Phytochemistry, 1973, Vol. 12, pp. 1737 to 1740. Pergamon Press. Printed in England.

MACULATIN: AN ISOMER OF UVEDALIN EPOXIDE FROM *POLYMNIA MACULATA*

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(*Received* 18 *January* 1973. *Accepted* 1 *Fedruary* 1973)

Key Word Index—*Polymnia maculata*; Compositae; germacranolide; maculatin; isomer of uvedalin epoxide.

Abstract—The isolation of a new germacranolide, maculatin IIc or IId, from *Polymnia maculata* Cav. is reported.

INTRODUCTION

IN A communication dealing with constituents of North American *Polymnia* species, we deduced[1] gross structures Ia and Ib for uvedalin and polydalin, two germacradienolides from *Polymnia uvedalia* (L.) L.*

Uvedalin epoxide (4,5-epoxyuvedalin) was subsequently shown[4] to be identical with enhydrin[5] from *Enhydra fluctuans* Lour.; thus a recent X-ray study of enhydrin bromohydrin (IIa)[6] permits definition of the relative stereochemistry of uvedalin epoxide as IIb and that of uvedalin and polydalin as IIIa and IIIb respectively.†

We now report isolation from *Polymnia maculata* Cav. of a new germacranolide maculatin. Direct comparison of maculatin and its derivatives with uvedalin epoxide leads to the conclusion that maculatin possesses structure IIc (i.e. is a stereoisomer of uvedalin epoxide where the isomerism resides in the stereochemistry of the 5-carbon side chain) or IId.

* Formulae Ia and Ib of Ref. 1 are redrawn to conform with the convention proposed recently by Rogers *et al.*[2] This requires renumbering of the ring carbon atoms. Since in the redrawn formulae, the lactone ring is closed to C-6, the strongly negative Cotton effect of uvedalin reported by us[1] now suggests *trans*-fusion of the γ-lactone ring if the empirical rule relating the sign of the Cotton effect to the nature of the lactone ring junction[3] were applicable to $\Delta^{1(10)}$-*cis*, Δ^{4}-*trans*- as well as to $\Delta^{1(10)}$-*trans*, Δ^{4}-*trans*- germacradienolides and the absolute configuration were as depicted. However, as epoxidation results in *reversal* of the sign of the Cotton effect (for uvedalin epoxide, λ_{max} 243 nm, $[\theta]$ +8980, for maculatin λ_{max} 242 nm, $[\theta]$ +7060) without of course altering the configuration at C-6, it is evident that application of the rule to systems of the type under discussion here is fraught with danger.

† The results of the X-ray analysis dispose of the suggestion[7] that the two ester functions of uvedalin and its epoxide should be interchanged as in IId.

[1] HERZ, W. and BHAT, S. V. (1970) *J. Org. Chem.* **35**, 2605.
[2] ROGERS, D., MOSS, G. P. and NEIDLE, S. (1972) *J.C.S. Chem. Commun.* 142.
[3] STÖCKLIN, W., WADDELL, T. G. and GEISSMAN, T. G. (1970) *Tetrahedron* **26**, 2397.
[4] JOSHI, B. S., KARMAT, V. N. and FUHRER, H., (1971) *Tetrahedron Letters* 2373.
[5] KRISNASWAMI, N. R., SESHADRI, T. R. and VEDANTAM, T. N. C. (1969) *Current Sci.* **38**, 284.
[6] KARTHA, G., GO, K. J. and JOSHI, B. S. (1972) *J.C.S. Chem. Commun.* 1327.
[7] ALI, E., GHOSH DASTIDAR, P. P., PAKRASHI, S. C., DURHAM, L. J. and DUFFIELD, A. M. (1972) *Tetrahedron* **28**, 2285.

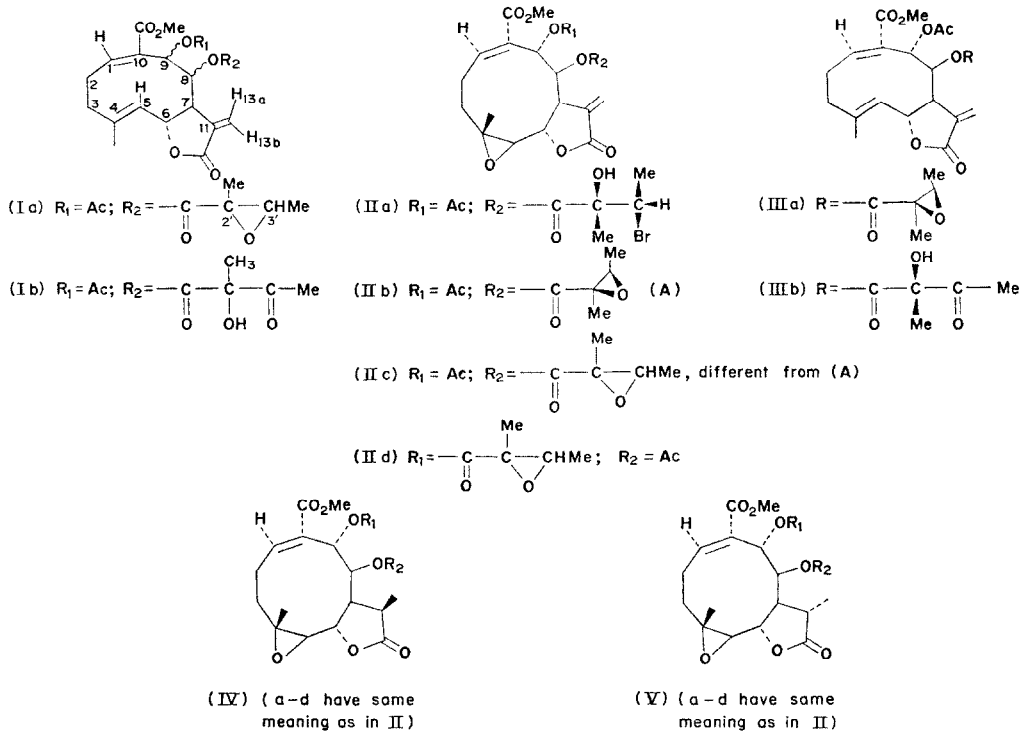

TABLE 1. NMR SPECTRA OF MACULATIN,

Compound	H-3	H-5	H-6	H-7	H-8	H-9
Enhydrin	7·15*dd*	2·69*d*	4·28*t*	3·0*m*	6·70*dd*	5·86*d*
	(10·2, 7)	(9·5)	(9·5)		(8·4, 1·4)	(8·5)
Maculatin	7·16*dd*	2·72*d*	4·28*t*	3·04*m*	6·71*dd*	5·81*d*
	(10·2, 7)	(9·5)	(9·5)		(8·4, 1·4)	(8·5)
IVb	7·12*dd*	2·57*d*	4·49*t*		6·27*dbr*	5·81*d*
	(10·2, 7)	(9·5)	(9·5)		(7·8)	(7·8)
IVc (or IVd)	7·11*dd*	2·58*d*	4·45*t*		6·29*dbr*	5·80*d*
	(10·3, 7)	(9·5)	(9·5)		(7·8)	(7·8)
Vb	7·17*dd*	2·57*d*	4·15*t*		6·30*dbr*	5·87*d*
	(10·2, 7)	(9·5)	(9·5)		(8·5)	(8·5)
Vc (or Vd)	7·16*dd*	2·58*d*	4·13*t*		6·28*dbr*	5·86*d*
	(10·2, 6·8)	(9·5)	(9·5)		(8·7)	(8·7)

* Run in $CDCl_3$ solution at 90 MHz on a Bruker HFX-10 NMR spectrometer using TMS as internal *q*—quartet, *m*—multiplet whose center is given, *br*—slightly broadened singlet. Unmarked signals are correspond to one proton unless otherwise specified; signals in last five columns correspond to three protons.

DISCUSSION

Maculatin, $C_{23}H_{28}O_{10}$, m.p. 226–8°, $[\alpha]_D^{25}$ −74·8°, had an NMR spectrum which differed only minimally from that of uvedalin epoxide (see Table 1), the chief variations being slight but reproducible shifts in the signals of H-9, H-13 and C-3′ methyl. The two compounds were indistinguishable on TLC, but exhibited different rotations and slightly different IR spectra as KBr pellets, but not in solution.*

Catalytic hydrogenation of maculatin gave a compound, m.p. 172–6°, which differed from a substance, m.p. 199°, previously obtained[4] by hydrogenation of uvedalin epoxide (enhydrin).† On the basis of model considerations (more facile adsorption on the catalyst surface from the bottom) we tentatively formulate these substances as IVb (from enhydrin) and IVC (or IVd). A second set of dihydro derivatives, probably Vb (m.p. 213–5°) and Vc (or Vd, m.p. 106–10°), was obtained by $NaBH_4$ reduction of uvedalin and subsequent epoxidation, on the one hand, and by $NaBH_4$ reduction of maculatin on the other. While the components of each pair were indistinguishable on TLC and had almost superimposable NMR spectra (Table 1), the IR spectra (KBr pellets) showed some significant differences; however the NMR spectra clearly differentiated between the two sets.

Our analysis of the NMR spectra of maculatin and its derivatives, carried out with the aid of spin decoupling in the manner previously discussed for uvedalin,[1] will not be described in detail here but leads to the same carbon skeleton and distribution of functional groups around the ring as deduced previously for uvedalin epoxide (IIb). The identity of coupling constants and near-identity of chemical shifts demonstrated in Table 1 requires that the two substances possess the same configuration and conformation in the periphery of the ring. Hence the difference between maculatin and IIb must either be due to a reversal in the

* There was no significant m.p. depression between maculatin and our sample of IIb, m.p. 218–20°. However, the latter m.p. was reached only once; generally the m.p. of uvedalin epoxide was in the range 180–4°. The m.p. of enhydrin is reported as 185–6°,[5] 185°[4] and 184°.[7]

† This substance was kindly supplied by Dr. B. S. Joshi in the course of work intended to establish the identity of enhydrin with uvedalin epoxide or maculatin.

ENHYDRIN AND RELATED COMPOUNDS*

H-13	H-3′	C-10	Me C-2′	C-3′	Co_2Me	Ac
6·32*d* (3·4) 5·83*d* (3)	3·02*q* (5·5)	1·71	1·44	1·16*d* (5·5)	3·82	2·04
6·37*d* (3·4) 5·89*d* (3)	3·04*q* (5·5)	1·74	1·46	1·24*d* (5·4)	3·83	2·08
1·16*d* (7·2)†	3·06*q* (5·6)	1·67	1·47	1·26*d* (5·2)	3·82	1·99
1·22*d* (7·5)†	3·07*q* (5·5)	1·69	1·51	1·29*d* (5·5)	3·83	1·97
1·30*d* (6·5)†	3·08*q* (5·5)	1·69	1·50	1·28*d* (5·7)	3·83	2·04
1·31*d* (7)†	3·08*q* (5·5)	1·69	1·53	1·29*d* (5·5)	3·82	2·00

standard. Values are in ppm, multiplicities are indicated by the usual symbols: *d*—doublet, *t*—triplet; singlets. Figures in parentheses are coupling constants or line separations. Figures in first eight columns

† Three protons.

attachment of the two acyl residues to C-8 and C-9, as in IId, or must reside in stereoisomerism of the five-carbon ester side chain, as in IIc. The amount of maculatin on hand was not sufficient to permit settlement of this ambiguity. However, since the H-2′, 2′-methyl and 3′-methyl signals in the maculatin and uvedalin epoxide series are not significantly different, it seems likely that the side chain in IIc and IId, like that of IIb, is derived from angelic, not tiglic acid, and that if, the structure of maculatin is IIc, the epoxy acid moiety is enantiomeric with that present in IIb.

EXPERIMENTAL

M.ps were determined in capillaries and are uncorrected. IR spectra were run as KBr pellets on a Perkin-Elmer Model 257 grating spectrometer, rotations in $CHCl_3$. Analyses were performed by Dr. F. Pascher, Bonn, Germany.

Maculatin. 4·5 kg of *Polymnia maculata* Cav., collected by Dr. E. L. Tyson 2 miles S.W. of Cerro Punta, Panama in February 1970 (Tyson No. 5943 on deposit in herbarium of Florida State University) was extracted in the usual manner.[8] The crude gum, wt 12 g, was chromatographed over 200 g of silicic acid (Mallinckrodt 100 mesh), 400 ml fractions being collected in the following order: FR. 1–10 C_6H_6, fr. 11–20 C_6H_6–$CHCl_3$ (3:1), fr. 21–30 C_6H_6–$CHCl_3$ (1:), fr. 31–40 C_6H_6–$CHCl_3$ (1:3), fr. 41–50 $CHCl_3$, fr. 51–60 $CHCl_3$–MeOH (97:3), fr. 61–70 $CHCl_3$–MeOH (19:1), 71–80 $CHCl_3$–MeOH (9:1). All fractions were monitored by TLC. Fractions 32–38 which showed one major spot were combined and allowed to crystallize. Repeated recrystallization from ethylacetate-hexane afforded 0·3 g of maculatin, m.p. 226–8°, $[\alpha]_D^{25}$ −74·8° (*C* 2·55), IR bands at 1775 (sh), 1760, 1750, 1719, 1660 and 1630 cm^{-1} (Calc. for $C_{23}H_{30}O_{10}$: C, 59·48; H, 6·08; O, 34·45. Found: C, 58·78; H, 6·12; O, 64·42%).

Reduction of maculatin. A solution of 58 mg of maculatin in 5 ml EtOAc was stirred with 20 mg 10% Pd–C catalyst in H_2 at room temp. and pressure until H_2 uptake had ceased. The solution was filtered and evaporated *in vacuo* and the residue (IVc or IVd) recrystallized repeatedly from EtOAc–hexane, yield 40 mg, m.p. 172–6° (Calc. for $C_{23}H_{30}O_{10}$: C, 59·22; H, 6·48; O, 34·30. Found: C, 58·99; H, 6·56; O, 34·08%). (b) To a solution of 52 mg maculatin in 5 ml MeOH was added 43 mg $NaBH_4$ in 4 ml MeOH at 0°. The mixture was stirred at room temp. for 1 hr and acidified with dil. HCl. The solvent was evaporated *in vacuo*, and the residue extracted with $CHCl_3$. The washed and dried extract was evaporated and the residue was recrystallized from EtOAc–hexane, yield 35 mg, m.p. 106–10° (Calc. for $C_{23}H_{30}O_{10}$: C, 59·22; H, 6·48; O, 34·30. Found: C, 58·90; H, 6·56; O, 34·32%). CD *curves.* (MeOH, 0·52 mg/ml). *Uvedalin epoxide.* $[\theta]_{281}$ −442 (min); $[\theta]_{275}$ O; θ_{243} +8980 (max); $\theta_{232.5}$ O, $[\theta]_{216}$ −85 400 (min). *Maculatin.* $[\theta]_{283}$ −294 (min); $[\theta]_{270}$ O; $[\theta]_{242}$ +7060 (max); $[\theta]_{235}$ O; $[\theta]_{215}$ −81 000 (min).

Acknowledgements—This work was supported in part by U.S. Public Health Service Research Grant CA-13121 from the National Cancer Institute and a grant from Hoffmann-La Roche, Inc.

[8]HERZ, W. and HÖGENAUER, G. (1962) *J. Org. Chem.* **27**, 905.