2.5 ml. of 1.0 *N* ethanolic KOH solution. After brief shaking 5.0-ml. portions of 1.0 *N* ethanolic HCl were added and the solutions diluted to 25.0 ml. Portions of the solutions were centrifuged and the spectra run against similarly prepared blanks.

D.—The double reverse was achieved by treating a 5.0-ml. aliquot of the reverse (acidic) solution with 5.0 ml. of 1.0 *N* ethanolic KOH, diluting to 25.0 ml., centrifuging and running against a similarly prepared blank.

Anaerobic Attempt to Recover Flavothebaone from Dilute Base.—A stock solution of flavothebaone was de-oxygenated with N_2 for 0.5 hour as was an ethanolic KOH solution. Some of the stock solution was pipetted into the KOH solution while continuing to sweep with N_2. The solution turned orange-yellow but became light yellow after a few minutes. An evacuated gas cell was attached to the system and a portion of the solution was thereby withdrawn. The ultraviolet spectrum of this yellow sample was the same as those of the red-brown solutions obtained without the above precautions. A portion of the alkaline solution was poured into ethanolic H_2SO_4, centrifuged and the spectrum taken. It was the same as the spectrum given by flavothebaone after acidification of the basic solution as listed in Table I.

ITHACA, N. Y.

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

7-Azaindole. IV. The Hydrogenation of 7-Azaindole and Related Compounds[1,2]

BY MICHAEL M. ROBISON, FLORENCE P. BUTLER AND BONNIE L. ROBISON

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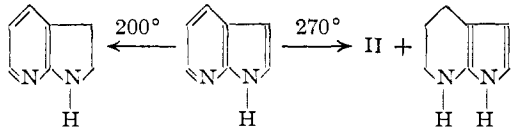
High-pressure hydrogenation of 7-azaindole (I) in neutral medium at 200° produces 2,3-dihydro-7-azaindole (II), while at higher temperatures the pyrroline ring is cleaved to yield 2-amino-3-ethylpyridine (IV). In acid medium, however, the ring is hydrogenated at atmospheric temperature and pressure to form 2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]pyridine (VI). The structure of this product was demonstrated by comparison with the corresponding hexahydro compounds obtained from the reductions of 1-methyl-7-azaindole (VII) and 7-methyl-7H-pyrrolo[2,3-b]pyridine (IX). 1,7-Dimethyl-1H-pyrrolo[2.3-b]pyridinium iodide (XV), on the other hand, reacts with five moles of hydrogen under similar conditions and 1-methyl-3-(2-methylaminoethyl)-piperidine hydroiodide (XVI) is formed. Miscellaneous derivatives of 7-azaindole including a number resulting from ring closure across the 1- and 7-positions are also described.

In 1943, Kruber[3] attempted to cleave the pyrrole ring of 7-azaindole (I) by high-pressure hydrogenolysis with a nickel catalyst in decalin solution. He reported that the pyrrolopyridine, unlike indole which can be cleaved to form *o*-ethylaniline,[4] reacts with one mole of hydrogen at 200° to form 2,3-dihydro-7-azaindole (II), and that at 250–270° a tetrahydroazaindole is produced as well. On the basis of its formation of a dibenzoyl derivative, Kruber proposed the structure 4,5,6,7-tetrahydro-7-azaindole (III) for the latter, but no conclusive evidence was offered for the structure of either hydrogenation product. An interest in "7-azaindoline" as an intermediate for the preparation of 7-



II I III

azaindoles substituted in the pyridine ring led us to reinvestigate the course of these hydrogenations and to extend the investigation to related reductions.

Hydrogenation of 7-azaindole at the prescribed[3] temperature and pressure with an aged W-4 Raney nickel catalyst[5] afforded a dihydro compound apparently identical with that described by Kruber. Evidence in support of the azaindoline structure was obtained from the ultraviolet spectrum of the compound (Fig. 1). The absorption maxima in the

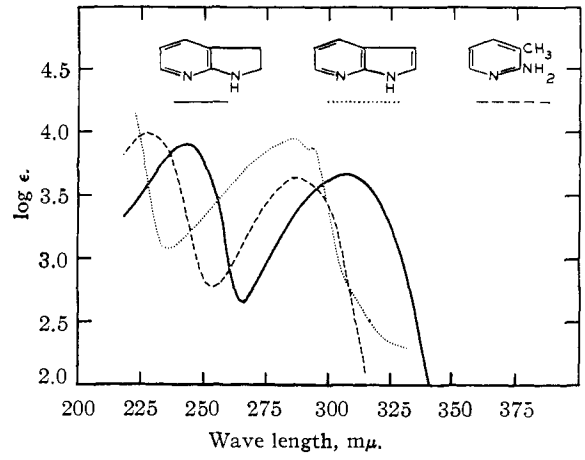


Fig. 1.

spectrum of the dihydro derivative show a bathochromic shift relative to the 7-azaindole absorption and the spectrum of II is more comparable to that of 2-amino-3-picoline, although the peaks in the latter spectrum also occur at a shorter wave length. Similar relationships are noted between the spectra of 2-methylindole,[6] 2-methylindoline[6] and *o*-toluidine[7] and between those of indene and hydrindene.[8] Although such a comparison does not provide conclusive evidence for the 2,3-dihydro structure, it does lend strong support to such a formulation. Attempts at substitution reactions in the pyridine ring of the dihydro compound are anticipated and these, if successful, will serve to confirm the structure.

In this Laboratory it was found that hydrogena-

(1) This investigation was supported by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Preceding paper, M. M. Robison and B. L. Robison, THIS JOURNAL, **78**, 1247 (1956).

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

(4) J. Von Braun, O. Bayer and G. Blessing, *ibid.*, **57**, 392 (1924).

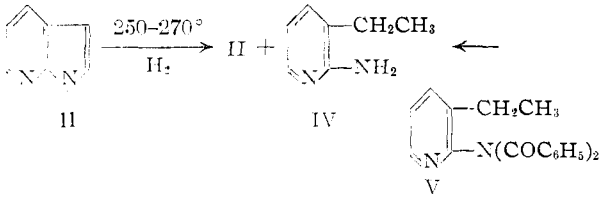
(5) A. A. Pavlic and H. Adkins, THIS JOURNAL, **68**, 1471 (1946).

(6) H. Kondo and H. Katsura, *Ber.*, **73**, 1424 (1940).

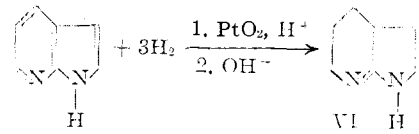
(7) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

(8) R. A. Morton and A. J. A. De Gouveia, *J. Chem. Soc.*, 911 (1934).

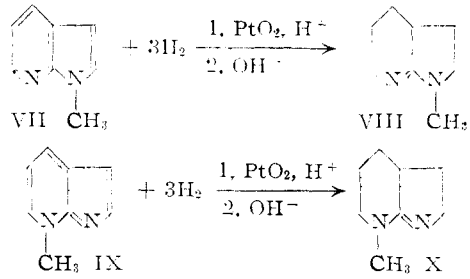
tion of azaindole at 250–270° afforded a mixture of the dihydro compound and a slightly more volatile material, as reported by Kruber.[3] Although distillation equipment capable of effecting a completely clean separation was not available, the ultraviolet spectra of the lower-boiling fractions were measured. These spectra were inconsistent with the pyrrole structure but corresponded very closely to the spectrum of 2-amino-3-picoline (see Fig. 1 and Experimental). The aminopyridine derivative likely to be formed in the reaction would be the known[9] 2-amino-3-ethylpyridine (IV) resulting from hydrogenolysis of the pyrrole ring and it was found that the low-boiling fractions did consist mainly of this "tetrahydro compound" contaminated by the 7-azaindoline. The identity of the purified crystalline material was demonstrated by mixture melting point of the amine and of its picrate with authentic samples of these compounds. Further, since 2-amino-3-picoline[10] and 2-aminopyridine[11] readily form dibenzoyl derivatives, it seemed possible that the "tetrahydro derivative" of Kruber was actually the hydrogenolysis product. The dibenzoyl derivative V melted at 166°, in fair agreement with the melting point (168°) reported by Kruber, but the discrepancies in the physical constants of the amine itself and in the melting points of the picrate (210.5°, reported[3] m.p. 200°) make it impossible to state with certainty that the products were actually the same.



A number of early experiments were directed toward the preparation of 7-azaindoline (II) under milder conditions. It has been reported[12] that an N-carbethoxy group in pyrrole derivatives greatly facilitates hydrogenation, and an unsuccessful attempt was made to hydrogenate 1-carbethoxy-7-azaindole at atmospheric pressure with the active W-4 Raney nickel.[5] 7-Azaindole also was recovered unchanged after prolonged treatment with refluxing ethereal lithium aluminum hydride, in agreement with results observed with indole itself.[13] In a further search for mild reduction conditions hydrogenation in acid medium was tried, since the pyridine ring undergoes facile reduction in such circumstances.[14] It was found that 7-azaindole reacts with 3 moles of hydrogen at atmospheric temperature and pressure when stirred with Adams catalyst in aqueous ethanolic hydrochloric acid. The product, which is considered to be 2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]pyridine (VI), is a strong base ($pK_b \sim 2.3$) and has an



intense infrared absorption band, attributable to the >C=N— stretching vibration, at 1652 cm.$^{-1}$ (KBr disk) or 1635 cm.$^{-1}$ ($CHCl_3$ solution). In an effort to provide closely-related spectral models to ascertain the position of the >C=N— bond, 1-methyl-7-azaindole (VII) and 7-methyl-7H-pyrrolo[2,3-b]pyridine (IX)[15] were also hydrogenated. The products were assigned the structures 1-methyl-2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]-pyridine (VIII) and 7-methyl-2,3,3a,4,5,6-hexahydro-7H-pyrrolo[2,3-b]pyridine (X) on the bases of the absence of >NH stretching absorptions in their infrared spectra and the occurrence of



>C=N— bands at 1657 and 1615 cm.$^{-1}$, respectively (pure liquids), or at 1652 and 1610 cm.$^{-1}$ (chloroform solutions). The closer agreement of the >C=N— absorption frequencies in the spectra of VI and VIII is at least strongly suggestive of the $\Delta^{7(7a)}$-structure, rather than the $\Delta^{1(7a)}$-structure corresponding to X. Further support for this formulation is to be found in a thorough-going series of investigations by Witkop,[16] who has found that the >C=N— absorption of hexahydroindole (XI) occurs at a lower frequency (1647 cm.$^{-1}$) than that of octahydroquinoline (XII, 1658 cm.$^{-1}$) and who has noted further that the corresponding hydrochlorides exhibit $>C{=}\overset{+}{N}H$ absorptions at 1684 and 1695 cm.$^{-1}$, respectively. The hydrochloride of VI shows absorption at 1684 cm.$^{-1}$ (KBr) and is lacking an "immonium band" in the 4.5–5.5 μ region. The absence of such a band is expected for a cyclic amidine of this type.[16c]

Further investigations of VI included dehydrogenation with palladium-on-charcoal. That the ring system had not been ruptured in the reduction was demonstrated by the formation of 7-azaindole. Early experiments also included benzoylation by several methods. From all of these a product was isolated whose analysis corresponded to the *di-*

(9) M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 457 (1955).

(10) O. Seide, *Ber.*, **57**, 1802 (1924).

(11) E. H. Huntress and H. C. Walter, *J. Org. Chem.*, **13**, 735 (1948).

(12) H. Adkins and H. L. Coonradt, THIS JOURNAL, **63**, 1563 (1941).

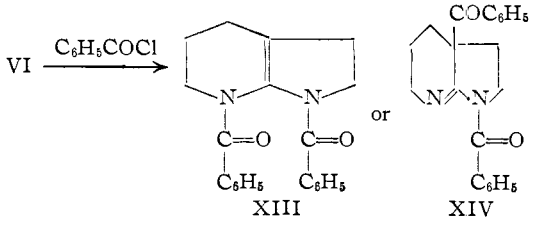
(13) P. L. Julian and H. C. Printy, *ibid.*, **71**, 3206 (1949).

(14) H. S. Mosher in Elderfield's "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. 1, p. 633.

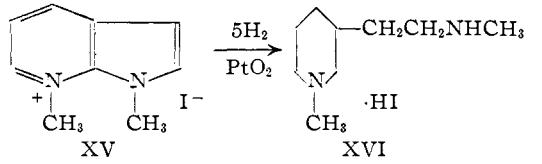
(15) M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 6554 (1955).

(16) (a) B. Witkop, *ibid.*, **78**, 2873 (1956); (b) **76**, 5597 (1954); (c) *Experientia*, **10**, 420 (1954).

benzoyl derivative of VI. In contrast to these results neither VIII nor X would form benzoyl derivatives under similar conditions. The structure of the acylation product is not clear. On the basis of structure VI, possibilities include either XIII or XIV for the derivative. On hydrolysis in concentrated hydrochloric acid an 87% yield of benzoic acid was obtained from the material, though the amine itself could not be isolated. Further experiments, however, demonstrated that the amine is relatively unstable to aqueous acid or base. The infrared spectrum of the dibenzoyl derivative provides no conclusive evidence for either structure, though it seems to favor structure XIV, since in the double-bond stretching region two strong absorptions are noted at 1635 and 1677 cm.$^{-1}$ as well as a shoulder at 1650 cm.$^{-1}$. On the basis of the available evidence, however, the exact structure must remain in doubt. In conjunction with the benzoylation studies, it may be noted that the amine was found to react in a 1:1 molar ratio with phenyl isocyanate. This result is in agreement with the proposed structure.



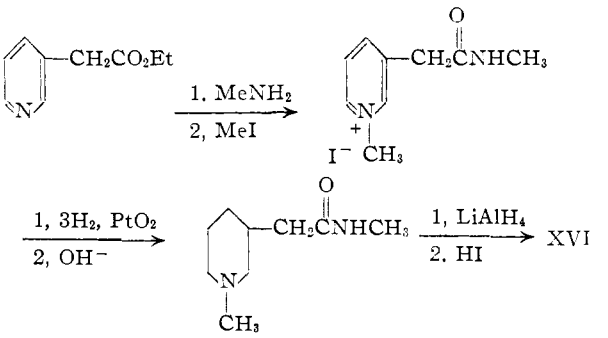
As an extension of the above reductions it was of interest to investigate the course of hydrogenation of 1,7-dimethyl-1H-pyrrolo[2,3-b]pyridinium iodide (XV). Rather surprisingly, at atmospheric temperature and pressure this compound absorbed



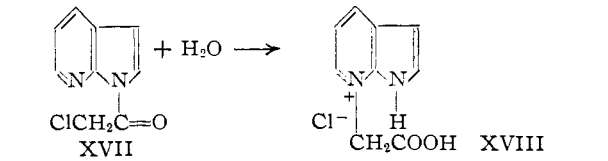
a fourth mole of hydrogen as rapidly as the first three and a fifth mole somewhat more slowly. Further, addition of hydriodic acid to the aqueous ethanol solutions completely prevented hydrogen uptake. The reaction of five moles of hydrogen indicated that one of the rings had been opened, and by analogy to the course of hydrogenation of compound IX in *neutral* medium,[15] it was expected that this would be the pyrrolidine ring. That the compound isolated was indeed the piperidine derivative XVI was demonstrated by comparison with an authentic sample, prepared by an unequivocal synthesis as shown below.

Some earlier experiments were directed to the preparation of tricyclic derivatives of azaindole by ring closure across the two nitrogen atoms, with the expectation of studying hydrogenations and other reactions in this series. Thus 1-chloroacetyl-7-azaindole (XVII) was prepared to attempt to form by intramolecular alkylation at the 7-position a product analogous to the imidazo[1,2-a]pyridine derivative obtained[17] on similar treatment of 2-

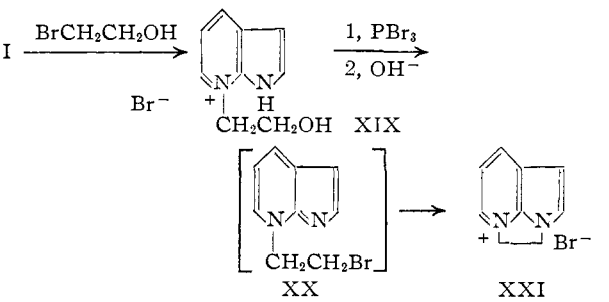
(17) A. E. Chichibabin, *Ber.*, **57**, 2092 (1924).



aminopyridine. On standing exposed to the atmosphere, or more readily on heating in water, the compound did undergo alkylation, but only with concomitant hydrolysis of the amide linkage to form the 7-carboxymethyl-1H-pyrrolo[2,3,-b]pyridinium chloride (XVIII).

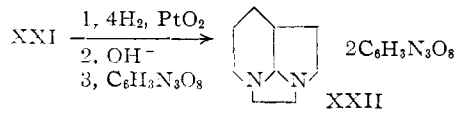


Because of the facile cleavage of the amide linkage, work was discontinued on the chloroacetyl compounds and attempts were made to construct an *ethano* bridge across the nitrogens according to a second scheme. Alkylation of 7-azaindole with



2-bromoethanol proceeded normally[15] to form 7-(2-hydroxyethyl)-1H-pyrrolo[2,3-b]pyridinium bromide (XIX). Treatment of this salt with phosphorus tribromide apparently replaced the alcohol function by bromine to form the corresponding 2-bromoethyl salt and on basification a yellow color developed, indicating the formation of a 7-alkyl-7H-pyrrolo[2,3-b]pyridine.[15] When this was immediately extracted into ether and the solution warmed the color was largely discharged and a white salt, apparently impure XXI, was formed. Numerous attempts to purify this quaternary bromide were unsuccessful, however. Some analyses indicated the possibility of solvates, but the only satisfactory result obtained was that for the picrate corresponding to XXI. Several experiments were carried out on the hydrogenation of the crude bromide, with an apparent reaction of approximately four molar equivalents of hydrogen. From the reduction mixture a distyphnate was prepared whose analysis was satisfactory for XXII, but because of the large percentage of styphnic acid in the adduct these analytical data provided no conclusive information about the hydrogenation state. As a con-

sequence of the extreme intractability of the compounds in this series work thereon was discontinued.



Experimental[18,19]

2,3-Dihydro-7-azaindole (II).—7-Azaindole, when hydrogenated by the method of Kruber,[3] afforded a product which in this Laboratory was found to melt at 83.0–85.0° (reported m.p. 78°). The compound, which is more water-soluble than 7-azaindole, gives only a yellow-green color on treatment with aqueous sodium nitroprusside and sodium hydroxide and the color changes to a pale green on acidification. These results are in contrast to the exceptionally strong blue-green → blue color reaction with azaindole.[9] The benzoyl derivative, prepared by the method of Kruber, melted at 119.5–121.5° (reported m.p. 120°).

2-Amino-3-ethylpyridine (IV).—Hydrogen at 78 atmos. was added to a bomb containing 22.4 g. of 7-azaindole, 100 ml. of decalin and 5 g. of W-4 Raney nickel and the apparatus was shaken and heated for 14 hours. The temperature was brought to 270° and the pressure-drop corresponded to approximately 2.5 moles of hydrogen per mole of compound. The yellow solution, which had a strong ammoniacal odor, was filtered through Celite and extracted with three 10-ml. portions of concentrated hydrochloric acid. The water layer was evaporated to a low volume *in vacuo*, treated with excess potassium carbonate and extracted with chloroform. The chloroform solution was dried over potassium carbonate and distilled. The product, together with some dihydro compound, was collected in four fractions (total 4.67 g.) boiling over the range 114° (12 mm.) to 135° (10 mm.). After the high-boiling fractions had crystallized partially, the crystals were separated (m.p. 78–82°, undepressed on admixture with authentic dihydro compound) and the combined oils redistilled. A fraction boiling at 116–118° (12 mm.) was relatively pure 2-amino-3-ethylpyridine. This material, which had $n^{24}D$ 1.5728 and d^{20}_4 1.047, was used as such for the ultraviolet spectrum. Absorption maxima occurred at 230 mμ (log ε 3.95) and 290 mμ (log ε 3.67) and a minimum was found at 258 mμ (log ε 2.93). Kruber[3] reported b.p. 133–134° (15 mm.), $n^{20}D$ 1.57117 and d^{20}_4 1.0891 for his tetrahydro compound. The boiling point of 2-amino-3-ethylpyridine[9] (as obtained from the amination of 3-ethylpyridine and contaminated with 2-amino-5-ethylpyridine) is 122.5–128.5° (18 mm.). When the product was chilled to induce crystallization and the solid pressed on porous tile and recrystallized from low-boiling petroleum ether, white plates were obtained, m.p. 41.0–41.5° alone and m.p. 41.5–43.5° on admixture with authentic 2-amino-3-ethylpyridine (reported[9] m.p. 43–45°).

2-Amino-3-ethylpyridine Picrate.—This adduct was prepared by reaction of the recrystallized amine with picric acid in 95% ethanol and recrystallization from the same solvent. There were obtained yellow needles, m.p. 210.0–211.0° dec. On admixture with picrate prepared from authentic amine (m.p. 209.0–210.5° dec.) these melted at 208.5–210.5° dec.

Anal. Calcd. for $C_7H_{10}N_2 \cdot C_6H_3N_3O_7$: C, 44.45; H, 3.73. Found: C, 44.61; H, 3.62.

2-(Dibenzoylamino)-3-ethylpyridine (V).—This derivative was prepared by the method of Huntress and Walter[11] for 2-(dibenzoylamino)-pyridine except that the crude product was washed with ethanol, with 5% hydrochloric acid and with 5% sodium bicarbonate to remove monobenzoyl compound and colored impurities. The yield of washed product, which had m.p. 159.5–162.5°, was 53%. It was found that recrystallization from ethanol[11] resulted in a material with a wide melting range, but recrystallization from 1:3 benzene–cyclohexane afforded white prisms, m.p. 165.5–166.5°.

Anal. Calcd. for $C_{21}H_{18}N_2O_2$: N, 8.48. Found: N, 8.40.

(18) Melting points are corrected, boiling points uncorrected.

(19) Analyses by Drs. Weiler and Strauss, Oxford, England, except for some nitrogen determinations carried out by a semimicro Kjeldahl technique in this Laboratory.

1-Carbethoxy-7-azaindole.—To a stirred solution of 5.90 g. of 7-azaindole and 3.95 g. of dry pyridine in 50 ml. of anhydrous ether a solution of 5.40 g. of ethyl chloroformate in 50 ml. of dry ether was added over a period of one hour. The mixture was refluxed for 3.5 hours, cooled and filtered from the precipitate of pyridine hydrochloride, which was washed with four 25-ml. portions of ether. The combined ether solutions were dried over sodium sulfate, the solvent was removed and the residue was chilled to form oily crystals which, after pressing on filter paper and washing with low-boiling petroleum ether, weighed 7.61 g. (80%), m.p. 42.0–48.5°. The analytical sample was recrystallized from the same solvent as long white filaments, m.p. 47.0–49.5°.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.31; N, 14.73. Found: C, 63.28; H, 5.28; N, 15.1.

Treatment of 7-Azaindole with Lithium Aluminum Hydride.—To a stirred solution of 145 mg. of lithium aluminum hydride in 15 ml. of dry ether was added a solution of 236 mg. of 7-azaindole in the same quantity of solvent. The mixture was refluxed 11 hours, the hydride decomposed and the ether dried and evaporated. Light-tan azaindole (0.21 g.) was recovered, m.p. 107.0–108.0°.

2,3,3a,4,5,6-Hexahydro-1H-pyrrolo[2,3-b]pyridine (VI).—A mixture of 2.36 g. of 7-azaindole, 50 ml. of 95% ethanol, 10 ml. of concentrated hydrochloric acid and approximately 0.5 g. of pre-reduced Adams catalyst was stirred with hydrogen for 12 hours, during which time about 103% of the theoretical hydrogen was absorbed. The colorless solution was evaporated *in vacuo* and the oily residue was treated with a few milliliters of water and excess potassium carbonate and extracted with ether. Evaporation of the dried extracts furnished an oily solid, which after pressing on porous tile, weighed 1.88 g. (76%) and melted at 88–96°. The analytical sample was obtained on recrystallization from low-boiling petroleum ether as white filaments, m.p. 103.5–104.5°. The ultraviolet spectrum of a cyclohexane solution of the compound shows only a shoulder extending into the quartz ultraviolet range, log ε (214 mμ) 3.72. A chloroform solution of the material shows infrared absorption at 3420 cm.$^{-1}$ (>NH) and a >C=N—band at 1635 cm.$^{-1}$ with a slight shoulder at 1665 cm.$^{-1}$ The pK_b, taken as equal to pOH at half-neutralization, is 2.3.

Anal. Calcd. for $C_7H_{12}N_2$: C, 67.68; H, 9.76; N, 22.56; neut. equiv., 124.2. Found: C, 67.70; H, 9.67; N, 22.52; neut. equiv., 125.1, 124.5.

When 0.25 g. of the compound was refluxed 4 hours with 10 ml. of concentrated hydrochloric acid and the solution evaporated, basified and extracted as in the preparation, only 0.06 g. of unchanged starting material, accompanied by an intractable oil, was recovered. When the same quantity of amine was refluxed 3 hours with 5 ml. of 5% sodium hydroxide and worked up in the same fashion, only a small quantity of oil was isolated.

Hydrochloride of Hexahydroazaindole.—After several unsuccessful attempts to precipitate this salt from anhydrous ether, the amine was treated with excess concentrated hydrochloric acid and the solution evaporated to dryness. The semi-liquid residue was dried at 60° (1 mm.) for 6 hours, during which period it became fairly hard. The exceptionally hygroscopic solid was quite soluble in most organic solvents. It could be recrystallized, albeit not satisfactorily, from dry benzene. The shiny white plates had m.p. 143.5–147.0°.

Anal. Calcd. for $C_7H_{13}N_2Cl$: C, 52.33; H, 8.15; N, 17.44. Found: C, 51.66; H, 8.10; N, 16.20.

Dehydrogenation of Hexahydroazaindole.—A mixture of 0.25 g. of the amine and 0.12 g. of 5% palladium-on-charcoal was heated at 250° for 3 hours in a nitrogen atmosphere. The mixture was extracted with hot cyclohexane and the extract was filtered through a bed of Darco and evaporated to yield 68 mg. of oily, yellow solid. This was pressed on porous tile and washed with cyclohexane, then dissolved in a few milliliters of 5% hydrochloric acid and treated with Darco. Precipitation with sodium bicarbonate afforded white solid, m.p. 105.0–106.0° both alone and on admixture with 7-azaindole. The product gave a positive sodium nitroprusside test.[9]

Dibenzoyl Derivative of VI.—Benzoyl chloride (1.12 g.) was added rapidly to a stirred mixture of 0.50 g. of amine, 10 ml. of anhydrous pyridine and 20 ml. of dry benzene and the solution was heated at 65° for 0.5 hour, during which

time a heavy oil layer separated. The mixture was then poured into 200 ml. of water and extracted as directed in Shriner, Fuson and Curtin.[20] Evaporation of the benzene layer left a residue which was dried *in vacuo* and washed with cold ethyl acetate. The resulting 0.79 g. (59%) of cream-colored solid had m.p. 140–144°, and was insoluble in dilute acid. The analytical sample was obtained on recrystallization from 1:3 ethanol–water as large leaves, m.p. 143.5–147.5°. No means of narrowing the melting range was found.

Anal. Calcd. for $C_{21}H_{20}N_2O_2$: C, 75.87; H, 6.08; N, 8.43. Found: C, 75.62; H, 5.93; N, 8.63.

When the reaction was carried out with equimolar quantities of benzoyl chloride and amine, only the dibenzoyl product was isolated, but in greatly reduced yield. Benzoylation in sodium hydroxide or in an ethereal suspension of potassium carbonate gave the same results.

When 664 mg. of the derivative was refluxed 5 hours with 5 ml. of concentrated hydrochloric acid and the cooled solution extracted with ether, 426 mg. (87%) of benzoic acid, m.p. 122.0–123.0° (undepressed on admixture with authentic acid), was obtained. Evaporation, basification and extraction of the water layer afforded only 23 mg. of oil.

1-Phenylcarbamyl-2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]pyridine.—Equimolar quantities of the hydrogenation product and phenyl isocyanate were mixed and the solid product was dissolved in 5% hydrochloric acid and filtered to remove traces of diphenylurea. The amide was precipitated by base in 93% yield and recrystallized from *n*-hexane for analysis. The resulting fine, white needles had m.p. 86.5–89.0° (cloudy melt). A narrower melting range could not be attained.

Anal. Calcd. for $C_{14}H_{17}N_3O$: N, 17.27. Found: N, 17.20.

7-Methyl-2,3,3a,4,5,6-hexahydro-7H-pyrrolo[2,3-b]pyridine (X).—A solution of 3.085 g. of IX[15] in 50 ml. of 95% ethanol and 10 ml. of concentrated hydrochloric acid reacted with 105% of the theoretical volume of hydrogen when reduced under the conditions employed for 7-azaindole. The hydrogenation mixture was worked up by the usual method except that the base was extracted into chloroform and distilled. There was thus obtained a 68% yield of hygroscopic, colorless oil, b.p. 108° (22 mm.) to 109° (18 mm.). The redistilled analytical sample had b.p. 105–106° (18 mm.), $n^{25}D$ 1.5077 and $d^{23.5}_4$ 0.996. The pK_b, determined by titration, was found to be 2.5.

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27; neut. equiv., 138.2. Found: C, 69.42; H, 10.08; N, 20.80; neut. equiv., 139.1.

An attempt to benzoylate this amine by the pyridine method using a 1.5:1 molar excess of benzoyl chloride was unsuccessful. No oil layer separated during the reaction period and the product from the extracts consisted of a very small quantity of dark oil from which crystals of benzoic acid separated on standing.

1-Methyl-7-azaindole (VII).—It was found that this compound can be prepared in greatly improved yield by a modification of the method previously described.[15] 7-Azaindole (5.90 g.) was dissolved in 100 ml. of dry xylene and refluxed and stirred in a nitrogen atmosphere with 2.40 g. of sodium hydride for 3 hours. The suspension was cooled, 14.20 g. of methyl iodide in 25 ml. of xylene was added and the mixture was refluxed again for 1.5 hours. Excess hydride was then decomposed by the addition of ethanol after which the xylene layer was extracted with a mixture of 100 ml. of water and 25 ml. of concentrated hydrochloric acid in three portions. The acid solution was then made basic and steam distilled directly after which the procedure was as previously described.[15] The faintly-yellow product from one distillation had b.p. 114–122° (25 mm.) and $n^{19}D$ 1.5978, and weighed 4.10 g. (62%). Use of a still larger mole-ratio of sodium hydride and methyl iodide was not tried, but it seems probable that such a procedure might further improve the yield.

1-Methyl-2,3,3a,4,5,6-hexahydro-1H-pyrrolo[2,3-b]pyridine (VIII).—When 5.766 g. of VII was hydrogenated in the same quantity of solvent and under the conditions described above, the theoretical quantity of hydrogen reacted. When the residue from the evaporation was made basic, however, a red color developed. Evaporation of the chloroform extracts and distillation afforded only 1.68 g. (28%) of pale-yellow oil, b.p. 108–113° (16 mm.), together with a large, red, non-volatile residue. On redistillation a colorless, intensely hygroscopic liquid was obtained which had b.p. 106° (15 mm.), d^{26}_4 0.995 and $n^{24}D$ 1.5158.

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.76; H, 10.32; N, 19.70.

The results of an attempted benzoylation were the same as in the case of the 7-methyl compound. From 0.55 g. of amine was obtained 0.31 g. of a brown oil which could not be induced to crystallize.

Hydrogenation of XV.—When 2.756 g. of XV[15] in 120 ml. of 5:1 ethanol–water was stirred with hydrogen in the presence of pre-reduced Adams catalyst from 0.5 g. of platinum oxide, four moles of hydrogen was taken up in 12 hours and a fifth mole reacted in another 15 hours. Filtration, evaporation and drying *in vacuo* left 2.7 g. of sticky, yellow solid which was recrystallized from acetonitrile under nitrogen. The recovery of white, crystalline material from the first recrystallization was typically only about 50%. The analytical sample of 1-methyl-3-(2-methylaminoethyl)-piperidine hydroiodide (XVI) had m.p. 140.0–142.0° (cloudy melt).

Anal. Calcd. for $C_9H_{21}N_2I$: C, 38.03; H, 7.45; N, 9.86. Found: C, 38.07; H, 7.51; N, 9.99.

N-Methyl-3-pyridineacetamide.—Ethyl 3-pyridineacetate[21] (24.78 g.) was dissolved in 50 ml. of aqueous methylamine which had been saturated at 0°, and the flask was stoppered tightly and allowed to stand for 71 hours. The solution was filtered to remove a small amount of insoluble impurity and evaporated to dryness *in vacuo*. On chilling, the residue crystallized affording a hygroscopic, slightly oily solid. This was boiled with cyclohexane and chilled to cause resolidification after which the hydrocarbon was decanted and the residue dried thoroughly *in vacuo*. The product (m.p. 56–64°) weighed 22.89 g. (theoretical yield 22.53 g.). No solvent was found from which the material could be recrystallized. For attempted purification it was subjected to several evaporative distillations in a sublimation apparatus at 140° (0.5 mm.), but the white product had m.p. 61–65°. No method was found to narrow the melting range and the analytical results were 1–3% low.

N-Methyl-3-pyridineacetamide Picrate.—This derivative was prepared by reaction of equimolar quantities of the amide and picric acid in 95% ethanol and recrystallization from the same solvent. The yellow needles had m.p. 177.5–178.5°.

Anal. Calcd. for $C_8H_{10}N_2O \cdot C_6H_3N_3O_7$: C, 44.33; H, 3.45; N, 18.47. Found: C, 44.49; H, 3.11; N, 18.40.

1-Methyl-3-(N-methylcarbamylmethyl)-pyridinium Iodide.—To 0.30 g. of amide was added 1.42 g. of methyl iodide and the mixture was allowed to stand overnight. The excess methylating agent was decanted and the crystalline product dried *in vacuo* to yield 0.59 g. (100%) of light-yellow solid, m.p. 117–125°. The analytical sample was obtained as pale-yellow needles from acetonitrile, m.p. 127.0–128.0°.

Anal. Calcd. for $C_9H_{13}N_2OI$: C, 37.00; H, 4.49; N, 9.59. Found: C, 37.44; H, 4.48; N, 9.66.

The reaction also was run on a 0.15 molar scale using only 0.5 mole of methyl iodide. With such quantities, however, efficient cooling is necessary to avoid overheating and loss of product.

N,N'-Dimethyl-3-piperidineacetamide.—The methiodide (30.73 g.) and approximately 1.5 g. of reduced Adams catalyst were added to 135 ml. of 80% ethanol and hydrogenated at an initial pressure of 3 atmospheres. After 34 hours, reaction had ceased and the pale-gold solution was filtered through Celite and evaporated to dryness. Water (25 ml.) and a small quantity of sodium bisulfite were added and the mixture was made strongly basic with potassium carbonate and extracted with chloroform. The extracts were dried over potassium carbonate and evaporated. The residue crystallized readily on drying *in vacuo* to yield 16.01 g. (89%) of a white solid, m.p. 76–79°. The

(20) R. L. Shriner, R. C. Fuson and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1956, p. 226.

(21) R. L. Malan and P. M. Dean, THIS JOURNAL, **69**, 1797 (1947).

analytical sample was recrystallized from cyclohexane as white filaments, m.p. 82.0–83.0°.

Anal. Calcd. for $C_9H_{18}N_2O$: C, 63.47; H, 10.68; N, 16.45. Found: C, 63.33; H, 10.48; N, 16.10.

1-Methyl-3-(2-methylaminoethyl)-piperidine Hydroiodide (XVI).—To a stirred suspension of 1.5 g. of lithium aluminum hydride in 75 ml. of dry tetrahydrofuran, a solution of 3.41 g. of the piperidine amide in 25 ml. of tetrahydrofuran was added over a 20-minute period. The mixture was refluxed with stirring for 8 hours, 0.75 g. more hydride being added after 2 hours. The excess reducing agent was decomposed with ethanol, approximately 50 ml. of saturated aqueous potassium hydroxide was added and the layers were separated. The aqueous layer was washed with additional ether and the combined organic solutions were dried over potassium hydroxide. The solvent was evaporated and the product distilled, during which process an appreciable quantity of water-soluble solid residue separated. The distillation product weighed only 0.49 g. (16%) and had b.p. 68–74° (15 mm.). The amine was not investigated further as such but was converted directly to the hydroiodide XVI by addition of the theoretical quantity of aqueous hydriodic acid. Evaporation of the solution *in vacuo* afforded a white solid which after washing with acetonitrile weighed 0.83 g. and had m.p. 139.5–141.5°. Recrystallizations from this solvent in a nitrogen atmosphere produced the analytical sample, m.p. 141.5–143.0° (cloudy melt). On admixture with the hydrogenation product this melted at 142.0–143.5°.

Anal. Calcd. for $C_9H_{21}N_2I$: N, 9.86. Found: N, 9.87.

1-Chloroacetyl-7-azaindole (XVII).—To a stirred solution of 5.90 g. of 7-azaindole and 3.96 g. of anhydrous pyridine in 100 ml. of dry ether a solution of 5.55 g. of chloroacetyl chloride in 50 ml. of ether was added over a period of 35 minutes. During the addition the temperature was kept below −10°. Water (50 ml.) was then added to dissolve the yellow precipitate of pyridine hydrochloride, the layers were separated, the water layer was extracted with three 60-ml. portions of ether and the combined ether solutions were dried over magnesium sulfate. Evaporation of the solvent in a nitrogen stream at room temperature left a residue which crystallized partially on chilling. The crystals were separated from the oil by filtration and the latter was caused to deposit a small amount of additional solid on further cooling. The combined greenish-yellow crystals, after thorough pressing on filter paper, weighed 5.93 g. (61%) and melted at 102–105°. The analytical sample was obtained in the form of long, white needles from cyclohexane, m.p. 107.5–109.0.

Anal. Calcd. for $C_9H_7N_2OCl$: C, 55.53; H, 3.63; N, 14.40. Found: C, 55.91; H, 3.69; N, 14.52.

Attempted Cyclization of XVII.—When the chloroacetyl compound was allowed to stand exposed to the air for a month, it gradually liquefied, then resolidified. The resulting solid decomposed at about 212°. When 1.94 g. of the amide was heated 4 hours with 25 ml. of boiling water, the solid gradually dissolved and the solution became acidic. Evaporation of the colorless liquid *in vacuo* afforded an oil which, after drying over phosphorus pentoxide, was triturated with acetone to produce 1.02 g. (48%) of white solid, m.p. 216–218°. For analysis the strongly acidic compound was recrystallized from absolute ethanol through which gaseous hydrogen chloride was bubbled. The white 7-carboxymethyl-1H-pyrrolo[2,3-b]pyridinium chloride (XVIII) darkens at 190° and has m.p. 218.0–218.5° dec. The ultraviolet spectrum of a water solution has maxima at 224 mμ (log ε 4.30) and at 295 mμ (log ε 3.95) and a minimum at 252 mμ (log ε 2.70).

Anal. Calcd. for $C_9H_9N_2O_2Cl$: C, 50.83; H, 4.27; N, 13.18. Found: C, 51.28, 51.14; H, 4.40, 4.18; N, 12.99.

An attempt also was made to cyclize the amide in the absence of water. When the material was heated in refluxing xylene for 1.5 hours much decomposition ensued and no salt-like material separated from the solution. The polymeric products were not investigated further.

7-(2-Hydroxyethyl)-1H-pyrrolo[2,3-b]pyridinium Bromide (XIX).—A mixture of 5.90 g. of 7-azaindole and 31.2 g. of 2-bromoethanol was heated 1.5 hours on the steam-bath in a nitrogen atmosphere. The cooled mixture was poured into 300 ml. of ether and the white product was separated by filtration and dried *in vacuo*. There was thus obtained 10.69 g. (88%) of product with m.p. 161–168°. The analytical sample was prepared by recrystallization from *n*-propyl alcohol, m.p. 174.5–175.0°.

Anal. Calcd. for $C_9H_{11}N_2OBr$: C, 44.46; H, 4.57; N, 11.52. Found: C, 44.11; H, 4.84; N, 11.41.

Cyclizations of XIX.—To a stirred suspension of 2.43 g. of XIX in 50 ml. of dry toluene, which was maintained at 0°, a solution of 2.70 g. of phosphorus tribromide in 75 ml. of dry toluene was added over a period of 3 hours. Stirring was continued as the mixture was allowed to warm slowly to room temperature, after which it was allowed to stand overnight. The slurry was then refluxed gently for 2 hours, the toluene was decanted and the residue was covered with ether. Ice, followed by dilute sodium hydroxide solution, was added to the well-cooled mixture and the yellow ether layer was separated. The aqueous phase was then saturated with potassium carbonate and extracted with additional ether until the yellow color was removed completely. The extracts were dried briefly over magnesium sulfate and evaporated on the steam-bath to yield a yellow, oily solid. This was triturated with acetone and separated by filtration. The acetone solution was again evaporated to dryness to produce additional white solid which was separated in the same manner, the washings and evaporations being repeated until no additional product was obtained. The total yield of white solid, after one recrystallization from 1:4 absolute ethanol–carbon tetrachloride, was 0.82 g., m.p. 148.5–149.5° dec. Analytical results corresponding to a simple empirical formula were not obtained on recrystallization from this or other solvents. It was noted that after recrystallization the product *lost* weight on exposure to air while the weight remained *constant* on storing over phosphorus pentoxide. It was eventually determined that the material was a solvate containing carbon tetrachloride, for the desiccator-dried material gave a positive test for chlorine, on sodium fusion, as well as bromine. On exposure to air the carbon tetrachloride was lost, but was apparently replaced to some degree by water. Neither by this treatment nor on drying at elevated temperatures could a satisfactory sample be prepared. The ultraviolet spectrum of a water solution of a sample dried at 60° exhibits maxima at 230 mμ (log ε 4.20) and 292 mμ (log ε 3.94) and a minimum at 248 mμ (log ε (2.08), if the ε values are calculated on the basis of pure XXI.

From the supposed XXI, which can be named most simply as 1,7-ethano-1H-pyrrolo[2,3-b]pyridinium bromide, a picrate was prepared by reaction of 0.5 g. of the salt, 0.32 g. of sodium acetate trihydrate and 1.02 g. of picric acid in 30 ml. of water. Recrystallizations of the product from 95% ethanol produced the analytical sample, m.p. 146.0–147.0°.

Anal. Calcd. for $C_9H_9N_2 \cdot C_6H_2N_3O_7$: C, 48.26; H, 2.98; N, 18.76. Found: C, 48.42; H, 3.33; N, 18.3.

Hydrogenation of XXI.—A solution of 503 mg. of XXI in 25 ml. of 95% ethanol with Adams catalyst reacted with 3.64 molar equivalents of hydrogen in approximately 11 hours. The solution was filtered and evaporated to dryness and about one-third of the residue was treated with a solution of 0.49 g. of 2,4,6-trinitroresorcinol and 0.14 g. of hydrated sodium acetate in water. The resulting yellow precipitate was recrystallized from water and from methanol to produce the analytical sample of XXII, m.p. 195.5–196.0° dec.

Anal. Calcd. for $C_9H_{16}N_2 \cdot 2C_6H_3N_3O_8$: C, 39.26; H, 3.45; N, 17.44. Found: C, 39.14; H, 3.35; N, 17.7.

Absorption Spectra.—All ultraviolet spectra were measured on a Beckman model DU quartz spectrophotometer at concentrations varying from 10^{-4} to 5×10^{-5} *M*. The solvent was cyclohexane, unless otherwise specified. Infrared spectra were determined on either a Perkin–Elmer spectrophotometer or a Baird instrument by Dr. S. M. Nagy and associates at the Microchemical Laboratory, Massachusetts Institute of Technology.

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