D-Nor Steroids. III. Synthesis of Conformationally Defined Cyclobutylamines and Alcohols[1,2]

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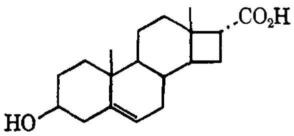
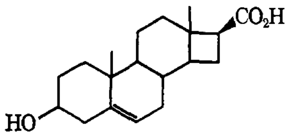
Abstract: Syntheses of the pseudoequatorial 16-amino- and hydroxy-D-norandrostanes **15** and **22**, the epimeric pseudoaxial D-norandrostanes **11** and **18**, and the corresponding *p*-toluenesulfonates **19** and **23** are described.

The D-nor steroids, first described in 1962,[5] have been the object of considerable recent attention.[6] One motive for developing syntheses of these compounds was the opportunity they provide for studying carbonium ion rearrangements of a cyclobutane ring held in a defined conformation by virtue of its *trans* fusion to the adjacent steroidal C ring. We recently reported the synthesis and deamination of the pseudoequatorial 3-methoxy-16β-amino-D-nor-1,3,5(10)-estratriene, but efforts to obtain the corresponding pseudoaxial 16α-amine or alcohol were unsuccessful.[2] We now outline the synthesis of a set of 16α- and 16β-substituted D-norandrostanes whose carbonium ion reactions are described in the accompanying paper.

Synthesis of the 3β-Methoxy-16-amino-D-norandrostanes. Since Muller, *et al.*,[5c] obtained both the 16α- and 16β-carboxylic acids from the irradiation of 3β-hydroxy-16-diazoandrost-5-en-17-one, whereas no significant amount of 16α product appears to form in the estrone series,[2,5a] dehydroisoandrosterone was chosen as our starting material in this work. The 16-diazo ketone was prepared from dehydroisoandrosterone essentially as described previously[5a] and irradiated to give a mixture of the epimeric 16-carboxylic acids, **1** and **2**. The minor component, 3β-hydroxy-D-norandrost-5-ene-16α-carboxylic acid (**1**), was readily obtained by digesting the mixture with methylene chloride and recrystallizing the residual **1** from methanol. The methylene chloride extract contained the 16β-acid **2**, which was most easily purified by treatment with diazomethane followed by chromatography over alumina. The methyl ester of **2** was then hydrolyzed to give **2** itself.



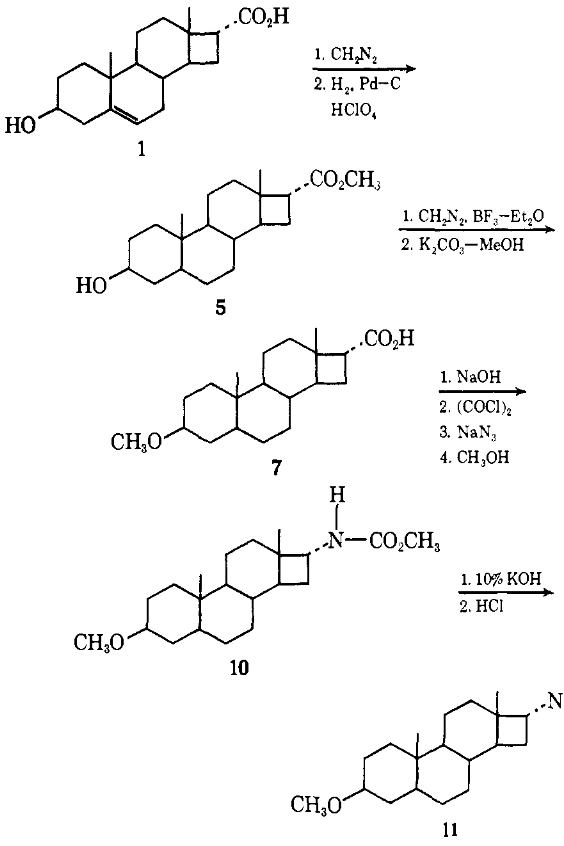
1



2

Acids **1** and **2** were the starting point for the preparation of the corresponding amines and alcohols. The reaction sequences are shown for the 16α series in Charts I and II; analogous procedures were used in the β series.

Chart I



Hydrogenation of the double bond of methyl 3β-hydroxy-D-norandrost-5-ene-16β-carboxylate proceeded readily using 10% palladium on charcoal at room temperature and 55 psi of hydrogen. While hydrogenation of the α isomer under these conditions gave only partial addition of hydrogen, addition of a catalytic amount of perchloric acid[7] resulted in complete hydrogenation. That the hydrogenation gave the desired 5α stereochemistry was confirmed by comparing the chemical and physical properties of **7** made as shown in Chart I with an authentic sample of **7** prepared independently from 3β-hydroxyandrostan-17-one.[8]

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[2] For part II, see J. Meinwald and J.-L. Ripoll, *J. Am. Chem. Soc.*, **89**, 7075 (1967).

[3] National Institutes of Health Predoctoral Fellow, 1963–1965.

[4] National Science Foundation Predoctoral Fellow, 1966–1969.

[5] (a) M. P. Cava and E. Moroz, *J. Am. Chem. Soc.*, **84**, 115 (1962); (b) J. L. Mateos and O. Chao, *Bol. Inst. Quim. Univ. Nacl. Auton. Mex.*, **13**, 3 (1961); (c) G. Müller, C. Huynh, and J. Mathieu, *Bull. Soc. Chim. France*, 296 (1962); (d) J. Meinwald, G. G. Curtis, and P. G. Gassman, *J. Am. Chem. Soc.*, **84**, 116 (1962).

[6] See ref 2 and papers cited therein.

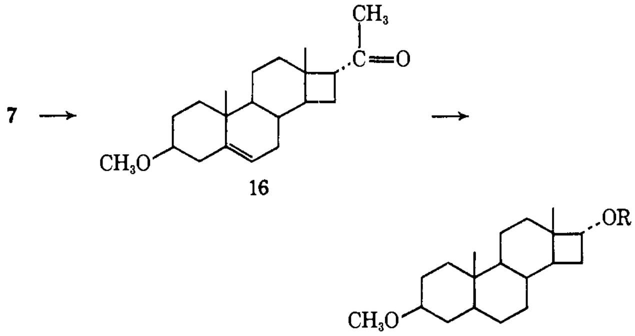
[7] E. B. Hershberg, E. Oliveto, M. Rubin, H. Staedle, and L. Kuhlen, *J. Am. Chem. Soc.*, 73, 1144 (1951).

[8] To show that epimerization during saponification had not occurred, a sample of 7 was esterified with diazomethane and examined by

The most effective route for the degradation of the 16-carboxylic acids to the corresponding amines was found to be the Curtius rearrangement. To prevent undesired complications, the 3β-hydroxy group of **6** was converted to a methoxyl function with diazomethane and boron trifluoride etherate.[9] The acid chloride **8** (λ_{max} 1790 cm^{-1}), prepared *via* oxalyl chloride treatment of the sodium salt of the carboxylic acid **7**,[10] was easily converted to the azide **9** (λ_{max} 2130 cm^{-1}) using sodium azide in acetone. The azide gave the methyl carbamate **10** (λ_{max} 3460 and 1735 cm^{-1}) upon heating in benzene–methanol. The structure of **10** is supported by a satisfactory elemental analysis and by its nmr and mass spectra; the 16α configuration follows from the known retention of configuration of the migrating group in the Curtius rearrangement.[11] 3β-Methoxy-D-norandrostanyl-16α-amine hydrochloride **11** was obtained in overall yield of 73% from the carboxylic acid **7** by treating the free amine, produced by ethanolic potassium hydroxide hydrolysis of **10**, with dry hydrogen chloride in ether.

Synthesis of the 3β-Methoxy-D-norandrostan-16-ols. Treatment of **7** with methyllithium gave an 84% yield of 3β-methoxy-16α-acetyl-D-norandrostane (**16**), characterized by its elemental analysis and the usual spectral data[12] (Chart II). The conversion of **16** to the corresponding 16α-acetoxy compound **17** was affected *via* the Baeyer–Villager reaction, which is known to procede with retention of configuration of the migrating group.[13] Because of the difficulty of separating a small amount of unchanged ketone from the acetate, the entire reaction mixture was treated with potassium carbonate and chromatographed through Florisil to give the desired 16α-alcohol **18** in 78% yield. The structure of **18** was substantiated by a satisfactory analytical and spectral data.

Chart II



16

17, R = COCH$_3$
18, R = H
19, R = SO$_2$C$_7$H$_7$

The 16α-*p*-toluenesulfonate **19** was obtained as a white, crystalline solid in good yield by stirring a pyridine solution of **18** for 3 days at 10° with excess *p*-toluenesulfonyl chloride. Procedures identical with those discussed above were used to convert the 16β-carboxylic acid to the corresponding alcohol **22**, and its *p*-toluenesulfonate **23**, making available the set of stereoisomeric D-nor steriods required for studying the cyclobutyl carbonium ion reactions of interest to us.

Experimental Section

Melting points were determined on a Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 257 grating infrared spectrophotometer or an Infracord. Nmr spectra were taken in carbon tetrachloride or deuteriochloroform with a Varian A-60A instrument. Mass spectra were recorded with an A.E.I. MS-902 spectrometer.[1] Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

3β-Hydroxy-D-norandrost-5-ene-16-carboxylic Acids (1) and (2). The procedure of Cava and Moroz[5a] was used with some modification to prepare **1** and **2**. Dehydroisoandrosterone was converted to its 16-oximino derivative as described by Stodola, Kendall, and McKenzie.[14] After acidification and filtration of the ethereal suspension, 16-oximinoandrost-5-en-3β-ol-17-one, mp 245–247°, was obtained in 91% yield and used without further purification. To a solution of 36 g (0.114 mole) of the oximino ketone in 750 ml of methanol and 144 ml of 5 *N* sodium hydroxide was added 56.6 ml (0.850 mole) of concentrated ammonia, and the solution cooled to 20°. As the solution was stirred and the temperature maintained at 20°, 265 ml (0.795 mole) of 3 *M* sodium hypochlorite was added dropwise. The reaction mixture was then allowed to warm up to room temperature and stirred for 6 hr. The reaction mixture was diluted with an equal volume of water, extracted with methylene chloride, and the combined methylene chloride extracts were washed several times with a saturated salt solution. The solvent was dried (MgSO$_4$), removed under reduced pressure, and the yellow solid recrystallized from acetone to give 21.6 g (60%) of diazo ketone, mp 201–202° dec.

A solution of 15 g (0.0477 mole) of the diazo ketone in 1000 ml of dioxane, 2500 ml of ether, and 500 ml of water was irradiated with a 450-W Hanovia lamp through a Pyrex filter until the diazo ketone was consumed. The photolysis mixture was then washed several times with water, dried (MgSO$_4$), and the solvent removed to leave a pale yellow residue. This was digested with 250 ml of methylene chloride, which was allowed to cool to room temperature and filtered to give 3.1 g of white powder. After recrystallization from methanol, 2.8 g (17%) of 3β-hydroxy-D-norandrost-5-ene-16α-carboxylic acid (**1**), mp 272–275°, in agreement with the literature value,[5c] was obtained.

The methylene chloride mother liquor was treated with diazomethane, the solution dried (MgSO$_4$), and the solvent removed. The residue was chromatographed through 350 g of neutral alumina, Brockman activity grade II, using 3:1 benzene–ether. The solid obtained was recrystallized from ether to give 9.2 g (58%) of methyl 3β-hydroxy-D-norandrost-5-ene-16β-carboxylate (**3**), mp 161–163°.[15]

3β-Methoxy-D-norandrostane-16α-carboxylic Acid (7). Excess diazomethane in methylene chloride was added to 5 g (16.5 mmoles) of the α-acid **1**. The product was recrystallized from hexane to give 4.3 g (83%) of methyl 3β-hydroxy-D-norandrost-5-ene-16α-carboxylate (**4**): mp 65–66°; infrared (CCl$_4$) 3630 (OH), 1740 cm^{-1} (C=O); nmr (CCl$_4$) τ 4.68 (m, 1, C=C—H), 6.33 (s, 3, CO$_2$CH_3), 6.80 (m, 1, C$_3$-H), 7.30 (d, 1, C$_{16}$-H), 8.78 (s, 3, C$_{13}$-CH_3), 8.98 (s, 3, C$_{10}$-CH_3), and the remaining ring protons from 7.6 to 8.7.

Hydrogenation at 50 psi and room temperature of a solution of 5 g (15.7 mmoles) of **4** in 150 ml of methanol containing 1 g of 10% Pd/C and 3 drops of perchloric acid was carried to completion (1–3 days) on a Parr apparatus. The catalyst was removed by filtration through Celite. The slightly yellow solid obtained by removing the solvent was dissolved in methylene chloride, washed with 10% sodium bicarbonate, dried (MgSO$_4$), filtered, and the solvent removed. After recrystallization from hexane, 4.1 g (82%) of methyl 3β-hydroxy-D-norandrostane-16α-carboxylate (**5**), mp 98–101°, was obtained: infrared (CCl$_4$) 3630 (OH) and 1740 cm^{-1} (C=O); nmr (CDCl$_3$) τ 6.39 (s, 3, CO$_2$CH_3), 6.85 (m, 1, C$_3$-H), 7.32 τ (d, 1, C$_{16}$-H), 7.95 (s, 1, OH), 8.89 (s, 3, C$_{13}$-CH_3), 9.23 (s, 3, C$_{10}$-CH_3), and the remaining ring protons from 7.8 to 9.0.

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glpc. The sample showed only one component which was identical with the original ester (6).

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(11) L. W. Jones and E. S. Wallis, *ibid.*, **48**, 169 (1926).

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(13) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 878 (1950).

(14) F. Stodola, E. C. Kendall, and B. F. McKenzie, *J. Org. Chem.*, **6**, 841 (1941).

(15) J. L. Mateos and R. Pozas, *Steroids*, **2**, 527 (1962).

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.93; H, 10.01.

To a solution of 5 g (15.6 mmoles) of **5** in methylene chloride cooled to 0° was added 3.12 ml (1.56 mmoles) of 0.5 *M* boron trifluoride etherate in 1:1 ether–methylene chloride. The reaction mixture is maintained at 0° or lower and diazomethane (78 mmoles) in methylene chloride was added dropwise. When the diazomethane was one-half added, the activity of the catalyst was restored by adding an additional 2.0 ml of the stock catalyst. After adding all the diazomethane, the reaction was stirred an additional 15 min, and the precipitate of polymethylene removed by filtration. The methylene chloride solution was washed with 10% sodium bicarbonate, dried ($MgSO_4$), filtered, and the solvent removed. The product, a clear, colorless oil, was chromatographed through 100–200 mesh Florisil to give 4.3 g (82%) of methyl 3β-methoxy-D-norandrostane-16α-carboxylate (**6**) as a clear, colorless oil: infrared (CCl_4) 1735 (C=O) and 1095 cm^{-1} (methoxy CO); nmr ($CDCl_3$) τ 6.31 (s, 3, $\mathrm{CO_2C}H_3$), 6.70 (s, 3, $\mathrm{OC}H_3$), 6.90 (m, 1, $\mathrm{C_3}$-H), 7.29 (d, 1, $\mathrm{C_{16}}$-H), 8.80 (s, 3, $\mathrm{C_{13}}$–$\mathrm{CH_3}$), 9.20 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the remaining protons from 7.7 to 9.0.

A mixture of 3.19 g (9.55 mmoles) of **6** in 100 ml of 3:1 methanol–containing 3 g of potassium carbonate was refluxed under nitrogen for 2 days. Most of the solvent was then removed under reduced pressure, the residue was diluted with water and acidified with 10% HCl. The mixture was twice extracted with chloroform. The chloroform extract was washed with water, dried ($MgSO_4$), filtered, and the solvent removed. After recrystallization from benzene, 2.6 g (85%) of 3β-methoxy-D-norandrostane-16α-carboxylic acid (**7**), mp 242–245°, was obtained: infrared (CCl_4) 3570, 3500–3100, 2800–2500 (CO_2H), 1720 (C=O), and 1120 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 6.68 (s, 3, $\mathrm{OC}H_3$), 6.85 (m, 1, $\mathrm{C_3}$-H), 7.25 (d, 1, $\mathrm{C_{16}}$-H), 8.81 (s, 3, $\mathrm{C_{13}}$-$\mathrm{C}H_3$), 9.19 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the remaining ring protons from 7.6 to 9.1.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.78; H, 10.03.

Methyl 3β-Methoxy-D-norandrostane-16α-carbamate (10). The α-carboxylic acid **7** was converted to the sodium salt by dissolving 2.6 g (8.12 mmoles) of **7** in 50 ml of ethanol containing 17.2 ml of 0.5 *M* sodium hydroxide (8.53 mmoles). Most of the solvent was removed under reduced pressure and the sodium salt of **7** was dried in a vacuum oven overnight at 50°. In 50 ml of dry benzene 2 g (5.85 mmoles) of the sodium salt of **7** was suspended and cooled. Four drops of dry pyridine and 1.0 ml (11.7 mmoles) of oxalyl chloride were added with vigorous stirring under nitrogen. After 45 min the benzene and excess oxalyl chloride were removed under reduced pressure. The viscous residue was extracted with benzene and filtered. When the benzene was removed, 1.93 g of the 16α-acid chloride **8**, a clear, colorless oil, remained: infrared (CCl_4) 1790 (C=O) and 1105 cm^{-1} (OCH_3).

To a solution of 1.93 g (5.68 mmoles) of freshly prepared **8** dissolved in 50 ml of dry acetone and cooled to 0° under nitrogen was added 0.74 g (11.4 mmoles) of sodium azide in 1.8 ml of distilled water. The reaction mixture was stirred for 15 min. diluted with 100 ml of water, and extracted with ether. The solution was dried ($MgSO_4$), filtered, and the ether removed to give a white, crystalline azide **9**: infrared (CCl_4) 2130 (azido group), 1715 (C=O), and 1100 cm^{-1} (OCH_3).

A solution of 2 g (5.8 mmoles) of **9** in 25 ml of 1:1 benzene–methanol was refluxed overnight under nitrogen. The solvent was removed, and the product recrystallized from methanol–water to give 1.7 g (85%) of methyl 3β-methoxy-D-norandrostane-16α-carbamate (**10**): mp 97–99°; infrared (CCl_4) 3460 (NH), 1735 (C=O), and 1095 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 4.75 (d, 1, $\mathrm{N}H$), 6.28 (m, 1, $\mathrm{C_{16}}$-H), 6.32 (s, 3, $\mathrm{CO_2\,C}H_3$), 6.67 (s, 3, $\mathrm{OC}H_3$), 6.85 (m, 1, $\mathrm{C_3}$-H), 8.90 (s, 3, $\mathrm{C_{13}}$-$\mathrm{C}H_3$), 9.17 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the remaining protons from 7.5 to 9.0; mass spectrum (70 eV) *m/e* (relative intensity) 349 (2), 334 (4), 318 (1), 302 (1), 289 (2), 274 (6), 248 (70), 233 (4), 216 (44), 201 (17), 190 (35), 173 (13), 161 (7), 138 (22), 128 (17), 109 (24). 108 (100), 107 (65), 106 (24), 101 (45), 95 (15), 93 (22), 91 (17), 81 (26), 79 (20), 71 (11), 69 (11), 67 (19), 55 (64), 43 (19), 40 (32).

Anal. Calcd for $C_{21}H_{35}O_3N$: C, 72.21; H, 10.03; N, 4.01. Found: C, 72.11; H, 10.15; N, 4.07.

3β-Methoxy-D-norandrostanyl-16α-amine Hydrochloride (11). A mixture of 3 g (8.6 mmoles) of **10** and 3 g (54.5 mmoles) of potassium hydroxide in 30 ml of 95% ethanol was refluxed under nitrogen for 3 days. The reaction mixture was diluted with water and extracted with chloroform. The chloroform was dried ($MgSO_4$), filtered, and the solvent removed to leave a clear, colorless oil: infrared ($CHCl_3$) 3680, 3380 (NH_2) and 1105 cm^{-1} (OCH_3). The amine was taken up in ether and hydrogen chloride bubbled through the solution to precipitate the amine hydrochloride **11** which was collected by filtration: infrared ($CHCl_3$) 3500–3050, 2700–2500 (NH_3), 1520 (CN), and 1095 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 6.53 (m, 1, $\mathrm{C_{16}}$-H), 6.70 (s, 3, $\mathrm{OC}H_3$), 6.85 (m, 1, $\mathrm{C_3}$-H), 8.89 (s, 3, $\mathrm{C_{13}}$-$\mathrm{C}H_3$), 9.20 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the remaining protons from 7.5 to 9.0.

Anal. Calcd for $C_{19}H_{34}NOCl$: C, 69.57; H, 10.45; N, 4.27; Cl, 10.82. Found: C, 69.65; H, 10.83; N, 4.25; Cl, 10.96.

Methyl 3β-Methoxy-D-norandrostane-16β-carboxylate (12). Hydrogenation of **3** followed by methylation with diazomethane and boron trifluoride etherate as described for the α isomer gave a 67% yield of **12**, mp 83–85°, after recrystallization from ethanol–water: infrared (KBr) 1730 (C=O) and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 6.21 (s, 3, $\mathrm{CO_2C}H_3$), 6.55 (s, 3, $\mathrm{OC}H_3$), 8.99 (s, 3, $\mathrm{C_{13}}$-$\mathrm{C}H_3$), 9.12 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the remaining protons from 6.6 to 9.2.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.56; H, 10.28.

3β-Methoxy-D-androstane-16β-carboxylic Acid (13). The conversion of **12** to **13** was carried out as described for the α isomer. The β-acid **13**, mp 200–201° was obtained in 87% yield: infrared (KBr) 3435 (CO_2H), 1695 (C=O), and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 0.46 (m, 1, $\mathrm{CO_2}H$), 6.68 (s, 3, $\mathrm{OC}H_3$), 8.98 (s, 3, $\mathrm{C_{13}}$-$\mathrm{C}H_3$), 9.20 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the other ring protons from 6.7 to 9.2.

Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.95; H, 10.07. Found: C, 74.39; H, 10.00.

Methyl 3β-Methoxy-D-norandrostane-16β-carbamate (14). The conversion of **13** to **14** was affected by the Curtius rearrangement as described for the α isomer. After recrystallization from hexane, an 84% yield (based on **13**) of **14**, mp 146–148°, was obtained: infrared (CCl_4) 3510 (NH), 1730 (C=O), and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 4.91 (d, 1, $\mathrm{N}H$), 6.39 (s, 3, $\mathrm{CO_2C}H_3$), 6.70 (s, 3, OCH_3), 9.09 (s, 3, $\mathrm{C_{13}}$-$\mathrm{C}H_3$), 9.19 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the remaining ring protons from 7.7 to 9.0.

Anal. Calcd for $C_{21}H_{35}NO_3$: C, 72.21; H, 10.03; N, 4.01. Found: C, 72.36; H, 10.00; N, 4.11.

3β-Methoxy-D-norandrostanyl-16β-amine Hydrochloride (15). Saponification of **14** gave **15** as colorless platelets, mp ~350°, in 74% yield: infrared (KBr) 3400 (NH_3) and 1095 cm^{-1} (OCH_3).

Anal. Calcd for $C_{19}H_{34}NOCl$: C, 69.57; H, 10.45; N, 4.27; Cl, 10.82. Found: C, 69.29; H, 10.41; N, 4.40; Cl. 10.59.

16α-Acetyl-3β-methoxy-D-norandrostane (16). To a solution of 2.5 g (7.8 mmoles) of the α-carboxylic acid **7** in 250 ml of benzene was added dropwise, with stirring, 14.1 ml (23.6 mmoles) of 1.67 *M* methyllithium in ether. The reaction mixture was stirred for 1 hr, quenched by pouring into ice water, and taken up in ether. The ether was washed with water, dried ($MgSO_4$), filtered, and the ether removed. After recrystallization from ethanol–water 2.1 g (84%) of **16**, mp 117–119°, was obtained: infrared (CCl_4) 1715 (C=O) and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 6.60 (s, 3, $\mathrm{OC}H_3$), 6.85 (m, 1, $\mathrm{C_3}$-H), 7.00 (d, 1, $\mathrm{C_{16}}$-H), 7.91 (s, 3, $\mathrm{COC}H_3$), 8.75 (s, 3, $\mathrm{C_{13}}$-$\mathrm{C}H_3$), 9.18 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the remaining protons from 7.6 to 9.1.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.15; H, 10.84.

3β-Methoxy-D-norandrostan-16α-ol (18). To a solution of 2.5 g (7.85 mmoles) of **16** in 75 ml of methylene chloride were added 3.2 g (15.7 mmoles) of 85% *m*-chloroperbenzoic acid and 34 mg of *p*-toluenesulfonic acid. The reaction mixture was stirred in the dark for 4 days at room temperature, then taken up in ether. The ether solution was washed with 10% sodium sulfite, 10% sodium bicarbonate, and water. The ethereal solution was dried ($MgSO_4$) and the ether removed to leave a white solid. This material was refluxed under nitrogen overnight in 300 ml of 3:1 methanol–water solution containing 2.5 g of potassium carbonate. The reaction mixture was extracted with ether, and the ether washed with water, dried ($MgSO_4$), filtered, and removed. After column chromatography of the residue through Florisil and recrystallization from hexane–ether, 0.72 g (78%) of **18**, mp 155–156°, was obtained: infrared (CCl_4) 3620 (OH) and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 6.00 (d, 1, $\mathrm{C_{16}}$-H), 6.74 (s, 3, $\mathrm{OC}H_3$) 6.90 (m, 1, $\mathrm{C_3}$-H), 7.72 (s, 1 OH), 9.05 (s, 3, $\mathrm{C_{13}}$-$\mathrm{C}H_3$), 9.20 (s, 3, $\mathrm{C_{10}}$-$\mathrm{C}H_3$), and the remaining ring protons from 7.8 to 9.0.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.80; H, 10.84.

3β-Methoxy-D-norandrostanyl 16α-*p*-Toluenesulfonate (19). To a solution of 170 mg (0.583 mmoles) of **18** in 2.0 ml of dry pyridine cooled to −20° was added 558 mg (2.92 mmoles) of freshly recrystallized *p*-toluenesulfonyl chloride. The flask was stoppered, shaken until the reaction mixture was homogeneous, and kept at *ca.* 10° for 3 days. The flask was cooled to 0°, water added to hydrolyze the excess of *p*-toluenesulfonyl chloride, and after 1 hr of stirring, the reaction mixture was poured into ice water and extracted with ether. The ethereal solution was washed with ice cold 50% HCl, cold 10% sodium bicarbonate, and water. The ether was removed below room temperature, and the white residue recrystallized from hexane to give 126 mg (49%) of **19**: mp 117–119°; infrared (CCl_4) 1600 (C=C), 1375, 1370, 1190, 1180 (OSO_2), and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 2.30 (q, 4, phenyl *H*), 5.28 (d, 1, C_{16}-*H*), 6.60 (s, 3, OCH_3), 6.90 (m, 1, C_3-*H*), 7.50 (s, 3, phenyl-CH_3), 8.95 (s, 3, C_{13}-CH_3), 9.18 (s, 3, C_{10}-CH_3), and the remaining protons from 7.8 to 9.0.

Anal. Calcd for $C_{26}H_{38}O_4S$: C, 69.92; H, 8.57; S, 7.18. Found: C, 69.56; H, 8.47; S, 7.29.

16β-Acetyl-3β-methoxy-D-norandrostane (20). The β-acid **13** was converted to **20**, mp 78–79°, in 56% yield as described for the α isomer: infrared (neat) 1710 (C=O) and 1100 cm^{-1} (OCH_3); nmr (CCl_4) τ 6.76 (s, 3, OCH_3), 8.09 (s, 3, $COCH_3$), 9.17, 9.20 (two s, 6, C_{13}- and C_{10}-CH_3), and the remaining ring protons from 7.0 to 9.1.

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.25; H, 10.74.

3β-Methoxy-D-norandrostan-16β-ol (22). The conversion of **20** to **22** was affected *via* the Baeyer–Villager sequence to give the 16β-acetoxy derivative **21** and hydrolyzed to **22** as described for the α isomer. Crystalline **22**, mp 173–174°, was obtained in 55% yield (based on **20**): infrared (KBr) 3610 (OH) and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 6.31 (m, 1, C_{16}-*H*), 6.70 (s, 3, OCH_3), 7.68 (s, 1, OH), 9.03 (s, 3, C_{13}-CH_3), 9.18 (s, 3, C_{10}-CH_3), and the remaining protons from 7.8 to 9.0.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.71; H, 11.02.

3β-Methoxy-D-norandrostanyl-16β-*p*-toluenesulfonate (23). The 16β-alcohol **22** was converted in virtually quantitative yield to **23** as described for the α isomer. White, crystalline **23**, mp 110.0–110.5°, was obtained: infrared (CCl_4) 1605 (C=C), 1390, 1380, 1190, 1180 (OSO_2), and 1105 cm^{-1} (OCH_3); nmr (CCl_4) τ 2.45 (q, 4, phenyl *H*), 5.70 (t, 1, C_{16}-*H*), 6.72 (s, 3, OCH_3), 6.90 (m, 1, C_3-H), 7.49 (s, 3, phenyl CH_3), 8.99 (s, 3, C_{13}-CH_3), 9.15 (s, 3, C_{10}-CH_3), and the remaining ring protons from 7.7 to 9.0.

Anal. Calcd for $C_{26}H_{38}O_4S$: C, 69.92; H, 8.57; S, 7.18. Found: C, 69.81; H, 8.49; S, 7.25.

D-Nor Steroids. IV. Carbonium Ion Rearrangements of Conformationally Defined Cyclobutanes[1,2]

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Abstract: Nitrous acid deamination of the pseudoequatorial D-norandrostanyl-16β-amine **2**, thermal decomposition of 16β-N-nitroso derivatives of **2**, hydrolysis of the 16β-diazotate salt, and solvolysis of the 16β-*p*-toluenesulfonate **28** gave the C-homo-D-bisnor steroids **7**, **8**, and **9**. In contrast, nitrous acid deamination of the pseudoaxial D-norandrostanyl-16α-amine **16**, hydrolysis of the 16α-diazotate salt, and acetolysis of the 16α-*p*-toluenesulfonate, **31**, gave the seco steroids **17** or **18** as the major products. Thermal decomposition of the 16α-N-nitrosoacetamide, **27**, gave the C-homo-D-bisnor steroids **9** and **15**, perhaps *via* the corresponding diazocyclobutane. In general, migration of the group *trans* and parallel to the p orbital of the developing cyclobutyl carbonium ion, so as to preserve maximum orbital overlap during rearrangement, seems to account for the course of these rearrangements.

Considerable data have been accumulated in recent years which indicate that the cyclobutane ring is nonplanar, with an angle between the two halves of the four-membered ring of 30–35°.[4] A direct consequence of this geometry is the differentiation of cyclobutyl substituents into pseudoequatorial and pseudoaxial types. The chemical consequences of this differentiation, however, have not been extensively explored. In particular, it is of interest to determine whether cyclobutanes will show steric control of the type so well documented for cyclohexanes during carbonium ion rearrangements. As in the case of the cyclohexanes themselves, polycyclic systems such as steroid derivatives simplify the study of conformational problems from both a theoretical and a practical point of view, compared to monocyclic systems. Recently at Cornell[5] and in other laboratories,[6] the deamination of some monocyclic cyclobutylamines has been investigated. Beyond this, several compounds in which the cyclobutane ring is fused to another ring in such a way as to provide defined conformations have shown that conformational control can be important in such reactions.[7,8] Our current results complement and contrast with these reports in several ways.

The 16-substituted D-nor steroids **1a** and **1b** (where X represents a suitable leaving group)[2] provide an excellent opportunity for studying the influence of reactant stereochemistry on the products resulting from cyclobutyl carbonium ion rearrangements, since the all-*trans* ring system is rigidly locked into a single confor-

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