

DOUBLE BOND CONFIGURATIONS OF

24-ETHYLIDINE STEROLS

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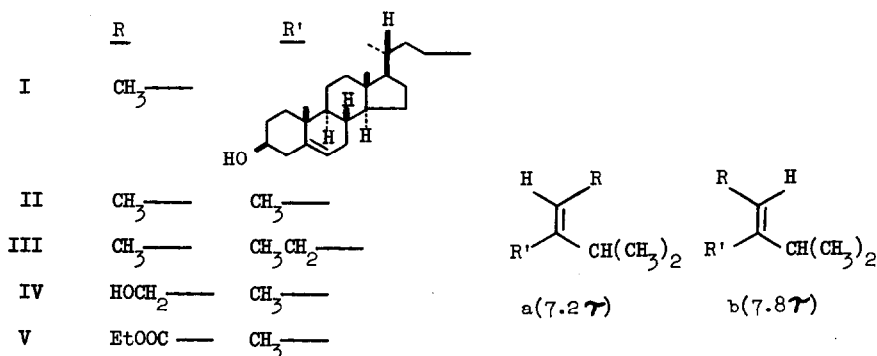
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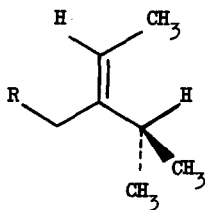
In 1960 the double bond configurations shown in Ia and Ib were assigned to fucosterol and isofucosterol, resp., by Dusza on the basis of an infrared comparison with the model compounds IIa and IIb<sup>2</sup>. However, the configurations of these model compounds had been assigned on unstated grounds in the American Petroleum Institute Catalog prior to 1960<sup>3a</sup>, and in 1960, Onesta and Castelfranchi obtained evidence which prompted them to reverse the configurations of IIa and IIb<sup>4</sup>. The new configurations were accepted by the American Petroleum Institute<sup>3b</sup>, but the evidence was not compelling, and the configurations of the sterols Ia and b were not reversed in print until Frost and Ward<sup>5</sup> did so on the basis of comparisons of the chemical shifts of the isopropyl methine hydrogens in the NMR with those of the cis and trans isomers of 4-methyl-2-pentene.

We now report: (1) While Dusza's ir method is successful in correlating Ia and b with IIa and b, it is not generally applicable, and should be replaced by the nmr method used by Frost and Ward<sup>5</sup>; (2) New evidence that the assignments of Onesta and Castelfranchi for IIa and b are correct; (3) Configurational assignments for the double bonds in IIIa and b, and for the naturally occurring 24-ethylidene sterols.

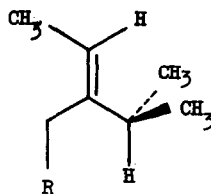


(1) Dusza found bands at 12.14, 12.30, 12.18 and 12.39 $\mu$  for fucosterol (Ib), isofucosterol (Ia), IIb, and IIa, resp., and from these values correlated Ib with IIb and Ia with IIa<sup>2</sup>. However, in trying to apply this method to IIIb and a, we found bands at 12.17 and 11.98, resp., and thus this method is of limited utility. Fortunately, in the nmr spectra of compounds I - IV and of all of the 24-ethylidene sterols we have examined, the heptet due to the isopropyl methinyl proton occurs at either  $7.2 \pm 0.1\tau$  (a series) or  $7.8 \pm 0.1\tau$  (b series), providing an easy means of correlation<sup>6</sup>.

This large difference is undoubtedly due to a change in population distribution of the various rotamers about the bond joining the isopropyl group to the double bond. The chief source of this change is non-bonded steric interactions between isopropyl methyls and vinyl methyls in the a series, and in this series, rotamers like VIa in which the isopropyl methinyl proton is near the vinyl methyl should predominate. Whether a substituent in the position of the isopropyl methinyl proton in VIa would be shielded or deshielded by a double bond has been a controversial point<sup>7</sup>; we think the low-field position of these protons in the a series strongly favors deshielding in this region<sup>8</sup>.



VIa



VIb

(2) Arguments in favor of the assignments shown for IIa and b follow.<sup>9</sup>

- a) Onesta and Castelfranchi<sup>4</sup> originally made these assignments because they felt after an examination of molecular models that more IIb than IIa should be formed in the pyrolysis of methylethylisopropylcarbonyl benzoate, a reaction they found to give 34% of the higher-boiling (7.8 $\tau$ ) stereoisomer and 11% of the lower.
- b) Frost and Ward<sup>5</sup> have correlated IIa and b with the 4-methyl-2-pentenes on the basis that the 7.8 $\tau$  isomer of II corresponds to the 7.7 $\tau$  isomer of the latter and the 7.2 $\tau$  isomer of II to the 7.4 $\tau$  isomer.
- c) The reaction between methyl isopropyl ketone and the Wittig reagent from triethyl phosphonoacetate<sup>10</sup> gave an excellent yield of a 4:1 mixture of Vb and a, resp., whose configurations (suggested by the yield ratio) could be assigned with considerable confidence from the chemical shifts of the  $\beta$ -methyl groups at 7.90 and 8.47 $\tau$ , resp.<sup>11</sup>. Lithium aluminum hydride reduction of this ester mixture gave a 4:1 mixture of the corresponding alcohols, IVb (isopropyl methinyl proton at 7.8 $\tau$ ) and a (7.2 $\tau$ ). To further correlate these alcohols with the hydrocarbons IIb and a, the alcohol mixture was reacted stereospecifically with  $\text{PBr}_3$ <sup>12</sup> followed by lithium aluminum hydride, giving a 4:1 mixture of IIb and a, resp.
- d) Ultraviolet irradiation of either IIa or b with di-tert-butyl sulfide in Pyrex<sup>13</sup> produced the same 76/24 mixture in which the 7.8 $\tau$  isomer predominated<sup>14</sup>.

(3) Using the 7.2 and 7.8 $\tau$  peaks, we have found the higher-boiling isomer in the case of III to be IIIa<sup>15</sup>; fucosterol (Ib = stigmasta-5, E-24(28)-diene-3 $\beta$ -ol) to be in the b series; and the other natural 24-ethylidene sterols, isofucosterol (Ia =  $\Delta^5$ -avenasterol = stigmasta-5, Z-24(28)-diene-3 $\beta$ -ol),  $\Delta^7$ -avenasterol (= stigmasta-7, Z-24(28)-diene-3 $\beta$ -ol), and citrostadienol<sup>16</sup> (=  $\alpha$ -sitosterol =  $\alpha_1$ -sitosterol = 4 $\alpha$ -methyl-5 $\alpha$ -stigmasta-7-Z-24(28)-dien-3 $\beta$ -ol) to be in the less stable a series.

#### Footnotes and References

1. Alfred P. Sloan Research Fellow. We also gratefully acknowledge financial support from the USPHS (GM-11721 to RBB).
2. J. P. Dusza, J. Org. Chem., **25**, 93 (1960).
3. a) Infrared Spectral Data, American Petroleum Institute, Research project 44, serial nos. 1796 and 1904 (1956); b) ibid., (1960).
4. R. Onesta and G. Castelfranchi, Chim. e Ind. (Milan), **42**, 735 (1960).
5. D. J. Frost and J. P. Ward, Tetrahedron Letters, 3779 (1968).
6. All nmr spectra were run in DCCL<sub>2</sub> on a HA-100 with internal TMS. This nmr method was reported by us at the second Natural Products Symposium, Kingston, Jamaica, January, 1968.
7. A. A. Bothner-By and J. A. Pople, Ann. Review of Phys. Chem., **16**, 54 (1965); J. W. ApSimon, W. G. Craig, P. V. Demarco, D. W. Mathieson, L. Saunders, and W. B. Whalley, Tetrahedron, **23**, 2357 (1967).
8. This effect shows to a much lesser extent with ethyl instead of isopropyl: The methylene in trans-3-methyl-2-pentene (analogous to IIb) absorbs at 8.03 $\tau$ , and the methylene in the cis isomer, at 7.98 $\tau$ .
9. While none of these arguments is by itself compelling, we consider the combination to far outweigh two which might be considered to favor the opposite assignments:
  - a) Dusza<sup>1</sup> claims to have obtained 9 parts of the lower-boiling (7.2 $\tau$ ) stereoisomer of II for each part of the higher from a Wittig reaction between methyl isopropyl ketone and triphenylphosphineethylidene. However, when we repeated this reaction, IIa and b were formed in very nearly equal amounts.
  - b) We tried to determine the configurations of IIa and b using the method of J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, J. Chem. Soc., 112 (1959), which involved adding isopropyl magnesium bromide to 3-chloro-2-butanone. However, the reaction was not very stereoselective, giving 70% of IIa (expected to be

- the minority isomer) and 30% of IIb. This contrasts with the addition of ethyl magnesium bromide to 3-chloro-2-butanone, which Cornforth found (and we have verified) gives 80-85% of trans-3-methyl-2-pentene (analogous to IIb). For recent discussions of difficulties in interpreting such "Cram's rule" additions, see G. J. Karabatsos, J. Am. Chem. Soc., 89, 1367 (1967), and references cited therein.
10. Aldrich Chemical Co.; this reagent in dry DMF was mixed with 0.9 eq NaOEt in EtOH, and after 1 hr, 1 eq ketone was added and the solution refluxed for 4 hrs.
  11. L. M. Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press Ltd., London, 1959, p. 121.
  12. R. B. Bates, J. H. Schauble, and M. Souček, Tetrahedron Letters, 1683 (1963).
  13. K. Gollnick and G. Schade, ibid., 689 (1968).
  14. As expected, IIIb predominated over IIIa to a lesser extent (64/36).
  15. This reversal in bp for IIIa and b as compared to IIa and b shows that the tentative generalization that trans-3-methyl-2-alkenes boil higher than their cis isomers (K. W. Greenlee and V. G. Wiley, J. Org. Chem., 27, 2304 (1962)) does not work with these compounds. The reason for the reversal is probably connected with the considerable differences in the shapes of the best conformations (VIa, VIb) which result when R = CH<sub>3</sub> as compared to the simpler case (VI, R = H).
  16. We have unequivocally shown the following compounds to be identical to citrostadienol: The sterol in slippery elm wood (Ulmus rubra Mühl), M. Fracheboud, J. W. Rowe, R. W. Scott, S. M. Fanega, A. J. Buhl, and J. K. Toda, Forest Products Journal, 18, 37 (1968); The  $\alpha_1$ -sitosterol from Solanum tuberosum L., K. Schreiber and G. Osske, Tetrahedron, 20, 2575 (1964), K. Schreiber and G. Osske, Experientia, 19, 69 (1963); The sterol from Betula verrucosa Ehrh. wood, J. Bergman, B. O. Lindgren, and C. M. Svahn, Acta Chem. Scand., 19, 1661 (1965); The sterol from Populus tremuloïdes Michx. bark, R. L. Hossfeld and W. T. Hunter, Tappi, 41, 358 (1958), R. L. Hossfeld and F. H. Kaufert, Forest Products J., 7, 437 (1957), I. A. Pearl and J. A. Harrocks, J. Org. Chem., 26, 1578 (1961); The  $\alpha$ -sitosterol from Populus tremula L., B. O. Lindgren and C. M. Svahn, Acta Chem. Scand., 20, 1763 (1966).