Tetrahedron Letters No. 18, pp 1611 - 1614.
0040-4039/79/0429-1611$02.00/0

REACTIONS OF 4-ACETOXY-2H-1,4-BENZOXAZIN-3-ONES WITH SOME NUCLEOPHILES

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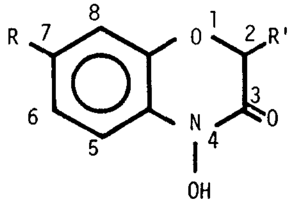
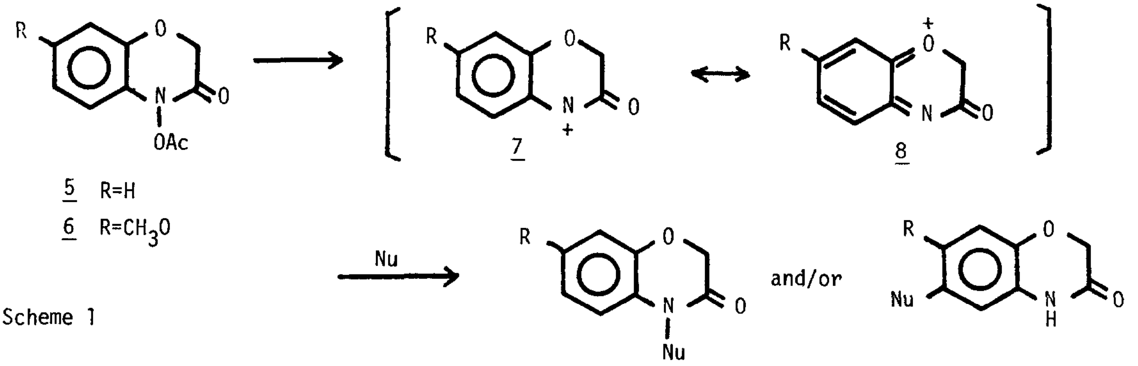
Summary O-Acetates of 4-hydroxy and 4-hydroxy-7-methoxy-2H-1,4-benzoxazin-3-ones reacted with nucleophiles such as phenols, indoles and ethanethiol The major reaction center is the positively-charged nitrogen atom In the reaction with 2-methylindole, 6-position of the benzoxazinone ring is another major reaction center

Several novel reactions of O-acetates of 4-hydroxy-2H-1,4-benzoxazin-3-one (1) and 4-hydroxy-7-methoxy-2H-1,4-benzoxazin-3-one (2) with some nucleophiles are presented in this paper These compounds were selected as model compounds of 2,4-dihydroxy-2H-1,4-benzoxazin-3-one (3) and 2,4-dihydroxy-7-methoxy-2H-1,4-benzoxazin-3-one (4) which are known as prohibitins contained in cereal plants such as maize and wheat,[1] and recently found to be mutagenic to bacteria by us [2] In order to obtain a chemical basis for understanding of the biological activities, we have investigated the reactions of 4-acetoxybenzoxazinones especially with



	R	R'
1	H	H
2	CH_3O	H
3	H	OH
4	CH_3O	OH

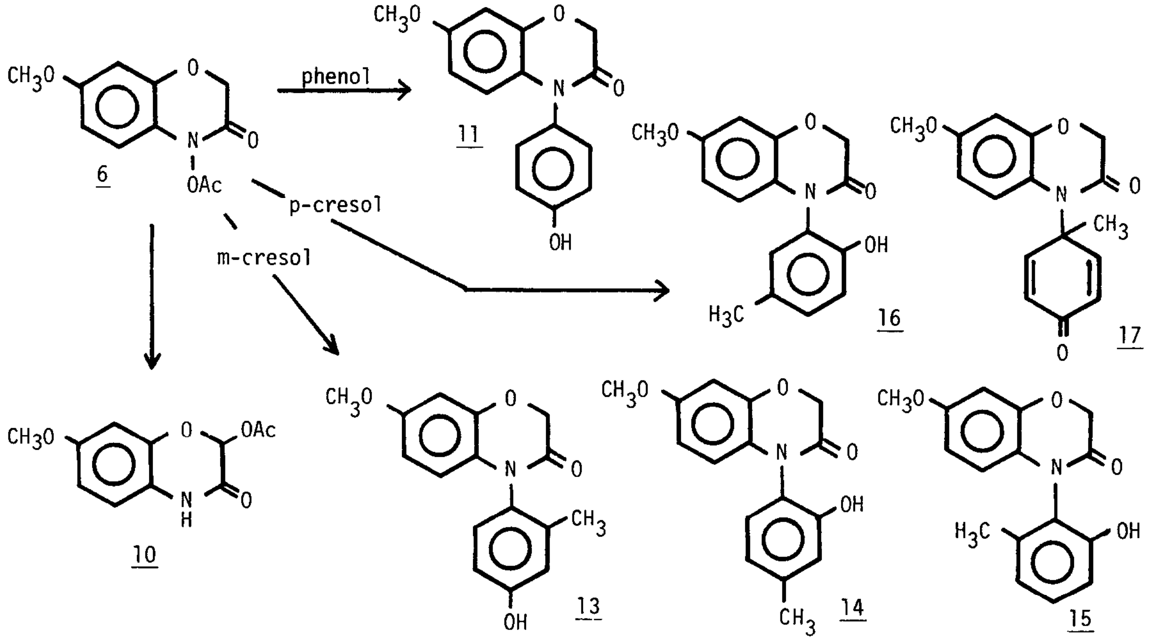


5 R=H
6 R=CH_3O

Scheme 1

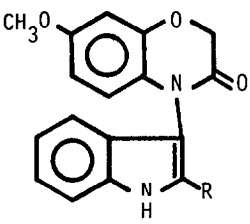
a few typical nucleophiles such as phenol, indole, and thiol, as expressed in scheme 1. A current concept in the chemical carcinogenesis study shows that O-esterification of arylhydroxamic acid is an important activation step in the heterolytic cleavage of N-O bond.[3] In fact, while the compounds 1 and 2 did not react with nucleophiles under mild conditions, 4-acetoxybenzoxazin-3-one (5) has been reported to rearrange to 6-acetoxybenzoxazin-3-one.[4] The reaction of 5 with phenol yielded 4-(p-hydroxyphenyl)-2H-1,4-benzoxazin-3-one (9) which is formed by substitution on the nitrogen atom by phenol in 5% yield only upon heating at 50°. Introduction of 7-methoxy group facilitates the reactions of nucleophiles on the positive nitrogen atom. In fact, the reactivity of 6 is so high that 6 could not be isolated in a crystalline state, and the decomposition at room temperature gave 2-acetoxy compound (10, 27%) and tar.[5]

The reaction of 6 with phenol rapidly proceeded in methylene chloride, and the major product was para-substituted phenol (11) in 33% yield accompanied with 2H-1,4-benzoxazin-3-one (12, 5%).[6] The structure of 11 was deduced from nmr [A_2B_2 signals of para-substituted phenol (at $\delta(CDCl_3)$ 7.08 and 6.82), the presence of all the hydrogens of the benzoxazinone ring, and the absence of the NH hydrogen]. Ortho-substituted phenol could not be isolated. However, the reaction with m-cresol in methylene chloride gave three isomeric products, 13 (19%), 14 (19%), and 15 (7%). These structures were analysed by nmr and comparison of uv spectra with 9. p-Cresol also reacted



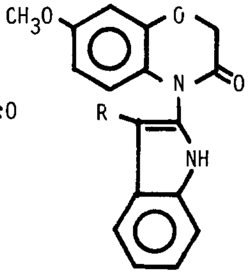
with 6 in methylene chloride giving 16 (18%) When the same reaction was conducted in tetrahydrofurane or benzene, the major product was cyclohexadienone derivative (17) isolated in yields of 18% (in THF) and 40% (in benzene). The structure of dienone, 17, was supported by nmr (olefinic hydrogens at δ($CDCl_3$) 6.68 and 6.24, and three aromatic hydrogens), ir (carbonyl absorbtion bands at 1665, 1675 and 1685 cm^{-1}, and the absence of NH nor OH absorbtion) The attack of the nitrogen atom on the ipso carbon atom of the p-cresol gives the structure

Reactions with indoles which are other nucleophiles of interest were studied The acetate, 6, reacted with indole in methylene chloride at 0° The major product was 3-substituted indole (18, 21%) whose structure was deduced from nmr (the absence of hydrogen at 3-position of indole and complete assignment of all the hydrogens on the benzoxazinone ring) The minor product was 2-substituted indole (19, 3%), whose structure was deduced from nmr (the hydrogen at 3-position was found at 6.42 ppm as a singlet) In the reaction of 3-methylindole, the 2-position of indole is the nucleophilic center, and the product 20 was isolated in only 5% yield, but an anticipated indoline derivative could not be found. The reaction of 6 with 2-methylindole in methylene chloride gave a compound 21 (36%), which showed a rather different spectroscopic character Nmr suggested the presence of NH and two singlet aromatic hydrogens and the compound showed a characteristic uv absorbtion (227 and 264 nm). The suggested structure 21 was finally confirmed by X-ray analysis 9) The indole nucleophile attacked the 6-position This is the same position as the acetoxy migration of 5. 4) Interestingly, the reaction in benzene gave 22 (24%), in addition to 21 (46%) The spectroscopic data of 22 is very close to 18



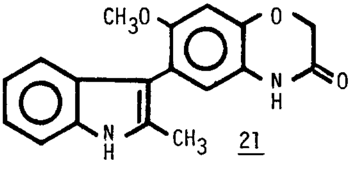
18 R=H

22 R=CH_3

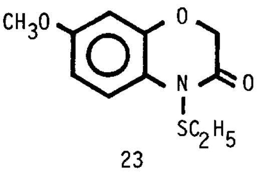


19 R=H

20 R=CH_3



21



23

Ethanethiol, another powerful nucleophile was also found to react with 6 rapidly at room temperature to give 23 (20%). Since all the hydrogens on the benzoxazinone ring were assigned by nmr while there was no ir absorbtion of NH band, the structure shown for 23 is plausible. The decomposition of 23 gave benzoxazinone (12).

In summary, the nitrogen atom is a major reaction center attacked by phenols, indoles, and ethanethiol. The presence of 7-methoxy group enhanced this reactivity. This is in accord with the heterolysis of N-O bond forming a species or transition state with positively-charged nitrogen (7) Nucleophiles attack 7 giving most of the products The probable related reactions are found in the reactions of phenylhydroxylamine with phenol,[10] and other aromatic compounds,[11,12] and of hydroxyaminofluorene with purine bases[13] The formation of 21 is interpreted by an attack of 2-methylindole on 8, a resonance tautomer of 7 [14] We beliebe that similar reactions may participate in the interactions of the prohibitins or mutagens with biological systems We are currently trying to prove this hypothesis Studies on solvent effects, reaction mechanisms, regioselectivity, influence of the hydroxy group at the 2-position, and synthetic application of the reaction are of chemical interest.

References and notes

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We reproduced this unusual reaction and proved the structures of the products by unambiguous synthesis Details will be published
5) 6 could be prepared by Schotten-Baumann acetylation of 2 in methylene chloride-sodium bicarbonate solution Methylene chloride solution could be concentrated to dryness at 0° The yield was about 80% The product yields in the reactions of 6 were calculated from the amount of 2 used in the preparation of 6
6) Every reaction of 6 with carbon nucleophiles appeared in this paper yielded 12 in 5-10% yield The formation of 12 may be interpreted by a participation of a triplet nitrenium ion,[7] electron transfer, or other mechanisms [8]
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(Received in Japan 24 January 1979)