Reactivity of 1*H*-Pyrrolo[2,3-*b*]pyridine. I. Synthesis of 3-Acetyl-7-azaindole and Related Compounds

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The behaviour of 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) towards several acylating reagents are reported. The preparation of 3-acetyl-7-azaindole, 3-chloroacetyl-7-azaindole and 3-(2-hydroxiethyl)-7-azaindole are described.

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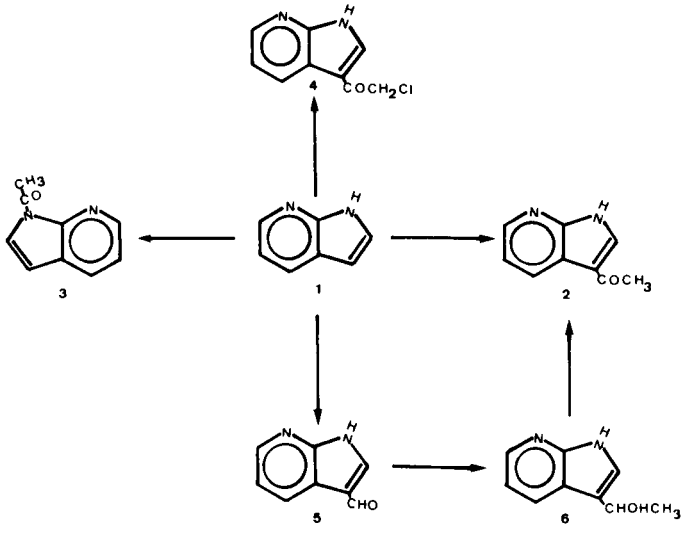
The isomeric monoazaindoles are convenient models for an investigation of intramolecular electronic interactions between π-electron deficient and π-electron excessive rings in bicyclic heteroaromatic systems. Fusion of an electron-withdrawing pyridine ring with an electron-releasing pyrrole ring to form an azaindole gives a system which retains certain chemical properties of both rings, but expectedly, of a lower order reactivity. Thus the pyrrole ring is attacked by electrophilic reagents in the 3-position like indole, although with greater difficulty. With respect to the acylation reaction, whereas azaindoles are readily acylated on the pyrrole nitrogen by warming on a water bath with an acid anhydride or with an acid chloride in the presence of carbonate or pyridine, the most useful acylation reaction on carbon of azaindoles, as with indoles is 3-formylation (1).

In the 7-azaindole series, no examples of a 3-acetyl derivative have been reported.

In this communication we wish to report the results of acylation of 7-azaindole, (**1**) using different acylating reagents. These reactions allowed us to isolate in good yield 3-acetyl-7-azaindole (2) which was prepared in our laboratory by an indirect method (Scheme I).

Scheme I



Due to the fact that formylation of azaindoles is carried out conveniently with the Vismeier reagent (2) and since the reaction involving indole, phosphorus oxychloride and *N,N*-dimethylcarboxamides has given a variety of 3-indolyl ketones (3) we tested the acylation of compound 1, using phoshorus oxychloride and *N,N*-dimethylacetamide as the reagents. As can be seen in Table I, compound **2** was not isolated. The 1-acetyl derivatives, (**3**) (11%) (4) and 75% of unchanged starting material were obtained from the reaction mixture. In Table I, the results obtained with the indole are reported. In the indole series other methods have been used for acylation. Thus 3-acetylindole, has been prepared by reaction of indole with acetic anhydride (5) or mild alkaline hydrolysis of 1,3-diacetylindole which is available from the reaction of indole with boiling acetic-acid anhydride for 24 hours (6).

We tested the acylation of 7-azaindole (1), under the experimental conditions described by Saxton (6) for the 3-acetylindole (experimental 2, Table I) isolating a substance (90%), the analysis and spectroscopic data of which are in good agreement with the 1-acetyl-7-azaindole (3). It seems reasonable to assume that the difference in reactivity between 7-azaindole and indole can be accounted for by the greater basic strength (pk_a = 4.59) of the former (7) compared to the latter (pk_a < 1). The protonation of the pyridine nitrogen has the effect of lowering the electron availability of the 3-position.

In a further attempt to achieve our objective we tested the acylation of **1** using acetic anhydride in the presence of anhydrous aluminum chloride. A white solid was isolated in 90% yield. Its spectra is in good agreement with the structure of compound **2**, previously prepared in our laboratory by an indirect method (see below). Among the by-products, the compound **3** (2%) was identified.

The same reaction, using as an acylation agent, 2-chloroacetyl chloride, gave **4** in high yield (81%). The 1-chloroacetyl-7-azaindole (8) was not detected. The ir spectra of compounds **2** and **4** showed complicated band splitting around 3000 cm^{-1} (9) and the absorption position for the NH proton in the nmr spectra is observed at 11.5 ppm for **2** and at 12.5 for **4** (in dimethyl sulphoxide). An alternative method of the preparation of compound 2 has

Table I

Experimental	Acylating reagent	Indole			7-azaindole		
		1-acetyl	3-acetyl	1,3-diacetyl	1-acetyl	3-acetyl	1,3-diacetyl
1	*N,N*-dimethyl-acetamide-phosphorus oxychloride	—	22.4% (3)	—	11%	—	—
2	Acetic-anhydride and acid acetic	—	—	50-60% (6)	90%	—	—
3	Acetic-anhydride-aluminum chloride		(a) (12)		2%	90%	—
4	Chloroacetyl-chloride-aluminum chloride		(b)	—		81%	—

(a) With anhydrous stannic chloride, indole itself gave mostly red tar. (b) 3-Chloroacetylindole could be prepared in fair yield by slow addition of the α-chloroacetyl chloride to indole and pyridine in dioxane at 60° (13).

Table II

^{1}H-NMR Spectra of 7-Azaidoles Derivatives

Compound	Chemical Shifts (ppm) (a)						J (cps)			
	C_2-H	C_3-H	C_4-H	C_5-H	C_6-H	Alkyl	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	Solvent
2	8.42 s		8.47 dd	7.20 dd	8.29 dd	2.52 s	7.5	1.6	4.7	DMSO-d_6
3	7.87 d	6.47 d (b)	7.77 dd	7.07 dd	8.27 dd	2.99 s	7.7	1.7	4.7	Deuteriochloroform
4	8.37 s		8.47 dd	7.23 dd	8.31 dd	4.92 s	8	1.7	5	DMSO-d_6
5	8.18 s		8.45 dd	7.23 dd	8.26 dd	(c)	8	1.5	5	Perdeuteriomethanol
6	7.34 s		8.11 dd	7.07 dd	8.24 dd	(d)	8	1.5	5	DMSO-d_6

(a) Abbreviations: dd = double doublet, s = singlet; (b) $J_{2,3}$ = 4 cps; (c) 9.83 s (CHO); (d) 1.53 (d, CH_3, J = 6.5 cps), 4.98 (c, -CH-).

been carried out in our laboratory by the condensation of 3-formyl-7-azaindole (**5**) (2) with methylmagnesium iodide and oxidation of the carbinal **6** formed (see Scheme I).

The preparation of compound **2** from **6** was achieved using anhydrous chromium trioxide as the oxidizing agent. Two different experiments were carried out. The oxidation of **6** using the chromium trioxide-pyridine complex in methylene chloride according to the procedure of Ratcliffe and Rodehorst (10), allowed us to isolate the compound **2** in 20% yield, while the use of hexamethylphosphoramide (11) as the solvent gave exclusively **2** in 99% yield.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R-12B spectrometer using TMS as an internal standard. Chemical shifts are reported as δ values in parts per million (ppm). Infrared spectra were measured on a Pye-Unicam SP 1100 spectrophotometer. Elemental analyses were performed by Instituto de Quimica Organica, Barcelona.

Acylation of 7-Azaindole (**1**).

A. With Phosphorus oxychloride and *N,N*-dimethylacetamide.

A 2.24 g sample of phosphorus oxychloride was slowly added to 3.2 ml of *N,N*-dimethylacetamide keeping the temperature below 5°. After the addition was complete, a solution of 1.18 g (10 moles) of 7-azaindole (1) in *N,N*-dimethylacetamide (1.8 ml) was added dropwise. The reaction mixture was heated to 90° for 2 hours, cooled, diluted with water and extracted with ether. The organic layer gave 0.176 g (11%) of compound **3**, 1-acetyl-7-azaindole, mp 67° recystallized from chloroform-hexane; ir (chloroform): 1710 cm^{-1} (CO); nmr, see Table II.

The aqueous layer was basified, extracted and the solvent removed. The solid obtained was identified as 7-azaindole (**1**) unchanged.

B. With Acetic Anhydride and Acetic Acid.

A solution of **1** (10 mmoles) in acetic anhydride (12 ml) and acetic acid (1.2 ml) was heated at reflux for 13 hours. After this time the reaction mixture was poured into water. A precipitate (90%) was formed which was identified as 1-acetyl-7-azaindole (**3**).

Identical results were obtained when the same reaction was carried out by heating in sealed tube for 22 hours.

C. With Acetic Anhydride in the presence of Anhydrous Aluminum Chloride.

To a solution of **1** (10 mmoles) in carbon disulphide (50 ml), 10 g of anhydrous aluminum chloride was slowly added. The reaction mixture was heated to 50° with stirring and 2.16 g of acetic anhydride was slowly added. The resulting solution was allowed to stir at 50° for 2 hours. After this time the solution was cooled to room temperature and 50 ml of water was slowly added. The organic layer was separated, dried and the solvent removed giving a residue which was purified and identified as **3** (2%).

A precipitate was obtained from the aqueous layer which was identified as **2**, 3-acetyl-7-azaindole, mp 206-207° (purified by sublimation (90%); ir (potassium bromide): 1645 cm^{-1} (CO); nmr see Table II.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.48; H, 5.03; N, 17.49. Found: C, 67.44; H, 5.01; N, 17.50.

3-Chloroacetyl-7-azaindole (**4**).

To a solution of **1** (10 mmoles) in carbon disulphide (50 ml), 10 g of anhydrous aluminum chloride was slowly added. The reaction mixture was heated to 50° with stirring and 1.154 g of chloroacetyl chloride in 5 ml of carbon disulphide was added dropwise. The resulting solution

was allowed to stir at 50° for 2 hours. After this time the solution was cooled at room temperature and 50 ml of water was slowly added. The aqueous layer was separated and a precipitate was obtained which was identified as **4**, mp 296-298°, recrystallizable from methanol, (82%); ir: (potassium bromide): 1650 cm^{-1}; nmr, see Table II.

Anal. Calcd. for $C_9H_7ClN_2O$: C, 55.54; H, 3.62; N, 14.39; Cl, 18.21. Found: C, 55.51; H, 3.60; N, 14.41; Cl, 18.20.

3-(2-Hydroxyethyl)-7-azaindole (**6**).

To solution of 3-formyl-7-azaindole (**5**) (2) (10 mmoles) in 1,2-dimethoxyethane (100 ml) a solution of mathylmagnesium iodide in ether (50 mmoles) was added dropwise. The ether was removed and the reaction mixture was heated at reflux for 4 hours. After this time a solution of ammonium chloride and hydrochloric acid in water was added (*p*H 6-7). The solution was extracted with methylene chloride and 1.25 g (77%) of **6** was obtained form the organic layer, mp 135°, recrystallizable from ethanol-chloroform; nmr, see Table II.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.62; H, 6.22; N, 17.23.

3-Acetyl-7-azaindole (**2**) from Oxidation of **6**.

Method A.

Chromium trioxide (0.47 g) was added to a magnetically stirred solution of 0.756 g of pyridine in 15 ml of methylene chloride. The flask was stoppered with a drying tube containing drierite and the solution stirred for 15 minutes at room temperature. After this time, a solution of the carbinol **5** (0.125 g) in methylene chloride was added. The reaction mixture was allowed to stir for 30 minutes. At the end of this period the solution was decanted from residue, condensed *in vacuo* and the residue then taken up in ether, filtered to remove insoluble chromium salts, washed with dilute aqueous base and dried over magnesium sulphate. Evaporation of the solvent at reduced pressure afforded the ketone **2** (20%).

Method B.

Chromium trioxide (2.1 g) was added to a magnetically stirred solution of 6 ml of hexamethyl phosphoramide and allowed to stir for 1 hour. At the end of this period, a solution of the carbinol **5** (1.66 g) in 8 ml of hexamethylphosphoramide was added and the reaction mixture was stirred for 6 hours. At the end of this period, the solution was poured into ice-water and extracted with methylene chloride. Only one product (compound **2**) was detected by thin layer chromatography the (yield estimated as 99%) but its isolation was not possible due to the difficulty in removing the solvent.

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