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123. Takenari Nakagome : Synthesis of Pyridazine Derivatives. VIII.[1] N-Oxidation of 3,4-Dimethylpyridazine Derivatives.

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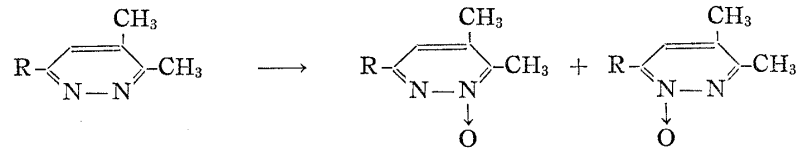
In Part III[2] and VII[1] of this series, the synthesis and the structural elucidation of 3-methylpyridazine N-oxide derivatives were reported. In continuation to the work, N-oxidation of 3,4-dimethylpyridazine and its derivatives was carried out.

3,4-Dimethylpyridazine (I)[3~5] was oxidized with hydrogen peroxide in glacial acetic acid in a usual way. Recrystallization and chromatographic separation of the product afforded two kinds of N-oxides, III, m.p. 149~150°, II, m.p. 110~111°, in 36% and 16% yield respectively, both of which regenerated the original 3,4-dimethylpyridazine (I) by catalytic reduction over palladized charcoal.

6-Chloro-3,4-dimethylpyridazine (IV),[4,5] was oxidized with perbenzoic acid in chloroform. When the crude product so obtained was subjected to catalytic dehalogenation over palladized charcoal in aqueous ammonia solution, II was mainly formed, in addition to a very minute amount of III, suggesting that the crude oxidized product consists of two 6-chloro-3,4-dimethylpyridazine N-oxides (V and VI). The chromatographic separation of this crude N-oxide through alumina column afforded pure 6-chloro-3,4-dimethylpyridazine 2-oxide (V), m.p. 109~110°, from the initial fraction eluted with benzene-chloroform mixture, although isomeric 6-chloro-3,4-dimethylpyridazine 1-oxide (VI) failed to be isolated in pure state. However, when the crude N-oxide was nitrated with fuming nitric acid in sulfuric acid, VI, m.p. 184~184.5°, was isolated, which was unaffected by the reagents and was readily separable from the nitrated product of V. The ultraviolet absorption spectra of these two isomers (V) and (VI) in 95% ethanol, with peaks at 262 and 321 mμ in the former and at 264.5 and 324 mμ in the latter, are very similar to those of pyridazine N-oxide derivatives reported in the previous papers.[2] Further, V was catalytically dehalogenated to yield II, while VI gave III.

In contrast with N-oxidation of I and IV, oxidation of 6-methoxy-3,4-dimethylpyridazine (VII) with hydrogen peroxide in glacial acetic acid gave a sole N-oxide (VIII) which was also prepared from the foregoing 6-chloro-3,4-dimethylpyridazine 2-oxide (V) on treatment with sodium methoxide.



Starting material

I : R=H
IV : R=Cl
VII : R=OCH_3

Products (Yield)

II (16%) III (35.5%)
V (83%) VI (0.7%)
VIII —

Chart I.

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1) Part VII. T. Nakagome : Yakugaku Zasshi, **82**, 1206 (1962).
2) Part III. *Idem* : *Ibid.*, **82**, 249 (1962).
3) J. Levisalles : Bull. soc. chim. France, **1957**, 1009 (C.A. **52**, 4656 (1958)).
4) R.H. Horning, E.D. Amstutz : J. Org. Chem., **20**, 707 (1955).
5) P. Schmidt, J. Druey : Helv. Chim. Acta., **37**, 1467 (1954).

Since 3-chloro-6-methylpyridazine was oxidized[2,6] only at the adjacent nitrogen to methyl group in view of the steric hindrance of chlorine atom, it seemed likely that N-oxidation of 6-chloro-3,4-dimethylpyridazine (IV) resulted in the formation of 2-oxide (V) as a principal product. This prediction was confirmed by a series of reactions analogous to those used for the characterization[1,2] of 3-chloro-6-methylpyridazine 1-oxide.

On hydrolysis with dilute sodium hydroxide solution V yielded 3,4-dimethyl-6-pyridazinol N-oxide (IX). Treatment of IX with dimethylsulfate in dilute sodium hydroxide solution gave a mixture of two products, separable by virtue of their different basicity. The basic component was identical with the foregoing 6-methoxy-3,4-dimethylpyridazine N-oxide (VIII). The structure of the second product (X) was established by its derivation to 1,3,4-trimethyl-6(1*H*)-pyridazinone (XI) by catalytic hydrogenation over palladized charcoal, which was also prepared by the treatment of the known 3,4-dimethyl-6(1*H*)-pyridazinone (XII) with dimethylsulfate in sodium hydroxide solution. In the latter case the isomeric 6-methoxy-3,4-dimethylpyridazine (VII) which might reasonably be formed was not obtained. The infrared spectra of X and XI showed absorption bands at 1681 cm^{-1} and at 1667 cm^{-1} respectively, attributable to the carbonyl group, and the ultraviolet spectrum of XI showed absorption maximum at 293 mμ closely corresponding to that of 1,3-dimethyl-6(1*H*)-pyridazinone at 294 mμ[7] in ethanol.

It became apparent, therefore, that the N-oxide group in IX and X is attached to the 2-position, and X is 1,3,4-trimethyl-6(1*H*)-pyridazinone 2-oxide and IX is 3,4-dimethyl-6-pyridazinol 2-oxide. Furthermore, IX does not color with ferric chloride solution, does not exhibit infrared absorption in the carbonyl region, and its ultraviolet spectrum shows two maxima at 252 and 315 mμ in 95% ethanol closely corresponding to those of 3-pyridazinol 1-oxide[2,8] and 6-methyl-3-pyridazinol 1-oxide,[2] giving further evidences supporting the assignment of the structure of IX.

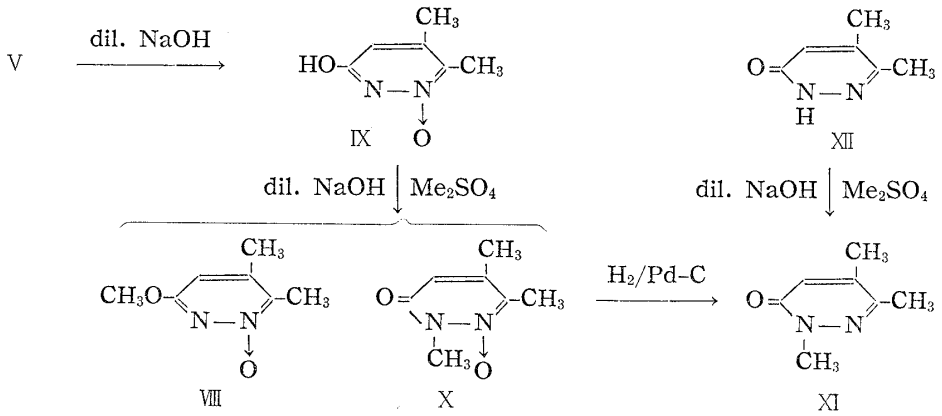

Chart 2.

It is concluded that among the N-oxides in the present work, II, V, VIII, and IX are 2-oxides, and III and VI are 1-oxides.

Itai and Natsume[9] described, in the recently published paper, that N-oxidation of 4-methoxypyridazine derivatives did not give preferentially 1-oxides, showing that the methoxyl group in 4-position exhibited only a weak polar effect to the ring nitrogen. The results of the present work similarly show that the effect of the methyl group in

6) H. Kano, M. Ogata, H. Watanabe, I. Ishizuka : This Bulletin, **9**, 1017 (1961).
7) W.G. Overend, L.M. Turton, L.F. Wiggins : J. Chem. Soc., **1950**, 3500.
8) H. Igeta : This Bulletin, **7**, 938 (1959).
9) T. Itai, S. Natsume : *Ibid.*, **10**, 643 (1962).

4-position was not so marked in the N-oxidation of 3,4-dimethylpyridazine derivatives, in contrast to 4-methyl-3,6-dimethoxypyridazine which afforded only 4-methyl-3,6-dimethoxypyridazine 1-oxide.[10,11]

Experimental*2

Oxidation of 3,4-Dimethylpyridazine (I)——To a solution of 30 g. (0.28 mole) of 3,4-dimethylpyridazine[3] in 400 cc. of AcOH was added 39 cc. of 30% H_2O_2 solution and the mixture was allowed to stand for 3~4 weeks at room temperature. The solution was concentrated in vacuum, water was added, and again concentrated. This procedure was repeated three times. The residual oil was basified with Na_2CO_3, extracted with $CHCl_3$ and the $CHCl_3$ layer was dried over anhyd. Na_2SO_4. After evaporation of $CHCl_3$, Et_2O was added to the residue, and crystals were filtered, washed with Et_2O, giving 28 g. (82%) of white crystals, m.p. 97~120°. This was repeatedly crystallized from benzene yielding 9.3 g. of colorless rods III, m.p. 149~150°. The combined mother liquor was evaporated and the residue was dissolved in benzene, which was poured on alumina column for chromatography. Elution with benzene afforded an initial fraction of 5.5 g. of colorless needles, m.p. 110~111°, after recrystallization from (iso-Pr)$_2$O and drying at 60~70° in vacuum. Yield, 16%. *Anal.* Calcd. for $C_6H_8ON_2$ (3,4-dimethylpyridazine 2-oxide (II)) : C, 58.05; H, 6.50; N, 22.57. Found : C, 58.56; H, 7.35; N, 22.25. UV $\lambda_{max}^{95\%\,EtOH}$ mμ (log ε): 258.5 (4.09), 312 (3.70). Picrate : Yellow plates (from MeOH-Et_2O), m.p. 118~119.5°. *Anal.* Calcd. for $C_6H_8ON_2 \cdot C_6H_3O_7N_3$: C, 40.80; H, 3.14; N, 19.83. Found : C, 41.07; H, 3.44; N, 19.41. Further elution afforded 2.9 g. of the foregoing III, m.p. 149~150°. Yield, 35.5%. *Anal.* Calcd. for $C_6H_8ON_2$ (3,4-dimethylpyridazine 1-oxide (III)) : C, 58.05; H, 6.50; N, 22.57. Found : C, 57.90; H, 6.43; N, 22.17. UV $\lambda_{max}^{95\%\,EtOH}$ mμ (log ε) : 264.5 (4.09), 312 (3.70). Picrate : m.p. 103~104°, yellow prisms (from Et_2O). *Anal.* Calcd. for $C_6H_8ON_2 \cdot C_6H_3O_7N_3$: C, 40.80; H, 3.14; N, 19.83. Found : C, 39.96; H, 3.62; N, 19.74. From the benzene mother liquor of recrystallization 6.3 g. (18%) of a mixture of both N-oxides was obtained.

Reduction of 3,4-Dimethylpyridazine N-Oxide (II) and (III)——A mixture of 0.1 g. of 3,4-dimethylpyridazine N-oxide, 15 cc. of MeOH and 0.5 g. of 5% Pd-C was shaken with H_2. After rapid absorption of 28 cc. of H_2 in 20 min., the reduction stopped. The catalyst was removed by filtration, and the filtrate was evaporated to dryness. The addition of picric acid in EtOH to the residue precipitated yellow crystals of

(i) (from 2-oxide (II)). m.p. 171~174°, 0.14 g. (52%).
(ii) (from 1-oxide (III)). m.p. 171~174°, 0.16 g. (56%).

A recrystallization from EtOH raised the melting point to 176~177°, undepressed on admixture with authentic specimen of picrate of 3,4-dimethylpyridazine, m.p. 176~177°.

Oxidation of 6-Chloro-3,4-dimethylpyridazine (IV)——To a $CHCl_3$ solution (500 cc.) containing 33.3g. (1.2 equivalent) of perbenzoic acid was added 20 g. of IV.[4] After 3 days at room temperature, $CHCl_3$ was removed in vacuum at 25~30°. The residue was made alkaline with aqueous Na_2CO_3 under cooling and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over K_2CO_3, evaporated to dryness. The crystalline residue was thinned with Et_2O for filtration, yielding 26 g. (83%) of crude N-oxide as colorless leaflets, m.p. 105~106°. Repeated recrystallization from (iso-Pr)$_2$O or benzene-hexane mixture did not raise the melting point of the product. Then, 2.6 g. of the crude N-oxide was dissolved in benzene, chromatographed on alumina. Each effluent was 100 cc. The benzene eluate gave 2.0 g. of m.p. 109~110°, which was recrystallized from (iso-Pr)$_2$O giving 1.8 g. of pure 6-chloro-3,4-dimethylpyridazine 2-oxide (V) as colorless needles, m.p. 109~110°. *Anal.* Calcd. for $C_6H_7ON_2Cl$: C, 45.39; H, 4.41; N, 17.65. Found : C, 45.51; H, 4.21; N, 17.01. UV $\lambda_{max}^{95\%\,EtOH}$ mμ (log ε) : 262 (3.95), 321 (3.71). Further elution with benzene and then with benzene-$CHCl_3$ (1:1) mixture gave 0.26 g., m.p. 104~105°, which was recrystallized from (iso-Pr)$_2$O to give colorless needles, m.p. 107~108°. The fraction eluted with $CHCl_3$ gave 0.13 g. This was recrystallized to colorless plates, m.p. 103~104°. No depression of melting point occured on admixture with the foregoing colorless needls, m.p. 109~110°. The eluate with $CHCl_3$-MeOH (1:1) gave no product.

6-Chloro-3,4-dimethylpyridazine 1-Oxide (VI)——A mixture of 6 g. of crude 3,4-dimethylpyridazine N-oxide, 20 cc. of conc. H_2SO_4 and 15.6 cc. of HNO_3 (d=1.48) was warmed at 70° for 6 hr. After cool, the mixture was poured on ice, extracted with $CHCl_3$ and the extract was evaporated, leaving behind 7.0 g. of crude product. This was dissolved in benzene, passed through a column of Florisil and the

*2 All melting points are uncorrected. Infrared spectra were measured with a Shimazu Infrared Spectrophotometer and ultraviolet spectra with a Shimazu RS-27 Recording Spectrophotometer.

10) Part V. T. Nakagome : Yakugaku Zasshi, 82, 1005 (1962).

11) M. Yanai, T. Kinoshita : Presented at the Kyushu Local Meeting of the Pharmaceutical Society of Japan on October 19th, 1962.

column was eluted with benzene, $CHCl_3$ and $CHCl_3$-MeOH mixture in that order. From the fraction eluted with benzene 6 g. of nitrated product was obtained, which will be reported in succeeding paper in detail. From the fraction eluted with $CHCl_3$-MeOH (20:1) mixture, a small amount of crystals was obtained. Discoloration was effected by treatment with alumina. Yield, 0.04 g. Recrystallization from benzene gave colorless rods, m.p. 184~184.5°. *Anal.* Calcd. for $C_6H_7ON_2Cl$: C, 45.39; H, 4.41; N, 17.65. Found : C, 45.75; H, 4.71; N, 17.88. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε) : 264.5 (4.05), 324 (3.67).

Catalytic Dehalogenation of Crude 6-Chloro-3,4-dimethylpyridazine N-Oxide——A mixture of 1 g. of the crude N-oxide (m.p. 105~106°) of IV, 0.1 g. of 5% Pd-C, 1 cc. of conc. NH_4OH and 200 cc. of water, was shaken with H_2. After about 40 min. 1 mole of H_2 was uptaken and the reduction stopped. The catalyst was filtered off, the filtrate was saturated with NaCl, extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, $CHCl_3$ was distilled off. The residue was washed with Et_2O, filtered, giving 0.7 g. of the product, m.p. 108~109°. This was dissolved in benzene and the solution was poured on alumina column for chromatography. The initial fraction eluted with benzene-$CHCl_3$ (4:1) mixture gave 0.7 g. (89%) of colorless crystals, m.p. 109~110°, which showed no depression on admixture with II. Further elution with benzene-$CHCl_3$ (1:1) mixture afforded 0.05 g. (0.6%) of colorless rods, m.p. 149~150° after recrystallization from benzene. No depression of melting point occured on admixture with III.

Catalytic Dehalogenation of V——Hydrogenation of 0.8 g. of V was carried out as described above for the crude N-oxide and the same treatment afforded 0.63 g. of the product. Recrystallization from $(iso\text{-}Pr)_2O$ and drying at 70~80° in vacuum yielded colorless needles, m.p. 110~111°, which were identified as 3,4-dimethylpyridazine 2-oxide (II) by admixture. Yield, 80%. Chromatographic separation of the crude product on alumina column failed to give isomeric III.

Catalytic Dehalogenation of VI——A mixture of 15 mg. of VI, 0.5 g. of 5% Pd-C, 1 cc. of conc. NH_4OH and 10 cc. of water was hydrogenated and worked up in the same manner as for V. Crystallization of the product from benzene gave colorless rods, m.p. 149~150°, identical with III.

6-Methoxy-3,4-dimethylpyridazine (VII)——A solution of 16 g. of 6-chloro-3,4-dimethylpyridazine and the MeONa from 2.8 g. (0.12 equivalents) of Na in 100 cc. of abs. MeOH was heated in a sealed tube on a boiling water bath for 2 hr. After removal of MeOH, water was added and the resulting solution was extracted with Et_2O. The extract was dried over anhyd. Na_2SO_4 and Et_2O was evaporated. The residue was digested with petr. benzin for filtration and colorless prisms, m.p. 70~71°, was obtained in quantitative yield. Crystallization from benzene did not raise the melting point *Anal.* Calcd. for $C_7H_{10}ON_2$: C, 60.85; H, 7.30; N, 20.28. Found : C, 61.04; H, 7.42; N, 20.47.

6-Methoxy-3,4-dimethylpyridazine 2-Oxide (VIII)——A mixture of 13.8 g. of VII, 17.5 cc. (1.5 equivalents) of 30% H_2O_2 and 100 cc. of AcOH was kept at 70~75° for 12 hr. Worked up in a manner described for N-oxidation of I, 13.8 g. of crude N-oxide was obtained, m.p. 97~98°, which was crystallized from $(iso\text{-}Pr)_2O$ to colorless prisms, m.p. 97.5~98.5°. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54; N, 18.17. Found : C, 54.79; H, 6.77; N, 18.00.

3,4-Dimethyl-6-pyridazinol 2-Oxide (IX)——A solution of 2.6 g. of V dissolved in 30 cc. of 10% NaOH was heated for 1.5 hr. on a boiling water bath. The solution was acidified with HCl, evaporated to dryness, and the residue was extracted with hot abs. EtOH, removing NaCl by filtration. The filtrate was concentrated to a small volume, the crystals that separated out were collected, m.p. 211° (decomp.). Yield, 1.6 g. (70%). This was twice recrystallized from EtOH giving colorless plates, m.p. 215° (decomp.). $FeCl_3$ test, negative. *Anal.* Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found : C, 51.43; H, 5.87; N, 20.18.

Reaction of IX with Dimethyl sulfate——To a solution of 1.4 g. of IX in 10 cc. of water, 3.8 g. (0.03 equivalent) of dimethyl sulfate was slowly added in portions with constant stirring, with simultaneous addition of 2*N* NaOH solution to neutralize the produced acid. After the reaction was complete, the solution was saturated with NaCl, extracted with $CHCl_3$. The $CHCl_3$ extract was washed with three 10 cc. portions of 4*N* HCl, then washed with water, dried over anhyd. Na_2SO_4 and $CHCl_3$ was distilled off. The residue (0.72 g.) was recrystallized from $(iso\text{-}Pr)_2O$ giving 0.3 g. (19.5%) of 1,3,4-trimethyl-6(1*H*)-pyridazinone 2-oxide (X) as colorless needles, m.p. 119~120°. *Anal.* Calcd. for $C_7H_{10}O_2N_2$: C, 54.53; H, 6.54; N, 18.17. Found : 54.09; H, 6.57; N, 18.67. IR : $\nu_{C=O}$ 1681 cm^{-1} (Nujol). The combined HCl layer was washed with $CHCl_3$, neutralized with Na_2CO_3, extracted with $CHCl_3$ and the $CHCl_3$ was dried over Na_2SO_4. Evaporation of $CHCl_3$ left 0.18 g. of the residue, which was recrystallized from $(iso\text{-}Pr)_2O$, using alumina for clarification, to yield colorless prisms, m.p. 97.5~98.5°, undepressed on admixture with VIII prepared from VII. Yield, 0.07 g. (4.5%).

1,3,4-Trimethyl-6(1*H*)-pyridazinone (XI)——(i) To a stirred solution of 3.7 g. of 3.4-dimethyl-6(1*H*)-pyridazinone[4] (XII) in 20 cc. of 2*N* NaOH, 3.8 g. of dimethylsulfate was slowly added below 40°. After the addition was complete, stirring was continued for 2 or 3 hr., adding NaOH solution to neutralize the formed acid. The solution was saturated with NaCl, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and on evaporation gave 3.95 g. (95%) of solid residue, m.p. 98~100°. Recrystallization from $(iso\text{-}Pr)_2O$ gave 2 g. of colorless plates, m.p. 102~103°, and a second crop of 1 g., m.p. 101~102° (73%). *Anal.* Calcd. for $C_7H_{10}ON_2$: C, 60.85; H, 7.30; N, 20.28. Found : C, 6115; H, 7.31; N, 19.96.

UV $\lambda_{max}^{95\%\,EtOH}$ mμ (log ε): 293 (3.47). $\lambda_{max}^{H_2O}$ mμ (log ε): 286 (3.48). IR: $\nu_{C=O}$ 1667 cm^{-1} (in Nujol). Picrate: yellow rods, m.p. 105~106° (from Et_2O). *Anal.* Calcd. for $C_7H_{10}ON_2 \cdot C_6H_3O_7N_3$: C, 42.51; H, 3.57; N, 19.07. Found: C, 42.64; H, 3.54; N, 19.14.

(ii) A mixture of 70 mg. of X, 10 cc. of water and 0.1 g. of 5% Pd-C was hydrogenated at an atmospheric pressure. After removal of the catalyst, the filtrate was saturated with NaCl, extracted with $CHCl_3$. After drying over Na_2SO_4, evaporation of $CHCl_3$ left 0.06 g. of crystals, which melted at 100°. Recrystallization from $(iso\text{-}Pr)_2O$ gave colorless plates, m.p. 102~103°, undepressed on admixture with XI prepared from XII as described in (i). Picrate: yellow rods, m.p. 106~107° (from Et_2O), identical with the picrate of XI prepared in (i).

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Summary

N-Oxidation of 6-chloro-3,4-dimethylpyridazine afforded two kinds of product (V and VI), the latter being in a very low yield. 6-Methoxy-3,4-dimethylpyridazine gave sole N-oxide (VIII). Catalytic dehalogenation of V and VI yielded 3,4-dimethylpyridazine N-oxide, II from V and III from VI respectively, both II and III being also obtained by N-oxidation of 3,4-dimethylpyridazine. V was derived to VIII.

N-Oxide group in II, V and VIII was concluded to be in the position adjacent to the methyl group from the derivation of V into 1,3,4-trimethyl-6(1*H*)-pyridazinone 2-oxide (X) by hydrolysis with dilute sodium hydroxide, followed by methylation with dimethyl sulfate and dilute alkali hydroxide. The structure of X was confirmed by the formation of 1,3,4-trimethyl-6(1*H*)-pyridazinone (XI) by catalytic reduction which was prepared by methylation of 3,4-dimethyl-6(1*H*)-pyridazinone. Consequently, the nitrogen further removed from the methyl group is oxidized in III and VI.

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