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Synthesis of Fused Imidazo-heterocyclic Systems

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The reaction of phenylacyl bromide and a variety of α-aminoheterocycles was investigated to determine its applicability to the preparation of fused imidazo-heterocyclic systems. The imidazo[1,2-a]pyrazine, imidazo[1,2-b]pyridazine, and imidazo[1,2-a]-benzimidazole systems and some variations of the imidazo[1,2-a]pyridine, imidazo[2,1-b]-thiazole, imidazotriazine, imidazo[2,1-b]-1,3,4-thiadiazole systems are described.

A long term interest in the pharmacological activity of imidazole derivatives has led us to investigate the preparation of various fused imidazo-heterocyclic systems. While our work was in progress certain imidazo[1,2-a]pyridines were reported to have diuretic (1,2) and anti-inflammatory activity (3) while 5-nitro-2-furyl substituted imidazo[1,2-a]-pyridines and imidazo[1,2-a]pyrimidines were claimed as antibacterial and antiprotozoal agents (4).

A variety of routes have been introduced for synthesis of imidazo systems (5, 6, 7, 8, 9). The original procedure of Tschitschibabin (10) involving condensation of an aminoheterocycle and an α-halo aldehyde or ketone was deemed most adaptable to extension and this route has been used in the current work. In our experience the procedure of Djerassi and Pettit (11) using dimethylformamide and sodium bicarbonate does not offer any advantage over heating the reactants in alcohol.

The condensation of 2-aminopyridine with phenacyl bromide gave I (R = phenyl) readily, but 2-amino-6-hydroxypyridine, 2,6-diaminopyridine (12), 2,3-diaminopyridine, 2-amino-6-acetamidopyridine, and 2-amino-6-bromopyridine led to no isolable products. 2-Amino-5-nitropyridine has been cyclized to the imidazo[1,2-a]pyridine with 1,2-dichloroethyl ether (13). Attempts with *p*-chlorophenacyl bromide in dimethylformamide-sodium bicarbonate or with phenacyl bromide in ethanol were unsuccessful. Phenacyl bromide in acetone, however, afforded a small amount of 6-nitro-2-phenylimidazo[1,2-a]pyridine (Ia). It appears likely (14,15) that the phenacyliminopyridone (III) was isolated first with cyclization occurring during recrystallization. Only a trace of Ib was isolated from 2-amino-3-nitropyridine.

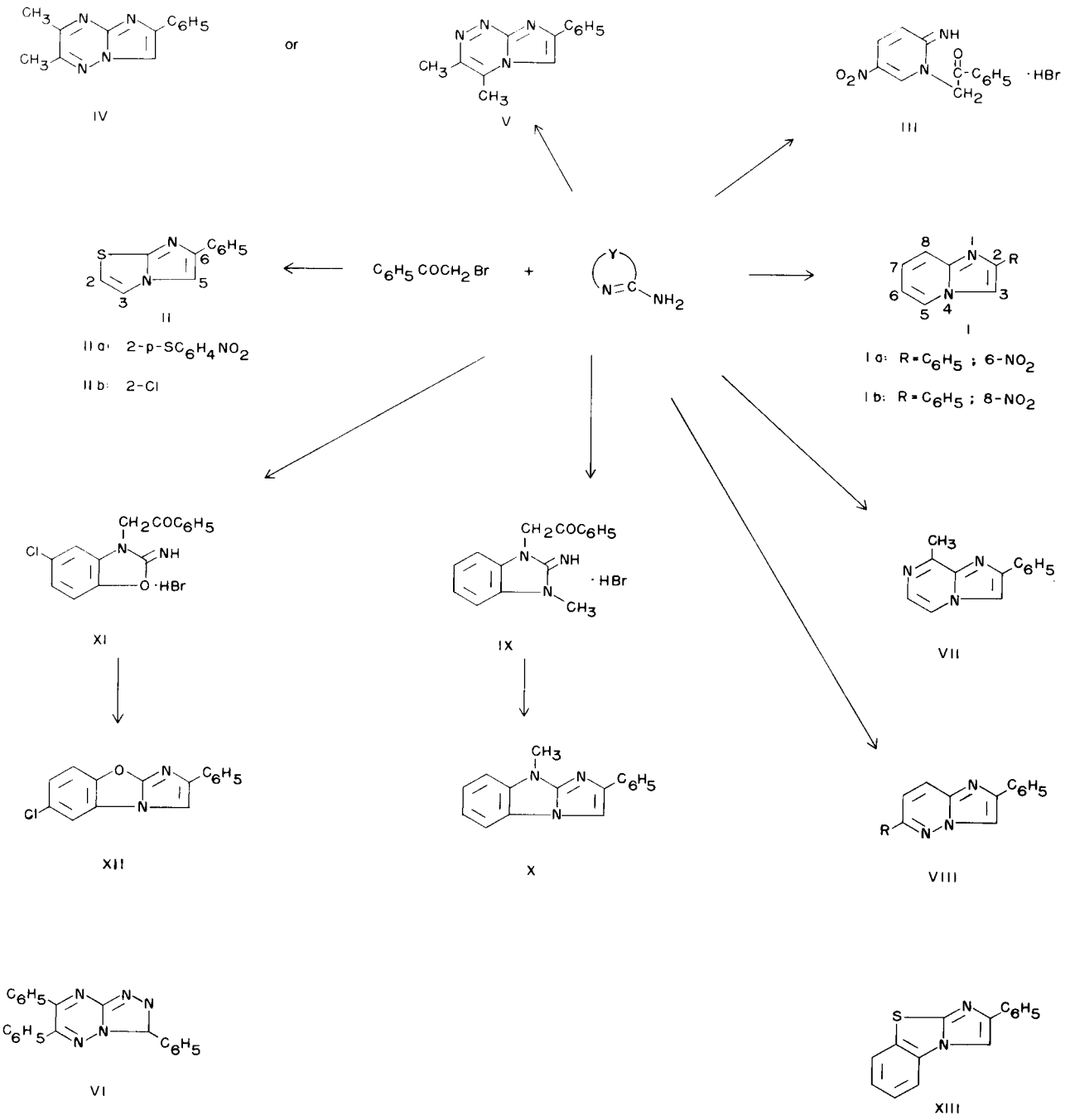
2-Aminopyrimidine gives imidazo[1,2-a]pyrimidines upon heating with phenacylhalides (16). However, our attempts to cyclize 2-amino-5-nitropyrimidine, 4-amino-6-chloropyrimidine, 2-methylthio-4-amino-6-chloropyrimidine, or 4-amino-6-acetamido pyrimidine with phenacyl bromide or 1,2-dichloroethyl ether failed.

The above results suggest that the electronic nature of substituents present in the aminoheterocyclic component may contribute to the success of the reaction. Further, although 2-aminothiazole is readily converted to imidazo[2,1-b]thiazoles (15), attempts with 2-amino-5-nitrothiazole and phenacyl bromide or 1,2-dichloroethyl ether failed. Similarly, 2-amino-5-*p*-nitrophenylmercaptothiazole afforded 2-(*p*-nitrophenylthio)-6-phenylimidazo[2,1-b]thiazole (IIa) but the conversion failed with 2-amino-5-*p*-nitrobenzenesulfonylthiazole. 2-Aminobenzothiazole gave the novel 2-phenylimidazo[2,1-b]benzothiazole XIII. 2-Chloro-6-phenylimidazo[2,1-b]thiazole (IIb) was readily prepared from the corresponding thiazole. The chlorine atom in IIb was unreactive.

3-Amino-5,6-dimethyl-1,2,4-triazine was converted to the imidazotriazine which may have either structure IV or V. This ring system from the phenyl substituted 1,2,4-triazines has been recently reported (17,18), though clarification of the direction of closure is not provided by this work. Since it has been shown (19,17) that the action of benzoyl chloride on 3-hydrazino-5,6-diphenyl-1,2,4-triazine leads to VI one might prefer structure IV. Recent work (20) on the direction of closure in substituted aminopyrimidines also favors IV.

The novel imidazo[1,2-a]pyrazine VII was readily formed from 2-amino-3-methylpyrazine. Surprisingly no product was obtained from 2-aminoquinoxaline under similar conditions. The pyridazine ring system was also amenable to this conversion, 3-amino-6-chloropyridazine and 3-amino-6-methoxypyridazine providing the imidazo[1,2-b]pyridazine system VIII. While this paper was in preparation this ring system was described by Yoneda and coworkers (21). Our data for VIII wherein R = Cl or OMe agree with that of the Japanese workers. VIII [R = $N(CH_2)_5$] was prepared by refluxing VIII (R = Cl) in excess piperidine. Attempts to convert VIII (R = Cl) to the primary amine with ethanolic ammonia yielded only starting material even at 125°/700 p.s.i. for 10 hours, while treatment at 170° under pressure for 15 hours gave intractable materials and a liquid $b._{3.5}$ 78° which was not characterized. Diamine derivatives VIII (R = $Et_2NCH_2CH_2NH$, $Me_2NCH_2CH_2CH_2NH$) were also prepared.

Recent work on the imidazo[2,1-b]-1,3,4-thiadiazole system (22,23) has been extended to the preparation of 2-(5-nitro-2-furyl-6-phenylimidazo[2,1-b]-1,3,4-thiadiazole from the active antibacterial agent 2-(5'-nitro-2'-furyl)-5-amino-1,3,4-thiadiazole (24), and a related compound from 2-amino-5-*p*-nitro-



phenylsulfonyl-1,3,4-thiadiazole. Interestingly the electron withdrawing group on this aminoheterocycle does not inhibit the reaction as was noted with the pyrimidines and thiazoles described above.

2-Aminobenzimidazole and phenacyl bromide gave no isolable product. However, 2-amino-1-methylbenzimidazole rapidly formed the intermediate ketimine IX which cyclized in hydrobromic acid to 2-phenyl-9*H*-imidazo[1,2-a]benzimidazole (X). Similarly 2-amino-5-chlorobenzoxazole formed XI, but this has resisted all attempts to effect the closure to XII.

Other aminoheterocycles which have proven resistant to this procedure have been various amino-1,3,5-triazines, 3-amino-5,8-diphenyl-1,2,4-triazocine, 2-amino-4,5-dimethyloxazole, 1-methyl-4-amino-6-benzyl-1*H*-pyrazolo[3,4-d]pyrimidine, and 1-methyl-3-amino-4-phenylpyrazole.

I (R = phenyl) has been shown (14,25,26) to have the 2- rather than 3-phenyl orientation. The structures for the materials described in this paper have similarly been assigned as 2-phenyl derivatives. The reaction is thus considered to proceed by initial attack of the halo ketone on the ring nitrogen followed by cyclization. This assignment is consistent with that used by the large majority of the workers in this area.

The only investigation made of the chemistry of these materials was to subject several of them to

catalytic hydrogenation. Thus 2-methylimidazo-[1,2-a]pyridine was converted to the 5,6,7,8-tetrahydro derivative with Pt in acetic acid (27). The 2-phenyl derivative behaved similarly however hydrogenation in methanol with Raney nickel was more satisfactory. The n.m.r. spectra of these materials in deuterochloroform clearly indicate that reduction takes place in the pyridine ring to give the 5,6,7,8-tetrahydro derivatives. Thus the peaks at low field for the pyridine ring protons (12) disappear in the products and a single peak for the imidazole proton and the multiplets for the four methylene groups are clearly evident. 6-Nitroimidazo[1,2-a]pyridine was converted to the 6-amino compound by reduction over Raney nickel in dimethyl formamide at low pressure and room temperature in contrast to the tin/hydrochloric acid procedure described by Takahashi (13).

These compounds have been evaluated in a variety of biological systems and possessed no outstanding activity, *per se*. However, the extension of the Tschitschibabin synthesis to other imidazoheterocyclic systems is continuing.

EXPERIMENTAL (28)

6-Nitro-2-phenylimidazo[1,2-a]pyridine (Ia).

A solution of 13.9 g. (0.1 mole) of 2-amino-5-nitropyridine and 19.9 g. (0.1 mole) of phenacyl bromide in 200 ml. of acetone was heated in a bomb for 4 hours at 65°. The mixture was cooled to room temperature and filtered to give 11.2 g. of pale yellow solid, m.p. 188-198°. Recrystallization several times from dimethylformamide gave the product, 2.0 g. (8.4%), m.p. 250-252°.

Anal. Calcd. for $C_{13}H_9N_3O_2$: C, 65.27; H, 3.79; N, 17.56. Found: C, 65.30; H, 3.50; N, 17.63.

8-Nitro-2-phenylimidazo[1,2-a]pyridine (Ib).

A mixture of 7 g. (0.05 mole) of 2-amino-3-nitropyridine and 10 g. (0.05 mole) of phenacyl bromide in about 300 ml. of ethanol was heated under reflux for 18 hours. Cooling to room temperature led to recovery of 3.4 g. (48.5%) of the starting material by filtration. The filtrate was concentrated to dryness *in vacuo* and the residue recrystallized from 2-propanol twice to give 2.5 g. of yellow solid, m.p. 234-236° (dec.) (prior sintering at 230°). This material was suspended in warm water made alkaline with aqueous sodium hydroxide and filtered. Two recrystallizations from 2-propanol gave a small amount of the product as a yellow solid, m.p. 140-142°.

Anal. Calcd. for $C_{13}H_9N_3O_2 \cdot {}^1/_2H_2O$: C, 62.90; H, 4.06; N, 16.93; H_2O, 3.63. Found: C, 62.91; H, 3.99; N, 17.28; H_2O, 3.25.

2-(*p*-Nitrophenylthio)-6-phenylimidazo[2,1-b]thiazole (IIa).

A mixture of 12.7 g. (0.05 mole) of 2-amino-5-*p*-nitrophenylmercaptothiazole and 10 g. (0.05 mole) of phenacyl bromide in 400 ml. of ethanol was heated under reflux for 6 hours. The mixture was filtered hot to give 10.6 g. of solid. Recrystallization from dimethylformamide gave 5.6 g. (26%) of the product as the hydrobromide salt, m.p. 285-288°.

Anal. Calcd. for $C_{17}H_{12}BrN_3O_2S_2$: C, 47.01; H, 2.79; N, 9.68. Found: C, 47.18; H, 2.85; N, 9.71.

2-Phenylimidazo[2,1-b]benzothiazole (XIII).

A solution of 15.0 g. (0.1 mole) of 2-aminobenzothiazole and 19.9 g. (0.1 mole) of phenacyl bromide in ethanol was heated under reflux for 3.5 hours and allowed to cool to room temperature. The white crystalline solid was removed by filtration and recrystallized from dimethylformamide to give 6 g. (18%) of the product as the hydrobromide salt, m.p. 267-270° (dec.) (prior sintering and change of crystal form from 245°).

Anal. Calcd. for $C_{15}H_{11}BrN_2S$: C, 54.39; H, 3.35; N, 8.46. Found: C, 54.23; H, 3.95; N, 8.68.

2-Chloro-6-phenylimidazo[2,1-b]thiazole (IIb).

A solution of 14.8 g. (0.1 mole) of 2-amino-5-chlorothiazole and 19.9 g. (0.1 mole) of phenacyl bromide in ethanol was heated under reflux for 24 hours. The mixture was allowed to cool to room temperature and filtered to give 13.8 g. of solid, m.p. 248-255° (dec.). The solid was suspended in water, treated with ammonium hydroxide and filtered to give 10 g. of product. Recrystallization from 2-propanol gave the pure material 7.6 g. (32%), m.p. 159-160.5°.

Anal. Calcd. for $C_{11}H_7ClN_2S$: C, 56.29; H, 3.01; N, 11.94. Found: C, 56.41; H, 2.93; N, 11.74.

2,3(or 3,4)-Dimethyl-6(or 7)-phenylimidazo[1,2-b or 2,1-c]-*as*-triazine (IV or V).

A suspension of 12.4 g. (0.1 mole) of 3-amino-5,6-dimethyl-1,2,4-triazine and 19.9 g. (0.1 mole) of phenacyl bromide in ethanol was heated under reflux for 6.5 hours, cooled to room temperature and filtered to give 17.7 g. of crude product. A portion of this material (5.7 g.) was recrystallized from ethanol to give 2.9 g. (9.5%) of pure product as the hydrobromide salt.

Anal. Calcd. for $C_{13}H_{13}BrN_4$: C, 51.16; H, 4.29; N, 18.36. Found: C, 51.42; H, 4.26; N, 18.35.

The remainder of the crude salt was dissolved in methanol, made alkaline with aqueous sodium hydroxide and poured into water to give 9.4 g. of solid. Recrystallization from ethanol provided 4 g. (18%) of product as the base, m.p. 218-219.5°.

Anal. Calcd. for $C_{13}H_{12}N_4$: C, 69.62; H, 5.40; N, 24.98. Found: C, 69.53; H, 5.26; N, 25.14.

8-Methyl-2-phenylimidazo[1,2-a]pyrazine (VII).

A mixture of 5.5 g. (0.05 mole) of 2-amino-3-methylpyrazine and 10 g. (0.05 mole) phenacyl bromide in ethanol was heated under reflux for 4 hours. The mixture filtered hot yielded 3.9 g. of white solid. Recrystallization from methanol provided the product as the hydrobromide salt, 2.5 g. (17%), m.p. 315-325° (dec.).

Anal. Calcd. for $C_{13}H_{12}BrN_3$: C, 53.81; H, 4.17; N, 14.48. Found: C, 54.12; H, 4.18; N, 14.60.

6-Chloro-2-phenylimidazo[1,2-b]pyridazine (VIII, R = Cl).

A mixture of 13 g. (0.1 mole) of 3-amino-6-chloropyridazine and 19.9 g. (0.1 mole) of phenacyl bromide in 500 ml. ethanol was heated under reflux for 3 hours, allowed to cool to room temperature, filtered and recrystallized from acetonitrile to give the product 9.7 g. (42%), m.p. 199-201°. Lit. (19) reports m.p. 200°.

Anal. Calcd. for $C_{12}H_8ClN_3$: C, 62.75; H, 3.51; N, 18.30. Found: C, 62.69; H, 3.55; N, 18.21.

2-Phenyl-6-piperidinoimidazo[1,2-b]pyridazine.

A solution of 8.7 g. of 6-chloro-2-phenylimidazo[1,2-b]pyridazine in excess piperidine was heated under reflux for 7 hours, poured into iced water, and the solid recrystallized from acetonitrile to give 6.7 g. (64%) of pure product, m.p. 168.5-170.5°. Lit. (19) reports 169°.

Anal. Calcd. for $C_{17}H_{18}N_4$: C, 73.35; H, 6.52; N, 20.13. Found: C, 73.57; H, 6.68; N, 20.05.

6-[(2-Diethylaminoethyl)amino]-2-phenylimidazo[1,2-b]pyridazine.

This material was prepared similarly to the piperidine analog above. Crystallization from acetonitrile and then from *n*-heptane gave the product (52%) as white plates, m.p. 116.5-118.5°.

Anal. Calcd. for $C_{18}H_{23}N_5$: C, 69.87; H, 7.49; N, 22.64. Found: C, 70.22; H, 7.14; N, 23.24.

6-[(3-Dimethylaminopropyl)amino]-2-phenylimidazo[1,2-b]pyridazine.

This material was prepared as indicated above. Crystallization from acetonitrile gave the product as white plates (69%), m.p. 169-170°.

Anal. Calcd. for $C_{17}H_{21}N_5$: C, 69.11; H, 7.17; N, 23.71. Found: C, 68.86; H, 6.89; N, 23.82.

2-(5-Nitro-2-furyl)-6-phenylimidazo[2,1-b]-1,3,4-thiadiazole.

A solution of 4.28 g. (0.02 mole) of 2-(5'-nitro-2'-furyl)-5-amino-1,3,4-thiadiazole and 4 g. (0.02 mole) of phenacyl bromide in dimethylformamide was heated for 4 hours at 85°. Cooling gave 1.7 g. of orange needles which upon recrystallization from dimethylformamide provided 1.3 g. (21%) of the desired product, m.p. > 300°.

Anal. Calcd. for $C_{14}H_8N_4O_3S$: C, 53.84; H, 2.58; N, 17.94. Found: C, 54.10; H, 2.69; N, 17.67.

2-[(*p*-Nitrophenyl)sulfonyl]-6-phenylimidazo[2,1-b]-1,3,4-thiadiazole.

A solution of 14.3 g. (0.05 mole) of 2-amino-5-*p*-nitrophenylsulfonyl-1,3,4-thiadiazole and 10 g. (0.05 mole) of phenacyl bromide in 500 ml. of acetone was heated under reflux for 19 hours. The acetone was removed *in vacuo* and the residue suspended in 500 ml. of ethanol and heated under reflux for 7 hours. Filtration and recrystallization from dimethylformamide afforded the product, 3.3 g. (17%), as yellow crystals, m.p. 277-279°.

Anal. Calcd. for $C_{18}H_{10}N_4O_4S_2$: C, 49.73; H, 2.61; N, 14.50. Found: C, 49.88; H, 2.46; N, 14.64.

2-(2-Imino-3-methyl-1-benzimidazolinyl)acetophenone (IX).

A solution of 7.4 g. (0.05 mole) of 2-amino-1-methylbenzimidazole and 10 g. (0.05 mole) of phenacyl bromide in 300 ml. of ethanol was stirred at room temperature. A heavy white solid formed shortly. Filtration gave 14.7 g. (83%) of product. A portion recrystallized from water gave the product as a white solid, m.p. crystals became green at 175°, sintered at 282° and melted at 292-295° (dec.).

Anal. Calcd. for $C_{16}H_{15}N_3O \cdot HBr \cdot 0.5H_2O$: C, 54.09; H, 4.83; N, 11.83; H_2O, 2.54. Found: C, 54.60; H, 4.79; N, 11.93; H_2O, 2.70.

2-Phenyl-9*H*-Imidazo[1,2-a]benzimidazole (X).

A suspension of 31 g. (0.087 mole) of the intermediate acetophenone in 500 ml. of 48% hydrobromic acid was heated under reflux for 6 hours, cooled, and filtered. The white solid was crystallized from methanol to give 12.5 g. (44%) of the product, m.p. 301-304° (dec., prior sintering).

Anal. Calcd. for $C_{16}H_{14}BrN_3$: C, 58.55; H, 4.30; N, 12.80; Br, 24.35. Found: C, 58.36; H, 4.53; N, 12.49; Br, 23.72.

2-[2-Imino-1-(6-chlorobenzoxazolinyl)]acetophenone (XI).

This material was prepared in a manner similar to the benzimidazole analog above. The product was obtained as the hydrobromide salt in 42% yield as a white powder, m.p. 265-267° (dec.).

Anal. Calcd. for $C_{15}H_{12}BrClN_2O_2$: C, 49.00; H, 3.29; N, 7.62. Found: C, 48.70; H, 3.05; N, 7.28.

5,6,7,8-Tetrahydro-2-phenylimidazo[1,2-a]pyridine.

A solution of 4.47 g. (0.023 mole) of 2-phenylimidazo[1,2-a]pyridine in 100 ml. methanol was hydrogenated at 25° and 50 p.s.i. over 1 g. Raney nickel. The mixture was filtered, the solvent removed *in vacuo* and the residue recrystallized from *n*-heptane to afford the product as a white powder, m.p. 104.5-106.5°, 3.9 g. (85%).

Anal. Calcd. for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 79.02; H, 7.15; N, 14.25.

6-Aminoimidazo[1,2-a]pyridine.

A solution of 5.7 g. of 6-nitroimidazo[1,2-a]pyridine in 250 ml. of dimethylformamide was hydrogenated at 27° and 50 p.s.i. over 2 g. Raney nickel. The mixture was filtered, the solvent removed *in vacuo* and to the residue added a saturated solution of hydrogen chloride in 2-propanol. The solid which resulted was recrystallized from methanol to give 1.8 g. (25%) of the product as the dihydrochloride salt, m.p. 239-243° (dec.).

Anal. Calcd. for $C_7H_9N_3Cl_2$: C, 40.80; H, 4.40; N, 20.39. Found: C, 40.94; H, 4.30; N, 20.14.

Acknowledgment.

The authors take this opportunity to thank Mr. Charles E. Childs and associates for microanalytical data, Dr. J. M. Vandenbelt and associates for the spectral data, and Mr. W. M. Pearlman for the hydrogenation experiments described herein.

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Received May 6, 1965 Ann Arbor, Michigan