Tetrahedron Letters No.3, pp. 199-202, 1970. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF HELIOXANTHIN

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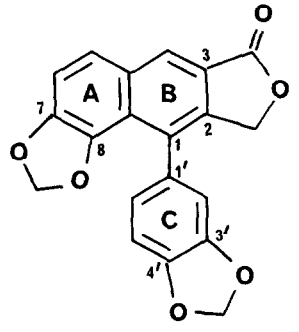
(Received in USA 19 November 1969; received in UK for publication 17 December 1969)

From the roots of Heliopsis helianthoides (L.) B.S.P. var. scabra Dunal, Jacobson isolated two non-crystalline, insecticidal amides which he named scabrin and heliopsin, and two crystalline, but inactive, products which were sparingly characterized.[1,2] Recently, Crombie and coworkers[3] have re-examined these latter products, named them helioxanthin and helianthoidin, and formulated them as lignans. Helioxanthin (1) joins the rapidly burgeoning group of naturally occurring lignans based on the 2,3-dimethylphenylnaphthalene framework, which are the subject of much current interest and include dehydropodophyllotoxin,[4] diphyllin,[5,6] justicidin A[5,7] and B,[7,8] taiwanin C[9] and E[9,10] and plicatinaphthol.[11] In several cases, since the available evidence did not permit distinction among alternative structural proposals, unequivocal synthesis was required and multi-step procedures have been reported.

We report here a total synthesis of helioxanthin (1) which fully confirms the proposed structure.



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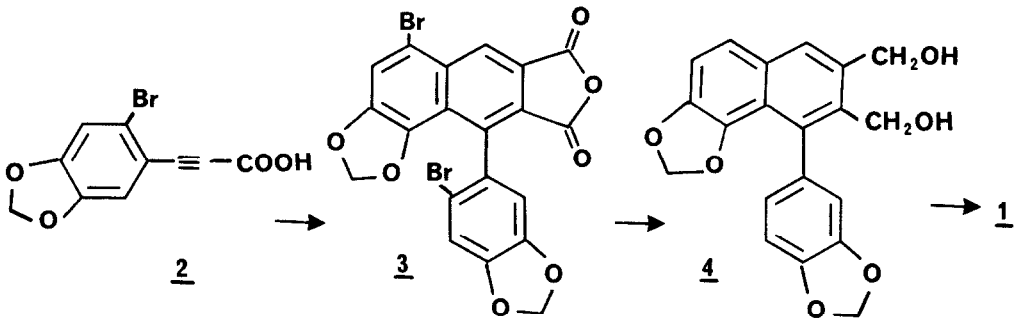
Treatment of 2-bromo-4,5-methylenedioxyphenylpropiolic acid (2) with dicyclohexylcarbodiimide in dimethoxyethane solution at -5 to -15° yielded

a product mixture from which 5-bromo-7,8-methylenedioxy-1-(2'-bromo-4', 5'-methylenedioxyphenyl)naphthalene-2,3-dicarboxylic acid anhydride (3) was separated by silica gel chromatography. The n.m.r. spectrum of 3, $C_{20}H_8Br_2O_7$ [δ 8.93(H-4), 7.77(H-6), 7.12(H-3'), 6.73(H-6'), 6.10 and 6.04 (ring A and C methylenedioxy groups)] is in complete accordance with the previously assigned structure.[12]



We have found that the reductive debromination of 3 to the diol, 2,3-bis-hydroxymethyl-7,8-methylenedioxy-1-(3',4'-methylenedioxyphenyl)naphthalene (4) by the action of lithium aluminum hydride and aluminum chloride in ether is capricious to reproduce but that the conversion is smoothly effected by employing tetrahydrofuran as solvent. In this way was obtained the diol, (4), $C_{20}H_{16}O_6$, whose n.m.r. spectrum has signals at δ 2.95 broad (two hydroxyls), 4.62 and 4.88 (two hydroxymethyls), 5.80 and 6.04 (two methylenedioxy groups), ca. 6.78 (ring C, three benzenoid protons), 7.16 (J 8.5) and 7.42 (J 8.5)(ring A benzenoid protons) and 7.77 (H-4); the signal patterns given by the benzenoid protons closely resemble those of dehydro-otobain.[12]

A satisfactory completion of the synthesis of helioxanthin required a selective oxidation of the C-3 hydroxymethyl group of the diol (4). This was achieved cleanly and in excellent yield by heating a solution of 4 in benzene under reflux for 30 minutes with the silver carbonate-celite reagent;[13] the crude product[14] on crystallization from ethanol yielded 7,8-methylenedioxy-1-(3',4'-methylenedioxyphenyl)-2-hydroxymethylnaphthalene-3-carboxylic acid lactone (1), $C_{20}H_{12}O_6$ as prisms, m.p. 243-244°, λ(EtOH) 219(25,400), 267(32,100), 289(2200) and 356 mμ(4000). A mixed m.p.

determination, nuclear magnetic resonance, mass spectra and infra-red spectra comparison with an authentic specimen of helioxanthin established their identity.[15]

We consider this three significant-step procedure to have useful and general application to the preparation of phenylnaphthalenes, and particularly to lignans of this type with carboxyl-derived functions at C-3.

Acknowledgment. The aid of an Institutional Research Grant from the American Cancer Society (IN-29) and a Research Grant (AM-13708) from the National Institute of Arthritis and Metabolic Diseases is gratefully acknowledged.

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14. Integration of the n.m.r. spectrum of the crude total product indicates that the isomeric lactone (i.e. from the 3-hydroxymethylnaphthalene-2-carboxylic acid), if at all present is in less than a 1:7 ratio.

15. Kindly provided by Professor L. Crombie, University of Nottingham, England.