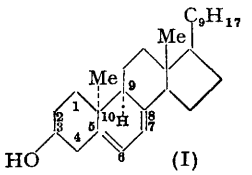
969. *Infra-red Spectra of Natural Products. Part I. The Stereochemistry of Lumistanol.*

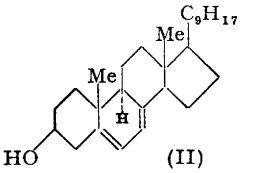
By A. R. H. Cole.

Infra-red measurements show that in lumistan-3β-ol the hydroxyl group is oriented in a polar direction. This fact, when considered with existing stereochemical knowledge, enables an unequivocal structure to be suggested for this compound.

Lumisterol (I) has been shown to differ from ergosterol (II) only in the orientation around $C_{(10)}$ (Kennedy and Spring, *J.*, 1939, 250). Doubt still exists, however, about the stereochemical configuration, especially at the 5-position, of the saturated hydrogenation product lumistanol. This was prepared as its acetate from dihydrolumisteryl acetate by Ahrens, Fernholz, and Stoll (*Annalen*, 1933, **500**, 109) and from lumisteryl acetate by Heilbron, Moffet, and Spring (*J.*, 1937, 411).



(I)



(II)

Attention has been drawn to this problem recently by Jones, Humphries, Herling, and Dobriner (*J. Amer. Chem. Soc.*, 1951, **73**, 3215). Infra-red measurements on a large number of 3-acetoxy-steroids indicate that the contour of an intense absorption band near 1240 cm.$^{-1}$ is related to the stereochemistry at the 3- and the 5-position. When the acetoxy-group is attached to the ring by a polar C–O bond (Barton, *Experientia*, 1950, **6**, 316) a group of two or three peaks is observed near 1240 cm.$^{-1}$, while for equatorially oriented acetoxy-groups there is only a single strong peak in this region. Lumistan-3β-yl acetate gives the complex type of band (see Jones *et al.*, *loc. cit.*, Fig. 4) indicating a polar acetoxy-group, in apparent contradiction to ergostan-3β-yl acetate which exhibits the expected simple (equatorial) absorption.

More recent infra-red work (Cole, Jones, and Dobriner, *J. Amer. Chem. Soc.*, in the press) has shown that in the spectra of the 3-hydroxy-steroids the intense band between

995 and 1055 cm.$^{-1}$, due to a C–O stretching vibration, may be used to distinguish between polar and equatorial hydroxyl substituents. In general an equatorial hydroxy-group absorbs at a higher frequency than the corresponding polar group. These observations have now been extended to cover lumistan-3β- and -3α-ol (*epi*lumistanol) and make it possible to put forward an unequivocal conformation for each of these compounds.

Experimental

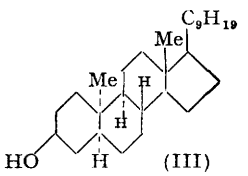
The infra-red spectra were measured on a Perkin–Elmer Spectrometer, Model 12c, equipped with a sodium chloride prism. Carbon disulphide solutions were employed in absorption cells 1 and 3 mm. in thickness and the spectra (shown in Fig. 1) are plotted by using the apparent molecular absorption coefficient $E_A = [\log_{10} (T_0/T)]/cl$ (Ramsay, *J. Amer. Chem. Soc.*, 1952, **74**, 72). The advantages of plotting infra-red spectra of large organic molecules quantitatively in this manner have been pointed out previously (Cole, Jones, and Dobriner, *loc. cit.*, and Jones, *Appl. Spectroscopy*, 1951, **6**, No. 1).

The lumistanol and *epi*lumistanol were kindly supplied by Dr. D. H. R. Barton. The former had been prepared by Heilbron, Moffet, and Spring (*loc. cit.*) and a portion of this sample was converted into *epi*lumistanol by oxidation to lumistanone and reduction by sodium and propanol (Ahrens, Fernholz, and Stoll, *loc. cit.*).

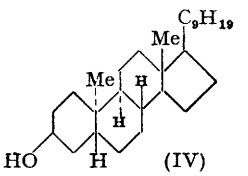
Results and Discussion

The intense absorption band due to the C–O stretching vibration lies at 1010 cm.$^{-1}$ in the spectrum of lumistan-3β-ol while for *epi*lumistanol it occurs at 1034 cm.$^{-1}$ (see Fig. 1). Thus the hydroxyl group in the former is oriented in a polar and in the latter in an equatorial direction, as suggested by the method of preparation of the *epi*lumistanol and in agreement with the complex band at 1240 cm.$^{-1}$ in the spectrum of lumistan-3β-yl acetate (Jones *et al.*, *loc. cit.*).

The various interconversions possible among the compounds related to vitamin D (for summary see Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd Edn., 1949, Reinhold Publ. Corp.) lead to the belief that they do not involve change in the stereochemical configurations of rings C and D, and it may be assumed that in lumistan-3β-ol they are the same as in ergostan-3β-ol. Models then show that there is only one possible structure (III) for lumistan-3β-ol which allows the hydroxyl group to be polar, if it is taken into account that the angular $C_{(10)}$-methyl group is α-oriented, and that the rings are in the thermodynamically more stable "chair" form.



(III)



(IV)

The stereochemical relations expressed by (III) are more apparent when drawn as in Fig. 2. The structure (IV), having a 5β-hydrogen atom, is not allowable, since the $C_{(1)}$–$C_{(10)}$-bond is polar with respect to ring B and (IV) requires that the $C_{(4)}$–$C_{(5)}$-bond be also polar and on the opposite side of the ring. *cyclo*Hexane rings can be fused at neighbouring carbon atoms only when both bonds are equatorial or when one is equatorial and the other polar (Johnson, *Experientia*, 1951, **7**, 315).

Reversal of the hydroxyl group and the hydrogen atom on $C_{(3)}$ in Fig. 2 gives the proposed conformation of *epi*lumistanol.

The $C_{(9)}$-isomer of lumistanol, hexahydropyrocalciferol (perhydrodehydrolumisterol) (Dimroth, *Ber.*, 1936, **69**, 1123) should now be represented by Fig. 3. The 3β-hydroxyl group in this structure is equatorially oriented and it would be useful to confirm this spectroscopically, but no sample has been available.

It may appear that (III) assumes that the hydrogen atom at $C_{(8)}$ is β-oriented but this is not so. If the configuration at $C_{(8)}$ were α (*i.e.*, B/C *cis*), then there would be two formally possible three-chair conformations for rings A, B, and C. Of these the α-conformation at

$C_{(5)}$ is eliminated because the β-configuration at $C_{(3)}$ would be equatorial. The conformation with the β-configuration at $C_{(5)}$ would explain the polar character of the $C_{(3)}$-hydroxyl group and remains a *formally* acceptable possibility. It is rejected, however, when the corresponding structure for the $C_{(9)}$-isomer hexahydropyrocalciferol is examined. If the 8-hydrogen atom is α-oriented, then in lumistanol the $C_{(7)}$–$C_{(8)}$-bond is polar and the $C_{(9)}$–$C_{(10)}$-bond is equatorial with respect to ring c. If now the bonds at $C_{(9)}$ are reversed to change the structure to that of hexahydropyrocalciferol, it is found that $C_{(9)}$–$C_{(10)}$ is polar

FIG. 1.

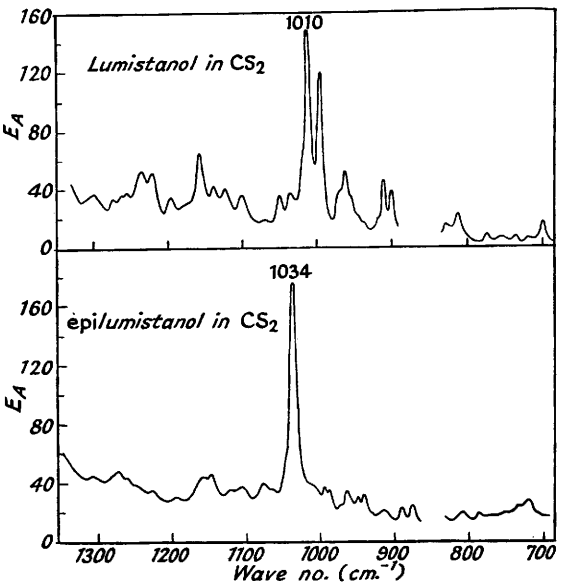


FIG. 2.

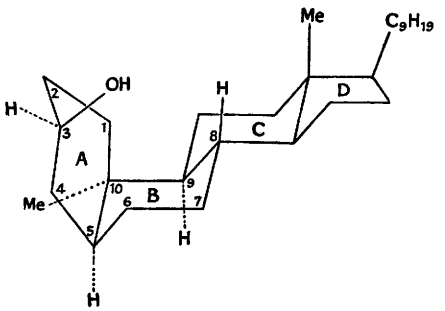
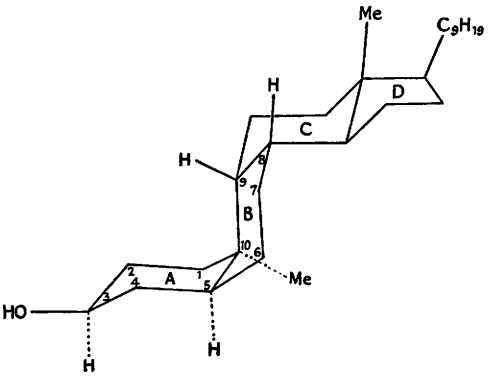


FIG. 3.



and on the opposite side of ring c from $C_{(7)}$–$C_{(8)}$ and this is not possible (Johnson, *loc. cit.*). Another reason for rejecting both $C_{(8)}$ α-conformations is that they would involve prohibitively strong steric repulsion between the $C_{(13)}$-methyl group on the one hand and the $C_{(7)}$–$C_{(8)}$-bond and, especially the $C_{(7)}$ β-hydrogen atom, on the other. As can be seen from a study of models, epimerisation of the $C_{(10)}$-methyl group removes the difficulty of placing the β-side of the lumisterol molecule on a catalyst surface, which is very apparent where the configurations at $C_{(10)}$ and $C_{(13)}$ are both β. Indeed the inversion of configuration at $C_{(10)}$ could hardly facilitate (as is observed experimentally) hydrogenation on the α-side at $C_{(8)}$, whereas it is obvious that it would facilitate the possibility of hydrogenation β at $C_{(8)}$.

In the suggested structure (Fig. 2) for lumistan-3β-ol the hydroxyl group and the 5-

hydrogen atom project on opposite sides of the molecule. Thus the suggestion by Jones *et al.* (*loc. cit.*, p. 3218) that the complex bands at 1240 cm.$^{-1}$ in the spectra of the polar acetates might be due to interaction of this hydrogen atom with the 3-acetoxy-group is probably incorrect. It seems that the contour of the " acetate band " at 1240 cm.$^{-1}$ is related to the orientation of the C–O bond only, and is not affected by that of the C–H at position 5.

A Fellowship from the Nuffield Foundation is gratefully acknowledged. The author is particularly grateful to Dr. D. H. R. Barton for stimulating discussions and help. Thanks are also offered to Mr. P. de Mayo (Birkbeck College, London) for preparing the *epi*lumistanol and to the Chester–Beatty Institute (London) for the use of the infra-red spectrometer.

UNIVERSITY OF WESTERN AUSTRALIA,
NEDLANDS, WESTERN AUSTRALIA.

[*Received, July 15th,* 1952.]