(C=C), 6.22 μ (C=C). Its ultraviolet spectrum exhibited no selective absorption down to 203 mμ.

Anal. Calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27. Found: C, 70.11; H, 9.61; N, 6.33.

A small amount of Va was treated with a solution of picric acid in a minimum amount of acetone. Addition of hexane precipitated the picrate, which, after recrystallization from acetone–hexane at room temperature, showed m.p. 168–169°; $[\alpha]_D$ +22.5° (*c* 1.2).

Anal. Calcd. for $C_{13}H_{21}NO_2 \cdot C_6H_3N_3O_7$: C, 50.44; H, 5.35; N, 12.39. Found: C, 50.17; H, 5.63; N, 12.88.

Benzoylation of the Unsaturated Amino Diol (IVa).—A mixture of IVa (1.67 g.), anhydrous pyridine (20 ml.,) and benzoyl chloride (3 ml.) was kept at room temperature for 3 days. After acidification with 3% hydrochloric acid, the solution was extracted with ether, the ether solution was washed with 3% aqueous sodium bicarbonate, then water, and dried over anhydrous sodium sulfate. Filtration and evaporation of the solution left an oily product (3.37 g.) which was chromatographed in ether on alumina (90 g.) ("Woelm" neutral, activity grade I). Elution with ether–ethyl acetate (30:1) afforded the benzoate IVb as an oil (1.52 g.); $\lambda_{max}^{CHCl_3}$ 2.93 (OH), 5.87 (C_6H_5CO–O), 6.17 μ (N–CO).

Oxidation of the Benzoate (IVb) with Potassium Permanganate.—A mixture of the benzoate IVb (580 mg.) and magnesium sulfate (2.5 g.) in acetone (10 ml.) was cooled at −10 to −2° with ice–salt, and a solution of potassium permanganate (1.2 g.) in aqueous acetone (80 ml.) was added dropwise while stirring over a period of 2.5 hr. During the addition, the temperature of the reaction mixture was maintained at −10 to −2°. Stirring was continued for 4.5 hr., and the solution was poured into methanol (20 ml.) and kept at room temperature overnight. After concentration of the solution *in vacuo*, the manganese dioxide was decomposed with sodium sulfite and 3% hydrochloric acid, and the solution was extracted with chloroform. The chloroform solution was washed with water and extracted with 3% sodium hydroxide. The alkaline solution was then acidified with 3% hydrochloric acid and extracted with chloroform. Washing of the extract with water, drying over anhydrous sodium sulfate and evaporation *in vacuo*, yielded a crystalline mass (250 mg.). This mixture of acids was subjected to sublimation at 65–70° (0.04 mm.) to remove benzoic acid, and the residue (124 mg.) was chromatographed in chloroform on Mallinkrodt's silicic acid (20 g.). Evaporation of the first eluate fraction and crystallization from ethyl acetate–hexane afforded N-benzoyl-L-(−)-pipecolic acid, m.p. 128.5–129°; $[\alpha]_D$ −45.5° (*c* 1.22); $\lambda_{max}^{CHCl_3}$ 5.84 (COOH), 6.16 μ (N–CO).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.85; H, 6.56; N, 6.12.

The infrared spectrum of this compound was identical in chloroform solution with synthetic N-benzoyl-DL-pipecolic acid.[8]

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Conversion of Morphine Alkaloids and Galanthamine to 1-Methyl-3a-(3′-methoxy-6′-methylphenyl)-4,2′-epoxyoctahydroindole

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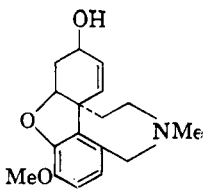
Cleavage of the B-ring of 14-hydroxydeoxydihydrocodeine (**2**) was achieved on its methine base **3** with loss of C-9 by a modified Prévost reaction, yielding the norseco compound **4**. The compound **4** was finally transformed to two isomers of 1-methyl-3a-(3′-methoxy-6′-methylphenyl)-4,2′-epoxyoctahydroindole (**15** and **17**), which has a carbon skeleton of mesembrane, one of the type of *Amaryllidaceae* alkaloids. The remaining isomer **24** was obtained by a multiple-step transformation from galanthamine (**1**). The stereochemistry of these isomers and their related compounds are discussed.

The structure of galanthamine (**1**) has been investigated by many workers.[1] Recently, Barton and Kirby[2] achieved its total synthesis. However, no direct evidence has been provided for its stereochemistry. In this paper, the authors' attempt was to confirm an absolute configuration of galanthamine by converting it to 1-methyl-3a-(3′-methoxy-6-methylphenyl)-4,2′-epoxyoctahydroindole, a compound which can be obtained from morphine alkaloids of known configuration.[3] Although we did not accomplish our purpose, the results obtained might be of some interest.



1

Hofmann degradation of 14-hydroxydeoxydihydrocodeine (**2**)[4] gave the methine base **3**, which showed absorption bands at 274, 300, and 313 mμ characteristic for the isoeugenol chromophore. A norseco compound **4** was obtained when **3** was treated under the condition of the Woodward modified Prévost reaction,[5] and the reaction mixture was made alkaline with potassium hydroxide. On the other hand, when aqueous ammonia was employed in place of potassium hydroxide, product **5** of composition $C_{21}H_{27}O_5N$[6] was afforded, which on treatment with potassium hydroxide was converted to **4**. The ultraviolet spectrum of **4** showed absorption bands at 231, 279, and 327 mμ which closely coincided with that of 3,4-dihydroxybenzaldehyde. Moreover, the infrared spectrum of **4** exhibited absorption bands at 1710 (six-membered cyclic ketone) and 1690 cm.$^{-1}$ (conjugated aldehyde). Therefore, it follows that **3** was not oxidized first to the

(1) W. C. Wildman, "The Alkaloids," Vol. VI, R. F. Manske, Ed., Academic Press, New York, N. Y., 1960, p. 289.

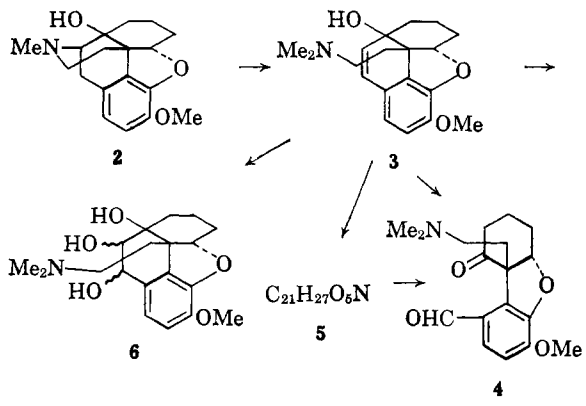
(2) D. H. R. Barton and G. W. Kirby, *Proc. Chem. Soc.*, 392 (1960); *J. Chem. Soc.*, 806 (1962).

(3) M. Mackay and D. C. Hodgkin, *ibid.*, 3261 (1955); J. Kalvoda, P. Buchschacher, and O. Jeger, *Helv. Chim. Acta*, **38**, 1847 (1955).

(4) A. C. Currie, J. Gillon, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 773 (1960); I. Seki, *Ann. Takamine Lab.* (Tokyo), **13**, 67 (1960).

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

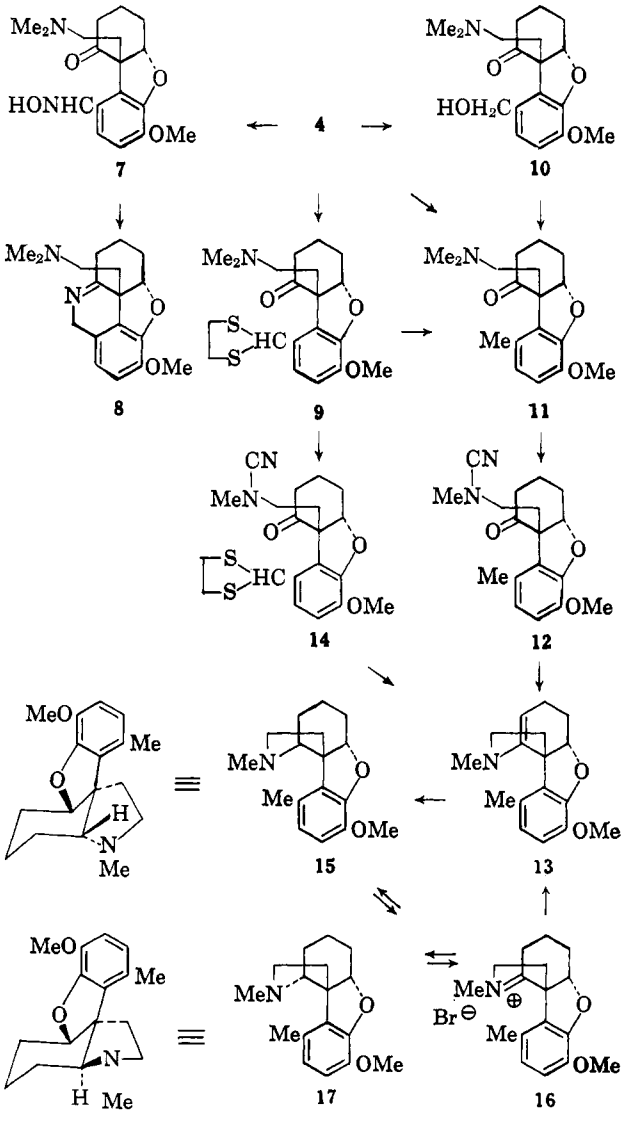
(6) Its molecular formula agrees with the addition of an acetyl group to the methine base **3**, and its infrared and n.m.r. spectra exhibit the characteristic absorption bands due to acetyl group.



triol **6** but directly to **4**.[7] The structure of **4** was supported by converting it to many derivatives.

An abnormal oxidation behavior of the Prévost reaction has occurred in the case of isophyllocladene, the allylic methyl group being replaced by a hydroxymethylene group.[8] On the other hand, an alkaline cleavage of a strained ring with a vicinal diol is also known.[9] However, in this case, the triol **6** was obtained from **3** by oxidation with osmium tetraoxide. Alkaline treatment of **6** recovered only a starting material. Therefore, it was shown that the triol **6** would not be a transitory intermediate in the formation of **4**. In the Prévost reaction with **3**, it can be considered that the allylic hydroxyl group would have participated in the formation of a cationic intermediate[10] to cleave the carbon–carbon linkage.

Treatment of **4** with an excess of hydroxylamine gave only the ketoaldoxime **7** even under a vigorous condition. The oxime **7** was catalytically reduced to an anil **8**, the infrared spectrum of which showed an absorption band at 1650 cm.$^{-1}$ (six-membered cyclic C=N).[11] Treatment of **4** with ethanedithiol in the presence of boron trifluoride gave monothioacetal **9**, which on desulfurization with hydrazine[12] yielded ketone **11**. Catalytic reduction of **4** gave alcohol **10**. On Clemmensen reduction of **10**, the keto group was unaffected, but the benzylic hydroxyl group was reduced, affording the keto compound **11**. From these results, the keto group is considered to be sterically hindered to a great degree. Analogously, Wolff–Kishner reduction of **4** also gave **11**. Finally, the intramolecular reaction of the keto group of **11** with a nitrogen atom was attempted to obtain octahydroindole derivatives **15** and **17** which also could be derived from galanthamine. The keto compound **11** reacted with cyanogen bromide to give the nor-N-cyano compound **12**, which was converted to an enamine **13** by treatment with aqueous alcoholic sodium hydroxide solution. The same enamine **13** also was obtained from **9** *via* the nor-N-cyano compound **14**. Catalytic hydrogenation of **13** in neutral medium gave only **15**, m.p. 125–126°. Oxidation of **15** in chloroform solution[13] with N-bromosuccinimide gave a quarternary azomethine **16**, which furnished the same enamine **13** by treatment with sodium hydroxide. Sodium borohydride reduction of **16** afforded the other isomeric octahydroindole derivative **17**, m.p. 117–119°, along with a small amount of **15**. On oxidation with N-bromo-

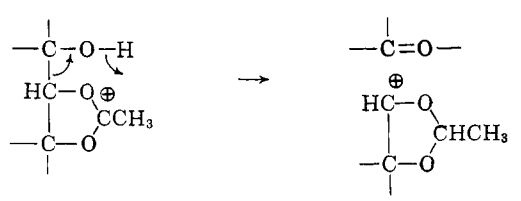


(7) The oxidation by a mixture of periodide and a suitable oxidizing agent would effect the elimination of C-9 of an allylic alcohol system, but in this case only the starting material was recovered. *Cf.* R. Pappo, D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Org. Chem.*, **21**, 478 (1956). Then we attempted hydroxylation of the double bond in the B-ring of 3 by the Woodward modified Prévost reaction followed by a cleavage of the resulting vicinal triol to obtain the norseco compound **4**. *Cf.* H. Rapoport, M. S. Chadha, and C. H. Lovell, *J. Am. Chem. Soc.*, **79**, 4694 (1957), for a discussion of the hydroxylation and cleavage of a double bond in the C-ring of morphine alkaloids. See also L. J. Sargent, L. H. Schwartzman, and L. F. Small, *J. Org. Chem.*, **23**, 1247 (1958).

(8) L. H. Briggs B. F. Cain, and B. R. Davis, *Tetrahedon Letters*, No. **17**, 9 (1960). This unexpected result was explained by subsequently finding that phyllocladene is isomerized to isophyllocladene by a trace of iodine in benzene.

(9) R. Anet, *ibid.*, 720 (1961).

(10) In this case, we postulate the following pathway.



(11) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

(12) V. Georgian, R. Harrison, and N. Gubisch, *ibid.*, **81**, 5834 (1959). In this literature, the authors stated that the presence of sodium hydroxide was not always necessary, but in our procedure an absence of alkali afforded only a starting material.

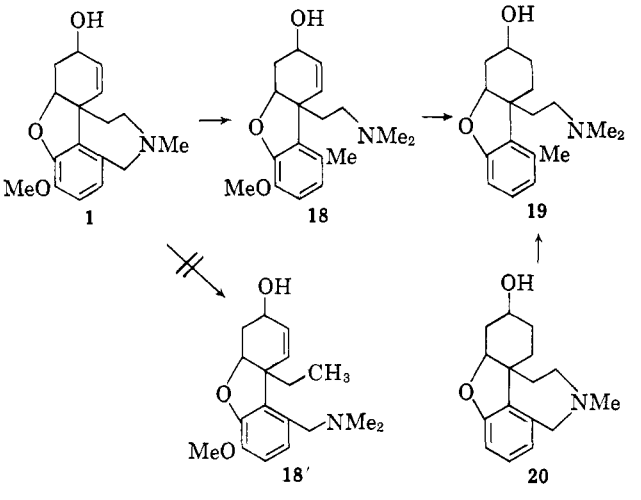
(13) This reaction did not occur in carbon tetrachloride solution even in the presence of dibenzoyl peroxide under irradiation. *Cf.* L. Horner, E. Winkelmann, K. H. Knapp, and W. Ludwig, *Ber.*, **92**, 288 (1959).

Octahydroindole derivatives **15** and **17** did not form a quarternary iodomethylate even after prolonged heating.

succinimide, **17** was converted into **16**. The formation of these two isomeric octahydroindole derivatives is explained by the fact that in morphine alkaloids the phenyl group is axial to the cyclohexane ring and the oxide ring fuses *cis* to C-ring.[3] The stereochemical assignment of **15** is based upon the catalytic hydrogenation of enamine **13** which as anticipated was affected from the less hindered side, *i.e.*, the side opposite to the pyrrolidine ring. The formation of the other isomer **17** may be rationalized by the concepts of steric approach control and product development control on the borohydride reduction.[14]

Then the authors attempted to convert galanthamine (**1**) to the octahydroindole derivative.

Emde degradation of galanthamine chloromethylate[15] yielded the methine base **18**. The methine base **18** was catalytically hydrogenated to dihydro compound **19** which was identified as the known Emde methine base **19**[16] of lycoramine (**20**). Therefore, the other possible structure **18′** for the methine base, is excluded.



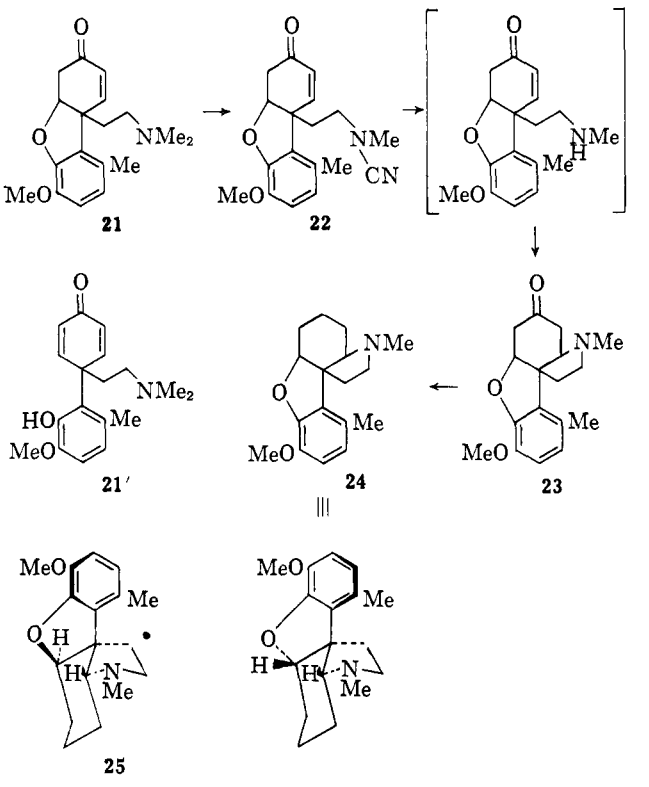
Oxidation of **18** with active manganese dioxide or Oppenauer oxidation yielded ketone **21** which showed no optical activity, due to an equilibration with its quinone type tautomer **21′**.[2]

The ketone **21** reacted with cyanogen bromide to give compound **22**. Treatment of **22** with potassium hydroxide caused decyanation and intramolecular β-amination of the α,β-unsaturated ketone simultaneously, to afford octahydroindole compound **23** which exhibited an expected absorption band at 1720 cm.$^{-1}$ but no absorption due to an α,β-unsaturated carbonyl group in an infrared spectrum. Wolff–Kishner reduction of **23** yielded **24** showing no absorption in the carbonyl region.

However, the infrared absorption bands of **24** were not coincident with those of **15** or **17** in chloroform.

Two (**15** and **17**) of the three isomers of 1-methyl-3a-(3′-methoxy-6′-methylphenyl)-4,2′-epoxyoctahydroindole were obtained from thebaine and the other one (**24**) from galanthamine.

The oxide ring in **15** and **17** must have the *cis*-fused configuration because the thebaine from which they are derived is known to possess the oxide ring of this



configuration. The experimental facts show that **15** and **17** should be epimers at position 7a (indole numbering). Considering the oxide ring fusion of the C-ring of thebaine as the *cis* configuration, two epimers are possible. When the octahydroindole ring fusion is *trans*, the phenyl group must be axial to the cyclohexane ring, and when it is *cis*, two conformational isomers for **15** can be theoretically considered; namely, the phenyl group axial **15** and equatorial **25** to the cyclohexane ring. However, the energy barrier between both structures **15** and **25** is not great enough to afford isolation of each compound. Consequently, the octahydroindole derivative **24** derived from galanthamine must have a different stereochemistry, *i.e.*, the *trans*-fused oxide ring. However, by these facts we could not fully establish the stereochemistry of galanthamine because the problem involved thermodynamic stability during the ring cleavage and closure of α,β-unsaturated ketones. Similar phenomena are also known in the cases of mesembrenine[17] and powellenone.[18] The compounds formed in all the cases must have the thermodynamically more stable configuration, which suggests that compound **24** obtained from galanthamine should have both oxide and pyrrolidine rings *cis*-fused. Although from the fact that **24** did not show an identical infrared spectrum with **15** or **17** obtained from thebaine, its oxide ring configuration is concluded to be *trans;* but there still remained an unclarified problem on the concept of thermodynamic stability of fusion of a five-membered ring with a six-membered ring.

Experimental

All melting points are uncorrected. Products were identified by mixture melting points and comparison of infrared spectra.

(14) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956); W. G. Dauben, E. J. Blanz, Jr., J. Jiu, and R. A. Micheli, *ibid.*, **78**, 3752 (1956).

(15) S. Uyeo and S. Kobayashi, *Pharm. Bull.* (Tokyo), **1**, 139 (1953).

(16) S. Ishiwata, *Yakugaku Zasshi*, **58**, 13 (1938).

(17) A. Popelak, G. Lettenbauer, E. Haack, and H. Spingler, *Naturwissenschaften*, **47**, 231 (1960).

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

14-Hydroxydeoxydihydrocodeine Methiodide.—According to established methods,[7] a 55% over-all yield of 14-hydroxydeoxydihydrocodeine (**2**), m.p. 118–119°, was obtained from thebaine. The **iodomethylate** was prepared as follows. A mixture of 10.0 g. of **2**, 50 ml. of methanol, and 20 ml. of methyl iodide was refluxed for 2 hr., and the solvent was removed under reduced pressure. The crystalline residue obtained was washed with cold acetone, yield, 13.0 g. An analytical sample, recrystallized from a methanol–acetone mixture, melted at 228–229°.

Anal. Calcd. for $C_{18}H_{23}O_3N \cdot CH_3I$: C, 51.58; H, 5.88; N, 3.16; I, 28.66. Found: C, 51.37; H, 5.63; N, 3.38; I, 28.40.

Methine Base 3.—To a preheated solution of 10.0 g. of the iodomethylate in water (100 ml.), 100 ml. of aqueous potassium hydroxide (40%) was added under stirring, and the reaction mixture was heated on a steam bath for 30 min. The crude product, extracted with benzene, was dried over magnesium sulfate and concentrated. The residual solid was recrystallized from *n*-hexane to give 6.3 g. of **3**, m.p. 128–129°. An analytical sample, recrystallized from *n*-hexane, melted at 128–129°; λ_{max}^{EtOH} 274, 300, and 313 mμ (ε 11,400, 4600, and 3500, respectively).

Anal. Calcd. for $C_{19}H_{25}O_3N$; C, 72.35; H, 7.99; N, 4.44. Found: C, 72.29; H, 7.70; N, 4.61.

Hydroxylation of Methine Base 3.—To a solution of 1.0 g. of osmium tetraoxide in 40 ml. of ether containing 0.78 ml. of pyridine, was added 1.2 g. of **3**. The solution became dark brown and was allowed to stand for 15 hr. The osmate ester, which, precipitated was collected, washed with ether, and dissolved in 60 ml. of methanol. The solution was heated under reflux for 4 hr. with a solution of 8 g. of sodium sulfite in 20 ml. of water, and extracted with chloroform after dilution with water. The extract was washed with water, dried over sodium sulfate, and evaporated; yield, 0.6 g.; m.p. 154–160°. An analytical sample sublimed *in vacuo* melted at 159–162°.

Anal. Calcd. for $C_{19}H_{27}O_5N$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.14; H, 7.77; N, 3.91.

Prévost Reaction of the Methine Base 3.—After addition of 5.4 g. of silver acetate to the solution of 5.0 g. of **3** in glacial acetic acid (100 ml.), powdered iodine (4.06 g.) was added in small portions with vigorous stirring over a period of 30 min. at room temperature. When all the iodine had been consumed, aqueous acetic acid (7.1 ml. of a solution prepared by diluting the glacial acetic acid to 50 ml. with 2.0 ml. of water) was added. The reaction mixture was then heated at 90–95° for 3 hr. with vigorous stirring. On cooling, it was treated with 12 g. of sodium chloride and insoluble salts were removed. The filtrate was evaporated under reduced pressure, the solids were taken up in methanol (50 ml.), filtered, and made slightly alkaline with concentrated ammonium hydroxide under cooling. The precipitates were collected and washed with water. The yield was 3.9 g.; m.p. 116–118°; $[\alpha]^{28}D$ −94° (*c* 2, in chloroform); λ_{max}^{EtOH} 291 mμ (ε 2900).

Anal. Calcd. for $C_{21}H_{27}O_5N$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.57; H, 7.30; N, 3.92.

Norseco Compound 4.—In the preceeding procedure of the acetate **5**, the residue obtained by evaporation of the acetic acid was neutralized with methanolic potassium hydroxide. and then treated with potassium hydroxide (3.0 g.) in water (10 ml.) and left overnight at room temperature. The reaction mixture was neutralized with acetic acid, concentrated to about one-fourth volume under reduced pressure, and, after dilution with water and treatment with potassium carbonate, extracted with benzene. The extract was washed with water, dried over magnesium sulfate, and evaporated. The residual oil was dissolved in a small amount of ether and cooled. The crystals which separated were then washed with cold ether; yield, 3.5 g.; m.p. 146–149°. An analytical sample was recrystallized from benzene–*n*-hexane mixture and melted at 149–150°; $[\alpha]^{28}D$ −52° (*c* 2 in chloroform); λ_{max}^{EtOH} 231, 279, and 327 mμ (ε 11,700, 12,400, and 7700, respectively).

Anal. Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.15; H, 7.34; N, 4.14.

The same compound was obtained from the acetate **5** by treating with potassium hydroxide in a similar manner. One gram of acetate **5** yields 0.87 g., m.p. 149–150°, of norseco compound **4**.

Ketoxime 7.—To a solution of **4** (5.0 g.) and hydroxylamine hydrochloride (1.5 g.) in 60 ml. of ethanol was added dropwise a solution of 2.0 g. of sodium carbonate in 60 ml. of water at 45° under stirring. The reaction mixture was stirred for 1 hr. at the same temperature. Dilution with water precipitated the oxime **7** as crystals; yield, 4.6 g., m.p. 188–189°. An analytical sample, recrystallized from a benzene–*n*-hexane mixture, melted at 188–189°.

Anal. Calcd. for $C_{18}H_{24}O_4N_2$: C, 65.04; H, 7.28; N, 8.43. Found: C, 65.24; H, 7.21; N, 8.23.

Catalytic Hydrogenation of the Ketoaldoxime 7.—Five grams of **7** in 30% acetic acid (100 ml.) was hydrogenated in the presence of 10% palladium–carbon (1.0 g.) under a hydrogen atmosphere at room temperature. The amount of hydrogen absorbed was about 800 ml. After removal of the catalyst, the solution was concentrated and treated with concentrated ammonium hydroxide. The liberated base was extracted with chloroform and the extract was dried over sodium sulfate and evaporated. The residual oil was distilled in vacuum, b.p. 145–155° (0.04 mm., bath temperature). The **monoiodomethylate** was prepared by treatment with methyl iodide in isopropyl ether under cooling with ice–water. An analytical sample recrystallized from ethyl acetate–methanol melted at 210–211° dec.

Anal. Calcd. for $C_{18}H_{24}O_2N_2 \cdot CH_3I$: C, 51.12; H, 6.05; N, 6.27; I, 28.47. Found: C, 51.29; H, 6.12; N, 6.20; I, 27.92.

Catalytic Hydrogenation of the Ketoaldehyde 4.—Five grams of **4** was hydrogenated in a mixture of acetic acid and ethyl acetate (1:1, 40 ml.) in the presence of platinum oxide (0.7 g.) at room temperature. After 30 min., the absorption of hydrogen amounted to the theoretical amount (1 mole). After removal of the catalyst, the solution was concentrated under reduced pressure, diluted with water, and treated with concentrated ammonium hydroxide. The crystalline precipitates were collected, washed with water, and recrystallized from an acetone–*n*-hexane mixture. The yield of alcohol **10**, m.p. 131–132°, was 4.5 g. An analytical sample, recrystallized from an acetone–*n*-hexane mixture, melted at 131–132°; $[\alpha]^{29}D$ +179° (*c* 2, in chloroform); λ_{max}^{EtOH} 290 mμ (ε 2800).

Anal. Calcd. for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.89; H, 7.66; N, 4.40.

Clemmensen Reduction of Alcohol 10.—Twenty grams of zinc dust was amalgamated by shaking with a solution of 2.0 g. of mercuric chloride in 20 ml. of water and 1 ml. of concentrated hydrochloric acid for 10 min. The liquid was then decanted and the amalgamated zinc was covered with 20 ml. of water and mixed with 3.0 g. of **10**. To the mixture was added 10 ml. of concentrated hydrochloric acid. The reaction mixture was gently refluxed for 10 hr. and a total of 10 ml. of concentrated hydrochloric acid was added at proper intervals. The mixture was cooled, filtered, treated with concentrated ammonium hydroxide, and extracted with benzene. The extract was washed with saline water, dried over magnesium sulfate, and evaporated. The residual oil was distilled in vacuum, b.p. 140–145° (0.07 mm.); yield, 2.55 g. An analytical sample was chromatographed on alumina (Merck) in benzene, sublimed, and recrystallized from *n*-pentane. This sample melted at 76–77°; $[\alpha]^{27}D$ +161° (*c* 2, in chloroform); λ_{max}^{EtOH} 291 mμ (ε 3000).

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.40; H, 8.28; N, 4.45.

Thioketalization of the Ketoaldehyde 4.—To a suspension of 1.0 g. of **4** in ethanedithiol (1.5 ml.), 1 ml. of boron trifluoride etherate was added. After the exothermic reaction, the reaction mixture became a paste. It was cooled, filtered, and washed with cold petroleum ether; yield, 1.1 g.; m.p. 141–143°. An analytical sample recrystallized from an acetone–petroleum ether mixture melted at 143–144°; λ_{max}^{EtOH} 296 mμ (ε 4400).

Anal. Calcd. for $C_{20}H_{27}O_3NS_2$: C, 61.05; H, 6.92; N, 3.56. Found: C, 60.93; H, 6.99; N, 3.82.

Desulfurization of the Thioacetal 9.—To a suspension of 3.0 g. of thioacetal in diethylene glycol (45 ml.) was added 80% hydrazine hydrate (12 ml.) and sodium hydroxide (6 g.). The mixture was gradually heated and kept at 170° for 20 min. The evolution of gas began at 120° and the total volume of the evolved gas, which was collected over water, was *ca.* 350 ml. The reaction mixture was extracted with benzene, and the extract was washed with water and dried over sodium sulfate. Evaporation of the benzene yielded 1.85 g., m.p. 71–74°. Recrystallization from *n*-pentane afforded a compound, m.p. 77–78°, which was identified as **11**.

Wolff–Kishner Reduction of the Ketoaldehyde 4.—A mixture of **4** (2.0 g.), diethylene glycol (120 ml.), 80% hydrazine hydrate (10 ml.), and potassium hydroxide (6 g.) was heated at 100° for 1 hr. and then kept at 160–180° for 3 hr. During this period, the evolved nitrogen gas amounted to about one mole equivalent. After cooling, the reaction mixture was extracted with benzene. The benzene extract was treated as in the preceding Clemmensen

reduction procedure. The product obtained was identical with **11**.

Reaction of the Ketone 11 with Cyanogen Bromide.—Cyanogen bromide (0.73 g.) was added to a solution of **11** (2.0 g.) in benzene (50 ml.) and the mixture was heated at 60° for 45 min. After cooling, the benzene solution was washed with 5% aqueous hydrogen chloride and water, and dried over sodium sulfate. The crystalline residue on evaporation of the solvent amounted to 1.75 g., m.p. 96–100°. An analytical sample, recrystallized from an acetone–*n*-hexane mixture, melted at 100–101°.

Anal. Calcd. for $C_{18}H_{22}O_3N_2$: C, 68.77; H, 7.05; N, 8.91. Found: C, 69.04; H, 7.35; N, 8.63.

Decyanation of the Nor-N-cyano Compound 12 and Ring Closure of the Resultant Enamine 13.—To a solution of 2.0 g. of **12** in 80% aqueous ethanol (10 ml.) was added potassium hydroxide (2.0 g.), and the mixture was heated at 110–120° in a sealed tube for 24 hr. The cooled reaction mixture was diluted with water and extracted with benzene. The extract was washed with water, dried over sodium sulfate, and evaporated. The solidified residue was unstable to air and had a tendency to change to red-colored resin. The reddish yellow solid was hydrogenated without further purification. It was dissolved in ethanol (50 ml.) and shaken with platinum oxide (0.43 g.) under a hydrogen atmosphere. The hydrogen volume absorbed amounted to 220 ml. for 30 min. Removal of catalyst and evaporation of the solvent afforded 1.3 g. of **15**, m.p. 122–125°. An analytical sample recrystallized from ethanol melted at 125.5–126°.

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.79; H, 8.58; N, 4.97.

Reaction of the Thioacetal 9 with Cyanogen Bromide.—Cyanogen bromide (0.3 g.) was added to a solution of **9** (1.0 g.) in benzene (20 ml.) and the mixture was heated at 60° for 45 min. After cooling, the benzene solution was washed with 5% aqueous hydrogen chloride and water, and dried over sodium sulfate. The oily residue obtained by evaporation of the benzene was crystallized by triturating with ether. The yield was 0.85 g., m.p. 155–157°. An analytical sample recrystallized from methanol melted at 158–158.5°.

Anal. Calcd. for $C_{20}H_{24}O_3N_2S_2$: N, 6.93. Found: N, 6.79.

Desulfurization and Ring Closure of 14.—To a suspension of **14** (3.0 g.) in diethylene glycol (40 ml.), sodium hydroxide (7 g.) and 80% hydrazine hydrate (10 ml.) were added, and the reaction mixture was gradually heated to 170° for 30 min. The total volume of evolved gas was *ca.* 500 ml. After dilution with water, the mixture was extracted with benzene. The extract was washed with water and dried over sodium sulfate. The oily product, obtained by evaporation of the benzene, was dissolved in ethanol (50 ml.) and hydrogenated with palladium–carbon (0.20 g.) under hydrogen atmosphere. Absorption of hydrogen corresponded to one mole. After filtration of the catalyst and concentration of the solvent, a crystalline product, 1.1 g., m.p. 123–125°, was obtained, which was identified as **15**.

Reaction of the Octahydroindole 15 with N-Bromosuccinimide.—To a solution of **15** (1.0 g.) in chloroform (50 ml.) was added N-bromosuccinimide (0.65 g.) and a trace amount of dibenzoyl peroxide, and the mixture was refluxed by irradiation with an infrared lamp for 1 hr. After concentration, 10 ml. of acetone was added to the mixture, which was then cooled. The crystals, which precipitated, were collected and weighed 0.87 g., m.p. 236–240° dec. An analytical sample, recrystallized from acetone, melted at 243–244° dec.

Anal. Calcd. for $C_{17}H_{22}O_2NBr$: N, 3.97. Found: N, 3.90.

Treatment of the Quarternary Azomethine 16 with Potassium Hydroxide.—To a preheated solution of **16** (1.0 g.) in water (10 ml.) was added 40% aqueous potassium hydroxide (10 ml.) and the reaction mixture was kept for 20 min. at 95–100° under stirring. The base which was liberated was extracted with benzene, and the extract was washed with water, dried over sodium sulfate, and evaporated. The oily residue was distilled *in vacuo*, b.p. 170° (0.005 mm., bath temperature); yield, 0.7 g. This oily product was hydrogenated with 10% palladium–carbon (0.3 g.) in ethanol as usual. The crystalline product, m.p. 122–124°, weighed 0.6 g. A sample recrystallized from methanol was identified as **15**.

Sodium Borohydride Reduction of the Quarternary Azomethine Base 16.—To a solution of **16** (1.0 g.) in ethanol (50 ml.) was added sodium borohydride (1.0 g.). The reaction mixture was heated at 60° for 3 hr., concentrated to one-third volume under slightly reduced pressure, made alkaline with 10% aqueous sodium hydroxide, and extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and evaporated to afford a crystalline residue (0.7 g.), m.p. 110–118°. The product (0.31 g.) which was repeatedly recrystallized from an ether–methanol mixture had a constant m.p. of 117–119° and its homogenity was examined by gas chromatography.

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.98; H, 8.58; N, 4.87.

Concentration of the mother liquor gave 0.31 g., m.p. 92–105°, which could not be separated by column chromatography on alumina; but gas chromatography showed the crude compound, m.p. 92–105°, to consist of **17**, m.p. 117–119°, and **15**, m.p. 125–126°, in a ratio of three to one.

Reaction of 17 with N-Bromosuccinimide.—N-Bromosuccinimide (0.26 g.) and a trace of dibenzoyl peroxide were added to a solution of **17** (0.30 g.) in chloroform (20 ml.), and the reaction mixture was refluxed by irradiation of an infrared lamp for 4 hr. and then concentrated. To the residue was added acetone (5 ml.) and the solution was cooled. The crystals were collected and washed with acetone; yield, 0.22 g.; m.p. 220–230° dec. The sample, m.p. 240–245° dec., which was recrystallized from acetone–methanol mixture, was identified as **16**.

Galanthamine Emde Methine Base 18.—Galanthamine iodomethylate[15] was converted to the chloromethylate by shaking with freshly prepared silver chloride as usual. An analytical sample recrystallized from an acetone–methanol mixture melted at 292–295°.

Anal. Calcd. for $C_{17}H_{21}O_3N \cdot CH_3Cl$: C, 63.90; H, 7.16; N, 4.14; Cl, 10.35. Found: C, 64.00; H, 7.15; N, 4.14; Cl, 10.51.

Sixty grams of 5% sodium amalgam was added to the solution of the **chloromethylate** (2 g.) in 50 ml. of water maintained at 100° at proper intervals for 12 hr. under stirring. After cooling, the reaction mixture was extracted with benzene, and the extract was washed with saline water, dried over sodium sulfate, and evaporated. There was obtained 1.4 g. of crystalline residue. The crude product melted at 142–145°.

An analytical sample recrystallized from acetone melted at 144–145°.

Anal. Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.21; H, 8.16; N, 4.40.

The **hydrochloride**, m.p. 198–200°, was recrystallized from methanol–acetone mixture.

Anal. Calcd. for $C_{18}H_{25}O_3N \cdot HCl$: C, 63.55; H, 7.64; N, 4.12; Cl, 10.44. Found: C, 63.40; H, 7.61; N, 4.04; Cl, 10.32.

Catalytic Hydrogenation of the Methine Base 18.—One gram of **18** was hydrogenated in 30 ml. of acetic acid in the presence of platinum oxide (0.3 g.) at room temperature. The absorption of hydrogen amounted to the theoretical amount (1 mole). After removal of the catalyst, the solution was concentrated under reduced pressure. The concentrated solution was diluted with water and treated with 10% sodium hydroxide. The liberated base was extracted with chloroform, and the extract was dried over sodium sulfate and evaporated. The residual oil was dissolved in ethanol containing hydrogen chloride and concentrated. There was obtained 1.0 g. of the crystalline hydrochloride, m.p. 205–210°.

An analytical sample, recrystallized from an acetone–methanol mixture, melted at 210–212°.

This sample was identified as lycoramine Emde methine base (**19**) prepared by Ishiwata's method.[16]

C-14, N-Seco Compound 21. (A) By Oxidation of the Emde Methine Base 18 with Manganese Dioxide.—Eighteen grams of active manganese oxide was added to a solution of **18** (2 g.) in chloroform (500 ml.) and the mixture was stirred for 6 hr. Filtration of manganese oxide and concentration of the solvent afforded 1.74 g. of a crystalline product, which was chromatographed in benzene on alumina (Merck, basic); elution with benzene gave 1.65 g. of crystalline product, m.p. 94–98°.

An analytical sample, recrystallized from an acetone–*n*-hexane mixture, melted at 96–98°.

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.68; H, 7.51; N, 4.52.

(B) By Oppenauer Oxidation of 18.—Three grams of aluminum isopropoxide was added to a solution of toluene (100 ml.) and cyclohexanone (100 ml.). The reaction mixture was refluxed for 7 hr. and, after cooling, extracted with 10% sodium carbonate and chloroform. The extract was dried over sodium sulfate and evaporated. There was obtained 0.80 g., m.p. 93–96°.

Reaction of the Seco Compound 21 with Cyanogen Bromide.—To a solution of **21** (1.0 g.) in benzene (50 ml.) was added 0.4 g. of cyanogen bromide, and the mixture was warmed at 60° for 1 hr. After cooling, the benzene solution was washed with 5% hydrogen chloride and water, and dried over sodium sulfate. An oily residue obtained by evaporation of the benzene was crystallized by trituration with ether; yield, 0.79 g.; m.p. 80–94°.

An analytical sample, recrystallized from an acetone–*n*-hexane mixture and ether, melted at 94° with presoftening at 82–83°.

Anal. Calcd. for $C_{18}H_{20}O_3N_2$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.91; H, 6.64; N, 8.84.

Decyanation of 22 and Ring Closure.—To a solution of 0.78 g. of **22** in ethanol (15 ml.) was added 20% potassium hydroxide (5 ml.), and the mixture was heated in a bath kept at 110° for 10 hr. After cooling, the reaction mixture was diluted with water and extracted with benzene. The extract was washed with water and dried over sodium sulfate Evaporation of the benzene afforded 0.43 g. of an oily product, which was chromatographed on alumina (Woelm, grade III). Elution with benzene afforded 0.23 g. of crystalline product. Elution with chloroform gave another 0.18 g. of an oily substance, which was not characterized.

An analytical sample, recrystallized from an acetone–*n*-hexane mixture, melted at 148–149°.

Anal. Calcd. for $C_{17}H_{21}O_3N$: C, 71.05; H, 7.37; N, 4.87. Found: C, 70.97; H, 7.32; N, 4.96.

Wolff–Kishner Reduction of the Keto Compound 23.—To a solution of the ketone **23** (1.0 g.) in diethylene glycol (50 ml.), 80% hydrazine hydrate (10 ml.) and potassium hydroxide (3.0 g.) were added, and the mixture was heated at 100° for 1 hr. and at 140–160° for 3 hr. During this time, 1 mole of nitrogen was evolved. After cooling, water (50 ml.) was added to the reaction mixture, and the mixture was extracted with benzene. The extract was washed with water and dried over sodium sulfate. Evaporation of the benzene afforded a semisolid product amounting to 0.79 g.

An analytical sample was purified by chromatography on alumina (Woelm, grade III), by elution with benzene and by sublimation, m.p. 85–86°.

Anal. Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.55; H, 8.35; N, 4.99.

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A Novel Reduction with Alkylmercaptans and a New Route to 2-Keto Steroids

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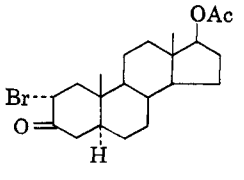
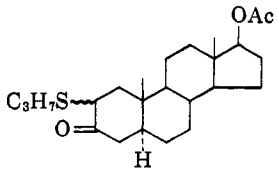
n-Propyl mercaptan reacts with 17β-acetoxy-2α-bromo-5α-androstan-3-one (I) to produce 17β-acetoxy-5α-androstan-2-one (IIIa). The intermediates have been shown to be 17β-acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II), 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI), and 2-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (VIII), in that order; hydrolysis of VIII produces the 2-ketone. Reduction of the intermediate 2,3-bis(*n*-propylmercapto)-5α-androst-2-en-17β-ol acetate (VI) by *n*-propyl mercaptan occurs only under strongly acidic conditions and in a symmetrical manner to produce 2- and 3-*n*-propylmercapto-5α-androst-2-en-17β-ol acetate (VIII and IX, respectively) in essentially equal quantities. 17β-Acetoxy-5α-androstan-2-one and -3-one can be separated quantitatively through preferential formation of a bisulfite adduct of the 3-ketone. Complete hydrolysis of the products from the above rearrangement with separation *via* the bisulfite reaction affords the 2-ketone (IIIa) in 41% yield and the 3-ketone in 49% yield.

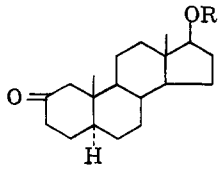
An attempt was made to prepare 17β-acetoxy-2ξ-*n*-propylmercapto-5α-androstan-3-one (II) from the corresponding 2α-bromo steroid (I) by heating the latter compound with *n*-propyl mercaptan in chloroform. Among the products of the reaction was 17β-acetoxy-5α-androstan-2-one (IIIa). This paper describes the investigation of this unusual reaction. The conditions which afford an optimum yield of the 2-ketone are given after the course of the reaction has been established.



I



II



IIIa, R = $COCH_3$
b, R = H
c, R = COC_2H_5

Replacement reactions at the C-2 of steroids have been plagued by rearrangements. For example, 2α-bromo-5α-cholestan-3-one reacts with potassium acetate in boiling acetic acid to give a 1:1 complex of 2α- and 4α-acetoxy-3-ketones.[1] At 200°, these same reactants give a Δ^5-4-keto steroid.[2] A different source of acetate ion, tetramethylammonium acetate, causes 2α-bromo-5α-cholestan-3-one to form 3β-acetoxy-5α-cholestan-2-one.[3] In the acid-catalyzed methanolysis of 2-acetoxytestosterone, the 2β-epimer yields 17β-hydroxy-5α-androstane-3,6-dione,[4] whereas the 2α-epimer yields 2-methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol.[5]

In the presently reported work a solution of 17β-acetoxy-2α-bromo-5α-androstan-3-one (I) and four molar equivalents of *n*-propyl mercaptan in chloroform was refluxed for six hours. Chromatography of the reaction products afforded 17β-acetoxy-5α-androstan-2-one (IIIa) in 23% yield, 17β-acetoxy-5α-androstan-3-one di-*n*-propylmercaptole (IV) in 9% yield, di-*n*-propyl disulfide in 75% yield, and a mixture of sulfur-containing oils. One portion of this oily mixture could be desulfurized with Raney nickel to give 5α-androstan-17β-ol acetate (V) in about 65% yield. When methanol was used as the solvent for recrystallization of the 2-ketone IIIa, the yield of 2-ketone dropped, and some dimethyl-

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