Clausenolide: a Novel Pentanortriterpenoid Furanolactone; *X*-Ray Crystal Structure

By DEBI P. CHAKRABORTY, PRANTOSH BHATTACHARYYA, and SATI P. BHATTACHARYYA
(*Department of Chemistry, Bose Institute, Calcutta* 700009, *India*)

JON BORDNER and GLENN L. A. HENNESSEE
(*Department of Chemistry, North Carolina State University, Raleigh, North Carolina* 27650)

and BORIS WEINSTEIN*
(*Department of Chemistry, University of Washington, Seattle, Washington* 98195)

Summary Clausenolide, a limonoid from *Clausena heptaphylla*, is shown by chemical, spectroscopic, and *X*-ray crystallographic studies to be a pentanortriterpenoid with a rearranged ring A.

ON the basis of taxonomic considerations, it became of interest to look for new limonoids[1] in *Clausena heptaphylla,* which is a rich source of carbazole alkaloids.[2] We here report the structure of clausenolide, the first pentanortriterpenoid with an unusual C–Me group at position 1 in the triterpene skeleton.

Clausenolide (I)† is a neutral compound, $C_{25}H_{32}O_8$, m.p. 150 °C, *m/e* 460 (M^+, 15·5%), 337 (100%), 277 (37·3%, $337-C_2H_4O_2$), and 42 ($C_2H_4O_2-H_2O$); $[\alpha]_D^{27}$ − 70·7° (*c* 1, $CHCl_3$); λ_{max} (ethanol) 206 and 270 nm (log ϵ 3·8 and 3·64), characteristic of a β-substituted furan and an isolated ketonic system; ν_{max} (Nujol) 3520, 3400, 1730, 1710, 1507, and 810 cm^{-1}, indicating the presence of several hydroxy functions, a δ-lactone system, an isolated six-membered ketone, and a β-substituted furan; n.m.r. ($CDCl_3$; 60 MHz) two α-furan protons (δ 7·4, 2H), a β-furan proton (δ 6·4, 1H), a furfurylic proton (δ 5·6, 1H), a proton attached to a secondary hydroxy-carbon atom (δ 4·5, 1H), two hydroxy protons (δ 4·0 and 2·5, s), an epoxide proton (δ 3·7, 1H, s), an oxomethylene group (δ 2·4, 2H), and five conventional C–Me groups (δ 1·6, 1·4, and 1·2–1·0), as well as a deshielded C–Me group (δ 1·5, *J* 2 Hz, non-equivalent methyls of an isopropyl unit). Based on these assignments, the limonoid must contain four additional rings.

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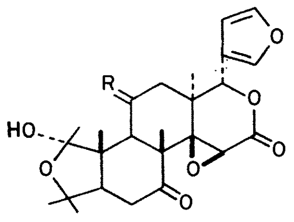
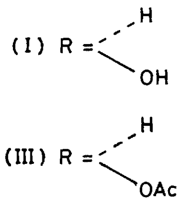
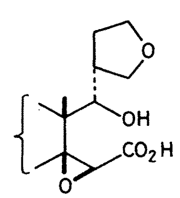
† We note that the systematic name of clausenolide is (1α,3aα,4aα, 4bβ, 6aα, 9α, 9aβ, 9bα, 10β,11aα)-1-(3-furanyl)decahydro-9,10-dihydroxy-4b,7,7,9,9a,11a-hexamethylfuro[3′,4′:5,6]naphth[2,1-*c*]oxireno[*d*]pyran-3,5(3a*H*,6*H*)-dione or (1*R**,3a*S**,3′*R**,5a*S**,6*S**,7*R**,9*R**,9a*S**,9b*S**)-7-[(*R**)-3-furylhydroxymethyl]decahydro-1,9-dihydroxy-1,3,3,5a,7,9b-hexamethyl-5-oxospiro[naphtho[1,2-*c*]-furan-6(3*H*),2′-oxirane]-3′-carboxylic acid δ-lactone (K. L. Loening, Director of Nomenclature, Chemical Abstracts Service, personal communication).







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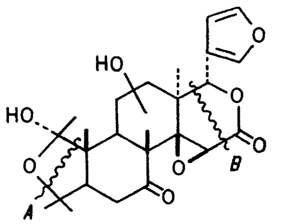

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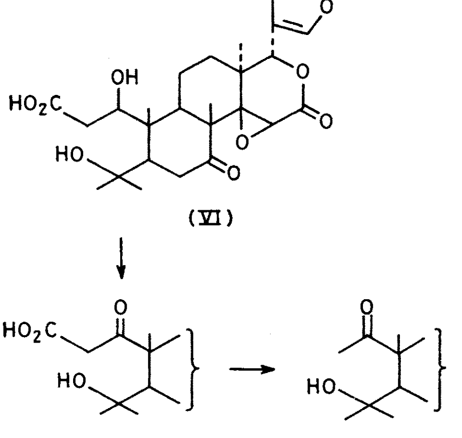

Clausenolide, on hydrogenation, produced hexahydroclausenolic acid (II), m.p. 174 °C; ν_{max} (Nujol) 3480, 3400, 1750, and 1710 cm^{-1}, consistent with the reduction of a β-substituted furan and the formation of a hydroxy acid from ring D. Acetylation yielded clausenolide monoacetate (III), m.p. 199 °C; *m/e* 502 ($M^+ - H_2O$), 379, 319 ($379 - MeCO_2H$), 301 ($319 - H_2O$), and 259; ν_{max} (Nujol) 3520, 1750, 1740, 1720, 1500, and 870 cm^{-1}, suggestive of the presence of a residual hydroxy group in either ring B or C. Sarret oxidation of clausenolide gave a six-membered ketone (IV), m.p. 195 °C; ν_{max} (Nujol) 3480, 1740, 1735, and 870 cm^{-1}; n.m.r. (partial) δ 2·7, consistent with the placement of the tertiary hydroxy in ring A and the new ketomethylene unit in ring C.

These findings can be expressed by the partial formula (V). Here, the high intensity peak at *m/e* 337 is accounted for by fragmentation along the wavy line *B*,[3] while the residual ion at *m/e* 277 represents the portion between the wavy lines *A* and *B*. By default, the $C_2H_4O_2$ fragment can be expanded to MeC(OH)O–, which forms part of ring A.

Full support for such a structure was obtained by a single-crystal *X*-ray diffraction analysis. Clausenolide crystallized from an acetone–toluene solution in the orthorhombic space group $P2_12_12_1$ with $a = 9{\cdot}344(2)$, $b = 21{\cdot}767(5)$, and $c = 13{\cdot}885$ Å.‡ A 1 Å data set (maximum $\sin\theta/\lambda = 0.5$) was collected at room temperature on a Syntex P$\bar{1}$ diffractometer using Cu-K_α radiation. A trial structure was obtained using a combination of direct methods (MULTAN[4]) and Fourier techniques. This trial structure was verified by a conventional full-matrix least-squares refinement. The later stages of refinement included a full-matrix treatment of scale factors, all non-hydrogen co-ordinates, and the anisotropic temperature factors in one matrix. Methylene and methine hydrogen positions were calculated; all other hydrogen positions were located by difference Fourier techniques. Hydrogen locations were added to the structure factor calculations in the later stages of refinement, but their parameters were not refined. The final *R*-index was 0·107. A difference Fourier revealed no missing or misplaced electron density in the vicinity of the clausenolide molecule. However, there was a higher than background residual density in the vicinity of a molecule of crystallization (toluene). Attempts simply to fit this disordered toluene did not prove to be entirely satisfactory, so investigation of the absolute configuration of the molecule was not attempted.§

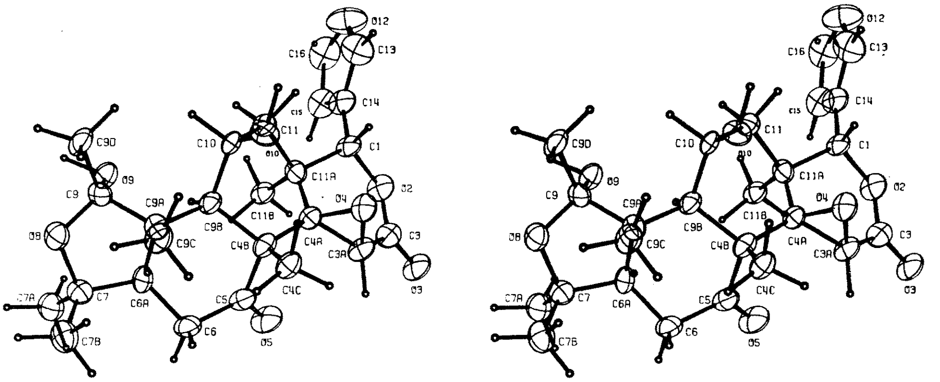

FIGURE. Stereoscopic view of the molecular structure of clausenolide.

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‡ Crystals were also grown from an acetone–benzene solution, but they contained a disordered benzene molecule of crystallization. Other solvents did not yield suitable crystals.

§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

If a heavy atom derivative of clausenolide can be prepared, then the disorder problem may be overcome and one could obtain the desired absolute configuration. A stereoplot of the molecule is given in the Figure. Full crystallographic details and parameters can be obtained from one of the authors (J. B.).

The genesis of the modified ring A in this pentanortriterpenoid can be visualized as proceeding by oxidation of deacetylnomilinic acid (VI)[5] to a β-keto acid (VII), followed by decarboxylation to a ketone (VIII), and ring closure to a hemiacetal system. Alternatively, hydroxylation and oxidation of nomilinic acid or isobacunoic acid would yield the same result.[6] The identification of such intermediates in nature would lend welcome support to these schemes.

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