On the Reactivity of 1-(*p*-Bromophenyl)-2-methyl-5-bromopyridazine-3,6-dione with Aliphatic Amines (1a,b)

Sylwester Baloniak and Henk C. van der Plas

Laboratory of Organic Chemistry, Agricultural University, 6703 BC Wageningen, The Netherlands

Received March 5, 1981

Reaction of 5-bromo-1-(*p*-bromophenyl)-2-methylpyridazine-3,6-dione with morpholine leads to formation of 1-(*p*-bromophenyl)-2-methyl-5-morpholinopyridazine-3,6-dione. The structure of the morpholino compound was established by the chemical methods and an X-ray crystal structure determination.

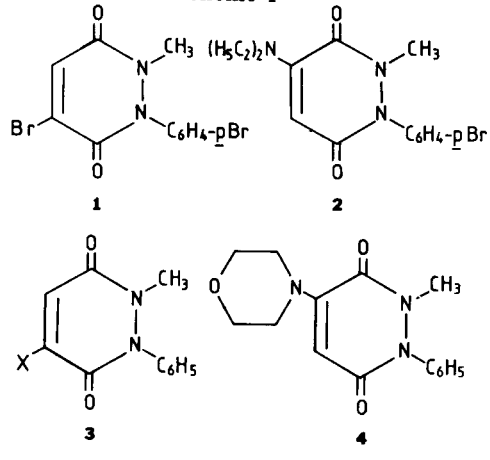
J. Heterocyclic Chem., **18**, 1109 (1981).

Reactions.

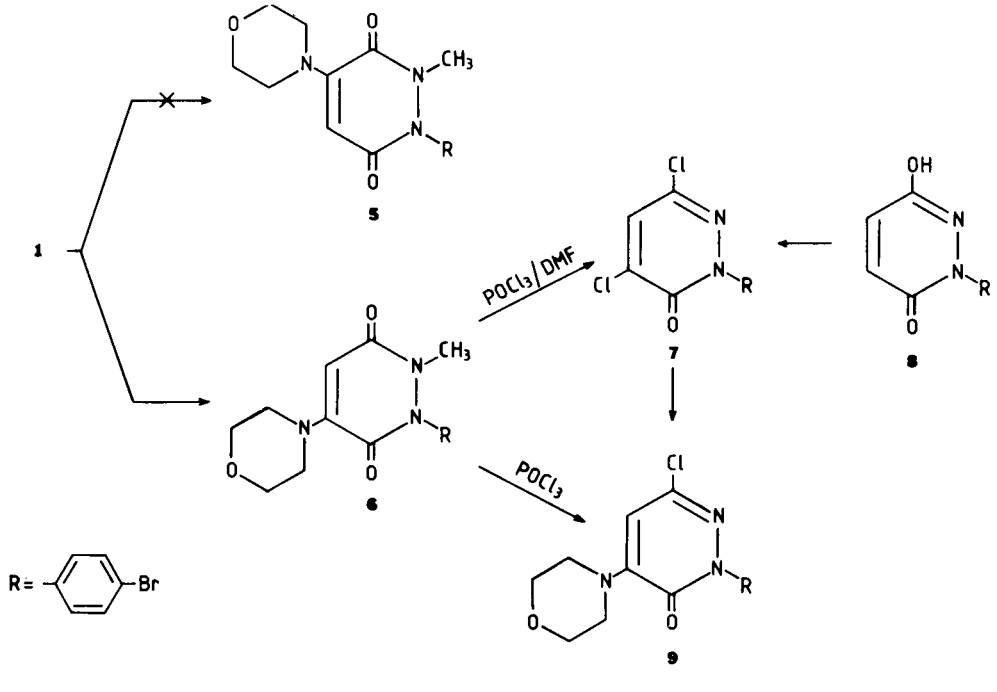
It has been reported (2-5) that 5-bromo-1-(*p*-bromophenyl)-2-methylpyridazine-3,6-dione (**1**), when subjected to a reaction with diethylamine in methanol, undergoes a cine substitution, leading to the formation of 1-(*p*-bromophenyl)-4-diethylamino-2-methylpyridazine-3,6-dione (**2**). The structures of **1** and **2** were firmly established by X-ray crystal structure determination (2). It has also been reported (6) that 5-chloro-2-methyl-1-phenylpyridazine-3,6-dione (**3**, X = Cl) with morpholine/acetone and 5-bromo-2-methyl-1-phenylpyridazine-3,6-dione (**3**, X = Br) with morpholine/benzene also lead to a cine substitution product *i.e.*, 2-methyl-4-morpholino-1-phenylpyridazine-3,6-dione (**4**).

We wish to report in this paper that **1**, when reacted with morpholine in ethanol gave not, as would be expected from the results mentioned above, the 4-morpholino compound (**5**) but 1-(*p*-bromophenyl)-2-methyl-5-morpholinopyridazine-3,6-dione (**6**). The structure determination is based on the following chemical reactions. Treatment of

Scheme 1



Scheme 2



0022-152X/81/061109-03$02.25

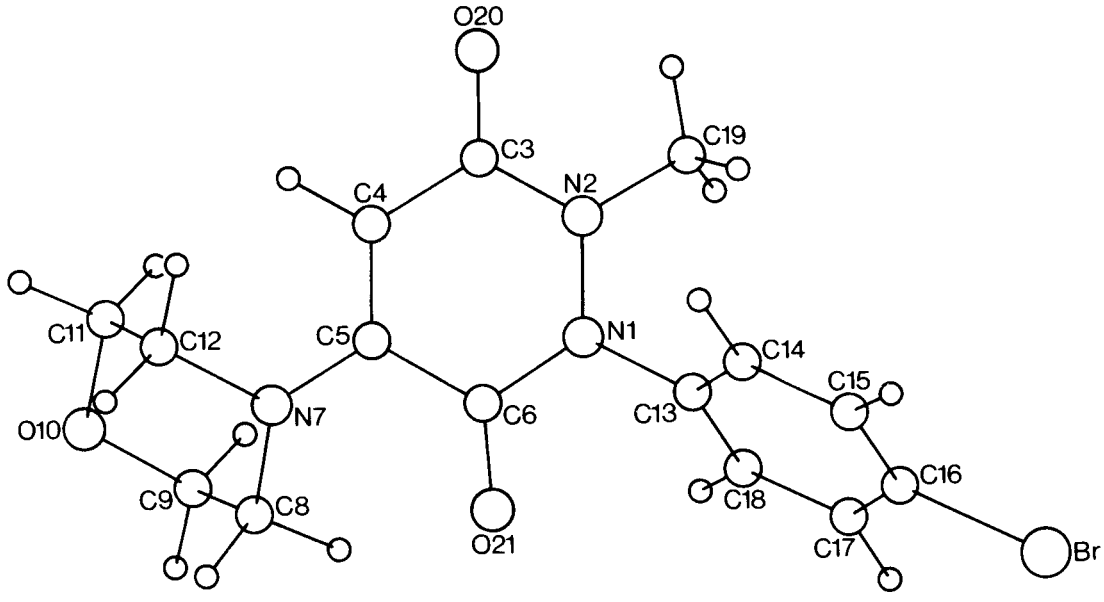


Figure 1

6 with phoshorus oxychloride in DMF gave 1-(*p*-bromophenyl)-3,5-dichloro-6-pyridazinone (**7**), being identical with the compound obtained on reaction of 1-(*p*-bromophenyl)-3-hydroxy-6-pyridazinone (**8**) with phosphorus oxychloride and phosphorus pentachloride (7). Treatment of **6** with phosphorus oxychloride and amination of **7** with morpholine gave the same product, *i.e.*, 1-(*p*-bromophenyl)-3-chloro-5-morpholino-6-pyridazinone (**9**). Although from the results of this set of reactions it is clear that in compound **6** the morholino group occupies position 5, we wanted to be sure that during the several reactions with phosphorus oxychloride no unexpected rearrangement has taken place. An X-ray crystal structure determination was carried out in order to prove unequivocally structure **6**. From this X-ray study structure **6** was confirmed.

X-Ray Structure Determination.

Crystals of the title compound are orthorhombic with space group $Pc2_1b$ and four molecules in a unit cell of dimensions a = 5.7428, b = 8.9717 and c = 29.312 Å. The crystal structure was determined from 1376 counter intensities by means of the heavy atom technique and refined to an R value of 0.055 (8).

The above mentioned results indicate to us that nucleophilic substitutions in the 5-halogenopyridazine-3,6-dione series do not always lead to cine substitution products as found so far, but that can also give products, in which the entering nucleophile is attached to the same carbon from which the leaving group has departed. Apparently two substitution mechanisms can operate in reactions with these 5-halogeno compounds *i.e.*, the $S_N(AE)^{cine}$ and the $S_N(AE)$ (9). Which factors determine the course of the substitution is not clear and is under investigation.

EXPERIMENTAL

1-(*p*-Bromophenyl)-2-methyl-5-morpholinopyridazine-3,6-dione (**6**).

1-(*p*-Bromophenyl)-2-methyl-5-bromopyridazine-3,6-dione (**1**) (0.5 g, 0.0013 mole) (10) was boiled with 6 ml of ethanol containing 0.2 g of morpholine for 2 hours. The residue obtained after evaporation of the solvent was crystallized from ethanol, pale yellow needles, mp 189-190°, yield 0.25 g (50%).

Anal. Calcd. for $C_{15}H_{16}BrN_3O_3$: C, 49.18; H, 4.37; N, 11.47. Found: C, 49.06; H, 3.49; N, 11.38.

1-(*p*-Bromophenyl)-3,5-dichloro-6-pyridazinone (**7**).

Compound **6** (0.5 g, 0.0013 mole), 5 ml of dimethylformamide and 2 ml of phosphorus oxychloride were heated at 150° for 0.5 hour. The reaction mixture was poured onto ice and the collected precipitate was crystallized from ethanol, colourless needles, m.p. 167-168°, yield 0.3 g (69.7%).

Anal. Calcd. for $C_{10}H_5BrCl_2N_2O$: C, 37.50; H, 1.56; N, 8.75. Found: C, 37.65; H, 1.51; N, 8.70.

The compound was identical with that obtained from 1-(*p*-bromophenyl)-3-hydroxy-6-pyridazinone (7).

1-(*p*-Bromophenyl)-3-chloro-5-morpholino-6-pyridazinone (**9**).

a.

Compound **6** (0.5 g, 0.0013 mole) was boiled in 10 ml of phosphorus oxychloride for 1 hour. The reaction mixture was poured onto ice and the precipitate crystallized from ethanol, colourless needles, m.p. 186-187°, yield 0.32 g (64%).

Anal. Calcd. for $C_{14}H_{13}BrClN_3O_2$: C, 45.37; H, 3.53; N, 11.34. Found: C, 45.39; H, 3.61; N, 11.24.

b.

1-(*p*-Bromophenyl)-3,5-dichloro-6-pyridazinone (**7**) (0.5 g, 0.0015 mole) and 0.15 g (0.0017 mole) of morpholine were boiled in 10 ml of ethanol for 2 hours and colourless needles, m.p. 186-187° was obtained, yield 0.45 g (78.9%). No melting point depression was observed after mixing with the compound prepared by method a.

REFERENCES AND NOTES

(1a) Paper VII on Pyridazines from our Laboratory; (b) For the previous paper see reference 2.

(2) C. Stam, J. J. Zwinselman, H. C. van der Plas and S. Baloniak, *J. Heterocyclic Chem.*, **16**, 855 (1979).

(3) S. Baloniak and A. Mroczkiewicz, *Ann. Pharm.* (Poznan), **12**, 53 (1976); S. Baloniak and A. Mroczkiewicz, *ibid.*, **12**, 65 (1976).

(4) S. Baloniak, A. Mroczkiewicz and M. Cagara, *Acta Pol. Pharm.*, **32**, 455 (1975).

(5) S. Baloniak, U. Thiel and M. Pacholzcyk, *ibid.*, **33**, 73 (1976).

(6) J. Druey, Kd. Meier and A. Stachelin, *Pharm. Acta Helv.*, **38**, 498 (1963).

(7) S. Baloniak and A. Mroczkiewicz, *Rocz. Chem.*, **48**, 399 (1974).

(8) Full details will be given in a paper to be submitted to *Acta Crystallographica.*

(9) For an explanation of this nomenclature for nucleophilic substitutions, we refer to H. C. van der Plas and F. Roeterdink, chapter on Six-membered Didehydroheteroarenes in Supplement C: "The Chemistry of Triple-bonded Groups", S. Patai and Z. Rappoport eds, in press.

(10) This compound was prepared according to the procedure given in reference 7 and in S. Baloniak and A. Mroczkiewicz, *Ann. Pharm. (Poznan)*, **12**, 53 (1976).