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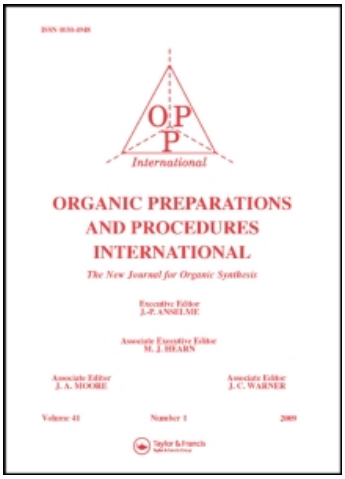

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ACIDIC PROPERTIES OF BENZIMIDAZOLES AND SUBSTITUENT EFFECTS. III.: THE SUBSTITUENT EFFECT ON THE IMIDAZOLE CYCLIZATION FROM N-(*m*-SUBSTITUTED-PHENYL) PICOLYLAMIDINES

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ACIDIC PROPERTIES OF BENZIMIDAZOLES AND SUBSTITUENT EFFECTS. III.[1]: THE SUBSTITUENT EFFECT ON THE IMIDAZOLE CYCLIZATION FROM N-(m-SUBSTITUTED-PHENYL)PICOLYLAMIDINES

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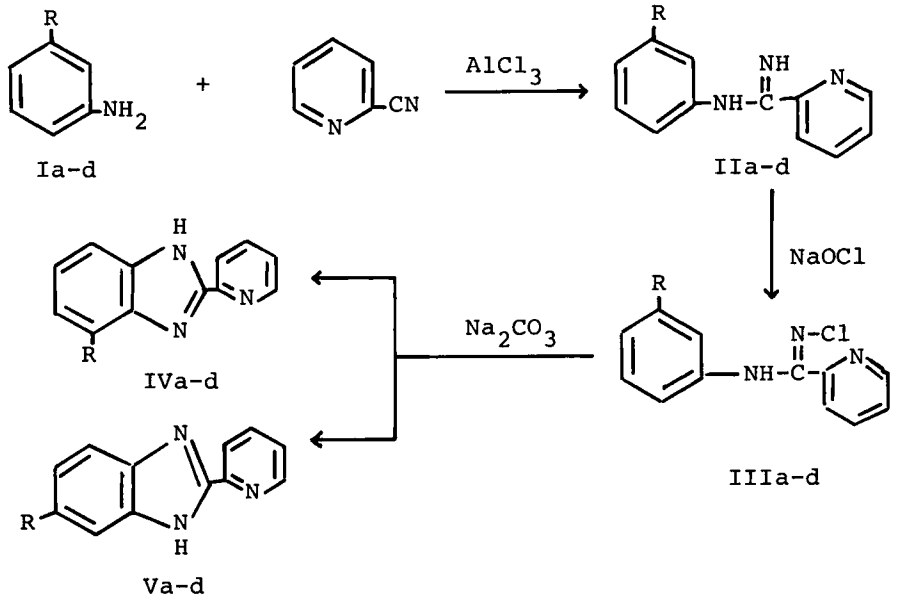
In the context of a study of the acidity of 2-(2-pyridyl)benzimidazoles,[1] we have found that the cyclization of N'-(m-substituted-phenyl)-picolylamidines(III) affords two isomers IV and V.



a) R=H; b) R=CH_3; c) R=OCH_3; d) R=NO_2

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The amidines II, obtained by the condensation of I with 2-cyanopyridine exhibited two secondary amine absorptions (νC=NH, -NH-) in the range of about 3300 to 3450 cm^{-1} similar to those of N-substituted-trichloroacetamidines,[2] shown in Table I. The nmr spectrum in 4% dimethylsulfoxide (DMSO) of II showed a broad single hydrogen peak at τ 3.00 to 4.00 for two protons of amidino group which disappeared upon the addition of D_2O. Their amidines afforded intermediate N-chloro compounds (III) whose nmr spectra showed a broad single hydrogen peak at τ -0.5 to -1.0 for one proton of secondary amino site. In general, the isolation of isomers IV and V can be carried out by fractional recrystallization from which 4 (or 7)-substituted-2-(2-pyridyl)benzimidazoles(IV) was separated first and the other ones(V) from the filtrate. The structural assignment of V was based on satisfactory elemental analyses, mass spectra and comparison with authentic samples of 5 (or 6)-substituted-2-(2-pyridyl)benzimidazoles, prepared from p-substituted-o-phenylene diamines and picolinic acid.[1] The structures of IV were assigned on the basis of elemental analyses and mass spectra. It is interesting Vc separated first from the cyclization of N'-(m-anisyl)picolylamidine(IIc); IVc precipitated gradually after adjustment to pH 8.0.

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Table I. Data of Preparation of Amidines II

Compd. No.	R	mp.,°C	Appearance (Recryst.solvent)	Yield(%)
IIa	H	189-191	colorless prisms ($MeOH-H_2O$)	87
IIb	CH_3	54-55	colorless needles (n-hexane)	63
IIc	OCH_3	66-67	colorless prisms (n-hexane)	51
IId	NO_2	117.5-118.5	light yellow needles (n-hexane-acetone)	73

Compd. No.	IR(KBr) $\nu_{C=NH}$	IR(KBr) ν_{-NH-}	Formula	Analysis(%) Calcd.(Found) C	H	N
IIa	3355	3460	$C_{12}H_{11}N\cdot HCl$	61.67 (61.55)	5.18 (5.23)	17.98 (18.01)
IIb	3295	3430	$C_{13}H_{13}N_3$	73.91 (73.76)	6.20 (6.38)	19.89 (19.76)
IIc	3335	3450	$C_{13}H_{13}N_3O$	68.70 (68.91)	5.77 (5.68)	18.49 (18.46)
IId	3355	3465	$C_{12}H_{10}N_4O_2$	59.50 (59.70)	4.16 (4.34)	23.13 (23.23)

Table II. Data of Cyclization of IV and V

II	R	Products: IV-type mp.,°C(lit.)	Yield(%)	V-type mp.,°C(lit.)	Yield(%)
IIa	H	219-220(219-220)[3]	75.0	–	
IIb	CH_3	144-144.5	22.0	159-160(158-160)[1]	60.0
IIc	OCH_3	100-102	13.0	133-134(133-134)[1]	32.0
IId	NO_2	214-215	24.5	211.5-212(211-212)[1]	38.0

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EXPERIMENTAL

All melting points were uncorrected. IR spectra were recorded on Nippon Bunko DS-701G Infrared Spectrophotometer. NMR spectra were taken with Nippon Denshi JNM-TMX60 in ca. 4% (w/v) DMSO solution with tetramethylsilane as an internal standard at 60 Mc.

N'-(m-Substituted phenyl)picolylamidines (II).- To a solution of 0.1 mole of a m-substituted aniline and 10.4 g.(0.1 mole) of 2-cyanopyridine in 40 ml. of sym-tetrachloroethane, 13.3 g. (0.1 mole) of powdered anhyd. $AlCl_3$ was gradually added and the mixture was then refluxed for 30 min. After cooling, the reaction mixture was poured into 1 l. of 5N NaOH aq. solution and extracted with 300 ml. of dichloromethane. The extract was dried over anhyd. Na_2CO_3 and HCl gas was then introduced to the extract cooled in an ice bath, during which period the crystalline hydrochloride of II separated. The crystalline mass was collected by suction and dissolved in 200 ml. of H_2O. The aqueous solution was neutralized with Na_2CO_3 to separate the crude amidine (II) which was recrystallized to give an analytical sample (Table I).

Cyclization from N'-(m-Substituted phenyl)picolylamidines (II). - The amidine (0.02 mole) was dissolved in 90 ml. of 50% aqueous MeOH and the pH adjusted to 3.0 with 10% HCl. To the solution was added dropwise 13 ml. of 10% NaOCl aq. solution for 5 min. at 10-20° and stirring was continued an additional 20 min. To the reaction solution was added 4 g. of Na_2CO_3 as a saturated aqueous solution and the mixture was heated for 1 hr. at reflux. After the reaction was over, the reaction mixture was kept overnight below 10° to separate the benzimidazoles(IV and

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V) which were isolated by fractional recrystallization. From their general behavior, IV was separated first and the filtrate was concentrated to give a crystalline mass of V.

Table III. Analytical Data of IV and V

Compd. No.	Appearance (Recryst. solvent)	Formula	Analysis (%) Calcd. (Found) C	H	N
IVa	colorless needles (benzene)	$C_{12}H_9N_3$	73.85 (74.17)	4.61 (4.63)	21.54 (21.33)
IVb	colorless needles (n-hexane-acetone)	$C_{13}H_{11}N_3$	74.62 (74.36)	5.31 (5.44)	20.08 (20.20)
IVc	colorless needles (n-hexane-acetone)	$C_{13}H_{11}N_3O$	69.32 (69.08)	4.92 (4.87)	18.66 (18.75)
IVd	light yellow needles (EtOH)	$C_{12}H_8N_4O_2$	60.00 (59.78)	3.37 (3.47)	23.32 (23.07)
Vb	colorless needles (n-hexane-acetone)	$C_{13}H_{11}N_3$	74.62 (74.81)	5.31 (5.29)	20.08 (20.23)
Vc	colorless needles (n-hexane-acetone)	$C_{13}H_{11}N_3O$	69.32 (69.44)	4.92 (4.90)	18.66 (18.72)
Vd	light yellow needles (EtOH)	$C_{12}H_8N_4O_2$	60.00 (59.80)	3.37 (3.40)	23.32 (23.16)

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