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The Alkylaminomethylation of Pyridazinol N-Oxides. V.[1] The Reaction of 3-Pyridazinol 1-Oxide with Formalin and Hydrohalogenic Acids

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The condensation reaction of a compound containing an active hydrogen with formaldehyde and a primary or secondary amine, which results replacement of the hydrogen by an alkylaminomethyl group, is known as the Mannich reaction. In this alkylaminomethylation, when an amine hydrochloride is used in the place of a free amine, the product is usually the hydrochloride of the Mannich base.

$$\begin{aligned} &\rangle\!\!\text{-H} + CH_2O + R_2NH \longrightarrow \rangle\!\!\text{-}CH_2NR_2 + H_2O \\ &\rangle\!\!\text{-H} + CH_2O + R_2NH\cdot HCl \longrightarrow \rangle\!\!\text{-}CH_2NR_2\cdot HCl + H_2O \end{aligned}$$

The present authors[1,3] have reported that the alkylaminomethylation of 3-pyridazinol 1-oxide (I) gives 6-alkylaminomethyl-3-pyridazinol 1-oxide. This paper describes remarkable contrast in the Mannich reaction of I using a free secondary amine and its hydrochloride as an amine component.

When I was treated with an equimolar mixture of 37% formalin and pyrrolidine in ethanol, a mono-Mannich base was obtained in 44% yield (Chart 1). Its structure was proved to be 6-pyrrolidinomethyl-3-pyridazinol 1-oxide (IIa) by means of nuclear magnetic resonance (NMR) spectroscopy, as noted in the experimental part.

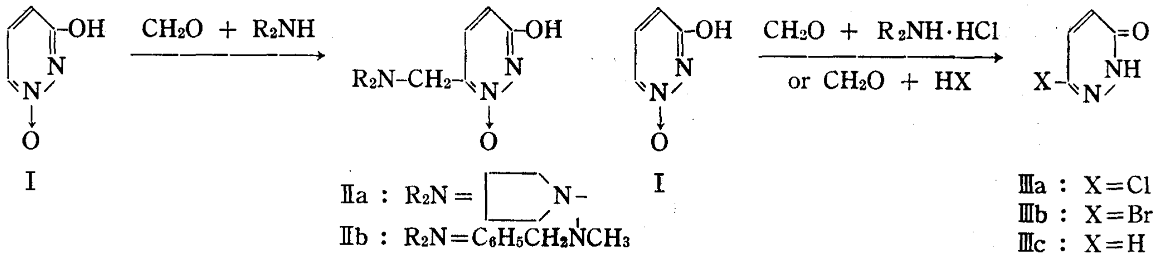

Chart 1

In contrast to the product (IIa) obtained in the alkylaminomethylation of I using a free secondary amine, as described above, treatment of I with 37% formalin and pyrrolidine hydrochloride in the presence of catalytic amount of hydrochloric acid did not give the expected hydrochloride of IIa but 6-chloro-3(2*H*)-pyridazinone (IIIa) in 6% yield, together with most of the starting material. Similarly, treatment of I with 37% formalin and N-methylbenzylamine gave 6-(N-methylbenzylaminomethyl)-3-pyridazinol 1-oxide (IIb) in 64% yield, but with N-methylbenzylamine hydrochloride, the product was also IIIa in 4% yield.

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1) Part IV: S. Kamiya, G. Okusa, M. Osada, M. Kumagai, K. Koshinuma, and A. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **16**, 939 (1968).

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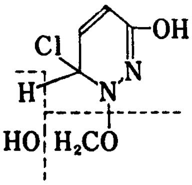
3) G. Okusa and S. Kamiya, *Chem. Pharm. Bull.* (Tokyo), **15**, 1172, 1733 (1967).

Thus, formation of IIIa should come from the reaction of I with formalin and hydrochloric acid. Actually, the reaction of I with a mixture of paraformaldehyde and concentrated hydrochloric acid at 70—75°, produced IIIa in 24% yield. When the same reaction was carried out under hydrogen chloride stream, the yield of IIIa reached to over 75%.

The same treatment of I with a mixture of paraformaldehyde and concentrated hydrobromic acid gave 6-bromo-3(2*H*)-pyridazinone (IIIb) in 37% yield and the desoxygenated product, 3(2*H*)-pyridazinone (IIIc) in 3% yield. On the other hand, with paraformaldehyde and concentrated hydroiodic acid, the product was only IIIc in 21% yield. In the case of 6-chloro-3-pyridazinol 1-oxide (IV), of which 6-position is blocked, this reaction did not occur and the starting material was recovered unchanged.

These reaction conditions are just the same as those for the chloromethylation of aromatic compounds. Since the rate-determining step of chloromethylation[4] is an electrophylic attack by $^{+}CH_2OH$, chloromethylation is like alkylaminomethylation[5] in the reaction mechanism. Consequently, this reaction can be explained as a reaction including 1,3-addition which is commonly observable in pyridine- and quinoline-N-oxides.[6]



V

The $^{+}CH_2OH$ produced by the reaction of formaldehyde and hydrochloric acid, first attacks the N-oxide function, and the Cl^- attacks the 6-position to form such an intermediate (V) which leads to loss of water and formaldehyde to give IIIa.

The possibility of this type of reaction for other heterocyclic N-oxides is under investigation.

Experimental[7]

6-Pyrrolidinomethyl-3-pyridazinol 1-Oxide (IIa) and 6-(N-Methylbenzylaminomethyl)-3-pyridazinol 1-Oxide (IIb)——To a suspended solution of 0.34 g (0.003 mole) of 3-pyridazinol 1-oxide in 5.0 ml of ethanol was added a solution of 0.5 ml of 37% formalin and 0.21 g (0.003 mole) of pyrrolidine in 3.0 ml of ethanol, and the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was evaporated to dryness under reduced pressure, the residue was dissolved in 10 ml of 10% hydrochloric acid and the solution was again evaporated to dryness under reduced pressure. The residue was dissolved in ethanol and ether was added. The separated crystals were filtered and recrystallized from ethanol to give colorless fine needles, mp 201—203°. Yield, 0.31 g (44%). NMR (10% solution in D_2O) τ: 2.84 (H^4, doublet, $J=6$ cps), 1.85 (H^5, doublet, $J=6$ cps), 5.36 (CH_2, singlet). *Anal.* Calcd. for $C_9H_{13}O_2N_3\cdot HCl$: C, 46.57; H, 6.09; N, 18.22. Found: C, 46.10; H, 6.07; N, 17.95.

6-(N-Methylbenzylaminomethyl)-3-pyridazinol 1-oxide (IIb) hydrochloride was similarly synthesized in 64% yield. Colorless granules (from a mixture of methanol and ethanol), mp 207—208° (decomp.). NMR (10% solution in D_2O) τ: 3.10 (H^4, doublet, $J=6$ cps), 1.85 (H^5, doublet, $J=6$ cps), 2.49 (C_6H_5, singlet), 6.94 (CH_2, singlet), 5.22 (NCH_3, singlet). *Anal.* Calcd. for $C_{13}H_{15}O_2N_3\cdot HCl$: C, 55.42; H, 5.72; N, 14.92. Found: C, 55.14; H, 6.12; N, 14.98.

6-Chloro-3(2*H*)-pyridazinone (IIIa) from 3-Pyridazinol 1-Oxide (I)——A mixture of 2.24 g (0.02 mole) of I, 0.90 g (0.03 mole) of paraformaldehyde and 10 ml of conc. hydrochloric acid was heated at 50—60° on a water bath for 3 hr. To the reaction mixture was added 0.90 g (0.03 mole) of paraformaldehyde again, and the mixture was heated at 70—75° for 0.5 hr with gently passing hydrogen chloride. The reaction mixture was evaporated to dryness, and the residue was recrystallized from ethanol to colorless pillars, mp 137—140°. IR ν_{max}^{KBr} cm^{-1}: 1610 (lactam-CO), 2800 (lactam-NH). This product was identical with

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4) I.N. Nazarov and A.V. Semenovskii, *Izv. Ak. N. SSSR, Otd. Khim. Nauk,* **1957**, 972 [*C.A.*, **52**, 4522 (1958)].

5) E.R. Alexander and E.J. Underhill, *J. Am. Chem. Soc.*, **71**, 4014 (1949); S.V. Lieberman and E.C. Wagner, *J. Org. Chem.*, **14**, 1001 (1949); J.H. Burckhalter, J.N. Well, and W.J. Meyer, *Tetrahedron Letters*, **1964**, 1353.

6) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam, 1969, p. 302—331.

7) All melting points are uncorrected. Infrared spectra were measured on a JASCO Model-IR infrared spectrophotometer and nuclear magnetic resonance spectra were measured on a Japan Electron Optics Model C-60H spectrometer.