The residue contained acetic acid as detected by the odor. The acetic acid was removed by appropriate extraction with bicarbonate. The oily product was chromatographed on a Florisil (10 g) column packed in benzene. Elution (50-ml fractions) with 10% acetone–Skellysolve B gave a viscous oil in fractions 2 and 3, which was identified as **N-benzoyl-N-formyl-5-aminopentan-2-one** (11) by its nmr spectrum: $\delta_{TMS}^{CDCl_3}$ 8.89 (–NCHO, singlet, 1 H), 3.72 (>NCH_2–, triplet, J = 6.5 Hz, 2 H), 2.53 (–$COCH_2$–, triplet, J = 6.5 Hz, 2 H), 2.13 (CH_3CO–, singlet, 3 H), 1.93 (–$CH_2CH_2CH_2$–, quintuplet, J = 6.5 Hz, 2 H). Fractions 5–11 contained a second product, which was identified as **N-benzoyl-5-aminopentan-2-one** (12) by its nmr spectrum [$\delta_{TMS}^{CDCl_3}$ 7.06 (–NH–, broad, 1 H), 3.35 (–NCH_2–, triplet, J = 6 Hz, 2 H), 2.53 (–$COCH_2$–, triplet, J = 6.5 Hz, 2 H), 2.10 (CH_3CO–, singlet, 3 H), 1.85 (–$CH_2CH_2CH_2$–, quintuplet, J = 6.5 Hz, 2 H)], and recovered starting material in a ratio of 2:1.

Chromic Acid Oxidation of 1. A. Isolation of 3-Benzoyl-3-azabicyclo[3.3.1]nonan-2-one (8).—Jones reagent (60 drops) was added to a solution of 1 (0.458 g) in acetone (10 ml) at room temperature over a period of 3 days. A thin layer chromatogram on silica gel (developed with 10% methanol–benzene and detected in iodine vapor) suggested that some 1 remained and a product less polar than 1. The organic material was isolated by removal of acetone, addition of water, and methylene chloride extraction. The organic material was chromatographed on Florisil (10 g) packed with Skellysolve B. Elution with 5% acetone–Skellysolve B gave the product in fractions 2–5. Recrystallization from acetone–Skellysolve B gave **8** as colorless crystals: mp 108–110°; $\nu_{C=O}$ 1695, 1670, $\nu_{C=C}$ 1625, 1600, 1575, 1490, $\nu_{C_6H_5}$ 735, 700 cm^{-1} in Nujol; $\delta_{CDCl_3}^{37°}$ 3.89 (–NCH_2–, doublet, J = 5 Hz, 2 H), 2.70 (–COCH–, broad singlet, half band width ~ 10 Hz, 1 H).

Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.35; H, 7.13; N, 5.82.

B. Isolation of N-Benzoyl-*cis*-3-aminomethylcyclohexanecarboxylic Acid (9).—In an experiment similar to the above, Jones reagent (45 ml) was added to 1 (6.97 g) over a period of 7 days. The organic material from the methylene chloride extract partially crystallized and from acetone–Skellysolve B, 1.15 g of crystalline solid, mp 178–182°, was obtained. The solid was insoluble in water but soluble in aqueous 5% sodium bicarbonate solution and was precipitated upon reacidification of the basic solution. Three recrystallizations of the solid from acetone–Skellysolve gave colorless crystals of **9**: mp 190–192°; ν_{NH} 3260, $\nu_{bonded\ OH}$ 3500–2300, $\nu_{C=O}$ 1700, 1650, 1635, $\nu_{amide\ II}$ 1550, $\nu_{C_6H_5}$ 700 cm^{-1} in Nujol; $\delta_{CDCl_3}^{37°}$ 8.76 (–NH–, triplet, J = 6 Hz, 1 H), 3.17 (–NCH_2–, triplet, J = 6 Hz).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.67; H, 7.28; N, 5.63.

Registry No.—1, 17037-72-8; 3, 21996-54-3; 4, 21996-55-4; 5, 21996-56-5; 6, 21996-57-6; racemic 6, 21996-58-7; 8, 22002-77-3; 9, 21996-59-8; 11, 21991-06-0; 12, 21991-07-1; 13, 21996-60-1; 14, 21996-61-2.

Acknowledgment.—We thank J. R. Heald, J. M. Noteboom, I. N. Pratt, M. J. Sutton, S. L. Towne, and H. M. Wiessner for technical assistance, and Dr. W. A. Struck and associates for physical and analytical data.

Hydrolytic Rearrangements of 19-Methanesulfonoxyandrost-4-ene-3,17-dione and 19-Methanesulfonoxyandrosta-3,5-dien-17-one

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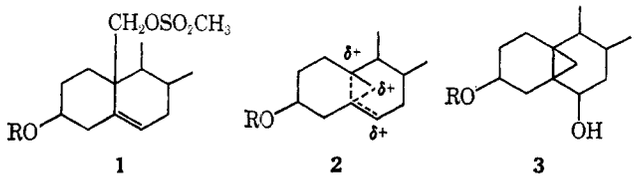
A study was made of the buffered hydrolyses of 19-methanesulfonoxyandrost-4-ene-3,17-dione (**4b**) and 19-methanesulfonoxyandrosta-3,5-dien-17-one (**5b**) for comparison with the results of hydrolysis of 19-substituted steroids with isolated Δ^5 double bonds. The acid-catalyzed rearrangements of 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (**28**) and 6β-hydroxy-5β,19-cycloandrostane-3,17-dione (**15**) are contrasted.

Participation of the isolated, homoallylic double bonds of Δ^5-19-substituted steroids **1** in kinetically controlled solvolyses has been found to lead to rearranged products **3** derived from 5β,19-cyclopropylcarbinyl cations **2**.[1] The present study of the buffered hydrolyses of 19-methanesulfonoxyandrost-4-ene-3,17-dione (**4b**) and 19-methanesulfonoxyandrosta-3,5-dien-17-one (**5b**) was undertaken to determine the effects of conjugation of the homoallylic double bonds on the nature of the products obtained.



1 2 3

19-Hydroxyandrost-4-ene-3,17-dione (**4a**) was prepared from 3β,19-dihydroxyandrost-5-en-17-one (**6**) by Oppenauer oxidation according to the procedure described in detail by Dauben and Ben-Efraim.[2] The methanesulfonate **4b** was prepared in essentially quantitative yield by treatment of **4a** with methanesulfonyl chloride in pyridine.

The preparation of 19-hydroxyandrosta-3,5-dien-17-one (**5a**) was based on a procedure which has been used to convert 10β-methyl-Δ^5-3β-hydroxy steroids into 10β-methyl-3,5-dienes.[3] 3β,19-Dihydroxy-17-ethylenedioxyandrost-5-ene (**7**) was prepared either directly from 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (**8**) by brief treatment with a small amount of water in dimethyl sulfoxide in the presence of a catalytic amount of sulfuric acid or by ketalization of 3β,19-dihydroxyandrost-5-en-17-one (**6**). Oppenauer oxidation of **7** gave 19-hydroxy-17-ethylenedioxyandrost-4-en-3-one (**9**) which was reduced with lithium tri-*t*-butoxyaluminum hydride in tetrahydrofuran to a mixture of the C_3-epimeric, allylic alcohols **10** according to the procedure of Klimstra and Colton.[4] The latter mixture was subjected to acid-catalyzed dehydration which occurred with concomitant hydrolysis of the

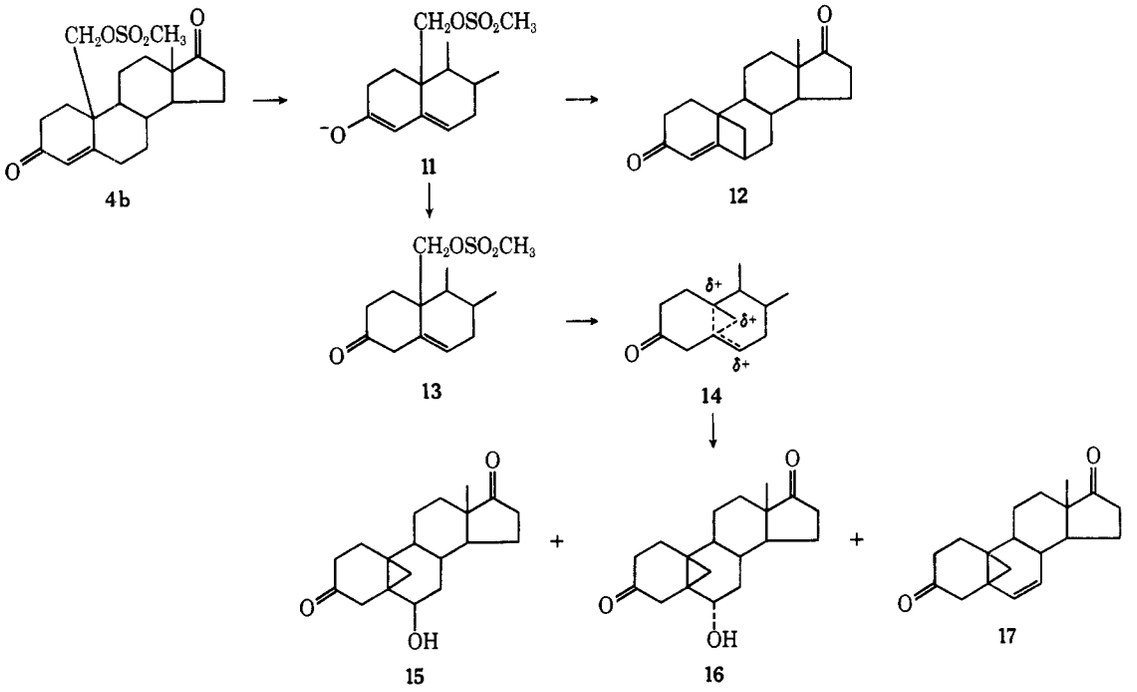
(1) (a) J. Tadanier, *J. Org. Chem.*, **31**, 3124 (1966); **31**, 3204 (1966). (b) O. Halpern, P. Crabbé, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964). (c) K. Syhora, J. A. Edwards, and A. D. Cross, *J. Org. Chem.*, **31**, 3411 (1966). (d) M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, **86**, 1528 (1964).

(2) W. G. Dauben and D. A. Ben-Efraim, *J. Med. Chem.*, **11**, 287 (1968).

(3) J. C. Eck, R. L. Van Peursem, and E. W. Hollingsworth, *J. Amer. Chem. Soc.*, **61**, 171 (1939).

(4) P. D. Klimstra and F. B. Colton, *Steroids*, **10**, 411 (1967).

SCHEME I



17-ketal leading to **5a**. The product (**5a**) was purified by chromatography followed by preparation of the *p*-nitrobenzoate (**5c**). The methanesulfonate (**5b**) was prepared from pure **5a** with methanesulfonyl chloride in pyridine, in the usual manner, characterized spectroscopically, and used without further purification.

Hydrolysis of **4b** required forcing conditions (autoclave, 120°, 45 hr) and led to the isolation of 6β,19-cycloandrost-4-ene-3,17-dione (**12**, 12%), 6β-hydroxy-5β,19-cycloandrostane-3,17-dione (**15**, 42%), 6α-hydroxy-5β,19-cycloandrostane-3,17-dione (**16**, 2.0%), and 5β,19-cycloandrost-6-ene-3,17-dione (**17**, 2.5%) (see Scheme I). A qualitative indication of the effect of the conjugation of the double bond of **4b** on the rate of hydrolysis was provided by the quantitative recovery of starting material under conditions adequate to effect complete reaction of 19-methanesulfonoxy steroids with isolated Δ^5 double bonds.[1]

The product **12** proved identical with that formed by treatment of **4b** with potassium *t*-butoxide in *t*-butyl alcohol as described by Wehrli, Schaffner, and Bonet-Sugrañes,[5] who postulated its formation under these conditions from the dienolate anion **11** (Scheme I).

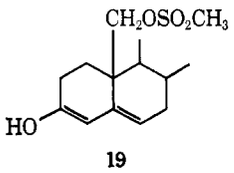
The configurations of the epimeric alcohols **15** and **16** were assigned on the basis of their relationship to the C_6-epimeric 3β-methoxy-6,17β-dihydroxy-5β,19-cycloandrostanes and their derived diacetates[1a] which was established by comparison of the nmr absorptions of their cyclopropyl and C_6 protons. In both the 3-keto and 3β-methoxy series the absorptions of the cyclopropyl protons of the 6-ols appeared as AB quartets. The chemical shifts (δ_{AB}) between the absorptions of the cyclopropyl protons of the 6β-hydroxy epimers were much greater (see Experimental Section) than those of the 6α-hydroxy epimers as a consequence of deshielding of the cyclopropyl protons which lie over the B rings by the neighboring 6β-hydroxyls.

(5) (a) J. J. Bonet, H. Wehrli and K. Schaffner, *Helv. Chim. Acta*, **45**, 2615 (1962). (b) J. J. Bonet, H. Wehrli and K. Schaffner, *ibid.*, **46**, 1776 (1963). (c) J. J. Bonet-Sugrañes, *Afinidad*, **22**, 326 (1965).

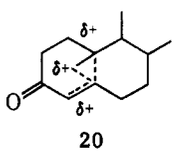
The absorptions of the C_6 protons of the epimers **15** and **16**, determined at 100 MHz, appeared as well-resolved quartets. The relative values of the separations between the outer peaks (5.9 Hz for the 6α proton of **15** and 14.7 Hz for the 6β proton of **16**) correspond to the relative values of the widths at half-height of the unresolved C_6 multiplets of the 3β-methoxy-6β- and -6α-acetoxy-5β,19-cycloandrostan-17β-acetates (6.5 Hz and 19 Hz, respectively) determined at 60 MHz.[1a]

The more abundant isomer **15** was oxidized with chromic anhydride in pyridine to 5β,19-cycloandrostane-3,6,17-trione **18** which showed the characteristic ir and uv spectra of a conjugated cyclopropyl ketone.

The products **15**, **16**, and **17** obtained by hydrolysis of the methanesulfonate **4b** are those expected to result from rearrangement of the unconjugated Δ^5-3 ketone, **13**, which may be formed under the reaction conditions (Scheme I). The possibility, however, that all of the products **12**, **15**, **16**, and **17** may be formed from the neutral dienol **19** under the conditions used in this work may not be ruled out.



19



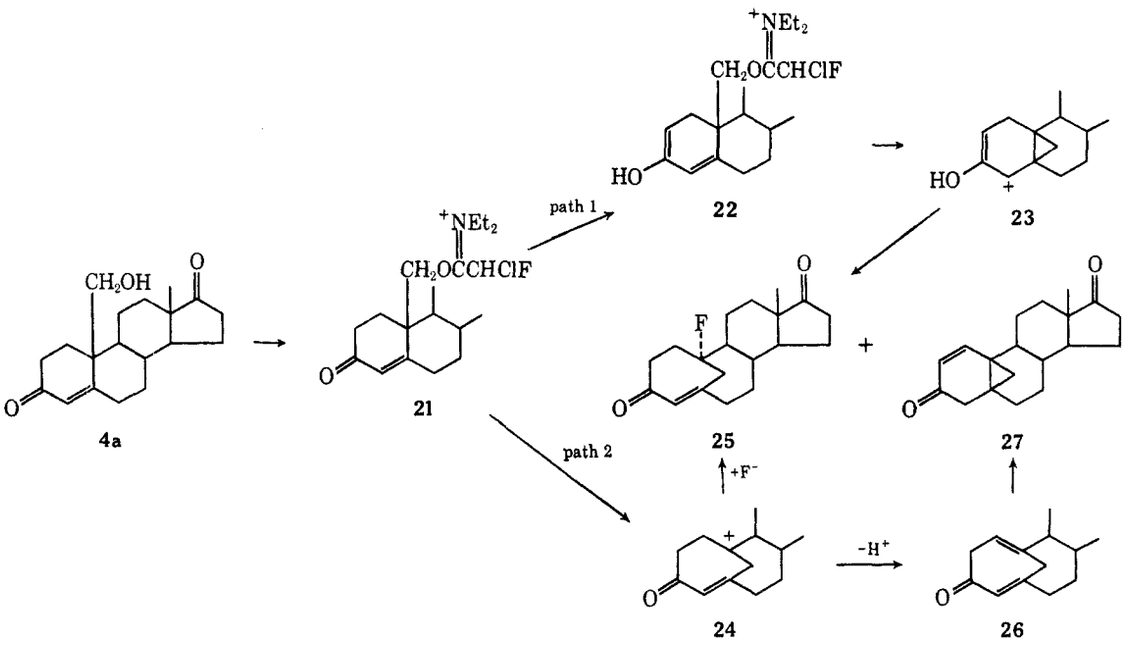
20

The failure to isolate products attributable to a cation such as **20** probably reflects the high energy of such an intermediate which would be a consequence of placing positive charge at C_4, adjacent to the C_3 carbonyl, to achieve effective stabilization by charge delocalization.

In this regard, the results of the buffered hydrolysis of **4b** offer an interesting contrast to those of Knox, *et. al.*,[6] who reported formation of 10β-fluoro-5,10-seco-5β,19-cycloandrost-4-ene-3,17-dione (**25**) and 5β,19-cycloandrost-1-ene-3,17-dione (**27**) on treatment of 19-hy-

(6) L. H. Knox, E. Velarde, and A. D. Cross, *J. Amer. Chem. Soc.*, **85**, 2533 (1963).

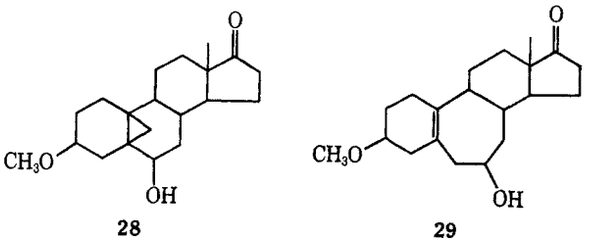
SCHEME II



droxyandrost-4-ene-3,17-dione (**4a**) with 2-chloro-1,1,2-trifluoroethyldiethylamine in refluxing acetonitrile for 2 hr. These authors proposed that the reaction occurred (path 1, Scheme II) by loss of N,N-diethylchlorodifluoroacetamide from the 2,4-dienol (**22**) of the adduct **21**. Since the methanesulfonate solvolysis differs from the reaction of **4a** with 2-chloro-1,1,2-trifluoroethyldiethylamine both in the ease of reaction and in the nature of the products formed, an attractive alternate mechanism (path 2, Scheme II) for the latter reaction consists of direct loss of N,N-diethylchlorodifluoroacetamide from **21** to form a cation such as **20**, the principle canonical structure of which might be expected to be **24** (Scheme II). It is, thus, suggested that the reaction of aliphatic alcohols with 2-chloro-1,1,-2-trifluorotriethylamine may be usefully classified with the family of reactions to which attention has recently been drawn by Beak and Trancik,[7] which, at least formally, is suitable for the generation of high energy cations by loss of a stable, nonnucleophilic leaving group. Other examples of reactions of this family include reactions of diazonium ions, isocarboxonium ions, and carboxylium ions.[7]

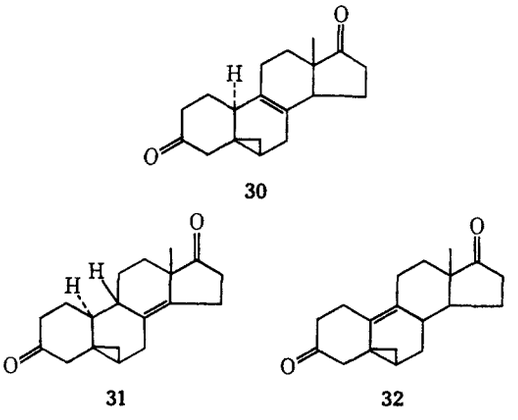
The recent paper of Wieland and Anner[8] provides further examples of the sensitivity of the nature of the rearrangements of steroid 19-substituted Δ^4-3 ketones to the reaction conditions.

Treatment of the cyclopropylcarbinol **15** with aqueous acetone, 0.2 *N* in sulfuric acid, under conditions which were adequate to effect essentially complete conversion of 3β-methoxy-6β-hydroxy-5β,19-cycloandrostan-17-one (**28**) into 3β-methoxy-7β-hydroxy-B-homoestr-5(10)-en-17-one (**29**),[1a] led to a 59% recovery of **15**, an ~5% yield of α,β-unsaturated ketone, which was detected in the ir spectrum of the total crude product, and the isolation of an elimination product (23% conversion) which has been assigned structure **30**



or **31**[9] on the basis of ir, uv, and nmr spectra (see Experimental Section) and its molecular ion peak at 284.

In the nmr spectrum of **30** (or **31**) the coupling constant (J = 17 Hz) of the AB quartet attributed to the absorption of the C_4-methylene protons was identical with that of the C_4-methylene protons of the isomeric, conjugated vinylcyclopropane **32**, reported



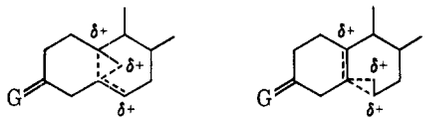
(7) P. Beak and R. J. Trancik, *J. Amer. Chem. Soc.*, **90**, 2714 (1968).
(8) P. Wieland and G. Anner, *Helv. Chim. Acta*, **52**, 453 (1969).

(9) The configurations at C_9 and C_{10} of the proposed structures **30** and **31** have been assigned on the assumption that the rearrangement involves intramolecular 1,2-hydrogen shifts. The latter have analogy in the well-known steroid backbone rearrangements.[10] Dreiding models suggest that **31** would be the much more stable of the two owing to the severe steric interaction between the 5β,6β-methylene group and the C_{13} methyl of **30**.

(10) J. W. Blunt, M. P. Hartshorne, and D. N. Kirk, *Tetrahedron Lett.*, 2125 (1966).

by Knox, *et. al.*[11] Although the chemical shifts of the low-field C_4-methylene protons of the isomeric vinylcyclopropanes were identical, the chemical shifts of their high-field counterparts were quite different [δ_A 2.82 and δ_B 1.64 for **30** (or **31**), and δ_A 2.82 and δ_B 2.35 for **32**].

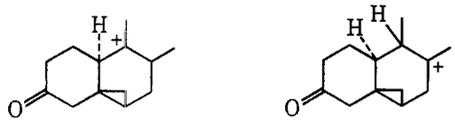
The 3-keto group of **15**, thus, both retards the rate of rearrangement, relative to the 3β-methoxy analog **28**, and alters the nature of the rearranged product. Although the conformational effect of replacing the sp^3 3 carbon of **28** with the sp^2 3 carbon of **15** might be expected to influence the rearrangements, the contrast between the two series may at least be rationalized on the basis of the expected electronic effect of the C_3 carbonyl. In the 3β-methoxy series, the rearrangement of **28** to **29** has been shown[1a] to occur *via* the isomeric cyclopropylcarbinyl cations **33a** and **34a**.



33 **34**

a, G = 3α-H, 3β-OCH_3
b, G = O

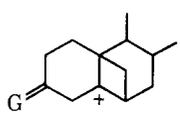
Since the dipole of the 3-keto group should oppose the development of positive charge in the A ring, the 3-keto cations **33b** and **34b** are expected to be destabilized relative to their 3β-methoxy counterparts and relative to rearranged cations such as **35** and **36** in which the positive charges are more distant from the C_3 carbonyl. This would be expected, both to retard



35 **36**

the rate of ionization of the conjugate acid of **15** and favor formation of the unconjugated vinylcyclopropane **30** or **31**.

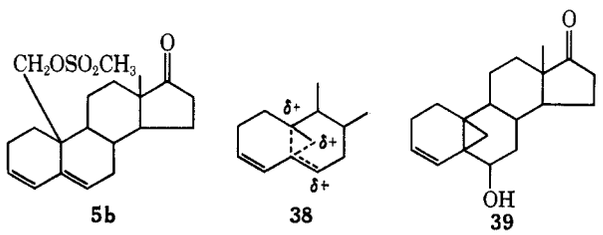
In addition, the nature of the rearrangement of a cation **33** to the isomeric cation **34** suggests a transition state such as **37** with electron deficiency at C_5. This



37

would further contribute to the decrease in the rate of rearrangement of **15**, since the transition state **37** (G=O) formed from **33b** has electron deficiency at C_5, β to the C_3 carbonyl.

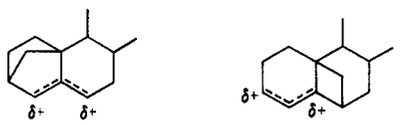
In contrast to the reaction of the dienolate anion **11**, which does not involve a carbonium-ion intermediate and which leads to cyclization at the terminal (C_6) carbon of the conjugated system to form **12**,[5] the parent diene **5b** reacts to form the 5β,19-cyclo-6β-ol **39**, which was isolated in 45% yield.



5b **38** **39**

The configuration at C_6 of **39** was established from the 100-MHz nmr spectrum by the fact that the peak separations of its C_6 quartet were identical with those of the C_6 quartet of 6β-hydroxy-5β,19-cycloandrostane-3,17-dione (**15**) (see Experimental Section).

The reaction of **5b** is thus analogous to those of 19-methanesulfonoxy steroids with isolated Δ^5 double bonds[1] and suggests that formation of **39** occurs *via* the Δ^3-cyclopropylcarbinyl cation **38**. Thus the presence of the Δ^3 double bond does not appreciably affect the course of the rearrangement, although cyclization at the terminal carbon atoms (C_3 or C_6) of the diene system would lead to the bridged, allylic cations **40** or **41**.



40 **41**

Experimental Section

Physical measurements were made with a Fisher-Johns melting point block; a Hilger and Watts polarimeter using 1% solutions in chloroform; a Perkin-Elmer, Model 421, grating ir spectrometer on 7% solutions in deuteriochloroform; Varian A-60 and HA-100 nmr spectrometers on deuteriochloroform solutions; a Cary, Model 11, uv spectrophotometer on methanol solutions; and an AEI MS-902 mass spectrometer. Nmr chemical shifts are expressed in δ units (parts per million).[12] Woelm alumina of activity III was used for column chromatography, unless otherwise specified. The petroleum ether used was a fraction boiling between 66 and 70°.

19-Methanesulfonoxyandrost-4-ene-3,17-dione (4b).—A solution of 1.0 g of 19-hydroxyandrost-4-ene-3,17-dione (**4a**)[2] in 30 ml of pyridine was cooled in an ice bath and 1.3 ml of methanesulfonyl chloride was added dropwise with magnetic stirring. After the addition was complete, the reaction mixture was allowed to stand in an ice bath for 2.5 hr and then shaken with a mixture of chloroform and water. The chloroform solution was washed with water, 5% $NaHCO_3$ solution, and then to neutrality with water. The chloroform solution was dried ($MgSO_4$) and the solvent was evaporated leaving 1.2 g of **4b**, mp 149–152°. Two recrystallizations of a 100-mg sample from acetone–petroleum ether gave 60 mg: mp 162–164°; $[\alpha]^{26}D$ +175° (lit.[5c,13] mp 157–158° dec; $[\alpha]D$ +85°).

Attempted Hydrolysis of 19-Methenesulfonoxyandrost-4-ene-3,17-dione (4b) in Refluxing Aqueous Acetone.—A solution prepared from 1.08 g of **4b**, 1.1 g of potassium acetate, 20 ml of water, and 60 ml of acetone was heated under reflux for 24 hr. The major portion of the acetone was evaporated under reduced pressure, and the product was isolated by chloroform extraction to yield 1.02 g of **4b**, mp 153–155°, not depressed on admixture

(11) L. H. Knox, E. Velarde, S. Berger, I. Delfin, R. Grezemkovski, and A. D. Cross, *J. Org. Chem.*, **30**, 4160 (1965).

(12) For convenience in reporting chemical shifts on a common scale, δ units are used throughout, in accord with the recommendations of the referees. The δ values reported for the characteristic peak positions of multiplets due to spin–spin coupling, which are functions of coupling constants, are valid only at the specified frequencies (60 MHz or 100 MHz) at which the spectra were determined. Individual peak positions of multiplets are reported to four significant figures to provide accurate estimates of peak separations.

(13) The apparent discrepancy in the rotations may be due to the fact that the rotation reported by Bonet-Sugrañes[5] was taken with a 0.5-dm tube, and the calculation of $[\alpha]D$ may not have been corrected for path length.

with starting material. Spectra (ir and nmr) were identical with those of starting material.

Hydrolysis of 19-Methanesulfonoxyandrost-4-ene-3,17-dione (4b).—A solution prepared from 8.5 g of **4b**, 8.5 g of potassium acetate, 160 ml of water, and 500 ml of acetone was heated in an autoclave at 120° for 45 hr. The major portion of the acetone was evaporated under reduced pressure and the resulting aqueous suspension was extracted with chloroform. The chloroform solution was washed with water, 5% sodium bicarbonate solution, and then to neutrality with water, and dried ($MgSO_4$). Evaporation of the chloroform left 7.3 g of a brown oil. Spectra (ir and nmr) showed the absence of methanesulfonate.

The product (7.2 g) was chromatographed on 700 g of alumina. Elution with 1:4 ether–benzene yielded 1.66 g of oil. This material was rechromatographed on alumina. The early fractions eluted with benzene contained 159 mg of 5β,19-cycloandrost-6-ene-3,17-dione **17**, mp 121–137°. Two recrystallizations from acetone–petroleum ether gave 75 mg of **17**: mp 143–146° (lit.[5] mp 141–142°); $\tilde{\nu}_{max}$ 3062, 3022, 1725, 1700 cm^{-1}; 60-MHz nmr, 5.367, 5.550, 5.733, 5.883 (C_6 H and C_7 H, q, low-field doublet broadened), 0.995, 1.017 (C_4 H, d), 0.92 (C_{18} H_3, s), 0.733, 0.833, 1.117, 1.217 (C_{19} H_2, q).

Further elution of the column with benzene gave 217 mg of mixtures (by tlc) which were not characterized, followed by 767 mg of 6β,19-cycloandrost-4-ene-3,17-dione (**12**), mp 123–128°. Recrystallization from acetone–petroleum ether yielded 555 mg of **12**, mp 131–132°. The infrared and nmr spectra were identical with those of the sample prepared from **4b** with KO-*t*-Bu in *t*-BuOH, as described below, and a mixture melting point showed no depression.

Elution of the original column with chloroform yielded 4.0 g of an orange crystalline solid. Two recrystallizations from acetone–petroleum ether gave 1.82 g of 6β-hydroxy-5β,19-cycloandrostane-3,17-dione (**15**) mp 200–203°; $[\alpha]^{25}D$ + 110°; $\tilde{\nu}_{max}$ 3598, 3440, 3058, 1727, 1702 cm^{-1}; 100-MHz nmr, 4.049, 4.062, 4.094, 4.108 (C_6 H, q), 2.482, 2.665, 2.710, 2.872 (C_4 H_2, q), 0.89 (C_{18} H_3, s), 0.399, 0.464, ···,[14] 0.995 (C_{19} H_2, q, δ_{AB} 0.88, J_{AB} = 6.5 Hz).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.48; H, 8.37.

Second and third crops of **15** (604 mg, mp 195–202°, and 332 mg, mp 190–198°, respectively) were obtained from the filtrates.

The material recovered from the mother liquors from the crystallization of **15** was chromatographed on a Sephadex column (90 × 2.5 cm, LH 20) in an ascending system with chloroform as the eluate to yield an additional 125 mg of **15**, mp 178–195°, and 134 mg of 6α-hydroxy-5β,19-cycloandrostane-3,17-dione (**16**). Two recrystallizations from acetone–petroleum ether gave 79 mg of **16**: mp 187–190°; $[\alpha]^{26}D$ +90°; $\tilde{\nu}_{max}$ 3612, 3460, 3050, 1728, 1700 cm^{-1}; 100-MHz nmr, 3.822, 3.878, 3.910, 3.969 (C_6 H, q), 2.420, 2.595, 2.880, 3.058 (C_4 H_2, q), 0.89 (C_{18} H_3, s), 0.425, 0.492, 0.510, 0.570 (C_{19} H_2, q, δ_{AB} 0.085, J_{AB} = 6.3 Hz).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 75.46; H, 8.67. Found: C, 75.66; H, 8.88.

6β,19-Cycloandrost-4-ene-3,17-dione (12).—The methanesulfonate (**4b**, 496 mg) was heated under reflux for 2 hr in an atmosphere of nitrogen in a solution prepared by dissolving 202 mg of potassium in 58 ml of *t*-butyl alcohol. The product was isolated by ether extraction and purified by chromatography on 15 g of alumina. Elution with benzene yielded 152 mg of crystals. Two recrystallizations from acetone–petroleum ether gave 81 mg of **12**: mp 130–132°; $[\alpha]^{24.5}D$ −77°; $\tilde{\nu}_{max}$ 1732, 1653 cm^{-1}; 60-MHz nmr, 5.64 (C_4 H, s), 3.208, 3.280, 3.375 (C_6 H, t), 0.99 (C_{18} H_3, s) [lit.[5a,b] mp 132°; $[\alpha]D$ −73°;[15] 60-MHz nmr, 5.59 (C_4 H, s), 0.97 (C_{18} H_3, s)].

5β,19-Cycloandrostane-3,6,17-trione (18).—To a solution of 406 mg of 6β-hydroxy-5β,19-cycloandrostane-3,17-dione (**15**) in 3 ml of pyridine was added a complex prepared from 467 mg of chromium trioxide and 5 ml of pyridine. The resulting suspension was allowed to stand overnight at room temperature. The product was isolated by extraction with ether (in which the product was only slightly soluble) and then chloroform to yield 291 mg of **18**, mp 154–160°. Two recrystallizations from acetone–petroleum ether provided the analytical sample (210 mg, mp 165–167°): $\tilde{\nu}_{max}$ 3070, 1730, 1703, 1673 cm^{-1}; λ_{max} 205 mμ (ε 4290); 100-MHz nmr, 2.85 (C_4 H_2, s, $W_{1/2}$ = 2 Hz), 1.055, 1.120, 2.665, 2.730 (C_{19} H_2, q), 0.94 (C_{18} H_3, s).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.16; H, 8.09.

3β,19-Dihydroxy-17-ethylenedioxyandrost-5-ene (7). A.—To a solution of 1.95 g of 6β,19-oxido-17-ethylenedioxy-3α,5α-cycloandrostane (**8**)[16] in 125 ml of dimethyl sulfoxide at room temperature was added, with stirring, 0.25 ml of water and 0.75 ml of concentrated sulfuric acid. Stirring was continued for 1 hr at room temperature and the resulting solution was shaken with 500 ml of chloroform and 1200 ml of 5% sodium bicarbonate solution. The chloroform layer was washed to neutrality with water and dried ($MgSO_4$). Evaporation of the chloroform left 1.69 g of **7**, mp 158–163°. The analytical sample, mp 167–168°, was prepared by recrystallization from benzene–petroleum ether and then from methanol–water. The ir and nmr spectra were identical with those obtained by ketalization of 3β,19-dihydroxyandrost-5-en-17-one (**6**) as described below.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.37; H, 9.26. Found: C, 72.42; H, 9.25.

B.—A mixture of 4.06 g of 3β,19-dihydroxyandrost-5-en-17-one (**6**),[16] 3.8 ml of ethylene glycol, 50 mg of *p*-toluenesulfonic acid monohydrate, and 250 ml of benzene was heated overnight under reflux using a water separator. The mixture was allowed to cool to room temperature and washed with water, 5% sodium bicarbonate solution, and then to neutrality with water, and dried ($MgSO_4$). Evaporation of the benzene left 4.4 g of **7**: mp 161–164°; $\tilde{\nu}_{max}$ 3597, 3448 cm^{-1}.

19-Hydroxy-17-ethylenedioxyandrost-4-en-3-one (9).—The Oppenauer oxidation was carried out by the procedure used by Dauben and Ben-Efraim[2] for the oxidation of 3β,19-dihydroxyandrost-5-en-17-one (**6**) to 19-hydroxyandrost-4-ene-3,17-dione (**4a**), but a work-up was employed which avoided steam distillation.

A solution prepared from 2.0 g of **7**, 28 ml of toluene, and 6.3 ml of cyclohexanone was heated under reflux with magnetic stirring for about 10 min during which time 8 ml of solvent was distilled. To the resulting solution was added a solution prepared from 0.6 g of aluminum isopropoxide, 6 ml of toluene, and 1.5 ml of cyclohexanone and reflux was continued with magnetic stirring for 15 min. The solution was cooled in an ice bath and 2.4 ml of acetic acid was added. The product was isolated by benzene extraction. After evaporation of the benzene, the higher boiling solvent remaining was removed by distillation under high vacuum. The product was triturated with petroleum ether, and removal of the supernatant left 2.0 g of **9**, mp 134–150°, suitable for use in subsequent steps.

The analytical sample was prepared by recrystallization from acetone–petroleum ether. A sample (204 mg) was recrystallized four times to yield 70 mg of pure **9**: mp 193–195°, $\tilde{\nu}_{max}$ 3619, 3440, 1658, 1614 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 73.10; H, 8.86.

19-(*p*-Nitrobenzoyloxy)androsta-3,5-dien-17-one (5c) and 19-Hydroxyandrosta-3,5-dien-17-one (5a).—To a magnetically stirred solution of 2.62 g of 19-hydroxy-17-ethylenedioxyandrost-4-en-3-one (**9**) (total crude material from the Oppenauer oxidation of **7**) in 50 ml of tetrahydrofuran, cooled to 0°, was added a freshly prepared solution of 10 g of lithium tri-*t*-butoxyaluminum hydride in 40 ml of tetrahydrofuran. The resulting solution was stirred at 0° for 15 min and then at room temperature for 3.5 hr. The reaction mixture was poured into 500 ml of 1:20 acetic acid–water solution, and the resulting aqueous mixture was extracted with ether. The ether solution was washed with water, 5% sodium bicarbonate solution, and then to neutrality with water. Evaporation of the solvent left 2.30 g of **10** as a white glass.

The crude allylic alcohol (**10**) thus prepared (2.26 g) was heated under reflux for 3 hr in a solution prepared from 226 ml of acetone and 82 ml of 1:10 sulfuric acid–water solution. The product (1.16 g of orange oil) was isolated by ether extraction and chromatographed on 120 g of alumina. Elution with 1:4 ether–benzene yielded 590 mg of 19-hydroxyandrosta-3,5-dien-17-one (**5a**) which was purified *via* the 19-*p*-nitrobenzoate **5c**.

The crude diene alcohol (1.45 g), accumulated from several runs carried out as described above, was allowed to stand at room temperature for 4 hr in a solution prepared from 1.96 g of *p*-nitrobenzoyl chloride and 25 ml of pyridine. Extraction with

(14) Peak appeared as a shoulder on the absorption peak of the C_{18} methyl group.

(15) The rotation (+8°) reported in ref 5a was later corrected in ref 5b.

(16) J. Tadanier, *J. Org. Chem.*, **28**, 1744 (1963).

chloroform yielded 2.54 g of an orange oil which was eluted through a short column of 25 g of alumina with 2 l. of benzene to yield 2.2 g of *p*-nitrobenzoate.

Two recrystallizations of material obtained in this manner (3.75 g) from acetone–petroleum ether yielded 1.93 g of pure 19-(*p*-nitrobenzoyloxy)androsta-3,5-dien-17-one (**5c**): mp 177–181°; $[\alpha]^{25}D$ −92°; $\tilde{\nu}_{max}$ 3020, 1720, 1648, 1604, 1524 cm^{-1}; λ_{max} 234 mμ (ε 23,500).

Anal. Calcd for $C_{26}H_{29}O_5N$: C, 71.71; H, 6.71; N, 3.22. Found: C, 71.76; H, 6.76; N, 3.16.

An additional 295 mg of **5c**, mp 180–183°, was obtained from the mother liquors by chromatography on alumina and crystallization.

A solution of 2.08 g of the *p*-nitrobenzoate **5c** in 140 ml of 5% methanolic potassium hydroxide solution was heated under reflux for 1 hr. Ether extraction followed by recrystallization from acetone–water solution yielded 1.05 g of 19-hydroxyandrosta-3,5-dien-17-one (**5a**): mp 120–125°; $[\alpha]^{25}D$ −92°; $\tilde{\nu}_{max}$ 3618, 3570, 3448, 3016, 1728, 1644 cm^{-1}; λ_{max} 234 mμ (ε 18,800); 100-MHz nmr, 5.5-6.1 (vinyl H's), 3.647, 3.680 ($C_{19}H_2$, d), 0.95 ($C_{18}H_3$, s).

A second crop of 120 mg of **5a**, mp 120–125°, was obtained from the mother liquors.

Preparation and Hydrolysis of 19-Methanesulfonoxyandrosta-3,5-dien-17-one (5b).—A solution of 1.06 g of 19-hydroxyandrosta-3,5-dien-17-one (**5a**) in 30 ml of pyridine was cooled in an ice bath and 1.3 ml of methanesulfonyl chloride was added with stirring. Stirring was continued with the reaction vessel in an ice bath for 30 min and the resulting solution was then allowed to stand at room temperature for 3 hr. The product was isolated by chloroform extraction including a washing with 5% sodium bicarbonate solution. The chloroform solution was dried ($MgSO_4$) and the solvent was evaporated leaving 1.40 g of a yellow glass. The ir and nmr spectra of the product were compatible with the structural assignment as 19-methanesulfonoxyandrosta-3,5-dien-17-one (**5b**) [$\tilde{\nu}_{max}$ 3020, 1729, 1648, 1350, 1168 cm^{-1}; 60-MHz nmr, 5.50–6.25 (vinyl H's), 4.050, 4.225, 4.272, 4.447 ($C_{19}H_2$, q), 2.97 ($-OSO_2CH_3$, s), 0.97 ($C_{18}H_3$, s)], and the crude product was used without further purification.

A solution of 1.34 g of **5b**, 1.21 g of potassium acetate, 35 ml of water, and 118 ml of acetone was heated under reflux for 26 hr. The resulting solution was diluted with 120 ml of water, and the major portion of the acetone was evaporated under reduced pressure. The aqueous suspension was extracted with ether, and the ether solution was washed with water, 5% sodium bicarbonate solution, and then to neutrality with water, and dried ($MgSO_4$). Evaporation of the ether left 1.04 g of a yellow oil. The 60-MHz nmr spectrum showed the absence of any methanesulfonate (no singlet at 2.97).

The product was heated under reflux for 1 hr in 100 ml of 2.5% methanolic potassium hydroxide solution. The product was isolated by ether extraction to yield 893 mg of an orange oil.

This product (353 mg) was chromatographed on a Sephadex (LH-20) column (90 × 2.5 cm) in an ascending system with chloroform as the eluent to yield 189 mg (45% based on **5a**) of 6β-hydroxy-5β,19-cycloandrost-3-en-17-one (**39**), mp 117–124°. Recrystallization from acetone–petroleum ether gave the analytical sample: mp 127–128°; $[\alpha]D$ +27°; $\tilde{\nu}_{max}$ 3601, 3448, 3062, 3022, 1730, 1638 cm^{-1}; λ_{max} 205 mμ (ε 5600); 100-MHz nmr, 5.892, 5.924, 5.990, 6.012 (C_4H, q), 5.41 (C_3H, m), 4.277, 4.290, 4.325, 4.336 (C_6H, q), 0.89 ($C_{18}H_3$, s), 0.769, 0.816, 0.982, 1.030 ($C_{19}H_2$, q).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.86; H, 9.18.

Acid-Catalyzed Rearrangement of 6β-Hydroxy-5β,19-cycloandrostane-3,17-dione (15).—A solution prepared from 507 mg of **15**, 6 ml of 1.4 *N* sulfuric acid and 32 ml of acetone was heated under reflux for 2 hr. The product was isolated by ether extraction to yield 480 mg of a white crystalline solid, mp 122–165°, which was chromatographed on 45 g of alumina. Elution with 1:5 chloroform–benzene gave 109 mg of 5β,6β-methanoandrost-8(9 or 14)-ene-3,17-dione (**30** or **31**), mp 141–149°. Recrystallization from acetone–water gave 77 mg: mp 150–152°; $[\alpha]^{26}D$ −90°; $\tilde{\nu}_{max}$ 3061, 1725, 1704 cm^{-1}; λ_{max} 210 mμ (ε 7400); 100-MHz nmr, 2.48 (C_8H_2, s, $W_{1/2}$ = 2 Hz), 1.555, 1.826, 2.745, 2.914 (C_4H_2, q), 0.91 ($C_{18}H_3$, s), 0.40–0.80 (cyclopropyl protons, m); molecular ion peak at *m/e* 284.

Elution of the column with chloroform gave 298 mg of **15**, mp 170–192°. Recrystallization from acetone–petroleum ether gave 218 mg, mp 194–200°. Both ir and nmr spectra were identical with those of starting materials.

Registry No.—**4b**, 5295-60-3; **5a**, 21899-70-7; **5b**, 21899-71-8; **5c**, 21889-72-9; **7**, 6037-79-2; **9**, 4677-42-3; **12**, 2352-95-6; **15**, 21899-76-3; **16**, 21899-77-4; **18**, 21899-78-5; **39**, 21899-79-6.

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2-(D-*arabino*-Tetrahydroxybutyl)pyrazine 4-N-Oxide. A Condensation Product of 2-Amino-2-deoxy-D-glucose Oxime and Glyoxal

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Condensation of 2-amino-2-deoxy-D-glucose oxime (**2**) or 2-amino-2-deoxy-D-mannose oxime (**6**) with glyoxal in water at room temperature gave 2-(D-*arabino*-tetrahydroxybutyl)pyrazine 4-N-oxide (**3**). The carbohydrate side chain of this compound was identical with that of 2,5-bis(D-*arabino*-tetrahydroxybutyl)pyrazine (fructosazine) (**9**) and 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline (**10**) according to nmr data.

In previous studies on heterocyclic compounds derived from carbohydrates, we have reported the formation of the "two-armed" pyrazines, 2,5-bis(D-*arabino*-tetrahydroxybutyl)pyrazine (fructosazine)[2a] (**9**) and 2,5-bis(D-*lyxo*-tetrahydroxybutyl)pyrazine (tagatosazine).[2b] As an extension of these studies, we report here the formation of one of the "one-armed" pyrazines. These pyrazines may have valuable medical applications, such as in chemotherapy of virus diseases, which we will report at a later date.

2-Amino-2-deoxy-D-glucose (**1**) reacts with hydroxylamine in methanol to form 2-amino-2-deoxy-D-glucose

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