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ACID-CATALYZED REARRANGEMENT OF AN EPOXY COUMARIN PHEBALOSIN THE REVISED STRUCTURE OF MURRALONGIN

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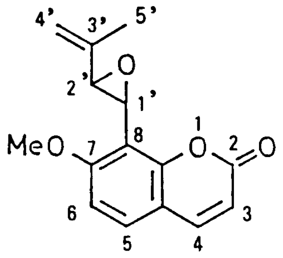
On treatment with acid, the well-known epoxy coumarin phebalosin (I) undergoes rearrangement to afford murralongin, a naturally occurring coumarin bearing an unusual isoprenoid unit. The structure of murralongin is reviewed, based on the hypothetical mechanism of rearrangement, and finally revised to (V) by X-ray crystalography.

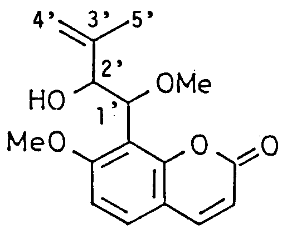
KEYWORDS —— phebalosin; murralongin; epoxy coumarin; revised structure; X-ray crystalography; rearrangement

Coumarin is one of the most widely distributed heterocyclic compounds in nature. A feature common to most naturally occurring coumarins is the presence of isoprenoid chains, either intact or partially degraded, of one or more units attached to a carbon atom of the aromatic nucleus, or to an oxygen atom, or to both. The isoprenyl coumarin occurs also in a variety of oxidized and skeletally rearranged forms, most of them biogenetically derived from the corresponding epoxide. Phebalosin (I), which occurs in some rutaceous plants,$^{1)}$ is perhaps the only coumarin bearing an epoxide group conjugated with a double bond in a single isoprenyl unit. In the course of chemical studies on Murraya paniculata (Rutaceae), we have encountered phebalosin and a number of related isoprenyl coumarins.$^{2)}$ The biogenetic interest in these coumarins has led us to investigate the reaction of phebalosin with acid. In this communication we report that treatment of phebalosin with acid furnishes murralongin, a well-known coumarin with an unprecedented isoprenoid unit, and we redefine the structure (VI) previously proposed for murralongin as (V).

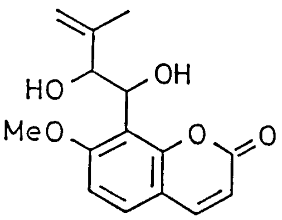
A solution of phebalosin in a mixture of MeOH and 10% sulfuric acid (1:1) was heated to 60°C for 5 h, then poured into water and extracted with chloroform. The chloroform extracts, which formed three spots on TLC, were purified by chromatography on SiO_2.$^{3)}$ Product 1 was found by spectroscopic analysis to be a methanol adduct (II) of phebalosin.$^{4)}$ The NMR spectrum of product 2 was very similar to that of product 1 except for the absence of an aliphatic methoxy group.$^{5)}$ It was finally identified as murrangatin (III) by direct comparison with an authentic sample.$^{6)}$ Product 3 was obtained as a minor product (10% yield). Its



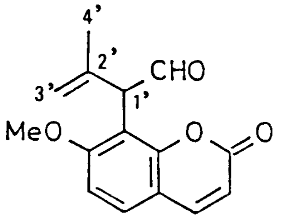
(I) phebalosin



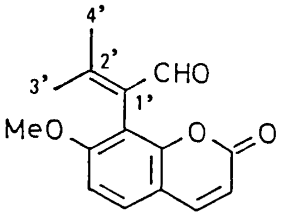
(II)



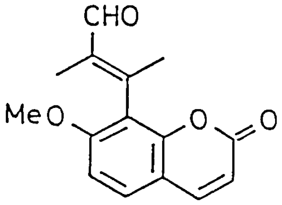
(III) murrangatin



(IV)



(V) murralongin



(VI)

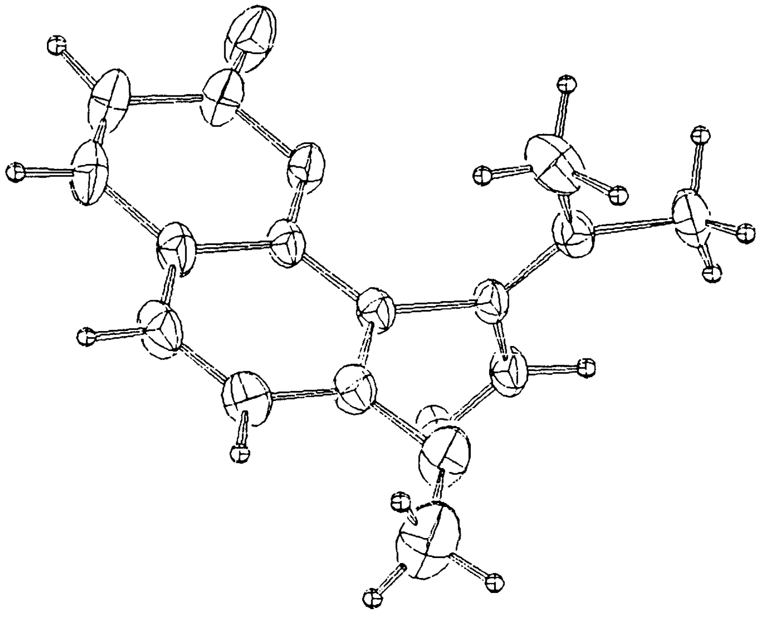


Fig. 1. Computer Generated Perspective Drawing of Murralongin (V)

^{1}H-and ^{13}C-NMR spectra showed an aldehyde, two methyls and a fully substituted double bond in addition to signals assignable to the 7-methoxy coumarin moiety.[7] This compound was identical to the authentic murralongin.[6]

The reaction of phebalosin with Lewis acid was also investigated since hydrolysis of an epoxide does not occur under this condition. When a large amount of BF_3-etherate was used,[8] the sole product obtained in this reaction was murralongin. On the other hand, treatment of phebalosin with a stoichiometrical amount of BF_3-etherate yielded a single product, distinct from murralongin on TLC. Since this compound was so labile as to be easily transformed into murralongin by treatment with mild acid, it is presumed to be an intermediate of this rearrangement reaction. Its structure was elucidated as (IV) by NMR spectroscopy.9) The formation of the intermediate (IV) in this reaction indicates that the migration of either a vinyl or coumarin skeleton to an adjacent carbon is essential for generating an aldehyde function from the epoxide. Perhaps this migration occurs in concert with the acid-catalyzed ring opening of the epoxide. Murralongin was first isolated from *Murraya elongata*10) and also occurs in *Murraya paniculata*.6,11) The structure of murralongin (VI) was deduced only from somewhat ambiguous analyses of spectral data.10) It is apparent that this structure cannot be adapted to the transformation of phebalosin into murralongin by way of an intemediate (IV). In order to confirm the structure of murralongin, a single crystal X-ray diffraction analysis12) was carried out and it was finally identified as (V), which disproves the previously assigned structure (Fig. 1). With respect to the mechanism of this rearrangement, two hypothetical pathways can be sketched (Fig. 2). Generally speaking, a ring opening of the epoxide occurs at the carbon atom that is better able to tolerate positive charge in the transition state. From this point of view, it appears that pathway A is preferable to B. This may be supported by the fact that a methoxy group, derived from methanol, is incorporated exclusively at the 1'-position as evidenced by the predominant formation of (II) in the hydrolysis of the epoxide (I) with a methanolic acid.

It has been reported that murralongin co-occurs with murrangatin, a hydrate form of phebalosin, in *Murraya paniculata*6,11) and *M. elongata*.10,13) So it seems reasonable to assume that this rearrangement is a chemical analogy of a reaction involved in the biosynthesis of murralongin.

ACKNOWLEDGEMENT We thank Dr. Jun-shan Yang, Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, China, for generously providing the authentic samples.

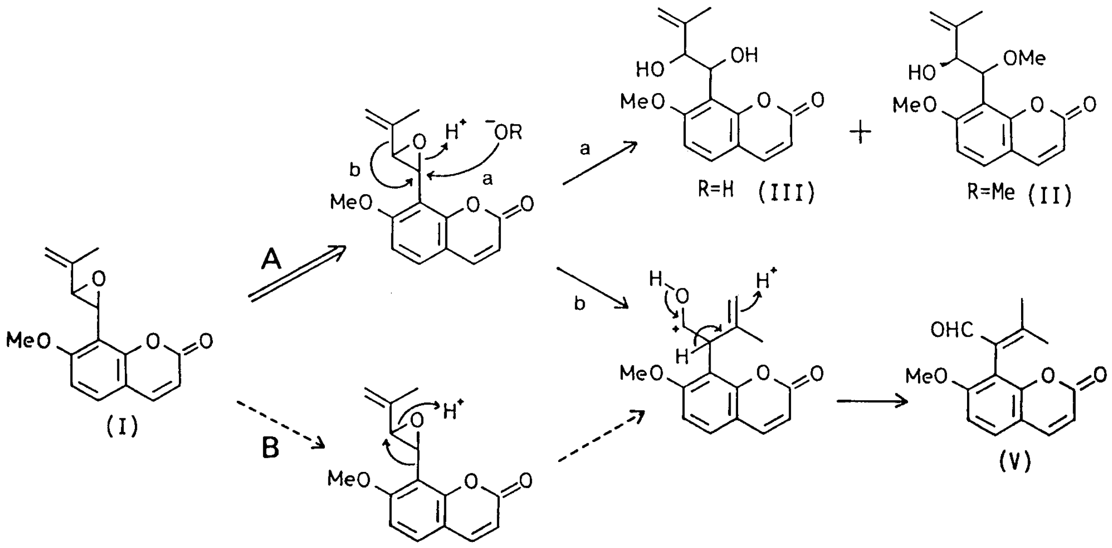


Fig. 2. Possible Mechanism of Rearrangement from Phebalosin to Murralongin

REFERENCES AND NOTES

1) D. B. M. Wickramaratne, V. Kumar and S. Balasubramaniam, Phytochemistry, **23**, 2964 (1984).

2) Unpublished. A previous report on this subject dealt with the isolation of indole alkaloids from this plant: T. Kinoshita, S. Tatara and U. Sankawa, Chem. Pharm. Bull., **33**, 1770 (1985).

3) The yields of the three products were as follows: product **1**, 55%; product **2**, 35%; product **3**, 10%.

4) ^{1}H-NMR ($CDCl_3$, 100 MHz) δ : 1.70(3H, dd, J=1.5 and 1.0Hz, 5'-H_3), 3.33(3H, s, 1'-OMe), 3.95(3H, s, 7-OMe), 4.70(2H, m, 4'-H_2), 4.90(1H, d, J=8.8Hz, 2'-H), 5.05(1H, d, J=8.8Hz, 1'-H), 6.27(1H, d, J=9.5Hz, 3-H), 6.87(1H, d, J=8.5Hz, 6-H), 7.41(1H, d, J=8.5Hz, 5-H), 7.62(1H, d, J=9.5Hz, 4-H). MS m/z : 290(M^+, 1%), 220(23%), 219(100%). These data are in good conformity with those for (II) reported in the literature: P. W. Chow, A. M. Duffield and P. R. Jefferies, Aust. J. Chem., **19**, 483 (1966).

5) mp 131°C (bezene-ether). ^{1}H-NMR ($CDCl_3$, 100MHz) δ : 1.79(3H, s, 5'-H_3), 3.97(3H, s, 7-OMe), 4.50(1H, d, J=8.5Hz, 2'-H), 4.60(2H, m, 4'-H_2), 5.30(1H, d, J=8.5Hz, 1'-H), 6.26(1H, d, J=9.5Hz, 3-H), 6.83(1H, d, J=8.5Hz, 6-H), 7.40(1H, d, J=8.5Hz, 5-H), 7.62(1H, d, J=9.5Hz, 4-H). MS m/z : 258(M^+-18, 1%), 219(16%), 206(23%), 205(100%).

6) J.-S. Yang and Y.-L. Su, Yaoxue Xuebao, **18**, 760 (1983).

7) mp 137-8°C (Et_2O). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76 ; H, 5.42. Found : C, 69.85 ; H, 5.43. MS m/z : 258(M^+, 100%), 229(21%), 215(94%), 214(24%), 201(27%), 199(40%), 187(57%), 171(32%). UVλ^{EtOH}_{max} nm : 324, 233. IRν^{KBr}_{max}cm^{-1} : 1725, 1655, 1600, 1490. ^{1}H-NMR ($CDCl_3$, 100MHz)δ : 1.79(3H, s, 3'-H_3), 2.43(3H, s, 4'-H_3), 3.84(3H, s, OMe), 6.23(1H, d, J=9.5Hz, 3-H), 6.90(1H, d, J=8.5Hz, 6-H), 7.45(1H, d, J=8.5Hz, 5-H), 7.65(1H, d, J=9.5Hz, 4-H), 10.22(1H, s, CHO). ^{13}C-NMR ($CDCl_3$, 25MHz)δ : 19.8(CH_3), 24.8(CH_3), 56.2(OMe), 107.6(CH), 112.8(CH and 2 x =C=), 128.5(CH), 129.0(=C=), 143.6(CH), 152.8(=C=), 159.5(=C=), 159.8(=C=), 160.9(=C=), 188.6(CHO).

8) After a mixture of phebalosin and BF_3-etherate in benzene was allowed to stand overnight, it was poured into water and extracted with benzene. The benzene extract was chromatographed on SiO_2 to give pure murralongin.

9) ^{1}H-NMR ($CDCl_3$, 100MHz) δ : 1.85(3H, br s, 4'-H_3), 3.88(3H, s, 7-OMe), 4.74(1H, br s, 1'-H), 4.89 and 5.06(1H each, m, 3'-H_2), 6.27(1H, d, J=9.6Hz, 3-H), 6.90(1H, d, J=8.6Hz, 6-H), 7.44(1H, d, J=8.6Hz, 5-H), 7.65(1H, d, J=9.6Hz, 4-H), 9.87(1H, s, 2'-CHO).

10) S. K. Talapatra, L. N. Dutta and B. Talapatra, Tetrahedron lett., **1973**, 5005.

11) K. Raj, S. C. Misra, R. S. Kapil and S. P. Popli, Phytochemistry, **15**, 1787 (1976).

12) Crystal data : $C_{15}H_{14}O_4$, M=258.27, monoclinic, space group $P2_1/n$, a=16.200 Å, b=7.625 Å, c=10.818 Å, β=92.92°, Z=4, Dx=1.28gcm^{-3}, V=1334.6 Å^3. The crystal structure was solved by direct methods. The least-squares refinement of the atomic positional and thermal parameters converged to R = 0.051 over 2429 statistically significant reflections.

13) S. K. Talapatra, L. N. Dutta and B. Talapatra, Tetrahedron, **29**, 2811 (1973).

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