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# Benzimidazole N-Oxides. VIII.[1] The Reactivity of Ethyl 1-Methyl-2-benzimidazolecarboxylate 3-Oxide and the Related Compounds

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Ethyl 1-methyl-2-benzimidazolecarboxylate 3-oxide (XVII) was synthesized from 1-methyl-2-benzimidazolecarboxaldehyde oxime 3-oxide *via* the corresponding nitrile (III) and imido ester (XIII). Both reactions of III and XIII with potassium hydroxide gave 1-methyl-2-benzimidazolol 3-oxide. From III, 2-carboxamide (XI), 2-thiocarboxamide derivatives and 6-hydroxy-1-methyl-2-benzimidazolecarbonitrile were obtained. L-2-(6-Hydroxy-1-methyl-2-benzimidazolyl)-$\Delta^2$-thiazoline-4-carboxylic acid was synthesized from III, which has an analogous structure to firefly luciferin but it was inactive as far as light production was concerned. From XIII, 2-amidrazone, 2-tetrazole derivative and 1,1′-dimethyl-2,2′-bibenzimidazole 3-oxide were prepared. Hydrolysis of III and XIII with hydrochloric acid gave 1-methylbenzimidazole 3-oxide. The corresponding amide XI, acid hydrazide and hydroxamic acid were obtained from XVII. Reaction of XVII with piperidine did not give the corresponding amide but a mixture of 1-methylbenzimidazole 3-oxide and piperidine urethan. 3-($\alpha$,$\beta$-Dimethoxycarbonyl-$\beta$-hydroxyvinyl)-2-ethoxycarbonyl-1-methylbenzimidazolium betaine was prepared from XVII and dimethyl acetylenedicarboxylate.

In previous papers of this series, it was showed that nucleophilic reagents attack 2-position selectively in 1-methylbenzimidazole 3-oxide[3] and 2-methyl group and/or 6-position in 1,2-dimethylbenzimidazole 3-oxide,[1] and that these N-oxides are very reactive compared with deoxygenated parent bases.

From these facts, it seems very interesting to study the behaviour of nucleophilic reagents towards a functional group on the 2-position of benzimidazole 3-oxide. This paper deals with syntheses and reactivities of benzimidazole 3-oxides bearing a functional group at the 2-position.

There has been no available literature for the synthesis of such compounds except one reported by Hayashi and Iijima[4] who obtained 2-phenylbenzimidazole 3-oxide from 2-phenylquinoxaline 4-oxide by treatment with hydrogen peroxide and potassium hydroxide and suggested that this method may be applicable to the preparation of other 2-substituted benzimidazole 3-oxides. The desired benzimidazole 3-oxides in the present paper were derived starting from 1-methyl-2-benzimidazolecarboxaldehyde oxime 3-oxide (II) which was obtained from 1,2-dimethylbenzimidazole 3-oxide (I) and isoamyl nitrite in the presence of sodium amide.[1]

Attempted dehydration of II with acetic anhydride or phosphoryl chloride by usual method gave 6-acetoxy-1-methyl-2-benzimidazolecarbonitrile (IV) or 6-chloro-1-methyl-2-benzimidazolecarbonitrile (V), respectively. The products would arise from further attack of the respective reagents on the primary product, 1-methyl-2-benzimidazolecarobonitrile 3-oxide (III). The compound III was obtained by using calculated amount of acetic anhydride in acetic acid. Another synthetic method for III was developed through thermal decomposi-

1) Part VII: S. Takahashi and H. Kanō, *Chem. Pharm. Bull.* (Tokyo), **14**, 1219 (1966).
2) Location: *Fukushima-ku, Osaka.*
3) S. Takahashi and H. Kanō, *Chem. Pharm. Bull.* (Tokyo), **12**, 783 (1964).
4) E. Hayashi and C. Iijima, *Yakugaku Zasshi*, **82**, 1093 (1962).

tion of 2-ethoxycarbonyloxyiminomethyl-1-methylbenzimidazole 3-oxide (VI), which was obtained by the reaction of II and diethyl pyrocarbonate in the presence of alkali.

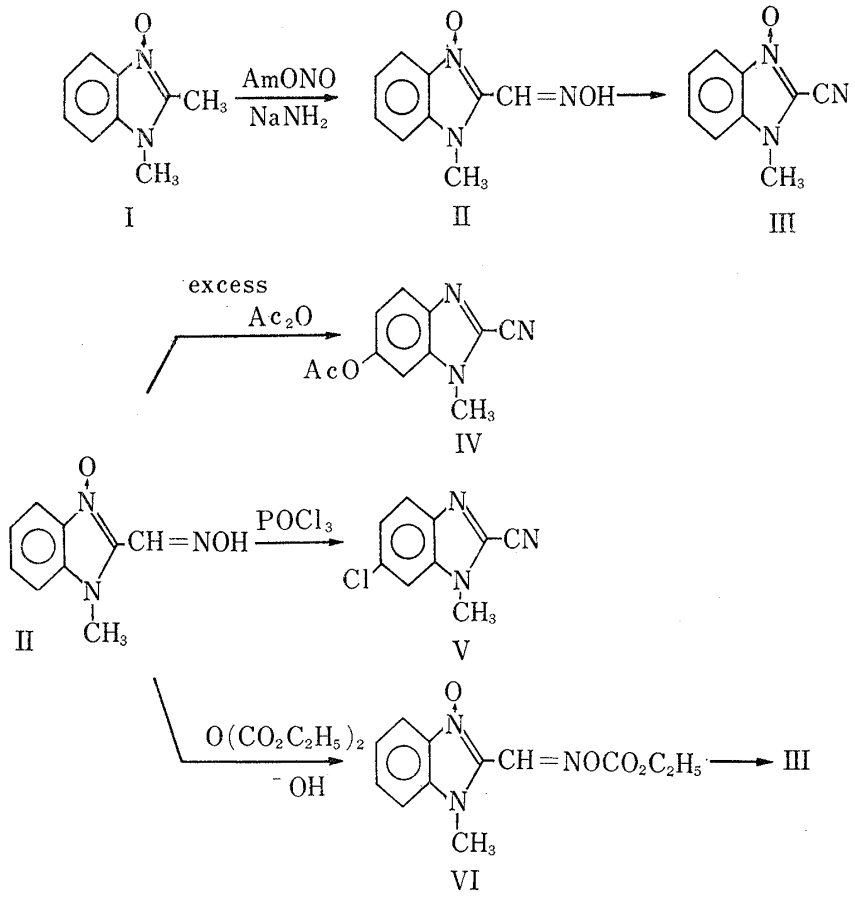


Chart 1

Heating of III with potassium hydroxide in methanol solution did not give the anticipated 1-methyl-2-benzimidazolecarboxylic acid 3-oxide or 2-carboxamide derivative but gave 1-methyl-2-benzimidazolol 3-oxide (VII). The formation of VII would involve the nucleophilic attack of hydroxide ion on the electron deficient 2-position of the imidazole ring instead of the attack at the cyano carbon. The same type of the reaction was reported in quinazoline[5] or quinoxaline[6] series. On the other hand, 1-methyl-2-benzimidazolecarbonitrile was hydrolyzed to 1-methyl-2-benzimidazolecarboxylic acid.[3]

The infrared spectrum showed that VII exists as its tautomeric form, 3-hydroxy-1-methyl-2-benzimidazolinone (VII') in the crystalline state. Methylation of VII with diazomethane yielded 3-methoxy-1-methyl-2-benzimidazolinone (VIII), whose infrared spectrum showed absorption band at 1700 $cm^{-1}$ (>C-O, broad).

The reaction of III with sodium methylmercaptide did not afford 2-methylthio-1-methylbenzimidazole 3-oxide.

As mentioned above, the reaction of III with acetic anhydride gave 6-acetoxy derivative IV, the structure of which was assigned by the infrared spectrum and by analogy with other substitution reactions of this series. Hydrolysis of IV with potassium hydroxide in methanol solution under the condition described in the Experimental afforded 6-hydroxy-1-methyl-2-benzimidazolecarbonitrile (IX). Treatment of IX with L-cysteine yielded L-2-(6-hydroxy-

5) T. Higashino, *Yakugaku Zasshi*, **80**, 1404 (1960).
6) E. Hayashi and C. Iijima, *Yakugaku Zasshi*, **84**, 156 (1964).

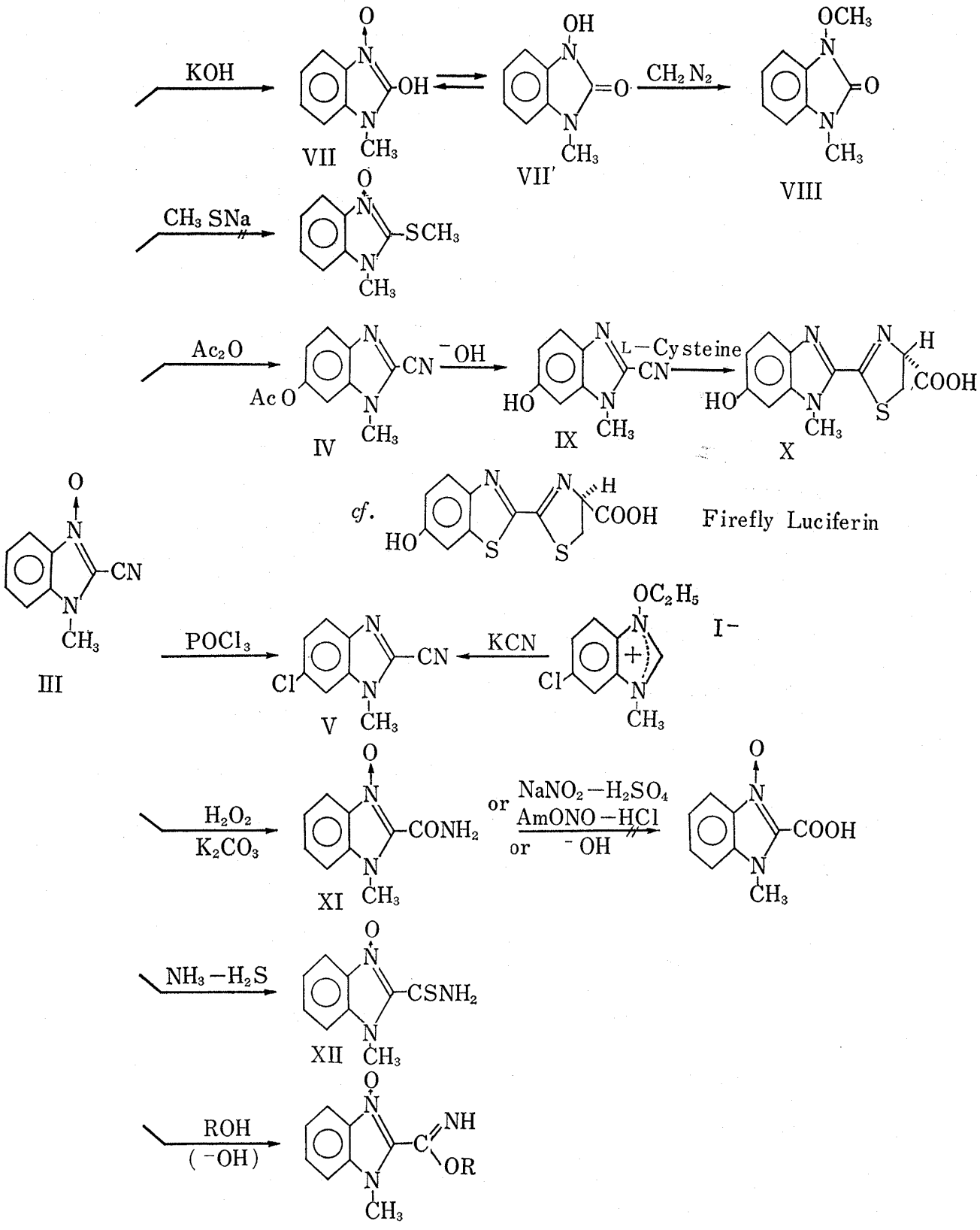


Chart 2

1–methyl–2–benzimidazolyl)–$\Delta^2$–thiazoline–4–carboxylic acid (X), which has an analogous structure to firefly luciferin reported by White, *et al.*,[7] but it was inactive as far as light production was concerned.[8]

Heating with phosphoryl chloride, III gave V. The structure of V was confirmed by comparison with a sample prepared by unambiguous method: 5–Chloro–2–nitro–N–methylaniline was formylated with acetic formic anhydride then the formanilide was reduced to 6–chloro–1–methylbenzimidazole 3–oxide by sodium borohydride in the presence of palladium-barium sulfate, a quaternary salt of which gave V by treatment with potassium cyanide.

1–Methyl–2–benzimidazolecarboxamide 3–oxide (XI) and 1–methyl–2–benzimidazolethiocarboxamide 3–oxide (XII) were obtained by the reactions of III with hydrogen peroxide–potassium carbonate and hydrogen sulfide–ammonia, respectively. Heating with concentrated hydrochloric acid, XI gave 1–methylbenzimidazole 3–oxide, which may be produced by hydrolysis to 1–methyl–2–benzimidazolecarboxylic acid 3–oxide followed by spontaneous decarboxylation owing to rather drastic condition. All attempts to lead to 1–methyl–2–benzimidazolecarboxylic acid 3–oxide from XI by diazotization with sodium nitrite–sulfuric acid, or isoamyl nitrite–hydrogen chloride method, or by hydroylsis with potassium hydroxide in methanol solution, did not succeed and only the starting material was recovered in all cases. Hofmann reaction of XI led to decompose and could not be confirmed the formation of 2–amino derivative.

III was readily converted to 1–methyl–2–benzimidazoleimidic acid ester 3–oxide (XIII) by refluxing in an alcoholic solution or by treating with cold alcoholic sodium hydroxide. The compound XIII can be served as a convenient starting material for various 2–substituted benzimidazole N–oxides. Reaction of XIII with potassium hydroxide in methanol solution gave VII similarly to the reaction of III. Reaction of XIII with hydrazine hydrate in alcohol solution gave 1–methyl–2–benzimidazolecarboimidohydrazide 3–oxide (XIV), which afforded 2–(5–tetrazolyl)–1–methylbenzimidazole 3–oxide (XV) by treatment with nitrous acid. Reaction of XIII with N–methyl–*o*–phenylenediamine dihydrochloride in methanol gave 1,1′–dimethyl–2,2′–bibenzimidazole 3–oxide (XVI).

Heating with concentrated hydrochloric acid, XIII gave 1–methylbenzimidazole 3–oxide, which may be yielded through 1–methyl–2–benzimidazolecarboxylic acid 3–oxide as in the case of III. However, treatment with dilute hydrochloric acid under mild condition, XIIIb gave ethyl 1–methyl–2–benzimidazolecarboxylate 3–oxide (XVII). The ester XVII reacted with methyl iodide, ammonia, and hydrazine hydrate to give 2–ethoxycarbonyl–3–methoxy–1–methylbenzimidazolium iodide (XVIII), XI and 1–methyl–2–benzimidazolecarbohydrazide 3–oxide (XIX), respectively. XIX could not be led to the acid azide derivative, but gave XVII by treatment with isoamyl nitrite and hydrochloric acid in ethanol. By the reaction with potassium hydroxide in alcoholic solution, XVII gave a mixture of VII and 1–methylbenzimidazole 3–oxide. Hydrolysis of XVII with hydrochloric acid gave 1–methylbenzimidazole 3–oxide.

1–Methyl–2–benzimidazolecarboxylic acid 3–oxide (XXI), which is unaccessible by direct hydrolysis of the corresponding nitrile III, imido ester XIII, or ester XVII, as mentioned above, was obtained by treatment of 1–methyl–2–benzimidazolehydroxamic acid 3–oxide (XX) with nitrous acid. The compound XX was easily prepared from XVII and hydroxylamine. The acid XXI was readily decarboxylated to 1–methylbenzimidazole 3–oxide within a week on standing even at room temperature.

The ester XVII reacted normally with monomethylamine to give 1,N–dimethyl–2–benzimidazolecarboxamide 3–oxide (XXII), but reacted abnormally with piperidine to yield 1–methylbenzimidazole 3–oxide and ethyl 1–piperidylcarboxylate. Further intensive work

7) E.H. White, F. McCapra, and G.F. Field, *J. Am. Chem. Soc.*, **85**, 337 (1963).
8) The authors are indebted to Prof. T. Goto (Univ. Nagoya) for this experiment.

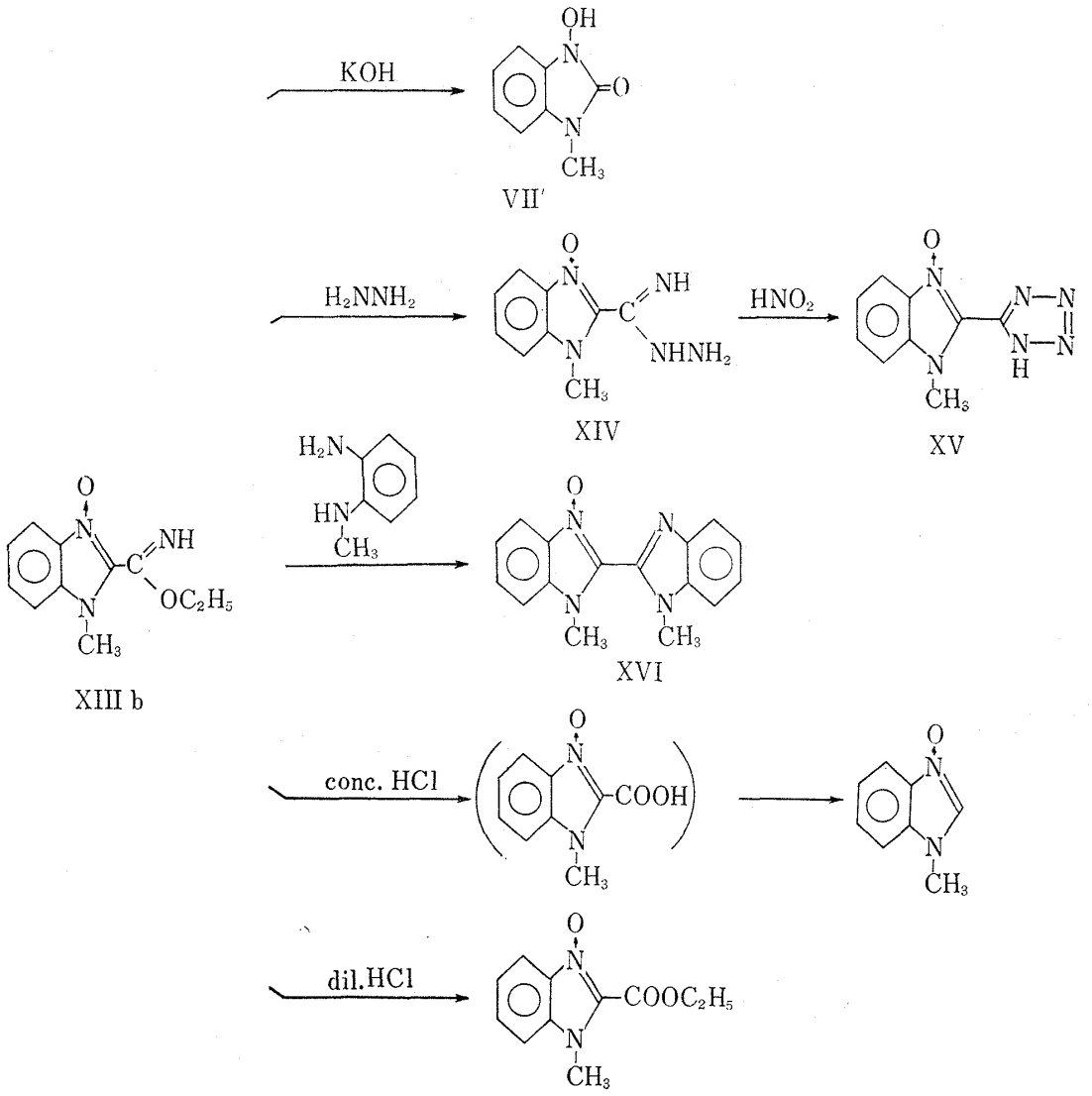


Chart 3

on this interesting reaction is in progress and will be reported later. The similar abnormal reaction was reported on reaction of esters of halogenoacetic acid with amines.[9]

We have reported that the reaction of 1,2-dimethylbenzimidazole 3-oxide and dimethyl acetylenedicarboxylate gave 3-(α,β-dimethoxycarbonyl-β-hydroxyvinyl)-1,2-dimethylbenzimidazolium betaine.[10] XVII reacted similarly with dimethyl acetylenedicarboxylate to give 3-(α,β-dimethoxycarbonyl-β-hydroxyvinyl)-2-ethoxycarbonyl-1-methylbenzimidazolium betaine (XXIII). Hydrolysis of XXIII with hydrochloric acid gave 3-(hydroxyoxalylmethyl)-1-methylbenzimidazolium chloride (XXIV), which was oxidized to 3-carboxymethyl-1-methylbenzimidazolium betaine (XXV) with potassium permanganate. To prove the structure, XXV was synthesized unambiguously as follows. Treatment of silver salt of benzimidazole with methyl bromoacetate gave methyl 1-benzimidazoleacetate (XXVI). Quaternization of XXVI with methyl iodide gave 3-(methoxycarbonylmethyl)-1-methylbenzimidazolium iodide (XXVII). XXVII was not hydrolyzed by treatment with hydro-

9) M.M. Joullié and A.R. Day, *J. Am. Chem. Soc.*, **76**, 2990 (1954); M.M. Joullié, *ibid.*, **77**, 6662 (1955); A.C. Pierce and M.M. Joullié, *J. Org. Chem.*, **28**, 658 (1963).
10) S. Takahashi and H. Kanō, *J. Org. Chem.*, **30**, 1118 (1965).

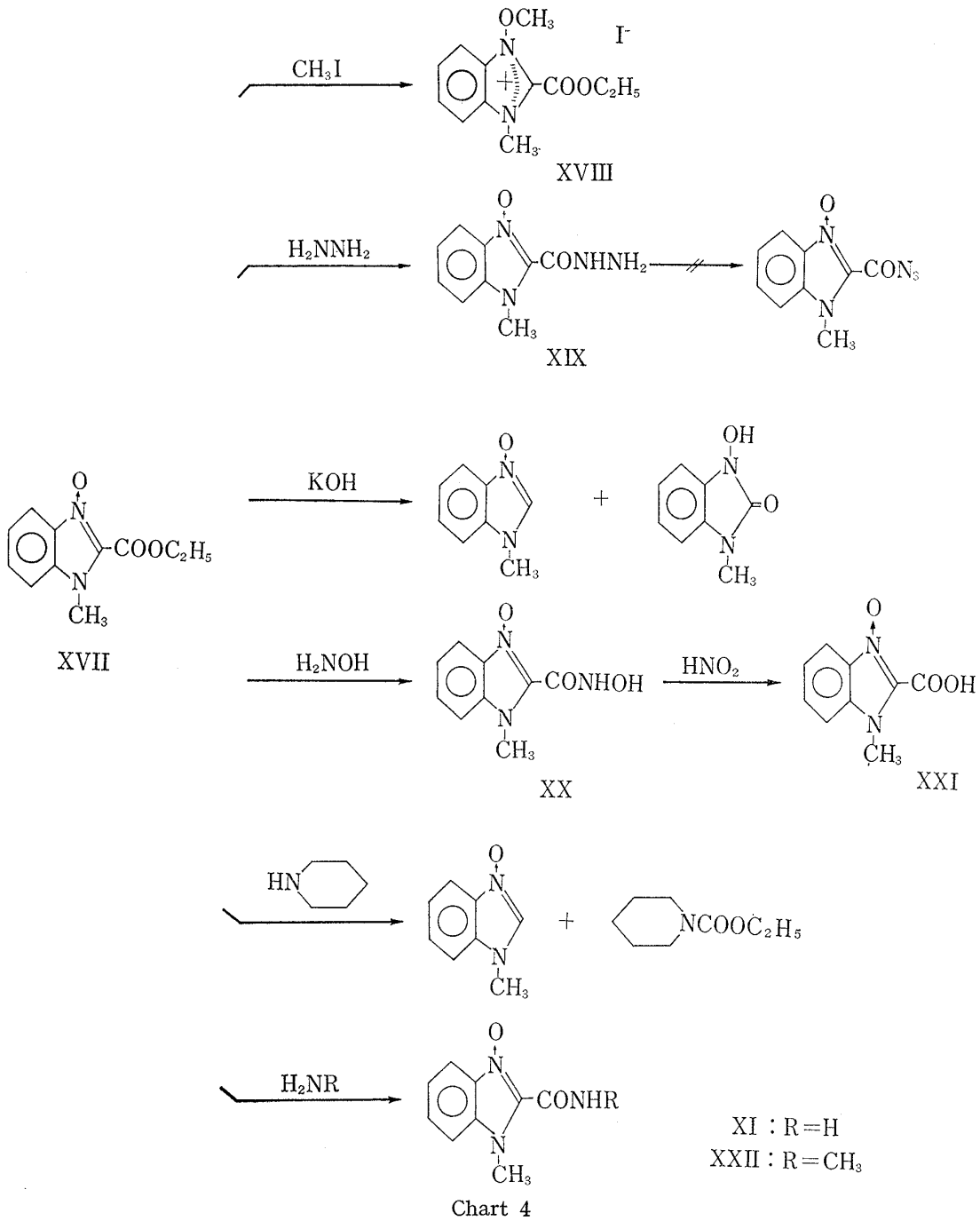


Chart 4

chloric acid or sodium hydroxide, but 3–(hydroxyaminocarbonylmethyl)–1–methylbenzimidazolium salt (XXVIII), which was obtained from XXVII and hydroxylamine, reacted with nitrous acid to give XXV. This betaine was identical in all respect with a specimen derived from XXIII. Heating of XXV with methyl iodide for a long time gave XXVII.

In the present investigation, it is noticeable that several uncommon reactions involving cleavage of the original functional groups at the 2–position of benzimidazole derivatives has been observed: The formation of the 2–hydroxy derivative VII from the nitrile III, imido ester XIII and ester XVII by treatment with alkali, the abnormal aminolysis of XVII and the extraordinary readiness of decarboxylation of the acid XXI.[11] These reactions may be related to the high electron deficiency of the 2–position bearing electron–withdrawing

11) J. Hine, N.W. Burske, M. Hine, and P.B. Langford, *J. Am. Chem. Soc.*, **79**, 1406 (1957).

groups and the stability of the resulting benzimidazole N–oxide carbanion effected by resonance contribution of the system as shown in Chart 5.

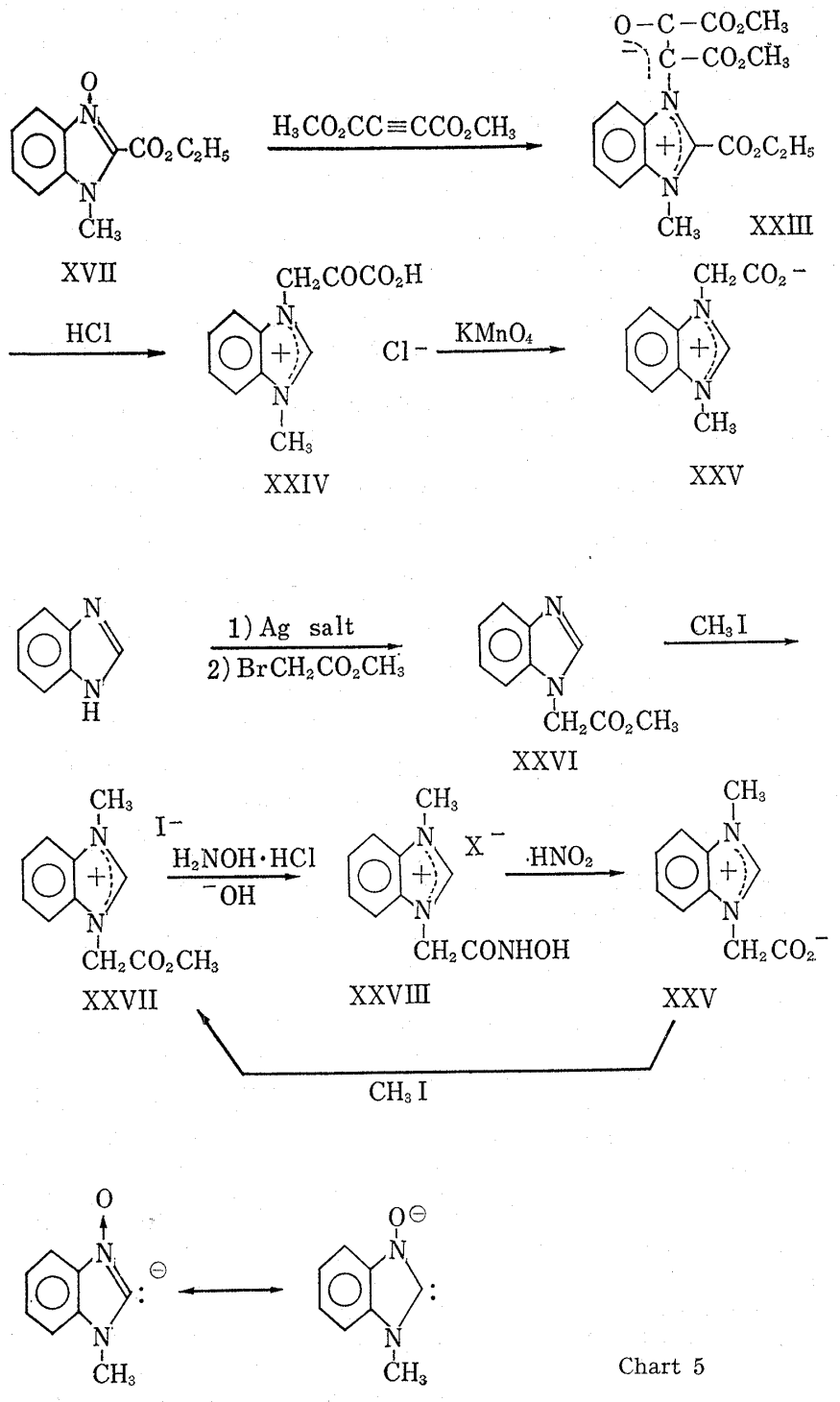


Chart 5

**Experimental**[12]

**1-Methyl-2-benzimidazolecarboxaldehyde Oxime 3-Oxide (II)**——To a suspension of 1,2-dimethylbenzimidazole 3-oxide (prepared from the dihydrate[13] (10.0 g, 0.051 mole) by azeotropic dehydration with

12) 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 with that of a sample prepared by an unequivocal route and if the sample had a melting point, it was also compared by mixed fusion. Infrared spectra were recorded with a Koken Infrared Spectrophotometer, Model IR-S.

13) S. Takahashi and H. Kanō, *Chem. Pharm. Bull.* (Tokyo), **11**, 1375 (1963).

chloroform) in liq. $NH_3$ (*ca.* 100 ml) was added powdered $NaNH_2$ (3.0 g, 0.077 mole) and then added iso-$C_5H_{11}ONO$ (8.9 ml, 0.066 mole) dropwise at $-70°$ during 10 min with stirring. After stirring at the temperature for 1 hr, it was allowed to rise to its boiling point and the resulting deep orange solution was stirred for an additional 2 hr, then the excess $NH_3$ was removed. The residue was dissolved in $H_2O$ (100 ml) and acidified with AcOH to give II as colorless precipitate (10.0 g). Recrystallization from EtOH–$H_2O$ or acetone gave colorless scales, mp 266° (decomp.).

**Reaction of II with Acetic Anhydride**——A solution of II (0.10 g) in $Ac_2O$ (1.0 ml) was heated on a water bath for 1 hr, then evaporated. The residue (0.10 g) was recrystallized from EtOH or AcOEt to give 6-acetoxy-1-methyl-2-benzimidazolecarbonitrile (IV) as colorless needles, mp 184—185°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: $\delta_{C-H}$ 869, 827, 801. *Anal.* Calcd. for $C_{11}H_9O_2N_3$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.66: H, 4.45; N, 29.73.

**Reaction of II with Phosphoryl Chloride**——To a solution of II (100 mg) in $CHCl_3$ (5.0 ml) was added $POCl_3$ (0.50 ml) and the resulting solution was heated under reflux for 2 hr, then evaporated. The residue was neutralized with aq. $NaHCO_3$ solution to give colorless crystals (75 mg), which was recrystallized from EtOH–$H_2O$ to give 6-chloro-1-methyl-2-benzimidazolecarbonitrile (V) as colorless needles, mp 189—190°. IR $\nu_{max}^{Nujol}$ $cm^{-1}$: $\delta_{C-H}$ 881, 820, 782. *Anal.* Calcd. for $C_9H_6N_3Cl$: C, 56.50; H, 3.13; N, 22.00. Found: C, 56.62; H, 3.59; N, 22.27.

**2-(Ethoxycarbonyloxyiminomethyl)-1-methylbenzimidazole 3-Oxide (VI)**——To a solution of II (0.82 g) in aq. NaOH solution (5%, 3.6 ml) was added diethyl pyrocarbonate (0.85 g) at a time with stirring and cooling in an ice-water bath. After stirring at the temperature for 0.5 hr, the resulting crystalline product was collected by filtration (0.90 g) and recrystallized from $CH_2Cl_2$–ether below 40° to give yellow scales, mp 202—204°. *Anal.* Calcd. for $C_{12}H_{13}O_4N_3$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.25; H, 5.15; N, 16.15.

**1-Methyl-2-benzimidazolecarbonitrile 3-Oxide (III)**——A) From II: A solution of II (1.90 g, 0.010 mole) and $Ac_2O$ (1.20 ml, 0.012 mole) in AcOH (40 ml) was heated on a water bath for 1 hr, then evaporated. The tarry residue (1.50 g) was solidified by addition of ether. Recrystallization from AcOEt gave colorless scales, mp 206° (decomp.). *Anal.* Calcd. for $C_9H_7ON_3$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.72; H, 4.36; N, 24.25.

B) From VI: A solution of VI (1.00 g) in acetone (20 ml) was heated under reflux for 0.5 hr, then evaporated. The residue was recrystallized from acetone to give colorless scales (0.55 g). VI also decomposed to III by only allowing to stand at room temperature within a week.

**1-Methyl-2-benzimidazolol 3-Oxide (VII)**——A solution of III (0.50 g) and KOH (0.70 g) in MeOH (7.0 ml) was heated under reflux for 1 hr, then evaporated. The residue was dissolved in $H_2O$ and neutralized with HCl to give colorless crystals. Recrystallization from acetone gave colorless prisms (0.3 g), mp 206—207°. *Anal.* Calcd. for $C_8H_8O_2N_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.83; H, 4.98; N, 17.54.

**3-Methoxy-1-methyl-2-benzimidazolinone (VIII)**——To a suspension of VII (0.30 g) in $CHCl_3$ (6.0 ml) and MeOH (3.0 ml) was added a solution of $CH_2N_2$ in ether and the resulting solution was allowed to stand at room temperature overnight. After evaporation, the residue was recrystallized from ether–*n*-pentane to give colorless prisms (0.25 g), mp 50—51°. *Anal.* Calcd. for $C_9H_{10}O_2N_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.65; H, 5.91; N, 15.60.

**Hydrogenolysis of VII**——A solution of VII (100 mg) in EtOH (10 ml) was shaken in $H_2$ atmosphere over Raney Ni (W-5, from 0.1 g alloy), $H_2$ of the calculated amount being absorbed during *ca.* 10 min. The catalyst was filtered off and the filtrate was evaporated to give a colorless product which was recrystallized from AcOEt (70 mg, mp 195—196°) and identified with 1-methyl-2-benzimidazolinone.[14]

**Reaction of III and Sodium Methylmercaptide**——To a solution of III (0.10 g) in MeOH (5.0 ml) was added a solution of $CH_3SNa$ in MeOH (20%, 0.30 ml) and the resulting solution was heated under reflux for 3 hr, then evaporated. The residue was separated with preparative TLC ($Al_2O_3$ with acetone) to give 1-methyl-2-benzimidazolecarboxamide 3-oxide (0.03 g) and several unidentified products.

**6-Acetoxy-1-methyl-2-benzimidazolecarbonitrile (IV)**——A solution of III (4.0 g) in $Ac_2O$ (20 ml) was heated on a water bath for 1 hr, then evaporated. Recrystallization from EtOH gave colorless prisms (3.8 g). This compound was identical with the above obtained one.

**6-Hydroxy-1-methyl-2-benzimidazolecarbonitrile (IX)**——A solution of IV (0.50 g) and KOH (0.3 g) in abs. EtOH (10 ml) was heated under reflux for 1 hr, then evaporated. The residue was dissolved in $H_2O$ and acidified with AcOH to give slightly yellow precipitate, which was collected by filtration (0.3 g) and recrystallized from DMSO–EtOH to give colorless short prisms, mp >250°. *Anal.* Calcd. for $C_9H_7ON_3$: C, 62.42; H, 4.07; N, 24.27. Found: C, 62.50; H, 4.24; N, 24.52.

**L-2-(6-Hydroxy-1-methyl-2-benzimidazolyl-$\Delta^2$-thiazoline-4-carboxylic Acid (X)**——To a solution of L-cystine (360 mg) in liq. $NH_3$ (70 ml) was added Na in a small pieces until a blue color persisted for 10 min with stirring (*ca.* 0.2 g) in $N_2$ atmosphere. After destruction the excess Na by addition of $NH_4Cl$, the $NH_3$ was allowed to evaporate in a stream of $N_2$. The residue was dissolved in $H_2O$ (10 ml) saturated with $N_2$ and the pH of the solution was adjusted to *ca.* 8 with 6 N HCl (*ca.* 3 ml).

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

A solution of IX (345 mg) and NaOH (80 mg) in $H_2O$ (10 ml) was added to the solution of cysteine obtained above, with stirring at room temperature in $N_2$ atmosphere. After stirring for an additional 3 hr and then standing overnight, the resulting solution containing a small amount of precipitate was filtered and the filtrate was acidified to pH *ca.* 3 with 1 N HCl to give a crystalline product (0.60 g). Recrystallization from EtOH–$H_2O$ gave white prisms, mp 194° (decomp.). $[\alpha]_D$ +5.5° (±0.1) ($c$=1.015 in DMF). *Anal.* Calcd. for $C_{12}H_{11}O_3N_3S$: C, 51.99; H, 4.00; N, 15.16; S, 11.54. Found: C, 51.97; H, 4.14; N, 15.16; S, 11.47.

**Reaction of III with Phosphoryl Chloride**——This reaction was carried out by the same procedure as for the reaction of II with $POCl_3$. 6-Chloro-1-methyl-2-benzimidazolecarbonitrile (V) was obtained by this reaction. Yield, 90%. This compound was identical with a sample obtained above.

**6-Chloro-1-methyl-2-benzimidazolecarbonitrile (V)**——A suspension of 5-chloro-2-nitro-N-methylaniline[15] (3.5 g) in acetic formic anhydride[16] (prepared from $Ac_2O$ 10.0 ml, HCOOH (98%) 4.0 ml) was warmed at 50° for 0.5 hr and allowed to stand overnight at room temperature, then evaporated. The residue was recrystallized from ether to give pale yellow plates (3.6 g), mp 72—74°. *Anal.* Calcd. for $C_8H_7O_3N_2Cl$: (5′-chloro-2′-nitro-N-methylformanilide): C, 44.76; H, 3.30; N, 13.06. Found: C, 44.74; H, 3.34; N, 13.20.

To a solution of $NaBH_4$ (2.0 g) in $H_2O$ (20 ml) were added a suspension of Pd–$BaSO_4$ (5%, 0.50 g) in $H_2O$ (5.0 ml)at a time and then a solution of the formanilide obtained above (2.0 g) in dioxane (20 ml) with stirring at room temperature during 15 min. After the addition, the stirring was continued for an additional 15 min. Removal of the catalyst and the solvents gave a colorless crystalline product, which was recrystallized from AcOMe to give colorless prisms (1.5 g), mp >250°. *Anal.* Calcd. for $C_8H_7ON_2Cl\cdot 2H_2O$ (6-chloro-1-methylbenzimidazole 3-oxide): C, 43.94; H, 5.08; N, 12.81. Found: C, 43.93; H, 5.16; N, 12.37.

A suspension of the N-oxide obtained above (1.0 g) in EtI (10 ml) was heated under reflux for 2 hr, then evaporated. The residue was extracted with cold $H_2O$ (5 ml) and the extract was evaporated. Recrystallization of the residue from EtOH–AcOEt gave colorless needles (0.6 g), mp 130° (decomp.). *Anal.* Calcd. for $C_{10}H_{12}ON_2ClI$ (6-chloro-3-ethoxy-1-methylbenzimidazolium iodide): C, 35.47; H, 3.57; N, 8.28. Found: C, 35.63; H, 3.61; N, 8.21.

To a solution of the above obtained quaternary salt (0.20 g) in $H_2O$ (2.0 ml) was added a solution of KCN (0.10 g) in $H_2O$ (1.0 ml) dropwise. A crystalline product which formed immediately was collected and recrystallized from EtOH–$H_2O$ to give V as white prisms (0.11 g), mp 194° (decomp.).

This compound was identified with a sample obtained from III.

**1-Methyl-2-benzimidazolethiocarboxamide 3-Oxide (XII)**——$H_2S$ gas was passed through a solution of III (0.20 g) in MeOH containing $NH_3$(saturated at 0°, 30 ml) for 1 hr at room temperature. After standing for 2 hr, the resulting orange solution was concentrated to *ca.* 5 ml and cooled to give a crystalline product (0.2 g), which was collected and recrystallized from acetone to give yellow prisms, mp 176—178°. *Anal.* Calcd. for $C_9H_9ON_3S$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.46; H, 4.44; N, 20.39.

**1-Methyl-2-benzimidazolecarboxamide 3-Oxide (XI) from III**——To a solution of III (0.20 g) in acetone (12 ml) were added $H_2O_2$ (30%, 3.0 ml) and aq. $K_2CO_3$ solution (10%, 8.6 ml), with stirring at room temperature. After stirring for 2 hr, the reaction mixture was allowed to stand overnight and a resulting crystalline product was collected. Recrystallization from MeOH gave colorless prisms or needles (0.19 g), mp 251° (decomp.). *Anal.* Calcd. for $C_9H_9O_2N_3$: C, 56.54; H, 4.75; N 21.98. Found: C, 56.69; H, 5.00; N, 21.95.

**Reaction of XI with Hydrochloric Acid**——A solution of XI (100 mg) in 6 N HCl (3.0 ml) was heated on a water bath for 1 hr, then evaporated. The residue was dissolved in $H_2O$ and neutralized to give colorless crystals, which was identified with the starting material (*ca.* 0.1 g). When the heating was continued for 8 hr, 1-methylbenzimidazole 3-oxide[13] was obtained (0.07 g).

**Reaction of XI with Nitrous Acid**——A) $NaNO_2$–$H_2SO_4$: To a solution of XI (100 mg) in conc. $H_2SO_4$ (0.20 ml) was added a solution of $NaNO_2$ (70 mg) in $H_2O$ (0.30 ml) dropwise with stirring and cooling in an ice-water bath. After stirring for an additional 1 hr, the resulting reaction mixture was diluted with $H_2O$ to give a crystalline product, which was dissolved in the solution by dilution and then precipitated again. The precipitate was collected and identified with the starting material (*ca.* 0.1 g).

B) AmONO–HCl: To a suspension of XI (191 mg) in abs. EtOH (20 ml) was added a solution of iso-$C_5H_{11}ONO$ (120 mg) in abs. EtOH (5.0 ml) with stirring and cooling in an ice-water bath, and added HCl–EtOH (20%, 0.20 ml) dropwise. The resulting mixture was stirred at room temperature for 8 hr, then evaporated. To the residue was added $H_2O$ (*ca.* 5 ml) and aq. $NH_3$ solution (10%, *ca.* 1 ml), and the precipitate was collected by filtration (185 mg), which was identical with the starting material.

**Reaction of XI with Potassium Hydroxide**——A solution of XI (0.10 g) and KOH (0.10 g) in MeOH (3.0 ml) was heated under reflux for 3 hr, then evaporated. The residue was dissolved in $H_2O$ and neutralized with 2 N HCl to give a colorless crystalline product (*ca.* 0.1 g), which was identified with the starting material. The same result was obtained by treating at 100° for 2 hr in a sealed tube.

15) J.W. Clark-Lewis and G.F. Katekar, *J. Chem. Soc.*, **1959**, 2825.
16) C.W. Huffman, *J. Org. Chem.*, **23**, 727 (1958).

**Attempted Hofmann Reaction of XI**——XI (0.19 g) was added to a solution of aq. NaOCl solution (12%, 0.80 g), NaOH (0.04 g) in $H_2O$ (0.80 ml) and the mixture was stirred at room temperature for 0.5 hr. The resulting solution was added dropwise with stirring to a boiling solution of aq. NaOH solution (20%, 0.5 ml). After stirring and heating for an additional 0.5 hr, the dark brown solution was evaporated and the residue was extracted with EtOH. Removal of the solvent gave only intractable resinous substances.

**Methyl 1-Methyl-2-benzimidazolecarboimidate 3-Oxide (XIIIa)**——This compound was obtained from III and MeOH by the same procedure as for the synthesis of the α-ethoxy compound mentioned below. Yield 60% (Method A, stirring 5 hr) or 90% (Method B). Recrystallization from acetone gave colorless prisms, mp 187—188°. *Anal.* Calcd. for $C_{10}H_{11}O_2N_3$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.66; H, 5.26; N, 20.23.

**Ethyl 1-Methyl-2-benzimidazolecarboimidate 3-Oxide (XIIIb)**——A) To a solution of III (0.10 g) in EtOH (2.0 ml) was added with stirring a solution of NaOH in EtOH (0.1%, 1.0 ml) and the resulting solution was allowed to stand for 1 hr at room temperature, then evaporated. The residue was recrystallized from acetone to give colorless prisms (0.06 g), mp 154—155°. *Anal.* Calcd. for $C_{11}H_{13}O_2N_3$: C, 60.26; H, 5.98; N, 19.15. Found: C, 59.94; H, 6.16; N, 19.10.

B) A solution of III (1.0 g) in EtOH (50 ml) was heated under reflux for 0.5 hr, then evaporated. The residue was recrystallized from acetone to give colorless prisms (1.1 g). This compound was identical with a specimen obtained above.

**Reaction of XIIIb with Potassium Hydroxide**——To a solution of XIIIb (0.20 g) in EtOH (1.0 ml) was added a solution of KOH (0.15 g) in EtOH (1.0 ml) and the resulting solution was heated under reflux for 2 hr, then evaporated. The residue was dissolved in $H_2O$ and neutralized with 6 N HCl to give a crystalline product (0.15 g). Recrystallization from AcOEt gave VII as colorless prisms, mp 205—206°, which was identified with a sample obtained above.

**1-Methyl-2-benzimidazolecarboimidohydrazide 3-Oxide (XIV)**——A solution of XIIIb (0.10 g) and $NH_2$-$NH_2 \cdot H_2O$ (80%, 0.10 ml) in EtOH (3.0 ml) was heated under reflux for 3 hr, then evaporated. The residue was recrystallized from iso-PrOH to give pale yellow prisms (0.09 g), mp 220° (decomp.). *Anal.* Calcd. for $C_9H_{11}ON_5$: C, 52.67; H, 5.40; N, 34.13. Found: C, 52.97; H, 5.69; N, 34.02.

**2-(5-Tetrazolyl)-1-methylbenzimidazole 3-Oxide (XV)**——To a solution of XIV (0.20 g) in 2 N HCl (10 ml) was added a solution of $NaNO_2$ (0.10 g) in $H_2O$ (0.30 ml) dropwise with stirring and cooling in an ice-water bath. A crystalline product which appeared immediately was collected by filtration and recrystallized from DMSO to give colorless prisms (0.15 g), mp >250°. *Anal.* Calcd. for $C_9H_8ON_6$: C, 50.00; H, 3.73; N, 38.88. Found: C, 49.73; H, 3.69; N, 38.91.

**1,1′-Dimethyl-2,2′-bibenzimidazole 3-Oxide (XVI)**——A solution of XIIIb (0.22 g) and N-methyl-*o*-phenylenediamine dihydrochloride (0.19 g) in MeOH (2.0 ml) was heated under reflux for 2 hr, then evaporated. The residue was dissolved in $H_2O$, neutralized with $NaHCO_3$ and extracted with $CHCl_3$. The extract was purified with preparative TLC ($Al_2O_3$, with $CHCl_3$) to give slightly yellow crystals (0.17 g). Recrystallization from AcOEt gave XVI, mp 120—125°, which was identical with a sample prepared from 1-methylbenzimidazole 3-oxide.[3]

**Reaction of XIIIb with Concentrated Hydrochloric Acid**——A solution of XIIIb (0.20 g) in conc. HCl (5.0 ml) was heated for 2 hr on a water bath, then evaporated. The residue was dissolved in $H_2O$, neutralized with $NaHCO_3$ and evaporated again. This residue was extracted with EtOH and recrystallized from AcOEt to give white prisms (0.12 g), which was proved to be 1-methylbenzimidazole 3-oxide.[13]

**Ethyl 1-Methyl-2-benzimidazolecarboxylate 3-Oxide (XVII)**——A solution of XIIIb (1.00 g) in 3 N HCl (25 ml) was heated at 50° for 1 hr, then evaporated. The residue was dissolved in $H_2O$ (10 ml), neutralized with $NaHCO_3$ and extracted with $CHCl_3$. Removal of the solvent gave a colorless crystalline product which was recrystallized from acetone to give colorless prisms or needles (0.75 g), mp 148—150°. *Anal.* Calcd. for $C_{11}H_{12}O_3N_2$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.65; H, 5.78; N, 12.52.

**Methyl 1-Methyl-2-benzimidazolecarboxylate 3-Oxide**——This compound was obtained from XIIIa by the same procedure as for the synthesis of XVII. Recrystallization from AcOMe gave colorless short prisms, mp 160° (decomp.). Yield 90%. *Anal.* Calcd. for $C_{10}H_{10}O_3N_2 \cdot H_2O$: C, 53.57; H, 5.39; N, 12.50. Found: C, 53.48; H, 5.47; N, 12.52.

**2-Ethoxycarbonyl-3-methoxy-1-methylbenzimidazolium Iodide (XVIII)**——A suspension of XVII (0.10 g) in $CH_3I$ (0.5 ml) was heated under reflux for 3 min then evaporated. The residue was recrystallized from EtOH-AcOEt to give yellow prisms (0.10 g), mp 150° (decomp.). *Anal.* Calcd. for $C_{12}H_{15}O_3N_2I$: C, 39.79; H, 4.18; N, 7.74. Found: C, 39.83; H, 4.31; N, 7.72.

**1-Methyl-2-benzimidazolecarboxamide 3-Oxide (XI) from XVII**——A solution of XVII (50 mg) in EtOH (1.0 ml) and $NH_3$-EtOH (saturated at 0°, 0.5 ml) was heated in a sealed tube on a water bath for 1 hr. After cooling, a precipitated product was collected (45 mg), which was identical with XI prepared from III.

**1-Methyl-2-benzimidazolecarbohydrazide 3-Oxide (XIX)**——To a solution of XVII (0.50 g) in EtOH (10 ml) was added $NH_2NH_2 \cdot H_2O$ (90%, 0.50 ml) dropwise with stirring. A crystalline product which precipitated immediately was collected by filtration (0.45 g) after standig for 10 min at room temperature and recry-

stallized from EtOH to give colorless short prisms, mp 228—230°. *Anal.* Calcd. for $C_9H_{10}O_2N_4$: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.67; H, 4.95; N, 27.12.

**Reaction of XIX with Nitrous Acid**——To a suspension of XIX (206 mg) in abs. EtOH (50 ml) was added a solution of iso-$C_5H_{11}ONO$ (120 mg) in EtOH (5 ml) with stirring and cooling in an ice–water bath, then added HCl–EtOH (20%, 0.20 ml) dropwise. The resulting solution was allowed to stand overnight at room temperature, and refluxed for 2 hr, then evaporated. The residue was dissolved in $H_2O$, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. Removal of the solvent gave colorless crystals (180 mg), which was recrystallized from acetone, mp 148—150°, and proved to be XVII.

**Reaction of XVII with Potassium Hydroxide**——A solution of XVII (100 mg) and KOH (50 mg) in EtOH (1.0 ml) was heated under reflux for 2 hr, then evaporated. The residue was dissolved in $H_2O$, neutralized with AcOH, and evaporated again. This residue was subjected to preparative TLC ($Al_2O_3$, with EtOH+$CHCl_3$=1:10) to give 1–methylbenzimidazole 3–oxide (58 mg) and VII (19 mg). These compounds were identified with their authentic specimens, respectively.

**Reaction of XVII with Hydrochloric Aicd**——This reaction was carried out by the same procedure as for the reaction of XIIIb with hydrochloric acid. 1–Methylbenzimidazole 3–oxide[13] (0.11 g) was obtained from XVII (0.20 g) by this reaction.

**1-Methyl-2-benzimidazolehydroxamic Acid 3-Oxide (XX)**——To a solution of XVII (110 mg) in EtOH (5.0 ml) was added a solution of $H_2NOH \cdot HCl$ (70 mg) and $NaHCO_3$ (160 mg) in $H_2O$ (2.0 ml) with stirring at room temperature. After stirring for an additional 1 hr, the solution was evaporated, the residue was dissolved in $H_2O$ and acidified with AcOH to give colorless crystals (0.10 g). Recrystallization from MeOH gave colorless prisms, mp 245° (decomp.) (turn brown at *ca.* 230°). *Anal.* Calcd. for $C_9H_9O_3N_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.38; H, 4.51; N, 20.49.

**1-Methyl-2-benzimidazolecarboxylic Acid 3-Oxide (XXI)**——To a suspension of XX (100 mg) in 1 N HCl (3.0 ml) was added a solution of $NaNO_2$ in $H_2O$ (*ca.* 20%) dropwise with stirring and cooling in an ice–water bath until starch–iodide paper turned blue. The compoud XX was dissolved in the solution and then a crystalline product was precipitated. After stirring and cooling for an additional 2 hr, the product was collected by filtration and washed with $H_2O$ (70 mg), which was purified by reprecipitating from aq. $NaHCO_3$ solution with AcOH, to give colorless needles, mp 70° (decomp.). *Anal.* Calcd. for $C_9H_8O_3N_2$: C, 56.25; H, 4.20; N, 14.58. Found: C, 55.88; H, 4.34; N, 14.82.

**1,N-Dimethyl-2-benzimidazolecarboxamide 3-Oxide (XXII)**——A solution of XVII (50 mg) in MeOH (0.5 ml) and $MeNH_2$–MeOH (saturated at 0°, 0.06 ml) was heated in a sealed tube at 70° for 2 hr, then evaporated. The residue (40 mg) was recrystallized from acetone to give colorless prisms, mp 184—185°. *Anal.* Calcd. for $C_{10}H_{11}O_2N_3$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.83; H, 5.61; N, 20.53.

**Reaction of XVII with Piperidine**——A solution of XVII (150 mg) and piperidine (0.07 ml) in abs. EtOH (1.0 ml) was heated at 60° for 2 hr, then evaporated (at *ca.* 20 mmHg, bath temperature 30°). The residue gave white precipitate (105 mg) by addition of ether (5.0 ml), which was proved to be 1–methylbenzimidazole 3–oxide.[13] From the filtrate, pale yellow oily substance was obtained (50 mg), which was purified by distillation using a small sublimation apparatus, and proved to be ethyl 1–piperidylcarboxylate. Identification of this urethan was also made by comparison of the retention time of gas–liquid chromatography with that of the authentic specimen prepared from piperidine and ethyl chloroformate (Apparatus: Varian Aerograph Model 1520–1B. Column: each stainless steel 5′×1/8″ O.D., 5% liquid phase on chromosorb W (60—80 mesh). Temperature: injector 200°, column 120°, detector (FID) 200°. Carrier Gas: $N_2$ 20 ml/min. Retention Time (adjusted): SE–30 2.02 min, PDEAS 1.27 min).

**3-(α,β-Dimethoxycarbonyl-β-hydroxyvinyl)-2-ethoxycarbonyl-1-methylbenzimidazolium Betaine (XXIII)**——To a solution of XVII (100 mg) in $CHCl_3$ (3.0 ml) was added a solution of dimethyl acetylenedicarboxylate (70 mg) in $CHCl_3$ (1.0 ml) dropwise with stirring and cooling in an ice–water bath, then the solution was allowed to stand at room temperature for 0.5 hr. The resulting orange solution was evaporated and the residue gave a crystalline product (130 mg) by addition of AcOEt. Recrystallization from AcOEt gave yellow microcrystals, mp 192—193°. *Anal.* Calcd. for $C_{17}H_{18}O_7N_2$: C, 56.35; H, 5.01; N, 7.73. Found: C, 56.05; H, 4.88; N, 7.55.

**3-Hydroxyoxalylmethyl-1-methylbenzimidazolium Chloride (XXIV)**——A solution of XXIII (200 mg) in 6 N HCl (2.0 ml) was heated under reflux for 3 hr, then evaporated. The residue was recrystallized from $H_2O$–acetone gave colorless plates (110 mg), mp 140° (decomp.). *Anal.* Calcd. for $C_{11}H_{11}O_3N_2Cl \cdot 2H_2O$: C, 45.44; H, 5.20; N, 9.64. Found: C, 45.65; H, 5.18; N, 9.74.

**3-Carboxymethyl-1-methylbenzimidazolium Betaine (XXV)**——To a solution of XXIV (180 mg) in $H_2O$ (5.0 ml) was added finely ground $KMnO_4$ with stirring at room temperature until the color of the oxidizing agent lasted for a time (*ca.* 110 mg). After removal of $MnO_2$ and $H_2O$, the residue was extracted with abs. EtOH to give a crystalline product, which was recrystallized from EtOH–AcOEt to give colorless prisms, mp >250°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2 \cdot H_2O$: C, 57.68; H, 5.81; N, 13.46. Found: C, 58.03; H, 5.86; N, 13.61.

**Methyl 1-Benzimidazoleacetate (XXVI)**——To a solution of $AgNO_3$ (17.0 g, 0.10 mole) in $H_2O$ (30 ml) were added EtOH (100 ml), then aq. $NH_3$ solution (30%) until the first precipitate dissolved (*ca.* 15 ml).

The resulting solution was added to a solution of benzimidazole (11.8 g, 0.10 mole) in EtOH (100 ml) to give white precipitate, which was collected by filtration and dried (20 g). To a suspension of the silver salt of benzimidazole (16.7 g, 0.074 mole, finely ground) in toluene (130 ml) was added methyl bromoacetate (11.4 g, 0.074 mole) dropwise with stirring and heating under reflux and, after the addition, stirring and heating were continued for 5 hr. The resulting solution was separated by decantation from the tarry residue and evaporated to give brown tar (4.3 g), which was chromatographed on alumina with $CHCl_3$ to give a crystalline product (2.7 g). Recrystallization from $CCl_4$ gave colorless needles, mp 85—86°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.32; H, 5.47; N, 14.45.

**3-(Methoxycarbonylmethyl)-1-methylbenzimidazolium Iodide (XXVII)**——A suspension of XXVI (1.8 g) in $CH_3I$ (5.0 ml) was heated under reflux for 1 hr, then evaporated. The residue (2.8 g) was recrystallized from MeOH–AcOMe to give colorless needles, mp 156—157°. *Anal.* Calcd. for $C_{11}H_{13}O_2N_2I$: C, 39.78; H, 3.95; N, 8.43. Found: C, 39.62; H, 4.09; N, 8.04.

**Attempted Hydrolysis of XXVII to XXV**——A) With HCl: A solution of XXVII (0.50 g) in 6 N HCl (5.0 ml) was heated under reflux for 5 hr, then evaporated. The residue was dissolved in $H_2O$, neutralized with aq. $NaHCO_3$ solution and evaporated again. This residue was extracted with abs. EtOH and the starting material (0.43 g) was recovered.

B) With NaOH: A solution of XXVII (0.10 g) and NaOH (0.20 g) in $H_2O$ (1.0 ml) and EtOH (3.0 ml) was heated under reflux for 2 hr, then evaporated. The residue was extracted with abs. EtOH, but no materials which showed absorption band in the reagion of 1600—1800 $cm^{-1}$ in infrared spectra, were obtained.

**3-Carboxymethyl-1-methylbenzimidazolium Betaine (XXV) from XXVII**——A solution of XXVII (150 (mg) and $H_2NOH \cdot HCl$ (70 mg) in MeOH (2.0 ml) was made alkaline with a solution of KOH in MeOH (10%) and allowed to stand for 1 hr at room temperature. After evaporation, the residue was extracted with abs. EtOH to give a crystalline poduct (100 mg) which was recrystallized from EtOH to give colorless short prisms, mp 140° (decomp.).[17]

To a solution of thus obtained hydroxamic acid (60 mg) in 1 N HCl (4.0 ml) was added dropwise a solution of $NaNO_2$ in $H_2O$ with stirring and cooling in an ice–water bath until starch–iodide paper showed blue color (5%, *ca.* 0.4 ml). Immediately, dark violet precipitate appeared. After stirring and cooling for an additional 10 min, the resulting mixture was filtered and the filtrate was evaporated. The residue was dissolved in $H_2O$, neutralized with $NaHCO_3$ and the solution was evaporated again. This residue was extracted with abs. EtOH to give colorless crystals (35 mg), which was recrystallized from EtOH–AcOEt, mp >250°, and identified with a specimen obtained above.

**3-(Methoxycarbonylmethyl)-1-methylbenzimidazolium Iodide (XXVII) from XXV**——A suspension of XXV (15 mg) in $CH_3I$ (1.0 ml) was refluxed for 15 hr, then evaporated. The residue (20 mg) was recrystallized from MeOH–AcOMe (mp 156—157°) and identified with a specimen prepared from methyl 1-benzimidazoleacetate and $CH_3I$.

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17) This compound is assumed to be a mixture of the iodide and the chloride by its analytical value.