REACTIONS OF 4-ACETOXY-2H-1,4-BENZTHIAZIN-3(4H)-ONE

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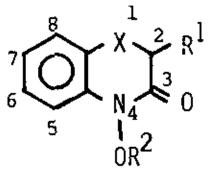
Abstract — 4-Acetoxy-2H-1,4-benzthiazin-3(4H)-one (5), a unique arylhydroxamic acid derivative, reacted with some nucleophiles. The position 2 of compound 5 is the center of high reactivity, and even benzene reacted with 5 nucleophilically at the position.

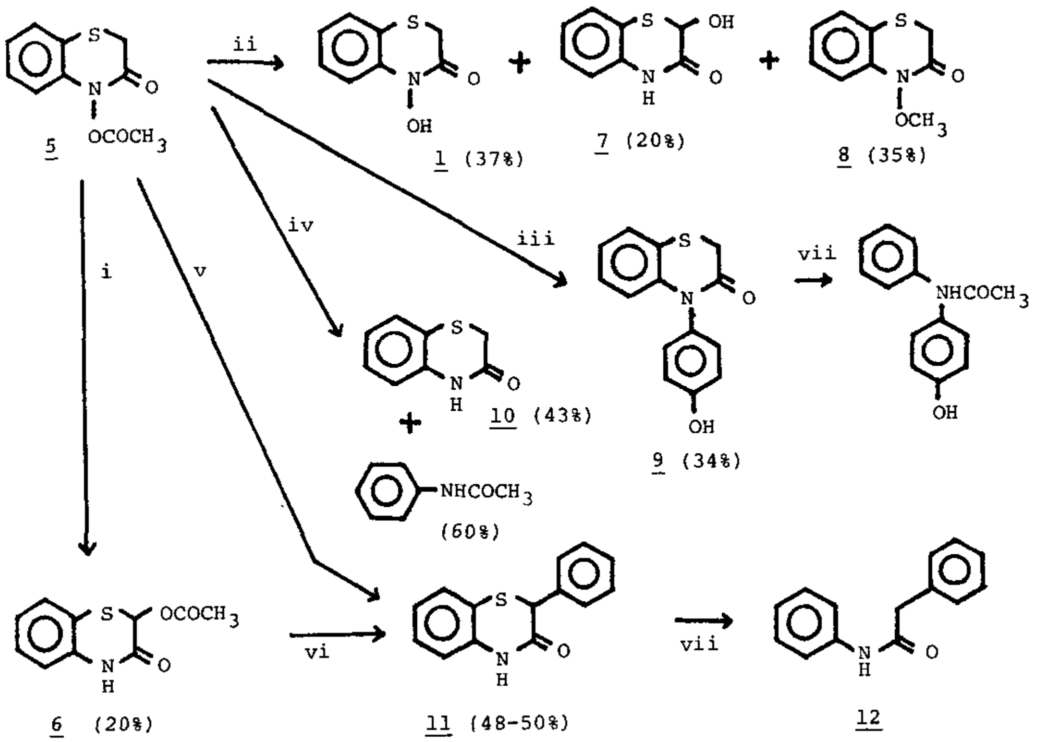
4-Hydroxy-2H-1,4-benzthiazin-3(4H)-one (1) is structurally related to 4-hydroxy-2H-1,4-benzoxazin-3(4H)-one (2), which is a model compound of a naturally occurring prohibitin, 2,4-dihydroxy-2H-1,4-benzoxazin-3(4H)-one (3).1) The reactions of 2 and its O-acetyl derivative (4) with chloride or acetate as nucleophiles have been reported.2,3) The reaction sites of 2 and 4 with these nucleophiles are mainly the position 5, 6 and 7 of the benzene ring moiety. Such carbon nucleophiles as phenol, cresol and aniline do not react with 2 or 4: for the heterolytic reactions with these nucleophiles, an electron donating group such as a methoxy group at the position 7 is required.4) In this paper, we report the reactions of 5 with some nucleophiles which are summarized in Scheme I.



	X	R^1	R^2
1:	S	H	H
2:	O	H	H
3:	O	OH	H
4:	O	H	COCH$_3$
5:	S	H	COCH$_3$

A reaction of 5 with acetate (reflux in acetic acid; reaction i in Scheme I) is the rearrangement of the 4-acetoxy group to the position 2, which gives 2-acetate (6), as reported by Coutts and Pound.5) The nucleophilic reaction at the position 2 of compound 5 seems to be an acid catalyzed reaction. In fact, when 5 was treated with methanol (reflux in MeOH for 20 hr), no detectable reaction occurred. However, a reaction of 5 in methanol containing CF$_3$COOH gave three major products, 1, 7 and 8 (reaction ii in Scheme I). Compounds 1 and 7 might be obtained by hydrolysis of the corresponding acetoxy or trifluoroacetoxy derivatives. Compound 8 is the product which can be obtained by the nucleo-

Scheme I



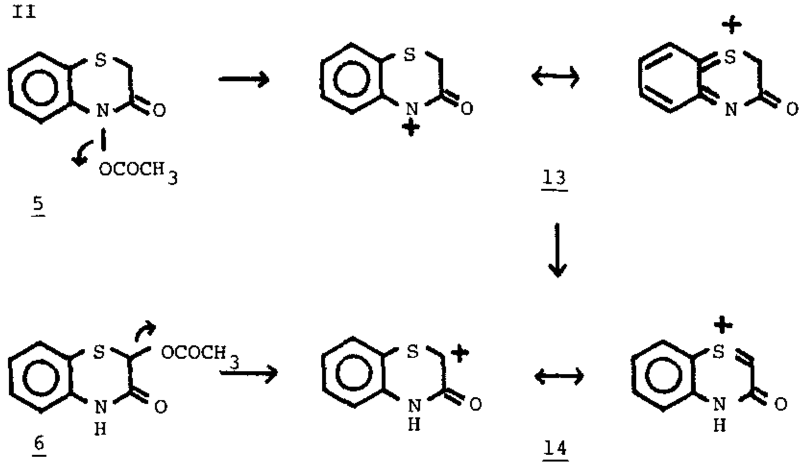
i: CH_3COOH, reflux. ii: $MeOH/CF_3COOH$, reflux. iii: Phenol/CF_3COOH, reflux. iv: Aniline/CF_3COOH, reflux. v and vi: Benzene/CF_3COOH, reflux. vii: Raney nickel. (All compounds shown in this scheme were correctly analyzed. The structures of the compounds were deduced from their ^{1}H-NMR, IR, mass spectroscopy, UV and elemental analysis.)

philic attack of methanol on 5, concerted with the heterolysis of the N-O bond.

Reactions of 5 with phenol (reaction iii in Scheme I) showed an enhanced reactivity of the compound compared with compound 4. While 4 did not react with phenol under a similar condition, 5 reacted with phenol at the position 4 (the nitrogen atom) to yield compound 9, whose structure was determined by conversion of 9 to *N-acetyl-4-hydroxydiphenylamine* as shown in the scheme. Aniline nucleophilically attacked the carbonyl carbon of the 4-acetoxy group of 5 to yield 10 and acetoanilide (reaction iv in Scheme I).

The most interesting reaction of 5 was found in the reaction with benzene

Scheme II



which is catalyzed by CF_3COOH (reaction v in Scheme I). Even benzene (a very weak nucleophile) reacted with 5 at the position 2 to give 11 in yield of 48%. The compound was desulfurized with Raney nickel to a derivative, 12, for identification. 2-Acetoxy derivative (6) also yielded compound 11 by reaction with benzene in the presence of CF_3COOH in yield of 50% (reaction vi in Scheme I). Reactions ii, v and vi in Scheme I showed an unexpectedly high reactivity at the position 2 of 5.

The reaction mechanism was considered to be as shown in Scheme II. Reactions of nucleophiles at the position 4 was explained by the formation of a cation, 13, by the heterolytic cleavage of N-O bond of 5, though S_N2-like mechanism could not be excluded completely. For the reaction with the weak nucleophile such as benzene which yields 2-substituted benzthiazinone, we considered a participation of a cation, 14. The cation, 14, was formed from cation 13 by tautomerization. The reactivity of cation 13 is not high enough to react with the weak nucleophile, benzene: only the strong nucleophile such as phenol and methoxide could trap the cation, 13. On the other hand, reactivity of cation 14 is so high that even benzene could react with the cation to give 11.

The enhanced reactivity of 5 compared with 4 (the facile heterolytic cleavage of the N-O bond) could be explained by the higher polarizability$^{6)}$ of the sulfur atom of 5 than the oxygen atom at the position 1 of 4, rather than the difference of the electron donating effects between sulfur and oxygen. The reaction mechanism for the formation of 2-substituted benzthiazinone may be strongly suggested by the reaction of 6 with benzene: the cation, 14, must participate in the reaction with benzene. The high reactivity of the position 2 of cation 14 would be rationallized by the smaller contribution of the sulfur atom to stabilize the neighbouring carbocation than that of an oxygen atom. The 3-carbonyl group also activates cation 14: the carbocation at the position 2 is so reactive that benzene can react at the position.

In conclusion, benzthiazinone (5) possesses a much higher reactivity than a structurally related benzoxazinone (4). The replacement of the oxygen at the position 1 with a sulfur atom caused a change of the high reactivity sites.

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