UDC 547.834.2[547.785.5].07

94. Torizo Takahashi, Ken Kanematsu, Ryota Oh-ishi, and Tamio Mizutani: Synthesis of Nitrogen-containing Cyclic Compounds. CXXIV.[1] Synthesis of Imidazopyridine Derivatives. (3).[2]

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The preceding paper from this laboratory described the syntheses of 3-substituted 6-chloro-3*H*-imidazo[*b*]pyridines. This paper is concerned with the synthesis of 1-substituted 6-chloro-1*H*-imidazo[*b*]pyridine, the Mannich reaction of 6-bromo-1*H*-imidazo[*b*]-pyridine, and the behavior of its product in the succeeding reaction.

Clark-Levis and Thompson[3] obtained 1-methyl-1*H*-imidazo[*b*]pyridin-2-ol by pyrolysis of ethyl N-methyl-2-amino-3-pyridinecarbamate which was prepared by methylation of ethyl 2-amino-3-pyridinecarbamate followed by reduction. Methylation of ethyl 2-bromo-5-chloro-3-pyridinecarbamate did not give the anticipated ethyl N-methyl-2-bromo-5-chloro-3-pyridinecarbamate and, therefore, 1-methyl-6-chloro-1*H*-imidazo[*b*]-pyridine was prepared according to the scheme shown in Chart 1.

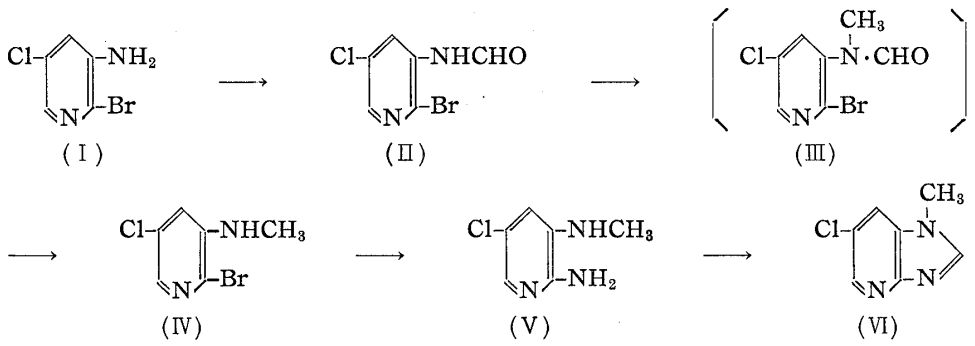

Chart 1.

Condensation of 2-bromo-3-amino-5-chloropyridine (I), prepared according to the method of Berrie, *et al.*[4] with formic acid in the presence of a small amount of acetic anhydride gave N-(2-bromo-5-chloro-3-pyridyl)formamide (II). A brown oily substance which was obtained by the methylation of (II) with dimethyl sulfate, decomposed on vaccum destillation and was used for the next hydrolysis without any purification. Hydrolysis of this oily substance (III) with conc. hydrochloric acid or caustic alkali did not give the expected results, but treatment with conc. ammonia water in a fused vessel at 100° gave 2-bromo-3-(methylamino)-5-chloropyridine (IV) in 30% yield.[*2]

2-Amino-3-(methylamino)-5-chloropyridine (V) was prepared by the reaction of (IV) with conc. ammonia water in the presence of a small amount of copper sulfate in a fused vessel at 130°. The diamine (V) was converted to 1-methyl-6-chloro-1*H*-imidazo-[*b*]pyridine (VI). On alkylation of 6-chloro-1*H*-imidazo[*b*]pyridine with methyl iodide as a methylation reagent, 3-methyl-6-chloro-1*H*-imidazo[*b*]pyridine was obtained besides a small amount of crystalline product of m.p. 203~205°, yield of which was 43%.

6-Bromo-1*H*-imidazo[*b*]pyridine (IX) was synthesized as shown in Chart 2.

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*2 This yield was calculated on (II).
1) Part CXXIII. T. Takahashi, M. Hayami: Yakugaku Zasshi **80**, 651(1960).
2) Part (2): This Bulletin, **7**, 602(1959).
3) J. W. Clark-Levis, M. J. Thompson: J. Chem. Soc., **1957**, 442.
4) A. H. Berrie, *et al.*: *Ibid.*, **1952**, 2042.

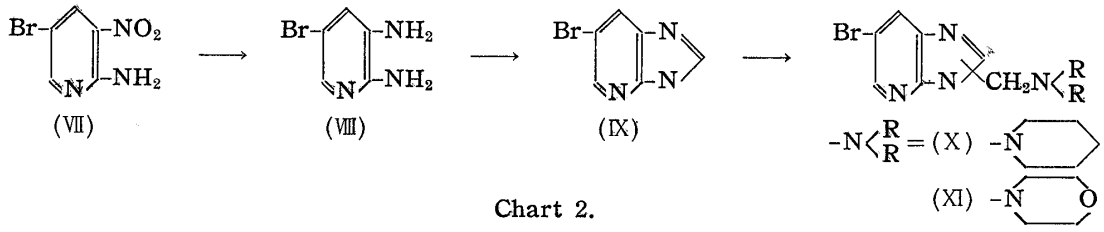

Chart 2.

These intermediate compounds, from 2-amino-3-nitro-5-bromopyridine (VII) to (IX), have been reported in the literature,[5] but the yield of the reduction of 2-amino-3-nitro-5-bromopyridine (VII) by Petrow's method[5] was not satisfactory. Therefore, (VII) was treated with hydrazine hydrate in ethanol solution, in the presence of palladium-carbon as a catalyst, and 2,3-diamino-5-bromopyridine (VIII) was obtained in 78% yield.

Condensation of (IX) with dialkylamines and paraformaldehyde by refluxing in isoamyl alcohol gave the corresponding dialkylaminomethyl compounds (X and XI) in a good yield.

For the structural proof of the Mannich base obtained as above the infrared spectra of (IX) and (X) were measured (Fig. 1).

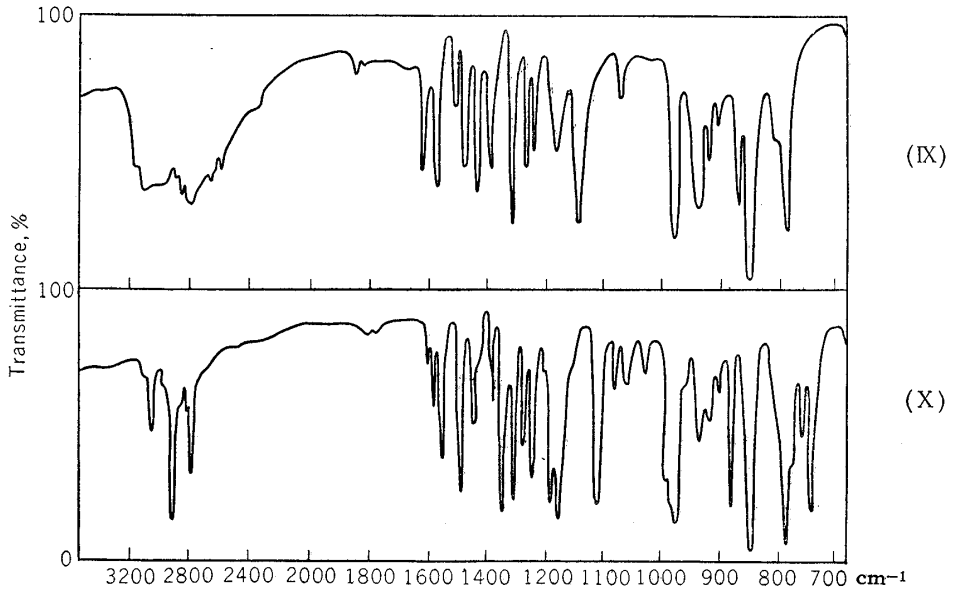

Fig. 1. Infrared Absorption Spectra of (IX) and (X) (in hexachlorobutadiene paste)

According to the report of Otting,[6] imidazole shows a sharp absorption at 3450 cm^{-1} in the vapor state and in dilute solution in chloroform, while in the solid state this absorption disappears and a new broad band appears with a peak at about 2800 cm^{-1} and a gradually weakening edge extending to the low frequency side to below 2300 cm^{-1}. Otting interpreted this new band as the $\overset{+}{N}$–H stretching absorption owing to the presence of an imidazole ring in a solid state in such ionic structures as shown in Chart 3.

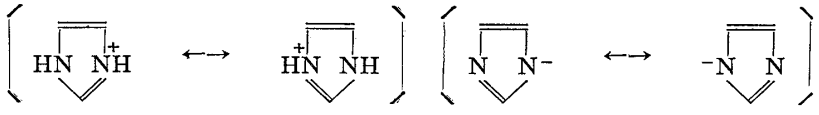

Chart 3.

5) V. Petrow, J. Saper: J. Chem. Soc., **1948**, 1389; H. Graboyes, A. R. Day: J. Am. Chem. Soc., **79**, 6421(1957).
6) W. Otting: Ber., **89**, 2887(1956).

It has been reported that the broad band near 2800 cm^{-1} of imidazole ring occurs in benzimidazole[7] and purine.[8] This characteristic absorption band arising from $\overset{+}{N}$–H bond is also observed in (IX) in the region of 3100~2300 cm^{-1} but (X) does not show such a broad absorption band and exhibits only two sharp absorption bands at 3060 and 2920 cm^{-1}, which can be assigned to the C–H groups. These fact are thought to indicate that on formation of (X), a piperidinomethyl was introduced into either one of the two nitrogen atoms in the imidazole ring of (IX) and that, as a result of it, the imidazole ring of (X) was inhibited to take such ionic structures as N–free imidazole ring. Therefore, (X) must be the N–substituted Mannich base, but it was not determined whether this substitution occurred in 1– or 3–position of (IX).

In order to investigate alkylation reaction of the above Mannich base, (X) was heated with aqueous solution of potassium cyanide and an unexpected elimination of piperidinomethyl group occurred to form (IX). (X) was refluxed with ethyl malonate in ethanol in the presence of sodium ethoxide and also deaminomethylated to (IX). According to the fact that the alkylating ability of the Mannich base is generally increased by converting it to its quaternary salt, (X) was quaternized with methyl iodide and the product (XII) was subjected to the reactions with potassium cyanide and ethyl malonate under the same conditions as in the case of (X) itself, from which the unexpected (IX) was also obtained. These results may be due to a mere decomposition of the Mannich base to its starting material but, on the other hand, they seem to indicate that migration of piperidinomethyl from (X) may occur under proper conditions.

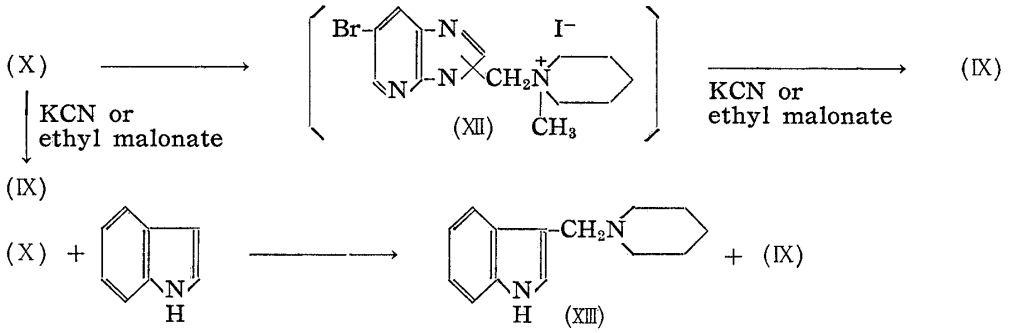

Chart 4.

When (X) and indole, whose Mannich base is extremely stable, was refluxed in toluene, the expected transaminomethylation occurred to give 3–(piperidinomethyl)indole (XIII) and (IX). The admixture of (XIII) with the sample of 3–(piperidinomethyl)indole obtained by a method of Kühn and Stein[9] showed no depression of the melting point.

Experimental

Ethyl 2-Bromo-5-chloro-3-pyridinecarbamate—To a mixture of 5 g. of (I) and 20 cc. of pyridine, 7 g. of chloroethyl carbonate was added dropwise at below 10° and stirred for 3 hr. at the same temp. Water was added to this reaction mixture and the separated product was recrystallized from petr. ether to colorless needles, m.p. 87°. Yield, 4.0 g. *Anal.* Calcd. for $C_8H_8O_2N_2BrCl$: C, 34.34; H, 2.86. Found: C, 34.55; H, 3.08.

N-(2-Bromo-5-chloro-3-pyridyl)formamide (II)—To a solution of 40 cc. of HCOOH (85%) and 10 cc. of Ac_2O, 3.5 g. of (I) was added and the solution was heated under reflux for 5 hr. Evaporation of the solution under reduced pressure and recrystallization of the residue from Et_2O and petr. ether gave colorless needles, m.p. 106~107°. Yield, 2.3 g. *Anal.* Calcd. for $C_6H_4ON_2BrCl$: C, 30.57; H,

7) B. A. Poraĭ-Koshits, *et al.*: Obshcheĭ Khim., **23**, 835(1953) [C. A., **48**, 4524(1954)].
8) C. H. Willits, *et al.*: J. Am. Chem. Soc., **77**, 2569(1955).
9) H. Kühn, O. Stein: Ber., **70**, 569(1937).

1.69; N, 11.89. Found : C, 30.72; H, 1.78; N, 12.08.

2-Bromo-3-(methylamino)-5-chloropyridine (IV)—(II) (5 g.) was boiled with Me_2CO (40 cc.), anhyd. K_2CO_3 (4 g.) was added to this reaction mixture during 10 min., and boiled for further 5 hr. Evaporation of the filtrate gave a brown oily substance. This oily substance, EtOH (20 cc.), and conc. ammonia (60 cc.) were heated in a fused vessel for 3 hr. at 100°. After cool, the solution was evaporated to dryness and extracted with Et_2O. After removal of the solvent, the residue was chromatographed on alumina. The petr. ether eluate, after evaporation of the solvent, gave (IV) which recrystallized from Et_2O and petr. ether to colorless needles, m.p. 43~44°. Yield, 1.4 g. *Anal.* Calcd. for $C_6H_6N_2BrCl$: C, 32.50; H, 2.70; N, 12.64. Found : C, 32.84; H, 2.91; N, 12.81.

2-Amino-3-(methylamino)-5-chloropyridine (V)—A mixture of (IV) (1.0 g.), conc. NH_4OH (30 cc.), water (5 cc.), and $CuSO_4$ (0.1 g.) was heated in a fused vessel for 20 hr. at 130°. After cool, the filtrate was extracted with Et_2O. Evaporation of the solvent and recrystallization from Et_2O and petr. ether gave (V) as colorless needles, m.p. 122~124°. Yield, 0.4 g. *Anal.* Calcd. for $C_6H_8N_3Cl$: C, 45.07; H, 5.07. Found : C, 45.22; H, 5.30.

1-Methyl-6-chloro-1*H*-imidazo[*b*]pyridine (VI)—A solution of 0.4 g. of (V) dissolved in 30 cc. of HCOOH (80%) was heated under reflux for 10 hr. Evaporation of the excess of HCOOH and recrystallization from benzene and Et_2O gave colorless prisms, m.p. 141°. Yield, 0.2 g. *Anal.* Calcd. for $C_7H_6N_3Cl$: C, 50.14; H, 3.58; N, 25.07. Found : C, 50.09; H, 3.69, N, 24.92.

Alkylation of 6-Chloro-1*H*-imidazo[*b*]pyridine—A mixture of 6-chloroimidazo[*b*]pyridine (1.5 g.), EtOH (30 cc.), and MeI (2.0 g.) was heated in a fused vessel for 10 hr. at 130°. After evaporation of the solvent, the reaction mixture was made alkaline with $NaHCO_3$ and filtered. The product was dissolved in Me_2CO and chromatographed on alumina. From petr. ether eluate, a crystalline product (0.15 g.) of m.p. 203~205° was obtained (recrystallized from Me_2CO). *Anal.* Found : C, 41.42; H, 3.34; N, 17.98.

UV-spectrum of this product resembled that of 1*H*-imidazo[*b*]pyridine but its structure was left undetermined.

EtOH eluate was evaporated and the residue was purified by dissolving it in ether and decolorizing with Norit. A brown oily product (0.7 g.) was confirmed as 3-methyl-6-chloro-1*H*-imidazo[*b*]-pyridine by mixed fusion of their picrates.

2,3-Diamino-5-bromopyridine (VIII)—A mixture of 3.0 g. of (VII), 7.2 cc. of hydrazine hydrate (80%), 0.3 g. of palladium-carbon, and 100 cc. of EtOH was heated under reflux for 1.5 hr. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue gave (VIII) after recrystallization from benzene as colorless needles, m.p. 158~160°. Yield, 2.0 g. No melting point depression occurred on admixture with an authentic sample of (VIII).

Condensation of (IX) with Piperidine and Paraformaldehyde—A mixture of 1.2 g. of (IX), 0.6 g. of piperidine, 0.3 g. of paraformaldehyde, and 20 cc. of iso-AmOH was refluxed for 3 hr. Evaporation of iso-AmOH *in vacuo* and recrystallization from Et_2O gave colorless needles, m.p. 119~120°. Yield, 1.0 g. *Anal.* Calcd. for $C_{12}H_{15}N_4Br$ (X) : C, 48.98; H, 4.80. Found : C, 48.84; H, 5.019.

Condensation of (IX) with Morpholine and Paraformaldehyde—A similar treatment of 1.2 g. of (IX), 0.6 g. of morpholine, 0.3 g. of paraformaldehyde, and 20 cc. of iso-AmOH gave colorless needles, m.p. 111~113°. Yield, 1.2 g. *Anal.* Calcd. for $C_{11}H_{13}ON_4Br$ (XI) : C, 44.46; H, 4.408. Found : C, 44.35; H, 4.628.

Reaction of (X) and KCN—A solution of 1.0 g. of (X) and 0.4 g. of KCN dissolved in 15 cc. of water was heated for 3 hr. on a water bath. The reaction mixture was evaporated to a small volume and set aside, and colorless crystals (IX) separated, m.p. 226~228° (from EtOH), undepressed on admixture with an authentic sample. Yield, 0.5 g. *Anal.* Calcd. for $C_6H_4N_3Br$ (IX) : C, 36.04; H, 2.035. Found : C, 36.25; H, 2.286.

Reaction of (X) and Ethyl Malonate—Ethyl malonate (1.0 g.) was added with stirring to a solution of 0.2 g. of Na in 30 cc. of dehyd. EtOH. After 30 min.'s stirring at room temperature, 2.0 g. of (X) was added to the mixture, the mixture was heated on a water bath for 4 hr., and evaporated to dryness. A small amount of water was added to the residue and the undissolved mass gave (IX), m.p. 226~228° (from EtOH), undepressed on admixture with an authentic sample. Yield, 1.1 g.

Reaction of (XII) and KCN—A solution of 2.0 g. of (X) and 0.8 g. of MeI dissolved in a small amount of EtOH was allowed to stand at room temperature for 12 hr. and excess EtOH was removed. As the product was slightly hygroscopic, it was used directly for the next reaction.

The reaction of (XII) prepared as above from 1.0 g. of (X) and 0.4 g. of KCN in the same manner as in the case of the reaction of (X) and KCN gave the same compound (IX). Yield, 0.5 g.

Reaction of (XII) and Ethyl Malonate—The reaction of (XII) prepared from 2.0 g. of (X), 0.2 g. of Na, and 1.0 g. of ethyl malonate in the same manner as in the reaction of (X) and ethyl malonate gave the same compound (IX). Yield, 1.0 g.

Reaction between (X) and Indole—A mixture of 2.0 g. of (X), 1.0 g. of indole, and 30 cc. of toluene was refluxed for 3 hr. After cool, colorless crystals separated from the reaction mixture, m.p. 225~

228° (from EtOH), undepressed on admixture with an authentic sample of (IX). Yield, 1.0 g. Evaporation of the mother liquor and recrystallization of the residue from EtOH gave colorless plates, m.p. 156~158°, undepressed on admixture with an authentic sample of (XIII). Yield, 0.9 g.

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Summary

1-Substituted 6-chloro-1*H*-imidazo[*b*]pyridine was prepared. The Mannich reaction of 6-bromoimidazo[*b*]pyridine and the behavior of its product in the alkylation reaction were described.

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95. Morizo Ishidate, Yoshio Sakurai, and Yutaka Kuwada : Studies on Carcinostatic Substances. XXIX.*1 1,1-Bis(2-chloroethyl)-hydrazine and its Derivatives as Tumor-inhibiting Agent.

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At present, in the field of study on preparing the anti-tumor derivatives of 2-chloroethylamine, it seems to be a new tendency to seek out derivatives with latent activity in order to improve their efficacy, i.e. to elevate their selectivity of action on the tumor tissues. In most works, however, they were confined to derivatives which might release the secondary amine, viz. bis(2-chloroethyl)amine, *in vivo* as an active component.

Studies have long been made to prepare compounds with latent activity, viz. masked derivatives, which could be activated by reduction *in vivo*, yielding the corresponding tertiary bis(2-chloroethyl)amine. Among them, N-methyl-bis(2-chloroethyl)amine N-oxide and N,N-bis(2-chloroethyl)isoxazolidinium halide[1] were proved so far to be the most promising, at least in animal experiments.

In this paper, an experiment to prepare the substituted derivatives of 1,1-bis(2-chloroethyl)hydrazine is described. A brief report[2] was already published in 1959 by the authors on the preparation of 1,1-bis(2-chloroethyl)hydrazine itself, because it was found at that time that Preussman[3] had independently published his work on the same compound.

This compound was found to have a strong biological activity, but it was particularly noticed that its chemical and biological activities diminished or were totally lost by substitution of its primary amino group with any other substituent. From this observation, it could be anticipated that an effective masked compound might be found among its

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3) R. Preussmann, *et al.* : Angew. Chem., **70**, 743(1958).