thio)carbonylthiamine (XLI) in 5 ml. of dihydropyran, 0.18 ml. of conc. HCl was added under stirring. After exothermic reaction had subsided, stirring was continued for 3 hr. Separated crystals were filtered, dissolved in a small amount of H_2O, and the solution was made alkaline and extracted with $CHCl_3$. The extract was dried over anhyd. $MgSO_4$ and evaporated. The oily residue was purified by chromatography on alumina and crystallized from petr. ether to form colorless prisms, m.p. 102~103°; yield, 0.3 g. Rf 0.76. *Anal.* Calcd. for $C_{20}H_{30}O_4N_4S_2$: C, 52.85; H, 6.65; N, 12.33. Found : C, 52.66; H, 6.98; N, 12.42.

O-(2-Tetrahydropyranyl)thiamine Propyl Disulfide (XL)——Prepared from 0.5 g. of Ⅷ, 5 ml. of 2,3-dihydropyran and 0.18 ml. of conc. HCl as described above. Colorless prisms, m.p. 80°; yield, 0.3 g, Rf 0.84. *Anal.* Calcd. for $C_{20}H_{32}O_3N_4S_2$: C, 54.53; H, 7.32; N, 12.72. Found : C, 54.45; H, 7.55; N, 12.35.

The authours express their deep gratitude to Prof. M. Tomita and Prof. S. Uyeo of Kyoto University and Dr. K. Takeda, Director of this laboratory, for their kind encouragement. Thanks are also due to Drs. Y. Matsui and K. Tori for IR and NMR spectral measurements, to the members of Analysis Room of this laboratory for elemental analysis.

Summary

The new thiamine derivatives, O-substituted derivatives of thiamine propyl disulfide, disulfide derivatives of thiamine and 2-hydroxy-3-carbamoyloxypropyl, 2-ethoxycarbonylethyl, 2-ethoxycarbonyloxyethyl, and their O-substituted derivatives were prepared. Also, O-2-tetrahydropyranyl derivatives of S-alkoxycarbonyl thiamine and thiamine propyl disulfide were prepared, and their primary screening tests were made.

(Received February 27, 1963)

[Chem. Pharm. Bull. 11 (11) 1375 ~ 1381]

UDC 547.785.5.02

215. Shirō Takahashi and Hideo Kanō : Benzimidazole N-Oxides. I. The Structure of Benzimidazole N-Oxide and Synthesis of its Derivatives.

(*Research Laboratory, Shionogi & Co., Ltd.*[*1])

Since the report by Ochiai[1] in 1942 on the synthesis and characterisic reactivity of pyridine N-oxide, many interesting studies on six-membered heteroaromatic N-oxides have been carried out. However, there are only a few reports on five-membered N-oxides. It appeared of interest to investigate syntheses and reactivities of benzimidazole N-oxide, the structure of which involves a five-membered heteroaromatic N-oxide. This paper, the first of a series, deals with the structure of benzimidazole N-oxide and synthesis of its derivatives.

Benzimidazole N-oxide was first synthesized by reduction of 2′-nitroformanilide with ammonium sulfide by von Niementowski.[2] He also prepared 2,6-dimethylbenzimidazole 3-oxide by dehydrobromination of 2,3-dibromo-2,6-dimethyl-2,3-dihydrobenzimidazole with potassium hydroxide.[3] Recently, Hayashi and Iijima[4] obtained 2-phenylbenzimidazole 3-oxide from 2-phenylquinoxaline 4-oxide by treatment with hydrogen

*1 Fukushima-ku, Osaka (高橋史郎，加納日出夫).

1) E. Ochiai, M. Ishikawa : Proc. Imp. Acad., Tokyo, **18**, 561 (1942).
2) St. von Niementowski : Ber., **43**, 3012 (1910).
3) *Idem* : *Ibid.*, **25**, 860 (1892).
4) E. Hayashi, C. Iijima : Yakugaku Zasshi, **82**, 1093 (1962).

NII-Electronic Library Service

peroxide and potassium hydroxide, and have suggested that this method may be applicable to the preparation of other 2-substituted benzimidazole 3-oxides. Many six-membered heteroaromatic N-oxides can be easily prepared from the parent bases by oxidation with organic peracid, but attempts to synthesize benzimidazole N-oxide using this method have been unsuccessful.[5,6]

The reductive ring-closure of N-acyl-*o*-nitroaniline derivatives with ammonium sulfide seems to be the most useful method for the synthesis of benzimidazole N-oxides. This procedure would involve reduction of the nitro group to the hydroxylamino group, and following, dehydrative ring-closure between the latter and the carbonyl group. Zinc in aqueous ammonium chloride solution is known as a reagent which reduces a nitro group to the hydroxylamino group. When 2′-nitroformanilide was heated with this reagent, benzimidazole N-oxide was obtained in a rather poor yield. But neither N-methyl-2′-nitroformanilide nor 2′-nitroacetanilide could be converted into the N-oxide derivative with this reagent.

It was further found that ring-closure between the hydroxylamino group and the carbonyl group does not take place, as in the following example : 2-(1-pyrrolidinyl)-2′-nitroacetanilide (I) was treated with ammonium sulfide to give 2-(1-pyrrolidinyl)-2′-hydroxylaminoacetanilide (II), but all further attempts to form the N-oxide (IV) through ring closure were unsuccessful.

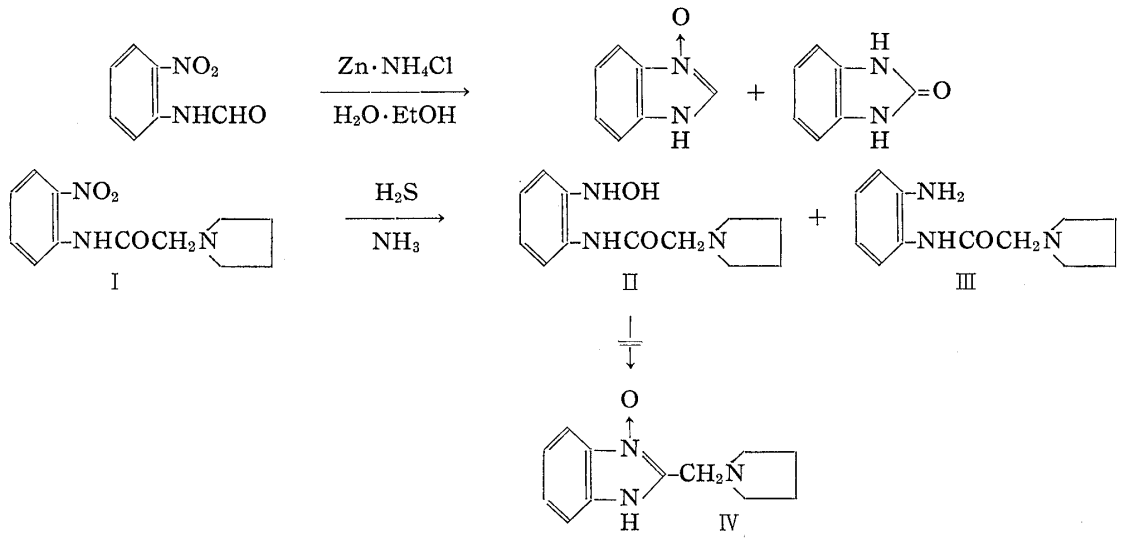


Chart 1.

There has been no report on the synthesis of 1-substituted benzimidazole 3-oxides, for example, 1-methylbenzimidazole 3-oxide. This compound is a very important one for the determination of whether benzimidazole N-oxide exists in the N-oxide form (XIV) or N-hydroxyl form (XV).

For synthesis of these N-oxides, N-acyl-N-substituted *o*-nitroanilines are key intermediates. Although 2′-nitroformanilide can be prepared from *o*-nitroaniline by refluxing with formic acid, N-substituted 2′-nitroformanilide (VI) could not be obtained by this procedure even under more drastic conditions. But when N-alkyl- and N-aralkyl-*o*-nitroanilines (V) were treated with acetic formic anhydride[7] at room temperature, their formyl derivatives were obtained in almost quantitative yields. N-alkyl- and

5) E. Hayashi, E. Ishiguro, M. Enomoto : Presented at the 80th Annual Meeting of the Pharmaceutical Society of Japan (1960).
6) D. J. Kew, P. F. Nelson : Austral. J. Chem., **15**, 792 (1962).
7) C. W. Huffman : J. Org. Chem., **23**, 727 (1958).

NII-Electronic Library Service

N-aralkyl-2′-nitroacetanilide (IX) were synthesized by the usual method. N-Phenyl-2′-nitroacetanilide was synthesized from 2-nitrodiphenylamine by heating with acetic anhydride in the presence of zinc chloride.[8] But N-phenyl-2′-nitroformanilide could not be obtained from 2-nitrodiphenylamine by treatment with acetic formic anhydride; when zinc chloride was present, this reaction resulted in the formation of N-phenyl-2′-nitroacetanilide rather than N-phenyl-2′-nitroformanilide.

Reduction of VI with ammonium sulfide gave 1-substituted benzimidazole 3-oxides (VII) together with considerable amounts of 1-substituted benzimidazoles (VIII). These benzimidazoles seemed to have been produced by ring-closure between the carbonyl group and the amino group derived from the nitro group by reduction.

In the same manner as described above 1-substituted 2-methyl benzimidazole 3-oxides (X) were prepared from IX. In this reaction, N-substituted 2′-aminoacetanilide (XII) and small amounts of 1-substituted 2-methylbenzimidazole (XI) were obtained as by-products. XII was easily converted into XI by heating in dilute hydrochloric acid.

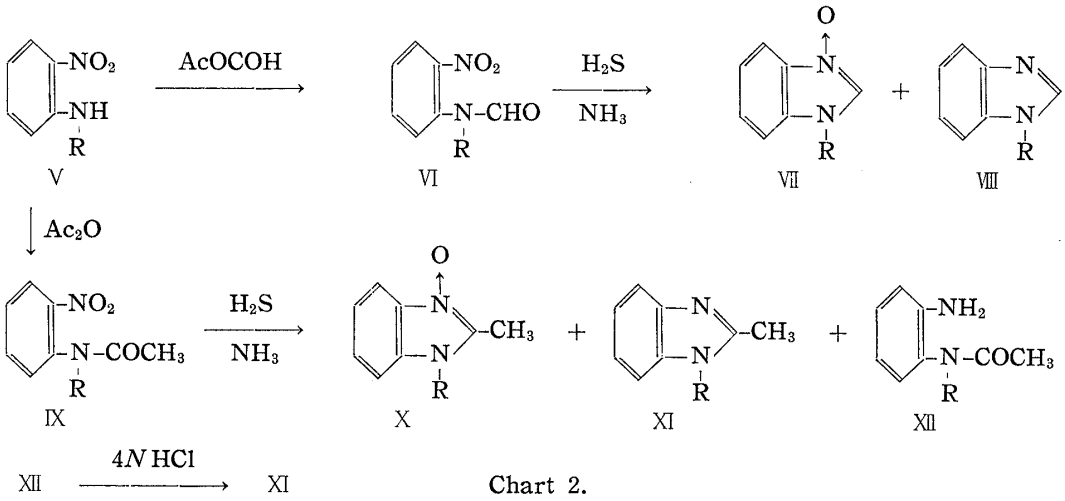


Chart 2.

These substituted benzimidazole 3-oxides are very soluble in water and alcohol, moderately soluble in acetone and ethyl acetate, and insoluble in non-polar solvents. They are also very hygroscopic and could not be obtained as anhydrous crystals. Benzimidazole N-oxide and its derivatives are readily deoxygenated by catalytic reduction in the presence of Raney-nickel.

Benzimidazole N-oxide was first regarded as an oxanhydro base (XIII) by von Niementowski,[2] and later Wright[9] and Hofmann[10] postulated further two tautomeric

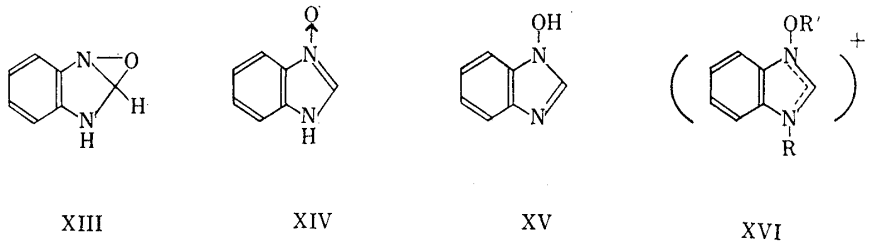


Chart 3.

8) F. Kehrmann, E. Baumgartner : Helv. Chim. Acta., **9**, 673 (1926).
9) J.B. Wright : Chem. Revs. **48**, 462 (1951).
10) K. Hofmann : "Imidazole and its Derivatives," 285 (1953). Interscience Publishers Inc., New York.

NII-Electronic Library Service

structures, XIV and XV, without any definite evidence. Recently, Kew and Nelson[6] assigned structure (XIV) to this compound on the bases of its physical and chemical properties; the melting point, solubility and some chemical reactivities.

Hayashi, *et al.*[5] reported that benzimidazole N-oxide reacted with diazomethane to give a mixture of 1-methylbenzimidazole 3-oxide and 1-methoxybenzimidazole. From this fact, the possibility of tautomerism in the benzimidazole N-oxide system, XIV and XV, would be expected.

In order to establish the structure of benzimidazole N-oxide, the ultraviolet spectra were compared with those of 1-methylbenzimidazole 3-oxide and 1-methoxybenzimidazole in some solvents.

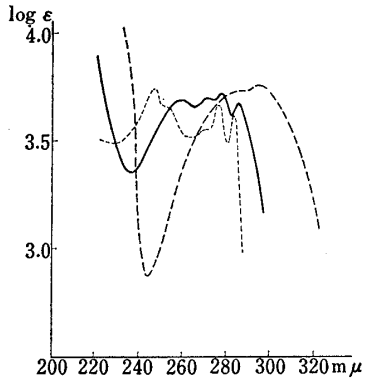


Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

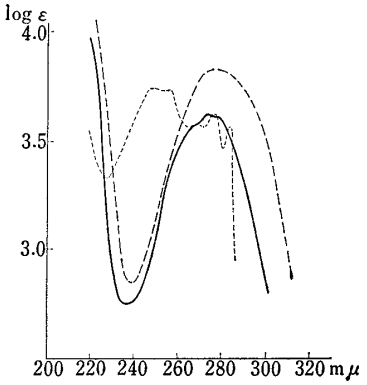


Fig. 2. Ultraviolet Absorption Spectra (in H_2O)

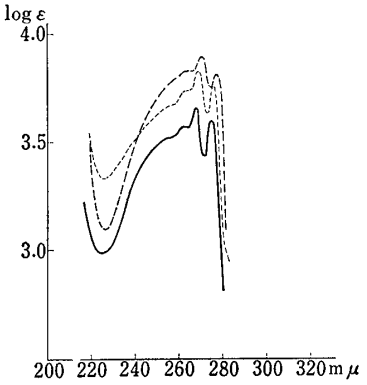


Fig. 3. Ultraviolet Absorption Spectra (in 0.1*N* HCl)

———— Benzimidazole N-oxide
– – – – 1-Methylbenzimidazole 3-oxide
------ 1-Methoxybenzimidazole

In ethanol solution, the spectrum of benzimidazole N-oxide closely resembles that of 1-methoxybenzimidazole, whereas in aqueous solution it resembles that of 1-methylbenzimidazole 3-oxide. These facts show that benzimidazole N-oxide exists predominantly in XV in ethanol solution and predominantly in XIV in aqueous solution (Figs. 1 and 2). In acidic solution, the spectra of these three compounds show similar curves, indicating that they exist in benzimidazolium cation (XVI) (Fig. 3).

Experimental*2

Reduction of 2′-Nitroformanilide with Zinc——NH_4Cl (1.0 g.) was added to a solution of 2′-nitroformanilide (2.0 g.) in 50% aq. EtOH (60 ml.) and following Zn dust (5.0 g.) was added in portions with stirring. The mixture was heated under reflux for 3 hr. The resulting grey mixture was filtered while hot and washed with hot EtOH. The mass was broken up into a powder and suspended in a dilute aq. NH_4OH solution. To the suspension was passed H_2S to decompose the Zn complex of benzimidazole N-oxide, and the precipitate was removed by filtration. The filtrate was evaporated and the crystalline residue was recrystallized from EtOH to give benzimidazole N-oxide (0.7 g.) m.p. 215° (decomp.) (Lit.[2] m.p. 210° and 212° (decomp.)). *Anal.* Calcd. for $C_7H_6ON_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.40; H, 4.33; N, 20.84. The filtrate from the reaction mass was evaporated and the residue was recrystallized from Me_2CO to give 2-benzimidazolinone (0.4 g.), m.p. >300° (Lit.[11] m.p. 305°).

Reduction of 2-(1-Pyrrolidinyl)-2′-nitroacetanilide (I) with Ammonium Sulfide——2′-Nitro-2-(1-pyrrolidinyl)acetanilide (3.0 g.) was dissolved in EtOH (120 ml.) containing concentrated aq. NH_4OH (6 ml.). To the solution was passed H_2S for 1 hr. After standing for an additional 1 hr., the crystals preci-

*2 All melting points were taken on a Kofler hot-stage and are uncorrected. Solvents were removed under reduced pressure. Infrared spectra were recorded with a Kōken Infrared Spectrophotometer, Model IR-S, and ultraviolet spectra were obtained by means of a Hitachi Recording Spectrophotometer, EPS-2.

11) O. Kym: J. Pr., [2], 75, 323 (1907).

NII-Electronic Library Service

pitated were collected by filtration (1.8 g.) and recrystallized from MeOH to give 2-(1-pyrrolidinyl)-2′-hydroxylaminoacetanilide (II), m.p. 148°(decomp.), as colorless scales. This compound was liable to decompose at an elevated temperature, even during recrystallization. *Anal.* Calcd. for $C_{12}H_{17}O_2N_3$: C, 61.25; H, 7.28; N, 17.86. Found: C, 61.08; H, 7.36; N, 17.51.

The filtrate from the hydroxylamino derivative was concentrated and cooled. The resulting crystalline product was collected and recrystallized from EtOH to give colorless plates (0.2 g.), m.p. 150~151°. *Anal.* Calcd. for $C_{12}H_{17}ON_3$ (2-(1-pyrrolidinyl)-2′-aminoacetanilide) (III): C, 65.72; H, 7.81; N, 19.16. Found: C, 65.50; H, 7.96; N, 18.83.

The IR spectrum of this compound was identical with that of the substance prepared by catalytic reduction of the above obtained II, and the mixed melting point showed no depression.

Attempted Cyclization of 2-(1-Pyrrolidinyl)-2′-hydroxylaminoacetanilide (II) to 2-(1-Pyrrolidinyl)-methylbenzimidazole 3-Oxide (IV)——The hydroxylamino compound was heated with 4*N* HCl or H_3PO_4, but the N-oxide could not be obtained.

N-Methyl-2′-nitroformanilide (VI, R=CH_3)——N-Methyl-*o*-nitroaniline (60 g., 0.4 mole) was added to AcOCOH, which was prepared from Ac_2O (95 ml., 1.0 mole) and HCOOH (98%, 38 ml., 1.0 mole). After standing overnight at room temperature, the resulting yellow solution was concentrated and the residual oil was dissolved in $CHCl_3$ (300 ml.), then neutralized with aq. $NaHCO_3$ solution. The $CHCl_3$ layer was separated, dried with Na_2SO_4, filtered, and evaporated to leave a yellow solid (69 g., 97%). Recrystallization from Et_2O gave pale yellow plates, m.p. 67~69°. *Anal.* Calcd. for $C_8H_8O_3N_2$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.51; H, 4.62; N, 15.34.

N-Ethyl-2′-nitroformanilide (VI, R=C_2H_5)——This compound was prepared form N-ethyl-*o*-nitroaniline by the same procedure mentioned above. Pale yellow prisms, yield 94%, m.p. 48~50°. *Anal.* Calcd. for $C_9H_{10}O_3N_2$: C, 55.66; H, 5.19; N, 14.43. Found: C, 55.61; H, 5.20; N, 14.20.

N-Benzyl-2′-nitroformanilide (VI, R=$CH_2C_6H_5$)——N-Benzyl-*o*-nitroaniline (23 g., 0.1 mole) was added to AcOCOH prepared from Ac_2O (28 ml., 0.3 mole) and HCOOH (98%, 11 ml., 0.3 mole). The mixture was stirred until the starting material dissolved and allowed to stand for 3 days at room temperature. The resulting pale yellow solution was evaporated, and Et_2O (30 ml.) was added to the residual oil to give pale yellow crystals (25 g., 97%). Recrystallization from AcOEt gave pale yellow prisms, m.p. 91~93°. *Anal.* Calcd. for $C_{14}H_{12}O_3N_2$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.40; H, 4.75; N, 10.91.

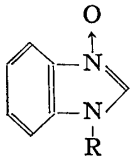
N-Ethyl-2′-nitroacetanilide (IX, R=C_2H_5)——A mixture of N-ethyl-*o*-nitroaniline (10.0 g.) and Ac_2O (9 ml.) was refluxed for 20 hr. The resulting yellow solution was evaporated, neutralized with aq. $NaHCO_3$ solution, and extracted with $CHCl_3$. The $CHCl_3$ layer was separated, dried, and evaporated to give a yellow oil which was solidified by cooling and rubbing (9.8 g.). Recrystallization from Et_2O and petr. ether gave yellow plates, m.p. 59~61°. *Anal.* Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.38; H, 5.82; N, 13.27.

N-Benzyl-2′-nitroacetanilide (IX, R=$CH_2C_6H_5$) (VII)——This compound was obtained from N-benzyl-*o*-nitroaniline (8.0 g.) and Ac_2O (7 ml.) by the same procedure mentioned above, yleld 7.8 g. Recrystallization from Et_2O gave pale yellow plates, m.p. 83~84°. *Anal.* Calcd. for $C_{15}H_{14}O_3N_2$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.74; H, 5.30; N, 10.40.

General Procedure for 1-Substituted Benzimidazole 3-Oxides (VII)——N-substituted 2′-nitroformanilide (20.0 g.) was added to a solution of EtOH (200 ml.) and EtOH-NH_4OH (saturated at 0°, 100 ml.). H_2S gas was passed into this mixture for about 2 hr. After standing overnight at room temperature, the resulting brown solution was concentrated to about 100 ml., and precipitated sulfur was filtered off and washed with EtOH. After removal of EtOH from the combined fitrate and washings, Me_2CO was added to the residual oil. The resulting white crystals were collected by filtration and recrystallized from AcOEt or Me_2CO to give white prisms, yield ca. 40%. From the filtrate N-substituted benzimidazole was obtained.

The compounds synthesized are listed in the Table I.

Table I. General Formula

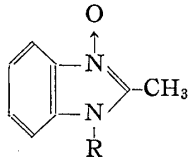


R	m.p.	Formula	Analysis (%) Calcd.			Found		
	(°C)		C	H	N	C	H	N
CH_3	60~62	$C_8H_8ON_2 \cdot 2H_2O$	52.16	6.57	15.21	52.37	6.87	14.94
C_2H_5	80~82	$C_9H_{10}ON_2 \cdot H_2O$	59.98	6.71	15.55	60.05	6.93	15.48
$CH_2C_6H_5$	47~50	$C_{14}H_{12}ON_2 \cdot 3H_2O$	60.42	6.52	10.07	60.76	6.73	10.24

NII-Electronic Library Service

General Procedure for 1-Substituted 2-Methylbenzimidazole 3-Oxides (X)——N-substituted-2′-nitroacetanilide[12] was treated in the same manner used for the formanilide. After the first crop of the N-oxide was collected, the filtrate was concentrated and chromatographed over alumina in $CHCl_3$ to give the second crop of the N-oxide, 1-substituted 2-methylbenzimidazole and N-substituted 2′-aminoacetanilide. The last compound was identified by mixed melting point and IR absorption spectrum with the authentic specimen, prepared by catalytic reduction of N-substituted 2′-nitroacetanilide.

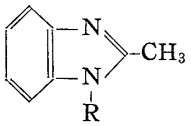
The compounds obtained in this reaction are listed in Tables II, III, and IV.

Table II. General Formula 

R	Yield	m.p.	Formula	Analysis (%) Calcd.			Found		
	(%)	(°C)		C	H	N	C	H	N
CH_3	80	65～70	$C_9H_{10}ON_2 \cdot 2H_2O$	54.53	7.12	14.13	54.51	7.28	14.27
C_2H_5	47	80～83	$C_{10}H_{12}ON_2 \cdot 2H_2O$	56.59	7.60	13.20	56.94	7.82	13.43
$CH_2C_6H_5$	59	83～85	$C_{15}H_{14}ON_2 \cdot H_2O$	70.29	6.29	10.93	70.25	6.51	10.83
C_6H_5	69	97～100 (164～165)[a]	$C_{14}H_{12}ON_2 \cdot 3/4H_2O$	70.72	5.72	11.78	70.43	5.83	11.78

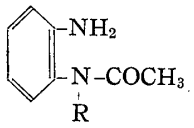
a) Anhydrous crystals

Cyclization of N-Substituted 2′-Aminoacetanilide (XII) to 1-Substituted 2-Methylbenzimidazole (XI)——In 4*N* HCl (5 ml.), XII (0.5 g.) was dissolved and the solution was heated on a water bath for 1 hr. After removal of the HCl, the residual oil was neutralized with aq. $NaHCO_3$ solution. The resulting substance was purified by a suitable method.

Table III. General Formula 

R	Yield (%)	m.p. (°C)	R	Yield (%)	m.p. (°C)
CH_3[13]	2	113～114	$CH_2C_6H_5$	12	197～199 (picrate)[a]
C_2H_5[14]	9	244～245 (picrate)	C_6H_5[12]	10	70～71

a) *Anal.* Calcd. for $C_{15}H_{14}N_2 \cdot C_6H_3O_7N_3$: C, 55.87; H, 3.80; N, 15.52. Found : C, 55.61; H, 3.92; N, 15.39.

Table IV. General Formula 

R	Yield	m.p.	Formula	Analysis (%) Calcd.			Found		
	(%)	(°C)		C	H	N	C	H	N
CH_3[12]	12	151～152	$C_9H_{12}ON_2$	65.83	7.37	17.06	65.89	7.34	16.76
C_2H_5	21	127～128	$C_{10}H_{14}ON_2$	67.38	7.92	15.72	67.37	8.06	15.92
$CH_2C_6H_5$	17	105～106	$C_{15}H_{16}ON_2$	74.97	6.71	11.66	75.13	6.78	11.43
C_6H_5[15]	17	110～111	$C_{14}H_{14}ON_2$	74.31	6.24	12.38	74.51	6.30	12.29

Catalytic Reduction of 1-Substituted Benzimidazole 3-Oxides (VII and X)——A solution of VII or X (ca. 0.2 g.) in MeOH (ca. 10 ml.) was shaken in a H_2 stream over Raney Ni (W-5, from 0.2 g. alloy), H_2 being absorbed within about 10 min. The catalyst was removed by filtration and washed with MeOH. The combined filtrate and washings were evaporated to give the corresponding benzimidazole.

1-Methoxybenzimidazole——Benzimidazole N-oxide (4.0 g.) was dissolved in a solution of NaOH (1.2 g.), H_2O (2 ml.), and MeOH (20 ml.), then MeI (4.5 g.) was added to the solution. The solution was

12) N-methyl-2′-nitroacetanilide : M. A. Phillips : J. Chem. Soc., **1929**, 2820.

NII-Electronic Library Service

warmed to 50° for 2 hr., and evaporated. The residual oil was extracted with Et_2O and dried. The Et_2O was removed from the extracts and the residue was distilled to give a colorless oil, b.p_5 98～99° (uncorr.). Yield 3.0 g. This compound was analysed as the picrate, yellow prisms (from MeOH), m.p. 202～204° (decomp.). *Anal.* Calcd. for $C_8H_8ON_2 \cdot C_6H_3O_7N_3$: C, 44.57; H, 2.94; N, 18.56. Found : C, 44.97; H, 3.25; N, 18.44.

The authors express their gratitude to Prof. Emeritus E. Ochiai of the University of Tokyo and Dr. K. Takeda, Director of this Laboratory, for their helpful guidance and encouragement. Thanks are due to Mr. I. Tanaka for ultraviolet spectral measurement, and to the members of the Analysis Room of this Laboratory for elemental analysis.

Summary

Previously unknown 1-substituted benzimidazole 3-oxides were synthesized by reductive ring-closure of N-acyl-N-substituted-*o*-nitroanilines. From the ultraviolet absorption spectra, it was shown that benzimidazole N-oxide exists as the N-oxide form in aqueous solution and as the N-hydroxyl form in ethanol solution.

(Received June 17, 1963)

13) O. Fischer : Ber., **25**, 2838 (1892).
14) R. Weidenhagen, G. Train, H. Wegner, L, Nordström : Ber., **75**, 1936 (1942).
15) E. J. Forbes, R. T. Wragg : Tetrahedron, 8, 79 (1960).

NII-Electronic Library Service