Tetrahedron Letters No.18, pp. 1325-1328, 1971. Pergamon Press. Printed in Great Britain.

STRUCTURE OF 7-HYDROXY-LATHYROL
A FURTHER DITERPENE FROM EUPHORBIA LATHYRIS L.

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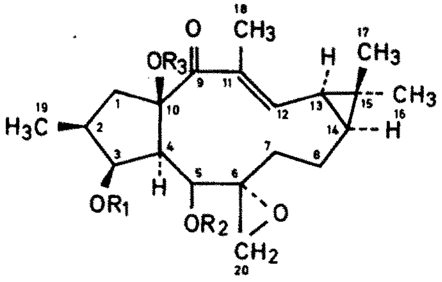
(Received in UK 15 March 1971; accepted for publication 25 March 1971)

By multistage Craig distribution of the hydrophilic neutral fraction of the seed oil of the caper spurge (Euphorbia lathyris L.) the crystalline compounds L_1, L_2, L_3 as well as the resinous compounds L_4 and L_5 were isolated (1,2). Recently, L_1 was characterized as 3-phenyl-acetate-5,10-diacetate I of the parent alcohol 6,20-epoxy-lathyrol II (3,4).

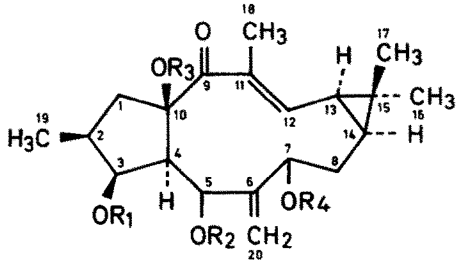
Compound L_2, $C_{38}H_{42}O_9$ (MS, anal.), m.p. 205-207°C is the diacetate-dibenzoate III of a diterpene alcohol IV (1,2) which we call 7-hydroxy-lathyrol. Spectral data of III: UV (MeOH): λ_{max} = 229, 273 nm; ε = 29800, 14200. The UV spectrum with maximum at 273 nm corresponds with that of I (λ_{max} = 273 nm; ε = 15000), indicating presence of the same chromophore in both molecules. IR (KBr): 1735, 1713 (CO), 1650, 1623 (C=C-CO), 907 ($C=CH_2$), 712 cm^{-1} (C_6H_5). The NMR spectrum ($CDCl_3$) indicates presence of two acetyl- (δ = 2,27, 1,37 ppm; 2 x 3H,S) and two benzoyl-groups (δ =7,3-8,2 ppm; 10 H,M). The signal of one of the acetyl groups at 1,37 ppm appears at extremely high field indicating strong shielding of its protons by an interatomic diamagnetic effect. It may be caused by the benzoyl groups and suggests a spatial neighbourhood of the ester groups concerned. Using D_5-pyridine as solvent, a paramagnetic shift of this acetyl group is noted (0,3 ppm), indicating a diminuation of the interaction between the ester groups. Additional NMR data of III ($CDCl_3$): H-12: 6,53, DD

($J_{12,13}$ = 11 cps, $J_{12,18}$ = 1-2 cps); H-5: 6,39, D ($J_{4,5}$ = 9 cps); H-3: 5,80, T ($J_{2,3}$ = $J_{3,4}$ = 3,5 cps); H-7: 5,55, T (J=6-7 cps); H_2-20: 5,53,S, 5,25, S; H-1a: 3,47, DD ($J_{1a,1b}$ = 14 cps, $J_{1a,2}$ = 8 cps); H-4: 2,99, DD ($J_{3,4}$ = 3,5 cps, $J_{4,5}$ = 9 cps); H-2: 2,4, M; H_3-18: 1,88, D ($J_{12,18}$ = 1-2 cps); H-13: 1,55, M; H_3-16, H_3-17: 1,34, S, 1,27, S; H_3-19: 1,02 ppm,D ($J_{2,19}$: 7 cps).



I: R_1 = $COCH_2C_6H_5$, R_2 = R_3 = $COCH_3$

II: R_1-R_3 = H



III: R_1-R_4 = 2 $COCH_3$, 2 COC_6H_5

IV: R_1-R_4 = H

V: R_1, R_2, R_4 = $COCH_3$, R_3 = H

Comparison of the NMR data specific for the parent alcohol with those of 6,20-epoxy-lathyrol (3,4) reveals structure IV for 7-hydroxy-lathyrol: instead of the signal of the protons of the epoxide group as noticed in the NMR spectrum of II, in III two singlets of protons of an exocyclic methylene group appear. Moreover, as compared to I the signal of a further geminal ester proton (5,55 ppm, T) is apparent in III. Since this proton has two coupling neighbours it is most probable that the additional hydroxyl group is attached to C-atom 7. If, alternatively this additional hydroxyl group would be attached to C-8 a dihedral angle of 90° of H-8 with one of the H-7 or with H-14 is to be postulated. All other signals correspond to those in the NMR spectrum of 6,20-epoxy-lathyrol. The doublet of a doublet at 3,47 ppm in the NMR spectra of the compounds I and II and also of III-V is related to proton H-1a. It is deshielded by its spatial neighbourhood to the carbonyl oxygen (as may be seen in Stuart-Briegleb models) and thus appears at rather low field.

Hydrolysis of III (0,5 m KOH in methanol) yields the parent alcohol IV, $C_{20}H_{30}O_5$ (MS), m.p. 222°-224°C from which by acetylation with Ac_2O/Py, 7-hydroxy-lathyrol-3,5,7-triacetate V is obtained, m.p. 161-162°C, NMR ($CDCl_3$): H-3: 5,56, T; H-5: 5,84, D; H-7: 5,15, T; OH-10: 3,50 ppm, S. $LiAlH_4$ reduction of the carbonyl group in IV affords a pentol (MS: parent ion m/e = 352) which exhibits a UV maximum at 213 nm (ε = 12900) indicating the presence of the vinyl-cyclopropane group (3,4).

The structure suggested for IV is confirmed and extended by X-ray diffraction analysis of V ($C_{26}H_{36}O_8$). Crystals suitable for the analysis were obtained from a 1:1 mixture of benzene and cyclohexane. The space group was found to be $P2_12_12_1$ with a = 18.34 Å, b = 12.22 Å and c = 11.43 Å; $\rho_{meas.}$ = 1.23 gcm^{-3}, $\rho_{calc.}$ = 1,23 gcm^{-3}, z = 4. Intensities were measured on a Siemens on-line single crystal diffractometer for $\theta \leq 70^\circ$ using CuKα radiation (θ/2θ scan and five-point measuring procedure). Of the 2726 independent reflections 61 were below the statistical detection limit.

The structure was solved by a virtually automatic direct procedure (5,6) based on the cyclic application of the triple-product relations (7) and Sayre's equation (8). Owing to the freedom of choice of the origin and the hand of the two enantiomorphic structures the phases of four strong projection reflections could be arbitrarily fixed. One three-dimensional and one further projection reflection were added assigning to them all combinations of the two phases 0° and 180° to give four phase sets. The phases of the 298 strongest unitary structure factors were determined by the cyclic procedure and the most probable solution chosen according to the Q-criterion (5). A U-Fourier synthesis with these phases revealed all 34 non-hydrogen atoms in the structure, the 31 highest peaks in the electron density distribution all corresponding to real atoms. Three cycles of isotropic and two cycles of anisotropic refinement yielded a preliminary R factor of 0.106. The molecular sceleton of V thus revealed is shown in Fig. 1a and 1b.

The absolute configuration of V was determined using the anomalous scattering of CuKα radiation by the oxygen atoms. Accurate intensity measurements were made on those Bijvoet pairs for which the calculated dispersion effects were strongest(9).

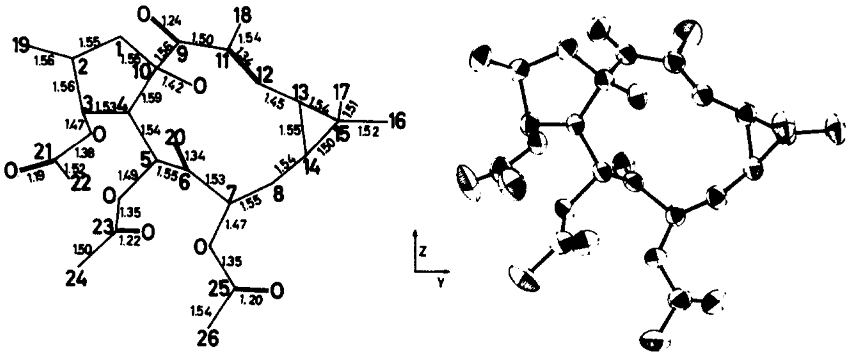


Fig. 1 (a) Diagram of molecule showing bond lengths after preliminary refinement R = 0.106. (b) yz projection. The ellipsoids illustrate the anisotropic thermal vibrations of the molecule. The x-axis points out of the plane of the paper.

The configuration shown in Fig.1 is absolute (see also I-V). It is identical with that of neophorbol and phorbol (10) respectively. This finding confirms the absolute configuration proposed (4) for some of the asymmetric centres of 6,20-epoxy-lathyrol (I) and the biogenetic relationships as assumed for the new lathyrol type of macrocyclic diterpenes (3,4) and phorbol as well as ingenol (11), the diterpene parent of the mono-esters L_4 and L_5, respectively.

REFERENCES

1. E.Hecker, Cancer Res. 28, 2338 (1968); Planta Medica, Supplement 1968, p. 24.
2. W.Adolf, H.Opferkuch and E.Hecker, Fette, Seifen, Anstrichmittel 70, 850 (1968).
3. W.Adolf, E.Hecker, A.Balmain, M.F.Lhomme, Y.Nakatani, G.Ourisson, G.Ponsinet, R.J. Pryce and T.S. Santhanakrishnan, Tetrahedron Letters 1970, 2241.
4. K.Zechmeister, M.Röhrl, F.Brandl, S.Hechtfischer, W.Hoppe and E.Hecker, W.Adolf, H.Kubinyi, Tetrahedron Letters 1970, 3071.
5. W.Hoppe et al., J.of Pure and Appl.Chem. 18, 465 (1969).
6. W.Hoppe, J.Gassmann, K.Zechmeister, Crystallographic Computing, 26.,Ed.F.R. Achmed, Munksgaard, International Booksellers and Publishers, Ltd. Kopenhagen 1970.
7. W.Cochran, Acta Cryst. 8, 473 (1955).
8. D.Sayre, Acta Cryst. 5, 60 (1952).
9. D.W.Engel, K.Zechmeister, M.Röhrl, F.Brandl, P.Narayanan, W.Hoppe, Nature, in the press.
10. W.Hoppe, F.Brandl, I.Strell, M. Röhrl, I. Gassmann and E.Hecker, H.Bartsch, G.Kreibich, Ch.v. Szczepanski, Angew.Chem. 79, 824 (1967); Angew.chem.internat.ed. 6, 809 (1967).
11. K.Zechmeister, F.Brandl, W.Hoppe and E.Hecker, H.J.Opferkuch, W.Adolf, Tetrahedron Letters 1970, 4075.