establish lower detection limits for the infrared–x-ray method; however, a conservative estimate is 15% of a minor conformer.

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Registry No.—I, 51-45-6; II HCl, 135-23-9; III HCl, 147-24-0; IV HCl, 22306-05-4; V, 67-48-1.

Supplementary Material Available. (1) Tables comparing the absorption maxima of the solid and solution ir spectra of choline chloride, methapyriline hydrochloride (II HCl), tripelennamine hydrochloride (IV HCl), histamine (I), and diphenhydramine hydrochloride (III HCl); and (2) detailed chemical shift data for the NMR spectra of methapyriline hydrochloride (II HCl), tripelennamine hydrochloride (IV HCl), and diphenhydramine hydrochloride (III HCl) (7 pages). Ordering information is given on any current masthead page.

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20-Methylcholesterol[1]

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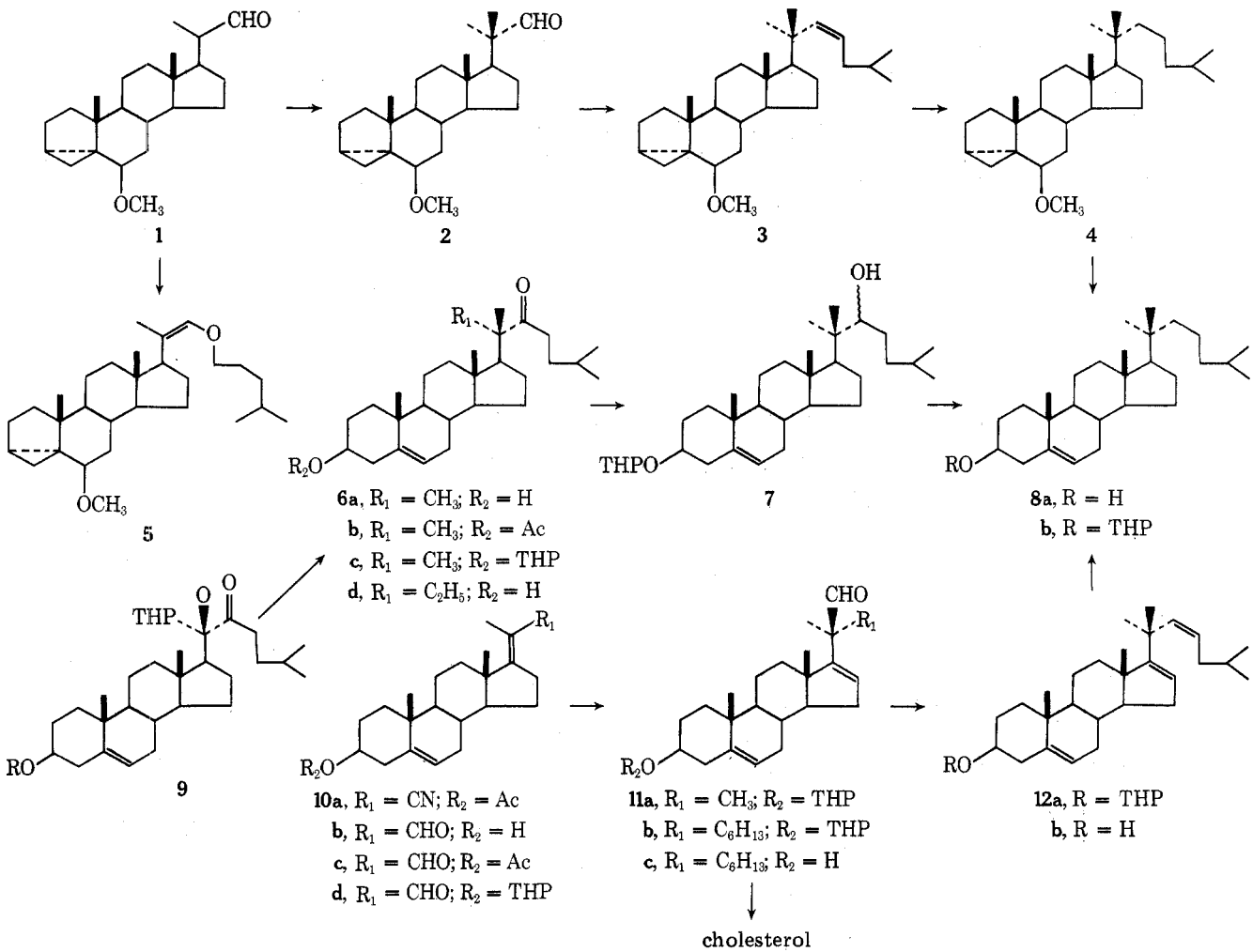
Three syntheses of 20-methylcholesterol (**8a**), resting on the alkylation of a C-20 anion with iodomethane, are described. The NMR signals of the 21- and the 28-methyl group are discussed in relation to the stereochemistry at C-20 of cholesterol and of 20-isocholesterol.

Within the framework of our studies[2] on the mechanism of the biodegradation of cholesterol to pregnenolone, we have investigated modifications[3] of the side chain of cholesterol. This paper describes syntheses of 20-methylcholesterol, a compound which cannot readily be metabolized by adrenals to pregnenolone and therefore was tested as a possible inhibitor both for the biosynthesis of cholesterol and for the biodegradation of cholesterol to pregnenolone.

The essence of the three syntheses described below consists in the generation of a carbanion at C-20, followed by its alkylation. Although there could be, a priori, a choice between the alkylation of a C-22 carbaldehyde with iodomethane, followed by the extension (of the aldehyde) to the complete cholesterol side chain, and the alkylation of a C-22 aldehyde with isohexyl bromide, followed by the conversion of the aldehyde to methyl, the second variant did not work: either the yield was poor, or the aldehyde suffered O-alkylation to give the enol ether **5**. This was revealed by its NMR spectrum, which lacked an aldehyde proton signal (δ 9–11) but indicated an olefinic methyl at δ 1.63, and also by its ir spectrum, giving a peak at 1660 cm^{-1}, commensurate with structures of similar enol ethers.[4]

The starting material for the first synthesis was the *i*-steroid aldehyde[5] **1**, which was alkylated with excess iodomethane (potassium *tert*-butoxide in *tert*-butyl alcohol) to give the α,α-dimethyl aldehyde **2** in 55% yield. The NMR spectrum of **2** shows a singlet at 9.66 ppm, in distinction to the doublet of the starting material **1**, where coupling (–CH–CHO) was observed. The stereoselectivity of this alkylation was studied by using iodomethane-d_3. The 250-MHz NMR indicates two



singlets for the C-20 methyls and the deuterated product shows relative intensities (for the two methyl peaks) of 3:2, indicating that the alkylation is only slightly stereoselective. The dimethyl aldehyde **2** was subjected to a Wittig reaction, according to Corey's procedure,[6] with isoamyltriphenylphosphonium bromide to give the olefin **3** in 60% yield. The olefin has the expected *Z* configuration as observed by Svoboda et al.[5] and others[7] in the formation of a cis olefin in similar cases. This is substantiated by the ir and NMR spectra (see Experimental Section). The dimethyl olefin **3** was catalytically reduced to give product **4**, which was solvolyzed to 20-methylcholesterol (**8a**) in 80% yield. The product is characterized by its two singlets at 0.85 and 0.92 ppm (*gem*-dimethyl) and by its mass spectrum, *m/e* 400.

The second synthesis involves the alkylation of (20*R*)-3β-hydroxy-20-tetrahydropyranyloxycholest-5-en-22-one (**9**).[8] This ketone was reduced in liquid ammonia with 2 equiv of calcium,[9] followed by the methylation of the resulting C-20 enolate with a large excess of iodomethane in tetrahydrofuran. The NMR of the alkylated product **6a** revealed an additional methyl peak (1.12 and 1.16 ppm, *gem*-dimethyl at C-20) and the mass spectrum showed the fragmentation of the 20–22 bond by the fragment *m/e* 315 ($M - C_6H_{11}O$).

The Alkylation at C-20 Is Stereospecific. The alkylation at the very hindered C-20 allows approach exclusively from the α side. The product of the iodomethane-d_3 alkylation shows in its NMR spectrum only one methyl peak at 1.11 ppm, indicative of a 28-CH_3 group and a 21-CD_3 group. The specific assignments for the C-20 *gem*-dimethyl peaks were obtained from the following considerations. (a) The doublet of the 21-methyl of (20*S*)-22-ketocholesterol is downfield (1.09 ppm), compared to the 21-methyl of its 20*R* isomer (1.00 ppm).[10] (b) The comparison of the 21-methyl peaks of a series of C-20 isomeric cholesteryl compounds[11] gave values of δ 0.91–0.95 for the 20*R* configuration and a range of δ 0.83–0.86 for the 20*S* configuration. In close analogy with these values, we assigned to the 21-methyl (below the plane) a value downfield relative to the 28-methyl (above the plane). After alkylation, the 3β-hydroxyl of **6a** was converted to its tetrahydropyranyl ether and the C-22 ketone reduced with lithium aluminum hydride. The mixture of epimeric alcohols at C-22 was mesylated and the mesylates reduced with lithium aluminum hydride to give 20-methylcholesterol tetrahydropyranyl ether (**8b**). Acid hydrolysis gave the desired 20-methylcholesterol (**8a**). The 100-MHz spectrum of 20-methylcholesterol (**8a**) reveals a downfield shift of the 18-methyl in comparison to cholesterol and to 20-isocholesterol.[12] The shift of 0.08 ppm is probably due to an interaction of the methyls 21 and 28.

The third synthesis rests on the alkylation of the aldehyde **10d.** This aldehyde was prepared by the reduction of the known (*E*)-3β-acetoxypregna-5,17(20)-diene-20-carbonitrile[13] (**10a**) with diisobutylaluminum hydride. Alkylation of the conjugated aldehyde **10d** with iodomethane gave product **11a** in a yield of 60%. The ir spectrum indicates the deconjugation of the carbonyl and the NMR spectrum shows singlets at 1.20 and 1.25 ppm, representing the *gem*-dimethyl at C-20. The stereoselectivity of this alkylation could be demonstrated since, contrary to the case of the saturated aldehyde **1** which was O-alkylated (see above) with isohexyl iodide, the conjugated aldehyde could be alkylated to 3β-hydroxycholesta-5,16-diene 20-carbaldehyde (**11c**) in 15% yield. The ir indicated a saturated aldehyde and the NMR spectrum showed a singlet for the 21-methyl at 1.22 ppm. The diene **11c** was

reduced over platinum oxide catalyst in 95% ethanol and gave 3β-hydroxycholest-5-ene 20-carbaldehyde which was not analyzed but directly decarbonylated to cholesterol with tris(triphenylphosphine)chlororhodium, a procedure[14] known to give a product with retention of configuration. The α,α-dimethyl aldehyde **11a** was subjected to a modified Wittig reaction[6] with isoamyltriphenylphosphonium bromide to give the triene **12a**, which was hydrolyzed to the 3β-hydroxy compound **12b** in an overall yield of 30%. Selective catalytic reduction of the triene **12b** with platinum oxide gave the title compound **8a**.

Assays[15] for inhibition of cholesterogenesis reveal 20-methylcholesterol to be inactive at a concentration of 1×10^{-4} M. The compound is equally inactive as inhibitor of cholesterol degradation (to pregnenolone) when tested in vivo under our standard conditions.[16]

Experimental Section

Melting points were determined on a Kofler melting point apparatus and are uncorrected. The NMR spectra were obtained in deuteriochloroform solution on a 60-MHz Varian EM360 and a 100-MHz Varian HA100D-15, with C1024 computer, using tetramethylsilane as an internal reference and the positions of the proton signals are expressed in parts per million downfield from tetramethylsilane signals. The mass analyses were obtained on an Atlas CH4, an ACI MS9, or an LKB 9000 spectrograph, using a direct insertion probe.

6β-Methoxy-20-methyl-3α,5-cyclo-5α-23,24-bisnorcholan-22-al (2) from 6β-Methoxy-3α,5-cyclo-5α-23,24-bisnorcholan-22-al (1). A solution of 1.4 g of potassium *tert*-butoxide in 30 ml of *tert*-butyl alcohol was added to a solution of 2.0 g of the aldehyde **1** in 20 ml of *tert*-butyl alcohol. After the addition of 3.5 ml (10 equiv) of methyl iodide the solution was stirred at room temperature for 18 h. Then the solution was poured on ice and the product isolated by extraction with ether. Chromatographic separation on Florisil gave, with the 2% ether in hexane eluates, 1.1 g (55%) of alkylated product **2** which could not be crystallized: ir 1705 (–CHO), 1090, 1010, and 960 cm^{-1} (6-OCH$_3$-*i*); NMR δ 0.75 (s, 3, 18-CH$_3$), 1.03 (s, 3, 19-CH$_3$), 1.12 [2s, 6, C-(CH$_3$)$_2$], 3.33 (s, 3, –OCH$_3$), 9.67 ppm (s, 1, –CHO).

Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.67; H, 10.89.

Attempted C-Alkylation of Aldehyde 1 with Isohexyl Bromide. Formation of Ether 5. A solution of 800 mg of potassium *tert*-butoxide in 20 ml of *tert*-butyl alcohol was added to a solution of 1 g of the aldehyde **1** in 20 ml of *tert*-butyl alcohol. After the addition of 4 ml (10 equiv) of 1-bromo-4-methylpentane (isohexyl bromide) the solution was stirred at 25 °C for 18 h. A small sample was removed and worked up as described for the alkylation with methyl iodide. Only starting material could be isolated. Therefore the solution was heated under reflux for 3 h and then cooled and poured on ice. The crude product was isolated by ether extraction and purified by chromatography on preparative thin layer plates. The bulk of the material was the least polar (using 5% ether in hexane), leading to the isolation of 260 mg of pure syrupy enol ether **5**: ir 1660 (vinyl ether), 1170, 1120, 1080 (ether bands), 1010 and 960 cm^{-1} (6-OMe-*i*); NMR δ 0.62 (s, 3, 18-CH$_3$), 0.88 [d, 6, 26,27-CH(CH$_3$)$_2$], 1.02 (s, 3, 19-CH$_3$), 1.63 (s, 3, 21-CH$_3$), 2.78 (m, 1, 6α-H), 3.34 (s, 3, –OCH$_3$), 3.66 (t, 2, J = 6 Hz, –OCH$_2$–), 5.83 ppm (m, 1, 22-H).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.06; H, 11.30.

(*Z*)-6β-Hydroxy-3α,5-cyclo-5α-20-methylcholest-22-ene 6-Methyl Ether (3) from 2. The suspension of 900 mg of sodium hydride in 15 ml of dimethyl sulfoxide was heated with stirring under nitrogen at 70–75 °C. After the hydrogen evolution ceased (ca. 45 min), the solution was cooled and the solution of 15.5 g of isoamyltriphenylphosphonium iodide in 50 ml of dimethyl sulfoxide was added quickly. To this red solution was added rapidly the solution of 5.4 g of 6β-methoxy-3α,5-cyclo-20-methyl-5α-23,24-bisnorcholan-22-al (**2**) in 75 ml of dimethyl sulfoxide. The combined solutions were heated with stirring under nitrogen at 55–60 °C for 3 h, then cooled and poured on ice. The crude product was isolated by extraction with ether. Chromatography on alumina gave with the hexane fractions 3.8 g (60%) of pure **3** as a syrup: ir 1010 cm^{-1} (–OMe); NMR δ 0.79 (s, 3, 18-CH$_3$), 0.91 [d, 6, J = 6 Hz, 26,27-CH(CH$_3$)$_2$], 1.02 (s, 3, 19-CH$_3$), 1.12 and 1.14 (2 s, 3, 3, 21- and 28-CH$_3$), 5.13 (d of t, 1, J_{23-22} = 12 and J_{23-24} = 6 Hz, 23-H), and 5.45 ppm (d of t, J_{22-23} = 12 and J_{22-24} = 1 Hz, 22-H).

Anal. Calcd for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.31; H, 11.72.

6β-Hydroxy-3α,5-cyclo-5α-20-methylcholestane 6-Methyl Ether (4) from 3. To the solution of 3.5 g of **3** in 200 ml of 95% ethanol was added 350 mg of 10% palladium on charcoal and the mixture was hydrogenated at room temperature and 30–35 psig for 18 h. The catalyst was removed by filtration and the ethanol evaporated. The 3.42 g (97%) of residue could not be crystallized, but appeared clean on TLC: ir 1010 and 960 cm^{-1} (6-OMe-*i*); NMR δ 0.77 (s, 3, 18-CH$_3$), 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH$_3$)$_2$], 0.86 (s, 3, 28-CH$_3$), 0.92 (s, 3, 21-CH$_3$), 1.01 ppm (s, 3, 19-CH$_3$).

Anal. Calcd for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 84.27; H, 12.23.

20-Methylcholesterol (8a) from 4. The solution of 3.4 g of the ether **4** in 90 ml of dioxane was heated to 80 °C and then 160 mg of *p*-toluenesulfonic acid and 32 ml of water were added. The solution was kept at 80 °C for 6 h, then cooled in ice, whereby the product crystallized. After one recrystallization from methanol 2.6 g (81%) of pure 20-methylcholesterol (**8a**), mp 122–124 °C, was obtained: ir 3400 cm^{-1} (–OH); NMR δ 0.75 (s, 3, 18-CH$_3$), 0.85 [d, 6, J = 6 Hz, 26,27 CH(CH$_3$)$_2$], 0.85 (s, 3, 28-CH$_3$), 0.92 (s, 3, 21-CH$_3$), 0.98 ppm (s, 3, 19-CH$_3$).

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.08. Found: C, 83.70; H, 12.06.

3β-Hydroxy-20-methylcholest-5-en-22-one (6a) from 9. Approximately 250 ml of anhydrous liquid ammonia was introduced into a 500-ml three-neck flask. While stirring vigorously 320 mg of calcium was added slowly. After the metal was dissolved, a solution of 2.0 g of (20*R*)-20-tetrahydropyranyloxy-22-ketocholesterol (**9**) in 30 ml of anhydrous tetrahydrofuran was added over a period of 0.5 h. After the blue-colored solution had turned colorless 50 ml of anhydrous tetrahydrofuran was added and the ammonia was allowed to evaporate. With most of the ammonia removed, 5 ml of methyl iodide in 10 ml of tetrahydrofuran was added and the solution was stirred at 25 °C overnight. A saturated solution of ammonium chloride was added and the mixture was extracted with ether. The ether solution was washed and dried and the solvent evaporated. The oily residue was chromatographed on a silica gel column which gave (5% ethyl acetate in benzene) 350 mg of pure alkylated product **6a**. Recrystallization from methanol furnished an analytical sample: mp 117–118 °C; ir 3330 (–OH) and 1680 cm^{-1} (>CO); NMR δ 0.73 (s, 3, 18-CH$_3$); 0.90 [d, 6, J = 6 Hz, 26,27-CH(CH$_3$)$_2$], 1.00 (s, 3, 19-CH$_3$), 1.12 (s, 3, 28-CH$_3$), 1.17 ppm (s, 3, 21-CH$_3$).

Anal. Calcd for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.10; H, 11.14.

3β-Acetoxy-20-methylcholest-5-en-22-one (6b). Acetylation of the alcohol **6a** with acetic anhydride and pyridine gave, after recrystallization from methanol, a pure analytical sample of the acetate **6b**: mp 119–120 °C; ir 1725 (–Ac), 1680 (–CO–), and 1240 cm^{-1} (Ac); NMR δ 0.72 (s, 3, 18-CH$_3$), 0.90 [d, 6, J = 6 Hz, 26,27-CH(CH$_3$)$_2$], 1.00 (s, 3, 19-CH$_3$), 1.13 (s, 3, 28-CH$_3$), 1.17 (s, 3, 21-CH$_3$), 2.04 ppm (s, 3, –OCOCH$_3$); mass spectrum *m/e* 396 (M – AcOH, 34%), 297 (M – AcOH – $C_6H_{11}O$, 100%).

Anal. Calcd for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 79.00; H, 10.46.

3β-Tetrahydropyranyloxy-20-methylcholest-5-en-22-one (6c). To the solution of 300 mg of the alcohol **6a** in 2 ml of 2,3-dihydropyran was added 1 drop of phosphorus oxychloride (25 °C, 18 h). The solution was poured into a chilled saturated sodium bicarbonate solution and extracted with methylene chloride. The extract was washed with water and dried over sodium sulfate and the solvent evaporated. After purification on TLC there was obtained 290 mg of solid **6c**, mp 104–105 °C, after recrystallization from methanol: NMR δ 0.71 (s, 3, 18-CH$_3$), 0.89 [d, 6, J = 6 Hz, 26,27-CH(CH$_3$)$_2$], 0.98 (s, 3, 19-CH$_3$), 1.12 (s, 3, 28-CH$_3$), 1.16 ppm (s, 3, 21-CH$_3$); mass spectrum *m/e* 396 (M – THPOH, 56%), 297 (M – THPOH – $C_6H_{11}O$, 57%), and 85 (100%).

Anal. Calcd for $C_{33}H_{54}O_3$: C, 79.46; H, 10.92. Found: C, 79.51; H, 10.76.

22-Hydroxy-20-methylcholesterol 3β-Tetrahydropyranyl Ether (22-Isomeric Mixture) (7). To the solution of 200 mg of the ketone **6c**, 100 mg of lithium aluminum hydride was added and the mixture heated under reflux for 18 h. The excess reagent was decomposed with 2 N sodium hydroxide. Solid sodium sulfate was added, and the precipitate was filtered off and washed with hot ethyl acetate. Evaporation of the filtrate gave, after purification on TLC, 120 mg of pure **7**, mp 139–140 °C after recrystallization from hexane: ir 3550 cm^{-1} (OH); NMR δ 0.78 (s, 3, 18-CH$_3$), 0.87 (s, 3, 28-CH$_3$), 0.89 [d, 6, J = 6 Hz, 26,27-CH-(CH$_3$)$_2$], 0.97 (s, 3, 21-CH$_3$), and 1.00 ppm (s, 3, 19-CH$_3$); mass spectrum *m/e* 398 (M – THPOH, 16%), 297 (M – THPOH – $C_6H_{13}O$, 12%), and 85 (100%).

Anal. Calcd for $C_{33}H_{56}O_3$: C, 79.14; H, 11.27. Found: C, 78.82; H, 11.17.

20-Methylcholesterol 3β-Tetrahydropyranyl Ether (8b). To a solution of 100 mg of the alcohol **7** in 1 ml of pyridine 2 drops of mesyl chloride was added and the solution left at 23 °C for 18 h. After the addition of water the product was extracted with methylene chloride, the organic phase washed, then dried, and the solvent evaporated. The crude residue (105 mg) was dried in a desiccator over phosphorus pentoxide and then added to a solution of 50 mg of lithium aluminum hydride in 5 ml of tetrahydrofuran and this solution heated under reflux overnight. The usual workup (see **7** above) gave, after recrystallization from methanol, 43 mg of pure **8b:** mp 100–101 °C; ir 1025 and 960 cm^{-1} (ether); NMR δ 0.75 (s, 3, 18-CH_3), 0.85 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 0.85 (s, 3, 28-CH_3), 0.92 (s, 3, 21-CH_3), 0.99 ppm (s, 3, 19-CH_3).

Anal. Calcd for $C_{33}H_{56}O_2$: C, 81.75; H, 11.64. Found: C, 81.52; H, 11.57.

20-Methylcholesterol (8a). The solution of 50 mg of the ether **7** in 2 ml of ethanol containing 2.5 mg of *p*-toluenesulfonic acid monohydrate was refluxed for 1 h. After cooling the solution was diluted with water and the product extracted with methylene chloride. After evaporation of the solvent the residue was recrystallized twice from methanol to give 35 mg of pure **8a:** mp 121–123 °C; ir 3400 cm^{-1} (–OH); NMR in all respects identical with that of the material obtained previously.

(20*S*)-3β-Hydroxy-20-ethylcholest-5-en-22-one (6d). The alkylation of 20α-tetrahydropyranyloxy-22-ketocholesterol (**9**) with ethyl bromide was carried out as described for the 20-methyl analogue above. Thus, 1.0 g of tetrahydropyranyloxy ketone gave 181 mg of alkylated material **6d,** mp 114–115 °C, after two recrystallizations from methanol: ir 3300 (–OH), 1680 cm^{-1} (CO); NMR δ 0.71 (s, 3, 18-CH_3), 0.80 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 0.98 (s, 3, 19-CH_3), and 1.12 ppm (s, 3, 28-CH_3); mass spectrum *m/e* 329 (M – $C_6H_{11}O$, 67%), 311 (M – $C_6H_{11}O$ – H_2O, 100%), and 271 (15%).

Anal. Calcd for $C_{29}H_{48}O_2$: C, 79.10; H, 10.71. Found: C, 78.77; H, 10.73.

(*E*)-3β-Hydroxypregna-5,17(20)-diene 20-Carbaldehyde (10b) and Its Acetate from 10a. The solution of 10 g of the nitrile **10a** in 200 ml of dry toluene was cooled to –70 °C under a nitrogen atmosphere, while stirring. Then 65.0 ml of a 20% solution of diisobutylaluminum hydride in hexane was added. The solution was kept at –70 °C for an additional 30 min and then kept at room temperature overnight. The solution was then poured into an ice-cold saturated solution of ammonium chloride, 2 N sulfuric acid was added until pH 3, and finally the product was extracted with methylene chloride. The organic phase was washed with water and with a saturated sodium bicarbonate solution and dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was chromatographed on a column of Florisil. The eluates with 10% ether in benzene furnished, after recrystallization from methanol, 8.1 g of **10b:** mp 137–138 °C; ir 3350 (–OH), 1645 and 1610 cm^{-1} (conjugated aldehyde); NMR δ 0.98 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.82 (s, 3, 21-CH_3), 2.90 (16-H), 5.42 (d, 1, 6-H), and 9.98 ppm (s, 1, –CHO).

Anal. Calcd for $C_{22}H_{32}O_2$·CH_3OH: C, 76.62; H, 10.07. Found: C, 76.57; H, 10.49.

Upon acetylation of the alcohol **10b** with acetic anhydride and pyridine, the acetate **10c** was obtained, mp 150–153 °C, after two recrystallizations from ether.

Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.95; H, 9.49.

(*E*)-3β-Tetrahydropyranyloxypregna-5,17(20)-diene 20-Carbaldehyde (10d) from 10b. To a solution of 8.1 g of the alcohol **10b** in 200 ml of tetrahydrofuran 8 ml of dihydropyran and 400 mg of *p*-toluenesulfonic acid were added. After standing for 4 h at room temperature, the solution was poured into a saturated solution of sodium bicarbonate and the mixture extracted with ether. The organic phase was washed with saline and water and dried, and the solvent was evaporated. The crude product was chromatographed on an alumina column, whereby the 10% ether in benzene eluates gave 8.9 g of ether **10d:** mp 143–146 °C; ir 1660 and 1610 (conjugated aldehyde), 1030 and 960 cm^{-1} (ether); NMR δ 0.98 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.82 (s, 3, 21-CH_3), 9.98 ppm (s, 1, –CHO).

Anal. Calcd for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.40; H, 9.69.

3β-Tetrahydropyranyloxy-20-methylpregna-5,16-diene 20-Carbaldehyde (11a) from 10d. To the solution of the anion of dimethyl sulfoxide, prepared as described for the preparation of **3** from **2,** the solution of 16.0 g of the conjugated aldehyde **10d** in 100 ml of tetrahydrofuran was added while stirring. After 1 h 4.0 g of iodomethane was added and stirring continued for 18 h. The solution was then poured into ice-cold water and the product was isolated by ether extraction. The ether extract was washed with a saline solution, then dried, and the ether evaporated off to give 12.7 g of crude residue. Upon chromatography on silica the benzene fractions furnished 10.1 g of α,α-dimethyl aldehyde **11a:** mp 146–148 °C; ir 1730 (aldehyde), 1025 and 955 cm^{-1} (THP ether); NMR δ 0.82 (s, 3, 18-CH_3), 1.03 (s, 3, 19-CH_3), 1.20 and 1.25 [2 s, 3, 3, –C(CH_3)$_2$], 9.33 ppm (s, 1, –CHO).

Anal. Calcd for $C_{28}H_{42}O_3$: C, 78.82; H, 9.92. Found: C, 78.70; H, 10.21.

(*Z*)-3β-Hydroxy-20-methylcholesta-5,16,22-triene (12b) from 11a. To the solution of the anion of dimethyl sulfoxide, prepared as described above, a solution of 5.40 g of isoamyltriphenylphosphonium iodide in 50 ml of dimethyl sulfoxide was added at once. To this deep red solution was added rapidly a solution of 1.0 g of the aldehyde **11a** in 70 ml of dimethyl sulfoxide. The combined solutions were heated, while stirring under nitrogen, to 60 °C for 5 h, then cooled and poured on ice. The crude product was isolated by extraction with ether. Chromatography on an alumina column gave with the benzene eluates 502 mg of olefin **12a** as a yellow syrup which could not be crystallized: ir 960 and 1040 cm^{-1} (ether); NMR δ 0.83 (s, 3, 18-CH)$_3$), 0.93 [d, 6, J = 6 Hz, 26,27-CH(CH_3)$_2$], 1.03 (s, 3, 19-CH_3), 1.23 [s, 3, 3, 21,28-C(CH_3)$_2$].

Without further purification, 400 mg of the ether **12a** was dissolved in 25 ml of methylene chloride and 25 ml of methanol. After the addition of 10 drops of concentrated hydrochloride acid the solution was left at room temperature overnight. The solvents were evaporated in vacuo and the residue chromatographed on silica TLC with benzene/10% ether. The product which was isolated by extraction from silica was recrystallized from acetone to give 286 mg of **12b:** mp 104–106 °C; ir 3350 cm^{-1} (OH); NMR δ 0.83 (s, 3, 18-CH_3), 0.95 [d, 6, 26,27-CH(CH_3)$_2$], 1.27 [2 s, 6, 21,28-C(CH_3)$_2$].

Anal. Calcd for $C_{28}H_{44}O$: C, 84.78; H, 11.18. Found: C, 84.64; H, 11.77.

20-Methylcholesterol (8a) from 12b. To a solution of 120 mg of the triene **12b** in 70 ml of 95% ethanol was added 12 mg of platinum oxide catalyst. The mixture was hydrogenated at 1 atm of hydrogen. After 110% of the calculated hydrogen was taken up the reaction was stopped, the ethanol evaporated in vacuo, the organic residue dissolved in methylene chloride, and the catalyst filtered off through Celite. The filtrate was evaporated to dryness and the residue crystallized from acetone to give 96 mg of **8a,** mp 120–123 °C, identical upon admixture with authentic standard. This material also had ir and NMR spectra indistinguishable from those obtained with material obtained previously by other syntheses.

3β-Hydroxycholesta-5,16-diene 20-Carbaldehyde (11c) from 10d. To a solution of the anion of dimethyl sulfoxide, prepared as described earlier, a solution of 2.0 g of the aldehyde **10d** in 20 ml of dimethyl sulfoxide was added. After 1 h 4.0 g of 1-bromo-4-methylpentane was added and the stirring continued overnight. The solution was now poured on ice and 2.1 g of crude product was isolated by ether extraction. Purification an preparative TLC gave 411 mg of relatively pure ether **11b** which could not be crystallized. Without further purification, the whole amount was hydrolyzed in a solution of 100 ml of tetrahydrofuran to which 5 drops of concentrated hydrochloric acid had been added and the solution let stand for 18 h. Dilution with water followed by extraction with methylene chloride gave 382 mg of a crude alcohol which was repeatedly recrystallized from methanol to give 315 mg of **11c:** mp 114–116 °C; ir 1680 (aldehyde), 960 and 1030 cm^{-1} (ether); NMR δ 0.82 (s, 3, 18-CH_3), 0.90 [d, 6, 26,27-CH(CH_3)$_2$], 1.03 (s, 3, 19-CH_3), 1.22 (s, 3, 21-CH_3), 9.32 ppm (s, 1, –CHO).

Anal. Calcd for $C_{28}H_{44}O_2$: C, 81.50; H, 10.75. Found: C, 81.53; H, 11.03.

Cholesterol from 3β-Hydroxycholesta-5,16-diene 20-Carbaldehyde (11c). A solution of 450 mg of the diene **11c** in 100 ml of 95% ethanol was reduced, at 1 atm, with hydrogen and 40 mg of prereduced platinum oxide. The reaction was stopped after 1.1 equiv of hydrogen was absorbed and the mixture was evaporated to dryness. The product was dissolved in methylene chloride and the catalyst was removed by filtration through Celite. The filtrate was evaporated to dryness and the residue filtered through a small column of alumina. The eluates gave 410 mg of 3β-hydroxycholest-5-ene 29-carbaldehyde which appeared as a single spot on TLC and was different from its starting material. The solution of 410 mg of this aldehyde and 1.0 g of tris(triphenylphosphine)chlororhodium in 50 ml of xylene was refluxed for 18 h, then cooled and 100 ml of ethanol added. The precipitated bis(triphenylphosphine)carbonylchlororhodium (670 mg, >80%) was removed by filtration, the filtrate evaporated to dryness in vacuo, and the residue chromatographed on an alumina column to give with the 5% ether in benzene eluates 211 mg of cholesterol, mp 149–150 °C, unchanged by admixture to an authentic sample. The ir and NMR spectra were idencal with those of an authentic standard.

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Synthesis and Cyclization of 21-Hydroxyethylthioprogesterone Derivatives

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Treatment of 21-*p*-toluenesulfonyloxyprogesterone with 2-mercaptoethanol gives 21-hydroxyethylthioprogesterone. Under reaction conditions which usually produce chlorination of primary alcohols 21-hydroxyethylthioprogesterone cyclizes to 17β-(5′,6′-dihydro-1′,4′-oxathiin-2′-yl)-4-androsten-3-one. Following acetylation of the 21-hydroxyethylthio group of the title compound, acid-catalyzed ketalization of the resulting acetate gives a resolvable mixture of 3-ethylene ketals of 21-acetoxyethylthio-5-pregnene-3,20-dione and 17β-(5′,6′-dihydro-1′,4′-oxathiin-2′-yl)-5-androsten-3-one. The anticipated 3,20-diethylene ketal of 21-acetoxyethylthio-5-pregnene-3,20-dione could not be detected in the reaction mixture using a variety of reaction conditions. The C-21 sulfur atom is believed to influence the courses of the deacetylation and cyclization reactions. Mechanisms are proposed to account for these results. Nuclear magnetic resonance, infrared, and ultraviolet spectral properties of the new steroid dihydroxathiins are discussed.

Steroid alkylating agents were previously synthesized in this laboratory to serve as active site directed irreversible inhibitors for studies of the steroid binding site of 20β-hydroxy steroid dehydrogenase (E.C.1.1.1.53).[1-3] One of a series of isomeric bromoacetoxyprogesterone derivatives, 4-pregnen-16α-ol-3,20-dione 16-bromoacetate, terminates pregnancy in rats.[4] Similarly, the steroid alkylating agent 4-estren-17β-ol-3-one 17-bromoacetate is an interceptive agent in rats and primates.[5] The benzylic halide 1,3,5(10)-estratriene-2,4-dibromomethyl-3-ol-17-one 3-*O*-methyl ether was found to be a persistent anti-estrogen.[6] Predictably, all of the bromoacetoxyprogesterone derivatives which were synthesized are susceptible to hydrolysis in aqueous media possessing pH values above 7.0. Indeed, following inactivation of 20β-hydroxy steroid dehydrogenase with 4-pregnen-6β-ol-3,20-dione bromoacetate, or 4-pregnen-11α-ol-3,20-dione bromoacetate, at pH 7.0, the enzyme is readily reactivated by adjusting the pH to 8.0 or 9.0.[7] Similar alkaline conditions produce hydrolytic cleavage of the ester bond in conjugates between steroid bromoacetates and nucleophilic amino acids.[2]

Steroid alkylating agents possessing greater stability toward hydrolysis over a broad pH range compared to the bromoacetates are desirable for our biological experiments. Therefore, we attempted to synthesize 21-(2′-chloroethylthio)progesterone, which was expected to have the desired chemical properties. The present report describes the synthesis of 21-(2′-hydroxyethylthio)progesterone and the results obtained when this steroid and its derivatives were treated under conditions conventionally employed for chlorination of primary alcohols.

11-Deoxycorticosterone (**1**, Scheme I) was converted to the corresponding 21-toluenesulfonate (**2**) by Borrevang's procedure.[8] Upon treatment of **2** with alkaline 2-mercaptoethanol 21-(2′-hydroxyethylthio)-4-pregnene-3,20-dione (**3**) was obtained. Reaction of **3** with thionyl chloride in chloroform,[9] or hexamethylphosphorus triamide and carbon tetrachloride in chloroform,[10] did not provide the expected 21-(2′-chloroethylthio)-4-pregnene-3,20-dione (**3b**) but instead gave a new compound **4**. This steroid does not exhibit a 1700-cm^{-1} ir absorption (characteristic of a C-20 carbonyl), but has a strong 1630-cm^{-1} absorption. Compound **4** possesses an unusually strong ultraviolet absorption [λ_{max} (CH_3OH) 238 nm (ϵ 24 000)], more thoroughly discussed below. Elemental analysis, NMR, ir, and uv spectral data of **4** support the structural