REACTIONS OF 10-THIAISOALLOXAZINE WITH PRIMARY AND SECONDARY ALCOHOLS

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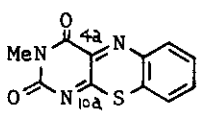
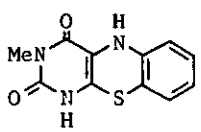
Abstract —— Reaction of 10-thiaisoalloxazine 1 with lower primary alcohols gives 4a,10a-diadducts 4 or 4a,10a-cyclic adducts 5 across the conjugated diimine moiety, whereas 1 oxidizes secondary alcohols in the neutral medium under irradiation with daylight to afford the corresponding carbonyl compounds.

Some years ago, an article from our laboratory described a preparative method for 10-thiaisoalloxazine 1 involving photochemical cyclization of 6-(2-azidophenylthio)uracil to dihydro-10-thiaisoalloxazine 2 followed by oxidation.[1] The present work was undertaken to examine an alteration in the reactivity of the conjugated diimine moiety of 1 by virtue of the replacement of the nitrogen (N-10) of isoalloxazine 3, a simple flavin model compound, by sulfur. The present results demonstrate that the reaction of 1 with lower primary alcohols



(1)



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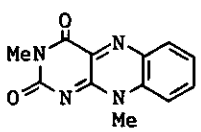

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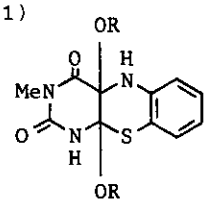
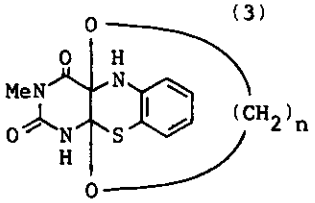


(4) a : R= Me
b : R= Et
c : R= n-Pr



(5) a : n= 2
b : n= 3
c : n= 4

gives 4a,10a-diadducts or 4a,10a-cyclic adducts across the conjugated diimine moiety, whereas 1 oxidizes secondary alcohols in the neutral medium under irradiation with daylight. These observations are a novel illustration of reactivities of the conjugated diimine bond in the isoalloxazine analogues.[2]

When 1 was dissolved in dry methanol at room temperature, a 1:2-adduct 4a was formed. Tlc analysis of the reaction mixture indicated the quantitative formation of 4a. The uv spectral change during the reaction showed two isosbestic points at 293 and 313 nm and the uv absorption of 4a was finally obtained. The planar structure of 4a was supported by microanalytical and spectral data[3] [^{1}H-NMR (DMSO-d_6, δ): 3.04 (3H, s, N-Me), 3.26 (3H, s, OMe), 3.47 (3H, s, OMe), 6.43-7.22 (4H, m, ArH), 7.13 (1H, br, NH), 9.25 (1H, br, NH); UV λ_{max}^{MeCN}nm(ϵ): 220 (2.5×10^4), 304 (4.0×10^3)]. Although the adduct 4a was stable in refluxing methanol, it reverted quantitatively to the starting material 1 upon heating at 150°C in a sealed tube without solvent.

Ethylene glycol also reacted with 1 at room temperature to give a novel cyclic adduct 5a. The uv spectrum of 5a [λ_{max}^{MeCN}nm(ϵ): 220 (2.5×10^4), 304 (4.0×10^3)] is superimposable on that of 4a.

Table 1 summerizes the result of adduct formation by the reaction of 1 with various primary alcohols. The reaction of 1 with primary alcohols such as n-propanol and butane-1,4-diol resulted in slow formation of the adduct only in low yields and recovered the starting material 1. The isoalloxazine 3 did not

Table 1. Reaction of 10-Thiaisoalloxazine 1 with Primary Alcohols[a]

Alcohol	Adduct	mp (°C)	Yield [b] (%)
MeOH	4a	135	95
EtOH	4b	140	85
n-PrOH	4c	129	20
$HO(CH_2)_2OH$	5a	221	90
$HO(CH_2)_3OH$	5b	232	35
$HO(CH_2)_4OH$	5c	-	trace

a A large excess amount of dry alcohols were employed. All reactions were carried out at 80°C for 4 h under an argon atmosphere. In the cases of diols, dry acetonitrile was used as solvent.

b Yields were estimated by hplc.

give any adducts under similar conditions, resulting in the recovery of 3. The reaction of 1 with secondary alcohols, however, did not give a detectable amount of the adduct and led to the reduction of 1. The uv spectrum of the solution of 1 in isopropanol gradually changed to show ultimately the absorption similar to that of the dihydro-10-thiaisoalloxazine 2 on standing at room temperature for a long period (about 3 days). On shielding from daylight, however, the reaction did not proceed. The formation of acetone in this reaction was proved by gas chromatography after its conversion into the corresponding pentafluorophenylhydrazone. Table 2 shows the yields of 2[4] and the corresponding carbonyl compounds obtained in the reactions of 1 with isopropanol, benzhydrol, and methyl mandelate.

Table 2. Reaction of 10-Thiaisoalloxazine 1 with Secondary Alcohols[a]

Alcohol	Dihydro-10-thiaisoalloxazine 2 Yield (%)[b]	Carbonyl compound Yield (%)[b,c]
i-PrOH	46	41
Ph-CHOH COOMe	78	60
Ph_2CHOH	85	89

a A large excess amount of dry alcohols were employed. Dry acetonitrile was used as solvent. All reactions were carried out in a pyrex flask at room temperature for 8 h under an argon atmosphere without shielding from daylight.
b Yields were estimated by hplc and gc.
c Yields based on 10-thiaisoalloxazine 1.

The reduction of 1 with the secondary alcohols, which occurs in place of addition to the conjugated diimine bond, is reasonably explained in terms of hydrogen abstraction from the low oxidation potential alcohols by an excited 1.[5] α-Oxy acid esters, α-ketols, and α-amino acids are oxidized by flavin and isoalloxazines in the presence of the base. These non-enzymatic observations accommodate that the initial step of the oxidation is the dissociation of the C-H bond adjacent to the carbonyl group followed by oxidation of the resulting carbanion.[2]

Oxidation of an intermediary carbanion, however, is not the sole mechanism available for the flavin-dependent oxidation. In particular, the substrates which have no structural elements for stabilization of the carbanionic species, as in the case of glucose oxidase, could be oxidized *via* alternate processes without the initial carbanion formation. Our observation in the oxidation of secondary alcohols by 1 in the neutral medium under mild conditions, although irradiation with daylight is requisite, provides a further example being suggestive of such an alternate process in the biological oxidation catalyzed by flavin.[6] Further studies for understanding the role of sulfur in 1 for the change of reactivity of the conjugated diimine and on the oxidation of other substrates by 1 are now in progress.

REFERENCES AND FOOTNOTES

1. T. Hiramitsu and Y. Maki, J. Chem. Soc. Chem. Commun., 1977, 557.
2. For recent reviews on the mechanisms of flavin-catalyzed redox reactions, see C. Walsh, Acc. Chem. Res., 1980, 13, 148; T. C. Bruice, ibid., 1980, 13, 256.
3. Satisfactory microanalytical and spectral data were obtained for all new compounds described here.
4. Contrary to dihydroisoalloxazine, the dihydro-10-thiaisoalloxazine 2 was fairly stable to autoxidation reverting to 10-thiaisoalloxazine 1 (half-life : ca. 6 h). Thus, quantitative analysis and isolation of 2 can be performed with ease.
5. Uv spectrum of 1 : $\lambda_{max}^{MeCN}(\epsilon)$: 226 ($2.0 \times 10^4$), 258 ($1.0 \times 10^4$), 283 ($1.5 \times 10^4$), 353 ($7.0 \times 10^3$), 450 ($5.0 \times 10^3$).
   Photoreduction of flavins in the presence of EDTA or mandelic acid has been well documented (cf. W. H. Walker, P. Hemmerich, and V. Massey, Eur. J. Biochem., 1970, 13, 258; D. L. Elliot and T. C. Bruice, J. Am. Chem. Soc., 1973, 95, 7901; P. F. Heelis, Chem. Soc. Rev., 1982, 11, 15).
6. After completion of this work, it has been communicated that cyclopentanol undergoes the autorecycling oxidation under neutral conditions at 120°C by 10-substituted pyrimido[5,4-g]pteridines, which have the same conjugated diimine moiety as that of flavins (cf. T. Nagamatsu, E. Matsumoto, and F. Yoneda, Chem. Lett., 1982, 1127).

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