

Structure of Lomatin, A New Coumarin

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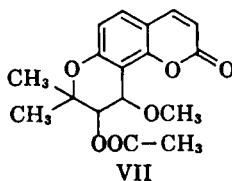
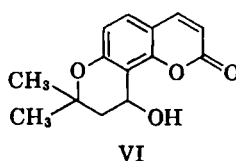
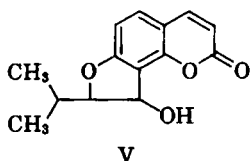
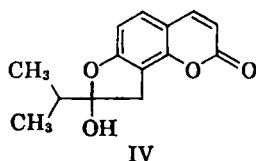
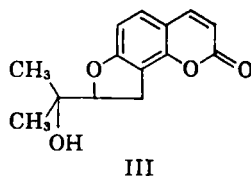
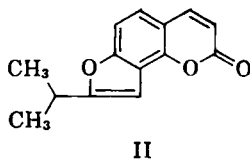
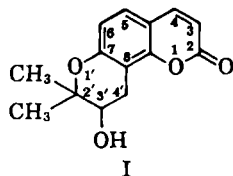
Examination of the coumarin content of the petroleum ether extract of *Lomatium nuttallii* (A. Gray) has revealed that the principal component is a compound, m.p. 187–188°, $[\alpha]_D^{25} + 74.8^\circ$ (EtOH), corresponding to the formula $C_{14}H_{14}O_4$. We have named this substance *lomatin*, and our structural studies indicate that it is (+)-3'-hydroxy-3',4'-dihydroseselin (I). Infrared spectra¹ (Nujol mull) show principal absorption frequencies at 3500 (free OH), 1700 (C=O), 1600 and 1487 (aromatic C=C), 1281 and 1075 cm^{-1} (OH deformation and C—O stretching). Ultraviolet spectra show λ_{max}^{EtOH} 246 $m\mu$ ($\log \epsilon$ 3.78), 257 (3.56), and 329 (4.11); λ_{min}^{EtOH} 242 $m\mu$ ($\log \epsilon$ 3.49), 252 (3.55), and 264.5 (3.30).

The nuclear magnetic resonance (NMR) spectrum of I showed absorption at 1.37 and 1.41 p.p.m. (*gem*-dimethyl) and at 2.6 p.p.m. (hydroxyl). Absorptions were observed at 2.93 and 3.11 p.p.m. ($J_{ab} = 5$ cps.) for the 4'-protons and at 3.89 p.p.m. ($J_{ab} = 5$ cps.) for the 3'-proton. Peaks at 6.16 and 7.60 p.p.m. ($J_{ab} = 10$ cps) are assigned to protons at positions 3 and 4, respectively, whereas protons at positions 6 and 5 are found to absorb at 6.77 and 7.22 p.p.m. ($J_{ab} = 8$ cps.), respectively. The hydroxyl proton absorption at 2.6 p.p.m. (concentration and temperature dependent) was eliminated by exchange with D_2O , confirming the infrared OH stretching at 3500 cm^{-1} . Formation of an acetate, m.p. 141°, combined with negative tests for phenol, conclusively showed the presence of an alcoholic hydroxyl group. Acid catalyzed dehydration yielded dihydroöroselone (II), confirming the suspected coumarin character of the nucleus. Furthermore, it revealed the presence of a ring system attached through an ethereal oxygen at position 7 to position 8.

Possible structures of the furanocoumarin type, based on II as a dehydration product, would be III, IV, and V. Of these, III is the structure of

columbianetin, unequivocally established previously (1). Structure IV would be a hemiketal ruled out by the insensitivity of lomatin to acid and by nonconformity to the NMR spectrum. Structure V likewise does not conform to the NMR spectrum but, in addition, is eliminated on the basis of the alkaline hydrolytic data on the acetate of I because esters derived from coumarins having a hydroxyl group on the benzylic carbon at position 8 of the coumarin nucleus are unusually sensitive to alkali, having half-lives of only a few minutes at best. Such esters are subject to a rapid S_N1 type of acyloxyl expulsion triggered by the neighboring phenoxide anion when the coumarin lactone ring is opened initially by base (2, 3). No such rapid hydrolysis was observed in the case of the acetate of I, inasmuch as the hydrolytic data showed a half-life of 28 minutes for this ester. The remaining structural possibilities were VI and I, assuming that a ring contraction could occur under the conditions of dehydration to yield II. Structure VI is eliminated by the hydrolytic arguments against V, although the NMR conceivably could be applicable. Thus, I was the most likely candidate, and this assignment was confirmed in two ways. The first was by marshaling the hydrolytic data for comparable compounds. A comparison with hydrolytic data reported by Willette and Soine (3) on 3'-acetoxy-4'-methoxy-3',4'-dihydroseselin (VII) with that of the acetate of I shows that the data are compatible with I. Compound VII has been shown to have a half-life of 8.5 minutes under similar conditions of alkaline hydrolysis which showed a half-life of 28 minutes for the acetate of I. Rabinovitch and Schramm (4) have shown that the relative rates of basic hydrolysis of 2-ethoxyethanol-1-acetate to ethyl acetate at 25° is 2.41. Portoghese and Malspeis (5) have, likewise, shown similar relative rates of basic hydrolysis for 2-methoxyethyl and ethyl esters of (\pm)- α -(2-piperidyl)-phenylacetic acid. The ratio of rates of hydrolysis of the acetate of I and VII (3.29) is in fair agreement with the above authors. Further evidence for a secondary alcohol function in I was obtained by comparing the NMR spectra of I and its acetate. It is well known (6) that a methine proton attached to a carbon bearing a secondary hydroxyl group usually exhibits absorption in the NMR at a frequency about 60 to 70 cps. higher than when

¹ The authors have previously but erroneously (3) reported that the absorption frequencies of (\pm)-I were 3636 (free OH), 1720 (C=O), 1295 and 1090 cm^{-1} (OH deformation and C—O stretching). The corrected values, identical with those of (+)-I, are given in this communication and were obtained with a Perkin-Elmer 521 grating infrared spectrophotometer.



the hydroxyl is acetylated. The frequency shift in the case of I and its acetate was 70 cps, in excellent agreement with its assigned character.

Finally, direct comparison of the NMR spectra of racemic I and its acetate² with their natural counterparts revealed that they were superimposable.

This represents the first report to our knowledge of the natural existence of I, although it may be pointed out that the structurally undefined hydroxy-containing coumarin recently reported by Hata *et al.* (7) from the roots of *Angelica formosana* Boiss., m.p. 187–188°, with the same empirical formula may well be identical with lomatin. The reported data, however, are not sufficient to make a firm identification. Finally, it should be noted that racemic I also has been reported by Mustafa *et al.* (8), in 1961, through controlled hydrolysis of visnadin with alcoholic

sulfuric acid, followed by aluminum isopropoxide reduction.

- (1) Willette, R. E., and Soine, T. O., *THIS JOURNAL*, **53**, 275(1964).
- (2) Smith, E., *et al.*, *J. Am. Chem. Soc.*, **79**, 3534(1957).
- (3) Willette, R. E., and Soine, T. O., *THIS JOURNAL*, **51**, 149(1962).
- (4) Rabinovitch, B., and Schramm, C. H., *J. Am. Chem. Soc.*, **72**, 627(1950).
- (5) Portoghesi, P. S., and Malspeis, L., *THIS JOURNAL*, **50**, 494(1961).
- (6) Jackman, L. M., "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 55.
- (7) Hata, K., *et al.*, *J. Pharm. Soc. Japan*, **83**, 611(1963).
- (8) Mustafa, A., *et al.*, *J. Org. Chem.*, **26**, 890(1961).

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² Previously prepared in these laboratories (3). It may be noted that the present work actually validates the well-accepted, but not necessarily proven, structure of racemic I.

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