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SYNTHESIS AND PHOTOREACTIONS OF SORBOPHENONES
A PHOTOCHEMICAL SYNTHESIS OF FLAVONE[1]

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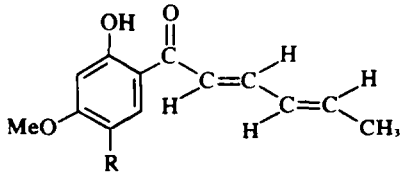
Abstract—A total synthesis of 5'-formyl-2'-hydroxy-4'-methoxy-(E,E)-sorbophenone, a cytotoxic metabolite of the fungus *Scytalidium* was accomplished in low yield. A model compound, 2'-hydroxy-4'-methoxy-(E,E)-sorbophenone was synthesized in better yield and this showed both cytotoxicity and activity in the P388 mouse leukemia screen. Irradiation of the latter sorbophenone caused cyclization to yield a mixture of the *cis* and *trans* isomers of 7-methoxy-2-(1'-propene)-chromanone. Similarly, irradiation of 2'-hydroxychalcone gave flavone in 53% yield.

Among the numerous metabolites we isolated[2] from the imperfect fungus *Scytalidium album* was 5'-formyl-2'-hydroxy-4'-methoxy-(E,E)-sorbophenone (**1**). Only a few mg were isolated from several hundred agar plates and the structure was proven[2] by spectral methods and analogy with some simple synthesized models. We discovered that **1** possessed relatively high cytotoxicity[3] and this was confirmed by the National Cancer Institute[4] (**1** = NSC 174259). In order to confirm the assigned structure of **1** we undertook a total synthesis.



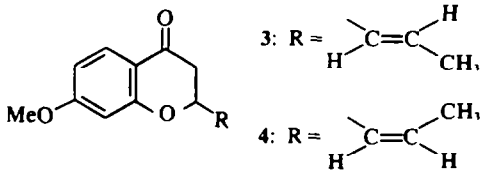
1: R = CHO
2: R = H

Because of the high cytotoxicity of **1**, we were also interested in the effect of structural modifications on cytotoxicity and attempted photochemical isomerization of the side chain in a model compound. A photocyclization was found to occur in addition to bond isomerization and this reaction was extended to provide a new synthesis of flavone from chalcone.

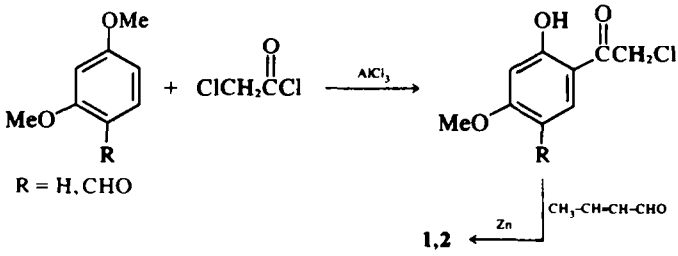
Synthesis. As a model reaction we followed the procedure[5] of Kuhn and Staab and converted *m*-dimethoxybenzene to 2-chloro-2'-hydroxy-4'-methoxyacetophenone and reacted the latter with crotonaldehyde to yield the known[5] 2'-hydroxy-4'-methoxysorbophenone (**2**) according to Scheme 1 (R=H). **2** was found[3] to be cytotoxic. The National Cancer Institute (**2** = NSC 178250) showed[4] **2** to be inactive against the L1210 (LE) *in vivo* antitumor screen, but active (T/C = 145 at 400 mg/kg) against the P388 (PS) screen.

In a similar manner, 2,4-dimethoxybenzaldehyde was converted in two steps to **1**, which proved to be identical to the isolated[2] natural product. Although **2** could be produced in good yield by this process, the yield of **1** was very low due to difficulties with the second step. The synthesis is being improved and modified in order to provide sufficient amounts for antitumor testing in animal systems.

Photochemistry. **2** was irradiated in benzene solution with the prospect that side chain double bond isomerizations might occur to produce structural variations for testing. A 73% yield of a colorless oil was isolated which showed one spot on TLC and a single peak in high pressure liquid chromatography and gas chromatography. A C,H analysis was obtained corresponding to an isomer of **2**. However, the UV and NMR spectra were not consistent with a simple double bond isomer. Indeed, the complexity of a number of the NMR peaks at 60 and 100 MHz led us to believe that the substance was actually an inseparable mixture of two substances and this was confirmed with 220 MHz NMR which allowed complete separation of peaks and a possible assignment of structure. These assignments (Experimental) indicated that the product was an approximate 1:1 mixture of **3** and **4**. Since we were unable to separate these compounds after many trials with



3: R =
4: R =

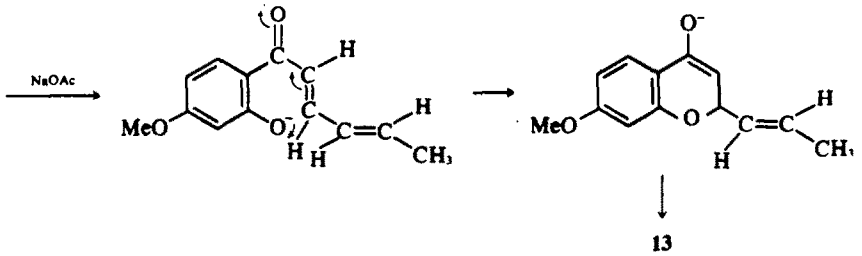


R = H, CHO

Scheme 1.

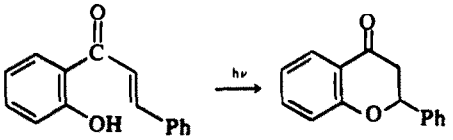
various types of chromatography, an independent synthesis of one was accomplished by simple base cyclization (Scheme 2).

A single compound was obtained in 24% yield and its structure assigned as 3 in accordance with the spectral data (Experimental) and the mechanism of Scheme 2 which is typical for the analogous synthesis of flavanones from chalcones. When the NMR of authentic 3 was subtracted from that of the photolysis mixture, the remaining peaks could be unequivocally assigned to 4.



Scheme 2.

The above photochemical synthesis of chromanones 3 and 4 led us to anticipate that such a procedure would also be applicable for a photochemical synthesis of flavanones from chalcones. We therefore irradiated 2'-hydroxychalcone (5) in benzene and indeed achieved a 53% yield of flavone (6).



5 6

Flavanones are usually synthesized by acid or base cyclization of chalcones, but occasionally problems are encountered with labile groups. The photochemical synthesis will provide an alternate flavanone synthesis method.

There are several mechanisms which could be suggested for the photocyclization we have observed. Phenols have a greatly increased pK_a in the excited state[6] and thus a photochemical analog of Scheme 2 is possible. External protic solvents are known[7] to undergo photoinduced addition to cycloalkenones and our observed reaction would be an intramolecular acyclic analog of those observed by Noyori and others.

The observed photocyclization of chalcone to flavone may be of importance in certain biosynthetic reactions. Thus, it has been shown[8] that light is an important factor in flavonoid biosynthesis in cell cultures of *Petrollinum hortense*. Although the emphasis has been placed[8] on enzyme activation, it is evident from our work that light would cause increased flavanoid production by direct irradiation or photosensitization processes since 2'-hydroxychalcones are the standard accepted biosynthetic precursors of flavonoids.

EXPERIMENTAL

Corrected m.ps were determined on a Thomas Hoover capillary m.p. apparatus. IR spectra were taken on Perkin–Elmer 267. NMR spectra were recorded on a Varian T-60 or JOEL-MH-100 and are reported as ppm from TMS as internal standard. HR-220 spectra were taken by Morgan–Schaffer, Montreal, Canada. UV spectra were measured using a Cary 17. Mass spectra were obtained using an AEI MS 12. Analyses were performed by Midwest Microlab, Ltd., Indianapolis, Indiana.

2-Chloro-2'-hydroxy-4'-methoxyacetophenone was prepared according to the method[5] of Kuhn and Staab. Thus, 13·8 g *m*-dimethoxybenzene (Aldrich Chemical Co.) in 15 ml CS_2 to which 13·5 g $AlCl_3$ was added, was reacted with 11·3 g chloroacetyl chloride in 10 ml CS_2. This procedure yielded 14 g (50% yield) 2-chloro-2'-hydroxy-4'-methoxyacetophenone.[5] A 10-fold scale up of the procedure was also successful. In a similar manner, 12·5 g 2,4-dimethoxybenzaldehyde (Aldrich Chemical Co.) in 12·5 ml CS_2 and 20 g $AlCl_3$ was reacted with 11·3 g chloroacetyl chloride to yield 6·0 g (22%) *2-chloro-5'-formyl-2'-hydroxy-4'-methoxyacetophenone* which was purified by recrystallization in MeOH and sublimation to give colorless crystals, m.p. 177–181°: NMR ($CDCl_3$) 4·04 (s, 3H, OCH_3), 4·74 (s, 2H, $COCH_2Cl$), 6·51 (s, 1H, aromatic), 8·29 (s, 1H, aromatic between carbonyl substituents), 10·28 (s, 1H, CHO), 12·37 (s, 1H, OH); IR (KBr) 1675 cm^{-1}; mass spec *m/e* 228, 230 (10 and 3·5%, M+). (Found: C, 52·23; H, 4·28. Calc. for $C_{10}H_9ClO_4$: C, 52·53; H, 3·97%).

2'-Hydroxy-4'-methoxy-(E,E)-sorbophenone, 2 was prepared according to the method[5] of Kuhn and Staab. Thus, 5 g 2-chloro-2'-hydroxy-4'-methoxyacetophenone was reacted with 13 g crotonaldehyde in 30 ml benzene with 70 mg $HgCl_2$ and 6 g freshly prepared mossy zinc to yield 1·3 g (24%) of 2, m.p. 108–109° (lit.[5] m.p. 111–112°). In a similar manner, 1 g 2-chloro-5'-formyl-2'-hydroxy-4'-methoxyacetophenone was reacted with 4 g crotonaldehyde in 10 ml benzene with 14 mg $HgCl_2$ and 2 g freshly prepared mossy zinc to yield a complex mixture which was purified by silica gel chromatography (elution with 4:1 hexane-$CHCl_3$) and then preparative layer chromatography on silica gel plates developed in benzene to yield 90 mg (10%) of 1, whose NMR, IR and TLC R_f values were identical with those of the isolated[2] natural substance.

7-Methoxy-2-(1'-propene)-chromanone (3, 4). A N_2-purged soln of 2 (90·8 mM) in 800 ml spectranalyzed benzene was irradiated (Hanovia 450-W lamp with Pyrex filter) and the reaction monitored by HPLC.[9] After 8 hr, the photolysate was evaporated and purified by PLC on silica gel (benzene). A band at R_f 0·1–0·2 which fluoresced blue under long wave length UV light was scraped from the plate and extracted into $CHCl_3$. A colorless oil (73%) was obtained which gave one spot on TLC in several systems, one peak on GLPC and one peak on HPLC and which analysed properly (see below) for an isomer of 2. It had the same mass spec and UV and nearly the same IR as pure 3 (see below). However, the 220 MHz NMR showed the isolate to be a 2:3 mixture of 3 and 4: NMR (220 MHz, $CDCl_3$) 1·75 (m, 6H. CH_3), 2·70 (m, 4H, C3), 3·81 (s, 3H, OCH_3 of 3), 3·82 (s, 3H, OCH_3 of 4), 4·89 (m, 1H, C2 of 3), 5·28 (m, 1H, C2 of 4), 5·71 (m, 2H, *trans* CH=CH of 3), 5·88 (m, 2H, *cis* CH=CH of 4), 6·44 (d, J = 2 c/s, 1H, C8 of 4), 6·45 (d, J = 2 c/s, 1H, C8 of 3), 6·57 (m, 1H, C6 of 4), 6·59 (m, 1H, C6 of 3), 7·83 (d, J = 8 c/s, 1H, C5 of 3), 7·85 (d, J = 8 c/s, 1H, C5 of 4). (Found: C, 71·72; H, 6·74. Calc. for $C_{13}H_{14}O_3$: C, 71·54; H, 6·46%).

7-methoxy-2-(1'-(E)-propene)-chromanone (3). To a soln of MeOH (75 ml), water (25 ml) and NaOAc (2·5 g) was added 100 mg of 2. The mixture was heated at reflux and monitored by HPLC.[9] After 96 hr, the soln was extracted with $CHCl_3$ and the residue

purified by prep TLC as above. A colorless oil was obtained in 24% yield and showed the typical[10] IR and UV of a chromanone: IR (film) 1660 (C=O) and 1600 cm^{-1} (C=C); UV (MeOH) 308 nm (4500), 270 (8460), 232 (11460), 212 (19100); mass spec *m/e* 218. The NMR ($CDCl_3$, 60 MHz) was distinctive for **3**: 1·75 (d, J = 5 c/s, 3H, Me), 2·70 (m, 2H, C3), 3·81 (s, 3H, OMe), 4·89 (m, 1H, C2), 5·71 (m, 2H, *trans* CH=CH), 6·45 (d, J = 2 c/s, 1H, C8), 6·59 (m, 1H, C6), 7·83 (d, J = 8 c/s, 1H, C5). (Found: C, 71·63; H, 6·64. Calcd for $C_{13}H_{14}O_3$: C, 71·54; H, 6·46%).

Flavone (**6**). A N_2-purged soln of **5** (Aldrich Chemical Co.) (1·3 mM in 800 ml of spectranalyzed benzene) was irradiated for 8 hr with a Hanovia 450 W lamp with Pyrex filter. The residue remaining after solvent evaporation was dissolved in a minimum of $CHCl_3$ and purified by prep TLC on silica gel (benzene). A band at R_f 0·4–0·5 with fluoresced blue under longwave UV light was removed from the plate and extracted with $CHCl_3$. Evaporation yielded **6** (53%), m.p. 74–75° (lit.[11] m.p. 75–76°) whose IR, UV and mass spectra were those reported[12] for **6**.

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[3]We are indebted to Dr. K. A. Larson, Department of Microbiology, Colorado State University for bioassays.

[4]We are indebted to Dr. Harry B. Wood of the National Cancer Institute for these bioassays.

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