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5β,12α-Cholajervane and Related Compounds[1]

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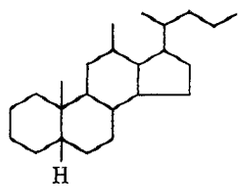
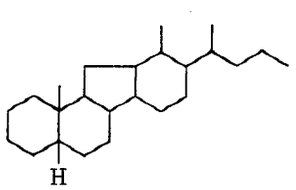
The three major cholajervenes obtained in the reactions, solvolysis of 5β-cholan-12α-ol mesylate, solvolysis of the 12-epimeric mesylate, and alkaline decomposition of 5β-cholan-12-one tosylhydrazone, were shown to be Δ^{12}, $\Delta^{13(18)}$, and $\Delta^{13(17)}$ isomers with α-H configurations at C-17, C-12 and C-17, and C-12, respectively. The three olefins were converted to a single hydrocarbon, 5β,12α-cholajervane, by hydrogenation and by dehydrogenation to a single compound which was demonstrated to have an aromatic D ring by spectral documentation. Diols and ketones corresponding to the three olefins were prepared and characterized. Mass spectral data of the hydrocarbons are presented.

In preliminary communications[2] we presented evidence that an earlier speculation[3] that a rearrangement product of 12α-cholanol mesylate[4] (5) has the 12-methyl-18-norcholane structure (I) was incorrect; instead it has the cholajervane structure[5] (II).



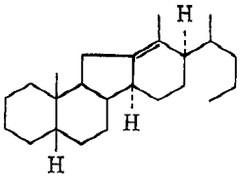
I



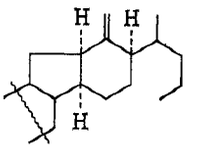
II

The original surmise of the 12-methyl-18-nor structure was based on analogy with the findings of Hirschmann and colleagues[6a] that rockogenin 12(β)-mesylate (**20a**) under solvolytic conditions rearranges into a *C*-nor-*D*-homo steroid, the ring expansion–contraction resulting from favorable conformational juxtaposition of the migrating and leaving bonds. Under similar solvolytic conditions a steroidal 12α-mesylate (**5**), with the angular methyl group at C-13 in an analogous trans-antiparallel relationship with the mesyloxy function, on rearrangement would be expected to undergo a favored Meerwein–Wagner shift to yield a compound of structure I.

When it was found that the two major rearranged products, **1** and **3**, formed when the 12α-mesylate **5** is refluxed in collidine, are also formed both in a similar reaction of the epimeric 12β-mesylate **6**, and in the alkaline decomposition of 12-cholanone tosylhydrazone[7] (**8**), the speculation favoring structure I for the products became dubious.[8] Confirmation of the *C*-nor-*D*-homo structure II for **1** and **3**, as well



1



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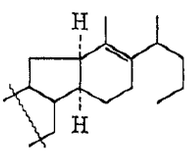

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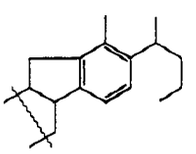

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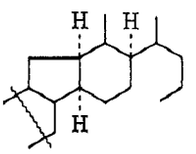


9

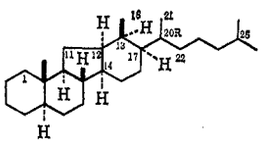
(1) Excerpted in part from the Ph.D. dissertation of R. C. E., University of Tennessee Medical Units, 1973.

(2) (a) F. C. Chang and R. C. Ebersole, *Tetrahedron Lett.*, 1985 (1968); (b) *ibid.*, 3521 (1968).

(3) F. C. Chang, *ibid.*, 2057 (1963).

(4) F. C. Chang, *J. Pharm. Sci.*, **53**, 1014 (1964). Improved syntheses of several 12-substituted 5β-cholane derivatives are reported in a companion to the present paper, R. C. Ebersole and F. C. Chang, *J. Org. Chem.*, **38**, 2713 (1973). All cholane and cholajervane compounds mentioned in this paper are of the 5β series; the designation 5β will be omitted in referring to these compounds.

(5) The name cholajervane was proposed[2b] to join the trivial names already in common use, jervane and etiojervane, with configuration and numbering as illustrated for jervane.



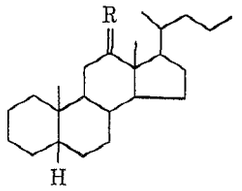
The name pregnajervane has been adopted to represent the C_{21} analog of the same series: W. F. Johns, *J. Org. Chem.*, **35**, 3524 (1970).

(6) (a) R. Hirschmann, C. S. Snoddy, C. E. Hiskey, and N. L. Wendler, *J. Amer. Chem. Soc.*, **76**, 4013 (1954); (b) J. Elks, G. H. Phillips, D. A. H. Taylor, and L. J. Wyman, *J. Chem. Soc.*, 1739 (1954).

(7) F. C. Chang, *J. Org. Chem.*, **30**, 2053 (1965).

(8) In all previously recorded rearrangements involving 12β-sulfonates and 12-tosylhydrazones, only rearranged products of the II type have been obtained.[6,11,13,25]

as for **2** which is obtained as an additional product in the reaction of **6**, follows from the characterization of an aromatic derivative **4** obtained by dehydrogenation of each of the three olefinic compounds.[2b]



5, R = H, α-OMs
6, R = H, β-OMs
7, R = H,H (Δ^{11})
8, R = NNHTs
28, R = O
29, R = H, α-OH
30, R = H, β-OH
31, R = H, α-OAc
32, R = H, β-OAc

This paper presents details of the experiments, and describes further characterization of the compounds and the formation of a common hydrocarbon, 5β,12α-cholajervane (**9**), from its three progenitor olefins.

The Cholajervenes.—Assignment of the double bond location in each of the three isomers **1**, **2**, and **3** was made on the basis of a known diagnostic method[9] supported by spectral evidence. The configurations of the olefins **1** and **2** were tentative, being based only on analogy with the corresponding compounds found in similar reactions in other steroidal series.[8] However, no $\Delta^{13(17)}$ analog was known,[10] although in the pregnajervane series such an isomer had been deduced[11] from ir and nmr evidence obtained from a mixture of seco ketones derived from an olefinic mixture.

Evidence is now available which essentially establishes the α-H configuration of all three olefins at centers 12 and 17 (when H is present). The evidence is mainly based on stereochemical considerations involved in the isomerism of **1** to **3** and of **2** to **1** and **3**, and in the hydrogenation of each of the three olefins by known methods to a common cholajervane.

It is reasonable to assume that the original configuration at C-17 is unchanged in the formation of olefin **1**, although rearrangement mechanisms are conceivable whereby inversion has taken place at that center. The arguments regarding configuration of the other compounds are initially based on assuming the α-H configuration at C-17 of **1**, but as will be evident in the sequel, independent compelling evidence supports that assignment. Each of the hydrogen atoms under discussion in the three olefins is allylic, and the isomerizations involved are 1,3-hydrogen shifts.

12α-Cholajervane.—Previous studies on steroids and other types of compounds having tetrasubstituted or hindered double bonds show that, under catalytic hydrogenation conditions, an allylic shift of hydrogen can take place. The catalyst is considered to approach from the less hindered side of the molecule, and both the hydrogen abstracted and the hydrogen inserted are on the same side as the catalyst.[12]

In this connection, **2** must be considerably hindered, as it does not undergo hydrogenation in PtO_2 even in acetic acid, but instead isomerizes to **1** and **3**. Thus, assuming the 17α-H configuration of **1**, the ready isomerization of **2** to **3** indicates that the catalyst approaches from the α side of the molecule, and isomerization to **1** would be expected also to involve the α side.

Hydrogenation of all three olefins to a single hydrocarbon, each in no less than 70% yield, lends support to the configurations assigned to **1**, **2**, and **3**. Catalytic hydrogenations carried out on both Δ^{12}- and $\Delta^{13(17)}$-*C*-nor-*D*-homo analogs are known to add predominantly from the α side in cis fashion, as documented by substantial evidence,[13] indicating that the α side of the molecule is more open for the approach of the catalyst. Accordingly, hydrogenation of **1** would be expected to give the 12α*H*,13α*H* and **3** the 13α*H*,17α*H* derivative. Diimide reduction has been shown to add cis from the less hindered side,[14] so that such a reduction of **2** would yield a 13α*H* product.

Considering the stereochemical selectivity of the hydrogenations as well as of the isomerization reactions, in order for the three isomers to yield predominantly the same hydrocarbon, the latter must have all α-H configurations at positions 12, 13, and 17. Thus the original tentative assignment for **1**, **2**, and **3** are correct,[15] in agreement with previous assignments for compounds analogous to **1** and **2** in other *C*-nor-*D*-homo series obtained by similar hydrogenations.[13]

The Cholajervanediols 10, 11, and 12.—The hydroxyl groups in the three osmylation products are assigned α configurations on the basis of cis hydroxylation from the unhindered side, in analogy to the hydrogenation assignments (see above). Nmr and ir data do not contribute significantly to configurational characterization of the tertiary hydroxyl groups, as previously indicated.[16,17]

Two additional diols, **14** and **15**, were isolated in minor yields from the diol mixtures obtained from the reactions of mesylate **5** and tosylhydrazone **6**; they were not found in the diol mixture from the reaction of the 12β-mesylate **6**. They are crystalline, isomeric with the other cholajervane diols, but

(9) J. Castells and G. D. Meakins, *Chem. Ind.* (*London*), 248 (1956); J. Castells, G. D. Meakins, and R. Swindells, *J. Chem. Soc.*, 2917 (1964).

(10) The original[9a] assignment of $\Delta^{13(17)}$ to the endocyclic olefin of the spirostane series was shown to be erroneous. It is actually the Δ^{12} isomer. J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron Lett.*, 119 (1965).

(11) J. M. Coxon, M. P. Hartshorn, D. N. Kirk, and M. A. Wilson, *Tetrahedron*, **25**, 3107 (1969).

(12) J. B. Bream, D. C. Eaton, and H. B. Henbest, *J. Chem. Soc.*, 1974 (1957).

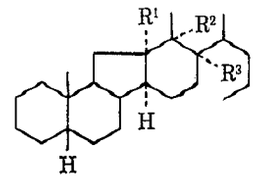
(13) (a) W. F. Johns, *J. Org. Chem.*, **29**, 2545 (1964); (b) H. Mitsuhashi and N. Kawahara, *Tetrahedron*, **21**, 1215 (1965); (c) T. Masamune, N. Sato, K. Kobayashi, I. Yamazaki, and Y. Tori, *ibid.*, **23**, 1591 (1967); (d) H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Lett.*, 2671 (1969); (e) J. W. Huffman, D. M. Alabran, and A. E. Ruggles, *J. Org. Chem.*, **33**, 1060 (1968); (f) T. Masamune, S. Murai, K. Orito, H. Ono, S. Numata, and H. Suginome, *Tetrahedron*, **25**, 4853 (1969).

(14) E. J. Corey, D. J. Pasto, and W. L. Mock, *J. Amer. Chem. Soc.*, **83** 2957 (1961).

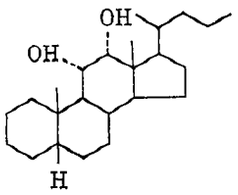
(15) Of the other seven cholajervane structures stereoisomeric at 12, 13, and 17, only the all β-H isomer would not require unusual regiospecific addition mechanisms for its formation, but then such a compound would be possible only if all the reactions are ones which proceed from the β side. Otherwise, for example, suppose **1** to be 17β-H. Expected cis addition from the α side to the Δ^{12} bond would give the 12α,13α,17β product, olefin **2** would have to be a 12α,17β isomer, **3** would be a 12α isomer; and, in order for **3** to be converted to the same hydrocarbon as was formed from **1**, addition to the $\Delta^{13(17)}$ bond would have to proceed in a trans regiospecific manner.

(16) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, **21**, 2489 (1965).

(17) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).



	R^1	R^2	R^3
10	OH	OH	H
11	H	OH	H (C-18 OH)
12	H	OH	OH



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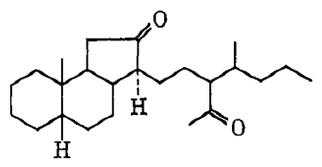

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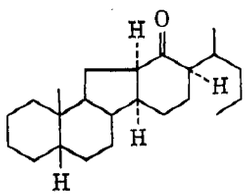

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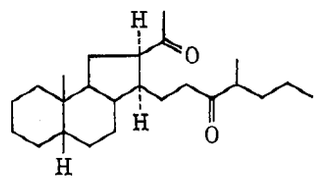


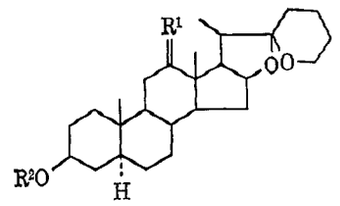
18

their structures have not been completely clarified. They are probably the αα or ββ diols from a single olefin, as on oxidation they gave the same ketone.

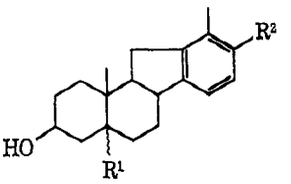
The D Ring Aromatic 4.—Conversion of all three olefins into a single hydrocarbon supplements the initial evidence of the same skeletal system provided by the successful aromatization of the three into **4**, but is more convincing because the hydrogenations conducted under mild conditions in each instance gave high yields of **9**, whereas the dehydrogenations required more vigorous conditions and afforded lesser yields.

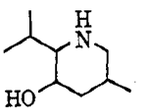
However, the cholajervane structure of these compounds requires separate documentation, which is available in the form of much spectral evidence. The nmr spectrum of **4** has in the aromatic region a two-proton (ortho) quartet which is virtually identical in chemical shift and splitting pattern with the corresponding signal exhibited in the nmr spectrum of **22**.[18] Both have their C-21 methyls (benzylic) as sharp doublets (J = 7 Hz) coupled with the C-20 protons which are quartets (J = 7 Hz) slightly obscured by overlapping signals, and the two have similar chemical shifts for the C-18 aromatic methyl protons (τ 7.84 for **4**, 7.78 for **22**). The C-19 methyl signal of **4** is at τ 8.97, which compares favorably with the value of τ 8.93 used for the C-19 methyl protons in the A/B-cis reference structure **23** in a nmr summary of 35 related aromatic D ring compounds.[19] Furthermore, uv spectra of **4** and veratramine[20] (**24**) are identical in shape and maxima of absorption.

Mass spectral analysis affords additional support for the structure of **4**. Its fragmentation pattern

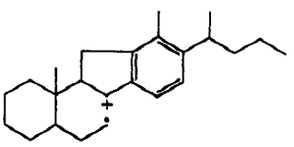


	R^1 (R^2 = Me succinyl[6a] or acetyl[11])
19	H, α-OTs
20a	H, β-OMs
20b	H, β-OTs
21	NNHTs

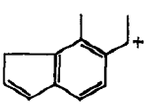


	R^1	R^2
22	α H	CHO
23	β H	H
24	Δ[5]	

resembles that of dihydroveratramine[21] in having in the higher mass range only one major ion, which is formed by fission of the side chain at the bond β to the ring. The second most intense fragment is a m/e 157 ion b which by plausible steps can be derived from a molecular ion a.



(M^+)a



b, m/e 157

Mass Spectra.—Prominent ions observed in the mass spectra of **4** and the other cholajervane derivatives prepared in this work are summarized in Table I. The

Table I

Prominent Ions in Mass Spectra of Cholajervanes

Ion	m/e (peak intensities, % of base peak) 1	2	3	9	4
M^+	328 (10)	328 (29)	328 (28)	330 (11)	324 (42)
M − 15		313 (22)	313 (8)		
M − 43 + 1		286 (75)			
M − 43[a]			285 (18)		281 (100)
M − 71 + 1[b]	258 (23)	258 (100)		258 (43)	
M − 71[c]	257 (100)	257 (92)	257 (13)	259 (100)	253 (9)
M − 85[d]		243 (67)			
	163 (9)	162 (67)		163 (23)	
	161 (10)	161 (63)	161 (26)		157 (12)[e]
149 ion[f]	149 (19)	149 (65)	149 (11)	149 (30)	
		148 (63)	133 (100)[e]	135 (15)	

[a] M − C_3H_7 (rupture of side chain at branch). [b] M − side chain + hydrogen rearrangement. [c] M − side chain. [d] M − side chain − CH_2. [e,f] See discussions in text. [e] May be artifact.

(18) R. W. Franck, G. P. Rizzi, and W. S. Johnson, *Steroids*, **4**, 463 (1964). We are indebted to Professor Johnson for a reference spectrum of compound **22**.

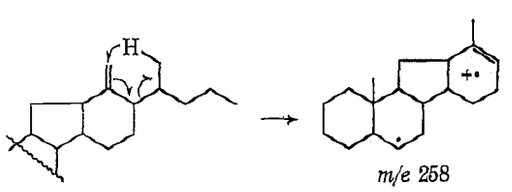
(19) T. Masamune, I. Yamazaki, K. Orito, and M. Takasugi, *Tetrahedron*, **27**, 3387 (1971).

(20) We thank Dr. Murle W. Klohs of Riker Laboratories for samples of veratramine and related compounds.

(21) H. Budzikiewicz, *Tetrahedron*, **20**, 2267 (1964).

most telling evidence supporting the six-membered D-ring structure in olefins **1**, **2**, **3**, and **9** is in the absence in their spectra of an ion corresponding to M − side chain − 42, which is a characteristic[22] frgament found in steroidal hydrocarbons substituted at C-17.

The fragmentation of the cholajervanes reflects the presence of a six-membered D ring, as it is known that alkyl cyclohexanes, unlike alkyl cyclopentanes, retain the cyclic structure in the fragmentation process.[23] The base peaks of **1** and **9** are *m/e* 257 and 259, respectively, both M − **71** ions, while the most intense peaks in the spectrum of **2**, of nearly equal intensity, are *m/e* 257 (M − 71) and 258 (M − 71 + 1). The net loss of side chain in **1** and **9** is consistent with the favored retention of the cyclic structure, the allylic 17,20 bond in **1** being favored for cleavage, and the same bond in **9** being favored in an alkyl cyclohexyl fragmentation. The two intense ions from **2** probably result from (1) an allylic cleavage to give *m/e* 257, and (2) fragmentation with a favorable, familiar hydrogen rearrangement, as depicted, to give the *m/e* 258 ion.



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The spectrum of **3** shows a quite different fragmentation pattern; in the higher mass range the most intense ion is at *m/e* 285 (M − 43); cleavage at 17,20 would be a higher energy process than at the 20,22 allylic bond. However the M − side chain ion *m/e* 257 is present in the spectrum, and could represent an isomerization of **3** to **1** or to **2**, although this rearrangement under chemical rearranging conditions proceeds in the reverse direction.

The presence of a significant *m/e* 149 and virtual absence of a *m/e* 151 ion in each of the spectra of **1**, **2**, **3**, and **9** (all 5β-cholajervanes) is of interest in connection with a recent publication[24] describing the feasibility of distinguishing between C-5 epimeric steroidal hydrocarbons substituted at C-17. 5α compounds showed a dominant *m/e* 149 ion while 5β epimers have two significant peaks, at *m/e* 149 and 151. Since deuterium-labeling studies[24] on the 17-substituted steroid hydrocarbons confirm the importance of rupture of the 13–17 bond in forming a molecular ion and consequent derivation of the *m/e* 151 ion, the absence of the latter ion in the cholajervane fragmentation can be explained on the basis that initial formation of such a molecular ion does not take place, because a 13,17 bond cleavage would mean disruption of the six-membered cyclic structure.

These and earlier studies by the same group of investigators[24] show that the formation of the *m/e* 149 ion, found ubiquitously in steroidal hydrocarbon spectra, is a complex process and results from several different fragmentation mechanisms. We must assume that the ion of the same *m/e* value derived from the cholajervanes also has a complicated genesis.

In Table I are listed lower *m/e* fragments which in reference to the known complexity of the *m/e* 149 ion probably are also of complex origin. They are included in the table mainly because the finding of the same (or differing only in one or two units) *m/e* fragments among the five compounds may be suggestive of related fragmentation processes.

Mechanism of Rearrangements.—The 12β-(equatorial) mesylate **6** reacts at a rate about 1300 times faster than the epimeric mesylate, as established by determination of the half-lives in solvolysis of the two compounds. Since solvolysis reaction rates of simple cyclic epimeric sulfonates (*e.g.*, *cis*- and *trans*-4-*tert*-butylcyclohexyl tosylates) are known to differ[25] only by a factor of a few units, with the axial epimer undergoing the faster reaction, the much faster reaction of the equatorial mesylate **6** must mean that solvolyses of **5** and **6** proceed by quite different mechanisms.

A recent study[11] of the two *C*-nor-*D*-homo steroid yielding reactions,[6,11,13,26] solvolysis of 12β-sulfonates and Bamford–Stevens decomposition[27] of 12-tosylhydrazones, has been published in which an attempt is made to explain the considerable variation in products and their yields in previously published work, on the basis of changes in mechanism caused by variation of solvent type and reaction temperature. Most of the study was carried out on the two hecogenin derivatives, rockogenin (12β) tosylate (**20b**) and hecogenin tosylhydrazone (**21**).

Our work on analogous reactions involving the 12β-mesylate **6** and the tosylhydrazone **8** were each conducted under a single set of reaction conditions, and the results independently would not be expected to shed much light on detailed mechanisms. However, since the conclusions from the paper cited rest on a consideration of products and yields, a comparison of our results with those reported in their study obtained under comparable conditions is in order.

The solvolysis of **5** in collidine under reflux should be comparable to the reaction of **20b** in pyridine under reflux, the main difference being in the temperature at reflux (171° *vs.* 115°). The difference in temperature could explain the lower proportion of the exo ($\Delta^{13(18)}$) olefin found in the reaction of **5**, but the total absence of the $\Delta^{13(17)}$ isomer among the products of their pyridine reaction, in contrast with the substantial yield in the reaction of **5**, is conspicuous. The consistent failure to find the $\Delta^{13(17)}$ isomer among the

(22) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, p 338; H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964, p 94; L. Tökes, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968); G. von Unruh and G. Spiteller, *Tetrahedron*, **26**, 3329 (1970).

(23) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 63.

(24) L. Tökes and B. A. Amos, *J. Org. Chem.*, **37**, 4421 (1972).

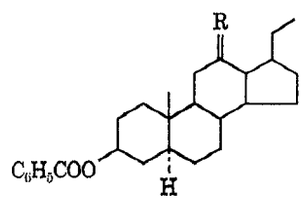
(25) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 96.

(26) H. Mitsuhashi and Y. Shimizu, *Tetrahedron*, **19**, 1027 (1963).

(27) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); W. Kirmse, B. G. von Bulow, and H. Schepp, *Justus Liebigs Ann. Chem.*, **691**, 41 (1966); R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967); G. Kaufman, F. Cook, H. Schechter, J. Bayliss, and L. Friedman, *ibid.*, **89**, 5736 (1967); K. Geibel, *Chem. Ber.*, **103**, 1637 (1970); A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **94**, 7081 (1972). (The last paper contains an extensive summary of references to the Bamford–Stevens reaction.)

products in all the reported rearrangement reactions of **20a**, **20b**, and **21** was attributed to the possible inductive effect of the 16-oxygen function.[11] This explanation receives some support from the fact that **5** without a substituent at C-16 does yield a $\Delta^{13(17)}$ olefin, and the only other indication that another such isomer is formed is from the indirect evidence derived from the rearrangement reaction involving the 12β-pregnanol tosylate derivative **25** mentioned above in discussing the $\Delta^{13(17)}$ olefin **3**. However, it should be pointed out that both the compounds **5** and **25** are unfettered by a fused E ring.

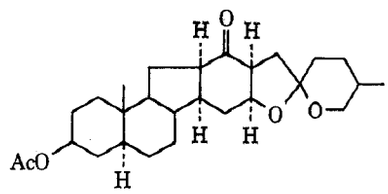
The most glaring discrepancies are found when the results of our experiments with the 12-substituted cholanes **6** and **8** are compared with those obtained with the two corresponding pregnane derivatives **25** and **26**. The latter results are not listed in Table I,



R

25 H,β-OTs

26 NNHTs



27

but are discussed in the final sections of the paper.[11] The cholanol and pregnanol derivatives compared are identical in the B, C, and D rings, with the C-17 hydrocarbon side chain three carbons longer in the former, and a difference[28] in the A/B ring junction. It was reported that the reactions 12β-tosylate **25** in potassium *tert*-butoxide and **25** in pyridine, and the tosylhydrazone **26** decomposition, all failed to produce either the Δ^{11} unrearranged olefin[29] or the exocyclic $\Delta^{13(18)}$-pregnajervene. The absence of the Δ^{11} compound in 12β solvolysis, and of the $\Delta^{13(18)}$ olefin in the decomposition, is consistent with our findings, but is contrary to the results for the $\Delta^{13(18)}$ olefin in our analogous former reaction, and for the Δ^{11} olefin in the latter.

No other studies of rearrangement reactions of 12α-sulfonates have been reported in the literature, although oils of undetermined structure formed as side products in early investigations[31] designed to prepare Δ^{11} compounds were obviously products of rearrangement. The work described here carried out under a single set of experimental conditions also does not warrant more than some tentative speculations on the course of the reaction. Solvolysis of the axial **5** in collidine is slow,[29] even much slower than such a reaction of an uncomplicated cyclic equatorial sulfonate, and probably undergoes preliminary formation of a carbonium ion, or ion pair, involving the sulfonyloxy group. Stabilization of the carbonium ion follows either by direct elimination to give the Δ^{11} cholene, or by rearrangement and subsequent eliminations of the rearranged ion to give the more stable olefins **1** and **3**, rather than the exocyclic **2**.

A clear explanation of why the angular methyl group at C-13 in a conformationally favorable trans-diaxial juxtaposition relative to the 12α-mesyloxy group does not rearrange is lacking, but steric factors appear to be important.[32]

There is ample evidence that reactions of 12α-sulfonates are sensitive to steric factors. In elimination on alumina,[33] the rate of reaction is dependent on whether there is an α substituent at C-17, whether the A/B ring junction is cis or trans fused, and on the bulk of the sulfonate group. A number of other reactions of 12-substituted steroids whose behavior is regarded as "anomalous" are unsatisfactorily explained probably because, among the various factors controlling the reactions, the very important steric factor is so difficult to assess. Some of these are the much discussed erratic reduction of 12 ketones,[34] the esterification of 12α[35] and 12β[36] alcohols, the Grignard reaction on 12 ketones,[37] and the inversion of migration order in tlc of certain 12-hydroxy derivatives.[38] The rearrangement of **5** appears to be another of the

(28) Two other differences are (1) the cholanol sulfonate **6** is a mesylate while the pregnanol sulfonate **25** is a tosylate, and (2) both **6** and the tosylhydrazone **8** are unsubstituted at C-3 while **25** and the tosylhydrazone **26** have 3β-acetoxy substituents. These differences in structure would affect the reactions, but should do so only minimally. The longer side chain of **6** and **8** is still alkyl and its effect should be largely of a steric nature, and, while it has been shown[33] that the conformation of the A/B rings and the size of an 12α-substituted sulfonate group are factors, they should not be decisive factors. Apart from the relative bulk of the mesyloxy and tosyloxy groups there are also electronic differences between the two, but in the instances where direct comparisons can be made between reactions of the tosylates[11] and mesylates[6] of the spirostan series, the results as reported are similar.

(29) In the initial publication on the *C*-nor-*D*-homo rearrangements[6a] the 12α-mesylate **19** was reported to yield after 15 hr at reflux in potassium *tert*-butoxide in *tert*-butyl alcohol largely unchanged starting material. The yield of olefin was about 10%, which was of the Δ^{11} compound; no rearranged product was found. In our earlier work on the preparation of unsaturated steroids, compound **5** was recovered essentially unchanged when refluxed under the same conditions, but in potassium *tert*-butoxide in DMSO at room temperature gave 11-cholene (65%), 12α-cholanol (29%), and no rearranged olefinic material.[30]

(30) F. C. Chang, *Steroids*, **4**, 55 (1964).

(31) J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946).

(32) Failure of the methyl group to rearrange to C-12 is especially interesting, as analogous migrations of that group to C-17 are well known (N. L. Wendler in "Molecular Rearrangements," part II, P. de Mayo, Ed., Wiley, New York, N. Y., 1964, p 1020) even though the leaving 17α substituent is pseudoaxial.

(33) G. Just and C. R. Engel, *J. Org. Chem.*, **23**, 12 (1958); C. R. Engel and S. F. Papadopoulos, *ibid.*, **26**, 2868 (1961).

(34) J. W. Huffman, D. M. Alabran, and T. W. Bethea, *J. Org. Chem.*, **29**, 2963 (1964); M. Alauddin and M. Martin-Smith, *ibid.*, **28**, 886 (1963); J. W. Huffman and J. T. Charles, *J. Amer. Chem. Soc.*, **90**, 6486 (1968); W. S. Murphy and D. F. Sullivan, *Tetrahedron Lett.*, 3707 (1971).

(35) R. T. Blickenstaff, K. Atkinson, D. Breaux, E. Foster, Y. Kim, and G. C. Wolf, *J. Org. Chem.*, **36**, 1271 (1971).

(36) M. E. Wall, F. I. Carroll, and G. S. Abernathy, Jr., *ibid.*, **29**, 604 (1964).

(37) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron Lett.*, 4469 (1965).

(38) 12α-Cholanol (**29**) migrates faster on silica gel plates than either its mesylate **5** or acetate **31**, contrary to the usual order (unpublished observations from this laboratory).

reactions which will remain "anomalous" until the steric factors are better known.[39]

In summary, a retrospective review of pertinent known work must lead one to the conclusion that, at the present stage of knowledge, a sufficient understanding of the three reactions which are available for the preparation of *C*-nor-*D*-homo steroids by rearrangement of 12-substituted steroids, to make possible a valid prediction of the products, is still not at hand. While the effect of solvent and reaction temperature is important, it seems clear that the course of the reactions is controlled as much by the structure and geometry of the reacting molecule, and precise knowledge concerning the steric factor is also needed.

The Ketones 16, 17, and 18.—The ketones derived from olefins **1**, **2**, and **3** *via* the respective diols were all crystalline products, and spectral data support the olefin structure assignments.

Ketone 16, having carbonyl groups corresponding to a five-ring ketone and a methyl ketone, by ORD determination shows a weak positive Cotton effect (a + 42), the direction of which agrees with an analysis of ORD aspects of hexahydroindanones.[40] The amplitude is smaller than might be expected, as the atoms C-8 and C-9 and the A ring are all in positive octants according to the octant rule; only the C-19 methyl group is in a negative octant. Perhaps the long β substituent at C-14 in a favorable conformation extends sufficiently into the negative front octant to influence the net Cotton effect.

Ketone 17 has carbonyl absorption characteristic of a cyclohexanone, and in its ORD spectrum exhibits a strong positive Cotton effect (a + 148) which is in disagreement with the value (a − 29) reported[41] for the spirostan ketone **27** which is analogous to **17**. It is not likely that lead tetraacetate oxidation of diol **17** has caused inversion at C-12 or C-17 when periodic acid or sodium periodate oxidation of the corresponding spirostanediol to **27** does not.[41] Inspection of a Dreiding model of **17** offers a possible explanation: with ring D in a distorted chair conformation,[18c,e] the A ring (A/B cis) is very prominently in the upper positive front octant, and the β substituent at C-17 could be partly in the lower positive front octant.

Ketone 18 by ir has carbonyl absorptions corresponding to a methyl ketone and an aliphatic (or C_6 ring) carbonyl group. As expected its ORD spectrum showed very small rotation over the entire uv range.

Experimental Section

General.—Melting points were determined on an electrical micro hot stage and are uncorrected. Combustion analyses were performed by Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Knoxville, Tenn. Infrared spectra were obtained using either a Perkin-Elmer Infracord Model 137, or Model 257 grating spectrophotometer. Optical rotation measurements were obtained with a Carl Zeiss photoelectric precision polarimeter using $CHCl_3$ as solvent. Ultraviolet spectra were measured in ethanol on a Perkin-Elmer Model 202 spectrophotometer. Gas–liquid chromatography was carried out on Hewlett-Packard Models 5750 or 402, or Varian Aerograph Model 700, chromatographs. Optical rotatory dispersion spectra were recorded on a Cary 60 spectropolarimeter at room temperature. Mass spectra were obtained either with a Jeolco Model JMS-01S, or with a Varian Model M66, or MS902, instrument. Either a Varian A-60A or HA-100 spectrometer was used for determination of nmr spectra. Tetramethylsilane was used as internal reference and chemical shifts are given on the τ scale.

Analytical thin layer chromatography and preparative thin layer chromatography (ptlc) were performed on glass plates layered (0.25 mm for tlc, 1.0 mm for ptlc) with silica gel G (Merck, Darmstadt). The plates used for ptlc were in addition impregnated with Ultraphor (Badische Anilin und Soda-Fabrik). Certain analytical tlc was done on layers containing silver nitrate (Stlc) prepared from silica gel in 7.5% silver nitrate–aqueous methanol solution, according to Gupta and Dev.[42] Analytical spots were visualized by spraying with ethanol–sulfuric acid–vanillin.[43] For cases where multiple development of plates was used, the abbreviation A,2× indicates that the plate was developed twice in solvent A (see below). Generally preparative plates required no spraying before being viewed under long wavelength (366 mμ) uv light. However, ptlc plates impregnated with silver nitrate required a preliminary spraying with 2′,7′-dichlorofluorescein[44] (0.1% in methanol) before viewing with uv radiation.

For column chromatography, either Florisil (60–100 mesh, Floridin Co.) or neutral aluminum oxide (activity grade I, Woelm Alumina) was used. Adsorbents treated with $AgNO_3$ (15%) were prepared as for tlc plates but were heated for 3 hr at 200° before use.

Solvents used for chromatographic development and elution are designated and abbreviated as follows: petroleum ether (bp 63–70°) (A), chloroform (B), ethyl acetate (C), ethyl ether (D), acetic acid (E), and acetone (F). A mixture of 50% Skelly B, 49% ethyl acetate, and 1% acetic acid is abbreviated ACE 50,49.

Solvolysis of 12α-Cholanol Mesylate (5).—A solution of **5** (10.0 g) in redistilled collidine (170 ml), after being heated at reflux for 4 hr, was stirred into a slush of ice–5% HCl and extracted with ether. The ethereal layer was washed successively with dilute acid, sodium bicarbonate solution, and water, dried with calcium sulfate, and evaporated to a dark oil. The oil (7.6 g), dissolved in petroleum ether and decolorized by passage over neutral alumina, was crystallized from THF–methanol to yield 11-cholene[45] (**7**) as colorless, elongated plates (1.4 g, 18%): mp 80.0–80.5°; $[\alpha]_D$ +36.6°; ir (KBr) 13.84 μ; nmr τ 9.28 (s, 3, C-18 or C-19 Me), 9.12 (s, 3, C-18 or C-19 Me), 4.58 [d of d, 1, $J_{11,12}$ = 10, $J_{9,11(or12)}$ = 2.5 Hz, C-11 (or C-12 H)], 3.87 [d of d, 1, $J_{11,12}$ = 10, $J_{9,12(or11)}$ = 2.5 Hz, C-12 (or C-11 H)].

The mother liquor was chromatographed on a $AgNO_3$–alumina column (900 g) and eluted with petroleum ether (monitored by Stlc). The early fractions produced an oil (1.52 g) which in acetone yielded 0.92 g (12%) of Δ^{12}-cholajervene[2a] (**1**) as colorless plates: mp 55.8–56.4°; $[\alpha]_D$ +2.5° (*c* 4.43); ir (KBr) 6.92 and 7.24 μ; nmr (100 MHz) τ 9.12 (s, 3, C-19 Me), 8.44 (s, 3, C-18 Me), 9.07 (d, 3, *J* = 7 Hz, C-21 Me).

Anal. Calcd for $C_{24}H_{40}$ (328.3130): C, 87.73;) H, 12.27. Found: C, 87.79; H, 12.26; M^+, 328.3116.

Continued elution provided another oily substance (0.40 g). Rechromatography of this material afforded $\Delta^{13(17)}$-12α-cholajervene[2b] (**3**) which, although shown to be homogeneous by Stlc and nmr, resisted attempts at crystallization: $[\alpha]_D$ −76.2° (*c* 2.99); nmr (100 MHz) τ 8.37 (s, 3, C-18 Me), 9.15 (s, 3, C-19 Me), 7.43[46] (q, 1, 20-H), 9.08 (d, 3, *J* = 7 Hz, C-21 Me). By

(39) An *ex post facto* speculation regarding the failure of the C-18 methyl group to shift, reflecting mainly observations from X-ray studies of the detailed geometry of steroid skeletons [H. J. Geise, C. Altona, and C. Romers, *Tetrahedron*, **23**, 439 (1967); C. Altona, H. J. Geise, and C. Romers, *ibid.*, **24**, 13 (1968)] is the following. The methyl group in a cholane molecule is distorted away sufficiently from coplanarity with the leaving 12α-mesyloxy substituent to render migration of the strained 13,14 bond a more favorable (lower energy) process than the shift of the 18-methyl group. By the same reasoning, one might conclude that, in the instances where the methyl group does undergo facile shift to C-17, the distortion must be in the direction of greater coplanarity of the C-18 methyl and the 17α substituent, as compared with the departure from coplanarity when the 17α group is pseudoaxial.

(40) W. Klyne, *Tetrahedron*, **13**, 29 (1961).

(41) J. M. Coxon, M. P. Hartshorn, and D. N. Kirk, *Aust. J. Chem.*, **18**, 759 (1965).

(42) A. S. Gupta and S. Dev, *J. Chromatogr.*, **12**, 189 (1963).

(43) J. S. Matthews, *Biochim. Biophys. Acta*, **69**, 163 (1963).

(44) C. B. Barrett, M. Dallas, and F. B. Padley, *J. Amer. Chem. Soc.*, **40**, 580 (1963).

(45) R. T. Blickenstaff and F. C. Chang, *J. Amer. Chem. Soc.*, **81**, 2835 (1959).

(46) D. Chapman and P. D. Magnus, "Introduction to Practical High Resolution Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1966, p 89.

double irradiation it was shown that the τ 7.43 and 9.08 signals are coupled.

Anal. Calcd for $C_{24}H_{40}$ (328.313): C, 87.73; H, 12.27. Found: C, 88.20; H, 12.20; M^+, 328.313.

Subsequent fractions from the column yielded 1.05 g of compound **7** (total yield of isolated product, 32%), in addition to several unresolved products (presumably olefins) in minor yield.

Solvolysis of 12β-Cholanol Mesylate[2a,4] (6).—A solution of **6** (5.33 g) was treated with collidine as with **5** for 1 hr, although the reaction was complete before 1 hr, as monitored by tlc. The product processed similarly was a residual oil (4.87 g) which was chromatographed on $AgNO_3$–alumina. The early fractions (1.19 g) dissolved in acetone gave 0.74 g (15%) of crystals found to be identical with **1**, according to tlc, glc, melting point, mixture melting point, ir, and nmr comparisons.

Intermediate fractions yielded a colorless oil (0.89 g, 24%) shown to be identical with **3** according to tlc, glc, ir, and nmr comparisons.

Material from later fractions when crystallized from acetone–benzene solution yielded 1.01 g (27%) of $\Delta^{18(18)}$-12α-cholajervene[2b] (**2**) as dense prisms: mp 36.0–37.2°; $[\alpha]_D$ +57.1° (*c* 3.23); ir (CS_2) 11.23 μ (methylenic double bond); nmr τ 9.10 (s, 3, C-19 Me), 9.10 (d, 3, J = 6 Hz, C-21 Me), 5.17, 5.30 (two perturbed 1-H singlets, >C=CH_2).

Anal. Calcd for $C_{24}H_{40}$ (328.313): C, 87.73; H, 12.27. Found: C, 87.80; H, 12.23; M^+, 328.309.

Other minor unresolved products were detected by glc and tlc.

Alkaline Decomposition of 12-Oxocholane *p*-Toluenesulfonylhydrazone[7] (8).—A mixture consisting of the tosylhydrazone **8** (0.20 g) added to a solution of Na metal (0.18 g) in ethylene glycol (8.0 ml) was maintained at a temperature of 150–170° in a nitrogen atmosphere for 1 hr, at which time evolution of gas had ceased. After being cooled the reaction mixture was poured into ice water and extracted with ether. The etheral extract was washed with water, dried with Na_2SO_4, and evaporated to yield a crude product which after passage over a Florisil column was a colorless oil (0.072 g). By tlc and glc analysis the oil was observed to consist of many more components than the products of the 12α- and 12β-mesylate solvolyses, but with olefins **1**, **3**, and **7** predominating. Isolation of the olefins was not attempted; estimation of the yields was done by glc quantitation and with confirmation of products by Stlc, as described in the next section.

Estimation of Total Yields.—The olefin yield values cited above for the two solvolysis reactions were yields obtained by isolation. The total yields of compounds **1**, **2**, **3**, and **7**, respectively, as estimated by glc (or glc and tlc) and summarized previously,[2b] are for solvolysis of **5**, 32, 0, 15, 40; for solvolysis of **6**, 35, 30, 25, 0; and for decomposition of **8**, 26, 0, 8, 24. The results previously reported were based on integration of peak areas with a disk integrator and use of an internal standard (2-cholestene). A subsequent reanalysis of the peak areas with a Dupont 310 curve resolver, corrected for detector response of the individual olefins, essentially confirms the published values.

Olefins **1** and **2** were not resolved by glc on the columns used (QF-1, OV-1, STAP), but were separated on Stlc plates. For the determination of the mixture from **6**, in which **1** and **2** are present, further analysis was effected by the method of visual comparison by tlc.[47]

Additional confirmation of the approximate ratios of olefins in the mixtures from the three rearrangement reactions was obtained by conversion to a mixture of diols which are readily resolvable by tlc, and subsequent spot-size estimation (see section below on diols).

Kinetic Measurements.—Half-life determinations of the solvolysis of mesylates **5** and **6** were carried out as follows. Solutions in collidine of **5** (5%) and **6** (8%) were prepared and 0.2-ml aliquots were sealed in 1-ml ampoules and placed in a constant-temperature bath at 100°. Ampoules were removed at intervals, and stored in a Dry Ice–acetone bath until an ir determination was made. Mesylate concentrations were determined directly on the collidine solutions by measurement at 10.5–11.5 μ and comparing absorption at the sharp maximum at 11.1 μ for **5**[4] and 11.0 μ for **6** with collidine solutions of known concentrations (base-line method[48]).

The half-life so determined for the reaction of **5** was 12.4 days (17,856 min); for **6**, 13.6 min (a factor in excess of 1300). At room temperature the spectrum of an 8% solution of **6** was unchanged over a period of 4 hr.

$\Delta^{12,14,16}$-Cholajervatriene (4). A. From Δ^{12}-Cholajervene (1).—Olefin **1** (0.138 g), xylene (4 ml), and 5% palladium on alumina catalyst[49] were heated in a sealed tube at 100°. Aliquots removed at various intervals examined by glc showed that reaction was slow, and **1** was first converted to **3** before further dehydrogenation occurred. At 48 hr the reaction was still incomplete, but it was stopped by cooling and addition of petroleum ether before filtering from the catalyst. Evaporation of solvent from the filtrate yielded an oil (0.116 g) composed of unchanged **1** (20%), **3** (20%), and **4** (60%), according to estimation by glc. The oil was chromatographed on $AgNO_3$–alumina. Uv-absorbing (267, 279 mμ) fractions (0.084 g) were combined and rechromatographed by ptlc (A,2×) to give **4** as a homogeneous oil: $[\alpha]_D$ +39.8° (*c* 3.72); ir (CS_2) 12.02, 12.29, 12.40 μ (aromatic); uv max (C_2H_5OH) 267 mμ (ε 810), 270, 275; nmr (100 MHz) τ 8.97 (s, 3, C-19 Me), 8.87 (d, 3, J = 7 Hz, C-21 Me), 7.84 (s, 3, C-18 Me), 7.08 (m, 1, C-20 proton), 3.20 (q, 2, aromatic).

Anal. Calcd for $C_{24}H_{36}$ (324.2824): C, 88.82; H, 11.18. Found: C, 88.79; H, 10.86; M^+, 324.2817.

Other methods of aromatization of **1** [palladium on charcoal in cymene,[50] *o*-chloranil[51] in DMF or in bis(2-methoxyethyl) ether, bromosuccinimide–collidine[52]] were all tried on **1** and found to be less satisfactory; for **2** and **3** the palladium on charcoal–cymene method gave the best yields (see below).

B. From $\Delta^{13(17)}$-12α-Cholajervene (3).—A solution (0.051 g) of $\Delta^{13(17)}$-cholajervene (**3**) in cymene (1 ml) was heated (100°) in a sealed tube with 0.118 g of 10% palladium on powdered charcoal for 44 hr. Filtration and evaporation of solvent afforded an oil (0.050 g) which was chromatographed over $AgNO_3$–alumina to obtain a homogeneous oil (0.017 g) shown to be identical with **4** by nmr, glc, tlc, uv, and ir determinations.

C. From $\Delta^{18(18)}$-Cholajervene (2).—Compound **2** by treatment with palladium on charcoal–cymene as in part B was found to be converted first to **3** before aromatization when monitored by glc. Estimated by comparison of peak heights, the ratio of **3** to **4** in the reaction product after 1 hr was 6.4:1, and after 24 hr, 1.4:1. Longer heating did not change the ratio appreciably. The proportion of **1** was uncertain at the early stages of the experiment inasmuch as compounds **1** and **2** are not resolved by glc (see below); although after 24 hr, when the reaction was stopped, the peak for **1** amounted to 15% of the total product, and tlc showed that olefin **2** is not present in the mixture. Confirmation of the identity of **3** and **4** was obtained by glc cochromatography with added samples of authentic **3** and **4**, and by tlc comparison.

Isomerization[6a,53] of 1 and 2. A. Formic Acid.—A solution of the exocyclic olefin **2** (0.100 g) in benzene (10 ml) was stirred with 98–100% formic acid (20 ml) at room temperature for 96 hr. Ether extraction followed by neutralization, drying, and removal of the solvent furnished an oil (0.090 g) composed of endocyclic olefins **1** (15%) and **3** (75%), according to glc analysis. The formation of olefins **1** and **3** was confirmed by tlc and subsequent isolation of diols **10** and **12** from the products of isomerization (see below, diol section).

A benzene solution of endocyclic olefin **1** was unchanged when treated similarly with formic acid. However, the reaction mixture afforded numerous olefin products when held at 60° for 113 hr under an atmosphere of nitrogen. Partial (40%) conversion to **3** was detected by chromatography (glc, tlc) and confirmed by isolation of diols from the osmylation reaction.

B. With PtO_2.—Compound **2** (0.010 g) shaken in a Parr apparatus with PtO_2 (0.070 g) in $CHCl_3$ (20 ml) was unchanged after 2 hr. Eight minutes after introduction of hydrogen **3** (30% by glc) was detected. In 2 hr, a mixture of **3** (59%) and **1** (35%) was observed (glc), which remained unaltered during further (24 hr) shaking.

C. With Other Reagents.—Olefins **1** and **2** were unchanged

(47) E. Stahl, "Thin-Layer Chromatography," Academic Press, New York, N. Y., 1965, p 47.

(48) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 209.

(49) Engelhard Industries, Newark, N. J.

(50) W. F. Johns, and I. Laos, *J. Org. Chem.*, **30**, 4220 (1965).

(51) E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *J. Chem. Soc.*, 3123 (1960).

(52) C. F. Hammer, D. S. Lange, J. B. Thompson, and R. Stevenson, *Tetrahedron*, **20**, 929 (1964); H. Mitsuhashi and S. Harada, *ibid.*, **22**, 1033 (1966).

(53) A recent publication is pertinent to this: N. L. Allinger and N. A. Pamphilis, *J. Org. Chem.*, **38**, 316 (1973).

by treatment with (1) collidine at 100°, (2) collidine–CH_3SO_3H (3:1 mixture), and (3) potassium *tert*-butoxide in DMSO at room temperature, and at 100°.

5β,12α-Cholajervane (9). A. From 1.—A solution of **1** (0.14 g) in methanol (140 ml) was shaken in a Parr apparatus with 5% rhodium on alumina catalyst (10.0 g) and hydrogen (3 atm) for 3 hr. The catalyst was filtered and successively washed with MeOH and $CHCl_3$. The combined filtrates, on removal of solvent, gave an oil (0.138 g) containing 85% (glc) of **9**. After chromatography over $AgNO_3$–alumina a fraction (0.116 g) crystallized from a tetrahydrofuran–acetone mixture to give 0.072 g of **9** as well-shaped prisms: mp 38.0–39.5°; $[\alpha]_D$ (cyclohexane) +62.2° (*c* 0.101); nmr (100 MHz) τ 9.11 (s, 3, C-19 Me), 9.17 (d, 3, J = 7 Hz, C-18 or C-21 Me), 9.24 (d, 3, J = 7 Hz, C-18 or C-21 Me), no resonance below 7.00; ir 3.42, 3.50 μ.

Anal. Calcd for $C_{24}H_{42}$ (330.3286): C, 87.19; H, 12.81. Found: C, 87.47; H, 12.49; M+, 330.3292.

B. From 2.—Olefin **2** (0.137 g) in benzene (1 ml) was introduced into a solution of $CuSO_4$ (0.006 g), 85% hydrazine hydrate (10 ml), and absolute ethanol (40 ml). Hydrogenation was complete after O_2 was bubbled through the refluxing hydrazine–oxygen–copper ion system[14] for 24 hr. The reaction mixture was extracted with ether, and the organic layer was washed successively with dilute acid, base, and water, then dried and freed of solvent. According to glc, the product contained **9** as the major (75%) component. Column chromatography over $AgNO_3$–alumina yielded a fraction (0.084 g) which crystallized from a tetrahydrofuran–acetone mixture to give 0.038 g of good crystalline product, which was identical with the **9** from part A, according to melting point, mixture melting point, $[\alpha]_D$, glc, tlc, nmr, ir, and mass spectral comparisons.

Catalytic hydrogenation of **2** with tris(triphenylphosphine)-rhodium chloride[54] with PtO_2 in acetic acid, with palladium on charcoal, with rhodium on charcoal, and with Raney nickel were all attempted and found to be less satisfactory than the diimide reaction. The reactions either yielded very complex mixtures which did include **9** (by glc) or, as in PtO_2 in acetic acid, resulted largely in isomerization but little hydrogenation.

C. From 3.—Olefin **3** (0.137 g) dissolved in methanol (140 ml) was shaken in a Parr apparatus with 5% rhodium on alumina catalyst (9.00 g) and hydrogen (3 atm) for 24 hr. The catalyst was removed by filtration, and concentration of the filtrate gave 0.130 g of oil, which according to glc contained 70% of **9**. After Sptlc, the oil crystallized as dense prisms (0.010 g) from a mixture of tetrahydrofuran–acetone. The crystalline material was found to be identical with **9** (melting point, mixture melting point, glc, tlc, nmr, $[\alpha]_D$, and mass spectrum).

Diols of Olefins 1, 2, and 3. A. 5β-Cholajervane-12α,13α-diol (10).[2,3]—To olefin **1** (0.100 g) dissolved in anhydrous ether (10 ml)–pyridine (0.1 ml was added at room temperature OsO_4 (0.100 g) and the mixture was allowed to stand for 4 days. After H_2S gas was bubbled (15 min) into the reaction mixture, suspended in CH_2Cl_2, the solution was filtered through Celite, washed with dilute HCl and water, and dried, and solvent removed. The resulting oil (0.094 g) contained a single diol, which in acetone afforded colorless needles of the 12α,13α-diol **10**: mp 159.2–160.1°; $[\alpha]_D$ +36° (*c* 4.3); ir (KBr) 2.95, 8.47, 8.98, 9.80, 10.14, 10.14, 10.53, 10.78 μ; nmr (100 MHz) τ 9.10 (s, 3, C-19 Me), 8.80 (s, 3, C-18 Me), 7.78, 7.43 (s, 2, 2-OH), 9.02 (d, 3, J = 6.5 Hz, C-21 Me).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.48; H, 11.68. Found: C, 79.45; H, 11.78; M+, 362.

B. 5β,12α-Cholajervane-13α,18-diol[2b] **(11)** was obtained by dihydroxylation of olefin **2** as in part A as elongated prisms when crystallized from acetone: mp 121° dec; $[\alpha]_D$ +36.8° (*c* 3.96); ir (KBr) 2.81, 2.92, 9.32, 9.47, 9.72, 9.97, 10.58 μ; nmr (CCl_4) τ 9.09 (s, 3, C-19 Me), 7.43 (s, 2, -OH), 6.46 (q, 2, J = 11 Hz, $-CH_2OH$).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.31; H, 11.66; M − 18, 344.

C. 5β,12α-Cholajervane-13α,17α-diol[2b] **(12)** was obtained by dihydroxylation of olefin **3** as in part A as prisms from a petroleum ether–acetone mixture: mp 166.3–166.9°; $[\alpha]_D$ −3.6° (*c* 4.5); ir (KBr) 2.82, 7.23, 8.47, 9.12, 9.63, 10.20, 10.38, 10.68 μ; nmr τ 9.05 (s, 3, C-19 Me), 8.93 (d, 3, J = 6 Hz, C-21 Me), 8.78 (s, 3, C-18 Me), 7.50, 7.63 (s, 2, 2-OH).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.15; H, 11.83; M+, 362.

D. 5β-Cholane-11α,12α-diol[3] **(13)**, isolated after osmylation of Δ^{11}-cholene (**7**) as in part A, was crystallized from acetone–methanol in the form of prisms: mp 118.0–119.3°; $[\alpha]_D$ +3.6° (*c* 5.00); ir (KBr) 2.92, 7.24, 9.11, 9.57, 9.79, 9.93, 10.41 μ; nmr τ 9.30, 8.93 (s, 6, 2 Me), 7.82 (s, 2, 2-OH), 6.12 (m, 2, C-11β H, C-12β H).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.43; H, 11.63.

Osmylation of Olefin Mixtures.—Each of the olefin mixtures obtained in the rearrangement reactions described above was dihydroxylated with OsO_4 and processed as for olefin **1**. The resulting diols were easily identified by tlc, and isolated by ptlc (developed 4×, $CHCl_3$).

From the olefin mixture of **5**, as expected, diols were isolated which were found to be identical with diols **10**, **12**, and **13**, obtained from olefins **1**, **3** and **7**, respectively (mixture melting point, tlc, ir).

A number of other diols were present as minor components in the mixture. Among these, two were isolated and obtained in crystalline form.

Diol 14 was obtained as fine needles from petroleum ether: mp 114.3–116.4°; $[\alpha]_D$ +5.9° (*c* 5.1); ir (KBr) 2.81, 2.86, 7.26, 8.78, 8.97, 9.61, 10.28, 10.98 μ; nmr (100 MHz) τ 9.08 (s, *ca.* 5, C-19 Me plus contribution from C-21 Me), 9.05 (d, *ca.* 3, C-21 Me), 9.02 (d, *ca.* 3, $CHCH_3$).

Anal. Calcd for $C_{24}H_{42}O_2$ (362,58): C, 79.50; H, 11.68. Found: C, 78.90; H, 11.68.

Diol 15 was obtained as prisms from petroleum ether: mp 113.5–114.0°; $[\alpha]_D$ −4.9° (*c* 4.3); ir (KBr) 2.94, 9.33, 9.88, 10.02, 10.34, 11.44 μ; nmr (100 MHz) τ 9.11 (s, 3, C-19 Me), 9.02 (d, *ca.* 3, C-12 Me), 8.93 (d, *ca.* 3, $CHCH_3$), 7.84, 7.47 (s, 2, 2-OH).

Anal. Calcd for $C_{24}H_{42}O_2$ (362.58): C, 79.50; H, 11.68. Found: C, 79.35; H, 11.96.

The olefin mixture from the reaction of mesylate **6** yielded three diols which were identical with diols **10**, **11**, and **12** prepared from olefins **1**, **2**, and **3**, respectively (mixture melting point, tlc, and ir).

Other minor unidentified products, probably isomeric diols, were observed by tlc, but diols **13**, **14**, and **15** were absent.

The olefin mixture from tosylhydrazone **8** yielded a diol mixture, from which were isolated by ptlc the same five diols (mixture melting point, tlc, ir) as were obtained from **5**, namely **10**, **12**, **13**, **14**, and **15**, the first three corresponding to olefins **1**, **3**, and **7** respectively.

A number of other minor products were present but unidentified.

The olefin mixture from the isomerization reactions reported above were also dihydroxylated. Diols were isolated which confirmed the presence of olefins detected by glc.

Oxidation of Diols to Ketones. 12,13-Seco-5β-cholajervane-12,13-dione[2a] **(16).**—Diol **10** (0.10 g) dissolved in a benzene (10 ml)–glacial acetic acid (10 ml) mixture was treated with $Pb(OAc)_4$ (0.20 g) for 12 hr. Ethylene glycol and water were added to the reaction solution, which was kept for 1 hr at room temperature in the dark. After extraction with ether, washing, desiccation, and removal of solvent, an oil was obtained which in petroleum ether crystallized as plates: mp 53.9–54.8°; $[\alpha]_D$ +91.8° (*c* 4.18); ORD (*c* 0.091, cyclohexane) $[\Phi]_{316}$ +2320°, $[\Phi]_{308}$ +2180°, $[\Phi]_{272}$ −1920°; ir (CCl_4) 5.72 (C_5-ring C=O), 5.83 (aliphatic C=O), 6.88, 7.08 ($-CH_2CO-$), 7.23, 7.39 μ (CH_3CO-); nmr τ 9.33 (s, 3, C-19 Me), 7.83 (s, 3, CH_3CO-).

Anal. Calcd for $C_{24}H_{40}O_2$ (360.56): C, 79.94; H, 11.18. Found: C, 79.60; H, 10.70; M+, 360.

18-Nor-5β,12α-cholajervan-13-one[2b] **(17).**—By similar lead tetraacetate oxidation of **11** and subsequent processing, an oil resulted which crystallized from petroleum ether as plates: mp 37.3–38.3°; $[\alpha]_D$ +13.4° (*c* 3.43); ORD (*c* 0.11, cyclohexane) $[\Phi]_{326}$ +6450°, $[\Phi]_{316}$ +3720°, $[\Phi]_{270}$ −8340°; ir (CS_2) 5.83 μ (C_6-ring C=O); nmr τ 9.11 (s, *ca.* 8, C-19 Me and contributions from C-21 and C-24 methyls).

Anal. Calcd for $C_{23}H_{38}O$ (330.53): C, 83.57; H, 11.59. Found: C, 83.83; H, 11.62; M+, 330.

13,17-Seco-5β,12α-cholajervane-13,17-dione[2b] **(18).**—Diol **12** similarly yielded an oil which in petroleum ether crystallized

(54) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

as plates: mp 68.0–68.6°; $[\alpha]_D$ −49.2° (*c* 3.66); ir ($CHCl_3$ 5.84 (C_6 ring or aliphatic C=O), 6.89 ($-CH_2CO-$), 7.25, 7.38 μ (CH_3CO-); nmr τ 7.83 (s, 3, CH_3CO-), 9.07 (s, 3, C-19 Me), 6.90, 7.60 (m, 1, C-20 H and C-12 H).

Anal. Calcd for $C_{24}H_{40}O_2$ (360.56): C, 79.94; H, 11.18. Found: C, 79.88; H, 10.98; M^+, 360.

Registry No.—**1**, 19534-78-2; **2**, 19594-93-5; **3**, 19594-94-6; **4**, 19654-71-8; **5**, 1251-13-4; **6**, 40429-72-9; **7**, 40429-73-0; **8**, 40429-74-1; **9**, 40429-75-2; **10**, 40429-76-3; **11**, 40429-77-4; **12**, 40429-78-5; **13**, 40429-79-6; **16**, 19654-72-9; **17**, 19594-96-8; **18**, 19594-98-0.

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Stereospecific Bromination of Methyl 3α,7α-Diacetoxy-12-oxocholanate, Catalyzed by Boron Trifluoride

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Methyl 3α,7α-diacetoxy-12-oxocholanate (1) failed to react with bromine in the presence of either hydrobromic acid or sodium acetate, but the monobromination of 1 catalyzed by BF_3 proved to be stereospecific, affording a high yield of the desired 11α-bromo ketone 2. However, the epimerization of 11β-bromo ketone 7, which was prepared by an alternative route, could only be achieved by HBr and not by BF_3. IBr, in the presence of BF_3 or HBr, was found to be very reluctant as a brominating agent for 1. Interpretation of the findings in terms of steric and stereoelectronic effects is offered. The pertinent spectroscopic data, including circular dichroism of the hitherto unknown two epimeric 11-bromo ketones, are given.

Bromination of keto steroids has been widely investigated. However, relatively few studies have been reported on 12-keto analogs.[1-3]

As part of a study we had interest in a stereoselective high-yield bromination of methyl 3α,7α-diacetoxy-12-ketocholanate (1).

Exposure of **1** to the action of bromine at 70°[1] in the presence of hydrobromic acid as a catalyst produced a complex mixture, with a low yield of bromo ketones **2** or **7**. Elimination of the catalyst[2] from the bromination reaction mixture (room temperature), or the addition of sodium acetate, did not induce much improvement in the reaction. None of the methods mentioned appears to be of any practical value, as evidenced by the nmr determinations of the reaction products.

A detailed study was undertaken to clarify the nature of the reaction and the factors determining the reactivity of the α hydrogens in **1**.

11-Bromo ketone **7** was prepared by an alternative method[2,4] (Scheme I).

The obtained 11β-bromo ketone **7** (yield 13%) was subjected to the action of hydrobromic acid in acetic acid solution.[3] The reaction was followed by tlc and nmr at various intervals. An almost complete conversion to the 11α-bromo epimer **2** was achieved after 48 hr.

To rationalize the above findings, namely the slow bromination of **1** and the facile epimerization of **7**, very low rate enolization in the parent compound **1** and enhanced enolization in its 11β-bromo derivative **7** are suggested.

To improve the reaction HBr was substituted by BF_3, a strong Lewis acid, known to be very effective as a catalyst in bromination reactions.[5]

Using bromine, in acetic acid, as the brominating agent and BF_3 as the catalyst, the desired 11α-bromo ketone **2** was obtained in a high yield of 95–97%. Only minor amounts of the 11β-bromo epimer **7** could be detected.

IBr, an effective reagent in the bromination of steroid aldehydes,[6] proved completely inactive in the presence of BF_3 or HBr. The combination, IBr and BF_3, effected a conversion of **1** to the corresponding acid (see Experimental Section).

Regarding epimerization of 11β-bromo ketone **7**, BF_3, in contrast to HBr, proved ineffective, even after long periods of time.

It appears that the action of BF_3 and HBr as catalysts is of an entirely different nature in effecting bromination and epimerization of **1** and **7**, respectively.

The configurations of the hitherto unknown epimers **2** and **7** were assigned by spectroscopic data. The nmr, ir, and uv data, given in the Experimental Section, are in full agreement with those reported on the 7-deoxy analogs. The circular dichroism curves of the two epimeric 11-bromo ketones and the mass spectra are given in Figure 1 and Table I, respectively.

Discussion

The preferential loss of an axial proton in the enolization of conformationally rigid cyclohexanones and the predominance of axial α-bromo ketone in kinetically

(1) H. B. Alter and T. Reichstein, *Helv. Chim. Acta*, **26**, 492 (1943).
(2) T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, **162**, 495 (1946).
(3) E. J. Corey, *J. Amer. Chem. Soc.*, **76**, 177 (1954).
(4) F. Nakada, R. Osawa, and K. Yamasaki, *Bull. Chem. Soc. Jap.*, **34**, 538 (1961).
(5) K. Takeda, T. Komeno, and K. Igarashi, *Chem. Pharm. Bull.*, **4**, 343 (1956).
(6) Y. Yanuka, R. Katz, and S. Sarel, *Chem. Commun.*, 849 (1968).