3-(trifluoroacetyl)-*d*-camphor (H(facam)), 3-(heptafluorobutyryl)-*d*-camphor (H(hfbc)), and 4,4,4-trifluoro-1-(2-thienyl)-1,3-butanedione (H(tta)) were obtained from Aldrich Chemical Co., Milwaukee, WI.

Synthesis. The $Ln(fod)_3$, $Ln(facam)_3$, $Ln(hfbc)_3$, $Ln(hfth)_3$, and $Ln(tta)_3$ chelates were synthesized and purified according to the procedure reported by Springer et al.[20] for the preparation of $Ln(fod)_3$ complexes or purchased from Aldrich Chemical Co. The Ag(fod) and Ag(tfa) complexes were prepared by the literature method.[9]

(a) Preparation of [4,4,4-Trifluoro-1-(2-thienyl)-1,3-butanedionato]silver(I), Ag(tta). A solution of 2.8 g of H(tta) in 20 mL of methanol was neutralized with 3.2 mL of 4 M NaOH and was then added to a vigorously stirred solution of 2.2 g of $AgNO_3$ in 50 mL of distilled water. As the ligand was added, a pale yellow solid immediately formed. The solid was collected by suction filtration and dried in vacuo over P_4O_{10} overnight. The product was stored in a light-proof container; mp 147-149 °C. Attempted sublimation of Ag(tta) and the other silver β-diketonates used in this study led to decomposition. Anal. Calcd for $Ag(C_8H_4O_2F_3S)$: C, 29.20; H, 1.22. Calcd for $Ag(C_8H_4O_2F_3S)\cdot H_2O$: C, 27.68; H, 1.74. Found: C, 27.22; H, 1.35.

(b) Preparation of [4,4,5,5,6,6,6-heptafluoro-1-(2-thienyl)-1,3-hexanedionato]silver(I), Ag(hfth). This compound was prepared by an identical procedure to that described for Ag(tta). The white solid had a melting point of 168-170 °C. Anal. Calcd for $Ag(C_{10}H_4O_2F_7S)$: C, 27.99; H, 0.94. Found: C, 27.91; H, 1.21.

NMR Studies. In most cases, small amounts of an insoluble material remained after dissolving the binuclear complexes in chloroform-*d*, and the following procedure was used for obtaining the NMR spectra. The required amounts of the lanthanide chelate and the silver β-diketonate were placed in a test tube and a solution of the substrate and 1% Me_4Si in chloroform-*d* was added. The test tube was stoppered, shaken for 2 min, and centrifuged. The supernatant was removed by pipet and placed in an NMR tube for analysis. Since the silver compounds are somewhat light-sensitive, the test tube and NMR tube were covered with aluminum foil prior to recording the spectrum.

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Registry No. $Yb(fod)_3$, 18323-96-1; $Yb(hfth)_3$, 85565-58-8; $Yb(tta)_3$, 14644-89-4; $Pr(fod)_3$, 17978-77-7; $Pr(hfth)_3$, 85565-59-9; $Pr(tta)_3$, 14644-86-1; $Pr(facam)_3$, 38053-99-5; $Pr(hfbc)_3$, 38832-94-9; $Yb(facam)_3$, 38054-03-4; Ag(fod), 76121-99-8; Ag(hfth), 85565-60-2; Ag(tta), 16029-33-7; Ag(tfa), 69070-40-2; cyclohexene, 110-83-8; toluene, 108-88-3; *dl*-camphene, 565-00-4; *d*-camphene, 5794-03-6; *l*-camphene, 5794-04-7.

(20) Springer, C. S., Jr.; Meek, D. W.; Sievers, R. E. *Inorg. Chem.* **1967**, *6*, 1105.

Favorskii Rearrangements of α-Halogenated Acetylcycloalkanes. 4.[1-3] Stereochemistry of Cyclopropanonic Rearrangements and the Influence of Steric Factors on the Competing Formation of α-Hydroxy Ketones†

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It is shown that the marked stereoselectivity, in favor of 17α-methylated etio acid derivatives, of Favorskii rearrangements in protic and polar media of 17-brominated 20-keto steroids—somewhat diminished by a bulky 12α-substituent, such as an acetoxy group—is due, to an appreciable extent, to the influence of the 18-methyl group. Thus, the rearrangement of 17-bromo-3β-acetoxy-18-nor-5α-pregnan-20-one, which was synthesized from 3β-acetoxy-5α-androstan-17-one, proceeds with potassium bicarbonate in aqueous methanol much less stereoselectively than analogous rearrangements of 13-methylated 17-bromo 20-ketones, and in its reaction with potassium methoxide in absolute methanol the yield of the 17β-methyl 17α-etio ester even exceeds that of the 17α-methylated rearrangement product, in contradistinction to the results of equivalent reactions of 13-methylated substrates. It is also shown that in the absence of the 18-methyl group a 17β-hydroxy 20-ketonic substitution product and related adducts are obtained in high proportion, and it is concluded that the quasi-absence of such products in analogous reactions of 13-methylated 17-bromo 20-keto steroids is essentially due to the steric impediment exerted by this group to the formation of intermediate epoxy ethers. The results presented agree with the hypothesis of a competition between concerted and nonconcerted cyclopropanone formations from α-halo enolates, in part dependent on the polarity and protonicity of the medium, or possibly with that of gradients of mechanisms, and they support the intermediacy of epoxy ethers in the formation of α-hydroxy ketones as side products of Favorskii rearrangements.

We have suggested[1,8,9] that the complex stereochemistry of cyclopropanonic Favorskii rearrangements, in particular of α-halogenated acetylcycloalkanes such as α-halogenated 20-keto steroids, may be explained by the assumption of a competition between a concerted cyclopropanone formation favored in an aprotic and mildly polar medium and by a nonconcerted pathway involving the intermediacy of a dipolar species, favored in a protic and polar medium, and by the assumption that in certain cases the two pathways may be operative simultaneously.[10] In the case

† Dedicated with admiration and gratitude to the memory of the late Dr. Hans Heusser (Feb 23, 1917-Oct 26, 1982), former Director, Hoffmann-La Roche & Co., Basle, Switzerland.

(1) Part 3: Engel, Ch. R.; Mérand, Y.; Côté, J. *J. Org. Chem.* **1982**, *47*, 4485.

(2) This publication represents paper 51 in our series "Steroids and Related Products". Paper 50: Bończa-Tomaszewski, Z.; Engel, Ch. R. *Steroids* **1982**, *39*, 107.

(3) Reported in part at the 46th Congress of the French-Canadian Association for the Advancement of Sciences (ACFAS), Ottawa, May 1978, and in part in a paper presented to the 28th Congress of the International Union of Pure and Applied Chemistry, Vancouver, Aug 1981.

(4) Abbreviated from part of the D.Sc. thesis of P.L., Université Laval, Quebec, Quebec, Canada, 1967.

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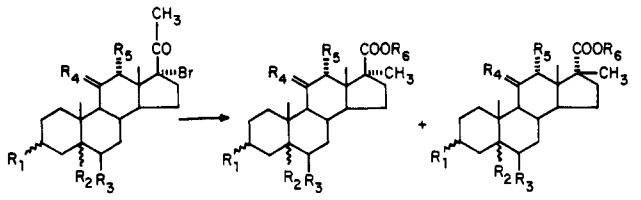
of asymmetry of the halogenated carbon atom of the α-halo ketone, the concerted reaction should lead stereospecifically, with inversion, to rearrangement products with a unique stereochemistry whereas in a reaction involving a delocalized intermediate, epimeric rearrangement products may be formed. We have further suggested that steric hindrance can favor the transformation of a dipolar intermediate into one of the two possible cyclopropanones and thus result in the formation, with high stereoselectivity, of one of the two possible epimeric rearrangement products. We have shown that the rearrangement of 17-bromo-3β-acetoxy-5-pregnen-20-one (1; R_1 = β-OAc, R_2 = R_3 = double bond, R_4 = H_2, R_5 = H) in the aprotic and mildly polar medium sodium methoxide–dimethoxyethane leads essentially to the rearrangement product with an inverted stereochemistry in position 17, the 17β-methylated 17α-etio ester (3; R_1 = β-OH, R_2 = R_3 = double

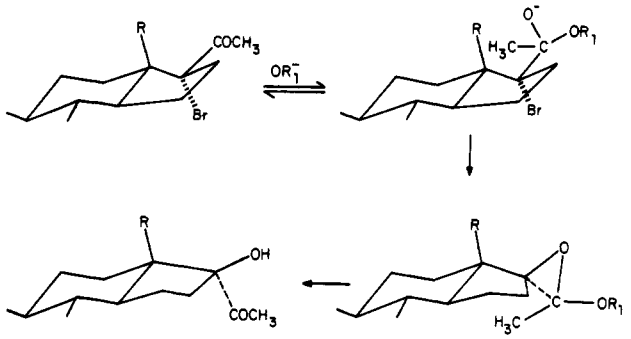


1 2 3

bond, R_4 = H_2, R_5 = H, R_6 = CH_3), whereas in the protic and polar medium potassium bicarbonate–methanol–water, 17α-methylated etio acid derivatives (2; R_1 = β-OH, R_2 = R_3 = double bond, R_4 = H_2, R_5 = H, R_6 = CH_3,H) are predominantly obtained.[8,9,12] In a medium of intermediate protonicity and polarity, mixtures of epimeric rearrangement products are formed.[8,9,12]

We attributed[8,9] the marked stereoselectivity observed in the rearrangement of 17-halogenated 20-keto steroids in polar and protic media to a considerable extent to the angular 18-methyl group, which can be considered to hinder the formation of the cyclopropanonic intermediate with a β configuration of its methylene group. This hypothesis seemed to be supported by the observation that in the case of the rearrangement of a 17-bromo 20-ketone with an 11-keto function (cf. 1; R_1 = α-OAc, R_2 = β-H, R_3 = R_5 = H, R_4 = O), in which the 18-methyl group is bent away from the centers involved in the formation of a 17β-methylene cyclopropanone, the stereoselectivity of the reaction is diminished.[8,9,12]

Scheme I



We now seem to have evidence that a bulkly substituent in position 12α, which might exert some hindrance to the formation of a cyclopropanone with an α configuration of its 17-methylene group, diminishes to a certain degree, but not drastically, the stereoselectivity of the rearrangement of 17-halogenated 20-keto steroids in media favoring the intermediacy of a dipolar species. When reinvestigating the rearrangement of 17-bromo-3α,12α-diacetoxy-5β-pregnan-20-one (1; R_1 = R_5 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2) with potassium bicarbonate in aqueous methanol, which had previously been carried out with an impure product,[8,13,14] with a crystalline, analytically pure substrate,[15] we found the ratio of the methylated and acetylated rearrangement product arising from a cyclopropanone intermediate with an α configuration of its methylene group, methyl 3α,12α-diacetoxy-17α-methyl-5β-etianate (2; R_1 = R_5 α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2, R_6 = CH_3), to the product arising from the 17-epimeric cyclopropanone, 3α-acetoxy-12α-hydroxy-17β-methyl-5β,17α-etianic acid lactone (20→12) (3; R_1 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2, R_5 = O—C_{20}=O, R_6 = >$C_{12\alpha}$H, to amount only to 13:1 and not, as in the case of 17-bromopregnenolone acetate, to 23:1.[8,19]

On the other hand, in order to verify the influence of the 18-methyl group on the stereoselectivity of the for-

(5) Abbreviated in part from a section of the M.Sc. thesis of J.Z., Université Laval, Quebec, Quebec, Canada, 1973.

(6) Abbreviated in part from a portion of the D.Sc. thesis of D.M., Université Laval, Quebec, Quebec, Canada, 1976.

(7) Abbreviated in part from the D.Sc. thesis of Y.M., Université Laval, Quebec, Quebec, Canada, 1976.

(8) Engel, Ch. R.; Roy, S. K.; Capitaine, J.; Bilodeau, J.; McPherson-Foucar, C.; Lachance, P. *Can. J. Chem.* **1970**, *48*, 361.

(9) Cf. also: (a) Engel, Ch. R.; Roy, S. K.; Bilodeau, J.; Lachance, P. "Abstracts A of Papers", 19th International Congress of Pure and Applied Chemistry, London, 1963, pp 53–54. (b) Engel, Ch. R. *Chimia* **1965**, *19*, 507.

(10) In a recent publication[1] we pointed out that instead of a competition between concerted and nonconcerted mechanisms, one could also take into consideration gradients of mechanisms, ranging from a reaction comprising a true dipolar intermediate to a pathway implying a "concerted" cyclopropanone formation, *stereochemically* equivalent to an S_N2 reaction, in which the disrotatory ring closure of the developing dipolar intermediate would commence before the bond to the leaving halogen is fully broken.[11] The gradients of mechanisms would thus correspond to the degree, dependent among other factors on the nature of the medium, to which the departure of the halogen substituent is effectively completed at the onset of the disrotatory ring closure.

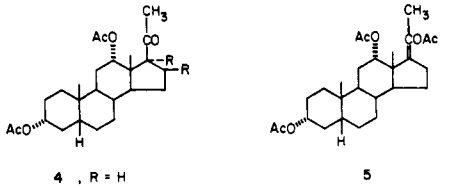
(11) Cf. also: Hunter, D. H.; Stothers, J. B.; Warnhoff, E. W. In "Rearrangements in Ground and Excited States"; de Mayo, P., Ed.; Academic Press: New York, 1980; Vol. I, p 381 ff.

(12) Cf. also the references quoted in ref 8.

(13) Engel, Ch. R.; Jennings, K. F.; Just, G. *J. Am. Chem. Soc.* **1956**, *78*, 6153.

(14) Engel, Ch. R.; Just, G.; Buttery, R. *Can. J. Chem.* **1961**, *39*, 1805.

(15) Bromination with molecular bromine in acetic acid, catalyzed by hydrogen bromide,[13] or with *N*-bromosuccinimide[14] of 3α,12α-diacetoxy-5β-pregnan-20-one (4) only affords an amorphous bromide which could not be adequately purified, due to its instability. The pure, crystalline 17-bromide (1; R_1 = R_5 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2) was now obtained by Fieser and Huang-Minlon's method[16,17] via the mixture of its geometrically isomeric enol acetates 5, under the conditions of Engel and Jahnke.[18] Interestingly, from its rearrangement product with potassium bicarbonate in aqueous methanol (cf. Experimental Section), the 16,17-dehydrobrominated product, 3α,12α-diacetoxy-5β-pregn-16-en-20-one (4a), was isolated in 4% yield. Its structure was proved by elemental and spectroscopic analyses and by direct dehydrobromination, in 91% yield, with lithium chloride in dimethylformamide.



4, R = H
4a, R = double bond

5

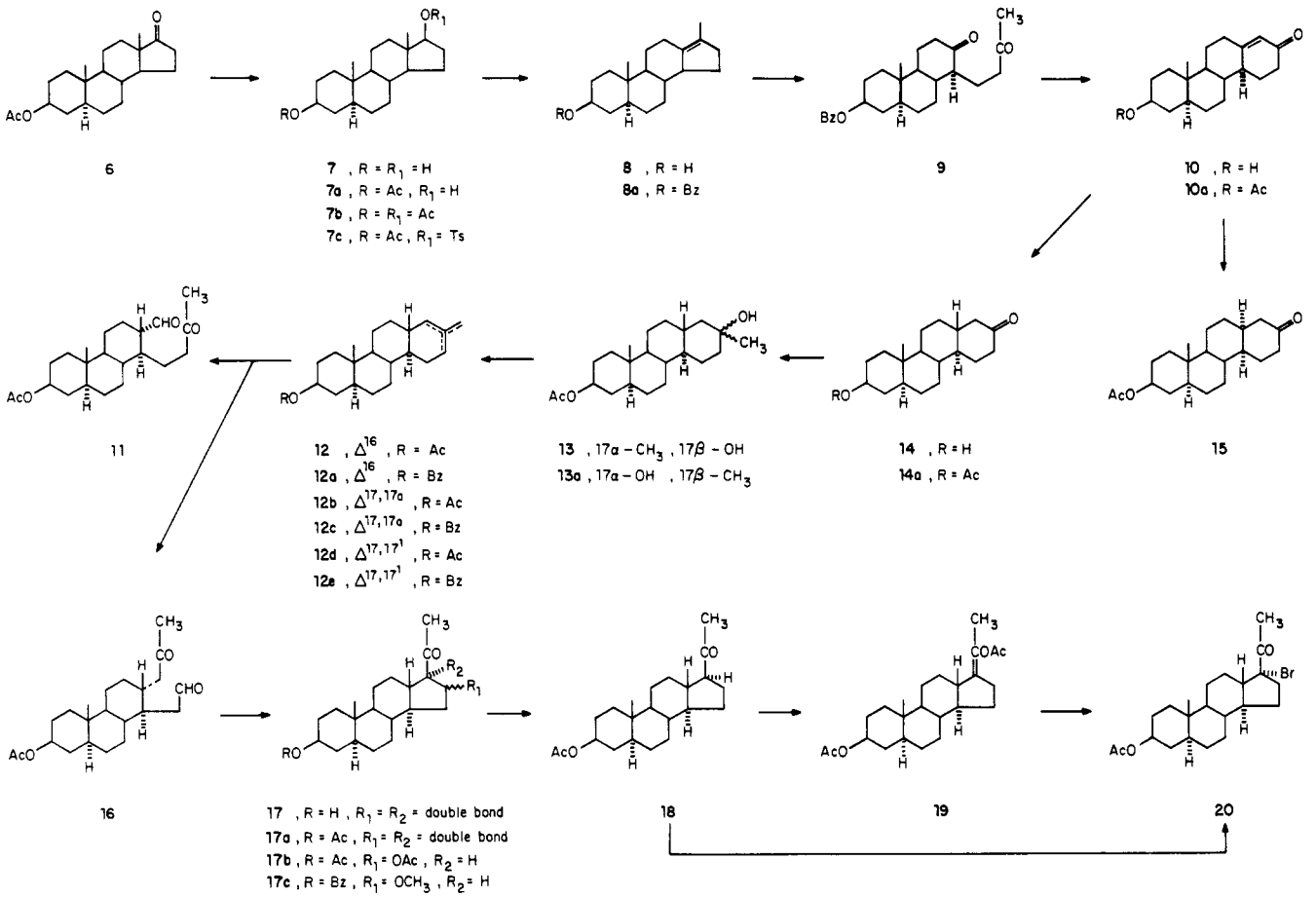
(16) Fieser, L. F.; Huang-Minlon, *J. Am. Chem. Soc.* **1949**, *71*, 1840.

(17) Cf. also: Heusser, H.; Engel, Ch. R.; Herzig, P. Th.; Plattner, Pl. A. *Helv. Chim. Acta* **1950**, *33*, 2229.

(18) Engel, Ch. R.; Jahnke, H. *Can. J. Biochem. Physiol.* **1957**, *35*, 1047.

(19) Cf. also: Deghenghi, R.; Schilling, G.; Papineau-Couture, G. *Can. J. Chem.* **1966**, *44*, 789.

Scheme II



mation in protic and polar media, from 17-halogenated 20-keto steroids, of 17α-methylene cyclopropanones, and thus of 17α-methylated etio acid derivatives, we decided to investigate rearrangements of a 17-bromo 20-ketone devoid of the 18-methyl group. We considered such experiments of interest also as a verification of our hypothesis[1,8,20,21] that the quasi-absence of substitution products in the reaction with bases of 17-halogenated 20-keto steroids is due to the impediment exerted by the 18-methyl group to the formation of epoxy ethers, in competition to the formation of cyclopropanones (cf. Scheme I). This assumption had already received some support from the observation[8] that, in contradistinction to rearrangements with bicarbonate in aqueous methanol of 17-brominated 20-ketones, the reaction with the same reagents of a 21-bromo 20-ketone, from which the formation of an epoxy ether should not be seriously hindered by the 18-methyl group, leads in a significant degree to a 21-hydroxy 20-ketone.[22]

For this investigation we chose 17-bromo-3β-acetoxy-18-nor-5α-pregnan-20-one (**20**) as the substrate, because A/B trans-fused 20-keto steroids have a shape similar to that of the 5-unsaturated products with which the majority of our previous experiments had been carried out and because the bromination of the corresponding 17-unsubstituted 20-ketones is simpler and not prone to the formation of side products arising from an allylic oxidation in position 7.[1]

Synthesis of 17-Bromo-3β-acetoxy-18-nor-5α-pregnan-20-one (20). For the synthesis of the unbrominated precursor of the bromo ketone **20**, 3β-acetoxy-18-nor-5α-pregnan-20-one (**18**), we followed essentially the method elaborated by Johns[23] and by Stork et al.[24] for the synthesis of 18,19-dinor steroids. The acetoxy androstanol **7a**, obtained in 86% yield by sodium borohydride reduction of 3β-acetoxy-5α-androstan-17-one (**6**, Scheme II), was transformed in 90% yield into its tosylate **7c** which was subjected, according to the procedure of Elks and Shoppee,[25] under the conditions employed by Madaeva,[26] to a Miescher–Kägi rearrangement[27] with ethylmagnesium bromide.[28] Since the resulting 18-nor-17-methyl-5α-androst-13(17)-en-3β-ol (**8**) crystallizes only with difficulty, it was converted in the crude state to the benzoate **8a**.[29] This product, obtained in 83% yield from tosylate **7c**, gave upon ozonolysis in methanol–dichloromethane, followed by reduction with zinc and acetic acid, 3β-(benzoyloxy)-17-methyl-18-nor-13,17-seco-5α-androstane-13,17-dione (**9**)[30] in 66% yield, which was cyclized with a 2% metha-

(20) Reference 4, p 98.
(21) Cf. also: Bordwell, F. G.; Frame, R. R.; Scamehorn, R. G.; Strong, J. G.; Meyerson, S. *J. Am. Chem. Soc.* **1967**, *89*, 6704.
(22) 21-Substituted 20-ketone derivatives are also formed in a considerable proportion by treatment of a 21-bromo 20-ketone with potassium methoxide in dimethoxyethane.[1]
(23) Johns, W. F. *J. Am. Chem. Soc.* **1958**, *80*, 6456; *J. Org. Chem.* **1961**, *26*, 4583; **1963**, *28*, 1856.
(24) Stork, G.; Khastgir, H. N.; Solo, A. J. *J. Am. Chem. Soc.* **1958**, *80*, 6457.
(25) Elks, J.; Shoppee, C. W. *J. Chem. Soc.* **1953**, 241.
(26) Madaeva, O. S. *Zh. Obshch. Khim.* **1957**, *27*, 2573.
(27) (a) Kägi, H.; Miescher, K. *Helv. Chim. Acta* **1939**, *22*, 683; (b) Miescher, K.; Kägi, H. *ibid.* **1949**, *32*, 761.
(28) The rearrangement by acetolysis with potassium acetate in acetic acid, according to the original procedure of Elks and Shoppee,[25] gave unsatisfactory results.
(29) The structures of all products were confirmed by combustion and spectral (UV, IR, ^{1}H NMR) analyses (cf. Experimental Section); only particular points of structural proofs are discussed in the General Section.
(30) It proved useful to protect, prior to ozonolysis, the 3β-alcohol by the formation of a benzoate rather than of an acetate.

nolic potassium hydroxide solution to 3β-hydroxy-18-nor-*D*-homo-5α-androst-13(17a)-en-17-one (**10**). It proved advantageous not to isolate the seco diketone **9**; proceeding in that fashion, one obtains the *D*-homo steroid **10** in over 60% yield from the androstene derivative **8a**. Whereas the catalytic reduction of the acetylated *D*-homoandrostenone (**10a**) with palladium on charcoal or palladium on calcium carbonate led to the cis *D*-homoandrostanone **15**, reduction with sodium and liquid ammonia, with addition of ammonium chloride,[31] gave the trans acetoxy ketone **14**, isolated as its acetate **14a** in 67% yield.[32] The trans stereochemistry of the Birch reduction product **14** could be inferred on conformational grounds[33] and was proved by its rotatory dispersion curve which shows a negative Cotton effect, corresponding according to the octant rule to a trans junction of rings C and D. The isomer **15**, resulting from the catalytic reduction, exhibits a positive Cotton effect.

Treatment of the acetoxy ketone **14a** with methylmagnesium iodide and reacetylation gave a mixture of isomeric tertiary 17-alcohols **13** and **13a**, which was dehydrated with phosphorus oxychloride to a mixture of isomeric Δ^{16},$\Delta^{17(17a)}$,$\Delta^{17(17^1)}$-18-nor-*D*-homoacetoxyandrostenes **12**, **12b**, and **12d**. Hydrolysis with sodium carbonate of the mixture and benzoylation gave the corresponding benzoates **12a,c,e** from which the isomer **12e**, whose double bond is exocyclic, could be isolated.

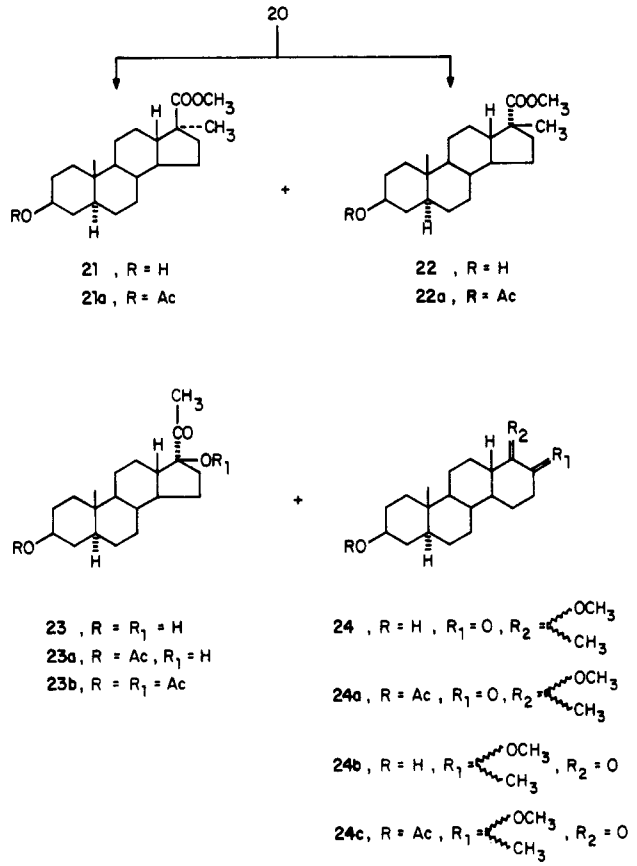
The original mixture of the acetates **12**, **12b**, and **12d**, whose proportion according to the integration of the olefinic ^{1}H NMR absorptions corresponded to 57:28:14, was enriched up to 81% in the Δ^{16} isomer **12** by Velluz's method[34] with *p*-toluenesulfonic acid and was then subjected to ozonolysis in dichloromethane–methanol, followed by reduction with zinc and acetic acid. The resulting, not separable (1:4) mixture of the isomeric acetoxy keto aldehydes **11** and **16**[35] was subjected to a Sarett cyclization[36] with an aqueous, dilute potassium or sodium hydroxide solution and reacetylated to give in 75% yield[37] 3β-acetoxy-18-nor-5α-pregn-16-ene (**17a**). From the mother liquors was obtained 3β,16ξ-diacetoxy-18-nor-5α-pregnan-20-one (**17b**). If the reacetylation is omitted, the free alcohol **17** can be isolated. When the reaction with sodium hydroxide is followed by treatment with sodium methoxide in methanol, a 16-methoxy derivative, isolated as its benzoate **17c**, is also formed. The structures of the 16-unsaturated 3-hydroxy 20-ketone **17**, of its acetate **17a**, and of its derivatives **17b** and **17c**, were confirmed by elemental and spectral analyses (cf. Experimental Section). In particular, acetate **17a** shows in the ultraviolet a maximum at 239 nm and a rotatory dispersion curve analogous to that of 16-unsaturated 20-keto steroids of the natural, 13-methylated series. Catalytic hydrogenation of the acetoxy enone **17a** over palladium on charcoal gave in practically quantitative yield 3β-acetoxy-18-nor-5α-pregnan-20-one (**18**). We attribute to its methyl ketone side chain the β configuration, as has been done by Stork[24] in an analogous case, because the approach of the 17-position is less hindered from the α side, even in the absence of the 18-methyl group. This assignment is in accord with the weak negative Cotton effect of ketone **18** which shows, in analogy with the findings of Wellman and Djerassi for 3β-acetoxyhexanordammar-20-one,[38] a minimum at 286 nm in its circular dichroism curve.

For the 17-bromination of the 18-norpregnanone **18** we prepared, as described for ketone **4**, the mixture of geometrically isomeric enol acetates **19** which was treated with bromine in acetic acid in the presence of potassium acetate.[18] The desired bromide **20** was obtained in 80% yield. The crystalline product was homogeneous, as determined by thin-layer analysis in various solvent systems and by triangle crystallizations. The same bromide can be obtained, albeit in much lower yield and less homogeneously, by *N*-bromosuccinimide bromination of the saturated ketone **18**. It seems logical to assign to the bromine substituent of bromo ketone **20** the α configuration since the approach from the α side should be even more favored for a bromine species than for hydrogen. The product shows in its rotatory dispersion curve a strong positive Cotton effect at 302 nm which indicates, according to the α-halo ketone rule,[39] its principal conformation to be analogous to that of 17α-unsubstituted 18-nor 20-ketones.[39d]

Favorskii Rearrangements of 17-Bromo-3β-acetoxy-18-nor-5α-pregnan-20-one (20). In a first series of experiments, we subjected the analytically pure bromo ketone **20** to the action of potassium bicarbonate in aqueous methanol, under the conditions previously used by our team.[8,13,14,17,40] The neutral fraction (96–97%) of the reaction product was reacetylated at room temperature with acetic anhydride in pyridine, and from the resulting mixture were isolated five components in the pure state by crystallization and by dry-column chromatography, the exact yields being determined gas chromatographically. The acetylated Favorskii rearrangement products methyl 3β-acetoxy-17α-methyl-18-nor-5α-etianate (**21a**) and methyl 3β-acetoxy-17β-methyl-18-nor-5α,17α-etianate (**22a**) were obtained in 25.1% and 5.5% yields, respectively. The structures of these products were determined by elemental, infrared, and ^{1}H NMR analyses (cf. Experimental Section). The α configuration of the 17-methyl substituent of the major, less polar, and less levorotatory epimer **21a** was firmly established by an X-ray crystallographic study by Fortier and Ahmed.[41]

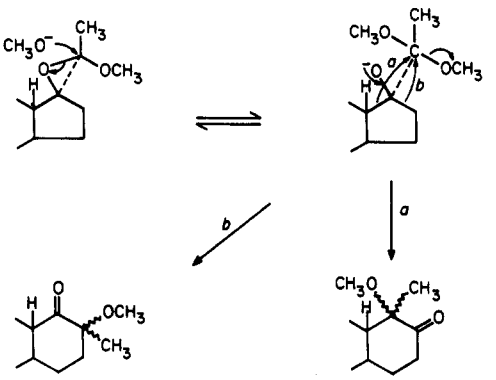
The main constituents of the acetylated reaction mixture were substitution products: 3β-acetoxy-17β-hydroxy-18-nor-5α,17α-pregnan-20-one (**23a**) and its acetate **23b**, their combined yield amounting to 61%, the 17-hydroxy derivative predominating.[42] Acetylation of the 17-hydroxy ketone **23a**, catalyzed by *p*-toluenesulfonic acid according to the method of Turner,[43] gave the above-mentioned diacetate **23b**, directly isolated from the reaction mixture. The constitution of the ketones **23a** and **23b** was established by elemental and spectral analyses (cf. Experimental Section), the presence of the methyl ketone moiety, apparent from the ^{1}H NMR spectra, also being confirmed

(31) Birch, A. J. *Q. Rev., Chem. Soc.* **1950**, *4*, 69.
(32) During the reaction with lithium and liquid ammonia, some of the reduction product of ketone **14**, 18-nor-D-homo-5α-androstane-3β,17α-diol, isolated as its diacetate, was formed. The equatorial 17α configuration of the 17-hydroxy group, to be expected on conformational grounds, was confirmed by the axial NMR signal of the 17-proton (cf. Experimental Section).
(33) Barton, D. H.; Robinson, C. H. *J. Chem. Soc.* **1954**, 3045.
(34) Velluz, L.; Amiard, G.; Heymes, R.; Goffinet, B. *Bull. Soc. Chim. Fr.* **1961**, 2166.
(35) This proportion was determined by integration of the aldehyde absorptions in the NMR.
(36) Poos, G. I.; Johns, W. F.; Sarett, L. H. *J. Am. Chem. Soc.* **1955**, *77*, 1026.
(37) In some runs, the yields of the cyclization reaction were lower.
(38) Wellman, K. M.; Djerassi, C. *J. Am. Chem. Soc.* **1965**, *87*, 60.
(39) (a) Djerassi, C.; Klyne, W. *J. Am. Chem. Soc.* **1957**, *79*, 1506. (b) Djerassi, C.; Osiecki, J.; Riniker, R.; Riniker, B. *Ibid.* **1958**, *80*, 1216. (c) Djerassi, C.; Fornaguera, I.; Mancera, O. *Ibid.* **1959**, *81*, 2383. (d) Cf. also: Djerassi, C.; Mitscher, L. A.; Mitscher, B. J. *Ibid.* **1959**, *81*, 947.
(40) Cf. also: Engel, Ch. R. *J. Am. Chem. Soc.* **1956**, *78*, 4727.
(41) Fortier, S.; Ahmed, F. R. *Acta Crystallogr., Sect. B* **1980**, *B36*, 994.
(42) The total yield of these products was consistent from one experiment to the other, but small variations in their relative abundance were observed, the approximate ratio of the 17-hydroxy and the 17-acetoxy derivatives amounting to 1.7:1.
(43) Turner, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 3489.



by Adachi's bromoform test.[44] Although the weakly positive Cotton effect of the hydroxy ketone **23a** would be compatible with a 17α-hydroxy configuration, a 17β-hydroxy configuration for the 20-ketones **23**, **23a**, and **23b** was probable, since, in general, epoxy ethers are opened by nucleophilic attack on the carbon atom bearing the ether substituent[45,46,50] and also because it is reasonable to assume that the acetoxy derivative **23b**, isolated from the reaction mixture, arose during the acetylation of the crude reaction product, under conditions which do not lend themselves to the acetylation of the quasi-axial tertiary hydroxyl group of a 17α-hydroxy 20-ketone. Drs. C. P. Huber and F. R. Ahmed from the National Research Council of Canada, Ottawa, to whom we are very grateful for their kind collaboration and whose detailed results will be published elsewhere, have confirmed the 17β-hydroxy configuration of the acetoxy hydroxy ketone **23a** by an X-ray crystallographic analysis.[51]

Scheme III



We also isolated from the acetylated reaction mixture, in approximately 2.3% yield, a product for which we tentatively suggest either structure **24a** or **24c** and which could arise by a D-homorearrangement of the epoxy ether intermediate (cf. Scheme III). In the infrared (in KBr) can be seen, apart from the 3-acetate adsorptions at 1730 and 1245 cm^{-1}, a carbonyl absorption at 1712 cm^{-1}, compatible with a 17- or 17a-keto function. The ^{1}H NMR spectrum confirms the presence of the 3-acetate group by the typical signal at δ 2 but exhibits no additional absorption in this region, attributable to a methyl ketone; it shows, on the other hand, three singlets, each corresponding to three protons, one at δ 0.73 which we attribute to the 19-methyl group, another at δ 1.16 which could correspond to the methyl group in positions 17 or 17a, and a third one at δ 3.05 which we assign to the methoxy group in positions 17 or 17a. The mass spectrum and elemental analysis of the product also agree with either of the proposed structures.

Very small quantities of three other products could be detected but were not further investigated.

In a second set of experiments the bromo ketone **20** was subjected to the action of potassium methoxide in absolute methanol, in a nitrogen atmosphere, but otherwise under the conditions previously used by our group.[8,17,52] The neutral reaction product (98.5%) was reacetylated as described above for the reaction with potassium bicarbonate in aqueous methanol. We isolated the same pure products as in the case of that reaction, the yields being again determined gas chromatographically. The 17α-methyl-18-noretianate **21a** was obtained in 14.8% yield and its 17-epimer **22a** in 15.2% yield; the 17β-hydroxy-18-nor-17α-pregnan-20-one **23a** and its 17-acetate **23b** were formed in 39.6% and 18.8% yields, respectively; the product to which we assign the *D*-homo structure **24a** or **24c** was isolated in 3.3% yield.

Discussion

Stereochemistry of Cyclopropanonic Favorskii Rearrangements in Protic Media. As can be seen, our hypothesis on the influence of the 18-methyl group on the stereochemical course of Favorskii rearrangements of 17-halogenated 20-keto steroids is indeed substantiated by the here-described experiments. In the highly protic and polar medium bicarbonate–methanol–water, in which we assume the reaction to proceed essentially via a delocalized intermediate,[1,8,9] the suppression of the 18-methyl group results in a significant diminution of the stereoselectivity of the reaction, the ratio of the 17α-methyl etio acid derivative to the 17β-methyl 17α-etio acid derivative being lowered from 23:1 for 17-bromopregnenolone acetate (1;

(44) Adachi, J. *J. Chem. Soc. Jpn.* **1950**, *71*, 566.
(45) Cf., inter alia: (a) Kende, A. S. *Org. React.* **1960**, *11*, 261. (b) Bergmann, M.; Mieckeley, A. *Ber.* **1931**, *64*, 802. (c) Loftfield, R. B.; Schaad, L. *J. Am. Chem. Soc.* **1954**, *76*, 35. (d) Stevens, C. L.; Farkas, E. *Ibid.* **1952**, *74*, 618. (e) Bordwell, F. G.; Scamehorn, R. G. *Ibid.* **1968**, *90*, 6751.
(46) It has, however, been reported[47] that epoxy ethers may also be hydrolyzed differently, and House et al.[48,49] reported cases in which α-chlorinated ketones whose chlorine atoms are bound to a quaternary carbon atom may lead with base to substitution products with overall retention of configuration.
(47) Temnikowa, T. I.; Kropacheva, E. N. *Zh. Obshch. Khim.* **1949**, *19*, 1917.
(48) House, O. H.; Thompson, H. W. *J. Org. Chem.* **1963**, *28*, 164.
(49) House, O. H.; Frank, G. A. *J. Org. Chem.* **1965**, *30*, 2948.
(50) We sincerely thank Dr. D. Taub from the Merck Sharp & Dohme Research Laboratories, Rahway, NJ, for an interesting and helpful discussion of this problem.
(51) The usual epoxy ether opening here observed makes it probable that the 17α-methoxy-20-oxopregnene isolated by Deghenghi et al.[19] in very low (0.5–2%) yield from the reaction product of 17-bromo-3β-acetoxy-5-pregnen-20-one with potassium bicarbonate or potassium carbonate in aqueous methanol, is not formed via a 20-methoxy 17β,20-epoxide.
(52) Engel, Ch. R.; Just, G. *J. Am. Chem. Soc.* **1954**, *76*, 4909.

Table I. Proportions of 17α- and 17β-Methyl Etio Acid Derivatives Formed in Favorskii Rearrangements of 17-Bromo 20-Keto Steroids in Relation to Starting Materials and Media

substrate	medium	proportion of 17α- and 17β-methyl etio acid derivatives	ref[a]
17-bromo-3β-acetoxy-5-pregnen-20-one	$KHCO_3$, CH_3OH, H_2O	23:1	8
	$KOCH_3$, CH_3OH	1.8:1	8
17-bromo-3α,12α-diacetoxy-5β-pregnan-20-one	$KHCO_3$, CH_3OH, H_2O	13:1	E
17-bromo-3α-acetoxy-5β-pregnane-11,20-dione	$KHCO_3$, CH_3OH, H_2O	5:1	8, 40
	$NaOCH_3$, CH_3OH	1:1	68; cf. 8
17-bromo-3β-acetoxy-18-nor-5α-pregnan-20-one	$KHCO_3$, CH_3OH, H_2O	4.5:1	E
	$KOCH_3$, CH_3OH	1:1.1	E

[a] The letter E refers to experiments described in the Experimental Section of this paper.

R_1 = β-AcO, R_2 = R_3 = double bond, R_4 = H_2, R_5 = H) or from 13:1 for 17-bromo-3α,12α-diacetoxy-5β-pregnan-20-one (1; R_1 = R_5 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2) to 4.5:1 for 17-bromo-3β-acetoxy-18-nor-5α-pregnan-20-one (**20**) (cf. Table I). We remark that this diminution of the stereoselectivity is much less pronounced if the comparison is made with a 13-methylated 11-ketonic 17-bromo 20-ketone such as 17-bromo-3α-acetoxy-5β-pregnane-11,20-dione (1; R_1 = α-OAc, R_2 = β-H, R_3 = R_5 = H, R_4 = O), in which the 18-methyl group is bent away from the β face of the reactive centers and in which electronic factors may also influence unfavorably the formation of a delocalized intermediate.[8,9]

In the less polar and less protic medium methoxide–absolute methanol, for which we suggest the reaction to proceed in part concertedly, with inversion, and thus to lead to a significant proportion of 17β-methylated 17α-etio acid derivatives,[1,8,9] the ratio of the 17α-methyl etio acid derivative to the 17β-methyl 17α-etio acid derivative is changed by removal of the 18-methyl group from 1.8:1 for 17-pregnenolone acetate to 1:1.1 for the 18-nor bromo ketone **20**.[53] Again, the change is much less significant if the comparison of the reaction of the 18-nor bromo ketone **20** is made with that of the 13-methylated 11-oxo 17-bromo 20-ketone (cf. Table I).

We remark also that although the stereoselectivity of the rearrangement in a protic and polar medium in favor of the formation of a cyclopropanone with an α configuration of its methylene group is markedly diminished in the absence of the angular 18-methyl group, it is not abolished. This seems plausible if one considers that even in the absence of an 18-methyl group the β face of the molecule is more hindered than the α face, and this seems to be the case also in the region involved in the reaction studied, as evidenced by the high stereoselectivity of the hydrogenation of a 16-unsaturated 18-nor 20-ketone and of the bromination of an 18-nor 17,20-enol acetate (cf. above).

Influence of the 18-Methyl Group on the Formation of Substitution Products. The here-described experiments also strongly support our hypothesis[8,20,21] that the quasi-absence of substitution side products, in particular of α-hydroxy ketones, in the rearrangement of 17-halogenated 20-keto steroids is largely due to the steric impediment, exerted by the 18-methyl group, to the formation of intermediate epoxy ethers. Thus, while no 17-hydroxylated 20-ketone has ever been obtained in a rearrangement of a 17-bromo 20-ketone of the normal, 13-methylated series,[54] 57–62% of the acetylated reaction products of the here-described rearrangements of the 17-bromo 18-nor 20-ketone **20** consisted of the 17β-hydroxy 20-ketone **23a**, its acetate **23b**, and the *D*-homo adduct **24a** or **24c**, which presumably arises also from an epoxy ether intermediate. And whereas 17-bromo 20-ketones possessing the 18-methyl group, such as 17-bromopregnenolone acetate, afford with potassium bicarbonate in aqueous methanol some 95%, and with potassium methoxide in absolute methanol almost 90%, of rearrangement products, the yields of such adducts in identical reactions of the 18-nor 17-bromo 20-ketone **20** amount only to approximately 30%. Our findings also lend support to the hypothesis that the α-hydroxy ketone substitution products which often accompany Favorskii rearrangement products are normally formed via epoxy ether intermediates. Indeed, while the formation of such intermediates should be hindered by the 18-methyl group, it cannot be seen that this group should strongly impede the formation of substitution products by pathways comprising delocalized intermediates[55] or representing an S_N1 reaction.[56] Furthermore, these mechanisms, as well as a pathway involving an alkylidene epoxide intermediate (taken into consideration by House and Frank[49,59] for the formation of α-alkoxy ketone side products of Favorskii rearrangements), are ruled out, at least in the present instances, by the β configuration of the 17-hydroxy group of ketone **23**, since the approach of the hydroxylic nucleophile to the intermediates of such reactions should occur from the α face of the molecule.[60]

(53) We attribute, of course, this change in the stereochemistry of the reaction to the portion proceeding via a delocalized intermediate. The influence of the 18-methyl group on the stereochemistry of the rearrangement can also be accommodated when one assumes gradients of mechanisms instead of a competition between a concerted reaction and a pathway involving the intermediacy of a delocalized species.[1,10]

(54) The sole 17-substituted 20-ketone obtained in rearrangements of 17-halogenated 20-ketones has been a 17α-methoxy derivative, formed in less than 2% yield in reactions with potassium bicarbonate or potassium carbonate in aqueous methanol.[19]

(55) Cf., e.g.: Fort, A. W. *J. Am. Chem. Soc.* **1962**, *84*, 2620, 2625.

(56) As pointed out by a referee, the 18-methyl group could hinder a substitution reaction proceeding from an intermediate enol allylic halide.[57] This would, however, only hold if the ion pair formed by halide abstraction from such a species were to remain an intimate one, in which case—and this cannot be assumed with certainty in the instances under consideration, especially in the protic media employed—the reaction would be sterically equivalent to an S_N2 displacement. Otherwise, a sterically unhindered attack by the hydroxylic nucleophile from the α face would be possible. Actually, the very fact that attack from the β face would be considerably hindered should favor a reaction path leading from the originally formed intimate ion pair, for instance through a solvent-separated ion pair or a true carbocation,[58] by a reaction not hindered by the 18-methyl group, to a substitution product with retention of configuration; this does not correspond to the experimental results. Of course, in the case of a true S_N2 mechanism, the 18-methyl group would exert strong steric hindrance, but such a mechanism is entirely improbable in the reaction, in a polar medium, of a bromo ketone whose halogen substituent is attached to a quaternary carbon atom, linked itself to another quaternary carbon atom.

(57) Bordwell, F. G.; Carlson, M. W. *J. Am. Chem. Soc.* **1970**, *92*, 3377.

(58) Cf.: Shiner, V. J.; Fisher, R. D. *J. Am. Chem. Soc.* **1971**, *93*, 2553.

(59) Cf. also: Cookson, R. C.; Nye, M. J. *J. Chem. Soc.* **1965**, 2009.

Experimental Section

General Methods. The melting points were taken in evacuated capillaries, and the temperatures were corrected. For column chromatography, neutral aluminum oxide (Woelm) and Davison's silica gel 923 were used. For dry column chromatography, Woelm activity III silica gel was used, and for thin-layer chromatography Merck silica gel GF-254 and Baker silica gel 7G were employed. Gas chromatographic separations were performed in Professor G. Just's laboratory at McGill University with a Hewlett-Packard, F&M Scientific instrument with an incorporated recorder, Model 5750. The separation of each identified constituent was obtained with 3% OV-1 as liquid phase on Chromosorb W in a glass column measuring 3 mm in diameter and 180 cm in length at 238 °C with a nitrogen flow of 1.9 cm s^{-1}. A flame-ionization detector was used. The injections of each isolated product and of each mixture were performed in triplicate. The identities of the peaks were established by comparison of the retention times of the pure isolated product and of the various products contained in the mixtures. The quantitative determination of each product was obtained by comparison of the integration of the surfaces of the peaks in the mixtures with those obtained by injection of known quantities of pure products, means being established for every experiment. The surfaces were determined by weight and by triangulation.

Infrared spectra were recorded on Beckman IR-4 and IR-12 spectrophotometers and on a Perkin-Elmer 457 instrument, the ultraviolet spectra were determined on Beckman DK-1A and Zeiss DMR-21 instruments, and the ^1H NMR spectra were recorded at 60 MHz on a Varian A-60 spectrometer and at 90 MHz on a Bruker HX-90 spectrometer in deuteriochloroform, tetramethylsilane serving as internal reference at 0 Hz. The rotatory dispersion and circular dichroism curves were obtained on a JASCO ORD/UV-5 spectropolarimeter. The mass spectra were recorded on a Varian M-66 instrument.

The microanalyses were performed by Mr. A. Bernhardt, Max Planck Institute, Mülheim, Germany, by the late Dr. and Mrs. F. Pascher, Bonn, Germany, by Dr. G. Schilling, Ayerst Laboratories, Montreal, Canada, and by Dr. C. Daesslé, Montreal, Canada. We pay tribute to Dr. and Mrs. Pascher and express sincere thanks to Mr. Bernhardt, Dr. Schilling, Dr. Daesslé, and their staffs for their excellent cooperation.

17-Bromo-3α,12α-diacetoxy-5β-pregnan-20-one (1; $R_1 = R_5$ = α-OAc, R_2 = β-H, R_3 = H, $R_4 = H_2$). The solvent was slowly distilled from a solution of 30 g of 3α,12α-diacetoxy-5β-pregnan-20-one (4, mp 139–141 °C) and 8.43 g of *p*-toluenesulfonic acid in 1.5 L of absolute acetic anhydride for 8 h, and subsequently the volume was further reduced to approximately 100 mL in vacuo. The crude mixture was extracted with ether, and the ethereal solution was washed with water, a saturated $NaHCO_3$ solution, and with water and was dried over Na_2SO_4. The crude, dark brown, semicrystalline product (36.5 g) was chromatographed on 1 kg of Al_2O_3 (activity III). Petroleum ether–benzene (9:1 and 4:1) eluted 26.9 g (82%) of a mixture of the geometrically isomeric **3α,12α,20-triacetoxy-5β-pregn-17(20)-enes 5**, mp 160–166 °C. A sample was recrystallized twice from ether–hexane for analysis: fine, colorless needles; mp 172–174 °C; $[\alpha]^{26}_D$ +160.7° (*c* 1.000, $CHCl_3$); IR (KBr) ν_{max} 1735, 1245 cm^{-1} (acetates); ^1H NMR (60 MHz) δ 0.88 and 0.92 (2 s, 18- and 19-CH_3), 1.80 (s, 21-CH_3), 2.06 (s, 6 H, 3α,12α-CH_3COO), 2.10 (s, 3 H, 20-CH_3COO), 4.75 (m, 3β-H), 5.23 (m, 12β-H). Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.40; H, 8.75. Found: C, 70.59; H, 8.61.

To a solution of 20 g of the above-obtained mixture of the enol acetates 5 (mp 160–166 °C) in 250 mL of glacial acetic acid was added, with stirring at room temperature over a period of 15 min, a 2 N bromine solution in acetic acid to which a solution of 4.1 g of potassium acetate in 3 mL of water had been added. The mixture was allowed to remain at room temperature for another 15 min and was poured into ice–water. The precipitate was filtered, was washed with water, and was dried to give 20.8 g (97.2%) of crystalline **17-bromo-3α,12α-diacetoxy-5β-pregnan-20-one** (1; $R_1 = R_5$ = α-OAc, R_2 = β-H, R_3 = H, $R_4 = H_2$), mp 152–155 °C. One recrystallization from dichloromethane–methanol gave 18.05 g (83.6%) of pure product (mp 161.5–162.5 °C). A sample was recrystallized twice from dichloromethane–methanol for analysis: fine needles; mp 166–167 °C; $[\alpha]^{20}_D$ +44.8° (*c* 1.000, $CHCl_3$); IR (KBr) ν_{max} 1735 (acetates), 1710 (20-ketone), 1250 cm^{-1} (acetates); ^1H NMR (60 MHz) δ 0.82 (s, 3 H, 19-CH_3), 0.96 (s, 3 H, 18-CH_3), 2.02 (s, 3 H, 21-CH_3), 2.16 (s, 3 H, 3α-CH_3COO), 2.40 (s, 3 H, 12α-CH_3COO), 4.71 (m, 1 H, 3β-H), 5.15 (t, 1 H, 12β-H). Anal. Calcd for $C_{25}H_{37}O_5Br$: C, 60.36; H, 7.50; Br, 16.07. Found: C, 60.42; H, 7.62; Br, 16.22.

Rearrangement of 17-Bromo-3α,12α-diacetoxy-5β-pregnan-20-one (1; $R_1 = R_5$ = α-OAc, R_2 = β-H, R_3 = H, $R_4 = H_2$) with Potassium Bicarbonate in Aqueous Methanol. To a solution of 11 g of the above-described diacetoxy bromo ketone 1 ($R_1 = R_5$ = α-OAc, R_2 = β-H, R_3 = H, $R_4 = H_2$), mp 161.5–162.5 °C, in 375 mL of methanol was added a solution of 22 g of $KHCO_3$ in 75 mL of water, the mixture was refluxed for 4 h, and its volume was reduced in vacuo to about 100 mL. The product was poured into 1 L of cold water, and the crystalline precipitate was filtered, washed to neutrality, and dried. This gave 8.5 g of "neutral fraction I". The alkaline filtrate and the washings were combined and acidified in the cold with 2 N H_2SO_4 to a Congo blue reaction and extracted with chloroform. The organic layer was washed with water and was dried over sodium sulfate. Removal of the solvent gave 1.38 g of "acid fraction I" which was dissolved in 25 mL of absolute methanol and 45 mL of absolute ether and treated at 0 °C with 30 mL of a 1.8% ethereal diazomethane solution. After storage at room temperature for 20 h, the mixture was treated with a few drops of acetic acid, and the solvents were removed. The resulting product (1.53 g) was combined with the "neutral fraction I", and this mixture was refluxed with 170 mL of a 6.8% methanolic KOH solution for 4 h.[61] After addition of 40 mL of water the volume was reduced in vacuo to about 50 mL, and the product was poured into 1 L of cold water. The precipitate was extracted with ether, the ethereal solution was washed with water and was dried over Na_2SO_4. Removal of the solvent gave 8.2 g of "neutral fraction II".

The alkaline solution, the extraction of which had provided "neutral fraction II", and the water washings were combined and acidified with 2 N H_2SO_4 to the Congo blue reaction and extracted with $CHCl_3$. The organic layer was washed with water, was dried over Na_2SO_4, and was taken to dryness. The resulting "acid fraction II" (530 mg) was dissolved in 8 mL of absolute methanol and 15 mL of absolute ether and treated at 0 °C with 15 mL of a 2% ethereal diazomethane solution. A few drops of acetic acid were added, the solvent was removed, the product (530 mg) was dissolved in 2 mL of pyridine, and the mixture was refluxed for 90 min with 1 mL of acetic anhydride. The usual workup provided 610 mg of a yellow, crystalline product which was recrystallized from ether–hexane to afford 400 mg of authentic **3α-acetoxy-12α-hydroxy-17β-methyl-5β,17α-etianic acid lactone (20→12) (3; R_1 = α-OAc, R_2 = β-H, R_3 = H, $R_4 = H_2$, R_5 = O—C_{20}=O, R_6 = >$C_{12\alpha}$H)**: mp 140–142 °C (lit.[8] mp 138–140 °C); IR (KBr) ν_{max} 1776 (γ-lactone), 1732 and 1249 cm^{-1} (acetate). The identity of the product with an authentic sample was established by the determination of a mixture melting point and by the comparison of the IR and ^1H NMR spectra.

Neutral fraction II (8.2 g) was dissolved in 26 mL of pyridine and 14 mL of acetic anhydride, and the mixture was refluxed for 90 min. The usual workup provided 9.4 g of a crystalline product which, upon recrystallization from methanol, gave 6.8 g of **methyl 3α,12α-diacetoxy-17α-methyl-5β-etianate (2; $R_1 = R_5$ = α-OAc, R_2 = β-H, R_3 = H, $R_4 = H_2$, R_6 = CH_3)**: mp 159–160 °C (lit.[13] mp 161–161.5 °C); IR (KBr) ν_{max} 1742 (acetates),1732 (methyl ester), 1246 cm^{-1} (esters); ^1H NMR (90 MHz) δ 0.73 (s, 3 H), and 0.96 (s, 3 H) (18- and 19-CH_3), 1.27 (s, 3 H, 17α-CH_3), 1.99 (s, 3 H, 12α-CH_3COO), 2.06 (s, 3 H, 3α-CH_3COO), 3.70 (s, 3 H, $COOCH_3$), 4.71 (m, 1 H, 3β-H), 5.35 (t, 1 H, 12β-H). The identity of the product was established by the comparison of its IR spectrum with that of an authentic sample and by the determination of a mixture melting point.

Chromatography of the mother liquors of neutral fraction II on 100 g of aluminum oxide (activity III) provided another 1.65 g of the above-described 17α-methyl etio ester 2 ($R_1 = R_5$ = α-OAc,

(60) This would also be true in the case of a substitution reaction from an enol allylic halide, not implying the direct transformation of an intermediate intimate ion pair into the substitution product.[56]

(61) Under these conditions 17α-methyl etio esters are not hydrolyzed.

R_2 = β-H, R_3 = H, R_4 = H_2, R_6 = CH_3) (mp 159–161 °C), 150 mg of the above-described lactone **3** (R_1 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2, R_5 = O—C_{20}=O, R_6 = >$C_{12\alpha}$H) (mp 140–142 °C), and 350 mg of **3α,12α-diacetoxy-5β-pregn-16-en-20-one (4a**, mp 198–200 °C). A sample of this product was recrystallized twice from ether–hexane for analysis: colorless needles; mp 198–200 °C; $[\alpha]^{23}_D$ +125.7° (*c* 1.000, $CHCl_3$); UV (EtOH) λ_{max} 237 nm (log ε 4.05); IR (KBr) ν_{max} 1745 (acetates), 1677 and 1600 (Δ^{16}-20-ketone doublet), 1252 cm^{-1} (acetates); ^1H NMR (60 MHz) δ 0.94 (6 H, 18- and 19-CH_3), 1.95 (s, 3 H, acetate), 2.01 (s, 3 H, acetate), 2.23 (s, 3 H, CH_3CO), 4.75 (m, 1 H, 3β-H), 5.54 (t, 1 H, 12β-H), 6.75 (t, 1 H, 16-H). Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.87; H, 8.63.

In toto, 8.45 g (85%) of the diacetoxy 17α-methyl etianate **2** (R_1 = R_5 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2, R_6 = CH_3), 550 mg (6.6%) of the 17β-methyl acetoxy lactone **3** (R_1 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2, R_5 = O—C_{20}=O, R_6 = >$C_{12\alpha}$H), and 350 mg (3.9%) of the 16-unsaturated 20-ketone **4a** were obtained.

Dehydrobromination of 17-Bromo-3α,12α-diacetoxy-5β-pregnan-20-one (1; R_1 = R_5 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2) with Lithium Chloride and Dimethylformamide. A quantity of 1.963 g of bromide **1** (R_1 = R_5 = α-OAc, R_2 = β-H, R_3 = H, R_4 = H_2) was refluxed in 450 mL of dimethylformamide with 362 mg of LiCl for 1 h under nitrogen. The cooled solution was poured into 1 L of ice–water, and the precipitate was filtered, washed with water, and dried to afford 1.647 g (91%) of enone **4a**, mp 190/197–198 °C. One recrystallization from ether–hexane raised the melting point to 197–198 °C. The product was found to be identical with the above-described sample by the determination of a mixture melting point and by the comparison of the IR and NMR spectra.

3β-Acetoxy-17β-(tosyloxy)-5α-androstane (7c). To a solution of 17.9 g of 3β-acetoxy-5α-androstan-17-one (**6**, mp 113–115 °C) in 550 mL of absolute dioxane and 350 mL of absolute methanol was added 4.88 g of $NaBH_4$, and the mixture was stirred at room temperature for 6 h. After acidification with 2 N sulfuric acid to pH 3, the product was extracted with ether, and the ethereal solution was washed with water, a saturated $NaHCO_3$ solution, and with water and was dried over sodium sulfate. Evaporation of the solvent left 18.29 g of a crystalline product which, upon recrystallization from methanol, gave 15.572 (86% yield) of **3β-acetoxy-5α-androstan-17β-ol (7a)**: mp 101–103 °C (lit.[26,62] mp 114–116 °C, 148 °C); IR (KBr) ν_{max} 3400 (OH), 1740 and 1250 cm^{-1} (acetate). The mother liquors (2.718 g) were chromatographed on 270 g of silica gel. Ethyl acetate eluted 760 mg of **5α-androstane-3β,17β-diol (7**, mp 162–163 °C) which, upon recrystallization from acetone–hexane, melted at 164–165 °C (lit.[63] mp 168 °C): $[\alpha]^{23}_D$ +5.6° (*c* 1.000, EtOH) [lit.[64] $[\alpha]^{23}_D$ +6° ($CHCl_3$)]; IR (KBr) ν_{max} 3465, 3375, 3200 (hydroxyls), 1075, 1055, 1030 cm^{-1} (CO). The same product was obtained by hydrolysis of 28 mg of the above-described 3β-acetoxy-5α-androstan-17β-ol (**7a**) with 30 mg of potassium carbonate in 1 mL of water at reflux temperature. The 3β-acetoxy-5α-androstan-17β-ol (**7a**) was further characterized by its diacetate derivative **3β,17β-diacetoxy-5α-androstane (7b)**: mp 126–127 °C (lit.[63] mp 127–128 °C); $[\alpha]^{23}_D$ −0.7° (*c* 1.000, $CHCl_3$) [lit.[65] $[\alpha]^{14}_D$ −1.3° (acetone)]; IR (KBr) ν_{max} 1740 and 1250 cm^{-1} (acetates), obtained in the usual fashion.[66]

To a solution of 16.88 g of 3β-acetoxy-5α-androstan-17β-ol (**7a**, mp 101–103 °C) in 325 mL of pyridine was added 40 g of *p*-toluenesulfonyl chloride, and the mixture was kept at 55 °C for 96 h. The volume was reduced in vacuo to 100 mL, the product was extracted with ether, and the ethereal layer was washed with iced aqueous 2 N hydrochloric acid, with water, with an iced $NaHCO_3$ solution, and with water and was dried over Na_2SO_4. Evaporation of the solvent gave 24.5 g of a crystalline product, mp 169–170 °C. Recrystallization from dichloromethane–ether gave 21.9 g (89.7%) of **3β-acetoxy-17β-(tosyloxy)-5α-androstane (7c)**, mp 172–174 °C. A sample was recrystallized three times from dichloromethane–ether for analysis: colorless needles; mp 173–174 °C (lit.[26] mp 173–174.5 °C); $[\alpha]^{23}_D$ −17.0° (*c* 1.000, $CHCl_3$); UV (EtOH) λ_{max} 225 nm (log ε 4.07); IR (KBr) ν_{max} 1730 (acetate), 1600 (tosylate), 1250 cm^{-1} (acetate). Anal. Calcd for $C_{28}H_{40}O_5S$: C, 68.82; H, 8.25; S, 6.56. Found: C, 68.85; H, 8.35; S, 6.68.

3β-(Benzoyloxy)-17-methyl-18-nor-5α-androst-13(17)-ene (8a). A solution of 83.3 g of the acetoxy tosylate **7c** (mp 170–171 °C) in 1.8 L of absolute benzene was added dropwise with stirring to an ethylmagnesium bromide solution prepared from 53 g of magnesium, 187 mL of ethyl bromide, and 900 mL of absolute ether. The ether was removed by distillation until the solution reached 74 °C, and the mixture was refluxed for 3 h and then left at room temperature for 18 h. The mixture was cooled, was acidified with 2 N H_2SO_4 to pH 2 and was extracted with ether. The ethereal solution was washed with an iced $NaHCO_3$ solution and with water and was dried over Na_2SO_4. Removal of the solvent gave 51.8 g of an oily product, representing crude **17-methyl-18-nor-5α-androst-13(17)-en-3β-ol (8)**, which was dissolved in 350 mL of pyridine and treated at room temperature for 16 h with 72 mL of benzoyl chloride. After addition of ice, the mixture was poured into ice–water, and the precipitated crystals were filtered, washed with water, and dissolved in benzene. The organic solution was washed with water and was dried over Na_2SO_4. Evaporation of the solvent gave 64.3 g of a crystalline substance which was recrystallized from ether–ethanol to afford 50.1 g (77%) of **3β-(benzoyloxy)-17-methyl-18-nor-5α-androst-13(17)-ene (8a)**, mp 146–148 °C. A sample was recrystallized four times from ether for analysis: colorless plates; mp 148–149 °C; $[\alpha]^{24}_D$ −25.8° (*c* 1.000, $CHCl_3$); UV (EtOH) λ_{max} 228 nm (log ε 4.05); IR (KBr) ν_{max} 3018 (double bond), 1711 (ester), 1648 (double bond), 1596 and 1578 (aromatic), 1268, 706 cm^{-1} (benzoate); ^1H NMR (60 MHz) δ 0.78 (s, 19-CH_3), 1.62 (s, 3 H, 17-CH_3), 7.55 and 8.1 (m, aromatic protons). Anal. Calcd for $C_{26}H_{34}O_2$: C, 82.49; H, 9.05. Found: C, 82.68; H, 9.16.

The mother liquors were combined with 97 g of mother liquors of the recrystallization of 440 g of impure benzoate **8a** originating from analogous experiments, and this mixture was chromatographed on 1 kg of Al_2O_3 (activity II). Elutions with petroleum ether gave 66.8 g of a product which, upon recrystallization from ether–ethanol, afforded 32.4 g of pure benzoate **8a**, mp 146–148 °C. Thus the total yield of benzoate **8a** amounted to 83%.

3β-(Benzoyloxy)-17-methyl-18-nor-13,17-seco-5α-androstane-3,17-dione (9). (a) Through a solution of 15.563 g of 3β-(benzoyloxy)-17-methyl-18-nor-5α-androst-13(17)-ene (**8a**) in 600 mL of a (1:1) CH_3OH–CH_2Cl_2 mixture there was passed, at −70 °C for 160 min at a flow rate of 175 mL/min, an oxygen current containing 6% of ozone, until an intense blue color persisted. The solution was allowed to reach room temperature, and 28 g of zinc dust and 30 mL of glacial acetic acid were added. The mixture was heated on a water bath for the initiation of the reaction and was subsequently left at room temperature for 45 min. The product was extracted with ether, and the ethereal solution was washed with iced 2 N HCl, with water, with an iced $NaHCO_3$ solution and with water and was dried over Na_2SO_4. Evaporation of the solvent left 16 g of an oil which crystallized from ether–hexane (mp 106–108 °C) and which was chromatographed on 1 kg of silica gel. Benzene–ethyl acetate (9:1) eluted 11.2 g (66.5% yield) of **3β-(benzoyloxy)-17-methyl-18-nor-13,17-seco-5α-androstane-13,17-dione (9)**, mp 109–111 °C. A sample was recrystallized four times from ether–hexane for analysis: mp 113–114 °C; $[\alpha]^{23}_D$ +11.1° (*c* 1.000, $CHCl_3$); UV (EtOH) λ_{max} 228 nm (log ε 4.01); IR (KBr) ν_{max} 3025 (unsaturation), 1710 (ketones), 1600 and 1580 (aromatic), 1270, 710 cm^{-1} (benzoate); ^1H NMR (60 MHz) δ 0.83 (s, 3 H, 19-CH_3), 2.12 (s, 3 H, CH_3CO), 5.0 (m, 3α-H), 7.4 and 8.08 (m, aromatic protons). Anal. Calcd for $C_{26}H_{34}O_4$: C, 76.06; H, 8.34. Found: C, 76.31; H, 8.41.

(b) In another experiment, a solution of 11.9 g of the 3β-(benzoyloxy)-17-methyl-18-norandrostene **8a** in 325 mL of CH_3OH and 525 mL of CH_2Cl_2 was ozonized at −70 °C with an oxygen current containing 1.7% of ozone for 180 min at a flow rate of 360 mL/min. Reduction at room temperature with 22 g of zinc powder and 23 mL of glacial AcOH gave 14 g of 3β-(benzoyloxy)-17-methyl-18-nor-13,17-seco-5α-androstane-13,17-dione (**9**),

(62) Schering AG, Ger. Pat. 659543, 1934 (issued 1938). Cf.: "Elsevier's Encyclopedia of Organic Chemistry"; Elsevier: Amsterdam, Houston, London, New York, 1956; Series III, Vol. 14 Suppl., p 2016s.

(63) Ruzicka, L.; Goldberg, M. W.; Rosenberg, H. R. *Helv. Chim. Acta* **1935**, *18*, 1487.

(64) Wilds, A. L.; Djerassi, C. *J. Am. Chem. Soc.* **1946**, *68*, 2125.

(65) Shoppee, C. W. *Helv. Chim. Acta* **1940**, *23*, 740.

(66) The characterization of the monoacetate by the corresponding dihydroxy and diacetoxy derivatives seemed called for in view of the difference of melting points of our monoacetate **7a** and of those reported in the literature.

mp 104–105 °C. This product was used without purification in the next reaction (cf. below).

3β-Hydroxy-18-nor-*D*-homo-5α-androst-13(17a)-en-17-one (10). A solution of 72.8 g of crude, crystalline 3β-(benzoyloxy)-17-methyl-18-nor-13,17-seco-5α-androstane-13,17-dione (**9**, mp 104–105 °C), prepared as described above in section b, in 2.2 L of CH_3OH containing 1.4% of H_2O and 2% of KOH was refluxed for 3 h under nitrogen. Part of the solvent was distilled off, and the mixture was poured into ice–water. The crystalline precipitate was filtered, washed with water, and dried. The product (46 g, mp 173–185 °C) was recrystallized from CH_3OH–H_2O to afford 31 g (61% yield from the 18-nor-17-methyl-androstene **8a**) of 3β-hydroxy-18-nor-*D*-homo-5α-androst-13(17a)-en-17-one (**10**), mp 197–198.5 °C. A sample was sublimed at 0.02 mmHg and 125 °C for analysis: mp 197–198 °C (lit.[27b] mp 194–196 °C); $[\alpha]^{23}_D$ −38° (*c* 1.000, $CHCl_3$); UV (EtOH) λ_{max} 240 nm (log ε 4.25); IR (KBr) ν_{max} 3375 (OH), 1650 and 1610 cm^{-1} (α,β-unsaturated ketone doublet). Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.03; H, 9.64.

Acetate 10a. A quantity of 3.2 g of 3β-hydroxy-18-nor-*D*-homo-5α-androst-13(17a)-en-17-one (**10**) was acetylated in the usual fashion in 16 mL of pyridine with 8 mL of acetic anhydride. By chromatography of the reaction product (3.4 g) on 100 g of Al_2O_3 (activity III), 2.992 g (88.5%) of **3β-acetoxy-18-nor-*D*-homo-5α-androst-13(17a)-en-17-one (10a**, mp 134–136 °C) was obtained. A sample was sublimed at 0.02 mmHg and 90 °C for analysis: mp 137–138 °C; $[\alpha]^{23}_D$ −37.6° (*c* 1.000 in $CHCl_3$); UV (EtOH) λ_{max} 240 nm (log ε 4.28); IR (KBr) ν_{max} 1735 (acetate), 1675 and 1615 (α,β-unsaturated ketone doublet), 1250 cm^{-1} (acetate); ^1H NMR (60 MHz) δ 0.79 (s, 3 H, 19-CH_3), 2.02 (s, 3 H, CH_3COO), 4.70 (m, 3α-H), 5.82 (17a-H). Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.29; H, 8.95.

3β-Acetoxy-18-nor-*D*-homo-5α,13α-androstan-17-one (15). A quantity of 500 mg of 3β-acetoxy-18-nor-D-homo-5α-androst-13(17a)-en-17-one (**10a**, mp 134–136 °C) was hydrogenated in 50 mL of EtOH at atmospheric pressure for 90 min with 100 mg of a 5% palladium-on-charcoal catalyst. The catalyst was filtered off and was washed with CH_2Cl_2, and the filtrate and washings were taken to dryness to afford 500 mg (quantitative yield) of 3β-acetoxy-18-nor-*D*-homo-5α,13α-androstan-17-one (**15**), mp 170–172 °C. A sample was recrystallized three times from ether–hexane for analysis: colorless needles; mp 170–171 °C; $[\alpha]^{23}_D$ −12.1° (*c* 1.000, $CHCl_3$); ORD (*c* 1.000, CH_3OH) $[\alpha]_{400}$ +4°, $[\alpha]_{350}$ +12°, $[\alpha]_{310}$ +44°, $[\alpha]_{292}$ +64° (max), $[\alpha]_{278}$ +20°, $[\alpha]_{274}$ 0°, $[\alpha]_{272}$ −20°, $[\alpha]_{256}$ −58° (positive Cotton effect); IR (KBr) ν_{max} 1735 (acetate), 1715 (ketone), 1240 cm^{-1} (acetate). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.92; H, 9.52.

Similar results were obtained when the hydrogenation was performed with a 4% palladium-on-calcium carbonate catalyst in the presence of KOH.

3β-Acetoxy-18-nor-*D*-homo-5α,13β-androstan-17-one (14a). (a) From 3β-Hydroxy-18-nor-*D*-homo-5α-androst-13(17a)-en-17-one (10). A solution of 37.5 g of 3β-hydroxy-18-nor-*D*-homo-5α-androst-13(17a)-en-17-one (**10**, mp 197–198.5 °C) in 1.2 L of a 2:1 mixture of absolute dioxane and absolute ether was added dropwise and with stirring at −70 °C to a solution of 5 g of Li in 2 L of liquid NH_3. After 30 min of further stirring at −70 °C, 60 g of ammonium chloride was added in small portions until the color of the mixture became gray. The ammonia was evaporated on a steam bath under nitrogen. When the solution had reached 27 °C, it was poured into ice–water, and the precipitate was filtered, washed with water, and dried. Thus 35.8 g of crystals (mp 162.5–163.5 °C) representing **3β-hydroxy-18-nor-*D*-homo-5α,13β-androstan-17-one (14)** was obtained. This product was acetylated in the usual fashion in 300 mL of pyridine with 150 mL of acetic anhydride at room temperature for 12 h. The product was poured into water, and the precipitated crystals were filtered, were washed with water, and were dried. The resulting product (41.3 g, mp 123–125 °C) was recrystallized from ether–hexane to give 25.5 g (59.7%) of pure **3β-acetoxy-18-nor-*D*-homo-5α,13β-androstan-17-one (14a)**, mp 126.5–127.5 °C. The mother liquors (16.4 g) were combined with 53 g of mother liquors of equivalent purity obtained by an analogous reduction of 122 g of the enone **10** and were chromatographed on 1 kg of aluminum oxide (activity III). Elutions with petroleum ether–benzene mixtures (9:1, 4:1, 1:1) gave 25 g of ketone **14a**, mp 124–125 °C (total yield 65.6%). A sample was sublimed at 80 °C (0.02 mmHg) for analysis: coarse, short, colorless needles; mp 131.5–132 °C; $[\alpha]^{23}_D$ −30.2° (*c* 1.000, $CHCl_3$); ORD (*c* 0.100, CH_3OH) $[\alpha]_{400}$ −16°, $[\alpha]_{350}$ −104°, $[\alpha]_{312}$ −512° (min), $[\alpha]_{286}$ 0°, $[\alpha]_{280}$ +240°, $[\alpha]_{256}$ +608° (max), $[\alpha]_{230}$ +356° (negative Cotton effect); IR (KBr) ν_{max} 1740 (acetate), 1712 (ketone), 1250 cm^{-1} (acetate). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.95; H, 9.77.

(b) From 3β-Acetoxy-18-nor-*D*-homo-5α-androst-13-(17a)-en-17-one (10a). A solution of 510 mg of the acetoxy enone **10a** in 22 mL of a (1:1) mixture of absolute dioxane and absolute ether was added dropwise with stirring at −70 °C to a solution of 180 mg of lithium in 120 mL of liquid ammonia over a period of 5 min. After 20 min of further stirring, 1.5 g of ammonium chloride was added portionwise, and the solution turned from blue to gray. Ammonia was evaporated under a nitrogen current during 2 h, and the mixture was poured into ice–water and extracted with ether. The ethereal solution was washed with water, dried over sodium sulfate, and taken to dryness. The yellowish, crystalline residue (477 mg, mp 165–169 °C) was acetylated in the usual fashion in 2 mL of pyridine with 1 mL of Ac_2O. The oily product (510 mg) crystallized from hexane (mp 125–127 °C) and gave upon recrystallization from ether–hexane 340 mg (66%) of pure **3β-acetoxy-18-nor-*D*-homo-5α,13β-androstan-17-one (14a)**, mp 128–129 °C. The mother liquors (170 mg) were chromatographed on 5 g of aluminum oxide (activity III). Petroleum ether–benzene (4:1) eluted another 57 mg of ketone **14a**, mp 127–128 °C (total yield 77.3%).

In another experiment, 15 g of enone **10a** in 545 mL of a (1:1) mixture of absolute dioxane and absolute ether was reduced with 3.27 g of lithium in 1.7 L of liquid NH_3, worked up as described above, and acetylated with 50 mL of Ac_2O in 100 mL of pyridine. The product (15.7 g) was chromatographed on 450 g of Al_2O_3 (activity III), petroleum ether–benzene mixtures and pure benzene eluting 7.149 g (47.6%) of ketone **14a**, whereas earlier elutions with petroleum ether and petroleum ether–benzene (4:1) gave 3.15 g (20.6%) of **3β,17α-diacetoxy-18-nor-*D*-homo-5α,13β-androstane** (mp 183–184 °C). A sample was recrystallized five times from CH_2Cl_2–CH_3OH for analysis: mp 183–184 °C; $[\alpha]^{23}_D$ −8.4° (*c* 1.000, $CHCl_3$); IR (KBr) ν_{max} 1740, 1250 cm^{-1} (large acetate bands); ^1H NMR (60 MHz) δ 0.75 (s, 19-CH_3), 2.0 (s, 6 H, 2 CH_3COO), 4.7 (m, large, 2 H, axial 3α- and 17β-protons). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.29; H, 10.02.

3β-Acetoxy-17ξ-methyl-18-nor-*D*-homo-5α,13β-androstan-17ξ-ols (13, 13a). Under nitrogen, a solution of 7.4 g of 3β-acetoxy-18-nor-*D*-homo-5α,13β-androstan-17-one (**14a**) in 480 mL of absolute benzene was added dropwise and with stirring to a methylmagnesium iodide solution prepared in 480 mL of absolute ether from 5 g of magnesium and 13 mL of methyl iodide. The ether was evaporated, the mixture was refluxed for 2 h, the excess Grignard reagent was destroyed with 20% aqueous ammonium chloride, and the mixture was poured into ice–water. The ether extract was washed with aqueous 0.1 N sodium thiosulfate, with a cold 20% solution of NH_4Cl, and with water. After the mixture had been dried over Na_2SO_4, the solvent was removed, and the crystalline residue (6.7 g) was acetylated in 80 mL of pyridine with 40 mL of Ac_2O at room temperature. The usual workup gave 7.5 g (97%) of a product crystallizing from ether–hexane (mp 155–158 °C) and representing a mixture of the acetoxy alcohols **13** and **13a**. By fractional crystallization from ether–hexane, 4.2 g (56%) of **3β-acetoxy-17α-methyl-18-nor-*D*-homo-5α,13β-androstan-17β-ol (13**, mp 161–163 °C) was isolated.[67] A sample was recrystallized three times from ether for analysis: prisms; mp 162–163 °C; $[\alpha]^{23}_D$ −31.0° (*c* 1.000, $CHCl_3$); IR (KBr) ν_{max} 3415 (OH), 1740, 1720 (split band, acetate), 1265 and 1250 (split band, acetate); IR (CCl_4) ν_{max} 3450 (weak OH band), 1735 (acetate), 1243 cm^{-1} (acetate). Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.79; H, 10.42.

(67) The configuration of the 17-hydroxy-17-methyl-*D*-homoandrostane derivatives **13** and **13a** is tentatively assigned on the basis of the fact that the dehydration of the pure alcohol **13**, for which we suggest an axial (17β) stereochemistry of the 17-hydroxy group, leads to a mixture of the $\Delta^{16,17}$ and $\Delta^{17,17a}$ olefins **12** and **12b**, whereas that of the mixture of alcohols **13** and **13a** also affords the $\Delta^{17,17^1}$ olefin **12d** (cf. below).

(68) Wendler, N. L., personal communication; cf. ref 8.

The mother liquors were taken to dryness and recrystallized from CH_3OH to give 438 mg (5.8%) of **3β-acetoxy-17β-methyl-18-nor-*D*-homo-5α,13β-androstan-17α-ol (13a)**, mp 125–126 °C. A sample was sublimed at 0.02 mmHg and 90 °C for analysis: mp 126–127 °C; $[\alpha]_D^{23}$ −27.2° (*c* 1.000, $CHCl_3$); IR (KBr) ν_{max} 3360 (OH), 1740 and 1240 cm^{-1} (acetate). Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.73; H, 10.43.

Dehydration of the 3β-Acetoxy-17ξ-methyl-18-nor-*D*-homo-5α,13β-androstan-17ξ-ols (13, 13a). (a) Dehydration of Alcohol 13. A solution of 1.5 g of the acetoxy alcohol **13** (mp 161–163 °C), to which we assign tentatively the 17β-hydroxy configuration, in 25 mL of pyridine was treated at 0 °C with 1.5 mL of phosphorous oxychloride. The mixture was allowed to reach room temperature and was stored for 16 h. Subsequently, in the cold, the excess phosphorus oxychloride was destroyed with ice, and the product was poured into ice–water. The ether extract was washed with iced 2 N HCl, with a cold $NaHCO_3$ solution, and with water and was dried over sodium sulfate. Evaporation of the solvent gave 1.464 g of a colorless oil which crystallized from EtOH (mp 86–89 °C). By recrystallization from EtOH, 391 mg of crystals melting at 98–99 °C was obtained. According to the integration of the NMR peaks of the 17a-H and 16-H protons (δ 5.16 and 5.37), this product contained approximately 80% of **3β-acetoxy-17-methyl-18-nor-*D*-homo-5α,13β-androst-16-ene (12)** and about 20% of **3β-acetoxy-17-methyl-18-nor-*D*-homo-5α,13β-androst-17(17a)-ene (12b)**. A sample of this mixture was recrystallized three times from ethanol for analysis: fine, colorless crystals; mp 97–98 °C; $[\alpha]_D^{23}$ −88.9° (*c* 1.000, $CHCl_3$); UV (cyclohexane) λ_{max} 188 nm (log ε 1.84); IR (KBr) ν_{max} 1740, 1243 cm^{-1} (acetate); ^1H NMR (60 MHz) δ 0.78 (s, 3 H, 19-CH_3), 1.60 (s, 3 H, 17-CH_3), 2.0 (CH_3COO), 4.7 (m, 3α-H), 5.16 (17a-H), 5.37 (d) (16-H). Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 80.04; H, 10.39.

(b) Dehydration of the Mixture of Alcohols 13 and 13a. A quantity of 3.4 g of the mixture of the acetoxy alcohols **13** and **13a** (mp 164–166 °C), obtained from ketone **14a**, was treated with 3.4 mL of $POCl_3$ as described above. Ether extraction gave 3 g of a yellowish product which was adsorbed on 90 g of aluminum oxide (activity II). Hexane–benzene (9:1) eluted 1.341 g of a product crystallizing from ethanol (mp 85–88 °C). Further elutions with the same solvent mixture gave 1.193 g of a product melting between 91 and 94 °C. The two products were recrystallized separately from EtOH to give 1.186 g of a mixture of the olefins **12** and **12b** (mp 97–98 °C). The mother liquors (1.6 g) were hydrolyzed, as described, in 520 mL of CH_3OH with 760 mg of K_2CO_3 dissolved in 100 mL of H_2O and 100 mL of CH_3OH. The resulting product (1.3 g) was benzoylated, as described previously, in 10 mL of pyridine with 2 mL of benzoyl chloride. Thus 1.6 g of a crystalline product (mp 140–145 °C) was obtained. It was dissolved in CCl_4 and chromatographed on Al_2O_3 (activity II). Hexane–benzene (9:1 and 4:1) eluted 1.063 g of a product melting between 159 and 165 °C. Recrystallization from dichloromethane–ether gave 819 mg of a product (mp 165–166 °C) which, according to the integration of the olefinic protons in its NMR spectrum, contained an 8:2 mixture of **3β-(benzoyloxy)-17-methyl-18-nor-*D*-homo-5α,13β-androst-16-ene (12a)** and **3β-(benzoyloxy)-17-methyl-18-nor-*D*-homo-5α,13β-androst-17(17a)-ene (12c)**. A sample of that mixture was recrystallized three times from dichloromethane–ether for analysis: mp 166–167 °C; $[\alpha]_D^{23}$ −62° (*c* 1.000, $CHCl_3$); UV (EtOH) λ_{max} 228 nm (log ε 4.2); IR (KBr) ν_{max} 3025 (unsaturation), 1650 (double bond), 1600 and 1580 (aromatic), 1270 and 710 cm^{-1} (ester); ^1H NMR (60 MHz) δ 0.78 (s, 3 H, 19-CH_3), 1.60 (s, 3 H, 17-CH_3), 5.17 (s, 17a-H), 5.37 (d, 16-H), 7.47 and 8.10 (m, aromatic protons). Anal. Calcd for $C_{27}H_{36}O_2$: C, 82.60; H, 9.24. Found: C, 82.81; H, 9.33.

The above-described mixture obtained by chromatography also contained some 17,17[1]-unsaturated product **12e** with an exocyclic methylene group, as evidenced by the ^1H NMR spectrum (60 MHz): δ 0.78 (19-CH_3), 1.60 (17-CH_3), 4.6 (=CH_2), 4.17 (s, 17a-H), 5.33 (d, 16-H), 7.47 and 8.13 (m, aromatic protons). The mother liquors of the above-described crystallizations were recrystallized from ether–ethanol to give 80 mg of a product (mp 133–137 °C), representing essentially **3β-(benzoyloxy)-17-methylene-18-nor-*D*-homo-5α,13β-androstane (12e)**. A sample was recrystallized from ether–ethanol for analysis: mp 149–150 °C; $[\alpha]_D^{23}$ −43.6° (*c* 1.000, $CHCl_3$); UV (EtOH) λ_{max} 228 nm (log ε 4.1); IR (KBr) ν_{max} 1725 (ester), 1665 (=CH_2), 1605 and 1585 (aromatic), 1270, 710 cm^{-1} (benzoate); ^1H NMR (60 MHz) δ 0.83 (s, 19-CH_3), 4.60 (CH_2=), 5.16 (m, 3α-H), 7.53 and 8.08 (m, aromatic protons). Anal. Calcd for $C_{27}H_{36}O_2$: C, 82.61; H, 9.24. Found: C, 81.97; H, 9.31.

(c) Dehydration of the Mixture of the Acetoxy Alcohols 13 and 13a and Equilibration of the Resulting Olefins. A quantity of 37.7 g of the epimeric mixture of the *D*-homo 17-alcohols **13** and **13a** was dehydrated as described above in 600 mL of pyridine with 37 mL of $POCl_3$. The workup and extraction, as described above, of the reaction product gave 34.4 g of an oily material: ^1H NMR (90 MHz) δ 0.77 (s, 19-CH_3), 1.65 (s, 17-CH_3), 2.00 (s, CH_3COO), 4.49–4.90 (integration 1.28 H, m, 3α-H and vinylic protons), 5.10 (integration 0.28 H, m, 17a-H), 5.32 (integration 0.57 H, m, 16-H). This product, together with 18.5 g of an analogous product prepared from 20.5 g of an analogous mixture of the alcohols **13** and **13a**, was dissolved in 2.8 L of absolute benzene and was refluxed for 90 min with 2.8 g of *p*-toluenesulfonic acid. The product was poured into water and was extracted with ether. The ethereal solution was washed with an iced saturated $NaHCO_3$ solution and with water and was dried over Na_2SO_4. Evaporation of the solvent gave 52.3 g of a semicrystalline mixture of the isomeric acetoxy olefins **12**, **12b** and **12d**: ^1H NMR (90 MHz) δ 0.77 (s, 19-CH_3), 1.65 (s, 17-CH_3), 2.00 (s, CH_3COO), 4.49–4.90 (integration 1.04 H, m, 3α- and vinylic protons), 5.10 (integration 0.23 H, m, 17a-H), 5.32 (integration 0.75 H, m, 16-H). Recrystallization from EtOH afforded 35.1 g of crystalline material (mp 97–98 °C) which contained, according to the integration of the ^1H NMR absorptions of the olefinic protons, 81% of **3β-acetoxy-17-methyl-18-nor-*D*-homo-5α,13β-androst-16-ene (12)** and 19% of **3β-acetoxy-17-methyl-18-nor-*D*-homo-5α,13β-androst-17(17a)-ene (12b)**.

Ozonolysis of the Mixture of 3β-Acetoxy-17-methyl-18-nor-*D*-homo-5α,13β-androst-16-ene (12) and 3β-Acetoxy-17-methyl-18-nor-*D*-homo-5α,13β-androst-17(17a)-ene (12b). At −70 °C, an oxygen current containing 1.7% of ozone was passed for 40 min at a flow rate of 360 mL/min through a solution of 20 g of the mixture, described above in section c, of the isomeric *D*-homoandrostenes **12** and **12b**, dissolved in 600 mL of a 2:1 CH_2Cl_2–CH_3OH mixture. Subsequently, 20 g of zinc powder and 20 mL of glacial acetic acid were added at room temperature, and the mixture was stirred for 30 min, filtered, and poured into ice–water. The CH_2Cl_2 extract was washed with a saturated $NaHCO_3$ solution and with water and was dried over Na_2SO_4. Evaporation of the solvents gave 23.6 g of an oily, not separable mixture of **3β-acetoxy-18-nor-16,17-seco-16-oxo-5α,13β-pregnan-20-one (16)** and **3β-acetoxy-17-methyl-18-oxo-13,17-seco-5α,13α-androstan-17-one (11)**: IR (KBr) ν_{max} 2705 (aldehydes), 1730 (ketones), 1740 and 1250 cm^{-1} (acetates); ^1H NMR (60 MHz) δ 0.76 (s, 19-CH_3), 1.94 (CH_3COO), 2.05 (CH_3CO), 3.6 (m, 3α-H), 9.46 (d, CHO, 11), 9.75 (t, CHO, 16). According to the integration of the peaks in the region of δ 9–10, the proportion of aldehydes **16** and **11** amounted approximately to 4:1. This mixture was used as such in the following reaction.

3β-Acetoxy-18-nor-5α,13β-pregn-16-en-20-one (17a), 3β,16ξ-Diacetoxy-18-nor-5α,13β-pregnan-20-one (17b), and 3β-(Benzoyloxy)-16ξ-methoxy-18-nor-5α,13β-pregnan-20-one (17c). (a) To 650 mg of the above-described mixture of the keto aldehydes **16** and **11** was added 100 mL of an aqueous 2.5% KOH solution, a few milliliters of water was evaporated in vacuo, and the mixture was refluxed for 3.5 h in a nitrogen atmosphere. The product was poured into ice water and was extracted with a (3:1) ether–dichloromethane mixture. The organic solution was washed with water and was dried over Na_2SO_4. Evaporation of the solvent gave 700 mg of an oily product which was acetylated in the usual manner in 2 mL of pyridine with 1 mL of Ac_2O. The resulting oily product (772 mg) was absorbed on 20 g of Al_2O_3 (activity III). Petroleum ether and petroleum ether–benzene mixtures (9:1 and 4:1) eluted 464 mg (75% from the mixture of the keto aldehydes **16** and **11**, 73.8% from the mixture of the D-homoandrostenes **12** and **12b**) of **3β-acetoxy-18-nor-5α,13β-pregn-16-en-20-one (17a)**, mp 124–127 °C. A sample was recrystallized three times from methanol for analysis: colorless needles; mp 141–142 °C; $[\alpha]_D^{23}$ +37.3° (*c* 1.000, $CHCl_3$); ORD (*c* 0.1000, CH_3OH) $[\alpha]_{500}$ +80°, $[\alpha]_{450}$ +140°, $[\alpha]_{400}$ +240°, $[\alpha]_{370}$ +520°, $[\alpha]_{346}$ +780° (max), $[\alpha]_{330}$ +320°, $[\alpha]_{324}$ 0°, $[\alpha]_{310}$ −800°, $[\alpha]_{300}$ −1200°, $[\alpha]_{286}$ −1360° (min), $[\alpha]_{270}$

−1320° (positive Cotton effect); UV (EtOH) λ_{max} 239 nm (log ϵ 3.8); IR (KBr) ν_{max} 1740 (acetate), 1665 and 1585 (Δ^{16}-20-ketone doublet), 1250 cm^{-1} (acetate); ^1H NMR (60 MHz) δ 0.75 (s, 19-CH_3), 1.90 (CH_3COO), 2.12 (CH_3CO), 4.3 (q, 16-H), 4.5 (m, 3α-H). Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.83; H, 9.40.

Further elutions with petroleum ether–benzene mixtures gave 165 mg (mp 178–180 °C; 22.7% from the mixture of the keto aldehydes **16** and **11**) of **3β,16ξ-diacetoxy-18-nor-5α,13β-pregnan-20-one (17b)**. The product was recrystallized four times from methanol for analysis: colorless needles; mp 181–182 °C; $[\alpha]^{23}_D$ −32° (*c* 1.000, $CHCl_3$); IR (KBr) ν_{max} 1740 (large, acetates), 1713 (ketone), 1250 cm^{-1} (large, acetates). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.10; H, 9.03.

(b) To a solution of 370 mg of the above-described mixture of the keto aldehydes **16** and **11** in 2 mL of CH_3OH was added 20 mL of H_2O, the volume of the mixture was reduced to 18 mL, and it was treated, for 5 h at 85 °C under nitrogen and with stirring, with 0.4 mL of aqueous 1 N NaOH. The product was poured on ice and was extracted with ether. The ethereal solution was washed with water and was dried over Na_2SO_4. Removal of the solvent gave 280 mg of a yellowish oil. A portion of 140 mg of this product was dissolved in 2 mL of absolute CH_3OH and added to a solution of $NaOCH_3$, prepared from 140 mg of Na and 7 mL of CH_3OH. The mixture was refluxed for 20 min, poured into ice–water, and extracted with ether. The ethereal solution was washed with water and was dried over Na_2SO_4, and the solvent was evaporated. The oily residue (105 mg) was chromatographed on 3.5 g of Al_2O_3 (activity III). Hexane–benzene (1:4) eluted 68 mg of a crystalline product [mp 149–153 °C; IR (KBr) ν_{max} 3500, 3400 (OH), 1705 (ketone), 1090 cm^{-1} (CH_3O)]; it was dissolved in 0.4 mL of pyridine and benzoylated with 0.2 mL of benzoyl chloride. The usual workup gave 80 mg (34%) of **3β-(benzoyloxy)-16ξ-methoxy-18-nor-5α,13β-pregnan-20-one (17c)**, mp 130–132 °C. A sample was recrystallized from methanol for analysis: short, clustered needles; mp 143–145 °C; $[\alpha]^{23}_D$ −10.4° (*c* 0.500, $CHCl_3$); UV (EtOH) λ_{max} 228 nm (log ϵ 3.95); IR (KBr) ν_{max} 3060 (unsaturation), 1725 (carbonyls), 1605 and 1585 (aromatic), 1270 (ester), 1105 (16ξ-OCH_3), 710 cm^{-1} (ester); ^1H NMR (60 MHz) δ 0.79 (s, 19-CH_3), 2.10 (CH_3CO), 3.10 (s, 3 H, 16-OCH_3), 3.78 (16-H), 4.8 (m, 3α-H), 7.15 and 7.75 (m, aromatic protons). Anal. Calcd for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.59; H, 8.49.

To a solution in 1 mL of CH_3OH of the other half (140 mg) of the product obtained as described above by reaction of the keto aldehydes **16** and **11** with NaOH was added another 25 mL of aqueous 1 N NaOH, and the mixture was refluxed for 2.5 h under nitrogen. The product was precipitated into ice–water and was extracted with ether. The organic solution was washed with water, dried over Na_2SO_4, and taken to dryness. The oily residue (110 mg) was chromatographed on Al_2O_3 (activity III). Petroleum ether–benzene (1:4) eluted 68 mg (44%) of **3β-hydroxy-18-nor-5α,13β-pregn-16-en-20-one (17)**, mp 144–147 °C. The product was recrystallized three times from ether–hexane for analysis: colorless needles; mp 160–161 °C; $[\alpha]^{23}_D$ +46.8° (*c* 1.000, $CHCl_3$); UV (EtOH) λ_{max} 239 nm (log ϵ 3.94); IR (KBr) ν_{max} 3425 (OH), 1650 and 1580 cm^{-1} (α,β-unsaturated ketone doublet); ^1H NMR (60 MHz) δ 0.77 (s, 19-CH_3), 1.95 (OH), 2.2 (s, 3 H, CH_3CO), 3.57 (m, 3α-H), 6.73 (q, 16-H). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.60; H, 9.96.

3β-Acetoxy-18-nor-5α,13β-pregnan-20-one (18). A quantity of 3.8 g of 3β-acetoxy-18-nor-5α,13β-pregn-16-en-20-one (**17a**, mp 140–141 °C) in 475 mL of EtOH was hydrogenated at atmospheric pressure in the presence of 760 mg of 5% palladium on charcoal. After 4 h, the catalyst was filtered off and was washed with CH_2Cl_2. The filtrate and washings were taken to dryness to give 3.8 g of crystalline 3β-acetoxy-18-nor-5α,13β-pregnan-20-one (**18**), mp 104–105 °C. A sample was recrystallized three times from hexane for analysis: colorless plates; mp 107–108 °C; $[\alpha]^{23}_D$ +14.6° (*c* 1.000, $CHCl_3$); CD (*c* 1.00, CH_3OH) $[\Theta]_{316}$ 0, $[\Theta]_{302}$ −229, $[\Theta]_{292}$ −458, $[\Theta]_{286}$ −492 (min), $[\Theta]_{280}$ −458, $[\Theta]_{268}$ −229, $[\Theta]_{248}$ 0 (negative Cotton effect); IR (KBr) ν_{max} 1740 (acetate), 1713 (ketone), 1250 cm^{-1} (acetate); ^1H NMR (60 MHz) δ 0.75 (s, 19-CH_3), 1.93 (s, CH_3COO), 2.03 (s, CH_3CO), 4.5 (m, 3α-H). Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.53; H, 9.91.

17-Bromo-3β-acetoxy-18-nor-5α,13β-pregnan-20-one (20). (a) Via the Enol Diacetates 19. As described for the preparation of the isomeric mixtures of the enol acetates **5**, 600 mg of 3β-acetoxy-18-nor-5α,13β-pregnan-20-one (**18**, mp 101.5–103 °C) was treated for 7 h with 46 mL of Ac_2O and 172 mg of *p*-TsOH. The usual workup gave 705 mg of an oil which was chromatographed on 30 g of Al_2O_3 (activity III). Elutions with petroleum ether–benzene (1:1) gave 564 mg of a semicrystalline mixture of the ***cis*- and *trans*-3β,20-diacetoxy-18-nor-5α,13β-pregn-17(20)-enes (19)**: IR (KBr) ν_{max} 1740 and 1240 cm^{-1} (large bands, 3β,20-acetates); ^1H NMR (90 MHz) δ 0.77 (s, 19-CH_3), 1.78 (s, 21-CH_3), 2.00 (s, 3β-CH_3COO), 2.08 (s, 20-CH_3COO), 4.47–4.90 (m, 3α-H). To 3 mL of a solution of 160 g of bromine in 1 L of AcOH was added 147 mg of KOAc in 0.1 mL of H_2O, and 2.5 mL of this mixture was added dropwise and with stirring, in the course of 20 min, to 564 mg of the above-described mixture of the cis and trans enol acetates **19**, dissolved in 9.8 mL of acetic acid. Subsequently, the product was precipitated into ice–water containing a dilute sodium bisulfite solution, and the mixture was extracted with ether. The ethereal layer was washed with an iced dilute $NaHCO_3$ solution and with water, dried over Na_2SO_4, and taken to dryness in vacuo. There was obtained 590 mg (80% yield from ketone **18**) of **17-bromo-3β-acetoxy-18-nor-5α,13β-pregnan-20-one (20)**: mp 105–106 °C; $[\alpha]^{25}_D$ +45.5° (*c* 1.080, $CHCl_3$). For analysis, a sample was recrystallized three times from methanol: colorless needles; mp 117.5–118 °C; $[\alpha]^{24}_D$ +57.5° (*c* 0.900, $CHCl_3$); ORD (*c* 0.018, CH_3OH) $[\alpha]_{400}$ +138°, $[\alpha]_{350}$ +555°, $[\alpha]_{330}$ +1278°, $[\alpha]_{319}$ +1430° (max), $[\alpha]_{302}$ 0°, $[\alpha]_{275}$ −2054° (min), $[\alpha]_{260}$ −1860° (positive Cotton effect); IR (KBr) ν_{max} 1735 (acetate), 1710 (ketone), 1250 cm^{-1} (acetate); ^1H NMR (90 MHz) δ 0.77 (s, 19-CH_3), 2.00 (s, CH_3COO), 2.41 (s, CH_3CO), 4.70 (m, 3α-H). Anal. Calcd for $C_{22}H_{33}O_3Br$: C, 62.11; H, 7.82; Br, 18.79. Found: C, 62.04; H, 8.00; Br, 18.70.

(b) By *N*-Bromosuccinimide Bromination of Ketone 18. A solution of 4.4 g of 3β-acetoxy-18-nor-5α,13β-pregnan-20-one (**18**) in 160 mL of absolute CCl_4 was refluxed with 3.4 g of NBS for 7 min under irradiation with a 660-W photoflood lamp. After cooling, the solution was washed with iced aqueous 0.1 N sodium thiosulfate and with ice–water and was dried over Na_2SO_4. Evaporation of the solvent left 5.2 g of a dark brown oil which was absorbed on 520 g of silica gel. Benzene–ethyl acetate (50:1) eluted 3.8 g of a product which crystallized from CH_3OH (mp 96–102 °C). Recrystallization from CH_3OH gave 1.2 g (22% yield) of bromide **20**, mp 108–110 °C. The analytical sample was obtained by two further recrystallizations from CH_3OH: mp 116–117 °C; $[\alpha]^{23}_D$ +53.7° (*c* 0.775, $CHCl_3$). Its spectral characteristics were identical with those of the product described in section a. Anal. Calcd for $C_{22}H_{33}O_3Br$: C, 62.11; H, 7.82; Br, 18.79. Found: C, 62.20; H, 7.62; Br, 19.03.

On crystallization of the mother liquors, no bromide **20** of comparable purity could be obtained.

Rearrangement of 17-Bromo-3β-acetoxy-18-nor-5α,13β-pregnan-20-one (20) with Potassium Bicarbonate in Aqueous Methanol. To a solution of 890 mg of analytically pure 17-bromo-3β-acetoxy-18-nor-5α,13β-pregnan-20-one (**20**, mp 117.5–118 °C) in 45 mL of CH_3OH was added a solution of 2 g of $KHCO_3$ in 8.5 mL of water, and the mixture was refluxed under nitrogen for 4 h. The product was poured into ice–water and extracted with ether. The ethereal solution was washed with water and was dried over Na_2SO_4. Evaporation of the solvent gave 666 mg of a crystalline substance (mp 158–162 °C) which gave a negative Beilstein test. The aqueous phase of the extraction and the water washings were combined, acidified with dilute H_2SO_4 to pH 2, and extracted with CH_2Cl_2. The organic solution was washed with water and was dried over Na_2SO_4. Evaporation of the solvent gave 29 mg of an oily product which was not further investigated.

The neutral fraction was acetylated at room temperature overnight with 2 mL of Ac_2O in 4 mL of pyridine. The usual workup gave 770 mg of a crystalline product (mp 151–155 °C). A portion of 701 mg of this mixture was recrystallized from ether–hexane to afford 196 mg (28.4%) of **3β-acetoxy-17β-hydroxy-18-nor-5α,17α-pregnan-20-one (23a)**, mp 156–157 °C. For analysis, a sample was recrystallized three times from ether–hexane: colorless platelets; mp 168–169 °C; $[\alpha]^{31}_D$ +20.7° (*c* 1.000, $CHCl_3$); ORD (*c* 0.034, CH_3OH) $[\alpha]_{400}$ +56.2°, $[\alpha]_{350}$ +89.8°,

$[\alpha]_{322}$ +118° (max), $[\alpha]_{308}$ +101.1°, $[\alpha]_{300}$ +73° (min), $[\alpha]_{290}$ +101.1° (positive Cotton effect); IR (CCl_4) ν_{max} 3610, 3470 (OH), 1740 (acetate), 1705 (20-ketone), 1235 (acetate), 1030 cm^{-1} (OH); ^1H NMR (90 MHz) δ 0.78 (s, 19-CH_3), 2.00 (s, CH_3COO), 2.22 (s, CH_3CO), 4.50–4.83 (m, 3α-H); mass spectrum, *m/e* 362 (M^+), 319 (M – CH_3CO, base peak), 305, 259; positive bromoform test by Adachi's procedure.[44] Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.82; H, 9.38. The structure and configuration of the product was confirmed by a crystallographic X-ray analysis by Drs. C. P. Huber and F. R. Ahmed, National Research Council of Canada, Ottawa, Canada.

The mother liquors were subjected to dry-column chromatography (60 × 3 cm column) on silica gel with petroleum ether–ether (4:1) as the developing solvent. The following products were isolated in increasing order of polarity.

(1) **Methyl 3β-acetoxy-17α-methyl-18-nor-5α-etianate (21a)**: 181 mg (25.2%); mp 105.5–106 °C. For analysis, a sample was recrystallized three times from methanol: colorless prisms; mp 106–106.5 °C; $[\alpha]^{31}_D$ –6.9° (*c* 0.990, $CHCl_3$); IR (KBr) ν_{max} 1735 (esters), 1250 (acetate), 1235 cm^{-1} (methyl ester); ^1H NMR (90 MHz) δ 0.78 (s, 19-CH_3), 1.07 (s, 17-CH_3), 2.00 (s, CH_3COO), 3.64 (s, 3 H, $COOCH_3$), 4.68 (m, 3α-H). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.22; H, 9.80.

The 17α-methyl configuration was confirmed by Fortier and Ahmed[41] by an X-ray crystallographic study.

(2) An oil (28 mg) which was subjected to thin-layer chromatography on silica gel (7% ethyl acetate in hexane). Thus, 10 mg of **methyl 3β-acetoxy-17β-methyl-18-nor-5α,17α-etianate (22a**, mp 92–97 °C) was obtained. The identity of this product with authentic material, described in the rearrangement experiment with $KOCH_3$ in absolute CH_3OH (cf. below), was established by the comparison of the infrared spectra and by the determination of a mixture melting point.

(3) A compound (21 mg) to which we ascribe either the structure of **3β-acetoxy-17aξ-methoxy-17aξ-methyl-18-nor-*D*-homo-5α,13β-androstan-17-one (24a)** or of **3β-acetoxy-17ξ-methoxy-17ξ-methyl-18-nor-*D*-homo-5α,13β-androstan-17a-one (24c)**, mp 177–185.5 °C. For analysis, a sample was recrystallized three times from ether–hexane: colorless platelets; mp 199–200 °C; $[\alpha]^{29}_D$ –50.2° (*c* 1.170, $CHCl_3$); IR (KBr) ν_{max} 1730 (acetate), 1712 (17- or 17a-ketone), 1245 cm^{-1} (acetate); ^1H NMR (90 MHz) δ 0.73 (s, 3 H, 19-CH_3), 1.16 (s, 3 H, 17- or 17a-CH_3), 2.00 (s, 3 H, CH_3COO), 3.05 (s, 3 H, 17- or 17a-OCH_3), 4.68 (m, 3α-H); mass spectrum, *m/e* 376 (M^+), 361 (M – CH_3), 348 (M – CO), 333 (M – $COCH_3$), 319, 85 (base peak). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.81; H, 9.62.

(4) A mixture (16 mg) of three products which was not further investigated.

(5) A product (36 mg) which, upon recrystallization from ether–hexane, gave 11 mg of **3β,17β-diacetoxy-18-nor-5α,17α-pregnan-20-one (23b)**, mp 148–150.5 °C. Another 84 mg of the same product (mp 154.5–156 °C) was obtained also in the following fraction. For analysis, a sample was recrystallized four times from ether–hexane: colorless platelets; mp 161–161.5 °C; $[\alpha]^{29}_D$ +13.8° (*c* 0.790, $CHCl_3$); ORD (*c* 0.020, CH_3OH) $[\alpha]_{400}$ +114°, $[\alpha]_{350}$ +156°, $[\alpha]_{320}$ +208°, $[\alpha]_{290}$ +260° (inflexion), $[\alpha]_{250}$ +395°; IR (KBr) ν_{max} 1735 (acetates), 1710 (20-ketone), 1250 cm^{-1} (acetates); ^1H NMR (90 MHz) δ 0.77 (s, 19-CH_3), 2.00 (s) and 2.03 (s) (3-CH_3COO and 17-CH_3COO), 2.10 (s, CH_3CO), 4.68 (m, 3α-H); mass spectrum, *m/e* 404 (M^+), 361 (M – CH_3CO), 344 (M – CH_3COOH), 319, 301, 241 (M – CH_3CO – $2CH_3COOH$, base peak). Anal. Calcd for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.33; H, 8.96.

(6) **3β-Acetoxy-17β-hydroxy-18-nor-5α,17α-pregnan-20-one (23a)**: 95 mg (13.8%) [59 mg, mp 141–146.5 °C; 36 mg, mp 138–142.5 °C]. The identity of the product was established by the comparison of the infrared spectra and by the determination of a mixture melting point with the above-described product, obtained directly by crystallization.

Acetylation of 3β-Acetoxy-17β-hydroxy-18-nor-5α,17α-pregnan-20-one (23a). To a solution of 35 mg of 3β-acetoxy-17β-hydroxy-18-nor-5α,17α-pregnan-20-one (**23a**) in 0.8 mL of glacial AcOH and 0.4 mL of Ac_2O was added 35 mg of *p*-TsOH, and the mixture was stored at room temperature for 18 h, cooled to 0 °C, treated with a few milliliters of CH_3OH, poured into ice–water, and extracted with ether. The ethereal solution was washed with an iced saturated $NaHCO_3$ solution and with water and was dried over Na_2SO_4. Evaporation of the solvents gave 36 mg of crystals (mp 156–157.5 °C) which gave on recrystallization from ether–hexane 21 mg of **3β,17β-diacetoxy-18-nor-5α,17α-pregnan-20-one (23b)**, mp 158–159 °C. The product was identified with the one isolated from the acetylated rearrangement product by the determination of a mixture melting point and by the comparison of the infrared spectra.

The results of this reaction were confirmed by a second experiment with 535 mg of analytically pure bromo ketone **20**, dissolved in 27 mL of CH_3OH, and treated, as described above, with 1.2 g of $KHCO_3$ in 5.1 mL of H_2O.

Quantitative Analysis by Gas Chromatography. According to the procedure outlined above in the General Methods, the acetylated neutral fraction of the reaction product was analyzed gas chromatographically with the following results: the product contained 25.1% of methyl 3β-acetoxy-17α-methyl-18-nor-5α-etianate (**21a**), 5.5% of methyl 3β-acetoxy-17β-methyl-18-nor-5α,17α-etianate (**22a**), 20.5% of 3β,17β-diacetoxy-18-nor-5α,17α-pregnan-20-one (**23b**), and 34.3% of 3β-acetoxy-17β-hydroxy-18-nor-5α,17α-pregnan-20-one (**23a**). The amount of the *D*-homo steroid **24a** or **24c** contained in the mixture corresponded approximately to 2.3%, as established by weight (since the retention time of this product is very close to that of the diacetoxy ketone **23b**).

Rearrangement of 17-Bromo-3β-acetoxy-18-nor-5α,13β-pregnan-20-one (20) with Potassium Methoxide in Absolute Methanol. Under nitrogen, there was added to a refluxing solution of potassium methoxide (prepared from 186 mg of potassium and 21 mL of absolute methanol), in the course of 10 min and portionwise, 898 mg of analytically pure 17-bromo-3β-acetoxy-18-nor-5α,13β-pregnan-20-one (**20**, mp 117.5–118 °C), and the mixture was refluxed under nitrogen for another 2 h. Subsequently, 4 mL of CH_3OH was added, the mixture was again heated for 20 min, its volume was reduced in vacuo to 15 mL, and the product was poured into ice–water and was extracted with ether. The ethereal solution was washed with cold 2 N H_2SO_4, with water, with an iced saturated $NaHCO_3$ solution, and with water and was dried over Na_2SO_4. Evaporation of the solvents gave 724 mg of crystals (mp 154–160 °C) which gave a negative Beilstein test. The aqueous phase of the extraction and the washings were combined, acidified to pH 3 with dilute H_2SO_4, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and taken to dryness. The oily residue (12 mg) was not further investigated.

The neutral fraction was acetylated at room temperature for 18 h with 2 mL of Ac_2O in 4 mL of pyridine. The usual workup gave 799 mg of crystalline material (mp 115–118 °C), a portion of 726 mg of which was recrystallized from ether–hexane to give 223 mg (32%) of **3β-acetoxy-17β-hydroxy-18-nor-5α,17α-pregnan-20-one (23a)**, mp 149–152 °C. Its identity was established by comparison of its infrared spectrum with that of the product obtained in the reaction with $KHCO_3$ in aqueous CH_3OH (cf. above) and by the determination of a mixture melting point. The mother liquors were subjected to dry column chromatography (60 × 3 cm column) on silica gel, petroleum ether–ether (4:1) being used as the developing solvent. The following products were isolated.

(1) **Methyl 3β-acetoxy-17α-methyl-18-nor-5α-etianate (21a)**: 92 mg (12.7%); mp 104.5–105.5 °C. This product was identified by the determination of a mixture melting point and by spectral comparisons with the product obtained in the previous experiment.

(2) **Methyl 3β-acetoxy-17β-methyl-18-nor-5α,17α-etianate (22a)**: 79 mg (11%); mp 102–104 °C. The product was identical with the one isolated in the previous experiment. For analysis, it was recrystallized three times from CH_3OH: colorless platelets; mp 114.5–115 °C; $[\alpha]^{31}_D$ –10.6° (*c* 0.490, $CHCl_3$); IR (CCl_4) ν_{max} 1733, 1245 cm^{-1} (large acetate and methyl ester bands); ^1H NMR (90 MHz) δ 0.77 (s, 19-CH_3), 1.23 (s, 17β-CH_3), 2.00 (s, CH_3COO), 3.63 (s, 3 H, $COOCH_3$), 4.65 (m, 3α-H). Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.58; H, 9.56.

(3) The compound (23 mg) to which we assign either the structure of **3β-acetoxy-17aξ-methoxy-17aξ-methyl-18-nor-*D*-homo-5α,13β-androstan-17-one (24a)** or of **3β-acetoxy-17ξ-methoxy-17ξ-methyl-18-nor-*D*-homo-5α,13β-androstan-17a-one (24c)**, mp 173–180 °C. This product was identified by spectral comparisons and by a mixture melting point determination with

the equivalent product isolated in the previous experiment.

(4) **3β,17β-Diacetoxy-18-nor-5α,17α-pregnan-20-one (23b)**: 144 mg (16.4%); mp 155–157 °C. This product was identified with the equivalent product isolated in the previous experiment in the usual fashion.

(5) **3β-Acetoxy-17β-hydroxy-18-nor-5α,17α-pregnan-20-one (23a)**: 52 mg (7.5%); mp 145–151 °C. This product was identified in the usual fashion by comparison with the product isolated in the previous experiment.

The results of this experiment were confirmed by repetition with 401 mg of analytically pure bromo ketone **20** and with $KOCH_3$ prepared from 80 mg of potassium and 9.4 mL of absolute CH_3OH.

Quantitative Analysis by Gas Chromatography. The gas chromatographic determination (cf. above) of the proportion of the isolated products in the acetylated reaction mixture gave the following results: 14.8% of methyl 3β-acetoxy-17α-methyl-18-nor-5α-etianate (**21a**), 15.2% of methyl 3β-acetoxy-17β-methyl-18-nor-5α,17α-etianate (**22a**), 18.8% of 3β,17β-diacetoxy-18-nor-5α,17α-pregnan-20-one (**23b**), 39.6% of 3β-acetoxy-17β-hydroxy-5α,17α-pregnan-20-one (**23a**). The reaction mixture contained approximately 3% of the *D*-homo-18-norandrostane derivative to which we assign either structure **24a** or **24c**, as determined by weight since its retention time is similar to that of the diacetoxy ketone **23b**.

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Ultraviolet Light Induced Dechlorination of Vicinal Polychlorocyclohexanes with Triethylamine[1]

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Photochemical dechlorination of *trans*- and *cis*-1,2-dichlorocyclohexanes (*t*- and *c*-DCC) in the presence of triethylamine (TEA) results in predominant dechlorination to form cyclohexene, where higher reactivity of the trans isomer over that of the cis ($\Phi_{t\text{-DCC}}/\Phi_{c\text{-DCC}} = 4.8$) is observed. Four stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexanes, i.e., benzene hexachlorides (BHCs), were similarly dechlorinated to give their stereoselective benzene tetrachlorides (BTC), which mainly lose two adjacent chlorine atoms with a trans configuration to each other among the six chlorines available in BHC. Quantum efficiencies for the dechlorination of the four isomers α-, β-, γ-, and δ-BHC are 0.072, 0.060, 0.19, and 0.11, respectively, which correlate with their reduction potentials, implying that the reaction may be initiated by an electron transfer from TEA to BHC.

Organochlorine insecticides such as DDT [1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane], DTE [1,1,1,2-tetrachloro-2,2-bis(*p*-chlorophenyl)ethane], and BHC (1,2,3,4,5,6-hexachlorocyclohexane) are generally considered to be persistent environmental pollutants. However, several workers reported that under anaerobic conditions (such as in sewage sludge, the sediment of lake bottoms, and the soil of flooded fields) some of the organochlorine compounds, e.g., γ-BHC, were decomposed in a rather short period.[2] Similarly, electrochemical reduction[3] and radiolysis[4] of γ-BHC were found to give 3,4,5,6-tetrachlorocyclohex-1-enes (BTC) followed by subsequent dechlorination to benzene.

Photochemical instability of amine–halomethane systems was noticed by several workers.[5,6] Thus, the irradiation of CCl_4 solutions of aliphatic amines rapidly develops crystalline precipitates, the amine hydrochloride along with simultaneous formation of chloroform.[7]

(1) Contribution No. 297.

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