Reactivity of 1*H*-Pyrrolo[2,3-*b*]pyridine. II. Synthesis of 3-(β-Haloethyl)-7-azaindole

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The preparation of 3-(2-chloroethyl)-7-azaindole and 3-(2-bromoethyl)-7-azaindole are described.

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Due to an interest in the study of the reactivity of azaindole systems, we now report the results of the reactions which allowed us to prepare 3-(β-haloethyl)-7-azaindole derivatives **1** from 7-azaindole (Scheme I).

Direct alkylation (route a), the metalation of 3-bromo-7-azaindole (**3**) (route b) and reduction of the carbonyl group of 3-haloacetyl compounds **5** (route c), are the routes tested simultaneously us [1,3]. The positive results obtained in the acylation of 7-azaindole (**2**) under Friedel-Crafts conditions [1] prompted us to explore the alkylation on such a system.

Thus, by the reaction of compound **2** (route a) with ethylene oxide and stannic chloride under the conditions described by Julia [4] for the indole series did not allow us to isolate compound **4** which was prepared in our laboratory by an indirect method (route b). However, under more drastic conditions (aluminum chloride in carbon disulphide and heating the reaction mixture for 30 minutes at 50°) the formation of 1-(2-hydroxyethyl)-7-azaindole (**6**) in 71% yield was observed.

When 2-chloro-1-hydroxyethane was used as the alkylating agent to obtain **1a** under different conditions (aluminum chloride, carbon disulphide, room temperature, 2 hours; boron trifluoride etherate, carbon disulphide, 50°, 2 hours) [5] 90% of unchanged starting material was recovered. In view of these results the 3-(2-hydroxyethyl)-7-azaindole (**4**) was prepared by regiospecific alkylation of the 1,3-dianion formed by metalation of the 3-bromo-7-azaindole (**3**) [6] (route b). Among the different conditions attempted, the reaction between two equivalents of *n*-butyllithium with one equivalent of compound **3** at -5° for 1 hour and then the addition of ethylene oxide keeping the temperature at 0° for 3 hours, gave the higher yields of compound **4** (57%). The formation of byproduct **6** was observed in a low yield (4%) and 19% of 7-azaindole (**2**) was recovered from the reaction mixture.

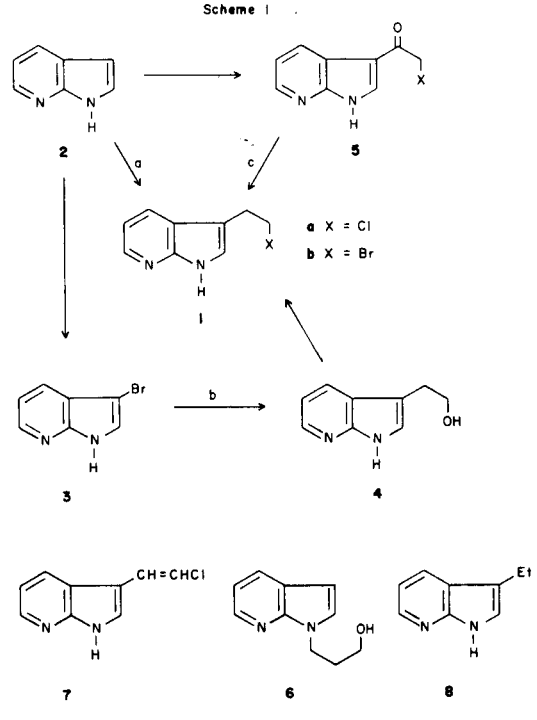
Subsequently, by reaction of compound **4** with phosphorus tribromide in an inert solvent, methylene chloride [4] or 1,2-dimethoxyethane [7] allowed us to isolate 21% and 19% respectively of compound **1b**. The low yields observed are probably due to the insolubility of the azaindole derivatives under the acidic conditions generated in the reaction mixture. We also prepared compounds **1** by reduction of 3-chloroacetyl-7-azaindole (**5a**) and 3-bromoacetyl-7-azaindole (**5b**) (route c). This route was viable because of the accesibility of the precursors **5**, as reported in our preceding paper [1].

In our hands, the reduction of **5a** with mixtures of aluminum chloride-lithium aluminum hydride [8] (molar ratio chloride/hydride lower than 2:1) led to 65% of 3-(2-chloroethyl)-7-azaindole (**1a**) (only 25% of **1a** was obtained pure) and 11% of a product identified as 3-(2-chlorovinyl)-7-azaindole (**7**) [9].

By contrast the preparation of the hydride adding aluminum chloride to a suspension of lithium aluminum hydride in an inert solvent, followed by the addition of the product at room temperature, allowed us to isolate 92% of compound **1a** without significant dehalogenation (lower than 3%).

The reduction of 3-bromoacetyl-7-azaindole (**5b**) under the same conditions gave 3-(2-bromoethyl)-7-azaindole (**1b**) in 90% yiled. When the compound **5b** was reduced by addition of lithium aluminum hydride to a suspension of the

Scheme I



product with aluminum chloride, 62% of **1b** and 24% of compound **8** were obtained.

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 part per million (ppm). Infrared spectra were measured on a Pye-Unicam SP 1100 spectrophotometer. Elemental analysis were performed by the Instituto de Química Orgánica, Barcelona.

3-(2-Chloroethyl)-7-azaindole (**1a**).

Method A.

To a solution of 0.7 g (3.6 mmoles) of 3-chloroacetyl-7-azaindole (**5a**) [1] in 200 ml of anhydrous 1,2-dimethoxyethane, 1.45 g (10.9 mmoles) of anhydrous aluminum chloride was slowly added, followed by addition of 0.33 g (8.7 mmoles) of lithium aluminum hydride. The mixture was refluxed for 3.5 hours. After this time 50 ml of water was added and the mixture was extracted with chloroform. The organic layer was dried and the solvent removed. The residue was purified by chromatography on a silica-gel column to obtain 0.16 g (25%) of white solid, mp 103-105°; nmr (deuteriochloroform): δ 3.12 (t, CH_2, 2H, $J_{8,9}$ = 6.7 Hz), 3.67 (t, CH_2Cl, 2H), 6.90 (dd, H-5, 1H, $J_{4,5}$ = 7.7 Hz, $J_{5,6}$ = 4.7 Hz), 7.13 (s, H-2, 1H), 7.78 (dd, H-4, 1H, $J_{4,6}$ = 1.7 Hz), 8.18 (dd, H-6, 1H), 11.8 (s, OH, 1H).

Anal. Calcd. for $C_9H_9ClN_2$: C, 59.84; H, 5.02; Cl, 19.63; N, 15.51. Found: C, 59.93; H, 5.08; Cl, 19.63; N, 15.51.

On elution with methylene chloride 0.05 g (11%) of a byproduct was obtained identified as 3-(2-chlorovinyl)-7-azaindole (**7**), mp 166-167°; nmr (deuterated dimethylsulfoxide): δ 6.42 (m, ethenyl-H, 1H), 7.10-7.25 (m, ethenyl-H, 1H, H-5, 1H), 8.1-8.4 (m, H-2, H-4, H-6, 3H), 11.2 (s, NH, 1H).

Anal. Calcd. for $C_9H_7ClN_2$: C, 60.52; H, 3.95; Cl, 19.85; N, 15.68. Found: C, 60.45; H, 3.90; Cl, 19.97; N, 15.60.

Method B.

To a suspension of 0.4 g of lithium aluminum hydride, 2.78 g (20.8 mmoles) of anhydrous aluminum chloride in 50 ml of anhydrous 1,2-dimethoxyethane, 1.02 g (5.2 mmoles) of **5a** in 200 ml of anhydrous 1,2-dimethoxyethane was added dropwise. After 40 minutes at room temperature 30 ml of water was added. The extraction with methylene chloride afforded 0.87 g (92%) of **1a**.

3-(2-Hydroxyethyl)-7-azaindole (**4**).

To a solution of 20 mmoles of *n*-butyllithium (1.6 *N*) in 20 ml of anhydrous ether at -5° under an atmosphere of nitrogen, 2.1 g (10 mmoles) of 3-bromo-7-azaindole (**3**) [6] in 30 ml of anhydrous 1,2-dimethoxyethane was slowly added. After one hour at this temperature, 1.48 g (33 mmoles) of ethylene oxide in 10 ml of 1,2-dimethoxyethane was added. This mixture was maintained at 0° for 5 hours. Then 10 ml of water and 10 ml of hydrochloric acid was added. The aqueous layer was basified and extracted with methylene chloride. This organic layer was concentrated and chromatographed on an alumina column using benzene as the eluent to obtain 0.97 g (57%) of a white solid, mp 93-94°; ir (potassium bromide): 3340 cm^{-1} (OH); nmr (deuteriochloroform): δ 2.87 (t, CH_2, 2H, $J_{8,9}$ = 6.7 Hz), 3.80 (t, CH_2OH, 2H), 4.7 (s, OH, 1H), 6.75 (dd, H-5, 1H, $J_{4,5}$ = 7.7 Hz, $J_{5,6}$ = 5.0 Hz), 6.90 (s, H-2, 1H), 7.67 (dd, H-4, 1H, $J_{4,6}$ = 1.5 Hz), 7.97 (dd, H-6, 1H).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27; Found: C, 66.63; H, 6.15; N, 17.21.

3-Bromoacetyl-7-azaindole (**5b**).

To a solution of 7.54 (64 mmoles) of **2** in 200 ml of carbon disulphide 30.0 g of anhydrous aluminum chloride was slowly added. The reaction mixture was heated to 50° with stirring and 12.9 g (64 mmoles) of bromoacetyl bromide in 50 ml of carbon disulphide was added dropwise. The resulting solution was allowed to stir at 50° for 40 minutes and 250 ml of water was slowly added. The aqueous layer was separated and the solvent removed to give a residue which was recrystallized from methanol and 11.5 g (75%) of white solid was obtained, mp 280-282°; nmr (deuterated dimethylsulfoxide): δ 4.70 (s, CH_2, 2H), 7.22 (dd, H-5, 1H, $J_{4,5}$ = 7.7 Hz, $J_{5,6}$ = 4.8 Hz), 8.30 (m, H-6, 1H), 8.42 (m, H-4, 1H), 8.60 (s, H-2, 1H), 12.7 (s, NH, 1H).

Anal. Calcd. for $C_9H_7BrN_2O$: C, 45.22; H, 2.95; Br, 33.42; N, 11.72. Found: C, 45.28; H, 2.99; Br, 33.36; N, 11.77.

1-(2-Hydroxyethyl)-7-azaindole (**6**).

To a solution of 7-azaindole (**2**) (1.20 g, 10 mmoles) in 50 ml of carbon disulphide, 5.0 g of anhydrous aluminum chloride was slowly added. The reaction mixture was heated to 50° with stirring and 5 ml of ethylene oxide was added. The resulting solution was allowed to stir at 50° for 30 minutes. Then the solution was cooled to room temperature and 50 ml of water was slowly added. The aqueous layer was extracted with chloroform, basified and extracted again with chloroform. This last organic layer was dried and the solvent was removed. Recrystallization of the residue in chloroform-carbon tetrachloride gave 1.18 g (71%) of white solid, mp 110°; ir (potassium bromide): 3050 cm^{-1} (OH); nmr (deuterated dimethylsulfoxide): δ 3.93 (t, CH_2, 2H, $J_{8,9}$ = 5.3 Hz), 4.27 (s, OH, 1H), 4.70 (t, CH_2OH, 1H), 4.70 (t, CH_2OH, 2H), 6.53 (d, H-3, 1H, $J_{2,3}$ = 2.5 Hz), 6.87 (dd, H-5, 1H, $J_{4,5}$ = 7.7 Hz, $J_{5,6}$ = 6.0 Hz), 7.60 (d, H-2, 1H), 8.13 (dd, H-6, 1H, $J_{4,6}$ = 1.2 Hz).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.67; H, 6.11; N, 17.32.

3-(2-Bromoethyl)-7-azaindole (**1b**).

From **5b**. Method A.

To a suspension of 0.39 g (10.3 mmoles) of lithium aluminum hydride in 50 ml of anhydrous 1,2-dimethoxyethane, 2.7 g (20 mmoles) of anhydrous aluminum chloride was slowly added, while cooling in a water bath. Then 1.18 g (5 mmoles) of **5b**, in 200 ml of anhydrous 1,2-dimethoxyethane was added dropwise. The mixture was stirred for 40 minutes and then 30 ml of water was added. The solution was extracted with methylene chloride and the organic layer concentrated to give 0.98 g of a residue which was purified by chromatography on a silica-gel column and 0.89 g (90%) of a white solid was obtained, mp 112-114°; nmr (deuteriochloroform): δ 4.4 (m, alquil-H, 4H), 6.97 (dd, H-5, 1H, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 5 Hz), 7.17 (s, H-2, 1H), 7.83 (dd, H-4, 1H, $J_{4,6}$ = 1.5 Hz), 8.22 (dd, H-6, 1H), 11.8 (S, NH, 1H).

Anal. Calcd. for $C_9H_9BrN_2$: C, 48.02; H, 4.03; Br, 35.50; N, 12.45. Found: C, 48.17; H, 4.20; Br, 35.45; N, 12.38.

Method B.

To a solution of 1.19 g (5 mmoles) of **5b** in 200 ml of anhydrous 1,2-dimethoxyethane heated at reflux, 2.74 g (20.5 mmoles) of anhydrous aluminum chloride was slowly added with stirring. Then 0.39 g (10.3 mmoles) of lithium aluminum hydride was added with care. The mixture was allowed to stir at room temperature for 40 minutes and after this time 50 ml of water was slowly added. The solution was extracted with methylene chloride and the organic layer dried and concentrated to give 0.87 g of an oil formed which consisted of 62% of **1b** and 20% of 3-ethyl-7-azaindole (**8**); nmr (deuteriochloroform): δ 1.2 (t, CH_3, 3H), 2.7 (c, CH_2, 2H), 7.00-8.25 (complex signal, azaindole ring-H, 5H).

From **4**. Method A.

To 0.52 g (3 mmoles) of **4** in 10 ml of anhydrous methylene chloride, 0.92 g (3.4 mmoles) of phosphorus tribromide in 5 ml of solvent was added. After 4 hours at room temperature the mixture was extracted with aqueous sodium hydrogen carbonate. The organic layer was dried and the solvent removed. The residue was purified by chromatography on silica-gel column to give 0.14 g (21%) of an oil identified as **1b**.

Method B.

To 0.41 g (2.5 mmoles) of **4** in 30 ml of anhydrous 1,2-dimethoxyethane, 0.92 g (3.4 mmoles) of phosphorus tribromide in 10 ml of 1,2-dimeth-

oxyethane was added. After 24 hours at room temperature the reaction mixture was treated as in method A and 0.11 g (19%) of **1b** as an oil was obtained.

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[9] The ^{1}H-nmr (DMSO-d_6/TFA) showed two doublets at 6.53 and 7.15 ppm but the variations that an halogen atom produces in the coupling constant and the unavailability of the other isomer has not permitted the assignment of the *E* or *Z* configuration.