[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

The Conversion of Diosgenin to Cortisone *via* 11-Ketosteroids of the 5β-Series

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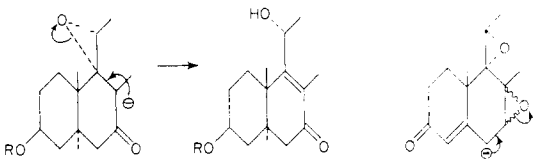
7ξ,8ξ,9α,11α-Diepoxy-Δ⁴-22a-spirosten-3-one (III), available in seven steps from diosgenin, has been converted by base-catalyzed rearrangement followed by hydrogenation to 9α,11α-epoxy-22a,5β-spirostan-8ξ-ol-3-one (V). Dehydration and rearrangement of V was accomplished in one step by means of boron trifluoride to yield the Δ⁸-3,11-dione (VI) and this was transformed by successive reductions with lithium in liquid ammonia and then sodium borohydride to the known cortisone intermediate 22a,5β-spirostan-3α-ol-11-one (VIIb).

All of the present commercial syntheses of cortisone, starting from either bile acids or microbiological transformation products, employ intermediates of the 5β (rings A/B *cis*) series,[2] thus facilitating greatly the ultimate introduction of the requisite Δ⁴-3-keto moiety. Of the many partial, chemical syntheses of cortisone from ring C unsubstituted steroids,[3] all but one involve intermediates of the less desirable 5α (rings A/B *trans*) configuration and thus require a more complicated procedure for the introduction of the Δ⁴-3-keto grouping.[2,3] The one exception,[4] utilizing 5β-steroids, consists in the application of the Fieser dichromate oxidation[5] to Δ^7,9(11)-22a,5β-spirostadien-3α-ol acetate.[6] An elegant device for the eventual introduction of the Δ⁴-3-keto grouping has been reported by the Manchester group[7] in that all reactions are carried out with 5α-hydroxy steroids, the 4,5-double bond being formed in the last step by dehydration rather that by conventional bromination–dehydrobromination. We are now presenting a reaction sequence which, starting with 5α-hydroxy sapogenins, proceeds through 11-oxygenated intermediates with the desirable 5β-configuration and which for the first time utilizes a 7,8;9,11-diepoxide. Such diepoxides have been isolated earlier,[8] but no synthetic applications have been recorded for them.

The seven-step conversion of diosgenin acetate (I) *via* the peroxide II to 7ξ,8ξ;9α,11α-diepoxy-Δ⁴-22a-spirosten-3-one (III) has been described recently.[9] Since the latter contains a vinylogous epoxy-ketone grouping, it was anticipated by analogy to the base-catalyzed rearrangement[10,11] of 9α,11α-epoxy-7-ketones to Δ⁸-11α-hydroxy-7-ketones (A → B) that similar treatment (C) would produce the corresponding 9α,11α-epoxy-Δ^4,6-dien-8ξ-ol-3-one (IV) and this indeed proved to be the case.



The rearrangement product IV possessed the typical[12] ultraviolet absorption maximum at 278 mμ and upon catalytic hydrogenation consumed two equivalents of hydrogen with formation of the corresponding tetrahydro derivative V. Since the catalytic hydrogenation of Δ^4,6-dien-3-ones proceeds essentially in the same manner[13] as that of the simple Δ⁴-en-3-one and since the presence of 11α-substituents is known to favor formation of reduction products with the 5β-configuration,[14] it was not unexpected that the hydrogenation proceeded in a uniform manner yielding a single isomer which by its subsequent transformations was shown to possess the desired 5β-configuration V. Dehydration *cum* rearrangement[15] was accomplished by short treatment (two minutes) with boron trifluoride in benzene solution furnishing Δ⁸-22a,5β-spirostene-3,11-dione (VI). For comparison purposes, an authentic sample of the corresponding 5α-isomer, Δ⁸-22a,5α-spirostene-3,11-dione (IX) was prepared by oxidation of the known[16] Δ⁸-22a, 5α-spirosten-3β-ol-11-one and it is pertinent to mention that this 5α-isomer IX was the predominant product in the catalytic hydrogenation of Δ^4,8-22a-spirostadiene-3,11-dione (VIII).[9] This represents a further example of the strong directing

(1) Syntex Postdoctorate Research Fellow, 1953-1954.

(2) *Cf.* C. Djerassi in "Vitamins and Hormones," Vol. XI, Academic Press, Inc., New York, N. Y., 1953, pp. 205–238; G. Rosenkranz and F. Sondheimer in "Fortschritte der Chemie Org. Naturstoffe," Vol. X, Springer Verlag, Vienna, 1953, pp. 274–389.

(3) *Cf.* C. Djerassi and G. Rosenkranz in "Ciba Foundation Colloquia on Endocrinology," Vol. VII, Churchill Ltd., London, 1953, pp. 79–95; G. Rosenkranz, F. Sondheimer, O. Mancera, J. Pataki, J. H. Ringold, J. Romo, C. Djerassi and G. Stork in "Recent Progress in Hormone Research," Vol. VIII, Academic Press, Inc., New York, N. Y., 1953, pp. 1–25.

(4) G. Rosenkranz, M. Velasco, C. Djerassi and F. Sondheimer, THIS JOURNAL, **75**, 4430 (1953).

(5) L. F. Fieser, J. E. Herz and W. Huang, *ibid.*, **73**, 2397 (1951); L. F. Fieser, W. Huang and J. C. Babcock, *ibid.*, **75**, 116 (1953).

(6) R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 4654 (1951).

(7) P. Bladon, H. B. Henbest, E. R. H. Jones, B. J. Lovell and G. F. Woods, *J. Chem. Soc.*, 125 (1954).

(8) (a) P. Bladon, H. B. Henbest, E. R. H. Jones, G. W. Wood, D. C. Eaton and A. A. Wagland, *ibid.*, 2916 (1953); (b) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **75**, 3477 (1953).

(9) C. Djerassi, A. J. Lemin, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2346 (1954).

(10) G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951); C. Djerassi, O. Mancera, J. Romo and G. Rosenkranz, *ibid.*, **75**, 3505 (1953).

(11) C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, *ibid.*, **74**, 1712 (1952).

(12) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

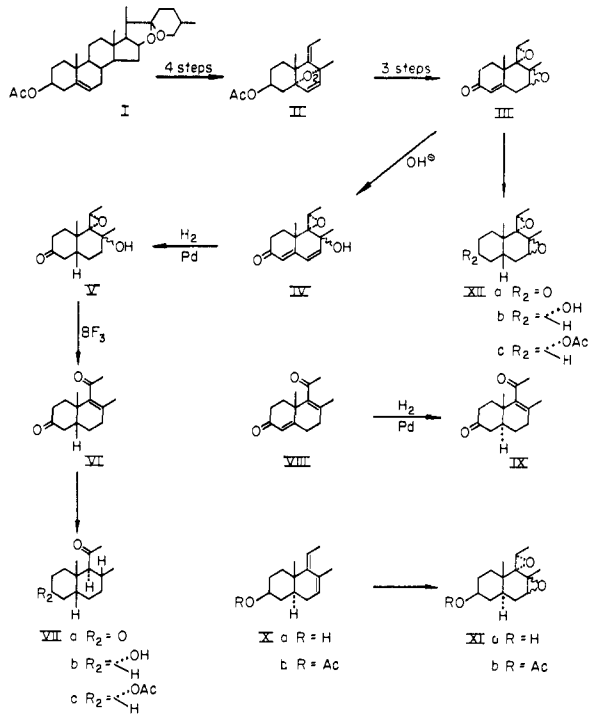
(13) C. Djerassi, R. Yashin and G. Rosenkranz, THIS JOURNAL, **74**, 422 (1952).

(14) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 3711 (1952); O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, **75**, 1286 (1953).

(15) An unsuccessful attempt to carry out a similar reaction sequence with a 9α,11α-epoxy-8α-hydroxysteroid bearing also a 5α-hydroxy substituent has been recorded by H. H. Inhoffen and W. Mengel (*Ber.*, **87**, 146 (1954)).

(16) C. Djerassi, W. Frick, G. Rosenkranz and F. Sondheimer, THIS JOURNAL, **75**, 3496 (1953).

influence of an 11-keto group toward 5α-hydrogenation in such Δ^4-3-ketones.[17]



Stereospecific reduction of the 8,9-double bond of VI was accomplished by the standard lithium–ammonia procedure[18] and the resulting saturated 3,11-dione (VIIa) was selectively reduced[14] at C-3 with sodium borohydride yielding 22a,5β-spirostan-3α-ol-11-one (VIIa) and upon acetylation the derived acetate VIIc. The further transformations of the acetate VIIc to cortisone have already been recorded.[4,19]

In connection with the above described hydrogenations (IV → V; VIII → IX) there was also examined the behavior of the starting diepoxide (III) under these conditions. The principal reduction product was again the 5β-isomer, 7ξ,8ξ;9α,11α-diepoxy-22a,5β-spirostan-3-one (XIIa), which was reduced further with sodium borohydride to the corresponding 3α-alcohol. To support these structure assignments an authentic sample of the isomeric 7ξ,8ξ;9α,11α-diepoxy-22a,5α-spirostan-3β-ol (XIa) was prepared by treatment of $\Delta^{7,9(11)}$-22a,5α-spirostadien-3β-ol (Xa)[20] with excess monoperphthalic acid; the two products (XIIb and XIa) as well as their acetates (XIIc and XIb) were completely different.

Acknowledgment.—We are grateful to Syntex S. A., Mexico City, for a generous gift of certain steroid intermediates.

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

(20) G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1950).

Experimental[21]

9α,11α-Epoxy-$\Delta^{4,6}$-22a-spirostadien-8ξ-ol-3-one (IV).—A mixture of 0.18 g. of 7ξ,8ξ;9α,11α-diepoxy-Δ^4-22a-spirosten-3-one (III),[9] 30 cc. of 95% ethanol, 0.016 g. of potassium hydroxide and 2 cc. of water was allowed to stand at room temperature for 50 minutes, the course of the rearrangement being followed spectrophotometrically. Dilution with water, extraction with ether, washing and evaporation furnished in quantitative yield a colorless solid with m.p. 155–157°. Recrystallization from ether gave plates with m.p. 157–159° while recrystallization from acetone–hexane yielded needles, m.p. 199–201°. The analytical sample, obtained from the latter pair of solvents, exhibited the constants: m.p. 201–202°, $[\alpha]^{25}D$ +345°, λ_{max}^{EtOH} 278 mμ, log ε 4.34, $\lambda_{max}^{CHCl_3}$ 6.0 μ.

Anal. Calcd. for $C_{27}H_{36}O_5$: C, 73.60; H, 8.24. Found: C, 73.70; H, 8.23.

9α,11α-Epoxy-22a,5β-spirostan-8ξ-ol-3-one (V).—A solution of 0.4 g. of the above dienone IV in 40 cc. of ethyl acetate was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure with 0.4 g. of 10% palladized charcoal catalyst for 1.5 hours at which time the hydrogen consumption corresponded to *ca.* 2.2 equivalents. Filtration of the catalyst and evaporation to dryness gave 0.39 g. of crystals with m.p. 191–194°. Recrystallization from methanol raised the m.p. to 197–199°, $\lambda_{max}^{CHCl_3}$ 2.90 and 5.88 μ.

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.44; H, 9.05.

Δ^8-22a,5β-Spirostene-3,11-dione (VI).—To a solution of 0.2 g. of the saturated hydroxy-keto epoxide V in 50 cc. of benzene, dried by distilling 10 cc., was added 0.2 g. of boron trifluoride etherate in 8 cc. of benzene and the mixture was refluxed for 2 minutes. Addition of water, extraction with ether and evaporation gave 0.19 g. of a yellow oil which was chromatographed on 10 g. of neutral alumina (activity I). Elution with benzene–ether (9:1) followed by crystallization from methanol produced 0.04 g. of colorless crystals with m.p. 190–191°, $[\alpha]^{25}D$ +48°, λ_{max}^{EtOH} 252 mμ, log ξ 3.95, $\lambda_{max}^{CHCl_3}$ 5.89 and 6.0 μ.

Anal. Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 76.18; H, 8.94.

22a,5β-Spirostane-3,11-dione (VIIa).—To a stirred solution of 0.3 g. of lithium in 180 cc. of liquid ammonia at −40° was added 0.69 g. of the unsaturated dione VI dissolved in 70 cc. of dry ether. After 10 minutes the blue color disappeared whereupon 5 g. of ammonium chloride was added and the solution was allowed to warm to room temperature. Ether was added, the solution was washed well with water, dried, evaporated and the residue in 30 cc. of acetone was oxidized directly with 4 cc. of a stock solution containing 66.6 g. of chromium trioxide, 25 cc. of sulfuric acid and 225 cc. of water. After standing at room temperature for 30 minutes, water was added and the solution was processed in the customary manner by ether extraction; yield 0.51 g., m.p. 195–199°. Recrystallization from methanol yielded colorless crystals with m.p. 204–206°, $[\alpha]^{25}D$ −22°, $\lambda_{max}^{CHCl_3}$ 5.86 μ.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.67; 9.51.

22a,5β-Spirostan-3α-ol-11-one (VIIb).—A solution of 0.1 g. of the saturated diketone VIIa in 10 cc. of pyridine was treated with 0.05 g. of sodium borohydride, dissolved in 5 cc. of pyridine and 0.1 cc. of water and allowed to stand at room temperature for 5 hours. Acidification with dilute hydrochloric acid, extraction with ether, washing, drying and evaporation furnished 0.08 g. of crystalline material with m.p. 189–193° which on recrystallization from ether–hexane produced the analytical sample with m.p. 192–194°, $[\alpha]^{25}D$ −33°, $\lambda_{max}^{CHCl_3}$ 5.89 μ.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.31; H, 9.83. Found: C, 75.07; H, 9.68.

(21) Melting points are corrected (Kofler block). Rotations and infrared spectra (Baird Associates recording double beam infrared spectrophotometer, 0.1 mm. cells) were measured in chloroform solution. The microanalyses were carried out by Geller Laboratories, Hackensack, New Jersey.

The acetate VIIc, after recrystallization from ether–hexane, possessed m.p. 184–186° undepressed upon admixture with an authentic sample,[4] $[\alpha]^{25}D$ +6°, $\lambda_{max}^{CHCl_3}$ 5.78 and 5.89 μ; identity was confirmed by infrared comparison.

Anal. Calcd. for $C_{29}H_{44}O_5$: C, 73.69; H, 9.38. Found: C, 73.95; H, 9.55.

Δ^8-22a,5α-Spirostane-3,11-dione (IX). (a) **By Hydrogenation of $\Delta^{4,8}$-22a-Spirostadiene-3,11-dione (VIII).**—The catalytic hydrogenation of 0.18 g. of the diene–dione VIII[9] was carried out exactly as described above for IV and resulted in the uptake of 1.1 equivalents of hydrogen after 1 hour. The crude crystalline material (0.18 g.) exhibited m.p. 190–195° and was chromatographed on 30 g. of neutral alumina (activity III). Elution with benzene–ether (9:1) and recrystallization from methanol gave needles, m.p. 210–212°, $[\alpha]^{25}D$ + 79°, λ_{max}^{EtOH} 253 mμ, log ϵ 3.97, $\lambda_{max}^{CHCl_3}$ 5.88 and 6.0 μ.

Anal. Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 76.06; H, 8.91.

(b) **By Oxidation of Δ^8-22a,5α-Spirosten-3β-ol-11-one.**—This unsaturated keto alcohol (0.2 g.)[16] in 20 cc. of pyridine was oxidized with 0.2 g. of chromium trioxide in 20 cc. of pyridine for 14 hours at room temperature. Dilution with water, followed by extraction with ether, washing with dilute acid and water, drying, evaporation and recrystallization from methanol furnished the dione IX with m.p. 209–212°, undepressed when mixed with a sample prepared according to (a); the infrared curves of the two samples were superimposable.

7ξ,8ξ;9α,11α-Diepoxy-22a,5β-Spirostan-3-one (XIIa).—The catalytic hydrogenation of 0.5 g. of the unsaturated diepoxide III[9] in 30 cc. of ethyl acetate was carried out in the standard manner with 10% palladized charcoal catalyst. The crude product (0.5 g., m.p. 224–228°) was chromatographed on 50 g. of neutral alumina (activity III) and the benzene–ether eluates were recrystallized from methanol; needles, m.p. 228–230°, $[\alpha]^{25}D$ −30°, $\lambda_{max}^{CHCl_3}$ 5.89 μ.

Anal. Calcd. for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65. Found: C, 73.37; H, 8.70.

7ξ,8ξ;9α,11α-Diepoxy-22a,5β-spirostan-3α-ol (XIIb).—The above diepoxy ketone XIIa (0.2 g.) in 15 cc. of methanol was reduced for 20 minutes at room temperature with 0.03 g. of sodium borohydride dissolved in 4 cc. of methanol and 0.5 cc. of water. The crude product (0.19 g., m.p. 221–225°) was recrystallized from methanol; m.p. 228–231°, $[\alpha]^{25}D$ −37°, no carbonyl absorption in the infrared.

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.71; H, 9.14.

The acetate XIIc was recrystallized from methanol and exhibited m.p. 268–270°, $[\alpha]^{25}D$ −12°, $\lambda_{max}^{CHCl_3}$ 5.79 μ.

Anal. Calcd. for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.53; H, 8.79.

7ξ,8ξ;9α,11α-Diepoxy-22a,5α-Spirostan-3β-ol (XIa).—A solution of 1.0 g. of $\Delta^{7,9(11)}$-22a,5α-spirostadien-3β-ol (Xa)[20] in 50 cc. of chloroform was treated with an excess of an ethereal solution of monoperphthalic acid for 24 hours at room temperature. After washing with sodium bicarbonate and water, drying, evaporation and crystallization from chloroform–methanol, there was obtained 0.85 g. of the diepoxide XIa with m.p. 284–288°, $[\alpha]^{25}D$ −57°.

Anal. Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 73.07; H, 9.08.

The acetate XIb was recrystallized from methanol-chloroform whereupon it melted at 312–316°; reported[8b] for a sample prepared by epoxidation of the diene acetate Xb, m.p. 312–316°.

DETROIT 1, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL AND BIOLOGICAL RESEARCH SECTION, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

Steroidal Cyclic Ketals. X.[1] 16-Hydroxylated Steroids. I. The Preparation of 16α-Hydroxyprogesterone

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Reaction of Δ^5-pregnene-16α-benzyloxy-3β-ol-20-one acetate (II) with ethylene glycol (benzene, *p*-toluenesulfonic acid) gave the 20-ethylene ketal IIIb which on treatment with lithium–liquid ammonia–alcohol was converted into the 3β,16α-diol (IV). The 3-hydroxyl group of the latter could be preferentially oxidized to afford Δ^4-pregnene-16α-ol-3,20-dione 20-ethylene ketal (VI). Acid hydrolysis gave 16α-hydroxyprogesterone (VIIa). Proof of the non-rearrangement of the double bond on ketalization of a Δ^{16}-20-ketone also has been presented.

In the past few years a number of 16α-hydroxylated steroids have been isolated as metabolites from and pregnant mare's human urine.[2] The interest aroused has stimulated attempts to produce, synthetically, these compounds and also any possible metabolic precursors. The successful synthesis of Δ^4-pregnene-16α-ol-3,20-dione acetate (VIIb)[3] and Δ^4-pregnene-16α,21-diol-3,20-dione diacetate[4] and its enzymatic hydrolysis product has been reported. More recently, Cole and Julian[5] have described a procedure for the introduction of a 16α-hydroxyl group by an atypical opening of a 16α,17α-oxide by chromous salts. Δ^4-Pregnene-16α-ol-3,20-dione (VIIa) and Δ^4-pregnene-16α,21-diol-3,20-dione, among other compounds, were prepared successfully in this manner. It is interesting to note that both of these compounds have been prepared by microbiological hydroxylation of progesterone[6] and desoxycorticosterone,[7] respectively.

The purpose of the work described in this report was to investigate chemical methods which would give in a facile manner 16α-hydroxylated pregnene derivatives, and which would allow concomitantly complete control of the labile 16α-hydroxyl group. It seemed possible to utilize our experience with the protective ethylene ketal group[8] to accomplish this end. In particular, our efforts were directed to a synthesis of Δ^4-pregnene-16α-ol-3,20-dione (VIIa) as a desirable example.

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(3) H. Hirschmann, F. B. Hirschmann and J. W. Corcoran, *Federation Proc.*, **12**, 218 (1953).

(4) H. Hirschmann, F. B. Hirschmann and G. L. Farrel, THIS JOURNAL, **75**, 4862 (1953).

(5) W. Cole and P. L. Julian, *J. Org. Chem.*, **19**, 131 (1954).

(6) D. Perlman, E. Titus and J. Fried, THIS JOURNAL, **74**, 2126 (1952).

(7) E. Vischer, J. Schmidlin and A. Wettstein, *Helv. Chim. Acta*, **37**, 321 (1954).

(8) See ref. 1 and preceding papers.