NH_4Cl (50 mg.) was added to this solution and liq. NH_3 was evaporated at room temperature. The residue was diluted with H_2O, extracted with $CHCl_3$, washed with H_2O, dried over Na_2SO_4 and evaporated leaving a crystalline substance (43 mg.), which was chromatographed on Al_2O_3 to give manogenin (Ⅵa, 25 mg.), m.p. 243~245° and Ⅷ (4 mg.), colorless needles (from AcOEt), m.p. 240~241°, $[\alpha]_D^{23}$ $-62\pm5°$ (c=0.38), Rf value 0.18. *Anal.* Calcd. for $C_{27}H_{44}O_5$: C, 72.28; H, 9.89. Found: C, 72.50; H, 10.01. The physical data of Ⅷ is consistent with those of agavogenin in the literature.[2]

Summary

The steroidal constituents of *Hosta montana* F. MAEKAWA *var. liliiflora* F. MAEKAWA was investigated, and seven sapogenins were isolated. These sapogenins were tigogenin (Ia), hecogenin (Ⅱa), 9-dehydrohecogenin (Ⅲa), gitogenin (Ⅳa), neogitogenin (Va), manogenin (Ⅵa) and 9-dehydromanogenin (Ⅶa).

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111. Shirō Takahashi and Hideo Kanō: Benzimidazole N-Oxides. III.*1 The Reactivity of 1-Methylbenzimidazole 3-Oxide.

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In previous papers, it was reported that benzimidazole N-oxide exists in two tautomeric forms; the N-oxide form and N-hydroxy form,[1] and that the reactivity of N-alkoxybenzimidazole, a derivative of the latter, is similar to that of ordinary heteroaromatic N-oxide or N-alkoxyquarternary salt.*1

The present work is concerned with the reactivity of 1-methylbenzimidazole 3-oxide (I), the N-oxide group of which is fixed in contrast to that of 1-unsubstituted benzimidazole N-oxide. The preparation and catalytic deoxygenation of I has been already reported.[1]

Treatment of I with phosphorus trichloride, which is a known procedure[2] for deoxygenation of amine N-oxide, gave a mixture of 1-methylbenzimidazole (Ⅱ) and 1-methyl-2-chlorobenzimidazole (Ⅲ) in a nearly equal yield.

By the reaction with acetic anhydride, I gave a product, the analytical value of which corresponded to the one expected from the reaction of other heteroaromatic N-oxides; 1-methyl-2-acetoxybenzimidazole (Ⅳ). But, as in the case of benzimidazole N-oxide[3], there is a possibility that the product may be 1-methyl-3-acetyl-2-benzimidazolinone (V). The infrared spectrum of this compound supports the structure (V), showing a very strong, rather broad band at 1720 cm^{-1} (in Nujol mull).

It was reported*1 that 1-ethoxybenzimidazole reacted readily with hydrazine hydrate and sodium hydrogensulfite. I also reacted with these reagents to give 1-methyl-2-hydrazinobenzimidazole (Ⅵ) and sodium 1-methyl-2-benzimidazolesulfonate (Ⅶ), respectively. But the rates of these reactions were slower than those with 1-ethoxybenzimidazole.

*1 Part Ⅱ. S. Takahashi, H. Kanō: This Bulletin, **12**, 282 (1964).
*2 Fukushima-ku, Osaka (高橋史郎, 加納日出夫).
1) S. Takahashi, H. Kanō: This Bulletin, **11**, 1375 (1963).
2) M. Hamana: Yakugaku Zasshi, **71**, 263 (1951).
3) D. J. Kew, P. F. Nelson: Austral J. Chem., **15**, 792 (1962).

The reaction of I with sulfuryl chloride or phosphoryl chloride gave 1-methyl-2-chlorobenzimidazole (III) in good yields. III was also obtained from I and tosyl chloride, but the yield was poor.

The reaction of I with phosphorus trichloride mentioned above, would involve the initial formation of phosphoryl chloride, resulting from the reaction of I and the trichloride followed by rapid chlorination of the remaining I.

The Reissert reaction was applied to heteroaromatic N-oxide to introduce a nitrile group.[4] I gave 1-methyl-2-benzimidazolecarbonitrile (VIII) by this reaction in good yield. 1-Methyl-2-benzimidazolecarboxamide, which is a common by-product of this reaction, was not obtained under the conditions described in the Experimental.

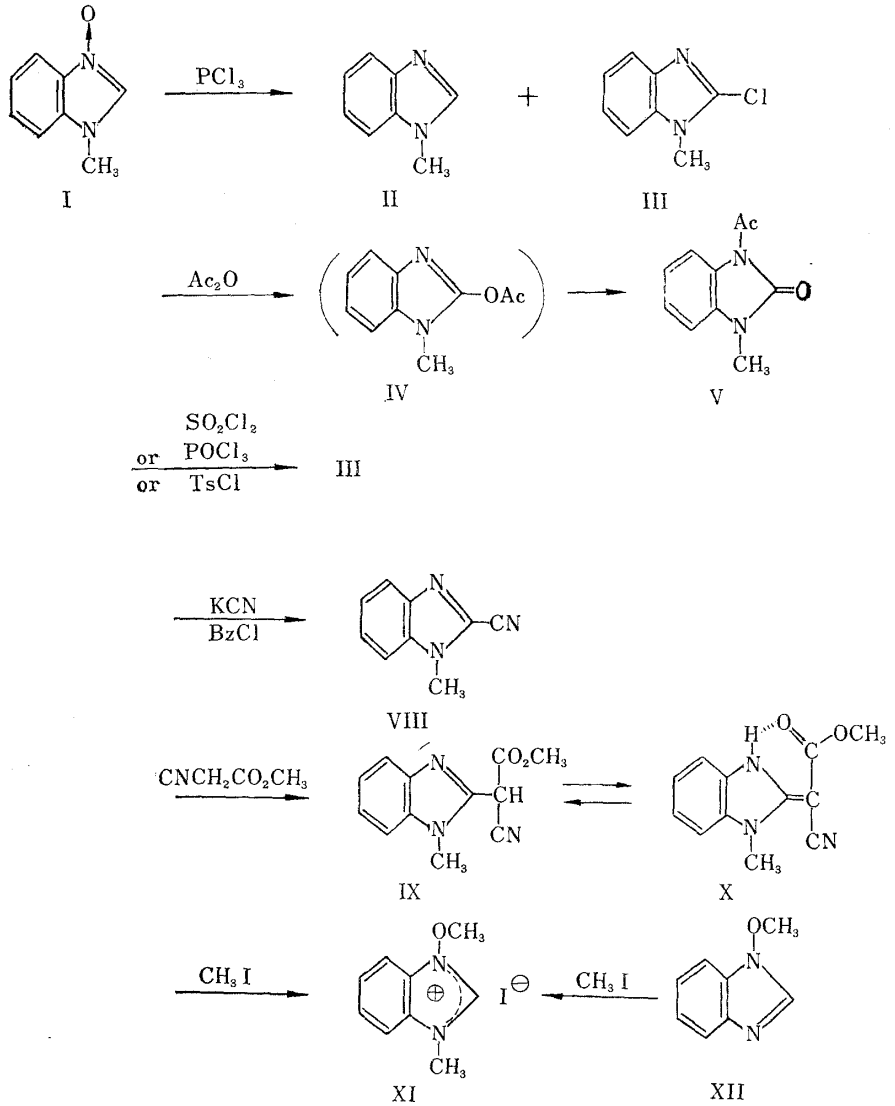

Chart 1.

When I was heated with methyl cyanoacetate, methyl α-cyano-1-methyl-2-benzimidazoleacetate (IX) was obtained. The infrared spectrum of IX was different from the expected one; the spectrum contains bands at 3290, 2250, and 1644 cm^{-1}, assignable to NH, CN, and CO, respectively. The position of the carbonyl group deviates considerably from the region of ordinary esters and the presence of a secondary amino group

4) M. Henze: Ber., **69**, 1566 (1936).

can not be anticipated from the structure (IX). From these spectral properties, it seems that the structure of this compound is better represented by a tautomeric formula of IX (X). The compound gave 1,2-dimethylbenzimidazole by acid or alkali hydrolysis, and following spontaneous decarboxylation. The compound (X) was also readily obtained in better yield by the reaction of I and methyl cyanoacetate in the presence of acetic anhydride at low temperature, as already shown by Hamana and Yamazaki[5] in quinoline- and pyridine-N-oxide derivatives.

I reacted with methyl iodide to give 1-methyl-3-methoxybenzimidazolium iodide (XI), which was also obtained from 1-methoxybenzimidazole (XII) and methyl iodide. From this fact, it is clear that the π-electrons on the imidazole ring of XI are delocalized similarly to those of 1,2,3,5(or 6)-tetramethylbenzimidazolium iodide[6].

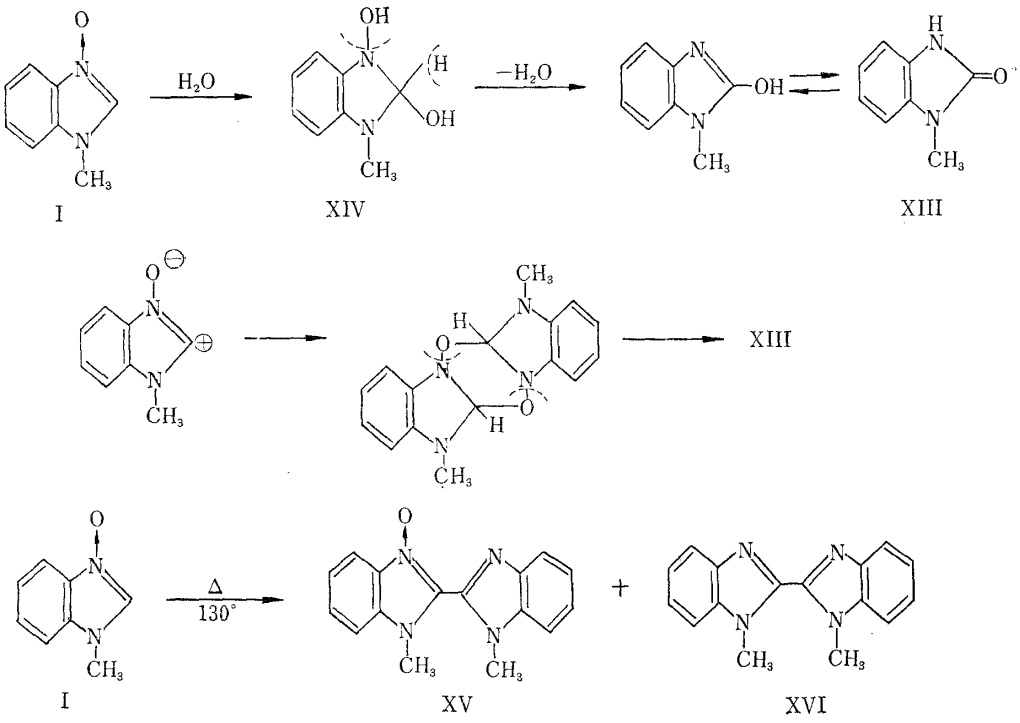

Chart 2.

I is stable in crystalline state, but in solution it is liable to rearrange to 1-methyl-2-benzimidazolinone (XIII); refluxing of the chloroform or acetone solution for several hours or allowing the solution to stand for a few weeks at room temperature was sufficient to complete the rearrangement.

Landquist[7] and Ciamician, *et al.*[8] reported that quinoxaline N-oxides were converted into quinoxalinol derivatives by the action of ultraviolet rays.

In our case, the effect of ultraviolet rays to the migration was negligible; the rate of migration of I, measured by relative intensity of the carbonyl stretching band of XIII in the infrared spectrum, in chloroform solution placed in a dark room was nearly equal to that of the one exposed to daylight. In the spectrum, the band at 1319 cm^{-1} diminishes as the reaction proceeds, so this band was assigned as the N→O group of I.

5) M. Hamana, M. Yamazaki : This Bulletin, **11**, 415 (1963).
6) K. Hofmann : "Imidazole and its Derivatives," 256 (1953). Interscience Publishers Inc., New York.
7) J.K. Landquist : J. Chem. Soc., **1953**, 2830.
8) G. Ciamician, P. Silber : Ber., **34**, 2040 (1901).

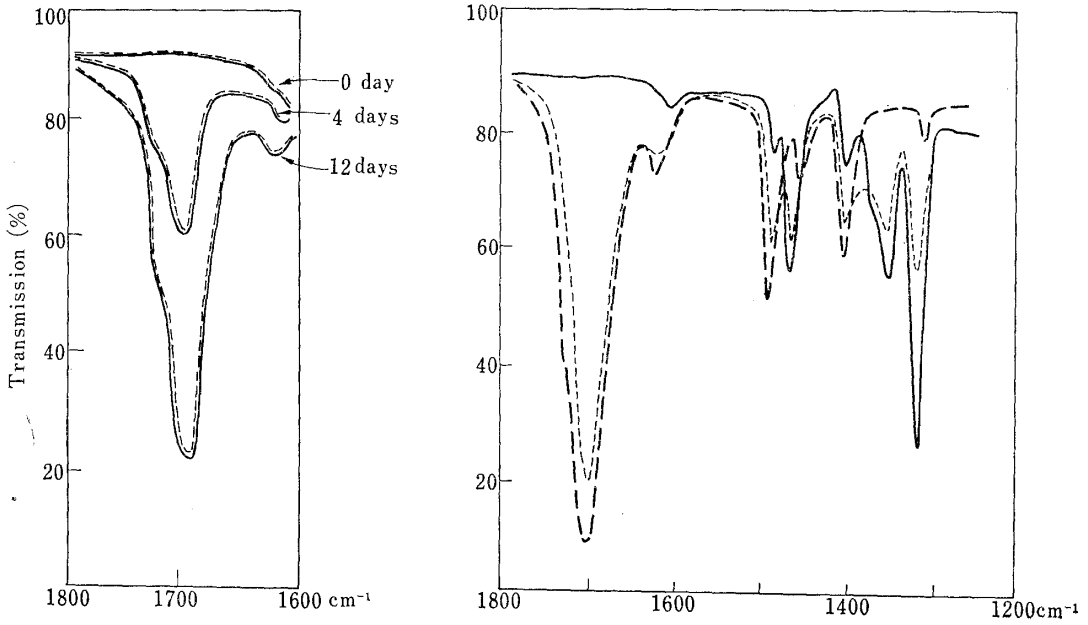

Fig. 1.

——— Exposed to daylight
– – – – – Kept in a dark room

——— 1-Methylbenzimidazole 3-oxide (in $CHCl_3$)
– – – – – After standing the above solution for 12 days at room temperature
— — — 1-Methyl-2-benzimidazolinone (in $CHCl_3$)

The conversion of I into XIII would involve one the following alternative routes : i) by addition of water I is converted into 1-methyl-2,3-dihydro-2,3-benzimidazolediol (XIV), whose dehydration gives XIII. ii) cyclo-addition of two molecules of I takes places, then N-O bond is cleaved to give XIII.

By heating benzimidazole N-oxide with water in a sealed tube, von Niementowski[9] obtained a derivative of the N-oxide, which was assigned as 2,2′-bibenzimidazole 3,3′-dioxide by Kuhn and Blau.[10] When I was heated without solvent at 130°, a mixture of 1,1′-dimethyl-2,2′-bibenzimidazole 3-oxide (XV), and a small amount of 1,1′-dimethyl-2,2′-bibenzimidazole (XVI) was obtained.

So far as the present experimental results are concerned, it may be concluded that the chemical behaviour of I is closely similar to that of ordinary six-membered heteroaromatic N-oxide, except for a few specific reactions to benzimidazole N-oxide.

Experimental*3

Deoxygenation of I with Phosphorus Trichloride——To a solution of I (I′, 0.45 g.) in $CHCl_3$ (3.0ml.), a solution of PCl_3 (0.30 ml.) in $CHCl_3$ (3.0 ml.) was added dropwise with stirring and cooling. The resulting solution was heated under reflux for 5 min. After cooling, the solution was made alkaline with 10% aq. NH_3 and the H_2O layer was separated and extracted with $CHCl_3$, which was added to the $CHCl_3$ layer. The extracts was chromatographed on alumina from $CHCl_3$ to give 1-methyl-2-chlorobenz imidazole (III) (0.18 g.) then 1-methylbenzimidazole (II) (0.16 g.).

*3 All melting points were taken on a Kofler hot-stage and are uncorrected. Solvents were removed under reduced pressure. 1-Methylbenzimidazole 3-oxide dihydrate (I′) was dehydrated to 1-methylbenzimidazole 3-oxide (I) azeotropically with $CHCl_3$, unless otherwise stated. I obtained by this method melted at 128~130°. Each identification was made by comparison of the IR spectrum with that of a sample prepared by an unequivocal route and if the sample had melting point, it is also made by mixed fusion. IR spectra were recorded with a Kōken Infrared Spectrophotometer, Model IR-S.

9) St. von Niementowski : Ber., **43**, 3012 (1910).
10) R. Kuhn, W. Blau : Ann., **615**, 99 (1958).

Ⅲ was recrystallized from petr. benzin to give colorless scales, m.p. 117~118°. *Anal.* Calcd. for $C_8H_7N_2Cl$: C, 57.66; H, 4.24; N, 16.81. Found: C, 57.79; H, 4.33; N, 16.44.

This compound was identified with an authentic specimen.[11]

Ⅱ, m.p. 63~65°, was identified with an authentic specimen.[12]

1-Methyl-3-acetyl-2-benzimidazolinone (V)——A mixture of I (I′, 0.30 g.) and Ac_2O (3.0 ml.) was heated on a water bath for 10 min. After removal of excess Ac_2O, H_2O was added to the residue to give colorless crystals. The product was recrystallized from EtOH–H_2O to give colorless prisms, m.p. 121~122°. *Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.36; H, 5.34; N, 15.04.

Hydrolysis of 1-Methyl-3-acetyl-2-benzimidazolinone (V)——A solution of V (0.10 g.) in 4*N* HCl (3.0 ml.) was refluxed for 0.5 hr. then evaporated. The residue was dissolved in H_2O and neutralized with aq. $NaHCO_3$ solution to give colorless crystals. The product was recrystallized from EtOH to give colorless prisms, m.p. 196~197°. *Anal.* Calcd. for $C_8H_8ON_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.88; H, 5.48; N, 19.11.

This compound was identified with authentic 1-methyl-2-benzimidazolinone[13] (Ⅻ).

1-Methyl-2-hydrazinobenzimidazole (VI)——A mixture of I′ (0.45 g., without dehydration) and NH_2-$NH_2 \cdot H_2O$ (2.5 ml., 90%) was heated on a water bath for 3 hr. After removal of the excess hydrate, 2*N* HCl was added to the residue and the solution was cooled to give 1-methyl-2-hydrazinobenzimidazole·HCl (0.30 g.), which was recrystallized from H_2O–EtOH, m.p. >290°. This compound was identified with an authentic specimen.[11]

1-Methyl-2-benzimidazolesulfonic Acid——I′ (0.30 g., without dehydration) was added to a solution of $NaHSO_3$ (0.30 g.) in H_2O (2.0 ml.). The resulting solution was heated on a water bath for 0.5 hr., then acidified with 6*N* HCl to give a white precipitate, quantitatively. Recrystallization from EtOH–H_2O gave colorless prisms, m.p. >300°. *Anal.* Calcd. for $C_8H_8O_3N_2S \cdot \frac{1}{2}H_2O$: C, 43.44; H, 4.10; N, 12.66. Found: C, 43.73; H, 4.25; N, 12.40.

Reaction of I with Sulfuryl Chloride——To a solution of I (I′, 0.50 g.) in $CHCl_3$ (5.0 ml.) was added a solution of SO_2Cl_2 (1.0 ml.) in $CHCl_3$ (5.0 ml.) dropwise with stirring and cooling in an ice-water bath. The solution turned deep violet then orange. The resulting solution was heated under reflux for 10 min., then evaporated. The residue was made alkaline with aq. $NaHCO_3$ solution then extracted with $CHCl_3$. The $CHCl_3$ extract was chromatographed on alumina from $CHCl_3$ to give 1-methyl-2-chlorobenzimidazole. Recrystallization from petr. benzin gave colorless needles (0.40 g.), m.p. 117.0~117.5°. This compound was identified with an authentic specimen.[11]

Reaction of I with Phosphoryl Chloride——This experiment was carried out by the same procedure as above mentioned. Yield, 90%. Ⅲ obtained here was identified with above obtained one.

Reaction of I with Tosyl Chloride——A solution of TsCl (0.50 g.) in $CHCl_3$ (3.0 ml.) was added dropwise to a solution of I (I′, 0.50 g.) in $CHCl_3$ (5.0 ml.) with stirring and cooling. The resulting dark red solution was heated under reflux for 5 min. then evaporated. The residue was chromatographed on alumina from $CHCl_3$ to give Ⅲ as colorless crystals (0.25 g.).

Reissert Reaction of I——To a solution of KCN (0.20 g.) in H_2O (1.5 ml.) was dissolved I′ (0.40 g., without dehydration), then added BzCl (0.32 ml.) with shaking and cooling in an ice-water bath. Immediately, a crystalline product precipitated. After standing for 10 min. at room temperature, the product was collected by filtration and recrystallized from CCl_4 to give colorless prisms (or scales), m.p. 178~179° (0.30 g.). *Anal.* Calcd. for $C_9H_7N_3$ (1-methyl-2-benzimidazolecarbonitrile) (Ⅷ): C, 68.77; H, 4.49; N, 26.74. Found: C, 68.76; H, 4.43; N, 26.68.

Hydrolysis of VIII——To a solution of KOH (0.20 g.) in MeOH (5.0 ml.) was added Ⅷ (0.20 g.) and the resulting solution was refluxed for 2 hr. After cooling, the precipitated product (0.25 g.) was collected by filtration and dissolved in a small amount of H_2O then acidified with conc. HCl to give colorless crystals (0.15 g.). Recrystallization from H_2O (under 70°) gave colorless prisms, m.p. 103° (decomp.). This compound was identified with authentic 1-methyl-2-benzimidazolecarboxylic acid.[14]

Methyl α-Cyano-1-methyl-2-benzimidazoleacetate (IX)——1) A mixture of I (I′, 3.0 g.) and methyl cyanoacetate (2.5 g.) was heated on a water bath. In the course of 5 hr., a crystalline product separated. After heating for 7 hr., MeOH was added to the mixture and the product was collected by filtration (1.0 g.). Recrystallization from MeOH gave colorless silky needles, m.p. 252~253°. *Anal.* Calcd. for $C_{12}H_{11}O_2N_3$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.71; H, 4.72; N, 18.12.

2) To a mixture of I (I′, 0.30 g.) and methyl cyanoacetate (0.30 g.), Ac_2O (0.30 ml.) was added dropwise with stirring and cooling in an ice bath. Immediately, a crystalline product precipitated. The mixture was allowed to stand at room temperature for 0.5 hr., then MeOH was added to the mixture

11) N. P. Bednyagina, I. Ya. Postovskii: J. Gen. Chem. (U. S. S. R.), **30**, 1456 (1960).
12) G. R. Beaven, *et al.*: J. Pharm. and Pharmacol., **1**, 957 (1949).
13) A. Hunger, J. Kebrle, A. Rossi, K. Hoffmann: Helv. Chim. Acta, **44**, 1273 (1961).
14) P. W. Alley, D. A. Shirley: J. Org. Chem., **23**, 1791 (1958).

and the product was collected by filtration and washed with MeOH (0.30 g., colorless prisms). Recrystallization from MeOH gave colorless silky needles, m.p. 252~253°. This compound was identified with above-obtained one.

Hydrolysis of IX——1) With alkali : IX (0.33 g.) was added to a solution of KOH (0.15 g.) in MeOH (4.0 ml.) and the mixture was heated on a water bath in a sealed tube for 10 hr. After cooling, the resulting precipitate was filtered off and the filtrate was neutralized with 6*N* HCl then evaporated. The residue was extracted with abs. EtOH. After evaporating, the residue (0.11 g.) was recrystallized from petr. benzin to give colorless prisms, m.p. 113~114°. This compound was identified with authentic 1,2-dimethylbenzimidazole.[15]

2) With acid : A mixture of IX (0.30 g.) and 4*N* HCl (15 ml.) was heated under reflux for 5 hr. In the course of 1 hr., the starting material dissolved in the solution. After evaporation, the residue was neutralized with aq. $NaHCO_3$ solution. The resulting solution was evaporated again and the residue was treated by the same procedure as above-mentioned to give 1,2-dimethylbenzimidazole (0.15 g.), m.p. 113~114°.

3-Methoxy-1-methylbenzimidazolium Iodide (XI)——1) From I : A mixture of I (I′, 0.30 g.) and MeI (2.0 ml.) was heated under reflux for 10 min. The starting material dissolved in the solution then a crystalline product precipitated. After cooling, the product (0.46 g.) was collected by filtration and recrystallized from EtOH-AcOEt to give colorless prisms, m.p. 140° (decomp.). *Anal.* Calcd. for $C_9H_{11}ON_2I$: C, 37.26; H, 3.82; N, 9.66. Found : C, 37.54; H, 4.04; N, 10.11.

2) From XII : XII (0.20 g.) was added to MeI (1.0 ml.) and the solution was heated under reflux for 0.5 hr. Within 5 min., the product separated. By treating as described above, XI was obtained in quantitative yield.

Rearrangement of I to 1-Methyl-2-benzimidazolinone (XIII)——A solution of I in Me_2CO was heated under reflux for 8 hr. or allowed to stand at room temperature for a few weeks. Evaporation of the solution gave XIII in quantitative yield. Recrystallization from Me_2CO gave colorless prisms, m.p. 196~197°.

This compound was identified with an authentic specimen.[13]

Pyrolysis of I——I (I′, 0.15 g.) was heated on an oil bath at 130° for 5 hr. and the resulting brown tar was chromatographed on alumina from $CHCl_3$ to give 1,1′-dimethyl-2,2′-bibenzimidazole (XVI) (0.02 g.) then 1,1′-dimethyl-2,2′-bibenzimidazole 3-oxide (XV) (0.07 g.).

XVI was recrystallized from EtOH to give colorless plates, m.p. 211~212°. This compound was identified with a specimen prepared from 2,2′-bibenzimidazole[16] by methylation with dimethyl sulfate in the presence of alkali.

XV was recrystallized from AcOEt to give colorless needles, m.p. ca. 120° (monohydrate) and 215° (decomp.) (anhydrous crystals). This compound was identified with a specimen.[17]

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Summary

The reactivity of 1-methylbenzimidazole 3-oxide (I), which is a five-membered heteroaromatic N-oxide, was investigated. Deoxygenation with phosphorus trichloride, reactions with acetic anhydride and some anionide reagents, and the Reissert reaction were examined. Normal products were obtained in all cases, a result which can be expected from the reactions of the six-membered N-oxide. I reacted with methyl cyanoacetate to give methyl α-cyano-1-methyl-2-benzimidazoleacetate. I and 1-methoxybenzimidazole reacted with methyl iodide to give 1-methyl-3-methoxybenzimidazolium iodide in both cases. In solution, I is liable to rearrange to 1-methyl-2-benzimidazolinone and pyrolysis of I gave 1,1′-dimethyl-2,2′-bibenzimidazole 3-oxide and 1,1′-dimethyl-2,2′-bibenzimidazole.

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15) O. Fischer : Ber., **25**, 2838 (1892).
16) H. Hübner : Ann., **209**, 339 (1881).
17) S. Takahashi, H. Kanō : Tetrahedron Letters, **1963**, 1687.