Notes

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Acidic Properties of Benzimidazoles and Substituent Effects. V.[1] Protection of Benzimidazoles by N-Alkyl Bond Formation using Vinylpyridines

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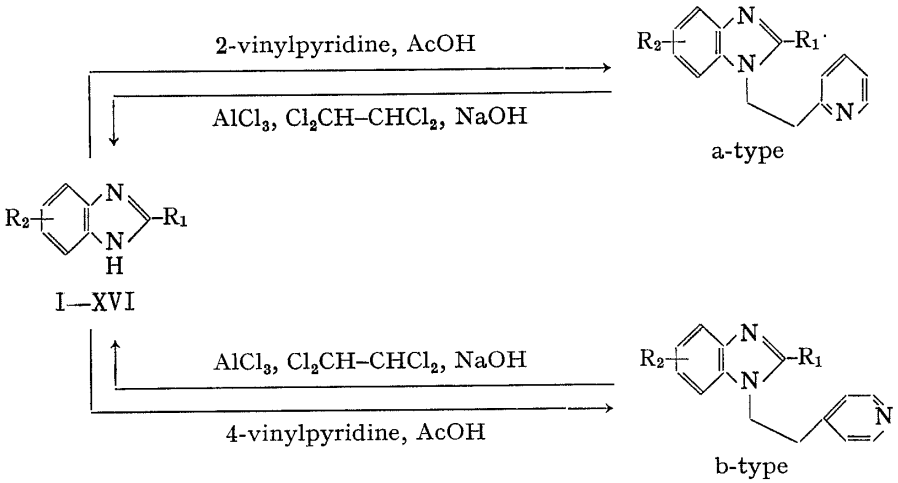
Vinylpyridines were utilized for protection of the benzimidazole N–H bond to give 1-(2-pyridylethyl)-benzimidazoles. The reaction was found to progress smoothly when glacial acetic acid was used as a catalyst. In the alkylation of 5- or 7-substituted-2-arylbenzimidazoles with vinylpyridines, the yield decreased with increasing electron-attracting effect of the substituent groups in the benzimidazole ring. On the other hand, the removal of pyridylethyl groups by the use of aluminum chloride as a catalyst was kinetically examined; a large excess of sodium hydroxide was used for decomposition of the intermediate adduct of aluminum chloride. The rate increased somewhat when electron-releasing substituent groups were present in the benzimidazole ring. 1-[2-(2-Pyridyl)ethyl]-2-arylbenzimidazoles were resistant to removal of their (2-pyridyl)ethyl groups. 4-Vinylpyridine can be used more efficiently as a protecting agent.

Keywords——2-pyridylbenzimidazoles; protection with vinylpyridines for imidazole; 1-(2-pyridylethyl)-benzimidazoles; substituent effect on N-alkylation of benzimidazoles; rate of removal of pyridylethyl groups by aluminum chloride catalyst

In the course of studies on the protection of imidazole ring N–H bonds, attempts to employ alkyl groups for protection have enjoyed only limited success on account of the difficulties in easily removing the alkyl group.[2–4]

Since alkylation at the 1-position of benzimidazole takes place readily merely on heating with vinylpyridines,[5] the dealkylation of 1-pyridylethyl bonds by the use of aluminum chloride has been developed.[6] The present study was undertaken to examine the alkylations of 5- or 7-substituted-2-arylbenzimidazole derivatives with 2- and 4-vinylpyridines in the presence



R_1=H, CH_3, phenyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-quinolyl, 4-quinolyl
R_2=H, CH_3, $COOC_2H_5$, Cl, NO_2

Chart 1

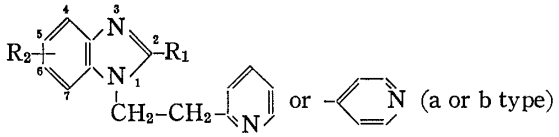
of a carboxylic acid, as well as the factors affecting removal of their pyridylethyl groups by aluminum chloride treatment.

The reactivity of vinylpyridines was investigated in the synthesis of 5- or 7-substituted-2-arylbenzimidazoles with a pyridylethyl substituent at the 1-position, using various aliphatic acids as catalysts. The N-alkyl bond formation was found to progress smoothly when glacial acetic acid was used and to be influenced by the substituent group on the benzimidazole ring. The removal of pyridylethyl groups occurred upon heating with aluminum chloride and it appeared that the substituent group on the benzimidazole ring affected the rate of the removal.

Experimental

Preparation of 1-[2-(2- or 4-Pyridyl)ethyl]-5- or 7-substituted-2-arylbenzimidazoles (a and b Type Compounds)——5- or 7-Substituted-2-arylbenzimidazoles for use as starting materials were prepared in the same manner as in our earlier report.[1)]

Table I. Analytical Data for 1-[2-(2- or 4-Pyridyl)ethyl]-2-arylbenzimidazoles



Compd. No.	R_1	R_2	mp(°C) (lit.)	Appearance (Recryst. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Yield (%)
Ia	H	H	57 (54)[3)]	Colorless needles (Petr. ether–ether)	$C_{14}H_{13}N_3$	75.31 (75.60)	5.87 (5.80)	18.82 (18.62)	89.7
Ib	H	H	101 (101)[3)]	Colorless prisms (*n*-Hexane–Me_2CO)	$C_{14}H_{13}N_3$	75.31 (75.11)	5.87 (5.99)	18.82 (18.94)	69.5
IIa	CH_3	H	77 (75)[3)]	Colorles needles (Petr. ether–ether)	$C_{15}H_{15}N_3$	75.92 (76.08)	6.37 (6.16)	17.71 (17.64)	93.7
IIb	CH_3	H	132 (129)[3)]	Colorless needles (CCl_4)	$C_{15}H_{15}N_3$	75.92 (75.79)	6.37 (6.24)	17.71 (17.99)	76.0
IIIa	Phenyl	H	82 (80—81)[3)]	Colorless powder (*n*-Hexane)	$C_{20}H_{17}N_3$	80.24 (80.06)	5.73 (5.91)	14.04 (13.94)	71.0
IIIb	Phenyl	H	129	Colorless needles (*n*-Hexane–Me_2CO)	$C_{20}H_{17}N_3$	80.24 (80.51)	5.73 (5.68)	14.04 (13.91)	23.4
IVa	2-Pyridyl	H	80—81 (75.5)[5)]	Colorless needles (H_2O–EtOH)	$C_{19}H_{16}N_4$	75.97 (76.13)	5.37 (5.26)	18.66 (18.71)	63.3
IVb	2-Pyridyl	H	110 (113.5)[5)]	Colorless needles (*n*-Hexane–Me_2CO)	$C_{19}H_{16}N_4$	75.97 (76.18)	5.37 (5.26)	18.66 (18.91)	65.0
Va	3-Pyridyl	H	bp 97 (20 Torr)	Light yellow liquid	$C_{19}H_{16}N_4$	75.97 (76.16)	5.37 (5.40)	18.66 (18.44)	67.0
Vb	3-Pyridyl	H	bp 98 (6 Torr)	Light yellow liquid	$C_{19}H_{16}N_4$	75.97 (76.24)	5.37 (5.13)	18.66 (18.73)	22.7
VIa	4-Pyridyl	H	102	Light yellow prisms (Petr. ether–ether)	$C_{19}H_{16}N_4$	75.97 (76.07)	5.37 (5.26)	18.66 (18.77)	65.0
VIIa	2-Quinolyl	H	123	Colorless needles (*n*-Hexane–Me_2CO)	$C_{23}H_{18}N_4$	78.83 (78.73)	5.18 (5.29)	15.99 (15.78)	69.0
VIIb	2-Quinolyl	H	136	Light yellow needles (Petr. ether–ether)	$C_{23}H_{18}N_4$	78.83 (78.66)	5.18 (5.02)	15.99 (16.22)	66.0
VIIIa	4-Quinolyl	H	90	Colorless needles (*n*-Hexane–Me_2CO)	$C_{23}H_{18}N_4$	78.83 (79.06)	5.18 (5.12)	15.99 (16.08)	57.0
VIIIb	4-Quinolyl	H	141	Colorless prisms (Petr. ether–ether)	$C_{23}H_{18}N_4$	78.83 (78.69)	5.18 (5.21)	15.99 (16.07)	43.4
IXa	2-Pyridyl	5-CH_3	bp 122 (6 Torr)	Light yellow liquid	$C_{20}H_{18}N_4$	76.40 (76.85)	5.77 (5.49)	17.82 (17.65)	82.0
IXb	2-Pyridyl	5-CH_3	bp 135 (5 Torr)	Light yellow liquid	$C_{20}H_{18}N_4$	76.40 (76.86)	5.77 (5.49)	17.82 (17.50)	68.8
Xa	2-Pyridyl	7-CH_3	90	Colorless needles (Petr. ether–ether)	$C_{20}H_{18}N_4$	76.40 (76.61)	5.77 (5.66)	17.82 (17.62)	76.9

Compd. No.	R_1	R_2	mp(°C) (lit.)	Appearance [Recryst. solvent]	Formula	Analysis (%) Calcd (Found) C	H	N	Yield (%)
Xb	2-Pyridyl	7-CH_3	142—143	Colorless needles (n-Hexane–Me_2CO)	$C_{20}H_{18}N_4$	76.40 (76.15)	5.77 (5.82)	17.82 (18.20)	38.2
XIa	2-Pyridyl	5-Cl	95	Colorless needles (Petr. ether–ether)	$C_{19}H_{15}ClN_4$	68.16 (68.02)	4.52 (4.80)	16.74 (16.59)	82.0
XIb	2-Pyridyl	5-Cl	114	Colorless needles (n-Hexane–Me_2CO)	$C_{19}H_{15}ClN_4$	68.16 (68.07)	4.52 (4.68)	16.74 (16.93)	65.8
XIIa	2-Pyridyl	7-Cl	116	Colorless needles (n-Hexane)	$C_{19}H_{15}ClN_4$	68.16 (68.03)	4.52 (4.31)	16.74 (16.48)	53.0
XIIb	2-Pyridyl	7-Cl	148	Colorless needles (n-Hexane–Me_2CO)	$C_{19}H_{15}ClN_4$	68.16 (68.21)	4.52 (4.38)	16.74 (16.69)	44.8
XIIIa	2-Pyridyl	5-NO_2	137	Light yellow needles (n-Hexane–Me_2CO)	$C_{19}H_{15}N_5O_2$	66.07 (65.89)	4.38 (4.69)	20.28 (20.34)	63.8
XIIIb	2-Pyridyl	5-NO_2	163	Light yellow needles (n-Hexane–Me_2CO)	$C_{19}H_{15}N_5O_2$	66.07 (66.21)	4.38 (4.31)	20.28 (20.14)	40.6
XIVa	2-Pyridyl	7-NO_2	163	Yellow needles (n-Hexane–Me_2CO)	$C_{19}H_{15}N_5O_2$	66.07 (65.96)	4.38 (4.51)	20.28 (20.35)	8.7
XIVb	2-Pyridyl	7-NO_2	167	Light yellow prisms (n-Hexane–Me_2CO)	$C_{19}H_{15}N_5O_2$	66.07 (66.01)	4.38 (4.58)	20.28 (20.14)	1.4
XVa	2-Pyridyl	5-$COOC_2H_5$	80	Colorless powder (Petr. ether–ether)	$C_{22}H_{20}N_4O_2$	70.95 (71.25)	5.41 (5.38)	15.05 (15.19)	75.2
XVb	2-Pyridyl	5-$COOC_2H_5$	171	Colorless powder (n-Hexane–Me_2CO)	$C_{22}H_{20}N_4O_2$	70.95 (71.01)	5.41 (5.38)	15.05 (15.19)	58.0
XVIa	2-Pyridyl	5-OCH_3	bp 100 (6 Torr)	Light yellow liquid	$C_{20}H_{18}N_4O$	72.70 (72.54)	5.49 (5.81)	16.96 (17.02)	86.6

Table II. Spectrophotometric Data

Compd. No.	Concn. ($\times 10^{-5}$)	λ_{max} (nm)[a]	log ε_{max}
IVa	5.0	308	4.23
IVb	5.0	308	4.21
IXa	4.2	313	4.22
IXb	3.1	314	4.25
Xa	4.2	305	4.22
Xb	5.0	305	4.21
XIa	5.0	313	4.26
XIb	5.0	314	4.23
XIIa	5.0	304	4.29
XIIb	5.0	305	4.25
XIIIa	5.0	325	4.26
XIIIb	5.0	324	4.20
XIVa	5.0	335	4.14
XIVb	5.0	335	4.16

a) In ethanol.

Kinetic Measurement——a) Preparation of Sample: A 10 ml aliquot of 0.05 M solution of 1-(2-pyridylethyl)-2-arylbenzimidazoles in dry 1,1,2,2-tetrachloroethane (bp 147°C) was pipetted into a 30 ml flask and then a thermometer was inserted into the solution. After the temperature of the benzimidazole solution had been adjusted to 140°C (±0.5°C), the reaction was initiated by the addition of 6.7 mg of powdered anhyd. $AlCl_3$. After the desired interval, the reaction was quenched by cooling the mixture to 5°C and the mixture was then poured into 8 ml of 5 N NaOH. After being shaken for 5 min, the whole was extracted with dichloromethane (2×7 ml) and the organic layer was washed with 20 ml of H_2O. The extract was evaporated to dryness *in vacuo*. The residue was dissolved in 2 ml of EtOH and subjected to the following analysis.

b) Detection: Preparative thin layer chromatography was done on silica gel plates prepared in our laboratory using Silica-layer G-10 (Nakarai Chemicals, Ltd.). A 0.01 ml aliquot of the sample was applied to the starting line of this plate (20×20 cm). The plate was developed in benzene–$CHCl_3$–EtOH (15:5:1).

Table III. Dealkylation of 1-[2-(2- or 4-Pyridyl)ethyl]-2-arylbenzimidazoles to 2-Arylbenzimidazoles

Starting material	Benzimidazole	mp (°C)[a]	Yield (%)
IIIa	III	293—294	40
IVa	IV	219—220	30
IVb	IV	219—220	85
VIIa	VII	195	26
VIIb	VII	195	82
IXa	IX	158—160	22
IXb	IX	158—160	90
Xa	X	144—145	38
Xb	X	144—145	93
XIa	XI	140—141	13
XIb	XI	140—141	85
XIIa	XII	132—133	23
XIIb	XII	132—133	70
XIIIa	XIII	211—212	12
XIIIb	XIII	211—212	70
XIVa	XIV	214—215	18
XIVb	XIV	214—215	80

a) The benzimidazoles after removal of the pyridylethyl groups were identical (mixed melting point test) with the corresponding benzimidazole prepared in ref. 1.

After development, the plate was air-dried, and then the blue-fluorescent spot at *Rf* 0.27—0.35 was eluted with 5 ml of EtOH at about 50°C. The ultraviolet spectrum of the eluate was measured on a Hitachi EPS-3T machine, and the concentrations of 1-(2-pyridylethyl)-2-arylbenzimidazoles were determined from a calibration curve with considerable accuracy in the concentration range from 2.0 to 7.0×10^{-5} M. The initial rates were followed for 15 to 30 min at 140°C. Plots of the reciprocal of remaining 1-(2-pyridylethyl)-2-arylbenzimidazoles against time were linear, and the rates of dealkylation were calculated from them.

c) Dealkylation of 1-(2-Pyridylethyl)-2-arylbenzimidazoles, Typical Procedure: Powdered anhyd. $AlCl_3$ (0.003 mol) was added to a solution of 1-(2-pyridylethyl)-2-arylbenzimidazole (0.003 mol) in 50 ml of dry tetrachloroethane, and the mixture was heated at 140°C for 5 h. When the reaction was over, the reaction mixture was cooled to 5°C and then poured into 100 ml of 5 N aq. soln. After being shaken for 5 min, the whole mixture was extracted with dichloromethane. The extract was washed with H_2O, dried over anhyd. Na_2CO_3 and evaporated to dryness *in vacuo*. The residue was recrystallized to give the corresponding 2-arylbenzimidazole (Table III).

Results and Discussion

Substituent Effects on N-Alkyl Bond Formation with 2- and 4-Vinylpyridines

The protection of the N–H bond of benzimidazoles (I to XVI) can be accomplished by alkylation with 2- or 4-vinylpyridines in the presence of acetic acid to form 1-[2-(2- or 4-pyridyl)ethyl]-benzimidazoles (Ia, b to XVIa, b). The infrared (IR) spectra of the a and b type compounds formed exhibited characteristic C–H streching absorptions in the range of 2900 to 3000 cm^{-1}, while secondary amine absorptions of the imidazole ring were completely absent. In general, peak groups 92 mass units (pyridylmethylene) apart from their parent peaks (M^+) were characteristic in the fragmentation patterns. As regards the scope of the reactions, the substituent effects of 5- or 7-substituted-2-(2-pyridyl)-benzimidazoles (IX to XVI) were examined; some data are shown in Fig. 1. The amount of alkylation tended to decrease with increasing electron-attracting power of a substituent in the benzimidazole ring. The available evidence indicates that the yield is related to the acidity of the benzimidazoles. On the other hands, in our study of the reactivity of vinylpyridines with acids, it was found that the use of double the molar quantity of glacial acetic acid raised the yields of the N-alkylations. Changes in the acid series from C_2H_5- to C_3H_7-COOH had little further effect upon the yield; for instance, when 2-(2-pyridyl)-benzimidazole (IV) was reacted with 4-vinylpyridine in the presence of acids: HCOOH, IVb in 40% yield$<C_2H_5COOH$, *n*-C_3H_7COOH, IVb

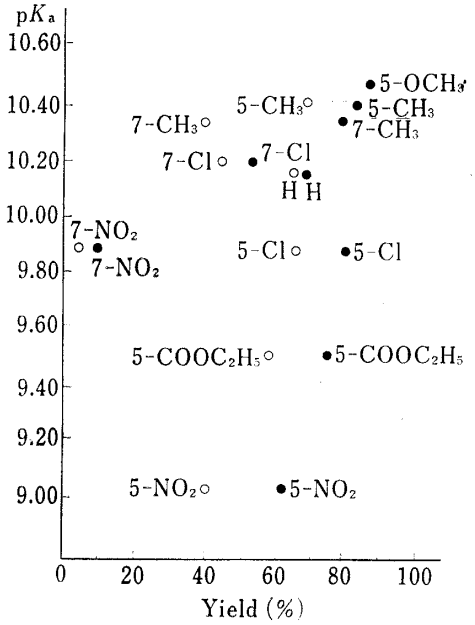


Fig. 1. Correlation of pK_a Values[a] of 5- or 7-Substituted-2-(2-pyridyl)benzimidazoles and Yields of Their a and b Type Compounds

●: a type, ○: b type.
a) Data are taken from ref. 1.

Table IV. Rate Constants for the Dealkylation by Aluminum Chloride

Compd. No.	Rate constant k ($1 \cdot mol^{-1} \cdot min$)[a]	Rel. rate
IVb	640	1.00
IXb	900	1.41
Xb	1160	1.81
XIb	490	0.76
XIIb	280	0.44
XIIIb	390	0.61
XIVb	490	0.76

a) The k values are the averages of at least four determinations. The measurements are accurate to within 1%.

in 55% yield<CH_3COOH, IVb in 65% yield. However, 1-(2-pyridylethyl)-2-(2-pyridyl)-7-nitrobenzimidazoles (XIVa, b) were obtained in less than 10% yields and prolongation of the reaction time did not lead to any increase in the yield, although the pK_a value of XIV is close to that of 5-chloro-2-(2-pyridyl)benzimidazole (XI), which affords XIa, b in more than 60% yields. The magnitude of the drop in yields of XIVa, b suggests a large steric blocking effect of the nitro group at the imidazole N–H site.

Factors affecting the Removal of Pyridylethyl Groups

In order to observe the initial increase in rates upon addition of aluminum chloride, the reactions of 1-(2-pyridylethyl)-benzimidazoles (IVa, b and IXa, b to XIVa, b) with aluminum chloride in tetrachloroethane were carried out at 140°C for 30 min and instantaneously quenched by addition of sodium hydroxide aqueous solution. A small increase in the rate of removal of pyridylethyl group can be attributed to addition of aluminum chloride with heating to 140°C, and the initial reaction was second-order. The remaining 1-(2-pyridylethyl)-benzimidazole was measured by spectrophotometry after isolation by thin layer chromatography, in which the 1-(2-pyridylethyl)-benzimidazole was always determined as a blue-fluorescent spot at *Rf* 0.27—0.35, while the corresponding benzimidazole appeared at *Rf* 0.7—0.8 under ultraviolet light.

The ability of electron-releasing substituent groups in the benzimidazole ring to increase the rate of removal of (4-pyridyl)ethyl group was in the order: 5-NO_2, XIIIb (0.61)<5-Cl, XIb (0.76)<H, IVb (1.00)<5-CH_3, IXb (1.41). However, the a type compounds, 1-[2-(2-pyridyl)ethyl]-2-arylbenzimidazoles, proved reluctant to liberate their (2-pyridyl)ethyl groups, as indicated in Table III. This might be because aluminum chloride as a Lewis acid catalyst links more effectively to the nitrogen of pyridine in the (2-pyridyl)ethyl site. Consequently, 4-vinylpyridine can be used more efficiently as a protecting agent.

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References and Notes

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Total Synthesis of (±)-Malyngolide

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(±)-Malyngolide, which is an antibiotic isolated from a marine blue-green alga, was synthesized starting from 2-ethoxycarbonylcyclopentanone.

Keywords——malyngolide; antibiotic; selective oxidation; selective reduction; Baeyer–Villiger oxidation

Malyngolide is a recently discovered antibiotic isolated from the marine blue-green alga, *Lyngbya majuscula* GOMONT,[1] and its structure was determined as **1**. Recently, an elegant total synthesis of (—)-malyngolide has been reported by Mukaiyama *et al.*[2]

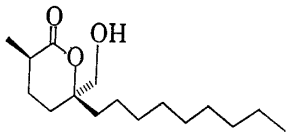

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Fig. 1

As a part of a general project aimed at the elucidation of the structure-activity relationships of antimicrobial substances[3], we selected malyngolide as a parent compound and firstly planned to synthesize it by a route which is applicable to the synthesis of its analogs.

The synthetic route to (±)-malyngolide is illustrated in Chart 1.

2-Ethoxycarbonyl-2-nonylcyclopentanone (**3**) was prepared by the reaction of 2-ethoxycarbonylcyclopentanone (**2**)[4] with nonyl bromide in the presence of sodium hydride in N,N-dimethylformamide at 100—110°C in 82.5% yield.

For conversion of the keto ester (**3**) to a ketol (**5**), it is necessary to reduce the ester group selectively in the presence of the keto group. There is no good method so far available for that purpose, although many procedures are available for the reduction of a ketone or aldehyde in the presence of an ester or lactone.[5] Therefore, we examined firstly reduction of both keto and ester groups and successive selective oxidation of the secondary alcohol in the diol (**4**). Thus, reduction of the keto ester (**3**) with lithium borohydride gave the diol (**4**) in 71.4% yield, and this product was oxidized selectively with bromine and hexamethylphosphoramide (HMPA)[6] to give the ketol (**5**) in 72.2% yield. Secondary, we employed the method of enolate formation in combination with hydride reduction which was first developed by Barton for the reduction of steroidal ketones.[7] Thus, the keto ester (**3**) was treated with lithium diisopropylamide (LDA) at —76°C in tetrahydrofuran (THF) to form a lithium enolate, which was reduced with lithium aluminum hydride at the same temperature to afford the desired ketol (**5**) in 63.5% yield.

Baeyer–Villiger oxidation of the ketol (**5**) with *m*-chloroperbenzoic acid in the presence of sodium bicarbonate in chloroform gave a lactone (**6**) as a sole product in 81.8% yield. The protection of the hydroxyl group in **6** was accomplished in 78.6% yield by treatment with