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Synthesis of *N*-Acetylbenzimidazole Derivatives

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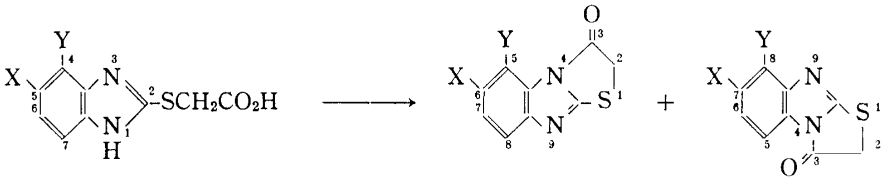
For the structure determination of thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one derivatives (**2** or **3**) they were converted to the corresponding 1-acetylbenzimidazoles (**4**) by desulfurization. The latter compounds (**4**) were alternatively prepared by the cyclization of 2-aminoacetanilide derivatives (**5**) with CS_2 in dimethylformamide (DMF), followed by desulfurization with Raney Ni. However, the reactions of **5** with ethyl orthoformate/H_2SO_4 in DMF gave a mixture of **4** and its acetyl-rearranged product (**7**).

Keywords——acetyl group; rearrangement; thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one; *N*-acetylbenzimidazoles; ethyl orthoformate; carbon disulfide; desulfurization

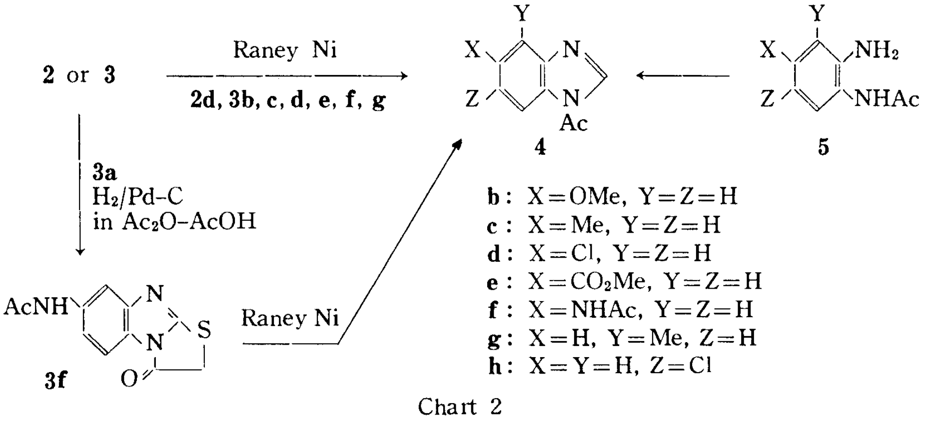
In the previous paper[1] we reported that the cyclization of 5-substituted-2-benzimidazothiolacetic acid (2-benzimidazothiolacetic acid is abbreviated as BTA) (**1**, Y=H) gave two kinds of thiazolo[3,2-*a*]benzimidazole-3(2*H*)-one(TBI) (**2** and **3**, Y=H) in a ratio of 1:1, in contrast to earlier results,[2] and that the same reaction of 4-substituted BTA (**1g**) gave the 8-methyl TBI (**3g**) predominantly. The structures of these cyclized products (**2** and **3**) were suggested by the ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum, in which C_5-H is shifted downfield by the anisotropic effect of lactam carbonyl at the 3-position. However, this method left some ambiguity, especially in the case of 6-nitro TBI (**2a**), in which the shift value of C_5-H was rather small. In this paper we report the structure determination of **2** and **3** by chemical means.



1 **2** **3**

a: $X=NO_2$, Y=H
b: X=OMe, Y=H
c: X=Me, Y=H
d: X=Cl, Y=H
e: $X=CO_2Me$, Y=H
f: X=NHAc, Y=H
g: X=H, Y=Me

Chart 1



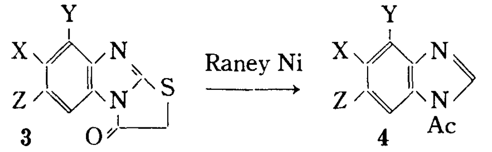
b: X=OMe, Y=Z=H
c: X=Me, Y=Z=H
d: X=Cl, Y=Z=H
e: $X=CO_2Me$, Y=Z=H
f: X=NHAc, Y=Z=H
g: X=H, Y=Me, Z=H
h: X=Y=H, Z=Cl

Chart 2

In order to distinguish the structures **2** from **3** it is sufficient to determine the structure of one of them. Our method consists of the conversion of TBI (**2** or **3**) to bicyclic acetylbenzimidazole (**4**) by desulfurization and an alternative synthesis of the latter (**4**) from the corresponding 2-aminoacetanilide (**5**) (Chart 2). 7-Nitro TBI (**3a**) was converted to acetamino TBI (**3f**) before desulfurization, since the desulfurization would be accompanied by reduction of the nitro group.

Desulfurization of TBI (**2** or **3**) was successfully carried out with Raney Ni to give the acetylbenzimidazole (**4**), accompanied by the deacetylated product in the cases of the chloro TBI (**2d** and **3d**). The results are listed in Table I.

Table I. Desulfurization of TBI (**2** and **3**) with Raney Ni to Acetylbenzimidazole (**4**)

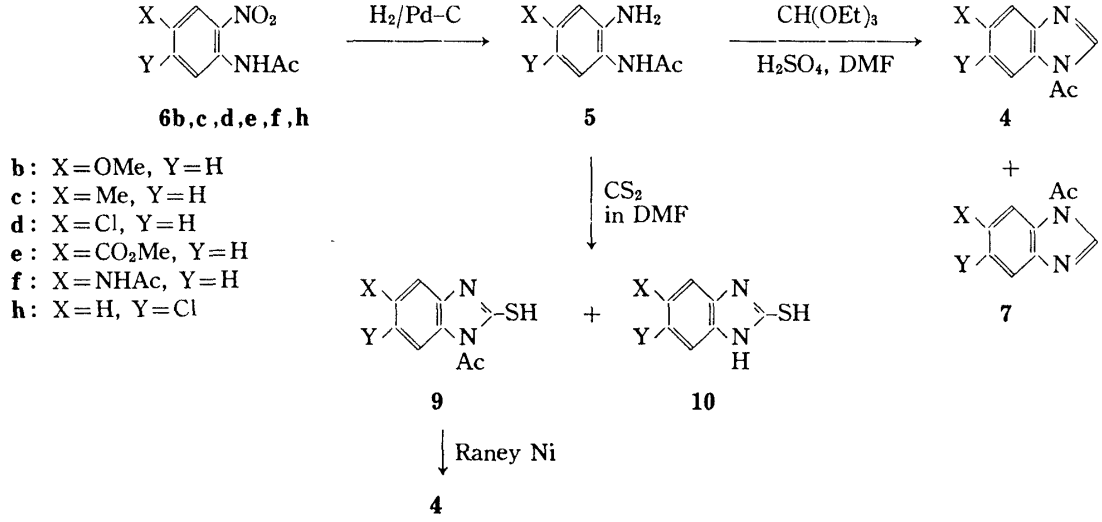


Starting material (2,3)	Product			By-product Yield (%)
		Yield (%)	mp (°C)	
3b (X=OMe, Y=Z=H)	**4b**	26.3	131—133	
3c (X=Me, Y=Z=H)	**4c**	54.7	124—125	
2d (X=Y=H, Z=Cl)	**4h**	3.8	126—128	20.9[a]
3d (X=Cl, Y=Z=H)	**4d**	12.2	122—123	19.1[a]
3e (X=CO_2Me, Y=Z=H)	**4e**	48.0	177—179	
3f (X=NHAc, Y=Z=H)	**4f**	24.5	197—199	
3g (X=H, Y=Me, Z=H)	**4g**	68.5	68— 69	

a) Deacetylated product[5-chlorobenzimidazole, mp 127—128°C (lit,5) mp 124—126°C)].

Thus, we sought to carry out an alternative synthesis of acetylbenzimidazole (**4**) by cyclization of the corresponding 2-aminoacetanilide (**5**). 4-Substituted 2-aminoacetanilide (**5**) was prepared by the reduction of the corresponding nitro compound (**6**). The chemistry of the 4-methyl compound (**4g**) will be described later in this paper.

The preparation of *N*-acylbenzimidazole derivatives (**4**) *via* cyclization of the corresponding 2-acylaminoaniline such as 2-aminoacetanilide (**5**) has never been reported. Thus, we

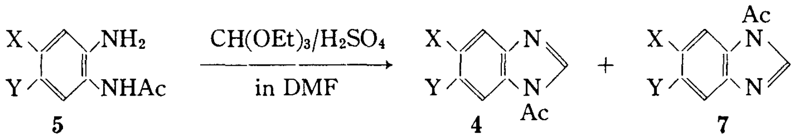


b: X=OMe, Y=H
c: X=Me, Y=H
d: X=Cl, Y=H
e: X=CO_2Me, Y=H
f: X=NHAc, Y=H
h: X=H, Y=Cl

Chart 3

applied the usual conditions for conversion of phenylenediamine to benzimidazole to the cyclization of 2-aminoacetanilide (**5**). However, the reaction of 2-amino-4-methoxyacetanilide (**5b**) with formic acid[4] gave only a complex mixture as determined by thin layer chromatography (TLC). Next, **5b** was allowed to react with ethyl orthoformate/H_2SO_4 in dimethylformamide[5] (DMF) and was found to give two products, **4b** (mp 131—133 °C) and **7b** (mp 115—116.5 °C). The same treatment of other 4-substituted 2-aminoacetanilides (**5c**, **d**, **e**, **f**) with ethyl orthoformate/H_2SO_4 in DMF similarly gave two kinds of *N*-acetylbenzimidazole derivatives (**4** and **7**). 2-Amino-5-chloroacetanilide (**5h**), an isomer of 2-amino-4-chloroacetanilide (**5d**), also gave a similar result as listed in Table II. These results showed that the cyclization of 2-aminoacetanilide (**5**) with ethyl orthoformate was undoubtedly accompanied by the rearrangement of an acetyl group. Therefore, this method was not suitable for the preparation of authentic 1-acetyl-5-substituted benzimidazole (**4**). As we presumed that the acetyl rearrangement occurs under acidic conditions, we examined the

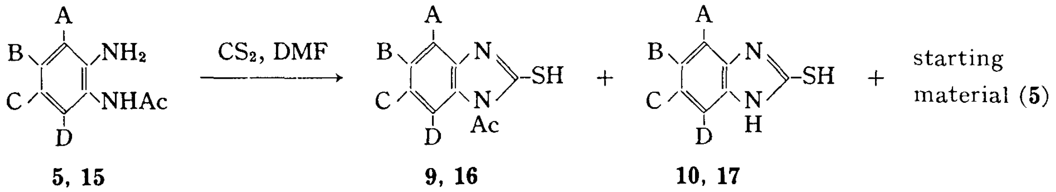
TABLE II. Cyclization of 4- or 5-Substituted-2-aminoacetanilide (**5**) with Ethyl Orthoformate/H_2SO_4 in DMF to *N*-Acetylbenzimidazoles (**4** and **7**)



Starting material (**5**)	Yield (%) Combined	Isolated **4**	Isolated **7**	mp (°C) **4**	mp (°C) **7**
5b (X=OMe, Y=H)	49.5	23.5	21.1	125—128	115—116.5
5c (X=Me, Y=H)	57.7	28.8[a]	28.8[a]	119—120	Not isolated
5d (X=Cl, Y=H)	38.6	24.2	14.4	122.5—123	124—126
5e (X=CO_2Me, Y=H)	40.0	30.0	10.0	174—176	155—157
5f (X=NHAc, Y=H)	39.5	16.9	22.6	197—199	179—181
5h (X=H, Y=Cl)	45.5	11.7	33.8	122—123	124—126

[a] The yield was calculated from ^{1}H-NMR data obtained with shift reagent.[1]

TABLE III. Cyclization of 4-, 5-, or 6-Substituted 2-Aminoacetanilide (**5** or **15**) with CS_2 in DMF to *N*-Acetylbenzimidazolethiol (**9**, **16**) and Deacetyl Compound (**10**, or **17**)



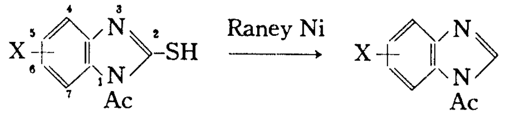
Starting material (**5**, **15**)	Reaction time (h)	Product (%) **9**, **16**	mp (°C)	Deacetyl compound[1] (**10**, **17**)	Recovered st. material (**5**) (%)
5b (B=OMe, A=C=D=H)	89	**9b** 59.1	204—205	**10b** 11.4	—
5c (B=Me, A=C=D=H)	120	**9c** 48.9	200.5—202	**10c** 21.3	—
5d (B=Cl, A=C=D=H)	167	**9d** 29.0	207—209	**10d** 16.1	29.7
5e (B=CO_2Me, A=C=D=H)	256	**9e** 25.9	233—235	**10e** 29.2	—
5f (B=NHAc, A=C=D=H)	66	**9f** 13.9	>260 (dec.)	**10f** 23.9[a]	—
5h (C=Cl, A=B=D=H)	46	**9h** 18.0	199.5—200.5	**10d** 30.0	—
15 (A=B=C=H, D=Me)	20.5	**16** 23.4	>270 (dec.)	**17** 8.1	—

[a] mp 297°C (dec.) (lit,[7] mp 300—307°C).

cyclization under neutral and milder conditions. Montgomery *et al.*[6] reported the cyclization of 4,5-diaminopyrimidine with carbon disulfide (CS_2) in DMF to 9-mercaptopurine. We applied these neutral conditions to the cyclization of 4-substituted 2-aminoacetanilide (**5**).

Thus 2-amino-4-methoxyacetanilide (**5b**) was treated with CS_2 in DMF at room temperature. The reaction proceeded slowly to yield two products, the expected 1-acetyl-5-methoxybenzimidazolethiol (**9b**, mp 204—205 °C) and 6-methoxybenzimidazolethiol (**10b**).[1] The latter compound (**10b**) was probably formed by hydrolysis of the first product (**9b**), because this compound was found to be slowly hydrolyzed when separately treated under the same cyclization conditions. Other 2-aminoacetanilides (**5**) also gave the corresponding acetylbenzimidazolethiol (**9**), although accompanied with the hydrolyzed product (**10**), as listed in Table III. The thiols (**9**) thus obtained were desulfurized with Raney Ni under neutral conditions to give the corresponding acetylbenzimidazole (**4** or **7**) as a single product (Table IV). Each acetylbenzimidazole (**4** or **7**) was found to be identical with the sample obtained from the corresponding TBI (**2** or **3**) by desulfurization. These results clearly demonstrate the correctness of our view[1] on the structure of TBI (**2** and **3**, Y=H), based on the ^{1}H-NMR spectrum.

Table IV. Desulfurization of *N*-Acetylbenzimidazolethiol (**9**) to *N*-Acetylbenzimidazole (**4**, **7**, **18**)



9, **16**, **19** **4**, **7**, **18**

Starting material	Product	
	Yield (%)	mp (°C)
9b (X=5-OMe)	**4b** 63.6	134—135
9c (X=5-Me)	**4c** 40.2	124—125
9d (X=5-Cl)	**4d** 29.3	125—126
9e (X=5-CO_2Me)	**4e** 50.8	180—182
9f (X=5-NHAc)	**4f** 41.9	203—205
9h (X=6-Cl)	**7d** 29.6	125—126
16 (X=7-Me)	**18** 34.7	81— 82.5
19 (X=4-Me)	**4g** 57.2	65— 66

Next, we describe the structure determination of 8-methyl TBI (**3g**). This can also be achieved by preparing the desulfurized product (**4g**) by an alternative route. In order to prepare the desulfurized product (**4g**), 3-methyl-2-nitroaniline (**11**) should be required, but **11** was hard to obtain. Thus, commercial 1-methyl-6-nitroaniline (**12**), an isomer of **11**, was used as a starting material for preparing an isomer of **4g**, 1-acetyl-7-methylbenzimidazole (**18**) (Chart 4).

The aniline (**12**) unexpectedly gave an *N*,*N*-diacetyl compound (**13**) under usual acetylation conditions (heating with Ac_2O). Partial hydrolysis of the *N*,*N*-diacetyl compound (**13**) with conc. HCl in AcOH gave the acetanilide (**14**), which was converted to 2-amino-6-methylacetanilide (**15**) by catalytic hydrogenation.

The 2-aminoacetanilide (**15**) thus obtained was allowed to react with CS_2 in DMF to give the desired acetylbenzimidazolethiol (**16**), accompanied with the deacetyl benzimidazolethiol[1] (**17**) as a by-product. The former (**16**) was desulfurized by Raney Ni to give 1-acetyl-7-methylbenzimidazole (**18**), which was found to be an isomer of the main product (**3g**) formed in the cyclization of 4-methyl BTA (**1g**). Accordingly the structure of **3g** was indirectly determined. For direct confirmation, 2-aminoacetanilide (**15**) was treated with ethyl orthoformate/H_2SO_4

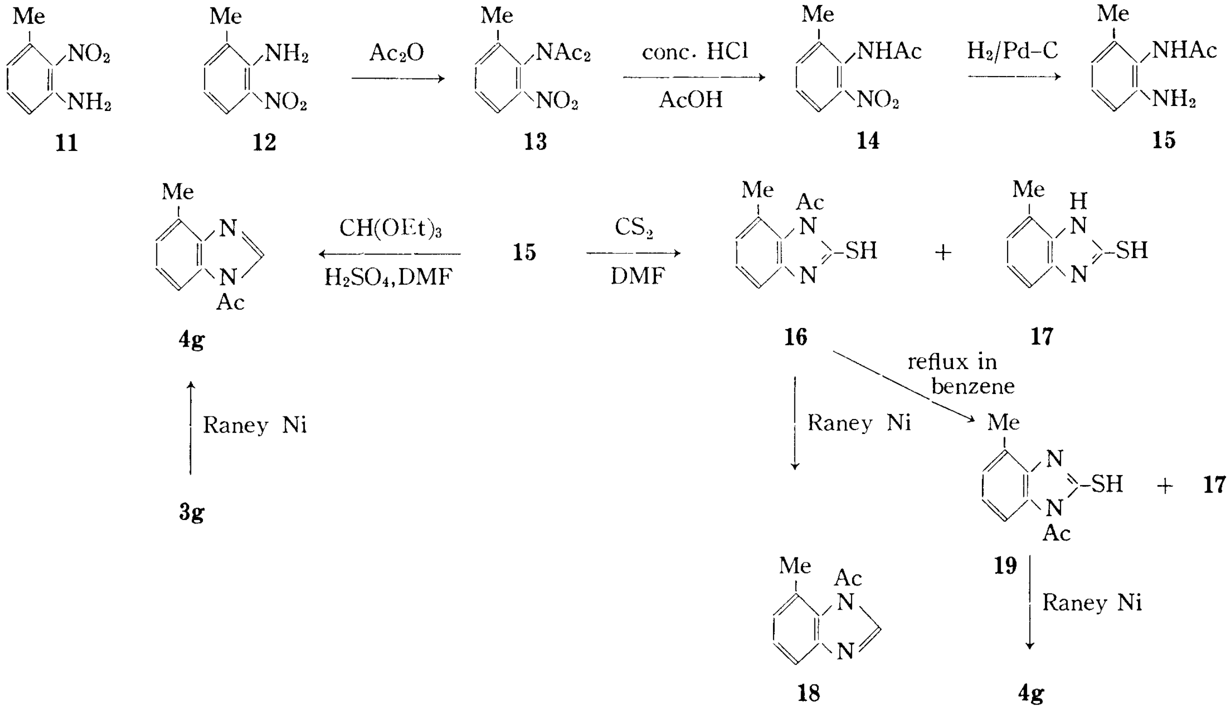


Chart 4

in DMF. This reaction resulted in the formation of a single compound, $C_{10}H_{10}N_2O$, in contrast to the same reactions of 4-substituted 2-aminoacetanilides (5). This product was not 1-acetyl-7-methylbenzimidazole (**18**), but the acetyl-rearranged product, 1-acetyl-4-methylbenzimidazole (**4g**), which was identical with the sample prepared from 9-methyl TBI (**3g**). The fact that the cyclization reaction of **15** with ethyl orthoformate gave only an acetyl rearranged product suggested that the similar compound **16** would undergo acetyl rearrangement easily. Thus, heating the 1-acetyl-7-methylbenzimidazolethiol (**16**) in benzene (or AcOEt) gave an isomer (**19**). Desulfurization of **19** gave 1-acetyl-4-methylbenzimidazole (**4g**), which was identical with the sample obtained from 8-methyl TBI (**3g**). Thus, the proposed structure of the cyclization product[1] (**3g**) was also found to be correct.

During the present study we found an interesting *N*,*N*-acyl rearrangement. This will be described in detail in a subsequent paper.

Experimental

All melting points were measured on a micro melting point hot stage (Yanagimoto) and are uncorrected. Infrared (IR), ^{1}H-NMR and mass spectra (MS) 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. Chemical shifts in the ^{1}H-NMR spectra are given in δ-values referred to internal tetramethylsilane (TMS), and the assignments 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 GF_{254}, 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; br, broad. All starting materials were commercially available compounds unless otherwise stated.

7-Acetamidothiazolo[3,2-*a*]benzimidazole-3(2*H*)-one (**3f**)——7-Nitrothiazolo[3,2-*a*]benzimidazole-3(2*H*)-one[1] (**3a**) (350 mg) was dissolved in a mixture of Ac_2O (11 ml) and AcOH (55 ml) and hydrogenated over 5% Pd-C (450 mg). After uptake of hydrogen ceased, the catalyst was filtered off. The filtrate and washings were combined and evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel using AcOEt–benzene (3: 2) to give recovered **3a** (10 mg) and the acetamide (**3f**) (211 mg, 56.8%). Recrystallizations of **3f** from AcOEt–benzene gave colorless plates, mp 252°C (dec.). *Anal.* Calcd for $C_{11}H_9N_3O_2S$: C, 53.43; H, 3.67; N, 16.99. Found: C, 53.60; H, 3.49; N, 17.04. IR $\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 3300—3100 (NH), 1740 (lactam C=O), 1690 (acetamido C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.06 (3H, s, $COCH_3$), 4.58 (1H, s, $-CH_2S-$), 7.38 (1H, dd, $J=2.0$ and 10.0 Hz, C_6–H), 7.73 (1H, d, $J=10.0$ Hz, C_5–H), 7.90 (1H, d, $J=2.0$ Hz, C_8–H), 10.00 (1H, br s, NH). MS *m/z*: 247 (M^+), 249 (M^++2, 5.2% intensity of M^+), 242 (M−42, base peak).

General Procedure for Desulfurization of Thiazolo[3,2-*a*]benzimidazole-3(2*H*)-one (TBI) (3) with Raney Ni to Acetylbenzimidazole (4)——Raney Ni(W_4) [prepared from alloy (0.9—2.6 g)] was added to a solution of TBI (3) (0.24—0.84 mmol) in AcOEt (5—200 ml) and the mixture was refluxed for 0.5—1.5 h. Raney Ni was filtered off, and the combined filtrate and washings (AcOEt) were evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel and recrystallized from an appropriate solvent to give 4. The products were identified by comparison with authentic samples (Tables II, IV).

Preparation of 4- or 5-Substituted 2-Aminoacetanilide (5)——The corresponding 2-nitroacetanilide (6) was hydrogenated over 5% Pd-C to give 5.

TABLE V. The Characterization Data for 1-Acetyl-5-(4) and 1-Acetyl-6-substituted Benzimidazoles (7)

Compound	Formula	Recrystallization solvent	Crystal form	Analysis (%) Calcd (Found)			IR $\nu_{max}^{CHCl_3}$ cm^{-1}
				C	H	N	C=O
4c	$C_{10}H_{10}N_2O$	Benzene–Hexane	Colorless plates	68.95 (69.04	5.79 5.61	16.08 15.96)	1700
4d	$C_9H_7ClN_2O$	AcOEt–Hexane	Colorless needles	55.54 (55.66	3.62 3.52	14.39 14.27)	1725
7d	$C_9H_7ClN_2O$	Benzene–Hexane	Colorless needles	55.54 (55.77	3.62 3.59	14.39 14.11)	1720
4e	$C_{11}H_{10}N_2O_3$	AcOEt–Benzene	Yellow needles	60.54 (60.36	4.62 4.62	12.84 12.80)	1720
7e	$C_{11}H_{10}N_2O_3$	Benzene–Hexane	Yellow needles	60.54 (60.28	4.62 4.45	12.84 12.69)	1720
4f	$C_{11}H_{11}N_3O_2$	AcOEt	Colorless needles	60.82 (60.67	5.11 5·12	19.34 19.21)	1710
7f	$C_{11}H_{11}N_3O_2$	AcOEt–Benzene	Colorless prisms	60.82 (60.69	5.11 5.09	19.34 19.11)	1725
4g	$C_{10}H_{10}N_2O$	Benzene–Hexane	Colorless needles	68.95 (68.86	5.79 5.63	16.08 15.88)	1725
18	$C_{10}H_{10}N_2O$	Benzene–Hexane	Colorless plates	68.95 (68.72	5.79 5.74	16.08 15.72)	1735

Compound	^{1}H-NMR($CDCl_3$) δ: ppm, J: Hz					
	$COCH_3$	C_2-H	C_4-H	C_5-H	C_6-H	C_7-H
4c	2.48[b] (s)	8.78 (s)	7.53 (dif. s)	2.48[a] (s)	7.20 (dif. d, $J=8.0$)	8.02 (d, $J=8.0$)
4d	2.75 (s)	8.32 (s)	7.25 (d, $J=2.0$)	— —	7.35 (dd, $J=2.0$ and 8.0)	8.13 (d, $J=8.0$)
7d	2.76 (s)	8.28 (s)	7.73 (d, $J=8.0$)	7.31 (dd, $J=2.0$ and 8.0)	—	8.22 (d, $J=2.0$)
4e	2.81 (s)	8.95 (s)	8.26 (d, $J=2.0$)	3.91[a] (s)	7.92 (dd, $J=2.0$ and 9.0)	8.24 (d, $J=9.0$)
7e	2.79 (s)	8.45 (s)	7.75 (d. $J=8.0$)	8.08 (dd, $J=2.0$ and 8.0)	3.96[a] (s)	8.84 (d, $J=2.0$)
4f	2.74[b] (s)	8.75 (s)	8.07 (d. $J=2.0$)	2.08[a] (s)	7.45 (dd, $J=2.0$ and 9.0)	8.01 (d. $J=9.0$)
7f	2.78[b] (s)	8.72 (s)		7.60 (2H, dif. s)	2.10[a] (s)	8.52 (dif. s)
4g	2.75 (s)	8.28 (s)	2.70[a] (s)		7.10—7.40 (2H, m)	8.00 (dd, $J=2.0$ and 7.0)
18	2.77 (s)	8.25 (s)		7.10—7.68 (3H, m)		2.69[a] (s)

a) Methyl signal. b) Solvent for ^{1}H-NMR: DMSO-d_6.

i) 2′-Amino-*p*-acetanisidide (**5b**): Brown needles (from benzene–AcOEt), mp 155—156.5°C (lit,10) mp 150—150.5°C). *Anal.* Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.91; H, 6.77; N, 15.24. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3420 (NH), 1635 C=O).

ii) 2′-Amino-*p*-acetotoluidide (**5c**): Light brown needles from benzene–AcOEt, mp 131—132°C (lit,9) mp 130—131°C). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.34; N, 17.06. Found: C, 66.07; H, 7.39; N, 16.96. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3340 (NH), 1620 (C=O).

iii) 2′-Amino-4′-chloroacetanilide (**5d**): Colorless needles from benzene–AcOEt, mp 141.5—143°C (lit,10) mp 144°C). *Anal.* Calcd for $C_8H_9ClN_2O$: C, 52.05; H, 4.91; N, 15.17. Found: C, 52.36; H, 4.90; N, 14.85. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3350 (NH), 1630 (C=O).

iv) Methyl 4-Acetamido-3-aminobenzoate (**5e**): Methyl 4-acetamido-3-nitrobenzoate,11) mp 124—125 °C, prepared by esterification of 3-nitro-4-acetamidobenzoic acid,12) was hydrogenated over 5% Pd-C (1.0 g) under atmospheric pressure at room temperature. The crude product (3.6 g) was recrystallized from MeOH to give pale yellow needles, mp 197—199°C. *Anal.* Calcd for $C_{10}H_{12}N_2O_3$: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.53; H, 5.72; N, 13.52. IR ν_{max}^{Nujol} cm^{-1}: 3430, 3350, 3170 (NH), 1715, 1650 (C=O). ^{1}H-NMR (CD_3OD) δ: 2.34 (3H, s, $COCH_3$), 3.89 (3H, s, CO_2CH_3), 7.28—7.50 (3H, m, aromatic H).

TABLE VI. Characterization Data for 1-Acetyl Substituted-2-benzimidazolethiols (**9**, **16**, **19**) (See Table III)

Compound	Formula	Recrystallization solvent	Crystal form	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{Nujol} cm^{-1} C=O
9b	$C_{10}H_{10}N_2O_2S$	AcOEt–Benzene	Colorless needles	54.04 (54.09	4.54 4.48	12.60 12.57)	1675
9c	$C_{10}H_{10}N_2OS$	AcOEt–Benzene	Light yellow plates	58.23 (58.54	4.89 4.92	13.58 13.33)	1680
9d	$C_9H_7ClN_2OS$	AcOEt	Colorless needles	47.69 (47.83	3.11 3.05	12.36 11.92)	1705
9e	$C_{11}H_{10}N_2O_3S$	AcOEt–Benzene	Colorless needles	52.79 (53.03	4.03 4.05	11.19 10.87)	1680
9f	$C_{11}H_{11}N_3O_2S$	EtOH	Light yellow prisms	53.00 (53.36	4.45 4.29	16.86 16.79)	1650
9h	$C_9H_7ClN_2OS$	AcOEt–Benzene	Colorless needles	47.69 (47.64	3.11 3.14	12.36 12.50)	1720
16	$C_{10}H_{10}N_2OS$	AcOEt–Benzene	Colorless needles	58.23 (57.99	4.89 4.85	13.58 13.23)	1745
19	$C_{10}H_{10}N_2OS$	AcOEt–Benzene	Colorless needles	58.23 (58.19	4.89 4.75	13.58 13.13)	1715

Compound	^{1}H-NMR (DMSO-d_6) δ: ppm, *J*: Hz C_4-H	C_5-H	C_6-H	C_7-H	$COCH_3$
9b	6.70 (d, *J*=2.0)	3.85a) (s)	6.84 (dd, *J*=2.0 and 9.0)	7.92 (d, *J*=9.0)	3.05 (s)
9c	6.96 (dif. s)	2.38a) (s)	7.02 (dif. d., *J*=8.0)	7.84 (d, *J*=8.0)	3.00 (s)
9d	7.12 (dif. s)	— —	7.30 (dd, *J*=2.0 and 8.0)	7.94 (d, *J*=8.0)	2.98 (s)
9e		3.92a)	7.64—8.12 (3H, m)		3.06 (s)
9f	7.75 (d, *J*=2.0)	2.10a) (s)	7.19 (dd, *J*=2.0 and 8.0)	7.89 (d, *J*=8.0)	3.00 (s)
9h	7.14 (d, *J*=9.0)	7.36 (dd, *J*=3.0 and 9.0)	— —	7.96 (d, *J*=3.0)	3.34 (s)
16		7.02—7.16 (3H, m)		2.25a) (s)	3.06 (s)
19	2.46a) (s)	7.08—7.16 (2H, m)		7.72—7.86 (1H, m)	3.06 (s)

a) Methyl signal.

v) 2,5-Diacetamidoaniline (**5f**): Light brown powder from 50% EtOH, mp 242—244°C (lit,[13] mp 231—232°C). *Anal.* Calcd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.74; H, 6.46; N, 20.19. IR ν_{max}^{Nujol} cm^{-1}: 3380—3100 (NH), 1640 (C=O).

vi) 2′-Amino-5′-chloroacetanilide (**5h**): 5′-Chloro-2′-nitroacetanilide[14] (**6h**) (3.0 g), mp 117—119°C (lit,[14a] mp 117—118°C), was hydrogenated over 5% Pd-C under atmospheric pressure at room temperature. The crude product (2.35 g, 91%) was recrystallized from AcOEt–hexane to give pale yellow needles, mp 130—132°C. *Anal.* Calcd for $C_8H_9ClN_2O$: C, 52.05; H, 4.91; N, 15.17. Found: C, 52.23; H, 4.86; N, 14.85. IR ν_{max}^{Nujol} cm^{-1}: 3350, 3200 (NH), 1630 (C=O). ^{1}H-NMR (CD_3OD) δ: 2.28 (3H, s, $COCH_3$), 6.71 (1H, d, J=8.0 Hz, $C_{3'}$-H), 6.95 (1H, dd, J=2.0 and 8.0 Hz, $C_{4'}$-H), 7.15 (1H, d, J=2.0 Hz, $C_{6'}$-H). MS *m/z*: 186 (M^++2, 35.4% intensity of M^+), 184 (M^+).

General Procedure for the Reaction of 4- or 5-Substituted 2-Aminoacetanilide (5) with Ethyl Orthoformate/H_2SO_4[5] in DMF——A solution of 2-aminoacetanilide (**5**) (2.8 mmol) in DMF (1.0 ml) containing ethyl orthoformate (1.8 ml) and one drop of H_2SO_4 was heated at 120—150°C (bath temperature) until the starting material (**5**) was no longer detectable by TLC (30—80 min). Then the reaction mixture was poured into water, and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel using a mixture of AcOEt and hexane of appropriate ratio as an eluent to give 1-acetyl-5-(**4**) and 1-acetyl-6-substituted benzimidazole (**7**) in every case. The results are listed in Table II and the results of characterization in Table V. The methoxy compounds (**4b** and **7b**) have already been reported.[1]

General Procedure for the Reaction of 4- or 5-Substituted 2-Aminoacetanilide (5) with CS_2 in DMF——CS_2 (8.8 ml) was added to a solution of **5** (8.5 mmol) in DMF (12 ml) and the whole was stirred at room temperature until the starting material (**5**) was no longer detectable or the reaction proceeded no further as determined by TLC. The reaction mixture was poured into water, and extracted with AcOEt. The extract was dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed over silica gel using a mixture of benzene–AcOEt of appropriate ratio as an eluent to give sulfur, 1-acetyl-5- or 6-substituted 2-benzimidazolethiol (**9**), 5-substituted 2-benzimidazolethiol,[1,7] (**10**) and the starting material (**5**), in that order of elution. The results are listed in Table III and the results of characterization of **9** in Table VII.

General Procedure for the Desulfurization of the *N*-Acetyl-2-benzimidazolethiol (9)——Raney Ni(W_4) [prepared from alloy (2.0 g)] was added to a solution of the thiol (**9**) (200—300 mg) in AcOEt (20—50 ml) and the mixture was refluxed for 40—50 min. The Raney Ni was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was purified by column chromatography over silica gel using a mixture of AcOEt and benzene of appropriate ratio as an eluent to give *N*-acetylbenzimidazole (**4**). The products **4** were found to be identical with the compounds prepared by desulfurization from the corresponding TBI (**2** or **3**). The results are listed in Table IV.

***N*,*N*-Diacetyl-6-nitro-*o*-toluidine (13)**——6-Nitro-*o*-toluidine (**12**) (6.00 g) was dissolved in Ac_2O (33 ml) and the mixture was heated at 120°C (bath temperature) for 12.5 h. The reaction mixture was poured into ice-water and the precipitated crystals (7.70 g, 83.7%), mp 58—59°C, were collected. This compound was difficult to recrystallize. IR ν_{max}^{Nujol} cm^{-1}: 1720—1700 (C=O). ^{1}H-NMR (CD_3OD) δ: 2.28 (9H, s, aromatic $-CH_3$ and $COCH_3 \times 2$), 7.40—7.76 (2H, m, C_3- and C_4-H), 7.95 (1H, dd, J=2.5 and 8.0 Hz, C_5-H). High resolution MS: Calcd for $C_{11}H_{12}N_2O_4$: 236.0798. Found: 236.0796.

6′-Nitro-*o*-acetotoluidide (14)——The diacetyl compound (**13**) (500 mg) was dissolved in a mixture of conc.HCl (3.0 ml) and AcOH (15 ml), and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was evaporated to dryness *in vacuo* without heating. The residue was recrystallized from 50% EtOH to give the pale yellow needles (346 mg, 85%), mp 158—159°C (lit,[15] mp 158°C). IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1670 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.08 (3H, s, $COCH_3$), 2.32 (3H, s, aromatic $-CH_3$), 7.20—7.56 (2H, m, $C_{3'}$- and $C_{4'}$-H), 7.71 (1H, dd, J=2.0 and 7.0 Hz, $C_{5'}$-H), 9.78 (1H, br s, NH).

6′-Amino-*o*-acetotoluidide (15)——A solution of the nitro compound (**14**) (2.00 g) was hydrogenated over 5% Pd-C (400 mg) under atmospheric pressure at room temperature. The catalyst was filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue (1.44 g, 85.4%) was recrystallized from benzene–AcOEt to give colorless needles, mp 150—152°C. *Anal.* Calcd for $C_9H_{12}N_2O$; C, 65.83; H, 7.34; N, 17.06. Found: C, 65.89; H, 7.40; N, 17.02. IR ν_{max}^{Nujol} cm^{-1}: 3450—3100 (NH), 1640 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.14 (6H, s, aromatic $-CH_3$ and $COCH_3$), 3.64 (2H, br s, NH_2), 6.52—7.23 (4H, m, NH and aromatic H).

1-Acetyl-7-methyl-2-benzimidazolethiol (16)——See the general procedure for the reaction with CS_2 and Table III for the preparation, and Table VII for the characterization data.

1-Acetyl-7-methylbenzimidazole (18)——See the general procedure for desulfurization and Table IV for the preparation, and Table VI for the characterization data.

1-Acetyl-4-methylbenzimidazole (4g)——i) a) 1-Acetyl-4-methyl-2-benzimidazolethiol (**19**): A solution of the 7-methyl compound (**16**) (105 mg) in benzene (10 ml) was refluxed for 2 h. The solvent was distilled off *in vacuo* and the residue was chromatographed over silica gel using a mixture of AcOEt–hexane (1:8) as an eluent. The first eluate gave **19** (80 mg, 75%), which was recrystallized from benzene–AcOEt to provide colorless needles, mp 250—252°C. *Anal.* Calcd for $C_{10}H_{10}N_2OS$; C, 58.23; H, 4.89; N, 13.58. Found: C, 58.19; H, 4.75; N, 13.13. IR ν_{max}^{Nujol} cm^{-1}: 3150 (NH), 1715 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.46

(3H, s, aromatic $-CH_3$), 3.06 (3H, s, $COCH_3$), 7.12 (2H, m, C_5– and C_6–H), 7.80 (1H, m, C_7–H), 13.20 (1H, br s, NH). MS *m/z*: 206 (M^+), 164 (M−42, base peak).

The second fraction was the deacetylated compound[1] (**17**) (18 mg, 23%). This rearrangement was also observed in other solvents, such as AcOEt.

b) 1-Acetyl-7-methylbenzimidazole (**4g**) from the Thiol (**19**): The thiol (**19**) (80 mg) was treated with Raney Ni(W_4) [prepared from alloy (1.3 g)] according to the general procedure. See Table IV for the result. The product was identical with the sample obtained from TBI (**3g**).

ii) Reaction of the Amine (**15**) with Ethyl Orthoformate/H_2SO_4 in DMF: The amine (**15**) (200 mg) was treated with ethyl orthoformate/H_2SO_4 in DMF according to the general procedure. The yield was 86 mg (41%). The characterization data are shown in Table VI. This compound was identical with the sample obtained by desulfurization of TBI (**3g**).

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