

$\lambda_{\max}^{1\% \text{ KOH in abs. EtOH}}$  241  $m\mu$  ( $\epsilon$  16,650) and 308  $m\mu$  ( $\epsilon$  20,100);  $\nu_{\max}$  1760, 1682, 1655 and 1610  $\text{cm}^{-1}$ ;  $[\alpha]^{25D} +102^\circ$  ( $c$  0.956),  $[M]_D +335$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{30}\text{O}_3$  (328.44): C, 76.79; H, 8.59. Found: C, 76.43; H, 8.81.

$\Delta^{4,17(20)}$ -Pregnadiene-20-ol-3,16-dione 20-Acetate (V).—A solution of 0.215 g. of the trione IV in 5 ml. of pyridine and 3 ml. of acetic anhydride was allowed to stand 16 hours at room temperature, poured into water, extracted with ether and ethyl acetate, and the combined extracts were treated with Norite and dried. Evaporation gave an oil. Six crystallizations from dilute acetone afforded 0.032 g. (13%) of the enol acetate V, m.p. 203–203.5°;  $\lambda_{\max}$  242  $m\mu$  ( $\epsilon$  26,400);  $\lambda_{\max}^{1\% \text{ KOH in abs. EtOH}}$  241  $m\mu$  ( $\epsilon$  16,400) and 308  $m\mu$  ( $\epsilon$  21,200);  $\nu_{\max}$  1755, 1725, 1679, 1652, 1625 and 1170  $\text{cm}^{-1}$ ;  $[\alpha]^{25D} -30^\circ$  ( $c$  0.531),  $[M]_D -112$ .

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{30}\text{O}_4$  (370.47): C, 74.56; H, 8.16. Found: C, 74.83; H, 8.36.

$\Delta^4$ -Pregnene-16 $\beta$ -ol-3,20-dione (VIa).—To a refluxing mixture of 0.83 g. of the 16 $\beta$ -ol bis-ketal IIIa in 100 ml. of methanol was added 6 ml. of 8% (v./v.) sulfuric acid. The reaction was allowed to proceed for 3 minutes and then was

added to ice-water. The mixture was filtered to give 0.54 g. of solid, m.p. 188–194.5°. Several crystallizations from acetone–petroleum ether gave 0.245 g. of the 16 $\beta$ -ol dione VIa, m.p. 202–203°;  $\lambda_{\max}$  240  $m\mu$  ( $\epsilon$  16,500);  $\nu_{\max}$  3420, 1712, 1658 and 1615  $\text{cm}^{-1}$ ;  $[\alpha]^{25D} +192^\circ$  ( $c$  1.91),  $[M]_D +645$ .

*Anal.* Calcd. for  $\text{C}_{21}\text{H}_{30}\text{O}_3$  (330.45): C, 76.32; H, 9.15. Found: C, 76.06; H, 9.02.

$\Delta^4$ -Pregnene-16 $\beta$ -ol-3,20-dione 16-Acetate (VIb).—A solution of 272 mg. of VIa in 4 ml. of pyridine and 2 ml. of acetic anhydride was allowed to stand at room temperature for 16 hours, poured into ice-water, and filtered to give 264 mg. of crude acetate VIb, m.p. 185–193°. Several crystallizations from acetone–petroleum ether yielded 110 mg. (36%) of VIb, m.p. 202–203°;  $\lambda_{\max}$  240  $m\mu$  ( $\epsilon$  17,100);  $\nu_{\max}$  1745, 1721, 1680, 1625 and 1250  $\text{cm}^{-1}$ ;  $[\alpha]^{25D} +103^\circ$  ( $c$  0.3),  $[M]_D +384$ .

The analytical sample was obtained necessarily by sublimation, otherwise the analytical results invariably indicated solvation.

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{32}\text{O}_4$  (372.49): C, 74.16; H, 8.66. Found: C, 74.19; H, 8.80.

PEARL RIVER, NEW YORK

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

## Terpenoids. XVII.<sup>1</sup> The Cactus Triterpenes Thurberogenin and Stellatogenin<sup>2</sup>

BY CARL DJERASSI, E. FARKAS,<sup>3</sup> L. H. LIU<sup>3</sup> AND G. H. THOMAS<sup>3</sup>

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Degradative evidence is presented on the basis of which it is suggested that the two cactus triterpenes thurberogenin and stellatogenin possess structures XLII and XLIII based on a betulinic acid skeleton.

In the first paper of this series<sup>4</sup> we described the isolation from the cactus *Lemaireocereus thurberi* of a new triterpene which was named "thurberogenin." The substance possessed the empirical formula  $\text{C}_{30}\text{H}_{46}\text{O}_3$ , formed a monoacetate and in the infrared exhibited a band at *ca.* 5.65  $\mu$  which was assigned to a five-membered lactone ring. Subsequently, an investigation of *Lemaireocereus stellatus*<sup>5</sup> and other cacti<sup>5,6</sup> led to the isolation of another triterpene lactone, "stellatogenin" ( $\text{C}_{30}\text{H}_{48}\text{O}_4$ ) which could be correlated<sup>5</sup> with thurberogenin. Since stellatogenin is much more abundant as well as more widely distributed<sup>5,6</sup> this has made available a sufficient supply of these two triterpenes so that degradation studies could be initiated and these form the subject of the present paper. It should be noted that except for the cactus triterpene dumortierigenin,<sup>7</sup> no tri-

terpenes so far have been encountered in nature which possess a lactone ring.

**Reactions of the Double Bond.**—Thurberogenin gives essentially no color with tetranitromethane<sup>8</sup> and does not show<sup>7</sup> any high terminal ultraviolet absorption typical<sup>9</sup> of the 12–13 double bond of triterpenes of the  $\alpha$ - and  $\beta$ -amyrin series (I, II). Nevertheless, the presence of a reactive double bond could be demonstrated by several reactions: (a) thurberogenin (X) can be hydrogenated with platinum oxide in glacial acetic acid to a dihydro derivative (XI); (b) thurberogenin can be oxidized readily with perbenzoic acid to yield an epoxide (XII)<sup>5</sup>; (c) selenium dioxide in acetic acid transforms thurberogenin acetate into an  $\alpha,\beta$ -unsaturated aldehyde (XIV) ( $\lambda_{\max}^{\text{EtOH}}$  222  $m\mu$ ,  $\log \epsilon$  4.01) which in turn can be hydrogenated with palladium to a dihydroaldehyde (XV).

These reactions eliminate completely from consideration an  $\alpha$ -(I) or  $\beta$ -amyrin (II) skeleton, since those triterpenes<sup>10</sup> behave differently under such conditions, but rather suggest that thurberogenin belongs to the rare class of lupeol triterpenes of which only three members are known<sup>10</sup>: lupeol

(XXII) transformation (*cf.* D. H. R. Barton and N. J. Holness, *J. Chem. Soc.*, 78 (1952)).

(8) The earlier reported (ref. 4) light yellow color may have been due to some contamination, possibly with oleanolic acid.

(9) T. G. Halsall, *Chemistry & Industry*, 867 (1951).

(10) For the sake of brevity, references to the original literature are not given when they apply to well-known reactions of pentacyclic triterpenes since these are summarized quite adequately in review articles by O. Jeger (in L. Zechmeister's "Progress in the Chemistry of Organic Natural Products," Springer, Vienna, 1951, Vol. 7, p. 1) and by D. H. R. Barton (in E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Press, Houston, Texas, 1953, Vol. IIB, p. 726).

(1) Paper XVI, C. Djerassi, G. H. Thomas and H. Monsimer, *THIS JOURNAL*, **77**, 3579 (1955).

(2) (a) We are indebted to the Division of Research Grants of the U. S. Public Health Service for generous financial assistance (Grant No. G-3863) in support of this work. (b) Presented at the XIV International Congress of Pure and Applied Chemistry, Zürich, July 22, 1955.

(3) Postdoctorate research fellow at Wayne University.

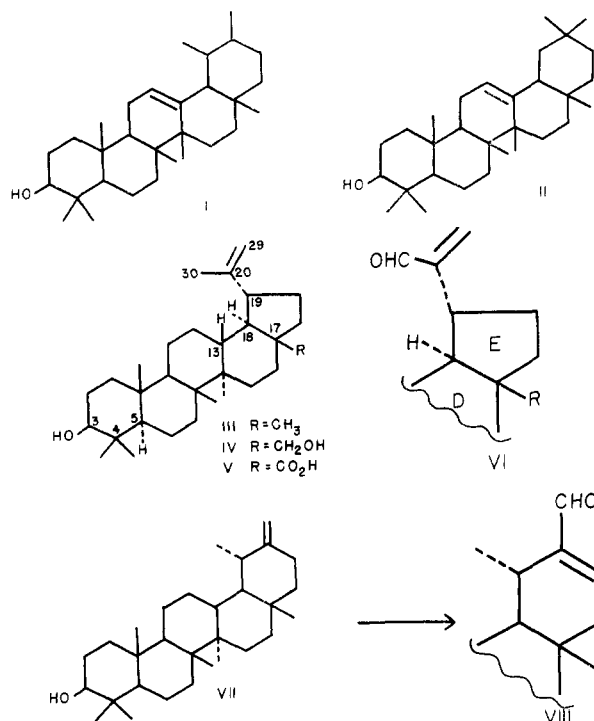
(4) Paper I, C. Djerassi, L. E. Geller and A. J. Lemin, *THIS JOURNAL*, **75**, 2254 (1953).

(5) Paper XI, C. Djerassi, L. H. Liu, E. Farkas, A. E. Lippman, A. J. Lemin, L. E. Geller, R. N. McDonald and B. J. Taylor, *ibid.*, **77**, 1200 (1955).

(6) To be published.

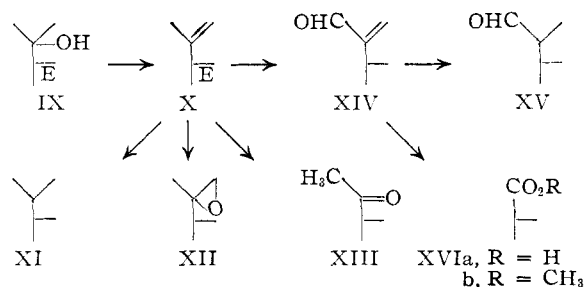
(7) Paper VI, C. Djerassi, E. Farkas, A. J. Lemin, J. C. Collins and F. Walls, *THIS JOURNAL*, **76**, 2969 (1954). While a definite decision cannot as yet be made whether the intact lactone ring is indeed present in the plant glycosides or whether it is produced during the acid hydrolysis, it was shown in that paper that the lactone ring of dumortierigenin, thurberogenin and stellatogenin could not have been formed in the manner recorded for the oleanolic acid  $\rightarrow$  iso-oleanolic acid lactone

(III), betulin (IV) and betulinic acid (V). Additional support for a terminal methylene group was adduced by the ozonolysis of thurberogenin acetate<sup>11</sup> which produced formaldehyde and a nor-ketone XIII, further characterized as the oxime. It should be noted that all of these reactions also would be consistent with those reported<sup>12</sup> for the terminal ring of taraxasterol (VII) except that the  $\alpha,\beta$ -unsaturated aldehyde VIII, produced by selenium dioxide oxidation of VII, exhibits  $\lambda_{\text{max}}^{\text{EtOH}}$  234  $\mu$  by virtue of its higher degree of substitution as compared to the unsaturated aldehyde VI<sup>13</sup> derived from lupeol (III).



A taraxasterol skeleton (VII) for thurberogenin could be excluded unequivocally by ozonization of its derived unsaturated aldehyde XIV which resulted, in complete analogy<sup>14</sup> to betulin (IV), in the loss of two carbon atoms and the formation of a bisnor-acid XVIa which for adequate characterization was transformed into the methyl ester (XVIb). It should be noted that the hydroxyl group and the five-membered lactone ring of thurberogenin remained unaffected during these transformations, which establish rigorously the presence of an isopropenyl group. It has been demonstrated earlier<sup>5</sup> that stellatogenin (IX) differs from thurberogenin (X) only in the presence of an additional tertiary

hydroxyl group and that stellatogenin 3-monoacetate could be dehydrated to thurberogenin acetate.<sup>15</sup> The following partial structures (IX  $\rightarrow$  XVI) depict the reactions discussed so far.



**The Structure of Ring A.**—Oxidation of thurberogenin with the chromium trioxide-pyridine reagent<sup>16</sup> yielded thurberogenone (XVIIIa) which exhibited two infrared carbonyl bands ( $\lambda_{\text{max}}^{\text{CHCl}_3}$  5.66 and 5.90  $\mu$ ), the latter corresponding to a six-membered (or larger) ring ketone. A similar product (XVIIIb) was obtained when dihydrothurberogenin was oxidized (or ozonized<sup>11</sup>) and conversion of the latter (XVIIIb) to a dibromo derivative XIXb indicated the presence of at least two hydrogen atoms adjacent to the newly formed carbonyl group. By analogy to most of the known pentacyclic triterpenes,<sup>10</sup> it was assumed that this is the typical  $3\beta$ -hydroxyl function in ring A flanked by a 4,4-dimethyl moiety and the correctness of this assumption was demonstrated as follows. Reduction of thurberogenone (XVIIIa) with sodium borohydride regenerated thurberogenin (XVIIa) and since the carbonyl group of XVIII is quite reactive (facile oxime formation), the hydroxyl group is most likely equatorial and hence  $\beta$ -oriented<sup>17</sup> (provided rings A and B are *trans*-fused as has so far been the case with every known pentacyclic triterpene<sup>10</sup>).

One of the typical reactions<sup>10</sup> of ring A of the pentacyclic triterpenes with the  $3\beta$ -hydroxyl function is the ring contraction accompanying dehydration with phosphorus pentachloride; ozonolysis of the rearrangement product XX then yields acetone and the corresponding five-membered A-nor-ketone XXI. When those conditions were applied to dihydrothurberogenin (XVIIb) ring contraction was observed and the crystalline dehydration product (XXb) upon ozonolysis furnished acetone and A-nor-dihydrothurberogenone (XXIb) with infrared carbonyl bands at 5.64  $\mu$  (lactone) and 5.78  $\mu$  (five-membered ring ketone). The presence in thurberogenin and stellatogenin of a ring A structure (XVII) typical of that found in the other pentacyclic triterpenes<sup>10</sup> appears to be proved beyond reasonable doubt.

**The Five-membered Lactone Ring.**—The presence of a five-membered lactone ring in thurberogenin and stellatogenin has so far been indicated

(11) When the ozonolysis was carried out with free thurberogenin, the  $3\beta$ -hydroxyl group was oxidized at the same time. Similarly, in a model experiment in which 18-iso-oleanolic acid lactone (XXII) was subjected to ozonolysis conditions, 18-iso-oleanonic acid lactone was obtained in good yield.

(12) T. R. Ames, J. L. Beton, A. Bowers, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 1905 (1954).

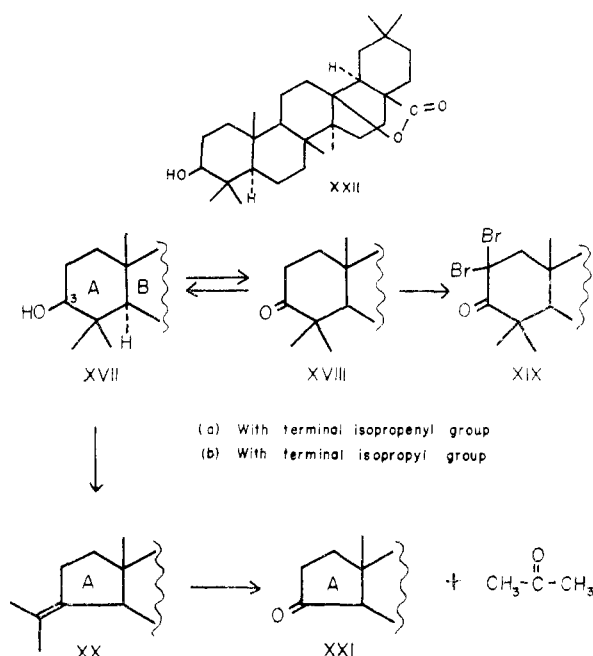
(13) The ultraviolet absorption maximum of the unsaturated aldehyde VI in the lupeol or betulin series has been reported at 225  $\mu$  (L. Ruzicka and G. Rosenkranz, *Helv. Chim. Acta*, **23**, 1312 (1940); E. R. H. Jones and R. J. Meakins, *J. Chem. Soc.*, 1337 (1940)).

(14) J. M. Guider, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 3024 (1953).

(15) That no skeletal rearrangement had occurred during this dehydration was proved (ref. 5) by the fact that lithium aluminum hydride reduction of thurberogenin oxide (XII) yielded a tetrol identical with the one obtained by similar reduction of stellatogenin (IX).

(16) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *This Journal*, **75**, 422 (1953).

(17) D. H. R. Barton (*J. Chem. Soc.*, 1027, footnote 23 (1953)) pointed out that sodium borohydride reduction of reactive cyclohexanones generally leads to the equatorial alcohol.

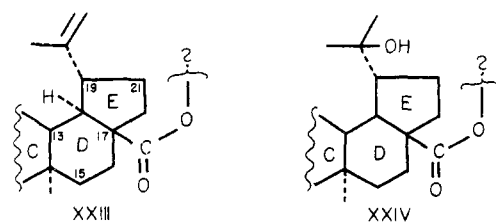


only by the infrared band at *ca.* 5.65  $\mu$ . Thurberogenin is unchanged by chloroform-hydrogen chloride (conditions<sup>7</sup> under which oleanolic acid lactone is converted chiefly to the free acid) and while it has been possible to open the ring by warming with alkali, immediate relactonization was encountered upon acidification or when methylation was attempted. A similar behavior is exhibited by 18-iso-oleanolic acid lactone (XXII).

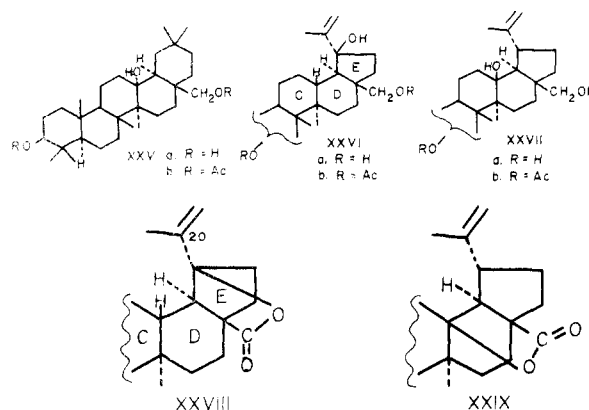
In view of the fact that thurberogenin is accompanied in the cactus<sup>4</sup> by oleanolic acid and stellatogenin<sup>5</sup> by oleanolic acid and betulinic acid (V), we feel justified in assuming tentatively that the carbonyl group of the lactone ring of thurberogenin and stellatogenin originates at C-17, this assumption being based on the premise that these two substances possess a normal triterpene skeleton. The earlier demonstration of the presence of an isopropenyl group in thurberogenin and the co-existence of stellatogenin and betulinic acid (V) in the same cactus would permit the further assumption that these two cactus triterpenes are based on a betulinic acid skeleton (partial structures XXIII and XXIV). The main difference in the behavior of these lactones and the known<sup>7</sup> synthetic lactones of the oleanolic acid series (*e.g.*, XXII) is the position of the infrared lactone band,<sup>18</sup> which in the case of thurberogenin and stellatogenin is at an appreciably lower wave length. Apparently, this is a reflection of the greater degree of strain in a lactone ring formed across a *trans*-hydrindane system (*cf.* XXVIII).

On the basis of partial structure XXIII for thurberogenin, only four alternatives (positions 13, 15, 19, 21) remain for consideration as termination points of the five-membered lactone ring. With the model 18-iso-oleanolic acid lactone (XXII), lithium aluminum hydride reduction readily formed a triol (XXVa) which was characterized further as the

(18) *Cf.* Table I in ref. 7 and D. H. R. Barton and P. deMayo, *J. Chem. Soc.*, 3111 (1953).



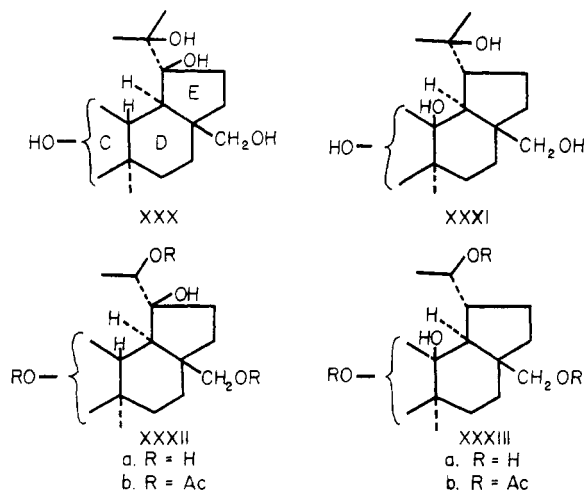
3,28-diacetate XXVb. Similar reduction of thurberogenin afforded a triol (XXVIa or XXVIIa) which also formed a diacetate (XXVIb or XXVIIb); the latter proved to be stable to chromium trioxide thus proving that the hydroxyl group involved in the lactone ring must have been tertiary rather than an axially oriented, secondary hydroxyl function (positions 15 or 21). The same series of reactions also was carried out in the dihydro series with identical results. Keeping in mind the assumptions made earlier on biogenetic grounds, the partial structure of thurberogenin can be defined more precisely as XXVIII or XXIX, stellatogenin being the corresponding derivative with a tertiary hydroxyl group at C-20.



**The Structures of Thurberogenin and Stellatogenin.**—In order to differentiate between the two alternatives XXVIII and XXIX, several experiments were carried out with the lithium aluminum hydride reduction products. The tertiary hydroxyl group in the model triol diacetate XXVb as well as in the corresponding thurberogenin derivative XXVIb or XXVIIb was found to be surprisingly resistant to dehydration, and more vigorous conditions, as outlined in the experimental section, led to unidentifiable products, possibly due to skeletal rearrangement. Attention was turned next to the tetrol (partial structures XXX or XXXI) obtained<sup>5</sup> by lithium aluminum hydride reduction of either stellatogenin or thurberogenin oxide (XII) since only one (XXX) of the two alternatives possesses a vicinal glycol system. The substance was not attacked by lead tetraacetate over a period of 48 hours.

Since the stability of the tetrol may have been due to its di-tertiary nature (XXX), the 30-nor-ketone XIII derived from thurberogenin acetate was reduced with lithium aluminum hydride to yield the corresponding 30-nor-tetrol (partial structures XXXIIa or XXXIIIa) and which readily formed a triacetate (XXXIIb or XXXIIIb). This tetrol also

did not consume any lead tetraacetate, nor did it yield any ketonic material upon oxidation with sodium bismuthate<sup>19</sup> even when heated. The tentative conclusion was reached, therefore, that these results indicated the absence of a vicinal glycol system and that partial structures XXVII, XXIX, XXXI and XXXIII were the correct ones.

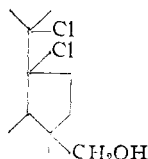


In view of the spectacular results achieved in the treatment of lupeol derivatives with various acidic reagents<sup>12</sup> which resulted in ring enlargement and the correlation of a considerable number of triterpenes of the lupeol (III) and taraxasterol (VII) groups, numerous experiments along similar lines were carried out with thurberogenin. The complex mixtures which resulted did not lead to any definite conclusions and will not be considered further at this time. However, certain experiments with the triol (XXVIIa or XXVIIa) derived from thurberogenin led us to question the conclusion reached above on the basis of the negative glycol cleavage experiments, namely, that the lactone ring terminated at C-13 as depicted in XXIX.

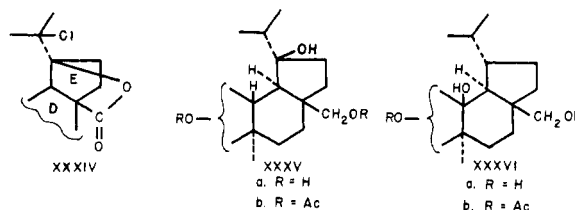
Treatment of thurberogenin or stellatogenin with hydrogen chloride in ethanol furnished a chlorine-containing product which could not be obtained pure but in which the chlorine atom was almost certainly substituted at C-20 (e.g. XXXIV) since catalytic dechlorination produced dihydrothurberogenin (XI). When the same reaction conditions were applied to the triol (XXVIIa or XXVIIa) a dichloro-diol ( $C_{30}H_{50}Cl_2O_2$ ) of unknown constitution was isolated, the net effect having been addition of hydrogen chloride to the double bond (as in the case of thurberogenin itself) and replacement of one of the hydroxyl groups (presumably the tertiary one as in the conversion of stellatogenin to XXXIV).<sup>20</sup> However, when the dihydro-triol (XXXVa or XXXVIa) was subjected to the same conditions, it was recovered essentially unchanged.

(19) C. J. W. Brooks and J. K. Norymberski, *Chemistry & Industry*, 804 (1952); *Biochem. J.*, **55**, 371 (1953).

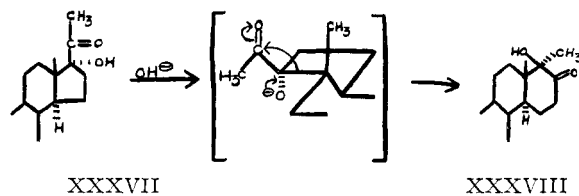
(20) We do not wish to imply, however, that this product had necessarily the structure



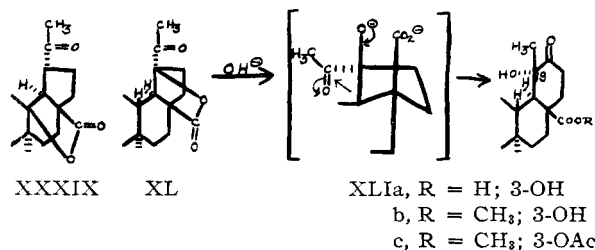
Since the only difference in the two reactions was the presence or absence of the terminal double bond, the latter should have no effect (unless a skeletal rearrangement is involved) on the replacement of the tertiary hydroxyl group by chloride if structures XXVIIa and XXXVIa were correct, but it would indeed have a marked effect, by virtue of allylic activation, if the alternate structures XXVIa and XXXVa were the correct ones and this actually proved to be the case.



An apparently decisive decision was made in the following manner. 17-Hydroxy-20-ketosteroids (XXXVII) undergo base-catalyzed ring enlargement to XXXVIII ("D-homo rearrangement") and the stereochemical requirements of this rearrangement recently have been considered in detail.<sup>21</sup>

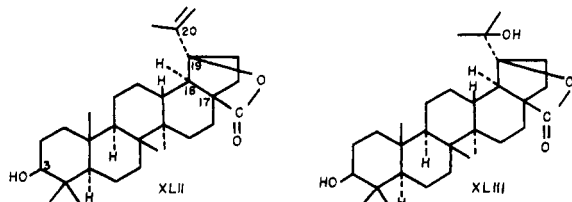


The 30-nor-ketone, obtainable by ozonization of thurberogenin acetate, should, in the light of the above deductions, possess structure XXXIX or XL. As has been mentioned earlier, the lactone ring of thurberogenin (or stellatogenin) can be opened with base but closes immediately upon acidification. If partial structure XXIX for thurberogenin is the correct one, then the nor-ketone must be XXXIX and it should not be affected by base. On the other hand, the isomeric formulation XXVIII would give rise to a nor-ketone XL which possesses all of the structural requirements for ring enlargement to an E-homo derivative XLI which now should be incapable of relactonization because the resulting hydroxyl group (at C-19) would be equatorial. In fact, when this experiment was carried out, an acid (XLIa) was produced which was characterized as the methyl ester XLIIb and methyl ester acetate XLIIc; the analytical and infrared spectral data were fully consistent with these formulations.



(21) R. B. Turner, *THIS JOURNAL*, **75**, 3484 (1953).

Returning to the basic assumption—namely, that both triterpenes possess a normal triterpene skeleton and that the lactone carbonyl is attached to position 17—one can now tentatively assign structure XLII to thurberogenin and XLIII to stellatogenin. Assuming the same stereochemistry as in lupeol (III), there is considerable hindrance around the 19–20 bond<sup>22</sup> and this would appear to be at the present time the only explanation for the resistance of glycols such as XXX and XXXII toward lead tetraacetate and sodium bismuthate. It should be emphasized that a conclusive structure assignment can be made only when thurberogenin has been correlated with a triterpene of known constitution. Such experiments are contemplated as soon as additional supplies of cactus become available.



### Experimental<sup>23</sup>

**Dihydrothurberogenin (XI).**—A solution of 167 mg. of thurberogenin acetate (m.p. 250°,  $[\alpha]_D^{25} +22^\circ$ )<sup>24</sup> in glacial acetic acid was hydrogenated at room temperature and atmospheric pressure with 10 mg. of platinum oxide overnight. Filtration of the catalyst, concentration, dilution with water, filtration and recrystallization from methanol-chloroform yielded 112 mg. of dihydrothurberogenin acetate as transparent platelets, m.p. 261–263°,  $[\alpha]_D^{25} +55^\circ$ ,  $\lambda_{\max}^{\text{chlf}} 5.66$  and  $5.81 \mu$ .

*Anal.* Calcd. for  $C_{32}H_{48}O_4$ : C, 77.06; H, 10.11. Found: C, 77.11; H, 10.34.

Dihydrothurberogenin was produced by refluxing 179 mg. of the acetate for 2 hours with 7% methanolic potassium hydroxide, filtering the potassium salt and acidifying it in ethanol suspension. The lactone was extracted with ether and processed in the usual manner; crystallization from methanol-chloroform gave 110 mg. of needles, m.p. 325–328°,  $[\alpha]_D^{25} +35^\circ$ ,  $\lambda_{\max}^{\text{chlf}} 5.66 \mu$ .

*Anal.* Calcd. for  $C_{30}H_{46}O_3$ : C, 78.89; H, 10.59. Found: C, 79.09; H, 10.68.

The substance also could be obtained by hydrogenation of free thurberogenin, but that route was less desirable because of the relative insolubility of the starting material. Acetylation of dihydrothurberogenin thus obtained yielded the same acetate as described above.

**Selenium Dioxide Oxidation of Thurberogenin Acetate.**—A solution of 4.88 g. of thurberogenin acetate and 4.5 g. of sublimed selenium dioxide in 130 cc. of glacial acetic acid was refluxed for 2 hours. The solvent was removed *in vacuo*, water was added and the product was extracted with ether. After washing with 2% sodium hydroxide solution and water, drying and evaporation, the reddish solid was chromatographed on alumina (activity II). Elution with benzene-ether (8:2) furnished 2.2 g. of colorless, crystalline unsaturated aldehyde (XIV) which was recrystallized from methanol-chloroform; m.p. 292–295°,  $[\alpha]_D^{25} +120^\circ$ ,  $\lambda_{\max}^{\text{chlf}} 5.63$  (lactone), 5.80 (acetate) and  $5.93 \mu$  (unsaturated aldehyde),  $\lambda_{\max}^{\text{EtOH}} 222 m\mu$ ,  $\log \epsilon 4.01$ .

*Anal.* Calcd. for  $C_{32}H_{46}O_5$ : C, 75.26; H, 9.08. Found: C, 74.62; H, 9.49.

(22) Cf. p. 1912 of ref. 12.

(23) Melting points were determined on the Kofler block. Unless noted otherwise, rotations and infrared spectra (Baird double beam recording infrared spectrometer using 0.1 mm. cells) were measured in chloroform solution. The microanalyses were carried out by Geller Laboratories, Hackensack, New Jersey.

(24) Cf. footnote 21 in ref. 5.

A sample of the unsaturated aldehyde (0.65 g.) was hydrogenated with 0.1 g. of 5% palladized charcoal catalyst in 90 cc. of tetrahydrofuran. Hydrogen uptake was complete within 5 minutes, whereupon the catalyst was filtered and the saturated aldehyde XV was isolated in the usual manner; yield 0.44 g., m.p. 238–241° (from methanol-chloroform),  $[\alpha]_D^{25} +46^\circ$ ,  $\lambda_{\max}^{\text{chlf}} 5.65$  and  $5.80 \mu$  (more intense than in XIV due to saturated aldehyde and acetate), no high selective ultraviolet absorption.

*Anal.* Calcd. for  $C_{32}H_{48}O_5$ : C, 74.96; H, 9.44. Found: C, 74.92; H, 9.61.

**Ozonolysis of Acetoxythurberogenin.**—Thurberogenin acetate (206 mg.) was ozonized (ca. 1.5% ozone) at 20° in glacial acetic acid for 0.5 hour and the ozonide was decomposed by steam distillation into dimedon solution. The latter solution, after standing in the ice-box for 2 days, gave a 38% yield of the dimedon derivative of formaldehyde (m.p. 186–188°). The residue from the steam distillation was extracted with ether-chloroform and washed with sodium carbonate and aqueous sodium chloride solution. After removal of the solvent, the solid was recrystallized from methanol-chloroform to furnish 103 mg. of the acetoxy 30-nor-ketone XL as plates, m.p. 314–318° with change in crystalline form at 270–280° and partial sublimation at ca. 300°,  $[\alpha]_D^{25} +30^\circ$ ,  $\lambda_{\max}^{\text{chlf}} 5.66$ , 5.80 and  $5.88 \mu$ .

*Anal.* Calcd. for  $C_{31}H_{46}O_5$ : C, 74.66; H, 9.30. Found: C, 74.17; H, 9.03.

The oxime was prepared in the standard manner (ethanol-pyridine, 0.5 hour, steam-bath) and was recrystallized from methanol-chloroform; m.p. 264–267°.

*Anal.* Calcd. for  $C_{31}H_{47}NO_5$ : N, 2.73. Found: N, 2.86.

**Ozonolysis of Thurberogenin.**—Ozonolysis of thurberogenin (364 mg.) in the manner described above for the acetate produced 107 mg. of the 30-nor-3,29-diketone, m.p. 254–257°,  $\lambda_{\max}^{\text{chlf}} 5.66$  and  $5.89 \mu$ . Attempted acetylation regenerated the starting material.

*Anal.* Calcd. for  $C_{29}H_{42}O_4$ : C, 76.61; H, 9.31. Found: C, 77.14; H, 9.40.

**18-Isoöleanonic Acid Lactone.**—Ozonolysis of 200 mg. of 18-isoöleanonic acid lactone (XXII)<sup>7</sup> in the same manner gave 123 mg. of the 3-keto lactone, m.p. 349–353° (from methanol-chloroform),  $[\alpha]_D^{25} +41^\circ$ ,  $\lambda_{\max}^{\text{chlf}} 5.70$  and  $5.88 \mu$ . The same product (150 mg.) was obtained when 250 mg. of XXII was oxidized with chromium trioxide in pyridine solution.

*Anal.* Calcd. for  $C_{30}H_{48}O_3$ : C, 79.24; H, 10.20. Found: C, 79.42; H, 10.45.

**Ozonolysis of Unsaturated Aldehyde Derived from Thurberogenin.**—A solution of 1.55 g. of the above described unsaturated aldehyde XIV from the selenium dioxide oxidation of thurberogenin acetate in 80 cc. of glacial acetic acid and 3 cc. of chloroform was ozonized at room temperature for 4 hours and then steam distilled. The non-volatile residue was extracted with ether which in turn was washed with 5% potassium hydroxide solution. A small amount of gel was filtered and added to the aqueous, alkaline washes which were acidified with dilute acid. The precipitated bisnor-acid XVIa was taken up in ether and methylated with diazomethane prepared from 2 g. of N-nitrosomethylurea. Chromatography of the ester on 20 g. of neutral alumina (activity II), elution with hexane-benzene and recrystallization from methanol-chloroform produced 0.38 g. of the acetoxy bisnor-methyl ester XVIb as colorless needles, m.p. 220–223°,  $[\alpha]_D^{25} +30^\circ$ ,  $\lambda_{\max}^{\text{chlf}} 5.66$ , 5.80 and shoulder at  $5.82 \mu$ .

*Anal.* Calcd. for  $C_{31}H_{46}O_6$ : C, 72.34; H, 9.01. Found: C, 72.09; H, 9.10.

From the original ether solution there was obtained 0.61 g. of neutral material which was not investigated further.

**Thurberogenone (XVIIIa).**—Thurberogenin (0.245 g.) in 4 cc. of pyridine was treated at 0° with 0.3 g. of chromium trioxide in 8 cc. of the same solvent. After 10 hours at room temperature the reaction mixture was processed in the customary manner. Purification was accomplished by chromatography and recrystallization from chloroform-methanol; yield 0.12 g. of colorless rods, m.p. 234–237°,  $[\alpha]_D^{25} +35^\circ$ ,  $\lambda_{\max}^{\text{chlf}} 5.66$  and  $5.90 \mu$ .

*Anal.* Calcd. for  $C_{30}H_{44}O_2$ : C, 79.60; H, 9.80. Found: C, 79.52; H, 9.71.

The oxime was prepared in the usual way and recrystallized from methanol-chloroform; m.p. 253–256°.

*Anal.* Calcd. for  $C_{30}H_{45}NO_2$ : N, 3.00. Found: N, 2.72.

**Dihydrothurberogenone (XVIIIb).**—Following the above procedure, 91 mg. of dihydrothurberogenin was oxidized with the chromium trioxide-pyridine complex; yield 61 mg. of long needles, m.p. 255–258°,  $[\alpha]_D^{25} +63^\circ$ ,  $\lambda_{max}^{chl}$  5.66 and 5.90  $\mu$ . The same ketone was obtained in somewhat lower yield by ozonolysis of dihydrothurberogenin in acetic acid followed by steam distillation.

*Anal.* Calcd. for  $C_{30}H_{42}O_3$ : C, 79.24; H, 10.20. Found: C, 79.09; H, 10.22.

A sample (96 mg.) of the ketone in 40 cc. of glacial acetic acid was brominated at 30° with 0.55 cc. of a bromine-acetic acid solution (1.256 g. of bromine in 10 cc. of acetic acid). After 2 hours, a crystalline solid separated whereupon 10 drops of 4 *N* hydrogen bromide in acetic acid was added and stirring continued at 30–35° for 3 hours. The precipitated solid was filtered and combined with a second crop obtained on addition of water. Recrystallization of the solid (100 mg.) from methanol-chloroform led to **di-bromo-dihydrothurberogenone (XIXb)**, m.p. 262–264°,  $[\alpha]_D^{25} +27^\circ$ ,  $\lambda_{max}^{chl}$  5.65 and 5.85  $\mu$ .

*Anal.* Calcd. for  $C_{30}H_{44}Br_2O_3$ : C, 58.80; H, 7.24; Br, 26.11. Found: C, 58.79; H, 7.40; Br, 26.05.

**Sodium Borohydride Reduction of Thurberogenone.**—Thurberogenone (104 mg.) was left at room temperature for 1 hour with 22 mg. of sodium borohydride in 20 cc. of absolute ethanol. After addition of a few drops of acetic acid, water was added, the product was extracted with ether and the crude solid was acetylated directly with acetic anhydride-pyridine. Chromatography on alumina and recrystallization from methanol-chloroform led to 62 mg. of thurberogenin acetate; identity was established by comparison of physical constants and infrared spectra.

**Ring Contraction of Dihydrothurberogenin.**—Dry nitrogen was bubbled with stirring through a mixture of 500 mg. of dihydrothurberogenin, 650 mg. of phosphorus pentachloride and 100 cc. of purified hexane for 6 hours at room temperature. At the end of that period, saturated sodium chloride was added and 85 mg. of recovered dihydrothurberogenin was removed by filtration. The organic layer was washed with sodium carbonate solution, water, dried and evaporated. The colorless solid was chromatographed on 25 g. of alumina (activity I–II) and eluted with hexane containing a small amount of benzene. The first six crystalline fractions (total weight 160 mg.) were rechromatographed to remove a small but persistent Beilstein-positive impurity and then recrystallized; m.p. 213–216°,  $[\alpha]_D^{25} +30^\circ$ , yellow color with tetranitromethane.

*Anal.* Calcd. for  $C_{30}H_{46}O_2$ : C, 82.12; H, 10.57. Found: C, 82.62; H, 10.24.

A sample (0.20 g.) of the olefin XXb (corresponding in purity to the above, once-chromatographed 160 mg.) was ozonized in acetic acid solution at 20° as described above for thurberogenin acetate. The reaction mixture was steam distilled into an alcoholic solution of dimedon and after standing in the ice-box overnight (no precipitate), it was steam distilled in turn into an alcoholic solution of 2,4-dinitrophenylhydrazine. The solution was extracted with benzene, dried and chromatographed on alumina. Acetone 2,4-dinitrophenylhydrazone (67 mg.) was eluted with benzene and after recrystallization yielded 30 mg. of the pure derivative, m.p. 123–125°, undepressed upon admixture with authentic material.

The residue from the original ozonolysis steam distillation was extracted with ether and the ether-soluble material was chromatographed. **A-Nor-dihydrothurberogenone (XXIb)** was recrystallized from methanol-chloroform whereupon it showed m.p. 223–225°,  $[\alpha]_D +150^\circ$ ,  $\lambda_{max}^{chl}$  5.64 and 5.78  $\mu$ .

*Anal.* Calcd. for  $C_{27}H_{40}O_3$ : C, 78.59; H, 9.77. Found: C, 78.53; H, 9.97.

**Some Reactions of the Lactone Ring of Thurberogenin, Stellatogenin and 18-Isoöleanolic Acid Lactone.**—Dry hydrogen chloride gas was bubbled for 2 hours through a solution of 0.10 g. of thurberogenin in 30 cc. of chloroform.

No acidic material was encountered on extraction and the starting material was recovered unchanged from the chloroform solution as demonstrated by mixture melting point and infrared comparison.

When thurberogenin (57 mg.) was refluxed for 3 hours with 15 cc. of 15% methanolic potassium hydroxide, no neutral material was extracted with chloroform. Acidification of the alkaline solution and recrystallization from methanol yielded approximately 80% of thurberogenin. A similar behavior was observed when stellatogenin was refluxed for 18 hours with 5% methanolic potassium hydroxide solution.

In an attempt to methylate thurberogenin, it was left in moist ether with diazomethane for 3 days; infrared examination of the product showed no ester band and the spectrum was identical with that of the starting material. In a second experiment, thurberogenin (250 mg.) was converted into the potassium salt by refluxing for 2 hours in 30 cc. of methanol-dioxane with 600 mg. of potassium hydroxide. After letting stand overnight, 1.5 g. of dimethyl sulfate was added with stirring and methanolic potassium hydroxide added dropwise over a period of several hours to maintain the pH above 7. Dilution with water and extraction with chloroform yielded over 80% of recovered thurberogenin.

**18-Isoöleanolic acid lactone (XXII)** was converted into the potassium salt as shown above for thurberogenin. The salt was dissolved in 40 cc. of methanol and 1.1 equivalents of silver nitrate in the minimum amount of water was added in order to convert the substance into the silver salt. After stirring for 10 minutes, the calculated amount of methyl iodide was added and after an additional 30 minutes, the mixture was filtered and the filtrate was concentrated. Dilution with water and extraction with chloroform gave a nearly quantitative recovery of the starting lactone; no ester band was observed in the infrared spectrum.

**18 $\alpha$ -Oleanane-3 $\beta$ ,13 $\beta$ ,28-triol (XXVa).**—18-Isoöleanolic acid lactone (XXII) (0.24 g.) was reduced with 2.2 g. of lithium aluminum hydride in 190 cc. of tetrahydrofuran in the manner described earlier<sup>7</sup> for oleanolic acid lactone, the crucial factor being the method of decomposition of the reaction mixture. Recrystallization from methanol-chloroform furnished 0.2 g. of colorless crystals of the triol, m.p. 284–286°,  $[\alpha]_D +4^\circ$ .

*Anal.* Calcd. for  $C_{30}H_{52}O_3$ : C, 78.20; H, 11.38. Found: C, 78.03; H, 11.52.

Acetylation with acetic anhydride-pyridine yielded long, colorless needles of the **3,28-diacetate XXVb**, m.p. 242–244°,  $[\alpha]_D^{25} +28^\circ$ ,  $\lambda_{max}^{chl}$  5.79  $\mu$ .

*Anal.* Calcd. for  $C_{34}H_{56}O_5$ : C, 74.95; H, 10.36; acetyl, 15.72. Found: C, 74.72; H, 10.43; acetyl, 15.04.

Approximately 75–80% of the pure triol diacetate XXVb was recovered unchanged when attempts were made to effect dehydration by either treating it at room temperature for 30 minutes with thionyl chloride in pyridine or by refluxing it for 2 hours with phosphorus oxychloride in pyridine. Boron trifluoride in boiling benzene did affect the substance but no pure product could be isolated from that reaction mixture.

**Lithium Aluminum Hydride Reduction of Thurberogenin.**—Following the above conditions, 0.25 g. of thurberogenin led to 0.11 g. of the triol XXVIa, m.p. 250–253°,  $[\alpha]_D^{25} +36^\circ$ .

*Anal.* Calcd. for  $C_{30}H_{50}O_3$ : C, 78.55; H, 10.99. Found: C, 78.13; H, 10.77.

An attempt to remove the tertiary hydroxyl function in the triol proved abortive by the method<sup>28</sup> employed successfully with nerolidol and other allylic alcohols. A solution of 300 mg. of the triol in 15 cc. of tetrahydrofuran was added to 50 cc. of liquid ammonia followed by 1.5 cc. of ethanol and 1.5 g. of potassium metal. After stirring for 9.5 hours at –60°, ammonium chloride was added, the ammonia allowed to evaporate and more tetrahydrofuran was added. The latter was washed, dried, evaporated and the residue was acetylated. Chromatography led to 0.27 g. of diacetate, m.p. 197–200°, which was shown to be identical with the diacetate prepared by direct acetylation of the triol.

The diacetate XXVIb was recrystallized from methanol as long needles, m.p. 198–200°,  $[\alpha]_D^{25} +42^\circ$ .

(25) A. J. Birch, K. M. C. Mostyn and A. R. Penfold, *Australian J. Chem.*, **60**, 391 (1953).

*Anal.* Calcd. for  $C_{34}H_{54}O_5$ : C, 75.23; H, 10.03; acetyl, 15.90. Found: C, 75.40; H, 9.73; acetyl, 15.85.

The above diacetate was recovered unchanged when treated for one hour with chromium trioxide under conditions<sup>26</sup> adequate for the oxidation of 18 $\alpha$ -oleanane-3 $\beta$ ,19 $\alpha$ -diol.

When the triol diacetate XXVIb was refluxed with phosphorus oxychloride in pyridine solution for 10 hours, no dehydration was observed and the starting material was recovered unchanged. Refluxing in benzene solution for 1 hour with boron trifluoride caused reaction, but the glassy product ( $\lambda_{\text{max}}^{\text{EtOH}}$  213 m $\mu$ ,  $\log \epsilon$  4.3) could not be crystallized or purified even after chromatography.

Selenium dioxide oxidation of the diacetate XXVIb (1.5 g.) in the manner described above for thurberogenin acetate yielded 0.92 g. of the corresponding unsaturated 30-aldehyde, m.p. 216–219°,  $[\alpha]_D^{25}$  +28°,  $\lambda_{\text{max}}^{\text{CHCl}_3}$  5.80, 5.92 and 8.0  $\mu$ ,  $\lambda_{\text{max}}^{\text{EtOH}}$  222 m $\mu$ ,  $\log \epsilon$  4.01.

*Anal.* Calcd. for  $C_{34}H_{52}O_6$ : C, 73.34; H, 9.41. Found: C, 73.38; H, 9.14.

**Lithium Aluminum Hydride Reduction of Dihydrothurberogenin.**—Similar reduction of 0.525 g. of dihydrothurberogenin produced 0.39 g. of the corresponding triol XXXVa, m.p. 300–302°,  $[\alpha]_D$  +35°.

*Anal.* Calcd. for  $C_{30}H_{50}O_3$ : C, 78.20; H, 11.38. Found: C, 78.22; H, 11.34.

The diacetate (XXXVb) exhibited m.p. 208–211°,  $[\alpha]_D^{25}$  +45°.

*Anal.* Calcd. for  $C_{34}H_{50}O_5$ : C, 74.95; H, 10.36. Found: C, 74.77; H, 10.39.

**Lithium Aluminum Hydride Reduction of 20-Nor-29-ketothurberogenin Acetate (XL).**—Lithium aluminum hydride reduction of 0.80 g. of chromatographically purified 3-acetoxy-30-nor-ketone (XL) was carried out as described for the other compounds of this series and produced after recrystallization from 95% ethanol 0.49 g. of the tetrol XXXIIa, m.p. 312–315°, no infrared carbonyl band.

*Anal.* Calcd. for  $C_{28}H_{46}O_4$ : C, 75.28; H, 10.89. Found: C, 75.48; H, 10.83.

The triacetate XXXIIb crystallized as rods from methanol; m.p. 220–222°,  $[\alpha]_D$  +29°.

*Anal.* Calcd. for  $C_{35}H_{56}O_7$ : C, 71.39; H, 9.59. Found: C, 71.03; H, 9.32.

A suspension of the tetrol XXXIIa (100 mg.) in 20 cc. of 50% acetic acid was stirred for 18 hours with 3 g. of sodium bismuthate, conditions under which the model  $\Delta^5$ -pregnen-3 $\beta$ ,17 $\alpha$ ,20-triol was oxidized completely in 30 minutes. Dilution with water, neutralization with potassium hydroxide solution, filtration and recrystallization from methanol gave 80 mg. of recovered tetrol, further identified by its infrared absorption spectrum in nujol mull. Similar results were obtained when the reaction was carried out in dilute acetic acid–tetrahydrofuran solution. On repeating the reaction in refluxing 50% acetic acid followed by steam distillation, no trace of acetaldehyde could be obtained *via* the dinitrophenylhydrazones; the tetrol could not be recovered in a pure state from the steam distillation residue but no infrared carbonyl absorption was observed in the crude product. A quantitative lead tetraacetate oxidation in glacial acetic acid for 48 hours at room temperature

showed no consumption of the reagent. Similar negative results were encountered with the tetrol XXX obtained earlier<sup>5</sup> from the lithium aluminum hydride reduction of stellatogenin or thurberogenin oxide.

**Reaction of Thurberogenin and Derivatives with Ethanolic Hydrogen Chloride.**—A solution of 250 mg. of thurberogenin in 150 cc. of absolute ethanol was saturated at 0° with dry hydrogen chloride gas and then kept at room temperature for 10 days. The product, obtained by dilution with water and extraction with ether, was chromatographed carefully on alumina (activity II–III). The benzene–ether eluates possessing the same melting point were combined (0.175 g.) and recrystallized from methanol–chloroform to constant melting point without, however, obtaining a sample with a satisfactory analysis.

*Anal.* Calcd. for  $C_{30}H_{48}ClO_3$ : C, 73.30; H, 9.64; Cl, 7.20. Found: C, 75.27; H, 9.94; Cl, 4.77.

Precisely the same compound (130 mg.) was obtained (mixture melting point and infrared spectrum) when 200 mg. of stellatogenin was treated in a similar fashion. The substance is presumably the impure 20-chloro derivative XXXIV since dechlorination with WR-4 Raney nickel catalyst in ethanol at room temperature and atmospheric pressure (24 hours) furnished 127 mg. of pure dihydrothurberogenin starting with 210 mg. of thurberogenin which had been treated with hydrogen chloride. It should be noted that thurberogenin itself is not reduced by Raney nickel under those conditions.

When 300 mg. of the triol XXVIa, obtained by lithium aluminum hydride reduction of thurberogenin, was treated in a like manner with ethanolic hydrogen chloride, careful chromatography followed by recrystallization from chloroform–methanol produced 120 mg. of a dichloro derivative,<sup>20</sup> m.p. 207–211°,  $[\alpha]_D^{27}$  +44°.

*Anal.* Calcd. for  $C_{30}H_{46}Cl_2O_3$ : C, 70.20; H, 9.75; Cl, 13.82. Found: C, 69.61; H, 9.94; Cl, 13.91.

A similar reaction with the corresponding saturated triol XXXVa yielded no chlorine-containing material and over 50% of the pure starting material was recovered.

**Base-catalyzed Ring Enlargement of Acetoxy-30-nor-29-ketothurberogenin (XL).**—A solution of 600 mg. of the acetoxy nor-ketone in 50 cc. of 5% methanolic potassium hydroxide was refluxed for 18 hours. Dilution with water and extraction with ether yielded only a negligible neutral fraction. The acidic material XLIa which precipitated on acidification of the aqueous layer was extracted with ether and methylated directly with excess diazomethane. Chromatography of the crude product on 15 g. of alumina (activity II) and elution with benzene and benzene–ether mixtures followed by crystallization from methanol gave 0.38 g. of the *E*-homo methyl ester XLIIb, m.p. 192–194°,  $[\alpha]_D$  –36°,  $\lambda_{\text{max}}^{\text{CHCl}_3}$  2.78 and 2.90–2.95  $\mu$  (multiple hydroxyl absorption), 5.80 and 5.84  $\mu$ .

*Anal.* Calcd. for  $C_{30}H_{48}O_5$ : C, 73.73; H, 9.90. Found: C, 73.19; H, 9.83.

Acetylation with acetic anhydride–pyridine and recrystallization from methanol led to colorless rods of the 3-monoacetate XLIIc, m.p. 227–232°,  $[\alpha]_D$  –26°,  $\lambda_{\text{max}}^{\text{CHCl}_3}$  5.80–5.83  $\mu$  (broad band).

*Anal.* Calcd. for  $C_{32}H_{50}O_6$ : C, 72.41; H, 9.50. Found: C, 72.54; H, 9.56.

DETROIT, MICHIGAN

(26) T. R. Ames, G. S. Davy, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 2868 (1952).