(d) **With Sulfuric Acid.**—A mixture of 200 mg. of diazo ketone VIII, 20 cc. of 15% sulfuric acid and 3 cc. of ethanol was heated under reflux for 20 minutes. Evaporation of an ether extract of the reaction mixture yielded 120 mg. (83%) of crystalline **3-bromo-α,2,5-trihydroxyacetophenone (XXII)** which separated from ether in cream colored prisms, m.p. 166–168°. The triol produced a green color with ferric chloride solution.

Anal. Calcd. for $C_8H_7BrO_4$: C, 38.88; H, 2.85. Found: C, 38.55; H, 2.99.

Hydrolysis of α,2,5-triacetoxy-3-bromoacetophenone (XIX, 40 mg.) was accomplished by heating under reflux for 5 minutes with a mixture of 10 cc. of water, 0.5 cc. of 36% hydrochloric acid and 2 drops of 48% hydroiodic acid. Upon cooling the solution, 15 mg. (58%) of crystalline triol (XXII) was obtained, which did not depress the m.p. of the triol prepared from diazo ketone VIII and sulfuric acid.

2,3,5-Triacetoxy-α-diazoacetophenone (IX) was prepared in 77% yield from 2,3,5-triacetoxybenzoyl chloride (VI)[9] in the manner previously described[4] and formed cream colored needles, m.p. 135–138°.

Anal. Calcd. for $C_{14}H_{12}N_2O_7$: C, 52.50; H, 3.77. Found: C, 52.85; H, 3.77.

2,3,5-Triacetoxy-α-bromoacetophenone (XVII).—The aforementioned diazoketone (2 g.) was slowly added to a saturated solution of hydrogen bromide in glacial acetic acid. After 10 minutes the acetic acid was removed under reduced pressure and the residue was heated on the steam-bath for 1 hour with 7 cc. of acetic anhydride and 1 drop of concentrated sulfuric acid. When the reaction mixture was poured onto ice there was obtained 1.6 g. of crystalline solid. Two crystallizations from ethanol yielded colorless needles, m.p. 81–82°.

Anal. Calcd. for $C_{14}H_{13}BrO_7$: C, 45.06; H, 3.51. Found: C, 45.19; H, 3.76.

α,2,3,5-Tetraacetoxyacetophenone (XX). (a) **From 2,3,5-Triacetoxy-α-diazoacetophenone (IX).**—The diazo ketone (150 mg.) was added slowly to boiling acetic acid (4 cc.) and the solution was then boiled for 5 minutes. The solvent was removed under reduced pressure and the residue was evaporatively distilled in vacuum. Upon scratching the distillate under ethanol it finally crystallized and one crystallization from ethanol produced colorless prisms (70 mg., 42%), m.p. 112–113°.

Anal. Calcd. for $C_{16}H_{16}O_9$: C, 54.54; H, 4.58. Found: C, 54.28; H, 4.78.

(9) R. E. Corbett, C. H. Hassall, A. W. Johnson and A. R. Todd, *J. Chem. Soc.*, 1 (1950).

(b) **From 2,3,5-Triacetoxy-α-bromoacetophenone (XVII).**—A mixture of 300 mg. of the bromo ketone, 132 mg. of silver acetate and 20 cc. of dry acetic acid was refluxed for one hour. The filtered solution was evaporated in vacuum and the residue was crystallized from ethanol; yield 150 mg. (53%) of tetraacetate (XX), which did not depress the m.p. when mixed with a sample prepared from the diazo ketone as previously described.

3,5-Diacetoxy-α-diazoacetophenone (XXV).—A mixture of 8 g. of 3,5-dihydroxybenzoic acid,[10] 30 cc. of acetic anhydride and 3 drops of sulfuric acid was warmed on a steam-bath for 25 minutes and then poured onto 200 g. of ice. The solid **3,5-diacetoxybenzoic acid** was crystallized from a mixture of benzene and ethanol and formed colorless prisms, m.p. 156–158°, yield 11.5 g. (93%).

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.21; H, 4.36.

3,5-Diacetoxybenzoyl chloride was prepared from the aforementioned acid in 84% yield, and separated from a mixture of benzene and Skellysolve B in colorless needles, m.p. 84–85°.

Anal. Calcd. for $C_{11}H_9ClO_5$: C, 51.47; H, 3.53. Found: C, 51.60; H, 3.33.

3,5-Diacetoxy-α-diazoacetophenone (XXV) was prepared from 3,5-diacetoxybenzoyl chloride in the manner previously described for the isomeric 2,5-diacetoxy-α-diazoacetophenone[4]; yield 85% of yellow prisms from ether, m.p. 94–95°.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.84. Found: C, 54.98; H, 3.60.

3,5-Diacetoxy-α-bromoacetophenone was obtained when diazo ketone XXV was treated with hydrogen bromide in the manner described for preparation of bromo ketone XVII; m.p. 61–62°.

Anal. Calcd. for $C_{12}H_{11}BrO_5$: C, 45.73; H, 3.52. Found: C, 46.03; H, 3.34.

α,3,5-Triacetoxyacetophenone (XXIV) was prepared in 81% yield from diazo ketone XXV and in 75% yield from 3,5-diacetoxy-α-bromoacetophenone by methods analogous to those described for preparation of tetraacetate XX. The ester separated in colorless needles from methanol, m.p. 86–87°.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.79. Found: C, 57.10; H, 4.92.

(10) N. L. Drake (Ed.), "Organic Syntheses," Vol. 21, John Wiley and Sons, New York, N. Y., 1941, p. 27.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

α-Iodoketones. Part 4.[1] The Reaction of N-Iodosuccinimide with Enol Acetates of Δ^4-3-Ketosteroids[2]

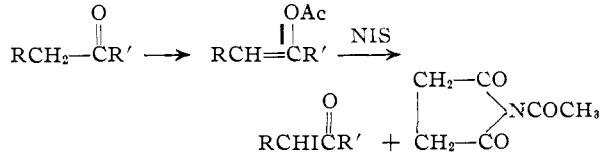
BY CARL DJERASSI, J. GROSSMAN AND G. H. THOMAS

RECEIVED FEBRUARY 8, 1955

Enol acetates of Δ^4-3-ketosteroids react with N-iodosuccinimide at room temperature to produce the corresponding 6-iodo-Δ^4-3-ketones and some reactions of this class of compounds have been studied. Taking advantage of the greater reactivity toward N-iodosuccinimide of unsaturated enol acetates as compared to saturated ones, progesterone has been converted into 17α-hydroxyprogesterone *via* its dienol acetate by selective reaction with the $\Delta^{3,5}$-3-acetoxy system, followed by deiodination at C-6, perbenzoic acid oxidation at C-17(20) and base treatment.

We have recently recorded[3] a novel synthesis of α-iodo ketones which involves reaction of an enol acetate with N-iodosuccinimide (NIS).

The only α,β-unsaturated enol acetate which has so far been examined[1] has been the steroidal enol acetate II, derived from a Δ^{16}-20-ketosteroid (I),

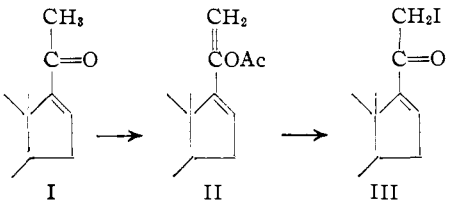


and this led in excellent yield to the corresponding Δ^{16}-21-iodo-20-ketone (III), thus opening a new preparative path to the cortical hormone side chain.

(1) Part 3, C. Djerassi and C. T. Lenk, THIS JOURNAL, **76**, 1722 (1954).

(2) We are indebted to the Research Corporation of New York for a Frederick Gardner Cottrell grant in support of this work.

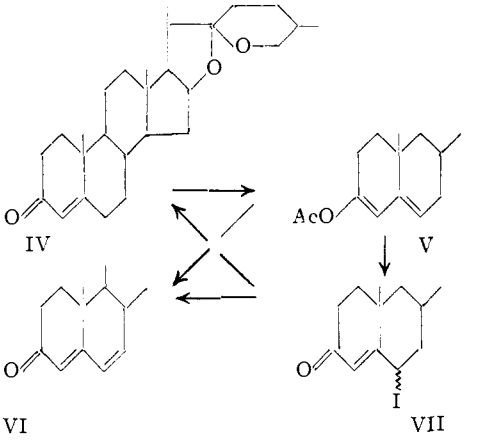
(3) C. Djerassi and C. T. Lenk, THIS JOURNAL, **75**, 3493 (1953).



I II III

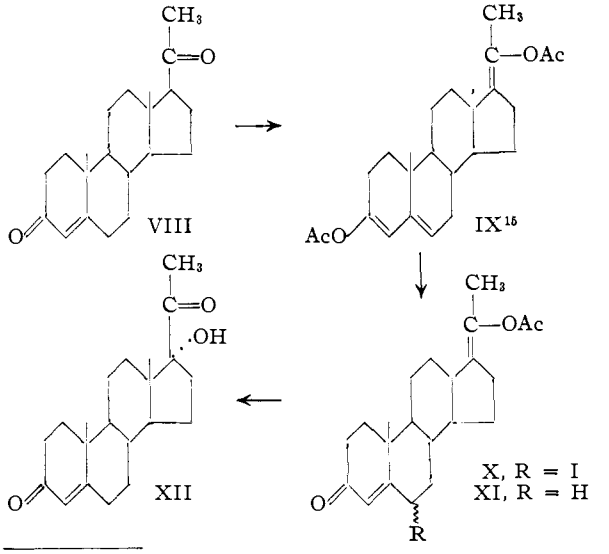
In order to examine further the scope of this reaction, we have investigated the behavior of an enol acetate (V) of a typical Δ^4-3-ketosteroid such as Δ^4-22a,25a-spirosten-3-one[4] (Δ^4-diosgenone)[5] (IV) with N-iodosuccinimide. When the enol acetate V was treated with NIS in the standard manner,[3] *i.e.* heating in dioxane solution for *ca.* 45 minutes, there was isolated in poor yield $\Delta^{4,6}$-22a,25a-spirostadien-3-one (VI).[6,7] In contrast to the earlier studied enol acetates[8] where essentially no reaction was observed at room temperature, the present example readily underwent reaction at room temperature, to produce in good yield an iodine-containing product which proved to be Δ^4-6ζ-iodo-22a,25a-spirosten-3-one (VII). That the iodine atom was not substituted at C-23 was demonstrated by the ease with which it could be removed with reagents such as sodium bisulfite (preferred), sodium iodide or chromous chloride and by the ultraviolet absorption maximum at 248 mμ (as compared to 242 mμ for the starting ketone IV). Such a bathochromic shift already has been observed earlier with 6-bromo-Δ^4-3-ketones.[8] Attempts to replace the 6-iodine atom by acetate with or without rearrangement[9] failed to yield any pure product, but treatment with 2,4-dinitrophenylhydrazine[10,11] or semicarbazide[11,12] resulted in dehydroiodination[13] and formation of the 2,4-dinitrophenylhydrazone or semicarbazone of the $\Delta^{4,6}$-dien-3-one.[6]

The above model experiments clearly illustrate that there exists a considerable difference in the reactivity of enol acetates of saturated[8] and unsaturated ketones toward N-iodosuccinimide and this encouraged us to examine a polyfunctional example in order to determine whether the ready reaction of unsaturated enol acetates could be used to synthetic advantage. While the optimum conditions have not been determined, the feasibility of such a procedure is exemplified below for the conversion of progesterone (VIII) to 17α-hydroxyprogesterone (XII).



IV V VI VII

The simplest procedure for the introduction of the important 17α-hydroxy group into 20-keto-steroids is that of Kritchevsky and Gallagher[14] which involves conversion to the $\Delta^{17(20)}$-enol acetate, epoxidation with peracid and brief treatment with base. In order to utilize this method in the synthesis of adrenal hormones possessing also the Δ^4-3-keto grouping so essential for biological activity, the 17α-hydroxyl group has to be introduced *prior* to elaboration of the Δ^4-3-keto moiety since no methods are available at the present time whereby an enol acetate can be formed selectively with a 20-keto function in the presence of the unsaturated ketone grouping in ring A. By the use of the NIS–enol acetate reaction, it has been possible now to reverse the order of these steps and to introduce the 17α-hydroxy substituent into a steroid which already contains the requisite unsaturated ketone system in ring A.



VIII IX[15] XII X, R = I XI, R = H

(4) For a slight revision of the sapogenin nomenclature, see C. Djerassi and J. Fishman, THIS JOURNAL, **77**, Aug. 5 (1955).

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

(6) R. Marker and D. L. Turner, *ibid.*, **63**, 771 (1941).

(7) J. Romo, H. J. Ringold, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 1873 (1951).

(8) *Cf.* C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, THIS JOURNAL, **72**, 4534 (1950).

(9) Acetolysis of 6-bromo-Δ^4-3-ketosteroids with potassium acetate leads to the rearranged 2α-acetoxy-Δ^4-3-ketone (F. Sondheimer, St. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *ibid.*, **75**, 4712 (1953); L. F. Fieser and M. A. Romero, *ibid.*, **75**, 4716 (1953); J. Herran, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 5531 (1954)).

(10) V. R. Mattox and E. C. Kendall, *ibid.*, **70**, 882 (1948).

(11) C. Djerassi, *ibid.*, **71**, 1003 (1949).

(12) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952).

(13) In order to show that dehydroiodination of α-iodoketones with 2,4-dinitrophenylhydrazine proceeds in the same manner as reported (ref. 10, 11) for analogous bromo derivatives, 2-iodocholestan-3-one (G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, *ibid.*, **72**, 4077 (1950)) was treated with this reagent and afforded smoothly the known (ref. 11) Δ^1-cholesten-3-one 2,4-dinitrophenylhydrazone.

(14) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949), and later papers.

(15) The isomeric di-enol acetate, $\Delta^{3,5,20}$-pregnatriene-3,20-diol diacetate already has been prepared by R. B. Moffett and D. I. Weisblat (THIS JOURNAL, **74**, 2183 (1952)). The product of the acetic anhydride–acetyl chloride reaction is apparently the 3-mono-enol acetate (U. Westphal, *Ber.*, **70**, 2128 (1937); L. Ruzicka and W. H. Fischer, U. S. Patent 2,248,438 (1941)).

Progesterone (VIII), the most readily available steroid hormone, was transformed into its dienol acetate IX ($\Delta^{3,5,17(20)}$-pregnatriene-3,20-diol diacetate)[15] and then treated at room temperature with NIS. The resulting 6-iodo-Δ^4-3-ketone (X) still retained the enol acetate grouping in the side chain as demonstrated by its infrared spectrum ($\lambda_{max}^{CHCl_3}$ 5.76 and 8.25 μ in addition to the 6.0 μ band) and by the mild reduction with sodium bisulfite which furnished the previously unknown crystalline 20-monoenol acetate (XI) of progesterone. The structure of this enol acetate XI was clearly defined by the spectral, rotatory and analytical data and by its conversion to 17α-hydroxyprogesterone (XII) with perbenzoic acid followed by warming with alkali.

Experimental[16]

$\Delta^{3,5}$-22a,25a-Spirostadien-3-ol Acetate (V).—A solution of 5.0 g. of Δ^4-diosgenone (IV)[8] was refluxed for 1.5 hours with 15 cc. of acetic anhydride and 15 cc. of acetyl chloride and most of the solvent was removed *in vacuo*. The precipitated solid was filtered and recrystallized from methanol–benzene; yield 3.5 g., m.p. 173–174°, $[\alpha]D$ −164°, λ_{max}^{EtOH} 235 mμ, log ϵ 4.20; $\lambda_{max}^{CS_2}$ 5.70 and 8.25 μ.

Anal. Calcd. for $C_{29}H_{42}O_4$: C, 76.61; H, 9.31. Found: C, 76.49; H, 9.33.

Reaction of $\Delta^{3,5}$-22a,25a-Spirostadien-3-ol Acetate with N-Iodosuccinimide. (a) At Room Temperature.—N-Iodosuccinimide[3] (2.0 g., Arapahoe Chemicals, Boulder, Colo.) was added to a solution of 2.0 g. of the above enol acetate V in 20 cc. of dioxane and after slight warming to ensure that all of the reagent had dissolved, the vessel was left at room temperature in the dark for 24 hours. Potassium iodide solution was added to the dark brown colored reaction mixture followed by 10% sodium thiosulfate solution and ice. The precipitated **6-iodo-Δ^4-22a,25a-spirosten-3-one (VII)** was collected and recrystallized from methanol–acetone; yield 1.51 g., m.p. 126–128°, $[\alpha]D$ −94°; λ_{max}^{EtOH} 248 mμ, log ϵ 4.08; $\lambda_{max}^{CHCl_3}$ 6.00 μ.

Anal. Calcd. for $C_{27}H_{39}IO_3$: C, 60.22; H, 7.30. Found: C, 60.63; H, 7.45.

(b) At 90°.—Equal amounts (0.5 g.) of the enol acetate V and NIS were heated in 2 cc. of dioxane for 45 minutes at 90° and the reaction mixture processed as described under (a). The crude product was chromatographed on 20 g. of alumina and elution with benzene–ether (9:1) followed by crystallization from acetone–ethanol yielded 0.05 g. of **$\Delta^{4,6}$-22a,25a-spirostadien-3-one (VI)**, m.p. 199–204°, undepressed upon admixture with authentic material,[6,7] λ_{max}^{EtOH} 285 mμ, log ϵ 4.36.

Reactions of 6-Iodo-Δ^4-22a,25a-spirosten-3-one (VII). (a) With Sodium Bisulfite.—A solution of the 6-iodo-Δ^4-3-ketone VII (0.3 g.) in 30 cc. of chloroform was shaken for 30 minutes with 50 cc. of a 10% solution of sodium bisulfite at which time no more color developed in the organic layer. Washing with water, drying and evaporation gave a quantitative yield of solid (m.p. 162–172°) which showed a negative Beilstein test. Recrystallization from acetone–ethanol furnished 0.15 g. of pure Δ^4-diosgenone (IV), m.p. 184–186°, $[\alpha]D$ −10°, λ_{max}^{EtOH} 242 mμ, log ϵ 4.20; identity with authentic material was established by mixture melting point and infrared comparison.

(b) With Sodium Iodide.—After refluxing 0.3 g. of iodo ketone VII with 0.5 g. of sodium iodide in 10 cc. of acetone for 12 hours, the solution was diluted with water containing some sodium thiosulfate and extracted with ether. The crude product (0.24 g.) showed the presence of a small amount of $\Delta^{4,6}$-dien-3-one (λ_{max}^{EtOH} 284 mμ, log ϵ 3.85) which could be removed only by chromatography whereupon 0.07 g. of Δ^4-diosgenone (IV), m.p. 183–186°, λ_{max}^{EtOH} 242 mμ, log ϵ 4.18, was isolated.

(c) With Chromous Chloride.—Reduction of 2 g. of the 6-iodo ketone in acetone solution for 10 minutes with chromous chloride, prepared[17] from 10 g. of chromic chloride, and chromatography of the crude product yielded 1.18 g. of a mixture of Δ^4-(IV) and $\Delta^{4,6}$-3-ketone VI, m.p. 178–179°. Recrystallization from acetone–ethanol raised the m.p. to 187–191° without, however, effecting a separation (λ_{max}^{EtOH} 242 and 284 mμ, log ϵ 4.13 and 4.15).

(d) With Semicarbazide.—A mixture of 0.5 g. of iodo ketone, 0.48 g. of semicarbazide hydrochloride, 0.48 g. of sodium acetate and 125 cc. of glacial acetic acid was kept for 2 hours at 70° under nitrogen, 7 cc. of pyruvic acid and 14 cc. of water were added and the mixture maintained for an additional 2 hours at that temperature. The product was extracted with ethyl acetate, washed thoroughly with dilute alkali and purified by chromatography and recrystallization from ethanol–acetone; yield 0.15 g., m.p. 205–208°, undepressed on admixture with authentic $\Delta^{4,6}$-dien-3-one (VI),[7] λ_{max}^{EtOH} 284 mμ, log ϵ 4.45.

(e) With 2,4-Dinitrophenylhydrazine.—To a hot solution of 0.2 g. of iodo ketone in 5 cc. of glacial acetic acid was added 0.1 g. of 2,4-dinitrophenylhydrazine and heating (*ca.* 100°) continued for 3–4 minutes. The solution was cooled, the bright red dinitrophenylhydrazone of the $\Delta^{4,6}$-dien-3-one VI was filtered and recrystallized from ethanol–chloroform; yield 0.15 g., m.p. 263–268°, undepressed when mixed with a sample of hydrazone prepared from VI, typical[18] ultraviolet absorption maxima (chloroform) at 310 and 404 mμ, log ϵ 4.17 and 4.56.

Anal. Calcd. for $C_{33}H_{42}N_4O_6$: C, 67.09; H, 7.17; N, 9.49. Found: C, 67.02; H, 7.21; N, 9.06.

Reaction of 2-Iodocholestan-3-one with 2,4-Dinitrophenylhydrazine.[19]—A solution of 0.5 g. of 2-iodocholestanone[13] in 20 cc. of acetic acid was treated with 0.225 g. of 2,4-dinitrophenylhydrazine in the above described manner to yield 0.51 g. of Δ^1-cholesten-3-one 2,4-dinitrophenylhydrazone, m.p. 219–221°, $\lambda_{max}^{CHCl_3}$ 381 mμ, log ϵ 4.41; identity with an authentic specimen[11] was established in the usual manner.

$\Delta^{3,5,17(20)}$-Pregnatriene-3,20-diol Diacetate (IX).—A solution of 10 g. of progesterone (VIII), kindly supplied by Syntex, S.A., Mexico City, in 50 cc. of isopropenyl acetate was refluxed with 0.05 cc. of concd. sulfuric acid, concentrated to one-half of the original volume and then diluted with ether. The crude product, obtained after evaporation of the washed and dried ether solution, was heated for 2 hours with 60 cc. of acetic anhydride and 0.5 g. of *p*-toluenesulfonic acid,[20] 30 cc. of solvent being collected during that period. After addition of ice and ether, the solution was processed in the usual manner and the crude product was purified by passage in benzene–hexane solution through a column of 80 g. of ethyl acetate-washed alumina. Crystallization from methanol furnished 6.3 g. of the enol acetate, m.p. 126–131°, suitable for the next step. The analytical sample exhibited the following constants: m.p. 138–140°, $[\alpha]D$ −151°, λ_{max}^{EtOH} 235 mμ, log ϵ 4.23, $\lambda_{max}^{CS_2}$ 5.70 and 8.2 μ.

Anal. Calcd. for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.13; H, 8.67.

The enol acetate was recovered unchanged (infrared spectrum) when shaken in methylene dichloride solution for 3 hours with 10% sodium bisulfite solution. It was important to demonstrate this stability since such treatment is required in the next step.

$\Delta^{4,17(20)}$-Pregnadien-20-ol-3-one 20-Acetate (Progesterone 20-Monoenol Acetate) (XI).—The above dienol acetate (IX) (0.63 g.) in 7 cc. of dioxane was treated in the usual manner (V → VII) with 0.44 g. of NIS for 24 hours at room temperature. The crude product,[21] dissolved in methylene dichloride, was shaken for 2 hours with 50 cc. of 10% sodium bisulfite solution, washed with water, dried, evaporated and

(16) Melting points are uncorrected. Unless noted otherwise, rotations and infrared spectra (Baird double beam recording spectrophotometer using 0.1-mm. cells) were measured in chloroform solution. The microanalyses were carried out by Geller Laboratories, Hackensack, N. J.

(17) See p. 4080 of ref. 13.

(18) C. Djerassi and E. Ryan, THIS JOURNAL, **71**, 1000 (1949).

(19) This experiment was carried out by Dr. J. J. Beereboom.

(20) As demonstrated by H. Vanderhaeghe, E. R. Katzenellenbogen, K. Dobriner and T. F. Gallagher (THIS JOURNAL, **74**, 2810 (1952)), such treatment will convert any Δ^{20}-enol acetate into the $\Delta^{17(20)}$-isomer.

(21) The spectral data of the crude compound (m.p. 80–87°, found: I, 22.53; calcd.; I, 26.34) are consistent with the 6-iodo structure (X), λ_{CHCl_3} 5.76, 6.00 and 8.25 μ.

chromatographed on 15 g. of ethyl acetate-washed alumina; yield 0.21 g., m.p. 165–170°. The analytical sample was recrystallized from methanol; m.p. 170–171°, $[\alpha]_D$ +100°, λ_{max}^{EtOH} 240 mμ, log ε 4.18; $\lambda_{max}^{CS_2}$ 5.72, 5.98 and 8.2 μ.

Anal. Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.67; H, 8.95.

17α-Hydroxyprogesterone (XII).—A sample (150 mg.) of the monoenol acetate XI in 5 cc. of chloroform was treated at 0° with 30 cc. of 0.1 *N* perbenzoic acid (in chloroform) and left for 3 hours at room temperature. After washing with dilute sodium hydroxide and water, the solvent was removed and the residue was warmed on the steam-bath for 3 minutes with 2 cc. of 4% methanolic potassium hydroxide. Dilution with water and extraction with ether furnished 125 mg. of crude product which was chromatographed on 5 g. of ethyl acetate-washed alumina and recrystallized from methanol; yield 55 mg., m.p. 218–220°, $[\alpha]_D$ +100°. The identity of this substance with 17α-hydroxyprogesterone synthesized by an alternate procedure[22] was established by infrared comparison and mixture melting point determination.

(22) G. Rosenkranz, J. Pataki, St. Kaufmann, J. Berlin and C Djerassi, THIS JOURNAL, **72**, 4081 (1950).

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Digitogenin

BY DONALD L. KLASS, MARY FIESER AND LOUIS F. FIESER

RECEIVED JANUARY 24, 1955

Digitogenin has been related directly to gitogenin by elimination of the most hindered hydroxyl group. Gitogenin has been shown to be 22a,5α-spirostane-2α,3β-diol by a partial synthesis through the 2β,3β-diol. Evidence for the location of the third hydroxyl in digitogenin at C_{15} is presented; this group probably has the β-configuration. A new sapogenin, the normal isomer of digitogenin, has been isolated from a commercial preparation of digitonin.

When this work was initiated, more than two years ago, digitogenin (Ia) was tentatively regarded as a 5α,22a-spirostane-2,3,15-triol,[1] but only the position (but not configuration) of the 2,3-glycol group was known with reasonable certainty from an indirect correlation of digitogenin with gitogenin, 5α,22a-spirostane-2,3-diol.[2] The third hydroxyl group was shown to be adjacent to an asymmetric center bearing a hydrogen atom and was originally placed at C_6,[3] and then at C_{15},[4] mainly on the basis of exclusion evidence.[5]

We have achieved a direct conversion of digitogenin into gitogenin in the following way. On treatment with ethyl chloroformate in dioxane–pyridine the 2,3-dicathylate (Ib) is obtained in good yield.[6] Oxidation with sodium dichromate gives a keto dicathylate II, which forms a 2,4-dinitrophenylhydrazone without difficulty, but which is reduced by the Huang-Minlon modification of the Wolff–Kishner reaction in very low yield (4%). The carbonyl group is eliminated, however, without difficulty by desulfuration of the ethylenethioketal, and the product is the dicathylate of gitogenin (IIIb), from which the free diol is obtained on hydrolysis.

In the meantime the probable structure of gitogenin has been shown to be 22a,5α-spirostane-2α,-3β-diol (IIIa) by a partial synthesis[7] involving a sequence of reactions for which the stereochemistry has been established in the cholesterol series[8] and by non-identity with the 2α,3α-diol and the 2β,3α-diol, prepared a few years ago by partial synthesis.[9] We have prepared the fourth possible isomer, the 2β,3β-diol, by *cis*-hydroxylation of Δ²-22a,5α-spirostene (IV)[9] with silver acetate, iodine and moist acetic acid.[10] Although two products are possible, only one diol could be isolated from the reaction (57% yield), and since it differs from the 2α,3α-diol, it is evidently the 2β,3β-diol. As expected, it forms an acetonide, which also differs from the acetonide of the 2α,2α-diol, and it is readily oxidized to gitogenic acid.[11] When the 2β,3β-diol is heated with sodium ethoxide in a sealed tube at 180°, the 2β-hydroxyl group (axial) rearranges to the more stable 2α-configuration (equatorial) with formation of gitogenin. The identity was established by mixed melting point and infrared comparisons. However, gitogenin prepared by this partial synthesis or from digitogenin (above) does not give a purple color with concentrated sulfuric acid, a test which is said to be characteristic for this sapogenin.[7,9] The color reaction probably is due to an impurity,[12] since gitogenin isolated from *Digitalis purpurea*[13] gives only light yellow to colorless solutions in the reagent.

Further evidence that the 2- and 3-hydroxyl groups of digitogenin are *trans* to each other is that the sapogenin is not dehydrated on sublimation

(1) Nomenclature: *Chem. Ind.*, June 23, 1951, SN 1.

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

(3) R. Tschesche and A. Hagedorn, *ibid.*, **69**, 797 (1936).

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

(5) For reviews of early literature see Elsevier's "Encyclopaedia of Organic Chemistry," Vol. 14, Series III, 1940, p. 286; L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Chapt. VIII, Reinhold Publ. Corp., New York, N. Y., 1949.

(6) Acetylation with acetic anhydride and sodium acetate (reflux temperature) gives a mixture of di- and triacetates, from which only the latter has been obtained pure [A. Windaus and K. Weil, *Z. physiol. Chem.*, **121**, 62 (1922)]. The diacetate is formed on treatment with warm acetic anhydride and pyridine [H. B. MacPhillamy, THIS JOURNAL, **62**, 3518 (1940)].

(7) J. Herran, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 5531 (1954).

(8) L. F. Fieser and M. A. Romero, *ibid.*, **75**, 4716 (1953).

(9) J. Pataki, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 5375 (1951).

(10) For examples of this method see D. Ginsburg, *ibid.*, **75**, 5746 (1953), and L. B. Barkley, *et al.*, *ibid.*, **76**, 5014 (1954).

(11) Our diol differs from a diol assigned the 2β,3β-configuration by J. Herran, *et al.*[7] However, the method used in this other partial synthesis could well lead to mixtures and the only evidence presented for the presumed structure is oxidation to gitogenic acid and non-identity with the other possible 2,3-diols. The rate of oxidation with lead tetraacetate has been reported [C. Djerassi and R. Ehrlich, *J. Org. Chem.*, **19**, 1351 (1954)].

(12) Possibly Δ⁴-yuccagenin (personal communication of Dr. F. Sondheimer).

(13) We are indebted to Dr. W. A. Jacobs, Rockefeller Institute, for this material.