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178. Shirō Takahashi and Hideo Kanō: Benzimidazole N-Oxides. IV.*1 1,3-Dipolar Cycloaddition Reaction with 1-Methylbenzimidazole 3-Oxide.*2

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Many kinds of 1,3-dipolar cycloaddition reactions have been explored recently,[1] and heteroaromatic N-oxides are regarded as a potential 1,3-dipolar system, reacting with appropriate dipolarophiles to give the products which have conceivably arisen from initial cycloadducts. The 1,3-dipolar cycloaddition of phenanthridine N-oxide with phenyl isocyanate was first reported by Hayashi.[2] Lately several examples in pyridine N-oxide, isoquinoline N-oxide and phenanthridine N-oxide have been added by Huisgen.[1,3]

As a part of our program of studies on benzimidazole N-oxide, the present investigation was undertaken to see if 1-methylbenzimidazole 3-oxide (I) could behave as a 1,3-dipole; this N-oxide having a five-membered heteroaromatic system unlike the above cited examples.

Reaction of I with phenyl isocyanate in chloroform at room temperature gave 1-methy-2-anilinobenzimidazole (II), which would have arisen from the initial cycloadduct by ring cleavage and subsequent decarboxylation. By the same procedure, II was also obtained from I and phenyl isothiocyanate. In this reaction, the evolution of carbonyl sulfide was confirmed by converting it into ammonium thiocarbamate. The product (II) obtained above was identified with a sample prepared from 1-methyl-2-chlorobenzimidazole and aniline.

I reacted vigorously with dimethyl acetylenedicarboxylate and methyl propiolate in chloroform at room temperature to give dimethyl 1-methyl-2-benzimidazoloxalacetate (III) and methyl α-formyl-1-methyl-2-benzimidazolacetate (VII), respectively, in good yields.

The structures of these compounds were confirmed by the following methods. The presence of an enolizable carbonyl in these compounds was deduced by the positive color reaction with ferric chloride. By alkaline hydrolysis in methanol, III gave oxalic acid and 1-methyl-2-benzimidazolacetic acid (IV), which was readily decarboxylated to 1,2-dimethylbenzimidazole (V). By treating III with hydroxylamine, methyl 1-methyl-2-benzimidazolacetate (VI) and oxalylhydroxamic acid were obtained. Alkaline hydrolysis of the methyl ester VI also gave the acid (IV).

Similarly, VII was also converted into IV by alkaline hydrolysis and to VI by treatment with hydroxylamine.

Reaction of the above-obtained ester VI with dimethyl oxalate or methyl formate in the presence of sodium methoxide in ether reproduced III or VII, respectively.

Both III and VII showed no signal peak characteristic of the methine proton in the nuclear magnetic resonance spectra (in $CDCl_3$) but showed absorption bands assignable

*1 Part III. S. Takahashi, H. Kanō: This Bulletin, **12**, 783 (1964).

*2 The outline of this work was published in Tetrahedron Letters, No. 25, 1687 (1963).
Although, in the communication, the reaction of 1-methylbenzimidazole 3-oxide with carbon disulfide was reported as a 1,3-dipolar cycloaddition reaction, an alternative explanation of this reaction through the intermediate $\rangle\overset{+}{N}-O-C\langle^{S}_{S}{}^{-}$ (cf. M. Hamana, *et al.*: This Bulletin, **10**, 969 (1962)) is also probable and this reaction has been omitted in the present paper.

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1) R. Huisgen: Angew. Chem., **75**, 604 (1963).
2) E. Hayashi: Yakugaku Zasshi, **81**, 1030 (1961).
3) H. Seidl, R. Huisgen: Tetrahedron Letters, No. 29, 2023 (1963).

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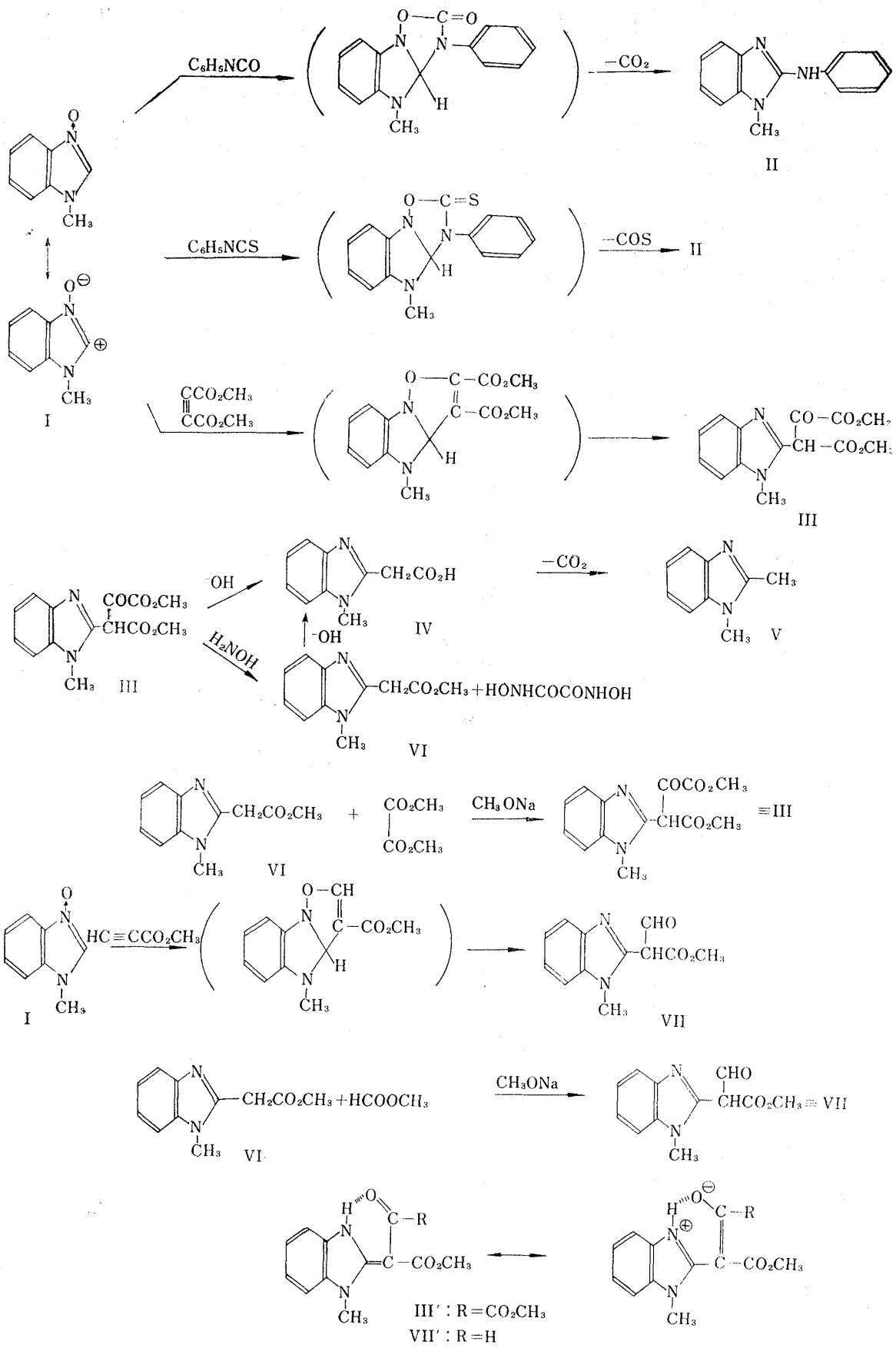

Chart 1.

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to NH or OH stretching band in the infrared spectra (ca. 3305 cm^{-1} and 3200~2400 cm^{-1}, respectively in Nujol), so these structures may be expressed by the isomeric structures of Ⅲ and Ⅶ (Ⅲ′ and Ⅶ′), respectively.

When I was heated with benzonitrile, an anticipated product 1-methyl-2-benzamidobenzimidazole (Ⅷ) along with 1,1′-dimethyl-2,2′-bibenzimidazole 3-oxide (Ⅸ), and a small amount of 1,1′-dimethyl-2,2′-bibenzimidazole (X) was obtained. Since the last two compounds can be produced by self-condensation of I,*1 it would involve the competitive reactions between cycloaddition and self-condensation. The ratio of Ⅷ to Ⅸ (1:4) suggests that the reaction rate of I with benzonitrile is slower than that of self-condensation of I.

The product Ⅷ was identified with a sample prepared from 1-methyl-2-aminobenzimidazole and benzoyl chloride in the presence of alkali.

I was treated with phenyl isocyanide in chloroform at the reflux temperature and gave Ⅱ and 1-methylbenzimidazole. The formation of Ⅱ may be rationalized by assuming that phenyl isocyanide is oxidized by the N-oxide to phenyl isocyanate which reacts with the remaining N-oxide to give Ⅱ.

Deoxygenation of pyridine N-oxide with phenyl isocyanide in the presence of halogen was recently reported.[4]

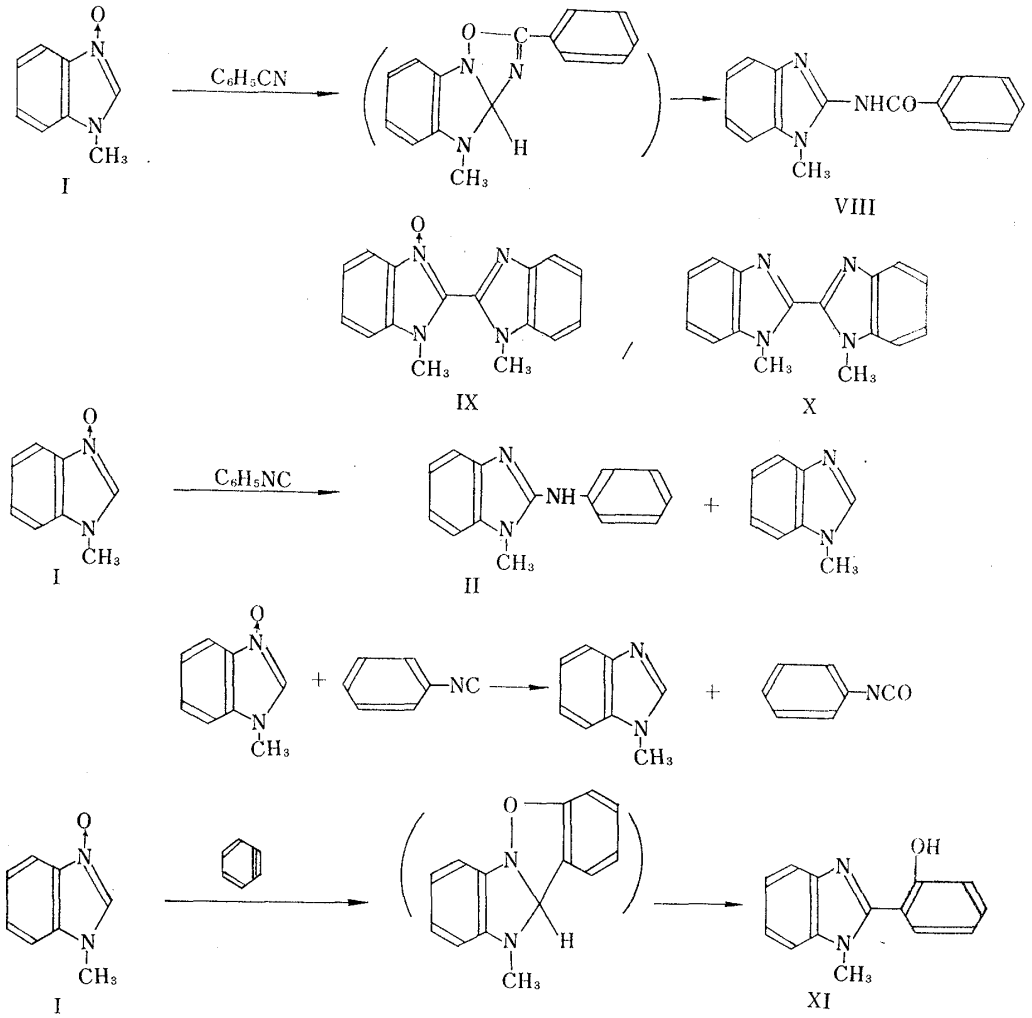

Chart 2.

4) H. W. Johnson, Jr., P. H. Daughhetee, Jr. : J. Org. Chem., **29**, 246 (1964).

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I reacted with benzyne produced by heating benzenediazonium-2-carboxylate[5] in *tert*-butanol to give 1-methyl-2-(*o*-hydroxyphenyl)benzimidazole (Ⅺ), which was identified with a sample prepared by heating N-methyl-*o*-phenylenediamine and salicylic acid in the presence of phosphorous pentoxide.

In the reaction of I with these dipolarophiles, no anticipated cycloadducts could be isolated, but it seems likely that the initial formation of the cycloadducts is followed by ring opening to stable rearomatized products. From the present experiments and the available data[1~3] on the reaction conditions of cycloaddition in six-membered heteroaromatic N-oxides, I seems to be more reactive than six-membered heteroaromatic N-oxides.

Experimental*4

Reaction of 1-Methylbenzimidazole 3-Oxide (I) with Phenyl Isocyanate——To a solution of I (I′, 0.50 g., 0.0027 mole) in $CHCl_3$ (3.0 ml.) was added phenyl isocyanate (0.33 g., 0.0028 mole) dropwise with shaking and cooling. After standing for 1 hr. at room temperature, the resulting crystalline product was collected by filtration (0.44 g.). Recrystallization from $CHCl_3$ gave colorless short prisms, m.p. 201~202°. *Anal.* Calcd. for $C_{14}H_{13}N_3$ (1-Methyl-2-anilinobenzimidazole)[6] (Ⅱ): C, 75.31; H, 5.87; N, 18.82. Found: C, 75.10; H, 5.73; N, 18.57.

This compound was identified with a sample prepared from 1-methyl-2-chlorobenzimidazole[7] (0.10 g.) and aniline (0.15 ml.) by heating (150°, 5 hr.).

Reaction of I with Phenyl Isothiocyanate——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 ethanolic ammonia. In the flask, a solution of I (I′, 0.50 g.) in $CHCl_3$ (5.0 ml.) was placed and nitrogen gas was passed through to expel a gas product from the reaction flask to the ammonia containing flask. A solution of phenyl isothiocyanate (0.40 g.) in $CHCl_3$ (2.5 ml.) was then added dropwise. The reaction mixture was treated by the same procedure as above mentioned to give Ⅱ (63%).

The gaseous product gave a crystalline product (ca. 0.1 g.) by the reaction with ammonia, which was identified with authentic ammonium thiocarbamate.[8]

Reaction of I with Dimethyl Acetylenedicarboxylate——To a solution of I (I′, 2.50 g., 0.0136 mole) in $CHCl_3$ (15 ml.) was added dimethyl acetylenedicarboxylate (1.93 g., 0.0136 mole) dropwise with shaking and cooling in an ice-water bath. After the addition, the resulting solution was allowed to stand for 1 hr. at room temperature, then evaporated. To the residue was added AcOEt and the crystalline product was collected by filtration (3.50 g.). Recrystallization from MeOH gave colorless short prisms, m.p. 185° (decomp.). *Anal.* Calcd. for $C_{14}H_{14}O_5N_2$ (Dimethyl 1-methyl-2-benzimidazoloxalacetate) (Ⅳ): C, 57.93; H, 4.86; N, 9.65. Found: C, 58.15; H, 5.03; N, 9.59. NMR (τ): 2.58 (benzene ring, complex pattern), 6.15($COOCH_3$), 6.27 ($N\text{-}CH_3$), 6.30 ($COOCH_3$).

Hydrolysis of III——To a solution of KOH (1.0 g.) in MeOH (10 ml.) was added Ⅲ (0.80 g.) and the resulting solution was heated under reflux for 1 hr. A precipitated product (0.46 g., potassium oxalate) which separated within a few minutes after heating was filtered off and the filtrate was concentrated to ca. 3 ml. then cooled to give colorless scales (0.63 g.). This product was dissolved in H_2O (ca. 1.0 ml.) and acidified with 6*N* HCl to give colorless crystals (0.35 g.). Recrystallization from H_2O (under 60°) gave colorless scales, m.p. 75° (decomp.). *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$ (1-Methyl-2-benzimidazolacetic acid) (Ⅳ): C, 63.15; H, 5.30; N, 14.73. Found: C, 63.10; H, 5.18; N, 15.00.

*4 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 Kōken Infrared Spectrophotometer, Model IR-S. NMR spectra were obtained in $CDCl_3$ solution containing tetramethylsilane as an internal reference on a Varian A-60 analytical NMR spectrometer. 1-Methylbenzimidazole 3-oxide dihydrate (I′) (S. Takahashi, H. Kanō: This Bulletin, **11**, 1375 (1963)) was dehydrated to I azeotropically with $CHCl_3$.

5) M. Stiles, R. G. Miller, W. Burckhardt: J. Am. Chem. Soc., **85**, 1792 (1963).
6) cf. 13).
7) N. P. Bednyagina, I. Ya. Postovskii: J. Gen. Chem. U. S. S. R. (Eng. Transl.), **30**, 1456 (1960).
8) H. L. Wheeler, B. Barnes: Am. Chem. J., **22**, 141 (1898).

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This compound was readily decarboxylated, even by allowing to stand at room temperature for a few weeks or heating on a water bath for a few minutes. In the latter case, after decomposition, the product which solidified again melted at 113~114°. Recrystallization from iso-Pr_2O gave colorless prisms, which was identical to authentic 1,2-dimethylbenzimidazole.[9]

Reaction of III with Hydroxylamine——To a solution of $NH_2OH \cdot HCl$ (1.14 g., 0.0163 mole) and AcONa (1.37 g., 0.0163 mole) in H_2O (7.0 ml.) and MeOH (25 ml.) was added III (1.50 g., 0.0049 mole). After standing for 1 day the solution was evaporated and the residue was triturated with $CHCl_3$. The $CHCl_3$ solution was evaporated to give colorless oil, which was solidified by cooling and rubbing (1.05 g.). Recrystallization from iso-Pr_2O gave colorless prisms, m.p. 66~68°. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$ (Methyl 1-methyl-2-benzimidazolacetate) (VI): C, 64.69; H, 5.92; N, 13.72. Found: C, 64.87; H, 6.03; N, 13.53.

This compound gave the hydrate by recrystallization from H_2O, colorless needles, m.p. 41~43°. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2 \cdot H_2O$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.64; H, 6.52; N, 12.61.

From the residue triturated with $CHCl_3$, oxalylhydroxamic acid was obtained. Recrystallization from 0.5*N* HCl gave colorless plates, m.p. 180° (decomp.). *Anal.* Calcd. for $C_2H_4O_4N_2$: C, 20.00; H, 3.36; N, 23.33. Found: C, 19.92; H, 3.47; N, 23.19.

Hydrolysis of VI——A solution of VI (0.35 g.) in KOH-MeOH (10%, 3.0 ml.) was heated under reflux for 2 hr. After cooling, the crystalline product was collected by filtration and dissolved in H_2O (ca. 0.5 ml.) then the solution was acidified by 6*N* HCl to give colorless crystals (0.20 g.), m.p. 75° (decomp.), which was identical with above obtained IV.

Dimethyl 1-Methyl-2-benzimidazoloxalacetate (III)——To a solution of VI (0.67 g., 0.0033 mole) and dimethyl oxalate (0.39 g., 0.0033 mole) in abs. Et_2O (5.0 ml.) was added CH_3ONa (0.18 g., 0.0033 mole). The mixture was heated under reflux for 40 hr., and the resulting white precipitate was collected by filtration and washed with Et_2O (0.52 g.). The precipitate was dissolved in H_2O (3 ml.) and neutralized with 6*N* HCl to give colorless crystals (0.35 g.). Recrystallization from MeOH gave colorless short prisms, m.p. 185° (decomp.), which was identical with the above-obtained III.

Reaction of I with Methyl Propiolate——This experiment was carried out by the same procedure as for the reaction with dimethyl acetylenedicarboxylate. Recrystallization from MeOH or Me_2CO gave colorless short prisms, m.p. 183° (decomp.). Yield, 90%. *Anal.* Calcd. for $C_{12}H_{12}O_3N_2$ (Methyl α-formyl-1-methyl-2-benzimidazolacetate) (VII): C, 62.06; H, 5.21; N, 12.06. Found: C, 62.13; H, 5.31; N, 11.83. NMR (τ): 0.29 (CHO), 2.65 (benzene ring, complex pattern), 6.19, 6.23 ($N-CH_3$ and $COOCH_3$).

Hydrolysis of VII——This experiment was carried out by the same procedure as for the hydrolysis of III. This reaction gave colorless crystals, m.p. 75° (decomp.), which was identical with the above-obtained IV. Yield, 65%.

Reaction of VII with Hydroxylamine——This experiment was carried out by the same procedure as for the reaction with III. This reaction gave colorless crystals, m.p. 66~68°, which was identical with the above-obtained VI. Yield, 60%.

Methyl α-Formyl-1-methyl-2-benzimidazolacetate (VII)——VI (0.50 g., 0.00245 mole) was added to a mixture of methyl formate (0.30 ml., 0.0049 mole) and CH_3ONa (0.20 g., 0.0037 mole) in abs. Et_2O (3 ml.). The mixture was allowed to stand in a sealed tube at room temperature for 10 days with occasional shaking. A precipitated product was collected and dissolved in a small amount of H_2O and the solution was neutralized with 6*N* HCl to give a crystalline product (0.25 g.). Recrystallization from Me_2CO gave colorless short prisms, m.p. 183° (decomp.), which was identical to the above obtained VII.

Reaction of I with Benzonitrile——A mixture of I (I′, 2.0 g.) and benzonitrile (1.1 ml.) was heated at 120° under nitrogen stream for 6 hr. The resulting brown crystalline mass was chromatographed on alumina from $CHCl_3$ to give 1,1′-dimethyl-2,2′-bibenzimidazole[10] (X) (0.20 g.) then 1-methyl-2-benzamidobenzimidazole (VIII) (0.40 g.) and 1,1′-dimethyl-2,2′-bibenzimidazole 3-oxide (IX) (1.20 g.) as the last fraction.

X was recrystallized from EtOH to give colorless prisms or plates, m.p. 211~212°. *Anal.* Calcd. for $C_{16}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.35; H, 5.63; N, 21.33.

This compound was identified with a sample prepared by a method described below.

VIII was recrystallized from EtOH to give colorless prisms, m.p. 161~162°. *Anal.* Calcd. for $C_{15}H_{13}ON_3$: C, 71.69; H, 5.21; N, 16.72. Found: C, 71.77; H, 5.43; N, 16.69.

This compound was identified with a sample prepared by a method described below.

IX was recrystallized from AcOEt to give colorless needles, m.p. 120~130° (hydrate), 215° (decomp.) (anhydrous). *Anal.* Calcd. for $C_{16}H_{14}ON_4 \cdot H_2O$: C, 64.85; H, 5.44; N, 18.91; H_2O, 6.08. Found: C, 65.13; H, 5.55; N, 18.59; H_2O, 6.11.

This compound was reduced to X catalytically in MeOH over Raney Ni.

1-Methyl-2-benzamidobenzimidazole (VIII)——To a mixture of 1-methyl-2-aminobenzimidazole (0.25 g.) in aq. $NaHCO_3$ solution (5%, 10 ml.) was added a solution of benzoyl chloride (0.20 ml.) in benzene (2.0 ml.) with shaking. The starting material dissolved in the solution, and then a crystalline product

9) M. A. Phillips: J. Chem. Soc., **1929**, 2820.
10) cf. P. W. Alley, D. A. Shirley: J. Org. Chem., **23**, 1791 (1958).

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precipitated. After standing for 10 min. at room temperature, the product was collected (0.25 g.) and recrystallized from EtOH to give colorless needles, m.p. 161~162°.

1,1'-Dimethyl-2,2'-bibenzimidazole (X)——To a solution of 1,1'-bibenzimidazole[11] (0.10 g.) in Me_2CO (10 ml.) containing aq. NaOH solution (20%, 1.0 ml.) was added dimethyl sulfate (0.29 g.) dropwise, then the solution was heated under reflux for 1 hr. After evaporating, the residue was triturated with abs. EtOH. Removal of the solvent gave a crystalline product, which was recrystallized from EtOH to give colorless plates (0.08 g.), m.p. 211~212°.

Reaction of I with Phenyl Isocyanide——A solution of I (I', 0.46 g., 0.0025 mole) and phenyl isocyanide (0.26 ml., 0.0025 mole) in $CHCl_3$ (5.0 ml.) was refluxed for 3 hr., then evaporated. The residue was chromatographed on alumina from AcOEt to give II (0.20 g.) then 1-methylbenzimidazole (0.10 g.) and from MeOH to give 1-methyl-2(3*H*)-benzimidazolinone[12] (0.26 g.).

II obtained here (m.p. 201~202°) was identical to the above-obtained one.

1-Methylbenzimidazole,[13] m.p. 64~66°. and 1-methyl-2(3*H*)-benzimidazolinone,[14] m.p. 196~197°, were identified with authentic specimens, respectively.

Reaction of I with Benzyne——To a solution of I (I', 0.70 g.) in *tert*-BuOH (10 ml.) was added benzenediazonium-2-carboxylate[5] (1.00 g.) and the resulting mixture was heated at 45° for 3 hr. with stirring, then allowed to stand overnight at room temperature. After evaporation, the brown residue was chromatographed on alumina from $CHCl_3$ to give a crystalline product (0.50 g.). Recrystallization from MeOH gave colorless short prisms, m.p. 170~171°. *Anal.* Calcd. for $C_{14}H_{12}ON_2$ (1-Methyl-2-(*o*-hydroxyphenyl)benzimidazole) (XI): C, 74.99; H, 5.38; N, 12.49. Found: C, 74.93; H, 5.41; N, 12.50.

1-Methyl-2-(*o*-hydroxyphenyl)benzimidazole[15] (XI)——A mixture of N-methyl-*o*-phenylenediamine dihydrochloride (0.5 g.), salicylic acid (0.4 g.) and phosphorous pentoxide (0.4 g.) was heated at 180° for 1 hr. After cooling, the reaction product was dissolved in aq. Na_2CO_3 solution (10%), and the solution was extracted with $CHCl_3$. The $CHCl_3$ layer was separated, dried then evaporated to give a dark orange oily substance, which was chromatographed on alumina from $CHCl_3$ to give colorless crystals. Recrystallization from MeOH gave colorless short prisms (0.1 g.), m.p. 170~171°.

This compound was identical with the above-obtained one.

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Summary

1-Methylbenzimidazole 3-oxide reacted with phenyl isocyanate, phenyl isothiocyanate, dimethyl acetylenedicarboxylate, and methyl propiolate, at room temperature and with benzonitrile, phenyl isocyanide, and benzyne on heating to give 1-methyl-2-anilinobenzimidazole (II), II, dimethyl 1-methyl-2-benzimidazoloxalacetate, methyl α-formyl-1-methyl-2-benzimidazolacetate, 1-methyl-2-benzamidobenzimidazole, II, 1-methyl-2-(*o*-hydroxyphenyl) benzimidazole, respectively.

Although the initial cycloadducts could not be isolated, these reactions can be best explained as occurring *via* 1,3-dipolar cycloaddition.

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11) H. Hübner: Ann., **209**, 339 (1881).
12) cf. *1.
13) G. R. Beaven, *et al.*: J. Pharm. and Pharmacol., **1**, 957 (1949).
14) A. Hunger, J. Kebrle, A. Rossi, K. Hoffmann: Helv. Chim. Acta, **44**, 1273 (1961).
15) cf. O. Fischer: Ber., **25**, 2826 (1892).

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