[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH, NEW BRUNSWICK, N. J.]

Transformations of Eburicoic Acid. IV. Side-Chain Degradation to 14-Methylpregnane Derivatives

BY DAVID ROSENTHAL, PAUL GRABOWICH, EMILY F. SABO, AND JOSEF FRIED[1]

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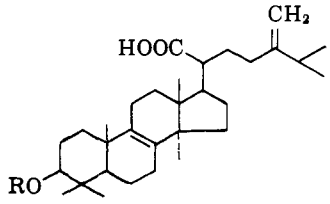
The 9-carbon side chain present in a variety of tetracyclic triterpenoid acids of fungal origin as exemplified by eburicoic acid (I) is degraded in five steps to the corticosterone side chain without impairing the nuclear double bond. The resulting 14-methylpregnane derivatives can be further modified by known methods to analogs of progestational and corticoid hormones. A novel method for the preparation of α-pyrones and their reduction with lithium aluminum hydride is described.

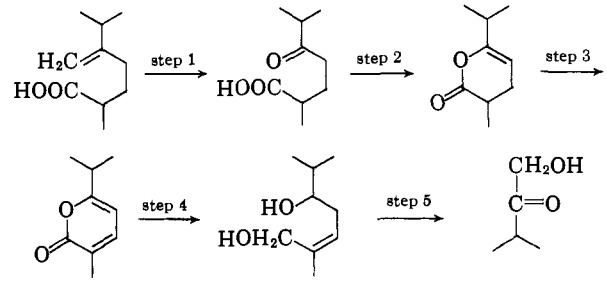
In three preliminary communications we have described the conversion of the tetracyclic triterpene eburicoic acid (I) to hormone analogs possessing the pregnane,[2a] androstane,[2b] and A-norpregnane[3] skeleton. We now wish to present a detailed account of that phase of our work dealing with the degradation of eburicoic acid to pregnane derivatives possessing the progesterone and deoxycorticosterone side chain.



I, R = H
Ia. R = Ac

Eburicoic acid was first isolated by Kariyone and Kurunu[4] from *Fomes officinalis* Fris., its name derived by these authors from the Japanese word for that fungus. It was re-isolated a decade later by Gascoigne, *et al.*,[5] and by Lahey and Strasser[6] from the mycelium of *Polyporus anthracophilus* Cooke grown naturally on *Eucalyptus regnans* wood, under which conditions it occurs as the acetyl derivative (Ia). Gascoigne, *et al.*,[7] were able to culture this and related Basidiomycetes of the genus *Polyporus* on a synthetic medium and found that under these modified conditions the unacetylated acid was produced in yields of 10–20% of the dried weight of the mycelium. The acid was easily isolated by extraction of the mycelium with organic solvents and purified by recrystallization. Efforts to facilitate the preparation of eburicoic acid led to the abandonment of the surface growth method in favor of submerged culture,[8] which made it possible to shorten the growth period from 3–4 months to 10 days without altering the yield of the acid per gram of mycelium. The chemistry of eburicoic acid as well as that of several of the other tetracyclic triterpenoid acids has been investigated by the group of Alexander Robertson in Liverpool, and it is to this laboratory that we owe its complete structure. An excellent summary of this work has been presented.[9]

All naturally occurring steroidal hormone precursors have a side chain attached to carbon atom 17 of the nucleus, which may range from five carbon atoms in the case of the bile acids to ten in some of the plant sterols. Many ingenious degradative schemes have been devised in response to the need for steroids possessing either the 2-carbon side chain of the corticoid and progestational hormones or for such lacking a side chain altogether as do the androgenic and estrogenic hormones. The 9-carbon side chain of eburicoic acid and related fungal acids such as polyporenic acid C and tumulosic acid is identical in its skeletal structure with that of ergosterol, but unlike that of the latter possesses a free carboxyl group in position 21 and a double bond joining carbon atoms 24 and 28. It has been our objective to make maximum use of these functional groups in such a manner as to have the carboxyl group in position 21 become the hydroxymethylene group of the corticosterone side chain and to utilize both the carboxylic acid function and the double bond to effect introduction of a double bond into the 20(22)-position, later to be oxidatively cleaved to furnish the 20-keto group. The introduction of such a double bond in a minimum number of steps is indeed an important aim in all steroidal side-chain degradation schemes. In our case this was to be accomplished by converting the 24(28)-double bond to a keto group (step 1) which would permit ring closure to an enol lactone (step 2) into which the essential 20(22)-double bond could then be introduced (step 3) by dehydrogenation to the stable α-pyrone system. Reduction of the carbonyl function with or without concomitant reduction of the conjugated enolic double bond at C-23 (step 4) should then permit oxidative removal of the 6-carbon fragment (step 5) to form the 2-carbon side chain of corticosterone. All these steps were to leave untouched the sensitive 8,9-double bond either for its own sake to study its effect on biological activity or as a handle for further operations.



The ozonolysis of acetyleburicoic acid (Ib) has already been described by Gascoigne, *et al.*,[5] but the resulting keto acid was not obtained in crystalline form. Closer study of the reaction revealed that the nuclear double bond in eburicoic acid is not entirely resistant to attack by ozone and that the reaction at that site, which leads to the formation of the 7,9(11)-diene system, is slower by an order of magnitude than ozonolysis of the side-chain double bond. Thus by conducting

(1) To whom requests for reprints should be sent at Ben May Laboratory for Cancer Research, University of Chicago, Chicago, Ill.

(2) (a) D. Rosenthal, J. Fried, P. Grabowich, and E. F. Sabo, *J. Am. Chem. Soc.*, **84**, 877 (1962); (b) G. Krakower, J. W. Brown, and J. Fried, *J. Org. Chem.*, **27**, 4710 (1962).

(3) J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **84**, 4356 (1962).

(4) T. Kariyone and G. Kurunu, *J. Pharm. Soc. Japan*, **60**, 110, 318 (1940); *Chem. Abstr.*, **35**, 461 (1941).

(5) R. M. Gascoigne, J. S. E. Holker, B. J. Ralph, and A. Robertson, *Nature*, **166**, 652 (1950).

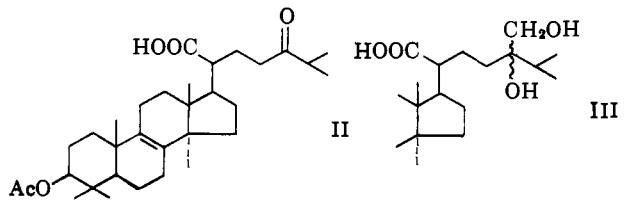
(6) F. N. Lahey and P. H. A. Strasser, *J. Chem. Soc.*, 873 (1951).

(7) R. M. Gascoigne, J. S. E. Holker, B. J. Ralph, and A. Robertson, *ibid.*, 2346 (1951).

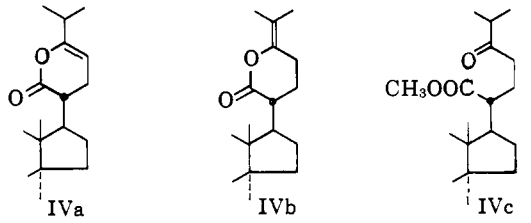
(8) S. C. Pan and W. R. Frazier, *Biotechnol. Bioeng.*, **4**, 303 (1962).

(9) J. Simonsen and W. C. J. Ross, "The Terpenes," Vol. 5, The University Press, Cambridge, 1957, p. 1.

the reaction at −60° and using 1 mole equivalent of ozone the desired norketo acid II was obtained in crystalline form with a minimum of diene formation.

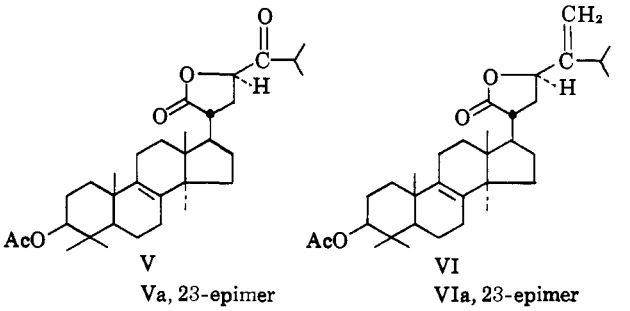


Alternatively, this acid could be obtained by hydroxylation of the 24(28)-double bond with osmium tetroxide to form the 3-acetoxy-24,28-dihydroxy acid (III) followed by lead tetraacetate cleavage. Enol lactonization of the δ-keto acid II with acetic anhydride and sodium acetate as described by Woodward, *et al.*,[10,11] gave a mixture of isomeric lactones from which the expected more abundant endocyclic double bond isomer IVa (α-lactone) was isolated by fractional crystallization. The presence of the enol lactone grouping in this compound was evident from the carbonyl absorption at 5.69 μ in the infrared and the position of the double bond from the single proton absorption at 5.17 τ in the n.m.r. Ozonolysis of this lactone gave a good yield of isobutyric

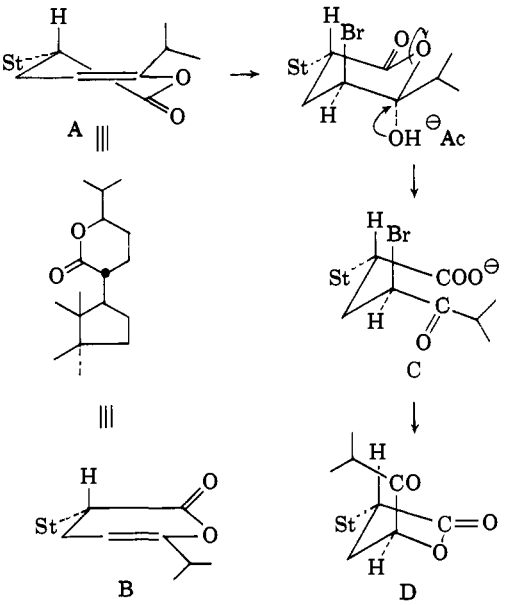


acid as the sole volatile product which was identified by comparison of the infrared spectrum of its sodium salt with that of an authentic sample.[12] Attempted saponification with aqueous potassium carbonate in methanol led exclusively to the known keto methyl ester IVc. Careful chromatography of the total lactone mixture on neutral alumina furnished the isomer IVb (β-lactone), which yielded acetone on ozonolysis and whose n.m.r. spectrum lacked olefinic proton absorption and showed three protons each at 8.29 and 8.38 τ (=C(CH₃)₂). In practice the mixture of α- and β-lactones could be used directly in the dehydrogenation step leading to the α-pyrone VIII.

Before describing this step we wish to digress for a moment to discuss the reaction of the α-lactone IVa with N-bromosuccinimide. When carried out in the presence of an acetate buffer this reaction furnished in almost quantitative yield a single bromine-free product, melting at 230–232°, which on the basis of its infrared spectrum (bands at 5.60 and 5.79 μ) and analysis was formulated as the keto lactone V. A lactone possessing this structure and melting at 231–233° had previously been described by Holker, *et al.*,[13] as the product of the reaction of acetyleburicoic acid with selenium dioxide followed by ozonolysis. A sample of this lactone prepared by the procedure of the English authors proved identical in all respects with our lactone V. On repeating the published procedure



we obtained during the chromatographic purification of the selenium dioxide product VI a second, isomeric lactone, which undoubtedly represents the expected 23-epimer VIa. The latter was converted by ozonolysis to the corresponding keto lactone Va. It is significant that in contrast to the selenium dioxide oxidation of acetyleburicoic acid the reaction of the enol lactone IVa with NBS is completely stereospecific and yields but a single substance. It is possible to assign the stereochemistry of the lactone V (and therefore also of the other γ-lactones Va, VI, and VIa) if one makes the well-substantiated assumption of *trans*-diaxial attack of the elements of hypobromous acid on the favored half-chair conformation A, in which the steroid nucleus is equatorial, followed by attack of the intermediate carboxylate anion C on carbon atom 23 with inversion of configuration. The sterically acceptable half-boat B by undergoing axial attack by bromonium ion would likewise lead ultimately to the same intermediate C. The alternative half-chair and half-boat conformations in which the steroid nucleus is axial are considered unlikely. Moreover, a transition state airising from such



a conformation would involve a most unfavorable 1,3-diaxial interaction between the steroid nucleus and the entering bromine atom. That the intermediate anion C readily undergoes lactonization was shown by first preparing the bromo acid VII from IVa with N-bromosuccinimide in the presence of perchloric acid and effecting its conversion into the lactone V with sodium acetate at room temperature.

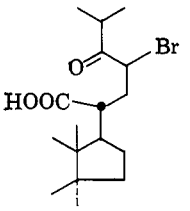
We now wish to return to step 3 of our main degradative sequence, the dehydrogenation of the enol lactones IVa and IVb to the α-pyrone VIII. A large number of dehydrogenating agents such as selenium dioxide, mercuric acetate, bromine, etc., were tried before it was discovered that this reaction could be performed

(10) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(11) Under these same conditions acetyleburicoic acid gave the stable mixed anhydride with acetic acid, lending support to the view that such an anhydride is an intermediate in the lactonization of II; *cf.* ref. 10.

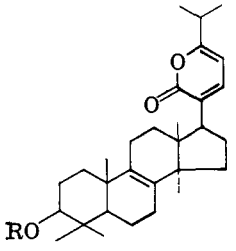
(12) E. Childers and G. W. Struthers, *Anal. Chem.*, **27**, 737 (1955).

(13) J. S. E. Holker, A. D. G. Powell, A. Robertson, J. J. H. Simes, R. S. Wright, and R. M. Gascoigne, *J. Chem. Soc.*, 2422 (1953).

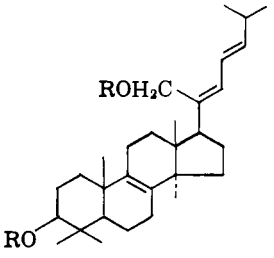


VII

cleanly and in good yield with 10% palladium-on-charcoal in boiling *p*-cymene. It was found that while lower boiling hydrocarbons such as xylene alone or in the presence of maleic anhydride led to the formation of the pyrone in small yield, the boiling point and aromatic nature of *p*-cymene provided optimum conditions for the dehydrogenation to occur.[14] In order to obtain maximum yields it was found practicable to remove traces of water by azeotropic distillation. Under such conditions the pure α-lactone IVa furnished a 75% yield of the pure pyrone VIII. As has already been mentioned, the β-lactone IVb could likewise be dehydrogenated to VIII but in this case the yields were only 60% and the reaction time had to be extended from 2 to 6 hr. Presumably the catalyst first causes isomerization to the endocyclic double bond isomer. The pyrone VIII had the expected spectral characteristics, an ultraviolet maximum at 305 mμ (ϵ 8900) and infrared bands at 5.90, 6.11, and 6.35 μ. Its n.m.r. spectrum showed two olefinic protons as doublets at 2.89 and 4.10 τ (J 7 c.p.s.). The lower field signal is assigned to the less shielded C-22 proton. Resonance

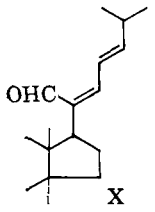


VIII, R = Ac
VIIIa, R = H
VIIIb, 3-ketone

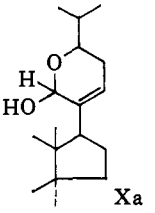


IX, R = H
IXa, R = Ac

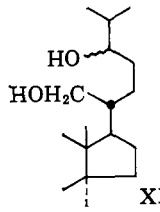
stabilization of α-pyrones is of a low order as demonstrated by their ready cleavage by alkaline reagents.[15] The system under discussion here, however, is remarkably stable to alkali, permitting hydrolytic removal of the acetyl group in position 3 without attack on the pyrone system. This unusual stability is ascribed to steric hindrance at the 21-carbonyl group and parallels the well-known resistance of the carboxylic acid derivatives of eburicoic acid and related triterpenoid acids to attack by nucleophilic reagents. Perhaps the most convincing demonstration of this hindrance is the survival of the α-pyrone system in potassium hydroxide in ethylene glycol at 150°. This well-documented resistance to attack by nucleophilic species provided ample grounds for the prediction that only the most effective donors of hydride ion would be able to attack the pyrone system in the next step of our contemplated scheme. This proved indeed to be the case. Sodium borohydride was without effect on VIII and refluxing lithium borohydride in tetrahydrofuran led only to removal of the ester group at C-3. Lithium aluminum hydride in boiling tetrahydrofuran, on the other hand, converted the pyrone acetate VIII in a not entirely expected, yet eminently useful, reaction to the conjugated diene IX. The ultraviolet spectrum of this compound (λ_{max}^{alc} 243 mμ (ϵ 31,000))[16] clearly indicated a conjugated dienic system and the two oxygen atoms demonstrated by elemental analysis were shown to be alcoholic by the formation of a diacetate (IXa). The n.m.r. spectrum shows three olefinic protons in a complex coupling pattern between 320 and 400 c.p.s. and two protons at 5.80 τ for the 21-methylene group. The allylic nature of the 21-hydroxyl group was convincingly demonstrated by oxidation of IX with manganese dioxide, which afforded the trienal X, exhibiting the expected spectral characteristics, notably the low field single proton absorption at -0.26 τ and the C–H– stretching absorption at 3.70 μ for the newly-formed aldehyde group. When the reaction time was extended from 24 to 72 hr., a second crystalline substance, transparent in the ultraviolet, of the formula $C_{30}H_{48}O_3$ could be isolated in 10% yield. This compound was assigned structure Xa and it is assumed to be formed from the trienal X by hydration of the 23-double bond followed by hemiacetal formation.



X



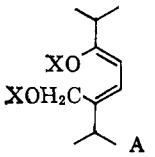
Xa



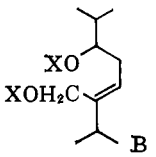
XI

The lithium aluminum hydride reduction of the pyrone VIII afforded in 5% yield a by-product of the composition $C_{30}H_{52}O_3$, which forms a triacetate, is transparent in the ultraviolet, lacks vinyl proton absorption in the n.m.r. and is therefore formulated as XI. This structural assignment is supported by the isolation of the same substance in 25% yield from the reaction of the mixture of enol lactones IVa and IVb with lithium aluminum hydride.

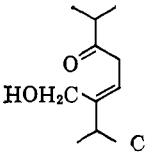
The unexpected course of the lithium hydride reduction requires comment. It had been envisioned that hydride attack would occur initially at the carbonyl group with the formation of the enolic intermediate A, which could either be further reduced to the diol B or



A



B



C

X = complex aluminum cation

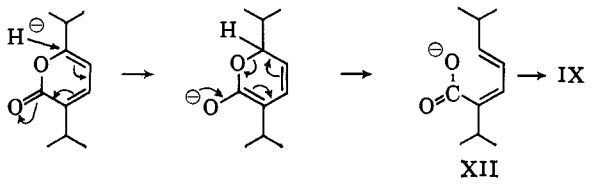
resist reduction and yield the keto alcohol C after hydrolysis. It is probable that the by-product XI arises in this fashion. The formation of the main reaction product IX, however, is more satisfactorily explained if one assumes primary attack of hydride ion at the end of the conjugated system (C-24) with scission of the carbon–oxygen bond to yield the doubly unsaturated carboxylate anion XII, which then suffers further reduction to IX.[17] However, a search for such a substi-

(14) The dehydrogenation conditions devised here have been successfully applied in the dehydrogenation of a dihydroindanone derived from isojervine to the corresponding indanone; *cf.* O. Wintersteiner and M. Moore, *Tetrahedron Letters*, 795 (1962).

(15) J. Fried in "Heterocyclic Compounds," Vol. 1, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1950, p. 354.

(16) The ultraviolet maximum for this compound is bathochromically displaced by 11 mμ over the value calculated by Woodward's rules (*J. Am. Chem. Soc.*, **64**, 72 (1942)). This may be a reflection of the steric strain introduced into the system by the presence of the bulky steroid nucleus.

(17) The mechanistic considerations invoked here for the formation of the trienol IX may be extended to make some predictions regarding the stereochemistry of the dienic system in IX and XVII. Identity of configuration of this unsaturated system in both IX and XVII follows from the virtually

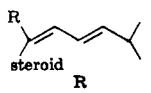


XII

tuted sorbic acid derivative among the products of this reaction, even under milder conditions, was unsuccessful. Evidence that the α-pyrone system is susceptible to δ-attack by nucleophilic reagents was available from the work of Fried and Elderfield[18] who found that

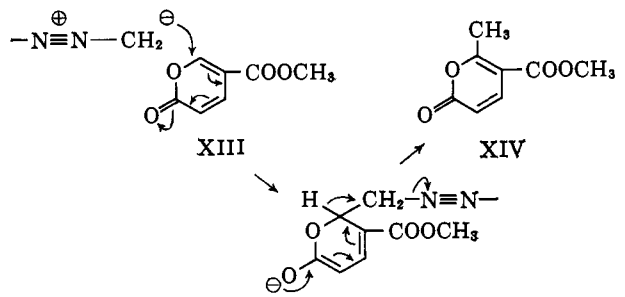
TABLE I

ULTRAVIOLET AND INFRARED SPECTRA FOR 20(22),23-DIENES

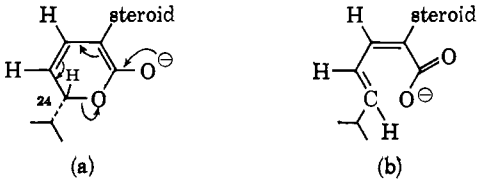


R

	Compound	λ_{max}^{alc}, mμ	ε	[λ_{max}^{Nujol}, μ]
CH_2OH	IX	243	31,000	5.64, 5.85, 6.02, 6.21
CH_2OH	XVII	243	30,000	5.60, 5.80, 6.08, 6.20
CH_2OAc	IXa	243	32,000	5.75, 5.92, 6.10, 6.25
CHO	X	291	20,200	6.00, 6.13, 6.33
COOH	XVI	252	17,300	5.94, 6.08, 6.23
$COOCH_3$	XVIa	254	17,700	5.86, 6.09, 6.21



identical vinyl proton splitting patterns in the n.m.r., their identical ultraviolet spectra, and the identity of their infrared spectra in the C=C— stretching region. Moreover, since the oxidation, reduction, and methylation reactions at C-21 involved in the preparation of X, XVI, and XVIa are known not to cause *cis–trans* isomerization, all of these compounds should also possess the same stereochemistry. The reasoning goes as follows: The intermediate anion (a) would represent the position of the electrons just prior

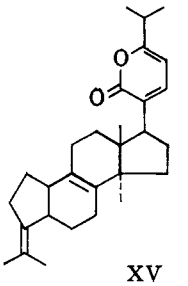


to the cleavage of the ring. As the carbon–oxygen bond is breaking, the tetrahedral carbon atom 24 becomes trigonal by the twisting of the two substituents into the plane of the incipient double bond. For steric reasons, this process would most likely proceed in the direction of the more stable *trans* configuration (b) for the γ,δ-double bond, leaving the α,β-double bond in its original configuration which is defined here as *trans* with regard to the bulkiest substituent, the steroid nucleus. The same would, of course, apply to the 24-epimer arising by hydride attack from the underside of the α-pyrone ring. The structures given in this paper all show this *trans–trans* stereochemistry. An attempt to verify these conclusions by an analysis of the ultraviolet and infrared spectra for our compounds (Table I) in the light of published data for all the stereoisomeric hexa- and deca-2,4-dienols and the deca-2,4-dienoic acids and their methyl esters (L. Crombie, *J. Chem. Soc.*, 1007 (1955); L. Crombie, S. H. Harper, and R. J. D. Smith, *ibid.*, 2754 (1957); A. Butenandt, H. Hecker, and H. G. Zachau, *Ber.*, **88**, 1189 (1955)) proved of limited value because of the uncertainty regarding the influence of the steroid nucleus on this system. It is possible, however, to exclude a *cis* arrangement at the 23-double bond in view of the high extinction coefficients for the dienols IX and XVII when compared with those reported in the above papers. Such an arrangement would require unfavorable planarity-distorting interactions at *both* double bonds, causing a decrease in extinction coefficient.

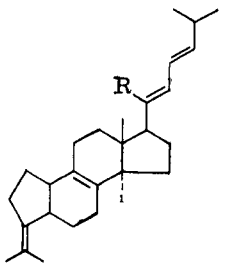
(18) J. Fried and R. C. Elderfield, *J. Org. Chem.*, **6**, 577 (1941).

methyl coumalate (XIII) reacts with diazomethane to form the methyl ester of 6-methylcoumalic acid (XIV).

While it was not possible to isolate the expected sorbic acid intermediate from the above reaction of VIII with lithium aluminum hydride, the analogous reaction with the pyrone XV yielded both the carboxylic acid XVI and the primary alcohol XVII. The ratio of the two products could be changed in favor of the alcohol by extending the reaction time. The ultraviolet spectrum of the acid (λ_{max}^{alc} 252 mμ (ε 17,300)), its conversion into the methyl ester XVIa, and their reduction to the alcohol XVII provide convincing evidence for the sorbic acid structure XVI. Moreover, the isolation of the acid at short reaction times and of the alcohol after longer exposure as well as the conversion of the former into the latter with lithium aluminum hydride are taken as evidence for the postulated reaction sequence. Similar observations have been made independently by Vogel,[19] who isolated 3-methylsorbic acid from the reduction of 4,6-dimethyl-α-pyrone with lithium aluminum hydride in ether at 10–20°. Failure to isolate the acid corresponding to XVI in the reduction of the pyrone VIII may be ascribed to the greater solubility of its salt thereby providing for more ready reduction to the unsaturated alcohol IX.



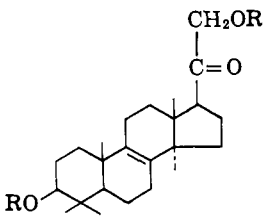
XV



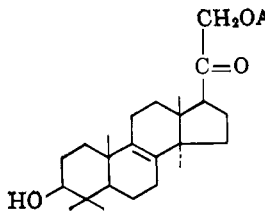
XVI, R = COOH
XVIa, R = $COOCH_3$
XVII, R = CH_2OH

The ozonolysis of both the trienediol IX and its diacetate IXa proceeded in 60 and 43% yield to the keto diol XVIII and its diacetate XVIIIa, respectively. Both XVIII and XVIIIa exhibited the characteristic features of the corticosterone side chain. Thus they reduced Tollens and tetrazolium reagents and XVIIIa showed infrared bands at 5.73 and 5.78 μ typical for that system. The 21-methylene group gave rise to a typical AB quartet in the n.m.r. spectrum of the acetate, which coalesced to a singlet in the free ketol. Both XVIII and XVIIIa are important intermediates for further work. The former has been converted quantitatively into the 21-monoacetate XIX by acetylation with 1 mole of acetic anhydride to serve as an intermediate for further operations in ring A. The latter has been selectively saponified with potassium carbonate to the 3-monoacetate XX, which in turn has been utilized for the reductive removal of the 21-hydroxyl group *via* the 21-mesylate XXI and 21-iodide XXII to form the hydroxy ketone XXIII. Oxidation of the latter with Jones reagent gave the 3,20-diketone XXIV. Applying the well-known chromic acid oxidation of Δ^8-14-methyl steroids to their 7,11-diketones to the diacetate XVIIIa afforded the enedione XXV in 75% yield. The yield in this reaction is considerably higher with this substrate than with Δ^8-lanostene and other long side-chain-containing compounds. This is ascribed to the presence in the pregnene derivative XVIIIa of but one tertiary carbon atom susceptible to hydroxylation by hot chromic acid.[20]

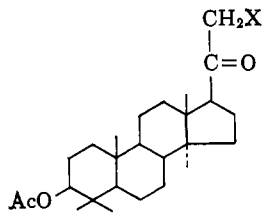
(19) G. Vogel, *Chem. Ind.* (London), 268 (1962).



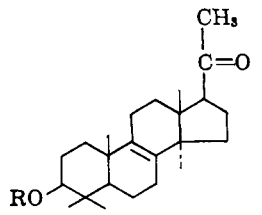
XVIII, R = H
XVIIIa, R = Ac



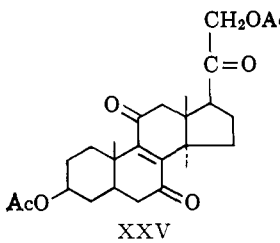
XIX



XX, X = OH
XXI, X = OSO_2CH_3
XXII, X = I



XXIII, R = H
XXIIIa, R = Ac
XXIV, 3-ketone



XXV

Experimental

All melting points are uncorrected in capillaries. Rotations are in chloroform unless otherwise specified. Ultraviolet spectra were determined on a Cary 11, infrared spectra on a Perkin–Elmer 21, and nuclear magnetic resonance spectra on a Varian A-60 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard.

Isolation of Eburicoic Acid (I) from the Mycelium of *Polyporus Sulfureus*.—A total of 6.6 kg. of the dried mycelium of *Polyporus sulfureus* (containing soy solids derived from the medium) derived from a 150-gal. fermentation using a soy bean medium as described in detail by Pan and Frazier[8] was divided in five portions and each portion extracted in a large Soxhlet extractor first with hexane (10 l.) for 18 hr. to remove lipids and then with chloroform (10 l.) for 72 hr. Cooling of the chloroform extracts and filtration gave a combined first crop of 586 g. of eburicoic acid followed by a second crop of 55 g. when the pooled mother liquors were concentrated. An additional 80 g. of material obtained by further concentration of the chloroform mother liquors contained mainly other products. The hexane solutions, on standing, deposited an additional 8 g. of eburicoic acid. Recrystallization of the first and second crops from ethanol–chloroform with the aid of Darco G60 gave a total of 495 g. of pure eburicoic acid (I), m.p. 282–284°, lit. 283°,[4] 292°,[5] 292–293°.[6] The acid was positively identified by conversion into many of the derivatives cited in ref. 5 and 6.

Acetyleburicoic Acid (Ia).—To a cooled solution of 500 g. of eburicoic acid (I) in 2.37 l. of pyridine was added 700 ml. of acetic anhydride. After standing overnight at room temperature, the excess acetic anhydride was decomposed by the addition of 100 ml. of ice followed after 30 min. by 4 l. of water. The precipitate of crude acetyleburicoic acid was collected and dissolved in 4 l. of chloroform. The chloroform solution was washed with 1 *N* hydrochloric acid, water, and 5% potassium bicarbonate solution and concentrated to 2 l. After the addition of 2 l. of methanol, the solution was reconcentrated to a volume of 2 l., treated with decolorizing charcoal and the filtered solution concentrated again. The acetyleburicoic acid was collected in two crops: crop 1, 419 g., m.p. 240–244°; crop 2, 33.5 g., m.p. 235–238° (lit.[6,7] m.p. 256–257°).

Ozonolysis of Acetyleburicoic Acid (Ia). 3β-Acetoxy-Δ⁸-lanostene-24-one-21-oic Acid (II).—Through a solution of 51.3 g. (0.1 mole) of acetyleburicoic acid (Ia) in a mixture of 500 ml. of chloroform and 500 ml. of ethyl acetate, cooled in a Dry Ice–acetone bath, was passed 0.1 mole of ozone contained in 89 l. of oxygen. The resulting solution was allowed to warm to −10° when it was diluted with 50 ml. of glacial acetic acid. Powdered zinc was then added in portions with stirring and the temperatures allowed to rise to +15° but not higher. A total of 25 g. of zinc was required and after 2.5 hr. an aliquot of the reaction mixture no longer blued starch–iodide reagent in a test tube. The reaction mixture was filtered and the zinc and zinc salts washed thoroughly with ethyl acetate. The ethyl acetate–chloroform filtrate was washed thoroughly with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. A total of 56 g. of the crude keto acid II was obtained. It was used without further purification in the lactonization step.

The keto acid II was obtained in pure crystalline form by chromatography on neutral alumina or silica gel. For this purpose a solution of 14 g. of the above crude acid was dissolved in 50 ml. of benzene and charged to a column containing 280 g. of alumina; 50% chloroform–benzene (9 l.) eluted 1.9 g. of pure acid melting at 234–236°, which was followed by 1.2 g. of acid when the eluent was changed to 75% chloroform in benzene (3 l.). An additional 1.3 g. of pure acid was obtained with chloroform (5 l.). The column was then stripped with 5% acetic acid in chloroform (2 l.) which eluted 10.4 g. of crude material which was dissolved in 100 ml. of benzene and rechromatographed on 200 g. of silica gel. Elution with benzene (750 ml.) gave 4 g. of amorphous material which was followed by crystalline acid (2.4 g.) when the eluent was changed to chloroform (8 l.). The pure acid had the properties: m.p. 236–238°, $[\alpha]^{23}D$ +52° (*c* 0.49), $\lambda_{max}^{CS_2}$ 5.78 and 5.90 μ; λ_{max}^{Nujol} 5.83–5.90, 8.05, 9.76, and 9.94 μ.

Anal. Calcd. for $C_{32}H_{50}O_5$ (514.72): C, 74.67; H, 9.79. Found: C, 74.64; H, 9.54.

Alternatively, the keto acid II was prepared as follows:

(a) **3β-Acetoxy-Δ⁸-eburicene-24,28-diol-21-oic Acid (III).**—To a solution of 2 g. of acetyleburicoic acid (Ia) in 20 ml. of benzene and 2 ml. of pyridine was added dropwise a solution of 1 g. of osmium tetroxide in 10 ml. of benzene. Addition was complete in 1 hr. and the reaction mixture was allowed to remain at room temperature for an additional 4 hr. The dark solution was diluted with 76 ml. of dioxane and saturated with hydrogen sulfide for 15 min. The resulting suspension was filtered with the aid of Celite and the filtrate evaporated to dryness. The residue (2.1 g.) was triturated with acetone leaving 1.5 g. of the dihydroxy acid III melting at 238–242°. Recrystallization of this material from 95% ethanol furnished the pure dihydroxy acid, m.p. 246–248°; λ_{max}^{Nujol} 2.95, 5.80, 6.05, and 8.00–8.10 μ.

Anal. Calcd. for $C_{33}H_{54}O_6$ (546.76): C, 72.49; H, 9.96. Found: C, 72.76; H, 9.92.

(b) **3β-Acetoxy-Δ⁸-lanostene-24-one-21-oic Acid (II).**—A solution of 1.17 g. of the 24,28-dihydroxy acid III in 200 ml. of 0.0108 *M* lead tetraacetate solution in glacial acetic acid was allowed to stand at room temperature for 35 min. A few drops of ethylene glycol was then added to reduce excess lead tetraacetate and the solution was concentrated *in vacuo* and diluted with water. The resulting suspension was extracted with ethyl acetate and the ethyl acetate extract washed several times with water, dried over sodium sulfate, and evaporated *in vacuo*. The resulting crude product (1.07 g.) on recrystallization from acetone furnished 700 mg. of the keto acid II, m.p. 225–227°, $[\alpha]^{23}D$ +50° (*c* 0.43).

Anal. Calcd. for $C_{32}H_{50}O_5$ (514.72): C, 74.67; H, 9.79. Found: C, 74.32; H, 9.50.

Although this acid was lower melting, its infrared spectrum was identical with that of the product obtained by ozonolysis. This was confirmed by conversion into the known methyl ester, m.p. of the crude product 170–172°, lit.[7] 177–178°.

Enol Lactonization of 3β-Acetoxy-Δ⁸-lanostene-24-one-21-oic Acid (II). 3β-Acetoxy-Δ⁸,²³-lanostadiene-24-ol-21-oic Acid 21→24-Lactone (α-Lactone) (IVa) and 3β-Acetoxy-Δ⁸,²⁴-lanostadiene-24-ol-21-oic Acid 21→24-Lactone (β-Lactone) (IVb).—To a solution of 15.4 g. of crude 3β-acetoxy-Δ⁸-lanostene-24-one-21-oic acid (II) (obtained directly by decomposition of the ozonized acetyleburicoic acid with zinc and acetic acid) in 150 ml. of acetic anhydride was added 3.75 g. of anhydrous sodium acetate and the resulting suspension was heated under reflux for 10 hr. Upon cooling, the acetic anhydride solution was decanted from the sodium acetate and the latter washed thoroughly with benzene. The combined acetic anhydride–benzene solutions were evaporated to dryness *in vacuo;* the residue was redissolved in benzene and filtered from precipitated sodium acetate. The clear benzene solution was evaporated to dryness leaving a mixture of the α- and β-enol lactones (15.1 g.). Separation was achieved by chromatography on neutral alumina as follows: The total residue was dissolved in 50 ml. of benzene and 50 ml. of hexane and charged to a column containing 300 g. of neutral alumina. Elution with 250 ml. of benzene–hexane 1:1 produced 3.1 g. of crude crystalline α-lactone IVa, which after crystallization from 95% ethanol was analytically pure; m.p. 172–174°, $[\alpha]^{23}D$ +37°; λ_{max}^{Nujol} 5.69, 5.78, 5.93 (weak), 8.05, 12.05, 12.63, and 13.30 μ. The 12.05 and 12.63 μ bands are diagnostic for the α-lactone and are absent in the β-lactone to be described below; n.m.r. 5.17 τ (d, *J* 5 c.p.s.) (23-proton).

(20) S. F. St. André, H. B. McPhillamy, J. A. Nelson, A. C. Shabica, and C. R. Scholz, *J. Am. Chem. Soc.*, **74**, 5506 (1952).

Anal. Calcd. for $C_{32}H_{48}O_4$ (496.70): C, 77.37; H, 9.73. Found: C, 77.41; H, 9.82.

Continued elution of the alumina column with benzene (8 l.) produced a total of 4 g. of material in 12 fractions, all of which melted between 150–160° and represent a mixture of the α- and β-lactones. Rechromatography of this mixture was necessary to obtain the pure β-lactone. For this purpose all the fractions were combined (4 g.), dissolved in 20 ml. of benzene and 80 ml. of hexane, and charged to a column of 120 g. of neutral alumina. Elution with benzene–hexane 2:8 produced in the first 500 ml. 827 mg. of the pure α-lactone, which was followed on elution with the same solvent mixture (5.5 l.) and with benzene–hexane 1:1 (2 l.) by a total of 2.9 g. of material, representing a mixture of α- and β-lactones melting at 158–160°. Continued elution of the column with benzene (9 l.) yielded a total of 1.2 g. of material which after recrystallization from ethanol constituted pure 3β-acetoxy-$\Delta^{8,24}$-lanostadiene-24-ol-21-oic acid 21→24-lactone (β-lactone) (IVb); 404 mg., m.p. 190–191°, $[\alpha]^{23}D$ +64° (*c* 0.87); λ_{max}^{Nujol} 5.70, 5.79, 5.97 (weak), 8.08, 11.50, 11.80, and 13.50 μ. The 11.80 μ band is absent in the α-lactone. The n.m.r. spectrum showed no absorption in vinyl region; 8.29 and 8.38 τ $\left(=C\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}\right)$

Anal. Calcd. for $C_{32}H_{48}O_4$ (496.70): C, 77.37; H, 9.73. Found: C, 77.56; H, 9.73.

Since it is not necessary to separate the α- and β-lactones for dehydrogenation to the pyrone VIII, the chromatographic procedure could be simplified considerably. Thus the crude mixture of enol lactones IVa and IVb derived from the ozonolysis of 200 g. of acetyleburicoic acid was dissolved in 1 l. of hexane and filtered through a column containing 1 kg. of neutral alumina. A total of 4 l. of hexane eluted 119 g. of crystalline material which on recrystallization from 500 ml. of methanol furnished 84 g. of the mixed α- and β-lactones melting at 160–162°; total yield 40%.

Ozonolysis of α-Lactone IVa.—A solution of 51 mg. of α-lactone IVa in 5 ml. of carbon tetrachloride was cooled to 0° and ozonized with 1.5 mole equivalents of ozone. The mixture was poured into 10 ml. of distilled water and refluxed for 20 min. It was then placed in a distillation flask, and 6 ml. of aqueous distillate was collected after removal of the carbon tetrachloride. Titration of the distillate with standard sodium hydroxide solution indicated 40% of one mole equivalent of volatile acid. The neutralized solution was evaporated to dryness, dissolved in 1 drop of water, and crystallized by the addition of 3 drops of acetone. The infrared spectrum[12] of the dried product (KBr pellet) was identical with that of authentic sodium isobutyrate and very different from those of *n*-propionate, *n*-butyrate, *n*-valerate, and isovalerate.

Ozonolysis of β-Lactone IVb.—A solution of 24 mg. of the β-lactone IVb in 5 ml. of glacial acetic acid was ozonized at about 10° with 5 molar equivalents of ozone. The reaction mixture was poured into 10 ml. of water and 6 ml. was distilled off from a micro-Claisen flask into a chilled solution of 2,4-dinitrophenylhydrazine hydrochloride in water (prepared by saturating the free base in 2 *N* HCl at 0° and filtering the solution). The dried fine, yellow precipitate weighed 8 mg., m.p. 117–120°. One recrystallization gave m.p. 123–124°. The infrared spectrum of the original crystals was identical with that of an authentic specimen of acetone 2,4-dinitrophenylhydrazone. The solubility of the derivative in the solution accounts for 2 additional mg. of 2,4-dinitrophenylhydrazone; total: 10 mg. or 90% yield. Under identical conditions the α-lactone gave no detectable precipitate.

Methanolysis of the α-Lactone IVa.—To a solution of 20 mg. of the α-lactone IVa in 3 ml. of methanol was added 0.20 ml. of 10% aqueous potassium carbonate. The cloudy solution was shaken for 1 hr. during which time a heavy precipitate had formed. An additional 10 ml. of methanol was added to dissolve the precipitate and the clear solution was allowed to stand at room temperature overnight. The solution was then evaporated to small volume, poured into water, and filtered. The dried precipitate weighed 14 mg., m.p. 167–168°. Its infrared spectrum was identical with that of an authentic sample of methyl 3β-acetoxy-Δ^8-lanostene-24-one-21-oate (IVc) prepared by the ozonolysis of methyl acetyleburicoate.[6] Further crystallization raised the melting point to 178–179°; lit. 181–183°,[6] 177–178°.[7]

Anal. Calcd. for $C_{33}H_{52}O_5$ (528.75): C, 74.96; H, 9.91. Found: C, 74.90; H, 9.99.

Mixed Anhydride of Acetyleburicoic Acid with Acetic Acid.—A solution of 500 mg. of acetyleburicoic acid and 7 mg. of anhydrous sodium acetate in 5 ml. of acetic anhydride was refluxed for 4 hr. The mixture was evaporated to dryness *in vacuo*, taken up in ether, washed with sodium bicarbonate solution and saturated sodium chloride, and dried over sodium sulfate. Evaporation of the filtered extract yielded a residue which crystallized at once. Recrystallization from hexane and cooling to −20° gave 197 mg. of crystals, m.p. 104–106°. Further crystallization from hexane raised the melting point to 106–107°, $[\alpha]^{23}D$ +48°; λ_{max}^{Nujol} 5.51, 5.75, 6.10, and 11.29 μ.

Anal. Calcd. for $C_{35}H_{54}O_5$ (554.78): C, 75.77; H, 9.81. Found: C, 75.37; H, 9.52.

Reaction of α-Lactone IVa with NBS and Sodium Acetate. 3β-Acetoxy-(23R)-Δ^8-lanostene-23-ol-24-one-21-oic Acid 21→23-Lactone (V).—To a solution of 209 mg. (0.42 mmole) of 3β-acetoxy-$\Delta^{8,23}$-lanostadiene-24-ol-21-oic acid 21→24-lactone (IVa) in 15 ml. of pure dioxane and 8 ml. of an acetate buffer (prepared by dissolving 6.6 g. of anhydrous NaOAc and 6.6 ml. of glacial HOAc in 100 ml. of H_2O) was added over a period of 5 min. a solution of 153 mg. (0.86 mmole) of N-bromosuccinimide in 15 ml. of dioxane. After an additional 5 min., excess water was added and the resulting crystalline product was filtered; yield 200 mg., m.p. 223–226°. Recrystallization from ethyl acetate–hexane gave 114 mg. of V, m.p. 230–232°. From the mother liquor an additional 18 mg. was obtained; λ_{max}^{Nujol} 5.60, 5.80, and 7.95 μ. This material was shown by direct comparison to be identical in every respect with material prepared from acetyleburicoic acid by selenium dioxide oxidation followed by ozonolysis as reported by Holker, *et al.*[13] These authors report m.p. 233–235°, $[\alpha]D$ +59°.

Anal. Calcd. for $C_{32}H_{48}O_5$ (512.70): C, 74.96; H, 9.44. Found: C, 74.98; H, 9.52.

3β-Acetoxy-23-bromo-(23S)-Δ^8-lanostene-24-one-21-oic Acid (VII).—To a solution of 50 mg. of 3β-acetoxy-$\Delta^{8,23}$-lanostadiene-24-ol-21-oic acid 21→24-lactone (IVa) (0.101 mmole) in 3 ml. of dioxane was added 3 ml. of 0.167 *N* aqueous perchloric acid followed by a solution of 37 mg. (0.205 mmole) of N-bromosuccinimide in 3 ml. of dioxane. After 5 min. the mixture was diluted with water and the resulting crystals filtered, washed with water, and dried *in vacuo* at room temperature. This material represents the essentially pure bromo acid (VII).

Anal. Calcd. for $C_{32}H_{49}O_5Br$: Br, 13.46. Found: Br, 13.81.

N-Chlorosuccinimide did not react with the α-lactone IVa under either of the above sets of conditions. The bromo acid VII could be converted to the lactone V as follows: To a solution of 20 mg. of the bromo acid VII in 3 ml. of dioxane was added 50 mg. of sodium acetate in 1 ml. of water. After 20 min. at room temperature water was added and the product extracted with chloroform. Evaporation of the chloroform extract furnished 12 mg. (69%) of the keto lactone V, m.p. 226–228°.

Selenium Dioxide Oxidation of Acetyleburicoic Acid (Ia). 3β-Acetoxy-(23R)-$\Delta^{8,24(28)}$-eburicadiene-23-ol-21-oic Acid 21→23-Lactone (VI) and its (23S)-Epimer (VIa).—A solution of 3 g. of acetyleburicoic acid (Ia) and 333 mg. of selenium dioxide in 45 ml. of glacial acetic acid and 1.5 ml. of water was heated under reflux for 3 hr. The reaction mixture was filtered and poured into ice water and the resulting precipitate filtered, triturated well with water, and dried in a vacuum oven at 70°. The resulting material (3.1 g.) was dissolved in 20 ml. of benzene and 80 ml. of hexane and chromatographed on 70 g. of neutral alumina. No solid material was eluted with benzene–hexane (1:1), but when the eluent was changed to benzene there was isolated from a total of 3 l. of eluent, a total of 580 mg. of crystalline material which on crystallization from 95% ethanol furnished 427 mg. of the methylene lactone VI, m.p. 205–207°. This material on recrystallization from 95% ethanol melted at 210–212°, $[\alpha]D$ +51.5° (*c* 0.92); λ_{max}^{Nujol} 5.63, 5.80, 6.07, and 8.00 μ; lit.[13] m.p. 214–215°, $[\alpha]D$ +49°.

From the mother liquors of this material there was obtained 146 mg. of a second lactone VIa, not isolated by the British workers, which melted at 188–190°. An additional 46 mg. of this material was obtained by continuing the elution of the column with 1 l. of benzene; $[\alpha]D$ +42° (*c* 0.50); λ_{max}^{Nujol} 5.63, 5.76, 6.07, and 8.00 μ.

Anal. Calcd. for $C_{33}H_{50}O_4$ (510.73): C, 77.60; H, 9.87. Found: C, 77.39; H, 9.58.

3β-Acetoxy-(23S)-Δ^8-lanostene-23-ol-24-one-21-oic Acid 21→23-Lactone (Va).—A solution of 75 mg. of the lactone VIa in 2.5 ml. of chloroform and 2.5 ml. of ethyl acetate was ozonized with 1.5 meq. of ozone at the temperature of a Dry Ice–acetone mixture. The ozonide was reduced with hydrogen over a 10% palladium-on-carbon catalyst (5 mg.), the catalyst removed by filtration, and the solvent evaporated to dryness *in vacuo*. The residue (73 mg.) on crystallization from 95% ethanol furnished 42 mg. of material melting at 200–202°. The analytically pure material had m.p. 215–217°, $[\alpha]D$ +93° (*c* 0.53); λ_{max}^{Nujol} 5.60, 5.80, and 7.96 μ.

Anal. Calcd. for $C_{32}H_{48}O_5$ (512.70): C, 74.96; H, 9.44. Found: C, 74.86; H, 9.28.

3β-Acetoxy-$\Delta^{8,20(22),23}$-lanostatriene-24-ol-21-oic Acid 21→24 Lactone (α-Pyrone) (VIII).—A suspension of 180 mg. of 10% palladium-on-charcoal in 25 ml. of *p*-cymene was dried by azeotropic removal of approximately 3 ml. of solvent until the temperature of the vapor was over 170°. To this mixture was added 250 mg. of the thoroughly dried α-enol lactone IVa and the re-

sulting suspension heated under reflux with stirring for 2 hr. under a blanket of nitrogen. The mixture was cooled, filtered, and the solvent removed *in vacuo*. The residual crystalline material on recrystallization from absolute ethanol furnished the pure α-pyrone VIII in 75% yield, m.p. 228–228.5°, $[\alpha]^{23}D$ −114°, λ_{max}^{alc} 305 mμ (ϵ 8900); λ_{max}^{Nujol} 5.79, 5.90, 6.11, 6.35, 8.05, 11.90, and 12.69 μ.

Anal. Calcd. for $C_{32}H_{46}O_4$ (494.68): C, 77.69; H, 9.37. Found: C, 77.77; H, 9.43.

When the β-enol lactone IVb was substituted for the α-lactone IVa the reaction time had to be prolonged to 6 hr. In this case the yield of the pyrone VIII was 60%. For unknown reasons, out of many lots of Eastman terpene-free and practical *p*-cymene employed in this reaction, one lot of terpene-free material gave very poor yields of VIII.

A mixture of α- and β-enol lactones (84 g., m.p. 160–162°) was dehydrogenated with 84 g. of 10% palladium-on-charcoal in 1700 ml. of *p*-cymene for 6 hr. yielding after recrystallization from alcohol–chloroform 49 g. of the pure α-pyrone VIII, m.p. 226–228°, yield 58%.

$\Delta^{8,20(22),23}$-Lanostatriene-3β,24-diol-21-oic Acid 21→24-Lactone (VIIIa).—To a solution of 6.2 g. of 3β-acetoxy-$\Delta^{8,20(22),23}$-lanostatriene-24-ol-21-oic acid 21→24-lactone (VIII) in 250 ml. of dioxane was added under nitrogen 125 ml. of 1.5 *N* KOH in methanol. After 3 hr. at room temperature the mixture was diluted with 400 ml. of water and the suspension neutralized with 6 *N* sulfuric acid. Chloroform was then added and the layers separated. The chloroform–dioxane extract was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residual solid (5.9 g.) melted at 242–246° and showed a trace of the acetate VIII on thin layer chromatography. Crystallization from ethyl acetate gave 4.2 g. (57%) of pure material, m.p. 262–264°, $[\alpha]^{25}D$ −146° (*c* 0.76), λ_{max}^{alc} 305 mμ (ϵ 10,500); λ_{max}^{Nujol} 2.79, 5.86, 6.08, and 6.31 μ.

Anal. Calcd. for $C_{30}H_{44}O_3$ (452.65): C, 79.60; H, 9.80. Found: C, 79.50; H, 9.83.

The following hydrolysis procedure demonstrates the stability of the pyrone system to alkali: To a solution of 510 mg. of potassium hydroxide in 10 ml. of ethylene glycol was added 73 mg. of the finely ground α-pyrone acetate VIII. The suspension was stirred and immersed in an oil bath held at a temperature of 150°. After 5 min. there resulted a clear, pale yellow solution which was heated for an additional 4 min. and then cooled; 25 ml. of water was added and the mixture extracted with ether. The ether extract was washed with saturated sodium chloride solution, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The crystalline residue (60 mg.) on recrystallization from acetone furnished 30 mg. of the α-pyrone 3-ol VIIIa, m.p. 254–255°.

$\Delta^{8,20(22),23}$-Lanostatriene-3-one-24-ol-21-oic Acid 21→24-Lactone (VIIIb).—To a solution of 128 mg. of $\Delta^{8,20(22),23}$-lanostatriene-3β,24-diol-21-oic acid 21→24-lactone (VIIIa) in 30 ml. of Merck reagent acetone was added at room temperature 0.2 ml. of a solution prepared by dissolving 200 mg. of chromium trioxide and 320 mg. of concentrated sulfuric acid in 1 ml. of water (Jones reagent). After 10 min. methanol was added to reduce excess chromium trioxide and the solution was diluted with water and concentrated *in vacuo*. The resulting suspension was extracted with chloroform, the chloroform extract dried over sodium sulfate, and evaporated to dryness *in vacuo;* 77 mg. of the 3-ketone VIIIb, m.p. 228–230°, was obtained, which after crystallization from acetonitrile gave the pure substance, m.p. 236–238°, $[\alpha]^{25}D$ −139° (*c* 1.14); λ_{max}^{Nujol} 5.87, 6.08, 6.30, 12.02, and 12.63 μ; λ_{alc}^{max} 305 mμ (ϵ 9200).

Anal. Calcd. for $C_{30}H_{42}O_2$ (415.63): C, 79.95; H, 9.39. Found: C, 80.21; H, 9.54.

$\Delta^{8,20(22),23}$-Lanostatriene-3β,21-diol (IX).—A solution of 5 g. of the α-pyrone VIII in 210 ml. of freshly distilled tetrahydrofuran was added over a 15-min. period to a refluxing solution of 5 g. of lithium aluminum hydride in 125 ml. of tetrahydrofuran with stirring under a blanket of nitrogen. Reflux was continued for an additional 2 hr. and the solution was cooled to room temperature. Saturated sodium sulfate solution was added carefully until all the lithium aluminum hydride was decomposed, following which the reaction mixture was shaken with several 200-ml. portions of benzene and the resulting extracts decanted from the inorganic salts until all the organic material was extracted. The benzene–tetrahydrofuran solution was dried over sodium sulfate and evaporated to dryness *in vacuo*. The resulting residue (4.6 g.) was dissolved in 100 ml. of benzene and the solution chromatographed on 100 g. of neutral alumina washing the column with 800 ml. of benzene to remove some impurities. The trienediol IX was obtained by elution with 2800 ml. of 10% chloroform in benzene. The combined eluates were evaporated to dryness and recrystallized from ether which resulted in 2.06 g. (46% yield) of the pure trienediol IX, m.p. 166–168°, $[\alpha]^{23}D$ +68° (chf.), λ_{max}^{alc} 243 mμ (ϵ 31,000); λ_{max}^{Nujol} 3.10, 5.64, 5.85, 6.02, and 6.21 μ; n.m.r.: three olefinic protons in a complex splitting pattern between 320 and 400 c.p.s., two protons at 5.80 τ (21-CH_2), which on addition of D_2O resolves to an AB quartet at 5.72 and 5.88 τ (*J* 25 c.p.s.).

The trienediol IX is unstable when stored in the presence of light and air. After 1 month at room temperature, peroxides were detected with starch–KI reagent; the intensity of the ultraviolet absorption maximum had decreased by about 40% and the melting point was 10° lower. The diacetate IXa showed no significant decrease in melting point and ultraviolet extinction coefficient after standing for 2 years.

The diacetate IXa was prepared as follows: A solution of 500 mg. of the trienediol IX in 5 ml. of anhydrous pyridine and 0.5 ml. of acetic anhydride was allowed to stand at room temperature overnight. Removal of the reagents *in vacuo* left a residue which on crystallization from methanol furnished 505 mg. of the pure diacetate IXa, m.p. 131–132°, $[\alpha]^{23}D$ +87°, λ_{max}^{alc} 243 mμ (ϵ 32,100); λ_{max}^{Nujol} 5.75, 5.92, 6.10, 6.25, and 8.19 μ.

Anal. Calcd. for $C_{34}H_{52}O_4$ (524.75): C, 77.82; H, 9.99. Found: C, 77.75; H, 10.01.

Continued elution of the alumina column with 25% chloroform in benzene (600 ml.) produced little material. When this solvent mixture was replaced by chloroform (1:1) there was eluted 200 mg. of crystalline material which after recrystallization from acetone furnished 134 mg. of Δ^8-lanostene-3β,21,24ξ-triol (XI), m.p. 199–200°, $[\alpha]^{23}D$ +37° (*c* 0.96); λ_{max}^{alc} no selective absorption; λ_{max}^{Nujol} 3.00 μ.

Anal. Calcd. for $C_{30}H_{52}O_3$ (416.72): C, 78.20; H, 11.38. Found: C, 78.25; H, 11.33.

The triacetate was prepared with pyridine and acetic anhydride at room temperature. Recrystallization from methanol gave prisms, m.p. 74–78°, $[\alpha]D$ +46° (*c* 1.09); λ_{max}^{Nujol} 5.75, 8.05 μ.

Anal. Calcd. for $C_{36}H_{58}O_6$ (586.82): C, 73.68; H, 9.96. Found: C, 73.51; H, 9.99.

Lithium Aluminum Hydride Reduction of the Mixture of α- and β-Lactones (IVa and IVb). Δ^8-Lanostene-3β-21,24ξ-triol (XI).—A mixture of α- and β-lactones IVa and IVb (200 mg., m.p. 158–160°), was reduced with lithium aluminum hydride in freshly distilled tetrahydrofuran exactly as described for the reduction of the α-pyrone VIII. The material remaining after evaporation of the solvent (118 mg.) was dissolved in 10 ml. of benzene and chromatographed on 4 g. of neutral alumina. Benzene (300 ml.) eluted 42 mg. of material. Benzene–chloroform 9:1 (300 ml.) eluted 15 mg. of material. The desired triol XI was eluted with chloroform (300 ml.) and amounted to 50 mg., which after two recrystallizations from acetone melted at 197–198° and showed no depression in melting point with the triol derived from the lithium aluminum hydride reduction of the α-pyrone VIII. The infrared spectra of the two samples were identical in every detail.

$\Delta^{8,20(22),23}$-Lanostatriene-3β-ol-21-al (X).—To a solution of 250 mg. of the trienol IX in 25 ml. of chloroform was added 7.5 g. of activated manganese dioxide prepared according to Attenburrow, *et al.*,[21,22] and the mixture shaken in the dark for 24 hr. The mixture was filtered, the manganese dioxide washed well with chloroform, and the filtrate evaporated to dryness *in vacuo*. The crystalline residue on recrystallization from methanol afforded 120 mg. of the unsaturated aldehyde X, which after recrystallization from the same solvent gave the pure substance, m.p. 129–130°, $[\alpha]D$ +111° (*c* 1.02); λ_{max}^{alc} 291 mμ (ϵ 20,200); λ_{max}^{Nujol} 3.03, 3.70, 6.00, 6.12, and 6.33 μ.

Anal. Calcd. for $C_{30}H_{46}O_2$ (438.67): C, 82.13; H, 10.57. Found: C, 81.63; H, 10.33.

The aldehyde X is extremely unstable. Standing at room temperature for a few days leads to uncrystallizable decomposition products.

21,24ξ-Oxido-$\Delta^{8,20(22)}$-lanostadiene-3β,21-diol (Xa).—To a solution of 100 mg. of the trienol IX in 10 ml. of chloroform was added 3.0 g. of manganese dioxide[21,22] and the mixture shaken violently for 72 hr. in the dark. The solution was then filtered, evaporated to dryness, and the residue crystallized from acetonitrile. There was isolated 11 mg. of the hemiacetal Xa, m.p. 186–187°; no ultraviolet absorption above 215 mμ, λ_{max}^{KBr} 2.87, 5.84 (w), and 6.07 (w) μ.

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 78.89; H, 10.59. Found: C, 79.15; H, 10.45.

3-Isopropylidene-14-methyl-$\Delta^{8,20(22),23}$-A-norcholestatriene-24-ol-21-oic Acid 21→24-Lactone (XV).—To a suspension of 104 mg. of $\Delta^{8,20(22),23}$-lanostatriene-3β,24-diol-21-oic acid 21→24-lactone (VIIIa) in 50 ml. of toluene, which was cooled to 0–5° with ice and protected from light, 108 mg. of phosphorus pentachloride was added while a rapid stream of helium was bubbled through

(21) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(22) An activated manganese dioxide preparation purchased from Beacon Chemical Industries, Cambridge 40, Mass., gave the same result.

the magnetically stirred solution. The reaction was quenched after 12 min. with excess 10% potassium carbonate solution and the organic phase was extracted three more times with this reagent, washed with saturated sodium chloride solution, dried over sodium sulfate, filtered, and the solvent evaporated *in vacuo*. Beautiful, fine needles (78 mg., 78% yield) of 3-isopropylidene-14-methyl-$\Delta^{8,20(22),23}$-A-norcholestatriene-24-ol-21-oic acid 21→24-lactone (XV) separated from absolute ethanol; m.p. 182–185°, $[\alpha]^{23}D$ −165° (*c* 0.51), λ_{max}^{alc} 305 mμ (ε 10,300); λ_{max}^{Nujol} 5.78, 6.10, 6.33, and 9.08 μ.

Anal. Calcd. for $C_{30}H_{42}O_2$ (434.64): C, 82.90; H, 9.74. Found: C, 83.20; H, 9.49.

3-Isopropylidene-14-methyl-$\Delta^{8,20(22),23}$-A-norcholestatriene-21-ol (XVII) and 3-Isopropylidene-14-methyl-$\Delta^{8,20(22),23}$-A-norcholestatriene-21-oic Acid (XVI).—A solution of 240 mg. of 3-isopropylidene-14-methyl-$\Delta^{8,20(22),23}$-A-norcholestatriene-24-ol-21-oic acid 21→24-lactone (XV) in 10 ml. of freshly distilled tetrahydrofuran was added dropwise under nitrogen to a refluxing stirred suspension of 240 mg. of lithium aluminum hydride in tetrahydrofuran over a 5-min. period. The reaction mixture was then heated under reflux for an additional 15 min., cooled, and decomposed with *ca.* 1 ml. of saturated sodium sulfate solution. The resulting precipitate was filtered off and washed three times with benzene. The combined filtrates were dried over sodium sulfate and evaporated to give 200 mg. of a clear oil. This was dissolved in 5 ml. of benzene and 5 ml. of hexane and chromatographed on 20 g. of activity V neutral alumina. Elution with 5% hexane and benzene gave 45 mg. of crystalline material, m.p. 89–90°, which after recrystallization from methanol furnished the pure isopropylidene-14-methyl-$\Delta^{8,20(22),23}$-A-norcholestatriene-21-ol (XVII), m.p. 112–113°, $[\alpha]^{23}D$ +48° (*c* 1.43); λ_{max}^{alc} 243 mμ (ε 29,800); λ_{max}^{Nujol} 3.00, 5.60, 5.80, 6.08, 6.20, and 9.99 μ; n.m.r.: three protons in a complex splitting pattern between 325 and 380 c.p.s., two protons at 5.81 τ (21-CH_2). The lower melting crystals represent a solvate with methanol, which on melting loses solvent and on cooling resolidifies and melts again at 115–116°.

Anal. Calcd. for $C_{30}H_{46}O$ (422.67): C, 85.24; H, 10.97. Found: C, 85.32, H, 10.89.

Continued elution of the column with 5% methanol in chloroform furnished 100 mg. of acidic material, which on crystallization from methanol afforded the pure 3-isopropylidene-14-methyl-$\Delta^{8,20(22),23}$-A-norcholestatriene-21-oic acid (XVI), m.p. 169–170°, $[\alpha]^{23}D$ +86° (*c* 0.75), λ_{max}^{alc} 252 mμ (ε 17,300); λ_{max}^{Nujol} 5.94, 6.08, 6.23, and 10.24 μ.

Anal. Calcd. for $C_{30}H_{44}O_2$ (436.65): C, 82.51; H, 10.16. Found: C, 82.29; H, 9.88.

When the reaction time was prolonged to 1 hr., the ratio of products was shifted in favor of the tetraeneol XVII.

The best yield of the tetraeneol XVII was obtained when the α-pyrone XV (400 mg.) in 18 ml. of dry ether was reduced with 300 mg. of lithium aluminum hydride in 20 ml. of ether for 3 hr. at room temperature. The crude product (368 mg.) on recrystallization from methanol gave 260 mg. of pure XVII, m.p. 90–94° (solvate), yield 67%.

Methyl 3-Isopropylidene-14-methyl-$\Delta^{8,20(22),23}$-A-norcholestatriene-21-oate (XVIa).—The methyl ester XVIa was prepared with diazomethane in methanol–ether and recrystallized from methanol; m.p. 126–128°; λ_{max}^{alc} 254 mμ (ε 17,700), $[\alpha]^{23}D$ +77° (*c* 1.04); λ_{max}^{Nujol} 5.86, 6.09, 6.21, 8.29, and 10.19 μ.

Anal. Calcd. for $C_{31}H_{46}O_2$: C, 82.61; H, 10.29. Found: C, 82.76; H, 10.39.

Reduction of Methyl 3-Isopropylidene-$\Delta^{8,20(22),23}$-A-norcholestatriene-21-oate (XVIa) with Lithium Aluminum Hydride.—The methyl ester XVIa (104 mg.) was reduced with 15 mg. of lithium aluminum hydride in 50 ml. of ether at room temperature for 2 hr. After decomposition with little water the mixture was filtered and the solvent evaporated to give 60 mg. of crystals (m.p. 68–70°) from methanol, 60% yield. The infrared spectrum of this material was identical with that obtained by reduction of the α-pyrone derivative XV.

3β,21-Diacetoxy-4,4,14α-trimethyl-Δ^{8}-5α-pregnene-20-one (XVIIIa).—A solution of 100 mg. of the trienenol diacetate IXa in 10 ml. of ethyl acetate was ozonized at −25° with 3 mole equivalents of ozone. To the resulting solution was added at room temperature 0.5 ml. of acetic acid and then portionwise a total of 1 g. of zinc dust until a negative starch–iodide test was observed, which required about 3 hr. The mixture was filtered, washed with a saturated salt solution, dried over sodium sulfate, and evaporated to dryness *in vacuo*. A crystalline residue (82 mg.) was obtained which on recrystallization from methanol yielded 37 mg. of material melting at 182–184° (43%). Further crystallization from methanol furnished analytical material, m.p. 187–188.5°, $[\alpha]^{23}D$ +101° (*c* 0.22); λ_{max}^{Nujol} 5.73 (shoulder), 5.78, 8.03, 9.30, 9.70, and 9.88 μ; n.m.r.: two protons in an AB pattern, doublets at 5.33 τ (*J* 17 c.p.s.) and 5.46 τ (*J* 17 c.p.s.) (21-CH_2).

Anal. Calcd. for $C_{28}H_{42}O_5$ (458.61): C, 73.32; H, 9.23. Found: C, 73.10; H, 9.02.

3β-Acetoxy-4,4,14α-trimethyl-Δ^{8}-5α-pregnene-21-ol-20-one (XX).—To a solution of 995 mg. of the diacetate XVIIIa in 250 ml. of methanol was added with stirring under helium 5 ml. of 10% oxygen-free potassium carbonate. After 2 hr. at room temperature 0.55 ml. of glacial acetic acid was added followed by the addition of water and the methanol was removed *in vacuo*. The resulting suspension was chilled, filtered, and the precipitate washed and dried *in vacuo*. The crystals (885 mg., 98%) melted at 200–201°. The analytically pure monoacetate XX was obtained, m.p. 202–205°, $[\alpha]^{23}D$ +93° (*c* 0.38); λ_{max}^{Nujol} 2.83, 5.78, 5.86, and 7.98 μ; n.m.r.: two protons at 5.83 τ (singlet, 21-CH_2).

Anal. Calcd. for $C_{26}H_{40}O_4$ (416.58): C, 74.96; H, 9.68. Found: C, 75.14; H, 9.64.

3β-Acetoxy-21-mesyloxy-4,4,14α-trimethyl-Δ^{8}-5α-pregnene-20-one (XXI).—To a solution of 880 mg. of the 3β-monoacetate XX in 22 ml. of anhydrous pyridine was added at 0°, 0.25 ml. (1.5 mole equiv.) of methanesulfonyl chloride. The reaction was allowed to remain at 0° for 2.75 hr., when it was stopped by the addition of a small amount of ice. After 30 min. the solution was concentrated *in vacuo* to one-fourth of its volume, chloroform and water were added, and after separation of the phases the chloroform solution was washed with dilute sulfuric acid, water, and then with dilute sodium bicarbonate keeping the extract cool at all times. The chloroform extract was dried over sodium sulfate, filtered, and evaporated to dryness *in vacuo* leaving the 21-mesylate XXI as a crystalline residue (935 mg., 89%) melting at 147–150°. Analytically pure material was obtained from methanol, m.p. 156–157°, $[\alpha]^{23}D$ +101° (*c* 1.07); λ_{max}^{KBr} 5.78, 7.38, 8.04, and 8.53 μ.

Anal. Calcd. for $C_{27}H_{42}O_6S$ (494.66): C, 65.55; H, 8.55. Found: C, 65.67; H, 8.49.

3β-Acetoxy-21-iodo-4,4,14α-trimethyl-Δ^{8}-5α-pregnene-20-one (XXII).—A solution of 820 mg. of the crude 21-mesylate XXI and 2.16 g. of sodium iodide in 30 ml. of acetone was refluxed for 10 min. on the steam bath. Water was added and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and the solvent removed *in vacuo*. The residue on recrystallization from methanol furnished 790 mg. (90%) of the 21-iodo compound XXII, m.p. 159–160° (blackening at 185°), $[\alpha]^{23}D$ +136° (*c* 1.08); λ_{max}^{KBr} 5.75, 5.87, and 8.00 μ.

Anal. Calcd. for $C_{26}H_{39}O_3I$ (526.48): C, 59.31; H, 7.46. Found: C, 59.37; H, 7.49.

3β-Acetoxy-4,4,14α-trimethyl-Δ^{8}-5α-pregnene-20-one (XXIIIa).—To a solution of 784 mg. of the iodo compound XXII in 17 ml. of dioxane was added 15.3 ml. of a 5% sodium bisulfite solution and the resulting mixture refluxed for 1 hr. on the steam cone. Water and chloroform were added and after separation of the layers, the chloroform phase was washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo;* 550 mg. of material was obtained and an additional 45 mg. by extraction of the aqueous layer with ethyl acetate. Recrystallization from methanol furnished the pure pregnene derivative XXIIIa (533 mg.) in 87% yield, m.p. 169–170°, $[\alpha]^{23}D$ +116° (*c* 1.7); λ_{max}^{KBr} 5.79, 5.85, and 7.97 μ.

Anal. Calcd. for $C_{26}H_{40}O_3$ (400.58): C, 77.95; H, 10.07. Found: C, 77.97; H, 10.09.

4,4,14α-Trimethyl-Δ^{8}-5α-pregnene-3β-ol-20-one (XXIII).—A solution of 500 mg. of the pregnene 3-acetate XXIIIa in 100 ml. of 1 *N* ethanolic KOH was allowed to stand at room temperature for 20 hr., when crystals had appeared in the solution. The mixture was neutralized with 4 *N* sulfuric acid, diluted with water, the ethanol removed *in vacuo*, and the aqueous suspension extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated *in vacuo*. There remained a crystalline residue (430 mg.) which after recrystallization from methanol furnished the analytically pure hydroxy ketone XXIII (390 mg.) in 88% yield, m.p. 254–256°, λ_{max}^{KBr} 2.83 and 5.86 μ, $[\alpha]^{23}D$ +122° (*c* 1.23); n.m.r.: 7.88 τ (21-CH_3).

Anal. Calcd. for $C_{24}H_{38}O_2$ (358.54): C, 80.39; H, 10.68. Found: C, 80.39; H, 10.62.

4,4,14α-Trimethyl-Δ^{8}-5α-pregnene-3,20-dione (XXIV).—To a solution of 12 mg. of the hydroxy ketone XXIII in 8 ml. of reagent grade acetone was added with stirring 0.27 ml. of a solution containing 20 mg. of chromium trioxide and 32 mg. of sulfuric acid per milliliter of 90% aqueous acetone. The reaction was allowed to proceed for 15 min. when it was stopped by the addition of a few drops of 95% ethanol. Water was added and the steroid extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated to dryness *in vacuo*. There remained 11 mg. of a crystalline residue, which after recrystallization from acetone furnished the pure 3,20-diketone XXIV, m.p. 203–204°, $[\alpha]^{23}D$ +136° (*c* 0.52), λ_{max}^{KBr} 5.85 μ.

Anal. Calcd. for $C_{24}H_{36}O_2$ (356.53): C, 80.85; H, 10.18. Found: C, 80.74; H, 10.28.

3β,21-Diacetoxy-4,4,14α-trimethyl-Δ⁸-5α-pregnene-7,11,20-trione (XXV).—To a solution of 23 mg. of the Δ⁸-pregnene 3,21-diacetate (XVIIIa) in 2 ml. of glacial acetic acid maintained at 77–78° was added with stirring over a 20-min. period a solution of 20 mg. of chromium trioxide in 1 ml. of glacial acetic acid. After a total reaction time of 25 min. the mixture was cooled to room temperature, the bulk of the acetic acid removed *in vacuo* and the residue taken up in water and chloroform. The chloroform extract was washed three times with water, dried over sodium sulfate, and the solvent removed *in vacuo*. The residue (24 mg.) crystallized readily from methanol furnishing 18 mg. of the trione diacetate XXV, 75% yield, m.p. 191–192°, $[\alpha]^{23}D$ +107° (*c* 0.59), λ_{max}^{alc} 268 mμ (ε 8100); λ_{max}^{Nujol} 5.74, 5.82, 6.00, and 8.00–8.10 μ.

Anal. Calcd. for $C_{28}H_{38}O_7$ (486.58): C, 69.11; H, 7.83. Found: C, 68.82; H, 7.89.

4,4,14α-Trimethyl-Δ⁸-5α-pregnene-3β,21-diol-20-one (XVIII). A solution of 684 mg. (1.56 mmoles) of the triene diol IX in 40 ml. of ethyl acetate was ozonized at −20° with 2.1 mole equivalents of ozone containing 0.81 mmole of ozone per liter of gas. The ozonolysis mixture was allowed to stand at −20° for 30 min. It was then decomposed at room temperature by the addition of 2 ml. of glacial acetic acid and 10 g. of zinc dust (in portions). The mixture was stirred for 1 hr., when it no longer gave a positive test with potassium iodide–starch reagent, filtered, washed with water, dried over sodium sulfate, and the solvent removed *in vacuo*. A crystalline residue remained (605 mg.) which on recrystallization from methanol–ethyl acetate furnished 358 mg. (62%) of the ketol XVIII melting at 214–216°. Crystallization from the same solvent furnished the pure compound, m.p. 225–227°, $[\alpha]^{23}D$ +113°, λ_{max}^{Nujol} 2.80 and 5.88 μ.

Anal. Calcd. for $C_{24}H_{38}O_3$ (374.54): C, 76.96; H, 10.23. Found: C, 76.85; H, 10.20.

21-Acetoxy-4,4,14α-trimethyl-Δ⁸-5α-pregnene-3β-ol-20-one (XIX).—To a solution of 1.0 g. of the carefully vacuum-dried (100°) pregnenediol XVIII in 25 ml. of pyridine was added 299 mg. of acetic anhydride (1.1 equiv.) and the mixture allowed to stand at room temperature for 18 hr. The reagents were evaporated *in vacuo* and the residual crystalline residue recrystallized from chloroform–methanol. There was obtained 800 mg. of the 21-monoacetate XIX, m.p. 198–199°, $[\alpha]D$ +119° (*c* 1.10); λ_{max}^{Nujol} 2.71, 5.72, 5.80, and 8.10 μ; n.m.r.: two protons in two doublets at 5.33 τ (*J* 17 c.p.s.) and 5.45 τ (*J* 17 c.p.s.) (21-CH_2).

Anal. Calcd. for $C_{26}H_{40}O_4$ (416.58): C, 74.97; H, 9.70. Found: C, 74.97; H, 9.48.

21-Acetoxy-4,4,14α-trimethyl-Δ⁸-5α-pregnene-3,20-dione (XXIV).—A solution of 25 mg. of the 21-acetate XIX in 5 ml. of acetone was oxidized with 0.5 ml. of a solution containing 20 mg. of chromium trioxide and 32 mg. of concentrated sulfuric acid per milliliter of 90% aqueous acetone. The reaction was allowed to proceed for 15 min. when excess chromium trioxide was decomposed by the addition of methanol. Water and chloroform were added and the chloroform extract washed with water, dried over sodium sulfate, and evaporated to dryness. The diketone XXIV crystallized readily from methanol and melted at 172–173°, $[\alpha]^{23}D$ +131° (*c* 1.13); λ_{max}^{Nujol} 5.71, 5.78, 5.90, and 8.10 μ.

Anal. Calcd. for $C_{26}H_{38}O_4$ (414.56): C, 75.32; H, 9.24. Found: C, 75.27; H, 9.28.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, URBANA, ILL., AND THE CONVERSE LABORATORY OF HARVARD UNIVERSITY, CAMBRIDGE 38, MASS.]

Synthesis of a β-Amyrin Derivative, Olean-11,12;13,18-diene[1]

BY E. J. COREY, HANS-JÜRGEN HESS, AND STEPHEN PROSKOW

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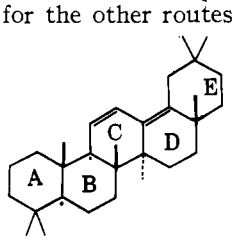
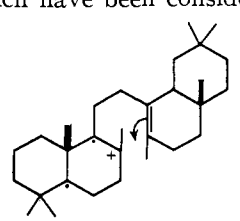
The construction of the pentacyclic ring system of the β-amyrin derivative olean-11,12;13,18-diene has been accomplished by joining a precursor containing the A and B rings to a monocyclic intermediate with a preformed E ring and then closing ring D by an internal aldol reaction and ring C by internal cation–olefin addition.

We have previously reported in a preliminary note[2] a synthetic route to olean-11,12;13,18-diene (I), a well-known pentacyclic triterpene derivative in the β-amyrin series. Details of this synthesis are provided in the present paper. The main object of the investigation was to test the possibility of forming the pentacyclic nucleus by cyclization of a tetracyclic intermediate containing rings A, B, D, and E *via* cationic intermediates, *e.g.*, II. This general approach to the pentacyclic nucleus is attractive because the synthesis of the necessary intermediates is clearly feasible and because the total number of steps required appears to be smaller than for the other routes which have been considered.



I



II

In addition there is a parallel with the proposed biosynthetic processes[3,4] and the reactions which have been employed for the synthesis of pentacyclosqualene (8,8′-cycloonocerene).[5,6] As in previous work,[6] we chose to deal with substances lacking the 3-hydroxyl group of the naturally occurring β-amyrin derivatives for the sake of operational convenience. The choice of the diene I as the synthetic objective was governed in part by the fact that this substance is resistant to isomerization under the acidic conditions which are generally used for cationic cyclization of olefins as is dramatically illustrated by the formation of this system from the ursan-11,12;13,18-diene system under drastic conditions.[7]

In general terms the synthesis of I was carried out along the following lines. An intermediate which contained rings A and B (VI) was prepared and coupled to a monocarbocyclic structure (X) ultimately to comprise ring E. The D ring was then produced by an aldol cyclization and finally the C ring was closed by an acid-catalyzed internal addition reaction.

(1) This work was supported by the National Science Foundation.

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