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

Imidazo[α]pyridines

Imidazo[β]pyridine

Imidazo[γ]pyridine

Recently some interesting biological results have been reported for benzimidazole derivatives in the field of bacterial-growth inhibitors. Imidazo[β]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[β]pyridine were synthesized in this laboratory to test their pharmacological activity, but little information is available concerning the synthesis of N-substituted imidazopyridine. Weidenhagen and Train synthesized some 1,2-dialkylimidazo[γ]pyridine, and Clark-Levis, et al obtained 1-methyl-2-hydroxylimidazo[β]pyridine.

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

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

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\begin{align*}
&\text{(I) Cl} \quad \text{NO}_2 \quad \text{Br} \\
&\text{(II) R = CH}_3 \\
&\text{(III) R = C}_2\text{H}_5 \\
&\text{(IV) R = CH}_3\text{C}_2\text{H}_5 \\
&\text{(V) R = CH}_2\text{CH}_2\text{N(CH}_3)_2 \\
&\text{(VI) R = CH}_3 \\
&\text{(VII) R = C}_2\text{H}_5 \\
&\text{(VIII) R = CH}_3\text{C}_2\text{H}_5 \\
&\text{(IX) R = CH}_2\text{CH}_2\text{N(CH}_3)_2 \\
&\text{(X) R = CH}_3, \quad R' = H \\
&\text{(XI) R = CH}_3, \quad R' = \text{CH}_3 \\
&\text{(XII) R = CH}_3\text{C}_2\text{H}_5, \quad R' = H \\
&\text{(XIII) R = C}_2\text{H}_5, \quad R' = \text{CH}_3 \\
&\text{(XIV) R = CH}_3\text{C}_2\text{H}_5, \quad R' = \text{CH}_3 \\
\end{align*}
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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. Reaction of (I) with

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*1 Yoshida-Konoe-cho, Sakyo-ku, Kyoto (高橋żej, 米田文彦, 大石俊太).
1) Part CXIV: This Bulletin, 6, 611 (1958).
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[2,1-b]pyridines (X and XII) by heating with formic acid, and also to 2,3-dimethyl- and 2-methyl-3-ethyl-6-chloroimidazo[2,1-b]pyridines (XI and XII) 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[2,1-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 diamine derivative (IX) was effected with stannous chloride in conc. hydrochloric acid and (IX) was converted to 3-(2-dimethylaminoethylamino)-6-chloroimidazo[2,1-b]pyridine (XV) by heating with formic acid. These compounds were oily substances except 3-benzyl-6-chloroimidazo[2,1-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.

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Experimental*2

2-Methylamino-3-nitro-5-chloropyridine (II)—A mixture of 8.0 g. of (I) and 13 cc. of aqueous MeNH₄(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 C₁₅H₁₄O₂N₈Cl: 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 C₁₅H₁₆O₂N₈Cl: 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 C₁₅H₁₂O₂N₈Cl: 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 C₁₅H₁₄O₂N₈Cl·HBr: C, 53.17; H, 4.30. Found: C, 52.90; 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. SnCl₄ 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 C₁₅H₁₂N₈Cl: 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 C₁₅H₁₄N₈Cl: 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.
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 $C_{11}H_{12}N_8Cl$: C, 61.67; H, 5.13. Found: C, 61.45; H, 5.02.

$\text{2-(2-Dimethylaminoethylamino)-3-amin-5-chloropyridine (IX)}$—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 $C_{16}H_{14}N_4Cl\cdot2C_2H_4O_2$: C, 37.48; H, 3.12. Found: C, 37.50; H, 3.28.

$\text{3-Methyl-6-chloroimidazo(b)pyridine (X)}$—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 $C_{17}H_{18}N_3Cl\cdotC_2H_4O_2N_3$: C, 39.84; H, 2.26. Found: C, 39.56; H, 2.57.

$\text{3-Ethyl-6-chloroimidazo(b)pyridine (XI)}$—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 $C_{15}H_{14}N_4Cl\cdotC_2H_4O_2N_3$: C, 40.92; H, 2.67. Found: C, 41.20; H, 2.87.

$\text{2,3-Dimethyl-6-chloroimidazo(b)pyridine (XI)}$—A solution of 0.8 g. of (VI) dissolved in 15 cc. of Ac₂O was heated under reflux for 5 hr. Excess of Ac₂O 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 $C_{16}H_{18}N_3Cl\cdotC_2H_4O_2N_3$: C, 40.52; H, 2.67. Found: C, 41.14; H, 2.82.

$\text{2-Methyl-3-ethyl-6-chloroimidazo(b)pyridine (XIII)}$—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 $C_{17}H_{18}N_3Cl\cdotC_2H_4O_2N_3$: C, 42.40; H, 3.06. Found: C, 42.32; H, 3.28.

$\text{3-Benzyl-6-chloroimidazo(b)pyridine (XIV)}$—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 $C_{19}H_{13}N_3Cl$: C, 64.07; H, 4.16. Found: C, 64.04; H, 4.30.

$\text{3-(2-Dimethylaminoethylamino)-6-chloroimidazo(b)pyridine (XV)}$—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 $C_{18}H_{13}N_3Cl\cdot2HCl\cdotH_2O$: C, 38.05; 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 $C_{19}H_{13}N_3Cl\cdotC_2H_4O_2N_3$: 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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