Synthesis of 3,4-Dihydro-2*H*-pyrano[3,2-*c*]pyridine

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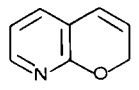
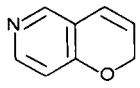
Among the fundamental heterocycles resulting from the ring fusion of the pyran and pyridine nucleus, up to now the only ones actually known are 2*H*-pyrano[2,3-*b*]-pyridine (**1**) and 2*H*-pyrano[3,2-*c*]pyridine (**2**).

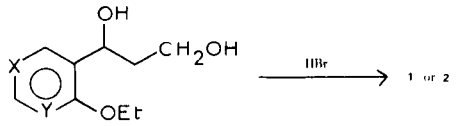


1



2

They have been prepared from suitably *ortho*-disubstituted pyridines, the last step of the synthesis involving the cyclisation of an *ortho*-ethoxypyridylpropanediol such as **3** (1,2).

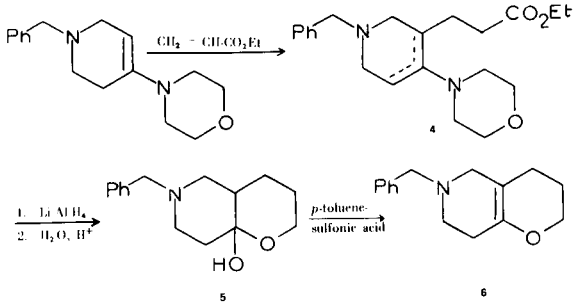


3a X = CH, Y = N
b X = N, Y = CH

Compound **1** has thus been obtained in 60% yield (1), but in the case of the 4-ethoxy derivative **3b**, a higher temperature was necessary for the cyclisation; so that the isomer **2** could not be produced with a yield better than 23% (2), which limits the practical value of this synthesis.

This difference has been explained in terms of a greater resistance to cleavage and a lower nucleophilicity of 4-pyridinol ethers as compared to their 2-isomers (2).

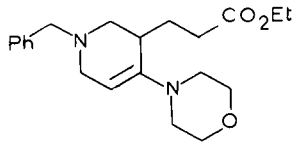
We wish to report here our preliminary results in search of a novel route to pyrano[3,2-*c*]pyridines.



5 6

The first steps of the proposed synthesis are an extension to nitrogen compounds of the first steps of Borowitz's synthesis of large ring keto lactones (3,4).

Condensation of the morpholine enamine of 1-benzyl-4-piperidone (5,6) with ethyl acrylate furnished the enamine ester **4**. Concerning the structure of this product, two possible isomeric structures would be expected: based on enamine stabilities structure **4a** would seem to be the favored isomer. This view was confirmed by pmr which indicated a 65% content of isomer **4a** as shown by integration of an ethylenic proton at 4.65 ppm, present in **4a** but absent in its isomer which possesses a fully substituted double bond.

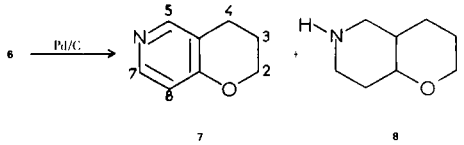


4a

Lithium aluminum hydride reduction of the ester function followed by acid hydrolysis proceeded in 65% yield affording the bicyclic hemiketal **5** as a solid (m.p. 135°), the ir spectrum of which exhibited no carbonyl absorption in the solid state.

Dehydration of the hemiketal **5** was performed in 89% yield by refluxing **5** in toluene with *p*-toluenesulfonic acid and separating the water formed.

The last step involves dehydrogenation and debenzylation of the bicyclic enol ether **6**. It was realized by refluxing for 48 hours this last product in xylene, in the presence of 10% palladium/carbon. An example of an analogous reaction has been reported by Belsky in the case of *N*-benzyl-6-aza-2-methylchromone (5).



7 8

The dihydropyranopyridine **7** was thus obtained in a 49% isolated yield; in addition of **7**, the debenzylation step furnished the perhydro derivative **8** that could be

easily removed by using benzenesulfonyl chloride.

Attempts to reduce the amount of the perhydro derivative **8** in order to improve the yield of the aromatization step, and functionalization of the resulting dihydropyranopyridine in the 4-position, 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. Pmr spectra were recorded on a Varian A-60 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 = singlet; d = doublet; t = triplet; q = quartet; m = multiplet.

Morpholine Enamine of 1-Benzyl-4-piperidone or 4-(1-Benzyl-1,2,3,6-tetrahydro-4-pyridyl)morpholine.

A solution of 1-benzyl-4-piperidone (94.5 g., 0.5 mole) and morpholine (87 g., 1 mole) in dry toluene (300 ml.) was refluxed in a flask equipped with a water separator until no further separation of water was observed. This took from 8 to 10 hours. After removal of the toluene and excess morpholine under reduced pressure on a water bath, the residue was distilled, giving the expected enamine, b.p. 154-157°/0.2 torr (102 g., 85%), reported b.p. 146-150°/0.1 torr (5), b.p. 175°/0.5 torr (6); n_D^{20} = 1.5649; ir: 1660 cm^{-1} (enamine); pmr (deuteriochloroform): 2-2.90 (complex multiplets, 8H), 2.90-3.15 (complex multiplet, 2H, N-CH_2-CH=), 3.50-3.90 (6H, 2 benzylic H and 4H of CH_2-O-CH_2), 4.56 (t, 1H, ethylenic H), 7.35 (m, 5H, aromatic H).

Morpholine Enamine of 1-Benzyl-3-carbethoxyethyl-4-piperidone (**4**) or 4-(1-Benzyl-3-carbethoxyethyl-1,2,3,6-tetrahydro-4-pyridyl)-morpholine.

A mixture of the morpholine enamine of 1-benzyl-4-piperidone (118 g., 0.457 mole) and ethyl acrylate (50.3 g., 0.503 mole) in absolute ethanol (250 ml.), protected from moisture by a drying tube, was refluxed for 20 hours. After removal of solvent; the residue was distilled to give the morpholine enamine of 1-benzyl-3-carbethoxyethyl-4-piperidone **4** as a viscous oil, 140 g. (0.391 mole, 85%), b.p. 189-196°/0.2 torr; n_D^{20} = 1.5356. The ir spectrum of **4** exhibited peaks at 1730 cm^{-1} (ester) and 1640 cm^{-1} (enamine); pmr (deuteriochloroform): 1.26 (t, 3H, CH_3 of ethyl), 1.7-3.2 (complex multiplets, 13.35H), 3.50-3.90 (complex multiplet including singlet of 2 benzylic H centered at 3.58, 6H), 4.11 (q, 2H, CH_2 of ethyl), 4.65 (t, 0.65H, ethylenic proton), 7.38 (s, 5H, aromatic H).

6-Benzyl-8a-hydroxy-3,4,4a,5,6,7,8,8a-octahydro-2*H*-pyrano-[3,2-*c*]pyridine (**5**).

A solution of the enamine ester **4** (86 g., 0.24 mole) in dry ether (250 ml.) was added dropwise at ice-bath temperature to a well stirred suspension of lithium aluminium hydride (9.1 g., 0.24 mole) in dry ether (250 ml.). The stirring was carried on and the mixture heated to boiling for 4 hours. To the cooled solution was slowly added ethanol (31 ml.) and then dilute sulfuric acid (20%, 375 ml.). The aqueous layer was heated to 60° for 4 hours then set aside overnight at room temperature. The cooled solution was basified with saturated sodium carbonate solution, filtered and extracted with chloroform. The dried solution was evaporated to leave the crude ketoalcohol which existed only as the hydroxy ether tautomer **5**. Recrystallization from benzene gave pure **5**, m.p. 135° (43.3 g., 0.175 mole, 73%). The ir spectrum of **5** (potassium bromide) showed a broad hydroxyl band centered at 3380 cm^{-1} and no carbonyl band. The pmr spectrum (deuteriochloroform) exhibited a singlet at 7.34 (aromatic H) a singlet at 3.54 (benzylic H), and a hydroxyl band at 2.7-3.5 which was affected by dilution.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.67. Found: C, 72.95; H, 8.74; N, 5.70.

6-Benzyl-3,4,5,6,7,8-hexahydro-2*H*-pyrano[3,2-*c*]pyridine (**6**).

Compound **5** (45 g., 0.182 mole) was dissolved in dry toluene (400 ml.), a few crystals of *p*-toluenesulfonic acid (about 1 g.) were added and the solution was refluxed for 15 hours; the water produced was collected in a water separator. The cooled solution was treated with solid potassium carbonate, filtered, evaporated under reduced pressure then distilled to give 37 g. (89%) of **6** as a colorless oil: b.p. 123-125°/0.1 torr; n_D^{20} = 1.5575; ir: 1700 cm^{-1}, 1245 cm^{-1} (vinylic ether); pmr (deuteriochloroform): 2.84 (s, 2H, 4-CH_2), 3.93 (t, 2H, 2-CH_2), 3.57 (s, 2H, benzylic H), 7.36 (s, 5H, aromatic H) and complex multiplets centered at 1.65-2.75.

Anal. Calcd. for $C_{15}N_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.27; H, 8.14; N, 6.16.

3,4-Dihydro-2*H*-pyrano[3,2-*c*]pyridine (**7**).

A solution of **6** (22.3 g., 0.098 mole) in dry xylene (200 ml.) was refluxed for 48 hours in the presence of 10% palladium/-carbon (2.5 g.). The cooled solution was filtered and evaporated under reduced pressure to give 12.2 g. of residue. A mixture of the residue (12.2 g.), benzenesulphonyl chloride (24 g., 18 ml.) and a 5% solution of sodium hydroxyde (400 ml.) was shaken vigorously until the odour of the acid chloride had disappeared. The mixture was allowed to cool and the insoluble oil was extracted with ether (150 ml. then 3 x 75 ml.). The ether layer was extracted with dilute hydrochloric acid (5%, 5 x 75 ml.) to remove all the tertiary amine present. The aqueous layer was made alkaline by addition of dilute sodium hydroxyde solution (10%, 200 ml.) then extracted with ether (5 x 100 ml.). The dried solution was filtered, evaporated and distilled to give 6.5 g. of 3,4-dihydro-2*H*-pyrano[3,2-*c*]pyridine (**7**) (49%), b.p. 73-74°/0.8 torr; n_D^{20} = 1.5502; ir: 3025 cm^{-1} (pyridine C-H), 1590, 1575, 1490 cm^{-1} (pyridine ring), 1280, 1260 cm^{-1} (aromatic ether); pmr (deuteriochloroform) δ: 2.00 (m, 2H, 3-CH_2), 2.73 (t, 2H, J_{3-4} = 6.25 Hz, 4-CH_2), 4.20 (t, 2H, J_{2-3} = 5.25 Hz, 2-CH_2), 6.73 (d, 1H, J_{7-8} = 5 Hz, 8-H), 8.24 (s + d, 2H, J_{7-8} = 5 Hz, 5-H and 7-H).

Anal. Calcd. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.37. Found: C, 70.87; H, 7.06; N, 10.37.

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