[CONTRIBUTION FROM THE RESEARCH LABORATORIES, CHEMICAL DIVISION, MERCK & CO., INC.]

The Rearrangement of the Steroid C/D Rings[1]

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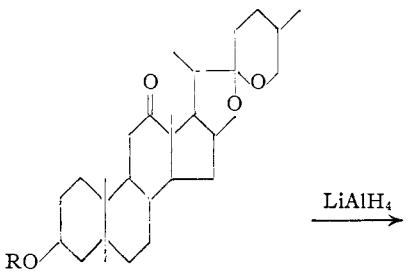
RECEIVED FEBRUARY 12, 1954

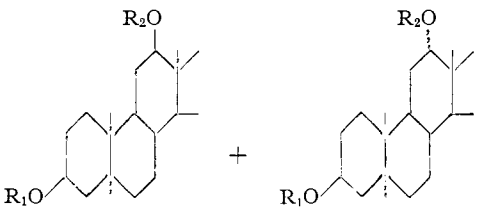
The relative configurations at C_{12} of rockogenin and 12-epi-rockogenin have been determined by correspondence of molecular rotation differences and saponification rates with the bile acid analogs. Chemical transformations of known steric course also support these assignments. Rockogenin in the form of its 12β-mesylate derivative (IIc) was observed to undergo rapid solvolytic rearrangement accompanied by C/D-ring contraction and expansion. Under the same conditions the mesylate derivative (IIIc) of 12-epi-rockogenin was recovered largely unchanged together with minor amounts of Δ^{11}-dehydrotigogenin. The synthesis is described of an 11-keto-$\Delta^{13(17a)}$-C-nor/D-homosapogenin exhibiting chromophoric characteristics markedly similar to those of jervine. The significance of the steroid C/D ring rearrangement is briefly discussed in the light of current theoretical considerations.

As part of a study concerned with C-ring transformations of hecogenin (I)[2] it became of interest to investigate the possibilities of converting this sapogenin into the corresponding Δ^{11}-ethenoid derivative. The reaction deviation attending the classical chemical approach[3] to this system constitutes the subject of the present account.

Hecogenin acetate (I) was reduced with lithium aluminum hydride to give a mixture of C_{12}-epimeric diols. The diol mixture was separated by fractional crystallization of the 3-methylsuccinate derivative[3a] yielding thereby essentially equal amounts of two pure isomers melting at 222–225° and 152–154°. Chromic acid oxidation of both isomers gave one and the same hecogenin 3-methylsuccinate (Ia) thereby establishing the C_{12}-epimeric character of the two diols. Saponification of the lower melting (154°) succinate derivative afforded a free diol, m.p. 218.5–220.5°, which gave a diacetate derivative, m.p. 206–209°. This diol, which was subsequently shown to possess the 12β-OH configuration (II) (see below), proved to be identical in all respects with natural rockogenin.[4]



I, R = CH_3CO–
Ia, R = $CH_3O_2C(CH_2)_2CO_2$–



II, $R_1 = R_2 = H$–
IIa $R_1 = CH_3O_2C(CH_2)_2CO$–, $R_2 = H$–
IIb $R_1 = R_2 = CH_3CO$–
IIc $R_1 = CH_3O_2C(CH_2)_2CO$–, $R_2 = CH_3SO_2$–

III
IIIa
IIIb
IIIc
IIId $R_1 = CH_3CO$–, $R_2 = CH_3SO_2$–

The residue from the original succinoylation of the diol mixture after essentially complete separation of the crystalline 3-methyl succinate derivatives was an intractable oil. The latter showed only weak hydroxyl absorption together with an intense ester band in the infrared. Saponification of this oil produced nearly pure rockogenin (II) in excellent yield. It appears therefrom that succinoylation of a 12β-hydroxyl group proceeds with considerably greater ease than with its 12α-epimer.[5]

The assignment of configuration to the C_{12}-epimeric diols II and III was deduced from the molecular rotation differences of the two diols and their respective diacetate derivatives IIb and IIIb as compared with the C_{12}-epimeric cholanates.[6] It is apparent from the molecular rotation comparisons given in Table I that rockogenin should be assigned the 12β-configuration. Confirmation of this configurational assignment was adduced from the rates of saponification of the two diacetate derivatives IIb and IIIb. Thus it is evident from Fig. 1 that the rate of saponification of the acetate function at C_{12}, as measured by the rate of consumption of two equivalents of alkali, is much faster for IIb than for IIIb. These results are again in accord with the relative rates of saponification of the corresponding C_{12}-epimeric acetoxy cholanates as determined by Koechlin and Reichstein[6a] and in conformity as well with the greater ease of hydroly-

(1) Preliminary accounts of this work were reported in Communications to THIS JOURNAL, **74**, 2693 (1952); **75**, 5135 (1953), as well as at the Symposium on Steroids, Gordon Research Conferences AAAS at New Hampton, N. H., August 2–7, 1953.

(2) For previous work in this series see: R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953).

(3) For a leading reference see: J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **29**, 654 (1946).

(3a) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949), employed the succinate derivatives to advantage in effecting the separation of the isomeric 7-hydroxy-1-keto-13-methylperhydrophenanthrenes.

(4) This represents the first time that the configuration at C_{12} of a sapogenin has been unequivocally established. See ref. 1.

(5) Succinoylation has been widely employed in the steroid field for effecting selective esterification at position 3 in the presence of a 12α-hydroxyl function; see for example: E. Schwenk, B. Riegel, R. B. Moffett and E. Stahl, THIS JOURNAL, **65**, 549 (1943); N. L. Wendler and T. Reichstein, *Helv. Chim. Acta*, **31**, 1713 (1948); see also ref. *f*, Table I.

(6) (a) B. Koechlin and T. Reichstein, *ibid.*, **25**, 918 (1942); (b) T. F. Gallagher and W. P. Long, *J. Biol. Chem.*, **162**, 521 (1946); (c) D. H. R. Barton and W. Klyne, *Chem. & Ind.*, 755 (1948); (d) E. Borgstrom and T. F. Gallagher, *J. Biol. Chem.*, **177**, 951 (1949); (e) see also Table I, ref. *c* and *d*.

TABLE I

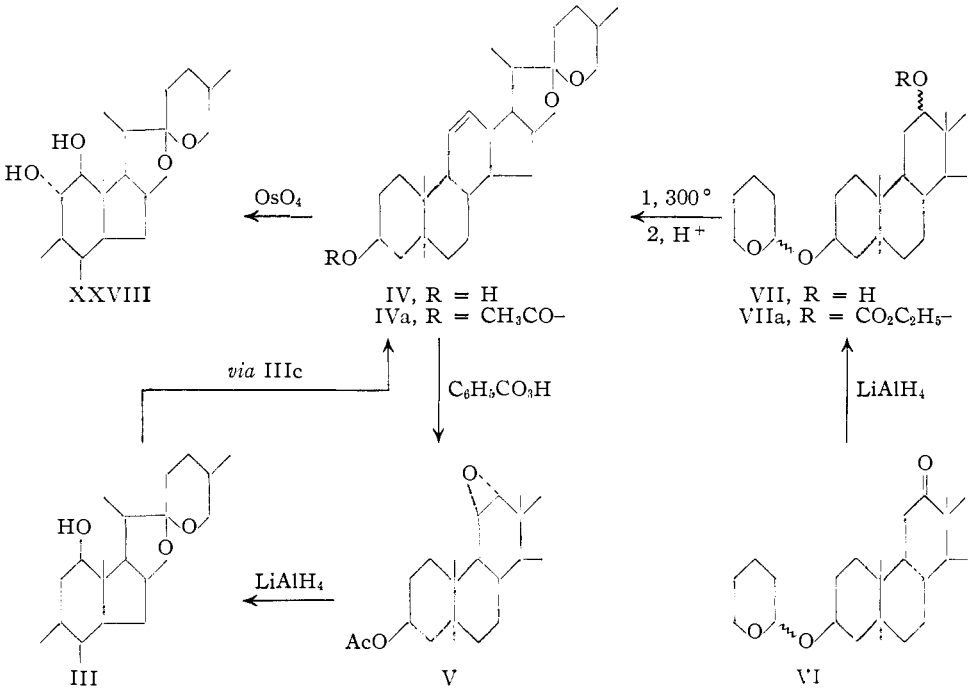
MOLECULAR ROTATIONS OF C-12 HYDROXYLATED STEROIDS

Compound	M_D	Compound	M_D	$M_D^{12\alpha-12\beta}$
12-Epi-rockogenin	-182^{0a}(chf.)	Rockogenin	-292^{0a}(chf.)	+110°
	-140^{a} (an.)		-276^{a} (an.)	+136
	-149^{b} (chf.)		-276^{b} (chf.)	+127
12-Epi-rockogenin 3-methyl succinate	-217^{a} (chf.)	Rockogenin 3-methyl succinate	-326^{a} (chf.)	+109
12α-Hydroxycholanic acid	$+164^{c}$ (an.)	12β-Hydroxycholanic acid	$+143^{c}$ (an.)	+ 21
Methyl 3α,12α-dihydroxycholanate	$+227^{d}$ (an.)	Methyl 3α,12β-dihydroxycholanate	$+177^{e}$ (an.)	+ 50
Methyl 3α-acetoxy-12α-hydroxyetianate	$+237^{f}$ (chf.)	Methyl 3α-acetoxy-12β-hydroxyetianate	$+161^{f}$ (chf.)	+ 76
12-Epi-rockogenin 3,12-diacetate	-77.5^{a} (an.)	Rockogenin 3,12-diacetate	-338^{a} (an.)	+260
	-77.0^{b} (chf.)		-332^{b} (chf.)	+255
Methyl 3-keto-12α-acetoxyetianate	$+527^{f}$ (chf.)	Methyl 3-keto-12β-acetoxyetianate	+262 (chf.)	+265
Methyl 3α,12α-diacetoxyetianate	$+644^{f}$ (chf.)	Methyl 3α,12β-diacetoxyetianate	+366 (chf.)	+278
Methyl 3α,12α-diacetoxycholanate	$+463^{e}$ (an.)	Methyl 3α,12β-diacetoxycholanate	$+279^{e}$ (an.)	+184

[a] See Experimental section. The solvent abbreviations indicated in the table are: chf. = chloroform, an. = acetone. [b] See reference 8. [c] M. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **26**, 2097 (1943). [d] T. Reichstein and M. Sorkin, *ibid.*, **25**, 797 (1942). [e] B. Koechlin and T. Reichstein, *ibid.*, **25**, 918 (1942). [f] S. Pataki, K. Meyer and T. Reichstein, *ibid.*, **36**, 1295 (1953).

sis associated with equatorial ester groupings.[7,8]

The 3-methylsuccinate derivatives of rockogenin (IIa) and 12-epi-rockogenin (IIIa) were converted to their respective 12-mesylate derivatives IIc and IIIc with methanesulfonyl chloride in pyridine.



Treatment of the 12α-mesylate IIIc with potassium *t*-butoxide in refluxing *t*-butyl alcohol for 15 hours resulted largely in the recovery of unchanged mesylate derivatives together with the formation of *ca.* 10% of an olefin. The latter was subsequently shown to be identical with Δ^{11}-dehydrotigogenin (IV) by comparison with a sample prepared by pyrolysis of the ethyl carbonate derivative VIIa[9] obtained from hecogenin (I). Osmylation of Δ^{11}-dehydrotigogenin (IV) produced the triol XXVIII[10] and treatment with perbenzoic acid correspondingly afforded the oxido derivative V[10]; the latter on reductive opening with lithium aluminum hydride gave 12-epi-rockogenin (III) thereby confirming the configuration of the rockogenins deduced earlier (see above) on the basis of physical evidence.

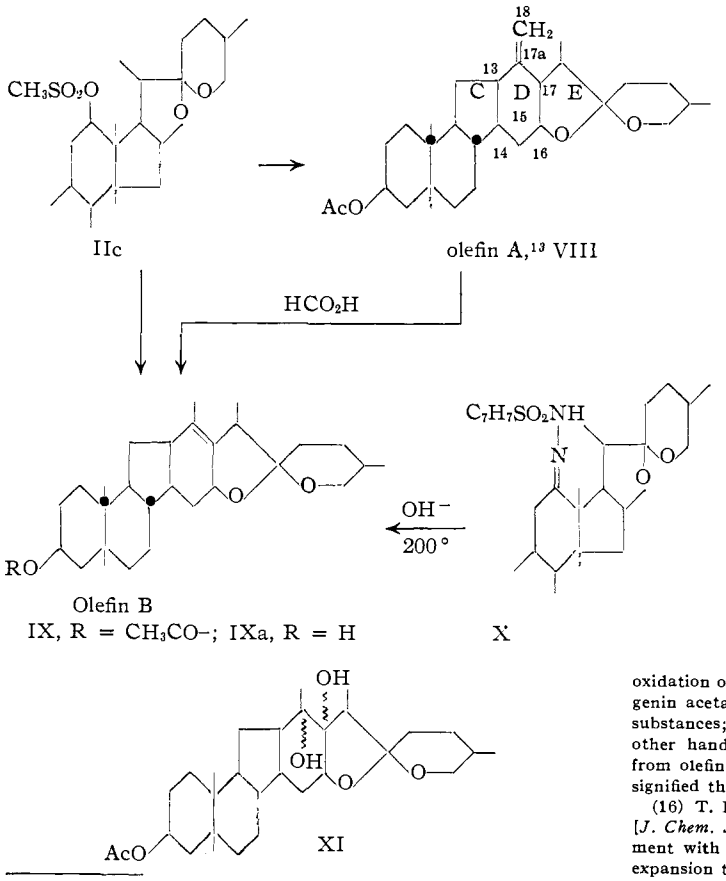
(7) D. H. R. Barton, *Experientia*, **6**, 316 (1950).

(8) C. Sannié and H. Lapin [*Bull. soc. chim.*, 1080 (1952)] recently separated the two diols II and III by paper chromatography. The physical constants reported by these authors for the epimeric rockogenins and the diacetates are in reasonable agreement with our reported[1] values.

(9) G. L. O'Connor and H. R. Nace [THIS JOURNAL, **74**, 5454 (1952)] have recently observed that the carbonate esters of cholestanol and cholesterol can be pyrolyzed in excellent yield to the corresponding olefins. We found that it was not possible to prepare the xanthogenic ester corresponding to VIIa.

(10) The action of peracids on Δ^{11}-cholenic esters has been shown to give exclusively the 11α,12α-oxide. See J. Press and T. Reichstein, *Helv. Chim. Acta*, **25**, 878 (1942); B. McKenzie, W. McGuckin and E. C. Kendall, *J. Biol. Chem.*, **162**, 555 (1946); T. F. Gallagher and W. P. Long, *ibid.*, **162**, 495 (1946).

Treatment of the 12β-mesylate IIc with potassium *t*-butoxide in refluxing *t*-butyl alcohol produced two olefins which were separated by fractional crystallization of their acetate derivatives. The less soluble olefin A, m.p. 221–225°, exhibited a sharp well-defined band in the double bond region of its infrared spectrum at 6.08 μ and an intense band at 11.26 suggesting an exocyclic methylenic double bond.[11] Olefin A was epoxidized with perbenzoic acid to give a crystalline oxido derivative; reductive cleavage of this oxide with lithium aluminum hydride afforded a diol that gave only a monoacetate on room temperature acetylation with acetic anhydride in pyridine. This same diol, moreover, reverted in large measure to the original olefin A on refluxing with acetic anhydride. This behavior strongly suggested that the new hydroxyl group was tertiary in character, a result, moreover, to be anticipated from the reductive scission of an oxide derived from an exocyclic methylene group.[12] This conclusion was confirmed by the failure of the diol monoacetate to undergo oxidation with chromic acid. It was apparent at this stage on purely chemical grounds that olefin A could neither be the Δ^{11}- nor the Δ^{9}-olefinic[2] systems and therefore had to



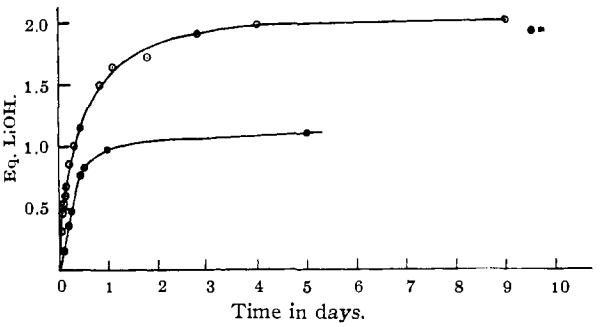


Fig. 1.—Relative saponification rates at 25° for: O, rockogenin diacetate; ●, 12-epi-rockogenin diacetate; ●*, separate sample heated at 74° for 6 hr., consumed 1.93 eq. of base.

be a product of molecular rearrangement.[14,15]

Hydroxylation of olefin A with osmium tetroxide afforded a triol which in turn gave a diacetate derivative on room temperature acetylation with acetic anhydride in pyridine. Periodic acid oxidation of the triol produced formaldehyde (60%) together with a quantitative yield of a nor-ketone. The latter possessed normal carbonyl absorption at 5.84 μ in the infrared spectrum characteristic of a 6-ring ketone. Olefin A was thereby established to be a rearranged olefin containing a methylene group exocyclic to a 6-membered ring. It will be evident from subsequent evidence presented that olefin A and the nor-ketone as well as their intermediate transformation products possess the abnormal steroid ring skeleton bearing a 5-membered C-ring and a 6-membered D-ring.

Olefin B, the second olefin produced from the decomposition of the 12β-mesylate derivative IIc, was found to be the endocyclic $\Delta^{13(17a)}$ or $\Delta^{17(17a)}$-double bond isomer (IX) of olefin A. This was established by the conversion of VIII → IX with formic acid at room temperature.[16] Olefin B ex-

(11) See for example: N. Sheppard and G. B. B. N. Sutherland, *Proc. Roy. Soc.* (*London*), **A196**, 195 (1949).

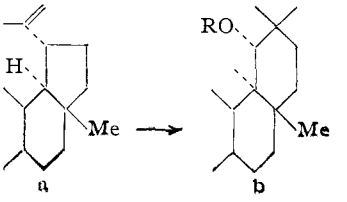
(12) W. G. Brown, in "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1951, Vol. VI, Chapt. X, p. 469.

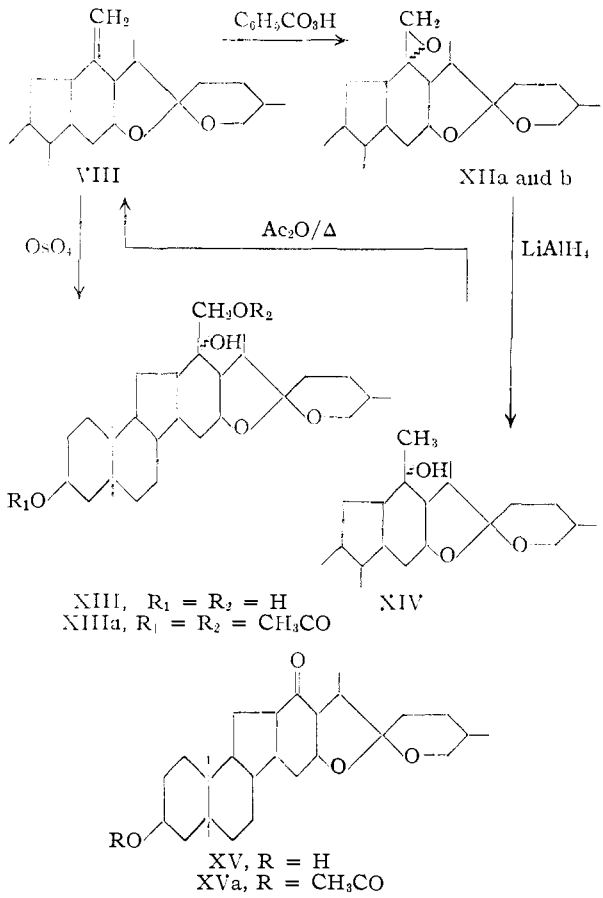
(13) It follows from the geometry of the rearrangement (see later) that rings C, D and E are *cis*-fused with the 13, 14, 16 and 17 hydrogens α-oriented behind the plane of the ring system. Ring D in all probability possesses the boat conformation since models indicate the attainment thereby of a more planar system.

(14) Rearrangement of the 12β-mesylate IIc was also found to occur even in the absence of added alkoxide ion, *e.g.*, on refluxing a *t*-butyl alcohol solution of IIc. Since the exocyclic olefin was observed to isomerize on treatment with formic acid, it is apparent that the absence of base may affect the ratio in which the isomeric rearranged olefins are produced.

(15) Additional considerations excluding the Δ^{11}- as well as the Δ^{9}-structures for olefin A were as follows: Reductive cleavage of an oxide derived from a Δ^{11}-olefin followed by oxidation of its monoacetate derivative should have given either hecogenin acetate or 11-ketotigogenin acetate both of which were known substances; $\Delta^{9(11)}$-dehydrotigogenin and its oxide derivative, on the other hand, were both known individuals and markedly different from olefin A and its derived oxide. These facts, therefore, clearly signified that olefin A was a product of molecular rearrangement.

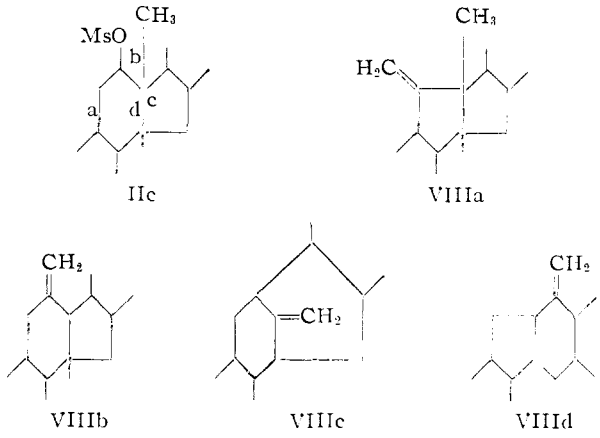
(16) T. R. Ames, G. S. Davy, T. G. Halsall and E. R. H. Jones, [*J. Chem. Soc.*, 2868 (1952)] have reported that lupeol (a) on treatment with formic acid at room temperature was converted by ring-expansion to a derivative of 18(α)-oleanane-2$''\beta''$,19α-diol (b). It is



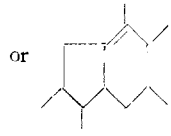


hibited no absorption in the double bond region of the infrared spectrum and was transformed with osmium tetroxide to a triol which gave only a monoacetate XI by room temperature acetylation. Olefin B, moreover, was synthesized by an entirely unrelated route involving the alkaline decomposition of the *p*-toluenesulfonyl hydrazone derivative of hecogenin (X).[17] This method reasonably restricts the position of the double bond in the resultant olefin[18] to either $\Delta^{13(17a)}$ or $\Delta^{17(17a)}$.

A consideration of the possible exocyclic methylenic systems related to olefin A which could arise in consequence of Wagner rearrangement of IIc, is reasonably restricted to the structures represented by formulas VIIIa–VIIId.

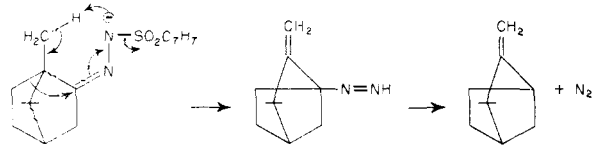


Structure VIIIa represents a highly strained system possessing a *trans* fusion of two 5-membered rings which implies a high energy barrier to its

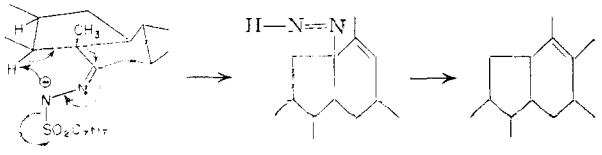


significant that olefin A did *not* revert to the normal steroid skeleton under these conditions nor was it found possible to effect this reversion with hot formic acid—conditions employed successfully by H. Kägi and K. Miescher [*Helv. Chim. Acta*, **22**, 683 (1939), **32**, 761 (1949)] for the rearrangement of 17α-androstanol to ψ-androstene.

(17) Compare the conversion of camphor *p*-toluenesulfonyl hydrazone to camphene; W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952). In view of the known decomposition of diazocamphene to tricyclene [H. Meerwein and K. van Emster, *Ber.*, **53**, 1815 (1920)], the mechanics of these transformations appear most reasonably interpreted by a concerted process, *viz.*

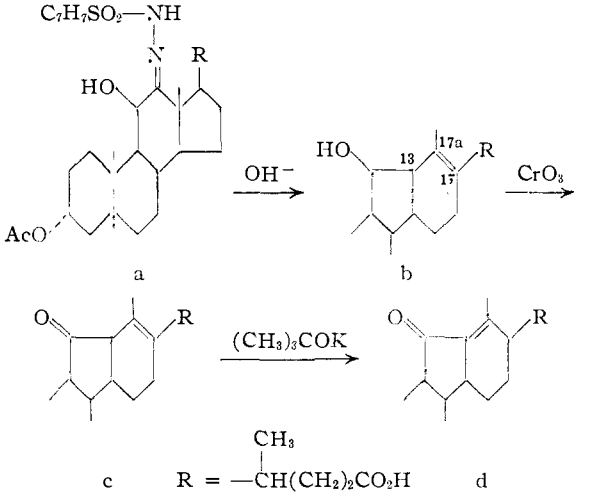


In extrapolating this interpretation to hecogenin *p*-toluenesulfonylhydrazone (X), it is evident from the spatial arrangement of atoms about the C/D ring system that only olefin B[18] can reasonably arise in consequence to this type of concerted rearrangement.



The antiparallel disposition of the C$_{13}$-methyl group with respect to the hydrazone residue makes unlikely a concerted pathway with involvement of a C$_{18}$-hydrogen atom; consequently olefin A should not arise in significant amounts as was indeed observed to be the case.

(18) We have tentatively chosen to formulate olefin B as the $\Delta^{13(17a)}$ isomer on the basis of evidence derived from incomplete work in the cholic acid series indicated below.



Thus compound (c) exhibited little if any absorption in the ultraviolet whereas this substance after treatment with base gave rise to characteristic absorption at 2525 Å. These observations support the $\Delta^{13(17a)}$ assignment to olefin B as given by formula IX.

A cleavage experiment designed to take advantage of the allylic ether oxygen in the $\Delta^{13(17a)}$ structure (sodium and butanol) was unrewarding. The decomposition of the tosylhydrazone of ψ-hecogenin, on the other hand, resulted in the re-establishment of the spiro ketal side chain.

formation.[19] Since, moreover, the norketone obtained from glycol–oxidation of olefin A exhibits normal 6-ring ketone absorption in the infrared at 5.84 μ,[20] structure VIIIa can be eliminated as a possibility. Structure VIIIb is the product of an improbable two-stage Wagner–Meerwein rearrangement involving successively the C_{13}–CH_3 and C_{12}–H. In view of the *trans*-character of Wagner–Meerwein rearrangements,[21] moreover, if structure VIIIb were to be formed, it would more probably arise from the 12α-mesylate (IIIc) than from the 12β-mesylate (IIc); the latter has been conclusively shown not to be the case. Jones and his associates[22] have demonstrated that ketones possessing α-methylene groups exhibit a characteristic band in the infrared due to α-methylene bending. This band appears at 1400–1440 cm.$^{-1}$ (6.95–7.14 μ) for 6-ring ketones and disappears after deuterium exchange with the α-hydrogen atoms. Hecogenin (I) was found to exhibit an intense band at 1429 cm.$^{-1}$ (7 μ) which disappeared after deuterium exchange. The nor-ketone derived from olefin A, on the other hand, showed no absorption band in the region 1370 to 1453 cm.$^{-1}$ (6.87–7.3 μ). Since the ketone derived from VIIIb would be expected to exhibit a band in this region, its absence in the spectrum of the nor-ketone further argues against structure VIIIb for the olefin. Structure VIIIc could not arise from the rearrangement of IIc by a concerted path since a complete space reorientation of ring C would be required in order to accommodate *cis*-bonding at C_{12} and C_{14} as necessitated by the bridgehead character of the resultant bicyclo[3.3.1]nonanone system. Equilibration of the nor-ketone, derived from olefin A, in deuterium oxide resulted in the introduction of two deuterium atoms. This exchange implies the ability of the nor-ketone to exist in some measure as an enol under the conditions of the equilibration. In view of the restricted bridgehead character of a ketone derived from VIIIc, it is highly improbable that it would undergo deuterium exchange to any measurable extent.[23] In view of these considerations the only structure for olefin A which is consistent with all the facts is structure VIIId.[24]

The structures of the rearranged olefins VIII and IX as deduced from chemical evidence, derive additional support from considerations concerned with the functional role of geometrical factors in controlling the course of Wagner–Meerwein rearrangements in general. Thus it has become generally accepted that *coplanarity* of the migratory groups in the rearranging species is an essential geometrical prerequisite in the promotion of Wagner–Meerwein rearrangements.[7,21,25] In consequence moreover of the anti-parallel relationship of departing and migrating groups attained through coplanarity, a concerted process of bond-breaking and bond-forming with its implicit steric acceleration is to be inferred. Elaborate experimental support for this concept has been provided by countless studies on the rates of solvolytic rearrangement of epimeric systems.[26] In the light of these considerations it is apparent that the geometrical requirements for a C/D ring contraction–expansion process are fulfilled only in the case of the transformation of rockogenin (12β, IIc) to olefin A (VIII) and olefin B (IX).

The kinetics of solvolysis of the C_{12}-epimeric mesylate derivatives IIc and IIIc was determined in acetic acid at 65° by titration of the liberated methanesulfonic acid with sodium acetate[27] followed potentiometrically. The half-lives for the first-order solvolyses of the 12β-mesylate IIc and the 12α-mesylate IIIc were found to be 8.6 minutes and 39.7 hours, respectively (Figs. 2 and 3). The significant difference in rates of solvolysis of the two epimeric mesylates could be interpreted as indicating a factor of geometrical promotion operative in IIc but absent in IIIc.[28]

The rearrangement–dehydration of the C_{12}-epimeric rockogenins finds an interesting parallel in the case of β- and epi-β-amyrin.[29] Whereas β-amyrin rearranges with ring contraction to XVI in a manner similar to IIc, epi-β-amyrin on the other hand undergoes simple dehydration to XVII, comparable with IIIc.

(19) R. P. Linstead and E. M. Meade, *J. Chem. Soc.*, 935 (1934); W. E. Grigsby, J. Hind, J. Chanley and F. H. Westheimer, THIS JOURNAL, **64**, 2606 (1942); E. E. van Tamelen, *ibid.*, **73**, 3444 (1951).

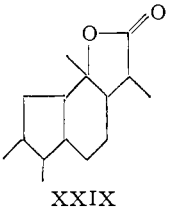
(20) 5-Ring ketones absorb in the infrared at *ca.* 5.75 μ; R. N. Jones, V. Z. Williams, M. J. Whalen and K. Dobriner, *ibid.*, **70**, 2024 (1948).

(21) See, for example, P. D. Bartlett and I. Pöckel, *ibid.*, **59**, 820 (1937).

(22) R. N. Jones, A. R. H. Cole, *ibid.*, **74**, 5648 (1952); R. N. Jones, A. R. H. Cole and B. Nolin, *ibid.*, **74**, 5662 (1952). We are grateful to Dr. Jones for informing us of his observations in advance of their publication.

(23) A. C. Cope and E. S. Graham, [THIS JOURNAL, **73**, 4702 (1951)] employed similar arguments to explain the failure of 1-bromobicyclo[3.3.1]nonane-9-one to brominate. These authors pointed out that enolization of this ketone to accommodate bromination would require the formation of a double bond at a bridgehead position which is not possible for steric reasons (Bredt's rule). V. Prelog, P. Barman and M. Zimmermann [*Helv. Chim. Acta*, **32**, 1284 (1949)] have observed the failure of angular β-keto acids derived from bicyclo[3.3.1]-nonan-9-one to decarboxylate under normal conditions. In this case the transition state to decarboxylation is believed to require double bond character at the bridgehead position, a requirement which is sterically incapable of fulfillment by considerations implicit in the Bredt rule.

(24) It is of interest that M. Sorkin and T. Reichstein [*ibid.*, **27**, 1631 (1944)] in a study concerned with the lactonization of the 3α,12-dihydroxy-bis-nor-cholanic acids observed the formation of a series of lactones. In order to account for the product multiplicity these authors formulated the various Wagner–Meerwein rearrangement possibilities including that of the C-nor/D-homo-lactone (XXIX).



XXIX

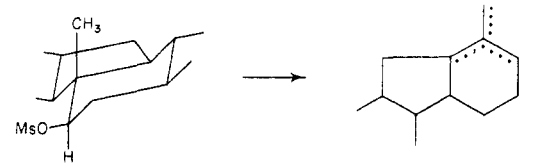
(25) D. H. R. Barton and E. Miller, THIS JOURNAL, **72**, 1066 (1950); D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953); M. L. Dhar, E. D. Hughes, C. K. Ingold, *et al.*, *ibid.*, 2093 (1948); P. I. Pollak and D. Y. Curtin, THIS JOURNAL, **72**, 961 (1950).

(26) See for example: S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan and H. Marshall, *ibid.*, **74**, 1127 (1952), and references therein.

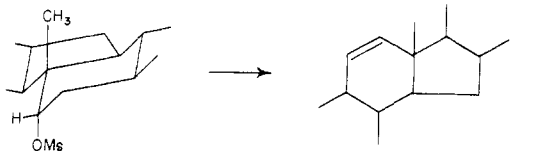
(27) Method of Winstein, *et al.* See for example: S. Winstein, E. Grunwald and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

(28) Compare for example the relative rates of solvolysis of the epimeric exo- and endo-nor-bornyl-*p*-bromotoluene sulfonates (ref. 27).

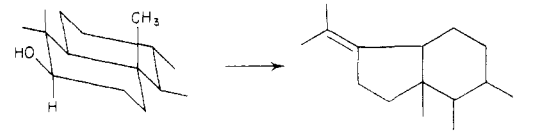
(29) O. Jeger, "Fortschritte der Chemie organischer Naturstoffe," Springer Verlag, Wien, 1950, vol. VII, p. 65.



IIc



III c



β-Amyrin XVI

Epi-β-amyrin XVII

Additional instances of C/D ring rearrangement with derivatives of hecogenin have been observed.

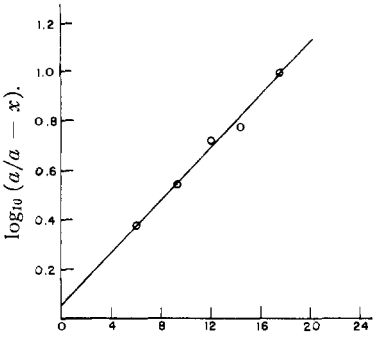


Fig. 2.—Solvolysis rate determined in acetic acid at 64.4 ± 0.2° for: rockogenin-3-methyl succinate-12(β)-mesylate; $K_{avg.}$ = 1.34 × 10^{-3} sec.$^{-1}$; $T/2$ 8.6 min.

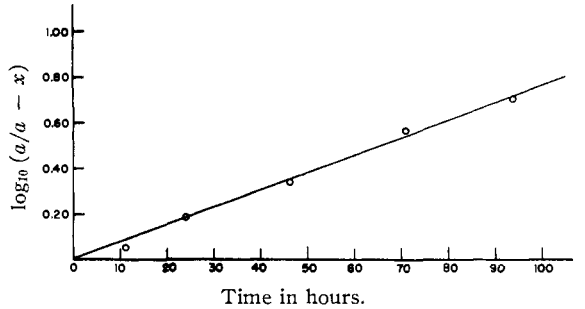
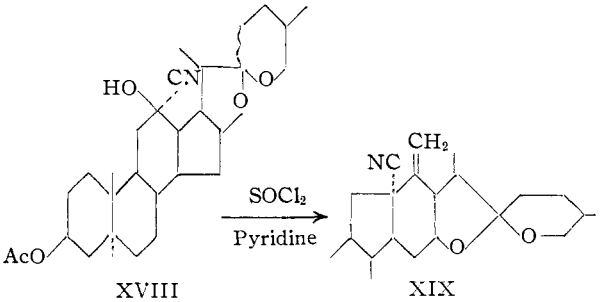
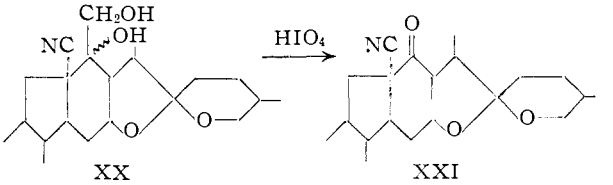


Fig. 3.—Solvolysis rate determined in acetic acid at 64.4 ± 0.2° for: 12-epi-rockogenin-3-methyl succinate-12(α)-mesylate; $K_{avg.}$ = 1.74 × 10^{-2} hr.$^{-1}$; $T/2$ 39.7 hr.

In particular the cyanohydrin derivative XVIII was found to rearrange smoothly to the angular cyano derivative of olefin A XIX on treatment with thionyl chloride in pyridine. The structure of XIX was established by osmylation to give the glycol XX followed by periodate cleavage to the nor-ketone XXI and formaldehyde 80%.

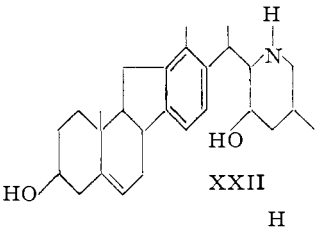


XVIII XIX

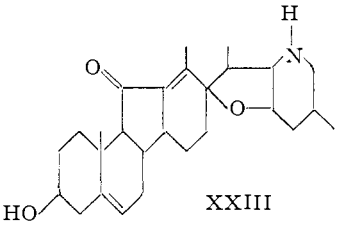


XX XXI

Recently excellent evidence has been presented for the C-nor/D-homo ring system in the steroid alkaloids veratramine (XXII) and jervine (XXIII).[30] In view thereof, the present work suggests the possibility that the biogenesis of these alkaloids might conceivably arise *via* a rearrangement pathway similar to that under discussion. These and other considerations encouraged the search for a synthetic route to the sapogenin counterpart of jervine whereby a direct comparison with the chromophoric system advanced[30] for this alkaloid would be possible.



XXII



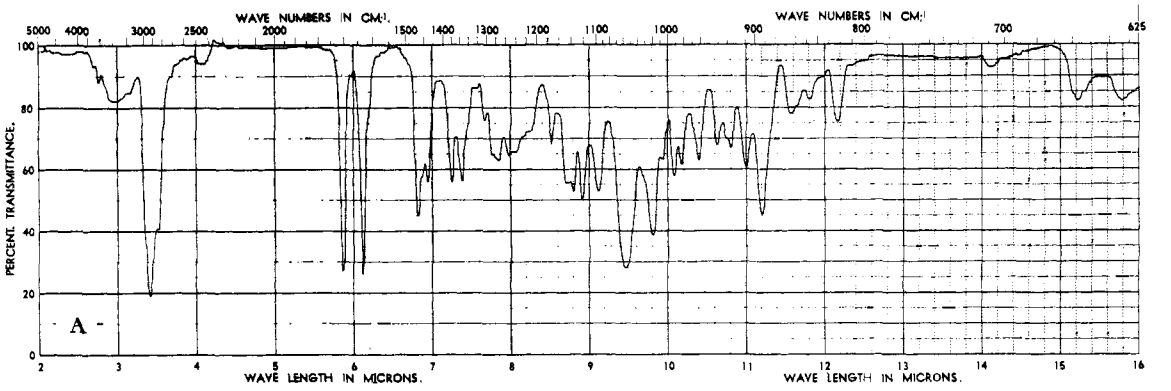
XXIII

To this end attempts to effect solvolytic rearrangement of the 12-mesylate derivative of 11-ketorockogenin (XXIVa) were totally unavailing.[31] Conversion of the diketone XXV[32] to its toluene-

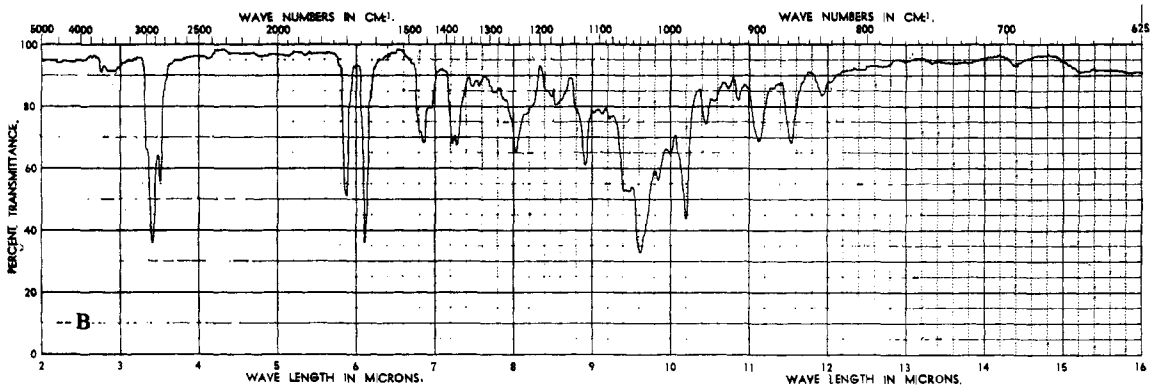
(30) Ch. Tamm and O. Wintersteiner, THIS JOURNAL, **74**, 3842 (1952); O. Wintersteiner and M. Moore, *ibid.*, **75**, 4938 (1953); J. Fried and A. Klingsberg, *ibid.*, **75**, 4929 (1953), and references cited in these papers.

(31) The course of this reaction will constitute the subject of a future report.

(32) This compound was first described by C. Djerassi, H. Ringold and G. Rosenkranz, THIS JOURNAL, **73**, 5513 (1951).



(A)

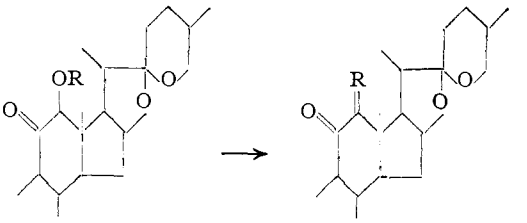


(B)

Fig. 4.—Infrared spectra determined in chloroform solution: (A) jervine (XXII); (B) $\Delta^{13(17a)}$-22a, 5α-C-*nor*/D-homospirostene-3β-ol-11-one (XXVI).

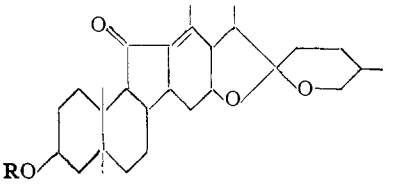
p-sulfonylhydrazone derivative XXVa, however, followed by treatment with potassium hydroxide in refluxing ethylene glycol resulted in the formation of the 11-keto-$\Delta^{13(17a)}$-C-nor/D-homosapogenin XXVI together with substantial amounts of the ketol XXIV.[33]

The ultraviolet spectrum of XXVI was found to be essentially the same as that of jervine, and the infrared spectra in the C=O and C=C regions of both substances, exhibited an unusual band intensity relationship (Fig. 4).



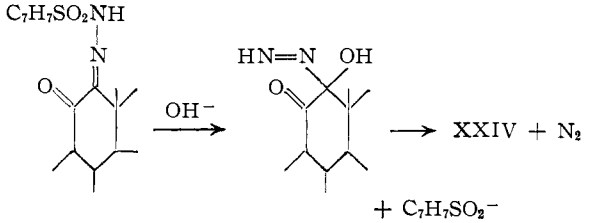
XXIV, R = H
XXIVa, R = CH_3SO_2–

XXV, R = O=
XXVa, R = $C_7H_7SO_2NHN$=

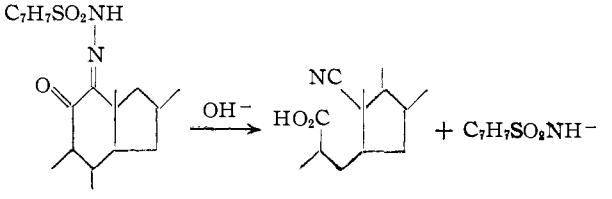


XXVI, R = H
XXVIa, R = CH_3CO–

(33) In addition to the rearrangement-degradation of XXVa (see footnote 18) the competitive decomposition of XXVa → XXIV by the following route is suggested



An alternate decomposition path, which was, however, *not* observed is the following close analogy to the second-order Beckmann cleavage [A. Werner and A. Piguet, *Ber.*, **37**, 4295 (1904)].



Acknowledgment.—The authors are indebted to Mrs. H. Gager for the rate studies described in this paper, to Messrs. R. Walker and N. Trenner for the infrared spectra and to Mr. R. N. Boos and staff as well as Mr. B. Arison for the analytical data reported. Appreciation is also expressed to Messrs. H. Slates and R. Miller for the execution of certain experiments.

Experimental[34]

Rockogenin (22a,5α-Spirostane-3β,12β-diol) and 12-Epi-rockogenin (22a,5α-Spirostane-3β,12α-diol).—Hecogenin acetate (I) (60.0 g.) in dry tetrahydrofuran (1.35 l.) was added gradually to a stirred solution of lithium aluminum hydride (9.65 g.) in dry ether (650 cc.) under nitrogen at a rate just fast enough to maintain gentle refluxing (addition time *ca.* one-half hour). When the addition was complete the reaction mixture was allowed to stir for an additional two hours. The excess lithium aluminum hydride was decomposed by the careful addition of ethyl acetate, with ice cooling, until no more reaction was observed followed by treatment with a saturated solution of sodium sulfate and with anhydrous magnesium sulfate.[35] Filtration followed by evaporation of the solvents gave 54.9 g. (100% yield) of a white amorphous solid which showed no carbonyl absorption in the infrared spectrum.

The crude mixture of the epimeric diols was dissolved in 300 cc. of dry redistilled pyridine, treated with 109 g. of succinic anhydride and heated on a steam-bath in a nitrogen atmosphere for 3 hours and 45 minutes. At the end of this period most of the pyridine was removed *in vacuo* on the steam-bath and the residue was dissolved in a mixture of chloroform and ethyl acetate containing enough ether to make the organic layer lighter than water. After washing successively with 2.5 *N* hydrochloric acid and with water, the organic layer was treated with 5.5 g. of Darco (G-60), filtered and taken to dryness. The mixture thus obtained as an amorphous solid amounted to 66.8 g. The latter was esterified by passing diazomethane into a solution of the crude acids in a 300-cc. mixture of equal amounts of methanol, chloroform and ethyl acetate. During the addition of the diazomethane a heavy crystalline precipitate began to separate in the flask and in the diazomethane delivery tube. Methylation was therefore continued by adding the diazomethane as an ethereal solution from a dropping funnel until an excess was present. The solid which had precipitated was removed by filtration (fraction 1) affording 9.73 g. of **12-epi-rockogenin 3-methyl succinate (IIIa)**, m.p. 215–221°. An analytical sample of elongated prisms prepared by repeated recrystallization from acetone melted at 222.2–225°, $[\alpha]D$ −39.7° (chf.).

Anal. Calcd. for $C_{32}H_{50}O_7$: C, 70.29; H, 9.22. Found: C, 70.08; H, 8.94.

Concentration of the mother liquor gave two additional fractions amounting to 4.90 g. of less pure IIIa, m.p. *ca.* 206–215°. After the isolation of a fourth crop (3.07 g., m.p. 186–204°) constituting a mixture of the 12-epimeric 3-methyl succinates IIa and IIIa, 15.85 g. (fraction 5) of **rockogenin 3-methyl succinate (IIa)** was obtained as aggregates of prisms, m.p. 146.5–148.5°. An analytical sample was recrystallized from acetone, melted at 152–154°, $[\alpha]D$ −59.6° (chf.).

Anal. Calcd. for $C_{32}H_{50}O_7$: C, 70.29; H, 9.22. Found: C, 70.44; H, 9.46.

A sixth crop of less pure IIa (1.52 g.) melted at 141–153°, bringing the over-all yield of crystalline material obtained to about 51% of the theoretical.

Chromatography of the oily residue constituting about half of the reaction mixture afforded only small additional amounts of IIa and IIIa. The non-crystallizable oil showed only weak hydroxyl absorption together with an intense ester band in the infrared. This material could be hydrolyzed to rockogenin, characterized as the diacetate (see below), m.p. and mixed m.p. with an authentic specimen 201–205°.

Saponification of 0.369 g. of 12-epi-rockogenin 3-methyl succinate (IIIa), m.p. 223–225°, was carried out by refluxing a solution (32 cc.) of an equal mixture of tetrahydrofuran and methanol with 7.5 cc. of 8% aqueous potassium hydroxide for 2.5 hours. The reaction mixture was allowed to stand at room temperature overnight and the **12-epi-rockogenin** was isolated by removal of most of the organic solvents *in vacuo* followed by addition of water. The diol thus obtained in quantitative yield melted at 220–222.5°. A sample, m.p. 218–220°, $[\alpha]D$ −42.1° (chf.), −32.4° (acetone), obtained by recrystallization from methanol was dried at 140° and analyzed.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 75.40; H, 10.22.

A 0.292-g. sample of 12-epi-rockogenin was acetylated with 5.5 cc. of acetic anhydride in an inert atmosphere at reflux temperature for two hours and then at room temperature overnight. The excess reagents were removed *in vacuo* to give a foam which was crystallized from methanol. The **12-epi-rockogenin diacetate (IIIb)** was thus obtained as prisms (0.234 g.), m.p. 153–157.5°. In a capillary the sample melted at 152.5–154.5°. One additional recrystallization from acetone–water raised the m.p. to 156–159°, $[\alpha]D$ −15° (acetone).

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.25; H, 9.34.

Saponification of rockogenin 3-methyl succinate IIa (1.0 g., m.p. 151–153°) was carried out essentially as described above for the 12α-isomer affording 0.80 g. of **rockogenin**, m.p. 209–211°. Recrystallization from methanol of a sample prepared essentially as described gave large prisms, melting at 216–220°, $[\alpha]D$ −63.0° (chf.).

Anal. Calcd. for $C_{27}H_{44}O_4 \cdot CH_3OH$: C, 72.37; H, 10.41. Found: C, 72.55; H, 10.48.

A sample of the solvated rockogenin was dissolved in ether and taken to dryness affording prisms, m.p. 218.5–220.5°, $[\alpha]D$ −63.8° (acetone).

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.96; H, 10.25. Found: C, 74.79; H, 10.00.

This specimen did not depress the m.p. of an authentic sample of rockogenin isolated[36] from *agave gracilipes* and the infrared spectra of the two samples were identical (reported[37] m.p. 220°). A mixed m.p. with a sample of 12-epi-rockogenin showed a slight depression (210.5–213.5°).

Acetylation of rockogenin (II) in refluxing acetic anhydride as described above for the 12-epimeric diol III gave prisms of **rockogenin diacetate (IIb)**, m.p. 200–207.5°. Upon recrystallization from methanol the m.p. of an analytical sample was 201–208.5°, capillary m.p. 206–209° (reported[37] m.p. 206°), $[\alpha]D$ −65.4° (acetone).

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.36; H, 9.36.

A mixed m.p. with a sample[36] prepared from natural rockogenin was not depressed. Identity of the synthetic and the natural materials was further established by comparison of their infrared spectra.

Hecogenin Methyl Succinate (Ia): (A) From **Hecogenin (I).**—A 2.0-g. sample of hecogenin was dissolved in 30 cc. of dry pyridine and heated with 4.7 g. of succinic anhydride on a steam-bath in a nitrogen atmosphere for 3.75 hours. The reaction product was worked up essentially as described above for the succinoylation of the epimeric rockogenins and the acid was subsequently esterified with an ethereal solution of diazomethane. Evaporation of the solvents gave after trituration with ether, 2.11 g. (84% yield) of the desired methyl succinate, m.p. 180–184°. Two recrystallizations from ether–petroleum ether afforded an analytical sample, m.p. 184–187°, $[\alpha]D \pm 0°$ (chf.).

Anal. Calcd. for $C_{32}H_{48}O_7$: C, 70.55; H, 8.88. Found: C, 70.53; H, 8.74.

(B) From **Rockogenin 3-Methyl Succinate (IIa).**—To a cooled solution of 0.300-g. sample of IIa, m.p. 151–154°, in 10 cc. of acetic acid was added dropwise 4.7 cc. of a chromic acid solution prepared by dissolving 0.088 g. of chromic anhydride in 10 cc. of acetic acid. The oxidation was allowed to proceed at room temperature overnight and excess oxidizing agent was then decomposed with methanol. After removing most of the acetic acid *in vacuo* the residue was taken up in ether and was washed successively with cold 2 *N* sulfuric acid, with water, sodium carbonate and again with water. Concentration of the dried ethereal solution afforded 0.190 g. of the keto ester, capillary m.p. 184.5–185.5°. One recrystallization from ether–petroleum ether gave Ia, m.p. 185–188°, $[\alpha]D \pm 0°$ (chf.).

(34) All m.p.'s reported were taken on a micro hot-stage unless otherwise noted and are corrected.

(35) Method of R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, THIS JOURNAL, **74**, 4223 (1952).

(36) Kindly supplied by Dr. L. A. Sweet of Parke, Davis & Co., Detroit, Mich.

(37) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).

(C) From 12-Epi-rockogenin 3-Methyl Succinate (IIIa).—A 0.300-g. sample of IIIa dissolved in 12 cc. of acetic acid was oxidized exactly as described above for the 12β-epimer. The keto ester thus obtained had a capillary m.p. of 184.5–185°, $[\alpha]_D$ −2.5° (chf.). A mixed m.p. with specimen prepared as described under A and B above was not depressed.

Rockogenin 3-Methyl Succinate-12-Mesylate (IIc).—Traces of moisture were removed from 11.02 g. of rockogenin 3-methyl succinate (IIa), m.p. 151–153°, by azeotropic distillation with benzene. The resulting dry compound was dissolved in 120 cc. of dry pyridine and with swirling treated with 7.0 cc. of methanesulfonyl chloride. The reaction mixture was protected from atmospheric moisture and kept at room temperature overnight. The excess methanesulfonyl chloride was decomposed by gradual transfer of the reaction mixture to an excess of ice and water and the resulting precipitate was removed by filtration. The solid was washed thoroughly with water and on drying gave the 12β-mesylate in quantitative yield as prisms, m.p. 130–134.5° dec. This material was entirely satisfactory for use in the subsequent step. In one run the crude reaction product was isolated as a different crystalline modification, m.p. 153–155° dec. In general it was observed that on recrystallization of the crude product the m.p. dropped. An analytical sample prepared by recrystallization from acetone melted at 127–132° dec., $[\alpha]_D$ −48.4° (chf.).

Anal. Calcd. for $C_{35}H_{52}O_9S$: C, 63.43; H, 8.39; S, 5.13. Found: C, 63.85; H, 8.45; S, 5.18.

The isomeric **12-epi-rockogenin 3-methyl succinate-12-mesylate (IIIc)** was prepared in the same manner from 12-epi-rockogenin 3-methyl succinate (IIIa) (2.20 g., m.p. 222–224.5°). The crude mesylation product obtained in quantitative yield (2.51 g.) melted at about 183–189° dec. An analytical sample prepared by recrystallization from acetone–petroleum ether (b.p. 66–67°) melted at 141°, resolidified at 145° and finally melted at 185–188° with darkening, $[\alpha]_D$ −13.4° (chf.).

Anal. Calcd. for $C_{35}H_{52}O_9S$: C, 63.43; H, 8.39; S, 5.13. Found: C, 63.90; H, 8.56; S, 5.28.

Δ^{11}-22a,5α-Spirostene-3β-ol (IV): (A) From IIIc.—To a stirred solution of potassium *t*-butoxide in *t*-butyl alcohol, prepared from 0.48 g. of potassium in 14 cc. of *t*-butyl alcohol, was added a suspension of 1.35 g. of 12-epi-rockogenin 3-methyl succinate-12-mesylate (m.p. 183–188°) in 36 cc. of *t*-butyl alcohol and the mixture was refluxed in a nitrogen atmosphere for about 52 hours. In the course of the reaction an additional 20 cc. of *t*-butyl alcohol was added. The reaction mixture was cooled, diluted with 10 cc. of water and 25 cc. of methanol and most of the *t*-butyl alcohol was removed on the steam-bath *in vacuo*. The residue was refluxed with a mixture of methanol, tetrahydrofuran and aqueous sodium hydroxide, concentrated *in vacuo* and diluted with water. The aqueous layer was extracted with a mixture of ether and chloroform and the organic extracts were washed free of base, dried and concentrated to dryness. The solvated, semi-solid residue was readily crystallized from methanol–water affording 0.240 g. (27% yield) of prisms which gave a positive test for unsaturation with tetranitromethane and melted at 188–192° (capillary m.p.). In the course of a m.p. determination on the micro hot-stage it was observed that the opaque prisms began to change to needles at 157°. An analytical sample, m.p. 191–192.5°, $[\alpha]_D$ −34.1° (chf.), was obtained by an additional recrystallization from methanol–water.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 77.98; H, 10.35.

Acetylation of the above olefin (m.p. 191–192.5°) with acetic anhydride and pyridine at room temperature afforded Δ^{11}-22a,5α-spirostene-3β-ol acetate (IVa) as small prisms m.p. 195–203°. This material was satisfactory for use in the epoxidation step. (See below comparison with IVa prepared from VIIa.)

In another experiment 1.08 g. of IIIc was refluxed with potassium *t*-butoxide in *t*-butyl alcohol essentially as above but for about 16 hours. The product was acetylated with refluxing acetic anhydride and chromatographed to yield 0.061 g. of IVa, m.p. 203.5–209.5°. A mixed m.p. with a sample of $\Delta^{9(11)}$-22a,5α-spirostene-3β-ol acetate[2] (m.p. 200–205°) was depressed (195–203°). The major product from the chromatographic purification (0.27 g.) was 12-epi-rockogenin-3-acetate-12-mesylate, m.p. 173–176° $\lambda\lambda_{max}^{Nujol}$ 5.78 μ, 8.0 μ (CH_3CO), 7.4–7.5 μ, 8.5 μ (CH_3SO_2).

Anal. Calcd. for $C_{30}H_{48}O_7S$: S, 5.80. Found: S, 6.03.

(B) From VIIa. **Hecogenin tetrahydropyranyl ether (VI)** was prepared by adding 0.06 cc. of phosphorus oxychloride to a suspension of 5.0 g. of hecogenin in 50 cc. of purified dihydropyran with vigorous shaking after the addition of each drop. Shaking was continued until the solid had dissolved (*ca.* 5 min.) and the solution was maintained at 25–30° for 2 hours. The reaction mixture was made basic by the addition of 20 cc. of 5% methanolic potassium hydroxide, poured into 100 cc. of 75% methanol and the solid[38] filtered and washed with 25 cc. of 75% methanol. Crystallization from 95% ethanol gave 3.05 g. (51%) of hecogenin tetrahydropyranyl ether, m.p. 209–213°. The oil which had separated from the combined filtrate and washings was extracted with petroleum ether and the dried extract concentrated *in vacuo* to a sirup which deposited crystals on trituration with 75% methanol. Recrystallization from 95% ethanol gave 1.86 g. (31% yield) of product, m.p. 207–211°. The analytical sample melted at 209–213°. The infrared spectrum showed no hydroxyl absorption.

Anal. Calcd. for $C_{32}H_{50}O_5$: C, 74.66; H, 9.79. Found: C, 74.91; H, 9.50.

Reduction of the above hecogenin tetrahydropyranyl ether VI (5.0 g.) with 0.76 g. of lithium aluminum hydride was carried out essentially as described for the reduction of hecogenin acetate. The resulting mixture of **rockogenin and 12-epi-rockogenin tetrahydropyranyl ethers (VII)** was crystallized from ethyl acetate to yield 3.88 g. (77.5%) of crystalline material m.p. 202–225°. An additional 0.76 g. (15%) of material, m.p. 188–196°, was obtained from the mother liquor. Subsequent recrystallization afforded an analytical sample, m.p. 231–250°. The infrared spectrum exhibited hydroxyl absorption at 2.92 μ and no absorption in the carbonyl region.

Anal. Calcd. for $C_{32}H_{52}O_5$: C, 74.34; H, 10.14. Found: C, 74.18; H, 10.23.

The 12-Ethyl Carbonate Derivative of Rockogenin and Epi-rockogenin-3-tetrahydropyranyl Ether (VIIa) was prepared from a solution of 3.61 g. of the above mixture (VII) (m.p. 202–225°) in 360 cc. of benzene and 14.5 cc. of pyridine by rapid addition of 14.5 cc. of ethyl chlorocarbonate in 72 cc. of benzene. The mixture was stirred at room temperature for 16 hours, the excess chlorocarbonate decomposed with water and the benzene solution washed with water and concentrated *in vacuo*. The solid was crystallized from acetone–methanol in two fractions: (1) 2.95 g. (72%), m.p. 184–215° (Found: C, 71.83; H, 9.55) and (2) 0.86 g. (21%), m.p. 180–187° (Found: C, 71.76; H, 9.43.). Calcd. for $C_{35}H_{56}O_7$: C, 71.39; H, 9.59.

The infrared spectra of the two fractions showed carbonyl absorption at 5.77 μ but no hydroxyl absorption.

A mixture of ethyl carbonate derivatives VIIa, 0.30 g., was pyrolyzed in a nitrogen atmosphere at 285° for 2 hours and the pyrolysate evaporatively distilled in high vacuum. The distillate (0.24 g.), which set to a hard glass on cooling was refluxed for 5 minutes with 10 cc. of methanol containing 0.15 cc. of concentrated hydrochloric acid. Concentration and dilution with water afforded crystalline material which was purified by recrystallization from dilute methanol; wt. 0.072 g. (34% yield)[39] of IV, m.p. 153–155°.

This compound was characterized as its acetate prepared from a 0.050-g. sample by heating on the steam-bath with 0.5 cc. of pyridine and 1.0 cc. of acetic anhydride for one hour to give 0.041 g. of colorless prisms from ethyl acetate, m.p. 201–204°, $[\alpha]_D$ −42.7° ($CHCl_3$). The infrared spectrum in the solid state was identical with that of the olefin obtained from IIIc as described under (A) above.

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.45; H, 9.61.

Conversion of Δ^{11}-22a,5α-Spirostene-3β-ol Acetate to Tigogenin Acetate (XXVII).—Hydrogenation of 0.067 g. of the acetate IVa over 0.010 g. of platinum oxide in 10 cc. of ethyl acetate afforded 0.048 g. of **22a,5α-spirostane-3β-ol acetate (XXVII)** as the first crop from acetone–methanol, m.p. 200–205°, $[\alpha]_D$ −69.0° (chf.). The melting point

(38) In a 15-g. run only an oil separated at this point; when worked up as described above there was obtained 15.66 g. (87.4%) of hecogenin tetrahydropyranyl ether.

(39) In subsequent runs with 1.0-g. samples, yields of only 15% could be realized.

was undepressed on admixture with authentic material, m.p. 202–207°, $[\alpha]_D$ −69.7° (chf.), prepared by acetylation of the Wolff–Kishner[37] reduction product of hecogenin (reported[37] m.p. 204–206°).

11α,12α-Oxido-22a,5α-spirostane-3β-ol Acetate (V).—A 0.116-g. sample of Δ^{11}-22a,5α-spirostene-3β-ol acetate (0.208 millimole), m.p. 195–203°, was epoxidized with 0.607 millimole of perbenzoic acid in 2.05 cc. of benzene at about 5° for 16 hours and then at room temperature for four hours. After diluting with ether, excess oxidizing agent was decomposed with aqueous sodium thiosulfate and the benzoic acid was extracted with a 5% aqueous sodium carbonate solution. The organic layer was then washed with water and with a saturated salt solution, dried and taken to dryness. The crude epoxide was recrystallized from methanol containing small amounts of chloroform to afford 0.050 g. of V, m.p. 220–226°. One additional recrystallization from the same solvent gave a sample melting at 225–230°. A capillary m.p. was 221–226°.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.56; H, 9.26.

Reduction of 11α,12α-Oxido-22a,5α-spirostane-3β-ol Acetate.—A 0.030-g. sample of the epoxide V in 6 cc. of anhydrous tetrahydrofuran was added dropwise with stirring to about 0.1 g. of lithium aluminum hydride in 5 cc. of anhydrous ether. After the addition was complete the mixture was refluxed for 45 minutes and the reaction was then worked up essentially as described for the reduction of hecogenin acetate. From the reduction reaction it was possible to isolate 12-epi-rockogenin, identified by comparison of its infrared spectrum with that of an authentic specimen.

22a-5α-Spirostane-3β,11α-12α-triol (XXVIII).—A 0.062-g. sample of Δ^{11}-22a,5α-spirostene-3β-ol, m.p. 186–191°, was dissolved in a mixture of 3 cc. of benzene and 0.4 cc. of pyridine and allowed to stand with an excess of osmium tetroxide at room temperature for eight days. The osmate ester was isolated and decomposed with sodium sulfite essentially as described for the preparation of XX (see below). The crude triol (0.067 g.) was crystallized from methanol to afford prisms, m.p. 222–227°. An analytical sample, m.p. 221–225°,[40] was prepared by adsorption of the triol on acid-washed alumina, elution with ether–methanol (7:3) followed by recrystallization from dilute methyl alcohol.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 72.05; H, 9.68.

$\Delta^{17a(18)}$-22a,5α-C-Nor/D-homo-spirostene-3β-ol Acetate (VIII) (a).—To a stirred solution of potassium *t*-butoxide in *t*-butyl alcohol (prepared from 3.40 g. of potassium in about 310 cc. of *t*-butyl alcohol) was added 10.0 g. of rockogenin 3-methyl succinate-12-mesylate, m.p. 128–135° dec., and the mixture was refluxed in a nitrogen atmosphere for about 18 hours. In the course of the reaction an additional 50 cc. of *t*-butyl alcohol was put in. The reaction was cooled, diluted with 15 cc. of water, 75 cc. of tetrahydrofuran and 150 cc. of methanol and refluxed two more hours under nitrogen. Solvents were removed *in vacuo*, water being added periodically to aid in the removal of the *t*-butyl alcohol. The solid which had precipitated was removed by filtration and was washed free of base. The crude olefin displayed a great tendency to solvate with a variety of solvents giving gels which were difficult to crystallize, but the compound was readily isolated as the acetate after refluxing with acetic anhydride (57 cc.) for 30 minutes. The $\Delta^{17a(18)}$-22a,5α-C-nor/D-homo-spirostene-3β-ol acetate which separated from the acetic anhydride solution on cooling was removed by filtration and freed of colored impurities by washing with acetic acid to afford 3.95 g. (54% yield), m.p. 208–221°. (The mother liquor was set aside for the isolation of IX—see below.) One recrystallization of the crude VIII gave the pure olefin (2.29 g.), m.p. 221–225°, and a second crop (0.850 g.), m.p. 210–216.5°, $\lambda_{max}^{CS_2}$ 6.08 μ, 11.26 μ. An analytical sample of the olefin acetate melted at 221–225.5°, $[\alpha]_D$ −80.6° (chf.).

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.21; H, 9.92.

$\Delta^{17(17a)}$-22a,5α-C-Nor/D-homo-spirostene-3β-ol acetate (IX) was isolated from the mother liquor of the acetylation reaction described above by concentration and dilution with water. After crystallization from methanol 1.110 g. was obtained, m.p. 141–142.5°. An analytical sample, prepared by recrystallization from methanol, melted at 142–144°, $[\alpha]_D$ −52.6° (chf.).

Anal. Calcd. for $C_{29}H_{44}O_4$: C, 76.27; H, 9.71. Found: C, 76.03; H, 9.72.

Alternatively IX was prepared from the **toluene-*p*-sulfonylhydrazone derivative of hecogenin (X).** The latter was prepared from 8.60 g. of hecogenin and 7.44 g. of toluene-*p*-sulfonylhydrazide in 300 cc. of ethanol in the presence of 2 cc. of concentrated hydrochloric acid by refluxing for 30 minutes and boiling for an additional 15 minutes after the condenser was removed. The product crystallized after the addition of an equal volume of water to afford 6.1 g., m.p. 258° dec. A second crop (3.4 g., m.p. 260–262°) brought the yield to 79%. An analytical sample, prepared by recrystallization from methanol, melted at 259–260° dec., $\lambda_{max}^{CH_3OH}$ 226 mμ (log ε 4.09).

Anal. Calcd. for $C_{34}H_{50}O_5N_2S$: S, 5.35. Found: S, 5.54.

The conversion of X to IX was carried out by suspending 1.2 g. of the sulfonylhydrazone in 25 cc. of a 1 *N* solution of sodium in ethylene glycol. The reaction mixture was heated in a nitrogen atmosphere. When the inside temperature reached 110–150°, a vigorous evolution of nitrogen ensued and the solid slowly dissolved, whereby the solution became cloudy and an oil separated on the surface of the solvent. After the temperature had reached 170° (total heating period about 30 minutes) no further gas evolution was noted. The mixture was maintained at 170° for 15 more minutes and then allowed to cool. Water was added and the product, which had crystallized in part on cooling, was extracted into petroleum ether and washed free of base. The dried solution on evaporation yielded a foam which resembled the isomeric $\Delta^{17a(18)}$-olefin VIII in its tendency to become solvated. A sample (0.71 g., m.p. 113–123°) was obtained from dilute methanol. An analytically satisfactory specimen of **$\Delta^{17(17a)}$-22a,5α-C-nor/D-homo-spirostene-3β-ol (IXa)** was prepared by evaporative distillation at 180–220° (0.01 mm.) of a sample which had been twice recrystallized from methanol.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 77.95; H, 10.00.

Acetylation of IXa at 100° with 2 cc. of pyridine and 3 cc. of acetic anhydride for 45 minutes gave after concentration, extraction into ether and removal of the solvent an oil which was crystallized from dilute methyl alcohol. The olefin acetate thus obtained in 78% yield from the alcohol IXa was identical with material prepared by solvolysis of the 12β-mesylate IIc as described above.

Isomerization of VIII to IX.—A 0.200-g. sample of the exocyclic olefin acetate VIII was shaken for seven days in a mixture of 12 cc. of anhydrous benzene and 20 cc. of 98–100% formic acid. The layers were separated and the benzene layer was diluted with ether and washed neutral with water. The dried solution yielded 0.194 g. of a foam which showed no significant absorption in the 6 μ and in the 11.24 μ regions. This material was triturated with methanol giving 0.146 g. of the endocyclic olefin acetate IX, m.p. 123–135°. One further recrystallization raised the m.p. to 142–144° undepressed on admixture of IX prepared by either method described above.

22a,5α-C-Nor/D-homo-spirostane-3β,17αξ,18-triol 3,18-Diacetate (XIIIa).—To a solution of 0.99 g. of the olefin acetate VIII, m.p. 219–223.5°, in 25 cc. of dry benzene and 0.61 cc. of dry, redistilled pyridine was added 0.64 g. of osmium tetroxide. The reaction mixture was kept at room temperature for six days. The mixture was diluted with benzene and washed free of pyridine with dilute (2.5 *N*) hydrochloric acid. A small amount of osmate ester which separated was removed by filtration, washed with ether and combined with the main material at a later stage. The filtrate was washed free of acid with water and the solution taken to dryness *in vacuo* to yield the bulk of the black amorphous ester. The osmate ester was decomposed by refluxing in 200 cc. of ethanol with 2.18 g. of sodium sulfite dissolved in 50 cc. of water for 1.5 hours. To effect com-

(40) It has been shown [O. Wintersteiner, M. Moore and K. Reinhardt, *J. Biol. Chem.*, **162**, 707 (1946); T. F. Gallagher, *ibid.*, **162**, 539 (1946)] that osmylation of a Δ^{11}-double bond affords the α-*cis*-diol in the bile acid series. A triol, m.p. 262–263°, isomeric with XXVIII and formulated as 22a,5α-spirostane-3β,11β,12β-triol was prepared by C. Djerassi, H. Martinez and G. Rosenkranz [*J. Org. Chem.*, **16**, 1278 (1951)] from XXIV by reduction with lithium aluminum hydride.

plete saponification the mixture was then refluxed with 1.5 cc. of a 30% aqueous solution of sodium hydroxide for 1.5 hours. The solution was concentrated and water was added. After chilling for several hours the triol which had separated was removed by filtration and washed free of base. The yield was 0.95 g. (97.5%), m.p. 198–208°. The m.p. of this triol was found to be quite variable and was not sharp. Thus a sample of the above specimen melted at 180–190° after recrystallization from chloroform–benzene and at 195–205° after one further recrystallization from benzene.

An aliquot (0.72 g.) of the triol melting at 195–205° was acetylated with 5 cc. of anhydrous pyridine and 5 cc. of acetic anhydride at room temperature overnight. The reaction product was worked up in the usual manner[41] to give a quantitative yield of the triol diacetate XIIIa, m.p. 212–219°. A more finely divided sample melted at 210–215°. An analytical sample prepared by recrystallization from ethyl acetate–petroleum ether melted at 211–216°; this compound exhibited a hydroxyl peak at 2.8 μ.

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08. Found: C, 70.03; H, 9.37.

Saponification of the above triol diacetate XIIIa (0.0375 g.), m.p. 211–216°, in 10 cc. of methanol with 1 cc. of a 2.5 *N* sodium hydroxide solution (at room temperature overnight followed by 1.5 hours at reflux temperature) afforded the triol XIII, m.p. 195–209°, in 99% yield (0.0313 g.).

In one experiment 3.08 g. of the olefin acetate VIII was osmylated and the ester decomposed essentially as described above. The crude product was acetylated directly to give a 91% yield of the triol diacetate XIIIa, m.p. 211–217°.

22a,5α-C-Nor/D-homo-18-nor-spirostan-3β-ol-17a-one (XV).—To a solution of 0.610 g. of the triol XIII, m.p. 180–190°, in 52 cc. of ethanol were added 0.336 g. of periodic acid dihydrate and 3 cc. of water. The reaction mixture was kept at room temperature overnight and the alcohol was then removed *in vacuo* (without heating). The residue was distributed between ether and a 5% aqueous solution of sodium bicarbonate. The ethereal solution was washed twice more with base, then with water until neutral and finally with a saturated salt solution. After removal of the solvent the residue amounted to 0.570 g. (100%), m.p. 170–176°. An analytical sample obtained by recrystallization from ether–petroleum ether (b.p. 66–67°) melted at 179–183°, $[\alpha]_D$ −93.8° (chf.). A capillary m.p. was 180–181.5°.

Anal. Calcd. for $C_{26}H_{40}O_4$: C, 74.96; H, 9.68. Found: C, 75.01; H, 9.66.

A sample of the ketone, m.p. 171–176°, was acetylated with pyridine and acetic anhydride at room temperature overnight. The reaction mixture was worked up in the usual manner[41] and the product was recrystallized from acetone to afford XVa, m.p. 227–232°, $[\alpha]_D$ −95.1°. The sample changed from plates to needles above 200°. This compound showed no absorption maximum between 6.87 and 7.3 μ, whereas hecogenin acetate exhibited a λ_{max} at 7.0 μ.[22]

Anal. Calcd. for $C_{28}H_{42}O_5$: C, 73.33; H, 9.23. Found: C, 73.84; H, 9.10.

In one experiment 0.195 g. of the triol XIII, m.p. 174–186°, dissolved in 15 cc. of ethanol, was treated with a solution of 0.099 g. of periodic acid dihydrate in 0.9 cc. of water at room temperature for 12 hours. A 2-cc. aliquot was then removed, diluted with 0.06 cc. of 2 *N* sulfuric acid and with 8 cc. of water and steam distilled. The distillate was found to contain 1 mg. of formaldehyde by chromotropic acid titration.[42]

The bulk of the reaction mixture was diluted with 30 cc. of water and extracted with ether. After washing with a saturated salt solution the organic layer afforded the ketone XV (0.074 g., m.p. 177–181°).

To the combined aqueous layers was added 50 drops of a 10% solution of 1,1-dimethylcyclohexane-3,5-dione and the mixture was concentrated in the hot. Upon cooling, the dimedone derivative of formaldehyde separated; m.p. and m.m.p. with an authentic sample 191°.

(41) The work-up procedure consisted in the dissolution of the residue in ether, washing successively with dilute hydrochloric acid, water, bicarbonate, and finally water and saturated salt solution. After drying over magnesium sulfate the ether was distilled *in vacuo*.

(42) C. E. Bricker and W. A. Vail, *Anal. Chem.*, **22**, 720 (1950).

17aξ,18-Oxido-22a,5α-C-nor/D-homo-spirostane-3β-ol Acetate (XIIa).—A 0.730-g. sample of the exocyclic olefin acetate VIII (1.6 millimoles), m.p. 218.5–225°, was epoxidized with 1.76 millimoles of perbenzoic acid in 50 cc. of benzene at about 5° for about 23 hours. After diluting with ether the benzoic acid was extracted with a sodium carbonate (5%) solution. The organic layer was then washed free of base with water and finally with a saturated salt solution, dried and taken to dryness. The crude epoxide (91% yield) which gave a negative test for unsaturation with tetranitromethane was dissolved in a mixture of 8 cc. of benzene and 11 cc. of petroleum ether and adsorbed on 35 g. of alumina. After elution of small amounts (about 0.020 g.) of unsaturated material, 0.220 g. of epoxide (m.p. ranging from 205–229° to 211–230°) was eluted with petroleum ether–benzene mixtures. A single recrystallization from acetone raised the m.p. of the hexagonal prisms to 234.5–238°, $[\alpha]_D$ −79° (chf.). The m.p. was unchanged on further recrystallization.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.62; H, 9.33.

17aν,18-Oxido-22a,5α-C-nor/D-homo-spirostane-3β-ol 3-acetate (XIIb)[43] was obtained from the more polar benzene–petroleum ether eluates. After several recrystallizations from acetone–petroleum ether, the needles melted at 206–213°, $[\alpha]_D$ −57.0° (chf.). The possibility that this material was still to some degree contaminated by the higher melting epoxide cannot be ruled out.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.85; H, 9.70.

22a,5α-C-Nor/D-homo-spirostane-3β,17aν-diol 3-Acetate XIV.—The more dextrorotatory epoxide XIIb (0.400 g.) dissolved in 60 cc. of dry tetrahydrofuran was added to lithium aluminum hydride (0.20 g.) in dry ether (60 cc.) over a 5-minute interval. Stirring was continued for 1 hour and 45 minutes at room temperature and then for 30 minutes at reflux temperature. The reaction mixture was worked up as described for the hydride reduction of hecogenin acetate (see above) and afforded 0.370 g. of an amorphous solid. A 0.260-g. sample of this crude reduction product was acetylated with acetic anhydride and pyridine at room temperature overnight. The excess reagents were removed *in vacuo* at about 40° and the residue was taken up in ether, washed with water until neutral and then with a saturated salt solution. From the dried solution 0.260 g. of a diol monoacetate, m.p. 172–183°, was obtained. The infrared spectrum showed both hydroxyl and acetoxy absorption. An analytical sample prepared by repeated recrystallization from ether–petroleum ether melted at 185–188°.

Anal. Calcd. for $C_{29}H_{46}O_5$: C, 73.38; H, 9.77. Found: C, 72.94; H, 9.63.

The diol monoacetate was recovered unchanged after treatment of a solution of 0.100 g. dissolved in 3 cc. of acetic acid with 1.67 cc. of a solution prepared by dissolving 0.0915 g. of chromic anhydride in 10 cc. of acetic acid for 3.5 hours.

In one experiment the lower melting epoxide was reduced with lithium aluminum hydride as described above. The resulting diol was refluxed with acetic anhydride for two hours affording the slightly impure olefin acetate VIII, m.p. 212–220°, which gave a positive test for unsaturation with tetranitromethane and which showed the characteristic peak at 6.08 μ and at 11.26 μ in the infrared.

22a,5α-C-Nor/D-homo-spirostane-3β,17ξ,17aξ-triol 3-Acetate XI.—To a solution of 2.50 g. of the endocyclic olefin acetate IX in 65 cc. of dry benzene containing 1.54 cc. of anhydrous pyridine was added 1.63 g. of osmium tetroxide. The reaction mixture was kept at room temperature for 17 days. The solution was added to 75 cc. of a 2.5 *N* solution of hydrochloric acid and the resulting precipitate (fraction A) was removed by filtration, washed with ether and then with water. The filtrates were washed free of acid with water and taken to dryness. The resulting dark residue was combined with fraction A initially separated by filtration and the osmate ester was then decomposed by refluxing for 2.25 hours in 245 cc. of ethanol with 5.82 g. of sodium sulfite dissolved in 40 cc. of water. The mixture was filtered hot and any undecomposed osmate ester thus removed by filtration was again refluxed with sodium sulfite in aqueous alcohol. After filtration the combined filtrates were

(43) The letter ν is here employed to denote a compound of unknown sterochemistry isomeric with the 17aξ-compound XIIa.

concentrated *in vacuo* and extracted with ether. After drying over magnesium sulfate the ethereal solution afforded 2.88 g. of the crude triol which was acetylated with pyridine and acetic anhydride at room temperature overnight. The product was worked up in the usual manner[41] to give about 3 g. of the crude triol monoacetate XI. Recrystallization from acetone–petroleum ether gave 1.45 g., m.p. 213–217°. An analytical sample, obtained from acetone–petroleum ether, melted at 215–218°, $[\alpha]D$ −39.3° (chf.).

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08. Found: C, 71.00; H, 9.45.

22a,5α-Spirostane-3β-ol-11,12-dione 12-*p*-Toluenesulfonylhydrazone (XXVa).—A mixture of 22a,5α-spirostane-3β-ol-11,12-dione,[32] 2.73 g. (0.0061 mole), and *p*-toluenesulfonylhydrazide, 2.43 g. (0.013 mole), was dissolved in 50 cc. of acetic acid and allowed to stand at room temperature for ten hours. The derivative was precipitated by the addition of water and, after a suitable aging period, it was filtered and recrystallized from methanol–water, affording 2.92 g. (80%), m.p. 158–160° dec.

Anal. Calcd. for $C_{34}H_{48}O_6N_2S$: N, 4.57. Found: N, 4.84.

$\Delta^{13(17a)}$-22a,5α-C-Nor/D-homo-spirostene-3β-ol-11-one (XXVI).—The above hydrazone XXVa (2.75 g.) was refluxed in a nitrogen atmosphere with a solution of 5 g. of potassium hydroxide in 90 cc. of ethylene glycol for one-half hour. The product, 1.94 g. of a white powder, was precipitated by the addition of water to the cooled solution and acetylated at room temperature with 15 cc. of acetic anhydride and 10 cc. of pyridine. The resulting 2.17 g. of amorphous acetate, on treatment with petroleum ether deposited 0.290 g. of crystalline 22a,5α-spirostane-3β,12β-diol-11-one diacetate, m.p. 222–225°. One recrystallization from methanol gave 0.230 g., m.p. 224–228° undepressed on admixture with an authentic sample.[44]

The petroleum ether mother liquor was chromatographed on 75 g. of acid-washed alumina from which the desired α,β-unsaturated ketone was eluted with (1:1) petroleum ether–benzene and crystallized from methanol to give 0.288 g., m.p. 177–179°. Recrystallization from acetone–methanol gave 0.240 g. of irregular transparent plates of XXVIa, m.p. 178.5–179.5°, $[\alpha]D$ −80.7° ($CHCl_3$), $\lambda\lambda_{max}^{CH_3OH}$ 255 mμ (log ε 4.18), 350 mμ (2.87).

Anal. Calcd. for $C_{29}H_{42}O_5$: C, 74.01; H, 9.00. Found: C, 73.74; H, 8.92.

A 0.120-g. sample of the acetate was saponified by refluxing in a nitrogen atmosphere with 10 cc. of 10% methanolic potassium hydroxide for 2 hours. After recrystallization from methanol–water XXVI was obtained as white needles; wt. 0.090 g., m.p. 190–192°, $[\alpha]D$ −78.4° ($CHCl_3$), $\lambda\lambda_{max}$ 255 mμ (log ε 4.17), 350 mμ (2.88).

An additional quantity (0.092 g.) of ketol diacetate, m.p. 223–226°, was obtained by further elution with ether.

Cyanohydrin of hecogenin acetate (XVIII) was prepared[45] by the addition of 14.5 g. of potassium cyanide over a period of 20 minutes to an externally cooled solution of 5.0 g. of hecogenin acetate dissolved in a mixture of 13.9 cc. of glacial acetic acid, 60 cc. of methanol and 40 cc. of chloroform. After the addition was complete the reaction was stirred for 15 more minutes at 0° and then for one hour at room temperature. The cyanohydrin which had separated was removed by filtration, washed with water and with ethyl acetate to afford 2.56 g., capillary m.p. 266–269° dec. with previous sintering. One recrystallization from chloroform–petroleum ether gave an analytically pure sample, capillary m.p. 271–275° dec. with previous sintering.

Anal. Calcd. for $C_{30}H_{45}O_5N$: C, 72.11; H, 9.08; N, 2.80. Found: C, 72.39; H, 9.13; N, 2.93.

The initial filtrate was shaken with a 5% aqueous solution of sodium sulfate and with more ethyl acetate. The organic layer afforded an additional 2.53 g. of lower melting cyanohydrin (capillary m.p. 236–243°). The work-up and purification of the mother liquors afforded in addition material exhibiting intermediate m.p. behavior. Very possibly the reaction resulted in the formation of epimeric cyanohydrins but no attempt was made to effect separation of the two specimens (see also m.p. reported below).

Alternatively[46] the cyanohydrin was prepared as follows: an 11.0-g. sample of hecogenin acetate was dissolved in 20 cc. of chloroform and 0.35 cc. of triethylamine and 9.5 cc. of petroleum ether was added. To the cooled solution 4.0 cc. of anhydrous hydrogen cyanide was added. After stirring for about one minute the solution became cloudy and set to a gel. After stirring at room temperature for two more hours the cyanohydrin, contaminated by polymerized hydrogen cyanide, was filtered, sucked as dry as possible on the funnel and then dried for 15 minutes in a vacuum desiccator to afford 8.8 g., m.p. 266–270° dec. with sintering from 255°. This material, which was shown to contain 1.15% of water by Karl Fischer titration, was satisfactory for use in the dehydration experiment.

$\Delta^{17a(18)}$-13α-Cyano-C-nor/D-homo-22a,5α-spirostene-3β-ol Acetate (XIX).—A solution of 8.12 g. of the above cyanohydrin XVIII, m.p. 266–270° (dec. with previous sintering), in 75 cc. of anhydrous pyridine was chilled and the solution treated with 2.7 cc. of thionyl chloride. The mixture was kept at room temperature overnight and then filtered through Super-cel to remove tarry impurities. The filtrate was poured into about 600 cc. of ice and water. The solid precipitate was extracted into ethyl acetate and washed with dilute hydrochloric acid, with a dilute solution of sodium bicarbonate and with a saturated salt solution. The solution was concentrated and on addition of an equal volume of petroleum ether the olefin, m.p. 216.5–219.5° (2.61 g.), separated as slightly tan needles. A single recrystallization from ethyl alcohol afforded 2.25 g., m.p. 220–221°.

The mother liquors from the initial crystallization were concentrated to dryness to give 5.0 g. of solid material from which 1.19 g. of white fluffy needles, m.p. 207–214°, and 0.235 g. of prisms, m.p. 240–243° dec., could be isolated. These fractions have not yet been examined further.

Dehydration of the cyanohydrin, capillary m.p. 248–253° dec., prepared by the potassium cyanide–acetic acid method afforded the rearranged olefin acetate, m.p. 220–221.5° after repeated recrystallization from acetone–petroleum ether.

Anal. Calcd. for $C_{30}H_{43}O_4N$: C, 74.80; H, 9.00; N, 2.91. Found: C, 75.24; H, 8.69; N, 2.93.

13α-Cyano-22a,5α-C-nor/D-homo-18-nor-spirostan-3β-ol-17a-one (XXI).—To a solution of 0.500 g. of XIX, m.p. 218.5–221.5°, in 6 cc. of anhydrous benzene and 0.352 cc. of distilled pyridine was added *ca.* 0.295 g. of osmium tetroxide. The black reaction mixture was kept at room temperature for about seven days. At the end of this time the reaction mixture was treated with 0.065 cc. of allyl acetate and allowed to stand for one hour. After diluting the mixture with chloroform, 0.3 g. of Super-cel was added followed by the dropwise addition of 1.03 cc. of concentrated hydrochloric acid for a five-minute period with vigorous stirring. After stirring for 3.5 hours the precipitate was removed by filtration and washed several times with hot chloroform. The filtrate was washed successively with water, 5% aqueous sodium bicarbonate, water and finally with a saturated salt solution. After removal of the solvents *in vacuo* a dark oil was obtained which was refluxed with 85 cc. of ethanol and 4.0 g. of sodium sulfite dissolved in 25 cc. of water for two hours. After filtration, the black residue was washed repeatedly with ethanol and the combined filtrates and washings were concentrated and diluted with water. The oil which had separated was extracted into a mixture of ether and ethyl acetate. The organic layer was washed with a saturated salt solution, dried and taken to dryness. The resulting oil was completely saponified by refluxing with an aqueous alcoholic solution of potassium hydroxide. The gummy solid which separated after the addition of ice-water was separated by filtration and recrystallized from dilute alcohol affording 0.273 g. of crude **13α-cyano-22a,5α-C-nor/D-homo-spirostane-3β,17aξ,18-triol (XX)**, melting at *ca.* 220° with previous melting and resolidification at about 190°. The infrared spectrum revealed the presence of hydroxy and cyano groups but no carbonyl peaks.

To a solution of 0.091 g. of the above triol in 5 cc. of ethanol were added 0.043 g. of periodic acid dihydrate and then 0.5 cc. of water. The reaction mixture was kept at room

(44) C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951).

(45) This procedure was based on an unpublished experiment carried out with a 12-keto steroid in the bile acid series by Dr. K. Pfister.

(46) We are indebted to Dr. M. Tishler for suggesting this method of preparation.

temperature overnight. A 1-cc. aliquot was diluted with 4 cc. of water and 0.03 cc. of 2 *N* sulfuric acid and then distilled. The distillate was found to contain 0.87 mg. of formaldehyde (83% of theory) by chromotropic acid titration.

The bulk of the reaction mixture was diluted with water and the cyano ketone separated by filtration. The crude ketone melted at 121–123° and exhibited bands in the infrared at 3.1 μ (OH), 4.58 μ (CN) and 5.80 μ (CO). It was found later that the m.p. depended on the rate of heating. Thus a sample melting ordinarily at about 125° was found to melt at 221–235° when heated very slowly to 130°. An analytical sample was prepared by recrystallization from methanol–water, m.p. 237–238°.

Anal. Calcd. for $C_{27}H_{39}O_4N$: C, 73.43; H, 8.90. Found: C, 73.82; H, 9.17.

Saponification Rate Determinations of the Diacetates of Rockogenin and 12-Epi-rockogenin.—Solutions containing 0.0960-millimole samples of the diacetates in 55 cc. of ethanol were treated with a solution containing 0.4140 meq. of lithium hydroxide and the total volume of the solutions was brought to 80 cc. with water. The temperature was maintained at 25.0 ± 0.2°. Aliquots were removed at intervals, treated with an excess of hydrochloric acid and back-titrated potentiometrically with alkali.

Rockogenin diacetate consumed one equivalent of base in about eight hours and two equivalents in four days. The diacetate of 12-epi-rockogenin, however, took up only one equivalent of alkali in 24 hours. In one experiment 0.0099 millimole of 12-epi-rockogenin diacetate dissolved in ethanol was treated with 0.0135 meq. of lithium hydroxide and diluted to 10 cc. with ethanol. After heating at 74° for six hours, 1.93 equivalents (96.5% of the theory) had been consumed.

Determination[47] of the Rates of Acetolysis of the 3-Methyl Succinate-12-mesylate Derivatives of Rockogenin and 12-Epi-rockogenin.—An 0.0041 *N* solution of IIc in acetic acid (m.p. 16.3°) was divided into aliquots which were kept frozen in sealed ampules until the beginning of the experiment. Acetolysis was carried out at 64.4 ± 0.2°. The rate of reaction was determined by potentiometric titration of 5-cc. aliquots with a solution of sodium acetate.

The first order rate constant for IIIc was similarly determined on a 0.0039 *N* solution.

Deuteration of 22a,5α-C-Nor/D-homo-18-nor-spirostane-3β-ol-17a-one (XV).—Butanol (46 cc.) was washed successively with two 24-cc. and three 10-cc. portions of deuterium oxide. A 0.054-g. sample of XIIa (m.p. 179–183°) was refluxed with 12 cc. of the above deuterized butanol in the presence of 0.240 g. of potassium hydroxide for 48 hours. The solution was concentrated *in vacuo* and cooled. A large excess of methanol was added, the solution was filtered and the product isolated by the addition of water. The infrared spectrum of the product, m.p. about 179–183°, was very similar to the starting material but differed in detail. Analysis by infrared spectroscopy of the water formed on combustion revealed the presence of 4.2 ± 0.1% D (85% of the theory for two gram atoms). XV was recovered unchanged (m.p., m.m.p., infrared spectrum) on treatment with potassium hydroxide in butanol under these conditions.

(47) See reference 27 for method.

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NOTES

A Route to Monosubstituted Ferrocene Compounds

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RECEIVED APRIL 15, 1954

Thus far relatively few monosubstituted ferrocene (bis-cyclopentadienyliron) compounds have been reported.[1] We have found that ferrocene can be metalated conveniently with *n*-butyllithium to yield a mixture of the mono- and dimetalated products, with the former predominating.

The metalation mixture can be carbonated in the usual way to yield the mono- and the disubstituted acids, separable by fractional crystallization. The methyl ester of the mono-acid can be prepared in conventional fashion.

The pK_a of the mono-acid, determined in ethanol–water solution (2:1 by volume), is 6.78, while that of benzoic acid under identical conditions is 6.32. This indicates that the ferrocene acid is weaker by approximately a factor of 3 than benzoic acid.

If the metalation product is treated with triphenylchlorosilane, a mixture of mono- and bis-triphenylsilylferrocene results, which again can be separated by fractional crystallization. It would seem that this metalation procedure may thus be a key in preparing other monosubstituted ferrocene types.

It is of interest that ferrocene does undergo the metalation reaction with *n*-butyllithium. Benzene itself does not react appreciably with this reagent, indicating that the hydrogen atoms in ferrocene are more acidic.

Experimental

Preparation of Acids.—A solution of 5.0 g. (0.027 mole) of ferrocene[2] in 75 ml. of anhydrous ether was placed in an oven-dried 3-neck flask fitted with a stirrer, a dropping funnel and a water-cooled condenser. To this 0.08 mole of *n*-butyllithium was added dropwise with stirring. The stirring was stopped after one hour and the mixture was allowed to stand for 24 hours under an atmosphere of nitrogen.

The reaction mixture was poured jetwise with stirring into a Dry Ice ethereal slush. Cold water was added cautiously after the Dry Ice had disappeared and the two layers were separated. The water layer was acidified with 6 *N* hydrochloric acid whereupon 0.4 g. of a mixture of crude acids precipitated out. An elemental analysis of the mixture indicated it to be approximately 70% ferrocenemonocarboxylic acid and 30% dicarboxylic acid. On this basis, the reaction gave a 65% total yield of acids, or a 35% conversion.

The crude acids were separated by fractional crystallization from glacial acetic acid. The reddish brown crystals of the mono-acid did not melt up to 200° and then slowly decomposed.

Anal. (monocarboxylic acid) Calcd. for $C_{11}H_{10}O_2Fe$: C, 57.4; H, 4.29. Found: C, 57.0; H, 4.36.

Preparation of Methyl Esters.—Each acid was esterified, using methanol and a trace of mineral acid. The esters were recrystallized from a methanol–water mixture. The methyl ester of the dicarboxylic acid melted at 114–115°.[1] The methyl ester of ferrocenemonocarboxylic acid melted at 70–71°.

(1) R. B. Woodward, M. Rosenblum and M. C. Whiting, THIS JOURNAL, **74**, 3458 (1952); P. L. Pauson, *ibid.*, **76**, 2187 (1954).

(2) T. J. Kealy and P. L. Pauson, *Nature*, **168**, 1039 (1951). See also G. Wilkinson, *et al.*, THIS JOURNAL, **74**, 2125 (1952).