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EUPHORBETIN : A NEW BICOUMARIN FROM EUPHORBIA LATHYRIS L.

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A number of novel diterpenes[1-4], triterpenes[5] and plant pigments[6,7] have so far been isolated from Euphorbia lathyris. We wish to report in this communication, the isolation of a new bicoumarin, 'euphorbetin', from the seeds of this plant.

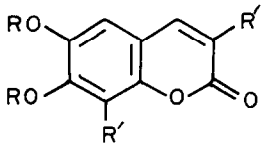
The seeds were extracted with pet. ether, chloroform and alcohol successively. The alcohol extract on concentration furnished esculetin (Ia), $C_9H_6O_4$* (M^+ 178), m.p. 269-71°, ν_{max}^{Nujol} cm^{-1} : 3300, 3200 (hydroxyl), 1660 (lactone), 1610 (phenyl); NMR : δ (DMSO) 6.25 (1H, d, J = 10 Hz), 3-H; 6.85 (1H, S), 8-H; 7.08 (1H, S), 5-H; 7.98 (1H, d, J = 10 Hz), 4-H; diacetate $C_{13}H_{10}O_6$ (Ib), m.p.135-37°, ν_{max}^{Nujol} cm^{-1} : 1760 (acetate), 1725 (lactone), 1625 (phenyl); NMR : δ (DMSO) 2.12 (3H, S), 6-$OCOCH_3$; 2.35 (3H, S), 7-$OCOCH_3$; 6.62 (1H, d, J = 10 Hz), 3-H; 7.53 (1H, S), 8-H; 7.78 (1H, S), 5-H; 8.16 (1H, d, J = 10 Hz), 4-H; dimethyl ether $C_{11}H_{10}O_4$ (Ic), m.p. 144-46°, λ_{max}^{EtOH} nm (log ε) : 209 (4.35), 230 (4.3), 295 (3.8), 342 (4.1); ν_{max}^{Nujol} cm^{-1} : 1725 (lactone), 1620 (phenyl) ; NMR : δ ($CDCl_3$) 3.92 (1H, S), 6-OCH_3; 3.98 (3H, S), 7-OCH_3; 6.26 (1H, d, J = 10 Hz), 3-H; 6.82 (1H, S), 8-H; 6.85 (1H, S), 5-H; 7.6 (1H, d, J = 10 Hz), 4-H.

The seeds were further extracted with alcohol for a longer period. The extract was boiled with MeOH and filtered to remove traces of esculetin. The residue was then refluxed with 6% alc.HCl. The hydrolysate was crystallised from a large volume of alcohol when euphorbetin precipitated out as light yellow crystals, $C_{18}H_{10}O_8$ (IIa), m.p.>320°, ν_{max}^{Nujol} cm^{-1} : 3250 (hydroxyl),

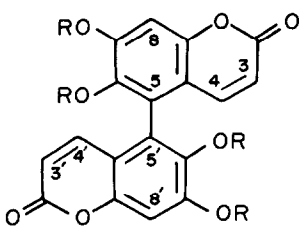
* The compounds reported in this communication gave satisfactory analysis.

1665 (lactone), 1600 (phenyl). It is very sparingly soluble in the usual organic solvents. It forms a tetra acetate $C_{26}H_{18}O_{12}$ (IIb), m.p.235-37°, ν_{max}^{Nujol} cm^{-1} : 1760 (acetate), 1730 (lactone), 1600 (phenyl). Methylation with dimethyl sulphate and K_2CO_3 in anhydrous acetone afforded the tetra methyl ether $C_{22}H_{18}O_8$ (IIc) (M^+ 410); m.p. 230-32°, λ_{max}^{EtOH} nm (log ε) : 210 (4.58), 223 (4.55), 300 (4.19), 337 (4.35); ν_{max}^{Nujol} cm^{-1} : 1725 (lactone), 1600 (phenyl); NMR : δ ($CDCl_3$) 3.66 (3H, S), $-OCH_3$; 4.07 (3H, S), $-OCH_3$; 6.23 (1H, d, J = 10 Hz); 7.08 (1H, S); 7.17 (1H, d, J = 10 Hz).

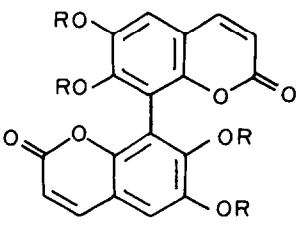
The molecular composition and methoxyl estimation of IIc (4 OMe) and the similarity of UV spectra with that of Ic indicated II to be a dimer of I. The symmetrical nature of the molecule was revealed by the NMR spectrum of IIc and by its mass spectrum (doubly charged ion at m/e 205). The presence of a doublet at δ 6.23 ppm in IIc ascribed to 3-H of a coumarin ruled out a 3-3' or 4-4' dimeric structure. So euphorbetin can be represented by structure II or III.



Ia. R = H, R′ = H
Ib. R = $COCH_3$, R′ = H
Ic. R = CH_3, R′ = H
Id. R = CH_3, R′ = Cl



IIa. R = H
IIb. R = $COCH_3$
IIc. R = CH_3



III

On comparison of NMR spectra of methyl ethers of esculetin and euphorbetin it is observed that the chemical shifts for 4-H as also for a methoxyl group

were located at a higher field positions in the latter, whereas the aromatic proton singlet moved down field. Methoxyl groups at 6 or 6' position and protons in 4 or 4' position in IIc would be shielded by the ring current of the adjacent non planar benzene ring and are therefore expected to resonate at a higher frequency[8,9] Structure III cannot explain the high shielding of the protons at 4 & 4' positions and was therefore ruled out. The low field shift of the signal for 8,8' protons on the other hand is most probably due to the inductive effect of the other coumarin ring.

In the mass spectrum of IIc the molecular ion is the base peak, initial loss of OCH_3 is very facile compared to loss of CH_3; m/e 379 (50%), m/e 395 (7%). The mass fragmentation pattern is as follows : m/e 410 (M^+), 100%; 395 ($M-CH_3$), 7%; 379 ($M-OCH_3$); 50%; 364 ($M-OCH_3-CH_3$), 82%; 349 ($M-OCH_3-2CH_3$), 13%; 336 ($M-OCH_3-CH_3-CO$), 31%; 321 ($M-OCH_3-2CH_3-CO$), 16%; 308 ($M-OCH_3-CH_3-2CO$), 14%; 293 ($M-OCH_3-2CH_3-2CO$), 21%; 205 (M^{++}), 35%.

Euphorbetin represents the first example of 5:5' bicoumarin. The other C-C bicoumarins so far isolated from natural sources are dicoumarol (Sweet clover)[10], bicoumol (Ladino clover)[11], matsukaze lactone (Boenninghausenia albiflora)[12], kotamin and desmethyl kotamin (Aspergillus flaucus)[13].

The synthesis of 8:8' dimer of Ic was attempted for comparison purposes through the electrophillic chlorination of the compound with SO_2Cl_2 and charcoal[14] in tetrachloroethane followed by Ullmann reaction[15] with activated copper bronze in DMF but without success. Chlorination by above method actually produced 3:8 dichloro, 6:7-dimethyl esculetin (Id), m.p. 224-25°, ν_{max}^{Nujol} cm^{-1} : 1725 (lactone), 1600 (phenyl); NMR : δ ($CDCl_3$) 3.88 (S, 3H), 6-OCH_3; 3.95 (S, 3H), 7-OCH_3; 6.82 (S, 1H), 5-H; 8.13 (S, 1H), 4-H.

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References:

1. W. Adolf & E. Hecker, A. Balmain, F.M. Lhomme, Y. Nakatani, G. Ourisson, G. Ponsinet, R.J. Pryce and T.S. Santhanakrishnan, L.G. Matyukhina and I.A. Saltikova, Tetrahedron Letters, 2241 (1970) and refs. therein.
2. K. Zechmeister, M. Rohrl, F. Brandl, S. Hechtfischer, W. Hoppe, E. Hecker, W. Adolf and H. Kubinyi, Tetrahedron Letters, 3071 (1970).
3. K. Zechmeister, F. Brandl, W. Hoppe, E. Hecker, H.J. Opferkuch and W. Adolf, Tetrahedron Letters, 4075 (1970).
4. P. Narayanan, M. Rohrl, K. Zechmeister, D.W. Engel, W. Hoppe, E. Hecker and W. Adolf, Tetrahedron Letters, 1325 (1971).
5. P.K. Dutta and R.N. Chakravarti, Phyto. Chem., 10, 2250 (1971).
6. K. Dumkow, Z. Naturforsch, B, 24, 358 (1969).
7. R. Jaretzky and W. Kohler, Chem. Zentr., 1, 303 (1943).
8. J.P. Ferris, C.B. Boyce and R.C. Briner, J. Amer. Chem. Soc., 93, 2942 (1971).
9. T.R. Govindachari and P.C. Parthasarathy, Tetrahedron, 27, 1013 (1971).
10. M.A. Stahmann, C.F. Huebner and K.P. Link, J. Biol. Chem., 138, 513 (1941).
11. R.R. Spencer, S.C. Witt, R.E. Lundin & E.M. Bickoff, J. Agr. Food Chem., 15(3), 536 (1967).
12. T. Miyazaki & S. Mihashi, Chem. Pharm. Bull. (Tokyo), 12(10), 1232, 1236 (1964).
13. G. Buchi, D.H. Klaubert, R.C. Shank, S. Weinreb & G.N. Wagan, J. Org. Chem., 36, 1143 (1971).
14. Oesterreichische Stickstoffwerke A.G., Chem. Abstr., 66, 46215q(1967).
15. N. Kornblum and D.L. Kendall, J. Amer. Chem. Soc., 74, 5782 (1952).