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1,2,8-TRIOXYGENATED XANTHONES FROM *KIELMEYERA PETIOLARIS*[1]

O. R. Gottlieb,[a] M. Taveira Magalhães[a,c] and G. M. Stefani[b]
Departamento de Química Orgânica, Universidade de Brasília, Brasília, Brazil[a]
Instituto de Química Básica, Universidade de Minas Gerais, Belo Horizonte, Brazil[b]
Department of Chemistry, Royal College of Advanced Technology, Salford, Lancashire, England[c]

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Abstract—The structures of 2,8-dihydroxy-1-methoxyxanthone and 1,2-dimethoxy-8-hydroxyxanthone are proposed for two constituents of *Kielmeyera petiolaris* (Spr.) Mart.

Two crystalline constituents (I and II) were isolated from the benzene extract of *Kielmeyera petiolaris* (Spr.) Mart., a tree which, like other species of the Guttiferae family currently under investigation,[2] grows abundantly on the central Brazilian plateau. Elementary analysis, mol. wt. determination and UV spectroscopy indicate dihydroxymethoxyxanthone (I) and dimethoxy-hydroxyxanthone (II) structures. Furthermore, since methylation with dimethyl sulphate converts the compounds into one and the same trimethoxy derivative, both xanthones possess an identical oxygenation pattern.

Indeed, in the aromatic region, the NMR spectra of I and II (in trifluoroacetic acid) are very similar, showing a pair of doublets (τ 2·4 and 2·6, J 9·5 c/s), a triplet (τ 2·3, J 8·5 c/s) and two quartets (τ3·0 and 3·1, J 8·5 and 1·0 c/s). This coupling pattern suggests the presence of two *ortho* protons on one ring and three vicinal protons on the other ring, and is thus compatible with oxygenation of the xanthone skeleton at positions 1,2,5; 3,4,5; 1,2,8 or 1,5,6.[3] The first two structural alternatives can be eliminated, since they contain a proton (at C-8), vicinal to the strongly electron withdrawing carbonyl group. Even though, in this case, a hydroxyl or methoxyl group would be present at position 5, the quartet corresponding to the proton at C-8 would

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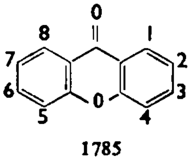
[1] For a preliminary report see Part IV of this series: L. D. Antonaccio, G. M. Stefani, O. R. Gottlieb and M. Taveira Magalhães, *Anais acad. brazil. ciênc.* in press.

[2] Cf. Part V of this series: O. R. Gottlieb, M. Taveira Magalhães, M. Camey, A. A. Lins Mesquita and D. de Barros Corrêa, *Tetrahedron* **22**, 1777 (1966).

[3] The numbering system is based on xanthene-9-one as the basic skeleton, following the rules given in Handbook for Chemical Society Authors, Special Publication No. 14, The Chemical Society, London, 1960.



be expected to appear at 2·02.[4] The last of these alternatives can be ruled out, since the trimethoxyxanthone derived from the natural compounds shows pronounced depression of the m.p. upon admixture of an authentic sample of 1,5,6-trimethoxyxanthone[5] (quoted as 3,4,8-trimethoxyxanthone).

The UV spectra of the compounds, as well as those of their derivatives, are informative. Addition of aluminium chloride to both I and II causes similar bathochromic shifts in their absorption spectra, establishing the presence of hydroxyl groups at the 8 (or equivalent 1) position. Upon acetylation of the dihydroxymethoxyxanthone (I)a di-O-acetyl-derivative results, the UV spectrum of which is comparable to that of 1-methoxyxanthone (Table 1). This suggests the existence of a 1-methoxy-8-hydroxy system and only the second hydroxy group remains to be located.

Addition of boric acid, while leaving the UV spectrum of compound I unaltered, causes a shift of the maxima of its demethylated derivative. The second hydroxyl can, consequently, be located only at position 2, *ortho* to the methoxyl group.

TABLE 1. COMPARISON OF UV ABSORPTION MAXIMA, mμ (ε): 2,8-DIACETOXY-1-METHOXYXANTHONE/MONOMETHOXYXANTHONES (solvent: EtOH)

2,8-Diacetoxy-1-methoxyxanthone	236 (52,800)	243 (55,300)	272 (14,100)	295 (4,400)	347 (9,000)
1-Methoxyxanthone	237 (34,800)	245 (31,400)	276 (8,200)	295 (7,800)	346 (8,100)
2-Methoxyxanthone	236 (42,700)	249 (37,000)		303 (4,900)	359 (7,100)
3-Methoxyxanthone	236 (39,600)		267 (9,900)	301 (15,600)	325 (10,000)
4-Methoxyxanthone	235 (32,400)	248 (39,500)	273		346 (5,800)

TABLE 2. UV ABSORPTION MAXIMA, mμ (ε), OF 1,2,8-TRIOXYGENATED XANTHONES (solvent: EtOH)

1,2,8-Trihydroxyxanthone	241 (26,000)	265 (36,400)	290 (7,800)	338 (8,800)
2,8-Dihydroxy-1-methoxyxanthone (I)	238 (26,800)	262 (32,800)	290 (5,200)	322 (4,400)
1,2-Dimethoxy-8-hydroxyxanthone (II)	238 (29,800)	260 (35,200)	290 (5,600)	322 (5,000)
1,2,8-Trimethoxyxanthone	241 (49,500)		284 (8,100)	311 (9,500)

The structure of 2,8-dihydroxy-1-methoxyxanthone is, therefore, proposed for compound I. Formulation of II as 1,2-dimethoxy-8-hydroxyxanthone follows, since II can be synthetized by partial methylation of I with diazomethane. It is known that methylation or demethylation of oxygen functions at carbons 1 or 8 give rise to considerable spectral shifts (Table 2). The fact that both I and II have practically identical UV spectra indicates that diazomethane reacts with a hydroxyl group at C-2 and not at C-8. Furthermore, the abundance of the $(M-15)^+$ fragment in the mass spectrum of II (89 % of base peak), as compared to the analogous fragment formed from I (12 %), is probably due to the tendency of formation of a quinonoid structure, assisted by expulsion of a methyl from a 2-methoxy group.

An independent, if indirect, confirmation of the proposed structure for compound II was provided as follows. Positive ferric chloride and cobaltinitrite[6] tests respectively indicate the hydroxyl as vicinal to the carbonyl and an unsubstituted aromatic position. De-etherification of II affords a derivative which is easily decomposed in alkaline

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[4] O. R. Gottlieb, M. Taveira Magalhães and F. Scheinmann, forthcoming publication.

[5] G. D. Shah and R. C. Shah, *J. Sci. Ind. Research, India* **15B**, 630 (1956).

[6] F. Feigl, *Spot Tests in Organic Analysis* (6th Edition), p. 200, Elsevier, Amsterdam (1960).

medium and gives a positive titanium trichloride reaction.[7] Two of the hydroxyls of the demethylated compound and, consequently, the two methoxyls in II, must, therefore, be located in vicinal positions. Of the four structural alternatives compatible with these data, only the 6,7-dimethoxy-1-hydroxyxanthone is known[8] (quoted as 2,3-dimethoxy-8-hydroxyxanthone). The m.p. of this compound (228–231°), when compared with II (173–174°), precludes their identity. 3,4-Dimethoxy-1-hydroxyxanthone, m.p. 169–170°,[9] and 5,6-dimethoxy-1-hydroxyxanthone, m.p. 183–185°, were synthesized by diazomethane methylation of the previously described 1,4-dihydroxy-3-methoxyxanthone[10] and 1,5,6-trihydroxyxanthone[5] (quoted as 3,4,8-trihydroxyxanthone) respectively. Direct comparison prove that these dimethoxyhydroxyxanthones are not identical with II, which is therefore, 1,2-dimethoxy-8-hydroxyxanthone.

The occurrence of 2,8-dihydroxy-1-methoxyxanthone and 1,2-dimethoxy-8-hydroxyxanthone in Guttiferae is exceptional from the standpoint of chemical taxonomy. 1,8-Substitution, in the form of the 1,2,6,8 or 1,3,5,8-oxygenation pattern, has, until now, only been found in xanthones isolated from the Gentianaceae family.

EXPERIMENTAL

Unless otherwise stated NMR spectra were determined as trifluoroacetic acid solutions, using tetramethylsilane as internal standard, in a Varian A-60 spectrometer. Chemical shifts are given on the τ scale. Coupling constants, J, are in c/s. s = singlet, d = doublet, t = triplet, q = quartet, o = octet, m = multiplet. IR spectra were determined as nujol mulls, using a Perkin–Elmer Infracord model 137 B spectrometer. Only significant bands are quoted. UV spectra were determined as 95% EtOH solutions, using a Beckman DU spectrophotometer. Mass spectra were obtained using a Consolidated Electrodynamics Corporation model 103-C spectrometer operating at an ionizing voltage of 70 eV. All mol. wts quoted were obtained by mass spectrometry. M.ps were determined using a Kofler hot stage microscope and are uncorrected. Separations by column chromatography were carried out using Merck Kieselgel 0·05–0·20 mm and TLC separations were carried out with Merck Kieselgel G.

Isolation procedure. Trunk wood (10 kg) of *Kielmeyera petiolaris* was separated from its bark, reduced to powder and extracted with benzene in a Soxhlet apparatus. The solution was concentrated and washed exhaustively with conc Na_2CO_3 aq. The clear aqueous solution was acidified and extracted with $CHCl_3$. Both, the benzene and the $CHCl_3$-solutions, were dried and evaporated.

The carbonate soluble portion of the extract was dissolved in benzene, and the solution was washed repeatedly with small volumes of dil Na_2CO_3aq, which were then acidified separately. While the first washings yielded only resinous masses, the later ones precipitated yellow crystals (I, 2,8-dihydroxy-1-methoxyxanthone; 0·17 g).

The carbonate insoluble portion of the extract was washed with hexane and the resulting solid was dissolved in a hot mixture of benzene–hexane (6:1) which, upon cooling, precipitated yellow crystals (II, 1,2-dimethoxy-8-hydroxyxanthone; 0·16 g).

2,8-*Dihydroxy*-1-*methoxyxanthone*. Compound I was obtained, after recrystallizations from EtOH, as yellow needles, m.p. 197–199°; M.W. 258. (Found: 65·21; H, 3·92; OCH_3, 11·89. $C_{14}H_{10}O_5$ requires: C, 65·11; H, 3·87; OCH_3, 12·10%.) λ_{max} Table 2. No alteration in presence of AcONa or H_3BO_3 + AcONa. λ_{max}^{NaOH} 254, 275, 350 mμ (ε resp. 31,400; 25,300; 4,000); $\lambda_{max}^{AlCl_3}$ 238, 277, 311, 350 mμ (ε resp. 28,800; 28,500; 6,200; 4,000). ν_{max} 3330, 1647, 1607, 1583 cm^{-1}. τ 7-H 3·08 (q, J 8·0, 1·0), 6-H 2·30 (t, J 8·0), 5-H 2·91 (q, J 8·0, 1·0) 4-H 2·60 (d, J 9·5), 3-H 2·41 (d, J 10·0), 1-OCH_3 5·90 (s).

1,2-*Dimethoxy*-8-*hydroxyxanthone*. Compound II was obtained, after recrystallizations from EtOH, as yellow needles, m.p. 173–174°, M.W. 272. (Found: C, 65·88, H, 4·74, OCH_3, 22·65

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[7] F. Weygand and E. Csendes, *Chem. Ber.* **85**, 45 (1952).

[8] H. F. Dean and M. Nierenstein, *J. Chem. Soc.* 802 (1920).

[9] A. A. Lins Mesquita, Ph.D. Thesis, Universidade de Minas Gerais, Brasil (1965).

[10] V. V. Kane, A. B. Kulkarni and R. C. Shah, *J. Sci. Ind. Research, India* **18B**, 75 (1959).

$C_{15}H_{12}O_5$ requires: C, 66·17, H, 4·41, 2 OCH_3, 22·79%.) Gibbs test: λ_{max} 665 mμ (ε13,500). λ_{max} Table 2. No alteration in presence of AcONa. λ_{max}^{NaOH} 238, 263, 326 mμ (ε resp. 37,600; 17,800; 7,000); $\lambda_{max}^{AlCl_3}$ 238, 276, 310, 351 mμ (ε resp. 31,900; 30,800; 6,700; 4,400). ν_{max} 1647, 1607, 1574, 827 cm^{-1}. τ 7-H 3·16 (q, J 8·5, 1·0), 6-H 2·30 (t, J 8·5), 5-H 3.00 (q, J 8·5, 1·0), 4-H 2·62 (d, J 10·0), 3-H 2·36 (d, J 9·5), 1,2-OCH_3 5·81 (s), 5·96 (s).

A solution of I (15 mg) in dry ether was treated with excess ethereal diazomethane at room temp. The solution was kept overnight. Evaporation and crystallization of the residue gave yellow needles, m.p. and mixed m.p. with the above 1,2-dimethoxy-8-hydroxyxanthone, 173–174°. Identical TLC and superimposable IR spectra confirmed the identity.

1,2,8-*Trimethoxyxanthone.* Dimethyl sulphate (0·4 ml) and calcinated K_2CO_3 (0·4 g) were added to a solution of II (35 mg) in dry acetone (10 ml). The mixture was maintained under reflux for 12 hr, cooled to room temp and filtered. Evaporation of the solvent left a residue which was treated with ammonia (0·2 ml) and water (10 ml). The precipitate was filtered and crystallized from cyclohexane–acetone (1:1) yielding white cubes, m.p. 153–155°, λ_{max} Table 2. No alteration in presence of NaOH; ν_{max} 1658, 1615, 1603, 1580 cm^{-1}; τ ($CDCl_3$) 7-H 3·29 (q, J 8·0, 1·0), 6-H 2·50 (t, J 8·0), 5-H 3·10 (q, J 8·0, 1·0), 4-H 2·91 (d, J 10·0), 3-H 2·75 (d, J 10·0), 1,2,8-OCH_3 5·96 (s), 6·01 (s), 6·10 (s).

2,8-*Diacetoxy*-1-*methoxyxanthone.* Compund I (10 mg) was dissolved in a mixture of pyridine–Ac_2O 1:1 (0·2 ml) and allowed to stand overnight at room temp. Following addition of ice water, the mixture was extracted with $CHCl_3$. The organic solution was washed successively with 10% HCl, 1% NaOHaq, water and dried. Evaporation of the solvent and crystallization of the residue from EtOH yielded white needless m.p. 165–167°. λ_{max} Table 1. τ ($CDCl_3$) 7-H 3·10 (q, J 7·0, 1·0) 6-H 2·40 (t, J 8·0), 5-H 2·73 (q, J 7·0, 1·0), 4-H 2·84 (d, J 9·0), 3-H 2·68 (d, J 9·0), 1-OCH_3 6·13 (s), 2,8-OAc 7·56 (s), 7·68 (s).

1,2,8-*Trihydroxyxanthone.* A solution of II (50 mg) in dry benzene (7 ml) was boiled under reflux with $AlCl_3$ (0·45 g) for 8 hr. After addition of a second portion of the reagent (0·25 g), heating was continued for a further 12 hr. After concentration to about 2·5 ml, HCl (1·5 ml) and AcOH (2 ml) were added. After 30 min at reflux and cooling, water (10 ml) was added. The solid which precipitated was filtered and washed with water. Recrystallization of the reaction product from benzene afforded bright yellow needles, m.p. 234–237°.

The same procedure, when applied to I, afforded a product whose identity with the above mentioned 1,2,8-trihydroxyxanthone was established by mixed m.p., chromatographic and spectral comparison; λ_{max} Table 2. No alteration in presence of AcONa. Addition of NaOH causes decomposition. $\lambda_{max}^{AlCl_3}$ 243, 268 sh, 286, 315 sh, 367 mμ (ε resp. 25,600; 20,300; 27,600; 8,400 8,800). $\lambda_{max}^{H_3BO_3+AcONa}$ 254, 268, 278 sh, 336 mμ (ε resp. 24,900; 35,600; 29,400; 9,200).

1,2,8-*Triacetoxyxanthone.* 1,2,8-Trihydroxyxanthone was acetylated by the Ac_2O–pyridine procedure. Crystallization of the reaction product from benzene yielded white needles, m.p. 225–227°. λ_{max} 235 sh, 244, 268, 344 mμ (ε resp. 42,600; 46,900; 12,200; 7,600).

3,4-*Dimethoxy*-1-*hydroxyxanthone.* 1,4-Dihydroxy-3-methoxyxanthone[10] was methylated by the diazomethane procedure. Crystallization of the reaction product from EtOH yielded yellow needles, m.p. 169–170°. λ_{max} 234, 259, 305, 365 mμ (ε resp. 27,200; 26,600; 11,200; 3,700). No alteration in presence of AcONa. λ_{max}^{NaOH} 231, 270, 295 mμ (ε resp. 27,100; 17,000; 12,500). $\lambda_{max}^{AlCl_3}$ 266, 274 mμ (ε resp. 25,700; 22,000). ν_{max} 1655, 1610, 1567, 764 cm^{-1}.

5,6-*Dimethoxy*-1-*hydroxyxanthone.* 1,5,6-Trihydroxyxanthone[5] was methylated by the diazomethane procedure. Crystallization of the reaction product from $CHCl_3$–EtOH yielded yellow rectangular rods, m.p. 183–185°. λ_{max} 235 sh, 243, 268, 310, 354 mμ (ε resp. 45,800; 49,000; 11,000 19,800; 7,600). No alteration in presence of AcONa. λ_{max}^{NaOH} 236, 275, 294 mμ (ε resp. 55,000; 21,200; 15,000). λ_{max} 235, 250, 278, 332 mμ (ε resp. 39,500; 32,000; 27,800; 28,600). $\lambda_{max}^{AlCl_3}$ 1653, 1620 cm^{-1}.

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