Journal of Natural Products
Vol. 47, No. 1, pp. 123-126, Jan-Feb 1984

NEW XANTHONES ISOLATED FROM *CENTAURIUM LINARIFOLIUM*

M. PARRA, M.T. PICHER, E. SEOANE, and A. TORTAJADA

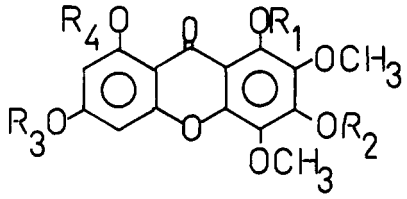
Department of Organic Chemistry, Faculty of Chemistry, University of Valencia, Valencia, Spain

ABSTRACT.—*Centaurium linarifolium* contains 1,6-dihydroxy-3,5-dimethoxyxanthone and two new compounds identified as 1,8-dihydroxy-2,3,4,6-tetramethoxyxanthone and 1,6-dihydroxy-3,5,7,8-tetramethoxyxanthone by spectroscopic evidence and chemical transformation into known compounds.

Centaurium linarifolium (Lamark) G. Beck, a plant known previously as *Erithraea barrelieri*, is used in folk medicine as a digestive, antipyretic, and a drug helpful in increasing blood circulation. No previous work is mentioned in the literature on this species. However, different xanthones have been isolated from the family of Gentianaceae (1-5) and at least two, gentisine and isogentisine, from *Gentiana lutea*, (6). For this reason, we made this study, and we wish now to report on xanthones isolated from *C. linarifolium*.

RESULTS AND DISCUSSION

The hexane extract represented 5.72% of the dry weight of the plant. From this extract, a phenolic fraction (1.83% of hexane extract) was separated, and its chromatography on a silica gel column afforded three crystalline yellow compounds, A, B, and C.



1a: $R_1=R_4=H$; $R_2=R_3=CH_3$
1b: $R_1=R_2=R_3=R_4=CH_3$
1c: $R_1=R_3=CH_3$; $R_2=R_4=H$
1d: $R_4=H$; $R_1=R_2=R_3=CH_3$
1a′: $R_1=R_4=CH_3CO$; $R_2=R_3=CH_3$
1c′: $R_1=R_3=CH_3$; $R_2=R_4=CH_3CO$

1,8-DIHYDROXY-2,3,4,6-TETRAMETHOXYXANTHONE (**1a**).—Compound A, mp 173-174°, is a new compound identified as 1,8-dihydroxy-2,3,4,6-tetramethoxyxanthone. The relative intensity of isotopic molecular ions gave the molecular formula $C_{17}H_{16}O_8$. The three maxima of the uv spectrum are characteristic of the xanthone skeleton. Of eight oxygens, two belong to the xanthone skeleton as a carbonyl (ir, 1655 cm-1) and an ether (ir, 1245, 1210, 1160 cm-1) group; four of them are methoxyl groups (^{1}H-nmr, three singlets of 12 H at δ 4.2, 4.0, 3.9); and two are hydroxyl groups (^{1}H-nmr, two singlets at δ 11.8 and 11.9 each of 1 H). These hydroxyl groups are placed at C-1 and C-8 on the following evidence: (a) they appear at very a low field in ^{1}H-nmr due to the chelation with the carbonyl group; (b) they are not seen in the ir spectrum due to this double chelation; and (c) uv maxima in MeOH did not change by addition of either NaOAc or NaOAc + H_3BO_3, which means a remarkable diminished acidity, due again to double chelation. However, uv maxima in MeOH show a strong bathochromic shift by the addition of $AlCl_3$, which is not destroyed by HCl (7). There are only two aromatic protons that are *meta* to each other as they are split

by J_m = 1.3 Hz (^{1}H-nmr, two doublets δ 6.4 and 6.3). They must be placed at C-5, C-7 (or C-2, C-4). The remaining places in the xanthone skeleton are occupied by four methoxyl groups. This situation is confirmed by the major fragmentation in ms. The major fragments (M-15), (M-CH_2O), and (M-CH_3-CO) require methoxyl groups at C-4 and C-2 (8).

The final identification was made by its methylation to 1,2,3,4,6,8-hexamethoxyxanthone (**1b**) described in the literature (9).

1,6-DIHYDROXY-3,5,7,8-TETRAMETHOXYXANTHONE (**1c**).—Compound C, mp 178-179°, is a new compound, identified as 1,6-dihydroxy-3,5,7,8-tetramethoxyxanthone. The relative intensity of isotopic molecular ions afforded the molecular formula $C_{17}H_{16}O_8$. The three uv maxima are characteristic of the xanthone skeleton. Of the eight oxygens two belong to the xanthone skeleton as a carbonyl (ir, 1660 cm^{-1}) and an ether (1210, 1195, 1160 cm^{-1}); four of them are methoxyl groups (^{1}H-nmr, three singlets of 12 H at δ 3.9-4.0); and two are hydroxyl groups (ir, 3250 cm^{-1}; ^{1}H-nmr singlet at δ 13.5; preparation of diacetate derivative). One hydroxyl group must be placed at C-1 (or C-8). Its signal in ^{1}H-nmr appears at low field (δ 13.5), and uv maxima in MeOH undergo a strong bathochromic shift in the presence of $AlCl_3$, which did not disappear with HCl (10). There are only two aromatic protons, split by a small J_m = 1.3 Hz, which is characteristic of reciprocal *meta* position. They should be placed either at C-1, C-3 (equivalent C-6, C-8) or C-2, C-4 (equivalent C-5, C-7). The high field (δ 6.5, 6.3) at which they appear suggests the positions C-2, C-4; the signal of C-1H should be about δ 7.8 (11). The second hydroxyl group must be located either at C-3 or C-6; this xanthone shows strong acidic character, and its uv spectrum in MeOH suffers a bathochromic shift when NaOAc is added. Of the two possible positions, we have chosen C-6 because uv spectra in (MeOH+NaOMe) and (MeOH+NaOAc) are superimposable and the 1,3-dihydroxyxanthones are not strong acids that give superimposable spectra (10). In addition, the δ values of protons at C-2, C-4 (or C-5, C-7) in the acetate derivative are consistant with a 1-acetoxy-3-methoxyxanthone (δ 6.85 and 6.60). Values required by a 1,3-diacetoxyxanthone would be δ 7.35 and 6.86 (12). The other four methoxyl groups should be placed at C-3, C-5, C-7, and C-8. This situation is in agreement with the major ms spectrum fragmentations (M-CH_3; M-CH_3-CO) which require OMe at C-5 and C-7 (8). An alternative formula, which would explain spectroscopic properties, might be the structure of 1,6-dihydroxy-2,3,4,8-tetramethoxyxanthone, but this structure is excluded by a positive Gibbs test which requires a free position *para* to the hydroxyl group. Final identification was made by its conversion into 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone (**1d**), described in the literature (4), and comparison with an authentic sample.

EXPERIMENTAL

The melting points were determined on a Büchi apparatus. The uv spectra were measured on a Perkin-Elmer Ultraviolet-Visible Spectrophotometer, model 575. The ir spectra were recorded in KBr pellets on a Perkin-Elmer 281 spectrophotometer. ^{1}H-nmr spectra were recorded in the stated solvents on a Perkin-Elmer R-12B (60 MHz) instrument with TMS as internal standard. Mass spectra were taken with a Varian-160 Spectrometer at 70 eV.

EXTRACTION AND FRACTIONATION.—The plant was collected at "Simat de Valldigna" in Valencia, Spain, and classified by Dr. Mansanet, Professor of Botany at the University of Valencia. Stems and leaves of *C. linarifolium*, dried at room temperature (3.35 kg), were extracted with hexane (20 liters). The hexane extract (191.88 g, 5.72% of dried plant) was separated with Na_2CO_3 and NaOH into neutral, acidic, and phenolic fractions. The phenolic fraction (3.502 g; 1.83% of hexane extract) was chromatographed on silica gel (105 g) from which hexane-Et_2O eluted successively three yellow crystalline products: A (154 mg) eluted with hexane-Et_2O (8:2); B (43 mg), hexane-Et_2O (3:1); and C (208 mg), hexane-Et_2O (45:55).

1,8-Dihydroxy-2,3,4,6-tetramethoxyxanthone (**1a**).—Compound A was identified as 1,8-dihydroxy-

2,3,4,6-tetramethoxyxanthone on the following data: mp 173-174° (from $CHCl_3$-EtOH); uv λ max (log ε) (MeOH) 234 (4.01), 259 (4.05), 333 (4.16) nm. These maxima do not change, by addition of either NaOAc or NaOAc+H_3BO_3; λ max (MeOH+$AlCl_3$) 277, 330sh, 373 nm, which does not change by addition of HCl; ir (KBr) 3100-2850, 1655, 1615, 1595, 1560, 1470, 1370, 1270, 1245, 1210, 1160, 1130, 1090, 1055, 850, 810, 775, 700 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 11.9 and 11.8 (2s, 2H, OH-1 and OH-8), 6.4 (d, J=1.3 Hz, H-2), 6.3 (d, J=1.3 Hz, H-4), 4.2, 4.0, 3.9 (3s, 12H, 4 OCH_3); ms *m/z* 348 (86.1, M^+), 333 (100, M-15), 318 (31.2, M-CH_2O), 305 (15.2, M-CH_3-CO), 303 (52.8, M-CH_2O-CH_3), 288 (49.8, M-CH_2O-2CH_3), 273 (31.2), and 245 (52.9).

1,6-Dihydroxy-3,5-dimethoxyxanthone.—Compound B, needles from Me_2CO mp 194-196°, was identified as 1,6-dihydroxy-3,5-dimethoxyxanthone by comparison with uv, ms, and ^{1}H-nmr spectral data reported in the literature (13, 14).

1,6-Dihydroxy-3,5,7,8-tetrametoxyxanthone (**1c**).—Compound C was identified as 1,6-dihydroxy-3,5,7,8-tetramethoxyxanthone on the following data: mp 178-179° (from Me_2CO); uv λ max (MeOH) (log ε) 253 (4.09), 321 (4.19), 360 (4.24) nm; λmax (MeOH+NaOMe) 247, 265sh, 368 nm; these maxima are superimposable with those obtained from (MeOH+NaOAc) and from (MeOH+NaOAc+H_3BO_3); λ max (MeOH+$AlCl_3$) 256sh, 268, 347, 409 nm; no change by adding HCl; ir (KBr) 3250, 3020-2840, 1660, 1605, 1580, 1490, 1465, 1355, 1320, 1210, 1195, 1160, 1145, 1050, 905, 820, 755 cm^{-1}; ^{1}H-nmr (CD_3COCD_3, 60 MHZ) δ 13.5 (s, 1H, OH-1), 6.5 (d, J=1.3 Hz, 1H, H-7), 6.3 (d, J=1.3 Hz, 1H, H-5), 4.0-3.9 (3s, 12H, 4 OCH_3); ms *m/z* 348 (58.1, M^+), 333 (100, M-CH_3), 305 (40.1, M-CH_3-CO), 290 (50.8, M-2CH_3-CO), 288 (19, M-2CH_3-CH_2O), 273 (14.8, M-CH_2O-3CH_3), and 245 (14.9, M-3CH_3-CH_2O-CO).

1,8-Diacetoxy-2,3,4,6-tetramethoxyxanthone (**1a'**).—Compound A, 1,8-dihydroxy-2,3,4,6-tetramethoxyxanthone (30 mg, 0.09 mmol) was treated at room temperature with Ac_2O (1.0 ml, 7.4 mmol) in pyridine for 40 h. After working up, the reaction product was 1,8-diacetoxy-2,3,4,6-tetramethoxyxanthone (21 mg, 56%) mp 144° (from MeOH); ir (KBr) 3020-2840, 1760, 1630, 1600, 1560, 1460, 1405, 1370, 1300, 1205, 1160, 1115, 1080, 1050, 895, 835 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 6.85 (d, J=2 Hz, 1H, H-7), 6.60 (d, J=2 Hz, 1H, H-5), 4.1-3.85 (4s, 12H, 4 OCH_3), 2.45 and 2.40 (2s, 2 $OCOCH_3$).

1,6-Diacetoxy-3,5,7,8-tetramethoxyxanthone (**1c'**).—Compound C, 1,6-dihydroxy-3,5,7,8-tetramethoxyxanthone (30 mg, 0.09 mmol) was treated in pyridine with Ac_2O (1.0 ml, 7.4 mmol) at room temperature. The reaction product worked up was 1,6-diacetoxy-3,5,7,8-tetramethoxyxanthone (18 mg, 48%) mp 135-136° (from MeOH); ir (KBr) 3015-2840, 1770, 1660, 1630, 1590, 1570, 1470, 1415, 1365, 1300, 1200, 1155, 1105, 1060, 960, 895, 820 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 6.85 (d, J=2 Hz, 1H, H-7), 6.60 (d, J=2 Hz, 1H, H-5), 4.0 and 3.9 (2s, 12H, 4 OCH_3), 2.50 and 2.45 (2s, 6H, 2 $OCOCH_3$).

1-Hydroxy-3,5,6,7,8-pentamethoxyxanthone (**1d**).—Compound C, 1,6-dihydroxy-3,5,7,8-tetrametoxyxanthone (30 mg, 0.09 mmol) in Et_2O was treated with CH_2N_2 (excess). The reaction product worked up was 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone (16 mg, 51%), mp 107-108° (from methanol); uv λ max (log ε) (MeOH) 256 (4.45), 314 (4.54), 358 (4.60) nm; λ max (MeOH+NaMeO) 247, 257, 274sh, 318 nm; the same maxima in (MeOH+NaOAc); λ max in (MeOH+$AlCl_3$) 260, 273sh, 320, 345sh nm, which did not change by HCl; ir (KBr) 3010-2840, 1655, 1610, 1590, 1560, 1410, 1350, 1290, 1195, 1165, 1095, 1060, 1040, 830, 815 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 13.2 (s, 1H, OH-1), 6.4 (d, J=1.3 Hz, 1H, H-7), 6.3 (d, J=1.3 Hz, 1H, H-5), 4.1-3.9 (4 s, 15H, 5 OCH_3).

1,3,5,6,7,8-Hexamethoxyxanthone (**1b**).—Compound A, 1,8-dihydroxy-2,3,4,6-tetramethoxyxanthone (30 mg, 0.09 mmol) in dry Me_2CO was treated with K_2CO_3 (1,2 g) and dimethyl sulphate (1, 2 ml) at reflux for 16 h. The reaction product worked up was 1,3,5,6,7,8-hexamethoxyxanthone (15 mg, 46%) mp 157-159° (from EtOH); uv λ max (log ε) (EtOH) 204 (4.35), 249 (4.22), 303 (3.85), 336sh nm; ir (KBr) 3020-2830, 1665, 1620, 1590, 1460, 1405, 1360, 1300, 1195, 1130, 1065, 960, 810 cm^{-1}; ^{1}H-nmr ($CDCl_3$, 60 MHz) δ 6.50 (brs, 1H, H-4), 6.30 (brs, 1H, H-2), 4.1-3.9 (6s, 18H, 6 OCH_3).

ACKNOWLEDGMENTS

We are indebted to Dr. G. Sullivan, Professor at the College of Pharmacy, University of Texas at Austin, Texas for the specimen of 1-hydroxy-3,5,6,7,8-pentamethoxyxanthone which he kindly sent to us.

LITERATURE CITED

1. R.K. Chaudhuri and S. Ghosal, *Phytochemistry* **10**, 2425 (1971).
2. G.H. Stout, E.N. Christensen, W.J. Balkenhol, and K.L. Stevens, *Tetrahedron* **25**, 1961 (1969).
3. P. Rivaille, J. Massicot, M. Guyot, and V. Plouvier, *Phytochemistry*, **8**, 1533 (1969).
4. G. Sullivan, F.D. Stiles, K.H.A. Rosler, *J. Pharm. Sci.*, **66**, 828 (1977).
5. A.J. Quillinan and F. Scheinmann, *J. Chem. Soc., Perkin Trans.* **I**, 1329 (1973).
6. L. Canonica and F. Pelizzoni, *Gazz. Chim.*, **85**, 1007 (1955).

7. R. Somanathan and M.U.S. Sultanbawa, *J. Chem. Soc. Perkin Trans.* **I**, 1935 (1972).
8. P. Arends, P. Helboe, and J. Moller, *Org. Mass, Spectrom.*, **7**, 667 (1973).
9. S. Ghosal, R.K. Chaudhuri, and A. Nath, *J. Indian Chem. Soc.*, **48**, 589 (1971).
10. A.A. Lins Mesquita, D. de Barros Corrêa, O.R. Gottlieb, and M. Taveira Magalhães, *Analyt. Chim. Acta*, **42**, 311 (1968).
11. D. Barraclough, H.D. Locksley, F. Scheinmann, M.T. Magalhães, and O.R. Gotlieb, *J. Chem. Soc.*, **B**, 603 (1970).
12. J. Massicot, J.P. Marthe, and S. Heitz, *Bull. Soc. Chim. Fr.*, 2712 (1963).
13. S. Ghosal, R.K. Chaudhuri, and A. Nath, *J. Pharm. Sci.*, **62**, 137 (1973).
14. S. Ghosal, D. Jaiswal, K. Biswas, *Phytochemistry*, **17**, 2119 (1978).

Received 17 March 1983