[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE, THE WEIZMANN INSTITUTE OF SCIENCE]

Synthesis of 4-Methylated Steroids[1]

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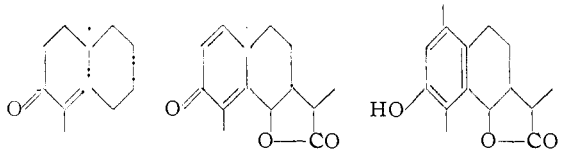
Two methods of synthesis of 4-methyl-Δ^4-cholesten-3-one (Xa) are described. The first involves the reaction of the enol lactone VIa with ethylmagnesium bromide, followed by treatment with base. The second, which proceeds only in poor yield, involves the direct monomethylation of Δ^4-cholesten-3-one (IVa). The first method is applied to the synthesis of 4-methyltestosterone (Xb) and 4-methylprogesterone (Xd). 4-Methyltestosterone acetate (Xc) is dehydrogenated with selenium dioxide to 4-methyl-1-dehydrotestosterone acetate (XIc), which on dienone–phenol rearrangement and saponification produces 1,4-dimethylestradiol (XIIb). This rearrangement is an exact parallel in the steroid series to the santonin–desmotroposantonin rearrangement.

The possibility that a substance isolated in these laboratories from grapefruit oil was a 4-methylated steroid first aroused our interest in this class of compound. Such substituted steroids, in particular the 4-methyl-Δ^4-3-ketones (type X), were unknown, although in the bicyclic series the analogous 3-keto-4,9-dimethyl-Δ^4-octahydronaphthalene (I)[2] and substituted derivatives are well known. Thus, the sesquiterpenes α-cyperone[3a] and carissone[3b] contain the system I, and other derivatives have been



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described in connection with studies related to the synthesis of santonin (II).[4] 4-Methylated steroidal Δ^4-3-ketones have furthermore become of considerable interest recently in view of the announcement that certain steroidal Δ^4-3-ketones methylated at the C-2 position possess higher biological activities than the unmethylated hormones.[5]

The preparation of a 4-methyl-Δ^4-3-ketone was first investigated in the cholesterol series. Two successful routes were found, both proceeding from Δ^4-cholesten-3-one (IVa) itself. The first utilized the enol lactone VIa, readily prepared from IVa through ozonolysis to the keto-acid Va, followed by heating with sodium acetate and acetic anhydride.[6] It is known that the enol lactone on reaction with methylmagnesium iodide, followed by base cyclization of the product, regenerates Δ^4-cholesten-3-one in high yield.[7] The analogous treatment of VIa with ethylmagnesium bromide when carried out with one equivalent at room temperature or below (conditions which have been used with the methyl Grignard reagent[6b,7a,8]) was unsatisfactory. However, when an excess of ethylmagnesium bromide was used in refluxing ether–benzene, the required 4-methyl-Δ^4-cholesten-3-one (Xa) was obtained in 65% yield after base cyclization.[9] The structure of Xa was confirmed by the infrared spectrum which indicated the presence of an α,β-unsaturated ketone and especially by the ultraviolet spectrum. The latter (λ_{max} 251 mμ, log ϵ 4.18) is in good agreement with the value (λ_{max} 252 mμ) to be expected of an α,β,β-trisubstituted α,β-unsaturated ketone with one exocyclic double bond.[10] Other substances containing the same chromophoric system as Xa have been shown to exhibit similar absorption (λ_{max} 248–251 mμ, log ϵ 4.13–4.21).[2,3,4,6b]

The substance produced by the reaction of Δ^4-cholesten-3-one with the ethyl Grignard reagent, which on base treatment furnishes the 4-methyl-Δ^4-3-ketone Xa, is presumably the unsaturated hemiketal VIIa or the corresponding diketone (*cf.* ref. 7b). No attempt at isolation of this intermediate was made in view of the known lability of the corresponding methyl compound.[7b] However, two further substances were produced by the Grignard reaction and could be isolated after the base treatment. The more polar of the two was a comparatively high melting substance, saturated to tetranitromethane, exhibiting an associated hydroxyl band at 3.08 μ, but no carbonyl bands in the infrared. The empirical formula appeared to be $C_{30}H_{54}O_2$, and we believe this compound to be the hemiketal VIIIa derived from VIa by reaction with two equivalents of the Grignard reagent. It has previously been reported[6b] that enol lactones of type VI on reaction with methylmagnesium iodide may yield a polar high-melting "over-reacted" product which very probably has a structure analogous to VIII. The other substance obtained from VIa and ethylmagnesium bromide was less polar than the 4-methyl-Δ^4-3-ketone Xa, was unsaturated to tetranitromethane and in the infrared showed no hydroxyl band but a medium intensity band at 5.98 μ. The empirical formula was $C_{30}H_{52}O$ and all these observations are consistent with the enol

(1) Presented in part at the 19th Meeting of the Chemical Society of Israel, June 11, 1956 (*cf. Bull. Research Council Israel*, **5A**, 283 (1956)).

(2) F. D. Gunstone and R. M. Heggie, *J. Chem. Soc.*, 1437 (1952); F. J. McQuillin, *ibid.*, 528 (1955); M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956).

(3) (a) *Inter al.* R. Howe and F. J. McQuillin, *J. Chem. Soc.*, 2423 (1955), and previous papers; (b) K. Mohr, O. Schindler and T. Reichstein, *Helv. Chim. Acta*, **37**, 462 (1954); D. H. R. Barton and E. J. Tarlton, *J. Chem. Soc.*, 3492 (1954).

(4) *Inter al.* Y. Abe, *et al.*, THIS JOURNAL, **75**, 2567 (1953); **78**, 1116, 1422 (1956).

(5) J. A. Hogg, F. H. Lincoln, R. W. Jackson and W. P. Schneider, *ibid.*, **77**, 6401 (1955).

(6) (a) R. B. Turner, *ibid.*, **72**, 579 (1950); (b) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(7) (a) G. I. Fujimoto, *ibid.*, **73**, 1856 (1951); (b) R. D. H. Heard and P. Ziegler, *ibid.*, **73**, 4036 (1951).

(8) *Cf.* L. B. Barkley, M. W. Farrar, W. S. Knowles, H. Raffelson and Q. E. Thompson, *ibid.*, **76**, 5014 (1954).

(9) After completion of this part of our work, we were informed by Prof. E. R. H. Jones that this substance had also been prepared in his laboratory. An account of this preparation has now been published (G. D. Meakins and O. R. Rodig, *J. Chem. Soc.*, 4679 (1956)). The reported negative rotation ($[\alpha]_D$ −108°) *versus* our positive value ($[\alpha]_D$ +110°) is presumably a misprint.

(10) R. B. Woodward, THIS JOURNAL, **64**, 76 (1942).

ether structure IX, the dehydration product of VIII.[11]

The other route to 4-methyl-Δ^4-cholesten-3-one involves the direct methylation of Δ^4-cholesten-3-one by means of methyl iodide and *t*-potassium butoxide in *t*-butyl alcohol. This reaction, when carried out with 3 molar equivalents of the potassium alkoxide, is known to produce 4,4-dimethyl-Δ^5-cholesten-3-one in over 60% yield.[12] The process presumably proceeds *via* the desired monomethylation product Xa, but the latter can only be formed in high yield by the monomethylation of IVa if this reaction takes place appreciably faster than the further methylation of Xa to the 4,4-dimethyl-Δ^5-compound. Unfortunately no indication of the first step occurring faster than the second could be found, as evidenced by the fact that the dimethylation of Δ^4-3-ketones can be brought about by means of methyl iodide and potassium *t*-butoxide in *t*-butyl alcohol even at room temperature[13] and that the further methylation of the 4-methyl-Δ^4-3-ketone Xa (obtained by the route described above) to the corresponding 4,4-dimethyl-Δ^5-3-ketone occurs very readily (see Experimental). Nevertheless the monomethylation of Δ^4-cholesten-3-one was studied under different conditions. It was found that when conditions were used so that unchanged ketone remained, already much of the dimethyl ketone was formed. However, the presence of the monomethyl ketone Xa could be detected by ultraviolet spectroscopy, and under suitable conditions this compound could be isolated in about 5% yield. Although this constitutes a one-step synthesis of Xa, the first-mentioned route is to be preferred in view of the much higher yield and ease of isolation of the product.

Methods for producing 4-methyl-Δ^4-3-ketones having been worked out in the cholesterol series, we applied the preferred one for making available the 4-methylated hormones in the testosterone, esterone and progesterone series. The enol lactone VIc readily obtained by ozonolysis of testosterone or of its acetate and treatment of the resulting keto acid with acetic anhydride and sodium acetate,[7a,14] was allowed to react with excesss ethylmagnesium bromide. Base treatment of the product then furnished 4-methyltestosterone (Xb) in *ca.* 25% yield,[15] and 40% of the keto-acid Vb could be recovered. 4-Methyltestosterone (Xb), as well as the corresponding 17-acetate (Xc), showed the expected maximum in the ultraviolet at 251 mμ.

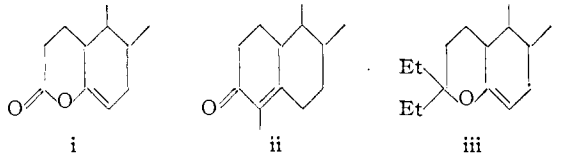
It has been shown that steroidal Δ^4-3-ketones may be dehydrogenated to the corresponding $\Delta^{1,4}$-dien-3-ones by means of selenium dioxide,[16] preferably in a tertiary alcohol containing some acetic acid.[17] We have found that 4-methyl-Δ^4-3-ketones may similarly be dehydrogenated, for 4-methyltestosterone (Xb) under these conditions produced 4-methyl-1-dehydrotestosterone (4-methyl-$\Delta^{1,4}$-androstadien-17β-ol-3-one) (XIb). Similarly, 4-methyltestosterone acetate (Xc) gave the acetate XIc.[18] Both XIb and XIc showed ultraviolet maxima at 244 mμ (log ϵ 4.16), in good agreement with the spectra of the various stereoisomers of santonin (II) (λ_{max} 242–246 mμ, log ϵ 4.01–4.27),[4] which contain the identical chromophoric system. The infrared spectra showed the doublets at 6.17 and 6.23 μ in the double bond region, typical of $\Delta^{1,4}$-dien-3-ones.[19]

In addition to the expected dienones, the selenium dioxide dehydrogenation of Xb and Xc produced selenium-containing substances (*cf.* ref. 17a), which are now being investigated.

The various stereoisomers of santonin (II) on treatment with acids[4,20] (most conveniently with acetic anhydride–sulfuric acid and subsequent saponification[21]) yield the desmotroposantonins (III), this reaction being the classical example of the so-called dienone–phenol rearrangement. The exact parallel in the steroid series was realized when 4-methyl-1-dehydrotestosterone acetate (XIc) was treated with *p*-toluenesulfonic acid in acetic anhydride and the product was saponified, thereby producing 1,4-dimethylestradiol (XIIb). The structure of this substance was confirmed by its ultraviolet spectrum (λ_{max} 288 mμ, log ϵ 3.23), very similar to that of the desmotroposantonins (λ_{max} 290 mμ, log ϵ 3.33–3.46)[4] and exhibiting the expected bathochromic shift compared to estradiol (λ_{max} 280 mμ, log ϵ 3.30)[22] and 1-methylestradiol (λ_{max} 284 mμ, log ϵ 3.28).[22]

In the progesterone series, the keto-acid Vd obtained by the ozonolysis of progesterone was converted to the enol lactone enol acetate VIe (stereo-

(11) Since this manuscript was prepared, J. A. Hartman, A. J. Tomasewski and A. S. Dreiding (THIS JOURNAL, **78**, 5662 (1956)) have described the obtention of 4-methyl-19-nortestosterone acetate (ii) from the enol lactone i derived from 19-nor-testosterone, by reaction with ethylmagnesium iodide and base. The sole by-product isolated from this reaction was the enol ether iii, analogous to our by-product IX. It



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was considered that the "over-reacted" material[5b] derived from enol lactones of type VI with methylmagnesium iodide therefore had a structure analogous to iii (and IX). However, this "over-reacted" material is polar and high-melting, like VIII, whereas the enol ethers iii and IX are non-polar (less polar than the corresponding 4-methyl-Δ^4-3-ketones) and comparatively low-melting.

(12) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *ibid.*, **76**, 2852 (1954).

(13) D. Elad and F. Sondheimer, *Bull. Research Council Israel*, **5A**, 269 (1956).

(14) C. C. Bolt, *Rec. trav. chim.*, **57**, 905 (1938); F. L. Weisenborn, D. C. Remy and T. L. Jacobs, THIS JOURNAL, **76**, 552 (1954).

(15) Drs. G. Rosenkranz and H. J. Ringold of Syntex S.A., Mexico City, have kindly informed us that they have independently prepared this substance by the same method (H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, in press).

(16) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *ibid.*, **21**, 239 (1956).

(17) (a) C. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); (b) S. A. Spilfogel, T. A. P. Posthumus, M. S. de Winter and D. A. van Dorp, *Rec. trav. chim.*, **75**, 475 (1956).

(18) T. Miki (*J. pharm. Soc. Japan*, **75**, 403, 410 (1955)) and Y. Abe, *et al.* (latest reference of footnote 4), have now also described the dehydrogenation of 4-methyl-Δ^4-3-ketones in the decalin series (type I) to the corresponding dienones with selenium dioxide in acetic acid and pyrolysis of the product.

(19) R. N. Jones, P. Humphries, E. Packard and K. Dobriner, THIS JOURNAL, **72**, 86 (1950).

(20) *Cf.* G. R. Clemo, R. D. Haworth and E. Walton, *J. Chem. Soc.*, 1110 (1930).

(21) Huang-Minlon, Chien-Pen Lo and Ju-Yung Chu, THIS JOURNAL, **65**, 1780 (1943).

(22) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953), Table 31.

isomeric mixture at C-20).[23] Reaction with ethylmagnesium bromide and base treatment, as previously, then produced 4-methylprogesterone (Xd) with the typical ultraviolet maximum at 251 mμ. In addition, a polar comparatively high-melting saturated by-product could again be isolated, to which the hemi-ketal structure VIIId is assigned.

In Table I, the molecular rotations ($[M]_D$) of the various 4-methyl-Δ^4-3-ketones are compared with those of the parent Δ^4-3-ketones. It can be seen that in all cases the introduction of the 4-methyl group results in an appreciable increase in the $[M]_D$, ranging from +91 in the cholestenone to +130 in the progesterone series. A similar increase is observed in passing from $\Delta^{1,4}$-dien-3-ones to the corresponding 4-methyl compounds. It is of interest to note that whereas testosterone and its acetate have almost the identical $[M]_D$, the increase in the $[M]_D$ which occurs in acetylating 1-dehydrotestosterone is also observed in the 4-methyl-1-dehydro series.

In preliminary assays carried out by the Endocrine Laboratories (Madison, Wis.), 4-methyltestosterone was found to possess *ca.* 40% of the androgenic and 120% of the myothrophic activity of testosterone, when tested by injection in castrated immature mice. 4-Methylprogesterone had *ca.* 50% of the progestational activity of progesterone, when tested by subcutaneous injection in estrogen-primed rabbits.

(23) G. I. Fujimoto and J. Prager, THIS JOURNAL, **75**, 3259 (1953).

TABLE I

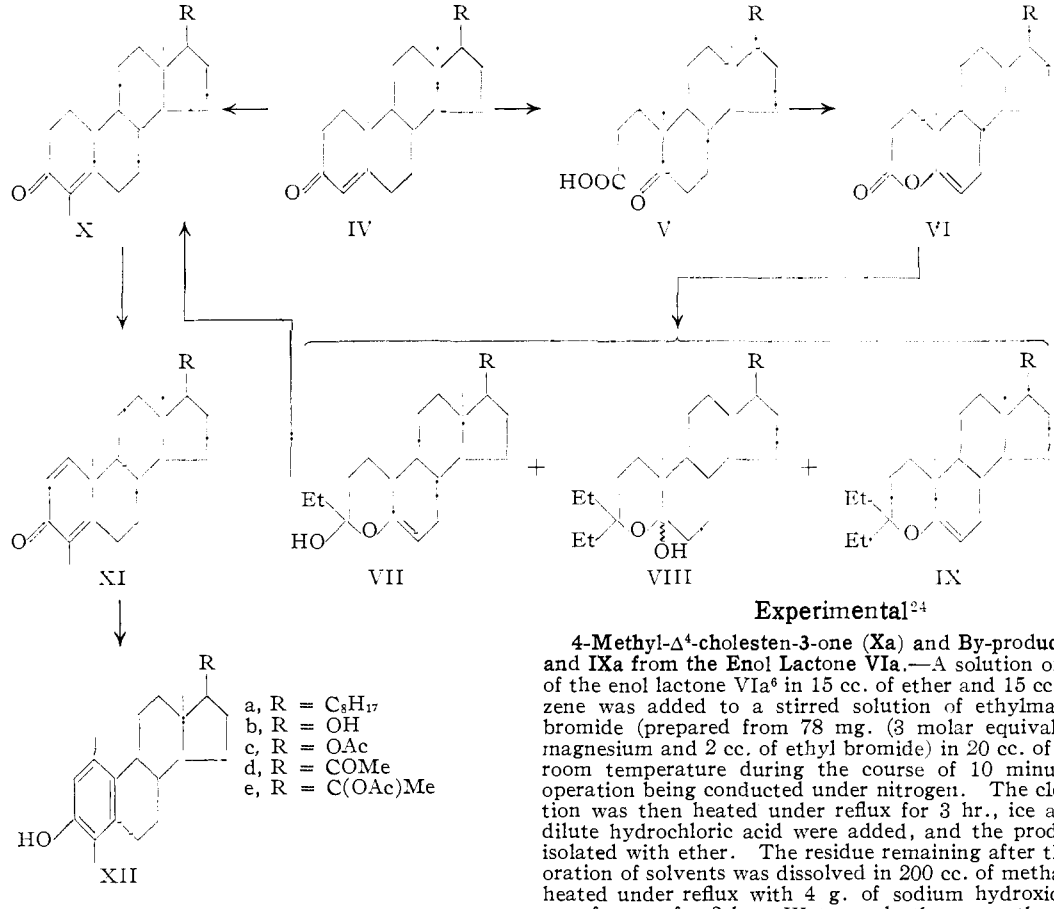
MOLECULAR ROTATION DATA OF 4-METHYL-Δ^4-3-KETONES

Series	$[M]_D$ of Δ^4-3-ketone	$[M]_D$ of 4-methyl-Δ^4-3-ketone	$\Delta[M]_D$
Δ^4-Cholesten-3-one	+342[a]	+438	+96
Testosterone	+314[b]	+405	+91
Testosterone acetate	+317[b]	+420	+103
Progesterone	+641[b]	+771	+130
1-Dehydrotestosterone	+57[c]	+138	+81
1-Dehydrotestosterone acetate	+92[c]	+205	+113

[a] L. F. Fieser, THIS JOURNAL, **75**, 4377 (1953). [b] F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *ibid.*, **75**, 4712 (1953). [c] H. H. Inhoffen, G. Zühlsdorff and Huang-Minlon, *Ber.*, **73**, 451 (1940).

Various reactions of the 4-methylated steroids described in this paper are now being investigated and will be reported in a subsequent publication.

Acknowledgment.—We are indebted to Dr. G. Rosenkranz of Syntex S.A., Mexico City, for the generous supply of steroidal starting materials.



Experimental[24]

4-Methyl-Δ^4-cholesten-3-one (Xa) and By-products VIIIa and IXa from the Enol Lactone VIa.—A solution of 0.42 g. of the enol lactone VIa[6] in 15 cc. of ether and 15 cc. of benzene was added to a stirred solution of ethylmagnesium bromide (prepared from 78 mg. (3 molar equivalents) of magnesium and 2 cc. of ethyl bromide) in 20 cc. of ether at room temperature during the course of 10 minutes, the operation being conducted under nitrogen. The clear solution was then heated under reflux for 3 hr., ice and then dilute hydrochloric acid were added, and the product was isolated with ether. The residue remaining after the evaporation of solvents was dissolved in 200 cc. of methanol and heated under reflux with 4 g. of sodium hydroxide in 40 cc. of water for 2 hr. Water and ether were then added, and the product, obtained by the evaporation of the dried ether extract, was chromatographed on 15 g. of alumina.

(24) Melting points are uncorrected. Rotations were determined (at 20°) in chloroform solution unless specified otherwise. Ultraviolet spectra were measured in 95% ethanol solution on a Unicam Model S.P. 500 spectrophotometer and infrared spectra in chloroform solution on a Baird double beam recording spectrophotometer [for brevity only bands in the hydroxyl region (2.8–3.2 μ) and carbonyl region (5.5–6.4 μ) are reported]. Analyses were carried out in our microanalytical department under the direction of Mr. Erich Meier.

The solid fractions (56 mg., 12%) eluted with pentane yielded the enol ether IXa (see below). The next solid fractions, eluted with pentane–benzene (9:1) on crystallization from ether–methanol furnished 285 mg. (66%) of 4-methyl-Δ^4-cholesten-3-one, m.p. 102–103°, $[\alpha]_D$ +110°, λ_{max} 251 mμ (log ε 4.18), λ_{max} 6.02 and 6.18 μ.

Anal. Calcd. for $C_{28}H_{46}O$: C, 84.35; H, 11.63. Found: C, 84.39; H, 11.65.

The fractions eluted with ether on crystallization from ether–pentane gave 66 mg. (14%) of the hemi-ketal VIIIa, m.p. 175–176°, $[\alpha]_D$ +31°, λ_{max} 2.91 and 3.08 μ.

Anal. Calcd. for $C_{30}H_{54}O_2$: C, 80.65; H, 12.18. Found: C, 80.29; H, 12.07.

The enol ether IXa, eluted first from the column, on crystallization from ether–methanol showed m.p. 103–104°, $[\alpha]_D$ +1°, λ_{max} 5.98 μ.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.93; H, 12.28.

4-Methyl-Δ^4-cholesten-3-one (Xa) by Direct Methylation of Δ^4-Cholesten-3-one (IVa).—A solution of 300 mg. of potassium (3 molar equivalents) in 10 cc. of *t*-butyl alcohol was added to a boiling solution of 1 g. of Δ^4-cholesten-3-one in 30 cc. of benzene. Methyl iodide (3 cc.) in 30 cc. of benzene was then added and refluxing was continued for 5 minutes. The solution was cooled, 0.5 cc. of water was added and the solvents were evaporated to dryness under reduced pressure. Ether was added, the insoluble potassium iodide was collected and the filtrate was evaporated. Crystallization of the residue from methanol yielded 450 mg. of 4,4-dimethyl-Δ^5-cholesten-3-one,[12] m.p. 172–174°, no high-intensity absorption in the ultraviolet. The mother liquors (λ_{max} 243 mμ, log ε 4.01 and 250 mμ, log ε 3.95) were chromatographed on 20 g. of alumina. The fractions eluted with pentane furnished another 35 mg. of the 4,4-dimethyl-Δ^5-3-ketone (total yield 45%). The next solid fractions, eluted with pentane–benzene (9:1), on crystallization from ether–methanol produced 54 mg. (5%) of 4-methyl-Δ^4-cholesten-3-one, m.p. 101–103°, λ_{max} 251 mμ (log ε 4.16). The m.p. was undepressed on admixture with the sample prepared from VIa and the infrared spectra were identical. Further elution with pentane–benzene (8:2) gave an oil (102 mg.) which was not further investigated. Finally, pentane–benzene (6:4) eluted 150 mg. (15%) of unchanged Δ^4-cholesten-3-one, m.p. 79–81°.

When the methylation of cholestenone was carried out with 1 mol. of potassium *t*-butoxide and 1 mol. of methyl iodide (boiling for 15 minutes), 7.5% of the 4,4-dimethyl ketone, 3% of the 4-methylcholestenone (Xa) and 70% of unchanged starting material were obtained.

Methylation of 4-Methyl-Δ^4-cholesten-3-one (Xa) to 4,4-Dimethyl-Δ^5-cholesten-3-one.—Potassium (15 mg., 3 molar equivalents) dissolved in 0.5 cc. of *t*-butyl alcohol was added to a boiling solution of 50 mg. of 4-methyl-Δ^4-cholesten-3-one in 1.5 cc. of benzene. A solution of 0.5 cc. of methyl iodide in 5 cc. of benzene was added and boiling was continued for 5 minutes. The reaction mixture was worked up as described above for the methylation of Δ^4-cholesten-3-one. Crystallization of the residue (after removal of potassium iodide) from ether–methanol produced 32 mg. of 4,4-dimethyl-Δ^5-cholesten-3-one, m.p. 170–172°, undepressed on admixture with a sample prepared by the above-described method.

4-Methyltestosterone (Xb).—A solution of ethylmagnesium bromide (prepared from 0.41 g., 2 molar equivalents, of magnesium) in 40 cc. of ether was added dropwise to a stirred solution of 2.8 g. of the enol lactone acetate VIc[7a] in 50 cc. of ether and 50 cc. of benzene during 15 minutes, under nitrogen. The reaction mixture in which a heavy precipitate had formed was heated under reflux for 2 hr. and was then cooled and decomposed with dilute hydrochloric acid. Isolation with ether yielded a product which was triturated with 250 cc. of ether and the insoluble over-reacted material (0.76 g.), m.p. 273–276°, $[\alpha]_D$ +8° (pyridine) was collected. The filtrate was evaporated, and the residue was heated under reflux for 2 hr. with 1 g. of potassium hydroxide in 30 cc. of methanol. The neutral product was isolated with ether and chromatographed on 30 g. of alumina. The fractions eluted with benzene and benzene–ether (9:1) on crystallization from ether–pentane yielded 0.64 g. (25%) of 4-methyltestosterone, m.p. 172–173°, $[\alpha]_D$ +134°, λ_{max} 251 mμ (log ε 4.16); λ_{max} 2.82, 6.01 and 6.20 μ.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.52; H, 10.06.

The acetate Xc crystallized from methanol as needles, m.p. 158–160°, $[\alpha]_D$ +122°, λ_{max} 251 mμ (log ε 4.17); λ_{max} 5.78, 6.00 and 6.20 μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.89; H, 9.13.

The acidic material obtained after the base treatment on crystallization from acetone furnished 1.05 g. (40%) of recovered keto-acid Vb,[14] m.p. 202–203°.

4-Methyl-1-dehydrotestosterone (XIb).—4-Methyltestosterone (250 mg.) and selenium dioxide (125 mg.) were heated under reflux with 5 cc. of *t*-butyl alcohol and 0.05 cc. of glacial acetic acid under nitrogen for 8 hr., another 125 mg. of selenium dioxide was then added and refluxing was continued for another 16 hr. Ether and water were added, the organic layer was washed with sodium carbonate solution and water, dried and evaporated. The residue was chromatographed on 10 g. of alumina and the fractions eluted with benzene and benzene–ether (9:1) were crystallized from ether–hexane and sublimed in high vacuum. This procedure yielded 72 mg. (29%) of 4-methyl-1-dehydrotestosterone, m.p. 188–190°, $[\alpha]_D$ +46°, λ_{max} 244 mμ (log ε 4.16); λ_{max} 2.90, 6.01, 6.17 and 6.23 μ.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.76; H, 9.30.

Further elution of the chromatogram with ether yielded 75 mg. of a selenium-containing substance, m.p. *ca.* 290° (dec. with separation of red selenium).

4-Methyl-1-dehydrotestosterone Acetate (XIc).—4-Methyltestosterone acetate (400 mg.) in 8 cc. of *t*-butyl alcohol and 0.08 cc. of glacial acetic acid was dehydrogenated with two lots of selenium dioxide (2 × 200 mg.) as described above for the corresponding alcohol. Chromatography on 16 g. of alumina and crystallization of the fractions eluted with pentane–benzene (9:1 and 8:2) from pentane–ether yielded 84 mg. (21%) of 4-methyl-1-dehydrotestosterone acetate, m.p. 175–176°, $[\alpha]_D$ +60°, λ_{max} 245 mμ (log ε 4.17); λ_{max} 5.78, 6.02, 6.17 and 6.22 μ.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.02; H, 8.71.

The fractions eluted with pentane–benzene (2:1) on crystallization from acetone yielded 64 mg. of a selenium-containing substance, m.p. 240–245° dec.

4-Methyl-1-dehydrotestosterone acetate could alternatively be prepared by acetylating the free alcohol XIb (described above) with acetic anhydride and pyridine at room temperature.

1,4-Dimethylestradiol (XIIb).—A solution of 55 mg. of 4-methyl-1-dehydrotestosterone acetate and 15 mg. of *p*-toluenesulfonic acid in 5 cc. of acetic anhydride was heated on the steam-bath for 3 hr. The residue obtained by isolation with ether was heated under reflux with 0.5 g. of potassium hydroxide in 15 cc. of methanol for 1 hr., under nitrogen. Addition of water, isolation with ethyl acetate and crystallization from methylene chloride–methanol produced 35 mg. (73%) of 1,4-dimethylestradiol as long needles, m.p. 125–129°, $[\alpha]_D$ +155°, λ_{max} 288 mμ (log ε 3.23); λ_{max} 2.88 and 3.08 μ. This substance contained solvent of crystallization as evidenced by the bubbling observed at the m.p. and by the low carbon content. The solvent-free diol could only be obtained by sublimation at 140–160° in high vacuum.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.62; H, 9.65.

4-Methylprogesterone (Xd).—A solution of ethylmagnesium bromide (prepared from 0.67 g., 2.5 molar equivalents, of magnesium) in 50 cc. of ether was added to a stirred solution of 4 g. of the enol lactone enol acetate VIe[23] in 75 cc. of ether and 75 cc. of benzene during 15 minutes under nitrogen. The mixture was heated under reflux for 2.5 hr., cooled and decomposed with dilute hydrochloric acid. The residue remaining after evaporation of the dried organic extract was heated under reflux with 1.5 g. of potassium hydroxide in 50 cc. of methanol for 2 hr. under nitrogen. Ice was added and the non-acidic material was isolated with ether in the usual way. The resulting oil (2.8 g.) was chromatographed on 100 g. of alumina. The fractions eluted with pentane–benzene (9:1, 8:2 and 7:3) on crystallization from

ether–methanol gave 4-methylprogesterone (0.36 g.) as needles, m.p. 155–157°, $[\alpha]D$ +235°, λ_{max} 251 mμ (log ε 4.18); λ_{max} 5.84, 6.00 and 6.20 μ.

Anal. Calcd. for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82. Found: C, 80.60; H, 9.69.

The fractions eluted with ether on crystallization from acetone–hexane yielded the hemi-ketal VIIId, m.p. 178–180°, $[\alpha]D$ +37°, λ_{max} 2.96 and 5.84 μ.

Anal. Calcd. for $C_{24}H_{40}O_3$: C, 76.55; H, 10.71. Found: C, 76.14; H, 10.60.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Acid-catalyzed Rearrangement of Cinenic Acid. III.[1] Structure and Synthesis of the Lactonic Product

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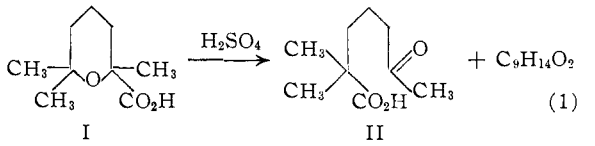
A crystalline lactone, isolated in 15% yield after treatment of α-cinenic acid (I) with concentrated sulfuric acid, has been shown to possess structure III. This lactone has been synthesized using a two-step procedure involving the Diels–Alder addition of isoprene to ethyl methacrylate and lactonization of the resultant adduct. The formation of III from I involves a reaction sequence which is unrelated to the carboxyl transfer process which produces geronic acid (II).

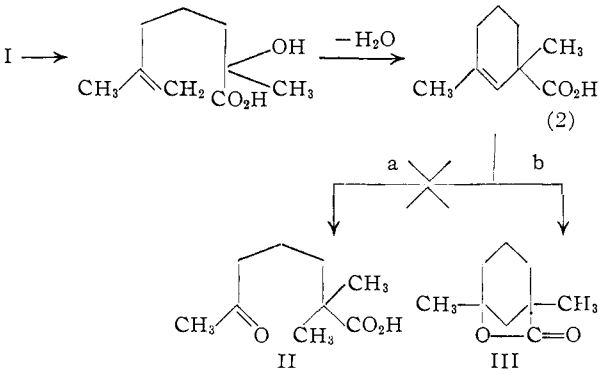
Introduction

As a continuation of our study of the acid-catalyzed rearrangements of α-cinenic acid (I), we have investigated the structure of the crystalline lactone, $C_9H_{14}O_2$, which is formed in about 15% yield when α-cinenic acid is isomerized to geronic acid (II) (see eq. 1).[2,3] The results of these synthetic and degradative studies are presented below.



I II (1)

On the basis of a mechanism for the formation of II which is now known to be erroneous (eq. 2a), Rupe derived formula III[2] for the lactonic product (eq. 2b). The support for this formulation, aside



(2)

II III

from these "theoretical" considerations, came only from the observations that the lactone was saturated (therefore bicyclic) and that it could be hydrolyzed to a hydroxy-acid which dehydrated to regenerate the original lactone. Since this rather incomplete evidence in favor of III is weakened by the discovery that the formation of II involves a carboxyl transfer process rather than the path shown in equation 2,[4] we have sought a rigorous proof of the lactone structure.

Structure Proof

The rearrangement of I was carried out as previously described, and a crystalline lactone, m.p. 50–51°, was obtained from the neutral portion of the product. A Kuhn–Roth determination indicated the presence of two C-methyl groups. The infrared spectrum of the crystalline lactone (in Nujol) showed a maximum at 5.60 μ. More significantly, in chloroform solution the lactone showed maximal absorption at 5.67 μ. Since these findings were in accord with the proposed structure, an independent synthesis of this structure was undertaken as the simplest method of unambiguous identification. The method chosen for the synthesis is outlined in Chart 1. Diels–Alder addition of isoprene to ethyl methacrylate gave a *mixture* of adducts, not easily separable into its individual components by fractional distillation. The formation of both of the theoretically possible products was anticipated, and ensured the success of the synthesis. Treatment of the mixture with sulfuric acid in acetic acid gave a mixture of lactones, from which III, m.p. 50–51°, and IV, m.p. 48–49°, were isolated by distillation and purified by crystallization. These were the lactones to be expected from acid-catalyzed cyclization following Markownikoff's rule. In accord with the structural assignments, III showed lactonic absorption at 5.67 μ (in chloroform) while IV showed absorption at 5.80 μ (in chloroform). The reported carbonyl bands for the known models

VI VII

VI and VII are at 5.67 and 5.76 μ, respectively.[5] Finally, III was degraded in good yield to *m*-xylene (identified by conversion to its trinitro derivative, as well as by its infrared and ultraviolet spectra) by

(1) Presented at the 131st National Meeting, American Chemical Society, Miami, Florida, April, 1957. For the previous paper in this series see J. Meinwald and C. C. Cornwall, THIS JOURNAL, **77**, 5991 (1955).

(2) H. Rupe and C. Liechtenhan, *Ber.*, **41**, 1278 (1908).

(3) H. Rupe and H. Hirschmann, *Helv. Chim. Acta*, **16**, 505 (1933).

(4) J. Meinwald, THIS JOURNAL, **77**, 1617 (1955).

(5) R. Grewe, A. Heinke and C. Sommer, *Chem. Ber.*, **89**, 1978 (1956).