Selective Demethylation of Polymethoxyxanthones with Aqueous Piperidine

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Abstract □ Data are presented for selective demethylation of eight polymethoxyxanthones with aqueous piperidine. Clarification and rationalization of the present and previous observations are made. The mechanism is defined in terms of both resonance effects and steric factors.

Keyphrases □ Xanthones, various polymethoxy—selective demethylation with aqueous piperidine □ Polymethoxyxanthones, various—selective demethylation with aqueous piperidine □ Demethylation, selective—various polymethoxyxanthones with aqueous piperidine

Interest in selective demethylation of polymethoxyxanthones stems from its use in structure elucidation (allocation of hydroxy–methoxy substituents) and in the synthesis of naturally occurring xanthones (1). Demethylation of 1-methoxyxanthones, with added methoxy groups in the A and B rings, with aluminum chloride produced 1-hydroxy derivatives (2). However, mixtures resulted with this reagent if the methyl ethers were sensitive to acidic reagents (1). Demethylation with basic reagents, on the other hand, was thought to involve 3- and/or 6-methoxy groups since oxygen functions *para* to the carbonyl group of the xanthone nucleus are poorest in electrons. Accordingly, demethylation of 2,3-dimethoxy-, 2,3,4-trimethoxy-, and 1-hydroxy-3,4,7-trimethoxyxanthones with either aqueous piperidine or tetramethylammonium hydroxide under reflux furnished the corresponding 3-hydroxy derivatives (3).

Some anomalies, however, were created by a subsequent report (4) that demethylation with aqueous piperidine was not entirely selective since the reaction was dependent on the number and position of methoxy groups in the xanthone nucleus and on the extent of heating with the demethylating agent. Thus, 1,2,3-trimethoxyxanthone was reported (4) to give 1-methoxy-2,3-dihydroxyxanthone instead of the expected 1,2-dimethoxy-3-hydroxyxanthone. Likewise, 2,3,4-trimethoxyxanthone, contrary to the earlier study (3), was reported to furnish 2-hydroxy-3,4-dimethoxyxanthone, 1,7-dimethoxyxanthone gave 1-hydroxy-7-methoxyxanthone, and 1,8-dimethoxy- and 1,3,5-trimethoxyxanthones were unreactive (4). The purposes of this paper are to sort out the anomalies and to propose a plausible mechanism of this demethylation reaction.

EXPERIMENTAL

Compounds—Xanthones III and VI–VIII were available from previous investigations of *Canscora decussata* (5), *Polygala arillata* (6), and *Swertia bimaculata* (7). Xanthones I, IV, and V were prepared by using previously reported (2, 8) procedures; xanthone II was obtained from the present investigation.

Reaction—In a typical experiment, 1,3-dimethoxyxanthone (I), 0.30 g, in piperidine (6 ml) and water (6 ml) was refluxed for 60 hr. The cooled mixture was poured into 4 *N* HCl. The resulting suspension was extracted with chloroform (3 × 100 ml). The chloroform layer was washed with 2 *N* HCl and water and dried with anhydrous magnesium sulfate. Evaporation of the solvent gave a residue (0.26 g), which showed three major spots on TLC on silica gel G[1]: R_f 0.78, 0.19, and 0.12 [solvent of benzene–acetic acid (20:1); iodine vapor was used for staining].

The xanthones were separated into homogeneous entities by column chromatography over silica gel[2] (60–120 mesh). Benzene and benzene–ethyl acetate (90:10) were used as eluents. The benzene eluates afforded the unchanged parent compound (0.024 g), followed by 1-hydroxy-3-methoxyxanthone (0.132 g), and 1,3-dihydroxyxanthone (0.033 g). The benzene–ethyl acetate eluates gave a brown polymeric compound (0.028 g). The other xanthones (II–VIII), when treated and processed similarly, also afforded unchanged material (8–20%) and some polymeric compounds (5–15%) in addition to the hydroxymethoxyxanthones (Table I).

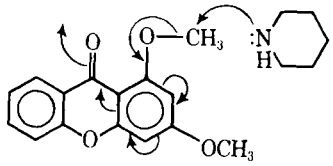
RESULTS AND DISCUSSION

Xanthones I–VIII, when refluxed (40–60 hr) with aqueous piperidine, yielded unchanged starting material and intractable polymeric compounds in addition to the selectively demethylated hydroxymethoxyxanthones (Table I). The time of heating produced significant effects only with VIII. Thus, 40 hr of refluxing afforded the corresponding 1,6-dihydroxyxanthone, while 60 hr resulted in the corresponding 1,3,6-trihydroxy derivative. The identity of the compounds was established on the basis of UV absorption (5, 9) and PMR (5, 8, 10) spectra and by direct comparison with authentic samples where possible.

These results indicate that demethylation of 1-methoxy-, 1,3-dimethoxy-, and those xanthones containing added methoxy group(s) in the B ring (5- and/or 7-position) would take place preferentially at the 1-position. With a preformed 1-hydroxy substituent or in the absence of an oxygen function at the 1-position, the 3-position would be demethylated. In consonance with this conclusion, 1-hydroxy-3-methoxyxanthone and 2,3,4-trimethoxyxanthone produced 1,3-dihydroxyxanthone and 2,4-dimethoxy-3-hydroxyxanthone, respectively.

With an added methoxy group at the 2-position, the demethylation occurred at this position. Thus, 1,2,3-trimethoxyxanthone and 1,2,3,4,7-pentamethoxyxanthone produced 1,3-dimethoxy-2-hydroxyxanthone and 1,4,7-trimethoxy-2,3-dihydroxyxanthone, respectively. A small amount of 1-methoxy-2,3-dihydroxyxanthone was also produced from the first compound, thereby supporting a previous report (4). A methoxy group flanked by *ortho*-substituents may be pushed out (1, 11) of the benzene ring and its behavior modified accordingly.

A pleasing double application of the demethylation was accomplished in the synthesis of 1,6-dihydroxy-3,5,7-trimethoxy- and 1,3,6-trihydroxy-5,7-dimethoxyxanthones by varying the heating time. The 1- and 6-methoxy groups were preferentially demethylated within 40 hr of heating; with 60 hr of heating, the 3-methoxy group was demethylated. These xanthones were encountered among about two dozen compounds of this class found in *C. decussata* Schult (Gentianaceae) (11).



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[1] E. Merck, Darmstadt, West Germany.
[2] British Drug Houses or Woelm Pharma GmbH & Co.

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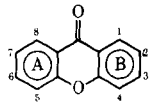
Table I—Selective Demethylation of Polymethoxyxanthones



Compound	Substituents	Demethylation Substituents	Yield, %
I	1,3-$(OCH_3)_2$	1-OH-3-OCH_3	44
		1,3-$(OH)_2$	11
II	1-OH-3-OCH_3	1,3-$(OH)_2$	65
III	1,3,5-$(OCH_3)_3$	1-OH-3,5-$(OCH_3)_2$	40
		1,3-$(OH)_2$-5-OCH_3	8
IV	1,3,7-$(OCH_3)_3$	1-OH-3,7-$(OCH_3)_2$	45
		1,3-$(OH)_2$-7-OCH_3	10
V	2,3,4-$(OCH_3)_3$	2,4-$(OCH_3)_2$-3-OH	52
VI	1,2,3-$(OCH_3)_3$	1,3-$(OCH_3)_2$-2-OH	55
		1-OCH_3-2,3-$(OH)_2$	5
VII	1,2,3,4,7-$(OCH_3)_5$	1,4,7-$(OCH_3)_3$-2,3-$(OH)_2$	38
VIII	1,3,5,6,7-$(OCH_3)_5$	1,6-$(OH)_2$-3,5,7-$(OCH_3)_3$	22
		1,3,6-$(OH)_3$-5,7-$(OCH_3)_2$	36

The ease of *O*-demethylation is a function of resonance and steric factors. In compounds that are sterically less strained (I–IV), preferential demethylation occurs at C-1, followed by C-3 (and C-6), as could have been predicted on the basis of resonance factors (IX). Furthermore, since C-1 is more hindered than C-3 and C-6, the former should demethylate more readily. The selective demethylation at C-3 in V is caused by the relief of steric strain. However, this reaction can be explained as well in terms of simple resonance. In compounds having substitution at three or four adjacent carbon atoms, as in VI–VIII, the relief of steric strain is so important that it takes precedence over resonance effects, and one observes *O*-demethylation at C-2, C-3, and C-6, with C-2 demethylation being caused by the relief of steric strain.

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South American Plants III: Isolation of Fulvoplumierin from *Himatanthus sucuuba* (M. Arg.) Woodson (Apocynaceae)

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Abstract □ The bark of *Himatanthus sucuuba* was screened for pharmacological and anticancer activities. The lactone, fulvoplumierin ($C_{14}H_{12}O_4$), was isolated from the *n*-hexane fraction. The identity was proven by elemental analysis and IR, mass spectral, and melting-point determinations. Reference samples were used for comparison.

Keyphrases □ Fulvoplumierin—isolated from *Himatanthus sucuuba* bark, evaluated for pharmacological and anticancer activity □ *Himatanthus sucuuba*—fulvoplumierin isolated from bark, evaluated for pharmacological and anticancer activity □ Antineoplastic activity—fulvoplumierin isolated from *Himatanthus sucuuba* bark, evaluated

In the search for new drugs from plants growing in the Upper Amazon Valley in Peru, several hundred species were evaluated for antitumor[1] and other pharmacological activities[2]. Plants with known medicinal folk uses received priority.

One plant, "bellaco caspi," *Himatanthus sucuuba* (M. Arg.) Woodson (Apocynaceae)[3], has several uses. Infusions, decoctions, and poultices prepared from the stem bark are used as a vermifuge and laxative and for treating arthritis, "tumors," boils, hernias, and swellings. A 50% ethanol–water extract of the stem bark showed anti-inflammatory activity in the carrageenan-induced edema method and was marginally active against the human epidermoid carcinoma of the nasopharynx (KB) test system. Frac-

[1] Tests were performed at the Drug Evaluation Branch, Drug Research and Development Division of the Cancer Treatment, National Cancer Institute, National Institutes of Health, Bethesda, MD 20014.

[2] All tests were performed at the Natural Products Research Laboratories, Rockville, MD 20851.

[3] The plant was collected in Peru in April 1968. Identification was made by Dr. J. J. Wurdak, Smithsonian Institution, Washington, D.C. A herbarium specimen was deposited at the Smithsonian Institution.

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