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# XANTHONOLIGNOIDS FROM *KIELMEYERA CORIACEA**

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**Key Word Index**—*Kielmeyera coriacea*; Guttiferae; synthesis; kielcorin; *cis*-kielcorin; kielcorin B; xanthonolignoids.

**Abstract**—The synthesis of kielcorin and the tentative identification of kielcorin B (5-hydroxymethyl-6-guaiacyl-2,3:3′,2′,4′-methoxyxanthone-1,4-dioxane), isomeric xanthonolignoids of *Kielmeyera coriacea* are reported.

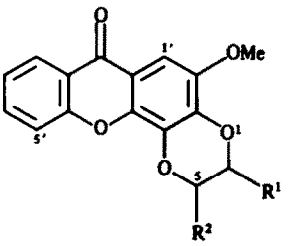
## INTRODUCTION

The presence of kielcorin in several *Kielmeyera* (Guttiferae) species was mentioned briefly in previous papers [2, 3]. Of the two alternative structures **1a** and **1b** which were subsequently proposed [4] the former was shown to represent kielcorin [5]. The present paper reports the synthesis of **1a** and of *cis*-kielcorin (**1c**). To kielcorin B, a companion compound of **1a** in *Kielmeyera coriacea* Mart., structure **2** was tentatively assigned.

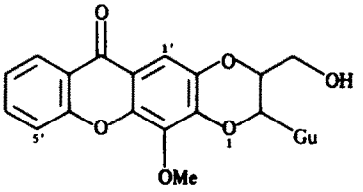
## RESULTS AND DISCUSSION

The synthesis of **1a** involved as starting materials salicylic acid (**3a**), pyrogallol (**4a**) and coniferyl alcohol (**5**). The two former were converted via **3b** (yield 30%) and via **4b** (75%) [6] → **4c** (30%) → **4d** (80%) [7], respectively, into **3c** (80%) and **4e** (60%). Friedel–Crafts condensation of the end products of these reaction sequences gave the benzophenone **6** (80%) [8] subsequently converted via **7a** (30%) [8] to 3,4-dihydroxy-2-methoxyxanthone (65%) [9]. The oxidative coupling of catechols and coniferyl alcohol (**5**) with $Ag_2O$ in $C_6H_6$ has been used successfully in the synthesis of eusiderin [10] and silybin [11]. Application of the procedure to **7b** + **5** and chromatographic fractionation of the reaction product led to kielcorin (**1a**), *cis*-kielcorin (**1c**) and a mixture of two compounds with probable structures **8a** and **8b**.

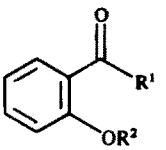
The spectra obtained for synthetic **1a** were identical with the spectra of naturally occurring kielcorin. This, however, is not conclusive evidence for the structure since the spectra of iso-kielcorin (**1b**) may not be significantly different. Thus *a priori* it was thought that the *para* (**1a**) or *meta* (**1b**) relationship of the benzoyloxy groups with respect to the carbonyls could provide diagnostic NMR chemical shift differences. Although the study of models (**10a** vs **10b** [11], **10c** vs **10d** [12]) indeed indicated shifts of $\delta$ to occur in the expected directions (Table 1), the differences between the observed values for **1a** and the calculated values (based on mean shifts of $\delta$ of the models) for **1b** are slight. Considering additionally that the vast predominance of **1a** in the synthetic mixture diminishes spectral resolution, no assertion as to the presence or absence of **1b** can be made and *vice versa*.




**1a** $R^1$ = Gu, $R^2$ = $CH_2OH$, $R^1/R^2$ *trans*
**1b** $R^1$ = $CH_2OH$, $R^2$ = Gu, $R^1/R^2$ *trans*
**1c** $R^1$ = Gu, $R^2$ = $CH_2OH$ $R^1/R^2$ *cis*

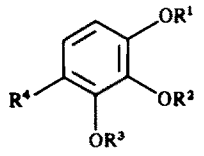



**2**

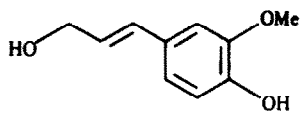



**3a** $R^1$ = OH, $R^2$ = H
**3b** $R^1$ = OH, $R^2$ = Me
**3c** $R^1$ = Cl, $R^2$ = Me

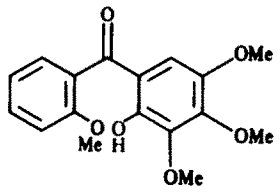
* Part 40 in the series "The Chemistry of Brazilian Guttiferae". For Part 39 see Ref. [1]. Dedicated to the memory of our mentor and friend Professor Joaquim António de Barros Polónia (1925–1985).



**4a** $R^1 = R^2 = R^3 = R^4 = H$
**4b** $R^1 = R^2 = R^3 = H$, $R^4 = Ac$
**4c** $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = Ac$
**4d** $R^1 = R^2 = Me$, $R^3 = H$, $R^4 = OH$
**4e** $R^1 = R^2 = R^3 = Me$, $R^4 = OMe$



**5**



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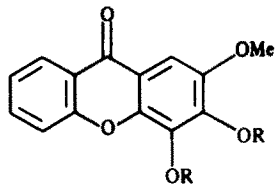
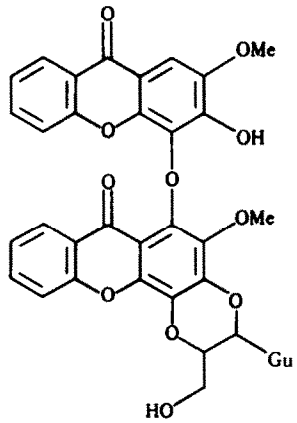
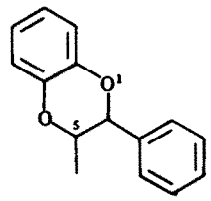


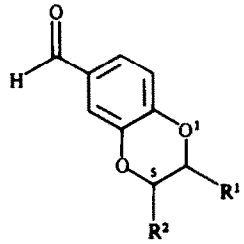
**7a** R = Me
**7b** R = H



**8a** Gu/$CH_2OH$ *trans*
**8b** Gu/$CH_2OH$ *cis*



**9a** Ph/Me *trans*
**9b** Ph/Me *cis*



**10a** $R^1$ = Gu, $R^2 = CH_2OH$
**10b** $R^1 = CH_2OH$, $R^2$ = Gu
**10c** $R^1$ = Gu$^1$, $R^2$ = Me
**10d** $R^1$ = Me, $R^2$ = Gu$^1$

Gu – 4 - hydroxy - 3 - methoxyphenyl (guaiacyl)
Gu$^1$ – 4 - benzyloxy - 3 - methoxyphenyl

Fortunately our synthetic kielcorin was identical in one more respect, namely the opening of the dioxane ring by alkali [5], with the natural product. Thus the identification of **1a** relies on the postulate that **1b** would not react with alkali [5]. Besides, the formation of **1b**, in nature as well as in the laboratory, would contradict the regioselectivity of the oxidative coupling reaction deduced by mechanistic considerations [11].

With respect to other spectral features, that however also do not differentiate **1a** and **1c**, the $^{13}C$ NMR signals due to the methoxyls were recorded at $\delta$ 56.57 and 56.69. Thus both these groups are vicinal to at least one unsubstituted aromatic position and **1a** indeed includes a 2-methoxy- and not, as in **2**, a 4-methoxyxanthone moiety. The *trans* vs *cis* arrangement of the substituents at C-5 and C-6, respectively, in **1a** and **1c** was recognized by comparison of $^1H$ NMR data. The analogous data for model compounds **9a** vs **9b** [13] (Table 2) confirm these stereochemical assignments.

The relevant MS ions of the **8a** + **8b** mixture were recorded at *m/z* 514 (highest mass, probably representing

Table 1. $^1H$ NMR chemical shifts ($\delta$) of *trans*- (**1a**) and iso- (**1b**) kielcorins, *para* (**10a**, **10c**) and *meta* (**10b**, **10d**) model benzyloxybenzaldehydes

| | **1a** | **1b** | **10a** | **10b** | **10c** | **10d** | $\Delta\delta$ | $\Delta\delta$ |
|---|---|---|---|---|---|---|---|---|
| H | | Calc. | [11] | [11] | [12] | [12] | **10b–10a** | **10d–10c** |
| 5 | 4.39 | 4.41 | 4.05 | 4.05 | 4.16 | 4.20 | 0.00 | 0.04 |
| 6 | 5.07 | 5.00 | 5.04 | 4.96 | 4.68 | 4.62 | −0.08 | −0.06 |

Table 2. $^1$H NMR chemical shifts ($\delta$), multiplicities (m) and coupling constants ($J_{H\text{-}5,H\text{-}6}$ in Hz) of *trans*- (**1a**) and *cis*- (**1c**) kielcorins, *trans*- (**9a**) and *cis*- (**9b**) model dioxans

| | **1a** | | | **1c** | | | **9a**[13] | | | **9b**[13] | | | $\Delta\delta$ | $\Delta\delta$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | $\delta$ | m | $J$ | $\delta$ | m | $J$ | $\delta$ | m | $J$ | $\delta$ | m | $J$ | **1c–1a** | **9b–9a** |
| 5 | 4.39 | *m* | | 4.96 | *m* | | 4.00 | *m* | | 4.51 | *m* | | 0.57 | 0.51 |
| 6 | 5.07 | *d* | 9 | 5.47 | *d* | <4 | 4.52 | *d* | 8 | 5.10 | *d* | 3 | 0.40 | 0.58 |

a 2 × **7b** − 2H fragment), 436 (**1a**), 432 (**1a** − 4H), 258 (base peak, **7b**) and 180 (**5**). The $^1$H NMR is also consistent with the structure of compounds formed by oxidative coupling of **7a** + **1a** (**8a**) and **7a** + **1c** (**8b**). On the one hand the H-1′ signal was registered at half the intensity of the H-8′ signal and at lower field ($\delta$7.35) than the H-1′ signal of **1a** ($\delta$7.17) [but not of **1c** ($\delta$7.34)]. On the other hand all signals attributed to xanthone protons appear twice at slightly different $\delta$ values. The dioxane H-5 and H-6 also give rise to two pairs of signals: 4.41 (*m*) and 5.05 (*J* = 9 Hz), 4.86 (*m*) and 5.76 (*J* small), typical, respectively, of *trans*- (**1a**) and *cis*- (**1c**) kielcorins (*cf.* Table 2).

Certain crude kielcorin fractions *ex Kielmeyera coriacea*, upon repeated crystallizations, surprisingly led to products of lower and larger melting ranges. The phenomenon was accompanied by the separation from the original H-5 NMR multiplet of **1a** ($\delta$4.39) of a signal ($\delta$4.14) endowed with precisely the same contour. The spectrum of the product with the highest enrichment in the additional compound showed a 6:1 intensity ratio of these signals. The major component of the mixture is of course kielcorin (**1a**). The minor component cannot be iso-kielcorin (**1b**) or *cis*-kielcorin (**1c**) (*cf.* spectral data) and is tentatively identified with **2**. In this structure, designated kielcorin B, the inductive diminution of electron density by the xanthone heterocycle on H-5 of **1a** is absent and the corresponding signal should indeed appear at relatively higher field.

## EXPERIMENTAL

*Preparation of kielcorin* (**1a**). Compounds **7b** (0.4 g) and **5** (0.3 g) were dissolved in anhydrous $C_6H_6$ (500 ml) and $Me_2CO$ (160 ml). $Ag_2O$ (1.05 g) was added. The mixture was stirred in darkness at room temp. (7 hr). Filtration and evapn gave a crude product (0.63 g) which was chromatographed (silica gel, $CHCl_3$ and $CHCl_3$–MeOH, 1:1) yielding **1a** (65 mg), **1c** (20 mg), **8a** + **8b** (40 mg) and mixture of polar products.

(±)-*Kielcorin* (**1a**). Mp and lit. [2] mp 250–251° ($CHCl_3$–EtOH). $^1$H NMR (300 MHz, DMSO): $\delta$9.29 (*s*, PhOH), 8.18 (*dd*, *J* = 7, 2 Hz, H-8′), 7.84 (*td*, *J* = 7, 2 Hz, H-6′), 7.66 (*dd*, *J* = 9, 2 Hz, H-5′), 7.47 (*td*, *J* = 7, 2, H-7′), 7.17 (*s*, H-1′), 7.09 (*br s*, H-2″), 6.93 (*dd*, *J* = 8, H-5″), 6.86 (*dd*, *J* = 8, H-6″), 5.16 (*s*, $CH_2OH$), 5.07 (*d*, *J* = 8 Hz, H-6), 4.39 (*m*, *J* = 8 Hz, H-5), 3.75 (*dd*, *J* = 12, 3.6 Hz, $CH_2$), 3.86 and 3.81 (2*s*, 2 OMe). $^{13}$C NMR (20 MHz, DMSO): $\delta$174.60 (C-9′), 155.17 (C-4b′), 147.60 (C-3″), 147.28 (C-4″), 145.71 (C-2′), 142.48 (C-4a′), 139.36 (C-3′), 134.54 (C-6′), 132.35 (C-4′), 126.55 (C-1″), 125.72 (C-8′), 124.06 (C-7′), 120.75 (C-6″), 120.63 (C-8a′), 117.88 (C-5′), 115.38 (C-5″), 113.79 (C-9a′), 112.10 (C-2″), 96.42 (C-1′), 77.75 (C-6), 76.27 (C-5), 59.83 ($CH_2$), 56.69 and 56.57 (2 OMe). MS (rel. int.) *m/z*: 436 $[M]^+$ (90), 418 (18), 299 (23), 258 (36), 256 (24), 243 (20), 228 (32), 180 (86), 162 (27), 151 (16), 137 (100), 124 (98).

(±)-cis-*Kielcorin* (**1c**). Mp 265–268° ($Me_2CO$). $^1$H NMR (300 MHz, DMSO): $\delta$8.14 (*d*, *J* = 7.5 Hz, H-8′), 7.79 (*td*, *J* = 7.5 and 1.5 Hz, H-6′), 7.66 (*dd*, *J* = 7.5 and 1.5 Hz, H-5′), 7.43 (*td*, *J* = 7.5 and 1.5 Hz, H-7′), 7.34 (*s*, H-1′), 7.28 (*s*, H-2″), 7.17 (*d*, *J* = 7.5 Hz, H-5″), 6.89 (*d*, *J* = 7.5 Hz, H-6″), 5.47 (*d*, *J* small, H-6), 4.96 (*m*, H-5), 3.97 and 3.79 (2*s*, 2 OMe), 3.91 and 3.80 ($CH_2$). MS (rel. int.) *m/z*: 436 $[M]^+$ (2), 432 (40), 404 (10), 269 (10), 258 (100), 243 (46), 225 (20), 215 (20).

*Mixture* (**8a** + **8b**). $^1$H NMR (300 MHz, DMSO): $\delta$8.18 (*dd*, *J* = 7, 2 Hz, H-8′), 8.13 (*dd*, *J* = 7, 2 Hz, H-8′), 7.83 (*td*, *J* = 7.7, 2 Hz, H-6′), 7.74 (*td*, *J* = 7.7, 2 Hz, H-6′), 7.69 (*dd*, *J* = 7, 2 Hz, H-5′), 7.61 (*dd*, *J* = 7, 2 Hz, H-5′), 7.46 (*td*, *J* = 8.8, 2 Hz, H-7′), 7.36 (*s*, H-1′), 7.35 (*s*, H-1′), 7.23 (*s*, H-2″), 6.94 (*d*, *J* = 7 Hz, H-5″, **8b**), 6.87 (*d*, *J* = 8 Hz, H-5″, **8a**), 6.79 (*d*, *J* = 8 Hz, H-6″), 5.75 (H-6, **8b**), 5.05 (*d*, *J* = 11 Hz, H-6, **8a**), 4.86 (*m*, H-5, **8b**), 4.41 (*m*, H-5, **8a**). MS (rel. int.) *m/z*: 514 (2), 436 (2), 432 (2), 258 (100), 243 (56), 228 (24), 215 (20), 180 (10), 157 (20).

(±)-*Kielcorin* (**1a**) + (±)-*kielcorin B* (**2**). A crude natural sample of kielcorin *ex Kielmeyera coriacea* (16 mg) [2] was submitted to repeated column and thin layer chromatography (silica gel, $CHCl_3$). The final product (7 mg) consisted of a 6:1 mixture of **1a** and **2**. $^1$H NMR (300 MHz, DMSO, only the signals attributed to **2** are given): $\delta$9.26 (*s*, PhOH), 8.21 (*dd*, *J* = 7, 2 Hz, H-8′), 7.86 (*td*, *J* = 9, 9.2 Hz, H-6′), 7.69 (*dd*, *J* = 9, 2 Hz, H-5′), 7.49 (*dd*, *J* = 7, 7.2 Hz, H-7′), 7.22 (*s*, H-1′), 7.07 (*s*, H-2″), 6.92 (*dd*, *J* = 9, 2 Hz, H-6″), 6.84 (*d*, *J* = 9 Hz, H-5″), 5.12 (*d*, *J* = 7 Hz, H-6′), 4.14 (*m*, H-5), 3.87 and 3.79 (2*s*, 2 OMe).

*Preparation of intermediates.* Methylation of **3a** gave **3b**. This (5.56 g) was added in small portions to a boiling soln of $SOCl_2$ (6 ml) in anhydrous $C_6H_6$ (10 ml). Subsequently another portion of $SOCl_2$ (8 ml) was added. The soln was refluxed (30 min) and evapd to yield **3c** (5.4 g). Compound **4b** was prepared from $Ac_2O$, AcOH and pyrogallol (**4a**) according to [6] except for the order of addition of pyrogallol to $Ac_2O$ which was inverted. Methylation ($Me_2SO_4$, $K_2CO_3$, $Me_2CO$) of **4b** (3.5 g) gave **4c** (1.2 g), mp 75–77°. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 1640, 1613, 1587, 1504, 1282, 1090. $^1$H NMR (60 MHz, $CDCl_3$): $\delta$12.53 (*s*, PhOH), 7.52 (*d*, *J* = 9 Hz, H-4), 6.52 (*d*, *J* = 9 Hz, H-5), 3.97, 3.90 (2*s*, 2 OMe), 2.60 (*s*, Me). Compound **4d** was prepared from **4c**, 10% aq. NaOH and 3% aq. $H_2O_2$ according to [7]. $^1$H NMR (60 MHz, $CDCl_3$): $\delta$6.63 (*d*, *J* = 9 Hz, H-6), 6.35 (*d*, *J* = 8 Hz, H-5), 3.90, 3.80 (2*s*, 2 OMe). $Me_2SO_4$-Methylation of **4d** gave **4e**, $^1$H NMR (60 MHz, $CDCl_3$): $\delta$6.60 (*s*, H-4, H-5), 3.90 (*s*, 2 OMe), 3.80 (*s*, 2 OMe). Compound **6** was prepared according to [8] using **3c** and **4e**. IR $\nu_{max}^{KBr}$ cm$^{-1}$: 2941, 1773, 1656, 1603, 1587, 1477, 1295. $^1$H NMR (60 MHz, $CDCl_3$): $\delta$12.77 (*s*, PhOH), 7.52 (*dd*, *J* = 8, 2 Hz, H-6′) 7.40–6.86 (*m*, H-3′,4′,5′), 6.59 (*s*, H-6), 4.03, 3.96, 3.80, 3.60 (4*s*, 4 OMe). Compound **7a** was prepared by cyclization of compound **6** [8]. Compound **7b** was prepared by selective demethylation of compound **7a** [9]. $^1$H NMR (60 MHz, $d_6$-$Me_2CO$): $\delta$8.27 (*dd*, *J* small, H-8), 8.6–7.3 (m, H-5,6,7), 7.30 (*s*, H-1), 4.00 (*s*, OMe).

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## REFERENCES

1. Oliveira, W. G. de, Mesquita, A. A. L., Lima, R. A. de, Gottlieb, O. R. and Gottlieb, H. E. (1984) *Phytochemistry* **23**, 2390.
2. Gottlieb, O. R., Mesquita, A. A. L., Silva, E. M. da and Melo, M. T. de (1969) *Phytochemistry* **8**, 665.
3. Gottlieb, O. R., Mesquita, A. A. L. and Nagem, T. J. (1971) *Phytochemistry* **10**, 2253.
4. Castelão Jr, J. F., Gottlieb, O. R., Lima, R. A. de, Mesquita, A. A. L., Gottlieb, H. E. and Wenkert, E. (1977) *Phytochemistry* **16**, 735.
5. Nielsen, H. and Arends, P. (1978) *Phytochemistry* **17**, 2040.
6. Badhawar, I. C. and Venkataraman, K. (1943) *Org. Synth. Coll. Vol.* II, 304.
7. Baker, W., Jukes, E. H. T. and Subramanyam, C. A. (1934) *J. Chem. Soc.* 1681.
8. Quillinan, A. J. and Scheinmann, F. (1973) *J. Chem. Soc. Perkin Trans. 1* 1329.
9. Gottlieb, O. R., Magalhães, M. T., Camey, M., Mesquita, A. A. L. and Barros Corrêa, D. de (1966) *Tetrahedron* **22**, 1777.
10. Merlini, L. and Zanarotti, A. (1975) *Tetrahedron Letters* 3621.
11. Merlini, L., Zanarotti, A., Pelter, A., Rocheford, M. P. and Hänsel, R. (1980) *J. Chem. Soc. Perkin Trans 1* 775.
12. Su, T. L., Schulz, J. and Hänsel, R. (1977) *Chem. Ber.* **110**, 3867.
13. Proietti, G., Corsano, S. and Castagnino, E. (1981) *J. Heterocycl. Chem.* **18**, 415.