Synthesis of New Heterocycles. 3,4-Dihydropyrano[2,3,4-*hi*]indolizine and Derivatives [1]

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Interaction of the lithium derivative of 2,3-dihydro-4*H*-pyrano[3,2-*b*]pyridine with the diethyl acetal of bromoacetaldehyde, followed by hydrolysis and subsequent ring closure afforded the novel heterocycle 3,4-dihydropyrano[2,3,4-*hi*]indolizine which was inacessible by the Tschitschibabin method. However, the 2-phenyl derivative was easily prepared by the Tschitschibabin method.

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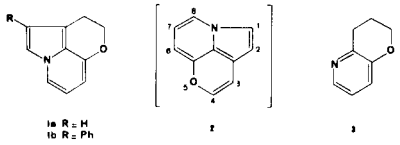
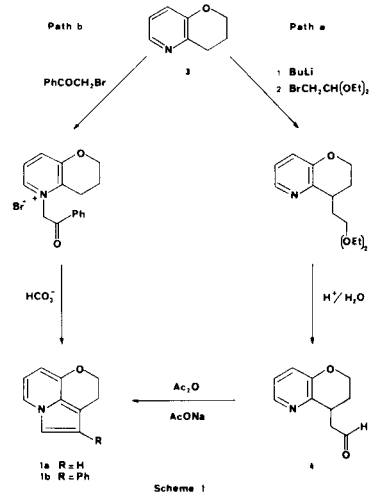
In connection with our work on fundamental heterocycles and indolizine compounds, it appeared that the structure of type **1** was relatively unknown [2]. Specifically, the parent fundamental heterocycle **2** has not yet been described. In the course of this study, it seemed to us that annellation reactions performed on 2,3-dihydro-4*H*-pyrano[3,2-*b*]pyridine (**3**) previously synthesized by our group [3] could provide an entry into this novel heterocyclic system. This paper describes the synthesis of two derivatives of this fundamental structure belonging to the dihydro series: the dihydro compound itself **1a** and its 2-phenyl substituted derivative **1b**.



1a R = H
1b R = Ph

Nevertheless, it is a convenient method for the preparation of substituted indolizines, so we use it to obtain the phenyl derivative **1b** as depicted in path b. Condensation of 2,3-dihydro-4*H*-pyrano[3,2-*b*]pyridine with phenacyl bromide afforded a crude quaternary salt which was treated immediately by aqueous sodium bicarbonate at reflux. After alumina column chromatography, 2-phenyl-3,4-dihydropyrano[2,3,4-*hi*]indolizine (**1b**) was obtained in 90% yield and was characterized by ir, pmr and ms. For the unsubstituted heterocycle, the Tschischibabin reaction failed as it was described for the condensation of α-picoline with α-chloroacetaldehyde, thus it did not yield an indolizine. Rather this latter compound was synthesized in one step and in good yield by the cyclization of 3-(2-pyridyl)propanol in the presence of a dehydrogenation catalyst [6]. The intermediate in this reaction is probably 3-(2-pyridyl)propanal, an unstable aldehyde [7]. So in order to obtain compound **1a**, it was necessary to introduce into the 4-position of the pyran ring of 2,3-dihydro-4*H*-pyrano[3,2-*b*]pyridine, an alkyl chain bearing an ω-aldehyde function. The synthesis has been achieved as described in the following sequence. The condensation of an α-pyranopyridyllithium derivative with the diethyl acetal of bromoacetaldehyde afforded 4-(2'-diethoxy)ethyl-5-azachroman in 52% yield. Acidic hydrolysis produced the aldehyde **4** in high yield. By the action of acetic anhydride in the presence of sodium acetate, the latter was cyclized to **1a** which was isolated in a 45% yield after alumina column chromatography followed by distillation under reduced pressure. This novel heterocyclic compound was characterized by ir, pmr and ms. The formation of this compound can be ascribed to the same mechanism which was reported for the preparation of 8-acetoxyindolizine [8].



Scheme 1

Attempts to functionalize the resulting dihydropyranoindolizine in the 3-position in order to obtain the fundamental heterocycle **2** are presently under investigation.

EXPERIMENTAL

Melting points were determined in capillary tubes on a Büchi apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. The pmr spectra were recorded on a WP60 Bruker spectrometer. Chemical shifts are reported in parts per million (δ) downfield from TMS and were assigned on integral information and coupling patterns. The following abbreviations have been used: s = singulet, d = doublet, t = triplet, q = quartet, m = multiplet.

Mass spectra were taken on a R-10-10 Riber spectrometer under 70 ev.

2,3-Dihydro-4*H*-pyrano[3,2-*b*]pyridine (**3**).

This compound was obtained according to the procedure described by Krings [3,9]. It was obtained in a 50% yield by cyclization of 3-(3-hydroxy-2'-pyridyl)propanol [9], bp 95°/11 torr, n_D^{20} = 1,5452; ir: 2940 cm^{-1} (pyridine ring); pmr (deuteriochloroform): δ 2.07 (m, 2H, 3-H), 2.95 (t, 2H, 4-H), 4.17 (t, 2H, 2-H), 7.00 (m, 2H, 7-H and 8-H), 8.10 (m, 1H, 6-H); ms: $M^{+\cdot}$ 135 (91%), $C_3H_3^+$ 39 (100%).

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.17; H, 6.80; N, 10.30.

4-(2'-Diethoxy)ethyl-5-azachroman.

To a solution of 5-azachroman (1.35 g, 0.010 mole) in dry diethyl ether was added dropwise at ice bath temperature and under an inert atmosphere butyl lithium (6.9 ml, 0.011 mole 10% excess). The mixture was stirred at this temperature for 2 hours. To the cooled solution was added 1.71 ml of bromoacetaldehyde diethyl acetal (0.011 mole, 10% excess). The resulting mixture was stirred at 20° for 12 hours. After hydrolysis, extraction (diethylether) and drying (magnesium sulfate), the solution was filtered, evaporated and distilled to give the chroman derivative in a 52% yield, bp 165°/0.3 torr, n_D^{19} = 1.5139; ir: 2940 cm^{-1} (CH_2 antisymetric), 1775, 1595 cm^{-1} (pyridine ring), 1120-1050 cm^{-1} (C-O-C-O-C); pmr (deuteriochloroform): δ 1.2 (t, 6H, 2 CH_3 of ethyl), 1.5-2.8 (m, 4H, 4-(1'-CH_2), 2.8-3.3 (m, 1H, 4-H), 3.3-4 (m, 4H, CH_2 of ethyl), 4.25 (t, 2H, 2-H), 5.0 (t, 1H, acetal H), 7.1 (m, 2H, 7-H and 8-H), 8.25 (m, 1H, 6-H); ms: $M^{+\cdot}$ 251 (6.2%), 135 (100%).

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.93; H, 8.37; N, 5.58. Found: C, 66.89; H, 8.35; N, 5.72.

2-(5-Azachroman-4-yl)ethanal (**4**).

A solution of the preceding compound (2.51 g, 0.010 mole) and 11 ml of 1*N* hydrochloric acid in 50 ml of distilled water was heated at 50° for 4 hours. The cooled solution was neutralized with potassium carbonate and extracted continuously with diethyl ether during 12 hours. The dried solution was filtered and evaporated to give the unstable aldehyde **4** which was used immediately for the following preparation, $n_D^{19.5}$ = 1.5451; ir: 1710 cm^{-1} (aldehyde function), 1595, 1575, 1475, 1435 cm^{-1} (pyridine ring); pmr (deuteriochloroform): δ 0.9-4 (m, 5H, 3-H, 4-H and CH_2 median), 4-4.5 (m, 2H, 2-H), 7.15 (m, 2H, 7-H and 8-H), 8.2 (dd, 1H, 6-H), 10.1 (t, 1H, aldehyde proton).

3,4-Dihydropyrano[2,3,4-*hi*]indolizine (**1a**).

The following mixture was stirred at 20° for 12 hours: 1.7 g of compound **3** (0.010 mole), 0.82 g of anhydrous sodium acetate in 30 ml of acetic anhydride and 1 ml of acetic acid. After filtration, the resulting solution was evaporated under reduced pressure (50°, 5 torr). After chromatography on a neutral alumina column and distillation under reduced pressure, the pyranoindolizine was obtained in a 45% yield (0.68 g), bp 109°/0.2 torr; ir: 1650, 1530 cm^{-1} (indolizine ring), 1240 cm^{-1} (aryl ether); pmr (deuteriochloroform): δ 3.10 (t, 2H, 3-H, J_{3-4} = 5.4 Hz), 4.45 (t, 2H, 4-H, J_{3-4} = 5.4 Hz), 6.00 (dd, 1H, 6-H, J_{6-8} = 0.5 Hz, J_{6-7} = 6.8 Hz), 6.37 (dd, 1H, 7-H, J_{6-7} = 6.8 Hz, J_{7-8} = 7.3 Hz), 6.55 (d, 1H, 2-H, J_{1-2} = 2.5 Hz), 7.30 (d, 1H, 1-H, J_{1-2} = 2.5 Hz), 7.60 (dd, 1H, 8-H, J_{7-8} = 7.3 Hz, J_{6-8} = 0.5 Hz); ms: $M^{+\cdot}$ 159 (100%), 130 (63.6%).

Anal. Calcd. for $C_{10}H_9NO$: C, 75.47; H, 5.66; N, 8.81. Found: C, 75.02; H, 5.93; N, 8.80.

2-Phenyl-3,4-dihydropyrano[2,3,4-*hi*]indolizine (**1b**).

A mixture of 5-azachroman (**3**) (1.35 g, 0.010 mole) and phenacyl bromide (1.99 g, 0.010 mole) in 50 ml of dried acetone was refluxed under an inert atmosphere for 12 hours. After removal of solvent (40°, 15 torr) and addition of distilled water, the resulting solution was treated with an excess of sodium bicarbonate (3 g). After refluxing for 12 hours, the black insoluble oil was extracted with methylene chloride. The organic phase was treated with magnesium sulfate, filtered and evaporated under reduced pressure. The resulting crude indolizine was chromatographed on an alumina column (eluent, diethyl ether). After evaporation, the pure 2-phenyl-3,4-dihydropyrano[2,3,4-*hi*]indolizine was obtained in 90% yield (2.1 g), mp 66°; ir: 1650, 1530 cm^{-1} (indolizine ring), 1245 cm^{-1} (aryl ether); pmr (deuteriochloroform): δ 3.50 (t, 2H, 3-H), 4.50 (t, 2H, 4-H), 6.00 (d, 1H, 6-H), 6.50 (m, 1H, 7-H), 7.30-7.90 (m, 7H, 8-H, 1-H and phenyl H); ms: $M^{+\cdot}$ 235 (100%).

Anal. Calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.85; H, 5.56; N, 5.79.

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