Structures of Two Dimers Formed from Lomatin(9,10-Dihydro-9-hydroxy-8,8-dimethyl-8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-2-one) †

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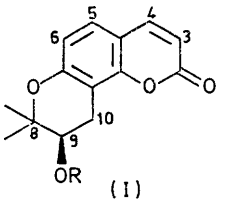
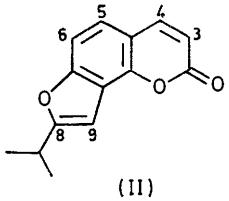
Treatment of lomatin (Ia) with toluene-*p*-sulphonic acid in xylene gives, along with dihydro-oroselone (II), two minor epimeric dimers, identified on the basis of spectral evidence, in which one of the benzodipyran units has rearranged. A nearly quantitative yield of dihydro-oroselone(II) was obtained from lomatin(Ia) by treatment with perchloric acid. Esters of lomatin (Ib and c) also yielded dihydro-oroselone (II), but the dehydration product seselin (IV) did not undergo this reaction. Mechanisms are discussed.

LOMATIN (9,10-dihydro-9-hydroxy-8,8-dimethyl-8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-2-one) (Ia) [1-3] has been shown to possess the 9*R*-configuration.[4] Several naturally occurring, physiologically active khellactone diesters have been synthesised from lomatin (Ia) in our laboratory.[2,5] In the light of results of experiments on coumarin dimers,[6] we have now studied the effect of acidic reagents on lomatin. With toluene-*p*-sulphonic acid in xylene it gave dihydro-oroselone (II) as the major product, along with two minor components. The formation of dihydro-oroselone (II) from (Ia) with acidic reagents has been observed earlier.[1] The two minor products, A and B, were characterised, on the basis of i.r., u.v., n.m.r., and mass spectra, as C-8 epimers, of the dimeric structure (III).



(I)

a; R = H
b; R = Ac
c; R = CO·CMe:CHMe



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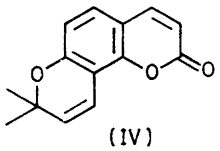
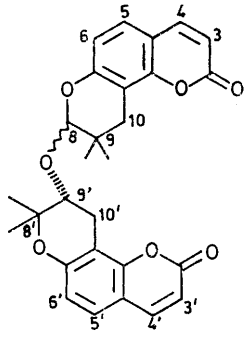


(IV)



(III)

The presence of coumarin function in compound A was revealed by i.r. absorptions at 1 725, 1 605, 1 565, and 835 cm^{-1}. The u.v. absorption [$\lambda_{max.}$ 214, 246, 256, and 327 nm (log ε 4.50, 3.85, 3.81, and 4.46)] indicated the absence of additional conjugation with the coumarin function. In the n.m.r. spectrum (see Figure) the pair of doublets (*J* 9.5 Hz) at τ 3.75 (2 H) and 2.35 (2 H) is assignable to protons at C-3, C-3', C-4, and C-4', respectively. The doublet (*J* 8.5 Hz) at τ 2.74 (2 H) is due to the C-5 and C-5' protons, and the corresponding coupled C-6 and C-6' protons exhibited two doublets (*J* 8.5 Hz) at τ 3.22 (1 H) and 3.28 (1 H). Singlets at τ 8.92 (6 H), 8.97 (3 H), and 9.03 (3 H) are assignable to four methyl groups at C-9 and C-8'. The singlet at τ 7.27 (2 H) can be assigned to two benzylic protons at C-10. The singlet at τ 5.03 (1 H) is assigned to the C-8 proton; its chemical shift is as expected [7] for O·CH·O. The two benzylic protons at C-10' and the adjacent C-9' tertiary proton (ABX system) exhibited three double doublets centred at τ 7.18 (1 H, *J* 17.0 and 7.5 Hz), 6.67 (1 H, *J* 17.0 and 5.5 Hz), and 5.93 (1 H, *J* 7.5 and 5.5 Hz).

Like compound A, compound B displayed absorption spectra typical of the coumarin system lacking additional conjugation. Its n.m.r. spectrum (see Figure) was in accord with the structure (III).

Hydrolysis of the compound A in acetic acid–hydrochloric acid resulted in a mixture of three products along with unhydrolysed starting material. The formation of lomatin (Ia) was shown by t.l.c. Separation and characterisation of the other products was not achieved owing to the complex nature of the mixture and the paucity of material. The formation of lomatin supports the presence of the lomatin unit and of the acetal function in compound A. Hydrolysis of compound B was not carried out owing to lack of material.

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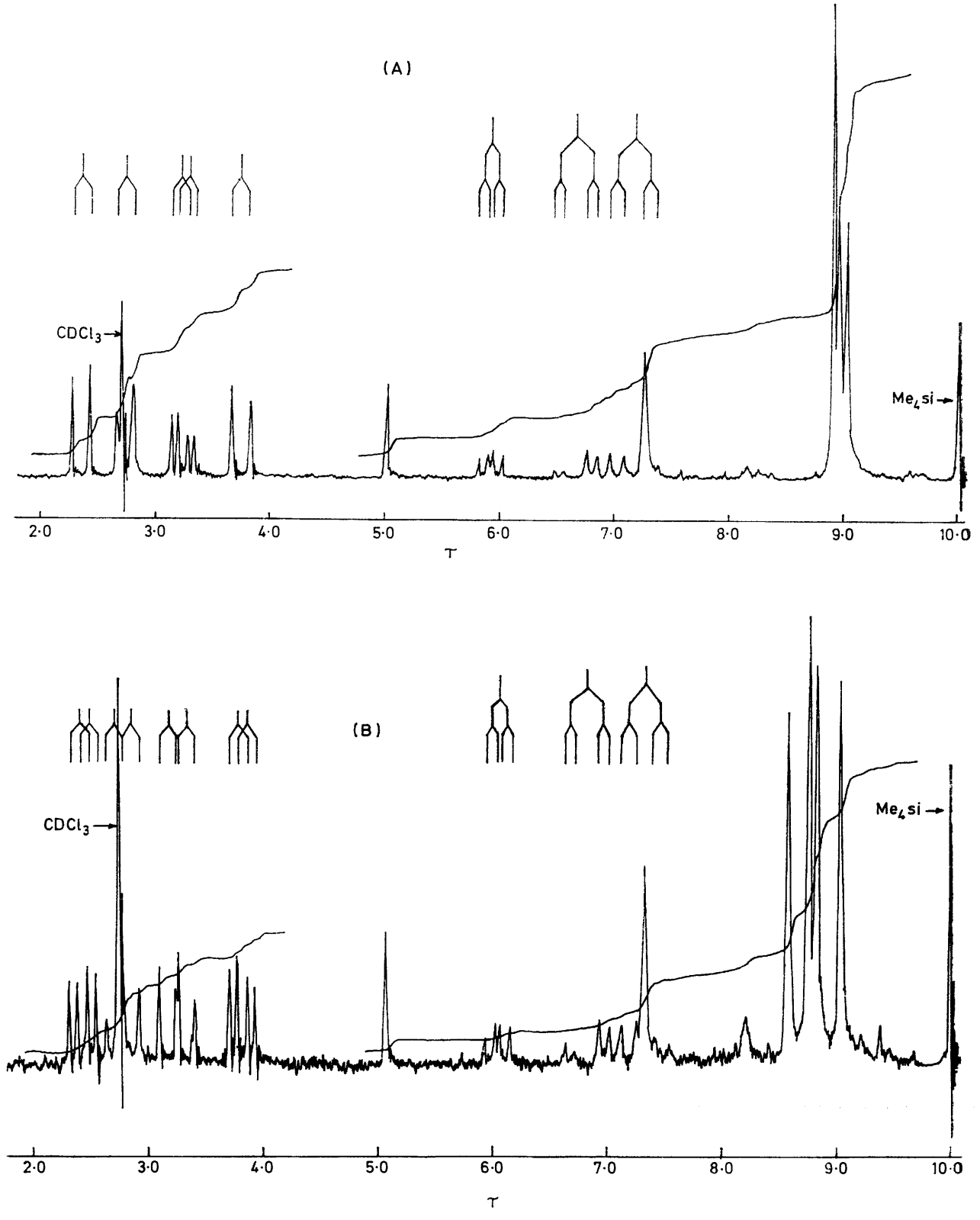
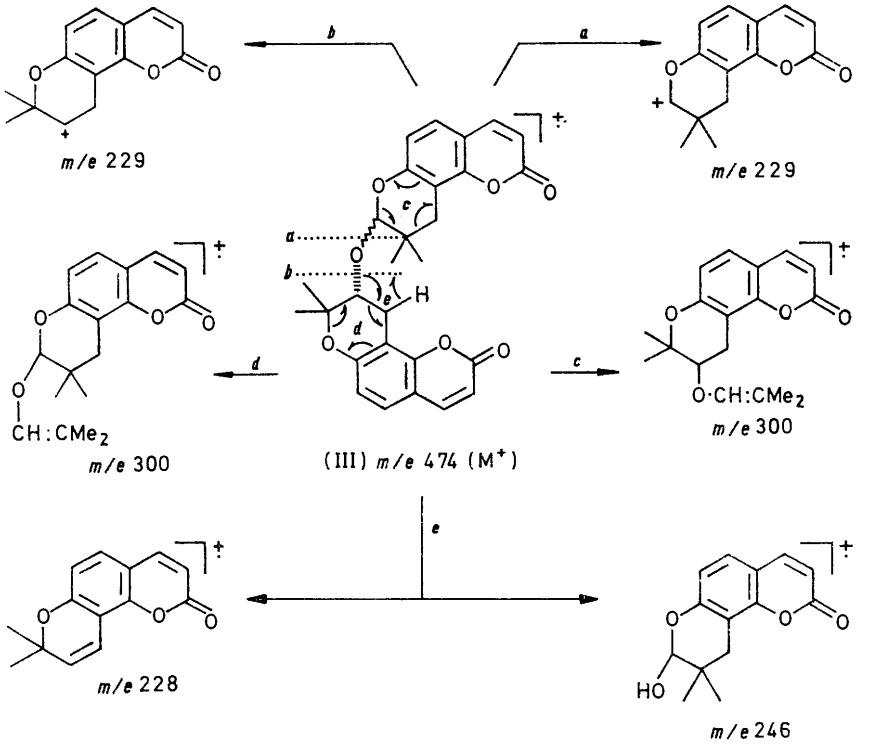


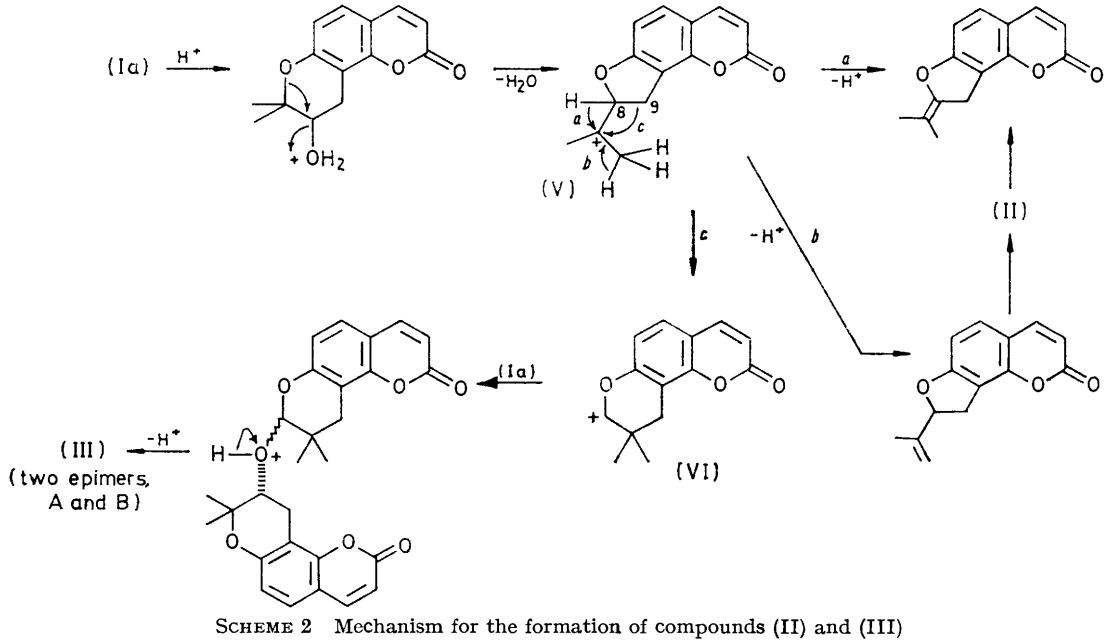
N.m.r. spectra of compounds A and B in $CDCl_3$

The major evidence in favour of the proposed C-8 epimeric structures is based on the n.m.r. spectra of compounds A and B. In both the cases the singlets around τ 5 (1 H), and 7.3 (2 H) revealed the presence of the 9,10-dihydro-9,9-dimethyl-2-oxo-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-8-oxy-unit, and the double doublets centred around τ 6 (1 H), 6.8 (1 H), and 7.3 (1 H) indicated the presence of the 9,10-dihydro-8,8-dimethyl-2-oxo-2*H*,8*H*-benzo[1,2-*b*:3,4-*b*']dipyran-9-oxy-unit. The formation of these products can be mechanistically explained as shown in Scheme 2.

Further, the mass spectra of A and B are similar and their fragmentation patterns support the structures assigned. The spectra exhibited the molecular ion at *m/e* 474 (doubly charged ion at *m/e* 237), and the base peak appeared at *m/e* 229 formed by cleavage of the ether



SCHEME 1 Mass spectral fragmentation of compounds A and B



SCHEME 2 Mechanism for the formation of compounds (II) and (III)

linkages on either side; see Scheme 1). The peaks at *m/e* 246 and 228 are due to proton displacements, and the peak at *m/e* 300 is due to retro-Diels–Alder cleavage of either of the pyran rings. Similar scissions are reported for the fragmentations of lomatin and its derivatives.[8] The other peaks in the spectra can be rationalized as further fragments of the monomer units.

The formation of dihydro-oroselone (II) from lomatin (Ia) was also observed with other acidic reagents (polyphosphoric acid, sulphuric acid, hydrobromic acid); a nearly quantitative yield was observed with perchloric acid in refluxing chloroform. In glacial acetic acid, treatment of lomatin (Ia) with perchloric or sulphuric acid gave the acetate (Ib) at room temperature, but dihydro-oroselone (II) was the only isolable product at 100—110 °C. Like lomatin, the acetate (Ib) and the angelate (Ic) (jatamansin) also yielded (II) on treatment with perchloric acid, whereas lomatin and its esters (Ia—c) were unchanged after treatment with boron trifluoride–ether complex. Dehydration of lomatin with pyridine–phosphoryl chloride gave seselin (IV), which was also formed by treatment of lomatin tosylate with collidine.[9] Seselin did not give dihydro-oroselone (II) on treatment with perchloric acid. The single-step transformation of lomatin and its esters (Ia—c) into dihydro-oroselone (II) is of biogenetic significance, as pyrano- and furo-coumarins co-occur in *Umbelliferae*.

The mechanism shown in Scheme 2 would explain the formation of compounds (II) and (III) from lomatin. In the presence of acid, lomatin (Ia) undergoes protonation and loss of water to give the ion (V), which on deprotonation followed by the double bond isomerization yields dihydro-oroselone. Migration of the 8,9-bond in (V) generates the ion (VI), which on nucleophilic attack by lomatin from either side, followed by loss of a proton, results in the two epimeric dimers A and B (III). The alternative formation of (II) *via* the dehydration product (IV) was excluded since seselin (IV) did not rearrange to (II) under identical conditions.

EXPERIMENTAL

U.v. spectra were measured for solutions in ethanol with a Perkin-Elmer 402 spectrophotometer. I.r. spectra were measured for Nujol mulls with a Perkin-Elmer 237B spectrophotometer. N.m.r. spectra were recorded for solutions in $CDCl_3$ at 60 MHz with tetramethylsilane as internal standard. Neutral silica gel (Riedel) activated at 120 °C for 5 h was used for column chromatography. Solutions were dried by standard techniques.

Treatment of Lomatin (Ia) *with Acidic Reagents* —(a) *With toluene-*p*-sulphonic acid.* A mixture of lomatin (Ia) (5 g), toluene-*p*-sulphonic acid (3.5 g), and xylene (125 ml) was stirred for 10 h at 140—150° (bath temperature) and then xylene was distilled off. The residue was extracted with chloroform, washed with water till neutral, dried, concentrated, and chromatographed over silica gel (140 g). Elution with hexane–ethyl acetate (8 : 1; 3.5 l) eluted dihydro-oroselone (8-isopropylfuro[2,3-*h*][1]benzopyran-2-one) (3 g). A mixture (900 mg) of compounds A and B and (Ia) was eluted by hexane–ethyl acetate (7 : 3; 3 l). Further elution with ethyl acetate gave a residue (400 mg) which did not yield any isolable products. Compounds A (200 mg) and B (180 mg) and lomatin (250 mg) were separated from the mixture and purified by repeated column chromatography and p.l.c. on silica [hexane–benzene–ethyl acetate (1 : 1 : 1)]. Dihydro-oroselone (II) was crystallized from hexane–ethyl acetate; m.p. and mixed m.p. 140—141° (Found: C, 73.55; H, 5.35. Calc. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3%); $\lambda_{max.}$ 206, 253, and 305 nm (log ε 4.35, 4.42, and 4.03); $\nu_{max.}$ 1 715, 1 610, 1 578, 1 403, 1 372, 1 362, and 1 300 cm^{-1}; τ 8.64 (6 H, d, *J* 7 Hz), 6.88 (1 H, m), 3.65 (1 H, d, *J* 9.5 Hz), 3.29 (1 H, s), 2.69 (2 H, s), and 2.21 (1 H, d, *J* 9.5 Hz). *Compound A* {9,9′,10,10′-*tetrahydro*-8′,8′,9,9-*tetramethyl*-8,9′-*oxybis*-8H-*benzo*[1,2-b:3,4-b′]*dipyran*-2-*one*} (III) was crystallized from hexane–ethyl acetate; m.p. 222—223° (Found: C, 71.0; H, 5.75. $C_{28}H_{26}O_7$ requires C, 70.9; H, 5.5%); $\lambda_{max.}$ 214, 246, 256, and 327 nm (log ε 4.50, 3.85, 3.81, and 4.46); $\nu_{max.}$ 1 725, 1 605, 1 565, 1 490, 1 400, 1 375, 1 367, and 1 335 cm^{-1}; for n.m.r. see main text, *m/e* 474 (M^+, 17%), 300(2), 246(3), 237(0.5), 229(100), 228(20), 213(17), 187(81), 175(18), 159(6.5), 147(2.8), and 131 (5). The isomer, *compound B* (III), a thick liquid, which was not crystallized, afforded a solid after drying under vacuum, m.p. 135—139° (Found: C, 71.05; H, 5.4%); $\lambda_{max.}$ 212, 246, 256, and 327 nm (log ε 4.53, 3.87, 3.83, and 4.37) $\nu_{max.}$ 1 725, 1 605, 1 568, 1 492, 1 402, and 1 375 cm^{-1}; τ 2.39, 2.47, 3.76, and 3.85 (each 1 H, d, *J* 9.5 Hz, H-3, -3′, -4, and 4′), 2.72, 2.85, 3.17, and 3.33 (each 1 H, d, *J* 8.5 Hz, H-5, -5′, -6, and -6′), 8.58, 8.76, 8.83, and 9.03 (each 3 H, s, 8′-, and 9-Me_2), 7.33 (2 H, s, 10-H_2), 5.07 (1 H, s, H-8), and 6.05 (1 H, *J* 7.5 and 5.5 Hz), 6.83 (1 H, *J* 17.0 and 5.5 Hz), and 7.32 (1 H, *J* 17.0 and 7.5 Hz) (ABX system); *m/e* 474 (M^+, 15.5%), 300(1.3), 246(4.9), 237(0.5), 229(100), 228(31), 213(25), 187(75), 175(29), 159(7), 147(4), and 131(2).

(b) *With polyphosphoric acid.* A mixture of lomatin (Ia) (200 mg) and polyphosphoric acid (2 ml), prepared by adding phosphoric oxide (14 g) to phosphoric acid (9 ml), was kept on a steam-bath for 2 h. The usual work-up and chromatography of the residue gave dihydro-oroselone (95 mg).

(c) *With hydrobromic acid.* A mixture of lomatin (Ia) (500 mg), hydrogen bromide in acetic acid (35%; 2 ml), and glacial acetic acid (2 ml) was kept on a steam-bath for 12 h, then worked up in the usual manner to give dihydro-oroselone (II) (340 mg).

(d) *With sulphuric acid.* A mixture of lomatin (Ia) (200 mg), 98% sulphuric acid (0.2 ml), and chloroform (10 ml) was refluxed for 4 h, then worked up as usual and purified to give dihydro-oroselone (II) (110 mg).

(e) *With perchloric acid in chloroform.* Lomatin (Ia) (250 mg) was dissolved in chloroform (10 ml) and perchloric acid (0.25 ml) was added. The mixture was refluxed for 4 h, then extracted with an excess of chloroform; the extract was washed with water and dried. Chromatography gave dihydro-oroselone (II) (208 mg).

(f) *With perchloric acid in acetic acid at room temperature.* A mixture of lomatin (Ia) (500 mg), perchloric acid (0.5 ml), and acetic acid (10 ml) was stirred for 8 h at room temperature. It was then extracted with chloroform and the extract was washed with water, sodium hydrogen carbonate solution, and water, then dried and concentrated. The residue, on chromatography over silica gel (25 g) and elution with hexane–ethyl acetate (4 : 1; 500 ml), yielded lomatin

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acetate (Ib) (430 mg); elution with hexane–ethyl acetate (2 : 1; 500 ml) eluted unchanged (Ia) (100 mg). Lomatin acetate was crystallized from benzene; m.p. and mixed m.p. 136—137° (Found: C, 66.55; H, 5.8. Calc. for $C_{16}H_{16}O_5$: C, 66.65; H, 5.6%).

(g) *With sulphuric acid in acetic acid at room temperature.* A mixture of lomatin (Ia) (500 mg), sulphuric acid (0.5 ml), and glacial acetic acid (10 ml) was stirred at room temperature for 6 h, then worked up and chromatographed over silica gel (20 g), as in (f), to give lomatin acetate (Ib) (520 mg) and lomatin (Ia) (30 mg).

(h) *With perchloric acid in acetic acid at* 100—110 °C. A mixture of lomatin (Ia) (500 mg), perchloric acid (0.5 ml), and acetic acid (10 ml) was stirred for 8 h at 100—110 °C (bath temperature). The usual work-up and chromatography gave dihydro-oroselone (II) (300 mg).

(i) *With sulphuric acid in acetic acid at* 100—110 °C. A mixture of lomatin (Ia) (500 mg), perchloric acid (0.5 ml), and acetic acid (10 ml) was stirred at 100—110 °C (bath temperature) for 6 h and worked up as usual to give dihydro-oroselone (II) (280 mg).

Hydrolysis of Compound A (III).—A mixture of compound A (III) (50 mg), concentrated hydrochloric acid (1 ml), acetic acid (5 ml), and water (1 ml) was stirred for 10 h at 100—110 °C. Acetic acid was removed under vacuum and the residue extracted with chloroform. The extract was washed with water, dried, and concentrated. T.l.c. (1 : 1 : 1 hexane–benzene–ethyl acetate) showed the residue to be a mixture of three products, including lomatin (Ia), along with unhydrolysed compound A.

Dehydration of Lomatin with Pyridine–Phosphoryl Chloride.—A mixture of lomatin (Ia) (200 mg), pyridine (2.5 ml), and phosphoryl chloride (0.2 ml) was warmed on a steam-bath for 5 min, left at room temperature for 6 h, poured into cold water, and extracted with chloroform. The organic layer was washed with water, dilute hydrochloric acid, dilute aqueous sodium hydrogen carbonate, and water, dried, and concentrated. The residue, after chromatography over silica gel (8 g) and elution with hexane–ethyl acetate (6 : 1; 400 ml), yielded seselin (IV) (80 mg), m.p. 119—120° (Found: C, 74.0; H, 5.5. Calc. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3%); $\lambda_{max.}$ 219, 285, 295, and 333 (log ε 4.45, 4.04, 4.09, and 4.12); $\nu_{max.}$ 1 720, 1 625, 1 595, 1 477, 1 400, 1 369, and 1 355 cm^{-1}; τ 8.52 (6 H, s), 4.32 (1 H, d, *J* 10 Hz), 3.90 (1 H, d, *J* 9 Hz), 3.38 (1 H, d, *J* 9 Hz), 3.11 (1 H, d, *J* 10 Hz), 2.83 (1 H, d, *J* 9 Hz), and 2.47 (1 H, d, *J* 9 Hz).

Treatment of Seselin with Perchloric Acid.—A mixture of seselin (IV) (200 mg), perchloric acid (0.2 ml), and chloroform (10 ml) was refluxed on a steam-bath for 4.5 h. The usual work-up and chromatography over silica gel (8 g) yielded unchanged seselin (90 mg), m.p. and mixed m.p. 119—120°. Elution with a polar solvent yielded a more polar compound.

Treatment of Lomatin Acetate (Ib) *with Perchloric Acid.*—A mixture of the acetate (Ib) (250 mg), perchloric acid (0.2 ml), and chloroform (10 ml) was refluxed for 5 h. The usual work-up and purification gave dihydro-oroselone (II) (175 mg).

Treatment of Lomatin Angelate (Ic) *with Perchloric Acid.*—The naturally occurring jatamansin (Ic) (250 mg) was dissolved in chloroform (10 ml) to which perchloric acid (0.2 ml) was added. The mixture was refluxed for 5 h and was then worked up in the usual way to give dihydro-oroselone (II) (155 mg).

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