

CHEMICAL STUDIES IN RELATION TO THE BIOSYNTHESIS OF SOME NATURAL BENZOFURANS AND RELATED COMPOUNDS. PART II*

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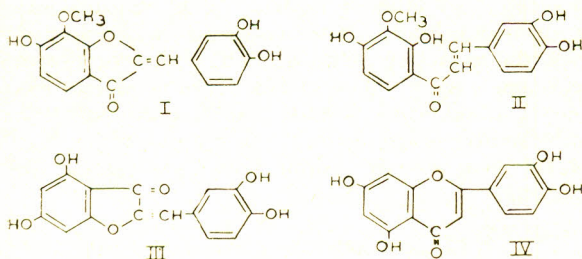
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4'-Methoxybenzylidene-coumaran-3-one (VI) on treatment with alcoholic alkali gave anisaldehyde. The other products obtained were the flavone (VIII) and a diketone (IX). Reduction of (VI) gave 2(4'-methoxy-benzyl)-3-hydroxy-dihydrobenzofuran. These reactions provide some chemical basis for the hypothesis that benzalcoumarones probably derived by the condensations of benzaldehydes and coumaranones are involved in the biosynthesis of flavones and related substances.

Introduction

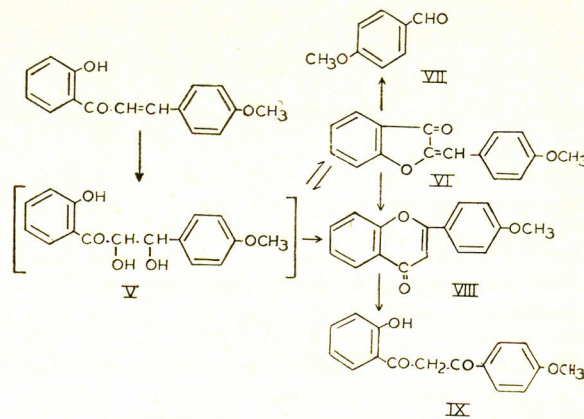
Little work of a biochemical nature has been done on the possibility of biosynthesis of flavones and related substances including furanoid compounds from benzalcoumaranones, but it appears certain that oxidation processes play an important role in the formation of these compounds in plants.¹⁻⁶ The present investigation while primarily concerned with providing some further chemical evidence in support of the hypothesis that coumarones could be derived from benzalcoumaranones has also produced some unexpected and at the same time quite interesting results. One of the results which has been of particular significance was the formation of the flavone (VIII) from benzylidenecoumaranone (VI) by the action of alcoholic alkali. Leptosidin (I), a benzalcoumaranone, has been isolated from *Coreopsis grandiflora* and it is significant that 2',4',3,4-tetrahydroxy-3'-methoxy chalcone (II) has also been isolated from this plant. The co-occurrence of the coumaran-3-one aureusidin (III) and the flavone luteolin (IV) in *Antirrhinum majus* is equally noteworthy.



Such co-existence and structural relations, besides indicating the biosynthetic relationships among the different groups of compounds mentioned above, also suggest that coumaran-3-ones may be derived from benzylidenecoumaranone by loss of the benzylidene group. The most

plausible mechanism for the removal of the benzylidene group would be, however, by means of a reverse-aldol reaction as shown in the case of 6-methoxy-2-isopropylidene-coumaran-3-one. Reduction of coumaran-3-one with sodium borohydride could then give coumarone (cf. Part I of this series).

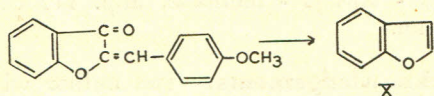
The oxidation process mentioned above appears to be vitally connected with the formation of flavones and related substances from benzalcoumaranones as shown in the following scheme.



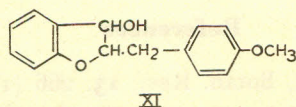
Although the co-occurrence of benzalcoumaranone and flavone is less frequently encountered in nature, the one in *Antirrhinum majus* indicates that these compounds are interconvertible. The most probable mechanism involved in this interconversion would be, however, dependent upon the opening of the ring and formation of the intermediate (V). Formation of the flavone from benzalcoumaranone in the laboratory lends support to this view. While it may be argued that the reaction is not analogous to a cellular process it is certain that the same results could be achieved under conditions approximating to those obtaining in living cells.

*The work described in this paper was carried out in the Department of Organic Chemistry, University of Sydney, Australia.

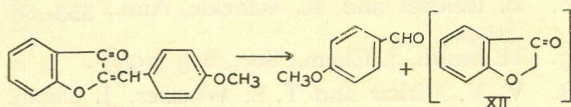
Reactions of 4'-Methoxybenzylidene-coumaran-3-one.—In order to provide some basis for a hypothesis such as that above, the reactions of 4'-methoxy-benzylidene-coumaran-3-one (VI) were studied. Reduction of (VI) with sodium borohydride⁷ was expected to yield coumarone (X) and/or related substances.



The only product of this reaction was a substance $C_{16}H_{16}O_3$ to which structure (XI) is assigned. An attempt to dehydrate it with dilute sulphuric acid proved unsuccessful.



4'-Methoxybenzylidene-coumaran-3-one (VI) was then examined to see whether a reverse aldol reaction could remove the benzylidene group as anisaldehyde (VII) and leave coumaran-3-one (XII) or a derivative.



Treatment with very dilute alkali resulted only in the recovery of the starting material. Prolonged treatment with alcoholic alkali at room temperature gave mainly anisaldehyde which was identified as its 2:4-dinitrophenylhydrazone. It seems likely that coumaran-3-one formed under went degradation under the influence of alkali leading to the production of an unidentifiable polymeric material. A side reaction also occurred resulting in the formation of the flavone (VIII) and a diketone, 2-hydroxybenzoylanisoyl methane (IX), identified by mixed melting point with an authentic specimen prepared by a standard method⁸.

Experimental

Melting points are uncorrected. Microanalyses were carried out partly by the C.S.I.R.O. Micro-analytical Laboratory and partly by the Micro-analytical Laboratory, University of Sydney.

(a) *4-Methoxy-2'-hydroxychalcone*.—o-Hydroxyacetophenone (13.6 g.) was added to an aqueous alcoholic solution of sodium hydroxide (10 g.; water, 80 ml; ethanol, 50 ml.). The

solution was stirred and anisaldehyde (13.6 g.) slowly added, the temperature being maintained at 25°C. Vigorous stirring was continued for three hours at this temperature, and then the mixture was kept at 0°C. overnight. The solid yellow mass was acidified with acetic acid (15%). 4-Methoxy-2'-hydroxychalcone, m.p. 93-4°C., from methanol was obtained in good yield.

(b) *4-Methoxy-2'-hydroxychalcone Dibromide*.—4-Methoxy-2'-hydroxychalcone (10 g.) was dissolved in a minimum amount of carbon disulphide and the solution was cooled to 0°C. Bromine (20 ml.; 1 vol. bromine; 9 vol. carbon disulphide) was added with stirring, the temperature being kept below 10°C. The dibromide separated as granular yellow crystals, m.p. 137-8°C., from methanol.

(c) *4'-Methoxybenzylidene-coumaran-3-one*.—A mixture of the dibromide (10.5 g.) and absolute ethanol (200 ml.) was heated to boiling on a water bath. When the solid was completely dissolved sodium hydroxide (50% ; 10 ml.) was added and the mixture refluxed for ten minutes. The solution was immediately cooled and diluted with water. The crude product was filtered and washed several times on the filter with water. 4'-Methoxybenzylidene-coumaran-3-one, m. p. 138-9°C. from methanol was obtained in 60% of the theoretical yield.

(d) *Reduction of 4'-Methoxybenzylidene-coumaran-3-one with Sodium Borohydride*.—4'-Methoxybenzylidene-coumaran-3-one (500 mg.) was dissolved in absolute ethanol (25 ml.) by warming on a water bath. The system was filled with nitrogen and sodium borohydride (300 mg.) in ethanol added. The mixture was refluxed one hour. After cooling it was acidified with dilute acetic acid, diluted with water and extracted with ether. The combined extracts were washed with sodium bicarbonate solution and finally with water. Evaporation of the solvent gave an oily residue which crystallised on standing.

2(4'-Methoxybenzyl)-coumaran-3-ol, m.p. 114-5°C., was recrystallised from light petroleum (b.p. 60-90°C.). (Found: C, 74.7; H, 6.1. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3).

(e) *Alkaline Treatment of 4'-Methoxybenzylidene-coumaran-3-one*.—4'-Methoxybenzylidene-coumaran-3-one (1 g.) was dissolved in ethanol (50 ml.) and sodium hydroxide solution (50 ml.; 20%) added. The mixture was allowed to stand twenty-four hours at room temperature. After dilution with water it was extracted with ether.

Evaporation of the solvent gave a mixture of solid and oil which was diluted with a little methanol and filtered. 4'-Methoxy-flavone, m.p. 155°C., was recrystallised from methanol. (Found: C, 76.2; H, 4.9. $C_{16}H_{12}O_3$ requires C, 76.2; H, 4.8).

The methanolic mother liquors containing the oil gave a derivative with 2:4-dinitrophenylhydrazine hydrochloride, m.p. 250°C., not depressed in mixed melting point with an authentic specimen of anisaldehyde 2:4-dinitrophenylhydrazone.

The alkaline solution was acidified and extracted with ether. After evaporation of the solvent, *o*-hydroxybenzoyl-anisoyl methane, m.p. 111°C., from methanol, not depressed in mixed melting point with an authentic specimen was obtained. (Found: C, 70.7; H, 5.4. $C_{16}H_{14}O_4$ requires C, 71.0; H, 5.2).

(f) *o*-Anisoyloxy-acetophenone.—*o*-Hydroxyacetophenone (5 g.) was dissolved in pyridine (10 cc.) and anisoyl chloride (6.5 g.) added. The mixture was heated fifteen minutes on a water bath and allowed to stand at room temperature for one hour. It was then poured into dilute hydrochloric acid (2N). *o*-Anisoyloxyacetophenone separated in good yield (8 g.), and was recrystallised from ethanol, m.p. 111°C.

(g) *o*-Hydroxybenzoyl-anisoyl-methane.—*o*-Anisoyloxy-acetophenone (5 g.) was added to

powdered sodium (400 mg.) in dry toluene (35 ml) and refluxed three hours. After cooling the mixture was acidified with dilute acetic acid (1:1). The aqueous layer was separated and the toluene diluted with ether and extracted with sodium hydroxide (5%). Acidification of the alkaline extract resulted in the separation of *o*-hydroxybenzoyl-anisoyl-methane, m.p. 112°C., from methanol.

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