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A NOVEL CYCLIZATION REACTION OF *o*-CARBOXYPHENYL AND *o*-CARBAMOYLPHENYL SULFOXIDES

FORMATION OF BENZOXATHIANE, DIHYDROBENZOTHIAZINE AND BENZOISOTHIAZOLINE DERIVATIVES[1]

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Abstract—When *o*-carboxyphenyl or *o*-carbamoylphenyl sulfoxide was heated with a large excess of acetic anhydride at 100–130° for 1–3 h, 6-membered heterocyclic compounds, *i.e.*, 3,1 - benzoxathian-4 - one and 2,3 - dihydro - 1,3 - benzothiazin - 4 - one, and a 5-membered heterocyclic compound, *i.e.*, 1,2-benzoisothiazolin-3-one were obtained in good yield.

Cyclization would take place by the initial intramolecular nucleophilic attack of either the sulfinyl O atom at *ortho*-carbonyl carbon or the N atom of the amide group at *ortho*-sulfinyl S atom to give a 5-membered cyclic acyloxysulfonium salt or aminosulfonium salt, which undergoes an intramolecular Pummerer rearrangement to afford the heterocyclic compounds.

INTRODUCTION

The oxygen exchange and racemization reactions of *o*-carboxyphenyl phenyl sulfoxide in both sulfuric acid[2] and acetic anhydride[3] are anchimerically assisted as compared to those of other substituted diphenyl sulfoxides.

As an extension of the neighboring group effect, we have studied possible neighboring group effect of carboxyl group or amide group in the Pummerer reaction and have found a novel cyclization to afford 2,3 - dihydro - 1,3 - benzothiazin - 4 - one, 3,1-benzoxathian - 4 - one or 1,2 - benzoisothiazolin - 3 - one in the reaction of *o*-carboxyphenyl or *o*-carbamoylphenyl sulfoxide with acetic anhydride.

It is well known that the Pummerer reaction does take place when alkyl sulfoxide is treated with acylating agent to afford α-substituted sulfide in which the substituent is derived from the outer nucleophile other than acyloxyl group.[4] However, in the case of *o*-carboxy- and *o*-carbamoylphenyl sulfoxides an apparently different type of intramolecular Pummerer reaction is taking place.

This paper presents a detailed account of the study of this novel cyclization reaction of alkyl *o*-carboxyphenyl and *o*-carbamoylphenyl sulfoxides.

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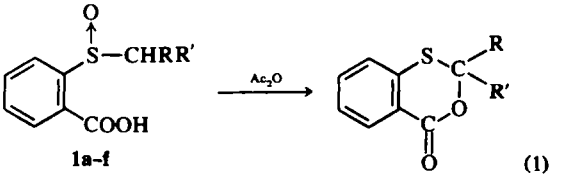
RESULTS

Reaction of o-carboxyphenyl sulfoxide

Cyclization took place when alkyl *o*-carboxyphenyl sulfoxides (**1**) were heated with a large excess of acetic anhydride. After removing excess acetic anhydride and volatile products, the residue was purified by column chromatography, and 2-substituted 3,1 - benzoxathian - 4 - one (**2**) obtained in high yields (Eq 1).

Yields, m.ps and IR data of benzoxathiane derivatives (**2**) are listed in Table 2.

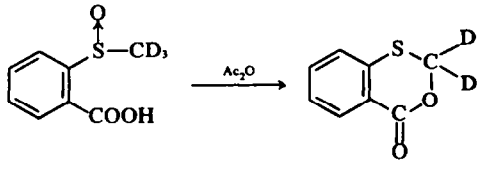


1a–f (1)

a: R = H, R' = H
b: R = H, R' = Me
c: R = H, R' = Et

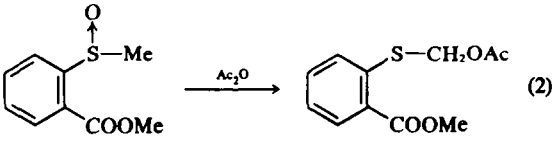
2a–f

d: R = H, R' = Ph
e: R = H, R' = *p*-Cl—C$_6$H$_4$
f: R = Me, R' = Me



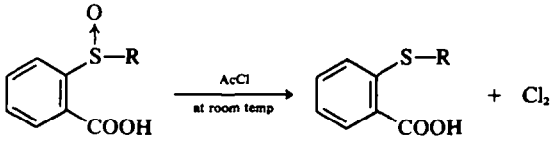
Since the yield was nearly quantitative, this reaction is the best synthetic procedure for obtaining compound **2**. Other methods hitherto-known have limited application since the products are obtained only in poor yields.[5] Moreover, 2,2-disubstituted benzoxathiane derivative (**2f**) and 2-deuterated isomer can be easily prepared only by this method; the other general method is the condensation of thiosalicylic acid with aldehyde only to produce 2-monosubstituted benzoxathiane derivatives.[5]

The cyclization reaction is possible only when the sulfoxide contains a free carboxyl group at the *ortho* position. When *o*-carbomethoxyphenyl methyl sulfoxide was heated with a large excess of acetic anhydride, acetoxymethyl *o*-carbomethoxyphenyl sulfide was obtained as the only product of normal Pummerer rearrangement. (Eq 2)



(2)

Meanwhile, the reaction of **1** with acetyl chloride, another acylating agent, proceeds very easily to afford *o*-carboxyphenyl sulfide in a good yield with evolution of chlorine gas.[6] (Eq 3)



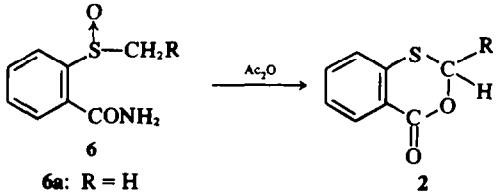
R = Me, Et, Ph, CH_2Ph (3)

Reaction of o-carbamoylphenyl sulfoxide

Benzyl *o*-phenylcarbamoylphenyl sulfoxide (**3a**) reacted with a large excess of acetic anhydride and yielded the 6-membered heterocyclic compound, 2,3 - diphenyl 2,3 - dihydro - 1,3 - benzothiazin - 4 - one (**4a**) in good yield (80%). Benzyl *o*-methylcarbamoylphenyl sulfoxide (**3b**) was also cyclized to give N-methyldihydrobenzothiazine derivative (**4b**) in 75% yield under similar conditions.

While in the reaction of benzyl *o*-carbamoylphenyl sulfoxide (**3c**) with a large excess of acetic anhydride yielded a 5-membered heterocyclic compound, 2-acetyl 1,2 - benzoisothiazolin - 3 - one (**5**) was obtained in good yield (90%) with the concomitant formation of benzyl acetate.

However, the reaction of alkyl *o*-carbamoylphenyl sulfoxide (**6**) with acetic anhydride is somewhat different from those of benzyl *o*-carbamoylphenyl sulfoxides (**3**). (Eq 5)



(5)

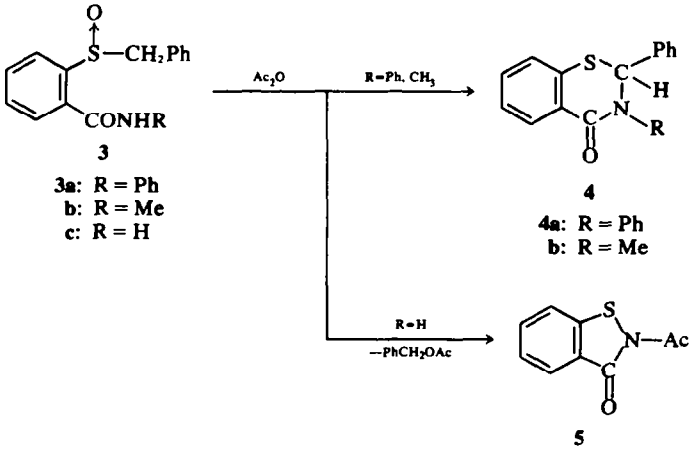
6
6a: R = H
b: R = Me

2

When *o*-carbamoylphenyl methyl sulfoxide (**6a**) was heated with acetic anhydride, a 6-membered heterocyclic compound containing no N atom, 3,1 - benzoxathian - 4 - one (**2a**) was produced in 44% yield together with acetoxymethyl *o*-acetylcarbamoylphenyl sulfide as the product of normal Pummerer rearrangement reaction.

In this cyclization both the intramolecular and the intermolecular Pummerer reactions are presumed to take place competitively, and under more drastic conditions (140° for 2 h) the intermolecular Pummerer reaction occurs preferentially to give acetoxymethyl *o*-acetylcarbamoylphenyl sulfide (90%) and benzoxathiane derivative (**2a**) in only 5% yield.

Similarly, 2-methyl 3,1 - benzoxathian - 4 - one (**2b**) was produced in 29% yield upon heating ethyl



3
3a: R = Ph
b: R = Me
c: R = H

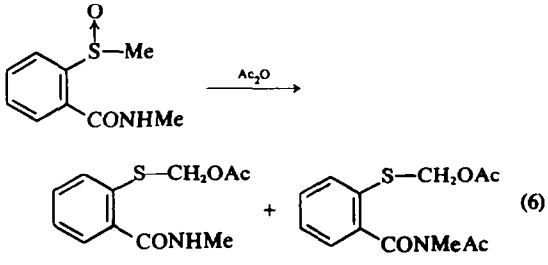
4
4a: R = Ph
b: R = Me

(4)

5

o-carbamoylphenyl sulfoxide (**6b**) with acetic anhydride. (Eq 5)

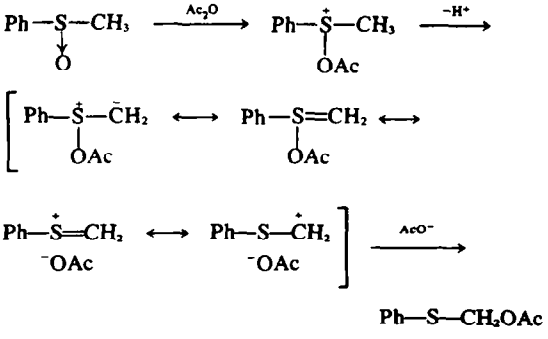
Whereas, in the reaction of methyl *o*-methylcarbamoylphenyl sulfoxide with acetic anhydride, no cyclized product was obtained and the normal intermolecular Pummerer reaction took place predominantly as shown below.



(6)

DISCUSSION

The mechanism of normal Pummerer reaction with acetic anhydride has been well studied[7] and the overall picture of the reaction can be depicted as follows.

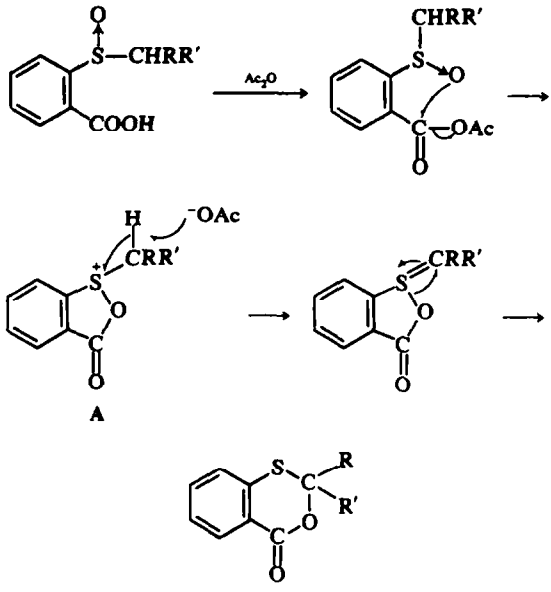


The order of reactivity for alkyl groups attached to the S atom of the sulfoxide in the normal Pummerer reaction appears to fall in the order; methyl > n-alkyl > sec-alkyl ≫ benzyl.[4,7] However, in this cyclization reaction benzyl, *p*-chlorobenzyl and isopropyl *o*-carboxyphenyl sulfoxides (**1d**, **1e** and **1f**) were found to cyclize as readily as the Me isomer (**1a**).

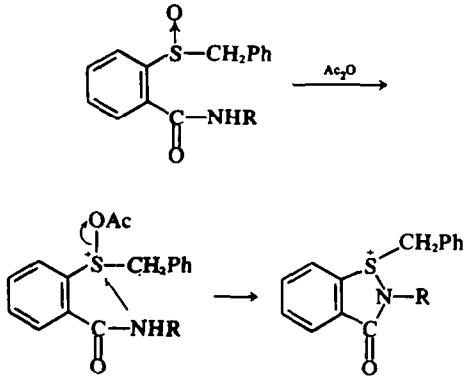
The apparent lack of the steric effect in this cyclization reaction may suggest that the initial acylation step is somewhat different from that of the normal Pummerer reaction.

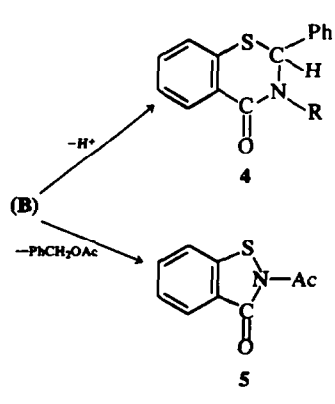
The most likely mechanism for the cyclization seems to involve the formation of an incipient 5-membered cyclic acyloxysulfonium salt (**A**), followed by proton removal and subsequent 1,2-shift of carboxyl group from the S atom to the C atom to afford the cyclized product (**2**). (Scheme 1)

In the reaction of benzyl *o*-carbamoylphenyl sulfoxide (**3**), the cyclization proceeds presumably through a prior formation of a 5-membered cyclic aminosulfonium salt (**B**), followed by either the



SCHEME 1.





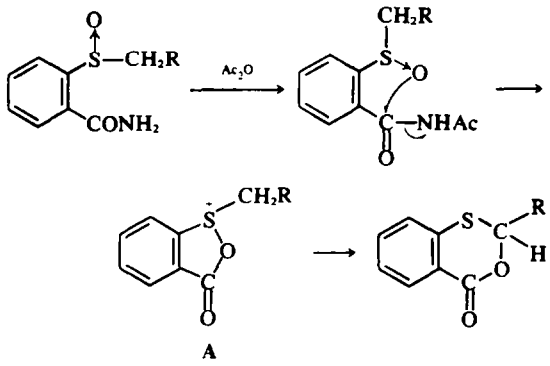
SCHEME 2.

attack of acetate anion at benzylic carbon to afford 1,2 - benzoisothiazolin - 3 - one (**5**) and benzyl acetate or the abstraction of α-proton of intermediate (**B**) and the subsequent 1,2-shift of amino nitrogen from the S atom to the C atom to afford dihydrobenzothiazine derivative (**4**). (Scheme 2)

The difference in the reactivities of benzyl *o*-carbamoylphenyl sulfoxide (**3**) are assumed to be dependent on the stabilities of intermediate (**B**), since N-acetyl benzoisothiazoline derivative is more stable than the N-Me or the N-Ph isomer, and hence the attack of acetate anion at benzylic carbon of N-acetyl intermediate **B** would be more facile than that of N-Me or N-Ph intermediate **B**.

Whereas the cyclization of *o*-carbamoylphenyl methyl (or ethyl) sulfoxide (**6**) would take place by the initial acetylation of amide nitrogen, followed by the attack of sulfinyl O atom at carbonyl C atom of *ortho* acetylcarbamoyl function to give a 5-membered cyclic acyloxysulfonium salt (**A**), which then undergoes an intramolecular Pummerer rearrangement to afford benzoxathiane derivative (**2**). (Scheme 3)

This interpretation would be conceivable in view of the following observations; namely, the sulfinyl O atom of the methyl sulfoxide (**6**) is more basic than that of benzyl sulfoxide (**3**), and the intramolecular nucleophilic attack of sulfinyl oxygen at carbonyl carbon of *o*-acetylcarbamoylphenyl



SCHEME 3.

methyl sulfoxide derived from the acetylation of *o*-carbamoylphenyl methyl sulfoxide (**6a**) is more facile than that of methyl *o*-methylcarbamoylphenyl sulfoxide.

EXPERIMENTAL

Materials

o-Carboxyphenyl sulfide was synthesized from the alkylation of thiosalicyclic acid with alkyl halide in aqueous EtOH in the presence of NaOH. The following R–S–C_6H_4COOH-*o* were prepared. (R and m.p. °C); Me, 169–170 (lit[8] 168–169); Et, 134–135 (lit[9] 130–131); n-Pr, 121–122 (lit[10] 121); i-Pr, 114–115 (lit[11] 116–117); CH_2Ph, 186–187 (lit[12] 189); *p*-Cl–$C_6H_4CH_2$, 218–219 (lit[13] 222).

Table 1. M.ps and analytical data of sulfoxides, R–S(O)–C_6H_4–R′-*o*

R	R′	m.p. (°C)	Anal. % C	Found (Calcd) H	N
Me	COOH	175 (dec)	(lit[8] 175 (dec))		
Et	COOH	155 (dec)	54·16 (54·53)	4·89 (5·08)	
n-Pr	COOH	154 (dec)	55·94 (56·58)	5·50 (5·70)	
i-Pr	COOH	144 (dec)	56·68 (56·58)	5·71 (5·70)	
$PhCH_2$	COOH	170 (dec)	64·74 (64·60)	4·39 (4·65)	
p-Cl–$C_6H_4CH_2$	COOH	175 (dec)	56·62 (57·05)	3·46 (3·76)	
Me	$CONH_2$	188 (dec)	52·22 (52·44)	4·59 (4·95)	7·75 (7·64)
Me	$CONHCH_3$	157 (dec)	54·19 (54·80)	5·26 (5·62)	7·15 (7·10)
Et	$CONH_2$	160 (dec)	54·69 (54·80)	5·36 (5·62)	6·68 (7·10)
$PhCH_2$	$CONH_2$	171 (dec)	64·36 (64·84)	4·97 (5·05)	5·43 (5·40)
$PhCH_2$	$CONHCH_3$	163 (dec)	65·54 (65·91)	5·49 (5·53)	5·05 (5·12)
$PhCH_2$	CONHPh	186 (dec)	70·82 (71·62)	4·85 (5·11)	4·55 (4·18)

Table 2. Yield, m.p. and IR data of **2**

R	R′	Yield (%)	m.p. (°C) b.p. (°C/mmHg)	IR(CCl_4) ν_{CO} (cm^{-1})
H	H	97	45–47 (lit[19] 47–47·5)	1743
H	CH_3	95	55–56 (lit[20] 57)	1742
H	C_2H_5	93	35–36[a]	1742
H	Ph	98	90–91 (lit[21] 83–84)	1743
H	*p*-Cl–C_6H_4	99	115·5–116·5 (lit[22] 116–117)	1744
CH_3	CH_3	95	105–107/0·5[b]	1739

[a] Found: C, 61·46; H, 5·09%. Calcd for $C_{10}H_{10}O_2S$: C, 61·83; H, 5·19%.
[b] Found: C, 61·22, H, 4·76%. Calcd for $C_{10}H_{10}O_2S$: C, 61·83; H, 5·19%.

o-Carbamoylphenyl sulfide was synthesized from the reaction of the corresponding acid chloride with an amine. The following R–S–C_6H_4CONHR'-*o* were prepared. (R, R' and m.p.); Me, H, 148–149 (lit[14] 149–150); Me, Me, 142–143 (lit[15] 140); Et, H, 130–131 (lit[16] 131–132); $PhCH_2$, H, 150–151 (lit[17] 152–153); $PhCH_2$, CH_3, 135–136.

o-Carboxyphenyl sulfoxide was synthesized by the oxidation of the corresponding sulfide with bromine-pyridine complex in aqueous pyridine soln according to our previously reported method.[18] The sulfoxides obtained were recrystallized from acetonitrile, EtOAc or alcohol. M.ps and analytical data are summarized in Table 1.

o-Carbamoylphenyl sulfoxide was synthesized by the oxidation of the corresponding sulfide with $NaIO_4$ in aqueous EtOH or bromine-pyridine complex in aqueous pyridine. The sulfoxides obtained were recrystallized from acetonitrile or EtOAc. M.ps and analytical data are summarized in Table 1.

o-Carboxyphenyl trideuterated methyl sulfoxide was synthesized by the H–D exchange reaction of *o*-carboxyphenyl methyl sulfoxide in NaOD–D_2O soln by heating under reflux (2 h). The sulfoxide obtained was nearly completely (> 95%) labeled with deuterium, since no Me signal in NMR measurement was observed.

o-Carbomethoxyphenyl methyl sulfoxide was prepared by the ester exchange reaction of *o*-carboxyphenyl methyl sulfoxide and EtOAc. The sulfoxide, colorless oil, obtained was confirmed by the NMR and IR measurement.

Acetic anhydride, obtained commercially, was treated with anhyd NaOAc. After refluxing for several h, it was distilled. b.p. 139·5–140°.

General procedure for the reaction of sulfoxide with acetic anhydride. Sulfoxide was treated with a large excess of Ac_2O at 100–130° for 1–3 h until any spot of the starting sulfoxide in TLC disappeared. An excess Ac_2O and any volatile product were evaporated at reduced pressure, and then products obtained were isolated by column chromatography (silica gel, benzene as eluent).

o-Carboxyphenyl sulfoxides (**1**). Alkyl *o*-carboxyphenyl sulfoxides (2 mmole) were heated with a large excess of Ac_2O (*ca* 20 ml) at 100° for 1–2 h. After removing excess Ac_2O and any volatile product *in vacuo*, the remaining residue was purified by column chromatography, and then 2-substituted 3,1 - benzoxathian - 4 - one was obtained, yield, m.p. and IR data are listed in Table 2.

Benzyl o-carbamoylphenyl sulfoxide (**3c**). Ac_2O (60 ml) containing benzyl *o*-carbamoylphenyl sulfoxide (2·59 g) was heated at 130° for 3 h, and then the product obtained was chromatographed through silica gel column to obtain an equimolar mixture (2·1 g) at first elution and then 2-acetyl 1,2 - benzoisothiazolin - 3 - one (0·8 g). The mixture was separated by developing on silica gel TLC for 3 days with n-hexane–benzene (10:1 v/v) as the eluent. Thus 2-acetyl 1,2 - benzoisothiazolin - 3 - one (1·80 g) and benzyl acetate (0·9 g) were obtained, and the former was recrystallized from EtOAc. m.p. 138–140° (lit[23] 139°).

Benzyl o-phenylcarbamoylphenyl sulfoxide (**3a**). The title sulfoxide (300 mg) was heated with 10 ml Ac_2O at 130° for 3 h. After the usual work-up 2,3-diphenyl 2,3 - dihydro - 1,3 - benzothiazin - 4 - one (230 mg) was obtained and recrystallized from EtOAc-hexane. m.p. 137–139° (lit[24] 138–140°).

Benzyl o-methylcarbamoylphenyl sulfoxide (**3b**). The title sulfoxide (310 mg) was heated with 20 ml of Ac_2O at 130° for 3 h, and 2-phenyl 3-methyl 2,3 - dihydro - 1,3 - benzothiazin - 4 - one (220 mg) was obtained. m.p. 79–81° (lit[25] 81·5°).

o-Carbamoylphenyl methyl sulfoxide (**6a**). (i) *o*-Carbamoylphenyl methyl sulfoxide (400 mg) was heated with 10 ml Ac_2O at 100° for 5 h, and then an excess Ac_2O was evaporated at reduced pressure, followed by chromatography through silica gel column to give 3,1 - benzoxathian - 4 - one (160 mg) at the first elution and then acetoxymethyl *o*-acetylcarbamoylphenyl sulfide (270 mg), m.p. 106–108°, at the second elution.

(ii) The sulfoxide (260 mg) was heated with 10 ml Ac_2O at 140° for 2 h. 3,1 - Benzoxathian - 4 - one (44 mg) and acetoxymethyl *o*-acetylcarbamoylphenyl sulfide (196 mg) were obtained.

o-Carbamoylphenyl ethyl sulfoxide (**6b**). *o*-Carbamoylphenyl ethyl sulfoxide (300 mg) was heated with 15 ml of Ac_2O at 130° for 3 h. After the usual work-up 2-methyl 3,1 - benzoxathian - 4 - one (80 mg) was obtained, but several other products could not be identified.

Methyl o-methylcarbamoylphenyl sulfoxide. Ac_2O (10 ml) containing methyl *o*-methylcarbamoylphenyl sulfoxide (200 mg) was heated at 120° for 3 h. The product obtained was separated through silica gel column to give acetoxymethyl *o*-methylcarbamoylphenyl sulfide (130 mg), m.p. 113–115°, and acetoxymethyl o-acetylmethylcarbamoylphenyl sulfide (140 mg), colorless oil.

o-Carbomethoxyphenyl methyl sulfoxide. The sulfoxide (300 mg) was heated with Ac_2O (10 ml) at 120° for 3 h. The product obtained was chromatographed through a silica gel column to give acetoxymethyl *o*-carbomethoxyphenyl sulfide (100 mg), colorless oil, at the first elution and then the starting sulfoxide (200 mg).

o-Carboxyphenyl trideuterated methyl sulfoxide. The title sulfoxide (200 mg) was heated with Ac_2O (10 ml) containing 1 ml AcOH at 100° for 1 h. After the usual work-up 2,2 - dideuterated 3,1 - benzoxathian - 4 - one (190 mg) obtained was nearly completely labeled (> 95%) with deuterium from the observation of the NMR measurement.

Reaction of o-carboxyphenyl sulfoxide with acetyl chloride. An acetyl chloride soln containing any one of the sulfoxides (*ca* 300 mg) was kept at room temp and the reduction was found to proceed with evolution of Cl_2 gas. After an excess acetyl chloride and any volatile product were evaporated at reduced pressure, the corresponding sulfides were obtained nearly quantitatively and identified by comparing the physical properties with those of the authentic samples.

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