

SYNTHESIS OF THE ISOQUINUCLIDINE RING SYSTEM

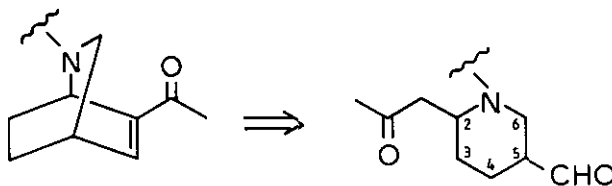
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Abstract - The formation of the biochemically important isoquinuclidine ring system by intramolecular condensation of an appropriately substituted piperidine-5-carbaldehyde derivative 6 is described. The direct acylation of the intermediate  $\alpha$ -aminonitrile 5a (prepared by the modified Polonovski reaction) to the piperidine-5-carbaldehyde derivative 6 could be achieved only in low yield. However, if the  $\alpha$ -aminonitrile 5a was transformed, before the acylation, to the "dimer" 7 of tetrahydroanabasine type, the piperidine-5-carbaldehyde derivative 6 could be obtained in much higher total yield.

In connection with our efforts to develop new and useful methods for the preparation of the isoquinuclidine (2-azabicyclo[2.2.2]octane) ring system, present in the Iboga alkaloid series<sup>1</sup>, we recently described a new route based on the 5,2-bridging of appropriately substituted 3,4,5,6-tetrahydropyridine equivalents.<sup>2</sup>

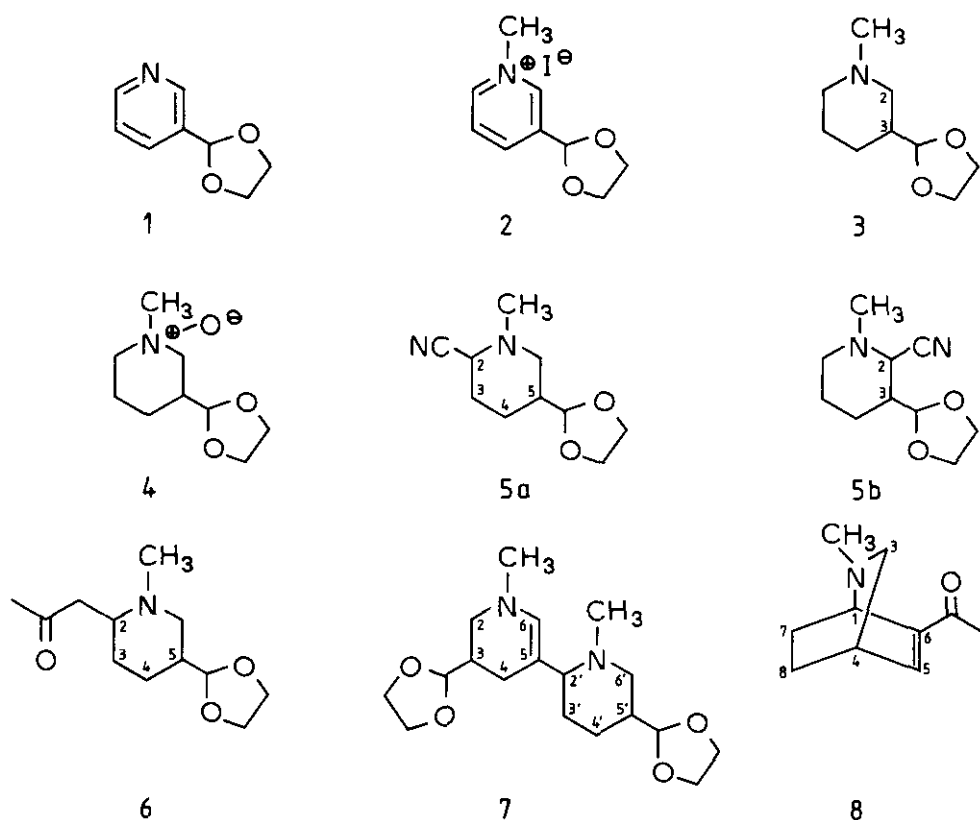
An alternative approach to this crucial problem would be the 2,5-bridging of suitably substituted piperidine-5-carbaldehyde derivatives. In the present communication we report a successful use of this approach for the synthesis of the isoquinuclidine ring system.



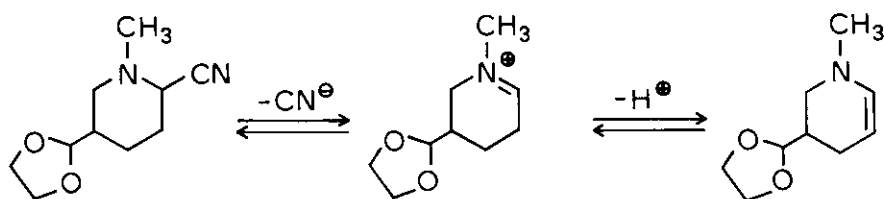
For the preparation of the necessary appropriately substituted piperidine-5-carbaldehyde derivatives (under the protected form, *e.g.* acetal) the modified Polonovski reaction<sup>3-5</sup> seemed to be well suited.

Acetalization of pyridine-3-carbaldehyde with ethylene glycol yielded the corresponding pyridine-3-carbaldehyde acetal 1, which was alkylated with methyl iodide to the corresponding methyl salt 2. Catalytic hydrogenation of the salt furnished the N-methylpiperidine-3-carbaldehyde acetal 3, which was treated with H<sub>2</sub>O<sub>2</sub> to yield the corresponding N-oxide 4. The N-oxide was subjected to the modified Polonovski reaction<sup>3-5</sup> conditions and the intermediate iminium salts were reacted with KCN to give  $\alpha$ -aminonitriles (2-cyanopiperidines) 5a and 5b (approx. 3:1).<sup>6</sup>

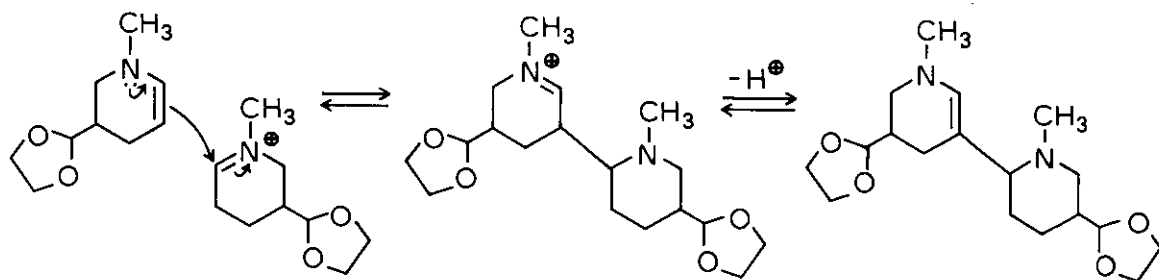
Treatment of the mixture of  $\alpha$ -aminonitriles 5a and 5b (*vide infra*) with AgBF<sub>4</sub> and sodium methylacetoacetate produced the desired ketopiperidine 6 only in low yield.<sup>7</sup> As the efforts to obtain the ketopiperidine 6 in higher yield by this procedure did not succeed, we decided to modify the synthetic strategy.



The tendency of 3,4,5,6-tetrahydropyridines (or their equivalents, e.g. 2-cyanopiperidines) to form "dimers" of tetrahydroanabasine-type, combined with the equilibrium existing in hydroxylic solvents between the "dimers" and the corresponding monomers,<sup>8-10</sup> suggested the means to an alternative approach to the problem (Schemes 1 and 2).



Scheme 1



Scheme 2

Indeed, treatment of the mixture of  $\alpha$ -aminonitriles 5a and 5b with  $AgBF_4$  in dry THF yielded the "dimer" 7<sup>11</sup> (it turned out to be more economical to carry out the "dimer" formation step without prior separation of the two  $\alpha$ -aminonitrile isomers), which upon acylation with methyl acetoacetate in MeOH/H<sub>2</sub>O afforded the ketopiperidine 6 in much higher yield than did 5a in the direct acylation (vide supra). When the ketopiperidine 6 was refluxed in 5% HCl the desired isoquinuclidine 8 was obtained in 53% yield.

#### EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 spectrophotometer using liquid film between NaCl crystals. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (<sup>1</sup>H-NMR) and 15.04 MHz (<sup>13</sup>C NMR). Chemical shift data are given in ppm downfield from TMS (internal standard,  $\delta = 0$ ); s, d, dd, t, q and m designate singlet, doublet, doublet of

doublets, triplet, quartet and multiplet, respectively. Mass spectrometry was performed on a Jeol JMS-D-100 apparatus and Kratos MS 80 RFA Autoconsole/DS 55 apparatus (high resolution).

#### Pyridine-3-carbaldehyde acetal 1

Pyridine-3-carbaldehyde (Fluka) (0.99 g, 9.25 mmol) was dissolved in 20 ml of benzene. p-Toluene-sulphonic acid monohydrate (1.80 g, 9.47 mmol) was added and the mixture was refluxed for 5 min. Redistilled ethylene glycol (0.63 g, 10.16 mmol) was added and refluxing was continued using a Dean and Stark apparatus for 4 h. By this time 0.4 ml water had separated. The cooled mixture was shaken with 20 ml 10% Na<sub>2</sub>CO<sub>3</sub>. Phases were separated and the aqueous layer was extracted several times with CH<sub>2</sub>Cl<sub>2</sub>. The combined extracts were washed with water, and worked up normally to give 1 1.21 g (87%) as a pale yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 4.08 (m, 4H), 5.85 (s, 1H). MS m/z 151 (M<sup>+</sup>), 150, 106, 73 (100%).

#### Pyridinium salt 2

Acetal 1 (1.18 g, 7.81 mmol) was dissolved in 20 ml of MeOH and CH<sub>3</sub>I (1.5 ml, 24.0 mmol) was added. The mixture was refluxed overnight and worked up normally to give 2 (2.02 g, 88%) as yellow crystals, mp 182°C.

#### N-Methylpiperidine-3-carbaldehyde acetal 3

Pyridinium salt 2 (0.92 g, 3.14 mmol) was hydrogenated with PtO<sub>2</sub> (0.090 g) in 20 ml of MeOH over night. Normal work-up yielded 3 (0.39 g, 73%) as a pale yellow liquid. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.26 (s, 3H), 3.88 (m, 4H), 4.66 (d, 1H, J = 3.6 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) C(2) 56.55, C(3) 40.19, C(4) 24.41, C(5) 24.61, C(6) 55.91, >NCH<sub>3</sub> 46.49, -OCHO- 105.58, -CH<sub>2</sub>CH<sub>2</sub>- 64.54 (2C). MS m/z 171 (M<sup>+</sup>), 99, 73, 58, 57, 44 (100%).

#### N-Oxide 4

Piperidine 3 (0.49 g, 2.87 mmol) was dissolved in 20 ml of CH<sub>2</sub>Cl<sub>2</sub>:MeOH (1:1) and 30% H<sub>2</sub>O<sub>2</sub> (1.5 ml, 13 mmol) was added. The solution was stirred at 55°C for 48 h. Excess peroxide was destroyed by the addition of 60 mg of 10% Pd/C and stirring was continued at 55°C for 2 h. The mixture was filtered and evaporated. Normal work-up yielded 4 (0.52 g, 97%) as white hygroscopic crystals.

$\alpha$ -Aminonitriles 5a and 5b

N-Oxide 4 (0.62 g, 3.32 mmol) was dissolved in 8 ml of dry  $\text{CH}_2\text{Cl}_2$ , cooled to  $0^\circ\text{C}$  and stirred under an atmosphere of argon. Trifluoroacetic anhydride (1.0 ml, 7.32 mmol) was added dropwise over a period of 15 min. KCN (0.33 g, 5.00 mmol) in 1.7 ml of  $\text{H}_2\text{O}$  was added and the pH of the aqueous layer was adjusted to pH 5 by the addition of solid NaOAc. The mixture was stirred at rt for 30 min and basified to pH 10 with 10% aq.  $\text{Na}_2\text{CO}_3$ . Normal work-up yielded a mixture of the isomeric compounds 5a and 5b (approx. 3:1) (0.52 g, 80%). IR 2240 (w) (CN)  $\text{cm}^{-1}$  (both isomers).  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.38 (s, 3H), 3.90 (m, 4H), 4.60-4.84 (m, 1H) (both isomers).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) C(2) 53.96, C(3) 27.60, C(4) 20.58, C(5) 39.61, C(6) 50.97,  $>\text{NCH}_3$  43.83,  $-\text{OCHO}-$  104.80,  $-\text{CH}_2\text{CH}_2-$  64.54 (2C), CN 115.77 (major isomer 5a) C(2) 55.19, C(3) 42.72, C(4) 20.58, C(5) 23.76, C(6) 50.00,  $>\text{NCH}_3$  43.50,  $-\text{OCHO}-$  103.82,  $-\text{CH}_2\text{CH}_2-$  64.54 (2C), CN 114.20 (minor isomer 5b). MS  $m/z$  196 ( $\text{M}^+$ ), 170, 169, 123, 96, 73 (100%) (both isomers).

Dimer 7

A mixture of  $\alpha$ -aminonitriles 5a and 5b (160 mg, 0.82 mmol) was dissolved in 30 ml of dry THF.  $\text{AgBF}_4$  (0.16 g, 0.82 mmol) was added in 1.0 ml of dry THF and the mixture was stirred protected from light at rt for 10 min. 10%  $\text{NH}_4\text{OH}$  (20 ml) was added and stirring was continued for 10 min. Layers were separated and worked up normally to give 7 (90 mg, 65%). IR 1665, 1595 (s) ( $>\text{NC}=\text{C}$ )  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.10 (s, 3H), 2.54 (s, 3H), 3.89 (t, 8H), 4.63 (d, 1H,  $J = 3.4$  Hz), 4.80 (d, 1H,  $J = 3.4$  Hz), 5.77 (s, 1H).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) C(2) 50.54, C(3) 37.21, C(4) 21.43, C(5) 110.77, C(6) 134.08, C(2') 70.00, C(3') 30.97, C(4') 25.45, C(5') 40.32, C(6') 57.53,  $>\text{NCH}_3$  42.72,  $>\text{N}'\text{CH}_3$  43.83,  $-\text{OCHO}-$  105.84,  $-\text{OC}'\text{HO}-$  105.45,  $-\text{CH}_2\text{CH}_2-$  64.54 (4C). MS  $m/z$  338 ( $\text{M}^+$ ), 294, 265, 73 (100%).

Ketopiperidine 6

Dimer 7 (110 mg, 0.33 mmol) was dissolved in  $\text{MeOH}/\text{H}_2\text{O}$  (1:1, 2 ml). Methyl acetoacetate (0.39 g, 3.36 mmol) was added and the mixture was refluxed overnight. Most of the methanol was evaporated and the residue was extracted with  $\text{CH}_2\text{Cl}_2$ . Combined extracts were extracted with 5% HCl and the acidic aqueous phase was washed with ether. After neutralisation with solid  $\text{NaHCO}_3$  the solution was worked up normally to give 6 (89 mg, 60%) as a pale yellow oil. IR 1710 (s) (C=O)  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  2.17 (s, 3H), 2.21 (s, 3H), 3.90 (m, 4H), 4.63 (d, 1H,  $J = 3.7$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) C(2) 59.09, C(3) 30.71, C(4) 25.13, C(5) 40.06, C(6) 57.53,  $>\text{NCH}_3$  43.11,  $\text{COCH}_3$  31.23,  $\text{COCH}_2-$  48.63, CO 207.32,  $-\text{OCHO}-$  105.64,  $-\text{CH}_2\text{CH}_2-$  64.74 (2C). MS  $m/z$  227 ( $\text{M}^+$ ), 170 (100%).

### Isoquinuclidine 8

Compound 6 (39 mg, 0.17 mmol) was dissolved in 5% HCl (10 ml) and the solution was refluxed for 2 h. It was then neutralised with solid NaHCO<sub>3</sub> and worked up normally to give 8 (15 mg, 53%) as a pale yellow oil. IR 1660 (s) (C=O), 1605 (s) (C=C) cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 2.13 (s, 3H), 2.32 (s, 3H), 7.33 (dd, 1H, J<sub>1</sub> = 6.7 Hz, J<sub>2</sub> = 1.7 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>) C(1) 51.30, C(3) 55.32, C(4) 24.35, C(5) 143.24, C(6) 143.76, C(7) 26.04, C(8) 21.36, >NCH<sub>3</sub> 44.67, COCH<sub>3</sub> 31.82, CO 195.24. MS m/z 165 (M<sup>+</sup>), 137, 136 (100%). Found: 165.1160 (mass spectrometry). Calc. for C<sub>10</sub>H<sub>15</sub>NO: 165.1154.

### REFERENCES AND NOTES

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7. The "dimer" 7 was isolated from the reaction mixture in good yield (presence of an external base).
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10. Unpublished results from our laboratory.
11. Alternatively, the "dimer" 7 could be prepared, although in lower yield, directly from the N-oxide 4 without trapping the intermediate iminium salt with KCN.

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