the para effect is the result of a conformational variation between the para and ortho,meta isomers and not a spectroscopic one. From the previously proposed quadrant rule,[3] the orientation of the ^1L_b transition moment in the para isomers that exhibit the above effect is expected to lie perpendicular to the long molecular axis of the cholesteryl molecules, while the average direction of the ^1L_b transition in the ortho and meta isomers, on the other hand, is expected to lie parallel with the long molecular axis of the solvent molecules.

In general, large rotational strengths are again associated with the intensity of the transition and unusually high intensity LCICD is associated with the presence of methoxy groups.

Conclusion

LCICD studies on benzene and some of its substituted derivatives show both spectroscopic and conformational effects as a function of aromatic ring substitution. The signs of the CD within the ^1L_b electronic transition in monosubstituted benzenes show variations which depend on the electronic behavior (ortho-, para-, or meta-directing properties) of the substituent, similar to that found in MCD studies.[9] We have concluded that the change in LCICD sign as a function of aromatic ring substituent is a result of a spectroscopic change within the benzene electronic transitions and not a result of a conformational variation, as a function of substituent, in the liquid crystal.

The LCICD behaviors of some ortho-, meta-, and para-disubstituted benzene derivatives show an interesting trend where the para isomer possesses oppositely signed CD bands from the less symmetrical ortho and meta derivatives. We believe the latter phenomena to be a result of conformational variation between the isomers in a cholesteric mesophase of a single chirality.

Acknowledgment. Stimulating discussions with Drs. W. H. H. Gunther, G. Johnson, J. E. Kuder, H. Scheraga, and H. Erying are gratefully acknowledged.

D-Nor Steroids. VI. Stereochemical Effects on Carbonium Ion Reactions of C/D Cis D-Nor Steroids[1]

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Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14850. *Received July 19, 1973*

Abstract: An improved synthesis of 16-diazo-17-keto steroids, used for the preparation of C/D cis 16α- and 16β-substituted D-nor steroids, is described. The results of deamination and solvolysis reactions of these D-nor steroids in both the 16α and 16β series are presented. Product and rate studies indicate that *both* series behave as if the 16 substituent occupies a pseudoequatorial conformation. While this is expected for the 16α compounds, it can be rationalized for the 16β cases only by assuming that these compounds exist in an unusual conformation, in which ring C occurs as a boat. Severe nonbonded repulsions between a 16β substituent and nearby axial protons in the normal steroid conformation make this assumption plausible, and it is confirmed by X-ray crystallographic analysis. In this way, the anomalous behavior of these C/D cis D-nor steroids can be readily explained.

Carbonium ion reactions of cyclobutanes have been the subject of much investigation.[2] The C/D trans-fused D-nor steroids provide a series of compounds which have been especially appropriate for the examination of carbonium ion reactions of cyclobutanes of defined conformation.[3] In the present work, we describe the preparation, characterization, and chemical behavior of the corresponding C/D cis D-nor steroids, in which unanticipated conformational effects come into play.

Syntheses. The requisite 16-substituted C/D cis D-nor steroids were prepared *via* photochemical Wolff rearrangement[4,5] of the appropriate 16-diazo-17-keto steroid (**5**, Chart I), for which an improved preparation has been developed. Photochemical equilibration of dehydroisoandrosterone (**1**)[6] affords the C/D cis starting material **2**, from which the desired diazo ketone **5** was prepared. The usual route to such diazo ketones has been the chloramine oxidation of the corresponding oximino ketone,[5] and this sequence has been applied to **2** itself.[7] In our hands, however, only a low yield (*ca.* 25%) of **5** could be obtained, and in view of the difficulty in preparing the cis-fused starting material, a more efficient synthesis involving the "diazo transfer" technique[8,9] was developed. Formylation of **2** with sodium hydride and ethyl formate in dimethylformamide gave the 16-formyl-17-keto steroid, which exists largely as the enol **3**. Treatment of **3** with diethylamine in refluxing ethanol gave the enamine **4**, which reacted

(1) The partial support of this research by grants from the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, is acknowledged with pleasure.

(2) For a leading reference, see P. v. R. Schleyer and V. Buss, *J. Amer. Chem. Soc.*, **91**, 5880 (1969).

(3) J. Meinwald and T. N. Wheeler, *J. Amer. Chem. Soc.*, **92**, 1009 (1970).

(4) P. A. S. Smith, "Molecular Rearrangements," Vol. 1, P. DeMayo, Ed., Interscience, New York, N. Y., 1963.

(5) J. C. Mateos and O. Chao, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **13**, 3 (1961); M. P. Cava and E. Moroz, *J. Amer. Chem. Soc.*, **84**, 115 (1962); J. Meinwald, G. G. Curtis, and P. G. Gassman, *ibid.*, **84**, 116 (1962).

(6) A. Butenandt, A. Wolff, and P. Karlson, *Ber. Deut. Chem. Ges. B*, **74**, 1308 (1941); A. Butenandt and L. Poshmann, *ibid.*, **77**, 394 (1944).

(7) G. Muller, C. Huynh, and J. Mathieu, *Bull. Soc. Chim. Fr.*, 296 (1962).

(8) W. von E. Doering and C. DePuy, *J. Amer. Chem. Soc.*, **75**, 5955 (1953); M. Regitz, *Angew. Chem., Int. Ed. Engl.*, **6**, 733 (1967); M. Rosenberger, P. Yates, J. B. Hendrickson, and W. Wolf, *Tetrahedron Lett.*, 2285 (1964).

(9) J. B. Hendrickson and W. Wolf, *J. Org. Chem.*, **33**, 3610 (1968).

Chart I

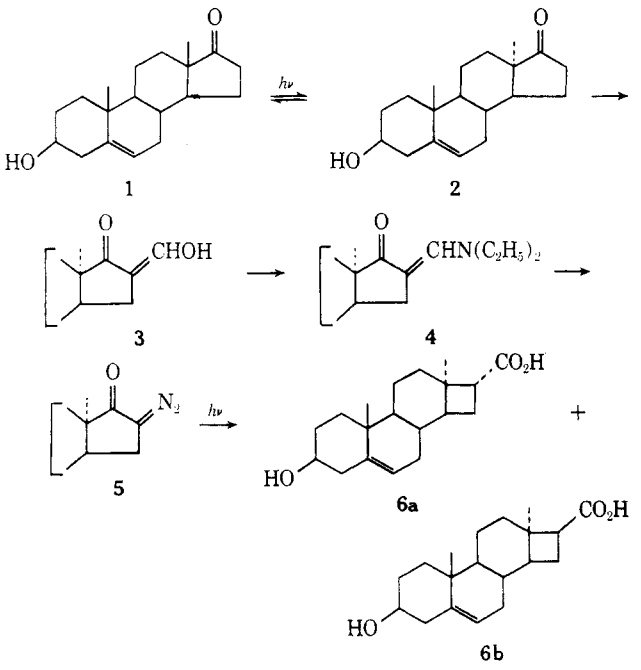
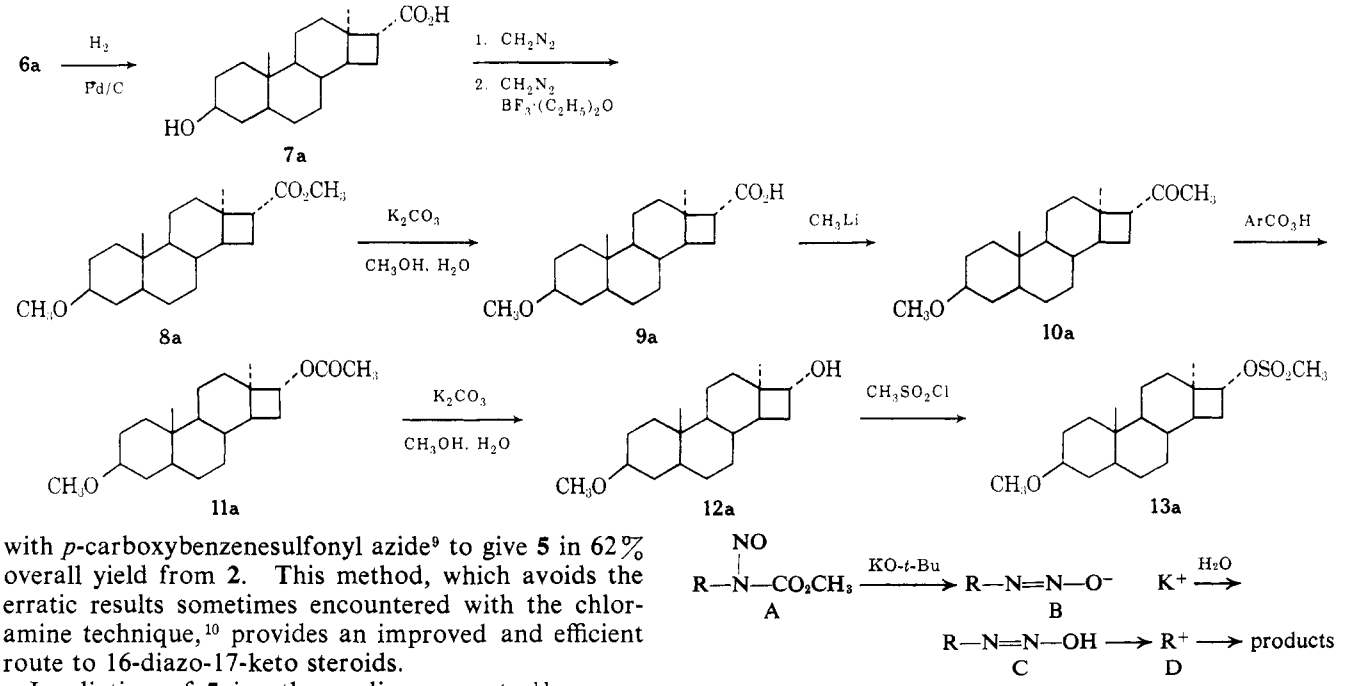


Chart II



with *p*-carboxybenzenesulfonyl azide[9] to give **5** in 62% overall yield from **2**. This method, which avoids the erratic results sometimes encountered with the chloramine technique,[10] provides an improved and efficient route to 16-diazo-17-keto steroids.

Irradiation of **5** in ether–*p*-dioxane–water[11] gave a mixture of two acids, **6a** and **6b**. The major one of these acids had been obtained earlier by Muller and coworkers,[7] who assigned it the 16α configuration (**6a**) on the basis of a circular dichroism comparison of the corresponding methyl ketone with pregnenolone.[7] This comparison seemed insecure to us, especially since the 16β epimer in the D-nor steroid series was not then available. In the present work, both epimeric carboxylic acids were obtained from the photochemical ring contraction, and since the assignment of their configurations was critical to an understanding of the subsequent chemistry, this question was reexamined. While chemical and spectral studies gave us only ambiguous answers, X-ray crystallographic studies on the corresponding saturated methyl ketones (**10a** and **10b**)[12] served to confirm the earlier configurational assignment and, in addition, gave some very interesting conformational insights (*vide infra*).

The syntheses of the corresponding 16-methanesulfonates and 16-methylcarbamates followed well established pathways[11] and are sufficiently summarized (for the 16α series) in Charts II and III.

Reactions in the 16α Series. Deaminations were accomplished using the base cleavage of *N*-nitrosocarbamates (A), which under anhydrous conditions yield diazotate salts (B) as initial products.[13] Upon aqueous quenching, these salts protonate to give diazotic acids (C),[14] the key intermediates in the nitrous acid deamination of amines, and it is for this reason that the two reactions are closely related.[15] In particular, if the diazotic acid is secondary, products arising from the corresponding carbonium ion (D) are observed.[14] The mildness of the reaction conditions and the nonacidic reaction medium make this deamination technique especially attractive.

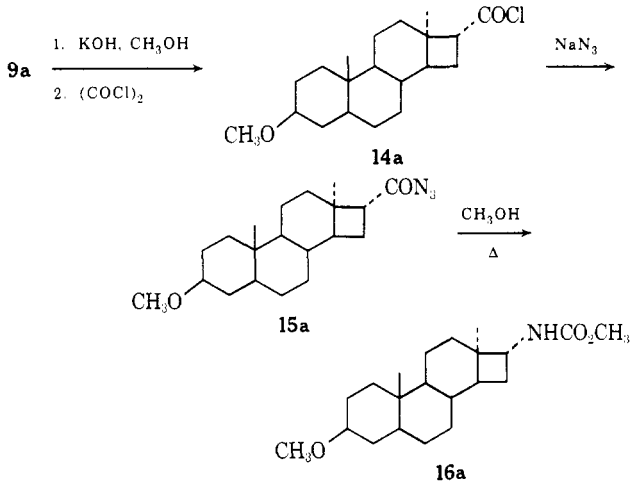
The 16α carbamate (**16a**) was converted into the corresponding *N*-nitrosocarbamate (**17a**) by treatment

with dinitrogen tetroxide in methylene chloride. Potassium *tert*-butoxide cleavage of **17a** was carried out in ether at −25°; quenching with water, followed by appropriate work-up and chromatography, gave two oily fractions. The more polar of these (63%) consisted of a mixture of the initial carbamate (**16a**, 11%) and the 16α alcohol (**12a**, 89%), corresponding to replacement of the nitrogen substituent with retention of configuration.

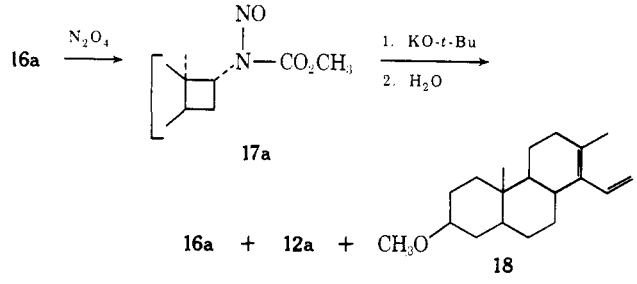
The less polar fraction proved to be a conjugated

(10) T. N. Wheeler, Ph.D. Thesis, Cornell University, June 1969.
(11) J. Meinwald, L. L. Labana, and T. N. Wheeler, *J. Amer. Chem. Soc.*, 92, 1006 (1970).
(12) J. Meinwald, A. J. Taggi, P. A. Luhan, and A. T. McPhail, *Proc. Nat. Acad. Sci. U. S.*, in press.
(13) A. Hantzsch and M. Lehmann, *Ber. Deut. Chem. Ges.*, 35, 899 (1902).
(14) R. A. Moss, *J. Org. Chem.*, 31, 1802 (1966).
(15) E. H. White and D. J. Woodcock, "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968.

Chart III



diene (**18**, 9%) resulting from opening of ring D.[16] In the ultraviolet, this diene showed λ_{max}^{hexane} 238 nm. The gc–mass spectrum showed a strong molecular ion at *m/e* 274. Vinyl and allylic methyl groups were apparent in the nmr spectrum of this diene, and microozonolysis confirmed the presence of a terminal methylene group.



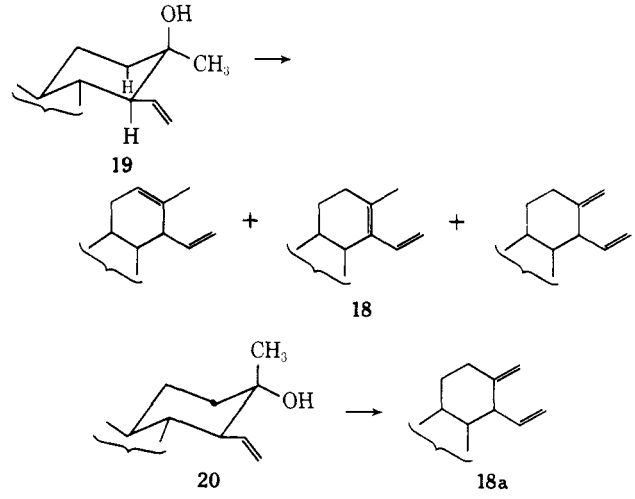
Solvolysis of the 16α mesylate (**13a**) in buffered aqueous tetrahydrofuran at room temperature, followed by preparative thin-layer chromatography of the product mixture, gave three fractions. The least polar of these (25%) was found to be identical with the diene (**18**) previously obtained from the deamination of **16a**. The second component (20%) was assigned the unsaturated alcohol structure **19** on the basis of spectral and chemical evidence (see the Experimental Section for additional details). Dehydration of **19** with phosphorus oxychloride in dry pyridine[17] gave a mixture of at least two dienes (gc–mass spectrum, *m/e* 274). The mixture showed λ_{max}^{hexane} 238 nm, as well as end adsorption. When the mixture was heated with hydrochloric acid in methanol, the intensity of the longer retention time peak decreased, while that of the peak of the shorter retention time increased. The position of the λ_{max} remained unchanged, while the end adsorption vanished. Of the structures for the unsaturated alcohol compatible with these observations, **19** appears most attractive, since both its formation and its dehydration can be rationalized more easily than those of competing possibilities (*vide infra*).

(16) An alternative structure for this diene, which fits the spectral data equally well, is one which interchanges the positions of the methyl and vinyl groups attached to ring C. Mechanistic reasons, however, lead us to favor structure **18**, as discussed in connection with the solvolysis results.

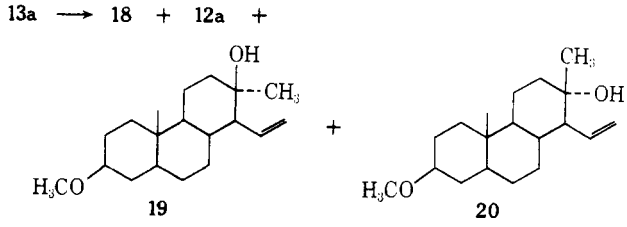
(17) L. H. Sarett, *J. Amer. Chem. Soc.*, **70**, 1454 (1948); S. Bernstein, R. Littell, and J. H. Williams, *ibid.*, **75**, 4830 (1953).

The most polar fraction from the solvolysis of **13a** yielded two components on silica gel plates impregnated with silver nitrate. One of these was identified as the 16α alcohol, **12a** (21%), again corresponding to replacement of the leaving group with retention of configuration. Spectral and chemical data (see the Experimental Section) suggested the remaining component (11%) to be **20**, epimeric with the previously described **19**. Phosphorus oxychloride dehydration of **20** gave a single diene **18a** with only end absorption in the ultraviolet. Infrared and nmr spectra of the diene indicated the presence of vinyl and vinylidene groups. Heating this diene with hydrochloric acid in methanol gave rise to a product with the same gc retention time and ultraviolet absorption as the previously described conjugated diene (**18**).

The stereochemical assignments for **19** and **20** are simply accommodated by the assumption that **19** has an axially oriented hydroxyl group, which is able to undergo trans diaxial elimination in three directions, while **20** has an equatorial hydroxyl, which can eliminate only toward the methyl group to give a single olefin.



In summary, solvolysis of **13a** proceeds as outlined below. The close relationship between this solvolysis and the deamination of **16a** is apparent.



Reactions in the 16β Series. Nitrosation and deamination of the 16β carbamate (**16b**) were carried out as described for **16a**. A small, nonpolar fraction (11%) of the product proved to be a mixture of olefins which was not further investigated. In addition, some carbamate (**16b**, 20%) was recovered. The chief reaction product (51%), however, was readily identified as the C-homo-D-bisnor steroid **21**, characterized in a previous study.[3] This compound, now obtained as a crystalline solid, is formed free of the corresponding epimer at C-13.

Solvolysis of the 16β-methanesulfonate, **13b**, was found to give this same C-homo-D-bisnor steroid **21**

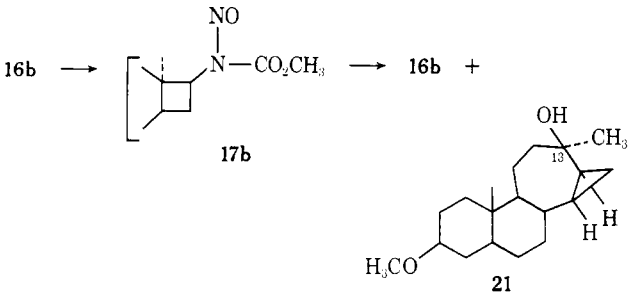
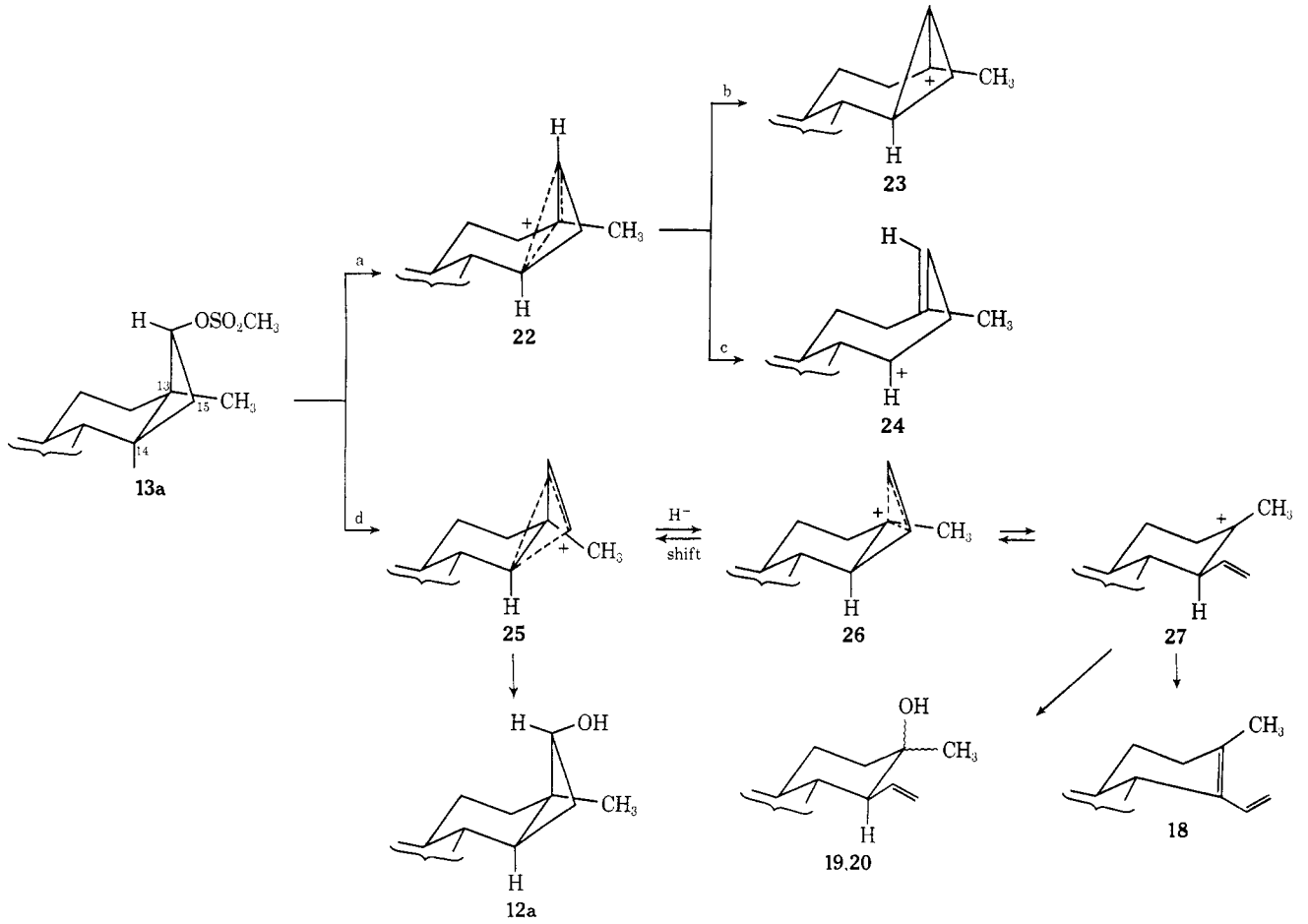


Chart IV



in practically quantitative yield, again, free of any stereoisomer.

$$\mathbf{13b} \xrightarrow[K_2CO_3]{THF\text{-}H_2O} \mathbf{21}$$

The rate of hydrolysis of **13b** in 60% aqueous acetone was determined by titrating liberated acid in a pH-Stat at pH 7.5 (25.1°). The data gave good first-order plots for at least 4 half-lives. The rate was found by least-squares analysis to be $2.79 \pm 0.01 \times 10^{-4}$ sec^{-1} (average of two runs, ± standard error).[18] This rate may be compared with that for the hydrolysis of cyclobutyl toluenesulfonate under the same conditions, reported as 4.61×10^{-5} sec^{-1}.[19,20] The comparison implies that *the solvolysis of* **13b** *is accompanied by anchimeric assistance.* Since the solvolysis of **13a** is even faster than that of **13b**, it too must involve participation of a cyclobutane ring bond.

Discussion

Considering first the solvolysis of **13a**, inspection of Dreiding models and, subsequently, of X-ray crystallographic results[12] shows that the C-13–C-14 and C-14–C-15 bonds have the proper orientation to overlap with the developing p lobe at C-16. The possible consequences of such participation are outlined in Chart IV.

Participation of the C-13–C-14 bond (path a) would lead to bridged ion **22**, which could collapse to a trans-fused tertiary cyclopropylcarbinyl ion (**23**, path b) or a trans cyclooctenyl ion (**24**, path c). Clearly, these would be highly strained species, and the transition states leading to their formation might be expected to be unfavorable if less strained alternatives were accessible.

Participation of the C-14–C-15 bond (path d) would give the bridged ion **25**, which could equilibrate with the more stable ion **26** by the migration of a hydride ion from C-15 to C-16.[21] (This step might also involve a

(18) The hydrolysis rate of **13a** was not studied because of experimental difficulties, although it was observed that **13a** was qualitatively more reactive than **13b**.

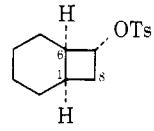
(19) P. v. R. Schleyer, D. LePerchec, and D. J. Raber, *Tetrahedron Lett.*, 4389 (1969).

(20) The rate ratio for solvolysis of methanesulfonates *vs.* toluenesulfonates is expected to be less than 10. This estimate may be obtained by applying the linear free energy relation for leaving groups obtained by K. H. Lohmann, Ph.D. Thesis, MIT, 1959, assuming that the reaction system constant γ is 1.0. A recent study of various leaving groups in cyclobutyl solvolyses [D. D. Roberts, *J. Org. Chem.*, **37**, 1510 (1972)] indicates this factor may be less (on the order of 0.75–1.5).

(21) K. B. Wiberg and J. G. Pfeiffer, *J. Amer. Chem. Soc.*, **92**, 553 (1970).

vinyl group migration, for which there is ample precedent.[22]) Bridged ion **26** can then collapse to the tertiary ion **27**, from which the observed epimeric alcohols (**19** and **20**) and diene (**18**) can arise. Attack of water at C-16 of the initially formed **25** would account for the observed formation of **12a**, the retention of configuration resulting from two successive inversions at C-16.

Wiberg and Pfeiffer observed results very similar to these in their study of the acetolysis of the *cis*-bicyclo-[4.2.0]octyl-7-toluenesulfonates.[21] In the case of **28**,



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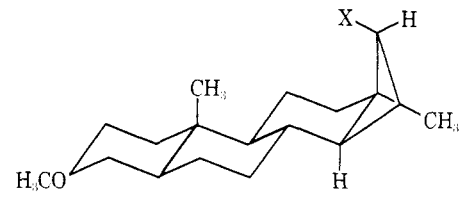
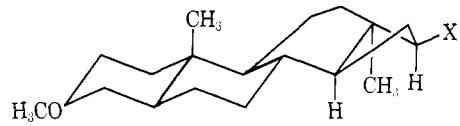
the initial products are derived from a 2-vinylcyclohexyl cation, rather than the strained *trans*-bicyclo-[5.1.0]octyl or *trans*-cyclooctenyl cations. Wiberg points out that disrotatory opening of the C-1–C-8 bond restores the somewhat flattened cyclohexane ring to a normal chair form, giving this route an additional advantage over C-1–C-6 bond cleavage.[21] An analogous effect is expected in the D-nor steroids. The chief difference between the two cases, therefore, is simply the additional hydride migration step in the solvolysis of **13a**, which permits formation of a tertiary rather than a secondary cation.

The deamination of *N*-nitrosocarbamate **17a** parallels the solvolytic results just discussed. In this case, the major product was the unrearranged alcohol, **12a**, which could arise either from ion **25** or from the often observed internal return of hydroxide ion from the intermediate diazotic acid (C).[15,23] The strongly basic medium would then be expected to favor deprotonation of **27** to give diene **18**.

The anchimerically assisted solvolysis of the 16β-methanesulfonate **13b** appears at first sight to be straightforward, since it is expected that cyclobutyl derivatives should give rise to cyclopropylcarbinyl products *via* cationic intermediates. Inspection of Dreiding models, however, shows that a 16β substituent should occupy a pseudoaxial conformation (if the remainder of the steroid skeleton retains its normal conformation, as shown in formula E), making anchimeric assistance impossible.[24] If, however, ring C were to adopt a skew-boat conformation, the 16β substituent would then become pseudoequatorial, and the observed assisted ring contraction might be readily understood. Since molecular models reveal that there would be very severe nonbonded interactions between a 16β substituent and the axial protons at C-8 and C-11 of E, it is not implausible that an alternative conformation (formula F) in which these interactions are relieved at the cost of a skew boat ring C might be preferred.



E

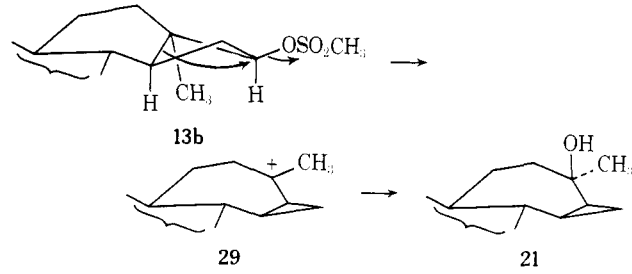


F

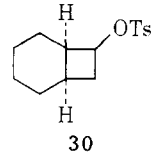
Recent X-ray crystallographic results obtained on the 16β-methyl ketone **10b** show that ring C is indeed a distorted boat in the solid state and that the 16β substituent does occupy a pseudoequatorial position,[12] exactly as anticipated on the basis of these chemical studies and model considerations.

The solvolysis (and deamination) results are accommodated, therefore, as shown in Chart V. Of the

Chart V



various paths available to **13b**, direct formation of the tertiary cyclopropylcarbinyl intermediate **29**, perhaps concerted with stereospecific addition of water to give **21**, appears to be the preferred pathway. It may be noted that in Wiberg's study[21] of the acetolysis of the analogous bicyclo[4.2.0]octyl-7-toluenesulfonate **30**,



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vinylcyclohexyl, cyclooctenyl, and cyclopropylcarbinyl products were all observed. In this case, however, all of the competing processes involved secondary cations. The reduced complexity of the D-nor steroid example may simply reflect the ability of the angular methyl substituent to direct the rearrangement by stabilization of the cyclopropylcarbinyl intermediate.

In summary, while the carbonium ion reactions of the cyclobutyl system contained within the D-nor steroids described in this work are somewhat different from those previously found in simpler, conformationally mobile bicyclic compounds, these reactions are readily interpreted when the electronic effects of the angular methyl group and the conformational effects revealed in the X-ray studies are taken into account.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 337 grating spectrophotometer. Nuclear magnetic resonance spectra were obtained on the following instruments: 60 MHz, Varian A60-A; 90 MHz, Bruker HX-90 equipped with a Digilab Pulse Fourier

(22) S. Julia, J. P. Lavaux, S. R. Pathak, and G. H. Whitman, *J. Chem. Soc.*, 2633 (1964); J. W. Wilt, C. T. Parsons, C. A. Schneider, D. G. Schultenover, S. J., and W. J. Wagner, *J. Org. Chem.*, **33**, 694 (1968), footnote 46b; H. Tanida, K. Tor, and K. Kitahonoki, *J. Amer. Chem. Soc.*, **89**, 3212 (1967); J. C. Fairlie, R. McCrindle, and R. D. H. Murray, *J. Chem. Soc. C*, 2115 (1969).

(23) R. A. Moss and C. M. Lane, *J. Amer. Chem. Soc.*, **89**, 5655 (1967); R. A. Moss, F. C. Shulman, and E. Emery, *ibid.*, **90**, 2731 (1968).

(24) K. B. Wiberg, R. A. Fenoglio, V. Z. Williams, Jr., and R. W. Ubersax, *J. Amer. Chem. Soc.*, **92**, 568 (1970).

Transform system; and 100 MHz, Varian HA-100. All chemical shift values are quoted in τ units. Ultraviolet spectra were obtained on a Cary 14 spectrophotometer. Mass spectra were recorded on an AEI MS-902 mass spectrometer. Mass spectra are not reported in detail, since little structural information could be derived from them. Gas chromatography–mass spectrometry (gc–ms) was performed on a Perkin-Elmer 270 instrument, using a 6 ft by $^1/_8$ in. column, with 5% OV-1 on 60–80 mesh Gas Chromosorb Q. Gas chromatography was performed on an Aerograph Hy-Fy 600 instrument equipped with a flame ionization detector. The column was a 6 ft by 1/8 in. 6% OV-1 on 60–80 mesh Chromosorb P. The carrier gas was nitrogen at 18 psi and 60 ml/min. The injector temperature was 280°. The column temperatures are reported with the corresponding experiment. Melting points were obtained on a Kofler hot-stage microscope. Microanalysis was performed by Galbraith Laboratories, Inc.

Analytical thin-layer chromatography was performed on silica gel Eastman Chromagram sheets. Preparative thin-layer chromatography was performed on 20 × 20 cm glass plates coated with a 0.75-mm layer of E. Merck silica gel GF_{254}. Column chromatography was performed using 100–200 mesh Florisil.

Hexane refers to Fisher "ACS Certified Hexanes (mixture of isomers)" that was redistilled before use. Petroleum ether refers to the 60–70° boiling fraction that was also redistilled, the fraction boiling at 66–68° being used. Tetrahydrofuran (THF) was distilled from lithium aluminum hydride.

(13α)-Androst-5-en-3β-ol-17-one (2). A solution of 25 g of **1** (0.087 mol; obtained from Searle Chemicals, Inc., and recrystallized twice from methanol before use) in 2 l. of dry ether was prepared in a large photolysis flask equipped with a quartz immersion well, Pyrex filter, Hanovia 450-W mercury arc lamp, and a nitrogen inlet tube extending to the bottom of the flask. The solution was purged with dry nitrogen for 2 hr, then irradiated for 150 hr. Gc monitoring (250° oven temperature) indicated this to be the optimum time. The ether was removed by distillation and the residue dissolved in 200 ml of absolute methanol. Girard's Reagent T (16.5 g, 0.097 mol) and 15 ml of glacial acetic acid were added and the solution refluxed for 1.5 hr. The resulting yellow solution was cooled, poured into 300 ml of water, and extracted with three 500-ml portions of ether. The combined ether extracts were washed twice with 250-ml portions of saturated sodium bicarbonate and once with 250 ml of water and dried over magnesium sulfate. The solution was concentrated to approximately 75 ml, then stored for several days at −20°. The resulting white solid was filtered and washed with cold ether to give 6.0 g (24%) of **2**. Recrystallization of a small sample from ethanol–water gave white needles, mp 182–185° (lit.[7] mp 187°). The crude material was sufficiently pure to use in the following steps.

16-(*N*,*N*-Diethylamino)methylene-(13α)-androst-5-en-3β-ol-17-one (4). A dry, three-necked flask equipped with a nitrogen inlet and mechanical stirrer was charged with 11.0 g of a 57% oil dispersion of sodium hydride (0.262 mol). The oil was removed by slurrying the sodium hydride with several portions of petroleum ether and decanting the supernatant liquid. A solution of 12.0 g (0.042 mol) of **2** and 13.2 ml of ethyl formate (12.2 g, 0.165 mol, freshly distilled from phosphorous pentoxide) in 200 ml of dimethylformamide (stored over calcium hydride and distilled *in vacuo* prior to use) was cooled to −20°. This solution was added to the sodium hydride and stirred vigorously. A few drops of methanol were added to initiate the reaction. When the reaction had started, as evidenced by gas evolution, the reaction flask was immersed in an ice bath and maintained at 0° for 5 hr, then overnight at room temperature. Excess sodium hydride was decomposed with water. The mixture was poured into 600 ml of water, and Celite was stirred in. The resultant suspension was filtered through a thick Celite pad and the filter cake washed with water to give a dark brown filtrate. The filtrate was acidified with concentrated hydrochloric acid and the resulting tan solid was removed by filtration and washed with water. Drying *in vacuo* gave 12.1 g (92%) of the 16-formyl steroid **3**. This material gave a positive test with ferric chloride:[25] ir ($CHCl_3$) 3565 (free OH), 3420 (associated OH), and a series of four bands at 1740, 1710, 1670, and 1600 cm^{-1} (β-dicarbonyl). This material was not further purified but used directly in the next step.

A solution consisting of 24.2 g (0.076 mol) of **3**, 24 ml of diethylamine, and a few milligrams of *p*-toluenesulfonic acid dissolved in 1200 ml of absolute ethanol was prepared in a 2-l. flask equipped with a magnetic stirrer, a Soxhlet extractor charged with 24 g of predried Linde molecular sieve, Type 4A, and a nitrogen atmosphere.[26] The solution was refluxed with stirring for 50 hr. The solvent was removed and the residue recrystallized from acetone to give, in two crops, 22.0 g (77%) of **4**: mp 199–203°; infrared ($CHCl_3$) 3580 (free OH), 3390 (associated OH), 1670 (C=O), and 1668 (conjugated C=C) cm^{-1}; nmr ($CDCl_3$) 9.16 (3 H, s, CH_3 on C-10), 9.05 (3 H, s, CH_3 onC-13), 8.80 (6 H, t, J = 7 Hz, NCH_2CH_3), 6.65 (4 H, q, J = 7 Hz, NCH_2), 6.5 (1 H, broad, C-3 proton), 4.62 (1 H, broad s, C-6 proton), 2.62 (1 H, m, $=CHNEt_2$), and the remaining protons from 7.0 to 9.0. Further recrystallization from acetone gave an analytical sample, mp 201–203°. *Anal.* Calcd for $C_{24}H_{37}NO_2$: C, 77.58; H, 10.04; N, 3.77. Found: C, 77.70; H, 10.14; N, 3.77.

16-Diazo-(13α)-androst-5-en-3β-ol-17-one (5). A solution of 20.0 g (0.054 mol) of **4** and 13.5 g (0.062 mol) of *p*-carboxybenzenesulfonyl azide[9] in 800 ml of THF, in a flask protected from light, was refluxed for 48 hr. The solution was cooled, poured into 600 ml of water, and extracted twice with 400-ml portions of ether. The combined ether extracts were washed twice with 250-ml portions of saturated sodium bicarbonate and once with saturated brine. Drying over magnesium sulfate, removal of the solvent, and crystallization of the residue from acetone gave 14.7 g (87%) of **5** as bright yellow crystals, mp 192–199°, with rapid decomposition and gas evolution (lit.[7] mp 210°). The melting point of **5** remained constant even after three recrystallizations from acetone.

3β-Hydroxy-*D*(13α)-norandrost-5-ene-16α-carboxylic Acid (6a). A solution of 7.5 g (23.9 mmol) of diazo ketone **5** in 1250 ml of ether, 500 ml of *p*-dioxane, and 250 ml of water[11] was prepared in a 2-l. photolysis vessel equipped with a magnetic stirrer and a nitrogen inlet. A slow stream of nitrogen was bubbled through the solution for several hours, and it was then irradiated for 28 hr using a Hanovia 450-W mercury arc lamp through a Corex filter. The aqueous layer was removed and the organic layer washed eight times with 200-ml portions of water, then once with saturated brine. The solution was dried over magnesium sulfate and the solvent removed to give a yellowish solid. This solid was refluxed with methylene chloride for 1 hr. After cooling, the solid 16α acid **6a** was removed by filtration and washed with cold methylene chloride. Recrystallization from methanol gave, in two crops, 3.5 g (48%) of **6a**, mp 240–246° dec (lit.[7] mp 254°). The melting point of this product did not change even on repeated recrystallization from methanol.

The methylene chloride mother liquor was retained in order to obtain the 16β acid (*vide infra*).

3β-Hydroxy-*D*(13α)-norandrost-5-ene-16β-carboxylic Acid (6b). The methylene chloride mother liquors obtained above were extracted six times with a total of 200 ml of 0.5 *N* sodium hydroxide solution. The combined basic extracts were washed once with methylene chloride, then acidified with 2 *N* hydrochloric acid. The resulting suspension was extracted three times with methylene chloride. The combined organic extracts were washed once with saturated brine and dried over magnesium sulfate. Removal of the solvent gave 1.7 g of a yellowish solid. Recrystallization from methylene chloride gave 1.4 g (19%) of the impure 16β acid (**6b**) as yellow crystals: mp 160–175°; ir ($CHCl_3$) 3565 (free OH), 3260 (associated OH), 1722 (associated C=O), 1700 (free C=O) cm^{-1}; nmr (DMSO-d_6) 9.17 (3 H, s, CH_3 on C-10), 8.75 (3 H, s, CH_3 on C-13), 7.26 (1 H, m, C-16 proton), 6.7 (1 H, broad, C-3 proton), 5.8 (approximately 1.8 H, very broad, associated OH), 4.75 (1 H, broad s, C-6 proton), 1.92 (approximately 0.2 H, s, free OH), and the remaining ring protons from 7.5 to 9.1.

Attempts at purification by recrystallization did not improve the melting point significantly. Further purification was therefore effected later in the reaction sequence.

3β-Methoxy-*D*(13α)-norandrostane-16α-carboxylic Acid (9a). A solution of 2.0 g of 16α acid **6a** in 200 ml of methanol was placed in a Parr bottle containing 400 mg of 10% palladium-on-charcoal catalyst and hydrogenated at room temperature and 47 psi for 24 hr. Filtration through Celite and removal of the solvent gave 2.0 g of **7a** as a white solid: ir (KBr) 3390 (OH), 1695 (C=O) cm^{-1}; nmr (DMSO-d_6) 9.23 (3 H, s, CH_3 on C-10), 8.97 (3 H, s, CH_3 on C-13), 6.95 (1 H, t, J = 8 Hz, C-16 proton), 6.6 (1 H, broad, C-3 proton), 5.5 (approximately 1.8 H, very broad, associated OH), 1.92 (approximately 0.2 H, s, free OH), and the remaining ring protons from 7.5 to 9.1. An analytical sample, mp 222–225°, was prepared by re-

(25) C. R. Hauser, E. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 59 (1954).

(26) G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

crystallization from methanol–water. *Anal.* Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.42; H, 9.80.

Approximately 49 mmol of diazomethane was generated in 300 ml of ether by treating 6.45 g of 80% *N*-nitrosomethylurea with 50% aqueous potassium hydroxide. This solution was added slowly to a well-stirred suspension of 3.0 g (9.9 mmol) of **7a** in 100 ml of ether maintained at 0°. When the addition was complete, the solution was stirred at 0° for 1 hr, then warmed to room temperature. Excess diazomethane was removed with a stream of nitrogen. Removal of the solvent gave 3.0 g of the 16α-ester as a colorless oil which subsequently crystallized: ir ($CHCl_3$) 3580 (free OH), 3440 (associated OH), 1728 (C=O) cm^{-1}; nmr ($CDCl_3$) 9.12 (3 H, s, CH_3 on C-10), 8.97 (3 H, s, CH_3 on C-13), 7.40 (1 H, s, OH), 7.05 (1 H, t, J = 8 Hz, C-16 proton), 6.4 (1 H, broad, C-3 proton), 6.36 (3 H, s, OCH_3), and the remaining ring protons from 7.3 to 9.0.

A solution of 3.0 g (9.4 mmol) of the 16α ester in 50 ml of methylene chloride was subjected to methylation using boron trifluoride etherate and diazomethane as described previously.[11,27] The methylene chloride was removed and the residue taken up in ether. The solution (which often contained suspended polymethylene) was washed with saturated sodium bicarbonate, water, and saturated brine and dried over magnesium sulfate. Removal of the solvent gave 3.3 g of a yellowish oil which crystallized slowly on standing. This material was chromatographed on 220 g of Florisil with petroleum ether–acetone as eluent to give 2.9 g of **8a**, which solidified from an oil: ir ($CHCl_3$) 1727 (C=O), 1095 (OCH_3) cm^{-1}; nmr ($CHCl_3$) 9.73 (3 H, s, CH_3 on C-10), 8.97 (3 H, s, CH_3 on C-13), 7.55 (1 H, broad m, C-14 proton), 6.88 (1 H, partially obscured m, J = 8 Hz, C-16 proton), 6.66 (3 H, s, OCH_3), 6.36 (3 H, s, CO_2CH_3), 6.9 (1 H, broad, C-3 proton), and the remaining ring protons from 8.0 to 9.0. This material was not purified further but was used directly in the next step.

A solution of 2.9 g of **8a** and 2.9 g of anhydrous potassium carbonate in 185 ml of methanol and 45 ml of water was refluxed under nitrogen for 48 hr. Most of the solvent was removed under reduced pressure. The residue was dissolved in water and the solution acidified with 2 *N* hydrochloric acid to give a curdy white precipitate. This mixture was extracted twice with ether. The combined ether extracts were washed with saturated brine and dried over magnesium sulfate. Removal of the solvent gave a white solid which was recrystallized from hexane to give 2.6 g (83%, based on 3.0 g of **6a**) of 16α acid **9a**: mp 141.5–143°; ir ($CHCl_3$) 3490 (free OH), 3100 (associated OH), 1735 (associated C=O), 1700 (free C=O), 1095 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.20 (3 H, s, CH_3 on C-10), 8.88 (3 H, s, CH_3 on C-13), 7.60 (1 H, broad, C-14 proton), 6.83 (1 H, partially obscured multiplet, J = 8 Hz, C-16 proton), 6.8 (1 H, broad, C-3 proton), 6.65 (3 H, s, OCH_3), ~1.03 (approximately 0.4 H, s, CO_2H), and the remaining protons from 7.8 to 9.0. *Anal.* Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.07. Found: C, 74.90; H, 10.07.

A small sample of **9a** was treated with diazomethane; the product was found to have an nmr spectrum identical with that of **8a**, hence no epimerization occurred during saponification of **8a**.

16α-Acetyl-3β-methoxy-*D*(13α)-norandrostane (10a). A dry, three-necked flask equipped with a nitrogen inlet, magnetic stirrer, and serum cap was charged with 1.75 g (5.45 mmol) of **9a** and 90 ml of ether. The solution was cooled in an ice bath. Ten milliliters of a 1.67 *M* (16.7 mmol) solution of methyllithium in ether was added *via* syringe. A precipitate formed immediately. The mixture was stirred for 0.5 hr at 0°, then for 4.5 hr at room temperature. The reaction mixture was added dropwise to 100 ml of rapidly stirred ice–water. Approximately one-quarter of the reaction mixture was added in this way; the water–ether mixture was transferred to a separatory funnel and the ice–water replaced. This procedure was followed until all of the reaction mixture was quenched.[28]

The aqueous layer was removed and washed once with ether. The combined ether extracts were washed once with saturated brine and dried over magnesium sulfate. Removal of the solvent and crystallization from hexane afforded 1.3 g (75%) of the 16α-methyl ketone **10a**: mp 111.5–113°; ir (CCl_4) 1710 (C=O), 1175 (CCOC), 1102 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.20 (3 H, s, CH_3 on C-10), 9.02 (3 H, s, CH_3 on C-13), 8.02 (3 H, s, $COCH_3$), 7.50 (1 H, broad, C-14 proton), 6.75 (1 H, partially obscured m, J = 8 Hz, C-16 proton), 6.8 (1 H, broad, C-3 proton), 6.65 (3 H, s, OCH_3), and the remaining ring protons from 7.8 to 9.0. *Anal.* Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.96; H, 10.90.

3β-Methoxy-*D*(13α)-norandrostan-16α-ol (12a). A solution of 1.1 g (3.5 mmol) of **10a**, 1.2 g (5.8 mmol) of 85% *m*-chloroperbenzoic and a few milligrams of *p*-toluenesulfonic acid in 50 ml of methylene chloride was refluxed in the dark for 4 days. The solution was cooled, diluted with 50 ml of ether, and washed once each with 10% aqueous sodium bisulfite, saturated sodium bicarbonate, and saturated brine. Drying over magnesium sulfate and removal of the solvent gave 1.25 g of the 16α acetate **11a** as a yellowish oil: ir (CCl_4) 1735 cm^{-1} (C=O), and 1095 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.18 (3 H, s, CH_3 on C-10), 8.97 (3 H, s, CH_3 on C-13), 8.00 (3 H, s, CH_3CO_2), 6.8 (1 H, broad, C-3 proton), 6.66 (3 H, s, OCH_3), 4.95 (1 H, t, J = 8 Hz, C-16 proton), and the remaining ring protons from 7.4 to 9.0.

The oily product from above (1.25 g) and 1.25 g of anhydrous potassium carbonate were dissolved in 50 ml of methanol and 13 ml of water. The mixture was refluxed under a nitrogen atmosphere for 18 hr. The solution was cooled and most of the solvent removed under reduced pressure. The residue was taken up in ether and water, the organic layer removed, and the aqueous layer extracted with ether. The combined ether extracts were washed with saturated brine and dried over magnesium sulfate. Removal of the solvent gave 0.9 g of a crystalline solid. This solid was chromatographed on 160 g of Florisil with petroleum ether–acetone as eluent to give 0.8 g (79%) of the 16α alcohol **12a** as a white crystalline solid with a characteristic strong odor. This compound could be recrystallized from methanol–water or sublimed under vacuum to give pure **12a**: mp 110–111.5°; ir (CCl_4) 3495 (free OH), 3330 (associated OH), and 1095 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.27 (3 H, s, CH_3 on C-10), 8.97 (3 H, s, CH_3 on C-13), 7.11 (1 H, s, OH), 6.8 (1 H, broad, C-3 proton), 6.67 (3 H, s, OCH_3), 5.82 (1 H, t, J = 8 Hz, C-16 proton), and the remaining ring protons from 7.7 to 9.1. *Anal.* Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.93; H, 11.01.

Methyl 3β-Methoxy-*D*(13α)-norandrostane-16α-carbamate (16a). The potassium salt of **9a** was prepared by dissolving 2.0 g (6.24 mmol) of **9a** in 25 ml of 0.5 *N* (12.5 mmol) methanolic potassium hydroxide. The solvent was removed and the salt dried at 0.5 Torr and room temperature for 1 hr, then overnight at 0.5 Torr and 80°.

The dried salt was cooled, 20 ml of benzene added, and the suspension stirred under nitrogen. To this suspension was added 2.1 ml (3.2 g, 25.0 mmol) of oxalyl chloride. The reaction mixture was stirred at room temperature for 0.5 hr, then refluxed for a few minutes. The solvent and excess oxalyl chloride were removed under reduced pressure. The residue was extracted with benzene and filtered under nitrogen. Removal of the solvent gave the acid chloride **14a** as a viscous oil, showing carbonyl absorption at 1795 cm^{-1} in the infrared (CCl_4).

The crude acid chloride was dissolved in 35 ml of acetone and stirred under nitrogen at 0°. A solution of 1.21 g (18.7 mmol) of sodium azide in 3 ml of water was added rapidly. A white precipitate formed immediately. The mixture was stirred at 0° for 15 min, then poured into water and extracted three times with ether. The combined ether extracts were washed twice with saturated brine and dried over magnesium sulfate. Removal of the solvent gave the acyl azide **15a** as white crystals, which was characterized only by its ir spectrum (CCl_4): 2120 (–N_3) and 1714 (C=O) cm^{-1}. The acyl azide was used immediately in the following step.

A solution of the above azide in 100 ml of 1:1 methanol–benzene was refluxed for 24 hr. The solvent was removed and the residue chromatographed on 150 g of Florisil with petroleum ether–acetone as eluent. The eluate was crystallized from hexane to give 1.84 g (84%) of the 16α-methylcarbamate **16a** as white needles, mp 147–148.5°. Further recrystallization from hexane gave an analytical sample: mp 148–148.5°; ir (CCl_4) 3435 (NH), 1727 (C=O), 1505 (–NHCO–), and 1098 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.22 (3 H, s, CH_3 on C-10), 8.98 (3 H, s, CH_3 on C-13), 6.65 (3 H, s, OCH_3), 6.8 (1 H, broad, C-3 proton), 6.35 (3 H, s, CO_2CH_3), 5.68 (1 H, broad q, J = 9 Hz, C-16 proton), 4.87 (1 H, d, J = 9 Hz, NH), and the remaining ring protons from 6.9 to 9.1. *Anal.* Calcd for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 72.21; H, 10.26; N, 4.14.

3β-Methoxy-*D*(13α)-norandrostane-16β-carboxylic Acid (9b). Three grams of crude 16β-acid **6b**, 600 mg of 10% palladium-on-charcoal catalyst, and 200 ml of methanol were placed in a Parr bottle and hydrogenated at 47 psi overnight. Work-up as described for the 16α isomer **7a** gave 3.0 g of the reduced acid **7b** as a white solid: ir ($CHCl_3$) 3580 (free OH), 3300 (associated OH), 1730

(27) E. Muller and W. Rundel, *Angew. Chem.*, **70**, 105 (1958).

(28) This work-up was necessary to prevent formation of the corresponding tertiary alcohol: *cf.* H. O. House and T. M. Bare, *J. Org. Chem.*, **33**, 943 (1968).

(associated C=O), 1700 (free C=O) cm^{-1}; nmr ($CDCl_3$) 9.23 (3 H, s, CH_2 on C-10), 8.77 (3 H, s, CH_3 on C-13), 7.16 (1 H, t, J = 9 Hz, C-16 proton), 6.4 (1 H, broad, C-3 proton), 4.43 (1 H, s, CO_2H), and the remaining protons from 7.6 to 9.0. A small amount (*ca.* 5%) of the 16α isomer could be detected by a shoulder on the τ 9.23 singlet. This material was used without further purification.

The 16β-methyl ester was prepared in the same fashion as the 16α isomer. Acid **7b** (3.0 g, 9.4 mmol) yielded 3.2 g of the ester, as an oil: ir (CCl_4) 3601 (free OH), 3350 (associated OH), and 1740 (C=O) cm^{-1}; nmr ($CDCl_3$) 9.27 (3 H, s, CH_3 on C-10), 8.82 (3 H, s, CH_3 on C-13), 7.22 (1 H, t, J = 9 Hz, C-16 proton), 7.15 (1 H, s, OH), 6.5 (1 H, broad, C-3 proton), 6.36 (3 H, s, CO_2CH_3), and the remaining ring protons from 7.5 to 9.0.

The methyl ether **8b** was prepared in the same manner as the 16α isomer **8a**. Thus 3.2 g of 16β ester gave 3.2 g of crude **8b** as an oil which subsequently crystallized. Chromatography on 220 g of Florisil with petroleum ether–acetone as eluent gave 2.6 g of **8b** as a white solid: ir (CCl_4) 1733 (C=O), and 1095 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.25 (3 H, s, CH_3 on C-10), 8.80 (3 H, s, CH_3 on C-13), 7.13 (1 H, t, J = 9 Hz, C-16 proton), 6.7 (1 H, broad, C-3 proton), 6.65 (3 H, s, OCH_3), 6.33 (3 H, s, CO_2CH_3), and the remaining ring protons from 7.5 to 9.0. The shoulder on the τ 9.25 singlet due to the 16α epimer could still be seen.

This material was not further characterized but was saponified as described for the 16α isomer, **8a**. Saponification of 2.6 g of **8b** gave a white solid which was crystallized from acetone to give 1.9 g (60%) of **9b**, as white crystals: mp 197–200°; ir ($CHCl_3$) 3490 (free OH), 3250 (associated OH), 1735 (associated C=O), 1700 (free C=O), and 1090 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.25 (3 H, s, CH_3 on C-10), 8.78 (3 H, s, CH_3 on C-13), 7.12 (1 H, t, J = 9 Hz, C-16 proton), 6.7 (1 H, broad, C-3 proton), 6.65 (3 H, s, OCH_3), −1.10 (approximately 0.5 H, s, CO_2H), and the remaining ring protons from 7.6 to 9.1. The shoulder on the τ 9.25 peak due to the 16α isomer could no longer be seen. Further recrystallization of this material gave an analytical sample, mp 201.5–203.5°. *Anal.* Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.07. Found: C, 75.08; H, 10.18.

16β-Acetyl-3β-methoxy-*D*(13α)-norandrostane (10b). The 16β-acetyl compound **10b** was prepared in the same manner as the 16α epimer **10a**, except that a different solvent was used. Thus 1.5 g (4.7 mmol) of **9b** dissolved in 60 ml of 1:1 ether–THF was treated with 15 ml (25 mmol) of 1.67 *M* methyllithium solution. After work-up as described earlier, the resulting residue was chromatographed on 220 g of Florisil with petroleum ether–acetone as eluent to give two fractions, one containing **10b** (0.83 g) and the other (0.58 g) **10b** contaminated with the corresponding tertiary alcohol. Rechromatography of the second fraction gave additional **10b**, bringing the total to 1.11 g (75%). Recrystallization from pentane gave an analytical sample: mp 115–116.5°; ir (CCl_4)1720 (C=O), 1172 (CCOC), and 1097 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.28 (3 H, s, CH_3 on C-10), 8.72 (3 H, s, CH_3 on C-13), 8.02 (3 H, s, $COCH_3$), 7.07 (1 H, t, J = 8 Hz, C-16 proton), 6.9 (1 H, broad, C-3 proton), 6.70 (3 H, s, OCH_3), and the remaining ring protons from 7.7 to 9.1. *Anal.* Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.25; H, 10.95.

3β-Methoxy-*D*(13α)-norandrostan-16β-ol (12b). A solution of 0.83 g (2.6 mmol) of **10b**, 1.0 g (5.3 mmol) of 85% *m*-chloroperbenzoic acid, and a few milligrams of *p*-toluenesulfonic acid in 50 ml of methylene chloride was refluxed in the dark for 96 hr. Work-up as for the 16α acetate (**11a**) gave 0.91 g of the 16β acetate **11b** as an oil: ir (CCl_4) 1734 (C=O) and 1098 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.23 (3 H, s, CH_3 on C-10), 8.87 (3 H, s, CH_3 on C-13), 8.00 (3 H, s, CH_3CO_2–), 7.37 (1 H, d of t, J = 8 and 12 Hz, C-14), 6.8 (1 H, broad, C-3 proton), 6.68 (3 H, s, –OCH_3), and 5.35 (1 H, t, J = 8 Hz, C-16 proton), and the remaining ring protons from 8.0 to 9.1.

Hydrolysis of this acetate in the same way as **11a** gave 0.64 g of **12b** as an oil which slowly crystallized. Chromatography on 140 g of Florisil with petroleum ether–acetone as eluent gave 0.53 g (70%) of **12b** as a white solid. Crystallization from pentane gave prismatic needles; mp 101–102°; ir (CCl_4) 3585 (OH) and 1098 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.25 (3 H, s, CH_3 on C-10), 8.96 (3 H, s, CH_3 on C-13), 7.43 (1 H, d of t, J = 8 and 12 Hz, C-14 proton), 7.12 (1 H, s, OH), 6.9 (1 H, broad, C-3 proton), 6.68 (3 H, s, OCH_3), 6.18 (1 H, t, J = 8 Hz, C-16 proton), and the remaining ring protons from 7.9 to 9.0. *Anal.* Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.27; H, 11.10.

Methyl 3β-Methoxy-*D*(13α)-norandrostane-16β-carbamate (16b). The 16β carbamate **16b** was prepared in the same way as the 16α carbamate **16a**. Thus 1.0 g (3.1 mmol) of **9b** gave 0.90 g (83%) of **16b** as white needles: mp 102–104.5°; ir (CCl_4) 3435 (NH), 1728 (C=O), 1498 (–NHCO–), and 1100 (OCH_3) cm^{-1}; nmr ($CDCl_3$) 9.25 (3 H, s, CH_3 on C-10), 8.89 (3 H, s, CH_3 on C-13), 7.4 (1 H, m, C-14 proton), 6.8 (1 H, broad, C-3 proton), 6.66 (3 H, s, OCH_3), 6.35 (3 H, s, CO_2CH_3), 6.2 (*ca.* 1 H, m obscured by singlet at 6.35, C-16 proton), 4.82 (1 H, d, NH), and the remaining ring protons from 7.8 to 9.0. *Anal.* Calcd for $C_{21}H_{35}NO_3$: C, 72.17; H, 10.09; N, 4.01. Found: C, 71.92; H, 10.22; N, 3.88.

Base-Catalyzed Rearrangement of Methyl 3β-Methoxy-*D*(13α)-norandrostane-16α-*N*-nitrosocarbamate (17a). A solution of 0.25 g (0.72 mmol) of the 16α carbamate **16a** in 10 ml of methylene chloride was cooled (ice bath) in a flask equipped with a magnetic stirrer, drying tube, and serum cap. Anhydrous sodium acetate (0.50 g, 6.1 mmol) was added. A 1.0 *M* methylene chloride solution of dinitrogen tetroxide (5 ml, 5 mmol) was injected through the serum cap.[29] Stirring was continued at ice temperature for 1 hr. The reaction mixture was poured into ice water and extracted with ether. The organic layer was removed and washed with ice-cold 10% sodium bicarbonate, ice-cold water, and saturated brine. Drying over magnesium sulfate and removal of the solvent at 0° gave the *N*-nitrosocarbamate **17a**, as yellow crystals, which was characterized by its infrared spectrum (CCl_4): 1757 cm^{-1} (C=O) with a small absorbance at 1730 cm^{-1} (C=O) corresponding to the residual carbamate.

This *N*-nitrosocarbamate was decomposed by injecting it (dissolved in 15 ml of dry ether) into a slurry of 0.32 g (2 mmol) of potassium *tert*-butoxide in dry ether maintained at −25° under nitrogen. Stirring was continued at −25° for 1 hr, and the suspension was allowed to warm to 0° and was then quenched with water. The mixture was transferred to a separatory funnel and extracted with ether. The ether extracts were washed with water and with saturated brine. Drying over magnesium sulfate and removal of the solvent gave 0.21 g of a yellow oil. Chromatography on 30 g of Florisil with hexane–acetone as eluent gave two fractions. The less polar material, fraction A (18 mg, 9%), obtained as an oil and identified as diene **18**, had the following spectral data: ir (CCl_4) 3060 (olefinic CH), 1095 (OCH_3), and 905 (–CH=CH_2) cm^{-1}; nmr ($CDCl_3$) 9.23 (3 H, s, CH_3 on C-10), 8.42 (3 H, broad s, CH_3 on C-13), 6.8 (1 H, broad, C-3 proton), 6.62 (3 H, s, OCH_3), 4.8 (3 H, m, –CH=CH_2), and the remaining ring protons from 7.6 to 9.1; uv λ_{max}^{hexane} 238 nm; gc–ms parent ion at *m/e* 274. The presence of a terminal methylene group was confirmed by ozonolysis and identification of the resultant formaldehyde as described below.

Fraction B (0.13 g, 63%) proved by its nmr spectrum to be a mixture of the 16α alcohol **12a** (89%) and the original carbamate **16a** (11%).

Ozonolysis and Detection of Formaldehyde. The method outlined here is a modification of the method of Moore and Brown.[30] A solution of *ca.* 2 mg of the compound to be ozonized was dissolved in 1 ml of methylene chloride. This solution was ozonized at −80° until the blue color of ozone was observed in the solution. Excess ozone was removed with a stream of nitrogen. The solvent was removed and the residue dissolved in several drops of methanol. Three drops of a freshly prepared solution of 4,4-dimethylcyclohexane-1,3-dione (dimedone, *ca.* 100 mg/ml) was added and the solution warmed on a stream bath.

A sample of this solution was then analyzed gas chromatographically. The column temperature, usually greater than 190°, was adjusted to suit the individual analysis. Identification was made by comparison with an authentic sample of the formaldehyde bis-dimedone derivative.[31] The following controls were performed for each analysis: ozonolysis of the compound and similar work-up, but omitting the dimedone solution; ozonolysis and work-up of methylene chloride alone; gc analysis of dimedone solution; and gc analysis of ozonolysis mixture before work-up.

Preparation and Solvolysis of 3β-Methoxy-*D*(13α)-norandrostanyl-16α-methanesulfonate (13a). A solution of 300 mg (1.03 mmol) of **12a** in 6 ml of dry pyridine was cooled and stirred magnetically in an ice bath. Freshly distilled methanesulfonyl chloride (0.24 ml, 0.35 g, 3.08 mmol) was added. Needles of pyridinium hydrochloride began to form immediately. The solution was stirred for several hours at 0°, then stored at 5°. After 24 and 48 hr, 0.12 ml (0.17 g, 1.54 mmol) of fresh methanesulfonyl chloride was added and the reaction mixture returned to the refrigerator. The reaction mixture was allowed to stand for an additional 48 hr

(29) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6008 (1955).
(30) B. P. Moore and W. J. Brown, *J. Chromatogr.*, **60**, 157 (1972).
(31) E. C. Horning and M. C. Horning, *J. Org. Chem.*, **11**, 95 (1946).

at 5° after the last addition of acid chloride. It was then poured into ice–water and extracted three times with ether. The combined ether layers were washed with cold water, with cold 2 *N* hydrochloric acid, and with saturated brine. Drying over magnesium sulfate at 0° and removal of the solvent gave 0.37 g (91%) of **13a** as a yellow oil. Preliminary experiments showed this material to be quite reactive; the nmr spectrum of this compound often showed peaks corresponding to solvolysis products. Because of its reactivity, this material was characterized only by its nmr spectrum ($CDCl_3$): 9.25 (3 H, s, CH_3 on C-10), 8.85 (3 H, s, CH_3 on C-13), 7.05 (3 H, s, OSO_2CH_3), 6.8 (1 H, broad, C-3 proton), 6.68 (3 H, s, OCH_3), 5.05 (1 H, t, J = 8 Hz, C-16 proton), and the remaining ring protons from 7.6 to 9.1.

Solvolysis of the mesylate was carried out under nitrogen in 60 ml of 1:1 THF–water, buffered with 0.37 g of anhydrous potassium carbonate, for 24 hr at room temperature. Most of the solvent was then removed under reduced pressure. Water was added and the residue was extracted three times with ether. The combined ether extracts were washed with saturated brine and dried over magnesium sulfate. Removal of the solvent gave 0.29 g of a yellow oil. Preparative thin layer chromatography with 1:1 pentane–ether as eluent gave three fractions. The fastest moving fraction (A, 71 mg, 25%) was found to be spectrally identical with the diene **18** obtained from the basic decomposition of **17a**.

The second fraction (B, 57 mg, 20%), obtained as an oil, had the following spectral characteristics: ir (CCl_4) 3600 (OH), 3060 (olefinic CH), 1095 (OCH_3), 995 and 905 ($-CH=CH_2$) cm^{-1}; nmr ($CDCl_3$) 9.20 (3 H, s, CH_3 on C-10), 8.88 (3 H, s, CH_3 on C-13), 6.8 (1 H, broad, C-3 proton), 6.63 (3 H, s, OCH_3), 4.8 (3 H, m, $-CH=CH_2$), and the remaining ring protons from 8.0 to 9.1; gc–ms parent ion at *m/e* 292. The presence of a terminal methylene group was confirmed by the ozonolysis procedure described above. These data, combined with the dehydration experiments described below, indicate the structure to be **19**.

The slowest moving fraction (117 mg) proved by its nmr spectrum to be a mixture of two components, which could be resolved by thin-layer chromatography on silica gel plates impregnated with silver nitrate (ether eluent).[32] The faster moving component (C, 60 mg, 21%) was recrystallized from pentane. This material was found to be the 16α-alcohol **12a** by comparison of its melting point and spectral data with those of the authentic material.

The slower moving component (D, 32 mg, 11%) obtained as a white solid, mp 126–127°, had the following spectral data: ir (CCl_4) 3560 (OH), 3060 (olefinic CH), 1095 (OCH_3), 995 and 915 ($-CH=CH_2$) cm^{-1}; nmr ($CDCl_3$) 9.23 (3 H, s, CH_3 on C-10), 8.92 (3 H, s, CH_3 on C-13), 6.9 (1 H, broad, C-3 proton), 6.68 (3 H, s, OCH_3), 4.77 (3 H, m, $-CH=CH_2$), and the remaining protons from 8.0 to 9.1; gc–ms molecular ion at *m/e* 292, and an $M^+ - H_2O$ ion at *m/e* 274.2331 (calcd for $C_{19}H_{30}O$, 274.2297). The presence of a terminal methylene group was confirmed by the ozonolysis procedure described above.

These data, combined with the dehydration experiments described below, indicate the structure of this compound to be **20**.

Dehydration of 16α-Mesylate Solvolysis Fraction B. Dehydration of 11 mg of fraction B with phosphorus oxychloride in pyridine, and appropriate work-up, gave 9 mg of an oil. Gas chromatographic analysis (198° column temperature) showed two peaks, one at T_r = 5.7 min, the other at T_r = 6.4 min. Gc–ms showed both components to have molecular ions at *m/e* 274, indicating both are dehydration products of B.

The ultraviolet spectrum of this mixture showed λ_{max}^{hexane} 238 nm indicating a conjugated diene, as well as end absorption.

A sample of this mixture dissolved in methanol and heated with 2 drops of 1:1 hydrochloric acid–water and reanalyzed on the gc showed the peak at 6.4 min decreasing and the peak at 5.7 min increasing. An ultraviolet spectrum after this treatment showed the same λ_{max} but no end absorption.

It was also found that the dehydration product after acid treatment cochromatographed (gc as well as thin layer chromatography with 1:1 hexane–acetone or ether as eluents) with diene **18**.

Dehydration of 16α-Mesylate Solvolysis Fraction D. Treatment of 13 mg of fraction D as described for fraction B gave 8 mg of oily yellow crystals which appeared as one gc peak at T_r = 5.7 min (at 198°). This material was identified as **18a** by its spectral data: ir (CCl_4) 3060 (olefinic CH), 1095 (OCH_3), 910 ($-CH=CH_2$), and 890 ($=CH_2$) cm^{-1}; nmr ($CDCl_3$, 90 MHz Fourier transform, residual proton of $CDCl_3$ as internal standard) 9.28 (s, CH_3 on C-10), 6.9 (broad, 3α proton), 6.67 (s, OCH_3), 5.45 and 5.33 (two doublets, J = 2 Hz, $C=CH_2$), 4.90 (broad multiplet, vinyl group), and the remaining ring protons from 7.2 to 9.1. The ultraviolet spectrum (hexane) showed only end absorption. The mass spectrum showed a parent ion at *m/e* 274. When a sample of this material was heated in methanol solution with 1 drop of 1:1 hydrochloric acid–water, the gc was unchanged but the uv spectrum of the product was now identical with that of a similarly treated sample of the dehydration products obtained from fraction B.

Base-Catalyzed Rearrangement of Methyl 3β-Methoxy-*D*(13α)-norandrostane-16β-*N*-nitrosocarbamate (17b). The 16β carbamate **16b** was nitrosated in the same way as the 16α epimer **16a**. Thus 0.29 g (0.84 mmol) of **16b** gave the *N*-nitrosocarbamate **17b** as a yellow oil. The infrared spectrum (CCl_4) showed the presence of the *N*-nitrosocarbamate by an absorbance at 1758 cm^{-1} (C=O), as well as residual carbamate by absorbances at 3435 (NH) and 1735 (C=O) cm^{-1}.

This mixture was treated with potassium *tert*-butoxide followed by water quenching as described earlier. Work-up gave 0.22 g of a yellow oil. Preparative thin-layer chromatography with ether as eluent gave three bands. The fastest moving fraction (25 mg, 11%) was shown by its nmr spectrum to be a mixture of several olefinic components which were not further investigated.

The slowest moving fraction (45 mg, 20%) proved by its nmr spectrum and melting point (102–104°, after crystallization from pentane) to be recovered carbamate **16b**.

The remaining fraction (112 mg, 51%) proved to be identical with the C-homo-D-bisnor alcohol **21** by comparison of its nmr and infrared spectra and its thin-layer chromatographic behavior (1:1 hexane–acetone, ether as eluents) to those of an authentic sample.[3] Crystallization from pentane gave an analytical sample of **21**, mp 121–122°. *Anal.* Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.91; H, 11.24.

No nmr or chromatographic evidence for the presence of the C-13 epimeric alcohol[3] was obtained.

Preparation and Solvolysis of 3β-Methoxy-*D*(13α)-norandrostanyl-16β-methanesulfonate (13b). The 16β-mesylate **13b** was prepared in the same way as the 16α epimer. Thus 0.30 g (1.03 mmol) of the 16β alcohol **12b** gave 0.34 g of the mesylate **13b**, which crystallized on standing. This material was characterized only by its nmr spectrum ($CDCl_3$): 9.23 (3 H, s, CH_3 on C-10), 8.87 (3 H, s, CH_3 on C-13), 7.28 (1 H, d of t, J = 8 Hz, 12 Hz, C-14 proton), 7.05 (3 H, s, OSO_2CH_3), 6.9 (1 H, broad, C-3 proton), 6.68 (3 H, s, OCH_3), 5.35 (1 H, t, J = 8 Hz, C-16 proton), and the remaining ring protons from 7.8 to 9.1.

This mesylate was solvolyzed under the same conditions as the 16α epimer. Work-up gave 0.26 g (*ca.* 99%) of an oil which had an nmr spectrum identical with that of the *endo*-C-homo-D-bisnor alcohol **21**. Again, no epimeric alcohol[3] was observed by nmr. Recrystallization from pentane gave 0.22 g (83%) of pure **21**, mp 119–121°.

Kinetics of Hydrolysis of 13b. The rate of hydrolysis of **13b** in 60% (v/v) aqueous acetone was followed at pH 7.5 in a Radiometer Automatic titrator, Model TTlc, by titrating the liberated acid with 0.1 *N* sodium hydroxide. The kinetic runs were performed at 25.1° under a nitrogen atmosphere. The sample size was approximately 7.5 mg (*ca.* 2.0×10^{-5} mol) in 10 ml of solvent. A plot of $\log [c_0/(c_0 - c)]$ *vs.* time (c_0 = equivalents of base added at time = ∞, c = total equivalents of base added at time = t) gave a straight line for at least 4 half-lives. Least-squares analysis of the data gave a rate of $2.79 \pm 0.01 \times 10^{-4}$ sec^{-1} (average of two runs), with a correlation coefficient better than 0.999. The error quoted is a standard error.

(32) L. J. Morris, *Chem. Ind. (London)*, 1238 (1962).