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STEREOCHEMISTRY OF ISOKHELLACTONE DERIVED COUMARINS FROM *PEUCEDANUM ARENARIUM**

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Key Word Index—*Peucedanum arenarium* var. *arenarium*; Umbelliferae; stereochemistry; natural coumarins; xanthalin, peuarenarine, peuarenine, isokhellactone.

Abstract—Previously xanthalin and two new pyranocoumarins, peuarenarine and peuarenine, had yielded on alkaline hydrolysis *cis*-isokhellactone (*cis*-3',4'-dihydroxy-3',4'-dihydroxanthyletin). The configuration of these products has been now established as 3'(*R*),4'(*R*). Additionally, *cis*- and *trans*-methylisokhellactones, *cis*-isokhellactone diacetate and *cis*-isokhellactone dibenzoate have been obtained.

INTRODUCTION

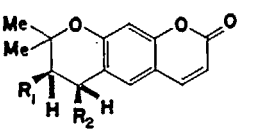
In earlier communications [1–3] the presence of xanthalin (1) and two new pyranocoumarins peuarenarine (2) and peuarenine (3) was reported. *Cis*-configuration was established [3] for the above compounds as well as for the parent glycol, isokhellactone (4). The stereochemistry and absolute configuration of these, and related products, are now discussed.

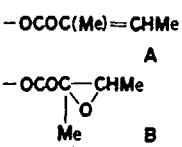
RESULTS AND DISCUSSION

Treatment of the natural diesters (1–3) in dioxane with aqueous potassium hydroxide led to the *cis*-diol (4) mp 217–219° [2]. After several recrystallizations of this product from methanol the mp rose to 227–229°, $[\alpha]_D^{25}$ −21.5° (*c* 0.22, pyridine), $[\alpha]_D^{25}$ +38.6° (*c* 0.14, EtOH), $[\alpha]_D^{25}$ +47.7° (*c* 0.22, MeOH). Sano *et al.* [4] have recently prepared the (−)-*cis*-diol, mp 226–228° $[\alpha]_D$ −43.8° (MeOH) and the (+)-*trans*-diol, mp 229–231° $[\alpha]_D$ +144.2° from the coumarin decursin. The new (+)-*cis*-diol (4) obtained from the natural coumarins of *Peucedanum arenarium* is therefore the third component of the four possible isomers. The absolute configuration of the (−)-*cis*-diol has been determined [4] as 3' (*S*), 4' (*S*) and that of the (+)-*trans*-diol as 3' (*S*), 4' (*R*). Therefore the (+)-*cis*-diol (4) prepared by alkaline hydrolysis of the coumarins (1–3) should be 3' (*R*), 4' (*R*). The proposed absolute configuration was confirmed by its hydrogenation over Adam's catalyst to give 3,4-dihydrodecursinol (5) $C_{14}H_{10}O_4$, mp 141–142°, $[\alpha]_D$ −25.2° (MeOH) whereas Sano *et al.* [4] have reported mp. 140–142° and $[\alpha]_D$ +29.7° (MeOH) for the corresponding enantiomer.

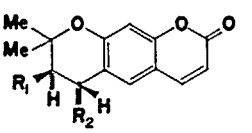
The *cis*-products in this series of linear pyranocoumarins have been encountered not only among natural products, but they have also been synthesized after acetylation and benzoylation of the (+)-*cis*-diol to its *cis*-diacetate (6) and *cis*-dibenzoate (7).

The only *trans* product prepared in this series has been *trans*-methylisokhellactone (8). Treatment of the natural coumarins with methanolic potassium hydroxide at room temperature or under reflux led to a mixture of the *cis*- and *trans*-products (8 and 9) in a ratio of approx.

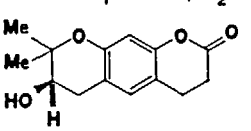




(1) xanthalin, R_1 = R_2 = A
(2) peuarenorine, R_1 = A, R_2 = B
(3) peuarenine, R_1 = R_2 = B
(4) isokhellactone, R_1 = R_2 = OH
(6) isokhellactonediacetate, R_1 = R_2 = OCOMe
(7) isokhellactonedibenzoate, R_1 = R_2 = $OCOC_6H_5$
(9) cis-methylisokhellactone, R_1 = OH, R_2 = OMe
(10) cis-3'-acetyl-4'-methylisokhellactone
R_1 = OCOMe, R_2 = OMe



(8) trans-methylisokhellactone
R_1 = OH, R_2 = OMe
(11) trans-3'-acetyl-4'-methylisokhellactone
R_1 = OCOMe, R_2 = OMe



(5) 3,4-dihydrodecursinol

* Unless otherwise stated UV spectra were measured in EtOH IR in $CHCl_3$ and NMR in $CDCl_3$ at 100 MH_3.

Part 9 in the series "Natural Coumarins". For part 8 see Zheleva A. B., Mahandru M. M. and Bubeva-Ivanova L. (1976), *Phytochemistry* **15**, 209.

1 : 1, mp 136–138°. The isomers were separated by PLC to give (−)-*trans*- and (+)-*cis*-methylisokhellactones (8 and 9). The new products now make available all the four possible optical isomers, since (−)-*cis*- and (+)-*trans*-methylisokhellactones have been reported by Hata *et al.* [5]. Acetyl derivatives of the (−)-*trans*- and (+)-*cis*-methylisokhellactones were also prepared and saponification of these acetates with potassium hydroxide in acetone regenerated the starting methylisokhellactones.

EXPERIMENTAL

Isokhellactone (4). A mixture of **1**, **2** and **3** (3 g) in dioxane (30 ml) was treated with 10% KOH (200 ml) for 2 hr under reflux. After cooling the soln was acidified with 10% H_2SO_4, diluted (600 ml H_2O) and extracted with EtOAc. The extract was dried and concentrated to give **4**, mp 227–229°, lit. 217–219° [3].

Isokhellactonediacetate (6). Acetylation of **4** with C_5H_5N–AC_2O gave **6**, mp 147–147.5°, $[\alpha]_D^{25}$ −58.8° (c 0.16, $CHCl_3$). (Found: C, 62.25; H, 5.01, M^+ 346, $C_{18}H_{18}O_7$ requires: C, 62.42; H, 5.20%). UV λ_{max}^{EtOH} nm (log ε) 220 (4.05), 246(3.28), 257(3.36), 300*sh*(400), 324(4.22). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735, 1630, 1565, 1492, 1390, 1375, 1320, 1300. NMR: δ 7.57 (1H, *d*, *J* = 10 Hz, H − 4), 6.23 (1H, *d*, *J* = 10 Hz, H − 3), 7.28 (1H, *s*, H − 5), 6.78 (1H, *s*, H − 8), 6.18 (1H, *d*, *J* = 4 Hz, H − 4'), 5.33 (1H, *d*, *J* = 4 Hz, H − 3'), 1.43 (6H, *s*, >C(Me)), 2.05 (3H, *s*, OCO Me), 2.13 (3H, *s*, OCOMe).

Isokhellactonedibenzoate (7). Benzoylation of **4** with benzoylchloride-C_6H_6–C_5H_5N gave **7**, mp 89–90°, $[\alpha]_D^{25}$ +0.13° (c 0.08, $CHCl_3$). (Found: C, 71.25; H, 5.01, M^+ 470, $C_{28}H_{22}O_7$ requires C, 71.48; H, 4.68%). UV λ_{max}^{EtOH} nm (log ε): 220 (4.10), 246 (3.35), 257 (3.50), 300*sh* (4.20), 324 (4.30). IR ν_{max}^{CHCl3} cm^{-1}: 1715–1740, 1630, 1602, 1586, 1565, 1492, 1466, 1451, 1390, 1372. NMR: δ 7.89 (1H, *d*, *J* = 10 Hz, H − 4), 6.21 (1H, *d*, J = 10 Hz, H − 3), 6.88 (1H, *s*, H − 8), 6.58 (1H, *d*, *J* = 4 Hz, H − 4'), 5.71 (1H, *d*, *J* = 4 Hz, H − 3'), 1.56 (6H, *s*, >$C(CH_3)_2$), 7.20–7.90 (11H, *brd m.*, H − 5 and 2 C_6H_5COO).

Methylisokhellactones, cis (**9**) *and trans* (**8**). The coumarin diesters (**1–3**) dissolved in MeOH (50 ml) were heated under reflux with 10% aq KOH (200 ml., 2 hr). The reaction mixture was cooled, acidified (10% H_2SO_4), diluted with H_2O (600 ml) and extracted with EtOAc. The extract was dried and conc to give a mixture of **4**, **8** and **9**. Column chromatography on neutral alumina gave a mixture of **8** and **9** and pure **4**. After PLC of the above mixture in $CHCl_3$–Me_2CO (9 : 1), pure **8** and **9** were isolated. *Cis*-methylisokhellactone (**9**), mp 104–105°, $[\alpha]_D^{25}$ +57.2° (c 0.18, MeOH) (lit [5] mp 71.5°, $[\alpha]_D$ −52.9 (MeOH) for the enantiomer). (Found: C, 65.10; H, 5.65; M^+ 276, $C_{15}H_{16}O_5$ requires C, 65.21; H, 5.79%.) UV λ_{max}^{EtOH} nm (log ε): 220(4.15), 247(3.45), 257(3.60), 300*sh*(4.24), 324 (4.38). IR ν_{max}^{Nujol} cm^{-1}: 3540, 3480, 1720, 1625, 1560, 1490, 1330, 1305, 1290, 1140. NMR (in C_5D_5N): δ 7.62 (1H, *d*, *J* = 10 Hz, H − 4), 6.29 (1H, *d*, *J* = 10 Hz, H − 3), 7.69 (1H, *s*, H − 5), 6.76 (1H, *s*, H − 8), 4.58 (1H, *d*, *J* = 3.5 Hz, H − 4'), 4.16 (1H, *d*, *J* = 3.5 Hz, H − 3'), 3.50 (3H, *s*, OMe), 1.68 and 1.32 (3H each, *s*, >$C(Me)_2$). *Trans*-methylisokhellactone (**8**): mp 72–74°, $[\alpha]_D^{25}$ −76° (*c* 0.55, EtOH), $[\alpha]_D^{25}$ −73° (c 0.24, MeOH) (lit [5] mp 94–96°, $[\alpha]_D$ +92.3° (MeOH) for the enantiomer). (Found: C, 65.15; H, 5.60, M^+ 276, $C_{15}H_{16}O_5$ requires C, 65.21; H, 5.79%). UV λ_{max}^{EtOH} nm (log ε): 220 (4.08), 247 (3.35), 257 (3.52), 300*sh* (4.17), 324 (4.30). IR ν_{max}^{Nujol} cm^{-1}: 3422, 1720, 1625, 1560, 1495, 1352, 1330, 1290, 1090. NMR (in C_5D_5N): δ 7.59 (1H, *d*, *J* = 10 Hz, H − 4), 6.25 (1H, *d*, *J* = 10 Hz, H − 3), 7.62 (1H, *s*, H − 5), 6.80 (1H, *s*, H − 8), 4.57 (1H, *d*, *J* = 7.6 Hz, H − 4'), 4,07) 1H, *d*, *J* = 7.6 Hz, H − 3'), 3.68 (3H, *s*, OMe), 1.59 and 1.46 (3H each, *s*, >$C(Me)_2$).

Cis- *and* trans-*acetylmethylisokhellactone* (**10** and **11**). *Cis*-methylisokhellactone (**9**) was acetylated to give a small amount of a resinous residue of **10**. NMR: δ 7.58 (1H, *d*, *J* = 10 Hz, H − 4), 6.19 (1H, *d*, *J* = 10 Hz, H − 3), 7.54 (1H, *s*, H − 5), 6.74 (1H, *s*, H − 8), 5.41 (1H, *d*, *J* = 4 Hz, H − 4'), 4.52 (1H, *d*, *J* = 4 Hz, H − 3'), 3.58 (3H, *s*, OMe), 2.04 (3H, *s*, OCOMe), 1.24 and 1.38 (6H, >$C(Me)_2$). Accordingly, **8** gave **11**, mp 136–137°, $[\alpha]_D^{25}$ −44° (*c* 0.79, EtOH) (lit [5] mp 130–132° $[\alpha]_D$ +77.0° (EtOH) for the enantiomer). (Found: C, 64.00; H, 5.55, M^+ 318, $C_{17}H_{18}O_6$ requires C, 64.15; H, 5.66%). UV λ_{max}^{EtOH} nm (log ε): 220 (4.05), 246 (3.26), 257 (3.30), 300*sh* (4.00), 324 (4.22). NMR: δ 7.59 (1H, *d*, *J* = 10 Hz, H − 4), 6.21 (1H, *d*, *J* = 10 Hz, H − 3), 7.42 (1H, *s*, H − 5), 6.75 (1H, *s*, H − 8), 5.22 (1H, *d*, *J* = 5 Hz, H − 4'), 4.30 (1H, *d*, *J* = 5 Hz, H − 3'), 3.50 (3H, *s*, OMe), 2.10 (3H, *s*, OCOMe), 1.24 (*s*) and 1.38 (*d*) (6H, >$C(Me)_2$).

REFERENCES

1. Bubeva-Ivanova, L. and Zheleva, A. (1972) *Sbornik Trudove NIHFI*, **7**, 179.
2. Zheleva, A., Bubeva-Ivanova, L. and Spassov S. L. (1971) *Z. Naturforsch.* **26b**, 113.
3. Zheleva, A., Soine T. O. and Bubeva-Ivanova, L. (1972) *J. Pharm. Sci.* **61**, 1643.
4. Sano K., Yosioka, I. and Kitagawa, I. (1973) *Chem. Pharm. Bull.* **21**, 2095.
5. Hata K. and Sano, K. (1969) *Yakugaku Zasshi*, **89**, 549.