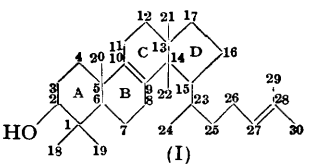
116. *Triterpenoids. Part X.* The Stereochemistry of Lanostadienol (Lanosterol).*

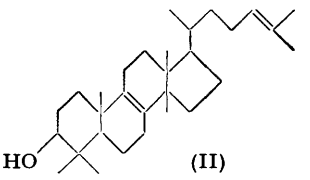
By C. S. Barnes, D. H. R. Barton, J. S. Fawcett, and B. R. Thomas.

On the basis of molecular-rotation and conformational arguments configurations have been assigned to all the asymmetric centres in lanostanol and certain of its derivatives. The conclusions reached are in excellent agreement with those recently adduced by Curtis, Fridrichsons, and Mathieson (*Nature*, 1952, **170**, 321) on the basis of *X*-ray diffraction studies. A preliminary account of our views has already been published (Barnes, Barton, Cole, Fawcett, and Thomas, *Chem. and Ind.*, 1952, 426).

The solution of the constitutional problem for lanostadienol (see preceding paper and references there cited) invites inquiry into the stereochemistry of the molecule. On the basis of conformational (Barton, *Experientia*, 1950, **6**, 316) and generalised molecular-rotation arguments (Klyne, *J.*, 1952, 2916; Stokes and Werner Bergmann, *J. Org. Chem.*, 1951, **16**, 1817; 1952, **17**, 1194) a purely chemical solution to the problem can be adumbrated. Two formulæ, (I) and (II), for lanostadienol are here considered. The first of these is the constitution of lanostadienol on the assumed applicability of the isoprene rule. The second non-isoprenoid formula is the only other solution to the problem which is possible on chemical evidence. That the latter is the correct solution has been argued by Curtis, Fridrichsons, and Mathieson (*loc. cit.*) on the basis of *X*-ray diffraction data.



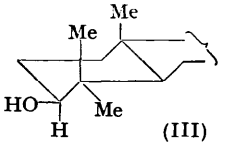
(I)



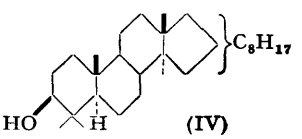
(II)

We commence by accepting the generalised molecular-rotation arguments of Klyne (*loc. cit.*) that rings A and B are *trans*-fused as in the other triterpenoids that have been investigated (see Barton and Holness, *J.*, 1952, 78). Since the angular methyl group at $C_{(5)}$ has the same configuration as the angular methyl group at $C_{(10)}$ in steroids (Klyne, *loc. cit.*) we envisage that it projects above the plane of the paper in the β-configuration.

The hydroxyl group at $C_{(2)}$ in lanostadienol is equatorial (cf. Barton, *loc. cit.*) as shown by its stability towards attempted epimerisation (Wieland, Pasedach, and Ballauf, *Annalen*,



(III)



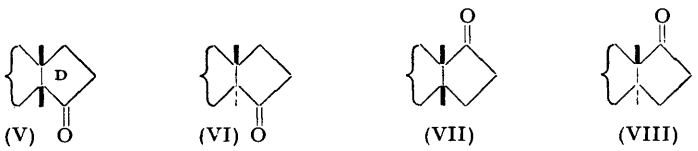
(IV)

1937, **529**, 68) and by its regeneration (in suitable derivatives) on reduction of the appropriate ketones with sodium and alcohol (*inter al.*, Marker, Wittle, and Mixon, *J. Amer.*

* Part IX, preceding paper.

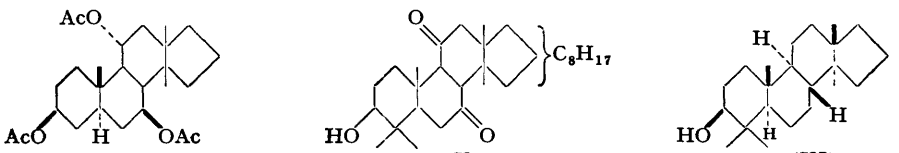
Chem. Soc., 1937, **59**, 1368; Marker and Wittle, *ibid.*, p. 2289). It must therefore have the 2β-configuration as in (III), a conclusion which is confirmed (cf. Barton, *loc. cit.*; Barton and Holness, *loc. cit.*) by the well-established dehydration + rearrangement observed on treatment with phosphorus pentachloride (Dorée, McGhie, and Kurzer, *J.*, 1947, 1467; Ruzicka, Montavon, and Jeger, *Helv. Chim. Acta*, 1948, **31**, 818; Dorée, McGhie, and Kurzer, *Nature*, 1949, **163**, 140; *J.*, 1949, S 167). We have previously (Barton, Fawcett, and Thomas, *J.*, 1951, 3147) advanced arguments that the $C_{(13)}$ methyl group must be on the same side of the molecule as the $C_{(5)}$ methyl group; therefore the appropriate partial stereochemistry in (IV) may be deduced.

The stereochemistry of the $C_{(14)}$ methyl group can be established (Barnes, Barton, Cole, Fawcett, and Thomas, *loc. cit.*) by the generalised molecular rotation method. Four possibilities (V), (VI), (VII), and (VIII) have to be considered for ring D of the 2β : 8β : 11α-triacetoxylanan-15(or 17)-one described in the preceding paper. To differentiate between them the molecular-rotation contribution of the keto-group is required. This was determined by Wolff–Kishner reduction of the ketone, followed by reacetylation, to give



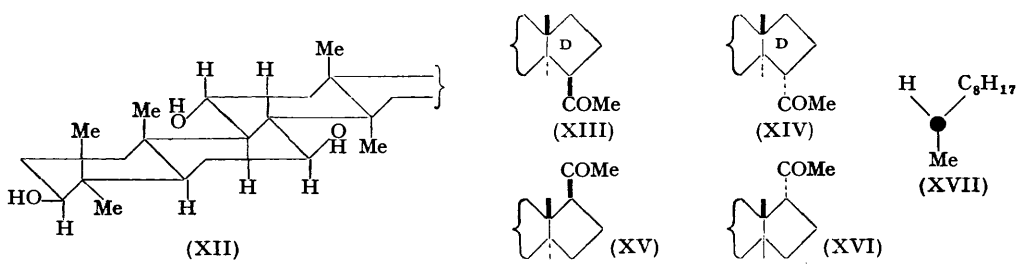
(V) (VI) (VII) (VIII)

2β : 8β : 11α-triacetoxylanane (IX), which was further characterised by conversion into the corresponding triketone, lanane-2 : 8 : 11-trione. The difference in molecular rotation between the triacetoxylanane and the derived ketone was +110°, whilst that between the triketone and the corresponding tetraketone (see preceding paper) was +90°. The approximate molecular rotation contributions to be expected for structures (V) to (VIII) are (Klyne, *loc. cit.*) −500°, +250°, +500°, and +250° respectively. Clearly the experimental data exclude (V) as compared with (VI) and favour (VIII) relative to (VII).



(IX) (X) (XI)

It is now appropriate to discuss the ring fusion of compounds with rings B and C saturated. Such compounds are prepared *via* 2-hydroxylanostane-8 : 11-dione (X). We have shown (see Experimental section) that this diketone is stable to vigorous alkaline treatment and therefore both $C_{(9)}$ and $C_{(10)}$ must be in the more stable configuration. On the basis of conformational arguments (Barton, *loc. cit.*), especially those advanced by W. S. Johnson (*Experientia*, 1951, **7**, 315; cf. Turner, *J. Amer. Chem. Soc.*, 1952, **74**, 2118; W. S. Johnson, *ibid.*, in the press) the configurations at $C_{(9)}$ and $C_{(10)}$ must be *trans* relative to each other



(XII) (XIII) (XIV) (XVII) (XV) (XVI)

and *anti* relative to $C_{(14)}$ and $C_{(5)}$. We thus reach the stereochemical conclusions summarised for lanan-2-ol in (XI). Since sodium and alcohol reductions of ketone groups afford the thermodynamically more stable equatorial configurations (Barton, *loc. cit.*), the

stereochemistry of the lanostane-2 : 8 : 11-triol described in the preceding paper must be 2β : 8β : 11α- [see (XII)] in agreement with the ease of acylation (cf. Heusser, Anliker, and Jeger, *Helv. Chim. Acta*, 1952, **35**, 1537).

There remains for consideration the stereochemistry of the side chain. Of the four possible alternatives, (XIII)—(XVI), (XIII) is equivalent to (XVI), and (XIV) to (XV), on the basis of generalised molecular rotations. As Table 1 clearly shows, the molecular-rotation contribution of the side chain in appropriate methyl ketones, with respect to the corresponding *iso*octyl side chain compounds, corresponds closely to that for a 17β-acetyl group in the steroid series. On this count the lanostadienol side chain must be fused 15α based on (I) or 17β based on (II). This conclusion is also in agreement with the fact that the acetyl group and therefore, because of the method of synthesis, the side chain is fused to the ring system in the thermodynamically more stable configuration (McGhie and Pradhan, personal communication). On the basis of equatorial and polar bonds (with respect to ring C; see Barton, *loc. cit.*) this also means that the configuration must be 15α or 17β.

TABLE 1.

Compound	$[M]_D$ in $CHCl_3$: With *iso*octyl side chain	With side chain replaced by –COMe	Δ	Refs.
2-Hydroxylanostan-11-one	+275°	+410°	+135°	1, 2, 3
11-Ketolanostan-2-yl acetate	+291	+455	+164	1, 2, 3
Cholestanol	+ 89	+290	+201	4, 5
Cholestanyl acetate	+ 60	+277	+217	4, 5
17-*iso*Cholestanol	− 95	−248	−153	5, 6

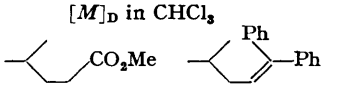
[1] Voser, Montavon, Günthard, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 1893. [2] Voser, Jeger, and Ruzicka, *ibid.*, 1952, **35**, 503. [3] McGhie, Pradhan, Cavalla, and Knight, *Chem. and Ind.*, 1951, 1165; McGhie, Pradhan, and Cavalla, *J.*, 1952, 3176. [4] Barton, *J.*, 1946, 1116. [5] Shoppee, *J.*, 1949, 1671. [6] $[M]_D$ for 17-*iso*cholestanol is assumed to be the same as that for 17-*isoallo*pregnane (Casanova and Reichstein, *Helv. Chim. Acta*, 1949, **32**, 647). The introduction of the 3β-hydroxyl group and the change from the saturated ethyl to the saturated *iso*octyl side chain can have but little effect on optical rotation (cf. Barton and Klyne, *Chem. and Ind.*, 1948, 755; Klyne, *loc. cit.*).

TABLE 2.

	$[M]_D$ in $CHCl_3$: No side chain	*iso*Octyl side chain	Δ	Refs.
2β : 8β : 11α-Triacetoxylanane	+81°	+170°	+89°	1
Androstane	+ 5	+ 91	+86	2
Androstan-3β-ol	+ 3	+ 89	+86	2, 3

[1] Exptl., this paper. [2] Barton and Klyne, *Chem. and Ind.*, 1948, 755. [3] Barton, *J.*, 1946, 1116.

TABLE 3.

Compound	$[M]_D$ in $CHCl_3$: 17-Subst. = 	Δ	Refs.
Lanane derivatives.			
2β-Hydroxy-11-ketolanane	+250°	+397°	+147°	1
8 : 11-Diketolanane	+266	+390	+124	2
Steroid derivatives.			
3β-Hydroxyandrost-5-ene	−198	− 74	+124	3, 4
3β-Hydroxyandrostane	+ 74	+204	+130	3, 5
3β-Acetoxyandrostane	+ 48	+183	+135	3, 5
3α-Acetoxytestane	+186	+345	+159	3, 5
3β-Acetoxy-11-ketotestane	+319 *	+458	+139	6, 7, 8, 9

* The literature values (refs. 6, 7, and 8) are for acetone solution. The calculated molecular rotation has been corrected for chloroform solution by the correction factor of +20° found applicable by Barton and Brooks (ref. 3) for various bile acid 12-keto-derivatives.

[1] Voser, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1952, **35**, 503. [2] Voser, Mijovic, Jeger, and Ruzicka, *ibid.*, 1951, **34**, 1585. [3] Barton and Brooks, *J.*, 1949, 2596. [4] Meystre, Wettstein, and Miescher, *Helv. Chim. Acta*, 1947, **30**, 1022. [5] Meystre and Miescher, *ibid.*, 1946, **29**, 33. [6] Lardon and Reichstein, *ibid.*, 1943, **26**, 586. [7] Hicks and Wallis, *J. Biol. Chem.*, 1946, **162**, 641. [8] Wintersteiner and Moore, *ibid.*, p. 725. [9] Wettstein and Meystre, *Helv. Chim. Acta*, 1947, **30**, 1262.

A further interesting aspect of the molecular-rotation properties of the lanostane side chain is brought out in Table 2. Again there is excellent agreement for a 15α- or 17β-fused side chain.

The remaining centre of asymmetry in the lanostadienol molecule is that at $C_{(23)}$. The configuration at this centre can be derived from molecular-rotation considerations. The change from the weak chromophore of a $C_{(26)}$-carbomethoxy-group to the corresponding strongly chromophoric diphenylethylene derivative (see Table 3) is attended by a change in molecular rotation of about +140 units. This molecular-rotation difference may be regarded as determined in the main part by the configuration at $C_{(23)}$. As shown in Table 3 exactly the same molecular-rotation difference is observed in the steroid series, where the corresponding centre of asymmetry at $C_{(20)}$ is of defined orientation (Wieland and Miescher, *Helv. Chim. Acta*, 1949, **32**, 1922). We conclude that $C_{(23)}$ in lanostane compounds has the configuration indicated in (XVII). The latter depicts the view looking down the bond from the tetracyclic nucleus towards $C_{(23)}$. The conclusion reached is, of course, independent of the attachment of the side chain to $C_{(15)}$ or $C_{(17)}$.

It is instructive to compare the stereochemical conclusions in the present paper with those reached by Curtis, Fridrichsons, and Mathieson (*loc. cit.*) from *X*-ray diffraction studies on lanostenol iodoacetate. It is gratifying to find that, *mutatis mutandis* with regard to $C_{(15)}$ or $C_{(17)}$ for the attachment of the side chain, there is complete agreement at every relevant centre of asymmetry.

Experimental

General techniques were as in the preceding paper.

2β : 8β : 11α-*Triacetoxylanane*.—2β : 8β : 11α-Triacetoxylanan-17-one (see preceding paper) (400 mg.) was heated with hydrazine hydrate (4 ml.) and saturated ethanolic sodium ethoxide (6 ml.) at 190° for 15 hours. After working up in the usual way the product was re-acetylated and then chromatographed over alumina (Peter Spence; Grade H). Elution with 9 : 1 benzene–ether afforded 2β : 8β : 11α-*triacetoxylanane* (240 mg.), m. p. 150—151° (from methanol), $[\alpha]_D$ +18° (*c*, 1·1), $[M]_D$ +91° (Found: C, 68·85; H, 9·15. $C_{28}H_{44}O_6,CH_3{\cdot}OH$ requires C, 68·45; H, 9·5%). There was no carbonyl band in the ultra-violet spectrum.

Lanane-2 : 8 : 11-*trione*.—The foregoing triacetate (100 mg.) was hydrolysed with ethanolic potassium hydroxide, and the derived lanane-2β : 8β : 11α-triol in " AnalaR " acetic acid (10 ml.) was oxidised with chromium trioxide (100 mg.) at room temperature overnight. After working up in the usual way the product was chromatographed over alumina (Peter Spence; Grade H). Elution with 1 : 1 benzene–ether furnished the *trione* (45 mg.), m. p. 236—238° (from methanol), $[\alpha]_D$ +51° (*c*, 0·88), $[M]_D$ +175°, $\lambda_{max.}$ 285 mμ (ε, 140). It was sublimed for analysis (Found: C, 77·25; H, 9·10. $C_{22}H_{32}O_3$ requires C, 76·7; H, 9·35%).

Action of Alkali on 8 : 11-*Diketolanostanyl Acetate*.—The diketo-acetate (100 mg.), m. p. 222°, $[\alpha]_D$ +56° (*c*, 2·70), was refluxed with ethanolic potassium hydroxide (10%; 4 ml.) for 1 hour. After working up in the usual way and reacetylation with pyridine–acetic anhydride overnight at room temperature, recrystallisation from chloroform–methanol gave back starting material (65 mg.), m. p. and mixed m. p. 220—221°, $[\alpha]_D$ +56° (*c*, 2·15).

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