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C-22 KETALS RELATED TO THE SAPOGENINS*

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Abstract—Reduction of 5,6-dihydrokryptogenin diacetate with Raney nickel in ethanol reduced the 16-ketone group and gave a mixture of a 22-ethyl ketal with a hemiketal. Both undergo elimination reactions very readily to yield the Δ^{22}-bond isomer of pseudotigogenin diacetate. The conversions are reversible and are catalyzed by acetic acid and in neutral solution by calcium sulfate and other surfaces. Alkaline hydrolysis followed by cyclization with acetic acid converted both the ketal and the Δ^{22}-olefin to tigogenin. The relative stabilities of ketal epimers at C-22 are discussed and related to the stereochemistry of the sapogenins and the *cyclo*pseudosapogenins.

THREE years ago an attempt was made to deduce the configuration of the sapogenins at C-22 by conformational analysis.[1] In the case of the sapogenins which belong to the so-called *iso* series, an unambiguous selection seemed possible that agreed with that preferred for various reasons also by other workers.† In the normal series only a tentative conclusion was drawn. The chief uncertainty was whether the difference (*A*) in interactions that would result from an interchange of the axial and equatorial substituents at C-25 would exceed the difference (*B*) in the eclipsed interactions of the substituents at C-20 and C-22 that would result from an interchange of the C-23 methylene and the pyranoid oxygen. On the basis of Pitzer's estimates of the rotational barriers of propane and butane we suggested that (*A*) was larger than (*B*). Since that time, Dauben and Pitzer[3a] have raised the original estimate for butane from 3600 to a value of 4400 to 6100 cal and state that no reliable calculation has been possible. This revision invalidated our argument that the *normal* and *iso*sapogenins differ in their configuration at C-22.

Before this development we had started a study of model substances related to the sapogenins in order to obtain a better estimate of (*B*). While this work was in progress two important communications appeared which bear on this problem. Callow and Massy-Beresford[4] have related sapogenins of the *normal* and of the *iso* series by reactions designed not to change the configuration at C-22 and have concluded that both series possess identical configurations at this asymmetric center and differ in their conformations at C-25. This result is to be expected if (*A*) is smaller than (*B*).

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† For review of the earlier literature see Hirschmann *et al.*[1] The assignment originally made by Wall and Serota was revised.[2]

[1] H. Hirschmann, F. B. Hirschmann and J. W. Corcoran, *J. Org. Chem.* **20**, 572 (1955).

[2] M. E. Wall, S. Serota and C. R. Eddy, *J. Amer. Chem. Soc.* **77**, 1230 (1955).

[3] M. S. Newman, *Steric Effects in Organic Chemistry*. Wiley, New York (1956): [(a)] W. G. Dauben and K. S. Pitzer, *Op. cit.* pp. 8, 15 and 24; [(b)] D. J. Cram, *Op. cit.* p. 304; [(c)] F. H. Westheimer, *Op. cit.* p. 533.

[4] R. K. Callow and P. N. Massy-Beresford, *Chem. & Ind.* 1146 (1956); *J. Chem. Soc.* 4482 (1957).

On the other hand, Wall and Walens[5] have presented evidence in support of the thesis[6] that *cyclo*pseudosapogenins of the two series differ in their configurations at C-22 and agree in their conformations at C-25. This leads to the conclusion that (*A*) is larger than (*B*). In view of this apparent contradiction,* it seems of interest to report our findings on monocylic C-22 ketals, such as (III), since their stability should no longer be dependent on their configuration at C-25.

A possible route to such compounds was suggested by the work of Kaufmann and Rosenkranz,[7] who reduced kryptogenin and its diacetate with Raney nickel in alcohol and observed selective reduction of the 16-keto group. The resulting free compound, which occurs as a hemiketal at least in the crystalline state,[8] readily cyclized with acid to form diosgenin.[7] The amorphous diacetate gave pseudodiosgenin diacetate on treatment with phosphorus oxychloride and pyridine as well as on boiling with tetrahydronaphthalene or acetic anhydride. This suggested a hemiketal structure also for the diacetate. With a view to studying the relative stabilities of the two isomers permitted by asymmetry at C-22, we repeated the reduction of kryptogenin diacetate.

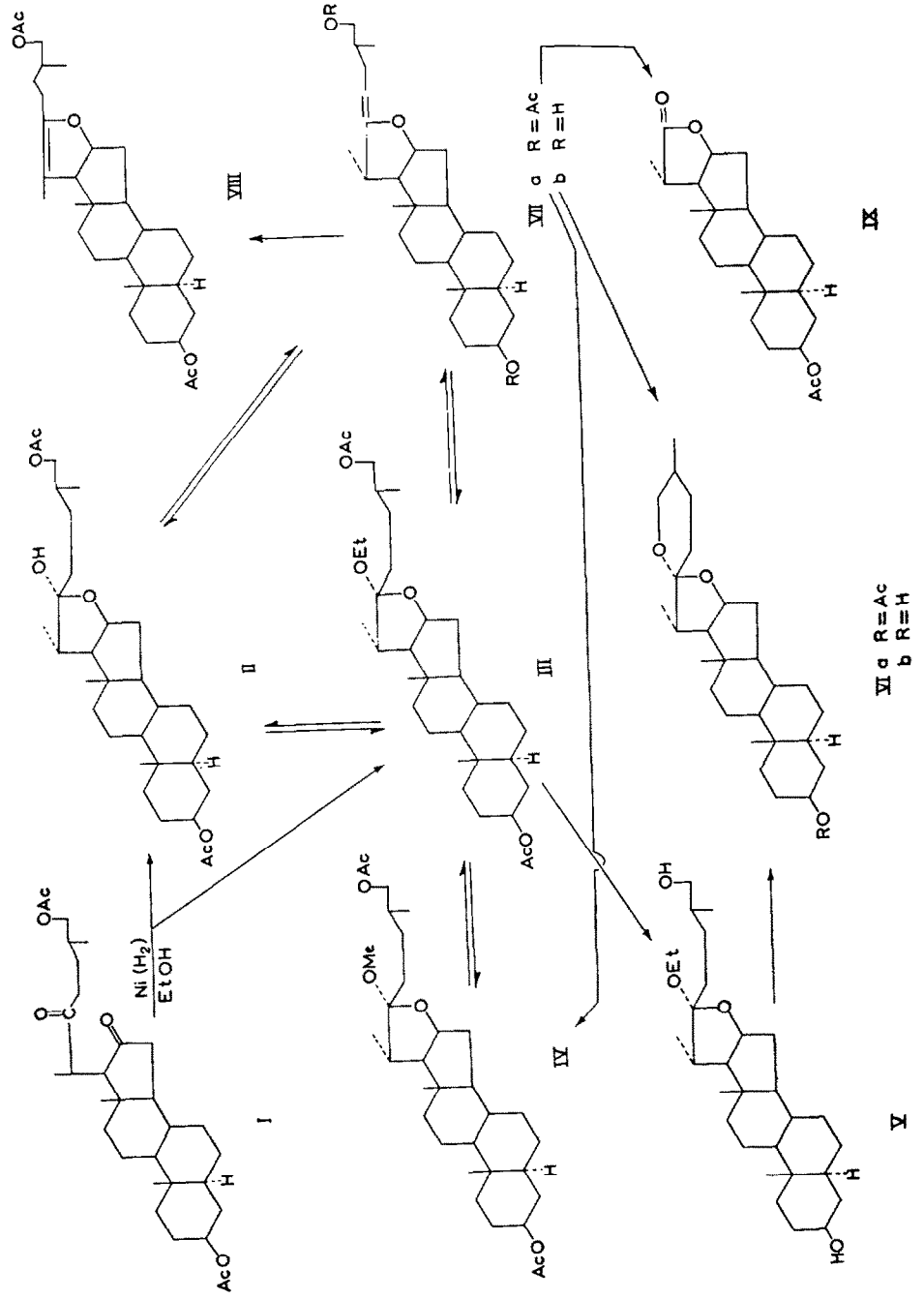
Our reduction product, which no longer possessed the absorption band at 5·82 μ of the 22-ketone group,† proved to be a mixture which could be separated by crystallization into a hydroxylic and non-hydroxylic component. Completely analogous results were obtained in the reduction of 5,6-dihydrokryptogenin diacetate (I). The two reduction products (II) and (III) were closely related. The hydroxylated compound (II) yielded the non-hydroxylic product (III) in the presence of ethanol and acetic acid at room temperature, while dilute acetic acid reversed this process. Compound (III) gave a new substance (IV) with methanol and acetic acid, which reverted to the starting compound with ethanol and acetic acid. All three products (II), (III) and (IV) showed maxima at 5·77 and 8·08 μ of such intensity as to indicate the presence of two acetoxy groups but had no other carbonyl peak. The origin of these compounds and their very facile interconversions in the presence of acid suggested that they represented a hemiketal and an ethyl and a methyl ketal, respectively. Their composition was consistent with this view, which received further support from the conversion of (III) to tigogenin (VIb) by alkaline hydrolysis and cyclization in alcoholic acetic acid. This demonstrated that only the carbonyl group at C-16 had been reduced by the nickel hydrogenation of compound (I), while the one at C-22 had been masked by derivatization.

Attempts to chromatograph either the original reduction mixture or the pure ketal (III) on silica gel–Celite led to the destruction of the ketal and yielded mixtures

* This conflict was not recognized by Wall,[6] who rationalized the different assignments for the *cyclo*pseudosapogenins ("20 β-series") as follows: "A different situation occurs in the 20 β-series. In this case the C_{21} methyl is replaced by a much smaller hydrogen atom, and models show no interaction in either of the two C_{22} possibilities." While this analysis described the situation to the rear of ring E, it took no account of the replacement of a hydrogen by the much larger methyl on the frontal side.

† Our measurement for kryptogenin diacetate agrees with reports on this[9] and other[8] 16-substituted 22-ketones, but differs from observations[10] for 22-monoketones which were found to absorb near 5·87 μ.

[5] M. E. Wall and H. A. Walens, *Chem. & Ind.* 818 (1957).
[6] M. E. Wall, *Experientia* **11**, 340 (1955).
[7] S. Kaufmann and G. Rosenkranz, *J. Amer. Chem. Soc.* **70**, 3502 (1948).
[8] R. S. Miner and E. S. Wallis, *J. Org. Chem.* **21**, 715 (1956).
[9] C. R. Eddy, M. E. Wall and M. K. Scott, *Analyt. Chem.* **25**, 266 (1953).
[10] W. Tarpley and C. Vitiello, *Appl. Spectroscopy* **9**, 69 (1955). I. Scheer, M. J. Thompson and E. Mosettig, *J. Amer. Chem. Soc.* **79**, 3218 (1957).


Ni (H2)
EtOH
I
II
III
IV
V
VI a R=Ac
b R=H
VII a R=Ac
b R=H
VIII
IX
OAc
OH
OEt
OMe
OR
=O
AcO
RO
HO

containing the hemiketal (II) and an amorphous product (VIIa), characterized by an absorption band of the same wavelength (5·91 μ) and similar intensity as the double-bond stretching band of the vinyl ether group in pseudotigogenin diacetate (VIII).[11] Like pseudotigogenin,[12] (VIIa) was not altered by hydrogenation with platinum in a neutral solvent. On the other hand, (VIIa) differed from pseudotigogenin diacetate not only in several bands in the finger-print region of the infrared spectrum (Table 1), but also in its chemical behavior. On treatment with ethanol and acetic acid (VIIa) furnished the ethyl ketal (III), while pseudotigogenin diacetate was recovered unchanged. Alkaline hydrolysis of (VIIa) gave the crystalline parent compound (VIIb), which was converted to tigogenin (VIb) in ethanolic acetic acid. Pseudotigogenin with methanolic* acetic acid[13] yielded an isomer, *cyclo*pseudotigogenin. Oxidation of (VIIa) with chromic acid gave the known[14] 3β-acetoxy-16β-hydroxybisnor*allo*-cholanic 22 → 16-lactone (IX) as the main product. These observations show that the new vinyl ether (VIIa) is the Δ^{22}-bond isomer of pseudotigogenin diacetate and make it very probable that the C-21 methyl in (VIIa) as well as in the ketals and the hemiketal is directed towards the rear just as it is in the reaction products (VI) and (IX).[15] The position of the double bond admits the possibility of *cis–trans* isomerism. We are uncertain whether our preparations represent a single geometric isomer, since the instability of (VIIa) interfered with attempts towards its fractionation. Chromatography on silica gel–Celite led to contamination with the hemiketal (II) and drastic spectral changes occurred even on standing evidently owing to autoxidation.

The marked differences in the spectra of (VIIa) and (VIII) permitted their use as a diagnostic tool in following the course of eliminations at C-22. Treatment of the ethyl ketal (III) with a mixture of benzene and acetic acid at room temperature caused desaturation and gave the Δ^{22}-isomer, while boiling in ethanol and acetic acid furnished slowly the *endo*cyclic olefin. The greater stability of this isomer could be demonstrated also at room temperature by a conversion of (VIIa) to (VIII) in the presence of acetic and phosphoric acids. The *exo*cyclic product was obtained when benzene solutions of (III) were shaken with Drierite (anhydrous calcium sulfate). The process can be reversed in alcoholic solution and requires rather large amounts of the catalyst. Complete eliminations occurred more readily with the hemiketal and gave compound (VIIa) of good spectral purity. The reactions catalyzed by Drierite are probably mechanistically distinct from those proceeding with acid, since our preparation of calcium sulfate, when suspended in water, acted as an acceptor rather than a donor of hydrogen ions. The process was viewed as surface catalysis and was expected to show a preference for *cis* elimination to yield the more stable isomer, whereas the acid-catalyzed reaction normally favors the formation of the more stable product by *trans* elimination.[3b] Since our reactions when conducted under the mildest conditions gave the less stable isomer by both modes of elimination, the result probably does not reflect the relative positions of the ethoxy group to the hydrogen at C-20, but rather suggests that the abstraction of this hydrogen is retarded by steric hindrance. There is good

* Ethanol has been used with other pseudosapogenins.[3]

[11] A. L. Hayden, P. B. Smeltzer and I. Scheer, *Analyt. Chem.* **26**, 550 (1954).
[12] R. K. Callow, D. H. W. Dickson, J. Elks, R. M. Evans, V. H. T. James, A. G. Long, J. F. Oughton and J. E. Page, *J. Chem. Soc.* 1966 (1955).
[13] M. E. Wall and H. A. Walens, *J. Amer. Chem. Soc.* **77**, 5661 (1955).
[14] R. Tschesche and A. Hagedorn, *Ber. Dtsch. Chem. Ges.* **68**, 1412 (1935).
[15] J. W. Corcoran and H. Hirschmann, *J. Amer. Chem. Soc.* **78**, 2325 (1956).

TABLE 1. INFRARED ABSORPTION MAXIMA BETWEEN 7·55 AND 11·25 μ*

Compound	Wavelength (μ)																
(II)				8·50	8·68	8·82	9·09	9·32[b]		**9·74**	10·06[i]	**10·19**	**10·30**	10·42[i]	10·64[b]	10·89[b]	11·17
(III)			8·43	8·54	8·67	8·82	**9·02**		**9·41**	**9·75**	10·03	**10·20**[b]		10·42		10·87	11·16
(IV)			8·36	8·54	8·67	8·82	**9·08**		**9·38**	**9·75**	10·01[i]	10·21[i]		10·42	10·63[b]	10·92[b]	11·21
(VIa)		7·71		**8·52**	8·66	8·84	9·11	**9·31**	**9·49**	**9·76**	10·06	**10·19**		**10·42**		**10·85**	**11·12**
				G	H	J	K		N					R			
(VIIa)	7·64	7·73		**8·54**	8·66	8·83		9·27		**9·73**	10·07	10·18		**10·40**	10·61	10·94[b]	11·17
(VIII)		7·69	8·42	8·59	8·67	8·83	9·01	9·28		**9·69**		10·17		10·43[b]	10·62		11·16

* Solvent was carbon disulfide. The following are omitted from this Table. Very weak maxima and inflexions, the strong ester peaks at 8·06 μ in (VIa) and at 8·08 μ in the other compounds, as well as the peak of (VIa) at 9·93 μ and the inflexions of (III) at 9·85, of (IV) at 9·85 and 9·95, of (VIa) at 9·24 and 10·50, of (VIIa) at 8·20, and of (VIII) at 8·22 and 9·83 μ. i = inflexion. b = broad. Strong bands are in bold face type. The capital letters refer to the band designations of R.N. Jones, E. Katzenellenbogen and K. Dobriner, (*J. Amer. Chem. Soc.* **75**, 158 (1953), for *iso*sapogenins but list only those which occur in the spectra of both (III) and (IV) with intensity and position comparable to those in (VIa). Absorption frequencies and a curve have been published for (VIa) by Eddy *et al.*[9] and a curve for (VIII) by Callow *et al.*[12]

evidence that an external* base is restrained from supporting the ionization of hydrogen at the frontal face of C-20, because the reverse process, the protonation of the $\Delta^{20(22)}$ double bond of pseudosapogenin, proceeds much faster from the rear, although the product, *cyclo*pseudosapogenin,† is less stable than the one resulting from frontal protonation (VIb). Therefore the formation of the *exo*cyclic isomer in an ionic process does not prove a *cis* relationship of the ethoxy group to the hydrogen at C-20.

The only elimination mechanism which would avoid complications from steric hindrance effects appears to be a unimolecular pyrolysis.[16] It could not be realized with our substrate. The results of pyrolyses of compound (III), which were conducted in evacuated tubes without solvent, depended on the surface of the vessel. Clean glass tubes gave mixtures of the two olefins in which the *exo*cyclic isomer generally predominated. As the reaction temperature was lowered from 195° to 158°, the elimination of alcohol became increasingly incomplete and reversible. This suggested surface catalysis of the elimination. Other workers[16,17] have observed such catalysis repeatedly and were able to prevent it by coating the wall with a carbonaceous residue. Pyrolysis of (III) at 158° in tubes pretreated by exposure to hot ethylene[17] went to completion and gave the *endo*cyclic isomer. However, this need not have been the primary reaction product, since (VIIa) under the same conditions was isomerized to (VIII). Finally a silvered tube gave (VIIa) as the sole olefinic product. The reaction at 158° could not be carried to completion by lengthening the reaction time, but its apparent end-point did not constitute a true equilibrium, since treatment of the pyrolysis product with a large excess of ethanol caused only a moderate increase in (III). Evidently the silver-lined surface likewise participated in the elimination.

In the presence of acetic acid ketals could be formed from other full or half ketals or from the Δ^{22}-olefin. Since the latter was obtained with the same catalyst from ketals in a medium free of hydroxylic compounds, it is possible that the ketal exchange involves the olefin as an intermediate. However, regardless of the mechanism, the main steric effects should be those governing the reaction at C-22, since it is close to the C-21 methyl, while a trigonal C-23 appears to be about equally accessible from either side. If the steric result depends on the degree of steric hindrance towards the approach of the alcohol, the faster reaction should be the one from the front to yield a product in which the C-23 methylene is eclipsed by the C-21 methyl. As pointed out before,[1] this is the less stable isomer. The compound actually isolated from the reaction must have the stable configuration. The ethyl ketal in methanol and acetic acid is converted completely to the methyl ketal in less than 10 min, but undergoes no spectrographic changes in ethanol and acetic acid when kept for a period twenty times as long. Even after boiling, no isomer of (III) could be detected. Another indication for the stable configuration of the ketals is the addition or exchange reaction involving an alcohol function at C-26. The reactions proceed at room temperature under the same conditions; the same considerations as to the probable mechanism of the faster

* The hydrogen at C-23 is also more accessible to an internal base such as the furanoid oxygen or the C-26 acetoxy group if these should play a role in the elimination. (Cf. R. T. Arnold, *Helv. Chim. Acta* **32**, 134 (1949).)

† This configuration at C-20, which was first proposed by Wall and co-workers, has been accepted by most investigators. An additional argument in its favor will be given below.

[16] D. H. R. Barton, A. J. Head and R. J. Williams, *J. Chem. Soc.* 453 (1952); *Ibid.* 1715 (1953).
[17] F. Daniels and P. L. Veltman, *J. Chem. Phys.* **7**, 756 (1939).

reaction should apply, and again the product (tigogenin) is the stable isomer at C-22. Evidently the reaction conditions furnish sufficient activation to permit the approach of the alcohol from the more hindered side. Accordingly, we assign to the ketals and the hemiketal the stable structures indicated in formulas (II) to (V) and presume that their epimers are rather short lived under the conditions of our reactions.* These considerations provide an additional argument[5] against the suggestion[18] that *cyclo*pseudotigogenin is the 22-epimer of (VIb) because the cyclization product of (VIIb) contained no detectable amounts of *cyclo*pseudotigogenin, although *cyclo*pseudosapogenins do not isomerize to sapogenins under the conditions of the reaction.[2]

Our observations demonstrate that C-22 ketals can undergo bond ruptures and bond formations at C-22 under neutral conditions. No similar exchange reactions with aliphatic alcohols have been described for the known bicyclic ketals and none are to be expected, since the cyclization of pseudotigogenin and of (VIIb) with the C-26 carbinol group proceed in the presence of a large excess of a competing external alcohol. This different behavior could be caused by the lesser thermodynamic stability or by the greater flexibility of the monocyclic compounds. If stability is the important factor, exchange reactions analogous to those found with the less stable monocyclic ketals might also occur with the unstable C-22 epimers of the known *spiro* ketals and result in a change of their configuration at C-22. In that case it may not be sufficient merely to avoid acid conditions if the configuration at C-22 is to be preserved in a reaction that alters the relative stabilities of C-22 epimers. In view of this it does not seem superfluous to point out that our data are consistent with the assignment of Callow for the natural sapogenins and are not in conflict with the seemingly opposing assignment made by Wall for the *cyclo*pseudosapogenins.

Equilibration of the *iso* and normal sapogenins shows an equilibrium constant of 1/3 to 1/4 which at 350°K corresponds to ΔF of 760 to 960 cal.[19,6] The free-energy difference (A) caused by an exchange of an axial for an equatorial methyl at C-25 can now be estimated as about 900 cal.† On the other hand, if the normal and *iso*-sapogenins both possess an equatorial methyl at C-25 and differ in their configuration at C-22, their stability difference (B) should approximate that between ketal (III) and its epimer. If the difference were no larger than about 1000 cal, the detection of this epimer of (III) or (IV) should have been possible by spectrographic means after exposure to acid and alcohol inasmuch as the ketal group gives rise to strong bands, which can hardly be assumed to be invariant to a change of configuration. We

* The alternative possibility that the transition states are more nearly tetrahedral than trigonal and therefore favor the more stable configurations at C-22, would also account for our observations.

† Estimate based on a ΔF of about 1800 cal between equatorial and axial methyl*cyclo*hexane.[20] Our earlier[1] estimate of 800 $\pm$ r cal included a term (r) for the skewed interaction between the pyranoid oxygen and the C-27 methyl. In the light of the recent discussion of Dauben and Pitzer [3a] this term should be small or negligible, since a staggered methyl does not lead to the same non-bonded interactions as are present in axial *cyclo*hexanol. On the other hand, the sum of the two skewed interactions between an axial furanoid oxygen and C-24 and C-26 cannot be neglected but should aproximate 800 to 900 cal[20,21] On the basis of these values the difference between the two conformations (XVb) and (XVIb) that were shown in our older analysis[1] reduces to the interaction of C-21 with the axial H at C-26 in (XVIb). Judging from the rapid increase in ΔF with increasing bulk of an axial alkyl group,[20] this term (s) must be large and hence (XVIb) appreciably less stable than (XVb). It seems justified, therefore, to eliminate (XVIb) from this discussion.

[18] R. K. Callow and V. H. T. James, *Chem. & Ind.* 691 (1954).
[19] M. E. Wall, S. Serota and L. P. Witnauer, *J. Amer. Chem. Soc.* 77, 3086 (1955).
[20] S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.* 77, 5562 (1955).
[21] S. J. Angyal and D. J. McHugh, *Chem. & Ind.* 1147 (1956).

conclude therefore that only (*A*) agrees with the experimentally determined value for sapogenin equilibration, while (*B*) is larger than this. If the angle between corresponding bonds were the same in the sapogenins and *cyclo*pseudosapogenins, this conclusion should apply to both. However, normal bond angles cannot prevail if the configuration at C-20 is inverted, because this would lead to a prohibitively short distance[15] between C-18 and C-21. This strain should result in a displacement of C-21 towards the plane of ring *E* in such a way that the angular deflections are held to a minimum.[3c] This distortion lengthens the distance of C-21 from the proximal substituent at C-22 in ring *F* and thereby diminishes the difference (*B*). Consequently our findings cannot be applied to the *cyclo*pseudosapogenins. We cannot estimate the magnitude of this effect, but, if the distortion of the molecule reduces (*B*) to a value less than (*A*), the assignments of Wall and of Callow would be reconciled.

The key step used in demonstrating identical configurations at C-22 for *cyclo*-pseudotigogenin and tigogenin consisted in a hydrogenation of a $\Delta^{20(21)}$-unsaturated sapogenin with platinum in non-specified neutral solvents.[5] Since nickel evidently can substitute an ethoxy for a hydroxy group* at C-22 as indicated by the conversion of (I) to (III), we have tested the stability of compound (III) to the action of platinum in methanol. At least with the amounts of catalyst used no appreciable exchange was observed.

The formation of the *exo*cyclic vinyl ether (VIIa) is in contrast to the eliminations described for the reduction product of Kaufmann and Rosenkranz[7] and for the sapogenins which always yielded the $\Delta^{20(22)}$-isomer.† The reason for this difference probably lies in the milder reaction conditions used by us. In fact, the more facile abstraction of a proton from C-23 rather than from C-20, which characterized our eliminations in the presence of acetic acid, may have its counterpart in certain acid-catalyzed reactions of the sapogenins such as bromination[22] and deuterium exchange.[23]‡ If preferential protonation occurs on that oxygen which is not part of the furanoid ring, just as it must be in the acid-catalyzed desaturation of compound (III), the hydrogen most easily substituted at C-23 can be expected to be the equatorial one, since this bond would be coplanar with and antiparallel to the strongest electron-withdrawing group. Other workers[22,24] have suggested the axial conformation for the primary bromination product in analogy to observations with *cyclo*hexanones. Spectrographic observations[25] indicate, however, that the predominant[22] monobromide of tigogenin possesses an equatorial bromine.

* In this case we prefer this explanation to the one given for the alkylation of amines by alcohols in the presence of nickel, as the latter process requires conditions which permit the dehydrogenation of the alcohol to the aldehyde (either no added hydrogen or high temperatures). L. T. Plante, W. G. Lloyd, C. E. Schilling and L. B. Clapp, *J. Org. Chem.* **21**, 82 (1956); L. T. Plante and L. B. Clapp, *J. Org. Chem.* **21**, 86 (1956).

† The presence of the Δ^{22}-isomer as a contaminant of some preparations of pseudosapogenin diacetates has been suspected by A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones and A. G. Long, *J. Chem. Soc.* 2807 (1955). Our results do not verify their predictions as to the optical rotation of the *exo*cyclic product. Its possible role as an intermediate in other reactions of the sapogenins has been discussed by D. H. Gould, H. Staeudle and E. B. Hershberg, *J. Amer. Chem. Soc.* **74**, 3685 (1952).

‡ Admittedly the site of these reactions has not been proven beyond doubt, but since two hydrogens can be replaced by either deuterium or bromine at least one should come from C-23. Reaction at C-23 has been assumed in virtually all discussions of this topic.

[22] M. E. Wall and H. W. Jones, *J. Amer. Chem. Soc.* **79**, 3222 (1957); and references cited in this paper.
[23] R. K. Callow, V. H. T. James and P. N. Massy-Beresford, *Chem. & Ind. (Rev.)* 26 (1956).
[24] D. A. H. Taylor, *Chem. & Ind.* 1066 (1954).
[25] D. H. R. Barton, J. E. Page and C. W. Shoppee, *J. Chem. Soc.* 331 (1956).

EXPERIMENTAL*†

3β, 26-Diacetoxy-25a-cholestane-16,22-dione (5,6-dihydrokryptogenin diacetate) (I). A solution of 677 mg of kryptogenin diacetate in 127 ml of 95% ethanol was stirred magnetically with 1·5 g of pre-reduced 1% palladium–calcium carbonate[1] in an atmosphere of hydrogen. The product was freed of catalyst by passage through a short column of silica gel–Celite and recrystallized from methanol and from ligroin to give 541 mg of compound (I), m.p. 121–123·5°. The spectrum retained the carbonyl peaks (5·77 and 5·82 μ) of the starting compound, but lost those at 12·28 and 12·45 μ (Δ^5).[26] A m.p. of 121–123° has been reported for (I) obtained with different catalysts.[27]

22a-Ethoxy-5α, 25a-furostan-3β, 26-diol diacetate (III). A solution of 261 mg of 5,6-dihydrokryptogenin diacetate (I) in 20 ml of absolute ethanol and a suspension of 2·3 g of freshly prepared Raney nickel[28]‡ in 3 ml of the same solvent were shaken in an atmosphere of hydrogen for 70 min. Gas uptake ceased after 35 min. The catalyst was removed by centrifugation and the product was recrystallized from 95% ethanol. Compound (III) had m.p. 154–157°. The yield was 160 mg. The analytical sample was dried at 80° and showed $[\alpha]_D$—35° (*c*, 0·4 in ethanol). *Anal.* Calcd. for $C_{33}H_{54}O_6$: C, 72·48; H, 9·96. Found: C, 72·73; H, 10·22 per cent. The ratio of (III) to (II) as determined by the infrared spectrum of the crude reduction product was very much lower, when 138 mg of (I) in 95% ethanol were shaken with 238 mg of nickel and only 48 mg of (III) were obtained.

A solution of 2·5 mg of compound (III) in 1·5 ml of methanol was heated under reflux for 1 hr. The dried residue showed the infrared spectrum of (III). Chromatography of (III) on magnesium silicate–Celite led to a complex mixture, which showed the vinyl ether band.

5α,25a-Furostan-3β,22a,26-triol 3,26-diacetate (II). A solution of 50 mg of compound (III) in 3·75 ml of 80% acetic acid was kept at 25° for 2 hr and then equilibrated rapidly between alcohol-free ether and more than 2 equivalents of aqueous sodium carbonate. The ether phase was washed with more carbonate and repeatedly with water and was evaporated to dryness. The residue on recrystallization from light petroleum gave 43 mg of hemiketal (II). M.p.s of 112–114·5° and of 99–102° were observed for two different preparations, which possessed identical infrared spectra (λ_{max} 2·79, 5·77 μ, and those in Table I). $[\alpha]_D^{23}$—23° (*c*, 0·5 in 95% ethanol). *Anal.* Calcd. for $C_{31}H_{50}O_6$: C, 71·77; H, 9·72. Found C, 71·87; H, 10·00 per cent.

* All melting points reported are corrected. Unless when noted otherwise, compounds were dried at room temperature for analysis and physical measurements, and infrared spectra were measured in carbon disulfide in 1 per cent solutions. Compound (VIb), which is less soluble, was examined also as a pressing in potassium bromide. The silica gel (Davison)–Celite (2:1) used in chromatography was pre-washed (K. N. Trueblood and E. W. Malmberg, *J. Amer. Chem. Soc.* **72**, 4112 (1950)). The unwashed product when suspended in water lowered its pH from 5·9 to 5·4, while Drierite raised it to 7·1. The ligroin used had boiling range of 90–96°, and the light petroleum 60–70°. The ether extracts of the reaction products were evaporated at room temperature under a current of nitrogen. No sodium sulfate or other chemical drying agent was employed.

† The stereonomenclature used follows the proposal of C. Djerassi, T. T. Grossnickle and L. B. High, *J. Amer. Chem. Soc.* **78**, 3166 (1956). Specifically, the terms "22a" and "25a" denote configurations identical with those in tigogenin.

‡ The W-5 catalyst used was prepared on 0·1 scale and washed with 5 l. of water. Excessive washing and too rapid stirring gave an inactive product.

[26] H. Hirschmann, *J. Amer. Chem. Soc.* **74**, 5357 (1952).
[27] R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *J. Amer. Chem. Soc.* **69**, 2199 (1947); A. L. Nussbaum, A. Sandoval, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.* **17**, 426 (1952).
[28] H. Adkins and H. R. Billica, *J. Amer. Chem. Soc.* **70**, 695 (1948).

A sample heated under reflux in 95% ethanol for 70 min showed no change in spectrum.

22a-Methoxy-5α,25a-furostan-3β,26-diol diacetate (IV). A solution of 11 mg of ketal (III) in 0·8 ml of dry methanol and 0·2 ml of glacial acetic acid was kept at room temperature for 200 min and worked up as described for (II). Recrystallization from methanol gave the methyl ketal (IV), m.p. 112·5–117°. The bands at 9·08 and 9·38 μ serve best for the differentiation of this compound. *Anal.* Calcd. for $C_{32}H_{52}O_6$: C, 72·14; H, 9·84. Found: C, 71·71; H, 10·10 per cent.

5α,25a-Δ²²-Furosten-3β,26-diol diacetate (VIIa). A solution of 21·3 mg of the hemiketal (II) in 1 ml of benzene was shaken with 400 mg of Drierite at room temperature for 8 hr in the dark. Compound (VIIa) (18·7 mg) was obtained by centrifuging and four washings with benzene. (Losses due to adsorption occurred consistently. To prevent this a trial run was treated with methanol just before centrifuging. The product contained about 45 per cent of (IV).) Olefin (VIIa) showed λ_{max} at 5·77, 5·91 μ and those given in Table 1. Material with the same absorption characteristics was obtained from (III) adsorbed on 55 parts of silica gel–Celite in a fraction eluted with benzene containing 5 per cent of ether. Complete conversion of 31 mg of (III) to (VIIa) by shaking with Drierite required three treatments (550, 520 and 1280 mg of calcium sulfate) to yield (VIIa), with $[\alpha]_D^{23}$ + 3° (*c*, 0·6 in 95% ethanol).

Product (VIIa) contaminated with (II) resulted when 3 mg of (III) were kept in 1·2 ml of dry benzene and 0·25 ml of dry acetic acid for 200 min at room temperature and worked up as described for (II). A sample of the olefin (VIIa) stored for 5 weeks lost its absorption band at 5·91 μ and showed new absorption in the hydroxyl and ketone region. All experiments recorded for (VIIa) were done on freshly prepared samples that had been checked spectrographically.

3β-Acetoxy-16β-hydroxybisnorcholanic 22→16-lactone (IX). A mixture of 16 mg of olefin (VIIa), 16 mg of chromium trioxide and 3·8 ml of 99·5% acetic acid was kept at 25° for 270 min. Excess of oxidant was reduced with methanol and the product was extracted with ether. The neutral fraction (13 mg) clearly showed the peak of the normal lactone at 8·51 μ, but not that of its 20-epimer at 8·61 μ.[15] It was hydrolyzed with potassium hydroxide and *tert.*-butanol[29] for 3 hr at room temperature and again separated into neutral (3·4 mg with λ_{max} 240 mμ and extinction equivalent[29] to 1·2 mg of 3β-hydroxy-Δ¹⁶-*allo*pregnen-20-one*) and acidic compounds. The latter were relactonized with hydrochloric acid and the product (6·8 mg) was acetylated with acetic anhydride and pyridine at room temperature. The acetate had the infrared spectrum of 3β-acetoxy-16β-hydroxybisnor*allo*cholanic 22→16-lactone and upon recrystallization from 95% ethanol and from methanol showed m.p. 217–220°, undepressed by admixture of a reference sample.[15]

22a-Ethoxy-5α,25a-furostan-3β,26-diol (V). A mixture of 30 mg of ethyl ketal (III), 9 ml of methanol and 0·6 ml of 5% aqueous potassium carbonate was warmed gently to effect solution and kept at room temperature for 24 hr. The mixture was concentrated to about 2 ml under a current of nitrogen and distributed between ether and water. The ether phase yielded 24 mg of residue, which was recrystallized from ethanol and from acetone. The compound melted with evolution of gas at about

* The most likely explanation for the formation of this product is a shift of the double bond by chromic acid analogous to the one observed with phosphoric acid.

[29] M. E. Wall, H. E. Kenney and E. S. Rothman, *J. Amer. Chem. Soc.* **77**, 5665 (1955).

200–205°. *Anal.* Calcd. for $C_{29}H_{50}O_4$: C, 75·28; H, 10·89. Found: C, 75·22; H, 11·14 per cent. This sample was dried at room temperature; another which was dried at 80° lost about 3 per cent of its weight and gave C, 75·93; H, 10·65 per cent, suggesting that partial elimination of ethanol had occurred.

5α,25a-Δ²²-Furosten-3β,26-diol (VIIb). Olefin (VIIa) (18·5 mg in 4·5 ml of methanol) was hydrolyzed with 0·4 ml of 5% potassium carbonate under nitrogen for 24 hr. The product (15·5 mg) was isolated by ether extraction and recrystallized from acetone. Fine needles were obtained, which showed partial or complete fusion near 152°, followed by resolidification on further heating. The final m.p. (209°) suggests conversion to tigogenin during heating. Only the sample used for combustion was dried at 100°. *Anal.* Calcd. for $C_{27}H_{44}O_3$; C, 77·83; H, 10·65. Found: C, 77·40; H, 10·87 per cent. The principal peaks include λ_{max}^{KBr} 5·91, 7·64, 7·73, 8·19, 8·59, 8·83, 9·25, ~9·59, 10·18, 10·40 and 10·62 μ. This product, which was handled in glassware pre-washed with carbonate and with water, was free of tigogenin in spectrographically detectable amounts. When these precautions were not taken, recrystallization from alcoholic solvents led to a mixture of (VIIb) and (VIb).

Other conversions catalyzed by acetic acid. In general reactions were performed on 2·5 mg samples of starting compound, which were dissolved in four volumes of the alcohol listed (usually 0·4 ml) and one volume of glacial acetic acid and maintained at room temperature. Reaction times in min are given in parentheses. Products were isolated as described for (II) and examined spectrographically without purification. In every case the curve of the crude product was in very close agreement with that obtained with our best reference specimen. Reaction (*a*) (III) + methanol (200) → (IV); (*b*) (III) + methanol (10) → (IV); (*c*) (IV) + ethanol (200) → (III); (*d*) (VIIa) + methanol (10) → (IV); (*e*) (VIIa) + ethanol (180) → (III); (*f*) (II) + ethanol (10) → (III); (*g*) (VIII) + ethanol (200) → (VIII); (*h*) (III) + ethanol (200) → (III). [The product of (*h*) was chromatographed on paper in the system *iso*octane, methanol and water (20 : 17 : 3 by volume) and treated with trichloroacetic acid in 95% ethanol.[30] As with pure (III), only a single spot was seen (R_F 0·84). A larger run (15·2 mg) of reaction (*h*) was recrystallized once from 95% ethanol. The crystals melted at 153–156°, the mother liquor (1·8 mg) showed signs of some decomposition, but consisted mainly of ketal (III).] (*i*) (V) (9·8 mg) + ethanol (2·6 ml) (135) → (VIb) [identity confirmed by m.p. (205–209°) and mixture m.p. and by m.p. (203–209°), mixture m.p. and infrared spectrum of acetate]; (*j*) (VIIb) + ethanol (10) → (VIb) [the purity of the crude reaction product was confirmed by infrared spectroscopy after acetylation, the identity also by the m.p. and mixture m.p. (both 209°) of the recrystallized acetate]; (*k*) when 2·3 mg of (III), 2 ml of ethanol and 0·5 ml of acetic acid were heated under a reflux, the product showed only maxima attributable to either (III) or (VIII). (III) predominated after 2, (VIII) after 8½ hr.

Pyrolyses. All reactions were run in small glass tubes, which were evacuated and sealed. The tubes were inserted into a pre-heated microbomb oven and removed from it hot at the end of the reaction time. The opened tubes were dried to remove ethanol and their contents were examined spectrographically. Differentiation of (VIIa) and (VIII) was facilitated by the fact that (VIIa) has extinction minima at 8·44 and 7·69 μ and (VIII) at 8·56 μ, which nearly coincide with maxima of the other

[30] C. de Courcy, *J. Endocrinol.* **14**, 164 (1956). This procedure is a modification of one introduced by E. Heftmann and A. L. Hayden, *J. Biol. Chem.* **197**, 47 (1952).

olefin. Compound (III) was estimated by the apparent extinction at 9·41 μ. In the conditions specified below the first figure refers to the reaction temperature, the second to the time in minutes:

(i) *Clean glass tubes.* About 2·5 mg of (III) (*a*) 195°, 180; (*b*) 186°, 20; (*c*) 170°, 15; (*d*) 157°, 20; (*e*) 158°, 30. The ratio of (VIIa) to (VIII) varied irregularly as it increased in the sequence (*c*), (*a*), (*e*), (*d*), (*b*), the content of (III) from (*a*) to (*e*) was about 0, 13, 15, 22, 20 per cent, respectively. (*f*) (VIII) 158°, 280 showed no change; (*g*) product of (*a*) 195°, 240 was almost completely converted to (VIII); (*h*) product of (*e*) + 1 ml of methanol 158°, 30 → mixture of (IV), (VIIa) and (VIII).

(ii) *Tubes coated with carbonaceous residue.* These were obtained by keeping tubes which had been evacuated and then filled with ethylene at 450° for 17 hr. Pyrolyses of either (III) or (VIIa) for 30 min at 158° gave (VIII) runs *i*, *j*.

(iii) *Silvered tubes.* These were pre-treated with Tollen's reagent and lactose, and then thoroughly washed and dried: (*k*) (III) 158°, 30 → (VIIa) and (III) (ca. 28%); (l) (III) 158°, 90 → (VIIa) and (III) (ca. 34 per cent); product of (*k*) + 0·2 ml of methanol 158°, 30 → (IV) and (VIIa); product of (l) + 0·25 ml of ethanol 158°, 30 → (VIIa) and (III) (ca. 40 per cent).

Other reactions of 5α,25a-Δ^{22}-furosten-3β,26-diol diacetate (VIIa). A solution of 2·7 mg of (VIIa) in 2 ml of methanol was shaken with 320 mg of Drierite for 8 hr. About 55 per cent was converted to (IV).

A solution of 3·5 mg of (VIIa) in 6 ml of dry dioxan was stirred magnetically with 18 mg of platinum (which had been pre-reduced and washed with dry dioxan) in an atmosphere of hydrogen for 135 min. No change in spectrum was observed.

When this material was treated with 0·9 ml of acetic acid and 0·1 ml of concentrated hydrochloric acid at 23° for 15 hr, the product no longer showed absorption at 5·91 μ. There was new carbonyl absorption near 5·83 μ, but no hydroxyl peak. The Beilstein test was positive.

A solution of 2·3 mg of (VIIa) in 0·95 ml of acetic and 0·05 ml of 85% phosphoric acids was kept at room temperature for 200 min. The product isolated as described for (II) gave an infrared spectrum characteristic of (VIII).

Treatment of ketal (III) *with platinum.* Compound (III) (3·2 mg), 25 mg of Adam's platinum dioxide catalyst and 6 ml of methanol were shaken with hydrogen for 90 min. The product was no longer completely soluble in carbon disulfide, evidently owing to partial deacetylation. The spectrum was essentially that of ketal (III), but showed a weak shoulder at 9·08 μ (cf. Table 1, compound (IV)) which was not seen in a control without platinum.

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