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17. Takanobu Itai and Sachiko Natsume: Potential Anti-cancer Agents. Ⅷ.[1] Nitration of Pyridazine 1-Oxide. (1).

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It has been reported[2,3] that the nitration of both 3,6-dimethyl- and 3,6-dialkoxypyridazine 1-oxide produced their 4-nitro 1-oxide derivatives under relatively mild conditons in good yields. The nitration of 3-methoxypyridazine 1-oxide was carried out with a mixed acid by Igeta[4] and Nakagome[5] independently, and 3-methoxy-4-nitropyridazine 1-oxide was obtained as a main product in common with both workers. 3-Methoxy-4,6-dinitropyridazine 1-oxide was a sole by-product in the case of Igeta, whereas Nakagome observed the formation of 3-methoxy-6-nitro compound and its 1-oxide as by-products in the nitration reaction. This discrepancy might arise from the difference of their reaction conditions. All of these 4-nitro 1-oxide derivatives were found to possess bacteriostatic and carcinostatic activities in vitro.[6,7] Therefore, it may be anticipated that 4-nitro derivative of pyridazine 1-oxide itself has a similar biological activity.

The nitration of pyridazine 1-oxide I[*2] was found to require vigorous conditions, contrary to the above cases. When I was treated with a large excess of fuming nitric acid in concentrated sulfuric acid, carefully keeping the temperature at 130~140° for a long period of time, a mono nitro compound of light yellow needles Ⅱ, m.p. 150~151°, was obtained as a sole reaction product in 22% yield with a recovery of the starting material in 26% yield. However, when it was treated below 100°, no reaction took place, the most part of the starting material being recovered unchanged. The mononitro compound Ⅱ obtained here was quite unstable to caustic alkali. Red resinous substance was immediately deposited by an addition of alcoholic alkali at room temperature and Ⅱ could not be regenerated by its acidification.

It is well-established that α- or γ-position to N-oxide is nitrated in the series of alkoxy substituted pyridazine N-oxides owing to the electromeric effect of N-oxide function, so that this nitration product Ⅱ may be assumed to be either 4- or 6-nitropyridazine 1-oxide. Ⅱ was hydrogenated to monoaminopyridazine Ⅲ, m.p. 130°, after an absorption of four molar equivalents of hydrogen over Raney-Nickel according to Hayashi and co-workers' method.[8] It was found that Ⅲ was not 3-aminopyridazine,[9] but was identical with 4-aminopyridazine, firstly prepared by Kuraishi,[10] by mixed

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*2 C.F. Koelsch, W.H. Gumprecht: J. Org. Chem., **23**, 1603 (1958). Koelsch *et al.* claimed that pyridazine was oxidized to its mono N-oxide in a good yield by standing with 1 molar equivalent of 30% hydrogen peroxide in glacial acetic acid at room temperature for 4 weeks and that the presence of an excess of hydrogen peroxide and an elevation of reaction temperature decreased the yield. Authors, however, obtained the same mono N-oxide by treating with two molar equivalents of hydrogen peroxide at 100° for 7 hr. in a better yield. Details are shown in the experimental part.

1) Part Ⅶ. T. Itai, G. Ito: This Bulletin, **10**, 1141 (1962).
2) T. Itai, H. Igeta: Yakugaku Zasshi, **75**, 966 (1955).
3) T. Itai, S. Sako: This Bulletin, **9**, 149 (1961).
4) H. Igeta: *Ibid.*, 8, 550 (1960).
5) T. Nakagome: Yakugaku Zasshi, **80**, 712 (1960).
6) M. Nakamura, F. Miyazawa, S. Iwahara, T. Itai, *et al.*: Eisei Shikenjo Hokoku, **78**, 157 (1960).
7) F. Miyazawa, S. Iwahara, T. Itai, *et al.*: *Ibid.*, **79**, 307 (1961).
8) E. Hayashi, H. Yamanaka, K. Shimizu: This Bulletin, **7**, 141 (1959).
9) E.A. Steck, R.P. Brundage, L.T. Fletcher: J. Am. Chem. Soc., **76**, 3226 (1954).
10) T. Kuraishi: This Bulletin, **4**, 137 (1956).

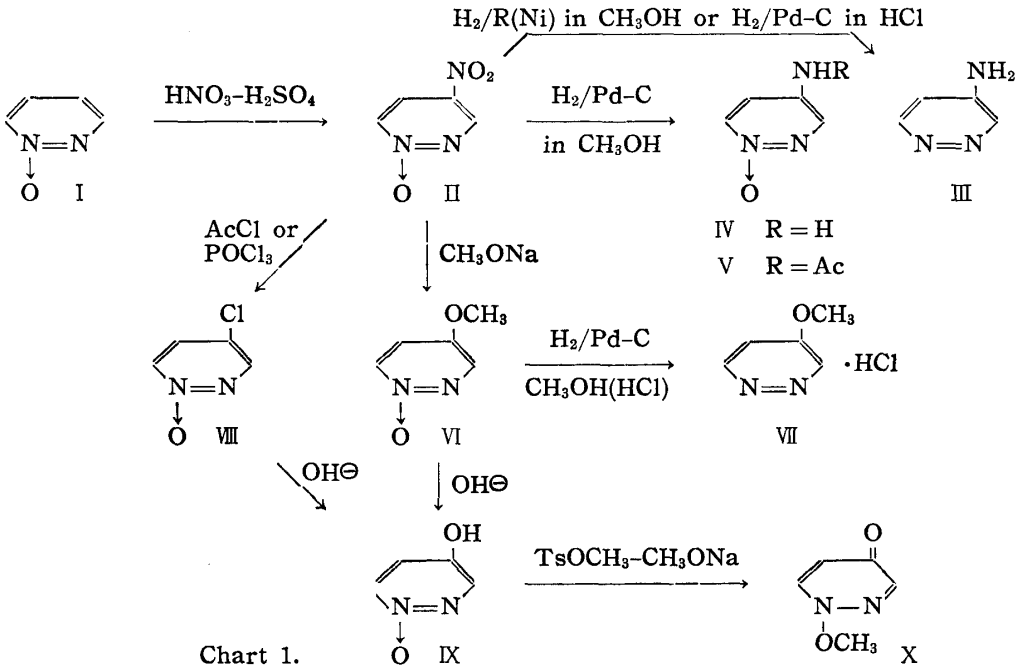

Chart 1.

melting points and by a comparison of infrared absorption spectra. III was also obtained by hydrogenation over palladium-charcoal in methanolic solution containing hydrochloric acid. Therefore, II could be assumed to be most likely 4-nitropyridazine 1-oxide.

On the other hand, 4-aminopyridazine N-oxide (IV) was produced when reduction was carried out over palladium-charcoal in neutral solvent, whereupon it was observed that the hydrogenation proceeded quite rapidly until the absorption of two molar equivalents of hydrogen and a further uptake of one molar hydrogen became slower. This behavior has been observed[11] in the case of catalytic hydrogenation of 4-nitro N-oxide derivatives of pyridine and quinoline under similar conditions.

IV was acetylated with acetic anhydride at 100° to its mono N-acetate V. An attempt to convert this monoacetate to 4-amino-6-hydroxypyridazine[12] under a usual condition was unsuccessful. With an expectation obtaining the same kind of rearrangement product, IV was treated with phosphoryl chloride at 80°, but any 4-aminochloropyridazine could not be detected.

The nitro group of II behaved as the usual γ-nitro group of six-membered heteroaromatic N-oxides and was susceptible to nucleophyllic substitution as expected. Thus, II was readily converted to 4-methoxypyridazine N-oxide (VI), m.p. 124~125°, in 64% yield by standing in methanolic sodium methoxide for 1 hour at room temperature, and VI was transformed to 4-methoxypyridazine hydrochloride (VII),[13] m.p. 147~148°, after an absorption of one molar equivalent of hydrogen over palladium-charcoal in methanolic solution containing hydrochloric acid. When the substitution reaction of II with the methoxy group was carried out in boiling methanol, the yield of VI decreased to only 8%.

II was also convertible to 4-chloropyridazine N-oxide (VIII), m.p. 119~121°, in a very good yield by treatment with acetyl chloride at 35° for 3 hours, accompanied by the formation of nitrogen dioxide. When II was heated with phosphoryl chloride in boiling

11) E. Ochiai, M. Katada : Yakugaku Zasshi, **63**, 186 (1943); E. Ochiai, T. Naito : *Ibid.*, **64**, 206 (1944).
12) T. Kuraishi: This Bulletin, **6**, 332 (1958).
13) K. Eichenberger, R. Rometsch, J. Druey : Helv. Chim. Acta., **39**, 1755 (1956).

water bath, VIII was produced in 65% yield but the treatment of II at reflux temperature resulted in the formation of VIII in a lower yield. The expected dichloropyridazine could not be isolated.

On hydrolysis of VI or VIII in alkaline medium, 4-pyridazinol N-oxide (IX), m.p. 285° (decomp.), was obtained. When IX was treated with methyl *p*-toluenesulfonate and sodium methoxide in methanolic solution, quite hygroscopic needles X, m.p. 80°, were obtained, whose picrate gave the analytical values corresponding to the picrate of monomethyl derivative of IX. X is obviously different from VI in respect to melting point and ultraviolet or infrared absorption spectra, and furthermore, X possesses a pyridone type of carbonyl band in its infrared spectrum, and ultraviolet absorption spectrum of X was resembling to that of 1-methyl-4(1*H*)-pyridazinone[13] (Table I). Judging from these data, this methylation product X should be 1-methoxy-4(1*H*)-pyridazinone, and thus, the nitration product II should be 4-nitro derivative since *β*-hydroxy N-oxide would behave in different manner.

Table I.

	λ_{max}^{EtOH} (ε_{max})	λ_{max}^{HCl} (ε_{max})
X	272 mμ (11020)	261 mμ[a] (8700)
	269 mμ (14800)	252 mμ[b] (10650)

a) in *N* HCl *b*) in 2*N* HCl

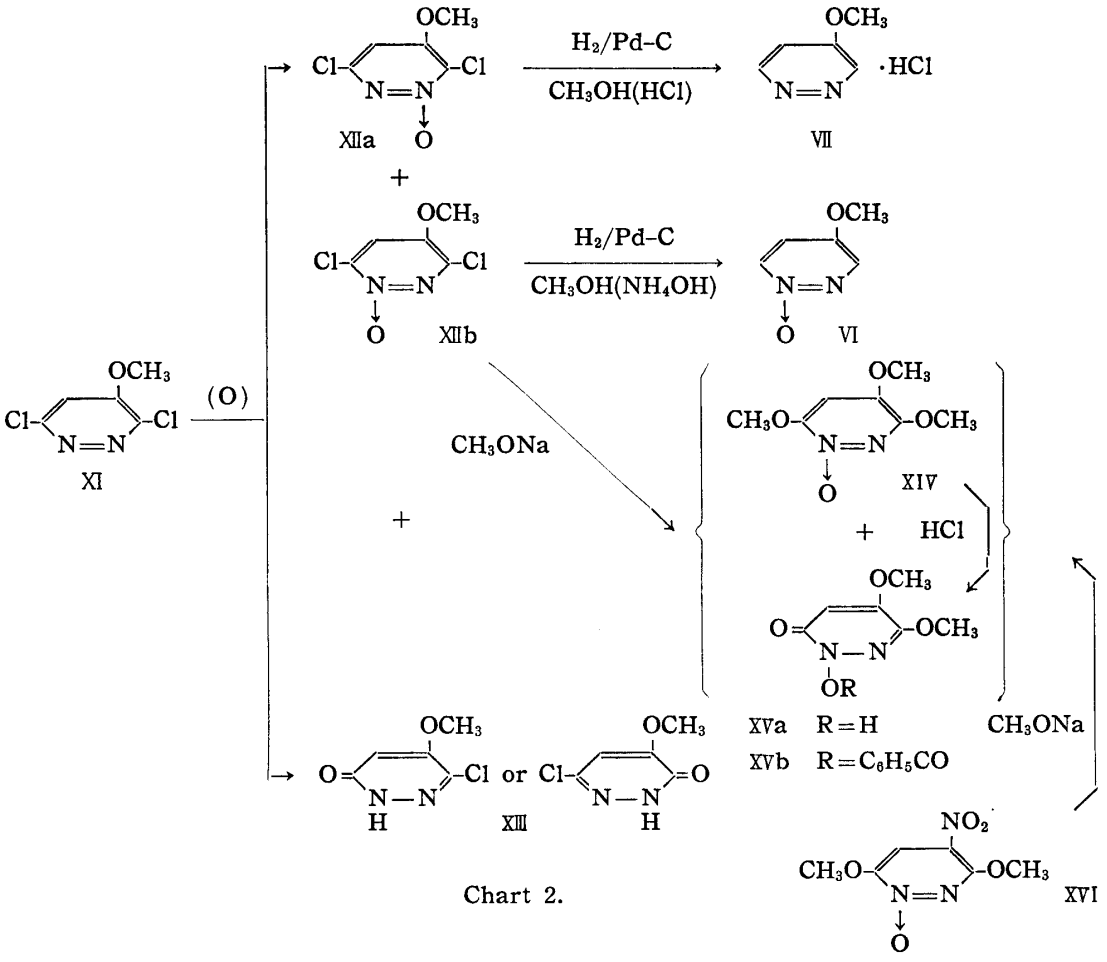

Chart 2.

In order to verify the position of this nitro group chemically, a series of reactions was investigated starting from 4-methoxy-3,6-dichloropyridazine (XI)[13] as shown in

Chart 2. When XI was treated with monoperphthalic acid in ethereal solution at room temperature, two kinds of mono N-oxides, XIIa, m.p.162.5~164°, and XIIb, m.p. 174.5°, were isolated in 4.5% and 12.2% yields respectively, accompanied by a recovery of 45% of the starting material. In addition to these substances, a small amount of white needles XIII, m.p. 286°(decomp.), was obtained as a by-product, which gave the analytical values corresponding to monochloromonomethoxypyridazinone and had a pyridone type carbonyl band at 1660 cm^{-1} and a band of NH bonding at 3080 cm^{-1} in its infrared region. Therefore, XIII must be either 4- or 5-methoxy-6-chloro-3(2*H*)-pyridazinone, produced by hydrolysis of the more reactive chlorine atom in the starting meterial XI.

When XIIb, was treated with methanolic sodium methoxide, two products XIV, m.p. 119°, and XVa, m.p. 236°(decomp.) were obtained. XIV was identified as 3,4,6-trimethoxypyridazine 1-oxide, whose structure had been determined by Igeta,[1,4] by mixed melting points and the comparison of their infrared spectra. XVa gave the analytical values corresponding to demethylated product of XIV and had hydroxamic acid type bands near 2700 cm^{-1} and at 1662 cm^{-1} in its infrared region. Furthermore, the hydroxamic acid benzoate bands ($NOCOC_6H_5$ type CO at 1770 cm^{-1} and α-pyridone type CO at 1664 cm^{-1}) were detected in the infrared absorption spectrum of the benzoyl derivative XVb, so that XVa is 2-hydroxy-5,6-dimethoxy-3(2*H*)-pyridazinone, which may result in the cleavage of the methoxy group adjacent to the N-oxide group with sodium methoxide. In fact, XVa was obtained from known 4-nitro-3,6-dimethoxypyridazine 1-oxide XVI with an excess of sodium methoxide accompanied by 3,4,6-trimethoxypyridazine 1-oxide (XIV), and further, XVa was produced also by heating XIV with dilute hydrochloric acid. Consequently, correlations of XIIb to XIV and XVI have been established that the N-oxide group in XIIb located at *p*-position to 4-methoxy group. When XIIb was hydrogenated over palladium-charcoal in alkaline medium, 4-methoxypyridazine 1-oxide was obtained after an absorption of two molar equivalents of hydrogen, and the hydrogenated product was identical in all respects with VI, which was directly derived from II as stated above. Therefore, the structure of the nitration product of pyridazine 1-oxide with the mixed acid was rigorously confirmed to be 4-nitropyridazine 1-oxide (II).

Analytical data of XIIa fit to an N-oxide of XI and the isomeric structure XIIa to XIIb was proved by ready hydrogenation to 4-methoxypyridazine hydrochloride with 3 molar hydrogen absorption over palladium-charcoal in methanolic solution containing hydrochloric acid.

Biological activities of some of these pyridazine 1-oxide derivatives were tested and it was found[7] that 4-nitropyridazine 1-oxide (II) had quite similar antibacterial and anti-cancer activity *in vitro* as well as 4-nitro-3,6-disubstituted pyridazine 1-oxides. The details will be described elsewhere.

Experimental

Pyridazine 1-Oxide (I)——The results of the oxidation of pyridazine with AcOH-H_2O_2 under various conditions were shown in Table II. It was obvious from the Table that the production of I were highly affected by reaction temperatures, and contrary to Koelsch's description,*2 the best yield was observed when the oxidation was carried out at 100° using 2 mol. equiv. of H_2O_2 (reaction No. 5).

Table II.

No.	Pyridazine (g.)	AcOH (cc.)	30% H_2O_2 (mol. equiv.)	Reaction time (hr.)	Temperature (°C)	Product: Recovery g.(%)	Product: N-Oxide g.(%)
1	18.8	150	2	8	65~ 72	11.6(62)	4.5(20)
2	13.5	100	3	12	65~ 72	8.0(59)	4.1(25)
3	11.5	100	3	11	80~ 85	5.7(50)	4.3(31)
4	13.7	100	3	12	98~100	—	14.2(86)
5	15.9	160	2	7	98~100	—	16.9(89)

To a solution of 15.9 g. of pyridazine in 162 cc. of glacial AcOH was added 22.3 cc. (1 mol. equiv.) of 30% H_2O_2 and the mixture was heated on a boiling water bath. After 4 hr., an additional 1 mol. equiv. of H_2O_2 was added and heating was continued further for 4 hr. The reaction mixture was treated as usual, and the distillation of the crude product *in vacuo* gave 16.9 g. (88.6%) of I, a very hygroscopic solid, b.p$_4$ 138~140°, m.p. 38~40°. UV $\lambda_{max}^{H_2O}$ mμ (log ε) : 254 (4.02), 300 (3.65). IR : $\nu_{max}^{CHCl_3}$ 1325 cm^{-1}. I was identical with the material, prepared according to Koelsch's description, in all respects.

Perchlorate : Colorless fine dice, m.p. 183~184°(from MeOH). *Anal.* Calcd. for $C_4H_4ON_2 \cdot \frac{1}{2}HClO_4$: C, 32.83; H, 3.10; N, 19.15. Found : C, 32.55; H, 2.93; N, 19.28.

Nitration of Pyridazine 1-Oxide (I)——Twenty grams of I was dissolved in 200 cc. of conc. H_2SO_4 under cooling and to this solution was added 35 cc. of fuming HNO_3 (d=1.50) dropwise during 4.5 hr., carefully keeping at 130~140° with stirring. After the mixture was kept at the same temperature for 4 hr., 5 cc. of additional HNO_3 was added dropwise and heating was continued furthermore for 4 hr. The addition of 5 cc. of HNO_3 and heating were repeated again. After cooled, the mixture was poured into ca. 1000 g. of cracked ice and after being allowed to stand for 5 hr., it was extracted with about 2000 cc. of $CHCl_3$ repeatedly. The combined extract was dried over Na_2SO_4 and evaporated. The crystalline residue was recrystallized from MeOH to give light yellow needles II, m.p. 150~151°, 4.2 g.

Residual aqueous layer after $CHCl_3$ extraction was partially neutralized with ca. 400 g. of $NaHCO_3$ until the yellowish color of the solution changed slightly orange and the mixture was extracted with $CHCl_3$, which afforded an additional crop of II, m.p. 149~151°, 2.3 g. Overall yield of II, 6.5 g. (22.1%). *Anal.* Calcd. for $C_4H_3O_3N_3$: C, 34.05; H, 2.14; N, 29.79. Found : C, 34.13; H, 2.07; N, 30.09. UV : $\lambda_{max}^{95\%\ EtOH}$ 332 mμ (log ε 4.20). IR ν_{max}^{Nujol} cm^{-1} : 1592, 1582 (doublet), 1350.

When the aqueous solution was made completely alkaline with $NaHCO_3$ and extraction with $CHCl_3$ afforded 5.2 g. of recovery of I.

II changes reddish resinous substance by an addition of alcoholic KOH. II was strongly adsorbed on Al_2O_3.

Catalytic Hydrogenation of II over Raney-Ni——Raney-Ni, freshly prepared from 1 g. of Ni-Al alloy, and 0.1 cc. of glacial AcOH were added to a suspension of 0.2 g. of II in 30 cc. of MeOH and the mixture was shaken in H_2 were stream. The first 3 mol. equiv. of H_2 were taken up within 4 min., and further absorption of the next 1 mol. equiv. of H_2 required 35 min. The catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was neutralized with satd. $NaHCO_3$, and extracted with AcOEt. After drying over Na_2SO_4, AcOEt was evaporated to give. 0.08 g. (59%) of white crystals III, m.p. 130°, which was identical with authentic 4-aminopyridazine[10] by mixed melting points and a comparison of UV and IR spectra.

Catalytic Hydrogenation of (II) over Pd-C——i) In an acidic medium : A suspension of 0.1 g. of II in the mixture of 20 cc. of MeOH and 20 cc. of 5% HCl was hydrogenated over 20% Pd-C (prepared from 0.1 g. of C and 4.2 cc. of 1% $PdCl_2$). 4 mol. equiv. of H_2 was absorbed within 10 min. The catalyst was filtered off, the filtrate was evaporated under reduced pressure, the residue was dissolved in a small amount of H_2O and neutralized with satd. $NaHCO_3$. It was extracted with AcOEt, removal of which gave 10 mg. of colorless crystals, m.p. 127~129°, undepressed on admixture with III.

ii) In MeOH : A suspension of 0.3 g. of II in 150 cc. of MeOH was hydrogenated over 20% Pd-C (prepared from 0.1 g. of C and 4.2 cc. of 1% $PdCl_2$). First 2 mol. equiv. of H_2 were absorbed within 2 min., but the absorption of next one mol. equiv. of H_2 required 90 min. The reaction mixture was treated as usual and recrystallization of the crude product from AcOEt afforded 105 mg. (44%) of 4-aminopyridazine 1-oxide as yellowish needles, m.p. 222~224°(decomp.).

Diazoreaction : Positive. Red-color by addition of 5% $FeCl_3$. *Anal.* Calcd. for $C_4H_5ON_3$: C, 43.24; H, 4.54; N, 37.83. Found : C, 43.54; H, 4.72; N, 37.81. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) : 224 (3.44), 293 (4.30), 343 (3.57). IR ν_{max}^{KBr} cm^{-1} : 3290, 3173, 1640, 1259.

HNO_3 salt : m.p. 184°(decomp.) (by addition of conc. HNO_3 in AcOH solution and recrystallization from AcOH). *Anal.* Calcd. for $C_4H_5ON_3 \cdot HNO_3$: C, 27.59; H, 3.47; N, 32.18. Found : C, 27.77; H, 3.76; N, 32.40.

Treatment of IV with Ac_2O : A suspension of 80 mg. of IV in 5 cc. of Ac_2O was heated at 100° for 1 hr. After an excess of Ac_2O was evaporated under reduced pressure, the crystalline residue (95 mg.), m.p. 235~238°, was recrystallized from EtOH to fine needles V, m.p. 239°. *Anal.* Calcd. for $C_6H_7O_2N_3$: C, 47.05; H, 4.61; N, 27.44. Found : C, 47.25; H, 4.56; N, 27.76. IR ν_{max}^{KBr} cm^{-1} : 3225, 1686.

Forty milligrams of V was refluxed with 3 cc. of Ac_2O for 5 hr. and the reaction mixture was treated as usual but any 5-amino-3-pyridazinol was not detected, giving only a small amount of black non-crystalline powder, m.p. >360°.

4-Methoxypyridazine 1-Oxide (VI)——To a solution of 0.3 g. of II in 100 cc. of MeOH was added a methanolic MeONa prepared from 0.08 g. of Na and 10 cc. of dehyd. MeOH. The mixture turned

immediately brown. After standing for 1.5 hr. at room temperature, the mixture was concentrated to dryness below 40° under reduced pressure. The red-colored residue was dissolved in 2 cc. of H_2O and extracted with $CHCl_3$, which was dried over Na_2SO_4 and evaporated. Almost colorless crystalline product, m.p. 105~110°, was recrystallized from Me_2CO-benzene to afford colorless needles VI, m.p. 124~125°, 172 mg. (64.2%). *Anal.* Calcd. for $C_5H_6O_2N_2$: C, 47.62; H, 4.80; N, 22.22. Found : C, 47.44; H, 5.27; N, 21.71. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) : 275 (4.33), 328 (3.64). IR : $\nu_{max}^{CHCl_3}$ 1278 cm^{-1}.

When 150 mg. of II was refluxed with a solution of 0.05 g. of Na in 15 cc. of MeOH for 2 hr., only 40 mg. (7.5%) of pure VI was obtained after purification.

Catalytic Hydrogenation of VI——A solution of 0.17 g. of VI in 5 cc. of MeOH and 20 cc. of 5% HCl was hydrogenated over 20% Pd-C. The reduction was discontinued after 1 mol. equiv. of H_2 uptake, and the mixture was treated as usual. The white crystalline product VII (0.14 g.), m.p. 147~148°, was obtained, which was identical with authentic 4-methoxypyridazine hydrochloride[13] in all respects.

4-Chloropyridazine 1-Oxide (VIII)——i) With AcCl : A mixture of 0.4 g. of II and 4.3 cc. of AcCl was allowed to stand at 35° for 3 hr. with occasional stirring. AcCl was removed under reduced pressure, the residue was neutralized with satd. $NaHCO_3$, extracted with $CHCl_3$ and it was evaporated after dried over Na_2SO_4. Crystalline residue (0.33 g; m.p. 117~120°) was recrystallized from benzene to yield 0.28 g. (76%) of colorless needles VIII, m.p. 119~121°. *Anal.* Calcd. for $C_4H_3ON_2Cl$: C, 36.80; H, 2.32; N, 21.46. Found : C, 36.86; H, 2.31; N, 21.69. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) : 274 (4.10), 328 (3.51). IR ν_{max}^{KBr} 1318 cm^{-1}.

ii) With $POCl_3$: a) At 100° : A mixture of 75 mg. of II and 2 cc. of $POCl_3$ was heated on a boiling water bath for 8 hr. After the excess of $POCl_3$ was removed under reduced pressure, the residue was neutralized with $NaHCO_3$, extracted with $CHCl_3$ and it was evaporated after dried over Na_2SO_4. The residue was purified over Al_2O_3 with $CHCl_3$ and 45 mg. (65%) of colorless needles, m.p. 119~121°, was obtained. This was undepressed with VIII on admixture, which was obtained in i).

b) At reflux temperature : A mixture of 0.1 g. of II and 1 cc. of $POCl_3$ was refluxed for 0.5 hr. After treating as above, only 30 mg. (33%) of VIII was obtained accompanied by a trace of yellowish oil and a dark bluish resinous substance.

4-Pyridazinol 1-Oxide (IX)——i) From 4-methoxypyridazine 1-oxide (VI) : A mixture of 0.3 g. of VI, 5 cc. of 5% KOH and 5 cc. of MeOH was refluxed for 1.5 hr. The reaction mixture was concentrated to dryness under reduced pressure, a small amount of H_2O was added to the residue and the mixture was acidified with HCl. A crystalline product (0.25 g., m.p. 274~278° (decomp.)) deposited and this was collected by filtration. From the filtrate, after evaporating to dryness, followed by extraction with Me_2CO-MeOH, 0.04 g. of crystals, m.p. 274~277° (decomp.) was obtained. The combined crystals were recrystallized from 80% MeOH to fine crystals IX, m.p. 283~285° (decomp.). Yield, 165 mg. (64%). Red-coloration by 5% $FeCl_3$. *Anal.* Calcd. for $C_4H_4O_2N_2$: C, 42.86; H, 3.60; N, 24.99. Found: C, 43.03; H, 3.54; N, 25.00. UV $\nu_{max}^{H_2O}$ mμ (log ε) : 276~277 (4.12), 305~315 (shoulder); $\lambda_{max}^{0.1N\ KOH}$ mμ (log ε) : 281 (4.13), 310~320 (shoulder); $\lambda_{max}^{0.1N\ HCl}$ mμ (log ε) : 267 (4.08), 310 (3.45).

ii) From 4-chloropyridazine 1-oxide (VIII) : A suspension of 0.21 g. of VIII in 4 cc. of 5% NaOH was heated at 100° for 30 min. After acidification with dil. HCl, the mixture was evaporated under reduced pressure, the residue was extracted with hot Me_2CO, which was evaporated. The residue, after treatment with charcoal, crystallized from 80% MeOH to give 44 mg. of fine needles, m.p. 278~282° (decomp.), identical with the material IX obtained in i) by the mixed melting points and a comparison of IR spectra.

Methylation of 4-Pyridazinol 1-Oxide (IX)——A solution of 75 mg. of IX and 130 mg. of TsOMe in methanolic MeONa from 10 cc. of MeOH and 20 mg. of Na was refluxed for 1 hr. The mixture was evaporated under reduced pressure and extracted with $CHCl_3$, which was dried over Na_2SO_4 and evaporated. Forty milligrams of a quite hygroscopic solid, m.p. 75~80°, was obtained. UV: $\lambda_{max}^{95\%\ EtOH}$ 272 mμ (log ε 4.04); $\lambda_{max}^{N\ HCl}$ 261 mμ (log ε 3.94). IR ν_{max}^{Nujol} cm^{-1} : 1651, 1600.

Picrate : Yellow needles, m.p. 133~134° (from MeOH). *Anal.* Calcd. for $C_5H_6O_2N_2 \cdot C_6H_3O_7N_3$: C, 37.19; H, 2.55; N, 19.72. Found : C, 37.16; H, 2.95; N, 19.79.

N-Oxidation of 4-Methoxy-3,6-dichloropyridazine (XI)——A solution of 4.5 g. of XI in 150 cc. of an ethereal solution of monoperphthalic acid (containing 16.4 mg. of active oxygen per cc.) was allowed to stand at room temperature for 10 days. After Et_2O was evaporated under reduced pressure at room temperature, $CHCl_3$ was placed over the residue. The mixture was neutralized with 10% NH_4OH under ice-cooling, and it was extracted thoroughly with $CHCl_3$. The combined $CHCl_3$ extract was washed with a small amount of H_2O, dried over K_2CO_3 and was evaporated. About 70 cc. of benzene was added to the residue and an insoluble solid was collected by filtration (60 mg., m.p. 255~270°) and recrystallized from MeOH to 20 mg. of colorless needles XIII, m.p. 284~286° (decomp.). *Anal.* Calcd. for $C_5H_5O_2H_2Cl$: C, 37.40; H, 3.14; N, 17.45. Found : C, 37.33; H, 3.41; N, 16.89. IR : ν_{max}^{KBr} 1662 cm^{-1}.

The filtrate was passed through Al_2O_3 column. From the first portion, eluted with benzene, 2.03 g. of the starting material was recovered. A crystalline solid obtained from the second eluate, was recrystallized from benzene to 0.14 g. of colorless needles XIIa, m.p. 162.5~164°. *Anal.* Calcd. for $C_5H_4O_2N_2Cl_2$: C, 30.79; H, 2.07; N, 14.37. Found : C, 31.10; H, 2.17; N, 14.68. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) : 234~235 (4.37), 268 (3.87), 311 (3.41). IR ν_{max}^{KBr} cm^{-1} : 1330, 1210, 1124.

The third fraction, eluted with benzene, was a mixture, m.p. 140~166°. This was divided into two fractions by passing through the other column of Al_2O_3 with benzene containing 0.5% of MeOH, 80 mg. of XIIa, m.p. 163°, and 90 mg. of XIIb, m.p. 172~174°, were obtained.

The fourth fraction eluted with benzene containing 0.5% of MeOH was almost pure XIIb, m.p. 172~174°, 0.51 g. Recrystallization from benzene gave colorless needles for an analytical sample, m.p. 174~174.5°. *Anal.* Calcd. for $C_5H_4O_2N_2Cl_2$: C, 30.79; H, 2.07; N, 14.37. Found : C, 31.08; H, 2.35; N, 14.28. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) : 278 (4.19), 348 (3.67). IR ν_{max}^{KBr} cm^{-1} : 1328, 1253, 1140.

The fifth fraction was a mixture, an yellowish oil containig a small amount of colorless crystalline substance. 30 mg.

The sixth fraction, eluted with $CHCl_3$ containing 20% of MeOH, m.p. 270~280°, 25 mg., was recrystallized from MeOH to 10 mg. of XIII, m.p. 282~285°(decomp.).

Treatment of 4-Methoxy-3,6-dichloropyridazine 1-Oxide (XIIb) with MeONa——A solution of 195 mg. of XIIb in 20 cc. of MeOH was refluxed with methanolic MeONa (prepared from 50 mg. of Na and 2 cc. of MeOH) for 1 hr. MeOH was evaporated under reduced pressure, the residue was dissolved in a small amount of H_2O and extracted with $CHCl_3$, which was dried over K_2CO_3 and evaporated. 25 mg. of crystalline residue, m.p. 112~116°, was recrystallized from benzene to give 15 mg. of XIV, m.p. 119°. No m.p. depression was observed on admixture with authentic 3,4,6-trimethoxypyridazine 1-oxide. IR ν_{max}^{KBr} cm^{-1} : 1286, 1243, 1026.

The aqueous layer was acidified with HCl and the crystals A which precipitated (m.p. 232°) were collected by filtration. The filtrate was extracted with $CHCl_3$, the crystalline residue, m.p. 230~232°, obtained fromthe extract, was combined with A and recrystallized from MeOH to colorless needles XVa, m. p. 235~236°(decomp.), 80 mg. Violet-coloration by $FeCl_3$. *Anal.* Calcd. for $C_6H_8O_4N_2$: C, 41.86; H, 4.68; N, 16.28. Found : C, 41.72; H, 4.45; N, 16.45. IR ν_{max}^{KBr} cm^{-1} : 2700, 1662.

Benzoylation of XVa : To a mixture of 60 mg. of XVa in 1 cc. of pyridine was added 0.1 g. of BzCl. The mixture was allowed to stand for 2 days at room temperature and poured into 4 cc. of ice-water. A reddish oil seperated, was crystallized by rubbing, and collected by filtration. 50 mg., m.p. 166°, XV. Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless needles for analytical sample, m.p. 169°. *Anal.* Calcd. for $C_{13}H_{12}O_5N_2$: C, 56.52; H, 4.38. Found : C, 56.53; H, 4.39. IR ν_{max}^{KBr} cm^{-1} : 1770, 1664.

Treatment of 3,6-Dimethoxy-4-nitropyridazine 1-Oxide (XVI) with MeONa——A suspension of 0.4 g. of XVI in 15 cc. of MeOH was refluxed with MeONa (prepared from 80 mg. of Na and 5 cc. of MeOH) for 75 min. MeOH was evaporated under reduced pressure, and the residue was extracted with $CHCl_3$ after an addition of a small amount of H_2O. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated. The crystalline residue (35 mg., m.p. 109~111°) was recrystallized from benzene to yield 25 mg. of colorless needles, XIV, m.p. 119°.

The aqueous layer was acidified with dil. HCl and the crystals B which precipitated were collected by filtration (0.3 g., m.p. 228~230°). The filtrate was concentrated to ca. 1 cc. and extracted with $CHCl_3$. The crystals obtained by evaporation of the extract (55 mg., m.p. 225~230°) were combined with the crystals B and recrystallized from MeOH to 0.16 g. of colorless needles, m.p. 235~236°(decom.). No m.p. depression was observed on admixture with XVa. IR : identical with that of XVa in all respects.

Hydrolysis of 3,4,6-Trimethoxypyridazine 1-Oxide (XIV)——A mixture of 70 mg. of XIV and 1 cc. of 10% HCl was heated on a boiling water bath for 20 min. HCl was evaporated under reduced pressure and the crystalline residue (60 mg.) was recrystallized from MeOH to 40 mg. of white needles, m.p. 235~236° (decomp.). No m.p. depression was observed on admixture with XVa. IR : identical with that of XVa in all respects.

Catalytic Hydrogenation of 4-Methoxy-3,6-dichloropyridazine 1-Oxide (XIIb)——A solution of 0.21 g. of XIIb in 40 cc. of MeOH containing 0.4 cc. of conc. NH_4OH was hydrogenated over 10% Pd-C, prepared from 0.1 g. of C and 1.9 cc. of 1% $PdCl_2$. The reduction was cut after the rapid absorption of 2 mol. equiv. of H_2. The catalyst was filtered off and MeOH was evaporated to dryness under reduced pressure. The residue was extracted with $CHCl_3$, which was dried and evaporated. The purification of the residue (m.p. 118~120°, 150 mg.) over Al_2O_3 with $CHCl_3$ gave 115 mg. (85%) of colorless needles, m.p. 124~125°. No m.p. depression was observed on admixture with VI. IR and UV : identical with those of VI in all respects.

Catalytic Hydrogenation of 4-Methoxy-3,6-dichloropyridazine 2-Oxide (XIIa)——A solution of 0.1 g. of XIIa in 20 cc. of MeOH containing 0.3 cc. of conc. HCl was shaken with 20% Pd-C in H_2 stream. Three mol. equiv. of H_2 were absorbed in 25 min. Treatment of the reaction mixture as usual, gave 70 mg. (93%) of colorless crystals, m.p. 147~148° (decomp.). The crystals were identical with

authentic 4-methoxypyridazine hydrochloride[13] by mixed melting points and by comparison of IR spectra.

Free base, m.p. 42~44° was obtained by passing the above hydrochloride in MeOH through Amberlite IRA 410 (OH^-). No m.p. depression was observed on admixture with authentic 4-methoxypyridazine.[13]

Picrate : m.p. 143~144°(from MeOH). *Anal.* Calcd. for $C_6H_6ON_2 \cdot C_6H_3O_7N_3$: C, 38.95; H, 2.67; N, 20.65. Found : C, 39.10; H, 2.66; N, 21.10.

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Summary

Pyridazine 1-oxide (I) was nitrated to 4-nitropyridazine 1-oxide (II) with a mixed acid under a vigorous condition. The structure of II was confirmed as follows. i) Hydrogenation of II itself and methoxypyridazine 1-oxide (VI), derived from II, gave the known 4-aminopyridazine and 4-methoxypyridazine, respectively. ii) Pyridazinol 1-oxide obtained by hydrolysis of VI formed N-methoxypyridazinone with methyl *p*-toluenesulfonate and sodium methoxide. iii) VI was identical with the compound obtained by hydrogenation of 4-methoxy-3,6-dicholoropyridazine 1-oxide, whose structure was established by its correlation to the known 3,4,6-trimethoxypyridazine 1-oxide. In addition, some reactions related to II were described.

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18. Katsura Morita, Shunsaku Noguchi, Hiroshi Kono, and Takuichi Miki : Synthesis of Polyhydroxysteroids. I. A Modified Degradation of the Diosgenin Side Chain.*1

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Side chain degradation of steroidal sapogenins has been carried out by Marker's method,[1,2] which involves transformation of sapogenins into pseudosapogenin acetates and subsequent chromic anhydride oxidation followed by hydrolysis to give pregnenolones. Owing to various improvements later performed by other investigators[3~5] the production yields of 3β-hydroxypregna-5,16-dien-20-one from diosgenin, for instance, are reported to be above 60%.

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