

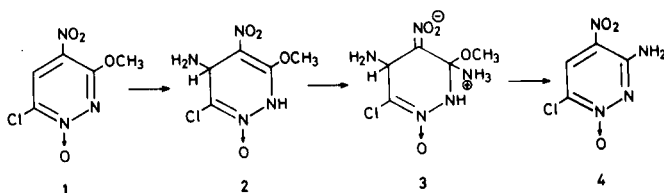
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Reaction of 3-chloro-6-methyl-4-nitropyridazine 1-oxide (**5**) with methanolic ammonia at 0° led to a replacement of the chlorine atom by a methoxy group as well as by an amino group. Reaction of the 3-methoxy-6-methyl-4-nitropyridazine 1-oxide (**6**) with the same reagent led to amino-demethoxylation; this replacement reaction was very slow. Attempts to perform these reactions with liquid ammonia failed. Pmr spectroscopy of solutions of compound **6** in methanolic ammonia revealed that no  $\sigma$ -adduct was present. However in liquid ammonia a 1:1  $\sigma$ -adduct at C-5 *i.e.* **12b** was formed. 3,6-Dimethoxy-4-nitropyridazine 1-oxide (**7**) gave with methanolic ammonia an amino-demethoxylation at C-6. No  $\sigma$ -adduct could be detected by pmr spectroscopy. However, in liquid ammonia convincing pmr data were obtained showing the presence of a 1:1  $\sigma$ -adduct at C-5.

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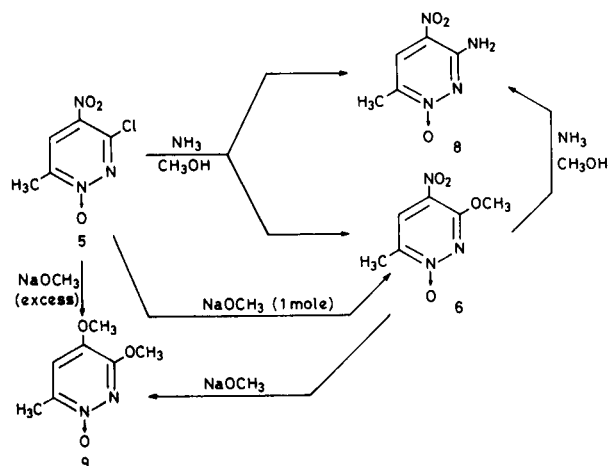
In the preceding papers (3,4) we reported that the reaction of 6-chloro-3-methoxy-4-nitropyridazine 1-oxide (**1**) with methanolic ammonia and with liquid ammonia gave 3-amino-6-chloro-4-nitropyridazine 1-oxide (**4**). The mechanism of this amino-demethoxylation was proposed to proceed through the  $\sigma$ -adduct **2**, since the pmr spectrum of a solution of **1** in methanolic ammonia and in liquid ammonia showed a singlet signal at 4.82 ppm, strongly indicating the presence of a hydrogen atom at a saturated carbon atom at position 5. The replacement of the methoxy group by an amino group took place in the nitrovinyl moiety of **2** *via* **3**.



Scheme I

In extending these studies, we investigated the amination of 3-chloro-6-methyl- (**5**), 3-methoxy-6-methyl- (**6**) and 3,6-dimethoxy-4-nitropyridazine 1-oxide (**7**) and looked for the possible intermediacy of Meisenheimer adducts by pmr spectroscopy. Reaction of 3-chloro-6-methyl-4-nitropyridazine 1-oxide (**5**) with methanolic ammonia at 0° for 1 hour gave 3-methoxy-6-methyl-4-nitropyridazine 1-oxide (**6**) and 3-amino-6-methyl-4-nitropyridazine 1-oxide (**8**). The structure assignment of **8** was based on i) the pmr spectrum (DMSO- $d_6$ ) showing the singlet signal (3H) of the methyl group at  $\delta$  2.26 ppm, the singlet (1H) of the ring proton at  $\delta$  8.55 ppm and a broad signal (2H) at  $\delta$  7.80-8.25 ppm ascribed to the presence of the amino group; ii) the ir spectrum (potassium bromide) featuring the NH stretching vibration absorptions at 3420  $cm^{-1}$  and 3250  $cm^{-1}$  and the  $N^+-O^-$  stretching vibration

at 1310  $cm^{-1}$ ; iii) the mass spectrum showing the molecular peak at  $m/e$  170 and a fragmentation peak at  $m/e$  153 (M-17, loss of OH from the  $N^+-O^-$  function and the methyl group) and iv) the elemental analysis ( $C_5H_6N_4O_3$ ). The structure of compound **6** was proved by identity with an authentic specimen (**5**) with respect to its melting point

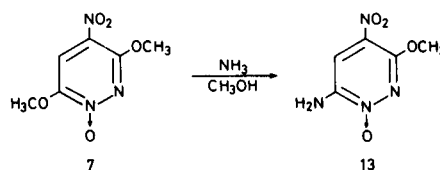


Scheme II

and its spectrum (potassium bromide).

On reacting 3-methoxy-6-methyl-4-nitropyridazine 1-oxide (**6**) with methanolic ammonia at 0° for 1 hour, amino-demethoxylation into **8** occurred. The rate of this reaction was very low, since the yield of **8** was only 8.8% and **6** could be recovered in a yield of 73%. Reaction of **6** at 50° for 1 hour gave **8** in a reasonable yield (62%). From these results, it was evident that the greater part of the 3-amino compound **8** obtained from the 3-chloro compound **5** by methanolic ammonia at 0° was not formed through the 3-methoxy compound **6**. Moreover, these reactions show that in compound **6** the 3-position has a higher reactivity towards nucleophiles than position 4. This was also found on reacting **5** with one mole of sodium

methoxide in absolute methanol at  $-20^{\circ}$  the 3-methoxy compound **6** being obtained in a reasonable yield (62%). This order of reactivity ( $3 > 4$ ) was in excellent agreement with the reactivity order found (6) in the reaction of halogenopyridazine 1-oxides with nucleophiles,  $5 > 3 > 6 > 4$ . The reaction of **5** with two moles of sodium methoxide in absolute methanol under refluxing was reported (5) to replace both the nitro group and the chlorine atom, yielding the 3,4-dimethoxy derivative **9**. In order to obtain some information on the mechanism of the aminodemethoxylation ( $6 \rightarrow 8$ ), we investigated the pmr spectrum of **6** in methanolic ammonia at  $0^{\circ}$ . We could not obtain any evidence for the intermediacy of a  $\sigma$ -adduct. This was an interesting contrast to our previous observation with the 3-methoxy compound **1** which gave under identical conditions a  $\sigma$ -adduct at C-5 *i.e.*, **2**. Apparently the presence of the electron-donating methyl group at position 6 instead of the electron-attracting chlorine atom made addition at position 5 in compound **6** disadvantageous. Since by pmr spectroscopy no evidence for an adduct at C-5 was formed in methanolic ammonia, we postulate that the formation of compound **8** from **6** took place *via* the  $\sigma$ -adduct at C-3 (**10b**). Similarly the conversion of  $5 \rightarrow 8$  and of  $5 \rightarrow 6$  will probably occur *via* **10a** and **11a**, respectively. It was evident that the formation of **10** or **11** must occur in a rate determining step of the reaction, since no considerable build-up of the intermediary  $\sigma$ -adduct has been observed. This was in agreement with the general theory on nucleophilic substitution reactions.



Scheme III

Attempts to aminate **6** with liquid ammonia at  $-33^{\circ}$  for 1 hour failed; no substitution product could be isolated and the starting material was recovered in a yield of 89%. Also treatment of compound **5** with liquid ammonia resulted in a strongly coloured reaction mixture from which no aminated product or starting material could be isolated. Surprisingly, however, we observed that in the pmr spectrum of **6** in liquid ammonia at  $-40^{\circ}$ , the proton at C-5 lies about 3.5 ppm at a higher field than in a solution in deuteriochloroform (see Table I and Table II). This led to the conclusion that in liquid ammonia the  $\sigma$ -adduct (**12b**) was present. The reason why in liquid ammonia a  $\sigma$ -adduct at C-5 was formed and not in methanolic ammonia was not quite obvious. It might be connected with the fact that ammonia in methanol was strongly solvated which decreased (7) the reactivity of the lone-pair of the ammonia in a nucleophilic addition. Reaction of 3,6-dimethoxy-4-nitropyridazine 1-oxide (**7**) with methanolic ammonia at  $0^{\circ}$  and with liquid ammonia at  $-33^{\circ}$  gave a complicated mixture from which no product could be isolated. However, when the reaction with

Table I

Chemical Shifts of the 4-Nitropyridazine 1-Oxides **5-8, 10** (Expressed in ppm)

	H (5)	CH <sub>3</sub>	CH <sub>3</sub> O	NH <sub>2</sub>
3-Chloro-6-methyl-4-nitropyridazine 1-Oxide ( <b>5</b> ) (a)	8.37	2.55	---	--
3-Methoxy-6-methyl-4-nitropyridazine 1-Oxide ( <b>6</b> ) (a)	8.20	2.48	4.12	--
3,6-Dimethoxy-4-nitropyridazine 1-Oxide ( <b>7</b> ) (a)	7.98	--	4.12; 4.14	--
3-Amino-6-methyl-4-nitropyridazine 1-Oxide ( <b>8</b> ) (b)	8.55	2.26	---	7.80-8.25 (broad)
3-Amino-6-methoxy-4-nitropyridazine 1-Oxide ( <b>10</b> ) (b)	8.00	--	3.98	6.84 (broad singlet)

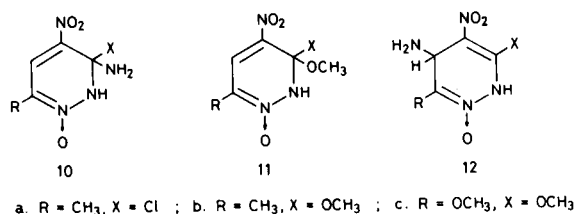
(a) Deuteriochloroform. (b) DMSO-d<sub>6</sub>.

Table II

Chemical Shifts of some 4-Nitropyridazine 1-Oxides Dissolved in Liquid Ammonia (Expressed in ppm)

	H (5)	CH <sub>3</sub>	CH <sub>3</sub> O
3-Chloro-6-methyl-4-nitropyridazine 1-Oxide ( <b>5</b> )	4.72	2.08	--
3-Methoxy-6-methyl-4-nitropyridazine 1-Oxide ( <b>6</b> )	4.68	2.08	3.65
3,6-Dimethoxy-4-nitropyridazine 1-Oxide ( <b>7</b> )	5.14	--	3.78; 4.08
4-Nitro-pyridazine 1-Oxide ( <b>1</b> )	4.55	--	--

methanolic ammonia was carried out at  $-20^{\circ}$ , an orange-coloured product was obtained which was assigned the structure of 6-amino-3-methoxy-4-nitropyridazine 1-oxide (**13**). This was based on the following results: i) the pmr spectrum (DMSO- $d_6$ ) showed the singlet signal (3H) of the methoxy group at  $\delta$  3.98 ppm, the singlet signal (3H) of the ring proton at  $\delta$  8.00 ppm and a broad singlet signal (2H) of the amino group at  $\delta$  6.84 ppm; ii) the ir spectrum (potassium bromide) clearly gave the NH stretching vibration absorptions at  $3375\text{ cm}^{-1}$  and  $3250\text{ cm}^{-1}$  and the  $\text{N}^+-\text{O}^-$  stretching vibration adsorption at  $1315\text{ cm}^{-1}$ ; iii) the mass spectrum gave the molecular peak at  $m/e$  186; and iv) the elemental analysis ( $\text{C}_5\text{H}_6\text{N}_4\text{O}_4$ ). This structure assignment was confirmed by an underpressed melting point when mixed with an authentic specimen (**8**).



Scheme IV

Attempts to obtain by pmr spectroscopy an indication about the possible intermediate in this amino-demethoxylation failed. No  $\sigma$ -adduct could be detected in the methanolic ammonia. However, a C-5 adduct between **7** and ammonia *i.e.*, **12c** was observed when liquid ammonia was used (see Table II). As indicated above no product could be obtained from the reaction mixture. The addition of liquid ammonia to C-5 in the 4-nitropyridazine 1-oxides **6** and **7** were in agreement with the results of the study of the kinetics of nucleophilic displacement reactions (6).

## EXPERIMENTAL

Melting points are uncorrected. The ir spectra were taken on a Hitachi EPI-G3 apparatus. The pmr spectra were recorded on a Jeol JNM C-60 H spectrometer. The spectra were taken in deuteriochloroform, DMSO- $d_6$ , using TMS (0 ppm) as internal standard. The mass spectra were recorded with an AEI MS 902 instrument.

a) The following starting materials were prepared by procedures given in the literature: 3-chloro-6-methyl-4-nitropyridazine 1-oxide (**5**) (5); 3-methoxy-6-methyl-4-nitropyridazine 1-oxide (**6**) (5); 3,6-dimethoxy-4-nitropyridazine 1-oxide (**7**) (9).

b) Reaction of 3-Chloro-6-methyl-4-nitropyridazine 1-Oxide (**5**) with Methanolic Ammonia.

A solution (10 ml.) of **5** (380 mg., 2 mmoles) in absolute methanol was saturated with ammonia at  $0^{\circ}$  for 1 hour. The solvent was removed *in vacuo* and the residue was separated by preparative tlc on silica gel using chloroform as eluent. Compound **6** was crystallized from methanol yielding 120 mg. (32%) of yellow prisms, m.p.  $98-99^{\circ}$ . The structure was identified by ir comparison (potassium bromide) with an authentic specimen (**5**)

and underpressed mixed melting point. 3-Amino-6-methyl-4-nitropyridazine 1-oxide (**8**) was crystallized from methanol to orange scales, m.p.  $213^{\circ}$ , yield 130 mg. (38%). The structure was further identified by ir comparison with an authentic specimen (10,11) and underpressed mixed melting point.

*Anal.* Calcd. for  $\text{C}_5\text{H}_6\text{N}_4\text{O}_3$  (170.13): C, 35.30; H, 3.55; N, 32.93. Found: C, 35.17; H, 3.40; N, 32.63.

c) Reaction of 3-Chloro-6-methyl-4-nitropyridazine 1-Oxide (**5**) with Sodium Methoxide in Absolute Methanol.

3-Chloro-6-methyl-4-nitropyridazine 1-oxide (**5**) (380 mg., 2 mmoles) was added at about  $-5^{\circ}$  to a solution of sodium methoxide in absolute methanol, prepared from absolute methanol (25 ml.) and sodium (48 mg., 2 mmoles). The mixture was kept at this temperature for an hour. The solvent was removed *in vacuo*, water was added and extracted with chloroform. After drying over magnesium sulfate, the chloroform was removed *in vacuo* and the residue was purified by column chromatography through silica gel, using chloroform as eluent. Recrystallization from methanol gave 230 mg. (62%) of **6**, yellow needles, m.p.  $98-99^{\circ}$ . This melting point was not depressed on admixture with authentic specimen of **6** (**5**).

d) Reaction of 3-Methoxy-6-methyl-4-nitropyridazine 1-Oxide (**6**) with Methanolic Ammonia.

A solution of **6** (370 mg., 2 mmoles) in 10 ml. of methanol was saturated with ammonia at  $0^{\circ}$  for 1 hour. The solvent was removed *in vacuo* and the residue was purified by preparative tlc of silica gel, using chloroform as eluent. Starting material (**6**) was recovered (270 mg., 73%). Compound **8** was crystallized from methanol to give orange scales, m.p.  $210^{\circ}$  (lit. (10,11)  $203-204^{\circ}$ ), yield 30 mg. (8.8%). When the reaction was carried out at  $50^{\circ}$  in a sealed tube, the yield of **8** increased to 62%.

e) Reaction of 3,6-Dimethoxy-4-nitropyridazine 1-Oxide (**7**) with Methanolic Ammonia.

A solution of **7** (400 mg., 2 mmoles) in absolute methanol was saturated with ammonia at  $-20^{\circ}$  for 1 hour. The solvent was removed *in vacuo* and the residue was purified by preparative tlc of silica gel, using ethyl acetate as eluent. Crystallization from ethyl acetate gave 100 mg. (27%) of 6-amino-3-methoxy-4-nitropyridazine 1-oxide (**13**), orange needles, m.p.  $183-184^{\circ}$  dec. It gave a completely identical ir spectrum (potassium bromide) with an authentic specimen of **13** (**8**).

*Anal.* Calcd. for  $\text{C}_5\text{H}_6\text{N}_4\text{O}_4$ : C, 32.26; H, 3.25. Found: C, 32.50; H, 2.98.

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