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A SYNTHESIS OF 16α-HYDROXY-20-KETOSTEROIDS AND THEIR CORRELATION WITH OTHER RING D SUBSTITUTED STEROIDS. THE CONFIGURATION OF THE SAPOGENIN SIDE CHAIN[1, 2]

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The natural occurrence of 16α-hydroxysteroids such as Δ^5-pregnene-3β,16α, 20α-triol (2) made it desirable to develop methods for their partial synthesis. The first procedure (3) for the introduction of the 16α-hydroxyl group into the pregnane skeleton aimed at the preparation of this urinary triol. It involved the base-catalyzed addition (4) of benzyl alcohol to a Δ^{16}-unsaturated 20-ketosteroid (I) and the hydrogenolysis of the resulting benzyloxy compound (II). In order to preserve the 5–6 double bond present in the starting compound the hydrogenolysis was carried out with sodium and alcohol. This choice prompted the prior reduction of the 20-keto group since 16-alkoxy-20-ketones readily eliminate the alcohol under the alkaline reaction conditions (2, 4). However 16-hydroxysteroids, if they occur in glandular extracts, are apt to be present not only as 20-alcohols but also as 20-ketones. We, therefore, searched for a modification of this process which would permit hydrogenolysis without need for the protection of the 20-keto group. This approach proved to be feasible and has been utilized for a preparation of 16α-acetoxyprogesterone.

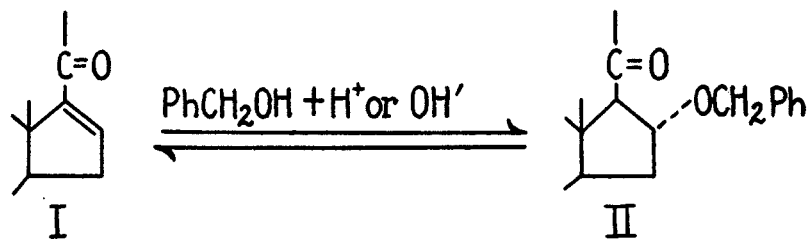


FIG. 1

Palladium supported on charcoal has been employed in other fields for the hydrogenolysis of benzyl ethers (5). In steroid chemistry palladium on various carriers has served mostly for the hydrogenation of ethylenic or acetylenic linkages. Palladium on calcium carbonate (6), in particular, has been used widely for the reduction of the 5–6 double bond, but palladium on charcoal in a medium of acetic acid (7), ethyl acetate (8) or alcohol (9) has also proved to be an effective

[1] Supported by a grant from the National Cancer Institute of the National Institutes of Health, Public Health Service.

[2] The preparation of 16α-acetoxyprogesterone and the degradation to androstanetriol was reported before the American Society of Biological Chemists on April 7, 1953 (1), and the argument in favor of structure XVa for smilagenin was presented in a discussion at the Gordon Conference on Steroids, August 2, 1954.

catalyst for this reaction. It was anticipated, therefore, that hydrogenation of an alcoholic solution of 3β-acetoxy-16α-benzyloxy-Δ^5-pregnen-20-one (IIIa) (3) with a palladium-carbon catalyst (10) would furnish 3β-acetoxy-16α-hydroxyallopregnan-20-one. Infrared analysis of the reaction product disclosed, however, that the twin peaks of the starting material near 12.3 and 12.5μ, which are characteristic of the 5–6 double bond in 3β-acetoxysteroids (11), had been retained (VIII). More detailed studies revealed that a selective hydrogenolysis of the benzyloxy group is possible with limited ratios of catalyst to substrate but that large amounts of catalyst reduce the olefinic bond as well. Shortly after this observation had been made, Hershberg, *et al.* (12) reported on the inertness of 5–6 double bonds in other selective reductions in which a commercial palladium-charcoal catalyst had been employed in neutral solvents such as alcohol or dioxane. The same workers also recorded the conversion of 17-ethinyltestosterone to 17-ethyltestosterone with this catalyst in dioxane. If the hydrogenolysis of the readily accessible[3] (though as yet non-crystalline) 16α-benzyloxyprogesterone proceeded with equal selectivity the reaction would afford a very simple route to 16α-hydroxyprogesterone. However, when we hydrogenated this benzyl ether with the same commercial catalyst in dioxane, the 4–5 double bond was reduced quite rapidly and before the hydrogenolysis of the benzyloxy group had been completed. It seemed more promising, therefore, to introduce the 4–5 double bond subsequent to the cleavage of the benzyl ether.[4]

To permit differential treatment of the hydroxyl groups at C-3 and C-16, the one at C-3 was esterified with formic acid while the other was still blocked with the benzyl group (IIIb). The formylation technique of Koechlin, *et al.* (14) proved well suited to this purpose. The chief merit of this ester as a protective group lies in its reactivity in solvolytic processes (14, 15) which exceeds by far that of the acetate. This lability did not complicate the hydrogenolysis of the benzyloxy group in alcohol or the acetylation of the resulting hydroxyl group with acetic anhydride and pyridine, as the desired 3β-formoxy-16α-acetoxy-Δ^5-pregnen-20-one (IV) could be obtained in good yield. This lability, however, permitted the liberation of the hydroxyl group at C-3 (V) without concomitant hydrolysis or elimination of the ester at C-16. The synthesis of 16α-acetoxyprogesterone (VI) was completed readily by bromination, oxidation with chromium trioxide, and debromination with chromous chloride (16). In marked contrast to 16α,17α-epoxides (17) little or no elimination at C-16 occurred under the strongly acidic conditions of the chromous chloride reduction. While this work was in progress Perlman, Titus, and Fried (18) reported a biosynthesis of 16-hydroxyprogesterone which was observed when progesterone was incubated with a strain of actinomyces. Through the kind cooperation of Dr. Wintersteiner

[3] $\Delta^{4,16}$-pregnadiene-3,20-dione adds alcohol only to the 16–17 double bond (4).

[4] A possible alternative, the protection of the Δ^4-3-ketone by ketalization to the Δ^5-unsaturated ketal (*cf.* 13) prior to reduction of the benzyloxyprogesterone, has not yet been explored. *Addendum:* While this paper was in press, Bernstein, Heller, and Stolar [*J. Am. Chem. Soc.*, **76**, 5674 (1954)] described another variant of the benzyl alcohol method in which a 20-ketal was used for the preparation of 16 α-hydroxyprogesterone.

and the investigators at the Squibb Institute a direct comparison of the acetates was possible which disclosed their identity. Perlman, *et al.* inferred the 16α configuration of their product from the negative contributions of the 16-hydroxyl group and of its acetate to the molecular rotation. Since 16β substituents in an appropriate molecular environment [as in methyl etianate (19)] can also make sizable negative contributions, the observed rotational shifts would not seem to constitute an entirely rigorous proof of configuration. The assignment is confirmed, however, by our synthesis which is sterically unambiguous. The orientation of VI at C-16 can be deduced from that of the benzyl ether (III) which had been converted previously (3) to the known 3β,16α,20α-triacetoxy-Δ^5-pregnene (IXa) and its 20-epimer (IXb) by means of lithium aluminum hydride, sodium and alcohol, and acetylation. The possibility that the second reduction step would alter the configuration at C-16 was considered most improbable and can now be

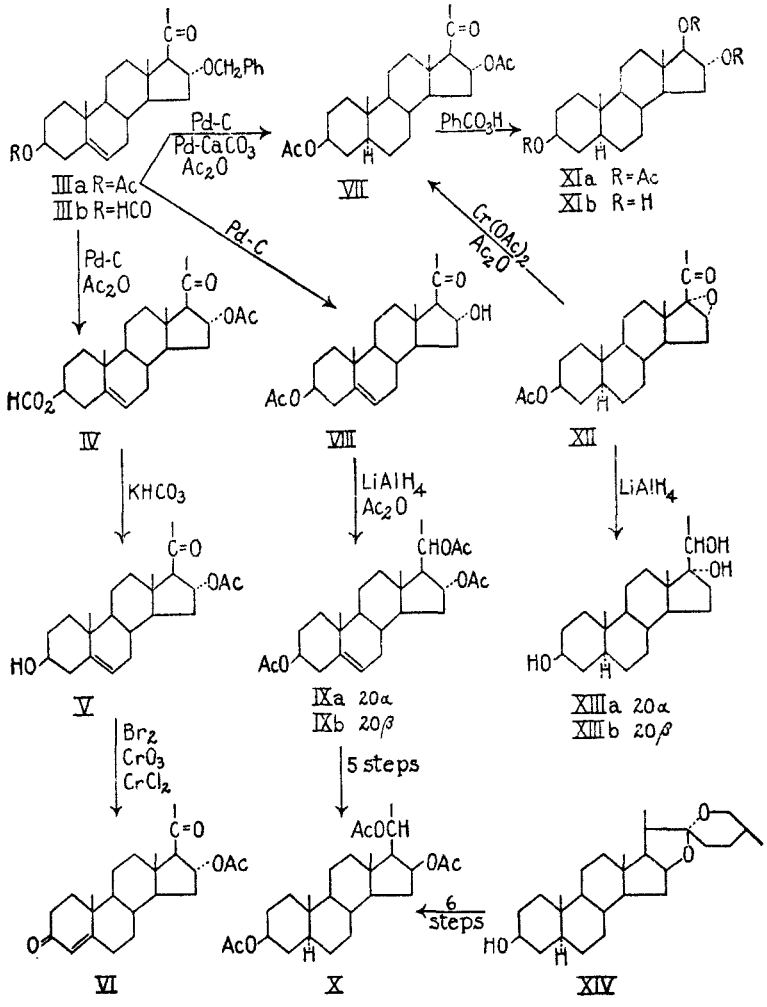


FIG. 2

excluded even further since catalytic hydrogenation (IIIa → VIII) followed by reduction with lithium aluminum hydride and acetylation yielded again the same pair of 20-epimeric triacetates (IXa and b). This new sequence represents an improved synthesis of the urinary excretion product, Δ^5-pregnene-3β,16α,20α-triol, since the yield of the 20α-epimer is substantially higher if the 16-alcohol rather than the benzyl ether is treated with lithium aluminum hydride.

In recent years 3 independent assignments have been made of the configuration at C-16 of steroids oxygenated in this position. Huffman and Lott (20) deduced the configuration of 16,17-glycols like Δ^5-androstene-3β,16α,17β-triol by correlation with known 17β-hydroxysteroids such as testosterone. Plattner and coworkers (21) reduced 3β-acetoxy-16,17-epoxyallopregnan-20-one (XII) to Reichstein's compounds J (XIIIb) and O (XIIIa) for which the α orientation of the 17-hydroxyls is now accepted (22, 23) and thus established the 16α configuration for the epoxide. In a study reported from this laboratory (24) it was pointed out that the reactions of the sapogenins (*e.g.* XIV) and pseudosapogenins are consistent only with the 16β,17β-configuration and this conclusion too seems to have met with general acceptance (*e.g.* 25). Sapogenins were degraded by Marker, *et al.* to 3,16,20-trihydroxypregnanes both in the 5-normal and allo (26) series. Since these reactions retain the configurations at C-16 (24) the products such as the triacetate X could be used as points of reference in determining the orientations of related structures including the triacetates IX (2, 3) discussed above.[5] While all 3 assignments rest on good evidence it is clear that the cogency of the steric arguments pertaining to C-16 and C-17 will gain considerably if it can be shown that the conclusions which were drawn independently are consistent with each other.

We have obtained a correlation between 16-hydroxypregnane derivatives and the 16,17-glycols by direct conversion. The 3β-acetoxy-16-benzyloxy-Δ^5-pregnen-20-one, to which we have assigned the 16α configuration (IIIa), was hydrogenated with palladium on charcoal and with palladium on calcium carbonate to give after acetylation a 3β,16-diacetoxyallopregnan-20-one (VII) which was oxidized with peroxybenzoic acid. The product was identical with the 3β,16,17-triacetoxyandrostane which according to the findings of Huffman and Lott possesses the 16α,17β-configuration (XIa). Since the conversion IIIa → VII → XIa can hardly affect the configuration at C-16, the identity of the triacetates shows that the steric assignment of III and VIII which is based on the configuration of the sapogenins at C-16 is consistent with the configurational assignment for androstanetriol which is based on the configuration of testosterone. Moreover, the degradation adds an example to the rather limited number of observations (27, 28)[6] on which we can base the view that peroxy acid oxidations of ketones pro-

[5] Moore (19) recently has linked also the cardiac aglycone, gitoxigenin, to this scheme of steric correlations.

[6] The important experiments of Gallagher and Kritchevsky (29) on the peroxy acid oxidations of 20-ketones provide the main argument for the configurations of 17-hydroxyetiocholanes and clarify the steric course of such degradations only if one considers the supplementary evidence pertaining to these 17-hydroxysteroids (29) as adequate to establish their configuration. A similar situation exists in other degradations (30).

ceed without inversion. *Trans* relationship can be deduced for the side chain and the acetoxy group in the starting compound (VII) (from the conversion VIII → X) and for the two vicinal acetoxy groups in the product (XI). The degradation of one 16,17-*trans* compound to another by a reaction involving only C-17 is consistent only with retention of configuration.[7]

Very recently Cole and Julian (17) described another two-step synthesis of 16-hydroxy-20-ketosteroids from Δ^{16}-20-ketones. It proceeds *via* the 16α,17α-epoxide which is reduced to a 16α-hydroxy-20-ketone with chromous acetate. Clearly, if the configurations assigned to compound III at C-16 and to XIII at C-17 are correct the 3β,16-diacetoxyallopregnan-20-one (VII) prepared from XII and from IIIa should be identical. This proved to be the case. Moreover, there are other examples (compound VIII and 16α,21-diacetoxyprogesterone)[8] which show that the benzyl alcohol method and the epoxide procedure give identical products. The conclusion therefore seems warranted that there is now a satisfactory correlation of configuration of ring D substituents between a group of compounds which includes 17-hydroxysteroids with and without a 17-alkyl side chain, 16-hydroxylated pregnanes, 16,17-glycols of the androstane series, and sapogenins.

Our argument (24) for the 16β configuration of the sapogenins was based mainly on considerations of stability. New observations (32, 33) seem to justify an attempt to apply such arguments also to the question of orientation at C-22. Scheer, Kostic, and Mosettig (33) have shown that smilagenin and sarsasapogenin differ in configuration at C-25. Their results, however, do not preclude the possibility that these compounds may possess different orientations also at C-22. Sarsasapogenin is stable to acid for moderate periods (33, 34) but is converted to smilagenin on prolonged exposure (35). Under acid conditions the spiroketal system of the sapogenins is highly reactive (36, 26a) and some of these reactions can be explained by tautomerism with a carbonyl form. Although no proven example of an isomerization at C-22 exists, there is every reason to believe that an unstable stereoisomer of a ketal at C-22 would isomerize quite readily when heated with mineral acid. It is inferred, therefore, that the natural spiroketals are the stable isomers with respect to C-22 and that smilagenin represents the most stable, and sarsasapogenin the second most stable isomer permitted by the asymmetry at C-22 and C-25. The two other steric forms probably are still un-

[7] The extent of this degradation depends quite markedly on the nature and configuration of the substituent at C-16. The yields realized here with a 16α-acetoxy compound were less than those reported by Fukushima and Gallagher (4) with the 16α-methoxy derivative but far superior to results we had obtained earlier with the 3β-acetoxy-16β-acyloxyallopregnan-20-one, that results from the oxidation of pseudotigogenin diacetate, since we failed to isolate the triester of adrostane-3β,16β,17β-triol. One would suspect that steric hindrance of the group at C-16 to the addition of peroxy acid to the 20-ketone is the main cause for the observed differences.

[8] After our announcement of the preparation of this compound (31), Drs. Julian and Cole very kindly informed us of their independent synthesis and provided material for a mixture melting point which showed no depression.

known.[9] Since the isomerizations of sapogenins were carried out in a medium of alcohol containing hydrochloric acid (36, 32, 34, 35) it may be argued that the results reflect the relative stabilities not of the sapogenins but of their oxonium salts. This would be correct if the majority of molecules under reaction conditions were present as oxonium compounds. This however is not to be expected. Ethers have been found to be weaker bases than water (42), a phenomenon which has been ascribed to steric strain (B-strain) (43). The presence of an electron-withdrawing group (alkoxy group) should render ketals still weaker bases than ethers.[9a] If the formation of oxonium salts introduces additional steric strain in sapogenins it would further reduce their basicity. Therefore, it seems justified to assume that in a medium containing more water than acid molecules, such as was used in the isomerization studies cited, the majority of sapogenin molecules is present in neutral form.

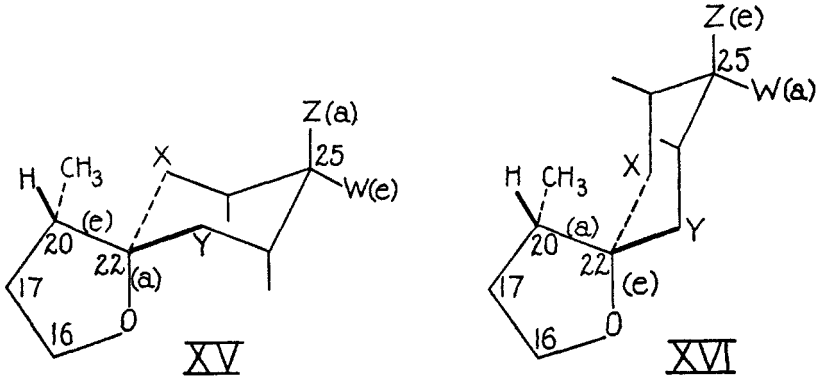
The most stable form of the sapogenin molecule should contain the pyranoid ring (F) as a chair (44). Such an arrangement is possible regardless of configuration and admits the possibility of two conformations for each of the 4 theoretically possible isomers. While these conformations would be expected to be interconvertible in solution, one conformation would predominate over the other if it is more stable. Eight different arrangements of the sapogenin structure, therefore, are to be considered which contain ring F as a chair (XV, XVI). Their essential differentiating features are the following: (a) the methyl group at C-25 is equatorial (*e*) or axial (*a*), (b) the oxygen of ring F or the C-23 methylene group is eclipsed by the methyl group at C-20, (c) C-20 or the oxygen at C-16 occupy an equatorial position with respect to ring F. A change in any of these 3 sets of alternatives will affect the interactions between non-bonded ring substituents. It is to be expected that these repulsions are the greater the larger the bulk of the interacting groups and that bulky groups exert a greater repulsive effect if they are axial than if equatorial (44).[10] Most observations in support of this view were made on cyclohexane derivatives but a similar situation seems to exist with those of tetrahydropyran (46). Hassel and Ottar (46) have postulated that the proximity of an axial hydroxymethyl and an axial hydroxyl group introduces greater

[9] Callow and James (37) have assigned these structures to the primary cyclization products of the pseudosapogenins. If this should prove to be correct, their rapid conversion to smilagenin and sarsasapogenin, respectively, would be consistent with the postulated order of stability. These primary cyclization products were recognized as being different from the naturally occurring sapogenins by several groups of investigators who proposed various structures and the following names: 20-isosapogenin (34), neosapogenin (37, 39), anasapogenin (38), and cyclopseudosapogenin (40). The argument given by Callow and James against isomerism at C-20 does not seem to be conclusive (see also 41).

[9a] One of the referees has pointed out that an opposing effect is to be expected from no-bond resonance (oxygen hyperconjugation). Unless this effect is unexpectedly large it should not raise the basicity of the spiroketals to the level of alcohol or water.

[10] Exceptions have been noted only in cases which permit the interaction of two strong dipoles (*e.g.* 45). No comparable situation exists in the sapogenin side chain. The effect of dipole interactions on the relative stabilities of the various structures XV and XVI is believed to be much smaller and has been ignored in this discussion, since it is not expected to alter the final result.

instability into a pyranose molecule than that of two axial hydroxyl groups and this has been recognized as one of the two main factors determining pyranoside conformations as ascertained experimentally by Reeves (47). There is evidence to show that the space requirements of oxygen bridges are less than those of methylene groups. The van der Waals radius of oxygen has been estimated as 1.4 Å, of the methylene group as 2 Å (48). In *o*-substituted biphenyls the methoxy group presents less of an obstacle to racemization by rotation around the pivotal bond than a methyl group (49). Similarly the estimated potential barrier towards rotation of methyl groups in methanol or dimethyl ether is less than in ethane or propane (50). Accordingly it would appear that the most stable arrangement of



	X	Y	Z	W	
XVa	O	CH_2	H	CH_3	XVIa
XVb	O	CH_2	CH_3	H	XVIb
XVc	CH_2	O	H	CH_3	XVIc
XVd	CH_2	O	CH_3	H	XVId

FIG. 3

the sapogenin molecule is one with these characteristics: (a) the methyl group at C-25 is equatorial, (b) the oxygen in ring F is eclipsed by the methyl at C-20 which places the methylene group C-23 in opposition to the hydrogen at C-20, (c) the oxygen at C-16 is axial and therefore C-20 is equatorial with respect to ring F. These specifications (XVa) define a configuration at C-25 which agrees with that determined unequivocally (51, 33) for the most stable compound, smilagenin. The configuration derived by the same internally consistent argument for C-22 therefore has received[11] additional experimental support. It seems quite probable, therefore, that smilagenin possesses partial structure XVa.

[11] It seems relevant to point out that our argument is not an *ad hoc* theory to fit the steric situation at C-25 since our conclusions were reached before James (51) reported on the absolute configuration of C-25.

Analogous considerations apply to other sapogenins of the so called 22-iso series such as diosgenin and tigogenin.

The stereoisomer second to smilagenin in stability would be expected to differ from it in the reversal of *one* of the three conditions that define the configuration and conformation of smilagenin. Indeed the reversal of any one of these specifications will invert the configuration at C-25 and hence lead to a structure (XVb, XVc, and XVIb) consistent with the proven orientation of sarsasapogenin at this site (33, 51). The most stable of these structures should represent sarsasapogenin. We have attacked the problem with the aid of a method developed by Pitzer which has been used successfully with aliphatic (52) and alicyclic hydrocarbons (53, 54). It requires in the present case of heterocyclic rings additional approximations [see *e.g.* (46)]. The transition XVa to XVc introduces an interaction similar to that found in the very unstable eclipsed form of butane (*i.e.* the planar *cis* arrangement). This however is compensated in part by the disappearance of the smaller interactions resulting from the opposition of the C-23 methylene to the hydrogen at C-20 and the pyranoid oxygen to the C-21 methyl. The energy difference between XVc and XVa is estimated as being less than the difference in rotational barriers of *n*-butane (3600 cal.) and propane (3300 cal.) (52) and therefore as less than 300 cal. The transition of XVa to XVb introduces two new interactions. One of these relates to the proximity of the axial methyl group at C-25 to the C-23 methylene and is of the type encountered in the skew form of butane, which is derived from the planar *cis* form by a 60° rotation around the central bond. The magnitude of this effect was found to be 800 (52, 55) to 900 (53) cal. The second steric strain results from the skew interaction between this methyl group and the oxygen of ring F. For reasons given above, its magnitude (r cal.)[12] is expected to be less than the corresponding skew interaction of butane. Regardless of the value of r, XVb should be less stable than XVc. If XVb is compared with XVIb the following differences are apparent: XVb has one skew interaction between carbons C-27 and C-23 (~800 cal.) and three skew interactions between carbon and oxygen (one between C-27 and the pyranoid oxygen, the others involving C-24 and C-26 with the furanoid oxygen) (3 r cal.). XVIb has two skew interactions involving carbons (C-20 with C-24 and C-26). One of these should be exceptionally large since the C-21 methyl group is held in close proximity to the axial hydrogen at C-26. The size of this increment over ~1600 cal.(s cal.) cannot be stated precisely. [For a somewhat similar case, the diaxial form of 1,3-dimethylcyclohexane, see (53).] Hence the energy difference between XVIb and XVa is estimated as (1600 + s − 2r) cal. and unless s is small compared to other interactions considered XVIb appears to be less stable than XVc. On the basis of this comparison XVc seems to be the most likely structure for sarsasapogenin and of other compounds of the so called normal series. Obviously such a proposal can only be *tentative* since the estimated stability dif-

[12] Studies on the rotational isomerism of 1-propanol should furnish the desired information, but unfortunately the result (820 ± 180 cals.) of a spectroscopic investigation (56) leaves some doubt as to the nature of the isomerism under study since ethanol too gave rise to isomers with similar differences in stability.

ferences are quite small compared with the uncertainty of the method in this case.

The discussion presented is based on the contention that the configurations of smilagenin and sarsasapogenin at C-20 are identical and agree with that of cholesterol. A steric correlation between the two sapogenins can be based on the identity of the C_{22} lactones that result from their oxidation (57). The two sapogenins can be linked to cholesterol through diosgenin which has been converted to smilagenin and to tigogenin (58). Another steric tie between 5α or Δ^5-sapogenins and those with 5β configuration is provided by the conversion of the lactone from sarsasapogenin to that of tigogenin (59). Since the last step in this transformation involves the reduction of a Δ^4-3-ketolactone with sodium and alcohol and since the esters of bisnorcholanic acids largely isomerize on treatment with alcoholic alkali (60), it might be argued that this reaction could have altered the configuration at C-20. It should be pointed out, therefore, that the difference in molecular rotations of the lactones derived from tigogenin and from sarsasapogenin is completely accounted for by their epimerism at C-5.[13] Moreover, studies from this laboratory have failed to demonstrate isomerization of the lactone from tigogenin on treatment with sodium methoxide. The probable cause for the difference between these esters and these lactones lies in the interference of the methyl groups (C-18 and C-21) which would result from the isomerization of the lactone at C-20 (41, 34). If this interpretation is correct the ease of lactonization observed for the oxidation products of the sapogenins would demonstrate the α orientation[14] of the carboxylate. The same orientation of the sapogenin side chain at C-20 can be deduced from the conversion of diosgenin to Δ^5-cholestene and cholesterol (64) and from the degradation of tigogenin acetate with peroxy acid to the 20-epimer of allopregnane-$3\beta,16\beta,20\beta$-triol (24).

The configuration of the sapogenin side chain has been the subject of several recent discussions. Our conclusions are at variance with those of Wall and Serota (35) who, without specifying conformations or configurations at C-25, proposed configurations at C-22 as in XVd for smilagenin and as in XVb for sarsasapogenin. Ziegler, Rosen, and Shabica (39) considered the cyclization of the pseudosapogenins as a *trans* addition to the 20–22 double bond and proposed structure XVa for diosgenin. As the compound is obtained under conditions which might permit equilibration at C-22, the postulated interrelationship of configurations at C-20 and C-22 is not necessarily preserved in the final product. This has been pointed out by Taylor (40), who proposed XVa for smilagenin and XVb for sarsasapogenin. His conclusions are based on the proven configurations at C-25, on structures deduced for the primary cyclization products of the pseudosapogenins, and on considerations of some of the factors which may be responsible for the greater stability of smilagenin than of sarsasapogenin. This argument, however, appears not to be fully conclusive for while Taylor has pointed out that

[13] $\Delta[M]_D^{5\alpha\text{-}5\beta}$ for the 3β-hydroxylactones: $-143°$ (61) $+125°$ (57) $= -18°$; standard value $-9°$ (62); for 3β-acetoxylactones: $-192°$ (61) $+124°$ (57) $= -68°$; standard value $-55°$ (62).

[14] The terms α and β are applied to C-20 in the sense advocated by Fieser and Fieser (63).

the transition XVc → XVd would be a very improbable interpretation of the conversion of sarsasapogenin to smilagenin, he has failed to consider the alternative reaction XVc → XVa. It seems, therefore, that Taylor's approach toward the determination of configuration of sarsasapogenin leads to the same problem of relative stabilities that we have discussed above. The results of bromination have also been adduced to elucidate sapogenin structures (35, 40). The interpretations thus far advanced would not seem to explain readily the report that the monobromination of a "22-iso" sapogenin, hecogenin acetate, gives rise to two isomeric monobromides which contain bromine in the side chain (65).

EXPERIMENTAL

All melting points reported are corrected. Compounds were dried for analysis, rotation and spectroscopy at 80° *in vacuo* except compound V which was dried at 100°. Infrared spectra were measured on solutions in carbon disulfide as described previously (11).

3β-Formoxy-Δ⁵,¹⁶-pregnadien-20-one. 3β-Hydroxy-Δ⁵,¹⁶-pregnadien-20-one[15] (301.2 mg.) was treated with benzyl alcoholic potassium hydroxide under nitrogen as described previously (3). The resulting mixture of starting compound and reaction product is very difficult to separate by chromatography prior to esterification. The material (384.6 mg.) was dissolved in 18 ml. of benzene and 9 ml. of formic acid (98–100%, product of Allied Chemical and Dye Corp., General Chemical Division) and kept at 50–53° under anhydrous conditions with the pressure reduced sufficiently to permit the distillation of about 15 ml. of liquid during 90 minutes. While moisture was still being excluded, the remaining benzene-formic acid solutions were concentrated further *in vacuo* and then distributed between ether and water. The ether layer was washed repeatedly with sodium bicarbonate and with water until neutral. All extractions were done in a cold room with chilled solvents in quick succession. The ether residue (386.4 mg.) in 4 ml. of benzene and 8 ml. of petroleum ether was chromatographed on a prewashed column of 20 gm. of a 2:1 mixture of silica gel (Davison, T-200) with Celite. The early and late eluates could not be induced to crystallize and were discarded. Fractions containing 3β-formoxy-Δ⁵,¹⁶-pregnadien-20-one crystallized on evaporation of the eluant (benzene). The crude product (135.5 mg.) was repeatedly recrystallized from acetone; m.p. 173–177°; $[\alpha]_D$ −47° (*c*, 0.6, chloroform). The infrared spectrum gave evidence for the presence of a Δ¹⁶-20-ketone (5.99μ), and of a formoxy group (5.79, 8.49μ) (66). In the 12μ region were several prominent absorption maxima: ∽11.87μ, 12.03μ [Δ¹⁶-20-ketone (67)] 12.22μ (Δ¹⁶-20-ketone and Δ⁵ in 3β-formates) and 12.49μ (Δ⁵).

Anal. Calc'd for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83.

Found: C, 77.18; H, 8.80.

3β-Formoxy-16α-benzyloxy-Δ⁵-pregnen-20-one (IIIb). The eluates which followed fractions containing formylated starting material in the above chromatogram were oily but they crystallized from methanol. This material (182.5 mg.) upon recrystallization from acetone gave 145.9 mg. of long needles melting at 128–129.5°. Analytical sample showed m.p. 130.5–131°; $[\alpha]_D^{25}$ −44° (*c*, 0.5, chloroform). The infrared spectrum included maxima at 5.86μ (20-ketone), at 5.79 and 8.48μ [formate (66)], at 12.44 and 12.23μ [Δ⁵ in 3β formates oxygenated at C-16 (11)], and at 13.66 and 14.36μ [benzyloxy group (3)].

Anal. Calc'd for $C_{29}H_{38}O_4$: C, 77.30; H, 8.50.

Found: C, 77.46; H, 8.63.

The yield of benzyl ether depends greatly on the purity of the benzyl alcohol. The product labelled purissimum of the Aldrich Co. has given 37% of pure IIIb. Hydrochloric

[15] The authors are indebted to Dr. J. J. Pfiffner of Parke, Davis and Company who generously supplied us with our starting material, 3β-hydroxy-Δ⁵,¹⁶-pregnadien-20-one; and to Dr. E. W. D. Huffman, Wheatridge, Colorado for the microanalyses reported in this paper.

acid also catalyzed the addition of benzyl alcohol to 3β-hydroxy-$\Delta^{5,16}$-pregnadien-20-one, while piperidine (68) did not.

3β-Formoxy-16α-acetoxy-Δ^5-pregnen-20-one (IV). A preparation (30.6 mg.) of palladium chloride on charcoal (made according to Mozingo's procedure C (10) was suspended in 95% ethanol and reduced with hydrogen. The catalyst was separated by centrifugation and washed 4 times with the same solvent. An alcoholic suspension (4 ml.) was shaken in an atmosphere of hydrogen until the volume remained constant and after the addition of 99.9 mg. of 3β-formoxy-16α-benzyloxy-Δ^5-pregnen-20-one (IIIb) in 25 ml. of 95% ethanol shaken again until the reaction ceased (110 minutes). The reaction product was separated from the catalyst and acetylated in 2 ml. of pyridine with 1 ml. of acetic anhydride at room temperature for 16 hours. The excess reagent was hydrolyzed by the slow addition of water to the chilled solution. The mixture was diluted with ether and washed with cold 1 *N* hydrochloric acid, with a cold sodium bicarbonate solution, and with water. The ether residue (88.1 mg) upon recrystallization from methanol gave 77.1 mg. of IV; m.p. 187–195°. The analytical sample was recrystallized from acetone-petroleum ether; m.p. 195–197.5° ± 2°; $[\alpha]_D^{26}$ −45° (*c*, 0.75, chloroform). The infrared spectrum gave evidence for the presence of formate (5.79 and 8.48μ), acetate (5.74 and 8.03μ), 20-ketone (5.84μ), and Δ^5 (12.22 and 12.45μ) (carbonyl maxima not fully resolved).

Anal. Calc'd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51.
Found: C, 71.77; H, 8.54.

While this procedure was well reproducible, hydrogenation runs with smaller amounts of substrate (60 mg.) and less catalyst (18 mg.) repeatedly came to a standstill before the hydrogenolysis was completed. However 25 mg. of IIIb with 41 mg. of catalyst took up hydrogen rapidly but gave a product with less intense Δ^5 peaks. Since the purification of the intermediate *3β-formoxy-16α-hydroxy-Δ^5-pregnen-20-one* entailed greater losses than that of the acetate, the carbinol was isolated only once from a standard run (100 mg.) and recrystallized repeatedly from acetone and from acetone-petroleum ether; m.p. 153.5–156.5°.

Anal. Calc'd for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95.
Found: C, 73.32; H, 8.95.

3β-Hydroxy-16α-acetoxy-Δ^5-pregnen-20-one (V). A solution of 35.7 mg. of 3β-formoxy-16α-acetoxy-Δ^5-pregnen-20-one (IV) in 12 ml. of methanol was treated with 0.36 ml. of 1 *N* aqueous potassium bicarbonate. A precipitate formed which dissolved after swirling for 15 minutes. The mixture was kept at 23° for another hour. The product which was isolated by distribution between ether and water gave upon recrystallization from acetone 26.8 mg. of fine rods melting at 239–243°. Further recrystallization raised the m.p. to 241–245°, with decomposition. The infrared spectrum of a sample mulled with Nujol showed a hydroxyl peak near 2.85μ, carbonyl peaks at 5.81 and 5.93μ, and a complex (!) ester peak (two strong maxima at 7.97 and 8.04 and an inflexion near 7.91μ). The bands in the 12μ region were at 11.99, 12.41, and 12.50μ. The compound was too insoluble in carbon disulfide to permit precise measurements. The curve indicated approximately normal carbonyl peaks (5.75 and 5.88μ) and a simple ester peak at 8.03μ.

Anal. Calc'd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15.
Found: C, 73.76; H, 9.33.

16α-Acetoxy-Δ^4-pregnene-3,20-dione (VI). A solution of 18.2 mg. of 3β-hydroxy-16α-acetoxy-Δ^5-pregnen-20-one (V) in 1.8 ml. of acetic acid was treated with an equimolar amount of bromine in 0.6 ml. of the same solvent. After adding 4.9 mg. of chromium trioxide in 0.5 ml. of 90% acetic acid, the mixture was kept at 21° for 2 hours. The excess oxidant was reduced with 0.3 ml. of methanol, the mixture diluted with 6 ml. of acetone, and treated with 3 ml. of chromous chloride reagent (2) for 30 minutes under nitrogen at 22°. After the addition of water the neutral fraction was isolated by ether extraction and by washing with water, sodium bicarbonate, and water. It contained 16.8 mg. of an oil that crystallized from carbon disulfide. Recrystallization from acetone-petroleum ether furnished 10.6 mg. of needles melting at 133–137°. Aliquots of the analytical sample (which had been purified by adsorption on a magnesium silicate-Celite column and elution with benzene containing 5%

ether and by several recrystallizations) showed various melting points (135°, 137° and 140°). This appears to be due to allotropism since samples of various m.p. gave evidence of interconversion upon reheating of the resolidified melts. $[\alpha]_D^{27}$ +99° (*c*, 0.5, 95% ethanol); $\lambda_{max.}^{95\%\ EtOH}$ 240.5 mμ, ε 17000. Carbonyl peaks at 5.74, 5.84, and 5.95μ, ester peak at 8.05μ. Supplementary evidence for Δ⁴-3-ketone: maxima at 11.53, 12.85, and ∽14.57μ (66).

Anal. Calc'd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66.

Found: C, 74.14; H, 8.69.

A sample of biosynthetic 16α-hydroxyprogesterone (18) supplied by the Squibb workers was acetylated. This acetate showed a double melting point (135 and 138°) which was not depressed on admixture of VI prepared from V. The infrared curves of both preparations were in very close agreement. Lit. m.p. 134–135°; $[\alpha]_D$ +107° ($CHCl_3$) (18).

3β,16α-Diacetoxyallopregnan-20-one (VII) (*a*). *From 3β-acetoxy-16α-benzyloxy-Δ⁵-pregnen-20-one* (IIIa). A mixture of 74.9 mg. of compound IIIa (3), 63 mg. of palladium-charcoal (prepared according to Mozingo, prereduced and washed as described above), and 12.5 ml. of 95% ethanol were shaken in an atmosphere of hydrogen for 90 minutes. The crude reaction product was freed of catalyst, dissolved in 8 ml. of 95% ethanol, and hydrogenated in the presence of 402 mg. of a 1% palladium-calcium carbonate catalyst (69). The product (56.8 mg.) was acetylated in 2 ml. of pyridine with 1 ml. of acetic anhydride at room temperature for 18 hours. The acetate (60.6 mg.) upon recrystallization from methanol gave 45 mg. of needles melting at 172–174.5° with sintering at 168°. A purer specimen (m.p. 177.5–178.5°) was obtained by chromatography on magnesium silicate-Celite and recrystallization; $[\alpha]_D^{26}$ +17° (*c*, 0.6, chloroform). The infrared spectrum showed no Δ⁵-peaks in the 12μ region. The ester peak was broad and had a simple contour (8.04μ). Carbonyl peaks were at 5.75 and 5.84μ.

Anal. Calc'd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15.

Found: C, 71.89; H, 9.23.

(*b*). *From 3β-acetoxy-16α,17α-epoxyallopregnan-20-one* (XII). To an aqueous solution of 1.324 gm. of sodium acetate trihydrate which was layered with petroleum ether were added 2 ml. of chromous chloride solution (2). Under the protection of petroleum ether the resulting precipitate was centrifuged, washed 4 times with cool water which had been boiled, and suspended in 2 ml. of such water. This suspension was added to a tube containing 39.7 mg. of compound XII in 6 ml. of acetic acid. The tube was sealed *in vacuo* and agitated on a slow rocker for 16 hours. The mixture was distributed between water and ether. The ether phase was washed with cold hydrochloric acid, cold bicarbonate and water, and taken to dryness. The residue (38.6 mg.) was freed of some Δ¹⁶-20-ketone by chromatography on silica gel-Celite and then acetylated with acetic anhydride (1 ml.) in pyridine at room temperature for 16 hours. The resulting product (29.5 mg.) gave 24.7 mg. of pure 3β,16α-diacetoxyallopregnan-20-one (VII); m.p. 176–178°; $[\alpha]_D^{29}$ +20° (*c*, 0.7, chloroform).

Anal. Calc'd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15.

Found: C, 71.71; H, 9.34.

There was no depression of the melting point when a sample was admixed with a specimen of VII prepared from IIIa. The infrared spectra were in good accord.

3β,16α,17β-Triacetoxyandrostane (XIa). A solution of perbenzoic acid in benzene [0.4 ml., 1 *M*, prepared according to Kolthoff and co-workers (70) and concentrated to >1 *M* *in vacuo*] was added to 69.8 mg. of 3β,16α-diacetoxyallopregnan-20-one (VII, prepared from IIIa). After the solution had stood at room temperature for 3 days a second aliquot (0.4 ml.) of perbenzoic acid solution was added. The mixture was kept for another 4 days when it was distributed between ether and water. The ether phase was washed with sodium carbonate and with water and gave 72.1 mg. of crystalline residue which was separated by means of Girard's reagent T. The ketonic fraction (46.2 mg.) which was obtained from the Girard derivative after a 30-minute hydrolysis with 1 *N* hydrochloric acid in the refrigerator (to avoid elimination reactions at C-16), was reoxidized with 0.2 ml. of 2 *M* perbenzoic acid for 7 days. The resulting non-ketonic fraction (15.1 mg.) was combined with the one obtained before (22.1 mg.) and chromatographed on 885 mg. magnesium silicate-Celite (1:1). The

crystalline fractions upon recrystallization from methanol gave 19.8 mg. of 3β,16α,17β-triacetoxyandrostane (XIa) [m.p. 174.5–177.5°; $[\alpha]_D^{28}$ −43° (*c*, 0.48, 95% ethanol)] and 6.3 mg. (m.p. 173–176.5°).

Anal. Calc'd for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81.

Found: C, 69.09; H, 9.05.

The m.p. remained unchanged on admixture of a sample which had been obtained (71) by reduction of natural 3β,16α,17β-triacetoxy-Δ⁵-androstene. Comparison of the infrared spectra of the saturated triacetates and a mixture m.p. of the free triols (XIb) confirmed the identity of the two preparations.

3β-Acetoxy-16α-hydroxy-Δ⁵-pregnen-20-one (VIII). A mixture of 106.3 mg. of 3β-acetoxy-16α-benzyloxy-Δ⁵-pregnen-20-one (IIIa), 32.9 mg. of palladium-charcoal catalyst (prepared according to Mozingo, prereduced, washed and equilibrated with hydrogen as described above), and 25 ml. of 95% ethanol were shaken in an atmosphere of hydrogen until the gas uptake ceased (135 minutes). The catalyst was removed by passing the suspension through a short column of silica gel-Celite and washed with ethanol. The residue (86.0 mg.) of the ethanol solutions was recrystallized from butanone to yield 39.6 mg. of heavy prisms. An additional crop of 23.6 mg. was obtained from the mother liquors by chromatography (silica gel-Celite (2:1), elution with benzene + 30% ether), and recrystallization. A finely powdered sample showed m.p. 165.5–166.5° followed by resolidification and final m.p. 169–170.5°, $\lambda_{max.}^{95\% \text{ EtOH}}$ 285 mμ (ε ∽43), $\lambda_{min.}$ 244 mμ, $[\alpha]_D^{27}$ −7° (*c*, 0.9, 95% ethanol). Lit. m.p. 172° (17).

Anal. Calc'd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15.

Found: C, 73.88; H, 9.39.

As judged from infrared spectra dioxane could be substituted for alcohol as solvent in the hydrogenolysis, while benzene could not. When 4 mg. of IIIa in alcohol were hydrogenated for 105 minutes in the presence of 200 mg. of the prereduced and washed palladium-charcoal catalyst, and then acetylated, the crude product (1.3 mg.) showed no Δ⁵ peaks in the 12μ region and gave an infrared spectrum similar to VII.

Reduction of 3β-acetoxy-16α-hydroxy-Δ⁵-pregnen-20-one (VIII). A solution of 39.6 mg. of VIII in 25 ml. of dry ether was kept in an ice-bath and stirred while 8 ml. of an ethereal solution of lithium aluminum hydride (prepared from 220 mg. of hydride and 30 ml. of dry ether) was added dropwise during 30 minutes. After the addition of an additional 18 ml. of the hydride solution (5 minutes) stirring was continued for 45 minutes. The product (34.7 mg.) was isolated in the usual manner (72), acetylated in pyridine with acetic anhydride at room temperature, and chromatographed on alumina as described previously (3). The earlier eluates gave 11.0 mg. of platelets, m.p. 166.5–168.5°, which were identified as *3β,16α, 20β-triacetoxy-Δ⁵-pregnene* (IXb) (3) by mixture m.p. and by comparison of the infrared spectra. The later eluates gave 7.0 mg. of needles, m.p. 177.5–179°, identical with *3β,16α, 20α-triacetoxy-Δ⁵-pregnene* (IXa) (3) as shown again by mixture m.p. and infrared spectrum.

To test whether the mode of mixing the reactants had any effect on the proportion of the 20-epimers, two aliquots of an ethereal solution of VIII (each containing 11.8 mg. in 10 ml. of ether) were each treated with 39 mg. of lithium aluminum hydride in 10 ml. of ether. In one run the hydride was added dropwise (31 minutes) to the steroid, in the other the steroid to the hydride (57 minutes). The products were acetylated and showed infrared spectra in very close accord with each other (approximately 40% 20α) but contained less 20α than the mixture obtained in the larger scale run described above.

The hydrogenolysis of the benzyloxy group and the reduction of the 20-keto group of IIIa can be carried out in a single step with a nickel catalyst (73) in 95% ethanol. The spectrum of the acetylated product was indicative of a smaller proportion of the 20α isomer (IXa).

SUMMARY

A method for the preparation of 16α-hydroxy-20-ketosteroids has been described and applied to the partial synthesis of 16α-acetoxyprogesterone.

Steric correlations have been carried out which complete the links between a variety of steroids substituted in ring D. These include 17-hydroxysteroids with and without a side chain at C-17, 16-hydroxylated pregnanes, 16,17-glycols of the androstane series, and sapogenins.

Stability data and a conformational analysis of sapogenins suggest that smilagenin and other compounds of the so called 22-iso series have the partial structure XVa. In the sarsasapogenin series the expected stability differences between possible structures are smaller and the results more uncertain. They favor the partial structure XVc.

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