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Received January 28, 1980

Synthetic approaches to the preparation of perhydrofuro[2,3-*c*]pyridin-2-one derivatives as analogs of pilocarpine are reported. Derivatives of the desired ring system were obtained from iodolactonization of the appropriate tetrahydropyridyl esters.

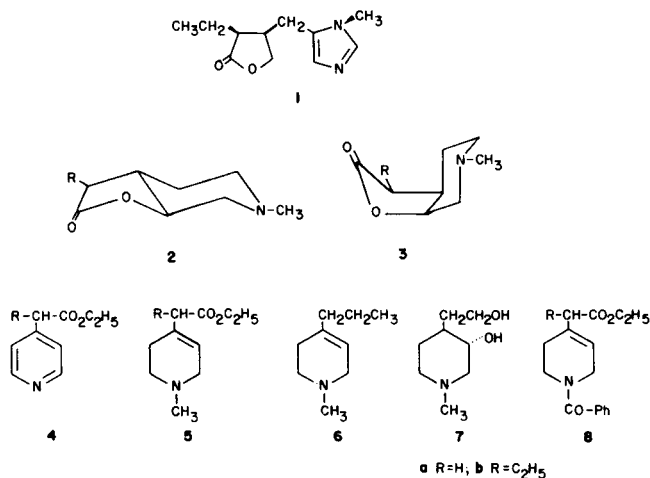
J. Heterocyclic Chem., 17, 1609 (1980).

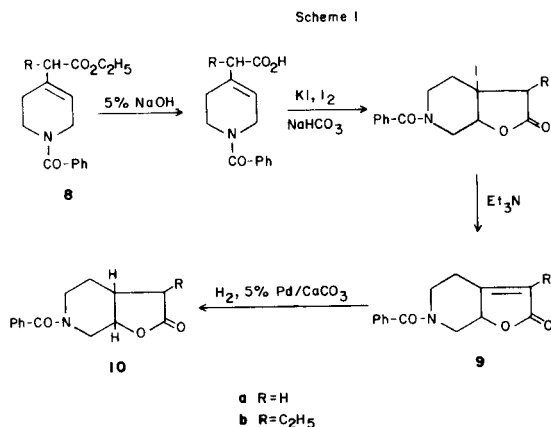
As part of a study aimed at examining the structural and conformational requirements of pilocarpine (**1**) essential for cholinergic activity, the synthesis of the perhydrofuro[2,3-*c*]pyridine analogs **2** and **3** was attempted. Previous studies by Hanssen, *et al.* (1), had indicated that a series of 3-ethyl-4-dialkylaminoalkyldihydro-2-(3*H*)furanones related to isopropylamine and homoisopropylamine possess parasympathomimetic effects albeit weaker than pilocarpine, suggesting that the imidazole ring of pilocarpine is not essential for cholinergic activity. Analogs **2** and **3** represent conformationally restricted derivatives of pilocarpine in which the imidazole ring has been replaced by a simple alkylamine moiety fused to the lactone ring.

Ethyl 4-pyridylacetate (**4a**) was prepared by the method of Katritzky (2) while **4b** was prepared by the alkylation of 4-pyridylacetonitrile with ethyl tosylate and subsequent hydrolysis and esterification. Each was converted to its methiodide salt and reduced by the method of Lyle (3) to give **5a** and **5b**, respectively. Cyclization of **5a** was attempted under the following conditions: (a) refluxing with 48% hydrobromic acid and glacial acetic acid (4); (b) refluxing with 50% sulfuric acid (5); (c) refluxing with 48% hydrobromic acid, 50% sulfuric acid in glacial acetic acid; (d) hydrolysis of **5a** with 10% sodium hydroxide to the corresponding acid, then refluxing as in (a); (e) hydrolysis of **5a** with 10% sodium hydroxide followed by refluxing as in (b). Under the first three conditions, the only identifiable recovered product was **5a**. In the latter two cases, only intractable tarry materials were obtained. Refluxing **5b** under the conditions in (a) specified above yielded only the product resulting from hydrolysis and decarboxylation (**6**). Proof of structure of **6** was easily obtained by comparison of this product with that resulting from sodium borohydride reduction of the methiodide salt of 4-*n*-propylpyridine. Because of the difficulties encountered in the cyclization of **5a** and **5b** to the *cis*-lactone, approaches to the synthesis of **2** [which could then be isomerized to **3** (6,7)] were explored. It was anticipated that oxidative hydroboration of **5a** would yield a *trans*-hydroxy acid which could then be subsequently cyclized to **2** under acidic conditions. However, treating **5a** under these conditions yielded only the diol **7**. Because of the difficulties encountered in attempts to cyclize the un-

saturated esters containing a basic amine function it was decided to reinvestigate these reactions using a benzoyl blocking group on nitrogen. However, when either **8a** or **8b** (**8**) was treated with 48% hydrobromic acid in glacial acetic acid, only an unidentifiable tarry material and benzoic acid were isolated. Treatment of **8a** under hydroboration conditions yielded only a reddish gummy material and benzoic acid. We then directed our efforts to the approach outlined in Scheme I.

Alkaline hydrolysis of **8a** yielded the corresponding acid along with some benzoic acid. Treatment of the acid under iodolactonization conditions (9) gave an iodolactone whose stereochemistry was presumed to be *cis* based on observations reported (8) for the corresponding carbocyclic system. Triethylamine-induced dehydrohalogenation gave the unsaturated lactone **9a** which was identical in all respects with the lactone obtained by the method of Sundberg, *et al.* (10). Subsequent reduction gave the saturated lactone **10a**. In a similar manner, **10b** was prepared from **8b**. In a final attempt to prepare the target compounds **2** and **3**, the approach outlined in Scheme II was tried using the *N*-methyl derivatives **5a** and **5b**. However, only intractable tars were obtained on treating the corresponding acids with potassium iodide and iodine.





EXPERIMENTAL

The ir spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer. Nmr spectra were determined on a Jeolco Model C-60-HL spectrometer. Refractive indices were obtained on a Bausch and Lomb refractometer. Melting points were obtained on a Mel-Temp capillary melting point apparatus and are uncorrected. Elemental analysis was performed by Dr. A. Bernhardt, Microanalytisches Laboratorim, Max Planck Institute für Kohlenforschung, Mulheim (Ruhr), West Germany. The uv spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer.

2-(4-Pyridyl)butyronitrile.

According to the procedure described by Schulze (11), 82.2 g. (0.501 mole) of 4-chloromethylpyridinium chloride dissolved in 600 ml. of dimethylsulfoxide at room temperature was added dropwise, with stirring, to a suspension of 105.0 g. (1.61 mole) of (dried) potassium cyanide in 150 ml. of dimethylsulfoxide. The mixture was cooled and the temperature kept below 40° for 2.5 hours, then treated with 800 g. of potassium carbonate in 2500 ml. of water and 72 ml. of 40% potassium hydroxide, whereupon two layers formed. Water was added until the mixture became homogeneous and the solution was extracted with ether (8 × 400 ml.). The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated under reduced pressure to give a brown residue, which was distilled at 95-98° (0.1 mm) to yield 20.1 g. (34%) of the nitrile, m.p. 36-38°. Sodium hydride (8.5 g. of 50% mineral oil dispersion, 0.177 mole) was added to a cooled and stirred solution of 20.0 g. (0.177 mole) of 4-pyridylacetonitrile in 70 ml. of dimethylformamide. After hydrogen ceased to evolve, 35.4 g. (0.177 mole) of ethyl *p*-toluenesulfonate in 70 ml. of dry toluene was added slowly to the dark solution with stirring and the resulting mixture stirred at room temperature for 15 hours. The precipitated sodium *p*-toluenesulfonate was removed by filtration, and the filtrate was concentrated under reduced pressure to about a volume of 50 ml. Water was added to the oily residue and the product was extracted several times with ether. The ether extracts were shaken twice with 3*N* hydrochloric acid and the acidic extracts rendered alkaline with sodium carbonate. The liberated base was extracted with ether and the ether extracts were dried over sodium sulfate, filtered and the solvent evaporated under reduced pressure. The residual oil was distilled at 94-96° (0.15 mm) to yield 11.3 g. (43.7%) of the nitrile as a colorless oil, n_D^{20} 1.5095; picrate (ethanol), m.p. 155-157°.

Anal. Calcd. for C₉H₁₀N₂: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.68; H, 6.82; N, 18.89.

Ethyl 2-(4-Pyridyl)butyrate (4b).

2-(4-Pyridyl)butyronitrile (14.2 g., 0.097 mole) in 125 ml. of concentrated hydrochloric acid was heated for 30 minutes on a water bath, cooled, 150 ml. of absolute ethanol was added, and the resulting mixture refluxed for 18 hours. The reaction mixture was concentrated under

reduced pressure to about 125 ml., poured into 400 ml. of water, made alkaline with sodium carbonate and extracted with chloroform (4 × 150 ml.). The organic extracts were dried over magnesium sulfate, filtered and the solvent was removed by distillation under reduced pressure to give 13.5 g. of a residue which was distilled at 64-66° (0.15 mm) to yield 10.7 g. (57.1%) of the product; n_D^{20} 1.4935; ir (liquid film): 1735 (C=O saturated ester), 1595 and 1565 cm⁻¹ (C=C and C=N aromatic pyridine ring); nmr (carbon tetrachloride): δ 0.90 (t, 3, CH₃-CH₂-CH-), 1.21 (t, 3, CH₃-CH₂-O-CO-), 1.96 (m, 2, CH₃-CH₂-CH-), 3.50 (t, 1, CH₃-CH₂-CH-), 4.13 (q, 2, CH₃-CH₂-O-CO-), 7.33 (m, 2, H₃ and H₅ of the pyridine ring), and 8.66 (m, 2, H₂ and H₆ of the pyridine ring). Glc (Perkin-Elmer 900) using a column (213 cm X 0.0514 cm) containing 10% SE-30 on Chromosorb W indicated that the liquid contained only one major component.

Anal. Calcd. for C₁₁H₁₃NO₂: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.24; H, 7.98; N, 7.34.

1-Methyl-4-*n*-propyl-1,2,5,6-tetrahydropyridine (6).

The procedure described for the synthesis of 5a (8) was followed using 13.1 g. (0.05 mole) of 4-*n*-propylpyridine methiodide in 300 ml. of methanol and 7.57 g. (0.2 mole) of sodium borohydride. After working up the reaction mixture as described previously, the residue was distilled at 64-66° (0.05 mm) to yield 5.1 g. (52.7%) of a colorless liquid; n_D^{20} 1.4619; ir (liquid film): 2780, 2740 and 2680 (C-H stretching associated with the pair of electrons on the nitrogen atom), 1680 cm⁻¹ (C=C trisubstituted alkene); nmr (carbon tetrachloride): δ 0.90 (t, 3, CH₃-CH₂-CH₂-), 1.36 (m, 2, CH₃-CH₂-CH₂-), 2.00 (m, 4, CH₃-CH₂-CH₂- and -CH₂- at C₅), 2.23 (s, 3, N-CH₃), 2.43 (m, 2, -CH₂- at C₆), 2.8 (m, 2, -CH₂- at C₂), and 5.27 (broad singlet, 1, olefinic proton H₃, W_{1/2} = ~ 8 Hz).

Anal. Calcd. for C₉H₁₁N: C, 77.63; H, 12.31; N, 10.06. Found: C, 77.44; H, 12.49; N, 10.01.

Hydroboration of 5a.

A solution of 9.2 g. (0.05 mole) of 5a (8) in 30 ml. of dry 1,2-dimethoxyethane and diborane (which was generated externally from 3.3 g. of sodium borohydride and 21.2 g. of boron fluoride ethyl ether) was flushed to the solution with the aid of a stream of dry nitrogen gas. The reaction mixture was stirred for 2 hours, cooled to 0° and treated with 80 ml. of 6*N* sodium hydroxide and 10 ml. of 30% hydrogen peroxide. The resulting mixture was heated on a steam bath for 2 hours. The mixture was concentrated to about one-third of its volume under reduced pressure, and then acidified with concentrated hydrochloric acid and refluxed for 24 hours. The mixture was concentrated under reduced pressure, rendered alkaline with sodium carbonate, saturated with sodium chloride and extracted with chloroform (3 × 150 ml.). The chloroform extracts were dried over magnesium sulfate, filtered, and the solvent was removed under reduced pressure to give a residue which solidified after several hours. Recrystallization from *n*-hexane-ethanol gave 1.1 g. (13%) of a solid product which was identified as 1-methyl-3-hydroxy-4- β -hydroxyethylpiperidine (7); picrate (ethanol), m.p. 310-312° dec.; ir (potassium bromide): 3320 cm⁻¹ (OH-associated), no carbonyl absorption; nmr (deuterium oxide): δ 2.08 (broad signal, 6), 3.05 (s, 3, N-CH₃), 3.53 (broad signal, 5), and 4.35 (broad signal, 1).

Anal. Calcd. for C₁₄H₂₀N₂O₂ (picrate): C, 43.30; H, 5.19; N, 14.43. Found: C, 43.49; H, 5.33; N, 14.57.

6-Benzoyl-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridin-2-(7aH)one (9a).

A solution of 4.5 g. (0.0164 mole) of 7a (8) in 40 ml. of 5% sodium hydroxide was refluxed for 12 hours. The solution was cooled and acidified with 10% hydrochloric acid (some benzoic acid was isolated during acidification) and extracted with chloroform (4 × 50 ml.). The chloroform extracts were dried over magnesium sulfate, filtered and the solvent was evaporated under reduced pressure to yield 3.0 g. of a pale yellow solid which was dissolved in 62 ml. of 0.5*N* sodium bicarbonate and allowed to stir for 18 hours with a solution of 2.5 g. of iodine and 9.96 g. of potassium iodide dissolved in 30 ml. of water. The oily precipitate was extracted with ether, and the ethereal extract was washed with sodium bisulfite and saturated sodium bicarbonate solution suc-

cessively (until the coloration of iodine disappeared), and dried over sodium sulfate, filtered and evaporated under reduced pressure to yield 2.2 g. of dark brown residue. An ethereal solution of the residue was refluxed overnight with 8.0 g. of triethylamine, filtered, and evaporated under reduced pressure. The residue was chromatographed on silica gel (50-200 mesh E. Merck. AG. Germany) using 40% ether in benzene as an eluting solvent to give 480 mg. (10%) of **9a** m.p. 158-159°, lit. (10) m.p. 160-165°.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.02; H, 5.39; N, 5.88.

6-Benzoyl-3a,4,5,6,7,7a-hexahydrofuro[2,3-c]pyridin-2-(3*H*)one (**10a**).

A solution of 360 mg. (0.00147 mole) of **9a** in 50 ml. of ethanol was hydrogenated at room temperature for 18 hours on a Parr low pressure hydrogenator at 44 psi using 100 mg. of 5% palladium on calcium carbonate as a catalyst. Removal of the catalyst and evaporation of the solvent under reduced pressure produced an oil which was purified by chromatography using 50.0 g. of silica gel (50-200 mesh E. Merck-AG. Germany) and 40% ether in benzene as an eluting solvent to give 344 mg. (95.4%) of an oil which failed to crystallize from *n*-hexane-ether; ir (potassium bromide): 1770 (C=O saturated 5-membered γ -lactone), and 1630 cm^{-1} (C=O amide); nmr (deuteriochloroform): δ 1.16-3.50 (complex multiplets, 9), 4.33 (m, 1) and 7.46 (s, 5, aromatic phenyl protons).

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.59; H, 6.31; N, 5.88.

6-Benzoyl-3-ethyl-4,5,6,7-tetrahydrofuro[2,3-c]pyridin-2-(7a*H*)one (**9b**).

The procedure followed was essentially that used to prepare **9a**, using 5.0 g. (0.016 mole) of **8b**, 2.8 g. of iodine and 10.5 g. of potassium iodide. The crude iodolactone (2.5 g.) was subjected to dehydrohalogenation with 8.0 g. of triethylamine in anhydrous ether. After working up the reaction mixture as described previously, the residue was chromatographed on silica gel (E. Merck-AG. Germany) using 40% ether in benzene as the eluting solvent to yield 530 mg. of an oil residue which was crystallized from *n*-hexane-ether to give 500 mg. (11.5%) of **9b**, m.p. 150-153°; ir (potassium bromide): 1750 cm^{-1} (C=O $\Delta^{\alpha,\beta}$ -butenolide); nmr (deuteriochloroform): δ 1.64 (t, 3, CH_3-CH_2), 2.60-3.53 (m, 6), 4.06-4.50 (m, 3), and 7.66 (s, 5, aromatic phenyl protons).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.66; H, 6.38; N, 5.26.

6-Benzoyl-3-ethyl-3a,4,5,6,7,7a-hexahydrofuro[2,3-c]pyridin-2-(3*H*)one (**10b**).

The procedure followed was essentially similar to that used to prepare (**10a**) using 500 mg. (0.0018 mole) of **9b** in 70 ml. of ethanol and 100 mg. of 5% palladium on calcium carbonate as a catalyst. After working up the reaction mixture as previously described, the oil obtained was purified using 40.0 g. of silica gel (50-200 mesh E. Merck-AG. Germany) and 40% ether in benzene as an eluting solvent to give 410 mg. (83.3%) of an oil; ir (liquid film): 1770 (C=O, saturated 5-membered γ -lactone), and 1630 cm^{-1} (C=O amide); nmr δ (deuteriochloroform): 1.13 (t, 3, CH_3-CH_2), 2.60-3.53 (complex multiplets, 8), 4.30 (broad signal, 3), and 7.60 (s, 5, aromatic phenyl protons).

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.33; H, 7.15; N, 5.21.

Acknowledgment.

This research was supported in part by a Faculty Research Grant, University of Mississippi and in part by the Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi.

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