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Reactivity of 2,4(5)-Dialkylimidazoles. Synthesis of 6,7,8,9-Tetrahydro-5*H*-imidazo[1,5-*a*][1,4]diazepine Derivatives

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6,7,8,9-Tetrahydro-5*H*-imidazo[1,5-*a*][1,4]diazepine derivatives (IV) were synthesized by the reaction of formalin with 1-γ-aminopropylimidazole derivatives (III) prepared by cyanoethylation and then catalytic hydrogenation of the imidazole derivatives (I).

From a series of studies on the reactivity of 2,4(5)-dialkylimidazoles (I)[2] we have reported on their reaction with formalin forming hydroxymethylated imidazoles[3] and dihydropyrazine derivatives,[3,4] the latter being Mannich reaction products derived from two imidazole molecules and two formaldehyde molecules. Considering that ring formation should be possible between the unsubstituted 5(4)-position and appropriate substituents at the 1(3)-nitrogen atom, we first tried the effect of cyanoethylation at the nitrogen atom. There are many reports on reactions resulting in substitution on the imidazole ring[5] but little is known about the addition reaction of acrylonitrile to the imidazole ring except about cyanoethylation of benzimidazole[6] and photochemical addition to phenylimidazole.[7] This may be because N-cyanoethylated products do not lead to physiological active natural products, such as histidine or nucleic acids. In a previous short communication[8] we reported the synthesis of 6,7,8,9-tetrahydro-5*H*-imidazo[1,5-*a*][1,4]diazepines, which have a new ring system. This paper gives a full account of this work.

Refluxing of 2,4(5)-dialkylimidazoles (Ia—f) with acrylonitrile in ethanol yielded 1-β-cyanoethylimidazoles (IIa—f) in high yield (Table I). The infrared (IR) spectra of IIa—f showed the characteristic absorption of a nitrile group at about 2250 cm^{-1}, but not that of an N-free imidazole ring at about 3200—2300 cm^{-1}. Structure (II) was assigned to the products for the following reasons. Masui, *et al.* found from proton magnetic resonance (PMR) spectral data, that alkylation of 2,4(5)-dialkylimidazole with methyl iodide occurred at either nitrogen atom, but that alkylation of *n*-butyl bromide, which is more bulky, only occurred at the less hindered nitrogen atom. On cyanoethylation, the less hindered nitrogen atom should be attacked by the bulky acrylonitrile group. IIa—f were converted to 1-γ-aminopropylimidazoles (IIIa—f) by reduction with $LiAlH_4$ or catalytic hydrogenation over Raney Ni in

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2) *a*) M. Masui, K. Suda, M. Yamauchi, and C. Yijima, *J. C. S. Perkin I*, **1972**, 1955; *b*) M. Masui, H. Miyata, K. Suda, and M. Yamauchi, *ibid.*, **1972**, 1960.
3) M. Masui, K. Suda, M. Inoue, K. Izukura, and M. Yamauchi, *Chem. Pharm. Bull.* (Tokyo), **22**, 2359 (1974).
4) M. Masui, K. Suda, M. Yamauchi, and N. Yoshida, *Chem. Pharm. Bull.* (Tokyo), **21**, 1387 (1973).
5) *a*) K. Hoffmann, "The Chemistry of Heterocyclic Compounds," Part I, ed. by A. Weissberger, Interscience, New York, 1953, p. 99; *b*) E.S. Schipper and A.R. Day, "Heterocyclic Compounds," Vol. 5, ed. by T.C. Elderfield, Wiley, New York, 1957, p. 194; *c*) M.R. Grimmett, "Advances in Heterocyclic Chemistry," Vol. 12, ed. by A.T. Katritzky and A.J. Boulton, Academic Press, New York, 1970, p. 103.
6) *a*) British Patent 457621 [*Chem. Abstr.*, **31**, 3068 (1937)]; *b*) L.S. Efros and B.A. Porai-Koshits, *Zhur. Obshchei Khim.*, **23**, 697 (1953) [*Chem. Abstr.*, **48**, 7603 (1954)].
7) Y. Ito and T. Matsuura, *Tetrahedron Letters*, **1974**, 513.
8) M. Yamauchi and M. Masui, *Chem. & Ind.*, **1976**, 31.

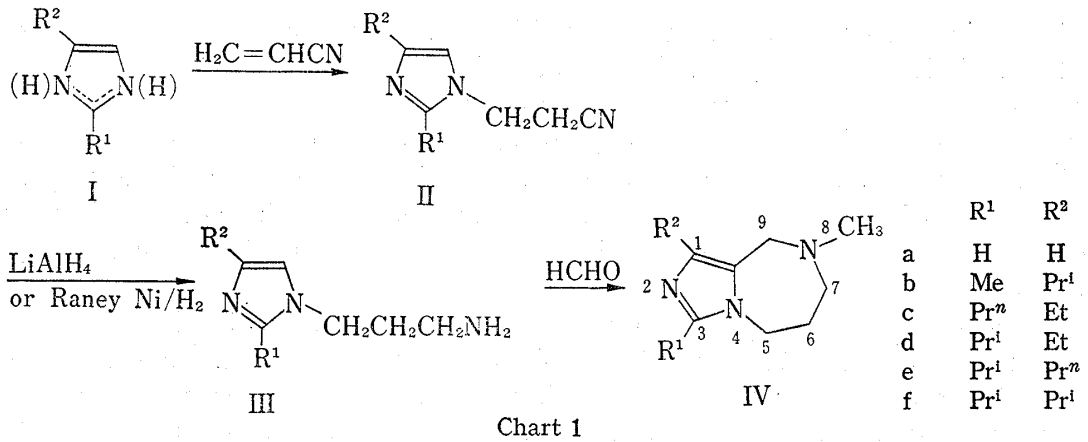

Chart 1

TABLE I. 1-β-Cyanoethyl-2,4-dialkylimidazoles

	bp(°C)	(mmHg)	Yield (%)[a]	Formula	mp(°C)	Picrate Analysis (%) Calcd. C	H	N	Found C	H	N
a	145	(0.5)	98.0	$C_{12}H_{10}O_7N_6$	116—117	41.15	2.88	24.00	41.14	2.94	23.87
b	140	(0.06)	87.0	$C_{16}H_{18}O_7N_6$	113—114	47.29	4.47	20.68	47.14	4.60	20.62
c	132	(0.08)	97.5	$C_{17}H_{20}O_7N_6$	114—115	48.57	4.80	19.99	48.30	4.77	19.71
d	130	(0.04)	77.1	$C_{17}H_{20}O_7N_6$	141	48.57	4.80	19.99	48.29	4.77	19.68
e	119	(0.03)	93.2	$C_{18}H_{22}O_7N_6$	104	49.77	5.10	19.35	50.19	5.03	19.09
f	134	(0.06)	88.4	$C_{18}H_{22}O_7N_6$	175	49.77	5.10	19.35	49.94	5.12	19.25

a) distilled

TABLE II. 1-γ-Aminopropyl-2,4-dialkylimidazoles

	bp(°C)	(mmHg)	Yield (%)[a]	Formula	mp(°C)	Dipicrate Analysis (%) Calcd. C	H	N	Found C	H	N
a	117	(2.0)	91.3	$C_{18}H_{17}O_{14}N_9$	225	37.06	2.94	21.61	37.23	3.11	21.92
b	128	(0.5)	79.8	$C_{22}H_{25}O_{14}N_9$	158	41.31	3.94	19.72	41.60	4.06	19.54
c	125	(0.02)	76.5	$C_{23}H_{27}O_{14}N_9$	163	42.27	4.16	18.96	42.37	4.27	19.04
d	122	(0.02)	87.2	$C_{23}H_{27}O_{14}N_9$	117	42.27	4.16	18.96	42.25	4.35	19.05
e	122	(0.02)	70.9	$C_{24}H_{29}O_{14}N_9$	210	43.18	4.38	18.88	43.05	4.53	18.87
f	108	(0.02)	70.9	$C_{24}H_{29}O_{14}N_9$	211	43.18	4.38	18.88	43.40	4.57	18.68

a) distilled

TABLE III. PMR Spectral Data on II and III (ppm)

	II 2-H	4-H	5-H	>N-CH₂— (triplet J)	—CH₂-CN (triplet J)	III 2-H	4-H	5-H	>N-CH₂— (triplet J)	—CH₂— (quintet J)	—CH₂-NH₂ (triplet J)
a	7.50	7.02	6.96	4.22(6.5)	2.78(6.5)	7.45	7.01	6.89	4.03(7.0)	1.87(7.0)	2.67(7.0)
b			6.56	4.10(7.0)	2.72(7.0)			6.47	3.86(7.0)	1.81(7.0)	2.72(7.0)
c			6.54	4.11(7.0)	2.71(7.0)			6.48	3.87(7.0)	1.84(7.0)	2.73(7.0)
d			6.53	4.10(7.0)	2.68(7.0)			6.45	3.88(7.0)	1.83(7.0)	2.73(7.0)
e			6.54	4.09(6.7)	2.67(6.7)			6.46	3.88(7.0)	1.84(7.0)	2.73(7.0)
f			6.53	4.10(6.7)	2.68(6.7)			6.46	3.89(7.0)	1.84(7.0)	2.74(7.0)

ethanol containing ammonia. The yields of III obtained by Raney Ni reduction are shown in Table II. PMR data on II and III are shown in Table III.

It is known[2b,5b] that the ring proton adjacent to the alkylated nitrogen atom in N-alkylimidazoles gives a signal at a higher field than the ring proton of the parent imidazoles, so the ring protons of IIa and IIIa with a signal at a higher field were assigned to position 5. The ring protons of IIa and IIIa show signals at a lower field than those of IIb—f and IIIb—f. Introduction of an alkyl group into the imidazole ring tends to shift the signal of the ring proton to a higher field.

In IIIb—f it seems that position 5 is the only reaction site in the ring, and that III is converted to a 5—7 ring system by an intramolecular Mannich reaction. When IIIf had been treated with formalin under the usual conditions of the Mannich reaction many products were separated by thin-layer chromatography, but these products could not be isolated in pure states. However, the hydroxymethylation procedure reported by Godefroi, *et al.*[9] was successfully applied to these aminopropylimidazoles as a Mannich reaction condition; When IIIb—f were treated with formalin in buffered medium (acetic acid–sodium acetate), 6,7,8,9-tetrahydro-1,3-dialkyl-8-methyl-5*H*-imidazo[1,5-*a*][1,4]diazepines (IVb—f) were isolated from the reaction mixture (Table IV).

Table IV. 6,7,8,9-Tetrahydro-5*H*-imidazo[1,5-*a*][1,4]diazepines

	bp(°C)	(mmHg)	Yield (%)[a]	Dipicrate							
				Formula	Decomp. p(°C)	Analysis (%) Calcd. C	H	N	Found C	H	N
a	110	(1.0)	45.2	$C_{20}H_{19}O_{14}N_9$	220	39.42	3.14	20.68	39.43	3.18	20.47
b	105	(0.04)	32.7	$C_{21}H_{27}O_{14}N_9$	216	43.31	4.09	18.94	43.48	4.14	18.99
c	108	(0.04)	37.9	$C_{25}H_{29}O_{14}N_9$	196	44.19	4.30	18.55	44.05	4.43	18.51
d	98	(0.07)	58.7	$C_{25}H_{29}O_{14}N_9$	225	44.19	4.30	18.55	44.05	4.38	18.56
e	105	(0.04)	42.6	$C_{26}H_{31}O_{14}N_9$	208	45.02	4.51	18.17	45.12	4.83	18.49
f	109	(0.4)	47.2	$C_{26}H_{31}O_{14}N_9$	220	45.02	4.51	18.17	45.05	4.70	18.32

a) separated by column chromatography and distilled

In IIIa positions 2, 4 and 5 should all be able to condense with the branch at position 1. In particular, position 2 surrounded by two nitrogen atoms seems to be an active reaction site. Thus we expected to obtain another imidazodiazepine ring system from IIIa through a Mannich reaction. In the PMR spectrum of IVa (Table V), two imidazole ring protons show signals at 6.83 and 7.32 ppm. Since the latter was assigned to the ring proton surrounded by the two nitrogen atoms, it is clear that no reaction occurred at position 2 of IIIa. In addition the similarity in the signal patterns of IVa and IVb—f suggests that these products have the same ring system. If condensation could occur at position 4 of IIIa, the bicyclo[5,2,1] ring system (V) produced should have a different signal pattern and the proton at position 10 would show a signal at a higher field than the observed value (6.83 ppm) owing to the electronic effect of alkyl groups introduced in the neighboring positions 1 and 7 (*cf.* in IIb—f and IIIb—f the ring proton at position 5 shows a signal at about 6.5 ppm). From these facts we concluded that the condensation occurred at position 5, and that the product was 6,7,8,9-tetrahydro-8-methyl-5*H*-imidazo[1,5-*a*][1,4]diazepine. Thus this procedure seems to be a general method for preparation of 6,7,8,9-tetrahydro-5*H*-imidazo[1,5-*a*][1,4]diazepine. PMR data on IV are shown in Table V.

The usual Mannich reaction product of III should be VI, but the product isolated was IV, in which N-methylation had occurred at position 8. To clarify the mechanism of N-methyla-

9) E.F. Godefroi, H.J.J. Loozen, and J. Luderer-platje, *Recl. Trav. Chim. Pays-Bas*, **91**, 1383 (1972).

Table V. PMR Spectral Data on IV (ppm)

	1-H	3-H	5-H_2	6-CH_2	7-CH_2	N-CH_3	9-CH_2
a	6.83	7.32	4.03	1.83	2.96	2.28	3.70
b			3.89	1.76	2.95	2.27	3.66
c			3.93	1.79	2.95	2.30	3.65
d			3.93	1.79	2.92	2.29	3.63
e			3.94	1.79	2.93	2.29	3.63
f			3.95	1.79	2.29	2.29	3.68

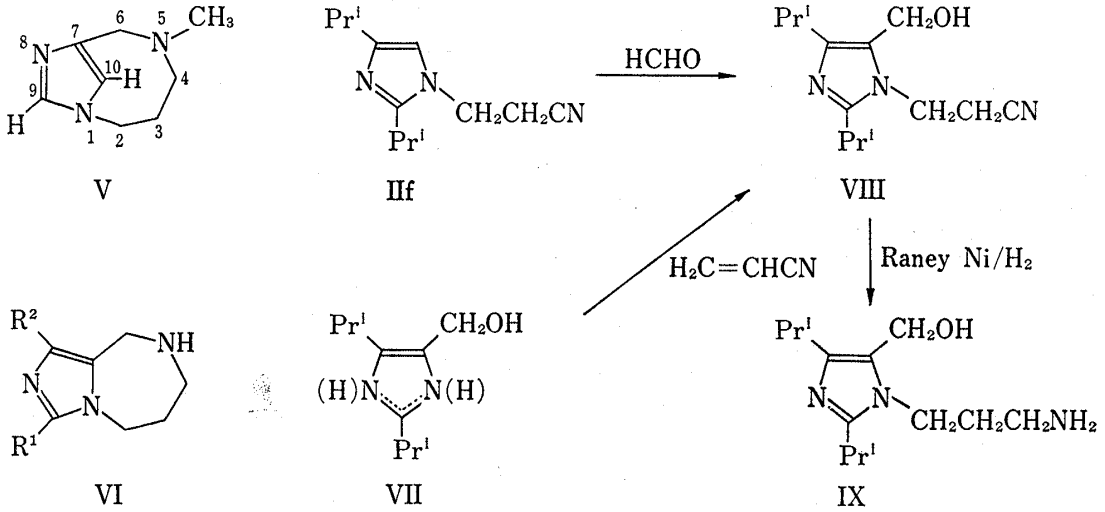

Chart 2

tion we attempted to synthesize VI. When IIf was treated with formalin in a sealed tube at 120° for 3 hours, the hydroxymethylated product (VIII) was isolated in poor yield. VIII was also obtained quantitatively by cyanoethylation of 2,4(5)-diisopropyl-5(4)-hydroxymethylimidazole (VII).[3] Catalytic hydrogenation of VIII over Raney Ni in ethanol containing NH_3 at 100 atm. and 100° gave an oily product in poor yield, from which crystalline salts such as the picrate, hydrochloride and oxalate were not obtained. We expected that hydrogenation of the nitrile group of VIII should result in dehydrative condensation between the amino group and the hydroxyl group and should yield VI. From PMR spectral data, the oily product was assigned structure IX; the signal at 4.55 ppm due to the methylene proton of the hydroxymethyl group appears as a singlet and the signals at 4.00 (triplet), 1.88 (quintet) and 2.71 ppm (triplet) are assigned to the methylene protons of the $>N-CH_2CH_2-CH_2NH_2$ group. Attempts to convert IX to VI by treatment with KOH,[10] HCl[11] or Raney Ni[12] were unsuccessful. IX was not converted to IV in acetate buffer, so it is not an intermediate in formation of IV. In formate solution, IIIb reacted with formalin yielding IVb in similar yield to that in acetate buffer, and IIIf was also converted to IVf with formalin by heating under a nitrogen atmosphere or standing at room temperature. This suggests that IV is mainly formed through the usual Mannich reaction process,[3,13] but that somewhat rapid N-methylation is involved.

10) Y. Sprinzak, *J. Am. Chem. Soc.*, **78**, 3207 (1956).
11) F.B. Slezak, H.Bluestone, T.A. Magee, and J.H. Wotiz, *J. Org. Chem.*, **27**, 2181 (1962).
12) S.M. McElvain and L.W. Bannister, *J. Am. Chem. Soc.*, **76**, 1126 (1954).
13) T.F. Cunnings and J.R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

Another possible pathway, that is, that monomethylation of III takes place before the Mannich reaction, seems improbable, since secondary amines react as readily in the Leuckart reaction as primary amines to give tertiary amines.[14]

Experimental[15]

1-β-Cyanoethylimidazoles (IIa—f)——A mixture of imidazoles (Ia—f), excess acrylonitrile and ethanol was refluxed for 3 hours. Excess acrylonitrile and the solvent were evaporated off and the residue was distilled under reduced pressure to give 1-β-cyanoethylimidazoles (IIa—f) in high yields (Table I).

1-γ-Aminopropylimidazoles (IIIa—f); $LiAlH_4$ Reduction——To a solution of excess $LiAlH_4$ in ether, a solution of II in ether was added drop-wise and the mixture was refluxed for 5 hours. Decomposition of excess hydride was effected by addition of ethyl acetate. Hydrolysis was then brought about by the addition of 10% NaOH solution. Continuous extraction of the aqueous layer with ether for 20 hours gave 1-γ-aminopropylimidazoles (IIIa—f).

Raney Ni Reduction——A solution of II in ethanol containing ammonia was placed in a hydrogenation bomb with excess Raney Ni (W-6). Hydrogenation was carried out at 100° for 3 hours under an initial pressure of 100 atm. Then the catalyst was removed by filtration and the solvent was evaporated off. Distillation of the residue gave IIIa—f in the yields shown in Table II.

6,7,8,9-Tetrahydro-5*H*-imidazo[1,5-*a*][1,4]diazepines (IVa—f)——A mixture of 1-γ-aminopropylimidazole (7 mmole), 1.0 g of sodium acetate $3H_2O$, 0.6 ml of acetic acid and 5 ml of formalin was refluxed for 5 hours. The reaction mixture was cooled and poured into 10 volumes of water. Then it was made alkaline with saturated potassium carbonate solution, and extracted with chloroform. The extract was dried and distilled, and the residue was subjected to chromatography. Diazepine derivatives (IVa—f) were eluted as the first fraction with chloroform–methanol (10: 1 v/v) (Table IV).

1-β-Cyanoethyl-2,4-diisopropyl-5-hydroxymethylimidazole (VIII)——*a*) Hydroxymethylation of 1-β-Cyanoethyl-2,4-diisopropylimidazole (IIf): A mixture of IIf (665 mg) and excess formalin was heated in a sealed tube at 120—130° for 6 hours. The reaction mixture was cooled and poured into 5 volumes of water and extracted with chloroform. The extract was dried and distilled and the resulting crystalline residue was recrystallized from chloroform–*n*-hexane to give 277 mg (36.3%) of VIII. Mass Spectrum *m/e*: 235.(M^+) mp 164—164.5°. *Anal.* Calcd. for $C_{13}H_{21}ON_3$: C, 66.35; H, 9.00; N, 17.86. Found: C, 66.17; H, 9.06; N, 17.80. PMR δ: 4.60 (2H, s, $-C\underline{H}_2OH$), 4.21 (2H, t, J=7.0 Hz, $>NC\underline{H}_2CH_2CN$), 2.88 (2H, t, J=7.0 Hz, $-NCH_2C\underline{H}_2CN$).

b) Cyanoethylation of 2,4(5)-Diisopropyl-5(4)-hydroxymethylimidazole (VII): A mixture of VII (102 mg), acrylonitrile (2 ml) and MeOH (5 ml) was refluxed for 6 hours. Evaporation of excess acrylonitrile and the solvent gave VIII in quantitative yield.

Raney Ni Reduction of 1-β-Cyanoethyl-2,4-diisopropyl-5-hydroxymethylimidazole (VIII)——A solution of VIII (120 mg) in ethanol containing ammonia was placed in a hydrogenation bomb with excess Raney Ni (W-6). The hydrogenation was carried out at 100° for 3 hours under an initial pressure of 100 atm. The catalyst was removed by filtration and the solvent was evaporated off. The residue was distilled under reduced pressure to give 50 mg of IX. $bp_{0.5}$ 160—165° (bath temp.). PMR δ: 4.55 (2H, s, $-C\underline{H}_2OH$), 4.00 (2H, t, J=7.0 Hz, $>NC\underline{H}_2CH_2CH_2NH_2$), 1.88 (2H, quintet, J=7.0 Hz, $>NCH_2C\underline{H}_2CH_2NH_2$), 2.71 (2H, t, J=7.0 Hz, $>NCH_2CH_2C\underline{H}_2NH_2$).

Reaction of IIIb with Formalin in Formic Acid–Sodium Formate——A mixture of IIIb (500 mg), sodium acetate (340 mg), formic acid (0.23 ml) and formalin (2.5 ml) was refluxed for 10 hours. The reaction mixture was mixed with 10 volumes of water, made alkaline with saturated potassium carbonate solution, and extracted with chloroform. The extract was dried and distilled, and chromatography of the residue gave 160 mg of IVb.

14) M.L. Moore, "Organic Reactions," Vol. 5, John Wiley & Sons, Inc., New York, 1949, p. 301.

15) IR absorption spectra were recorded with a Hitachi EPI-G3 spectrophotometer, mass spectra with a Hitachi Perkin RMU-6E mass spectrometer, and PMR spectra with a Hitachi R-22 spectrometer with tetramethylsilane as internal reference in $CDCl_3$. Extracts were dried over anhyd. Na_2SO_4. Column chromatographies were carried out on silica gel (Mallinckrodt) using a mixture of chloroform and methanol as eluent.