Synthesis of 24,28-Didehydroaplysterol and *X*-Ray Crystal Structure of Aplysterol: Unusual Marine Sterols

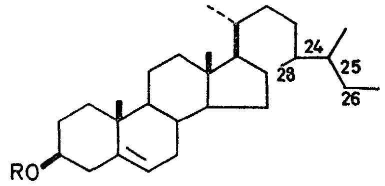
By Pietro De Luca, Mario De Rosa, Luigi Minale,* Reffaella Puliti, and Guido Sodano
[*Laboratorio per la Chimica e Fisica di Molecole di Interesse Biologico del C.N.R., Via Toiano, 2 - Arco Felice(NA) Italy*]

and Federico Giordano and Lelio Mazzarella
(*Istituto Chemico, Università degli Studi, Napoli, Italy*)

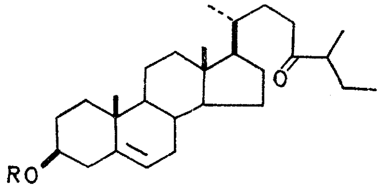
Summary The synthesis of 26-methyl-24-methylenecholesterol establishes this as the 24,28-didehydroaplysterol, isolated from the sponge *Verongia aerophoba*; the structure of 24,26-dimethylcholesterol, previously suggested for aplysterol, occurring in the same sponge as the principal sterol, has been confirmed by single-crystal *X*-ray diffraction studies of its *p*-iodobenzoate derivative, which also showed the stereochemistry to be 24*R*,25*S*.

Recently we reported the occurrence in the marine sponge *Aplysina* (= *Verongia*) *aerophoba* of two novel sterols, aplysterol (**1a**) and 24,28-didehydroaplysterol (**2a**), which on the basis of spectral and chemical evidence, were characterized as 26-methyl homologues of 24-methyl- and 24-methylene-cholesterol, respectively,[1] without side-chain stereochemical implications. The addition of an "extra" carbon atom to the normal cholesterol skeleton at C-26 is without previous parallel.

In order to confirm unambiguously the structures of these sterols, which seem to be confined solely to the *Verongia* species,[2] and to establish the stereochemistry of side-chains, we now report the synthesis of 24,28-didehydroaplysteryl acetate (**2b**) and the *X*-ray determination of the crystal structure of the 3-*p*-iodobenzoate derivative of aplysterol (**1b**).

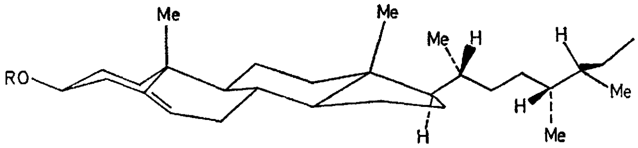


(1) a; R = H
b; R = *p*-Iodobenzoyl
(2) a; R = H, $\Delta^{24(28)}$
b; R = Ac, $\Delta^{24(28)}$



(3) a; R = Ac
b; R = H

The synthesis of (**2b**) was accomplished *via* a Wittig reaction of the 26-methyl-24-oxocholesteryl acetate (**3a**). Reaction between 3β-acetoxy-Δ^5-cholenyl chloride and di-s-butylcadmium[3] (prepared from Bu^{s}Br) afforded a mixture of ethyl and s-butyl esters together with the ketone (**3a**); the free 3-hydroxy-group of this compound (**3b**; epimeric at C-25) was isolated in 15% yield by saponification† followed by SiO_2 chromatographic purification. Treatment of (**3b**) with acetic anhydride in pyridine gave the acetate (**3a**) [m.p. 94—96° (MeOH); m/e 396 ($M^+ -$ $MeCO_2H$), 296, 255, 253, and 213; singlets at δ 0·68 (13-Me), 1·01 (10-Me), and 1·94 (MeCO) and multiplets at δ 4·49 (C*H*OAc) and 5·37 (CH=C)] which was converted into (**2b**; yield 60%) by treatment with $CH_3{:}PPh_3$ (room temp. for 1 h and then 5 h at 65°). Crystallization from MeOH gave pure (**2b**; epimeric at C-25), m.p. 120—122° (natural m.p. 113—114°), identical with natural 24,28-didehydroaplysteryl acetate as shown by t.l.c. ($SiO_2/AgNO_3$), g.l.c.,‡ i.r., and n.m.r. data. The mass spectrum of the synthetic (**2b**), m/e 394, 296, 255—253, and 213 differs from that of the natural one in the absence of a peak at m/e 310, which is present in the mass spectrum of the latter,[1] and is attributable to an impurity. Furthermore, the stanyl acetates, obtained on hydrogenaion of both natural and synthetic (**2b**), were identical (g.l.c.).



FIGURE

The *p*-iodobenzoate derivative (**1b**) was prepared by esterification of (**1a**) with *p*-iodobenzoyl chloride in pyridine and crystallized from acetone [m.p. 151—154° (decomp.)]. Crystals were monoclinic, space group $P2_1$, with unit cell dimensions: $a = 12{\cdot}52(3)$, $b = 9{\cdot}10(2)$, $c = 14{\cdot}62(3)$ Å, $\beta = 92{\cdot}48° \pm 0{\cdot}20°$, $U = 1665$ Å^3, $Z = 2$, $D_m = 1{\cdot}26$ g cm^{-3}. Intensities of 2648 reflections were collected by an "on line" Siemens diffractometer (Cu-K_α radiation), using a single crystal of roughly cylindrical shape (0·1 mm thick) and 2040 were considered observed. The data were collected at room temp. by the moving-crystal, moving-counter technique. No correction for absorption was applied.

The structure was solved using the normal heavy-atom and Fourier synthesis technique, and refined by the block-diagonal least-squares method, using isotropic thermal parameters. In the last four cycles, anisotropic thermal parameters and anomalous dispersion corrections for the iodine atoms were taken into account, the absolute configuration being chosen on the basis of the known configuration at C(10) and C(13).

The atomic scattering factors used were computed from the function given by Cromer and Mann.[4] No attempt was made to locate the hydrogen atoms. The final discrepancy factor was 10·8%. In the Figure a projection of the molecule ($R{=}IC_6H_4CO{-}$) is shown. *X*-Ray analysis confirms the structure previously deduced by chemical methods[1] and in addition, it establishes the *R* and *S* configuration for the carbon atoms C(24) and C(25), respectively.

All bond distances and angles are in good agreement with the values found for this class of compounds.[5] The dihedral angles of the rings A, B, and C compare well with the values found in other Δ^5-steroids, and indicate that rings A and C are chairs and that ring B is a half chair.[6,7] The conformation of the cyclopentane ring D can be described in terms of the two parameters Δ and ϕ_m as defined by Altona *et al.*[8] The values found for aplysterol, $\Delta = 2°$ and $\phi_m = 45°$, are close to those of an ideal half-chair conformation.

(*Received*, 30*th July* 1973; *Com.* 1099.)

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† The esters proved difficult to separate from the ketone (**3a**).

‡ G.l.c. analyses were performed on a 2 m 1% OV-1 column at 245°.

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