methanol (75 ml) at 0–5 °C. After 18 h at room temperature, the solution was heated on the steam bath until ether boiled mildly and then the solvent was removed on the rotary evaporator. The residue (6.8 g) was dissolved in ether/$CHCl_3$ (1:1, 300 ml) and extracted with 2% K_2CO_3 (300 ml). The organic layer was dried over anhydrous K_2CO_3 and evaporated to give 4.2 g of **12**. This material was dissolved in methanol (10 ml) and excess methanolic HCl added. Evaporation and recrystallization of the residue from methanol/benzene gave **12** HCl as the hydrate: 2.0 g; mp 142–144 °C; NMR δ 1.14 (d, 3, J = 6.6 Hz), 3.66 (s, 3), 3.78 (s, 6), 6.8 (s, 2).

Anal. Calcd for $C_{20}H_{32}ClNO_6$: C, 57.44; H, 7.72; N, 3.35; Cl, 8.48; H_2O, 4.34. Found: C, 57.05, H, 7.82; N, 3.31; Cl, 8.26; H_2O, 4.56.

12-Carbomethoxy-2,3,11-trimethoxy-9-methyl-5,8,8a,11,-12,12a,13,13a-octahydro-6*H*,9*H*-benzo[*a*]pyrano[3,4-*g*]quinolizine (14). A solution of triphenylmethylsodium in ether[11] was prepared from triphenylmethyl chloride (42 g) in anhydrous ether (1000 ml). This was added under nitrogen pressure to a solution of **12** (6.1 g) in dry dioxane[12] (150 ml) at 15 °C until the deep red color of triphenylmethylsodium persisted. Methyl formate (4.8 g) was added and the solution stirred for 16 h while the ice water cooling bath warmed to room temperature. The entire mixture was poured into 2.4 M HCl (320 ml). The aqueous layer was extracted with ether (2 × 300 ml) and evaporated to dryness under reduced pressure and the resulting solid azeotroped twice with methanol. The residue (11.1 g) containing crude product and inorganic material was dissolved in 3.4% methanolic HCl (38 g) and refluxed for 3.5 h. The reaction mixture was evaporated to dryness and the residue distributed between ether (200 ml) and 5% K_2CO_3 (100 ml). The aqueous layer was separated and extracted with ether (2 × 100 ml). The combined ether solutions were dried over anhydrous K_2CO_3 and evaporated to give 3.9 g of **14**.

12-Carbomethoxy-2,3-dimethoxy-9-methyl-5,8,8a,12a,13,-13a-hexahydro-6*H*,9*H*-benzo[*a*]pyrano[3,4-*g*]quinolizine Hydrochloride (2 HCl). A solution of 14 (3.9 g) and *p*-toluenesulfonic acid (2.3 g) in $CHCl_3$ (350 ml) was azeotroped for 120 h using a Dean-Stark apparatus containing concentrated H_2SO_4 (20 ml) in the trap. The reaction mixture was poured into 5% K_2CO_3 (100 ml). The $CHCl_3$ layer was separated and the aqueous layer extracted with $CHCl_3$ (2 × 100 ml). The combined $CHCl_3$ solutions were dried over anhydrous K_2CO_3 and the solvent removed on the rotary evaporator. The crude oil was triturated with benzene to give four crops of crystalline material. Infrared spectroscopy indicated that three crops (1.8 g) consisted essentially of the desired compound. Intense bands at 1680 and 1600 cm^{-1} indicated the carbonyl and the conjugated double bond, respectively, of the desired compound; a small band at 1725 cm^{-1} indicated the presence of an impurity. The remaining crop of material (164 mg) showed strong absorption at 1725 cm^{-1} and was not combined with the above material for purification as the hydrochloride. The 1.8-g sample described above and 4.2 g of material obtained from 16 g of **14** in five separate reactions were combined and dissolved in ether (900 ml). The solution was dried (Na_2SO_4) and the hydrochloride salt was precipitated with anhydrous hydrogen chloride. The entire mixture was evaporated under reduced pressure and the remaining semisolid recrystallized from methanol/ether to give 3.7 g of **2** HCl as the two-thirds hydrate, mp 181–186 °C.

Anal. Calcd for $C_{21}H_{28}ClNO_5 \cdot \frac{2}{3}H_2O$: C, 59.81; H, 7.07; N, 3.31; Cl, 8.31; H_2O, 2.82. Found: C, 60.10; H, 7.06; N, 3.41; Cl, 8.47; H_2O, 2.55.

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Registry No.—**2**, 60184-19-2; **2** HCl, 60209-13-4; **3**, 60209-14-5; **5** HCl epimer A, 60184-20-5; **5** HCl epimer B, 60209-15-6; **6**, 60184-21-6; **6** β-methyl epimer, 60209-16-7; **12**, 60184-22-7; **12** HCl, 60209-17-8; **14**, 60184-23-8.

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Stereospecific Synthesis of the Four 20,22-Epoxycholesterols and of (*Z*)-20(22)-Dehydrocholesterol[1]

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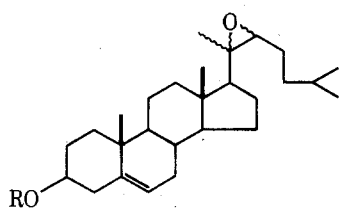
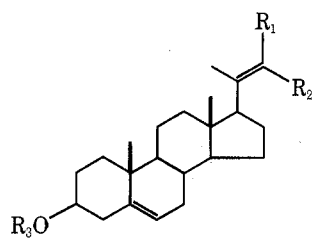
(20*R*,22*S*)-, (20*R*,22*R*)-, and (20*S*,22*R*)-epoxycholesterol have been synthesized stereospecifically from (20*R*,22*R*)-, (20*R*,22*S*)-, and (20*S*,22*S*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**4a**, **5a**, and **21**), respectively, via their 22-mesylates. (*Z*)-20(22)-Dehydrocholesterol has been prepared by pyrolysis of the 1,3-dioxolane derivative of (20*R*,22*S*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**5a**). The stereoselective oxidations of (*E*)-3β-acetoxy-5,20(22)-cholestadiene with *m*-chloroperbenzoic acid gave (20*S*,22*S*)-20,22-epoxycholesterol (after hydrogenolysis of the 3β-acetate) and with osmium tetroxide yielded **21**. A total stereoselectivity has been obtained in the synthesis of the glycol (20*R*,22*R*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**4a**) from the aldehyde (20*R*)-3β-acetoxy-20-tetrahydropyranyloxypregn-5-ene-20-carbaldehyde (**10b**) by an isoamylmagnesium bromide Grignard reaction.

In continuation of our work[3–5] on the mechanism of the biochemical conversion of cholesterol to pregnenolone and in view of suggestions[6–8] that 20,22-epoxycholesterol (**1a–d**)[9] and 20(22)-dehydrocholesterol (**2a,b**)[9] are obligatory intermediates in the biochemical transformation of cholesterol to pregnenolone, mediated by mitochondrial preparations of the rat adrenal cortex, it appeared important to prepare such sterols by stereospecific syntheses. There is no mention of the configuration of either the 20,22 double bond or of the 20,22-epoxide by these authors.[6–8] However, since

(20*R*,22*R*)-20,22-dihydroxycholesterol (**4b**) is a proven intermediate[3,4] immediately before the appearance of pregnenolone, it is tempting to speculate that if (a) 20(22)-dehydrocholesterol and 20,22-epoxycholesterol are "essential intermediates", as claimed by Kraaipoel et al.,[6-8] and if (b) these biochemical reactions proceed similarly to the chemical interconversions we present, then this would suggest the sequence (*Z*)-20,22-dehydrocholesterol → (20*R*,22*S*)-20,22-epoxycholesterol → (20*R*,22*R*)-20,22-dihydroxycholesterol. We have tested these two putative intermediates, the *E* olefin **2b**, and the three other 20,22-epoxides **1b**, **1c**, and **1d** and



1a, 20*R*, 22*S*; R = H
b, 20*R*, 22*R*; R = H
c, 20*S*, 22*S*; R = H
d, 20*S*, 20*R*; R = H
e, 20*R*, 22*R*; R = Ac
f, 20*S*, 22*S*; R = Ac



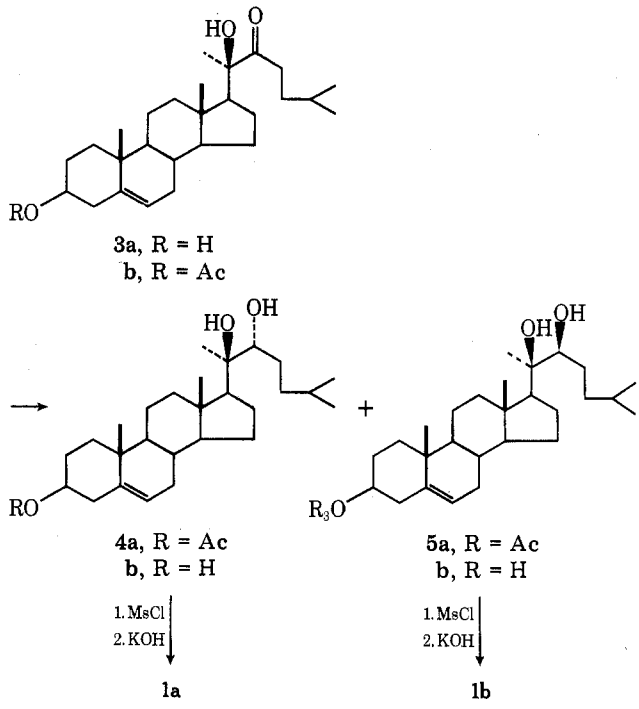
2a, R_1 = H; R_2 = C_5H_{11}; R_3 = H
b, R_1 = C_5H_{11}; R_2 = H; R_3 = H
c, R_1 = H; R_2 = C_5H_{11}; R_3 = Ac
d, R_1 = C_5H_{11}; R_2 = H; R_3 = Ac

found them not to be involved as intermediates in the metabolism of cholesterol to pregnenolone. A preliminary report concerning this has already appeared.[10] Since the epoxides and olefins can be synthesized stereoselectively via the corresponding 1,2-glycols,[11,12] we concentrated our efforts on the syntheses of these diols.

On the basis of our previous work,[13] we devised a synthetic route for **4a** and **5a** as shown in Scheme I.

Reduction of the acetate **3b**[13] with sodium borohydride gave the isomeric alcohols **4a** and **5a** in a ratio of 1:6 (85% yield), which could readily be separated by HPLC. Lithium aluminum hydride reduction of **4a** and of **5a** gave the known triols[13] **4b** and **5b**. Since this scheme was not suited for the preparation of large amounts of the more desirable 22*R* isomer **4b**, an alternate method, which had already been applied to the synthesis of crustecdysone,[14] was applied to the synthesis of **4b**. As outlined in Scheme II, treatment of pregnenolone acetate (**6**), first with acetone cyanohydrin and then with dihydropyran, gave a crude product which was separated[15] by fractional crystallization into the pure 20*R* isomer **7b**[13] and the 20*S* isomer **8b**. The isomer **7b** underwent a normal Grignard reaction to give **3a**. In the case of the isomer **8b**, however, the Grignard reaction led exclusively to a reductive cleavage of the C-20 hydroxy function to give (20*R*)-3β-acetoxycholest-5-en-22-one (**11b**). The cyanohydrin **7b** was reduced with diisobutylaluminum hydride to yield the imine which was then hydrolyzed to the aldehyde **10a**. Acetylation of **10a** with pyridine–acetic anhydride gave the acetate **10b** in 45% overall yield. The product showed ir absorption at 2680 and 1695 (–CHO), 1720 and 1245 (–$COOCH_3$), 1025 and 960

Scheme I



3a, R = H
b, R = Ac

4a, R = Ac
b, R = H

5a, R = Ac
b, R = H

1. MsCl
2. KOH

1a **1b**

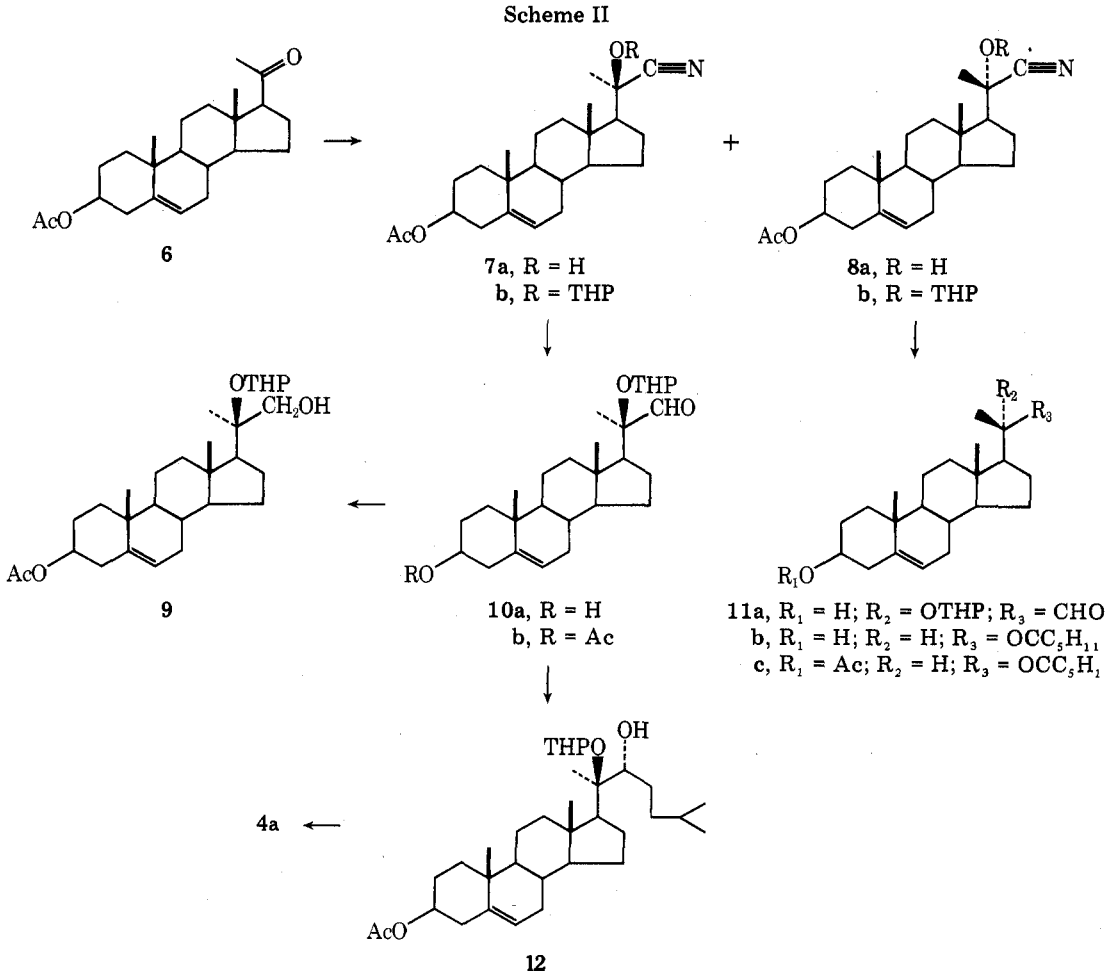
cm^{-1} (THP ether). The NMR spectrum gave signals at 9.75 (s, 1 H, –CHO), 4.67 (m, 1 H, –OCHO–), 1.02 (C-19 methyl), 0.78 ppm (C-18 methyl). Treatment of the aldehyde **10b** with isoamylmagnesium bromide at −70 °C gave three products (see Experimental Section) from which the desired product **12** could be isolated. The ir spectrum of **12** showed absorption at 3350 (–OH), 1720 and 1245 (–$COOCH_3$), 1025 and 960 cm^{-1} (THP ether) and the NMR spectrum (100 MHz) revealed the completed side chain 0.85 and 0.91 (26/27-CH_3), 2.02 (–$OCOCH_3$), and 4.75 ppm (–OCHO–). The mass spectrum showed peaks at *m/e* 444 ($M^+ - 102$), 429 ($M^+ - 117$), 426 ($M^+ - 120$), 384 ($M^+ - 162$), 85 (base peak). Removal of the tetrahydropyranyl protective group of **12** with dilute hydrochloric acid gave the acetate glycol **4a**. For routine syntheses crude **12** was converted, without purification of intermediates, to **4a**, which was readily obtained pure by preparative TLC. However, the reaction of the 20*S* aldehyde with isoamylmagnesium bromide, under the same conditions as used for **12**, yielded a galaxy of unidentified products which were not further investigated.

The epoxides **1a** and **1b** were synthesized by conventional procedures. Treatment of (20*R*,22*R*)-20,22-dihydroxycholesterol 3β-acetate (**4a**) and (20*R*,22*S*)-20,22-dihydroxycholesterol 3β-acetate (**5a**) with freshly distilled methanesulfonyl chloride in pyridine gave the 22-mesylates which were directly converted by aqueous potassium hydroxide treatment to the corresponding epoxides **1a** and **1b**, in yields of 66 and 80%, respectively. The mass spectra of these epoxides showed major peaks at *m/e* 400 (M^+, base peak), 385 ($M^+ - 15$), 382 ($M^+ - 18$). The products had a strong ir absorption at 3350 cm^{-1} (–OH) and the NMR spectra gave a characteristic signal for **1a** at 2.7 (22-H) and at 2.65 ppm (22-H) for **1b**.

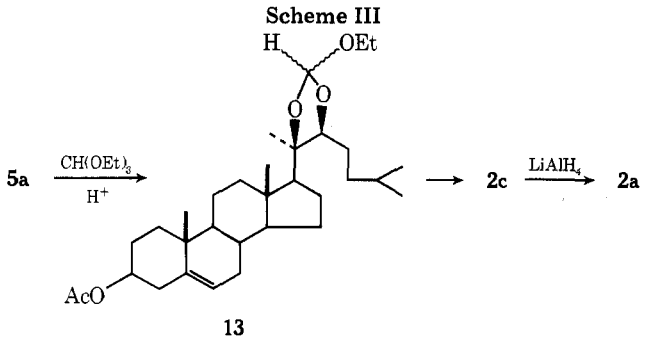
In addition to the already known (*E*)-20(22)-dehydrocholesterol[16-18] we sought the corresponding *Z* isomer **2a**. This was prepared according to Scheme III.

Following the procedure of Eastwood et al.,[19,20] the glycol **5a** was reacted with triethyl orthoformate to give the 1,3-dioxolane **13**, which, without further purification, was pyrolyzed at reduced pressure under acidic conditions. The resulting acetate **2c** was hydrogenolyzed with lithium aluminum hydride to give **2a** in an overall yield of 45%. Table I shows the

Scheme II



Scheme III



striking differences in melting point and the proton resonances of the NMR spectra of **2c** and of **2d,** a difference also borne out by their ^{13}C NMR spectra.[21] In addition an alternate synthesis (Scheme IV) was carried out in order to provide labeled substrates for biological experiments.[10]

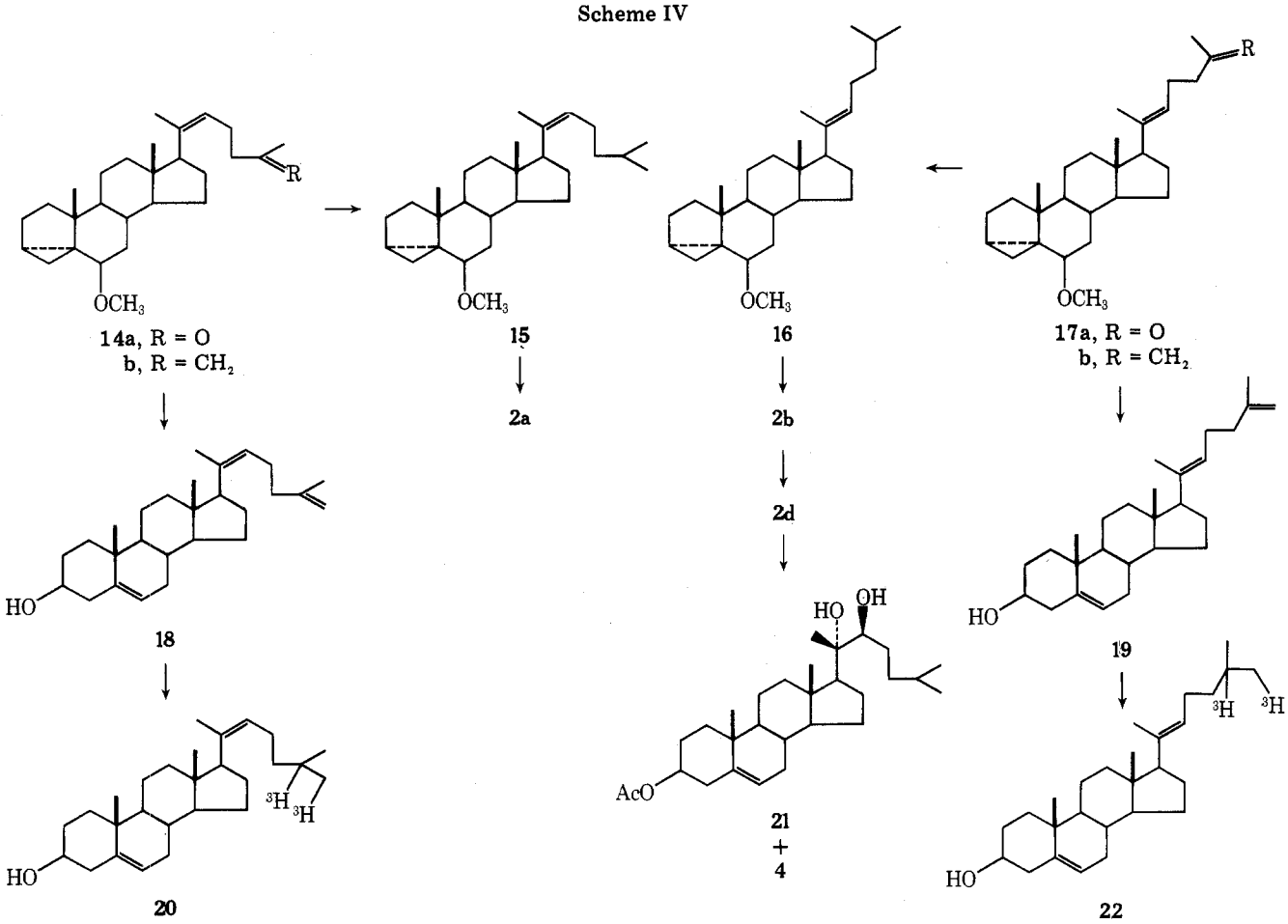
The known (*Z*)- and (*E*)-20(22)-dehydro ketones[22] **14a** and **17a** were treated with methylenetriphenylphosphorane to give their respective 20(22),25-dienes, **14b** and **17b.** Selective hydrogenation of the terminal double bond over tris(triphenylphosphine)rhodium chloride gave the desired *E* isomer **16** and the *Z* isomer **15,** which were hydrolyzed to **2b** and **2a** under the condition of McKennis.[23] This reduction was also carried out with tritium (experimental details will be given in a subsequent communication) to give the 25,26-tritiated products **20** and **22,** respectively.

Olefins **2a** and **2b** were each selectively oxidized with *m*-chloroperbenzoic acid. The oxidation of the *E* olefin gave two epoxides **1b** and **1c** in the ratio of 2:3. Only after acetylation could the mixture be separated on preparative TLC. Their respective configurations were established by comparison with the epoxide **1b** of known configuration, since it was derived from the known glycol **5a.**[24] The NMR spectra of these two epoxides (from **2b**) show different signals for the 18-CH_3 and for the 22-H (see Table I). As opposed to the epoxidation of the *E* isomer **2b,** the *Z* isomer **2a** gave only one epoxide upon treatment with *m*-chloroperbenzoic acid. This product had the 20*R*,22*S* configuration and was identical in all respects with an authentic sample of **1a,** obtained from **4a** (Scheme I). The stereospecific attack of the 20(22) double bond of this reaction can readily be explained by steric hindrance.[11,25] Selective oxidation of **2d** with osmium tetroxide followed by hydrolysis of the formed osmates with aqueous sodium bisulfite in pyridine gave (20*R*,22*R*)- and (20*S*,22*S*)-3β,20,22-trihydroxycholest-5-ene 3β-acetate (**4a** and **21**) (76% yield) in a ratio of 1:13. Their configurations were established by comparison with an authentic sample of **4a** in Scheme I and the proton chemical shifts of 21-CH_3 define the C-20 configuration.[26] These two glycols were separated by HPLC and the

Table I

	δ, ppm			
	18-Me	21-Me	22-H	Mp, °C
1b	0.80		2.65	135–137
1c	0.68		2.82	123–125
2c	0.69	1.72	5.29	82–83
2d	0.54	1.61	5.15	123–125

Scheme IV



20*S*,22*S* glycol **21** was converted, as indicated in Scheme I, to the epoxide **Id.**

Experimental Section

General. Low-resolution mass spectra were measured with either a LKB 9000 mass spectrometer or Finnigan 1015 mass spectrometer. NMR spectra, reported in parts per million, were obtained in $CDCl_3$ solution using tetramethylsilane as internal reference. The 60-MHz NMR spectra were taken on a Varian Associates DA-60 spectrometer, and the 100-MHz NMR spectra were run on a Varian Associates HA-100 spectrometer. The microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y., and Instranal Laboratory, Inc., Rensselaer, N.Y. All melting points reported are uncorrected.

All preparative thin layer chromatography (TLC) plates were 20 × 20 cm, and 1000-mm thick silica gel.

Anhydrous tetrahydrofuran was prepared by distillation from lithium aluminum hydride. Anhydrous dimethyl sulfoxide was obtained by vacuum distillation from calcium hydride into 4A molecular sieves. Anhydrous methylene chloride was provided by washing with concentrated sulfuric acid, then with aqueous potassium carbonate and water, followed by drying over calcium chloride, and distillation from P_2O_5.

$NaBH_4$ Reduction of Acetate Ketol 3b to Alcohols 4a and 5a. To the stirred solution of 1.6 g of **3b**[13] in 35 ml of tetrahydrofuran and 20 ml of methanol in an ice bath, 314 mg of sodium borohydride was added slowly. The mixture was then stirred for 30 min in the ice bath and at 25 °C for 2 h. After dilute hydrochloric acid solution had been added to consume the excess hydride, the reaction mixture was poured into ice water. The resulting precipitate was filtered, washed with water, and dried to give 1.55 g of a mixture of alcohols, which were separated by HPLC. This separation was carried out in methylene chloride–methanol (1:4) on 2 × 8 ft Bondapak C18/Porasil B column. The 22*R* and 22*S* isomers, **4a** and **5a**, were completely resolved in two recycles in a ratio of 1:6. The former had the longer retention time, and the smaller R_f.

4a had mp 192–194 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 3.40 (m, 1 H, C-22 proton), 2.03 (s, 3 H, CH_3COO–), 1.23 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.88 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.48; H, 10.47.

5a had mp 182–184 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 3.23 (m, 1 H, C-22 proton), 2.03 (s, 3 H, CH_3COO–), 1.27 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.88 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.41; H, 10.23.

(20*R*)-3β-Acetoxy-20-(2′-tetrahydropyranyloxy)pregn-5-ene-20-carbonitrile (7b) and (20*S*)-3β-Acetoxy-20-(2′-tetrahydropyranyloxy)pregn-5-ene-20-carbonitrile (8b). A mixture of **6** (50 g), potassium cyanide (5 g), and 230 ml of acetone cyanohydrin was stirred for 3 h at room temperature and poured into 750 ml of water. The resulting precipitate was filtered and washed with water–acetic acid (49:1), ethanol, and ether–hexane (1:5), and dried in a vacuum desiccator overnight to give 40 g of mixture of **7a** and **8a.**

To a cooled solution of crude cyanohydrin mixture (40 g) and *p*-toluenesulfonic acid (800 mg) in 450 ml of anhydrous tetrahydrofuran was added 50 ml of dihydropyran. The mixture was allowed to stand overnight, poured into cold saturated sodium bicarbonate solution, and extracted thoroughly with methylene chloride. The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give 50 g of nitriles **7b** and **8b** in ca. 1:1 ratio, as well as a small amount of unchanged cyanohydrin which could be removed by recrystallizations from methanol. The combined crystals were then recrystallized from cyclohexane to enrich the 20*R* isomer **7b** in the crystal portion and the 20*S* isomer in the filtrate. Pure **7b** could be obtained by five to eight recrystallizations from cyclohexane. The 20*S* isomer enriched mixture was recrystallized from methanol (four to six times) to give pure **8b. 8b** had a greater R_f than **7b** (2% ethyl acetate in benzene as eluent).

7b had mp 219–222 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 5.08 (m, 1 H, –OCHO–), 4.60 (m, 1 H, C-3 proton), 2.03 (s, 3 H, CH_3COO–), 1.60 (s, 3 H, C-21 methyl), 1.03 ppm (s, 6 H, C-18 and C-19 methyls).

8b had mp 179–180 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 5.13 (m, 1 H, –OCHO–), 4.60 (m, 1 H, C-3 proton), 2.03 (s, 3 H, CH_3COO–), 1.63 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.97 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{43}NO_4$: C, 74.16; H, 9.23; N, 2.98. Found: C, 73.94; H, 9.16; N, 3.21.

(20*R*)-3β-Acetoxy-20-(2′-tetrahydropyranyloxy)pregn-5-ene-20-carbaldehyde (10b). To a solution of 2 g of **7b** in 150 ml of anhydrous ether and 60 ml of anhydrous benzene at −70 °C, 20 ml of a 20% solution of diisobutylaluminum hydride in hexane was slowly added with a syringe and under a nitrogen atmosphere. The resulting solution was stirred for 15 h at room temperature. The aluminum complex was decomposed by cautious addition of a cold 2 N sodium hydroxide solution in the ice bath and the mixture was stirred for an additional 30 min at room temperature. The ether layer was separated from the aqueous layer which was extracted with ether. The ethereal extract was filtered with the aid of Celite, dried (Na_2SO_4), and evaporated in vacuo. To the resulting residue in 10 ml of ethanol, 2 ml of acetic acid and 3.5 ml of water were added while stirring for 30 min at room temperature. Then the mixture was diluted with water and the resulting precipitate filtered and washed thoroughly with water. After drying 1.24 g of hydroxy aldehyde **10a** was obtained which was sufficiently homogeneous on TLC to be converted to **10b:** NMR δ (60 MHz) 9.75 (s, 1 H, –CHO), 5.37 (m, 1 H, C-6 proton), 4.67 (m, 1 H, –OCHO–), 1.34 (s, 3 H, C-21 methyl), 1.02 (s, 3 H, C-19 methyl), 0.78 ppm (s, 3 H, C-18 methyl).

The acetate aldehyde **10b** was prepared by dissolving **10a** in 10 ml of pyridine and 1 ml of acetic anhydride. The solution was allowed to stand overnight at room temperature, after which time it was dumped into ice. By recrystallization from methanol 0.9 g was obtained: 151–153 °C; NMR δ (60 MHz) 9.72 (s, 1 H, –CHO), 5.37 (m, 1 H, C-6 proton), 4.67 (m, 1 H, –OCHO–) 4.58 (m, 1 H, C-3 proton), 2.03 (s, 3 H, CH_3COO–), 1.34 (s, 3 H, C-21 methyl), 1.02 (s, 3 H, C-19 methyl), 0.78 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.69; H, 9.50.

(20*S*)-3β-Hydroxy-20-(2′-tetrahydropyranyloxy)pregn-5-ene-20-carbaldehyde (11a). The solution of 2 g of **8b** in 150 ml of anhydrous ether was converted to 1.1 g of **11a** in the same manner as described for **10b:** mp 113–116 °C; ir (KBr pellet) 3540 (OH), 1710 and 2680 (C=O), 1025 and 960 cm^{-1} (THP ether); NMR δ (60 MHz) 9.73 (s, 1 H, –CHO), 5.37 (m, 1 H, C-6 proton), 4.67 (m, 1 H, –OCHO–), 1.42 (s, 3 H, C-21 methyl), 1.00 (s, 3 H, C-19 methyl), 0.78 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.29; H, 9.69.

(20*R*,22*R*)-3β,20,22-Trihydroxycholest-5-ene 3β-Acetate (4a) from 10b. To a stirred solution of **10b** (300 mg) in 30 ml of anhydrous methylene chloride, cooled to −70 °C under a nitrogen atmosphere, was added dropwise over a period of 5 min 30 ml of a solution of isoamylmagnesium bromide, which was prepared from 500 mg of magnesium, 3.5 ml of isoamyl bromide, and 15 ml of anhydrous ether, and in the end the ether was replaced by dry methylene chloride (40 ml). Then the dry ice bath was removed and immediately 15 ml of saturated sodium sulfate solution was added dropwise. After stirring at room temperature for 30 min, the mixture was dried (Na_2SO_4) and filtered through a Celite plug, and the solvent evaporated in vacuo to give 360 mg of crude oily alcohol **12.** An aliquot of the crude product was purified on a preparative TLC (15% acetone in hexane as eluent), revealing three compounds in a ratio of 1:12:2 (in order of increased polarity). The least polar fraction was identical with starting material **10b** in all aspects. The middle fraction **12** had NMR δ (100 MHz) 5.37 (m, 1 H, C-6 proton), 4.75 (m, 1 H, –OCHO–), 2.02 (s, 3 H, CH_3COO–), 1.28 (s, 3 H, C-21 methyl), 1.01 (s, 3 H, C-19 methyl), 0.88 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.80 ppm (s, 3 H, C-18 methyl); mass spectrum (70 eV) *m/e* 459 ($M^+ - 85$), 442 ($M^+ - 102$), 427 ($M^+ - 117$), 424 ($M^+ - 120$), 382 ($M^+ - 162$), 85 (base peak).

Anal. Calcd for $C_{34}H_{56}O_5$: C, 74.95; H, 10.36. Found: C, 74.89; H, 10.93.

The most polar fraction **9** had NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.73 (m, 1 H, –OCHO–), 3.72 and 3.23 (2 d, 2 H, J = 12 Hz, $-CH_2OH$), 2.03 (s, 3 H, CH_3COO–), 1.37 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.80 ppm (s, 3 H, C-18 methyl).

To the solution of crude **12** in 4 ml of THF–H_2O (9:1) 0.05 N hydrochloric acid solution was added until it became turbid. The mixture was stirred for 20 h and poured into cold saturated sodium bicarbonate solution. The mixture was extracted with methylene chloride and back-washed with saturated sodium chloride solution and water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The crude product was cleaned on preparative TLC (20% acetone in hexane as eluent) to give 70 mg of **4a** which was identical with the authentic sample (Scheme I) in all aspects.

Grignard Reaction of 8b with Isoamylmagnesium Bromide (11c). Following the method of Chaudhuri et al.,[24] 2 g of **8b** was reacted with isoamylmagnesium bromide and the resulting imine was hydrolyzed in acetic acid and benzene. The crude product **11b,** without further purification, was acetylated in the usual manner. Recrystallization from methanol gave 650 mg of **11c**[27] with mp 139–140 °C, and identical ir and NMR spectra with a sample of authentic material.

(20*R*,22*S*)-20,22-Epoxycholesterol (1a) and (20*R*,22*R*)-20,22-Epoxycholesterol (1b). To the ice-cold solution of 200 mg of acetate glycol **4a** in 1.5 ml of pyridine was added 0.14 ml of methanesulfonyl chloride (freshly distilled at atmospheric pressure). The solution was kept in the ice bath for 10 min and at room temperature for 20 min. Then the solution of 380 mg of potassium hydroxide in 3 ml of water was added and, after heating under reflux for 30 min, the solution was cooled to room temperature and slowly diluted with water. The precipitate was filtered, washed thoroughly with water, and dried to give 194 mg of crude epoxide. Purification by preparative TLC (15% acetone in hexane at eluent), followed by recrystallization from methanol, gave 115 mg of **1a:** mp 113–114 °C; NMR δ (100 MHz) 5.37 (m, 1 H, C-6 proton), 3.50 (m, 1 H, C-3 proton), 2.68 (m, 1 H, C-22 proton), 1.28 (s, 3 H, C-21 methyl), 1.01 (s, 3 H, C-19 methyl), 0.89 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.79 ppm (s, 3 H, C-18 methyl); mass spectrum (22.5 eV) M^+ *m/e* 400 (base peak).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.68; H, 10.86.

Conversion of 5a to 1b. When 200 mg of **5a** was treated in the same manner as described above, 140 mg of epoxide **1b** was obtained: mp 135–137 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 3.50 (m, 1 H, C-3 proton), 2.65 (m, 1 H, C-22 proton), 1.33 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.80 ppm (s, 3 H, C-18 methyl); mass spectrum (22.5 eV) M^+ *m/e* 400 (base peak).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.94; H, 10.81.

(*Z*)-3β-Hydroxycholesta-5,20(22)-diene (2a). A solution of acetate glycol **5a** (500 mg), ethyl orthoformate (4 ml), and benzoic acid (10 mg) was stirred at 110 °C for 3 h. To the crude 1,3-dioxolane **13,** after evaporation of the solvent in vacuo, 100 mg of benzoic acid was added. The mixture was heated at 170–175 °C for 15 min at 5 Torr. After cooling, the oily product was dissolved in ether and the solution was washed with saturated sodium bicarbonate solution, dried (Na_2SO_4), and evaporated in vacuo. The crude product was purified by column chromatography over alumina. Elution with hexane gave 220 mg of olefin **2c.** An analytical sample was prepared by recrystallization from methanol: mp 82–83 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 5.29 (m, 1 H, C-22 proton), 4.60 (m, 1 H, C-3 proton), 2.03 (s, 3 H, CH_3COO–) 1.72 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.88 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.69 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.76; H, 10.71.

2a was prepared by the addition of 200 mg of **2c** in 10 ml of anhydrous ether to 25 mg of $LiAlH_4$ in 15 ml of anhydrous ether and stirring at reflux for 30 min under anhydrous conditions. The excess hydride was decomposed by cautious addition of 2 N sodium hydroxide solution. Finally the precipitate was filtered with the aid of Celite and washed with methylene chloride. Evaporation of the solvent gave 172 mg of syrup which failed to crystallize: NMR δ (100 MHz) 5.37 (m, 1 h, C-6 proton), 5.29 (m, 1 H, C-22 proton), 3.50 (m, 1 H, C-3 proton), 1.72 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.88 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.69 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.38; H, 11.53.

(*Z*)-6β-Methoxy-3α,5-cyclo-5α-cholesta-20(22),25-diene (14b) and (*E*)-6β-Methoxy-3α,5-cyclo-5α-cholesta-20(22),25-diene (17b). A mixture of 78 mg of 54.3% sodium hydride mineral oil dispersion in 1.4 ml of anhydrous dimethyl sulfoxide was stirred at 70 °C under a nitrogen atmosphere until no hydrogen evolution could be detected. The mixture was cooled to room temperature and a solution of 0.63 g of methyltriphenylphosphonium bromide in 5 ml of anhydrous dimethyl sulfoxide was added, immediately producing a yellowish solution. Then a solution of 350 mg of **14a**[22] in 2 ml of anhydrous tetrahydrofuran was added and the resulting mixture was stirred at 60 °C for 3 h. The reaction mixture was then cooled and poured into ice water. The mixture was extracted thoroughly with

hexane and the combined extracts were washed with water and saturated sodium chloride solution, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over alumina. Elution with hexane gave 240 mg of oily diene **14b:** NMR δ (60 MHz) 5.30 (m, 1 H, C-22 proton), 4.70 (s, 2 H, >C=CH_2), 3.35 (s, 3 H, $-OCH_3$), 2.78 (m, 1 H, >CHOMe), 1.73 (s, 6 H, C-21 and C-26 methyls), 1.03 (s, 3 H, C-19 methyl), 0.72 (s, 3 H, C-18 methyl), 0.30–0.67 ppm (m, 3 H, cyclopropyl); mass spectrum (22.5 eV) *m/e* 396 (M^+), 381 ($M^+ - 15$), 364 ($M^+ - 32$), 349 ($M^+ - 47$), 285 ($M^+ - 111$), 253 (base peak, $M^+ - 143$).

Anal. Calcd for $C_{28}H_{44}O$: C, 84.78; H, 11.18. Found: C, 84.67; H, 11.11.

Conversion of 17a to 17b. When 350 mg of **17a** was treated in the same manner as described above, 200 mg of **17b** was obtained as oil: NMR δ (60 MHz) 5.18 (m, 1 H, C-22 proton), 4.70 (s, 2 H, >C=CH_2), 3.32 (s, 3 H, $-OCH_3$), 2.78 (m, 1 H, >C**H**OCH_3), 1.73 (s, 3 H, C-27 methyl), 1.65 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.58 (s, 3 H, C-18 methyl), 0.30–0.67 ppm (m, 3 H, cyclopropyl); mass spectrum (22.5 eV) *m/e* 396 (M^+), 381 ($M^+ - 15$), 364 ($M^+ - 32$), 349 ($M^+ - 47$), 285 ($M^+ - 111$), 253 (base peak, $M^+ - 143$).

Anal. Calcd for $C_{28}H_{44}O$: C, 84.78; H, 11.18. Found: C, 84.99; H, 11.26.

(*Z*)-6β-Methoxy-3α,5-cyclo-5α-cholest-20(22)-ene (15) and (*E*)-6β-Methoxy-3α,5-cyclo-5α-cholest-20(22)-ene (16). To a solution of 160 mg of diene **14b** in 2.5 ml of benzene, 25 mg of tris(triphenylphosphine)rhodium chloride was added and the homogeneous solution was stirred under an atmosphere of hydrogen and stopped when the theoretical amount of hydrogen had been absorbed (ca. 6 h). The solution was filtered through a dry column of 15 g of alumina. The column was washed with hexane and the combined solvent fractions were evaporated in vacuo to give 90 mg of **15:** NMR δ (100 MHz) 5.30 (m, 1 H, C-22 proton), 3.33 (s, 3 H, $-OCH_3$), 2.78 (m, 1 H, >CHOMe), 1.70 (s, 3 H, C-21 methyl), 1.02 (s, 3 H, C-19 methyl), 0.87 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.70 (s, 3 H, C-18 methyl), 0.30–0.67 ppm (m, 3 H, cyclopropyl).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.58; H, 11.64.

E olefin **16** was prepared from **17b** in the manner described above for the *Z* isomer (60% yield): NMR δ (60 MHz) 5.20 (m, 1 H, C-22 proton), 3.35 (s, 3 H, $-OCH_3$), 2.78 (m, 1 H, >CHOMe). 1.30 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.58 (s, 3 H, C-18 methyl), 0.30–0.67 ppm (m, 3 H, cyclopropyl).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.24; H, 11.57.

(*Z*)-3β-Hydroxycholesta-5,20(22)-diene (2a) and (*E*)-3β-Hydroxycholesta-5,20(22)-diene (2b). To 2 ml of dioxane containing 1.5 ml of water at room temperature under a nitrogen atmosphere, 100 mg of **15** in 1.1 ml of dioxane was added and the mixture heated to 80–85 °C until it became homogeneous. Then 5.5 mg of *p*-toluenesulfonic acid was added and heating was continued at 80 °C for 6 h. The reaction mixture was cooled, poured into saturated sodium bicarbonate solution, and extracted with ether. The ethereal extract was washed with water, and dried (Na_2SO_4). The residue, after removal of the solvent in vacuo, was purified by preparative TLC (10% ethyl acetate in benzene as eluent) to give 87 mg of oily diene **2a** which was identical in all respects with the material from Scheme III.

The *E* diene **2b**[16-18] was prepared in the same manner as described above to give the known product in 89% yield.

Selective Oxidation of 2b with *m*-Chloroperbenzoic Acid, 1b and 1c. To a cold solution of 450 mg of diene **2d** in 9 ml of methylene chloride, 200 mg of *m*-chloroperbenzoic acid in 9 ml of methylene chloride was added. The mixture was allowed to stand for 20 h at 0–2 °C and then was transferred to a separatory funnel with the aid of more methylene chloride. The organic layer was washed with 2 N sodium hydroxide solution, water, and brine, and dried (Na_2SO_4). The residue, after removal of solvent in vacuo, was purified by preparative TLC (5% acetone in hexane) to give 147 mg of **1e** and 219 mg of **1f.** The former had the greater R_f. An analytical sample was prepared by recrystallization from methanol.

1e had mp 103–104 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 2.63 (m, 1 h, C-22 proton), 2.03 (s, 3 H, CH_3COO-), 1.32 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.90 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.80 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.91; H, 10.49.

1f had mp 91–93 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 2.82 (m, 1 H, C-22 proton), 2.03 (s, 3 H, CH_3COO-), 1.30 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.90 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.68 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.79; H, 10.39.

1c was prepared by treating **1f** with lithium aluminum hydride in the same manner as described for **2a** (92% yield). An analytical sample was prepared by recrystallization from methanol: mp 123–125 °C; NMR δ (60 MHz) 5.73 (m, 1 H, C-6 proton), 3.50 (m, 1 H, C-3 proton), 2.82 (m, 1 H, C-22 proton), 1.30 (s, 3 H, C-21 methyl), 1.02 (s, 1 H, C-19 methyl), 0.92 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.68 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.92; H, 11.13.

Oxidation of 2a to 1a with *m*-Chloroperbenzoic Acid. 2a (150 mg) was oxidized with *m*-chloroperbenzoic acid in the same manner as described above. The crude product was purified by preparative TLC to give 102 mg of **1a** which was identical with the authentic sample in all aspects.

(20*S*,22*S*)-20,22-Dihydroxycholesterol 3β-Acetate (21). A mixture of 1.7 g of **2d** and 1 g of OsO_4 in 70 ml of anhydrous ether was allowed to stand at room temperature for 19 h. Then the solvent was evaporated in vacuo. To this mixture was added 100 ml of pyridine and 3.5 g of sodium bisulfite in 80 ml of water, and stirred at room temperature for 18 h. This mixture was poured into water and extracted with ether. The ethereal extract was washed with 2 N hydrochloric acid solution, saturated sodium bicarbonate solution, and water, and dried (Na_2SO_4). Purification on preparative TLC (20% acetone in hexane as eluent) gave 1.4 g of glycol mixture **21** and **4a** which were separated by HPLC in a ratio of 13:1 in the same system as described for **4a** and **5a.** The former had the shorter retention time. An analytical sample was prepared by recrystallization from methanol: mp 175–178 °C; NMR δ (60 MHz) 5.37 (m, 1 H, C-6 proton), 4.60 (m, 1 H, C-3 proton), 3.72 (m, 1 H, C-22 proton), 2.03 (s, 3 H, CH_3COO-), 1.07 (s, 3 H, C-21 methyl), 1.03 (s, 3 H, C-19 methyl), 0.90 (d, 6 H, J = 6 Hz, C-26 and C-27 methyls), 0.88 ppm (s, 3 H, C-18 methyl).

Anal. Calcd for $C_{29}H_{48}O_4$: C, 75.60; H, 10.50. Found: C, 75.81; H, 10.30.

Epoxide **1d** was prepared from **21** (300 mg) in the same manner as described in Scheme I. Purification by preparative TLC (15% acetone in hexane as eluent) gave 185 mg of epoxide **1d.** An analytical sample was prepared by recrystallization from methanol: mp 133–135 °C; NMR δ (100 MHz) 5.37 (m, 1 H, C-6 proton), 3.50 (m, 1 H, C-3 proton), 2.45 (m, 1 H, C-22 proton), 1.30 (s, 3 H, C-21 methyl), 1.01 (s, 3 H, C-19 methyl), 0.90 (s, 3 H, C-18 methyl), 0.89 ppm (d, 6 H, J = 6 Hz, C-26 and C-27 methyls).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.90; H, 10.91.

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Registry No.—**1a,** 60132-86-7; **1b,** 60084-21-1; **1c,** 60132-87-8; **1d,** 60182-58-3; **1e,** 60084-22-2; **1f,** 60132-88-9; **2a,** 60132-89-0; **2b,** 59905-87-2; **2c,** 60132-90-3; **2d,** 54548-85-5; **3b,** 60084-23-3; **4a,** 60084-24-4; **5a,** 60183-23-5; **6,** 1778-02-5; **7a,** 60182-59-4; **7b,** 60084-25-5; **8a,** 60132-91-4; **8b,** 60084-26-6; **9,** 60084-27-7; **10a,** 60084-28-8; **10b,** 60134-79-4; **11a,** 60084-29-9; **12,** 60084-30-2; **13,** 60084-31-3; **14a,** 53139-52-9; **14b,** 60084-32-4; **15,** 60084-33-5; **16,** 60084-34-6; **17a,** 53139-53-0; **17b,** 60084-35-7; **21,** 60132-92-5; isoamyl bromide, 107-82-4.

References and Notes

(1) This work was supported by the U.S. Public Health Service Grant AM-03419 from the Institute of Arthritis, Metabolism and Digestive Diseases and from the National Science Foundation Research Grant GB-38612.
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Stereochemistry of 1,3-Cyclohexadienes. Conformational Preferences in 9-Substituted 9,10-Dihydrophenanthrenes

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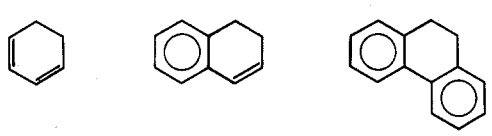
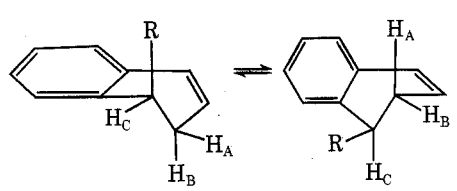
A series of 9-R-9,10-dihydrophenanthrenes [R = CH_3, CN, $C(CH_3)_3$, $COCH_3$, CO_2CH_3, $CO_2CH_2CH_3$, OH, $Si(CH_3)_3$] as well as two related 5,6-dihydrochrysenes, are studied by NMR analysis of the three spin H_9, H_{10}, $H_{10'}$ system. The coupling constants thus obtained are then used to determine the conformational preferences of these mobile ring systems with regard to the location of substituents in pseudoaxial or pseudoequatorial positions. All substitutes except cyano were found to preferentially adopt the pseudoaxial conformation.

The majority of studies concerned with the stereochemistry of 1,3-cyclohexadiene ring systems (**1–3**) have dealt with



1 **2** **3**

derivatives of 1,2-dihydronaphthalene (**2**).[1-5] In the case of 1-substituted 1,2-dihydronaphthalenes, NMR investigations into the equilibrium between **4a′** and **4e′** were carried out by computer analysis of the ABC spectra resulting from the benzylic and allylic protons.[2-4] In both **4a′** and **4e′** the protons



4a′ **4e′**

H_B and H_C interact in a pseudoaxial/pseudoequatorial relationship and the spin interactions are equivalent, leading to a J_{ae} coupling constant which is independent of the position of equilibrium, and values of 6.8 Hz have been determined.[2] On the other hand, protons H_A and H_C interact as pseudoequatorial/pseudoequatorial in **4a′** and pseudoaxial/pseudoaxial in **4e′**, and the time average value of this coupling constant is directly related to the conformational populations. Thus, using values of J_{aa} = 16 and J_{ee} = 2 Hz, and the relationship

$$J_{AC} = xJ_{ee} + (1 - x)J_{aa} \quad (1)$$

the fraction (x) of the conformations with the group in the pseudoaxial position was calculated for a number of R groups.[4]

Although the 9,10-dihydrophenanthrene system (**3**) would appear to be closely related, discrepancies have been noted in comparing coupling constant data with the dihydronaphthalenes. Thus, one report[1] based on ^{13}C satellite resonances provides values of 8.3 and 5.8 Hz for **3**, presumably corresponding to the average $\frac{1}{2}(J_{aa} + J_{ee})$ value (9.4 in **2**) and to J_{ae} (7.0 in **2**), respectively. Furthermore, 9,10-dihydro-4,5-dimethylphenanthrene shows $\frac{1}{2}(J_{aa} + J_{ee})$ = 10.59 and J_{ae} = 3.97 Hz,[6] whereas the values for 9-dimethylamino-9,10-dihydro-4,5-dimethylphenanthrene are $\frac{1}{2}(J_{aa} + J_{ee})$ = 7.92 and J_{ae} = 3.5 Hz.[7] Katritzky et al.[2] have suggested that the contrast between 1,2-dihydronaphthalene and 9,10-dihydrophenanthrene may be due to differences in dihedral angles, although de la Mare et al.[5] have presumed approximately equal dihedral angles for both systems in a more recent NMR study. Furthermore, these latter workers have suggested that their coupling constant data for *cis*- and *trans*-9-acetoxy-10-chloro-9,10-dihydrophenanthrene compare favorably with the corresponding values for 9-dimethylamino-9,10-dihydro-4,5-dimethylphenanthrene when electronegativities are taken into account. However, a recent NMR investigation[6] on 9,10-dihydro-4,5-dimethylphenanthrene itself has suggested a much larger dihedral angle between the benzene rings in this system as a result of 4- and 5-methyl steric interaction.

We now report NMR special analysis of a series of 9-substituted 9,10-dihydrophenanthrenes (**5a′** ⇌ **5e′**). These studies were conducted in order to obtain accurate coupling constant data for comparison with the 1,2-dihydronaphthalene ring system and to determine the conformational preferences of the 9 substituents.

Since H_9 and H_{10} are dipseudoequatorial in **5a′** and dipseudoaxial in **5e′**, $J_{9,10}$ is expected to reflect the relative contributions from each conformation. On the other hand, H_9