indicated by the value of the reaction constant −0.51 can be attributed to the fact that the influence of the substituent on k_{forward} and $k_{\text{rev.}}$ change differently with σ.

As the formation constant β_1 of benzoylacetanilide-Fe (III) complex was shown to be given by relation (15), the overall reaction constant, ρ_1, for the formation of this 1:1 complex species will be given by

$$\rho_1 = \rho_2 - \rho_{-2} - \rho_a \tag{17}$$

where ρ_2, ρ_{-2} and ρ_a are the reaction constants for the chelate formation, chelate decomposition, and the acid dissociation of the ligand respectively. Substituting the values −1.693, −0.51 and +0.933 of ρ_1, ρ_2 and ρ_a respectively in equation (17) would yield a value of +0.257 for the reaction constant, ρ_{-2}, of the dissociation of the 1:1 chelate species. As expected the process of the dissociation of the complex is favoured by electron-withdrawing substituents.

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Acylation of 2-Cyanomethylbenzimidazole

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An acylation of 2-cyanomethylbenzimidazole (**2**), which has the NH and the active methylene group as active site, in acetone by the Schotten-Baumann method was carried out. The acylation occurred at the nitrogen of the imidazole ring when **2**, itself, was used as a base. In these experiments, **2** was condensed with acetone to give 2-(1-cyano-2-methyl-1-propenyl)benzimidazole (**4a**) in the presence of trimethylamine as a base, however, **2** could not react with acetone in the presence of pyridine as a base.

Keywords——acylation; 2-cyanomethylbenzimidazole; Schotten–Baumann method; basicity; active methylene

The chemistry of benzodiazepine series has extensively been studied.[2] Recently, we have synthesized 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (**1**) by the reaction of *o*-phenylenediamine with ethoxymethylenemalononitrile.[3] The ring transformations of **1** were reported[4] and one of them afforded 2-cyanomethylbenzimidazole[5] (**2**). This paper deals with some interesting reactions, especially acylation of **2**, which was found during studies on structural determination of products obtained from the transformation of **1**.

Compound **2** did not dissolve in water, so that acylation of **2** by the Schotten-Baumann method was tried in acetone. The above experiment in the presence of pyridine as a base did not give an acylated compound but gave the hydrochloride **3**, unexpectedly. On the other hand, when trimethylamine (40% in water) was employed as a base, the free base **2** reacted with the solvent to give only 2-(1-cyano-2-methyl-1-propenyl)benzimidazole (**4a**). This result should be due to the reaction of the carbonyl group in acetone with the active methylene group in **2**. In these experiments, pyridine acts as a catalyst for hydrolysis of

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[1] Location: *Shirokane, Minato-ku, Tokyo, 108, Japan.*

[2] G.A. Archer and L.H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).

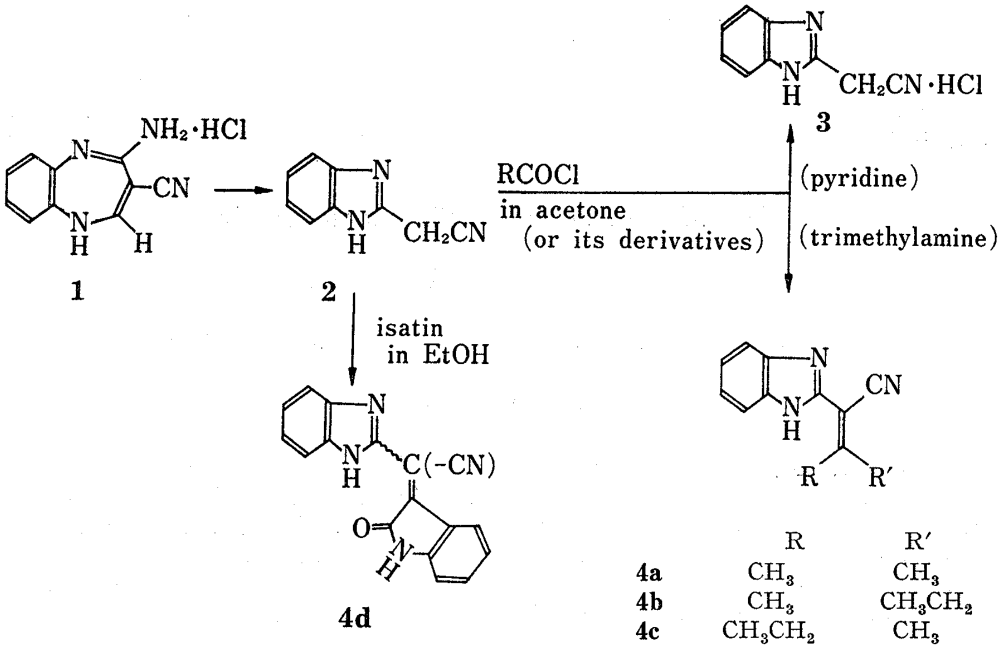
[3] Y. Okamoto and T. Ueda, *J. Chem. Soc., Chem. Commun.*, 367 (1975).

[4] Y. Okamoto and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **23**, 1391 (1975).

[5] Y. Okamoto and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), "submitted."

acyl chloride, and trimethylamine acts as a catalyst for abstraction of proton from the active methylene group.

Methyl ethyl ketone also reacted with **2** in the presence of trimethylamine to give a mixture of geometric isomers of 2-(1-cyano-2-methyl-1-butenyl)benzimidazole (**4b** and **4c**). Signals of methyl protons were observed in the nuclear magnetic resonance (NMR) spectrum of the isomeric mixture as two triplets and two singlets.[6] Intensity of the triplet at a higher field (1.07 ppm) is considerably weaker than that at a lower field (1.20 ppm). The triplet signal at 1.07 ppm should be attributed to the methyl protons in the ethyl group of **4c** which might be located at the *cis*-position to the aromatic ring, and the triplet at 1.20 ppm to the methyl protons in the ethyl group of **4b** which might be located at the *trans*-position to the aromatic ring. Two singlet signals of methylprotons at 2.32 (weak) and 2.35 (strong) ppm



	R	R'
4a	CH_3	CH_3
4b	CH_3	CH_3CH_2
4c	CH_3CH_2	CH_3

Chart 1

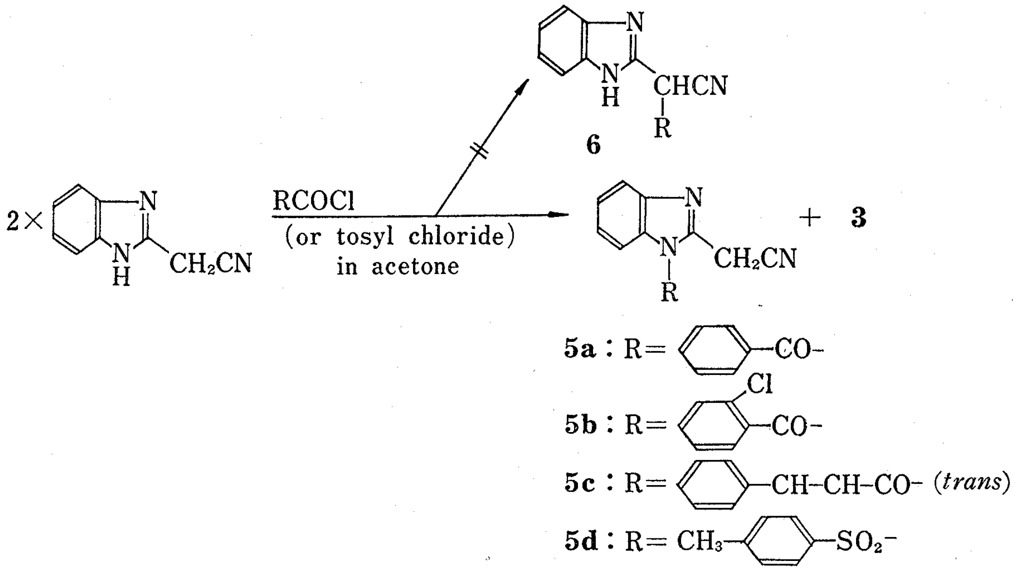


Chart 2

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[6] All chemical shifts were measured from the signal of tetramethylsilane as an internal standard.

Table I. Benzimidazole Derivatives

Compound (No)	mp (°C)	Yield (%)	Recryst. solvent	Formula	Analysis					
					Calcd.			Found		
					C	H	N	C	H	N
4a	216—217	87	EtOH+H_2O	$C_{12}H_{11}N_3$	73.07,	5.62,	21.31	72.87,	5.63,	21.25
4b+**4c**	167—168	70	EtOH+H_2O	$C_{13}H_{13}N_3$	73.90,	6.20,	19.89	73.78,	6.31,	19.93
5a	186—188	52	EtOH	$C_{16}H_{11}N_3O$	73.55,	4.24,	16.08	73.34,	4.50,	16.37
5b	163—164	43	EtOH	$C_{16}H_{10}ClN_3O$	64.98,	3.41,	14.21	64.79,	3.54,	14.43
5c	147—148	26	EtOH	$C_{18}H_{13}N_3O$	75.24,	4.56,	14.63	75.42,	4.41,	14.82
5d	172—173	50	EtOH	$C_{16}H_{13}N_3O_2S$	61.72,	4.21,	13.50	61.55,	4.54,	13.47

should be due to the corresponding structures **4c** and **4b**, respectively. Steric factors appeared to have strong influence on the reaction with acetophenone and only a small amount of an oily substance was formed. On the other hand, a cyclic ketone such as isatin (2,3-diketoindoline) easily reacted with **2** to give violet crystals, 2-(2-benzimidazolyl)-2-(1,2-dihydro-2-oxo-3*H*-indol-3-yliden)ethanenitrile (**4d**), in 93% yield, when refluxed in ethanol in the absence of a catalyst. This compound was hardly soluble in ordinary organic solvents, so that the structure was deduced from its infrared (IR) absorption ($\nu_{C\equiv N}$ 2220 cm^{-1}, very weak) and mass analysis (M^+ 286).

Acylation of 2-cyanomethylbenzimidazole (**2**) was carried out by utilizing the basicity of **2** itself. A mixture of 2 equivalent mol of **2** and 1 equivalent mol of tosyl chloride in acetone was refluxed and the precipitated **3** was filtered off. The filtrate was concentrated under a reduced pressure to give a tosylated compound, 1-tosyl-2-cyanomethylbenzimidazole (**5d**), in 50% yield. The NMR spectrum of **5d** indicated that the tosylation occurred not at the active methylene carbon but at the nitrogen of the imidazole ring. The signal of methylene protons in **5d** appeared at 4.40 ppm (10% solution in $CDCl_3$). Compounds obtained in the above experiments are listed in Table I.

Pyridine and trimethylamine were not effective catalysts for the acylation. One of the reasons for this might be the difference in basicity of the catalysts. The order of the basicity is as follows: trimethylamine>**2**>pyridine. In conclusion, it should be noted that the basicity of **2** should be used for the acylation of **2** by the Schotten-Baumann method.

Experimental[7]

2-(1-Cyano-2-methyl-1-propenyl)benzimidazole (4a)——To a solution of 0.1 g of 2-cyanomethylbenzimidazole (**2**) in 30 ml of acetone was added a few drops of trimethylamine (40% solution in water). The mixture was refluxed on a water-bath for 10 min, and the solvent was evaporated under a reduced pressure to give crystals which were recrystallized from ethanol and water to give 0.11 g (87%) of the crystals, mp 148—149°.

A mixture of the geometric isomers, (**4b**) and (**4c**), was also synthesized from the reaction of methyl ethyl ketone with **2** by the same method described above.

2-(2-Benzimidazolyl)-2-(1,2-dihydro-2-oxo-3*H*-indol-3-yliden)ethanenitrile (4d)——To a solution of 1.0 g of 2-cyanomethylbenzimidazole in 150 ml of ethanol was added 0.95 g of isatin, and the mixture was refluxed on a water-bath for 1 hr. The violet crystals that precipitated were filtered off and washed with ethanol to give 1.7 g (94%) of (**4d**), mp 260°; MS *m/e*: 286 (M^+); IR ν_{max}^{KBr} cm^{-1} 2220 (C≡N).

General Procedure for Acylation of 2——To a solution of 0.52 g of **2** in 50 ml of acetone was added dropwise 0.22 g of benzoyl chloride. After the mixture had been refluxed on a water-bath for 30 min, the precipitated crystals were filtered off, and the filtrate was concentrated under a reduced pressure to give crystals. Recrystallization from ethanol gave colorless plates of (**5a**) in 52% yield (0.22 g), mp 186—188°.

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[7] All melting points are uncorrected. The IR spectra were recorded on a Japan Spectroscopic Model IRA-1 spectrometer. The NMR and mass spectra were obtained on a Varian T 60 and a JMS-01S spectrometer (Japan Electron Optics Laboratory Co., Ltd.).