SYNTHETIC APPROACHES TOWARDS BICOUMARINS

SYNTHESIS OF EUPHORBETIN AND ISOEUPHORBETIN

P. K. Dutta, P. C. Majumder and N. L. Dutta*
Indian Institute of Experimental Medicine, Calcutta-32, India

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The isolation of euphorbetin **1a** and isoeuphorbetin **2a**, the novel bicoumarins from the seeds of *Euphorbia lathyris*, and their structure elucidation, have been reported previously.[1,2] Attempted synthesis of this class of compounds via different routes is reported in this communication.

Owing to the ready availability of esculetin **3a** from *E. lathyris* (yield 0·1%), it was decided to exploit this as the starting material. Bicoumarins have been earlier synthesised[3,4] from coumarins by halogenation followed by Ullmann reaction. However the usual halogenating agents would attack esculetin **3a** at C_8 in preference to C_5. Although this approach is expected to lead to the hitherto-unreported 8,8′-bicoumarinyl derivative rather than the naturally occurring 5,5′- or 5,8′-dimers we followed this route since the product would be of interest for comparison purposes.

Esculetin dimethyl ether **3a**, prepared from esculetin with dimethyl sulphate and K_2CO_3 in acetone, was subjected to electrophilic chlorination with SO_2Cl_2 in tetrachloroethane in the presence of charcoal.[5] The product, m.p. 224–25°, showing IR absorption at 1725 cm^{-1} (coumarinyl lactone) was assigned the formula $C_{11}H_8O_4Cl_2$ on the basis of elementary analysis. From the known behaviour of coumarins towards electrophilic reagents this was expected to be 3,8-dichloro derivative **3c**. The NMR spectrum, which showed two one-proton singlets at δ 8·13 and δ 6·85 ppm, ascribed to the 4-H and 5-H respectively, and two three-proton singlets at δ 3·98 and 3·92 ppm, ascribed to aromatic methoxy groups, is in agreement with this structure.

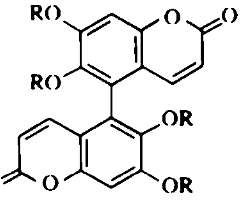
The dichloro derivative **3c** was thereafter subjected to Ullmann reaction by refluxing with activated copper bronze in DMF.[6] It remained unchanged at the end of 8 h reflux although two sites of dimerisation were available in the system. Failure of Ullmann reaction with some 3-chlorocoumarins has been reported by other workers.[7]

As a modification of the above procedure the 3,4-double bond of esculetin dimethyl ether was first hydrogenated to avoid halogenation at C_3. The dihydro-derivative **3d**, m.p. 88–90°, ν_{max}^{Nujol} 1770 cm^{-1} (dihydrocoumarinyl lactone[8]), was then brominated to obtain the 8-bromo derivative **3e**, m.p. 124°. Ullmann reaction of this compound was expected to form the tetrahydro 8,8′-dimer which could then be dehydrogenated using reagents such as DDQ. However, it also remained unaffected under the conditions of the Ullmann reaction.

Oxidative coupling of phenols in presence of potassium ferricyanide to produce biphenyl derivatives as used in the synthesis of a dimeric alkaloid[9] from corypalline was then resorted to and the syntheses of the natural bicoumarins (**1b** and **2b**) were finally achieved by this route. Thus an alkaline solution of esculetin **3a** was treated with potassium ferricyanide in an atmosphere of nitrogen. The reaction product after acidification and subsequent conversion to the methyl ether followed by chromatography yielded at least five distinct components (compounds A–E) besides unchanged esculetin dimethyl ether **1b**.

Compound A, m.p. 230–32°, was found to be identical (m.m.p., NMR and IR spectra) with euphorbetin tetramethyl ether **1b**.

Compound B, crystallised from methanol in needles, m.p. 199–200°, could be characterised as isoeuphorbetin tetramethyl ether **2b**. The identity was again confirmed by m.m.p., IR and NMR spectra.



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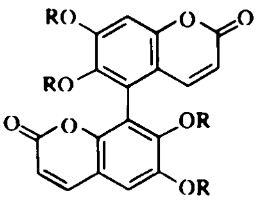

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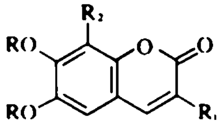
a: R = H
b: R = CH_3



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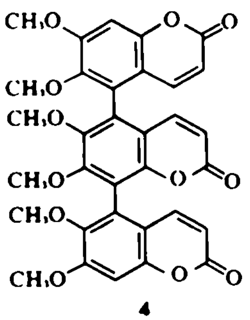
a: R = R_1 = R_2 = H
b: R = CH_3, R_1 = R_2 = H
c: R = CH_3, R_1 = R_2 = Cl
d: 3,4-dihydro, R = CH_3, R_1 = R_2 = H
e: 3,4-dihydro, R = CH_3, R_1 = H, R_2 = Br



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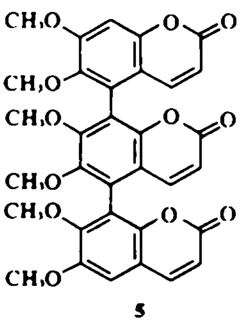

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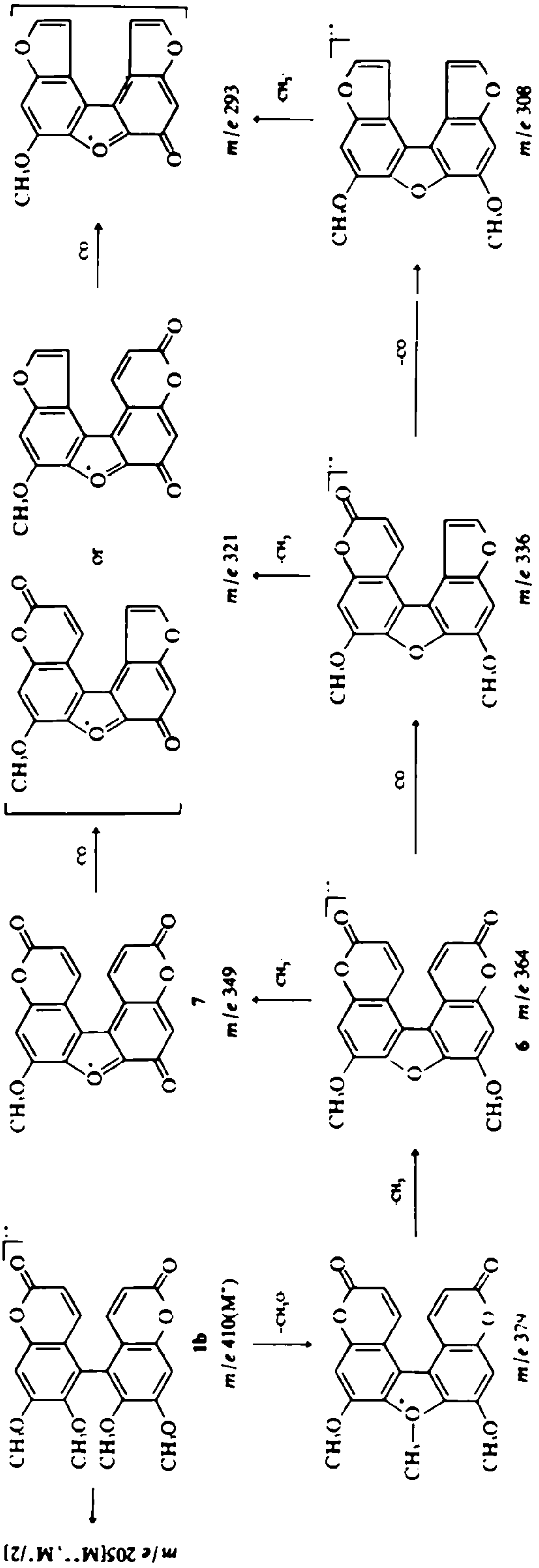


Fig. 1. Proposed mass spectral fragmentation of euphorbetin tetramethylether 1b.

Compound C, $C_{33}H_{26}O_{12}$ (M^+ 614), m.p. > 300° showed the characteristic band for coumarinyl lactone (1725 cm^{-1}) in its IR spectrum. Its ultraviolet spectrum showed maxima at 224 (log ϵ 4·76), 298 (log ϵ 4·36) and 332 (log ϵ 4·45) nm. The molecular formula and spectral similarity with **1b**, **2b** and **3b** indicated it to be a trimer of **3b**. The NMR spectrum showed signals for six methoxyl groups at δ 3·7 (6H, s), 3·75 (6H, s) and 4·07 (6H, s). The peaks at δ 6·26 (2H, d, J = 10 Hz) and 6·3 (1H, d, J = 10 Hz) could be ascribed to the three C_3-protons of the coumarinyl system. A multiplet integrating for five protons was observed between δ 7·07–7·23 ppm. The doublet nature of all the signals for C_3-protons ruled out any trimeric structure involving the 3 or 4 positions of the coumarin ring. Again since the chemical shift of the C_4-proton of esculetin dimethyl ether is δ 7·6 ppm, the absence of any signal in this region in the spectrum of compound C clearly indicated shielding of all the C_4-protons by adjacent aromatic rings as observed[1] with **1b**. This left only one possible structure **4** for the trimer. The shielding of four methoxyl groups (signals at δ 3·7 and δ 3·75) is readily explained by the proposed structure, which is also consistent with the fragmentation pattern (*vide infra*).

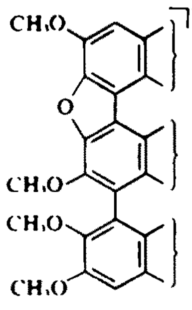
Compound D, $C_{44}H_{34}O_{16}$ (M^+ 818), m.p. > 300° and compound E, $C_{33}H_{26}O_{12}$ (M^+ 614), m.p. 230° appear to be a tetramer and a trimer of **3b** respectively on the basis of spectral similarity (UV, IR). Although obtained in amounts insufficient for full characterisation, a tentative structure **5** could still be proposed for compound E on the grounds that (i) its mass fragmentation pattern is similar to that of **4**; (ii) none of the products isolated from the reaction mixture (**1b**, **2b** and **4**) contain the 8 : 8′-linkage.

Surprisingly the 8,8′- or 3,3′-dimer[10] or a biphenyl ether-type product[9] were not encountered although their formation would be anticipated in view of the results obtained with ferricyanide oxidation on similar systems.

Compounds **1b**, **2b**, **4** and **5** showed in their mass spectra a characteristic fragmentation pattern which deserves comment. The spectrum of **1b** did not follow the usual fragmentation pattern of coumarins (cf. esculetin dimethyl ether[11]). Thus initial elimination of a OCH_3 group from the molecular ion is much more facile compared to that of CH_3; *m/e* 379 (50%), *m/e* 395 (7%). Again loss of 28 mass units (CO) from the molecular ion is not observed. A very prominent peak is observed at *m/e* 364, possibly formed by successive loss of 31 (OCH_3) and 15(CH_3) mass units from the molecular ion to produce the ion **6**. Formation of such species **6** has been suggested in biflavonoid systems.[12] Further loss of a methyl radical leads to the ion at *m/e* 349 which presumably has an orthoquinonoid type of structure **7** (cf. cularine alkaloids[13]). Successive loss of 28 mass units (CO) is supposed to form the peaks at *m/e* 336 and 308 from **6** (*m/e* 364) and at *m/e* 321 and 293 from **7** (*m/e* 349). The peak at *m/e* 205 might be due to doubly charged (M^{++}) molecular ion as found for symmetric molecules[14,15] or due to $M^+/2$ formed by rupture of the biphenyl bond and is more prominent in the symmetrical dimer **1b** as compared to the unsymmetrical one **2b**. The mass fragmentation scheme is shown in figure 1.

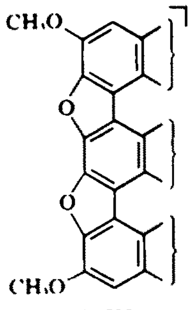
The mass spectrum of isoeuphorbetin tetramethyl ether **2b** is comparable to that of the symmetrical dimer **1b** in peak positions though the relative intensities of the fragments are mostly reduced in the former case.

The mass fragmentation of the trimers (**4** and **5**) follows the above pattern to give prominent peaks at *m/e* 568 **8** and *m/e* 522 **9**. Peaks at *m/e* 540, 494, 466 and 438 can be accounted for as before by assuming successive loss of 28 (CO) mass units from **8** and **9**. This pattern is thus in agreement with the proposed structures for the trimers.



m/e 568

8



m/e 522

9

EXPERIMENTAL

All m.ps were recorded in open capillaries and are uncorrected. IR and UV spectra were recorded in Perkin-Elmer Infracord (137) and Hilger-Watts Uvispek (007) spectrophotometer respectively. The mass spectra were recorded in Hitachi (RMU-6L) instrument at 80 eV with an ionising current of 80 μa using a direct inlet system. The NMR spectra were recorded on a 60 MHz Varian Instrument (A-60 or T-60) in $CDCl_3$ and the chemical shifts are expressed in ppm from TMS as internal standard.

Esculetin dimethyl ether **3b**

To a solution of esculetin **3a** (2·00 g) in dry acetone (100 ml) anhydrous K_2CO_3 (10 g) and dimethyl sulphate (10 ml) were added. The mixture was refluxed for 15 h and the hot acetone solution filtered. The residue after removal of solvent was crystallised from methanol to furnish needles of **3b** (1·7 g), m.p. 144–6°; UV: λ_{max}^{EtOH} (log ϵ), 230 (4·3), 295 (3·8) and 342 (4·1) nm; IR: ν_{max}^{Nujol} 1725 and 1620 cm^{-1} (α-pyrone); NMR: δ 3·92 (3H, 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). (Found: C, 63·96; H, 4·95, Calc. for $C_{11}H_{10}O_4$: C, 64·08; H, 4·89%).

3,8-dichloro-6,7-dimethoxy coumarin **3c**

To a solution of **3b** (500 mg) in dry sym-tetrachloroethane (30 ml) containing a catalytic amount of charcoal (10 mg) was added dropwise sulphuryl chloride (3·4 g, 0·06 mole) during 15 min. The mixture was then refluxed for 3 hr, cooled and the catalyst filtered off. The filtrate was distilled under vacuum to furnish a solid which crystallised from methanol in needles (400 mg), m.p. 224–25°; IR: ν_{max}^{Nujol} 1725, 1600 cm^{-1}; NMR: δ 3·88 (3H, s, 6-OCH_3) (3H, s, 7-OCH_3), 6·92 (1H, s, 5-H), 8·13 (1H, s, 4-H). (Found: C, 48·29; H, 2·98; $C_{11}H_8O_4Cl_2$ requires: C, 48·18, H, 2·92%).

Attempted Ullmann condensation of **3c**

3c (350 mg) and dry dimethyl formamide (30 ml) were placed in a three necked flask equipped with a reflux condenser and a stirrer. The solution was heated to reflux and then 2 g of activated copper bronze was added in one portion. Refluxing was continued for 4 hr after which another 2 g of copper bronze was added; refluxing was continued for another 4 hr. The reaction mixture was cooled, poured into a large volume of water and extracted with ether. The ethereal solution was washed thoroughly with water and dried (Na_2SO_4). The residue on removal of solvent was crystallised from ethanol to afford unchanged **3c**.

3,4-Dihydro-6,7-dimethoxy coumarin **3d**

A solution of **3b** (1·0 g) in 95% ethanol (100 ml) was hydrogenated over Pd/C (200 mg, 10%) at room temperature and atmospheric pressure. The catalyst was filtered off and the solvent evaporated. The residue obtained was taken up in ether washed thoroughly with water and dried (Na_2SO_4). Removal of solvent followed by crystallisation from methanol yielded needles of **3d**

(600 mg), m.p. 88–90°; IR: ν_{max}^{Nujol} 1770, 1600 cm^{-1}. (Found: C, 63·32; H, 5·88. Calc. for $C_{11}H_{12}O_4$: C, 63·45; H, 5·81%).

8-Bromo-3,4-dihydro-6,7-dimethoxy coumarin 3e

To a solution of 3d (500 mg) in glacial acetic acid (10 ml) containing a small amount of iron powder (catalyst) a 10% solution of bromine in the same solvent (3 ml) was added during 15 min with stirring. The mixture was then heated over water bath for 3 hr. The reaction mixture was diluted with a large volume of cold water and extracted with ether. The ethereal solution was washed repeatedly with cold water and dried (Na_2SO_4). Removal of solvent followed by crystallisation from methanol afforded 3e (200 mg), m.p. 124°, IR: ν_{max}^{Nujol} 1770 cm^{-1}. (Found: C, 45·74; H, 3·89. $C_{11}H_{11}O_4Br$ requires: C, 45·83; H, 3·82%).

Attempted Ullmann condensation of 3e

The above bromocompound (150 mg) was refluxed in dimethyl formamide (20 ml) with activated copper bronze (2 g) as before. After usual work up the product obtained was found to be *unchanged starting material.*

Ferricyanide oxidation of 3a *and methylation of the product*

Esculetin 3a (2 g) was added to an aqueous soln of KOH (2 g in 50 ml) in an atmosphere of N_2 at 0° and a soln of $K_3[Fe(CN)_6]$ (3·5 g in 100 ml water) was then slowly added with stirring to the alkaline soln over a period of 30 min. Stirring was continued for 1 hr at room temp. and for a further 15 min over a steam-bath. The soln was neutralised with 5N HCl, cooled and filtered. The residue was washed thoroughly with water, dried and methylated as before with dimethyl sulphate (10 ml) and anhydrous K_2CO_3 (10 g) in dry acetone (100 ml) for 20 hr. The residue obtained after usual work up was chromatographed over silica gel (60 g). Benzene eluates on crystallisation from methanol afforded needles of 3b (300 mg), m.p. 142°.

Benzene chloroform (9:1) eluate on crystallisation from methanol afforded needles of euphorbetin tetramethyl ether **1b** (500 mg), m.p. 232–34°, UV: λ_{max}^{EtOH} (log ϵ) 223 (4·55), 300 (4·19), 337 (4·35) nm; IR: ν_{max}^{Nujol} 1725, 1600 cm^{-1}; NMR: δ 3·65 (6H, s, 6 & 6-OCH$_3$), 4·05 (6H, s, 7 & 7′-OCH$_3$), 6·17 (2H, d, J = 10 Hz, 3 & 3′-H), 7·03 (2H, s, 8 & 8′-H), 7·12 (2H, d, J = 10 Hz, 4 & 4′-H); MS: *m/e* (rel. intensity) 410 (M^+, 100), 395 (7), 379 (50), 364 (82), 349 (13), 336 (31), 321 (16), 308 (14), 293 (21), 205 (35). (Found: C, 64·31; H, 4·48. $C_{22}H_{18}O_8$ requires: C, 64·39; H, 4·42%).

Benzene:chloroform (85:15) eluate yielded a solid which on crystallisation from methanol afforded needles of isoeuphorbetin tetramethyl ether **2b** (100 mg), m.p. 200–202°, UV: λ_{max}^{EtOH} (log ϵ) 222 (4·60), 294 (4·19), 336 (4.34) nm; IR: ν_{max}^{Nujol} 1725, 1715, 1600, 1580 cm^{-1}; NMR: δ 3·68 (6H, s, 6 & 7′-OCH$_3$), 3·97 (6H, s, 7&6′-OCH$_3$), 6·12 (1H, d, J = 10 Hz) and 6·32 (1H, d, J = 10 Hz), 3 & 3′-H, 6·9 (1H, s, 8-H), 7·05 (1H, s, 5′-H), 7·08 (1H, d, J = 10 Hz, 4-H), 7·7 (1H, d, J = 10 Hz, 4′-H); MS: *m/e* (rel. intensity) 410 (M^+, 100), 395 (20), 379 (34), 364 (64), 349 (8), 336 (36), 321 (25), 308 (7), 293 (18), 205 (22). (Found: C, 64·17; H, 4·47. $C_{22}H_{18}O_8$ requires: C, 84·39; H, 4·42%).

Benzene:chloroform (65:35) eluate on crystallisation from ethanol afforded needles of 4 (100 mg), m.p. > 300°; UV: λ_{max}^{EtOH} (log ϵ) 224 (4·76), 298 (4.36) and 332 (4·45) nm; IR: ν_{max}^{Nujol} 1725, 1600 cm^{-1}, NMR: δ 3·7 (6H, s); 3·75 (6H, s); 4·07 (6H, s); 6·26 (2H, d, J = 10 Hz); 6·3 (1H, d, J = 10 Hz); 7·07–7·23 (5H, m); MS: *m/e* (rel. intensity), 614 (M^+, 100), 599 (5), 583 (21), 568 (33), 555 (4), 553 (4), 540 (5), 537 (8), 525 (5), 522 (5), 509 (5), 494 (6), 466 (4), 438 (3), 307 (M^{++}, 15), 299·5 (doubly charged ion from 599·6). (Found: C, 64·38; H, 4·35. $C_{33}H_{26}O_{12}$ requires: C, 64·49; H, 4·26%).

Benzene:Chloroform (1:1) eluates, an intimate mixture of two compounds (D and E) were further separated by preparative TLC over silica gel (plate thickness: 0·6 mm; solvent: ethyl acetate-benzene 7:3).

Compound D, crystallised from methanol (20 mg), m.p. > 300°; UV: λ_{max}^{EtOH} (log ϵ) 223 (4·92), 298 (4·55) and 328 (4·58) nm; IR: ν_{max}^{Nujol} 1725, 1600 cm^{-1}; MS: *m/e* (rel. intensity) 818 (M^+, 100), 803 (2), 787 (21), 772 (7), 757 (3), 741 (2), 726 (2), 711 (1), 695 (1), 680 (1), 488 (2). (Found: C, 64·39; H, 4·25. $C_{44}H_{34}O_{16}$ requires: C, 64·54; H, 4·19%).

Compound E 5 crystallised from methanol (10 mg), m.p. 230°; UV: λ_{max}^{EtOH} (log ϵ) 221 (4·69), 297 (4.31) and 335 (4·35) nm; IR: ν_{max}^{Nujol} 1725, 1600 cm^{-1}; MS: *m/e* (rel. intensity) 614 (M^+, 100), 599 (3), 583 (24), 568 (15), 555 (3), 553 (4), 540 (3), 537 (2), 525 (2), 522 (4), 509 (2), 494 (4), 466 (23), 438 (2). (Found: C, 64·31; H, 4·39. $C_{33}H_{26}O_{12}$ requires: C, 64·49; H, 4·26%).

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