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" E U P H O R B I A S T E R O I D "

(Epoxy-lathyrol)

A new tricyclic diterpene from Euphorbia lathyris L.

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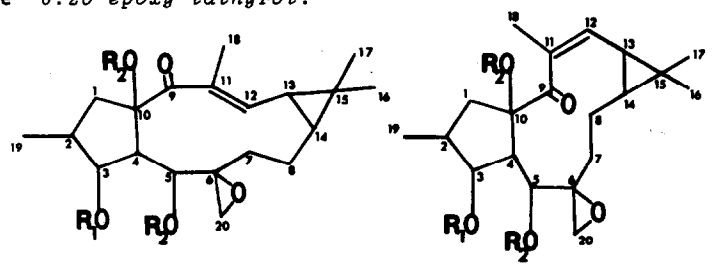
Dilution of the seed oil of the caper spurge (Euphorbia lathyris L,) with acetone results in the separation of a crystalline compound, m.p.199,5°C, previously named "euphorbiasteroid" (1-7). This substance is in fact the diacetate-phenylacetate 1 of a diterpene alcohol (cf.7) 2, for which we propose the name *6:20-epoxy-lathyrol.*[¶] [†]



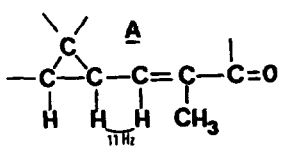
1, R_1=PhAc, R_2=Ac
2, R_1=R_2=H

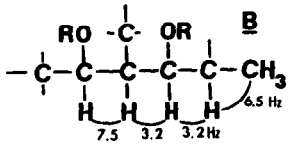
Euphorbiasteroid has the molecular formula $C_{32}H_{40}O_8$ (MS, anal.). Its NMR spectrum shows the presence of two acetates (δ=2.05, 2,15; 2x3H, S), and a phenylacetate (δ=7.25, 5H; 3.59, 2H). Alkaline hydrolysis of 1 (0.5% KOH in methanol) provides the parent alcohol 2, $C_{20}H_{30}O_5$ (MS, anal.), m.p.204-207°C, and phenylacetic acid. Alcohol 2 forms a DNPH, and on acetylation gives two monoacetates and a diacetate (with Ac_2O/Py), or a triacetate (with Ac_2O/TsOH).

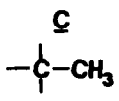
[¶] Euphorbiasteroid is identical with "substance L_1", m.p.199-200°C, obtained from the hydrophilic neutral fraction of the seed oil (8,9). From the same source are isolated compounds "L_3", a derivative of lathyrol which contains a 6(20)double-bond (10), and "L_2", a derivative of 7-hydroxy-lathyrol (11).

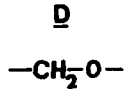
[†] Structure 1 was presented by G.O. at the 3rd Natural Products Symposium, University of Jamaica, Mona, on 9 January, 1970.

From the NMR spectra of 1 and 2 and decoupling experiments in various solvents, the following structural elements may be deduced (δ values indicated):



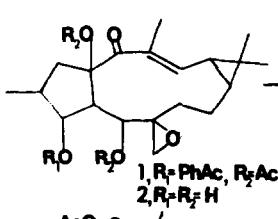


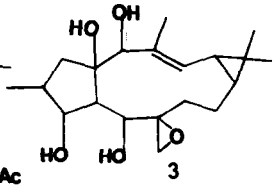


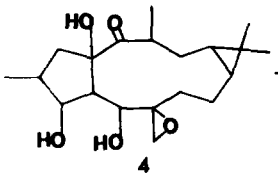


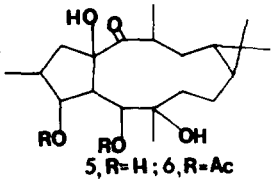
1	1.46	6.59	1.84	6.24	5.47	0.67	1.21	2.39
2	1.40	6.71	1.87	4.38	1.87 4.22	1.10	1.15	2.58

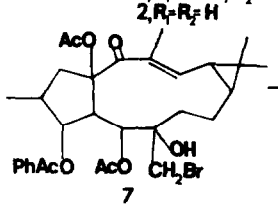
Additional evidence for part structure A is obtained from the UV maximum of 2 at 273 nm (ε=15 000), which moves to 214 nm (ε=13 400) on borohydride reduction of the carbonyl group to give the vinyl-cyclopropane 3, m.p. 177-179°C.

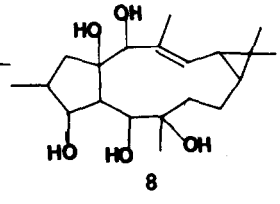


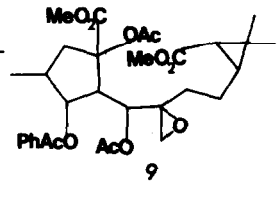


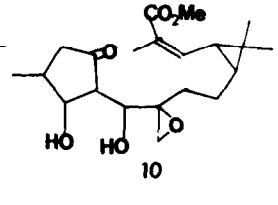






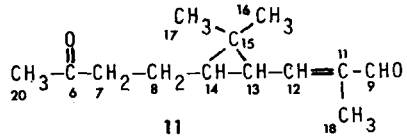






Hydrogenation of 2 over 10% Pd/C gives the dihydro-derivative 4 which, on prolonged treatment, is further reduced to the tertiary alcohol 5; m.p. 180-182°C. Acetylation of 5 (Ac_2O/Py) gives a 3,5-diacetate 6, m.p. 192-194°C, the NMR spectrum of which clearly shows the additional methyl resonance for the HO—C—CH_3 group (δ=1.24, S, 3H). This evidence indicates the presence of an epoxide of the type >C—CH_2 in compound 1, a conclusion which is confirmed by its conversion with HBr to the bromohydrin 7, m.p.160-161°C.

$LiAlH_4$ reduction of 2 affords the pentol 8, which on acetylation forms a 3,5,9-triacetate (H-9: δ=5.51, S, 1H). Ozonolysis of 1 followed by methylation (CH_2N_2) provides the diester 9, thus confirming part structure A. Periodate oxidation of 2, followed by methylation, gives the cyclopentanone-ester 10 (IR,KBr:1740, 1697, 1630 cm^{-1}; UV: λ_{max}236 nm, ε=13 600). In the periodate oxidation of the pentol 8, cleavage occurs at two sites, to give the aldehyde-methyl ketone 11 (IR,KBr:1710, 1670 cm^{-1}; UV: λ_{max}262 nm, ε=20 000).



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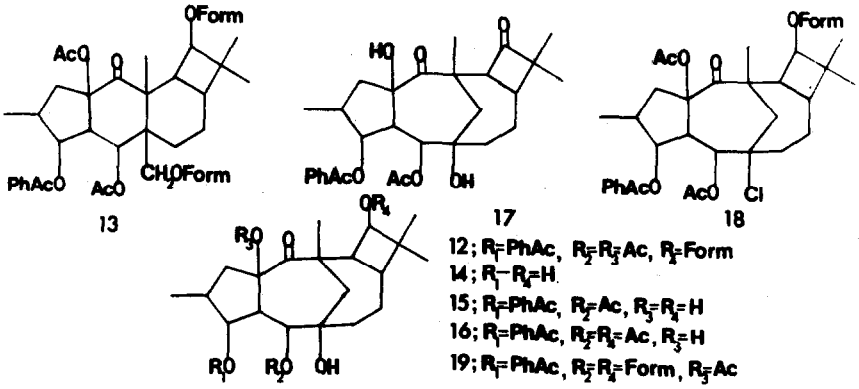
NMR: 1.13, 1.20: H_3-16, H_3-17, S
1.70: H_2-8, M; 1.80: H_3-18, D;
2.13: H_3-20, S; 2.50: H_2-7, T;
6.30: H_{12}, DD.

The above data lead unambiguously to the formulation of structure 1, or an isomer with ester groups interchanged. The relative positions of the ester groups were elucidated by a study of the *acid rearrangement* products of euphorbiasteroid. Treatment of 1 with $AcOH/HClO_4$, CF_3CO_2H or, preferably, HCO_2H, results in *transannular cyclisations* and *rearrangement* to give products of types 12 and 13 (with acetate or trifluoracetate groups instead of formate in the first two cases).



12; R_1=PhAc, R_2=R_3=Ac, R_4=Form
14; R_1–R_4=H
15; R_1=PhAc, R_2=Ac, R_3=R_4=H
16; R_1=PhAc, R_2=R_4=Ac, R_3=H
19; R_1=PhAc, R_2=R_4=Form, R_3=Ac

The monoformate 12, m.p.227-230°C, can be fully hydrolysed (1% KOH/MeOH) to the pentol 14, m.p.175°C, or selectively (Na_2CO_3) to the triol 15, m.p.99-101°C, which has retained the C-3 and C-5 ester functions (NMR). This identifies the tertiary ester of 1, at C-10, as an acetate. Compound 15 can be acetylated to the phenylacetate-diacetate 16, m.p.187-190°C, or oxidised (Jones' reagent) to the cyclobutanone 17, m.p.258-260°C (IR,$CHCl_3$: 1773 cm^{-1}). In addition, the tertiary bridge-head hydroxyl of 12 reacts with thionyl chloride to give the bridge-head chloride 18, m.p.255-258°C.

Prolonged heating of the ester 12 in formic acid leads to formolysis of the secondary acetate group, giving the diformate 19, the NMR spectrum of which suggests that the acetate replaced by formate is at C-5, thus placing the phenylacetate group at C-3.

In each of these rearranged substances, the characteristic NMR pattern due to fragment 8 is retained; H-13 now gives the expected doublet (J=11 Hz). The same structurally significant patterns are observed in the NMR spectrum of the diformate 13 (m.p.172-174°C), besides a singlet for the new primary $-CH_2$-OForm group.

The compounds 12 and 13 can be considered as formed from 1 by intramolecular alkylation of the enone of C-11, by either terminus of the (protonated) epoxide, followed by ring expansion of the cyclopropyl-carbonium ion produced to a cyclobutyl ion (and, in the case of 13), by esterification of the new

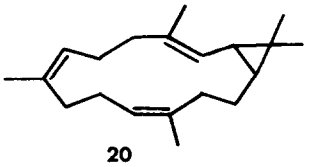
primary alcohol formed).

The carbon skeleton of 1 is directly derived from that of geranyl-geraniol by three cyclisations; it is a tricyclic relative of cembrene (12) and the duvatrienols (13). The skeleton of phorbol (14) differs from that of lathyrol only by the additional cyclisation C-8/C-9,potentially a plausible one as an internal vinylogous ketolisation. Thus, we have used here the phorbol numbering.

A recent X-ray analysis has confirmed structure 1 (15) and elucidated the trans-configuration of the double bond,and the relative configuration of the asymmetric centres, left undecided by our results.

All substances mentioned have been characterised by MS,NMR,IR and UV spectra, by CD (when relevant), and most by analysis. Measurements and stimulating discussions of NMR spectra by Prof.M.Anteunis, Gent, and Dr.A.Mannschreck, Heidelberg, are gratefully acknowledged (W.A., E.H.), as well as support by The Royal Society (A.B.), the CNRS (M.F.L.,Y.N.,T.S.S.; Laboratoire Associé No.31) and the CIBA Foundation (R.J.P.).

Note added 18 March,1970: The diterpene hydrocarbon casbene,20, biogenetically related to lathyrol, has recently been reported (16) as a cyclisation product of geranyl-geraniol pyrophosphate with enzyme preparations of castor bean (Ricinus communis L.,Euphorbiaceae).



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Bibliography:

1 -Y.Tahara, Ber.,23, 3347 (1890).
2 -N.F.Dublyanskaya, Pharmaz.Pharmakol.,8, 1 (1937).
3 -Id., ibid., 9, 8 (1937).
4 -N.F.Dublyanskaya and I.A.Remezow, ibid., 10, 7 (1937).
5 -N.F.Dublyanskaya, ibid., 11-12, 50 (1937).
6 -R.Jaretzky and W.Kohler, Arch.Pharm.,281, 256 (1943).
7 -W.Trzebny, Roczn.Chem., 40, 55 (1966).
8 -E.Hecker, Cancer Research, 28, 2338 (1968).
9 -W.Adolf, H.Opferkuch and E.Hecker, Fette, Seifen, Anstrichm., 70, 825 (1968)
10-W.Adolf and E.Hecker, in preparation.
11-M.Röhrl et al.,in preparation.
12-W.G.Dauben, W.E.Thiessen and P.R.Resnick, J.Amer.Chem.Soc., 84, 2015 (1962).
13-D.L.Roberts and R.L.Rowland, J.Org.Chem., 27, 3989 (1962).
14-E.Hecker, Naturwissenschaften, 54, 282 (1967); E.Hecker et al.,Tetrahedron Letters, 3165 (1967); Hoppe et al.,Hecker et al.,Angew.Chem. Intern.Ed., 6, 809 (1967); Petterson et al., Chem.Comm.,716 (1967).
15-K.Zechmeister, M.Röhrl, F.Brandl, S.Hechtfischer, W.Hoppe and E.Hecker, W.Adolf and H.Kubinyi, Angew.Chem., in press.
16-D.R.Robertson and C.A.West, Biochemistry, 9,70 and 80 (1970).