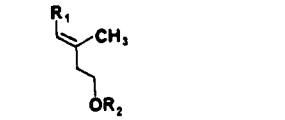
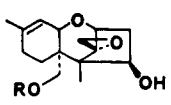
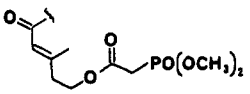
in which the growing macrocyclic chain is first attached to C(15)–OH and the macrocycle closed by a lactonization reaction involving C(4)–OH.

Treatment of 3-butyn-1-ol with Me_3Al (3.0 equiv) and Cl_2ZrCp_2 (0.25 equiv) followed by trichloroethyl chloroformate (1.1 equiv) according to Negishi's procedure[9] afforded ester **4**[10] in 20–25% yield. Treatment of **4** with 1.2



4 $R_1 = CO_2CH_2CCl_3$, $R_2 = H$
5 $R_1 = CO_2CH_2CCl_3$, $R_2 = COCH_2PO(OCH_3)_2$
6 $R_1 = CO_2H$, $R_2 = COCH_2PO(OCH_3)_2$
10 $R_1 = CO_2H$, $R_2 = TBDMS$
11 $R_1 = I$, $R_2 = H$





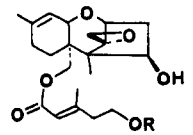
7, R =

8, R =

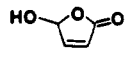
9, R =

equiv of the mixed anhydride prepared from trifluoroacetic anhydride and dimethylphosphonoacetic acid[11] (CH_2Cl_2, pyridine, 94% yield) yielded **5**, deprotection of which (Zn, THF, KH_2PO_4) gave acid **6** in 76% yield. Esterification of verrucarol (**2**) with **6** (1.5 equiv), DCC, and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 according to Hassner's method[12] afforded trichothecene monoester **7** in 34–55% yield as a 3:1 mixture of *E*/*Z* olefin isomers together with up to 19% of diene **8** (ca. 3:1 olefin mixture) and 19% of phosphonoacetate **9**. Although a number of coupling methods (DCC, mixed anhydrides, etc.) proved to be highly selective[5a] for the primary hydroxyl group of **2**, we were not able to eliminate the formation of **8**, **9**, or (*Z*)-**7**. Moreover, we were unable to separate (*E*)-**7** from its olefin isomer.

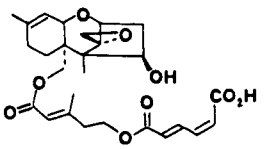
A parallel series of coupling experiments was performed by using acid **10**. This intermediate was prepared initially from **4** [(i) TBDMS-Cl, imidazole, DMF; (ii) Zn, THF, KH_2PO_4; 59% for both steps], but a higher yielding sequence proceeded from 3-butyn-1-ol via vinyl iodide **11**[9] [(i) TBDMS-Cl, imidazole, DMF; (ii) *n*-BuLi, Et_2O, –60 °C; (iii) CO_2, –78 °C; 67% yield of **10** from **11**; 43% overall yield from 3-butynol]. Thus, treatment of verrucarol with **10** (1.5 equiv), DCC, and DMAP in CH_2Cl_2 (6 h, 23 °C) afforded ester **12** as a 4:1 mixture of *E* and *Z* olefin isomers in 82–85% yield; careful separation of such mixtures by silica gel chromatography afforded pure (*E*)-**12** in 56–60% overall yield along with 14–16% of (*Z*)-**12**.[13] Deprotection



12, R = TBDMS
13, R = H
7, R = $COCH_2PO(OCH_3)_2$



14



15

of (*E*)-**12** by treatment with HOAc and H_2O in THF (3:1:1, 4 h, 23 °C) smoothly provided **13** (96%), a known degradation product of verrucarin J,[14] acylation of which [$(MeO)_2POCH_2CO_2H$ (1.1 equiv), DCC, DMAP, CH_2Cl_2], gave pure (*E*)-phosphonate **7** in 53% yield (33% of **13** was recovered).[15] Condensation of **7** with malealdehydic acid (**14**)[16] by using the procedure outlined previously[5g] afforded verrucarin J seco acid **15** reproducibly in 57–58% yield. Finally, **15** was treated with pivaloyl chloride (2 equiv) and triethylamine (3 equiv) in CH_2Cl_2 (0.01 M) to form the mixed anhydride which was treated in situ with 4-pyrrolidinopyridine to effect ring closure (23 °C, 2 h). In this manner verrucarin J was isolated by chromatography in 55–60% yield which, following recrystallization from $CHCl_3$–ether, was identical in all the usual respects with an authentic sample generously provided by Professor B. B. Jarvis.[17]

Acknowledgment. This research was supported by the National Cancer Institute (Grant No. CA 26830), the National Science Foundation and the Whitaker Health Sciences Fund (Predoctoral Fellowships to T.A.B), and the Merck Co. We are grateful to Professor B. B. Jarvis for providing a sample of natural verrucarin J for comparative purposes and to Drs. T. W. Doyle and T. Kaneko of Bristol Laboratories for a generous supply of anguidine.

Supplementary Material Available: ^1H NMR data for compounds **10**, (*E*)-**12**, (*Z*)-**12**, (*E*)-**13**, (*Z*)-**13**, (*E*)-**7**, **15**, and synthetic verrucarin J (3 pages). Ordering information is given on any current masthead page.

(8) Compound **3** (R = $CH_2CH_2SiMe_3$) has been synthesized by a combination of the methods reported in our preliminary studies[5g] and those described herein. A C(15)-monoprotected derivative of verrucarol was prepared by treating **2** with $HO_2C(CH_2)_3OTBDMS$, DCC, and 4-(dimethylamino)pyridine (DMAP) in CH_2Cl_2 (70% yield).

(9) Rand, C. L.; Van Horn, D. E.; Moore, M. W.; Negishi, E. *J. Org. Chem.* **1981**, *46*, 4093.

(10) The spectroscopic properties (250- or 270-MHz ^1H NMR, IR, mass spectrum) of all new compounds were in accord with the assigned structures.

(11) Donovan, S. F.; Avery, M. A.; McMurry, J. E. *Tetrahedron Lett.* **1979**, 3287.

(12) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

(13) Condensation of **2** and **10** with Mukaiyama's salt afforded *E* esters exclusively but in low yield and with poor regioselectivity [60:40 C(15) vs. C(4)]: Mukaiyama, T.; Usui, M.; Shimada, E.; Saigo, K. *Chem. Lett.* **1975**, 1045. Other procedures (mixed anhydride, 2-pyridylthiol ester, CDI[5d]) led to mixtures of olefin isomers, and the Mitsunobu procedure failed altogether.

(14) Tamm originally reported that **13** possessed a *Z* double bond.[6] The spectroscopic properties of (*E*)-**13**, however, are identical with those previously reported for the naturally derived compound. Moreover, we have prepared authentic (*Z*)-**13** by deprotection of (*Z*)-**12** with CH_3CO_2H in aqueous THF (3:1:1; 86% yield), which leaves little doubt that the natural material possesses an *E* double bond.

(15) The yield of **7** is not improved substantially when larger excesses of dimethylphosphonacetic are employed; diacylation [C(4) and C(5′)] is a serious problem under such conditions.

(16) Doerr, I. L.; Willette, R. E. *J. Org. Chem.* **1973**, *38*, 3878.

(17) (a) Synthetic verrucarin J isolated by chromatography was contaminated with ~10% of an isomer which was removed during the crystallization step. (b) Also isolated from the ring closure step was 30% of an isomer tentatively assigned the *E,E*-configuration for the muconate diester linkage. This compound (R_f 0.5) is easily separated from **1** (R_f 0.7 in 1:1 ether–CH_2Cl_2) by silica gel chromatography. A report on the synthesis of other isomers of **1** will be published in due course.

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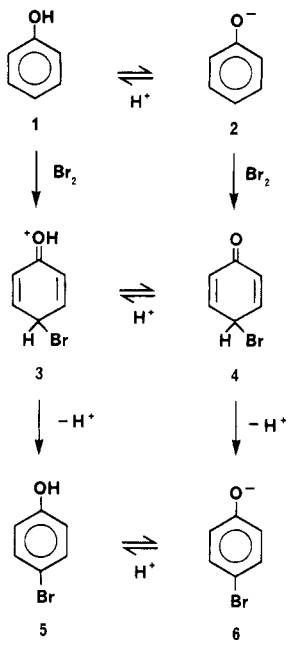
Observation of the Cyclohexadienone Intermediate in the Aqueous Bromination of Phenol

Summary: The unstable 4-bromo-2,5-cyclohexadienone intermediate involved in the aqueous bromination of phenol has been observed for the first time by stopped-flow UV spectrophotometry (λ_{max} ~240 nm, ϵ ~10 000). In the pH range 0–6 its rearrangement to *p*-bromophenol occurs by acid-catalyzed and uncatalyzed pathways. The intermediate derived from 2,6-dimethylphenol behaves similarly but rearranges more slowly and so is more easily studied.

0022-3263/83/1948-0759$01.50/0

Scheme I



Starting from *p*-cresol one can also observe the cyclohexadienone resulting from bromine attack ipso to the *p*-methyl group. It rearranges relatively slowly by a route that is acid catalyzed and bromide ion catalyzed. However, this route accounts for only about 10% of the reaction; the major pathway presumably results from bromine attacking at an ortho position.

Sir: Electrophilic bromination of simple phenols apparently proceeds via 2,5-cyclohexadienone intermediates,[1-3] such as **4** in Scheme I. Phenols bearing bulky substituents at positions 2 and 6 react with bromine in acetic acid to give cyclohexadienones of sufficient lifetime to be observable by conventional means[2] or flow NMR[3] and in one case to be isolable.[2] Heretofore there has been no direct observation of such intermediates in aqueous brominations nor has the intermediate **4**, derived from unsubstituted phenol **1**, ever been detected. We now report that such observations are possible with the use of stopped-flow UV spectrophotometry.[4]

In aqueous solutions of pH 0–4 phenol reacts with bromine with a second-order rate constant[5] of 4.2×10^5 M^{-1} s^{-1}; above pH 4.5 reaction is via phenoxide ion at a diffusion-controlled rate.[7] These results were obtained by monitoring the disappearance of bromine at 270–275 nm (tribromide ion maximum at 267 nm).[4] However, if one monitors the reaction at 240–245 nm, one sees an increase in absorbance followed by a slower decrease.[9] This we ascribe to the formation and decay of the cyclohexadienone **4**, since various of its derivatives have absorption maxima in the region of 240–260 nm (see ref 2, 3, 10 and references therein) and bromination under our conditions leads predominantly to the para product **5**. Analyzing the latter part of the decay curves, we obtain first-order rate constants that are independent of the initial concentrations of phenol, bromine, or bromide ion, as required for an intermediate such as **4**.

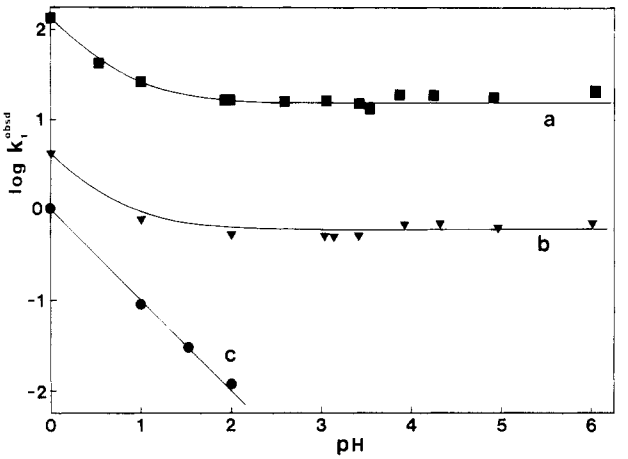


Figure 1. pH–rate profiles for the decay of 4-bromo-2,5-cyclohexadienones. At 25 °C, I = 0.1 (KBr). (a) Intermediate **4** derived from phenol. (b) Intermediate derived from 2,6-dimethylphenol. (c) Intermediate **8** derived from ipso bromine attack upon *p*-cresol, [KBr] = 0.1 M.

The disappearance of **4** varies with pH according to eq 1 (see Figure 1), with constants k_H = 110 M^{-1} s^{-1} and k_0

$$k_{obsd} = k_H[H^+] + k_0 \quad (1)$$

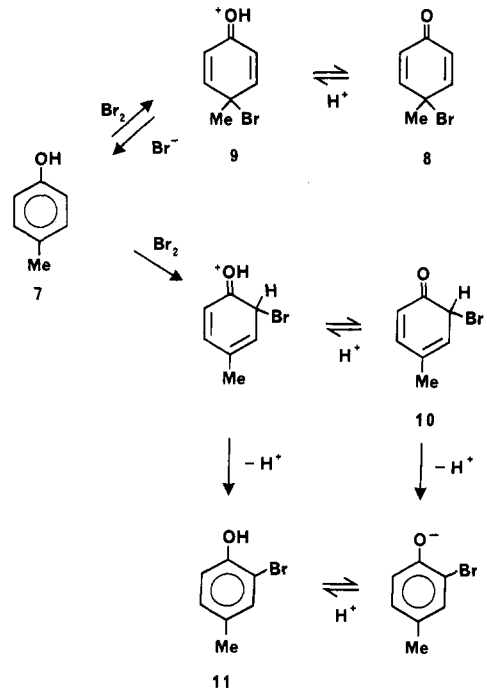
= 15 s^{-1}. The two terms in eq 1 are probably due to water abstracting the C-4 proton of the protonated intermediate **3** and water abstracting the same proton from the cyclohexadienone **4**,[11] respectively. The involvement of water acting as the base in the latter case is supported by the observation of a solvent isotope effect of 1.6.[13,14] Taken as a whole our results are consistent with the overall mechanism depicted in Scheme I.

We have also studied the aqueous bromination of 2,6-dimethylphenol. We reasoned that the corresponding cyclohexadienone intermediate should be more easily observed since the initial attack of bromine should be faster, but the deprotonation step should be slower. These expectations were realized. Monitoring the decay of the intermediate at 250 nm, we obtained the first-order rate constants depicted in Figure 1. Again the pH dependence of these constants follows eq 1, suggesting similar modes of decomposition as for the intermediate **4**.

Phenols show greater reactivity for bromine attack at para positions than at ortho.[6,15] This suggested to us that with a para-substituted phenol, initial bromine attack

(1) de la Mare, P. B. D. "Electrophilic Halogenation"; Cambridge University Press: Cambridge, 1976; Chapter 7.
(2) de la Mare, P. B. D. *Acc. Chem. Res.* **1974**, *7*, 361 and references therein.
(3) Fyfe, C. A.; Van Veen, L., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 3366.
(4) The equipment and techniques used were as described in other recent work: (a) Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *J. Am. Chem. Soc.* **1982**, *104*, 7219. (b) Tee, O. S.; Paventi, M. *Ibid.* **1982**, *104*, 4142. (c) Tee, O. S.; Berks, C. G. *J. Org. Chem.* **1980**, *45*, 830.
(5) At 25 °C, I = 1.0 M (KBr), corrected for tribromide ion formation.[4c] The value is essentially the same at I = 0.1 M (KBr). Bell and Rawlinson[6] give a value of 1.8×10^5 M^{-1} s^{-1}, obtained electrochemically and extrapolated to zero ionic strength.
(6) Bell, R. P.; Rawlinson, D. J. *J. Chem. Soc.* **1961**, 63.
(7) The apparent second-order rate constant is about 2.4×10^{10} M^{-1} s^{-1}. This high value, seemingly above diffusion controlled,[8] probably contains a contribution from reaction with tribromide ion[6] and may also be high due to some polybromination. These questions will be addressed in a full paper.
(8) Ridd, J. H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1.
(9) Normal concentrations used were as follows: phenol, 0.5 mM; bromine, 0.05–0.1 mM; potassium bromide, 0.1 M. Temperature was controlled at 25 °C. Under these conditions and with pH 2–4, bromine disappearance at 275 nm and intermediate appearance at 240 nm have a rate constant of about 85 s^{-1}. The subsequent decrease at 240 nm has a rate constant of 15 s^{-1}.
(10) Cook, K. L.; Waring, A. J. *J. Chem. Soc., Perkin Trans. 2*, **1973**, 84.
(11) The kinetically indistinguishable alternative of hydroxide ion attacking the conjugate acid **3** can be ruled out. Judging by similar derivatives in the literature,[10,12] the pK value of **3** must be less than −3. This requires an unreasonable rate constant of more than 10^{18} M^{-1} s^{-1} for hydroxide attack in order to explain our value of k_0.
(12) Vitullo, V. P.; Grossman, N. *J. Am. Chem. Soc.* **1972**, *94*, 3844.
(13) At pH(pD) = 3.6, so the solvent isotope effect refers to the k_0 process.
(14) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275.
(15) For example, we find k_2 = 15 000 M^{-1} s^{-1} for *o*-bromophenol and 4400 for *p*-bromophenol.

Scheme II



might occur ipso to the substituent. Support for this idea comes from the work of Fischer and Henderson who have isolated 4-chloro-2,5-cyclohexadienones resulting from ipso chlorine attack upon *p*-alkylphenols in nonaqueous solvents.[16] Using *p*-cresol (7) as substrate in aqueous bromination, we find that we can indeed observe an intermediate at about 250 nm. However, the absorbance change associated with its disappearance is small (only 10% of that found for 4 or its dimethyl analogue), and the major portion of the product appears before the intermediate disappears. The first-order decay of the intermediate, presumed to be the 2,5-cyclohexadienone 8, shows acid catalysis (Figure 1) *and* is linearly dependent upon bromide ion concentration.

Our observations for *p*-cresol are rationalized by Scheme II. The substrate is mainly attacked by bromine at an ortho position to give a 2,4-cyclohexadienone **10**, which is converted through to product fairly quickly.[17] A minor amount (~10%) of bromine attack occurs ipso to give the observed intermediate 8. This undergoes debromination by bromide ion attack upon the protonated form **9** to give back *p*-cresol and bromine and so is eventually converted to the ortho bromo product 11.

In summary, we have observed the formation and decay of intermediates in the aqueous bromination of phenol, 2,6-dimethylphenol, and *p*-cresol. They exhibit kinetic and spectral properties[19] that are consistent with them being 4-bromo-2,5-cyclohexadienones.

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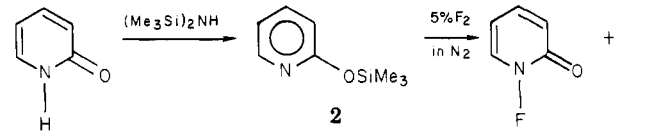
1-Fluoro-2-pyridone: A Useful Fluorinating Reagent

Summary: 1-Fluoro-2-pyridone (mp 50–53 °C) has been prepared by reaction of 5% fluorine in nitrogen and 2-(trimethylsiloxy)pyridine in $FCCl_3$ at −78 °C. After sublimation, the pyridone is used as a selective fluorinating agent in the preparation of some fluoromalonates.

Sir: Since many organic compounds acquire interesting new properties on the introduction of a fluorine atom, methods of selectively introducing fluorine into organic molecules are of interest. Many of the procedures now used to prepare fluorinated molecules employ extremely reactive, corrosive, toxic, and often gaseous materials that require specialized equipment. We wish to report the synthesis of a solid organic molecule, 1-fluoro-2-pyridone, that shows potential as a fluorine transfer agent. 1-Fluoro-2-pyridone (1) was chosen as a potentially selective fluorinating reagent[1] because of several attractive features: (1) the labile N–F linkage, (2) the aromatizability of the pyridone nucleus after fluorination (a driving force for reaction), (3) the likelihood that the compound would be solid, and (4) the absence of toxic or explosive reaction byproducts. Furthermore, a synthetic route to 1 was readily envisioned. Because of the affinity of silicon for fluorine as well as a low-energy six-membered transition state available for reaction, 2-(trimethylsiloxy)pyridine[3] (2) was chosen for treatment with 5% fluorine in nitrogen[4] (eq 1). Furthermore, use of the siloxypyridine eliminated the possibility of interference by HF that might occur during fluorination of the unsubstituted pyridone, 3.



3 2 1

Me_3SiF (1)

1-Fluoro-2-pyridone (1) is particularly notable because no unusual safety precautions are required for either its preparation or its use. The fluorination system was constructed entirely from glass vessels and Tygon tubing; Kel-F was used to lubricate the joints. The diluted fluorine[4] was passed through solid NaF and into the reactor,

(16) Fischer, A.; Henderson, G. N. *Can. J. Chem.* **1979**, *57*, 552.
(17) 2,4-Cyclohexadienones (e.g., **10**) are kinetically much less stable than the 2,5-isomers.[16,18]
(18) Miller, B. *Acc. Chem. Res.* **1975**, *8*, 245.
(19) The absorption maxima for 4, 2,6-dimethyl-substituted 4, and 8 are about 240, 250, and 250 nm, respectively. In the first two cases the extinction coefficients are about 10 000, as found for isolable 2,5-cyclohexadienones (see ref 2, 3, 10 and references therein). In contrast, the isomeric 2,4-cyclohexadienones have maxima around 310 nm and somewhat smaller extinction coefficients.[20]
(20) Miller, B. *J. Am. Chem. Soc.* **1970**, *92*, 6246, 6252. Quinkert, G.; Durner, G.; Kleiner, E.; Haupt, E.; Leibfritz, D. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 556. Lasne, M. C.; Ripoli, J. L. *Tetrahedron Lett.* **1980**, *21*, 463.

(1) Attempts to prepare *N*-fluorosuccinimide from succinimide or one of its salts (potassium, sodium, calcium, or silver) and various fluorinating agents (fluorine, trifluoromethyl hypofluorite, or perchloryl fluoride) in a variety of solvents (water, freon, chloroform, acetonitrile, methylene chloride, or trifluoroacetic acid) at temperatures ranging from −78 °C to room temperature were unsuccessful. Recently, *N*-fluoroperfluorosuccinimide has been prepared,[2] however its chemistry was not reported.
(2) Yagupol'skii, Ya. L.; Savina, T. I. *Zh. Org. Khim.* **1981**, *17*, 1330.
(3) Buchanan, M. J.; Cragg, R. H.; Steltner, A. *J. Organomet. Chem.* **1976**, *120*, 189.
(4) Available from Air Products. Although other fluorinating agents such as CF_3OF might have produced a higher yield of **3**, these reagents generally generate toxic gaseous products (e.g., COF_2) and are more expensive than fluorine diluted with nitrogen.

0022-3263/83/1948-0761$01.50/0