group. The spectrum of the hydrochloride showed long-range deshielding of an anomeric proton along with other ring protons, possibly induced by the electric field of an ammonium cation. The long-range deshielding due to an acetamido group was weaker than an ammonium group. It was observed in a variety of the derivatives that H_1 of α-glucopyranoses resonated at lower field with greater $J_{1,2}$ values than those of α-mannopyranoses. The differences presented ready distinction between the two isomers.

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166. Shirō Takahashi and Hideo Kanō: Benzimidazole N-Oxides. Ⅶ.*1 The Reactivity of 1,2-Dimethylbenzimidazole 3-Oxide.

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

In the previous paper of this series,[1] we have reported that 1-methylbenzimidazole 3-oxide is very reactive at the 2-position for nucleophilic reagents showing similar chemical behavior to six-membered heteroaromatic N-oxides, except a few peculiar reactions.

In connection with the previous investigation, this paper deals with the reactivity of 1,2-dimethylbenzimidazole 3-oxide (I), the 2-position of which has no replaceable hydrogen atom.

Schulenberg and Archer[2] have reported that 2-methyl-1-phenylbenzimidazole 3-oxide is obtained by catalytic reduction of N-phenyl-2′-nitroacetanilide in absolute ethanol in the presence of hydrogen chloride. A modification of this method provided a more convenient synthesis of I from N-methyl-2′-nitroacetanilide than the previous ammonium-hydrogen sulfide method.[3]

The N-oxide I was deoxygenated by phosphorus trichloride, sulfur dioxide, sodium hydrogensulfite, and sodium borohydride besides by catalytic reduction with Raney nickel.[3] Although, it was reported that heteroaromatic N-oxides are indifferent towards sulfur dioxide in contrast to aliphatic N-oxides,[4] more recently the deoxygenation reaction has been discovered on 2-phenylquinoxaline N-oxide.[5]

As an example of deoxygenation of heteroaromatic N-oxide with sodium borohydride, the conversion of 1,2,3,4-tetrahydrophenazine dioxide into cis-1,2,3,4,4a,5,10,10a-octahydrophenazine has been reported recently.[6]

In six-membered nitrogen-heteroaromatic compounds, mobility of the hydrogen atoms of the methyl groups are generally enhanced when the methyl groups are in conjugation with the ring-nitrogen atom by inductive effect of the hetero atom. The mobility was estimated chemically by the capacity for condensing with carbonyl, nitroso

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*1 Part Ⅵ. S. Takahashi, H. Kanō: This Bulletin, **14**, 375 (1966).

*2 Fukushima-ku, Osaka (高橋史郎, 加納日出夫).

1) S. Takahashi, H. Kanō: This Bulletin, **12**, 783 (1964).
2) J. W. Schulenberg, S. Archer: J. Org. Chem., **30**, 1279 (1965).
3) S. Takahashi, H. Kanō: This Bulletin, **11**, 1375 (1963).
4) B. Umezawa: *Ibid.*, **8**, 698 (1960).
5) E. Hayashi, C. Iijima: Yakugaku Zasshi, **82**, 1093 (1962).
6) M. J. Haddadin, C. H. Issidorides: Tetrahedron Letters, No. 36, 3253 (1965).

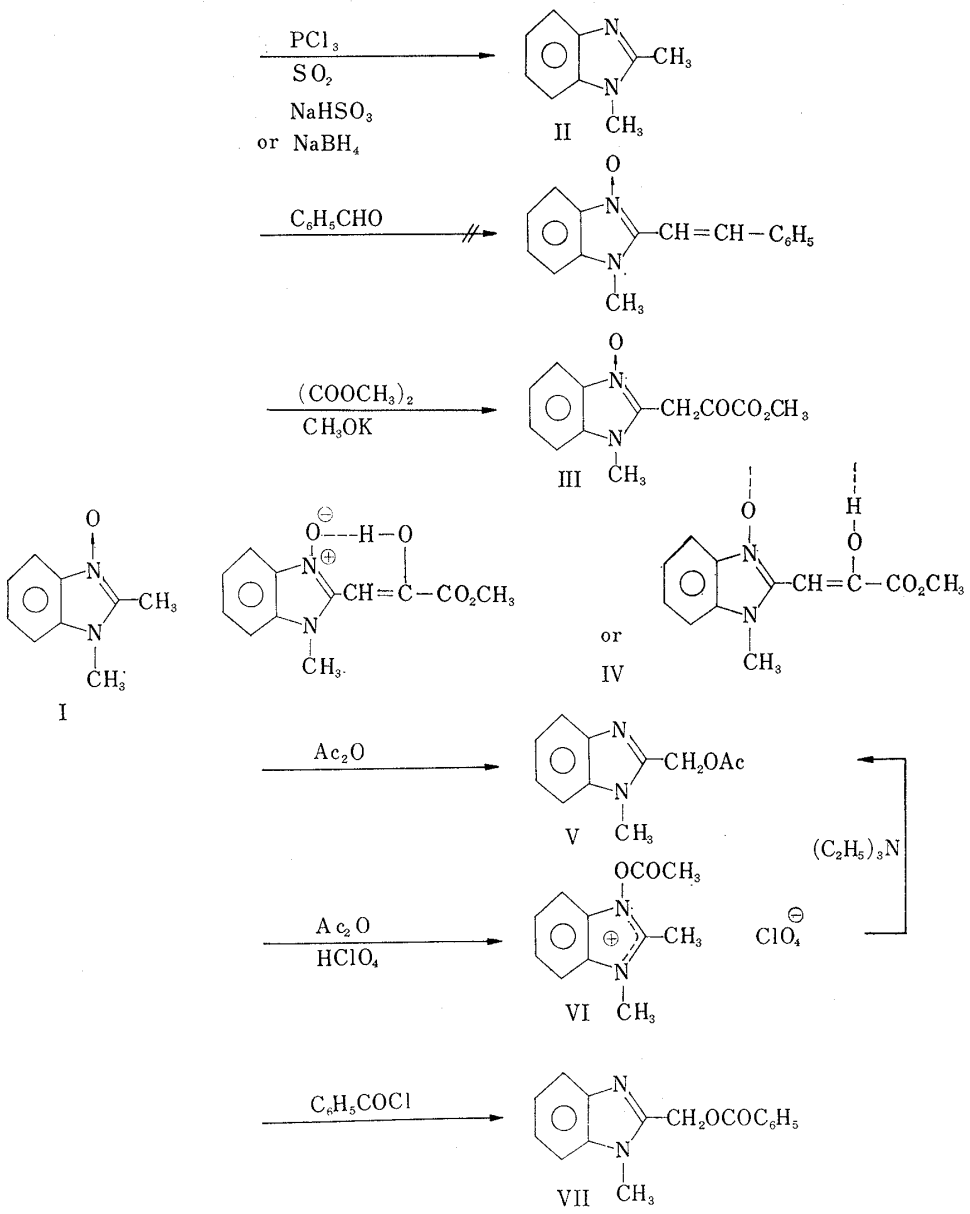

Chart 1.

and diazo compounds.[7] In some cases, the methyl groups of heteroaromatic N-oxides are more reactive than those of the parent bases, and in the other cases, contradictory results are obtained. On the latter cases, it has been assumed that a positive charge on the nitrogen atom which causes enhancement of the reactivity is partly compensated by electrons of the oxygen atom, as was shown by dipole moment measurements.[7]

The N-oxide I did not react with benzaldehyde in the presence of piperidine or zinc chloride, although 1,2-dimethylbenzimidazole gave 2-styryl derivative.[8] In contrast, I reacted readily with dimethyl oxalate to give 2-methoxalylmethyl-1-methylbenzimidazole 3-oxide (III) in good yield; whereas 1,2-dimethylbenzimidazole has been shown to give ethyl 1-methyl-2-benzimidazolepyruvate in poor yield, even on the prolonged reaction with diethyl oxalate.[9]

7) For example, see I. M. Mishina, L. S. Efros : J. Gen. Chem. U. S. S. R. (Engl. Transl.), **32**, 2185 (1962).
8) L. N. Pushkina, S. A. Mazalov, I. Ya. Postovskii : *Ibid.*, **32**, 2585 (1962).
9) W. Borsche, W. Doeller : Ann., **537**, 65 (1938).

The nuclear magnetic resonance spectrum of III shows signal peaks at τ (in $CDCl_3$) 2.30~2.80 (4H, benzene ring protons, complex pattern), 3.82 (1H,-CH=, singlet), 6.13 (3H, $COOCH_3$) and 6.30 (3H, N-CH_3), which suggests that this compound exists as intra or internal hydrogen bonded form (IV).

The condensation reaction of I with *p*-dimethylaminonitrosobenzene or *p*-nitrobenzenediazonium chloride did not occur.

Many reports have been published concerning the reaction of α- or γ-picoline N-oxide with acetic anhydride[10] or that of quinaldine N-oxide with benzoyl chloride.[11] The N-oxide I also reacted with these reagents and gave 2-acetoxymethyl-1-methylbenzimidazole (V) and 2-benzoyloxymethyl-1-methylbenzimidazole (VII). On the reaction with acetic anhydride in the presence of perchloric acid, an intermediate, 3-acetoxy-1,2-dimethyl-benzimidazolium perchlorate (VI) was obtained as in some six-membered heteroaromatic N-oxides.[10c,12] The perchlorate VI gave V by treatment with triethyl amine in acetonitrile.

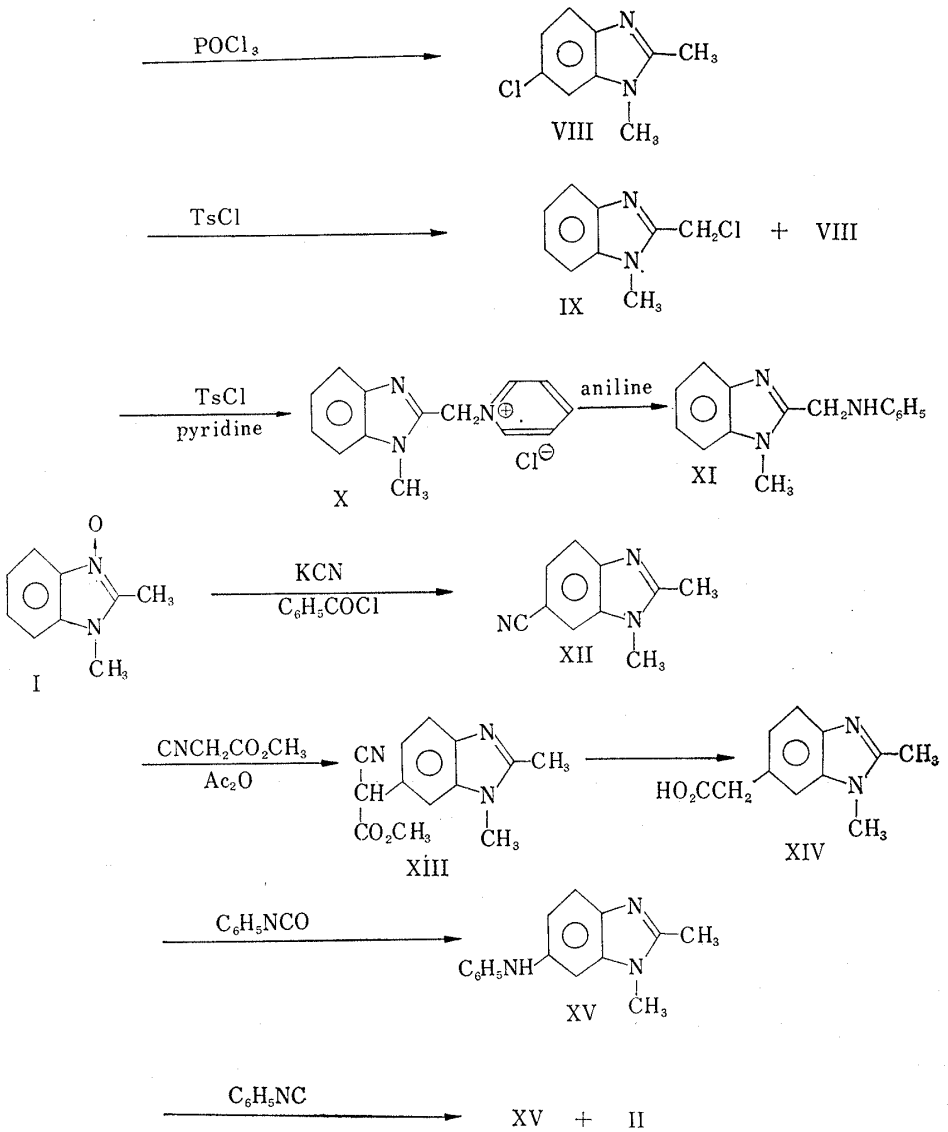

Chart 2.

10) For example, see *a*) S. Oae, T. Kitao Y. Kitaoka : J. Am. Chem. Soc., **84**, 3359 (1962); *b*) *Idem* : *Ibid.*, **84**, 3362 (1962); *c*) V. J. Traynelis, P. L. Pacini : *Ibid.*, **86**, 4917 (1964).

11) S. Oae, S. Kozuka : Tetrahedron, **20**, 2671 (1964).

12) C. W. Muth, R. S. Darlak : J. Org. Chem., **30**, 1909 (1965).

By the reaction with phosphoryl chloride, the N-oxide I gave 6-chloro-1,2-dimethylbenzimidazole (Ⅷ) in good yield, but with tosyl chloride, I gave a mixture of Ⅷ and 2-chloromethyl-1-methylbenzimidazole (Ⅸ) in nearly equal amounts.

As in pyridine N-oxides and quinoline N-oxides,[13] the N-oxide I reacted with tosyl chloride in the presence of pyridine to give the pyridinium salt (X), which was characterized as its dipicrate, and X was treated with aniline to give 2-anilinomethyl-1-methylbenzimidazole (Ⅺ). The nuclear magnetic resonance spectrum of Ⅺ shows the presence of $-CH_2-$group (τ, 5.63 in $CDCl_3$) and the absence of $C-CH_3$ group. This structure was confirmed by comparison with an authentic sample prepared from 2-chloromethyl-1-methylbenzimidazole and aniline.[14]

On treatment with potassium cyanide and benzoyl chloride, the N-oxide I gave 1,2-dimethyl-6-benzimidazolecarbonitrile (Ⅻ) in very poor yield.

The reaction of I with methyl cyanoacetate in the presence of acetic anhydride gave a crystalline compound, the analytical value of which corresponded to methyl 1,2-dimethylbenzimidazolecyanoacetate. The existence of signal peaks of three methyl groups (τ (in $CDCl_3$) 6.06 ($COOCH_3$), 6.28 ($N-CH_3$) and 7.22 ($C-CH_3$)) suggests the cyanoacetate group is attached to the benzene ring. Hydrolysis of the ester gave 1,2-dimethylbenzimidazoleacetic acid, the decarboxylation of which into a methyl derivative for structure decision failed. However, the structure of methyl 1,2-dimethyl-6-benzimidazolecyanoacetate (XIII) was assigned by analogy with other substitution reactions of this series.

The reaction of N-oxides of phenanthridine,[15a] pyridine,[15b] isoquinoline[15b] and 1-methylbenzimidazole[15c] with phenyl isocyanate was shown to give their deoxygenated bases with an anilino substituent on the adjacent position to the original N-oxide group. This reaction has been explained by 1,3-dipolar cycloaddition reaction mechanism. The N-oxide I gave 6-anilino-1,2-dimethlbenzimidazole (XV) by the reaction with phenyl isocyanate. The position of the anilino group was assumed by nuclear magnetic resonance spectrum showing the survival of the $C-CH_3$ group, and confirmed by comparison with an authentic sample prepared from 6-acetamido-1,2-dimethylbenzimidazole and bromobenzene by Ullmann reaction.

The facts that the reaction of I and phenyl isocyanate gave no 5-anilino isomer and a cross reaction of 1-ethyl-2-methylbenzimidazole 3-oxide with phenyl isocyanate in the presence of 1,2-dimethylbenzimidazole gave only 6-anilino-1-ethyl-2-methylbenzimidazole, suggest the mechanism of this reaction involves an anhydro-base type intermediate as shown in Chart 3.

The reaction of I with phenyl isocyanide also gave XV together with the deoxygenated base Ⅱ, which would involve initial formation of phenyl isocyanate *via* oxidation of the isocyanide by the N-oxide as proposed previously in the similar reaction of 1-methylbenzimidazole 3-oxide.[15c]

The N-oxide I gave 2-hydroxyiminomethyl-1-methylbenzimidazole 3-oxide (XVI) on the reaction with isoamyl nitrite in the presence of sodium amide, as known in several other heteroaromatic N-oxides having a methyl group.

As a co-ordination compound of the N-oxide I, a complex with boron trifluoride (XVII) was obtained in good yield.

13) M. Hamana, *et al.*: Yakugaku Zasshi, **84**, 23, 28, 35, 42 (1964).
14) G. K. Hughes, F. Lions: J. Proc. Roy. Soc. N. S. Wales, **71**, 209 (1938) (Chem. Abstr., **32**, 5831 (1938)).
15) *a*) E. Hayashi: Yakugaku Zasshi, **81**, 1030 (1961); *b*) R. Huisgen: Angew. Chem., **75**, 604 (1963); *c*) S. Takahashi, H. Kanō: This Bulletin, **12**, 1290 (1964).

From these experimental results, it may be concluded that the reactivity of the N-oxide I is very similar to that of the six-membered heteroaromatic N-oxide bearing methyl group at the α- or γ-position to the ring nitrogen atom.

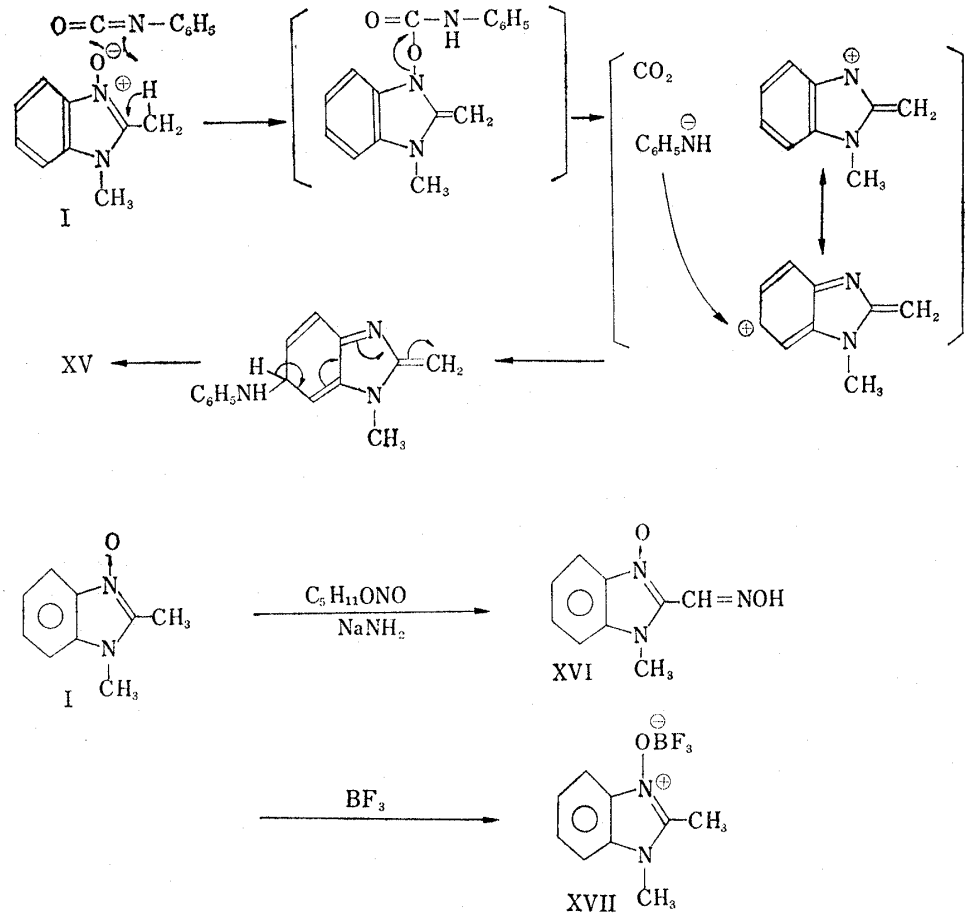

Chart 3.

Experimental*3

1,2-Dimethylbenzimidazole 3-Oxide (I)——A mixture of N-methyl-2′-nitroacetanilide (5.0 g.), EtOH (99 %, 60 ml.), conc. HCl (4.0 ml.) and Pd-charcoal (5%, 1.0 g.) was shaken in H_2 atmosphere. When H_2 gas of *ca.* 1.1 times of theoretical amount had been absorbed, the reduction was stopped. After removal of the catalyst and solvent, the residue was neutralized and recrystallized from AcOEt to give colorless prisms (3.5 g., 74%).

By the same method of Schulenberg and Archer (PtO_2 catalyst),[2] the N-oxide was obtained in yield of 66%.

Deoxygenation of I. With Phosphorus Trichloride——To a solution of I (I′, 0.20 g., 1.0 mmole) in $CHCl_3$ (1.5 ml.) was added a solution of PCl_3 (0.12 ml., 1.3 mmole) in $CHCl_3$ (1.0 ml.) with stirring and cooling in an ice-water bath. After the addition, the solution was heated under reflux for 5 min. The cooled solution was made alkaline with aq. NH_3 and the $CHCl_3$ layer was separated, and the water layer was extracted with $CHCl_3$. The combined $CHCl_3$ solution was concentrated and chromatographed on alumina with $CHCl_3$ gave 1,2-dimethylbenzimidazole (II) as colorless crystals (0.14 g.), m.p. 113~114°, which was identified with an authentic specimen.[16]

*3 All melting points were taken of 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. NMR spectra were obtained in $CDCl_3$ solution containing tetramethylsilane as an internal reference on a Varian A-60 analytical NMR spectrometer. 1,2-Dimethylbenzimidazole 3-oxide dihydrate[3] (I′) was dehydrated by azeotropic distillation with $CHCl_3$ in case of necessity.

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

With Sulfur Dioxide——Into a solution of I (I′, 0.20 g., 1.0 mmole) in $CHCl_3$ (10 ml.) was passed SO_2 gas for 0.5 hr. After standing for 3 hr. at room temperature, the solution was evaporated and the residue was dissolved in H_2O. The solution was made alkaline with aq. $NaHCO_3$ and extracted with $CHCl_3$. Evaporation of the solvent gave II (0.13 g.) as a colorless crystals, m.p. 110～113°, which was purified by recrystallization from petr. benzine and identified with an authentic specimen.[16]

With Sodium Hydrogensulfite——A solution of I′ (0.10 g., 0.5 mmole) and $NaHSO_3$ (0.06 g., 0.6 mmole) in H_2O (1.0 ml.) was heated on a water bath for 6 hr. After evaporation, the residue was dissolved in H_2O and made alkaline with aq. NH_3 to give II (0.06 g.) as colorless crystals, m.p. 111～113°, which was purified and identified with an authentic specimen.[16]

With Sodium Borohydride——To a solution I′ (0.20 g., 1.0 mmole) in EtOH (2.0 ml.) was added a solution of $NaBH_4$ (0.08 g., 2.0 mmole) in EtOH (4.0 ml.) with stirring at room temperature, and the solution was heated under reflux for 3 hr., then evaporated. The residue was extracted with $CHCl_3$ and the extract was chromatographed on alumina with $CHCl_3$ to give II (0.08 g.) and the starting material, I (0.03 g.).

Attempted Condensation Reaction of I with Benzaldehyde——1) A solution of I (I′, 0.10 g., 0.5 mmole) and benzaldehyde (0.06 ml., 0.6 mmole) in MeOH (3.0 ml.) containing piperidine (3 drops) was heated under reflux for 5 hr. After evaporation, the residue was treated with ether to give colorless crystals (0.10 g.), which was shown to be the starting material, I, by IR spectrum.

2) A mixture of I (I′, 0.20 g., 1.0 mmole), benzaldehyde (0.15 ml., 1.5 mmole) and $ZnCl_2$ (0.15 g.) was heated at 120° for 10 min. The cooled mixture was dissolved into H_2O, and the solution was made alkaline with aq. NH_3 (10%). After evaporation, the residue was extracted with $CHCl_3$. Removal of the solvent gave colorless crystal (0.15 g.), which was the starting material recovered.

Reaction of I with Dimethyl Oxalate——To a solution of MeOK in MeOH, prepared by dissolving K (0.20 g., 5.1 mmole) in MeOH (3.0 ml.) in N_2 atmosphere, was added dimethyl oxalate (0.60 g., 5.1 mmole) and the solution was stirred for 15 min. To the resulting solution was added a solution of I (I′, 1.10 g., 5.5 mmole) in MeOH (3.0 ml.) with stirring. After stirring for an additional 30 min., the solution was allowed to stand for 1 day and then evaporated. The yellow residue was dissolved into a small amount of H_2O and neutralized with HCl and extracted with $CHCl_3$. Removal of the solvent gave 2-methoxalylmethyl-1-methylbenzimidazole 3-oxide (III) as yellow crystals (1.18 g.), which was recrystallized from acetone gave yellow prisms, m.p. 199～200° (decomp.). *Anal.* Calcd. for $C_{12}H_{12}O_4N_2$: C, 58.06; H, 4.78; N, 11.29. Found: C, 58.17; H, 4.94; N, 11.14.

Attempted Condensation Reaction of I with *p*-Nitrosodimethylaniline——To a solution of I (I′, 0.40 g., 2.0 mmole) in MeOH (10 ml.) were added a solution of *p*-nitrosodimethylaniline (0.30 g., 2.0 mmole) in MeOH (5 ml.) and aq. Na_2CO_3 (satd., 2 drops). The resulting solution was heated under reflux for 3 hr., and then evaporated. Chromatography of the residue on alumina with $CHCl_3$ gave only the starting materials.

Attempted Coupling Reaction of I with *p*-Nitrobenzenediazonium Chloride——To a solution of I (I′, 0.60 g., 3.0 mmole) and AcONa (1.25 g.) in glacial AcOH (10 ml.) was added a solution of diazonium chloride prepared from *p*-nitroaniline (0.42 g., 3.0 mmole) with stirring at 3～5°. After the solution was stirred for an additional 4 hr. at room temperature, the solution was made alkaline with aq. Na_2CO_3 and allowed to stand overnight, and then evaporated. The residue was extracted with $CHCl_3$, and then with absolute EtOH, but a condensation product was not obtained from these extracts.

Reaction of I with Acetic Anhydride——A solution of I (I′, 0.50 g.) in Ac_2O (10 ml., large excess) was heated on a water bath for 10 min. After removal of the excess reagent, to the residue was added H_2O and the solution was made alkaline with aq. NH_3, and extracted with $CHCl_3$. Removal of the solvent left colorless crystals (0.25 g.), which was recrystallized from isopropyl ether to give 2-acetoxymethyl-1-methyl benzimidazole (V) as colorless prisms, m.p. 68～69°. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.72; H, 6.01; N, 13.51.

This compound was identified with an authentic specimen[17] (lit., m.p. 76～78°).

3-Acetoxy-1,2-dimethylbenzimidazolium Perchlorate (VI)——To a solution of I (I′, 0.30 g., 1.5 mmole) in AcOH (3.0 ml.) and Ac_2O (6.0 ml. large excess) was added a solution of $HClO_4$ (60%, 0.30 g., 1.8 mmole) in Ac_2O (2.0 ml.) dropwise during 10 min. with stirring and cooling in an ice-water bath. After cooling for an additional 20 min., white crystals which formed by scratching were collected by filtration and washed with anhydrous ether in a dry N_2 atmosphere. The product (0.3 g.), colorless small prisms, m.p. 168～171°, IR ν_{max}^{Nujol} 1822 cm^{-1}. *Anal.* Calcd. for $C_{11}H_{13}O_6N_2Cl$: C, 43.36; H, 4.30; N, 9.19. Found: C, 43.44; H, 4.43; N, 9.30.

2-Acetoxymethyl-1-methylbenzimidazole (V) from VI——A mixture of VI (0.15 g., 0.5 mmole), $(C_2H_5)_3N$ (0.14 ml., 1.0 mmole) in CH_3CN (5.0 ml.) was heated under reflux for 2 hr., then evaporated. The residue was extracted with $CHCl_3$ and the extract was chromatographed on alumina with $CHCl_3$ to give

17) N. A. Zakharova, B. A. Porai-Koshits, L. S. Efros: Zhur. Obshcheĭ Khim., **23**, 1225 (1953) (Chem. Abstr., **47**, 12367 (1953)).

colorless crystals (0.06 g.), m.p. 68~69°, which was identified with above obtained one and with an authentic specimen.[17]

Reaction of I with Benzoyl Chloride——To a solution of I′ (0.30 g., 1.5 mmole) in aq. NaOH (10%, 10 ml.) was added BzCl (0.35 ml., 3.0 mmole) dropwise with stirring. The resulting crystalline product was collected by filtration and washed with ether (0.25 g.). Recrystallization from EtOH–AcOEt gave 2-benzoyloxymethyl-1-methylbenzimidazole (Ⅶ) as colorless plates, m.p. 147~148°. *Anal.* Calcd. for $C_{16}H_{14}O_2N_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.27; H, 5.43; N, 10.35.

This compound was identified with an authentic specimen.[17]

Reaction of I with Phosphoryl Chloride——To a solution of I (I′, 0.60 g., 3.0 mmole) in $CHCl_3$ (10 ml.) was added a solution of $POCl_3$ (0.41 ml., 4.5 mmole) in $CHCl_3$ (2.0 ml.) dropwise with stirring and cooling in an ice-water bath, and the resulting solution was heated under reflux for 4 hr., then evaporated. To the residue was added crashed ice and neutralized with aq. $NaHCO_3$ and then extracted with $CHCl_3$. Evaporation of the solvent gave 6-chloro-1,2-dimethylbenzimidazole (Ⅷ) (0.5 g.) as colorless crystals, which was recrystallized from petr. benzine to give colorless needles, m.p. 156~157°. *Anal.* Calcd. for $C_9H_9N_2Cl$: C, 59.84; H, 5.02; N, 15.51. Found: C, 59.92; H, 5.08; N, 15.45.

This compound was identified with an authentic specimen.[18]

Reaction of I with Tosyl Chloride——To a solution of I (I′, 0.30 g., 1.5 mmole) in $CHCl_3$ (3.0 ml.) was added a solution of TsCl (0.29 g., 1.5 mmole) in $CHCl_3$ (2.0 ml.) and the solution was heated under reflux for 30 min. A precipitated product which separated on cooling was collected (0.2 g.) by filtration and the filtrate was evaporated to give another product (0.4 g.). The former was suspended in H_2O and neutralized with aq. $NaHCO_3$ to give 6-chloro-1,2-dimethylbenzimidazole (Ⅷ) (0.10. g), m.p. 156~157°, which was identical with above-obtained one. The latter was chromatographed on alumina with $CHCl_3$ to give 2-chloromethyl-1-methylbenzimidazole (Ⅸ) (0.13 g.), m.p. 93~95°, which was identified with an authentic specimen.[19]

Reaction of I with Tosyl Chloride in Pyridine——To a solution of I (I′, 0.40 g., 2.0 mmole) in pyridine (4.0 ml.) was added TsCl (0.45 g., 2.4 mmole) and the resulting solution was heated on a water bath for 2 hr. Removal of the excess pyridine left a reddish brown tarry substance, which gave a crystalline picrate by a usual method. Recrystallization from EtOH–H_2O gave yellow plates, m.p. 244~246° (decomp.). *Anal.* Calcd. for $C_{14}H_{14}N_3 \cdot C_6H_2O_7N_3 \cdot C_6H_3O_7N_3$ (1-(1-methyl-2-benzimidazolemethyl)pyridinium picrate): C, 45.82; H, 2.82; N, 18.49. Found: C, 46.13; H, 3.07; N, 18.75.

2-Anilinomethyl-1-methylbenzimidazole (XI)——A mixture of the crude tarry pyridinium salt, obtained above (used the same amount of the starting materials), and aniline hydrochloride (2.0 g.) was heated under HCl gas stream at 180° for 3 hr. The resulting orange tarry substance, which solidified on cooling, dissolved in H_2O and neutralized with aq. Na_2CO_3. The excess aniline was removed by steam-distillation and the residue was extracted with $CHCl_3$. The extract was chromatographed on alumina with $CHCl_3$ to give colorless crystals, which were recrystallized from AcOEt–petr. benzine or CCl_4 to give colorless plates, m.p. 148~150°. *Anal.* Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.15; H, 6.67; N, 17.62.

The compound was identified with an authentic specimen[14] (lit., m.p. 118°).

Reaction of I with Potassium Cyanide——To a stirring mixture of I′ (0.50 g., 2.5 mmole), KCN (3.0 g., excess), H_2O (30 ml.) and $CHCl_3$ (30 ml.) was added a solution of BzCl (0.50 ml., 4.3 mmole) in $CHCl_3$ (2.0 ml.) dropwise under cooling in an ice-water bath. After stirring was continued for an additional 5 min., the $CHCl_3$ layer was separated, concentrated and chromatographed on alumina with AcOEt to give 1,2-dimethyl-6-benzimidazolecarbonitrile (Ⅻ) (0.10 g.) as colorless crystals, which was recrystallized from CCl_4 to give colorless scales, m.p. 210~212°, and identified with a sample.*1

Reaction of I with Methyl Cyanoacetate——To a mixture of I (I′, 0.50 g., 2.5 mmole) and methyl cyanoacetate (2.5 ml., excess) was added Ac_2O (0.50 ml., 5.0 mmole) dropwise with stirring and cooling in an ice-water bath. After standing for 30 min., the resulting solution was chromatographed on alumina with $CHCl_3$ to give methyl 1,2-dimethyl-6-benzimidazolecyanoacetate (XIII) (0.05 g.) as colorless crystals. Recrystallization from acetone–isopropyl ether gave colorless prisms, m.p. 255~257° (decomp.). *Anal.* Calcd. for $C_{13}H_{13}O_2N_3$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.22; H, 5.71; N, 17.26.

Hydrolysis of XIII——A suspension of XIII (0.04 g.) in 6*N* HCl (2.0 ml.) was heated under reflux for 8 hr., then evaporated. The residue was dissolved in H_2O and the acidity of the solution was adjusted to pH 4 with aq. $NaHCO_3$ and evaporated again. This residue was extracted with abs. EtOH, and removal of the solvent gave 1,2-dimethyl-6-benzimidazoleacetic acid (XIV) (0.03 g.) as colorless crystals. Recrystallization from EtOH–AcOEt gave colorless needless, m.p.>250°. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2 \cdot 2H_2O$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.79; H, 6.70; N, 11.73.

Attempted Decarboxylation of XIV——A mixture of XIV obtained above (30 mg.) and Cu-powder (200 mg.) was placed in a small flask and heated *in vacuo* (0.10 mm. Hg) at 200° (bath temperature). After

18) J. H. Ridd, B. V. Smith: J. Chem. Soc., **1960**, 1363.
19) J. Büchi, H. Zwicky, A. Aebi: Arch. Pharm., **293**, 758 (1960).

heating for 2 hr., the mixture was extracted with MeOH, but any trimethylbenzimidazole[20] was not detected by thin layer chromatography (Al_2O_3).

Reaction of I with Phenyl Isocyanate——To a solution of I (I′, 0.30 g., 1.5 mmole) in $CHCl_3$ (5.0 ml.) was added a solution of C_6H_5NCO (0.20 ml., 1.8 mmole) in $CHCl_3$ (3.0 ml.) dropwise with stirring and cooling in an ice-water bath. The resulting reddish brown solution was allowed to stand at room temperature for 30 min., then evaporated. The residue, which solidified by scratching, was recrystallized from AcOEt to give 6-anilino-1,2-dimethylbenzimidazole (XV) (0.3 g.) as colorless needles, m.p. 200～202°. *Anal.* Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.71; H, 6.55; N, 17.34.

The same compound was obtained by the reaction of I with phenyl isothiocyanate. Yield, 40%.

This compound was identical with a sample prepared below.

6-Anilino-1,2-dimethylbenzimidazole——A mixture of 5(6)-nitro-2-methylbenzimidazole (6.0 g.) and $(CH_3)_2SO_4$ (3.0 ml.) was heated on a water bath for 1 hr. To the cooled mixture was added aq. NaOH (10%, 50 ml.) to give slightly brown crystals, which were collected by filtration and washed with the aq. NaOH, then H_2O to give a mixture of 5- and 6-nitro-1,2-dimethylbenzimidazole (the ratio[21] was nearly 1:1 determined by chromatography in small amount. In preparative scale, separation of them was incapable by means of recrystallization or column chromatography).

A suspension of the above-obtained mixture of 5- and 6-nitro-1,2-dimethylbenzimidazole in EtOH (100 ml.) was shaken in H_2 atmosphere in the presence of Adams catalyst (PtO_2, 0.30 g.). After the reduction had completed, the solvent and catalyst were removed and Ac_2O (15.0 ml.) was added to the residue. The resulting solution was heated on a water bath for 20 min., then evaporated. The residue was dissolved in H_2O and neutralized with aq. NH_3 to give colorless crystals (3.0 g.), which was recrystallized from H_2O (30 ml.). The insoluble product (1.0 g.) was 5-acetamido-1,2-dimethylbenzimidazole, which was recrystallized from EtOH–H_2O, m.p. 248～249°. Evaporation of the filtrate gave 6-acetamido-1,2-dimethylbenzimidazole (1.5 g.) on cooling, was recrystallized from H_2O to give white needles or prisms, m.p. 220～225°. *Anal.* Calcd. for $C_{11}H_{13}ON_3 \cdot 1/2H_2O$: C, 62.24; H, 6.65; N, 19.80. Found: C, 62.52; H, 6.78; N, 19.83.

A mixture of 6-acetamido-1,2-dimethylbenzimidazole (1.20 g.), KI (70 mg.), Cu-power (70 mg.), K_2CO_3 (0.90 g.) and bromobenzene (10 g.) was heated under reflux with stirring and sometimes H_2O which formed was removed by co-distillation with a small amount of the bromobenzene. After heating for 20 hr., the insoluble materials were filtered off and the filtrate was concentrated and chromatographed on alumina with $CHCl_3$ to give 6-acetanilido-1,2-dimethylbenzimidazole (1.76 g.), slightly brown oily substance.

A solution of the acetyl derivative obtained above (0.60 g.) and NaOH (0.6 g.) in H_2O (0.8 ml.) and MeOH (5.0 ml.) was heated in a sealed tube on a water bath for 6 hr. The resulting brown solution was concentrated and chromatographed on alumina with $CHCl_3$ to give colorless crystals (0.47 g.). Recrystallization from EtOH–H_2O gave colorless needles, m.p. 200～202°.

6-Anilino-1-ethyl-2-methylbenzimidazole——This compound was obtaind from 1-ethyl-2-methylbenzimidazole 3-oxide (dihydrate[3] 0.30 g.) and C_6H_5NCO (0.20 ml.) by the same procedure as for the 1,2-dimethyl compound mentioned above. Recrystallization from AcOEt gave colorless plates (0.25 g.), m.p. 176～178°. *Anal.* Calcd. for $C_{16}H_{17}N_3$: C, 76.46; H, 6.82; N, 16.72. Found: C, 76.39; H, 6.91; N, 16.72.

Cross Reaction of 1-Ethyl-2-methylbenzimidazole 3-Oxide with Phenyl Isocyanate in the Presence of 1,2-Dimethylbenzimidazole——To a solution of 1-ethyl-2-methylbenzimidazole 3-oxide (0.50 g., 2.4 mmole) and 1,2-dimethylbenzimidazole (0.30 g., 2.0 mmole) in $CHCl_3$ (5.0 ml.) was added a solution of C_6H_5NCO (0.39 ml., 3.6 mmole) in $CHCl_3$ (3.0 ml.) with stirring and cooling in an ice-water bath. After standing for 30 min. at room temperature, the solution was evaporated. To the residue was added acetone to give colorless crystals (0.45 g.), which was shown to be pure 6-anilino-1-ethyl-2-methylbenzimidazole by the NMR spectrum.

Reaction of I with Phenyl Isocyanide——A solution of I (I′, 0.60 g., 3.0 mmole) and C_6H_5NC (0.45 ml., 4.5 mmole) in $CHCl_3$ (6.0 ml.) was heated under reflux for 6 hr. The solution was concentrated and chromatographed on alumina with a mixture of $CHCl_3$ and AcOEt (3:1) to give II (0.17 g.) and then XV (0.10 g.), m.p. 200～201°, which was identified with a sample obtained above.

Reaction of I with Isoamyl Nitrite——To a suspension of I (I′, 0.50 g., 2.5 mmole) in liq. NH_3 (*ca.* 50 ml.) was added powdered $NaNH_2$ (0.12 g., 3.0 mmole) and then added iso-$C_5H_{11}ONO$ (0.35 g., 3.0 mmole) dropwise at −50～−60° with stirring. After being maintained at the temperature for 30 min., 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 a small amount of H_2O and acidified with AcOH to give 2-hydroxyiminomethyl-1-methylbenzimidazole 3-oxide (XVI) as colorless precipitate (0.4 g.). Recrystallization from EtOH–H_2O gave colorless scales, m.p. 266° (decomp.). *Anal.* Calcd. for $C_9H_9O_2N_3$: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.37; H, 4.86; N, 21.94.

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

21) M. A. Phillips (J. Chem. Soc., **1931**, 1143) reported that by this procedure, 6-nitro-1,2-dimethylbenzimidazole was obtained in 100:1 ratio to 5-nitro isomer.

In one run, the product of m.p. 256° (decomp.), which have the satisfactory analytical figures for XVI was obtained. This compound was heated with 6*N* HCl on a water bath for 30 min. to give the higher melting isomer obtained above, therefore, this compound may be unstable form of XVI.

Boron Trifluoride Complex of 1,2-Dimethylbenzimidazole 3-Oxide (XVII)——To a solution of I (I′, 0.40 g., 2.0 mmole) in $CHCl_3$ (5.0 ml.) was added BF_3–ether (0.50 ml., 3.9 mmole) dropwise with stirring at room temperature, and the solution was allowed to stand for 30 min. In a few minutes, colorless crystals separated from the resulting turbid solution. The mixture was cooled and filtered to give the complex as colorless crystals (0.45 g.). Recrystallization from acetone to give the complex as colorless crystals (0.45 g.). Recrystallization from acetone to give colorless prisms, m.p. 206～208°. *Anal.* Calcd. for $C_9H_{10}ON_2 \cdot BF_3$: C, 46.99; H, 4.39; N, 12.18. Found: C, 47.17; H, 4.27; N, 12.12.

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Summary

Deoxygenation of 1,2-dimethylbenzimidazole 3-oxide (I) proceeded by treatment with phosphorus trichloride, sulfur dioxide, sodium hydrogensulfite and sodium borohydride besides by catalytic reduction with Raney nickel. The methyl group at C-2 of I seemed less reactive than that of the parent base and did not condense with benzaldehyde, *p*-dimethylaminonitrosobenzene or *p*-nitrobenzenediazonium chloride. However, I reacted with dimethyl oxalate in the presence of alkali to give 2-methoxalylmethyl-1-methylbenzimidazole 3-oxide in good yield. The reactions of I with acetic anhydride, benzoyl chloride, phosphoryl chloride, tosyl chloride, tosyl chloride-pyridine, potassium cyanide-benzoyl chloride, methyl cyanoacetate-acetic anhydride, phenyl isocyanate, phenyl isocyanide and isoamyl nitrite-sodium amide were examined. By these reactions, 2-substituted methyl-1-methylbenzimidazole and/or 6-substituted 1,2-dimethylbenzimidazole were obtained. As a co-ordination compound, the boron trifluoride complex of I was obtained.

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167. Zen-ichi Horii, Takushi Kurihara, Shigeo Yamamoto, Ming-Ching Hsü, Chuzo Iwata, Ichiya Ninomiya, and Yasumitsu Tamura: Studies on Ergot Alkaloids and Related Compounds. XIII.*1 Syntheses and Stereochemistries of 4-Methyl-1,2,3,-4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylic Acids.

(*Faculty of Pharmaceutical Sciences, Osaka University**2)

In the preceding paper*1, ethyl *anti*-4-methyl-2,3,4,4a,5,6-hexahydrobenzo[*f*]quinoline-2-carboxylate (I) and ethyl *trans-anti*-4-methyl-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline-2-carboxylate (III) have been prepared as simplified analogues of lysergic acid and shown to possess a marked oxytocic activity. In view of this result, it appears of

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*1 Part XII: This Bulletin, **13**, 420 (1965).

*2 Toneyama, Toyonaka, Osaka (堀井善一, 栗原拓史, 山本重雄, 徐 明 郷, 岩田宙造, 二宮一弥, 田村恭光).