and worked up in the usual way. Thus a clear gum (**15b**, almost quantitative yield) was obtained which crystallized on standing for 5 days. A tlc examination of **15b** indicated it to be approximately 95% pure; infrared spectrum showed λ_{max} 2.91 μ (NH) and absence of carbonyl absorption.

Without further purification, hydrazone **15b** (0.15 g, 0.50 mmol) was dissolved in toluene (5 ml, previously dried over sodium) and added portionwise, over 1.5 hr, to a heated (100°) and stirred solution of potassium *t*-butoxide[30] (0.11 g, 0.98 mmol, freshly sublimed) in toluene (4 ml). The temperature was then raised so that the mixture refluxed gently. A tlc examination (alumina GF, 1% CH_3OH-$CHCl_3$) after 3 hr indicated that most of the hydrazone had reacted; therefore, another equivalent (0.55 g, 0.49 mmol) of potassium *t*-butoxide was added and refluxing was continued another hour. The mixture was cooled, H_2O was added, and the product was extracted into $CHCl_3$. The usual work-up gave a brownish oil, 0.12 g, which appeared mostly as three components on tlc (20% CH_3OH-$CHCl_3$) but as one peak for the desired **2** on vpc. Sublimation of the crude oil at 110° gave a light yellow sublimate which spontaneously crystallized, 0.10 g. The latter was further purified by preparative tlc (20% CH_3OH-$CHCl_3$) and afforded 0.05 g (36%) of crystalline **2**, mp 115–120°. Sublimation at 90°, crystallization from CH_3OH-H_2O, and one further sublimation gave the analytical sample: mp 122–124°; $[\alpha]^{20}D$ −10° (*c* 1.1); nmr δ 2.33 (6 H, aromatic CH_3 and N-CH_3), 3.83 (3 H, OCH_3), 4.50 (multiplet, C-6a H).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.95; H, 8.45.

(30) Obtained from MSA Research Corp., Callery, Pa.

Registry No.—**2**, 17278-09-0; **3**, 115-37-7; **7**, 17245-36-2; **9b**, 17245-37-3; **10**, 17245-38-4; **11a**, 17245-39-5; **11b**, 15357-89-8; **12**, 17245-41-9; **13**, 17245-42-0; **14**, 17245-43-1; **15a**, 17245-44-2; **16a**, 17245-45-3.

Acknowledgment.—The authors wish to express their gratitude to Dr. Everette L. May of these laboratories for many helpful discussions and to Dr. G. W. A. Milne, National Heart Institute, for the mass spectra.

Transformations in the Morphine Series. IV.[1a] Conversion of Thebaine into 1-Methyl-3a-(3′-hydroxy-6′-methylphenyl)-4,2′-oxidooctahydroindole by Two Different Routes. A Rearrangement *via* an Aziridinium Intermediate[1b]

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The synthesis of octahydroindole **5a** by two different routes is discussed. Reduction ($LiAlH_4$) of mesylate **3b** gave, through the aziridinium intermediate **4**, rearrangement product **5a**. This structure was proved by an independent synthesis. Thus, ketone **6** on reduction ($NaBH_4$) gave alcohols **7a** and **8a**. Mesylation of **7a** gave **7c** which on heating in benzene gave **9a**. Ionic exchange converted **9a** into its bromide form **9b**. Dry distillation of **9b** afforded **5a**, which was correlated with a racemic sample of the same compound reported by Japanese workers. The stereochemistry of **7a** and **8a** were proven by nmr analysis of their respective acetates, **7b** and **8b**. Compound **5a** was inactive as an analgesic in mice, while the phenolic **5b** had an ED_{50} of 25 mg/kg, as determined by the hot-plate method.

In the preceding paper of this series,[1a] the synthesis of the methanobenzofuro[3,2-*d*]azocine **1** from the corresponding ketone **2** was accomplished by a modified Wolff–Kishner reduction but only after numerous other approaches failed. The intention of this paper is to discuss the rearrangement that occurred during one of these approaches, the synthesis of this rearranged product by another route, and its identification with a degradation product obtained from the naturally occurring alkaloid, galanthamine.[2]

Sodium borohydride reduction of **2** readily afforded the axial (α, with respect to the carbocyclic ring) alcohol **3a**.[1a] Actually, the conformation of the hydroxyl in **3a** was not immediately apparent, but in the light of further work and the synthesis of the diastereomer by another route (as described later) it was assigned the α configuration. Tosylation of **3a** in pyridine failed, starting material being recovered, whereas mesylation in pyridine readily esterified the alcohol to give the mesylate **3b**. The latter was not stable, and, if allowed to remain overnight, it gradually decomposed to a more polar compound. As previously described,[1a] $LiAlH_4$ treatment of **3b** gave a 39% yield of what had initially[3] been assigned structure **1**.

The instability of **3b** suggested the possibility of an intermediate aziridinium (*viz.*, **4**) being formed during $LiAlH_4$ treatment. If the mesylate exists in the configuration shown (**3b**), then the 1,2-*trans* diaxial arrangement of the nitrogen and mesyl group is ideal for an internal displacement of the latter group by the pair of electrons on the nitrogen. This then would lead to the formation of either compound **1** or the octahydroindole **5a**, depending on the point of attack of the hydride ion. The formation of aziridinium and cyclic ammonium compounds through displacement of leaving groups by tertiary nitrogen, and of their ring opening by hydride ion, is well documented[4] (Scheme I).

That this rearrangement occurred to the octahydroindole **5a** has now been proven by an independent synthesis and direct comparison with an authentic racemic sample.[2] The starting material for the

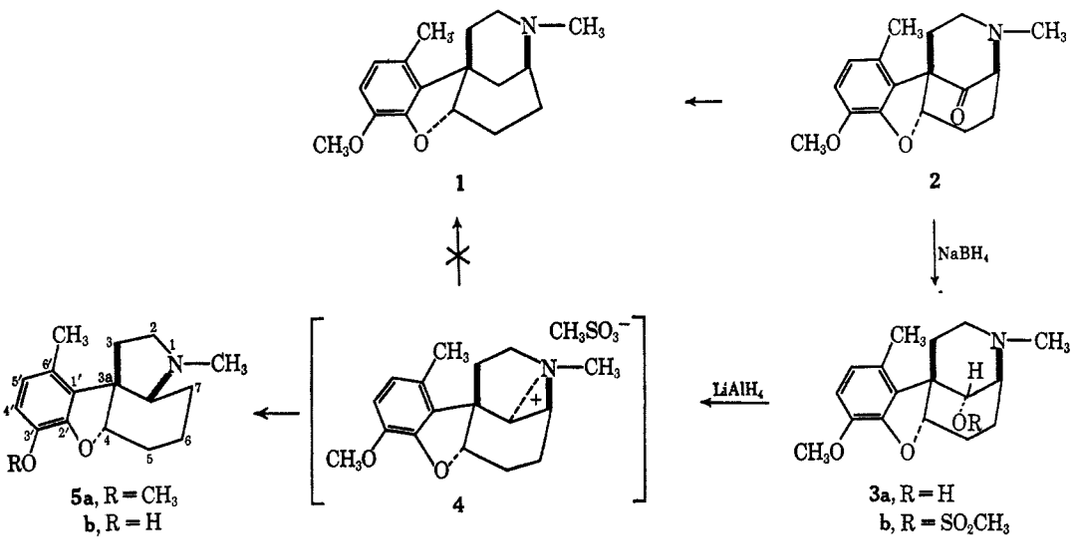
(1) (a) Part III: M. Mokotoff and L. J. Sargent, *J. Org. Chem.*, **33**, 3551 (1968). (b) Presented in part at the 156th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, Atlantic City, N. J. Sept 1968. (c) University of Pittsburgh, School of Pharmacy, Pittsburgh, Pa. 15213.

(2) H. Mishima, M. Kurabayashi, and I. Iwai, *ibid.*, **28**, 2621 (1963).

(3) M. Mokotoff and L. J. Sargent, 154th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, Chicago, Ill., Sept 1967, Abstracts, p 20P.

(4) (a) S. Okuda, S. Yamaguchi, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **13**, 1092 (1965); (b) E. M. Fry, *J. Org. Chem.*, **30**, 2058 (1965); (c) E. Wenkert and N. V. Bringi, *J. Amer. Chem. Soc.*, **81**, 1474 (1959); (d) C. Hootele, J. Pecher, U. Renner, and R. H. Martin, *Chimia*, **21**, 133 (1967); [*Chem. Abstr.*, **67**, 43983*y* (1967)]; (e) J. Harley-Mason, A.-ur-Rahman, and J. A. Beisler, *Chem. Commun.*, 743 (1960); (f) K. Biemann and M. Friedmann-Spiteller, *J. Amer. Chem. Soc.*, **83**, 4805 (1961).

SCHEME I



alternate synthesis was the methyl ketone **6**, prepared as previously described.[1a] Reduction of **6** with $NaBH_4$ gave a mixture of the epimeric alcohols **7a** and **8a**. Column chromatography of this mixture on silica gel afforded the α alcohol **7a** in 90% yield and the β alcohol **8a** in 6% yield. These assignments are based on the nmr data for alcohols **7a** and **8a** and their respective acetates **7b** and **8b**. The α alcohol **7a** showed hydroxyl proton at δ 3.07, whereas β alcohol **8a**, which can hydrogen bond to the nitrogen, showed hydroxyl proton further downfield at δ 4.32, at approximately equal concentrations and temperature; both protons were exchangeable with D_2O. It is known that the band position of a proton is very sensitive to hydrogen bonding, causing downfield shifts.[5] Furthermore, β acetate **8b** showed a three-proton singlet at δ 2.07, the usual place for an acetate methyl, whereas the α acetate **7b** showed the acetate methyl resonance upfield at δ 1.53. This upfield shift is readily explained when one examines a model of **7b** and notes that the acetate methyl lies perpendicular to the plane of the aromatic ring and thus is quite shielded,[6] a conformation which is not possible with β acetate **8b**.

When ketone **6** was reduced catalytically with Pt and H_2, an 84% yield of pure **7a** was obtained.[7] The high stereospecificity of the reduction could perhaps be attributed to prior complexing of the amine function with the catalyst surface[8a] or to assistance of hydride ion transfer by participation of the amine function.[8b]

Cyclization to the octahydroindole system was effected by conversion of α alcohol **7a** into its corresponding mesylate **7c** and refluxing the latter in benzene. Because of the proximity of the nitrogen to the mesylate, a facile cyclization[4] occurred, thus affording a 70% yield of crystalline methanesulfonate salt **9a**. The nmr spectrum supported the structure of **9a** with five singlet methyl peaks at δ 2.43 (aromatic CH_3), 2.70 ($CH_3SO_3^-$), 3.42 and 3.63 [$^+N(CH_3)_2$, shifted downfield and separated into two peaks], and 3.87 (OCH_3).

Compound **9a** was converted into the bromide salt **9b** by ion exchange with Amberlite IRA-400 AG in the bromide form.[9] The nmr spectrum of **9b** in D_2O showed resonance for only four singlet methyl peaks at δ 2.47 (aromatic CH_3), 3.27 and 3.48 [$^+N(CH_3)_2$, separated into two peaks], and 3.88 (OCH_3). Dry distillation of **9b** eliminated methyl bromide and afforded octahydroindole **5a** in 59% yield (Scheme II). This compound was identical in all respects (infrared spectrum, melting point, mixture melting point, and $[\alpha]D$) with **5a** prepared *via* $LiAlH_4$ reduction of the mesylate **3b**.

Conversion of **5a** into phenol **5b** was effected in 87% yield by refluxing with 48% HBr. The structure was substantiated by the following data: λ_{max} 2.77 μ (phenolic OH); nmr δ 5.55 (broad, phenolic H) and absence of OCH_3 signal; mass spectral molecular ion at *m/e* 259.

Mishima and coworkers[2] reported the preparation of the racemic octahydroindole **5a** by a degradative scheme from the alkaloid, galanthamine. Direct comparison of the Mishima sample[10] and our sample in the infrared showed them to be identical in $CHCl_3$ solution but different in the solid state (KBr pellet). This is to be expected[11] since the Mishima sample from galanthamine is racemic, whereas **5a**, as prepared by both routes from thebaine, is optically active. Although the optical rotation ($[\alpha]D$) of **5a** from thebaine is 0, it has a specific rotation ($[\alpha]^{C_2H_5OH}$) of $-104°$ at 310 mμ in its ORD curve. On the other hand, **5a** as prepared from galanthamine[2] shows no optical activity either at the D line of sodium or in its ORD curve.

May and coworkers[12] have established, in systems analogous to **2**, that one can direct the course of reduction of certain α-amino ketones depending on

(5) Roy H. Bible, Jr., "Interpretation of NMR Spectra. An Empirical Approach," Plenum Press, New York, N.Y., 1965, p 59.

(6) See ref 5, pp 17 and 18. The author wishes to thank Dr. E. D. Becker of these institutes for helpful discussions concerning some of the nmr data.

(7) Alcohol **7a** is identical with the previously reported alcohol **10**[1a] which was isolated as a by-product in the Raney nickel reduction of the dithioacetal ketone **9b**.[1a]

(8) (a) H. O. House, H. C. Muller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963), and references therein; (b) T. Matsumoto, T. Nishida, and H. Shirahama, *ibid.*, **27**, 79 (1962).

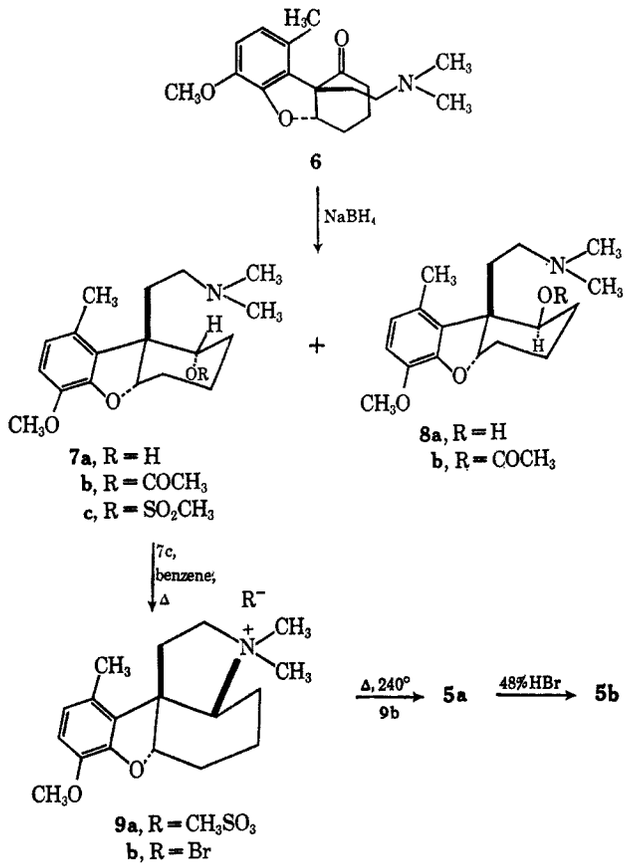
(9) B. M. Iselin and J. C. Sowden, *J. Amer. Chem. Soc.*, **73**, 4984 (1951).

(10) The author thanks Dr. H. Mishima, Sankyo Co., Ltd., Tokyo, Japan, for a generous supply of racemic **5a**.

(11) A. Goosen, E. V. O. John, F. L. Warren, and K. C. Yates, *J. Chem. Soc.*, 4038 (1961).

(12) (a) E. L. May and H. Kugita, *J. Org. Chem.*, **26**, 188 (1961); (b) E. L. May, H. Kugita, and J. H. Ager, *ibid.*, **26**, 1621 (1961); (c) H. Kugita and E. L. May, *ibid.*, **26**, 1954 (1961); (d) S. Saito and E. L. May, *ibid.*, **26**, 4536 (1961).

SCHEME II



whether there is a free pair of electrons available on the nitrogen or not. Thus, the free base **10** was converted into the α isomer **11** by either catalytic hydrogenation or hydride reduction, while the β isomer **12** was produced from the quaternary salt **13** under comparable conditions[8a,12] (Scheme III). It was, therefore, expected that $NaBH_4$ reduction of the free base **2** would give the α alcohol **3a**. This has been substantiated by the ready formation of the aziridinium intermediate **4** and subsequent rearrangement to **5a**, which one would expect only from a *trans*-diaxial arrangement as in **3b**. If, however, the mesyl group was in the β position, then $LiAlH_4$ treatment would be more likely to give compound **1**. Following the work of May, *et al.*,[12] the methobromide **14** (prepared as previously reported)[1a] was reduced with $NaBH_4$ to **15** which on dry distillation afforded the equatorial (β, with respect to the carbocyclic ring) alcohol **16a**. This alcohol had a different ir spectrum from that of **3a**, yet gave the same mass spectral fragmentation pattern as **3a**. This could be expected for isomeric alcohols. Furthermore, the higher melting point of **16a** (190.5–191.5°) compared with that of **3a** (145–146°) supported the β configuration of the hydroxyl in **16a** since only in this configuration can the hydroxyl hydrogen bond with the nitrogen. Alcohol **16a** gave a stable mesylate **16b**, which could be isolated in crystalline form. However, $LiAlH_4$ treatment of **16b** did not give **1** nor cause rearrangement to **5a**, but simply caused O–S cleavage to **16a** (Scheme III), a further substantiation of the β configuration of **16a**.

The analgetic activities of **5a** and **5b** were determined in mice by the hot-plate method.[13] Compound **5a** showed no activity while **5b** had an ED_{50} of 25 mg/kg, approximately one-third the activity of codeine.[14]

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are corrected. Microanalyses were performed by the Analytical Services Section of this institute, under the direction of Dr. William C. Alford. Mass spectra were determined on both an LKB Model 9000 and an Associated Electronics Industries, MS-9, mass spectrometer. The nmr spectra were determined as solutions in $CDCl_3$ with TMS as internal standard (unless stated otherwise) on a Varian A-60 spectrometer. Chemical shifts are recorded as δ values in parts per million. Optical rotations were determined in $CHCl_3$ (unless stated otherwise) on a Rudolph 338 polarimeter or a Perkin-Elmer 141 automatic polarimeter and are corrected to the nearest degree. All extractions utilized $CHCl_3$ (unless stated otherwise) with Mayer reagent as an end point test; the pooled $CHCl_3$ solutions were combined, washed twice with H_2O, dried with Na_2SO_4, and concentrated under reduced pressure. Skellysolve B refers to petroleum ether of bp 66–75°.

9b-[2-(Dimethylamino)ethyl]-3,4,4a,9b-tetrahydro-6-methoxy-9-methyl-1α(2H)-dibenzofuranol (7a) and 1β Alcohol 8a.—Compound **6** (1.00 g, 3.30 mmol) was dissolved in CH_3OH (45 ml) and treated dropwise while stirring with a solution of $NaBH_4$ (0.50 g, 13 mmol) in CH_3OH (15 ml). After an additional 20 min the solution was diluted with excess H_2O. The bulk of the CH_3OH was removed under reduced pressure, and the product was extracted in the usual way. The resulting light orange oil was chromatographed on a column of silica gel (50 g) which was packed as a slurry in 10% benzene–ether. By gradually increasing the polarity, the higher R_f component or α alcohol **7a** (0.90 g) was eluted with 7% CH_3OH–$CHCl_3$ and solidified on standing. Repeated crystallization from Skellysolve B gave the analytical sample of **7a**: mp 98–98.5°; $[\alpha]^{25}D$ −26° (*c* 1.0); nmr, δ 3.85 (4 H, C-1β H hidden under OCH_3 peak); mass spectral molecular ion at *m/e* 305.

Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 71.02; H, 8.84; N, 4.45.

A portion of **7a** was converted into its acetate **7b** with pyridine and acetic anhydride by the usual procedure: $\lambda_{max}^{CHCl_3}$ 5.79 μ (acetate).

By increasing the polarity to 10% CH_3OH–$CHCl_3$, the lower R_f component or β alcohol **8a** was eluted and gave 0.06 g of noncrystalline homogeneous product: nmr, δ 4.05 (multiplet, C-1α H); mass spectral molecular ion at *m/e* 305. A small portion of **8a** was crystallized from acetone–Skellysolve B: mp 225–230°. The much higher melting point of the β alcohol **8a** compared with that of the α alcohol **7a** is indicative of hydrogen bonding between the amine and OH functions in the former compound. The remainder of **8a** was converted into its acetate **8b** as described above for **7b**: $\lambda_{max}^{CHCl_3}$ 5.75 μ (acetate).

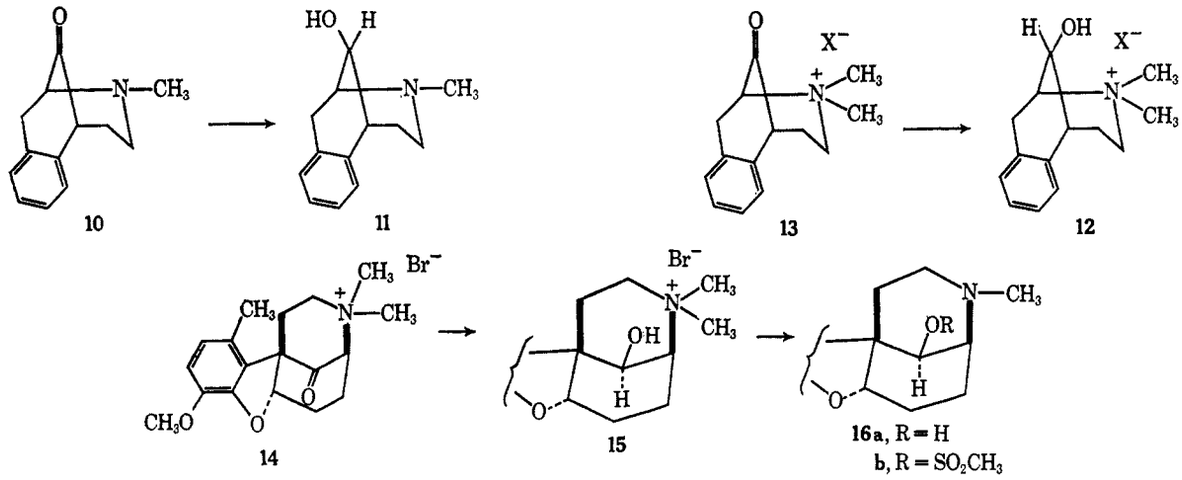
The α alcohol **7a** could be more readily obtained by catalytic reduction of ketone **6**. Thus 1.00 g (3.30 mmol) of **6** in CH_3OH (50 ml) was added to a suspension of Pt (from reduction of 0.5 g of PtO_2) in CH_3OH (50 ml) and hydrogenated under 1 atm of H_2 for 24 hr (calculated uptake of H_2, 80 cc; observed, 85 cc). The catalyst was filtered and the filtrate was concentrated to a gum which was crystallized from Skellysolve B; the yield in three crops was 0.84 g (84%), mp 97–98°, and it was uncontaminated with the β alcohol **8a**.

1,1-Dimethyl-3a-(3′-methoxy-6′-methylphenyl)-4,2′-oxidooctahydroindole Methanesulfonate Salt (9a).—The alcohol **7a** (0.40 g, 1.38 mmol) dissolved in pyridine (5 ml) and cooled in ice was treated dropwise with a cold solution of methanesulfonyl chloride (0.80 ml) in pyridine (3 ml). This solution was stirred at 0° for 2 hr, decomposed with an ice–water mixture, and extracted in the usual way with CH_2Cl_2. The resulting oily mesylate **7c** was dissolved in benzene (40 ml) and refluxed overnight on a steam bath, and the resulting tan crystalline product was collected and crystallized from $CHCl_3$–ether. The yield was 0.37 g (70%) of **9a**, mp 215.5–216.5°. Repeated crystallizations, once utilizing Norit, gave the colorless analytical sample: mp 214.5–216°; $[\alpha]^{25}D$ +19° (*c* 1.0).

(13) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). The author thanks Mrs. L. Atwell for these data.

(14) A. E. Jacobson and E. L. May, *J. Med. Chem.*, **8**, 563 (1965).

SCHEME III



Anal. Calcd for $C_{19}H_{29}NO_5S$: C, 59.50; H, 7.62; N, 3.65. Found: C, 59.45; H, 7.31; N, 3.83.

1,1-Dimethyl-3a-(3′-methoxy-6′-methylphenyl)-4,2′-oxidooctahydroindole Bromide Salt (9b).—Amberlite IRA-400 AG (55 g) ion-exchange resin (Rohm and Haas) was converted into the bromide form by stirring with three 100-ml portions of 4.8% aqueous HBr, followed by three washings with H_2O. A portion of the above-prepared resin was added to a solution of **9a** (0.25 g, 0.65 mmol) dissolved in H_2O (25 ml). The mixture was stirred for 4 hr and filtered, and the resin was stirred for 15 min with fresh H_2O. Pooling of the aqueous solutions and concentration to dryness, under reduced pressure, gave the crude product. The latter was dissolved in $CHCl_3$, dried (Na_2SO_4), and concentrated to a solid mass which was crystallized from $CHCl_3$–ether, yielding 0.24 g (quantitative) of methobromide **9b**, mp 242–248° dec uncor. The analytical sample had mp 251–252° dec uncor and $[\alpha]^{25}D$ +29° (*c* 1.25).

Anal. Calcd for $C_{18}H_{26}NO_2Br$: C, 58.70; H, 7.12; N, 3.80; Br, 21.70. Found: C, 58.49; H, 7.25; N, 3.65; Br, 21.99.

1-Methyl-3a-(3′-methoxy-6′-methylphenyl)-4,2′-oxidooctahydroindole (5a).—Alcohol **3a**[15a] (1.25 g, 4.3 mmol) in pyridine (15 ml) was cooled in ice and treated dropwise with a cold solution of methanesulfonyl chloride (2.0 ml) in pyridine (8 ml). After stirring for 1.5 hr at 0°, H_2O and ice were added and the mixture was extracted with CH_2Cl_2 in the usual way. Concentration gave a yellow oil (**3b**). The latter was not purified further but was immediately dissolved in purified tetrahydrofuran (60 ml), heated to reflux under a nitrogen atmosphere, and treated dropwise with a clear ethereal solution of $LiAlH_4$ (30 ml, *ca.* 1.5 *M*). This mixture was stirred and refluxed for 40 min, cooled for 20 min, and decomposed, while cooling, with a little H_2O and excess $CHCl_3$. The organic layer was separated by filtration and the inorganic material was extracted twice with boiling $CHCl_3$. The combined $CHCl_3$ solutions were worked up in the usual way and concentrated to a yellow oil which slowly crystallized. Sublimation of the latter at 100° under high vacuum and crystallization of the sublimate from CH_3OH–H_2O afforded 0.46 g (39%) of colorless crystalline **5a**. Recrystallization and sublimation gave the analytical sample: mp 91.5–92.5°; $[\alpha]^{25}D$ +19° (HBr salt, *c* 0.77, H_2O);[15] nmr, δ 2.30, 2.33 (3 H each, N-CH_3 and aromatic CH_3), 3.90 (3 H, OCH_3), 4.47 (multiplet, C-4 H).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.46; H, 8.19; N, 5.36.

Short-path, dry distillation of **9b** (0.105 g, 0.28 mmol) under high vacuum at an air-bath temperature of 240° gave a crystalline sublimate (62 mg). Crystallization of this sublimate from CH_3OH–H_2O yielded, in two crops, 46 mg (59%) of **5a**, mp 92.5–93°, which was identical (infrared spectrum, melting point, mixture melting point, and $[\alpha]D$) with a sample prepared as reported above.

1-Methyl-3a-(3′-hydroxy-6′-methylphenyl)-4,2′-oxidooctahydroindole (5b).—Methyl ether **5a** (0.40 g, 1.5 mmol) and 48% of aqueous HBr (5.0 ml) were heated to reflux for 20 min in a preheated (160°) oil bath. Upon cooling, crystals of the HBr salt of **5b** appeared which were dissolved in H_2O and converted into the free base by basification with NH_4OH. The resulting mixture was extracted in the usual manner, thereby giving a tan solid which was crystallized from CH_3OH–H_2O, yielding (in two crops) 0.33 g (87%) of phenol **5b**, mp 143–144°. Two sublimations at 120° gave the analytical sample: mp 142–142.5°; $[\alpha]^{25}D$ +20°(HBr salt, *c* 1.0, H_2O);[16] nmr, δ 2.28 (6 H, singlet with shoulder when spectrum expanded, aromatic CH_3 and N-CH_3), 4.55 (multiplet, C-4 H).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.07; H, 8.06; N, 5.28.

2,3,4,5,6,6a-Hexahydro-8-methoxy-3,11-dimethyl-1H-4,11b-methanobenzofuro[3,2-*d*]azocin-12β-ol (16a).—Methobromide **14**[15a] (0.30 g, 0.79 mmol) dissolved in CH_3OH (25 ml) was treated dropwise with a solution of $NaBH_4$ (0.20 g) in CH_3OH (10 ml), stirred for 1.5 hr, and decomposed with H_2O (20 ml). After stirring another 15 min, the solution was concentrated to a solid which was further dried *in vacuo* over P_2O_5. The solid was crystallized from CH_3OH–ether and gave 0.27 g of **15**. Without further purification, all of **15** was subjected to short-path, dry distillation under high vacuum at an air-bath temperature of 220°. The resulting crystalline material was first washed directly in the tube with a small amount of isopropyl ether to remove contaminating impurities. The remaining crystalline material was dissolved in $CHCl_3$ and concentrated to dryness, giving 0.18 g of **16a** as colorless crystals. The analytical sample was obtained by repeated crystallizations from isopropyl ether: mp 190.5–191.5°; $[\alpha]^{25}D$ +13° (*c* 0.84); mass spectral molecular ion at *m/e* 289.

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01. Found: C, 70.78; H, 8.06.

Registry No.—Thebaine, 115-37-7; **5a**, 17245-66-8; **5b**, 17245-67-9; **7a**, 17245-68-0; **8a**, 17322-75-7; **9a**, 17245-70-4; **9b**, 17245-71-5; **16a**, 17245-72-6.

Acknowledgment.—The author wishes to express his gratitude to Drs. Everette L. May and Lewis J. Sargent of this laboratory for many helpful discussions.

(15) The free base **5a** had zero rotation $[\alpha]D$ in both $CHCl_3$ and CH_3OH.

(16) The free base **5b** had $[\alpha]^{25}D$ +1 (*c* 1.0).