STUDIES TOWARDS 3,4-DIMETHOXY-1-METHYL-1,2-DIHYDRO-PYRIDINE, SO-CALLED ARECOLIDINE, OR ITS TAUTOMERS

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Dedicated to Prof. A. R. Katritzky on occasion of his 65th birthday

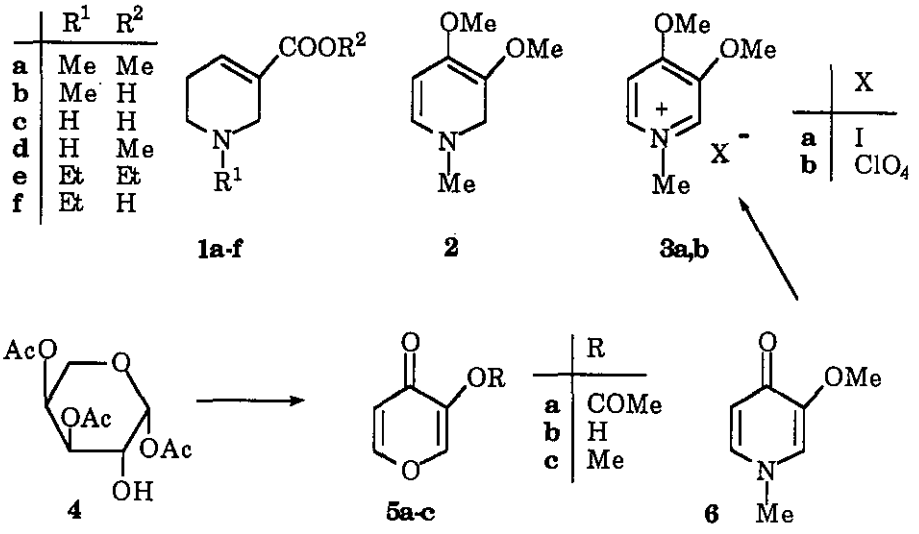
Abstract- Different synthetic paths towards the title compound (**2**) lead to intermediates (**3**, **11**, **13**, **14**, **15**, and **17**). All of these, but especially **3** and **14** are very close to the target molecule or its tautomers. These, however, turn out to be too unstable for isolation. Thus, the structure of the compound described as arecolidine must be wrong.

Introduction

The main alkaloid of the areca nut (*Areca catechu* L.) , arecoline (**1a**), is a well-known pharmaceutical agent.[1] H. Emde reported 1915 on the isolation of an isomer named arecolidine from mother liquors of the industrial **1a** purification.[2] Tentative structure (**2**) was assigned to the compound, but there is no biosynthetic relationship to the other minor alkaloids from the same plant, arecaidine (**1b**), guvacine (**1c**), and guvacoline (**1d**). Although arecolidine has never been reisolated or firmly established in its structure the compound is mentioned even in recent handbooks and articles.[1,3] Having done research on other methoxypyridines,[4] we felt hydro compounds like **2** or its double bond isomers should be rather unstable. An attempted reisolation directly from areca nuts in our laboratory did not meet with success.[5] Thus, Emde's compound may very well have been an artifact from the technical work-up. We decided therefore to attempt the synthesis of **2** or its tautomers.

Approach I

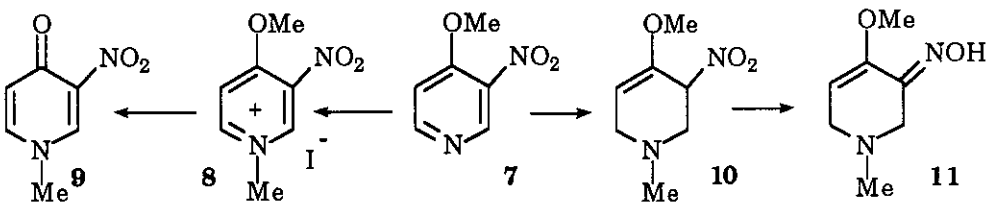
The most straightforward path towards **2** appeared to be a reduction of 3,4-dimethoxy-*N*-methylpyridinium salts (**3a,b**). A useful starting material was 1,3,4-triacetyl-α-D-xylo-pyranose (**4**) [6] which could be transformed into **5a** by an adaptation of Chittenden's method to prepare kojic acid:[7] **4** was treated with DMSO / acetic anhydride which resulted in a one-pot oxidation-transesterification-elimination to yield 79% of **5a**. This was hydrolyzed giving **5b** (91%), methylated (**5c**, 65%), and finally reacted with methylamine whereby 3-methoxy-1-methyl-4-pyridone (**6**, 69%) was formed. Conversion with methyl iodide in acetonitrile led to oily **3a** which proved to be rather unstable. On attempted crystallization from hot solvents, MeI was split off again. Crystalline (**3b**) could be obtained, however, when the methylation was performed with dimethyl sulfate and 40% perchloric acid was added thereafter.



Reduction was attempted with H_2 / Pt or Pd in various solvents, $NaBH_4$, $LiAlH_4$, $Na_2S_2O_4$, or $NaAlH_2(OCH_2CH_2OMe)_2$. In line with the observed sensitivity of **3a**, all reduction experiments with both salts failed. Either no reaction occurred at all or a mixture of decomposition products was obtained.

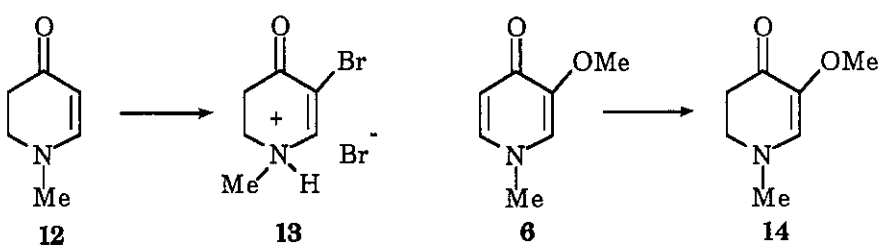
Approach II

4-Methoxy-3-nitropyridine (**7**) is easily available *via* nitration of 4-pyridone, reaction with phosphorus pentachloride and then with methanol.[8] It could be *N*-methylated with methyl iodide, but the salt (**8**) decomposed easily by demethylation. This process led to the more stable pyridone (**9**) instead of direct reversal to **7** . Borohydride reduction of **7** gave 81% of **10** under mild conditions. Whereas a variety of literature conditions[9] did not yield the respective ketone, it was possible to prepare the oxime (**11**) in a *Nef* -like reaction developed by McMurry.[10] All further experiments towards de-oximation (hydrolysis, oxidation, trans-oximation) gave only decomposition.



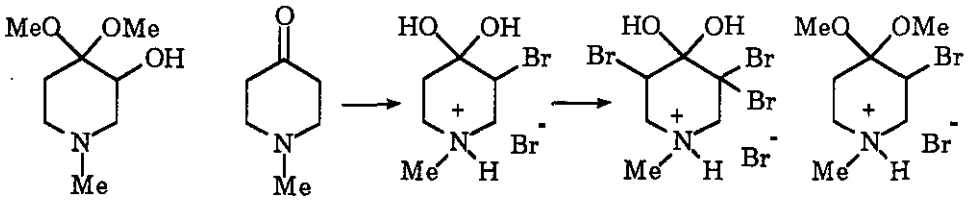
Approaches IIIa/b

N-Methyl-2,3-dihydro-4(1*H*)-pyridinone (**12**)[11] was brominated to yield the hydrobromide (**13**). This compound is stable only as the salt. Attempts to liberate the base, to substitute the bromide in 3-position, or to ketalize resulted in fast tarring. On the other hand, **6** was reduced successfully with $NaAlH_2(OCH_2CH_2OMe)_2$ to give **14** as the only isomer. **14** turned out to be an extremely unstable oil that could be handled solely in solution and was characterized only by nmr and ms spectroscopy. Reaction of this material with LDA/ methyl iodide at -78 °C resulted in immediate tarring.



Approaches IVa/b

3-Hydroxy-4,4-dimethoxy-1-methylpiperidine (**15**) is available from *N*-methylpiperidone with iodosobenzene diacetate / MeOH / KOH.[12] All efforts to oxidize the hydroxy group (*e.g.*, by Swern oxidation variants, MnO_2, PCC, CrO_3/HOAc, $NaClO_2$, Br_2) either did not show any effect or led to decomposition. When *N*-methyl-4-piperidone was brominated with 1 or 3 molar equivalents of Br_2, the hydrobromide-hydrates (**16** or **17**) were obtained. Ketal (**18**) could be prepared from **16** with orthoformate. Again all experiments towards further substitution and/or oxidation and elimination reactions of **16** - **18** were totally futile.



15 **16** **17** **18**

Discussion

It is known from the literature that 1,2- or 1,6-dihydropyridines are reasonably stable if they carry electron withdrawing groups conjugated to the enamine structural element. Compounds lacking this type of stabilization seem to be rather sensitive towards oxidation and polymerizations. These expectations are confirmed fully by the present results.

Some of our new compounds (**3, 11, 13, 14, 15,17**) are very close to the target molecule(s). **3** and especially **14** are actually only one step removed from **2** . It is quite apparent, however, that the stability of compounds decreases the closer the target structure is approached. This is illustrated best by the fast decomposition of the free base of **13** (3-bromo-5,6-dihydro-1-methyl-4(1*H*)-pyridinone) and of **14** (2,3-dihydro-5-methoxy-1-methyl-4(1*H*)-pyridinone). Thus, *if there really is a natural product arecolidine, an isomer of arecoline, it cannot have structure* **2** .

The question remains: what was it that Emde isolated as "arecolidine" (mp 110°C, no CHN analysis) and characterized by molecular analyses of hydrochloride-hydrate (mp 95-98°C),

hydrobromide (sintering from 235°C, decomp. 268-271°C), chloroaurate (decomp. 219-220°C), chloroplatinate (sintering from 214°C, decomp. 222-223°C), methiodide (decomp. 264°C), and chloroaurate of methyl derivative (decomp. 252°C) ?

An exhaustive literature search for likely arecoline ($C_8H_{13}NO_2$) isomers and the melting points of their derivatives furnished as the only somewhat matching candidate *N*-ethyl-1,2,5,6-tetrahydronicotinic acid (**1f**). The recorded melting / decomposition points are: *hydrochloride* 223-233°C, *chloroaurate* 214-215°C, *chloroplatinate* 229°C. **1f** *itself, however,* was described as an oil. We prepared compound (**1f**) by $NaBH_4$ reduction of *N*-ethyl-nicotinic acid ethyl ester bromide (to give **1e**) and subsequent hydrolysis. The oil was distilled *in vacuo* and could be crystallized thereafter. Its melting point is 181°C, and hydrochloride and hydrobromide have mp 204 and 170-173°C in our hands. Thus, the data for **1f** and "arecolidine" do not agree. The very hygroscopic character of compound (**1f**) and its salts, however, make the melting point determinations difficult, and the formation of further crystalline hydrates seems possible. In the last analysis it can only be stated that the literature structure for "arecolidine" must be wrong.

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EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Ir spectra were recorded on a Beckman Acculab 8. ^{1}H-Nmr spectra were recorded on a Varian EM 360 spectrometer working at 60 MHz or on a Bruker AM 300 instrument working at 300 MHz (75.45 MHz for ^{13}C-nmr spectra). New compounds for which no C,H,N analysis is given are too unstable. Mass spectra were measured with a Varian MAT 311A, EI (70eV).

3-Carboxyethyl-N-ethyl-1,2,5,6-tetrahydropyridine (**1e**):

Nicotinic acid ethyl ester (36.5 g, 0.24 mol) and ethyl bromide (263 g, 2.41 mol) in 360 ml of CH_3CN were refluxed for 2 d. The solution was concentrated, the residue (ca. 65 g) was diluted with 625 ml of MeOH and cooled to 0°C. $NaBH_4$ (19 g, 0.5 mol) was added slowly, and stirring was continued for 2 h at room temperature. MeOH was distilled off (temperature <50°C), and the residue was hydrolized with 600 ml of H_2O. After extraction with ether and drying (Na_2SO_4) the solvent was removed and the red residue was distilled in a Kugelrohr apparatus. Yield (**1e**): 24.6 g (54%), bp 60-70°C/0.05 mbar; 9.3 g. (A higher boiling fraction contained a mixture of dihydropyridines, bp 130-135°C/0.05 mbar).- Ir: 2985, 2800, 2760, 1705, 1250 cm^{-1}. ^{1}H-Nmr (300 MHz/$CDCl_3$): δ 1.15 (t, J=7.2, 3H, $NCH_2\underline{CH_3}$), 1.29 (t, J=7.2, 3 H, $OCH_2\underline{CH_3}$), 2.37 (m, 2 H(5)), 2.55 (m, 4 H, $NC\underline{H_2}CH_3$ and H(6)), 3.19 (AB system, J=2.9, 2 H(2)), 4.20 (q, J=7.2, 2 H, $OC\underline{H_2}CH_3$), 7.01 (m, H(4)).

N-Ethyl-3-carboxy-1,2,5,6-tetrahydropyridine (**1f**):

a) basic hydrolysis: **1e** (1 g, 5.46 mmol) and KOH (0.3 g, 5.46 mmol) in 20 ml of EtOH were refluxed for 5 h. The solution was treated with 10% HCl to pH=6 and concentrated *in vacuo*. The residue was extracted two times with 20 ml of AcOEt. Removal of solvent after drying (Na_2SO_4) gave a red oil of **1f**, red oil (0.4 g, 47%). Sublimation (90-130°C/0.01 mbar) in a Kugelrohr apparatus left white hygroscopic crystals, mp 181°C.

b) acidic hydrolysis: **1e** (1 g, 5.46 mmol) in 100 ml of H_2O was treated with HCl (conc.) or HBr (conc.) to pH=1. After refluxing for 12 h, the solution was concentrated to dryness. The salts were crystallized from acetone/petroleum ether. To prepare the free base, the residue was taken up in a little EtOH and treated with Et_3N to pH=6. Removal of solvent after filtration gave a red oil of **1f** (0.7 g, 83%). Sublimation (90-130°C/0.01 mbar) in a Kugelrohr apparatus left white hygroscopic crystals, mp 181°C; hydrochloride: mp 204°C; hydrobromide: mp 170-173°C. Anal.Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.00; H, 8.30; N 9.04. Ir: 3600-3200, 2910, 2400-2200, 1590, 1370, 1340, 760, 730 cm^{-1}. ^{1}H-

Nmr (300 MHz/DMSO-d_6): δ 1.35 (t, J=7.2, 3 H, $NCH_2\underline{CH_3}$), 2.51 (m, 2 H(5)), 3.06 (m, 4 H, NCH_2CH_3 and H(6)), 3.73 (m, 2 H(2)), 6.85 (m, H(4)).

3.4-Dimethoxy-N-methylpyridinium iodide (**3a**):

6 (0.9 g , 7 mmol) and 10 ml of methyl iodide in 10 ml of MeCN were heated at 50°C for 8 h. Evaporation of the solvent yielded 2 g of a brownish viscous oil (**3a**). This decomposed on attempted crystallization. ^{1}H-Nmr (60 MHz/DMSO-d_6): δ 3.86, 3.96 (2 s, 3 H each, OMe), 4.10 (s, 3 H, NMe), 7.53 (d, J=5, H(5)), 8.43 (d, J=5, H(6)), 8.53 (s, H(2)).

3,4-Dimethoxy-N-methylpyridinium perchlorate (**3b**):

6 (0.6 g, 4.2 mmol) and dimethyl sulfate (1.33 g, 10 mmol) were heated at 80°C for 2 h. At 0°C the solution was diluted with 2.7 ml of $HClO_4$ (70%). Ether was added dropwise to beginning turpidity, and the solution was kept at -15°C for 3-7 d. Very hygroscopic colourless crystals of **3b** were filtered off and were stored over P_2O_5. Yield: 900 mg (85%), mp 118-123°C. Anal. Calcd for $C_8H_{12}ClNO_6$: C, 37.88; H, 4.77; N, 5.52. Found: C, 37.73; H, 4.98; N, 5.38. ^{1}H-Nmr (60 MHz/DMSO-d_6): δ 3.90, 4.00 (2 s, 3 H each, OMe), 4.10 (s, 3 H, NMe), 7.50 (d, J=7.61, 1 H(5)), 8.40 (s, H(2)), 8.50 (d, J=7.6, H(6)). ^{13}C-Nmr (DMSO-d_6): δ 46.61 (NMe), 57.42 (OMe), 57.93 (OMe), 109.08 (C(5)), 128.82 (C(6)), 141.34 (C(2)), 146.12 (C(3)), 160.11 (C(4)).

3-Acetoxy-4-pyrone (O-acetylpyromeconic acid : **5a**):

4 [6] (20 g, 72.5 mmol) in 220 ml of DMSO and 120 ml of Ac_2O were stirred for 3 d at room temperature. The slightly yellowish solution was concentrated at 70°C and distilled in a Kugelrohr apparatus. Yield (**5a**): 8.8 g (79%), bp 90-100°C/0.2 mbar, mp 92°C (from EtOH) (lit.,[13]: 93°C). Ir: 3060, 1730, 1650, 1410, 1370,1300, 1220, 1160 cm^{-1}. ^{1}H-Nmr (300 MHz/$CDCl_3$): δ 2.34 (s, 3 H, Me), 6.50 (d, J=5.6, H(5)), 7.76 (dd, J=0.9 and 5.6, H(6)), 7.90 (d, J = 0.9, H(2)).

3-Hydroxy-4-pyrone (pyromeconic acid : **5b**) :

A suspension of **5a** (5 g, 32.5 mmol) in 100 ml of H_2O was refluxed for 2 h. Vacuum concentration followed by Kugelrohr distillation and recrystallization from Et_2O gave 3.3 g (91%) of white crystals (**5b**), bp 80-100°C/18 mbar, mp 117°C (lit.,[14]: 118°C). Ir: 1640, 1610, 1450, 1390, 1310, 1235, 1190, 1100 cm^{-1}. ^1H-Nmr (60 MHz/$CDCl_3$): δ 6.43 (d, J=6, H(5)), 7.73 (d, J=6, H(6)), 7.80 (s, H(2)).

3-Methoxy-4-pyrone (O-Methylpyromeconic acid : **5c**):

5 b (3 g, 27 mmol), 4 ml of methyl iodide, and 200 mg of solid K_2CO_3 were heated in 50 ml of MeCN at 50°C for 24 h. After cooling, the suspension was filtered, the solvent was removed *in vacuo*, and the residue was sublimated (140°C/1.5 mbar). Yield (**5c**): 2.2 g (65%), mp 94°C (lit.,[15]: 94.5°C). Ir: 1630, 1610, 1450, 1340, 1250, 1200, 1180, 1110, 1025, 980 cm^{-1}. ^1H-Nmr (60 MHz/$CDCl_3$): δ d 3.70 (s, 3H, OMe), 6.27 (d, J=5, H(5)), 7.52 (s, H(2)), 7.62 (d, J=5, H(6)).

3-Methoxy-N-methyl-4-pyridone (N,O-Dimethylpyromeconaminic acid : **6**):

5c (2 g, 16 mmol) in 70 ml of an aqueous solution of methyl amine (40%) were refluxed for 8 h. Evaporation of the solvent and crystallization from MeOH/Et_2O (4:1) gave 1.5 g (69%) of slightly brownish crystals (**6**), mp 90°C (lit., [15]: 92°C). Ir: 1620, 1570, 1500, 1435, 1290, 1240, 1170, 1170, 1020, 935 cm^{-1}. ^1H-Nmr (60 MHz/$CDCl_3$): δ 3.5 (s, 6H, 2 Me groups), 5.87 (d, J=7, H(5)), 7.26 (s, H(2)), 7.40 (d, J=7 H(6)).

4-Methoxy-N-methyl-3-nitro-pyridinium iodide (**8**):

7[8] (3.2 g, 21 mmol) and 20 ml of methyl iodide in 20 ml of CH_2Cl_2 were stirred for 72 h at room temperature. Crude **8** precipitated as yellow-orange crystals. Yield: 5.9 g (95%), mp 110°C (decomp.). Ir: 1590, 1530, 1300, 1210, 990, 825, 750 cm^{-1}. ^1H-Nmr (60 MHz/DMSO-d_6): δ

4.24 (s, 3H, OMe), 4.27 (s, 3H, NMe), 8.08 (d, J=7.4, H(5)), 9.07 (dd, J=7.4 and 1.6, H(6)), 9.77 (d, J=1.6, H(2)).

4-Methoxy-N-methyl-3-nitro-1,2,3,6-tetrahydropyridine (**10**):

$NaBH_4$ (3.85 g, 101 mmol) was added slowly to **8** (24 g, 81.1 mmol) in 250 ml of H_2O and 250 ml of ether at room temperature. After 5 min the Et_2O-phase was separated, and the aqueous phase was extracted three times with ether. The combined organic layer was dried (Na_2SO_4), filtered over silica gel and concentrated. Yield: 11.23 g (81%) of crude **10**. Recrystallization from Et_2O/petroleum ether (3:1) gave white crystals (6 g), mp 60°C. Anal. Calcd for $C_7H_{12}N_2O_3$: C, 48.83; H, 7.01; N, 16.26. Found: C, 48.80; H, 6.74; N, 16.04. Ir: 1670, 1530, 1445, 1380, 1360, 1330, 1280, 1260, 1210, 1130, 1060, 990, 980 cm^{-1}. ^{1}H-Nmr (300 MHz /$CDCl_3$): δ 2.36 (s, 3H, NMe), 2.79 (m, 2 H(2)), 3.36 (m, 2 H(6)), 3.61 (s, 3 H, OMe), 4.88 (m, H(3)), 5.06 (m, H(5)). ^{13}C-Nmr ($CDCl_3$): δ 44.74 (N-Me), 52.70 (C(2)), 55.04 (O-Me), 56.25 (C(6)), 83.09 (C(3)), 100.20 (C(5)), 146.65 (C(4)).

4-Methoxy-N-methyl-1,6-dihydro-3(1H)-pyridinone oxime (**11**):

To **10** (500 mg, 2.9 mmol) in 6 ml of MeOH was added NaOMe (160 mg, 3 mmol) and the solution was stirred for 0.5 h at room temperature. After cooling to 0°C a solution was added which contained $TiCl_3$ (1.9 g, 12.2 mmol) and NH_4OAc (2.8 g, 36 mmol) in 14 ml of H_2O. Stirring was continued for 2 h at 10°C, and the yellow suspension was treated with further $TiCl_3$ (480 mg, 3.1 mmol) and NH_4OAc (700 mg, 9 mmol) in 4 ml of H_2O. After 8 h at room temperature $Tl(NO_3)\cdot 3H_2O$ (2 g, 5.8 mmol) was added and stirring was continued for 15 h at 20°C. The slightly basic aqueous layer was extracted with $CHCl_3$, dried (Na_2SO_4) and concentrated. Yield (**11**): 400 mg (80%) after sublimation at 135°C/0.4 mbar, mp 100°-158°C (decomp.). Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.03. Found: C, 53.94; H, 7.66; N, 17.93. Ir: 3200-2700, 1635, 1605, 1485, 1450, 1380, 1260, 1235, 1200, 1170, 1105, 980, 950, 880 cm^{-1}. Ms (EI): m/z = 156 (M+). ^{1}H-Nmr (300 MHz/DMSO-d_6): δ 2.24 (s, 3 H, NMe), 3.00

(d, J=4.1, H(6)), 3.27 (s, 2 H(2)), 3.49 (s, 3 H, OMe), 5.24 (t, J=4.1, H(5)), 11.05 (s, 1 H, NOH). ^{13}C-Nmr (DMSO-d_6): δ 44.61 (N-Me); 50.82 (C(6)), 52.13 (C(2)), 54.27 (OMe), 101.95 (C(5)), 148.01 (C(4)), 148.21 (C(3)).

3-Bromo-N-methyl-1,6-dihydro-4(1H)-pyridinone hydrobromide (**13**):

Bromine (1.44 g, 9 mmol) was added dropwise to an ice cooled solution of **12** [11] (1 g , 9 mmol) in 20 ml of CH_2Cl_2. After 3 h at -15°C the yellow crystals were separated by filtration. Yield (**13**): 2.3 g (94%), mp 130°C (decomp.). Anal. Calcd for $C_6H_9Br_2NO$: C, 26.60; H, 3.59; N, 5.40. Found: C, 26.93; H, 3.35; N, 5.17. Ir: 3000-2300, 1640, 1550, 1380, 1300, 1200, 1160, 1005, 985 cm^{-1}. ^{1}H-Nmr (300 MHz/DMSO-d_6): δ 2.45 (t, J=8.0, 2 H(5)), 3.06 (s, 3 H, NMe), 3.46 (t, J=8.0, 2 H(6)), 7.82 (s, H(2)), 9.46 (br s, NH).

3-Methoxy-N-methyl-1,6-dihydro-4(1H)-pyridinone (**14**):

A solution of $NaH_2Al(OCH_2CH_2OMe)_2$ (1 g, 3.47 mmol, 70% in toluene) was added dropwise to **6** (0.2 g, 1.44 mmol) in 50 ml of THF at 0°C. Stirring was continued for 2 h at 0°C and 2h at 25°C. The fair-red solution was added quickly to 10 ml of 1 N NaOH and 50 ml of $CHCl_3$ and the two layers were stirred intensely for 0.5 h. The organic phase was separated and the aqueous phase was extracted three times with $CHCl_3$. Removal of solvent after drying (Na_2SO_4) and Kugelrohr distillation gave 50 mg (25%) of an oil (**14**), bp 95-100°C/0.8 mbar). Ir: 2980, 2880, 2810, 1635, 1590, 1310, 1280, 1235, 1200, 1180, 1090 cm^{-1}. Ms (EI): m/z = 141 (M+). ^{1}H-Nmr (300 MHz/$CDCl_3$): δ 2.51 (t, J=7.9, 2 H(5)), 2.95 (s, 3 H, NMe), 3.29 (t, J=7.9, 2 H(6)), 3.62 (s, 3 H, OMe), 6.95 (s, H(2)). ^{13}C-Nmr ($CDCl_3$): δ 35.73 (C(5)), 43.13 (NMe), 49.62 (C(6)), 60.88 (OMe), 134.08 (C(3)), 146.57 (C(2)), 185.65 (C(4)).

3-Hydroxy-4,4-dimethoxy-N-methylpiperidine (**15**):

N-Methyl-4-pyridone (3 g, 26.55 mmol) were added to an ice cooled solution of 4.5 g (80.2 mmol) of KOH in 30 ml of MeOH. At 0°C the solution was treated slowly with iodosobenzene

diacetate (9.2 g, 28.56 mmol) within 45 min. After stirring for 36 h at room temperature the solvent was removed and the residue was taken up in 20 ml of H_2O. The aqueous layer was extracted with CH_2Cl_2 and dried (Na_2SO_4). Evaporation of solvent and crystallization from ether gave 1.5 g (32%,**15**), mp 109°C (lit., [10]: 110°C). Ir: 3300, 3040, 2930, 2780, 1460, 1440, 1350, 1290, 1250, 1210, 1145, 1110, 1080, 1060, 1040, 1010 cm^{-1}. ^1H-Nmr (300 MHz/$CDCl_3$): δ 1.87 ppm (m, 2H, H(5) and OH), 2.08 (dt, J=4.3 and 10.9, H(5)), 2.27 (s, 3 H, NMe), 2.39 (dd, J=1.8 and 11.8, 1 H(2)), 2.61 (m, 1 H(2)), 2.77 (m, 2 H(6)), 3.22 and 3.26 (2 s, 3 H each, OMe), 3.73 (m, H(3)).

3-Bromo-N-methyl-4-piperidone hydrate hydrobromide (**16**):

N-Methyl-4-piperidone (5 g, 44.18 mmol) in 20 ml of HBr (48%) was treated with 7.06 g (44.2 mmol) of Br_2 at 0°C. After stirring for 5 min at 0°C 10 ml of EtOH were added and the light-yellow crystals were filtered off. Yield (**16**): 9.1 g (75%), mp 136°C. Anal. Calcd for $C_6H_{13}Br_2NO_2$: C, 24.76; H, 4.50; N, 4.81. Found: C, 24.75; H, 4.43; N, 4.78. Ir: 3490, 3290, 2930, 2700, 1460, 1410, 1400, 1200, 1190, 1110, 1100, 1025 cm^{-1}.

N-Methyl-3,3,5-tribromo-4-piperidone hydrate hydrobromide (**17**):

N-Methyl-4-piperidone (10 g, 88.37 mmol) in 50 ml of HBr (48%) were treated dropwise with 42.66 g (267 mmol) of Br_2 at 0°C. After 15 min the solution was completely decolourized. White crystals precipitated on addition of 50 ml of EtOH. Recrystallization from EtOH gave 32 g (84%, **17**), mp 164°C (decomp.). Ir: 3400-2500, 1440, 1370, 1320, 1280, 1210, 1190, 1130, 1110, 1095, 1040, 1020, 985 cm^{-1}. Anal. Calcd for $C_6H_{11}NO_2Br_4$: C, 16.06; H, 2.47; N, 3.12. Found: C, 16.41; H, 2.55; N 3.29. ^1H-Nmr (300 MHz/DMSO-d_6): δ 2.90 (s, 3 H, NMe), 3.42 (m, 1 H(6)), 3.66 (m, 1 H(6)), 4.07 (d, J=13.4, 1 H(2)), 4.38 (d, J=13.4, 1 H(2)), 4.67 (dd, J=12.3 and 4.3, H(5)).

3-Bromo-4,4-dimethoxy-N-methyl-piperidine hydrobromide (**18**):

16 (1.5 g, 5.16 mmol), 10 ml of MeOH and 10 ml of trimethyl orthoformate were stirred at room temperature for 15 h under argon. Removal of solvent (T<30°C) and crystallization from MeOH/Et_2O gave 1.1 g (67%) of colourless crystals (**18**), mp 112°C. Ir: 3260, 3240, 2920, 2680, 1460, 1300, 1150, 1110, 1080, 1040 cm^{-1}. The compound was very unstable.

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