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

Steroids and Triterpenoids of Citrus Fruit. III.[1] The Structure of Citrostadienol, a Natural 4α-Methylsterol[2]

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The structure of the citrus peel-oil constituent citrostadienol is shown to be 4α-methyl-$\Delta^{7,24(28)}$-stigmastadien-3β-ol (4α-methyl-24-ethylidene-Δ^7-cholesten-3β-ol) (Ia).

The isolation and characterization of citrostadienol from Israeli grapefruit and orange-peel oil was reported in the previous paper of this series.[1] This substance, m.p. 162–164°, $[\alpha]D$ +24°, γ_{max} 209 mμ (ε 5,500),[25] had the apparent composition $C_{30}H_{50}O \pm CH_2$ and evidence was presented that it was a doubly unsaturated 3β-hydroxy-5α-steroid[3] or tetracyclic triterpene, one of the double bonds being located at the Δ^7- or $\Delta^{8(9)}$-position. We now describe experiments which show citrostadienol to be 4α-methyl-$\Delta^{7,24(28)}$-stigmastadien-3β-ol (4α-methyl-24-ethylidene-Δ^7-cholesten-3β-ol) (Ia).[4]

A clue as to the nature of the side-chain of citrostadienol was provided by the fact that acetaldehyde was obtained through ozonolysis, or preferably through successive hydroxylation of citrostadienol acetate with osmium tetroxide and treatment with periodic acid. This observation suggested the presence of the $\Delta^{24(28)}$-stigmastene (24-ethylidene-cholestane) side-chain, previously found in the algae sterols fucosterol[5] and sargasterol.[6] It may be noted that β-sitosterol (24-ethylcholesterol), a companion of citrostadienol from which the latter was separated only with difficulty,[1] contains the corresponding saturated side-chain.

It has been pointed out previously[1] that the molecular rotation (M_D) data for citrostadienol resemble those of the tetracyclic triterpenes rather than the sterols, the shift in M_D in passing from the natural alcohol to its acetate (Δ_1) being positive rather than negative.[7] Two observations, however, ruled out a normal tetracyclic triterpene (4,4,14-trimethyl-sterol) structure. Firstly, treatment of citrostadienol with phosphorus pentachloride in benzene[8] did not cause contraction of ring A to an isopropylidene-cyclopentane derivative (as judged by the non-formation of acetone or of a cyclopentanone after ozonolysis of the product) and the 4,4-dimethyl-3β-hydroxy-5α-grouping therefore appeared to be absent. Secondly, hydrogenation of citrostadienol acetate in acetic acid over a platinum catalyst resulted in the uptake of one molar equivalent of hydrogen and yielded isocitrostenol acetate, which was saponified to isocitrostenol. The latter no longer contained the side-chain double bond since ozonolysis gave no acetaldehyde. The ultraviolet spectrum (λ_{max} 210 mμ, ε 10,500)[25] clearly indicated the nuclear double bond to have migrated to the $\Delta^{8(14)}$-position[9] and this was confirmed by the fact that isocitrostenol acetate no longer reacted positively in the Fieser selenium dioxide test.[10] The presence of a 14-methyl group is therefore excluded.

Although citrostadienol could not be a 4,4-dimethyl-3β-hydroxy sterol, the anomalous molecular rotation data were indicative of a sterol structure with an additional alkyl group (or groups) near to the 3β-hydroxy function. Further information was provided by the complete hydrogenation of citrostadienol acetate or of isocitrostenol acetate over platinum in acetic acid containing hydrochloric acid. These conditions are known to effect the hydrogenation of $\Delta^{8(14)}$-steroids[11] and the saturated citrostanol acetate was indeed obtained. Saponification yielded citrostanol which could be oxidized to the saturated ketone citrostanone by means of chromium trioxide in acetic acid.

In the course of our recent studies on ring A-methylated saturated steroids,[12] we prepared a number of ring A methylated cholestan-3β-ols. It was found that the Δ_1-values for the 2α methyl and 2,2-dimethyl derivatives are −179 and −42, respectively, while the corresponding values for the 4α- and 4,4-dimethyl derivatives are +73 and +41. The Δ_1-value for citrostanol is +61, suggestive of a 4α-methyl or 4,4-dimethyl-3β-ol structure. The latter has, however, already been ruled out and citrostanol therefore appeared to be 4α-methylstigmastan-3β-ol (VIIa).

At this stage synthetic work was undertaken. It has been shown that Δ^4-3-ketones can be monomethylated directly at C-4 by means of methyl iodide and potassium *t*-butoxide in boiling *t*-butyl alcohol.[13] Under these conditions Δ^4-stigmasten-3-

(1) For Part II, see A. Weizmann and Y. Mazur, *J. Org. Chem.*, **23**, 832 (1958).

(2) Presented in part before the Organic Chemistry Division at the 133rd Meeting of the American Chemical Society, San Francisco, Calif., April, 1958.

(3) The 3-hydroxy group is in the β-configuration as citrostadienol gives an insoluble digitonide. The 5α-configuration is based on the fact that the 3β-hydroxy group is equatorial since lithium aluminum hydride reduction of citrostadienone regenerates citrostadienol in high yield and since citrostadienol acetate exhibits a single unsplit band at 1252 cm.$^{-1}$ (in Nujol) in the infrared (*cf.* R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **73**, 3215 (1951)).

(4) For a preliminary communication, see Y. Mazur, A. Weizmann and F. Sondheimer, *ibid.*, **80**, 1007 (1958).

(5) I. M. Heilbron, R. F. Phipers and H. R. Wright, *J. Chem. Soc.* 1572 (1934); D. H. Coffey, I. M. Heilbron and F. S. Spring, *ibid.*, 738 (1936); H. B. MacPhillamy, THIS JOURNAL, **64**, 1732 (1942).

(6) K. Tsuda, R. Hayatsu, Y. Kishida and S. Akagi, *ibid.*, **80**, 921 (1958).

(7) *Cf.* D. H. R. Barton, *J. Chem. Soc.*, 813 (1945).

(8) *Inter al.* C. Dorée, J. F. McGhie and F. Kurzer, *ibid.*, 1467 (1947); L. Ruzicka, M. Montavon and O. Jeger, *Helv. Chim. Acta*, **31**, 818 (1948).

(9) *Cf.* P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

(10) L. F. Fieser, THIS JOURNAL, **75**, 4395 (1953).

(11) *Cf.* H. Wieland and G. Coutelle, *Ann.*, **548**, 270 (1941).

(12) Y. Mazur and F. Sondheimer, THIS JOURNAL, **80**, 5220 (1958).

(13) F. Sondheimer and Y. Mazur, *ibid.*, **79**, 2906 (1957); N. W. Atwater, *ibid.*, **79**, 5315 (1957).

one (III)[14] yielded the corresponding 4-methyl compound IV with its characteristic ultraviolet maximum at 251 mμ,[13] besides 4,4-dimethyl-Δ^5-stigmasten-3-one (V). Reduction of 4-methyl-Δ^4-stigmasten-3-one (IV) with lithium in liquid ammonia yielded as major product 4α-methylstigmastan-3-one (VI), also obtained by the catalytic hydrogenation of IV in ethanol over a palladium–charcoal catalyst and subsequent treatment with aqueous sulfuric acid in boiling ethanol. The analogous reactions have been carried out previously in the cholesterol series[12] and the evidence for assigning the 4α-methyl-5α-configuration to the product has been presented. Reduction of the saturated ketone VI with lithium aluminum hydride smoothly produced 4α-methylstigmastan-3β-ol (VIIa) which was the minor product obtained from the lithium–ammonia reduction of the α,β-unsaturated ketone IV and which was further characterized as the acetate VIIb. The three synthetic substances VI, VIIa and VIIb proved to be identical in every respect with citrostanone, citrostanol and citrostanol acetate, respectively. The nature of the carbon skeleton of citrostadienol was therefore elucidated and isocitrostenol must be 4α-methyl-$\Delta^{8(14)}$-stigmasten-3β-ol (IIa).

There remained the task of determining the position of the nuclear double bond of citrostadienol. The ultraviolet spectrum rules out the $\Delta^{8(14)}$-position and only the Δ^7- or $\Delta^{8(9)}$-positions can account for the double bond shifting to $\Delta^{8(14)}$ on hydrogenation in acetic acid over platinum.[15] To differentiate between the two formulations Ia and VIII, citrostadienol was allowed to react with excess of osmium tetroxide and the resulting pentol was acetylated with acetic anhydride and pyridine at room temperature. Under these conditions the Δ^7-structure Ia was expected to yield a pentol triacetate (4α-methylstigmastane-3β,7α,8α,24,28-pentol 3,7,28-triacetate) (IXb), while the $\Delta^{8(9)}$-isomer VIII should produce a pentol diacetate (4α-methylstigmastane-3β,8α,9α,24,28-pentol 3,28-diacetate) (Xb) or possibly an unsaturated tetrol triacetate.[16] In fact, elemental analysis of the product clearly showed it to be the pentol triacetate IXb. The pentol structure IXa for the osmium tetroxide oxidation product was further indicated through its cleavage by means of lead tetraacetate (and subsequent acetylation) to the diketo aldehyde XI, showing the aldehyde C–H stretching band at 2793 cm.$^{-1}$ in the infrared.[17] Under these conditions, the pentol Xa should have given a triketone. The nuclear double bond in citrostadienol is therefore at Δ^7 and the complete structure is 4α-methyl-$\Delta^{7,24(28)}$-stigmastadien-3β-ol (Ia).

At the same time as our announcement of the structure of citrostadienol,[4] Djerassi, Mills and Villotti[18] reported the cactus constituent lophenol to be 4α-methyl-Δ^7-cholesten-3β-ol[19] and evidence has been presented by us that α_1-sitosterol (obtained from grain oil)[20] is also a 4α-methyl sterol.[21] The occurrence of 4α-methyl sterols, an intermediate type between the sterols and the tetracyclic triterpenes, is therefore comparatively widespread in the plant kingdom. This finding, taken together with the recent report that the *Eucalyptus* constituent cycloeucalenol[22] is a 4α,14α-dimethyl sterol,[23] strongly suggests that the biosynthesis of plant sterols proceeds by the demethylation of squalene cyclization products, as has been shown for cholesterol by biochemical experiments in animals.[24]

Experimental[25]

Isocitrostenol Acetate (IIb).—Citrostadienol acetate (200 mg., m.p. 142–143°, $[\alpha]_D$ + 43°)[1] dissolved in 25 cc. of glacial acetic acid was shaken in hydrogen over 50 mg. of a platinum oxide catalyst. About 1 molar equivalent of hydrogen had been absorbed in 1 hour and uptake had stopped. The catalyst was removed, the solvent was evaporated under reduced pressure and the product was isolated with ether. Crystallization from ether–methanol gave 155 mg. of isocitrostenol acetate as needles with m.p. 129–130°, $[\alpha]_D$ + 41°.

Anal. Calcd. for $C_{32}H_{54}O_2$: C, 81.64; H, 11.56. Found: C, 81.42; H, 11.52.

Isocitrostenol (IIa).—The acetate IIb (100 mg.) was hydrolyzed by being boiled for 2 hr. with 200 cc. of 3% potassium hydroxide in methanol. Isolation with ether and crystallization from ether–methanol gave 82 mg. of isocitrostenol as needles with m.p. 152–153°, $[\alpha]_D$ + 23°, λ_{max} 210 mμ, ε 10,500. The same substance was obtained when free citrostadienol was hydrogenated in acetic acid over platinum and the product was hydrolyzed with potassium hydroxide in boiling methanol.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 84.14; H, 12.15.

Citrostanol Acetate (VIIb). (a) **From Citrostadienol Acetate.**—Citrostadienol acetate (250 mg.) dissolved in 30 cc. of glacial acetic acid containing 2 drops of concentrated hydrochloric acid was shaken in hydrogen over 100 mg. of a

(14) R. E. Marker and E. L. Wittle, THIS JOURNAL, **59**, 2704 (1937); E. R. H. Jones, P. A. Wilkinson and R. H. Kerlogue, *J. Chem. Soc.*, 391 (1942); D. H. R. Barton and E. R. H. Jones, *ibid.*, 599 (1943).

(15) *Cf.* H. P. Sigg and T. Reichstein, *Helv. Chem. Acta*, **39**, 1507 (1956).

(16) H. Wieland and W. Benend (*Ber.*, **75**, 1708 (1942)) stated that the triol obtained by the osmium tetroxide hydroxylation of dihydrozymosterol benzoate (now known to be $\Delta^{8(9)}$-cholesten-3β-ol benzoate) and subsequent saponification formed a triol diacetate. However, L. F. Fieser and M. Fieser ("Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 3rd edition, 1949, p. 291) have pointed out that the German workers had made an error in calculating the theoretical analytical values and that in fact the reported analysis indicated the acetylated product to be the diacetate of a mono-anhydro derivative.

(17) *Cf.* L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen & Co. Ltd., London, 1956, pp. 135–136.

(18) C. Djerassi, J. S. Mills and R. Villotti, THIS JOURNAL, **80**, 1005 (1958).

(19) This structure was also assigned by W. W. Wells and D. H. Neiderhiser (*ibid.*, **79**, 6569 (1957)) to a sterol isolated from rat feces, with rather different physical properties to lophenol. No conclusive proof for the assigned structure was given and the substance appears to be inhomogeneous (*cf.* Y. Mazur and F. Sondheimer, succeeding paper).

(20) *Inter al.*, E. S. Wallis, S. Bernstein, *et al.*, *ibid.*, **58**, 2446 (1936); **61**, 2308 (1939); *J. Org. Chem.*, **7**, 103 (1942).

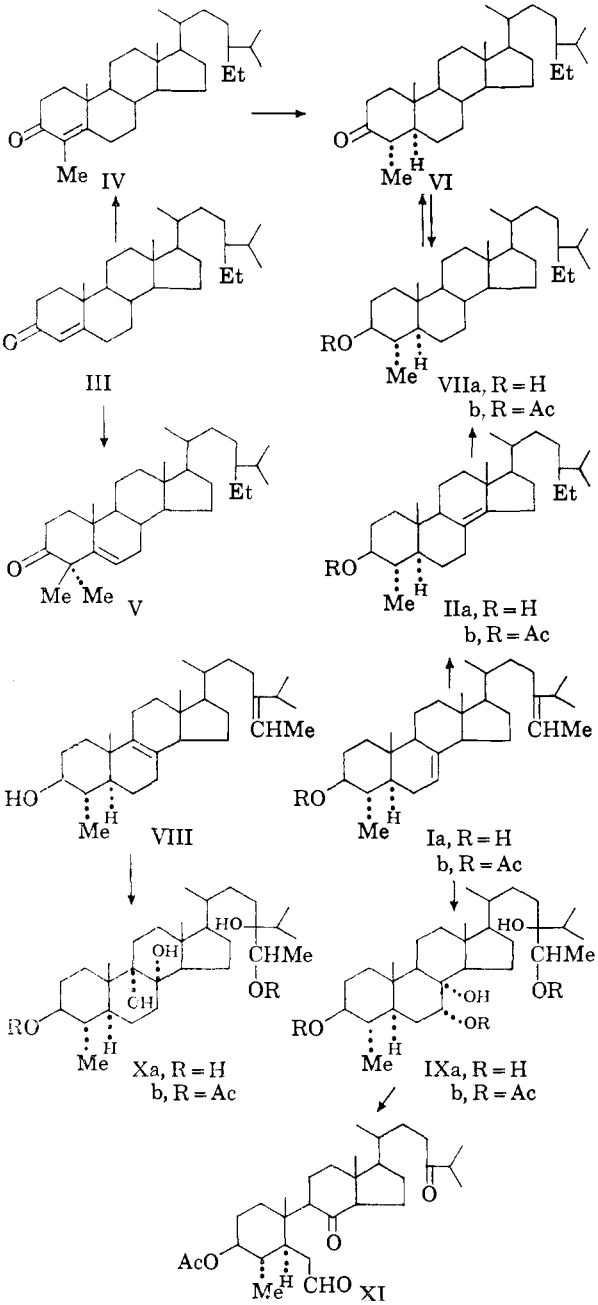
(21) Y. Mazur, A. Weizmann and F. Sondheimer, *Bull. Research Council Israel*, **7A**, 82 (1958). It should be noted that this paper has been abstracted incorrectly (*C.A.*, **52**, 12888 (1958)).

(22) J. S. G. Cox, F. E. King and T. J. King, *J. Chem. Soc.*, 1384 (1956).

(23) J. S. G. Cox, F. E. King and T. J. King, *Proc. Chem. Soc.*, 290 (1957).

(24) *Cf.* K. Bloch, *et al.*, *J. Biol. Chem.*, **218**, 319 (1956); **226**, 941 (1957); *Federation Proc.*, **15**, 323 (1956); THIS JOURNAL, **79**, 684 (1957).

(25) Melting points are uncorrected. The alumina used for all chromatograms was Merck acid-washed alumina. Rotations were determined at room temperature in chloroform solution. Ultraviolet spectra were taken 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 with sodium chloride optics. Analyses were carried out in our microanalytical laboratory under the direction of Mr. Erich Meier.



platinum oxide catalyst. After 6 hr. another 2 drops of concentrated hydrochloric acid was added and the hydrogenation was allowed to proceed overnight. The catalyst was removed and the product, isolated by means of ether, was chromatographed in pentane solution on 10 g. of alumina. The fractions eluted with 250 cc. of pentane yielded 130 mg. of citrostanol acetate as bushy needles with m.p. 138–140°. Two crystallizations from ether–methanol led to the analytical sample with m.p. 144–145°, $[\alpha]_D$ + 39°.

Anal. Calcd. for $C_{32}H_{56}O_2$: C, 81.29; H, 11.94. Found: C, 81.12; H, 11.88.

(b) From Isocitrostenol Acetate (IIb).—The hydrogenation was carried out with 100 mg. of isocitrostenol acetate, 20 cc. of glacial acetic acid, 1 drop of concentrated hydrochloric acid and 25 mg. of platinum oxide. After removal of the catalyst, the product was isolated with ether and the residue after removal of ether was dissolved in 50 cc. of carbon tetrachloride. This solution was washed twice with 10 cc. of cold acetic anhydride containing 2 cc. of concentrated sulfuric acid, in order to remove unsaturated impurities. The carbon tetrachloride solution then was washed with water, dried and evaporated. Crystallization from ether–methanol yielded 52 mg. of the saturated acetate VIIb as needles with m.p. 143–144°, undepressed on admixture with the sample made by method a.

Citrostanol (VIIa).—Citrostanol acetate (150 mg.) was boiled for 2 hr. with 200 cc. of a 3% methanolic potassium hydroxide solution. Isolation of the product with ether and crystallization from ether–methanol gave 121 mg. of citrostanol with m.p. 186–187°, $[\alpha]_D$ + 28°.

Anal. Calcd. for $C_{30}H_{54}O$: C, 83.65; H, 12.64. Found: C, 83.84; H, 12.60.

Citrostanone (VI).—A solution of 125 mg. of citrostanol (VIIa) in 10 cc. of glacial was treated with a solution of 60 mg. of chromic acid in 10 cc. of 90% acetic acid at 23°. The mixture was allowed to stand at this temperature for 16 hr. and the excess of chromic acid was then decomposed by the dropwise addition of methanol. Isolation with ether and crystallization from ether–methanol furnished 98 mg. of citrostanone as needles with m.p. 152–153°, $[\alpha]_D$ + 19°.

Anal. Calcd. for $C_{30}H_{52}O$: C, 84.04; H, 12.23. Found: C, 83.88; H, 12.21.

4-Methyl-Δ⁴-stigmasten-3-one (IV.)—A solution of 2 g. of Δ⁴-stigmasten-3-one (III) (m.p. 90–91°)[14] in 20 cc. of *t*-butyl alcohol was added to a boiling solution of 0.3 g. of potassium in 20 cc. of *t*-butyl alcohol. Methyl iodide (0.71 g.) in 100 cc. of *t*-butyl alcohol then was added dropwise to the boiling solution during 5 hr. After being boiled for a further 0.5 hr., the mixture was cooled, water was added and the product was isolated with ether in the usual way. The resulting material was dissolved in 25 cc. of pentane and chromatographed on 80 g. of alumina. The first fractions eluted with pentane on crystallizations from methanol yielded 0.045 g. of 4,4-dimethyl-Δ⁵-stigmasten-3-one (V) with m.p. 102–103°, $[\alpha]_D$ + 6°, no high-intensity absorption in the ultraviolet, $\nu_{max}^{CS_2}$ 1705 cm.$^{-1}$.

Anal. Calcd. for $C_{31}H_{52}O$: C, 84.48; H, 11.89. Found: C, 84.26; H, 11.80.

Further elution with pentane and crystallization from ether–methanol furnished 0.75 g. of 4-methyl-Δ⁴-stigmasten-3-one (IV) with m.p. 127–130°. The analytical sample showed m.p. 130–131°, $[\alpha]_D$ + 99°, λ_{max} 251 mμ, ε 15,500, ν_{max} 1670 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{50}O$: C, 84.44; H, 11.81. Found: C, 84.45; H, 11.70.

The last fractions eluted with pentane–benzene (9:1) furnished 0.61 mg. of the starting material III with m.p. 90–91°.

4α-Methylstigmastan-3-one (VI) from 4-Methyl-Δ⁴-stigmasten-3-one (IV). (a) By Catalytic Hydrogenation.—A solution of 100 mg. of 4-methyl-Δ⁴-stigmasten-3-one (IV) in 20 cc. of absolute ethanol was shaken in hydrogen over 25 mg. of a 10% palladium–charcoal catalyst. After 15 minutes exactly 1 molar equivalent of hydrogen had been absorbed and uptake stopped. The catalyst was removed and washed with hot ethanol. Aqueous sulfuric acid (2 cc., 20%) was added to the combined filtrates (200 cc.) and the solution was boiled under reflux for 2 hr. Ice then was added and the product was isolated by means of ether. The resulting material was dissolved in pentane and chromatographed on 16 g. of alumina. The fractions eluted with 30 cc. of pentane yielded 41 mg. of 4α-methylstigmastan-3-one (VI) with m.p. 148–149°. Two crystallizations from ether–methanol led to a pure sample with m.p. 153–154°, $[\alpha]_D$ + 19°, no high-intensity absorption in the ultraviolet. There was no depression in m.p. on admixture with the sample of citrostanone described above and the infrared spectra were completely identical.

(b) By Reduction with Lithium in Ammonia.—A solution of 150 mg. of 4-methyl-Δ⁴-stigmasten-3-one (IV) in 10 cc. of ether was added dropwise during 5 minutes to a stirred solution of 100 mg. of lithium in *ca.* 25 cc. of liquid ammonia. The reaction mixture was stirred for another 5 minutes and 2 g. of ammonium chloride then was added. The ammonia was allowed to evaporate, the residue was diluted with water and the product was isolated with ether. The resulting material was chromatographed in pentane solution on 10 g. of alumina. The crystalline fractions eluted with pentane on crystallization from ether–methanol yielded 77 mg. of the saturated ketone VI with m.p. 152–154°, $[\alpha]_D$ + 19°. There was no depression in m.p. on admixture with the

sample prepared by method a or with citrostanone and the infrared spectra of all the three materials were identical.

The chromatography fractions eluted with benzene gave 52 mg. of 4α-methylstigmastan-3β-ol (VIIa) with m.p. 178–184°. Two crystallizations from methanol yielded a pure sample, m.p. 186–187°, undepressed on admixture with a specimen prepared by the method described below.

4α-Methylstigmastan-3-β-ol (VIIa).).—A solution of 75 mg. of 4α-methylstigmastan-3-one (VI) in 15 cc. of dry ether was added to 100 mg. of lithium aluminum hydride in 10 cc. of ether and the mixture was heated under reflux for 1 hr. Decomposition with dilute sulfuric acid, isolation with ether and crystallization from methanol gave 61 mg. of 4α-methylstigmastan-3β-ol (VIIa), m.p. 187–188°, $[\alpha]D + 28°$. The m.p. was undepressed on admixture with a sample of citrostanol and the infrared spectra were absolutely identical.

The acetate VIIb was prepared by means of acetic anhydride and pyridine (overnight, room temperature). Two crystallizations from methanol gave a pure sample, m.p. 143–144°, $[\alpha]D + 38°$. Identity with citrostanol acetate was established by mixture m.p. determination and infrared comparison.

Acetaldehyde from Citrostadienol. (a) By Ozonolysis.—A stream of 3% ozonized oxygen was passed through a solution of 200 mg. of citrostadienol in 20 cc. of carbon tetrachloride at 0° for 25 minutes. Water (10 cc.) then was added and the mixture was distilled into a cooled solution of 200 mg. of 2,4-dinitrophenylhydrazine in 6 cc. of ethanol and 14 cc. of 40% aqueous sulfuric acid. The resulting precipitate was collected, washed with water, dried, dissolved in benzene and chromatographed on 15 g. of alumina. The benzene fractions on evaporation and crystallization from ethanol furnished 32 mg. (30%) of acetaldehyde 2,4-dinitrophenylhydrazone with m.p. 162–164°. The m.p. was undepressed on admixture with an authentic sample (m.p. 162–164°) and the infrared spectra were completely identical.

(b) By Successive Hydroxylation and Periodic Acid Cleavage.—Osmium tetroxide (125 mg.) was added to a solution of 100 mg. of citrostadienol acetate in 10 cc. of dry dioxane and the mixture was allowed to stand at room temperature in the dark for 48 hr. A stream of hydrogen sulfide was then passed through the mixture for 15 minutes, the black precipitate was removed and the product was isolated by means of ethyl acetate. It then was dissolved in 10 cc. of dioxane and a solution of 250 mg. of periodic acid hydrate in 2 cc. of water was added. After being left overnight at room temperature, the solution was distilled into a cooled solution of 100 mg. of dinitrophenylhydrazine in 3 cc. of methanol and 7 cc. of 40% aqueous sulfuric acid. The resulting precipitate, on purification as in the ozonolysis experiment, yielded 42 mg. (88%) of acetaldehyde 2,4-dinitrophenylhydrazone with m.p. 163–164°, undepressed on admixture with an authentic sample.

4α-Methylstigmastane-3β,7α,8α,24,28-pentol 3,7,28-Triacetate (IXb) and the Acetoxy-diketo-aldehyde XI.—A solution containing 95 mg. of citrostadienol and 130 mg. of osmium tetroxide in 15 cc. of pyridine was allowed to stand for 48 hr. in the dark. The pyridine was evaporated under reduced pressure and the residue was boiled for 90 minutes with 1.5 g. of sodium sulfite in 10 cc. of water and 10 cc. of ethanol. The product was then isolated with ether and ethyl acetate and one-half of the resulting crude pentol IXa was acetylated with 1.5 cc. of pyridine and 1.5 cc. of acetic anhydride overnight at room temperature. The acetate was isolated with ether in the usual way and chromatographed in benzene on 5 g. of alumina. The only crystalline material was eluted with ether and on crystallization from ether–pentane yielded the pentol triacetate IXb as needles with m.p. 221–222°.

Anal. Calcd. for $C_{36}H_{60}O_8$ (pentol triacetate IXb): C, 69.64; H, 9.74. Calcd. for $C_{34}H_{58}O_7$ (pentol diacetate Xb): C, 70.55; H, 10.10. Found: C, 69.55; H, 9.77.

The second half of the crude pentol IXa was dissolved in 4 cc. of glacial acetic acid, and 300 mg. of lead tetraacetate in 20 cc. of acetic acid was added. After being allowed to stand overnight at room temperature, the mixture was diluted with water and the product was isolated with ether. The resulting material was acetylated with acetic anhydride in pyridine at room temperature and the product was again isolated with ether. The acetate was dissolved in pentane–benzene (2:1) and chromatographed on 5 g. of alumina. The substance eluted with benzene on crystallization from ether–pentane gave the acetoxy-diketo-aldehyde XI as plates with m.p. 151–153°, showing a well defined aldehyde band in the infrared (ν_{max} 2793 cm.$^{-1}$).

Anal. Calcd. for $C_{30}H_{48}O_5$: C, 73.73; H, 9.90. Found: C, 73.53; H, 9.88.

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

Synthesis of 4α-Methyl-Δ^7-steroids. The Interrelationship of Cholesterol, Citrostadienol and Lophenol

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The methylation of Δ^7-cholesten-3-one (II) has been shown to proceed at C-4 and to result in 4α-methyl-Δ^7-cholesten-3-one (III). Reduction of the latter with lithium aluminum hydride yielded 4α-methyl-Δ^7-cholesten-3β-ol (IVa). The last mentioned substance also was obtained from the citrus sterol citrostadienol (I) by partial ozonolysis to 4α-methyl-Δ^7-cholesten-3β-ol-24-one (VIIIa), followed by reduction of the 24-keto group through Wolff–Kishner reduction. The 4α-methyl-Δ^7-cholesten-3β-ol (IVa) obtained by either route proved to be identical with the cactus sterol lophenol to which structure IVa had been assigned. It is shown that the molecular rotation contribution of the 24-ethylidene group in citrostadienol is anomalous and it is proposed that the Δ$^{24(28)}$-double bond in the citrus sterol exists in the opposite configuration to that in the algae sterols fucosterol and sargasterol. The suggestion is made that the grain oil sterol α_1-sitosterol is the Δ$^{24(28)}$-isomer of citrostadienol.

We recently have shown the citrus sterol citrostadienol to be 4α-methyl-24-ethylidene-Δ^7-cholesten-3β-ol (I).[1] It seemed to us to be of interest to interrelate this substance with an authentic Δ^7-cholestene derivative by converting it through removal of the 24-ethylidene group to 4α-methyl-Δ^7-cholesten-3β-ol (IVa) and to synthesize the latter. This scheme, the realization of which is described in this paper, became of additional interest when it was announced that 4α-methyl-Δ^7-cholesten-3β-ol (IVa) is obtainable from two natural sources: the cactus constituent lophenol was shown to be IVa[2] and the latter structure also was assigned tentatively to a sterol isolated from rat feces,[3] although the two natural products did not seem to be identical.[2]

(1) Y. Mazur, A. Weizmann and F. Sondheimer, THIS JOURNAL, **80**, 1007, 6293 (1958).

(2) C. Djerassi, J. S. Mills and R. Villotti, *ibid.*, **80**, 1005 (1958).

(3) W. W. Wells and D. H. Neiderhiser, *ibid.*, **79**, 6569 (1957).