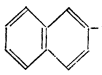
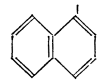
The authors express their gratitude to Mr. Matsui, the Director of this Laboratory, and Prof. K. Tsuda of the University of Tokyo for encouragement throughout this work, and especially thank for kind advices of Dr. Y. Okajima. Thanks are also due to Mr. T. Onoe, Mr. H. Nagashima, Miss C. Furukawa for microanalysis, and Miss N. Sawamoto and Mr. N. Higosaki for the measurement of infrared and ultraviolet spectra.

Summary

It has been reported that 2-naphthyl allylic ethers undergo the Claisen rearrangement to give naphthol derivatives. 2-naphthyl propargyl ether derivatives,  -O·$CH_2C{\equiv}C$-R (R=H, CH_3, Ph.), replacing the double bond of allylic ethers by a triple bond, do not undergo the Claisen rearrangement but a new ring-closure to give 3*H*-naphtho[2,1-*b*]pyran derivatives. Moreover, 1-naphthyl derivatives, 
also undergo the same ring-closure to give 4-phenyl-2*H*-naphtho[1,2-*b*]pyran. The structures of new pyran derivatives obtained by the new ring-closure were confirmed by the melting point, infrared and ultraviolet spectra of the authentic samples which were synthesized by another routes.

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148. Takanobu Itai and Shigeru Sako : Potential Anti-cancer Agents. V. 3,6-Disubstituted 4-Nitropyridazine 1-Oxides and their Derivatives.

(*National Institute of Hygienic Sciences*[*1])

On the nitration of 3-methoxy- and 3,6-dimethoxy-pyridazine 1-oxides had been reported by Itai and Igeta,[1] Igeta,[2,3] and by Nakagome.[4] In our third paper[5] of this series, syntheses of 3,6-dialkoxy-4-nitropyridazine 1-oxides and their anti-cancer actions were reported. Synthesis of 3-alkoxy-6-chloropyridazine 1-oxides were given in our fourth paper.[6] Now, nitration of 3-methoxy- and 3-hydroxy-6-chloropyridazine 1-oxides and reactions of their products will be reported in this paper.

On hydrolysis of 3-methoxy-6-chloropyridazine 1-oxide (Ia) with 5% sodium hydroxide, 6-chloro-3-pyridazinol 1-oxide (Ib) was produced. Nitration of these two compounds was carried out with sulfuric acid-nitric acid at 50°, which occurred rather easily, but was more difficult than for 3-methoxy- or 3,6-dimethoxypyridazine 1-oxides. As nitration did not occur of 3-methoxypyridazine, it was clear that contribution of

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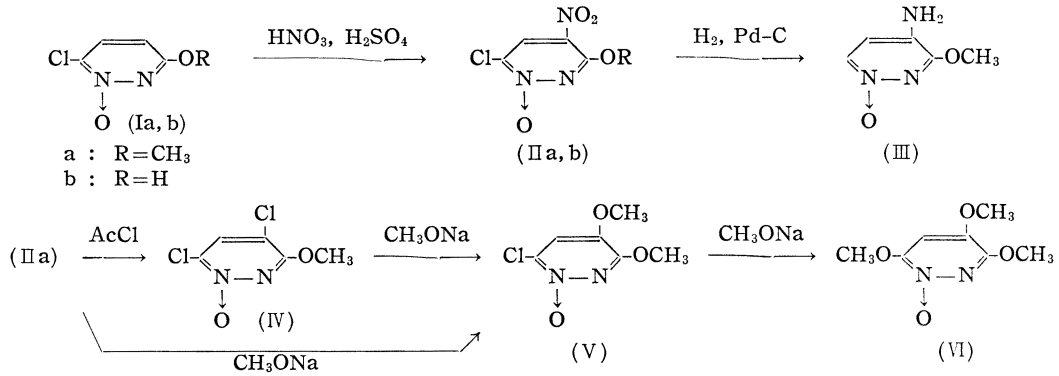
1) T. Itai, H, Igeta : Yakugaku Zasshi, **75**, 966 (1955).
2) H. Igeta : This Bulletin, **7**, 938 (1959).
3) *Idem* : *Ibid.*, **8**, 550 (1960).
4) T. Nakagome : Yakugaku Zasshi, **80**, 712 (1960).
5) T. Itai, S. Sako : This Bulletin, **9**, 149 (1961).
6) *Idem* : *Ibid.*, **10**, 989 (1962).

+M effect of N-oxide was large. But at this time, chlorine in 6-position seemed to offer rather preventing effect to the reaction, comparing to the cases of 3-methoxy- or 3,6-dimethoxypyridazine 1-oxides. The nitro compound from (Ia) was reduced by catalytic hydrogenation to the corresponding amino compound. This was identified by admixture melting point determination with 3-methoxy-4-aminopyridazine 1-oxide, obtained by H. Igeta.[3] As the result, it was found that the nitro group was located in 4-position.

A reaction of acetyl chloride with (IIa) gave expected 3-methoxy-4,6-dichloropyridazine 1-oxide (IV), which was converted to dimethoxychloro- pyridazine N-oxide by the reaction with one mole of sodium methoxide at room temperature. When (IIa) was treated similarly as (IV), same dimethoxy-chloropyridazine N-oxide was produced. Then, it was conclu ded that both of the products were 6-chloro-3,4-dimethoxypyridazine1-oxide, and the nitro or chloro groups in 4-position were more reactive than chlorine in 6-position. By warming (V) with sodium methoxide, 3,4,6-trimethoxypyridazine 1-oxide (VI) was obtained. This was confirmed by mixed melting point determination with the authentic substance, given by H. Igeta.[3]



Experimental

6-Chloro-3-pyridazinol 1-Oxide (Ib)——A mixture of 1.00 g. of (Ia) and 10 cc. of 5% NaOH was heated on a steam bath for 2 hr. The resulting solution was concentrated to a small volume and neutralized with conc. HCl. Deposited colorless needles were collected, m.p. 224~225°(decomp.). Yield, 651 mg., 71%. The needles were recrystallized from water, m.p. 224~225°(decomp.). *Anal.* Calcd. for $C_4H_3O_2N_2Cl$: C, 32.78; H, 2.06. Found : C, 32.72; H, 2.19.

3-Methoxy-4-nitro-6-chloropyridazine 1-Oxide (IIa)——To a solution of 3.00 g. of (Ia) in 9 cc. of conc. H_2SO_4, 2 cc. of HNO_3 (d=1.38) was added and the mixture was heated at 50° for 3 hr. The mixture was poured on ice, the pale yellow precipitate that separated out was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and $CHCl_3$ was evaporated. The residue was recrystallized from EtOH to yellow needles, m.p. 144~145°. Yield, 2.48 g., 65%. *Anal.* Calcd. for $C_5H_4O_4N_3Cl$: C, 29.21; H, 1.96; N, 20.44. Found : C, 29.30; H, 2.05; N, 20.81.

4-Nitro-6-chloro-3-pyridazinol 1-Oxide (IIb)——To a solution of 426 mg. of (Ib) in 1.2 cc. of conc. H_2SO_4, 0.4 cc. of HNO_3 (d=1.38) was added and the mixture was heated at 50° for 3 hr. After cooling, the mixture was poured on ice, the yellow precipitate separated out was collected and washed with a small amount of water, m.p. 208~210°(decomp.). Yield, 295 mg., (53%). Recrystallization from benzene-EtOH gave yellow needles, m.p. 214~215°(decomp.). *Anal.* Calcd. for $C_4H_2O_4N_3Cl$: C,25.08; H, 1.05. Found : C, 25.62; H, 1.67.

Catalytic Hydrogenation of (IIa); Formation of 3-Methoxy-4-aminopyridazine 1-Oxide (III)——To a solution of 207 mg. of (IIa) in 20 cc. of EtOH, 0.2 g. of 9% Pd-C was added. The mixture was hydrogenated at atmospheric pressure and room temperature. The reduction stopped after 4 equivalent of H_2 had been absorbed. The catalyst was filtered off and EtOH was evaporated from filtrate. The residue was dissolved in water, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and concentrated to a small volume. After cooling, the deposited

colorless needles were collected, m.p. 180°(decomp.). Yield, 77 mg., 54%. Admixture with 3-methoxy-4-aminopyridazine 1-oxide prepared from 3-methoxy-4-nitropyridazine 1-oxide by H. Igeta[3] showed no depression of m.p. and their IR spectra had also same absorption. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3160, 1485, 1315, 1240, 1020, 973.

3-Methoxy-4,6-dichloropyridazine 1-Oxide (IV)——A mixture of 509 mg. of (IIa) and 3 cc. of AcCl was heated on a steam bath for 30 min. Excess of AcCl was distilled off under reduced pressure, the residue was neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4, passed through a column of activated alumina and $CHCl_3$ was evaporated from the effluent. 205 mg. of colorless crystals (m.p. 133~148°) were recrystallized from petr. benzin to colorless needles, m.p. 153~154°. Yield, 82 mg. *Anal.* Calcd. for $C_5H_4O_2N_2Cl_2$: C, 30.79; H, 2.07. Found: C, 30.40; H, 2.35.

3,4-Dimethoxy-6-chloropyridazine 1-Oxide (V) i) Reaction of (IV) with MeONa——To a solution of 82.5 mg. of (IV) in 1.8 cc. of MeOH, 0.5 cc. of MeOH solution of MeONa (Na; 20 mg./cc.) was added and the mixture was allowed to stand for 1 hr. at room temperature. MeOH was distilled off under reduced pressure, 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. The residue was dissolved in benzene-$CHCl_3$, passed through an alumina layer and eluted with $CHCl_3$. $CHCl_3$ was evaporated from the effluent, the residue (m.p. >180°) was recrystallized from benzene to colorless needles, m.p. 188~190°(decom.). Yield, 38 mg., 47%. Admixture with 3,4-dimethoxy-6-chloropyridazine 1-oxide prepared from (IIa) showed no depression of m.p. and their IR spectra had also same absorption.

ii) Reaction of (IIa) with MeONa——To a solution of 210 mg. of (IIa) in 4 cc. of MeOH, 1.2 cc. of MeOH solution of MeONa (Na; 20 mg./cc.) was added and mixture was allowed to stand for 1 hr. at room temperature. MeOH was distilled off under reduced pressure, 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. The residue (m.p. 180~182°, 185 mg.) was recrystallized from benzene to colorless, needles, m.p. 188~190°(decomp.). Yield, 143 mg. 73%. *Anal.* Calcd. for $C_6H_7O_3N_2Cl$: C, 37.81; H, 3.70. Found: C, 37.98; H, 3.85.

Reaction of (V) with MeONa; Formation of 3,4,6-Trimethoxypyridazine 1-Oxide (VI)——To a solution of 62 mg. of (V) in 5 cc. of MeOH, 1 cc. of MeOH solution of MeONa (Na; 20 mg./cc.) was added, the mixture was heated on a steam bath for 10 min. and then allowed to stand for 50 min. at room temperature. MeOH was distilled off under reduced pressure, 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. The residue was recrystallized from benzene to colorless prisms, m.p. 116~118°. Yield, 12 mg. Admixture with 3,4,6-trimethoxypyridazine 1-oxide prepared from 3-dimethoxy-4,6-dinitropyridazine 1-oxide by H. Igeta[3] showed no depression of m.p. and their IR spectra had also same absorption. IR ν_{max}^{KBr} cm^{-1}: 1615, 1350, 1280, 1240, 1025, 995.

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Summary

When 3-methoxy- and 3-hydroxy-6-chloropyridazine 1-oxides (Ia, b) were nitrated with nitric acid and concentrated sulfuric acid, mono-nitro compounds (IIa. b) were produced. (IIa) was shown as 4-nitro compound. (IIa) was converted to 3-methoxy-4,6-dichloropyridazine 1-oxide (IV) with acetyl chloride. The reaction of (IIa) and (IV) with sodium methoxide occurred at their 4-positions respectively.

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