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ADDITIONAL NEW XANTHONES ISOLATED FROM *CENTAURIUM LINARIFOLIUM*

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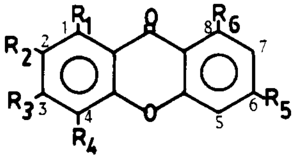
In studying *Centaurium linarifolium* (Lamark) G. Beck, used in folk medicine, we reported on the new xanthones isolated (1). That report described the isolation and characterization of 1,6-dihydroxy-3,5-dimethoxyxanthone (B), 1,8-dihydroxy-2,3,4,6-tetramethoxyxanthone (A), and 1,6-dihydroxy-3,5,7,8-tetramethoxyanthone (C). We now wish to report on additional compounds isolated and characterized. These are 1,8-dihydroxy-3,4,6-trimethoxyxanthone (**X**$_1$), 1,8-dihydroxy-2,6-dimethoxyxanthone (**X**$_2$), 1,3,8-trihydroxy-2,4,6 trimethoxyxanthone (**D**), and two new xanthones **X**$_3$ and **E** with two alternative structures.



X$_1$: $R_1=R_6=OH; R_3=R_4=R_5=OCH_3; R_2=H$
X$_2$: $R_1=R_6=OH; R_2=R_5=OCH_3; R_3=R_4=H$
D: $R_1=R_3=R_6=OH; R_2=R_4=R_5=OCH_3$
X$_3$: $R_1=R_3=R_6=OH; R_2$ or $R_4=OCH_3; R_5=R_4$ or $R_2=H$
E: $R_3=R_6=OH; R_1=R_2$ or $R_4=OCH_3; R_5=R_4$ or $R_2=H$

RESULTS AND DISCUSSION

Compound **X**$_1$ was identified as 1,8-dihydroxy-3, 4, 6-trimethoxyxanthone by the following evidence: Its molecular formula given by isotopic molecular ions is $C_{16}H_{14}O_7$, and the three maxima of its uv spectrum are characteristic of the xanthone skeleton. Of seven oxygens, two belong to the xanthone skeleton as carbonyl (ir, 1630 cm^{-1}) and ether (ir, 1270, 1210, 1170 cm^{-1}) groups, three of them are methoxyl groups (pmr, 2 s of 9H at δ 3.96 and 3.86), and two are hydroxyl groups that must be placed at C-1 and C-8 for three reasons: (a) their proton signals appear at very low field (2 s, at δ 11.95 and 11.90), (b) they are not seen in the ir spectrum due to chelation with the CO group, and (c) uv maxima in MeOH show a bathochromic shift on addition of $AlCl_3$, but they do not change on addition of NaOAc. There are only three aromatic protons, one is a singlet and two are *meta* to each other ($J=2.0$ Hz). There are only two possible structures consistent with the distribution of three OCH_3 groups, and these protons—namely, 1,8-dihydroxy-2,3,6-trimethoxyxanthone and 1,8-dihydroxy-3,4,6-trimethoxyxanthone. The former structure is that of a compound described by Chaudhuri and Ghosal (2), and its properties are different from those of compound **X**$_1$; therefore, the structure of **X**$_1$ should be the latter. Very recently, Takagi and Yamaki (3) described a compound with the structure of 1,8-dihydroxy-3,4,6-trimethoxyxanthone from *Erythraea centaurium*, whose properties coincide perfectly with those of compound **X**$_1$.

Compound **X**$_2$ was identified as 1,8-dihydroxy-2,6-dimethoxyxanthone as follows: Its molecular formula was $C_{15}H_{12}O_6$ (isotopic ions), and its uv maxima were characteristic of a xanthone skeleton. Of six oxygens, two belong to the xanthone skeleton as CO and ether groups based on ir spectra, two of them are methoxyl groups (pmr, 2 s at 3.88 and 3.83 for 6H), and two are OH groups placed at C-1 and C-8 for the same reasons given for **X**$_1$. There are four aromatic protons, two at reciprocal *ortho*-positions ($J=9.3$ Hz) and two at reciprocal *meta*-positions ($J=2.0$ Hz). There are only two possible structures consistent with these data: 1,8-dihydroxy-4,6-dimethoxyxanthone (4) and 1,8-dihydroxy-2,6-dimethoxyxanthone (5). A compound having the latter structure was isolated some years ago from different plants and coincides with $\mathbf{X}_2$ (5).

Compound D was identified as 1,3,8-trihydroxy-2, 4, 6-trimethoxyxanthone on the following evidence. Its molecular formula given by molecular isotopic ions was $C_{16}H_{14}O_8$. Of eight oxygens, two are part of the xanthone skeleton as a CO (ir, 1665 cm^{-1}) and an ether oxygen (ir, 1200, 1085, 1045), three are methoxyl groups (pmr, 3 s at 3.98, 3.95, and 3.87 for 9H), and the other three are OH groups (ir, 3400 cm^{-1}). Two OH groups are placed at C-1 and C-8 since the signals of their protons appear at low field (2 s, at δ 11.98 and 11.95), and uv maxima of the compound in MeOH undergo a bathochromic shift by addition of $AlCl_3$. The third OH group must be placed either at C-3 or C-6 in view of the strong acidic character of the compound (uv maxima undergo a bathochromic shift with NaOAc). There are only two aromatic protons, which are at reciprocal *meta*-positions, and they should be placed at C-5 and C-7 or at C-2 and C-4. Therefore, there are two possible formulas: 1,3,8-trihydroxy-2,4,6-trimethoxyxanthone or 1 6,8-trihydroxy-2,3,4-trimethoxyxanthone, but the pmr of the triacetate militates against the latter structure and supports the former, because aromatic protons of the latter structure should appear at lower field [about δ 7.35 for H-7 and 6.86 for H-5 (6)] while our compound showed absorptions at 6.82 and 6.57 ppm. Recently (1982) Nesta and Nikolaeva (7) have reported the same compound with about the same melting point, isolated from *Erythraea centaurium*.

Compound $\mathbf{X}_3$ was identified as either 1,3,8-trihydroxy-2-methoxyxanthone or 1,3,8-trihydroxy-4-methoxyxanthone on the following evidence: Its molecular formula was established as $C_{14}H_{10}O_6$ by low and high resolution ms, and the presence of a xanthone skeleton was supported by ir and uv spectra. There are two hydroxyl groups placed at C-1 and C-8 (since uv maxima in MeOH showed a bathochromic shift on addition of $AlCl_3$) and one hydroxyl group placed at C-3 or C-6 (since uv maxima in MeOH+$NaOCH_3$ are superimposable with those in MeOH+NaOAc). The pmr spectrum showed four aromatic protons. The signal of one proton is a singlet and should be placed at C-2 or C-4, while the signals of the three others provided an ABX system and should be located on the other ring. Finally, the methoxyl group (pmr δ 3.88, 3H) must be located at either C-2 or C-4. According to the above evidence, compound $\mathbf{X}_3$ should have the structure of either 1,3,8-trihydroxy-2-methoxyxanthone or 1, 3, 8-trihydroxy-4-methoxyxanthone. Neither of these structures has previously been mentioned in the literature.

Compound **E** was identified as either 3,8-dihydroxy-1,4-dimethoxyxanthone or 3,8-dihydroxy-1,2-dimethoxyxanthone on the following evidence: Its molecular formula was shown to be $C_{15}H_{12}O_6$ by low and high resolution ms. Two oxygens belong to the xanthone skeleton (ir, 1655, 1160, 1095 cm^{-1}); two other oxygens are hydroxyl groups, one at C-8 (pmr, δ 12.79 and uv, bathochromic effect by addition of $AlCl_3$) and another one 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-3 because the compound's uv spectra in (MeOH+NaOMe) and (MeOH+NaOAc) are superimposable and 6,8-dihydroxyxanthone is not a strong enough acid to give superimposable spectra (8). The last two oxygens are methoxyl groups (pmr, δ 3.99, and 3.77, 6H). There are four aromatic protons, which cannot be placed on C-1 or C-8 since their signals should appear at lower field (about δ 8.0) (9). One of these four aromatic protons is a singlet that must be placed on C-2 or C-4, and the remaining three protons form an ABX system and should be located in the other ring, which bears a methoxyl group at C-1. Therefore, compound **E** should be identified with either 3,8-dihydroxy-1,4-dimethoxyxanthone or 3,8-dihydroxy-1,2-dimethoxyxanthane, neither of which are mentioned in the literature.

EXPERIMENTAL

The mps were determined on a Kofler 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. Pmr spectra were recorded in the stated solvents on a Perkin-Elmer R-12B (60 MHz) instrument, and a Varian Aerograph CFT-20 (80 MHz) instrument, with TMS as internal standard. Mass spectra were taken with a Varian-160 Spectrometer at 70 eV.

EXTRACTION AND FRACTIONATION.—*C. linarifolium* was collected and authenticated as described by Parra *et al.*, (1). We obtained from the leaves and stems of the plant (3.35 kg) a hexane extract (5.72% of dry plant), which was fractionated into neutral, acidic, and phenolic fractions, as is described in the first report (1). The phenolic fraction (3.502 g) was chromatographed on silica gel (105 g), from which hexane-Et_2O of increasing polarity eluted 98 fractions, combined into six groups, as Table 1 shows.

Compounds A,B,C,**D**,**E**, crystallized directly from the eluate. The residue contained in the mother liquor of crystallization was again recrystallized from other solvents, and so $\mathbf{X}_1$,$\mathbf{X}_2$,$\mathbf{X}_3$ were obtained. Compounds A,B,C were described in the first report.

1,8-Dihydroxy-3,4,6-trimethoxyxanthone: Compound $\mathbf{X}_1$, yellow powder from Me_2CO (24 mg) mp 225-227° (lit. 236-237°), was identified as 1,8-dihydroxy-3,4,6-trimethoxyxanthone by comparison with uv, ms, and pmr spectral data reported in the literature (3). The diacetate derivative made with Ac_2O and pyridine had mp 177-178° (from Me_2CO).

1,8-Dihydroxy-2,6-dimethoxyxanthone: Compound $\mathbf{X}_2$, orange crystals from Me_2CO (11 mg) mp 187-189° (lit. 189-190°), was identified as 1,8-dihydroxy-2,6-dimethoxyxanthone by comparison with uv, ms, and pmr spectral data reported in the literature (5). The diacetate derivative made with Ac_2O and pyridine has mp 205-207° (from Me_2CO).

1,3,8-Trihydroxy-2,4,6-trimethoxyxanthone: Compound **D**, yellow crystals from MeOH (43 mg) mp 215-217° (lit. 213-215°), was identified as 1,3,8-trihydroxy-2,4,6-trimethoxyxanthone by comparison with uv, ms, and pmr spectral data reported in the literature (7). The triacetate derivative made with Ac_2O and pyridine had mp 213-216° (from Me_2CO).

1,3,8-Trihydroxy-2-methoxy or 1,3,8-trihydroxy-4-methoxyxanthone: Compound $\mathbf{X}_3$ identified with one of two possible structures on the following data: pale yellow crystals (6 mg) mp 262-264° (from Me_2CO); one peak in gc after trimethylsilylation; uv λ max (MeOH) nm (log ϵ) 222 sh, 247 (3.87), 274 sh, 316 (3.57), 368 (3.15); λ max (MeOH+NaOMe) 233, 254, 291, 350; these maxima are superimposable with those in (MeOH+NaOAc); maxima with ($MeOH+NaOAc+H_3BO_3$) are the same as in MeOH; λ max ($MeOH+AlCl_3$) 221, 245, 266, 280, 340, 420, which do not change by addition of HCl; ir (KBr) 3470 (sharp), 3250 (broad), 1650, 1615, 1580, 1460, 1340, 1210, 1155, 1090, 990, 925, 780 cm^{-1}; pmr (CD_3COCD_3, 80 MHz) δ 7.68 (dd, J=6.6 and 4.8 Hz, 1H, H-6 part X of a system ABX), 7.33-7.24 (m, 2H, H-5 and H-7, AB part of the system ABX), 6.54 (s, 1H, H-2 or H-4), 3.88 (s, 3H, OCH_3); ms *m/z* (rel. int.), 274 (71.9, M^+), 259 (75.7, $M-CH_3$), 256 (20.8, $M-H_2O$), 231 (100, $M-CH_3-CO$), 228 (12.4, $M-H_2O-CO$), 202 (15.0, $M-CH_3$-

TABLE 1. Crystalline Compounds Isolated from Six Groups of Eluates in the Chromatography of the Phenolic Fraction of *Centaurium linarifolium* from Silica Gel

Eluate	Fractions	Proportion of hexane-Et_2O	Crystalline compounds
I	20-25	(8:2)	A+$\mathbf{X}_1$
II	26-40	(8:2)	A+$\mathbf{X}_2$
III	57-75	(3:1)	B
IV	80-85	(50:50)	**D**+$\mathbf{X}_3$
V	88-92	(45:55)	C
VI	93-95	(45:55)	**E**

CO-CHO); found by high resolution ms 274.0475^7, $C_{14}H_{10}O_6$ require 274.0474.

3,8-Dihydroxy-1,4-dimethoxy or 3,8-dihydroxy-1,2-dimethoxyxanthone: Compound **E**, identified with one of two possible structures on the following data: yellow crystals (4 mg) mp 170-172° (from $CHCl_3$); one peak in gc after trimethylsilylation; uv λ max (MeOH) nm 222, 252, 275 sh, 312, 370; λ max (MeOH+NaOMe) the same as in (MeOH+NaOAc) 244, 268, 287, 323 sh, 404 sh; maxima in (MeOH+NaOAc+H_3BO_3) the same as in MeOH; λ max (MeOH+$AlCl_3$) 222, 246, 267, 283, 335, 420, which do not change by addition of HCl; ir (KBr) 3440, 3110-2830, 1655, 1620, 1500, 1450, 1300, 1160, 1095, 1070, 1005, 810, 790, 745, 735, 715 cm^{-1}; pmr (DMSO-d_6, 80 MHz) δ 12.79 and 10.52 (2s, 2H, OH-8 and OH), 7.60 (dd, J=6.2 and 3.3 Hz), 1H, H-6, part X of a system ABX), 7.35-7.27 (m, 2H, H-5 and H-7, part *AB* of a system ABX), 6.82 (s, 1H, H-2 or H-4), 3.99, 3.77 (2s, 6H, 2 OCH_3); ms *m/z* (rel. int.), 288 (88.6, M^+), 273 (100, M-CH_3), 259 (15.2, M-CHO), 245 (78.3, M-CH_3-CO), 202 (23.6, M-$2CH_3$-2CO); found by high resolution ms 288.0629^6, $C_{15}H_{12}O_6$ require 288.0630.

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