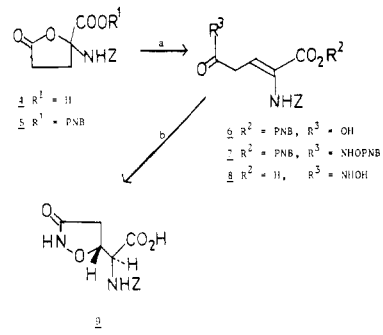
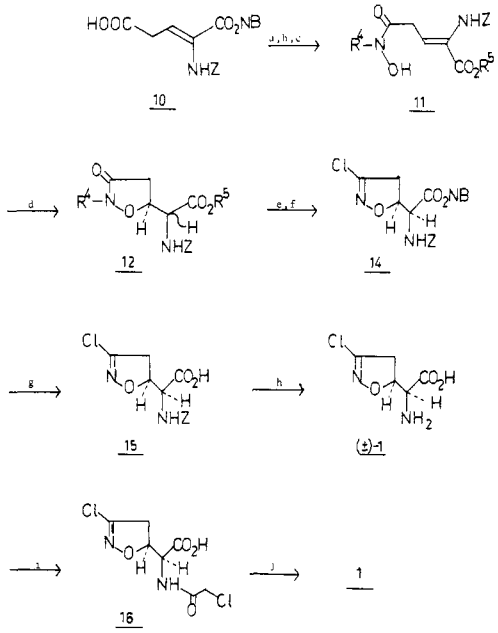
Scheme II[a]



[a] (a) DBU, THF, 0 °C; (b) 2.15 equiv of 1 N NaOH, reflux.

Scheme III[a]



[a] (a) DCC, *N*-hydroxysuccinimide, THF; (b) **13**; (c) anhydrous KF, EtOH; (d) dilute aqueous $NaHCO_3$; (e) PCl_5, CH_3NO_2; (f) column chromatography; (g) Al-Hg, ether; (h) $(COCl)_2$–DMF/benzene; (i) *p*-nitrophenyl chloroacetate;[15] (j) hog kidney acylase I.

1 was readily achieved via the chloroacetyl derivative **16**[8i] by means of hog kidney acylase I, affording optically pure AT-125 (57%), $[\alpha]^{20}_{378}$ +135° (c 0.159, H_2O).

This sequence involves eight separate steps, including deprotections, from the known and readily available **7**, and only one chromatographic separation, i.e., that of the oximino chloride **12** and its diastereomer.

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An Unusual Nucleophilic Attack on a Carbonyl Oxygen. Reaction of a Positively Charged Oxygen Atom

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Protonation on the nitrogen atom of *p*-benzoquinone monoimine (**1**) should give a species (**2**) with a positively charged oxygen atom,

Chart I

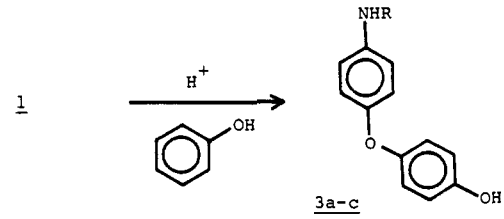
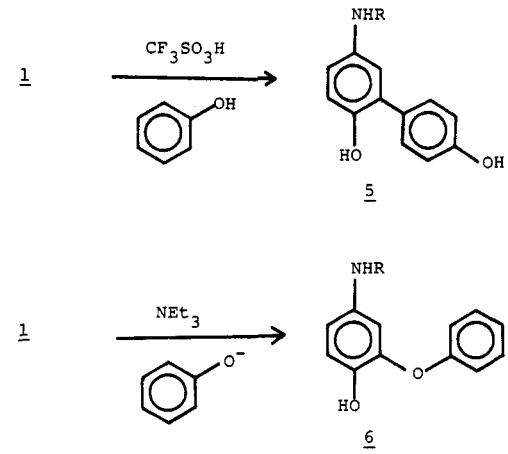
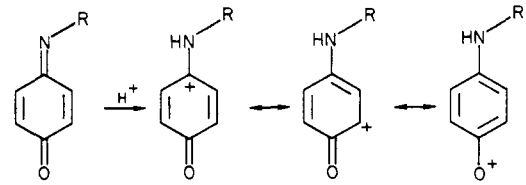


Chart II



a phenoxenium ion. In this paper we wish to report the discovery of a pathway which involves the species **2** in the reaction of *N*-acyl-*p*-benzoquinone imines (**1a–c**) with phenol, aniline, and dimethylaniline. This is an example of nucleophilic attack on an oxygen atom of a carbonyl group.



1a, R = SO_2CH_3
b, R = $COCH_3$
c, R = COPh-*p*-NO_2

2a-c

The chemistry of benzoquinone imines has been extensively studied by Adams.[1] The only known example of a reaction of the oxygen atom of **1** is the reaction with dialkyl phosphites.[2] Recently, attention has been paid to *N*-acetylbenzoquinone imine (**1b**), since the compound is believed to be a toxic reactive metabolite of phenacetin and phenacetamol.[3] It is clearly important to delineate the conditions under which nucleophiles react with the electrophilic compound.

The reaction of *N*-(methanesulfonyl)-*p*-benzoquinone imine (**1a**, R = Ms)[4,5] with excess phenol (20–100 equiv) in a solvent such as tetrahydrofuran, benzene, or methylene chloride proceeded smoothly at room temperature for 10 h (Chart I). The major product was 4-(methanesulfonylamino)phenyl 4-hydroxyphenyl ether (**3a**, R = Ms) isolated in 88% yield. The reaction site is

(1) Adams, R.; Reifschneider, W. *Bull. Soc. Chim. Fr.* **1958**, 23.
(2) Titov, E. A.; Avdeenko, A. P. *Obshch. Khim.* **1971**, *41*, 797; *Chem. Abstr.* **1971**, *75*, 63343, 76448.
(3) Calder, I. C.; Healey, K.; Yong, A. C.; Ham, K. N.; Yange, J. D. *Biol. Oxid. Nitrogen, Proc. Int. Symp., 2nd* **1978**, 308. Nelson, S. N. *Ibid.*, **1978**, 319. Calder, I. C.; Creek, M. J. *Aust. J. Chem.* **1976**, *29*, 1801. Shudo, K.; Ohta, T.; Orihara, T.; Nagao, M.; Takahashi, Y.; Sugimura, T. *Mutat. Res.* **1978**, *58*, 367.
(4) Adams, R.; Looker, C. R. *J. Am. Chem. Soc.* **1951**, *73*, 1145.
(5) All the new compounds were correctly analyzed and identified with authentic samples prepared by unambiguous reactions.

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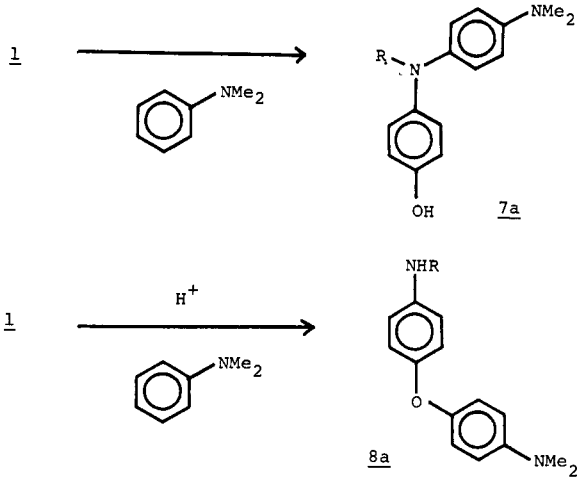
Chart III



the *oxygen* atom of the quinone imine. Another product identified was 4-hydroxymethanesulfonylanilide (**4a**), the formation of which could be explained as due to an oxidoreduction between **1a** and **3a**. The reduction of **1a** to **4a** was effected by the reaction of **1a** with isolated **3a**. The presence of excess phenol and high dilution increased the yield of **3a** and decreased the formation of **4a**. The presence of an acid, trifluoroacetic acid (TFA, 2 equiv to **1a**), increased the reaction rate: the reaction (**1** → **3**) is acid catalyzed. The formation of **3a** was not affected by air, light, benzoyl peroxide, azobis(isobutyronitrile), diphenyl(trinitrophenyl)hydrazyl, *m*-dinitrobenzene, or 1,1-diphenylethylene.

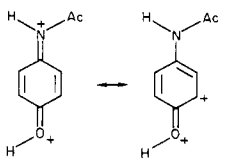
Reaction under strongly acidic conditions (5 equiv of trifluoromethanesulfonic acid) gave a diphenyl derivative **5a**.[6] Addition of triethylamine to the reaction also abolished the formation of the diphenyl ether **3a** and gave another diphenyl ether, **6a** (Chart II).[7]

The reaction of **1a** with excess *N*,*N*-dimethylaniline in methylene chloride in the presence of a catalytic amount of acid gave 4-(dimethylamino)-*N*-(4-hydroxyphenyl)methanesulfonylanilide (**7a**) in 50–60% yield. However, addition of excess protonic acid partially changed the reaction site from the nitrogen atom to the oxygen atom. Thus, a diphenyl ether (**8a**) was formed in 20–30% yield in the presence of TFA (5–10 equiv to dimethylaniline), though accompanied with **7a** (30–35%) (Chart III). This confirmed that the reaction on the oxygen atom requires the presence of a proton.

The reaction of **1a** with aniline proceeded similarly, but the yield of the corresponding products was low (15%) because of their instability under the reaction conditions. *N*-Acetyl- and *N*-(*p*-nitrobenzoyl)-*p*-benzoquinone imines (**1b** and **1c**) reacted similarly with phenol in methylene chloride, leading to formation of diphenyl ethers **3b** and **3c**, respectively. In these cases too, acid is required for the reaction at the oxygen atom.

The reaction on the oxygen atom can be explained as involving the *N*-protonated *N*-acyl-*p*-benzoquinone imine,[8] a kind of phenoxenium ion (**2**), which reacts with nucleophilic phenol or anilines.[9] Carbonyl polarization against atomic electronegativity is made possible by the aromatization of the protonated species, and the cation is stabilized by the acylamino group. No reasonable pathway which leads to **3** or **8** by rearrangement of an intermediate product is conceivable. A homolytic or radical chain mechanism cannot be involved, since the reaction is not affected by radical scavengers nor initiators. A reaction on the oxygen and carbon atoms of the *p*-nitrophenoxenium ion with anisole has been reported,[10] while unsubstituted phenoxenium ion reacts with the phenyl ring but not the oxygen atom in the reaction with phenol.[11] The present phenoxenium ion **2** must be more stable than the above species; this is consistent with the preferred attack at the para position of phenol.[12] It does not react with anisole on the oxygen atom in the presence of 2 equiv of TFA.[12] Concerning the attack on the carbonyl oxygen, the Perkow reaction can be cited as a related reaction, though its mechanism is not clear.[13] Few reactions of nucleophiles on positively charged heteroatoms, especially on oxygen and nitrogen, are known.[14] In view of the data presented above, we believe that the stabilized phenoxenium ion is an interesting chemical species, like the unsubstituted phenoxenium ion previously reported.[11] We are continuing to investigate various aspects of positively charged heteroatoms.

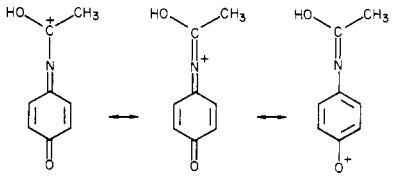
(6) This reaction may involve formation of an O,N-diprotonated species:



A similar species, the protonated species of *p*-nitrosophenol, has been proposed by: Olah, G. A.; Donovan D. J. *J. Org. Chem.* **1978**, *43*, 1743. Trifluoromethanesulfonic acid can double protonate *N*-phenylhydroxylamines to give iminium–benzenium dications (Okamoto, T.; Shudo, K.; Ohta, T. *J. Am. Chem. Soc.* **1975**, *97*, 7184). A similar reaction catalyzed by $AlCl_3$ has been reported by: Adams, R.; Eiler, K. R. *J. Am. Chem. Soc.* **1951**, *73*, 1149.

(7) This is a usual nucleophilic reaction of quinone imines.[1]

(8) O-Protonation of the acyl oxygen atom is equally possible and gives a phenoxenium ion such as **2'b**



2'b

(9) Concerted (**1** → **3**) and stepwise (**1** → **5**) pathways suggested by a referee are better defined by general and specific acid catalyses, respectively. However, two separate pathways from a single reactant to different products by general and specific acid catalyses are unlikely, because in a general acid catalysis the best catalyst is the strongest acid, the lyonium ion, which is also the catalyst in a specific acid catalysis. In addition the reaction **1** → **3** seems to be specific acid catalyzed, since it does not occur in PhOH/PhO^-. Consequently, we interpreted the formation of **5** as involving a doubly protonated species.[6]

(10) Abramovitch, R. A.; Inbasekaran, M.; Kato, S. *J. Am. Chem. Soc.* **1973**, *95*, 5428.

(11) Endo, Y.; Shudo, K.; Okamoto, T. *J. Am. Chem. Soc.* **1977**, *99*, 7721. *p*-Nitrophenoxenium ion prepared from *p*-NO_2PhONHTs with benzene gave only 2-hydroxy-5-nitrobiphenyl (unpublished result).

(12) Stock, L. M.; Brown, H. C. *Adv. Phys. Org. Chem.* **1965**, *1*, 36. Klopman, G. "Chemical Reactivity and Reaction Path"; Wiley: New York, 1974; p 81. More stable electrophiles attack more para positions. For example, benzenediazonium ion reacts with phenol at its para position and does not have enough reactivity to react with anisole.

(13) Lichetenthaler, F. W. *Chem. Rev.* **1961**, *61*, 607. Borowitz, I. J.; Anschel, M.; Firstenberg, S. *J. Org. Chem.* **1967**, *32*, 1723. Allen, J. F. *J. Am. Chem. Soc.* **1957**, *79*, 3071.

(14) Gassman, P. G. *J. Am. Chem. Soc.* **1980**, *102*, 1214.

Direct Determination of the Temperature Dependence of the Reactions of a Singlet Carbene. Intersystem Crossing and the Cyclopropanation of Olefins by Fluorenylidene in Acetonitrile Solution

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We recently reported the first direct spectroscopic observation of a singlet carbene in fluid solution at room temperature.[1]

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