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Shigeru Sako: Syntheses of Pyridazine Derivatives. II.[1] The Reactivity of Chlorine Atom in 3- or 6-Position of Chloropyridazine 1-Oxide.

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It was reported in part I of this series that the chlorine in 3 position was more reactive than the chlorine in 6 position of 3,6-dichloropyridazine 1-oxide (I) in the nucleophilic substitution.[1] Present paper describes the reactivity of chlorine in position 3 or 6 of monochloropyridazine 1-oxide.

3-Chloropyridazine 1-oxide had already been synthesized by H. Igeta.[2] 6-Chloropyridazine 1-oxide (IV) was prepared by adding powdered copper to a solution of 6-aminopyridazine 1-oxide[3] diazotized in hydrochloric acid. As shown in Table, when 3-chloropyridazine 1-oxide (III) and (IV) were separately allowed to stand with sodium methoxide for 30 minutes at 30°, 77% of 3-methoxypyridazine 1-oxide (VI) and 84% of 6-methoxypyridazine 1-oxide (VII) were obtained respectively. Though reaction was continued for 1 hour for 3-chloropyridazine (II), the yield of 3-methoxypyridazine (V) was only 33%. When they were heated with ethylamine on a steam bath for 1 hour, III and IV gave 72% of 3-ethylaminopyridazine 1-oxide (IX) and 79% of 6-ethylaminopyridazine 1-oxide (X) respectively, but 97% of starting material was recovered from II. By heating at 120~130° for 3 hours, II gave 40% of 3-ethylaminopyridazine (VIII), which was identical with the reduction product of 3-ethylamino-6-chloropyridazine (XI). III and IV reacted with ethylamine even at 28°, and gave their ethylamino derivatives in several percent yields.

Table I.

	Chloropyridazines	Agent	Reaction		Reaction product	Yield (%)
			Temp.	Time		
II	3-chloro	MeONa	30°	1 hr.	V	33
III	3-chloro 1-oxide	MeONa	30°	30 min.	VI	77
IV	6-chloro 1-oxide	MeONa	30°	30 min.	VII	84
II	3-chloro	$EtNH_2$	steam bath	1 hr.	VIII	— (97%*)
II	3-chloro	$EtNH_2$	120~130°	3 hr.	VIII	40 (34%*)
III	3-chloro 1-oxide	$EtNH_2$	steam bath	1 hr.	IX	72
III	3-chloro 1-oxide	$EtNH_2$	28°	5 hr.	IX	3.5
IV	6-chloro 1-oxide	$EtNH_2$	steam bath	1 hr.	X	79
IV	6-chloro 1-oxide	$EtNH_2$	28°	5 hr.	X	4 (93%*)

* Recovery of starting material

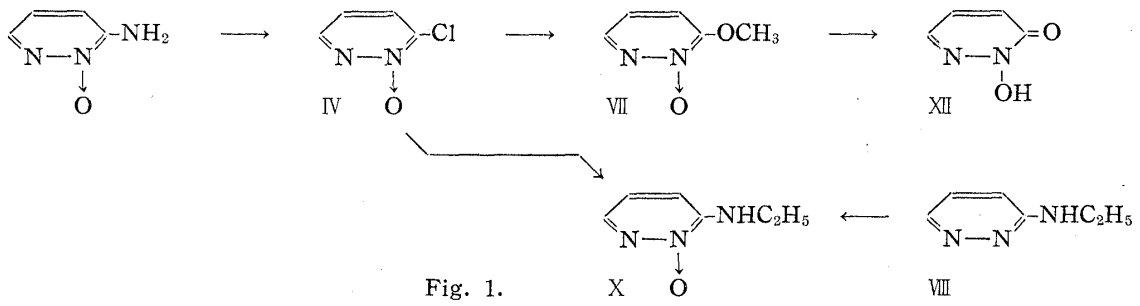

Fig. 1.

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1) S. Sako: This Bulletin, **10**, 956 (1962).
2) H. Igeta: This Bulletin, 8, 559 (1960).
3) T. Itai, T. Nakashima: This Bulletin, **10**, 347 (1962).

From these results, it is found that different from the case of I, the chlorine in 3 or 6 position of monochloropyridazine 1-oxides has almost same reactivity, and they are more reactive than 3-chloropyridazine (II). VII was hydrolyzed by 5% NaOH to a hydroxy derivative XII, which gave brownish red coloration with aqueous ferric chloride. As its infrared spectrum shows strong absorption at 1670 cm^{-1} attributed to C=O, it seemed that XII was 2-hydroxy-3(2*H*)-pyridazinone like 2-hydroxy-6-methoxy-3(2*H*)-pyridazinone.[4] The ultraviolet absorption spectrum of XII in ethanol showed two maxima (λ_{max}^{EtOH} mμ (log ε) : 230 (3.73), 310 (3.50), corresponding those in the spectrum of 1-hydroxy-2(1*H*)-pyridone (λ_{max}^{EtOH} mμ (log ε) : 228 (3.86), 305 (3.66)).[5] VIII was oxidized by hydrogen peroxide in glacial acetic acid to X.

Experimental

6-Chloropyridazine 1-Oxide (IV)——To a solution of 5.27 g. of 6-aminopyridazine 1-oxide dissolved in 20 cc. of water and 28 cc. of 35% HCl, 5 g. of $NaNO_2$ was added in small portions under ice cooling, followed by 0.2 g. of Cu powder. The mixture was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated to dryness. The white solid (4.2 g.) was recrystallized from benzene, colorless prisms, m.p. 157~158°. Yield, 3.8 g., 61%. *Anal.* Calcd. for $C_4H_3ON_2Cl$: C, 36.80; H, 2.32; N, 21.46. Found : C, 37.05; H, 2.79; N, 22.04.

Formation of 3-Methoxypyridazine (V)——A mixture of 412.2 mg. of II, 8 cc. of MeOH and 6 cc. of MeOH solution of MeONa (Na : 20 mg. per cc.) was allowed to stand for 1 hr. at 30°. MeOH was distilled off under reduced pressure, a small amount of water was added to the residue, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated. IR spectrum of the extract (dark red liquid, 382.8 mg.) showed that it was a mixture of II and V. On addition of picric acid to an ethereal solution of the extract, a picrate was formed. The picrate was recrystallized from EtOH, yellow needles, m.p. 103~105°. Yield, 404.4 mg., 33%. m.p. rose to 109~111° by further recrystallization. Admixture with an authentic sample showed no depression of m.p.

Formation of 3-Methoxypyridazine 1-Oxide (VI)——A mixture of 622.0 mg. of III, 12 cc. of MeOH and MeONa in MeOH (6 cc. containing 120 mg. of Na) was allowed to stand for 30 min., and treated as described above. The extract (m.p. 76~78°, 595.8 mg., 99%) was recrystallized from benzene-isopropyl ether, colorless needles, m.p. 79~80°. Yield, 462.8 mg., 77%. Admixture with an authentic sample showed no depression of m.p., and their IR spectra had also same absorptions.

6-Methoxypyridazine 1-Oxide (VII)——A mixture of 609.2 mg. of IV, 12 cc. of MeOH and MeONa in MeOH (6 cc. containing 120 mg. of Na) was allowed to stand for 30 min. with occasional shaking, and treated as described above. The extract (m.p. 121~123°, 562.8 mg., 96%) was recrystallized from benzene, colorless scales, m.p. 126~127°. Yield, 494.2 mg., 84%. *Anal.* Calcd. for $C_5H_9O_2N_2$: C, 47.62; H, 4.80. Found : C, 47.62; H, 4.95.

3-Ethylaminopyridazine (VIII)——i) A mixture of 9 g. of XI, 90 cc. of EtOH, 8 cc. of 28% NH_4OH and 0.4 g. of 6% Pd-C was hydrogenated. After removal of the catalyst by filtration, the solvent was evaporated to dryness, the residue was mixed with small amount of water and $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated to dryness. The extract was recrystallized from petr. benzine-benzene, colorless needles, m.p. 93~94°. Yield, 5.3 g., 75%. *Anal.* Calcd. for $C_6H_9N_3$: C, 58.51; H, 7.37; N, 34.12. Found : C, 58.47; H, 7.13; N, 34.08. Picrate; yellow needles, m.p. 157~158° (from EtOH). *Anal.* Calcd. for $C_6H_9N_3 \cdot C_6H_3O_7N_3$: C, 40.91; H, 3.43; N, 23.86. Found : C, 41.10; H, 3.20; N, 23.91.

ii) A mixture of 674.0 mg. of II, 12 cc. of EtOH and 1.8 g. of 70% aqueous solution of ethylamine was heated in a sealed tube at 120~130° for 3 hr. The solvent was distilled off under reduced pressure, and the residue was treated as described above. IR spectrum of the extract (323.2 mg.) showed that it was mixture of II and VIII. This formed a picrate in Et_2O, m.p. 148~150°, 832 mg. 40%. The picrate was recrystallized from EtOH, yellow needles, m.p. 154~156°, undepressed on admixture with picrate of VIII prepared from XI. The ethereal mother liquid was washed with NaOH solution, and the aqueous layer was extracted with ether. The combined ether layer was dried over anhyd. K_2CO_3, and ether was evaporated to dryness. 231.2 mg. of white crystals, m.p. 35°, were obtained. Its IR spectrum showed same absorption with that of II. 34% of II was recovered.

3-Ethylaminopyridazine 1-Oxide (IX)——A mixture of 622.4 mg. of III, 12 cc. of EtOH and 1.8 g. of 70% ethylamine was heated in a sealed tube on a steam bath for 1 hr. After treating as described above, the extract (623.4 mg., hygroscopic) was washed with warm Et_2O, and white crystals, m.p. 75~78°, was obtained (463.2 mg., 70%). Recrystallization from AcOEt gave colorless plates, m.p. 79~80°.

4) T. Nakagome : Yakugaku Zasshi, **81**, 1048 (1961).
5) E. Shaw : J. Am. Chem. Soc., **71**, 67 (1949).

Anal. Calcd. for $C_6H_9ON_3$: C, 51.78; H, 6.52; N, 30.20. Found : C, 51.51; H, 7.48; N, 30.38. This formed a picrate in AcOEt, m.p. 128~130°, 717.0 mg. Ethereal washings also gave same picrate, m.p. 126~129°, 153.6 mg. The total picrate; 870.6 mg., 72%. The picrate was recrystallized from AcOEt, yellow needles m.p. 131~132°. *Anal.* Calcd. for $2C_6H_9ON_3 \cdot C_6H_3O_7N_3$: C, 42.60; H, 4.17; N, 24.85. Found : C, 42.62; H, 4.07; N, 24.62.

6-Ethylaminopyridazine 1-Oxide (X)——A mixture of 627.2 mg. of IV, 12 cc. of EtOH and 1.8 g. of 70% aqueous ethylamine was treated as described above. The extract (m.p. 95~110°, 664.0 mg.) was recrystallized from benzene-petr. benzine, colorless prisms, m.p. 113~114°. Yield, 526.8 mg., 79%. *Anal.* Calcd. for $C_6H_9ON_3$: C, 51.78; H, 6.52; N, 30.20. Found : C, 52.10; H, 6.03; N, 30.52.

N-Oxidation of VIII; Formation of X——A mixture of 2.573 g. of VIII, 26 cc. of glacial AcOH and 2.6 cc. of 30% H_2O_2 was heated for 6 hr. at 60°. 1.7 cc. of 30% H_2O_2 was added to the mixture, and heating was continued for 6 hr. more. After distilling off the solvent under reduced pressure, the residue was neutralized with $NaHCO_3$, adding simultaneously some water. The mixture was extracted with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated to dryness. The residual brownish viscous liquid was dried in vacuum desiccator. The solid, so obtained, was dissolved in benzene-$CHCl_3$, passed through a column of activated alumina, and eluted with benzene-$CHCl_3$. The solvent was evaporated from the eluates, the residue melted at not less than 90° were collected, and recrystallized from benzene, colorless prisms, m.p. 113~115°. Yield, 569 mg., 20%. Admixture with X prepared from IV showed no depression of m.p., and their IR spectra had also same absorption.

2-Hydroxy-3(2*H*)-pyridazinone (XII)——A mixture of 301.6 mg. of VII and 5 cc. of 5% NaOH was heated on a steam bath for 1 hr. After acidification of the solution, water was distilled off under reduced pressure, the residue was recrystallized from benzene, colorless prisms, m.p. 167~168°, 83.2 mg. *Anal.* Calcd. for $C_4H_4O_2N_2$: C, 42.86; H, 3.60; N, 24.99. Found : C, 42.76; H, 3.73; N, 24.41.

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