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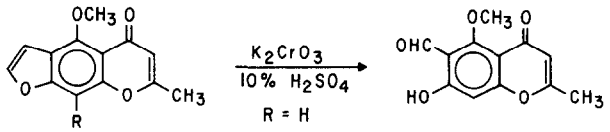
Catalytic Osmylation and Oxypalladation of Khellin. Two Useful Methods for Furan Ring Degradation. Replacement of the Furan Ring by an Isoxazole Ring.

Ronald B. Gammill* and Sharon A. Nash
The Upjohn Company
Kalamazoo, Michigan 49001

Abstract: Two oxidation reactions are described which result in the selective degradation of the furan ring in khellin. Conversion of these products to previously inaccessible analogues is described.

Khellin **1** is one of the oldest medicinal agents known to man.[1] Plant extracts containing khellin were used by the Egyptians 3000 years ago for the treatment of renal and biliary colic. The recent discovery of khellin's lipid-altering activity in man and antiatherosclerotic activity in animal models has renewed interest in preparing furochromone analogues.[2] It is interesting to note that over the past forty years a number of pyrone ring and C-4/C-9 methoxyl modifications of khellin have appeared in the literature.[3] This is mainly due to the availability of numerous degradation products of khellin which can be utilized in the reconstruction of many furochromone analogues. However, modification of the furan ring found in khellin, whether it be simple substitution or replacement of that ring with another heterocycle, has not appeared. It seems quite clear that a major reason for the absence of such analogues is the lack of methodology for the selective degradation of the furan ring in khellin to suitable synthetic intermediates capable of being used to reconstruct the desired furan ring modifications.[4]

The chromic acid oxidation of visnagin, a closely related analogue to khellin, has been known for years to afford the hydroxyaldehyde **3** in good yield.[5] Unfortunately, our attempts to extend this oxidation to khellin, historically the more pharamacologically interesting compound of the two,[6] has not been successful. This is perhaps not too surprising since chromic acid is capable of oxidatively demethylating para-methoxy aromatics to yield quinones.[7]



1 R = OCH_3 Khellin
2 R = H Visnagin

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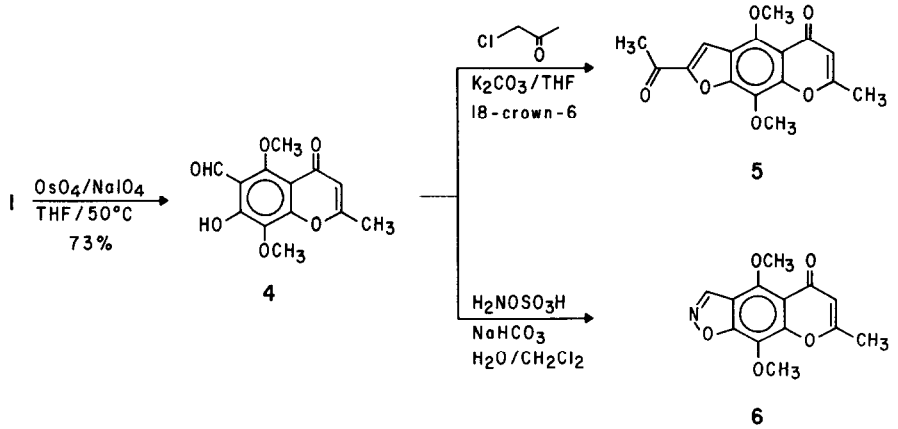
We would like to report in this letter two distinctively different and efficient methods for the selective oxidation of the furan ring in khellin. These oxidations lead to two versatile synthons for A ring (furan) modifications.

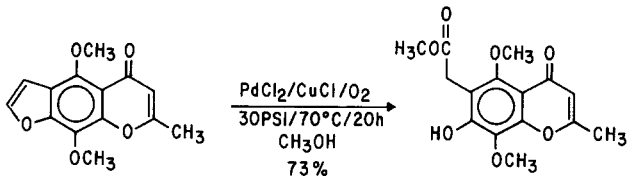
In general little attention has been directed toward the cleavage of the furan ring in benzofurans. Both iron (III) catalyzed oxidation using hydrogen peroxide [8] and ozonolysis[9] of benzofuran leads to low yield mixtures of salicylaldehyde, o-hydroxyphenylacetic acid, in the latter case some catachol is produced. While the oxidation of benzofuran with m-chloroperbenzoic acid has not been described, the success realized with furan derivatives[10] lead us to attempt such an oxidation using khellin as our substrate. Unfortunately, those attempts were unsuccessful. Attempts to combine an oxymetallation-oxidation procedure using either mercury or thallium were only partially successful[11] and ultimately lead us to investigate the catalytic osmylation described below.

Catalytic osmylation of khellin in THF at 50°C in the presence of $NaIO_4$ (2.2 equiv) afforded the hydroxyaldehyde **4**[12,13] in 73% yield. This methodology complements the chromic acid oxidation of visnagin which yields **3**. To place the versatility of **4** in perspective, we describe the preparation of a C-2 furan ring analogue and an analogue in which the furan ring has been replaced by an isoxazole ring. Treatment of hydroxyaldehyde **4** with chloroacetone in refluxing THF in the presence of potassium carbonate and 18-crown-6 resulted in the formation of the 2-acetyl furochromone **5**[14] in 53% yield. This two step, one pot conversion of **4** to **5** illustrates both the efficiency of analogue preparation using **4** and the added benefit of generating additional functionality (ketone) for subsequent manipulations.



The isoxazole analogue **6** was prepared from **4** by slow addition of O-sulfonic acid hydroxylamine to the aldehyde in a two phase system (water/methylene chloride) containing $NaHCO_3$ (2 equiv.).[15] This reaction provided the isoxazole analogue **6**[16] in 79% yield.

A second method for oxidizing the furan ring in khellin which gives rise to another versatile analogue synthon was also developed. Catalytic oxidation of khellin with palladium chloride ($CuCl/O_2$/30psi) in methanol at 70°C for 20 hours afforded the hydroxy ester 7[17] in 73% yield. This reaction nicely complements the osmylation described above.



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The methodology described above provides access to important furan ring modifications necessary for properly evaluating furochromones in the lipid area. In addition, it provides precedents for similar oxidations on other systems containing the benzofuran system.

References and Notes

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4. Another reason for the lack of furan ring analogues in the khellin series is the lack of flexibility incorporated into earlier total syntheses efforts in this area. For an example of more recent methodology that addresses the question of versitile synthetic building blocks see: R.B. Gammill and B.R. Hyde, *J. Org. Chem.*, 48, 3863 (1983).

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7. O.C. Musgrave, *Chem. Rev.*, 69, 499 (1969). While small amounts of khellin quinone could be detected in our oxidation, this chronic acid oxidation generally gave a complex mixture of products in very low yield.

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10. G. Schulte, P.J. Scheuer and O.J. McDonnell, *Helv. Chim. Acta.*, 63, 2159 (1980); for another successful oxidation which also results in an interesting rearrangement see: S.B. Gingerich, W.H. Campbell, C.E. Bricca, P.W. Jennings and C.F. Campana, *J. Org. Chem.*, 46 2589 (1981).

11. The details of these oxymetallations will appear in the full account of this work.

12. All new compounds were characterized by IR, UV, MS, NMR and these data were consistent with the assigned structure. Satisfactory combustion analyses were also obtained for new compounds.

13. **4**; Mp 199-202°; IR (mull) 2954, 2925, 2855, 1667, 1642, 1575, 1472, 1425, 1394, 1347, 1319, 1283, 1230, 1136, 1046, 980 cm^{-1}; ^1H-NMR ($CDCl_3$, δ) 11.01 (s,1H), 10.34 (s,1H), 4.02 (s,3H), 3.96 (s,3H), 2.38 (s,3H); UV (EtOH) λ_{max} (ε): 217 (12,500), 219 sh (12,400), 261 (29,900), 272 (29,450), 300 sh (2,750), 375 sh, (1,200).

14. **5**; Mp 184-5°C; IR (mull) 1675, 1623, 1483, 1366, 1288, 1110, 1059 cm^{-1}; ^1H-NMR ($CDCl_3$, δ) 7.72 (s,1H), 6.06 (s,1H), 4.23 (s,3H), 4.10 (s,3H), 2.63 (s,3H), 2.40 (s,3H); UV (EtOH) λ_{max} (ε): 228 sh (16,200), 2.45 (21,300), 282 (29,900), 337 (10,450).

15. D.S. Kemp and R.B. Woodward, *Tetrahedron*, 21, 3019 (1965).

16. **6**; Mp 280-2°C; IR (mull), 1666, 1641, 1617, 1602, 1475, 1435, 1394, 1217, 1143 cm^{-1}; ^1H-NMR ($CDCl_3$, δ) 8.94 (s,1H), 6.06 (s,1H), 4.23 (s,3H), 4.20 (s,3H), 2.39 (s,3H); UV (EtOH) λ_{max} (ε): 230 (27,800), 252 (24,950), 260 (23,400), 272 sh (8,400), 315 (6,200).

17. **7**; Mp 173-7°C; IR (mull) 2950, 2931, 2867, 2854, 1733, 1652, 1595, 1562, 1488, 1462, 1436, 1431, 1398, 1373, 1358, 1335, 1308, 1190, 898 cm^{-1}; ^1H-NMR ($CDCl_3$, δ) 6.1 (s,1H), 4.0 (s,3H), 3.9 (s,3H), 3.8 (s,2H), 3.7 (s,3H), 2.4 (s,3H); UV (EtOH) λ_{max} (ε): 208 (19,150), 228 (21,050), 248 (20,250), 254 (21,400), 268 sh (7,800), 293 (8,100), 342 sh (2,100).

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