Tetrahedron. Vol 29, pp 2811 to 2814 Pergamon Press 1973 Printed in Great Britain

THE STRUCTURE AND STEREOCHEMISTRY OF MURRANGATIN

A NEW MONOMERIC COUMARIN FROM *MURRAYA ELONGATA*[a] ALPH. DC.

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(*Received in the UK* 19 *April* 1973; *Accepted for publication* 11 *May* 1973)

Abstract—The structure 1 for murrangatin, a new monomeric coumarin isolated from the leaves of *Murraya elongata* has been elucidated by spectroscopic and chemical evidence, and confirmed by its chemical correlation with phebalosin (7) suggesting its stereochemistry as 1 or its mirror image.

Murraya koenigii Spreng (Rutaceae) has recently proved to be a rewarding source of a number of interesting new carbazole alkaloids,[1] and *Murraya paniculata* has been found to contain coumarins.[2,3] We were thus induced to examine *Murraya elongata*[4] on which no report of any previous investigation is available for novel chemotaxonomic information. This species, indigenous to Burma, is a shrub introduced in some gardens of West Bengal. Evidence for the structure and stereochemistry of murrangatin (1), a new monomeric coumarin isolated from the leaves of this plant is now presented.

Murrangatin (1), m.p. 133°, $C_{15}H_{16}O_5$, $[\alpha]_D$-3°, showed UV absorption characteristics of a 7-alkoxycoumarin chromophore.[5] The presence of coumarin CO, intramolecular H-bonded diol and $=CH_2$ was indicated from its IR spectrum.

The PMR spectrum of 1 confirmed the presence of the 7-methoxy-8-substituted coumarin system[6] showing the characteristic coumarin doublets at 6·21 (*H*-3) and 7·60 ppm (*H*-4, $J_{3,4}$ = 10 Hz), a pair of doublets at 7·39 (*H*-5) and 6·86 ppm (*H*-6, $J_{5,6}$ = 8·5 Hz) and a sharp 3H singlet at 3·97 ppm (O*Me* at C-7, the oxygenation site of all natural coumarins). The remaining signals due to the $C_5H_9O_2$ side chain at C-8 comprise a finely split doublet at 1·75 ppm (3H, 3′-C*H*$_3$, J = 1 Hz—coupling with one vinylic proton at C-4′), a broad signal at 3·27 ppm (2H, 1′-O*H* and 2′-O*H*, disappearing on deuteration), another broad 1H signal at 5·29 ppm (sharpening in D_2O to a clear doublet, J = 8·5 Hz, *H*-1′), and a doublet at 4·54 ppm (J = 8·5 Hz, *H*-2′)—partially hidden under a broad 2H singlet at 4·61 ppm (4′-*H*'s). The side chain was thus identified as 3′-methyl-but-3′-ene-1′2′-diol, attached to C-8′ through C-1′ leading to the expression 1 for murrangatin.

The mass spectrum of 1, fully consistent with its structure, showed an extremely weak parent ion at *m/e* 276 (0·25%) due to the ready fission of the 1′-2′ bond, benzylic as well as allylic and also α— to both the oxygens, giving rise to a stable ion *a* which appeared as the base peak[7] at *m/e* 205; charge retention in the eliminated side chain formed the *m/e* 71 ion *b* of low intensity (3·5%). The other significant peaks were at *m/e* 206 (24%) due to the ion *c* formed by H transfer from the eliminated side chain to the coumarin moiety during 1′-2′ bond cleavage, *m/e* 191 (*c*—CH_3, 6%), 175 (*a*—CH_2O, 11%, m*149), and 162 (*a*—CH_3—CO, 8·4%).

The PMR and mass spectra of the diacetate (2), dihydro (3), dihydro diacetate (4) and acetonide (5) derivatives of 1 were also in excellent accord with their assigned structures. The formation of 5 supported the vicinal nature of the two OH functions. The mass fragmentation of 5, following a number of independent routes, is quite interesting and deserves special mention (Scheme 1, Cou = 7-methoxy coumarin-8-yl). The most abundant peak is attributable to the radical ion *e* at *m/e* 112, generated as shown: charge retention on the aromatic part with simultaneous intramolecular H capture or H loss gave rise to the ion *a* or *f*.

The location of a 1′,2′-dihydroxy side chain at position 8 was established by the formation of 8-formyl-7-methoxy coumarin (6) by Jones oxidation of murrangatin.

Structure 1 for murrangatin was finally confirmed by the formation of its (±) variety from an authentic sample of (±) phebalosin[8] (7). Since phebalosin was postulated to have *trans* stereochemistry (7) on the basis of vicinal coupling constant[9], $J_{1',2'}$ = 2 Hz, (−) murrangatin is predicted to have *erythro*- configuration **10** or its mirror image. However, its absolute configuration remains unsettled as yet.

Murrangatin is not an artifact arising out of phebalosin (7), since (a) 7 did not undergo hydrolysis under the condition of isolation of 1 and (b) 1 and not 7 was present in the original extract of the plant material as indicated by TLC. It is quite

[a]This work was presented at the 8th IUPAC symposium on 'The Chemistry of Natural Products', New Delhi, India, February 6–12, 1972, *Abstract*, p. 87.

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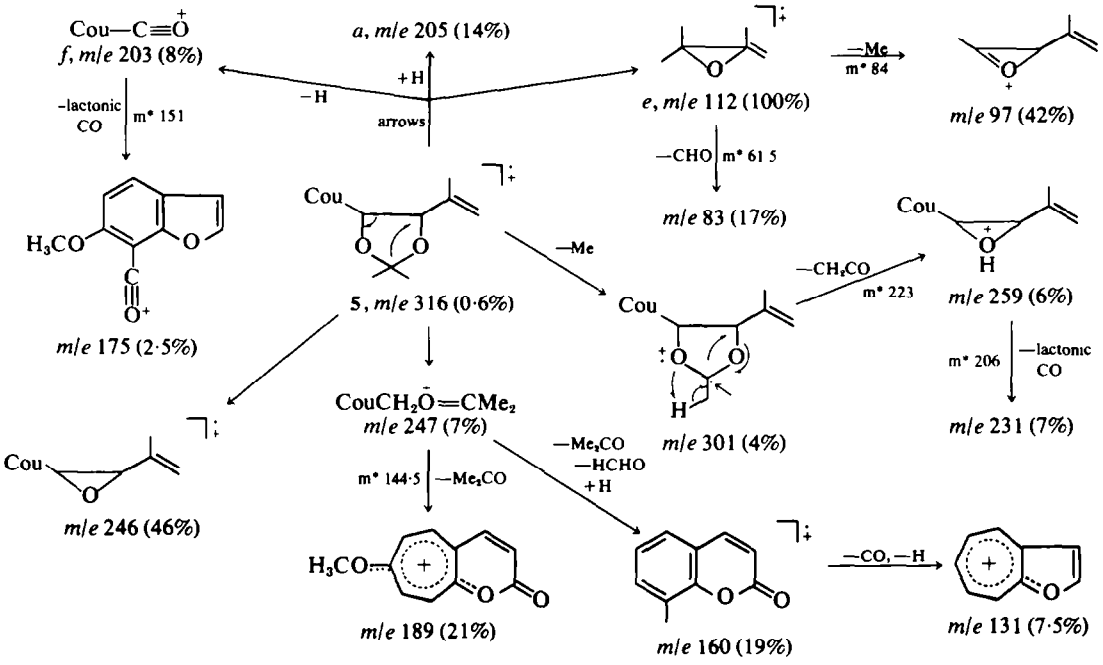
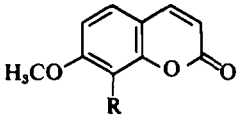
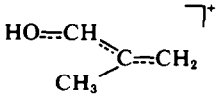


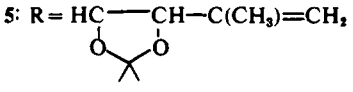
SCHEME 1. Mass fragmentation of murrangatin acetonide (**5**).



1: R = CHOH—CHOH—C(CH$_3$) = CH$_2$
2: R = CHOAc—CHOAc—C(CH$_3$) = CH$_2$
3: R = CHOH—CHOH—CH(CH$_3$)$_2$
4: R = CHOAc—CHOAc—CH(CH$_3$)$_2$

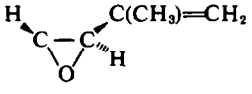


b, *m/e* 71

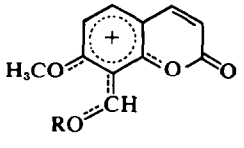


5: R = HC—CH—C(CH$_3$)=CH$_2$

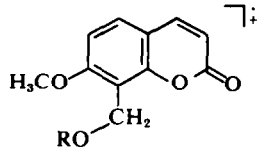
6: R = CHO



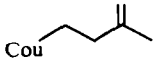
7: R =



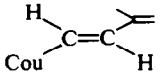
a, R = H, *m/e* 205
a', R = COCH$_3$, *m/e* 247



c, R = H, *m/e* 206
c', R = COCH$_3$, *m/e* 248



8
Cou = 7-methoxy coumarin-8-yl



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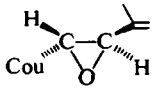
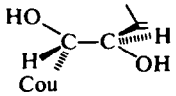


7



Erythro-(1'S, 2'R)
10

probable that 1 is formed in the plant cell from its immediate precursor 7, the latter being biosynthesised from 8-isopentenyl umbelliferone methyl ether (8), presumably via its *trans*-1′,2′-dehydro derivative (9), through preferential epoxidation. However, this speculative biogenetic sequence demands feeding experiments for its confirmation. The side chain in murrangatin is unique and seems not to have been incorporated by any other natural product; moreover, such oxygenation at both 1′ (benzylic) and 2′ positions is also rarely encountered in coumarins.

EXPERIMENTAL

All m.ps were determined in open capillaries in a H_2SO_4 bath and are uncorrected. IR spectra were taken as KBr pellets with a Perkin Elmer Infra-cord (Model 137) instrument. $[\alpha]_D$ Values were taken in $CHCl_3$ by Mr. P. Mazumdar of IIEM, Calcutta-32 in a Hilger-Watts M-511 Microptic photoelectric polarimeter and UV spectra are for solns in 95% EtOH, measured in a Beckman Spectrophotometer, Model DK 2. PMR spectra were determined in $CDCl_3$ with a Varian A-60D spectrometer. Mass spectra were recorded in AEI MS9 spectrometer operating at 70 e.V. using the direct insertion probe. Petrol refers to light petroleum, b.p. 60–80°. Silica gel (100–200 mesh) of M/s Gouri Chemicals, Calcutta was used for column chromatography. The analytical samples were routinely dried at 80° over P_2O_5 for 24 hr in *vacuo*.

Isolation of murrangatin (1). Dried and powdered leaves (700 g) were exhaustively extracted in a Soxhlet apparatus for 40 hr successively with petrol and $CHCl_3$. The residues of the extracts were dissolved in C_6H_6 and chromatographed. The fractions eluted with C_6H_6—$CHCl_3$ (1:1) and $CHCl_3$ furnished residues which on repeated chromatography yielded pure murrangatin (yield 0·05% and 0·07% from petrol and $CHCl_3$ extracts respectively) crystallising from Et_2O—$CHCl_3$ mixture as needles, m.p. 133°, $[\alpha]_D$ −3° (*c* 0·49), R_f 0·52 (silica gel; $CHCl_3$—MeOH 93:7); intense blue-violet fluorescence under UV; λ_{max} 317 nm (log ε, 4·13), 258 (3·51), 254 (3·50), 248 (3·52); λ_{min} 266 (3·31), 256 (3·49), 252 (3·48)—unaffected by alkali; ν_{max} 1713 (coumarin CO), 1603 (aromatic), 1565 (α-pyrone double bond), 3490 (intramolecular H-bonded diol), 1265 and 1123 (*sec*—OH) and 910 cm^{-1} (=CH_2); M^+ 276. (Found: C, 65·03; H, 5·80. $C_{15}H_{16}O_5$ requires; C, 65·21; H, 5·84%).

Murrangatin diacetate (2). A mixture of 1 (40 mg), Ac_2O (10 drops) and fused NaOAc (8 mg) was kept at room temp overnight. Working up in the usual way furnished 2 crystallising from Et_2O as shining needles (38 mg), m.p. 124°, $[\alpha]_D$ +3·3° (*c* 1·53); ν_{max} 1725 (coumarin CO), 1603 (aromatic), 1575 (α-pyrone double bond), 910 (=CH_2) cm^{-1}; PMR signals at 6·24 (1H, *d*, *J* = 10 Hz, *H*-3), 7·57 (1H, *d*, *J* = 10 Hz, *H*-4), 7·40 (1H, *d*, *J* = 9 Hz, *H*-5), 6·83 (1H, *d*, *J* = 9 Hz, *H*-6), 3·97 (3H, *s*, 7-OCH_3), 6·69 (1H, *d*, *J* = 9 Hz, *H*-1′), 6·09 (1H, *d*, *J* = 9 Hz, *H*-2′), 2·03 and 2·06 (3H, *s*, each, 1′-OCOCH_3 and 2′-OCOCH_3), 1·65 (3H, *t*, *J* = 1 Hz, 3′-CH_3), and 4·74 and 4·93 ppm (1H, *m*, each, 4′-H_2). In the mass spectrum major peaks were recorded at *m/e* 360 (0·1, M^+), 301 (0·8, M^+−OAc, 300 (4·2, M^+−AcOH), 258 (4·4, 300-CH_2CO, m*222), 248 (3·4, *c*′, M^+−$C_6H_9O_2$+H), 247 (7·3, *a*′, M^+—$C_6H_9O_2$), 206 (15·7, *c*, *c*′−CH_2CO), 205 (100, *a*, *a*′−CH_2CO, m* 170), 190 (3, *a*−Me), 175 (3·5, *a*−CH_2O, m* 149), 162 (3%, 190−CO). (Found: C, 63·20; H, 5·57. $C_{19}H_{20}O_7$ requires C, 63·33; H, 5·59%).

Dihydromurrangatin (3). A solution of 1 (80 mg) in aldehyde free 95% EtOH (15 ml) was magnetically stirred for 2 hr in presence of 10% Pd-C (20 mg) in H_2 at little over 1 atmosphere. The H_2 uptake corresponded to one mole equiv per mole of 1. Removal of the catalyst by filtration and evaporation of the solvent under reduced pressure yielded on oily residue. The latter furnished 3 crystallising from Et_2O as light needles (36 mg), m.p. 107°; ν_{max} 3450 (OH), 1725 (coumarin CO), 1603 (aromatic), 1573 (α-pyrone double bond), 1260 and 1120 (*sec* OH), no band for =CH_2; PMR signals at 6·24 (1H, *d*, J = 10 Hz, *H*-3), 7·62 (1H, *d*, J = 10 Hz, *H*-4), 7·40 (1H, *d*, J = 9 Hz, *H*-5), 6·88 (1H, *d*, J = 9 Hz, *H*-6), 3·95 (3H, *s*, 7-OCH_3), and 5·28 and 3·87 ppm (1H, *b*, each, *H*-1′ and *H*-2′ resolving on D_2O exchange to *d* and *dd* respectively, $J_{1',2'}$ = 8 Hz and $J_{2',3'}$ = 4 Hz), 2·82 (2H, *b*, 1′-O*H* and 2′-O*H*, disappeared on deuteration), 1·45 (1H, *m*, *H*-3′) and 0·97 (6H, *d*, J = 6 Hz, 3′-(CH_3)$_2$). Mass spectrum: major peaks at *m/e* 278 (1·6, M^+), 261 (2·9, M^+—OH), 260 (2·0, M^+—H_2O), 245 (4·5, M^+—H_2O—Me), 218 (19·6, M^+—OH—$CHMe_2$), 217 (43·3, M^+—H_2O—Me—CO), 206 (80·4, *c*, M^+—C_4H_9O+H), 205 (100, *a*, M^+—C_4H_9O), 191 (97·1, *c*−Me), 189 (64·1, *c*−OH), 178 (70·6, *c*−CO), 175 (70·8, *a*−CH_2O), 163 (54·3, *c*−Me—CO), 162 (62·5, *a*−Me—CO), 161 (56·7%, 189−CO). (Found: C, 64·58; H, 6·58. $C_{15}H_{18}O_5$ requires C, 64·74; H, 6·52%).

Dihydromurrangatin diacetate (4). A mixture of 3 (20 mg), Ac_2O (6 drops) and fused NaOAc (5 mg) was kept overnight at room temp and worked up in the usual way to afford 4 crystallising from petrol-Et_2O mixture as light needles (18 mg), m.p. 142°, $[\alpha]_D$ −2·7° (*c* 1·5); ν_{max} 1740 (coumarin CO), 1605 (aromatic) and 1575 cm^{-1} (α-pyrone double bond), OH band absent; PMR signals at 6·25 (1H, *d*, J = 10 Hz, *H*-3), 7·58 (1H, *d*, J = 10 Hz, *H*-4), 7·41 (1H, *d*, J = 9 Hz, *H*-5), 6·85 (1H, *d*, J = 9 Hz, *H*-6), 3·98 (3H, *s*, 7-OCH_3), 6·54 (1H, *d*, J = 6·5 Hz, *H*-1′) 5·64 (1H, *dd*, J = 5 Hz and 6·5 Hz, *H*-2′), 1·99 and 2·05 (3H, *s*, each, 1′-OCOCH_3 and 2′-OCOCH_3), 1·72 (1H, *b*, H-3′) and 0·93 ppm (6H, *d*, J = 6 Hz, 3′-(CH_3)$_2$). Mass spectrum: major peaks at *m/e* 362 (93, M^+), 302 (6·4, M^+—AcOH), 290 (84·1, M^+—CH_2CO—CH_2O), 260 (47·8, M^+—AcOH—CH_2CO), 248 (8·3, *c*′, M^+—$C_6H_{11}O_2$+H), 247 (89·8, *a*′, M^+—$C_6H_{11}O_2$), 206 (79·6, *c*, *c*′−CH_2CO), 205 (100, *a*, *a*′−CH_2CO), 191 (45·2, *c*−Me), 190 (51, *a*−Me), 189 (73·9, *c*−OH), 177 (29·3, *a*−CO), 175 (70·7, *a*−CH_2CO), 162 (70·6%, *a*−CO—Me). (Found: C, 63·01; H, 6·11, $C_{19}H_{22}O_7$ requires C, 62·98; H, 6·12%).

Murrangatin acetonide (5). A mixture of 1 (62 mg) and 5 ml of dry Me_2CO (made 0·1 N with conc H_2SO_4) was stirred magnetically for 6 hr at room temp. The mixture on working up in the usual way furnished the corresponding acetonide (5) crystallising from petrol-Et_2O mixture as needles (60 mg), m.p. 137°, $[\alpha]_D$ +2·4° (*c* 1·25); ν_{max} 1725 (coumarin CO), 1603 (aromatic), 1575 (α-pyrone double bond) and 895 (=CH_2) cm^{-1}; PMR signals at 6·24 (1H, *d*, J = 10 Hz, *H*-3), 7·59 (1H, *d*, J = 10 Hz, *H*-4), 7·40 (1H, *d*, J = 9 Hz, *H*-5), 6·86 (1H, *d*, J = 9 Hz, *H*-6), 3·95 (3H, *s*, 7-OCH_3), 5·56 (1H, *d*, J = 9 Hz, *H*-1′), 5·01 (1H, *d*, J = 9 Hz, *H*-2′), 4·87 and 4·96 (1H, *m*, each, 4′-H_2), 1·54 (3H, *s*, 3′-CH_3), and 1·71 and 1·76 ppm (3H, *s*, each, C(CH_3)$_2$ of acetonide moiety). (Found: C, 68·17; H, 6·35. $C_{18}H_{20}O_5$ requires C, 68·34; H, 6·37%).

Jones oxidation of 1 *to* 6. To a soln of 1 (30 mg) in 2 ml Me_2CO at 0° a soln of CrO_3 (30 mg) in 2 ml 14 N H_2SO_4

was added dropwise till a permanent yellow colour persisted. The mixture upon usual work up furnished a gummy residue which on chromatography yielded the oxidation product 6, crystallising from alcohol (8 mg), m.p. 210° (lit.[8] 213°). Mass spectrum: major peaks at *m/e* 204 (100, M^+), 176 (30·8, M^+—CO), 175 (12·8, M^+—CHO), 161 (7·0, M^+—CO—Me), 147 (16·3%, M^+—CO—CHO).

Conversion of (±) *phebalosin* (7) *to* (±) *murrangatin* (1). A soln of 7 (25 mg) in dioxan (5 ml) was kept overnight with 1·5 N HCl (5 ml). Usual work up afforded (±) murrangatin, crystallising from Et_2O-$CHCl_3$ mixture as needles (20 mg), m.p. 132°, $[\alpha]_D = 0°$, identified with natural murrangatin by m.p., mixed m.p., TLC and spectral properties.

Acknowledgements—Sincere thanks are accorded to Dr. B. C. Das (CNRS, France), Dr. S. C. Pakrashi (IIEM, Calcutta), Dr. R. S. Kapil (CDRI, Lucknow), Dr. A. Chakraborty IIT, Kanpur) for spectral measurements and to Professor P. R. Jefferies (Australia) for the generous gift of an authentic sample of (±) phebalosin. Financial assistance from CSIR (India) by way of a Research Fellowship to one of us (L.N.D.) is gratefully acknowledged.

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