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CONSTITUENTS OF MAMMEA AMERICANA L., V. (1)

SOME SIMPLE MONO-AND DIHYDROXYXANTHONES

R.A. Finnegan, J.K. Patel, and P.L. Bachman (2)

Department of Medicinal Chemistry, School of Pharmacy,

State University of New York at Buffalo, Buffalo, N.Y., 14214

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In an earlier article, the isolation of 2-hydroxyxanthone from mamey seed extracts was described (3) and its unique position among naturally occurring xanthones noted. Recently, the presence of 2-methoxyxanthone in Kielmeyra coriacea Mart. (4), (another member of the family Guttiferae) as well as in M. americana L. (5) has also come to light. We now wish to report that 4-hydroxyxanthone, 1,7-dihydroxyxanthone (euxanthone), and 1,5-dihydroxyxanthone (see the figure) co-occur with the 2-hydroxy isomer in M. americana, and to emphasize the bearing of these findings on current biogenetic theory.

4-Hydroxyxanthone.

During the course of our original chromatographic separation of 2-hydroxyxanthone, a second crystalline substance was isolated from immediately preceding fractions in substantially lesser amount. After being recrystallized twice (ethanol-isohexane) and sublimed (160° at 0.2 mm.), this substance showed m.p. $245.0\text{-}246.0^{\circ}$. (Kofler hot stage, corrected); ν_{max}^{KBr} 3322, 1653 (shoulder), 1647, 1613, 1605, 905, 748 cm^{-1}; λ_{max}^{EtOH} 235, 250,

282, 290, 353 mμ; $\lambda_{max}^{EtOH-NaOH}$ 235, 269, 301, 311, 402 mμ (6). In spite of what now seem to be obvious spectoscopic clues to the identity of this compound, microanalytical data led to its formulation as a "C_{12}" phenol and further work was deferred until a larger amount of this material could be obtained. This has now been accomplished along with the re-isolation of 2-hydroxyxanthone and the pair of isomeric dihydroxyxanthones described below. On reexamining the properties of the "C_{12}" phenol, we realized that, except for the analytical figures, all its properties were in excellent accord with those reported in the literature for 4-hydroxyxanthone (7). This correlation was supported by the results of a second microanalysis (Found: C, 73.60; H, 3.52) which were in close agreement with theory (8). Verification of this structural assignment was completed by direct comparison with an authentic sample. Thus, Ullmann condensation of guaiacol with o-chlorobenzoic acid followed by cyclization and demethylation provided 4-hydroxyxanthone identical in all respects with the natural product.

1,7-Dihydroxyxanthone (Euxanthone).

During chromatography on silica columns of an ethanol extract of mamey seed residue (oil removed), there was obtained, immediately after elution of 2-hydroxyxanthone, a bright yellow semi-solid. Crystallization from a mixture of chloroform and isohexane provided yellow needles, m.p. 240-241°. Microanalytical data led to a $C_{13}H_8O_4$ formulation and the spectroscopic propertie of this substance were compatable with a dihydroxyxnathone structure. A search of the literature suggested three possible isomers: the 1,4-, 3,4-, and the 1,7-dihydroxy derivatives. The latter seemed more likely on phytochemical grounds since euxanthone has previously been encountered in Platonia insignis Mart. (9,10), another member of Guttiferae. The preparation of an authe

specimen of euxanthone, whose properties were identical with those of the natural product, verified this conclusion; thus, M. americana L. may be added to the growing list of Guttiferae which produce this substance (11,12).

Our synthesis of euxanthone followed the classical Ullmann method (10, 13). We were also able to obtain this product, although in low yield, from the modified (14) Michael-Kostanecki (10) reaction of 2,5-dihydroxybenzoic acid with resorcinol. An alternative approach, utilizing the condensation of 2,6-dihydroxybenzoic acid with hydroquinone, failed to provide euxanthone but instead produced 1,6-dihydroxyxanthone. This result has been independently observed and discussed just recently by others (12).

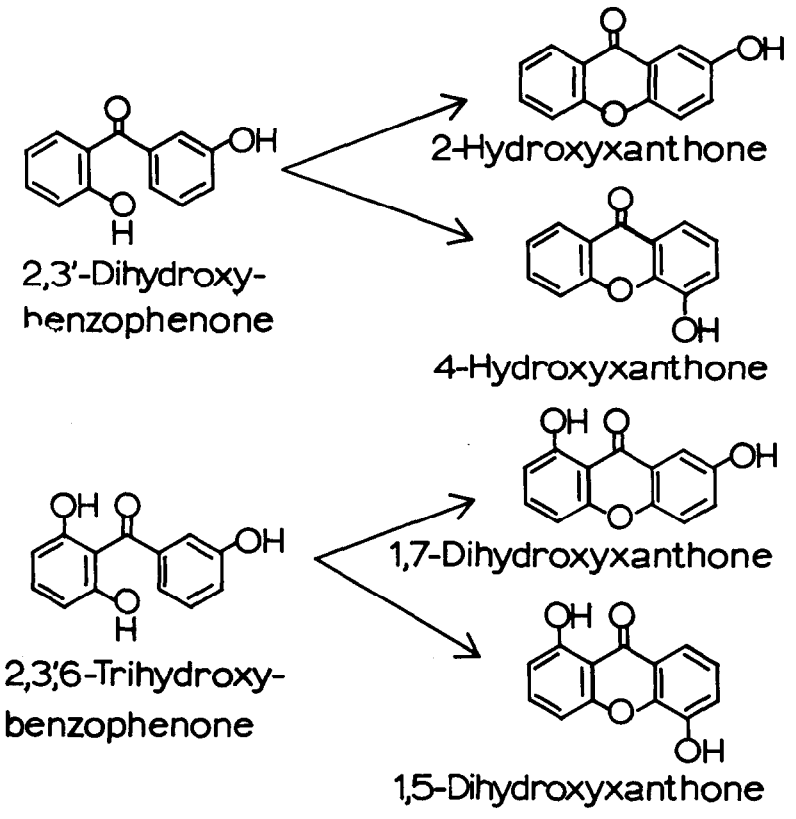
1,5-Dihydroxyxanthone.

During the silica gel column chromatography referred to above, before the elution of 4-hydroxyxanthone, there was obtained a yellow crystalline solid which, after several recrystallizations from chloroform-isohexane mixtures, had m.p. 260-261 and for which the formula $C_{13}H_8O_4$ was deduced from microanalytical and molecular weight data. The infrared (ν_{max}^{KBr} 3413, 1645 cm^{-1}) and ultraviolet (λ_{max}^{EtOH} 252, 318, 378 mμ, log e 4.62, 3.92, 3.73; $\lambda_{max}^{EtOH-NaOH}$ 252, 318, 358, 416 mμ, log e 4.62, 3.82, 3.98 3.86) spectra were typically xanthone-like. Among the known dihydroxyxanthones, both the 1,3-isomer, m.p. 260°, and the 1,6-isomer, m.p. 258-259°, were ruled out by direct comparison of unambigously prepared samples with the natural product. Our attention then became focused on the possibility that the unknown was the previously unreported 1,5-dihydroxyxanthone. In view of our identification of the three xanthones already described, this possibility was uniquely supported by the biogenetic considerations discussed below. Accordingly, the 1,5-isomer was synthesized by the following sequence of reactions.

The diazonium fluoborate salt derived from the commercially available 2-methyl-3-chloroaniline was decomposed in refluxing methanol to produce 2-chloro-6-methoxytoluene, which in turn was oxidized to 2-chloro-6-methoxybenzoic acid. Ullmann coupling of this acid with guaiacol afforded a diphenyl ether which was cyclized by treatment with acetyl chloride and sulfuric acid. The resulting 1,5-dimethoxyxanthone, m.p. 190°, then yielded the desired 1,5-dihydroxyxanthone after treatment with aluminum chloride. This synthetic product has m.p. 265-266°. Its infrared and ultraviolet spectra were indistinguishable from those of the plant derived material and the mixture melting point was 261-263°. The somewhat lower melting point of the natural xanthone is not surprising under the circumstances and is most likely the result of slight contamination by 4-hydroxyxanthone.

A Note on the Biogenesis of Xanthones.

The suggestion has recently been advanced that natural xanthones fall into two groups which reflect differing modes of biogenesis (15). One group consists of those apparently derived from an appropriate 2,2'-dihydroxybenzophenone by a cyclodehydration sequence, while the other comprises those conveniently regarded as arising from a 2,3'-dihydroxybenzophenone by an oxidative coupling reaction. Although the extent to which the oxidative coupling route to xanthones prevails in nature has been a matter of mild debate (16), the overall simpler pattern of xanthone biogenesis which results from consideration of both types of ring closure (17) cannot be gainsaid. We believe that our observation of the coexistence not only of the 2- and 4-hydroxyxanthone isomers, but also (*a fortiori*) the 1,5- and 1,7-dihydroxyxanthones in the same species is in elegant accord with their respective derivation by oxidative coupling from common benzophenone precursors. These connections are illustrated in the figure below.



In view of the biogenetic relationship between certain benzophenones and 4-arylcoumarins (18) (neoflavanoids) (19), the presence in M. americana of a number of 4-phenylcoumarins (1,5) along with members of the xanthone class would seem to provide an additional unifying link to patterns of biogenesis among phenolic oxygen-heterocycles. Further studies on mamey seed constituents are in progress.

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