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A Plausible Chemical Analogy for Biosynthesis of 2-Arylbenzofuran of Isoflavonoid Origin and its Application to Synthesis of Vignafuran

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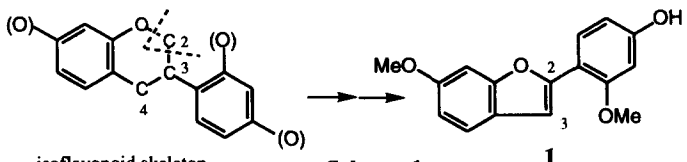
Abstract: Treatment of 2-hydroxy-isoflav-3-ene with acid afforded 2-arylbenzofuran in good yield, and a mechanism for this chemical conversion involving loss of one carbon unit was described. This reaction scheme was suggested as a plausible chemical analogy for the corresponding biosynthetic process of 2-arylbenzofuran of isoflavonoid origin, and a new biosynthetic scheme depicting 2-hydroxy-isoflav-3-ene as the possible common intermediate for both 2-arylbenzofuran and 3-arylcoumarin was proposed. Synthesis of a potent antimicrobial 2-arylbenzofuran phytoalexin, vignafuran, was also achieved by use of this chemical scheme. Copyright © 1996 Published by Elsevier Science Ltd

The occurrence of 2-arylbenzofurans in nature is restricted to either legumes or mulberry and its related plants.[1,2,3] However, these compounds are of increasing interest since many of them have been recognized as phytoalexins, a group of secondary metabolites produced *de novo* as defensive substances by plants against fungal infection. Those known from mulberry and its allies are thought to differ biogenetically from those of leguminous origin. The former are characterized by the location of the oxygen functionality of 2-phenyl group at the 3'- and 5'-positions and are derived from oxidative cyclization of the corresponding stilbene precursors.[4,5] On the other hand, those of leguminous origin possess the oxygen functionality commonly at the 2'- and 4'-positions in the 2-phenyl group and are considered to be members of the isoflavonoid family although they have a C_6-C_2-C_6 skeleton, one carbon short of that of the ordinary isoflavonoid.[1,6] Vignafuran (**1**) is typical of such 2-arylbenzofuran, which was isolated as a potent fungicidal phytoalexin from microorganism-infected cowpea (*Vigna unguiculata*) leaves.[7]



isoflavonoid skeleton **1**

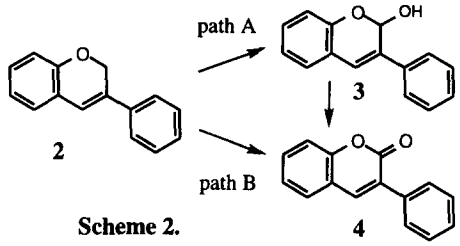
Scheme 1.

Extensive tracer experiments demonstrated that vignafuran is derived from an isoflavonoid precursor through contraction of its heterocyclic ring involving loss of the C-2 carbon (Scheme 1),[6] but its biosynthetic process remains undefined. In this paper the author presents one-step chemical conversion of 2-hydroxy-isoflav-3-ene (**3**) (3-phenyl-2*H*-1-benzopyran-2-ol) to 2-arylbenzofuran (**6**) as a chemical analogy for the plausible 2-arylbenzofuran biosynthesis of leguminous origin. Synthesis of vignafuran by use of this chemical scheme is also described.

More than a dozen of isoflavonoid classes have been known from natural sources up to the present.[1] Accumulation of knowledge on the natural co-occurrence and chemical interconversions of various isoflavonoids has helped postulate a possible biogenetic scheme to interrelate them, and this scheme has been substantiated or often corrected by increasing experimental evidence. However, there are still several classes of isoflavonoids that are missing from the latest version of the isoflavonoid biogenetic scheme because of the lack of persuasive biosynthetic evidence. 2-Arylbenzofurans are a class of these isoflavonoids that must await further experimentation, and no hypothetical biogenetic precursor has been suggested.

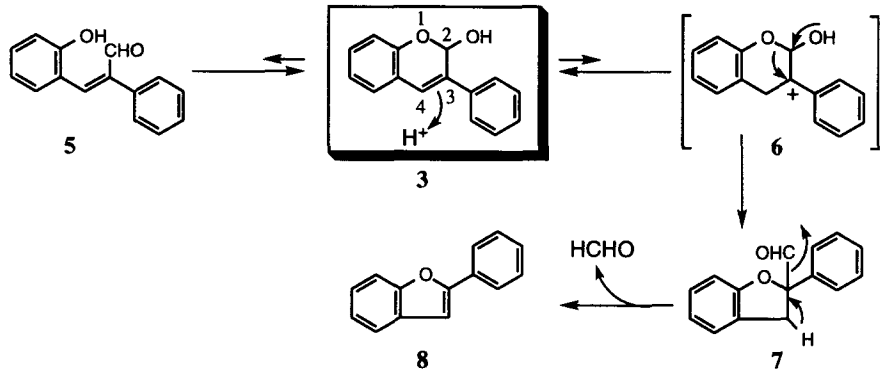
A characteristic feature encountered in the 2-arylbenzofuran biosynthesis will be undoubtedly contraction of the heterocyclic ring of the corresponding isoflavonoid precursor resulting in elimination of one carbon unit. Chemical conversion of isoflavylium perchlorate to 2-arylbenzofuran by treatment with H_2O_2 was reported earlier as a possible chemical analogy for 2-arylbenzofuran biosynthesis.[8] This conversion was postulated as proceeding through the corresponding deoxybenzoin intermediate resulting from oxidative cleavage of isoflavylium-3,4-epoxide. However, this process will not be a chemical basis for the 2-arylbenzofuran biosynthesis, because it involves, as biosynthetic intermediates, several chemical species that have yet to be discovered in nature.

Undoubtedly, either isoflav-3-ene (**2**; 3-phenyl-2*H*-1-benzopyran) or 3-arylcoumarin (**4**; 3-phenyl-2*H*-1-benzopyran-2-one) is the most proximate class of isoflavonoids to 2-arylbenzofuran. However, it can hardly be imagined that a ring contraction process involving loss of the C_1 unit, which is a necessary step for formation of the furan ring, results from these two isoflavonoids. 3-Arylcoumarin is supposed to arise from allylic oxidation of isoflav-3-ene.[1] A previously proposed biosynthetic scheme from isoflav-3-ene to 3-arylcoumarin seems to be based on a report on autoxidative conversion from pterocarpene (6*H*-benzofuro[3,2-*c*]benzopyran) to coumestan (6*H*-benzofuro[3,2-*c*]benzopyran-6-one),[9] and thus this process is believed to proceed in one step (path B; Scheme 2).[1] From the viewpoint of enzymatic oxidation, such type of oxidation is unlikely in a secondary metabolic process. Alternatively, this oxidation may be postulated as a combination of two independent oxidation processes: monooxygenation of allyl methylene of isoflav-3-ene and subsequent dehydrogenation of the resulting C-2 hydroxyl (path A; Scheme 2). In this scheme 2-hydroxy-isoflav-3-ene (**3**) can be envisaged as the proximate biosynthetic intermediate for 3-arylcoumarin, but its role has never been referred to in the isoflavonoid biogenesis. It was also of interest to investigate whether 2-hydroxy-isoflav-3-ene can be interrelated chemically with another class of isoflavonoids, particularly 2-arylbenzofuran. Thus, 2-hydroxy-isoflav-3-ene (**3**)[10] was prepared by reduction of 3-arylcoumarin[11] with DIBAL, and was then subjected to chemical conversion under various conditions. Conversion of **3** to 2-arylbenzofuran (**8**) was successfully achieved in 78% yield on its treatment with acid.[12] It is the C-2 carbon that was eliminated in this chemical conversion, since 2-arylbenzofuran resulting from the conversion of [2-^{13}C]-2-hydroxy-isoflav-3-ene[13] retained no ^{13}C label. It is readily speculated



Scheme 2.

that compound **3** is isomerized mainly to its acyclic stilbene isomer **5** [(*E*)-α-(2-hydroxyphenylmethylene)-benzeneacetaldehyde] and, to a lesser extent, to a cyclic coumaran isomer **7** (2-formyl-2-phenyl-2,3-dihydro-

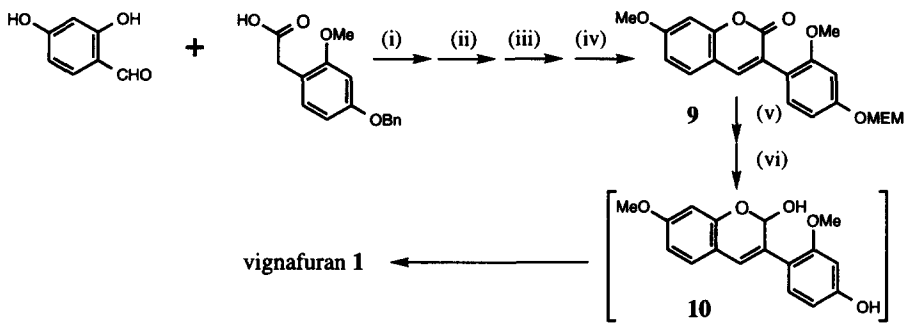


Scheme 3. A Possible Mechanism for Chemical Conversion of 2-Hydroxy-isoflav-3-ene to 2-Arylbenzofuran

benzofuran) under acidic condition. Compound **3** and its two isomers (**5** and **7**) would exist in equilibrium, and only the isomer **7** would undergo deformylation to give rise to 2-arylbenzofuran (**8**). The isomerization from **3** to **7** would be effected by formation of a cation (**6**) at the 3-position resulting from protonation to the 3,4-double bond and subsequent migration of the 1,2-bond to this cation as illustrated in Scheme 3. The isomer **7** is unlikely to be derived by direct cyclization of its acyclic isomer **5** since an electron-absorbing aldehyde group will not allow formation of the corresponding cation. The ratio of the isomer **7** in the equilibrium mixture may be small, but irreversible elimination of formaldehyde from this isomer giving rise to 2-arylbenzofuran would lean the equilibrium toward formation of this isomer. A possible mechanism for one-step chemical conversion of 2-hydroxyisoflav-3-ene (**3**) to 2-arylbenzofuran (**8**) involving loss of the C_1 carbon unit as summarized in Scheme 3. This was further substantiated by the finding that a deuterium label at C-2 of 2-hydroxyisoflav-3-ene (**3**)[12] was lost during its conversion to 2-arylbenzofuran (**8**).

Synthesis of vignafuran (**1**) was successfully achieved according to the above chemical process as shown in Scheme 4 (56% overall yield from **9**).[14] Though attempts to isolate a hypothetical biosynthetic precursor of vignafuran, 3-(4'-hydroxy-2'-methoxyphenyl)-7-methoxy-2*H*-1-benzopyran-2-ol (**10**), met with failure, there is no doubt that formation of vignafuran proceeded *via* **10**. 2-Hydroxy-isoflav-3-ene and its analogues have yet to be encountered in nature, but this chemical conversion suggests a biosynthetic scheme of 2-arylbenzofurans of the isoflavonoid origin where 2-hydroxy-isoflav-3-ene serves as a common precursor for both 3-arylcoumarin and 2-arylbenzofuran. This will supplement the previously proposed biosynthetic scheme of the isoflavonoid. Synthesis of several naturally occurring 2-arylbenzofurans has been reported in view of their importance as biologically active substances.[15,16] It is noteworthy that the above chemical scheme may prove valueable as a new tool for synthesis of biologically active 2-arylbenzofurans since 3-arylcoumarins are readily available from aldol condensation of the corresponding *o*-hydroxybenzaldehyde and phenylacetic

acids (Scheme 4).



(i) $AcONa/Ac_2O$; (ii) $NaOH/(CH_3O)_2SO_2$; (iii) H_2/Pd-C; (iv) NaH/CH_3OCH_2Cl; (v) DIBAL; (vi) H^+

Scheme 4.

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10. 2-Hydroxy-isoflav-3-ene (**3**) was prepared from reduction of 3-arylcoumarin[11] by use of DIBAL in toluene at -78°. Yield: 41%. Mp. 94-96° (benzene-hexane). λ_{max}^{MeOH} nm: 207, 289; ν_{max}^{KBr} cm^{-1}: 3300, 1483, 1452, 1204; ^1H NMR (100MHz, $CDCl_3$) δ: 6.77 (1H, s, 2-H), 6.9-7.6 (10H, m, Ar-H and 4-H); ^{13}C NMR (25MHz, $CDCl_3$) δ: 91.6 (2-C), 116.6, 121.6, 122.1, 125.4, 127.3, 127.5, 128.2, 128.9, 130.0, 135.7, 149.4; EI-MS (rel. int., %): 224 (M^+, 94), 206 (100).
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12. Procedure: a solution of 2-hydroxy-isoflav-3-ene (**3**) in 2N H_2SO_4 (THF-H_2O) was kept under reflux for 2 hr. The reaction mixture was diluted with H_2O and extracted with ether. The ether solution was dried and evaporated to dryness. The residue was crystallized from MeOH to give 2-arylbenzofuran (**8**). Yield: 78%. mp. 120-121° (lit.[8] 118°). [2-*d*]-2-Hydroxy-isoflav-3-ene was also prepared in the same manner using *d*-DIBAL.
13. Preparation: [1-^{13}C]-Phenylacetonitrile was prepared from benzyl bromide and $K^{13}CN$ (*ca.* 30% enriched), and was then hydrolyzed on reflux in 20% ethanolic KOH to furnish [1-^{13}C]-phenylacetic acid. Over all yield: 82%. [2-^{13}C]-2-Hydroxy-isoflav-3-ene was prepared according to the above scheme.[10]
14. Procedure: DIBAL was added at -78° to a solution of 2',7-dimethoxy-4'-methoxymethyl-3-arylcoumarin (**9**) in CH_2Cl_2 until fluorescence of the reaction mixture on irradiation with UV (365 nm) disappeared. The reaction mixture was then evacuated without heating. 2N H_2SO_4 (THF-H_2O) was added to the residue and this mixture was refluxed 3 hr. Workup in the usual manner afforded vignafuran (**1**) in 56 % yield.
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