15 g. of manganese dioxide at room temperature for 4 hours. The oxide was then removed by filtration and washed well with chloroform. Crystallization of the product from chloroform–ether furnished 1.26 g. (84%) of Δ^{4}-22a-spirosten-3-one, m.p. 183–185°, $[\alpha]^{20}_{D}$ −6°, λ_{max} 240 mμ, log ε 4.24, identified with an authentic sample (m.p. 185–186°, $[\alpha]^{20}_{D}$ −8°) by mixture melting point.

Δ^{5}-22a-Spirosten-3β-ol-7-one Acetate (IV).—A solution of 0.50 g. of Δ^{5}-22a-spirosten-3β,7α-diol 3-acetate (m.p. 190–193°, $[\alpha]^{20}_{D}$ −155°)[9] in 50 cc. of benzene was shaken with 5 g. of manganese dioxide for 24 hours at room temperature. The crystalline residue, after removal of the dioxide and solvent, showed λ_{max} 234 mμ, log ε 4.10, indicating the reaction to have proceeded to 83% completion. Crystallization from methanol furnished 0.29 g. (58%) of Δ^{5}-22a-spirosten-3β-ol-7-one acetate with m.p. 198–199°, $[\alpha]^{20}_{D}$ −158°, λ_{max} 234 mμ, log ε 4.18, $\nu_{max}^{CHCl_3}$ 1726 and 1674 cm.$^{-1}$, identified with an authentic specimen (m.p. 197–198°, $[\alpha]^{20}_{D}$ −163°[9]) by mixture melting point and infrared comparison.

$\Delta^{9(11)}$-22a,5α-Spirosten-3β-ol-12-one (VI).—A solution of 0.50 g. of $\Delta^{9(11)}$-22a,5α-spirostene-3β,12ξ-diol (V) (m.p. 200–203°)[10] (most probably a mixture of C-12 stereoisomers) in 50 cc. of chloroform was shaken with 5 g. of manganese dioxide for 10 hours at room temperature. The total product showed λ_{max} 238 mμ, log ε 4.07, indicating 81% oxidation. Crystallization from chloroform–acetone yielded 0.38 g. (76%) of the $\Delta^{9(11)}$-12-one (VI) with m.p. 221–223°, λ_{max} 238 mμ, log ε 4.16, $\nu_{max}^{CHCl_3}$ 1670 cm.$^{-1}$ and free hydroxyl band, identified with an authentic specimen (m.p. 223–225°)[11] by mixture melting point and infrared comparison.

$\Delta^{5,17(20)}$-Pregnadien-3β-ol-21-al Acetate (VIII).—A solution of 0.80 g. of $\Delta^{5,17(20)}$-pregnadiene-3β,21-diol (m.p. 193–196°)[12] in 80 cc. of chloroform was shaken with 8 g. of manganese dioxide for 5 hours at room temperature. The crystalline residue with λ_{max} 244 and 284 mμ, log ε 4.25 and 3.54, respectively, was acetylated (pyridine–acetic anhydride, room temperature, 24 hours), and the product was crystallized from methanol. In this manner 0.50 g. of the 21-aldehyde VIII with m.p. 183–186° was obtained, raised on further crystallization from chloroform–methanol to 186–187°, $[\alpha]^{20}_{D}$ −58°, λ_{max} 244 mμ, log ε 4.36, $\nu_{max}^{CHCl_3}$ 1718 and 1670 cm.$^{-1}$ (reported[13] m.p. 184–185°, $[\alpha]^{20}_{D}$ −60°, λ_{max} 244 mμ, log ε 4.44). A further small quantity of VIII could be obtained by chromatography of the mother liquors.

Testosterone (XI) from Δ^{4}-Androstene-3,17-dione (IX).—A solution of 50 g. of Δ^{4}-androstene-3,17-dione in 300 cc. of dry tetrahydrofuran was added with stirring and ice cooling to 15 g. of lithium aluminum hydride in 1.5 l. of tetrahydrofuran during 30 minutes, and the mixture was then heated under reflux for 1 hour. The excess reagent was decomposed by the careful addition of ethyl acetate, and concentrated aqueous sodium sulfate was then added until the precipitate began to adhere to the sides of the flask. Finally *ca.* 100 g. of solid sodium sulfate was added, the salts were removed by filtration and washed well with tetrahydrofuran. Evaporation of solvent yielded 50.4 g. of a mixture of Δ^{4}-androstene-3β,17β-diol (Xa) and the 3α,17β-diol (Xb) as a white powder with m.p. 165–171°, no appreciable absorption in the ultraviolet.

The above solid was finely ground in a mortar, then suspended in 1250 cc. of chloroform, and stirred with 250 g. of manganese dioxide for 10 hours at room temperature. The dioxide was removed by filtration, washed thoroughly with hot chloroform, and the combined chloroform solutions were evaporated to dryness. Crystallization from acetone–hexane furnished 38.2 g. of testosterone with m.p. 152–153°, $[\alpha]^{20}_{D}$ +108°, λ_{max} 240 mμ, log ε 4.23, as first crop, and 6.9 g. with m.p. 150–152° as second and third crops (total over-all yield 45.1 g. or 90%). Identity of the combined crops with an authentic sample was established by mixture melting point determination and infrared comparison.

Essentially identical results were obtained when the initial reduction was carried out with sodium borohydride in boiling aqueous alcohol.

Δ^{4}-Pregnen-20β-ol-3-one (XIVa) from Progesterone (XII).—Progesterone (5.0 g.) was reduced with lithium aluminum hydride, as described above for Δ^{4}-androstene-3,17-dione. The total reduction product (5.0 g.) with m.p. 162–172°, no appreciable absorption in the ultraviolet, in 500 cc. of chloroform, was stirred with 50 g. of manganese dioxide for 24 hours at room temperature. Crystallization of the product from ether–pentane furnished 3.3 g. (66%) of Δ^{4}-pregnen-20β-ol-3-one (XIVa) with m.p. 166–168°, raised on further crystallization to 174–175°, $[\alpha]^{20}_{D}$ +86°, λ_{max} 240 mμ, log ε 4.23, $\nu_{max}^{CHCl_3}$ 1660 cm.$^{-1}$ and free hydroxyl band[21] (reported m.p. 171–172°, $[\alpha]^{24}_{D}$ +84°[17]; m.p. 169–171°, $[\alpha]^{20}_{D}$ +83°[16b]; m.p. 174–175°, $[\alpha]_{D}$ +90°[16c]).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.48; H, 10.22.

The acetate XIVb was crystallized from acetone–hexane, and exhibited m.p. 161–162°, $[\alpha]^{20}_{D}$ +134°, λ_{max} 240 mμ, log ε 4.22, $\nu_{max}^{CHCl_3}$ 1718 and 1660 cm.$^{-1}$ (reported m.p. 159–159.5°, $[\alpha]^{25}_{D}$ +140°[17]; m.p. 159–161°, $[\alpha]^{20}_{D}$ +137°[16b]; m.p. 161–162°, $[\alpha]_{D}$ +129°[16c]).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.83; H, 9.76.

MEXICO CITY, D. F.

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[21] The lower melting 20α-isomer of XIVa[16c,17] which presumably was formed to some extent,[16] was probably present in the mother liquors, but no attempt at isolation was made.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. LI.[1] $\Delta^{4,6}$-Dien-3-ones[2,3]

BY FRANZ SONDHEIMER, C. AMENDOLLA AND G. ROSENKRANZ

RECEIVED JUNE 25, 1953

Both Δ^{4}-3-ones (II) and Δ^{5}-3β-ols (IV) are oxidized by means of manganese dioxide to the corresponding $\Delta^{4,6}$-dien-3-ones (III). The conversion of IV to III is a useful preparative method for the latter, and the generality of this type of oxidation is demonstrated by its application to a number of different Δ^{5}-3β-ols (IV). The intermediate in the oxidation of IV to III is shown to be almost certainly the Δ^{5}-3-one (V).

In the previous paper of this series[1] it was shown that steroidal Δ^{4}-3β-ols (I) were oxidized smoothly to the corresponding Δ^{4}-3-ones (II) by means of manganese dioxide at room temperature. It was found, however, in one experiment in which the oxidation was allowed to proceed for an unusually long time (24 hours) that a new ultraviolet absorption maximum at 284 mμ of low intensity, in addition to the expected one at 240 mμ, appeared in the product. Since it had been shown that the Δ^{4}-3-one (II) was the primary product, it follows that this system must slowly be further attacked by the manganese dioxide, and indeed when an authentic Δ^{4}-3-one (Δ^{4}-22a-spirosten-3-one) was shaken with manganese dioxide at room temperature for 24

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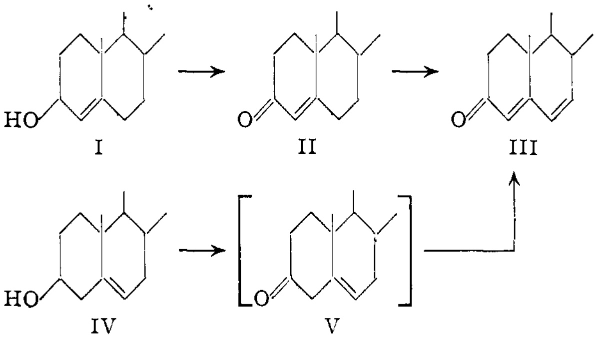
[1] Steroids. L. F. Sondheimer, C. Amendolla and G. Rosenkranz, THIS JOURNAL, **75**, 5930 (1953).

[2] Presented in part at the Los Angeles Meeting of the American Chemical Society, March, 1953.

[3] A preliminary announcement of part of this work has been published (F. Sondheimer and G. Rosenkranz, *Experientia*, **9**, 62 (1953)).

hours, a low intensity maximum at 284 mμ again appeared. In order to ascertain the nature of the material responsible for this new maximum, the reaction of Δ^4-22a-spirosten-3-one with manganese dioxide was carried out in boiling benzene. The product in this case showed a 284 mμ band of considerably increased intensity, and it was possible to isolate the 284 mμ absorbing material and identify it as $\Delta^{4,6}$-22a-spirostadien-3-one. It thus became evident that manganese dioxide is capable of causing direct dehydrogenation of a Δ^4-3-one (II) to the $\Delta^{4,6}$-dien-3-one (III). This cannot, however, be considered a preparative method for the latter, since even by chromatographic means it was found very difficult and wasteful to separate the unchanged Δ^4-3-ketone (II) from the required dienone (III).[4]



Fortunately it was observed that the readily available Δ^5-3β-ols (IV) with manganese dioxide at room temperature also yielded the corresponding $\Delta^{4,6}$-dien-3-ones (III), and again the conversion could be considerably improved by carrying out the reaction in refluxing benzene. In this case, as would be expected, the products may be separated very easily from the more polar starting materials by simple chromatography, and this oxidation procedure constitutes a convenient and general synthesis of steroidal $\Delta^{4,6}$-dien-3-ones. A variety of the latter have been prepared by this method, and the results are set out in Table I (all oxidations were carried out in refluxing benzene, reaction time 8 hours). Examples no. 1–4 illustrate oxidations of compounds with comparatively non-reactive side chains. In no. 5 two different reactive functions are present, and the Δ^{16}-20β-ol grouping is oxidized to the Δ^{16}-20-one as well as the Δ^5-3β-ol to the dienone. In no. 6 it is shown that the saturated 20β-ol grouping is unattacked, although (no. 7) the saturated 17β-ol function appears to be oxidized to some extent. In nos. 9 and 10 it is demonstrated that the reaction is applicable to compounds containing the 17α-hydroxy-20-ketone grouping. That no "D-homo" rearrangement had occurred in these cases was indicated by the fact that a compound such as pregnane-17α,21-diol-3,20-dione 21-acetate (dihydro Substance S 21-acetate)[5] was recovered unchanged when heated with manganese dioxide,[6] and by an independent synthesis of 6-dehydro Substance S 21-acetate from Substance S 21-acetate by bromination at C-6 with N-bromosuccinimide, followed by collidine dehydrobromination (*cf.* ref. 4). Since it has been shown[4] in the case of 6-dehydrocortisone 21-acetate that a $\Delta^{4,6}$-dien-3-one (III) may be reduced to the Δ^4-3-one (II) with zinc in benzene–acetic acid, the present procedure allows the conversion of a Δ^5-3β-ol (IV) to the Δ^4-3-one (II) in cases (such as with compounds containing the important 17α-hydroxy-20-one function) where the Oppenauer method is inapplicable.

The above-described process for oxidizing Δ^5-3β-ols to the $\Delta^{4,6}$-dien-3-ones by means of manganese dioxide is similar to that of Wettstein[7] by which the same conversion is effected with aluminum *t*-butoxide and benzoquinone in boiling toluene. The two methods seem to result in similar conversions, but the presently reported one appears to be preferable for a number of reasons, such as (a) ease of carrying out the reaction and isolating the product; (b) a considerable amount of starting material is usually recovered and may be recycled to increase the total yield; (c) the method is applicable to compounds containing the Oppenauer sensitive 17-ol-20-one grouping[8]; (d) the method may be used for the preparation of $\Delta^{4,6}$-dien-3-ones with saturated hydroxy groups elsewhere in the molecule without having to protect these, although some further oxidation may occur (*cf.* no. 7).

In view of the fact that Δ^4-3-ones (II) can give rise to $\Delta^{4,6}$-dien-3-ones (III), as described above, the idea was entertained that the former might be intermediates in the oxidation of IV to III. This was not, however, considered likely, since in no case in the latter type of oxidation was there observed any material with an ultraviolet absorption maximum at 240 mμ typical of II. Moreover, the rate of oxidation of IV to III appeared to be appreciably faster than that of II to III. A more likely intermediate was the Δ^5-3-one (V), the intermediate in the Wettstein type of oxidation.[7] This was shown to be almost certainly the case by subjecting such an unconjugated ketone, Δ^5-pregnene-3,20-dione,[9] to oxidation with manganese dioxide. One hour at room temperature resulted in almost complete conversion to the $\Delta^{4,6}$-dien-3-one, 6-dehydroprogesterone. It thus became apparent that in the transformation of IV to III the first step is a slow oxidation of the alcohol to the β,γ-unsaturated ketone V, followed by rapid oxidation to the dienone.

Experimental[10]

Manganese Dioxide.—The dioxide employed for all the oxidations described in this paper was prepared from potas-

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[4] Similar difficulties in separating a Δ^4-3-one from the $\Delta^{4,6}$-dien-3-one were reported in the cortisone series by V. R. Mattox, E. L. Woroch, G. A. Fleisher and E. C. Kendall (*J. Biol. Chem.*, **197**, 261 (1952)).

[5] B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, THIS JOURNAL, **73**, 189 (1951).

[6] On the other hand, compounds containing the 17α,21-diol-20-one grouping unprotected at C-21 were degraded to the 17-ketones with manganese dioxide. The cleavage of other α-ketols and α-glycols by means of manganese dioxide will be described in a subsequent communication.

[7] A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940).

[8] Even with a compound containing the 21-acetoxy-20-one grouping (21-acetoxy-Δ^5-pregnen-3β-ol-20-one, no. 8), the Wettstein method appears to result in only a very low yield.[7]

[9] V. Westphal and J. Schmidt-Thomé, *Ber.*, **69**, 889 (1936).

[10] Melting points are uncorrected. Rotations were determined at 20° in chloroform, and ultraviolet absorption spectra in 95% ethanol solution, unless stated otherwise. We are indebted to Srta. Paquita Revaque for these measurements, and to Srta. Amparo Barba for the microanalyses.

TABLE I

No.	Starting material (IV)	Product (III)	Conversion, %	Crystall. solvent	Properties[a]	Reported properties[b]
1	Δ^5-22a-Spirosten-3β-ol (diosgenin)	$\Delta^{4,6}$-22a-Spirostadien-3-one[c]	31	Acetone–ether	M.p. 210–212°. $[\alpha]_D$ −56°. λ_{max} 284 mμ. log ϵ 4.47	M.p. 205–207°. $[\alpha]^{20}_D$ −55°[d]
2	Cholesterol	$\Delta^{4,6}$-Cholestadien-3-one	27	Methanol	M.p. 80–81°. $[\alpha]_D$ +31°. λ_{max} 284 mμ. log ϵ 4.48	M.p. 80.5–81.5°. $[\alpha]^{24}_D$ +33°[e]
3	Δ^5-Androsten-3β-ol-17-one	$\Delta^{4,6}$-Androstadiene-3,17-dione[c]	38	Acetone–ether	M.p. 172–173°. $[\alpha]_D$ +135°. λ_{max} 284 mμ. log ϵ 4.47	M.p. 168–170°. $[\alpha]^{20}_D$ +138°[f]
4	Δ^5-Pregnen-3β-ol-20-one	$\Delta^{4,6}$-Pregnadiene-3,20-dione (6-dehydroprogesterone)[c]	34	Acetone	M.p. 145–146°, $[\alpha]_D$ +185°. λ_{max} 284 mμ. log ϵ 4.50	M.p. 147–148°. $[\alpha]^{18}_D$ +149 (EtOH)[g]
5	$\Delta^{5,16}$-Pregnadiene-3β,20β-diol[h]	$\Delta^{4,6,16}$-Pregnatriene-3,20-dione (6,16-bisdehydroprogesterone)	27	Chloroform–acetone	M.p. 253–256°. $[\alpha]_D$ +144°. λ_{max} 240 mμ. log ϵ 4.21 and 284 mμ, log ϵ 4.48	Calcd. for $C_{21}H_{26}O_2$: C. 81.23; H. 8.44. Found: C. 81.58; H. 8.69
6	Δ^5-Pregnene-3β,20β-diol[h]	$\Delta^{4,6}$-Pregnadien-20β-ol-3-one	31	Chloroform–acetone	M.p. 197–199°. $[\alpha]_D$ +15°. λ_{max} 284 mμ. log ϵ 4.49	Calcd. for $C_{21}H_{30}O_2$: C. 80.21; H. 9.62. Found: C. 80.41; H, 9.97
7	Δ^5-Androstene-3β,17β-diol	(a) $\Delta^{4,6}$-Androstadien-17β-ol-3-one (6-dehydrotestosterone)	16	Acetone	M.p. 209–211°. $[\alpha]_D$ +74°. λ_{max} 284 mμ. log ϵ 4.50	M.p. 209–211°,[g] $[\alpha]^{20}_D$ +77°[f]
		(b) $\Delta^{4,6}$-Androstadiene-3,17-dione[c]	11	Acetone–ether	M.p. 171–173°. $[\alpha]_D$ +136°. λ_{max} 284 mμ. log ϵ 4.46	See no. 3
8	21-Acetoxy-Δ^5-pregnen-3β-ol-20-one	21-Acetoxy-$\Delta^{4,6}$-pregnadiene-3,20-dione (6-dehydrodesoxycorticosterone acetate)	21	Ether–pentane	M.p. 114–115°. $[\alpha]_D$ +164°. λ_{max} 284 mμ. log ϵ 4.49	M.p. 115–116°, $[\alpha]^{18}_D$ +151° (EtOH)[g]
9	Δ^5-Pregnene-3β,17α-diol-20-one[i]	$\Delta^{4,6}$-Pregnadien-17α-ol-3,20-dione	25	Acetone–ether	M.p. 240–242°. $[\alpha]_D$ +21°. λ_{max} 284 mμ. log ϵ 4.48	Calcd. for $C_{21}H_{28}O_3$: C. 76.79; H, 8.59. Found: C, 77.13; H, 8.77
10	Δ^5-Pregnene-3β,17α,21-triol-20-one 21-acetate[j]	$\Delta^{4,6}$-Pregnadiene-17α,21-diol-3,20-dione 21-acetate (6-dehydro Substance S acetate)	30	Acetone–ether	M.p. 220–222°. $[\alpha]_D$ +104°. λ_{max} 284 mμ. log ϵ 4.47	Calcd. for $C_{23}H_{30}O_5$: C. 71.48; H. 7.82. Found: C. 71.64; H. 8.15

[a] See footnote 10. [b] Analyses given for new compounds. [c] Identified by direct comparison with an authentic specimen. [d] J. Romo, H. J. Ringold, G. Rosenkranz and C. Djerassi, *J. Org. Chem* , **16**, 1873 (1951). [e] A. L. Wilds and C. Djerassi, THIS JOURNAL, **68**, 1712 (1946). [f] C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann and J. Pataki, *ibid.*, **72**, 4534 (1950). [g] A. Wettstein, *Helv. Chim. Acta*, **23**, 388 (1940). [h] Prepared by lithium aluminum hydride reduction of the corresponding C-20 ketone. [i] P. L. Julian, E. W. Meyer and I. Ryden, THIS JOURNAL, **72**, 367 (1950). [j] J. Heer and K. Miescher, *Helv. Chim. Acta*, **34**, 359 (1951).

sium permanganate and manganese sulfate, as described previously.[11]

Reaction of Δ^4-22a-Spirosten-3-one with Manganese Dioxide. (a) At Room Temperature.—A solution of 1.5 g. of Δ^4-22a-spirosten-3-one (λ_{max} 240 mμ, log ϵ 4.23) in 150 cc. of chloroform was shaken with 15 g. of manganese dioxide at room temperature for 24 hours. The total product exhibited λ_{max} 240 and 284 mμ, log ϵ 4.21 and 3.14, respectively, indicating a *ca.* 5% conversion to the $\Delta^{4,6}$-dien-3-one.

(b) **At 72°.**[12]—The reaction was carried out for 24 hours with 1.5 g. of Δ^4-22a-spirosten-3-one and 15 g. of manganese dioxide in 150 cc. of refluxing benzene, with stirring. The product showed λ_{max} 240 and 284 mμ, log ϵ 4.02 and 4.08, respectively, indicating a *ca.* 40% conversion to the $\Delta^{4,6}$-dien-3-one. After chromatographic purification on alumina and repeated crystallization from acetone–ether, a small quantity of $\Delta^{4,6}$-22a-spirostadien-3-one with m.p. 210–211° $[\alpha]^{20}_D$ −53°, λ_{max} 284 mμ, log ϵ 4.46 (*cf.* Table I, no. 1), was obtained.

Reaction of Δ^5-22a-Spirosten-3β-ol (Diosgenin) with Manganese Dioxide. (a) At Room Temperature.—A solution of 1 g. of diosgenin in 100 cc. of benzene was shaken with 10 g. of manganese dioxide for 24 hours. The total product showed λ_{max} 284 mμ, log ϵ 3.69 (*ca.* 16% conversion to dienone). After being shaken for a further 24 hours, the substance exhibited λ_{max} 284 mμ, log ϵ 3.92 (28% conversion to dienone). By chromatography on alumina a 20% yield of $\Delta^{4,6}$-22a-spirostadien-3-one could be isolated. Very similar results were obtained with other Δ^5-3β-ols.

(b) **At 72°.**[12] **Typical Procedure for All Oxidations Shown in Table I.**—A stirred solution of 1.5 g. of diosgenin in 150 cc. of benzene was boiled under reflux with 15 g. of manganese dioxide for 8 hours. The dioxide was removed by filtration, washed very well with hot benzene (in other cases it was found necessary to wash with hot chloroform or acetone), and the filtrate was evaporated to dryness. The residue showed λ_{max} 284 mμ, log ϵ 4.10 (43% conversion to dienone) and was chromatographed on 45 g. of alumina. The fractions eluted with hexane yielded 0.46 g. (31%) of $\Delta^{4,6}$-22a-spirostadien-3-one with m.p. 206–209°, λ_{max} 284 mμ, log ϵ 4.45, which on further crystallization from acetone–ether furnished material with properties indicated in Table I (no. 1). The fractions eluted with hexane–benzene (2:1 and 1:1) yielded recovered diosgenin.

All the other Δ^5-3β-ols shown in Table I were oxidized by this procedure, on the same scale. In those cases where the starting material was insoluble in hot benzene, the reaction was run in suspension with the finely ground solid.

Conversion of Δ^4-Pregnene-17α,21-diol-3,20-dione 21-Acetate (Substance S Acetate) to $\Delta^{4,6}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate.[13]—Substance S 21-acetate (5.0 g.) was converted to the 6-bromo compound by means of N-bromosuccinimide in chlorobenzene–carbon tetrachloride solution, containing pyridine, exactly as described by Mattox, *et al.*,[4] for cortisone 21-acetate. Crystallization from acetone–ether yielded 4.2 g. (70%) of product with m.p. 182–183° dec., $[\alpha]^{20}_D$ +65°, λ_{max} 242 mμ, log ϵ 4.25.

Anal. Calcd. for $C_{23}H_{31}O_5Br$: C, 59.09; H, 6.68; Br, 17.11. Found: C, 58.78; H, 6.61; Br, 17.39.

The bromo compound (1.2 g.) was heated under reflux with 15 cc. of redistilled γ-collidine under nitrogen for 30 minutes. The collidine hydrobromide (0.45 g.) was removed by filtration, the filtrate was diluted with ether and washed successively with dilute hydrochloric acid, sodium bicarbonate solution and water. Evaporation of the dried solution and crystallization from acetone–ether furnished 0.49 g. (50%) of 6-dehydro Substance S acetate with m.p. 221–223°, $[\alpha]^{20}_D$ +102°, λ_{max} 284 mμ, log ϵ 4.48. Identity

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(11) O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(12) Boiling point of benzene in Mexico, D.F.

(13) This experiment was kindly carried out by Dr. J. Romo of these laboratories.

with the specimen obtained by manganese dioxide oxidation (Table I, no. 10) was demonstrated by mixture melting point determination and infrared comparison.

Reaction of Δ^5-Pregnene-3,17-dione with Manganese Dioxide.—A solution of 0.20 g. of Δ^5-pregnene-3,17-dione (m.p. 163–165°, no high intensity absorption in the ultraviolet, quantitatively converted to progesterone with a trace of acid)[9] in 20 cc. of benzene was shaken at room temperature with 2 g. of manganese dioxide for 1 hour. The total product exhibited λ_{max} 284 mμ, log ϵ 4.41, and 6-dehydroprogesterone with m.p. 143–145° could easily be isolated after one crystallization.

MEXICO CITY, D. F.

[CONTRIBUTION NO. 1135 FROM STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

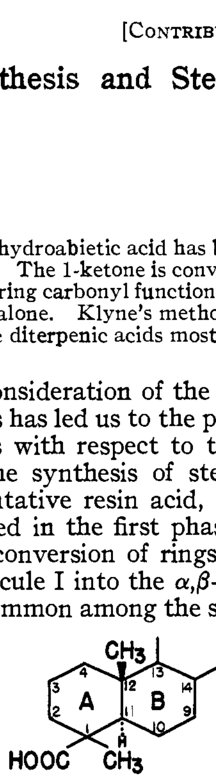
Synthesis and Stereochemistry of the 3-Keto-Δ^4-steroidal System from Diterpenic Acids[1a,b]

BY HAROLD H. ZEISS AND WILLIAM B. MARTIN, JR.[1c]

RECEIVED JULY 28, 1953

Dehydroabietic acid has been degraded by a series of reactions, including Hofmann elimination, to 1-ketonordehydroabietane. The 1-ketone is converted to 2-keto-$\Delta^{1,11}$-nordehydroabietene, a 3-keto-Δ^4-steroidal system, by a new method of moving a ring carbonyl function to an adjacent ring carbon atom. This method is applied also in the conversion of α-decalone to β-decalone. Klyne's method of molecular rotational differences is used to demonstrate that the C-12 angular methyl group of the diterpenic acids most probably has the steroidal β-configuration.

Consideration of the structures of the diterpenic acids has led us to the present investigation of these acids with respect to their use as source material in the synthesis of steroidal substances. A representative resin acid, dehydroabietic acid, is employed in the first phase of this problem, namely, the conversion of rings A and B of the resin acid molecule I into the α,β-unsaturated ketonic system II common among the steroidal hormones.



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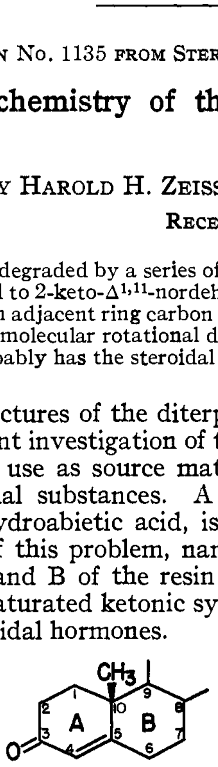

II

The degradation of dehydroabietic acid (III) at C-1 to 1-ketonordehydroabietane (IV),[2] previously believed to have been achieved by chromic acid oxidation of diphenyl-*t*-dehydroabietinol[3] and subsequently shown to be erroneous,[4] has been accomplished by a series of reactions including Hofmann elimination. In the course of this present work Jeger, *et al.*,[4] reported the preparation of IV by treatment of dehydroabietinol with phosphorus pentachloride followed by ozonolysis of the olefinic mixture containing the desired exocyclic olefin. Stork and Burgstahler[5] subsequently have synthesized *dl*-IV.

The acid chloride of III, by reaction with sodium azide followed by decomposition and rearrangement of the acid azide in xylene at 90°, is converted smoothly into dehydroabietane-1-isocyanate (V). The infrared spectrum of V is characterized by an intense band at 2220 cm.$^{-1}$ (4.5 μ) and the lack of the carbonyl band of III at 1680 cm.$^{-1}$ (5.9 μ). Treatment of V with mineral acid to obtain the corresponding primary amine is unsatisfactory; but reduction of V with lithium aluminum hydride[6] yields N-methyldehydroabietane-1-amine (VI). Reductive methylation of VI with formalin in formic acid gives rise to N,N-dimethyldehydroabietane-1-amine (VIII), which on further methylation with methyl iodide eliminates trimethylamine spontaneously, although slowly, at room temperature. The three β-carbon atoms, having one, two and three hydrogen atoms, may compete in this elimination. The Hofmann elimination rule leads to the prediction of predominant elimination at the C-1 methyl group, and this is found to be the case by the isolation of $\Delta^{1\text{-exo}}$-dehydroabietene (VIII). Alternately, the solid, unstable quaternary iodide from VII may be isolated, treated with silver oxide and thermally decomposed to VIII. Or, VI may be quaternized directly with methyl iodide and decomposed to VIII with equally satisfactory results.[7] The exocyclic nature of the double bond in VIII is substantiated by the appearance of absorption bands at 1650 cm.$^{-1}$ (6.1 μ) and at 880 cm.$^{-1}$ (11.3 μ) in the infrared spectrum of the olefin. From the ozonolysis of VIII at low temperature, ketone IV is obtained whose infrared spectrum (Fig. 1) is the same as that of Jeger's ketone and of the synthetic *dl*-ketone.[5] The 2,4-dinitrophenylhydrazone of IV melts between 85–86° in agreement with that derivative reported by Jeger.[4,8]

Of the several methods known for moving a ring carbonyl function to an adjacent ring carbon atom

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[1] (a) Taken from the dissertation submitted by W. B. Martin, Jr., to the Faculty of the Graduate School, Yale University, 1953, in candidacy for the degree of Doctor of Philosophy. (b) Presented in part at Buffalo, N. Y., March 26, 1952; Abstr. 121st Meeting, Amer. Chem. Soc., p. 41K; (c) E. I. du Pont de Nemours Fellow, 1951–1952.

[2] Nomenclatural usage in this paper follows the suggestion of J. L. Simonsen and D. H. R. Barton, "The Terpenes," Vol. III, Cambridge Univ. Press. 1952, p. 391, by which dehydroabietic acid becomes dehydroabietane-1-carboxylic acid.

[3] H. H. Zeiss, THIS JOURNAL, **70**, 858 (1948).

[4] A. Brossi, H. Gutmann and O. Jeger, *Helv. Chim. Acta*, **33**, 1730 (1950); H. H. Zeiss, THIS JOURNAL, **73**, 497 (1951).

[5] G. Stork and A. Burgstahler, *ibid.*, **73**, 3544 (1951).

[6] The reduction of an isocyanate to a methylamine, with lithium aluminum hydride, hithertofore unreported, to our knowledge was first performed by W. von E. Doering and K. B. Wiberg (unpublished results).

[7] The facile elimination is attributed to the excessive steric strain obtaining in the quaternary salt.

[8] The ketone itself, on standing for several months, crystallized, m.p. 50.5–51°; semicarbazone, m.p. 216–216.5°. Jeger has reported 30–32° and 204–205°, respectively, for these compounds. NOTE ADDED IN PROOF.—The isolation of a new C-1 ketone by R. P. Jacobsen, THIS JOURNAL, **75**, 4709 (1953), allows the presumption that Jeger's ketone is a *cis–trans* mixture.