Synthesis of Substituted 4- and 6-Azaindoles[1a]

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The syntheses of 5-methoxy- and 5-benzyloxy-4- and -6-azaindoles are described. Condensation of 2-methyl-3-nitropyridine and of 6-methoxy- and 6-benzyloxy-2-methyl-3-nitropyridine with diethyl oxalate afforded the corresponding ethyl 3-nitro-2-pyridinepyruvates, which, on hydrogenation, were transformed into ethyl 4-azaindole-2-carboxylate and its substituted derivatives. Hydrolysis of the ethyl 4-azaindole-2-carboxylates and of the isomeric 6-azaindole-2-carboxylates, prepared similarly from the 3-nitro-4-pyridinepyruvates, afforded the corresponding azaindole-2-carboxylic acids, which could not be decarboxylated by the usual methods. Decarboxylation was achieved when the lithium salt of 5-methoxy- and 5-benzyloxy-4-azaindole-2-carboxylic acid was treated with iodine, and the corresponding 2,3-diiodo-4-azaindole was obtained which on hydrogenation afforded the 5-methoxy- and 5-benzyloxy-4-azaindole. Alternatively, the ethyl 4-azaindole-2-carboxylates and the ethyl 6-azaindole-2-carboxylates were reduced to the corresponding 2-formylazaindoles, which were then easily decarbonylated over chlorotris(triphenylphosphine)rhodium to the substituted azaindoles.

The 4-azaindoles are a little studied family of heterocycles of which few members and derivatives have been prepared. The main reason for this is that the synthetic methods used for the preparation of 4-azaindoles, as well as those used for the preparation of the isomeric 5-, 6-, and 7-azaindoles, are of limited range owing to the harsh reaction conditions on which they depend.[2] The 4-azaindoles were usually prepared by a Madelung-type cyclization of an N-acyl-2-methyl-3-aminopyridine at high temperature in the presence of a strong base.[3-5] In another synthetic approach to 4-azaindoles, modeled on the Fischer indole synthesis, isopropyl methyl ketone 3-pyridylhydrazone was cyclized to a 3-substituted 4-azaindolenine,[6] but the severe reaction conditions limit the usefulness of this method for the synthesis of substituted 4-azaindoles with sensitive groups. More recently,[7] 4-azaindole was obtained by the cyclization of a formamidine derivative of 2-methyl-3-aminopyridine under conditions which resemble the Madelung-type cyclization. The literature on the synthesis of 6-azaindoles is also very sparse, and the methods employed resemble those used for the synthesis of 4-azaindoles.[8,9]

Since the azaindoles are an interesting group of heterocycles from the standpoint of their biological activity as analogs of physiologically active indoles,[4,10] we undertook the synthesis of 5-methoxy- and 5-benzyloxy-4-azaindole and of 5-methoxy- and 5-benzyloxy-6-azaindole, in order to use them as intermediates and models for the synthesis of 5-hydroxyazaindole bases. To achieve this we examined the reductive cyclization of properly substituted ethyl 3-nitropyridinepyruvates, and found it to be a reaction which proceeds well under mild conditions and results in good yields of the substituted azaindoles.

Discussion

The key reaction for the synthesis of 4-azaindoles was the successful condensation of 2-methyl-3-nitropyridine (**3**) and of 6-methoxy- (**1**) and 6-benzyloxy-2-methyl-3-nitropyridine (**2**), with diethyl oxalate in the presence of base to yield the corresponding ethyl 3-nitro-2-pyridinepyruvates **4**, **5**, and **6**. Although similar condensations have failed in the past,[11] we found the reaction to take place readily and in good yields in the presence of potassium ethoxide. This extended to the 2-methylpyridine series the reaction which we described for the 4-methylpyridine series.[12] Thus the *o*-nitro group sufficiently enhanced the acidity of the methyl group; it is known that 2-methylpyridine does not condense with diethyl oxalate, whereas its N-oxide does.[13,14] The corresponding ethyl pyridinepyruvates **4**, **5**, and **6** were isolated as potassium enolates and liberated from their salts at pH 3.

The nitropyridine **3** was prepared from 6-chloro-2-methyl-3-nitropyridine by reduction with copper and acetic acid,[15] and the nitropyridines **1** and **2** were also prepared from 6-chloro-2-methyl-3-nitropyridine by the usual methods.[16] The nmr and ir data showed that the pyruvates existed mainly as enols; nevertheless when they were hydrogenated at atmospheric pressure they cyclized to the corresponding ethyl 4-azaindole-2-carboxylates **7**, **8** and **9**. The hydrogenation of the ethyl 6-benzyloxy-3-nitro-2-pyridinepyruvate (**5**) was carried out over platinum oxide; the others were reduced over palladium on charcoal; and the esters were hydrolyzed to the corresponding acids **10**, **11**, and **12** in good yields.

(1) (a) This work was supported by the Consejo Nacional de Investigaciones (Argentina) and the National Institutes of Health (GM-11973 and AI-04888). (b) Career investigator of the Consejo Nacional de Investigaciones (Argentina).

(2) For references on azaindole ring synthesis prior to 1965, see B. Frydman, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 3530 (1965). Recent azaindole syntheses are (a) Madelung-type: R. E. Willete, *J. Chem. Soc.*, 5874 (1965); (b) *via* hydrazones: A. H. Kelly and J. Parrick, *Can. J. Chem.*, **44**, 2455 (1966); G. Tacconi and A. Perotti, *Ann. Chim.* (Rome), **55**, 810, 1223 (1965); (c) *via* haloalkylpyridines: L. N. Yakhontov, M. Ya Uritskaya, and M. V. Rubstov, *Khim. Geterotsikl. Soedin.*, 918 (1965).

(3) C. R. Clemo and C. A. Swan, *J. Chem. Soc.*, 198 (1948).

(4) T. K. Adler and A. Albert, *ibid.*, 1794 (1960).

(5) J. C. Clayton and J. Kenyon, *ibid.*, 2953 (1950).

(6) G. E. Ficken and J. D. Kendall, *ibid.*, 584 (1961).

(7) R. R. Lorenz, B. F. Tullar, C. F. Koelsch, and S. Archer, *J. Org. Chem.*, **30**, 2531 (1965).

(8) W. Hertz and D. R. K. Murty, *ibid.*, **25**, 2242 (1960).

(9) O. Süs and K. Möller, *Ann.*, **599**, 233 (1956).

(10) T. K. Adler and A. Albert, *J. Med. Chem.*, **6**, 482 (1963); M. R. Bell, J. O. Hoppe, H. E. Lape, D. Wood, A. Arnold, and W. H. Selberis, *Experientia*, **23**, 298 (1967).

(11) W. Herz and D. R. K. Murty, *J. Org. Chem.*, **26**, 122 (1961); G. M. Badger and R. P. Rao, *Aust. J. Chem.*, **17**, 1399 (1964).

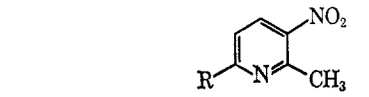
(12) B. Frydman, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, **87**, 3530 (1965).

(13) R. Adams and S. Miyano, *ibid.*, **76**, 3168 (1954).

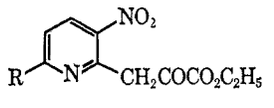
(14) The attempted condensation of 3-methyl-4-nitropyridine under the same reaction conditions afforded only the 1,2-di(3′-nitro-4′-pyridyl)ethylene (75%): mp 240–241°; nmr (TFA), δ 8.4 (s, 2, −CH=CH−), 8.7 (d, 2, J = 7 Hz, C-5 H), 9.3 (d, 2, J = 7, C-6 H), 9.8 (s, 2, C-2 H). See also E. C. Taylor and J. S. Driscoll, *J. Org. Chem.*, **26**, 3796 (1961).

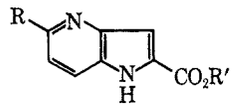
(15) H. E. Baumgarten and K. Cook, *ibid.*, **22**, 138 (1957).

(16) H. E. Baumgarten and H. Chien-Fan Tsu, *J. Amer. Chem. Soc.*, **74**, 3830 (1952).



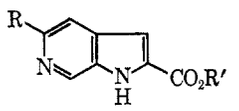
1, R = OCH_3
2, R = $OCH_2C_6H_5$
3, R = H



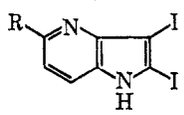


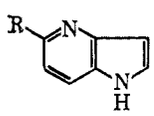
4, R = OCH_3
5, R = $OCH_2C_6H_5$
6, R = H

7, R = OCH_3; R′ = C_2H_5
8, R = $OCH_2C_6H_5$; R = C_2H_5
9, R = H; R′ = C_2H_5
10, R = OCH_3; R′ = H
11, R = $OCH_2C_6H_5$; R′ = H
12, R = H; R′ = H



13, R = OCH_3; R′ = C_2H_5
14, R = $OCH_2C_6H_5$; R′ = C_2H_5
15, R = OCH_3; R′ = H
16, R = $OCH_2C_6H_5$; R′ = H





17, R = OCH_3
18, R = $OCH_2C_6H_5$

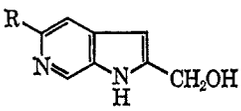
19, R = OCH_3
20, R = $OCH_2C_6H_5$
21, R = H

The ethyl 5-methoxy- (**13**) and 5-benzyloxy-6-azaindole-2-carboxylates (**14**) were obtained by a sequence of reactions analogous to those described above for the 4-azaindole derivatives.[12] When subjected to hydrolysis they gave the corresponding 6-azaindole-2-carboxylic acids **15** and **16** in good yield. All the azaindole-2-carboxylic acids, **10**, **11**, **12**, **15**, and **16**, showed an unexpected resistence to decarboxylation. They could not be decarboxylated by heating alone or in solvents, by pyrolysis of their salts, by employing the Hunsdiecker reaction or its modifications,[17] or by procedures employing lead tetraacetate.[18] However, when 5-methoxy-4-azaindole-2-carboxylic acid (**10**) or its 5-benzyloxy analog **11** were transformed into their lithium salts and treated with iodine in aqueous solution, the corresponding 2,3-diiodo derivatives **17** and **18** were obtained in good yields. The reaction did not take place with the sodium or potassium salts of the acids and 4-azaindole-2-carboxylic acid (**12**) itself did not react. The 2,3-diiodo-4-azaindoles **17** and **18** underwent hydrogenolysis to the corresponding 4-azaindoles **19** and **20**. 5-Methoxy-4-azaindole (**19**) was thus prepared in 36% over-all yield starting from 6-methoxy-2-methyl-3-nitropyridine (**1**), and 5-benzyloxy-4-azaindole (**20**) was prepared in 9% over-all yield.

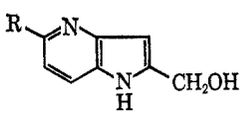
Several properties of 5-methoxy-4-azaindole (**19**) are of interest. The methyl group can be cleaved with 48% hydrobromic acid, and the 5-oxo-4,5-dihydro-1H-pyrrolo[3,2-*b*]pyridine (**34**) was obtained in 96% yield. The α-pyridone structure was assigned to **34** instead of the 5-hydroxy-4-azaindole structure on the basis of the bathochromic shift of 25 mμ in its uv absorption and of the amide band in its ir spectrum. When a Vilsmeier reaction (dimethylformamide and phosphorous oxychloride) was carried out with **19**, 3-formyl-5-methoxy-4-azaindole (**35**) was obtained in 40% yield. The reaction failed when ethyl 5-methoxy-4-azaindole-2-carboxylate (**7**) was used, as could be expected. However, the yield was consistently lower than that usually obtained in the indole series, probably owing to the electron-withdrawing effect of the pyridine nucleus.

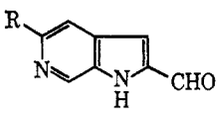
The same effect was present in the reactions of Mannich base **36**. Although the base **36** was obtained in the usual way it did not react, as such or as its quaternary salt, with sodium or potassium cyanide or with diethyl sodiomalonate. A similar effect was observed by Okuda and Robison[19] for the Mannich base of 5-azaindole. The alkylating properties of 7-azagramine[20] and of 4,7-diazagramine[21] are similar to those of gramine; so it must be assumed that in these azaindoles the electron-withdrawing properties of the pyridine or pyrazine moieties do not effect the C-3 position.

Since most of the azaindolecarboxylic acids which we obtained could not be decarboxylated, the possibility of decarbonylating the corresponding aldehydes was considered. By reduction of the substituted ethyl 6-azaindole-2-carboxylates **13** and **14** and of the ethyl 4-azaindole-2-carboxylates **7**, **8**, and **9** with lithium aluminum hydride in tetrahydrofuran, the corresponding 2-hydroxymethyl azaindoles **22**, **23**, **24**, **25**, and **26**



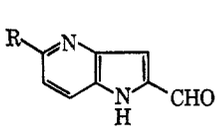
22, R = OCH_3
23, R = $OCH_2C_6H_5$

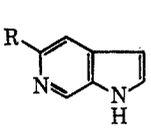


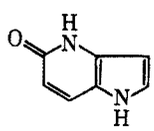


24, R = OCH_3
25, R = $OCH_2C_6H_5$
26, R = H

27, R = OCH_3
28, R = $OCH_2C_6H_5$



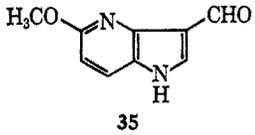


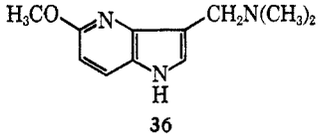


29, R = OCH_3
30, R = $OCH_2C_6H_5$
31, R = H

32, R = OCH_3
33, R = $OCH_2C_6H_5$

34





35

36

were obtained in good yields in both series. The alcohols were then easily oxidized to the corresponding aldehydes **27**, **28**, **29**, **30**, and **31** by manganese dioxide in ether–tetrahydrofuran solution. Heating the aldehydes above the melting points, at atmospheric pressure or *in vacuo*, did not yield the expected

(17) S. J. Cristol and W. Firth, Jr., *J. Org. Chem.*, **26**, 280 (1961); **27**, 2711 (1962).

(18) J. K. Kochi, *J. Amer. Chem. Soc.*, **87**, 2500 (1965); D. H. R. Barton, H. P. Faro, E. P. Serebryakov, and N. F. Woolsey, *J. Chem. Soc.*, 2439 (1965).

(19) S. Okuda and M. Robison, *J. Org. Chem.*, **24**, 1008 (1959).

(20) M. M. Robison and B. L. Robison, *J. Amer. Chem. Soc.*, **77**, 457 (1955).

(21) S. Klutchko, H. V. Hansen, and I. R. Meltzer, *J. Org. Chem.*, **30**, 3454 (1965).

TABLE I

SYNTHESIS AND PROPERTIES OF SUBSTITUTED 4-AZAINDOLES AND 6-AZAINDOLES

Compound	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2-Hydroxymethyl-5-methoxy-4-azaindole (**24**)[a]	125–130	87	$C_9H_{10}N_2O_2$	60.7	5.7	15.7	60.5	5.6	15.7
2-Hydroxymethyl-5-benzyloxy-4-azaindole (**25**)[a,b]	192–194	43	$C_{15}H_{14}N_2O_2$	70.9	5.5	11.0	70.7	5.3	11.0
2-Hydroxymethyl-4-azaindole (**26**)[a,c]	198–200	59	$C_8H_8N_2O$	64.9	5.4	18.9	64.8	5.3	18.7
2-Hydroxymethyl-5-benzyloxy-6-azaindole (**23**)[a]	125–127	48	$C_{15}H_{14}N_2O_2$	70.9	5.5	11.0	70.6	5.2	10.9
2-Formyl-5-methoxy-4-azaindole (**29**)[d]	175–177	82	$C_9H_8N_2O_2$	61.4	4.6	15.9	61.4	4.7	15.8
2-Formyl-5-benzyloxy-4-azaindole (**30**)[d,e]	188–190	77	$C_{15}H_{12}N_2O_2$	71.4	4.8	11.1	71.3	4.5	11.0
2-Formyl-5-benzyloxy-6-azaindole (**28**)[d]	155–156	50	$C_{15}H_{12}N_2O_2$	71.4	4.8	11.1	71.2	4.6	11.2
2-Formyl-4-azaindole (**31**)[d,f]	210–212	46	$C_8H_6N_2O$	65.8	4.1	19.2	65.9	3.8	18.9
5-Methoxy-4-azaindole (**19**)[g]	114–117	49	$C_8H_8N_2O$	64.9	5.4	18.9	65.0	5.6	18.8
5-Benzyloxy-4-azaindole (**20**)[g]	148–152	45	$C_{14}N_{12}N_2O$	75.0	5.4	12.5	74.9	5.3	12.4
4-Azaindole (**21**)[g,h]	123–126	45	$C_7H_6N_2$	71.2	5.1	23.7	71.1	5.3	23.5
5-Benzyloxy-6-azaindole (**33**)[g]	152–154	48	$C_{14}H_{12}N_2O$	75.0	5.4	12.5	74.8	5.2	12.3

[a] Prepared according to procedure A. [b] Uv max 306 mμ (ε 17,300). [c] Uv max 295 mμ (ε 15,000). [d] Prepared according to procedure B. [e] Uv max 310 mμ (ε 19,200), sh 325 (18,200). [f] Uv max 319 mμ (ε 18,600). [g] Prepared according to procedure C. [h] Lit.[4] mp 127°.

azaindoles. Heating in solvents in the presence of peroxides resulted in mixtures of products. Finally, a good procedure was found by heating the aldehydes in decalin at 300° for a short time in the presence of the chlorotris(triphenylphosphine)rhodium complex,[22] which afforded the azaindoles **32**, **33**, **19**, **20**, and **21** in fair yield (Table I). The 4-azaindoles and 6-azaindoles with no substituents at C-2 or C-3, as well as the 2-hydroxymethyl derivatives, gave a positive Ehrlich reaction on heating; the ethyl azaindole-2-carboxylates and the 2-formylazaindoles did not react with the Ehrlich reagent. The synthesis of various derivatives of the 4- and 6-azaindoles described in the present work will be the subject of future publications.

Experimental Section[23]

6-Benzyloxy-2-methyl-3-nitropyridine (**2**).—6-Chloro-2-methyl-3-nitropyridine[16] (60 g, 0.34 mol) was added to a solution of 8.5 g (0.37 g-atom) of sodium in 1200 ml of benzyl alcohol. The mixture was left at room temperature for 12 hr, then heated at 85° during 1 hr, and the benzyl alcohol was evaporated at reduced pressure at 90° (10 mm). The crystalline residue was washed with two 250-ml portions of water and recrystallized from ethanol. Slightly colored prisms (67 g, 79%) were obtained: mp 86–88°; uv max 298 mμ (ε 9400).

Anal. Calcd for $C_{13}H_{12}O_3N_2$: C, 63.9; H, 4.9; N, 11.5. Found: C, 64.1; H, 4.9; N, 11.5.

6-Methoxy-2-methyl-3-nitropyridine (**1**) was obtained by the action of methanolic sodium methoxide on the 6-chloro-2-methyl-3-nitropyridine as described;[16] **1** had mp 64–65° (lit.[16] mp 65°).

2-Methyl-3-nitropyridine (**3**).—To a solution of 19 g of 6-chloro-2-methyl-3-nitropyridine in 36 ml of glacial acetic acid was added 30 g of copper powder in portions during 30 min, while the mixture was heated at reflux with constant stirring. The heating and stirring was continued until the mixture became too thick to stir (approximately 30 min); then it was diluted with 500 ml of water, made alkaline with solid sodium carbonate, and steam distilled. The 7 l. of steam distillate was extracted with ether; the ethereal extract was dried (Na_2SO_4) and concentrated; and the residual oil was precipitated as a picrate from 100 ml of ethanol. The picrate was crystallized from ethanol yielding 14.7 g (44%), mp 122–124°.

Anal. Calcd for $C_{12}H_9O_9N_5$: C, 39.2; H, 2.4; N, 19.1. Found: C, 39.3; H, 2.4; N, 19.0.

The 2-methyl-3-nitropyridine was obtained as a free base (6.6 g, 43%) by dissolving the picrate in aqueous ethanolamine and extracting the pyridine into ether.

Ethyl 6-Methoxy-3-nitro-2-pyridinepyruvate (**4**).—To a solution of 1200 ml of absolute ether and 96 ml of absolute ethanol was added 16.8 g (0.45 g-atom) of potassium, and the mixture was stirred until all the potassium dissolved; 60 ml (0.45 mol) of diethyl oxalate was then added, followed after 5 min by 60 g (0.4 mol) of 6-methoxy-2-methyl-3-nitropyridine (**1**); and the red mixture was stirred for 36 hr. The red potassium enolate was removed by filtration, washed thoroughly with ether, dried, suspended in 1500 ml of water, and decomposed by adjusting the solution to pH 4 with acetic acid and precipitating the pyruvate which was crystallized from ethanol: 45 g (71%); mp 123–124°; uv max 328 mμ (ε 16,500); ir, 3300 (enolic OH), 1695 cm^{-1} (ester CO); nmr, δ 1.5 (t, CH_3), 4.4 (q, $\mathbf{CH_2}CH_3$), 6.8 (d, J = 10 Hz, C-5 H), 7.6 (s, $\mathbf{CH}$=C—OH), and 8.5 (d, J = 10, C-4 H).

Anal. Calcd for $C_{11}H_{12}O_6N_2$: C, 49.2; H, 4.5; N, 10.4. Found: C, 49.3; H, 4.5; N, 10.6.

Ethyl 6-benzyloxy-3-nitro-2-pyridinepyruvate (**5**) was prepared following the same procedure used for the synthesis of the 6-methoxy derivative **4**. From 48 g of 6-benzyloxy-2-methyl-3-nitropyridine (**2**) was obtained 32 g (50%) of ethyl 6-benzyloxy-3-nitro-2-pyridinepyruvate (**5**), mp 109–111° (from ethanol).

Anal. Calcd for $C_{17}H_{16}O_6N_2$: C, 59.3; H, 4.7; N, 8.1. Found: C, 59.6; H, 4.5; N, 8.0.

Ethyl 3-Nitro-2-pyridinepyruvate (**6**) was prepared following the same procedure used for the synthesis of the 6-methoxy derivative **4**. From 14 g of 2-methyl-3-nitropyridine (**3**) was obtained 11.4 g (47%) of ethyl 3-nitro-2-pyridinepyruvate (**6**): mp 140°; uv max 250 mμ (ε 18,200), 315 (1200).

Anal. Calcd for $C_{10}H_{10}O_5N_2$: C, 50.4; H, 4.2; N, 11.7. Found: C, 50.4; H, 4.2; N, 11.7.

Ethyl 5-Methoxy-4-azaindole-2-carboxylate (**7**).—Ethyl pyridinepyruvate (**4**) (5 g) was dissolved in 100 ml of ethanol and reduced during 45 min at 20 psi with hydrogen over 2 g of 10% palladium on charcoal. The catalyst was filtered and washed with ethanol. The combined filtrate and washings were concentrated *in vacuo* to 10 ml; 25 ml of water was added; and the suspension was cooled at 5° for several hours. The resulting precipitate was filtered, dried, and sublimed at 110° (0.01 mm) giving 3.3 g (80%) of **7**: mp 134–135°; uv max 301 mμ (ε 11,000), 314 (13,500), 320 (13,800); nmr, δ 7.6 (d, J = 5 Hz, C-6 H), 8.6 (d, J = 5, C-7 H), 8.0 (s, C-3 H).

Anal. Calcd for $C_{11}H_{12}O_3N_2$: C, 59.9; H, 5.5; N, 12.7. Found: C, 59.9; H, 5.6; N, 12.7.

Ethyl 4-azaindole-2-carboxylate (**9**) was prepared following the same procedure used for the synthesis of the 5-methoxy derivative **7**. From 6 g of ethyl 3-nitro-2-pyridinepyruvate (**6**) was obtained 3 g (63%) of **9**: mp 179°; sublimed at 125° (5 μ); uv max 305 mμ (ε 19,300), 312 (16,300).

Anal. Calcd for $C_{10}H_{10}O_2N_2$: C, 63.1; H, 5.3; N, 14.7. Found: C, 63.1; H, 5.1; N, 14.5.

(22) J. Tsuji and K. Olmo, *Tetrahedron Lett.*, 3969 (1965).

(23) All melting points were taken on the Köfler block; uv absorptions were measured in ethanol; ir spectra were obtained on potassium bromide wafers; and nmr spectra were taken in deuteriochloroform, unless otherwise noted, with internal TMS (δ 0). Tlc was run on silica-coated plates, and the Ehrlich reagent (2% *p*-dimethylaminobenzaldehyde in 6 *N* hydrochloric acid) was used as developer at 100°. Microanalyses were performed by the Microchemical Laboratory, University of California at Berkeley, Berkeley, Calif. Nmr spectra were determined at the Department of Organic Chemistry, Faculty of Sciences, University of Buenos Aires, Buenos Aires.

Ethyl 5-Benzyloxy-4-azaindole-2-carboxylate (8).—Ethyl 6-benzyloxy-3-nitro-2-pyridinepyruvate (**5**) (10 g) was suspended in 150 ml of ethanol and reduced with hydrogen at atmospheric pressure over 1 g of platinum oxide until the theoretical amount of hydrogen was consumed (40 min). The catalyst was removed; the ethanol was evaporated to dryness; and the oily residue was dissolved in a small amount of chloroform and adsorbed on a neutral alumina column (40 × 3 cm) prewashed with chloroform. The azaindole was eluted with chloroform (1 l.); the chloroform was evaporated *in vacuo;* and the crystalline residue was recrystallized from acetone–water and sublimed at 115° (0.01 mm) giving 4 g (50%) of **8**: mp 106–110°; uv max 229 mμ (ε 12,300), 312 (14,900), 318 (15,400).

Anal. Calcd for $C_{17}H_{16}O_3N_2$: C, 68.9; H, 5.4; N, 9.5. Found: C, 69.2; H, 5.6; N, 9.6.

5-Methoxy-4-azaindole-2-carboxylic Acid (10).—Ethyl 5-methoxy-4-azaindole-2-carboxylate (**7**) (10 g) dissolved in 300 ml of 2 *N* sulfuric acid was heated under reflux for 3 hr, after which the solution was adjusted to pH 4 with solid sodium carbonate and cooled at 5° or several hours. The resulting precipitate was removed by filtration, dried, and crystallized from ethanol–water giving 8.5 g (97%) of **10**: mp 280° dec; uv max 315 mμ (ε 15,500), 295 (11,000).

Anal. Calcd for $C_9H_8O_3N_2$: C, 56.3; H, 4.2; N, 14.6. Found: C, 56.3; H, 4.2; N, 14.5.

5-Methoxy-6-azaindole-2-carboxylic acid (15) was prepared following the same procedure used for the obtention of **10**. From 10 g of ethyl 5-methoxy-6-azaindole-2-carboxylate (**13**)[12] was obtained 7 g (80%) of **15**: mp 220° (from ethanol); uv max 278 mμ (ε 15,100), 287 (18,000), 335 (4400).

Anal. Calcd for $C_9H_8O_3N_2$: C, 56.3; H, 4.2; N, 14.6. Found: C, 56.3; H, 4.2; N, 14.8.

5-Benzyloxy-4-azaindole-2-carboxylic Acid (11).—Ethyl 5-benzyloxy-4-azaindole-2-carboxylate (**8**) (6 g) dissolved in 100 ml of 2 *N* aqueous potassium hydroxide was heated under reflux for 1 hr, after which the solution was adjusted to pH 4 with glacial acetic acid and cooled at 5° for several hours. The resulting precipitate was filtered, dried, and purified by dissolution in dilute ammonium hydroxide and precipitation with acetic acid giving 4.4 g (73%) of **11**: mp 300° dec; uv max 315 mμ (ε 15,000), 318 (16,400).

Anal. Calcd for $C_{15}H_{12}O_3N_2$: C, 67.1; H, 4.5; N, 10.4. Found: C, 66.8; H, 4.5; N, 10.4.

5-Benzyloxy-6-azaindole-2-carboxylic acid (16) was prepared following the same procedure used for the preparation and purification of **11**. From 5 g of ethyl 5-benzyloxy-6-azaindole-2-carboxylate (**14**)[24] was obtained 3 g (70%) of **16**, mp 310°.

Anal. Calcd for $C_{15}H_{12}O_3N_2$: C, 67.1; H, 4.5; N, 10.4. Found: C, 66.8; H, 4.3; N, 10.2.

4-Azaindole-2-carboxylic acid (12) was prepared following the same procedure used in the synthesis of **11** and **16**. From 5 g of ethyl 4-azaindole-2-carboxylate (**9**) was obtained 3.8 g (90%) of 4-azaindole-2-carboxylic acid: mp 320° (from water); uv max 309 mμ (ε 14,200).

Anal. Calcd for $C_8H_6O_2N_2$: C, 59.2; H, 3.7; N, 17.3. Found: C, 59.1; H, 3.8; N, 17.1.

2,3-Diiodo-5-methoxy-4-azaindole (17).—5-Methoxy-4-azaindole-2-carboxylic acid (**10**) (10 g, 0.04 mol) was dissolved in 850 ml of a 1 *N* aqueous lithium hydroxide solution; 50 g (0.2 mol) of iodine dissolved in 540 ml of methanol was added; and the mixture was stirred for 3 hr at room temperature. The excess of iodine was then destroyed with sodium sulfite. The solution was adjusted to pH 8 with solid sodium carbonate and extracted thoroughly with ten 150-ml portions of chloroform. The dried chloroform extracts (Na_2SO_4) were evaporated to dryness *in vacuo*, and the brown crystalline residue (18 g, 82%) was used directly in the next step. It could be purified by recrystallization from benzene–methylcyclohexane and sublimation at 150° (0.01 mm): mp 185–189°; R_F 0.76 (benzene–chloroform 1:1).

Anal. Calcd for $C_8H_6N_2OI_2$: C, 24.0; H, 1.5; N, 7.0. Found: C, 24.3; H, 1.6; N, 7.3.

5-Methoxy-4-azaindole (19).—The crude diiodo-4-azaindole **17** (9 g) was dissolved in 200 ml of ethanol; 25 g of sodium acetate trihydrate was added; and the solution was reduced at 20 psi with hydrogen during 12 hr over 2 g of 10% palladium on charcoal. The catalyst was removed and washed with ethanol. The combined filtrate and washings were evaporated *in vacuo*, and the residue was dissolved in 20 ml of water and extracted with five 10-ml portions of chloroform. The dried (Na_2SO_4) chloroform extracts were evaporated *in vacuo*, and the residue was sublimed at 90° (1 μ) giving 2.7 g (81%) of **19**: mp 114–117°; R_F 0.20 (benzene–chloroform 1:1); uv max, 301 mμ (ε 11,800), 305 (10,900); nmr, δ 4.0 (s, OCH_3), 6.6 (d, J = 10 Hz, C-6 H), 7.3 (t, C-2 H and C-3 H), 7.6 (d, J = 10, C-7 H).[25]

Anal. Calcd for $C_8H_8ON_2$: C, 64.9; H, 5.4; N, 18.9. Found: C, 65.0; H, 5.6; N, 18.8.

Examination of the hydrogenation reaction by tlc after 3 and 6 hr indicated the formation of intermediate monoiodo-5-methoxy-4-azaindoles (R_F 0.50 and 0.35) during the process. For the alternative synthesis of 5-methoxy-4-azaindole (**19**) see Table I.

2,3-Diiodo-5-benzyloxy-4-azaindole (18) was prepared following the same procedure used in the synthesis of 2,3-diiodo-5-methoxy-4-azaindole (**17**). From 3.6 g of 5-benzyloxy-4-azaindole-2-carboxylic acid (**11**) was obtained 4.5 g (71%) of crude **18**, which was purified by crystallization from benzene: mp 172–176°; R_F 0.80 (benzene–chloroform 1:1).

Anal. Calcd for $C_{14}H_{10}N_2I_2O$: C, 35.3; H, 2.1; N, 5.9. Found: C, 35.6; H, 2.0; N, 5.5.

5-Benzyloxy-4-azaindole (20) was prepared by the same procedure used in the synthesis of 5-methoxy-4-azaindole (**19**), and the hydrogenation was completed in 6 hr. From 4.5 g of crude **18** was obtained 1.5 g (65%) of **20**: mp 148–152°; uv max 301 mμ (ε 11,000); R_F 0.25 (benzene–chloroform 1:1).

Anal. Calcd for $C_{14}H_{12}ON_2$: C, 75.0; H, 5.4; N, 12.5. Found: C, 74.9; H, 5.3; N, 12.4.

The alternative synthesis of **20** is described in Table I.

2-Hydroxymethyl-5-methoxy-6-azaindole (22). Procedure A.—Ethyl 5-methoxy-6-azaindole-2-carboxylate (**13**) (8 g) dissolved in 400 ml of tetrahydrofuran was slowly added with constant stirring to a suspension of 2 g of lithium aluminum hydride in 100 ml of tetrahydrofuran. The resulting mixture was heated at reflux for 4 hr, and then 600 ml of ice water was added. The solution was adjusted to pH 12 with concentrated sodium hydroxide solution and extracted with ten 200-ml portions of ether. The dried (Na_2SO_4) ether extracts were evaporated *in vacuo*. The crystalline residue was recrystallized from methanol giving 3.4 g (48%) of **22**: mp 168–170°; uv max 270 mμ (ε 7570), 275 (7650), 313 (5160); R_F 0.06 (1% ethanol in chloroform).

Anal. Calcd for $C_9H_{10}O_2N_2$: C, 60.8; H, 5.9; N, 15.7. Found: C, 60.7; H, 5.6; N, 15.7.

2-Formyl-5-methoxy-6-azaindole (27). Procedure B.—2-Hydroxymethyl-5-methoxy-6-azaindole (**22**) (2 g) was dissolved in a mixture of 60 ml of tetrahydrofuran and 500 ml of ether; 20 g of manganese dioxide was added; and the mixture was stirred for 24 hr at room temperature. The oxidant was removed and washed with ether. The combined filtrate and washings were evaporated *in vacuo*, and the crystalline residue was recrystallized from benzene–cyclohexane, giving 1.7 g (76%) of **27**: mp 174–178°; uv max 290 mμ (ε 16,300), 299 (18,000); nmr (TFA), δ 9.8 (s, CHO); R_F 0.23 (1% ethanol in chloroform).

Anal. Calcd for $C_9H_8O_2N_2$: C, 61.4; H, 5.0; N, 15.9. Found: C, 61.4; H, 4.6; N, 15.9.

5-Methoxy-6-azaindole (32). Procedure C.—The aldehyde **27** (300 mg) and chlorotris(triphenylphosphine)rhodium (100 mg) were suspended in 6 ml of decalin and heated at 300° for 30 min in a sealed vessel. The mixture was extracted with five 2-ml portions of 4 *N* hydrochloric acid. The aqueous solution was washed twice with 5 ml of ether, alkalized with a concentrated sodium hydroxide solution, and reextracted with five 3-ml portions of chloroform. The dried (Na_2SO_4) chloroform extract was evaporated *in vacuo*, and the crystalline residue was sublimed at 90° (1 μ), giving 130 mg (48%) of **32**: mp 122–124°; uv max 267 mμ (ε 5500), 273 (5260), 313 (5200).

Anal. Calcd for $C_8H_8ON_2$: C, 64.9; H, 5.4; N, 18.9. Found: C, 64.7; H, 5.4; N, 18.8.

(24) B. Frydman, S. Reil, M. E. Despuy, and H. Rapoport, *J. Amer. Chem. Soc.*, submitted for publication.

(25) In the nmr spectra of indoles in $CDCl_3$, there was a pronounced chemical shift in the triplets (NH coupling) corresponding to the α hydrogens (δ 7.0) and the β hydrogens (δ 6.5) which indicated the greater electron density at the β position of indole. The collapse of both signals in **19** into one triplet at δ 7.3 indicated not only the close similarity of both hydrogens, but also the diminished electron density in the pyrrole ring of 4-azaindoles.

5-Oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridine (34).—5-Methoxy-4-azaindole (19) (1 g) was dissolved in 20 ml of 48% hydrobromic acid, and the mixture was heated under reflux for 2.5 hr. It was then evaporated to dryness; the residue was dissolved in 4 ml of water; and the solution was adjusted to pH 7 with solid sodium carbonate. The precipitate was filtered, dried, crystallized from methanol, and sublimed at 220° (1 μ), giving 825 mg (96%): mp 280–289°; uv max 330 mμ (ϵ 12,700).

Anal. Calcd for $C_7H_6ON_2$: C, 62.7; H, 4.5; N, 20.9. Found: C, 62.4; H, 4.5; N, 20.9.

3-Dimethylaminomethyl-5-methoxy-4-azaindole (36).—5-Methoxy-4-azaindole (19) (1 g) was dissolved in 60 ml of 1-butanol; 400 mg of paraformaldehyde and 1 g of dimethylamine hydrochloride were added; and the mixture was heated at reflux for 30 min and evaporated to dryness *in vacuo*. The residue was dissolved in 50 ml of 4 *N* hydrochloric acid, washed twice with 100 ml of ether, alkalized with solid potassium carbonate, and extracted several times with chloroform. The dried (Na_2SO_4) chloroform extracts were evaporated *in vacuo*, and the oily residue was dissolved in 50 ml of ethanol and precipitated as a dipicrate. The dipicrate was centrifuged, washed twice with 20 ml of cold ethanol, and recrystallized from methanol to yield 3.3 g (75%), mp 174–176°.

Anal. Calcd for $C_{23}H_{21}O_{15}N_9$: C, 41.6; H, 3.1; N, 19.0. Found: C, 41.4; H, 3.0; N, 18.9.

The free base was recovered by dissolution of the dipicrate in 90% aqueous acetone and passage through an IRA-400 (HCO_3) ion-exchange resin[26] column: nmr (D_2O), δ 3.1 [s, $N(CH_3)_2$], 4.8 (s, CH_2), 8.3 (s, C-2 H).

3-Formyl-5-methoxy-4-azaindole (35).—5-Methoxy-4-azaindole (15) (200 mg, 1.2 mmol) dissolved in 0.1 ml of dimethylformamide was added to a mixture of 0.12 ml (1.3 mmol) of phosphorous oxychloride and 0.4 ml of dimethylformamide cooled at 0°; the solution was heated at 70° for 2 hr and was cooled. Then 2 ml of ice water was added. The crystalline precipitate was centrifuged, dried, and crystallized from ethanol giving 85 mg (40%) of **35**: mp 145–147°; ir, 1720 cm^{-1} (CHO).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.3; H, 4.5; N, 15.9. Found: C, 61.6; H, 4.7; N, 16.2.

Registry No.—**2**, 17288-26-5; **3** monopicrate, 17288-27-6; **4**, 17288-28-7; **5**, 17288-29-8; **6**, 17288-30-1; **7**, 17322-90-6; **8**, 17288-31-2; **9**, 17288-32-3; **10**, 17288-33-4; **11**, 17288-34-5; **12**, 17288-35-6; **15**, 17288-36-7; **16**, 17288-37-8; **17**, 17288-38-9; **18**, 17288-39-0; **19**, 17288-40-3; **20**, 17288-41-4; **21**, 272-49-1; **22**, 17288-43-6; **23**, 17288-44-7; **24**, 17288-45-8; **25**, 17288-46-9; **26**, 17288-47-0; **27**, 17288-48-1; **28**, 17288-49-2; **29**, 17288-50-5; **30**, 17288-51-6; **31**, 17288-52-7; **32**, 17288-53-8; **33**, 17288-54-9; **34**, 17322-91-7; **35**, 17288-55-0; **36** dipicrate, 17288-56-1.

(26) J. M. Bobbitt, *J. Org. Chem.*, **22**, 1729 (1957).

Bridgehead Nitrogen Heterocycles. I. A Convenient Synthesis of Pyrazolo[1,5-*a*]pyridines[1]

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Cyclization of 2-alkyl-1-aminopyridinium salts (2) with acyl or aroyl chlorides in pyridine solution provides a convenient synthesis of derivatives of the title ring system (3). With 1-amino-2-methyl- and 1-amino-2,6-dimethylpyridinium iodides and benzoyl chloride, intermediate pyridinium betaines (6) were isolated unless prolonged reaction times were employed. Acylation at the 3 position occurs extremely readily in this ring system. Spectral data for derivatives of this ring system are described.

The direct amination of tertiary amines with hydroxylamine-O-sulfonic acid to yield the corresponding hydrazinium salts[2] has been applied to the preparation of 1,2-diaminopyridinium salts which underwent an extremely facile cyclization with aliphatic acids or acid chlorides to *s*-triazolo[1,5-*a*]pyridine derivatives.[3] The ease of amination of 2-alkylpyridines (1) to 2-alkyl-1-aminopyridinium salts (2) with hydroxylamine-O-sulfonic acid[2] suggested that cyclization of these salts with acyl chlorides might provide an extremely simple and direct synthesis of the pyrazolo[1,5-*a*]pyridine ring system (3). In this communication we describe the successful synthesis of this ring system by this route which now makes it readily available.

Pyrazolo[1,5-*a*]pyridine and its 2-phenyl derivative have been prepared previously[4a] by potassium ferricyanide oxidative ring closure of the corresponding 2-(2-aminoethyl)pyridines. Oxidation of pyrazolo[1,5-*a*]pyridine with potassium permanganate was shown to give pyrazole-3-carboxylic acid,[4a] clearly establishing that ring closure had occurred in the oxidation process. This was also indicated by the uv absorption spectrum of the system.[4b] A more complex substituted derivative has also been reported,[4c] and, by 1,3 dipolar addition type reactions to azomethine imines, fused[4d] and reduced[4e] pyrazolo[1,5-*a*]pyridine derivatives have been obtained. This last route has recently been used[4f] for the preparation of a variety of pyrazolo-[1,5-*a*]pyridine derivatives and is an effective complement to the synthetic procedures described below. In this present study several alkylpyridine derivatives were aminated at position 1 in moderately good yield, either with hydroxylamine-O-sulfonic acid or with its potassium salt.[2] The resulting 1-aminopyridinium salts (2) (Table I) were found to be extremely reactive toward acetyl chloride in pyridine, and cyclization occurred in a very short time. The 1-amino-2-methylpyridinium salts failed to give cyclic products with benzoyl chloride unless prolonged reaction times (24 hr) were used. With shorter reaction periods, pyridinium betaines were isolated as the sole products from the reaction mixtures. Moreover, the 1-amino-2-methylpyridinium salts always resulted in cyclic products which were acylated (acetyl or benzoyl group) in the 3 position. At no time was it possible to obtain a

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(2) R. Gosl and A. Meuwsen, *Chem. Ber.*, **92**, 2521 (1959).

(3) K. T. Potts, H. R. Burton, and J. Bhattacharyya, *J. Org. Chem.*, **31**, 260 (1966).

(4) (a) J. D. Bower and G. A. Ramage, *J. Chem. Soc.*, 4506 (1957); (b) J. D. Bower, *ibid.*, 4510 (1957); (c) E. C. Taylor and K. S. Hartke, *J. Amer. Chem. Soc.*, **81**, 2452 (1959); (d) R. Huisgen, R. Grashey, P. Laur, and H. Leitermann, *Angew. Chem.*, **72**, 416 (1960); (e) H. Beyer, K. Leverenz, and H. Schilling, *ibid.*, **73**, 272 (1961); (f) V. Boekelheide and N. A. Fedoruk, *J. Org. Chem.*, **33**, 2062 (1968).