The mixture was poured onto ice, extracted with $CHCl_3$, $CHCl_3$ was distilled off and the residue was recrystallized from MeOH to yellow prisms, m.p. 144~145°. Yield, 65 mg. *Anal.* Calcd. for $C_5H_5O_3N_3$: C, 38.71; H, 3.25; N, 27.05. Found: C, 38.80; H, 3.36; N, 26.65.

4-Methyl-5-aminopyridazine (XV)——A mixture of 200 mg. of XIV, 2 cc. of MeOH, 1 cc. of 10% HCl-MeOH and 0.1 g. of 10% Pd-C was subjected to hydrogenation. Four moles of H_2 per mole of XIV were absorbed. The catalyst was filtered, the filtrate was neutralized with methanolic NH_3 solution, and the solvent was evaporated. The residue was extracted with AcOEt. AcOEt was evaporated. The residue was recrystallized from AcOEt to give 50 mg. of colorless prisms, m.p. 137~138°. *Anal.* Calcd. for $C_5H_7N_3 \cdot \frac{1}{2}H_2O$: C, 50.83; H, 6.83; N, 35.57; H_2O, 7.61. Found: C, 50.54; H, 7.01; N, 35.10; H_2O, 8.01.

3-Amino-5-methylpyridazine (XVIII)——A mixture of 700 mg. of XVI, 10 cc. of MeOH, 2 cc. of methanolic NH_3 and 0.1 g. of 10% Pd-C was subjected to hydrogenation. One mole of H_2 per mole of XVI was absorbed. The catalyst was filtered, the solvent was removed and the residue was extracted with AcOEt. AcOEt was evaporated. The residue was recrystallized form AcOEt to yield 300 mg. of colorless prisms, m.p. 183~184°. *Anal.* Calcd. for $C_5H_7N_3$: C, 55.03; H, 6.47; N, 38.51. Found: C, 55.13; H, 6.57; N, 38.22.

4-Amino-4-methylpyridazine (XIX)——A mixture of 1.0 g. of XVII, 10 cc. of MeOH, 2 cc. of methanolic NH_3 and 0.2 g. of 10% Pd-C was subjected to hydrogenation. When the reaction mixture was treated in the same way as described above, 500 mg. of XIX as colorless prisms, m.p. 200°(decomp.) was obtained. *Anal.* Calcd. for $C_5H_7N_3$: C, 55.03; H, 6.47; N, 38.51. Found: C, 55.03; H, 6.49; N, 38.68.

The authors express their gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo and Dr. K. Takeda, Director of this laboratory, for their helpful guidance and encouragement. Thanks are also to Dr. T. Kubota, Dr. Y. Matsui, Mr. I. Tanaka and Mr. M. Takasuka for ultraviolet and infrared spectral measurements, and to I. Ishizuka for carrying out gas chromatography, and to the members of the analysis room of this laboratory for elemental analysis.

Summary

4-Methylpyridazine 1-oxide (IV) and 2-oxide (V) were synthesized from 4-methylpyridazine (III). Nitration of IV could not be accomplished, but V gave 4-methyl-mononitropyridazine 2-oxide (XIV) in low yield. The nitro group of XIV was proved to be in 5-position.

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9. **Haruyuki Watanabe, Masaru Ogata, and Hideo Kano**: Pyridazines. III.[1,2] The Dipole Moments and the Structures of Monomethylpyridazine N-Oxides.[3]

(*Research Laboratory, Shionogi & Co., Ltd.*[*1])

In the foregoing papers of this series,[1,2] the synthesis of all possible monomethylpyridazine N-oxides, namely 3-methylpyridazine 1-oxide (IV), 2-oxide (III), 4-methylpyridazine 1-oxide (IX) and 2-oxide (XII) were reported. The structures of two isomeric 3-methylpyridazine N-oxides (IV and III) were established, however, those of two 4-methylpyridazine N-oxides (IX and XII) were presumed only by analogy.

[*1] Fukushima-ku, Osaka (渡辺春幸, 尾形 秀, 加納日出夫).

[1] Part I: M. Ogata, H. Kano: This Bulletin, **11**, 29 (1963).

[2] Part II: *Idem*: *Ibid.*, **11**, 35 (1963).

[3] A preliminary report of a part of this work was published as the Communication to the Editor in this Bulletin **9**, 1017 (1961).

The present investigation was undertaken to examine the dipole moments of eight available pyridazine N-oxides, including IV, III, IX, and XII, in order to obtain further evidences for determining the structure of these compounds.

Experimental

The materials, listed in Table I, were synthesized and purified according to the procedure already reported.[1,2] Some of these materials were hygroscopic and they were desirable to be prevented from moisture. Hygroscopic solid samples were requested to store under high vacuum in the presence of phosphorus pentoxide in the dark at least for 5 days. Liquids were used immediately after distillation, or otherwise stored in small desiccator maintaining in a refrigerator at 0°C if it was impossible. These samples were weighed out in a dry air.

The measurements of the dielectric constants were carried out in benzene at a low concentration at 25° by means of a heterodyne beat apparatus provided with a platinum cell.[4] For each solute, determinations were made with a solution at four different concentrations appropriately chosen below 1.5 weight per cent. The graphical plot of the dielectric constant as well as the density of solutions against the concentration in weight per cent gave linear dependence within experimental errors. The slopes of these straight lines were evaluated by the leastsquares method and the molar polarization of the solute was calculated by the similar method to that introduced by Halverstadt and Kumler,[5] differing in that densities were used instead of the specific volumes. The deformation polarization of each compound was assumed to be 1.05 times as much as the molar refraction approximated with the sum of atomic refractions for the D line. As to the values of moments, no serious errors have not been introduced by this assumption, henceforce probable errors being estimated at less than 0.02 D.

The results are shown in Table I, in which α and β are, respectively, the changes of the dielectric constant and density of solutions with the weight fraction of the solute; others are followed to the usual notations.

Table I. Dipole Moments of Some Derivatives of Pyridazine and Its N-Oxide in Benzene Solutions at 25°

Compound		m.p./b.p. (°C)	α	β (g./cc.)	P_2 (cc.)	MR_D	μ (D)
No.	Substituent in pyridazine						
I	3-Methyl-6-chloro	58	17.43	0.29	451.2	32.46	4.51
II	3-Methyl	b 204	19.98	0.16	380.6	27.62	4.13
III	3-Methyl N-oxide	84	27.29	0.30	590.9	30.03	5.23
IV	3-Methyl N-oxide	69.5	27.32	0.33	590.1	30.03	5.23
V	3-Methyl-6-chloro N-oxide	164	21.33	0.36	609.9	34.86	5.29
VI	4-Methyl	98/11	23.43	0.18	440.9	27.62	4.48
VII	3-Chloro-4-methyl	47	18.98	0.27	490.0	32.46	4.72
VIII	3-Chloro-4-methyl N-oxide	149	24.51	0.37	695.8	34.86	5.67
IX	4-Methyl N-oxide	84	32.42	0.32	696.5	30.03	5.70
X	4-Methyl-6-chloro	33	19.60	0.29	504.0	32.46	4.79
XI	4-Methyl-6-chloro N-oxide	128	24.36	0.32	694.6	34.86	5.67
XII	4-Methyl N-oxide	135/4	30.54	0.29	658.6	30.03	5.53
XIII	N-Oxide	39	31.02	0.35	581.3	24.76	5.21
XIV	4-Nitro 1-oxide	150	4.42	0.48	139.2	31.05	2.28
XV	3-Methyl-5-nitro 2-oxide	119	5.50	0.36	191.6	35.70	2.71
XVI	3-Methyl-5-nitro-6-chloro 2-oxide	103.5	6.64	0.53	262.2	40.18	3.28

Discussion

A molecular moment may be calculated by using the accepted bond moments.[6] To calculate what moment a molecule might be expected to have, the moment associated with a group is more useful than that associatd with merely one bond, because greater

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[4] Y. Kurita, M. Kubo: J. Am. Chem. Soc., **79**, 5460 (1957).

[5] I.F. Halverstadt, W.D. Kumler: J. Am. Chem. Soc., **64**, 2988 (1942).

[6] C.P. Smyth: "Dielectric Behavior and Structure," MeGraw-Hill, Book Co., New York, 253 (1955).

uniformity of environment is obtained by using a group moment. And further, the group moments obtained from solution measurements are the ones to be used for the calculation of the moments measured in solution, as mutual inductive effects between solvent and solute molecules are then contained in both the observed and the calculated values, although these effects may be altered to a certain extent by the presence of other groups.

The group moments of methyl groups attached to pyridazine ring, a pyridazine and a C-Cl bond, may be calulated from the moments of Ⅵ, Ⅷ, and Ⅹ by a simple vector analysis,*2 assuming the plane hexagonal Kekulé model of the ring. The calculations are shown in detail to illustrate the method.

$$4.72^2 = 4.48^2 + X^2 - 2 \times 4.48X \cos\alpha$$

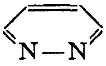
$$4.79^2 = 4.48^2 + X^2 + 2 \times 4.48X \cos\alpha$$

$$X = \mu(\mathrm{C{-}Cl}) = 1.59$$

$$\cos\alpha = 0.0371$$

$$4.48 \cos\alpha = \mu(\mathrm{C{-}CH_3}) \cos 60^\circ$$

$$\mu(\mathrm{C{-}CH_3}) = 0.33$$



$= 4.15$

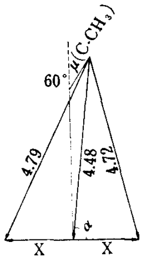


Chart 1.

These group moments of $C-CH_8$ and C-Cl are in good agreement with the accepted values 0.37~0.4 and 1.58, respectively.6) The moment for pyridazine is also in good agreement with the theoretical value 4.077) which differs slightly from the observed one 3.94 D in dioxane.7) This discrepancy may be attributed to the solvent effect. These group moments receive further confirmation from the results of compounds I and Ⅱ. Assuming these group moments, the moments of I and Ⅱ can be calculated to be 4.58 D and 4.16 D, respectively, in good agreement with the observed ones 4.51 D and 4.13 D.

The moment of pyridazine N-oxide is the resultants of the moments of pyridine, 2.22 D7) and its N-oxide, 4.24 D,8) but how much these component moments may be modified by the ortho effect in pyridazine N-oxide molecule remains to be examined. Neglecting this effect, the moment of pyridazine N-oxide is calculated as 5.68 D, the direction of which makes an angle of 19°50′ with the N-O bond. This calculations can be illustrated conveniently by choosing a line parallel to N-N bond as an *x* axis and a line perpendicular to it as the *y* axis as shown in Chart 2. The observed value for pyridazine N-oxide ⅩⅢ, 5.21 D, is smaller than 5.68 D, the resultant of the moments of pyridine and its N-oxide. This discrepancy can be regarded as a measure of the ortho effect. On the other hand, while the angle between *y* axis in Chart 2 and the resultant moment of pyridazine N-oxide is affected to some extent by the ortho effect, one can assume 30°—19°30′ =10°10′ for the angle as good approximation. Then it becomes easy to calculate the moments for the derivatives of pyridazine N-oxides.

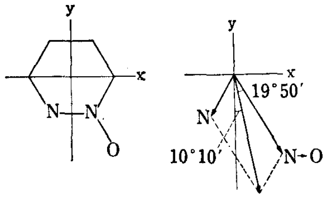


Chart 2.

In Chart 3, the methods of preparation of 3-methylpyridazine N-oxides are represented schematically with the observed moments and theoretical moments in parentheses. The theoretical moments were obtained by the following calculation :

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*2 Although other set of group moments was used in the preliminary report3) assuming 0.37 D for $C-CH_3$, now it is not necessary to assume any group moment because sufficient data are available to determine all group moments without any assumption of group moment.

7) Ref. 6), p. 343.

8) E.P. Linton : J. Am. Chem. Soc., **62**, 1945 (1940).

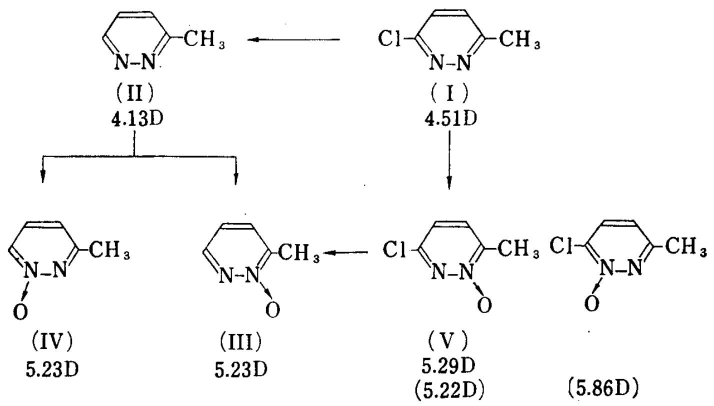


Chart 3.

$$\text{1-oxide}: \quad \mu_y = 5.21 \cos 10°10'$$

$$\mu_x = 5.21 \sin 10°10' + 1.59 + 0.33$$

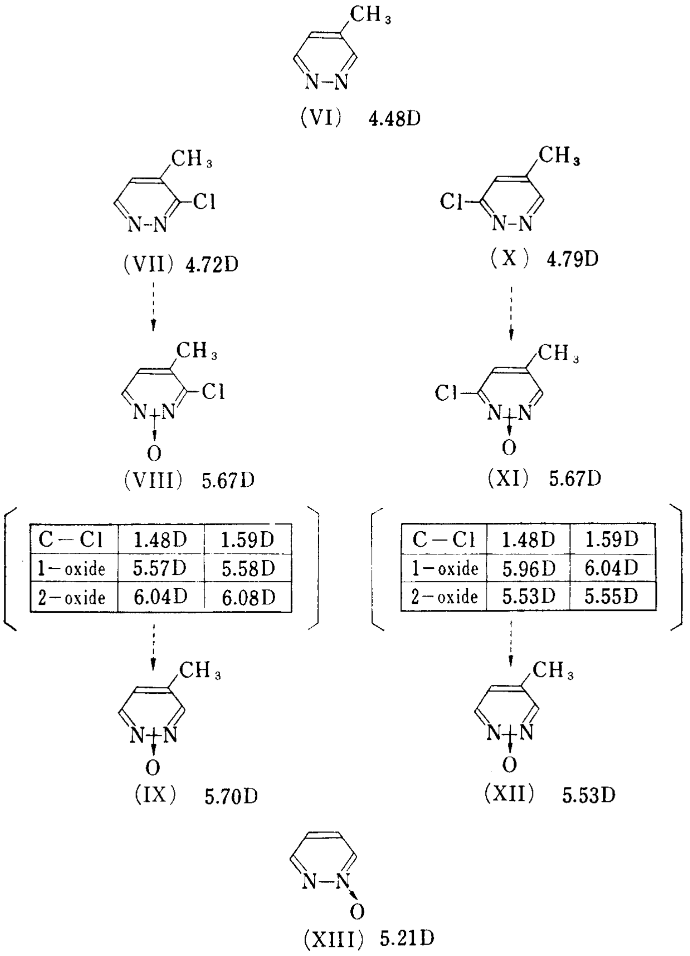
$$\mu = \sqrt{\mu_x^2 + \mu_y^2} = 5.86$$

$$\text{2-oxide}: \quad \mu_y = 5.21 \cos 10°10'$$

$$\mu_x = 5.21 \sin 10°10' - 1.59 - 0.33$$

$$\mu = 5.22$$

Although the group moment values and angles between the group moments are necessarily approximate, it is clear that the 1-oxide have much pretty higher moments to be assigned to compound V. The agreement between the calculated value 5.22 D for



C−Cl	1.48D	1.59D
1−oxide	5.57D	5.58D
2−oxide	6.04D	6.08D

C−Cl	1.48D	1.59D
1−oxide	5.96D	6.04D
2−oxide	5.53D	5.55D

Chart 4.

2-oxide and the observed one, 5.29 D is admitted exactly within the errors of experiment and calculation for 3-methyl-6-chloropyridazine 2-oxide (V). This is consistent with and confirms the conclusion in the previous paper[1] that the compound V is 2-oxide. Here, it should be mentioned that the observed moment for III is quite the same to IV. While the moment of IV is expected to be larger than that of III, there is no difference between the observed values for them 5.23 D, which are very close to that of pyridazine N-oxide XIII, 5.21 D. This fact may be attributed, at least in part, to the solvent effects. The molecular shape of III departs from that of a sphere to elevate the apparent moment value by the solvent effect[9] and that of IV does to lower.

In Chart 4, the methods of preparation of 4-methylpyridazine N-oxides are illustrated schematically, along with the observed moments and theoretical moments. in parentheses. Since it is known that IX has the same molecular structure to that of XII except the position of oxygen, one must be 1-oxide and the other 2-oxide. When VIII and XI are subjected to catalytic reduction, they give IX to and XII, respectively. Therefore it is natural to consider that the position of oxygen atom in VIII is the same to that in IX, and XI has an N-O group on the other side.

First, let it be assumed for both VIII and IX to be 1-oxide. The molecular moment of VIII may be treated as the resultant of the moments of IX and C-Cl, but in order to calculate the theoretical moments for the 3-chloro-4-methylpyridazine 1-oxide, it is necessary to find the direction of 4-methylpyridazine 1-oxide. This can be performed by approximating the direction with that of vector sum of methyl group and pyridazine N-oxide XIII, as illustrated in Chart 5 and the following equations.

$$\begin{cases} \mu_x = 5.21 \sin 10°10' + \mu(\text{C-CH}_3) \cos 60° \\ \mu_y = 5.21 \cos 10°10' + \mu(\text{C-CH}_3) \sin 60° \end{cases}$$

$$5.70 = \sqrt{\mu_x^2 + \mu_y^2}$$

$$\alpha = 13°15'$$

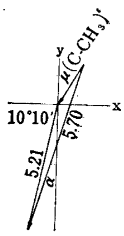


Chart 5.

where α is the angle between the y axis and the direction of the resultant moment.

Then one can easily calculate the theoretical moment for 3-chloro-4-methylpyridazine 1-oxide, using the group moments, 1.59 D for C-Cl and 5.70 D for IX, and get 5.58 D. If 1.48 D is used for C-Cl bond as in the preliminary report,[3] this value becomes 5.57 D. These results are listed in Chart 4. Then, assuming VIII and IX as 2-oxide together, similar calculations can be applied for these hypothetical molecules and derive the results in Chart 4, i.e. 6.04 D for C-Cl 1.48 D and 6.08 D for C-Cl 1.59 D.

In spite of the variation of C-Cl bond moment, it is clear that the observed value of VIII 5.67 D is in good agreement with the calculated values 5.57 D and 5.58 D for 1-oxide.

The theoretical moments of 4-methyl-6-chloropyridazine 1-oxide and 2-oxide can be calculated in the same way as described above, using the observed values for X, XII, and XIII. It becomes 5.96 D for 1-oxide when C-Cl is 1.48 D, and 6.04 D when C-Cl is 1.59 D, and for 2-oxide 5.53 D when 1.48 D, 5.55 D when 1.59 D. These circumstances are shown in Chart 4. The agreement between these calculated values and the observed ones in Chart 4 is excellently admitted for 2-oxide, and it is likely that VIII and IX are 1-oxide and XI and XII are 2-oxide. But a possibility cannot be ruled out that the reductions of VIII and XI caused migration of oxygen atom to the opposite side, for instance, VIII was 1-oxide and IX was 2-oxide. Even in this case, the calculated values for VIII and XI remain unchanged and the conclusions for VIII and XI do not change

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[9] R.H. Wiswall, Jr., and C.P. Smyth : J. Chem. Phys., **9**, 356 (1941).

neither, and only the positions of N→O group in IX and XII become meager. The theoretical moments of 4-methylpyridazine 1-oxide and 2-oxide can be calculated by simple vector summation to be 5.58 D and 5.52 D respectively as compared to IX 5.70 D and XII 5.53 D. This calculation suggests that IX is 1-oxide and XII is 2-oxide. The observed value for IX, 5.70 D, is also in good agreement with 5.61 D, the resultant moment of 4-methylpyridine N-oxide 4.50 D10) and pyridine 2.22 D.

Based upon the above discussion, it can be concluded that IV, VIII, and IX are 1-oxides and III, V, XI, and XII are 2-oxides.

Dipole moments of some nitroderivatives of 3-methylpyridazine N-oxides were also measured to confirm their molecular structures, the values of which were normal for the structures predicted in the previous paper.1) These values are listed in Table I.

The authors express their appreciation to Prof. Emeritus E. Ochiai and Dr. K. Takeda, Director of the laboratory, for their helpful advices and encouragements.

Summary

Dipole moments of 3- and 4-methylpyridazine N-oxides and their related compounds were measured in order to determine the positions of N→O group in these compounds, and the following conclusions were derived.

1. It was confirmed that IV was 1-oxide and III and V were 2-oxides.
2. In 4-methyl derivatives, VIII and IX are 1-oxides and XI and XII are 2-oxides.

(Received January 17, 1962)

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10) A.N. Sharpe and S. Walker: J. Chem. Soc., **1961**, 4522.

UDC 615.711.76[615.785]-015.25:547'118.5

10. **Masayasu Kimura***1: Molecular Pharmacological Studies on Drug-Receptor Complexes System in Drug Action. I. Antagonism to Acetylcholine of Organophosphorous Compounds.*2

(*Faculty of Pharmaceutical Sciences, University of Toyama*)

Using organophosphorous compounds, known well as insecticides, the present studies were initiated to extend the research field further and the author had been studying on an acetylcholine (ACh)-receptor complex in drug action.

In recent years, considerable attention has been paid to the action of the organophosphorous poison against mammals, which is mainly due to the direct inhibition against cholinesterase (ChE) activity, and there exists in reality a considerable literature on the pharmacological treatment of anti-ChE poisoning by organophosphorous compounds and its detoxication. From a clinical point of view, it is now well established that atropine as well as 2-pyridinealdoxime methiodide (PAM) have to be given as the antidotes against organophosphorous compounds. Likewise, from many of the

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*1 5-Okuda, Toyama (木村正康).

*2 This was presented at the 13th Annual Meeting of the Pharmaceutical Society of Japan (April 1960, in Tokyo).