

Derivatives of 1*H*-imidazo[4,5-*b*]pyridine

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Dedicated to Professor Allan R. Day

The synthesis of five derivatives of 2-methylimidazo[4,5-*b*]pyridine, three imidazo[4,5-*b*]pyridines and two aminopyridines is reported. An improved procedure for replacing halogens for the preparation of aminopyridines is described. The preliminary screening of four of the imidazo[4,5-*b*]pyridines did not indicate useful antimetabolite or antihistaminic properties.

Improvements in the amination procedure of Maier-Bode (2) and Schickh, *et.al.*, (3) permitted amination of larger quantities of chloro- and bromopyridines with improved yields. A relatively high yield procedure for recovering 2,3-diaminopyridine (II) with greater stability to air oxidation was developed. It was found that fusion of II with glycollic acid produced 2-hydroxymethylimidazo[4,5-*b*]pyridine (III) in high yield. *Via* the 2-chloromethylimidazo[4,5-*b*]pyridine hydrochloride (IV), derivatives of 2-aminomethylimidazo[4,5-*b*]pyridines were readily prepared in good yields.

EXPERIMENTAL

General Information.

All analyses were performed by Sarah M. Woods, University of Pennsylvania, Division of Organic Chemistry, Analytical Laboratory. Melting points are corrected and were determined in a Wagner and Meyer (4) melting point bath. The 2-aminopyridine and 2-amino-5-methylpyridine were obtained from Reilly Tar and Chemicals Co.

Amination Procedure.

Concentrated ammonia containing 20 g./ℓ. of cuprous chloride was cooled to 0° and saturated with ammonia to about 35% ammonia content (1). The aminations were carried out in a stirring autoclave. Generally, eight hours was sufficient. After removal of water, the residue was treated with excess 50% sodium hydroxide. The product recovery depended on the particular compound.

2,3-Diaminopyridine (II).

Two moles (316 g., 210 ml.) of 3-bromopyridine was reacted with 550 ml. of I for eight hours at 170-180°. The mixture was worked up as described. The product recovered by ether extraction and vacuum distillation was converted to 2-chloro-3-aminopyridine (Ib) by the procedure of Schickh, *et.al.*, (3). The amination of Ib required 16 hours at 130-140°. After addition of sodium hydroxide, water was first removed under vacuum and completely by azeotropic distillation with xylene. The dry residue was distilled at 1-2 mm, and II was collected as a slurry in cold xylene. As required, II was filtered from the xylene slurry and vacuum dried. Light colored II was available for several months. Over-all, a 46% yield based on 3-bromopyridine was obtained.

2-Hydroxymethylimidazo[4,5-*b*]pyridine (III).

Neither the Phillips procedure (5), fusion with chloroacetic acid, nor heating with chloroacetic anhydride would convert II to the desired IV. Fusion with glycollic acid readily cyclized II to III in 81% yield. Crystals from water melted at 219-220°, unchanged by recrystallization from ethanol/cyclohexane.

Anal. Calcd. for C₇H₇N₃O: C, 56.36; H, 4.73; N, 28.17. Found: C, 56.24; H, 4.52; N, 28.30.

2-Chloromethylimidazo[4,5-*b*]pyridine Hydrochloride (IV).

Compound III (14.9 g., 0.1 mole) was dissolved/slurried in 25 ml. absolute ethanol. Dry hydrogen chloride was passed in as long as any precipitate formed. The product was collected, dried without purification, m.p. 239°, yield, 18.5 g. (100%). This III hydrochloride was suspended in 100 ml. of dry chloroform and refluxed with 35 ml. thionyl chloride for two hours. The slightly rose-colored slurry was filtered hot. The 2-chloromethylimidazo[4,5-*b*]pyridine hydrochloride (IV) was vacuum dried. A white powder, 19.6 g. (95%), melted at 255°. Without purification, it was suitable for conversion to amino derivatives. The free base was a very potent sternutator and produced underarm rash if there had been prior exposure to 2-chloromethylbenzimidazole (ARD). Compound IV was also very irritating.

2-(Dibutylaminomethyl)imidazo[4,5-*b*]pyridine (V).

By adding IV to five moles of the chosen secondary amine, refluxing for two hours, the aminomethyl compounds were isolated *via* the hydrochloride. Compound IV (14.2 g., 0.07 mole) was converted to V hydrochloride. This was converted to V by adding sodium bicarbonate to a cold dilute alcohol solution. Dried V was crystallized from hexane as soft, glistening platelets in 78% yield, M.P. 102-103°.

Anal. Calcd. for C₁₅H₂₄N₄: C, 69.26; H, 9.26; N, 21.48. Found: C, 69.39; H, 9.34; N, 21.53.

2-(Morpholinomethyl)imidazo[4,5-*b*]pyridine (VI).

After 16.3 g. (0.08 mole) IV was refluxed with 35 g. of morpholine, 100 ml. benzene precipitated VI hydrochloride. The free base, VI, was obtained as fine hard micro-needles after the second recrystallization from ethanol-cyclohexane, 85% yield, m.p. 166-167°.

Anal. Calcd. for C₁₁H₁₄N₄O: C, 60.59; H, 6.51; N, 25.66. Found: C, 60.50; H, 6.58; N, 25.89.

2-(Piperidinomethyl)imidazo[4,5-*b*]pyridine (VII).

The reaction product of 16.3 g. of IV and 34 g. of piperidine was precipitated as VII hydrochloride by addition of 100 ml. of hexane. The recovered VII was a buff tacky solid which required a second recrystallization from ethylcyclohexane to yield VII (52%), m.p. 154°.

Anal. Calcd. for C₁₂H₁₆N₄: C, 66.65; H, 7.45; N, 25.90. Found: C, 66.71; H, 7.34; N, 25.98.

6-Aminoimidazo[4,5-*b*]pyridine Dihydrochloride (VIII).

The conversion of 2-aminopyridine to 2-amino-5-nitropyridine

(X) was based on the procedure of Caldwell and Kornfeld (6). In a 2 mole scale synthesis, a yield of 66% was obtained as orange-yellow crystals from methanol. The 8% yield of 2-amino-3-nitropyridine was removed by steam distillation. Bromination of X by the Tschitschibabin and Tjashelowa (7) procedure on a one mole scale (139 g.) produced 198 g. (91%) of 2-amino-3-bromo-5-nitropyridine (XI), m.p. 219-220° after one crystallization from ethanol.

One-half mole (109 g.) of XI was aminated for 16 hours at 130-140°. The product crystallized once from 1-butanol melted at 258-259°. The 26 g. yield of 2,3-diamino-5-nitropyridine (XII) was only 36%.

Refluxing 15.4 g. (0.1 mole) of XII for two hours with 50 ml. of formic acid produced the formamide. The excess formic acid was removed under aspirator vacuum at 100°, 0.5 g. of sodium carbonate was added and the mixture was heated for two hours at 150°. The 6-nitroimidazo[4,5-*b*]pyridine (XIII) was extracted with boiling ethanol, and was recrystallized from ethanol (Norite) as pale buff, silky needles, m.p. 308-310°.

When catalytic hydrogenation failed, XIII was reduced by the Petrow and Saper (8) procedure using iron and alcoholic hydrogen chloride. The almost white VIII melted at 257-259°, yield from 3.2 g. XIII (0.02 mole) was 2.2 g. (55%).

Anal. Calcd. for $C_6H_8N_4Cl_2$: C, 34.75; H, 3.89; N, 27.06; Cl, 34.21. Found: C, 34.69; H, 3.95; N, 26.98; Cl, 34.42.

2-Amino-3-nitro-5-methylpyridine (XIV).

The procedure of Vaughan, *et al.*, (9) was used to nitrate 324 g. (3 moles) of 2-amino-5-methylpyridine. Two crystallizations from 3-pentanol yielded XIV, m.p. 190-191° in 64% yield.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.07; H, 4.62; N, 27.44. Found: C, 47.22; H, 4.59; N, 27.42.

2,3-Diamino-5-methylpyridine (XV).

Palladium on charcoal did not effectively hydrogenate XIV. The tacky product could neither be purified nor converted to an imidazole. The Petrow and Saper (8) procedure proceeded well. A buff product was obtained by distillation *in vacuo* of the dry reaction mixture. Crystallization from xylene-anisole yielded white clusters, m.p. 139-140°, yield 17.3 g., (86%). This diamine was less sensitive to air oxidation than II.

Anal. Calcd. for $C_6H_9N_3$: C, 58.52; H, 7.37; N, 34.12. Found: C, 58.70; H, 7.21; N, 34.07.

6-Methylimidazo[4,5-*b*]pyridine (XVI).

Formic acid was an inefficient agent for converting XV to the imidazole. Ethyl orthoformate, 35 ml., 10 g. of XV, one hour reflux, gave a crude product melting at 120-125°. Distillation at 5 mm and two crystallizations from xylene yielded a white product, m.p. 146-147°. The 8.3 g.-yield was 77%.

Anal. Calcd. for $C_7H_7N_3$: C, 63.14; H, 5.31; N, 31.55. Found: C, 63.07; H, 5.56; N, 31.38.

6-Imidazo[4,5-*b*]pyridyl Carboxylic Acid (XVII).

Compound XVI (2.66 g., 0.02 mole) dissolved in 5 ml. of water was refluxed for 15 minutes with 100 ml. of 0.4 M potassium permanganate. When the purple color disappeared, the mixture was acidified with dilute sulfuric acid and ether extracted.

Crystallization and recrystallization from pH 3 water (drop, dilute sulfuric acid) yielded 1.2 g. (36%) of XVII, m.p. 310-312°.

Anal. Calcd. for $C_7H_5N_3O_2$: C, 51.57; H, 3.10; N, 25.71. Found: C, 51.46; H, 3.18; N, 25.63.

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