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110. Torizo Takahashi, Fumiro Yoneda, and Ryota Oishi : Synthesis of Nitrogen-containing Cyclic Compounds. CXV.[1] Synthesis of Imidazopyridine Derivatives. (2).

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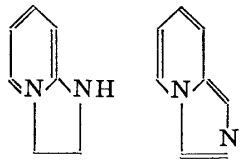
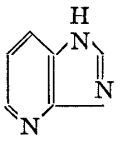
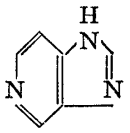
In imidazopyridine system formed by fusion of pyridine and imidazole ring, the following four isomers are possible.



Imidazo[*a*]pyridines



Imidazo[*b*]pyridine



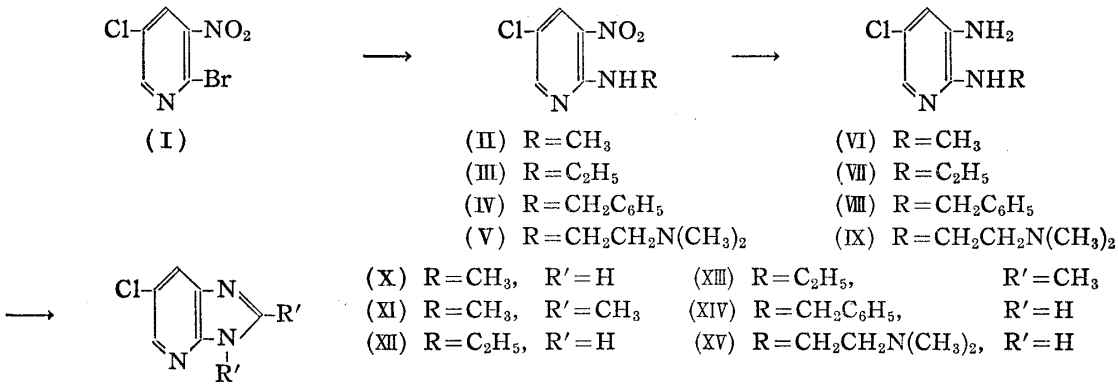
Imidazo[*c*]pyridine

Recently some interesting biological results have been reported for benzimidazole derivatives in the field of bacterial-growth inhibitors.[2] Imidazo[*b*]pyridine is structurally related both to those compounds and purines that have outstanding pharmacological actions.

It seemed of interest, therefore, to test physiological activity of their derivatives and a large number of derivatives have been synthesized for this purpose. Some derivatives of 2-benzylimidazo[*b*]pyridine were synthesized in this laboratory to test their pharmacological activity,[3] but little information is available concerning the synthesis of N-substituted imidazopyridine. Weidenhagen and Train[4] synthesized some 1,2-dialkylimidazo[*c*]pyridine, and Clark-Levis, *et al.*[5] obtained 1-methyl-2-hydroxyimidazo[*b*]pyridine.

Therefore, some compounds related to N-substituted imidazo[*b*]pyridine having substituent in 3-position were prepared.

The compounds were synthesized according to scheme shown in Chart 1.



(I)

(II) R=CH_3
(III) R=C_2H_5
(IV) R=$CH_2C_6H_5$
(V) R=$CH_2CH_2N(CH_3)_2$

(VI) R=CH_3
(VII) R=C_2H_5
(VIII) R=$CH_2C_6H_5$
(IX) R=$CH_2CH_2N(CH_3)_2$

(X) R=CH_3, R′=H
(XI) R=CH_3, R′=CH_3
(XII) R=C_2H_5, R′=H
(XIII) R=C_2H_5, R′=CH_3
(XIV) R=$CH_2C_6H_5$, R′=H
(XV) R=$CH_2CH_2N(CH_3)_2$, R′=H

Chart 1.

The starting material for these compounds is 2-bromo-3-nitro-5-chloropyridine (I) which was prepared according to the method of Berrie, *et al.*[6] Reaction of (I) with

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1) Part CXIV : This Bulletin, **6**, 611 (1958).
2) D. W. Woolley : J. Biol. Chem., **152**, 225(1944).
3) T. Takahashi, F. Yoneda, S. Yoshimura : This Bulletin, **6**, 443 (1958).
4) R. Weidenhagen, C. Train : Chem. Ber., **75**, 1936(1942).
5) J. W. Clark-Levis, M. J. Thompson : J. Chem. Soc., **1957**, 442.
6) A. H. Berrie, *et al.* : *Ibid.*, **1952**, 2042.

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hydrous methyl- and ethylamine in a sealed vessel using alcohol as a solvent gave 2-methylamino- and 2-ethylamino-3-nitro-5-chloropyridines (II and III) in a good yield. The nitro compounds were reduced to the corresponding diamines (VI and VII) with stannous chloride in conc. hydrochloric acid. Finally the diamines were converted to 3-methyl- and 3-ethyl-6-chloroimidazo[*b*]pyridines (X and XII) by heating with formic acid, and also to 2,3-dimethyl- and 2-methyl-3-ethyl-6-chloroimidazo[*b*]pyridines (XI and XIII) by heating with acetic anhydride. 2-Benzylamino-3-nitro-5-chloropyridine (IV) was obtained almost quantitatively by the reaction of (I) with benzylamine in benzene solution. This derivative was converted into 2-benzylamino-3-amino-5-chloropyridine (VIII) with reduced iron in acid ethanol in a good yield.

Condensation of 2-benzylamino-3-amino-5-chloropyridine with formic acid gave 83% yield of 3-benzylamino-6-chloroimidazo[*b*]pyridine (XIV).

2-(2-Dimethylaminoethylamino)-3-nitro-5-chloropyridine hydrobromide (V) was also prepared by heating (I) with 2-dimethylaminoethylamine in ethanol solution. Reduction of 2-(2-dimethylaminoethylamino)-3-nitro-5-chloropyridine to its diamino derivative (IX) was effected with stannous chloride in conc. hydrochloric acid and (IX) was converted to 3-(2-dimethylaminoethylamino)-6-chloroimidazo[*b*]pyridine (XV) by heating with formic acid. These compounds were oily substances except 3-benzyl-6-chloroimidazo[*b*]pyridine (XIV) and, therefore, they were confirmed as their picrate and hydrochloride. The results of pharmacological test of these compounds will be discussed later.

The authors are grateful to the members of the Analysis Center of the University of Kyoto for the microanalyses.

Experimental*2

2-Methylamino-3-nitro-5-chloropyridine (II)—A mixture of 8.0 g. of (I) and 13 cc. of aqueous $MeNH_2$ (25%) in 60 cc. of EtOH was heated at 100° in a sealed vessel for 2 hr. After cool, light yellow needles were collected by filtration and water was added to the filtrate until no more precipitate appeared. The combined product was recrystallized from EtOH to yield 5.7 g. (90%) of light yellow needles, m.p. 148~150°. *Anal.* Calcd. for $C_6H_6O_2N_3Cl$: C, 38.40; H, 3.20. Found: C, 38.63; H, 3.48.

2-Ethylamino-3-nitro-5-chloropyridine (III)—This was prepared from (I) by the method described above. The product was purified by recrystallization from EtOH. Yield, 95%. Yellow needles, m.p. 86~87°. *Anal.* Calcd. for $C_7H_8O_2N_3Cl$: C, 41.68; H, 3.97. Found: C, 41.42; H, 4.19.

2-Benzylamino-3-nitro-5-chloropyridine (IV)—A mixture of 2.0 g. of (I) and 3.0 g. of benzylamine in 20 cc. of benzene was heated under reflux for 1 hr. After cool, white crystals were filtered off, the filtrate was concentrated to a small volume, and cooled to crystallize the product as yellow needles. These were washed with water and dried. Recrystallization from MeOH gave yellow crystals (2.1 g.), m.p. 104~105°. *Anal.* Calcd. for $C_{12}H_{10}O_2N_3Cl$: C, 54.65; H, 3.76. Found: C, 54.68; H, 3.91.

2-(2-Dimethylaminoethylamino)-3-nitro-5-chloropyridine Hydrobromide (V)—This was obtained in 37% yield by treatment of (I) with 2-dimethylaminoethylamine using EtOH as a solvent, by the method described above. Yellow needles (from EtOH), m.p. 188~189°. *Anal.* Calcd. for $C_9H_{13}O_2N_4Cl \cdot HBr$: C, 33.17; H, 4.30. Found: C, 32.90; H, 4.51.

2-Methylamino-3-amino-5-chloropyridine (VI)—3.0 g. of (II) was added gradually to a mixture of 11 g. of anhyd. $SnCl_2$ in 30 cc. of conc. HCl. The solution was heated for 30 min., evaporated to dryness under a reduced pressure, and the white residue was made alkaline with 40% NaOH solution with cooling. The mixture was shaken with ether and the ether layer separated and evaporated. Crystallization of the residue from ether-petr. ether gave (VI) as needles, m.p. 132°; yield, 0.8 g. *Anal.* Calcd. for $C_6H_8N_3Cl$: C, 45.71; H, 5.07. Found: C, 45.59; H, 4.93.

2-Ethylamino-3-amino-5-chloropyridine (VII)—This was obtained in 47% yield from (III) by the method described above, and crystallized from ether-petr. ether as needles, m.p. 107~108°. *Anal.* Calcd. for $C_7H_{10}N_3Cl$: C, 48.97; H, 5.83. Found: C, 49.04; H, 6.06.

2-Benzylamino-3-amino-5-chloropyridine (VIII)—A mixture of 1.5 g. (IV), 3.5 g. reduced iron, 20 cc. EtOH, 2 cc. water, and 0.1 cc. conc. HCl was heated under reflux for 1 hr. and the reaction

*2 All m.p.s are uncorrected.

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mixture was filtered. The filtrate and washings were evaporated to a very small volume and made alkaline with NaOH. The precipitated black solid was dried and extracted with boiling benzene. Evaporation of the benzene solution and recrystallization from ether-petr. ether gave gray plates, m.p. 113° (1.0 g., 85%). *Anal.* Calcd. for $C_{12}H_{12}N_3Cl$: C, 61.67; H, 5.13. Found: C, 61.45; H, 5.02.

2-(2-Dimethylaminoethylamino)-3-amino-5-chloropyridine (IX)—This was prepared from (V) by the same method as for (VI). The product was purified by dissolving it in ether and decolorizing with Norit. Pale yellow oil.

Picrate: Yellow needles (from acetone), m.p. 202°(decomp.). *Anal.* Calcd. for $C_9H_{15}N_4Cl \cdot 2C_6H_3O_7N_3$: C, 37.48; H, 3.12. Found: C, 37.50; H, 3.26.

3-Methyl-6-chloroimidazo[*b*]pyridine (X)—A solution of 1.0 g. of (VI) dissolved in 15 cc. of HCOOH (85%) was heated under reflux for 5 hr. Evaporation of the excess of formic acid under a reduced pressure, followed by purification by dissolving it in ether and decolorizing with Norit gave brown oil (0.6 g.).

Picrate: Yellow plates (from EtOH), m.p. 207°. *Anal.* Calcd. for $C_7H_6N_3Cl \cdot C_6H_3O_7N_3$: C, 39.84; H, 2.26. Found: C, 39.56; H, 2.57.

3-Ethyl-6-chloroimidazo[*b*]pyridine (XII)—This was obtained in 45% yield from (VII) as a light brown oily substance by the method described above.

Picrate: Yellow needles (from acetone), m.p. 183~184°. *Anal.* Calcd. for $C_8H_8N_3Cl \cdot C_6H_3O_7N_3$: C, 40.92; H, 2.67. Found: C, 41.20; H, 2.87.

2,3-Dimethyl-6-chloroimidazo[*b*]pyridine (XI)—A solution of 0.8 g. of (VI) dissolved in 15 cc. of Ac_2O was heated under reflux for 5 hr. Excess of Ac_2O was removed and the residue was purified by dissolving it in ether and decolorizing with Norit. Light brown oily substance (0.4 g.).

Picrate: Yellow needles (from acetone), m.p. 224°(decomp.). *Anal.* Calcd. for $C_8H_8N_3Cl \cdot C_6H_3O_7N_3$: C, 40.92; H, 2.67. Found: C, 41.14; H, 2.82.

2-Methyl-3-ethyl-6-chloroimidazo[*b*]pyridine (XIII)—This was prepared in 80% yield from (VII) by the method described above, but reaction time was 7 hr., and the product was pale yellow oily substance.

Picrate: Yellow needles (from acetone), m.p. 212~213°. *Anal.* Calcd. for $C_9H_{10}N_3Cl \cdot C_6H_3O_7N_3$: C, 42.40; H, 3.06. Found: C, 42.32; H, 3.28.

3-Benzyl-6-chloroimidazo[*b*]pyridine (XIV)—A solution of 0.5 g. of (VIII) dissolved in 10 cc. of formic acid (80%) was heated at 170° under reflux for 3 hr. Evaporation of excess formic acid gave (XIV) (0.7 g., 60%) as needles, m.p. 111°, from petr. ether and benzene. *Anal.* Calcd. for $C_{13}H_{10}N_3Cl$: C, 64.07; H, 4.16. Found: C, 64.04; H, 4.30.

3-(2-Dimethylaminoethylamino)-6-chloroimidazo[*b*]pyridine (XV)—This was obtained in 50% yield from (IX) by the method used for (X). Reaction time was 8 hr. Light yellow oil.

Hydrochloride: Needles (from ether-petr. ether), m.p. 205°. *Anal.* Calcd. for $C_{10}H_{13}N_4Cl \cdot 2HCl \cdot H_2O$: C, 38.03; H, 5.38; N, 17.74. Found: C, 38.11; H, 5.59; N, 17.81.

Picrate: Yellow needles (from acetone), m.p. 213~214°. *Anal.* Calcd. for $C_{10}H_{13}N_4Cl \cdot C_6H_3O_7N_3$: C, 42.33; H, 3.52. Found: C, 42.42; H, 3.75.

Summary

N-Substituted imidazo[*b*]pyridines having substituent in 3-position were prepared.

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