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STRUCTURE OF THE XANTHONOLIGNOID KIELCORIN

HANNE NIELSEN and PETER ARENDS

Department of Chemistry BC, Royal Danish School of Pharmacy, 2 Universitetsparken, DK-2100 Copenhagen Ø, Denmark

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Key Word Index—*Hypericum*; Guttiferae; xanthonolignoid; kielcorin; structural identification.

INTRODUCTION

The structure of kielcorin, a xanthonolignoid from *Kielmeyera coriacea*, has recently been reported [1] as (**1**) or the alternative (**2**). We hereby present results which confirm the constitution shown in (**2**) for kielcorin isolated from several species of *Hypericum* (*H. androsaemum*, *H. calycinum*, *H. maculatum* and *H. perforatum*). None of the samples of kielcorin from these sources exhibited appreciable optical activity nor did, contrary to the original report, an authentic sample. The possibility of ready racemization was experimentally ruled out and kielcorin may thus be considered a naturally occurring mixture of (**2**) and its enantiomer.

RESULTS AND DISCUSSION

The benzyl ether moiety present in kielcorin proved resistant to hydrogenolysis, even under conditions used for phenyldioxan [2], and it was not hydrolysed by HCl–HOAc [3, 4]. Treatment with aqueous NaOH led to opening of the dioxan ring. The hydrolysis product (**3**) reverted to kielcorin under conditions of EI–MS, but its MW was confirmed by FD–MS.

The resultant phenolic group in (**3**) is situated at C-3′ of the xanthone nucleus as proved by UV spectroscopy [5]. The values for $\lambda_{NaOAc}-\lambda_{MeOH}$ and for $\varepsilon_{NaOAc}/\varepsilon_{MeOH}$ of the K-band were almost coincident with those for 3-hydroxy-2,4-dimethoxyxanthone and well separated from those of 4-hydroxy-2,3-dimethoxyxanthone.

When basic hydrolysis was conducted in the presence of EtOH a second product (**4**), identified by FD–MS as an ethyl derivative of (**3**), was isolated. Apart from the relevant ethoxy group signals, the PMR spectra of (**3**) and (**4**) differed significantly only as regards the low-field methine proton, i.e. that attached to the benzylic carbon. It resonates at δ 5.46 in (**3**) but at δ 4.98 in (**4**). The difference is in excellent agreement with that observed between the values for the corresponding protons of butane-1,3-diol and its 3-methyl ether [6]. Basic hydrolysis of the benzylic ether linkage in kielcorin is probably initiated by ionization of the *para* phenolic group since the corresponding monomethyl ether remains unchanged under these conditions. The mechanism may be visualized as proceeding via an intermediate of quinoid structure [7].

The [α]-values at 400 and 300 nm reported for kielcorin in dioxan [1] are far from negligible. No details regarding type of instrument nor concentration of solutions were given. Taking into account the large absorptivity of the compound and imposing reasonable limitations on the absorbance of the measuring solution, the angles of rotation will however be close to the limits of error. In practice it was not possible to make readings at 365 nm, the lower limit of the polarimeter used. At higher wavelengths [α] was ab. zero and CD measurements in the region 400–220 nm showed $\Delta\varepsilon \approx 0$ for isolated compounds and authentic sample alike.

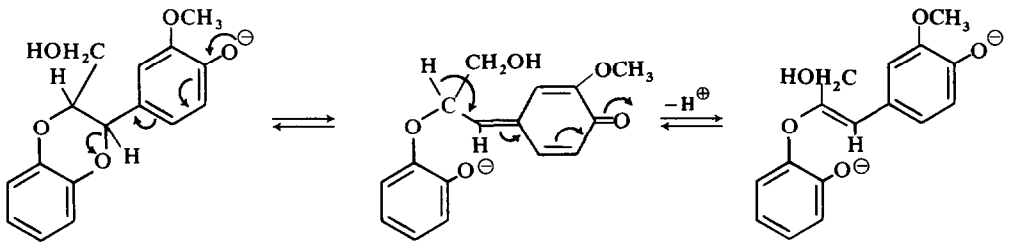
The structurally similar benzodioxan moiety present in dehydrosilybin (**5**) was reported [8] to racemize under basic conditions. A plausible mechanism for this reaction would require reversible removal of the nonbenzylic methine proton from the opened dioxan ring with concomitant loss of configurational identity (Scheme 1). This proton should thus be exchangeable with deuterium under basic conditions. However, neither kielcorin nor an authentic sample of (**5**) showed this behaviour. Instead, exchange of the aromatic protons at C-6 and C-8 took place in (**5**) in accordance with reactions of other phenols [9]. Since the relative configuration in kielcorin has been established as *trans* [1], the natural product must include both the 5*R*, 6*R* and the 5*S*, 6*S* enantiomers of 5-hydroxymethyl-6-(4″-hydroxy-3″-methoxyphenyl)-2,3: 3′,4′-(2′-methoxyxanthono)-1,4-dioxan. Authentic (**5**) was subsequently found to be a racemate. This implies that the structural assignments for silybin may need reinvestigation.

EXPERIMENTAL

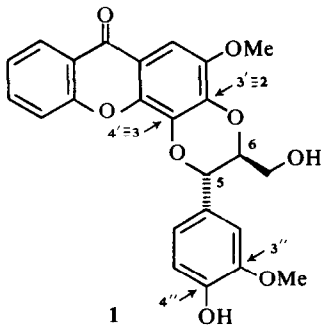
Extraction and purification. Dried roots of *Hypericum androsaemum*, *H. calycinum* (cultivated), *H. maculatum* and *H. perforatum* (wild) were powdered, defatted with petrol and extracted with $CHCl_3$. Purification included column chromatography on Sephadex LH-20 (MeOH) and on Si gel ($C_6H_6 \rightarrow$ EtOAc), affording kielcorin in yields ranging from 0.003 to 0.013% (dry wt), cryst. from $CHCl_3$–EtOH, mp 254–255.5° (corr.). λ_{max}^{MeOH}, ν_{max}^{KBr}, PMR, ^{13}C-NMR and MS data were in close agreement with those reported [1]. Identity was verified by TLC, UV and IR comparison with an authentic sample. $[\alpha]_\lambda^{20} \approx 0°$ (Perkin-Elmer 141 polarimeter) (dioxan: *c* 0.5) for λ between 436 and 589 nm. $\Delta\varepsilon_\lambda \approx 0$ (Dichrographe III CNRS-Roussel-Jouan) (MeOH) for λ between 220 and 400 nm.

Hydrolysis product (**3**). 9.5 mg kielcorin in 10 ml 2N NaOH under N_2 were heated at 90° for 2 hr, then acidified, extracted with $CHCl_3$ and chromatographed on a Si gel column ($CHCl_3 \rightarrow$ EtOAc), affording 6 mg (**3**). MS (Varian MAT-CH5 instrument with an EI/FI/FD ion source) EI 70 eV, 180°C, *m/e* (rel. int.): 436 (45) [$M^+ - H_2O$], 419 (14), 418 (45), 299 (75), 270 (25), 258 (32), 243 (16), 181 (15), 180 (96), 162 (45), 137 (100), 124 (49), FD, *m/e*: 455 [$M^+ + 1$]. λ_{max}^{MeOH} nm (log ε): 230 (4.52), 281 (3.88), 312 (3.83), 354 (3.63). $\lambda_{max}^{MeOH+NaOAc}$ nm (log ε): 213 (4.58), 281 (3.98), 378 (4.02). PMR (270 MHz, $(CD_3)_2CO$), δ(TMS)): 6.8–8.2 (8 aromat. H), 5.46 (1H, *d*, J = 4 Hz, —O—C<u>H</u>—Ph), 4.31 (1H, *m*, —O—C<u>H</u>—CH_2—), 4.15 (1H, *dd*, J = 7 and 13 Hz, —C<u>H</u>HOH), 3.95 (3H, *s*, —OCH_3), 3.75 (3H, *s*, —OCH_3), 3.70 (1H, *dd*, J = 4 and 13 Hz, —OCH<u>H</u>OH).

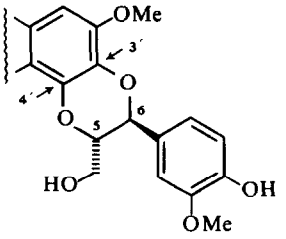
Ethanolysis product (**4**). Hydrolysis as above but with 6 ml EtOH added and 0.5 hr heating led after work-up to 6 mg (**4**) besides 2.5 mg of (**3**). EI–MS, 70 eV, 150°C, *m/e* (rel. int.): 482 (5) [M^+], 436 (34), 418 (6), 299 (7), 258 (10), 243 (6), 181 (83), 180 (34), 138 (91), 137 (36), 120 (100). FD–MS, *m/e*: 483 [$M^+ + 1$]. λ_{max}^{MeOH} as for (**3**). PMR (90 MHz, $(CD_3)_2CO$), (δ(TMS)): 4.98 (1H, *d*, J = 4 Hz, —O—C<u>H</u>—Ph), 3.61 (2H, *q*, J = 7 Hz,



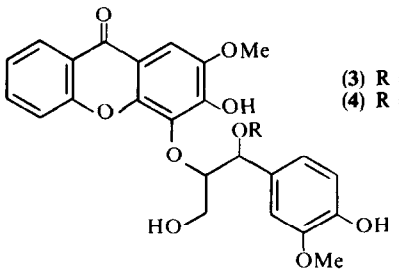
Scheme 1



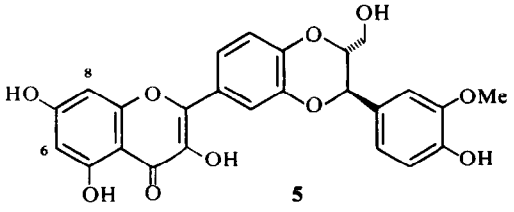
1



2



(3) R = H
(4) R = Et



5

—O—C<u>H</u>$_2$—CH$_3$), 1.24 (3H, *t*, *J* = 7 Hz, —O—CH$_2$—C<u>H</u>$_3$), other signals as for (**3**).

Kielcorin mono-Me ether was prepared by reaction with CH_2N_2 in Et_2O–MeOH (9 + 1) followed by column chromatography on Si gel (CH_2Cl_2 → $CHCl_3$).

Attempted proton-deuterium exchange. 5 mg kielcorin, (**5**), resp. in 1 ml of $(CD_3)_2CO$ were added 5 mg of K_2CO_3 and 50 μl of D_2O and heated at 90° in closed vessels for 0.5 hr. After acidification with 20% DCl in D_2O and standing for 12 hr the mixtures were extracted with $CHCl_3$, the extracts evapd and the PMR spectra in DMSO-d_6 for kielcorin and in C_5D_5N for (**5**) recorded. The spectrum of kielcorin was virtually unchanged; TLC revealed slight hydrolysis to (**3**). In the spectrum of (**5**) the signals corresponding to H-6 and H-8 had disappeared.

Optical activity of (**5**). $[\alpha]_\lambda^{20} = 0°$ (dioxan; *c* 0,6). $\Delta\varepsilon_\lambda \approx 0$ (MeOH) for λ between 220 and 350 nm.

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REFERENCES

1. Castelão, J. F., Jr., Gottlieb, O. R., De Lima, R. A., Mesquita, A. A. L., Gottlieb, H. E. and Wenkert, E. (1977) *Phytochemistry* **16**, 735.
2. Baker, R. H., Cornell, K. H. and Cron, M. J. (1948) *J. Am. Chem. Soc.* **70**, 1490.
3. Geissman, T. A. and Mojé, W. (1951) *J. Am. Chem. Soc.* **73**, 5765.
4. Dreyer, D. L. (1970) *J. Org. Chem.* **35**, 2294.
5. Correa, D. B., Silva, L. G. F., Gottlieb, O. R. and Gonçalves, S. J. (1970) *Phytochemistry* **9**, 447.
6. Szymanski, H. A. and Yelin, R. E. (1968) *NMR Band Handbook*, p. 182. IFI/Plenum, New York–Washington.
7. Gierer, J. and Norén, I. (1962) *Acta Chem. Scand.* **16**, 1713.
8. Pelter, A. and Hänsel, R. (1975) *Chem. Ber.* **108**, 790.
9. Kirby, G. W. and Ogunkoya, L. (1965) *J. Chem. Soc.*, 6914.