Catalytic hydrogenation of PSa and PSm diacetates followed by alkaline hydrolysis yielded the known DPSa and DPSm[12] which were found to be *identical* to D20-iSa and D20-iSm, respectively.

Mild oxidation of 20-iSa and 20-iSm with CrO_3-pyridine[13] gave the respective 3 keto derivatives; 3 keto-20-iSa (m.p. 151°, $[\alpha]^{25}D$ +20°, strong ketonic band at 1714 kr.; Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.24; H, 10.04); 3 keto-20-iSm (m.p. 162°, $[\alpha]^{25}D$ −55°; ketonic band at 1714 kr.; Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.14; H, 10.18). Reflux with alcoholic HCl resulted in formation of the known 3 keto-Sa (sarsasapogenone), m.p. 223° and 3 keto-Sm (smilagenone), m.p. 188° identical with the products of CrO_3–pyridine oxidation of Sa and Sm.

Mild oxidation of 20-iSa and 20-iSm with CrO_3–acetic acid yielded amorphous acids which on treatment with KOH in *t*-butyl alcohol were smoothly *cleaved* to the known 16-pregnen-3,20-dione, (m.p. 200–201°, $[\alpha]^{25}D$ +69.3°, $\lambda_{max.}$ 239 mμ, log ε 3.98). Similar treatment of D20-iSa and D20-iSm also resulted in formation of 16-pregnen-3,20-dione. Under similar oxidative conditions the linkage between C_{20} and C_{22} in Sa, Sm, DSa, DSm is not affected.

The data presented permit a reasonably certain assignment of configuration of steroidal sapogenins at C_{20}. Molecular models constructed for the two possible geometrical isomers show that I is under relatively little strain whereas in II the methyl groups attached to carbons 13 and 20 put a tremendous strain on ring E. The configuration II is assigned to 20-isosapogenins. It is in accord with the *facile oxidative cleavage* of such compounds and their dihydro analogs, and with the formation of pseudosapogenins on *refluxing* with acetic anhydride. Configuration I is assigned to the more stable naturally occurring steroidal sapogenins. Formation of 20-isosapogenins is not confined to sarsasapogenin and smilagenin but has been observed with diosgenin, tigogenin and hecogenin indicating it is a general reaction.

The configuration of cholesterol and related sterols and bile acids at C_{20} is still unsettled. Fieser and Fieser assigned the non-relative designations 20-a or 20-b to differentiate the side chains of such steroids.[14] Based largely on optical rotation differences, they later assigned (in terms of their C_{20} convention) the relative configuration 20-beta to the side chains of cholesterol and bile acids.[15,16] Klyne[17] deduced from the X-ray studies of Carlisle and Crowfoot[18] that the cholesterol side chain has the 20-alpha configuration.

There is now available direct chemical evidence which completely substantiates Klyne's formulation for cholesterol. Marker and Turner[19] converted diosgenin to cholesterol by a route which could not affect the acid stable C_{20} configuration (I) found in all natural steroidal sapogenins. Marker and coworkers[20,21] also showed that diosgenin, tigogenin and smilagenin all have the same side chain, a fact also confirmed by infrared studies.[8,9] Consequently the side chain configurations of cholesterol and smilagenin at C_{20} are identical. We have shown that the C_{20} configuration of smilagenin is 20-alpha. Hence cholesterol and most other natural sterols and bile acids which have been related to it have the 20-alpha configuration with respect to the rest of the molecule.

These findings confirm by an independent route the previous conclusions of Wieland and Miescher.[22] These workers showed that Δ^5-3β-acetoxy-bisnor-cholenic acid could be converted to Δ^5-pregnen-3β,-20α-diol as a result of the action of perbenzoic acid. Turner[23] later showed that this type of reaction proceeds with retention of configuration. Hence the bisnor-cholenic acid and the longer chain bile acids from which it can be derived have the 20-alpha configuration.

(12) R. E. Marker and E. Rohrmann, THIS JOURNAL, **62**, 521 (1940).

(13) G. I. Poos, G. E. Arth, R. E. Beylen and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(14) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publ. Corp., New York, N. Y., 1949, pp. vi–viii.

(15) L. F. Fieser and M. Fieser, ref. 14, pp. 412–419.

(16) L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948).

(17) W. Klyne, *Chemistry and Industry*, 426 (1951).

(18) C. H. Carlisle and D. Crowfoot, *Proc. Roy. Soc. (London)*, **184A**, 64 (1945).

(19) R. E. Marker and D. L. Turner, THIS JOURNAL, **63**, 767 (1941).

(20) R. E. Marker, T. Tsukamoto and D. L. Turner, *ibid.*, **62**, 2525 (1940).

(21) R. E. Marker, E. Rohrmann and E. M. Jones, *ibid.*, **62**, 1162 (1940).

(22) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(23) R. B. Turner, THIS JOURNAL, **72**, 878 (1950).

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RECEIVED MARCH 13, 1954

STEROIDAL SAPOGENINS. XX. CONFIGURATION OF SPIROKETAL SIDE CHAIN AT CARBON 22[1]

Sir:

In a recent communication Scheer, Kostic and Mosettig[2] state that Sa[3] and Sm are not isomeric at both C_{22} and C_{25} as previously believed[4] but differ only at C_{25}. We feel this view is incorrect. Not only is there excellent evidence available to show that Sa and Sm are isomeric at C_{22}, but in view of the establishment of the configuration of steroidal sapogenins at C_{20}[1] it is now possible for the first time to designate the actual configuration of Sa and Sm at C_{22}.

The evidence that Sa and Sm are isomeric at C_{22} is convincing: (a) Sa and Sm have different infrared spectra in the region 850–1350 K.[5,6] These are believed to be due to the vibrations of the –C–O–C–O–C– spiroketal system constrained by the two E and F rings. When this system is disrupted, as in

(1) Paper XIX. M. E. Wall, C. R. Eddy and S. Serota, THIS JOURNAL, **76**, 2849 (1954).

(2) I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **75**, 4871 (1953).

(3) Abbreviations used in this paper: Sa = sarsasapogenin, Sm = similagenin, P = pseudo, D = dihydro, 20-i = 20-iso. Thus D20-iSa = dihydro 20-isosarsasapogenin.

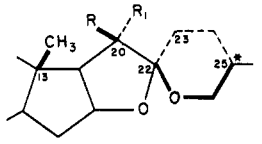
(4) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 846 (1939).

(5) M. E. Wall, C. R. Eddy, M. L. McClennan and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952).

(6) R. N. Jones, E. Katzenellenbogen and K. Dobriner, THIS JOURNAL, **75**, 158 (1953).

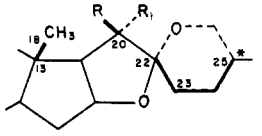
formation of dihydrosapogenins, these characteristic bands disappear.[5,6] As we have shown previously,[1] Sa and Sm are identical at C_{20} and isomerism at C_{25} has no effect on infrared spectra. Therefore the spectral differences between Sa and Sm must be due to isomerism at C_{22}. (b) Prolonged refluxing of 22b-spirostanes, such as Sa or its dihydroxy analog, with alcoholic hydrochloric acid converts them to the isomeric 22a series.[4,7,8] This can be possible only if Sa and Sm were isomeric at C_{22}. (c) Djerassi, Martinez, and Rosenkranz[9] have shown that Sa under proper conditions forms a *23-dibromide* whereas Sm and other 22a-spirostanes form only *23-monobromides*. We have confirmed this. Again this difference is possible only if Sa and Sm are *isomeric* at C_{22}.

The bromination data in conjunction with the established configuration at C_{20}[1] permits, for the first time, assignment of configuration at C_{22}. Molecular models corresponding to IA and IIA in Fig. 1 were constructed. On account of the hindrance of the methyl group attached to C_{20} it is impossible to construct a 23-dibromide of IA. Therefore it is Sm. A 23-dibromide can easily be constructed from IIA. Therefore it is Sa. By analogy we assign configurations IB and IIB to 20-iSm and 20-iSa, respectively.[1] In this case 20-iSm should form a dibromide and experiments to confirm this will be reported at a later date.



I-A Smilagenin
R = H. R_1 = CH_3

I-B 20-Isosmilagenin
R = CH_3. R_1 = H



II-A Sarsasapogenin
R = H. R_1 = CH_3

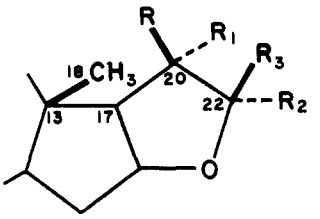
II-B 20-Isosarsasapogenin
R = CH_3. R_1 = H

Fig. 1.—Configurations of sarsasapogenin and smilagenin and their 20-isoanalogs at carbons 20 and 22.

Scheer, Kostic and Mosettig[2] converted Sa and Sm to identical 16,22-epoxycoprostan-3β-ol derivatives via catalytic hydrogenation, selective tosylation at C_{26}, followed by $LiAlH_4$ reduction. Using a somewhat modified procedure involving catalytic hydrogenation of the 3-acetates, tosylation at C_{26}, replacement of tosyl with iodine, followed by zinc–acetic acid reduction, hydrolysis, and formation of the nicely crystalline 3-3,5-dinitrobenzoates, we confirmed these workers' findings: 16,22-epoxycoprostan-3β-ol-3[3,5-dinitrobenzoate, m.p. 236–237°, $[\alpha]_D^{25}$ +6.2°. Calculated for $C_{34}H_{48}N_2O_7$: C, 68.51; H, 8.12. Found: C, 68.38; H, 8.20].

This, however, *does not prove* that Sa and Sm are identical at C_{22}. This would be true only if DSa and DSm retain configuration at C_{22} during hydrogenation. We wish to present evidence that during catalytic hydrogenation the configuration of DSm at C_{22} probably is changed from that of Sm and becomes identical to that of DSa, whereas DSa does not change configuration.

On catalytic hydrogenation 20-iSa and 20-iSm give dihydro derivatives D20-iSa and D20-iSm identical to those obtained from similar hydrogenation of PSa and PSm diacetates.[1] Therefore, the location of the hydrogen atom at C_{20} in dihydropseudosapogenins is known, *i.e.*, it is identical to that of 20-isosapogenins as in IB and IIB.[10] Since catalytic hydrogenation of an olefinic bond usually results in a *cis* configuration,[11] we assign formulations IIIA and IIIB, Fig. 2, to D20-iSm = PDSm and D20iSa = PDSa. Entrance of the hydrogen atoms on the rear faces of C_{20} and C_{22} is in complete accord with the structures of PSa and PSm in which the front faces of C_{20}-C_{22} are almost completely shielded by methyl groups attached to C_{18} and C_{20}.



IIIA. D_{20}iSm = DPSm. R = CH_3. R_1 = R_2 = H. R_3 = $-(CH_2)_2-\overset{H}{\underset{CH_3}{C}}-CH_2OH$

IIIB. D_{20}iSa = DPSa. R = CH_3. R_1 = R_2 = H. R_3 = $-(CH_2)_2-\overset{CH_3}{\underset{H}{C}}-CH_2OH$

IVA. DSm. R_1 = CH_3. R = R_2 = H. R_3 = $-(CH_2)_2-\overset{H}{\underset{CH_3}{C}}-CH_2OH$

IVB. DSa. R_1 = CH_3. R = R_2 = H. R_3 = $-(CH_2)_2-\overset{CH_3}{\underset{H}{C}}-CH_2OH$

Fig. 2.—Configuration of dihydro and dihydro 20-iso-analogs of sarsasapogenin and smilagenin.

From a consideration of the formulations in Figs. 1 and 2, it is seen that catalytic hydrogenation of 20-iSm (IB) to form D20-iSm (IIIA) involves a *change* in C_{22} configuration to that identical with D20-iSa (IIIB). Formation of IIIB from 20-iSa (IIB) does not involve a change in C_{22} configuration. Hence D20-iSm and D20-iSa are now isomeric only at C_{25}. It is most probable that hydrogenation of Sm (IA) and Sa (IIA) to DSm (IVA) and DSa (IVB), respectively, involves a similar mechanism. Accordingly, the formation of the same 16,22-epoxy-coprostan-3β-ol from Sm and Sa

(7) M. E. Wall, C. R. Eddy, S. Serota and R. F. Mininger, *ibid.*, **75**, 4437 (1953).

(8) We have confirmed Marker's findings in regard to the conversion of Sa to Sm[4] and have found the spectral differences associated with 22b- and 22a-spirostanes.[5,6]

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

(10) Hydrogenation of sapogenins does not affect the configuration at C_{20}. For example Sa, which is stable to CrO_3 oxidation, hydrogenates to DSa likewise stable, 20-iSa unstable to CrO_3 oxidation, hydrogenates to D20-iSa which is equally unstable.

(11) G. W. Wheland, "Advanced Organic Chemistry," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1949, pp. 297–298.

is not incompatible with C_{22} isomerism of these sapogenins.

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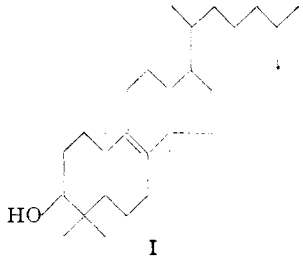
THE SYNTHESIS OF LANOSTENOL

Sir:

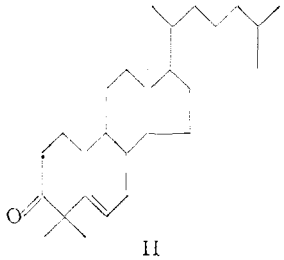
We wish to record the conversion of cholesterol into the naturally occurring tetracyclic triterpene lanostenol (dihydrolanosterol)(I). These results



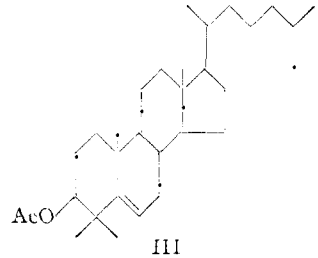
I

constitute the first total synthesis[1] of a tetracyclic triterpene, and provide rigorous confirmation in detail of the remarkable structural and stereochemical relationships, between the lanostane group and the steroids, which have been brought to light in recent years through degradative,[2] deductive,[3] biochemical,[4] and physical[5] studies.

Direct methylation of either Δ^4- or Δ^5-cholestenone-3[6] in dry *tert*-butanol with potassium *tert*-butoxide (3 moles) and methyl iodide (6 moles) gave 4,4-dimethyl-Δ^5-cholestenone-3 (II) (63%), m.p. 176–177°, $[\alpha]_D$ +1 (*c* 2.07)[7] (*Anal.* Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 84.14; H, 11.91), which was reduced by lithium aluminum hydride to 4,4-dimethylcholesterol

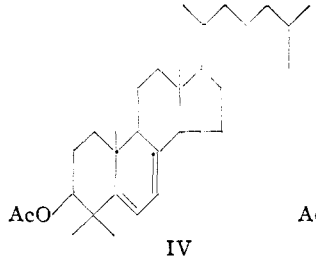


II

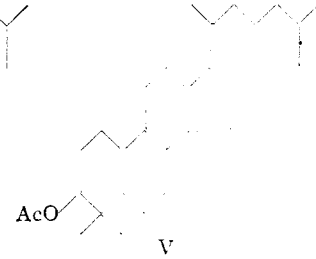


III

(75%), m.p. 150–151°, $[\alpha]_D$ − 64° (*c* 1.16) (*Anal.* Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.54; H, 11.98), and converted to the corresponding *acetate* (III), m.p. 136–137°, $[\alpha]_D$ −48° (*c* 2.15) (*Anal.* Calcd. for $C_{31}H_{52}O_2$: C, 81.52; H, 11.48. Found: C, 81.21; H, 11.34). Treatment of (III) in carbon tetrachloride with N-bromosuccinimide, followed by collidine, gave 3β-acetoxy-4,4-dimethyl-$\Delta^{5,7}$-cholestadiene (IV) (56–58%), m.p. 151–152° (vac.),[8] $[\alpha]_D$ −107° (*c* 1.27), $\lambda\lambda_{max.}$ 273 mμ (ϵ 11,200), 282 mμ (ϵ 11,000)[9] (*Anal.* Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.86; H, 11.00), which was converted by hydrogen chloride in chloroform (−40°), followed by

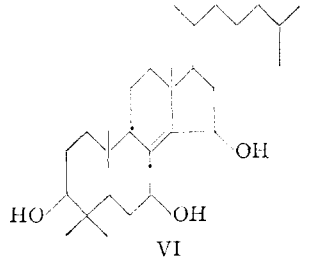


IV

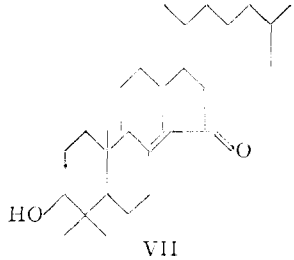


V

anhydrous ammonia in methanol (−60°), to 3β-acetoxy-4,4-dimethyl-$\Delta^{7,14}$-cholestadiene (V), m.p. 123–125° (vac.), $[\alpha]_D$ −140° (*c* 1.24), $\lambda_{max.}$ 244 mμ (ϵ 11,000) (*Anal.* Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.88; H, 11.05). Oxidation of (V) by perphthalic acid in ether, followed by hydrolysis with ethanolic potash, gave a *triol* (75%), very probably (VI),[10] m.p. 240–241°



VI



VII

(vac.) (*Anal.* Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28), which with hydrogen chloride in ethanol furnished 3β-hydroxy-4,4-dimethyl-15-keto-$\Delta^{8(14)}$-cholestene (VII) (30%), m.p. 161–162° (vac.), $[\alpha]_D$ +135° (*c* 1.44), $\lambda_{max.}$ 261 mμ (ϵ 14,700), IR (C=O, C=C) 5.89 μ, 6.15 μ (*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 80.99, H, 11.08). The *benzoate* of (VII), m.p. 154–155° (vac.), $[\alpha]_D$ +137° (*c* 1.56), $\lambda\lambda_{max.}$ 232 mμ (ϵ 17,000), 260 mμ (ϵ 16,600), IR (OC=O + C=O, C=C) 5.84 + 5.88 μ, 6.15 μ (*Anal.* Calcd. for $C_{36}H_{52}O_3$: C, 81.15; H, 9.84. Found: C, 80.85; H, 9.92) on direct methylation in dry *tert*-butanol with potassium *tert*-butoxide (56 moles) and methyl iodide (112 moles) gave 3β-benzoyloxy-4,4,14-trimethyl-15-keto-Δ^7-cholestene (IX) (67%), m.p. 212–213° (vac.), $[\alpha]_D$ +84° (*c* 1.42), $\lambda\lambda_{max.}$ 229 mμ (ϵ 15,200), 273 mμ (ϵ 1020), 281 mμ (ϵ 800), IR

(1) For total synthesis of cholesterol, see R. B. Woodward, F. Sondheimer and D. Taub, THIS JOURNAL, **73**, 3548 (1951); R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952); H. M. E. Cardwell, J. W. Cornforth, S. R. Duff, H. Holtermann and R. Robinson, *J. Chem. Soc.*, 361 (1953).

(2) W. Voser, M. V. Mijovic, H. Heusser, O. Jeger and L. Ruzicka, *Helv. Chim. Acta*, **35**, 2414 (1952), and many earlier papers; C. S. Barnes, D. H. R. Barton, A. R. H. Cole, J. S. Fawcett, and B. R. Thomas, *J. Chem. Soc.*, 571 (1953), and earlier papers.

(3) W. Klyne, *J. Chem. Soc.*, 2916 (1952); C. S. Barnes, D. H. R. Barton, J. S. Fawcett and B. R. Thomas, *ibid.*, 576 (1953).

(4) E. Kyburz, B. Riniker, H. R. Schenk, H. Heusser and O. Jeger, *Helv. Chim. Acta*, **36**, 1891 (1953); R. B. Woodward and K. Bloch, THIS JOURNAL, **75**, 2023 (1953).

(5) R. G. Curtis, J. Fridrichsons and A. McL. Mathieson, *Nature*, **170**, 321 (1952); J. Fridrichsons and A. McL. Mathieson, *J. Chem. Soc.*, 2159 (1953).

(6) For a rapid and convenient preparation of these ketones from cholesterol, see L. F. Fieser, THIS JOURNAL, **75**, 5421 (1953).

(7) All rotations were measured in chloroform.

(8) Taken in a capillary sealed off at a pressure of 3 mm.

(9) All ultraviolet spectra were measured in 95% ethanol.

(10) *Cf.* C. S. Barnes, D. H. R. Barton and G. F. Laws, *Chemistry and Industry*, 616 (1953); D. H. R. Barton and G. F. Laws, *J. Chem. Soc.*, 52 (1954).