3.5 hr. and then concentrated under reduced pressure and diluted with cold, dilute hydrochloric acid. After the resulting mixture had been extracted with ether, the ethereal extract was washed with aqueous sodium bicarbonate, dried, and concentrated. The residual colorless oil (92 mg.) contained[7] at least two components. Chromatography of an 80-mg. portion on 4 g. of Woelm alumina (activity grade II) separated 42 mg. of the more rapidly eluted component (eluted with benzene). Crystallization of this material from an ether–petroleum ether mixture afforded 26 mg. of **hydroxy ketal isopropyl ester 18** as white prisms, m.p. 112–113°. A mixture of this product with the starting methyl ester **14** melted at 88–94°. The product has infrared absorption[11] at 3450 (associated O–H) and 1706 cm.$^{-1}$ (hydrogen-bonded ester C═O) with intense ultraviolet[12] end absorption (ϵ 10,600 at 215 mμ) and weak absorption (ϵ 450 or less) in the region 250–270 mμ.

Anal. Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83; mol. wt., 360. Found: C, 69.93; H, 7.76; mol. wt., 360 (mass spectrum).

A New Indole Synthesis[1]

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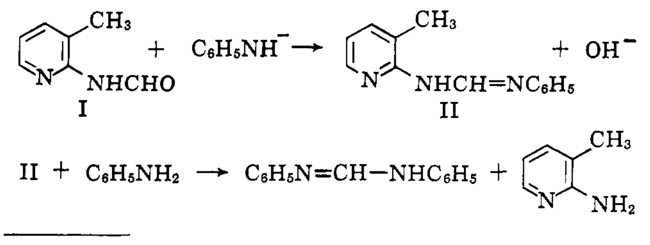
Cyclization of N-(3-methyl-2-pyridyl)-N′-methyl-N′-phenylformamidine and the corresponding isomers, 2-methyl-3-pyridyl- and 3-methyl-4-pyridylformamidines, in the presence of sodium N-methylanilide in boiling N-methylaniline furnished the three isomeric pyrrolopyridines (azaindoles). When this reaction was applied to N-(2-tolyl)-N′-methyl-N′-phenylformamidine in mineral oil at 300°, indole itself was obtained in over 75% yield.

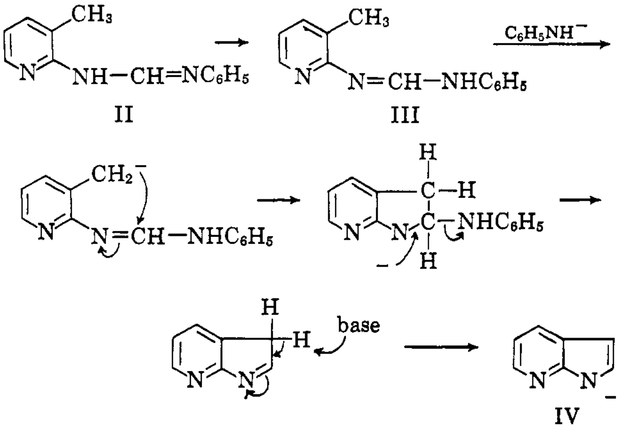
In connection with another problem, the need arose for a preparative synthesis of 1H-pyrrolo[2,3-*b*]pyridine (7-azaindole) that was adaptable for large-scale work. This compound was prepared by Robison[4] who heated a mixture of N-(3-methyl-2-pyridyl)formamide (I) with 6 equiv. of sodium anilide and 2 equiv. of potassium formate without solvent at 300° to obtain the desired product in about 45% yield on a 0.3 *M* scale. This method was patterned after one of Tyson's modifications of the Madelung synthesis[5] for preparing indole. Although Tyson did not establish the course of the reaction, his investigation revealed that the addition of potassium formate to the reaction mixture and the use of either potassium *o*-toluidide or sodium anilide rather than potassium *t*-butoxide helped to increase the yield of indole. The role of the potassium formate is not clear. Tyson suggested that the salt serves as a source of carbon monoxide *in situ* which reacts with the alkali metal toluidide to form the corresponding alkali *o*-formotoluidide which then condenses to form indole.

Repetition of Robison's work revealed that the reaction mixtures were almost intractable and rarely furnished the desired compound in the reported yield. It was found that, by incorporating several modifications including the use of mineral oil as a diluent, fairly consistent yields of 50–63% could be achieved (see Experimental section). In this work it was noted that considerable quantities of N,N′-diphenylformamidine were produced as a by-product, which may have arisen according to the following scheme.



Although the reaction of diarylamidines with aromatic amines has been shown by Roberts[6] to be acid catalyzed, the same authors also found that arylformimidates react slowly at room temperature with aromatic amines to furnish diarylformamidines in the presence of sodium *t*-butoxide.

It is also possible that the 7-azaindole was being formed by a base-catalyzed cyclization of II.



If this hypothesis were correct, then a more suitable precursor for the *in situ* formation of the mixed formamidine, II, should furnish 7-azaindole more readily. When ethyl N-(3-methyl-2-pyridyl)formimidate (V) was heated with 3 moles of sodium anilide in mineral oil at 300°, 7-azaindole was produced in 40% yield, thus obviating the use of potassium formate.

It was felt that the formamidine III was reacting with base in another sense to form the ion VI and that prevention of this reaction would substantially increase the yield of IV. Indeed, the use of sodium N-methylanilide permitted the reaction to be carried out at 200° with a concomitant increase in yield to 52%. The use of N-methylaniline thus has a twofold purpose in that it also prevents the formation of the tautomer II.

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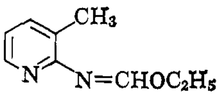
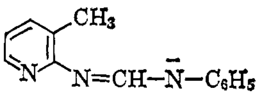
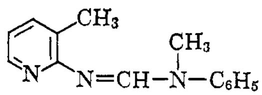
[4] M. M. Robinson and B. L. Robison, *J. Am. Chem. Soc.*, **77**, 6554 (1955); **77**, 457 (1955). Using this method, 6-methyl-7-azaindole and 4-methyl-7-azaindole were prepared in 13 and 24% yield, respectively, by ring closure of the apposite 2-formamidodimethylpyridines: A. Albert and R. E. Willette, *J. Chem. Soc.*, 4063 (1964).

[5] F. T. Tyson, *J. Am. Chem. Soc.*, **72**, 2801 (1950).

[6] R. M. Roberts, R. H. DeWolfe, and J. H. Ross, *ibid.*, **73**, 2277 (1951).


V


VI


VII

Under identical reaction conditions the yield fell to 38% at 300°, confirming the fact that 7-azaindole *is not stable at elevated temperatures in the presence* of strong base.[7]

Optimum conditions for the cyclization were realized when the preformed formamidine VII was used. This compound was prepared in 88% over-all yield by treating 2-amino-3-methylpyridine with ethyl orthoformate, followed by condensation of the resulting formimidate with N-methylaniline.[8] Treatment of VII with 1.5 equiv. of sodium N-methylanilide in refluxing N-methylaniline (198°) gave 7-azaindole in 80% yield.

The corresponding 1H-pyrrolo[3,2-*c*]pyridine (5-azaindole), and 1H-pyrrolo[3,2-*b*]pyridine (4-azaindole), were prepared by the same procedure in yields of 51 and 10%, respectively. It is probable that the instability of the compounds at the temperatures of the cyclization is responsible in part for the poorer yields.

Indole itself was prepared from N-(2-tolyl)-N′-methyl-N′-phenylformamidine. Cyclization did not proceed well at 200°, but at 300° occurred smoothly within 30 min. to afford indole in 76% yield. 6-Methylindole and 7-methylindole were prepared similarly.

Experimental

Ethyl N-(3-Methyl-2-pyridyl)formimidate (V).—A mixture of 327.3 g. (3.03 moles) of 2-amino-3-methylpyridine, 890 g. (6.0 moles) of triethyl orthoformate, and 6 ml. of 6 *N* alcoholic hydrochloric acid was heated under a distilling column for 5 hr. during which time 400 ml. of ethanol was collected while the pot temperature rose from 115 to 145°. The excess triethyl orthoformate was then distilled at atmospheric pressure to give 255 g. of the ortho ester, b.p. 144–146°. Vacuum distillation of the residue yielded 358 g. of the formimidate, b.p. 117–120° (20 mm.), n^{26}D 1.5220.[9] The pot residue amounted to 94 g. and was chiefly bis(3-methyl-2-pyridyl)formamidine, m.p. 85–86°, which, upon treatment with 98 g. of triethyl orthoformate, yielded an additional 90 g. of the desired formimidate. The total yield thus amounted to 448 g. or 90% of theory.

N-(3-Methyl-2-pyridyl)-N′-methyl-N′-phenylformamide (VII).—A solution of 281 g. (1.71 moles) of ethyl N-(3-methyl-2-pyridyl)formimidate and 366 g. (3.42 moles) of N-methylaniline was slowly heated. At 110° ethanol began to distil and, as the pot temperature reached 185°, about 90% of the theoretical amount of ethanol had been collected. Then the reaction mixture was subjected to vacuum distillation to recover 184 g. of N-methylaniline, b.p. 90–92° (20 mm.). The residue, which weighed 397 g. (calcd. 385 g.), solidified on standing and was almost pure unsymmetrical formamidine suitable for use in the next step.

A sample distilled at 154–155° (0.5 mm.), crystallized on standing, and, after recrystallization from *n*-pentane, melted at 68–69°.

Anal. Calcd. for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.39; H, 6.84; N, 18.78.

7-Azaindole (IV). A. From N-(3-Methyl-2-pyridyl)-N′-methyl-N′-phenylformamidine.—Under a nitrogen stream 20.5 g. (0.525 mole) of sodamide was added portionwise to 113 g. (1.05 moles) of N-methylaniline. This mixture was heated slowly and with efficient stirring to reflux and kept at reflux temperature for 30 min. A warm solution of 79.0 g. (0.35 mole) of N-(3-methyl-2-pyridyl)-N′-methyl-N′-phenylformamidine in 25 ml. of N-methylaniline was added during 15 min. Excess N-methylaniline was allowed to distil until a total of 130 ml. was collected during 20 min. After cooling, hydrolysis of the sodium compounds was effected by slow addition of 200 ml. of water. The mixture was extracted three times with ether and the extracts were dried over Drierite and then freed of ether. N-Methylanaline was removed by distillation through a 12-in. Claisen column at 88–90° (15 mm.). The residue was distilled under high vacuum to yield 33.1 g. (80%) of 7-azaindole, b.p. 100–118° (0.5 mm.).

The distillate was recrystallized from isopropyl acetate to yield 31.5 g., m.p. 104–106°, lit.[4] m.p. 105–106°.

B. From N-(3-Methyl-2-pyridyl)formamide.—A 12-l. flask, equipped with a stainless steel stirring rod and blade (Teflon blades and glass rods could not stand the load of the viscous reaction mixture) was charged with 1770 g. (19 moles) of aniline and 5 g. of nickel oxide [prepared by heating $Ni(NO_3)_2 \cdot 6H_2O$ over a Bunsen burner until the evolution of nitric oxide ceased]. The mixture was heated to 160° and 6 g. of sodium was added. The reaction is slow at first but then becomes exothermic and proceeds very rapidly. Therefore, after the reaction had definitely been initiated, external heating was discontinued and 239 g. of sodium was added at a rate to maintain the temperature between 160 and 170°. Then the mixture was heated at 180° until all of the sodium had reacted. A total of 1.5 l. of mineral oil was added and the temperature was raised to 280°, allowing the excess aniline to distil. A solid mixture of 408 g. (3.0 moles) of N-(3-methyl-2-pyridyl)formamide and 505 g. (6.0 moles) of potassium formate was added portionwise over a 10-min. period as rapidly as the heavy fuming permitted. The mixture was heated at 290–300° for 45 min. (It was essential to keep the mixture in suspension during this time.) After cooling to about 200° the mineral oil was decanted. The cooled, solid, black mass was covered with 4 l. of ether and then hydrolyzed by slow addition of 2 l. of water with slight cooling. After all of the solid had dissolved, the layers were separated and the aqueous layer was extracted twice with ether. The combined ethereal solutions were extracted with dilute hydrochloric acid. The acid solution was washed with ether and then made basic with 35% sodium hydroxide. The organic materials were extracted with ether and the extracts were dried over Drierite. After removal of the ether the residue was distilled and a 202-g. (57%) fraction boiling at 100–113° (0.5 mm.) was collected. The distillate was recrystallized (95% recovery) from isopropyl acetate and the 7-azaindole melted at 104–106°.

C. From Ethyl N-(3-Methyl-2-pyridyl)formimidate.—Under a nitrogen stream 39 g. (1.0 mole) of sodamide was added portionwise to 236 g. (2.2 moles) of N-methylaniline. This mixture was heated slowly and with efficient stirring to reflux and kept at reflux temperature for 30 min. Then the mixture was allowed to cool to 120° and 41 g. (0.25 mole) of ethyl N-(3-methyl-2-pyridyl)-formimidate was added carefully. The reaction was heated at 200° for 1 hr. while a total of 150 ml. of N-methylaniline was collected. After cooling the residue was worked up as described above in method A. A total of 15.5 g. (52%) of 7-azaindole, b.p. 100–112° (0.5 mm.), was collected and the recovery of N-methylaniline was 93%.

Ethyl N-(3-Methyl-4-pyridyl)formimidate.—Using the procedure for V, ethyl N-(3-methyl-4-pyridyl)formimidate was prepared in 88% yield from 4-amino-3-picoline, b.p. 141–143° (27 mm.), n^{25}D 1.5224. This was sufficiently pure for use in the next step.[9]

N-(3-Methyl-4-pyridyl)-N′-methyl-N′-phenylformamidine.—Heating ethyl N-(3-methyl-4-pyridyl)formimidate with 2 equiv. of N-methylaniline at 190° gave N-(3-methyl-4-pyridyl)-N′-methyl-N′-phenylformamidine in 81% yield, b.p. 160–170° (0.2 mm.), which, after recrystallization from *n*-heptane, melted at 60–61°.

Anal. Calcd. for $C_{14}H_{15}N_3$: C, 74.64; H, 6.71; N, 18.65. Found: C, 74.69; H, 6.85; N, 18.72.

5-Azaindole.—By treating 38.5 g. (0.17 mole) of N-(3-methyl-4-pyridyl)-N′-methyl-N′-phenylformamidine with 20 g. (0.51 mole) of sodamide and 109 g. (1.02 moles) of methylaniline as described above in the synthesis of 7-azaindole, method A, a total

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(7) O. Kruber, *Ber.*, **76**, 128 (1943).

(8) N. M. Roberts, *J. Am. Chem. Soc.*, **72**, 3603 (1950).

(9) This formimidate is not stable and it should be converted at once to the formamidine.

of 17.5 g. of crude 5-azaindole was obtained, b.p. 105–125° (0.1 mm.). The product was purified by crystallizing the oxalate from absolute alcohol and recrystallization from methanol–water to give 19.0 g. of 5-azaindole oxalate, m.p. 192–193° dec.

Anal. Calcd. from $C_7H_6N_2 \cdot C_2H_2O_4$: C, 51.92; H, 3.87. Found: C, 52.06; H, 4.01.

The free base was liberated and recrystallized from isopropyl acetate to give 10.2 g. (51%) of 5-azaindole, m.p. 112–113°, lit.[10] m.p. 111.5–112.5°.

Ethyl N-(2-Methyl-3-pyridyl)formimidate.—Ethyl N-(2-methyl-3-pyridyl)formimidate was prepared in 71% yield from 3-amino-2-methylpyridine, according to the procedure described for V [b.p. 104–105° (5.0 mm.), $n^{25}D$ 1.5207] and used in the following step.[9]

N-(2-Methyl-3-pyridyl)-N′-methyl-N′-phenylformamidine.—A solution of 48 g. (0.292 mole) of ethyl N-(2-methyl-3-pyridyl)-formimidate and 62.5 g. (0.584 mole) of N-methylaniline was heated for 4 hr. during which time the temperature rose slowly to 170°. Since only 7 ml. of ethanol was collected, the mixture was heated on a steam bath overnight. The excess N-methylaniline was removed under reduced pressure and the residue was fractionated to give 53.0 g. (81%), b.p. 135–137° (0.1 mm.). The distillate crystallized on standing and a sample recrystallized from *n*-hexane melted at 63–64°.

Anal. Calcd. for $C_{14}H_{15}N_3$: N, 18.64; neut. equiv., 225.3. Found: C, 18.63; neut. equiv., 225.0.

4-Azaindole.—A total of 51 g. (0.226 mole) of N-(2-methyl-3-pyridyl)-N′-methyl-N′-phenylformamidine was treated with 17.7 g. (0.452 mole) of sodamide in 97 g. (0.904 mole) of N-methylaniline according to the procedure described above for IV, method A.

The crude product, 6.3 g., distilled at 120–185° (5 mm.).

The distillate was converted to the oxalate in absolute alcohol. Recrystallization from water–methanol gave 4.6 g. of 4-azaindole oxalate, m.p. 201–202° dec.

Anal. Calcd. for $C_7H_6N_2 \cdot C_2H_2O_4$: neut. equiv., 104.1. Found: neut. equiv. (base), 107.0; neut. equiv. (acid), 105.6.

Conversion of the oxalate to the free base gave 2.9 g. of 4-azaindole, m.p. 127–128°, lit.[11] m.p. 127–128°.

N-(2-Tolyl)-N′-methyl-N′-phenylformamidine.—A solution of 57.3 g. (0.375 mole) of phosphorus oxychloride in 150 ml. of dry benzene was added dropwise to a solution of 100 g. (0.74 mole) of N-methylformanilide in 150 ml. of benzene. The mixture was stirred 4 hr. and allowed to stand at room temperature overnight. A solution of 40.5 g. (0.375 mole) of *o*-toluidine in 150 ml. of benzene was added at 33–35° over a period of 30 min. The mixture was stirred for 5 hr. at room temperature and then it was added rapidly to a solution of 170 ml. of 35% sodium hydroxide in 1 l. of ice–water. The layers were separated and the aqueous layer was re-extracted with 800 ml. of ether. The combined extracts were dried over potassium carbonate and the solvents were removed *in vacuo*. The residue was crystallized from 150 ml. of isopropyl alcohol. The yield was 56.0 g., m.p. 98–101°. Vacuum distillation of the filtrate furnished 53 g. of N-methylformanilide, b.p. 130° (15 mm.), and the residue yielded an additional 7.5 g. of product, m.p. 98–100° after recrystallization from isopropyl acetate. The total yield corresponds to 75%.

Anal. Calcd. for $C_{15}H_{16}N_2$: C, 80.35; H, 7.18; N, 12.45. Found: 80.16; H, 7.31; N, 12.74.

Indole.—Under a stream of nitrogen 19.5 g. (0.5 mole) of sodamide was carefully added to 107 g. (1.0 mole) of N-methylaniline. The addition was slightly exothermic. The mixture was heated slowly and with efficient stirring to boiling and refluxed for 30 min. Without cooling, 100 ml. of mineral oil was added and the internal temperature was raised to 290°, allowing the N-methylaniline to distil over. To this mixture 56.0 g. (0.25 mole) of N-(2-tolyl)-N′-methyl-N′-phenylformamidine was added over a 5-min. period and heating was continued at 300° for 35 min. When the temperature had dropped to about 100°, the mineral oil was decanted. The solid black residue was covered with 200 ml. of ether and hydrolyzed by slow addition of 100 ml. of water. The aqueous layer was extracted twice with ether. The combined extracts were dried over Drierite. The ether was removed and vacuum distillation of the residue gave 22.3 g. of indole (76.5%), b.p. 128–133° (28 mm.).

N-(2,6-Dimethylphenyl)-N′-methyl-N′-phenylformamidine.—This compound was prepared from 2,6-xylidine in 71% yield using the procedure described above for N-(2-tolyl)-N′-methyl-N′-phenylformamidine. The product was distilled at 147–165° (0.3 mm.) and the distillate was crystallized from *n*-pentane, m.p. 47–49°.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.54; H, 7.67; N, 12.07.

7-Methylindole.—The above formamidine was heated with 3 equiv. of sodium N-methylanilide at 250° for 15 min. following the procedure for indole. The product distilled at 83–86° (0.3 mm.) and recrystallization of the distillate gave an 80% yield of 7-methylindole, m.p. 84–85°, lit.[12] m.p. 85°.

N-(2,5-Dimethylphenyl)-N′-methyl-N′-phenylformamidine.—The product was obtained in 62% yield from 2,5-xylidine as described in the preparation of N-(2-tolyl)-N′-methyl-N′-phenylformamidine, b.p. 165–173° (0.3 mm.). The distillate was recrystallized from *n*-hexane, m.p. 79–81°.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.61; H, 7.52; N, 11.83.

6-Methylindole.—The above formamidine was cyclized in the presence of 3 equiv. of sodium N-methylanilide by heating at 250° for 15 min. as described above in the procedure for indole.

The product distilled at 148–155° (20 mm.), $n^{25}D$ 1.5987, and the yield was 65% of theory. The picrate melted at 159–160°, lit.[13] m.p. 160–161°.

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[12] O. Kruber, *Ber.*, **59**, 2753 (1926).

[13] W. H. F. Sasse, *J. Chem. Soc.*, 526 (1960).