STEROIDS CCLXXIV[1]. BIOLOGICALLY-ACTIVE LABILE ETHERS IV[2]. THE SYNTHESIS OF 22-OXA-25-AZACHOLESTEROL AND RELATED COMPOUNDS

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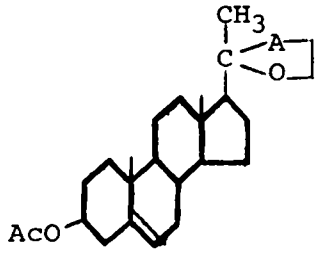
The cyclic ethylene ketal of 3β-hydroxypregn-5-en-20-one undergoes cleavage of the ketal ring by lithium aluminum hydride and aluminum trichloride. Chemical manipulation of the primary hydroxyl in the resultant 20β-(2-hydroxyethyl) ether led to numerous 20β sidechain structural variants, among them 22-oxa-25-azacholesterol.

The incessant flow of novel synthetic steroids has repeatedly uncovered new, and often unexpected, correlations of enhanced biological activity with specific structural modifications. Among the later discoveries has been that of Ercoli and his co-workers who found that certain cyclopentenyl and related ethers in the androstane series showed an activity substantially higher than the activity of the free alcohols for administration by the oral route[3]. Enhancement of the oral activity by protection of sensitive alcohol functions as a labile ether group has since been

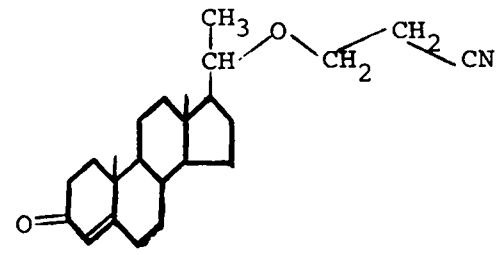
successfully extended in the Syntex Laboratories with the development of novel potent anabolic agents[4] and estrogens[5]. In these cases the chemically-sensitive unit chosen was the readily-prepared tetrahydropyran-2-yloxy ether moiety. The general concept of labile ethers has been discussed with reference to possible alternative acid- and base-sensitive chemical structures[2]. There was announced simultaneously a new group of estrogens, of high activity by oral administration, bearing the 17β-(2-substituted ethoxy) group[2]. The key step in the synthesis of such derivatives was the cleavage of a 17-cyclic ethylene ketal or hemithioketal ring by a metal hydride - Lewis acid reagent. Extension of this procedure to the analogous 3β-hydroxy-pregn-5-en-20-one cyclic ethylene ketals and monothioketals is now reported. An extra stimulus to the investigations was provided by reports[6] of powerful oral hypocholesterolemic activity for 20,25-diazacholesterol[7] and the related 20α-(2'-dialkylaminoethyl)amino-pregn-5-en-3β-ols[8]. However, later work has shown that such agents function primarily by inhibition of the conversion of desmosterol to cholesterol[9] and accumulation of desmosterol in body tissue is known to be associated with undesirable side effects.

3β-Hydroxypregn-5-en-20-one-3-acetate cyclic ethylene ketal (I) was reductively cleaved with lithium aluminum hydride-aluminum trichloride reagent[10] to afford 20β-(2-hydroxyethoxy)-pregn-5-en-3β-ol (IIa). The 20β-configuration is assigned from a consideration of the probable reaction

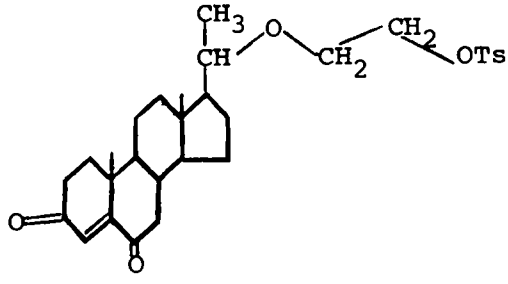
mechanism[10], in which it is envisaged that the thermodynamically most stable configuration will develop at the carbon bearing the ether oxygen, and on the basis of chemical evidence (vide infra). Acetylation of the diol IIa furnished the diacetate IIb which was selectively hydrolyzed to obtain 20β-(2-hydroxyethoxy)-pregn-5-en-3β-ol acetate (IIc). Oxidation of this diol monoacetate IIc with chromic oxide-pyridine reagent[11] led to the aldehyde IId. The related acid IIe was obtained when the diol monoacetate IIc was treated with chromic acid oxide in acetone-sulfuric acid reagent[12] followed by hydrolysis of the 3-acetate ester. Exposure of the diol monoacetate IIc to mesyl chloride-pyridine gave the acetate-mesylate diester IIf, while treatment of the diol IIa with one equivalent of mesyl chloride furnished the primary mesylate IVg. Similarly, the diol IIa was converted to the diol monotosylate IIh which was readily acetylated to give the acetate-tosylate diester IIi. Displacement of the tosylate by cyanide ion was achieved when the ester IIi was kept overnight on the steam bath with potassium cyanide in dimethylformamide. The 20β-(2-cyanoethyl) ether IIj which resulted was hyrolyzed to the 3β-alcohol IIk and this was then oxidized, without purification, under Oppenauer conditions to yield 20β-(2-cyanoethoxy)-pregn-4-en-3-one (III). An attempt to oxidize the diol monotosylate IIh with chromic acid[12] to the pregn-5-en-3-one analog led instead to 20β-(2-hydroxyethoxy)-pregn-4-ene-3,6-dione p-toluenesulfonate (IV) with



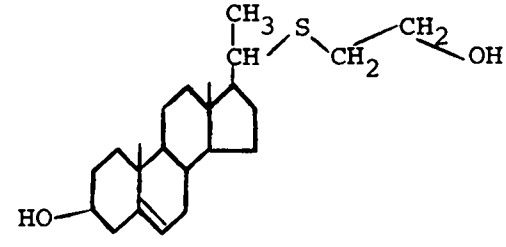
I A = O
V A = S



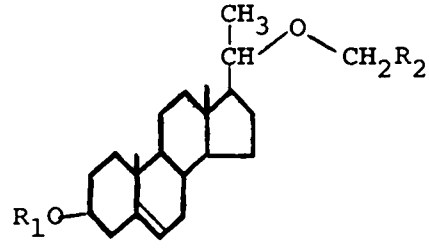
III



IV



VI



II

a, R_1 = H, R_2 = CH_2OH

b, R_1 = Ac, R_2 = CH_2OAc

c, R_1 = Ac, R_2 = CH_2OH

d, R_1 = Ac, R_2 = CHO

e, R_1 = H, R_2 = CO_2H

f, R_1 = Ac, R_2 = CH_2OMs

g, R_1 = H, R_2 = CH_2OMs

h, R_1 = H, R_2 = CH_2OTs

i, R_1 = Ac, R_2 = CH_2OTs

j, R_1 = Ac, R_2 = CH_2CN

k, R_1 = H, R_2 = CH_2CN

l, R_1 = H, R_2 = $CH_2N(CH_3)_2$

m, R_1 = H, R_2 = $CH_2{}^{+}NH(CH_3)_2Cl^{-}$

n, R_1 = Ac, R_2 = CH_2N⟨⟩

o, R_1 = H, R_2 = CH_2N⟨⟩

p, R_1 = H, R_2 = CH_2O-⟨O⟩

q, R_1 = Ac, R_2 = CH_2I

r, R_1 = H, R_2 = CH_2F

characteristic ultraviolet absorption maxima at 226 and 252 mμ. The nitrile IIj was cleaved by hot strong alkali to pregn-5-ene-3β,20β-diol, an elimination reaction considered to proceed by initial abstraction of proton α to nitrile. The stereochemistry at C-20 is not expected to be affected in this reaction and the 20β orientation of the side chain is established therefore.

When the acetate-tosylate diester IIi was allowed to react with dimethylamine under pressure, followed by mild alkaline hydrolysis, there was obtained 20β-(2-dimethylaminoethoxy)-pregn-5-en-3β-ol (IIl, 22-oxa-25-azacholesterol), further characterized as its hydrochloride salt IIm. Similarly, the tosylate IIi was readily displaced to give the N-piperidylethyl ether IIn with retention of the 3β-acetate ester group. Hydrolysis gave the corresponding free alcohol IIc. For bioassays the tetrahydropyranyl ether IIp of the diol 3-acetate IIc, and two 20β-(2-halogenoethyl) ethers were synthesized. The iodo derivative IIq was arrived at by an appropriate displacement reaction upon the tosylate IIi. Exposure of the diol monoacetate IIc to the ubiquitous 2-chloro-1,1,2-trifluoro-triethylamine reagent[13], followed by hydrolysis of the 3β-acetate led smoothly to the desired fluoro analog IIr.

Having prepared a series of 20β-ethers of pregn-5-ene-3β,20β-diol attention was switched next to the 20β-thio analogs. When 3β-hydroxypregn-5-en-20-one 3-acetate cyclic monothioketal (V)[14] was treated with lithium aluminum hydride-aluminum trichloride reagent[10] the sole isolable product was the 20β-[(2-hydroxyethyl)thio]ether VI. Preferential

cleavage at the C-0 link of the monothioketal is well precedented[10,15]. Attempts to convert the (2-hydroxyethyl)thioether VI to a series of (2-substituted ethyl) thioethers revealed that the thioethers are less stable than their 22-oxa analogs II. The lesser stability of 17β-thioethers versus the 17β-ethers was noted earlier[2]. Moreover, since the reductive cleavage of the monothioketal V proceeded in unattractive yield further investigation of the 20β-thioethers was not pursued.

Biological activities of the various compounds prepared in this work will be reported elsewhere by Dr. R. I. Dorfman and his colleagues.

EXPERIMENTAL[16]

20β-(2-Hydroxyethoxy)-pregn-5-en-3β-ol (IIa). - A solution of 7.5 g. of lithium aluminum hydride in 300 ml. of ether was added slowly to an ice-cold, stirred solution of 100 g. of aluminum trichloride in 300 ml. of ether. After 1 hr. a solution of 18.2 g. of the ketal I in 100 ml. of tetrahydrofuran was added and the reaction mixture stirred overnight. Following destruction of the excess of hydride with ethyl acetate, saturated aqueous sodium sulfate solution was added and the inorganic material was collected at the filter, washing with ethyl acetate. The organic layer of the filtrate was separated, dried and evaporated in vacuo to yield 9.8 g. of crude 20β-(2-hydroxyethoxy) ether IIa, m.p. 147-153°. Recrystallization from benzene-hexane gave the analytical sample, m.p. 183-185°; $[\alpha]_D$ −68°; νmax 3300, 1450, 1375, 1350, 1320, 1120, 1088, 1055, 965 and 890 cm^{-1}.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.20; H, 10.56; O, 13.24. Found: C, 76.27; H, 10.52; O, 13.44.

20β-(2-Hydroxyethoxy)-pregn-5-en-3β-ol diacetate (IIb). A solution of 5 g. of the above diol IIa in 25 ml. of pyridine and 10 ml. of acetic anhydride was kept 1 hr. at 80° and then poured into water. Isolation with methylene chloride in the normal manner led to 6.3 g. of an anhydrous solid. Several crystallizations from methylene chloride-methanol furnished 5.2 g. of the pure diacetate derivative

IIb, m.p. 103-105°; $[\alpha]_D$ - 52°; νmax 1730, 1455, 1380, 1245, 1115, 1050, 1035, 1015, 975, 940, 915 and 850 cm^{-1}.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.85; H, 9.35.

20β-(2-Hydroxyethoxy)-pregn-5-en-3β-ol 3-acetate (IIc). A solution of 5 g. of the diacetate IIb in 3 ml. of water and 497 ml. of methanol containing 0.001% of sodium bicarbonate was maintained under reflux during 0.5 hr. Dilution with water followed by extraction with methylene chloride and evaporation of the washed and dried extracts afforded a solid which was chromatographed over alumina. Thereby were separated 230 mg. of unreacted diester IIb, 2.45 g. of the desired monoacetate IIc, and 1.09 g. of the diol IIa. Recrystallization of the monoacetate from hexane-methylene chloride gave an analytical specimen, m.p. 134-136°; $[\alpha]_D$ - 65°; νmax 3325, 1740, 1375, 1250, 1120, 1070 and 1040 cm^{-1}.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.97; O, 15.82. Found: C, 74.24; H, 9.79; O, 15.69.

Oxidation of 20β-(2-hydroxyethoxy)-pregn-5-en-3β-ol 3-acetate. - a) The monoacetate IIc (1 g.) was added in small portions to a cooled slurry of 1 g. of chromium trioxide in 8 ml. of pyridine and the whole kept 18 hr. at room temperature[11]. Work up in the normal manner led to 770 mg. of amorphous material. Chromatography on neutral alumina and elution with hexane-benzene mixtures furnished 320 mg. of crystalline aldehyde IId, m.p. 142-149°. By recrystallization from hexane-methylene chloride there was obtained a sample, m.p. 147-150°; $[\alpha]_D$ - 55°; νmax 1760, 1735, 1320, 1250, 1190, 1130 and 1040 cm^{-1}.

Anal. Calcd. for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51; O, 15.90. Found: C, 74.93; H, 9.30; O, 16.12.

b) Oxidation of 1 g. of the diol monoacetate IIc in 50 ml. of acetone at room temperature with chromic acid in acetone-sulfuric acid[12] and work-up in the usual way yielded an amorphous solid acid. Without further purification this solid was promptly dissolved in 50 ml. of 4% methanolic potassium hydroxide and the solution kept 45 min. at reflux. After being cooled and neutralized with dilute hydrochloric acid the aqueous mixture was extracted with ethyl acetate. Evaporation of the washed and dried extracts left 550 mg. of crude free acid, m.p. 218-223°. Several crystallizations from methanol-acetone gave the analytical sample of 20β-(2-carboxymethoxy)-pregn-5-en-3β-ol (IIe), m.p. 227-230°; $[\alpha]_D$ - 6°; νmax 3300 (broad absorption); 2550, 1730, 1460, 1380, 1130, 1040, 1030 and 960 cm^{-1}.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64; O, 17.00. Found: C, 73.36; H, 9.80; O, 17.20.

20β-(2-Hydroxyethoxy)-pregn-5-en-3β-ol 3-acetate 20β-(2-methanesulfonate) (IIf). - A mixture of 1.5 g. of the diol monoacetate IIc and 0.5 ml. of methane sulfonyl chloride in 12 ml. of anhydrous pyridine was allowed to react for 1.5 hr. at 0-5°. Dilution with water, then filtration, gave 1.68 g. of mixed acetate-mesylate ester IIf, m.p. 120-123°. Recrystallization from methylene chloride-methanol provided a pure specimen, m.p. 122-124°; $[\alpha]_D$ - 49°; νmax 1738, 1355, 1250, 1185, 1130, 1040, 1015, 970, 930 and 810 cm^{-1}.

Anal. Calcd. for $C_{26}H_{42}O_6S$: C, 65.71; H, 8.77; O, 19.88; S, 6.64. Found: C, 65.07; H, 8.98; O, 19.92; S, 6.87.

20β-(2-Hydroxyethoxy)-pregn-5-en-3β-ol 20β-(2-methanesulfonate) (IIg). - Exposure of 1 g. of the diol IIa to 1.05 molar equivalents of mesyl chloride in 10 ml. of anhydrous pyridine as outlined above furnished, following chromatography over alumina, 670 mg. of the diol monomesylate IIg, m.p. 149-155°. The analytical sample was prepared by several crystallizations of crude IIg from hexane-ether-methylene chloride and showed m.p. 160-164°; $[\alpha]_D$ - 52°; νmax 3220, 1174, 1020, 970, 930 and 811 cm^{-1}.

Anal. Calcd. for $C_{24}H_{40}O_5S$: C, 65.46; H, 9.16; O, 18.10; S, 7.28. Found: C, 65.13; H, 9.33; O, 18.05; S, 7.17.

20β-(2-Hydroxyethoxy)-pregn-5-en-3β-ol 20β-(2-p-toluenesulfonate) (IIh). - Treatment of 1 g. of the diol IIa overnight at room temperature with 520 mg. (1 equivalent) of p-toluenesulfonyl chloride and 10 ml. of dry pyridine followed by work-up in the normal manner gave 600 mg. of an amorphous solid. By chromatography over neutral alumina there were obtained 220 mg. of the monotosylate IIh followed by 300 mg. of the starting diol IIa. Recrystallization of the monotosylate IIh from methylene chloride-methanol afforded the analytical sample, m.p. 145-147°; $[\alpha]_D$ - 53°; λmax 224-226 (log ε 4.09), 262 (log ε 2.77) and 274 mμ (log ε 2.64); νmax 3475, 1605, 1455, 1355, 1195, 1180, 1135, 930, 810 and 780 cm^{-1}; n.m.r. 38.5 (s., 18-H), 61 (s., 19-H), 61 (d., J 6 c.p.s., 21-H), 146 (s., $ArCH_3$), 191-235 (m., H-C-O), 316 (m., 6-H) and 450.5 c.p.s. (q., J 8.5 c.p.s., at 432, 440.5, 460.5 and 469 c.p.s., ortho aromatic protons).

Anal. Calcd. for $C_{30}H_{44}O_5S$: C, 69.72; H, 8.58; O, 15.48; S, 6.20. Found: C, 69.87; H, 8.53; O, 15.41; S, 6.23.

20β-(2-Hydroxyethoxy)-pregn-5-en-3β-ol 3-acetate 20β-(2-p-toluenesulfonate) (IIi). - Treatment of 600 mg. of the above-mentioned monotosylate IIh with acetic anhydride

and pyridine in the usual way gave 680 mg. of crude acetate-tosylate mixed ester IIi. Purification was achieved by filtration through neutral alumina, followed by crystallization from methylene chloride-methanol, giving 390 mg. of the acetate-tosylate IIi, m.p. 107-108°; $[\alpha]_D$ - 56°; λmax 224-226 (log ε 4.06), 262 (log ε 2.74) and 274 mμ (log ε 2.62); νmax 1730, 1620, 1355, 1242, 1181, 1178, 1134, 1035, 1020, 935, 810 and 783 cm^{-1}.

Anal. Calcd. for $C_{32}H_{46}O_6S$: C, 68.71; H, 8.30; S, 5.74. Found: C, 69.00; H, 8.69; S, 5.56.

20β-(2-Cyanoethoxy)-pregn-5-en-3β-ol acetate (IIj). - A solution of 750 mg. of the acetoxy tosylate (IIi) in 75 ml. of dimethylformamide was heated to 85° for 16 hrs. with 750 mg. of potassium cyanide. After cooling, water was added and the precipitate which formed was extracted with ethyl acetate, washed with water until neutral, dried, and evaporated *in vacuo*. There was obtained 640 mg. of semi-crystalline material which was recrystallized from methylene chloride-methanol, affording 500 mg. of the nitrile (IIj), m.p. 92-98°. The analytical sample showed, m.p. 102-103°; $[\alpha]_D$ - 60°; νmax 2245, 1740, 1385, 1249, 1120 and 1040 cm^{-1}.

Anal. Calcd. for $C_{26}H_{39}O_6N$: C, 75.50; H, 9.51; O, 11.61; N, 3.38. Found: C, 75.38; H, 9.65; O, 11.63; N, 3.34.

20β-(2-Cyanoethoxy)-pregn-4-en-3-one (III). - Selective hydrolysis of the 3-acetoxy grouping of IIj was effected by refluxing 500 mg. of this derivative for 20 min. in 20 ml. of 1% potassium hydroxide in methanol. After work-up in the usual way there was obtained 420 mg. of amorphous material, presumably (IIk). This product, which could not be obtained crystalline, was submitted to Oppenauer oxidation in toluene (7 ml.), with cyclohexanone (4 ml.) and aluminum isopropoxide (715 mg.), for half an hour at reflux temperature. After steam distillation, followed by extraction, 380 mg. of amorphous material was obtained. Chromatography on neutral alumina furnished 220 mg. of the α,β-unsaturated ketone (III), m.p. 129-130°. Recrystallization from acetone-hexane gave the pure sample, m.p. 134-135°; $[\alpha]_D$ + 87°; λmax 242 mμ (log ε 4.22); νmax 2245, 1668, 1619, 1375, 1340, 1270, 1228, 1185, 1100, 965, 935 and 855 cm^{-1}.

Anal. Calcd. for $C_{24}H_{35}O_2N$: C, 78.00; H, 9.55; O, 8.66; N, 3.79. Found: C, 77.74; H, 9.45; O, 8.68; N, 3.97.

20β-(2-Hydroxyethoxy)-pregn-4-ene-3,6-dione 20β-(2-p-toluenesulfonate) (IV). - When 1.24 g. of the monotosylate IIh was treated with an excess of chromic acid in sulfuric acid-acetone reagent[12], under the usual conditions there

was obtained 1.3 g. of amorphous material. This product was purified by filtration through 40 g. of neutral alumina to afford 600 mg. of the pregn-4-ene-3,6-dione derivative IV, m.p. 128-131°. Further crystallization from ether-hexane provided the analytical sample, m.p. 132-133°; $[\alpha]_D$ - 49°; λmax 226 (log ε 4.25) and 252 mμ (log ε 4.06); νmax 1693, 1675, 1660, 1602, 1222, 1195, 1177, 1125, 1100, 1025, 925, 818 and 780 cm^{-1}.

Anal. Calcd. for $C_{30}H_{40}O_6S$: C, 68.16; H, 7.63; O, 18.15; S, 6.06. Found: C, 67.98; H, 7.73; O, 17.99; S, 5.95.

20β-(2-Dimethylaminoethoxy)-pregn-5-en-3β-ol (III). - A slow stream of dimethylamine was passed through a solution of 1.5 g. of the acetoxy tosylate IIi in 20 ml. of diglyme until the latter was saturated. The reaction tube was then sealed and heated to 90° for 18 hrs. after which the cooled mixture was poured into water, extracted with methylene chloride and washed until neutral. Evaporation of the dried extracts in vacuo furnished 1.05 g. of an amorphous product. This was subjected to the action of 2% methanolic potassium hydroxide hydrolysis on the steam bath in the normal manner. Work-up then afforded 850 mg. of 22-oxa-25-azacholesterol (III). Several crystallizations from acetone-water gave 560 mg. of pure compound, m.p. 123-125°; $[\alpha]_D$ - 59°; νmax 3400, 1370, 1110 and 1075 cm^{-1}.

Anal. Calcd. for $C_{25}H_{43}O_2N$: C, 77.07; H, 11.13; O, 8.20; N, 3.60. Found: C, 76.45; H, 11.21; O, 8.64; N, 3.17.

The hydrochloride salt IIm was prepared by passing a stream of hydrogen chloride gas through a solution of 0.7 g. of the dimethylamino derivative III in 125 ml. of ether during 15 minutes. The white salt separated out and was collected at the filter, washing with ether. Recrystallization from methylene chloride-ether furnished 570 mg. of the hydrochloride IIm, m.p. 236-240°; $[\alpha]_D$ - 63°. νmax 3380, 2650, 1380, 1110, 1065 and 970 cm^{-1}.

Anal. Calcd. for $C_{25}H_{44}O_2NCl$: C, 70.49; H, 10.41; O, 7.49; N, 3.29; Cl, 8.32. Found: C, 69.98; H, 10.43; O, 7.70; N, 3.76; Cl, 8.44.

20β-(2-N-Piperidinoethoxy)-pregn-5-en-3β-ol acetate (IIn). - A solution consisting of 900 mg. of the acetate tosylate (IIi) in 4 ml. of piperidine was kept at reflux for 17 hr. After being cooled, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water until neutral, dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The amorphous product (690 mg.) which was obtained was passed through 30 g. of neutral alumina to pro-

vide 290 mg. of a substance, m.p. 102-110°. Crystallization from methylene chloride-methanol gave a pure sample of the N-piperidinoethoxy derivative (IIn), m.p. 112-114°; $[\alpha]_D$ - 38°; νmax 1739, 1370, 1240, 1140, 1130 and 1040 cm^{-1}.

Anal. Calcd. for $C_{30}H_{49}O_3N$: C, 76.38; H, 10.47; N, 2.97. Found: C, 76.45; H, 10.35; N, 3.19.

20β-(2-N-Piperidinoethoxy)-pregn-5-en-3β-ol (IIo). - A solution of 1 g. of the 3β-acetate IIn in 100 ml. of 2% potassium hydroxide in methanol was kept at room temperature for 16 hr. The alkaline mixture was neutralized with a dilute acetic acid solution and then concentrated in vacuo. Extraction with methylene chloride afforded a crude product which was purified by passage through 40 g. of silica gel giving 360 mg. of the N-piperidinoethoxy derivative IIo, m.p. 134-140°. Recrystallization from methylene chloride-methanol-water gave a pure sample, m.p. 139-141°; $[\alpha]_D$ -51°; νmax 3200, 1370, 1100 and 1085 cm^{-1}.

Anal. Calcd. for $C_{28}H_{47}O_2N$: C, 78.27; H, 11.03; O, 7.45; N, 3.26. Found: C, 78.38; H, 10.81; O, 7.63; N, 3.44.

20β-(2-[(tetrahydropyran-2-yl)oxy]ethoxy)-pregn-5-en-3β-ol (IIp). - A mixture of 1 g. of the monoacetate (IIc) in 80 ml. of anhydrous benzene, 2 ml. of dihydropyran and 40 mg. of p-toluenesulfonic acid was kept 72 hr. at room temperature. The reaction mixture was then poured into water and extracted with benzene. Evaporation of the dried solution gave 2 g. of an amorphous residue which was hydrolyzed by 2% methanolic potassium hydroxide solution to furnish 990 mg. of the tetrahydropyranyl ether IIp, m.p. 82-88°. The analytical sample was obtained by crystallization from hexane-acetone, m.p. 94-96°; $[\alpha]_D$ - 39°; νmax 3300, 1370, 1130, 1080, 1055, 1042, 1025, 995 and 875 cm^{-1}.

Anal. Calcd. for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38; O, 14.33. Found: C, 75.33; H, 10.56; H, 14.29.

20β-(2-Iodoethoxy)-pregn-5-en-3β-ol acetate (IIq). - A solution of 1 g. of the acetoxy tosylate (IIi) and 1 g. of sodium iodide in 40 ml. of diglyme was heated under reflux for 2 hr. Dilution with water afforded 1.18 g. of crude material which after several crystallizations from ether-methanol gave the analytical sample of the 2-iodoethyl ether (IIq), m.p. 91-92°; $[\alpha]_D$ - 24°; νmax 1735, 1370, 1240, 1105, 1040, 1020, 1010, 955, 935, 905, 885, 872, 845 and 805 cm^{-1}.

Anal. Calcd. for $C_{25}H_{39}O_3I$: C, 58.34; H, 7.64; O, 9.32; I, 24.66. Found: C, 58.81; H, 7.73; O, 9.26; I, 24.15.

20β-(2-Fluoroethoxy)-pregn-5-ene-3β-ol (IIr). - A solution of 2 g. of the monoacetate (IIc) in 20 ml. of methylene chloride was left 24 hr. at room temperature with 1.38 g. of 2-chloro-1,1,2-trifluorotriethylamine. The reaction mixture was evaporated to dryness in vacuo and the crude product which was obtained was hydrolyzed by refluxing for 30 min. with 100 ml. of 0.9% potassium hydroxide in methanol solution. The 1.9 g. of amorphous material obtained by extraction was purified by filtration through 200 g. of silica gel, giving 650 mg. of fluoro-derivative (IIr), m.p. 150-154°. Recrystallization from methylene chloride-hexane gave the analytical sample, m.p. 152-155°; $[\alpha]_D$ - 56°; νmax 3300, 1370, 1125 and 1055 cm^{-1}.

Anal. Calcd. for $C_{23}H_{37}O_2F$: C, 75.78; H, 10.23; F, 5.21. Found: C, 75.80; H, 10.05; F, 5.01.

20β-([2-Hydroxyethyl]thio)-pregn-5-en-3β-ol (VI). - A solution of lithium aluminum hydride (0.114 g.) in 10 ml. of ether was added slowly to 877 mg. of aluminum trichloride in 11 ml. of ether. To this reagent was added a solution of 2 g. of the monothioketal V[14] dissolved in 30 ml. of dioxane and the whole was then kept under reflux during 5 hr. The reaction mixture was then worked-up by cautious addition of ethyl acetate and aqueous sodium sulfate followed by extraction with ethyl acetate. The washed and dried extracts were evaporated and the resulting amorphous residue subjected to chromatographic separation over alumina. Benzene-hexane (1:4) eluant removed 500 mg. of unchanged monothioketal V. Elution of the column with benzene-ether (9:1) gave 700 mg. of 3β-hydroxypregn-5-en-20-one and a 7:3 mixture of the same solvents finally removed the desired (2-hydroxyethyl)thioether VI in 30% overall yield, m.p. 127-131°. Recrystallization from benzene-hexane gave an analytical sample, m.p. 147-150°; $[\alpha]_D$ - 86°; νmax 3260, 1370, 1050 and 1010 cm^{-1}.

Anal. Calcd. for $C_{23}H_{38}O_2S$: C, 72.97; H, 10.12; O, 8.45; S, 8.46. Found: C, 73.11; H, 9.93; O, 8.54; S, 8.42.

Pregn-5-ene-3β,20β-diol. - A solution of the cyanoethoxy derivative IIj (220 mg.) in ethylene glycol (10 ml.) containing potassium hydroxide (2 g.) and water (0.8 ml.) was heated under reflux for 72 hrs. After cooling, the reaction mixture was poured into water, saturated with sodium chloride, and extracted with ethyl acetate. The organic layer was washed with water until neutral, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The crude crystalline material (115 mg.; m.p. 150-200°) was recrystallized from methylene chloride-hexane to provide a pure sample of pregn-5-ene-3β,20β-diol, m.p. 198-200°; $[\alpha]_D$ - 73°. This compound was shown to be identical with an authentic sample by m.p., mixed m.p., and comparison of the infrared spectra.

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16. Except where stated otherwise rotations are for chloroform solutions, ultraviolet spectra are for ethanol solutions, and infrared spectra are for potassium bromide discs. Melting points were taken on the Fisher-Johns block and are uncorrected. Microanalyses are by either Mid-West Microlaboratories, Indianapolis 20, Indiana, or by A. Bernhardt, Muhlheim (Ruhr), Germany. Alumina used for chromatography was neutralized by stirring with ethyl acetate and reactivated by heating at 120° for 72 hrs. Unless stated otherwise the alumina had activity grade III, as defined by H. Brockmann and H. Schodder, BER, 74, 73 (1941). In the presentation of n.m.r. data, s. = singlet, d. = doublet, t. = triplet, q. = quartet, and m. = multiplet.