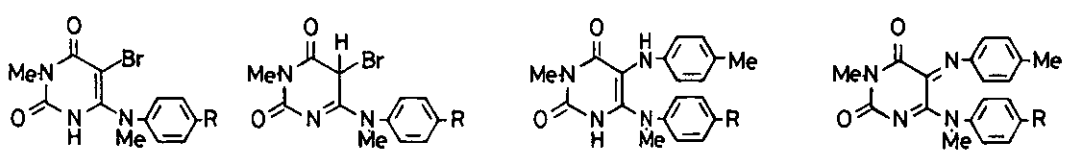
PREPARATION AND REDUCING PROPERTY OF 5,6-DIANILINOPYRIMIDINEDIONES

Magoichi Sako, Yutaka Kojima, Kosaku Hirota, and Yoshifumi Maki*
Gifu College of Pharmacy, 6-1, Mitahora-higashi 5 Chome, Gifu 502, Japan

Abstract —— 5,6-Dianilinopyrimidinediones (3), prepared with ease by the reaction of 6-anilino-5-bromopyrimidinediones (1) with p-toluidine, are fairly stable to autoxidation but possess the capacity reducing a disulfide bond under mild conditions.

Recently, we have reported[1] that 5-bromo-6-(N-methylanilino)pyrimidinediones (1) undergo the reductive debromination with ease in the presence of electron donors. The reaction could be reasonably explained in terms of the involvement of a tautomeric form (2), containing the C(5)-bromine significantly activated by adjacent carbonyl and acylimino functions. From the structural point of view, nucleophilic substitution on the C(5)-position of 2 can be expected to occur smoothly. These considerations prompted us to investigate the reaction of 1 with aromatic amines.

In this paper, we describe occurrence of the facile displacement of the C(5)-bromine in 1 by toluidine and the reducing property of the products, 5,6-dianilinopyrimidinediones (3). The compounds (3) are fairly stable to autoxidation but reduce disulfides to the corresponding mercaptans under mild conditions. The present results are of interest in connection with the 1,5-dihydroflavin chemistry.



1 2 3 4

a): R= Br, b): R= Me

A mixture of 5-bromo-3-methyl-6-(N-methyl-p-bromoanilino)pyrimidine-2,4(1H,3H)-dione (1a)(1.0 mM)[2] and excess amount of p-toluidine (10.0 mM) in dimethyl sulfoxide (4 ml) was stirred at room temperature for 4 h. After the reaction mixture was poured into a cold 0.5 N-HCl solution, recrystallization of the collected precipitates from ethanol gave 3-methyl-6-(N-methyl-p-bromoanilino)-5-(p-toluidino)pyrimidine-2,4(1H,3H)-dione (3a), mp 255°C, as white plate crystals in 94 % yield. The structure of the product (3a) was supported by its microanalytical results and spectral data [mass m/e 415 (M^+); ir(KBr) 3340 (NH),1700 (C=O) cm ; uv(MeCN) 210 (2.5×10^4), 247 (2.0×10^4), 299 (1.3×10^4) nm; nmr(DMSO-d_6, δ) 2.10 (3H, s, ArMe), 3.07 (3H, s, NMe), 3.15 (3H, s, NMe), 6.25 (1H, b, deuterium exchangeable NH), 6.25-7.35 (8H, m, aromatic protons), 11.08 (1H, b, deuterium exchangeable NH)].

Similarly, the reaction of 5-bromo-3-methyl-6-(N-methyl-p-toluidino)pyrimidine-2,4(1H,3H)-dione (1b) with toluidine gave the corresponding 5,6-dianilinopyrimidinedione (3b), mp 233°C, in 90 % yield.

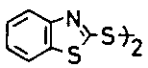
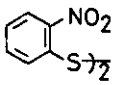
Although it has been demonstrated that the nucleophilic substitution on the C(5)-position of 6-unsubstituted 5-bromopyrimidinediones by amines takes place only under drastic conditions,[3] the reaction of the 6-anilino-5-bromopyrimidinediones (1) with toluidine smoothly occurred even under mild conditions as expected to give the 5,6-dianilinopyrimidinediones (3) in high yields.

Stirring a solution of (3a, 0.01 mM) in acetonitrile (100 ml) at room temperature in a stream of oxygen resulted in the slow formation of 3-methyl-5-(p-methylanilidene)-6-(N-methyl-p-bromoanilino)pyrimidine-2,4(3H,5H)-dione (4a),[4] mp 143°C, (a half life of 3a = ca. 0.5 day). Tlc and hplc analyses of the reaction mixture proved the quantitative conversion of 3a to 4a . The uv spectral change during the reaction showed two isosbestic points at 240 and 348 nm. Analogous results were also obtained in the case of 3b . These facts apparently indicate that the 5,6-dianilinopyrimidinediones (3) are fairly stable to autoxidation.

When an equimolar mixture (0.1 mM) of 3a and (benzothiazol-2-yl) disulfide in acetonitrile (40 ml) was stirred at room temperature under an argon atmosphere for 1 day, the 5-anilidene-6-anilinopyrimidinedione (4a) and 2-mercaptobenzothiazole were isolated in low yields, respectively. The reaction was markedly facilitated by the employment of hexamethylphosphorylamide or dimethylformamide as a solvent. Analogous results were obtained in the reaction of 3a and (2-

nitrophenyl) disulfide or lipoamide, though prolonged reaction time was required for the progress of the reaction. The results of these reactions are summarized in Table I.

Table I Reactions of 5,6-dianilinopyrimidinediones (3a) with disulfides[a)]

Disulfide	Solvent	Reaction Time (day)	5-Anilidene-6-anilinopyrimidinediones (4a) Yield (%)[b)]
	MeCN	1	33
	HMPA	1	87
	DMF	1	95
	HMPA	10	31
Lipoamide	HMPA	10	15

a) Formation of the mercaptans was proved by tlc analysis of the reaction mixture. In the cases of (benzothiazol-2-yl) disulfide and lipoamide, the corresponding mercaptans were isolated and identified with those authentic samples, respectively.
b) Yields were estimated by hplc analysis of the reaction mixtures.

The redox reaction between 3 and the disulfides was suppressed to some degree upon shielding from daylight or by the addition of a small amount of p-dinitrobenzene which is a one-electron trapping reagent.[5] These observations suggest that a one-electron transfer process could be involved in the present reaction. The use of flavin mimics such as isoalloxazines and deazaisoalloxazines has been enlightening in the development of chemical insight in the flavin-catalyzed biochemical redox reactions.[6] The details of the chemical reactivities of 1,5-dihydroflavins, however, still remain equivocal because of their high sensitivity to autoxidation and the lack of suitable model compounds. The present results show that the 5,6-dianilinopyrimidinediones (3) may be utilized as an open-ring mimic of the 1,5-dihydroflavins which is readily available.[7,8]

REFERENCES AND FOOTNOTES

1 M. Sako, K. Hirota, and Y. Maki, Chem. Pharm. Bull., 1983, 31, 3496; idem, Tetrahedron, 1983, 39, 3919.

2 M. Sako, M. Suzuki, M. Tanabe, and Y. Maki, J. Chem. Soc., Perkin I, 1981, 3114.

3 For example, 5-anilinopyrimidine-2,4(1H,3H)-dione was prepared by treatment of 5-bromopyrimidine-2,4(1H,3H)-dione with aniline in refluxing ethylene glycol for 2 h. cf. F. R. Gerns and G. H. Hitchings, U.S. patent, 1966, 3238208 (Chem. Abstr., 1966, 64, 17617e).

4 The oxidation product (4a) was obtained with ease by treatment of 3a with 2,3-dichloro-5,6-dicyanobenzoquinone as reddish purple needles in almost quantitative yield. 4a : mass m/e 413(M^+); ir(KBr) 1710 (C=O), 1670 (C=O) cm^{-1}; uv(MeCN) 231 (2.1×10^4), 243 (2.0×10^4), 334 (6.0×10^3), 400-600 (shoulder) nm; nmr(DMSO-d_6,δ) 2.22 (3H, s, ArMe), 3.06 (3H, s, NMe), 3.51 (3H, s, NMe), 6.22-8.31 (8H, m, aromatic protons).

5 N. Kornblum, Angew. Chem. Int. Ed., 1975, 14, 734; N. Ono, R. Tamura, and A. Kaji, J. Am. Chem. Soc., 1983, 105, 4017.

6 For recent reviews concerning mechanisms of flavin catalysis, see C. Walsh, Acc. Chem. Res., 1980, 13, 148; T. C. Bruice, ibid., 1980, 13, 256; H. Dugus and C. Penny, 'Bioorganic Chemistry. A Chemical Approach to Enzyme Action', Springer-Verlag, New York, 1981, p 460.

7 Recently, preparation and study of a low-potential dihydroflavin mimic was reported by Bruice et al. cf. E. B. Skibo and T. C. Bruice, J. Am. Chem. Soc., 1983, 105, 3304 and 3316.

8 Only an example of the open-ring flavin analogue has been reported, i.e., 5-amino-6-hydroxy (or amino)pyrimidine-2,4(1H,3H)-dione catalyzes oxidation of benzylamine in a stream of oxygen. Cf. S. Ito, T. Kaneko, and K. Higashi, Nippon Kagaku Kaishi, 1981, 902.

Received, 29th December, 1983