^{0.1\ N\ KOH}$ 245 mμ (ε 7400), 290 (4220); $\nu_{max}^{CHCl_3}$ 3540 (OH), 1282 and 1240 cm^{-1} (OCH_3).

Anal. Calcd for $C_{10}H_{13}NO_2$ (179.22): C, 67.02; H, 7.31; N, 7.82. Found: C, 66.97; H, 7.54; N, 7.92.

Preferential O-Demethylation of 2,3-Dihydro-6,7-dimethoxy-1(4H)-naphthalenone (14).—A solution of 1 g of **14**[17] in 40 ml of a mixture of 48% aqueous hydrobromic acid and glacial acetic acid (1:1) was heated at 115° for 5 hr. The solvent was removed under reduced pressure, and the residue was purified by preparative tlc on silica gel (ten plates, 20 × 20 mm; silica gel DSF-5, Camag, 1-mm thickness; the mobile phase was benzene–ethyl acetate (8:2)). The plates were developed three times. Four zones detectable by ultraviolet light were removed from the plates and each was eluted with 100 ml of ethyl acetate. The silica gel was removed by filtration and the filtrates were evaporated under reduced pressure. From the first zone (highest R_f value) 162 mg of crystalline material was obtained which, after three recrystallizations from ether–petroleum ether (30–60°) gave 69 mg (7%) of starting material **14**, mp 97–98°. A mixture melting point with authentic material[17] showed no depression. The second zone (86 mg) was recrystallized from ether–petroleum ether (30–60°) to yield 37 mg (4%) of **2,3-dihydro-6-hydroxy-7-methoxy-1(4H)-naphthalenone (16)**, mp 115–118°. Recrystallization from the same solvent gave 27 mg of analytically pure **16**: mp 117–119.5°; $\nu_{max}^{CHCl_3}$ 3530 (OH), 1670 (C=O), 1620 and 1586 (phenyl), 1280 (OCH_3), and 1230 cm^{-1} (OH); for uv data taken in ethanol and ethanol saturated with sodium acetate, see Figure 4; λ_{max} (in 0.002 *M* sodium ethoxide) 254 mμ (ε 9470), 295 (3400) (sh), 348 (27,600); pK_a 7.8.

Anal. Calcd for $C_{11}H_{12}O_3$ (192.22): C, 68.73; H, 6.29. Found: C, 68.60; H, 6.50.

The third zone gave 326 mg of crystalline material which was recrystallized from ether to afford 259 mg (28%) of **2,3-dihydro-7-hydroxy-6-methoxy-1(4H)naphthalenone (15)**, mp 148–152°. Two recrystallizations from ether yielded 166 mg of pure **15**: mp 149–152°; $\nu_{max}^{CHCl_3}$ 3555 (OH), 1675 (C=O), 1620 (phenyl), 1288 and 1271 (OCH_3), and 1232 cm^{-1} (OH); for uv data taken in ethanol and ethanol saturated with sodium acetate, see Figure 3; λ_{max} (in 0.002 *M* sodium ethoxide) 253 mμ (ε 23,300), 285 (8200), 365 (5450); nmr ($CDCl_3$), δ 2.08 (2 H, m, CH_2-3), 2.60 and 2.88 (2 H each, t, J = 6 cps, CH_2-2 and CH_2-4), 3.95 (3 H, s, OCH_3), 5.85 (1 H, exchangeable with D_2O, s, OH), 6.70 and 7.60 (1 H each, s, C_5–H and C_8–H); pK_a 9.6.

Anal. Calcd for $C_{11}H_{12}O_3$ (192.22): C, 68.73; H, 6.29. Found: C, 68.92; H, 6.41.

The last zone gave 83 mg of solid material which, on crystallization from ether–petroleum ether (30–60°), yielded 21 mg (2%) of **2,3-dihydro-6,7-dihydroxy-1(4H)-naphthalenone (17)**, mp 186–192°. After two recrystallizations from the same solvent, **17** melted at 192–195°.[18]

Registry No.—**3**, 15287-89-5; **4**, 15287-90-8; **4** HCl, 15287-91-9; **6**, 15287-92-0; **8**, 15287-93-1; **9a**, 15287-94-2; **9b**, 15287-95-3; **10**, 15287-96-4; **11**, 1078-27-9; **12a**, 15287-98-6; **12b**, 15287-99-7; **13a**, 1010-72-6; **15**, 15288-01-4; **16**, 15288-02-5.

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(14) In ref 8 compound **11** is reported to have mp 260–263°, while ref 9 gives mp 247–249°.

(15) This compound was prepared by Dr. A. Bruderer of F. Hoffmann-La Roche and Co. Ltd., Basle, and has mp 260–261°.

(16) H. W. Gibson, in a private communication (University of Notre Dame, Department of Chemistry, Notre Dame, Ind.) reported mp 177–179°.

(17) This compound was prepared by Dr. K. Fahrenholtz of these laboratories.

(18) Reference 11 gives mp 195°.