

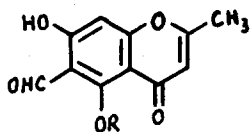
NATURAL CHROMONES-VII. A NEW TOTAL
SYNTHESIS OF VISNAGIN

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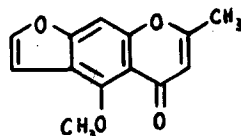
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The literature contains a number of total syntheses of visnagin (I), a constituent of *Ammi visnaga* L., most of which (1) are based on the initial elaboration of a suitably substituted benzofuran derivative followed by the construction of a 2-methyl-7-pyrone moiety linearly onto it. Two syntheses (2,3) start from a ready-built chromone residue and proceed by formation of the furan ring.



II: R=CH₃; X:R=H



I

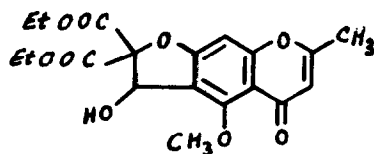
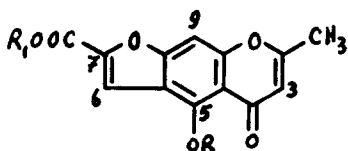
In the present work, a synthesis of visnagin was realized by the use of 2-methyl-5-methoxy-6-formyl-7-hydroxychromone (II) by condensation with diethyl bromomalonate. When the reaction was conducted in a boiling acetone solution containing potassium carbonate for 30 hours, 2-methyl-5-methoxy-6,7-(2',3'-furo)-chromone-5'-carboxylic acid ethyl ester (III) (m.p. 188-190°) resulted. Reducing the reaction period to 12 hours gave a mixture of III and the dicarboxylic acid diethyl ester IV (m.p. 168-170°); the latter was the sole product from a condensation performed in ethanolic solution containing potassium hydroxide. The structure III finds support in the n.m.r. spectrum (4) which contains a slightly broadened and shorten-

ed signal at δ 6.01 (C-3 proton), 7.76 (C-9) and 7.20 (furanoid β -proton at C-6); the latter two signals exhibit long range coupling effect which doubles each ($J_{69} = 1.5$ c.p.s.). That IV is an intermediate towards the formation of III in the potassium carbonate experiment was proven by effecting this transformation (IV \longrightarrow III) by the action of the carbonate alone. The structure of IV is supported by n.m.r. data which show signals arising from two ethyl, one methoxyl and one methyl groups along with a singlet (δ 5.96) due to the C-3 proton and one (δ 6.47) due to the single benzenoid proton (C-9), but the spectrum, surprisingly, contains no evidence for hydroxyl group and was not changed upon treatment with D_2O or after heating (80°). The formation of intermediates (not isolated) with structures analogous to IV was previously assumed (5) to take place during the synthesis of some benzofuran derivatives by condensation of a suitable salicylaldehyde with diethyl bromomalonate.

Subsequent saponification of the ester groups in III and IV with mineral acid was found to be considerably influenced by the nature of solvent. Thus while hydrolysis with ethanolic hydrochloric acid affected only the C-5 methoxyl group in III (to give V, m.p. $213-214^\circ$), the use of aqueous solution affected both ester and ether groups, giving rise to VI (m.p. $315-318^\circ$) from III, IV and VII. Methylation of VI with diazomethane gave the ester VIII (m.p. $277-279^\circ$), and with methyl iodide gave the ether-ester IX (m.p. $223-225^\circ$). The desirable 5-methoxy free carboxylic acid (VII) was obtained (m.p. $295-297^\circ$) only by careful saponification of III with sulphuric acid in acetic acid solution. Final decarboxylation of VII with copper bronze in quinoline solution afforded visnagin (I), which was identical with the natural product (mixed m.p., $139-140^\circ$, and IR spectra), in reasonable yield.

A formal total synthesis of visnagin was also realized starting

from 2-methyl-5,7-dihydroxy-6-formylchromone (X) which has been prepared (3) from phloroglucinaldehyde through condensation with ethyl acetoacetate in diphenyl ether by a modification (6) of the original Simonis (7) and Mentzer (8) reactions. Condensation of X with diethyl bromomalonate, not



III: $R=CH_3, R_1=C_2H_5$; V: $R=H, R_1=C_2H_5$;
 VI: $R=R_1=H$; VII: $R=CH_3, R_1=H$;
 VIII: $R=H, R_1=CH_3$; IX: $R=R_1=CH_3$

IV

manageable in acetone-potassium carbonate, was made in ethanolic alkali to give a mixture containing the 5-hydroxy analogue of IV. Saponification with potassium carbonate or hydrochloric acid in acetone solution afforded a mixture comprising V which was then methylated to III. Transformation into visnagin then follows as described before via VII.

Satisfactory elemental analysis and spectral data were obtained for all products.

We are deeply indebted to Professor A.V. Robertson (University of Sydney) for the n.m.r. measurements (made in $CDCl_3$, with reference to T.M.S.).

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