SYNTHESIS OF THE ISOQUINUCLIDINE RING SYSTEM

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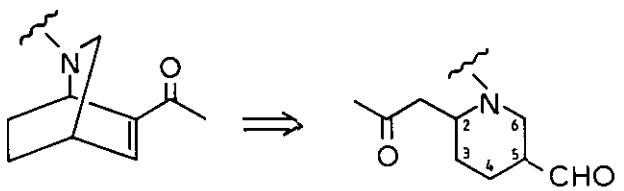
Abstract - The formation of the biochemically important isoquinuclidine ring system by intramolecular condensation of an appropriately substituted piperidine-5-carbaldehyde derivative 6 is described. The direct acylation of the intermediate α-aminonitrile 5a (prepared by the modified Polonovski reaction) to the piperidine-5-carbaldehyde derivative 6 could be achieved only in low yield. However, if the α-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[1], we recently described a new route based on the 5,2-bridging of appropriately substituted 3,4,5,6-tetrahydropyridine equivalents.[2]

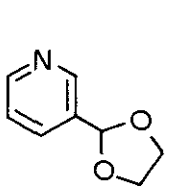
An alternative approach to this crucial problem would be the 2,5-bridging of suitably substituted piperidine-5-carbaldehyde derivatives. In the present communication we report a successful use of this approach for the synthesis of the isoquinuclidine ring system.



For the preparation of the necessary appropriately substituted piperidine-5-carbaldehyde derivatives (under the protected form, e.g. acetal) the modified Polonovski reaction[3-5] 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_2O_2 to yield the corresponding N-oxide 4. The N-oxide was subjected to the modified Polonovski reaction[3-5] conditions and the intermediate iminium salts were reacted with KCN to give α-aminonitriles (2-cyanopiperidines) 5a and 5b (approx. 3:1).[6]

Treatment of the mixture of α-aminonitriles 5a and 5b (vide infra) with $AgBF_4$ and sodium methylacetoacetate produced the desired ketopiperidine 6 only in low yield.[7] As the efforts to obtain the ketopiperidine 6 in higher yield by this procedure did not succeed, we decided to modify the synthetic strategy.



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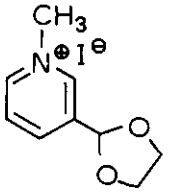

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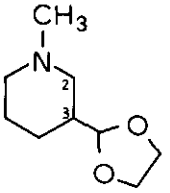

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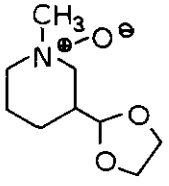

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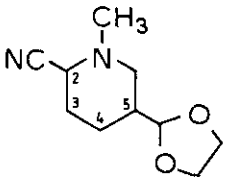
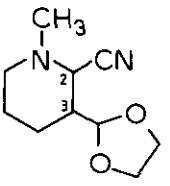


5a



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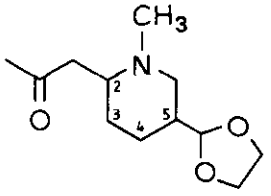

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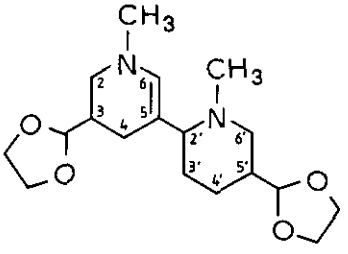

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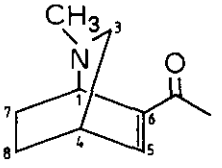

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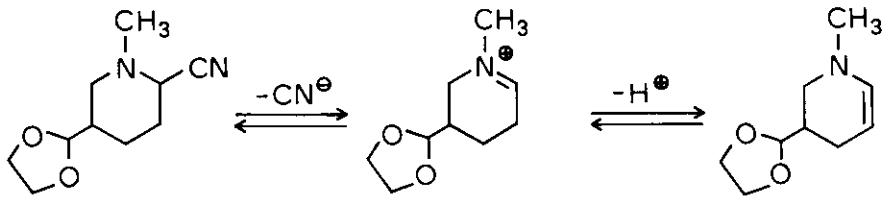
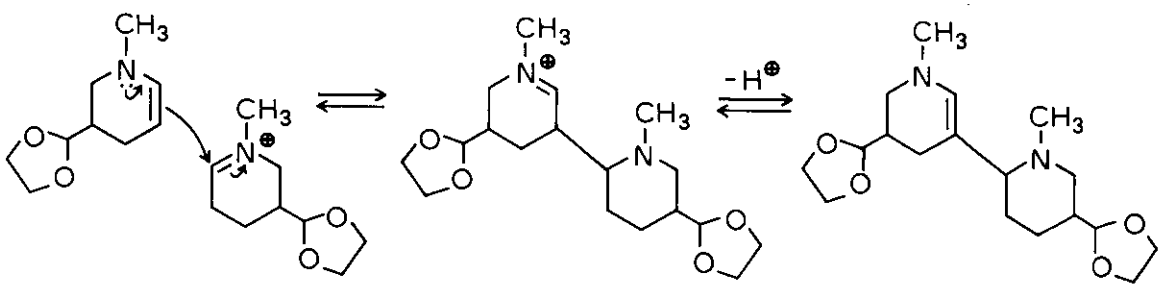
The tendency of 3,4,5,6-tetrahydropyridines (or their equivalents, e.g. 2-cyanopiperidines) to form "dimers" of tetrahydroanabasine-type, combined with the equilibrium existing in hydroxylic solvents between the "dimers" and the corresponding monomers,[8-10] suggested the means to an alternative approach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



Scheme 1



Scheme 2

Indeed, treatment of the mixture of α-aminonitriles 5a and 5b with $AgBF_4$ in dry THF yielded the "dimer" 7[11] (it turned out to be more economical to carry out the "dimer" formation step without prior separation of the two α-aminonitrile isomers), which upon acylation with methyl acetoacetate in $MeOH/H_2O$ 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. ^1H and ^{13}C NMR spectra were recorded on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS (internal standard, δ = 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-Toluenesulphonic 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_2CO_3. Phases were separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined extracts were washed with water, and worked up normally to give 1 1.21 g (87%) as a pale yellow oil. ^1H NMR ($CDCl_3$) δ 4.08 (m, 4H), 5.85 (s, 1H). MS m/z 151 (M^+), 150, 106, 73 (100%).

Pyridinium salt 2

Acetal 1 (1.18 g, 7.81 mmol) was dissolved in 20 ml of MeOH and CH_3I (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_2 (0.090 g) in 20 ml of MeOH over night. Normal work-up yielded 3 (0.39 g, 73%) as a pale yellow liquid. ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.88 (m, 4H), 4.66 (d, 1H, J = 3.6 Hz). ^{13}C NMR ($CDCl_3$) C(2) 56.55, C(3) 40.19, C(4) 24.41, C(5) 24.61, C(6) 55.91, $>NCH_3$ 46.49, -OCHO- 105.58, $-CH_2CH_2-$ 64.54 (2C). MS m/z 171 (M^+), 99, 73, 58, 57, 44 (100%).

N-Oxide 4

Piperidine 3 (0.49 g, 2.87 mmol) was dissolved in 20 ml of CH_2Cl_2:MeOH (1:1) and 30% H_2O_2 (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.

α-Aminonitriles 5a and 5b

N-Oxide 4 (0.62 g, 3.32 mmol) was dissolved in 8 ml of dry CH_2Cl_2, cooled to 0°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 H_2O 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. Na_2CO_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) cm^{-1} (both isomers). ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.90 (m, 4H), 4.60-4.84 (m, 1H) (both isomers). ^{13}C NMR ($CDCl_3$) C(2) 53.96, C(3) 27.60, C(4) 20.58, C(5) 39.61, C(6) 50.97, $>NCH_3$ 43.83, -OCHO- 104.80, $-CH_2CH_2-$ 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, $>NCH_3$ 43.50, -OCHO- 103.82, $-CH_2CH_2-$ 64.54 (2C), CN 114.20 (minor isomer 5b). MS m/z 196 (M^+), 170, 169, 123, 96, 73 (100%) (both isomers).

Dimer 7

A mixture of α-aminonitriles 5a and 5b (160 mg, 0.82 mmol) was dissolved in 30 ml of dry THF. $AgBF_4$ (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% NH_4OH (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) (>NC=C) cm^{-1}. ^1H NMR ($CDCl_3$) δ 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}C NMR ($CDCl_3$) 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, $>NCH_3$ 42.72, $>N'CH_3$ 43.83, -OCHO- 105.84, -OC'HO- 105.45, $-CH_2CH_2-$ 64.54 (4C). MS m/z 338 (M^+), 294, 265, 73 (100%).

Ketopiperidine 6

Dimer 7 (110 mg, 0.33 mmol) was dissolved in $MeOH/H_2O$ (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 CH_2Cl_2. Combined extracts were extracted with 5% HCl and the acidic aqueous phase was washed with ether. After neutralisation with solid $NaHCO_3$ the solution was worked up normally to give 6 (89 mg, 60%) as a pale yellow oil. IR 1710 (s) (C=O) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.17 (s, 3H), 2.21 (s, 3H), 3.90 (m, 4H), 4.63 (d, 1H, J = 3.7 Hz). ^{13}C NMR ($CDCl_3$) C(2) 59.09, C(3) 30.71, C(4) 25.13, C(5) 40.06, C(6) 57.53, $>NCH_3$ 43.11, $CO\underline{C}H_3$ 31.23, $CO\underline{C}H_2-$ 48.63, CO 207.32, -OCHO- 105.64, $-CH_2CH_2-$ 64.74 (2C). MS m/z 227 (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 $NaHCO_3$ 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^{-1}. ^1H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.32 (s, 3H), 7.33 (dd, 1H, J_1 = 6.7 Hz, J_2 = 1.7 Hz). ^{13}C NMR ($CDCl_3$) 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, $>NCH_3$ 44.67, $COCH_3$ 31.82, CO 195.24. MS m/z 165 (M^+), 137, 136 (100%). Found: 165.1160 (mass spectrometry). Calc. for $C_{10}H_{15}NO$: 165.1154.

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7. The "dimer" 7 was isolated from the reaction mixture in good yield (presence of an external base).
8. N.J. Leonard and F.P. Hauck, Jr., J. Am. Chem. Soc., 1957, 79, 5279.
9. S.J. Martinez and J.A. Joule, Tetrahedron, 1978, 34, 3027.
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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