tricia A. McVeigh).—β-Nitrostyrene[4] (7.46 g., 0.0500 mole) and indole (5.86 g., 0.0500 mole) were warmed on a steam-bath just long enough to form a clear, homogeneous, orange-red solution. The container was stoppered and set aside for two months. At the end of this period the solution had become a clear, immobile, reddish glass. The glass was dissolved in ethanol by warming on a steam-bath. Hot water was added to the point of incipient cloudiness and the solution was allowed to crystallize. Addition of water to the mother liquor from the first crystallization yielded a small second crop of crystals. The combined crude yield of tan-colored crystals was 10.4 g. (0.0391 mole, 78%). Two or three recrystallizations from ethanol–water yielded 3-(1-phenyl-2-nitroethyl)-indole (8.8 g., 0.033 mole, 66%), m.p. 99–100°.

(b) **From β-Nitrostyrene and Indole at Steam-bath Temperature.**—β-Nitrostyrene (13.9 g., 0.0932 mole) and indole (10.0 g., 0.0854 mole) were heated on a steam-bath for 4.5 hours until the odor of β-nitrostyrene was no longer evident. Crystallization of the reaction solution from ethanol yielded 3-(1-phenyl-2-nitroethyl)-indole (12.3 g., 0.0462 mole, 54%), m.p. 99–100°.

(c) **From β-Nitrostyrene and Indolemagnesium Iodide.**—Indolemagnesium iodide was prepared by the method of Baker[2] from magnesium turnings (1.36 g., 0.0560 g. atom), ethyl iodide (7.78 g., 0.0499 mole) in absolute ethyl ether (20 cc.) and indole (5.85 g., 0.0499 mole) in absolute ethyl ether (35 cc.). A solution of β-nitrostyrene (7.15 g., 0.0479 mole) in absolute ethyl ether (40 cc.) was added slowly, with stirring, to the ice-cooled solution of indolemagnesium iodide. During the addition a yellow-brown, gummy residue formed. The mixture was stirred for one-half hour at room temperature and then treated with a solution of acetic acid (60 cc.) in water (200 cc.). The aqueous and ethereal layers were separated. The aqueous layer was neutralized with sodium carbonate and then extracted three times with ether. The ethereal layer was washed with aqueous sodium carbonate solution until the evolution of carbon dioxide ceased. The ethereal layer was then combined with the ether extracts and the combined solution dried over calcium chloride. The ether solvent was replaced by ethanol and the solution treated with decolorizing charcoal. The solution was concentrated by vacuum distillation and allowed to crystallize at −10°. The crude product was recrystallized twice from ethanol–water, yielding white, rod-like crystals of 3-(1-phenyl-2-nitroethyl)-indole (5.0 g., 0.0188 mole, 39%), m.p. 99–100°; ν_{NH} (cm.$^{-1}$) 3480 in $CHCl_3$, 3380 in Nujol; ν_{NO_2} (cm.$^{-1}$) 1532 in Nujol, 1380 in $CHCl_3$.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.29): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.23; H, 5.29; N, 10.29.

3-(1-Phenyl-2-aminoethyl)-indole (IIIa).—3-(1-Phenyl-2-nitroethyl)-indole (5.7 g., 0.0214 mole) in absolute ethanol (60 cc.) and platinic oxide (0.100 g.) were treated with hydrogen at 36 p.s.i. in a Parr low pressure hydrogenation apparatus for ten hours. The catalyst was filtered off and the filtrate concentrated by vacuum distillation. The solution slowly turned deep brown in contact with air. Since cooling produced no crystals, the ethanol solvent was replaced by benzene, from which the product readily crystallized. Recrystallization yielded white 3-(1-phenyl-2-aminoethyl)-indole (2.8 g., 0.0118 mole, 55%), m.p. 130.5–131.5°; ν_{NH} (cm.$^{-1}$) 3510, 3400 in $CHCl_3$.

Anal. Calcd. for $C_{16}H_{16}N_2$ (236.30): C, 81.32; H, 6.83; N, 11.86. Found: C, 81.47, 81.59; H, 7.08, 6.95; N, 11.69.

3-(1-Phenyl-2-nitropropyl)-indole (IV).—β-Methyl-β-nitrostyrene[5,6] (5.33 g., 0.0327 mole) and indole (3.83 g., 0.0327 mole) were warmed on a steam-bath until a clear, orange-red solution was formed. The flask was stoppered and set aside for 70 days. The dark solution was treated with absolute ethanol and, after being allowed to evaporate overnight, deposited pink crystals (0.14 g.), m.p. 159–160°. Three more crops of crystals were increasingly impure. Recrystallization from ethanol–water, with charcoal, yielded a total of 1.53 g. (0.00546 mole, 16%), m.p. 159–161°. The analytical sample of 3-(1-phenyl-2-nitropropyl)-indole melted at 161–162°; ν_{NH} (cm.$^{-1}$) 3480 in $CHCl_3$, 3440 in CS_2, 3420 in Nujol; ν_{NO_2} (cm.$^{-1}$) 1557 or 1540 in Nujol, 1391 or 1362 in $CHCl_3$.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$ (280.31): C, 72.84; H, 5.75; N, 9.99. Found: C, 72.84, 73.07; H, 5.75, 6.06; N, 9.59, 9.98.

(4) D. E. Worrall in "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 413.

(5) E. Knoevenagel and L. Walter, *Ber.*, **37**, 4502 (1904).

(6) H. B. Hass, A. G. Susie and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

MINNEAPOLIS 14, MINNESOTA

[CONTRIBUTION FROM THE MOORE LABORATORY OF CHEMISTRY, AMHERST COLLEGE]

7-Azaindole. I. Synthesis and Conversion to 7-Azatryptophan and Other Derivatives

BY MICHAEL M. ROBISON AND BONNIE L. ROBISON

RECEIVED AUGUST 10, 1954

7-Azaindole (II) has been prepared in yields as high as 51% by the Madelung cyclization of 2-formamido-3-picoline (I) in the presence of sodium anilide and potassium formate. The indole was converted to 7-azagramine (III) which was used to alkylate acetamidomalonic ester. The product (IV) was converted to 7-azatryptophan (V) by hydrolysis and decarboxylation. That the side-chain was attached at the 3-position was shown by conversion of the intermediate gramine to 3-methyl-7-azaindole (VIII) which was prepared for comparison by cyclization of 2-formamido-3-ethylpyridine (XI). Several new derivatives of 3-ethylpyridine also are described.

7-Azaindole (II, 1-pyrrolo[2,3-b]pyridine) was obtained first from coal tar by Kruber,[1] who prepared derivatives and obtained evidence for the constitution of the compound by oxidation of its benzenesulfonamide to 2-benzenesulfonamidonicotinic acid and conversion of the latter to the known 2-aminonicotinic acid. The structure was confirmed later by the work of Clemo and Swan[2] who synthesized the substance in 3% yield by cyclization of 2-formamido-3-picoline in the presence of sodium ethoxide. These workers also prepared 2-methyl- and 2-ethyl-7-azaindole from the acetyl and propionyl derivatives of 2-amino-3-picoline. Miescher and Kägi[3,4] earlier prepared 7-azaoxindole and other compounds in which the pyrrole ring is partially oxidized, and Sucharda[5] synthesized several of the corresponding indoxyl compounds. Very little work has been reported, however, on the chemistry of 7-azaindole itself.

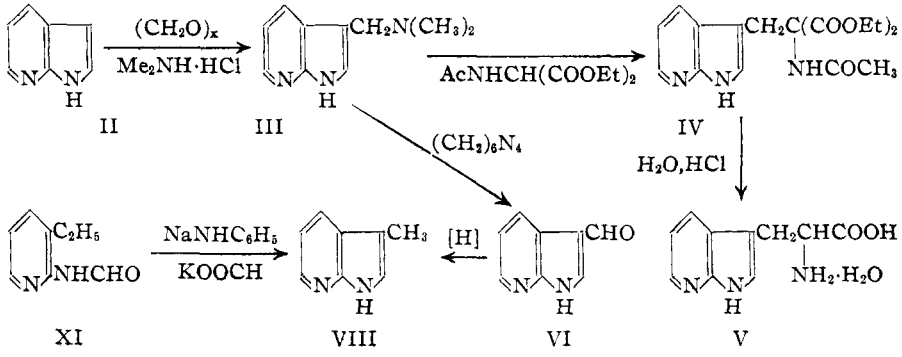
(1) O. Kruber, *Ber.*, **76**, 128 (1943).

(2) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 603 (1945).

(3) K. Miescher and H. Kägi, *Helv. Chim. Acta*, **24**, 1471 (1941).

(4) H. Kägi, *ibid.*, **24**, 141E (1941).

(5) E. Sucharda, *Roczniki Chem.*, **3**, 236 (1923); *C. A.*, **19**, 72 (1925).



Clemo[2] reported that the use of potassium ethoxide[6] instead of sodium ethoxide as a cyclization catalyst did not appreciably affect the yield of 7-azaindole. It was found in this Laboratory, however, that by the use of sodium anilide and potassium formate[7] yields of crude product as high as 51% could be obtained. The reaction could be run on a scale sufficient to produce 5–10 g. of material at one time. An attempt also was made to prepare 2-methyl-7-azaindole[2] by this method; 2-acetamido-3-picoline, however, apparently undergoes anilinolysis much more readily under these conditions than does the formamide. From the reaction was obtained an appreciable quantity of acetanilide but only an insignificant amount of impure product.

When 7-azaindole was treated with formaldehyde and dimethylamine in acetic acid[8] 3-dimethylaminomethyl-7-azaindole (III) was formed. It was later found that a better yield of this product could be obtained by treating the indole with paraformaldehyde and dimethylamine hydrochloride in refluxing *n*-butyl alcohol. Reaction of the product with acetamidomalonic ester in the presence of xylene and sodium hydroxide at 140°[9] produced ethyl α-acetamido-α-carbethoxy-β-(7-aza-3-indolyl)-propionate (IV).

Kruber[1] reported that 7-azaindole, unlike indole, is stable to acid but unstable to aqueous base. He found that the azacompound was not resinified even on prolonged heating with concentrated hydrochloric acid. A similar observation was made in this Laboratory; 7-azaskatole (VIII, *vide infra*) was recovered virtually quantitatively after a three-hour reflux period with the same acid. Accordingly, the intermediate IV was hydrolyzed and decarboxylated to 7-azatryptophan (V) in one step by treatment in this fashion.[10] The analysis of the product, which was obtained in 85% yield, indicated the presence of one mole of water per mole of aminoacid. Although the ultraviolet spectrum, which was very similar to that of 7-azagramine (Fig. 1), indicated that no cleavage of the ring had occurred in the hydrolysis, the water could not be removed by drying *in vacuo* at elevated temperatures. Therefore it was considered desirable to prepare a water-free derivative. From water a picrolonate was obtained which fulfilled this requirement.

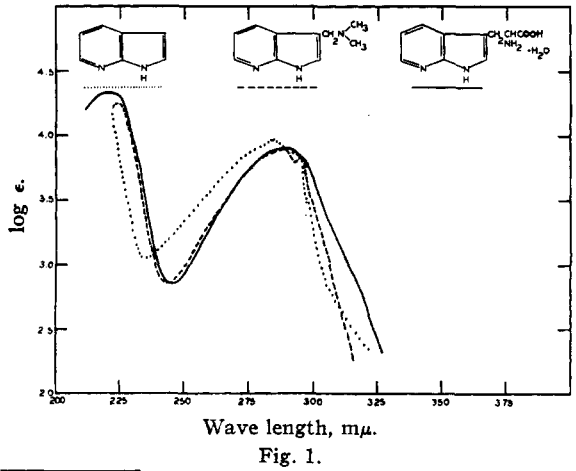


Fig. 1.

The aminoacid is being subjected to testing for biological activity. In preliminary tests it has been found that it serves as an inhibitor of tryptophan metabolism in *Tetrahymena pyriformis*[11] and that this effect is reversed by tryptophan. Detailed results will be reported elsewhere.

It was considered probable that, like indole, 7-azaindole would undergo the Mannich reaction at the 3-position; however, since little was known about the effects of the pyridine nitrogen on the pyrrole ring, it was necessary to confirm this assumption. To this end the Mannich base was converted to 7-azaindole-3-carboxaldehyde (VI) by reaction with hexamethylenetetramine in aqueous propionic acid.[12] Wolff–Kishner reduction of the aldehyde semicarbazone produced a methyl-7-azaindole which was different from 2-methyl-7-azaindole[2] but identical with 3-methyl-7-azaindole (VIII). The latter compound was prepared independently by the cyclization of 2-formamido-3-ethylpyridine (XI) in the presence of sodium anilide and potassium formate.

The 2-formamido-3-ethylpyridine precursor, 2-amino-3-ethylpyridine (X), was synthesized by amination of 3-ethylpyridine. Although cyclization of the formamide to an azaindole derivative provides direct evidence that the amine is 2-amino-3-ethylpyridine, rather than the 2,5-isomer, it was also converted to the known 2-chloronicotinic acid. This was done by transformation to 3-ethyl-2-pyridone (XII) and 2-chloro-3-ethylpyridine (XIII). The latter compound was oxidized to 2-chloronicotinic acid (XIV) which was prepared for comparison by the same sequence of reactions from 2-amino-3-picoline.[13]

(6) F. T. Tyson, THIS JOURNAL, **63**, 2024 (1941).
(7) F. T. Tyson, *ibid.*, **72**, 2801 (1950).
(8) H. Kuhn and O. Stein, *Ber.*, **70**, 567 (1937).
(9) E. E. Howe, A. J. Zambito, H. R. Snyder and M. Tishler, THIS JOURNAL, **67**, 38 (1945).
(10) *Cf.* N. F. Albertson, *ibid.*, **68**, 450 (1946).
(11) We wish to thank Drs. G. W. Kidder and Virginia C. Dewey of the Biological Laboratory, Amherst College, for performing these tests.
(12) H. R. Snyder, S. Swaminathan and H. J. Sims, THIS JOURNAL, **74**, 5110 (1952).
(13) O. Seide, *Ber.*, **57**, 1802 (1924).

Experimental[14,15]

7-Azaindole (II).—To sodium anilide, prepared by heating and stirring aniline (94.8 g.) and sodium hydride (21.6 g.) under nitrogen in a one-liter three-necked flask, 26.4 g. of dry potassium formate was added while the mixture was heated at 160°. After mixing, 20.4 g. of 2-formamido-3-picoline[2] was added and the temperature raised to 290–310° while stirring. Periodically the nitrogen stream and stirrer were stopped and aniline was distilled under water-pump vacuum, a total volume of 41–44 ml. being collected. The reaction was kept above 290° for 30–35 minutes; about 50 minutes usually elapsed between attainment of reaction temperature and cessation of heating, since the temperature usually fell during the distillations. The mixture was cooled under nitrogen, the tarry mass was decomposed quickly with water while cooling externally, and 51 ml. of glacial acetic acid was added to neutralize the strong base. The water layer was extracted with ether, the extracts dried, and the ether removed on the steam-bath. Distillation of the residue through a Vigreux column produced a low-boiling fraction, chiefly aniline, and a yellow solid intermixed with a red oil, b.p. 90–110° (1.5 mm.). The product was separated by filtration and pressed on filter paper. Refrigeration of the oil produced more solid; the total yield was 9.16 g. (51.8%). Recrystallization from cyclohexane produced 7.2 g. of light-yellow crystals, m.p. 102.5–104°. Evaporation of the mother liquors allowed recovery of 0.92 g. of cruder material. The analytical sample melted at 105–106° (reported[1,2] 107° and 106–107°).

Anal. Calcd. for $C_7H_6N_2$: C, 71.19; H, 5.09; N, 23.73. Found: C, 71.26; H, 5.06; N, 23.8.

Omission of the potassium formate, lowering of the reaction time to 15 minutes, or varying the quantities of potassium formate or sodium anilide either diminished or did not improve the yields.

7-Azaindole does not give the Ehrlich or pine-shaving reaction.[1,2] A sensitive color reaction is found on treatment of the compound with 5% sodium nitroprusside solution followed by dilute sodium hydroxide.[16] The dark blue-green color changes to blue, then violet, on addition of excess hydrochloric acid. Derivatives of the azaindole also give color tests in most cases, but these are usually less pronounced.

7-Azagramine (III).—In early experiments this was prepared by the method of Kuhn and Stein[3] except that the reaction period was extended to 72 hours and the product was salted out by addition of excess potassium carbonate, then washed with water and with ether. In the best reaction the yield of crude product was 54%, m.p. 145–151°. A sample was prepared for analysis by recrystallization from nitromethane and washing of the white blades with carbon tetrachloride, m.p. 157–158.5°.

Anal. Calcd. for $C_{10}H_{13}N_3$: C, 68.54; H, 7.48; N, 23.98. Found: C, 68.23; H, 7.63; N, 24.0.

It was later found that the following procedure afforded optimum yields. To 40 ml. of *n*-butyl alcohol were added 1.18 g. of 7-azaindole, 0.88 g. of dimethylamine hydrochloride and 0.33 g. of paraformaldehyde, and the mixture was refluxed for 30 minutes. The clear solution was then evaporated to dryness *in vacuo* and to the residue 10 ml. of water and 1 ml. of concentrated hydrochloric acid were added. The water layer was extracted with ether and then made strongly basic with potassium carbonate. The resulting precipitate, after drying and washing with ether, weighed 1.42 g. (81.1%) and melted at 144–152°.

Ethyl α-Acetamido-α-carbethoxy-β-(7-aza-3-indolyl)-propionate (IV).—Approximately 75–100 mg. of powdered sodium hydroxide was added to 3.50 g. of the unrecrystallized gramine and 4.34 g. of acetamidomalonic ester in 35 ml. of xylene, and the mixture was refluxed in a nitrogen atmosphere for nine hours. The hot liquid was filtered to remove sodium hydroxide and cooled. The resulting crystals were washed with benzene and with cyclohexane. There was obtained 5.02 g. (72.3%) of light-tan powder, m.p. 163.5–167°. A sample was purified for analysis by recrystallization from benzene; white filaments, m.p. 170–170.5°.

Anal. Calcd. for $C_{17}H_{21}N_3O_5$: C, 58.77; H, 6.09; N, 12.10. Found: C, 58.48; H, 6.13; N, 12.0.

α-Amino-β-(7-aza-3-indolyl)-propionic Acid (V).—Crude ester from the above preparation (3.47 g.) was dissolved in 20 ml. of concentrated hydrochloric acid and the mixture was refluxed for seven hours. The light-yellow liquid was evaporated to dryness *in vacuo*, the hygroscopic solid residue was dissolved in a few milliliters of water, and the solution was neutralized with dilute ammonium hydroxide. The aminoacid slowly precipitated as a cream-colored solid which was separated by filtration and washed with water. The yield of hydrated product was 84.8%, m.p. 262–264° dec. (uncor.). The compound was soluble in hot water but almost insoluble in alcohol and other organic solvents. It was first recrystallized from water from which it was deposited slowly in a poorly-defined crystal form. It was found that the addition of several volumes of acetone to the warm water solutions caused crystallization as white fluffy needles. The melting point, which varied with rate of heating, was 257–259° dec. (uncor.) when the block was pre-heated to 220°. The compound gave a positive Ninhydrin test.

Anal. Calcd. for $C_{10}H_{11}N_3O_2 \cdot H_2O$: C, 53.79; H, 5.88; N, 18.82. Found: C, 53.79; H, 6.03; N, 18.6.

7-Azatryptophan Picrolonate.—To a hot-water solution of 0.22 g. of the aminoacid was added approximately 0.3 g. of picrolonic acid, also in hot water. The resulting precipitate was filtered and recrystallized from water from which small yellow needles were deposited. The melting point was somewhat variable but was usually about 217–219°.

Anal. Calcd. for $C_{10}H_{11}N_3O_2 \cdot C_{10}H_8N_4O_5$: C, 51.17; H, 4.09; N, 20.88. Found: C, 50.86; H, 4.01; N, 21.1. Calcd. for $C_{10}H_{11}N_3O_2 \cdot H_2O \cdot C_{10}H_8N_4O_5$: C, 49.27; H, 4 35; N, 20.11.

7-Azaindole-3-carboxaldehyde (VI).—A solution of 7-azagramine (0.35 g.) and hexamethylenetetramine (0.28 g.) in 1.5 ml. of 66% propionic acid was added dropwise to a refluxing solution of 0.28 g. of hexamethylenetetramine in 1 ml. of the same solvent. The addition was carried out over a period of one hour and the solution was refluxed two hours more. The reaction, unlike that in the indole series,[12] was not complete in a shorter time. On addition of 6 ml. of water to the yellow solution and cooling, a white precipitate (0.16 g., 55%) of the aldehyde formed. Addition of base to the mother liquors produced a negligible amount of less pure material. The precipitate, which melted at 211–213.5°, was recrystallized from water. White needles were obtained, m.p. 214.5–215°. When the reaction was run on a scale five to ten times as large, yields were about 10% lower.

Anal. Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.15; N, 19.17. Found: C, 65.59; H, 4.36; N, 18.9.

7-Azaindole-3-carboxaldehyde Phenylhydrazone.—To a solution of 0.16 g. of VI in 15 ml. of boiling water a solution of phenylhydrazine in dilute aqueous acetic acid was added dropwise until no more precipitate formed. The mixture was cooled and 0.23 g. (89%) of phenylhydrazone was separated by filtration. The yellow product melted at 229–235° with decomposition. Recrystallization from ethanol–water produced golden plates, m.p. 231–232.5° dec.

Anal. Calcd. for $C_{14}H_{12}N_4$: C, 71.16; H, 5.13; N, 23.71. Found: C, 70.89; H, 5.33; N, 24.0.

7-Azaindole-3-carboxaldehyde Semicarbazone (VII).—To a solution of 0.80 g. of VI in 80 ml. of boiling water was added a solution of 1.35 g. of semicarbazide hydrochloride and 2.3 g. of sodium acetate trihydrate in water. After the formation of a transitory yellow coloration, a white solid precipitated. The mixture was heated on the steam-bath for 15 minutes, then cooled, and the product collected by filtration. The semicarbazone, which weighed 1.1 g. (99%), formed fine white filaments on recrystallization from a large volume of ethanol. These had no definite melting point, but browned gradually above 250° and decomposed completely between 290 and 310°.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.19; H, 4.47; N, 34.47. Found: C, 53.41; H, 4.52; N, 34.8.

7-Azaskatole (VIII) by Wolff–Kishner Reduction of VII.—The semicarbazone (1.25 g.) was added to a solution of 1.2

(14) Melting points are corrected unless designated (uncor.). These latter were taken on a Fisher–Johns melting-point block.

(15) Microanalyses by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(16) This test gives similar results with indole. *Cf.* Beilstein, "Handbuch der organischen Chemie," Verlag von Julius Springer, Berlin, 1935, Vol. XX, p. 307.

g. of sodium in 40 ml. of dry diethylene glycol and the mixture was heated under a nitrogen atmosphere. Reaction, as evidenced by gas evolution, set in at about 205° bath temperature. The bath was maintained at 210–225° for a period of one hour, though after the first 30 minutes the bubbling had ceased. During this period a small quantity of solid precipitated. The mixture was cooled and poured into 225 ml. of water containing 3.1 g. of glacial acetic acid. The resulting liquid, which contained solid in suspension, was extracted with ether. The ether extracts were washed with several portions of water, dried and evaporated. Sublimation of the tan residue at 120° (0.2 mm.) produced a white waxy solid which was dissolved in a few milliliters of dilute hydrochloric acid and reprecipitated with sodium bicarbonate solution to remove traces of glycol. There was thus obtained 0.45 g. (55%) of the skatole, m.p. 129–131°. After recrystallizations from *n*-hexane and from cyclohexane the white needles, which had only a faint odor reminiscent of that of 7-azaindole, melted at 130.5–132°. On admixture with 2-methyl-7-azaindole[2] (m.p. 134–135.5°) the sample melted at 91–105°.

Anal. Calcd. for $C_8H_8N_2$: C, 72.69; H, 6.11; N, 21.20. Found: C, 72.74; H, 6.17; N, 20.8.

2-Amino-3-ethylpyridine (X).—To 71.4 g. of 3-ethylpyridine[17] in 200 ml. of dry *p*-cymene 40 g. of finely-powdered commercial sodium amide was added. The mixture was heated with occasional shaking for nine hours at 150–155° in a metal-bath, cooled, and cautiously decomposed with water. It was then acidified with concentrated hydrochloric acid, the layers were separated, and the water layer was washed with several portions of ether. The aqueous layer was made strongly basic with solid sodium hydroxide and the resulting dark oil was extracted into ether. The extracts were dried, the ether removed, and a fraction boiling at 122.5–128.5° (18 mm.) was collected. On chilling, the 60.4 g. of distillate solidified to produce white crystals intermixed with light-yellow oil. The mixture was filtered and washed with low-boiling petroleum ether as quickly as possible. In the impure condition the solid tended to liquefy on exposure to the moisture of the air and much material was lost in the separation. It is probable that the oil is a mixture of 2-amino-3-ethylpyridine and 2-amino-5-ethylpyridine,[18] but it was not investigated further. The solid on recrystallization from low-boiling petroleum ether formed large silvery plates, m.p. 43–45°. The amine is not very soluble in water but liquefies immediately on contact with it.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.80; H, 8.27; N, 22.93. Found: C, 69.04; H, 8.29; N, 23.0.

2-Formamido-3-ethylpyridine (XI).—This compound was prepared by a modification of the method for the corresponding picoline.[2] At the end of the reaction period low-boiling materials were removed by distillation up to 40° (20 mm.) and the residue was cooled. The resulting moist white crystals were pressed on filter paper and then washed with water. From 12.4 g. of amine there was obtained, after one recrystallization from cyclohexane, 6.75 g. (44.3%) of white needles, m.p. 113–114.5°. The analytical sample had the same melting point.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.97; H, 6.72; N, 18.66. Found: C, 64.31; H, 6.64; N, 18.7.

When the amine was formulated directly as obtained from the distillation, only the above product was isolated, but in greatly reduced yield.

(17) T. I. Fand and C. F. Lutomski, THIS JOURNAL, **71**, 2931 (1949).

(18) *Cf.* A. E. Chichibabin and A. W. Kirsanov, *Ber.*, **57**, 1163 (1924), who obtained approximately equal quantities of the two analogous isomers on amination of nicotine.

7-Azaskatole (VIII) by Cyclization of XI.—The formamide (9.40 g.) was cyclized by the procedure for 7-azaindole, using 39.5 g. of aniline, 9.0 g. of sodium hydride and 11.0 g. of potassium formate. In the final distillation a fraction with b.p. 67–103° (0.4 mm.) was collected which crystallized partially on cooling. The solid was separated by filtration and washed with cyclohexane; yield 1.33 g. (16.1%), m.p. 126–130°. Recrystallization from the same solvent produced white needles, m.p. 131.5–133°. On admixture with the skatole obtained from the reduction the sample melted at 130.5–132.5°. The ultraviolet spectra of the two samples were essentially identical.

Treatment of the Skatole with Acid.—A 400-mg. sample of compound obtained from the cyclization (m.p. 130.5–132°) was dissolved in 5 ml. of concentrated hydrochloric acid and the mixture refluxed three hours. The colorless solution was evaporated to dryness *in vacuo*, the residue dissolved in a few milliliters of water and the solution neutralized with sodium bicarbonate. The suspension was extracted with ether and the ether dried and evaporated. The white crystalline residue weighed 385 mg. and had m.p. 130.5–133° both alone and on admixture with untreated starting material.

3-Ethyl-2-pyridone (XII).—The amine (14.25 g., m.p. 42.5–44°) was hydrolyzed by the method of Seide.[13] On addition of sodium carbonate to the reaction mixture, about 4 g. of white needles crystallized. These were apparently product with water of crystallization; on slow heating they melted at 120–121.5°, but on rapid heating at lower temperatures. After drying *in vacuo* they became dull in appearance and melted at the above temperature irrespective of rate of heating. The filtrate from the crystals was evaporated and treated as in the reference. The remainder of the product was obtained as a fraction of boiling point 183–186° (17 mm.) and melting point 119.5–121.5°. The total weight of dry product was 12.1 g. (84.3%). From cyclohexane a sample for analysis was obtained; shiny plates, m.p. 120.5–121.5°.

Anal. Calcd. for C_7H_9NO: C, 68.26; H, 7.38; N, 11.37. Found: C, 68.40; H, 7.42; N, 11.5.

2-Chloro-3-ethylpyridine (XIII).—This substance was also prepared by the method of Seide, except that the reaction period was increased to 3.5 hours, since hydrogen chloride evolution appeared to be slower than with the methyl compound. From 11.24 g. of 3-ethyl-2-pyridone there was obtained 4.74 g. (36.6%) of colorless oil, b.p. 98–100° (19 mm.), $n^{20}D$ 1.5270.

Anal. Calcd. for C_7H_8NCl: C, 59.33; H, 5.70; N, 9.89; Cl, 25.09. Found: C, 59.55; H, 5.55; N, 9.85; Cl, 24.9.

Oxidation of the Chloroethylpyridine.—A mixture of 3.70 g. of the chloro compound and 20 g. of potassium permanganate in 500 ml. of water was refluxed two hours. The manganese dioxide was removed by filtration and washed with boiling water and the combined aqueous solutions were neutralized with dilute sulfuric acid. Evaporation of the solution to 150 ml. and addition of hydrochloric acid to *p*H 1–2 produced white crystals. After recrystallization from water the product weighed 2.83 g. (68.5%). Both alone and on admixture with 2-chloronicotinic acid (prepared from 2-amino-3-picoline) the material melted at 194° with decomposition when heated rapidly in a sealed capillary (reported[13] m.p. 193°).

Ultraviolet Spectra.—All spectra were measured on a Beckman model DU quartz spectrophotometer. Compounds were made up to 10^{-4} molar concentration in cyclohexane, with the exception of the tryptophan, whose spectrum was measured from a water solution of the same concentration.

AMHERST, MASSACHUSETTS