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60. Takanobu Itai and Sachiko Natsume: Potential Anti-cancer Agents. IX.[1] Nitration of Pyridazine 1-Oxide. (2).

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In the preceding paper,[1] the authors have reported that pyridazine 1-oxide (I) was nitrated to 4-nitropyridazine 1-oxide (II) with mixed acid under vigorous conditions with recovery of a considerable amount of the starting material, and the nitro group of II was readily displaced with nucleophilic reagents. The present paper will describe the nitration of I with acyl nitrate.

Ochiai and Kaneko[2,3] applied the nitration with acyl nitrate for the first time to heteroaromatic N-oxides, and succeeded in the introduction of a nitro group at β-position to N-oxide of some derivatives of pyridine and quinoline. It is anticipated that the similar substitution would take place at 3- and/or 5-position of I, and it seems very interesting to examine the chemical and biological reactivities of these nitration products.

When I was treated with benzoyl chloride-silver nitrate in chloroform solution at a low temperature as described by Ochiai and Kaneko,[3] two kinds of new mononitropyridazine N-oxide, (III, m.p. 169°, and IV, m.p. 142~143°) were isolated in 33% and 0.8% yields respectively, accompanied with recovery of the starting material in 28% yield. III is quite unstable to alkali. On dissolving III in sodium bicarbonate solution, the color of the solution soon changed from yellow to red, and III could not be regenerated by acidifying the solution. IV is a little more stable than III, and after standing it in sodium bicarbonate solution for a short time, IV was recovered unchanged. But, with caustic alkalis, it changes to an unknown reddish substance immediately. Both III and IV were adsorbed strongly on alumina.

When acetyl chloride was used instead of benzoyl chloride, the same nitro compounds were obtained, but in lower yield of III (Table I).

Table I.

Reagents	Yields of III	Yields of IV	Recovery of I
C_6H_5COCl-$AgNO_3$	33%	0.8%	28%
CH_3COCl-$AgNO_3$	17%	0.8%	34.5%

III and IV gave analytical values corresponding to mononitropyridazine 1-oxide. Their infrared absorption spectra showed bands attributable to C-NO_2 group, but no bands of hydroxyl and carbonyl groups at all. Since they obviously differed from 4-nitropyridazine 1-oxide in respect of their melting points and ultraviolet and infrared spectra, they must be the two isomers among 3-, 5-, and 6-nitropyridazine 1-oxides.

The structure of IV was determined to be 5-nitropyridazine 1-oxide, because it formed known 4-aminopyridazine (V),[4] m.p. 127~129°, by hydrogenation over palladium-charcoal in methanolic solution containing hydrochloric acid.

III was proved to be 3-nitropyridazine 1-oxide from the following experiments. Hydrogenation of III under the same condition as in the case of IV, gave known

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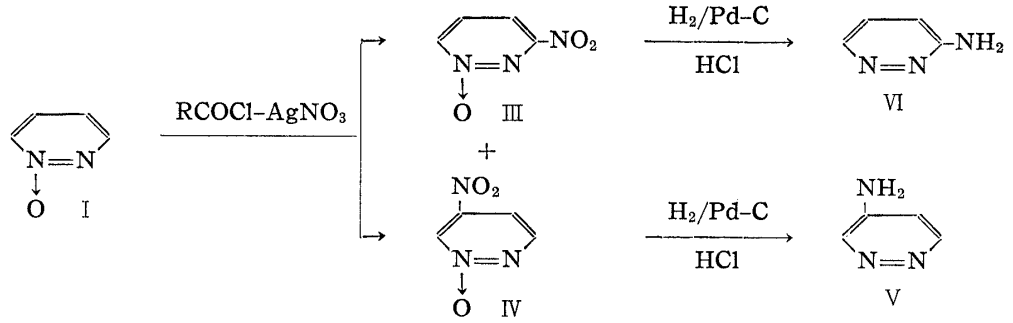
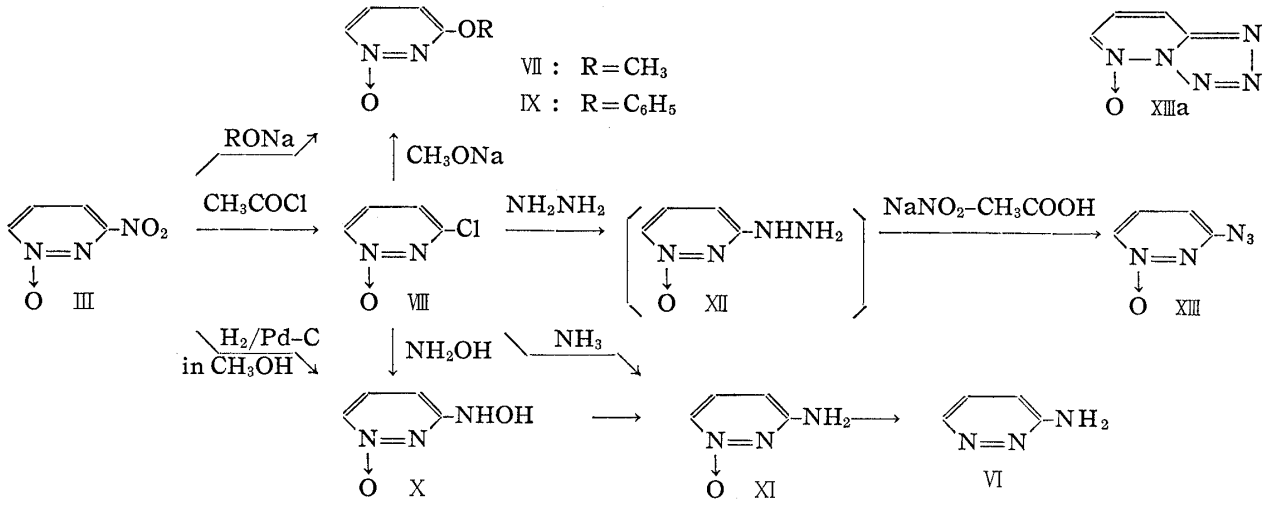
1) T. Itai, S. Natsume: This Bulletin, **11**, 83 (1963).
2) E. Ochiai, C. Kaneko: This Bulletin, **5**, 56 (1957) and following papers.
3) *Idem*: *Ibid.*, **7**, 267 (1959).
4) T. Kuraishi: This Bulletin, **4**, 132 (1956).



3-aminopyridazine (VI),[5] m.p. 170°, after four molar equivalents of hydrogen uptake. By standing at 30° with methanolic sodium methoxide, III was converted to monomethoxypyridazine 1-oxide (VII), m.p. 79~80°, in good yield. Both the mixed melting points determination and comparison of infrared spectra confirmed the identity of VII with 3-methoxypyridazine 1-oxide, whose preparation was first reported by Igeta and its structure has been rigorously established.[6] Furthermore, III was transformed by boiling with acetyl chloride to colorless needles VIII, m.p. 93°, identical with known 3-chloropyridazine 1-oxide[7] on admixture.



Since it was observed that 3-nitro group was reactive against nucleophilic reagents as mentioned above, some additional experiments were carried out and the results were compared with those of 4-nitropyridazine 1-oxide (II)[1] and 2-nitropyridine[8],*2 as shown in Table II. Deducing from the data, it may be concluded roughly, that nucleophilic attack to 3-position with alkaline reagents, takes place with the nearly same degree as the case of 4-nitropyridazine 1-oxide, and more easily than that of 2-nitropyridine, whereas, in the case with acidic reagents, 3-nitro group is displaced less easily than 4-nitro group.

*2 The nitro group of III was located concurrently at α-position against 2-N and β-position against 1-N of pyridazine 1-oxide, so that the similar reactivity to that of 2-nitropyridine was expected.

5) E. A. Steck, R. P. Brundage, L. A. Fletcher: J. Am. Chem. Soc., **76**, 3225 (1954).
6) H. Igeta: This Bulletin, **7**, 938 (1959). Igeta described 3-methoxypyridazine 1-oxide as hygroscopic crystals, b.p$_4$ 143°, but later, Nakagome repeated the N-oxidation reaction of 3-methoxypyridazine under the same condition and described that he obtained colorless needles, m.p. 79~80°, whose identity with Igeta's 3-methoxypyridazine 1-oxide was quite certain because both nitration products of their independent N-oxidation product were shown to be identical. See T. Nakagome: Yakugaku Zasshi, **81**, 554 (1961).
7) *Idem*: *Ibid.*, 8, 559 (1960).
8) M. Katada: Yakugaku Zasshi, **67**, 59 (1947).

Table II.

Reagent	Condition	3-NO_2-N→O (III)	4-NO_2-N→O (II)[1]	2-Nitropyridine[8]
CH_3ONa	30°, 1.5 hr.	77 % of 3-MeO-N→O 15 % of recovery	65 % of 4-MeO-N→O[1]	No reaction[8]
〃	reflux temp.	73 % of 3-MeO-N→O[a]	8 % of 4-MeO-N→O[b]	2-EtO-pyridine[c]
C_6H_5ONa	100°, 2 hr.	50 % of 3-C_6H_5O-N→O	——	No reaction[8]
CH_3COCl	35°, 3 hr.	2 % of 3-Cl-N→O 90 % of recovery	76 % of 4-Cl-N→O[1]	——
〃	reflux temp.	81 % of 3-Cl-N→O	——	——
$POCl_3$	55°, 5 hr.	——	20 % of 4-Cl-N→O 36 % of recovery	——
〃	70°, 3 hr.	No reaction	——	No reaction[8]

a) For 1 hr.
b) The yield was decreased with reflux.[1]
c) With C_2H_5ONa for 2 hr.[8]

The mode of the catalytic hydrogenation of III over palladium-charcoal in neutral solution, differs from the case in acidic medium. Rapid hydrogen absorption was observed up to two molar equivalents, and thereafter the absorption became quite slow. This behavior has been observed in the case of the hydrogenation of 4-nitro N-oxides of pyridine,[9] quinoline,[10] and of pyridazine[1] under the similar condition. When the reduction was stopped after the absorption of two moles of hydrogen, yellow needles X, m.p. 184°(decomp.), were obtained in 76 % yield as a sole product. X was identified as 3-hydroxyaminopyridazine 1-oxide on admixture with the compound prepared by treating 3-chloropyridazine 1-oxide (VIII) with hydroxylamine. Their identity was also confirmed by comparison of the infrared spectra. Further hydrogenation of X under the above condition gave two products, colorless needles of m.p. 139~141°(decomp.) and of m.p. 170°. It was found that the latter was 3-aminopyridazine (VI), and the former, m.p. 139~141°(decomp.), was identical with 3-aminopyridazine 1-oxide (XI)*3 prepared from VIII with alcoholic-ammonia. When the hydrogenation of III was stopped after three molar equivalents of hydrogen uptake, the formation of, X, XI, and VI was observed in 21 %, 32 %, and 10 % yields respectively. Therefore, it may be assumed that, in this case, the reduction of nitro group to hydroxyamino group takes place preferentially, corresponding to the first rapid absorption of two molar equivalents of hydrogen, and the further slow hydrogen absorption is required to reduce the hydroxyamino group to an amino group with simultaneous reduction of N-oxide group.

The chlorine atom at 3-position of VIII as well as the 3-nitro group in III, is susceptible to the attack of nucleophilic reagents, as observed in the above reactins with ammonia and with hydroxylamine. In addition, it was found that VIII was directly converted to 3-methoxypyridazine 1-oxide (VII) by sodium methoxide at room temperature in 79 % yield, and furthermore, VIII produced 3-azidopyridazine 1-oxide (XIII), m.p. 155~156° (decomp.), via 3-hydrazino pyridazine 1-oxide (XII) obtained by treatment with hydrazine under usual condition. XIII has azide bands near 2200 cm^{-1} in the infrared region, and therefore it is obvious that XIII exists hardly in its isomeric tetrazole structure XIIIa.

Rearrangement of III with tosyl chloride or deoxygenation of III with phosphorus trichloride was attempted under usual conditions and either of those reactions resulted in recovery of the most part of the starting material.

The test on carcinostatic and bacteriostatic activity of some of these compounds was

*3 The correlation of XI to an acetamidopyridazine N-oxide was proved, which was obtained in small yield as a by-product on N-oxidation of 3-acetamidopyridazine, accompanied with the mainly produced 6-acetamidopyridazine 1-oxide. See T. Itai, T. Nakashima : This Bulletin, **10**, 346, 936 (1962).

9) E. Ochiai, M. Katada : *Ibid.*, **63**, 186 (1943).
10) E. Ochiai, T. Naito : *Ibid.*, **64**, 206 (1944).

carried out[11] in our Institute, and it was found that III possessed no activity to Ehrlich ascite carcinoma *in vivo*, while III showed strong activity against *Staphylococcus aureus*, *Escherichia coli*, *Shigella flexneri* 2a and *Candida albicans in vitro*. Details will be published elsewhere.

Experimental

Nitration of Pyridazine 1-Oxide (I) with Acyl Nitrate——a) With BzCl-$AgNO_3$: To a well-cooled solution of 5 g. (0.052 mole) of I in 40 cc. of $CHCl_3$ was added 6 cc. (7.32 g., 0.052 mole) of BzCl, and 9.7 g. (0.057 mole) of finely powdered $AgNO_3$ was added in small portions keeping below −10° under stirring. was continued for 4 hr. at the same temperature, and the mixture was allowed to stand for 4 days. Stirring AgCl and a yellow precipitate (A) which separated were collected by filtration, washed with cold $CHCl_3$ twice and extracted thoroughly with hot $CHCl_3$. The yellow extract was concentrated to dryness and the crystalline residue was recrystallized from MeOH to yield 2.15 g. of yellow needles III, m.p. 166°. Soluble in satd. $NaHCO_3$ and in 10% NaOH. Not regenerated by acidification of these alkaline solutions. Adsorbed strongly on Al_2O_3. *Anal.* Calcd. for $C_4H_3O_3N_3$: C, 34.05; H, 2.14; N, 29.79. Found : C, 34.28; H, 1.79; N, 30.09. IR ν_{max}^{KBr} cm^{-1} : 1543, 1523, 1337, 1324. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) : 232 (4.02), 281 (3.99), 350 (3.73).

The mother liqour was concentrated to dryness and the residue was separated by SiO_2 chromatography into fractions.

The first fraction, eluted with benzene-$CHCl_3$ (9:1), was identified as BzOH, 51 mg.

The second fraction, eluted with the above solvent, was identified as nearly pure IV, m.p. 141～142°, 22 mg. Soluble in $NaHCO_3$ and NaOH. This was recrystallized from MeOH to yellow needles, m.p. 142～143°, for analytical samples. *Anal.* Calcd. for $C_4H_3O_3N_3$: C, 34.05; H, 2.14. Found : C, 34.48; H, 2.39. IR ν_{max}^{KBr} cm^{-1} : 1567, 1518, 1360, 1280. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) : 217 (3.97), 241 (4.02), 370 (3.24). The third fraction, eluted with fhe same solveut, was recrystallized from MeOH, to 45 mg. of III, m.p. 167～169°.

The fourth fraction, eluted with $CHCl_3$, was a brown syrupy mixture, 100 mg.

The fifth fraction, eluted with $CHCl_3$, was identical with the starting material I, 270 mg. Perchlorate, 184°.

The insoluble residue, after extracting (A) with hot $CHCl_3$, was extracted with hot MeOH, and from the MeOH extract, 0.06 g. of an additional III was obtained after evaporation and recrystallization.

The filtrate and washings which were obtained after filtrating (A), were combined and evaporated. To the residue 30 cc. of H_2O and 60 cc. of Et_2O was added, and insoluble substance was collected by filtration, and recrystallized from MeOH to give 0.12 g. of III, m.p. 169°. The filtrate was extracted with Et_2O, and the Et_2O extract gave 5.9 g. of BzOH after drying and evaporation. The aqueous layer was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ repeatedly. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated. The residue was purified by SiO_2 chromatography as above. 40 mg. of IV, m.p. 142～143°, 45 mg. of III, m.p. 169°, and 1.12 g. of I were obtained.

b) With AcCl-$AgNO_3$: To a well-cooled solution of 5 g. (0.052 mole) of I in 50 cc. of $CHCl_3$ was added 4.1 cc. (4.5 g., 0.057 mol.) of AcCl, and to this mixture 9.7 g. (0.057 mole) of finely powdered $AgNO_3$ was added in small portions keeping below −10° under stirring. Stirring was continued at the same temperature for 1.5 hr. After standing for 3 days at room temperature, the reaction mixture was treated as above, 1.26 g. (17.2 %) of III, 57 mg. (0.85%) of IV, and 1.72 g. of recovery of I were obtained.

Catalytic Hydrogenation of 5-Nitropyridazine 1-Oxide (IV)——A solution of 0.042 g. of IV in 15 cc. of 50% MeOH containing 1 cc. of conc. HCl was hydrogenated over 20% Pd-C. After 4 mol. equiv. of H_2 uptake, the catalyst was removed and the solvent was evaporated. Hygroscopic crystalline residue was dissolved in a small amount of MeOH and transformed to its picrate (54 mg.) by adding methanolic solution of Na picrate. Recrystallization of the picrate from MeOH gave yellow needles, m.p. 226～228° (decomp.), undepressed with the picrate, m.p. 228° (decomp.), of authentic 4-aminopyridazine on admixture. *Anal.* Calcd. for $C_4H_5N_3 \cdot C_6H_3O_7N_3$: C, 37.04; H, 2.49; N, 25.92. Found; C, 37.46; H, 2.68; N, 26.41.

Free base V, m.p. 127～129°, was obtained by passing the above picrate in MeOH through Amberlite IRA 410 (OH^-). No melting point depression with authentic 4-aminopyridazine[4] was observed.

Catalytic Hydrogenation of 3-Nitropyridazine 1-Oxide (III)——a) Over Pd-C in acidic medium : A suspension of 145 mg. of III in a mixture of 30 cc. of MeOH and 30 cc. of 4% HCl was hydrogenated over 20% Pd-C (prepared from 4.2 cc. of 1% $PdCl_2$ and 0.1 g. of C). The hydrogenation was stopped

11) The tests were performed by Dr. F. Miyazawa and Dr. T. Matsushima, Division of Microbiology in this Institute. A part of results : F. Miyazawa, S. Iwahara, T. Itai, *et al.* : Eisei Shikenjo Hokoku, **79**, 307 (1961).

after rapid absorption of 4 mol. equiv. of H_2 and the reaction mixture was treated as usual. Nearly colorless crystals, 100 mg. were obtained and this was purified through picrate by addition of 1 mol. equiv. of Na picrate and recrystallization from EtOH. The picrate (100 mg., 31%), m.p. 248~249°, was undepressed with the picrate[5] of 3-aminopyridazine on admixture.

By passing the above picrate in MeOH through Amberlite IRA 410 (OH^-), 3-aminopyridazine (VI), m.p. 170°, was produced, which was undepressed with authentic specimen[5] on admixture.

b) Over Pd-C in neutral medium : i) 3-Hydroxyaminopyridazine 1-oxide (X). A mixture of 1.08 g. of III and 20% Pd-C (prepared from 0.2 g. of C and 8.4 cc. of 1% $PdCl_2$) in 100 cc. of MeOH was shaken in H_2 stream. After rapid absorption of 2 mol. equiv. of H_2, the reduction was stopped. Faint yellow crystals deposited. The reaction mixture was warmed, and while hot, the catalyst was filtered off and washed thoroughly with hot MeOH. The filtrate was combined with the washings and evaporated to dryness. Recrystallization of the residue from EtOH gave 0.74 g. (76%) of faint yellow plates X, m.p. 184° (decomp.). It is soluble in 10% HCl, and dissolves red-colored in satd. $NaHCO_3$, 10% Na_2CO_3 and 10% NaOH. It reduces Fehling solution. *Anal.* Calcd. for $C_4H_5O_2N_3$: C, 37.80; H, 3.97; N, 33.06. Found : C, 38.08; H, 3.75; N, 32.74. UV $\lambda_{max}^{95\%\,EtOH}$ mμ (log ε) : 229 (4.17), 262 (4.14), 341 (3.63). IR ν_{max}^{KBr} : 3160 cm^{-1}.

ii) 3-Aminopyridazine 1-oxide (XI) : A mixture of 1.06 g. of III and 20% Pd-C (prepared from 0.2 g. of C and 8.4 cc. of 1% $PdCl_2$) in 200 cc. of MeOH was hydrogenated as above. After 3 mol. equiv. of H_2 uptake, the reduction was stopped, and the mixture was treated as above. The crystalline residue was recrystallized from MeOH to 0.2 g. (21%) of 3-hydroxyaminopyridazine 1-oxide (X), m.p. 182° (decomp.), identical with the material obtained in i), by mixed melting point and comparison of IR spectra.

The mother liquor was concentrated to dryness, the residue was dissolved in MeOH and a methanolic solution of picric acid was added. The yellow crystals which deposited were collected by filtration and recrystallized from MeOH to yellow needles (0.25 g., 10%), m.p. 248~249°. No melting point depression on admixture with the picrate of 3-aminopyridazine.

The filtrate was allowed to stand over Amberlite IRA 410 (OH^-) overnight. The resin was removed by filtration, the filtrate was evaporated and the residue was recrystallized from AcOEt to 0.27 g. (32%) of nearly colorless needles XI, m.p. 139~141°. *Anal.* Calcd. for $C_4H_5ON_3$: C, 43.24; H, 4.54, N, 37.83. Found : C, 43.45; H, 4.10; N, 37.25. UV $\lambda_{max}^{95\%\,EtOH}$ mμ (log ε) : 217 (4.23), 246~248 (4.13), 338~340 (3.74). IR ν_{max}^{KBr} cm^{-1} : 3340, 3300, 3210, 1632.

Catalytic Hydrogenation of 3-Hydroxyaminopyridazine 1-Oxide (X)——A mixture of 0.2 g. of X and 0.12 g. of 20% Pd-C in 50 cc. of MeOH was shaken in H_2 stream. The reduction was stopped after 1 mol. equiv. of H_2 uptake and the mixture was treated as above. 60 mg. (12%) of the picrate of VI, m.p. 245~249°, and 75 mg. (43%) of XI, m.p. 139~141°, were obtained.

Reaction of 3-Nitropyridazine 1-Oxide (III) with NaOMe——a) At 30° : To a suspension of 0.2 g. of III in 70 cc. of anhyd. MeOH was added methanolic MeONa prepared from 40 mg. of Na and 7 cc. of MeOH. The mixture was allowed to stand at 30° for 1.5 hr. (III went into solution slowly). The insoluble substance was filtered and washed with benzene. Recrystallization of it gave 30 mg. of III, m.p. 168~169° (15%). The filtrate was combined with the washings and evaporated under reduced pressure. After an addition of a small amount of H_2O, the residue was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. The crystalline residue was recrystallized from benzene to 137 mg. (77%) of colorless dice VII, m.p. 79~80°. No melting point depression on admixture with authentic 3-methoxypyridazine 1-oxide.[6] IR and UV : identical with those of authentic sample in all respects.

b) At reflux temperature : To a solution of 0.4 g. of III in 50 cc. of hot MeOH was added 10 cc. of methanolic NaOMe prepared from 80 mg. of Na. The mixture was refluxed for 1 hr. and treated as above. 0.26 g. (73%) of colorless dice VII was obtained.

Reaction of III with AcCl——a) At reflux temp. : A suspension of 0.59 g. of III in 15 cc. of AcCl was refluxed until all of III went into solution (It required ca. 9 hr.). AcCl was distilled off under reduced pressure, and the crystalline residue was recrystallized from $(iso\text{-}Pr)_2O$ to give 0.36 g. of VIII, m.p. 93°. No melting point depression on admixture with authentic 3-chloropyridazine 1-oxide.[7] An additional crop of VIII, 80 mg., was obtained by purification of the mother liquor through Al_2O_3 using $CHCl_3$. Total yield of VIII, 0.44 g., 81%. UV $\lambda_{max}^{95\%\,EtOH}$: 266 mμ (log ε, 4.00). IR ν_{max}^{KBr} : 1340 cm^{-1}; identical with that of authentic sample.

b) At 35° : A suspension of 0.1 g. of III in 1 cc. of AcCl was allowed to stand at 35° for 3 hr. The mixture was concentrated to dryness under reduced pressure, the residue was extracted with hot $(iso\text{-}Pr)_2O$ repeatedly. From the combined $(iso\text{-}Pr)_2O$ extract, after evaporation and purification by Al_2O_3 chromatography with $CHCl_3$, 2 mg. of 3-chloropyridazine 1-oxide (VIII) was obtained. The insoluble substance in hot $(iso\text{-}Pr)_2O$, was nearly pure III, m.p. 167~169°, 90 mg.

3-Phenoxypyridazine 1-Oxide (IX)——To a solution of 0.4 g. of Na dissolved in 0.7 g. of C_6H_5OH with warming, 0.15 g. of III was added. The mixture was heated at 100° for 1 hr. C_6H_5OH was removed *in vacuo*, H_2O was added to the residue, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract

was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue in $CHCl_3$ was passed through Al_2O_3 column and the combined $CHCl_3$ eluate was evaporated. The residue was recrystallized from benzene to give colorless needles, m.p. 115~116°. Yield, 100 mg., 50%. *Anal.* Calcd. for $C_{10}H_8O_2N_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.50; H, 4.53; N, 14.70.

Treatment of VIII with NH_2OH——To a saturated solution of 0.27 g. of $NH_2OH \cdot HCl$ in MeOH was added 0.27 g. of K_2CO_3 in a small amount of H_2O. KCl which deposited was filtered off. The filtrate was added to a solution of 80 mg. of VIII in 3 cc. of MeOH. After refluxing for 5.5 hr., the reaction mixture was concentrated to dryness, diluted with a small amount of H_2O and extracted with $CHCl_3$. Evaporation of the $CHCl_3$ extract gave 22 mg. of crystals (m.p. 80~90°), which were recrystallized from $(iso\text{-}Pr)_2O$ to yield colorless needles, m.p. 90~92°. No depression on admixture with the starting material. The substance which was insoluble in $CHCl_3$ and H_2O, was collected by filtration, and recrystallized from EtOH, to 6 mg. of yellow crystals, m.p. 182~183° (decomp.), identical with 3-hydroxyaminopyridazine 1-oxide (X), obtained by partial hydrogenation of III, on admixture and by comparison of IR spectra.

Reaction of VIII with NH_3——A mixture of 0.2 g. of VIII, 5 cc. of EtOH and 3 cc. of 28% of NH_4OH was heated at 120° for 4 hr. in a sealed tube. The reaction mixture was treated with charcoal, evaporated to dryness under reduced pressure. The residue was extracted with hot AcOEt repeatedly and the combined AcOEt extract was evaporated. Recrystallization of the residue from AcOEt gave 0.05 g. of 3-aminopyridazine 1-oxide (XI), m.p. 140~141°, which was identical with the product obtained by the reduction of III, on admixture and by comparison of IR spectra.

The mother liquor was concentrated to dryness. Purification of the residue by Al_2O_3 chromatography with $CHCl_3$ gave 60 mg. of the starting material VIII.

Reaction of VIII with MeONa——To a solution of 0.17 g. of VIII in 10 cc. of MeOH was added methanolic MeONa (from 30 mg. of Na and 5 cc. of MeOH). The mixture was allowed to stand overnight at room temperature and evaporated under reduced pressure. After an addition of a osmall amount f H_2O, the residue was extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and evaporated. Purification of the residue by Al_2O_3 chromatography using benzene gave 130 mg. (79%) of white crystals, m.p. 78~80°. Beilstein's reaction, negative. This was identical with authentic 3-methoxypyridazine 1-oxide on admixture.

3-Azidopyridazine 1-Oxide (XIII)——A mixture of 0.05 g. of VIII and 0.04 cc. of 80% $NH_2NH_2 \cdot H_2O$ in 1 cc. of 99% EtOH was refluxed for 1 hr., cooled and concentrated to dryness under reduced pressure. The residue was dissolved in 1 cc. of AcOH, to which an aqueous solution of 0.03 g. of $NaNO_2$ was added under cooling. Crystalline product which deposited was collected by filtration and recrystallized from 99% MeOH to yield nearly colorless plates, m.p. 155~156°. Yield, 30 mg., 57%. *Anal.* Calcd. for $C_4H_3ON_5$: C, 35.04; H, 2.21; N, 51.09. Found: C, 34.82; H, 2.52; N, 51.12. IR ν_{max}^{KBr} cm^{-1}: 2180, 2150, 1250.

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Summary

Nitration of pyridazine 1-oxide (I) with acyl nitrate afforded two kinds of β-nitropyridazine 1-oxide, i.e., 3-nitropyridazine 1-oxide (III) as a main product and 5-nitropyridazine 1-oxide (IV) as a poorly yielded by-product. Structural correlations of those nitro compounds to known pyridazine derivatives were achieved by catalytic hydrogenations or nucleophilic displacement reactions of the active nitro group. Furthermore, some nucleophilic substitution reactions of III and 3-chloropyridazine 1-oxide were described.

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