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**Cyclization of [(4- or 5-Substituted-2-benzimidazolyl)thio]acetic Acids.
Isolation and Identification of Two Possible Isomers of
Substituted Thiazolo[3,2-*a*]benzimidazol-3(2H)-one**

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Cyclizations of [(5-substituted-2-benzimidazolyl)thio]acetic acid (**2a—e**) to the corresponding thiazolo[3,2-*a*]benzimidazol-3(2H)-one (**5** and **6**) were successfully carried out by heating **2a—e** in Dowtherm A or Ac₂O/pyridine, and gave the two possible isomers (**5a—e** and **6a—e**) in a ratio of nearly 1:1 in all cases. Separation of **5** and **6** was successfully carried out, and their structures (namely, the direction of cyclization) were suggested on the basis of the NMR spectra. Dowtherm A was more effective than Ac₂O/pyridine, particularly for the cyclization of [(5-nitro-2-benzimidazolyl)thio]acetic acid (**2a**), which had been reported not to be cyclized with other reagents. Similar cyclization of [(4-methyl-2-benzimidazolyl)thio]acetic acid (**2f**) preferentially gave 8-methylthiazolo[3,2-*a*]benzimidazol-3(2H)-one (**6f**).

Keywords—cyclization; isomer; Dowtherm A; Ac₂O/pyridine; 2-benzimidazothiolacetic acid, thiazolo[3,2-*a*]benzimidazol-3(2H)-one

Preparations of thiazolo[3,2-*a*]benzimidazol-3(2H)-one (TBI) (**1**) and their derivatives—[(especially alkylidene derivatives (**1a**)] at the 2-position have been reported in many papers¹⁾ in view of their potential physiological activities. The nitro group forms a part of various drugs such as chloramphenicol, pyrrolnitrin,^{2a)} nitrofurantoin derivatives,^{2b)} azomycin,^{2c)} ilamycin,^{2d)} and so on, we were therefore interested in preparing the nitro derivative of TBI (**1**) in order to study its pharmacological activity. However, for the same purpose Chizhevskaya³⁾ tried the cyclization of [(5-nitro-2-benzimidazolyl)thio]acetic acid (**2a**) [(2-benzimidazolyl)thioacetic acid is abbreviated as BTA] to the corresponding nitro TBI with dicyclohexylcarbodiimide/pyridine, which was reported to be a better reagent than the usual Ac₂O/pyridine,⁴⁾ but without success. We also attempted the cyclization of the same compound (**2a**) and were able to achieve it. Furthermore, we found the general formation of two isomeric products (**5** and **6**) in the cyclization of 4- or 5-substituted BTA (**2**), whereas previous authors had reported only one of the isomers (TBI) in the cyclization of 4- or 5-substituted BTA. In this paper we report the details.

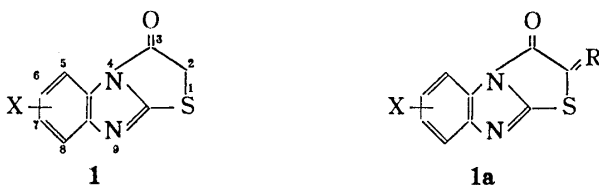


Chart 1

5-Nitro BTA (**2a**) was prepared starting from commercially available *o*-phenylenediamine derivative (**3a**) according to the reported method.³⁾ 5-Nitro BTA (**2a**) thus obtained was allowed to react under various cyclization conditions, such as Ac₂O/pyridine, ClCO₂Et/NEt₃, ClCO₂Et/LiOH, PPE, or refluxing in xylene or tetralin, but failed to cyclize. Finally, heating 5-nitro BTA (**2a**) in Dowtherm A⁵⁾ [an eutectic mixture of biphenyl (26.5%) and phenyl ether (73.5%)] gave a solid, mp 219—222 °C in 75.8% yield. However, as this solid was found to consist of two components having very similar *R_f* values on thin-layer chromatography (TLC), they

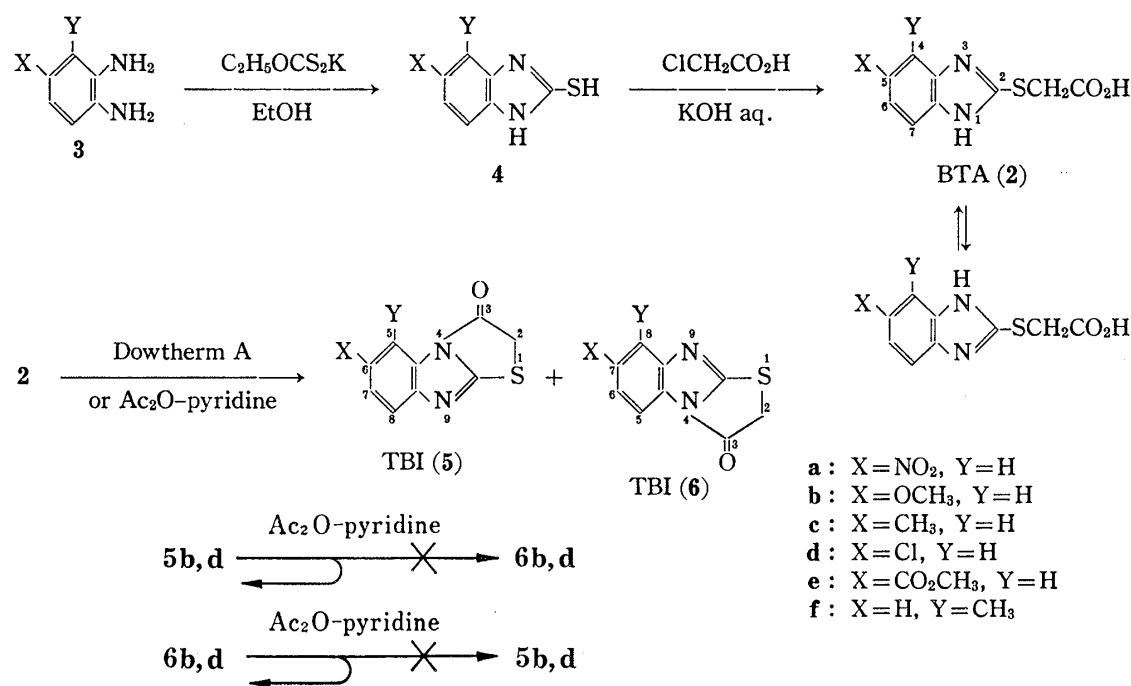


Chart 2

were separated by a combination of fractional recrystallization from ethyl acetate and column chromatography over silica gel into two compounds, **5a** (having the smaller R_f value) and **6a**. Both were found to have the same molecular formula of $\text{C}_9\text{H}_5\text{N}_3\text{O}_3\text{S}$, by elemental analysis and mass spectroscopy (MS, m/e 235: M^+). In the infrared (IR) spectrum both show a carbonyl band due to a five membered lactam at 1740 cm^{-1} , respectively. Furthermore, on treatment with methanol they readily gave the same methyl ester (**7a**), mp $153\text{--}154^\circ\text{C}$, which was identical with a sample prepared from the carboxylic acid **2a** by the usual method. These findings confirmed that the cyclization products (**5a** and **6a**) were the target compounds, but with a difference of cyclization direction. The formation of the two isomers (**5** and **6**) may easily occur in the cyclization of 5-substituted BTA (**2**) to the corresponding TBI. However, previous workers reported the formation of only one of the two possible isomers, that is, 6-substituted TBI (**5**), when 5-methoxy,⁶⁾ 5-methyl,⁷⁾ or 5-chloro⁸⁾ BTA (**2**) was cyclized. The discrepancy between previous workers' results and ours prompted us to reinvestigate the cyclization of other 5-substituted BTAs (**2**). In addition to this, we intended to compare our method for cyclization using Dowtherm A with the usual method using $\text{Ac}_2\text{O/pyridine}$. Other 5-substituted BTA were prepared as well as 5-nitro BTA (Chart 2).

First, 5-methoxy BTA (**2b**) was allowed to react with $\text{Ac}_2\text{O/pyridine}$ according to the reported method.⁶⁾ In this reaction, two products, **5b** (known,⁶⁾ mp $161\text{--}163^\circ\text{C}$) and **6b** (unknown, mp $152\text{--}154^\circ\text{C}$), were formed, in contrast to the previous report⁶⁾ (Table I). These two products were found to have the same molecular formula of $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2\text{S}$ by elemental

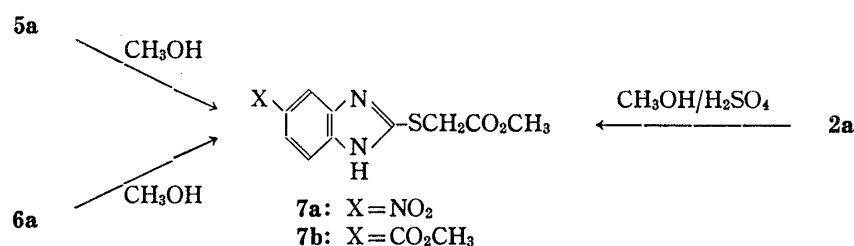


Chart 3

TABLE I. The Yields of TBI (5 and 6) obtained by Cyclization of BTA (2)

Starting material	Method ^{a)}	Combined yield (%)	Ratio of 5: 6 by NMR	Isolated yield (%)		mp (°C)	
				5	6	5	6
2a (X=NO ₂ , Y=H)	A	75.8	1.0:1.0	4.6	20.6	224—226	230—232
	B	0	—	—	—	—	—
2b (X=OCH ₃ , Y=H)	A	79.6	1.0:1.3	26.3	19.9	161—163 ^{b)}	152—154
	B	44.0	1.0:1.1	Not tried		—	—
2c (X=CH ₃ , Y=H)	A	51.5	1.0:1.0	Not tried		199—201 ^{c)}	138—139
	B	69.2	1.0:1.0	9.0	3.6	—	—
2d (X=Cl, Y=H)	A	95.2	1.0:1.0	39.5	40.4	195—197 ^{d)}	181.5—182
	B	88.4	1.0:1.0	41.1	36.3	—	—
2e (X=CO ₂ CH ₃ , Y=H)	A	60.3	1.3:1.0	20.2	14.7	187—189	193—195
	B	26.5	1.1:1.0	Not tried		—	—
2f (X=H, Y=CH ₃)	A	59.4	1.0:18.5	Not tried		—	193—194 ^{e)}
	B	78.2	1.0:8.0	—	48.5	—	—

a) A: Dowtherm A, B: Ac₂O-pyridine, b) lit.⁷⁾ mp 154°C, c) lit.⁸⁾ mp 183—184°C, d) lit.⁹⁾ mp 183—184°C, e) lit.⁷⁾ mp 191—192°C.

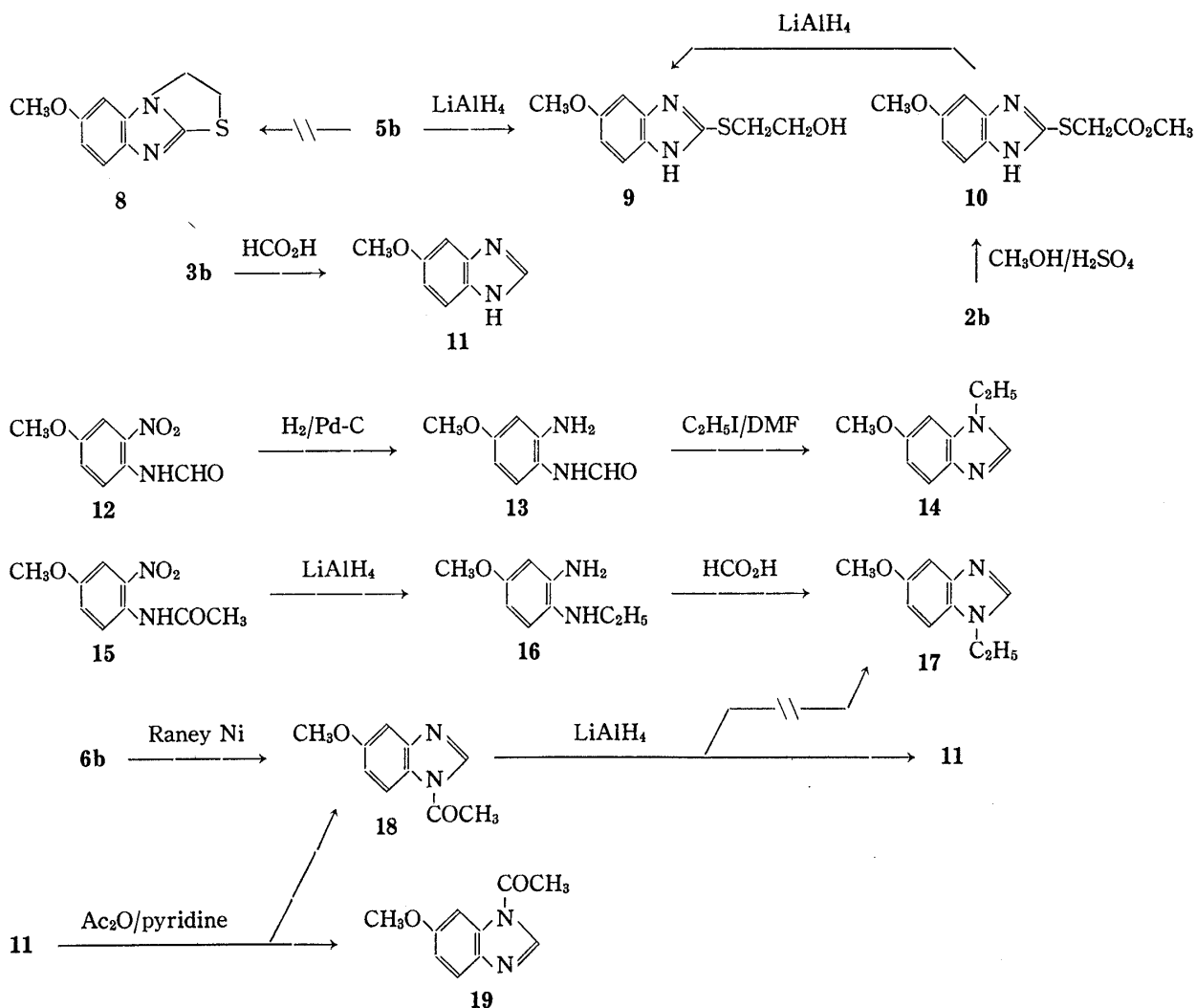


Chart 4

analysis and MS (m/e 220: M^+). Their IR spectra show a five-membered lactam carbonyl band at 1745 cm^{-1} . Therefore, they should be cyclized products.

The direction of cyclization was suggested by analysis of the NMR spectrum as follows. Since tricyclic TBI should be coplanar, $C_5\text{-H}$ must be deshielded relative to other aromatic proton by the anisotropic effect of lactam carbonyl. Thus, we attempted to prepare the C_3 -decarbonyl compound (8), in which no proton would be deshielded, for comparison with **5b**. However, treatment of **5b** with lithium aluminum hydride gave the ring-opened alcohol (9) and thiol⁶⁾ (4b), instead of the C_3 -decarbonyl compound (8). The structure of the alcohol (9) was determined by comparison with an authentic sample prepared by reduction of the ester (10). As the C_3 -decarbonyl compound (8) could not be obtained, we chose 5-methoxy BTA (**2b**) as a reference compound in order to compare its aromatic protons with the corresponding ones of the cyclized products (**5b** and **6b**). Table II lists the chemical shifts of protons on the benzene ring of **2b**, **5b**, and **6b**, and Table III lists the difference values of chemical shifts between the protons of **2b**, and the corresponding⁹⁾ ones of **5b** or **6b**. These data reveal that $C_5\text{-H}$ ($J=2.0$ Hz) in **5b** is shifted downfield (0.40 ppm) most markedly and $C_5\text{-H}$ ($J=9.0$ Hz) in **6b** is similarly shifted (0.42 ppm). This result suggested that the structures (direction of cyclization of **5b** and **6b**) should be as shown in Chart 2, based on a comparison of bicyclic BTA (**2b**) with tricyclic TBI (**5b** and **6b**). The former exists in tautomers at the imidazole ring, while the latter does not. If this tautomerism significantly influences the proton chemical shifts of

TABLE II. NMR Data for BTA (**2**) and TBI (**5** and **6**) in $\text{DMSO}-d_6$ (δ , ppm)

Compound	Chemical shift (J : Hz)			
	$C_4\text{-H}$	$C_6\text{-H}$	$C_7\text{-H}$	$-\text{SCH}_2-$
2a ($X=\text{NO}_2$, $Y=\text{H}$)	8.31 (d, $J=2.0$)	8.06 (dd, $J=2.0$ and 9.0)	7.59 (d, $J=9.0$)	4.24 (s)
2b ($X=\text{OCH}_3$, $Y=\text{H}$)	6.94 (d, $J=2.0$)	6.69 (dd, $J=2.0$ and 9.0)	7.30 (d, $J=9.0$)	4.02 (s)
2c ($X=\text{CH}_3$, $Y=\text{H}$)	7.21 (d, $J=2.0$)	6.90 (dd, $J=2.0$ and 9.0)	7.29 (d, $J=9.0$)	4.10 (s)
2d ($X=\text{Cl}$, $Y=\text{H}$)	7.46 (d, $J=2.0$)	7.08 (dd, $J=2.0$ and 9.0)	7.41 (d, $J=9.0$)	4.11 (s)
2e ($X=\text{CO}_2\text{CH}_3$, $Y=\text{H}$)	8.02 (d, $J=2.0$)	7.78 (dd, $J=2.0$ and 8.0)	7.50 (d, $J=8.0$)	4.20 (s)
2f ($X=\text{H}$, $Y=\text{CH}_3$)	a)	6.89—7.35 (3H, m)		4.20 (s)

Compound	Chemical shift (J : Hz)				
	$C_2\text{-H}$	$C_5\text{-H}$	$C_6\text{-H}$	$C_7\text{-H}$	$C_8\text{-H}$
5a ($X=\text{NO}_2$, $Y=\text{H}$)	4.70 (s)	8.48 (d, $J=2.0$)	—	8.26 (dd, $J=2.0$ and 10.0)	7.73 (d, $J=7.0$)
6a ($X=\text{NO}_2$, $Y=\text{H}$)	4.65 (s)	7.98 (d, $J=9.0$)	8.22 (dd, $J=2.0$ and 9.0)	—	8.35 (d, $J=2.0$)
5b ($X=\text{OCH}_3$, $Y=\text{H}$)	4.59 (s)	7.34 (d, $J=2.0$)	3.81 ^{b)} (s)	6.95 (dd, $J=2.0$ and 9.0)	7.46 (d, $J=9.0$)
6b ($X=\text{OCH}_3$, $Y=\text{H}$)	4.59 (s)	7.72 (d, $J=9.0$)	6.89 (dd, $J=2.0$ and 9.0)	3.81 ^{b)} (s)	7.15 (d, $J=2.0$)
5c ($X=\text{CH}_3$, $Y=\text{H}$)	4.59 (s)	7.64 (d, $J=2.0$)	2.43 ^{b)} (s)	7.14 (dd, $J=2.0$ and 9.0)	7.44 (d, $J=9.0$)
6c ($X=\text{CH}_3$, $Y=\text{H}$)	4.59 (s)	7.69 (d, $J=9.0$)	7.11 (dd, $J=2.0$ and 9.0)	2.43 ^{b)} (s)	7.36 (d, $J=2.0$)
5d ($X=\text{Cl}$, $Y=\text{H}$)	4.62 (s)	7.79 (d, $J=2.0$)	—	7.36 (dd, $J=2.0$ and 9.0)	7.60 (d, $J=9.0$)
6d ($X=\text{Cl}$, $Y=\text{H}$)	4.62 (s)	7.82 (d, $J=9.0$)	7.32 (dd, $J=2.0$ and 9.0)	—	7.64 (d, $J=2.0$)
5e ($X=\text{CO}_2\text{CH}_3$, $Y=\text{H}$)	4.63 (s)	8.28 (d, $J=2.0$)	3.88 ^{b)}	7.96 (dd, $J=2.0$ and 9.0)	7.62 (d, $J=9.0$)
6e ($X=\text{CO}_2\text{CH}_3$, $Y=\text{H}$)	4.63 (s)	7.90 (dif. s)	7.89 (dif. m)	3.88 ^{b)} (s)	8.04 (dif. s)
6f ($X=\text{H}$, $Y=\text{CH}_3$)	4.63 (s)	7.65 (m)	7.18 (2H, m)		2.52 ^{b)} (s)

a) $C_4\text{-H}$, b) Methyl signal.

TABLE III. Proton Shifts (Δ Value) of 6-Substituted (5) and 7-Substituted TBI (6) from the Corresponding Protons of BTA (2)

Compound	C ₅ -H	C ₆ -H	C ₇ -H	C ₈ -H
5a	-0.17	—	-0.20	-0.14
6a	-0.39	-0.16	—	-0.04
5b	-0.40	—	-0.26	-0.16
6b	-0.42	-0.20	—	-0.21
5c	-0.43	—	-0.24	-0.15
6c	-0.40	-0.21	—	-0.15
5d	-0.33	—	-0.28	-0.19
6d	-0.41	-0.24	—	-0.18
5e	-0.26	—	-0.18	-0.12
6e	-0.40	-0.11	—	-0.02
6f	-0.53	-0.06	-0.06	—

Minus signs denote low-field shifts.

the benzene ring, 5-methoxy BTA (2b) might not be suitable as a reference compound for methoxy TBI (5b and 6b).

Thus, in order to investigate whether the tautomerism influences the proton chemical shifts on the benzene ring or not, we attempted to examine the NMR spectra of 5-methoxybenzimidazole (11), 1-ethyl-6-methoxybenzimidazole (14) and 1-ethyl-5-methoxybenzimidazole (17) as model compounds. 5-Methoxybenzimidazole (11) was prepared according to the reported method.¹⁰ The 1-ethyl-6-methoxy compound (14) was prepared starting from 2'-nitro-*p*-formanisidide (12), which was reduced to the amine (13). Treatment of the amine (13) with ethyl iodide, followed by spontaneous cyclization gave the desired 1-ethyl-6-methoxy compound (14). The 1-ethyl-5-methoxy compound (17) was prepared starting from 2'-nitro-*p*-acetoanisidide (15). Treatment of 15 with lithium aluminum hydride for conversion of the N-acetyl group to an ethyl group was accompanied by the simultaneous reduction of the nitro group to give the diamine (16). The diamine (16) was too labile to characterize, but the structure was clear from the MS [m/e 166 (C₉H₁₄N₂O): M⁺] and the absence of nitro group absorption in the IR spectrum. The diamine (16) was treated with formic acid according to the general method¹¹ for benzimidazole synthesis to give the 1-ethyl-5-methoxy compound (17).

TABLE IV. Chemical Shifts (δ , ppm, DMSO- d_6) of Benzenoid Protons of 5-Methoxy-(11), 1-Ethyl-6-methoxy-(14), and 1-Ethyl-5-methoxybenzimidazole (17).

Compound	Proton		
	C ₄ -H	C ₆ -H	C ₇ -H
11	7.45	6.79	7.07
14	7.57(0.12)	6.80(0.01)	7.13(0.06)
17	7.47(0.02)	6.87(0.08)	7.18(0.11)

Figures in parenthesis are difference (Δ) values from 11.

Chemical shift values of benzenoid protons of the above compounds (11, 14, and 17) are collected in Table IV. The figures in parentheses are difference values from the corresponding protons of the reference compound (11). These values are 0.12 ppm or less, which are small enough to indicate that the effect of tautomerism upon the proton chemical shifts is negligible. Thus, the above-mentioned method should be valid.

For further characterization of 5b and 6b, 6b was desulfurized with Raney Ni to give the 1-acetyl compound (18). A further supply was obtained by acetylation of 11, and was treated

with lithium aluminum hydride for conversion to the 1-ethyl-5-methoxy compound (17). However, this reduction resulted in the formation of the N-unsubstituted compound (11).

The products (5b and 6b) could not be separated quantitatively by column chromatography, and in order to assess the ratio of the products (5b and 6b) accurately, we measured the NMR spectrum of the mixture before separation. However, no suitable C₂-H or methoxy group signal of these compounds (5b and 6b) was available for integration. Thus, we used a shift reagent, tris(dipivalomethanato)europium [Eu(DPM)₃], for separation of the signals. As europium could coordinate with carbonyl oxygen¹²⁾ of these molecule (5b and 6b), methoxy group or C₂-H signals, or both, were expected to separate. The published method¹²⁾ was used. The results are shown in Fig. 1; the methoxy groups of each compound were satisfactorily separated. Integration gave a ratio of 5b: 6b=1.0: 1.1.

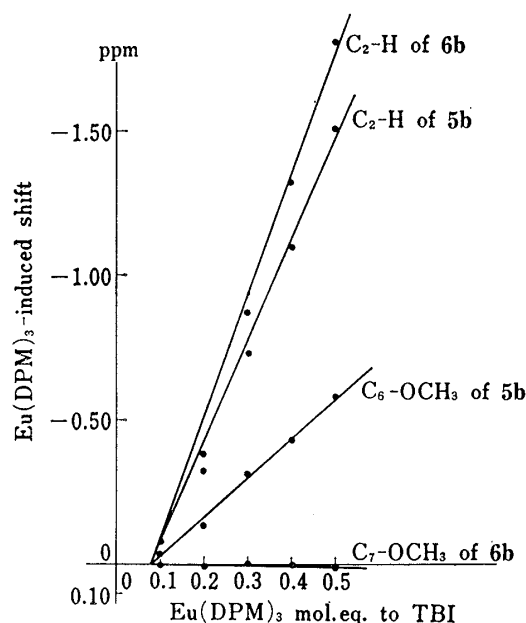


Fig. 1. The Measured Eu(DPM)₃-induced Shifts of 6-(5b) and 7-Methoxy TBI (6b)

Minus signs denote lower-field shifts.

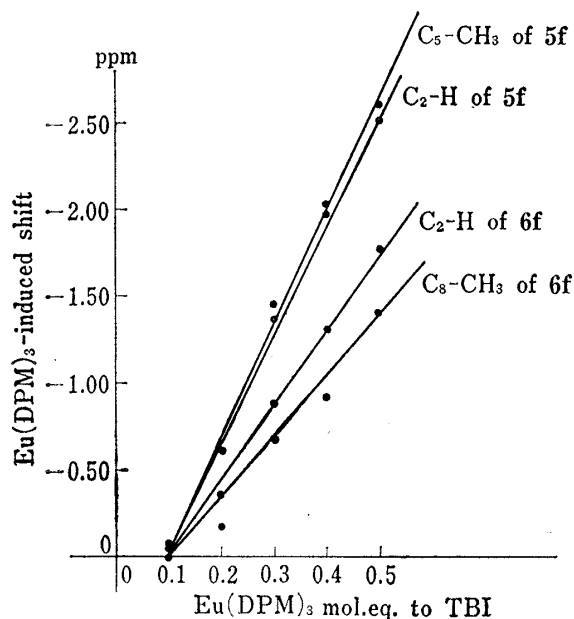


Fig. 2. The Measured Eu(DPM)₃-induced Shifts of 5-(5f) and 8-Methyl TBI (6f)

Minus signs denote lower-field shifts.

Next, 5-methoxy BTA (2b) was allowed to react in Dowtherm A. This reaction also resulted in the formation of two cyclized products (5b and 6b). The ratio was 5b: 6b=1.0: 1.3. As regards yields, the Dowtherm A method (79.6%) was superior to the Ac₂O/pyridine method (44.0%) (Table I).

Our reinvestigation revealed that the cyclization of 5-methoxy BTA (2b) gave two cyclized products (5b and 6b). The same treatment of the known 5-methyl (2c), 5-chloro (2d), and unknown 5-methoxycarbonyl BTA (2e) gave two cyclized products, 6-substituted (5) and 7-substituted TBI (6), respectively. By analysis of their NMR spectra the structures were deduced and the formation ratio was estimated as described for methoxy TBI (5b and 6b). The results are listed in Tables I and II, showing that the Dowtherm A method is superior to the generally used Ac₂O/pyridine method, especially for nitro BTA (2a). The formation ratio differs slightly due to substituents on the benzene ring. This may be explained by the basicity of the nitrogen, situated *para* to the substituent, which should be strengthened by an electron-donating group or weakened by an electron-withdrawing one. However the fact that 5-nitro BTA (2a) gave the ratio of 1: 1 lead us to the conclusion that the ratio is roughly unity for all cases, so that the 5-substituent of BTA (2) has only a minor electronic effect on the cyclization.

Subsequently, we attempted to investigate why our results and previous workers' results were different for the cyclization of 5-substituted BTA (2). This difference might be because 6-substituted TBI (5) is thermodynamically more stable than the corresponding 7-substituted TBI (6). If so, they might have used reaction conditions under which 6-substituted TBI (5) was preferentially formed. In order to ascertain this, 6-methoxy (5b), 7-methoxy (6b), 6-chloro (5d), and 7-chloro TBI (6d) were allowed to react under the cyclization conditions (heating in Ac_2O /pyridine). However, no isomerization occurred at all (Chart 2). We therefore concluded that previous workers might have failed to obtain the other isomer in the work-up procedure, if both isomers were formed in their experiments. Their assignment of the products coincides with ours.

Finally we attempted the same reaction on 4-methyl BTA⁷⁾ (2f), whose 4-methyl substituent might exert some steric effect. The cyclization of this compound (2f) was also reported⁷⁾ to give only 8-methyl TBI.

Treatment of 4-methyl BTA (2f) as described for 5-substituted BTA (2) resulted in the predominant formation of 8-methyl TBI (6f), which was easily isolated by recrystallization, whereas no minor product, 5-methyl TBI (5f), could be isolated. The existence of a minor amount of 5-methyl TBI (5f) was suggested by observation of its (5f) methyl signal in the $\text{Eu}(\text{DPM})_3$ -induced NMR spectrum of the reaction mixture. The structure (cyclization direction) of 6f was suggested by analysis of the NMR spectrum as in the cases of methoxy TBI (5b and 6b) (Fig. 2). In the NMR spectrum of 6f, the C_5 -proton appears to be isolated from other aromatic protons at lower field. However, as the corresponding proton in 4-methyl BTA (2f) is buried in aromatic protons, the difference value could not be estimated accurately. This result shows that 4-substituted BTA cyclizes preferentially to the sterically less hindered 1-position. Thus, we concluded that steric effects rather than electronic ones of substituents on the benzene ring govern the direction of cyclization of BTA (2).

Experimental

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. IR, NMR and mass spectra were obtained with Shimadzu IR-400, Hitachi R-24B (60 MHz) and JEOL JMN-4H-100 (100 MHz), and JEOL JMS-01-SG-2 spectrometers, respectively. In the NMR spectra chemical shifts are given in δ -values referred to the internal tetramethylsilane (TMS), and the assignment of all NH and OH signals were confirmed by observing the disappearance of their signals after addition of D_2O . Mass spectra were measured by the direct inlet system. For column chromatography, Kieselgel 60 (70–230 mesh), Merck, and for TLC, Kieselgel GF₂₅₄, Merck, were used. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; m, multiplet; dif, diffused; sh, shoulder.

5-Carboxy-2-benzimidazolethiol (4, X=CO₂H, Y=H)—The following procedure was used, according to the general method.¹³⁾ A mixture of commercial 3,4-diaminobenzoic acid (3, X=CO₂H, Y=H) (500 mg) and potassium ethyl xanthate (1.50 g) in EtOH (10 ml) and water (21 ml) was refluxed for 4 h. After cooling, the reaction mixture was acidified (pH 3–4) with 20% AcOH. The separated crystals were collected and recrystallized from 50% EtOH to give pale brown leaflets (364 mg, 56.7%, mp > 290°C. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 1675 (CO₂H). MS m/e : 194 (M⁺). This compound was used for the following reaction without further purification.

4- or 5-Substituted BTA, [(4- or 5-Substituted-2-benzimidazolyl)thio]acetic Acid (2)—General Procedure: A solution of KOH (7.00 g, 125 mmol) in water (50 ml) was added to a mixture of the thiol (4) (26 mmol) and chloroacetic acid (3.50 g, 37 mmol) in EtOH (50 ml). The resulting solution was refluxed for 6 h. Decolorizing carbon was then added, and after 10 min removed by filtration. The filtrate was acidified (pH 3–4) with 20% AcOH, and stored in a refrigerator overnight. The separated product was collected by filtration and recrystallized from 50% EtOH.

5-Nitro BTA, [(5-Nitro-2-benzimidazolyl)thio]acetic Acid (2a): 70.8% yield, mp 203–205°C (lit.,³⁾ mp 215–216°C). *Anal.* Calcd for C₉H₇N₃O₄S: C, 42.69; H, 2.79; N, 16.60. Found: C, 42.90; H, 2.67; N, 16.43.

5-Methoxy BTA, [(5-Methoxy-2-benzimidazolyl)thio]acetic Acid (2b): 55.7% yield, mp 196–198°C (lit.,⁶⁾ mp 190°C).

5-Methyl BTA, [(5-Methyl-2-benzimidazolyl)thio]acetic Acid (2c): 54.1% yield, mp 205–207°C (lit.,⁷⁾ mp 201°C).

5-Chloro BTA, [(5-Chloro-2-benzimidazolyl)thio]acetic Acid (**2d**): 58.2% yield, mp 194—196°C (lit.,⁹) mp 197°C). *Anal.* Calcd for $C_9H_7ClN_2O_2S$: C, 44.54; H, 2.90; N, 11.54. Found: C, 44.33; H, 2.86; N, 11.29.

5-Carboxy BTA, [(5-Carboxy-2-benzimidazolyl)thio]acetic Acid (**2**, X=CO₂H, Y=H): 88.5% yield, colorless leaflets, mp 250—260°C (dec.). *Anal.* Calcd for $C_{10}H_8N_2O_4S$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.45; H, 3.18; N, 11.67. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3300—2400 br (NH and COOH), 1715, 1675 (COOH). NMR (DMSO-*d*₆) δ : 4.05 (2H, s, -SCH₂-), 7.46 (1H, d, *J*=8.0 Hz, C₇-H), 7.66 (1H, dd, *J*=2.0 and 8.0 Hz, C₆-H), 8.00 (1H, d, *J*=2.0 Hz, C₄-H). MS *m/e*: 252 (M⁺).

5-Methoxycarbonyl BTA, [(5-Methoxycarbonyl-2-benzimidazolyl)thio]acetic Acid (**2e**): a) Methyl [(5-Methoxycarbonyl-2-benzimidazolyl)thio]acetate (**7b**): A suspension of dicarboxylic acid (**2**, X=CO₂H, Y=H) (500 mg) in abs. MeOH was saturated with dry HCl gas under ice-cooling. The mixture was refluxed for 2.5 h and then the solvent was evaporated off *in vacuo*. The residue was dissolved in AcOEt, washed with 5% Na₂CO₃ and dried over MgSO₄. Removal of the solvent *in vacuo* gave the diester (**7b**), 290 mg (51.7%), which was recrystallized from benzene-MeOH to give pale yellow leaflets, mp 136—137°C. *Anal.* Calcd for $C_{12}H_{12}N_2O_4S$: C, 51.42; H, 4.32; N, 9.99. Found: C, 51.40; H, 4.22; N, 9.62. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3200 (NH), 1735, 1690 (C=O). NMR (DMSO-*d*₆) δ : 3.69 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 4.28 (2H, s, -SCH₂-), 7.50 (1H, d, *J*=8.0 Hz, C₇-H), 7.86 (1H, dd, *J*=2.0 and 8.0 Hz, C₆-H), 8.01 (1H, d, *J*=2.0 Hz, C₄-H). MS *m/e*: 280 (M⁺).

b) 5-Methoxycarbonyl BTA (**2e**): A suspension of the diester (**7b**) (2.00 g) in conc. HCl (12 ml) and AcOH (60 ml)¹⁴ was heated at 42—43°C (bath temperature) for 4.5 h. The mixture was then cooled and the solvent was evaporated off *in vacuo*. The resulting residue was washed with AcOEt and dried to give the monoester (**2e**) (1.61 g). Recrystallizations from 20% MeOH gave colorless needles (1.24 g, 65.5%), mp 209—210°C. *Anal.* Calcd for $C_{11}H_{10}N_2O_4S$: C, 49.62; H, 3.79; N, 10.52. Found: C, 49.57; H, 3.65; N, 10.50. IR $\nu_{\max}^{\text{Nujol}}$ cm⁻¹: 3400 br, 3200 br (NH), 1710—1680 (C=O). NMR (DMSO-*d*₆) δ : 3.88 (3H, s, OCH₃), 4.20 (2H, s, -SCH₂-), 5.00 (2H, br s, OH and NH), 7.50 (1H, d, *J*=8.0 Hz, C₇-H), 7.78 (1H, dd, *J*=2.0 and 8.0 Hz, C₆-H), 8.04 (1H, d, *J*=2.0 Hz, C₄-H). MS *m/e*: 266 (M⁺).

4-Methyl BTA[(4-Methyl-2-benzimidazolyl)thio]acetic Acid (**2f**): 69.6% yield, mp 224—226°C (lit.,⁷) mp 220—221°C).

Elemental analysis of the known BTA (**2**) was done only on the products having lower melting point than that reported in the literature.

Cyclization of 4- or 5-Substituted BTA (2**). Formation of Two Isomers of [Thiazolo[3,2-*a*]benzimidazol-3(2H)-one] (**5** and **6**)**—a) Dowtherm A Method: A suspension of 4- or 5-substituted BTA (3.6 mmol) in Dowtherm A⁵ (10 ml) was heated at 190—206°C (bath temperature) for 20 min, then cooled. The resulting

TABLE V. Characterization of Cyclized Products, TBI (**5** and **6**)

Compound	Recrystallization solvent	Crystal form	Formula	Analysis (%)			IR $\nu_{\max}^{\text{Nujol}}$ cm ⁻¹ C=O
				Calcd (Found)			
				C	H	N	
5a	AcOEt	Light yellow Needles	C ₉ H ₅ N ₃ O ₃ S	45.96 (46.05)	2.14 2.07	17.86 17.71)	1740
6a	AcOEt	Light yellow Needles	C ₉ H ₅ N ₃ O ₃ S	45.96 (45.89)	2.14 2.06	17.86 18.10)	1740
5b	EtOH	Pale pink Plates	C ₁₀ H ₈ N ₂ O ₂ S	54.53 (54.59)	3.66 3.50	12.72 12.41)	1745
6b	EtOH	Light brown Needles	C ₁₀ H ₈ N ₂ O ₂ S	54.53 (54.57)	3.66 3.46	12.12 12.44)	1745
5c	EtOH	Light yellow Needles	C ₁₀ H ₈ N ₂ OS	58.80 (58.91)	3.95 3.80	13.72 13.34)	1745
6c	EtOH	Light yellow Needles	C ₁₀ H ₈ N ₂ OS	58.80 (58.59)	3.95 3.94	13.72 13.46)	1735
5d	Benzene	Light yellow Leaflets	C ₉ H ₅ ClN ₂ OS	48.11 (48.39)	2.24 2.20	12.47 12.41)	1745
6d	Benzene	Colorless Needles	C ₉ H ₅ ClN ₂ OS	48.11 (48.06)	2.24 2.10	12.47 12.76)	1750
5e	AcOEt	Colorless Needles	C ₁₁ H ₈ N ₂ O ₃ S	53.22 (53.26)	3.25 3.18	11.28 10.98)	1730br
6e	AcOEt	Colorless Needles	C ₁₁ H ₈ N ₂ O ₃ S	53.22 (53.30)	3.25 3.20	11.28 11.03)	1745, 1710
6f	EtOH	Light yellow Needles	C ₁₀ H ₈ N ₂ OS	58.80 (58.90)	3.95 3.81	13.72 13.29)	1750

The MS spectrum of each compound has the M⁺ peak as the base peak.

crystals were collected in the case of 5-nitro BTA. In other cases, hexane was added to the cooled solution in order to separate the crystals [Dowtherm A was evaporated off before adding hexane, in the case of 5-methyl BTA (**2c**)]. The crude products thus obtained were purified on a short column of silica gel with AcOEt–benzene (1:10) or acetone–benzene (1:8) as an eluent for measurement of the NMR spectrum. Care was taken that the mixture (**5** and **6**) should not be separated during the purification process.

For isolation of the mixture into 6-substituted (**5**) and 7-substituted TBI (**6**), the mixture was first recrystallized from an appropriate solvent as shown in Table V. This procedure gave 7-substituted TBI (**6a**) in the case of the nitro compound or 6-substituted TBI (**5**) in other cases. The residue obtained by evaporation of the mother liquor to dryness was recrystallized to give another isomer (**6b**) in the case of the 7-methyl compound, or chromatographed carefully over silica gel with AcOEt–benzene (1:10), acetone–benzene (1:8), or AcOEt–hexane (1:3) as an eluent to give 6-substituted TBI (**5**) and 7-substituted TBI (**6**). The data for characterization of TBI (**5** and **6**) are shown in Table V.

b) Ac_2O /Pyridine Method: A solution of 4- or 5-substituted BTA (**2**) (7.5 mmol) in Ac_2O (1.5 ml) and pyridine (2.3 ml) was heated at 90°C (bath temperature) for 10 min. The reaction mixture was poured into water and the crystals that separated were collected by filtration with suction, or the mixture was evaporated to dryness *in vacuo* when the products were oily (in the case of **2f**). Measurement of the NMR spectra and purification were as described for the Dowtherm A method.

Measurement of the NMR Spectrum using Shift Reagent—a) Method and Conditions of Measurement: A sample (a mixture of **5** and **6**) (*ca.* 20 mg) was accurately weighed and dissolved in CDCl_3 (0.3 ml). $\text{Eu}(\text{DPM})_3$ was successively added to this solution (0.1, 0.2, 0.3, 0.4, and 0.5 molar equivalent). The NMR spectra of the resulting solutions were measured with TMS as an internal standard, and good straight lines were obtained on plotting the induced shift values against concentration of $\text{Eu}(\text{DPM})_3$ for each signal in this range (Fig. 1 and 2).

b) Assignment of Signals: Signals were assigned by comparison of the NMR spectrum of a sample (a mixture of **5** and **6**) with 6-substituted TBI (**5**) or 7-substituted TBI (**6**). The figures show methoxy TBI (**5b** and **6b**) (Fig. 1) and 5- (**5f**) and 8-methyl TBI (**6f**) (Fig. 2) as examples. The ratios thus obtained are shown in Table I. In the case of nitro TBI (**5a** and **6b**), $\text{C}_2\text{-H}$ is separated in the absence of $\text{Eu}(\text{DPM})_3$.

Methyl [(5-Nitro-2-benzimidazolyl)thio]acetate (7a**)**—a) From 6-Nitro TBI (**5a**): A solution of **5a** (2.1 mg) in MeOH (3 ml) was refluxed for 3 h. Removal of the solvent *in vacuo* gave the ester (**7a**), mp 151–153°C, which was identical with an authentic sample.

b) From 7-Nitro TBI (**6a**): **6a** (2.4 mg) was treated as described for **5a** to give the ester (**7a**) (2.6 mg), mp 152–154°C, which was identical with an authentic sample.

c) Preparation of an Authentic Sample of the Ester (**7a**): A suspension of 5-nitro BTA (**2a**) (107 mg) in MeOH (3 ml) containing conc. H_2SO_4 (0.04 ml) was refluxed for 2 h. The solvent was evaporated off *in vacuo*. The residue was dissolved in AcOEt, then the solution was washed with dil. NaHCO_3 , and dried over MgSO_4 . The residue obtained by removal of the solvent was chromatographed over silica gel with AcOEt–hexane (2:3) as an eluent to give pale yellow rods (97 mg, 86.6%), mp 149–151°C, which were recrystallized from AcOEt–hexane. *Anal.* Calcd for $\text{C}_{10}\text{H}_6\text{N}_3\text{O}_4\text{S}$: C, 44.94; H, 3.39; N, 15.72. Found: C, 44.75; H, 3.18; N, 15.31. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3275 (NH), 1715 (C=O). NMR (CD_3OD) δ : 3.74 (3H, s, OCH_3), 4.00 (2H, s, $-\text{SCH}_2-$), 7.50 (1H, d, $J=9.0$ Hz, $\text{C}_7\text{-H}$), 8.09 (1H, dd, $J=2.0$ and 9.0 Hz, $\text{C}_6\text{-H}$), 8.32 (1H, d, $J=2.0$ Hz, $\text{C}_4\text{-H}$), MS m/e : 267 (M^+).

2-[(5-Methoxy-2-benzimidazolyl)thio]ethanol (9**)**—a) Reduction of 6-Methoxy TBI (**5b**): LiAlH_4 (35 mg) was added to a solution of 6-methoxy TBI (**5b**) (50 mg) in anhyd. THF (3 ml). The mixture was refluxed for 1.3 h. After cooling, the reaction mixture was treated with 3% NaOH (0.5 ml) and filtered by suction. The residue was washed with AcOEt. The combined filtrate and washings were dried over MgSO_4 , and evaporated to dryness *in vacuo* to give a crude product (46 mg), which was chromatographed over silica gel with benzene–AcOEt (1:1) as an eluent to give 5-methoxy-2-benzimidazoethiol (**4b**) (8 mg, 18.4%) as colorless fine columns, mp 260°C (dec.) (lit.,⁶ mp 252°C). Further elution with the same solvent gave the alcohol (**9**) (19 mg, 37.3%) as colorless needles, mp 89–91°C, which were recrystallized from benzene. The product was identical with an authentic sample.

b) Preparation of the Authentic Alcohol (**9**): i) Methyl [(5-Methoxy-2-benzimidazolyl)thio]acetate (**10**): A solution of 5-methoxy BTA (**2b**) (1.02 g) in MeOH (8 ml) containing conc. H_2SO_4 (0.3 ml) was refluxed for 4 h, then cooled. The solvent was evaporated off *in vacuo*. The residue was diluted with water, followed by basification with dil. NaHCO_3 , and extracted with AcOEt. The organic layer was washed with water, dried over MgSO_4 , and concentrated *in vacuo*. The residue (1.130 g, 100%) was recrystallized from benzene to give colorless needles, mp 77–78°C. *Anal.* Calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3\text{S} \cdot 1/2\text{H}_2\text{O}$: C, 50.56; H, 5.02; N, 10.72. Found: C, 50.68; H, 5.06; N, 10.35. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm^{-1} : 3500 (NH), 1735 (C=O). NMR (CDCl_3) δ : 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.96 (2H, s, $-\text{SCH}_2-$), 6.80 (1H, dd, $J=9.0$ and 2.0 Hz, $\text{C}_6\text{-H}$), 6.97 (1H, d, $J=2.0$ Hz, $\text{C}_4\text{-H}$), 7.38 (1H, d, $J=9.0$ Hz, $\text{C}_7\text{-H}$).

ii) The Authentic Alcohol (**9**): LiAlH_4 (500 mg) was added to a solution of the ester (**10**) (876 mg) in anhyd. THF (7 ml) under ice-cooling. The mixture was stirred for 15 min under ice-cooling and for a further 15 min at room temperature. When the reaction was complete, the reaction mixture was worked-up as described for the reduction of 6-methoxy TBI (**5b**). The crude product (787 mg) was chromatographed

over silica gel with benzene-AcOEt (2:3) as an eluent to give crystals (477 mg, 60.8%). Recrystallizations from benzene-AcOEt gave colorless needles, mp 91–92°C. *Anal.* Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.39; N, 12.49. Found: C, 53.58; H, 5.39; N, 12.67. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3300–2400 (NH and OH). NMR (CDCl_3) δ : 3.30 (2H, t, SCH_2CH_2), 3.77 (3H, s, OCH_3), 4.09 (2H, t, $\text{CH}_2\text{CH}_2\text{OH}$), 6.80 (1H, dd, $J=3.0$ and 9.0 Hz, $\text{C}_6\text{-H}$), 6.95 (1H, d, $J=3.0$, $\text{C}_4\text{-H}$), 7.30 (1H, d, $J=9.0$, $\text{C}_7\text{-H}$). Signals due to OH and NH were too broad to be observed.

2'-Nitro-*p*-formaniside¹⁵ (12)—Commercial 2'-nitro-*p*-anisidine (3.515 g) was added to a mixture of 83% formic acid (20 ml) and Ac_2O (1.98 ml) under ice-cooling and stirred at room temperature for 1.5 h. The reaction mixture was poured into water and the resulting crystals were collected by filtration. Recrystallization from 70% EtOH gave pale orange plates (3.40 g, 82.7%), mp 145–147°C (lit.¹⁵) mp 150–151°C. *Anal.* Calcd for $\text{C}_8\text{H}_8\text{N}_2\text{O}_4$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.82; H, 4.12; N, 14.17. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3270 (NH), 1660 (C=O). NMR (CDCl_3) δ : 3.87 (3H, s, OCH_3), 7.20 (1H, dd, $J=2.0$ and 8.0 Hz, $\text{C}_6\text{-H}$), 7.65 (1H, d, $J=2.0$ Hz, $\text{C}_3\text{-H}$), 8.49–8.70 (2H, m, CHO and $\text{C}_6\text{-H}$), 10.00 (1H, br.s, NH).

2'-Amino-*p*-formaniside (13)—A solution of the nitro compound (12) (3.00 g) in EtOH (290 ml) was hydrogenated at room temperature under normal pressure with 5% Pd-C (500 mg). When the uptake of hydrogen had ceased, the catalyst was removed. Concentration of the filtrate and washings *in vacuo* without heating gave a solid (2.22 g, 89.0%), which was recrystallized from benzene-AcOEt to give colorless needles, mp 139–140°C. *Anal.* Calcd for $\text{C}_8\text{H}_{10}\text{N}_2\text{O}_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.55; H, 5.98; N, 16.65. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3350, 3250 (NH), 1640 (C=O). MS m/e : 166 (M^+).

1-Ethyl-6-methoxybenzimidazole (14)—The amino-formyl compound (13) (300 mg) was added to a solution of ethyl iodide (309 mg) in DMF (3 ml). The mixture was heated at 68–82°C (bath temperature) for 1.5 h, poured into ice-water, basified with dil. NaHCO_3 (pH 8–9), and extracted with benzene. The organic layer was washed with water, dried over anhyd. K_2CO_3 , and concentrated *in vacuo* to give an oily residue (176 mg). The residue was chromatographed over silica gel with $\text{CH}_2\text{Cl}_2\text{-MeOH}$ (25:1) as an eluent to give an oil (155 mg, 48.9%). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : no characteristic band. NMR ($\text{DMSO}-d_6$) δ : 1.45 (3H, t, $J=7.0$ Hz, CH_2CH_3), 3.82 (3H, s, OCH_3), 4.25 (2H, q, $J=7.0$ Hz, NCH_2CH_3), 6.80 (1H, dd, $J=2.0$ and 8.0 Hz, $\text{C}_6\text{-H}$), 7.13 (1H, d, $J=2.0$ Hz, $\text{C}_4\text{-H}$), 7.57 (1H, d, $J=8.0$ Hz, $\text{C}_7\text{-H}$), 8.06 (1H, s, $\text{C}_2\text{-H}$). MS m/e : 176 (M^+). Picrate: Yellow needles, mp 197–198°C, recrystallized from 80% EtOH. *Anal.* Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O} \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 47.41; H, 3.73; N, 17.28. Found: C, 47.49; H, 3.58; N, 17.35.

2-Amino-N₁-ethyl-*p*-acetaniside (16)— LiAlH_4 (273 mg) was added to a suspension of 2'-nitro-*p*-acetaniside¹⁶ (15) (500 mg) in anhyd. THF (10 ml) under ice-cooling. The mixture was stirred under ice-cooling for 1 h, then treated with 3% NaOH (1 ml). The precipitates were filtered off, and the filtrate and washings were dried over anhyd. K_2CO_3 . Removal of the solvent *in vacuo* gave a dark brown oil (472 mg). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : 3235 br (NH), no C=O or NO_2 band. MS m/e : 166 (M^+). This compound was used for the following reaction without further purification, since it was very labile.

1-Ethyl-5-methoxyimidazole (17)—A mixture of the amine (16) (472 mg) and 83% formic acid (1.2 ml) was refluxed for 2.5 h. After cooling, the reaction mixture was basified (pH 9–10) with 10% NaOH and extracted with Et_2O . The organic layer was washed with water and dried over anhyd. K_2CO_3 . Removal of the solvent *in vacuo* gave an oil (173 mg), which was chromatographed over silica gel with $\text{CH}_2\text{Cl}_2\text{-MeOH}$ (20:1) as an eluent to give a pale brown oil (142 mg, 33.6%). IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1} : no characteristic band. NMR ($\text{DMSO}-d_6$) δ : 1.45 (3H, t, $J=7.0$ Hz, CH_2CH_3), 3.80 (3H, s, OCH_3), 4.25 (2H, dd, $J=7.0$ Hz, NCH_2CH_3), 6.86 (1H, dd, $J=2.0$ and 8.0 Hz, $\text{C}_6\text{-H}$), 7.17 (1H, d, $J=2.0$ Hz, $\text{C}_4\text{-H}$), 7.45 (1H, d, $J=8.0$ Hz, $\text{C}_7\text{-H}$), 8.12 (1H, s, $\text{C}_2\text{-H}$). MS m/e : 176 (M^+). Picrate: Yellow needles, mp 237–238°C, recrystallized from 60% EtOH. *Anal.* Calcd for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O} \cdot \text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 47.41; H, 3.73; N, 17.28. Found: C, 47.62; H, 3.48; N, 17.56.

1-Acetyl-5-methoxybenzimidazole (18)—a) Raney Ni(W_4) [prepared from alloy (0.9 g)] was added to a solution of 7-methoxy TBI (6b) (52 mg) in AcOEt (5 ml), and the mixture was refluxed for 30 min, then cooled. The Ni catalyst was filtered off, and the combined filtrate and washings were concentrated *in vacuo* to give an oily residue (16 mg). The residue was chromatographed over silica gel with AcOEt-benzene (3:2) as an eluent to give crystals. Recrystallizations from hexane-benzene gave colorless needles, mp 131–133°C. This compound was identical with one of the two products prepared by acetylation of 5-methoxybenzimidazole (11).

b) A solution of 5-methoxybenzimidazole (11) (203 mg) in Ac_2O (0.2 ml) and pyridine (0.2 ml) was refluxed for 3 h. After cooling, the reaction mixture was evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel with hexane-benzene (1:1) as an eluent. The first eluate yielded 1-acetyl-5-methoxybenzimidazole (18) (41.6 mg, 14.6%), which was recrystallized from hexane-benzene to give pale yellow prisms, mp 136–138°C. *Anal.* Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.93; H, 5.29; N, 14.51. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 1735 (C=O). NMR (CDCl_3) δ : 2.72 (3H, s, COCH_3), 3.88 (3H, s, OCH_3), 7.02 (1H, dd, $J=2.0$ and 9.0 Hz, $\text{C}_6\text{-H}$), 7.26 (1H, d, $J=2.0$ Hz, $\text{C}_4\text{-H}$), 8.10 (1H, d, $J=8.0$ Hz, $\text{C}_7\text{-H}$), 8.31 (1H, s, $\text{C}_2\text{-H}$). This compound was identical with a sample prepared from 7-methoxy TBI (6b). Further elution with same solvent gave 1-acetyl-6-methoxybenzimidazole (19) (51 mg, 18.8%), which was recrystallized from hexane-benzene to give colorless needles, mp 112–113.5°C. *Anal.* Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.00; H, 5.19; N, 14.57. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1} : 1735 (C=O). NMR

(CDCl₃) δ : 2.70 (2H, s, COCH₃), 3.88 (3H, s, OCH₃), 7.02 (1H, dd, $J=2.0$ and 9.0 Hz, C₆-H), 7.69 (1H, d, $J=9.0$ Hz, C₇-H), 7.79 (1H, d, $J=2.0$ Hz, C₄-H), 8.31 (1H, s, C₂-H).

5-Methoxybenzimidazole (11)—a) From 1-Acetyl-5-methoxybenzimidazole (18): LiAlH₄ (30 mg) was added to a suspension of the acetyl compound (18) (40 mg) in anhyd. THF (3 ml). The mixture was refluxed for 1 h, and then treated with 3% NaOH (0.15 ml). The precipitates were filtered off and washed with AcOEt. The combined filtrate and washings were dried over MgSO₄ and concentrated *in vacuo*. The residue (29 mg, 92.3%) was recrystallized from benzene-AcOEt to give pale yellow prisms, mp 116–118°C, which were identical with an authentic sample.

b) Preparation of an Authentic Sample of 11:¹⁰ The free base obtained from commercial 4-methoxy-*o*-phenylenediamine·2HCl was allowed to react with 83% formic acid according to the reported method.¹⁰ The yield was 50.0%. Recrystallizations from hexane-benzene-AcOEt gave pale yellow prisms, mp 118–120°C (lit.¹⁰ mp 123°C). *Anal.* Calcd for C₈H₈N₂O: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.79; H, 5.41; N, 18.70. IR $\nu_{\text{max}}^{\text{Nujol}}$ cm⁻¹: 3100 br (NH). NMR (DMSO-*d*₆) δ : 3.69 (3H, s, OCH₃), 6.79 (1H, dd, $J=2.0$ and 8.0 Hz, C₆-H), 7.07 (1H, d, $J=2.0$ Hz, C₄-H), 7.45 (1H, d, $J=8.0$ Hz, C₇-H), 8.04 (1H, s, C₂-H). MS *m/e*: 148 (M⁺).

Attempted Isomerization of Methoxy TBI (5b and 6b) and Chloro TBI (5d and 6d) with Ac₂O-Pyridine—A solution of 5b, 6b, 5d, or 6d (5 mg) in Ac₂O (0.05 ml)-pyridine (0.15 ml) was heated at 85–100°C (bath temperature) for 1 h. No isomerization was found to occur as judged by TLC.

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References and Notes

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