0.14 g (63%) of 2-phytylphenol (IX) as a colorless oil. Ultraviolet data appear in Table I; the nmr data are in Table II.

*Anal.* Calcd for $C_{26}H_{44}O$: C, 83.9; H, 11.8. Found: C, 83.5; H, 11.8.

**General Procedures for the Preparation of 2-Multiprenylphenols (III and V). A. Acid-Catalyzed Isoprenylation of Phenol and 2-Methoxyphenol (Guaiacol).**—To a solution of 0.02 mole of phenol or 2-methoxyphenol and 0.005 mole of the appropriate multiprenyl alcohol in 25 ml of redistilled dioxane, was added dropwise 1.5 ml of freshly distilled boron trifluoride etherate in 5 ml of dioxane. After a reaction period of 3 to 5 hr, the solution was poured into a mixture of three volumes of water and two volumes of ether. The organic phase was separated, dried, and evaporated. The oily residue was subjected to preparative thin layer chromatography as described. Spectral data for the 2-multiprenylphenols (III, V) and 4-multiprenylphenols (XI, XII) prepared in this way are recorded in Tables I and II.

By this procedure by isoprenylation of phenol were prepared 2-phytylphenol (IX), 2-geranylphenol (III, $n = 2$), 2-farnesylphenol (III, $n = 3$), and 2-nonaprenylphenol (III, $n = 9$). Similarly, by isoprenylation of guaiacol were prepared 2-geranyl-6-methoxyphenol (V, $n = 2$) and 2-farnesyl-6-methoxyphenol (V, $n = 3$). In each case the corresponding 4-multiprenyl isomer (XI, XII) was observed by thin layer chromatography; only those for which spectral data are given in Tables I and II were actually isolated and characterized. In the $BF_3$-catalyzed reaction of guaiacol with solanesol[16] the desired 2-nonaprenyl-6-methoxyphenol (V, $n = 9$) was present (tlc) in low yield, but was not isolated since the base-catalyzed procedure (see below) had been shown to be superior for the preparation of this compound.

**B. Base-Catalyzed Isoprenylation of Phenol and 2-Methoxyphenol (Guaiacol).**—A solution of 0.02 mole of phenol or 2-methoxyphenol in 5 ml of anhydrous benzene was added dropwise to a suspension of 0.025 mole of sodium hydride in 15 ml of dry benzene maintained under nitrogen. After 2 hr, a solution of 0.02 mole of the appropriate multiprenyl bromide in 10 ml of anhydrous benzene was added dropwise. After 24 hr, the reaction mixture was washed with water, and the organic phase was dried and evaporated. The residue was subjected to preparative thin layer chromatography as described. Spectral data for the 2-multiprenylphenols (III, V) and multiprenyl phenyl ethers prepared in this way are recorded in Tables I and II.

By this procedure were prepared 2-phytylphenol (IX), 2-decaprenylphenol (III, $n = 10$), 2-phytyl-6-methoxyphenol, 2-nonaprenyl-6-methoxyphenol (V, $n = 9$), and 2-decaprenyl-6-methoxyphenol (V, $n = 10$). In each case the corresponding O-multiprenyl isomer was shown to be present by thin layer chromatography on alumina as described. Spectral data for these O-multiprenyl derivatives isolated and characterized are recorded in Tables I and II.

**Registry No.**—III ($n = 2$), 10232-02-7; III ($n = 3$), 10232-03-8; III ($n = 9$), 10248-68-7; III ($n = 10$), 614-92-6; V ($n = 2$), 10232-05-0; V ($n = 3$), 10248-69-8; V ($n = 9$), 10232-06-1; V ($n = 10$), 7762-53-0; VIII, 10232-08-3; IX, 10232-09-4; X, 10232-10-7; XIa, 10232-11-8; XIb ($n = 2$), 10232-12-9; XIb ($n = 3$), 10232-13-0; XII ($n = 2$), 10232-14-1; XII ($n = 3$), 10232-15-2; XII ($n = 9$), 10232-16-3; 2-phytyl-6-methoxyphenol, 10232-17-4; 2-methoxyphenyl phytyl ether, 10232-18-5; 2-methoxyphenyl decaprenyl ether, 10232-19-6.

**Acknowledgment.**—This research was partially supported by funds from the Merck Sharp and Dohme Research Laboratories, Rahway, N. J., and we express our appreciation to Dr. Max Tishler. Solanesol and the intermediate, 3,7,11,15,19,23,27,31,35,39-decamethyltetraconta-6,10,14,18,22,26,30,34,38-nonaen-1-yn-3-ol[16] were generously provided by Dr. O. Isler and Professor Dr. Pl. A Plattner of F. Hoffmann-La Roche and Co. Ltd., Basel, Switzerland.

# The Grignard Addition to Steroidal Cyclic Ketals

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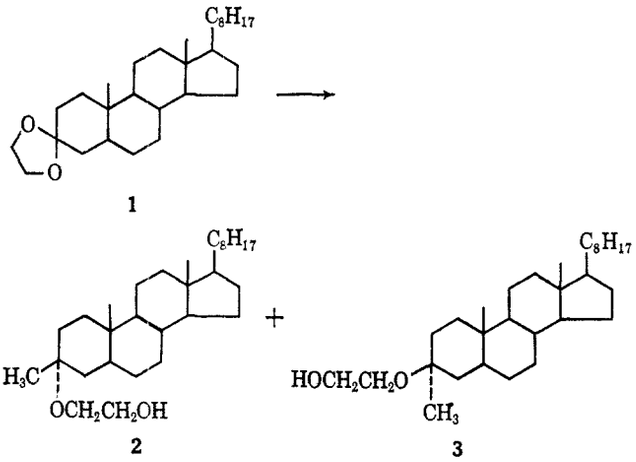
Grignard reagents, in boiling benzene solution, added to steroidal 3-, 17-, and 20-cyclic ketals, effected cleavage of the heterocyclic ring and formation of tertiary glycol ethers.

In a previous communication[1] we described the Grignard addition to cyclic ketals and acetals in boiling benzene solution. The products of such reactions with cyclic ketals are tertiary glycol ethers, and with cyclic acetals the products are secondary glycol ethers. Similar reactions have been reported by Feugeas[2] on cyclic ketals of halogenated saturated ketones, by Zepter[3] on C-20 steroidal ethylene ketals, by Bible[4] on the ethylene ketal of estrone methyl ether, and by Blomberg, *et al.*,[5] and Shostakovskii, *et al.*,[6] on 2-alkyl-1,3-dioxolanes. We wish to report the results of our work in the steroid series.

Ketals, generally, are stable under Grignard reaction conditions.[7] However, their stability is reduced when the reaction is performed in hot benzene instead of ether, which is the usual solvent used for such Grignard reactions,[8] and the heterocyclic ring is cleaved. Thus, by using benzene as a solvent we were able to add Grignard reagents at the C-3, C-17, and C-20 positions of the steroid molecule and concomittantly to open the ketal rings at these positions.

Reaction of cholestan-3-one ethylene ketal (**1**) with methylmagnesium bromide in boiling benzene solution gave two isomeric glycol ethers which were separated by chromatography on alumina and identified as 3$\beta$-methyl-3$\alpha$-(2-hydroxyethoxy)cholestane (**2**), and 3$\alpha$-methyl-3$\beta$-(2-hydroxyethoxy)cholestane (**3**). That **2** was the axial glycol ether and **3** the equatorial glycol ether was determined by the ease of elution of **2** from the chromatographic column and by examination of the

(1) R. A. Mallory, S. Rovinski, and I. Scheer, *Proc. Chem. Soc.*, 416 (1964).
(2) A. Feugeas, *Bull. Soc. Chim. France*, 2568 (1963).
(3) R. Zepter, *J. Prakt. Chem.*, **26**, 174 (1964).
(4) R. H. Bible, Jr., U. S. Patent 3,081,315 (1963); *Chem. Abstr.*, **59**, 10180b (1963).
(5) C. Blomberg, A. O. Vreugdenhil, and T. Homsma, *Rec. Trav. Chim.*, **72**, 355 (1963).
(6) M. F. Shostakovskii, A. S. Atavin, and B. A. Trofinov, *Zh. Obshch. Khim.*, **34**, 2088 (1964).
(7) C. Djerassi, "Steroid Reactions," Holden-Day, Inc., San Francisco, Calif., 1963, Chapter I.
(8) According to Zepter[3] Grignard reagents form a complex both with ether and the dioxolane ring. However, when benzene is used as a solvent, the dioxolane ring is free of competition, and it can thus be cleaved.



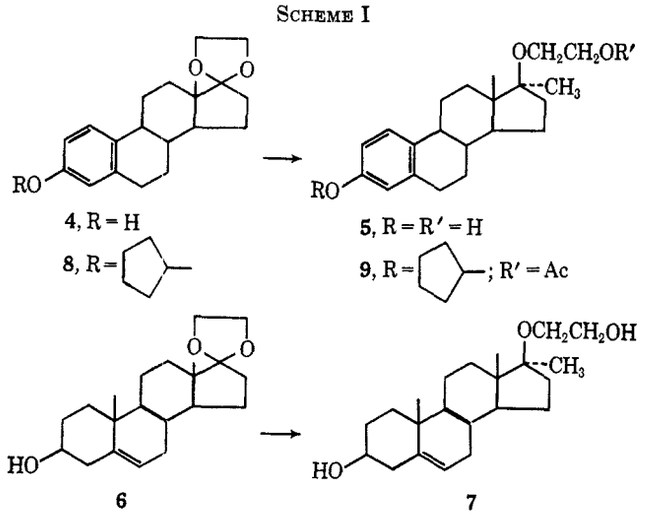
1

2 3

nmr spectra of the compounds and comparison of the C-19 methyl shift with model compounds. In both **2** and 3$\beta$-methylcholestan-3$\alpha$-ol the signal of the C-19 protons appears at 46 cps ($\delta$ 0.77), whereas in **3** and 3$\alpha$-methylcholestan-3$\beta$-ol, *i.e.*, the equatorial glycol ether and the equatorial alcohol, respectively, the resonance of the C-19 protons is slightly deshielded and appears at 50 cps ($\delta$ 0.83).

The reaction of methylmagnesium bromide with cyclic ketals at the C-17 position gave only one product. Thus the ketal derivatives of estrone (**4**), dehydroepiandrosterone (**6**), and 3-cyclopentoxyestrone (**8**) gave the corresponding 17$\alpha$-methyl-17$\beta$-(2-hydroxyethoxy)glycol ethers **5**, **7**, and **9**, respectively, attack of the Grignard reagent being assumed from the less hindered $\alpha$ side. (See Scheme I.)

SCHEME I

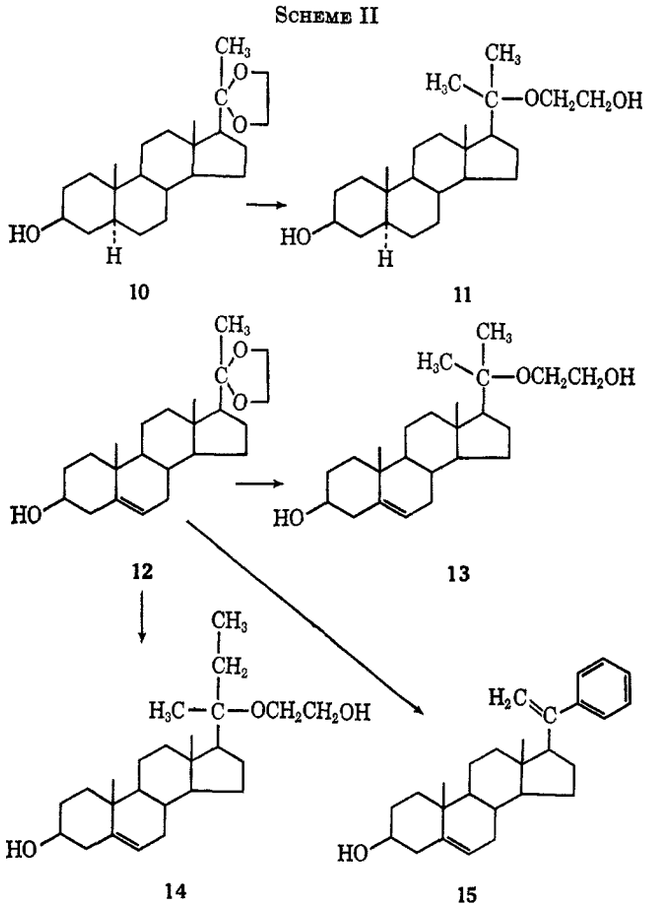


4, R = H
8, R =
5, R = R′ = H
9, R = ; R′ = Ac

6 7

Addition at the C-20 position also occurred under the same reaction conditions. Allopregnan-3$\beta$-ol-20-one ethylene ketal (**10**) and pregn-5-en-3$\beta$-ol-20-one ethylene ketal (**12**) gave the corresponding glycol ethers **11** and **13**, respectively. Ethylmagnesium bromide added to **12** to give the tertiary glycol ether (**14**), whereas addition of a bulkier Grignard reagent such as phenylmagnesium bromide caused dehydration at C-20 giving rise to 20-phenylpregna-5,20-dien-3$\beta$-ol (**15**) [$\lambda_{max}^{EtOH}$ 232 m$\mu$ ($\epsilon$ 8500)] and with appropriate nmr signals for a C-20 vinylidene group at $\delta$ 5.11 (doublet, $J$ = 6 cps). (See Scheme II.) Similarly, dehydration occurred when methylmagnesium bromide was added to pregna-5,16-dien-3$\beta$-ol-20-one 3-acetate 20-ethylene ketal (**16**) thereby yielding the known[9] bisnorchola-5,-16,20-trien-3$\beta$-ol acetate (**17**), $\lambda_{max}^{EtOH}$ 239 m$\mu$ ($\epsilon$ 18,961).

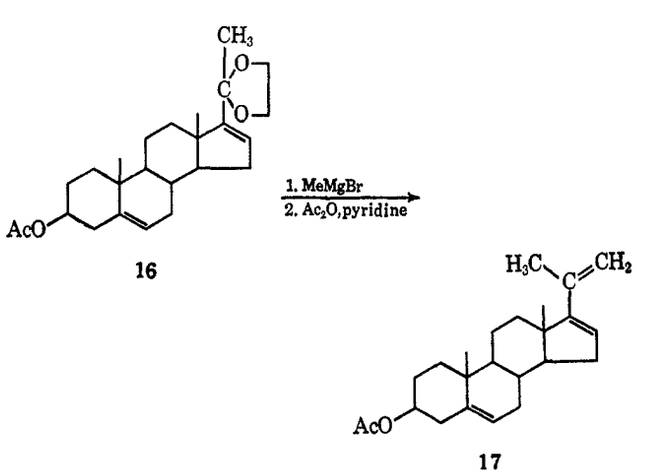
SCHEME II



10 11

12 13

14 15

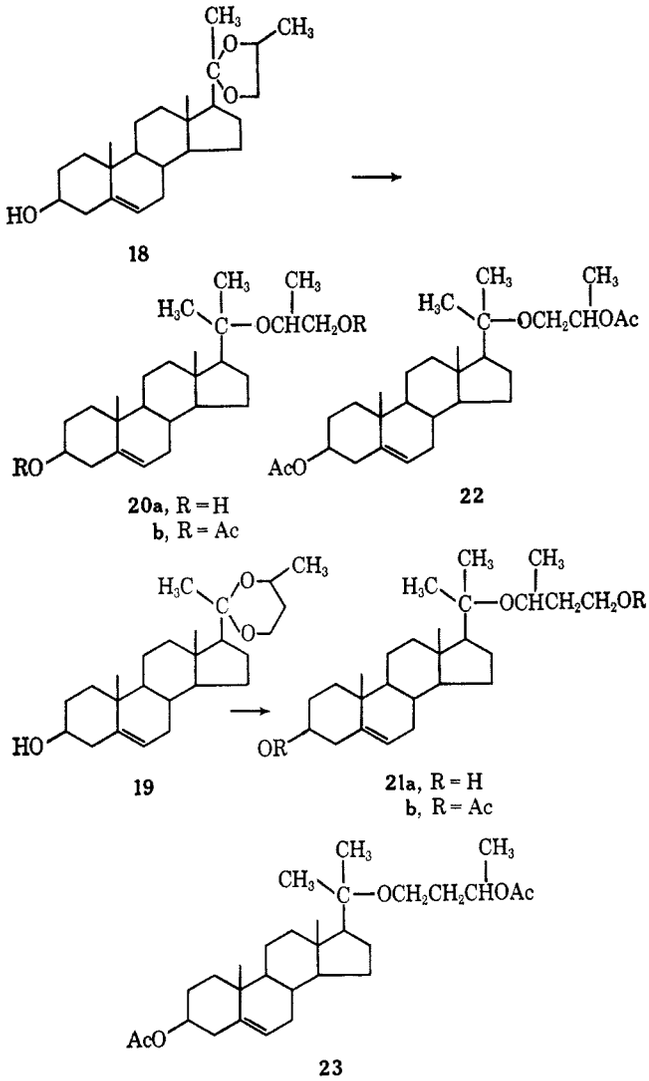


16 17

Cleavage of ketals with Grignard reagents was not limited to simple 1,3-dioxolanes. Variously substituted 1,3-dioxolanes as well as 1,3-dioxanes were cleaved. Thus, the 4-methyl-1,3-dioxolane derivative of pregnenolone (**18**) and the 4-methyl-1,3-dioxane analog (**19**) upon treatment with methylmagnesium bromide afforded 20-methyl-20-($\beta$-hydroxyisopropoxy)-pregn-5-en-3$\beta$-ol (**20a**) and 20-methyl-20-(3-hydroxy-1-methylpropoxy)pregn-5-en-3$\beta$-ol (**21a**), respectively. (See Scheme III.) Ring opening to the primary hydroxyl compounds was demonstrated by nmr analysis

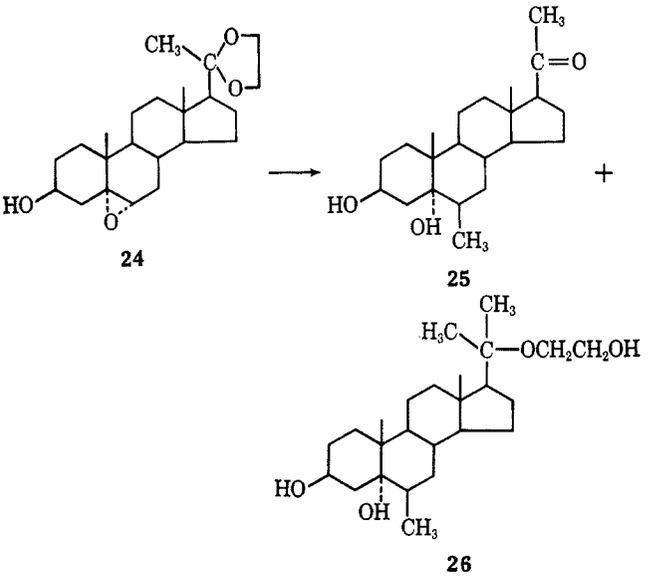
(9) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

SCHEME III



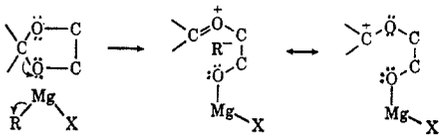

of the derived diacetates (**20b** and **21b**).[10] The alternative structures for the heterocyclic, ring-opened compounds may be represented as **22** and **23**. Both **20b** and **21b** require the presence of two protons next to the acetoxy group on the side chain and one methine proton next to an oxygen in the form of an ether linkage whereas the reverse is true in alternative structures **22** and **23**. It would also be expected that the resonance of a methine proton next to an acetoxy function would be somewhere near $\delta$ 5.30 as shown in the model compound methyl $\beta$-acetoxybutyrate,[11] whereas the resonance of a methine proton adjacent to an ether linkage would be somewhere near 3.55 as observed with 3-methoxybutanol-1.[12] Since the appropriate nmr signals in diacetate **21b** are a triplet at $\delta$ 4.05 corresponding to two methylene protons adjacent to an acetoxy function and a sextet at 3.75 owing to a methine proton adjacent to an ether linkage, we interpret this result as favoring structure **21a** rather than **23**. In **20b** the chemical-shift difference between the methine hydrogen and the methylene hydrogen was small, resulting in one three-proton signal at $\delta$ 3.89. Since no signal was observed near $\delta$ 5.00 we interpret this evidence as favoring primary hydroxyl compound **20a**.[13]

The products were more varied when two groups capable of reacting with Grignard reagents were present in the molecule. Reaction of 5$\alpha$,6$\alpha$-epoxypregnan-3$\beta$-ol-20-one ethylene ketal (**24**) with methylmagnesium bromide gave two products, the known 6$\beta$-methylpregnane-3$\beta$,5$\alpha$-diol-20-one[14] (**25**) and 6$\beta$,20-dimethyl-20-(2-hydroxyethoxy)pregnane-3$\beta$,5$\alpha$-diol (**26**). The addition of methylmagnesium bromide to the bisethylene ketal of progesterone (**27**) gave a complex mixture from which five crystalline products

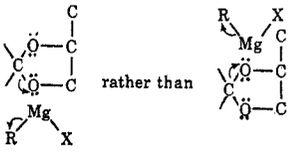



were isolated by chromatography on alumina (after regeneration of carbonyl groups by acid hydrolysis) and identified as the following: the known bisnorchola-4,20-dien-3-one[15] (**28**), $\lambda_{max}^{EtOH}$ 240 m$\mu$ ($\epsilon$ 16,500), appropriate nmr signals for the C-20 vinylidene group at $\delta$ 4.76 (doublet, $J$ = 8 cps) and for the C-20 methyl group at 1.76; 3$\beta$-methyl-3$\alpha$-(2-hydroxyethoxy)bisnorchola-5,20-diene[16] (**29**), nmr signals at $\delta$ 1.04 (C-19 protons), 4.76 (doublet, $J$ = 7 cps, the vinylidene group at C-20), and 1.76 (C-20 methyl group);

(13) If one assumes the basic mechanism of the addition is



then the formation of **20** and **21** rather than **22** and **23** is apparent. The Grignard reagent would tend to favor attack on the less hindered ketal oxygen of compounds **18** and **19** thus opening the ring to form primary alcohols, *i.e.*




(14) L. Miramontes, P. Aguinaco, and M. A. Romero, *J. Am. Chem. Soc.*, **82**, 6153 (1960).

(15) C. Meystre and K. Miesher, *Helv. Chim. Acta*, **32**, 1758 (1949).

(16) Only one of the possible isomers was isolated. From the resonance of the C-19 methyl protons in the nmr spectrum the $\alpha$ configuration was assigned to the glycol chain at the 3 position in **29**, **30**, and **32**, since a $\beta$ configuration is expected to shift the signal of the C-19 protons further downfield.

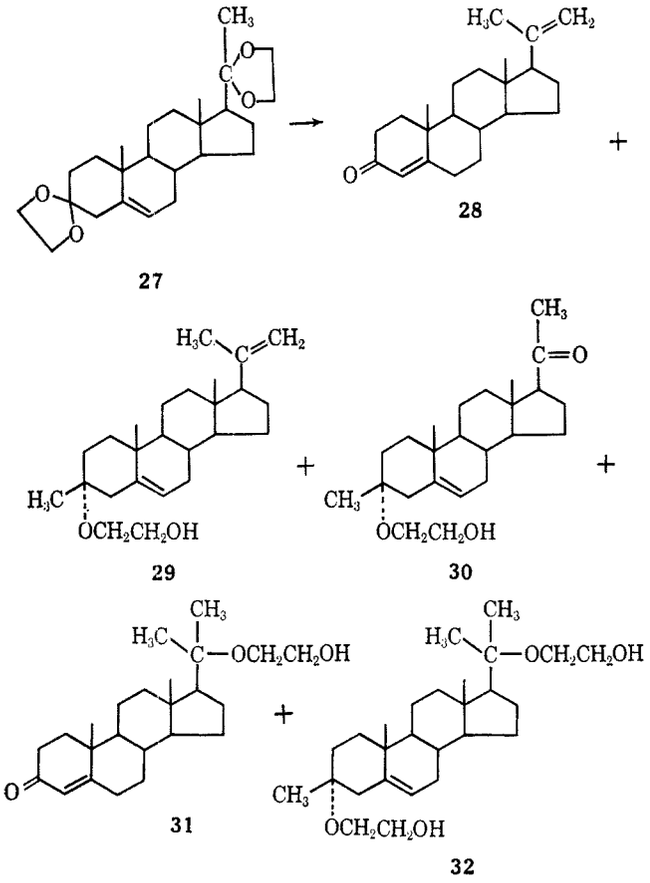
(10) We are grateful to Dr. N. S. Bhacca of Varian Associates for the determination and interpretation of the nmr spectra of these two diacetates.

(11) Varian NMR Spectra Catalog, Varian Associates, Palo Alto, Calif., 1966, Spectrum No. 182.

(12) Reference 11, Spectrum No. 120.

3β-methyl-3α-(2-hydroxyethoxy)-5-pregnen-20-one[16] (**30**), nmr signals at δ 1.04 (C-19 protons), 2.10 (C-20 methyl groups); 20-methyl-20-(2-hydroxyethoxy)-pregn-4-en-3-one (**31**), $\lambda_{max}^{EtOH}$ 240 mμ (ε 16,500); and 3β,20-dimethyl-3α,20-di(2-hydroxyethoxy)pregn-5-ene[16] (**32**), nmr signals at δ 1.04 (C-19 protons). (See Scheme IV.)

SCHEME IV




Some reactions of the glycol ethers are noteworthy. The glycol chain was stable under basic conditions thus permitting Oppenauer oxidations of compounds **7** and **13** to corresponding unsaturated ketones **33** and **31** (identical with one of the products obtained from the action of methylmagnesium bromide on **27**). The primary hydroxyl function of the glycol reacted in a normal fashion. Diethylaminohydrochloride **35** was obtained from **31** *via* intermediate tosylate **34**. The glycol chain could be cleaved under mild conditions. Thus, **13** was converted to the known 5-allo-20-methyl-pregnan-3β-ol[17] (**36**) by hydrogenation over platinum in acetic acid. (See Scheme V.)

The Grignard addition to nonsteroidal cyclic acetals and ketals will be reported in subsequent papers.

## Experimental Section

Melting points were determined on a Fisher-Jones apparatus and are uncorrected. Infrared spectra were recorded with a Beckman IR-5; nmr spectra were obtained with the Varian A-60 spectrometer using deuteriochloroform solutions with tetramethylsilane as an internal standard; ultraviolet spectra were determined in ethanol solution, unless otherwise noted, with a Cary Model 11 recording spectrophotometer. Rotations were measured at 25° in approximately 1% solutions in chloroform unless otherwise noted.

**General Procedure for Preparing Ketals.**—A solution of 0.5 mole of a steroid ketone, 0.75 mole of a glycol, and 0.3 to 1.5 g of *p*-toluenesulfonic acid monohydrate in 300–500 ml of dry benzene was boiled under reflux from 5 to 72 hr, cooled, and then stirred while adding an excess of ammonium hydroxide and 200 ml of water. The aqueous layer was discarded. The organic layer and any precipitate which was present were combined and concentrated to dryness *in vacuo*. The solid residue was crystallized from a suitable solvent.

**3-β-Methyl-3α-(2-hydroxyethoxy)cholestane (2).**—A mixture of 20 g (0.046 mole) of cholestanone ethylene ketal[18] (**1**), 2000 ml of dry benzene, and 200 ml of 3 *M* methylmagnesium bromide in ether was boiled under reflux with stirring for 16 hr, cooled to 5°, and treated with 1000 ml of a 25% aqueous ammonium acetate solution. The benzene layer was separated, dried over anhydrous magnesium sulfate, and concentrated to dryness *in vacuo*. The oily residue was chromatographed on alumina (Woelm, neutral, grade 1). The fraction eluted with 0.5% methanol in ether was crystallized from acetone to yield 7.87 g of **2**: mp 104.5–105°; $[\alpha]_D$ +25°; nmr signals at δ 0.67 (C-18 protons), 0.77 (C-19 protons), 0.83, 0.92, 1.32 (methyl groups), 3.34 (triplet, $J$ = 5 cps), and 3.62 (triplet, $J$ = 5 cps) (the two methylene groups of the glycol chain).

*Anal.* Calcd for $C_{30}H_{54}O_2$: C, 80.65; H, 12.18. Found: C, 80.48; H, 12.16.

The **carbamate** of **2** crystallized from ether–pentane: mp 143–144°. *Anal.* Calcd for $C_{31}H_{55}NO_3$: C, 76.02; H, 11.32; N, 2.86. Found: C, 75.91; H, 11.15; N, 2.80.

**3α-Methyl-3β-(2-hydroxyethoxy)cholestane (3).**—Elution of the column from the preparation of **2** with 2% methanol in ether gave 7.84 g of compound **3** after crystallization from acetone: mp 104.5–105° (resolidified and then remelts at 119°); $[\alpha]_D$ +34°; nmr signals at δ 0.69 (C-18 protons), 0.83 (C-19 protons), 0.93 and 1.23 (methyl groups), 3.72 (broad, the two methylene groups of the glycol chain). A mixture with **2** melted below 90°. Examination of the infrared spectra of compounds **2** and **3** confirmed the nonidentity of these isomers.

*Anal.* Calcd for $C_{30}H_{54}O_2$: C, 80.65; H, 12.18. Found: C, 80.60; H, 12.18.

The **carbamate** of **3** crystallized from acetone: mp 180–180.5°. *Anal.* Calcd for $C_{31}H_{55}NO_3$: C, 76.02; H, 11.32; N, 2.86. Found: C, 75.98; H, 11.12; N, 3.09.

**17α-Methyl-17β-(2-hydroxyethoxy)estra-1,3,5(10)-trien-3-ol (5).**—Five grams (0.0159 mole) of estrone ethylene ketal[19] was boiled under reflux for 24 hr with methylmagnesium bromide (sixfold excess) in benzene. The crude oil which was obtained upon treatment of the reaction mixture as described for the preparation of **2** (above) was chromatographed on silicic acid. Elution with 35% ethyl acetate in benzene gave 2.35 g of **5** after crystallization from benzene: mp 152.5–153.5°, $[\alpha]_D$ +44°.

*Anal.* Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.60; H, 9.16.

The **acetate** of **5** crystallized from methanol: mp 94.5–95°. *Anal.* Calcd for $C_{23}H_{32}O_4 \cdot 0.5H_2O$: C, 72.41; H, 8.72. Found: C, 72.41; H, 8.09.

**17α-Methyl-17β-(2-acetoxyethoxy)estra-1,3,5(10)-trien-3-ol Cyclopentyl Ether (9).**—Reaction of 12.7 g (0.332 mole) of estrone cyclopentyl ether ethylene ketal (**8**) with methylmagnesium bromide (as described above) afforded an oily product which was acetylated to yield 2.99 g of **9** melting at 100–100.5°, $[\alpha]_D$ −60°.

*Anal.* Calcd for $C_{28}H_{40}O_4$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.09.

**17α-Methyl-17β-(2-hydroxyethoxy)androst-5-en-3β-ol (7).**—Fifty grams (0.15 mole) of dehydroepiandrosterone ethylene ketal[20] treated with methylmagnesium bromide for 72 hr (see preparation of **2**) gave 19.6 g of **7**: mp 165–167° from acetone; $[\alpha]_D$ −64°; nmr signals at δ 0.90 (C-18 protons), 1.05 (C-19 protons), 1.22 (C-17 methyl group), 3.51 (multiplet for the two methylene groups of the glycol), and 5.30 (the vinyl hydrogen at C-6).

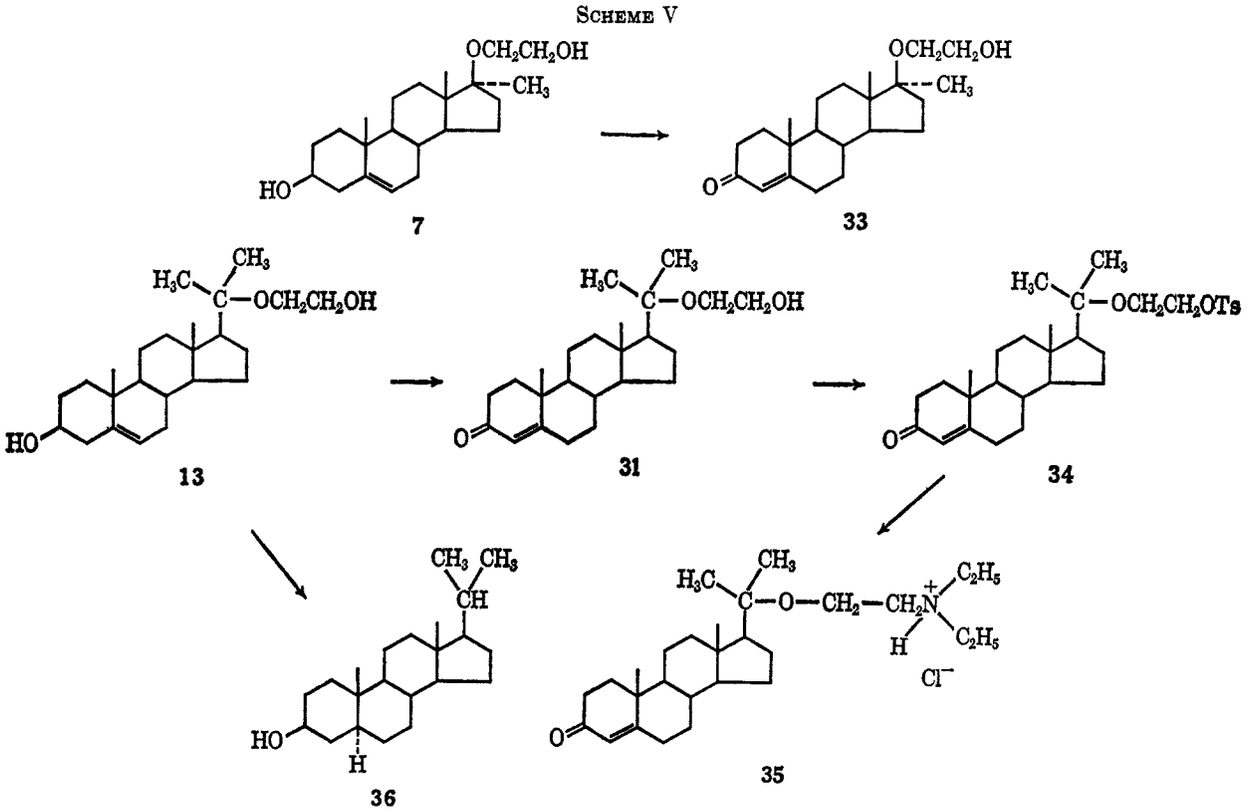
(17) J. P. Dusza and W. Bergmann, *J. Org. Chem.*, **25**, 79 (1960).

(18) H. J. Dauben, B. Löken, and H. J. Ringold, *J. Am. Chem. Soc.*, **76**, 1359 (1954).

(19) G. C. Buzby, Jr., R. A. Edgren, J. A. Fisher, G. A. Hughes, R. C. Jones, K. Ledig, T. W. Patteson, R. Rees, H. Smith, L. L. Smith, D. M. Teller, and G. R. Wendt, *J. Med. Chem.*, **7**, 755 (1964).

(20) S. Julia, C. Neuville, and M. Davin, *Bull. Soc. Chim. France*, 297 (1960).

SCHEME V




*Anal.* Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.69; H, 10.46.

**17α-Methyl-17β-(2-hydroxyethoxy)androst-4-en-3-one (33).**—A solution of 10 g (0.0287 mole) of **7** in 3 l. of toluene and 400 ml of cyclohexanone was dried by distillation of 250 ml of solvent, then 400 ml (0.12 mole) of a 6% solution of aluminum isopropylate in toluene was added, and the mixture was boiled under reflux for 25 min with stirring. The reaction mixture was cooled, diluted with water, and acidified with 5% hydrochloric acid; the organic layer was separated and dried over potassium carbonate and concentrated to dryness *in vacuo*. The residue was dissolved in benzene and chromatographed on 300 g of silicic acid. The fraction eluted with 15% ethyl acetate in benzene crystallized from acetone to yield 4.0 g of **33**: mp 165.5–166.5°, $[\alpha]_D$ +86°, $\lambda_{max}$ 240 mμ (ε 16,200).

*Anal.* Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.13; H, 9.92.

**20-Methyl-20-(2-hydroxyethoxy)allopregnan-3β-ol (11).**—Treatment of 3 g (0.0083 mole) of allopregnan-3β-ol-20-one ethylene ketal[21] (**10**) with methylmagnesium bromide as described for the preparation of **2** gave 2.15 g of **11** as white crystals from methylene chloride: mp 197.5–199.5°, $[\alpha]_D$ +6° (pyridine).

*Anal.* Calcd for $C_{24}H_{42}O_3$: C, 76.14; H, 11.18. Found: C, 76.02; H, 10.92.

The **diacetate** (acetic anhyride–pyridine, room temperature overnight) crystallized from methanol: mp 99–101.5°. *Anal.* Calcd for $C_{28}H_{46}O_5$: C, 72.69; H, 10.02. Found: C, 72.99; H, 10.03.

**20-Methyl-20-(2-hydroxyethoxy)pregn-5-en-3β-ol (13).**—In a similar fashion **20 methyl-20-(2-hydroxyethoxy)pregn-5-en-3β-ol** (**13**) was obtained from pregn-5-en-3β-ol-20-one ethylene ketal[22] (**12**) as white crystals from chloroform: mp 190–192°, $[\alpha]_D$ −44° (pyridine).

*Anal.* Calcd for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.41; H, 10.62.

The **diacetate** crystallized from methanol: mp 74.5–75°. *Anal.* Calcd for $C_{28}H_{44}O_5$: C, 73.00; H, 9.63. Found: C, 73.11; H, 9.54.

**20-Methyl-20-(2-hydroxyethoxy)pregn-4-en-3-one (31).**—As described above for the preparation of **33**, 10 g (0.0266 mole) of **13** gave 5.77 g of **31** which crystallized from ethyl acetate: mp 158–159°; $[\alpha]_D$ +81°; $\lambda_{max}$ 241.5 mμ (ε 16,172); nmr signals at δ 0.88 (C-18 protons), 1.20 (C-19 protons and one of the two methyl groups at C-20), 1.27 (C-20 methyl group), 3.56 (multiplet, methylene groups of the glycol), 5.71 (C-4 vinyl hydrogen).

*Anal.* Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.94; H, 10.09.

The **acetate** melted at 103–104° after crystallization from methanol–water. *Anal.* Calcd for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 74.76; H, 9.52.

The **semicarbazone** of the acetate melted at 208–210°. *Anal.* Calcd for $C_{27}H_{43}N_3O_4$: C, 68.46; H, 9.15. Found: C, 68.41; H, 9.19.

Treatment of **31** with *p*-toluenesulfonyl chloride in cold pyridine gave a crystalline **tosylate** melting at 121–123° which was treated with diethylamine in the usual way to give **20-methyl-20-(2-diethylaminoethoxy)pregn-4-en-3-one hydrochloride (35)**, mp 189–190° (from acetone).

*Anal.* Calcd for $C_{28}H_{48}ClNO_2$: C, 72.14; H, 10.38; N, 3.01. Found: C, 72.11; H, 10.28; N, 2.91.

**20a-Ethyl-20-(2-hydroxyethoxy)pregn-5-en-3β-ol (14).**—Reaction of **12** with ethylmagnesium bromide for 3 hr and work-up in the usual way gave **20a-ethyl-20-(2-hydroxyethoxy)pregn-5-en-3β-ol**[23] (**14**) which was crystallized from methylene chloride: mp 175–178°, $[\alpha]_D$ −47°.

*Anal.* Calcd for $C_{25}H_{42}O_3$: C, 76.87; H, 10.84. Found: C, 76.84; H, 10.88.

The **diacetate** melted at 77–78°. *Anal.* Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.57; H, 9.79.

**20-Phenylpregna-5,20-dien-3β-ol (15).**—Treatment of 5 g (0.0139 mole) of **12** with phenylmagnesium bromide for 5 hr in the usual way and normal work-up yielded 2.57 g of **15** as crystals from methanol: mp 150–151°; $[\alpha]_D$ +18°; $\lambda_{max}$ 232 mμ (ε 8500); nmr signals at δ 0.59 (C-18 protons), 0.95 (C-19 protons), 5.11 (doublet, $J$ = 6 cps, C-20 vinylidene group), 5.31 (C-6 vinyl hydrogen), 7.30 (C-20 phenyl group).

*Anal.* Calcd for $C_{27}H_{36}O$: C, 86.11; H, 9.64. Found: C, 86.02; H, 9.62.

The **acetate** melted at 111–112°: $[\alpha]_D$ +21°, $\lambda_{max}$ 232 mμ (ε 9000). *Anal.* Calcd for $C_{29}H_{38}O_2$: C, 83.21; H, 9.15. Found: C, 83.61; H, 9.24.

(21) W. Schutt and C. Tamm, *Helv. Chim. Acta*, **41**, 1730 (1958).

(22) W. J. Adams, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and B. Sturgeon, *J. Chem. Soc.*, 4490 (1956).

(23) The absolute stereochemistry at C-20 has not been determined. However, assuming backside attack of the Grignard reagent, the ethyl group would add to place the methyl group in the β position. However, in lieu of absolute proof the ethyl is designated "a" rather than α.

**Bisnorchola-5,16,20-trien-3β-ol Acetate (17).**—Pregna-5,16-dien-3β-ol-20-one acetate ethylene ketal (16)[24] upon treatment with methylmagnesium bromide gave an oily product whose infrared spectrum indicated the presence of a vinylidene group ($\nu_{max}$ at 825 $cm^{-1}$) and whose ultraviolet absorption ($\lambda_{max}$ 239 mμ) indicated a conjugated system. Acetylation of the oil gave a crystalline product (from methanol) which proved to be **17**: mp 126.5–127.5°; $[\alpha]D$ −78°; $\lambda_{max}$ 238 mμ (ε 18,960) (isooctane) [lit.[9] mp 124.5–126°, $[\alpha]D$ −76°, $\lambda_{max}$ 239 mμ (16,220)]; nmr signals at δ 1.00 (C-19 protons), 1.27 (C-18 protons), 1.92 (C-20 methyl group), 2.06 (C-3 acetoxyl protons), 5.00 (doublet, $J$ = 10 cps, C-20 vinylidene group), 5.43 (C-6 vinyl hydrogen), 5.80 (C-16 vinyl hydrogen).

*Anal.* Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.31; H, 9.42.

**20-Methyl-20-(β-hydroxyisopropoxy)pregn-5-en-3β-ol (20a).**—Methylmagnesium bromide was treated with pregn-5-en-3β-ol-20-one 1,2-propylene ketal (**18**) (mp 147–149°; C, 77.16; H, 10.82) to give **20a** as crystals from methylene chloride: mp 213–216°, $[\alpha]D$ −52°.

*Anal.* Calcd for $C_{25}H_{42}O_3$: C, 76.87; H, 10.84. Found: C, 76.96; H, 10.80.

The **diacetate** (**20b**) crystallized from acetone, melted at 111–113°: nmr signals at δ 0.88 (C-18 protons), 1.01 (C-19 protons), 1.11, 1.23, 1.27 (methyl groups), 2.04, 2.10 (acetoxyls), 3.89 (the methine proton next to the ether linkage and the two methylene protons adjacent to the acetoxyl function on the side chain), 5.36 (C-6 vinyl hydrogen).

*Anal.* Calcd for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 73.34; H, 9.76.

**20-Methyl-20-(3-hydroxy-1-methylpropoxy)pregn-5-en-3β-ol (21a).**—Pregn-5-en-3β-ol-20-one 1,3-butylene ketal (**19**) (mp 161–163°; C, 77.28; H, 10.64) was treated with methylmagnesium bromide to yield **21a**: mp 217–220° (crystallized from methylene chloride), $[\alpha]D$ −14° (pyridine).

*Anal.* Calcd for $C_{26}H_{44}O_3$: C, 77.17; H, 10.96. Found: C, 77.16; H, 10.82.

The **diacetate**, (**21b**), obtained as crystals from methanol, melted at 103°: nmr signals at δ 0.83 (C-18 protons), 1.01 (C-19 protons), 1.08, 1.17, 1.25 (methyl groups), 2.04 (acetoxyl groups), 3.75 (sextet, the methine proton adjacent to the ether linkage), 4.05 (triplet, the methylene group next to the acetoxyl function on the side chain), 5.40 (C-6 vinyl hydrogen).

*Anal.* Calcd for $C_{30}H_{48}O_5$: C, 73.73; H, 9.90. Found: C, 73.83; H, 9.82.

**6β,20-Dimethyl-20-(2-hydroxyethoxy)pregnane-3β,5α-diol (26).**—Chromatography on silicic acid of the residue obtained from the work-up of the reaction of 5 g (0.0133 mole) of 5α,6α-epoxypregnan-3β-ol-20-one ethylene ketal (**24**, mp 197–199°; C, 73.52; H, 9.79), with methylmagnesium bromide gave two major fractions of crystalline material. Elution with 20% ethyl acetate in benzene gave 1.6 g of a crystalline material melting at 213–215°, $[\alpha]D$ +57°, which was shown to be **6β-methylpregnan-3β,5α-diol-20-one** (**25**) (*vide infra*) (lit.[14] mp 208–211°, $[\alpha]D$ +59). Elution with 50% ethyl acetate in benzene gave 1.9 g of **26** which crystallized from acetone: mp 185.5–186.5°, $[\alpha]D$ +61° (methanol).

*Anal.* Calcd for $C_{25}H_{44}O_4$: C, 73.48; H, 10.85. Found: C, 73.47; H, 10.61.

**Reaction of Methylmagnesium Bromide with the Bisethylene Ketal of Progesterone (27).**—Treatment of 20 g (0.0479 mole) of **27**[25] with a sixfold excess of methylmagnesium bromide for 16 hr in the usual manner afforded an oily residue which was evidently a complex mixture of various products. The oil was treated with 90% methanol containing a trace amount of *p*-toluenesulfonic acid to hydrolyze unreacted ketal. Chromatography on silicic acid of the resultant hydrolyzed mixture gave five crystalline products. Elution with 5% ethyl acetate in benzene yielded 1.99 g of **bisnorchola-4,20-dien-3-one** (**28**): mp 159–160°; $[\alpha]D$ +109; $\lambda_{max}$ 240 mμ (ε 16,500) (lit.[15] mp 155–160°, $[\alpha]D$ +105°); nmr signals at δ 0.66 (C-18 protons), 1.20 (C-19 protons), 1.73 (C-20 methyl group), 4.76 (doublet, $J$ = 8 cps, C-20 vinylidene group), 5.75 (C-4 vinyl hydrogen).

*Anal.* Calcd for $C_{22}H_{32}O$: C, 84.56; H, 10.32. Found: C, 84.73; H, 10.55.

Further elution with 10% ethyl acetate in benzene gave 2.1 g of **3β-methyl-3α-(2-hydroxyethoxy)bisnorchola-5,20-diene** (**29**) (from acetone) which melted at 134.5–135.5°: $[\alpha]D$ −30° (methanol); nmr signals at δ 0.62 (C-18 protons), 1.04 (C-19 protons), 1.10 (C-3 methyl group), 1.73 (C-20 methyl group), 3.60 (multiplet, the two methylene groups of the glycol chain), 4.80 (C-20 vinylidene group), 5.30 (C-6 vinyl hydrogen).

*Anal.* Calcd for $C_{25}H_{40}O_2$: C, 80.59; H, 10.82. Found: C, 80.64; H, 10.77.

Continued elution with 15% ethyl acetate in benzene yielded 2.34 g of crystalline **3β-methyl-3α-(2-hydroxyethoxy)pregn-5-en-20-one** (**30**): mp 168–168.5°, $[\alpha]D$ +44° (methanol); nmr signals at δ 0.66 (C-18 protons), 1.03 (C-19 protons), 1.1 (C-3 methyl group), 2.10 (C-20 methyl group), 3.60 multiplet (glycol methylene groups), 5.25 (C-6 vinyl hydrogen).

*Anal.* Calcd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23. Found: C, 76.80; H, 10.07.

The fraction eluted with 20% ethyl acetate in benzene gave 2.78 g of **31**, identical (infrared, nmr, melting point, optical rotation) with the material described above as obtained from Oppenauer oxidation of compound **13**.

The fifth product was obtained by elution with 25% ethyl acetate in benzene and crystallization from acetone. The crystalline **3β,20-dimethyl-3α,20-di(2-hydroxyethoxy)pregn-5-ene** (**32**, 4.58 g) melted at 152–153°: $[\alpha]D$ −16.5° (methanol); nmr signals at δ 0.83 (C-18 protons), 1.02 (C-19 protons), 1.10 (C-3 methyl group), 1.18, 1.27 (the two methyl groups at C-20), 3.62 (multiplet, the glycol methylenes), 5.71 (C-6 vinyl hydrogen).

*Anal.* Calcd for $C_{27}H_{46}O_4$: C, 74.61; H, 10.67. Found: C, 74.49; H, 10.52.

**Bisnorcholan-3β-ol (36).**—A mixture of 1.13 g of **13**, 0.15 g of Adams catalyst, and 60 ml of acetic acid was stirred in a hydrogen atmosphere for 3 hr at room temperature and pressure. Crystallization from acetone gave 0.74 g of **36** melting at 151°: $[\alpha]D$ +7° (lit.[17] mp 145–146°, $[\alpha]D$ +9.3°), nmr signals at δ 0.68 (C-18 protons), 0.82 (C-19 protons), 0.92, 1.01 (*gem*-dimethyl at C-20), 1.72 (C-3 hydroxyl), 3.46 (C-3 hydrogen).

*Anal.* Calcd for $C_{22}H_{38}O$: 82.95; H, 12.03. Found: C, 82.86; H, 11.78.

The **acetate** (from methanol) melted at 127–127.5°: $[\alpha]D$ 0° (lit.[17] mp 122–123°, $[\alpha]D$ −1.9°). *Anal.* Calcd for $C_{24}H_{40}O_2$: C, 79.94; H, 11.18. Found: C, 79.79; H, 11.21.

**Registry No.**—**2**, 10060-15-8; carbamate of **2**, 10026-28-5; **3**, 10026-29-6; carbamate of **3**, 7780-44-1; **5**, 10026-30-9; **9**, 10026-31-0; **7**, 6173-94-0; **33**, 10026-33-2; **11**, 7780-45-2; diacetate of **11**, 10026-34-3; **13**, 10028-40-7; diacetate of **13**, 6193-90-4; **31**, 7780-47-4; acetate of **31**, 7780-48-5; semicarbazone of the acetate of **31**, 10026-35-4; **35**, 7780-49-6; **14**, 10083-91-7; diacetate of **14**, 7785-06-0; **15**, 10039-00-6; acetate of **15**, 10026-36-5; **17**, 7780-50-9; **20a**, 10039-01-7; **20b**, 10039-02-8; **21a**, 10026-37-6; **21b**, 10026-38-7; **26**, 6193-91-5; **28**, 7676-45-1; **29**, 7780-53-2; **30**, 7780-54-3; **32**, 10039-03-9; **36**, 7780-55-4; acetate of **36**, 7780-56-5.

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(24) S. Bernstein, M. Heller, and S. Stolar, *J. Am. Chem. Soc.*, **76**, 5674 (1954).

(25) F. Sondheimer, M. Velasco, and G. Rosenkranz, *ibid.*, **77**, 192 (1955).