9β,10α-Androst-4-ene-3,17-dione (X).—9β,10α-Testosterone (30 g) in 600 ml of acetone was oxidized at 0° with 29.8 ml of 8 *N* chromic acid reagent. After the normal work-up with methylene chloride, the crude product was recrystallized from aqueous ethanol to afford 18.2 g of needles, mp 153.5–156.0°. A second crop, after further crystallization, afforded an additional 4.5 g of product, mp 151–153°.

***cis*-9β,10α-Pregna-4,17(20)-dien-3-one (VIII).**—A solution of 15.0 g of 9β,10α-androst-4-ene-3,17-dione in 150 ml of dry methanol was heated to reflux under nitrogen and treated with 8.0 ml of freshly distilled pyrrolidine. After 10 min at reflux, protecting from light, the orange solution was allowed to cool to room temperature, whereupon the enamine spontaneously crystallized. After cooling well in the freezer the crystals were filtered, washed well with dry methanol, and dried at 35°, affording 15.88 g of product. This material was dissolved in 300 ml of dry benzene containing a few drops of pyrrolidine and added to a solution of ethylidenetriphenylphosphorane in 600 ml of DMSO (prepared from 10.54 g of 54% sodium hydride dispersion and 99 g of ethyltriphenylphosphonium iodide). After heating at 50–55° overnight (protecting from light), 100 ml of 10% potassium hydroxide solution and 300 ml of methanol were added. Heating (50°) was continued for 1.5 hr. The reaction was then cooled, neutralized with acetic acid, and diluted with water. After extraction with three portions of ether, the combined extract was washed with water and 5% sodium bicarbonate solution, dried, and evaporated. The crude product was chromatographed on silica gel. Benzene and benzene–ethyl acetate (99:1) eluted 7.77 g of crystalline material which upon recrystallization from aqueous methanol weighed 5.62 g and had mp 111–114°. Further recrystallization from ether–hexane raised the melting point to 114.5–115.5°. This material was identical with the above-prepared sample by tlc and nmr analysis.

9β,10α-Pregna-4,16-diene-3,20-dione (IX).—A solution of VIII (1.0 g) and hematoporphyrine (20 mg) in 35 ml of pyridine was treated with a fine stream of oxygen while being illuminated with a series of two 15-W fluorescent lamps. After 4.5 hr, 5 ml of acetic anhydride was added, and the reaction mixture was allowed to stand at room temperature (somewhat exothermic) for 45 min and was then heated at 60° for an additional 30 min. After dilution with water, the product was extracted with methylene chloride and the organic phase washed thoroughly with 2 *N* HCl and then with 5% sodium bicarbonate solution. After drying, the methylene chloride solution was slurried with 15 g of neutral alumina (grade II) and filtered. The crystalline residue obtained after evaporation of the solvent was recrystallized twice from ether–petroleum ether to afford 562 mg of product, mp 151–153°. One further recrystallization raised the melting point to 165.5–167.0°, and this material was identical with an authentic sample[12] of this substance.

Registry No.—II, 10104-25-3; III, 17244-02-9; IVa, 17244-03-0; Va, 17244-04-1; VII, 17244-05-2; VIII, 17244-06-3; X, 571-45-9.

Acknowledgment.—We are indebted to Dr. V. Toome for the ultraviolet spectra, to Drs. F. Vane and T. Williams for the nmr spectra, and to Drs. A. Steyermark and F. Scheidl for the microanalyses. The valuable technical assistance of Mr. Harold Lucas and Mr. Fred DiMaria is greatly appreciated.

Transformations in the Morphine Series. III.[1a] Conversion of Thebaine into Methanobenzofuro[3,2-*d*]azocines

MICHAEL MOKOTOFF[1b] AND LEWIS J. SARGENT

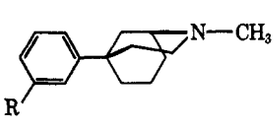
Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

Received April 1, 1968

The synthesis of phenylmorphans containing an ether bridge comparable with that in morphine was undertaken. Thebaine was converted, by reported procedures, into 6-deoxy-14-hydroxydihydrocodeine (**4**), and the latter was converted into its methine base **5**, which was hydroxylated (OsO_4); periodate cleavage of triol **6** gave keto-aldehyde **7**. Selective reduction of ethylene dithioacetal **9b** with Raney nickel afforded **11b**. Bromination and cyclization gave **13**, which was hydrogenolyzed to **14**. Dry distillation eliminated CH_3Br, yielding **15a**. The carbonyl group in **15a** was reduced ($NaBH_4$) to the alcohol **16a**, which was mesylated to **16b**. The latter on treatment with $LiAlH_4$ unexpectedly gave the rearranged octahydroindole **17**. A modified Wolff–Kishner reduction of **15a**, by way of the intermediate hydrazone **15b**, afforded the desired methanobenzofuro[3,2-*d*]azocine **2**. Compound **15a** was inactive as an analgetic in mice while **2** had a potency about one-half that of codeine.

Earlier reports from this laboratory described the synthesis and biological activity of two compounds whose structures are related to morphine, namely 2-methyl-5-phenylmorphan[2,3] (**1a**) and 5-(*m*-hydroxyphenyl)-2-methylmorphan[2,3] (**1b**).

Compound **1b** had an analgesic potency equal to morphine, whereas **1a** was slightly less effective than meperidine; both were somewhat more toxic than morphine. It should be noted that both **1a** and **1b** are racemates, while morphine is levorotatory and meperidine is optically inactive.



1a, R = H
b, R = OH

It has been recognized for some time that certain structural features of morphine should be embodied in any modification of its structure in order to retain analgesic potency. They are (1) the phenyl nucleus, (2) the quaternary carbon attached to this nucleus, and (3) the tertiary nitrogen two carbon atoms (C-15 and C-16 in **3**) removed from the quaternary carbon. Further, it was the consensus that the tertiary nitrogen should be in a six-membered-ring formation.[4] Cleavage of the ether bridge and substitution in the aromatic nucleus of morphine appear to decrease activity,[5] while the pronounced analgesic properties of the

(1) (a) Part II: L. J. Sargent and B. C. Joshi, *J. Med. Chem.*, **11**, 336 (1968). (b) Author to whom correspondence should be addressed at the University of Pittsburgh, School of Pharmacy, Pittsburgh, Pa.

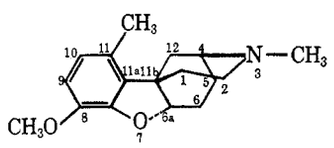
(2) E. L. May and J. G. Murphy, *J. Org. Chem.*, **19**, 618 (1954); **20**, 1197 (1955).

(3) According to *Chemical Abstracts* nomenclature, these compounds are 2-methyl-5-phenyl-2-azabicyclo[3.3.1]nonane and 2-methyl-5-(*m*-hydroxyphenyl)-2-azabicyclo[3.3.1]nonane, respectively.

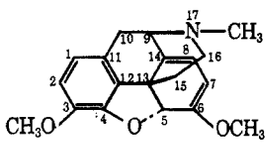
(4) E. L. May and L. J. Sargent in "Analgetics," G. deStevens, Ed., Academic Press Inc., New York, 1965, p 123.

(5) E. L. May in "Medicinal Chemistry," 2nd ed, A. Burger, Ed., Interscience Publishers, Inc., New York, 1960, p 311.

morphinans[6] and 6,7-benzomorphans[6] demonstrate that the oxygen bridge apparently is not essential for activity. Therefore, it appears that, to retain analgesic activity in a morphine transformation product, one should either have an intact ether bridge or none at all. Since the phenylmorphans (**1a** and **b**) represent the case in which the ether bridge is absent, we sought to prepare an analogous derivative with the ether bridge intact (*viz.*, **2**).



2



3

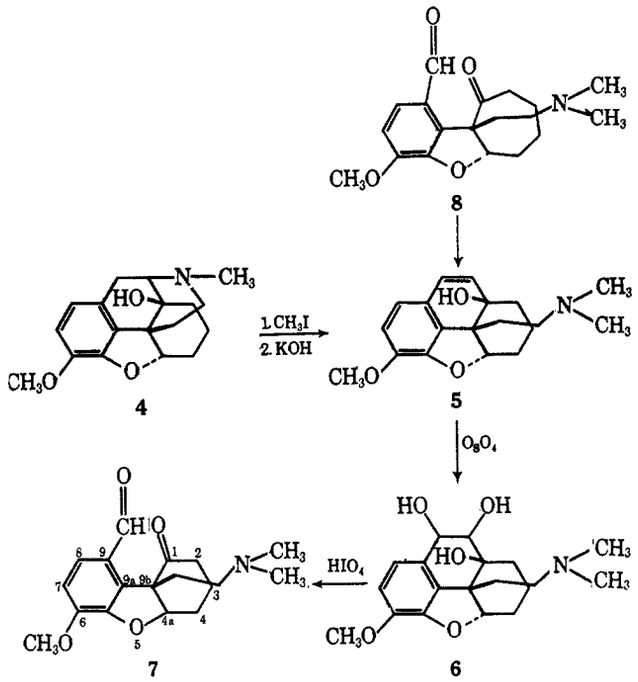
In the light of a recent publication by Mishima, *et al.*,[7] the most promising route to structure **2** appeared to be through degradation of the alkaloid, thebaine (**3**). Since thebaine is optically active, the final product, **2**, would be expected to be optically active, in contrast to the totally synthetic, racemic phenylmorphans (**1a** and **b**).

An important intermediate in the planned degradation was 6-deoxy-14-hydroxydihydrocodeine (**4**), which was prepared as outlined by Currie, *et al.*,[8] starting with 14-hydroxycodeinone.[9] Although this procedure was longer than the sequence outlined by Mishima, *et al.*,[7] it was much easier to obtain (35% over-all yield) compound **4** by this method.

In order to introduce a double bond between C-9 and C-10, **4** was degraded (Hofmann) to the methine base **5**, in 86% yield. Based on the report of Mishima, *et al.*,[7] we had originally planned to cleave the 9,10 bond in **5** with simultaneous loss of C-9 by use of the Woodward-modified Prevost reaction,[10] to the reported[7] 9b-[2-(dimethylamino)ethyl]-3,4,4a,9b-tetrahydro-6-methoxy-9-oxo-1(2H)-dibenzofuranone (**7**). However, a later paper[11] indicated that the ketoaldehyde **7**, as reported earlier,[7] was in error and was subsequently corrected to that of structure **8** containing a seven-membered-ring ketone.

In the light of this development we had to devise an alternate method of preparing **7**. Although Iwai, *et al.*,[11] suggested that **7** could be prepared by the periodate oxidation of the triol **6**, they reported no procedures nor physical data. Thus, in a modification of a procedure by Mishima, *et al.*,[7] methine **5** was oxidized with osmium tetroxide followed by cleavage of the osmate ester *via* exchange with mannitol,[12] affording the triol **6**. The latter was not crystallized but was subjected to periodate cleavage in acetate

SCHEME I



8

4

5

7

6

buffer[13] (pH 5.2), yielding (42% from **5**) the desired ketoaldehyde **7** (Scheme I). It was necessary to work in acidic medium in view of the finding that tertiary amines consume periodate in alkaline solution[14] while the ionic (protonated) forms do not, an observation confirmed by Rapoport, *et al.*,[13] with several codeine derivatives.

Spectroscopic data supported the structure of the ketoaldehyde **7**. The observed infrared split peak at 5.86 and 5.95 μ was attributed to a six-membered ketone and aromatic aldehyde, respectively. The nmr spectrum showed a singlet at δ 10.17 for the aldehyde proton, while the mass spectrum gave a molecular ion at m/e 317.

In order to realize our planned synthesis, it was necessary to retain the keto group while selectively reducing the aldehyde in **7** to a methyl group. Although Iwai, *et al.*,[11] reported carrying out this conversion by Wolff–Kishner reduction (Huang-Minlon modification), they reported no physical data for their compound except the mass spectral molecular ion. We were unable to effect this conversion by their method, obtaining only a crude product whose infrared spectrum showed the absence of any carbonyl peak.[15]

We were able to obtain the desired product by selective conversion of the aldehyde into its ethylene dithioacetal, followed by desulfurization with Raney nickel. Thus, the ketoaldehyde **7** was dissolved in excess 1,2-ethanedithiol and treated with boron trifluoride etherate. The product isolated was the desired dithioacetal **9a**, obtained as a complex with boron trifluoride. That **9a** was a complex was shown by positive fluorine analysis and the fact that it was water soluble and convertible into the free base **9b** with 1 *N* NaOH. It is not surprising that **9a** was

(6) J. Hellerbach, O. Schnider, H. Besendorf, B. Pellmont, N. B. Eddy, and E. L. May, "Synthetic Analgesics," part II, Pergamon Press, New York, 1966.

(7) H. Mishima, M. Kurabayashi, and I. Iwai, *J. Org. Chem.*, **28**, 2621 (1963).

(8) A. C. Currie, J. Gillan, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 773 (1960).

(9) (a) I. Kh. Fel'dman and A. I. Lyutenberg, *Chem. Abstr.*, **40**, 6489 (1946); (b) T. B. Zalucky and G. Hite, *J. Med. Chem.*, **3**, 615 (1961).

(10) R. B. Woodward and F. V. Brutcher, Jr., *J. Amer. Chem. Soc.*, **80**, 209 (1958).

(11) I. Iwai, A. Koshiro, M. Kurabayashi, H. Mishima, S. Uyeo, and K. Yamomoto, *Chem. Commun.*, 118 (1965). This paper was brought to our attention in correspondence with Dr. Mishima.

(12) S. M. Kupchan, and S. D. Levine, *J. Amer. Chem. Soc.*, **86**, 701 (1964).

(13) H. Rapoport, M. S. Chadha, and C. H. Lovell, *ibid.*, **79**, 4694 (1957).

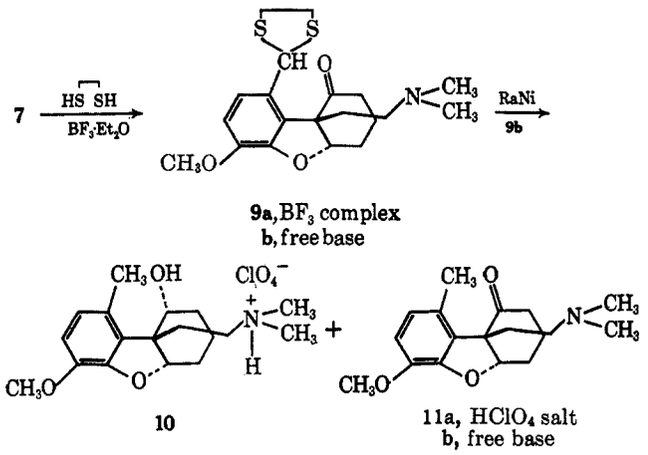
(14) E. H. Flynn, M. V. Sigal, Jr., P. F. Wiley, and K. Gerzon, *ibid.*, **76**, 3121 (1954).

(15) After the completion of this work, the paper by S. Uyeo, A. Koshiro, H. Irie, and K. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 582 (1967), describing the preparation of **11b** by another route, came to our attention.

first isolated as the addition product since Kraus and Brown[16] have shown that primary, secondary, and tertiary amines readily form 1:1 addition complexes with boron trifluoride. The free base **9b** resisted attempts at crystallization but analyzed correctly. Its infrared spectrum was devoid of aldehyde carbonyl and showed a single peak at 5.85 μ for the six-membered ketone. The nmr spectrum of the free base **9b** was devoid of a signal for aldehyde proton but instead showed resonance at δ 3.42 (4 H, multiplet) for the dithioethylene group, and at 5.78 (singlet) for the dithioacetal proton.

Initial attempts at desulfurization of the dithioacetal **9b** with W-2 Raney nickel in ethanol gave a product which appeared as a two-component mixture on tlc. The lower R_f component was converted into its perchlorate and identified as alcohol **10** by elemental analysis and infrared and mass spectral data. The α stereochemistry was assigned to **10** on the basis of its synthesis by another route and structure proof as reported elsewhere.[17] The higher R_f component was converted into its perchlorate and identified as the desired methyl ketone **11a** (Scheme II).

SCHEME II



In order to prevent the reduction of the ketone (to the alcohol) a less active catalyst was necessary. Spero, *et al.*,[18] had a similar problem which was solved by deactivating the Raney nickel in refluxing acetone. Utilizing this procedure we eliminated the undesired **10** and were able to obtain, by purification through its perchlorate, the free base **11b**: yield 40%. The structure was supported by physical data: λ_{max} 5.86 (six-membered ketone); nmr signals at δ 2.16 (3 H, aromatic CH_3) and 2.21 [6 H, N-$(CH_3)_2$]; mass spectral molecular ion at *m/e* 303.

A distinct problem in obtaining a satisfactory yield was the tenacity with which **11b** was adsorbed on the Raney nickel. Even prolonged extraction (Soxhlet) did not effectively remove all the product. An improvement in the yield and ease of purification of **11b** were later accomplished by the substitution of commercial Raney nickel[19] for the deactivated W-2 form. The commercial Raney nickel required no deactivation and **11b** could be isolated in crystalline form (65% yield) without purification through its perchlorate salt.

In order to effect cyclization of **11b** to a six-membered nitrogen-containing ring it was first necessary to brominate α to the carbonyl function. It was anticipated that bromination with 1 equiv of bromine in acetic acid would selectively react α to the carbonyl rather than on the aromatic nucleus. However, this was not the case, and in initial experiments bromination with 1 equiv of bromine followed by cyclization with NH_4OH afforded an acetone-soluble product, assigned the structure **12**, and an acetone-insoluble product, assigned the structure **13**. The assignment of **12** was based on analytical data, the observance of only one aromatic proton in the nmr spectrum, the presence of molecular ions at *m/e* 381 and 383 in the mass spectrum, and the fact that it failed to cyclize. When the bromination was conducted in the presence of 2 equiv of bromine and the product cyclized, only the bromo methobromide **13** was isolated (80% yield). Thus, bromination occurs on the aromatic ring as well as α to the carbonyl, the latter bromine being displaced by the nitrogen in an SN2 reaction upon basification with NH_4OH. That bromination also occurred on the aromatic ring was not unexpected[20] since the latter is activated by a *p*-oxygen function.

Hydrogenolysis of the aromatic bromine in **13** was readily accomplished with 10% Pd/C, affording a 77% yield of **14**. Dry distillation of **14** eliminated methyl bromide and afforded **15a** in 79% yield. The latter structure was confirmed spectroscopically: λ_{max} 5.77 μ (ketone); nmr signals at δ 2.24 and 2.40 (3 H each, N-CH_3, aromatic CH_3); mass spectral molecular ion at *m/e* 287.

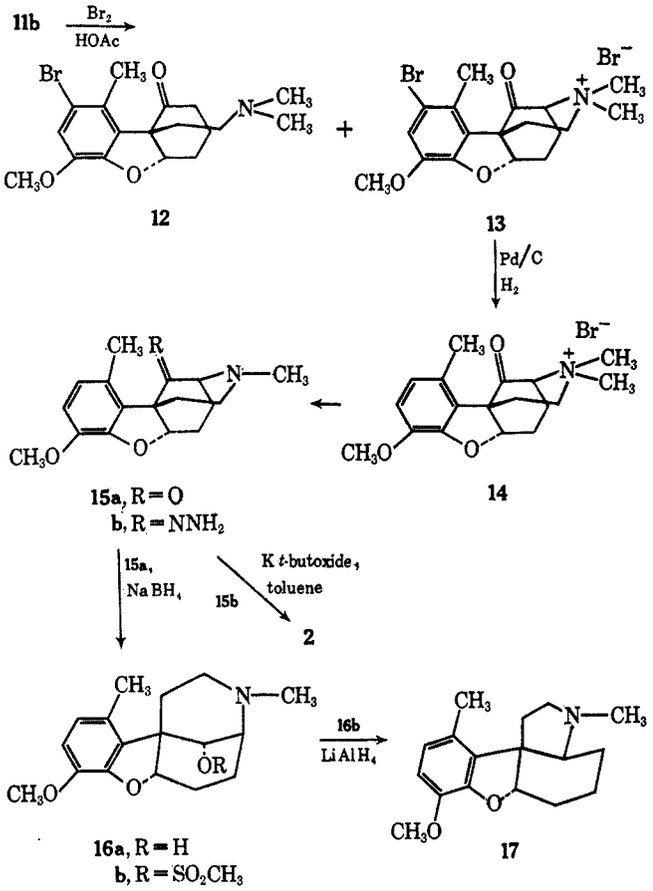
Attempts were made to reduce the carbonyl group in **15a** to the corresponding hydrocarbon *via* Wolff–Kishner reduction (Huang-Minlon modification) in a manner utilized for the synthesis[2] of **1a**; however, only noncarbonyl-containing, intractable mixtures were obtained. This result is not surprising since it has been reported[21] that, in the Wolff–Kishner reaction of many α-amino ketones and related compounds, an elimination competes with the normal reduction and in some instances is the predominant reaction.[22] In view of this, an alternate route (assuring the integrity of the ether bridge) was devised which involved the reduction of the carbonyl to the respective alcohol, followed by mesylation and elimination *via* hydride displacement. Thus, $NaBH_4$ reduction smoothly afforded the alcohol **16a** in 97% yield, later identified as the α alcohol.[17] Mesylation in pyridine readily esterified the alcohol to give the mesylate **16b**. Because of thei nstability of the latter it was not purified but, instead, dissolved in tetrahydrofuran and immediately treated with $LiAlH_4$. Nucleophilic displacement of the mesylate group gave a 39% yield of a compound which initially had been assigned the structure **2**;[23] there was

(16) C. A. Kraus and E. H. Brown, *J. Amer. Chem. Soc.*, **51**, 2690 (1929).
(17) M. Mokotoff, *J. Org. Chem.*, **33**, 3556 (1968).
(18) G. B. Spero, A. V. McIntosh, Jr., and R. H. Levin, *J. Amer. Chem. Soc.*, **70**, 1907 (1948).
(19) Raney active nickel catalyst, grade no. 28, W. R. Grace and Co., Chattanooga, Tenn.
(20) L. F. Small, H. M. Fitch, and W. E. Smith, *ibid.*, **58**, 1457 (1936); M. Gates and M. S. Shepard, *ibid.*, **84**, 4125 (1962).
(21) M. F. Grundon, H. B. Henbest, and M. D. Scott, *J. Chem. Soc.*, 1855 (1963).
(22) N. J. Leonard and S. Gelfand, *J. Amer. Chem. Soc.*, **77**, 3269, 3272 (1955).
(23) M. Mokotoff and L. J. Sargent, 154th National Meeting of the American Chemical Society, Division of Medicinal Chemistry, Chicago, Ill., Sept 1967, Abstracts, p 29P.

observed a mass spectral molecular ion at m/e 273.174 by peak matching (calculated m/e 273.172). The mesylate **16b** has now been shown to have, instead, rearranged to the octahydroindole **17** *via* an aziridinium intermediate. The mechanism of this rearrangement, and the synthesis of **17** by another route, is the subject of a subsequent paper.[17]

After many other fruitless approaches, the desired **2** was finally obtained by a modified Wolff–Kishner reduction first introduced by Cram, *et al.*,[24] and expanded upon by Grundon and coworkers.[21] Thus, the ketone **15a** was converted into its hydrazone **15b** and decomposed to the desired methanobenzofuro[3,2-*d*]azocine **2** by refluxing in toluene with potassium *t*-butoxide. The physical data for **2** were consistent with the structure shown but entirely different from that of **17**; there was observed a mass spectral molecular ion at m/e 273 (Scheme III).

SCHEME III



The analgetic activities of **2** and **15a** were determined in mice by the hot-plate method.[25] Compound **15a** showed no activity while **2** had a potency approximately one-half that of codeine.[26]

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are corrected. Microanalyses were done 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 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) by Mrs. E. Peake on a Rudolph 338 polarimeter, and are corrected to the nearest degree. Infrared spectra were recorded in $CHCl_3$ (unless stated otherwise) on a Perkin-Elmer Infracord spectrophotometer. All extractions utilized $CHCl_3$ (unless stated otherwise) with Mayer reagent as test; the pooled $CHCl_3$ solutions were combined, washed twice with H_2O, dried with Na_2SO_4, and concentrated under reduced pressure. For vapor phase chromatography (vpc) a 6-ft, glass column was packed with 1% SE 30 on Gas-Chrom P, 100/120 mesh, and used isothermally at 220°. All thin layer chromatography (tlc) was carried out using silica gel.

14-Hydroxycodeinone was prepared according to the procedure of Fel'dman and Lyutenberg[9a] and Zalucky and Hite.[9b]

14-Hydroxycodeine was prepared according to the procedure of Sargent, *et al.*[27]

6-Deoxy-14-hydroxydihydrocodeine (4) was prepared as outlined by Currie, *et al.*[8]

Methine base 5 was prepared according to the procedure of **Mishima**, *et al.*[7]

9b-[2-Dimethylamino)ethyl]-3,4,4a,9b-tetrahydro-6-methoxy-9-oxo-1(2H)-dibenzofuranone (7).—A solution of methine base **5** (12.5 g, 40 mmol) in pyridine (8 ml) and ether (300 ml) was treated with osmium tetroxide (11.0 g, 43 mmol), stirred for 2 hr, and left overnight. The osmate ester was separated *via* centrifugation and washed several times with ether. The combined ether washings were treated with another 1.0 g of osmium tetroxide and allowed to stand for 3–5 hr; the resulting brown precipitate was combined with the first crop of osmate ester. The latter was hydrolyzed by dissolving in $CHCl_3$ (475 ml) and vigorously stirring for 20 hr with 700 ml of 1.7% KOH solution containing 110 g of mannitol. After separation of the organic from the aqueous phase, the latter was washed once with $CHCl_3$ and the combined $CHCl_3$ solutions were worked up as usual. Benzene was added to the residue, and the system was again concentrated to remove traces of pyridine. The residual semicrystalline triol **6** (10.1 g) [which could be crystallized from benzene–petroleum ether (bp 66–75°), mp 160–165° dec] was suitable for further work.

The triol was dissolved in 1 l. of acetate buffer, pH 5.2 (100 ml of 1 *M* NaOH plus 146 ml of 1 *M* acetic acid plus enough H_2O to make 1 l.), and treated with sodium metaperiodate (18.6 g, 87 mmol). After 23 hr, 300 ml of 0.1 *N* sodium arsenite was added to decompose the excess periodate, giving a black precipitate which dissolved to a red-brown solution when basified with excess NH_4OH. This solution was extracted with CH_2Cl_2 in the usual way, thereby affording a tan crystalline residue which was crystallized from purified isopropyl ether. The yield of light yellow crystals was (in three crops) 5.4 g (42% based on methine base **5**). Additional pure material could be obtained by chromatography of the mother liquors on a column of silica gel (0.05–0.20 mm, Brinkmann) prepared as a slurry in 50% benzene–ether. The desired product **7** was eluted with 6% CH_3OH–$CHCl_3$.

A portion of **7** was purified by preparative tlc (silica gel HF, 15% CH_3OH–$CHCl_3$ as mobile phase) and crystallized from purified isopropyl ether: mp 121–121.5°; $[\alpha]^{20}D$ −8° (*c* 1.07); nmr, δ 5.13 (multiplet, C-4a H).

Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 67.85; H, 7.41; N, 4.36.

9b-[2-(Dimethylamino)ethyl]-3,4,4a,9b-tetrahydro-6-methoxy-9-oxo-1(2H)dibenzofuranone 9-Ethylene Dithioacetal (9b).—The ketoaldehyde **7** (6.3 g, 20 mmol), was dissolved in an excess of 1,2-ethanedithiol (8.7 ml, 104 mmol) and treated with redistilled BF_3–etherate (3.9 ml) while stirring. Upon cooling, the yellow solution set to a hard mass. After 20 min the solid was collected with petroleum ether (bp 35–60°), pulverized, and again collected with the same solvent. The crude yellow product was crystallized from acetone–isopropyl ether, yielding (in two crops) 8.8 g of **9a**. The free base **9b** was obtained by dissolving **9a** in 300 ml of hot H_2O, filtering, cooling, and basifying with excess 1 *M* NaOH. The liberated gum was separated by centrifugation,

(24) D. J. Cram, M. R. V. Sahyun, and G. R. Knox, *J. Amer. Chem. Soc.*, **84**, 1734 (1962).

(25) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exptl. Therap.*, **107**, 385 (1953). We are indebted to Mrs. L. Atwell for these data.

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

(27) L. J. Sargent, L. H. Schwartzman, and L. F. Small, *J. Org. Chem.*, **23**, 1247 (1958). This procedure gave better yields than the method of Currie, *et al.*[8]

washed with H_2O, dissolved in $CHCl_3$, and worked up in the usual manner; concentration yielded **9b** as a yellow gum (6.9 g, 88%). The latter resisted attempts at crystallization. For analytical purposes a specimen was purified on one preparative tlc plate (silica gel HF, 15% CH_3OH–$CHCl_3$ as mobile phase), and submitted as an oil.

Anal. Calcd for $C_{20}H_{27}NO_3S_2$: C, 61.03; H, 6.92; S, 16.29. Found: C, 60.83; H, 6.72; S, 16.29.

9b-[2-(Dimethylamino)ethyl]-3,4,4a,9b-tetrahydro-6-methoxy-9-methyl-1α(2H)-dibenzofuranol $HClO_4$ (10) and 9b-[2-(Dimethylamino)ethyl]-3,4,4a,9b-tetrahydro-6-methoxy-9-methyl-1-(2H)-dibenzofuranone (11).—Initial attempts to desulfurize **9b** were made with freshly prepared W-2 Raney nickel[28] that was not deactivated. In one run, **9b** (0.15 g) was refluxed with 3 g of W-2 Raney nickel in 20 ml of C_2H_5OH for 5 hr. Filtration and evaporation of the C_2H_5OH left an oil which appeared as two components on tlc. The oil was purified on one preparative tlc plate (silica gel HF, 15% CH_3OH–$CHCl_3$ as mobile phase) and yielded two products. The lower R_f component, which showed no ir carbonyl absorption, was converted into its perchlorate and purified by crystallization from absolute C_2H_5OH, yielding colorless crystals of **10**: mp 204.5–206.5°; λ_{max}^{Nujol} 2.80 μ (hydroxyl); mass spectral molecular ion at *m/e* 305.

Anal. Calcd for $C_{18}H_{28}ClNO_7$: C, 53.26; H, 6.95; Cl, 8.74. Found: C, 53.03; H, 6.92; Cl, 8.48.

The higher R_f component was converted into its perchlorate and identified as **11a**. Crystallization from absolute C_2H_5OH yielded the analytical sample as colorless crystals, mp 165–166.5°.

Anal. Calcd for $C_{18}H_{26}ClNO_7$: C, 53.53; H, 6.49; N, 3.47; Cl, 8.78. Found: C, 53.33; H, 6.37; N, 3.58; Cl, 8.62.

However, when freshly prepared W-2 Raney nickel was deactivated by refluxing in acetone, only the desired **11b** was obtained. Thus, **9b** (2.0 g, 5.0 mmol) was dissolved in acetone (30 ml) and added to a refluxing, stirred mixture of 20 g of W-2 Raney nickel (previously refluxed for 2 hr in 70 ml of acetone). After 3 hr, an examination of an aliquot by vpc showed some starting material. Therefore another 10 g of deactivated W-2 Raney nickel was added, and the mixture was refluxed another 4.5 hr. The acetone was decanted and the catalyst was extracted (Soxhlet) overnight with acetone. Concentration of the combined acetone solutions yielded an oil which was converted into the perchlorate and crystallized from absolute C_2H_5OH. The perchlorate (1.2 g) was dissolved in hot H_2O (30 ml), cooled, basified with 1 *M* NaOH, and extracted in the usual way. Concentration gave crystalline **11b**, which upon recrystallization from *n*-hexane gave (in three crops) light yellow crystals (0.60 g, 40%), mp 82–84°.

A substantial increase in yield was obtained by utilizing commercial Raney nickel.[19] It did not have to be deactivated and could be used directly in acetone. Thus, a solution of **9b** (5.0 g, 12.7 mmol) in 150 ml of acetone was treated with 50 g of Grace Raney nickel[19] and refluxed 6 hr, and another 10 g of catalyst was added. After refluxing overnight the acetone solution was decanted from the catalyst, concentrated to a semicrystalline product, partially dissolved in H_2O, and rendered alkaline with 1 *M* NaOH. The product was extracted in the usual way, thereby affording 2.05 g of buff-colored crystalline **11b**. Further extraction of the catalyst for 30 hr (Soxhlet) with acetone and the above work-up gave 0.3 g of **11b**. An additional extraction (48 hr, *n*-C_3H_7OH, Soxhlet) gave another 0.15 g of **11b**; the total crystalline yield was 2.5 g (65%), suitable for the next step.

The analytical sample had mp 85–85.5°; $[\alpha]^{20}D$ +213° (*c* 0.89) (lit.[15] mp 79–81°; $[\alpha]^{23}D$ +211°); nmr δ 5.10 (multiplet, C-4a H).

Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.23; H, 8.31; N, 4.64.

9b-[2-(Dimethylamino)ethyl]-3,4,4a,9b-tetrahydro-6-methoxy-8-bromo-9-methyl-1(2H)-dibenzofuranone (12) and 2,3,4,5,6,6a-Hexahydro-8-methoxy-10-bromo-3,11-dimethyl-1H-4,11b-methanobenzofuro[3,2-*d*]azocin-12-one Methobromide (13).—Compound **11b** (0.10 g, 0.33 mmol) was dissolved in acetic acid (2 ml) and, while stirring at a bath temperature of 50–55°, treated with 1.0 ml of Br_2–acetic acid solution (0.18 ml of Br_2 in 10 ml of acetic acid, 0.34 mmol). The reaction was run in the dark for 3 hr and concentrated to a small volume, and the product precipitated with ether. The resulting tan material was partially dissolved in 4 ml of H_2O, covered with 25 ml of ether in a separatory funnel, and rapidly shaken with 0.1 ml of NH_4OH.[29] After the layers were separated, the aqueous phase was again extracted with 25 ml of ether and the combined ether solutions were concentrated to an oil which was warmed with a few milliliters of acetone. The crystals that formed were collected and identified as bromo methobromide **13**. Upon concentration to dryness the mother liquor afforded a tan crystalline material whose tlc (silica gel, 15% CH_3OH–$CHCl_3$ as mobile phase) showed compound **13** at the origin and another component with R_f 0.6–0.7. Preparative tlc gave the latter component, which on crystallization from CH_3OH–H_2O and one sublimation gave an analytical sample of bromo compound **12**: mp 102–103°; nmr δ 2.15 (3 H, aromatic CH_3), 2.23 [6 H, $N(CH_3)_2$], 5.05 (multiplet, C-4a H), 7.05 (1 H, aromatic).

Anal. Calcd for $C_{18}H_{24}BrNO_3$: C, 56.55; H, 6.33. Found: C, 56.90; H, 6.44.

When 2 equiv of Br_2 were used only the bromo methobromide **13** was isolated. Thus, 2.65 g (8.8 mmol) of **11b** dissolved in acetic acid (45 ml) was treated dropwise, in the dark at 50–55°, with a solution of 0.93 ml of Br_2 in 10 ml of acetic acid (18 mmol). The product was isolated after 2.5 hr by concentration and precipitation with ether, as above. The tan material was partially dissolved in 60 ml of H_2O and covered with 100 ml of ether in a separatory funnel, and the mixture was shaken rapidly with 2 ml of NH_4OH. Work-up as above and warming with acetone gave (in two crops) 3.25 g (80%) of the desired bromo methobromide **13**. Several crystallizations from CH_3OH–ether gave light yellow crystals, mp 235–239° dec uncor.

Anal. Calcd for $C_{18}H_{23}Br_2NO_3$: C, 46.87; H, 5.03; Br, 34.66. Found: C, 46.67; H, 5.08; Br, 34.07.

2,3,4,5,6,6a-Hexahydro-8-methoxy-3,11-dimethyl-1H,4,11b-methanobenzofuro[3,2-*d*]azocin-12-one Methobromide (14).—Compound **13** (3.45 g, 7.5 mmol) was dissolved in 300 ml of warm CH_3OH, cooled, and hydrogenolyzed with 1.8 g of 10% Pd/C in an atmosphere of H_2 for 60 hr. The catalyst was separated and boiled for 1 hr with fresh CH_3OH, and the combined solutions were concentrated to a small volume. Ether was added until crystallization ensued to yield 2.2 g (77%). A second crop was obtained, but its ir spectrum identified it as mostly starting material. Several crystallizations from CH_3OH–ether gave colorless, solvated crystals of **14**: mp 263–265° dec uncor; λ_{max}^{Nujol} 2.87 (CH_3OH of crystallization), 5.73 μ (ketone).

Anal. Calcd for $C_{18}H_{24}BrNO_3 \cdot {}^1/_2CH_3OH$: C, 55.79; H, 6.58; Br, 20.07. Found: C, 55.77; H, 6.64; Br, 19.95.

2,3,4,5,6,6a-Hexahydro-8-methoxy-3,11-dimethyl-1H-4,11b-methanobenzofuro[3,2-*d*]azocin-12-one (15a).—Dry distillation of **14** (0.85 g, 2.2 mmol), under high vacuum at an air-bath temperature of 240°, gave a pale yellow crystalline sublimate. The sublimate was crystallized from purified isopropyl ether yielding colorless needles (0.45 g, mp 162–163°). A second crop, slightly less pure, weighed 0.05 g (total yield 0.50 g, 79%). The analytical sample had mp 162.5–163°; $[\alpha]^{20}D$ −192° (*c* 0.43); nmr δ 5.02 (quartet, C-6a H).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.08; H, 7.09; N, 4.96.

2,3,4,5,6,6a-Hexahydro-8-methoxy-3,11-dimethyl-1H-4,11b-methanobenzofuro[3,2-*d*]azocin-12α-ol (16a).—Compound **15a** (1.35 g, 4.7 mmol) was dissolved in warm CH_3OH (100 ml), cooled, and treated dropwise, while stirring, with a solution of $NaBH_4$ (0.72 g) in 20 ml of CH_3OH. After stirring for 45 min at room temperature, 90 ml of H_2O was added and stirring was continued for another 30 min. The solution was concentrated to a small volume and the aqueous mixture was extracted in the usual manner. The crystalline residue was recrystallized from isopropyl ether, affording (in three crops) 1.32 g (97%) of colorless crystals. The analytical sample of **16a** had mp 145–146°; $[\alpha]^{20}D$ −37° (*c* 1.0); λ_{max} 2.80 μ (OH); 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, 70.25; H, 8.28.

2,3,4,5,6,6a-Hexahydro-8-methoxy-3,11-dimethyl-1H-4,11b-methanobenzofuro[3,2-*d*]azocine (2).—Ketone **15a** (0.20 g, 0.70 mmol) dissolved in absolute C_2H_5OH (12 ml) was treated with 95% hydrazine (1.2 ml) and gently refluxed until a tlc examination (20% CH_3OH–$CHCl_3$) indicated no more ketone (4 hr). The solution was concentrated to dryness, dissolved in $CHCl_3$,

(28) R. Mozingo in "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

(29) J. G. Murphy, J. H. Ager, and E. L. May, *J. Org. Chem.*, **25**, 1386 (1960).

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]

MICHAEL MOKOTOFF[1c]

Laboratory of Chemistry, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

Received April 1, 1968

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).