crystallized *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-

(1) Partial support of this research was provided by National Institutes of Health Research Grant GM 10090; we acknowledge their support with pleasure. Mass spectra were recorded by the Cornell high-resolution mass spectral facility sponsored by Grant FR 00355 from the National Institutes of Health.

(2) For part III, see J. Meinwald, L. L. Labana, and T. N. Wheeler, *J. Am. Chem. Soc.*, **92**, 1006 (1970).

(3) National Science Foundation Predoctoral Fellow, 1966–1969.

(4) (a) A. Almenningen, O. Bastiansen, and P. N. Skancke, *Acta Chem. Scand.*, **15**, 711 (1961); (b) J. D. Dunitz and V. Schomaker, *J. Chem. Phys.*, **20**, 1703 (1952); (c) J. B. Lambert and J. D. Roberts, *J. Am. Chem. Soc.*, **85**, 3710 (1963); (d) J. B. Lambert and J. D. Roberts, *ibid.*, **87**, 3884, 3891 (1965); (e) G. W. Rathjens, Jr., N. K. Freeman, W. D. Gwinn, and K. S. Pitzer, *J. Am. Chem. Soc.*, **75**, 5634 (1953).

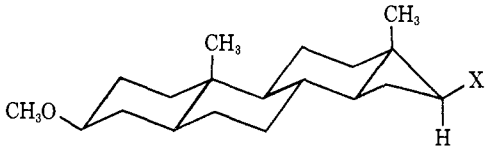
(5) L. L. Labana, Ph.D. Thesis, Cornell University, 1965.

(6) (a) I. Lillien and R. A. Doughty, *Tetrahedron Letters*, 3953 (1967); (b) I. Lillien, G. F. Reynolds, and L. Handloser, *ibid.*, 3475 (1968).

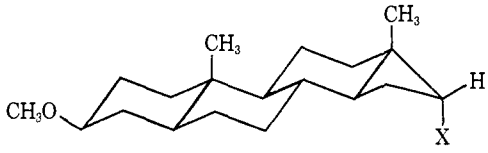
(7) K. B. Wiberg and J. G. Pfeiffer, *J. Am. Chem. Soc.*, **90**, 5324 1968).

(8) J. Meinwald and J.-L. Ripoll, *ibid.*, **89**, 7075 (1967).

mation. The results of deaminating, by several methods, a pair of stereoisomeric 16-amino D-nor steroids and their derivatives as well as the results of solvolyzing the corresponding 16-*p*-toluenesulfonates will be presented.

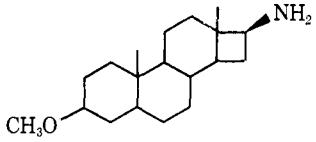


1a

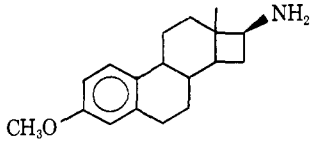


1b

Carbonium Ion Rearrangements of the Amines and Their Derivatives. The deamination of the 16β-amine **2** was carried out by treating a solution of its hydrochloride in 50% aqueous acetic acid at $-10°$ with sodium nitrite. The product was a viscous, yellow oil which showed hydroxylic (3610 cm^{-1}), cyclopropyl (3060 cm^{-1}), weak acetate ester (1735 cm^{-1}), and nitrate ester (1632 cm^{-1}) absorptions in its infrared spectrum. Lithium aluminum hydride reduction of the entire reaction mixture gave a colorless oil free of ester absorptions, which was separated into two major components (C, in 69% yield and B, in 18% yield) by column chromatography on Florisil. Of these components, C and B were characterized as **7** and **8**, although only C could be obtained crystalline.



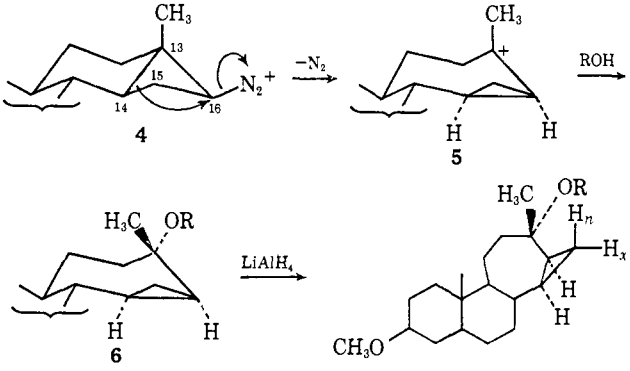
2



3

In analogy with the results reported by Meinwald and Ripoll[8] for the deamination of 3-methoxy-16β-amino-D-nor-1,3,5(10)-estratriene (**3**), the most probable reaction path for **2** was considered to be that outlined in Chart I. Framework molecular orbital models

Chart I



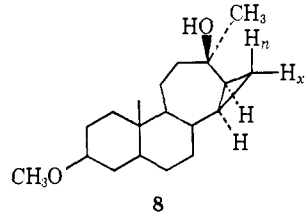
4 5 6

7, R = H
12, R = CO_2CH_3
15, R = Ac

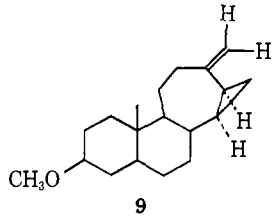
suggest that the C_{16}–N bond deviates by only *ca.* 10° from being parallel to the C_{13}–C_{14} bond.[9] Therefore, as nitrogen is lost from the diazonium salt **4**, the C_{13}–C_{14} bond is in a position to migrate readily to fill the developing p orbital at C_{16}. This generates the tertiary cyclopropylcarbinyl carbonium ion **5**, which adds a nucleophile predominantly from the less-hindered α side of the steroid to give **6**. The stereochemistry of **6** shown in Chart I is based on the usual assumptions that inversion of configuration occurs at both rearrangement origin (C_{13}) and its terminus (C_{16}), whereas retention is expected from the migrating group (C_{14}).

Elemental analysis, spectral data, and chemical evidence support the C-homo-D-bisnor steroid structure shown in Chart I for **7**. In the infrared spectrum of **7** is a strong free hydroxyl absorption at 3610 cm^{-1} and a cyclopropyl carbon–hydrogen stretching absorption at 3060 cm^{-1}. The nmr spectrum of **7** is particularly helpful in elucidating its stereochemistry. It shows a three-proton singlet at τ 8.98 for the C_{13}-methyl, a three-proton singlet at 9.31 for the C_{10}-methyl, and a high-field one-proton multiplet at τ 9.85 for the *endo*-methylene cyclopropyl proton (H_n). The unusually high upfield chemical shift of H_n is attributed to the shielding of the seven-membered ring above which it lies. The remainder of the nmr spectrum of **7** shows three protons at 6.70 (singlet) for the methoxy group, one proton at 6.90 (multiplet) for the C_3-hydrogen, one proton at 7.91 (singlet, exchanges with deuterium oxide) for the hydroxyl group, and the remaining ring protons at 7.9–9.5. The mass spectrum shows a molecular ion at *m/e* 292 and peaks at 277, 274, and 260 attributed to loss of CH_3, H_2O, and CH_3OH. The tertiary nature of the hydroxyl groups in **7** and **8** was shown by their failure to acetylate or oxidize under mild conditions.

Component B from the deamination of the 16β-amine **2** was a clear, colorless oil which resisted all attempts at crystallization. It was assigned the structure **8**, epimeric with **7**, on the basis of the spectral data (summarized in the Experimental Section) and the observation that dehydration of both **7** and **8** with phosphorus oxychloride in pyridine gave a single major exocyclic olefin, **9**, in *ca.* 70% yield. The structure of **9** is supported by the appearance of a cyclopropyl carbon–hydrogen stretching at 3070 cm^{-1} and the characteristic carbon–hydrogen bending of a terminal methylene group at 890 cm^{-1}.[10] The nmr spectrum of **9** shows a two-proton multiplet for the olefinic protons at τ 5.15, the C_{10}-methyl as a singlet at 9.20, and cyclopropyl protons at 9.2–9.8. Finally, the minor deamination product **8** does not show a high-field methylene cyclopropyl proton in its nmr spectrum, as does **7**. Apparently the shielding of H_n in **8** by the seven-membered ring is compensated for by the deshielding by the neighboring β-hydroxy group.



8



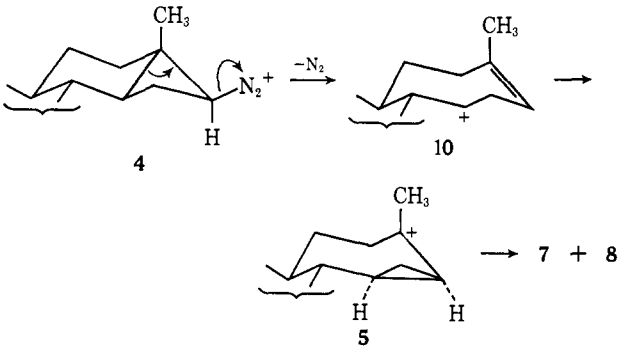
9

(9) The detailed structures of the 16-substituted epimeric D-nor steroids are being examined by Dr. Everly Fleisher of the University of Chicago.

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

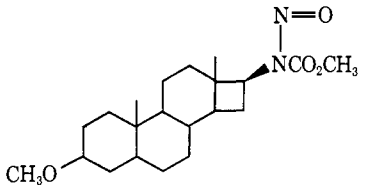
Although the formation of these products is well accommodated by the scheme shown in Chart I, a variant of this possibility is outlined in Chart II. This pathway

Chart II

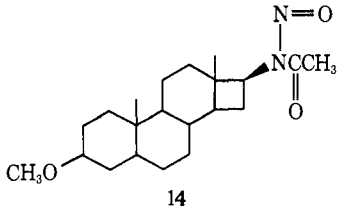


deserves serious consideration because it is of importance in the recently reported work of Wiberg and Pfeiffer.[7] In the hope of trapping a product derived from the hypothetical homoallylic cation **10**, in this sequence, the deamination of several derivatives of **2** was carried out.

The thermal decomposition of N-alkyl-N-nitrosoamides and N-alkyl-N-nitrosourethans has been well studied by White[11] and others.[12] The first step involves rearrangement of the nitroso compound to a diazo ester, which then rapidly decomposes to esters and olefins; the exact mechanism for this decomposition depends upon solvent polarity and the type of amine. For nitrosoamides of secondary carbinamines, the decomposition involves dissociation of the diazo ester into an ion pair, extrusion of nitrogen to form a second ion pair, and the formation of either esters or olefins from the latter ion pair. Since collapse of the ion pair in nonpolar solvents to form esters should be very fast, any intermediates corresponding to **10** should have a good chance of being trapped. Methyl 3β-methoxy-D-norandrostane-16β-N-nitrosocarbamate (**11**) was prepared using the general technique described by White.[11a] Thermal decomposition of **11** at 75° in carbon tetrachloride buffered with sodium carbonate gave a mixture from which two components could be obtained and characterized. One component (32% yield) was identified from its infrared and nmr spectra as the olefin **9**. The other component (40% yield) was a clear, colorless oil assigned structure **12** (see Chart I) on the basis of the spectral data.



11



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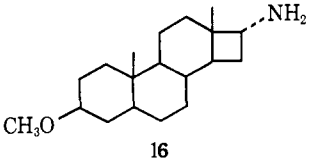


16

Similarly, 3β-methoxy-16β-acetamido-D-norandrostane (**13**) was prepared by treating **2** with excess acetic anhydride in pyridine. Nitrosation of **13** with nitrogen tetroxide gave 3β-methoxy-D-norandrostane-16β-N-nitrosoacetamide (**14**). Thermal rearrangement of **14** at 45° in carbon tetrachloride buffered with sodium carbonate gave a 50% yield of **9** and a 42% yield of a clear, colorless oil characterized as **15** (Chart I) largely on the basis of the spectral data given in the Experimental Section.

A third method of deaminating amines is the solvolysis of alkyl diazotates produced by treating nitrosocarbamates with potassium *t*-butoxide[13]

$$RNCO_2CH_3 + t\text{-BuOK} \longrightarrow RN{=}N{-}OK + t\text{-BuOCOCH}_3$$

Addition of water to the diazotate salt involves a rapid proton transfer to produce a diazotic acid

$$RN{=}N{-}OK + H_2O \longrightarrow RN{=}NOH + KOH$$

Two modes of decomposition are available to the diazotic acid in basic media

$$RN{=}NOH \xrightarrow{-N_2,\,-OH} R^+ \longrightarrow \text{products}$$

$$RN{=}NOH \xrightarrow[H_2O]{-H^+,\,-OH^-} RN_2\ (\text{diazoalkane}) \longrightarrow \text{products}$$

The partition between carbonium ion derived products and products resulting from diazoalkanes is dependent upon the structure of the alkyl group and the nature of the reaction medium. In general, secondary alkyl diazotates seem to decompose in aqueous solution to give carbonium ion derived products unless some structural feature is present to stabilize the diazoalkane.[14]

The diazotate salt prepared from **11** was hydrolyzed in ether–water to give 88% of the C-homo-D-bisnor steriod alcohol **7** and 8% of the olefin **9**.

In summary, the nitrous acid deamination of the 16β-amine, the thermal decomposition of two N-nitroso derivatives of the 16β-amine, and the decomposition of the 16β-diazotate all give products derived from the cyclopropylcarbinyl cation **5**. It would seem that the carbonium ions (or closely related species) from the pseudoequatorial 16β-substituted D-norandrostanes are rearranging directly to **5**, in analogy to the preliminary result already reported in the estrone series,[2] rather than proceeding first to either an unrearranged cyclobutyl cation or the homoallylic cation **10**.

The nitrous acid deamination of 3β-methoxy-D-norandrostanyl-16α-amine (**16**) was carried out under the

(11) (a) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955); (b) *ibid.*, **77**, 6011 (1955); (c) *ibid.*, **77**, 6014 (1955); (d) E. H. White and C. Aufdermarsh, Jr., *ibid.*, **83**, 1174 (1961); (e) *ibid.*, **83**, 1179 (1961).

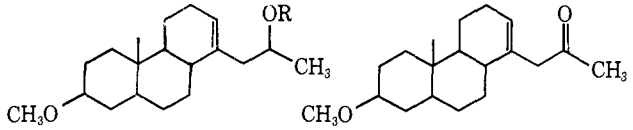
(12) R. Huisgen and H. Reimlinger, *Ann.*, **599**, 183 (1956).

(13) R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966).

(14) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1968, p 462 ff.

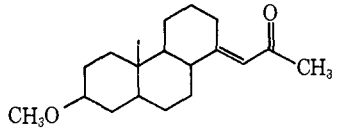
same conditions used for the β-amine. The product was a viscous yellow oil which showed only hydroxyl and ester absorptions in the infrared. The total product was reduced with lithium aluminum hydride to give a clear, colorless oil which showed only hydroxyl (3610 cm^{-1}) absorption in the infrared. Chromatography of the mixture through Florisil gave three fractions: A (12%), B (12%), and C (76%). Fraction A appeared to be a complex mixture of olefins, and was not characterized further.

The major component (C) was a clear, colorless oil assigned structure **17** only after a host of more obvious structures had been considered and rejected on the basis of the data summarized below. Thus, C showed a broad hydroxyl absorption at 3600 cm^{-1} and a weak double bond stretching absorption at 1650 cm^{-1} in the infrared. The nmr spectrum of C showed one olefinic proton at τ 4.70 (broad singlet), one proton at 6.15 (multiplet) for a proton α to a hydroxyl group, three protons at 8.83 (doublet, J = 6 cps) for a secondary methyl group, three protons at 9.18 (singlet) for the C_{10}-methyl, and the remaining expected absorptions. The mass spectrum of C showed the molecular ion at *m/e* 292, loss of CH_3 (277), H_2O (274), and CH_3OH (260). Ozonolysis of C gave a crude product which showed the carbonyl (1730 cm^{-1}) and carbon–hydrogen stretching absorptions (2710 cm^{-1}) of an aldehyde as well as a ketone carbonyl (1718 cm^{-1}) in the infrared. Oxidation of C with Collins' reagent[15] followed by preparative thin layer chromatography gave a clear, colorless oil formulated as **19**. The infrared spectrum of **19** showed a carbonyl at 1718 cm^{-1}. The nmr spectrum of **19** showed one olefinic proton at τ 4.70 (broad singlet), three protons at 6.71 (singlet) for the methoxy group, one proton at 6.85 (multiplet) for the C_3-hydrogen, two protons at 7.03 (broad singlet), for the allylic methylene group α to a carbonyl group, three protons at 7.95 (singlet) for the acetyl methyl, three protons at 9.18 (singlet) for the C_{10}-methyl, and the various ring protons at 7.5–9.0. The mass spectrum of **19** showed the expected molecular ion at *m/e* 290 and a base peak at 43, corresponding to the fragment $[O{\equiv}CCH_3]^+$ formed by



17, R = H
18, R = Ac

19



20

cleavage α to the carbonyl group. The ultraviolet spectrum of **19** shows no absorption above 210 mμ. However, upon warming a solution of **19** in ethanol with 30% HCl, the ultraviolet spectrum developed a strong absorption with λ_{max} 242 mμ ($\epsilon \cong$ 12,000), in accord with expectations for the α,β-unsaturated ketone **20**.[16]

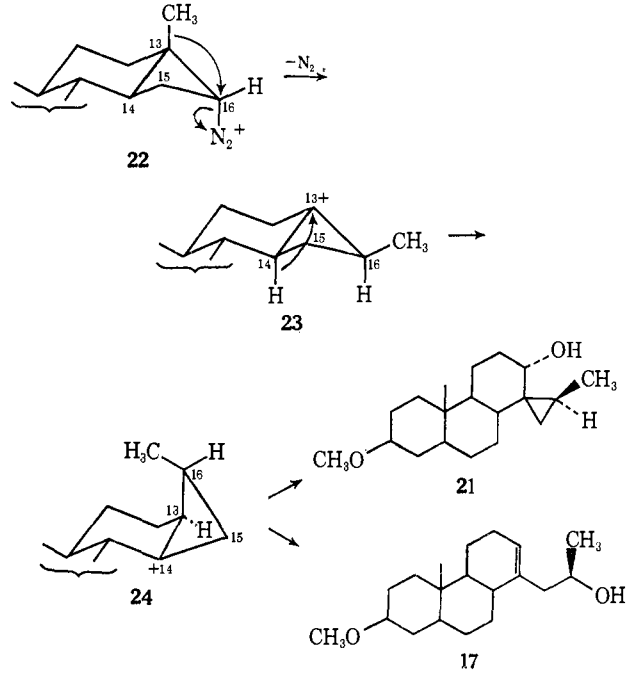
(15) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Letters*, 3363 (1968).

(16) R. S. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., p 100.

The minor deamination product (B) from **16** is tentatively formulated as **21**. The structure assignment rests mainly on the spectral data (summarized in the Experimental Section) and the oxidation of **21** with Sarett's reagent to a compound showing carbonyl absorption at 1695 cm^{-1}. Conjugation of the ketone with a cyclopropane ring would be expected to lower the frequency of the carbonyl absorption by *ca.* 20 cm^{-1}.[10]

A reasonable pathway to the major and minor products from the pseudoaxial α-amine **16** deamination is outlined in Chart III. The first step after forming the

Chart III



diazonium salt **22** is migration of the antiperiplanar C_{13}-methyl to C_{16} as nitrogen is lost. This produces the bridgehead carbonium ion **23** which suffers a further hydride shift from C_{14} to C_{13} to give **24**. In the final step the spirocyclopropane **21** is formed if the nucleophile attacks at C_{13} with accompanying ring contraction, or the seco steroid **17** is formed if the nucleophile attacks at C_{16} with accompanying formation of a homoallylic system.

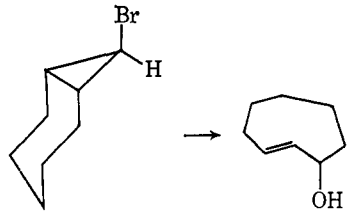
The 16α-nitrosocarbamate (**25**) was prepared by treating methyl 3β-methoxy-D-norandrostane-16α-carbamate with nitrogen tetroxide. Subsequent treatment with potassium *t*-butoxide, followed by hydrolysis of the 16α-diazotate, gave a 63% yield of seco product **17**.

Surprisingly, the thermal decomposition of 3β-methoxy-D-norandrostane-16α-N-nitrosoacetamide (**27**) at 40–45° in carbon tetrachloride buffered with sodium carbonate gave a 58% yield of the vinyl cyclopropane **9** and a 25% yield of the C-homo-D-bisnor steroid acetate **15**. A possible explanation for the formation of these products, characteristic of the 16β series, is that the thermal rearrangements of both 16-N-nitrosoacetamides (or at least, that of **27**) may be proceeding through the corresponding diazocyclobutane, from which the isolated products can be easily derived.

***p*-Toluenesulfonate Solvolyses.** In general, the tosylate solvolysis experiments followed closely the pattern established in our deamination studies. The solvolysis of 3β-methoxy-D-norandrostanyl 16β-*p*-toluenesulfo-

nate (**28**) was carried out under the carefully controlled conditions which had permitted the isolation of *trans*-cyclooct-2-en-1-ol (**30**) from *exo*-bicyclo[5.1.0]oct-8-yl bromide (**29**) (Chart IV); *i.e.*, a solution of **28** in dioxane–water containing calcium carbonate was stirred for 3 days at room temperature.[7,17] The product was separated into its components by column chromatography on Florisil to give the epimeric C-homo-D-nor alcohols **7** (28%) and **8** (48%).

Chart IV

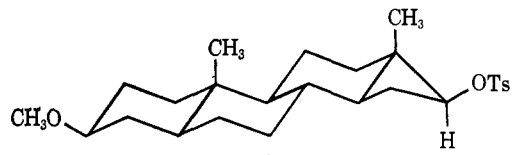


29 **30**

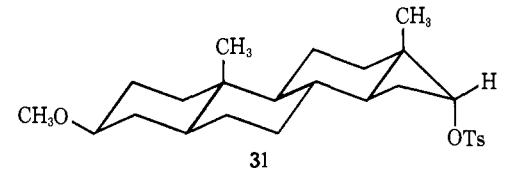
The rate of acetolysis of **28** was measured spectrophotometrically by observing the decrease in absorbance (λ_{max} 261 mμ) of **28** with time.[18] The rate constant was found to be 1.99 hr^{-1} (5.53×10^{-4} sec^{-1}) at 29° for the acetolysis. The rate of acetolysis of cyclobutyl tosylate at 29° was calculated to be 4.98×10^{-3} hr^{-1};[19] **28** thus undergoes acetolysis about 400 times as fast as cyclobutyl tosylate, which would seem to be indicative of anchimeric assistance by the C_{13}–C_{14} bond. The products from the acetolysis of the 16β-tosylate **28** were the rearranged olefin **9** (25%) and the acetate **15** (60%).

The acetolysis of 3β-methoxy-D-norandrostanyl 16α-*p*-toluenesulfonate (**31**) was first attempted by heating it in acetic acid which was 0.5 *M* in potassium acetate at 60° for 3 days. A sample of the reaction mixture gave unchanged **31**. However, after 3 days at 120° the reaction was complete. Column chromatography of the reaction mixture gave two fractions: A, in 25% yield and B, in 60% yield. A, although apparently homogeneous on tlc, seemed from its nmr spectrum to be a complex mixture, and was not further characterized. B was found to be the acetate **18** corresponding to **17**, the major product from the deamination of the 16α-amine. Thus, treating **17** with acetic anhydride in pyridene gave a product identical with B in all respects. Attempts to measure the rate of acetolysis of **31** spectrophotometrically were unsuccessful, since only erratic results were observed, indicative of possible unappreciated complications. In any event, the qualitative unreactivity of the pseudoaxial 16α-tosylate compared to the 16β pseudoequatorial isomer is striking.

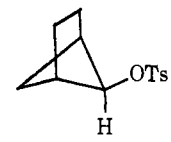
Comparison of the Carbonium Ion Rearrangements of 16-Substituted D-Nor Steroids with Those of Other Cyclobutyl Systems. Although an exact rate constant for the acetolysis of the 16α-*p*-toluenesulfonate **31** could not be measured, it was clearly much smaller than that of the 16β isomer **28**. Wiberg and Fenoglio[20] found a similar difference in the acetolysis rates of *endo*- and *exo*-5-bicyclo[2.1.1]hexyl *p*-toluenesulfonates **32** and **33**. The *endo* isomer **32**, analogous in geometry



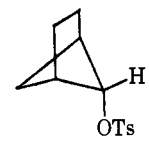
28



31



32

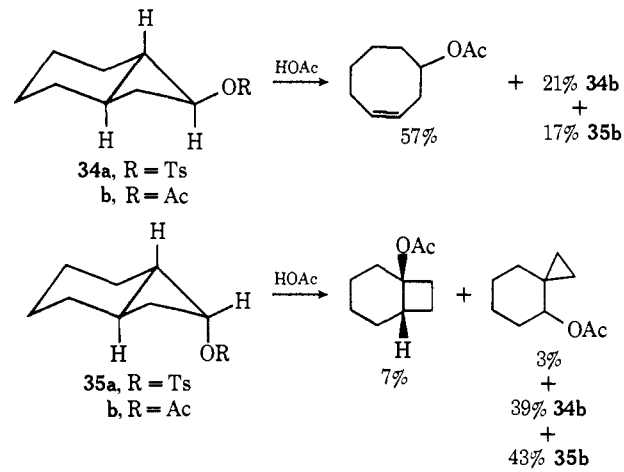


33

to the 16β-*p*-toluenesulfonate **28**, undergoes acetolysis 10^6 times faster than the *exo* isomer **33**, analogous to the 16α ester. Since these observations seem reasonable on stereoelectronic grounds, it is especially remarkable that the rates of acetolysis (relative to cyclobutyl tosylate) of the closely related *trans*-bicyclo[4.2.0]octyl 7-tosylates, **34** and **35**, have been found very recently to be equally slow (0.05 that of cyclobutyl tosylate) for both the pseudoequatorial ester, **34a**, and the pseudoaxial ester, **35a**.[7]

The products derived from the parent bicyclic nuclei **34** and **35** (Chart V) show marked differences from those derived from their steroidal analogs, **28** and **31**. Note

Chart V

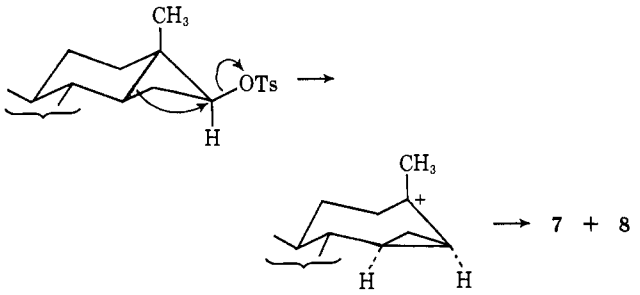


that the pseudoaxial tosylate **35a** gave only 10% of rearranged products upon acetolysis, and **34a** gave 57% rearranged material, whereas the D-norsteroidal tosylates **28** and **31** gave apparently total rearrangement. (At least no unrearranged products could be detected.) One difference of possible significance between **31** and **35a** is the greater migratory aptitude of the antiperiplanar methyl group compared to the hydride. In both pairs of epimers, there would seem to be a greater relief of nonbonding repulsions accompanying the observed rearrangements in the steroidal cases.

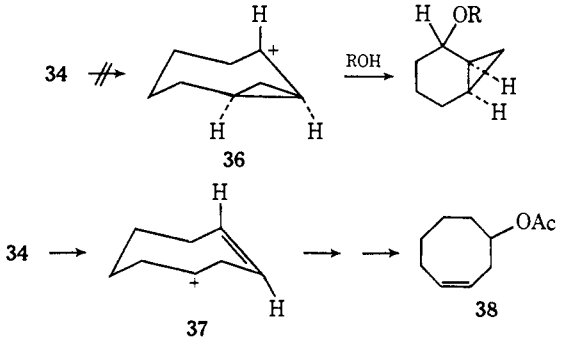
The rearrangement paths for the pseudoequatorial **28** and **34a**, which would appear from models to have similar geometries, are again different in detail. Migration of the bridging bond to give a tertiary cyclopropyl-

(17) G. H. Whitham and M. Wright, *Chem. Commun.*, 294 (1967).
(18) G. C. Swain and C. R. Morgan, *J. Org. Chem.*, **29**, 2097 (1964); (b) N. C. G. Campbell, D. M. Muir, R. R. Hill, J. H. Parish, R. M. Southam, and M. C. Whiting, *J. Chem. Soc., B*, 355 (1968).
(19) J. D. Roberts and V. C. Chambers, *J. Am. Chem. Soc.*, **73**, 5034 (1951).
(20) K. B. Wiberg and R. Fenoglio, *Tetrahedron Letters*, 1273 (1963).

carbinyl cation directly is apparently favored for the D-nor steroid **28**, since this produces an energetically favorable intermediate. Similar migration of the



bridging bond in **34a** to give a secondary cyclopropylcarbinyl cation (**36**) is apparently not as favorable. On the other hand, cleavage of the bridging bond in **34** to produce a (*trans*) homoallylic cyclooctenyl cation **37**, with relief of the strain inherent in the cyclobutane, followed by reaction with the solvent to give **38** apparently competes favorably in this case.



Despite these differences, which clearly reflect specific structural features of the substrates chosen, these studies on the D-nor steroids clearly indicate that there can be dramatic conformational control of both reaction products and reaction rates for such systems; conformational effects would appear to be of an importance in these cyclobutanes comparable to that already well established for the cyclohexanes.

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 a Perkin-Elmer 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 mass spectrometer.[1] Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Nitrous Acid Deamination of 2. 3β-Methoxy-13α-hydroxy-C-homo-D-bisnorandrostane (7) and Its 13β-Hydroxy Epimer 8. To a solution of 3.0 g (9.15 mmoles) of **2** in 105 ml of 1:1 acetic acid–water stirred under nitrogen at −10° was added 7.5 g (109 mmoles) of sodium nitrite in small portions over a 4-hr period. The reaction mixture was kept for 12 hr at 0°, then allowed slowly to warm up to room temperature and diluted with 150 ml of ice water. The reaction mixture was neutralized with potassium carbonate, extracted with ether, and the ether washed with 5% HCl, 10% sodium bicarbonate, and water. The ether was dried ($MgSO_4$), filtered, and removed to give 2.95 g of a pale-yellow oil: infrared (CCl_4) 3610 (OH), 3060 (cyclopropyl CH), and 1632 cm^{-1} (nitrate ester).

The crude product was dissolved in 100 ml of ether and added to a mixture of 1.13 g (29.8 mmoles) of lithium aluminum hydride in ether. After stirring overnight the excess hydride was destroyed by the successive addition of 1.5 ml of water, 1.5 ml of 15% sodium hydroxide, and 4.5 ml of water. The ether phase was obtained by filtration, washed, dried ($MgSO_4$), filtered, and the ether removed to give 2.65 g of clear, colorless oil: infrared (CCl_4) 3610 (OH) and 3060 cm^{-1} (cyclopropyl CH). Column chromatography of this material on 100–200 mesh Florisil afforded successively 0.105 g (4% from **2**) of product A, 0.481 g (18%) of product B (**8**), 1.882 g (69%) of product C (**7**), and 0.240 g (9%) of product D. The nmr spectra of products A and D indicated each to be a complex mixture, and they were not further studied. Product C (**7**) was recrystallized from ether–hexane to give 1.4 g of white, crystalline solid: mp 111–112°; infrared (CCl_4) 3610 (OH), 3060 (cyclopropyl CH), and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 6.70 (s, 3, OCH_3), 6.90 (m, 1, C_3-*H*), 7.91 (s, 1, O*H*), 8.98 (s, 3, C_{13}-CH_3), 9.31 (s, 3, C_{10}-CH_3), 9.85 (m, 1, *endo*-methylene cyclopropyl C*H*), and the remaining ring protons from 7.9 to 9.5; mass spectrum (70 eV) *m/e* (relative intensity) 292 (31), 277 (18), 275 (4), 260 (8), 259 (12), 246 (8), 245 (4), 243 (15), 242 (12), 232 (15), 227 (23), 219 (25), 202 (25), 199 (25), 187 (31), 173 (15), 159 (12), 147 (31), 133 (34), 120 (25), 107 (100), 91 (45), 81 (72), 79 (44), 77 (25), 71 (84), 67 (66), 55 (59), 43 (94), 41 (75), and 28 (30).

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.08; H, 10.92. Found: C, 78.05; H, 10.90.

Product B (**8**) was a clear, colorless oil which resisted all attempts at crystallization but appeared to be a single compound from tlc on silica gel: infrared (CCl_4) 3610 (OH), 3060 (cyclopropyl CH), and 1095 cm^{-1} (OCH_3); nmr (CCl_4) τ 6.70 (s, C, OCH_3), 6.90 (m, 1, C_3-*H*), 8.65 (s, 3, C_{13}-CH_3), 9.23 (s, 3, C_{10}-CH_3), and the remaining ring protons from 7.8 to 9.7; mass spectrum (70 eV) *m/e* (relative intensity) 292 (8), 277 (6), 276 (4), 275 (3), 274 (50), 260 (22), 259 (25), 246 (8), 244 (20), 242 (93), 227 (73), 202 (36), 187 (52), 173 (31), 159 (37), 147 (46), 133 (65), 120 (10), 107 (69), 91 (73), 81 (100), 79 (77), 77 (36), 71 (36), 67 (39), 55 (45), 43 (52), 41 (65), and 28 (78).

Attempted Acetylation of 7 and 8. To a solution of 30 mg of **7** or **8** in 0.5 ml of pyridine was added 10 drops of acetic anhydride. The reaction mixture was shaken and allowed to stand overnight at room temperature. The mixture was diluted with water, extracted with ether, and the ether washed with cold 5% HCl, 10% sodium bicarbonate, and water. After drying and removing the ether, a clear oil was obtained which showed essentially the infrared spectrum of **7** or **8** with less than 5% carbonyl absorption.

Attempted Oxidation of 7 and 8. To a solution of 75 mg of **7** or **8** in 2 ml of pyridine was added 2 ml of Sarett's reagent. The reaction flask was stoppered and kept at room temperature for 3 days with periodic shaking. The reaction mixture was poured into ice water, extracted with ether, and the ether washed with cold 50% HCl, 10% sodium bicarbonate, and water. The ether was dried and removed to leave 49 mg of a colored oil whose ir showed a moderate, broad, unresolved absorption in the carbonyl region. When this oil was examined on silica gel tlc plates, three or four poorly resolved components could be seen.

Dehydration of 7 and 8 to 9 Using Phosphorus Oxychloride in Pyridine. To a solution of 500 mg (1.71 mmoles) of **7** in 10 ml of pyridine cooled to 0° was added 2.0 ml (7.78 mmoles) of phosphorus oxychloride. The reaction mixture was stirred at 0° under nitrogen for 3 hr, allowed to warm up to room temperature, and stirred an additional 12 hr. The mixture was then poured into ice water, extracted with ether, the ether washed with cold 50% HCl, 10% sodium bicarbonate, and water. The ethereal solution was dried ($MgSO_4$), filtered, and the solvent removed to leave 450 mg of a clear, colorless oil. This was chromatographed on 50 g of neutral alumina (Brockmann Grade I) with 95:5 benzene–ether to give 340 mg (72%) of **9** as a clear, colorless oil: infrared (CCl_4) 3070 (cyclopropyl CH), 1650 (C=C), 1100 (OCH_3), and 890 cm^{-1} (vinyl CH); nmr (CCl_4) τ 5.15 (m, 2, olefinic *H*), 6.65 (s, 3, OCH_3), 6.90 (m, 1, C_3-*H*), 9.20 (s, 3, C_{13}-CH_3), and the remaining protons from 7.6 to 9.8.

Using the same procedure, 0.73 g (2.5 mmoles) of **8** was dehydrated with phosphorus oxychloride in pyridine to give 440 mg (64% of a clear, colorless oil whose infrared and nmr spectra were identical with those of **9** obtained by dehydration of **7**.

Thermal Rearrangement of Methyl 3β-Methoxy-D-norandrostane-16β-N-nitrosocarbamate (11). To a solution of 1.0 g (2.86 mmoles) of methyl 3β-methoxy-D-norandrostane-16β-carbamate in 50 ml of carbon tetrachloride was added 0.98 g (12 mmoles) of anhydrous sodium acetate and the reaction mixture stirred under nitrogen and cooled to −5°. Through a septum, 4.8 ml (11.8 mmoles) of 2.48 *M* nitrogen tetroxide in carbon tetrachloride was added. Stirring was continued for 1 hr, then the yellow solution was poured into ice water, washed with cold 10% sodium bicarbonate, dried ($MgSO_4$), and the solvent removed at 0° to give brilliant yellow crystals of **11**: infrared (CCl_4) 1760 (C=O), 1520 (CN), and 1105

cm^{-1} (OCH_3); nmr (CCl_4) τ 5.92 (s, 3, CO_2CH_3), 6.28 (t, 1, C_{16}-*H*), 6.68 (s, 3, OCH_3), 6.90 (m, 1, C_3-*H*), 9.10 (s, 3, C_{13}-CH_3), 9.25 (s, 3, C_{10}-CH_3), and the remaining ring protons from 7.4 to 9.0.

A solution of 850 mg (2.12 mmoles) of **11** in 35 ml of carbon tetrachloride containing 1 g of sodium carbonate was heated overnight at 75°. The solution, colorless at the end of this time, was filtered and the solvent removed to leave a slightly colored oil which was chromatographed through 100–200 mesh Florisil to give 186 mg (32% from the carbamate) of product A whose infrared and nmr spectra were identical with those of **9** and 296 mg (40%) of product B (**12**) as a clear, colorless oil: infrared (CCl_4) 3070 (cyclopropyl CH), 1745 (C=O), 1270, 1265 (ester CO), and 1100 cm^{-1} (methoxy CO); nmr (CCl_4) τ 6.28 (s, 3, OCO_2CH_3), 6.70 (s, 3, OCH_3), 6.90 (m, 1, C_3-*H*), 8.55 (s, 3, C_{13}-CH_3), 9.20 (s, 3, C_{10}-CH_3), 9.83 (m, 1, *endo*-methylene cyclopropyl *CH*), and the various other ring protons from 7.8 to 9.7.

Thermal Rearrangement of 3β-Methoxy-D-norandrostane-16β-N-nitrosoacetamide (14). 3β-Methoxy-16β-acetamido-D-norandrostane (**13**) was prepared by adding 3 drops of acetic anhydride to 100 mg (0.31 mmole) of **2** in 0.5 ml of pyridine. The stoppered mixture was allowed to stand for 2 days at room temperature, then diluted with water, and extracted with ether. The ether extract was washed with 5% HCl, 10% sodium bicarbonate, and water. The ether solution was dried ($MgSO_4$), filtered, and the ether removed to leave a white solid. Recrystallization of this material from ether–hexane gave 70 mg (65%) of **13**: mp 180–183°; infrared ($CHCl_3$) 3450 (NH), 1695 (C=O), 1500 (CN), and 1105 cm^{-1} (OCH_3).

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.65; H, 10.51; N, 4.20. Found: C, 75.49; H, 10.66; N, 4.11.

Nitrosation of **13** was carried out exactly as described for **11** to give yellow, crystalline **14**: infrared (CCl_4) 1745 (C=O), 1510 (CN), and 1110 cm^{-1} (OCH_3); nmr (CCl_4) τ 6.28 (t, 1, C_{16}-*H*), 6.67 (s, 3, OCH_3), 7.20 (s, 3, $COCH_3$), 9.10 (s, 3, C_{13}-CH_3), 9.25 (s, 3, C_{10}-CH_3), and the remaining protons at 7.4–9.0.

The freshly prepared **14** (1.0 g, 2.0 mmoles) was thermally rearranged at 45° in carbon tetrachloride exactly as described for **11**. After chromatography, 410 mg (50%) of product A, which gave infrared and nmr spectra identical with those of **9**, and 380 mg (42%) of product B (**15**) were obtained. Product B (**15**) was a clear, colorless oil: infrared (CCl_4) 3060 (cyclopropyl CH), 1735 (C=O), 1250 (ester CO), and 1100 cm^{-1} (methoxy CO); nmr (CCl_4) τ 6.70 (s, 3, OCH_3), 6.90 (m, 1, C_3-*H*), 8.05 (s, 3, $COCH_3$), 8.60 (s, 3, C_{13}-CH_3), 9.22 (s, 3, C_{10}-CH_3), 9.75 (m, 1, *endo*-methylene cyclopropyl *CH*), and the remaining protons at 7.5–9.3; mass spectrum (70 eV) *m/e* (relative intensity) 334 (1), 290 (3), 274 (41), 259 (19), 247 (13), 242 (33), 232 (10), 227 (48), 212 (10), 201 (15), 188 (18), 172 (15), 159 (15), 147 (31), 133 (31), 119 (36), 91 (64), 81 (68), 67 (45), 60 (37), 55 (40), and 44 (100).

Base-Catalyzed Decomposition of 11. A solution of **11** prepared from 1.0 g (2.86 mmoles) of the corresponding β-carbamate in 30 ml of ether was injected through a septum into a slurry of 0.672 g (6.0 mmoles) of potassium *t*-butoxide stirring in dry ether, under nitrogen, at −30°. After 30 min the precipitate of diazotate salt was collected by filtration under nitrogen and washed with 100 ml of ether. The precipitate was then suspended in 50 ml of ether, stirred vigorously under nitrogen, cooled to −5°, and quenched with 5 ml of water. The reaction mixture was extracted with ether, and the ether extract was washed with water, dried ($MgSO_4$), filtered, and removed to leave a white solid. Column chromatography of this material on Florisil gave 63 mg (8%) of **9** as a clear oil and 0.735 g (88%) of **7** as a crystalline solid, mp 112–113°.

Nitrous Acid Deamination of 3β-Methoxy-D-norandrostanyl-16α-amine Hydrochloride (16). The procedure used in the nitrous acid deamination of 1.90 g (5.62 mmoles) of **16** was the same used for **2**. After reducing the crude product with lithium aluminum hydride and chromatographing on Florisil, three fractions were obtained: 0.162 g of A (12%), 0.163 g (12%) of B, and 0.945 g (76%) of C. Fraction A appeared from its nmr spectrum to be a complex mixture of olefins and was not further studied. Component B (**21**) was a clear, colorless oil which could not be crystallized: infrared (CCl_4) 3610 (OH), 3060 (cyclopropyl CH), and 1100 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 6.70 (s, 3, OCH_3), 6.85 (m, 2, C_3-*H* and *CH*OH), 7.55 (s, 1, O*H*), 9.03 (d, J = 6 cps, 3, $CHCH_3$), 9.30 (s, 3, C_{10}-CH_3), and the remaining protons from 7.5 to 10.0.

Component C (**17**), the major product, was also a clear, colorless oil which could not be crystallized: infrared (CCl_4) 3620, 3560 (OH), 1650 (C=C), and 1100 cm^{-1} (OCH_3); nmr (CCl_3) τ 4.70 (m, 1, olefinic *H*), 6.15 (m, 1, *CH*OH), 6.67 (s, 3, OCH_3), 6.85 (m, 1, C_3-*H*), 8.83 (d, J = 6 cps, 3, $CHCH_3$), 9.18 (s, 3, C_{10}-CH_3), and the remaining protons from 7.7 to 9.1; mass spectrum (70 eV) *m/e* (relative intensity) 292 (57), 277 (12), 275 (11), 274 (47), 259 (5), 258 (5), 251 (7), 250 (29), 245 (7), 241 (9), 234 (8), 233 (7), 231 (9), 226 (13), 215 (7), 200 (16), 186 (22), 160 (12), 158 (14), 147 (22), 134 (40), 133 (40), 130 (14), 118 (36), 106 (100), 94 (28), 91 (53), 89 (67), 80 (57), 78 (63), 76 (32), 66 (40), 54 (40), 44 (60), 40 (57).

Oxidation of 21 with Sarett's Reagent. Compound **21** (49 mg) was oxidized with Sarett's reagent as described for **7** and **8**. The product was a pale yellow oil: infrared (CCl_4) 3060 (cyclopropyl CH), 1695 (C=O), and 1100 cm^{-1} (OCH_3).

Oxidation of 17 with Collins Reagent. To a solution of 155 mg (0.53 mmoles) of **17** in 33 ml of methylene chloride was added 1.64 g (6.36 mmoles) of dipyridine–chromium(VI) oxide, and the flask stoppered and allowed to remain overnight at room temperature. The reaction mixture was then washed with cold 10% HCl, 10% sodium bicarbonate, and water. After drying ($MgSO_4$) and removing the solvent, the residue was subjected to preparative thin layer chromatography on silica gel G. This gave 6.3 mg (41%) of a single major component, **19**, as a clear, colorless oil: infrared (CCl_4) 1718 (C=O) and 1100 cm^{-1} (OCH_3); nmr (CCl_4) τ 4.70 (s, 1, olefinic *H*), 6.71 (s, 3, OCH_3), 6.85 (m, 1, C_3-*H*), 7.03 (s, 2, $COCH_2C$=C), 7.95 (s, 3, $COCH_3$), 9.18 (s, 3, C_{10}-CH_3), and the remaining ring protons at 7.5–9.5; mass spectrum (70 eV) *m/e* (relative intensity) 290 (22), 275 (5), 262 (4), 258 (4), 243 (7), 233 (21) 232 (98), 230 (3), 225 (4), 218 (4), 200 (32), 190 (15), 159 (12), 119 (15), 107 (61), 105 (22), 95 (22), 81 (22), 66 (22), 55 (23), 43 (100), 28 (50); uv spectrum (ethanol) transparent above 210 mμ. When 10 ml of 6.25×10^{-5} *M* solution of **19** in ethanol was warmed with 3 drops of 30% HCl, the uv gave λ_{max} 242 mμ ($\epsilon \cong 12{,}000$).

Ozonolysis of 17. Ozone was bubbled through a solution of 50 mg (0.17 mmoles) of **17** in 10 ml of hexane at room temperature until precipitation of the powdery white ozonide appeared complete. After centrifuging, the hexane was decanted off the ozonide, 10 ml of 50% aqueous acetic acid was added, the solution cooled to 0°, and 150 mg of zinc dust added. After stirring for 3 hr, the reaction mixture was poured into water and extracted with ether. The mixture was brought to pH 9 by adding potassium carbonate, and filtered through Celite. The ether phase of the filtrate was washed with 10% sodium bicarbonate, dried ($MgSO_4$), filtered, and the ether removed to yield 35 mg of a clear, colorless oil: infrared (CCl_4) 3610–3420 (OH), 2710 (aldehyde CH), 1730 (aldehyde C=O), 1718 (ketone C=O), and 1100 cm^{-1} (OCH_3).

Base-Catalyzed Decomposition of Methyl 3β-Methoxy-16α-N-nitrosocarbamate (25). In exactly the same procedure described for **11**, 1.0 g (2.86 mmoles) of 16α-carbamate was converted to crystalline yellow **25**: infrared (CCl_4) 1760 (C=O), 1520 (CN), and 1105 cm^{-1} (OCH_3); nmr (CCl_4) τ 5.85 (s, 3, CO_2CH_3), 6.05 (m, 1, C_{16}-*H*), 6.70 (s, 3, OCH_3), 8.75 (s, 3, C_{13}-CH_3), 9.15 (s, 3, C_{10}-CH_3), and the remaining ring protons at 7.1–9.0.

The diazotate salt of **25** was prepared as described for **11**. The hydrolysis of 450 mg of the 16α-diazotate gave 391 mg of a clear, colorless oil. After chromatography through Florisil, 245 mg (63%) of a clear, colorless oil identified from its infrared and nmr spectra as **17** was obtained.

Thermal Rearrangement of 3β-Methoxy-D-norandrostane-16α-nitrosoacetamide (27). 3β-Methoxy-16α-acetamido-D-norandrostane (**26**) was prepared as described for the β isomer, **13**. From 1.09 g (3.22 mmoles) of the 16α-amine hydrochloride **16**, 0.72 g (67%) of **26**, mp 209–211°, was obtained after recrystallization from ether: infrared (CCl_4) 3450 (NH), 1695 (C=O), 1500 (CN), and 1105 cm^{-1} (OCH_3); nmr ($CDCl_3$) τ 3.19 (d, J = 6 cps, 1, N*H*), 6.10 (t, J = 6 cps, 1, C_{16}-*H*), 6.65 (s, 3, OCH_3), 6.90 (m, 1, C_3-*H*), 7.98 (s, 3, $COCH_3$), 8.89 (s, 3, C_{13}-CH_3), 9.16 (s, 3, C_{10}-CH_3), and the remaining protons from 7.5 to 9.0, mass spectrum (70 eV) *m/e* (relativity intensity) 333 (4), 318 (1), 290 (1), 286 (2), 274 (6), 248 (12), 233 (2), 216 (18), 201 (10), 190 (13), 173 (5), 159 (3), 147 (5), 138 (8), 120 (4), 118 (31), 117 (26), 95 (7), 93 (8), 91 (5), 86 (100), 81 (10), 70 (12), 55 (6), 44 (14), and 42 (13).

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.65; H, 10.51; N, 4.20. Found: C, 75.62; H, 10.76; N, 4.05.

The nitrosation of **26** was carried out as described for **11**, to give crystalline yellow **27**: infrared (CCl_4) 1745 (C=O), 1520 (CN), and 1105 cm^{-1} (OCH_3). Nitrosoamide **27** was decomposed at 40–45° in carbon tetrachloride as described for **11**. From the decomposition of **27** prepared from 1.0 g (3.0 mmoles) of **26** after chromatography on Florisil, 474 mg (58%) of **9** and 247 mg (25%) of **15** were obtained.

Solvolysis of 3β-Methoxy-D-norandrostanyl 16β-*p*-Toluenesulfonate (28). To a solution of 0.710 g (1.59 mmoles) of **28** in 50 ml of 3:1 dioxane–water was added 0.710 g (7.10 mmoles) of calcium carbonate, and the reaction mixture stirred under nitrogen at room

temperature for 3 days. The reaction mixture was filtered, diluted with water, and extracted with ether. The ether extract was removed to leave 525 mg of a clear, colorless oil. This material was separated into three components by preparative thin layer chromatography on silica gel G. Fraction 1, 17 mg (3%), was not further investigated. Component 2, 251 mg (48%), was a transparent, colorless oil which was determined to be **8** from its infrared and nmr spectra. Component 3, 145 mg (28%), was a white solid which proved to be **7**.

Determination of the Acetolysis Rate of 28. The rate of acetolysis was followed spectrophotometrically by measuring the decrease in absorbance of **28** (λ_{max} 261 mμ) with time. A stock solution of 25 ml of acetic acid which was 1.50×10^{-3} *M* in **28** and 1.50×10^{-3} *M* in anhydrous sodium acetate was prepared, *ca.* 3 ml of the solution placed in a uv cell and allowed to equilibrate to the temperature inside the sample chamber of the Beckman DU spectrophotometer (**29**). The reference cell was filled with pure acetic acid. Table I gives the measurements which were taken in a sample run. From the data in Table I, a plot of $-\ln (D - D_\infty)$ *vs.* time gave a straight line the slope of which gave $k = 2.03$ hr^{-1}. The average value of k obtained from three runs was 1.99 hr^{-1}.

Acetolysis of 3β-Methoxy-D-norandrostanyl 16α-*p*-Toluenesulfonate (31). A solution of 695 mg (1.56 mmoles) of **31** in 0.5 *M* potassium acetate–acetic acid (50 ml) was stirred at 120° under nitrogen for 3 days. The reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with 10% sodium bicarbonate, then with water, dried ($MgSO_4$), filtered, and the ether removed to leave 490 mg of a slightly yellow oil. After column chromatography of this material on Florisil, two fractions were obtained. Fraction 1 was 125 mg (25%) of a clear, slightly colored oil which showed a complex number of absorptions in the nmr. This material appeared to be a mixture of several compounds and was not further investigated. Fraction 2 was 292 mg (60%) of a clear, colorless oil, **18** which was found to be identical with the acetate obtained by treating **17** with acetic anhydride in pyridine: infrared (CCl_4) 1740 (C=O), 1260, 1245 (ester C—O), and 1100 cm^{-1} (OCH_3); nmr (CCl_4) τ 4.80 (s, 1, olefinic *H*), 5.00 (m, 1, C*H*OAc), 6.70 (s, 3, O*CH*$_3$), 6.90 (m, 1, C_3-*H*), 8.02 (s, 3, CO*CH*$_3$), 8.80 (d, J = 6 cps, 3, CH-C*H*$_3$), 9.15 (s, 3, C_{10}-C*H*$_3$), and the remaining ring protons at 7.7–9.0; mass spectrum (70 eV) *m/e* (relative intensity) 334 (2), 319 (1), 302 (1), 292 (1), 290 (1), 274 (100), 259 (4), 242 (10), 227 (6), 213 (2), 202 (3), 187 (3), 173 (2), 159 (3), 148 (30), 134 (25), 119 (6), 107 (30), 91 (11), 81 (10), 79 (14), 71 (6), 68 (9), 55 (6), 43 (40), and 29 (2).

Table I

Time, sec × 10^2	D	$D - D_\infty$	$-\ln (D - D_\infty)$
0	1.333	0.356	1.033
1.25	1.317	0.340	1.079
2.14	1.298	0.321	1.136
3.25	1.287	0.310	1.171
3.86	1.273	0.296	1.217
4.53	1.263	0.285	1.255
6.08	1.245	0.268	1.317
8.61	1.216	0.239	1.431
1.294	1.173	0.196	1.630
1.882	1.123	0.146	1.924
2.602	1.077	0.100	2.302
3.657	1.033	0.056	2.882
4.904	1.003	0.026	3.650
5.008	1.000	0.023	3.772
5.620	0.990	0.013	4.343
	0.977		

Cycloamyloses as Enzyme Models. Effects of Inclusion Complex Formation on Intramolecular Participation

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Abstract: Cycloheptaamylose forms complexes with mono-*p*-carboxyphenyl esters of 3-substituted glutaric acids and markedly depresses the rates of intramolecular carboxylate ion attack. However, cycloheptaamylose does not form any covalent intermediates in the reaction; it is involved only as a binding site. The sensitivity of the rate depressions to added cycloheptaamylose depends primarily upon the reactivities of the complexes. The 3-methyl, 3,3-dimethyl, and 3-isopropyl glutarate esters form complexes which show little or no reactivity compared to the free esters. The complex of the 3-phenyl glutarate ester, however, is only slightly less reactive than the free 3-phenyl glutarate ester. There appears to be no relationship between the relative reactivities of the free glutarate esters and those of the complexed esters. Consequently, the specificity of binding in these complexes can induce large changes in overall relative reactivity. This model study supports the idea that specificity in enzymic reactions may result from the geometry of binding the substrates to the enzymes, rather than resulting from the catalytic reactions themselves.

A major problem in enzymology is to explain the specificities observed in enzymic reactions. A number of hypotheses have been proposed[3] to account for specificity, but an evaluation of the importance of each of these ideas is difficult. The experimental evidence which model studies furnish in support or rejection of these various proposals involves only kinetic data. These data are very useful for discussing ideas about mechanisms of enzymic reactions, but they seldom contribute to an understanding of specificity. The main problem is to separate the study of binding from the catalytic reactions themselves in order to evaluate each factor independently.

Cycloamyloses have been utilized as enzyme models because of their ability to form inclusion complexes.[4-6]

(1) National Institutes of Health Postdoctoral Fellow, 1967–1969.
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(3) A number of reviews are available which explore these proposals: D. E. Koshland, Jr., and K. E. Heet, *Ann. Rev. Biochemistry*, **37**, 359 (1968); W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Co., Inc., New York, N. Y., 1969, p 282; M. L. Bender and F. J. Kezdy, *Ann. Rev. Biochemistry*, **34**, 49 (1965).
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