# Oxymetalation of Khellin. Solvomercuration, Osmylation, and Palladium-Catalyzed Oxidation of the Furan Ring in Khellin. The Synthesis of Highly Oxygenated Chromones and 2-Substituted Furochromones

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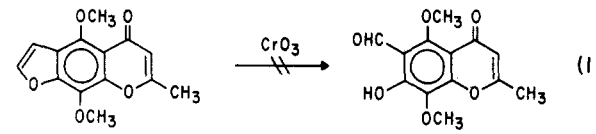
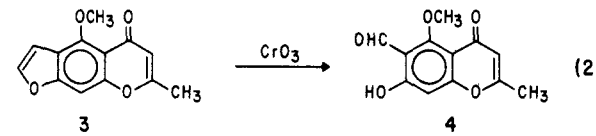
Oxidation of khellin with thallium(III) nitrate (TTN) in methanol results in the addition of two molecules of methanol across the 2,3-double bond in the furan ring. Oxidation of khellin with mercuric(II) nitrate ($Hg(NO_3)_2$) in aqueous THF followed by treatment with sodium metaperiodate ($NaIO_4$) afforded hydroxy aldehyde **2** in 24% yield. Catalytic osmylation of khellin, using $NaIO_4$ to reoxidize the osmium, in THF at 50 °C afforded hydroxy aldehyde **2** in 73% yield. Hydroxy aldehyde **2** underwent a smooth Dakin oxidation ($NaOH/H_2O_2$) to yield diol **13**. Alkylation of **13** with diiodomethane ($K_2CO_3$/DMF) afforded the methylenedioxy analogue **14** in 65% yield. Alkylation of **2** with chloroacetone in the presence of $K_2CO_3$/18-crown-6 in THF afforded the 2-acetylfurochromone **19** in 53% yield. The corresponding 2-carbomethoxy and benzoyl analogues, **17** and **18**, respectively, were also prepared but required a stepwise process. Oxidation of khellin with $PdCl_2$ under 30 psi of $O_2$ in the presence of CuCl in methanol afforded the hydroxy ester **27** in 73%. Hydrolysis of **27** resulted in clean conversion to acid **28**, which upon treatment with acetic anhydride afforded the lactone **7**.

The recent interest in the lipid-altering and antiatherosclerotic activity of khellin[1] has stimulated our interest in modifying the furochromone nucleus. During the past 40 years a wide variety of pyrone ring and C-4/C-9 alkoxyl modifications on khellin have appeared.[2] However, furan ring modifications of khellin, except for saturation of the ring, have gone unreported.[3] Most of the synthetic efforts directed toward the total synthesis of furochromones bearing the C-4 and/or C-9 methoxyl groups have likewise not seriously addressed the question of furan ring substitution (or modification).[4]

An approach to furan ring modifications that should nicely complement any total synthesis effort and perhaps offer a more desirable alternative to analogue synthesis due to the commercial availability of khellin is the direct functionalization or degradation/reconstruction of the furochromone nucleus, resulting in either a substituted furan ring or an entirely new heterocyclic ring. However, several problems immediately come to mind with this strategy. For example, treatment of khellin with electrophilic reagents, or attempts to regiospecifically generate an organolithium species at C-2 (furan ring) which could be trapped with electrophiles, is obviously problematic without first protecting the pyrone ring. The nucleophilic nature of the C-5 carbonyl oxygen in the pyrone ring suggests the need for perhaps more than 1 equiv of an electrophilic reagent and depending on the reagent in question one must be concerned with the stability of the C-4 methoxyl. For example, with $AlCl_3$ or $MgI_2$ the C-4 methoxyl is readily removed to yield the corresponding phenol.[5] Attempts to regiospecifically lithiate the C-2 position of the furan ring in khellin with the subsequent addition of an electrophile is likewise, as mentioned above, problematic because of the acidity of the C-7 methyl group in the pyrone ring. Thus one must deal with a dianion and undesired reaction on the pyrone unit.




1 Khellin 2




3 Visnagin 4

Degradation of the furan ring of furochromones is well documented in the literature.[6] For example, oxidation of visnagin (**3**) with chromic acid yields the hydroxy aldehyde **4** in good yield. However, treatment of khellin with chromic acid under identical conditions (and modifications thereof) used to oxidize **3** fail to yield hydroxyaldehyde **2**. There is little question that the failure to effect the conversion of **1** to **2** has suppressed the interest in furan

(1) For lipid-altering activity of furochromones in animal models, see: Gammill, R. B.; Day, C. E.; Schurr, P. E. *J. Med. Chem.* **1983**, *26*, 1672. Stevens, T. J.; Schurr, P. E.; Gammill, R. B.; Day, C. E. *Atherosclerosis* **1985**, *56*, 313. For lipid-altering activity in man, see: Harvengt, C.; Desager, J. P. *Int. J. Clin. Pharm. Res.* **1983**, *5*, 363.

(2) (a) For pyrone ring modification, see: Gammill, R. B.; Nash, S. A.; Mizsak, S. A.; *Tetrahedron Lett.* **1983**, 3435. Gammill, R. B. *J. Org. Chem.* **1984**, *49*, 5035. Watanabe, T.; Katayama, S.; Yamauchi, M. *J. Chem. Soc., Perkin Trans. 1* **1978**, 726. Abu-Shady, H.; Eid, A. I.; Ragab, F. A. *J. Pharm. Belg.* **1978**, *33*, 397. Dorofeenko, G.; Tkachenko V. V.; Mezheritskii, V. V. *Khim. Geterotsikl. Soedin.* **1973**, 1020. Eiden, F.; Rehu, U. *Chem. Ber.* **1974**, *107*, 1057. Rehee, U. *Arch. Pharm. (Weinheim, Ger.)* **1974**, *307*, 866. (b) For alkoxy modifications, see: Mustafa, A.; Sidky, M. M.; Mahran, M. R. *Ann. Chem.* **1965**, *684*, 187; **1967**, *704*, 182. Dann, O.; Volz, G. *Ann. Chem.* **1965**, *685*, 167. Musante, C.; Falutta, S. *Farmaco, Ed. Sci.* **1961**, *16*, 343. Martin, M.; Cantain, M.; Sado, M.; Zukerkavell, F.; Fourneau, J. P.; Linee, P.; Lacroix, P.; Quiniou, P.; van der Driessche, J. *Eur. J. Med. Chem. Chim. Ther.* **1974**, *9*, 563. Mustafa, A.; Starkovsky, N. A.; Zaki, E. *J. Org. Chem.* **1960**, *25*, 794. Kossakowski, J. *Acta. Pol. Pharm.* **1982**, *39*, 199.

(3) For a preliminary report on this work, see: Gammill, R. B.; Nash, S. A. *Tetrahedron Lett.* **1984**, *25*, 2953.

(4) For references to earlier syntheses see: Mustafa, A. "Furopyrans and Furopyrones" *The Chemistry of Heterocyclic Compounds*; Weissburger, A., Ed.; Wiley: New York; 1967; Vol. 23, p 103. For an example of more recent methodology that makes the synthesis of furan ring analogues more attractive, see: Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863.

(5) For demethylation with $AlCl_3$, see: Horton, W. J.; Paul, E. G. *J. Org. Chem.* **1959**, *24*, 2000. With $MgI_2$, see: Schönberg, A.; Sina, A. *J. Am. Chem. Soc.*, **1953**, *75*, 3265. With aniline hydrochloride, see: Schönberg, A.; Sina, A. *J. Am. Chem. Soc.* **1950**, *72*, 3396. With $HI/Ac_2O$, see: Clarke, J. R.; Robertson, A. *J. Chem. Soc.* **1949**, 302. Also see: Mukerjee, S. K.; Seshadri, T. R. *J. Sci. Ind. Res. Sect. B* **1954**, *13*, 400. With aromatic thiols, see: Schönberg, A.; Aziz, G. *J. Am. Chem. Soc.* **1953**, *75*, 3265.

(6) (a) Schönberg, A.; Badran, N.; Starkowsky, N. A. *J. Am. Chem. Soc.* **1955**, *75*, 4992; (b) **1955**, *77*, 1019.

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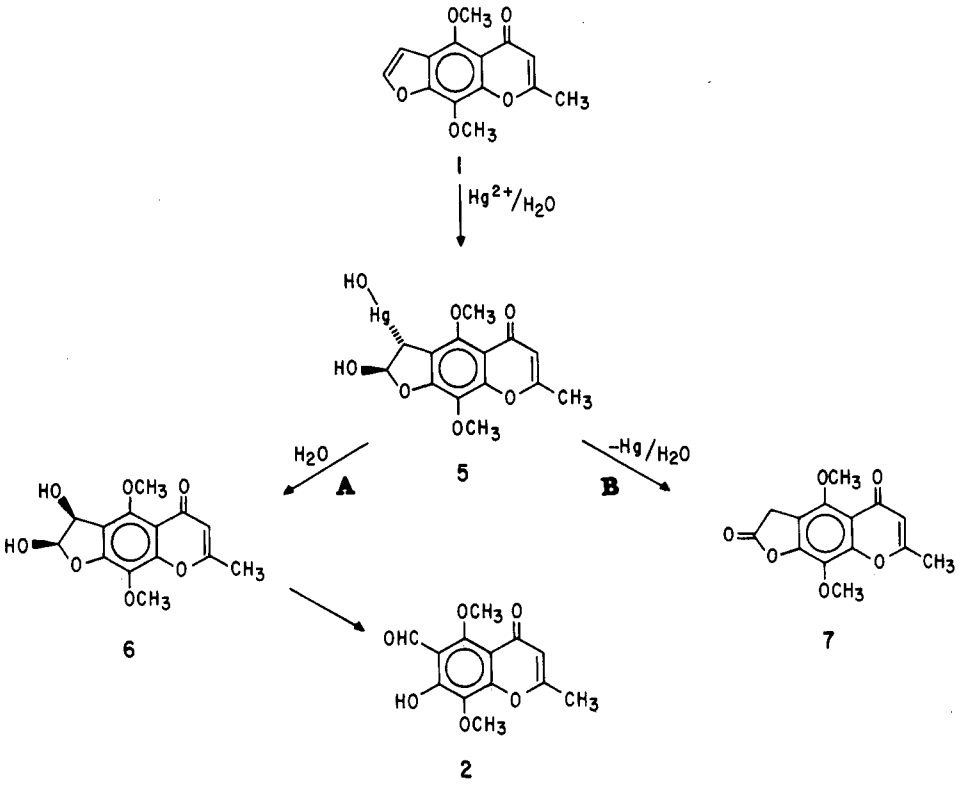
**Scheme I**



ring modification in the khellin series. The failure of the above oxidation is perhaps not surprising when one considers that chromic acid is known to effect oxidative demethylation of certain *p*-methoxy aromatics to yield quinones.[7]

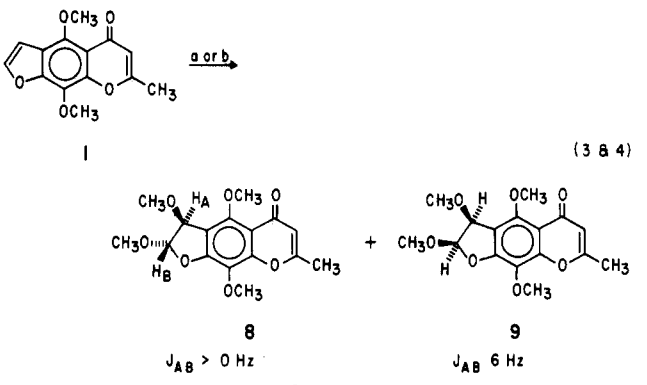
In general, little attention has been directed toward the cleavage of the furan ring in benzofurans. Maissnat has described an iron(III)-catalyzed oxidation of benzofuran using hydrogen peroxide[8] to give in low yield a mixture of salicylaldehyde and *o*-hydroxyphenylacetic acid. Ozonolysis[9] of benzofuran, as described by Wacek, yielded a mixture of salicylaldehyde, salicylic acid, and catechol. Neither Maissnat's iron(III)-catalyzed oxidation nor Wacek's ozonolysis procedure were particularly appealing to us because of the problem of over oxidation.

Several years ago McKillop and Taylor reported that treatment of benzofuran with thallium(III) nitrate (TTN) in methanol resulted in the clean formation of 2,3-dimethoxy-2,3-dihydrobenzofuran in modest yield.[10] This report stimulated us to consider utilizing oxymetalation chemistry as an entry to furan ring modifications in khellin.

## Data and Results

Mechanistically, two reaction pathways are possible for the oxymetallation of khellin. For example, as illustrated in Scheme I, solvomercuration in aqueous media would be expected to initially give the organomercurial **5**. Ionization or oxidation of **5** could then give the diol **6**, which upon oxidative cleavage would give the desired product **2**. On the other hand, if **5** lost the elements of Hg and $H_2O$, for example, through a hydride shift, the lactone **7** would result.

Treatment of a methanolic solution of khellin with thallium(III) nitrate (TTN) at room temperature as described by McKillop and Taylor afforded the *trans*-2,3-dimethoxydihydrofurochromone **8** in low yield. The problems associated with large-scale disposal of thallium waste, low yield, and the formation of emulsions upon workup of this reaction prompted us to consider other metals. We found a much cleaner and higher yielding

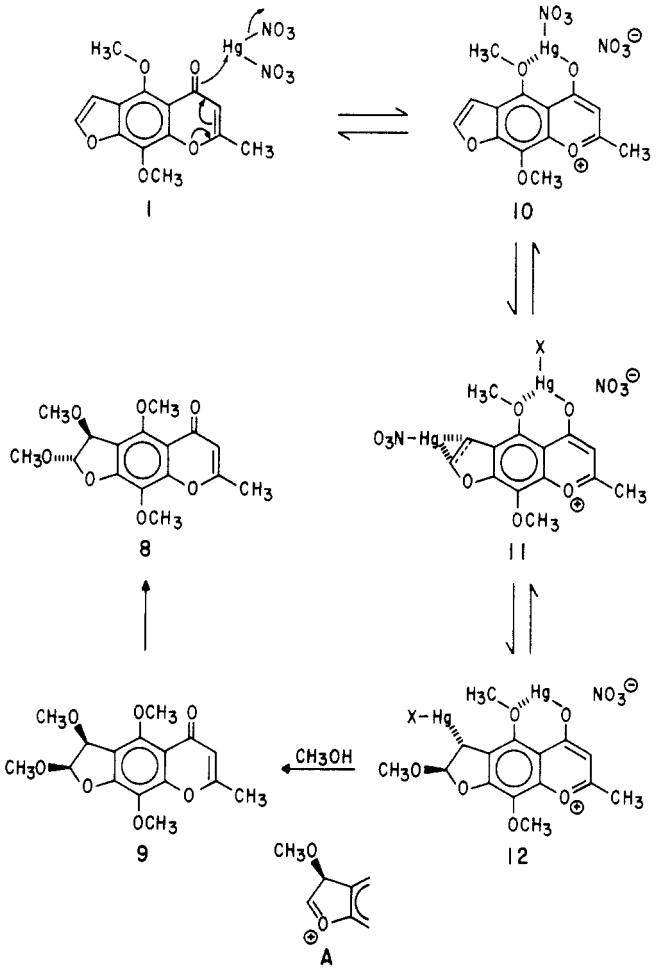


reaction by utilizing $Hg(NO_3)_2$ rather than TTN. In this latter case, when the reaction was stopped after 2 h, a 1/1 mixture of the trans/cis isomers **8** and **9** (66%) was obtained. Extending the reaction time to 24 h afforded only the trans isomer **8** (57%). The trans isomer does not show coupling between $H_a$ and $H_b$ which is consistent with molecular models that show a dihedral angle of ~90 degrees between these two hydrogens. The cis isomer shows a coupling of 6 Hz.

For complete conversion of khellin to **8**, 2 equiv of mercuric nitrate were required. This was not surprising since mercuric nitrate is an excellent electrophilic reagent

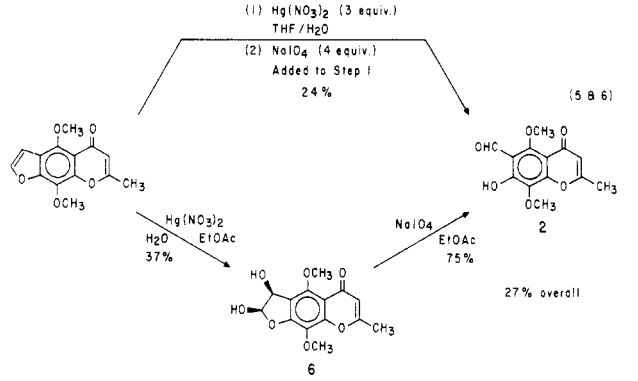
(7) Musgrave, O. C. *Chem. Rev.* **1969**, *69*, 499.
(8) Maissnat, J. M.; Bodronx, J. M.; Bovchoale, C.; Blanchard, M. *J. Mol. Catal.* **1980**, *9*, 237.
(9) Wacek, A. V.; Zeisler, F. *Monatsh. Chem.* **1952**, *83*, 5. Wacek, A.; Eppinger, H. O.; Bezard; A. V. *Chem. Ber.* **1940**, *73*, 521.
(10) McKillop, A.; Hunt, J. D.; Kiegle, F.; Bigham E.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3635.
(11) For two excellent reviews on organomercurial compounds, see: Arzoumanian, H.; Metzzer, J. *Synthesis* **1971**, 527. Larock, R. C. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 27.

**Scheme II**



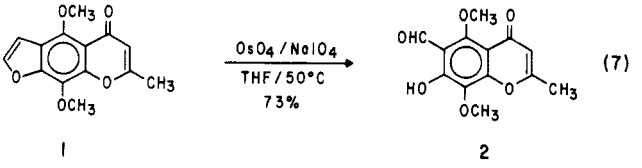
and likely forms a reversible complex with the C-5 carbonyl oxygen as illustrated in Scheme II. It is also possible, as pointed out by Shearer and Wright,[12] that the second mole of mercuric nitrate may be required for the subsequent oxidation of the organomercurial **12**, which ultimately leads to **9**. We feel, however, that in the case of khellin, if such an oxidation were taking place, we would see some conversion of khellin to **8** or **9** with a single equivalent of reagent; this was not the case. On the basis of these results we favor the solvomercuration–demercuration process illustrated in Scheme II.[13] Addition of methanol to intermediate **11** gives rise to the organomercurial **12**, which through solvolysis[13] yields the cis adduct **9**. Conversion of **9** to the thermodynamically more stable trans isomer **8** can be viewed as proceeding through the oxonium intermediate A.

We next carried out the oxymercuration in aqueous media in hopes of obtaining the corresponding diol, which upon oxidative cleavage would yield the desired hydroxy aldehyde **2**. Treatment of khellin with 2 equiv of mercuric nitrate in either aqueous THF or EtOAc lead to incomplete conversion to the desired *cis*-diol **6**. Extending the reaction time or heating the reaction had little effect on further conversion of **1** to **6**. Increasing the amount of $Hg(NO_3)_2$ to 3 equivalents did, however, lead to complete conversion of khellin to diol **6**. Treatment of **6** with 1.1 equiv of $NaIO_4$ in ethyl acetate then yielded the desired hydroxy aldehyde



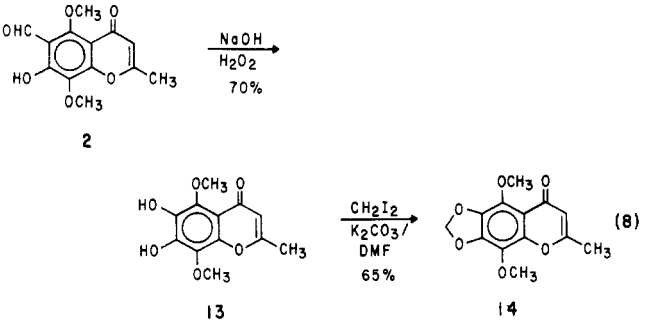
**2** in moderate yield. Chromone **2** could also be obtained without isolation of **6** by adding $NaIO_4$ directly to the diol reaction. While the yield of this latter process was comparable to the two step sequence, the drawback was the requirement of 4 equiv of $NaIO_4$ to effect complete conversion of the diol to **2**.

Aldehyde **2** could be obtained directly from khellin without isolation of the intermediate diol in much higher yield through osmylation. Catalytic osmylation of khellin in dioxane at room temperature using *N*-methylmorpholine *N*-oxide,[14] to regenerate the osmium tetraoxide, gave a 38% yield of the aldehyde along with a small amount of the diol (10%). Increasing the reaction tem-



perature to 50 °C resulted in a slightly lower yield (32%) of **2**. Encouraging results were obtained when $NaIO_4$[15] was used as the oxidant in the reaction. Treatment of khellin with catalytic $OsO_4$ in dioxane in the presence of 2.2 equiv of $NaIO_4$ afforded **2** in 61% yield with only trace amounts of the diol being detected by thin-layer chromatography. Further improvements were realized by changing the solvent to THF and heating the reaction to 50 °C. Under these latter reaction conditions the aldehyde was isolated in 73% yield on a 10-mmol scale and 44% yield on a 0.4-mol scale.

With hydroxy aldehyde **2** in hand, we explored the possibility of converting **2** to the 1,3-dioxolo[4,5-*g*]benzopyranone system **14**. This necessitated converting the C-6 aldehyde to a phenol, i.e., a Baeyer–Villiger oxidation. Oxidation of **2** using *m*-CPBA in refluxing methylene chloride appeared to afford **13**. However, a number of



(12) Shearer, D. A.; Wright, G. F. *Can. J. Chem.* **1955**, *33*, 1002.

(13) This process is consistent with earlier reports. Balbiano, L.; Paolini, V. *Chem. Ber.* **1902**, *35*, 2994; **1903**, *36*, 3575; **1904**, *37*, 225. Summerbell, R. K.; Kolb, G. H.; Graham, E. S.; Albred, A. L. *J. Org. Chem.* **1962**, *27*, 4461.

(14) VanRheenan, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

(15) Chinn, L. *Selection of Oxidants in Synthesis*; Marcel Dekker: New York, 1971; pp 160–162. Papps, R.; Allen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478. Also see: Rylander, P. N. *Organic Synthesis with Noble Metal Catalyst*; Academic: New York, 1973; 121.

**Scheme III**

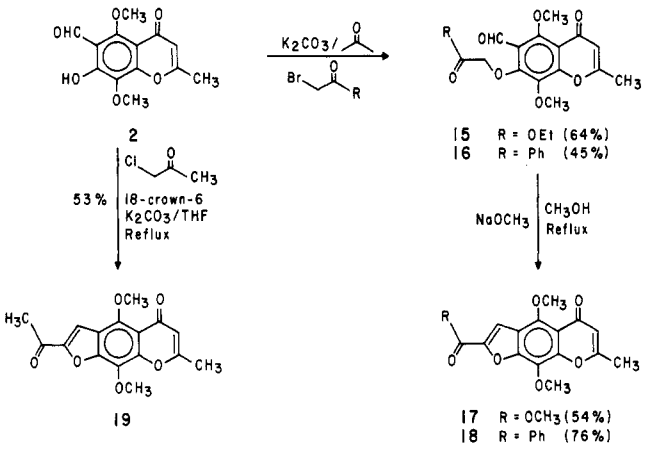


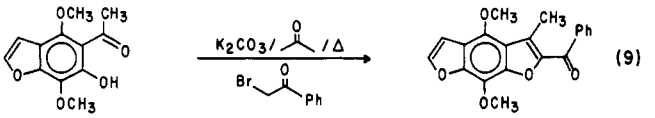

**Table I. Palladium-Catalyzed Oxidation of Khellin**

| $PdCl_2$, equiv | reacn conditions | solvent | catalyst (equiv) | results |
|---|---|---|---|---|
| 1.1 | 75–85 °C | $CH_3OH/CH_3CN$ | | no reacn |
| 2.2 | 80–85 °C | $DMF/H_2O$ | | no reacn |
| 2.1 | 70–80 °C, 2 h | $CH_3OH$ | | 7% |
| 1.1 | 25 psi/$O_2$, 45 °C | $CH_3OH$ | CuCl (1.1) | 40% |
| 10 (mol) % | 20 psi/$O_2$, room temp | $CH_3OH$ | CuCl (1.1) | 26% |
| 10 (mol) % | 30 psi/$O_2$, 65 °C/24 h | $CH_3OH$ | CuCl (1.1) | 73% |

byproducts were also produced in this reaction in almost equal amounts and forced us to seek an alternate method for this rearrangement. Despite the sensitivity of the pyrone ring to base, particularly to hydroxide, we found that diol **13** could readily be prepared via a Dakin oxidation.[16] Addition of hydrogen peroxide to an aqueous NaOH (1 equiv) solution of aldehyde at ambident temperature afforded **13** in 70% yield after column chromatography. This reaction is even more remarkable when one considers that these same reaction conditions at a slightly higher reaction temperature convert khellin to a hydroxy acid.[6a] The methylenedioxy unit was then introduced by using the method of Simpson, Daub, and Hayes.[17] Treatment of **13** with diiodomethane in DMF containing potassium carbonate afforded **14** in 65% yield.

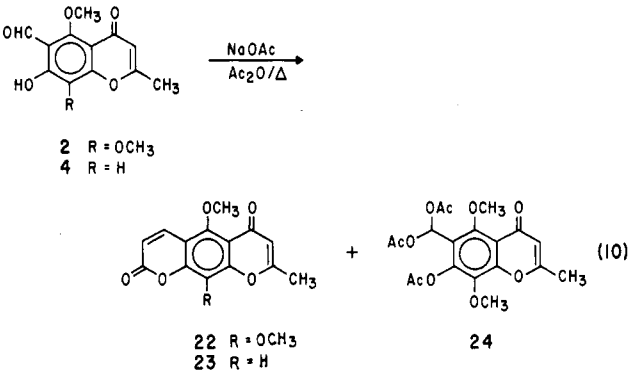
Chromone **2** also provided access to C-2 substituted furochromones in a straightforward fashion without interference from the pyrone ring. Alkylation of **2** with ethyl bromoacetate and $\alpha$-bromoacetophenone yielded ethers **15** and **16**, respectively (Scheme III). Because of the base-sensitive nature of the pyrone ring, the use of potassium carbonate in refluxing acetone was required to prepare these ethers. On the basis of the observations of Davies,[18] concerning the cyclization of similar substrates to furans, we attempted cyclization of **15** by treating the aldehyde ester with magnesium methoxide in methanol. Unfortunately, a number of new products were formed; however, none were the desired furochromone. Sodium hydride, in THF, also failed to yield **17**. Finally, we found that treatment of both **15** and **16** with 1 equiv of sodium methoxide in methanol cleanly afforded **17** and **18** in 54% and 76% yield, respectively. It is worth noting that these latter reaction conditions were least effective in furan formation for Davies.

Attempts to extend the above chemistry to chloroacetone failed. We did find, however, that alkylation of **2** with chloroacetone in refluxing THF containing 18-crown-6/$K_2CO_3$ afforded the 2-acetylfurochromone **19** directly and in good yield. We were, in fact, somewhat surprised when alkylation of **2** with $\alpha$-bromoacetophenone, using $K_2CO_3$ in refluxing acetone, did not afford **18** directly since we had found earlier that under such conditions, khellinone (**20**) was cleanly converted to the benzodifuran **21** in good yield.




(9)

The availability of the hydroxy aldehyde **2** also provided the opportunity to prepare the coumarinochromone **22**. In a similar case, Mustafa, Starkovsky, and Zaki[19] reported that treatment of **4** with an excess of sodium acetate in refluxing acetic anhydride for 5 h afforded a 36% yield of the benzodipyran **23**. We found that treatment of **2** with




(10)

excess sodium acetate in refluxing acetic anhydride for 5 h afforded a 16.5% yield of **22** and a 65% yield of **24**. Basic hydrolysis of **24** gave the hydroxy aldehyde **2**. A similar triacetate has been suggested as an intermediate by Kumanotani in the preparation of coumarin from salicylaldehyde using sodium acetate in acetic anhydride.[20]

## Palladium-Catalyzed Oxidation of Khellin

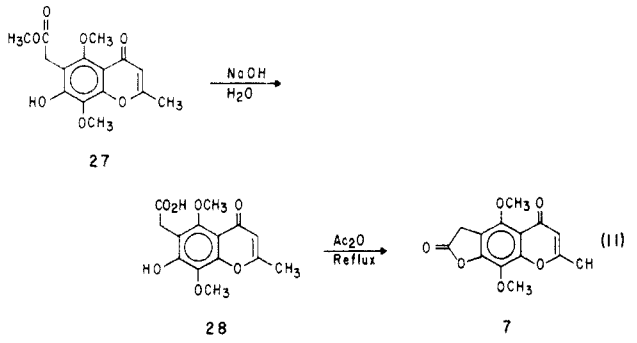
As noted in Scheme I there are two possible pathways oxymetalation can follow. In the case of khellin, oxymetalation appears to follow path "A". Thus the organomercural **5** undergoes solvolysis to yield the dihydroxy product.[12] In pursuit of the lactone **7** we investigated the palladium-mediated oxidation of khellin.

Attempts to oxidize khellin in the presence of $PdCl_2$ (stoichiometric) in mixed solvents ($CH_3OH/CH_3CN$ or $DMF/H_2O$) failed (see entries 1 and 2 in Table I).[21,22] However, in the presence of 2.1 equiv of $PdCl_2$ at 70–80

(16) The procedure of Hocking was used. Hocking, H. B. *Can. J. Chem.* **1973**, *51*, 2384.
(17) Simpson, J. E.; Daub, G. H.; Hayes, F. N. *J. Org. Chem.* **1973**, *38*, 1771.
(18) Davis, J. S. H.; McCrea, P. A.; Norris, W. L.; Ramage, G. R. *J. Chem. Soc.* **1950**, 3260.
(19) Mustafa, A.; Starkovsky, N. A.; Zaki, E. *J. Org. Chem.* **1961**, *26*, 523.
(20) Kumanotani, J.; Kuwata, T. *J. Soc. Org. Synth. Chem., Tokyo* **1953**, *11*, 388.
(21) Clement, W. H.; Selivitz, C. M. *J. Org. Chem.* **1964**, *29*, 241.
(22) Parshall, G. W. *Homogeneous Catalysis*; Wiley-Interscience: New York, 1980. Rylander, P. N. *Organic Synthesis with Noble Metal Catalysts*; Academic: New York, 1973. Bird, C. W. *Transition Metal Intermediates in Organic Synthesis*; Logos: London, 1976, p 88.

°C in methanol, a 7% yield of the hydroxy ester **27** was obtained. Further improvements on the reaction included making the reaction catalytic in palladium ($CuCl/O_2$) and extending the reaction time to 24 h. Under these conditions, the hydroxy ester **27** was obtained in 73% yield. A suggested mechanism for the conversion of **1** to ester **27** is provided in Scheme IV.

The desired lactone **7** was prepared by careful hydrolysis of **27** with 2 equiv of sodium hydroxide followed by refluxing in acetic anhydride. This provided lactone **7** in 50% yield.




## Experimental Section

**General Methods.** Mass spectra, infrared spectra, ultraviolet spectra, and combustion analysis were obtained by the Physical and Analytical Chemistry Department of The Upjohn Company. $^1H$ NMR spectra were obtained at 60 MHz in deuterochloroform solutions containing $Me_4Si$ as an internal standard. $^{13}C$ NMR were recorded on a Varian CFT-20 instrument. Infrared spectra were obtained on a Perkin-Elmer 197 spectrophotometer. Combustion analyses were also obtained from Micro-Analysis, Inc., Wilmington, DE. Thin-layer chromatography (TLC) was conducted with Merck glass plates precoated with silica gel 60 F-254. The TLC plates were visualized by UV light or iodine. Column chromatography was conducted at medium-pressure utilizing silica gel 60 (E. Merck, 230–400 mesh). All solvents for chromatography were reagent grade distilled in glass (Burdick and Jackson).

***trans*-2,3,4,9-Tetramethoxy-2,3-dihydro-7-methyl-5*H*-furo[3,2-*g*]benzopyran-5-one (8).** Khellin (26.0 g, 0.1 mol) was dissolved in methanol (600 mL), and to that solution was added $Hg(NO_3)_2{\cdot}H_2O$ (72.0 g, 0.21 mol) in a single portion. The resulting green solution was stirred at ambient temperature for 24 h. The methanol was then removed in vacuo and the resulting oil diluted with EtOAc and then water. The organic layer was dried and solvent removed in vacuo to afford a dark brown oil. Chromatography of that oil (30.0 g) over 900 g of Florisil (EtOAc) yielded 18.33 g (57%) of **8** as a white solid: mp 137–139 °C; IR (mull) 2952, 2925, 2908, 2870, 1665, 1622, 1602, 1484, 1462, 1422, 1386, 1351, 1206, 1115, 1083, 1061, 978, 891 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.05 (s, 1 H, vinyl), 5.55 (s, 1 H, C-2 H), 4.85 (s, 1 H, C-3 H), 4.05 (s, 3 H, Ar methoxy), 3.98 (s, 3 H, Ar methoxy), 3.62 (s, 3 H, $OCH_3$), 3.45 (s, 3 H, $OCH_3$), 2.35 (s, 3 H, $CH_3$); mass spectrum; *m/e* (relative intensity) 322 (26), 291 (9), 290 (12), 275 (8), 262 (18), 261 (19), 260 (21), 259 (100), 247 (13), 231 (16); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 231 (25400), 249 (sh, 23550), 253 (23850), 288 (6850). Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.59. Found: C, 59.54; H, 5.87.

***cis*-2,3-Dihydroxy-2,3-dihydro-4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*]benzopyran-5-one (6).** Khellin (26.0 g, 0.1 mol) was added to a mixture of EtOAc (500 mL) and $H_2O$ (200 mL). To that solution was added $Hg(NO_3)_2{\cdot}H_2O$ (102.9 g, 0.3 mol) in a single portion and the resulting solution stirred at room temperature for 1.5 h. During the reaction, a white solid separated from the solution. The solid was collected on a filter and air-dried to give 16.24 g of diol **6** of suitable purity for subsequent reactions: IR (mull) 2954, 2925, 2867, 2854, 1653, 1592, 1481, 1391, 1375, 1360, 1334, 1085, 1070, 1049, 895 $cm^{-1}$; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 6.00 (s, 1 H, olefinic), 5.72 (br, 1 H, C-2 H), 4.96 (br, 1 H, C-3 H), 3.86 (s, 6 H, methoxy), 3.31 (s, 2 H, OH's), 2.32 (s, 3 H, $CH_3$); mass spectrum, *m/e* (relative intensity) 294 (9), 276 (22), 265 (100), 263 (42), 261 (21), 247 (20), 233 (19), 220 (21), 207 (25), 205 (23); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 206 (15200), 231 (16900), 250 (sh, 17750), 254 (18250), 292 (5450); $^{13}C$ NMR ($Me_2SO$-$d_6$) 175.61, 163.39, 154.56, 152.26, 151.94, 127.68, 118.46, 111.62, 110.61, 109.53, 74.42, 61.28, 60.59, 19.20 ppm.

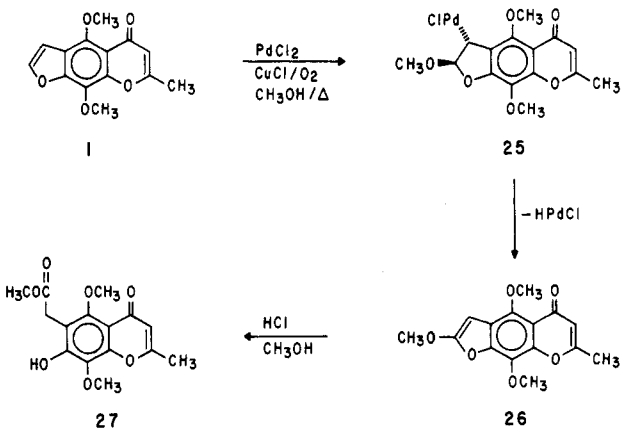
**6-Formyl-5,8-dimethoxy-7-hydroxy-2-methylchromone (2) via *N*-Methylmorpholine Oxide and Osmium Tetraoxide Oxidation.** *N*-Methylmorpholine oxide (3.32 g, 22 mmol, in water, 10 mL) was added to a dioxane solution (65 mL) of khellin (2.6 g, 10 mmol). Osmium tetraoxide (0.18 g, 0.7 mmol) was added to the above solution and stirred at ambient temperature for 46.5 h and then poured into a separatory funnel containing 2 N HCl and methylene chloride. Extraction with methylene chloride, washing the combined organic layers with brine, and filtering through sodium sulfate afforded 2.40 g of the crude product after evaporation of the solvent. The crude product was added to 105 g of silica gel packed in 1% methanol–methylene chloride. Taking 35-mL fractions, elution with 200 mL of 1%, 500 mL of 1.5%, 500 mL of 2%, 500 mL of 2.5%, 500 mL of 3%, and 1000 mL of 6% methanol–methylene chloride afforded 1.0 g (fractions 17–26, 38% yield) of aldehyde **2**, 0.2 g (fractions 51–82) of an unknown, and 0.3 g (fractions 83–120) of diol **6**. An analytical sample of aldehyde **2** was prepared by recrystallization from ethyl acetate–Skelly B to give pale yellow crystals: mp 199–202 °C; silica gel TLC: $R_f$ 0.4 (EtOAc); 0.6 (5% MeOH–$CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 11.01 (s, 1 H), 10.34 (s, 1 H), 6.03 (s, 1 H, olefinic), 4.02 (s, 3 H, $OCH_3$), 3.96 (s, 3 H, $OCH_3$), 2.38 (s, 3 H, $CH_3$); IR (mull) 2954, 2925, 2855, 1667, 1642, 1575, 1472, 1425, 1394, 1347, 1319, 1283, 1230, 1136, 1046, 980, 923, 864, 816, 782 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ ($\epsilon$) 217 (12500), 219 (sh, 12400), 261 (29900), 272 (29450), 300 (sh, 2750), 375 (sh, 1200); mass spectrum (high resolution), calcd for $C_{13}H_{12}O_6$ 264.0634, found 264.0646; mass spectrum *m/e* (relative intensity) 246 (16), 231 (30), 221 (87), 203 (18), 192 (43), 163 (36), 43 (100). Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 58.81; H, 4.62.

**6-Formyl-5,8-dimethoxy-7-hydroxy-2-methylchromone (2) from Diol 6.** The crude diol **6** (500 mg, 1.70 mmol) was added to an aqueous THF solution (35%) of $NaIO_4$ (400 mg, 1.87 mmol). After being stirred for 30 min, the reaction was diluted with EtOAc and the organic layer separated. The aqueous was back-extracted with EtOAc. The total organic was then dried ($MgSO_4$) and solvent removed in vacuo to give 340 mg of **2** (76%, mp 198–200 °C).

**6-Formyl-5,8-dimethoxy-7-hydroxy-2-methylchromone (2) via Sodium Periodate and Osmium Tetraoxide Oxidation.** A solution of khellin (2.6 g, 10 mmol) in dioxane (65 mL) and water (910 mL) was stirred at 50 °C in a round-bottom flask equipped with a magnetic stirrer. First osmium tetraoxide (0.25 g, 1 mmol) and then sodium periodate (4.7 g, 22 mmol) were added. After being stirred at 50 °C for 22 h, the reaction mixture was transferred to a separatory funnel containing 2 N HCl. Extraction with methylene chloride (3×), washing with brine, and filtering through sodium sulfate afforded 2.74 g of crude product after evaporation of the solvent. The crude product was added to 100 g of silica gel packed and eluted with 1% methanol–methylene chloride. Combining fractions 12–28 (35 mL/fraction) afforded 1.94 g (73% yield) of **2**; mp 199–201 °C.

**6-Formyl-5,8-dimethoxy-7-hydroxy-2-methylchromone (2). Large-Scale Reaction.** A solution of khellin (104 g, 0.4 mol) in dioxane (2.6 L) and water (0.4 L) was stirred in a three-neck round-bottom flask equipped with an overhead stirrer, a thermometer, and a heating mantle. First osmium tetraoxide (8 g, 0.032 mol) was added, and then $NaIO_4$ (188 g, 0.88 mol) was added over 30 min. The heating mantle temperature was slowly turned up so that the reaction mixture reached 53 °C after 2 h, where the reaction was maintained for 20 h. The reaction mixture was transferred to a portable separatory funnel containing 2 N HCl (2.6 L). Extraction with methylene chloride (2×, 4.6 L total), washing with 1 N sodium bisulfite (2 L) and brine (2 L), and filtering through sodium sulfate afforded 73.2 g of crude product after evaporation of solvent. The crude product was added in (2) halves to 300 g of silica packed with 1% methanol–methylene chloride on a flash column. Elution with 1% methanol–methylene chloride afforded 50.2 g of the aldehyde. Recrystallization from ethyl acetate gave 46.7 g (44% yield) of yellow crystalline **2**, mp 198–200 °C.

**Scheme IV**




**6,7-Dihydroxy-5,8-dimethoxy-2-methylchromone (13).** Aldehyde **2** (2.69 g, 10.2 mmol) was added to a solution of sodium hydroxide (0.41 g, 10.2 mmol) in water (967 mL). To the resulting dark solution was added hydrogen peroxide (30%, 5.4 mL). After being stirred at ambient temperature for 2.25 h, the reaction solution was poured into a separatory funnel containing brine, acidified with hydrochloric acid, and diluted with ethyl acetate. Extraction with ethyl acetate (6 × 150 mL) and filtration of the combined organic layers through sodium sulfate afforded 2.38 g of the crude product after evaporation of the solvent. The crude product was added to 170 g of silica gel packed in 3% methanol–methylene chloride. Elution with 500 mL of 3%, 500 mL of 5%, 500 mL of 7%, and 500 mL of 10% methanol–methylene chloride afforded 1.80 g of **13** (Fractions 21–32, 40-mL fractions, 70% yield). An analytical sample was prepared by crystallization from ethyl acetate–Skelly B: mp 189.0–190.0 °C; silica gel TLC, $R_f$ 0.4 (5% MeOH–$CH_2Cl_2$); IR (mull) 3383 (OH), 1649, 1600 (C=O), 1578 (C=C), 1465, 1431, 1276, 1179, (C–O/other) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.04 (s, 1 H, olefinic), 4.00 (s, 3 H, $OCH_3$), 3.95 (s, 3 H, $OCH_3$), 2.36 (s, 3 H, $CH_3$); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 212 (24200), 229 (sh, 19000), 252 (13000), 300 (7100), 323 (7350); mass spectrum (high resolution), calcd for $C_{12}H_{12}O_6$ 252.0634, found 252.0816; mass spectrum, *m/e* (relative intensity) 252 (parent, 82), 237 (91), 219 (45), 209 (100), 194 (41), 179 (31); melt solvate; 2.45% ethyl acetate. Anal. Calcd for $C_{12}H_{12}O_6$ and 2.45% EtOAc: C, 57.08; H, 4.89. Found: C, 57.03; H, 5.11.

**4,9-Dimethoxy-6-methyl-8*H*-1,3-dioxolo[4,5-*g*][1]-8-benzopyranone (14).** Diiodomethane (0.22 mL, 0.75 g, 2.75 mmol) in dimethylformamide (9 mL) was slowly added over 15 min to a solution of **13** (0.63 g, 2.5 mmol) and potassium carbonate (anhydrous, 0.75 g, 5 mmol) in dimethylformamide (12.5 mL) under nitrogen and stirring at 95 °C. After being stirred at 95 °C for an additional 1.25 h, the reaction solution was poured into a separatory funnel containing 50% brine and ether. Extraction with ether (5 × 150 mL), washing the combined organic layers with brine, and filtering through sodium sulfate afforded 0.75 g of crude product. Recrystallization from acetone–hexane at −20 °C afforded 0.43 g (65% yield) of **14** as a powder: mp 170.2–173.0 °C; silica gel TLC; $R_f$ 0.3 (EtOAc); IR (mull) 1655, 1618 (C=O), 1391, 1359, 1294, 1219 (C–O) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.05 (s, 2 H, $CH_2$), 6.02 (s, 1 H, olefinic), 4.02 (s, 3 H, $OCH_3$), 3.99 (s, 3 H, $OCH_3$), 2.33 (s, 3 H, $CH_3$); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 213 (23800), 239 (19600), 253 (14800), 286 (7200), 313 (sh, 5400); mass spectrum, *m/e* (relative intensity) 264 (parent, 100), 249 (52), 236 (72), 221 (61), 203 (19), 193 (23), 175 (38). Anal. Calcd for $C_{13}H_{12}O_6$: C, 59.09; H, 4.58. Found: C, 58.72; H, 4.67.

**6-Formyl-5,8-dimethoxy-7-[(ethoxycarbonyl)methoxy]-2-methylchromone (15).** To a solution of aldehyde **2** (10 g, 38 mmol), 18-crown-6 (1.0 g), and potassium carbonate (6 g, 40 mmol) in tetrahydrofuran (200 mL) was added ethyl bromoacetate (4.6 mL, 7 g, 42 mmol). After refluxing for 16.7 h, the reaction mixture was transferred to a separatory funnel containing 2 N HCl and ethyl acetate. Extraction with ethyl acetate (3 × 300 mL), washing with brine, and filtering through sodium sulfate afforded 16 g of crude product after evaporation of the solvent. The crude product was chromatographed (flash chromatography) over 300 g of silica gel to afford 8.56 g (64% yield) of **15**. An analytical sample was prepared by recrystallization from ether–hexane: mp 88.5–90.6 °C; silica gel TLC, $R_f$ 0.2 (EtOAc); IR (mull) 1760, 1692, 1657 (C=O), 1582, (C=C) 1583, 1470, 1387, 1352, 1141 (C–O/other) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 10.45 (s, 1 H, aldehyde), 6.08 (s, 1 H, olefinic), 4.86 (s, 2 H, $CH_2$), 4.26 (q, 2 H, $CH_2$, $J$ = 6 Hz), 3.96 (s, 3 H, $OCH_3$), 3.94 (s, 3 H, $OCH_3$), 2.38 (s, 3 H, $CH_3$), 1.29 (t, 3 H, $CH_3$, $J$ = 6 Hz); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 236 (22950), 254 (24600) 295 (sh, 5150); mass spectrum (high resolution), calcd for $C_{17}H_{18}O_8$ 350.1002, found 350.0989; mass spectrum, *m/e* (relative intensity) 350 (parent, 44), 277 (92), 263 (100), 249 (81), 233 (20), 219 (32), 205 (18). Anal. Calcd for $C_{17}H_{18}O_8$: C, 58.28; H, 5.18. Found: C, 58.01; H, 5.04.

**2-Carbomethoxy-4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*][1]benzopyran-5-one (17).** A solution of the ether **15** (1.0 g, 2.86 mmol), sodium methoxide (0.83 g, 25% MeOH solution, 3.8 mmol), and methanol (25 mL) was refluxed for 14 min. The reaction mixture was transferred to a separatory funnel containing 2 N HCl and ethyl acetate. Extraction with ethyl acetate (2×, 200 mL), washing with brine, and filtering through sodium sulfate afforded 1.21 g of crude product after evaporation of the solvent. The crude product was chromatographed (flash chromatography) over 85 g of silica gel (ethyl acetate) to give 0.49 g (54% yield) of **17**. An analytical sample was obtained by recrystallization from ethyl acetate–hexane: mp 202.1–203.1 °C; silica gel TLC, $R_f$ 0.2 (EtOAc); IR (mull) 1717, 1665 (C=O), 1618, (C=C) 1483, 1441, 1350, 1292, 1057, 758 (C–O/other) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.76 (s, 1 H, furan vinyl), 6.06 (s, 1 H, pyrone vinyl), 4.22 (s, 3 H, $OCH_3$), 4.10 (s, 3 H, $OCH_3$), 3.98 (s, 3 H, methyl ester), 2.39 (s, 3 H, $CH_3$); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 242 (24950), 271 (33800), 328 (27100); mass spectrum (high resolution), calcd for $C_{16}H_{14}O_7$ 318.0739, found 318.0727; mass spectrum, *m/e* (relative intensity) 318 (parent, 74), 303 (100), 289 (40), 274 (79), 235 (39), 93 (32), 77 (24), 59 (41), 53 (36). Anal. Calcd for $C_{16}H_{14}O_7$: C, 60.38; H, 4.43. Found: C, 59.90; H, 4.47.

**6-Formyl-5,8-dimethoxy-7-(benzoylmethoxy)-2-methylchromone (16).** Aldehyde **2** (5 g, 19 mmol), bromoacetophenone (3.76 g, 19 mmol), and anhydrous potassium carbonate (4.4 g, 32 mmol) were suspended in acetone (950 mL). After refluxing for 17.2 h, the reaction solution was transferred to a separatory funnel containing 2 N HCl and methylene chloride. Extraction with methylene chloride (3 × 300 mL), washing with brine, and filtering through sodium sulfate afforded 8.11 g of the product (oil) after evaporation of the solvent: silica gel TLC, $R_f$ 0.2 (80% EtOAc/Skelly-B); IR (mull) 1706, 1685, 1667 (C=O), 1578 (C=C), 1469, 1389, 1136, 1050, 965, 763, 692, 609 (C–O/Ar/other) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 10.49 (s, 1 H, aldehyde), 8.00–7.46 (m, 5 H, Ar), 6.08 (s, 1 H, olefinic), 5.58 (s, 2 H, $CH_2$), 3.98 (s, 3 H, $OCH_3$), 3.88 (s, 3 H, $OCH_3$), 2.36 (s, 3 H, $CH_3$); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 252 (36650), 290 (slsh, 7200), 305 (slsh, 5350); mass spectrum (high resolution), calcd for $C_{21}H_{18}O_7$ 382.1052, found 382.1038; mass spectrum, *m/e* (relative intensity) 382 (parent, 7), 349 (19), 277 (23), 263 (63), 259 (81), 247 (31), 219 (25), 105 (100), 91 (31), 77 (82). Anal. Calcd for $C_{21}H_{18}O_7$: C, 65.96; H, 4.74. Found: C, 65.93; H, 4.90.

**2-Benzoyl-4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*][1]-benzopyran-5-one (18).** A methanolic solution of ether **16** (2.4 g, 6.30 mmol) was added to sodium methoxide (1.40 g, 25% MeOH solution, 6.5 mmol), in methanol (48 mL) and refluxed for 14 min. The reaction mixture was transferred to a separatory funnel containing 2 N HCl and chloroform. Extraction with chloroform (2 × 200 mL) and filtration through sodium sulfate afforded 2.38 g of crude product after evaporation of the solvent. The crude product was added to 220 g of silica gel packed in 10% acetone–chloroform on a flash column. Elution with 10% acetone–chloroform gave 1.75 g (76% yield) of **18**. An analytical sample was prepared by recrystallization from ethyl acetate giving bright yellow crystals: mp 198.0–199.0 °C; silica gel TLC, $R_f$ 0.7 (10% acetone–chloroform); IR (mull) 1675, 1645 (C=O), 1611, 1594 (C=C), 1480, 1276, 1206, 1077 (C–O/other), 723 (Ar) $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.11–7.54 (m, 5 H, Ar), 7.73 (s, 1 H, furan vinyl), 6.08 (s, 1 H, pyrone vinyl), 4.26 (s, 3 H, $OCH_3$), 4.10 (s, 3 H, $OCH_3$), 2.14 (s, 3 H, $CH_3$); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 244 (23900), 264 (sh, 19600), 292 (28400), 350 (11450); mass spectrum (high resolution), calcd for $C_{21}H_{16}O_6$ 364.0947, found 364.0935; mass spectrum, *m/e* (relative intensity) 364 (parent, 90), 349 (74), 335 (35), 320 (30), 105 (100), 77 (86). Anal. Calcd for $C_{21}H_{16}O_6$: C,

69.23; H, 4.43. Found: C, 69.05; H, 4.64.

**2-Acetyl-4,9-dimethoxy-7-methyl-5*H*-furo[3,2-*g*][1]-benzopyran-5-one (19).** To a solution of aldehyde **2** (4.0 g, 15.1 mmol), 18-crown-6 (0.4 g), and potassium carbonate (2.4 g, 17.3 mmol) in tetrahydrofuran (80 mL) was added chloroacetone (91.5 mL, 18.7 mmol). After refluxing for 21.6 h, the reaction mixture was transferred to a separatory funnel containing 2 N HCl and methylene chloride. Extraction with methylene chloride (3 × 500 mL) and filtration through sodium sulfate afforded 5.43 g of crude product after evaporation of the solvent. The crude product was chromatographed over 250 g of silica gel packed in 10% acetone–chloroform. Elution with 10% acetone–chloroform (50 mL fractions) afforded 2.43 g (fractions 21–35, 53% yield) of **19**. An analytical sample was prepared by recrystallization from ethyl acetate–hexane: mp 184–185 °C; silica gel TLC, $R_f$ 0.4 (20% acetone–$CHCl_2$); IR (mull) 1675, 1623 (C=O), 1483, 1366, 1288, 1110, 1059 (C–O/other) $cm^{-1}$. $^1H$ NMR ($CDCl_3$) $\delta$ 7.72 (s, 1 H, furan vinyl), 6.06 (s, 1 H, pyrone vinyl), 4.23 (s, 3 H, $OCH_3$), 4.10 (s, 3 H, $OCH_3$), 2.63 (s, 3 H, acetyl), 2.40 (s, 3 H, $CH_3$); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 228 (sh, 16 200), 245 (21 300) 282 (29 900), 337 (10 450); mass spectrum (high resolution), calcd for $C_{16}H_{14}O_6$ 302.0801, found 302.079; mass spectrum, *m/e* (relative intensity) 302 (parent, 100), 287 (90), 273 (37), 258 (67), 231 (16), 217 (11), 203 (11). Anal. Calcd for $C_{16}H_{14}O_6$: C, 63.57; H, 4.67. Found: C, 63.30; H, 4.61.

**2-Benzoyl-3-methyl-4,8-dimethoxybenzo[1,2-*b*:5,4-*b*]difuran (21).** 4,7-Dimethoxy-5-acetyl-6-hydroxybenzofuran **20** (10.0 g, 42.3 mmol), $\alpha$-bromoacetophenone (8.42 g, 42.3 mmol), and potassium carbonate (10 g) were added to acetone (100 mL) and heated at reflux for 18 h. The reaction was cooled to room temperature and diluted with water and then extracted with ether. The organic extract was dried ($MgSO_4$) and solvent removed in vacuo to give a deep yellow solid. Recrystallization from EtOAc afforded 9.73 g (68%) of pure **21**: mp 123.9–124.8 °C; IR (mull) 2924, 2854, 1642, 1613, 1568, 1557, 1503, 1461, 1458, 1445, 1386, 1377, 1337, 1325, 1308, 1267, 1148, 1078, 928, 901, 739 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.15 (m, 2 H, Ar), 7.5 (m, 4 H, Ar), 7.0 (d, 1 H, $J$ = 2 Hz, olefinic), 4.2 (s, 3 H, $OCH_3$), 4.1 (s, 3 H, $OCH_3$), 2.8 (s, 3 H, $CH_3$); mass spectrum, *m/e* (relative intensity) 337 (22), 336 (95), 322 (22), 321 (100), 306 (7), 305 (9), 290 (7), 229 (28), 105 (22), 77 (20); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 220 (sh, 23 000), 225 (23 550), 230 (sh, (22 300), 270 (21 950), 326 (17 400), 365 (6950). Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.76. Found: C, 71.07; H, 4.74.

**5,10-Dimethoxy-8-methyl-2*H*,6*H*-benzo[1,2-*b*:5,4-*b*]dipyran-2,6-dione (22) and 6-(Diacetoxymethyl)-5,8-dimethoxy-7-acetoxy-2-methylchromone (24).** A suspension of aldehyde **2** (4.0 g, 15.1 mmol) and anhydrous sodium acetate (7.1 g, 86 mmol) was refluxed for 6 h in acetic anhydride (53 mL). After cooling, the reaction solution was transferred to a separatory funnel containing 2 N HCl and EtOAc. Extracting with EtOAc (2 × 400 mL), washing the combined organic layers with water and brine, and filtering through sodium sulfate afforded 5.70 g of a solid after evaporation of the solvent. The crude product was added to 200 g of silica gel packed in 25% Skelly-B/EtOAc. Taking 30-mL fractions and elution with 3 L of 25% Skelly B/EtOAc and 0.5 L of EtOAc afforded 4.0 g (fractions 10–18, 65% yield) of **24**. An analytical sample was prepared by recrystallization from EtOAc–ether, giving white crystalline **24**: mp 135.9–137.1 °C; silica gel TLC, $R_f$ 0.5 (EtOAc); IR (mull) 1781, 1767, 1752, 1668 (C=O's), 1591 (C=C), 1551, 1472, 1390, 1376, 1236, 1213, 1196, 1187, 1093, 1058, 979 $cm^{-1}$; $^1H$ NMR ($CDCl_3$), $\delta$ 8.14 (s, 1 H, CH), 6.10 (s, 1 H, pyrone vinyl), 3.99 (s, 3 H, $OCH_3$), 3.94 (s, 3 H, $OCH_3$), 2.41 (s, 3 H, $CH_3$), 2.38 (s, 3 H, acetyl), 2.06 (s, 6 H, acetyl); $^{13}C$ NMR ($CDCl_3$) 176.20, 168.37, 168.06, 163.79, 154.05, 152.87, 146.00 (d, $J$ = 4.1 Hz), 138.07, 119.36, 116.96, 112.22, (dd, $J$ = 168.1 Hz, $J$ = 3.6 Hz), 84.48 (d, $J$ = 174.7 Hz), 64.01 (q, $J$ = 146.0 Hz), 61.54 (q, $J$ = 146.0 Hz), 20.66 (q, $J$ = 129.9 Hz), 19.92 (dq, $J$ = 129.8 Hz, $J$ = 3.0 Hz) ppm;[23] UV (EtOH) $\lambda_{max}$ ($\epsilon$) 209 (sh, 15 800), 229 (31 900) 249 (sh, 16 050), 304 (5750); mass spectrum, *m/e* (relative intensity) 408 (parent, 1), 306 (31), 264 (65), 246 (16), 236 (49), 235 (20), 231 (30), 221 (100), 220 (14), 193 (28), 192 (19). Anal. Calcd for $C_{19}H_{20}O_{10}$: C, 55.59; H, 4.94. Found: C, 55.59; H, 5.06. Further elution of the column afforded 0.72 g (fractions 28–40, 16.5% yield) of **22**. An analytical sample was prepared by recrystallization from EtOAc to give crystalline **22**: mp 251.5–257.2 °C; silica gel TLC, $R_f$ 0.4 (EtOAc); IR (mull) 1757, 1733, 1671 (C=O's), 1616, 1589 (C=C), 1471, 1390, 1378, 1362, 1189, 1141, 1059 $cm^{-1}$ (C–O/other); $^1H$ NMR ($CDCl_3$) $\delta$ 8.10 (d, 1 H, coumarin vinyl, $J$ = 9.9 Hz), 6.40 (d, 1 H, coumarin vinyl, $J$ = 9.9 Hz), 6.10 (s, 1 H, pyrone vinyl), 4.07 (s, 3 H, $OCH_3$), 3.98 (s, 3 H, $OCH_3$), 2.42 (s, 3 H, $CH_3$); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 234 (16 200), 263 (22 300), 275 (23 250), 283 (sh, 21 900), 318 (11 150), 330 (9650); mass spectrum (high resolution), calcd for $C_{15}H_{12}O_6$ 288.0623, found 288.0634. Anal. Calcd for $C_{15}H_{12}O_6$: C, 62.50; H, 4.20. Found: C, 62.14; H, 3.91.

**Hydrolysis of 24.** A solution of the acetate **24** (100 mg, 0.24 mmol) and sodium hydroxide (2 N aqueous, 0.27 mL, 0.54 mmol) in THF was stirred at ambient temperature. After 4 days, the reaction was transferred to a separatory funnel containing 2 N HCl and $CH_2Cl_2$. The $CH_2Cl_2$ layer was filtered through sodium sulfate and evaporated to afford a white solid identical with **2** by TLC and $^1H$ NMR.

**6-(Carbomethoxymethyl)-7-hydroxy-2-methyl-5,8-dimethoxychromone (27).** Khellin (26.0 g, 0.1 mol), $PdCl_2$ (1.75 g, 9 mmol), and CuCl (11.0 g, 0.110 mol) were added to methanol (200 mL) and placed in a Parr hydrogenation apparatus. The mixture was degased and placed under 30 psi of $O_2$ pressure. The reaction was then heated to 70 °C with shaking for 24 h. The reaction was degased ($O_2$) and poured into methylene chloride (400 mL). The methylene chloride solution was washed with dilute HCl. The aqueous was extracted (3×, 500, 250, 100 mL). The combined extracts were dried ($MgSO_4$) and solvent removed in vacuo to give a dark oil that slowly solidified. Chromatography of that solid over Florisil (1 kg, 10% $CH_3OH/CH_2Cl_2$) afforded 22.54 g (73%) of the product as a white solid: mp 173–177 °C; IR (mull) 2950, 2931, 2867, 2854, 2855, 1733, 1652, 1595, 1562, 1488, 1462, 1436, 1431, 1398, 1373, 1358, 1335, 1308, 1234, 1190, 1167, 1116, 1058, 989, 965, 940, 917 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 6.1 (s, 1 H, pyrone vinyl), 4.0 (s, 3 H, $OCH_3$), 3.9 (s, 3 H, $OCH_3$), 3.8 (s, 2 H, $CH_2CO_2CH_3$), 3.7 (s, 3 H, $OCH_3$), 2.4 (s, 3 H, $CH_3$); mass spectrum, *m/e* (relative intensity) 309 (18), 308 (100), 279 (69), 261 (48), 249 (27), 247 (24), 235 (55), 234 (19), 233 (38), 205 (25); UV (EtOH) $\lambda_{max}$ ($\epsilon$) 208 (19 150), 228 (21 050), 248 (20 250), 254 (21 400), 268 (sh, 7800), 293 (8100), 342 (sh, 2100). Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.19. Found: C, 58.33; H, 5.26.

**6-Carboxy-5,8-dimethoxy-7-hydroxy-2-methylchromone (28).** A solution of ester **27** (10 g, 32.5 mmol) in tetrahydrofuran (760 mL) and aqueous sodium hydroxide (2 N, 38 mL, 76 mmol) was stirred at ambient temperature for 5 h. The reaction solution was poured into a separatory funnel containing ethyl acetate and 2 N HCl. Extracting with ethyl acetate, washing the combined organic layers with brine, and filtering through sodium sulfate afforded 9.2 g (96% yield) of **28** after evaporation of solvent. This material was of sufficient puriety for the subsequent step. An analytical sample was prepared by recrystallization from ethanol–ethyl acetate: mp 216.5–217.9 °C; silica gel TLC, $R_f$ 0.4 (5% MeOH–$CH_2Cl_2$); IR (mull) 3333, 3303 (C–OH), 1709, 1647 (C=O's), 1593 (C=C), 1487, 1460, 1448, 1399, 1358, 1307, 1247, 1199, 1120, 1052, 927, 850, 90 $cm^{-1}$ (C–O/other); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 11.4 (br, 1 H, acid), 6.00 (s, 1 H, pyrone vinyl), 3.80 (s, 3 H, $OCH_3$), 3.66 (s, 3 H, $OCH_3$), 3.53 (s, 2 H, $CH_2$), 2.34 (s, 3 H, $CH_3$); mass spectrum; *m/e* (relative intensity) 294 (parent, 88), 276 (79) 265 (44), 261 (100), 235 (50), 233 (92), 220 (39), 219 (38), 205 (84), 69 (39); equivalent weight calcd for $C_{14}H_{14}O_7$ 294, found 301. Anal. Calcd for $C_{14}H_{14}O_7$: C, 57.14; H, 4.79. Found: C, 56.82; H, 4.78.

**2-Oxo-(3*H*)-khellin (7).** A solution of acid **28** (4.61 g, 15.7 mmol) in acetic anhydride (100 mL) was immersed in an oil bath at 120 °C. After 25 min, the solution was removed and allowed to cool and the acetic anhydride removed under high vacuum. The crude product was added to 250 g of silica gel packed in 10% acetone–$CH_2Cl_2$. Elution with 10% acetone–$CH_2Cl_2$ (40-mL fractions) afforded 3.37 g (fractions 38–63, 78% yield) of lactone **7**. An analytical sample was prepared by recrystallization from $CH_2Cl_2$–hexane to afford crystalline **7**: mp 218.1–219.5 °C; silica gel TLC, $R_f$ 0.3 (EtOAc); $^1H$ NMR ($CDCl_3$) $\delta$ 6.10 (s, 1 H, pyrone vinyl), 4.06 (s, 3 H, $OCH_3$), 3.92 (s, 3 H, $OCH_3$), 3.84 (s, 2 H, $CH_2$), 2.38 (s, 3 H, $CH_3$); IR (mull), 1822, 1673 (C=O's), 1632 (C=C), 1462, 1387, 1352, 1142, 1077, 1039 $cm^{-1}$ (C–O/other); UV ($CHCl_3$) $\lambda_{max}$ ($\epsilon$) 249 (19 750), 304 (5350); mass spectrum, *m/e* (relative intensity) 276 (parent, 100), 261 (52), 247 (26), 233 (38), 205 (46),

(23) $^{13}C$ NMR is a gated spectrum where the decoupler is set to 0.

137 (18), 69 (26), 43 (17), 28 (21). Anal. Calcd for $C_{14}H_{12}O_6$: C, 60.87; H, 4.38. Found: C, 60.76; H, 4.40.

**Registry No.** 1, 82-02-0; 2, 92611-82-0; 6, 102830-25-1; 7, 102830-36-4; 8, 102830-23-9; 9, 102830-24-0; 13, 102830-26-2; 14, 102830-27-3; 15, 102830-28-4; 16, 102830-30-8; 17, 102830-29-5; 18, 102830-31-9; 19, 92611-83-1; 20, 484-51-5; 21, 102830-32-0; 22, 102830-34-2; 24, 102830-33-1; 27, 92611-85-3; 28, 102830-35-3; ethyl bromoacetate, 105-36-2; bromoacetophenone, 70-11-1; chloroacetone, 78-95-5.

# Bridgehead Hydrazines. 3. Unusual Photorearrangement of 1,4-Diphenylpyridazino[1,2-*b*]phthalazine-6,11-dione

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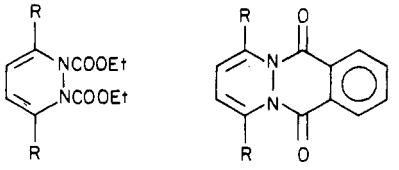
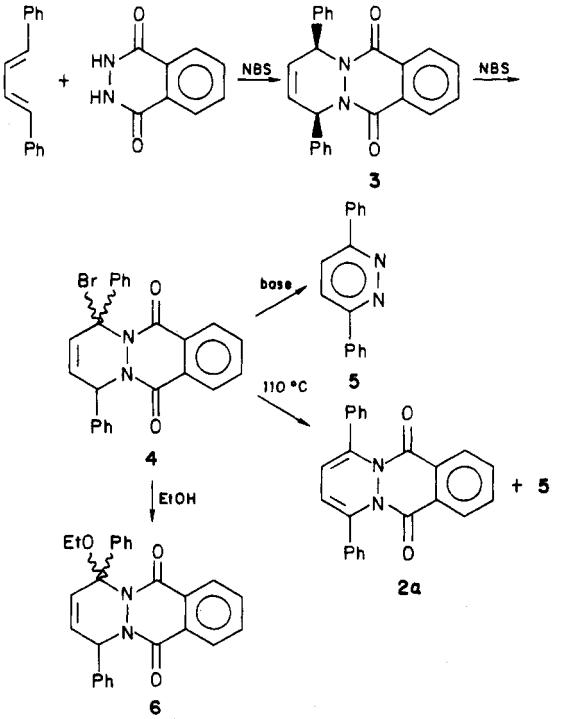
1,4-Diphenylpyridazino[1,2-*b*]phthalazine-6,11-dione (**2a**) was prepared through Diels–Alder reaction of phthalazine and 1,4-diphenylbutadiene, followed by allylic bromination and thermal 1,4-dehydrobromination. Upon photolysis, **2a** isomerized to an isoindolo[2,3-*a*]diazepine derivative, with an oxygen bridge across the seven-membered ring (**7**). A mechanism which involves an electrocyclic opening and a free radical cycloaddition is suggested.

The photoreactivity of 1,2-dihydro-1,2-diarylpyridazines is highly substituent dependent. Compound **1a**, for example, undergoes electrocyclic ring opening,[1] while **1b** gives, under the same conditions, mainly internal (2 + 2) cycloaddition.[2,3] We have recently reported[4] the synthesis and photolysis of the diazaanthraquinone **2b**. The photolysis resulted in (2 + 4) dimerization only and did not involve cleavage of the N–N bond. It was hoped that in analogy with **1a,b**, the introduction of two phenyl groups (**2a**) would direct the photolysis toward electrocyclic opening and formation of the diazecine ring system.




**Synthesis of 2a.** The Diels–Alder reaction of phthalazine (prepared in situ by NBS oxidation of phthalhydrazide) and *trans,trans*-1,4-diphenylbutadiene gave the tetrahydropyridazine **3** in 80% yield. Attempted direct selenium dioxide oxidation of **3** to **2a** (employed successfully in the synthesis of **1a**[5]) did not work. Allylic bromination of **3** with NBS proceeded smoothly and gave the bromide **4**, but all attempts to cause basic 1,4-dehydrobromination to **2a** resulted in complete removal of the phthaloyl portion and gave, even under very mild conditions, only 1,4-diphenylpyridazine **5**. It was noted that heating the bromide **4** to 110 °C (during melting point determination) caused orange-red coloring. We thus carried out pyrolysis of **4** on a preparative scale and obtained **2a** in 40% yield as a yellow-orange solid ($\lambda_{max}$ 402 nm). Analytical and spectral properties of **2a** were in accord with the proposed structure. The two vinylic hydrogens appeared in the NMR spectrum as one singlet ($\delta$ 6.12). It should be noted that the bromide **4** is very sensitive toward nucleophiles and reacted with ethanol to give the ethoxy derivative **6**. Although **4** was prepared by a free radical process and **6** by an $S_N1$ reaction, both were obtained as single stereoisomers.




**Photolysis of 2a.** The reaction proceeded rapidly, was solvent independent, and gave as the main product (70%) an isomer of **2a**. The NMR spectrum indicated loss of symmetry, as the two nonaromatic hydrogens appeared as two doublets [$\delta$ 5.93 and 5.40 ($J$ = 4.1 Hz)]. The IR car-

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