Rearrangements in Five-Membered Rings of Restricted Mobility[1]

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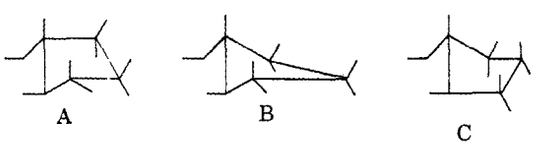
Base-catalyzed rearrangements of 16α-mesyloxy-17α-hydroxy steroid derivatives bearing a 17β-acetyl group in which the ketone is protected as the ethylene ketal proceed exclusively with ring contraction to four-membered D-ring derivatives. When the 17β substituent is an alkyl group, a competing rearrangement to 16-ketones occurs, presumably through intramolecular sulfonyl group transfer. The relative rates of these rearrangements seem to be influenced by electronic factors. *cis*-Bicyclo[3.3.0]octane derivatives bearing analogous functions also undergo ring contraction but to a lesser extent. Conformational reasoning is used to explain the rearrangement results.

In contrast to six-membered rings in which the relationship between reactivity and conformation has been extensively studied, the application of conformational reasoning to five-membered rings has played a minor role due to the mobility of cyclopentanes. This mobility can be reduced by fusion to a rigid system, providing an opportunity for the correlation of properties with specific conformations. Such studies would be appropriate in the five-membered D ring of steroids, due to the available information on their conformation. According to Brutcher, *et al.*,[2] the D ring can adopt three conformations (A, B, or C), depending on sub-

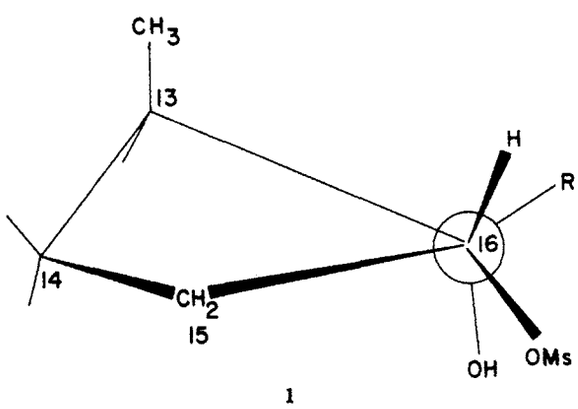


stituents present on the ring. Although these conformations do not allow complete *anti* coplanar relationship of ring bonds and bond attached to the ring, certain derivatives might adopt a conformation in which the four-center coplanar transition state, preferred in some ionic rearrangements, could be more easily attained.

A great number of rearrangements involving ring D are known,[3] but their outcome is usually determined by stereochemical considerations involving groups adjacent to ring D rather than by the conformation of the ring D itself.

The object of the present work was the investigation of base-catalyzed pinacol-type rearrangements of tertiary–secondary vicinal *cis*-diol monosulfonates located on five-membered rings of steroids or bicyclic systems. When such rearrangements occur in six-membered rings, they are known to result in ring contraction if the migrating bond in the ring and the leaving group adopt an *anti* coplanar conformation. In order to perform an analogous ring contraction of a five-membered to a four-membered ring, the necessary functions had to be placed in a way compelling the ring to adopt a conformation in which the bonds involved would be nearest to coplanarity. The appreciable angle strain involved in such a ring contraction also had to be taken into consideration; thus the occurrence of an alternative transformation could not be excluded *a priori*.

Steroidal D rings bearing a 17β side chain and 17α-hydroxy-16α-mesyloxy functions were considered conformationally appropriate for performing such rearrangements. Envelope C is considered to be the conformation of lowest energy for 17β-substituted D rings.[2] The 1,3-interaction between the 17α-hydroxyl and the 14α-hydrogen which might be expected to destabilize envelope C in favor of the half-chair B is counteracted by the presence of the 16α-mesyloxy grouping; examination of Dreiding models[4] shows that in conformation C the 1,3 interaction between the C-14 hydrogen and the C-16 group is weaker than in conformation B. The chances for a ring contraction in a base-promoted rearrangement were thus enhanced because in the envelope C the 13,17 bond and the leaving group are nearest to coplanarity[5,6] as seen in the Newman projection of the D ring, viewed from C-16 toward C-17 (1).



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Our studies were first conducted on a system bearing a 17β-acetyl side chain, in which the ketone was protected as the ethylene ketal in order to prevent the possibility of D-homoannulation occurring under basic conditions, because of the presence of the 17α-hydroxyl group. Thus 5α-pregn-16-en-3β-ol-20-one 3-acetate (I)[7] was converted into the corresponding ethylene ketal II and then hydroxylated with osmium tetroxide in pyridine, affording selectively the 16α,17α-diol derivative III. Treatment of III with methanesulfonyl chloride in pyridine yielded the mesylate IV, which, on exposure to potassium *t*-butoxide in *t*-butyl

(1) For preliminary reports regarding part of the present work, see (a) E. Ghera, *Tetrahedron Letters*, 4181 (1965), and (b) E. Ghera, *ibid.*, 17 (1966).

(2) (a) F. V. Brutcher, Jr., and W. Bauer, *J. Amer. Chem. Soc.*, **84**, 2236 (1962); (b) F. V. Brutcher, Jr., and E. J. Leopold, *ibid.*, **88**, 3156 (1966).

(3) For a review, see N. L. Wendler in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 1099.

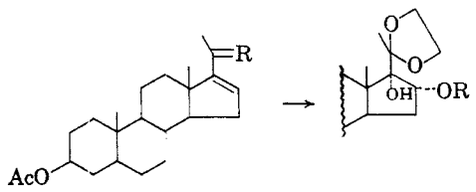
(4) A. S. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(5) The deviation from coplanarity of the involved bonds, as measured with the help of Dreiding models, is approximately 30 ± 5° for conformation C, 46 ± 5° for conformation B, and 64 ± 5° for conformation A. See ref 6 for measurements which allow the deduction of similar angles.

(6) A. D. Cross and P. Crabbé, *J. Amer. Chem. Soc.*, **86**, 1221 (1964).

(7) P. Crabbé, M. Perez, and G. Vera, *Can. J. Chem.*, **41**, 156 (1963).

alcohol solution, was converted into a mixture of crystalline products. Separation by column chroma-

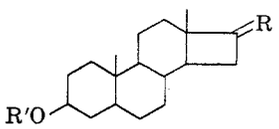


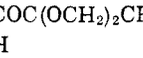
I, R = O
II, R = $(OCH_2)_2$
III, R = H
IV, R = Ms

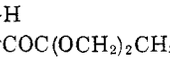
tography showed that this mixture consisted exclusively of two isomers, which have been formulated as the C-16 epimeric 3β-hydroxy-5α-21-methyl-21,21-ethylenedioxy-D-norpregnan-20-ones V and VI on the basis of both spectroscopic and degradative evidence. Both epimers exhibited a carbonyl band at 5.83 μ in their infrared spectra, the rather low wavelength absorption band for a ketone vicinal to a cyclobutane ring being due to the adjacent ethylenedioxy group.[8] The nmr spectrum of the major epimer (V), on which most of the identification work has been done, contained a double doublet corresponding to one proton at 3.16 ppm, which is attributed to the 16α-hydrogen split by the two C-15 protons. The signal of the ethylenedioxy grouping appeared as a singlet due to the magnetically equivalent environment of the four protons and the C-18 methyl protons resonated at 0.87 ppm. In the 16α epimer VI the C-18 methyl protons were deshielded, the signal being shifted to 1.26 ppm. This difference in the chemical shift of C-18 protons (23–24 cps), which has been found subsequently to be constant for other pairs of 20-keto-D-nor 16-epimers, is somewhat greater than the constant difference of 17 cps reported[9] for C-17 epimeric pregnane derivatives and is probably due to a change in the geometry of the angular methyl group relative to the C-20 ketone. In both 16α and 16β epimers the C-18 methyl protons appear shifted relatively downfield by comparison with analogous normal pregnane derivatives.[9] The assignment of configuration at C-16 has been confirmed by the Cotton effect in the ORD which is positive for the major isomer V and negative for VI.[10]

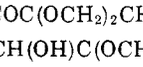
The composition of the mixture of the two epimers formed under the equilibrating conditions of the rearrangement could be determined by measurement of the optical rotation of the mixture, since the rotations of the pure epimers were known, and was found to be *ca.* 71% of V and 29% of VI. Treatment of either epimer with base under equilibrating conditions resulted in the formation of the same epimeric mixture as obtained from conversion of mesylate IV, thus proving that the carbonyl group was adjacent to the epimerizable center.

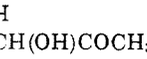
Unequivocal proof for the assigned structures was provided by chemical degradation. The removal of the ethylene ketal grouping, as a first step toward the intended degradation, could not be achieved with either epimer, even by prolonged heating with acid. The stability of the ketal grouping may be attributed to the difficulty of formation of an intermediate cation located α to a ketone. An analogous case of a stable α-keto ethylene ketal in a steroid side chain has been previously recorded,[8] although explained differently. Reduction of V by means of sodium borohydride in methanol afforded the diols VII (epimeric mixture) in which the ketal grouping could be easily cleaved under standard acidic conditions yielding the ketol derivatives VIII. Further reduction with lithium aluminum hydride afforded the triols IX which on cleavage with sodium periodate furnished an air-sensitive aldehyde X characterized by its infrared and nmr spectra. Acetylation of the C-3 hydroxyl group followed by oxidation using the Jones procedure[11] afforded the D-nor-16β-carboxylic acid, XI, identical with an authentic sample.[12]

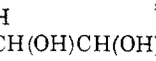


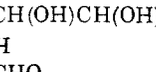
V, R =  ; R′ = H

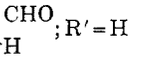
VI, R =  ; R′ = H

VII, R =  ; R′ = H

VIII, R =  ; R′ = H

IX, R =  ; R′ = H

X, R =  ; R′ = H

XI, R =  ; R′ = Ac

The generality of this ring contraction in steroid derivatives bearing the same substituents in ring D has been demonstrated by performing the rearrangement on an additional system with an aromatic ring A. The mesylate XVI was prepared starting from 3-acetoxy-19-norpregna-1,3,5(10),16-tetraen-20-one, XII (see Experimental Section), and rearranged under similar conditions to a mixture of epimers from which the major 16β-D-nor epimer XXIV has been isolated in a 52% yield. The relative magnitude of the two C-18 signals in the nmr spectrum showed that the ratio of epimers is similar to that found in the previously described rearrangement.

Thus the course of the base-catalyzed rearrangement in the systems described proceeds exclusively with ring contraction and provides a convenient method for the synthesis of various D-nor steroids.[13] Other products, which could have resulted by alternative 1,2 migration of the 17β side chain or by base-promoted elimination, have not been detected.

Our attention was next turned to the investigation of the influence which an electron-donating 17β-alkyl side chain might exercise on the ring-contracting

(8) For a similar effect associated with the vicinity of an ethylenedioxy grouping, see, *e.g.*, S. Bernstein, M. Heller, and W. S. Allen, *J. Org. Chem.*, **26**, 1333 (1961).

(9) M. B. Rubin and E. C. Blossey, *ibid.*, **29**, 1932 (1964).

(10) See G. Muller, C. Huinh, and J. Mathieu, *Bull. Soc. Chim. Fr.*, 296 (1962), for circular dichroism measurements of D-norpregnenolones.

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

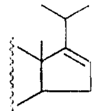
(12) J. Meinwald, G. G. Curtis, and P. G. Gasman, *J. Amer. Chem. Soc.*, **84**, 116 (1962). A sample of XI was obtained by the courtesy of Dr. H. Reimann of the Shering Corp.

(13) The only other method is the photolysis of diazo ketones which leads to D-nor-16-carboxylic acids. For literature data, see ref 1a.

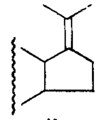
rearrangement. In rigid six-membered systems, where no ambiguity exists concerning the coplanarity of migrating and departing groups, the outcome of analogous ionic rearrangements depends only on the geometry of the molecule.[14] In the specific case of a five-membered ring in which this coplanarity is not completely achieved and the ring contraction is associated with appreciable angle strain, a change in electronic properties of the substituent could provide a reason for a different reaction course. The steric influence of a different 17β substituent (even if pseudo-equatorial) on the conformation of the D ring could be of some importance also. A 17β-*t*-butyl substituent would be sterically most similar to the side chain bearing the C-20 ethylene ketal group, although it involves some new interactions due to the six additional hydrogen atoms attached to the carbon atoms vicinal to C-20. However, attempts to condense *t*-butyllithium with androsterone, considered a possible route to the desired 17-*t*-butyl derivative, were unsuccessful, probably because of steric hindrance. Therefore, two other 16α-17α-dihydroxy derivatives, the first bearing a 17β-ethyl side chain (XVIII) and the second a 17β-isobutyl side chain (XXXI), were synthesized and their mesylates submitted to rearrangement conditions.

The synthesis of such steroidal systems presents difficulties and may be considered of intrinsic interest. One route would involve the preparation of Δ^{16}-17-alkyl derivatives which could be used for further hydroxylation of the 16,17 double bond. Thus the reduction of a C-20 ketone to a methylene group in common Δ^{16}-17-acetyl systems could provide intermediates with an ethyl side chain. However, the Wolff–Kishner reduction of α,β-unsaturated C-20 ketones is known to yield $\Delta^{17(20)}$ products,[15] whereas attempted preparation of Δ^{16}-20-thioketals, for the purpose of further reductive cleavage, was vitiated by 1,4 addition of ethanedithiol.[16]

Other possible intermediates, 17α-alkyl-17β-hydroxy derivatives, obtained by Grignard addition to 17-ketones, are usually rearranged on acid dehydration with migration of the angular C-18 methyl group or, in certain conditions, a 17,20 double bond can be formed. Only the simplest, Δ^{16}-17 methyl analog could be obtained by the pyrolysis of the corresponding 17β-acetate.[17] The use of 16α,17α-dihydroxy-20-keto derivatives as starting compounds for the reduction of the carbonyl group or alkylation at C-20 proved impractical in our hands because of the ease by which these compounds undergo D-homoannulation. The preparation of 20-methyl-5,16-pregnadien-3β-ol (partial structure i),

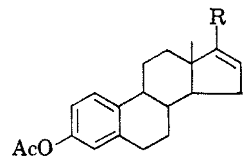


i

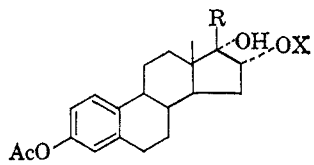


ii

which could serve for further hydroxylation, has been previously reported.[18] Repetition of the synthesis afforded a compound whose properties agreed with those reported but which exhibited no C-16 vinyl proton in the nmr spectrum. Since two methyl singlets appear at 1.59 and 1.72 ppm, it is suggested that the double bond is actually in the 17,20 position (partial structure ii).

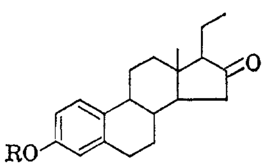


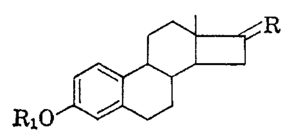
XII, R = $COCH_3$
XIII, R = $C(OCH_2)_2CH_3$
XIV, R = C≡CH



XV, R = $C(OCH_2)_2CH_3$; X = H
XVI, R = $C(OCH_2)_2CH_3$; X = Ms
XVII, R = C≡CH; X = H
XVIII, R = CH_2CH_3; X = H
XIX, R = CH_2CH_3; X = Ms
XX, R = CH_2CH_3; X = Ac
XXI, R = CH_2CH_3; X = Ts

The unreactivity of acetylenic bonds toward osmium tetroxide was exploited in the synthesis of the first system XVIII. Dehydration of 17α-ethinylestradiol 3-acetate with phosphorous oxychloride in pyridine afforded the enyne XIV in fair yield. Hydroxylation of the latter with osmium tetroxide in pyridine resulted in the exclusive formation of the 16α,17α-diol XVII as proven by nmr spectroscopic data. Catalytic hydrogenation afforded the 17β-ethyl derivative XVIII which was converted into the mesylate XIX. Treatment with potassium *t*-butoxide under conditions similar to those employed previously resulted in the conversion of XIX into a mixture of C-16 epimeric D-nor derivatives, separated as their acetates, XXV and XXVI, and an additional isomer, which was identified as 3-hydroxy-17β-ethyl-estra-1,3,5(10)trien-16-one (XXII). The percentage composition of the mixture was established by vpc analysis of the corresponding acetate mixture as 52% of 16β epimer (XXV), 20% of 16α epimer (XXVI), and 28% of XXIII.





XXII, R = H
XXIII, R = Ac

XXIV, R_1 = H; R_2 = COC$(OCH_2)_2CH_3$, H
XXV, R_1 = Ac; R_2 = $COCH_2CH_3$, H
XXVI, R_1 = Ac; R_2 = H, $COCH_2CH_3$
XXVII, R_1 = H; R_2 = OH, H
XXVIII, R_1 = H; R_2 = O

The stereochemical assignments for the C-16 epimers were made on the basis of the C-18 methyl signal in the nmr spectrum observed at 0.87 ppm in XXV and 1.27 ppm in XXVI and were confirmed by the signs of the Cotton effects of the ORD curves. The conversion of each epimer by base treatment into a mixture of both proved here too that the epimeric center is vicinal to the

(14) See ref 3, p 1084, for a review with references on this subject.

(15) R. Fischer, G. Lardelli, and O. Jeger, *Helv. Chim. Acta*, **33**, 1335 (1950).

(16) E. Ghera, unpublished results. See also J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Amer. Chem. Soc.*, **73**, 1528 (1951).

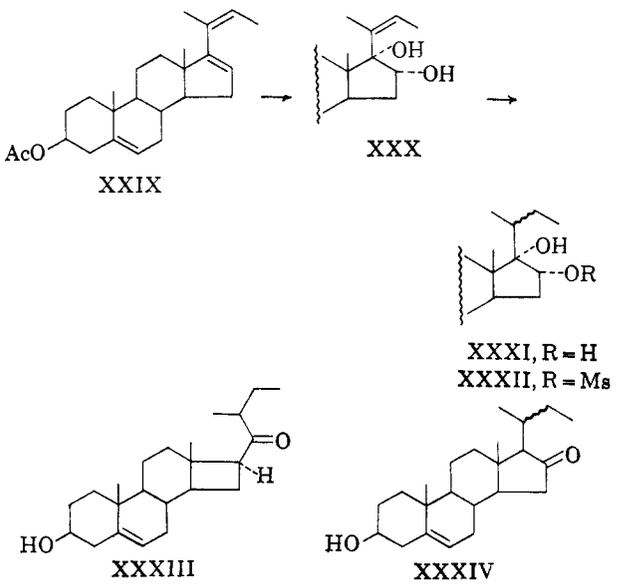
(17) C. Beard, J. M. Wilson, H. Budzikiewicz, and C. Djerassi, *ibid.*, **86**, 269 (1964).

(18) J. P. Dusza and W. Bergmann, *J. Org. Chem.*, **25**, 79 (1960).

carbonyl group. The degradative evidence was obtained by submitting a mixture of XXV and XXVI to Baeyer–Villiger oxidation followed by hydrolysis of the derived esters to a mixture of C-16 epimeric D-norestradiols XXVII. Oxidation by the Jones procedure[11] afforded D-norestrone XXVIII, the structure of which was established by the characteristic infrared carbonyl absorption band and by mass spectral evidence.

The third isomer obtained from the rearrangement exhibited in the infrared spectrum the absorption band of a five-membered cyclic ketone and, therefore, might have been expected to be a 16-substituted 17-ketone formed by the 1,2 migration of the side chain. Such a migration would be expected to compete with ring contraction in the case of ambiguous coplanarity conditions or due to sufficient mobility of the cyclopentane ring. However, this assumption was disproved by the negative Cotton effect of the ORD curve which was incompatible with the proposed structure but characteristic of 14α-17β-alkyl 16-ketones.[17] Moreover, treatment with sodium in deuteriomethanol resulted in exchange of three hydrogen atoms in ring D, as found by mass spectroscopic evidence: the M − 28 peak, representing the loss of C-6 and C-7,[19] remained unchanged after labeling whereas the intense M − 84 and M − 85 fragments, due to the loss of ring D in the original compound,[17] are shifted in the labeled compound to M − 87 and M − 88, showing that the exchange occurred only in ring D. These results substantiated the unexpected formation of the 16-ketone XXII and the latter assignment was confirmed by an independent synthesis of XXII using a Serini reaction which consists in the treatment of a 1,2-diol monoacetate with zinc.[20] This reaction, which has been utilized mainly for the conversion of 17-hydroxy-20-acetoxy steroidal derivatives to inverted 20-ketones, was found recently of synthetic use also in other systems.[21] Heating the triol diacetate XX with zinc followed by equilibration with base yielded a product identical in all respects with the ketone XXII.

The formation of a 16-ketone occurred to an even greater extent when a branched 17β-isobutyl-substituted system (XXXII) was submitted to base-catalyzed rearrangement. The synthetic route for the preparation of XXXII started from 3β-acetoxy-pregna-5,16-dien-20-one, which in a Wittig reaction with ethylidenetriphenylphosphorane yielded a single triene XXIX, to which the *trans* configuration may be assigned because *cis*-oriented methyl groups would imply a less favorable arrangement in the transition state.[22] The reaction of triene XXIX with osmium tetroxide (1.1 equiv) at low temperature resulted in the formation of XXX in good yield by selective hydroxylation of the 16,17 double bond from the α side, while the trisubstituted double bonds of the side chain and of ring B remained untouched. In agreement with the assigned structure the nmr spectrum showed a singlet at 1.67 ppm due to the C-21 methyl attached to a double bond. The upfield shift of the C-18 methyl signal (0.62 ppm) is explained by the restricted rotation of the side chain around the 17,20 bond, which forces the angular methyl group into the shielding cone of the 20,22 double bond. Catalytic hydrogenation of XXX affected only the side chain, yielding XXXI (C-20 epimers). Exposure of the corresponding epimeric 16-mesylates XXXII to potassium *t*-butoxide under the usual conditions resulted in formation of a mixture of isomers which exhibited in the infrared spectrum the 5.78-μ band due to the 16-ketones XXXIV (C-20 epimeric mixture) and the 5.88-μ band, characteristic for C-20 ketones in C-16 D-nor epimers. The percentage composition of the mixture of products obtained from the rearrangement showed a substantial increase in formation of 16-ketones (52%) at the expense of ring-contracted C-16 epimers (48%), compared with the 17β-ethyl-substituted series. These products were separated by extensive column chromatography and the assigned structures have been confirmed by characteristic spectroscopic data, analogous to those obtained in the previous series. The structure of the 16-ketones XXXIV was supported by their negative Cotton effects in the ORD and by introduction of three deuterium atoms in ring D by deuterium exchange.



XXIX XXX XXXI, R = H XXXII, R = Ms XXXIII XXXIV

An explanation of this latter rearrangement to 16-ketones by the participation of the neighboring 17α-*cis*-hydroxyl grouping was hardly acceptable in view of the basic conditions of the reaction. Moreover, the mesylate XIX was found stable and unreactive when exposed to different solvolytic conditions and the formation of oxides or ketones was not observed. However, ketones can be formed as a result of base-promoted reactions of epoxides[23] and therefore the behavior of a 17β-alkyl-substituted 16α,17α-oxido derivative in the basic conditions of the rearrangement was investigated. An appropriate derivative has been prepared by pyrolysis of 17α-methyl-17β-acetoxyandrostane which is known to yield a mixture of *endo*- and *exo*-cyclic olefins.[17] After treatment of the latter with *m*-chloroperbenzoic acid, the pure 16α,17α-oxide XXXV was separated and exposed to potassium *t*-butoxide in *t*-butyl alcohol but proved completely stable in these conditions.

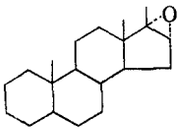
(19) C. Djerassi J. M. Wilson, H. Budzikiewicz, and J. W. Chamberlin, *J. Amer. Chem. Soc.*, **84**, 4544 (1962).

(20) For references on Serini reactions, see E. Ghera, M. Gibson, and F. Sondheimer, *ibid.*, **84**, 2953 (1962).

(21) E. Ghera and F. Sondheimer, *Tetrahedron Lett.*, 3887 (1964).

(22) See, *e.g.*, J. P. Dusza, *J. Org. Chem.*, **25**, 93 (1960), for a similar formation of one isomer.

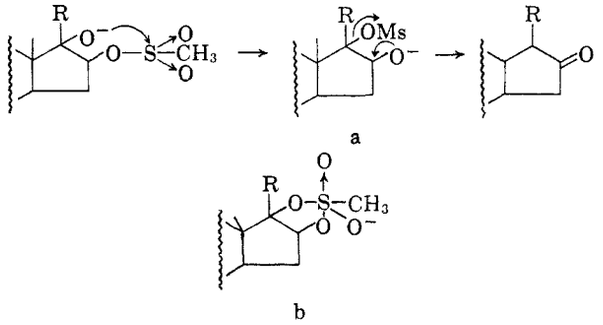
(23) J. K. Crandall and Luan-Ho Chang, *J. Org. Chem.*, **32**, 435 (1967).



XXXV

In view of these results, the possibility that the C-16 ketone originates from S–O bond cleavage in the mesylate has been taken into consideration. The base-catalyzed rearrangement would then proceed by intramolecular nucleophilic attack of the C-17 hydroxyl anion on the sulfur atom and cleavage of the S–O bond followed by a 1,2-hydrogen shift as shown in Scheme I (a); the pathway by which the transfer takes place could involve the formation of an intermediate cyclic "orthosulfonate" ion (b). Such a hypothesis seemed questionable in view of the well-documented behavior of similar *cis*-diol monosulfonates in six-membered ring systems[24] where base-catalyzed rearrangements occur by C–O bond cleavage in sulfonates; it should be noted, however, that the formation of a small amount

SCHEME I



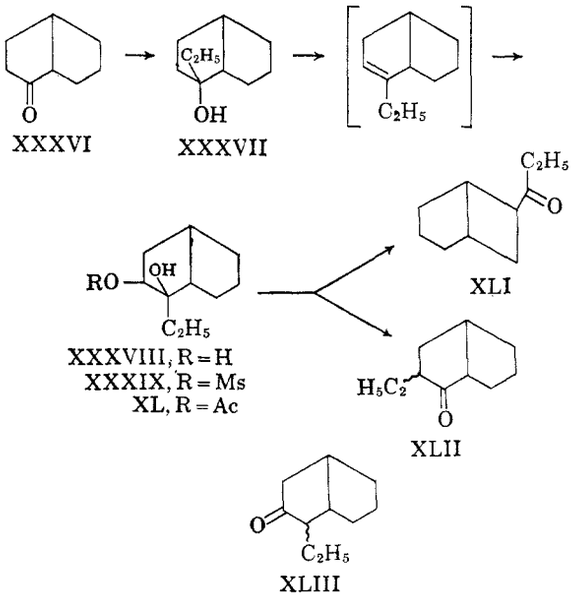
of a ketone which may have resulted by the cleavage of the S–O bond in a similar rearrangement has been observed in one instance.[25] The base-induced cleavage of the sulfur–oxygen bond has been reported to occur in "isolated" secondary sulfonate groups of carbohydrates[26] and in other systems where the displacement of the sulfonate ion by the attack of the nucleophile on carbon is sterically hindered.[27] A base-catalyzed, intramolecular sulfonyl group transfer has been reported recently in a carbohydrate system.[28]

Indirect evidence for the hypothesis of internal attack was obtained by submitting to identical rearrangement conditions the tosylate XXI instead of the mesylate XIX; the tosylate sulfur atom could be expected to be less susceptible to nucleophilic attack, due to resonance interaction with the aromatic system.[29] The composition of the mixture of products obtained from XXI, as determined by vpc analysis after acetylation, consisted from 96% D-nor epimers (XXV and XXVI) and only 4% XXIII, providing support for these considerations.

In summary, base-catalyzed reactions of the systems studied involve two competing reactions, ring contraction and rearrangement to 16-ketones. It would appear that the relative rates are influenced by electronic factors, the rate of the ring contraction being retarded by electron-donating C-17 substituents.

Finally, we investigated the behavior in analogous reactions of a *cis*-fused bicyclic derivative, *exo*-2-hydroxy-3-mesyloxy-*endo*-2-ethylbicyclo[3.3.0]octane (XXXIX) (Scheme II). Our purpose was to examine the scope of these rearrangements and their relationship to preferred conformations by using a five-membered ring of a fused system simpler than a steroid and of different strain and conformational properties.

SCHEME II



The mesylate XXXIX was prepared starting from the bicyclooctan-2-one XXXVI through the Grignard adduct XXXVII which yielded on dehydration the olefin with a trisubstituted double bond, as confirmed by the presence of a vinyl proton at 5.2 ppm in the nmr spectrum. The hydroxylation of the double bond with osmium tetroxide afforded, by attack from the less hindered side, a single, *exo*-diol XXXVIII (*vide infra*) which was converted into the corresponding mesylate.

Information on the preferred conformation of *cis*-bicyclo[3.3.0]octanes is hardly available. However, from examination of Dreiding models,[4] it seems reasonable to predict that the rings will adopt two envelope conformations in which the C-3 and C-7 atoms, respectively, will be out of the plane formed by four other atoms; in one of the envelopes the tip will be below the plane, whereas in the other it will be above, as shown in **2a**, the proposed conformation for *cis*-bicyclo[3.3.0]-octane. In this way the number of eclipsed bonds would be reduced, the 1,3 interactions between the C-2 and C-8 methylene groups and between the C-4 and C-6 groups being relieved through staggered arrangements.

(24) *Inter alia*, see N. L. Wendler, R. F. Hirschmann, H. L. Slates, and R. W. Walker, *J. Amer. Chem. Soc.*, **77**, 1632 (1955); R. B. Bates, G. Buchi, T. Matsura, and R. R. Schaffer, *ibid.*, **82**, 2327 (1960); Y. Mazur and M. Nussim, *ibid.*, **83**, 3911 (1961); N. L. Wendler, *Tetrahedron*, **11**, 213 (1960).

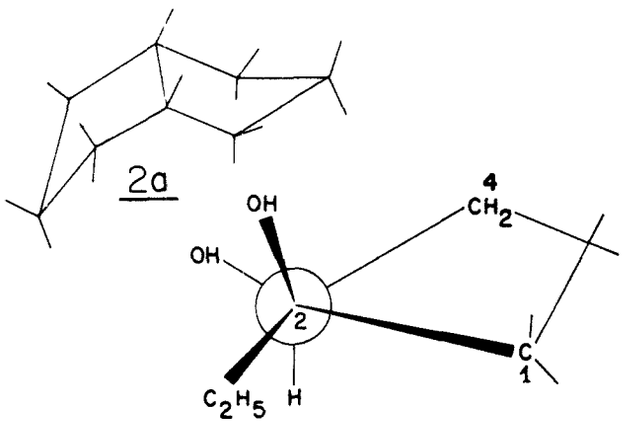
(25) N. L. Wendler and D. Taub, *J. Org. Chem.*, **23**, 953 (1958).

(26) S. P. Tipson, *Advan. Carbohydrate Chem.*, **8**, 207 (1953).

(27) *Inter alia*, see W. Huckel and H. Pietrzok, *Ann.*, **543**, 232 (1940); G. Stork, E. E. Van Tamelen, L. Y. Friedman, and A. W. Burgstahler, *J. Amer. Chem. Soc.*, **75**, 384 (1953); A. C. Cope and T. Y. Shen, *ibid.*, **78**, 5912 (1956).

(28) J. S. Brimacombe and L. C. N. Tucker, *Chem. Commun.*, 903 (1966).

(29) See, *e.g.*, E. T. Kaiser and D. H. Eargle, Jr., *J. Amer. Chem. Soc.*, **85**, 1821 (1965).



2b

Evidence for conformational preference in the substituted ring of the diol XXXVIII and mesylate XXXIX was provided by their respective nmr spectra. The C-3 *endo* proton of the diol, treated as the X portion of an ABX system, shows a triplet (J = 8.5 cps) with some broadening of the center line, whereas in the corresponding mesylate the same proton appears as a double doublet (J = 9 cps, J' = 7.5 cps). In spite of limitations imposed on the use of the Karplus relationship for the deduction of dihedral angles in strained five-membered rings containing electronegative substituents, it seems safe to assume that the two large J values exclude the possibility of bisection of the C-4 methylene group by the vicinal C-3 proton.[30] The substituted ring should thus adopt an envelope conformation with C-3 below the plane of the four other carbon atoms. The dihedral angle between the vicinal *cis*-hydroxyl groups in XXXVIII can be approximated as *ca.* 40° by the determination of the shift of OH stretching frequency in the infrared spectrum due to hydrogen bonding, using the modified Kuhn relationship.[2a] Thus the deviation from coplanarity of the migrating and departing groups would be of 20 ± 5° and the substituted ring of diol XXXVIII viewed from C-2 would appear as shown in **2b**.

The base-catalyzed rearrangement of XXXIX resulted in the formation of 2-propionylbicyclo[3.2.0]-heptane (XLI, 23%) and of the epimeric 3-ethylbicyclooctan-2-ones (XLII, 77%, about 1:1 epimeric ratio). The structure of propionylbicyclo[3.2.0]heptane followed from the characteristic mass spectral fragmentation (M − 29 and M − 57), absence of unsaturation, infrared carbonyl absorption at 5.86 μ, and the nmr spectrum of the corresponding semicarbazone which showed that the methylene group of the side chain is vicinal to the C=N bond (quartet at 2.22 ppm). As only one isomer has been detected by vpc with capillary column, it is formulated as *exo* substituted. The epimeric 3-ethyl-*cis*-bicyclooctan-2-ones have been identified by spectroscopic data and by independent synthesis from XXXVI and ethyl iodide. In the latter case the same ratio of epimers (about 1:1) has been obtained, showing their similar stability at equilibrium.[31] The presence of *cis*-2-ethyl-bicyclooctan-3-one XLIII, which could have been formed as described above in steroid rearrangements, has been ruled out by the preparation of the latter from the diol XXXVIII (by acid dehydration) and from acetate XL (by a Serini reaction). The epimeric composition of XLIII as obtained by the first method (84% *exo*- and 16% *endo*-ethyl epimer) agreed with the expected greater stability of *exo*-2-substituted bicyclooctan-3-ones, while the results of the Serini reaction (96% *exo* epimer), which was expected to proceed with inversion at C-2,[20] were in agreement with the *exo*-diol assignment for XXXVIII. Base treatment of the Serini product gave the same mixture of epimers as after acid dehydration.

The above observations show that ring contraction occurs also in the *cis*-bicyclo[3.3.0]octane system, though to a lesser extent than in the D ring of steroids. The difference in results between the two systems might be attributed to a greater mobility of the five-membered ring in the bicyclic system. Hence the 1,2 migration of the ethyl group, proceeding at a greater relative rate, can occur preferentially in the latter system in spite of the seemingly favorable conformational conditions for ring contraction. For the same reason the sulfonyl group transfer, which explains the formation of 16-ketones in the previously described rearrangements, does not take place in the bicyclic systems.

(30) See, for instance, ref 6 or P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964), for data on J in resembling strained systems and for references.

(31) See, *e.g.*, R. Granger, P. Nau, and J. Nau, *Bull. Soc. Chim. Fr.*, 1811 (1959), and preceding papers on the relative stability of 2- and 3-substituted *cis*-bicyclo[3.3.0]octanes.

Experimental Section[32]

3β-Acetoxy-20-ethylenedioxy-5α-pregn-16-ene (II).—A mixture of 750 mg of 3β-acetoxy-5α-pregn-16-en-20-one (I),[7] 100 ml of benzene, 7 ml of ethylene glycol, and 100 mg of *p*-toluenesulfonic acid was refluxed for 18 hr with stirring and azeotropic elimination of water with the help of a Dean–Stark separator. The solution was cooled, washed with aqueous sodium bicarbonate and water, dried, and the solvent was evaporated after addition of 1 drop of pyridine. Crystallization from methanol and 1 drop of pyridine yielded the ethylene ketal II (650 mg), mp 108–116°. The analytical sample melted at 120–122° (from methanol), $[\alpha]_D$ −4°.

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.32; H, 9.40.

3β-Acetoxy-20-ethylenedioxy-5α-pregnane-16α,17α-diol (III).—To a solution of II (1.1 g) in 12 ml of purified dry pyridine was added osmium tetroxide (1.2 g) in pyridine (16 ml) and the mixture stirred for 2.5 hr. A solution of 2 g of sodium bisulfite in 30 ml of water and 7 ml of pyridine was then added and vigorous stirring continued for 5 min. After addition of water the product was isolated with chloroform by work-up in the usual manner. Chromatography using hexane and 20% chloroform afforded 840 mg of crystals, mp 192–196°, homogeneous on tlc. The analytical sample, after two crystallizations from hexane and chloroform, melted at 202–204°: $[\alpha]_D$ −6°; infrared bands at 2.84, 5.79, 7.98, 9.69, and 10.50 μ; nmr signals at 0.82 (C-19), 0.32, (C-18), 1.35 (C-21), 2.01 (acetate), 3.9 ppm br (ethylene ketal).

Anal. Calcd $C_{25}H_{40}O_6$: C, 68.77; H, 9.24. Found: C, 68.92; H, 9.10.

3β-Acetoxy-16α-methanesulfonyloxy-20-ethylenedioxy-5α-pregnan-17α-ol (IV).—To the ice-cooled solution of III (650 mg) in pyridine (3 ml) was added methanesulfonyl chloride (0.4 ml) and the solution was set aside at room temperature for 14 hr. Addition of ice water, extraction with chloroform, and work-up

(32) Melting points are uncorrected and were determined on a Kofler block. Optical rotations were measured in chloroform (*ca.* 1% solution) unless indicated otherwise. Nmr spectra were run on a Varian A-60 spectrometer in deuteriochloroform, with tetramethylsilane as internal standard. Signals are given in parts per million. Infrared spectra were determined in chloroform solution, unless indicated otherwise. The phrase "work up in the usual manner" means that the organic layer is washed with diluted (5%) hydrochloric acid, aqueous sodium bicarbonate solution, and water, dried over anhydrous sodium sulfate, and the solvent evaporated. Florisil 60/100 mesh was used for column chromatography, unless indicated otherwise.

in the usual manner afforded the crude methanesulfonate which crystallized on trituration with pentane. Chromatography on silica BDH (elution with benzene and 10% chloroform) yielded 610 mg of purified IV, mp 190–193°. The analytical sample (from hexane–chloroform) melted at 193–194°: $[\alpha]_D$ −51°; infrared bands at 5.78, 7.48, 7.94, and 8.50 μ; nmr signals at 3.02 (methanesulfonate) and 4.06 ppm br (ketal).

Anal. Calcd for $C_{26}H_{42}O_8S$: C, 60.68; H, 8.23. Found: C, 60.45; H, 8.05.

16β,- (V) and 16α,3β-Hydroxy-21-methyl-21-ethylenedioxy-5α-D-norpregnan-20-ones (VI).—A solution of purified methanesulfonate IV (630 mg) in *t*-butyl alcohol (120 ml) was added under nitrogen to a solution of *t*-potassium butoxide prepared from 200 mg of potassium and 20 ml of *t*-butyl alcohol. After 6 hr stirring under nitrogen at 70° the solution was neutralized with acetic acid, diluted with water, and extracted several times with chloroform. The combined organic layers were washed with sodium chloride solution, dried, and evaporated under reduced pressure to yield 440 mg of crystalline material homogeneous on tlc (benzene–10% methanol or cyclohexane–30% ethyl acetate as developer), mol wt 376 (mass spectroscopy). Crystallization with methanol–10% water afforded a first crop (186 mg) of the 16-β epimer V, mp 164–169°. The mother liquor was chromatographed on neutral alumina (activity II) starting with hexane and proceeding to hexane and 10–15% chloroform. Elution provided first a small amount of the 16α epimer VI (mp 134–138°) followed by a mixture of V and VI while the later fractions yielded an additional amount of 80 mg of the 16-β epimer V. Recrystallization from methanol gave an analytical sample of V: mp 170–171°; $[\alpha]_D$ +73°; λ_{max}^{EtOH} 310 mμ (ε 63); infrared bands at 5.83 and 9.68 mμ; nmr signals at 0.83 (C-19), 0.87 (C-18), 1.38 (C-21 methyl), 4.0 (ethylene ketal), and 3.16 ppm (H-16, double doublet, J = 9 cps, J' = 6 cps); ORD in methanol (*c* 0.123), $[\phi]_{350}$ +4900°, $[\phi]_{337}$ +8700°, $[\phi]_{317}$ 0°, $[\phi]_{292}$ −8400°.

Anal. Calcd for $C_{23}H_{36}O_4$; C, 73.36; H, 9.64; Found: C, 73.05; H, 9.82.

The first eluted minor epimer VI (23 mg) was crystallized from hexane and chloroform: mp 139–141°; $[\alpha]_D$ +10°. In the infrared spectrum there were observed only fine structure differences from the spectrum of epimer V; nmr signals appear at 1.26 (C-18 protons) and 3.21 ppm (H-16); ORD in methanol (*c* 0.117), $[\phi]_{350}$ −1700°, $[\phi]_{333}$ −4100°, $[\phi]_{316}$ 0°, $[\phi]_{285}$ +6800°.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.12; H, 9.44.

Optical rotation of the epimeric mixture obtained from rearrangement (after chromatographic elimination of grease and impurities) $[\alpha]_D$ +55° (value used for the calculation of the ratio of epimers in the mixture).

Base-Catalyzed Equilibrations of D-Nor Epimers V and VI.—To a 1% methanolic solution of each epimeric ketone was added a 5% solution of potassium methoxide in methanol and the two resulting solutions were kept for 24 hr under nitrogen. Dilution with water and extraction with chloroform gave, in both cases, a mixture of the two 16-epimers, exhibiting in the nmr spectrum the 0.87 and 1.26 signals of C-18 protons of about the same relative magnitude as in the mixture obtained directly from rearrangement of IV.

Conversion of 16β-D-Nor Epimer V into 3β-Acetoxy-5α-D-norandrostane-16β-carboxylic Acid XI.—To 90 mg of V in 6 ml of methanol was added 40 mg of sodium borohydride and the mixture was stirred for 3 hr at room temperature. Isolation with chloroform yielded a crystalline mixture of diols VII (75 mg, no carbonyl absorption in infrared). The crude material was dissolved in methanol (8 ml) containing 1.5 ml of diluted sulfuric acid (8% v/v). After 3 hr reflux the solution was cooled, diluted with water, and extracted with chloroform. The extract was washed with sodium bicarbonate and sodium chloride solutions, dried, and concentrated *in vacuo* affording 60 mg of crystalline ketodiols VIII; mol wt 334 (mass spectrum); carbonyl absorption in the infrared spectrum at 5.85 μ. The crude product was dissolved in dry tetrahydrofuran (5 ml) and added to a suspension of lithium aluminum hydride (40 mg) in 5 ml of dry ether. After stirring for 2 hr at room temperature the excess reagent was decomposed with a solution of sodium sulfate in water and the mixture dried with anhydrous sodium sulfate. Filtration and hot chloroform washings afforded, after evaporation of the solvent from filtrate, 52 mg of isomeric, crystalline triols IX, the infrared spectrum of which showed strong OH at 2.96 μ and was devoid of carbonyl absorption. To the solution of triols IX (52 mg) in acetone (3 ml) was added 100 mg of sodium periodate in 2.5 ml of water and the mixture stirred for 5 hr. Dilution with water, extraction with chloroform, and evaporation of solvent without excessive heating afforded the unstable aldehyde X characterized by the nmr signal at 9.77 and infrared bands at 3.68 and 5.83 μ, mol wt 292 (mass spectrum). The crude aldehyde was acetylated and the obtained crude 3-acetate was oxidized by the Jones procedure,[11] with ice cooling. Extraction with chloroform afforded 20 mg of the D-nor acid XI, which crystallized by trituration with hexane. Sublimation (125°, 0.2 mm) afforded the pure acid, mp 237–239°, identical by tlc, mixture melting point, and infrared comparison with an authentic sample.[12]

3-Acetoxy-20-ethylenedioxy-19-norpregna-1,3,5(10),16-tetraene (XIII).—To a solution of 3-acetoxy-19-norpregna-1,3,5(10),-16-tetraen-20-one (XII, 300 mg)[33] in benzene (45 ml) and ethylene glycol (3.5 ml) was added *p*-toluenesulfonic acid (30 mg) and the solution refluxed for 8 hr, water being removed with the help of a Dean–Stark tube. The work-up (as described for ethylene ketal II) afforded a residue which was reacetylated overnight in the usual manner; extraction with chloroform containing traces of pyridine and purification by chromatography (elution with hexane and 20% chloroform) afforded 210 mg of XIII, mp 94–99°. The analytical sample (from methanol) melted at 103–104°, $[\alpha]_D$ +58°.

Anal. Calcd for $C_{24}H_{30}O_4$: C, 75.36; H, 7.91. Found: C, 75.52; H, 8.10.

3-Acetoxy-20-ethylenedioxy-19-norpregna-1,3,5(10)-triene-16α,17α-diol (XV).—To a solution of 550 mg of XIII in pyridine (6 ml) was added osmium tetroxide (500 mg) in 12 ml of pyridine and the mixture stirred for 3 hr. A solution of sodium bisulfite (1 g) in water (15 ml) was then added and the mixture stirred for additional 7 min. Extraction with chloroform and work-up in the usual manner yielded a solid residue which was chromatographed. Elution with hexane and 40% chloroform yielded 410 mg of XV, mp 204–209°. The analytical sample (from hexane and chloroform) melted at 210–212°: $[\alpha]_D$ +62°; infrared bands at 2.85, 5.75, 9.60, and 10.55 μ; nmr signals at 0.87 (C-18), 1.41 (C-21), 2.26 (acetate), and 4.01 ppm br (ethylene ketal).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.32; H, 7.80.

The corresponding **16-methanesulfonate XVI** was prepared by the method described for methanesulfonate IV. The analytical sample (from hexane and chloroform) melted at 202–203°: $[\alpha]_D$ +12°; infrared bands at 5.75, 7.48, 8.20, and 8.52 μ.

Anal. Calcd for $C_{25}H_{34}O_7S$: C, 60.73; H, 6.93. Found: C, 60.42; H, 6.72.

16β-3-Hydroxy-21-methyl-21-ethylenedioxy-19-nor-D-norpregna-1,3,5(10)-trien-20-one (XXIV).—The methanesulfonate XVI (215 mg) in *t*-butyl alcohol (100 ml) was reacted with *t*-potassium butoxide (from 80 mg of potassium and 10 ml of *t*-butyl alcohol), using the same conditions and work-up as described for the rearrangement of methanesulfonate IV. The obtained residue (164 mg) showed one spot on tlc and mol wt 356 (mass spectrum). Chromatography and crystallization of the fractions eluted with chloroform–hexane (1:1) afforded 78 mg of the 16-β epimer, XXIV, mp 184–189° (from chloroform and hexane, 52% yield); recrystallization raised the melting point to 193–194°; $[\alpha]_D$ +114°; carbonyl band in the infrared spectrum at 5.83 μ; nmr signals at 0.90 (C-18), 1.42 (C-21 methyl), 3.26 (H-16, double doublet, J = 9 cps, J' = 6 cps), 4.03 ppm s (ketal).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.43; H, 8.14.

The fractions which were eluted first and the mother liquor from crystallizations of the 16β epimer contained a mixture of the latter and of the 16α epimer which was not separated in pure state but identified by the 1.29-ppm (C-18) signal in the nmr spectrum.

3-Acetoxy-17-ethinylestra-1,3,5(10),16-tetraene (XIV).—A solution of 2.4 g of ethinylestradiol 3-acetate in 20 ml of dry pyridine and 1.3 ml of freshly distilled phosphorous oxychloride was stirred at 120° for 2 hr, cooled, and poured on 100 g of ice and 25 ml of hydrochloric acid. Extraction with ether containing 20% chloroform followed by washings of the organic layer with aqueous bicarbonate solution and water yielded, after drying and evaporation of the solvent, a residue (1.64 g) homogeneous on tlc, mp 104–109° (from methanol). Filtration

(33) C. Djerassi, G. Rosenkranz, J. Iriarte, J. Berlin, and J. Romo, *J. Amer. Chem. Soc.*, **73**, 1523 (1951).

through silica and recrystallization afforded the analytical sample: mp 115–116°; $[\alpha]_D$ +48°; infrared bands at 3.02, 4.77, 5.72, 8.30 μ.

Anal. Calcd for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55. Found: C, 82.26, H, 7.53.

3-Acetoxy-17β-ethinylestra-1,3,5(10)-triene-16α,17α-diol (XVII).—To a solution of the crude enyne XIV (1.63 g) in 80 ml of pyridine was added osmium tetroxide (1.5 g) and the mixture kept in dark at room temperature for 48 hr. A solution of 1.3 g of sodium metabisulfite in 210 ml of water and 150 ml of pyridine was then added and stirring continued for 1 hr. Addition of water and extraction with chloroform in the usual manner yielded a residue which was chromatographed. Elution with hexane and 40% chloroform yielded 1.02 g of XVII: mp 182–187°; the analytical sample melted at 186–188° (from hexane and ether); $[\alpha]_D$ +45°; infrared bands at 2.90, 3.01, 5.71, and 8.30 μ; nmr signals at 0.92 (C-18) 2.55 (acetylene proton), and 4.49 ppm br (C-16).

Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39. Found: C, 74.36; H, 7.32.

3-Acetoxy-17β-ethylestra-1,3,5(10)-triene-16α,17α-diol (XVIII).—A solution of 525 mg of XVII in 15 ml of ethyl acetate was stirred in hydrogen over 2% palladium on calcium carbonate. After absorption of 1.9 molar equiv (63 ml), the hydrogenation was stopped and the catalyst filtered. The residue was chromatographically purified (elution with 30% chloroform and hexane), yielding 480 mg of XVIII, mp 106–109°. The analytical sample melted at 112–113° (from ether and pentane): $[\alpha]_D$ +22°; nmr signals at 0.75 (C-18) and 0.98 ppm t (side-chain methyl).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.53; H, 8.35.

The corresponding diacetate XX was prepared by acetylation of XVIII and purified by chromatography (hexane and 15% chloroform as eluent): mp 140–141° (from hexane); $[\alpha]_D$ −19°.

Anal. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05. Found: C, 71.75; H, 7.88.

3-Acetoxy-17β-ethyl-16α-methanesulfonyloxyestra-1,3,5(10)-trien-17α-ol (XIX).—To a cooled solution of 500 mg of XVIII in 4 ml of pyridine was added a mixture of 0.5 ml of methanesulfonyl chloride and 0.5 ml of pyridine and the reaction mixture kept overnight at 10°. Addition of ice and isolation with chloroform in the usual manner yielded the crude XIX (540 mg) homogeneous on tlc, mp 169–176°. Recrystallization (ether and hexane) raised the melting point to 177–179°: $[\alpha]_D$ +9°; infrared bands at 5.71, 8.30, 7.32, and 8.50 μ; nmr signals at 0.78 (C-18), 1.03 t (side chain methyl), 3.02 (methanesulfonate), 4.95 ppm t (H-16, J = 6 cps).

Anal. Calcd for $C_{23}H_{32}O_6S$: C, 63.29; H, 7.39. Found: C, 63.65; H, 7.42.

Base-Catalyzed Rearrangement of Methanesulfonate XIX. Isolation of 3-Hydroxy-17β-ethylestra-1,3,5(10)trien-16-one (XXII) and of Epimeric 16β-XXV and 16α-XXVI-3-Acetoxy-21-methyl-19-nor-D-norpregna-1,3,5(10)trien-20-ones.—A solution of methanesulfonate XIX (1 g) in 650 ml of *t*-butyl alcohol was added to a solution of *t*-potassium butoxide (from 800 mg of potassium and 80 ml of *t*-butyl alcohol) and the reaction mixture stirred under nitrogen at 65° for 14 hr. Work-up (as described for the rearrangement of methanesulfonate IV) yielded 710 mg of residue homogeneous on tlc, mol wt 298 (mass spectroscopy). The infrared spectrum showed two carbonyl bands at 5.79 and 5.88 μ, the latter being of greater intensity. The 16-ketone XXII (70 mg) was separated by heating the residue with benzene and filtration of the formed crystals; it exhibited in the infrared spectrum (KBr) the 5.79-μ carbonyl band; mp 282–284°; $[\alpha]_D$ (pyr) −76°; ORD in tetrahydrofuran (*c* 0.085), $[\phi]_{350}$ −2980°, $[\phi]_{324}$ −10,170°, $[\phi]_{305}$ 0°, $[\phi]_{280}$ +11,330°.

Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.32; H, 8.57.

Because of its low solubility, the 16-ketone XXII was acetylated for vpc (*vide infra*) and nmr analysis (angular methyl at 0.73) and the purity of the noncrystalline acetate XXIII was checked by reconversion to XXII.

The remainder of the material from rearrangement (640 mg) was chromatographed and all fractions eluted first (hexane and 20–30% chloroform) which showed in the infrared spectrum only the 5.88-μ carbonyl band were combined, acetylated, and the acetate mixture chromatographed again. The fractions eluted first (70 mg, hexane and 60% benzene) showed in the nmr spectrum the presence of the angular methyl at 1.27 and consisted of the 16α epimer XXVI, which could not be obtained crystalline: $[\alpha]_D$ +46°; ORD in methanol (*c* 0.087), $[\phi]_{350}$ 0°, $[\phi]_{307}$ −4500°, $[\phi]_{291}$ 0°, $[\phi]_{265}$ +8800°.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.28. Found: C, 77.52; H, 8.24.

The corresponding semicarbazone formed readily and had mp 205–207°.

Anal. Calcd for $C_{23}H_{31}N_3O_3$: C, 69.49; H, 7.86; N, 10.57. Found: C, 69.18; H, 7.81; N, 10.22.

The following chromatographic fractions yielded 180 mg of 16β epimer XXV, mp 106–112° (from pentane and traces of chloroform). The analytical sample (from methanol) melted at 114–115°: $[\alpha]_D$ +145°; nmr bands at 0.87 (C-18), 1.06 t (C-21 methyl), 2.27 (acetate); the H-16 proton was superimposed on benzilic protons at about 3 ppm; ORD in methanol (*c* 0.089), $[\phi]_{350}$ +4600°, $[\phi]_{306}$ +11,050°, $[\phi]_{286}$ 0°, $[\phi]_{265}$ −9800°.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.28. Found: C, 77.45; H, 8.16.

In a separate experiment the mixture of products, as obtained from the rearrangement of XIX, was acetylated and submitted to vpc analysis (1% XE-60 on 100–120 mesh Gaschrom Q, 5 ft × 1.8 in. column), showing the composition: XXVI (20%, relative retention time 1), XXV (52%, retention time 1.3), and XXIII (28%, retention time 1.66).

The separate equilibration of ketones XXV and XXVI, as described for the epimers V and VI, yielded in both cases epimeric mixtures of the same composition, as determined by the relative magnitude of the C-18 angular methyl signals in the nmr spectrum.

Preparation and Rearrangement of *p*-Toluenesulfonate XXI.—To a solution of XVIII (110 mg) in pyridine (2 ml) was added *p*-toluenesulfonyl chloride (150 mg) and the solution kept at room temperature overnight. Addition of water, extraction with chloroform, and work-up in the usual manner yielded 120 mg of residue which was chromatographed on silica. Elution with hexane and 10% chloroform afforded 65 mg of XXI: mp 146–148°; analytical sample (from ether and pentane) melted at 149–150°; $[\alpha]_D$ +16°.

Anal. Calcd for $C_{29}H_{36}O_6S$: C, 67.95; H, 7.08. Found: C, 67.87; H, 6.85.

The treatment of XXI with base in conditions analogous to those used on methanesulfonate XIX yielded a residue homogeneous on tlc, which exhibited in the infrared spectrum the 5.88-μ carbonyl band and a shoulder at 5.79 μ. Acetylation followed by vpc analysis in conditions identical with those used on the rearrangement products obtained from XIX showed that the mixture consisted exclusively from XXVI (25%), XXV (71%), and XXIII (4%).

Conversion of D-Nor Epimers XXV and XXVI to D-Norestrone.—To a solution containing a mixture of the D-nor epimers XXV and XXVI (100 mg) in 0.8 ml of chloroform was added 180 mg of perbenzoic acid in 3 ml of chloroform and the mixture set aside at 10° for 4 weeks. The solution was diluted with chloroform, washed with aqueous sodium bicarbonate solution, and then with water. The organic layer was dried, concentrated, and the residue dissolved in a 1% methanolic potassium hydroxide solution and heated to reflux during 10 min. After cooling the solution was diluted with water and extracted with chloroform. The residue showed on tlc the presence of a polar product which was separated chromatographically (on elution with hexane and 40% chloroform) from some unoxidized material and identified as the epimeric mixture of D-norestradiols XXVII (52 mg, mp 205–220°): mol wt 258 (mass spectrum); hydroxyl bands at 2.79 and 2.92 μ (KBr) in the infrared spectrum. Oxidation of XXVII (45 mg) in a 3 ml of acetone by the Jones procedure at ice bath temperature, followed by chromatography of the obtained product (hexane and 20% chloroform), afforded D-norestrone XXVIII (23 mg). The analytical sample melted at 263–265°: $[\alpha]_D$ (pyr) +81°; carbonyl band in the infrared spectrum at 5.64 μ; mass spectrum, *m/e* 256 (molecular ion), 228, 214, 199, 186.

Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.45; H, 7.92.

Deuteration of Ketone XXII.—The ketone XXII (12 mg) was dissolved in deuteriomethanol (5 ml) containing 20% heavy water and 40 mg of sodium. After heating to reflux for 12 hr under nitrogen, the solution was concentrated *in vacuo* and heavy water was added. Extraction with chloroform gave 8 mg of 17,15,15-d_3-XXII, mp 266–272°, showing mass spectral peaks at 301 (M^+), *m/e* 286, 273, 214, and 213 as compared with 298

(M^+), *m/e* 283, 270, 214, and 213 in the parent, nonlabeled ketone.

Synthesis of Authentic 16-Ketone XXII.—The diacetate XX (55 mg) was thoroughly mixed with 1 g of zinc powder and the mixture was heated in a glass tube under nitrogen at 160° for 35 min. After cooling, warm chloroform was added and the zinc was removed by filtration. The residue obtained by evaporation of the solvent (38 mg) was dissolved in a 1% methanolic potassium hydroxide solution and left overnight at room temperature. Dilution with water and extraction with chloroform yielded a residue which showed on tlc two spots, one corresponding in R_f value to that of XXII and a second, more polar spot, due probably to the triol formed by hydrolysis of the unreacted diacetate XX. Chromatographic separation (elution with 25–30% chloroform and hexane) yielded 12 mg of the less polar compound which after crystallization (benzene) was found identical with the 16-ketone XXII by mixture melting point and infrared spectrum comparison.

3β-Acetoxy-20-ethylidenepregna-5,16-diene (XXIX).—A 1.37 *N* ethereal solution of butyllithium (19.8 ml, 27 mmol), was added to 12.48 g (30 mmol) of ethyltriphenylphosphonium iodide[34] in 120 ml of dry ether with swirling, under nitrogen. After 2 hr stirring a solution of 3β-acetoxypregna-5,16-dien-20-one (2.13 g, 6 mmol) in 100 ml of ether was added and the mixture was stirred for an additional 4 hr and then allowed to stand overnight. The ether was distilled off and at the same time dry tetrahydrofuran was added and the mixture refluxed for 4 hr. Water was then added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with water until neutral, dried, and the solvent evaporated. The residue was acetylated overnight and the obtained material was chromatographed, affording 190 mg of triene XXIX (elution with 10–15% chloroform and hexane) followed by unreacted starting material (940 mg). The triene was recrystallized by dissolution in a small amount of chloroform and addition of methanol: mp 129–131°; $[\alpha]_D$ −66°; λ_{max}^{isooct} 242 mμ (ε 13,800); nmr peaks at 0.97 (C-19), 1.07 (C-18), 1.57 d (J = 7 cps, C-23), 1.74 (C-21), 2.04 (acetate), 5.30–5.88 ppm br (three vinyl protons).

Anal. Calcd for $C_{25}H_{36}O_2$: C, 81.47; H, 9.85. Found: C, 81.40; H, 9.72.

3β-Acetoxy-20-ethylidenepregn-5-ene-16α,17α-diol (XXX).—To a stirred solution of the triene **XXIX** (200 mg) in 11 ml of pyridine, kept at −20° with the help of a Dry Ice–acetone bath, was added dropwise a solution of osmium tetroxide (154 mg, 1.1 equiv) in dry tetrahydrofuran (6 ml). After 1 hr the temperature was raised to −10° and after 1 additional hour the cooling was discontinued. After 3 hr from the starting of the reaction a solution of 1.7 g of sodium metabisulfite in 20 ml of pyridine and 28 ml of water was added and the mixture stirred for 1 hr at room temperature. Addition of water and extraction with chloroform in the usual manner yielded 165 mg of product homogeneous on tlc, mp 171–178°. The analytical sample (from chloroform and hexane) melted at 182–184°: $[\alpha]_D$ −102°; nmr bands at 0.62 (C-18), 0.97 (C-19), 1.69 (C-21, partly overlapping the C-23 doublet), 2.03 (acetate), 5.40 br (H-6), and 5.62 ppm br (H-22).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.32; H, 9.45.

3β-Acetoxy-20-ethylpregn-5-ene-16α,17α-diol (XXXI, C-20 Epimers).—Purified diene (170 mg) in dioxane was added to prereduced platinum oxide in the same solvent and stirred under hydrogen. After the fast absorption of 1 equiv of hydrogen the catalyst was filtered and evaporation of filtrate yielded 154 mg of the C-20 epimeric 16α,17α-diols XXXI, mp 146–165°, showing a single spot on tlc and nmr signals at 0.79 (C-18), 1.02 (C-19), 2.02 (acetate), 5.40 ppm br (H-6).

Anal. Calcd for $C_{25}H_{40}O_4$: C, 74.22; H, 9.97. Found: C, 74.34; H, 9.80.

The corresponding mixture of **C-20 epimeric 16-methanesulfonates XXXII** was prepared in 80% yield as described for methanesulfonate XIX and melted between 190 and 202°: nmr signals at 0.83 (C-18), 1.04 (C-19), and 3.08 ppm (methanesulfonate).

Anal. Calcd for $C_{26}H_{42}O_6S$: C, 64.71; H, 8.77. Found: C, 64.95; H, 8.60.

3β-Hydroxy-21-methyl-21-ethyl-16β-D-norpregn-5-en-20-one (XXXIII) and C-20 Epimeric Mixture of 3β-Hydroxy-20-ethylpregn-5-en-16-ones (XXXIV).—Treatment of methanesulfonate XXXII (540 mg) with base during 7 hr at 70° using the reagents and work-up as described for methanesulfonate XIX yielded 360 mg of residue which exhibited a single spot on tlc, mol wt 334 (mass spectrum), and showed two carbonyl bands, at 5.78 and 5.88, in the infrared spectrum. Complete chromatographic separation of all obtained isomers was precluded by their almost identical polarity. However, careful chromatography on 30 g of Florisil, using hexane and 20–30% chloroform, provided at first fractions containing the two C-16 substituted D-nor epimers which exhibited only the 5.88-μ carbonyl band in the infrared spectrum (115 mg). Two crystallizations from methanol and 10% water afforded the pure 16β epimer XXXIII: mp 131–132°; $[\alpha]_D$ +49°; nmr signals at 0.90 (C-18), 1.02 (C-19), 3.05 br (H-16), 5.40 ppm br (H-6); ORD in methanol (*c* 0.095), $[\phi]_{350}$ +1100°; $[\phi]_{315}$ +9059°, $[\phi]_{298}$ 0°, $[\phi]_{276}$ −12,600°.

Anal. Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.00; H, 10.36.

The mother liquor from crystallizations of XXXIII contained the corresponding 16α epimer (C-18 protons at 1.29 in the nmr spectrum and negative Cotton effect in ORD) which could not be obtained completely free from the major 16β epimer. Continued elution provided after some intermediate fractions a mixture of 20α- and 20β-ethyl 16-ketones XXXIV, which crystallized on trituration with pentane, melted in the range 79–96°, and exhibited the 5.78-μ carbonyl band in the infrared region. The mass spectrum showed the following fragmentation: *m/e* 344 (M^+), 326, 315, 311, 273, 259, and 213. ORD in methanol (*c* 0.092) showed $[\phi]_{370}$ −1150°, $[\phi]_{320}$ −10,300°, $[\phi]_{303}$ 0°, $[\phi]_{278}$ +10,700°.

Anal. Calcd for $C_{23}O_2H_{36}$: C, 80.18; H, 10.53. Found: C, 80.40; H, 10.62.

Deuteration of XXXIV (as described for XXII, with reflux for 1 hr) afforded 17,15,15-d_3-XXXIV, which showed the following peaks in mass spectrum: *m/e* 347 (M^+), 329, 318, 314, 276, 262, and 213.

The crude mixture obtained from rearrangement consisted from *ca.* 48% D-nor epimers and 52% 16-ketones XXXIV, as found by repeated chromatographic separation and by comparative infrared analysis: weighed amounts of D-nor epimers and of XXXIV were mixed and the sizes of the two carbonyl bands in the resulting mixture were compared with the relative sizes of the corresponding bands in the crude mixture of isomers.

Solvolytic Experiments with Methanesulfonate XIV.—The methanesulfonate XIV (100 mg) was submitted to the following reactions: reflux during 24 hr in 5 ml of glacial acetic acid containing 0.2 g of potassium acetate, reflux for 24 hr in *t*-butyl alcohol, stirring in 10 ml of *t*-butyl alcohol containing 2 ml of formic acid and 1 ml of water at 50° for 24 hr. The starting material was recovered unchanged from all these reactions. Prolonged boiling (48 hr) in glacial acetic acid (10 ml) in the presence of acetic anhydride (1 ml) resulted in the formation of a new unsaturated product (tetramitromethane test) due probably to the migration of the C-18 angular methyl and formation of a 13,14 double bond (no vinyl proton in nmr). The absence of a new carbonyl or oxide function in this product was proven by infrared and nmr spectroscopy.

Preparation and Treatment with Base of 17β-Methyl-16α,17α-oxido-5α-androstane (XXXV).—The pyrolysis of 17α-methyl-17β-acetoxy-5α-androstane[17] yielded a mixture of two olefins, the Δ^{16}-17-methyl derivative being the major component (70–80%, according to the magnitude of the vinyl proton shift at 5.26 in the nmr spectrum). This mixture (80 mg) was dissolved in 4 ml of chloroform and *m*-chloroperbenzoic acid (80 mg) was added. After being allowed to stand for 16 hr at room temperature the reaction mixture was diluted with chloroform, washed with sodium bicarbonate solution and water, dried, and evaporated. The residue (70 mg) was twice crystallized from methanol yielding the oxide XXXV (32 mg): mp 153–155°; $[\alpha]_D$ +25°; nmr signals at 0.74 and 0.78 (angular methyls), 1.35 s (C-17 methyl), and 3.18 ppm (H-16, $W_{1/2}$ = 2.5 cps).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.42; H, 11.23.

After being kept in the usual basic conditions (as described for the rearrangement of methanesulfonates) during 24 hr at 70°, the starting material was recovered unchanged (tlc, infrared, melting point).

***cis,exo*-1-Ethylbicyclo[3.3.0]octan-*endo*-1-ol (XXXVII).**—A solution of *cis*-bicyclo[3.3.0]octan-2-one[35] (XXXVI, 6.2 g) in 30 ml of dry ether was added to the reagent prepared from 2.4 g

(34) A. M. Kubriner and E. P. Oliveto, *J. Org. Chem.*, **31**, 24 (1966).

(35) A. C. Cope and W. R. Schmitz, *J. Amer. Chem. Soc.*, **72**, 3056 (1950).

of Mg, 15.6 g of ethyl iodide, and 150 ml of ether. The mixture was stirred overnight at room temperature, then treated with ice and diluted hydrochloric acid and extracted with ether. After removal of the solvent the residue was purified by distillation, yielding 4.8 g of the carbinol: bp 72–73° (5 mm); n_D 1.492.

Anal. Calcd for $C_{10}H_{18}O$: C, 86.88; H, 13.12. Found: C, 86.53; H, 13.20.

***cis,endo*-2-Ethylbicyclo[3.3.0]octane-*exo,exo*-2,3-diol (XXXVIII).**—Crude XXXVII (2.8 g) was refluxed in benzene (80 ml) and *p*-toluenesulfonic acid (200 mg) for 3 hr. The solution was then cooled, washed with aqueous sodium bicarbonate and water, dried, and concentrated to 30 ml at normal pressure. The nmr spectrum of this solution exhibited the presence of a vinyl proton (5.2 br). Osmium tetroxide (5 g) in ether (40 ml) was added to the above benzene solution of the olefin and the mixture was allowed to stand in the dark for 48 hr. Chloroform (60 ml) was then added and hydrogen sulfide passed through the mixture for 5 min using external cooling with cold water. After 2 hr the formed precipitate was removed by filtration, the filtrate evaporated, and the residue chromatographed. Elution with hexane and chloroform (1:1) yielded 1.2 g of XXXVIII: mp 82–83° (from pentane–ether); nmr signals at 0.98 t (methyl) and 3.78 ppm t (C-3, J = 8.5 cps); infrared bands (CCl_4), 3640 (free OH) and 3576 cm^{-1} (bonded OH); $\Delta\nu$ 64 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.35; H, 10.54.

The corresponding **3-acetate (XL)** had mp 73–74° (from pentane, at cold).

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.70; H, 9.45.

The corresponding **3-methanesulfonate (XXXIX)** was prepared in the usual way (6 hr, room temperature): mp 74–75° (from ether and pentane); nmr signals at 1.02 t (methyl) and 4.65 ppm dd (J = 8.5 cps, J' = 7.5 cps).

Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.22; H, 8.12. Found: C, 53.06; H, 8.16.

Base-Catalyzed Rearrangement of Methanesulfonate XXXIX.—A solution of XXXIX (330 mg) in 15 ml of ether was added to a solution of *t*-potassium butoxide (containing 80 mg of potassium) in 5 ml of *t*-butyl alcohol and the mixture stirred for 1.5 hr at 35° under nitrogen. Addition of water was followed by extraction with ether and removal of the solvent on a water bath at normal pressure with the help of a Vigreux column. The residue showed one homogeneous spot on tlc, the conversion being most probably near to quantitative. A vpc analysis using a 70-m glass capillary column coated with a ureide[36] showed the presence of three products: ***cis,exo*-2-propionylbicyclo[3.2.0]heptane XLI** (23%, relative retention time 100) and the epimeric ***cis*-3-ethylbicyclo[3.3.0]octan-2-ones XLII** (*endo* and *exo*, 77%, retention times 106 and 107.5, in about 1:1 ratio). The liquid bicycloheptane XLI was separated by chromatography of the residue on alumina Woelm activity I (elution with pentane and 1% ether) and showed a carbonyl band in the infrared spectrum at 5.86 μ, negative tetranitromethane test and mass spectral peaks at m/e 152 (M^+), 123, 95, and 85.

The corresponding semicarbazone had mp 172–173° (from methanol) and exhibited nmr signals at 1.06 t (methyl) and 2.23 ppm qu (methylene group vicinal to methyl).

Anal. Calcd for $C_{11}H_{19}ON_3$: C, 63.13; H, 9.15; N, 20.08. Found: C, 62.90; H, 8.96; N, 20.15.

The epimers XLII were eluted next and showed in the infrared spectrum a carbonyl band at 5.78 μ and in the mass spectrum m/e 152 (M^+) and 124; these peaks were shifted after deuteration (by the usual method described previously for the deuteration of 16-ketone XXXIV) to m/e 154 and 126.

(36) B. Feibush and E. Gil-Av, *J. Gas Chromatog.*, **5**, 257 (1967).

Preparation of Authentic *cis*-3-Ethylbicyclooctan-2-ones XLII.—To a solution of *t*-potassium butoxide (from 30 mg of potassium) in *t*-butyl alcohol was added bicyclooctan-2-one (XXXVI, 160 mg) in 5 ml of dry ether followed by ethyl iodide (140 mg) in 5 ml of ether and the mixture stirred under nitrogen for 7 hr at 70°. Addition of water and extraction with pentane yielded a mixture which contained, except unreacted starting material, the two epimers XLII in the same ratio as obtained from rearrangement (identification by vpc analysis[36] with injection of a mixed sample and mass spectrum).

Preparation of Epimeric *cis*-2-Ethylbicyclooctan-3-ones XLIII. A. By Acid Dehydration of XXXVIII.—The diol XXXVIII (30 mg) was dissolved in 3 ml of ethyl alcohol containing 0.2 ml of sulfuric acid and the solution was boiled under reflux for 1.5 hr. Isolation with ether yielded, after evaporation of the solvent at normal pressure, a material which showed one spot on tlc and a carbonyl band in the infrared spectrum at 5.77 μ; vpc analysis showed two peaks, corresponding to the *exo*-substituted epimer XLIII, 84%, retention time 112 (relative to previously described isomers) and the *endo* epimer XLIII (16%, retention time 128): mass spectral peaks, m/e 152 (M^+) and 124.

B. From the Acetate XL by a Serini Reaction.—To the acetate XL (40 mg) dissolved in 1.5 ml of toluene was added 500 mg of zinc and the mixture boiled under reflux, with stirring, during 14 hr. The zinc was removed by filtration and washed with ether and the filtrate washed with water, dried, and evaporated under normal pressure on a water bath. Vpc analysis in the previously mentioned conditions showed that the product contained mostly the *exo* epimer (96%) and only traces (4%) of the *endo* epimer. The semicarbazone of *exo* XLIII had mp 178–179° (from methanol).

Anal. Calcd for $C_{11}H_{19}ON_3$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.20; H, 9.32; N, 20.35.

Treatment of the Serini product with 1 *N* methanolic potassium hydroxide at room temperature (16 hr under nitrogen) increased the relative amount of the *endo* epimer to 16% (by vpc analysis).

Registry No.—II, 4787-61-5; III, 4787-62-6; IV, 4787-63-7; V, 4787-64-8; VI, 4787-65-9; XI, 4787-66-0; XIII, 4787-67-1; XIV, 14030-45-6; XV, 4787-68-2; XVI, 4787-69-3; XVII, 15261-27-5; XVIII, 14030-46-7; XIX, 14030-47-8; XX, 15476-25-2; XXI, 15493-83-1; XXII, 14038-18-7; 17,15,15-d_3-XXII, 15476-26-3; XXIV, 4787-70-6; XXV, 15476-19-4; XXVI, 14188-71-7; XXVI semicarbazone, 15493-85-3; XXVIII, 14038-17-6; XXIX, 15471-65-5; XXX, 14038-19-8; XXXI-20-α, 14188-73-9; XXXI-20-β, 15493-87-5; XXXII-20-α, 15493-67-1; XXXII-20-β, 15493-68-2; XXXIII, 14038-21-2; XXXIV-20-α, 15476-09-2; XXXIV-20-β, 15622-66-9; XXXV, 15493-70-6; XXXVII 15493-71-7; XXXVIII, 15476-10-5; XXXIX, 15476-18-2; XL, 15476-11-6; XLI, 15476-12-7; XLI semicarbazone, 15493-72-8; XLII (*endo*), 15476-13-8; XLII (*exo*), 15476-14-9; XLIII (*endo*), 15476-15-0; XLIII (*exo*), 15476-16-1; XLIII (*exo*) semicarbazone, 15476-17-2.

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