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Studies on Syntheses and Reactions of Methoxypyridazines. II. Methoxylation of 3,4,6-Trichloropyridazine^{1,2)}

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Methoxylation of 3,4,6-trichloropyridazine (**1**) with sodium methoxide was investigated in detail. Dimethoxylation of **1** afforded 6-chloro-3,4-dimethoxypyridazine (**5**) and a molecular complex (M) which is composed of **5** and 3-chloro-4,6-dimethoxypyridazine (**6**) in a ratio of 1 : 1. The nature of the complex (M) was examined by thermal and X-ray analyses. The molecular complex (M) was also obtained by monomethoxylation of 3,6-dichloro-4-methoxypyridazine (**3**) with sodium methoxide.

Keywords—3,4,6-trichloropyridazine; methoxylation; pyridazinone; dimethoxymonochloropyridazine; trimethoxypyridazine; molecular complex; thermal analysis; X-ray analysis

Our previous article described the result of methoxylation of 3,4,5-trichloropyridazine.²⁾ In this paper, we report some observations concerning the methoxylation of isomeric 3,4,6-trichloropyridazine (**1**), involving the formation of several types of methoxypyridazines and especially a unique molecular complex which is composed of 6-chloro-3,4-dimethoxypyridazine (**5**) and 3-chloro-4,6-dimethoxypyridazine (**6**).

Eichenberger *et al.*³⁾ obtained 3,6-dichloro-4-methoxypyridazine (**3**) in 70% yield⁴⁾ by monomethoxylation of **1** with NaOMe. On the other hand, Schönbeck and Kloimstein⁵⁾ reported that dimethoxylation of **1** with 2 eq of NaOMe afforded 6-chloro-3,4-dimethoxypyridazine (**5**) in 40% yield and a compound which was assigned as 3-chloro-4,6-dimethoxypyridazine (**6**) (mp 95–96 °C) in 52% yield.

From these reports it can be presumed that the monomethoxylated pyridazine **3** may be an intermediate in the formation of the dimethoxypyridazines **5** and **6**. Therefore, monomethoxylation of **3** with 1 eq of NaOMe was investigated in detail. The methoxylation resulted in the formation of two products, **5** and a molecular complex M in 44% and 47% yields, respectively.⁶⁾ The melting point of the complex M was identical with that of the compound **6** which was obtained by Schönbeck and Kloimstein⁵⁾ as described above. Some doubts concerning the structure of Schönbeck's compound **6**, however, arose from an examination of its proton nuclear magnetic resonance (¹H-NMR) spectral data. The ¹H-NMR spectrum of the complex M showed two sets of signals which are composed of those of **5** [δ 6.81 (1H, s, C₅-H), 3.98 (3H, s, OMe) and 4.17 (3H, s, OMe)] and **6** [δ 6.38 (1H, s, C₅-H), 4.10 (3H, s, OMe) and 3.96 (3H, s, OMe)] (Fig. 1 and Table I). The ratio of **5** and **6** in the complex M was determined to be 1 : 1 on the basis of the integral ratio of C₅-H in the ¹H-NMR spectrum. Reinvestigation of the dimethoxylation of **1** also gave **5** and M in the same yields as in the case of monomethoxylation of **3**. These results indicate that the complex M (Schönbeck's compound **6**) is a complex composed of **5** and **6** in a ratio of 1 : 1. Attempts to separate **5** from **6** in the complex M by fractional recrystallization from many kinds of solvents or by chromatography were unsuccessful.

Fig. 1. ¹H-NMR Spectra of Compounds 5, 6 and Complex M

Alkaline degradation of the complex M allowed isolation of **6**. After hydrolysis of the complex M with 5% NaOH at 100 °C for 20 min, the unresolved materials, which was proved to contain **5** and **6** in a ratio of 1 : 3 by ¹H-NMR spectral analysis, was collected and submitted to fractional recrystallization from MeOH to afford **6** as pure crystals together with the complex M. The melting point of **6** thus obtained was identical with that of **6** described by Landquist and Meek.⁷⁾ From 17.5 g of the complex M, 1.6 g of **6** was isolated. The above separation method is based on the fact that the methoxyl group at position 4 of **5** is hydrolyzed faster than that of **6**.

As described above, the methoxylation *via* **3** is unsatisfactory for the preparation of **6**. An

TABLE I. ¹H-NMR Spectral Data for Methoxypyridazines 2–8 (CDCl₃; δ ppm)

Product No.	C ₅ -H (each 1H, s)	OCH ₃ (each 3H, s)
2	7.50	4.18
3	6.98	4.06
4	7.16	4.17
5	6.81	3.98
		4.17
6	6.38	3.96
		4.10
8	6.29	3.89
		4.02
		4.10

Chart 2

alternative synthetic route *via* 3,4-dichloro-6-methoxypyridazine (**4**) leading to **6** was examined. The methoxypyridazine **4** has been prepared by Schönbeck and Kloimstein⁵⁾ by the treatment of 5,6-dichloro-3(2*H*)-pyridazinone (**10**) with diazomethane (Chart 2). However, the above reaction under Schönbeck's conditions gave another compound, 5,6-dichloro-2-methyl-3(2*H*)-pyridazinone (**11**),⁷⁾ in 52% yield in addition to **4** (16%). The structure of **11** was determined by comparison of the melting point and spectral data with those of the previously reported **11**.⁸⁾ The pyridazinone **11** was independently synthesized in 67% yield by methylation of **10** with methyl iodide in the presence of potassium carbonate as shown in Chart 2. It is noteworthy that the pyridazine **6** was synthesized by monomethoxylation of **4**. By chlorination of 6-chloro-3-methoxy-4(1*H*)-pyridazinone (**9**)⁵⁾ with phosphorus oxychloride, 4,6-dichloro-3-methoxypyridazine (**2**) was synthesized in 90% yield, and monomethoxylation of **2** afforded **5** in 91% yield.

The trimethoxylation of **1** with excess NaOMe was investigated. A solution of **1** and excess NaOMe in MeOH was refluxed and the reaction was monitored by ¹H-NMR spectroscopy. After 30 h, the ratio of **5**, **6** and trimethoxylated compound **8** was 5.4:1.5:1. These results indicate the very slow conversion of the dimethoxylated compounds **5** and **6** into **8**. After refluxing for 1 h, however, MeOH was evaporated off until the temperature of the

Fig. 2. DSC Curves of Compounds **5**, **6** and **M**, **M'** and Their Molten Mixture
a) **5**; b) **6**; c) **M**; d) **M'**; e) **6**=83%; f) **6**=24%.

Fig. 3. X-Ray Diffraction Patterns of Compounds **5**, **6** and **M**, **M'** and Physical Mixture of **5** and **6**

reaction mixture reached 80 °C, and then the mixture was further heated for 10 h to afford **8** and **9** in 55% and 9% yields, respectively.

The structure of the interesting complex **M** was examined by the thermal and X-ray analyses.

Thermal Analysis: The differential scanning calorimetry (DSC) curves of **5**, **6**, **M**, **M'** (the molten mixture of **5** and **6** in a weight ratio of 1 : 1) and molten mixtures of **5** and **6** in various weight ratios were recorded using a DSC apparatus (TA 3000, Mettler) in the range of 40–140 °C at a rate of 5 °C/min.

The measurement of each sample was repeated to obtain the DSC curves of physical mixture and molten mixture. Examples of the DSC curves are shown in Fig. 2. Sharp endothermic peaks owing to melting of **5**, **6**, **M** and **M'** appeared at 129, 110, 94 and 90 °C, respectively (Fig. 2a, 2b, 2c and 2d). The molten mixture containing 66–98% of **5** in **6** showed the melting of **5** and a eutectic peaks at around 110 and 80–88 °C, respectively (Fig. 2e), while

Fig. 4. X-Ray Diffraction Patterns of Compounds **5** and **6** and Their Eutectic Mixtures

Fig. 5. Phase Diagram

○, temperature of melting peaks; ●, temperature of pre-melting peaks.

the mixtures of 10–40% of **6** in **5** showed four peaks (Fig. 2f). This suggests the existence of complex phases at lower concentration ratios of **5**. The molten mixture containing 62.5% of **6** in **5** showed one sharp peak similar to that in Fig. 2d.

Powder X-Ray Analysis: Powder X-ray diffraction patterns of compounds **5**, **6**, **M**, **M'**, physical mixture of **5** and **6**, and the molten sample after thermal analyses were measured by using an X-ray diffractometer (RAD-rVB, Rigaku Denki; Cu- K_{α} ; 50 kV; 120 mA) with a non reflex sample holder (Fig. 3 and Fig. 4).

The diffraction patterns of **5**, **6**, **M**, **M'** were different, **M** and **M'** being polymorphs with 5 °C difference in their melting points. No changes due to melting were found for **5** and **6**. It was clear that **M** was not a simple mixture of **5** and **6**, since the physical mixture of **5** and **6** differed from **M** and **M'** in terms of the diffraction patterns. The patterns of the melts

containing 5—43%, 50—60% and 79—95% **6** were identical with those of the physical mixture of **5** and **M**, **M'** and the physical mixture of **6** and **M'**, respectively. When the weight percentage of **6** was 0—43, irregular shifts of diffraction peaks were found compared with the case of weight percentage >73.

The phase diagram of the mixture of **5** and **6** was drawn on the basis of DSC measurement (Fig. 5). The reasonable correspondence between the phase diagram in Fig. 5 and the changes of X-ray diffraction patterns in Fig. 3 suggested that **M** was not a simple crystalline mixture of **5** and **6** but a solid solution or a molecular compound formed when the equimolar mixture crystallized.

Experimental

Melting points were determined by the capillary method, and are uncorrected. ¹H-NMR spectra were taken on a Hitachi R-20B spectrometer (60 MHz), and chemical shifts are given in the (ppm) scale with tetramethylsilane as an internal standard.

Monomethoxylation of 3,6-Dichloro-4-methoxypyridazine (3)—A solution of 1 M NaOMe in MeOH (100 ml) was added to a stirred suspension of **3** (17.9 g) in MeOH (100 ml), and the mixture was heated under reflux for 1 h. The MeOH was evaporated off and water (50 ml) was added to the residue. The mixture was extracted with CHCl₃ and dried over K₂CO₃. The solvent was evaporated off and the residue was recrystallized from MeOH to give two products, 6-chloro-3,4-dimethoxypyridazine (**5**) and complex **M**. Compound **5**: 7.69 g (44%), mp 128—129 °C (lit.³) mp 130—131 °C). Complex **M**: 8.20 g (47%), mp 95—96 °C. *Anal.* Calcd for C₆H₇ClN₂O₂: C, 41.28; H, 4.04; N, 16.05. Found: C, 41.17; H, 3.97; N, 16.12.

Separation of 3-Chloro-4,6-dimethoxypyridazine (6) from Complex M—A mixture of complex **M** (17.5 g) and 5% NaOH solution (200 g) was heated with stirring at 100 °C for 20 min. The reaction mixture was extracted with CHCl₃. The organic layer was dried over K₂CO₃ and concentrated to dryness. The residue was recrystallized from MeOH to give 1.6 g (18%) of **6** as colorless crystals, mp 110—111 °C (lit.⁷) mp 110 °C). *Anal.* Calcd for C₆H₇ClN₂O₂: C, 41.28; H, 4.04; N, 16.05. Found: C, 41.41; H, 4.04; N, 16.04.

Reaction of 10 with Diazomethane—An ethereal solution of diazomethane [prepared from methylnitrosourea (5.15 g) and 5% KOH solution (15 ml)] in ether (50 ml) was added dropwise to a stirred suspension of **10** (4.95 g) in acetone (45 ml) at room temperature. After the evolution of N₂ gas had stopped, the solvent was evaporated off and the residue was recrystallized from *n*-hexane to give 1.80 g of 5,6-dichloro-2-methyl-3(2*H*)-pyridazinone (**11**), mp 97—98 °C (lit.⁸) mp 97—98 °C). The mother liquor was submitted to column chromatography on alumina using CHCl₃ as the eluent to afford an additional 1.0 g of **11** (total: 2.8 g, 52%) and 0.88 g (16%) of 3,4-dichloro-6-methoxypyridazine (**4**) as colorless crystals, mp 68—69 °C (*n*-hexane) (lit.⁵) mp 49—52 °C). **4**: *Anal.* Calcd for C₅H₄Cl₂N₂O: C, 33.55; H, 2.25; N, 15.65. Found: C, 33.20; H, 2.11; N, 15.40. **11**: *Anal.* Calcd for C₅H₄Cl₂N₂O: C, 33.55; H, 2.25; N, 15.65. Found: C, 33.41; H, 2.22; N, 15.54.

5,6-Dichloro-2-methyl-3(2*H*)-pyridazinone (11)—A mixture of **10** (1.65 g), K₂CO₃ (1.52 g) and iodomethane (1.56 g) in *N,N*-dimethylformamide (DMF) (20 ml) was stirred for 3 h at room temperature. The DMF was evaporated off under reduced pressure, then the residue was dissolved in a small amount of water and extracted with CHCl₃. The extract was dried over K₂CO₃ and concentrated to dryness. The residual solid was recrystallized from *n*-hexane to give 1.2 g (67%) of **11**, mp 97—98 °C, which was identical with a sample obtained above by the mixed melting point test.

3-Chloro-4,6-dimethoxypyridazine (6)—A solution of **4** (89.5 mg) in MeOH (2 ml) was added to a solution of 0.1 M NaOMe in MeOH (5 ml), and the mixture was refluxed for 1 h. The MeOH was evaporated off and water was added to the residue. The whole was extracted with CHCl₃ and the extract was dried over K₂CO₃. Removal of the solvent gave a solid, which were recrystallized from *n*-hexane to afford 62.8 mg (72%) of **6** as colorless crystals, mp 110—111 °C. This product was identical with a sample obtained from complex **M** by direct comparison of the ¹H-NMR spectra and by the mixed melting point test.

4,6-Dichloro-3-methoxypyridazine (2)—A mixture of **9** (16.1 g) and phosphorus oxychloride (153 g) was stirred at 80 °C until the crystals dissolved (a few min). The reaction mixture was poured into ice-water and slightly alkalinized by adding dil. NaOH solution. The mixture was extracted with CHCl₃, and the extract was dried over K₂CO₃ and evaporated to dryness. The residue was recrystallized from cyclohexane to give 16.1 g (90%) of **2** as colorless crystals, mp 80—81 °C. *Anal.* Calcd for C₅H₄Cl₂N₂O: C, 33.55; H, 2.25; N, 15.65. Found: C, 33.45; H, 2.22; N, 15.62.

6-Chloro-3,4-dimethoxypyridazine (5)—A 1 M NaOMe solution in MeOH (10 ml) was added to a solution of **2** (1.79 g) in MeOH (10 ml) and the mixture was refluxed for 1 h. The MeOH was removed *in vacuo* and water was added to the residue. The whole was extracted with CHCl₃. Evaporation of the solvent left crystals which were recrystallized from MeOH to give 1.60 g (91%) of **5**, mp 128—129 °C. This product was identical with a sample obtained from **3** by the mixed melting point test.

Trimethoxylation of 3,4,6-Trichloropyridazine (1)—A 1 M NaOMe solution in MeOH (200 ml) was added dropwise to an ice-cooled solution of **1** (9.15 g) in MeOH (50 ml) and then the mixture was heated for 1 h. The MeOH was evaporated off until the temperature of the reaction mixture reached 80 °C, and then the mixture was heated for 10 h and worked up as usual to afford 4.70 g (55%) of 3,4,6-trimethoxypyridazine (**8**) as colorless crystals, mp 121 °C (MeOH) (lit.⁹⁾ mp 121 °C). *Anal.* Calcd for C₇H₁₀N₂O₃: C, 49.41; H, 5.92; N, 16.46. Found: C, 49.31; H, 5.84; N, 16.27. The mother liquor was acidified (Congo red) with dil. HCl and the precipitate was collected and recrystallized from water to give 0.74 g (9%) of **9**, mp 225–228 °C. This product was identical with an authentic sample⁵⁾ by the mixed melting point test.

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References and Notes

- 1) A part of this work was presented at the Meeting of Tokai Branch, Pharmaceutical Society of Japan, Nagoya, Nov. 1984 and also at the 105th Annual Meeting of the Pharmaceutical Society of Japan, Kanazawa, Apr. 1985.
- 2) H. Nagashima, H. Oda, J. Hida, and K. Kaji, *Chem. Pharm. Bull.*, **35**, 421 (1987).
- 3) K. Eichenberger, R. Rometsch, and J. Druey, *Helv. Chem. Acta*, **39**, 1755 (1956).
- 4) We reexamined the same reaction and obtained **3** in 94% yield.
- 5) R. Schönbeck and H. Kloimstein, *Monatsh. Chem.*, **99**, 15 (1968).
- 6) Itai and Natsume isolated only **5** from the same reaction [T. Itai and S. Natsume, *Chem. Pharm. Bull.*, **10**, 643 (1962)].
- 7) J. K. Landquist and S. E. Meek, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2735.
- 8) Y. Maki, M. Takaya, and M. Suzuki, *Yakugaku Zasshi*, **86**, 487 (1966).
- 9) T. Itai and H. Igeta, *Yakugaku Zasshi*, **75**, 966 (1955).