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

7-Azaindole. V. Investigations of Alternative Syntheses of the Ring System[1,2]

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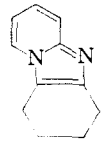
5,6,7,8-Tetrahydro-9H-pyrid[2,3-b]indole and 2,3-diphenyl-7-azaindole have been prepared by Fischer cyclizations of the corresponding pyridylhydrazones using polyphosphoric acid, though the method fails for a number of simpler pyridylhydrazones. 2-Aminopyridine-3-acetic acid, obtained in low yield by a sequence from 3-cyanomethylpyridine-N-oxide, has also been converted to 7-azaoxindole. A number of new pyridine derivatives prepared in this sequence are described.

7-Azaindole can be prepared on a conveniently large scale in approximately 50% yield by a Madelung-type cyclization of 2-formamido-3-picoline.[4] However, the exceedingly harsh cyclization conditions, employing sodium anilide at 300°, preclude the survival of almost any functional group, and the utility and generality of the synthesis are hence greatly diminished. Further, although substitution reactions take place readily at the 3-position of 7-azaindole,[4a,5] no direct method is available for introducing substituents into the pyridine ring or into the 2-position. The possible biological interest of 7-azaindole compounds bearing substituents in the six-membered ring prompted a search for more flexible and convenient syntheses of the nucleus.

The Fischer synthesis was first reinvestigated as a possible route to azaindoles, although this method has not yielded good results in the past. Thus Perkin and Robinson[6] were unable to effect a cyclization of acetone 2-quinolyl-hydrazone, though a number of condensing agents were tried, and Fargher and Furness[7] obtained similar negative results with a number of 2-pyridylhydrazones. More recently,[8] however, cyclohexanone 2-methyl-3-pyridylhydrazone has been converted to 1-methyl-5,6,7,8-tetrahydro-9H-pyrid[3,4-b]indole in low yield by the use of a zinc chloride catalyst. It was found in this Laboratory that cyclohexanone 2-pyridylhydrazone may be cyclized in polyphosphoric acid[9] to produce 5,6,7,8-tetrahydro-9H-pyrid[2,3-b]indole (I) in 53% yield. The structure of the product was demonstrated by dehydrogenation to 9H-pyrid[2,3-b]indole (II), which was identical with an authentic specimen prepared by the method of Witkop.[10] It may be noted that a German patent[11] claimed to have prepared the tetrahydro compound by condensation of 2-aminopyridine with 2-chlorocyclohexanone; this claim was subsequently questioned by Campbell and McCall,[12] who advanced the alternative 6,7,8,9-tetrahydropyrido[1,2-a]benzimidazole structure



(III) for the product. With the preparation of the authentic pyrid[2,3-b]indole the conclusions of the latter workers are confirmed. A Fischer type cyclization was also found to take place with desoxybenzoin 2-pyridylhydrazone to produce 2,3-diphenyl-7-azaindole. Proof of this structure stemmed from the positive test for active hydrogen given by the product and from comparison with the alternative 2,3-diphenylimidazo[1,2-a]pyridine, which was synthesized by reaction of desyl chloride with 2-aminopyridine. Reaction of α-halocarbonyl compounds with 2-aminopyridine is a general method for the preparation of the imidazo[1,2-a]-pyridine ring.[13]

It may be noted that Fischer cyclizations of the *phenylhydrazones* of the above two ketones take place under very mild conditions. For example, cyclohexanone phenylhydrazone produces tetrahydrocarbazole on gentle warming with aqueous hydrochloric acid.[14] Unfortunately it was found that cyclizations of pyridylhydrazones corresponding to more difficult cases in the benzene series do not take place in polyphosphoric acid even under very stringent conditions. Thus the 2-pyridylhydrazones of acetaldehyde, acetone and pyruvic acid failed to react exothermically and no cyclization products could be isolated from the reaction mixtures. On the basis of these experiences it appears that this cyclization is only practical in extremely favorable cases in the pyridine series.

A second, partially-successful approach to the 7-azaindole system required the preparation of suitable 2-substituted-3-pyridineacetic acid derivatives. To this end, 3-cyanomethylpyridine, which was synthesized in much improved yield by a modification of the method of Mosher and Tessieri,[15] was converted to its N-oxide IV. The oxide, on treatment with phosphorus oxychloride, reacted to produce 2-chloro-3-cyanomethylpyridine (V), a

(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, F. P. Butler and B. L. Robison, THIS JOURNAL, **79**, 2573 (1957).

(3) To whom inquiries should be addressed. CIBA Pharmaceutical Products, Inc., Summit, N. J.

(4) (a) M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 457 (1955); (b) **77**, 6554 (1955).

(5) M. M. Robison and B. L. Robison, *ibid.*, **78**, 1247 (1956).

(6) W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1973 (1913).

(7) R. G. Fargher and R. Furness, *ibid.*, 688 (1915).

(8) G. R. Clemo and R. J. W. Holt, *ibid.*, 1313 (1953).

(9) H. M. Kissman, D. W. Farnsworth and B. Witkop, THIS JOURNAL, **74**, 3948 (1952).

(10) B. Witkop, *ibid.*, **75**, 3361 (1953).

(11) J. Reitmann, German Patent 547,985, June 28, 1930; *C. A.*, **26**, 3514 (1932).

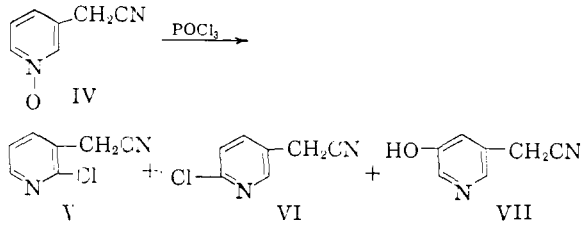
(12) N. Campbell and E. B. McCall, *J. Chem. Soc.*, 2411 (1951).

(13) A. E. Chichibabin, *Ber.*, **59**, 2048 (1926).

(14) W. C. Sumpter and F. M. Miller, "The Chemistry of Heterocyclic Compounds," Vol. 8, Interscience Publishers, Inc., New York, N. Y., 1954, p. 5.

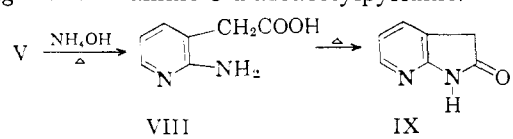
(15) H. S. Mosher and J. E. Tessieri, THIS JOURNAL, **73**, 4925 (1951).

smaller quantity of the unwanted 2-chloro-5-cyanomethylpyridine (VI) and a third compound, subsequently shown to be 3-hydroxy-5-cyanomethylpyridine (VII). Initially, an attempt was made to prove the structure of V by hydrolysis of both the chloro and cyano groups and decarboxylation of the resulting acid to the known 3-methyl-2-pyridone. From an acid hydrolysis, however, only 2-chloropyridine-3-acetic acid was isolated; the structures of both V and VI were therefore demonstrated by oxidation to the corresponding, known chloronicotinic acids. The identity of VII was established initially by a comparison of the



ultraviolet spectra of its neutral and basic solutions.[16] The bathochromic shift of the absorption maxima on changing to a medium of higher *p*H is characteristic of β-hydroxypyridines. The structure was further demonstrated by hydrolysis of the material to 3-hydroxypyridine-5-acetic acid and decarboxylation to the known[17] 3-hydroxy-5-picoline. Although such rearrangements to a "meta" position on a heterocyclic ring are well known in reactions of N-oxides with acetic anhydride,[16,18] they have apparently not been reported in the reactions with phosphorus oxychloride. The formation of the 3-hydroxy compound clearly cannot take place through a 3-chloro intermediate, but rather must result from an attack of some intermediate oxygen-containing phosphorus compound on the ring.

Compound V, on vigorous treatment with aqueous ammonia, was transformed to 2-aminopyridine-3-acetic acid (VIII) in very moderate yield. 2-Hydroxypyridine-3-acetic acid was formed as a by-product in the reaction, and was also prepared by a vigorous base-hydrolysis of 2-chloropyridine-3-acetic acid. The aminopyridine-acetic acid on heating to 225° was cyclized to 7-azaoxindole (IX), the properties of which were in agreement with those of the material prepared by Kägi[19] from 2-amino-3-diazoacetylpyridine.



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(16) S. Okuda, *Pharm. Bull. Japan*, **3**, 316 (1955).

(17) W. A. Jacobs and Y. Sato, *J. Biol. Chem.*, **181**, 56 (1949).

(18) *Cf.* M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956), and references cited therein.

(19) H. Kägi, *Helv. Chim. Acta*, **24**, 141E (1941).

Experimental[20,21]

Cyclohexanone-2-pyridylhydrazone.—Addition of 4.90 g. of cyclohexanone to 5.45 g. of 2-pyridylhydrazine[7] initiated an exothermic reaction. After about 10 minutes the turbid liquid crystallized on scratching, and the resulting white powder, after trituration with water, weighed 9.12 g. (96%) and melted at 90.5–92.5°. The analytical sample was prepared by recrystallizations from cyclohexane and from ethanol–water. In both cases some darkening of the solutions, indicating decomposition, was noted. The white plates sintered at about 85° and had m.p. 92–92.5°.

Anal. Calcd. for $C_{11}H_{15}N_3$: C, 69.81; H, 7.99. Found: C, 69.31; H, 8.07.

5,6,7,8-Tetrahydro-9H-pyrid[2,3-b]indole (I).—A mixture of 5.68 g. of the hydrazone and 18 g. of polyphosphoric acid[22] was heated gradually to about 160° with a thermometer in the liquid. Usually, a slight exothermic reaction was observed in these cyclizations at about 110° as the hydrazone dissolved. At 160° a vigorous exothermic reaction took place and the temperature rose to 220°, in spite of external cooling. When the reaction subsided, the mixture was cooled and dissolved in 100 ml. of water and the turbid solution was extracted with ether to remove non-basic materials, then neutralized with ammonium hydroxide. The resulting tan solid was sublimed at 110° (0.2 mm.) and recrystallized from ethanol–water. The off-white needles weighed 2.75 g. (53%) and had m.p. 155–156°. The analytical sample, prepared by further recrystallizations from the same solvent-pair, had the same m.p. and gave a positive active-hydrogen test with methylmagnesium iodide. The ultraviolet spectrum was similar to that of 3-methyl-7-azaindole. Maxima were observed at 228 mμ (log ε 4.32) and 292 mμ (log ε 3.97) and the minimum was found at 252 mμ (log ε 3.01).

Anal. Calcd. for $C_{11}H_{12}N_2$: C, 76.71; H, 7.03. Found: C, 76.49; H, 6.64.

9H-Pyrid[2,3-b]indole (II).—A mixture of one millimole of I, 0.1 g. of 5% palladium–charcoal and 5 ml. of Dowtherm was refluxed for 2 hours, cooled and added to 5 ml. of benzene. After filtration of the catalyst the solution was extracted with warm, dilute hydrochloric acid, from which 0.14 g. (82%) of product, m.p. 209–211°, was precipitated by addition of ammonium hydroxide. After recrystallization from benzene, the white needles melted at 210.5–211°. The authentic material prepared by the method of Witkop[10] melted at 210–212°, both alone and on admixture with the dehydrogenation product.

Desoxybenzoin 2-Pyridylhydrazone.—To a solution of 1.96 g. of desoxybenzoin in 1 ml. of glacial acetic acid was added 1.09 g. of 2-pyridylhydrazine. The turbid solution, which soon deposited a solid, was allowed to stand for 2.5 hours, after which the crystalline product was separated and muddled with dilute aqueous ammonia and with ethanol. Recrystallization from methanol afforded 1.4 g. of yellow crystals (49%), m.p. 105–110°. Further crystallizations from acetone–water and from ethanol were followed by an evaporative distillation at 160° (0.3 mm.) in a sublimation apparatus. The distillate, which crystallized on standing, had m.p. 110°.

Anal. Calcd. for $C_{19}H_{17}N_3$: C, 79.41; H, 5.96. Found: C, 79.40; H, 6.01.

2,3-Diphenyl-7-azaindole.—The cyclization was effected by heating 1.8 g. of the hydrazone with 8 g. of polyphosphoric acid at 110–120° for 1 hour. The mixture was cooled and stirred with 20 ml. of warm water and the two phases were extracted with benzene. The milky water layer and sticky solid were basified with ammonium hydroxide and separated, and the organic layer was extracted with ether. The residual cream-colored solid was separated by filtration, washed with water and with ether and recrystallized from *n*-butyl alcohol to yield 0.21 g. (12%) of crude, light-yellow crystals, m.p. 268–276°. Further recrystallizations from butyl alcohol and sublimation at 230° (0.1 mm.) produced fine, white crystals, m.p. 292.5–293.5°.

(20) Analyses by Drs. Weiler and Strauss, Oxford, England, except for some nitrogen analyses which were carried out by semi-micro Kjeldahl technique in this Laboratory.

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

(22) We wish to thank the Victor Chemical Works, Chicago, Ill., for a generous gift of this material.

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.41; H, 5.22. Found: C, 84.30; H, 5.01.

2,3-Diphenylimidazo[1,2-a]pyridine.—To a solution of 2.31 g. of desyl chloride[23] in 10 ml. of 95% ethanol was added 0.94 g. of 2-aminopyridine, and the orange solution was refluxed. When no reaction occurred, the ethanol was distilled and the temperature was raised to 130–140° for 1 hour, then to 190° for 5 minutes. Water and ammonium hydroxide were added to the cooled mixture, then sufficient acetone was added to cause crystallization of the sticky mass. Washing with acetonitrile left 1.14 g. (42%) of cream-colored powder, m.p. 148.5–150.5°. The analytical sample was prepared by recrystallizations from this solvent; shiny, white plates, m.p. 151–151.5°. The compound gave a negative test for active-hydrogen.

Anal. Calcd. for $C_{19}H_{14}N_2$: C, 84.41; H, 5.22; N, 10.36. Found: C, 84.66; H, 4.96; N, 10.51.

3-Cyanomethylpyridine.—To a stirred solution of 30 g. of sodium cyanide in 45 ml. of hot water, 250 ml. of 95% ethanol was added. A solution of 20 g. of 3-chloromethylpyridine hydrochloride[15] in a mixture of 50 ml. of 95% ethanol and 20 ml. of water was then added dropwise over a period of 40 minutes to the vigorously stirred, refluxing cyanide solution. Refluxing and stirring were continued for 1 hour, the solvent was evaporated *in vacuo* and the residue was extracted with six 100-ml. portions of ether.[2] After drying and evaporation of the solvent, distillation of the residue afforded a pale-yellow oil, b.p. 126° (7 mm.), $n^{20}D$ 1.5279. In three reactions the yields varied from 76.5 to 82.5%. Mosher and Tessieri,[15] who obtained a maximum yield of 34% by heating a premixed solution of the halide and cyanide, observed b.p. 91° (2 mm.) and $n^{20}D$ 1.5278.

3-Cyanomethylpyridine-N-oxide (IV).—A mixture of 55 ml. of glacial acetic acid, 15 ml. of 30% hydrogen peroxide and 11.0 g. of 3-cyanomethylpyridine was heated on the steam-bath for 12 hours, then cooled to room temperature; after addition of 10 ml. more hydrogen peroxide, the solution was heated 8 hours longer. Seventy milliliters of water was added, volatile reactants were evaporated *in vacuo* and the water addition and evaporation were repeated. The brown solid was extracted into chloroform and the solution was dried over potassium carbonate and evaporated. Recrystallization from chloroform–benzene afforded 10.8 g. of white plates (87%), m.p. 134.5–136°. The analytical sample was prepared by vacuum distillation at 180–182° (0.2 mm.) and a further recrystallization, m.p. 135.5–136.5°.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.67; H, 4.52; N, 20.89. Found: C, 62.90; H, 4.17; N, 21.30.

Treatment of IV with Phosphorus Oxychloride.—The oxide (10.0 g.) was added to 100 ml. of phosphorus oxychloride and the mixture was warmed slowly with vigorous shaking. After the solid dissolved, at about 100°, the red-brown solution was refluxed gently for 2 hours. The excess phosphoryl chloride was removed *in vacuo* and the residual brown sirup was poured onto 160 g. of ice. The tan precipitate was separated by filtration, washed, dried and recrystallized from ether–petroleum ether. The white needles of **2-chloro-3-cyanomethylpyridine (V)** had m.p. 84–86° and weighed 2.55 g. The analytical sample, prepared by further recrystallizations from the same solvent-pair, had m.p. 85–86°.

Anal. Calcd. for $C_7H_5N_2Cl$: C, 55.10; H, 3.30; N, 18.36. Found: C, 55.17; H, 3.30; N, 18.43.

The strongly acidic, aqueous filtrate from the chloro compound was extracted with five 50-ml. portions of chloroform and the extract was dried over magnesium sulfate and evaporated. The brown residue was adsorbed on a column of 80 g. of Fisher adsorption alumina from benzene solution. Elution with the same solvent afforded 1.14 g. more V (m.p. 83–85°) and 0.91 g. of the more strongly-adsorbed VI (m.p. 48–50°). The intermediate fractions from the chromatogram were combined with the mother liquors from the recrystallization of V and re-chromatographed on 50 g. of alumina. This process afforded 0.52 g. more V (m.p. 82–84°), 0.65 g. more VI (m.p. 48–50°) and 0.7 g. of the unresolved mixture. Thus the total yield of V was 4.21 g., or 37%, while the yield of VI was 1.56 g. (14%).

(23) A. M. Ward, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 159.

The 2-chloro-5-cyanomethylpyridine was purified for analysis by recrystallizations from ether–petroleum ether; white plates, m.p. 51–52°.

Anal. Calcd. for $C_7H_5N_2Cl$: N, 18.36. Found: N, 18.21.

The aqueous layer left from the chloroform extractions was adjusted to *p*H 4 with aqueous ammonia and again extracted with chloroform. It was then made basic with ammonia and the extraction repeated. From neither chloroform extract could any pure compound be isolated, only intractable tars being obtained. The water layer was next evaporated to dryness *in vacuo* and the residue was extracted with three 150-ml. portions of boiling acetone. Evaporation of the extracts and recrystallization of the residue from benzene–acetone afforded 0.78 g. (7.8%) of white **3-hydroxy-5-cyanomethylpyridine (VII)**, m.p. 177–180°. Further recrystallizations from the same solvent-pair produced white plates, m.p. 180–181°.

Anal. Calcd. for $C_7H_6N_2O$: N, 20.89. Found: N, 20.86.

The 3-pyridol gave an orange-red color with ferric chloride. An aqueous solution exhibited ultraviolet maxima at 216 mμ (ε 7570), 254 mμ (2320), 279 mμ (3880) and 319 mμ (1360), while minima were observed at 236 mμ (1370), 261 mμ (2140) and 300 mμ (876). In 0.25 *N* NaOH the values were: λ_{max} 241 mμ (9680) and 302 mμ (5320); λ_{min} 219 mμ (2520) and 265 mμ (786).

2-Chloropyridine-3-acetic Acid.—One-half gram of V was added to 20 ml. of concentrated hydrochloric acid and the mixture was refluxed for 5.5 hours, then evaporated to dryness *in vacuo*. The residue was triturated with water. Neither the solid nor its mother liquors gave any color with ferric chloride, thus indicating the absence of the pyridone grouping. The solid was dissolved in dilute sodium bicarbonate solution, a little insoluble material was separated by filtration and the acid was precipitated from the filtrate and recrystallized from benzene. The compound, m.p. 203–204°, was obtained in 76% yield (0.43 g.).

Anal. Calcd. for $C_7H_6NO_2Cl$: N, 8.16. Found: N, 8.17.

Oxidation of V.—The nitrile (265 mg.) was heated on the steam-bath with 614 mg. of potassium permanganate in 20 ml. of water until the color was discharged, in about 20 minutes. The manganese dioxide was separated and the filtrate saturated with carbon dioxide and evaporated to dryness *in vacuo*. The residue was taken up in water, a small quantity of insoluble material was separated by filtration, and the product was precipitated by acidification and recrystallized from water. The 232 mg. (85%) of 2-chloronicotinic acid had m.p. 192–193° dec. This oxidation product was also prepared from the 2-chloropyridine-3-acetic acid. Neither sample showed any melting point depression on admixture with authentic 2-chloronicotinic acid.[4a]

Oxidation of VI.—This nitrile was oxidized by the procedure employed with V. The 6-chloronicotinic acid, which was obtained in 50% yield, had m.p. 198–199° dec. alone[24], and m.p. 183–184° dec. on admixture with the 2-chloro isomer.

3-Hydroxypyridine-5-acetic Acid.—Ten milliliters of concentrated hydrochloric acid was added to 0.35 g. of VII and the mixture was refluxed 5 hours and evaporated to dryness *in vacuo*. The residue was dissolved in 10 ml. of water and treated with a saturated cupric acetate solution. The resulting greenish-blue precipitate was collected by filtration, washed with a small amount of cold water and suspended in 40 ml. of methanol. After hydrogen sulfide treatment, the copper sulfide was separated by filtration and the methanol evaporated. The yellow residue was recrystallized from methanol–methyl ethyl ketone as a white sand, m.p. 197° dec. The yield was 0.31 g. (78%).

Anal. Calcd. for $C_7H_7NO_3$: N, 9.15. Found: N, 8.85.

3-Hydroxy-5-methylpyridine.—Two-tenths gram of 3-hydroxypyridine-5-acetic acid was heated in a nitrogen atmosphere at 230° for 15 minutes, after which the residue was purified by sublimation at 135° (0.05 mm.). The white sublimate weighed 0.11 g. (77%) and melted at 134–137°. The analytical sample was prepared by recrystalli-

(24) M. J. Kabatschnik and M. M. Katznelson, *Ber.*, **68**, 399 (1935), report m.p. 197–198° dec.

zations from benzene as white prisms, m.p. 138.5° (reported[17] m.p. 137.5–139°).

Anal. Calcd. for C_6H_7NO: N, 12.84. Found: N, 12.65.

The picrate formed yellow needles from methanol, m.p. 189–190°.[25]

Reaction of V with Ammonia.—A mixture of 0.5 g. of 2-chloro-3-cyanomethylpyridine, 0.1 g. of hydrated copper sulfate and 15 ml. of concentrated ammonium hydroxide was heated in a sealed tube at 135 ± 10° for a period of 42 hours. Insoluble material was separated by filtration and the filtrate was evaporated to dryness *in vacuo* and treated with 5 ml. of cold water. The tan solid was separated and recrystallized from acetic acid–water to yield 105 mg. (19%) of white crystals, m.p. 215–217° dec. The analytical sample had m.p. 219–221.5° dec. after recrystallizations from the same solvent. The 2-aminopyridine-3-acetic acid (VIII), which is somewhat hygroscopic, was dried at 110° *in vacuo* for analysis.

Anal. Calcd. for $C_7H_8N_2O_2 \cdot {}^1/_2H_2O$: C, 52.17; H, 5.63. Found: C, 52.47; H, 5.78.

The aqueous filtrate from the crude product was treated with hydrogen sulfide, the resulting small quantity of copper sulfide separated and the filtrate evaporated to dryness *in vacuo*. The residue was extracted with hot absolute ethanol, which was evaporated. The new residue was dissolved in 5 ml. of absolute ethanol, 30 ml. of acetone was added, a small amount of insoluble material was separated and the solution was concentrated to one-third volume. The 0.11 g. of pale-orange precipitate was recrystallized from absolute ethanol–benzene and from water. There resulted 23 mg. (4.6%) of 2-hydroxypyridine-3-acetic acid, m.p. 240–241° dec. This material showed no melting-point depression on admixture with authentic compound prepared from the 2-chloropyridine-3-acetic acid (*vide infra*).

2-Hydroxypyridine-3-acetic Acid.—A solution of 0.16 g. of 2-chloropyridine-3-acetic acid in 10 ml. of 5% sodium hydroxide was heated in an autoclave at 200° for 4.5 hours. The brown mixture was filtered, acidified with concentrated hydrochloric acid and evaporated to dryness. The residue was extracted with boiling methanol and the solid from evaporation of the extract was recrystallized from water and from methanol. There was thus obtained 95 mg. (66.5%) of white crystals, m.p. 240–241° dec. The compound, which gave a red color with ferric chloride, was dried at 110° *in vacuo*.

Anal. Calcd. for $C_7H_7NO_3$: N, 9.15. Found: N, 9.12.

7-Azaoxindole (IX).—One-tenth gram of VIII was heated under nitrogen at 225° for 10 minutes, after which the residue was subjected to sublimation at 170° (10 mm.). The white needles, m.p. 175°, weighed 56 mg. (67% on the basis of the hemihydrate of VIII). The analytical sample, prepared by another sublimation, had the same melting point; Kägi[19] reported m.p. 175°.

Anal. Calcd. for $C_7H_6N_2O$: N, 20.89. Found: N, 21.18.

Absorption Spectra.—Ultraviolet spectra were determined with a Beckman model DU quartz spectrophotometer from 10^{-4} *M* solutions in cyclohexane, unless otherwise specified.

AMHERST, MASS.

(25) H. C. Chitwood, U. S. Patent 2,557,076, June 19, 1951; *C. A.*, **46**, 145 (1952), reported m.p. 187–188°.

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

7-Azaindole. VI. Preparation of 5- and 6-Substituted 7-Azaindoles[1]

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7-Azaindoline (2,3-dihydro-7-azaindole) behaves, as expected, like a substituted 2-aminopyridine and undergoes substitution reactions in the pyridine ring without accompanying reaction at the 3-position. Thus the substance was transformed *via* 1-nitro-7-azaindoline to the 5-nitro and 5-amino compounds, while treatment of 7-azaindoline-7-oxide with acetic anhydride produced two derivatives bearing oxygenated functions at the 5- and 6-positions, respectively. Since the substituted azaindolines could be dehydrogenated to azaindoles, these reactions provide a reasonably convenient route to this hitherto inaccessible class of substitution products.

Although 7-azaindole can be prepared in about 50% yield by cyclization of 2-formamido-3-picoline,[3] the extremely harsh conditions of the cyclization render impractical attempts to extend the preparation to azaindoles containing functional groups. Further, the 3-position of 7-azaindole, like that of indole, is most susceptible to substitution reactions,[3a,4] so that the azaindole nucleus itself does not offer ready entry into its pyridine ring. The possible biological interest of azaindoles bearing substituents in the six-membered ring prompted a search for methods of introducing such groups.

The most promising approach to the problem of blocking the pyrrole ring and allowing substitution in the pyridine ring appeared to be *via* 7-azaindoline (I). The structure of this substance, which was first prepared by Kruber,[5] was not demonstrated with certainty, though ultraviolet measurements appeared to substantiate it.[6] The success of several substitution reactions involving the reduction product, however, definitely confirms the 2,3-dihydro formulation.

The reaction of I with fuming nitric acid and sulfuric acid at low temperature produces 1-nitro-7-azaindoline (II) in high yield. The position of the nitro group was indicated by a negative active-hydrogen test and by analogy to the similar reaction which takes place with 2-methylaminopyridine.[7] The nitro compound II on warming with sulfuric acid, is converted to the isomeric 5-nitro-7-azaindoline (III), the site of substitution in which was again indicated by inference from the known case.[7] Further, reduction of the benzoyl derivative of III to 1-benzoyl-5-amino-7-azaindoline and treatment of the amine with nitrous acid afforded a

(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) CIBA Pharmaceutical Products, Inc., Summit, N. J.

(3) (a) M. M. Robison and B. L. Robison, THIS JOURNAL, **77**, 457 (1955); (b) **77**, 6554 (1955).

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