The Synthesis and Reactions of Certain Pyridazine 1-Oxides (1)

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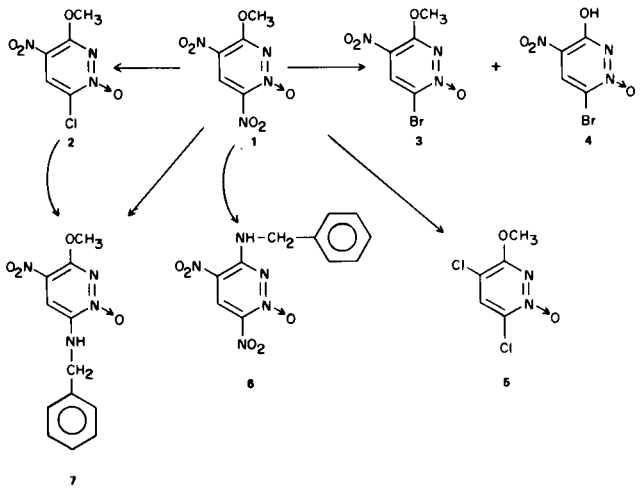
Received June 4, 1973

Nucleophilic displacement reactions under acidic and basic conditions have been studied with 4,6-dinitro-3-methoxypyridazine 1-oxide (**1**) and with 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**2**). Depending on the nature of the nucleophilic reagent and the conditions of the reaction we have found that the chloro group, the nitro group, as well as the methoxy group of **1** and **2** may be displaced by the nucleophile. This type of compound possesses significant *in vitro* antifungal activity.

Pyridazine *N*-oxides have been of interest in recent years because of their potent antimicrobial activity (2-4). As a continuation of a program initiated by Professor R. N. Castle (5), we selected 4,6-dinitro-3-methoxypyridazine 1-oxide (3) (**1**) for further study. When 4,6-dinitro-3-methoxypyridazine 1-oxide (**1**) was heated with dilute hydrochloric acid, an interesting reaction occurred. Instead of the anticipated cleavage of the methoxy group, one of the nitro groups was displaced by chlorine. The structure of this monochlorinated product was established as 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**2**). This product is identical to the product obtained by nitration of 6-chloro-3-methoxypyridazine 1-oxide following the procedures of Itai and Sako (6). This reaction provides an interesting example of an acid catalyzed nucleophilic displacement of a nitro group. This type of nucleophilic displacement is not without precedent, since the synthesis of 8-chlorotheophylline from 8-nitrotheophylline has been reported to occur under similar conditions (7).

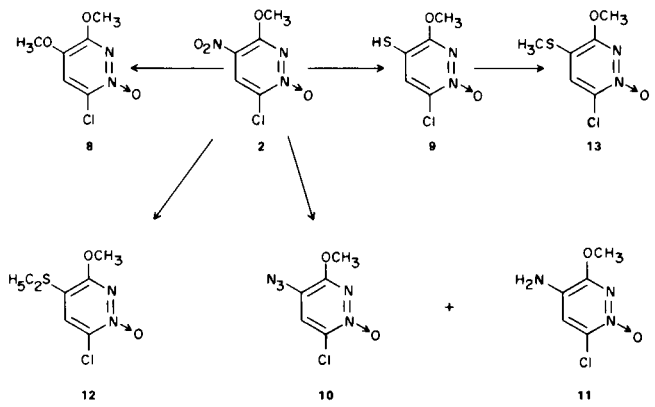


REACTION SCHEME A

An analogous treatment of 4,6-dinitro-3-methoxypyridazine 1-oxide (**1**) with dilute hydrobromic acid gave 6-bromo-3-methoxy-4-nitropyridazine 1-oxide (**3**) and 6-bromo-3-hydroxy-4-nitropyridazine 1-oxide (**4**). The structure of **3** was assigned on the basis of comparison of the spectral data with that of **2**. It is of interest that dilute hydrobromic acid does cleave the methoxy group to the corresponding 3-hydroxy derivative **4**. The reaction of 4,6-dinitro-3-methoxypyridazine 1-oxide (**1**) with acetyl chloride resulted in the unexpected displacement of both nitro groups to afford 4,6-dichloro-3-methoxypyridazine 1-oxide (**5**).

The reaction of **1** with basic nucleophiles provides an additional illustration of nucleophilic displacement reactions with compounds that contain competitive leaving groups. Refluxing an ethanolic solution of **1** with benzylamine afforded a mixture of 3-benzylamino-4,6-dinitropyridazine 1-oxide (**6**) and 6-benzylamino-3-methoxy-4-nitropyridazine 1-oxide (**7**). The structure of **7** was established by the unambiguous synthesis of **7** from 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**2**) and benzylamine in refluxing ethanol.

The compound 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**2**) provides an interesting model for studying leaving groups in nucleophilic substitutions of a heterocyclic *N*-oxide system. Theoretically the chloro, nitro, or methoxy groups could be replaced, depending on their position on the pyridazine *N*-oxide ring, as well as the type of nucleophilic reagent employed. The site of attachment of the incoming nucleophile can be readily determined by noting which group has been displaced. In conjunction with these studies, 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**2**) was treated with sodium methoxide to yield 6-chloro-3,4-dimethoxypyridazine 1-oxide (**8**), which is identical in all respects to the previously reported material (8).



REACTION SCHEME B

The ease of replacement of the 4-nitro group of 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (2) was further investigated under basic conditions with various nucleophiles. The reaction of **2** with sodium hydrosulfide, sodium ethylmercaptide and with sodium azide afforded the corresponding 6-chloro-3-methoxy-4-substituted pyridazine 1-oxide derivatives (see Reaction Scheme B). In each case, under the conditions employed, the 4-nitro group of **2** was replaced by the nucleophile. In the isolation and purification of the corresponding azido derivative **10**, we obtained 4-amino-6-chloro-3-methoxypyridazine 1-oxide (**11**) as a reduction product. The alkylation of 6-chloro-4-mercapto-3-methoxypyridazine 1-oxide (**9**) with methyl iodide gave the corresponding 6-chloro-3-methoxy-4-methylthiopyridazine 1-oxide (**13**) in good yield. The structure of **13** was verified by comparing the ultraviolet absorption spectrum with that of 6-chloro-4-ethylthio-3-methoxypyridazine 1-oxide (**12**).

The compounds (**1-13**) were evaluated for their antifungal activity by the broth dilution assay procedures. The data for the most potent antifungal compound, 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**2**) is given in Table I.

TABLE I

Antifungal Activity of
6-Chloro-3-methoxy-4-nitropyridazine 1-Oxide (**2**)

Organism	MIC (μg/ml.)	MLC (μg/ml.)
C. albicans	7.8	15.6
S. cerevisiae	7.8	15.6
C. diffluens	7.8	7.8
M. fulvum	7.8	7.8

EXPERIMENTAL (9)

6-Chloro-3-methoxy-4-nitropyridazine 1-Oxide (**2**).

A suspension of 2.0 g. of 3-methoxy-4,6-dinitropyridazine 1-oxide (3) (**1**) in 80 ml. of 10% hydrochloric acid was heated (oil bath) at 90° for 3-4 hours. Then the hot solution was filtered (sintered glass funnel) and chilled (ice bath or refrigerator) to produce 870 mg. (48%) of yellow crystals. Recrystallization from water gave yellow needles, m.p. 143-144° (lit. (6) reported m.p. 144-145°).

6-Bromo-3-methoxy-4-nitropyridazine 1-Oxide (**3**) and 6-Bromo-4-nitropyridazin-3-one 1-Oxide (**4**).

In an analogous manner to the preparation of **2**, 2.0 g. of **1** was suspended in 80 ml. of 10% aqueous hydrobromic acid and heated at 90° for 3 hours. The hot solution was filtered and cooled to 0°, then brought to *p*H 6-6.2 with concentrated ammonium hydroxide (17*M*) whereupon 6-bromo-3-methoxy-4-nitropyridazine 1-oxide (**3**) separated as a light yellow powder. Recrystallization from water gave 600 mg. (20% of light yellow needles, m.p. 135-137°; nmr (d_6 DMSO): s, 4.10 δ (CH_3O); s, 9.10 δ (C_5-H); uv (methanol): λ max (log ε max) = 250 nm (3.6), 285 nm (3.6), 285 nm (3.2), 367 nm (4.2).

Anal. Calcd. for $C_5H_4BrN_2O_4$: C, 24.01; H, 1.61; N, 16.80. Found: C, 23.98; H, 1.61; N, 16.62.

The filtrate at *p*H 6 was then made alkaline (*p*H 11) with sodium carbonate solution, whereupon the color changed from yellow to orange. The orange solution was evaporated (rotovac) and the residue extracted with 3 (150 ml.) portions of 2-propanol. Evaporation of the 2-propanol gave 100 mg. (4%) orange red solid which was recrystallized from methanol as red platelets, m.p. 230-230.5°; nmr (d_6-DMSO): s, 8.5 δ (C_5-H); uv (methanol); λ max (log ε max) = 230 nm (.38), sh 255 nm (3.6), sh 285 nm (3.4) and 372 nm (3.23).

Anal. Calcd. for $C_4H_2BrN_3O_4$: C, 20.35; H, 1.85; N, 17.80. Found: C, 20.38; H, 2.03; N, 17.61.

4,6-Dichloro-3-methoxypyridazine 1-Oxide (**5**).

A mixture of 1 g. of **1** and 11 ml. of acetyl chloride was refluxed, with the exclusion of moisture, for 3 hours. The mixture was cooled to room temperature and cautiously added to ice cold methanol with stirring. The resultant solution was evaporated (rotovac) and the residue was recrystallized twice from ethanol to afford 500 mg. (51%) of **5** as pale pink-yellow plates, m.p. 139-141°; uv (methanol): λ max (log ε max) = 220 nm (4.32), 267 nm (4.01), 340 nm (3.7).

Anal. Calcd. for $C_5H_4Cl_2N_2O_2$: C, 30.79; H, 2.06; N, 15.65; Cl, 36.36. Found: C, 30.82; H, 2.21; N, 15.50; Cl, 36.50.

6-Benzylamino-3-methoxy-4-nitropyridazine 1-Oxide (**7**) and 3-Benzylamino-4,6-dinitropyridazine 1-Oxide (**6**).

A mixture of 500 mg. (1.9 mmoles) of **7** and 500 mg. (excess) of benzylamine was refluxed in 15 ml. of ethanol for 3 hours. Upon cooling, a red solid precipitated. Recrystallization from ethanol afforded 200 mg. (36%) of **7** as red needles, m.p. 115-116°. To obtain a correct analysis, **7** was converted to the hydrochloride by dissolving in 20 ml. fo ethanol and adding ethanolic hydrogen chloride, then concentrating, diluting with ether, and chilling. Recrystallization from ethanol-ether gave the pure hydrochloride of **7**, m.p. 186-188°, yellow needles; uv (methanol): λ max (log ε max) = 225 nm (4.3), 257 nm (3.6), 305 nm (3.58), and 430 nm (3.47).

Anal. Calcd. for $C_{12}H_{12}N_4O_4$·HCl: C, 46.22; H, 4.81; N, 17.97. Found: C, 46.42; H, 4.91; N, 17.83.

Evaporation of the filtrate from the reaction (*e.g.*, after **7** was filtered) gave a red orange solid which was recrystallized from ethanol-hexane to afford 200 mg. (35%) of **6** as orange yellow plates, m.p. 158-159°; uv (methanol): λ max (log ε max) = 260 nm (3.8), 290 nm (3.85), 450 nm (3.7).

Anal. Calcd. for $C_{11}H_9N_5O_5$: C, 45.36; H, 3.09; N, 24.05. Found: C, 45.07; H, 3.03; N, 24.07.

6-Benzylamino-3-methoxy-4-nitropyridazine 1-Oxide (**7**): Alternate Procedure.

A mixture of 300 mg. of **2** (1.5 mmoles), 200 mg. (excess) of benzylamine and 20 ml. of ethanol was refluxed for 3 hours. The solution was allowed to cool to room temperature and 150 mg. (31%) of **7** was obtained as red needles, m.p. 115-116°. Conversion to the hydrochloride salt with ethanolic hydrogen chloride, yielded yellow needles, m.p. 186-188°. There was no melting point depression when this sample of **7**·HCl was mixed with the sample of **7**·HCl previously described, and the spectra of both samples were identical.

6-Chloro-3,4-dimethoxypyridazine 1-Oxide (**8**).

To a solution fo 60 mg. (1.2 mmoles) of sodium methoxide in 20 ml. of methanol was added 205 mg. (1.0 mmoles) of **2** and the mixture was stirred at room temperature for 3 hours. The mixture was evaporated (rotovac) and the residue was dissolved in 20 ml. of chloroform and filtered to remove sodium salts. Chromatography on silica gel with 3:1 chloroform-methanol and recrystallization of the product from heptane-benzene and then chloroform-pentane, afforded 185 mg. (93%) of **8** as a white powder, m.p. 187-189° (lit. (8), m.p. 188-190°.

Anal. Calcd. for $C_6H_7ClN_2O_3$: C, 37.77; H, 3.70; N, 14.70. Found: C, 37.47; H, 3.50; N, 14.57.

6-Chloro-4-mercapto-3-methoxypyridazine 1-Oxide (**9**).

A mixture of 420 mg. (2 mmoles) of **2** and 450 mg. (excess) of technical grade sodium hydrosulfide hydrate was refluxed in 10 ml. of absolute ethanol for 15 hours. The mixture was filtered and evaporated (rotovac) and the orange residue recrystallized twice from ethanol-benzene to afford 200 mg. (47%) of **9** as a yellow powder, m.p. 244-245° dec.; uv (methanol): λ max (log ε max) = 285 nm (3.8).

Anal. Calcd. for $C_5H_5ClN_2O_2S$: C, 31.16; H, 2.62; N, 14.54. Found: C, 31.30; H, 2.66; N, 14.72.

4-Azido-6-chloro-3-methoxypyridazine 1-Oxide (**10**) and 4-Amino-6-chloro-3-methoxypyridazine 1-Oxide (**11**).

A mixture of 220 mg. (1.1 mmoles) of **2** and 100 mg. (1.8 mmoles) of sodium azide was refluxed in 10 ml. of aqueous ethanol (1:1) for 3-4 hours. The solution was evaporated (rotovac) and the residue treated with 50 ml. of hot chloroform. The chloroform was cooled, filtered and eluted on a column of 10 g. of grade I neutral alumina (Baker) with 200-300 ml. of chloroform. The first material eluted consisted of 46 mg. (23%) of **10** as red crystals, washed with petroleum ether (30/60) and air dried. The crystals of **10** were analytically pure and had m.p. 93-94°; ir (potassium bromide): 2170^{-1} cm (N_3); uv (methanol): λ max (log ε max) = 230 nm (3.8), 290 nm (4.3), 345 nm (4.1).

Anal. Calcd. for $C_5H_4N_5O_2Cl$: C, 29.78; H, 1.99; N, 34.74. Found: C, 29.97; H, 1.86; N, 34.78.

Elution of the alumina column with 200-300 ml. of chloroform-methanol (3:1) gave a beige solid. Recrystallization from benzene-heptane gave 70 mg. (40%) of **11** as beige plates, m.p. 160-161°.

Anal. Calcd. for C $H_6N_3O_2Cl$: C, 34.20; H, 3.44; N, 23.93. Found: C, 34.40; H, 3.53; N, 24.20.

6-Chloro-4-ethylthio-3-methoxypyridazine 1-Oxide (**12**).

A mixture of 206 mg. (1 mmole) of **2** and 100 mg. (1.2 mmoles) of sodium ethylmercaptan were refluxed in 10 ml. of absolute ethanol for 3-4 hours. The solution was evaporated (rotovac) and the residue dissolved in 20 ml. of warm chloroform and cooled to room temperature. The chloroform solution was chromatographed on 10 g. of Baker grade I, neutral alumina (eluted with about 200 ml. fo chloroform) to yield 75 mg. (35%) of an ivory powder, m.p. 103-104°. One recrystallization from heptane-benzene gave white needles with m.p. 105-106°; uv (methanol): λ max (log ε max) = 237 nm (3.85), 274 nm (4.15), 304 nm (4.07) and 360 nm (3.6).

Anal. Calcd. for $C_7H_9ClN_2O_2$: C, 38.08; H, 4.11; N, 12.69. Found: C, 37.83; H, 4.15; N, 12.82.

6-Chloro-3-methoxy-4-methylthiopyridazine 1-Oxide (**13**).

A solution fo 150 mg. (0.78 mmoles) of **9** in 15 ml. of 15% ammonium hydroxide was treated with 300 mg. (excess) methyl iodide in 5 ml. of methanol at room temperature for 2-3 hours. The mixture was evaporated (rotovac), brought to *p*H 4-5 with a few drops of acetic acid and water (2-3 ml.) and evaporated (rotovac) again. The residue was then recrystallized from ethanol to yield 22 mg. (12%) of **13**, m.p. 133-135°. One recrystallization from benzene-pentane brought the melting point up to m.p. 145-146° (white needles); uv (methanol): λ max (log ε max) = 237 nm (3.8), 274 nm (4.1), 304 nm (4.0) and 360 nm (3.57).

Anal. Calcd. for $C_6H_7ClN_2O_2S$: C, 34.86; H, 3.42; N, 13.56. Found: C, 35.02; H, 3.50; N, 13.57.

Acknowledgment.

The authors are greatly indebted to Dr. M. P. Schweizer and his staff for spectral determinations and to Dr. L. N. Simon and his staff for the antifungal evaluations.

REFERENCES

(1) Presented at the Third International Congress of Heterocyclic Chemistry, Sendai (Japan), August 1971, paper B-26-8.

(2) T. Itai and S. Sako, *Chem. Pharm. Bull.* (Tokyo), 9, 149 (1949).

(3a) H. Igeta, *ibid.*, 7, 938 (1959); (b) H. Igeta, *ibid.*, 8, 550 (1960); (c) H. Igeta, *ibid.*, 8, 368 (1960).

(4) T. Nakagome, *Yakugaku Zasshi*, 81, 554 (1961).

(5) Private Communication from Professor R. N. Castle of Brigham Young University at Provo, Utah in 1970.

(6) I. Cacace and R. Masironi, *Ann. Chim.* (Rome), 47, 366 (1957).

(7) T. Itai and S. Sako, *Chem. Pharm. Bull.* (Tokyo), 10, 989 (1962).

(8) T. Itai and S. Natsume, *ibid.*, 10, 643 (1962).

(9) All analyses for C, H and N were performed by the Heterocyclic Corporation of Harrisonville, Missouri and analyses for other elements were performed by Galbraith Laboratories, Knoxville, Tennessee. Infrared spectra were obtained on the Perkin-Elmer 257-IR spectrophotometer. Ultraviolet spectra were obtained with the Perkin-Elmer 202-uv spectrophotometer. Proton magnetic resonance spectra were run on the Hitachi-Perkin Elmer R-20A high resolution spectrophotometer.