[JOINT CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY AND THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

The Stereochemistry of the Catalytic Hydrogenation of Δ^8-11-Keto Steroids. Synthesis of 8-Iso- and 14-Iso-11-keto Sapogenins[1]

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As illustrated in the sapogenin series, a steroidal Δ^8-11-ketone is readily isomerized with base to the corresponding 14β-isomer with the C/D *cis* fusion. In contrast to *chemical* reduction with lithium in liquid ammonia, which furnishes the "normal" B/C *trans* (8β, 9α) saturated 11-ketone, catalytic hydrogenation in the 14α-series leads to the corresponding B/C *cis* isomer (8α, 9α). Arguments, based on conformational analysis, are presented to support the assignment of configuration. Similar reactions in the 14β-series lead to one B/C *trans* (8β, 9α) and one B/C *cis* (8α, 9α) derivative but it is pointed out that in the absence of a reference compound, a secure structure assignment, based on conformational analysis, cannot be made which would differentiate the *chemical* from the *catalytic* reduction product.

Heusser and co-workers[5] have shown that the mono-epoxide of $\Delta^{7,9(11),22}$-ergostatrien-3β-ol acetate (ergosterol D acetate) is smoothly rearranged in the presence of boron trifluoride to an α,β-unsaturated ketone, which is not identical with the known Δ^8-7-ketone[6] and which possesses a carbonyl group unreactive to ketonic reagents. On that basis, the alternate Δ^8-11-keto structure was proposed[5] for the boron trifluoride rearrangement product which in turn would require that the starting material was the Δ^7-9,11-oxide. Rigorous proof of the correctness of this assumption was recently provided by the observation in both the ergosterol[7] and diosgenin[7,8] series that the rearrangement product III of the mono-epoxide II can be reduced chemically with lithium metal in liquid ammonia to produce (in the sapogenin series) the known 22a-5α-spirostan-3β-ol-11-one (VI) thus opening an attractive alternate route to cortisone. It is the purpose of the present paper to report on some isomerization and *catalytic* hydrogenation experiments of such a Δ^8-11-ketone in the sapogenin series.

From an experimental viewpoint, the preparation of the requisite mono-epoxide proved more advantageous with the propionate ester and $\Delta^{7,9(11)}$ 22a-5α-spirostadien-3β-ol (Ia),[9] readily available from diosgenin, was first converted to the propionate Ib and then oxidized with monoperphthalic acid. The resulting epoxide II was rearranged smoothly in *ca.* 70% yield to the corresponding Δ^8-11-ketone IIIb which exhibited the typical ultraviolet absorption maximum at 252 mμ and whose infrared spectrum was fully compatible with the assigned structure. Mild saponification (potassium carbonate) produced the free alcohol IIIa which could be repropionylated to the original ester IIIb. On the other hand, when the saponification was carried out by means of boiling 5% methanolic potassium hydroxide, there was isolated a new alcohol with an appreciably more positive rotation and which on propionylation yielded a new propionate. The presence of the intact Δ^8-11-keto moiety was demonstrated by the ultraviolet and infrared spectra and it was obvious, therefore, that isomerization had occurred at C-14 *via* the common anion to afford the 14β-isomer IV with rings C and D fused in the thermodynamically more stable *cis* configuration. An inspection of the infrared spectra of the two isomeric propionates IIIb and IVb shows interesting differences in the 9–10 μ region, a pronounced band at 9.50 μ apparently being characteristic of the *trans*-fused system.[9a] The same type of spectrum is found in the pair of alcohols IIIa and IVa and somewhat less pronounced in the hydrogenation products V and VII. This remarkably facile rearrangement thus offers a path to 14-iso(β)-11-keto steroids and synthetic work along these lines is now in progress.

As pointed out earlier,[10] in contrast to the known resistance of Δ^8-unsaturated sterols toward catalytic hydrogenation,[11] Δ^8-unsaturated 7-keto steroids undergo rapid reduction to afford *directly* the "natural" B/C *trans* (8β,9α) juncture, indicative of 1,4-addition to an enol system. It appeared, therefore, of very considerable interest to examine the stereochemical course of the catalytic hydrogenation of a Δ^8-11-ketone. When the propionate IIIb was subjected to the same hydrogenation conditions (palladized charcoal catalyst, room temperature, atmospheric pressure) which suffices for the complete reduction of Δ^8-22a-5α-spirostene-3β,11α-diol-7-one acetate[10] in two hours, at least ten times as long a period of time was necessary before saturation of the 8,9-double bond was achieved. The resulting product Vb was further characterized as the free keto alcohol Va, which proved to be completely different (notably in its rotation) from the known[10] "natural" (8β,9α) 22a-5α-spirostan-3β-ol-11-one (VI). Since the hydrogenation product was unchanged by boiling potassium hydroxide solution it must have been more stable than the isomer which would have been

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(5) H. Heusser, K. Eichenberger, P. Kurath, H. R. Daellenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951).

(6) H. E. Stavely and G. N. Bollenback, THIS JOURNAL, **65**, 1290 (1943).

(7) E. Schoenewaldt, L. Turnbull, E. M. Chamberlin, D. Reinhold, A. E. Erickson, W. V. Ruyle, J. M. Chemerda and M. Tishler, *ibid.*, **74**, 2696 (1952).

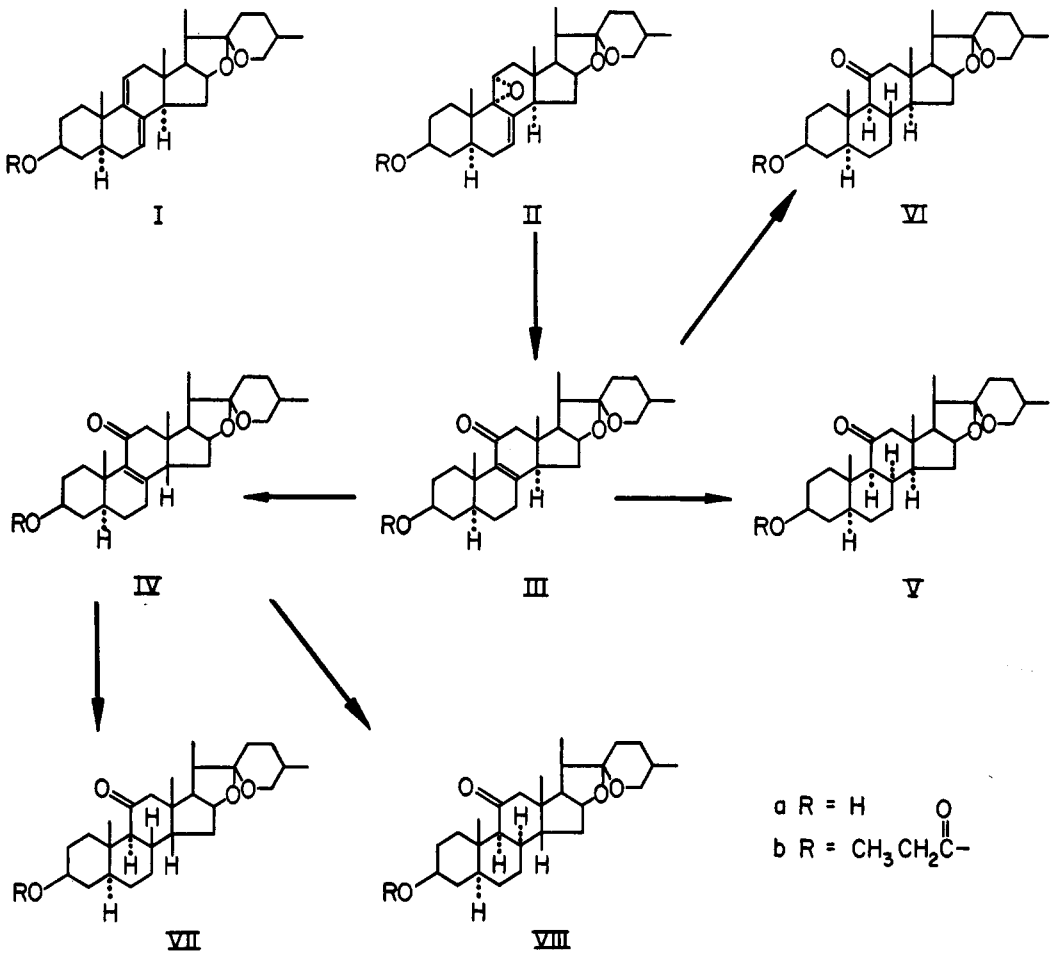
(8) F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952); F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1282 (1953).

(9) G. Rosenkranz, J. Romo, E. Batres and C. Djerassi, *J. Org. Chem.*, **16**, 298 (1951).

(9a) Prof. W. S. Johnson of the University of Wisconsin has made a similar observation (private communication).

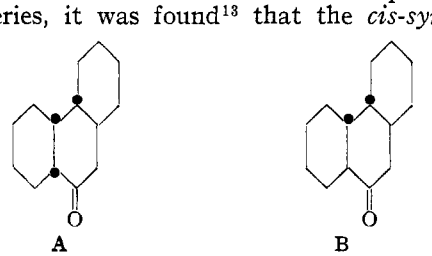
(10) *Inter al.*, C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712 (1952); *cf.* footnote 11 in that paper.

(11) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 214 (1949).



produced by isomerization at the carbon atom (C-9) adjacent to the keto function. Of the three possibilities (8β,9β, 8α,9α, 8α,9β), the 8β,9β-isomer *a priori* appears unlikely on steric grounds since it would involve adsorption on the catalyst surface and entrance of hydrogen on the highly hindered β-side. It was furthermore eliminated on chemical grounds since the hydrogenation product proved stable to alkali while the 8β,9β-11-ketone would be expected to be rearranged readily to the known 8β,9α-form. A distinction between the remaining two possibilities (8α,9α, 8α,9β) can be made with a fair degree of certainty on the basis of conformational analysis.[12]

The closest analogy to the presently studied cases is represented by the isomeric 9-ketoperhydrophenanthrenes[13] which have recently been examined by Johnson[14] from a conformational standpoint. In that series, it was found[13] that the *cis-syn-trans*



form (A) could not be isomerized to the *trans-syn-trans* isomer (B) and it was pointed out[14] that the latter could not assume an all chair conformation in contrast to A.

The presently described steroid case is more complicated by the presence of the angular methyl group at C-10 and, especially, the additional *trans*-fused ring D. As pointed out by Johnson[14] in the perhydrophenanthrene series, the *trans-syn-trans* isomer (B) must have the center ring B in the boat conformation since it is impossible to fuse ring C in a *trans* manner through two adjacent polar bonds. This is precisely the situation in our 8α,9β case where both the 9–11 and 8–14 bonds would be polar. However, an additional restriction is imposed in the steroid series by the *trans*-fused ring D in that *ring C* of the 8α,9β-isomer *must also be in the boat conformation* since otherwise ring D would have to be fused through two adjacent polar bonds (13–17 and 14–15). A similar analysis of the last possibility, the 8α,9α-isomer V shows that in contrast to the corresponding situation in the perhydrophenanthrene series[14] (where an all-chair conformation is possible) *one ring (B or C) must be in the boat conformation* in order to allow a *trans* attachment of ring D and circumvent the impossible situation of two adjacent polar bonds being involved in the *trans* ring juncture.

It is clear, therefore, that of these two possibilities, the 8α,9α (V) isomer, requiring only one boat, should be preferred over the alternate 8α,9β-

(12) *Cf.* D. H. R. Barton, *Experientia*, **6**, 312 (1950).
(13) R. P. Linstead and R. R. Whetstone, *J. Chem. Soc.*, 1428 (1950), and earlier papers.
(14) W. S. Johnson, *Experientia*, **7**, 315 (1951).

derivative with both rings B and C in the boat conformation. Since the α-side is precisely the one where conventional *cis*-addition of hydrogen would be favored on purely steric grounds coupled by the above conformational argument which parallels and augments that of Johnson[14] in the perhydrophenanthrene series, it seems highly probable that the product of the catalytic hydrogenation of the Δ^8-11-ketone III is the 8-iso(α)-11-ketone V.

Attention was turned next to the 14-iso(β)-series (IV), which is produced so readily by alkaline isomerization of the 14α-Δ^8-11-ketone III. Construction of a molecular model of the former shows that it differs from the essentially planar "natural" isomer III only by the fact that ring D is bent down toward the α-side, but as a consequence the β-side of the molecule appears appreciably less hindered while the α-side seems somewhat more hindered than their corresponding counterparts in III. As a result, it does not seem possible to predict from models on steric grounds alone which side would be favored for adsorption on the catalyst surface. Catalytic hydrogenation of IV proceeded at a markedly slower rate than that observed in III thus apparently reflecting the higher degree of hindrance (of the α- or β-sides in IV as compared to the α-side in III) observed in the model. The resulting hydrogenation product VIII again proved to be stable to alkali thus indicating that it was the thermodynamically more favored product over its C-9 epimer. Of the four possible structures (at C-8 and C-9) for the hydrogenation product of the 14-iso series, only one, the 8α,9β-isomer, requires one boat while the remaining *trans* (8β,9α) and the two *cis* isomers (8α,9α, 8β,9β) can assume all-chair conformations.[15] Since a *trans* derivative could be produced during *catalytic* hydrogenation only by 1,4-addition to an enol system or by an *in situ* rearrangement of an intermediate *cis* form, the most stable isomer might be expected to be formed directly in a *chemical* reduction since this has actually been observed[7,8] in the 14α-series (III → VI). The latter process does not involve adsorption and is not subject to subtle stereochemical effects as is the case in the catalytic hydrogenation.

When the 14-iso-Δ^8-11-keto propionate IV was reduced chemically with lithium in liquid ammonia in the previously described manner,[8] there was isolated (after saponification) an 11-keto alcohol, further characterized by its propionate. Both substances proved to be completely different from the corresponding derivatives obtained in the catalytic hydrogenation of IV. In spite of this, a secure assignment of configuration in this series is not yet possible since the conformational argument is considerably complicated (*cf.* Table I) by the fact that the five-membered ring D is now fused in a *cis* manner.

(15) The assignment of all-chair conformations for VII and VIII is made with the tacit assumption that *cis*-juncture of rings C and D does not involve also partial conversion of ring C from a chair to a boat form in order to relieve the "conventional" strain of the cyclopentane ring (based on conventional bond angles) inherent in any *cis*-hydrindane system in which the six-membered ring is in the chair conformation. However, essentially the same conclusion with respect to the relative stability of VII and VIII is reached if one applies Johnson's method (ref. 14) of maximum accumulation of equatorial bonds to the various isomers with ring C in the boat conformation.

TABLE I

NUMBER OF BOAT FORMS REQUIRED[a]

Isomer	14α Series	14β Series
8β,9α	None	None
8β,9β	One (B or C)	None
8α,9β	Two (B and C)	One (B)
8α,9α	One (B or C)	None

[a] These boat forms are required in order to permit *trans* attachment of the adjacent ring.

Just as in the 14α-series, two isomers can be eliminated with a fair degree of certainty for both the chemical and catalytic hydrogenation products. The 8β,9β-isomer would be expected to be isomerizable with base to the *trans* form, which was not the case since both reduction products were found to be stable to base; the 8α,9β-derivative can be eliminated since it requires ring B in the boat conformation (*cf.* Table I). On applying Johnson's[14] method of determining the number of equatorial and polar bonds by which the central ring is fused to its two neighbors, the tentative conclusion can be reached that the 8β,9α-isomer VII should be somewhat more stable and hence represent the lithium–ammonia reduction product, since it is connected by either four equatorial bonds or three equatorial and one polar (14–15) bond, depending on whether ring B or ring C is assumed to be the "central" ring. A similar analysis of the 8α,9α-form VIII indicates that it requires either three equatorial and one polar (8–14) bond or two equatorial and two polar bonds (9–10 and 13–17) and that it should represent the catalytic hydrogenation product.[16]

The opposite conclusion with respect to the above conformational argument can be reached if one considers a possible mechanism of the metal–ammonia reduction of α,β-unsaturated ketones. As pointed out to us by Professor A. L. Wilds of the University of Wisconsin, if such reduction involves attack of electrons first on the β-carbon (C-8 in this instance) followed by addition of a proton, then the stereochemical addition of the proton at C-8 would be the decisive factor since isomerization at the enolizable C-9 position would be governed by it. With such a view in mind, the *anti* form (with respect to the 8–14 bond) might be expected to be formed, a conclusion which leads to the correct result in the 14α-series (III → VI).[7,8] However, the same reasoning applied to the 14β-series would then indicate that the *chemical* reduction product is the B/C *cis* (8α,9α)-isomer VIII (*anti* backbone) and the *hydrogenation* product the B/C *trans* (8β,9α)-isomer VII (formed by initial *cis* addition on the β-side and *in situ* rearrangement during the long hydrogenation time).[16] No definite choice can yet be made between the above two possibilities but attempts to present an unequivocal proof are now in progress.

(16) Such a conclusion agrees with the observation in the 14α-series that the hydrogenation product was a *cis* compound formed by conventional *cis* addition of hydrogen from the catalyst surface. However, it is not clear from an inspection of models whether the angular methyl groups or ring D, which is now bent down to the α-side, have a greater hindering effect for adsorption on the catalyst surface. If it is the latter, then the initially formed hydrogenation product might well have been the 8β,9β-isomer which was rearranged to the alkali-stable *trans* form VII during the long hydrogenation.

Acknowledgment.—The authors are grateful to Professors W. S. Johnson and A. L. Wilds of the University of Wisconsin for interesting discussion.

Experimental[17]

$\Delta^{7,9(11)}$-22a-5α-Spirostadien-3β-ol Propionate (Ic).—The free-dien-3β-ol Ia[9] (40 g.) in 200 cc. of propionic anhydride and 40 cc. of pyridine was refluxed for 1 hr. and then allowed to stand at room temperature overnight. After dilution with water, filtration and recrystallization from chloroform–methanol and hexane–acetone there was obtained 32.5 g. of the propionate Ic with m.p. 179–180°, $[\alpha]^{22}D$ −13°, λ_{max}^{EtOH} 236, 242 mμ, log ϵ 4.12, 4.17.

Anal. Calcd. for $C_{30}H_{44}O_4$: C, 76.88; H, 9.46. Found: C, 77.18; H, 9.69.

9α,11α-Oxido-Δ^7-22a-5α-spirosten-3β-ol Propionate (II).—A solution of 20 g. of the above propionate Ib in 1 l. of dry ether was mixed with an ethereal solution of 1.1 equivalents of monoperphthalic acid. After 24 hours at room temperature, all of the peracid had been consumed and the ether solution was washed with sodium carbonate solution, dried and evaporated. Trituration with methanol afforded 16–18 g. of oxide with m.p. 218–223°, $[\alpha]^{20}D$ −91°, which did not exhibit any absorption in the 230–250 mμ region. The analytical sample was obtained by chromatography on alumina (activity II[18]) and elution with benzene followed by recrystallization from chloroform–methanol; m.p. 242–244°, $[\alpha]^{22}D$ −86°, $\lambda_{max}^{CHCl_3}$ 5.83 μ, yellow color with tetranitromethane.

Anal. Calcd. for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.45; H, 9.08.

Δ^8-22a-5α-Spirosten-3β-ol-11-one Propionate (IIIb).—The above oxide II (3.0 g.) in 120 cc. of dry thiophene-free benzene containing 10 drops of redistilled boron trifluoride etherate was allowed to stand at room temperature for 75 hours. The solution was diluted with ether, washed with sodium bicarbonate and water, dried and evaporated. The solid residue was chromatographed on 100 g. of alumina (activity III[18]) yielding the following three fractions: (a) benzene–hexane (1:1) eluates, 0.12 g., m.p. 150–160° which was not investigated further; (b) benzene and benzene–ether (4:1) eluates, 2.1 g. (70%) of IIIb with m.p. 198–200°, and (c) benzene–ether (1:1) and methanol eluates, 0.87 g. of oil. The analytical sample of the unsaturated ketone IIIb was obtained from chloroform–methanol, m.p. 204–205°, $[\alpha]^{22}D$ +52°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.08, $\lambda_{max}^{CHCl_3}$ 5.82 μ, 6.05 μ and 9.50 μ.

Anal. Calcd. for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.66; H, 9.36.

The ketone was recovered unchanged after refluxing for 8.5 hours with semicarbazide in ethanol solution.

Δ^8-22a-5α-Spirosten-3β-ol-11-one (IIIa).—In view of the facile alkaline isomerization at C-14, it was necessary to select the mildest possible conditions for the saponification of the propionate IIIb. Treatment of the propionate (230 mg.) with 100 mg. of potassium bicarbonate in 50 cc. of methanol and 10 cc. of water for 4 days at room temperature resulted in the nearly quantitative recovery of the starting material. It was necessary, therefore, to carry out the saponification with carbonate.

A mixture of 500 mg. of the propionate IIIb, 800 mg. of potassium carbonate, 10 cc. of water and 100 cc. of methanol was allowed to stand at room temperature for 48 hours and then concentrated to a small volume under reduced pressure. After addition of water and filtration the precipitate (450 mg.) was chromatographed on 15 g. of alumina (activity III[18]). The benzene eluates yielded 100 mg. of recovered starting material while from the benzene–ether (1:1) eluates there was obtained 340 mg. of the free alcohol IIIa with m.p. 200–202°, depressed to 180° upon admixture with the starting material. Two recrystallizations from dilute methanol raised the m.p. to 203–205°, $[\alpha]^{22}D$ +76°, $\lambda_{max}^{CHCl_3}$ 2.82 μ (hydroxyl group), 6.07 μ (Δ^8-11-ketone) and 9.50 μ. This latter band is the strongest in the 9–10 μ region and appears to be indicative of the C/D *trans* configuration.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.56; H, 9.24.

Repropionylation (propionic anhydride, pyridine, room temperature, 24 hours) of IIIa followed by recrystallization afforded the pure propionate IIIb in over 80% yield; the identity was established by mixed melting point, infrared spectra and rotation ($[\alpha]^{22}D$ +48°).

Δ^8-22a-5α-14-Iso(β)-spirosten-3β-ol-11-one (IVa).—A solution of 3.5 g. of Δ^8-22a-5α-spirosten-3β-ol-11-one propionate (IIIb) with m.p. 198–200° was refluxed for one hour with 350 cc. of 5% methanolic potassium hydroxide. After concentration *in vacuo*, dilution with water, extraction with chloroform, evaporation and recrystallization from ether–hexane, there was obtained 2.8 g. of the 14-iso-derivative IVa with m.p. 230–232°. Further recrystallization from the same solvent afforded the analytical sample with m.p. 234–235°, $[\alpha]^{22}D$ +110°, λ_{max}^{EtOH} 252 mμ, log ϵ 4.09, $\lambda_{max}^{CHCl_3}$ 2.82 and 6.05 μ; the infrared band at 9.50 μ typical of the 14α-derivatives IIIa and IIIb was absent.

Anal. Calcd. for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.60; H, 9.42.

Propionylation of the above keto alcohol IVa (100 mg.) with 2 cc. of pyridine and 1 cc. of propionic anhydride at room temperature for 20 hours followed by recrystallization from ethanol and ether–hexane led to 70 mg. of the analytical sample of the *propionate IVb* with m.p. 218–219°, depressed to 180–185° on admixture with IIIb, $[\alpha]^{22}D$ +91°, $\lambda_{max}^{CHCl_3}$ 5.82 and 6.05 μ; the characteristic 9.50 μ band of IIIb is absent.

Anal. Calcd. for $C_{30}H_{44}O_5$: C, 74.34; H, 9.15. Found: C, 74.18; H, 8.88.

22a-5α-8-Iso(α)-spirostan-3β-ol-11-one Propionate (Vb).—A mixture of 0.5 g. of Δ^8-11-ketopropionate IIIb, 250 mg. of 10% palladized charcoal (American Platinum Works, Newark, N.J.) and 80 cc. of ethanol was shaken in an atmosphere of hydrogen at room temperature and atmospheric pressure for 20 hours. Determination of the ultraviolet absorption maximum at 252 mμ indicated the presence of *ca.* 10% of unreduced material and the hydrogenation was completed by the addition of fresh catalyst and shaking overnight. After filtration of the catalyst and evaporation to dryness, the solid residue was chromatographed on 15 g. of alumina (activity II[18]) and the product was eluted with benzene; yield 0.42 g., m.p. 207–215°. One recrystallization from ethanol raised the m.p. to 213–215° (0.35 g.), while the analytical sample was obtained from acetone–hexane with m.p. 219–220°, $[\alpha]^{22}D$ −79°, $\lambda_{max}^{CHCl_3}$ 5.82 and 5.90 μ.

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found: C, 74.35; H, 9.69.

Saponification of 200 mg. of the propionate Vb with 500 mg. of potassium carbonate in 5 cc. of water and 50 cc. of methanol for two days at room temperature followed by recrystallization from acetone–hexane and dilute methanol produced 100 mg. of the analytical sample of **22a-5α-8-iso-(α)-spirostan-3β-ol-11-one (Va)** as small needles with m.p. 241–242°, $[\alpha]^{22}D$ −74°. The same product was obtained when the saponification was carried out with refluxing 10% methanolic potassium hydroxide for 2 hours indicating that the "stable" isomer was produced during the hydrogenation.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.06; H, 9.82.

Repropionylation of Va produced Vb with m.p. 218–220°, undepressed upon admixture with a sample of the propionate Vb obtained directly from the hydrogenation; the infrared spectra also proved to be identical.

22a-5α-8-Iso(α),14-iso(β)-spirostan-3β-ol-11-one (VIIIa).[19]—The catalytic hydrogenation of 1.0 g. of the unsaturated 14-iso ketone IVa was carried out in ethanol solution in the usual manner with 500 mg. of palladized charcoal for three days, at which time an aliquot exhibited no selective ultraviolet absorption at 252 mμ. The crude product was purified by chromatography on 30 g. of alumina (activity III[18]) and elution with benzene–ether (1:1) followed by recrys-

(17) Melting points are uncorrected. Rotations were determined on *ca.* 10-mg. samples in 2 cc. of chloroform in 1-dm. tubes and ultraviolet absorption spectra were measured in absolute ethanol solution. The infrared spectra were obtained with a Baird Associates recording double beam spectrophotometer in 0.1-mm. cells. The microanalyses were carried out in part by Messrs. M. Papo and R. Mullins (Wayne University) and partly by Srta. Amparo Barba (Syntex).

(18) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

(19) As pointed out more fully in the discussion, the stereochemistry of the B/C juncture is not yet established securely.

tallization from dilute methanol; yield 0.78 g., m.p. 160–162°. The analytical sample was obtained from dilute acetone as needles with m.p. 161–162°, $[\alpha]^{22}D$ −124°, $\lambda_{max}^{CHCl_3}$ 2.80 and 5.90 μ.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.18; H, 9.94.

The stability of the hydrogenation product was demonstrated when 150 mg. of VIIa was refluxed with 12 g. of potassium hydroxide, 10 cc. of water and 65 cc. of methanol for 2 hours. Dilution with water and one recrystallization from dilute alcohol furnished 130 mg. of crystals with m.p. 158–161°, which after one additional recrystallization was raised to m.p. 161–162°, undepressed on admixture with the starting material. The same results were obtained when sodium ethoxide in ethanol was used.

Propionylation of VIIIa in the usual manner followed by recrystallization from dilute methanol afforded the **propionate VIIIb** with m.p. 196–198°, $[\alpha]^{22}D$ −119°.

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found: C, 74.32; H, 9.60.

In order to determine whether there exists a difference in the rate of hydrogenation of the Δ^8-11-ketone depending upon the configuration at C-14, a sample of the 14-iso propionate IVb was hydrogenated with the same catalyst and solvent simultaneously with the above described hydrogenation of the 14-"normal" propionate IIIb. In contrast to the latter which was reduced to the extent of *ca.* 90% after 20 hours, the former had undergone only about 20% hydrogenation during the same period.

22a-5α-14-Iso(β)-spirostan-3β-ol-11-one (VIIa)[19].—A suspension of 0.44 g. of the Δ^8-14-iso propionate IVb in 20 cc. of ether was added in one portion with stirring to a solution of 20 mg. of lithium metal in 80 cc. of liquid ammonia. After disappearance of the blue color (less than 10 minutes), an additional 10 mg. of lithium was added and after 30 minutes, the excess metal was decomposed by the addition of a few drops of *t*-butyl alcohol followed by 0.5 g. of ammonium chloride. The ammonia was evaporated and 10 cc. of ethanol and 2 cc. of water were added to the residue and the mixture was allowed to stand at room temperature for 12 hours in order to complete the saponification of the propionate. The ethanol was removed under reduced pressure, the remainder was extracted with chloroform, washed well with water, dried and evaporated. Measurement of the ultraviolet absorption spectrum of the residue (0.42 g.) indicated the presence of less than 5% of unreduced starting material. For effective purification, it was necessary to chromatograph this material on 15 g. of alumina (activity II[18]); elution with benzene–ether (1:1) afforded 0.2 g. of colorless crystals of VIIa with m.p. 231–234°. The analytical sample was recrystallized once from dilute methanol and twice from ligroin and finally sublimed at 150° and 0.008 mm.; m.p. 234.5–235.5°, $[\alpha]^{22}D$ −3.3°, $\lambda_{max}^{CHCl_3}$ 2.78 and 5.88 μ.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 74.91; H, 9.94.

The **propionate** VIIb after recrystallization from dilute methanol and sublimation at 180° and 0.008 mm. exhibited m.p. 238–239°, $[\alpha]^{22}D$ −4.6°, $\lambda_{max}^{CHCl_3}$ 5.80 and 5.88 μ.

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found: C, 74.35; H, 9.59.

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Synthesis and Reactions of Chlorinated 3-Ketosteroids

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Chlorination of 3-ketoallosteroids by means of chlorine, sulfuryl chloride, pyridine perchloride hydrochloride or most advantageously *t*-butyl hypochlorite leads to the corresponding 2-chloro-3-ketones which can also be synthesized in one step from 3β-hydroxyallosteroids by simultaneous oxidation and chlorination. The position of the chlorine atom was proved by dehydrochlorination with 2,4-dinitrophenylhydrazine and by conversion *via* the pyridinium salt to the known nitrone. Evidence has also been adduced that the 2-chlorine atom possesses the α-configuration. Similar chlorination of 3-ketosteroids of the "5β" configuration produced the 4-chloroketones. A number of reactions of steroidal chloro ketones has been studied and compared with those of the brominated analogs.

4-Bromo-3-ketosteroids have proved to be of considerable importance[4] in the synthesis of Δ^4-3-ketosteroids and estrogens, while 2-iodoketones of the allo (5α) series represent the key intermediates[5] in the elaboration of the important Δ^4-keto moiety from allo ketones. Since bromo- and iodoketones differ markedly in some of their reactions, it appeared of interest to extend this work to the previously unknown chloro-3-ketosteroids and such an investigation was started at Wayne University (J.J.B. and C.D.). Independently, a study was undertaken at Harvard (D.G. and L.F.F.) to see if certain reactions of *t*-butyl hypochlorite reported in another connection[6] would be applicable to steroids, for example, to the chlorination of 3-ketosteroids.[7] Learning of each other's activities, we decided to complete the work in a joint investigation, which is reported in this paper.

The initial study of chlorination conditions was carried out with cholestane-3-one (Ia). Chlorine gas in carbon tetrachloride solution affords the 2-chloro derivative IIa in 35% yield while sulfuryl chloride under free radical conditions produces IIa in slightly higher yield; pyridine perchloride hydrochloride gives essentially the same results. *t*-Butyl hypochlorite proved to be the reagent of choice since in acetic acid solution up to 90% of 2-chlorocholestanone (IIa) can be isolated. Cholestane-3-one (Ia) itself is usually prepared by oxidation[8] of cholestane-3β-ol with sodium dichromate or chromic anhydride, but *t*-butyl hypochlorite is equally efficacious. It was thus found

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(4) See C. Djerassi, THIS JOURNAL, **71**, 1003 (1949) for leading references.

(5) G. Rosenkranz, C. Djerassi, *et al.*, *ibid.*, **72**, 1046, 4077, 4081 (1950); *Nature*, **168**, 28 (1951).

(6) J. J. Ritter and D. Ginsburg, THIS JOURNAL, **72**, 2381 (1950); D. Ginsburg, *ibid.*, **73**, 702, 2723 (1951); *Experientia*, **7**, 95 (1951).

(7) *Cf.* D. Ginsburg, *Bull. Res. Council Israel*, in press.

(8) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 139, and references cited therein.