method of Baker.[17] The greater sensitivity of this method is apparent from the fact that the quartets observed for the two ions were well resolved, while in the direct spectrum only broad peaks were observed. The INDOR spectrum of the methylcarboxonium ion is shown in Figure 3. The chemical shifts obtained by this method agree well with those obtained for the ions in FSO_3H–SbF_5 solution (Table I).

Experimental Section

Formic, acetic, and benzoic acids with 56% C^{13} enrichment of the carboxyl carbon atom were obtained from Merck Sharp and Dohme of Canada, Ltd. Carbon-13-enriched sodium propionate was prepared from ethylmagnesium bromide and carbon dioxide from 53% enriched barium carbonate following the procedure for sodium acetate-1-C^{14}.[18]

The carboxylic acid with C^{13} enrichment of the carboxyl carbon atom was dissolved at −80° in fluorosulfonic acid–antimony pentafluoride (1:1 *M*) using SO_2 as a diluent. A Varian Associates Model HA-60-IL spectrometer operating at 15.1 MHz with a Varian Associates Model V4331A probe adapted to accept a 17-mm dewar flask was used in conjunction with a V-4540 temperature controller. The solution was contained in a 13-mm nonspinning sample tube. A 56% C^{13}-enriched sample of methyl iodide contained in a concentrically mounted, sealed, 5-mm sample tube was used as a reference.[19] The spectra were calibrated by using an audiooscillator to generate side bands of the observed signals.

The method used for obtaining INDOR spectra has been described previously.[5,17] Proton spectra were recorded on a Varian Associates A-56-60-A nmr spectrometer.

Acknowledgments. Support of this work by a grant from the National Institutes of Health is gratefully acknowledged. Dr. E. B. Baker, Chemical Physics Laboratory, The Dow Chemical Company, Midland, Mich., is thanked for the INDOR spectrum.

(17) E. B. Baker, *J. Chem. Phys.*, 37, 911 (1962).

(18) A. Murray and D. L. Williams, "Organic Syntheses with Isotopes," Part I, Interscience Publishers, Inc., New York, N. Y., 1958, p 34.

(19) The relaxation time of methyl iodide in our experience was sufficiently short to permit facile homogeneity adjustment of the magnetic field. Dr. G. E. Maciel first observed the advantageous relaxation properties of methyl iodide (~2 sec). The shift of methyl iodide with respect to carbon disulfide was taken as 216.6 ppm: H. Spisecke and W. G. Schneider, *J. Chem. Phys.*, 35, 722 (1961).

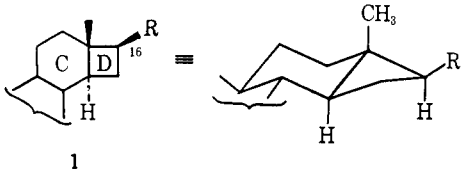
D-Nor Steroids. II. Carbonium Ion Reactions Yielding C-Homo-D-bisnor Steroids[1,2]

Jerrold Meinwald and Jean-Louis Ripoll[3]

Contribution from the Department of Chemistry, Cornell University, Ithaca, New York 14850. *Received August 4, 1967*

Abstract: Syntheses of the pseudo-equatorially substituted D-nor steroids **7** and **19** are described. Both the deamination of the 16β-amine **7** and attempted *p*-toluenesulfonate formation from the 16β-alcohol **19** result in the production of rearranged products with a C-homo-D-bisnor steroidal skeleton. These results correlate well with previous observations on the tendency of *endo*-5-substituted bicyclo[2.1.1]hexanes (in which the C_5 substituent also occupies a pseudo-equatorial position) to undergo particularly facile rearrangement involving participation of a cyclobutyl carbon–carbon bond.

Within the last half dozen years, many research groups, including one at Cornell, have described syntheses of D-nor steroids.[2,4] One of our original motivations for developing a route to this class of compounds was the opportunity they would provide to explore carbonium ion reactions of a cyclobutane ring held in a specific conformation by virtue of its *trans* fusion to a cyclohexane ring (*i.e.*, the adjacent C ring). Formula **1** shows the conformational situation of a



1

16β-substituted D-nor steroid; the 16β substituent occupies a pseudo-equatorial position in this configuration. The corresponding 16α compounds should have pseudo-axial conformations. We have planned to examine carbonium ion reactions such as deaminations and solvolyses in both the 16β and 16α series, and we now wish to report results obtained with the more readily accessible pseudo-equatorially (16β) substituted D-nor-1,3,5(10)-estratrienes.

Synthesis and Deamination of 3-Methoxy-16β-amino-D-nor-1,3,5(10)-estratriene

3-Methoxy-D-nor-1,3,5(10)-estratriene-16β-carboxylic acid (**2**) was prepared from estrone methyl ether[5] es-

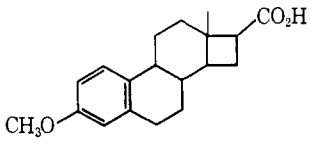
(1) Partial support of this research by the National Institutes of Health (GM-10090) and by Hoffmann-LaRoche, Inc., is acknowledged with pleasure.

(2) For part I, see J. Meinwald, G. G. Curtis, and P. G. Gassman, *J. Am. Chem. Soc.*, 84, 116 (1962). For some synthetic work complementary to that described in this manuscript, see R. Rausser, *et al.*, *Steroids*, in press.

(3) On leave (1965–1966) from the Laboratoire de Chimie Organique II, Faculté des Sciences, Université de Caen, Caen, France.

(4) (a) J. L. Mateos and O. Chao, *Bol. Inst. Quim. Univ. Nal. Auton. Mex.*, 13, 3 (1961); (b) M. P. Cava and E. Moroz, *J. Am. Chem. Soc.*, 84, 115 (1962); (c) G. Müller, C. Huynh, and J. Mathieu, *Bull. Soc. Chim. France*, 296 (1962); (d) A. Hassner, A. W. Coulter, and W. S. Seese, *Tetrahedron Letters*, 759 (1962); (e) H. Reimann, H. Schneider, O. Z. Sarre, C. Federbush, C. Towne, W. Charney, and E. P. Oliveto, *Chem. Ind.* (London), 334 (1963); (f) J. L. Mateos and R. Pozas, *Steroids*, 2, 527 (1962); (g) J. L. Mateos, O. Chao, and H. Flores R, *Tetrahedron*, 19, 1051 (1963); (h) A. Horeau and H. B. Kagan, *ibid.*, 20, 2431 (1964); (i) E. Ghera, *Tetrahedron Letters*, 4181 (1965); (j) G. Quinkert, C. Cimbollek, and G. Buhr, *ibid.*, 4573 (1966); (k) E. Ghera, *ibid.*, 17 (1967).

sentially as described previously.[4b] Although no basic product could be isolated from an attempted Schmidt



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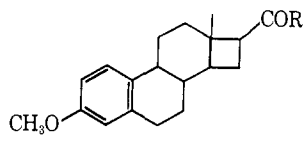
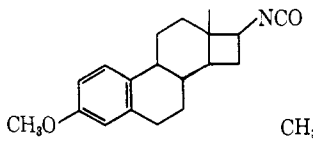


3, R = Cl
4, R = N_3

degradation of **2**,[6] the Curtius sequence proved a satis-



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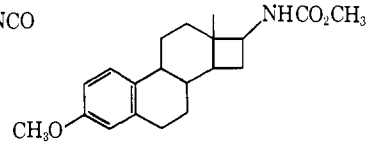
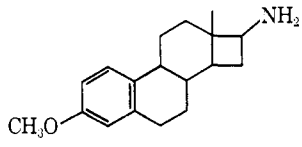


6

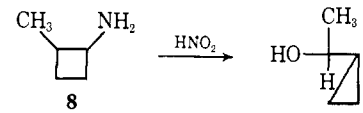
factory alternative route to the desired 16β-amino compound. Oxalyl chloride converted **2** into the corresponding acid chloride **3** (λ_{max} 5.50 μ), which reacted with sodium azide in acetone to give a mixture of the corresponding acyl azide **4** and isocyanate **5** (λ_{max} 4.65 and 4.38 μ). This mixture, after being refluxed in methanol, afforded crystalline 3-methoxy-D-nor-1,3,5-(10)-estratriene 16β-methylcarbamate (**6**) (λ_{max} 2.97 and 5.79 μ) in 47% over-all yield from **2**. The structure of **6** is supported by a satisfactory elementary analysis and by its nmr spectrum; the 16β configuration of this product follows from the known steric course of the Curtius degradation.[7] (A very small amount (*ca.* 5%) of the corresponding 16α-methylcarbamate could be obtained from the mother liquors when this sequence was carried through on crude **2**, but unfortunately, the amounts obtained were insufficient to permit complete characterization.) 3-Methoxy-16β-amino-D-nor-1,3,5(10)-estratriene (**7**) was obtained in 75% yield as its hydrochloride by treating the free amine, produced by ethanolic potassium hydroxide hydrolysis of **6**, with dry hydrogen chloride in ether.



7

The deamination of **7** was carried out by treating a solution of its hydrochloride in 50% aqueous acetic acid with sodium nitrite at 0°.[8] No basic component was recoverable after the usual work-up, and the crude neutral product consisted of a yellow, viscous oil showing hydroxylic (2.86 μ), acetate ester (5.76 μ), and nitrate ester (6.15 μ) absorptions in its infrared spectrum. Lithium aluminum hydride reduction of the entire fraction gave a colorless oil free of ester absorptions, which was subjected to chromatography over alumina to yield one major product (A, in 50% yield) and two minor products (B, 3%; C, 1%). Although each of these substances appeared homogeneous on the basis of tlc examination, only B could be obtained crystalline.

Before examining the data bearing on the structure of A, the chief deamination product, we shall consider what products might be reasonably expected on the basis of earlier studies of simple cyclobutylamine deamination reactions. Roberts, *et al.*, have studied the deamination of "*trans*"-2-methylcyclobutylamine (**8**) and found the ring contraction product, methylcyclopropylcar-

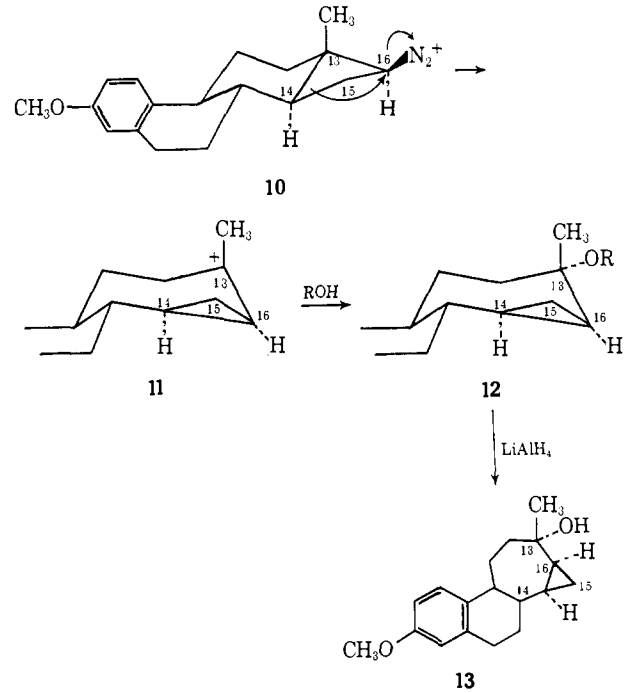


8 9

binol (**9**) (in modest yield), to be the only isolable product.[9] In an independent study,[10] we have found that the amine used in these experiments was probably a mixture of comparable amounts of *cis* and *trans* isomers of **8**, so that the possible influence of the stereochemistry of the amine on the course of this reaction might have gone unobserved. However, when the individual stereoisomers were prepared and subjected to the same reaction, the cyclopropylcarbinol **9** was found to form as a result of the deamination of each, so that no important stereochemical influence on the course of these reactions could be detected.[10]

Drawing on the analogy of this case, the simplest reaction path for **7** would appear to be contraction of ring D with concomitant expansion of ring C, as outlined (in stepwise fashion for clarity) in Chart I. Loss

Chart I



of nitrogen from the diazonium salt **10** and migration of the C_{13}–C_{14} bond would yield the tertiary carbonium ion

(5) We acknowledge with pleasure a generous gift of this starting material from the Schering Corporation.

(6) This reaction gave an 89% yield of the corresponding amine in the case of A-norcholestane-1-carboxylic acid (M. P. Cava and B. R. Vogt, *Tetrahedron Letters*, 2813 (1964)).

(7) See P. A. S. Smith in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 530 ff.

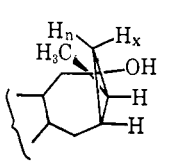
(8) Unpublished results of Dr. Lorraine Lunnemann Labana indicated that these experimental conditions give the simplest deamination products.

(9) M. S. Silver, M. C. Caserio, H. E. Rice, and J. D. Roberts, *J. Am. Chem. Soc.*, **83**, 3671 (1961).

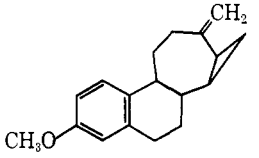
(10) L. L. Labana, Doctoral Dissertation submitted to Cornell University, 1965.

11, which could then combine with a nucleophile to give **12**. Assuming the quite generally observed[11] inversion of configuration at both the rearrangement origin (C_{16}) and its terminus (C_{13}), along with retention of configuration of the migrating group (C_{14}), the expected product becomes a *C-homo-D-bisnor steroid* with a *cis* C/D ring fusion (**12**). On this basis, formula **13** was considered a suitable working hypothesis for the structure of A.

Both chemical and physical evidence supports this assignment. Thus, A is recovered largely unchanged on treatment with acetic anhydride and pyridine, in accord with expectations for a tertiary alcohol. In its infrared spectrum, a carbon tetrachloride solution of A shows a well-resolved hydroxyl absorption at 2.96 μ. The nmr spectrum of A is especially useful, since it shows the presence of a unique cyclopropyl proton (τ 9.47–9.72), attributable to the *endo* proton (H_n) in partial formula **13a**.[12] The remainder of the nmr spectrum of A accounts for the phenyl protons (τ



13a

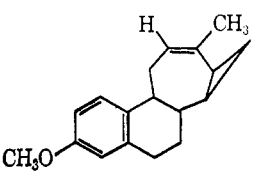


14

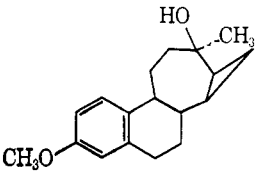
2.70–3.50, 3 H), the methoxyl group (singlet at τ 6.25, 3 H), the tertiary C_{18}-methyl group (singlet at τ 8.77, 3 H), and the hydroxyl group (τ 8.14). The other protons show complex absorption between τ 7.03 and 9.33, with the high-field absorption being indicative of additional cyclopropyl protons. The mass spectrum of this material showed its base peak at *m/e* 254, corresponding to an $(M - 18)^+$ fragment, as anticipated for the tertiary alcohol structure **13**.[13]

The dehydration of **13** provides further support for the above structural assignment. Treatment of **13** with phosphorus oxychloride in pyridine at room temperature[14] afforded a single product, assigned structure **14**, in 77% yield. In its infrared spectrum, disappearance of the hydroxylic absorption and the appearance of characteristic new maxima at 6.08 and 11.17 μ suggest the generation of an exocyclic methylene group.[15] A two-proton absorption at τ 5.14 in the nmr spectrum of **14**, replacing the previously observed hydroxylic and C_{18}-methyl absorption bands, confirms this conclusion. In its mass spectrum, olefin **14** showed its base peak at *m/e* 254.[13]

In contrast to this result, refluxing of an acidified methanolic solution of **13** led to two products, the chief of which is best accounted for on the basis of structure



15



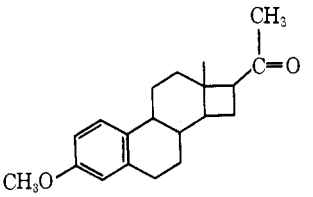
16

15. The main supporting evidence in this case is the appearance in the nmr spectrum of this product of a one-proton olefinic absorption (complex multiplet at τ 4.21–4.95) and an allylic C_{18}-methyl group (τ 8.20 singlet, 3 H). The high-resolution mass spectral parent peak at *m/e* 254.1656 confirmed the elemental composition of this olefin.[16] Treatment of the exocyclic olefin **14** with methanolic hydrogen chloride under comparable conditions also resulted in the formation of **15**.

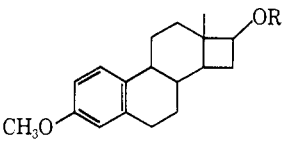
The minor, crystalline deamination product, B, is tentatively assigned formula **16**, epimeric with **13**. Its mass spectrum showed a base peak at *m/e* 254.[13] The structure assignment rests largely on the basis of spectral data (summarized in the Experimental Section) and a phosphorus oxychloride–pyridine dehydration to give **14** in 78% yield. Product C was not further examined.

Synthesis and Reactions of 3-Methoxy-16β-hydroxy-D-nor-1,3,5(10)-estratriene

3-Methoxy-D-nor-1,3,5(10)-estratriene-16β-carboxylic acid (**2**) reacted readily with methyllithium[17] to give the crystalline 16β-acetyl compound **17**, characterized by its elementary analysis and the usual spectral data.



17



18, R = $COCH_3$
19, R = H
20, R = $COCF_3$

Considerable difficulty was encountered in finding conditions suitable for the Baeyer–Villiger oxidation of **17** to the acetate **18**. A variety of procedures employing perbenzoic acid, *m*-chloroperbenzoic acid, and peracetic acid, with and without acid catalysts, were examined without success. In general, either unchanged starting material or uncharacterized products in which the aromatic A ring appeared to be destroyed were isolated. Finally, the storage in the dark of an ethereal solution of **17** containing a large excess of monoperphthalic acid at −3° for a month led to an 85% yield of the desired acetate **18** with only a few per cent of accompanying A-ring attack. Potassium carbonate in aqueous methanol converted **18** into the corresponding alcohol **19**, which gave the trifluoroacetate **20** on treatment with trifluoroacetic anhydride in pyridine.[18] All three compounds showed the expected spectral data, and the parent alcohol **19** gave the correct elementary analysis.

(11) For an excellent review of steroid rearrangements in particular, see N. L. Wendler in "Molecular Rearrangements," Vol. 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1019 ff.

(12) It would appear from an examination of molecular models that the *exo*-cyclopropyl proton (H_x) should be deshielded by the 13α-hydroxyl group, leaving H_n uniquely upfield. In contrast, in compound **16** (see below), no unique upfield proton appears in the nmr spectrum, and models suggest comparable deshielding of both H_x and H_n by the 13β-hydroxyl function.

(13) We are indebted to Dr. A. Duffield, Stanford University, for these mass spectral determinations.

(14) *Cf.* S. A. Julia and H. Heusser, *Helv. Chim. Acta*, **35**, 2080 (1952).

(15) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, Inc., San Francisco, Calif., 1962, p 24.

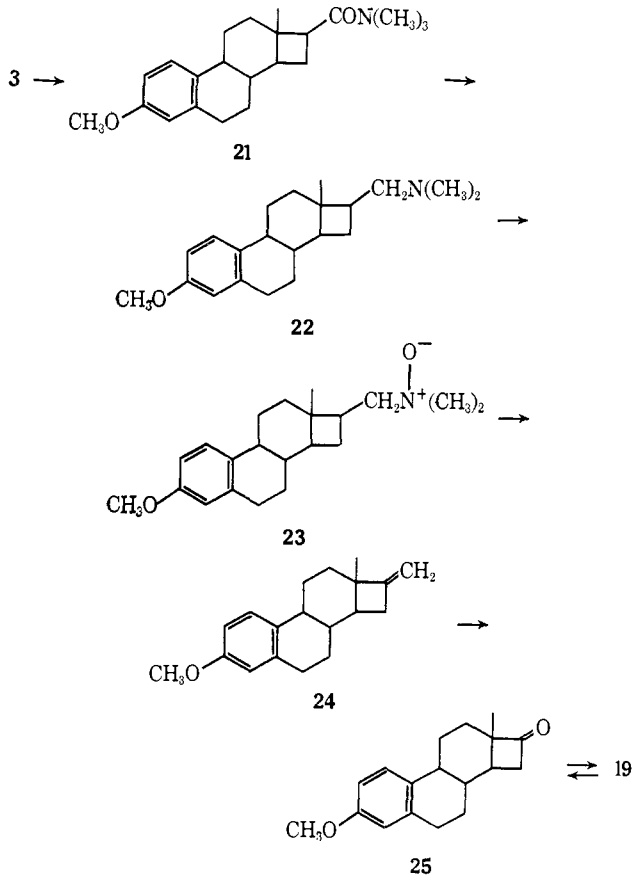
(16) We are grateful to Dr. R. Highet of the National Institutes of Health for this high-resolution spectrum, obtained on an A.E.I. MS-9 instrument.

(17) *Cf.* G. Müller, C. Huynh, and J. Mathieu, *Bull. Soc. Chim. France*, 296 (1962).

(18) *Cf.* B. W. Sands and A. T. Rowland, *Steroids*, 4, 175(1964).

An alternate synthesis of **19** was achieved as outlined in Chart II. The conversion of **3** to the exocyclic olefin

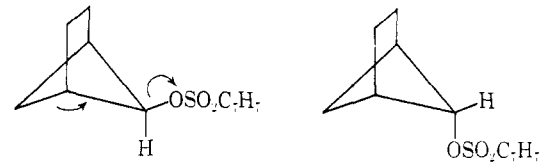
Chart II



24 proceeded smoothly,[19] although neither ozonolysis[20] nor Lemieux oxidation[21] gave any of the desired cyclobutanone. Osmium tetroxide oxidation[22] of **24** to the corresponding diol was also unsuccessful. Finally, ozonolysis conditions were found which gave a 10% yield of **25** as a crystalline solid (infrared maximum at 5.61 μ), along with an 85% recovery of starting material and 5% of an uncharacterized product in which the A ring appeared to have been attacked. Lithium aluminum hydride reduction of **25** proceeded entirely by α attack, to give the previously characterized 16β-alcohol **19**. Oppenauer oxidation of **19**[23] gave a 40% yield of **25**.

The trifluoroacetate **20** had been prepared in the hope that solvolysis of this ester would lead to carbonium ion derived products.[24] However, in 70% aqueous acetone, only unrearranged 16β-alcohol **19** was formed, indicating that acyl–oxygen fission was occurring in preference to the desired alkyl–oxygen fission. Attempts to prepare the *p*-toluenesulfonate of **19** were also frustrating in that only rearrangement products could be found under any conditions sufficiently vigorous to esterify the alcohol. Thus, using *p*-toluenesulfonyl chloride and pyridine at room temperature, the chief product was found to be the exocyclic olefin **14**, accompanied by lesser amounts of the epimeric tertiary alcohols **13** and **16**. The technique of Kochi and Hammond for the preparation of very sensitive *p*-toluenesulfonates[25] was also tried, but without success.

In summary, we have found that both the nitrous acid deamination of **7** and the attempted conversion of the alcohol **19** to the corresponding *p*-toluenesulfonate ester result in the formation of rearranged products possessing a C-homo-D-bisnor steroidal skeleton. These findings fit in well with those of Wiberg and Fenoglio,[26] who found that *endo*-5-bicyclo[2.1.1]hexyl *p*-toluenesulfonate (**26**) undergoes acetolysis (to give rearranged products) at a rate 10^6 times greater than the *exo* isomer **27**. The high reactivity of the pseudo-equatorially substituted **26**, associated with the participation of a neighboring cyclobutyl carbon–carbon bond, parallels the reactivity of the pseudo-equatorially substituted, 16β-D-nor steroids. It may be anticipated on this basis that the epimeric 16α-substituted D-nor steroids will show quite different behavior. Related work aimed at exploring this general area is now in progress.



Experimental Section

Infrared spectra were recorded using a Perkin-Elmer Infracord. Nmr spectra were taken in carbon tetrachloride or deuteriochloroform with a Varian A-60 instrument. Mass spectra were recorded with C.E.C. 21-103C and A.E.I. MS-9 (high-resolution spectra) mass spectrometers. Melting points were determined on a Kofler unit and are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

3-Methoxy-D-nor-1,3,5(10)-estratrlene-16β-carboxylic Acid (2). The procedure of Cava and Moroz[4b] was used with some modifications to prepare crude acid **2**. Estrone methyl ether was converted into its 16-oximino derivative as described by Litvan and Robinson.[27] After recrystallization, 16-oximinoestrone methyl ether, mp 166°, was obtained in 70% yield. To a solution of the above product (5 g) in THF (130 ml) were added 83 ml of a 4 *N* sodium hydroxide solution and 26.6 ml of concentrated ammonia. The solution was cooled to 10° under nitrogen and 66.5 ml of 5.25% sodium hypochlorite ("Clorox") was added dropwise with stirring over 1 hr. After stirring for 1 hr more, the reaction mixture was diluted with 500 ml of cold water; the yellow precipitate which had formed was filtered, washed, and dried, to give 4.1 g (83%) of crude 16-diazoestrone methyl ether, mp 133–136°. After chromatography of the crude product over neutral alumina in chloroform, followed by recrystallization from chloroform–methanol, there was obtained pure 16-diazoestrone methyl ether, mp 145–146°, in 64% over-all yield.

A mixture of this diazo ketone (4 g) and sodium bicarbonate (2.2 g) in 200 ml of THF and 180 ml of water was irradiated with a Hanovia 200-w mercury vapor lamp (using a Corex filter) until the starting material was all consumed. After addition of 500 ml of water, followed by extraction of some nonacidic product, the solution was acidified and cooled to 0°, when white crystals of crude acid **2** (mp 170–176°) separated (2.95 g, 76%). An analytical sample was obtained by further purification; it showed mp 188°, in agreement with the literature report.[4b]

(19) *Cf.* J. M. Conia and J. Gore, *Bull. Soc. Chim. France*, 735 (1963).
(20) *Cf.* J. M. Conia, P. Leriverend, and J. L. Ripoll, *ibid.*, 1803 (1961).
(21) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.* **33**, 1701 (1955).
(22) J. S. Baran, *J. Org. Chem.*, **25**, 257 (1960).
(23) A. Wettstein and C. Mystre, *Helv. Chim. Acta*, **30**, 1262 (1947).
(24) A. Moffat and H. Hunt, *J. Am. Chem. Soc.*, **80**, 2985 (1958).
(25) J. K. Kochi and G. S. Hammond, *ibid.*, **75**, 3443 (1953).
(26) K. B. Wiberg and R. Fenoglio, *Tetrahedron Letters*, 1273 (1963).
(27) F. Litvan and R. Robinson, *J. Chem. Soc.*, 1997 (1938).

3-Methoxy-D-nor-1,3,5(10)-estratriene 16β-Methylcarbamate (6). To 1 g of **2** (mp 170–176°) dissolved in 15 ml of benzene was added 1 ml of oxalyl chloride. The mixture was left overnight; after evaporation of the solvent, there remained 1.1 g of crude acid chloride **3**; infrared spectrum (KBr): 3.44, 5.50, 6.20, 6.68, 7.83, 7.96, 8.11, 8.86, 9.44, 9.68, 11.48, 12.33, 12.83, 13.03, and 13.93 μ. This material was dissolved in 10 ml of acetone and cooled to 0°, and to this solution was added dropwise 0.40 g of sodium azide in 1.5 ml of water. After stirring for 15 min, the mixture was diluted with 25 ml of water. The precipitated product (mixture of **4** and **5**) was filtered, washed, and dried; infrared spectrum (CCl_4): 3.42, 4.38, 4.65, 6.20, 6.68, 7.96, 9.35, 10.42, and 11.04 μ.

The crude mixture of **4** and **5** was dissolved in 15 ml of methanol and refluxed for 20 hr. The solvent was then removed and the residue (1.3 g) recrystallized twice from a mixture of benzene–hexane (1:9); 0.43 g (47%) of pure **6** (mp 166–167°) was thus isolated. An analytical sample (mp 167°) was obtained by chromatography over basic alumina and recrystallization; infrared spectrum (KBr): 3.00*, 3.41, 5.88*, 6.45, 6.66, 6.87, 7.77, 7.92, 8.03, 9.45, 9.70, 12.28, 12.38, and 12.82 μ (* bands at 2.97 and 5.79 μ in CCl_4).

The nmr spectrum in $CDCl_3$ (τ values) gave a quartet and a singlet at 2.68 and 3.41 (phenyl protons), a broad one-proton singlet at 5.10 (N–H), and methyl singlets at 6.21 (carbamate CH_3), 6.31 ($-OCH_3$), and 9.01 (angular CH_3); the remainder of the spectrum consisted of a broad absorption between 5.75 and 9.46.

Anal. Calcd for $C_{20}H_{27}O_3N$: C, 72.95; H, 8.26; N, 4.25. Found: C, 73.00; H, 8.24; N, 4.20.

3-Methoxy-16β-amino-D-nor-1,3,5(10)-estratriene (7). A mixture of 0.43 g of **6** and 0.5 g of potassium hydroxide in 5 ml of 95% ethanol was refluxed under nitrogen for 3 days; 20 ml of water was added, the ethanol boiled off under vacuum, and product **7** extracted with ether. The ethereal solution was washed with water, dried, and saturated with dry HCl, affording 0.3 g of the hydrochloride of **7** (75% yield; mp >300°); infrared spectrum (KBr): 2.95, 3.46, 6.21, 6.67, 6.84, 7.99, and 9.68 μ.

The nmr spectrum in $(CD_3)_2SO$ (τ values) showed a broad three-proton singlet at 1.46 (NH_3^+), phenyl protons between 2.75 and 3.43, methyl singlets at 6.31 ($-OCH_3$) and 8.91 (angular CH_3), one proton (adjacent to NH_3^+) at 6.50, and other protons between 7.05 and 9.15.

Anal. Calcd for $C_{18}H_{26}ONCl$: C, 70.25; H, 8.52; N, 4.55; Cl, 11.51. Found: C, 70.12; H, 8.35; N, 4.51; Cl, 11.62.

Nitrous Deamination of 7. 3-Methoxy-13α-hydroxy-C-homo-D-bisnor-1,3,5(10)-estratriene (13) and Its 13β-Hydroxy Epimer 16. The hydrochloride of **7** (2.85 g) was dissolved in 100 ml of 50% aqueous acetic acid and the solution was cooled to 0°. Sodium nitrite (7.1 g) was added in small portions, and the stirred mixture was kept for 12 hr at 0°, before being allowed to warm up to room temperature. After adding 120 ml of water to the reaction mixture and neutralizing with sodium carbonate, the products were extracted with ether. The ethereal solution was washed with 1% HCl and water, dried, and evaporated, affording 2.72 g of a viscous yellow oil; infrared spectrum (CCl_4): 2.86, 3.43, 5.76, 6.15, 6.63, 7.92, 8.06, and 9.60 μ.

The crude product was dissolved in ether (200 ml) and added dropwise to a refluxing suspension of lithium aluminum hydride (2.4 g) in 200 ml of ether; the mixture was refluxed overnight; water was added and the organic layer washed, dried, and evaporated, leaving 1.85 g of a colorless oil; infrared spectrum (CCl_4): 2.92, 3.41, 6.20, 6.65, 7.92, 8.05, 9.03, 9.55, and 11.04 μ.

Chromatography of the reduction product in chloroform over basic alumina afforded successively: 75 mg (3% from **7**) of product B (**16**), mp 103–104° after recrystallization from hexane; 1.29 g (50%) of product A (**13**), colorless oil; and 28 mg (1%) of product C, a yellow oil not further investigated. The infrared spectrum of product A (**13**) in CCl_4 showed absorption bands at 2.96, 3.45, 6.22, 6.68, 7.92, 8.03, 8.57, 9.02, 9.59, 10.61, 11.02, 11.51, and 11.76 μ.

The nmr spectrum of **13** in $CDCl_3$ (τ values) showed phenyl protons between 2.70 and 3.50 (3 H), methyl singlets at 6.25 ($-OCH_3$) and 8.77 (t-CH_3), a one-proton singlet at 8.14 (OH proton), and a one-proton multiplet between 9.47 and 9.72 (*endo* cyclopropyl proton); the remainder of the spectrum consisted of complex absorptions between 7.03 and 9.33.

The main infrared bands of B (**16**) in KBr were found at 2.86, 3.42, 6.18, 6.67, 9.06, 9.60, 10.91, and 12.32 μ. The nmr spectrum of **16** in CCl_4 (τ values) gave phenyl proton bands between 2.87 and 3.62, methyl singlets at 6.32 ($-OCH_3$) and 8.66 (t-CH_3), a one-proton singlet at 8.20 (OH), and a five-proton absorption between 9.04 and 9.63; the remainder of the protons were found between 7.19 and 8.81.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.40; H, 8.89. Found: C, 78.65; H, 9.08.

Attempted Acetylation of 13. Acetic anhydride (2 ml) was added to 0.2 g of **13** dissolved in 2 ml of pyridine, and the mixture was kept overnight at room temperature. Ether was then added, and the resulting solution was washed, dried, and evaporated. Chromatography over neutral alumina gave 23 mg (10%) of acetate of **13**, together with 0.13 g of unreacted **13**.

Dehydration of 13 Using Phosphorus Oxychloride in Pyridine. 3-Methoxy-C-homo-D-bisnor-1,3,5(10),13(18)-estratetraene (14). Phosphorus oxychloride (0.8 ml) was added dropwise to 0.2 g of **13** dissolved in 5 ml of pyridine and cooled to 0°; the mixture was kept at 0° for 1 hr and then at room temperature for 20 hr. After adding water to the reaction mixture, the product was extracted with ether. Chromatography over neutral alumina afforded 0.14 g (77%) of a colorless oil (**14**); infrared spectrum (neat) 3.43, 6.08, 6.21, 6.67, 6.91, 7.92, 8.09, 8.62, 9.61, and 11.17 μ.

The nmr spectrum in CCl_4 (τ values) showed phenyl absorption bands between 2.79 and 3.56, a two-proton resonance at 5.14 (exocyclic methylene), and a singlet at 6.29 ($-OCH_3$); other protons were found between 7.02 and 9.64.

Anal. Calcd for $C_{18}H_{22}O$: C, 85.00; H, 8.71. Found: C, 85.07; H, 8.69.

Dehydration of 13 Using Hydrochloric Acid in Methanol. 3-Methoxy-C-homo-D-bisnor-1,3,5(10),12-estratetraene (15). A solution of 0.1 g of **13** in 10 ml of methanol was refluxed for 2 hr with 0.5 ml of 10% HCl; water was then added and the product extracted with ether. After drying and removing the solvent, chromatography over neutral alumina afforded 70 mg (75%) of **15** as a colorless oil, together with 15 mg of an oil not further examined; infrared spectrum of **15** (CCl_4): 3.45, 6.17, 6.63, 6.80, 6.90, 7.87, 8.05, 8.57, 9.56, 11.81, and 14.56 μ. The nmr spectrum in CCl_4 (τ values) showed phenyl resonance lines between 2.90 and 3.62, a one-proton multiplet between 4.21 and 4.95 (olefinic proton), methyl singlets at 6.30 ($-OCH_3$) and 8.20 ($>CCH_3$); other protons appeared between 7.00 and 9.30. (The tetraene **14** also gave **15** quantitatively under the same experimental conditions.).

Dehydration of 16 with Phosphorus Oxychloride in Pyridine. Preparation of 14. Phosphorus oxychloride (0.4 ml) was added dropwise to a solution cooled to 0° of **16** (25 mg) in 2.5 ml of pyridine. The mixture was kept at 0° for 1 hr and then overnight at room temperature. Ether was then added, and the resulting solution was washed with water, dried, and evaporated. The infrared spectrum of the residue (18.3 mg, 78%) was identical with that of pure **14**.

3-Methoxy-16β-acetyl-D-nor-1,3,5(10)-estratriene (17). To 2.0 g of crude **2** in 120 ml of benzene was added 100 ml of a 2% ethereal solution of methyllithium. The mixture was kept at room temperature for 15 hr, water was then added, and the organic layer was washed, dried, and evaporated to afford 2.1 g of crude **17**, mp 80–120°. Chromatography over Florisil in benzene and recrystallization from 90% aqueous methanol gave 1.27 g (63%) of practically pure **17**, mp 130–133°. An analytical sample, mp 134–136°, was obtained by further recrystallization; infrared spectrum (KBr): 3.43, 5.88, 6.65, and 8.08 μ. Its nmr spectrum in CCl_4 (τ values) showed phenyl resonance lines between 2.93 and 3.56 and methyl singlets at 6.30 ($-OCH_3$), 8.07 ($-COCH_3$), and 9.10 (angular CH_3); other protons appeared between 5.85 and 9.57.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.48; H, 8.73. Found: C, 80.30; H, 8.68.

3-Methoxy-16β-acetoxy-D-nor-1,3,5(10)-estratriene (18). **17** (0.1 g) was dissolved in 20 ml of a 10% solution of monoperphthalic acid in ether. The mixture (protected from light) was stored for 1 month at −3°, and was then washed with sodium bicarbonate and water. After drying and evaporating the solvent, the crude product, by chromatography over acid alumina, gave 89 mg (85%) of practically pure **18**, mp 117–124°. Two recrystallizations from hexane afforded an analytical sample, mp 122–125°; infrared spectrum (KBr): 3.40, 5.69, 6.65, 7.90, 8.05, 9.48, 9.66, 11.47, and 12.42 μ. The nmr spectrum of **18** in CCl_4 (τ values) showed phenyl absorption bands between 2.65 and 3.45 and methyl singlets at 6.19 ($-OCH_3$), 7.94 ($-COCH_3$), and 8.96 (angular CH_3); other protons showed absorption between 6.96 and 9.20.

3-Methoxy-16β-hydroxy-D-nor-1,3,5(10)-estratriene (19). A solution of **18** (89 mg) in 20 ml of 75% methanol was refluxed for 2 hr with 0.1 g of potassium carbonate. After addition of water, the product was extracted with chloroform and purified by chromatography over basic alumina; alcohol **19** (mp 115–117°) was thus ob-

tained in practically quantitative yield, and was subsequently recrystallized three times from aqueous methanol to give an analytical sample, mp 120–121°; infrared spectrum (CCl_4): 3.06, 3.45, 6.19, 6.65, 6.85, 7.97, 8.07, 8.86, 9.20, 9.30, and 9.59 μ. Its nmr spectrum in CCl_4 (τ values) gave phenyl absorption bands between 2.69 and 3.55, methyl singlets at 6.27 ($-OCH_3$) and 8.98 (angular CH_3), and a one-proton multiplet at 6.13 (H adjacent to OH); the remainder of the absorption was found between 6.85 and 9.20.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.40; H, 8.89. Found: C, 79.31; H, 8.72.

Preparation and Hydrolysis of 3-Methoxy-16β-trifluoroacetoxy-D-nor-1,3,5(10)-estratriene (20). To a solution of 70 mg of **19** in 1.2 ml of pyridine, cooled to 0°, was added 1 ml of trifluoroacetic anhydride. The mixture was kept at room temperature for 18 hr, 2 ml of dioxane and 10 ml of water were then added, and the product was extracted with chloroform. After washing, drying, and evaporating the solvent, subsequent chromatography over Florisil afforded impure **20** (mp 90–105°) which was recrystallized twice from hexane, mp 111–113°; infrared spectrum (KBr): 3.40, 5.62, 6.67, 8.19, 8.53–8.68, 10.09, 11.47, 12.43, and 12.88 μ.

The nmr spectrum showed phenyl resonance lines between 2.84 and 3.55, a one-proton multiplet between 5.13 and 5.44 (H adjacent to $-COCF_3$), and methyl singlets at 6.27 ($-OCH_3$) and 8.95 (angular CH_3); other protons appeared between 7.00 and 9.00. Pure **20** was refluxed for 20 hr in 20 ml of 70% aqueous acetone; solvent was then evaporated under vacuum, and the product was extracted with chloroform. After washing, drying, and evaporating the solvent, subsequent chromatography over neutral alumina afforded only **19** in practically pure state.

3-Methoxy-16-methylene-D-nor-1,3,5(10)-estratriene (24). A solution of crude **3** (1.6 g) in 50 ml of benzene was added dropwise to 10 ml of a cold 30% dimethylamine solution in benzene. After 20 hr of stirring at room temperature, water was added and the organic layer separated, washed, dried, and evaporated. The residue consisted of 1.5 g of crude 3-methoxy-16β-N,N-dimethylamido-D-norestratriene (**21**), mp 135–141°. An analytical sample, mp 165–166°, was obtained by recrystallization from a hexane–benzene mixture; infrared spectrum (KBr): 3.40, 6.07, 6.62, 7.14, 8.04, 8.63, 9.55, 9.67, 11.62, and 12.31 μ.

The nmr spectrum of **21** in $CDCl_3$ (τ values) showed phenyl absorption lines between 2.71 and 3.37 and methyl singlets at 6.20 ($-OCH_3$), 7.03 ($-CON(CH_3)_2$), and 9.03 (angular CH_3); the remainder of the spectrum was found between 7.00 and 9.00.

A solution in ether (50 ml) of the crude amide **21** (1.5 g) was added dropwise to a refluxing suspension of lithium aluminum hydride (2 g) in 20 ml of ether. After refluxing for 20 hr, water was added, the ethereal phase was separated and washed with water, and the amine was extracted with 1% HCl. The aqueous acidic solution was washed with water and neutralized with sodium hydroxide and the free amine was extracted with ether. After the usual work-up, there was obtained 1.25 g of crude 3-methoxy-16β-N,N-dimethylaminomethyl-D-norestratriene (**22**), mp 63–67°. A pure sample, mp 70–71°, was obtained by recrystallization from hexane; infrared spectrum (KBr): 3.46, 6.23, 6.70, 6.90, 7.96, 9.55, 11.47, and 12.31 μ.

The nmr spectrum of **22** in CCl_4 (τ values) showed phenyl resonance bands between 2.86 and 3.56 and methyl singlets at 6.31 ($-OCH_3$), 7.90 ($-N(CH_3)_2$), and 9.06 (angular CH_3); the remaining protons gave resonance lines between 7.00 and 9.00.

Crude **22** (1.20 g) was dissolved in 50 ml of methanol, and 10 ml of 30% hydrogen peroxide was added at 0°. After 1 hr, the solution was allowed to warm up to room temperature and kept for 48 hr. The remaining hydrogen peroxide was destroyed with platinum, the solution was filtered and concentrated, and the amine oxide **23** was directly pyrolyzed at 180° (0.3 mm) for 15 min. Chloroform was added, and the solution was washed with 5% HCl. After drying and evaporating the solvent, chromatography over neutral alumina afforded 0.75 g (73% from **22**) of **24** as an oil which crystallized slowly.

An analytical sample, mp 57–58°, was obtained by recrystallization from 95% methanol; infrared spectrum (neat): 3.40, 5.94, 6.21, 6.65, 7.94, 8.05, 9.56, 11.39, and 12.51 μ.

The nmr spectrum of **24** in CCl_4 (τ values) showed phenyl absorption bands between 2.95 and 3.57, a two-proton quartet at 5.38 (exocyclic methylene), and methyl singlets at 6.31 ($-OCH_3$) and 8.90 (angular CH_3); the rest of the absorption lines appeared between 7.00 and 9.17.

Anal. Calcd for $C_{19}H_{24}O$: C, 85.00; H, 9.05. Found: C, 85.00; H, 8.90.

Ozonolysis of 24. 3-Methoxy-D-nor-1,3,5(10)-estratrien-16-one (25). A 0.017 *M* ozone solution was obtained by bubbling ozonized air through methylene chloride at −80° and was titrated with NaI and 0.1 *N* $Na_2S_2O_3$. This solution (22 ml) was added at −80° to 0.1 g of **24** dissolved in 10 ml of methylene chloride; after 10 min, 0.1 ml of pyridine was added and the solution allowed to warm up in cold water. The solution was washed with water and dried; the solvent was evaporated. Chromatography over neutral alumina afforded 10 mg of **25** (10%), together with unreacted **24** (85%) and A-ring-attacked product (5%). Ketone **25** was recrystallized twice from hexane, mp 102–103°; infrared spectrum (CCl_4): 3.42, 5.61, 6.19, 6.64, 6.83, 7.97, 8.08, and 9.59 μ. Its nmr spectrum in CCl_3 (τ values) gave phenyl absorption lines between 2.98 and 3.72 and methyl singlets at 6.36 ($-OCH_3$) and 8.82 (angular CH_3); other protons appeared between 6.81 and 9.32.

Anal. Calcd for $C_{18}H_{22}O_2$: C, 80.15; H, 8.10. Found: C, 79.98; H, 8.21.

Lithium Aluminum Hydride Reduction of 25. Preparation of 19. Ketone **25** (40 mg) was refluxed for 20 hr with 0.2 g of lithium aluminum hydride in 20 ml of ether. The product obtained after washing with water, evaporating the ether, and recrystallizing from aqueous methanol was pure **19**, mp 119–120°.

Oppenauer Oxidation of 19. Preparation of 25. **19** (0.1 g) was dissolved in 100 ml of toluene and 10 ml of cyclohexanone. Solvent (20 ml) was distilled in order to remove traces of water, and a solution of 1 g of aluminum isopropoxide in 30 ml of dry toluene was added dropwise. The mixture was boiled for 2 hr with slow distillation; 10 ml of a saturated aqueous solution of potassium sodium tartrate was added, solvents were removed by steam distillation, and the remaining aqueous phase was extracted with chloroform. After working up the reaction mixture, subsequent chromatography of the crude residue over neutral alumina afforded 40 mg of **25** (40%), mp 95–105°, together with unreacted **19** (33 mg) and degraded product (10 mg).

Attempted Preparation of 3-Methoxy-16β-hydroxy-D-nor-1,3,5(10)-estratriene *p*-Toluenesulfonate. Formation of 13, 14, and 16. *p*-Toluenesulfonyl chloride (1 g) was introduced into a solution of **19** (50 mg) in pyridine (2 ml) cooled to 0°; after 43 hr at room temperature, water was added, followed by a 10% aqueous solution of sodium bicarbonate until neutralization was achieved. The solution was extracted with ether. After work-up, three products were separated by chromatography over Florisil and characterized as **14** (principal product), **13**, and **16** (minor product).

Another attempt at preparation of the *p*-toluenesulfonate of **19** using the method of Kochi and Hammond,[25] was also unsuccessful