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CRYSTAL STRUCTURE AND STEREOCHEMISTRY OF INGOL-3,7,8,12-TETRAACETATE

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Several diterpene esters from the tigliane, daphnane and ingenane as well as from the macrocyclic lathyrane type (Fig.1) were isolated from several species of the plant family Euphorbiaceae (for an overview see loc. cit.1). For example, from the latex of the South African Euphorbia ingens E. Mey, several esters of the polyfunctional tetracyclic diterpenes ingenol[2)3)4)], 16-hydroxyingenol[4)5)] and the polyfunctional macrocyclic ingol[6)] were obtained. Ingol is one of the key derivatives of lathyrane and has achieved considerable interest as an antineoplastic agent[7)]. Further,ingol is of interest in connection with the biogenesis of the tumor promoting diterpene esters of the tigliane, daphnane and ingenane type[1)]. The structure and stereochemistry of ingenol was determined by X-ray crystallographic analysis of ingenol-3,5,20-triacetate[8)]. The structure of ingol was derived fom chemical and physical data without stereochemical assignments[6)]. We now report on the X-ray crystallographic analysis of ingol-3,7,8,12-tetraacetate obtained from naturally occurring esters by mild hydrolytic and acetylation procedures.

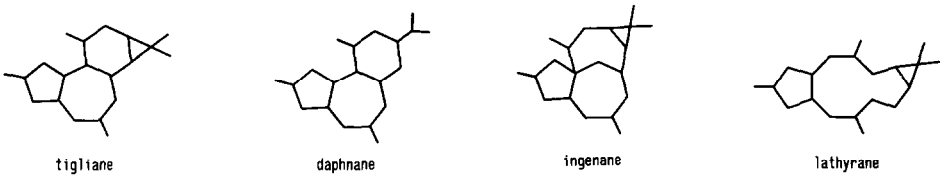

Fig.1: Diterpene skeletons

Ingol-3,7,8,12-tetraacetate was prepared as described previously[6)]. Crystallisation from diisopropylether gave white prisms (mp = 172-175°C) of size 0.7 x 0.2 x 0.2 mm. Crystal data: a = 21.222, b = 12.776, c = 10.756Å, space group $P2_12_12_1$, z = 4, d_m = 1.219, d_c = 1.217 g/cc. 2263 independent reflections (2017 observed $>2\sigma(I)$) were measured up to $\sin\theta/\lambda = 0.55$ Å^{-1} on an automated Siemens diffractometer with Cu Kα radiation (θ-2θ scanning, symmetrical 2° scan ranges, scan speed 1° min^{-1}). Data were scaled by Wilson statistics. The structure was solved with MULTAN[9)]. An E map from

the phase set with the best "combined figure of merit" using 400 E gave positions for 34 out of 38 nonhydrogen atoms. Subsequent Fourier maps revealed the positions of the other four atoms (excluding hydrogens). Refinement by full matrix least squares converged at R = 9.4%.

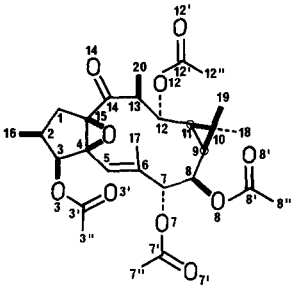

Fig.2: Structure of ingol-3,7,8,12-tetraacetate

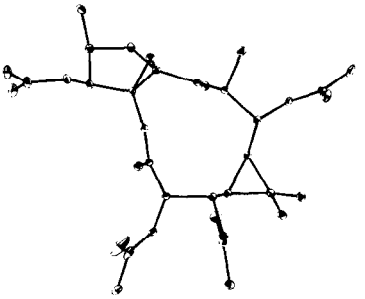

Fig.3: Crystal conformation of ingol with thermal ellipsoids, projection down c.

In contrast to lathyrol and its esters ingol-3,7,8,12-tetraacetate exhibits the 4β-lathyrane skeleton composed of three ring systems, i.e. cyclopentane, cycloundecane and cyclopropane (Fig.2 and 3). The junction between the cyclopentane and the macrocyclic ring is bridged by an epoxide ring at C4-C15, thereby fixing cis-configuration of the two positions interlinking the cyclopentane and the macrocyclic rings. Also the junction between the 11-membered and the cyclopropane ring (C9 and C11) has cis-geometry with respect to the cyclopropane methine hydrogens. The cyclopropane and the cyclopentane rings are exo with respect to the macrocycle. The distance between C5 and C6 of 1.32 Å clearly proves the presence of the $\Delta^{5,6}$ double bond which exhibits trans-configuration. By analogy to lathyrol and all other lathyrane-type diterpenes, for which the absolute configuration was determined, and supported by biogenetic considerations[1], α-configuration of 9-H and 11-H may be assumed.

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