The Structure of Carpesterol

Sir:

Although carpesterol (I, mp 251°, $[\alpha]^{27}\text{D}$ +67°) was first isolated from the lipid fraction of the Hindu medicinal plant, *Solanum xanthocarpum* (Schrad. and Wendl.), more than three decades ago,[1] no structural studies of the sterol have been reported. Because it was hoped that a structural knowledge of I would shed some light on the biogenetic pathway leading to solasodine,[2] which is the major alkaloid accompanying I in *S. xanthocarpum* and commonly found among many other *Solanum* species, we initiated the structural elucidation of I. We wish to report that X-ray crystallography has shown carpesterol (I) to be an elaboration of a (24*R*)-24-ethyllophenol skeleton (4α-methyl-5α-stigmast-7-en-3β-ol) heretofore not characterized from a natural source.[3]

High-resolution mass spectrometry established the empirical formula of I as $C_{37}H_{54}O_4$. Electron impact also revealed the marked lability of a $C_7H_6O_2$ fragment. That the labile group of I was due to a benzoyloxy function was confirmed by the appearance of five protons in the aromatic region of the nmr, by the isolation of benzoic acid from base hydrolysis, and by the presence of a strong absorption at 1710 cm^{-1} in the ir spectrum.

In addition to the oxygen bearing the benzoyl group, a second oxygen substituent is present as a free hydroxyl functionality ($\nu_{\max}$ 3590 cm^{-1}) which readily forms an acetate[1] and a benzoate.[4] The secondary disposition of the hydroxyl group follows from the formation of ketocarpesterol (II, mp 228–229°, $[\alpha]^{20}\text{D}$ +47°) *via* chromic oxidation of I.

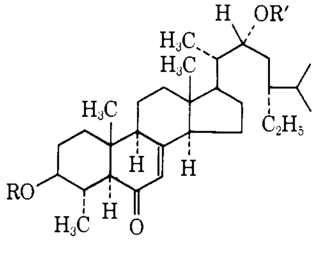
Although I exhibited a strong absorption at 1677 cm^{-1} in the ir attributable to an α,β-unsaturated ketone, the uv spectrum of I could not be used to further define the enone system because of the "masking effect" by the benzoyl chromophore also present in I. However, the more useful debenzoylcarpesterol diacetate (III) was readily prepared from I by successive treatment with $LiAlH_4$–THF, dicyanodichlorobenzoquinone–dioxane, and acetic anhydride–pyridine. The diacetate III (mp 205–206°, $\nu_{\max}$ 1686 cm^{-1}) gave a maximum in the uv at 245 mμ (ϵ 12,500) in good agreement with the calculated value[5] for a trisubstituted α,β-unsaturated ketone.

The determination of the functional groups and empirical formula of I prompted us to consider a tetracyclic triterpene as a trial structure. The triterpenoid nature of I was further indicated by the isolation of a methylated chrysene mixture from a selenium dehydrogenation experiment. Moreover, separation of 1,7-dimethylphenanthrene (pimanthrene) from the dehydrogenation product suggested the presence of methyl substituents at the 4 and 13 positions of the triterpenoid.

While the chemical investigation was in progress it was found that the *p*-iodobenzenesulfonate derivative (IV, pipsylate) of carpesterol formed triclinic plates (mp 126–127°) that were suitable for X-ray diffraction analysis. The space group was *P*1 since there was only one asymmetric molecule in the unit cell. The cell constants with estimated standard deviations in parentheses are $a = 7.466$ (2), $b = 10.981$ (3), $c = 13.187$ (3) Å; $\alpha = 92.75$ (3), $\beta = 96.76$ (2), $\gamma = 97.98$ (2)°. The density measured by the flotation method was 1.29 (calcd 1.30) g/cm^3. Using a Picker four-circle diffractometer with Mo Kα (Zr-filtered) radiation, the intensities of 2861 independent reflections were measured with a maximum $\sin\theta/\lambda$ of 0.545 Å^{-1}.

The iodine atom was placed at the unit cell origin. While it was possible to locate the sulfur atom from a Patterson map and two oxygen atoms and the benzene ring atoms of the pipsyl group from an electron density map phased with sulfur and iodine contributions, an electron density map using phases calculated for all known atoms still possessed the pseudocenter of symmetry generated by the very heavy iodine atom. It was not possible to distinguish one image of the molecule from the other on a basis of peak heights.

After several inconclusive attempts to fit a model based on chemical evidence, the pseudosymmetry was finally broken by means of a method suggested by Hoppe and Gassmann.[6] In this, all unassigned peaks in the electron-density map were selected which had peak heights greater than about 0.2 of that expected for a carbon atom. Structure factors were calculated for atoms (assumed to be carbon) at all these positions with occupancy factors based on a third degree polynomial of the observed electron density. Seven cycles of such weighted structure factor calculations followed by electron density maps based on them gradually enhanced the electron densities at the true positions and reduced all image peaks to less than the acceptance level. At this point the steroid nucleus and the attached groups were clearly defined. Subsequent least-squares refinement gave an *R* factor of 8.9%. Structure IV is a representation of the refined X-ray model. The mean estimated standard deviations for the bond lengths are 0.015, 0.030, and 0.020 Å for the steroid nucleus, for the side chain, and for the benzene rings, respectively. The corresponding deviations for the bond angles are 0.7, 1.5, and 1.1°.



I, R = C_6H_5CO; R′ = H
II, R = C_6H_5CO, 22-oxo
III, R = R′ = Ac
IV, R = C_6H_5CO; R′ = *p*-$IC_6H_4SO_2$

Apart from the pipsyl group, the thermal vibrations of the atoms are not markedly anisotropic. The tem-

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(1) I. Z. Saiyed and D. D. Kanga, *Proc. Indian Acad. Sci., Sect. A,* 4, 255 (1936).

(2) For a recent discussion of steroidal alkaloid biosynthesis, see K. Schreiber in "The Alkaloids," Vol. X, R. H. F. Manske, Ed., Academic Press, New York, 1968, pp 115–125.

(3) B. L. Williams, L. J. Goad, and T. W. Goodwin (*Phytochemistry,* **6**, 1137 (1967)) have reported the presence of small amounts of 24ζ-ethyllophenol in grapefruit peel in mixture with 24ζ-methyllophenol.

(4) M. P. Gupta and S. Dutt, *J. Indian Chem. Soc.,* **15**, 95 (1938).

(5) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, London, 1961, p 58.

(6) W. Hoppe and J. Gassmann, *Acta Crystallogr., Sect. B,* **24**, 97 (1968).

perature factor range is 2.4–4.4 Å^2 for the steroid nucleus, and 3.0–9.0 Å^2 for the side chain. Although the iodine atom has very anisotropic thermal parameters, and it is possible that a disorder model for the pipsyl group might produce somewhat better agreement, the present model seems adequate, as indicated by the *R* factor, for the aims of this structural study.

In addition to the unusual benzoyloxy substituent in the 3β configuration, the side-chain asymmetric centers are 20*S*, 22*R*, and 24*R* (stigmasterol configuration) as determined by internal comparison with the configurations at C-10 and C-13, assumed to be identical with cholesterol.

We believe the detailed structural information of carpesterol to be a logical part of the continuing clarification of phytosterol biosynthesis,[7] and perhaps carpesterol arises as the result of an intermediate bifurcation (as witnessed by the 22-hydroxyl function) in the sequence of events with which *S. xanthocarpum* synthesizes solasodine.

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(7) The role of 4α-methyl sterols in plant biosynthesis has been discussed by L. J. Goad in "Terpenoids in Plants," J. B. Pridham, Ed., Academic Press, London, 1967, pp 174–185.

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