The suspension was filtered, and the residue was extracted repeatedly[16] with hot water until ultraviolet absorption indicated completion of the extraction. The filtrate and extracts on evaporation to dryness at 40°, yielded 3.12 g (15.8 mmoles, 84%) of crude dicarboxylic acid. On purification by chromatography on Dowex-1 formate[6] followed by recrystallization from water, the product agreed fully in melting point, ultraviolet spectrum, and enzymological properties with the product isolated from bacterial culture media.[5]

Decarboxylation of 2-Methyl-3-hydroxypyridine-4,5-dicarboxylic Acid (VII).—Compound VII (197 mg, 1 mmole) was suspended in 10 ml of nitrobenzene in a small flask fitted with a nitrogen inlet tube and reflux condenser, with a carbon dioxide absorber connected to the condenser. Under a slow stream of nitrogen, the suspension was heated to 180–200° (oil bath) and maintained at this temperature until no more carbon dioxide was evolved (about 1 hr). The yield of carbon dioxide was 0.97 equiv. Most of the reaction products separated from the cooled nitrobenzene solution. The balance was obtained by extraction of the filtrate with 1 *M* aqueous ammonia in the presence of a little carbon tetrachloride to aid in the separation of the phases. The excess ammonia was evaporated, and the products were precipitated by adjusting the solution to pH 3.

The crude mixture was applied to a Dowex-1 formate column (2.2 × 28 cm) and eluted by increasing formic acid concentrations. The three major components, in order of elution, were VIII (eluted by 0.1 *M* formic acid, 35% yield), IX (eluted by 2 *M* formic acid, 33% yield), and unreacted starting material, VII (eluted by 5 *M* formic acid, 8%). Compound IX crystallized from water to give fine rods: mp 302–308° dec; λ_{max} (0.1 *M* HCl) 312 mμ (a_m 7200), (0.1 *M* NaOH) 307 mμ (a_m 5900), (0.1 *M* phosphate, pH 7.0) 307 mμ (a_m 5900).

Anal. Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.77; H, 4.56; N, 9.38.

Methyl 2-Methyl-3-hydroxypyridine-4-carboxylate (IX Methyl Ester).—Compound IX (200 mg, 1.3 mmoles) in 15 ml of methanol was saturated with hydrogen chloride and refluxed for 14 hr. The solvent was removed below 40°, 10 ml of water was added, and excess sodium bicarbonate was added. The product was extracted into three 25-ml portions of ethyl acetate, and the extract was dried with sodium sulfate. Upon partial evaporation and cooling, 145 mg (0.87 mmole, 67%) of the ester crystallized out. The ester sublimed at 100° and 14 mm (oil bath), forming colorless platelets on the seeded condenser: mp 48.5°; λ_{max} (0.1 *M* HCl) 315 mμ (a_m 7000), (0.1 *M* NaOH) 343 mμ (a_m 5500), (0.1 *M* phosphate, pH 7.0) λ_{max} 322 mμ (shoulder at 350 mμ) (a_m 4300).

Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.15; H, 5.27; N, 7.92.

2-Methyl-3-hydroxy-4-hydroxymethylpyridine Hydrochloride (X HCl). Compound IX methyl ester (150 mg, 1.1 mmoles) in 15 ml of dry ether was added dropwise to 40 mg of lithium aluminum hydride in 25 ml of ether. The solution was refluxed for 20 min; excess reductant was destroyed by addition of ethyl acetate. After evaporation to dryness, the residue was dissolved in water, applied to a Dowex-1 formate column, and eluted with 0.2 *M* formic acid. The eluate was evaporated to dryness and the residue was dissolved in water and applied to a Dowex-50 column (acid form). After washing with water the column was eluted with 5 *M* hydrochloric acid. The first ultraviolet-absorbing fraction (λ_{max} 283 mμ) was collected, concentrated to a small volume, decolorized with charcoal, and evaporated to dryness. After washing in ethanol, the crystalline product melted at 165–168° (lit.[17] mp 165–166°); λ_{max} (0.1 *M* HCl) 233 and 283 mμ (a_m 3000 and 6900, respectively), (0.1 *M* NaOH) λ_{max} 260 and 319 mμ (a_m 8000 and 5800, respectively), (0.1 *M* phosphate, pH 7.0) 248 and 312 mμ (a_m 6500 and 7600). The product is easily distinguished by chromotography and spectrum from the isomeric 2-methyl-3-hydroxy-5-hydroxymethylpyridine.[6]

Decarboxylation of 2-Methyl-3-methoxypyridine-4,5-dicarboxylic Acid (Va).—A suspension of Va (211 mg, 1 mmole) in 15 ml of nitrobenzene was heated under nitrogen to 180–190° for 0.5–1 hr as described earlier for VII. The compound dissolved completely, and the yield of carbon dioxide was quantitative. The decarboxylation product, which crystallized on cooling, was washed with benzene and ether, then sublimed at 180° (14 mm) to give a 90% yield of VIa as small, colorless prisms: mp 224°; λ_{max} (0.1 *M* HCl) 242 and 298 mμ (a_m 5100 and 9970, respectively), (0.1 *M* NaOH) 227 and 228 mμ (a_m 6700 and 7400), (0.1 *M* phosphate, pH 7.0), 227 and 288 mμ (a_m 6500 and 7400).

Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.79; H, 5.61; N, 8.64.

Decarboxylation of 2-Methyl-3-benzyloxypyridine-4,5-dicarboxylic Acid (Vb).—A suspension of Vb (2.87 g, 10 mmoles) in 40 ml of nitrobenzene was heated at 180–190° as described earlier. The compound dissolved completely; after 10 min CO_2 evolution ceased and the flask was cooled. The crude products were separated by filtration and ammonia extraction of the nitrobenzene layer as described earlier. The crude product (1 g) was suspended in 2 *M* hydrochloric acid (170 ml), heated, cooled, and filtered. The unreacted Vb remained on the filter. On adjusting the filtrate to pH 3, VIb crystallized as small plates: mp 230–231°; yield 43%; λ_{max} (0.1 *M* HCl) 242 and 297 mμ (a_m 7000 and 8900, respectively), (0.1 *M* NaOH) 287 mμ (a_m 6600), (0.1 *M* phosphate, pH 7.0) 287 mμ (a_m 6600).

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 68.94; H, 5.32; N, 5.67. Found: C, 69.12; H, 5.38; N, 5.76.

2-Methyl-3-hydroxypyridine-5-carboxylic Acid (VIII). A. From VIa.—One millimole (167 mg) of VIa was gently refluxed in 5–10 ml of 48% HBr for 4 hr, then evaporated to dryness under reduced pressure. The residue was dissolved in a little water, and the product was precipitated by adjusting to pH 3 and recrystallized from water (yield 70%). The compound was identical both in spectral and chromatographic properties with the product from natural sources;[6] like the latter, it sublimed at 280–300°, but on rapid heating underwent modification at about 305° and sublimed at 325–330°.

B. From VIb.—Crude VIb (2.3 g) in 1 l. of methanol–water (1:1, v/v) was hydrogenated at room temperature and pressure over 400 mg of palladium–charcoal catalyst. About 10.5 mmoles of hydrogen was absorbed. The filtrate was evaporated to 200 ml at 40°, applied to a column of Dowex-1 formate (4 × 42 cm), and eluted with formic acid. A total of 933 mg (6.1 mmoles) of VIII was obtained by evaporation of the appropriate fractions. The over-all yield (from Vb *via* VIb to VIII) was 36%.

Registry No.—III, 4753-19-9; IVb, 7442-21-9; Va, 7442-22-0; Vb, 7442-23-1; VIa, 7442-24-2; VIb, 7442-25-3; VIII, 7428-22-0; IX, 4328-92-1; X, 7442-27-5; IX methyl ester, 7442-72-0; X HCl, 7442-73-1.

(16) During the reaction a gray precipitate containing much of the product formed. This was prevented in later experiments by doubling the amount of solvent and increasing the water to 20–50% by volume.

(17) G. J. Martin, S. Avakian, and J. Moss, *J. Biol. Chem.*, **174**, 495 (1948).

Synthesis and Reactions of 5-Bromoskatole and 5-Bromo-1,3-dimethylindole[1a]

WAYLAND E. NOLAND AND CHARLES REICH[1b]

School of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

Received October 18, 1966

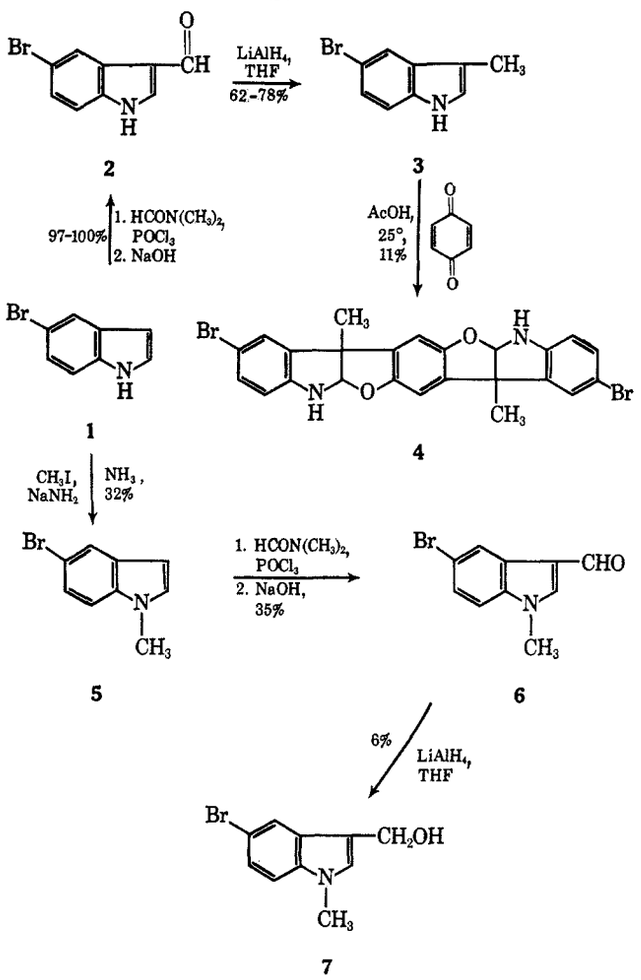
Skatole (3-methylindole) and 1,3-dimethylindole are appropriate model compounds for the more complex 3-alkylindoles, such as those derived biogenetically from tryptophan and tryptamine. We desired the benzene ring (*bz*) monobromoskatoles and 1,3-dimethylindoles as reference compounds for bromination studies and as synthetic intermediates. The synthesis of 5-bromoskatole (**3**) and 5-bromo-1,3-dimethylindole (**8**) is described here.

(1) (a) This investigation was supported in part by U. S. Public Health Service Research Grant No. CA-04073-05 from the National Cancer Institute. The work was presented in part by C. R. as a paper entitled "Synthesis of 5-Bromo-3-methylindole" at the Sixth Annual Undergraduate Chemistry Symposium, Macalester College, St. Paul, Minn., April 27, 1963, Abstracts pp 23–26; (b) Undergraduate Research Assistant 1962–1963;[1a] National Science Foundation Undergraduate Research Participant, summer 1963, supported by Grant No. NSF-GE-1143.

The commercially available 5-bromoindole (**1**) was formylated by the Vilsmeier procedure to the known[2] 5-bromoindole-3-carboxaldehyde (**2**). Reduction of **2** with lithium aluminum hydride in tetrahydrofuran (THF) gave the desired 5-bromoskatole (**3**). Reaction of 5-bromoskatole with *p*-benzoquinone in acetic acid gave a 2:1 adduct ($-H_2$), the structure of which (**4**) is assigned by analogy with that established[3] for the corresponding product of skatole and *p*-benzoquinone.

N methylation of 5-bromoindole to 5-bromo-1-methylindole (**5**, was accompanied by some debromination), Vilsmeier formylation to 5-bromo-1-methylindole-3-carboxaldehyde (**6**), and reduction with lithium aluminum hydride in tetrahydrofuran gave 5-bromo-1-methylindole-3-methanol (**7**, Scheme I). Isolation of

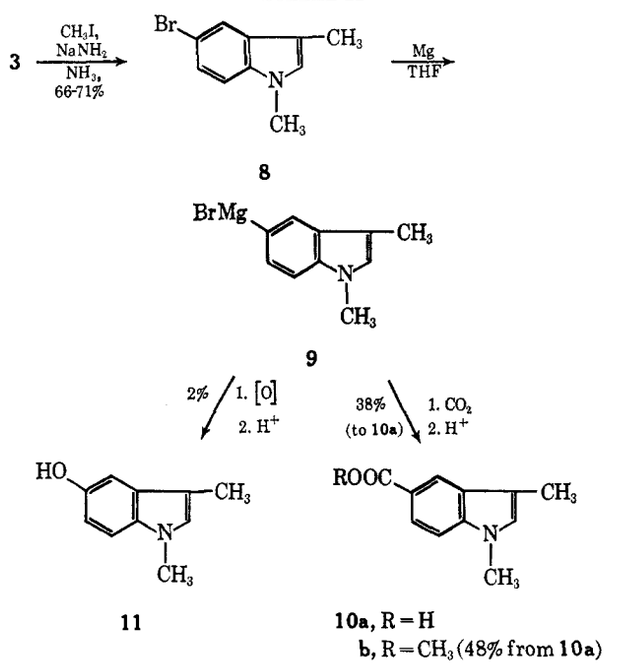
SCHEME I



the 3-methanol instead of the 3-methyl derivative is consistent with the generalization of Leete[4] that indole-3-methanol derivatives having an N-alkyl substituent (in contrast to an NH group[5]) are not reduced to 3-methylindoles with lithium aluminum hydride.

N methylation of 5-bromoskatole gave 5-bromo-1,3-dimethylindole (**8**). Metallation of **8** with magnesium in tetrahydrofuran gave the Grignard reagent, 1,3-dimethylindol-5-ylmagnesium bromide (**9**), as shown by carbonation to an acid, 1,3-dimethylindole-5-carboxylic acid (**10a**), which was also converted to a methyl ester (**10b**). Oxidation of the Grignard reagent (**9**) either with oxygen or with methyl borate and hydrogen peroxide[6] gave the corresponding phenol, physostigmol (**11**), a known degradation product[7] of the alkaloid physostigmine. To our knowledge, these examples (**8** → **9** → **10** and **11**) are the first preparations and uses of a Grignard reagent on the benzene ring portion of the indole nucleus. (See Scheme II.)

SCHEME II



Several approaches to the synthesis of the isomeric 5-bromo-2-methylindole were also investigated. The Fischer indole synthesis is reported to proceed[8] by heating acetone *p*-bromophenylhydrazone with zinc chloride (8[8a]–45 %[8d] yield), preferably in cumene under a nitrogen atmosphere.[8d] In our hands, when the Fischer indole synthesis was attempted with boron fluoride etherate in refluxing acetic acid for 2 hr, unchanged acetone *p*-bromophenylhydrazone was recovered in 53% yield. Heating of the latter compound in polyphosphoric acid to 130° caused a sudden temperature rise to 170°, with formation of a black, carbonaceous product. Attempted preparation[9] of 5-bromo-2-methylindole by the Madelung synthesis by heating 4′-bromo-*o*-acetotoluidide[10] with sodium amide according to the procedure for 2-methylindole[11] was

(2) G. Cavallini, F. Ravenna, and I. Grosso, *Farmaco* (Pavia) *Ed. Sci.*, **13**, 113 (1958); *Chem. Abstr.*, **52**, 20126 (1958).
(3) W. E. Noland and F. J. Baude, *J. Org. Chem.*, **31**, 3321 (1966).
(4) E. Leete, *J. Am. Chem. Soc.*, **81**, 6023 (1959).
(5) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).
(6) M. F. Hawthorne, *J. Org. Chem.*, **22**, 1001 (1957).
(7) F. Straus, *Ann. Chem.*, **406**, 332 (1914).
(8) (a) G. Quadbeck and E. Röhm, *Z. Physiol. Chem.*, **297**, 229 (1954); (b) V. Colo, B. Asero, and A. Vercellone, *Farmaco* (Pavia) *Ed. Sci.*, **9**, 611 (1954); *Chem. Abstr.*, **49**, 14733*c* (1954); (c) Farmaceutici Italia, S. A., British Patent 773,440 (July 3, 1954); *Chem. Abstr.*, **51**, 12147*d* (1957) (this is the patent covering ref 8b); (d) N. B. Chapman, K. Clarke, and H. Hughes, *J. Chem. Soc.*, 1424 (1965).
(9) J. T. Henderson and W. E. Noland, unpublished work, University of Minnesota, March 1966.
(10) (a) E. Wroblevsky, *Ann. Chem.*, **168**, 162 (1873); (b) prepared[9] in 90% over-all yield, mp 159.5–160.5°, from *o*-toluidine by the method for 2′-bromo-*p*-acetotoluidide: J. R. Johnson and L. T. Sandborn, "Organic Syntheses," Coll. Vol. I, A. H. Blatt, Ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p 111; *Org. Syn.*, **6**, 8 (1926).
(11) C. F. H. Allen and J. A. VanAllan, "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., John Wiley and Sons, Inc., New York, N. Y., 1955, p 597; *Org. Syn.*, **22**, 94 (1942).

unsuccessful. When the bath temperature had reached about 100°, a vigorous evolution of white fumes occurred and the black residue was left completely charred. A successful alternative to the Fischer indole synthesis with zinc chloride is the indoline method,[12] in which 2-methylindoline is brominated to 5-bromo-2-methylindoline (63% yield), which is then dehydrogenated with chloranil in refluxing xylene to 5-bromo-2-methylindole (54%).

Experimental Section

Melting points were determined on a calibrated Fisher-Johns hot stage. Ultraviolet spectra were determined on Bausch and Lomb Spectronic 505 or Beckman DK-2 spectrophotometers, and infrared spectra were determined on a Perkin-Elmer 21 spectrophotometer. Microanalyses were performed by Mrs. Olga Hamerston and her assistants, Lawrence L. Landucci, John H. Sellstedt, Mrs. Kathleen Nelson Juneau, and Brian H. Chollar at the University of Minnesota, or by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

5-Bromoindole (1).—The sample was obtained from the Aldrich Chemical Co.: mp 91–92°; λ_{max} (95% ethanol) 222 mμ (log ε 4.61), 280 (3.75), 287 (3.74), 297 (3.59); ν_{NH} (Nujol) 3400 ms, $\nu_{C=C}$ 1625 w, 1595 mw, 1560 m cm^{-1}.

5-Bromoindole-3-carboxaldehyde (2).—This compound, previously prepared by Cavallini, Ravenna, and Grosso[2] from 5-bromoindole in 13% yield by Vilsmeier formylation with N-methylformanilide, was prepared in the present work with N,N-dimethylformamide according to the procedure of James and Snyder[13] for indole-3-carboxaldehyde. Phosphorus oxychloride (25.9 cc, 0.283 mole) was added with stirring over a period of 0.5 hr to N,N-dimethylformamide (86 cc, 1.11 moles) and cooled to 10°, giving a pinkish orange solution. 5-Bromoindole (50.0 g, 0.255 mole) was then added rapidly with stirring but at a rate such that the temperature did not rise above 10°, giving a yellow solution. The solution was stirred at 10° for 1 hr and was then warmed to 35° and stirred at 35° for another hour, causing a thick, canary-yellow paste to set. Ice (100 g) was then added, with stirring, causing the paste to dissolve into a cherry-red solution. Additional ice (100 g) was added, and then a solution of sodium hydroxide (112.8 g, 2.82 moles) in water (300 cc) was added, dropwise with stirring until about one-third had been added and the solution had turned yellow-green. The resulting mixture was heated rapidly to the boiling point, causing evolution of dimethylamine and formation of a yellow-orange precipitate (56.0 g, 98%), mp 210°. Crystallization from ethanol gave a nearly white solid: mp 211° (lit.[2] mp 205°); λ_{max} (95% ethanol) 248 mμ (log ε 4.23), 260 inflection (4.16), 292 inflection (4.11), 296 (4.13); ν_{NH} (Nujol) 3150 ms, $\nu_{C=O}$ 1639 s, $\nu_{C=C}$ 1567 w, 1520 mw cm^{-1}.

Similar formylations, but on 48 and 150% of the scale described here, gave yields of 100%, mp 211°, and 97%, mp 204–210°.

5-Bromoskatole (3).—A solution of 5-bromoindole-3-carboxaldehyde (56.0 g, 0.250 mole) in dry tetrahydrofuran (dried over sodium, 350 cc) was added dropwise, with stirring, under nitrogen to a suspension of lithium aluminum hydride (19.0 g, 0.50 mole) in dry tetrahydrofuran (100 cc). The reaction was very exothermic, causing the tetrahydrofuran to reflux. The mixture was refluxed for 4 hr and then kept at room temperature for 24 hr. The excess lithium aluminum hydride (0.25 mole) was decomposed first with ethyl acetate (90 cc) and then with water (100 cc). The inorganic salts were separated by decantation and extracted with ether (2 l.). The combined decantate and ether extracts were concentrated until the volume of the ether layer was about 200 cc, and the water layer was separated. The ether layer was treated with charcoal (which removed no color), dried (Na_2SO_4), and evaporated, leaving after cooling an orange-yellow solid. Crystallization from petroleum ether (bp 60–68°) gave whitish tan crystals (40.8 g, 78%), mp 75–79°. Four recrystallizations of a sample from another run gave white, plate-like crystals, mp 79.5–80.5°, which become slightly yellow on contact with air: λ_{max} (95% ethanol) 228 mμ (log ε 4.58), 286 inflection (3.69), 291 (3.71), 300 inflection (3.61); ν_{NH} (Nujol) 3410 s, $\nu_{C=C}$ 1624 w, 1562 mw cm^{-1}.

Anal. Calcd for C_9H_8BrN (210.08): C, 51.45; H, 3.84; N, 6.67. Found: C, 51.39; H, 3.87; N, 6.73.

Similar reductions, but on 29 and 93% of the scale described here, gave yields of 40%, mp 78–79°, and 62%, mp 78–80°.

2,9-Dibromo-7b,14b-dimethyl-5a,7b,12a,14b-tetrahydrobisindolo[2,3-*b*:2′,3′-*b*′]benzo[1,2-*d*:4,5-*d*′]difuran (4).—A solution of 5-bromoskatole (3.00 g, 0.0143 mole) and *p*-benzoquinone (2.32 g, 0.0214 mole) in glacial acetic acid (25 cc) was stirred at room temperature for 3 days. The resulting black precipitate was filtered from the black solution and washed with more acetic acid until a tan solid remained. Crystallization from dioxane, with charcoal, gave a light gray powder (0.40 g, 11%), mp 267–270° dec.

In an earlier run, a solution of 5-bromoskatole (5.33 g, 0.0254 mole) and *p*-benzoquinone (3.62 g, 0.0334 mole) in glacial acetic acid (50 cc) was also stirred at room temperature for 72 hr. The resulting dark brown precipitate (2.55 g, 38%) was filtered and washed with ethanol. The dark brown solid was insoluble in 1,2,4-trichlorobenzene, but crystallization from N,N-dimethylformamide gave a white solid, mp 263–265° dec. Two recrystallizations from N,N-dimethylformamide gave a white solid, mp 264–265° dec, which was shown by its infrared spectrum in Nujol and by elemental analyses to contain N,N-dimethylformamide, probably occluded within the crystal lattice. Recrystallization from dioxane, however, gave white needles, mp 265–266° dec, which were free of solvent: λ_{max} (tetrahydrofuran) 234 mμ (log ε 4.42), 258 (4.37), 303 plateau (4.04), 328 (4.18); ν_{NH} (Nujol) 3390 m, $\nu_{C=C}$ 1601 m cm^{-1}.

Anal. Calcd for $C_{24}H_{18}Br_2N_2O_2$ (526.23): C, 54.78; H, 3.45; N, 5.32. Found: C, 54.58; H, 3.71; N, 5.09.

1-Benzyl-5-bromoindole.—The compound was prepared essentially by the procedure of Plieninger[14] for 1-benzylindole and 1-benzyl-4-bromoindole, except that the sodium amide was prepared from reaction of sodium, in the presence of a pinch of ferric nitrate, with the liquid ammonia used as the solvent for the reaction. Thus, sodium (7.04 g, 0.306 g-atom) in liquid ammonia (400 cc) with 5-bromoindole (50.0 g, 0.255 mole) and benzyl chloride (35.4 cc, 0.308 mole) gave, after extraction of the hydrolyzed residue with ether and chloroform (which proved to be a better solvent than ether) and crystallization of the yellow solid from methylene chloride–petroleum ether (bp 60–68°), yellowish crystals (46.5 g, 64%): mp 84–88°; λ_{max} (95% ethanol) 227 mμ (log ε 4.53), 281 (3.71), 290 (3.69), 302 inflection (3.50). One recrystallization from ethanol (which was found to be a better solvent) to which a little water was added gave shiny, white crystals (82% recovery): mp 87–88°[15] (lit.[16] mp 88–89° uncor); ν_{NH} (Nujol) none, $\nu_{C=C}$ 1605 mw, 1585 w, 1560 w cm^{-1}. Elemental analyses have not previously been reported.[16]

Anal. Calcd for $C_{15}H_{12}BrN$ (286.17): C, 62.95; H, 4.23; Br, 27.93; N, 4.89. Found: C, 62.68; H, 4.12; Br, 27.72. N, 4.70.

5-Bromo-1-methylindole (5).—The compound was prepared essentially by the procedure of Potts and Saxton[17] for methylation of indole to 1-methylindole. Thus, sodium (6.46 g, 0.281 g-atom) in liquid ammonia (400 cc) containing ferric nitrate nonahydrate (0.1 g) with 5-bromoindole (50.0 g, 0.255 mole) in anhydrous ether (50 cc) and methyl iodide (40.0 g, 0.282 mole) in anhydrous ether (40 cc) gave, after vacuum distillation of the residual red-brown oil, a forerun (1 cc), bp 75° (6.5 mm), and a main fraction as a colorless oil (38.9 g, 35 cc, 73%): bp 155° (6.5 mm), $n^{25}D$ 1.6376. Since a strong NH band was still present in the oil, the methylation procedure was repeated, using identical quantities except that the main fraction of the distillate was used in place of the 5-bromoindole. Vacuum distillation of the product gave a very pale yellow oil (17.0 g, 32%): bp 148° (4.8 mm), $n^{26}D$ 1.6322 [lit.[18] bp 147–148° (4 mm), $n^{20}D$ 1.6392]. A black tar remained as a residue from the distillation. The sample analyzed had $n^{26}D$ 1.6301; λ_{max} (95% ethanol) 227 mμ (log ε 4.51), 280 (3.77), 291 inflection (3.71), 303 inflection (3.56); ν_{NH}? (neat)

(12) A. P. Terent'ev, M. N. Preobrazhenskaya, A. S. Bobkov, and G. M. Sorokina, *J. Gen. Chem. USSR*, **29**, 2504 (1959).

(13) P. N. James and H. R. Snyder, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley and Sons, Inc., New York, N. Y., 1963, p 539; *Org. Syn.*, **39**, 30 (1959).

(14) H. Plieninger, *Chem. Ber.*, **87**, 127 (1954).

(15) We are indebted to Dr. S. P. Hiremath for purification of this sample. Microanalyses were performed by Dr. T. S. Prokopov at the University of Minnesota.

(16) G. Ehrhart and I. Hennig, *Arch. Pharm.*, **294**, 550 (1960).

(17) K. T. Potts and J. E. Saxton, *Org. Syn.*, **40**, 68 (1960).

(18) A. P. Terent'ev and M. N. Preobrazhenskaya, *J. Gen. Chem. USSR*, **29**, 322 (1959).

3390 vw, 3360 vw, $\nu_{C=C}$ 1620 mw, 1608 mw, 1575 m, 1564 m, 1513 ms, 1500 ms cm^{-1}. The elemental analyses suggest that some debromination had taken place.

Anal. Calcd for C_9H_8BrN (210.08): C, 51.45; H, 3.84; N, 6.67. Found: C, 55.46; H, 4.74; N, 7.81.

5-Bromo-1-methylindole-3-carboxaldehyde (6).—The procedure is that of James and Snyder[13] for the Vilsmeier formylation of indole to indole-3-carboxaldehyde. Phosphorus oxychloride (8.2 cc, 0.089 mole) was added, with stirring, over a period of 0.5 hr to N,N-dimethylformamide (27.3 cc, 0.352 mole) cooled to 10°, giving a pink solution. 5-Bromo-1-methylindole (15.0 g, 0.0714 mole) was then added dropwise, with stirring, at a rate such that the temperature of the resulting dark red paste did not rise above 10°. The mixture was stirred for 1 hr and then crushed ice was added, causing the dark red paste to become a cherry-red solution. A solution of sodium hydroxide (37.6 g, 0.94 mole) in water (200 cc) was added, dropwise with stirring until about one-third had been added and the solution had turned yellow-green, with the appearance of a precipitate. The remainder of the sodium hydroxide solution was added rapidly. The resulting suspension was heated to the boiling point for 1 hr, causing evolution of dimethylamine. The precipitate which settled out was crystallized from methylene chloride–petroleum ether (bp 60–68°), giving a yellow solid (5.97 g, 35%), mp 130–133°. Sublimation at 120° (1 mm) and recrystallization from methylene chloride–petroleum ether (bp 60–68°) gave very pale tan needles; mp 138°; λ_{max} (95% ethanol) 220 mμ (log ε 4.46), 253 (4.25), 301 (4.15); $\nu_{C=O}$ (Nujol) 1650 s, $\nu_{C=C}$ 1603 m, 1561 mw, 1530 ms cm^{-1}.

Anal. Calcd for $C_{10}H_8BrNO$ (238.09): C, 50.44; H, 3.39; N, 5.88. Found: C, 50.56; H, 3.36; N, 5.83.

5-Bromo-1-methylindole-3-methanol (7).—A solution of 5-bromo-1-methylindole-3-carboxaldehyde (5.18 g, 0.0218 mole) in dry tetrahydrofuran (100 cc) was added dropwise over a period of 2 hr to lithium aluminum hydride (1.66 g, 0.0438 mole) under a nitrogen atmosphere. The reaction was mildly exothermic, and the mixture turned pea green. The mixture was refluxed for 4 hr and then kept overnight. The excess lithium aluminum hydride was decomposed first with ethyl acetate and then with water. The inorganic salts were separated by decantation and extracted with ether. The ether layer and extracts were separated from the water, treated with charcoal, dried ($MgSO_4$), and evaporated, leaving a light brown oil, which solidified. Crystallization from ether gave a solid (0.3 g, 6%), mp 100–101°. Recrystallization from ether–petroleum ether (bp 60–68°) gave large, pinkish needles: mp 100–101°; λ_{max} (95% ethanol) 229 mμ (log ε 4.52), 284 inflection (3.69), 293 (3.69), 305 inflection (3.57); ν_{OH} (Nujol) 3330 ms, 3230 m, $\nu_{C=C}$ 1612 w, 1592 w, 1565 mw inflection, 1554 m cm^{-1}.

Anal. Calcd for $C_{10}H_{10}BrNO$ (240.10): C, 50.02; H, 4.20; N, 5.83. Found: C, 50.33; H, 4.34; N, 5.69.

5-Bromo-1,3-dimethylindole (8).—The procedure is that of Potts and Saxton[17] for the methylation of indole to 1-methylindole. Sodium (2.83 g, 0.123 g-atom) was added very slowly, with vigorous stirring, at a rate just sufficient to maintain a deep blue color, to liquid ammonia (400 cc) containing ferric nitrate nonahydrate (0.06 g). Thirty minutes after the addition was complete the blue color of the solution had disappeared and the light gray color of sodium amide was apparent. A solution of 5-bromoskatole (23.8 g, 0.113 mole) in anhydrous ether (50 cc) was then added slowly, with stirring, over a period of 30 min, followed by dropwise addition of a solution of methyl iodide (18.4 g, 0.130 mole) in anhydrous ether (19 cc). Stirring was continued for 1 additional hr, the ammonia was allowed to evaporate overnight, and the remaining ammonia was evaporated by heating on a steam bath for 30 min. Water (100 cc) and ether (100 cc) were added, the ether layer was separated, and the water layer was extracted with ether (two 50-cc portions). The combined ether layer and extracts were dried (Na_2SO_4) and evaporated. The residual oil was vacuum distilled, giving a viscous, yellow oil (16.6 g, 66%): bp 148° (1.5 mm); $n^{26}D$ 1.6236; λ_{max} (95% ethanol) 233 mμ (log ε 4.53), 289 inflection (3.63), 296 (3.64); ν_{NH} (neat) none, $\nu_{C=C}$ 1608 w, 1560 mw cm^{-1}.

Anal. Calcd for $C_{10}H_{10}BrN$ (224.10): C, 53.59; H, 4.50; N, 6.25. Found: C, 53.95; H, 4.32; N, 6.53.

The infrared spectrum was different from that of 5-bromo-1-methylindole.

In a similar run, using sodium (4.54 g, 0.197 g-atom) in liquid ammonia (500 cc) containing ferric nitrate nonahydrate (0.1 g) with 5-bromoskatole (37.7 g, 0.179 mole) in anhydrous ether (100 cc) and methyl iodide (28.0 g, 0.197 mole) in anhydrous ether (30 cc), 5-bromo-1,3-dimethylindole was obtained as a dark red oil (28.4 g, 71%), $n^{25}D$ 1.6220, ν_{NH} (neat) none.

1,3-Dimethylindole-5-carboxylic Acid (10a).—Magnesium turnings (1.3 g, 0.0535 g-atom) were dried by heating for 0.5 hr, and then dry tetrahydrofuran (25 cc) was added. 5-Bromo-1,3-dimethylindole (12.0 g, 0.0535 mole) was added dropwise under nitrogen, with vigorous stirring. A crystal of iodine was added and the mixture was refluxed for 5 hr until all of the magnesium had dissolved. Carbon dioxide was then passed in until the solution was saturated and had turned black. The solution was refluxed for 2 hr, kept overnight, and then hydrolyzed with aqueous 10% sulfuric acid. The tetrahydrofuran layer was separated, treated with charcoal, dried ($MgSO_4$), and evaporated. The dark brown residue was dissolved in aqueous 10% sodium bicarbonate, again treated with charcoal, and added slowly, with vigorous stirring, to aqueous 10% hydrochloric acid, giving a light brown precipitate (3.90 g, 38%), mp 228–231°. Crystallization from acetone–water gave white crystals: mp 237°; λ_{max} (95% ethanol) 248 mμ (log ε 4.60), 292 mμ (log ε 3.74); ν_{OH} (halocarbon oil) 2580 mw (broad), 2500 mw (inflection), 2200 w (inflection), $\nu_{C=O}$ 1670 s, $\nu_{C=C}$ 1605 m, 1570 mw cm^{-1}.

Anal. Calcd for $C_{11}H_{11}NO_2$ (189.21): C, 69.82; H, 5.86; N, 7.40. Found: C, 69.61; H, 6.03; N, 6.83, 6.74.

Methyl 1,3-Dimethylindole-5-carboxylate (10b).—A solution of 1,3-dimethylindole-5-carboxylic acid (1.0 g, 0.0053 mole) in methanol (75 cc) containing concentrated hydrochloric acid (20 drops) was refluxed for 3 hr and kept overnight. Ether (25 cc) was added, and the solution was washed with aqueous 10% sodium bicarbonate, treated with charcoal, dried ($MgSO_4$), and evaporated, giving a white solid (0.52 g, 48%), mp 74°. Three crystallizations from methanol–water gave white crystals: mp 76°; λ_{max} (95% ethanol) 251 mμ (log ε 4.63), 292 mμ (log ε 3.79); $\nu_{C=O}$ (Nujol) 1691 s, $\nu_{C=C}$ 1607 m, 1567 mw cm^{-1}.

Anal. Calcd for $C_{12}H_{13}NO_2$ (203.23): C, 70.91; H, 6.45; N, 6.89. Found: C, 70.68; H, 6.61; N, 6.80.

1,3-Dimethyl-5-indolol (Physostigmol, 11) by Oxidation of 1,3-Dimethylindol-5-ylmagnesium Bromide. A. With Oxygen.—A solution of 5-bromo-1,3-dimethylindole (5.0 g, 0.0223 mole) in dry tetrahydrofuran (25 cc) was added to magnesium turnings (0.544 g, 0.0224 g-atom). A crystal of iodine was added and the mixture was refluxed for 6 hr, during which all the magnesium dissolved. The solution was cooled to 0° and oxygen, which had been passed through concentrated sulfuric acid, ascarite, and then Dehydrite, was bubbled in, causing separation of a polymer-like precipitate. The mixture was kept overnight and then hydrolyzed with aqueous 10% sulfuric acid. Ether was added and the water layer was separated and extracted twice with ether. The combined ether layer and extracts were treated with charcoal, dried (Na_2SO_4), and evaporated, leaving a dark orange oil. Fractional distillation under vacuum gave a large forerun of 1,3-dimethylindole as a light yellow oil (1.34 g, 41%), bp 115–120° (10 mm), $n^{29.5}D$ 1.5877 [lit.[19] bp 119–120° (7 mm), $n^{25}D$ 1.5882[20]], and then a dark orange oil (0.83 g), bp 145–150° (2 mm), leaving a pot residue of 1.11 g. The dark orange oil was taken up in petroleum ether (bp 60–68°); light yellow crystals separated from the light yellow solution. These crystals were recrystallized from petroleum ether, giving fluffy, white needles (0.07 g, 2%): mp 98–100° (lit.[7] sinters faintly at 102°, mp 103°); λ_{max} (95% ethanol) 229 mμ (log ε 4.32), 283 (3.77), 310 (3.66), 320 inflection (3.56); ν_{OH} (Nujol) 3190 m broad, $\nu_{C=C}$ 1624 w, 1585 w cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO$ (161.20): C, 74.51; H, 6.88; N, 8.69. Found: C, 73.08, 74.25; H, 6.99, 7.86; N, 8.30.

B. With Methyl Borate and Hydrogen Peroxide.[6]—Dry tetrahydrofuran (50 cc) and 5-bromo-1,3-dimethylindole (6.20 g, 0.0276 mole) were added to magnesium turnings (0.73 g, 0.030 g-atom). A crystal of iodine was added and the mixture was refluxed for 3 hr until all the magnesium had dissolved. The solution was then added slowly under nitrogen to a solution of trimethyl borate (2.88 g, 3.13 cc, 0.0278 mole) in dry ether (50 cc) at −80°, causing a yellow paste to set. Aqueous 10% hydrochloric acid (20 cc) was then added, and the water layer was separated. The ether layer was washed twice with water and then aqueous 10% hydrogen peroxide was added, but there was no apparent reaction. The ether layer was separated, washed

(19) J. Meisenheimer, L. Angermann, O. Finn, and E. Vieweg, *Chem. Ber.*, **57**, 1753 (1924).

(20) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).

with aqueous 10% ferrous ammonium sulfate, and then extracted with aqueous 10% sodium hydroxide. The alkaline extract was acidified to litmus with aqueous 10% hydrochloric acid and extracted with ether. The ether extract was treated with charcoal, dried ($MgSO_4$), and evaporated, leaving a very small amount of green oil, which partially solidified upon being kept and cooled. The mixture was taken up in petroleum ether (bp 60–68°), and a white solid settled out (0.04 g, 1%), mp 98–100°. The infrared spectrum in Nujol was essentially identical with that of the sample prepared by oxidation with oxygen.

Registry No.—**3**, 10075-48-6; **8**, 10075-49-7; **1**, 10075-50-0; **2**, 877-03-2; **4**, 10086-59-6; 1-benzyl-5-bromoindole, 10075-51-1; **5**, 10075-52-2; **6**, 10102-94-0; **7**, 10075-53-3; **10a**, 10075-54-4; **10b**, 10075-55-5; **11**, 10102-95-1.

A One-Step Synthesis of 1,8-Naphthyridines[1]

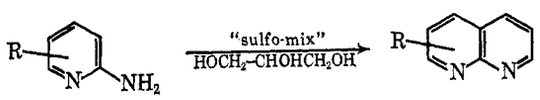
WILLIAM W. PAUDLER AND THOMAS J. KRESS

Department of Chemistry, Ohio University, Athens, Ohio

Received October 19, 1966

The scarcity of published papers dealing with the chemistry of the various isomeric naphthyridines can be ascribed to the difficulties encountered in attempts to prepare these compounds readily, and in good yields. Our interest in naphthyridines[2-4] has prompted us to investigate synthetic sequences for the preparation of larger amounts of the different naphthyridines. This note describes a facile synthesis of 1,8-naphthyridine and some of its methyl derivatives.

1,8-Naphthyridine has been prepared by Koller[5] and by Albert[6] by a five-step sequence starting with methyl 2-aminonicotinate, but this compound requires a multistep synthesis, and conversion to 1,8-naphthyridine proceeds in only 28% yield. Previous attempts to obtain 1,8-naphthyridines by the Skraup reaction on 2-aminopyridine have failed,[7] but in view of our recent success[2b,4] in applying the Skraup reaction to 4-aminopyridine, it became of interest to attempt this reaction with 2-aminopyridine.



1
R = H
R = 6-CH_3
R = 4-CH_3
R = 4,6-di-CH_3

2, R = H
3, R = 2-CH_3
4, R = 4-CH_3
5, R = 2,4-di-CH_3

The condensation of 2-aminopyridine employing Utermohlen's "sulfo-mix"[8a] and glycerol afforded 1,8-naphthyridine in 30% yield. It is of some interest to note that 1,5-naphthyridines[8b] as well as 1,6-naphthyridine[2b,4] are isolated from the reaction mixtures by steam distillation while 1,8-naphthyridine is not steam volatile under these conditions. It is conceivable that earlier reported failures[7] in attempts to apply the Skraup reaction to 2-aminopyridines might be accounted for by the traditional steam distillation procedures in isolating Skraup reaction products.

The structure proof of the 1,8-naphthyridine rests upon the identity of the reported melting points of the base itself, and of its picrate, as well as the analysis of the nmr spectrum, which clearly establishes the structure assignment.

The condensation of 6-methyl-, 4-methyl-, and of 4,6-dimethyl-2-aminopyridines with glycerol under similar reaction conditions as those employed for the preparation of the parent 1,8-naphthyridine yielded the 2-methyl-, 4-methyl-, and the 2,4-dimethyl-1,8-naphthyridines (compounds **3**, **4**, and **5**), respectively. The yields of these substituted 1,8-naphthyridines are between 10 and 20%.

The 2-methyl-1,8-naphthyridine obtained in this fashion was compared with an authentic sample of 2-methyl-1,8-naphthyridine prepared by the reaction sequence described by Brown[9] and the two compounds were shown to be identical. The physical constants of the other 1,8-naphthryidines, as well as the nmr spectra (Table I) are in agreement with the assigned structures.

Experimental Section[10]

1,8-Naphthyridine (**2**).—To a chilled, homogeneous mixture of 117 g of "sulfo-mix"[8a] and 25 g of anhydrous glycerol was added 7.5 g (0.08 mole) of 2-aminopyridine and 45 ml of water. The mixture was vigorously stirred in an oil bath at 130° for 5 hr, cooled in an ice bath, and made alkaline with concentrated aqueous sodium hydroxide. This solution was extracted with four 100-ml portions of chloroform. The combined chloroform extracts were then extracted with four 100-ml portions of aqueous hydrochloric acid (pH 3). The pH of the aqueous acid solution was adjusted to 5 and was reextracted with four 100-ml portions of chloroform. After several of these extractions the combined chloroform solutions were dried over anhydrous magnesium sulfate and evaporated to dryness. The solid residue of "crude" 1,8-naphthyridine (3.0 g, 30%), melted at 96–97° (lit.[6] 98°), picrate mp 207–208° (lit.[5] 207–208°), mol wt 130 (mass spectral value). Sublimation at 80° (0.3 mm) gave colorless, glassy needles (mp 98–99°, 2.95 g) of pure 1,8-naphthyridine.

2-Methyl-1,8-naphthyridine (**3**).—The same procedure was used as for the preparation of 1,8-naphthyridine except that 8.7 g (0.08 mole) of 2-amino-6-picoline was substituted for 2-aminopyridine. Three crystallizations from cyclohexane afforded white, cottony needles (1.2 g, 10%, mp 99–100°) of **8**. A mixture melting point with an authentic sample purified by sublimation (mp 99–100°) was not depressed. This melting point differs from that reported by Brown[9] (114–115°).

4-Methyl-1,8-naphthyridine (**4**).—The same general procedure was used except for the substitution of 8.6 g (0.08 mole) of 2-amino-4-picoline in place of 2-aminopyridine. 4-Methyl-1,8-naphthyridine [picrate mp 204–205° (lit.[11] 204–205°)] was obtained in 17% yield (2.0 g).

2,4-Dimethyl-1,8-naphthyridine (**5**).—The same procedure was followed except for the substitution of 2-amino-4,6-dimethylpyridine in place of 2-aminopyridine. The yield was 1.3 g

(1) This is paper V in the series "Naphthyridine Chemistry."
(2) (a) W. W. Paudler and T. J. Kress, *J. Heterocyclic Chem.*, **2**, 393 (1965); (b) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, **31**, 3055 (1966).
(3) W. W. Paudler and T. J. Kress, *Chem. Ind.* (London), 1557 (1966).
(4) T. J. Kress and W. W. Paudler, *Chem. Commun.*, 3 (1967).
(5) G. Koller, *Ber.*, **60**, 1918 (1927).
(6) A. Albert, *J. Chem. Soc.*, 1790 (1960).
(7) R. C. Elderfield, "Heterocyclic Compounds," Vol. 7, John Wiley and Sons, Inc., New York, N. Y., 1961, pp 198–236.
(8) (a) W. P. Utermohlen, Jr., *J. Org. Chem.*, **8**, 544 (1943); (b) H. Rapoport and A. Batcho, *ibid.*, **28**, 1753 (1963).
(9) E. Brown, *ibid.*, **30**, 1607 (1965).
(10) The nmr spectra were obtained with a Varian A-60 spectrometer. The purity of the compounds was ascertained by tlc [silica gel G, ethyl acetate–ether (20:80)]. The molecular weight was determined with a Hitachi Perkin-Elmer RMU-6E mass spectrometer (the mass spectral cleavage patterns of various naphthyridines will be described in a forthcoming paper).
(11) E. Ockiai and M. Miyaki, *Ber.*, **74**, 1115 (1941).