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Synthesis of 4,5-Di- and 1,4,5-Trisubstituted Imidazole Derivatives from 4,5-Dicyanoimidazole

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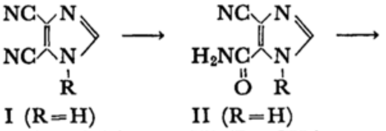
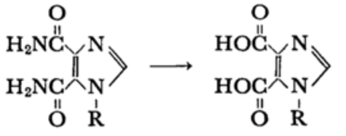
The chemical reactivities and the synthesis of various derivatives of 4,5-dicyanoimidazole formed by heating a solution of hydrogen cyanide in liquid ammonia were studied, as were the partial hydrolysis, hydrogenation, and addition reaction of cyano groups and the alkylation, cyanoethylation, and vinylation of the imidazole ring. From these experiments, a few new compounds were synthesized, which had been expected as intermediates of polymers containing imidazole rings.

In a previous paper,[1] the present authors have reported that adenine and 4,5-dicyanoimidazole were formed simultaneously by heating a solution of hydrogen cyanide in excess liquid ammonia. Though 4,5-dicyanoimidazole (I) has been already described in the literature,[2,3] the chemical properties of the compound have not yet been adequately described. This substance was recently found to be a valuable intermediate for the synthesis of various useful derivatives of imidazole and purine, *e.g.*, 4-amino-5-imidazolecarboxamide.[4] Furthermore, I may be expected to be a valuable intermediate for various polymers containing imidazole rings.

The present investigation was undertaken in order to clarify the reactivities of two cyano groups and one imino group of I and to prepare various imidazole derivatives.

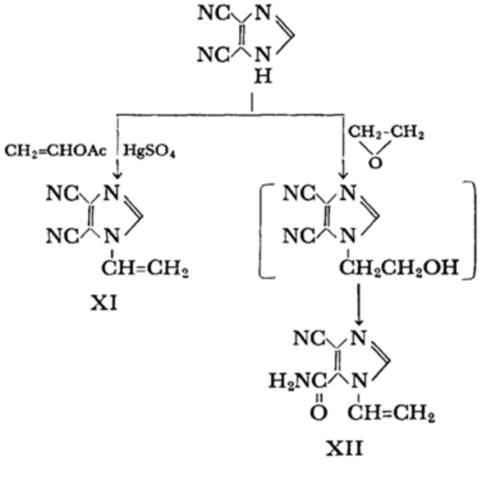


I (R=H) II (R=H)
I′ (R=CH_3) II′ (R=CH_3)



III (R=H) IV (R=H)
III′ (R=CH_3) IV′ (R=CH_3)

The partial hydrolysis[4] of I to 4-cyano-5-imidazolecarboxamide (II) had been achieved in a 90% yield by treatment with a 1 N sodium hydroxide solution. Under more drastic conditions, however, the hydrolysis of I could not be stopped at the diamide (III) stage, and 4,5-imidazoledicarboxylic acid (IV) was obtained in a 88% yield. In contrast with these findings, the hydrolysis of 1-methyl-4,5-dicyanoimidazole (I′) was found to occur hundreds of times faster than that of I. Consequently, whereas 1-methyl-4,5-imidazoledicarboxamide (III′) was obtained in a 80% yield, it was difficult to isolate 1-methyl-4-cyano-5-imidazolecarboxamide (II′) in a high yield. Besides, far more reduction of cyano groups of I′ was achieved than in the case of the reduction of I by lithium aluminium hydride or by catalytic hydrogenation (Raney Cobalt). The increased reactivities of the cyano groups of I′ may be due to the electron-releasing effect of the methyl group in the position 1. Attempts to prepare amidine and orthoester derivatives *via* iminoether[3] of I were unsuccessful. These data on the addition reactions indicate that the cyano groups of I are extremely different from those of malononitrile and benzonitrile. Hydrogen sulfide, however, reacted



XI

XII

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[1] H. Wakamatsu, Y. Yamada, T. Saito, I. Kumashiro and T. Takenishi, *J. Org. Chem.*, **31**, 2035 (1966).

[2] D. W. Woodward, U.S. Pat. 2534331 (1950).

[3] H. Bredereck and G. Schmötzer, *Ann.*, **600**, 95 (1956).

[4] Y. Yamada, I. Kumashiro and T. Takenishi, This Bulletin, **41**, 241 (1968).

TABLE 1. IMIDAZOLE DERIVATIVES

No.	Substituents			Yield %	Solv. of recrystn[a]	Mp °C (Bp)	Empirical formula
	R_1	R_2	R_3				
III	H	$CONH_2$	$CONH_2$	54	A	>300 d	$C_5H_6N_4O_2$
IV	H	CO_2H	CO_2H	88	A	280 — 282 d	$C_5H_4N_2O_4$
I′	CH_3	CN	CN	95[c]	B	89 — 89.5	$C_6H_4N_4$
II′	CH_3	CN	$CONH_2$	19	D	212 — 212.5	$C_6H_6N_4O$
III′	CH_3	$CONH_2$	$CONH_2$	80	B	268	$C_6H_8N_4O_2$
IV′	CH_3	CO_2H	CO_2H	70	B	253.5— 254 d	$C_6H_6N_2O_4$
V	H	CH_2NH_2	CH_2NH_2	40[b]	C	285 — 290 d	$C_5H_{10}N_4 \cdot 3HCl$
V	H	CH_2NH_2	CH_2NH_2	20[c]	C		
V	H	CH_2NH_2	CH_2NH_2	12[d]	C		
VI	CH_3	CH_2NH_2	CH_2NH_2	51[d]	C	265 — 268 d	$C_6H_{12}N_4 \cdot 3HCl$
VII	$C_6H_5CH_2$	CH_2NH_2	CH_2NH_2	45[d]	C	260 — 262 d	$C_{12}H_{16}N_4 \cdot 3HCl$
VIII	H	$CSNH_2$	$CSNH_2$	75	B	232 — 234 d	$C_5H_6N_4S_2$
IX	$CH_2CH{=}CH_2$	CN	CN	82	—	(148/1.5mmHg)	$C_9H_6N_4$
X	CH_2CH_2CN	CN	CN	90	D	95 — 96.5	$C_8H_5N_5$
XI	$CH{=}CH_2$	CN	CN	33	E	93.5— 94	$C_7H_4N_4$
XII	$CH{=}CH_2$	CN	$CONH_2$	60	B	191 — 191.5	$C_7H_6N_4O$
XIII	$COCH_3$	CN	CN	94	F	145 — 147.5	$C_7H_4N_4O$
XIV	$CH_2CH{=}CH_2$	CO_2H	CO_2H	70	B	204 — 205	$C_8H_8N_2O_4 \cdot \frac{1}{4}H_2O$

a) Solvents of recrystallization; A, dissolved in alkali and precipitated with hydrochloric acid; B,
b) Method A. c) Method B. d) Catalytic hydrogenation.

with I vigorously to form 4,5-imidazoledithiocarboxamide in a high yeild. I is a weakly acidic substance,[5] exhibiting different chemical reactivities than imidazole. Therefore, the imino group of I did not react with alkyl halide and dimethylsulfate, unless the basic substance was already present. The labile hydrogen atom of I was, however, readily added to acrylonitrile. In a similar fashion, I was converted to 1-vinyl-4-cyano-5-imidazolecarboxamide (XII) by the addition of ethylene oxide in the presence of sodium hydroxide as a catalyst. The imino group of I reacted with vinyl acetate in the presence of mercuric sulfate to form 1-vinyl-4,5-dicyanoimidazole (IX), though sodium salt of I did not react with vinyl halide in a nonaqueous solvent.

Experimental[6]

1-Methyl-4,5-dicyanoimidazole (I′). A) Into a solution of I (2.36 g, 20 mmol) in 0.2 N sodium hydroxide (100 m*l*), a 1 N silver nitrate solution (20 m*l*) was vigorously stirred. The precipitates were filtered, washed with water, and dried, and then treated with a solution of methyl iodide (1.25 m*l*, 20 mmol) in ether (50 m*l*) at 110°C for 2 hr in a sealed vessel. Silver iodide was then filtered out, and the clear etheral solution was evaporated to dryness. Crude I (1.68 g) was thus obtained. For further purification, the compound was recrystallized from hot water to give colorless crystals.

B) To a mixture of I (11.8 g, 0.1 mol) and sodium hydrogen carbonate (14.3 g, 0.17 mol) in 100 m*l* of water, dimethyl sulfate (14.3 m*l*, 0.15 mol) was added, drop by drop, over a 30-min period at 50—60°C. After the reaction mixture had been stirred at the same temperature for an additional hour, the product was extracted from the solution by ethyl acetate. The extract was washed with dilute aqueous sodium carbonate and water, and dried. The evaporation of the extract gave 12.5 g of I′.

1-Methyl-4-cyano-5-imidazolecarboxamide (II′). A solution of I′ (92 g) in 1.84 *l* of 0.5 N sodium hydroxide (as 50 v/v% aqueous ethanol) was allowed to stand at 24—25°C for 30 min. The solution was then neutralized with hydrochloric acid, and evaporated to 500 m*l*. The crystals formed were filtered off and washed with cold water. About five recrystallizations from ethanol gave an analytical sample of II′ (20 g).

4,5-Imidazoledicarboxamide (II). To a solution o I (2.36 g, 20 mmol) in 1.1 N sodium hydroxide (18 m*l*), 30% aqueous hydrogen peroxide (9.1 m*l*) was added, drop by drop, at 50—60°C over a 2-hr period. The solution was then neutralized with dilute hydrochloric acid, filtered, and the precipitates were washed with water and dried to give 1.66 g.

1-Methyl-4,5-imidazoledicarboxylic Acid (IV′). I′ (1.32 g, 10 mmol) was heated with a 6 N sodium

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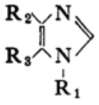
[5] pK*a* 5.2 at 18°C.

[6] The detailed data are listed in the table, in which the melting points and boiling point are uncorrected.



Ultraviolet absorption pH 1 λ_{max} mμ	ε	pH 13 λ_{max} mμ	ε	Carbon % Calcd	Found	Hydrogen % Calcd	Found	Nitrogen % Calcd	Found
		286		38.96	39.02	3.92	3.75	36.35	36.10
235,	8500	250,	5500	38.47	38.25	2.58	2.86	17.95	18.10
250,	10000	252,	7100	54.54	54.60	3.05	3.24	42.41	42.62
248,	7400	250.5,	7500	48.00	48.10	4.03	4.16	37.32	37.24
		257,	7200	42.85	42.65	4.80	4.95	33.32	33.51
227,	8600	237,	4400	42.36	42.26	3.56	3.57	16.47	16.31
				25.49	25.52	5.56	5.94	23.78	23.31
				28.87	29.23	6.06	6.09	22.45	22.36
				44.25	43.99	5.88	5.91	17.21	17.03
312,	11100	285,	9500	32.24	32.84	3.25	3.75	30.08	29.87
		333,	10800						
249.5,	9700	250,	8300	60.74	60.56	3.82	3.77	35.43	35.43
248.5,	11400	251,	7300	56.13	56.13	2.94	3.24	40.92	41.21
251,	13200	255.5,	9300	58.33	58.34	2.80	2.91	38.87	39.05
252		263.5		51.85	52.12	3.73	3.88	34.56	34.50
247.5, 14200 (at pH 7)				52.50	52.69	2.52	2.56	34.99	35.54
250		280		47.88	47.72	4.27	4.09	13.96	14.11

water; C, dilute hydrochloric acid; D, ethanol; E, methanol; F, dioxane.

hydroxide solution (10 m*l*) under refluxing for 1 hr and then neutralized with 3 N hydrochloric acid. The solution was cooled in an ice box. The precipitates were filtered, washed with cold water, and dried to give 1.19 g of the product.

4,5-Bis(aminomethyl)imidazole (V). A) To a suspension of lithium aluminum hydride (4.55 g, 0.12 mol) in tetrahydrofuran (400 m*l*), a solution of I (4.72 g, 40 mmol) in tetrahydrofuran (50 m*l*) was added, drop by drop, at 25—30°C. The mixture was stirred at 35—40°C for an additional 2 hr, and then water was added to the reaction mixture under cooling. Aluminum hydroxide was filtered out, and the filtrate was evaporated under reduced pressure. The brown residue was dissolved in water, and the aqueous solution was passed through a column of Amberite IR-120 (H^+ form). After washing with water, elution was effected with dilute aqueous ammonia. The eluate was evaporated to dryness under reduced pressure, and the residue was acidified with hydrochloric acid and decolorized. The solution was again evaporated to give crude 4,5-(bisaminomethyl)imidazole trihydrochloride (3.8 g), which showed a violet-red color when treated with ninhydrin.

B) To a solution of I (1.18 g, 10 mmol) in isoamyl alcohol (150 m*l*), sodium (11 g, 0.48 g atom) was added a little at a time under refluxing. When the metallic sodium had been dissolved completely, the solution was evaporated to dryness under reduced pressure. The isolation of V (0.47 g) was achieved in the way described in A.

C) A solution of I (0.5 g, 4.25 mmol) in methanol (20 m*l*) saturated with ammonia at 0°C was hydrogenated in the presence of Raney cobalt (0.7 g as alloy) under an initial hydrogen pressure of 110 kg/cm^2 and at a temperature in the range from 100 to 110°C. After the catalyst had been removed from the reaction mixture, the solution was evaporated to dryness under reduced pressure. V (0.12 g) was isolated in the way described in A.

4,5-Imidazoledithiocarboxamide (VIII). I (2.36 g, 20 mmol) and powdered sodium hydroxide as a catalyst (2 g) were added to liquid hydrogen sulfide (50 m*l* at −75°C), and the reaction mixture was heated at 70°C for 3 hr in a pressure vessel. The solution was then cooled and evaporated to dryness. Water (30 m*l*) was added and the pH adjusted to 2—3 with hydrochloric acid. A crude yellow product (2.79 g) was filtered out, washed, and recrystallized from hot water.

1-Allyl-4,5-dicyanoimidazole (IX). To a mixture of allyl bromide (18 g, 0.15 mol) and I (11.8 g, 0.1 mol) in 100 m*l* of water, sodium hydrogen carbonate (14.3 g, 0.17 mol) was added. The mixture was then heated at 80°C for 2 hr, and the cooled mixture was extracted with ether. The etheral solution was washed with dilute aqueous sodium carbonate and water, and then dried. After the evaporation of the etheral solution, the residual oil was distilled to give 13 g of IX.

1-(β-Cyanoethyl)-4,5-dicyanoimidazole (X). A mixture of I (1.18 g, 10 mmol) and powdered potassium hydroxide (100 mg) as a catalyst in acrylonitrile (20 m*l*) was heated at 120°C for 5 hr in a sealed tube, and then the solution was evaporated to dryness. Water (20 m*l*) was added and the pH adjusted to 7 with hydrochloric acid. The cooled solution gave 1.53 g of the product.

1-Vinyl-4,5-dicyanoimidazole (XI). To a solution of I (35.4 g, 0.3 mol) and mercuric acetate (12 g) in vinyl acetate (618 g, 7.2 mol), concentrated sulfuric acid (1.5 m*l*) was added. After the solution had been heated at 40—45°C for 48 hr, the precipitates were filtered and the excess vinyl acetate was removed under reduced pressure. The recrystallization of the residue from methanol gave 14.3 g of the product (IX).

1-Vinyl-4-cyano-5-imidazolecarboxamide (XII). A mixture of I (2.36 g, 20 mmol) and sodium hydroxide (0.4 g) as a catalyst in liquid ethylene oxide (10 m*l*) was carefully heated at 100°C for 3 hr in a pressure vessel. After the evaporation of the excess ethylene oxide, 1.95 g of XII were obtained by the recrystallization of the residue from hot water. The infrared spectrum (KBr) showed strong absorptions at 3025 (vinyl hydrogen), 2275 (cyano group), and 1670 cm^{-1} (amido group).

1-Acetyl-4,5-dicyanoimidazole (XIII).[7] To a solution of I (2.36 g, 20 mmol) and sodium hydrogen carbonate (0.42 g, 5 mmol) in 0.5 N sodium hydroxide (20 m*l*), acetic anhydride (2.04 g, 20 mmol) was added at 0—5°C. After 5 min, the resulting white precipitates (3.0 g) were filtered and recrystallized from dioxane. The infrared absorption spectrum (KBr) showed strong absorptions at 2270 (cyano group) and 1775 cm^{-1} (acetyl group).

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[7] The authors wish to thank Dr. Yoshioki Komachiya for his helpful suggestions regarding the synthesis of XIII.