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# Studies on Benzimidazoles and Related Compounds. III.[1] The Intramolecular Mannich Reaction of 2-Alkylaminomethylbenzimidazoles

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The intramolecular Mannich reaction of 2-alkylaminomethylbenzimidazole (II) provided 4-alkyl-1,3,4,5-tetrahydro-1,3,6-oxadiazepino[3,4-*a*]benzimidazole (III) in a good yield. Moreover, the amine (II) can be regenerated by treatment of III with 15% hydrochloric acid and its mechanism is speculated.

The Mannich reaction has known to be a convenient method of introducing aminomethyl group by the condensation of amine and aldehyde with compound containing an active hydrogen atom.[3]

Benzimidazole possesses an active hydrogen atom as the -NH-group in imidazole ring and reacts with diethylamine, piperidine, and morpholine in the presence of formalin[4] or paraformaldehyde.[5] On the other hand, 2-ethylbenzimidazole does not condense with amine and formalin at room temperature.[4] When a 2-hydroxyphenyl or a 4-hydroxybenzyl group was present in $C_2$-position of benzimidazole ring, the -NH-group did not undergo aminomethylation. Instead, aminomethyl group entered the preferential *ortho*-position of hydroxy group.[6] In these cases, the condensation is supposed to be affected by steric hindrance due to a substituent of $C_2$-position. Here we wish to report on the intramolecular Mannich reactioch of 2-alkylaminomethylbenzimidazole derivatives (IIa—d), in order to examine whether the formation of methylene bridge in case of these compounds would be possible or not.

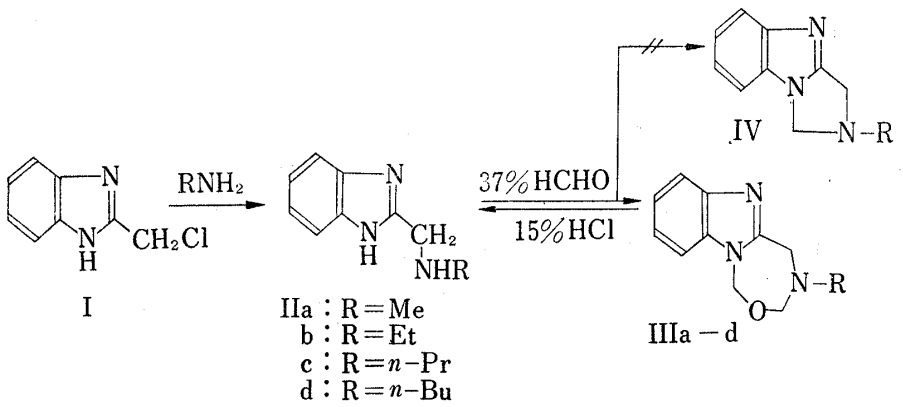


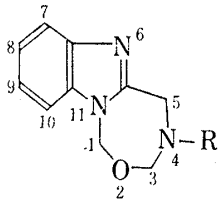

Chart 1

2-Methylaminomethylbenzimidazole (IIa)[7] in ethanol condensed with 37% formalin at room temperature (Chart 1). Infrared (IR) spectrum of the condensation product (IIIa),

1) Part II: S. Ishiwata and Y. Shiokawa, *Chem. Pharm. Bull.* (Tokyo), **17**, 2455 (1969).
2) Location: *No. 600, Kashiwagi-4-chome, Shinjuku-ku, Tokyo.*
3) F.F. Blicke, "Organic Reactions," Vol. I, ed., John Wiley and Sons, Inc., New York, N.Y., 1942, p. 303.
4) G.B. Bachman and L.V. Heisey, *J. Am. Chem. Soc.*, **68**, 2496 (1946).
5) T. Okuda, *Yakugaku Zasshi*, **80**, 205 (1960).
6) K. Hideg and H.O. Hankovszky, *Acta. Chem.* (Budapest), **53**(3), 271 (1967) [*C.A.*, **69**, 59156h (1968)].
7) A. Bloom and A.R. Day, *J. Org. Chem.*, **4**, 14 (1939).

isolated in 77.2% yield, showed the very intense absorption arising from $-CH_2OCH_2-$stretching vibration at 1165 $cm^{-1}$, and the absence of the characteristic absorption due to intermolecular hydrogen-bond (NH···N) at 3200—2400 $cm^{-1}$.[8] Further, its nuclear magnetic resonance (NMR) spectrum ($\tau$ in $CDCl_3$) indicated the presence of three methylene protons at 4.41, 5.21, and 5.69 as singlets, one methyl proton (N–Me) at 7.68 as singlet, three aromatic protons at 2.72 as multiplet, and one aromatic proton at 2.26 as multiplet (Table I).

Table I. Chemical Shifts ($\tau$) in $CDCl_3$



| | R | $C_7$–H (m) | Aromatic 3H (m) | $C_{(1)}H_2$ (s) | $C_{(3)}H_2$(s) | $C_{(5)}H_2$ (s) | R |
|---|---|---|---|---|---|---|---|
| IIIa | Me | 2.26 | 2.72 | 4.41 | 5.21 | 5.69 | 7.68 (s) |
| b | Et | 2.28 | 2.74 | 4.41 | 5.15 | 5.65 | 7.44 (q), 8.90(t) |
| c | *n*–Pr | 2.27 | 2.74 | 4.43 | 5.18 | 5.69 | 7.56(t), 8.49(six), 9.17(t) |
| d | *n*-Bu | 2.28 | 2.75 | 4.43 | 5.18 | 5.70 | 7.54(t), 8.65(m), 9.14(t) |

From these spectroscopic data, it was appeared that the Mannich reaction of IIa occurred at –NH– group of benzimidazole ring, but did not provide 2,3-dihydro-2-methyl-1*H*-imidazo-[1,5-*a*]benzimidazole (IV) which was expected from the reaction. The structure of the condensation product was assumed to be 1,3,4,5-tetrahydro-4-methyl-1,3,6-oxadiazepino[3,4-*a*]-benzimidazole (IIIa), which was cyclized by $-CH_2OCH_2-$ bridge between –NH– group of benzimidazole ring and amino group, from the spectral evidences and elemental analytical values.

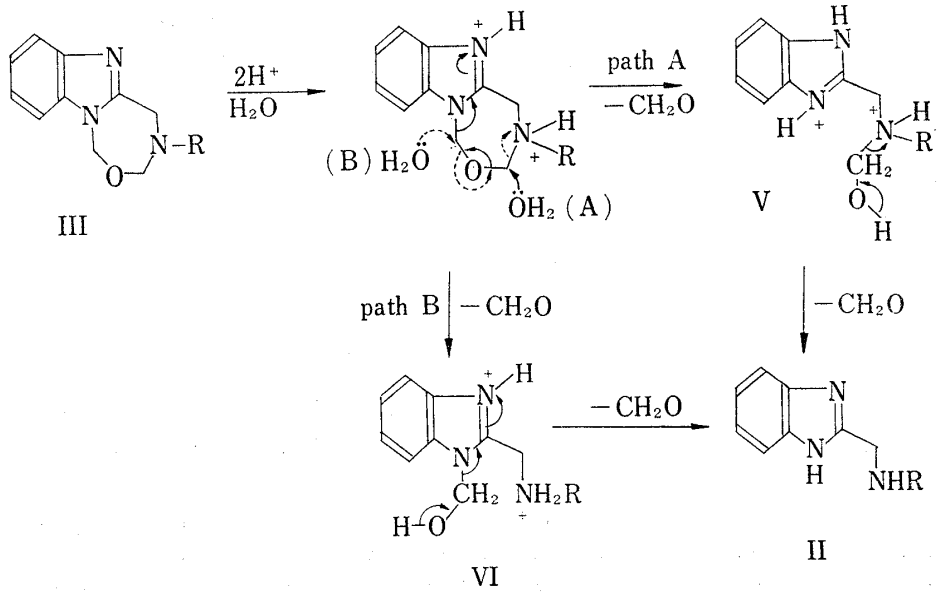



Chart 2

8) K.J. Morgan, *J. Chem. Soc.*, **1961**, 2343.

Similarly, the Mannich reaction of the other amines (IIb—d)[7,9] with 37% formalin provided the condensation products (IIIb—d) in 70.9—76.6% yield.

Analogous to the Pictet-Spengler reaction of 3-(3',4'-methylenedioxyphenyl)-octahydroindole,[10] it may be considered that the intramolecular Mannich reaction of the amine (II) provided the abnormal product (III) instead of IV because of ring strain.

The condensation product (IIId) was found to be very unstable toward dilute mineral acid as was expected; when IIId was dissolved in 15% aqueous hydrochloric acid at room temperature, the original amine (IId) was regenerated in 53% yield. Similar results were obtained by treatment of the other condensation products (IIIa—c) with hydrochloric acid. Moreover, small amounts of unknown compounds and unreacted III were obtained in every reaction. The so obtained amine was identified with the original amine (II) by the behavior on a thin-layer chromatogrum (TLC) and by IR and NMR spectral comparison.

The following mechanism was suggested to account for the regeneration of the original amine (II) on the basis of the fact that formaldehyde eliminated in a treatment of IIId with hydrochloric acid was trap as 2,4-dinitrophenylhydrazone (Chart 2). It may be considered that the intermediate (V) produced by nucleophilic attack of water at $C_3$-position of protonated III easily converts to the amine (II) (path A). Also, in path B, VI is expected to be unstable under this condition on the analogy of the following fact: 1-Hydroxymethylbenzimidazole[11] regarded as a model compound of VI was found to be unstable toward hydrochloric acid. Similar to V, therefore, the intermediate (VI) is supposed to change into II.

## Experimental[12]

**1,3,4,5-Tetrahydro-4-methyl-1,3,6-oxadiazepino[3,4-*a*]benzimidazole (IIIa)**——To a solution of the free amine (IIa), which was obtained by treatment of 2-methylaminomethylbenzimidazole dihydrochloride[7] (IIa 2HCl) (0.5 g) with conc. $NH_4OH$, in EtOH (15 ml) 37% formalin (1 ml) was dropwise added under cooling. After addition was completed, the solution was further stirred for 3 hr at room temperature and evaporated *in vacuo*. The residue was extracted with $CHCl_3$, the extract was washed with $H_2O$, dried over anhyd. $K_2CO_3$, and evaporated *in vacuo*. The product was recrystallized from benzene to give 0.335 g (77.2%) of colorless crystal, mp 227.5—228.5°. *Anal.* Calcd. for $C_{11}H_{13}ON_3$: C, 65.00; H, 6.45; N, 20.68. Found: C, 65.12; H, 6.41; N, 20.64. IR $cm^{-1}$ (KBr): $\nu_{-CH_2OCH_2-}$ 1165. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 245 (6700), 250 (shoulder) (6400), 270 (shoulder) (5400), 275 (7600), 282 (8200). NMR: (see Table I).

**4-Ethyl-1,3,4,5-tetrahydro-1,3,6-oxadiazepino[3,4-*a*]benzimidazole (IIIb)**——Prepared from IIb 2HCl[7] (0.5 g) as described for IIIa. Recrystallization from benzene gave 0.31 g (70.9%) of colorless crystal, mp 202—203°. *Anal.* Calcd. for $C_{12}H_{15}ON_3$: C, 66.34; H, 6.96; N, 19.34. Found: C, 66.59; H, 7.38; N, 19.72. IR $cm^{-1}$ (KBr): $\nu_{-CH_2OCH_2-}$ 1165. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 245 (6700), 250 (shoulder) (6400), 270 (shoulder) (5200), 275 (7600), 282 (8300). NMR: (see Table I).

**1,3,4,5-Tetrahydro-4-propyl-1,3,6-oxadiazepino[3,4-*a*]benzimidazole (IIIc)**——Prepared from IIc 2HCl[9] (0.5 g) as described for IIIa. Recrystallization from benzene gave 0.33 g (74.9%) of colorless crystal, mp 151.5—152.5°. *Anal.* Calcd. for $C_{13}H_{17}ON_3$: C, 67.50; H, 7.41; N, 18.17. Found: C, 67.31; H, 7.56; N, 18.47. IR $cm^{-1}$ (KBr): $\nu_{-CH_2OCH_2-}$ 1160. UV $\lambda_{max}^{EtOH}$ ($\varepsilon$): 246 (6700), 250 (shoulder) (6400), 270 (shoulder) (5300), 276 (7600), 283 (8300). NMR: (see Table I).

**4-Butyl-1,3,4,5-tetrahydro-1,3,6-oxadiazepino[3,4-*a*]benzimidazole (IIId)**——Prepared from IId 2HCl[7] (0.5 g) as described for IIIa. Recrystallization from benzene-*n*-hexane gave 0.34 g (76.6%) of colorless crystal, mp 141.5—142.5°. *Anal.* Calcd. for $C_{14}H_{19}ON_3$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.72; H, 7.79; N, 17.27. IR $cm^{-1}$ (KBr): $\nu_{-CH_2OCH_2-}$ 1162. UV $\lambda_{max}^{EtOH}$ m$\mu$ ($\varepsilon$): 245 (6400), 250 (shoulder) (6000), 270 (shoulder) (5100), 275 (7300), 282 (7900). NMR: (see Table I).

**Treatment of the Mannich Product (III) with 15% HCl**——The Mannich product (III) (0.1 g) was dissolved in 15% HCl (3 ml) at room temperature, the solution was made alkaline with conc. $NH_4OH$ under

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10) S. Tani and H. Irie, The 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968.
11) G. Weitzel, F. Schneider, A.M. Fretzdorff, K. Seynsche, and H. Finger, *Z. Physiol. Chem.*, **334**, 1 (1963).
12) Melting points were measured on a Yanagimoto Micro Melting Point Apparatus and uncorrected. NMR spectra were taken on a JNM-4H-100 spectrometer in $CDCl_3$ with tetramethylsilane as internal standard. IR and UV spectra were measured on a JASCO DS-301 IR spectrophotometer and on a Beckmann DB-G UV spectrophotometer.

cooling, and extracted with $CHCl_3$. The extract was washed with $H_2O$, dried over anhyd. $K_2CO_3$, and evaporated *in vacuo*. The residue, which showed three spots on a TLC (silica gel; $CHCl_3$–MeOH, 10:1), was dissolved in $CHCl_3$ and the solution was chromatographed on a silica gel (3 g) column. The main product was identified with the original amine (II) by the behavior on a TLC and by IR and NMR spectral comparison. Moreover, small amounts of unknown compounds and unreacted III were obtained.

IIa (0.015 g or 19% yield)
IIb (0.041 g or 51% yield)
IIc (0.048 g or 59% yield)
IId (0.046 g or 53% yield)

**Trapping of Formaldehyde**——To the solution of the Mannich product (IIId) (0.1 g) in 15% HCl (2 ml), a solution of 2,4-dinitrophenylhydrazine (0.162 g) in EtOH was added and the mixture was heated on a water bath in a few minutes. After cooling, the precipitate was filtered, washed with $H_2O$, and recrystallized from EtOH to give 0.12 g (70%) of reddish yellow crystals, mp 167°.

This compound was identified with authentic sample by mixed melting point determination and by IR spectral comparison.

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