hol 6. Distillation afforded a quantitative yield of colorless oil: bp 90–102° (bath temperature, 0.07 mm); λ_{max} (film) 2.99, 3.27, 6.06, 9.56, 9.88, 10.16, 11.23 mμ; δ_{TMS} (CCl_4) 5.37 (vinyl H in ring), 5.20 (doublet, J = 8.5 Hz, C=CHCHOH), 4.75 (C=CH_2), 1.76 (1 vinyl CH_3), 1.67 ppm (2 vinyl CH_3). *Anal.* Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.70; H, 11.13.

Preparation of α-Atlantone (13). Oxidation of allylic alcohol 12 was effected using the method developed by Ratcliffe and Rodehorst,[6] followed by conjugation of the crude α,β,β′,γ′-unsaturated ketone using a 0.50 M solution of sodium methoxide in methanol (5 ml/mmol of ketone); reaction time 15 min at room temperature. Extraction of the crude product with ether followed by fractional distillation afforded α-atlantone (13) as a yellow oil in 62% overall yield from alcohol **12**: bp 100–115° (bath temperature, 0.06 mm), 90% pure by vpc analysis,[10] oven temperature 220°, retention time 5.7 min). The nmr and ir spectral properties of the distilled product as well as its physical properties were identical with those previously reported[2] for α-atlantone.

Preparation of α,β-Unsaturated Nitrile 10. To a solution of 6.05 g (112 mmol) of sodium methoxide in 20 ml of absolute ethanol was added dropwise slowly over a period of 15 min a solution of 15.8 g (89.5 mmol) of diethyl cyanomethylphosphonate[13] in 50 ml of absolute ethanol. After this mixture was stirred for 10 min at room temperature, a solution of 7.372 g (53.3 mmol) of ketone 5 in 50 ml of absolute ethanol was added rapidly (with external cooling of the flask using a cold water bath). After 40 min at room temperature, the reaction mixture was poured into 800 ml of water and the product was isolated by extraction with pentane. Short-path distillation afforded nitrile 10 in 95% yield: bp 50–65° (bath temperature, 0.04 mm); 80% pure[14] by vpc analysis,[10] oven temperature 165°, retention time 7.7 min; λ_{max} (film) 4.52, 6.15, 8.66, 12.4 mμ (broad); δ_{TMS} (CCl_4) 5.38 (vinyl H in ring), 5.12 (C=CHCN), 2.06 (CH_3C=CHCN), 1.67 ppm (vinyl CH_3). *Anal.* Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38. Found: C, 81.69; H, 9.44.

Reduction of Nitrile 10. To a solution of 6.24 g (38.6 mmol) of nitrile 10 (contaminated with the corresponding Z stereoisomer) in 120 ml of dry benzene cooled to ~15° using a cold water bath was added dropwise rapidly a mixture of 35 ml of 1.62 M diisobutylaluminum hydride–benzene solution and 120 ml of dry benzene. After this mixture was stirred at room temperature for 4 hr, the flask was cooled in a water bath and 500 ml of saturated ammonium chloride solution was added (cautiously until the excess reagent had been hydrolyzed). This mixture was subsequently stirred vigorously at room temperature for 20 min before addition of 300 ml of 1 M H_2SO_4. The product was immediately isolated by extraction with ether and subsequently distilled to afford aldehyde 9 in 75% yield, bp 60–70° (0.03 mm). The ir and nmr spectral properties of this aldehyde were identical with those of the product obtained previously *via* oxidation of allylic alcohol 8.

Registry No.—5, 6090-09-1; 6, 826-57-3; 7, 51230-63-8; 8, 51230-64-9; 9, 51230-65-0; 10, 51230-66-1; 12, 51230-67-2; 13, 26294-59-7; methyl vinyl ketone, 78-94-4; isoprene, 79-79-5; methallyl chloride, 563-47-3.

References and Notes

(1) B. S. Panda, S. Krishnappa, S. C. Bisarya, and S. Dev, *Tetrahedron*, **27**, 841 (1971).
(2) R. J. Crawford, W. F. Erman, and C. D. Broaddus, *J. Amer. Chem. Soc.*, **94**, 4298 (1972).
(3) For structures of other members of the bisabolane family of sesquiterpenes, see T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds, Volume 2, Terpenes," Academic Press, New York, N. Y., 1972, pp 100–103.
(4) James H. Babler and Douglas O. Olsen, *Tetrahedron Lett.*, 351 (1974).
(5) (a) A. A. Petrov, *J. Gen. Chem. USSR*, **11**, 309 (1941). (b) A 4% impurity (retention time 2.7 min) *might* be methyl 3-methyl-3-cyclohexenyl ketone on the basis of experimental results previously reported in the literature. A. Manjarrez, T. Rios, and A. Guzman reported that a 95:5 mixture of these two isomeric ketones was obtained and separeted *via* conversion to the corresponding semicarbazones, using reaction conditions nearly identical with those employed in our synthesis. *Cf. Tetrahedron*, **20**, 333 (1964).
(6) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(7) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 1425 (1952).
(8) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, pp 682–709.
(9) Reactions were carried out under a nitrogen atmosphere. Unless indicated otherwise, the isolation of reaction products was accomplished by pouring the mixture into water or saturated brine and extracting thoroughly with the specified solvent. Anhydrous magnesium sulfate was used to dry the combined extracts, and the solvent was removed on a rotary evaporator under reduced pressure. Evaporative distillation refers to bulb-to-bulb (Kugelrohr) short-path distillation. Infrared spectra were obtained using a Beckman IR-5A infrared spectrophotometer and nmr spectra were recorded with a Varian A-60 nmr spectrometer. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. 60076.
(10) A 6 ft × 0.125 in. SE-30 column was used for this analysis.
(11) Available from Ventron Corporation, Alfa Products, Beverly, Mass. 01915.
(12) A minor component (retention time 4.0 min, <10% of the mixture was not identified but might be the Z allylic acetate.
(13) Available from Aldrich Chemical Co., Inc., Milwaukee, Wis. 53233.
(14) On the basis of the combustion analysis of this nitrile and its spectral properties, a 20% impurity (retention time 6.3 min) was assumed to be the Z stereoisomeric nitrile. Since the route to α-atlantone *via* the allylic rearrangement of alcohol 6 was highly stereoselective, no effort was made to separate this mixture and further characterize the components.

New Preparation of Desmosterol[1]

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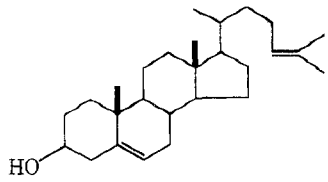
Two new syntheses of desmosterol (24-dehydrocholesterol) are described. The starting material is 3β-hydroxybisnorcholenic acid and 3β-hydroxynorcholenic acid, respectively.

Earlier investigations[3] of the catabolism of cholesterol, in this laboratory, led to the synthesis[4] of Δ^{16}-cholesterol and Δ^{17}-cholesterol, compounds which were to be tested as potential intermediates in the formation of side chain hydroxylated cholesterols. Desmosterol (1), a precursor[5] in the biosynthesis of cholesterol, may be considered as an intermediate in the synthesis of 24,25-dihydroxycholesterol, a side-chain analog of 24,25-dihydroxycholecalciferol,[6] which is a metabolite of vitamin D_3. It has already been reported[7] that desmosterol, on incubation with an enzyme preparation obtained from calf adrenal, produced 4-methyl-3-pentenoic acid and pregnenolone, suggesting that it could be a direct precursor of the steroid hormones. For these reasons we devised general methods of construction of the desmosterol side chain, which may easily be modified for the syntheses of hydroxy and alkyl derivatives.

In the earlier synthesis of 1 the 24,25 double bond was introduced by a Wittig reaction[8] involving a C_{24} steroid aldehyde as well as by the dehydration[9,10] of 25-hydroxycholesterol. We found[11] the latter method to be of little use for the synthesis of related compounds with a hydroxylated side chain. In recent years Bory,[12] Svoboda,[13] and Sheikh[14] have reported specific methods for the synthesis of 24-dehydrocholesterol derivatives bearing an additional double bond in the side chain.

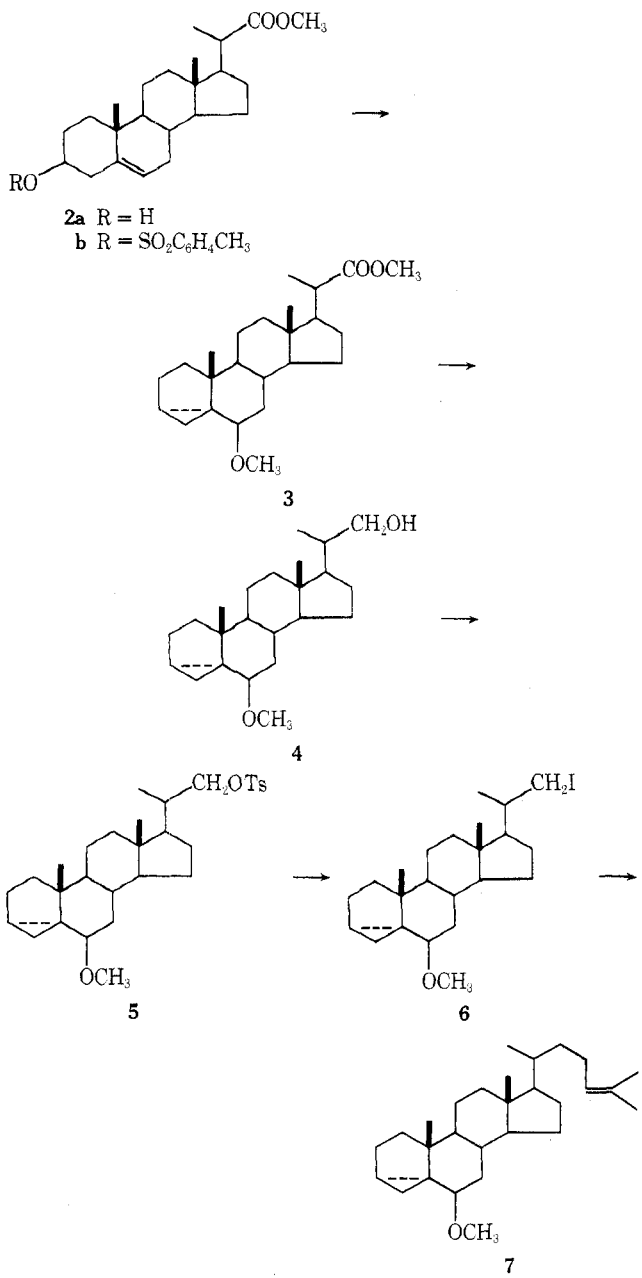


1

We now describe two new general syntheses of desmosterol, which can be extended toward the syntheses of compounds required by us in connection with biological oxidation studies. In these two methods we have chosen, as potential 24,25-unsaturated systems, dimethylallyl and dimethylvinyl residues to be joined to C_{22} and C_{23} steroid units, respectively.

It was reported[15] by Corey and Semmelhack that π-allylnickel halides[16] react with organic halides producing allyl-substituted molecules, a method successfully used by these authors in the synthesis of santalene.[15] A similar coupling procedure appeared quite attractive to us for the construction of the side chain in our projected synthesis of desmosterol. π-(Dimethylallyl)nickel bromide[16] was allowed to react with 22-iodo-3α,5-cyclo-23,24-bisnorcholan-6β-ol 6-methyl ether (**6**) (Chart I) leading to the formation of a crystalline 6β-methoxy-3,5-cyclodesmosterol derivative 7 in 65% yield. The nmr spectrum of 7 revealed characteristic olefinic methyl (26,27) protons at 96 and 100 Hz and a broad signal at 305 Hz for the 24 olefinic proton. Broad multiplets at 20–40 Hz and a sharp singlet and a triplet at 199 and 166 Hz, respectively, confirmed that the 6-methoxy i-steroid moiety in 7 remained unchanged under the condition of the reaction. Compound 7 was treated with aqueous dimethyl sulfoxide containing 0.3% perchloric acid, and desmosterol (1) was obtained in 60% yield. The purity of the material was established by melting point, ir, and nmr, as well as by comparison with an authentic sample.

Chart I



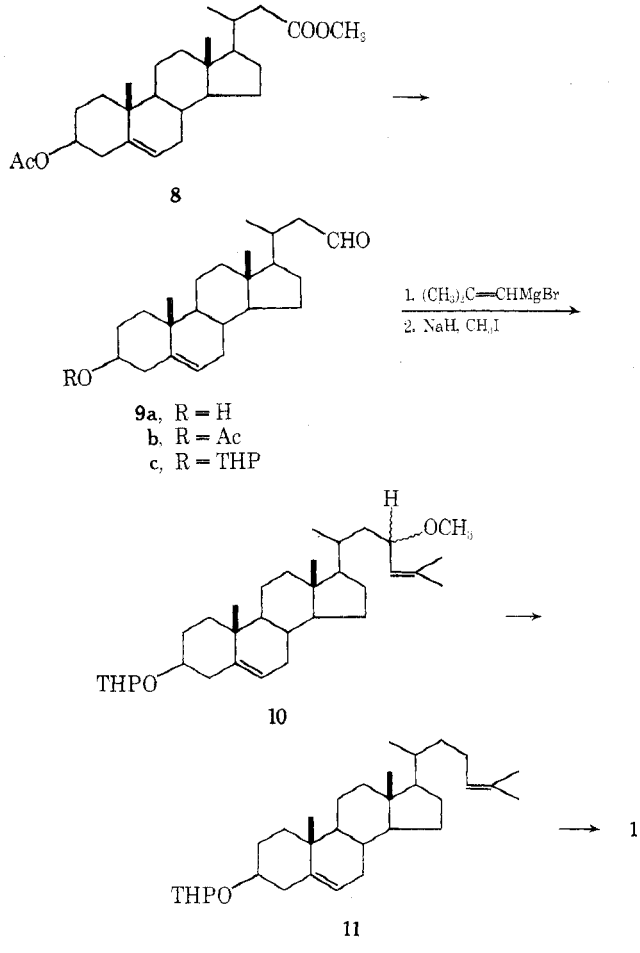
The synthesis of 6 was done in a straightforward manner starting from the methyl ester **2a** of readily available 3-hydroxybisnorcholenic acid. **2a** was converted to the 3β-tosyloxy derivative **2b** in the presence of *p*-toluenesulfonyl chloride. The tosyl ester was solvolyzed with methanol in the presence of pyridine and the product was filtered through alumina, resulting in the formation of the 3,5-cyclo-6β-methoxy derivative **3** as a syrup, which was found to be of sufficient purity for further conversion. It was reduced with lithium aluminum hydride and the crude product **4**, without further purification, was converted to the crystalline 22-tosyl derivative **5** in good yield. Its ir and nmr spectra (see Experimental Section) were in complete agreement with the proposed structure. Treatment of **5** with a boiling solution of sodium iodide in acetone gave the corresponding iodide as a crystalline material **6** in good yield. The overall yield of desmosterol (1) starting from **2a** was 20%.

We now describe the second seven-step synthesis (see Chart II) starting from methyl 3β-acetoxynorchol-5-enate (**8**) which could be prepared by the Arndt–Eistert homologation of the commercially available 3β-acetoxybisnorcholenic acid following the method[17] of Ryer and Gebert. The ester **8** was reduced with a solution of diisobutylaluminum hydride in hexane to the hydroxy aldehyde **9a** in greater than 90% yield. Its identity was established by its nmr spectra, exhibiting an aldehyde proton signal at 584 Hz but lacking that of an ester methyl proton. The crude product, without any further purification was converted to the tetrahydroxypyranyl ether **9c**, which was purified by filtration through a column of alumina and obtained as an amorphous solid. The purity of the product was established by its homogeneity of thin layer chromatography and its spectral data (see Experimental Section). Addition of the Grignard reagent[18] obtained from 1-bromo-2-methylpropene[19] to the THP ether aldehyde **9c** resulted in the formation of an allyl alcohol which was directly treated with sodium hydride and methyl iodide, resulting in the formation of the 23-isomeric mixture of the dimethylallyl methyl ether **10**. It was chromatographed on a column of alumina. Elution with hexane–benzene (1:1) gave **10** as an oil in 80% yield. Its nmr spectra exhibited methoxy proton signals at 191 Hz, strong but broad signals at 96–102 Hz due to the 26,27 olefinic methyls and THP ether methylene protons, and a broad signal at 303 Hz due to an olefinic proton, apparently at C-24. Lithium–ethylamine reduction[20] of **10** at 0° led to the formation of desmosterol tetrahydropyranyl ether (**11**) which was purified by filtration of its hexane solution through a column of alumina, followed by elution with benzene–hexane (1:20). It was obtained as a crystalline material in 50% yield.

In this connection, it may be emphasized that the present method of lithium–ethylamine-induced hydrogenolysis

of the methyl ether derivative of an allyl alcohol hardly produced any undesirable olefin, in contrast to the observations made during a similar reduction[4] of the tetrahydropyranyl ether of *cis*-$\Delta^{17(20)}$-22-hydroxycholesterol, resulting in the formation of a mixture of olefinic isomers. The scope of the present procedure and the advantages of the reduction of an allyl alcohol methyl ether over its ester will be described in a future publication.

Chart II



The tetrahydropyranyl ether **11** was readily cleaved under acidic treatment, giving crystalline desmosterol (**1**). The overall yield of **1** starting from **8** was 21%.

Experimental Section

Melting points are uncorrected. Nmr spectra, reported in hertz, were obtained in deuteriochloroform solution on a 60-MHz Varian Associates DA-60 spectrometer using tetramethylsilane as an external reference. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Methyl 3β-Tosyloxy-23,24-bisnorchol-5-en-22-oate (2b). A solution of 10 g of methyl 3β-hydroxy-23,24-bisnorchol-5-en-22-oate[21] (**2a**) and 13 g of *p*-toluenesulfonyl chloride in 160 ml of pyridine was left standing for 18 hr at 25°. Then water was added dropwise while stirring and the resulting precipitate was filtered off and washed with a large amount of water. Two recrystallizations from acetone–hexane gave 13.2 g of pure **2**: mp 145–147°; ir 1720 and 1245 ($COOCH_3$), 1180 and 1145 cm^{-1} (tosylate); nmr 41 ($18\text{-}CH_3$), 58 ($19\text{-}CH_3$), doublet centered at 70 (J = 6 Hz, $21\text{-}CH_3$), 147 ($CH_3C_6H_4$–), 218 ($COOCH_3$), 319 (6 H).

Anal. Calcd for $C_{30}H_{42}O_5S$: C, 70.01; H, 8.23; S, 6.23. Found: C, 69.44; H, 8.38; S, 6.52.

Methyl 3α,5-Cyclo-6β-methoxy-5α-23,24-bisnorcholan-22-oate (3). A solution of 10 g of the tosylate **2b** in 70 ml of pyridine and 1000 ml of methanol was heated on a steam bath for 3 hr, after which time the methanol was removed by distillation *in vacuo*. After the addition of water the mixture was extracted with ethyl acetate. The organic extract was washed with 2 *N* aqueous acetic acid, which removed all pyridine. Then the extract was washed with water, saturated bicarbonate, and saturated brine. After drying over anhydrous sodium sulfate and evaporation of solvent there was obtained 11.3 g of an oil, which was filtered through a column of alumina. The hexane–benzene eluates gave 7.2 g of a syrup which gave only one spot on tlc (10% ethyl acetate in benzene) and was not further purified before reduction, ir 1720 and 1248 ($COOCH_3$), 1090, 1010, and 960 cm^{-1} (6-OMe *i*).

3α,5-Cyclo-5α-23,24-bisnorcholane-6β,22-diol 6-Methyl Ether (4). To a suspension of 900 mg of lithium aluminum hydride in 100 ml of dry tetrahydrofuran was added a solution of 7.1 g of the ester **3** in 20 ml of tetrahydrofuran and the mixture was heated under reflux for 3 hr, then left at 25° for 18 hr. The excess reagent was decomposed with 2 *N* sodium hydroxide. Finally the precipitated salts were filtered off and washed with hot ethyl acetate. Evaporation of the filtrate gave 6.6 g of syrup which was not purified further, but appeared uniform on tlc (20% ethyl acetate in benzene), ir 3350 (OH), 1090, 1015, and 960 cm^{-1} (6-OMe *i*).

3α,5-Cyclo-22-tosyloxy-5α-23,24-bisnorcholan-6β-ol 6-Methyl Ether (5). To a solution of 6.0 g of the alcohol **4** in 100 ml of pyridine was added 5 g of *p*-toluenesulfonyl chloride. The solution was left standing for 24 hr at 23° and then, while cooling and with rapid stirring, the excess reagent was decomposed by dropwise addition of ice water. The crude tosylate crystallized in the aqueous pyridine and was collected by filtration. The solids were washed well with water and finally air dried at 25°. Recrystallization from ether and from benzene–hexane gave 6.1 g of tosylate **5**: mp 144–145°; ir 1190, 1170 (tosylate), 1090, 1010, and 980 cm^{-1} (6-OMe *i*); nmr 41 ($18\text{-}CH_3$), 61 ($19\text{-}CH_3$), 147 ($CH_3C_6H_4$–), broad multiplets at 20–40 (cyclopropyl hydrogens), 198 ($6\beta\text{-}OCH_3$), 166 (6α-H), multiplets centered at 233 (22-tosyloxymethylenes).

Anal. Calcd for $C_{30}H_{44}O_4S$: C, 71.97; H, 8.86; S, 6.39. Found: C, 71.74; H, 8.71; S, 6.67.

3α,5-Cyclo-22-iodo-5α-23,24-bisnorcholan-6β-ol 6-Methyl Ether (6). A solution of 6 g of tosylate **5** and 9 g of sodium iodide in 200 ml of dry acetone was heated under reflux on the steam bath for 10 hr. Then the acetone was evaporated off *in vacuo*, the residue was extracted with benzene, and the solution was dried over anhydrous sodium sulfate and evaporated. The crystalline residue was recrystallized from acetone–methanol to give 4.6 g of **6**: mp 110–112°; ir 1090, 1010, and 960 cm^{-1} (6-OMe *i*); nmr 45 ($18\text{-}CH_3$), 61 ($19\text{-}CH_3$), 198 ($6\beta\text{-}OCH_3$), broad multiplets at 20–40 (cyclopropyl hydrogens), 166 (6α-H).

Anal. Calcd for $C_{23}H_{37}OI$: C, 60.25; H, 8.58; I, 27.68. Found: C, 60.60; H, 8.36; I, 27.53.

3α,5-Cyclo-5α-cholest-24-en-6β-ol 6-Methyl Ether (7). A solution of 460 mg of the halide **6** in 5 ml of tetrahydrofuran was added at once to a solution of 520 mg of π-(dimethylallyl)nickel bromide[22] in 5 ml of tetrahydrofuran under argon at 25°. After 30 hr at 50°, the dark green mixture was poured into hexane. The hexane solution was washed with water, dried, and evaporated to give a syrup, which was chromatographed on alumina. The hexane–benzene eluates furnished 321 mg of prisms: mp 64–66° (acetone); ir 1090, 1010, and 960 cm^{-1} (6-OMe-i); nmr 43 ($18\text{-}CH_3$), 61 ($19\text{-}CH_3$), doublet centered at 56 (J = 6 Hz, $21\text{-}CH_3$), 96, 100 ($26,27\text{-}CH_3$), 199 ($6\beta\text{-}OCH_3$), broad multiplets at 20–40 (cyclopropyl hydrogens), 166 (6α-H), 305 (24 olefinic hydrogen).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.33; H, 11.68.

Desmosterol (1). To 50 ml of dimethyl sulfoxide was added 6 ml of water and 3 ml of 7% perchloric acid. This was cooled to 0° and 300 mg of **7** in 1 ml of tetrahydrofuran was added with stirring. After the solution was allowed to stand for 72 hr, it was poured over ice and extracted with ethyl acetate. The ethyl acetate extract was washed with water, saturated bicarbonate and saturated brine, dried, and evaporated. The residue, after two crystallizations from methanol, gave 166 mg of **1**, mp 120–122°, ir and nmr identical with those of authentic material.[10]

Diisobutylaluminum Hydride Reduction of Methyl 3β-Acetoxy-24-norchol-5-en-23-oate (8). 3β-Hydroxy-24-norchol-5-en-23-al (9a). To a cold stirred solution of 2 g of methyl 3β-acetoxy-24-norchol-5-en-23-oate (previously dried under vacuum) in 100 ml of dry toluene kept at −70° (Dry Ice–acetone) was added dropwise, with a syringe and under nitrogen, 105 ml of a 20% solution (1.41 mmol/ml) of diisobutylaluminum hydride in hexane and the stirring was continued for 2 hr at −70°. The aluminum complex was decomposed by careful addition of iced, saturated ammonium chloride solution followed by 86 ml of cold, dilute sul-

furic acid. The content of the reaction flask was transferred to a separatory funnel and extracted with ethyl acetate. The organic layer was separated, washed with water and saturated brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent yielded 1.6 g of the crude hydroxy aldehyde **9a** which was of sufficient purity for further transformation (see below). A small sample was crystallized from methylene chloride and ether: mp 127–129°; ir 3350 (OH), 2680, and 1695 cm^{-1} (CHO); nmr 44 (18-4_3), 61 (19-CH_3), 210 (3α-H), 322 (6-H), and 584 (CHO).

The 3-acetate **9b** was prepared by dissolving the crude hydroxy aldehyde (obtained from the above reduction experiment) in pyridine and adding excess acetic anhydride. The solution was allowed to stand overnight, after which time water was added and the mixture was extracted with ethyl acetate. After the pyridine was removed by extraction with cold, dilute hydrochloric acid, the ethyl acetate layer was washed with water, saturated sodium bicarbonate solution, and water. The solvent layer was separated, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. There was obtained 1.6 g (82%) of a crystalline product. An analytical sample was prepared by crystallization from ether: mp 125–130°; ir 2680 (CHO), 1720 (CH_3COO–), and 1695 (CHO); nmr 43 (18-CH_3), 62 (19-CH_3), 122 (acetate methyl), 280 (3α-H), 325 (6-H), and 586 (CHO).

Anal. Calcd for $C_{25}H_{38}O_3$: C, 77.67; H, 9.91. Found: C, 77.65; H, 9.82.

The tetrahydropyranyl ether **9c** was obtained in the following manner. The crude hydroxy aldehyde (see above), dissolved in 4 ml of dry methylene chloride, was treated with 3 equiv of dihydropyran and 4 drops of phosphorus oxychloride for 30 min at room temperature. The mixture was diluted with methylene chloride and poured into chilled sodium bicarbonate solution and the methylene chloride layer was separated. It was washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave an oil which was dissolved in hexane containing a small amount of benzene and chromatographed on 60 g of alumina. Elution with hexane–benzene (50%) gave the tetrahydropyranyl ether as an amorphous solid which failed to crystallize: 1.64 g (80%); ir 2680 and 1695 (CHO), 1025 and 960 cm^{-1} (THP ether); nmr 43 (18-CH_3), 61 (19-CH_3), 98 (THP methylenes), 280 (–OCHO–), 320 (6-H), and 584 (CHO).

Anal. Calcd for $C_{28}H_{44}O_3$: C, 78.45; H, 10.35. Found: C, 78.56; H, 10.50.

3β-Tetrahydropyranyloxy-23-methoxycholesta-5,24-diene (23-Isomeric Mixture) (10). In a flask were placed 240 mg of magnesium shavings, 1.5 ml of anhydrous tetrahydrofuran, and a trace of iodine. A drop of 1-bromo-2-methylpropene was added and the mixture was stirred under nitrogen at 30–40°. After a few minutes the brown color of the iodine began to fade to a cloudy yellow and after about 30 min the mixture became colorless but cloudy. As soon as the brown color started fading, a solution of 1.5 ml of 1-bromo-2-methylpropene in 1.5 ml of tetrahydrofuran was added carefully, one drop every 5–10 min, during the entire color change. When the mixture became colorless but cloudy, the dropwise addition was halted. The stirring was continued until the mixture became clear and colorless (1 hr from the start). The dropwise addition of the halide was resumed. Immediately the mixture started becoming yellow and began to boil increasingly and after a few minutes a complex precipitated out. The remaining halide was added with stirring over a period of 2 hr. In the end the mixture was boiled gently until the remaining traces of magnesium dissolved, leaving a clear, light-brown solution. It was diluted with 5 ml of tetrahydrofuran and then cooled slightly below room temperature. A solution of 856 mg of 3β-tetrahydropyranyloxy-24-norchol-5-en-23-al (**9c**) dissolved in 5 ml of tetrahydrofuran was added dropwise and the solution was gently heated under reflux for 30 min and then stirred at room temperature for 10 hr. The Grignard complex was decomposed by cautious additions of iced, saturated ammonium chloride solution. It was transferred to a separatory funnel and the tetrahydrofuran layer was removed. The aqueous layer was extracted with ether. The organic extracts were combined, washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, leaving behind a glassy residue. The ir spectra, while revealing the presence of a hydroxy group, did not show any characteristic band for aldehyde. The crude dry material was converted, without any further purification, to its methyl derivative. After washing carefully under nitrogen three times with dry hexane 500 mg of 53.4% sodium hydride in mineral oil, the residue was treated with 18 ml of anhydrous dimethyl sulfoxide. The mixture was warmed for about 1 hr, resulting in a clear solution of sodium methylsulfinyl methide. After cooling there was added a solution of the above allylic alcohol in 5 ml of tetrahydrofuran and then the solution was stirred for 3 hr under nitrogen at room temperature. After the dropwise addition of 6 ml of methyl iodide in the cold the mixture was stirred for 15 hr, after which time it was poured onto ice and water. It was extracted three times with ether and the combined ether extracts were thoroughly washed with saturated brine, dilute sodium thiosulfate solution, and water, and dried over anhydrous sodium sulfate. The solvent was evaporated and the crude product was purified by chromatography over alumina. Elution with hexane–benzene (50%) gave the allylic methyl ether **10** as a syrup: 0.8 g (80%); ir 1100 (–OMe), 1025 and 960 cm^{-1} (THP ether); nmr 40 (18-CH_3), 61 (19-CH_3), 191 (OCH_3), 96–102 (26,27 methyls and THP methylenes, 280 (OCHO) and 303 (24-H), 323 (6-H).

3β-Tetrahydropyranyloxycholesta-5,24-diene (11). A three-neck flask containing 500 mg of the ether **10** was fitted with a Dry Ice cold-finger condenser containing a mixture of Dry Ice and acetone and a drying tube, and 25 ml of anhydrous ethylamine was distilled (over sodium) directly into the flask. The mixture was stirred until a clear solution was obtained. Then 200 mg of lithium, cut into small pieces, was added rapidly and the stirring was continued for about 1 hr until a blue color persisted. Then the solution was filtered through glass wool into a saturated solution of ammonium chloride and extracted with three portions of 50 ml of ether. The combined ether extracts were washed with saturated brine, dried over anhydrous sodium sulfate, and distilled, yielding a partially crystalline residue. It was chromatographed over alumina, whereby elution with 5% benzene in hexane afforded a crystalline material. It was recrystallized from acetone, giving 225 mg of desmosterol tetrahydropyranyl ether (50%): mp 112–116°; ir 1125, 1012, and 900 cm^{-1} (THP ether); nmr 40 (18-CH_3), 60 (19-CH_3), doublet centered at 51 (J = 6 Hz, 21-CH_3), 98 and 100 (26,27 methyls and THP methylenes, 282 (OCHO) and 304 (24-4), 320 (6-H).

Anal. Calcd for $C_{32}H_{52}O_2$: C, 81.99; H, 11.18. Found: C, 82.24; H, 11.27.

Desmosterol (1). A 200-mg portion of the tetrahydropyranyl ether **11** was dissolved in 2 ml of tetrahydrofuran and heated gently at 40° for 5 min in the presence of 2 drops of concentrated hydrochloric acid. Then 5 ml of methanol was added and the solution was concentrated under a slow current of nitrogen, when a crystalline product separated out. It was cooled, filtered, and recrystallized from methanol, giving 115 mg (70%) of desmosterol: mp 120–122° (lit. mp 120–122°); nmr 41 (18-CH_3), doublet centered at 51 (J = 6 Hz, 21-CH_3), 61 (19-CH_3), 97 and 102 (26,27 methyls), 210 (3α-H) and 303 (24-H), 320 (6-H).

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Registry No.—**1**, 313-04-2; **2a**, 10527-79-4; **2b**, 51231-21-1; **3**, 51231-22-2; **4**, 51231-23-3; **5**, 51231-24-4; **6**, 51231-25-5; **7**, 51231-26-6; **8**, 33168-65-9; **9a**, 51231-27-7; **9b**, 10184-82-4; **9c**, 51231-28-8; **10** *R* isomer, 51231-29-9; **10** *S* isomer, 51231-30-2; **11**, 51231-31-3.

References and Notes

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(2) Chemistry Department, Westfield College, London, England.
(3) For our reviews see S. Burstein and M. Gut, *Advan. Lipid Res.*, **9**, 291 (1971); *Recent Progr. Horm. Res.*, **27**, 303 (1971); *Ann. N. Y. Acad. Sci.*, **212**, 262 (1973).
(4) N. K. Chaudhuri, R. Nickolson, J. G. Williams, and M. Gut, *J. Org. Chem.*, **34**, 3767 (1969).
(5) W. M. Stokes, W. A. Fish, and F. C. Hickey, *J. Biol. Chem.*, **220**, 415 (1956).
(6) (a) M. F. Holick, H. K. Schnoes, H. E. DeLuca, R. W. Gray, I. T. Boyle, and T. Suda, *Biochemistry*, **11**, 4251 (1972); (b) H. F. DeLuca, *N. E. J. Med.*, 289, 359 (1973).
(7) (a) DeW. S. Goodman, J. Avigan, and H. Wilson, *J. Clin. Invest.*, **41**, 2135 (1962); (b) K. Shimizu and M. Gut, *Steroids*, **6**, 301 (1965).
(8) D. R. Idler and U. H. M. Fagerlund, *J. Amer. Chem. Soc.*, **79**, 1988 (1957).
(9) W. Bergmann and J. P. Dusza, *J. Org. Chem.*, **23**, 459 (1958).
(10) U. H. M. Fagerlund and D. R. Idler, *J. Amer. Chem. Soc.*, **79**, 6473 (1957).

(11) Unpublished results from this laboratory.
(12) S. Bory, D. J. Lin, and M. Fetizon, *Bull. Soc. Chim. Fr.*, 1298 (1971).
(13) J. A. Svoboda, R. F. N. Hutchins, M. J. Thompson, and W. E. Robbins, *Steroids*, **14**, 469 (1969).
(14) Y. M. Sheikh, B. Twisch, and C. Djerassi, *Tetrahedron Lett.*, 3721 (1972).
(15) E. J. Corey and M. F. Semmelhack, *J. Amer. Chem. Soc.*, **89**, 2755 (1967).
(16) M. F. Semmelhack, *Org. React.*, **19**, 115 (1972).
(17) A. I. Ryer and W. H. Gebert, *J. Amer. Chem. Soc.*, **74**, 45 (1952).
(18) We are thankful to Professor J. Ficini of Paris for helpful suggestions on the preparation of this reagent.
(19) E. A. Braude and C. J. Timmons, *J. Chem. Soc.*, 2000 (1950).
(20) A. S. Ballsworth, H. B. Henbest, and T. I. Wrigley, *J. Chem. Soc.*, *1967 (1957)*.
(21) E. Fernholz, *Justus Liebigs Ann. Chem.*, **507**, 128 (1933).
(22) M. F. Semmelhack, Thesis, Harvard University, 1967.

General Methods of Synthesis of Indole Alkaloids. XIII. Oxindole Alkaloid Models[1,2]

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The synthesis of oxytryptophol and oxindoloindolizidine esters and methyl ketones is described. The determination of the stereochemistry of the acyl derivatives by ^1H and ^{13}C nmr spectral means is portrayed.

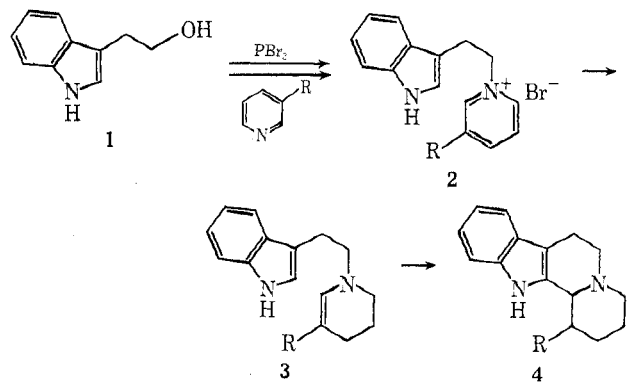
The transformation of tryptophol (**1**) into indoloquinolizidines (**4**) (Scheme I) represents the backbone of a general method of indole alkaloid synthesis.[4] As part of an endeavor to broaden the scope of the method, the possible replacement of the indole ring by the oxindole nucleus among early synthetic intermediates came under scrutiny. This modification offered great promise, since the resulting oxindoloindolizidine (**7**) could be envisaged in various stereochemical and substituted forms to be on the route to oxindole alkaloids of the rhyncophylline and mitraphylline types, to *Aspidosperma* alkaloids,[5] and to structures of even greater complexity. The incorporation of the oxindole system in the present scheme of synthesis appeared feasible at three stages of the reaction sequence: (a) by starting the sequence with oxytryptophol (**5**), (b) by oxidative conversion of indole **3** into oxindole **6** (followed by cyclization), and (c) by a related transformation of **4** into **7**. The following discussion focuses on these variations of Scheme I.

Bromination of tryptophol (**1**) in acetic acid gave a bromooxindole whose hydrogenolysis[6] led to oxytryptophol (**5**).[7] Unfortunately, in analogy with previous experience on *N*-methyloxindole compounds,[8] attempts of conversion of oxytryptophol (**5**) into an alkylating agent by the replacement of its hydroxy function by a leaving group failed. Thus, for example, treatment of **5** with hydrobromic acid yielded cyclopropane **8**.[9,10] As a consequence the preparation of oxindole equivalents of salts **2** appears a difficult task at best and the introduction of the oxindole unit is preferable at a later stage of Scheme I.

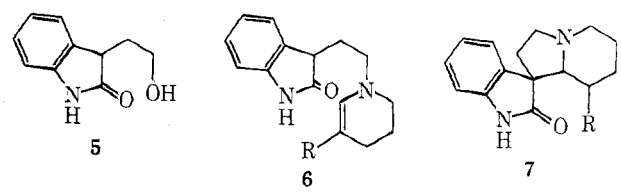
Treatment of ester **3b**[11] with aqueous *N*-bromosuccinimide[12] afforded a bromooxindole whose hydrogenolysis produced oxindole ester **7b** in one operation. Presumably the acid in the halogenating medium had effected the desired cyclization. The formation of three stereoisomers of **7b**, whose configuration is discussed later, indicated the cyclization to be nonspecific.

The customary procedure of an indole–oxindole conversion of type **4** → **7** involves initial oxidation with *tert*-butyl hypochlorite, base-catalyzed alcoholysis of the intermediate β-chloroindolenine, and acid hydrolysis of the resultant imino ether (Scheme II).[13] While this reaction sequence worked well for the simple indoloquinolizidine **4a**[11] and produced the **7a** diastereomers[14,15] therefrom, it proved difficult for **4** (R = Et)[14] and took an unusual course in the case of ketone **4c**.[16] Treatment of the latter with *tert*-butyl hypochlorite and subsequent hydroxide-

Scheme I

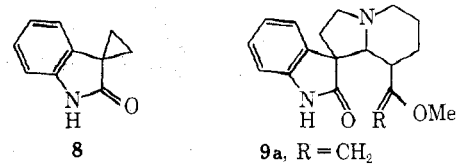


a, R = H; **b**, R = CO_2Me; **c**, R = Ac



a, R = H; **b**, R = CO_2Me; **c**, R = Ac

catalyzed methanolysis led to two oxindoles, instead of methoxyimines, and an unreacted chloroindolenine. The oxindoles proved to be an enol ether (**9a**) and a ketal (**9b**),



9a, R = CH_2
b, R = Me, OMe

whose mild acid hydrolysis converted them to stereoisomeric ketones (**7c**) of stereochemistry described below.

The unprecedented masking of a keto group in enol ether and ketal forms during a base-catalyzed operation, the formation of oxindoles instead of their imino ethers as a consequence of the rearrangement, and the ease of the reaction sequence appear interrelated and are interpreted most readily in terms of nucleophilic attack on the indolenine α-carbon site occurring intramolecularly. If it be assumed that methoxide first attacks the keto group and