An Etiojervane Analog of Testosterone

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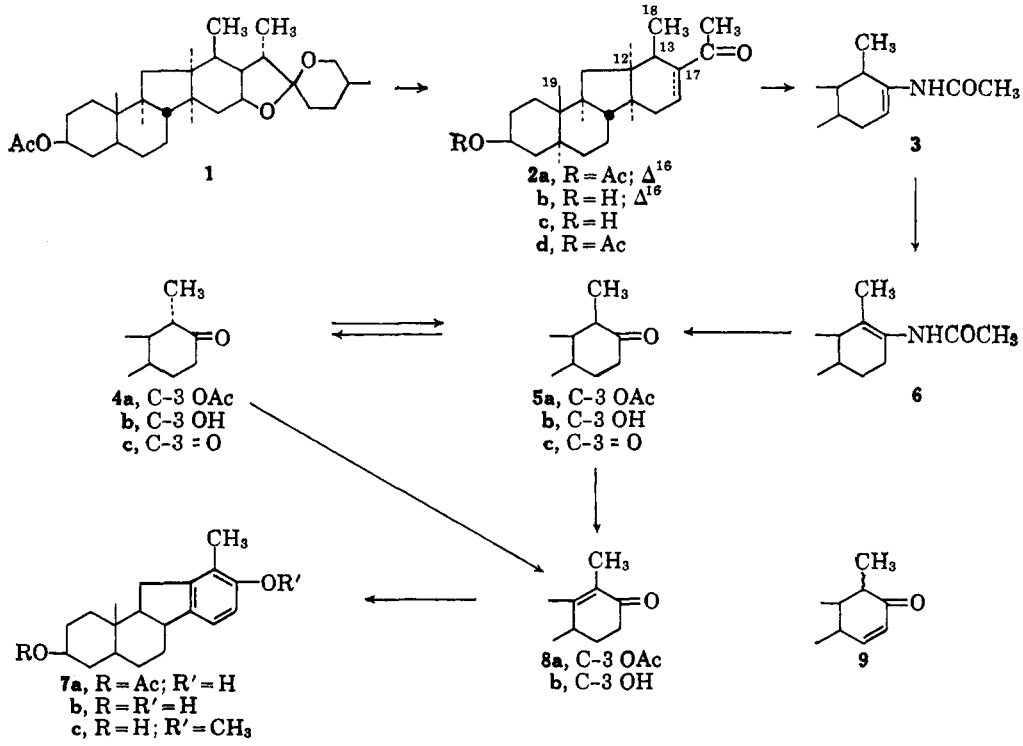
3β-Hydroxyetiojervan-17-one (**4b**) and its C-13 epimer **5b** have been prepared from the unsaturated ketone **2a**. From consideration of their O.R.D. curves and n.m.r. spectra, the former ketone is postulated to be in the steroid conformation as a twist form; the latter is in the nonsteroid conformation and affords an example of diamagnetic shielding. The preponderant ketone **4** has been converted to a variety of compounds including the aromatized compound **7** and the testosterone analog **12b**.

The unsaturated ketone **2a**, readily available[1,2] from the C-nor-D-homosapogenin (**1**), has provided a valuable starting point for the synthesis of etiojervane derivatives having the same C/D ring fusion (*cis*-α) found in the naturally occurring veratrum alkaloids.[3] Preparation of several androstane analogs in this series[4] was undertaken to explore their chemistry, stereochemistry, and biological activity.

SCHEME I



Degradation of the two-carbon side chain of ketone **2a** by use of the Beckmann rearrangement employed procedures described in pregnane chemistry.[5] Accordingly, the oxime of ketone **2a** was prepared and treated with phosphorus oxychloride in pyridine. Decomposition of the reaction mixture with cold water produced an enamide (**3**) different from that obtained when excess acid was present. Nonaqueous acid effected a rapid and essentially complete isomerization of enamide **3** to this second enamide (**6**) (see Scheme I). The difference between the two enamides was clearly disclosed by their respective n.m.r. spectra, the former showing a vinyl proton and a secondary methyl group, the latter a vinyl methyl group. The double bond migration involved is presumably a result of relief of steric strain and increase of hyperconjugative stability. The imine structure for either **3** or **6** was ruled out by the n.m.r. spectra: each compound shows a proton attached to nitrogen (a signal at 396 c.p.s., deleted by exchange with deuterium oxide). Neither enamide exhibits an ultraviolet maximum such as is shown by the corresponding pregnane derivatives; this is ascribed to an inhibition of resonance caused by steric interaction between the 18-methyl and the amide group.

Acid hydrolysis of either enamide **3** or **6** afforded a mixture of two hydroxy ketones, **4b** and **5b**. Separation of the components, achieved by chromatography and fractional crystallization, was followed easily by their distinctive n.m.r. spectra (see below). The two compounds were shown to be epimeric by virtue of their facile conversion with acid or base treatment to the same equilibrium mixture. The epimer **4b** was seen to predominate in this mixture (7:1). The less soluble

(1) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964).

(2) H. Mitsuhashi, K. Shibata, T. Sato, and Y. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **12**, 1 (1964).

(3) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 867.

(4) S. M. Kupchan and S. D. Levine [*J. Am. Chem. Soc.*, **86**, 701 (1964)] have recently reported the synthesis of similar compounds with a C/D-*trans* ring juncture.

(5) E. Testa and F. Fava, *Gazz. chim. ital.*, **87**, 971 (1957); G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).

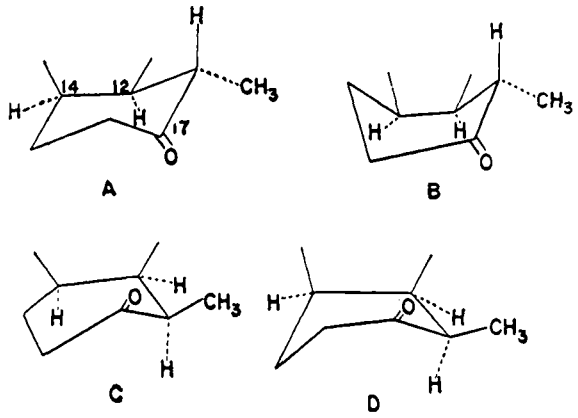


Figure 1.

major component (**4a**), in essentially pure form, could be obtained directly from the Beckmann rearrangement reaction mixture under controlled heterogeneous conditions.

To provide evidence for the stereochemical relationship of the saturated ketones **4** and **5** with the starting unsaturated ketone **2a**, the latter was reduced to its saturated derivative **2d**.[6] The facility of the reduction and the demonstrated stability[7] to isomerization of the double bond in the starting material **2a** make epimerization of the 13-methyl group very unlikely during the course of this reaction. Baeyer–Villager oxidation of **2d** followed by saponification and chromic acid oxidation yielded an unstable diketone **5c**, readily epimerized to the same stable diketone obtained by oxidation of the major hydroxy ketone **4b**. Since C-13 is not labilized in the formation of **5c** from the unsaturated ketone **2a**, the two are shown to have identical configurations.

Two carbon atoms, C-12 and C-13, in ketones **4** and **5** have unassigned stereochemistry. The remaining carbon atoms can be assumed to have the same configurations as found in hecogenin, since none of the intermediate reactions can effect epimerization of these positions. Lacking valid chemical criteria to establish the configurations at C-12 and C-13, the physical properties were investigated. The O.R.D. curve of the major ketone showed an unusually strong positive Cotton effect. Using as models the *enantiomeric* B-norcoprostan-3-one and (+)-*cis*-8-methylhydrindan-5-one, which show negative Cotton effects, the major ketone **4** clearly contains a *cis* (and α) C/D ring juncture,[7,8] an assignment in agreement with that made earlier on mechanistic grounds for the starting sapogenin **1**.[9] Further support for this assignment is gained from the recent demonstration that the C/D-*trans*-etiojervanes have the expected negative Cotton effect.[4]

The D-ring can exist theoretically in four possible conformations, two twist and two chair forms. Octant projections predict a positive Cotton effect for only two of these, the twist and chair forms analogous to the enantiomeric "steroid conformation"[8] of the A-ring, *i.e.*, that in which a C-13β substituent is axial (see Figure 1, A and B). From the enhanced amplitude of the O.R.D. curve, the predominance of the twist form can be inferred.[10] This conclusion is plausible because of the reduction in the traditional instability of the cyclohexane boat form both by the introduction of the carbonyl group and by twisting of the ring.[11,12] An additional increment of strain introduced by the fused-ring system may also render the twist form more stable than the chair form.

The principles of conformational analysis state that the equatorial position of a cyclohexane substituent is the preferred one.[13] The methyl group of the stable ketone **4** thus would lie on the α-face of the molecule, in either twist or chair form of the "steroid conformation".[14] Support for this assignment can be derived from the n.m.r. data (see below).

The O.R.D. curve of the epimeric, thus C-13β, methyl ketone **5** displays a negative Cotton effect rather than the expected positive curve. This change in sign is explained by the transformation of the D-ring into the nonsteroid conformation (C-13β equatorial, see Figure 1, C and D), for which either chair or twist form would be predicted from the octant rule to have a negative Cotton effect. Conformational change as a result of methyl group epimerization can be rationalized by noting in the steroid conformation the strong Van der Waal's interaction between the 13β- and the 19-methyl groups for either twist or chair form as well as a 13β-methyl–15β-hydrogen interaction in the twist form. By change of conformation these stresses are relieved. The amplitude of the O.R.D. curve indicates the chair form predominates. However, molecular models show that the stability of this form is decreased by strain introduced from the *cis*-fused C-ring, forcing four D-ring carbons to lie in a single plane. The corresponding twist form, almost in the classical boat conformation, has an octant projection which approximates that of the normal chair form, and conceivably could be the preferred form.

The n.m.r. spectra of the methyl ketones **4** and **5** allow ready distinction of the two compounds, but this distinction is found in the signal of the 19-methyl group rather than in the doublet of the 18-methyl. In normal epimerization the change from equatorial methyl to axial methyl is distinct in geometry and in the resultant n.m.r. signals.[15] The lack of change of the epimeric (18-) methyl group signals indicates a corresponding lack of change in geometry in the epimerization, possible by the postulated change from steroid (ketone **4**) to nonsteroid (ketone **5**) conformation. In this manner *both* ketones possess an equatorial methyl group.

The upfield shift (6 c.p.s.) of the 19-methyl group absorption in the n.m.r. from major to minor ketone also agrees with the conformational changes postulated,

(6) The stereochemistry at C-17 of this compound and its derivatives are assigned tentatively, and will be discussed in a later communication.

(7) We are indebted to Professor W. Klyne, Westfield College, University of London, for providing the O.R.D. measurements of ketones **4b** and **5b** and for several stimulating discussions relating to their interpretation.

(8) C. Djerassi and W. Klyne, *J. Chem. Soc.*, 2390 (1963), and references cited there.

(9) R. Anliker, O. Rohr, and H. Heusser, *Helv. Chim. Acta*, **38**, 1171 (1955).

(10) C. Djerassi and W. Klyne, *Proc. Natl. Acad. Sci. U. S.*, **48**, 1093 (1962); C. Djerassi, P. A. Hart, and E. J. Warawa, *J. Am. Chem. Soc.*, **86**, 78 (1964).

(11) N. L. Allinger, *ibid.*, **81**, 5727 (1959).

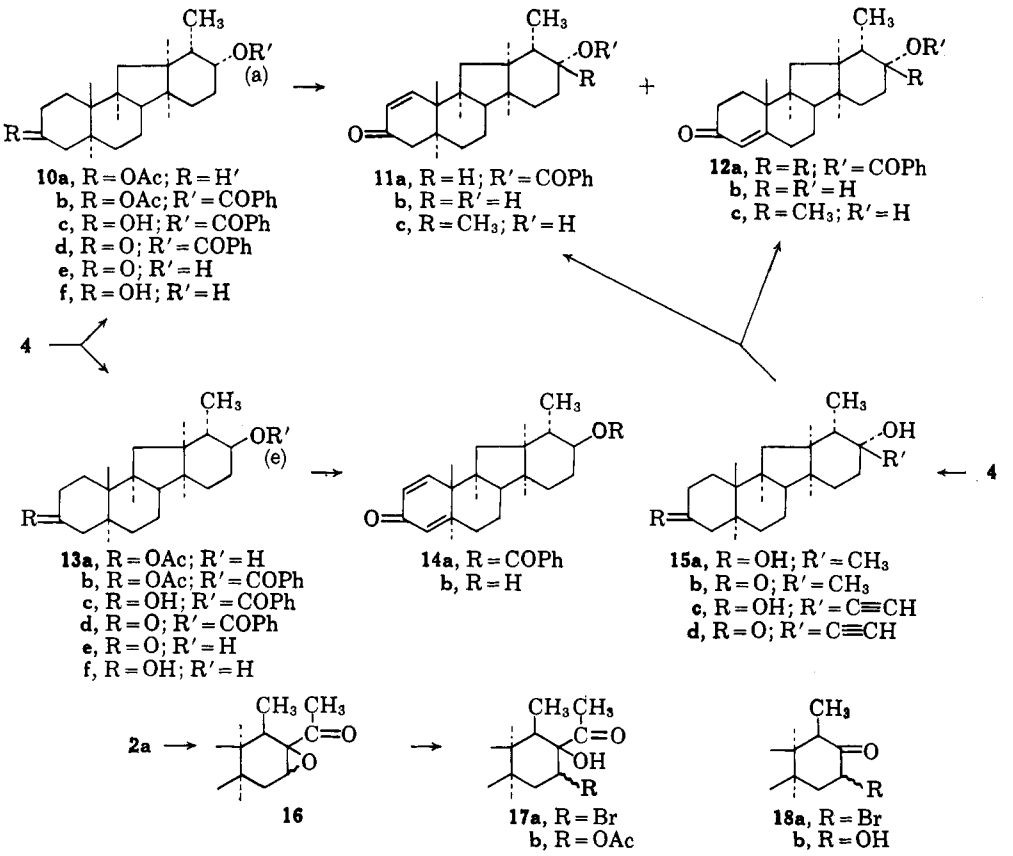
(12) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, and W. N. Hubbard, *ibid.*, **83**, 606 (1961).

(13) L. F. Fieser and M. Fieser, ref. 3, p. 14.

(14) The enhanced amplitude of the O.R.D. curve does not afford information which supports either configurational assignment: see C. Beard, C. Djerassi, J. Sicher, F. Sipos, and M. Tichy, *Tetrahedron*, **19**, 919 (1963).

(15) The shielding effect of a carbonyl function on the n.m.r. signals is discussed by R. L. Erskine and S. A. Knight, *Chem. Ind.*, (London), 1160 (1960).

SCHEME II



since in the nonsteroid conformation (ketone **5**) the 19-methyl group lies directly above the 17-carbonyl. This relationship is known to cause a diamagnetic shift.[15,16] In the major ketone (**4**) the distance between carbonyl and 19-methyl is greatly increased and the absorption of this methyl group reverts to the position found in its chemical antecedents. Having postulated the C-12 and C-13 configurations for ketones **4** and **5**, the stereochemical assignment is complete for these compounds and their precursors through compound **1**.

The unsaturated ketones **8** and **9** and their unconjugated isomers were of interest to allow study of the equilibration of C-14 and to allow substituent addition to the physiologically interesting C-12 and C-14 positions.[17] Monobromination–dehydrobromination of either ketone **4** or **5** led predominantly to the unsaturated ketone **8**, its structure being clearly indicated by the ultraviolet and n.m.r. spectra. Attempts to transform ketone **8** into either of its unconjugated isomers with acid (enol acetate formation) or base catalysis[18] were unrewarding.

Since no trace of unsaturated ketone **9** was found in the dehydrobromination mother liquors, alternate synthetic routes were investigated. The most direct of these entailed bromination of the enamide **3** under neutral conditions. The brominated material was hydrolyzed with dilute acid and was then dehydrobrominated. The unsaturated ketone fraction, a minor part of the resulting mixture, contained only ketone **8**.

Dibromination of ketone **4a** and subsequent dehydrobromination gave the phenol **7**. A milder alternate synthesis of the same phenol employed palladium–magnesium oxide dehydrogenation of unsaturated ketone **8a** at 80°.[19] Earlier attempts to effect this aromatization with N-bromosuccinimide or cupric chloride[20] were unsuccessful. The existence of the phenol affords proof of the size of the D-ring in compounds **1**–**5**. In addition, its n.m.r. spectrum confirms the relative position of the methyl group, oxygen atom, and the two aromatic protons. The methyl ether, prepared readily, was subjected to the lithium–ammonia reduction in an attempt to obtain ketone **9**. A small fraction of the product after acid hydrolysis was unsaturated ketone; this proved to be ketone **8b**, obtained previously.

Addition of substituents at C-16 in ketone **2a** produced compounds potentially degradable to 17-keto derivatives such as **18** and **9**.[21] Epoxidation of ketone **2a** proceeded very slowly to yield the oxide **16**, which was converted to the crystalline bromohydrin **17a** (see Scheme II). The 20-carbonyl group of this compound was too hindered to allow oxime formation while retaining the bromohydrin moiety. Borohydride reduction was successful; however, subsequent periodate cleavage of the resulting 17,20-glycol failed. The glycol monoacetate **17b** was prepared by osmium tetroxide catalyzed hydroxylation of ketone **2a**, but low yields discouraged further studies.

(16) O. L. Chapman, H. G. Smith, and R. W. King, *J. Am. Chem. Soc.*, **85**, 806 (1963).

(17) The hypotensive veratrum alkaloids are substituted at these positions. For leading references see L. C. Weaver, W. R. Jones, and S. M. Kupchan, *J. Pharm. Sci.*, **51**, 1144 (1962).

(18) H. J. Ringold and S. K. Malhotra, *Tetrahedron Letters*, 669 (1962).

(19) Belgian Patent 617,259 (1962).

(20) E. M. Kosower, W. J. Cole, G.-S. Wu, D. E. Cardy, and G. Meisters, *J. Org. Chem.*, **28**, 630 (1963).

(21) *Cf.* B. Ellis, D. Patel, and V. Petrow, *J. Chem. Soc.*, 800 (1958), for an analogous reaction sequence in the pregnane series.

Hydrogenation of the unsaturated ketone **8**, a potential synthetic entry to the C/D-*trans*-etiojervanes,[4] yielded almost entirely the *cis* ketone **4**. The reaction mechanism here is more complex than simple *cis* addition of hydrogen, a route which would provide the minor ketone **5**. (A separate experiment showed that the minor ketone **5** did not epimerize under the hydrogenation conditions.) Hydrogenation of 4-methylcholest-4-en-3-one affords a close precedent for this "*trans*" hydrogenation, since 4β-methylcholestanone is one of the products obtained.[22] Other mechanistic possibilities include stepwise reduction,[23] reduction of an unconjugated double bond isomer, and reduction of an enol (either homo- or heteroannular).[24] The addition of deuterium to the double bond of **8**[25] afforded a product completely lacking deuterium at C-13 as evidenced by the unchanged doublet of the C-18 methyl in the n.m.r. The stepwise hydrogenation as well as the simple *cis* addition are thus ruled out. Since addition of base during the hydrogenation did not enhance the reaction rate, the reduction probably does not involve the enol diene. The remaining mechanism, hydrogenation of a nonconjugated isomer, is presumably operative here.

To prepare the C-nor-D-homo analog of testosterone, the ketone **4a** was reduced with the bulky aluminohydride produced from triethylcarbinol.[26] The resulting mixture of isomers (**10a** and **13a**) was separable only after formation of the C-17 benzoate derivatives and hydrolysis of the C-3 acetate groups to yield the hydroxy benzoates **10c** and **13c** in roughly equal amounts.[27a] The n.m.r. spectrum of the first eluted isomer (**13c**) showed absorption for a 17-axial proton (broad signal at 285 c.p.s.).[27b] The later eluted isomer had a relatively sharp signal at 312 c.p.s., characteristic of an equatorial proton, thus axial benzoate group. The disparity in configurational assignment suggested by the order of elution (normally first for the axial ester)[13] and from the n.m.r. data can be attributed to the unusual steric hindrance found for the equatorial isomer, allowing it to be eluted first. Since there is no reason for a change from the "steroid conformation" of the parent ketone **4**, this conformation is assumed to be present here also; thus the equatorial ester group is on the β-face of the molecule.

Each of the hydroxy benzoates obtained was oxidized to the corresponding keto benzoate (**10d** and **13d**) and in turn hydrolyzed to its hydroxy ketone (**10e** and **13e**). Oxidation of each ketol led to the same diketone obtained by oxidation of the major ketone **4b**, demonstrating that no epimerization had occurred during the hydride reduction of the 17-carbonyl. The diol of each series was also obtained, the 17α-hydroxy derivative **10f** by lithium aluminum hydride reduction of the keto benzoate **10d**, and the 17β-hydroxy derivatives **13f** by hydrolysis of the 3-hydroxy benzoate **13c**. Diol **13f**, which contains an equatorial 17-hydroxyl group, was identical with the chief product of lithium–ammonia reduction of ketone **4**, and with the diol formed as a by-product in the selective hydrolysis of the mixed esters **10b** and **13b**; formation of this isomer in these two ways is consistent with the equatorial assignment for the 17-hydroxyl group.[13]

The C-17β benzoate **13d** was converted by dibromination and dehydrobromination to the dienone **14a**. Hydrolysis of the ester function provided the alcohol **14b**, the analog of 1-dehydrotestosterone.

The C-17α-benzoate **10d** was monobrominated. The monobromo compound was dehydrohalogenated with lithium bromide in dimethyl formamide to increase the proportion of Δ^4-ketone produced.[28] Product separation, aided by bisulfite adduct formation[29] and chromatography, yielded the desired isomer **12a**. A minor amount of the Δ^1-isomer **11a** was also found. Each of the isomers were saponified to the corresponding alcohols **11b** and **12b**, although the Δ^1-isomer was unusually resistant to hydrolysis.

Addition of methyl magnesium bromide to ketone **4a** produced a high yield of a single isomer **15a**. Since the Grignard reaction with a moderately hindered cyclohexanone derivative yields preponderantly the isomer with an axial hydroxyl,[30] the hydroxyl group of the adduct **15a** is assigned an α-configuration. This assignment must be regarded as tentative, however, because of the unusual steric factors involved. The C-3 hydroxyl was oxidized and the resulting ketone (**15b**) was subjected to monobromination–dehydrobromination. Chromatographic separation of the products yielded first the Δ^1-isomer **11c**. The following compound was the analog of methyl testosterone, the Δ^4-isomer **12c**.

Ethynylation of ketone **4** gave a single derivative, **15c**. Configurational assignment is made in analogy to the C-17 methyl derivative **15a**. The corresponding C-3 keto derivative **15d** was also prepared.

Experimental[31,32]

17-Acetyl-13β-etiojerv-16-en-3β-ol 3-Acetate 20-Oxime.—A solution of 17-acetyl-13β-etiojerv-16-en-3β-ol 3-acetate (**2a**, 7.5 g.)[1] and 8 g. of hydroxylamine hydrochloride in 200 ml. of pyridine was allowed to stand at room temperature overnight. Dilution with water gave a precipitate which was collected on a filter and washed thoroughly with water, yielding 7.8 g. of the oxime of **2a**: m.p. 205–210°; λ_{max} 2.77, 3.02, 5.78 μ; λ_{max} 234 mμ (log ϵ 4.18). Recrystallization from acetone did not change the melting point or ultraviolet extinction coefficient.

Anal. Calcd. for $C_{25}H_{35}NO_3$: C, 73.95; H, 9.45. Found: C, 74.13; H, 9.31.

When this oxime was prepared by boiling the components in pyridine for 90 min., a by-product (5%), isolable by chromatography, was crystallized from acetone–petroleum ether, to yield pure 17-acetyl-13β-etiojerv-16-en-3β-ol 20-oxime: m.p. 181–184°, λ_{max} 2.68 and 3.03 μ; $\Delta\nu$ 375 (multiplet, C=CH) c.p.s.

Anal. Calcd. for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03. Found: C, 76.30; H, 10.00.

(22) Y. Mazur and F. Sondheimer, *J. Am. Chem. Soc.*, **80**, 5220 (1958); E. L. Shapiro, T. Legatt, L. Weber, E. P. Oliveto, M. Tanabe, and D. F. Crowe, *Steroids*, **3**, 183 (1964).

(23) S. Siegel and B. Dmuchovsky, *J. Am. Chem. Soc.*, **84**, 3132 (1962).

(24) A. L. Wilds, J. A. Johnson, Jr., and R. E. Sutton, *ibid.* **72**, 5524 (1950).

(25) Catalytic addition of D_2 to unsaturated ketones has been employed by, *e.g.*, H. J. Ringold, M. Gut, M. Hayano, and A. Turner, *Tetrahedron Letters*, 835 (1962).

(26) Dr. P. D. Klimstra, of these laboratories, first employed this reagent and kindly suggested its use.

(27) (a) R. V. Brooks, W. Klyne, and E. Miller, *Biochem. J.*, **54**, 212 (1953); (b) Y. Kawazoa, Y. Sato, T. Okamoto, and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **11**, 328 (1963), and references cited there.

(28) B. J. Magerlein, *J. Org. Chem.*, **24**, 1564 (1959).

(29) P. D. Klimstra, U. S. Patent 3,018,296 (1962).

(30) G. Just and R. Nagarajan, *Experientia*, **18**, 402 (1962).

(31) We wish to thank Dr. R. T. Dillon and staff for the analyses, spectra, and rotations and Dr. E. G. Daskalakis and staff for the chromatographies reported.

(32) Infrared spectra were determined in chloroform, the ultraviolet spectra in methanol, and rotations in chloroform (1%). The n.m.r. spectra were run in deuteriochloroform on a Varian Model A-60 spectrometer at 60 Mc., with tetramethylsilane as an internal standard; $\Delta\nu$ = 0 c.p.s.

17-Acetamido-13β-etiojerv-16-en-3β-ol Acetate. (3).—A stirred solution of 0.60 g. of **2a** oxime in 10 ml. of pyridine at −5° was treated dropwise with a precooled solution of 1 ml. of phosphorus oxychloride in 10 ml. of pyridine over a 15-min. period. (The initial addition was very slow in order to prevent a rise in temperature.) After 2 hr. at −5° the solution was poured slowly into cold water and stirred vigorously for 25 min. The resulting precipitate was collected, washed with water, and dried, yielding 0.55 g. of crystals, m.p. 165–169°. Recrystallization of this material from methylene chloride–acetone gave pure enamide **3**: m.p. 175–178°; λ_{max} 2.89, 5.79, 5.93 μ; Δν 60 and 67 (C-18 CH_3), 378 (multiplet, C=CH), 396 (NH) c.p.s.; $[\alpha]_D$ +39°. The signal at 396 c.p.s. disappeared on D_2O exchange. No maximum was seen in the ultraviolet spectrum (log ϵ_{220} 3.67).

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45. Found: C, 73.69; H, 9.14.

The n.m.r. spectrum showed that enamide **3**, on prolonged standing in deuteriochloroform, isomerized to enamide **6**; thus care was necessary in obtaining the spectrum. The isomer **3** was stable to chromatography on silica, however, being eluted at 20% ethyl acetate in benzene.

17-Acetamidoetiojerv-13-en-3β-ol Acetate (6). A. Beckmann Rearrangement.—A solution of 8.3 g. of **2a** oxime in 50 ml. of pyridine was treated as described above with 10 ml. of phosphorus oxychloride in 50 ml. of pyridine. After completion of the reaction (2 hr.) the solution was poured into water and heated to 30° for 10 min. The insoluble material was filtered and washed with water, yielding 7.5 g. of product. Recrystallization of this material from methylene chloride–acetone gave 5.48 g. of the pure enamide **6**: m.p. 209–211°; λ_{max} 2.92, 5.79, 5.97 μ; Δν 95 (C=CCH_3), 396 (NH) c.p.s.; $[\alpha]_D$ −83°. The signal at 396 c.p.s. disappeared on D_2O exchange. No maximum was seen in the ultraviolet spectrum (log ϵ_{220} 3.80).

Anal. Calcd. for $C_{23}H_{35}NO_3$: C, 73.95; H, 9.45. Found: C, 74.11; H, 9.23.

B. Isomerization of Enamide 3.—To a slurry of 0.10 g. of the enamide **3** in 3 ml. of acetone was added 10 mg. of *p*-toluenesulfonic acid. The reaction mixture quickly became homogeneous and after 10 min. deposited a crystalline material. After a total of 15 min., the mixture was filtered using cold acetone to wash to crystals. The product, m.p. 193–198°, was identical in the infrared and n.m.r. with an authentic sample of **6**.

3β-Acetoxyetiojervan-17-one (4a).—A solution of 68 g. of **2a** oxime in 0.8 l. of pyridine was treated as described above with 60 ml. of phosphorus oxychloride in 300 ml. of pyridine. After 1 hr., the solution was poured slowly into 1.5 l. of water containing 0.5 l. of concentrated hydrochloric acid, maintaining the temperature at 45–55°. The resulting crystalline product was collected on a filter and washed with water, yielding 62 g. of the ketone **4a**, m.p. 155–161°. An n.m.r. spectrum showed this material to be essentially pure, containing none of the minor ketone (**5**). Recrystallization of a portion of the ketone from acetone yielded the pure sample: m.p. 175–177° (change in crystal form at 160°); λ_{max} 5.75 and 5.85 μ; Δν 50 (C-19 CH_3), 57 and 63 (C-18 CH_3) c.p.s.; $[\alpha]_D$ +123°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.76; H, 9.70. Found: C, 75.74; H, 9.65.

Extraction of the aqueous filtrate of the crude material with benzene afforded a mixture containing both ketones **4a** and **5a**.

If the aqueous hydrochloric acid was kept cold, a considerable amount of the enamide **6** could be isolated from the product.

3β-Hydroxyetiojervan-17-one (4b).—A solution of 0.30 g. of the enamide **6** in 50 ml. of methanol and 1 ml. of concentrated hydrochloric acid was heated at reflux for 2 hr. The methanol was distilled under reduced pressure and the resulting mixture was diluted with water. The resulting crystal mass was filtered and washed with water yielding 0.23 g. of the hydroxy compound **4b**, m.p. 156–159°. Recrystallization from ether yielded 0.16 g. of the analytically pure sample: m.p. 162–163°; λ_{max} 2.73 and 5.83 μ; Δν 48 (C-19 CH_3), 57 and 63 (C-18 CH_3) c.p.s.; $[\alpha]_D$ +145°; O.R.D.[7] in MeOH, $[\phi]^{pk}_{311\ m\mu}$ +10,650°, $[\phi]^{tr}_{270\ m\mu}$ −4425°, a = +216.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.46. Found: C, 78.65; H, 10.27.

Several attempts to effect a mild hydrolysis of the enamide to the acetoxy ketone **4a** by use of methanolic hydrochloric acid at room temperature were unsuccessful.

Acetylation of **4b** with acetic anhydride at 100° yielded the acetate **4a** identical in the infrared and n.m.r. with the authentic sample.

3β-Hydroxy-13β-etiojervan-17-one (5b).—Hydrolysis of 18 g. of the enamide **6** was carried out as described above yielding the hydroxy ketone **4b** as the major product. The mother liquors (4.7 g.) were chromatographed on 350 g. of silica. A mixture of the epimeric ketones (3.6 g.) was eluted with 10% ethyl acetate in benzene. Crystallization from acetone–petroleum ether produced two distinct types of crystals which were separated mechanically; heavy clusters of prisms, m.p. 147–155°, were identical in the infrared with the known ketone **4b**; a fine cottony crystal mass, m.p. 123–126°, was recrystallized three times more from the same solvent pair to give the pure epimeric ketone **5b**: m.p. 149–150°; λ_{max} 2.75 and 5.85 μ; Δν 42 (C-19 CH_3), 56 and 62 (C-18 CH_3) c.p.s.; $[\alpha]_D$ −166°; O.R.D.[7] in methanol, $[\phi]^{tr}_{311\ m\mu}$ −5905°, $[\phi]^{pk}_{270\ m\mu}$ +3500°, a = −94.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.80; H, 10.66.

The hydroxy ketone was acetylated with pyridine–acetic anhydride at room temperature for 24 hr. Dilution of the reaction with water gave a crystalline product which was purified by recrystallization from aqueous acetone to give the pure **3β-acetoxy-13β-etiojervan-17-one (5a)**: m.p. 137–138°; λ_{max} 2.75 and 5.85 μ; Δν 44 (C-19 CH_3), 56 and 61 (C-18 CH_3) c.p.s.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.58; H, 9.63.

Equilibration of Ketones 4 and 5.—A solution of 0.15 g. of ketone **4b** in 10 ml. of methanol and 1 ml. of 10% aqueous hydrochloric acid was heated at reflux for 2 hr. The solution was diluted with 50 ml. of water and filtered. The product was washed with water and dried, yielding 0.13 g. of material, m.p. 147–154°, $[\alpha]_D$ +83°. The n.m.r. showed clearly the C-19 methyl peaks for both epimers (42 and 48 c.p.s.).

A similar treatment of the 100 mg. of epimeric ketone **5** yielded 90 mg. of product, m.p. 135–150°, $[\alpha]_D$ +98°, with n.m.r. and infrared identical with the equilibrium mixture formed above. This rotational data implies that 15–20% of the minor epimer **5** is present at equilibrium.

Base-catalyzed epimerization of ketone **4** with aqueous potassium hydroxide in refluxing methanol was complete within 1 hr. as shown by the constancy of rotation ($[\alpha]_D$ +82°) at 1- and at 6-hr. intervals. The mixture produced was identical in infrared and n.m.r. spectra with that obtained by acid-catalyzed equilibration.

17β-Acetyl-13β-etiojervan-3β-ol (2c).—A solution of 2.0 g. of the unsaturated ketone **2b** in 30 ml. of ethanol containing 200 mg. of 5% palladium on carbon was stirred in a hydrogen atmosphere.[33] After 10 min. the reduction was complete and the mixture was filtered. Concentration of the filtrate gave a crystalline residue ($[\alpha]_D$ +38°) which was recrystallized twice from acetone–petroleum ether to yield 1.2 g. of the pure ketone **2c**: m.p. 154–156°; λ_{max} 2.78 and 5.85 μ; $[\alpha]_D$ +60°; O.R.D. in dioxane,[34] $[\phi]^{pk}_{303}$ +1450°, a = +116.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.36; H, 10.57.

Treatment of the ketone **2c** with pyridine–acetic anhydride at room temperature for 20 hr. afforded **17β-acetyl-13β-etiojervan-3β-ol acetate (2d)**, purified by recrystallization from ether–petroleum ether to give a sample, m.p. 131–133°, λ_{max} 5.78 μ, $[\alpha]_D$ +46°.

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.62; H, 10.07. Found: C, 76.32; H, 10.09.

13β-Etiojervane-3β,17α-diol.—A solution of 0.75 g. of the ketone **2d** in 20 ml. of formic acid, 3 ml. of water, and 2 ml. of 30% aqueous hydrogen peroxide was maintained at 70–75° for 1 hr. The cooled solution was diluted with water, and the product was isolated by extraction with benzene.[35] The product (0.55 g.) was boiled for 1 hr. in 50 ml. of methanol containing 10 ml. of 10% aqueous potassium hydroxide. The solution was extracted with benzene, yielding 0.35 g. of residue. Chroma-

(33) We wish to thank Mr. W. Selby and staff for the hydrogenations described here.

(34) Dr. N. L. McNiven, Worcester Foundation for Experimental Biology, kindly provided this O.R.D. data.

(35) The normal isolation procedure involved washing the organic extract with water and, if acidic, with aqueous potassium bicarbonate, drying over anhydrous magnesium sulfate and concentrating to dryness under reduced pressure (<50°).

tography of this material on silica afforded, by elution with 5% ethyl acetate in benzene, 60 mg. of starting material (infrared comparison). The crystalline diol (0.17 g.) was eluted with 10% ethyl acetate in benzene. Recrystallization from acetone–petroleum ether gave 0.10 g. of the diol, m.p. 169–170°, λ_{max} 2.75 μ.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 10.85. Found: C, 78.08; H, 11.03.

The same product was obtained by lithium aluminum hydride reduction of the diketone **5c**.

13β-Etiojervane-3,17-dione (5c).—A solution of 35 mg. of 13β-etiojervane-3β,17α-diol in 3 ml. of pyridine was added to a slurry of 0.10 g. of chromium trioxide in 2 ml. of pyridine[36] at 5° with stirring. After 20 min. the cooling bath was removed. After a total of 2 hr. the solution was diluted with water and extracted with ether.[35] The crude product (35 mg.) showed none of the epimer **4c** in the n.m.r. spectrum; the sample was recrystallized from ether to yield 12 mg. of the pure diketone **5c**: m.p. 169–170°; λ_{max} 5.83 μ; $\Delta\nu$ 54 (C-19 CH_3), 57 and 63 (C-18 CH_3) c.p.s.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.06; H, 9.73.

Etiojervane-3,17-dione (4c).—A solution of 45 mg. of the alcohol **4b** in 10 ml. of acetone was treated with 0.2 ml. of 4 *N* chromic acid solution.[37] After 5 min. the solution was diluted with water; the product was collected on a filter and washed with water, yielding 33 mg. of the pure diketone **4c**, m.p. 143–145°, λ_{max} 5.83 μ, $[\alpha]D$ +183°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.98; H, 9.94.

Alternatively, base-catalyzed equilibration of the unstable diketone **5c** readily afforded a mixture from which the preponderant constituent **4c** could be isolated.

3β-Acetoxyetiojerv-12-en-17-one (8a). A. From the Major Ketone (4a).—A solution of bromine in acetic acid (42 ml., 0.22 *M*) was added over a 10-min. period to 2.80 g. of the ketone **4a** in 30 ml. of acetic acid at 15°. Decolorization of the bromine was immediate. The solution was diluted with water and extracted with benzene. The extract was washed three times with water, and the solvent was removed (temperature below 45°), yielding 3.90 g. of a foam, λ_{max} 5.79 μ. The n.m.r. spectrum showed three distinct signals in the region ascribed to tertiary methyl groups, indicating a mixture of both C-13 bromo ketones had been formed.

A mixture of the crude bromoketone (3.80 g.) and 7 g. of magnesium oxide in 50 ml. of dimethylformamide was stirred at room temperature for 2 hr. An aliquot of the reaction mixture showed an unsaturated ketone band of medium intensity in the infrared. The remainder of the reaction mixture was heated to reflux under nitrogen for 1 hr. The solvent was removed under reduced pressure and the resulting solid was washed with benzene. The solution was washed three times with water and concentrated to dryness. The crystalline product, 2.25 g., was recrystallized from ether–methanol (Darco), yielding 1.15 g. of hard prisms, m.p. 162–164°, λ_{max} 246 mμ (log ϵ 4.12), and 0.26 g., m.p. 158–168°, λ_{max} 246 mμ (log ϵ 4.13). Recrystallization of a portion of this material from methylene chloride–methanol gave the pure unsaturated ketone **8a**, m.p. 167–168°, λ_{max} 5.78 and 6.02 μ, λ_{max} 246 mμ (log ϵ 4.19), $[\alpha]D$ +13°.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.11; H, 9.15.

Chromatography of the mother liquors (0.80 g.) on 70 g. of silica yielded 0.30 g. of material by elution with 1% ethyl acetate in benzene. Recrystallization from ether afforded 0.11 g. of the phenol **7a**, m.p. 199–206°, identical with the product described below. Elution with 2% ethyl acetate in benzene gave 0.25 g. of material, recrystallized from ether to yield an additional 0.20 g. of the unsaturated ketone **8a**, m.p. 167–168°. No evidence of the alternate unsaturated ketone (**9**) was found.

Although the bromination of **4a** was conducted successfully using pyridinium bromide perbromide as the brominating agent, the intermediate (axial?) bromo ketone appeared much less stable, decomposing on standing for a short period at room temperature.

Attempts to isomerize the unsaturated ketone were made with three reagents: acetic anhydride–perchloric acid, isopropenyl acetate–toluenesulfonic acid, and potassium *t*-butoxide.[18] With each of these reagents, on extended treatment a portion of the unsaturated ketone would disappear. That this was not simple bond isomerization was evidenced by the formation of mixtures of noncrystalline material which failed to regenerate the unsaturated ketone on treatment with aqueous base.

B. From the Minor Ketone 5a.—A solution of 80 mg. of the ketone **5a** in 5 ml. of acetic acid was treated with 90 mg. of pyridinium bromide perbromide and stirred at 20°. The reagent dissolved within 10 min. After an additional 5 min., the solution was diluted with water and extracted with benzene. A portion (56 mg.) of the product (113 mg.) in 5 ml. of dimethylformamide was added to 0.10 g. of magnesium oxide. The mixture was stirred at reflux under nitrogen for 1 hr. and then was poured into excess aqueous hydrochloric acid. The product was isolated by benzene extraction,[35] yielding 45 mg. of crystals. The material was essentially identical in the infrared with the authentic material (**8a**), and also showed no shift in the ultraviolet maximum (246 mμ).

3β-Hydroxyetiojerv-12-en-17-one (8b).—A solution of 0.35 g. of the acetate **8a** in 10 ml. of methanol and 2 ml. of 10% aqueous potassium hydroxide was heated at reflux for 30 min. The solution was diluted with water, and the resulting precipitate was collected on a filter, yielding 0.30 g. of crystals, m.p. 165–169°. Recrystallization from acetone–petroleum ether afforded 0.24 g. of pure **8b**, m.p. 168–170°, λ_{max} 2.91 and 6.08 μ, λ_{max} 247 mμ (log ϵ 4.17).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.10; H, 9.81.

Bromination–Dehydrobromination of the Enamide 3.—A mixture of 0.74 g. of the enamide **3** and 5 g. of anhydrous potassium carbonate in 30 ml. of chloroform was stirred vigorously at 5°. The mixture consumed 1.3 mole equiv. of an 0.85 *M* solution of bromine in carbon tetrachloride before the bromine color persisted. The mixture was filtered, and the filtrate was stirred vigorously with 30 ml. of water at room temperature for 3 hr. The solution became acidic very quickly. The organic layer was separated and the product was isolated in the usual manner.[35] A solution of the resulting stiff foam (0.96 g.) in 50 ml. of boiling dimethylformamide was stirred with 5 g. of magnesium oxide for 2 hr. The cooled solution was filtered and the product was isolated by benzene extraction.[35] The residue, 0.68 g., λ_{max} 248 mμ (log ϵ 3.74), was chromatographed on silica; no material was found which had an ultraviolet maximum at lower wave lengths (as would be expected for ketone **9**).

Etiojerva-12,15,17-triene-3,17-diol 3-Acetate (7a). A. From the Saturated Ketone 4a.—The acetate **4a** (1.60 g.) was dissolved in 20 ml. of acetic acid at 20°. To this solution was added 23 ml. of 0.39 *M* bromine–acetic acid solution over a 10-min. period. Bromine consumption was very rapid. The solution was diluted with water and extracted with benzene,[35] yielding 2.60 g. of a foam, λ_{max} 5.80 μ.

Anal. Calcd. for $C_{21}H_{31}BrO_3$: Br, 32.5. Found: Br, 32.4.

A solution of 2.55 g. of the bromide (as prepared above) in 300 ml. of dimethylformamide containing 10 g. of magnesium oxide was heated at reflux with stirring in an atmosphere of nitrogen for 40 min. The cooled mixture was filtered, diluted with water, and extracted with benzene. The noncrystalline product, 1.70 g., was chromatographed on 100 g. of silica. The crude phenol **7a**, 0.75 g., was obtained by elution with 1% ethyl acetate in benzene. Recrystallization from ether gave the pure phenol: m.p. 198–202°; λ_{max} 2.90 and 5.82 μ; λ_{max} 281 mμ (log ϵ 3.38); Δ 122 (−OAc), 128 ($PhCH_3$), quartet at 390, 397, 403, 410 (ArH_2) c.p.s.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.69; H, 8.76.

Elution with 2% ethyl acetate provided 90 mg. of unsaturated ketone **8a**, identified by ultraviolet and infrared spectra.

B. From the Unsaturated Ketone 8a.—A solution of 0.33 g. of the unsaturated ketone **8a** in 60 ml. of 2B ethanol was stirred at reflux with 0.50 g. of palladium–magnesium oxide catalyst[19] in an atmosphere of nitrogen. After 1 day an additional 0.50 g. of the same catalyst was added. After a total of 4 days, the mixture was filtered and the filtrate was concentrated to dryness. Chromatography of the resulting material (0.35 g.) on 150 g. of silica afforded 0.17 g. of the phenol **7a**, eluted with 0.5% ethyl acetate in benzene. Recrystallization from acetone–petroleum ether afforded 0.12 g. of phenol, m.p. 198–202°, identical with the authentic sample in the infrared.

Earlier attempts to aromatize the unsaturated ketone **8a** involved the use of N-bromosuccinimide in refluxing carbon

(36) For precautions, see G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1963).

(37) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

tetrachloride for 2 hr. and also cupric chloride–lithium chloride in dimethylformamide[20] at 85° for 2 hr. In neither case was any aromatic material produced as evidenced by the lack of absorption in the n.m.r. near 400 c.p.s.

Etiojerva-12,15,17-triene-3,17-diol (7b).—The acetate **7a** (0.65 g.) was added to 30 ml. of methanol and 5 ml. of 10% aqueous potassium hydroxide, and stirred at room temperature. The mixture quickly became homogeneous. After 3 hr., the solution was diluted with 2% aqueous hydrochloric acid, and the resulting precipitate, 0.63 g., m.p. 236–238°, was collected on a filter. Recrystallization from acetone–petroleum ether gave 0.52 g. of the pure phenol as an acetone solvate, m.p. 242–244°, λ_{max} 2.88 and 3.11 μ, λ_{max} 280 mμ (log ϵ 3.34), $[\alpha]D$ +23°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 77.01; H, 9.19.

Etiojerva-12,15,17-triene-3,17-diol 17-Methyl Ether (7c).—Methyl iodide (2 ml.), 2 g. of potassium carbonate, and 0.30 g. of the diol **7b** were heated in 20 ml. of refluxing 2B ethanol with stirring for 90 min. After distillation of half the solvent, the mixture was diluted with water and was filtered. The product, washed with water and dried, was dissolved in methanol and filtered. The filtrate was diluted with water to provide 0.28 g. of the ether **7c**, m.p. 162–163°, and 30 mg., m.p. 153–158°. The pure sample was obtained by recrystallization from aqueous methanol: m.p. 167–168°; λ_{max} 281 mμ (log ϵ 2.98), 285 (2.98), 290 (2.98); $\Delta\nu$ 128 ($ArCH_3$), 227 (OCH_3), 393, 402, 409, 417 (ArH_2) c.p.s.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.93; H, 9.64.

Birch Reduction of the Methyl Ether 7c.—A solution of 0.16 g. of the methyl ether **7c** in 125 ml. of 2B ethanol was added to 300 ml. of ammonia. Lithium wire (5 g.) was added over a 1-hr. period with two 50-ml. portions of ethanol. After 2 hr. the solution had decolorized and the ammonia was distilled. The product, isolated by benzene extraction,[35] was dissolved in 30 ml. of methanol and 2 ml. of 10% aqueous hydrochloric acid, and the resulting solution was heated at reflux for 1 hr. The cooled solution was diluted with water, and the product was isolated by benzene extraction.[35] The residue (0.13 g.) was chromatographed on 5 g. of silica. The crude unsaturated ketone fractions (65 mg.) were eluted with 10–20% ethyl acetate in benzene and exhibited maxima at 2.75, 5.81 (m), 6.01 (s) μ and at 245 (log ϵ 3.85) mμ; the n.m.r. spectrum showed no vinyl proton absorption.

16,17-Epoxy-17-acetyl-13β-etiojervan-3β-ol 3-Acetate (16).—To a solution of 1.50 g. of the unsaturated ketone **2a** in 20 ml. of chloroform was added five 30-ml. portions of 0.19 *M* perbenzoic acid in benzene solution at 2-day intervals. At periods less than 14 days, starting material was evident by inspection of the infrared spectra. After 14 days, the solution was stirred with 20 g. of calcium hydroxide for 30 min., was filtered and was retreated with a fresh 20 g. of calcium hydroxide. The filtrate from this treatment was concentrated to dryness, affording 1.50 g. of oil. The product was crystallized from methanol, yielding 0.50 g. of the epoxide **16**, m.p. 157–158°, and 0.20 g., m.p. 153–158°. Recrystallization of a portion from methylene chloride–methanol gave rods, m.p. 157–158°, λ_{max} 5.82 μ, $[\alpha]D$ +16°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.54; H, 9.14.

Chromatography of the mother liquors (0.65 g.) on 50 g. of silica afforded 0.35 g. of epoxide, eluted at 1% ethyl acetate in benzene, and recrystallized from methanol to yield 0.10 g. of **16**, m.p. 156–158°. Formation of the epoxide by use of trifluoroperacetic anhydride or alkaline hydrogen peroxide was less satisfactory.

16-Bromo-17-acetyl-13β-etiojervane-3β,17-diol 3-Acetate (17a).—A solution of 0.75 g. of the epoxide **16** and 10 ml. of 48% aqueous hydrobromic acid in 15 ml. of acetic acid gave a precipitate on mixing. The mixture was stirred at room temperature for 68 hr. and then was filtered. The precipitate was washed with water and aqueous potassium bicarbonate solution, yielding 0.20 g. of crystals, m.p. 188–190°. Recrystallization from methylene chloride–petroleum ether gave 0.19 g. of the pure material: m.p. 188–190°; λ_{max} 2.75, 5.75, and 5.81 μ; $\Delta\nu$ 238, 247, and 256 (–CHBr) c.p.s.

Anal. Calcd. for $C_{23}H_{35}BrO_4$: C, 60.65; H, 7.75. Found: C, 61.25; H, 8.00.

The bromohydrin **17a** remained unchanged after 18 days in pyridine with an excess of hydroxylamine hydrochloride.

The bromohydrin was reduced with sodium borohydride in methanol at room temperature for 18 hr. An n.m.r. spectrum of the amorphous product showed disappearance of the C-20 carbonyl but retention of the bromine atom. Treatment of this material with aqueous periodic acid in methanol containing a little pyridine for 20 hr. at room temperature gave a product which showed no spectral indication of cleavage of the glycol moiety.

17-Acetyl-13β-etiojervane-3β,16,17-triol 3,16-Diacetate (17b).—A solution of 0.50 g. of the acetate **2a** in 10 ml. of benzene containing 0.5 ml. of pyridine and 0.39 g. of osmium tetroxide was allowed to stand at room temperature for 18 hr. The black solution was diluted with 25 ml. of methanol, 10 ml. of benzene, and a solution of 3.5 g. of potassium carbonate and 3.5 g. of sodium sulfite in 35 ml. of water. The mixture was stirred at room temperature for 5 hr., was diluted with 50 ml. of chloroform, and was filtered through Super-cel, using chloroform to wash the filter cake. The pale green filtrate was diluted with water and extracted with chloroform.[35] The resulting product was triturated with ether leaving 0.18 g. of material, m.p. >300°, which showed no hydroxyl groups in the infrared. This material was not investigated further. The soluble portion was acetylated in pyridine–acetic anhydride at 100° for 30 min. The solution was cooled, diluted with water, and extracted with benzene. The residue, 0.54 g. of a dark foam, was chromatographed on silica. Elution with 5% ethyl acetate in benzene yielded the product, which was recrystallized from acetone–petroleum ether to yield 0.10 g. of the pure acetate **17b**: m.p. 173–175°; λ_{max} 2.78, 5.77, and 5.82 μ.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 69.20; H, 8.45.

Hydrogenation of the Unsaturated Ketone 8a.—A mixture of 0.70 g. of the unsaturated ketone **8a** and 70 mg. of 5% palladium–carbon catalyst in 50 ml. of 3A ethanol was stirred in an atmosphere of hydrogen. The uptake of hydrogen stopped when 1.0 mole equiv. had been absorbed (1.5 hr.). (The addition of 2 ml. of 10% aqueous potassium hydroxide slowed the reduction.) The mixture was filtered and the filtrate was concentrated to dryness, dissolved in ether, and filtered (Darco). The product (0.36 g., m.p. 164–166°) which precipitated on concentration of the ether solution was identical with an authentic sample of **4a**. The mother liquors were shown by the n.m.r. and infrared spectra to contain largely the same compound.

Repetition of the above experiment with 0.30 g. of ketone **8a** and the substitution of deuterium gas provided a crude product (0.28 g.) which showed an n.m.r. spectrum identical with that of the pure ketone **4a** in the 40–80-c.p.s. region; minor differences at lower fields were noted. Recrystallization of the crude product from acetone yielded 75 mg. of material, m.p. 173–175°. When dioxane was used as solvent, less than 10% of the product was reduced after 12 hr.

Hydride Reduction of Ketone 4a.—Triethylcarbinol (0.41 mole, 47.5 g.) in 30 ml. of tetrahydrofuran was added over a 30-min. period to a solution of 5.1 g. (0.135 mole) of lithium aluminum hydride in 200 ml. of tetrahydrofuran at 5°.[26] To this reagent at 5° was added a cooled solution of 15 g. of the ketone **4a** in 200 ml. of tetrahydrofuran over a 5-min. period. After 45 min. the solution was diluted with excess aqueous acetic acid and the product was isolated by methylene chloride extraction.[35] This material, 16 g. of oil, was chromatographed on silica, but failed to resolve into crystalline components (**10a** and **13a**). A center fraction, λ_{max} 2.72 and 5.78 μ, was submitted for analysis.

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.33; H, 10.28.

Paper, thin layer, or gas chromatography were not able to separate the components.

Etiojervane-3β,17α-diol 17-Benzoate (10c) and Etiojervane-3β,-17β-diol 17-Benzoate (13c).—A solution of 16 g. of alcohols **10a** and **13a** in 100 ml. of pyridine and 25 ml. of benzoyl chloride was heated at 100° for 15 min. The solution was cooled, diluted with 40 ml. of water, heated again at 100° for 30 min., and concentrated *in vacuo* to near dryness. The mixture was partitioned between ether and water, the organic layer being separated and washed several times with water and base. The product, obtained after distillation of the solvent, weighed 19 g., λ_{max} 5.82 μ, $[\alpha]D$ –16°. Again chromatography failed to separate the components.

The mixture of benzoates **10b** and **13b** in 600 ml. of methanol and a solution of 12 g. of potassium bicarbonate in 150 ml. of

water were stirred at reflux for 5 hr. The solution was concentrated and the product isolated by benzene extraction.[35] The resulting material (20 g.) was chromatographed on 2 kg. of silica. (Analysis of the crude product by n.m.r. indicated approximately equal amounts of **10c** and **13c**.) Elution with 0.5% ethyl acetate in benzene provided 0.8 g. of 3,17-diester. Eluted at 1% ethyl acetate in benzene was a total of 6.7 g. of material which crystallized from acetone to provide 2.85 g. of the pure 17β-benzoate (**13c**), m.p. 164–166°, λ_{max} 2.77 and 5.83 μ, Δν 47 (C-19 CH_3), $[\alpha]_D$ +12°.

Anal. Calcd. for $C_{26}H_{36}O_3$: C, 78.74; H, 9.15. Found: C, 78.69; H, 9.27.

This compound was obtained crystalline initially by lithium tri-*t*-butoxyaluminohydride reduction of keto benzoate **13d**.

Further elution with 1% ethyl acetate in benzene gave mixtures of the epimeric benzoates and then the pure α-isomer **10c**. Recrystallization from acetone of the later fractions eluted with 1% ethyl acetate–benzene afforded 2.4 g. of **10c**, m.p. 162–164°. Another recrystallization from acetone yielded the pure compound, m.p. 163–164°, λ_{max} 2.78 and 5.82 μ, Δν 47 (C-19 CH_3) and 311 c.p.s. (C-17β H, width at half height = 9 c.p.s.), $[\alpha]_D$ −61°. Admixture of **10c** and **13c** caused a depression in melting point.

Anal. Found: C, 78.97; H, 9.23.

Etiojervane-3β,17β-diol (**13f**).—Elution of the chromatographic column from the preceding experiment with ethyl acetate yielded 1.89 g. of material which was recrystallized from acetone to give 0.57 g. of the diol **13f**, m.p. 164–166°. Recrystallization from cyclohexane gave the analytical sample, m.p. 165–166°, λ_{max} 2.77 μ, Δν 190 (C-17α H) and 215 (C-3α H) c.p.s., $[\alpha]_D$ −23° (dioxane).

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 78.27; H, 11.04.

The same compound was obtained in good yield by saponification of the hydroxy benzoate **13c** or by lithium–ammonia reduction of the hydroxy ketone **4b**.

17β-Benzoyloxyetiojervan-3-one (**13d**).—A solution of 3.1 g. of the alcohol **13c** in 100 ml. of acetone was cooled to 5° and treated with an excess of 4 *N* chromic acid solution.[37] After 5 min. the solution was diluted with methanol and water; the resulting precipitate was collected on a filter and washed with water. The product, 2.79 g., m.p. 166–168°, was recrystallized from acetone to yield 2.10 g. of the ketone **13d**, m.p. 166–169°, λ_{max} 5.82 μ, $[\alpha]_D$ +34°.

Anal. Calcd. for $C_{26}H_{34}O_3$: C, 79.15; H, 8.69. Found: C, 78.98; H, 8.59.

17α-Benzoyloxyetiojervan-3-one (**10d**).—A solution of 0.85 g. of the alcohol **10c**, treated as above, yielded 0.85 g. of the pure ketone, m.p. 159–160°, λ_{max} 5.82 μ, $[\alpha]_D$ −32°.

Anal. Found: C, 78.96; H, 8.71.

17β-Hydroxyetiojervan-3-one (**13e**).—The benzoate **13d** (1.25 g.) in 40 ml. of *t*-butyl alcohol and 20 ml. of 10% aqueous potassium hydroxide was stirred at reflux for 24 hr. The mixture was diluted with water and the resulting precipitate was collected on a filter. A solution of the product in methylene chloride was dried and concentrated. The residue was crystallized from acetone–petroleum ether, yielding 0.65 g. of the pure material, m.p. 98–100°, λ_{max} 2.75 and 5.83 μ, $[\alpha]_D$ +7°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.61. Found: C, 78.26; H, 10.46.

A short chromic acid treatment of **13e** (40 mg.) afforded 25 mg. of the diketone **4c**, m.p. 142–145°, which was identical in the infrared with an authentic sample.

Etiojervane-3β,17α-diol (**10f**).—A solution of 0.60 g. of the keto benzoate **10d** in 10 ml. of tetrahydrofuran was added to a slurry of 0.5 g. of lithium aluminum hydride in 40 ml. of ether. The solution was stirred at reflux for 3.5 hr. The solution was treated sequentially with ethyl acetate, 1 ml. of water, and 1 ml. of 10% aqueous potassium hydroxide. The mixture was filtered and the filtrate was concentrated to dryness. The residue was crystallized from acetone–petroleum ether to yield 0.26 g. of the diol **10f**, m.p. 143–144°. Recrystallization from aqueous methanol gave a sample with the same melting point, λ_{max} 2.72 μ, Δν 215 (C-3α H) and 224 (C-17β H) c.p.s., $[\alpha]_D$ −35°.

Anal. Calcd. for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.92; H, 10.83.

17α-Hydroxyetiojervan-3-one (**10e**).—The benzoate **10d** (1.75 g.) was hydrolyzed as described above, yielding 0.55 g. of material, m.p. 163–164°, λ_{max} 2.75 and 5.85 μ, $[\alpha]_D$ −9°.

Anal. Calcd. for $C_{19}H_{30}O_2$: C, 78.57; H, 10.61. Found: C, 78.56; H, 10.39.

Brief oxidation of 40 mg. of **10e** with chromic acid–acetone gave 31 mg. of the diketone **4c**, m.p. 143–145°, identical in the infrared and n.m.r. spectra with an authentic sample.

17β-Hydroxyetiojerva-1,4-dien-3-one (**14b**).—A solution of 0.87 mmole of bromine in 5 ml. of methylene chloride and 15 ml. of acetic acid was added dropwise over a 20-min. period to a solution of 1.68 g. of the benzoate **13d** in 20 ml. of methylene chloride and 20 ml. of acetic acid at 15°. The solution was stirred for an additional 10 min. at 15°. The temperature was raised to 40° and maintained there for 1 hr. The solution was concentrated at reduced pressure (temperature less than 40°), yielding a crystalline residue which was triturated and washed with methanol on a filter yielding 1.80 g. of **2,4-dibromo-17β-benzoyloxyetiojervan-3-one**, m.p. 208–213°, λ_{max} 5.70 and 5.82 μ.

Anal. Calcd. for $C_{26}H_{32}Br_2O_3$: Br, 28.9. Found: Br, 28.2.

Magnesium oxide (2 g.) and 1.75 g. of the dibromo ketone in 40 ml. of dimethylformamide were stirred at reflux under an atmosphere of nitrogen for 2 hr. The solution was cooled and poured into iced aqueous sulfuric acid. The resulting precipitate was collected on a filter and washed with water, yielding 1.30 g. of crude dienone **14a**. This material was chromatographed on 60 g. of silica. The product, eluted with 5% ethyl acetate in benzene, was recrystallized from ether–cyclohexane to give the pure 17β-benzoyloxyetiojerva-1,4-dien-3-one: m.p. 95–98°; λ_{max} 5.83, 6.01, 6.18, 6.23 μ; λ_{max} 234 mμ (log ε 4.40). Several analyses on recrystallized material failed to give satisfactory results.

A stirred solution of 0.34 g. of benzoate **14a** in 30 ml. of *t*-butyl alcohol and 5 ml. of 10% aqueous potassium hydroxide was boiled under an atmosphere of nitrogen for 8 hr. The solvent was blown off in a stream of nitrogen and the residue was diluted with aqueous acetic acid. The resulting crystals (0.23 g., m.p. 240–245°) were recrystallized from methylene chloride–petroleum ether, affording 0.20 g. of the pure dienone **14b**, m.p. 245–248°; λ_{max} 2.73, 6.00, 6.15, 6.22 μ; λ_{max} 242 mμ (log ε 4.23).

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.48; H, 9.10.

2-Bromo-17α-benzoyloxyetiojervan-3-one.—A solution of 2.90 g. of the benzoate **10d** in 40 ml. of tetrahydrofuran and 40 ml. of acetic acid at −5° was treated dropwise over a 20-min. period with a solution of 13.3 ml. of 0.5 *M* bromine in acetic acid. After an additional 10 min. the solution was diluted with water and the product was isolated by benzene extraction. The residue, 3.0 g. of amorphous material, crystallized from ether; the product was filtered, yielding 1.60 g. of product, m.p. 150–153°. Two recrystallizations of this compound from acetone–petroleum ether gave 0.38 g. of the bromo ketone, m.p. 188–191°, λ_{max} 5.76 μ, λ_{max} 229 mμ (log ε 4.21) (benzoate absorption), $[\alpha]_D$ −25°.

Anal. Calcd. for $C_{26}H_{33}BrO_3$: C, 67.60; H, 6.69. Found: C, 67.22; H, 7.17.

17α-Benzoyloxyetiojerv-1-en-3-one (**11a**).—A solution of 3.0 g. of the bromo compound (as prepared above but without purification by crystallization) and 3 g. of lithium bromide in 30 ml. of dimethylformamide was heated in an atmosphere of nitrogen at 100° for 4 hr., and then heated at reflux for 1 hr. The solution was cooled and the inorganic salts were filtered. The product (2.75 g.) was isolated from the filtrate by benzene extraction,[35] and was dissolved in 250 ml. of ethanol and 210 ml. of water containing 40 g. of sodium bisulfite.[39] The solution was swirled for 3 min. and immediately was extracted three times with methylene chloride. The methylene chloride solution was washed with water, dried, and concentrated. The residue in 150 ml. of methanol was boiled with 28 g. of sodium bisulfite in 110 ml. of water for 2 hr. The solution was diluted with water and extracted with methylene chloride. The organic layer (solution A) was washed twice with water. The aqueous solutions were combined, made alkaline with sodium hydroxide, and heated with excess sodium hydroxide at 100° for 1 hr. The product, 0.43 g., was isolated by extraction with methylene chloride, crystallized from ether, and recrystallized from ether–petroleum ether to yield the pure unsaturated ketone **11a**, m.p. 158–162°, λ_{max} 5.80 and 5.92 μ, λ_{max} 229 mμ (log ε 4.39), $[\alpha]_D$ −39°.

Anal. Calcd. for $C_{26}H_{32}O_3$: C, 79.55; H, 8.22. Found: C, 79.48; H, 8.09.

17α-Hydroxyetiojerv-4-en-3-one (**12a**).—Solution A (from the preceding experiment) was concentrated and the residue (2.6 g.) was dissolved in 70 ml. of *t*-butyl alcohol and 10 ml. of 10% aqueous potassium hydroxide. The mixture was stirred at the reflux temperature for 18 hr. The organic solvent was evaporated in a stream of nitrogen, and the resulting mixture was diluted with

water. The product (1.25 g.), isolated by benzene extraction, was chromatographed on silica. The unsaturated ketone **12b**, eluted with 10% ethyl acetate in benzene, was recrystallized from acetone–hexane to provide the pure sample: m.p. 156–158°; λ_{max} 2.74, 5.99, 6.18 μ; λ_{max} 239 mμ (log ϵ 4.21); $[\alpha]_D$ +79°.

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.27; H, 9.77.

17α-Hydroxyetiojerv-1-en-3-one (11b).—A solution of 0.10 g. of the benzoate **11a** in 20 ml. of *t*-butyl alcohol and 5 ml. of 5% aqueous potassium hydroxide was stirred at reflux under nitrogen for 7 days. (After 1 day the only material isolated was unchanged starting material.) The butanol was distilled and the remaining mixture was extracted with benzene. The product was crystallized and recrystallized from ether–petroleum ether, yielding 30 mg. of the alcohol **11b**, m.p. 93–96°, λ_{max} 2.72 and 5.96 μ, λ_{max} 230 mμ (log ϵ 3.96).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 78.96; H, 9.89.

17β-Methyletiojervane-3β,17-diol (15a).—The ketone **4a** (1.0 g.) in 80 ml. of anhydrous ether was added over a 20-min. period to 20 ml. of 3 *M* methyl magnesium bromide in 50 ml. of anhydrous ether. The reaction mixture was heated at reflux for 20 hr., cooled in an ice bath, treated with 5 ml. of acetone, and acidified with dilute sulfuric acid. The product, 0.79 g. of amorphous material, was isolated by ether extraction and chromatographed on 80 g. of silica. The fractions eluted with 15% ethyl acetate in benzene were combined and recrystallized from acetone–petroleum ether to yield the pure **diol 15a**, m.p. 171–173°, λ_{max} 2.74 μ, $[\alpha]_D$ −36°.

Anal. Calcd. for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.53; H, 11.23.

17α-Hydroxy-17-methyletiojervan-3-one (15b).—The diol **15a** (0.38 g.) in 20 ml. of acetone was oxidized with 0.5 ml. of 4 *N* chromic acid solution[37] at 20°. After 10 min. the solution was diluted with water. The product was filtered and recrystallized twice from acetone–petroleum ether, affording the pure ketone **15b**, m.p. 140–142°, λ_{max} 2.74 and 5.84 μ, $[\alpha]_D$ −12°.

Anal. Calcd. for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59. Found: C, 79.10; H, 10.47.

17α-Hydroxy-17-methyletiojerv-1-en-3-one (11c) and **17α-Hydroxy-17-methyletiojerv-4-en-3-one (12c).**—Bromine (0.84 g.) in 3.0 ml. of methylene chloride was added dropwise over a 10-min. period to the ketone **15b** (1.59 g.) in 24 ml. of tetrahydrofuran at 5°. The solution was stirred for an additional 10 min. and then was neutralized with aqueous potassium bicarbonate. The product, isolated by benzene extraction, was dissolved in 10 ml. of dimethylformamide and added over a 10-min. period to 6 ml. of boiling dimethylformamide containing 0.80 g. of magnesium oxide. The mixture was stirred at reflux for an additional 45 min., cooled, and poured into ice–water. The product (1.57 g. of an oil), isolated by benzene extraction, was chromatographed on 150 g. of silica. The fractions eluted with 10% ethyl acetate in benzene yielded, after recrystallization from acetone–petroleum ether, the pure Δ^1-steroid **11c**: m.p. 139–140°; λ_{max} 2.75, 5.98, 6.25 μ; λ_{max} 229.5 mμ (log ϵ 3.95); $[\alpha]_D$ −30°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.44; H, 10.10.

Continued elution with 10% acetate in benzene afforded a second component, recrystallized from acetone–petroleum ether to give the Δ^4-ketone **12c**, m.p. 121–123°; λ_{max} 2.78, 6.00, 6.20 μ; λ_{max} 236 mμ (log ϵ 4.08).

Anal. Found: C, 79.20; H, 9.86.

17β-Ethynyletiojervane-3β,17-diol (15c).—Potassium hydroxide pellets (21 g.) in 115 ml. of diethylene glycol dimethyl ether and 9.2 ml. of diethylene glycol monoethyl ether were stirred vigorously with a metal stirrer at 135° under an atmosphere of nitrogen. After the pellets had liquified the stirred reaction mixture was cooled slowly to 0° while a fine suspension of potasium hydroxide was formed. The nitrogen atmosphere was replaced by the introduction of a stream of acetylene over the surface of the reaction mixture. (The gas was scrubbed with water and with concentrated sulfuric acid.) Upon saturation of the mixture with acetylene, 3.45 g. of the ketone **4b** in 25 ml. of diethylene glycol dimethyl ether was added. Acetylene passage was continued for 3 more hr. The reaction mixture was diluted with water and the resulting precipitate was separated by filtration, washed with water, dried, and then chromatographed on 120 g. of silica. The fractions eluted with 10% ethyl acetate in benzene were combined and recrystallized from acetone, yielding the pure adduct **15c**, m.p. 176–178°, λ_{max} 2.76 and 3.03 μ, $[\alpha]_D$ −34°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.40; H, 10.34.

17α-Hydroxy-17-ethynyletiojervan-3-one (15d).—A solution of 2.22 g. of the ethynyl compound **15c** in 200 ml. of acetone was oxidized with 2.0 ml. of 4 *N* chromic acid solution[37] at 20°. After 10 min. the solution was diluted with 3 ml. of 2-propanol and 100 ml. of water. The resulting precipitate was collected on a filter, washed with water, dried, and recrystallized three times from acetone to yield pure ketone **15d**, m.p. 215–221°; λ_{max} 2.74, 3.00, 5.80 μ; $[\alpha]_D$ −12°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.38; H, 9.43.

The Reaction of Some 1-Trihaloacetyl-8-methylazulenes with Base[1,2]

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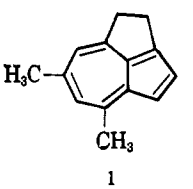
4,6,8-Trimethyl-, 1,4,6,8-tetramethyl-, 2,4,6,8-tetramethyl-, 4,6-diphenyl-8-methyl-, and 3,8-dimethyl-7-isopropylazulene have been acylated with trifluoro- and trichloroacetic anhydrides. Treatment of certain of the 1-trifluoroacetyl derivatives obtained with base has been found to produce a tricyclic alcohol. With certain of the 1-trichloroacetyl compounds, reaction with base resulted in the loss or transformation of the acyl group rather then cyclization. 1-Cyano-4,6,8-trimethylazulene was recovered unchanged after treatment with base.

The achievement of the tricyclic compound (1) by Hafner and Schneider[4] by means of a base-catalyzed cyclization involving the 8-methyl group, plus the discovery of a method for the direct introduction of a trihaloacetyl group into the 1-position,[5] led us to investigate the action of base on 1-trihaloacetyl-8-methylazulenes (*e.g.*, 2) as a possible new route to the ring system of 1.



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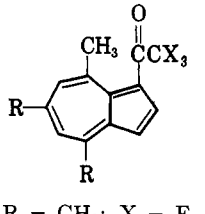

2, R = CH_3; X = F
2a, R = C_6H_5; X = F
2b, R = CH_3; X = Cl

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(3) National Science Foundation Predoctoral Fellow, summer 1959; National Institutes of Health Fellow, 1959-1961.

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(5) A. G. Anderson, Jr., and R. G. Anderson, *J. Org. Chem.*, **27**, 3578 (1962).