[Chem. Pharm. Bull. 12 (8) 866 ~ 872]

UDC 547.834.2.07

122. Yoshihisa Mizuno, Tokuo Itoh, and Kazuko Saito : Studies on Condensed Systems of Aromatic Nitrogenous Series. XXIV. Synthesis of 4-Substituted 1*H*-Imidazo[4,5-*c*]pyridines.*1

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In anticipation of synthetic work directed toward the synthesis of 4-amino-1-(β-D-ribofuranosyl)-1*H*-imidazo[4,5-*c*]pyridine (3-deazaadenosine) by the general method,[1] we have investigated both syntheses and chemical properties of a number of imidazo[4,5-*c*]-pyridines.[2] Our interest has been centered about 4-substituted 1*H*-imidazo[4,5-*c*]pyridines, among which 4-amino derivative (Ⅳ) has already been synthesized by Koegle, van der Want, and Salemink either by a ring closure of 2,3,4-triaminopyridine (XIII)[3] or by amination of the corresponding 4-chloro derivative (Ⅲ).[4] Both synthetic methods for Ⅳ involve 3-nitro-2,4-pyridinediol and are awkward for large scale operation, because of the many stages required even from 5-nitro-4,6-dihydroxynicotinic acid onward.*3,3,4)

As a new synthetic route to Ⅳ *via* Ⅲ, the chlorination of 1*H*-imidazo[4,5-*c*]pyridine 5-oxide (Ⅱ) with phosphoryl chloride[5] appeared attractive, since chlorination on the desirable position (on carbon 4 in Ⅱ) in preference to alternative, seemed very promising.[6] This approach to Ⅳ is summarized by a series of reactions outlined in Chart 1.

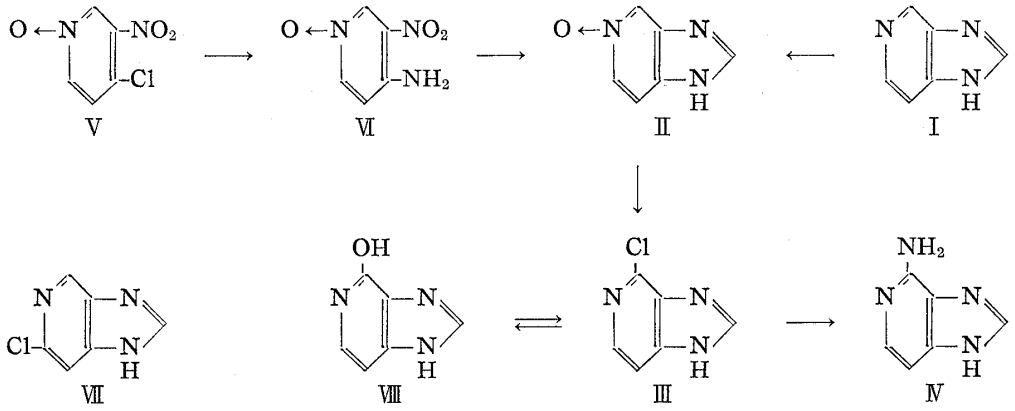

Chart 1.

*1 Part XXIII of this series; Y. Mizuno, T. Itoh, K. Saito : J. Org. Chem., **29**, in press (1964).

*2 Nishi-5, Kita-12, Sapporo, Hokkaido (水野義久, 伊藤憲夫, 斎藤和子).

*3 Koegle, *et al.* prepared 2,4-dihydroxy-3-nitropyridine-5-carboxylic acid by a four-step procedure, starting with acetonedicarboxylate; over-all yield of Ⅲ by this route was ca. 2% on the basis of the dicarboxylate.

1) J. Davoll, B. A. Lowy : J. Am. Chem. Soc., **73**, 1650 (1951).
2) Y. Mizuno, M. Ikehara, T. Itoh, K. Saito : J. Org. Chem., **28**, 1837 (1963).
3) F. Koegle, G. M. van der Want, C. A. Salemink : Rec. trav. chim., **67**, 29 (1948).
4) C. A. Salemink, G. M. van der Want : *Ibid.*, **68**, 1013 (1949).
5) Numerous examples of chlorination at the *ortho* position of aromatic N-oxide with $POCl_3$ (accompanied by concomitant deoxygenation of the N-oxide) have appeared in the literature; for example, see *a*) T. Kato : Yakugaku Zasshi, **75**, 1236 (1956); *b*) Y. Suzuki : This Bulletin, **5**, 78 (1957); *c*) G. Buchi, R. E. Mannig, F. A. Hochstein : J. Am. Chem. Soc., **84**, 3393 (1962).
6) This discussion is based on the fact that, for instance, 2-methyl-5-allyloxybenzothiazole, whose ring system is thio-counterpart of benzimidazole, was rearranged almost exclusively to 2-methyl-4-allyl-5-hydroxy derivative (a ratio of the yields of two isomeric products was 20:1); K. Nishizawa : Yakugaku Zasshi, **61**, 395 (1941); **63**, 441 (1943).

1*H*-Imidazo[4,5-*c*]pyridine (I) was mono-N-oxygenated by a standard method[7] to II in 74% yield. The product was purified by a cellulose powder column chromatography. The purified product was found to be identical with a sample, prepared by the alternate synthesis (*via* V→VI→3,4-diaminopyridine 1-oxide) : amination of 3-nitro-4-chloropyridine 1-oxide (V) gave rise to 3-nitro-4-aminopyridine 1-oxide (VI) which was in turn selectively reduced to 3,4-diaminopyridine 1-oxide. Its structural assignment rests upon the infrared and ultraviolet spectral data and the formation of 1*H*-imidazo[4,5-*c*]pyridine 5-oxide with the correct analysis. Because of the instability of the diamino-compound, this was handled as partially purified intermediate when used for the subsequent ring closure. The assignment of the 1*H*-imidazo[4,5-*c*]pyridine 5-oxide structure to a ring-closed product is based on the correct elementary analysis and the synthetic route, employed (Chart 1). On treatment of II with phosphoryl chloride, a chlorinated product was isolated whose analysis was compatible with the formula $C_6H_4N_3Cl$ and its properties resembled those reported for 4-chloro-1*H*-imidazo[4,5-*c*]pyridine.[4] The mixed melting point of the picrate of the product with that of the authentic sample,[4] did not show depression. Nuclear magnetic resonance spectrum of the chloro-derivative showed the presence of two doublets (458~463 c.p.s. and 488~493 c.p.s., both coupling constants were the same value : 5 c.p.s.), characteristic of AB-system in heterocycles (Fig. 1),[8] and was

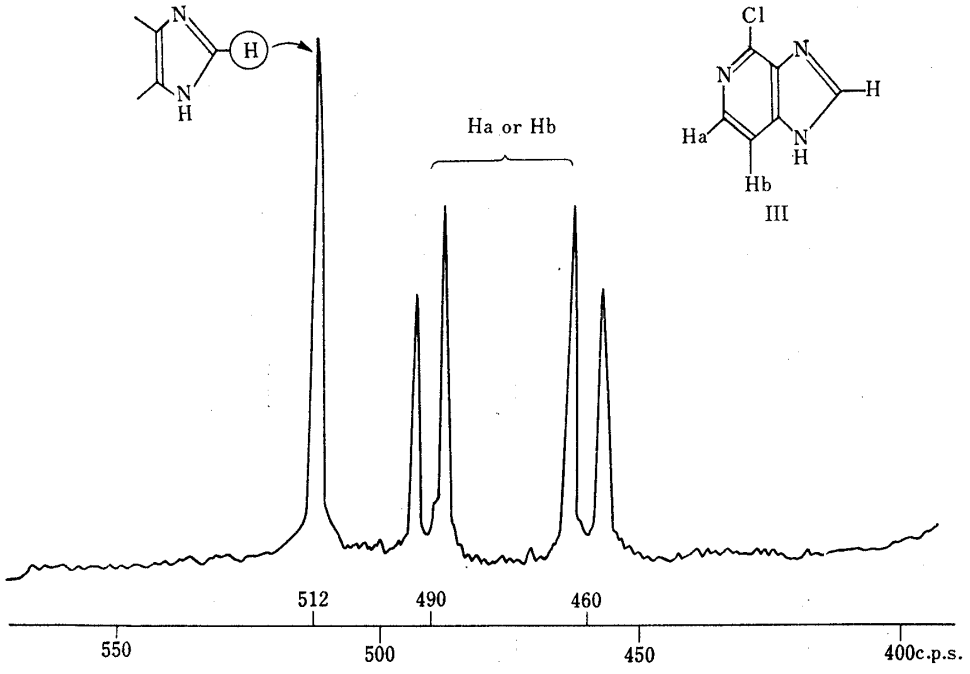

Fig. 1. Nuclear Magnetic Resonance Spectra of Chloro-1*H*-imidazo[4,5-*c*]pyridine, prepared from III were performed on Varian A60 Instrument using Dimethylsulfoxide as a Solvent and Tetramethylsilane as an Internal Standard

well compatible with the assigned structure, absolutely excluding the possibility that the product isolated might be another isomer (*viz.*, 6-chloro-derivative (VIII)). We examined the reaction mixture very carefully by the paper chromatographic technique, but failed to find any evidence for the formation of other isomers. It is to be noted that the reaction took place virtually at position 4, one of the two *ortho* position of 5-N-oxide of II.

7) E. Ochiai : J. Org. Chem., **18**, 535 (1953).
8) J. A. Pople, W. G. Schneider, H. J. Bernstin : "High-resolution Nuclear Magnetic Resonance," p. 267 and 269 (1959), McGraw-Hill Book Company, Inc., New York.

In connection with the present investigation, the work of the German chemists[9] is pertinent who reported that the reduction of 3-nitro-4-aminopyridine with staneous chloride (in the presence of concentrated hydrochloric acid) gave rise to 30% yield of 6-chloro-3,4-diaminopyridine. We repeated their procedure to prepare the supposed 3,4-diamino-6-chloro-derivative which was in turn supposed to be ring-closed to 6-chloro-1*H*-imidazo[4,5-*c*]pyridine (Ⅶ). However, the product isolated in 69% yield (X→Ⅲ in Chart 2) was, unexpectedly, identical with 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (Ⅲ), procured by the unequivocal synthesis,[4] showing that our sample of chloro-3,4-diaminopyridine, (prepared according to Koenig's procedure) should be assigned the 2-chloro-structure (X). Accordingly, Ⅲ could also be prepared by this route (*via* Ⅸ and X in

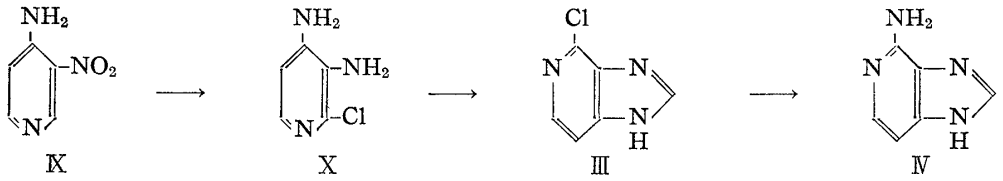

Chart 2.

Chart 2). For the preparation of Ⅲ, this route was found to be superior, in simplicity of procedure, to other routes, shown in charts. An over-all yield of Ⅲ by this route was 20% on the basis of Ⅸ.

Treatment of Ⅲ with ammonia and 60% perchloric acid gave rise to 4-amino-(3-deazaadenine, Ⅳ) and 1*H*-imidazo[4,5-*c*]pyridin-4-ol (3-deazahypoxanthine, Ⅷ), respectively. Ⅳ was also prepared from Ⅴ (*via* Ⅺ→XIII in Chart 3): treatment of 3-nitro-4-chloropyridine 1-oxide (Ⅴ) with phosphoryl chloride[10] gave rise to an isomeric mixture of Ⅺ and Ⅻ from which the former could be easily separated by fractional crystallization in 55% yield. Ⅺ was converted into Ⅳ by three-step procedure, essentially according

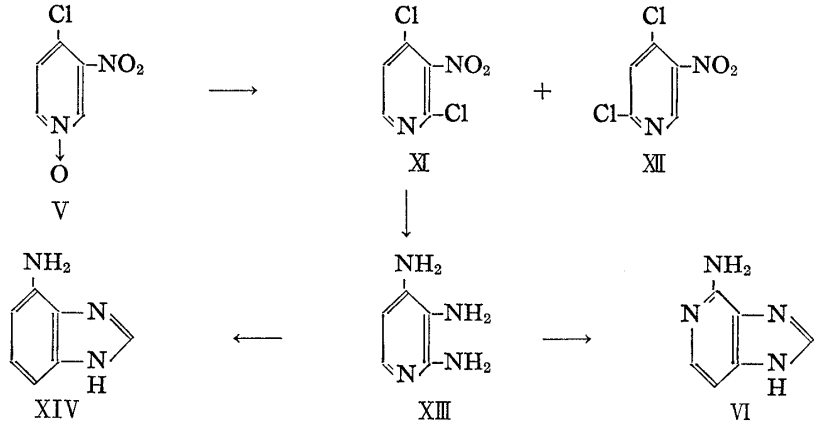

Chart 3.

*4 Koegle, *et al.* obtained 80.4% yield of 4-amino-1*H*-imidazo[4,5-*b*]pyridine (XIV) by the imidazole ring-closure of XIII, employing sodium dithioformate (in pyridine) as the condensing reagent, the direction of the ring-closure appeared to be dependent upon the condensing reagent employed and perhaps, upon other factors.*5

*5 A similar observation has been described by Hull[11] in the case of imidazole ring closure of 6-furylamino-4,5-diaminopyrimidine: this triamino derivative was ring-closed to 6-furfurylaminopurine (kinetin) in a quantitative yield with ethyl orthoformate (in acetic anhydride), whereas the isomeric 6-amino-9-furfurylpurine and kinetin were formed by ring closure of the same pyrimidine with formamide.

9) E. C. Koenig, M. Mields, H. Gurlet: Ber., **57**, 1179 (1924).
10) A. Hayashi: Yakugaku Zasshi, **70**, 142 (1947).
11) R. Hull: J. Chem. Soc., **1958**, 274.

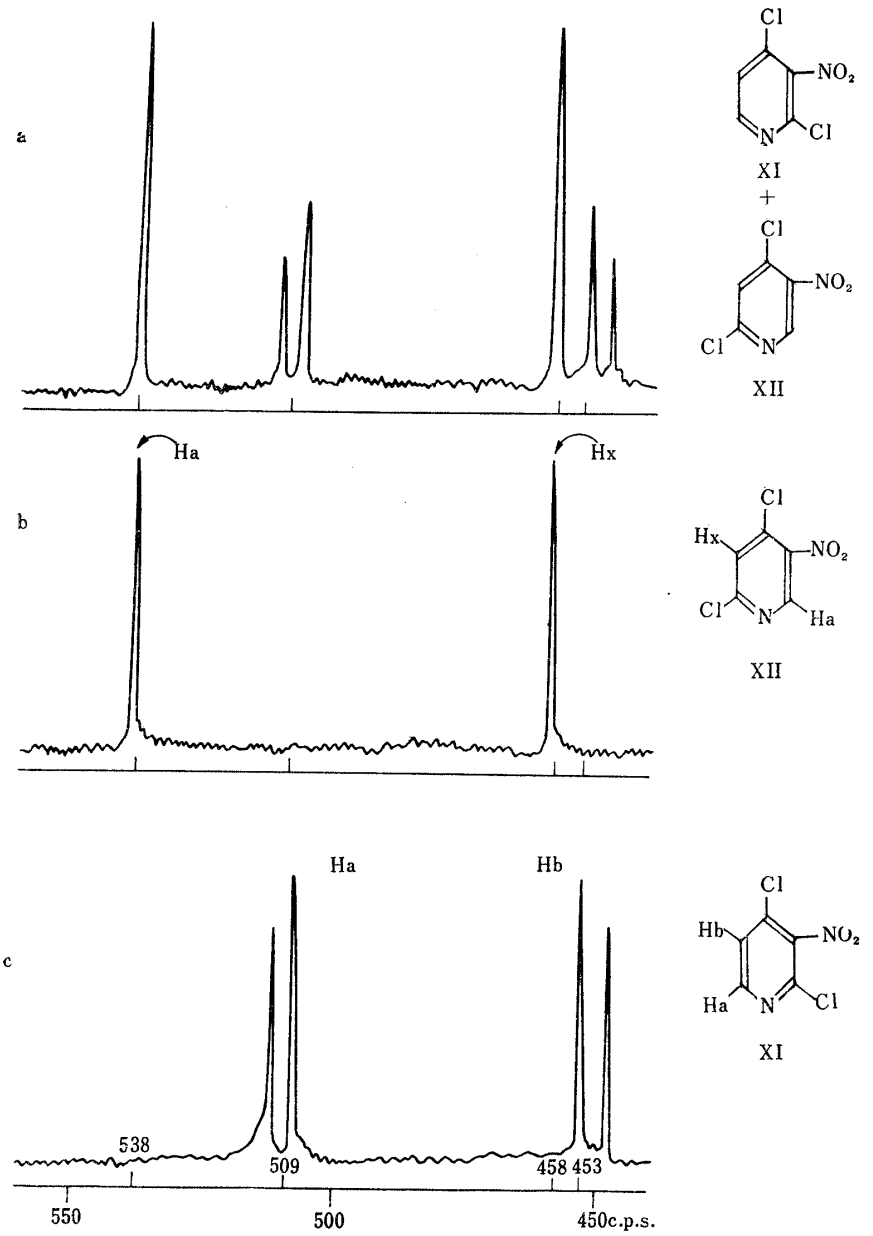

Fig. 2. Nuclear Magnetic Resonance Spectra of Dichloro-3-nitropyridines were determined as Fig. 1. Fig. 2a : As Equimolecular Mixture of XI and XII

to Koenig, *et al.*, except in the last step (imidazole ring-closure) where formic acid was employed instead of potassium dithioformate*4 as the condensing agent. Over-all yield of IV from V was 16%.

Experimental*6

1*H*-Imidazo[4,5-*c*]pyridine (3-Deazapurine, I)——I was prepared by a modification of Albert and

*6 Melting points of compounds which have not been described in the literature were corrected. UV spectra were recorded with a Beckmann Model DK-2 recording spectrophotometer. Molecular extinction coefficients were determined with a Shimadzu manual spectrophotometer. NMR spectra were determined on Varian A60 instrument using dimethyl sulfoxide as a solvent and tetramethylsilane as an internal standard. Except where noted, removal of the solvent was performed *in vacuo* (15～18 mm.). Paper chromatography was performed using the ascending technique. IR spectra were determined using a Koken Model DS-301 infrared recording spectrophotometer.

Pedersen's method.[12] 3,4-Diaminopyridine (4.28 g.) was refluxed with HCOOH (10 ml.) for 1 hr. Excess HCOOH was removed to afford a solid; this was dissolved in EtOH (100 ml.) and treated with $CaCO_3$ (ca. 3 g.) for 3 hr. and filtered and filtrate was concentrated to afford 3,4-diformylaminopyridine (wt., 6.05 g., 83%); after recrystallization from aq. EtOH, cubic crystals were obtained as monohydrate. m.p. 162~163° (decomp.). *Anal.* Calcd. for $C_7H_7O_2N_3 \cdot H_2O$: C, 45.90; H, 4.95; N, 22.94. Found : C, 45.95; H, 4.90; N, 22.96.

3,4-Diformylaminopyridine (9.00 g.) was submitted to a ring closure by sublimation *in vacuo* $b.p_{5\sim6}$ 140~150°, to I in an almost quantitative yield; wt., 5.85 g.; m.p. 163~166° (after recrystallization from AcOEt) (lit.,[12] 168~169°), picrate : m.p. 231~232° (lit.,[3] 231~232°); Rf 0.66 (BuOH-H_2O 84:16 v/v).

1*H*-Imidazo[4,5-*c*]pyridine 5-Oxide (II) (Method A)——1*H*-Imidazo[4,5-*c*]pyridine (I, 5.95 g., 0.05 mole) was oxidized at 55~56° with H_2O_2 (30%, 15 ml.) and glacial AcOH (150 ml.). The reaction was followed by paper chromatography using BuOH-H_2O (84:16 v/v) as the solvent system. After the reaction was almost complete (which required 95 hr.), the solvent was removed *in vacuo*; the residue was dissolved in EtOH and neutralized with $CaCO_3$ and filtered. The filtrate was concentrated to dryness. One-half of the residue (3.35 g.) was applied to a cellulose powder column (wt. of cellulose : 70 g., 37 × 3 cm. in diam.), employing BuOH-H_2O (84:16) as eluting solvent system (100 ml. of the eluate was collected as each fraction). The elution was followed both spectrophotometrically and by a paper chromatography. The first fraction contained only the starting material (I),*7 and the subsequent eight fractions (800 ml.) contained both I and a product (II), and fractions 10 and 11 (total volume : 200 ml.) gave after evaporation of the solvent, a pure 5-oxide (II); wt., 2.5 g. (74% yield). The sample gave correct combustion values, but this did not show sharp melting point : m.p. 220~250°. IR spectrum had a band at 1220 cm^{-1}, characteristic of aromatic N-oxide. Its picrate had sharp melting point of 234~235° (after recrystallization from EtOH). Mixed melting point with authentic sample, prepared by an alternate synthesis (*via* V→VI→3,4-diaminopyridine 1-oxide) was not depressed. UV: $\lambda_{max}^{N\,HCl}$ 264 mμ; $\lambda_{max}^{N\,NaOH}$ 290 mμ. Rf 0.22 (BuOH-H_2O=84:16); 0.76 (H_2O, adjusted to pH 10). *Anal.* Calcd. for $C_6H_5ON_3$: C, 53.33; H, 3.73; N, 31.10. Found : C, 53.43; H, 3.99; N, 30.99. *Anal.* Calcd. for $C_{12}H_8O_8N_6$ (picrate) : C, 39.57; H, 2.21; N, 23.08. Found : C, 39.56; H, 2.36; N, 22.96.

Method B——This procedure is similar to that employed by Vaughan, Krapcho, and English[13] for the preparation of 1*H*-imidazo[4,5-*b*]pyridine 4-oxide from 1*H*-imidazo[4,5-*b*]pyridine. A solution of I (2.40 g., 21 mmoles) in dioxane (75 ml.) was treated overnight at 15° with monoperphthalic acid (50 ml. of 0.3*N* Et_2O solution); during this period yellow glassy deposits separated and the supernatant liquor was decanted; the residue was treated with 10% HCl (2 × 6 ml., two equiv. of the base, employed) at 90° and cooled to 0° to separate phthalic acid; this was filtered off; wt., 1.67 g. To the filtrate was added hot Et_2O (100 ml.) and filtered while hot and the mixture was kept overnight at room temperature to separate a crude 5-oxide as the hydrochloride; wt., 0.89 g. Concentration of the filtrate gave a further crop; wt., 0.75 g. Paper chromatography of each sample after neutralization with NH_4OH showed the presence of a small amount of I. Purification was performed by a cellulose column chromatography, according to a procedure described in Method A. Yield of purified 5-oxide (II) was 1.15 g. (42.3%).

3-Nitro-4-chloropyridine 1-Oxide (V) (Method A) (from 3-Nitro-4-pyridinol 1-Oxide)——In a flask (100 ml.), fitted with a reflux-condenser and protected from the moisture with a calcium chloride tube, 3-nitro-4-pyridinol 1-oxide[10] (3.5 g.) was treated with $POCl_3$ (35 ml.) for 30 min. at 70~80°. The content of the flask was poured onto ice-H_2O, and neutralized with 10% Na_2CO_3 solution to deposit solids; these were collected by filtration; the filtrate was extracted with $CHCl_3$. Concentration of the filtrate *in vacuo* gave a further crop of the product; a total yield, 1.5 g. (39%); m.p. 137~138° (after recrystallization from Me_2CO, yellow needles), (lit.,[6] 137~138°).

Method B (from 1-Acetoxy-3-nitro-4(1*H*)-pyridone)——1-Acetoxy-3-nitro-4(1*H*)-pyridone[10] (2.0 g.) was treated with $POCl_3$ (2 ml.) at 90~100° (oil bath temp.). As worked up as in Method A, a crude V was obtained; wt., 1.2 g. Recrystallization from Me_2CO gave pure product; wt., 0.9 g. (63%); m.p. 137° (lit.,[10] 137~138°).

3-Nitro-4-aminopyridine 1-Oxide (VI)——To a solution of 3-nitro-4-chloropyridine 1-oxide (1.0 g.) in EtOH (10 ml.) was added NH_4OH (28%, 1 ml.) and the mixture was heated in a sealed tube for 1 hr. at 50~56°. After cooling, a small amount of a solid was filtered off and concentration of the filtrate gave a reddish, grey solid. This was recrystallized from aq. EtOH (1:1 v/v) to afford pure VI; wt., 150 mg. (16.8%); m.p. 235~237°. Rf 0.29 (BuOH-H_2O=84:16)· *Anal.* Calcd. for $C_5H_5O_3N_3$: C, 38.71; H, 3.25; N, 27.09. Found : C, 39.31; H, 2.90; N, 26.73

Preparation of 1*H*-Imidazo[4,5-*c*]pyridine 5-Oxide (II) from VI——A solution of VI (570 mg.) in aq. EtOH (EtOH-H_2O=2:1) was hydrogenated over Pd-C (4%, 1 ml.) until 220 ml. of H_2 was consumed (83% of the theoretical amount of H_2, required for the reduction of one nitro group), and filtered. The

*7 Identification was based on UV, IR, and mixed melting point in addition to Rf.

12) A. Albert, C. Pedersen : J. Chem. Soc., **1956**, 4683.

13) J. R. Vaughan, Jr., J. Krapcho, J. P. English : J. Am. Chem. Soc., **71**, 1885 (1949).

catalyst on carbon was washed with EtOH (2×20 ml.). Combined filtrate and washings were concentrated *in vacuo* to dryness (brown solid; wt., 370 mg.); UV : $\lambda_{max}^{N\,HCl}$ 285 mμ; $\lambda_{max}^{N\,NaOH}$ 276 mμ. The residue was, without purification, treated with HCOOH (50 ml.), until absorption maxima of the mixture completely shifted to those of the ring-closed product ($\lambda_{max}^{N\,HCl}$ 264 mμ; $\lambda_{max}^{N\,NaOH}$ 290 mμ); it required 2.5 hr. Excess HCOOH was removed *in vacuo* to afford a solid; this was dissolved in EtOH (20 ml.) and treated with $CaCO_3$ (300 mg.) for 3 hr. and filtered and the filtrate was concentrated to dryness to afford a solid. Removal of 1*H*-imidazo[4,5-*c*]pyridine (I) (deoxygenated by-product)*[8] by sublimation *in vacuo* (140~150°; 5~6 mm.) left a crude 5-oxide (II) as a residue (wt., 150 mg.); a part of the residue (30 mg.) was converted into the picrate; m.p. 234~235° (after recrystallization from EtOH). Mixed melting point with that of a sample prepared by oxidation of I by monoperphthalic acid did not show depression. IR spectra of both preparations were identical and indicated the presence of a band at 1220 cm^{-1}, characteristic of aromatic N-oxide.[14]

4-Chloro-1*H*-imidazo[4,5-*c*]pyridine (III) : Preparation of III from II——A suspension of 1*H*-imidazo[4,5-*c*]pyridine 5-oxide (II, 150 mg.) in $POCl_3$ (50 ml.) was refluxed until the oxide was completely dissolved. This required 7 hr. Excess $POCl_3$ was removed *in vacuo* to afford a residue. This was dissolved in H_2O (5 ml.) and the solution was neutralized with *N* NH_4OH and concentrated to dryness. The residue was dissolved in BuOH saturated with H_2O (50 ml.) and the combined aqueous washings contained only a negligible amount of III and discarded. Paper chromatography of the BuOH layer showed the presence of a single compound (a single spot in three solvent systems : Rf 0.73 in BuOH-H_2O; 0.84 in BuOH-pyridine-H_2O; 0.54 in H_2O adjusted to pH 10 with NH_4OH), and separated and concentrated to dryness. The residue weighed 74 mg. (43% yield). After recrystallization from H_2O, a pure sample of III was obtained (wt., 55.4 mg.). UV $\lambda_{max}^{pH\,7}$ mμ (ε) : 274 (5053), 267 (6060), 252 (4620); $\lambda_{min}^{pH\,7}$ mμ (ε) : 272 (4620), 256 (4340). The picrate melted at 174~175.9°, mixed melting point with that of authentic III[4] did not show depression. IR spectrum of the picrate was identical in every detail with that of the authentic III picrate. NMR spectra are given in Fig. 1. *Anal.* Calcd for $C_{12}H_7O_7N_6Cl$: C, 37.67; H, 1.84; N, 21.96. Found : C, 37.65; H, 2.00; N, 22.10.

4-Chloro-1*H*-imidazo[4,5-*c*]pyridine (III) from X——A solution of X*[9,9] (1.0 g., m.p. 218°) in methylcellosolve (14 ml.) was treated with formamidine acetate[15] (2.0 g.) for 1.5 hr. at 125°. As worked up as reported previously,[1] III was obtained in 69% yield; wt., 0.70 g. Rf 0.53 (H_2O, adjusted with NH_4OH to pH 10); 0.73 (BuOH-H_2O=84:16); UV λ_{max}^{EtOH} mμ : 274, 267, 252. *Anal.* Calcd. for $C_6H_4N_3Cl$: C, 46.92; H, 2.62; N, 27.23. Found : C, 47.22; H, 2.62; N, 27.35.

III was converted into the picrate; m.p. 176~177.6°; mixed melting point with that of a sample, prepared by an unequivocal synthesis,[3] did not show depression. IR spectrum of the picrate was identical to that of the picrate of the authentic sample. NMR spectra of III was very similar to those, given in Fig. 1. τ-Values were 1.83 and 2.33 (doublets); coupling constants were 5 c.p.s.

Preparation of 4-Amino-1*H*-imidazo[4,5-*c*]pyridine (IV) (3-Deazaadenine) from III——A solution of III (150 mg.) was treated in a sealed tube with NH_4OH (35%, 8 ml.) in the presence of $CuSO_4$ for 4 hr. at 160~170° and then for 10 hr. at 180~185°, and cooled. The mixture was concentrated *in vacuo* to dryness; the residue was dissolved in 3*N* HCl 5 ml.) and H_2S gas was passed through the resulting solution to remove Cu as CuS and the mixture was filtered; the filtrate was treated with activated carbon and filtered; the filtrate was concentrated *in vacuo* to dryness. Paper chromatography of the residue (after neutralization with NH_3) : Rf 0.19 (BuOH-H_2O=84:16); Rf of the authentic sample[3,4] 0.19 (in the same solvent system). The spot (Rf 0.19) was cut out and eluted with H_2O; absorption spectrum of the eluate had the same maxima as those of the authentic sample[3] (λ_{max} 260 mμ and 276 mμ). The rest of the residue was converted into the picrate whose IR spectra were determined and found to be identical with those of the authentic preparation.[3,4]

3-Nitro-2,4-dichloropyridine (XI) and 5-Nitro-2,4-dichloropyridine (XII)——A suspension of 3-nitro-4-chloropyridine 1-oxide (9.2 g.) in 300 ml. of $POCl_3$ was refluxed for 10 hr. and excess $POCl_3$ was removed *in vacuo* to afford yellow-colored resinous residue. The residue was poured onto ice-H_2O to separate semi-solid substance which was collected on a glass filter and air-dried on a porous plate; wt., 5.7 g. This sample was purified by distillation under reduced pressure (b.$p_{2\sim3}$ 72~78°). The purified sample had the same IR spectra as those of authentic sample of XI[3] and NMR spectra are given in Fig. 2.*[10] Yield was 5.5 g. (55%).

The filtrate was treated with three 250 ml. portions of $CHCl_3$ and the $CHCl_3$ solution was washed with H_2O and dried with Na_2SO_4 and filtered. Removal of $CHCl_3$ left oily substance (a mixture of XI

*[8] Sublimed sample had an absorption spectrum characteristic of I.

*[9] This sample was essentially prepared by Koenig and co-workers' method,[9] and the structure was corrected in the present investigation and procedure was slightly modified to give a better yield of X.

*[10] The spectra are well compatible with the assigned structure (XI).

14) H. Shindo : This Bulletin, 7, 407, 791 (1959).

15) E. C. Taylor, W. A. Ehrhart : J. Am. Chem. Soc., 82, 3138 (1960).

and XII). The sample was distilled under reduced pressure (b.$p_{2\sim3}$ 72~78°) to afford 2.17 g. of a mixture. NMR spectra showed that this was a 1:1 mixture of XI and XII (Fig. 2a).

Preparation of IV from XIII——XIII was prepared from XI essentially according to Koegle, *et al.*[3] XIII·HCl (0.35 g.) was refluxed with HCOOH (30 ml.) for 3 hr. and cooled. Concentration of the mixture *in vacuo* gave a residue; this was dissolved in conc. HCl (3 ml.) and to the solution was added an equal volume of EtOH to afford 0.12 g. (34%) of IV; m.p. 230~233°. UV spectrum of this sample was identical with that of a sample of 3-deazaadenine, prepared by Koegle's method.[3] IV was converted into the picrate whose IR spectrum was also identical with that of the authentic sample, prepared by the unambiguous synthesis.[3] *Anal.* Calcd. for $C_6H_8N_4Cl_2$ (dihydrochloride of IV): C, 34.80; H, 3.89; N, 27.06. Found: C, 34.83; H, 4.00; N, 26.65.

The authors wish to thank Dr. Ken'ichi Takeda, Director of the Shionogi Research Laboratories, for the determination of NMR spectra. They also wish to thank Mrs. Toyoko Tohma and Miss A. Maeda for the elementary analysis.

Summary

The evidences that the reported 6-chloro-3,4-diaminopyridine was actually 2-chloro-3,4-diaminopyridine (X) were presented. By employing X 4-amino-1*H*-imidazo[4,5-*c*]-pyridine (IV) was prepared *via* 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (III). An alternative synthetic method leading to IV was devised using 1*H*-imidazo[4,5-*c*]pyridine 5-oxide (II) as a key intermediate as follows. Oxidation of 1*H*-imidazo[4,5-*c*]pyridine (I) with hydrogen peroxide in acetic acid afforded the cerresponding 5-oxide (II); treatment of II with boiling phosphoryl chloride gave rise to III. 3-Nitro-2,4-dichloropyridine, useful intermediate for the synthesis of IV (*via* 3-nitro-2,4-diaminopyridine→2,3,4-triaminopyridine) was prepared by N-oxide-phosphoryl chloride reaction from 3-nitro-4-chloropyridine 1-oxide. Comparison of the several routes leading to IV has been made from a standpoint of the over-all yield.

(Received March 27, 1964)

[Chem. Pharm. Bull. 12 (8) 872 ~ 877]

UDC 615.766-015

123. Yukio Ishida and Kazuko Hara: Studies on Inhibitory Actions of Synthetic Peptides on the Effects of Oxytocin and Vasopressin.

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On the way of our studies with drug receptors of acetylcholine, barium chloride and oxytocin on the rat uterus, we found that the action of oxytocin was inhibited competitively by hydrogen ion and simple phenolic compounds. These results suggested that one of the active centres of oxytocin was tyrosine molecule in the peptide.[1~4]

In this report, many peptides containing tyrosine were synthesized for the purpose of obtaining more potent antagonistic substances against oxytocin. They showed more or less competitive inhibition to the contraction of rat uterus by oxytocin. Some peptides that did not contain tyrosine, on the other hand, exhibited no inhibitory action.

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1) K. Takagi, Y. Ishida, H. Moritoki, K. Hara: Yakugaku Zasshi, **81**, 1708 (1961).
2) Y. Ishida, H. Moritoki, K. Hara: *Ibid.*, **81**, 1713 (1961).
3) Y. Ishida: *Ibid.*, **81**, 1717 (1961).
4) *Idem*: *Ibid.*, **81**, 1722 (1961).