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Reaction of 2,4(5)-Dialkylimidazoles with Formaldehyde

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In the reaction of 2,4(5)-dialkylimidazoles, hydroxymethylated products (II) and dihydropyrazine derivatives (III) were obtained considerable yield in weakly acidic media, but poor yield in weakly basic media. These two reaction products (II) and (III) would be formed competitively.

There have been many reports on syntheses of the imidazole ring,[2] but few on its reactivity. Hydroxymethylation has been studied especially intensively since in this reaction an imidazole ring is introduced into histidine or histamine homologues. For example certain imidazoles having a methyl group[3] or benzyl group[4] in position 1 condense with formaldehyde to yield the corresponding 2-hydroxymethylimidazoles, while those with two substituents at positions 1 and 2 yield 5-hydroxymethyl- and 4,5-dihydroxymethylimidazoles.[5] On the other hand, hydroxymethylation of N-free imidazole has not been successful. Thinking that hydroxymethylation of N-free imidazoles should be possible using appropriate imidazole derivatives under appropriate reaction conditions we chose 2,4(5)-dialkylimidazoles[6] as starting materials. In a previous short communication[7] we reported the isolation of a novel Mannich reaction product (IIIh) on reaction of 2,4(5)-diisopropylimidazole with formaldehyde. in further studies on the reaction of 2,4(5)-dialkylimidazoles with formaldehyde, we obtained not only the dihydropyrazine derivatives (IIIa—h) but also the hydroxymethyl derivatives (IIa—h) under certain reaction conditions.

The hydroxymethylation procedure reported by Godefroi, *et al.*[5] was successfully applied to these imidazoles. When Ia—h were treated with formaldehyde in buffered medium (acetic acid–sodium acetate), 4(5)-hydroxymethylated products (IIa—h) and dihydropyrazine derivatives (IIIa—h) were isolated in the yields shown in Table I. The infrared (IR) spectra of IIa—h showed the characteristic absorption of an N-free imidazole ring at about 3200—2300 cm^{-1} (KBr). The nuclear magnetic resonance (NMR) spectrum of IIh (in CD_3OD), showed the signal of the methylene proton of the hydroxylmethyl group at 4.47 ppm. In the spectra of IIIa—h, besides signals of the side chain alkyl groups, the signal of the methylene proton of the dihydropyrazine ring were seen as a singlet at about 4.9 ppm (Table III).

The hydroxymethylated products (II) were also obtained in the following way. Treatment of I with benzyl chloride–potassium carbonate in methanol or with benzyl chloride–

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2) *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 R.C. Elderfield, Wiley, New York, 1957, p. 194; *c*) M.R. Grimmett, "Advance in Heterocyclic Chemistry," Vol. 12, ed. by A.R. Katritzky and A.J. Boulton, Academic Press, New York, 1970, p. 103.
3) R. Grindley and F.L. Pyman, *J. Chem. Soc.*, 3128 (1927).
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5) E.F. Godefroi, H.J.J. Loozen, and J. Luderer-platje, *Recl. Trav. Chim. Pays-Bas*, **91**, 1383 (1972).
6) *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, *J. C. S. Perkin I*, **1972**, 1960.
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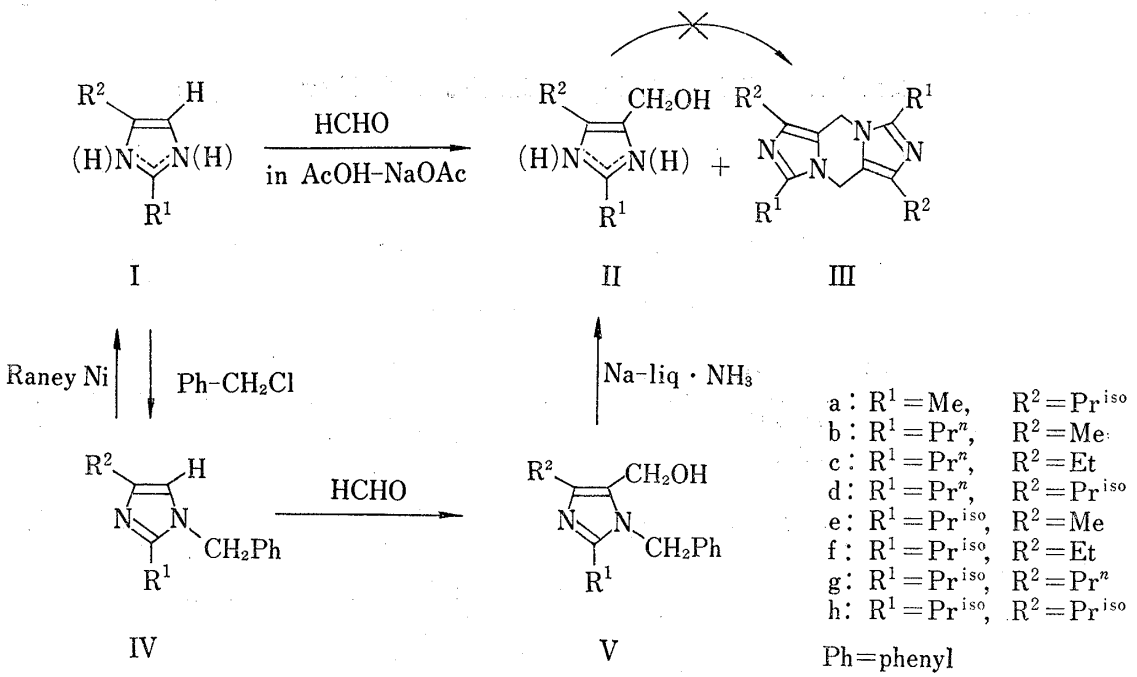


Chart 1

TABLE I. The Yields[a] of II and III on the Reaction of 2,4(5)-Dialkylimidazoles with Formaldehyde in Acetic Acid-Sodium Acetate

	R^1	R^2	II(%)	III(%)
a	Me	Pr^{iso}	23.2	26.0
c	Pr^n	Et	13.9	8.1
f	Pr^{iso}	Et	21.2	12.7
g	Pr^{iso}	Pr^n	10.6	17.3
h	Pr^{iso}	Pr^{iso}	26.5	23.2

a) The analyses were made by weighing each pure products, which were separated by column chlomatography.

TABLE II. 2,4(5)-Dialkyl-5(4)-hydroxymethylimidazoles

	R^1	R^2	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	Me	Pr^{iso}	168—170	$C_8H_{14}ON_2$	62.30	9.15	18.17	62.16	9.27	18.25
c	Pr^n	Et	158—159	$C_9H_{16}ON_2$	64.25	9.59	16.65	64.32	9.57	16.52
f	Pr^{iso}	Et	160	$C_9H_{16}ON_2$	64.25	9.59	16.65	63.91	9.60	16.52
g	Pr^{iso}	Pr^n	159—160	$C_{10}H_{18}ON_2$	65.89	9.96	15.37	65.68	9.84	15.57
h	Pr^{iso}	Pr^{iso}	160	$C_{10}H_{18}ON_2$	65.89	9.96	15.37	66.04	10.06	15.39

sodium amide in liquid NH_3[4] gave a single product, to which structure IV was assigned. Masui, *et al.*[6b] found from NMR spectral data, that alkylation of 2,4(5)-dialkylimidazole with methyl iodide occurred at either nitrogen atom, but that with the more bulky *n*-butyl bromide it occurred at the less hindered nitrogen atom. On benzylation, the less hindered nitrogen atom should be attacked by the bulky benzyl group. IV was readily reconverted to the star-

ting material by treatment with Raney Ni, and hence the N-benzyl group seemed to be a useful protecting group. On heating IV with formaldehyde in a sealed tube or in buffered medium, V was obtained. The NMR spectra of Va—h showed the signal of the methylene proton of

Table III. Dihydropyrazine Derivatives

	R^1	R^2	bp (mmHg)	δ ($CDCl_3$) (ppm) C–CH_2–N	Dipicrate Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	Me	Pr^{iso}	155—165 (0.03)	4.92	$C_{28}H_{30}O_{14}N_{10}$	46.03	4.14	19.17	46.32	4.31	19.21
c	Pr^n	Et	160—170 (0.03)	4.91	$C_{30}H_{34}O_{14}N_{10}$	47.49	4.52	18.46	47.49	4.53	18.19
f	Pr^{iso}	Et	160—170 (3)	4.94	$C_{30}H_{34}O_{14}N_{10}$	47.49	4.52	18.46	47.36	4.52	18.44
g	Pr^{iso}	Pr^n	120 (0.1)	4.90	$C_{32}H_{38}O_{14}N_{10}$	48.85	4.87	17.80	48.78	5.08	17.71
h	Pr^{iso}	Pr^{iso}	(77—78) *a)*	4.96	$C_{20}H_{32}N_4$	73.12	9.82	17.06	73.34	9.68	16.77 *b)*

a) mp *b)* free base

Table IV. 1-Benzyl-2,4-dialkylimidazoles

	R^1	R^2	bp (°C) (mmHg)	Yield (%)	Picrate Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	Me	Pr^{iso}	166—169 (0.38)	44	$C_{20}H_{21}O_7N_5$	54.17	4.77	15.80	54.22	4.75	15.66
b	Pr^n	Me	125 (0.15)	17	$C_{20}H_{21}O_7N_5$	54.17	4.77	15.80	54.36	4.84	15.66
d	Pr^n	Pr^{iso}	160 (0.6)	52	$C_{22}H_{25}O_7N_5$	56.04	5.35	14.86	56.05	5.49	14.87
e	Pr^{iso}	Me	111 (0.08)	41	$C_{20}H_{21}O_7N_5$	54.17	4.77	15.80	54.23	4.81	15.93
f	Pr^{iso}	Et	165—168 (0.35)	63	$C_{21}H_{23}O_7N_5$	55.14	5.07	15.31	55.08	5.11	15.29
g	Pr^{iso}	Pr^n	123—125 (0.15—0.30)	40	$C_{22}H_{25}O_7N_5$	56.04	5.35	14.86	55.85	5.35	14.70
h	Pr^{iso}	Pr^{iso}	124—126 (0.15) (47—49) *a)*	67	$C_{16}H_{22}N_2$	79.29	9.15	11.56	79.09	8.89	11.34 *b)*

a) mp *b)* free base

Table V. 1-Benzyl-2,4-dialkyl-5-hydroxymethylimidazoles

	R^1	R^2	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
a	Me	Pr^{iso}	183—186	25	$C_{15}H_{20}ON_2$	73.73	8.25	11.47	73.61	8.33	11.40
d	Pr^n	Pr^{iso}	105.5—106.5	33	$C_{17}H_{24}ON_2$	74.96	8.88	10.25	74.92	8.97	10.20
f	Pr^{iso}	Et	140—150 (0.09) *a)*	50	$C_{16}H_{23}ON_2Cl$	65.17	7.86	9.50	64.97	7.96	9.71 *b)*
h	Pr^{iso}	Pr^{iso}	131.5—132.5	47	$C_{17}H_{24}ON_2$	74.96	8.88	10.29	75.00	9.04	10.27

a) bp (mmHg) *b)* hydrochloride

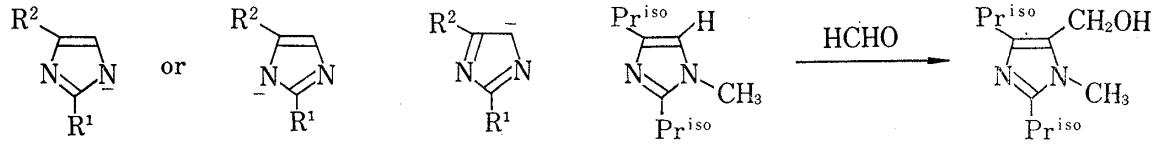
Table VI. NMR Spectral Data on IV and V (ppm)

	R^1	R^2	IV (in CCl_4) H	IV (in CCl_4) $-CH_2C_6H_5$	V (in $CDCl_3$) $-CH_2OH$	V (in $CDCl_3$) $-CH_2C_6H_5$
a	Me	Pr^{iso}	6.33(d)	4.86	4.48	5.17
b	Pr^n	Me	6.36(q)	4.92	4.40	5.19
d	Pr^n	Pr^{iso}	6.34(d)	4.93	4.46	5.19
e	Pr^{iso}	Me	6.33(q)	4.95	4.44	5.23
f	Pr^{iso}	Et	6.33(t)	4.92	4.43	5.22
g	Pr^{iso}	Pr^n	6.34(t)	4.97	4.44	5.26
			6.43(t)	4.96 (in $CDCl_3$)		
h	Pr^{iso}	Pr^{iso}	6.31(d)	4.92	4.44	5.19

the hydroxymethyl group at about 4.4 ppm, instead of that of the ring proton in the spectra of IVa—h, and the methylene proton signal of the benzyl group was shifted considerably down field, as the effect of the hydroxyl group compared to that in the spectra of IVa—h. Reduction of V with Raney Ni gave unexpectedly I instead of II. In this case not only N–C bond rupture but also C–C bond rupture occurred. In such a reaction, even if reduction takes place at the hydroxymethyl group, the hydroxymethyl group is probably converted to a methyl group by hydrogenolysis. It would be interesting to observe C–C bond fission instead of C–O bond fission as above. However, Birch reduction of V gave II in poor yield, together with IV and I.

In general hydroxymethylation of a heterocyclic aromatic system is believed to occur *via* electrophilic attack of protonated formaldehyde on the aromatic π-electron. Hydroxymethylation of 2,4(5)-disubstituted imidazoles is probably catalyzed by acid if the imidazole ring is not completely protonated under acidic conditions. In formate solution, 2,4(5)-diisopropylimidazole (Ih) reacted with formaldehyde yielding IIh and IIIh in a similar ratio to that in acetate buffer, but in hydrochloric acid solution the reaction did not take place. These results suggest that in weakly acidic buffered media, protonated formaldehyde attacks the neutral imidazole molecule which is in equilibrium with the protonated imidazole molecule.

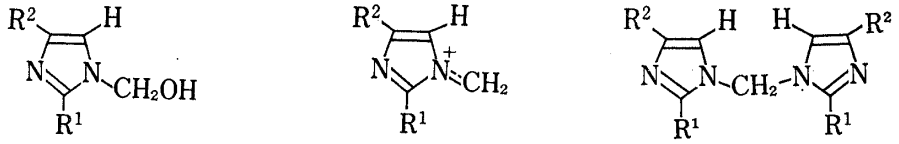
In borate buffer (pH 9.1), 2,4(5)-diisopropylimidazole (Ih) also reacted with formaldehyde yielding mainly IIh with a trace of IIIh. This suggests that in weakly basic medium, formaldehyde in the neutral form reacts with the neutral imidazole molecule or its conjugate base, VI or VII, yielding IIh and IIIh, and the predominant formation of IIh should be ascribed to the stronger nucleophilicity of the carbanion type VII.



VI VII VIII IX

Chart 2

There are two possible pathways for formation of II; i) by attack of formaldehyde on the carbon atom of the imidazole molecule and ii) a rearrangement pathway, that is, by attack of formaldehyde on the electron-rich basic nitrogen of the imidazole molecule to form aminomethylol (X), which should be an intermediate in formation of III, and then a shift of the N-hydroxymethyl group to the carbon atom at position 4(5). The former seems more likely since N-benzylimidazole (IV) and 1-methyl-2,4-diisopropylimidazole (VIII)[6b] gave the corresponding 5-hydroxymethylimidazole (IX) under similar reaction conditions. II was not



X XI XII

Chart 3

converted to III under similar reaction conditions so it is not an intermediate in formation of III. This, with the results mentioned above, suggests that the formations of II and III are competitive and that the dihydropyrazine derivative (III) is formed *via* the usual Mannich reaction mechanism. Cummings and Shelton[8] postulated that the Mannich reaction in basic media involves the condensation of a carbanion, derived from the active hydrogen compound, with an aminomethylol, R_2NCH_2OH, formed from the amine and formaldehyde. In acidic media, they suggested that the reaction involves the reaction of a carbonium ion, $R_2N\overset{+}{C}H_2 \leftrightarrow R_2\overset{+}{N}=CH_2$, derived from the aminomethylol or methylene bisamine formed in the reaction between the amine and formaldehyde, with the active hydrogen compound. In formation of the dihydropyrazine ring (III), we think that an intermediate, such as aminomethylol (X) or carbonium ion (XI) is formed from the imidazole and formaldehyde. Reaction between two X or XI or between X and XI gives III. Such an intermediate could react with nitrogen of the free imidazole yielding (XII), although no XII was detected.

Experimental[9]

Reaction of Imidazoles with Formalin; Method A (in a Sealed Tube)——A mixture of 2,4(5)-dialkylimidazole and excess formaldehyde was heated in a sealed tube at 120—130° for 3 hours. After cooling the reaction mixture was poured into 5 volumes of water and extracted with chloroform. The extract was dried and distilled and the resulting viscous oily material was subjected to chromatography. Dihydropyrazine derivatives were eluted as a first fraction.

Method B (in Acetic Acid-Sodium Acetate)——A mixture of 2,4(5)-dialkylimidazole (7 mmole), 1.0 g of sodium acetate·$3H_2O$, 0.6 ml of acetic acid and 5 ml of formaldehyde was refluxed for 20 hours. After cooling the reaction mixture was poured into 10 volumes of water, made alkaline with saturated potassium carbonate solution, and extracted with chloroform. The extract was dried and distilled, and the residue was subjected to chromatography. Dihydropyrazine derivatives were eluted as a first fraction and hydroxymethylated products as a later fraction. The yields of the two products are shown in Table I.

Reaction of 2,4(5)-Diisopropylimidazole with Formaldehyde in Formic Acid-Sodium Formate——A mixture of 2,4(5)-diisopropylimidazole (1.1 g), sodium formate (0.67 g), formic acid (0.45 ml) and formaldehyde (5 ml) was refluxed for 20 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 167 mg of IIIh and 424 mg of IIh.

1-Benzyl-2,4-dialkylimidazole——A mixture of 2,4(5)-dialkylimidazole (0.6 mmole), potassium carbonate (4.0 mmole), benzyl chloride (8.0 mmole) and methanol (30 ml) was refluxed for 15 hours. The solvent was evaporated off and the residue was mixed with water and extracted with chloroform. The extract was dried and distilled to give 1-benzyl-2,4-dialkylimidazole which was purified by silica gel chromatography and distillation.

1-Benzyl-2,4-dialkyl-5-hydroxymethylimidazoles——1-Benzyl-2,4-dialkylimidazoles were treated by Method A to give 1-benzyl-2,4-dialkyl-5-hydroxymethylimidazoles (Table V).

8) T.F. Cummings and J.R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

9) IR absorption spectra were recorded with a Hitachi EPI-G3 spectrophotometer, NMR spectra with a Hitachi Perkin-Elmer R-20A (60 Mc) and a Hitachi R-22 (90 Mc) spectrometer, and mass spectra with a Hitachi RMU-6E mass spectrometer. 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. The hydroxymethylation reagent used was 37% aqueous formaldehyde solution.

Reaction of 1-Benzyl-2-isopropyl-4-ethylimidazole Using Method B——1-Benzyl-2-isopropyl-4-ethylimidazole (1.15 g) was treated by Method B to obtain 1-benzyl-2-isopropyl-4-ethyl-5-hydroxymethylimidazole (1.17 g).

Reaction of 2,4(5)-Diisopropylimidazole with Formaldehyde in Borate Buffer——A mixture of 2,4(5)-diisopropylimidazole (315 mg), formaldehyde (2 ml) and borate buffer solution (ajusted to pH 9.1) (10 ml) was refluxed for 3.5 hours. The mixture was extracted with chloroform, and treated in the usual way yielding IIIh (5 mg) and IIh (34 mg).

Birch Reduction of 1-Benzyl-2,4-dialkyl-5-hydroxymethylimidazole——A solution of 1-benzyl-2,4-dialkyl-5-hydroxymethylimidazole in liquid NH_3 was treated with small pieces of sodium metal until a permanent blue color developed. Then ammonium chloride was added in small portions and the mixture was allowed to evaporate to dryness. The residue was mixed with water and extracted with chloroform. The extract was dried and evaporated to give 2,4(5)-dialkyl-5(4)-hydroxymethylimidazole and 2,4(5)-dialkylimidazole and 1-benzyl-2,4-dialkylimidazole.

Raney Ni Reduction of 1-Benzyl-2,4-diisopropyl-5-hydroxymethylimidazole——A mixture of 1-benzyl-2,4-diisopropyl-5-hydroxymethylimidazole (104 mg), excess Raney Ni, and ethanol was refluxed for 5 hours. The mixture was filtered and the filtrate was evaporated to give 51 mg of 2,4(5)-diisopropylimidazole.

1-Methyl-2,4-diisopropyl-5-hydroxymethylimidazole——1-Methyl-2,4-diisopropylimidazole (500 mg) was treated by Method A to give a crystalline material, which was recrystallized from *n*-hexane yielding 100 mg of 1-methyl-2,4-diisopropyl-5-hydroxymethylimidazole as colorless needles (mp 84—85°, M^+ *m/e* 196) (*Anal.* Calcd. for $C_{11}H_{20}ON_2$: C, 67.30; H, 10.27; N, 14.27. Found: C, 67.33; H, 10.41; N, 14.02.).