Nucleophilic Displacement Reactions of 3,6-Dichloropyridazine 1-Oxide with Sulphur Nucleophiles

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The displacement reaction of 3,6-dichloropyridazine 1-oxide with sodium sulphide took place at the 6-position to give 3-chloropyridazine-6-thiol 1-oxide, in contrast to the results with oxygen and nitrogen nucleophiles. Other sulphur nucleophiles (thiourea and phenylmethanethiol) also reacted at the 6-position; this is inconsistent with a previously reported reaction with potassium methanethiolate.

In the course of synthetic work on cephalosporins, the preparation of 6-chloropyridazine-3-thiol 1-oxide (I) was required. Since nucleophilic substitution reactions of 3,6-dichloropyridazine 1-oxide (II) have been reported to take place preferentially at the 3-position,[1] the reaction of compound (II) with sodium sulphide [2] was attempted. From subsequent reactions, however, it was demonstrated that the monosubstitution product obtained from (II) was 3-chloropyridazine-6-thiol 1-oxide (III).† Thus the monosubstitution product was treated with sodium methoxide to give a methoxypyridazinethiol *N*-oxide identical (n.m.r. and i.r. spectra) with material obtained from 6-chloro-3-methoxypyridazine 1-oxide (VI)[1a] by the method of Irikura.[3] Furthermore the samples of the disulphide (V) derived from (III) and (VI) *via* the thiol (IV) were indistinguishable. Compound (III) was also obtained from the reaction of the dichloro-derivative (II) with potassium hydrosulphide in methanol.

The preferred site of displacement reactions of (II) with other sulphur nucleophiles was investigated. Thus treatment with thiourea followed by oxidation with iodine gave 3,3′-dichloro-6,6′-dithiodipyridazine 1,1′-dioxide (VII), identical with the disulphide obtained by oxidation of 3-chloropyridazine-6-thiol 1-oxide (III). The reaction of phenylmethanethiol with (II) gave a monosubstitution product identical with the compound (VIII) obtained from the reaction of benzyl chloride with (III). Treatment of (III) with methyl iodide gave 3-chloro-6-methylthiopyridazine 1-oxide (IX), which on oxidation with *m*-chloroperbenzoic acid gave 3-chloro-6-methylsulphonylpyridazine 1-oxide (X).

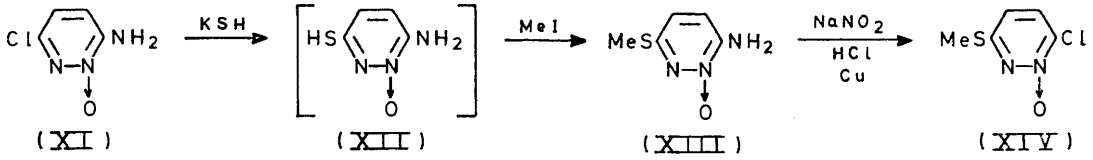
† For clarity, in this paper all pyridazine *N*-oxides are numbered so that the *N*-oxide grouping is at position 1.

[1] (*a*) S. Sako, *Chem. and Pharm. Bull.* (*Japan*), 1962, **10**, 956; (*b*) T. Nakagome, *Yakugaku Zasshi*, 1962, **82**, 244; (*c*) M. Tišler, and B. Stanovnik, *Adv. Heterocyclic Chem.*, 1968, **9**, 293.

[2] M. Ochiai *et al.*, U.S.P. 3,892,737.

[3] T. Irikura, K. Shirai, and S. Sato, *Yakugaku Zasshi*, 1964, **84**, 793.

It has been reported,[4] though without chemical evidence, that the reaction of potassium methanethiolate with 3,6-dichloropyridazine 1-oxide (II) gives 6-chloro-3-methylthiopyridazine 1-oxide. However, the n.m.r. spectrum and m.p. of our 3-chloro-6-methylthiopyridazine 1-oxide (IX) were closely similar to those reported for 6-chloro-3-methylthiopyridazine 1-oxide.* Also the n.m.r. spectrum and m.p. of our 3-chloro-6-methylsulphonylpyridazine 1-oxide (X) are very similar to those reported[4] for 6-chloro-3-methylsulphonylpyridazine 1-oxide.



(XI) (XII) (XIII) (XIV)

Because our chemical evidence clearly indicated that all the sulphur nucleophiles investigated attacked the 6-position of 3,6-dichloropyridazine 1-oxide (II), we synthesized 3-methylthio-6-chloropyridazine 1-oxide (XIV), in order to confirm further the designated structure (IX). Treatment of 6-amino-3-chloropyridazine 1-oxide (XI)[5] with potassium hydrosulphide gave 6-aminopyridazine-3-thiol 1-oxide (XII), which was without isolation converted into the methyl derivative (XIII). Diazotization of (XIII) followed by careful addition of copper powder afforded 6-chloro-3-methylthiopyridazine 1-oxide (XIV), which was different from compound (IX).

Thus the nucleophilic displacement reactions of 3,6-dichloropyridazine 1-oxide (II) with sulphur nucleophiles take place at the 6-position, in contrast to results with oxygen and nitrogen nucleophiles.[1] At present we do not have enough data to rationalize this difference in behaviour. It seems that the concept of 'hard' and 'soft' acids and bases[6] might give one possible explanation. Substitution reactions with carbon nucleophiles and an ambident species such as thiocyanate anion would be expected to be informative. However several reactions[7] have been noted in which the position of preferred nucleophilic attack in polyhalogenodiazines varies with changes of nucleophile and reaction conditions.

EXPERIMENTAL

N.m.r. spectra were taken (unless otherwise noted) with a Varian HA-100 spectrometer, with tetramethylsilane as internal standard in $CDCl_3$ or $(CD_3)_2SO$ and external standard in D_2O.

3-Chloropyridazine-6-thiol 1-Oxide (III).—(*a*) To a solution of sodium sulphide nonahydrate (4.35 g, 18 mmol) in water (50 ml) was added a solution of 3,6-dichloropyridazine 1-oxide (II) (1.0 g, 6 mmol) in dioxan (50 ml). The mixture was stirred for 10 h at room temperature and evaporated under reduced pressure. To the residue was added water (10 ml), and insoluble matter was filtered off. The filtrate was made acidic (10% HCl) and the separated solid was collected and washed with water to give a yellow *powder* (710 mg, 72%), m.p. 74—76° (Found: C, 29.3; H, 1.65; N, 16.85. $C_4H_3ClN_2OS$ requires C, 29.55; H, 1.85; N, 17.3%), δ ($CDCl_3$) (Varian T60 instrument) 7.14 and 7.88 (2 H, ABq, *J* 9 Hz, 4- and 5-H).

(*b*) A solution of potassium hydroxide (958 mg, 17.1 mmol) in absolute methanol (75 ml) was saturated with hydrogen sulphide, 3,6-dichloropyridazine 1-oxide (2 g, 12.1 mmol) was added, and the mixture was stirred for 5 h at room temperature, then evaporated under reduced pressure. Hydrochloric acid (5%; 10 ml) was added to the residue, which was then extracted with ethyl acetate. The solid obtained from the extract was dissolved in aqueous 5% sodium hydrogen carbonate (20 ml) and the solution was filtered and acidified (10% HCl). The separated solid was collected and washed with water to give a yellow powder (1.97 g, 70.2%), m.p. 73—75°, identical (n.m.r. spectrum) with the sample obtained in (*a*).

3-Methoxypyridazine-6-thiol 1-Oxide (IV).—3-Chloropyridazine-6-thiol 1-oxide (III) (488 mg, 3 mmol) was added to sodium methoxide solution [from sodium (690 mg, 30 mmol) in absolute methanol (50 ml)]. The mixture was refluxed for 2 h, then evaporated under reduced pressure. To the residue was added water (10 ml), and insoluble matter was filtered off. The filtrate was made acidic (3N-HCl) and the separated solid was collected and washed with water to give a yellowish powder (250 mg, 54%), m.p. 138—140° (from ethanol) (lit.,[3] 140—141°), identical (i.r. and n.m.r. spectra) with a sample obtained from 6-chloro-3-methoxypyridazine 1-oxide (VI).[1a]

3,3′-Dimethoxy-6,6′-dithiodipyridazine 1,1′-Dioxide (V).—To a solution of 3-methoxypyridazine-6-thiol 1-oxide (IV) (500 mg) in aqueous 5% sodium hydrogen carbonate (20 ml) was added dropwise a methanolic solution of iodine (5%) at room temperature with stirring until no more iodine was consumed. The separated solid was collected and recrystallized from chloroform–hexane to give yellowish *crystals* (385 mg, 75%), m.p. 212—213.5° (Found: C, 37.9; H, 3.15; N, 17.75. $C_{10}H_{10}N_4O_4S_2$ requires C, 38.2; H, 3.2; N, 17.8%), δ [$(CD_3)_2SO$] 3.86 (6 H, s, OCH_3) and 6.96 and 7.80 (4 H, ABq, *J* 9 Hz, 4-, 5-, 4′-, and 5′-H).

3,3′-Dichloro-6,6′-dithiodipyridazine 1,1′-Dioxide (VII).—(*a*) Treatment of 3-chloropyridazine-6-thiol 1-oxide (III) as above gave the disulphide (VII) as a yellowish *powder*, m.p. 239.5—240° (Found: C, 29.95; H, 1.3; N, 17.35. $C_8H_4Cl_2N_4O_2S_2$ requires C, 29.7; H, 1.3; N, 17.3%).

(*b*) A solution of 3,6-dichloropyridazine 1-oxide (II)

* Comparison of the i.r. spectra of the two compounds has recently established that they are identical (Professor M. Tišler, personal communication).

[4] T. Sega, A. Pollak, B. Stanovnik, and M. Tišler, *J. Org. Chem.*, 1973, **38**, 3307.

[5] (*a*) T. Itai and T. Nakashima, *Chem. and Pharm. Bull. (Japan)*, 1962, **10**, 936; (*b*) T. Horie and T. Ueda, *ibid.*, 1963, **11**, 114.

[6] R. G. Pearson, *J. Amer. Chem. Soc.*, 1963, **85**, 3533; *J. Chem. Educ.*, 1968, **45**, 581.

[7] R. G. Shephered and J. L. Fedrick, *Adv. Heterocyclic Chem.*, 1965 **4**, 145.

(330 mg, 2 mmol) and thiourea (168 mg, 2.2 mmol) in ethanol (12 ml) was refluxed for 1 h and evaporated under reduced pressure. To the residue were added water (20 ml) and aqueous 10% sodium hydroxide (10 ml), and the mixture was filtered; to the filtrate was added dropwise a methanolic solution of iodine (5%) at room temperature until no more iodine was consumed. The separated solid was collected and washed with water to give a yellowish powder (100 mg, 31%), identical (i.r. spectrum) with the sample obtained in (*a*).

3-*Chloro*-6-*methylthiopyridazine* 1-*Oxide* (IX).—To a solution of sodium hydrogen carbonate (136 mg, 1.66 mmol) and 3-chloropyridazine-6-thiol 1-oxide (III) (270 mg, 1.66 mmol) in water (7 ml), cooled in ice, were added methyl iodide (473 mg, 3.33 mmol) and acetone (2 ml). The mixture was stirred for 1 h at room temperature, then evaporated under reduced pressure. The separated *solid* was collected and recrystallized from ethyl acetate; yield 240 mg (82%), m.p. 194—197° (Found: C, 34.2; H, 2.85; N, 16.15. $C_5H_5ClN_2OS$ requires C, 34.0; H, 2.85; N, 15.95%), δ ($CDCl_3$) 2.46 (3 H, s, SCH_3) and 7.10 and 7.39 (2 H, ABq, *J* 9 Hz, 4- and 5-H).

3-*Chloro*-6-*methylsulphonylpyridazine* 1-*Oxide* (X).—To a solution of 3-chloro-6-methylthiopyridazine 1-oxide (IX) (60 mg, 0.31 mmol) in chloroform (4 ml) was added *m*-chloroperbenzoic acid (200 mg, 1.15 mmol); the mixture was stirred at room temperature for 1.5 h, chloroform (10 ml) was added, and the resulting solution was washed with aqueous 10% sodium hydrogen carbonate and then with saturated aqueous sodium chloride. The solid obtained from the chloroform layer was recrystallized from ethyl acetate–n-hexane to give *crystals* (60 mg, 92%), m.p. 155—157° (Found: C, 29.15; H, 2.35; N, 13.15. $C_5H_5ClN_2O_3S$ requires C, 28.8; H, 2.4; N, 13.4%), δ ($CDCl_3$) 3.40 (3 H, s, SO_2CH_3) and 7.27 and 8.26 (2 H, ABq, *J* 9 Hz, 4- and 5-H).

6-*Benzylthio*-3-*chloropyridazine* 1-*Oxide* (VIII).—(*a*) To a solution of sodium hydroxide (96 mg, 2.4 mmol) and phenylmethanethiol (297.6 mg, 2.4 mmol) in water (2.5 ml), cooled in ice, were added 3,6-dichloropyridazine 1-oxide (II) (330 mg, 2 mmol) and dioxan (0.6 ml). The mixture was stirred for 2 h and the separated *solid* was recrystallized from ethanol; yield 320 mg (63%), m.p. 180—184° (Found: C, 52.3; H, 3.5; N, 11.1. $C_{11}H_9ClN_2OS$ requires C, 52.25; H, 3.6; N, 11.1%), identical (i.r. spectrum) with the sample obtained from the following reaction.

(*b*) To a solution of sodium hydrogen carbonate (129 mg, 1.54 mmol) and 3-chloropyridazine-6-thiol 1-oxide (III) (250 mg, 1.54 mmol) in water (10 ml), cooled in ice, were added benzyl chloride (252 mg, 2.0 mmol) and acetone (5 ml). After being stirred for 2 h at room temperature, the mixture was evaporated under reduced pressure. The separated solid was collected and recrystallized from ethanol; yield 263 mg (72%), m.p. 181—184°.

6-*Amino*-3-*methylthiopyridazine* 1-*Oxide* (XIII).—A solution of potassium hydroxide (3 g, 53.5 mmol) in methanol (50 ml) cooled in ice was saturated with hydrogen sulphide. 6-Amino-3-chloropyridazine 1-oxide (XI) (2 g, 13.7 mmol) was added, and the mixture was heated at 130 °C for 12 h in a sealed vessel. The solvent was removed under reduced pressure and water (20 ml) was added to the residue. The clear solution was acidified to pH 3.5 with acetic acid and a small quantity of precipitate was removed by suction. To the filtrate were added sodium hydrogen carbonate (to pH 7.5) and then methyl iodide (2 ml, 32.2 mmol) with cooling in ice. The mixture was stirred for 2 h at room temperature then evaporated under reduced pressure to remove the excess of methyl iodide. The resulting solution was kept in a refrigerator to cause precipitation. The separated solid was collected and recrystallized from concentrated hydrochloric acid to give the *hydrochloride* of (XIII) as needles (1.2 g, 45%), m.p. 150—153° (Found: C, 30.55; H, 3.85; N, 21.55. $C_5H_7N_3OS$,HCl requires C, 31.0; H, 4.15; N, 21.7%), δ (D_2O) (Varian T60 instrument) 2.54 (3 H, s, SCH_3) and 7.44 (2 H, s, 4- and 5-H).

6-*Chloro*-3-*methylthiopyridazine* 1-*Oxide* (XIV).—To a suspension of 6-amino-3-methylthiopyridazine 1-oxide (XIII) hydrochloride (387 mg, 1.99 mmol) in a mixture of concentrated hydrochloric acid (5 ml) and water (1 ml) cooled in ice was added sodium nitrite (207 mg, 3.0 mmol) during 20 min. After a further 10 min a small quantity of copper powder was added. After stirring for 30 min, the separated solid was collected and purified by column chromatography on silica gel [$CHCl_3$–EtOH (3 : 4)] to yield the product (XIV), which was recrystallized (from $CHCl_3$–C_6H_6) to give slightly yellow *crystals* (25 mg, 7%), m.p. 169—172° (Found: C, 34.1; H, 2.7; N, 16.0 $C_5H_5ClN_2OS$ requires C, 34.0; H, 2.85; N, 15.95%), δ ($CDCl_3$) (Varian T60 instrument) 2.60 (3 H, s, SCH_3) and 6.91 and 7.60 (2 H, ABq, *J* 9 Hz, 4- and 5-H).

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