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### Summary

In the previous papers the reactions between aromatic, aliphatic and heterocyclic carboxylic acid hydrazides and either chloral or bromal in various alcohols were attempted and respective esters were obtained. In this paper the reactions of aromatic and aliphatic acid hydrazide with chloral in the presence of various amines were examined, leading eventually to reveal the formation of our expected acid amides as are shown in Table I and II. The intermediates in this reaction, 1-benzoyl-2-(2,2,2-trichloroethylidene) hydrazine (III: R=C<sub>6</sub>H<sub>5</sub>-, X=Cl) was found to form the amides (VI) when heated in amines. This fact indicated that the acid hydrazides converted to their amides through III.

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#### 52. Shirō Takahashi and Hideo Kanō: Benzimidazole N-Oxides. VI.\*1

Reaction of 3-Methoxy-1-methyl- and 1,2-dimethyl-benzimidazolium Iodide with Various Nucleophiles.

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The chemistry of N-alkoxy quaternary salts of pyridine and its related systems has been studied by several workers in recent years.<sup>1)</sup> In almost all the reactions reported, the formation of diverse products is best understood as resulting from various nucleophilic attacks on the quaternary salts *via* the following four courses (Chart 1).

The reaction of the quaternary salts with each of cyanide ion,<sup>2)</sup> Grignard reagents<sup>3)</sup> and some of ketones<sup>4)</sup> has been shown to yield the corresponding  $\alpha$ - or  $\alpha$ - and  $\gamma$ -substituted compound (course A). In some of these reactions, the decomposition *via* course C occurs concurrently. The reaction of 1-alkoxy-3- and 4-picolinium salts with thiophenoxide ions proceeds *via* course B, giving the corresponding arylmercaptomethylpyridines.<sup>5)</sup> When the quaternary salts are treated with alkali, the parent bases and an aldehyde are produced<sup>6)</sup> (course C). N-Alkoxy pyridinium halides decompose gradual-

\*1 Part V. S. Takahashi, H. Kanō: J. Org. Chem., 30, 1118 (1965).

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1) For a recent review on this topic, see T. Okamoto: Yūki Gōsei Kagaku Kyokaiishi, 19, 790 (1963).

2) W.E. Feely, E.M. Beavers: J. Am. Chem. Soc., 81, 4008 (1959); T. Okamoto, H. Tani: This Bulletin, 7, 130, 925 (1959); H. Tani: Yakugaku Zasshi, 80, 1419 (1960); 81, 142 (1961).

3) O. Cervinka: Chem. & Ind. (London), 1960, 1482; *Idem*: Collection Czechoslov. Chem. Commun., 27, 567 (1962); C. A., 57, 2188 (1962).

4) T. Okamoto, H. Takayama: This Bulletin, 11, 514 (1963).

5) L. Bauer, L. A. Gardella: J. Org. Chem., 28, 1323 (1965).

6) E. Ochiai, M. Katada, T. Naito: Yakugaku Zasshi, 64A, 210 (1944); W.E. Feely, W.L. Lohn, V. Boekerheide: J. Org. Chem., 22, 1135 (1957).

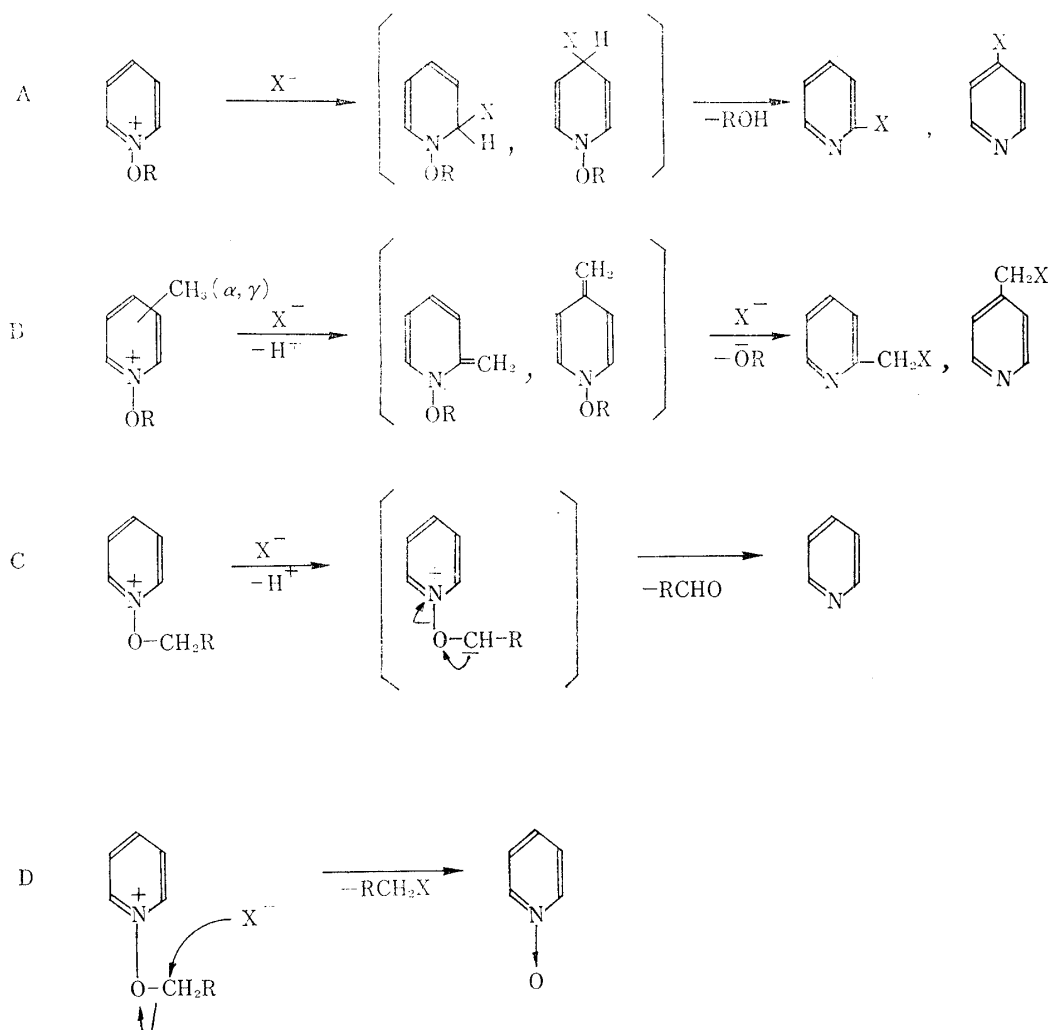


Chart 1.

ly to pyridine N-oxide and alkyl halide *via* course D. Similar decomposition of the salt on treatment with aniline gives the N-oxide and N-alkylaniline.<sup>1)</sup>

As a part of studies on benzimidazole N-oxides, we wish to report the reaction of 3-alkoxy-1-methylbenzimidazolium salts with various nucleophiles.

3-Methoxy-1-methylbenzimidazolium iodide (I) was obtained from 1-methylbenzimidazole 3-oxide and methyl iodide in quantitative yield,<sup>7)</sup> whereas quaternization of 1,2-dimethylbenzimidazole 3-oxide with methyl iodide gave, besides the desired 3-methoxy-1,2-dimethylbenzimidazolium iodide (II), the hemihydroiodide of the N-oxide, formaldehyde and 1,2-dimethylbenzimidazole. This side reaction will be discussed later. An alternative preparation of II was accomplished effectively by quaternization of 1-methoxy-2-methylbenzimidazole. Compound I reacted vigorously with potassium cyanide at room temperature to give 1-methyl-2-benzimidazolecarbonitrile (III) in quantitative yield. Reaction of I with sodium hydroxide yielded 1-methyl-2(3*H*)-benzimidazolinone (IV) unlike the cited example in pyridinium salts. With methylmagnesiumiodide, I gave 1,2-dimethylbenzimidazole (V).

Sodium hydrogensulfite, sodium methoxide and sodium isopropoxide reacted with I to give 1-methyl-2-benzimidazolesulfonic acid (VI), 2-methoxy- and 2-isopropoxy-1-

7) S. Takahashi, H. Kanō: This Bulletin, 12, 783 (1964).

methylbenzimidazole (VII and VIII), respectively. 2-*tert*-Butoxy-1-methylbenzimidazole could not be obtained by a similar procedure. The reaction of I with hydrazine hydrate, ammonia, methylamine and dimethylamine gave 2-hydrazino-1-methylbenzimidazole hydroiodide (IX), 2-amino-1-methylbenzimidazole (X), a mixture of 2-methylamino-1-methylbenzimidazole (XI) and its hydroiodide and 2-dimethylamino-1-methylbenzimidazole (XII) in good yield, respectively. Heating I with aniline on a water bath gave 2-anilino-1-methylbenzimidazole hydroiodide (XIII). When I was heated with methyl cyanoacetate or malononitrile, methyl 1-methyl-2-benzimidazolecyanoacetate (XIV) or 1-methyl-2-benzimidazolemalononitrile (XV) was obtained, respectively. The structure of XV was established by its conversion into V which was accomplished by acid hydrolysis and subsequent spontaneous decarboxylation.

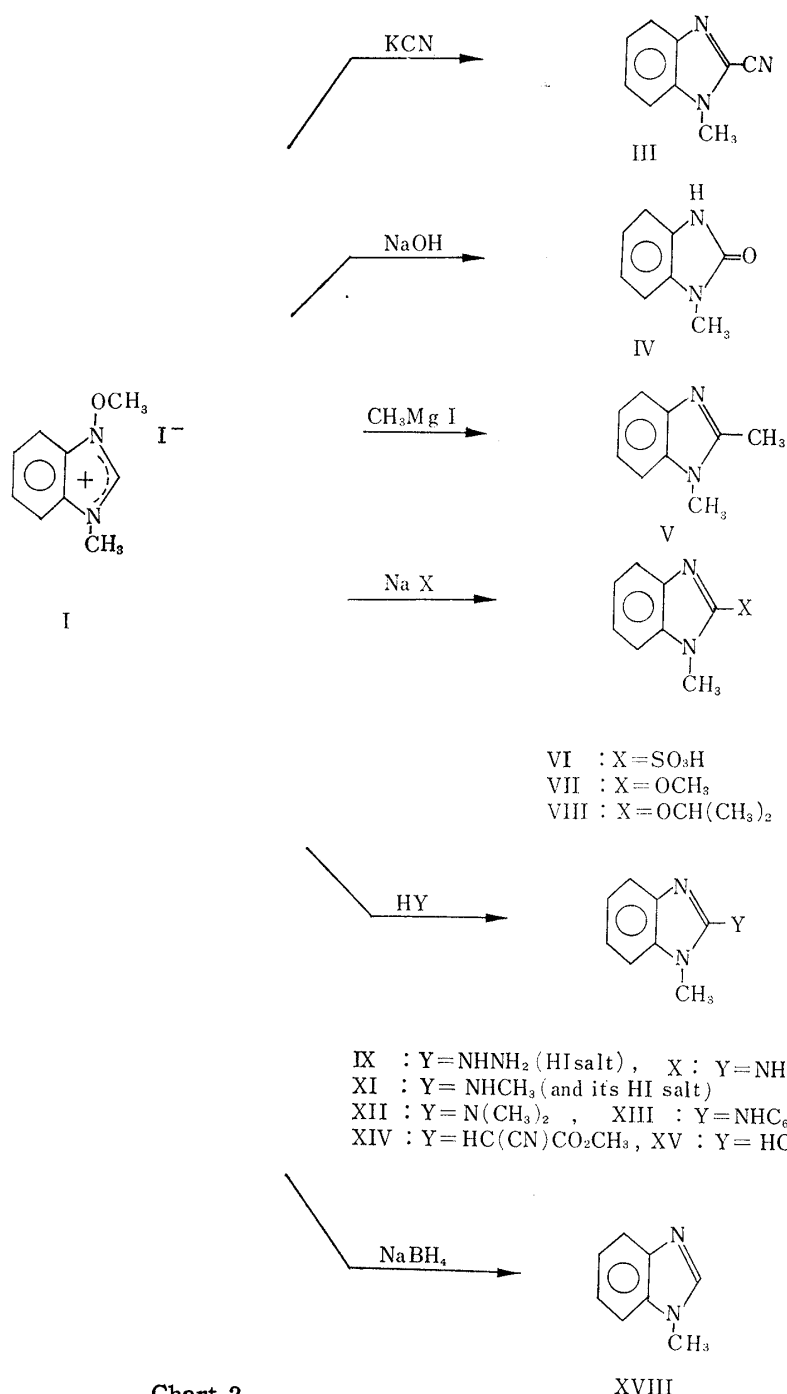


Chart 2.

XVIII

On the other hand, the reaction of II with potassium cyanide gave a mixture of 1,2-dimethyl-6-benzimidazolecarbonitrile (XVII) and V in nearly equal yields. The structure of XVII was confirmed as follows: NMR (nuclear magnetic resonance) and infrared spectra of the product showed that the cyano group is attached to the benzene ring. Hydrolysis of XVII with methanolic sodium hydroxide gave 1,2-dimethyl-6-benzimidazolecarboxylic acid, which was identified with a specimen prepared by permanganate oxidation of 1,2,6-trimethylbenzimidazole. The reaction of II with bases such as sodium hydroxide, sodium methoxide, hydrazine hydrate, sodium hydrogensulfite and ammonia gave only V in all cases. Treating either I or II with ethanolic sodium borohydride gave the parent base XVIII or V in quantitative yield.

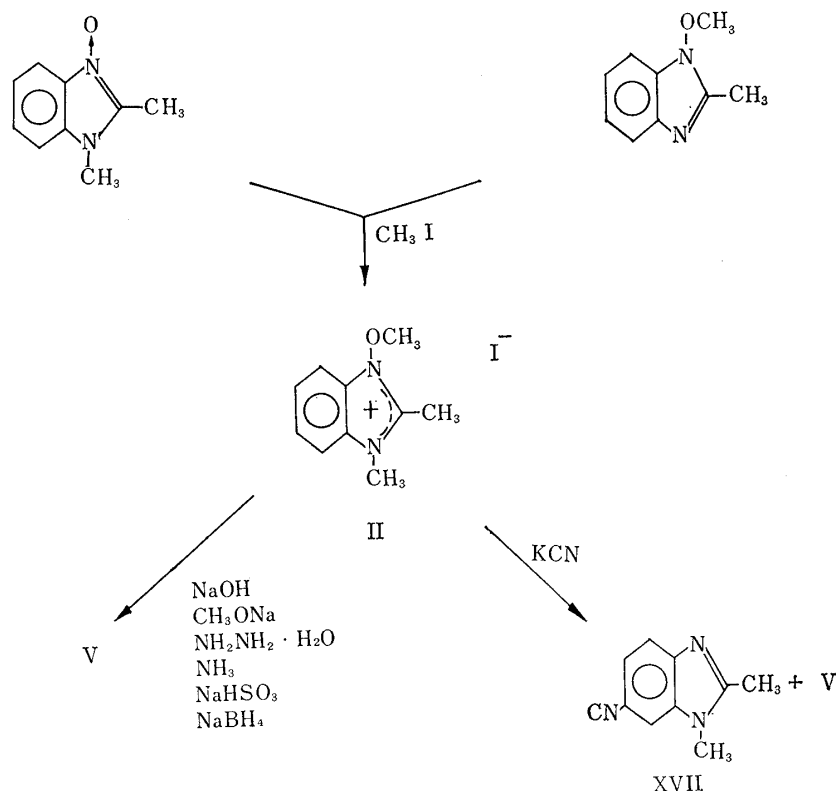


Chart 3.

All the substitution reactions of I described above seems to proceed through the A-type course, which is believed<sup>1,2)</sup> to involve N-alkoxydihydro base intermediate. However, the substitution reaction for I occurred in wider scope than that for pyridinium series. NMR study of I in deuterium oxide revealed that the 2-hydrogen of I is much labile, its deuterium exchange occurring even at room temperature without any catalyst. However, such deuterium exchange did not occur in N-alkoxypyridinium iodide under similar conditions. The extraordinary low  $\tau$  value ( $-1.00 \tau$  in  $\text{CDCl}_3$ ) of the 2-proton signal of I in NMR spectrum also indicates a high acidity of the proton. These facts suggest that the following alternative mechanism for the reactions of I with nucleophiles should be taken into consideration. Abstraction of the proton at the 2-position of I by the used nucleophile leads to a zwitterion intermediate (XX), whose carbene-type resonance hybrid (XX) undergoes further nucleophilic attack at the 2-position with concerted elimination of the methoxy group to produce the final product, 2-substituted-1-methylbenzimidazole.

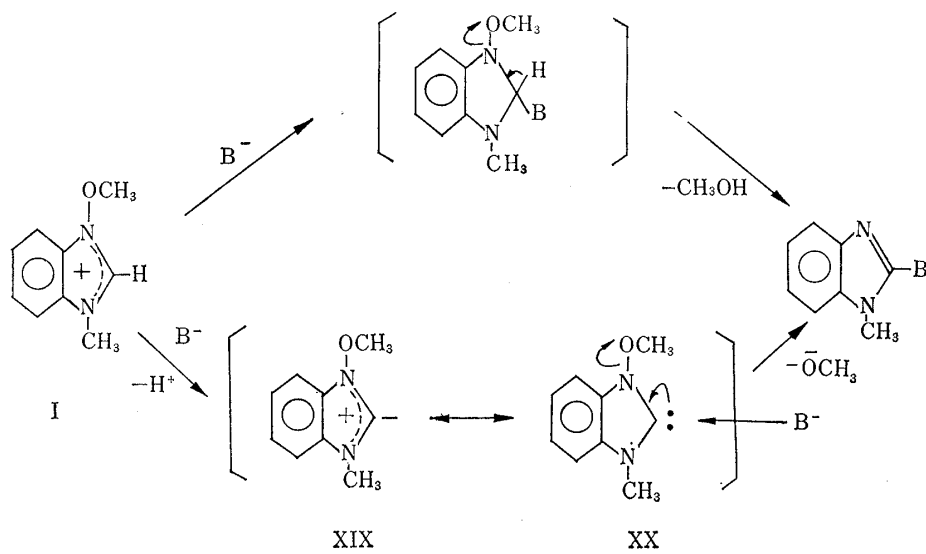


Chart 4.

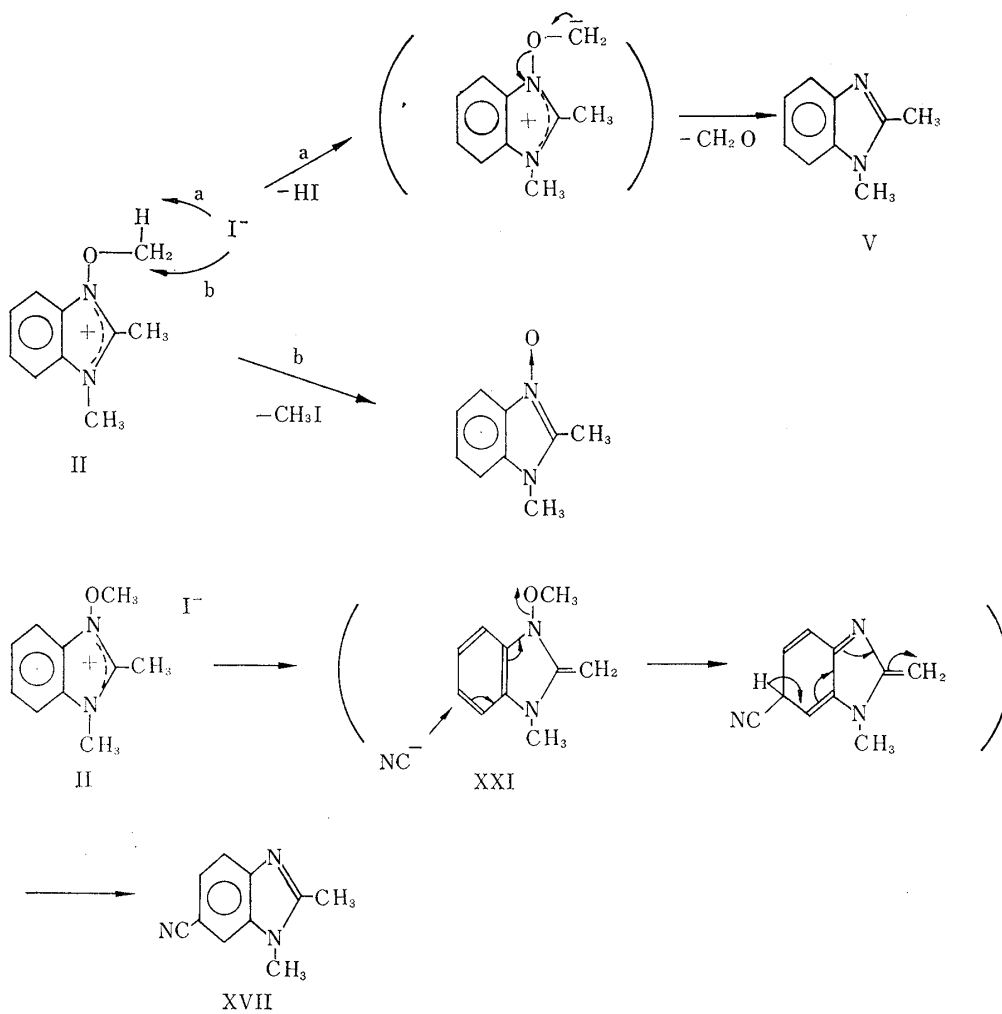


Chart 5.

Zwitterions of this type as reaction intermediates have received considerable attention since Breslow's studies<sup>8)</sup> on thiamine action, and some of evidence for zwitterion intermediates of the imidazole system have been presented recently.<sup>9)</sup>

The concurrent substitution reaction in II with potassium cyanide would involve initial abstraction of a proton from the active methyl group at 2-position (XXI) similarly to that in the B-course reaction. Further nucleophilic attack of the cyanide ion at 6-position with concerted departure of alkoxide ion restores aromaticity to form XVII. When this reaction was carried out in deuterium oxide, deuterium were incorporated in the methyl groups at 2-position of both XVII and V. However, the apparent difference of the ratio of the incorporated deuterium between XVII (0.75/3.0) and V (0.25/3.0) may support this mechanism. Since the formations of XVII and V are competitive, the partial deuterium exchange on V would occur at the stage of the quaternary salt II.

Decomposition of II into V with bases can be explained as occurring *via* the C-type course.

In the reaction of 1,2-dimethylbenzimidazole 3-oxide with methyl iodide, the quaternary salt, II, initially formed would be decomposed through both C- and D-type courses (Chart 5).

In supporting this mechanism, these by-products together with methyl iodide were obtained when a solution of II in chloroform was heated under reflux. In a sealed tube, this reaction gave 1,2,3-trimethylbenzimidazolium iodide and V.

The high electron-deficiency of 3-alkoxy-1-methylbenzimidazole 3-oxide derivatives were shown in their nuclear magnetic resonance spectra (Fig. 1).

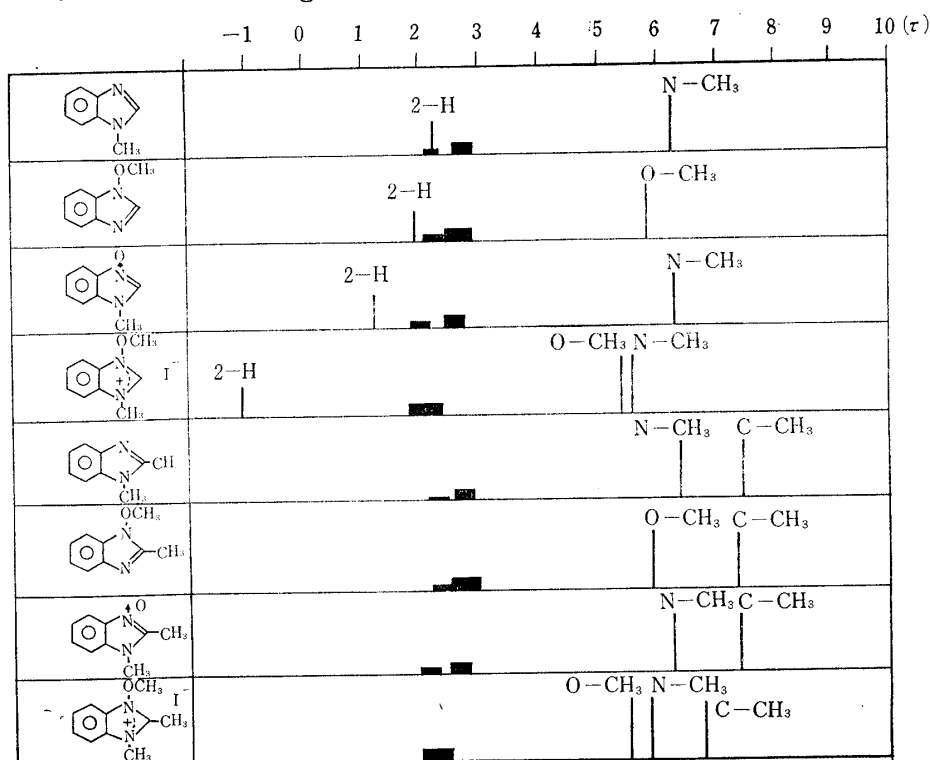


Fig. 1. Nuclear Magnetic Resonance Spectra of Benzimidazole Derivatives (in  $\text{CDCl}_3$ )

8) R. Breslow: J. Am. Chem. Soc., **76**, 1762 (1957).

9) H. W. Wanzlick: Angew. Chem. (Intern. ed.), **1**, 75 (1962); D. M. Lemal, K. I. Kawano: J. Am. Chem. Soc., **84**, 1761 (1962).

## Experimental\*3

**Reaction of 3-Methoxy-1-methylbenzimidazolium Iodide (I) with Potassium Cyanide**—To a solution of I (1.00 g., 3.5 mmoles) in H<sub>2</sub>O (5.0 ml.) was added a solution of KCN (0.27 g., 4.2 mmoles) in H<sub>2</sub>O (2.0 ml.) dropwise with stirring and cooling in an ice-water bath. Immediately, a crystalline product precipitated. After standing for 10 min., the crystals were collected by filtration and recrystallized from CCl<sub>4</sub> to give 1-methyl-2-benzimidazolecarbonitrile (III) as colorless prisms or scales; m.p. 178~179°. The yield was quantitative.

This compound was identified with a sample prepared from 1-methylbenzimidazole 3-oxide by Reisert reaction.<sup>7)</sup>

**Reaction of I with Sodium Hydroxide**—To a solution of I (0.50 g., 1.7 mmoles) in H<sub>2</sub>O (2.0 ml.) was added a solution of NaOH (0.08 g., 2.0 mmoles) in H<sub>2</sub>O (0.5 ml.) dropwise with stirring and cooling in an ice-water bath. Immediately, a colorless oil precipitated, which was solidified by rubbing. The product was collected by filtration and recrystallized from MeOH to give 1-methyl-2(3H)-benzimidazolinone (IV) as colorless prisms; m.p. 196~197°. The yield was quantitative.

This compound was identified with an authentic specimen.<sup>10)</sup>

**Reaction of I with Methylmagnesium Iodide**—To a solution of methylmagnesium iodide in ether (20 ml.), prepared from Mg (0.50 g., 21 mmoles) and CH<sub>3</sub>I (1.30 ml., 21 mmoles) in usual manner, was added finely ground I (0.60 g., 2.1 mmoles) with stirring at room temperature. The resulting dark green solution was heated under reflux for 1 hr. To the solution was added H<sub>2</sub>O under cooling to decompose the excess Grignard reagent and the ether layer was separated. The water layer was extracted with ether. The combined ether solution was dried and evaporated, and the residue was chromatographed on alumina with CHCl<sub>3</sub> to give 1,2-dimethylbenzimidazole (V) (0.25 g.) as colorless prisms, m.p. 113~114°, which was identified with an authentic specimen.<sup>11)</sup>

**Reaction of I with Sodium Hydrogensulfite**—To a solution of I (0.20 g., 0.7 mmole) in H<sub>2</sub>O (0.30 ml.) was added a solution of NaHSO<sub>3</sub> (0.10 g., 1.0 mmole) in H<sub>2</sub>O (0.50 ml.) dropwise with shaking. The product precipitated as colorless crystals. After standing for 10 min. at room temperature, the crystals were collected by filtration and recrystallized from EtOH-H<sub>2</sub>O to give colorless prisms, m.p. >300°, which was identified with 1-methyl-2-benzimidazolesulfonic acid, prepared from 1-methylbenzimidazole 3-oxide and NaHSO<sub>3</sub>.<sup>7)</sup> The yield was quantitative.

**Reaction of I with Sodium Methoxide**—Sodium (45 mg., 2.0 mmoles) was dissolved in MeOH (3.0 ml.), and the resulting solution was added to a solution of I (0.44 g., 1.5 mmoles) in MeOH (5.0 ml.) with stirring. After standing for 10 min. at room temperature, the solvent was removed and the residue was chromatographed on alumina with CHCl<sub>3</sub> to give 2-methoxy-1-methylbenzimidazole (VII) (0.23 g.) as colorless crystals. Recrystallization from *n*-pentane gave colorless needles or plates, m.p. 40~42°. *Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>ON<sub>2</sub>: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.25; H, 6.43; N, 17.35.

This compound was identified with a sample prepared from 2-methoxybenzimidazole<sup>12)</sup> and methyl iodide in the presence of alkali.

**Reaction of I with Sodium Isopropoxide**—Sodium (50 mg., 2.3 mmoles) was dissolved in iso-PrOH (5.0 ml.) with slight warming, and the resulting solution was added to a warm solution of I (0.50 g., 1.7 mmoles) in iso-PrOH (20 ml.). After heated on a water bath for 5 min., the solution was evaporated, and the residue was chromatographed on alumina with CHCl<sub>3</sub> to give 2-isopropoxy-1-methylbenzimidazole as a colorless oil (0.23 g.), which was analyzed as its picrate, yellow scales (from MeOH), m.p. 160° (decomp.). *Anal.* Calcd. for C<sub>11</sub>H<sub>14</sub>ON<sub>2</sub>·C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub>: C, 48.69; H, 4.09; N, 16.69. Found: C, 48.69; H, 4.33; N, 16.64.

**Attempted Reaction of I with Potassium *tert*-Butoxide**—To a solution of I (0.50 g., 1.7 mmole) in *tert*-BuOH (50 ml.) was added a solution of *tert*-BuOK, prepared by dissolving of K (70 mg., 1.8 mmole) in *tert*-BuOH (7.0 ml.) and the resulting solution was heated under reflux for 0.5 hr. After evaporation, the residue was chromatographed on alumina with CHCl<sub>3</sub>, but the resinous products obtained here were proved not to be the anticipated 2-*tert*-butoxy-1-methylbenzimidazole by IR spectra.

**Reaction of I with Hydrazine Hydrate**—To a solution of I (0.20 g., 0.7 mmole) in H<sub>2</sub>O (0.30 ml.) was added a solution of NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (90%, 0.10 ml., 1.8 mmoles) in water (0.10 ml.) with shaking. An

\*3 All melting points were taken on a Kofler hot-stage and are uncorrected. Solvents were removed under reduced pressure. Each identification was made by comparison of the infrared spectrum and if the sample had a melting point, it was also compared by mixed fusion. NMR spectra were obtained on a Varian A-60 analytical NMR spectrometer in CDCl<sub>3</sub> containing tetramethylsilane as an internal reference.

10) A. Hunger, J. Kebrle, A. Rossi, K. Hoffmann: *Helv. Chim. Acta*, **44**, 1273 (1961).

11) M. A. Phillips: *J. Chem. Soc.*, **1929**, 2820.

12) S. Takahashi, H. Kanō: *This Bulletin*, **12**, 282 (1964).

oily product precipitated, which was solidified by rubbing. Recrystallization from EtOH-AcOEt gave 2-hydrazino-1-methylbenzimidazole hydroiodide (X) (0.10 g.) as colorless needles, m.p. 242°(decomp.). *Anal.* Calcd. for  $C_8H_{10}N_4 \cdot HI$ : C, 33.12; H, 3.82; N, 19.31. Found: C, 33.32; H, 3.99; N, 19.11.

Neutralization of this hydroiodide by  $NaHCO_3$  gave 2-hydrazino-1-methylbenzimidazole.<sup>13)</sup>

**Reaction of I with Ammonia**—To a solution of I (0.20 g., 0.7 mmole) in  $H_2O$  (0.30 ml.) was added aq.  $NH_3$  (30%, 0.20 ml., 2.5 mmoles) with shaking and cooling in an ice-water bath. An oily product precipitated, which solidified immediately. Recrystallization from acetone- $CCl_4$  gave 2-amino-1-methylbenzimidazole (X) as colorless plates (0.10 g.), m.p. 208~209°.

This compound was identified with an authentic specimen.<sup>14)</sup>

**Reaction of I with Methylamine**—To a solution of I (0.50 g., 1.7 mmoles) in MeOH (2.0 ml.) was added methanolic- $CH_3NH_2$  (15%, 1.0 ml., 4.0 mmoles) dropwise with stirring and cooling in an ice-water bath. After standing for 1 hr. at room temperature, the resulting solution was evaporated and the residue was extracted with AcOEt.

The extracted part (0.08 g.) was recrystallized from AcOEt-petr. benzin to give 2-methylamino-1-methylbenzimidazole (XI) as colorless prisms, m.p. 185~186°. *Anal.* Calcd. for  $C_9H_{11}N_3$ : C, 67.05; H, 6.88; N, 26.07. Found: C, 67.38; H, 7.05; N, 25.81.

This compound was identified with a sample prepared from a methanolic solution of 2-chloro-1-methylbenzimidazole and  $MeNH_2$  by heating in a sealed tube at 120° for 3 hr.

AcOEt-insoluble part (0.35 g.) was recrystallized from MeOH-acetone to give 2-methylamino-1-methylbenzimidazole hydroiodide as colorless needles, m.p. 275°(decomp.). *Anal.* Calcd. for  $C_9H_{11}N_3 \cdot HI$ : C, 37.38; H, 4.18; N, 14.54. Found: C, 37.65; H, 4.35; N, 14.93.

Neutralization of this compound with  $NaHCO_3$  gave the free base obtained above.

**Reaction of I with Dimethylamine**—To a solution of I (0.20 g., 0.1 mmole) in MeOH (1.0 ml.) was added methanolic- $Me_2NH$  (20%, 0.70 ml., 2.5 mmoles) with stirring and cooling in an ice-water bath. After standing for 10 min. at room temperature, the solution was evaporated and the residue was chromatographed on alumina with  $CHCl_3$  to give 2-dimethylamino-1-methylbenzimidazole (XII) as a colorless oil (0.10 g.). This compound was analyzed as its picrate, yellow prisms, m.p. 191~192°(from acetone). *Anal.* Calcd. for  $C_{10}H_{13}N_3 \cdot C_6H_3O_7N_3$ : C, 47.52; H, 3.99; N, 20.79. Found: C, 47.68; H, 4.00; N, 20.59.

The free base XII was identified with a sample prepared from a methanolic solution of 2-chloro-1-methylbenzimidazole and  $Me_2NH$  by heating in a sealed tube at 120° for 3 hr.<sup>10)</sup>

**Reaction of I with Aniline**—A mixture of I (0.10 g., 0.35 mmole) and aniline (0.10 g., 1.1 mmoles) was heated on a water bath for 2 hr., and the resulting crystalline product was recrystallized from EtOH-AcOEt to give 2-anilino-1-methylbenzimidazole hydroiodide (XIII) as colorless needles (0.10 g.), m.p. 241~243°(decomp.). *Anal.* Calcd. for  $C_{14}H_{13}N_3 \cdot HI$ : C, 47.88; H, 4.02; N, 11.97. Found: C, 48.09; H, 4.16; N, 20.37.

Neutralization of this compound by  $NaHCO_3$  gave 2-anilino-1-methylbenzimidazole, which was identical with a sample.<sup>15)</sup>

**Reaction of I with Methyl Cyanoacetate**—To a solution of I (0.30 g., 1.0 mmole) in MeOH (3.0 ml.) was added  $CNCH_2CO_2CH_3$  (0.10 ml., 1.1 mmoles). After evaporating of the MeOH, the residual oil was heated at 120° for 10 min. Within a few minutes, a crystalline product precipitated. To the cooled mixture was added MeOH and the precipitate was collected by filtration to give methyl 1-methyl-2-benzimidazolecyanoacetate (XIV) (0.12 g.) as colorless needles, m.p. 250~252°(decomp.), which was identical with a sample.<sup>12)</sup>

**Reaction of I with Malononitrile**—A mixture of I (0.50 g., 1.7 mmoles) and  $CH_2(CN)_2$  (0.20 g., 3.0 mmoles) was heated on a water bath for 0.5 hr. The starting material dissolved into the solution then a crystalline product precipitated in a few minutes. To the cooled reaction mixture was added a small amount of EtOH and the precipitate was collected by filtration (0.25 g.). Recrystallization from EtOH gave 1-methyl-2-benzimidazolemalononitrile (XV) as colorless needles, m.p. >250°. *Anal.* Calcd. for  $C_{11}H_8N_4$ : C, 67.33; H, 4.11; N, 28.56. Found: C, 67.03; H, 4.41; N, 28.35.

**Hydrolysis of XV**—A suspension of XV (0.15 g.) in 6N HCl (10 ml.) was heated under reflux for 5 hr. Within 0.5 hr., the starting material dissolved into the solution. After evaporation, the residue was dissolved into a small amount of  $H_2O$  and neutralized with  $NaHCO_3$  then evaporated again. This residue was extracted with  $CHCl_3$  and removal of the solvent left a crystalline product (0.10 g.), which was recrystallized from petr. benzine to give colorless scales, m.p. 113~114°, and identified with an authentic specimen of V.<sup>11)</sup>

**Reaction of I with Sodium Borohydride**—To a solution of I (290 mg., 1.00 mmole) in EtOH (2.9 ml.) was added  $NaBH_4$  (40 mg., 1.05 mmoles) in small portions with stirring. After standing for a few

13) N. P. Bednyagina, I. Ya. Postovskii: *J. Gen. Chem. U. S. S. R.* (Eng. Transl.), **30**, 1456 (1960).

14) A. M. Simonov, N. D. Vitkevich: *Ibid.*, **30**, 610 (1960).

15) S. Takahashi, H. Kanō: *This Bulletin*, **12**, 1290 (1964).



minutes at room temperature, the resulting solution was evaporated and the residue was extracted with  $\text{CHCl}_3$ . Evaporation of the extract gave an oily residue, which was chromatographed on alumina with  $\text{CHCl}_3$  to give 1-methylbenzimidazole (XVII) as colorless crystals, m.p. 63~65°. The yield was quantitative.

This compound was identified with an authentic specimen of XVII.<sup>16)</sup>

**3-Methoxy-1,2-dimethylbenzimidazolium Iodide (II).** A) **Preparation from 1,2-Dimethylbenzimidazole 3-Oxide**—To a solution of 1,2-dimethylbenzimidazole 3-oxide, prepared from the N-oxide dihydrate<sup>17)</sup> (1.00 g.) by azeotropic dehydration with  $\text{CHCl}_3$  then dissolved into  $\text{CHCl}_3$  (10 ml.), was added  $\text{CH}_3\text{I}$  (3.0 ml. excess) with stirring and cooling in an ice-water bath. After standing for 2 hr. at room temperature, the resulting crystalline precipitate (0.3 g.) was filtered off and the filtrate was evaporated. The residue was recrystallized from EtOH-AcOEt gave colorless prisms (1.0~1.1 g.), m.p. 150~151° (decomp.). *Anal.* Calcd. for  $\text{C}_{10}\text{H}_{13}\text{ON}_2\text{I}$  (II): C, 39.49; H, 4.31; N, 9.21. Found: C, 39.64; H, 4.32; N, 9.31.

B) **The Experiment to Trap By-products**—A 20 ml. three-necked flask was fitted with a dropping funnel, a gas inlet tube, and a reflux condenser, and a delivery tube running from the top of the reflux condenser and reaching to the bottom of a flask containing a solution of 2,4-dinitrophenylhydrazine in phosphoric acid.<sup>18)</sup>

In the three-necked flask, ground 1,2-dimethylbenzimidazole 3-oxide, prepared from the dihydrate (1.00 g.) by azeotropic distillation with  $\text{CHCl}_3$ , was placed and  $\text{N}_2$  gas was passed through to expel a gaseous product from the reaction flask into another flask containing 2,4-dinitrophenylhydrazine. And then to the N-oxide was added methyl iodide at one time with magnetically stirring. The reaction was stopped after 0.3 hr.

The gaseous product gave 2,4-dinitrophenylhydrazone of formaldehyde as a crystalline product (0.05 g.), m.p. 166~168°, which was identified with a sample prepared from formaldehyde and 2,4-dinitrophenylhydrazine.

The reaction mixture was separated with  $\text{CHCl}_3$  to more soluble part and less soluble part. The former was recrystallized from EtOH-AcOEt to give II as colorless prisms (0.5 g.), m.p. 150° (decomp.), and the mother liquor was evaporated to give V (0.1 g.), m.p. 113~114°. The latter was recrystallized from MeOH to give 1,2-dimethylbenzimidazole 3-oxide hemihydroiodide (0.3 g.), as colorless or slightly brown hygroscopic prisms, m.p. 216° (decomp.). *Anal.* Calcd. for  $\text{C}_9\text{H}_{10}\text{ON}_2 \cdot 1/2\text{HI}$  (1,2-dimethylbenzimidazole 3-oxide hemihydroiodide): C, 47.80; H, 4.68; N, 12.39. Found: C, 48.04; H, 5.04; N, 12.57.

Neutralization of this compound with  $\text{NaHCO}_3$  gave 1,2-dimethylbenzimidazole 3-oxide.

C) **Preparation from 1-methoxy-2-methylbenzimidazole**—A solution of 1-methoxy-2-methylbenzimidazole (described below) (0.15 g.) in  $\text{CH}_3\text{I}$  (0.60 ml. excess) was heated under reflux for 10 min. After cooling, the resulting crystalline product was collected by filtration (0.18 g.). Recrystallization from EtOH-AcOEt gave colorless prisms, m.p. 150~151° (decomp.).

This compound was identical with II obtained above.

**1-Methoxy-2-methylbenzimidazole**—To a solution of 2-methylbenzimidazole 3-oxide<sup>19)</sup> (1.50 g., 10 mmoles) in MeOH (10 ml.) were added aq. KOH solution (0.60 g. in 2.0 ml. ca. 10 mmoles) and  $\text{CH}_3\text{I}$  (0.70 ml., 11 mmoles). The resulting solution was heated at 50° for 1 hr. then evaporated. The residual oil was extracted with ether, dried with  $\text{K}_2\text{CO}_3$  and distilled to give a colorless oil (1.2 g.) which solidified on cooling, b.p.<sub>4</sub> 103~105°, m.p. 39~41°. Recrystallization from *n*-pentane gave colorless prisms. *Anal.* Calcd. for  $\text{C}_9\text{H}_{10}\text{ON}_2$ : C, 66.65; H, 6.22; N, 17.27. Found: C, 67.00; H, 6.46; N, 16.92.

**Reaction of II with Potassium Cyanide**—To a solution of II (0.20 g., 0.66 mmole) in  $\text{H}_2\text{O}$  (0.50 ml.) was added a solution of KCN (0.20 g., 3.1 mmoles) in  $\text{H}_2\text{O}$  (0.30 ml.) dropwise with stirring and cooling in an ice-water bath. After the addition, the solution was allowed to stand at room temperature for 0.5 hr. Within a few minutes, a brown oil precipitated, which was solidified by rubbing. The mixture was extracted with  $\text{CHCl}_3$  and chromatographed on alumina with  $\text{CHCl}_3$ . The resulting product was washed with ether to give 1,2-dimethyl-6-benzimidazolecarbonitrile (XVIII) (0.04 g.) as ether insoluble part. Recrystallization from  $\text{CCl}_4$  gave colorless prisms, m.p. 210~211°. *Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{N}_3$ : C, 70.15; H, 5.30; N, 24.55. Found: C, 70.40; H, 5.35; N, 24.68.

The ether solution was evaporated to give V (0.04 g.).

**Hydrolysis of 1,2-Dimethyl-6-benzimidazolecarbonitrile (XVIII)**—To a solution of NaOH (0.10 g.) in  $\text{H}_2\text{O}$  (1.0 ml.) and MeOH (1.0 ml.) was added XVIII (0.050 g.), and the resulting solution was heated on a water bath for 5 hr., being allowed to evaporate the MeOH. The resulting cooled solution was neutralized with AcOH to give colorless crystals (0.04 g.). Recrystallization from EtOH- $\text{H}_2\text{O}$  gave colorless prisms or plates, m.p. >260°. *Anal.* Calcd. for  $\text{C}_{10}\text{H}_{10}\text{O}_2\text{N}_2$  (1,2-dimethyl-6-benzimidazolecarboxylic

16) G. R. Beaven, *et al.*: *J. Pharm. and Pharmacol.*, **1**, 957 (1949).

17) S. Takahashi, H. Kanō: *This Bulletin*, **11**, 1375 (1963).

18) G. D. Johnson: *J. Am. Chem. Soc.*, **73**, 5888 (1951).

19) St. von Niementowski: *Ber.*, **43**, 3012 (1910).

acid): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.45; H, 5.61; N, 14.83.

This compound was identified with a sample prepared below.

**1,2-Dimethyl-6-benzimidazolecarboxylic Acid**—To a suspension of 1,2,6-trimethylbenzimidazole<sup>16)</sup> (0.50 g., 3.1 mmole) in H<sub>2</sub>O (25 ml.) was added KMnO<sub>4</sub> (finely ground, 0.50 g., 3.1 mmoles) with stirring and heating on a water bath. After about 15 min., an additional KMnO<sub>4</sub> (0.50 g., 3.1 mmoles) was added. When the color of the permanganate disappeared (*ca.* 2 hr.), the hot reaction mixture was filtered, and the residue was washed with hot H<sub>2</sub>O. The filtrate and washings were combined and concentrated to *ca.* 10 ml., and acidified with AcOH to precipitate a crystalline product (0.30 g.). Recrystallization from EtOH-H<sub>2</sub>O gave colorless prisms or plates, m.p. >260°.

**Reaction of II with Sodium Hydroxide**—To a solution of II (0.20 g., 0.66 mmole) in H<sub>2</sub>O (0.5 ml.) was added a solution of NaOH (0.10 g., 2.5 mmoles) in H<sub>2</sub>O (0.5 ml.) dropwise with stirring and cooling in an ice-water bath. The resulting brown oil was extracted with CHCl<sub>3</sub> and chromatographed on alumina with CHCl<sub>3</sub> to give V. Recrystallization from petr. benzin gave colorless plates (0.07 g.), m.p. 113~114°, which was identified with an authentic specimen of V.<sup>11)</sup>

**Reaction of II with Sodium Methoxide**—Sodium (10 mg., 0.43 mmole) was dissolved in MeOH (0.5 ml.), and the resulting solution was added to a solution of II (0.10 g., 0.33 mmole) in MeOH (0.3 ml.). After standing for 0.5 hr. at room temperature, the solution was evaporated and the residue was extracted with CHCl<sub>3</sub>, chromatographed on alumina with CHCl<sub>3</sub>. Recrystallization from petr. benzin gave V as colorless plates (0.04 g.), m.p. 113~114°.

**Reaction of II with Hydrazine Hydrate**—A solution of II (0.10 g., 0.33 mmole) in NH<sub>2</sub>NH<sub>2</sub>·H<sub>2</sub>O (90%, 0.10 ml., 1.8 mmoles) was allowed to stand overnight at room temperature, which was extracted with CHCl<sub>3</sub> and worked up as described above to give V (0.04 g.).

**Reaction of II with Ammonia**—A solution of II (0.10 g., 0.33 mmole) in aq. NH<sub>3</sub> (5%, 1.0 ml., 3.0 mmoles) was heated at 70° in a sealed tube for 0.5 hr. After evaporation, the residue was extracted with CHCl<sub>3</sub> and worked up as described above to give V (0.04 g.).

**Reaction of II with Sodium Hydrogensulfite**—To a solution of II (0.30 g., 1.0 mmole) in H<sub>2</sub>O (0.60 ml.) was added a solution of NaHSO<sub>3</sub> (0.20 g., 1.9 mmoles) in H<sub>2</sub>O (1.0 ml.) dropwise with stirring at room temperature and the resulting solution was heated on a water bath for 5 min. After cooling, the resulting crystalline product was collected, and recrystallized from EtOH-AcOEt gave colorless needles (0.15 g.), m.p. 188~189°. *Anal.* Calcd. for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>·HI (V·HI): C, 39.43; H, 4.05; N, 10.22. Found: C, 39.00; H, 4.53; N, 10.23.

Neutralization of this compound with NaHCO<sub>3</sub> gave V.

**Reaction of II with Sodium Borohydride**—This experiment was carried out as for the reaction of I with NaBH<sub>4</sub> mentioned above. By this reaction, V was obtained in quantitative yield.

**Decomposition of II on Heating**—A) Under reflux. A solution of II (1.00 g.) in CHCl<sub>3</sub> (10 ml.) was placed in a 50 ml. two-necked flask fitted with a dropping funnel and a small widmer fractionating column, which was connected with a downward condenser. The solution was heated under gentle reflux and sometimes heated to boil vigorously to codistill the product of low boiling point with CHCl<sub>3</sub>. The solvent was supplied from the funnel to the reaction mixture to maintain the same volume during the reaction. After refluxing for 10 hr., the reaction mixture was cooled and the resulting crystalline product was collected by filtration (0.45 g.). This product was proved to be 1,2-dimethylbenzimidazole 3-oxide hemihydroiodide. The filtrate was evaporated and the residue was extracted with AcOEt. From the extract, V was obtained (0.06 g.) after recrystallization from petr. benzin, m.p. 113~114°. The extracted residue was dissolved in H<sub>2</sub>O, neutralized with NaHCO<sub>3</sub>, and evaporated. This residue was extracted with CHCl<sub>3</sub> and removal of the solvent gave another crop of V (0.15 g., m.p. 113~114°). The CHCl<sub>3</sub>-extracted residue was then extracted with abs. EtOH. From the extract, 1,2-dimethylbenzimidazole 3-oxide was obtained (0.15 g.).

To the solution of the product of low boiling point in CHCl<sub>3</sub> (*ca.* 60 ml.) was added pyridine (1.0 ml.) and the solution was heated under reflux for 1 hr. Removal of the solvent and the excess pyridine left a crystalline product (0.24 g., m.p. 116~118°), which was proved to be N-methylpyridinium iodide.<sup>20)</sup>

B) In a sealed tube. A solution of II (350 mg.) in CHCl<sub>3</sub> (5.0 ml.) was heated in a sealed tube on a water bath for 4 hr. After cooling, the resulting brown crystals were filtered (160 mg.) and recrystallized from MeOH to give 1,2,3-trimethylbenzimidazolium iodide as colorless plates or prisms, m.p. >250°. *Anal.* Calcd. for C<sub>10</sub>H<sub>13</sub>N<sub>2</sub>I: C, 41.68; H, 4.56; N, 9.72. Found: C, 41.83; H, 4.85; N, 9.51.

This compound was identified with a sample prepared from 1,2-dimethylbenzimidazole and methyl iodide by heating under reflux for 1 hr. without solvent.<sup>21)</sup>

The filtrate was evaporated and chromatographed on alumina with CHCl<sub>3</sub> gave V (130 mg.) as colorless crystals, m.p. 113~114°.

**Deuterium Exchange Experiment**—In a solution of I in deuterium oxide, the exchange rate (*t*<sub>1/2</sub>)

20) E. M. Kosower: J. Am. Chem. Soc., **77**, 3883 (1955).

21) cf. R. L. Shriner, P. G. Boermans: J. Am. Chem. Soc., **66**, 1810 (1944).

of the 2-hydrogen, measured by NMR spectrum ( $\tau$  0.20), was within 3 min. (at 34°, pH of an aqueous solution of I (0.10 mole) was 3.70).

**The Reaction of II with Potassium Cyanide in Deuterium Oxide**—To a solution of II (0.50 g.) in D<sub>2</sub>O (5.0 ml.) was added a solution of KCN (0.50 g.) in D<sub>2</sub>O (2.0 ml.) with stirring. The precipitated oil was worked up as described above. The intensive ratios of signal peaks of C-CH<sub>3</sub> groups to N-CH<sub>3</sub> groups of XVII and V obtained here in NMR spectra were 2.25/3.0 and 2.75/3.0, respectively.

The both 2-protons of the product XVII and V were not exchanged by deuterium in deuterium oxide under the same condition as the reaction was carried out.

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### Summary

Reactions of 1-methyl- or 1,2-dimethyl-3-methoxybenzimidazolium iodide (I or II) with various nucleophilic reagents (CN<sup>-</sup>, OH<sup>-</sup>, RO<sup>-</sup>, amines etc.) have been investigated.

Most of these reagents react with I to give the corresponding 2-substituted 1-methylbenzimidazole.

The reaction of II with these reagents generally affords 1,2-dimethylbenzimidazole (V) losing its methoxy group. Only with potassium cyanide, II undergoes substitution concurrently to give a mixture of 1,2-dimethyl-6-benzimidazolecarbonitrile and V.

The reaction mechanisms have been discussed as compared with those of N-alkoxy pyridinium salt, and a possible zwitterion intermediate for the reaction of I is noted.

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53. Hisao Matsumoto,\*<sup>1</sup>,\*<sup>2</sup> Hisakichi Matsumura,\*<sup>1</sup> and Sadao Iguchi\*<sup>3</sup> :  
Studies with Static Dialysis Method on the Release of Drugs  
from Nonionic Surfactant Solutions. I. Permeation of  
Tween 80 through Cellulose Membrane.

(Faculty of Pharmaceutical Sciences, Fukuoka University\*<sup>1</sup> and  
Faculty of Pharmaceutical Sciences, Kyushu University\*<sup>3</sup>)

There are many reports describing that surfactants influence the availability of solubilized drugs.<sup>1)</sup> It may be considered that the most important effect among them is on the permeability of drugs through biologic membrane, but its mechanism is not

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1) N. A. Allawala, S. Riegelman : J. Am. Pharm. Assoc., Sci. Ed., 42, 267 (1953); C. A. Lawrence, A. L. Erlanson : *Ibid.*, 42, 352 (1953).