ISOLATION OF (-)-PREORIXINE, A POSTULATED BIOSYNTHETIC KEY INTERMEDIATE OF (+)-ORIXINE AND RELATED QUINOLINE ALKALOIDS, FROM THE STEMS OF *ORIXA JAPONICA*[a]

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Abstract - A prenyl quinoline alkaloid (-)-preorixine was isolated from the stems of *Orixa japonica* (Rutaceae) and its structure was elucidated to be (-)-3-(2*S*,3-epoxy-3-methylbutyl)-2,4-dimethoxy-7,8-methylenedioxyquinoline. (-)-Preorixine is postulated as a biosynthetic key intermediate of (+)-orixine and related compounds.

Finely cut stems of *Orixa japonica* (Rutaceae) were extracted with hexane and the hexane extract was chromatographed over silica gel (eluted with $CHCl_3$ and $CHCl_3$-CH_3OH). Further purification of the alkaloid containing fraction by preparative tlc (developed with benzene-ethyl acetate) afforded (-)-preorixine (**1**, $C_{17}H_{19}NO_5$, mw 317, 0.007%)[1] together with orixinone (**2**, $C_{17}H_{19}NO_5$, mw 317, 0.017%) and (+)-orixine (**3**, $C_{17}H_{21}NO_6$, mw 335, 0.001%). Compounds (**2**) and (**3**) had been already isolated from the stem-barks and root-barks of *O. japonica*, respectively.[2,3] Compound (**1**) possesses the same molecular formula with that of **2** and showed

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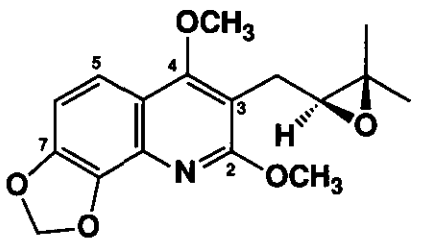
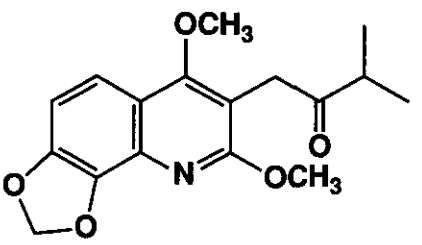
[a]Dedicated to Prof. Edward C. Taylor on the occasion of his 70th birthday.

similar spectroscopical characteristics. So, further comparison of the spectroscopical data of this compound was done with those of orixinone (**2**). In the ^{1}H nmr of **1**, a



1



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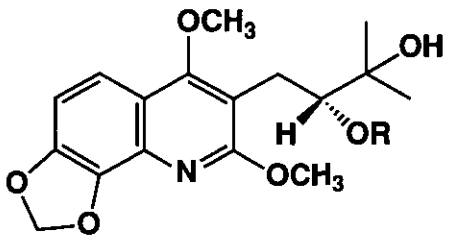

3 R = H

4 R = CHO

set of aromatic signal at δ 7.05 and 7.51 (each 1H, d, J = 8 Hz), a methylenedioxy signal at δ 6.20 and 6.21 (each 1H, d, J = 3 Hz) and two methoxyl signals at δ 3.98 and 4.12 (each 3H, s) are coincident with those of orixinone (**2**).[2] Whereas a septet signal at δ 2.80 (1H, septet, J = 7 Hz) and a singlet methylene signal at δ 3.86 (2H, s) shown in the ^{1}H nmr spectrum of orixinone (**2**) were not observed and a doublet signal at δ 1.20 (6H, d, J = 7 Hz) attributed to the geminal methyl moiety of **2** changed into two singlet methyl signals at δ 1.31 and 1.45 (each 3H, s). Instead in the ^{1}H nmr spectrum of **1**, AB_2 system at δ 2.89 (1H, dd, J = 9, 18 Hz), 3.03 (1H, dd, J = 6, 9 Hz) and 3.04 (1H, dd, J = 6, 18 Hz) was observed. In addition, unlike orixinone (**2**), **1** was optically active ($[\alpha]_D^{25}$ -7.5° (c = 0.8, $CHCl_3$)). From these findings it was elucidated that the compound (**1**) possesses an epoxide group in its prenyl moiety and the structure of this compound was concluded to be (-)-3-(2,3-epoxy-3-methylbutyl)-2,4-dimethoxy-7,8-methylenedioxyquinoline (**1**). Although partially optical active epoxide (**1**) with $[\alpha]_D$ -0.85° ($CHCl_3$)[4] was formerly synthesized as a possible biosynthetic intermediate of (+)-orixine, this is the first report of the natural

occurrence of **1** and we named this compound as (-)-preorixine (**1**). Stereochemistry of the chiral center of (+)-orixine (**3**) and related compounds had been extensively studied[4-7] and it was concluded that the chirality of C-2 of the prenyl moiety of (+)-orixine (**3**) was *R* and that of the corressponding (-)-epoxide (**1**) was *S*.

(-)-Preorixine (**1**) isolated herein was transformed into (+)-orixine (**3**) according to the previous report.[4] Thus, (-)-preorixine (**1**, 35.0 mg) was dissolved in 90% formic acid (2.0 ml) and stirred at room temperature under N_2 atomosphere for 7 h and the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was worked up to give a pale yellow oil (29.6 mg) and preparative tlc of this fraction using benzene-ethyl acetate (4:1) as a solvent afforded a monoformate ester (**4**, 12.8 mg, $[\alpha]_D^{28}$ +6.0° (c = 0.6, $CHCl_3$)).[8] Then the compound (**4**, 8.3 mg) was treated with a mixture of aq. 2*N* NaOH (0.5 ml) - CH_3OH (3.0 ml) at room temperature under N_2 atmosphere for 5 h to give (+)-orixine (**3**, 5.6 mg, $[\alpha]_D^{27}$ +22.1° (c = 0.28, $CHCl_3$)). The $[\alpha]_D$ values of the monoformate ester (**4**) and (+)-orixine (**3**) obtained from the synthesized **1** were +0.35° ($CHCl_3$) and +2.0° ($CHCl_3$),[4] respectively.

The co-occurrence of (-)-preorixine (**1**) with orixinone (**2**) and (+)-orixine (**3**) is quite interesting from the biosynthetic point of view because **1** is postulated as a biosynthetic precursor of the latter two compounds.[4] Epoxide derivatives of isoprenoid quinoline alkaloids have been considered as the key biosynthetic intermediates of not only isoprenyl quinoline alkaloids like (+)-orixine (**3**)[2,4] and (-)-edulinine[5] but also furo- and pyranoquinoline alkaloids such as balfourodine, skimmianine and flindersine[7,9] for a long time. Whereas to the best of our knowledge these envisaged epoxides have never been isolated from the natural sources and the demonstration of the occurrence of (-)-preorixine in the nature is noteworthy.

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REFERENCES AND NOTES

1. Uv λ_{max} ($CHCl_3$) 254, 316 nm; ir ν_{max} (KBr) 2949, 1640, 1609, 1580, 1518, 1479, 1374, 1350, 1278, 1233, 1205, 1112, 1061, 1040, 921, 900, 832, 809, 764 cm^{-1}; EIms (*m/z*) 317 (M+), 305, 288, 274, 246, 234, 216, 201; ^1H nmr ($CDCl_3$, δ) see text.
2. W. J. Donnelly and M. F. Grundon, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2116.
3. M. Terasaka, *Yakugaku Zasshi*, 1931, **51**, 707; *idem, ibid.*, 1933, **53**, 1046; *idem, Chem. Pharm. Bull.*, 1960, **8**, 523.
4. R. M. Bowman and M. F. Grundon, *J. Chem. Soc. (C)*,1967, 2368; J. F. Collins and M. F. Grundon, *Chem Commun.*, 1969, 1078; R. M. Bowman, J. F. Collins, and M. F. Grundon, *J. Chem. Soc., Perkin Trans. 1*, 1973, 626.
5. D. R. Boyd and M. F. Grundon, *J. Chem. Soc. (C)*, 1970, 556; D. Boulanger, B. K. Bailey, and W. Steck, *Phytochemistry*, 1973, ***12***, 2399.
6. R. M. Bowman, J. F. Collins, and M. F. Grundon, *Chem. Commun.*, 1967, 1131.
7. R. M. Bowman, G. A. Gray and M. F. Grundon, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1051.
8. Uv λ_{max} ($CHCl_3$) 254, 315 nm; ir ν_{max} (KBr) 3440, 2924, 1712, 1640, 1606, 1580, 1518, 1481, 1378, 1350, 1280, 1246, 1208, 1105, 1061, 1040, 923, 830, 809, 798, 767 cm^{-1}; EIms (*m/z*) 363 (M^+), 317, 302, 276, 260, 246, 232, 216, 201; ^1H nmr ($CDCl_3$, δ) 1.33 (3H, s, -C*H*$_3$), 1.37 (3H, s, -C*H*$_3$), 2.97 (1H, dd, *J* = 3, 14 Hz, -C*H*$_2$-CH(OCHO)-), 3.22 (1H, dd, *J* = 10, 14 Hz, -C*H*$_2$-CH(OCHO)-), 3.98 (3H, s, -OC*H*$_3$), 4.12 (3H, s, -OC*H*$_3$), 5.32 (1H, dd, *J* = 3, 10 Hz, -CH$_2$-C*H*(OCHO)-), 6.19 (1H, d, *J* = 2 Hz, -OC*H*$_2$O-), 6.20 (1H, d, *J* = 2 Hz, -OC*H*$_2$O-) 7.04 (1H, d, *J* = 9 Hz, C_6-H), 7.47 (1H, d, *J* = 9 Hz, C_5-H), 7.88 (1H, s, -OC*H*O).
9. M. F. Grundon and K. J. James, *Chem. Commun.*, 1971, 1311; R. M. Bowman, M. F. Grundon, and K. J. James, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1055.

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