[Chem. Pharm. Bull. 12 (3) 282 ~ 291]

UDC 547.785.5

40. Shirō Takahashi and Hideo Kanō : Benzimidazole N-Oxides. II.*1 The Reactivity of 1-Alkoxybenzimidazoles.

(*Shionogi Research Laboratory, Shionogi & Co., Ltd.**2)

In the first paper of this series, it was reported that benzimidazole N-oxide exists as its N-oxide form and/or as its N-hydroxy form depending upon the condition, and on the reaction with methyl iodide in the presence of alkali it gives 1-methoxybenzimidazole (Ia).

In the present work, the reactivity of 1-alkoxybenzimidazole (I) was studied and compared with the reactivity of normal heteroaromatic N-oxide and N-alkoxy-quarternary salt.

In many cases, heteroaromatic N-oxides were deoxygenated selectively by catalytic reduction over Raney nickel.[1] The alkoxy group of I was also eliminated by catalytic reduction with Raney nickel at ordinary temperature and pressure,[2] but the rate of the elimination was slower than that of deoxygenation of benzimidazole N-oxide. In the case of 1-allyloxybenzimidazole (Ic), the allyl group was saturated in the first step and then the resulting propoxy group was eliminated, in spite of the fact that the allyloxy group is eliminated before saturation of the double bond in some cases.[3]

On heating 1-ethoxybenzimidazole (Ib) with concentrated hydrochloric acid or hydrobromic acid in a sealed tube, the C-O bond of the ethoxy group was cleaved as ordinary ethers, and benzimidazole N-oxide was reproduced.

When I was heated with sodium alkoxide in alcohol at 100~150°, 2-alkoxybenzimidazole (II) was obtained in good yield, the alkoxy group of which had not come from the original alkoxy group but from the solvent.

N-Heteroaromatic compounds containing an alkoxy group at the α- or γ-position to the ring nitrogen atom often rearrange to N-alkyloxy derivatives on heating at high temperature. But, such a rearrangement was not observed with I even at the decomposition temperature. 2-Allyloxybenzimidazole (IIc) gave 1-allyl-2-(3*H*)-benzimidazolinone (III) on heating at 180° in quantitative yield. On the other hand, 2-ethoxybenzimidazole (IIb) did not change at 180°. When it was heated at 200~230°, intermolecular reaction occurred and a mixture of 2-(3*H*)-benzimidazolinone and 1-ethyl-2-ethoxybenzimidazole (IV) was obtained.

It is known that the N-alkoxy-quarternary salt of heteroaromatic N-oxide gives a cyano derivative by action of potassium cyanide.[4] Ib did not react with potassium cyanide at the boiling point of the ethanol solution, but at higher temperature it gave 2-benzimidazole carbamic acid (V) in poor yield.

Ib easily reacted with such weak nucleophilic reagents as hydrazine hydrate and sodium hydrogen sulfite on heating at 100° for a short time to give 2-hydrazinobenzimidazole (VI), and sodium 2-benzimidazolesulfonate (VII), respectively.

---

*1 Part I. S. Takahashi, H. Kanō : This Bulletin, **11**, 1375 (1963).

*2 Fukushima-ku, Osaka (高橋史郎, 加納日出夫).

1) E. Hayashi, H. Yamanaka, K. Shimizu : This Bulletin, **7**, 141, 146 (1959); E. Hayashi, H. Yamanaka, T. Higashino : *Ibid.*, **7**, 149 (1959).

2) E. Hayashi, E. Ishiguro, M. Enomoto : presented at the 80th Annual Meeting of the Pharmaceutical Society of Japan (1960).

3) E. Bergmann, H. Heimhold : J. Chem. Soc., **1935**, 1365; R. Baltzly, J. B. Buck : J. Am. Chem. Soc., **65**, 1984 (1943).

4) W. E. Feely, E. M. Beavers : J. Am. Chem. Soc., **81**, 4004 (1959).

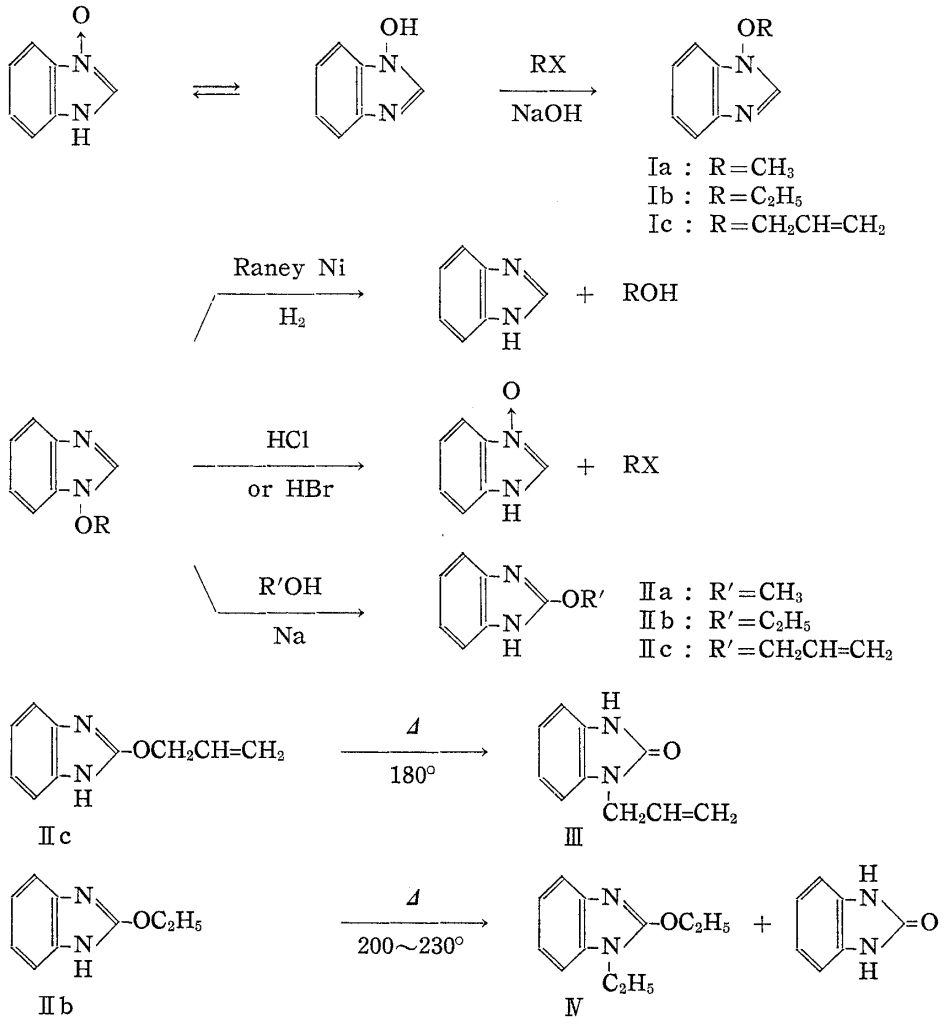

Chart 1.

The reaction of heteroaromatic N-oxides with acetic anhydride leading to acetoxy derivatives is well known. When Ib was heated with acetic anhydride on a water bath, then treated with water, it gave a labile oil, the analytical value of which corresponded to $C_{11}H_{14}O_3N_2$. This oil decomposed violently at 150~160° to give 1-acetyl-2-(3*H*)-benzimidazolinone (XI)[5] and ethanol. These facts suggest that the oily substance may be 2-acetoxy-3-ethoxy-2,3-dihydrobenzimidazole (X). On the other hand, when the reaction product of Ib with acetic anhydride was heated at 200° without treatment with water 1,3-diacetyl-2-(3*H*)-benzimidazolinone (IX)[5,6] was obtained. From these results, the reaction of Ib with acetic anhydride seems to proceed as shown in Chart 2; the reaction gave 1-ethoxy-2-acetoxy-3-acetyl-2,3-dihydrobenzimidazole (VIII), in the first step, which afforded IX at a high temperature. By action of water, VIII was hydrolyzed to X, which decomposed to XI on heating.

In these reactions, it seemed reasonable to assume that a nucleophilic reagent attacks the electron-deficient 2-position of 1-alkoxybenzimidazole, then elimination of alcohol occurs, giving 2-substituted benzimidazole.

It was reported that several heteroaromatic N-oxides react with phenylisocyanate to give derivatives substituted with an anilino group at the adjacent position to the ring

5) D. J. Kew, P. F. Nelson : Austral. J. Chem., **15**, 792 (1962).
6) N. F. Cheetham, W. F. Forbes, D. J. Kew, P. F. Nelson : *Ibid.*, **16**, 729 (1963).

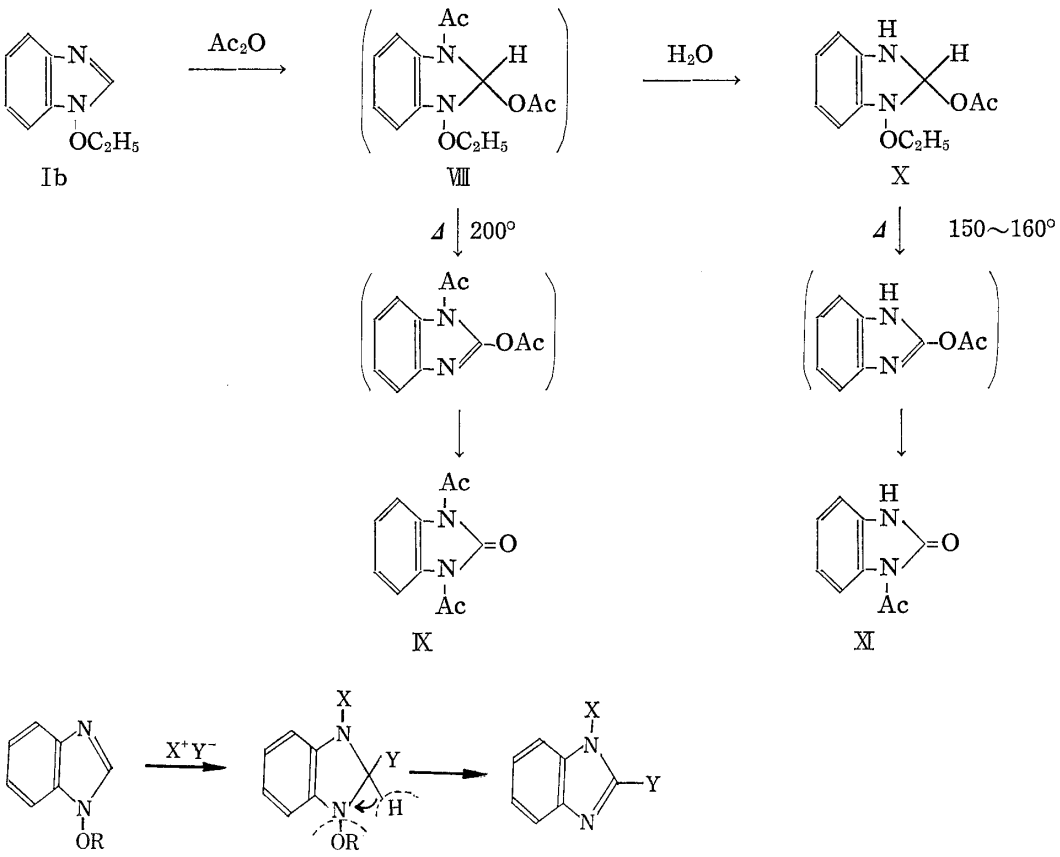

Chart 2.

nitrogen.[7,8] It is also known that benzimidazole reacts with phenyl isocyanate to give 2-phenylcarbamoylbenzimidazole (XIII).[9]

On heating with phenylisocyanate, Ib gave 1-ethoxy-2-phenylcarbamoylbenzimidazole (XII). Hydrogenolysis of XII gave XIII, which was identified with an authentic specimen prepared from 6*H*,13*H*-pyrazino[1,2-*a*:4,5-*a*']dibenzimidazole-6,13-dione and aniline.

Ib reacted with sulfuryl chloride to give a mixture of monochloro-1-ethoxybenzimidazole hydrochloride (XIV), chlorine atom of which attached to the benzene ring but the position was not determined, 1-ethoxy-2,4,5,6,7,-pentachlorobenzimidazole (XV) and 1-ethoxy-4,5,6,7-tetrachlorobenzimidazole (XVI). The structures were assigned from their elemental analyses and nuclear magnetic resonance spectra.

It is known that 1-alkylbenzimidazoles give 1-alkyl-2-aminobenzimidazoles on heating with sodium amide in N,N-dimethylaniline.[10] Ib reacted with sodium amide in N,N-

Table I Nuclear Magnetic Resonance Spectra of Chloro-1-ethoxybenzimidazole (τ)

Compound / Position	XIV (free base)	XV	XVI
2	1.99 (singlet)	—	2.35 (singlet)
Benzene ring	2.48	—	—
Ethyl (CH_2)	5.65 (quartet)	5.54 (quartet)	5.60 (quartet)
(CH_3)	8.58 (triplet)	8.47 (triplet)	8.48 (triplet)

7) E. Hayashi: Yakugaku Zasshi, **81**, 1030 (1961).
8) R. Huisgen: Angew. Chem., **75**, 604 (1963).
9) R. Gompper, E. Hoyer, H. Herlinger: Chem. Ber., **92**, 550 (1959).
10) A. M. Simonov, A. D. Garnovskiĭ: J. Gen. Chem. U. S. S. R., **31**, 114 (1961).

dimethylaniline exothermically to precipitate a crystalline product with evolution of ammonia gas. The structure of this compound was assigned as 1-ethoxy-2,2′-bibenzimidazole (XVII) by elemental analysis, molecular weight determination, and the infrared spectrum which shows the existence of NH group of the imidazole ring. Hydrogenolysis of XVII with Raney nickel gave 2,2′-bibenzimidazole (XVIII).

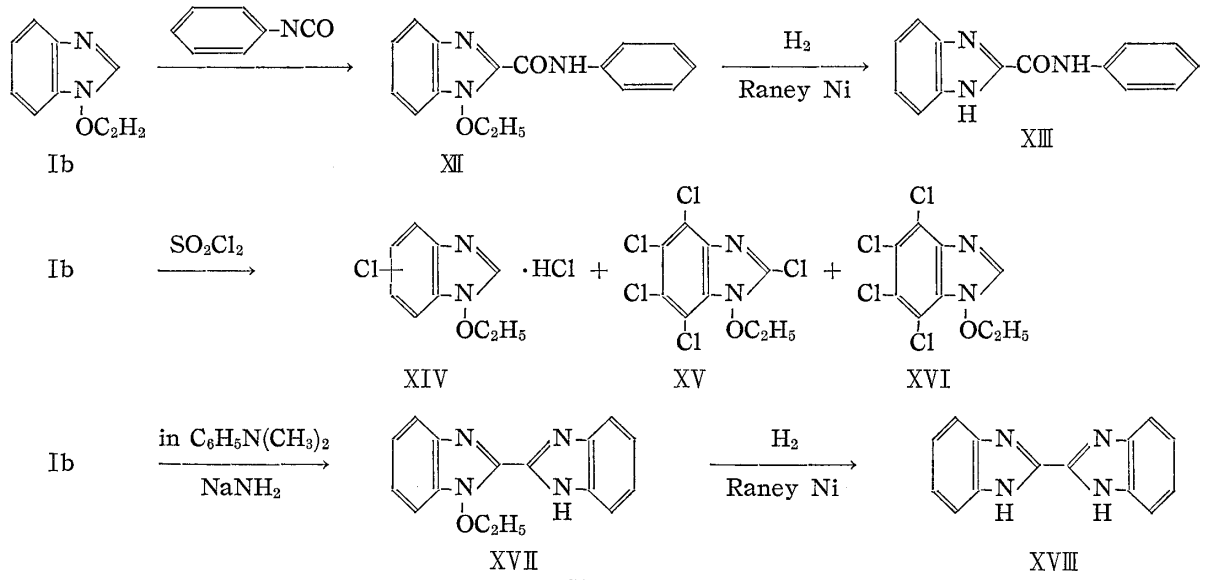

Chart 3.

Nitration is also one of the most important reactions of heteroaromatic N-oxides; pyridine N-oxide gives 4-nitropyridine N-oxide in good yield by treatment with potassium nitrate and sulfuric acid,[11] while pyridine itself can not be nitrated by the same reagent. Ib gave two mononitro derivatives, m.p. 77° and m.p. 104°, by treatment with a mixture of fuming nitric acid and concentrated sulfuric acid at room temperature, and the same reaction gave only a dinitro derivative on heating. By further treatment with the mixed acids on a water bath, both mononitro derivatives were converted into the same dinitro derivative, which was identical with the above-obtained dinitro compound. Catalytic reduction with Raney nickel converted both mononitro derivatives to the same 5 (or 6)-aminobenzimidazole (XXII). On the other hand, 2,4-dinitroformanilide was treated with ammonium sulfide followed with ethyl iodide to give 1-ethoxy-6-nitrobenzimidazole, m.p. 104°. This compound was identical with the above-obtained mononitro derivative of m.p. 104° (XX). These facts show that the other mononitro derivative of m.p. 77° is 1-ethoxy-5-nitrobenzimidazole (XIX) and the dinitro derivative is 1-ethoxy-5,6-dinitrobenzimidazole (XXI).

The amounts of XIX and XX obtained by this nitration were almost equal, being measured with infrared absorption spectra; the spectrum of XIX exhibited characteristic peak at 1080 cm^{-1}, and that of XX at 1110 cm^{-1}.

In order to compare electronic effects on the benzene ring of the ethoxy group and ethyl group, nitration of 1-ethylbenzimidazole (XXIII) was carried out under the same conditions.

At room temperature, XXIII gave two mononitro derivatives, m.p. 124° and m.p. 139°. Amounts of the isomers separated by column chromatography on alumina were nearly equal. By further nitration on heating, these two mononitro derivatives were converted into the same dinitro derivative, which was identical with the dinitro compound prepared directly from XXIII by nitration on a water bath.

11) E. Ochiai, M. Ishikawa, K. Arima : Yakugaku Zasshi, **63**, 79 (1943).

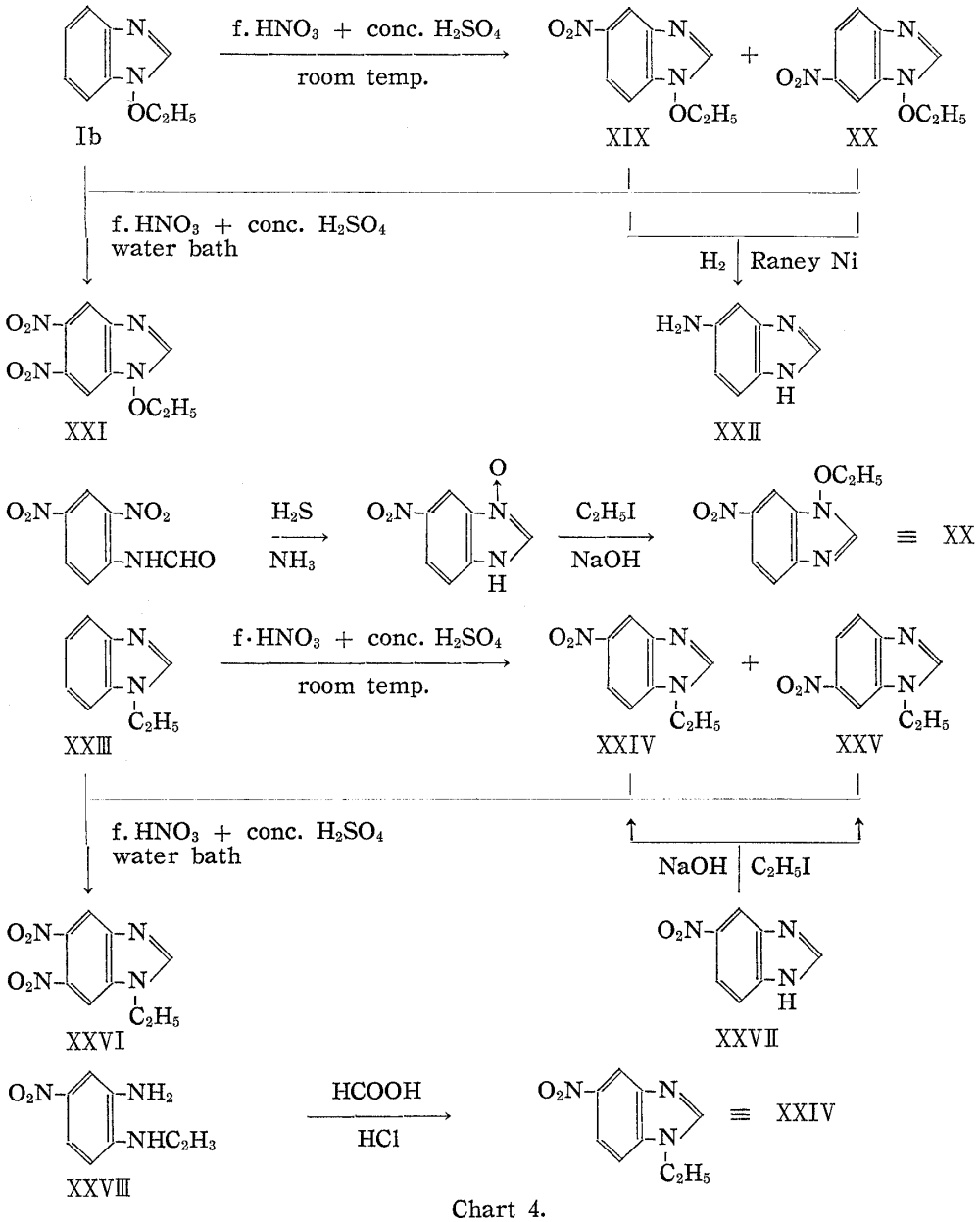

Chart 4.

To determine the structure of these compounds, the following experiments were carried out. 5(or 6)-Nitrobenzimidazole (XXVII) was converted into a mixture of 1-ethyl-5-nitrobenzimidazole (XXIV) and 1-ethyl-6-nitrobenzimidazole (XXV) by the action of ethyl iodide. Their melting points were 124° and 139°, respectively. These melting points and the infrared spectra were identical with those of the above-obtained mononitro derivative of m.p. 124° and 139°, respectively. By treatment with formic acid in hydrochloric acid, 2-ethylamino-5-nitroaniline (XXVIII) gave 1-ethyl-5-nitrobenzimidazole, the melting point and infrared spectrum of which were identical with those of the mononitro derivative of m.p. 139°. These facts show that the mononitro derivative of m.p. 139° is 1-ethyl-5-nitrobenzimidazole (XXIV), that of m.p. 124° is 1-ethyl-6-nitrobenzimidazole (XXV), and the dinitro derivative is 1-ethyl-5,6-dinitrobenzimidazole (XXVI).

Insofar as the nitration is concerned, it has been shown that the difference of electronic effect to benzene ring between the ethoxy group and ethyl group is negligible.

On the basis of the present investigation, it may be concluded that the chemical behaviour of 1-alkoxybenzimidazole is similar to that of an ordinary heteroaromatic

N-oxide and its N-alkoxy-quarternary salt, but the reactivity is not so large as the quarternary salt.

Experimental*3

1-Ethoxybenzimidazole (Ib)——Benzimidazole N-oxide (8.05 g., 0.060 mole) was added to a solution of NaOH (2.5 g., 0.063 mole) in H_2O (3 ml.) and EtOH (80 ml.). To this mixture, EtI (9.8 g., 0.063 mole) was added and the resulting solution was heated under reflux for 1 hr., then evaporated. H_2O was added to the residue and the separated oil was extracted with Et_2O. The Et_2O solution was dried and evaporated, and the residual oil was distilled under reduced pressure to give a colorless oil, $b.p_2$ 95°. Yield, 8.8 g. (90%). This compound was analyzed as the picrate. Yellow prisms (from Me_2CO), m.p. 191~193°. *Anal.* Calcd. for $C_9H_{10}ON_2 \cdot C_6H_3O_7N_3$: C, 46.04; H, 3.35; N, 17.90. Found : C, 46.05; H, 3.52; N, 17.77.

1-Allyloxybenzimidazole (Ic)——This compound was prepared from benzimidazole N-oxide and allyl bromide by the same procedure above mentioned. Coloress oil, $b.p_3$ 108°. Yield, 70%. Picrate : yellow prisms (from MeOH), m.p. 141~143°. *Anal.* Calcd. for $C_{10}H_{10}ON_2 \cdot C_6H_3O_7N_3$: C, 47.65; H, 3.25; N, 17.37. Found : C, 47.89; H, 3.47; N, 17.53.

Hydrogenolysis of 1-Methoxy- (Ia) and 1-Ethoxybenzimidazole (Ib)——A solution of Ia or Ib (ca. 0.5 g) in MeOH (ca. 10 ml.) was shaken in hydrogen atmosphere over Raney Ni (W-5, from 1 g. alloy), hydrogen of the calculated amount being absorbed during about 2 hr. The catalyst was filtered off and the filtrate was evaporated to give benzimidazole in quantitative yield.

Reduction of 1-Allyloxybenzimidazole (Ic)——A solution of Ic (0.50 g.) in EtOH (10 ml.) was shaken in hydrogen atmosphere over Raney Ni (W-5, from 0.5 g. alloy) until 1 mole of hydrogen had been absorbed. The catalyst was filtered off, and the filtrate was evaporated to give colorless oil (0.45 g.). Picrate, yellow needles (from EtOH), m.p. 130~131°. *Anal.* Calcd. for $C_{10}H_{12}ON_2 \cdot C_6H_3O_7N_3$ (1-propoxybenzimidazole picrate) : C, 47.41; H, 3.73; N, 17.28. Found : C, 47.71; H, 3.88; N, 17.14.

The IR spectrum of the oily substance was identical with that of 1-propoxybenzimidazole prepared from benzimidazole N-oxide and PrBr.

Hydrolysis of 1-Ethoxybenzimidazole (Ib) to Benzimidazole N-Oxide——A solution of Ib (0.50 g.) in conc. HCl (4.5 ml.) was heated in a sealed tube at 150° for 7 hr. The resulting brown solution was concentrated and neutralized with 10% aq. NH_3 solution to give a crystalline product. The crystals were collected and recrystallized from EtOH to give colorless plates, m.p. 226~228°. *Anal.* Calcd. for $C_7H_6ON_2$: C, 62.68; H, 4.51; N, 20.89. Found : C, 62.75; H, 4.74; N, 20.60.

The same result was obtained by use of conc. HBr instead of HCl.

2-Alkoxybenzimidazole (II)——1-Alkoxybenzimidazole (0.0025 mole) was added to a solution of Na (0.060 g., 0.0026 mole) in EtOH (5.0 ml.) and heated at 140° in a sealed tube. After 2 hr., the solution was evaporated and the residue was dissolved in H_2O, then neutralized with dil. AcOH to give 2-alkoxybenzimidazole, the alkoxy group of which was derived from EtOH of the solvent. The yields were almost quantitative.

2-Methoxybenzimidazole (IIa) : Colorless scales or prisms (EtOH-H_2O), m.p. 212~213°. *Anal.* Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44; N, 18.91. Found : C,64.97; H, 5.63; N, 18.94.

2-Ethoxybenzimidazole (IIb)[12] : Colorless plates (EtOH-H_2O), m.p. 165~166°. *Anal.* Calcd. for. $C_9H_{10}ON_2$: C, 66.65; H, 6.22; N, 17.27. Found : C, 66.65; H, 6.36; N, 17.44.

2-Allyloxybenzimidazole (IIc) : Colorless scales (EtOH-H_2O), m.p. 144~145°. *Anal.* Calcd. for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08. Found : C, 69.19; H, 5.73; N, 15.85.

Hydrolysis of 2-Ethoxybenzimidazole (IIb)[12]——A solution of 2-ethoxybenzimidazole (0.20 g.) in conc. HCl (3 ml.) was heated at 140° in a sealed tube for 5 hr. The resulting solution was diluted with H_2O, then neutralized with aq. NH_3 solution to give colorless crystals (0.15 g.). The product was identified with authentic 2(3*H*)-benzimidazolinone[13] by IR spectrum.

Rearrangement of 2-Allyloxybenzimidazole (IIc) to 1-Allyl-2(3*H*)-benzimidazolinone (III)——2-Allyloxybenzimidazole (0.3 g.) was heated at 180° for 2 hr. After cooling, the solid product was recrystallized from Me_2CO-petr. benzine to give colorless needles (0.3 g.), m.p. 99~100°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$ (III)[14] : C, 68.95; H, 5.75; N, 16.08. Found : C, 69.19; H, 5.93; N, 16.03.

---

*3 All melting points were taken on a Kofler hot-stage and are uncorrected. Solvents were removed under reduced pressure. Infrared spectra were recorded with a Kōken Infrared Spectrophotometer Model IR-S. NMR spectra were obtained in $CHCl_3$ solution containing tetramethylsilane as an internal reference on a Varian A-60 analytical NMR spectrometer.

12) T. Sandmeyer : Ber., **19**, 2650 (1886).
13) O. Kym : J. Pr., [2] **75**, 323 (1907).
14) J. Davoll, D. H. Laney : J. Chem. Soc., **1960**, 314.

This compound was identical with the substance prepared from N-allyl-*o*-phenylenediamine and urea.

Rearrangement of 2-Ethoxybenzimidazole (IIb)——2-Ethoxybenzimidazole (0.5 g.) was heated at 200~230° for 3 hr. The resulting mass was separated into an Me_2CO insoluble product and Me_2CO soluble products. The former (0.1 g.) was identified as 2(3*H*)-benzimidazolinone.[13] The latter, after removal of Me_2CO and recrystallization from CCl_4, gave the starting material (0.3 g.) and an oily substance (0.1 g.). The oil was identical with 1-ethyl-2-ethoxybenzimidazole (IV) prepared from IIb and EtI. This compound was analyzed as the picrate; m.p. 148~149° (from EtOH). *Anal.* Calcd. for $C_{11}H_{14}ON_2 \cdot C_6H_3O_7N_3$: C, 48.69; H, 4.09; N, 16.69. Found: C, 48.82; H, 4.15; N, 16.48.

Reaction of 1-Ethoxybenzimidazole (Ib) with Potassium Cyanide——To a solution of KCN (0.3 g.) in H_2O (1.0 ml.) were added EtOH (5 ml.) and Ib (0.50 g.). The solution was heated at 150° in a sealed tube for 2.5 hr., then evaporated. To the residue was added H_2O to give a crystalline product (0.10 g.), which was recrystallized from PrOH to give colorless needles, m.p. >300°. *Anal.* Calcd. for $C_8H_7ON_3$ (V): C, 59.62; H, 4.38; N, 26.07. Found: C, 60.00; H, 4.58; N, 25.87.

The IR spectrum of this compound was identical with that of an authentic specimen of 2-benzimidazolecarbamic acid.[15]

2-Hydrazinobenzimidazole (VI)——A mixture of Ib (0.50 g.) and hydrazine hydrate (90%, 2.5 ml.) was heated on a water bath with occasional skaking. Within a few minutes, the mixture became a solution. After one-half hour, the solution was evaporated to give a crystalline product, which was collected and washed with H_2O (0.40 g.). Recrystallization from EtOH gave colorless prisms, m.p. 211° (decomp.). *Anal.* Calcd. for $C_7H_8N_4$: C, 56.74; H, 5.44; N, 37.82. Found: C, 57.07; H, 5.63; N, 37.64.

The IR spectrum was identical with that of an authentic specimen.[16]

2-Benzimidazolesulfonic Acid (VII)——To a solution of sodium hydrogen sulfite (0.25 g.) in H_2O (1.0 ml.) was added Ib (0.20 g.), and the mixture was heated on a water bath for 5 min. with occasional shaking. The resulting solution was acidified with 6*N* HCl. The precipitated product was collected by filtration, washed with H_2O, and recrystallized from H_2O to give colorless prisms (0.20 g.), m.p. >300°. *Anal.* Calcd. for $C_7H_6O_3N_2S \cdot \frac{1}{2}H_2O$: C, 40.57; H, 3.41; N, 13.52. Found: C, 40.78; H, 3.60; N, 13.33.

The IR spectrum of this compound was identical with that of an authentic specimen.[17]

Reaction of 1-Ethoxybenzimidazole (Ib) with Acetic Anhydride——A mixture of Ib (1.0 g.) and Ac_2O (10 ml.) was heated on a water bath for 1 hr. The solution was concentrated, poured on cracked ice, then neutralized with aq. NH_3 solution to separate an oily substance. The oil was extracted with Et_2O and dried with Na_2SO_4. Removal of Et_2O gave a slightly brown viscous oil (1.2 g.). An analytical sample was purified by distillation using a small sublimation apparatus, colorless hygroscopic oil, b.p_2 ca. 110° (bath temperature). *Anal.* Calcd. for $C_{11}H_{14}O_3N_2$ (X): C, 59.45; H, 6.35; N, 12.60. Found: C, 59.85; H, 6.35; N, 12.73.

Thermal Decomposition of 2-Acetoxy-3-ethoxy-2,3-dihydrobenzimidazole (X)——In a flask fitted with a gas inlet tube and a gas exit tube leading to a flask immersed in a dry ice acetone bath, was placed X (1.00 g.) and heated in an oil bath. From the inlet tube, N_2 gas was passed through to expel the vaporized product from the reaction flask to the cooling one. When the temperature of the oil bath reached to 150~160°, a vigorous reaction occurred with solidification of the reactant and separation of a liquid, which was collected in the cooled flask (0.15 g.). The liquid was heated with phenyl isothiocyanate in a small sealed tube on a water bath for 3 hr. The resulting crystalline product was identified as phenylthiourethan[18] by comparison with an authentic sample. The solid product (0.50 g.) was purified by recrystallization from EtOH to colorless needles, m.p. 212~214°. *Anal.* Calcd. for $C_9H_8O_2N_2$ (XI): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.68; H, 4.59; N, 15.66. This compound was identified as 1-acetyl-2(3*H*)-benzimidazolinone by comparison with an authentic sample by mixed melting point and by IR spectra.

Thermal Decomposition of 1-Acetyl-2-acetoxy-3-ethoxy-2,3-dihydrobenzimidazole (VIII)——A mixture of Ib (0.5 g.) and Ac_2O (5 ml.) was heated on a water bath for 1 hr., and the excess anhydride was evaporated. The residual oil was treated as for 2-acetoxy-3-ethoxy-2,3-dihydrobenzimidazole except that the bath temperature was maintained at 200° for 10 min. H_2O was added to the product to give brown crystals. Recrystallization from EtOH gave colorless needles m.p. 153~154°. *Anal.* Calcd. for $C_{11}H_{10}O_3N_2$ (IX): C, 60.54; H, 4.62; N, 12.84. Found: C, 60.88; H, 4.74; N, 12.92.

This compound was identified as 1,3-diacetyl-2(3*H*)-benzimidazolinone by comparison with an authentic sample by the melting point and IR spectra.

1-Ethoxy-2-phenylcarbamoylbenzimidazole (XII)——A mixture of Ib (0.4 g.) and phenyl isocyanate (0.4 g.) was heated at 140° for 2 hr. The solidified product was chromatographed on alumina from benzene to give colorless crystals (0.6 g.). Recrystallization from EtOH or petr. benzine gave colorless

15) R. A. B. Copeland, A. R. Day: J. Am. Chem. Soc., **65**, 1072 (1943).
16) N. P. Bednyagina, I. Y. Postovskii: J. Gen. Chem. U. S. S. R., **30**, 1456 (1960).
17) J. G. Everett: J. Chem. Soc., **1930**, 2402.
18) A. W. Hofmann: Ber., **2**, 116 (1869).

needles, m.p. 129~130°. *Anal.* Calcd. for $C_{16}H_{15}O_2N_3$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.16; H, 5.39; N, 15.20.

2-Phenylcarbamoylbenzimidazole (XIII)——a) A solution of XII (0.20 g.) in EtOH (30 ml.) was shaken in hydrogen atmosphere over Raney Ni (W-5, from 0.4 g. alloy) until a calculated amount of hydrogen had been absorbed (ca. 1 hr.). After removal of the catalyst, the filtrate was evaporated to give colorless crystals (0.16 g.), which were recrystallized from EtOH to give colorless prisms, m.p. 242~243°. *Anal.* Calcd. for $C_{14}H_{11}ON_3$: C,70.87; H, 4.67; N, 17.71. Found: C, 71.05; H, 4.81; N, 17.41.

b) A mixture of 6*H*,13*H*-pyrazino[1,2-*a*:4,5-*a'*]dibenzimidazole-6,13-dione[15] (0.50 g.) and aniline (2.0 ml.) was heated at 120° in an oil bath for 1.5 hr. The pricipitated product was filtered, washed with EtOH and recrystallized from EtOH to give colorless prisms (0.60 g.), m.p. 241~242°. This compound was identical with the above-obtained one in all respects.

Reaction of 1-Ethoxybenzimidazole (Ib) with Sulfuryl Chloride——To SO_2Cl_2 (10 ml.) was added Ib (0.90 g.) dropwise with manual shaking and the solution was heated under reflux. In the course of 3 hr., crystalline products separated from the solution. After heating for an additional 3 hr., AcOEt was added to the mixture and the precipitate was collected by filtration. This product (0.60 g.) was recrystallized from EtOH-AcOEt to give colorless prisms m.p. 183° (decomp.). *Anal.* Calcd. for $C_9H_9ON_2Cl \cdot HCl$ (XIV): C, 46.37; H, 4.32; N, 12.02. Found; C, 46.11; H, 4.38; N, 12.28.

The filtrate was chromatographed on alumina from benzene to give crystals of m.p. 130~135° (0.3 g.) as the early fractions, then crystals of m.p. 125~128° (0.05 g.) as the late fractions.

The former product was recrystallized from petr. benzine to give colorless prisms, m.p. 135~136°. *Anal.* Calcd. for $C_9H_5ON_2Cl_5$ (XV): C, 32.32; H, 1.51; N, 8.38. Found: C, 32.52; H, 1.76; N, 8.15.

The latter product was recrystallized from EtOH to give colorless needles, m.p. 128~129°. *Anal.* Calcd. for $C_9H_6ON_2Cl_4$ (XVI): C, 36.02; H, 2.02; N, 9.34. Found: C, 35.51; H, 2.13; N, 9.16.

1-Ethoxy-2,2'-bibenzimidazole (XVII)——To a solution of Ib (0.80 g.) in N,N-dimethylaniline (4.0 ml.) was added powdered $NaNH_2$ (0.40 g.) at one time, and the mixture was occasionally shaken. Within a minute, the temperature of the mixture gradually rose, gas was evolved, and a copious amount of crystals separated. After standing for one-half hour at room temperature, the mixture was heated on a water bath for 1 hr., and cooled. The crystals were collected by filtration, washed with Et_2O, then triturated with dil. AcOH to give a pale yellow precipitate (0.55 g.). This was chromatographed on alumina from $CHCl_3$, then recrystallized from petr. benzine to give colorless plates, m.p. 152~154°. *Anal.* Calcd. for $C_{16}H_{14}ON_4$: C, 69.05; H, 5.07; N, 20.13. Found: C, 69.39; H, 5.24; N, 20.18.

2,2'-Bibenzimidazole (XVIII)——A solution of XVII (0.20 g.) in EtOH (20 ml.) was shaken in hydrogen atmosphere over Raney Ni (W-5, from 0.3 g. alloy). Owing to insolubility, the product precipitated. When no more hydrogen was absorbed (the time required was about one-half hour), the solvent was evaporated, the product dissolved in hot dimethylformamide and the catalyst was filtered off. The filtrate was evaporated and the residue (0.10 g.) was recrystallized from glacial AcOH to give colorless prisms, m.p. >300° (dried over KOH at 100°, 2 mm. Hg, for 5 hr.). *Anal.* Calcd. for $C_{14}H_{10}N_4$ (XVIII): C, 71.78; H, 4.30; N, 23.92. Found: C, 72.15; H, 4.36; N, 23.72.

The IR spectrum of this compound was identical with that of an authentic specimen.[19]

Nitration of 1-Ethoxybenzimidazole (Ib) at Room Temperature——To a mixture of fuming HNO_3 (d= 1.52, 1.0 ml.) and conc. H_2SO_4 (2.5ml.) was added Ib (1.00g.) dropwise with stirring. The solution was allowed to stand for 1 hr. at room temperature, then poured on cracked ice (ca. 15 g.). The crystalline precipitate was collected by filtration, neutralized with aq. NH_3 solution and extracted with $CHCl_3$. The $CHCl_3$ layer was separated, dried and evaporated to give pale yellow crystals (1.10 g.). Chromatography on alumina from $CHCl_3$ gave 1-ethoxy-6-nitrobenzimidazole (XX) melting in the range 100~103°, and then 1-ethoxy-5-nitrobenzimidazole (XIX) melting in the range 70~80°. The former was recrystallized from Et_2O to pale yellow prisms or plates (0.20 g.), m.p. 102~103°. *Anal.* Calcd. for $C_9H_9O_3N_3$ (XX): C, 52.17; H, 4.38; N, 20.28. Found: C, 52.37; H, 4.57; N, 20.49. The latter was recrystallized from Et_2O to pale yellow prisms or plates (0.40 g.), m.p. 75~77°. *Anal.* Calcd. for $C_9H_9O_3N_3$ (XIX): C, 52.17; H, 4.38; N, 20.28. Found: C, 52.08; H, 4.40; N, 20.01.

Reduction of 1-Ethoxy-5-nitrobenzimidazole (XIX)——A solution of XIX (0.20 g.) in EtOH (10 ml.) was shaken in hydrogen atmosphere over Raney Ni (W-5, from 0.5 g. alloy) until no more hydrogen was absorbed (ca. 2 hr.). The catalyst was filtered off, and the filtrate was evaporated to give colorless oil, which was solidified by cooling to colorless crystals (0.12 g.), m.p. 165~166°. This melting point was not depressed by admixture with authentic 5(or 6)-aminobenzimidazole.[20] IR spectrum of this compound was identical with that of the authentic specimen.

Reduction of 1-Ethoxy-6-nitrobezimidazole (XX)——The reduction was carried out by the same procedure as in the above-mentioned experiment. XX gave XXII by the reduction.

19) H. Hübner: Ann., **209**, 339 (1881).
20) M. Stäuble: Helv. Chim. Acta, **32**, 135 (1949).

Nitration of 1-Ethoxybenzimidazole (Ib) at High Temperature——To a mixture of fuming HNO_3 (d= 1.52, 1.5 ml.) and conc. H_2SO_4 (4.0 ml.) was added Ib (1.00g.) dropwise with stirring. The solution was heated on a water bath for 5 hr., then poured on cracked ice (ca. 20g.). The precipitate (1.00 g.) was collected, dried, chromatograhed on alumina from $CHCl_3$ and recrystallized from EtOH to give pale yellow scales, m.p. 137~138°. *Anal.* Calcd. for $C_9H_8O_5N_4$ (XXI): C, 42.86; H, 3.20; N, 22.22. Found; C, 43.13; H, 3.40; N, 22.13.

Nitration of 1-Ethoxy-5-nitrobenzimidazole (XIX)——To a mixture of fuming HNO_3 (0.3 ml.) and conc. H_2SO_4 (0.7 ml.) was added XIX (0.20 g.). The solution was heated on a water bath for 5 hr., then poured on cracked ice to give pale yellow crystals (0.2 g.). Recrystallization from EtOH gave pale yellow scales, m.p. 136~138°, which was identical with XXI above-obtained in all respects.

Nitration of 1-Ethoxy-6-nitrobenzimidazole (XX)——The nitration was carried out by the same procedure as for that of XIX. XX gave XXI by the nitration.

2′,4′-Dinitroformanilide——2,4-Dinitroaniline (13.3 g.) was added to acetic formic anhydride[21] which was prepared from Ac_2O (34.0 ml.) and HCOOH (98%, 14.0 ml.). The mixture allowed to stand for 2 days, then concentrated. Recrystallization of the residue from EtOH gave yellow scales (14.2 g.), m.p. 163~164°. *Anal.* Calcd. for $C_7H_5O_5N_3$: C, 39.82; H, 2.39; N, 19.90. Found: C, 40.05; H, 2.43; N, 19.57.

5-Nitrobenzimidazole 3-Oxide——H_2S was passed through the mixture of 2′,4′-dinitroformanilide (7.0 g.) in EtOH (300 ml.) containing EtOH-NH_3 (saturated at 0°, 20 ml.) for 3 hr. After standing overnight at room temperature, the resulting brown solution was concentrated to ca. 50 ml., and precipitated sulfur was filtered off and washed with EtOH. Removal of EtOH from the combined filtrate and washings gave brown crystals. Recrystallization from EtOH (ca. 1 L.) gave pale yellow plates (1.5 g.), m.p. 274° (decomp.). *Anal.* Calcd. for $C_7H_5O_3N_3$: C, 46.93; H, 2.81; N, 23.46. Found: C, 47.14; H, 2.83; N, 23.38.

1-Ethoxy-6-nitrobenzimidazole (XX) from 5-Nitrobenzimidazole 3-Oxide——To a solution of NaOH (0.16 g., 0.0040 mole) in H_2O (0.5 ml.) and EtOH (10 ml) was added the N-oxide (0.70 g., 0.0039 mole) then added EtI (0.60 g., 0.0039 mole). The solution was refluxed for 1hr., then evaporated. H_2O was added to the residue and separated oil was extracted with $CHCl_3$. The $CHCl_3$ layer was separated, dried and concentrated to give pale yellow crystals (0.60 g.). Recrystallization from Et_2O gave slightly yellow prisms, m.p. 104~105°. *Anal.* Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.38; H, 4.49; N, 20.43.

The IR spectrum of this compound was identical with that of XX prepared from Ib by nitration, and the mixed melting point showed no depression.

Nitration of 1-Ethylbenzimidazole (XXIII) at Room Temperature——The nitration was carried out by the same procedure as for that of Ib. The mixture of 1-ethyl-5-nitrobenzimidazole (XXIV) and 1-ethyl-6-nitrobenzimidazole (XXV) obtained from 1.00 g. of XXIII weighed 1.25 g. and 1.25 g. on two experiments. By chromatography on alumina from $CHCl_3$, the mixture was separated into a product melting in the range 120~123° (0.60 g., 0.56 g.) as the early fractions, and one melting in the range 130~134° (0.56 g., 0.57 g.) as the late fractions. The former product was assigned as XXV. Recrystallization from CCl_4 gave pale yellow plates, m.p. 123~124°. *Anal.* Calcd. for $C_9H_9O_2N_3$ (XXV): C, 56.54; H, 4.75; N, 21.98. Found: C, 56.61; H, 4.79; N, 21.87. The latter product was assigned as XXIV. Recrystallization from benzene gave pale yellow plates, m.p. 138~139°. *Anal.* Calcd. for $C_9H_9O_2N_3$ (XXIV): C, 56.54; H, 4.75; N, 21.98. Found: C, 56.65; H, 4.95; N, 21.73.

Nitration of 1-Ethylbenzimidazole (XXIII) at High Temperature——The nitration was carried out by the same procedure as for that of Ib. By the nitration, XXIII (1.0 g.) gave 1-ethyl-5,6-dinitrobenzimidazole (XXVI) (1.0 g.). Recrystallization from EtOH gave pale yellow prisms, m.p. 181~182°. *Anal.* Calcd. for $C_9H_8O_4N_4$: C, 45.76; H, 3.41; N, 23.72. Found: C, 46.00; H, 3.45; N, 23.53.

Nitration of 1-Ethyl-5-nitrobenzimidazole (XXIV) and 1-Ethyl-6-nitrobenzimidazole (XXV)——The nitration was carried out by the same procedure as for that of XIX. Both compounds (XXIV and XXV) gave the same dinitro derivative (XXVI) in good yields.

XXVI obtained here was identical with the compound above-obtained in all respects.

Ethylation of 5(or 6)-Nitrobenzimidazole (XXVII)——The ethylation was carried out by the same procedure as for that of 5-nitrobenzimidazole 3-oxide. The $CHCl_3$ extract chromatographed on alumina from $CHCl_3$ gave XXIV and XXV. XXIV and XXV obtained here were identified as being identical with the above-obtained ones respectively by mixed melting points and IR spectra.

1-Ethyl-5-nitrobenzimidazole (XXIV) from 2-(N-Ethylamino)-5-nitroaniline (XXVIII)——A mixture of XXVIII (0.80 g.),[22] HCOOH (98%, 0.4 ml.) and 4*N* HCl (6 ml.) was heated under reflux for 2 hr. The solution was concentrated and the residue was neutralized with aq. NH_3 solution to give colorless crys-

21) C. W. Huffmann: J. Org. Chem., **23**, 727 (1958).
22) K. Streitwolf, A. Fehrle: D. R. P. 489459; Frdl., **16**, 2619 (1931).

tals. Recrystallization from EtOH-H_2O gave slightly yellow plates (0.50 g.), m.p. 139~140°. *Anal.* Calcd. for $C_9H_9O_2N_3$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.61; H, 4.89; N, 21.83.

The IR spectrum of this compound was identical with that of XXIV above-obtained, and the mixed melting point showed no depression.

The authors are deeply grateful to Prof. Emeritus E. Ochiai of the Uneversity of Tokyo and Dr. K. Takeda, Director of this Laboratory, for their helpful advices and encouragements. Thanks are due to Mr. K. Aono for NMR spectral measurements, to the members of the Analysis Room of this Laboratory, and to Mr. S. Hashimoto for his technical assistance.

Summary

Reactions of 1-alkoxybenzimidazole (I) with nucleophilic reagents, acetic anhydride and some other reagents involving the nitrating mixture were examined. In these reactions, I behaves as an ordinary heteroaromatic N-oxide and its N-alkoxyquarternary salt, although the reactivity is not so large as the quarternary salt.

(Received November 21, 1963)

[Chem. Pharm. Bull. 12 (3) 291 ~ 298]

UDC 547.496.3 : 548.2 : 543.422.4

41. Masao Nishikawa and Akio Takabatake: Infrared Spectra of Thiourea and its Inclusion Compounds. V.*1 Use of Thiourea-d_4 as a Host Molecule.*2

(*Research Laboratories, Takeda Chemical Industries, Ltd.**3)

Considerable efforts have been devoted to investigations on the behavior of molecules trapped in clathrate compounds. Physicochemical methods, such as wide-line nuclear magnetic resonance,[1,2] magnetic susceptibility,[3] thermal analysis,[4] dielectric absorption,[5] electron spin resonance,[6] and infrared absorption,[7~9] are useful for such investigations. One of the authors (M. N.) also has attempted to study the state of guest molecules in thiourea channels by means of infrared spectroscopic analysis. Usually, absorption bands due to the host molecule (thiourea) are so strong that bands of guest molecules are masked by them almost completely and, consequently, all inclusion compounds exhibit nearly the same spectra when treated by ordinary Nujol mull or potassium bromide disk methods. By the technique described in previous papers of this series,*1, [10~12] however, some absorption bands of guest molecules can be observed in

*1 Part Ⅳ: This Bulletin, **11**, 1290 (1963).
*2 Presented at Symposium on Molecular Structure, Sendai, Oct. 3, 1963.
*3 Juso-nishino-cho, Higashiyodogawa-ku, Osaka (西川正夫, 高畑明夫).

1) D. F. R. Gilson, C. A. McDowell: Nature, **183**, 1183 (1959); *Idem*: Mol. Phys., **4**, 125 (1961).
2) H. Nakajima: Presented at International Symposium on Molecular Structure and Spectroscopy, Tokyo, September, 13, 1962.
3) H. Meyer, M. C. M. O'Brien, J. H. VanVleck: Proc. Roy. Soc., **A**, **243**, 414 (1957).
4) H. G. McAdie: Canad. J. Chem., **40**, 2195 (1962).
5) R. J. Meakins: Trans. Faraday Soc., **51**, 953 (1955).
6) O. H. Griffith, H. M. McConnell: Proc. Nat. Acad. Sci. U. S., **48**, 1877 (1962).
7) R. S. Drago, J. T. Kwon, R. A. Archer: J. Am. Chem. Soc., **80**, 2667 (1958).
8) R. A. Durie, R. J. Harrison: Spectrochim. Acta, **18**, 1505 (1962).
9) D. F. Ball, D. C. McKean: *Ibid.*, **18**, 933. (1963).
10) M. Nishikawa: Chem. & Ind. (Lonbon), 256 (1963).
11) *Idem*: This Bulletin, **11**, 977 (1963).
12) *Idem*: *Ibid.*, **10**, 1205 (1962).