was mixed with the α-tocopherol solution, an olive green coloration developed immediately and then faded to a brilliant yellow color in approximately 20 seconds. The benzene solution was concentrated *in vacuo*, and 0.53 g. of *m*-chlorobenzoic acid was collected on a filter. Another 0.16-g. sample was obtained by 0.5 *N* sodium bicarbonate extraction. On admixture with authentic *m*-chlorobenzoic acid, no depression of melting point was observed, m.p. 152–153°.

α-Tocoquinone.—The hydrocarbon layer from the above run was worked up as described in the previous section for α-tocoquinone. A 520-mg. sample (25%) was obtained which had an infrared spectrum identical with that obtained from a pure sample of α-tocoquinone.

Compound A.—From the yellow colored eluates from the alumina column, 410 mg. (20% yield) of compound A was obtained which had an infrared spectrum identical with that which was obtained above.

Compound B.—When 1.60 g. (5.15 mmoles) of bis-(*m*-chlorobenzoyl) peroxide in 20 ml. of benzene was mixed with 2.22 g. (5.15 mmoles) of α-tocopherol in 10 ml. of benzene and allowed to stand 15 minutes under a flow of nitrogen. When the reaction mixture was separated as previously described, 310 mg. (14% yield) of a slightly yellow colored oil, $n^{30}D$ 1.5134, was obtained from the forerun eluates. It had a molecular weight[14] of 448 and was insoluble in methanol and ethanol but readily soluble in non-polar solvents. It gave no reaction with acidic sodium iodide solution, saturated sodium hydrosulfite solution, or ferric chloride dipyridyl reagent (Emmerie and Engel test).

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.28; H, 11.56.

Ultraviolet spectrum: λ_{max}. 293 mμ (ε 2,150).

Infrared spectrum: 5.84 μ (carbonyl), 6.10 μ (double bond), 8.02 and 9.25 μ (ether).

Reaction of Benzoyl Peroxide with α-Tocopherol: 2,7,8-Trimethyl-2-(4′,8′,12′-trimethyltridecyl-1)-chroman-5,6-quinone.—In a 50-ml. erlenmeyer flask 0.80 g. (1.92 mmoles) of α-tocopherol was dissolved in 7 ml. of benzene, and to this solution a 0.46-g. (1.92 mmoles) solution of benzoyl peroxide in 10 ml. of benzene was added. The flask was stoppered and allowed to stand for 40 minutes. The solution was washed with 10% potassium carbonate, water and dried over sodium sulfate. After removal of the solvent, the red oil was poured on a 25 × 100 mm. Brockmann alumina column and developed with Skellysolve B. The large red band section was eluted with water and ether. On removal of the ether, 0.50 g. of red oil was obtained that had several absorption bands in the infrared in common with β-lapachone.

Anal. Calcd. for $C_{28}H_{46}O_3$: C, 78.08; H, 10.77. Found: C, 77.55; H, 11.32.

Acknowledgment.—The authors are grateful to Procter and Gamble Company for liberal financial support.

IOWA CITY, IOWA

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

7-Azaindole. II. Conversion to 7-Methyl-7H-pyrrolo[2,3-b]pyridine and Related Compounds[1,2]

BY MICHAEL M. ROBISON AND BONNIE L. ROBISON

RECEIVED JULY 25, 1955

Treatment of 7-azaindole (I) with methyl *p*-toluenesulfonate produced 7-methyl-1H-pyrrolo[2,3-b]pyridinium *p*-toluene sulfonate (IIa), which, on treatment with aqueous base, loses the elements of *p*-toluenesulfonic acid to form 7-methyl-7H-pyrrolo[2,3-b]pyridine (III). The structure of III was proved by catalytic hydrogenation and hydrogenolysis to 1-methyl-3-(2-aminoethyl)-piperidine (IV), which was identified as 1-methyl-3-[2-(1-(3-phenyl)-ureido)-ethyl]-piperidine (V). The urea was prepared for comparison by an independent synthesis from 3-(2-aminoethyl)-pyridine. The yellow 7H-pyrrolopyridine is a comparatively strong base, unlike the colorless 1-methyl-7-azaindole (VI, 1-methyl-1H-pyrrolo[2,3-b]pyridine), which was prepared by methylation of the sodio derivative of 7-azaindole with methyl iodide. Treatment of either compound III or VI with methyl iodide produces 1,7-dimethyl-1H-pyrrolo[2,3-b]pyridinium iodide (VII). Several new derivatives of 2-methylamino-3-picoline and of 3-(2-aminoethyl)-pyridine and an improved procedure for the large-scale preparation of 7-azaindole are also described.

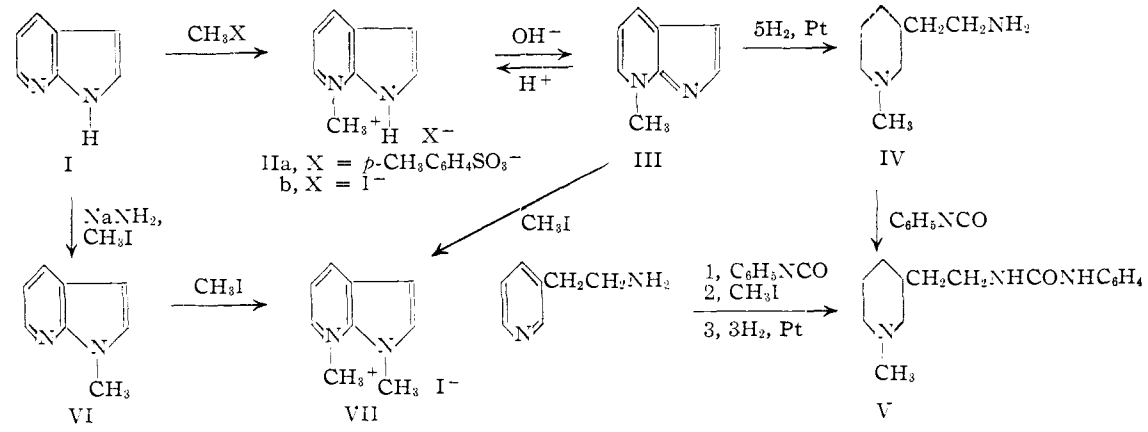
2-Aminopyridine on treatment with methyl iodide is methylated at the ring nitrogen to produce N-methyl-2-pyridonimine hydroiodide, which, on reaction with silver oxide or aqueous alkali, loses the elements of hydriodic acid to form N-methyl-2-pyridonimine. If, on the other hand, the amine is converted to its sodio derivative by the action of sodium amide in ether before the methylating agent is added, substitution occurs at the amino nitrogen.[3] In view of the structural relationship of 7-azaindole (I) to 2-aminopyridine, it seemed of interest to determine whether methylation reactions would take a similar course with the bicyclic compound. This was found to be the case. When 7-azaindole was treated with a refluxing benzene solution of methyl *p*-toluenesulfonate, methylation took place at the 7-position to produce 7-methyl-1H-pyrrolo[2,3-b]-pyridinium *p*-toluenesulfonate (IIa) in high yield. Treatment of the salt with base converted it to a hygroscopic yellow substance which was shown to be 7-methyl-7H-pyrrolo[2,3-b]pyridine (III).

The ultraviolet spectrum of the yellow compound is very different from the spectra of the 1H-pyrrolo[2,3-b]pyridines. In cyclohexane the compound exhibits a third absorption maximum at 385 mμ. In aqueous alkali the yellow color persists but the intensity is lower and the compound loses its color as the acidity of the medium is increased. In 10^{-3} *N* acid, 7-azaindole and the 7-methyl compound have similar spectra (Fig. 1), as would be ex-

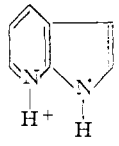
(1) This investigation was supported in part by a research grant, number C-2574 from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) Paper I of this series: M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 457 (1955).

(3) A. E. Chichibabin, R. A. Konowalowa and A. A. Konowalowa, *Ber.*, **54**, 814 (1921).



pected if the protonated species II and Ia are predominant in such a medium.



Ia

The 7H-pyrrolopyridine, like N-methyl-2-pyridonimine,[3] is a comparatively strong base. The pK_b was determined by measurement of the pH at half-neutralization and was found to be approximately 5.1, as compared with a value of 6.85 for 2-aminopyridine.[4] The compound gave a negative test for active hydrogen with the lithium aluminum hydride reagent.

N-Methyl-2-pyridonimine is readily hydrolyzed by boiling with aqueous sodium hydroxide to produce ammonia and N-methyl-2-pyridone.[3] 7-Methyl-7H-pyrrolo[2,3-b]pyridine, however, is not decomposed by aqueous base. When a sample was boiled with 20% aqueous sodium hydroxide for 5.25 hours, 90% of the starting material was recovered and no evidence of ammonia evolution was observed. Although Kruber[5] stated that 7-azaindole is sensitive to alkali, this statement apparently refers only to treatment with fused potassium hydroxide at high temperatures and not to solutions of aqueous base, as was stated earlier.[2] In this Laboratory it was observed that 94.5% of the compound may be recovered unchanged after boiling with 20% sodium hydroxide solution for six hours, and that not more than 0.82% of the theoretical amount of ammonia is evolved (based on one mole of ammonia per mole of 7-azaindole) under these conditions.

It was expected that if III were the correct structure for the yellow compound, catalytic hydrogenation would furnish a satisfactory means of structure proof. After saturation of the double bonds, one of the carbon–nitrogen bonds should undergo hydrogenolysis or solvolysis to form a piperidine or pyrrolidine derivative suitable for identification. This expectation was confirmed. On hydrogenation at atmospheric pressure with Adams catalyst, 4.94 moles of hydrogen was absorbed. When the product was treated with benzenesulfonyl chloride and alkali, an oil was obtained which was soluble either in acid or base but not in water, thus indicating the presence of primary and tertiary amine groups. It was therefore apparent that the pyrrolidine ring had been cleaved, rather than the piperidine ring, since in the latter case two secondary amine groups would have been formed, 3-[1-(3-methylamino)-propyl]-pyrrolidine being the product. Since only a small quantity of the strongly hygroscopic liquid piperidine derivative was available, it was converted directly to the phenylurea V. The yield in this latter step was 82% and the overall yield from compound III was 55.5%.

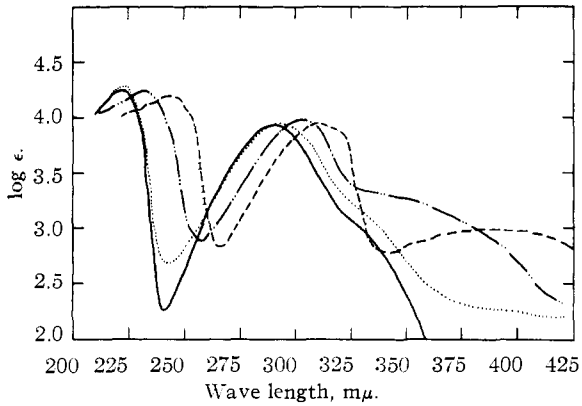


Fig. 1.—Spectra of: —, 7-azaindole in 0.001 N HCl; 7-methyl-7H-pyrrolo[2,3-b]pyridine: - - -, in cyclohexane; —··—, in 0.001 N NaOH; ....., in 0.001 N HCl.

The urea was prepared for comparison by an unequivocal synthesis. 3-Pyridineacetonitrile,[6] prepared from 3-pyridineacetamide,[7] was subjected to catalytic hydrogenation at low pressure in the presence of ammonia, using a Raney nickel catalyst. In this process only the nitrile group was reduced to produce the known[8] 3-(2-aminoethyl)-pyridine. This amine was converted to 1-phenyl-3-[2-(3-pyridyl)-ethyl]-urea by treatment with phenyl isocyanate, then to 1-methyl-3-[2-(1-(3-phenyl)-ureido)-ethyl]-pyridinium iodide by alkylation with

(4) Beilstein, "Handbuch der Organischen Chemie," Verlag von Julius Springer, Berlin, 1935, Vol. XXII, Erstes Ergänzungswerk, p. 629.

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

(6) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, THIS JOURNAL, **73**, 5752 (1951).

(7) M. Hartmann and W. Bosshard, *Helv. Chim. Acta*, **24**, 28E (1941).

(8) A. Dornow and W. Schacht, *Chem. Ber.*, **80**, 505 (1947).

methyl iodide. On catalytic hydrogenation at atmospheric pressure in the presence of Adams catalyst the methiodide absorbed 2.86 moles of hydrogen and 1-phenyl-3-[2-(3-(1-methyl)-piperidyl)-ethyl]-urea (V) was obtained in 84.4% yield. It was identical with the product prepared from the pyrrolopyridine as shown by mixture melting point and by paper chromatograms.

It may be noted that 7-azaindole would absorb no hydrogen in the presence of Adams catalyst at atmospheric pressure and room temperature. The 1H-pyrrolopyridine requires more stringent conditions for reduction. Thus Kruber[5] obtained a dihydro derivative of 7-azaindole by hydrogenation with a nickel catalyst at 200° and 118 atmospheres pressure and a tetrahydro compound when the temperature was raised to 250–270°, while Clemo and Swan[9] obtained dihydro derivatives of 2-methyl- and 2-ethyl-7-azaindole by the use of copper chromite catalyst at 180° and 160 atmospheres.

A number of attempts were made to prepare 1-methyl-7-azaindole. It was finally synthesized by treatment of 7-azaindole with sodium amide in refluxing xylene, followed by alkylation of the resulting sodio derivative with methyl iodide, also at this higher temperature. The 1-methyl derivative, which is a colorless liquid, has an ultraviolet spectrum very similar to that of 7-azaskatole[2] (Fig. 2), which provides evidence for the 1H-pyrrolo[2,3-b]-pyridine structure. The 1-methyl compound also gave a negative test for active hydrogen with the lithium aluminum hydride reagent. Attempts were also made to prepare the compound by a Madelung cyclization, as has been done in the case of 1-methylindole.[10] Neither the sodium anilide–potassium formate procedure[2] nor the potassium ethoxide procedure[11] afforded any of the product. The N-methyl-N-[2-(3-methyl)-pyridyl]-formamide for the cyclization was prepared by formylation[9] of 2-methylamino-3-picoline. This was obtained on methylation of 2-amino-3-picoline by a modification of the methods of Chichibabin and co-workers[3,12] for the preparation of 2-methylaminopyridine.

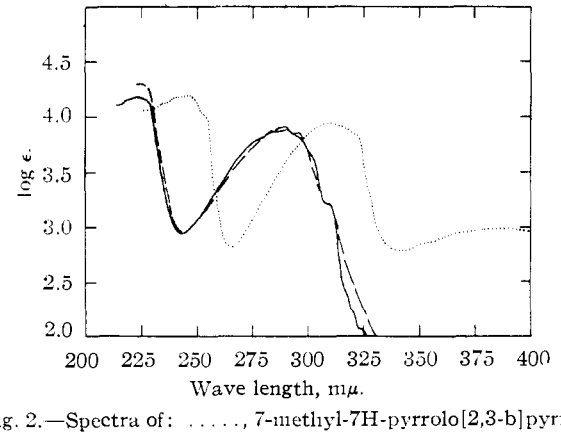


Fig. 2.—Spectra of: ....., 7-methyl-7H-pyrrolo[2,3-b]pyridine; —, 1-methyl-7-azaindole; – · – · –, 7-azaskatole.

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

(10) L. Marion and W. R. Ashford, *Can. J. Research*, **23B**, 26 (1945).

(11) F. T. Tyson, THIS JOURNAL, **63**, 2024 (1941).

(12) A. E. Chichibabin and I. L. Knunjanz, *Ber.*, **61**, 2215 (1928).

When the 7-methyl compound III was allowed to stand for 24 hours with methyl iodide at room temperature, 1,7-dimethyl-1H-pyrrolo[2,3-b]pyridinium iodide (VII) was formed. This quaternary salt was also prepared from 1-methyl-7-azaindole by similar treatment. In the latter case methylation proceeded less readily, for even after the reactants had stood for 60 hours at room temperature, reaction was only about 50% complete as shown by recovered VI. A similar situation obtains in the aminopyridine series. Treatment of either 2-methylaminopyridine or N-methyl-2-pyridonimine with methyl iodide results in the formation of 1-methyl-2-methylaminopyridinium iodide.[3]

Experimental[13,14]

7-Azaindole (I).—In an earlier paper[2] a procedure was described for the preparation of 7-azaindole by cyclization of 2-formamido-3-picoline in the presence of sodium anilide and potassium formate. Yields as high as 52% were obtained. Shortly after publication of that paper the supply of the particular brand of sodium hydride which had been used in the preparation of the sodium anilide was exhausted, and no more could be obtained. Using sodium hydride which is at present commercially available, the highest yield obtained by the procedure described was 36.5%. It was found, however, that by the use of Glas-Col heating mantles on both the upper and lower parts of the reaction flask the reaction temperature, 290–310°, could be attained without the troublesome vacuum-distillation step to remove aniline. When the mixture was maintained at this temperature with rapid stirring for 45 minutes without distillations, yields were actually higher than those obtained by the other procedure with the new sodium hydride. Further, the reaction could be run on a larger scale, since the extensive foaming experienced during the distillations was avoided. Thus in two reactions run in a 2-l. flask on a scale 1.5 and 2 times as large as that reported in the reference, yields of 11.3 and 15.8 g. (42.6 and 44.6%) of crude product were obtained. There is now no apparent reason why the process might not be carried out on a scale sufficient to produce 35–40 g. of the product at one time.

7-Methyl-1H-pyrrolo[2,3-b]pyridinium *p*-Toluenesulfonate (IIa).—To 5.90 g. of 7-azaindole in 75 ml. of dry benzene was added 11.1 g. of methyl *p*-toluenesulfonate and the solution was refluxed for 50 minutes. During the heating period the liquid separated into two layers. The mixture was cooled and allowed to stand overnight, during which time the product crystallized. It was separated by filtration and washed with ethyl acetate. The white crystals weighed 14.07 g. (92.6%) and melted at 130.5–132.0°. The product was purified by dissolution in boiling chloroform, addition of ethyl acetate to the cloud-point, and cooling. The white prisms had m.p. 134.0–134.5°.

Anal. Calcd. for $C_{15}H_{16}N_2O_3S$: C, 59.19; H, 5.30; N, 9.21; S, 10.54. Found: C, 58.93; H, 4.89; N, 8.86; S, 10.7.

When 7-azaindole was allowed to stand for three days with 4 equivalents of methyl iodide, the excess iodide evaporated and the product washed with ether, a solid was obtained whose weight corresponded to a quantitative yield of the methiodide IIb. A typical melting range, however, was 80–150°, and no method of obtaining a permanently sharp melting point was found. The analytical data indicated the presence of impurities.

7-Methyl-7H-pyrrolo[2,3-b]pyridine (III).—The crude *p*-toluenesulfonate (7.60 g.) was dissolved in 15 ml. of water and the solution was chilled in an ice-bath and saturated with potassium carbonate. A yellow oil separated. This was extracted into 600 ml. of ether in ten portions. The extracts were dried over potassium carbonate and evaporated to dryness. The resulting brown oil was dissolved in a minimum quantity of hot, 1:1 benzene–hexane and treated with Darco. The solvent was evaporated on the steam-bath and the residue was chilled to induce crystallization. The

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

(14) Analyses by Drs. G. Weiler and F. B. Strauss, Oxford, England, and by Dr. Joseph Alicino, Metuchen, N. J.

yellow-brown solid, after drying *in vacuo* over potassium hydroxide, weighed 2.85 g. The brown impurities were separated by distillation of the product in a sublimation apparatus equipped with a Dry Ice condenser. The process was carried out at 80–90° (bath) at 0.2 mm. From the above crude product was obtained 2.31 g. (70.0%) of yellow solid. The highest melting point observed was on a sample which had been dried in the melting-point tube *in vacuo* for several months; m.p. 48.5–50.5° (sealed capillary). After shorter drying periods in capillary tubes the observed melting points were as much as 5° lower. The solid liquified very rapidly on exposure to air. The analytical sample was recrystallized from cyclohexane–hexane and dried *in vacuo* over potassium hydroxide.

Anal. Calcd. for $C_8H_8N_2$: C, 72.69; H, 6.11; N, 21.20; neut. equiv., 132.2. Found: C, 71.71; H, 6.43; N, 21.4; neut. equiv., 133.0.

In the determination of the neutral equivalent by titration with a *p*H meter, the *p*OH at half-neutralization was taken as equal to the pK_b. The value obtained was 5.2.

When the methiodide IIb was treated with base and the product extracted into ether in a similar fashion, the 7H-pyrrolopyridine was obtained in 88% yield. In these earlier experiments purification was attempted by recrystallization alone, no distillation being carried out. The ultraviolet spectrum coincided with that of the product obtained from the *p*-toluenesulfonate, maxima being observed at 245 mμ (log ε 4.197), 309 mμ (log ε 3.945) and 385 mμ (log ε 2.991). The neutral equivalent and pK_b values also agreed, but the analytical results again indicated impurity. In two titrations, values of 132.3 and 133.2 were obtained for the neutral equivalent. The *p*H at half-neutralization was 8.9 in each case, corresponding to a value of 5.1 for pK_b.

Treatment of Compound III with Aqueous Base.—Amine obtained from hydrolysis of the *p*-toluenesulfonate and purified by distillation (m.p. 44–46°, 0.31 g.) was added to 20 ml. of 20% sodium hydroxide solution and the mixture refluxed for 5.25 hours. No basic gas was detected with litmus paper during this period. The solution was cooled and extracted with ether and the extracts were dried and evaporated. The residual oil, after drying for several days in a vacuum desiccator over potassium hydroxide, solidified on seeding with starting material. On admixture with starting material the recovered amine melted at 44–46°. The weight was 0.28 g.

7-Methyl-7H-pyrrolo[2,3-b]pyridine Picrate.—7-Methyl-1H-pyrrolo[2,3-b]pyridinium *p*-toluenesulfonate (1.38 g., m.p. 132–133°) was dissolved in 15 ml. of water and a solution of 1.14 g. of picric acid and 0.41 g. of anhydrous sodium acetate was added. The product was separated by filtration and recrystallized from acetone, from 95% ethanol and from water. There were thus obtained small, lemon-yellow needles, m.p. 209.5–210.5°.

Anal. Calcd. for $C_8H_8N_2 \cdot C_6H_3N_3O_7$: C, 46.54; H, 3.08; N, 19.39. Found: C, 46.77; H, 3.13; N, 19.3.

Treatment of 7-Azaindole with Aqueous Base.—7-Azaindole (273 mg., m.p. 105.0–106.5°) was added to 20 ml. of 20% aqueous sodium hydroxide and the mixture refluxed six hours. At the end of the reflux period the ammonia liberated, estimated acidimetrically, corresponded to 0.82% of the theoretical. The sodium hydroxide–7-azaindole mixture was extracted with ether and the extracts dried and evaporated. The residue of slightly pink 7-azaindole weighed 258 mg., m.p. 104.5–105.5°. On admixture with untreated starting material the sample melted at 105.0–106.5°.

Hydrogenation of 7-Methyl-7H-pyrrolo[2,3-b]pyridine.—Compound III, (692.5 mg., purified by distillation) was dissolved in 50 ml. of 95% ethanol and approximately 340 mg. of platinum catalyst from the reduction of platinum oxide was added. The mixture was stirred with hydrogen at atmospheric pressure for 25.5 hours, during which time 98.8% (4.94 moles) of the theoretical hydrogen was absorbed. The catalyst was separated by filtration and the solvent evaporated *in vacuo*. Benzene was added to the residual oil and the clear, colorless solution was dried over potassium carbonate. An attempt was made to distil the product, but because of the small quantity the loss by hold-up was too great and also only an unreliable boiling point, approximately 94–96° (19 mm.), could be obtained. All fractions of the product were therefore combined. The yellow oil weighed 506 mg. (67.8%). It was dissolved in 10 ml. of dry benzene, 429 mg. of phenyl isocyanate was added and the mixture allowed to stand at room temperature for 65 minutes. Evaporation of the benzene on the steam-bath in a stream of nitrogen left a yellow oil which crystallized readily on scratching. A few milliliters of water together with 4 ml. of 5% hydrochloric acid were added and the mixture was warmed slightly. A small quantity of acid-insoluble material was separated by filtration and the cloudy filtrate was treated with Darco and made strongly basic with excess potassium carbonate. The resulting oil crystallized on chilling and scratching. The light-tan 1-phenyl-3-[2-(3-(1-methyl)-piperidyl)-ethyl]-urea (V) was separated by filtration, washed with water and dried *in vacuo* over phosphorus pentoxide; the yield was 0.76 g. (82%), m.p. 85–92°. Recrystallizations from 1:2 ethanol–water produced a material which was apparently hydrated. This had a variable melting range of about five degrees between 85 and 100°. On drying, the crystals appeared to melt partially, then resolidify. When the dried material was recrystallized from cyclohexane and a sample dried *in vacuo* in a melting-point tube a melting point of 100.5–102.0° (sealed capillary) was observed.

Anal. Calcd. for $C_{15}H_{23}N_3O$: C, 68.92; H, 8.89; N, 16.07. Found: C, 68.72; H, 8.90; N, 15.8.

3-(2-Aminoethyl)-pyridine.—3-Pyridineacetonitrile[6] (5.88 g.) was added to 80 ml. of 95% ethanol, 20 ml. of concentrated ammonium hydroxide and an estimated 2–3 g. of Raney nickel, prepared by the method of Pavlic and Adkins.[15] The mixture was shaken with hydrogen at 2 atm. for 7 hours, during which time slightly more than 83% of the amount of hydrogen required for reduction of the nitrile group was absorbed. The catalyst was separated and the ethanol evaporated on the steam-bath. The residual solution was saturated with potassium carbonate and extracted with chloroform. After drying over potassium carbonate the extracts were distilled. There was obtained 4.21 g. (69.3%) of colorless 3-(2-aminoethyl)-pyridine, b.p. 114–119° (15 mm.). Dornow and Schacht[8] who prepared the amine by the Hofmann degradation of β-(3-pyridyl)-propionamide, reported a boiling point of 115.0–115.4° (14 mm.). For identification the amine was converted to its dipicrate. When it was treated with a hot-water solution of two equivalents of picric acid, a product was obtained which on recrystallization from water formed yellow needles, m.p. 213.5–214.0° dec. (reported[8] m.p. 211–212° dec.).

1-Phenyl-3-[2-(3-pyridyl)-ethyl]-urea.—The amine (1.22 g.) was dissolved in 10 ml. of dry benzene and 1.19 g. of phenyl isocyanate was added. Crystals formed on scratching after the mixture had stood for a few minutes. It was allowed to stand for 0.5 hour and the product was separated by filtration, washed with benzene and dried *in vacuo*. There was thus obtained 2.33 g. (96.7%) of white needles, m.p. 112.5–114.5°. The analytical sample was recrystallized from 1:9 ethanol–water and from benzene; m.p. 114.5–115.5°.

Anal. Calcd. for $C_{14}H_{15}N_3O$: C, 69.68; H, 6.28; basic N, 5.80. Found: C, 69.57; H, 6.07; basic N, 5.99.[16]

1-Methyl-3-[2-(1-(3-phenyl)-ureido)-ethyl]-pyridinium Iodide.—The pyridylurea (1.61 g.) was mixed with 9.5 g. of methyl iodide and allowed to stand under nitrogen for 26 hours. The excess methyl iodide was decanted and the residue dried *in vacuo*. There was thus obtained 3.07 g. of yellow solid, m.p. 78–82°. Excess methyl iodide was apparently retained in the product, since the theoretical yield was 2.56 g. A similar phenomenon was noted on methylation of compound III with the same alkylating agent (*vide infra*). In two preparations of the urea derivative, the excess weight corresponded approximately to 0.5 mole of extra methyl iodide per mole of derivative. Recrystallizations from absolute ethanol produced hygroscopic, colorless, translucent prisms. The melting point, which was somewhat variable, was approximately 71.5–74.5° (sealed capillary).

Anal. Calcd. for $C_{15}H_{18}N_3OI$: C, 47.00; H, 4.74; N, 10.96; I, 33.12. Found: C, 46.92; H, 5.21; N, 10.8; I, 33.16.

1-Phenyl-3-[2-(3-(1-methyl)-piperidyl)-ethyl]-urea (V).—To 60 ml. of 95% ethanol and approximately 340 mg. of

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

(16) These determinations, by perchloric acid titration, were carried out by J. F. Alicino.

reduced Adams catalyst was added 1.485 g. of recrystallized methiodide. On stirring with hydrogen at atmospheric pressure for 8 hours, the compound took up 95.2% (2.86 moles) of the theoretical hydrogen. The catalyst was separated and the colorless solution was evaporated to dryness *in vacuo*. Dissolution of as much of the product as possible in dilute hydrochloric acid followed by filtration to remove a small quantity of acid-insoluble material and treatment with excess potassium carbonate produced an oil, which crystallized on rubbing. There was thus obtained 853 mg. (84.4%) of crude product. On recrystallization from ethanol–water and from cyclohexane the same phenomena were observed as with the urea obtained from compound III. The analytical sample had m.p. 99.5–100.5° (sealed capillary). On admixture with the urea obtained from the pyrrolopyridine it melted at 100.5–102.0°. The two samples were also subjected to paper chromatography in *n*-butyl alcohol–acetic acid–water (60:15:25). The spots, which were detected by ultraviolet light (peak efficiency 253.7 mμ), had identical R_f values.

Anal. Calcd. for $C_{15}H_{23}N_3O$: C, 68.92; H, 8.89; N, 16.07. Found: C, 69.07; H, 8.69; N, 15.9.

1-Methyl-7-azaindole (VI).—Finely-powdered commercial sodium amide (1.95 g.) and 100 ml. of sodium-hydride-dried xylene were treated dropwise with stirring with a solution of 5.90 g. of dried 7-azaindole in 50 ml. of dry xylene over a period of about 10 minutes. During the addition most of the sodium amide appeared to dissolve. The mixture was refluxed for a period of eight hours, during which time a reddish solid precipitated on the sides of the flask and a basic gas was evolved. It was then cooled to room temperature and a solution of 7.1 g. of methyl iodide in 50 ml. of xylene was added with stirring over a 30-minute period. The suspension was then refluxed for another two hours. During the addition and heating periods the appearance changed. The red solid vanished and a white precipitate of sodium iodide formed. After the mixture had stood at room temperature overnight, 75 ml. of water and 20 ml. of concentrated hydrochloric acid were added. The layers were separated and the xylene was extracted with another similar quantity of dilute acid. The combined aqueous extracts were washed with ether and made basic with solid potassium carbonate. The liquid was extracted with 600 ml. of ether in six portions, the extracts dried and the solvent evaporated. Distillation of the residue produced 4 g. of a mixture which boiled over a 50° range. Paper chromatograms of this oil alongside of the known compounds indicated the presence not only of an unknown and of unreacted starting material (fluorescence and sodium nitroprusside[2] test), but also the probable presence of 7-methyl-7H-pyrrolo[2,3-b]pyridine and of 7-azaskatole. The presence of the latter was confirmed when crystals formed in the oil on standing. The crude skatole–indole mixture, after washing with cyclohexane, melted at 100–121° and on admixture with authentic 7-azaskatole[2] (m.p. 131–133°) at 110–126°. 7-Azaindole and 7-azaskatole are not appreciably steam-volatile and the relatively pure product was separated by passing steam through the mixture until the distillate was clear. The condensate, after treatment with potassium carbonate, was extracted with ether, the extract dried and the solvent removed. Distillation of the residue produced 1.28 g. (19.4%) of almost colorless oil, b.p. 106–110° (18 mm.), $n^{28}D$ 1.5948. On redistillation a colorless, hygroscopic oil was obtained, b.p. 112–116° (21 mm.), $n^{26}D$ 1.5959, d^{22}_4 1.107. On standing the oil developed a yellow color.

Anal. Calcd. for $C_8H_8N_2$: C, 72.69; H, 6.11; N, 21.20. Found: C, 72.33; H, 6.45; N, 20.9.

2-Methylamino-3-picoline.—2-Amino-3-picoline (21.6 g.) was dissolved in 100 ml. of sodium-dried ether and chilled in an ice-bath. Sodium amide (7.8 g.) was then added all at once, after which vigorous ebullition resulted. The mixture was refluxed for two hours, then cooled to room temperature, after which a solution of 28.4 g. of methyl iodide in 50 ml. of dry ether was added over a period of 35 minutes, with efficient stirring. The suspension was refluxed again for one hour, cooled and 40 ml. of water was added. Excess potassium carbonate was added, the layers were separated and the aqueous layer was extracted with additional portions of ether. The extracts were dried over potassium carbonate and distilled. There was obtained thus 20.75 g. of yellow oil, b.p. 105–115° (22 mm.).

The monomethyl derivative was separated from the dimethylaminopicoline and starting material by the method of Chichibabin and Knunjanz.[12] The crude alkylation product (65.94 g.) was dissolved in 200 ml. of dry pyridine and cooled in an ice-bath after which 170.2 g. of benzoyl chloride was added with swirling over a 12-minute period. The slurry was heated on the steam-bath for 0.5 hour, cooled, and poured into a mixture of 250 ml. of concentrated hydrochloric acid and 790 ml. of water which had previously been cooled to 0°, the temperature being kept below 10° during the addition. Benzoic acid and the dibenzoyl derivative of the starting material were separated by filtration and the filtrate was made basic and extracted with ether. The extracts were dried and distilled. After removal of the pyridine and dimethylaminopicoline the product distilled at 210° (22 mm.) to 220° (20 mm.). On cooling, 85.36 g. of pale-yellow N-methyl-N-[2-(3-methyl)-pyridyl]-benzamide, m.p. 96–98°, was obtained. An analytical sample was obtained by recrystallizations from 1:1 ethanol–water and from *n*-hexane as large clumps of white needles, m.p. 92.0–93.5°.

Anal. Calcd. for $C_{14}H_{14}N_2O$: C, 74.30; H, 6.25. Found: C, 74.65; H, 6.37.

The benzamide (85.36 g.) was refluxed for one hour with 202 ml. of concentrated hydrochloric acid, cooled and the benzoic acid removed by filtration. The filtrate was made strongly basic with potassium carbonate, the product extracted into ether, and the ether solution dried and distilled. Pure 2-methylamino-3-picoline was obtained in 82.6% yield from the benzoyl derivative as a colorless hygroscopic oil. The temperature at the start of the distillation was 114° (22 mm.) and at the end 115° (19 mm.). The analytical sample distilled at 113° (21 mm.) and melted at approximately 21°.

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.80; H, 8.27; N, 22.93; basic N, 11.47. Found: C, 68.35; H, 8.29; N, 22.76; basic N, 11.35.

N-Methyl-N-[2-(3-methyl)-pyridyl]formamide.—The amine (32.96 g.) was formylated by the method of Clemo and Swan for 2-amino-3-picoline,[9] with some modifications. The formamide was an oil and no precipitate was observed after the addition of the anhydride mixture to the ethereal solution of the amine. After two days, ether and other low-boiling materials were removed by distillation up to 60° (23 mm.), the residue was dissolved in 65 ml. of water and potassium carbonate was added in excess. The yellow oil was extracted into ether, dried and distilled. A colorless fraction (26.38 g., 65.0%) of b.p. 151–156° (19 mm.) was taken. The analytical sample distilled at 155° at the same pressure.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.97; H, 6.72; N, 18.66. Found: C, 64.35; H, 6.68; N, 18.8.

Attempted Cyclizations of the Formamide.—An attempt was first made to effect a Madelung cyclization in the presence of sodium anilide and potassium formate.[2] When the formamide was added, vigorous ebullition ensued. The reaction was carried out as usual and the mixture decomposed with water and acetic acid. Instead of extracting with ether at this stage, however, steam was passed through the mixture until the distillate became clear. Excess hydrochloric acid was added to the distillate and it was treated with Darco and filtered. Aniline was then removed by acetylation in the aqueous solution by the addition of excess acetic anhydride and sodium acetate[17] The precipitated acetanilide was removed by filtration and washed with water and dilute hydrochloric acid, and the filtrates were made basic with potassium carbonate. No liquid product was obtained and no odor of 1-methyl-7-azaindole was evident. The preparation was therefore abandoned at this stage.

A second attempt was made to effect the cyclization by the method of Tyson[11] using 1.5 moles of potassium ethoxide per mole of formamide. A reaction took place at 350° as indicated by ebullition and tar formation. The dark mass was maintained at this temperature for a period of 30 minutes, cooled, decomposed with water and steam distilled. The distillate was made acid with hydrochloric acid and extracted with ether to remove acid-insoluble material which was formed in the reaction. It was then made basic with potassium carbonate and extracted with ether and the extracts were dried and distilled. An oil was obtained, b.p.

(17) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, p. 165.

108–112° (18 mm.), $n^{30}D$ 1.5665. This was apparently 2-methylamino-3-picoline, which contained none of the azaindole desired, as shown by its complete conversion to the benzoyl derivative. It was dissolved in pyridine and treated with benzoyl chloride by the method of Chichibabin,[12] except that the benzoylation mixture, after heating, was poured into aqueous potassium carbonate and allowed to stand for 40 minutes, after which it was extracted with ether. After removal of ether and pyridine from the dried extracts the product distilled completely at 212° (19 mm.). On cooling the distillate crystallized; m.p. 91.5–96°.

1,7-Dimethyl-1H-pyrrolo[2,3-b]pyridinium Iodide (VII) from Compound III.—To 0.52 g. of compound III, purified by distillation, was added 5 ml. of methyl iodide and the mixture was allowed to stand under nitrogen for 28 hours. At the end of this period the excess alkylating agent was evaporated and the yellow, solid residue was dried in a vacuum desiccator. There was obtained 1.37 g. of product. This yield corresponds to 0.5 mole of extra methyl iodide per mole of monoalkylation product. Recrystallizations from absolute ethanol produced white needles, m.p. 249.5° with sharp decomposition. The melting point depended greatly on the rate of heating.

Anal. Calcd. for $C_9H_{11}N_2I$: C, 39.43; H, 4.05; basic N, 5.11. Found: C, 39.64; H, 4.02; basic N, 4.97.

When compound III, as obtained from the methiodide, was treated in a similar fashion with methyl iodide the same compound was obtained, also in a yield corresponding to 0.5 mole excess alkyl halide. In this case the white needles decomposed at 261°. The ultraviolet spectrum (water solvent) was essentially identical with that of the product obtained by alkylation of the 1-methyl-7-azaindole. Maxima were observed at 227 mμ (log ε 4.522) and at 296 mμ (log ε 3.888). The analytical data, however, again indicated the presence of impurities.

Compound VII by Methylation of 1-Methyl-7-azaindole.—Compound VI (652 mg.) was mixed with 5 ml. of methyl iodide and allowed to stand under nitrogen for a period of 60 hours, during which time a light-yellow solid was slowly deposited. The excess methyl iodide was evaporated in a stream of nitrogen and the residue was washed with cyclohexane. There was thus obtained 597 mg. (44.2%) of alkylation product. From the cyclohexane washings there was obtained, on evaporation, 275 mg. of starting material (42.2%). On recrystallization from absolute alcohol the product melted at 250.5° dec. On admixture with the alkylation product from compound III (obtained from the *p*-toluenesulfonate), a melting point of 251.5° dec. was observed. The ultraviolet spectrum of an aqueous solution had absorption maxima at 227 mμ (log ε 4.506) and at 296 mμ (log ε 3.882).

Anal. Calcd. for $C_9H_{11}N_2I$: C, 39.43; H, 4.05; N, 10.22; I, 46.29. Found: C, 39.65; H, 4.19; N, 10.4; I, 46.0.

Ultraviolet Spectra.—All spectra were measured on a Beckman model DU quartz spectrophotometer at concentrations ranging from 5×10^{-5} to 1.3×10^{-4} *M*. The solvent was in all cases cyclohexane unless otherwise specified.

AMHERST, MASSACHUSETTS

[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

Triazines. XIII. The Ring Cleavage of *s*-Triazine by Primary Amines. A New Method for the Synthesis of Heterocycles[1,2]

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Primary amines cleave *s*-triazine completely under evolution of ammonia and formation of the corresponding N,N′-disubstituted formamidines. Applied to suitable diamines, this reaction which occurs under mild conditions and with high yields provides a valuable method for the synthesis of various heterocycles, such as imidazolines, tetrahydropyrimidines, purines, benzoöxazoles and benzothiazoles.

During our recently reported studies of the halogenation of *s*-triazine[3] we tried to obtain, besides the described 2,4-dichloro-*s*-triazine,[4] the yet unknown monochloro-*s*-triazine by treating an excess of *s*-triazine with chlorine. Working up such reaction mixtures, after treatment with aniline in order to convert the unstable chlorides into the corresponding anilino-*s*-triazines, did not result in the expected 2-anilino-*s*-triazine, which has previously been prepared by a different route.[5a] However, besides 2,4-dianilino-*s*-triazine and 2,4,6-trianilino-*s*-triazine a considerable amount of N,N′-diphenylformamidine (IV) was found which could originate only from unreacted *s*-triazine still present in the chlorination mixture.

This assumption was confirmed by treating aniline with pure *s*-triazine; N,N′-diphenylformamidine was formed almost quantitatively with evolution of ammonia.[5b] The yield of the latter indicates that all three methine groups contained in the *s*-triazine ring participate in this peculiar ring cleavage, the only by-product being three moles of ammonia. The same reaction occurs as well with other aromatic, aliphatic, hydroaromatic and heterocyclic primary amines, under conditions which are given in general in the Experimental part of this paper. Table I lists some of the compounds obtained. These results recommend the reaction of *s*-triazine with primary amines as the best method for the synthesis of N,N′-symmetrical substituted formamidines.

Previously described procedures give often unsatisfactory results and are of limited applicability. Under any circumstances the present method is superior in yield and in ease of carrying out the reaction.

The reaction seems to be strictly limited to pri-

(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation, sponsored by the Olin Mathieson Chemical Corporation.

(2) Preceding communication: Ch. Grundmann, H. Schröder and W. Ruske, *Chem. Ber.*, **87**, 1865 (1954).

(2a) Presented before the Division of Organic Chemistry at the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, March 30, 1955.

(3) Ch. Grundmann and A. Kreutzberger, THIS JOURNAL, **77**, 44 (1955).

(4) Ch. Grundmann and E. Beyer, *ibid.*, **76**, 1948 (1954); I. Hechenbleikner, *ibid.*, **76**, 3032 (1954).

(5) (a) R. Hirt, H. Nidecker and R. Berchtold, *Helv. Chim. Acta*, **33**, 1365 (1950). (b) L. E. Hinkel, E E. Ayling and J. H. Beynon (*J. Chem. Soc.*, 678 (1935)), have already described the reaction of their "iminoformylcarbylamine"—which is in fact *s*-triazine—with aniline and some other aromatic amines obtaining aromatic disubstituted formamidines. Of course, on the basis of their false formula they were not able to interpret the mechanism correctly and they did not recognize the wide applicability of this reaction, especially for the synthesis of heterocycles.