explain the differences in the dispersion curves and no correlation between the steepness of the slope (implying the more rapid approach of a "maximum" or "minimum") and the degree of substitution of the double bond can be discerned. The latter would have been the most obvious explanation, the most highly substituted double bond absorbing toward higher wave length in which case its optically active absorption band (if one is indeed present) would appear sooner. An alternative explanation, which would take into consideration the relative distortion of the shape of the steroid molecule and consequent rotatory reflection by the introduction of double bonds at various positions, cannot as yet be put on a precise basis.

Experimental

With one exception,[16] all cholestenes (XI–XVI) were measured in dioxane solution, while the ketones (I–X) were investigated in methanol solution. The experimental procedure has already been outlined in detail[3a] and was also followed in this investigation except that all readings below 300 mμ were taken with a 150-watt xenon arc lamp (Hanovia 10-C-1). The lamp was operated on direct current with a special commercially available power supply unit.[8]

Cholestan-1-one (I) (C. Tamm and T. Reichstein): R.D. (Fig. 1): $[\alpha]_{700}$ +76°, $[\alpha]_{589}$ +115°, $[\alpha]_{245}$ +1774°, "max." $[\alpha]_{338}$ +403°, "min." $[\alpha]_{318}$ +374°, *c* 0.15, temp. 26–28°, λ_{max}^{MeOH} 285 mμ.[17]

Cholestan-2-one (II) (D. H. R. Barton), R.D. (Fig. 1): $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +59°, $[\alpha]_{250}$ −972°, "max." $[\alpha]_{310}$ +1632°, "min." $[\alpha]_{267}$ −1514°, *c* 0.1, temp. 23–26°, ultraviolet inflection, 286–290 mμ, log ε 2.24.

Cholestan-3-one (III)[3c], R.D. (Fig. 1): $[\alpha]_{700}$ +37°, $[\alpha]_{589}$ +55°, $[\alpha]_{245}$ −362°, "max." $[\alpha]_{307}$ +959°, "min." $[\alpha]_{267}$ −740°, *c* 0.1, temp. 29–31°.

Cholestan-4-one (IV) (L. F. Fieser and D. H. R. Barton), R.D. (Fig. 1): $[\alpha]_{700}$ +26°, $[\alpha]_{589}$ +29° $[\alpha]_{260}$ +1580°, "max." $[\alpha]_{267.5}$ +1650°, "min." $[\alpha]_{307.5}$ −780°, *c* 0.5, temp. 26–27°, λ_{max}^{MeOH} 290–295 mμ, log ε 1.56.

Cholestane-3,6-dione (V), (L. F. Fieser), R.D. (Fig. 2): $[\alpha]_{700}$ −15°, $[\alpha]_{589}$ +10°, $[\alpha]_{270}$ +667°, "max." $[\alpha]_{282}$ +944°, "min." $[\alpha]_{315}$ −521°, *c* 0.04, temp. 27–29°, λ_{max}^{MeOH} 294–296 mμ, log ε 1.75.

3β-Acetoxycholestan-6-one (VI), (R. C. Cookson), R.D. (Fig. 2): $[\alpha]_{700}$ −2°, $[\alpha]_{589}$ −17°, $[\alpha]_{240}$ +591°, "max." $[\alpha]_{270}$ +906°, "min." $[\alpha]_{306}$ −799°, *c* 0.1, temp. 24–26°, λ_{max}^{MeOH} 290–292 mμ, log ε 1.51.

3β-Acetoxycholestan-7-one (VII), (E. J. Corey), R.D. (Fig. 2): $[\alpha]_{700}$ −28°, $[\alpha]_{589}$ −36°, $[\alpha]_{250}$ −111°, "max." $[\alpha]_{274}$ +15°, "min." $[\alpha]_{310}$ −342°, *c* 0.1, temp. 25–27°, λ_{max}^{MeOH} 285–287 mμ, log ε 1.41.

Cholestan-3β-ol-15-one (VIII), (D. H. R. Barton), R.D. (Fig. 2): $[\alpha]_{700}$ +27°, $[\alpha]_{589}$ +49°, $[\alpha]_{250}$ −1230°, "max." $[\alpha]_{316}$ +1780°, "min." $[\alpha]_{275}$ −1835°, *c* 0.1, temp. 25–26°, ultraviolet inflection, 290–296 mμ, log ε 1.53.

Coprostan-16-one (IX), (E. Mosettig), R.D. (Fig. 2): $[\alpha]_{700}$ −77°, $[\alpha]_{589}$ −114°, $[\alpha]_{250}$ +2360°, "max." $[\alpha]_{276}$ +3800°, "min." $[\alpha]_{317}$ −3452°, *c* 0.1, temp. 25–26°, λ_{max}^{MeOH} 299–303 mμ, log ε 1.47.

D-Homoandrostan-3β-ol-17a-one (X), (W. Klyne), R.D. (Fig. 1): $[\alpha]_{700}$ −22°, $[\alpha]_{589}$ −38° $[\alpha]_{245}$ −577°, "max." $[\alpha]_{312}$ −166°, "min." $[\alpha]_{320}$ −193°, *c* 0.1, temp. 29–31°, λ_{max}^{MeOH} 275–277 mμ, log ε 1.70.

Cholest-1-ene (XI),[15] R.D. (Fig. 3): $[\alpha]_{700}$ +8.8°, $[\alpha]_{589}$ +20°, $[\alpha]_{300}$ +142°, *c* 0.1, temp. 23–25°.

Cholest-2-ene (XII),[15] R.D. (Fig. 3): $[\alpha]_{700}$ +47°, $[\alpha]_{589}$ +68°, $[\alpha]_{290}$ +445°, *c* 0.1, temp. 24–25°.

Cholest-3-ene (XIII),[15] R.D. (Fig. 3): $[\alpha]_{700}$ +30°, $[\alpha]_{589}$ +49°, $[\alpha]_{300}$ +410°, *c* 0.1, temp. 24–26°.

Cholest-4-ene (XIV),[15] R. D. (Fig. 3): $[\alpha]_{700}$ +39°, $[\alpha]_{589}$ +72.5°, $[\alpha]_{300}$ +448°, *c* 0.1, temp. 24–25°.

Cholest-5-ene (XV),[15] R.D. (Fig. 3): $[\alpha]_{700}$ −50°, $[\alpha]_{589}$ −64°, $[\alpha]_{300}$ −321°, *c* 0.1, temp. 24–27°.

Cholest-6-ene (XVI),[15,16] R.D. (Fig. 3): $[\alpha]_{700}$ −68°, $[\alpha]_{589}$ −93°, $[\alpha]_{290}$ −773°, *c* 0.1, temp. 26–28°.

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(17) P. Striebel and C. Tamm (*Helv. Chim. Acta*, **37**, 1094 (1954)) report λ_{max} 297 mμ in ether.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

The Constitution and Stereochemistry of Digitogenin[1]

BY CARL DJERASSI, THURMAN T. GROSSNICKLE[2] AND LEROY B. HIGH

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Degradative evidence is presented that digitogenin is 22a,25a,5α-spirostane-2α,3β,15β-triol (Ia), thus representing the first naturally occurring C-15 hydroxylated steroid. Attention is called to certain stereochemical features in fused hydrindanone systems.

The chemistry of digitogenin, the aglycone of the saponin digitonin, has been summarized adequately by Fieser and Fieser[3] who in 1949 pointed out that "the structure of digitogenin, the earliest known and most extensively investigated of all the sapogenins, is still uncertain." This was the existing state of affairs when we took up this structural problem in 1953, since no further publications on this subject had appeared in the intervening period. Our results, which have led to the elucidation of the structure and stereochemistry of this sapogenin, have been recorded in a series of preliminary communications[4–7] and we should now like to present the experimental details on which these brief reports were based.

Location of the Third Hydroxyl Group

The gross structural features of digitogenin had already been established by Tschesche,[8] who had subjected the oxidation product of digitogenin (I), digitogenic acid (now known to be II), to Wolff–Kishner reduction *via* its semicarbazone and had isolated a small amount of gitogenic acid (III), derivable by scission of ring A of gitogenin (IV).

(1) Supported by a research grant from the American Cancer Society through the Committee on Growth of the National Research Council.

(2) Monsanto Predoctorate Research Fellow, 1952–1954.

(3) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, chapter VIII.

(4) C. Djerassi and T. T. Grossnickle, *Chemistry & Industry*, 728 (1954).

(5) C. Djerassi, T. T. Grossnickle and L. B. High, *ibid.*, 473 (1955).

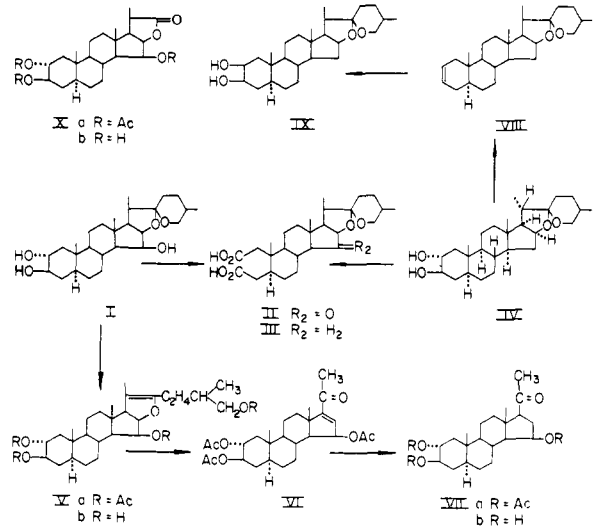
(6) C. Djerassi, L. B. High, T. T. Grossnickle, R. Ehrlich, J. A. Moore and R. B. Scott, *ibid.*, 474 (1955).

(7) C. Djerassi, L. B. High, J. Fried and E. F. Sabo, THIS JOURNAL, **77**, 3673 (1955).

(8) R. Tschesche, *Ber.*, **68**, 1090 (1935).

This sequence demonstrated that digitogenin must be x-hydroxy-22a,25a,5α-spirostane-2ξ,3ξ-diol[9,10] and Marker, *et al.*,[11] suggested on the basis of exclusion evidence that the remaining hydroxyl group is located at C-15. One aspect of digitogenin chemistry which could not be explained readily on the basis of such a structure was the report[11,12] that digitogenin did not undergo most of the reactions typical of the sapogenin spiroketal side chain, notably the degradation *via* the corresponding furosten to Δ^{16}-pregnen-20-ones.

Support for the C-15 location of the third hydroxyl group could be presented by infrared measurements[4] of digitogenic acid (II) and its derivatives, all of which showed a pronounced carbonyl band in chloroform solution at 5.73 μ, typical[13] of cyclopentanones; confirmation of this observation has been recorded recently.[14] More convincing infrared evidence is presented below with a derivative (XIIa) which does not contain any additional carbonyl bands (acid or ester). Furthermore, in striking contrast to Marker's reports,[11,12] it was found that the side chain of digitogenin could be degraded quite readily and the intermediate characterized (after saponification of the oily tetraacetate Va) as the crystalline $\Delta^{20(22)}$-5α-furostene-2,3,15,26-tetrol (Vb), which now lacked the infrared spiroketal bands and showed the typical[15] dextrorotatory spirostan $\rightarrow$ furosten shift. Chromium trioxide oxidation of the furosten tetraacetate (Va) in a biphasic system followed by treatment with alumina[16] led to Δ^{16}-allopregnene-2α,3β,15β-triol-20-one triacetate (VI). The hypsochromic shift (λ_{max}^{EtOH} 231 mμ as compared to *ca.* 238 mμ for other Δ^{16}-20-ketosteroids) of the ultraviolet absorption maximum represents further confirmation for the presence of a hydroxyl group at C-15 since it has also been observed in other γ-hydroxylated α,β-unsaturated steroid ketones.[17] Catalytic hydrogenation produced the saturated triacetoxy ketone VIIa, whose specific rotation was approximately 150° more positive than that of the Δ^{16}-ketone VI; this is remarkably high when compared to the usual dextrorotatory shift of *ca.* 40° accompanying such a structural change. This is a further illustration of the vicinal effect produced by a γ-substituent (at C-15) since the alternative explanation, *i.e.*, inversion at C-17, was excluded by saponification to the free trihydroxy-20-ketone VIIb and reacetylation to the original triacetate VIIa. Consequently, this eliminated the possibility that catalytic hydrogenation of VI had produced the thermodynamically unstable isomer at C-17 as a result of the orientation of the C-15 acetoxy group which had as yet not been established. Rigorous evidence for the location of the C-15 hydroxyl group by direct correlation with 15-hydroxyprogesterone[7] will be considered below. Warren and Canham[18] have reached the same conclusion concerning the placement of the third hydroxyl group of digitogenin on the basis of the periodate consumption of a lactone Xb, derived from this sapogenin, which corresponded to two vicinal glycol systems (2, 3 and 15, 16).



Correlation with Gitogenin

Tschesche's[8] correlation of digitogenin with gitogenin (IV) proceeded *via* the dicarboxylic acid II and consequently did not shed any light on the orientation of the hydroxyl groups since the asymmetric centers at positions 2, 3 and 15 had been destroyed. Conversion of digitogenin to gitogenin (or an isomer thereof) would automatically establish the stereochemistry in ring A and our attention

(9) Gitogenin and tigogenin have been interrelated *via* gitogenic acid (III) as well as through Δ^{2}-22a,25a,5α-spirosten (VIII) (see ref. 24). Since tigogenin can be obtained from diosgenin (*cf.* R. E. Marker, T. Tsukamoto and D. L. Turner, THIS JOURNAL, **62**, 2525 (1940)), all of the arguments pertaining to the configuration at C-20 and C-22 of diosgenin (for leading references see H. Hirschmann, F. B. Hirschmann and J. W. Corcoran, *J. Org. Chem.*, **20**, 572 (1955), and M. E. Wall, *Experientia*, **11**, 340 (1955)) also apply to digitogenin. V. H. T. James (*Chemistry & Industry*, 1388 (1953)) has related the configuration of C-25 in diosgenin with D-glyceraldehyde.

(10) For proposed nomenclature change of sapogenins at C-25, see I. Scheer, R. B. Kostic and E. Mosettig, THIS JOURNAL, **77**, 641 (1955), and C. Djerassi and J. Fishman, *ibid.*, **77**, 4291 (1955). In view of the uncertainty concerning isomerization at C-22 (see Hirschmann, *et al.*, ref. 9), it seems desirable for the time being to retain the "22a" and "22b" system in the original sense (G. Rosenkranz and C. Djerassi, *Nature*, **166**, 104 (1950); Ciba Conference on Steroid Nomenclature, *Chemistry & Industry*, June 23 (pp. SN 1-SN 11) (1951)) as has been generally accepted by workers in this field. The introduction (Wall, ref. 9) of the suffixes "D" and "L" to denote isomerism at C-25 rather than "a" and "b" by the standard steroid convention (*vide supra*) appears to us to be unwise since it simply complicates the nomenclature system even more by introducing a third set of suffixes which has never been employed in steroid chemistry and which does not offer any help as far as drawing structural formulas in the accepted sense is concerned. For instance, the absolute configuration of the steroids has been established at C-3 and at C-20 yet the suffixes D and L are not used in that connection.

(11) R. E. Marker, D. L. Turner and P. R. Ulshafer, THIS JOURNAL, **64**, 1843 (1942).

(12) R. E. Marke., R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **69**, 2183 (1947).

(13) *Cf.* R. N. Jones, P. Humphries and K. Dobriner, *ibid.*, **72**, 956 (1950).

(14) D. L. Klass, M. Fieser and L. F. Fieser, *ibid.*, **77**, 3829 (1955).

(15) *Inter al.*, C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 303 (1951); A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones and A. G. Long, *J. Chem. Soc.*, 2807 (1955).

(16) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, THIS JOURNAL, **75**, 4889 (1953).

(17) *Cf.* H. B. Henbest, E. R. H. Jones, G. W. Wood and G. F. Woods, *J. Chem. Soc.*, 4894 (1952); C. Amendolla, G. Rosenkranz and F. Sondheimer, *ibid.*, 1226 (1954); L. Dorfman, *Chem. Revs.*, **53**, 72 (1953).

(18) F. L. Warren and P. A. S. Canham, *Chemistry & Industry*, 727 (1954).

was, therefore, concentrated on this aspect of the problem.

Quantitative lead tetraacetate oxidation[6] of digitogenin showed $k = 1.63 \times 10^{-3}$ l.-mole^{-1} sec.$^{-1}$ as compared to 1.65×10^{-3} for gitogenin (IV); since this method has been found[19] to be very sensitive to stereochemical changes of the glycol moiety, this indicated that the two sapogenins were identical stereochemically insofar as ring A is concerned.

The two hydroxyl groups in gitogenin (IV) have been assigned[20] the $2\alpha,3\beta$-orientation since gitogenin was not identical with the synthetic[20] $2\alpha,3\alpha$- and $2\beta,3\alpha$-isomers and did not form an acetonide.[21] Synthetic verification followed shortly[22] but both the natural[20] and synthetic[22] specimens gave a purple color with concentrated sulfuric acid, believed[23] to be characteristic of $2\alpha,3\beta$-glycols while digitogenin did not produce any color under those conditions. A detailed examination of various gitogenin samples[6] demonstrated that this color was formed only with those samples which originated from sources which also contained the unsaturated analog yuccagenin (deep purple color with sulfuric acid) and that the color reaction was negative when such specimens were subjected to platinum oxide reduction. For the sake of completeness, the remaining isomer, 22a,25a,5α-spirostene-2β,3β-diol (IX), was synthesized[6] from Δ^2-22a,25a,5α-spirosten (VIII)[24] by a Prevost reaction in moist acetic acid[25,26]; in accordance with expectation, the product formed an acetonide, but did not give a color with concd. sulfuric acid, and was oxidized by lead tetraacetate[19] at a rate ($k = 31.9 \times 10^{-3}$ l.-mole^{-1} sec.$^{-1}$) substantially faster than the corresponding *trans*-glycols (I, IV).

MacPhillamy[27] has shown that under certain conditions digitogenin forms a diacetate. This has now proved to be the 2,3-diacetate Ib thus providing a means of operating at C-15 without destroying the asymmetric centers in ring A. Chromium trioxide oxidation of this diacetate Ib produced the corresponding ketone, digitogenone 2,3-diacetate (XI), which upon alkaline saponification furnished (14)-isodigitogenone (XIIa). This last substance possesses no other carbonyl groups aside from the 15-keto function and its infrared absorption spectrum exhibits a sharp cyclopentanone band at 5.73 μ in chloroform solution. That alkaline saponification of XI had been accompanied by isomerization was established by the fact that reacetylation gave a new diacetate, (14)-isodigitogenone 2,3-diacetate (XIIb). This isomerization could even be produced on alumina and was to be expected by analogy to the long known lability[28] of digitogenic acid (II) toward alkali leading to the isomer digitoic acid. This isomerization has been correctly interpreted[3] as involving isomerization of an adjacent enolizable center even before this center could be localized precisely. With the knowledge that the carbonyl group of digitogenone (XI) and hence also of digitogenic acid (II) is at C-15, only C-14 or C-16 could be implicated in the base-catalyzed isomerization. Inversion at C-16 appears unlikely on two grounds: (a) the spiroketal system would be very strained with a 16α-oxide bridge and, while such a system is not incapable of existence,[29] there seems to be no reason to suppose that it would be more stable than a D/E *cis* fusion. Furthermore, it is extremely improbable that such a system would exhibit (as it does) all of the characteristic infrared spiroketal bands which are so sensitive to even minor alterations.[30] (b) Digitogenin triacetate (Ic) is convertible to a triacetoxy lactone Xa which can be saponified[18,31] to the derived triol lactone Xb, a process which must have involved opening and reclosure of the lactone ring since the latter is rather susceptible to alkaline opening.[18,31] These steps do not involve epimerization at C-16 and the orientation of the oxygen at C-16 must be the same in digitogenin (I) as in the lactone X. This must be β, since it has been reported[32] that similar 16α-hydroxy acids do not lactonize.

From the above considerations, it follows that alkaline isomerization of 15-ketones of the digitogenin series (II, XI) must involve C-14 and it is now necessary to determine which isomer (14α or 14β) is more stable in order to deduce the configuration of digitogenin at that center. Tschesche's[3] Wolff–Kishner reduction of digitogenic acid (II) to gitogenic acid (III), the stereochemistry of which is known,[33] does not shed any light on the configuration of C-14 in digitogenin since (a) the reduction was carried out with only one epimer (alkali-labile) and (b) the reduction conditions involve strongly basic conditions which could have caused inversion at C-14. Attempts in our hands to convert digitogenone diacetate (XI) into its cycloethylene mercaptal failed by the zinc chloride (recovered starting material) or hydrogen bromide–acetic acid (inversion at C-14 without formation of derivative) pro-

(19) C. Djerassi and R. Ehrlich, *J. Org. Chem.*, **19**, 1351 (1954).

(20) J. Pataki, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 5375 (1951).

(21) The remaining alternative, the 2β,3β-isomer, was excluded because it was assumed that it would form an acetonide derivative, which indeed proved to be the case (see Experimental section of this paper and ref. 14).

(22) J. Herran, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **76**, 5531 (1954).

(23) G. Diaz, A. Zaffaroni, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **17**, 747 (1952).

(24) Gitogenin 2,3-dimesylate (IV) was treated with sodium iodide in acetone solution (*cf.* N. L. Wendler, H. L. Slates and M. Tishler, THIS JOURNAL, **74**, 4894 (1952)) to yield Δ^2-22a,25a,5α-spirosten (VIII) which proved to be identical with a sample of the olefin prepared from tigogenin tosylate (ref. 20).

(25) L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson *ibid.*, **76**, 5014 (1954); S. Winstein and R. E. Buckles, *ibid.*, **64**, 2784 (1942).

(26) Since submission of our original communication (ref. 6) on this subject, Klass, Fieser and Fieser (ref. 14) have described the synthesis of IX by this procedure while N. L. Wendler and H. L. Slates, *Chemistry & Industry*, 167 (1955), have employed it in the manogenin series.

(27) H. B. MacPhillamy, THIS JOURNAL, **62**, 3518 (1940).

(28) H. Kiliani, *Arch. Pharm.*, **231**, 448 (1893); H. Kiliani and A. Windaus, *Ber.*, **32**, 2201 (1899).

(29) N. L. Wendler, R. F. Hirschmann, H. L. Slates and R. W. Walker, *Chemistry & Industry*, 901 (1954); N. L. Owen and A. G. Peto, *ibid.*, 65 (1955).

(30) R. N. Jones, E. Katzenellenbogen and K. Dobriner, THIS JOURNAL, **75**, 158 (1953); C. R. Eddy, M. E. Wall and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

(31) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 2724 (1939).

(32) Private communication from Dr. A. Bowers; *cf.* A. Bowers, T. G. Halsall and G. C. Sayer, *J. Chem. Soc.*, 3070 (1954).

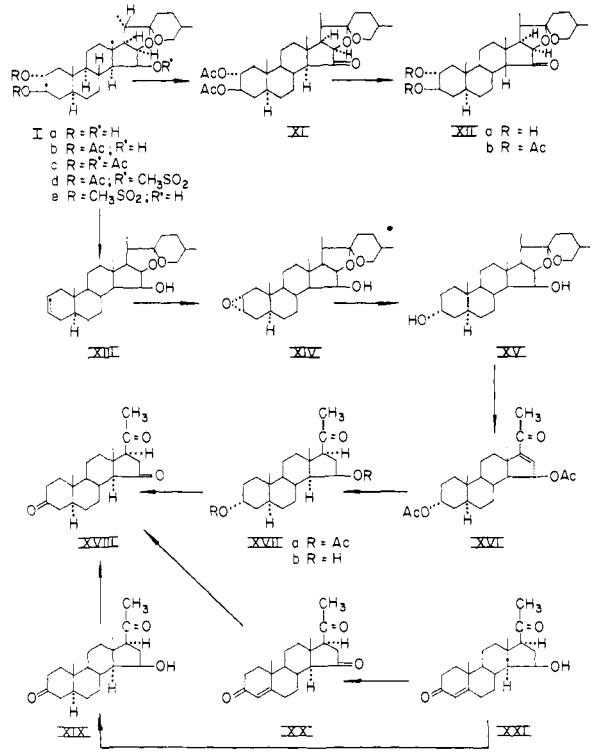
(33) Gitogenic acid and gitogenin have been correlated *via* tigogenin and diosgenin with the hormones and cholesterol, thus establishing the C/D *trans* juncture.

cedures.[34] Consequently, we had to resort to Huang-Minlon's modification[35] of the Wolff–Kishner reduction and *from both isomers (XI or XII), only gitogenin (IV) could be isolated as the sole pure product* in *ca.* 10–15% yield. Infrared examination of the mother liquors demonstrated extensive destruction of the spiroketal system probably due to elimination of the C-16 oxygen function.[36]

These results would lead to the tentative conclusion that digitogenone should be represented by XII, iso-digitogenone by XI and hence that digitogenin should possess a C/D *cis* juncture. This would be based on the assumption that since digitogenone was shown to be so labile to alkali, it is first isomerized to isodigitogenone under the alkaline conditions prevailing in the Wolff–Kishner reduction and then reduced to gitogenin, which is known[33] to possess the 14α(C/D *trans*) fusion. This would mean that digitogenin would be the first naturally occurring sapogenin with such a *cis* fusion but presumptive support for such a conclusion might be presented from two sides. Biogenetically, such an assumption is not so unlikely since digitogenin is one of the few sapogenins which occurs in the same plant together with cardiac glycosides and the latter are known to possess a C/D *cis* fusion, which would then simply be a reflection of a common biogenetic precursor with such a stereochemical feature. More importantly, Barton and collaborators[37] have reported that lithium–ammonia reduction of $\Delta^{8(14)}$-15-ketostenols yields a *single, alkali-stable* 15-ketostanol, which upon Wolff–Kishner reduction is transformed to the known stanol (*e.g.*, cholestan-3β-ol). They concluded that a C/D *trans* fused 15-ketostanol is more stable than the (unknown) *cis* isomer, a result which was quite unexpected and contrary to the generally accepted stability relationships[38] of *cis*- and *trans*-hydrindanones, particularly as applied to steroids.[39] An explanation for this apparent discrepancy has been offered on conformational grounds[40] and accepting the correctness of these views the above observed isomerization of digitogenone to isodigitogenone would represent a second instance in the steroid series where the *trans*-hydrindanone system is more stable.

Any arguments based on the Wolff–Kishner reductions described in the present paper are somewhat weakened by the poor yields and, more importantly, by the difference in the reactivity of the carbonyl groups. Thus, 14-isodigitogenone is recovered practically unchanged under conditions where digitogenone is converted to a large extent into the semicarbazone. It has been pointed out,[5] therefore, that an alternative explanation could be entertained based on a kinetic argument which would lead to the opposite conclusion. The first step in the Wolff–Kishner reduction must be hydrazone formation and if this is appreciably faster in the case of digitogenone, then in spite of the fact that this substance is the thermodynamically unfavored isomer, the reduction of the more stable isodigitogenone may proceed *via* the small amount of digitogenone always present in the equilibrium mixture. If correct, this would imply that digitogenone is represented by XI and 14-isodigitogenone by XII and that the base-catalyzed isomerization involves a conversion of a *trans*-hydrindanone to the *cis* isomer.

Support for this second explanation has been presented very recently[14] when it was observed that treatment of digitogenone (as the 2,3-dicathylate) with ethanedithiol in the presence of perchloric acid furnished a mercaptal which could be desulfurized in 69% yield to gitogenin. Isodigitogenone dicathylate did not react under those conditions.



An unambiguous solution of the stereochemical problem at C-14, which had assumed some importance because of its bearing on the general problem of relative stabilities of fused hydrindanones, required that the reaction sequence employed would obviate the possibility of inversion at C-14. Several experiments were carried out starting with digitogenin 2,3-diacetate 15-mesylate (Id) but without success. The mesylate was recovered unchanged after attempted displacement or elimination with potassium acetate in acetic acid and it was converted into digitogenin (Ia) when it was refluxed with either lithium aluminum hydride in tetrahydrofuran or with potassium ethyl mercaptide in *t*-

(34) The excellent boron trifluoride method (L. F. Fieser, THIS JOURNAL, **76**, 1945 (1954)) cannot be employed with sapogenins because of an unusual reaction with the spiroketal system (C. Djerassi, G. R. Pettit and G. H. Thomas, to be published).

(35) Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949).

(36) *Cf.* R. B. Turner, R. Anliker, R. Helbling, J. Meier and H. Heusser, *Helv. Chim. Acta*, **38**, 411 (1955); N. J. Leonard and S. Gelfand, THIS JOURNAL, **77**, 3272 (1955).

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

(38) For leading references see E. L. Eliel and C. Pillar, THIS JOURNAL, **77**, 3600 (1955).

(39) C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, *ibid.*, **75**, 3496 (1953), reported the base-catalyzed isomerization of Δ^8-11-ketosapogenins to the corresponding 14β-isomers.

(40) A. S. Dreiding, *Chemistry & Industry*, 992 (1954).

butyl alcohol for 3 days.[41] An alternative approach was, therefore, developed which involved correlation of digitogenin with a microbiological transformation product.[7]

Correlation of Digitogenin with Progesterone

Correlation of digitogenin with another steroid without eliminating the C-15 oxygen function requires suitable 15-oxygenated reference compounds and these seem to be provided by the recent discovery[42] that certain microörganisms are capable of introducing a hydroxyl group into position 15 of progesterone and desoxycorticosterone. Through the kind coöperation of Dr. J. Fried of the Squibb Institute for Medical Research, it has been possible to achieve such an interconversion and to settle the remaining stereochemical features of digitogenin. Fried and co-workers[42a] have shown that depending upon the microörganism, either 15α- or 15β-hydroxyprogesterone can be formed from progesterone and the orientation of the hydroxyl groups of the microbiological oxidation products has been established.[43] Catalytic hydrogenation of 15β-hydroxyprogesterone (XXI) in their hands had given both C-5 isomeric dihydro products and very brief oxidation of the 5α-isomer, allopregnane-3,20-dione-15β-ol (XIX), yielded allopregnane-3,15,20-trione (XVIII), also obtainable from 15β-hydroxyprogesterone (XXI) *via* the 15-ketone XX followed by hydrogenation. Allopregnane - 3,15,20 - trione (XVIII) thus appeared to be a very suitable reference compound and it has been possible to convert digitogenin into it by a sequence to be outlined below.

In order for this interconversion to be of stereochemical significance, two basic premises have to be established with respect to the stereochemistry of the reference substance XVIII. First, it has to be assumed that the microbiological oxidation of progesterone to 15β-hydroxyprogesterone (XXI) did not involve isomerization at C-14. This appears to be a reasonable assumption, since of the many microbiological oxidations carried out under a variety of conditions using different organisms and steroid substrates,[44] not a single one has involved inversion at an adjacent carbon atom. This is understandable since such hydroxylations do not seem to proceed through intermediate formation of a double bond.[45] Secondly, it has to be postulated that no inversion occurs in the oxidation of 15β-hydroxyprogesterone (XXI) or of its dihydro derivative XIX to the corresponding ketones XX and XVII. This seems also quite acceptable since the oxidation was carried out under very mild conditions and for a short period of time (less than 15 minutes). Furthermore, just as with digitogenone diacetate (XI), the oxidation products XVIII and XX were very labile to base and could be transformed to the more stable isomer, thus showing that the more labile ketone was indeed formed as the primary product in the oxidation.

The chief problem in the projected interconversion was the removal of the superfluous C-2 hydroxyl group of digitogenin (I) and this was accomplished by an adaptation of the method first employed by Wendler, Slates and Tishler[24] in their transformation of manogenin to hecogenin. Under mild conditions, digitogenin could be converted into the 2,3-dimesylate Ie without affecting the 15-hydroxyl function and heating with sodium iodide in acetone solution resulted in formation of the required olefin XIII. Epoxidation with perbenzoic acid to the 2α,3α-epoxide XIV[46] followed by lithium aluminum hydride reduction to 22a,25a,5α-spirostane-3α,15β-diol (XV) and standard side chain degradation produced Δ^{16}-allopregnene-3α,15β-diol-20-one diacetate (XVI), whose spectroscopic and rotatory properties closely paralleled that of VI. Catalytic hydrogenation afforded an oily acetate XVIIa which was saponified[47] to the crystalline allopregnane-3α,15β-diol-20-one (XVIIb) and oxidized with chromium trioxide. The resulting allopregnane-3,15,20-trione (XVIII) was identical in all respects (mixture melting point, infrared spectrum, rotation and mutarotation after addition of alkali) with a specimen derived from progesterone *via* the chemical-microbiological route.

We conclude from this successful interconversion that digitogenin is 22a,25a,5α-spirostane-2α,3β,-15β-triol (Ia)[48] and consequently that the base-catalyzed transformation of digitogenone (XI) to isodigitogenone (XII) involves the conversion of a *trans*-hydrindanone to a *cis*-hydrindanone, in spite of the fact that Wolff–Kishner reduction of either isomer gives the same *trans*-hydrindane (gitogenin (IV)). Whether this is in fact a general phenomenon applicable to all 15-keto steroids or whether it is a reflection of the additional spiroketal system attached to ring D remains to be determined. It is not inconceivable that the 15-ketostanols[37] are in fact 14β (C/D *cis*) derivatives which undergo the same kind of "kinetic" inversion during the Wolff–Kishner reduction as observed in the present paper but this remains to be established.[48a] The alkali isomerization of 15,20-diketones of the pregnane series (XVIII, XX) is formulated[7] tentatively as involv-

(41) *Cf.* G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, THIS JOURNAL, **75**, 384 (1953). The resistance of the 15-mesylate Id is somewhat reminiscent of the behavior of 12-epi-rockogenin 12-mesylate, which was recovered practically unchanged after being refluxed with potassium *t*-butoxide (*cf.* R. Hirschmann, C. S. Snoddy, Jr., C. F. Hiskey and N. L. Wendler, *ibid.*, **76**, 4013 (1954)).

(42) (a) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz and A. Borman, *Recent Progress in Hormone Research*, **11**, 149 (1955); (b) C. Meystre, E. Vischer and A. Wettstein, *Helv. Chim. Acta*, **38**, 381 (1955).

(43) J. Fried, R. W. Thoma, P. Grabowich and J. R. Gerke, to be published.

(44) A. Wettstein, *Experientia*, **11**, 465 (1955).

(45) *Cf.* M. Hayano and R. I. Dorfman, *J. Biol. Chem.*, **211**, 227 (1954); B. M. Bloom and G. M. Shull, THIS JOURNAL, **77**, 5767 (1955).

(46) The α-orientation is assumed by analogy to the epoxidation of VIII, where the stereochemistry was established (ref. 20).

(47) That this treatment does not involve any change at C-17 already has been demonstrated above with VII.

(48) The molecular rotation argument for the 15β-orientation is already summarized adequately in ref. 7 (footnote 8). The apparently opposite conclusion reached on molecular rotation arguments by Meystre, Vischer and Wettstein (ref. 42b) is in fact in agreement with our conclusions since their calculations are based on incorrect stereochemical assignments of their microbiological transformation products (*cf.* ref. 43). Klass, Fieser and Fieser (ref. 14) arrived at a 15β-assignment for the hydroxyl group on chemical grounds, but these are open to some objection in the absence of any knowledge concerning the behavior of the unknown 15-epimer of digitogenin.

(48a) NOTE ADDED IN PROOF.—The correctness of the original stereochemical assignment (ref. 37) in the sterol series has now been confirmed by the rotatory dispersion method (C. Djerassi, R. Riniker and B. Riniker, in press).

ing inversion *both* at C-14 and C-17 since 17β-acetyl-14β-steroids are inverted at C-17 by alkali[49] while 17α-acetyl-14β-steroids are not affected.[50] If this interpretation should prove to be correct in the light of experiments now under way with 15-keto steroids possessing different C-17 substituents (*e.g.*, ethyl), then the earlier conformational arguments[40] pertaining to rationalization of the relative stability of fused *cis*- and *trans*-hydrindanones appear to require modification.

One conclusion which can already be reached from our results is that at the present time, each example of hydrindanones should be examined on its own merit since subtle effects may alter the picture and that whenever possible, both isomers (*cis* and *trans*) should be investigated before a definite conclusion concerning relative stability is reached.

Experimental[51]

Digitogenin (I) and Derivatives.—The acid cleavage of 20 g. of digitonin (Hoffman–LaRoche, Inc., Nutley, N. J.) was carried out[52] by refluxing for 2 hours in an atmosphere of nitrogen with 200 cc. of 95% ethanol and 40 cc. of concd. hydrochloric acid. After cooling, the precipitate was collected and washed very well with water; yield 5.17 g., m.p. 273–275°. An additional 1.24 g. of **digitogenin** (Ia), m.p. 267–274°, could be obtained from the mother liquors, thus raising the total yield to 88%. Several recrystallizations of the first crop from dilute ethanol and from ethyl acetate–methanol afforded substantially pure digitogenin, m.p. 280–283°, $[\alpha]_D$ −75°, $\lambda^{CHCl_3}_{max}$ 2.81 and 2.90 (hydroxyl) and 10.22, 10.90, 11.14 and 11.53 μ (spiroketal). The substance gave no color with concd. sulfuric acid and was recovered in 90% yield when subjected to standard[20] acetonide formation conditions.

Digitogenic acid (II)[52] exhibited $\lambda^{CHCl_3}_{max}$ 2.8–4.2, 5.72 (cyclopentanone), 5.84 (acid), 10.23, 10.90, 11.18 and 11.55 μ (spiroketal) while the corresponding methyl ester showed $\lambda^{CHCl_3}_{max}$ 5.73, 5.78, 10.20, 10.90, 11.15 and 11.54 μ.

Since digitogenin from commercial digitonin is usually contaminated by gitogenin (IV) which must be removed completely in order for the subsequent conversion to gitogenin to be meaningful, all experiments involving the ketones XI and XII were carried out with chromatographically purified **digitogenin diacetate** (Ib).

In a typical experiment, 10.3 g. of digitogenin was acetylated at room temperature overnight with 20 cc. of acetic anhydride and 100 cc. of pyridine. The crude diacetate (11.5 g.), dissolved in 200 cc. of 1:1 hexane–benzene, was chromatographed on 350 g. of alumina. Elution with the same solvent yielded 1.19 g. of crude gitogenin (IV) diacetate. The bulk of the material (4.65 g., m.p. 213–228°) eluted with 1:4 hexane–benzene was recrystallized from methanol–chloroform to furnish 2.61 g. of diacetate Ib, m.p. 234–236°; twice recrystallized material (m.p. 238–240°) was used for the subsequent experiments. The analytical sample exhibited m.p. 241.5–242°, $[\alpha]_D$ −104°, $\lambda^{CHCl_3}_{max}$ 2.81, 5.75 5.78 μ.

Anal. Calcd. for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08. Found: C, 70.25; H, 9.19.

Elution with more polar solvents yielded partially hydrolyzed material, which was reacetylated and processed with another run.

Digitogenin 2,3-diacetate 15-mesylate (Id) was prepared by adding 0.2 cc. of mesyl chloride to an ice-cold solution of 1.4 g. of digitogenin diacetate (Ib) in 14 cc. of dry pyridine and letting stand at room temperature for 72 hours. The mixture was poured onto crushed ice, the precipitate was collected and washed well with dilute acid and dilute bicarbonate. Two recrystallizations of the crude solid (m.p. 182–192°) from ethanol led to 1.04 g. of the pure 15-mesylate, m.p. 208–210°, $[\alpha]_D$ −121°.

Anal. Calcd. for $C_{32}H_{50}O_9S$: C, 62.94; H, 8.20. Found: C, 63.01; H, 8.25.

Digitogenin dimesylate (Ie) was obtained when a solution of 10.46 g. of digitogenin in 85 cc. of pyridine was left in the refrigerator for 3 days with 5.0 cc. of mesyl chloride. Crystallization from methanol–chloroform gave 9.95 g., m.p. 263–265°, while the analytical sample exhibited m.p. 266–266.5°, $[\alpha]_D$ −85°.

Anal. Calcd. for $C_{29}H_{48}O_9S_2$: C, 57.63; H, 7.95. Found: C, 57.86; H, 7.76.

Degradation of Digitogenin (Ia) to **Δ^{16}-Allopregnene-2α,-3β,15β-triol-20-one Triacetate** (VI).—A mixture of 5.0 g. of digitogenin (Ia) in 15 cc. of acetic anhydride was heated in a sealed tube at 190° for 10 hours, cooled, poured into ice-water, extracted with ether, washed with bicarbonate solution, water, dried and evaporated. A 350-mg. portion of the oily tetraacetate Va was saponified with boiling 5% methanolic potassium hydroxide to yield, after recrystallization from ethyl acetate, **$\Delta^{20(22)}$-5α-furostene-2α,3β,15β,-26-tetrol** (Vb), m.p. 272–275°. $[\alpha]_D$ ± 0°, $\lambda^{CHCl_3}_{max}$ 3.0 (broad hydroxyl band) and 5.90 μ (furosten double bond[53]) but no spiroketal bands at 11.2 or 11.5 μ.

Anal. Calcd. for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 71.56; H, 9.68.

The remaining 6.54 g. of crude tetraacetate Va was dissolved in a mixture of 75 cc. of ethylene dichloride, 90 cc. of glacial acetic acid and 18 cc. of water, cooled to 10° and treated with stirring over a 30-minute period with 3.0 g. of chromium trioxide dissolved in 8 cc. of glacial acetic acid and 0.8 cc. of water. After an additional 2 hours at room temperature, chloroform was added and the organic phase was washed well with bicarbonate solution and water, dried and evaporated. The total crude "diosone" (6.47 g.), dissolved in 75 cc. of 3:2 hexane–benzene was placed on a column of 125 g. of unwashed (basic) alumina and left for 1 hour. Elution with benzene and benzene–ether mixtures led to 2.19 g. (41% over-all yield based on Ia) of Δ^{16}-allopregnene-2α,3β,15β-triol-20-one triacetate (VI).[54] The analytical sample was recrystallized from methanol, m.p. 185–187°, $[\alpha]_D$ −164°, λ^{EtOH}_{max} 231 mμ, log ϵ 3.97, $\lambda^{CHCl_3}_{max}$ 5.76–5.80, 5.98 and 6.27 μ.

Anal. Calcd. for $C_{27}H_{38}O_7$: C, 68.33; H, 8.07. Found: C, 68.27; H, 8.25.

Allopregnane-2α,3β,15β-triol-20-one (VII).[54]—The catalytic hydrogenation of the unsaturated ketone VI in ethyl acetate solution with 5% palladized charcoal catalyst proceeded in quantitative yield (m.p. 241–245° of crude product). Recrystallization from methanol furnished the **triacetate VIIa** as colorless prisms, m.p. 253–254°, $[\alpha]_D$ −16°, no high selective ultraviolet absorption.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.24; H, 8.37.

Refluxing of 0.62 g. of the above triacetate with 5% methanolic potassium hydroxide solution for 2 hours furnished 0.43 g. of crude triol VIIb, m.p. 207–233°, raised to 239–242°, $[\alpha]_D$ +63° after one recrystallization from acetone. The substance seems to exist in two polymorphic forms, since subsequently only material with m.p. 268–270°, $[\alpha]_D$ +65°, was obtained.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.10; H, 9.88.

(49) *Cf.* K. Meyer, *Helv. Chim. Acta*, **30**, 1976 (1947).

(50) *Cf.* P. A. Plattner, H. Heusser and A. Segre, *ibid.*, **31**, 249 (1948).

(51) Unless noted otherwise, melting points are uncorrected and were determined in evacuated capillaries, while rotations and infrared spectra were measured in chloroform solution. Alumina used for chromatography was neutral, activity II (Brockmann) unless specified otherwise. The microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, N. J., and Geller Laboratories, Hackensack, N. J.

(52) H. Kiliani and B. Merck, *Ber.*, **34**, 3562 (1901).

(53) A. L. Hayden, P. B. Smeltzer and I. Scheer, *Anal. Chem.*, **26**, 550 (1954).

(54) For molecular rotation comparisons, the missing constants of the corresponding 15-deoxy derivatives obtainable from gitogenin (IV) were needed and the required 2,3-diols from the Marker sample collection (*cf.* R. E. Marker, *et al.*, THIS JOURNAL, **69**, 2184 (1947)) were kindly furnished by Dr. J. A. Moore of Parke, Davis and Co. Acetylation of Δ^{16}-allopregnene-2α,3β-diol-20-one (m.p. 228–230°, $[\alpha]_D$ +41°) produced the corresponding 2,3-diacetate, m.p. 186–187.5°, $[\alpha]_D$ −15°. *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 72.08; H, 8.71. Found: C, 71.91; H, 8.84. Similar acetylation of allopregnane-2α,3β-diol-20-one (m.p. 238–239°, $[\alpha]_D$ +89°) led to the corresponding diacetate, m.p. 187.5–189°, $[\alpha]_D$ +29°. *Anal.* Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.65; H, 9.01.

Reacetylation of 100 mg. of the triol (acetic anhydride–pyridine, 1 hr. at 100°, 14 hours at 45°) yielded 120 mg. of the triacetate VIIa, m.p. 247–253°, raised to 252–254°, $[\alpha]D$ −14°, after one recrystallization from methanol. Identity with the above triacetate was established by mixture melting point determination and infrared comparison.

Digitogenone Diacetate (22a,25a,5α-Spirostane-2α,3β-diol-15-one Diacetate) (XI).—To a solution of 2.35 g. of chromatographically purified digitogenin 2,3-diacetate (Ib) in 235 cc. of acetone (distilled from permanganate) was added dropwise at 20° (external cooling) 2.5 cc. of 8 *N* chromic acid reagent[55] and the mixture was left at room temperature for 30 minutes. Dilution with ice-water, filtration of the product and recrystallization from methanol–chloroform furnished 1.61 g. of pure digitogenone diacetate (XI). The analytical sample was obtained from the same solvent mixture; m.p. 274–276°, $[\alpha]D$ −85°, $\lambda^{CHCl_3}_{max}$ 5.72, 5.76–5.78, 10.22, 10.84, 11.20 and 11.53 μ.

Anal. Calcd. for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 69.99; H, 8.70.

Purification could not be carried out by chromatography since in a test run using apparently neutral alumina, 14-isodigitogenone diacetate (XIIb) was produced in over 50% yield. The diacetate XI was recovered unchanged when it was treated for 4 days at 25° with ethanedithiol in dioxane solution in the presence of sodium sulfate and zinc chloride. When the reaction with ethanedithiol was carried out in glacial acetic acid solution in the presence of hydrogen bromide (4 hours, 25°), *ca.* 25% of the 14-isomer XIIb was isolated and no mercaptal formation was observed.

Standard treatment (1 hour, steam-bath) with Girard reagent T illustrated the relatively hindered nature of the 15-carbonyl group since only about 10% appeared in the ketonic fraction; 80% of unchanged diacetate XI was recovered from the non-ketonic portion.

Digitogenone 2,3-diacetate (XI) semicarbazone was prepared by the procedure used by Tschesche[6] in the case of digitogenic acid (II) and yielded 43% of the semicarbazone after 2 hours at 70° and overnight at 25°. Infrared examination of the mother liquors indicated appreciable quantities of unchanged ketone and heating at 70° for 3 hours with semicarbazide–sodium acetate in ethanol gave an additional 22% of the semicarbazone. The analytical sample was recrystallized from methanol whereupon it exhibited m.p. 249–251°, $[\alpha]D$ −205°, $\lambda^{CHCl_3}_{max}$ 2.83 and 2.98 (N–H), 5.75–5.78 (ester), 5.91 and 6.40 (semicarbazone), 10.22, 10.81, 11.21 and 11.53 μ (spiroketal).

Anal. Calcd. for $C_{32}H_{49}N_3O_7$: C, 65.39; H, 8.40. Found: C, 65.38; H, 8.45.

14-Isodigitogenone (22a,25a,5α,14β-Spirostane-2α,3β-diol-15-one) (XIIa).—A 0.5-g. sample of pure digitogenone diacetate (XI) (m.p. 274–276°) was refluxed for 2 hours with 2.5 g. of potassium hydroxide and 50 cc. of methanol; one recrystallization of the crude product from dilute acetone yielded 425 mg. of isodigitogenone (XIIa), m.p. 194–197°. Several recrystallizations from dilute ethanol afforded the analytical sample, m.p. 207–208°, $[\alpha]D$ −104°, $\lambda^{CS_2}_{max}$ 2.97 (broad), 5.73 (cyclopentanone), 10.21, 10.90, 11.17 and 11.53 μ.

Anal. Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.76; H, 9.39.

This is another stage where gitogenin (IV), present as an impurity in the starting digitonin, can be removed effectively. The gitogenin diacetate impurity is carried through up to the saponification *cum* isomerization step (XI → XIIa), where the high melting gitogenin (m.p. 273°) can be separated quite readily by crystallization from the more soluble isodigitogenone (XIIa).

Acetylation of isodigitogenone (XIIa) with acetic anhydride–pyridine at room temperature afforded 94% of crude **diacetate XIIb**, m.p. 268–275°, raised to 281–283° (70% yield) after recrystallization from methanol–chloroform. The analytical sample was obtained from the same solvent mixture, m.p. 283–284°, $[\alpha]D$ −132°, and exhibits an infrared band ($CHCl_3$) at 10.04 μ which is completely absent in XI.

Anal. Calcd. for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 70.27; H, 8.62.

(55) *Cf.* R. G. Curtis, I. Heilbron, E. R. H. Jones and G. F. Woods, *J. Chem. Soc.*, 461 (1953).

Alkaline saponification of the diacetate XIIb regenerated isodigitogenone (XIIa) in 96% yield.

Attempts to prepare a semicarbazone from 14-isodigitogenone diacetate (XIIb) under the conditions employed successfully in the case of XI, failed, only unreacted ketone being obtained. When the reaction time was increased to 8 hours, nearly 50% of starting material XIIb was recovered, but from the filtrate there was isolated 20–30% of a semicarbazone (m.p. 232–236° (Kofler)) which was not further purified for analysis. These experiments clearly show the increased steric hindrance around the 15-keto function in the 14-iso series (XII).

Wolff–Kishner Reduction of Digitogenone Diacetate (XI) to Gitogenin (IV).—A solution of 200 mg. of digitogenone diacetate (XI) in 7.5 cc. of 95% ethanol, 6.8 cc. of diethylene glycol and 0.9 cc. of 85% hydrazine hydrate was refluxed for 2.75 hours, 0.63 g. of potassium hydroxide was added and refluxing continued for 15 minutes. The condenser was removed, the temperature was permitted to rise to 150° and heating was continued at that temperature in a current of nitrogen for 13 hours. Dilution with ice and hydrochloric acid and isolation with chloroform gave 165 mg. of crude product (m.p. *ca.* 85°) which by infrared examination showed no more carbonyl group but rather extensive destruction of the spiroketal system. Several recrystallizations from dilute acetone afforded 30 mg. (18%) of somewhat impure gitogenin (IV), m.p. 255–265°, raised to 264–266° (10% yield) upon further recrystallization. Identity was established by mixture melting point determination, infrared comparison with an authentic sample[6] and by oxidation to gitogenic acid (III), m.p. alone or admixed with an authentic specimen, 244–246°.

When the reaction time was reduced to 4 hours, 11% of crude gitogenin (m.p. 254–257°) was obtained, but the presence of unreacted ketone and hydrazone was noted in the mother liquors by infrared spectral determination.

Wolff–Kishner Reduction of 14-Isodigitogenone (XIIa) to Gitogenin (IV).—The reduction was carried out essentially as above yielding 9% of gitogenin (IV), m.p. 267–268°, $[\alpha]D$ −63°, infrared spectrum and X-ray pattern[56] identical with that of authentic gitogenin.[6]

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.49; H, 10.07.

Gitogenin 2,3-diacetate exhibited m.p. 248–249°, $[\alpha]D$ −94°, and proved to be identical with the authentic derivative.[6]

Anal. Calcd. for $C_{31}H_{48}O_6$: C, 72.06; H, 9.36. Found: C, 72.21; H, 9.23.

Δ²-22a,25a,5α-Spirosten-15β-ol (XIII).—A mixture of 500 mg. of digitogenin 2,3-dimesylate (Ie), 2.0 g. of sodium iodide and 20 cc. of acetone was heated in a sealed tube at 110° for 48 hours and isolated in the standard manner.[24] Chromatography on 30 g. of alumina and elution with 3:1 hexane–benzene yielded 390 mg. of colorless solid, which was recrystallized from methanol; m.p. 203.5–205.5° (Kofler), $[\alpha]D$ −38°.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.08; H, 10.15.

2α,3α-Oxido-22a,25a,5α-spirostan-15β-ol (XIV).—The above olefin XIII (19.8 g.) in 250 cc. of chloroform was mixed with 250 cc. of a chloroform solution of perbenzoic acid (48 mg./cc.) and left at room temperature for 72 hours. The usual work-up[20] produced 19.9 g. of crude oxide, m.p. 175–180°; the analytical sample was purified by passage through a short column of alumina followed by several recrystallizations from methanol, m.p. 188–190°, $[\alpha]D$ −56°.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.34; H, 9.86.

22a,25a,5α-Spirostane-3α,15β-diol (XV).—The above epoxide (19.9 g.) was reduced with 7 g. of lithium aluminum hydride in 1 l. of ether as described for the 15-deoxysapogenin[20] and yielded 17.7 g. of the crude diol XV, m.p. 175–195°. Recrystallization from acetone yielded the analytical sample with a double m.p. 209–211° and 238–240° (Kofler), $[\alpha]D$ −74°.

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 74.95; H, 10.25. Found: C, 75.23; H, 10.02.

(56) Kindly carried out by Mr. R. B. Scott, Parke, Davis and Co., Detroit, Mich.

Δ^{16}-Allopregnene-3α,15β-diol-20-one Diacetate (XVI).—The side chain degradation of 4.38 g. of the diol XV was carried out exactly as described above for digitogenin and after recrystallization from methanol led to 1.79 g. of the unsaturated ketone XVI, m.p. 142–143°, $[\alpha]_D$ −152°, λ^{EtOH}_{max} 231 mμ, log ϵ 4.00.

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.74; H, 8.70.

Allopregnane-3α,15β-diol-20-one (XVIIb).—The above unsaturated ketone XVI (265 mg.) was hydrogenated as described for XI and yielded the saturated diacetoxyketone XVIIa as a colorless glass (no high selective ultraviolet absorption) which resisted all attempts at crystallization. Consequently, the material was directly saponified with 2% methanolic potassium hydroxide[47] to furnish a colorless solid (223 mg.) which was recrystallized from chloroform–hexane; m.p. 239–241°, $[\alpha]_D$ +59° ($CHCl_3$), +84° (pyridine).

Anal. Calcd. for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.37; H, 10.30.

Allopregnane-3,15,20-trione (XVIII).[57]—A solution of 26 mg. of allopregnane-3α,15β-diol-20-one (XVIIb) in 2.5 cc. of glacial acetic acid was treated dropwise over a period of 15 minutes with a 0.5% solution of chromium trioxide in 95% acetic acid until a definite excess of the reagent was noted (15.32 mg., theory 10.4 mg.). The excess reagent was destroyed with ethanol and the product was isolated by means of chloroform and crystallized; m.p. 222–223°, $[\alpha]_D$ +137°. The mutarotation (final value +55°) was determined by dissolving 6 mg. of the substance in 1.2 cc. of methanol, determining the rotation and then adding 0.02 cc. of 1.35 *N* methanolic potassium hydroxide solution and measuring the rotation at intervals until equilibrium was reached (*ca.* 15–20 hours). The substance proved to be identical by mixture melting point, infrared comparison, rotation and rate of mutarotation with samples prepared at the Squibb Institute[42,43] by two different routes from 15β-hydroxyprogesterone (XXI).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.72; H, 8.97.

22a,25a,5α-Spirostane-2β,3β-diol (IX).[26]—Gitogenin (IV) was converted into the 2,3-dimesylate with mesyl chloride in pyridine solution and recrystallized from methanol; m.p. 238–240°, $[\alpha]_D$ −79°.

(57) This experiment was carried out by Dr. Josef Fried and Miss Emily F. Sabo of the Squibb Institute for Medical Research (*cf.* ref. 7).

One gram of the dimesylate was heated in a sealed tube at 110° for 24 hours with 1.5 g. of sodium iodide and 20 cc. of dry acetone, water was added and the product (0.67 g.) was isolated by extraction with chloroform and recrystallized from acetone. The resulting **Δ^2-22a,25a,5α-spirosten (VIII)**, m.p. 182–184°, was shown to be identical by mixture melting point and infrared comparison with a specimen prepared[20] from tigogenin.

To a stirred solution of 400 mg. of the olefin VIII in 75 cc. of glacial acetic acid was added 270 mg. of freshly prepared silver oxide and the mixture was refluxed until clear. A trace (6.5 mg.) of acetic anhydride was added (to remove excess water formed during the above reaction), the solution was cooled to 20° and 255 mg. of iodine dissolved in acetic acid was added with stirring and heating was continued at 90–95° for 3 hours. The coagulated silver iodide was filtered, the filtrate evaporated to dryness *in vacuo*, taken up in hot methanol, boiled with a small amount of potassium bromide and again filtered. Saponification of the intermediate acetate was completed by adjusting the *p*H of the solution to 10 with methanolic potassium hydroxide solution and leaving overnight at room temperature. Dilution with water, extraction with chloroform, washing, drying and evaporation furnished 390 mg. of crude glycol, m.p. 218–230°. The analytical sample was purified by chromatography through a short alumina column and recrystallization from hexane–acetone and from methanol; m.p. 223–224° (flat plates from hexane–acetone) or 235–237° (needles from methanol) (Kofler), $[\alpha]_D$ −49°, rate of lead tetraacetate oxidation[58] in acetic acid solution,[19] k = 31.9 × 10^{-3} l.-mole^{-1} sec.$^{-1}$.

Anal. Calcd. for $C_{27}H_{44}O_4$: C, 74.95; H, 10.25. Found: C, 74.61; H, 10.29.

Oxidation of 40 mg. of the diol IX with chromium trioxide in acetic acid led to 20 mg. of gitogenic acid (III), m.p. and mixture m.p. 243–245°.

The acetonide was prepared by the acetone–*p*-toluenesulfonic acid method[20] and eluted from alumina with benzene; m.p. 239–241° (after recrystallization from acetone), depressed to 205–230° when mixed with the starting glycol IX, $[\alpha]_D$ −31°.

Anal. Calcd. for $C_{30}H_{48}O_4$: C, 76.22; H, 10.24. Found: C, 76.41; H, 10.36.

(58) The value of 3.69 × 10^{-3} reported earlier (ref. 19) was obtained with a product which proved to be chiefly gitogenin (see footnote in ref. 6).

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Decarboxylation *via* the Acid Chloride of Penta-*O*-acetyl-D-gluconic Acid[1a,1b]

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It has been found that the acid chloride of penta-*O*-acetyl-D-gluconic acid reacts with silver oxide and bromine in carbon tetrachloride solution to yield carbon dioxide and *aldehydo*-1-bromo-D-arabinose penta-*O*-acetate. The reaction in terms of carbon dioxide evolution is essentially quantitative. Although the reaction yields the same product that is obtained when a silver salt is treated with bromine, the use of the acid chloride eliminates the difficulties experienced in drying the silver salts.

In previous communications[2] it was shown that the silver salts of either alginic acid or penta-*O*-acetyl-D-gluconic acid would, when treated with bromine, react in the same manner as aromatic or aliphatic acids.[3] That is, the carboxyl group, which is lost as carbon dioxide, is substituted by bromine. The reaction is very sensitive to traces of water, the presence of which leads to the isolation of the unreacted free acid. The silver salts are also quite sensitive to heat and thus are difficult to dry thoroughly. In attempts to use acetic anhydride as a drying agent, it was observed that a carbon tetrachloride solution of the anhydride reacted with dry silver oxide and bromine to produce two moles of carbon dioxide per mole of acetic anhydride. When a carbon tetrachloride solution of acetyl chloride was treated with dry silver oxide and bromine, one

(1) (a) Published with the permission of The Bureau of Ordnance Navy Department. The opinions and conclusions are those of the author. (b) Presented in part at the 128th Meeting of the American Chemical Society, Minneapolis, Minn., September, 1955.

(2) F. A. H. Rice, Abstracts of the 127th Meeting of the Am. Chem. Soc., Cincinnati, O., **11E**, (1955); F. A. H. Rice and A. H. Johnson, THIS JOURNAL, **76**, 428 (1956).

(3) J. Kleinberg, *Chem. Revs.*, **40**, 381 (1947).