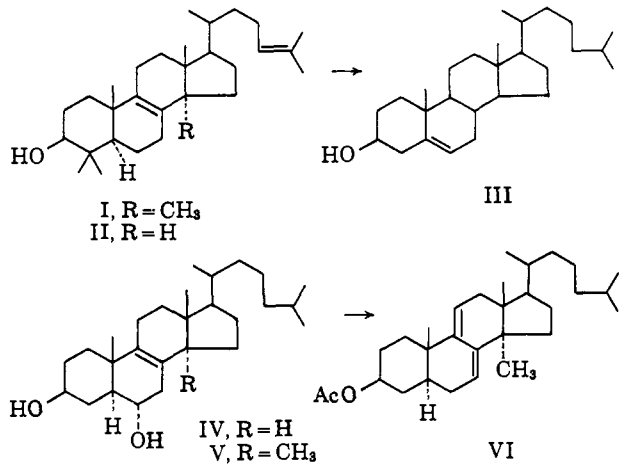
THE STRUCTURE OF THE CACTUS STEROL MACDOUGALLIN (14α-METHYL-Δ⁸-CHOLESTENE-3β,6α-DIOL)—A NOVEL LINK IN STEROL BIOGENESIS[1]

Sir:

The details of the biosynthesis of cholesterol and related sterols through the sequence mevalonate → farnesol → squalene → lanosterol are in general well documented.[2] One of the most interesting aspects involves the terminal stages in the conversion of lanosterol (I) to cholesterol (III), notably the demethylation[3] of lanosterol (I), which is believed to proceed through initial elimination of the 14α-methyl group, followed by oxidative removal of the two methyl groups at C-4. The operation of this path has been deomonstrated by Bloch and collaborators,[4] who noted the intermediacy of 14-norlanosterol (II) in cholesterol biosynthesis in the rat. Further support has been provided by the isolation, both from animals and plants, of 4-monomethyl sterols.[5]

The isolation and structure elucidation of lophenol[5a] (4α-methyl-Δ⁷-cholesten-3β-ol) from a cactus has prompted us to search for further links in the lanosterol (I) → cholesterol (III) transformation and we have concentrated on the cactus genera *Peniocereus* and *Wilcoxia*, both of which are characterized by large tuberous roots—a rare feature among the *Cactaceae*. The isolation and characterization of peniocerol (Δ⁸-cholestene-3β,6α-diol) (IV) from *Peniocereus fosterianus* Cut. has already been recorded[6] and mass spectral examination of the mother liquors indicated the presence of a higher homolog with an additional methyl group. Larger amounts of this new sterol, now named macdougallin (first isolated by Dr. R. D. H. Murray in our Laboratory), were encountered together with peniocerol (IV) in *Peniocereus macdougalli* Cut.[7] and its structure elucidation is reported herewith.

Chromatographic separation of macdougallin (V) and peniocerol (IV) was virtually impossible, but fractional crystallization of the diacetates proved successful, the purity of the fractions being established by mass spectrometery in view of the great similarity of their respective infrared spectra. Macdougallin diacetate exhibited m.p. 124–126°, $[\alpha]D$ +55.4° (all rotations in chloroform) as well as high terminal ultraviolet absorption (ϵ_{210} 4800, ϵ_{220} 1600). This latter feature, coupled with the absence of olefinic proton signals in the n.m.r. spectrum, requires the presence of a tetrasubstituted double bond. Alkaline saponification or exposure to lithium aluminum hydride provided the parent sterol, macdougallin (V), m.p. 173–174.5°, $[\alpha]D$ +71.8°, elementary analysis[8] and mass spectrometry establishing



the empirical formula $C_{28}H_{48}O_2$. In terms of elementary composition, macdougallin (V) thus represents x-methylpeniocerol, a peniocerol (IV) skeleton being assumed because of the close infrared spectral and chromatographic behavior of the two sterols. The *a priori* likely attachment of the extra methyl group at C-4 (as in lophenol[5a]) was excluded by partial saponification of macdougallin diacetate to the 6-monoacetate (amorphous) followed by chromium trioxide oxidation to the 3-keto-6-acetate (m.p. 117–117.5°, positive O.R.D. Cotton effect) and deuterium exchange, the presence of four exchangeable hydrogens being demonstrated by mass spectrometry.

Assuming an intact cholestane skeleton, these results leave only C-14 or the side chain as possible loci for the additional methyl group. An unambiguous answer could not be secured by n.m.r. spectrometry, but the C-14 attachment was made likely by the observation that the nuclear double bond would not be isomerized with acid nor reduced under acidic conditions, in contrast to the behavior[6] of peniocerol (IV). Definite proof for the location of the methyl group could be adduced by treatment of macdougallin diacetate with hydrogen chloride in acetic acid to gave 14α-methyl-Δ⁷,⁹⁽¹¹⁾-cholestadien-3β-ol acetate (VI), m.p. 77–78°, $[\alpha]D$ +66.3°, ϵ_{234}^{max} 16500, ϵ_{243}^{max} 19400 and ϵ_{251}^{max} 13900, which proved to be identical by mixture melting point determination and infrared comparison with an authentic sample, prepared by selenium dioxide–acetic acid oxidation of synthetic[9] 14α-methyl-Δ⁷-cholesten-3β-ol acetate.

Macdougallin is, therefore, 14α-methyl-Δ⁸-cholesthene-3β,6α-diol (V) and thus represents the first naturally occurring 14-monomethyl sterol. Its existence demonstrates that, at least in the cactus, demethylation in ring A can precede removal of the 14-methyl group of a lanosterol-like precursor and, furthermore, raises the question (resolvable by suitable biochemical experimentation) whether this alternate demethylation path may not also be operative in mammalian cholesterol biosynthesis.

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(2) "Ciba Foundation Symposium on the Biosynthesis of Terpenes and Sterols" (G. E. W. Wolstenholme and M. O'Connor, ed.), J. and A. Churchill, Ltd., London, 1959. For other recent reviews see J. W. Cornforth, *Pure Appl. Chem.*, **2**, 607 (1961); L. D. Wright, *Ann. Rev. Biochem.*, **30**, 525 (1961).

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(4) P. B. Schneider, R. B. Clayton and K. Bloch, *J. Biol. Chem.*, **224**, 175 (1957); F. Gautschi and K. Bloch, *J. Am. Chem. Soc.*, **79**, 684 (1957); F. Gautschi and K. Bloch, *J. Biol. Chem.*, **233**, 1343 (1958).

(5) (a) C. Djerassi, G. W. Krakower, A. J. Lemin, L. H. Liu, J. S. Mills and R. Villotti, *J. Am. Chem. Soc.*, **80**, 6284 (1958); (b) Y. Mazur, A. Weizmann and F. Sondheimer, *ibid.*, **80**, 6293 (1958); (c) D. H. Neiderhiser and W. W. Wells, *Arch. Biochem. Biophys.*, **81**, 300 (1959); (d) A. A. Kandutsch and A. E. Russell, *J. Biol. Chem.*, **235**, 2253, 2256 (1960).

(6) C. Djerassi, R. D. H. Murray and R. Villotti, *Proc. Chem. Soc.*, 450 (1961).

(7) Collected by Dr. D. K. Cox near La Escondida, Oaxaca (Mexico). We are indebted to Dr. Cox for numerous collections and to Dr. R. Villotti (Syntex, S. A., Mexico City) for the large-scale extractions performed in Mexico.

(8) All subtances reported in this communication gave satisfactory elementary analyses; in most instances the empirical formula was also confirmed by mass spectrometric measurements performed by Drs. M. Ohashi and J. M. Wilson.

(9) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957). We are thankful to Prof. D. H. R. Barton for providing us with this valuable intermediate.

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REACTIVE *o*-QUINONOID AROMATIC HYDROCARBONS OF THE PLEIADENE SERIES

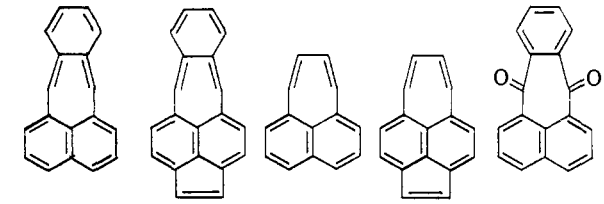
Sir:

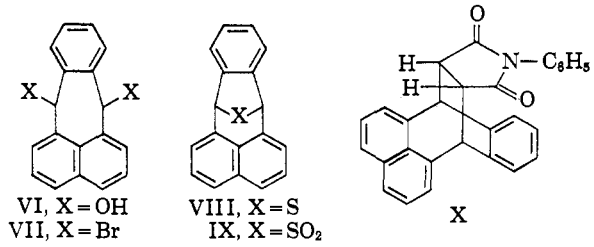
Whereas the known stable hydrocarbons naphthacene and benzo[*a*]anthracene may be viewed as derived from

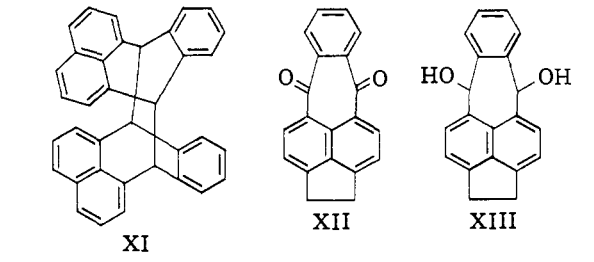
o-quinodimethane by fusion to the 2,3- and 1,2-positions of naphthalene, the corresponding *peri*-fused isomer, pleiadene (I),[1] has not been described and nothing is known concerning the stability of this system. The recently synthesized related hydrocarbons *peri*-cycloheptanaphthalene (III) and particularly *peri*-cycloheptaacenaphthylene (IV) show considerable aromatic stabilization, hydrocarbon IV being completely unaffected by maleic anhydride at 80° after eight and one-half days.[2a,b] We wish now to report that pleiadene (I) and its acenaphthylene analog acepleiadylene (II) are far more reactive species which appear not to be isolable, but which may be characterized as crystalline dimers and Diels–Alder adducts.[3]

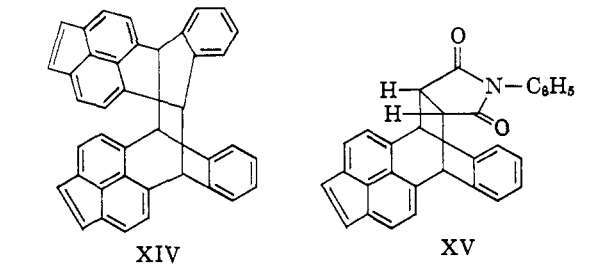
Reduction of 7,12-dihydropleiadene-7,12-dione (V)[4] with sodium borohydride gave, in 92% yield, diol VI, m.p. 198–200°. Reaction of VI with dry hydrogen bromide gave, in 90% yield, the corresponding dibromide VII, m.p. 134°. Phosphorus pentasulfide converted VII in 62% yield to the cyclic sulfide VIII, m.p. 177–178°; peracetic acid oxidation of VIII afforded, in 88% yield, the cyclic sulfone IX, m.p. 210–215° dec. Pyrolysis of sulfone IX at 210° in the presence of N-phenylmaleimide gave, in 70% yield, adduct X, m.p. 295–297°; under similar conditions in the absence of a dienophile there was obtained, in 51% yield, pleiadene dimer (XI), m.p. > 350° dec. The same dimer XI was formed in 86% yield by refluxing a benzene solution of dibromide VII with copper powder for fifteen minutes.

Sodium borohydride reduction of 5,10-dihydroacepleiadene-5,10-dione (XII)[5] afforded the corresponding diol XIII, m.p. 212–265° dec., in 80% yield. Solutions of XIII in dioxane containing a small amount of hydrochloric acid rapidly acquired an intense deep blue color which we ascribe to the hydrocarbon acepleiadylene (II), formed by a facile and unusual double vinylogous dehydration of diol XIII. Freshly prepared solutions of II showed absorption maxima at: λ_{max}^{diox} 227 mμ (log ε 4.32), 240 (4.23), 283 (4.23), 293 (4.25), 361 (4.53), 377 (4.69), 617 (3.14), 649 (3.17) and 674 (3.20). The blue color of solutions of II turned to yellow after standing at room temperature for 80 minutes, or on evaporation to dryness under all conditions tried; there was obtained, in 51% yield, the yellow acepleiadylene dimer (XIV), m.p. > 370° dec. When diol XIII was heated with N-phenylmaleimide in acidic dioxane on the steam-bath there was obtained, in 51% yield, the yellow adduct XV, m.p. 270–290° dec. Both XIV and XI showed an acenaphthylene type chromophore in the ultraviolet, in accord with the assigned structures, and both were easily reduced to the colorless acenaphthene type analogs.[6]









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(1) L. F. Fieser and M. A. Peters [*J. Am. Chem. Soc.*, **55**, 3010 (1933)] first proposed the name pleiadene for hydrocarbon I; on this basis the name acepleiadylene for II follows logically. In 1951 (ref. 2a) it was suggested that this nomenclature be changed so that the modified name pleiadiene might be reserved for the simpler compound III; in 1956 (ref. 2b) the name acepleiadylene was used to describe IV. At this time we feel compelled to return to the original nomenclature of Fieser and Peters, which is not only in common usage in several modern treatises, but which has been adopted recently as *official definitive nomenclature* (*i.e.*, pleiadene for I) by the IUPAC [*J. Am. Chem. Soc.*, **82**, 5553 (1960)].

(2) (a) V. Boekelheide, W. E. Langeland and C. Liu, *ibid.*, **73**, 2432 (1951); (b) V. Boekelheide and G. K. Vick, *ibid.*, **78**, 653 (1956).

(3) Melting points are uncorrected. Satisfactory analyses were obtained for all new compounds, the ultraviolet spectra of which were consistent with the assigned structures.

(4) A. Reiche, H. Sauthoff and O. Müller, *Ber.*, **65**, 1371 (1932).

(5) A. T. Peters and F. M. Rowe, *J. Soc. Dyers Colourists*, **59**, 52 (1943).

(6) The configuration of adducts X and XV and of dimers XI and XIV have been assigned tentatively on the basis of their ultraviolet absorption spectra. Details will be discussed in the full paper.