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Reactions of 6-(*N*-Methylanilino)-5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-dione with Benzyl Hydrosulfide and Benzylamine

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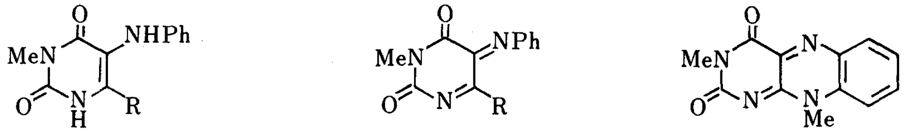
Treatment of 6-(*N*-methylanilino)-5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-dione (**2a**) with benzyl hydrosulfide or benzylamine under mild conditions without any catalyst resulted in the concurrent occurrence of a redox reaction and nucleophilic substitution at the C(6)-position of **2a** to give 5-anilino-6-(*N*-methylanilino)uracil (**1a**), 6-substituted 5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-diones (**2b**, **c**), and the oxidation product (dibenzyl disulfide or *N*-benzylidenebenzylamine). The substitution products **2b**, **c** also oxidized benzyl hydrosulfide and benzylamine under the same conditions.

Keywords——6-substituted 5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-dione; benzyl hydrosulfide; benzylamine; redox reaction; nucleophilic substitution; 6-substituted 5-anilinouracil

Recently, much attention has been paid to the chemical properties of the conjugated diimine bond (–N=C–C=N–) from both chemical and biochemical viewpoints. The cisoid type of this moiety has been shown to undergo the Diels–Alder type reaction as a diene component.[1] On the other hand, the oxidized form of flavin contains the transoid diimine moiety which plays a significant role in various biological oxidations.[2]

Our recent work[3] has demonstrated that oxidation of 5-anilino-6-(*N*-methylanilino)-uracils (*cf.* **1a**) affords 6-(*N*-methylanilino)-5-(*N*-phenylimino)pyrimidine-2,4-(3*H*,5*H*)-diones (*cf.* **2a**), possessing a transoid conjugated diimine moiety in the molecule, in high yields. The reactivity of **2a** toward substrates such as thiol and amino compounds is particularly intriguing, since **2a** can be regarded as a ring-opened analogue of 3,10-dimethylisoalloxazine (**3**) which is a simple flavin model compound.



1 **2** **3**

1
a: R=–NMePh(*p*-Br)
b: R=–SCH$_2$Ph
c: R=–NHCH$_2$Ph

2
a: R=–NMePh(*p*-Br)
b: R=–SCH$_2$Ph
c: R=–NHCH$_2$Ph

Chart 1

In this paper, we describe the oxidation of benzyl hydrosulfide and benzylamine by **2a**, which proceeds smoothly even under mild conditions without any catalyst. The oxidation, however, competes with nucleophilic substitution at the C(6)-position of **2a** by these substrates leading to 6-substituted 5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-diones **2b**, **c**. The substitution products **2b**, **c** also oxidize these substrates under the same conditions. The present results suggest that the conjugated diimine bond of **2a** is susceptible to nucleophilic addition and also possesses the capacity to oxidize thiol and amino compounds without any base catalyst.

A mixture of **2a** and an excess amount of benzyl hydrosulfide in acetonitrile was stirred overnight at room temperature under an argon atmosphere. Evaporation of the solvent and column chromatography of the residual oil gave **1a**, 5-anilino-6-benzylthio-3-methyluracil (**1b**), and 6-benzylthio-3-methyl-5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-dione (**2b**) in 22%, 25%, and 40% yields, respectively, together with *N*-methyl-*p*-bromoaniline (51%). The formation of a significant amount of dibenzyl disulfide in this reaction was proved by gas chromatographic (GC) analysis of the reaction mixture. When the reaction was carried out in the absence of **2a**, no formation of dibenzyl disulfide was observed. The reduced product **1a** was identical with an authentic sample. The structures of the products **1b** and **2b** were confirmed by their microanalytical results and spectral data (see the experimental section) and by oxidation of **1b** with 2,3-dichloro-5,6-dicyanobenzoquinone to give **2b**.

Treatment of the product **2b** with benzyl hydrosulfide under the conditions employed above afforded **1b** and dibenzyl disulfide in 15% and 12% yields, respectively. This finding clearly indicates that **2b** is a productive intermediate for the formation of **1b** in the reaction of **2a** with benzyl hydrosulfide.

Analogous results were also obtained on treatment of **2a** with benzylamine. The reaction of **2a** with an excess amount of benzylamine was carried out under conditions analogous to those employed in the above case.[4] After removal of the solvent, the residue was triturated with diethyl ether. The resulting precipitate was collected by filtration and chromatographed to separate **1a** (27%) and 5-anilino-6-benzylamino-3-methyluracil (**1c**) (56%). The formation of a large amount of *N*-benzylidenebenzylamine in this reaction was shown by nuclear magnetic resonance (NMR) spectroscopy of the filtrate and by the result of acid treatment leading to benzaldehyde. *N*-Methyl-*p*-bromoaniline was detected by thin layer chromatographic (TLC) analysis of the filtrate. The structure of **1c** was identical with that of a sample prepared by the reaction of 6-benzylamino-5-bromo-3-methyluracil with aniline.

Treatment of 6-benzylamino-3-methyl-5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-dione (**2c**) (prepared easily by the oxidation of **1c**) with benzylamine under the conditions employed above followed by acid treatment of the reaction mixture led to the isolation of **1c** and benzaldehyde in 87% and 78% yields, respectively.

The formation of the products **1b**, **c** in these reactions can be explained in terms of nucleophilic substitution at the C(6)-position of **2a** by the substrates followed by reduction of the resulting products **2b**, **c** by the substrates.

Thus, the 6-(*N*-methylanilino-5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-dione (**2a**) and the 6-substituted 5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-diones **2b**, **c** containing the conjugated diimine moiety in the molecule, possess the capacity to oxidize benzyl hydrosulfide and benzylamine.[5,6] It should be noted that the oxidation occurs smoothly even under mild conditions without any base catalyst.[2] In contrast to the case of **2a**, the isoalloxazine **3** did not react with these substrates under the conditions employed. These results indicate that the ring-opened analogue **2a** possesses an increased oxidation capacity compared with the parent isoalloxazine (**3**).

Experimental

All melting points were determined on a Yanagimoto micro hot stage apparatus and are uncorrected. Elemental analyses were performed at the Analytical Center in our university. Infrared (IR) spectra were recorded on a Hitachi 215 spectrometer in potassium bromide discs. Proton magnetic resonance (^{1}H-NMR) spectra were obtained on a

Hitachi R-24 B (60 MHz) spectrometer in deuteriodimethyl sulfoxide or deuteriochloroform containing tetramethylsilane as an internal standard. Mass spectra (MS) were measured at 75 eV with a JEOL JMS-D300 spectrometer and ultraviolet (UV) spectra with a Shimadzu UV-260 spectrophotometer. GC analyses were carried out with a Hitachi 023 instrument. Column chromatography was performed on silica gel (Wako gel C-300) using chloroform–acetone and chloroform as eluents. TLC analyses were carried out by using silica gel plates (Merck pre-coated plates, Silica gel 60 F-254) and mixed solvents (chloroform–acetone and benzene–ethyl acetate).

Preparation of 3-Methyl-6-(*N*-methyl-*p*-bromoanilino)-5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-dione (2a)——2,3-Dichloro-5,6-dicyanobenzoquinone (454 mg, 2.0 mmol) was added as a single batch to a stirred suspension of 5-anilino-3-methyl-6-(*N*-methyl-*p*-bromoanilino)uracil (**1a**) (802 mg, 2.0 mmol) [prepared by the reaction of 5-bromo-3-methyl-6-(*N*-methyl-*p*-bromoanilino)uracil[7] with aniline] in dry acetonitrile (40 ml) at room temperature and then stirring was continued until the solution took a clear reddish-purple color (for 0.5 h). After removal of the solvent under reduced pressure, column chromatography (chloroform) of the residue gave **2a** in 93% (743 mg) yield; mp 175—177 °C (from ethyl acetate–diethyl ether). *Anal.* Calcd for $C_{18}H_{15}BrN_4O_2$: C, 54.14; H, 3.79; N, 14.03. Found: C, 54.37; H, 3.87; N, 14.03. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1725 (C=O), 1680 (C=O). UV $\lambda_{\max}^{\text{MeCN}}$ nm (ε): 400—600 (shoulder), 320 (4.2×10^3), 247 (1.5×10^4), 229 (1.7×10^4), 222 (1.7×10^4), 216 (1.7×10^4). ^{1}H-NMR (in DMSO-d_6) δ: 3.10 (3H, br s, NMe), 3.58 (3H, br s, NMe), 6.34 (2H, d, $J=9$ Hz, phenyl ring protons), 7.19 (2H, d, $J=9$ Hz, phenyl ring protons), 7.30—7.80 (5H, m, phenyl ring protons). MS *m/z*: 399 (M$^+$).

The pyrimidinedione **2a** was also obtained (89% yield) by using *p*-quinone as an oxidizing agent, though heating of the solution and a prolonged reaction time (reflux for 9 h) were required for completion of the reaction.

Reaction of 2a with Benzyl Hydrosulfide——A mixrure of **2a** (400 mg, 1.0 mmol) and benzyl hydrosulfide (1.2 ml, 10.2 mmol) in dry acetonitrile (20 ml) was stirred overnight at room temperature under an argon atmosphere. After removal of the solvent under reduced pressure, the residual oil was chromatographed over silica gel (chloroform : acetone = 30 : 1) to isolate **1a** (88 mg, 22%), 5-anilino-6-benzylthio-3-methyluracil (**1b**) (85 mg, 25%); mp 169—170 °C. *Anal.* Calcd for $C_{18}H_{17}N_3O_2S$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.79; H, 5.05; N, 12.17. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3330 (NH), 3220 (NH), 1710 (C=O), 1630. UV $\lambda_{\max}^{\text{MeCN}}$ nm (ε): 315 (3.3×10^3), 281 (9.8×10^3), 242 (1.5×10^4). ^{1}H-NMR (in DMSO-d_6) δ: 3.13 (3H, s, NMe), 4.40 (2H, s, $-CH_2Ph$), 6.35—7.20 (5H, m, phenyl ring protons), 6.85 (1H, br, NH), 7.30 (5H, s, phenyl ring protons), 11.18 (1H, br, NH). MS *m/z*: 339 (M$^+$), 6-benzylthio-3-methyl-5-(*N*-phenylimino)pyrimidine-2,4(3*H*,5*H*)-dione (**2b**) (135 mg, 40%); mp 145—147 °C (from diethyl ether). *Anal.* Calcd for $C_{18}H_{15}N_3O_2S$: C, 64.09; H, 4.48; N, 12.46. Found: C, 63.94; H, 4.47; N, 12.33. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1725 (C=O), 1680 (C=O). UV $\lambda_{\max}^{\text{MeCN}}$ nm (ε): 503 (2.2×10^3), 351 (6.1×10^3), 285 (6.6×10^3), 224 (3.2×10^4). ^{1}H-NMR (in DMSO-d_6) δ: 3.08 (3H, s, NMe), 4.41 (2H, s, $-CH_2Ph$), 6.85—7.60 (10H, m, phenyl ring protons). MS *m/z*: 337 (M$^+$), and *N*-methyl-*p*-bromoaniline (95 mg, 51%).

GC analysis of the reaction mixture showed the formation of dibenzyl disulfide in 35% yield (based on **2a**).

Oxidation of 1b——2,3-Dichloro-5,6-dicyanobenzoquinone (207 mg, 0.9 mmol) was added as a single batch to a suspension of **1b** (275 mg, 0.8 mmol) in acetonitrile (10 ml) and then the mixture was stirred at room temperature for 1 h. After removal of the solvent under reduced pressure, the residue was extracted with chloroform. The extract was concentrated and then chromatographed over silica gel (chloroform) to isolate **2b** (252 mg, 92%).

Reaction of 2b with Benzyl Hydrosulfide——Under conditions similar to those employed in the case of **2a**, the reaction of **2b** (169 mg, 0.5 mmol) with benzyl hydrosulfide (0.6 ml, 5.1 mmol) was carried out. GC analysis of the reaction mixture showed the formation of dibenzyl disulfide in 12% yiled (based on **2b**). Chromatographic separation of the residue obtained after removal of the solvent yielded **1b** (26 mg, 15%) and the unchanged starting material **2b** (137 mg, 81%).

Reaction of 2a with Benzylamine——A mixture of **2a** (400 mg, 1.0 mmol) and benzylamine (1.0 ml, 9.2 mmol) in dry acetonitrile (20 ml) was stirred overnight at room temperature under an argon atmosphere. After removal of the solvent under reduced pressure, the residue was triturated with diethyl ether. The resulting precipitate was collected by filtration and chromatographed over silica gel (chloroform : acetone = 30 : 1) to yield **1a** (108 mg, 27%) and 5-anilino-6-benzylamino-3-methyluracil (**1c**) (180 mg, 56%); mp 238—240 °C (from methanol). *Anal.* Calcd for $C_{18}H_{18}N_4O_2$: C, 67.06; H, 5.63; N, 17.38. Found: C, 67.05; H, 5.64; N, 17.44. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3370 (NH), 3310 (NH), 1720, 1700 (C=O), 1645. UV $\lambda_{\max}^{\text{MeCN}}$ nm (ε): 273 (1.8×10^4), 244 (1.7×10^4). ^{1}H-NMR (in DMSO-d_6) δ: 3.02 (3H, s, NMe), 4.55 (2H, br d, $J=7.5$ Hz, $-CH_2Ph$), 6.35 (1H, br, deuterium-exchangeable NH), 6.54 (1H, br d, $J=7.5$ Hz, NH), 6.45—7.40 (5H, m, phenyl ring protons), 7.29 (5H, s, phenyl ring protons). MS *m/z*: 322 (M$^+$).

TLC analysis (chloroform : acetone = 30 : 1; benzene : ethyl acetate = 5 : 1) and the NMR spectrum of the filtrate showed the presence of significant amounts of *N*-methyl-*p*-bromoaniline and *N*-benzylidenebenzylamine. ^{1}H-NMR (in $CDCl_3$) δ: 4.70 (2H, br s, $-C\underline{H}_2Ph$), 8.25 (1H, br s, $-N=C\underline{H}Ph$). Benzaldehyde was obtained in 75% yield (based on **2a**) by treatment of the filtrate with 1 N HCl.

Preparation of 1c——Aniline (1.0 ml, 11 mmol) was added to a solution of 6-benzylamino-5-bromo-3-methyluracil (311 mg, 1.0 mmol) [prepared by bromination of 6-benzylamino-3-methyluracil[8] with *N*-bromosuccinimide] in DMSO (3.0 ml) and the mixture was stirred at room temperature for 1 d, then poured into a cold 1 N HCl solution. The resulting precipitate was collected by filtration, washed with diethyl ether, and recrystallized from methanol to isolate **1c** (254 mg, 79%).

Oxidation of 1c——2,3-Dichloro-5,6-dicyanobenzoquinone (256 mg, 1.1 mmol) was added to a suspension of **1c** (323 mg, 1.0 mmol) in acetonitrile (10 ml) and the mixture was stirred at room temperature for 1 h. After removal of the solvent under reduced pressure, the residue was extracted with chloroform. The extract was chromatographed over silica gel (chloroform : acetone = 50 : 1) to isolate **2c** (252 mg, 79%): mp 161—162 °C (from ethyl acetate–diethyl ether). *Anal.* Calcd for $C_{18}H_{16}N_4O_2$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.39; H, 5.03; N, 17.51. IR $\nu_{\max}^{\mathrm{KBr}}\,\mathrm{cm}^{-1}$: 3290 (NH), 1720 (C=O), 1665 (C=N). UV $\lambda_{\max}^{\mathrm{MeCN}}$ nm (ε): 465 (1.7×10^3), 276 (7.6×10^3), 215 (2.4×10^4). ^{1}H-NMR (in DMSO-d_6) δ: 3.04 (3H, s, NMe), 4.68 (2H, d, $J = 7$ Hz, $-\mathrm{C}\underline{\mathrm{H}}_2\mathrm{Ph}$), 6.80—7.60 (10H, m, phenyl ring protons), 9.40 (1H, br, deuterium-exchangeable NH). MS m/z: 320 (M^+).

Reaction of 2c with Benzylamine——Under conditions similar to those used in the case of **2a**, the reaction of **2c** (160 mg, 0.5 mmol) with benzylamine (0.5 ml, 4.6 mmol) in acetonitrile (5 ml) was carried out. After removal of the solvent under reduced pressure, the residue was washed with diethyl ether to isolate **1c** (140 mg, 87%) in a pure state. GC analysis of the solution obtained by treatment of the filtrate with 1 N HCl showed the presence of benzaldehyde (78% yield based on **2c**).

References and Notes

1) G. H. Sayed, M. S. Abd Elhalim, M. Y. El-Kady, and L. M. Abd Elwahab, *Indian J. Chem.*, **21B**, 589 (1982); W. Friedrichsen and A. Böttcher, *Heterocycles*, **16**, 1009 (1981).
2) For recent reviews concerning mechanisms of flavin catalysis, see C. Walsh, *Acc. Chem. Res.*, **13**, 148 (1980); T. C. Bruice, *ibid.*, **13**, 256 (1980); H. Dugas and C. Penney, "Bioorganic Chemistry. A Chemical Approach to Enzyme Action," Springer-Verlag, New York, 1981, p. 400.
3) M. Sako, Y. Kojima, K. Hirota, and Y. Maki, *Heterocycles*, **22**, 1021 (1984).
4) The formation of the substitution product **2c** in this reaction was monitored by TLC analysis during the reaction.
5) Oxidation of thiols by imino compounds under thermal conditions proceeds *via* the initial formation of an intermediary addition product, as already reported. *cf.* K. Harada, in "The Chemistry of Functional Groups. The Chemistry of the Carbon–Nitrogen Double Bond," ed. by S. Patai, International Publishers, New York, 1970, p. 255.
6) Recently, oxidation of benzylamine by pyrimido[4,5-*b*]quinoline-2,4(3*H*, 10*H*)-dione, which is a deazaflavin analogue, under thermal conditions has been reported. *cf.* F. Yoneda, Y. Sakuma, Y. Kadokawa, and A. Koshiro, *Chem. Lett.*, **1979**, 1467.
7) F. Yoneda, K. Shinozuka, K. Hiromatsu, R. Matsushita, Y. Sakuma, and M. Hamana, *Chem. Pharm. Bull.*, **28**, 3576 (1980).
8) G. Nuebel and W. Pfleiderer, *Chem. Ber.*, **95**, 1605 (1962).