3-Hydroxychromone.—Following procedure 1, 65% of the starting material was recovered, m.p. 178–179.5° (lit. 181°) and identified by comparison of infrared spectra. The yield was based only on recrystallized material.

3-Hydroxythiachromone.—Following procedure 1 only the starting material was recovered, m.p. 167–169° (lit. 172°), in about 90% yield and identified by comparison of infrared spectra.

Tropolone.—Procedure 3 was followed and a material was obtained that was thought to be a tropylium chloride as it gave a red-colored mineral acid test with Davidson AII indicator,[23] positive ferric chloride test, immediate precipitate with silver nitrate solution, and had an infrared spectrum typical of ionic compounds of pyronium type; *i.e.*, the spectrum was singularly devoid of well-defined bands, except for a sharp doublet at 6.26 and 6.29 μ, and very strong and broad hydroxyl absorption from 3.00 μ on. The simplicity of the spectrum of tropylium salts has been commented on earlier.[24,25] The yield of recovered tropolone, as hydrochloride, was 85%.

(23) D. Davidson, *J. Chem. Ed.*, **19**, 221, 532 (1942).

(24) W. v. E. Doering and L. H. Knox, THIS JOURNAL, **76**, 3203 (1954).

(25) W. G. Fateley and E. R. Lippincott, *ibid.*, **77**, 249 (1955).

Compounds E-I and E-I′ from α-Deoxykojic Acid and Methyl Acrylate.—Two products were obtained following procedure 1, but substituting 40 cc. of methyl acrylate for acrylonitrile. The first crop of 21.5 g. was E-I; m.p. after several recrystallizations from methanol was 219–220°.

Concentration of the mother liquor yielded 6.2 g. of E-I′, Recrystallization from methanol gave crystals that on slow heating melted at 110–115°, then resolidified and melted at 210–212°. Placed on a block at 205° the material decomposed, but at 170° it melted, resolidified and remelted around 200°. It seemed to be impure material and analysis also was unsatisfactory for any reasonable formula.

Anal. Calcd. for $C_{16}H_{18}O_8$ (E-I): C, 56.81; H, 5.36. Found: C, 56.68; H, 5.12. Calcd. for $C_{16}H_{18}O_8$ (E-I′): C, 56.81; H, 5.36. Calcd. for $C_{16}H_{20}O_9$: C, 53.9; H, 5.62; for $C_{15}H_{16}O_8$: C, 55.55; H, 4.97. Found: C, 55.35; H, 5.73.

Acknowledgment.—Analysis of A was by Miss M. Nielson. All other analyses were by Miss H. Beck.

EVANSTON, ILL.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS INC., AND THE INSTRUMENT DIVISION, VARIAN ASSOCIATES]

The Stereochemistry of Steroidal Sapogenins. III. N.m.r. Spectra

BY WILLIAM E. ROSEN, J. BENJAMIN ZIEGLER, ANTHONY C. SHABICA AND JAMES N. SHOOLERY

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Nuclear magnetic resonance spectra of steroidal sapogenins have been used to study the side chain stereochemistry. The spectra are consistent with structures previously proposed, in part on the basis of mechanistic considerations and in part on the basis of optical rotatory and chemical data.

The side chain stereochemistry of steroidal sapogenins has attracted considerable attention since Scheer, Kostic and Mosettig[1] proved that sapogenins of the so-called "normal" and "iso" series differed in absolute configuration at C-25. Only two of the four possible isomers in each series are known, and various attempts have been made to assign appropriate structures. Two sets of assignments were based on mechanistic considerations of the acid-catalyzed ring closures of the pseudosapogenins: (1) *trans*-addition of the proton and the C-26 oxygen across the C-20, C-22 double bond,[2] and (2) two-stage addition of the proton and C-26 oxygen across the C-20, C-22 double bond, with the proton addition resulting in a stabilized carbonium ion and the subsequent cyclization to form ring F always resulting in an equatorially oriented C-27.[3] Several other suggestions have been made, but only the set based on optical rotations[4] has also received serious consideration recently.

The elegant work of Callow and Massy-Beresford[5] eliminated from consideration the set which required equatorial C-27 groups in all structures, but rigorously established only that the thermodynamically stable spiroketals of the "normal" (25L) and the "iso" (25D) series did not differ at C-20 or at C-22. The greater stability of the "iso" series sapogenins permitted the assignment of structure I to sarsasapogenin ("normal" series sapogenin) and structure II to smilagenin ("iso" series sapogenin), assuming for ring F the chair form shown. The spiroketal isomer within the "normal" series which is thermodynamically less stable, but is kinetically favored under acid cyclizing conditions, has structure III according to both the "*trans*-addition" and "optical rotation" hypotheses. The two hypotheses differ, however, on the assignment of structure to the corresponding less stable spiroketal isomer in the "iso" series. Structure IV is expected according to the principle of *trans*-addition, and structure V was proposed on the basis of optical rotations.

We have examined the nuclear magnetic resonance spectra[6] of sarsasapogenin, neosarsasapogenin,[2a,7] smilagenin, neosmilagenin, diosgenin and

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

(2) (a) J. B. Ziegler, W. E. Rosen and A. C. Shabica, *ibid.*, **76**, 3865 (1954); **77**, 1223 (1955); (b) D. A. H. Taylor, *Chemistry & Industry*, 1066 (1954).

(3) Discussions at the Gordon Research Conference on the Chemistry of Steroids and Related Natural Products, New Hampton, N. H., August, 1954.

(4) M. E. Wall, *Experientia*, **11**, 340 (1955).

(5) R. K. Callow and P. N. Massy-Beresford, *Chemistry & Industry*, 1146 (1956); *J. Chem. Soc.*, 4482 (1957).

(6) Spectra were taken on deuterated chloroform solutions with a Varian Associates V-4300-C High Resolution Nuclear Magnetic Resonance Spectrometer operating at 60 mc. for hydrogen nuclei in a magnetic field of 14,096 gauss. Spectra were calibrated by the audio side band method with an accuracy of approximately ±1 c.p.s.

(7) (a) Various names have been used for these metastable spiroketal structures. We have retained the "neo" prefix in the absence of general agreement on nomenclature. (b) NOTE ADDED IN PROOF: The use of "cyclopseudosapogenins"[2b] for the unstable isomers has steadily gained favor, and promises to become generally accepted. We therefore withdraw our "neosapogenin" terminology in favor of "cyclopseudosapogenin."

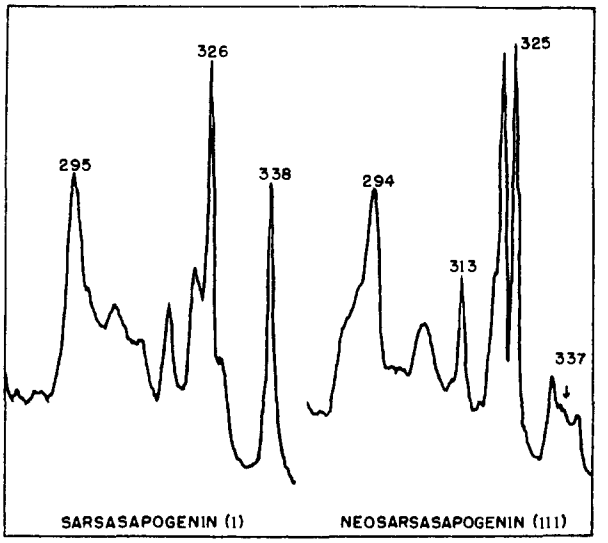


Fig. 1.—Nuclear magnetic resonance spectra of sarsasapogenin (I) and neosarsasapogenin (III).

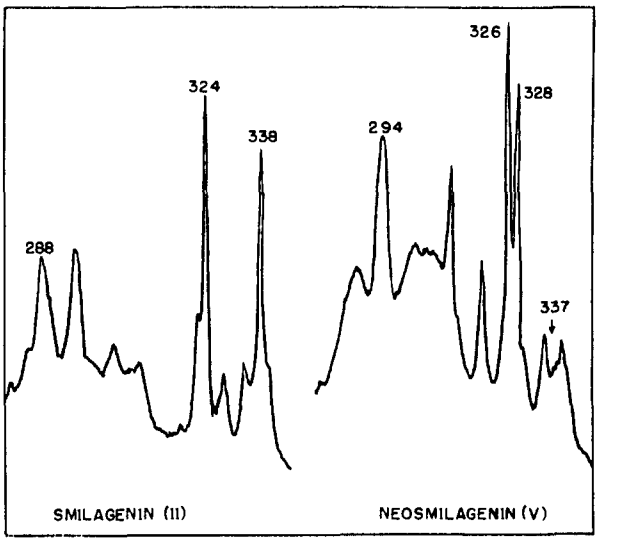
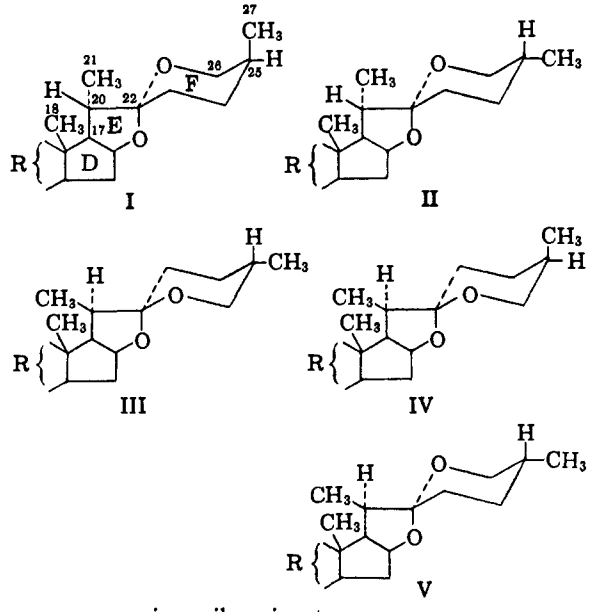


Fig. 2.—Nuclear magnetic resonance spectra of smilagenin (II) and neosmilagenin (V).

neodiosgenin, and have found that the n.m.r. curves of neosmilagenin and neodiosgenin are better explained by structure V (equatorial C-27 methyl group) than by structure IV (axial C-27 methyl group).



sarsasapogenin, smilagenin, etc.
R = $C_{13}H_{22}O$
diosgenin, etc.
R = $C_{13}H_{20}O$

The evidence is as follows. With sarsasapogenin (I) the C-19 methyl group gave a strong sharp peak at 326 c.p.s. (relative to the resonance of benzene, measured in an external annulus, arbitrarily chosen as 0) and the C-18 methyl group gave one at 338 c.p.s. as expected by analogy with several dozen other steroids.[8] Both the C-21 and C-27 methyl groups gave doublets[9] centered at 321 and at 326 c.p.s., which overlapped. The axial methyl group at C-25 therefore gave a resonance which was at least as low as 326 c.p.s. With neosarsasapogenin (III), the peak from the C-18 methyl group shifted from 338 c.p.s. to within a few cycles of the C-19 methyl group (strong peaks at 323 and 325 c.p.s.). In addition, one of the doublet methyl groups shifted up to 337 c.p.s. while the other moved down slightly to 317 c.p.s. The downward shift of the C-18 methyl group and one of the doublet methyl resonances can be attributed to steric interaction between C-18 and C-21.[11] The upward shift of one of the doublet methyl groups from 326 to 337 c.p.s. has therefore been attributed to the change of the C-27 methyl group from axial to equatorial.[12]

Smilagenin (II) (and diosgenin) gave the same C-18 methyl resonance position as did sarsasapogenin (338 c.p.s.). One of the doublet methyl resonances underlay the C-18 methyl group, confirming the assignment of this doublet position to an equatorial C-27 methyl resonance. With neosmilagenin (and neodiosgenin) the C-18 methyl resonance shifted down to the position of the C-19 methyl resonance (two strong peaks near 326 c.p.s.) as expected from the steric interaction with C-21. Significantly, the C-27 doublet resonance *remained* at 337 c.p.s., indicative of its equatorial conformation. The n.m.r. spectrum of neosmilagenin (and neodiosgenin) is therefore consistent with V but not with IV.[13]

(8) J. N. Shoolery and M. T. Rogers, THIS JOURNAL, **80**, 5121 (1958); n.m.r. spectra were done at 40 mc., and must be multiplied by 1.5 for comparing with these sapogenin spectra.

(9) Protons on adjacent carbon atoms (when there is free rotation about the C–C bond) are characteristically coupled, with a coupling constant of 6–9 c.p.s. Similar coupling of hydrogen peaks of methyl groups attached to CH groupings has been observed[10] with 6α- and 6β-methylprogesterone and with three different 16α-methyl steroids.

(10) Unpublished results, Varian Associates.

(11) A downward shift of 6 c.p.s. (from 313 to 307 c.p.s.) was also observed[10] for the C-19 methyl group in going from 6α-methylprogesterone to the hindered 1,3-diaxial 6β-methylprogesterone.

(12) With 6β- and 6α-methylprogesterone, the axial to equatorial transition (6β to 6α) resulted in the same upward shift of 11 c.p.s. (from 309 to 320 c.p.s.).[10] This quantitative agreement is probably fortuitous, since part of the shift with the 6-methylprogesterone pair must be due to release of the 1,3-diaxial interaction with C-19.

(13) M. E. Wall and H. A. Walens, THIS JOURNAL, **80**, 1984 (1958), have presented some chemical evidence in favor of structure V.

The acid-catalyzed cyclization of pseudosapogenins to neosapogenins and to sapogenins in terms of structures I, II, III and V is of interest mechanistically. The axial methyl group is energetically acceptable in the formation of the thermodynamically stable I by *trans*-ring closure of pseudosarsasapogenin. In the smilagenin series, however, ring-closure to the kinetically-favored (and thermodynamically-unfavored) spiroketal apparently proceeds in the *cis* fashion to V (equatorial methyl) because of a higher transition energy to the *trans*-product IV (axial methyl). The steric and mechanistic complexities of this system are clearly in need of further study.

SUMMIT, N. J., AND
PALO ALTO, CALIF.

[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

16-Hydroxylated Steroids. VI.[1] The Synthesis of the 16α-Hydroxy Derivatives of 9α-Substituted Steroids

BY SEYMOUR BERNSTEIN, ROBERT H. LENHARD, WILLIAM S. ALLEN, MILTON HELLER, RUDDY LITTELL, STEPHEN M. STOLAR, LOUIS I. FELDMAN AND ROBERT H. BLANK

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The synthesis of 9α-fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione (triamcinolone) (VIIIh) and other 9α-substituted-16α-hydroxy-steroids is described.

In an earlier communication[2] from this Laboratory, there was announced the synthesis of the 16α-hydroxy analogs of the interesting 9α-halo-corticoids. It is the purpose of this paper to expand upon this previous report.

Biological studies on 16α-hydroxyhydrocortisone (IIIa)[3,16] have demonstrated that this type of corticoid derivative still maintains a considerable activity in the usual types of assays (glycogen deposition, thymus involution and anti-inflammatory tests). It was, therefore, of interest to prepare the 16α-hydroxy derivatives of the more potent 9α-halo-steroids.[4]

Treatment of 21-acetoxy-4,9(11),16-pregnatriene-3,20-dione (I)[5] with osmium tetroxide in benzene and pyridine according to the procedure previously described[3] furnished 21-acetoxy-16α,17α-dihydroxy-4,9(11)-pregnadiene-3,20-dione (IIa). The conversion of I to IIa was also accomplished with potassium permanganate in acetone and a small amount of acetic acid according to the method of Petrow and co-workers.[6] Acetylation of IIa under mild conditions afforded the 4,9(11)-diene-16,-21-diacetate IIb. The method of Fried[4a,i] was then adapted for the introduction of the ring C substituents. The diene 16,21-diacetate IIb was treated with N-bromoacetamide and 10% perchloric acid in dioxane to give 16α,21-diacetoxy-9α - bromo - 11β,17α - dihydroxy - 4 - pregnene-3,20-dione (IIId). Reaction of the latter with anhydrous potassium acetate followed by reacetylation afforded 16α,21-diacetoxy-9β,11β-epoxy-17α-hydroxy-4-pregnene-3,20-dione (IVa). Prolonged treatment of the bromohydrin IIId with potassium acetate, or formation of the epoxide with potassium hydroxide in methanol, simultaneously deacetylated the product to furnish the epoxy 16α,-17α,21-triol IVb.

Addition of a saturated solution of hydrogen chloride in chloroform to a solution of the epoxy 16,21-diacetate IVa in chloroform yielded 16α,21-diacetoxy - 9α - chloro - 11β,17α - dihydroxy - 4-pregnene-3,20-dione (IIIe). Treatment of the latter with sodium methoxide in methanol gave 9α-chloro - 11β,16α,17α,21 - tetrahydroxy - 4 - pregnene-3,20-dione (IIIf) with an unexpectedly high melting point. Oxidation of the chlorohydrin 16,21-diacetate IIIe with a chromic anhydride–pyridine mixture[7] gave 16α,21-diacetoxy-9α-chloro-17α-hydroxy-4-pregnene-3,11,20-trione (VIa).

In a similar fashion reaction of the epoxy 16,21-diacetate IIIa with hydrogen fluoride in alcohol-free chloroform[8] afforded 16α,21-diacetoxy-9α-fluoro - 11β,17α - dihydroxy - 4 - pregnene - 3,20-dione (IIIg) in 33% yield. The free steroid, 9α-fluoro - 11β,16α,17α,21 - tetrahydroxy - 4 - pregnene-3,20-dione (9α-fluoro-16α-hydroxy-hydrocortisone (IIIh)), was obtained on hydrolysis with sodium methoxide in methanol. Oxidation of the fluorohydrin 16,21-diacetate IIIg in the manner described above yielded 16α,21-diacetoxy-9α-fluoro-17α-hydroxy-4-pregnene-3,11,20-trione (VIb).

Treatment of the fluorohydrin 16,21-diacetate IIIg with 2,4-dinitrophenylhydrazine in the usual manner furnished the expected mono-3-(2,4-di-

(1) Paper V, S. Bernstein, M. Heller, R. Littell, S. M. Stolar, R. H. Lenhard and W. S. Allen, THIS JOURNAL, **79**, 4555 (1957).

(2) S. Bernstein, R. H. Lenhard, W. S. Allen, M. Heller, R. Littell, S. M. Stolar, L. I. Feldman and R. H. Blank, *ibid.*, **78**, 5693 (1956).

(3) W. S. Allen and S. Bernstein, *ibid.*, **78**, 1909 (1956).

(4) (a) J. Fried and E. F. Sabo, *ibid.*, **75**, 2273 (1953); (b) **76**, 1455 (1954); (c) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restivo, A. Borman and F. M. Singer, *ibid.*, **77**, 4181 (1955); (d) R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett and M. Tishler, *ibid.*, **77**, 3166 (1955); (e) A. Nobile, W. Charney, P. L. Perlman, H. L. Herzog, C. C. Payne, M. E. Tully, M. A. Jevnik and E. B. Hershberg, *ibid.*, **77**, 4184 (1955); (f) J. A. Hogg, F. H. Lincoln, A. H. Nathan, A. R. Hanze, W. P. Schneider, P. F. Beal and J. Korman, *ibid.*, **77**, 4438 (1955); (g) E. Vischer, Ch. Meystre and A. Wettstein, *Helv. Chim. Acta*, **38**, 1502 (1955); (h) R. F. Hirschmann, R. Miller, J. Wood and R. E. Jones, THIS JOURNAL, **78**, 4956 (1956); (i) J. Fried and E. F. Sabo, *ibid.*, **79**, 1130 (1957).

(5) W. S. Allen and S. Bernstein, *ibid.*, **77**, 1028 (1955).

(6) G. Cooley, B. Ellis, F. Hartly and V. Petrow, *J. Chem. Soc.*, 4373 (1955)

(7) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

(8) Addition of tetrahydrofuran as an organic base according to the method of R. F. Hirschmann and co-workers[4h] increased the yield to 75–80%. We wish to thank Dr. S. Fox and M. Blicharz of the Lederle Laboratories Division for this information.