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# NOVEL PROPELLANE TYPE ADDUCTS OF 3-METHYL-10-THIAISOALLOXAZINE

Yoshifumi MAKI,* Miyuki TANABE, Magoichi SAKO, Kosaku HIROTA, and Kazunobu HARANO†

Gifu College of Pharmacy, 6-1, Mitahora-Higashi 5 Chome, Gifu 502

†Faculty of Pharmaceutical Science, Kumamoto University, 5-1, Oe-Honmachi, Kumamoto 862

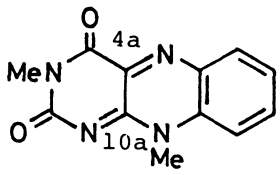
The reaction of 3-methyl-10-thiaisoalloxazine (2) with 1,2-ethanedithiol and 2-mercaptoethanol gave novel propellane type adducts 3a and 3b, respectively.

The use of flavin mimics such as isoalloxazines and deazaisoalloxazines[1] has been enlightening in the development of chemical insight in the flavin catalyzed redox reactions. In connection with the flavin redox chemistry, our special attention has been paid to the alternation of the reactivity of the conjugated diimine moiety by virtue of the chemical manipulation of the isoalloxazine ring.

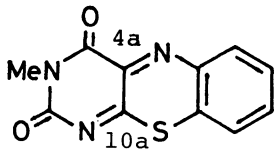
Along this line, our previous work[2] developed a photochemical preparative method of 3-methyl-10-thiaisoalloxazine (2) which possesses a sulfur atom in place of the N(10)-methyl group in 3,10-dimethylisoalloxazine (1).

The present paper describes that the reaction of 2 with 1,2-ethanedithiol or 2-mercaptoethanol produces a novel propellane type adduct 3a or 3b, which is apparently different from the behavior of the parent isoalloxazine (1).

The 10-thiaisoalloxazine (2)(1 mmol) was allowed to react with 1,2-ethanedithiol (10 mmol) in acetonitrile under nitrogen atmosphere at ambient temperature. The reaction was monitored by thin-layer chromatography and UV spectroscopy. After disappearence of 2, the reaction mixture was chromatographed over silica gel (solvent: chloroform) to give the propellane type adduct 3a, mp 270°C(decomp) in 60% yield. Microanalytical and spectral data supported



1



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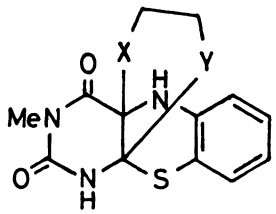

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Chart 1.

a: X= S, Y= S
b: X= O, Y= S
c: X= S, Y= O

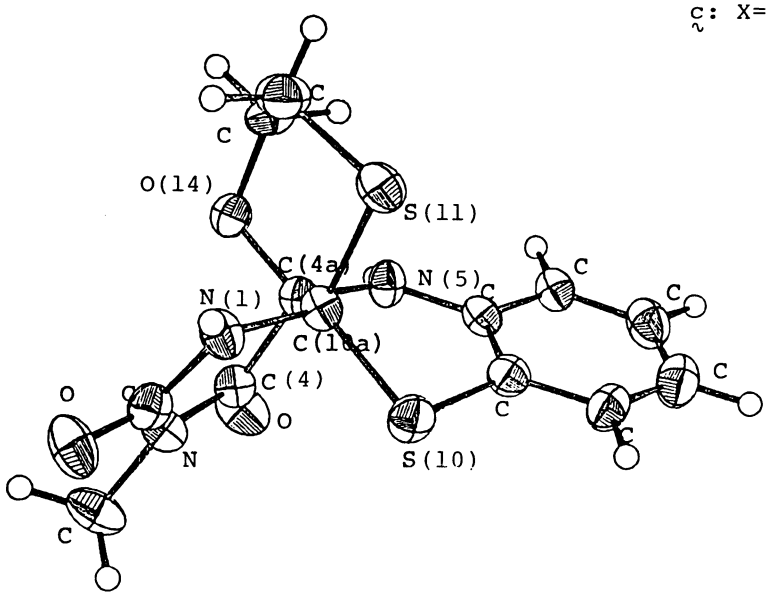


Fig. 1. ORTEP view of the propellane type adduct 3b.

the structure of 3a.[3] The propellane type adduct 3a was stable upon heating under reflux in acetonitrile for 3 h, whereas the pyrolysis of 3a at 250°C resulted in the conversion into 2 quantitatively.

Analogously, the reaction of 2 with 2-mercaptoethanol in acetonitrile gave a crystalline propellane type adduct 3b, mp 170°C(decomp), in 60% yield. The structure of the adduct 3b[3] was established by X-ray crystallographic analysis (see Fig. 1). Thus the alternative structure 3c was eliminated unambiguously.

Crystal data: $C_{13}H_{13}N_3O_3S_2$, monoclinic, space group $P2_1/a$, $a$=19.899(14), $b$=13.336(7), $c$=13.491(11) Å, $\beta$=157.01(3)°, $U$=1398.5 Å$^3$, $Dm$=1.508, $Dc$=1.535 g cm$^{-1}$ $z$=4. The data were obtained from an automatic, graphite-monochromated four-

circle diffractometer, using Mo-$K_\alpha$ radiation ($\lambda$=0.7107 Å). Of 1741 independent refractions, 1360 were treated as observed ($I$ 2.3 ($I$)). The crystal structure was solved by the direct method using the MULTAN series of programs[4] and refined by block-diagonal least squares to R=0.047.

Bond distances and angles relating to the $C_{4a}$- and $C_{10a}$-positions in the adduct 3b are listed in Table 1.

| Bond distances (Å) | | Bond angles (°) | | | |
|---|---|---|---|---|---|
| C(4a)-C(4) | 1.548(16) | C(4)-C(4a)-C(10a) | 110.26(89) | N(1)-C(10a)-C(4a) | 108.63(88) |
| C(4a)-N(5) | 1.422(14) | C(4)-C(4a)-N(5) | 111.86(90) | N(1)-C(10a)-S(10) | 107.32(74) |
| C(4a)-O(14) | 1.417(13) | C(4)-C(4a)-O(14) | 100.00(83) | N(1)-C(10a)-S(11) | 109.42(75) |
| C(4a)-C(10a) | 1.513(15) | C(10a)-C(4a)-O(14) | 112.09(87) | C(4a)-C(10a)-S(10) | 109.93(75) |
| C(10a)-N(1) | 1.447(14) | N(5)-C(4a)-C(10a) | 112.18(90) | S(11)-C(10a)-C(4a) | 112.02(76) |
| C(10a)-S(10) | 1.810(11) | N(5)-C(4a)-O(14) | 109.87(87) | S(11)-C(10a)-S(10) | 109.41(58) |
| C(10a)-S(11) | 1.807(11) | | | | |

Table 1. Bond distances and angles of the adduct 3b with their estimated standard deviations in brackets

The formation of 3b points that the initial addition site in the conjugated diimine moiety ($-N_1=C_{10a}-C_{4a}=N_5-$) of 2 is the 10a-position rather than the 4a-position, since the thiol group in the 2-mercaptoethanol is more nucleophilic than the hydroxy group. In fact, the reaction of 2 with methanol led to the formation of 4a,10a-diadduct quantitatively. However, treatment of 2 with 30% methylmercaptan in methanol gave exclusively 4a,10a-methylmercaptan diadduct.

Under analogous conditions, the isoalloxazine (1) was inert in the reaction with 1,2-ethanedithiol and 2-mercaptoethanol. In non-enzymatic reductions of flavins and analogues by thiol, however, strong kinetic evidence exists for an intermediacy of the thiol addition product across the azomethine bond ($-C_{4a}=N_5-$ of the isoalloxazine ring.[5-9]

As shown by the present experiments, the sulfur in 2 affects significantly on the reactivity of the conjugated diimine moiety, which involves the increased susceptibility to the nucleophilic addition and the alternation of the initial reaction site (4a→10a).

The present result provides a novel example in the reaction of the conju-

gated diimine bond and also has interesting mechanistic implication in connection with reduction of flavins by thiols.

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2) T. Hiramitsu and Y. Maki, J. Chem. Soc., Chem. Commun., 1977, 577.

3) The spectral data of 3a : IR(KBr)$cm^{-1}$; 3270(NH), 1720(C=O), 1675(C=O). UV (MeCN)nm(ε); 305(1.4x$10^3$), 213(4.5x$10^4$). NMR(DMSO-$d_6$) δ; 3.02(3H,s,N-Me), 2.80-3.70(4H,m,-$CH_2CH_2$-), 6.50-7.20(4H,m,ArH), 7.50(1H,br,NH), 9.78(1H,br, NH). The spectral data of 3b : IR(KBr)$cm^{-1}$; 3280(NH), 1725(C=O), 1670( C=O). UV(MeCN)nm(ε); 298(2.3x$10^3$), 218(3.1x$10^4$). NMR(DMSO-$d_6$)δ; 3.10(3H, s,NMe), 2.80-3.15(2H,m,-$CH_2$-), 3.80-4.50(2H,m,-$CH_2$-), 6.50-7.30(4H,m,ArH), 7.50(1H,br,NH), 9.78(1H,br,NH).

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