ALKYLATION OF 1-(3,4-DIMETHOXYBENZYL)-6,7-DIMETHOXY-ISOQUINOLINE (PAPAVERINE)

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Abstract - Alkylation of papaverine carbanion with various alkyl halides is described. Intramolecular ring formation is observed with 1-iodo-3-chloropropane as electrophile. 1-[1-(3,4-Dimethoxyphenyl-3-oxopropyl]-6,7-dimethoxyisoquinoline is studied.

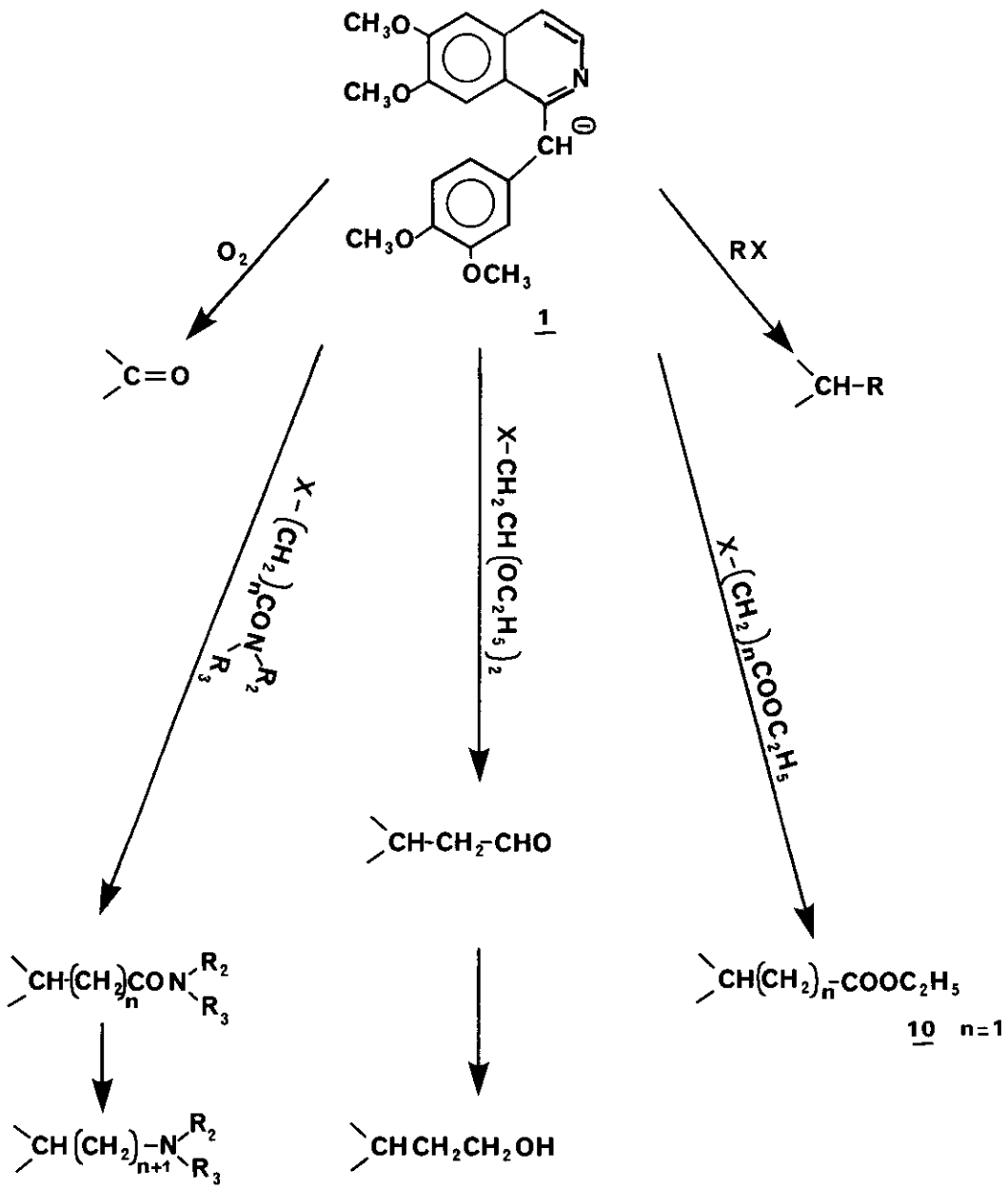
Derivatives of papaverine are few, despite their potential pharmacological interest[1]. In order to evaluate the cardiovascular properties of the alkyl derivatives of papaverine[2] a general method of preparation of its carbanion is needed and is described in the present work. The use of the papaverine carbanion in heterocyclic chemistry is discussed.

The weak acidity of the methylene hydrogens in papaverine has been shown by their oxidation by oxygen in presence of Triton B[3]. However the carbanion can be obtained via one of the three following conditions.

- sodamide liquid ammonia.
- sodamide hexamethylphosphoramide.
- butyllithium hexamethylphosphoramide.

With the first method giving the best results as shown by the very deep red color of the carbanion which developped in few minutes.

The reactivity of the carbanion towards electrophiles is shown in scheme 1. Carbanion 1 reacting with methyl iodide, allyl bromide or propyl bromide gives the corresponding alkyl derivative. Only mono-alkylated products are


CH3O
CH3O
N
CH⊖
CH3O
OCH3
1
O2
C=O
RX
CH-R
X-(CH2)nCONR2R3
X-CH2CH(OC2H5)2
X-(CH2)nCOOC2H5
CH-CH2-CHO
CH(CH2)nCONR2R3
CH(CH2)n+1-NR2R3
CHCH2CH2OH
CH(CH2)n-COOC2H5
10 n=1

Scheme 1

obtained and regioselective C alkylation is observed.

α or β-Halogenated esters or amides give alkylation products without elimination or addition on the ethoxy group (or amido group).

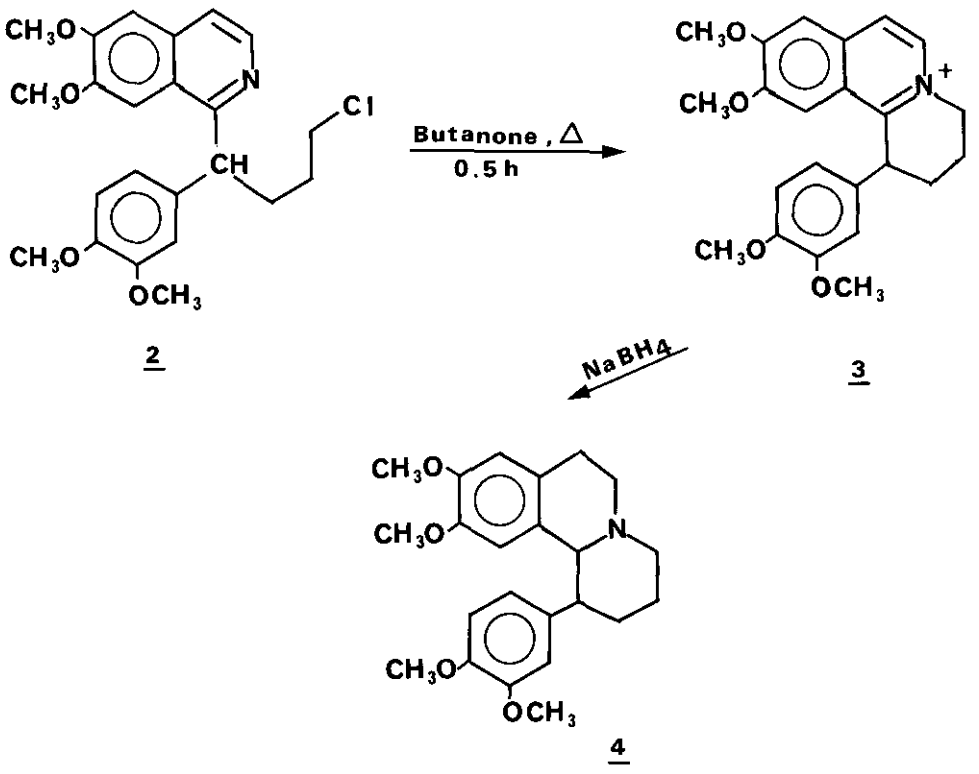
2,2-Diethoxyethyl bromide provides, after hydrolysis of compound 5, the aldehyde derivative 8 which can be isolated in basic media.

Bubbling oxygen in a solution of papaverine carbanion 1 gives the ketone papaveraldine[3,4]. The carbanion 1 can also react with aldehyde and ketone[5].

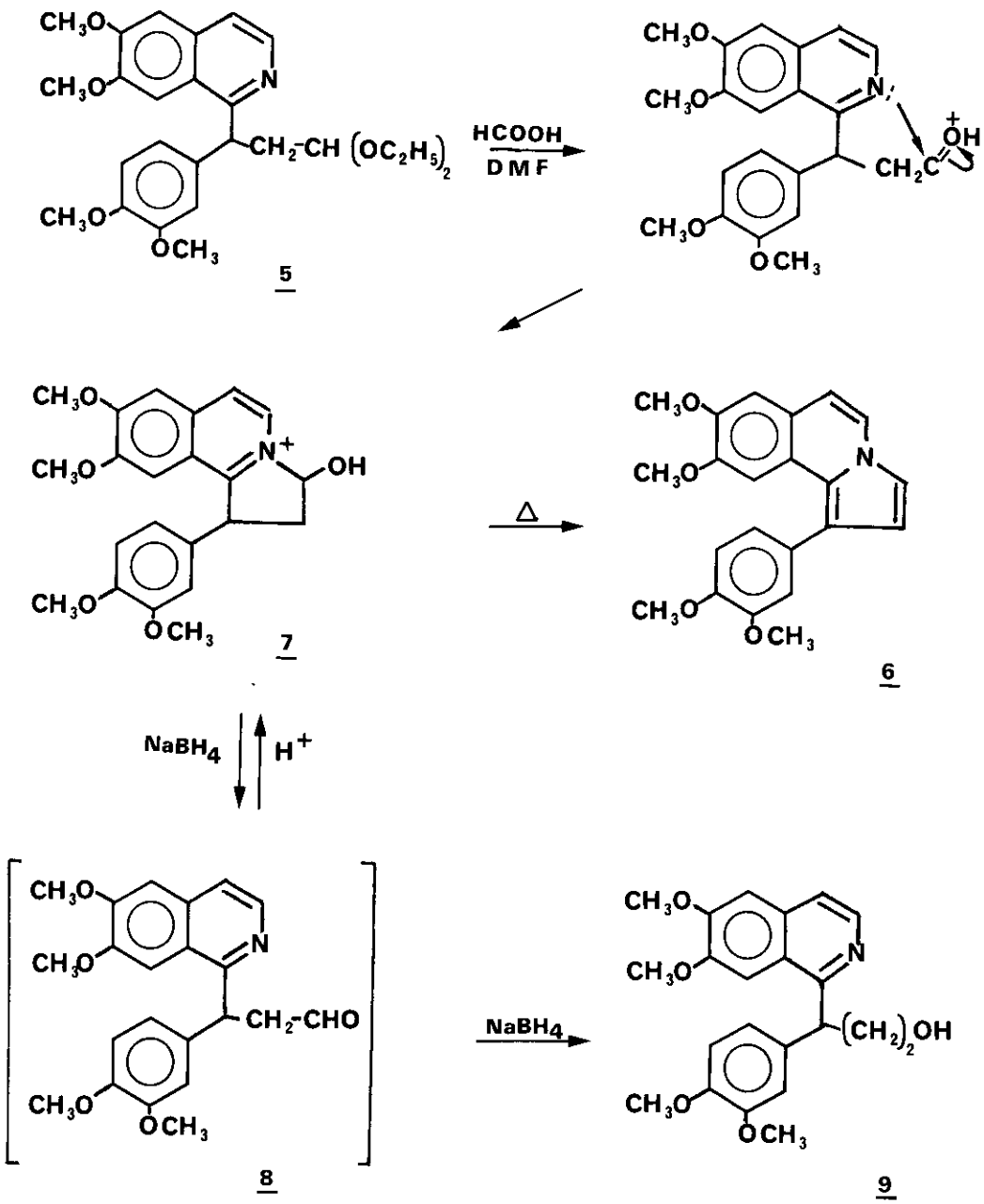
Intramolecular ring formation

The isoquinoline nitrogen of papaverine can be involved with functional alkyl derivatives, in the formation of heterocyclic compounds. (For related reactions see inter alia references[6,7]. Thus 1-chloro-3-iodopropane furnished compound 2 which on heating, produced an immonium salt 3; this in turn could be reduced by sodium borohydride to 4 as outlined in Scheme 2.

Scheme 2



2 3 4


CH3O
CH3O
N
CH2-CH (OC2H5)2
CH3O
OCH3
HCOOH
DMF
5
OH
CH2C
7
OH
Δ
6
NaBH4
H+
8
CHO
NaBH4
(CH2)2OH
9

Scheme 3

Again heating 5 in DMF/formic acid gave 6. Nucleophilic attack of the isoquinoline nitrogen on the protonated aldehyde yielded immonium salt which could be isolated and produced 6 on heating, as outlined in Scheme 3. Hydrolysis of the ketal 5 gave 8 which, in aciditic media produced the immonium salt 7. Compound 8 could be regenerated from 7 by adding a base as shown by NMR. Sodium borohydride reduction of 7 provided 9 which could also be directly obtained from 8. The easy cyclization of 8 to 7 occurred because of the preferred conformation of the nitrogen lone pair with respect to the carbonyl group. The NMR spectra of the ester 10 has an unexpectated coupling constant $\underset{X}{>}\underset{A,B}{CH-CH_2}-COOC_2H_5$ J_{AB} = 16 Hz J_{AX} = 8.9 Hz J_{BX} = 6.6 Hz implying interaction of the ethoxycarbonyl group with nitrogen. A similar interaction could be postulated for compound 8.

The methodology presented in the present work gives access to alkyl derivatives with functionality on the alkyl chain like amino alkyl chain (after reduction of the amide group). These new amino alkyl derivatives of papaverine with their pharmacological properties will be presented in a future paper.

EXPERIMENTAL

^1H NMR spectra were obtained on a Perkin-Elmer R24 B in $CDCl_3$ solution with Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin-Elmer spectrophotometer 257 using potassium bromide disks. The reported melting points are uncorrected.

Preparation of carbanion 1

Into a one litre three necked flask provided with stirring means and dry ice trap are successively introduced 300 ml of liquid ammonia, 0.3 g of sodium, 0.1 g of ferric chloride and then a further 0.8 g of sodium. The reaction mixture is stirred for 2 h, after which 10 g (0.0295 mole) of papaverine are added in small portions; a red solution is obtained after 2 h.

1-[1-(3,4-Dimethoxyphenyl)-ethyl]-6,7-dimethoxyisoquinoline :

To a solution of the carbanion 1 (7.1 g , 0.048 mole) of methyl iodide are slowly added; after stirring 1 h, 200 ml of dry toluene are added; ammonia is allowed to evaporate. When ambient temperature is reached 200 ml of water are added. The toluene layer is then decanted, washed, dried over anhydrous sodium sulfate and concentrated in vacuo; the oil obtained is chromatographed over a silica gel column (dichloromethane eluent) to give the product in 60% yield; mp 156°C; ^{1}H NMR: 8.45 (d, 1H, C<u>H</u>-N=), 7.15 (m, 6H, aromatic), 4.85 (q, 1H, C<u>H</u>CH$_3$ J=7Hz), 3.85 (4s, 12H, OC<u>H</u>$_3$), 1.85 (d, 3H, CHC<u>H</u>$_3$ J=7Hz).

1-[1-(3,4-Dimethoxyphenyl)-butyl] -6,7-dimethoxyisoquinoline :

The title compound is prepared as in the preceeding method, using propyl bromide instead of methyl iodide: yield 75%; mp 122°C; ^{1}H NMR: 8.45 (d, 1H, C<u>H</u>-N=), 7.15 (m, 6H, aromatic), 4.65 (t, 1H, C<u>H</u>), 3.85 (2s, 12H, OC<u>H</u>$_3$), 2.30 (m, 2H, CHC<u>H</u>$_2$), 1.30 (m, 2H, C<u>H</u>$_2$CH$_3$), 1.00 (t, 3H, CH$_3$).

1-[1-(3,4-Dimethoxyphenyl)-but-3-enyl] -6,7-dimethoxyisoquinoline :

Following the method described for methyl iodide but using allyl bromide as alkylating agent; the title compound (mp 112°C) is obtained in 70% yield. ^{1}H NMR: 8.40 (d, 1H, C<u>H</u>-N=), 7.10 (m, 6H, aromatic), 5.75 (m, 1H, CH$_2$-C<u>H</u>=), 5.00 (m, 2H, CH=C<u>H</u>$_2$), 4.70 (t, 1H, C<u>H</u>-CH$_2$), 3.85 (4s, 12H, OC<u>H</u>$_3$), 3.15 (m, 2H, >CH-C<u>H</u>$_2$-).

1-[1-(3,4-Dimethoxyphenyl)-3-ethoxycarbonylpropyl] -6,7-dimethoxyisoquinoline :

This is obtained in 70% yield using ethyl 3-bromopropionate as in the preceeding method; mp 115°C. IR (oil): 1725 cm^{-1}. ^{1}H NMR: 8.20 (d, 1H, C<u>H</u>-N=), 6.9 (m, 6H, aromatic), 4.65 (t, 1H, C<u>H</u>-CH$_2$), 4.00 (m, 2H, OC<u>H</u>$_2$), 3.75 (2s, 12H, OC<u>H</u>$_3$), 2.40 (m, 4H, C<u>H</u>$_2$C<u>H</u>$_2$), 1.20 (t, 3H, C<u>H</u>$_3$).

1-[1-(3,4-Dimethoxyphenyl)-2-(N,N-diethylaminocarbamoyl) ethyl] -6,7-dimethoxyisoquinoline :

Following the method described for methyl iodide but using N,N-diethyl-bromoacetamide as alkylating agent. Yield 90%; oil. ^{1}H NMR: 8.15 (d, 1H, C<u>H</u>-N=), 6.90 (m, 6H, aromatic), 5.30 (t, 1H, C<u>H</u>-CH$_2$), 3.65 (3s, 12H, OC<u>H</u>$_3$), 3.25 (m, 6H, C<u>H</u>$_2$), 1.10 (m, 6H, C<u>H</u>$_3$).

1-[1-(3,4-Dimethoxyphenyl)-2-(4-ethoxycarbonylpiperazinocarbonyl)-ethyl]-6,7-dimethoxyisoquinoline :

Same procedure as above but using 1-bromoacetyl-4-ethoxycarbonylpiperazine as alkylating agent. Oil. Yield 90%; IR: 1700 and 1640 cm^{-1}; ^1H NMR: 8.20 (d, 1H, C<u>H</u>-N), 6.95 (m, 6H, aromatic), 5.25 (t, 1H, C<u>H</u>-CH_2), 4.05 (q, 2H, O$C\underline{H}_2$), 3.70 (4s,12H, O$C\underline{H}_3$), 3.03 (m, 8H, N$C\underline{H}_2C\underline{H}_2$), 2.75 (q, 2H, $C\underline{H}_2$CO), 1.20 (t, 3H, $C\underline{H}_3$).

1-[1-(3,4-Dimethoxyphenyl)-3-oxo-propyl]-6,7-dimethoxyisoquinoline (8) :

This compound is obtained by the following sequence of reactions :

A/ Formation of the acetal intermediate: 1-[1-(3,4-dimethoxyphenyl)-3,3-diethoxypropyl]-6,7-dimethoxyisoquinoline.

To a solution containing 0.016 mole of the carbanion 1 described there is slowly added (5.3 g, 0.025 mole) of 2,2-diethoxy-ethyl bromide. After stirring for 1 h, 200 ml of dry toluene is added and the ammonia is allowed to escape. At ambient temperature, 200 ml of water is added and the whole is filtered over celite. The toluene solution is then decanted, washed, dried over anhydrous sulfate and concentrated. The oil obtained (9.5 g) is hydrolyzed without purification.

^1H NMR: 8.20 (d, 1H, C<u>H</u>-N=), 7.00 (m, 6H, aromatic), 4.70 (t, 1H, C<u>H</u>O), 4.25 (t, 1H, C<u>H</u>-CH_2), 3.75 (2s, 12H, O$C\underline{H}_3$), 3.30 (m, 4H, O$C\underline{H}_2$-), 2.40 (m, 2H, $C\underline{H}_2$), 1.10 (2t, 6H, $C\underline{H}_3$).

B/ Formation of the aldehyde: 1-[1-(3,4-dimethoxyphenyl)-3-oxo-propyl]-6,7-dimethoxyisoquinoline.

The compound (8.7 g, 0.014 mole) prepared in A above are hydrolyzed for 2 h at 50°C in 200 ml of 2% hydrochloric acid solution. After strong alkalisation with sodium carbonate, the mixture is extracted 3 times by 50 ml of dichloromethane. 7.25 g of an oil are obtained. Yield 95%. IR: 2730, 1715 cm^{-1} (CH=O). ^1H NMR: 9.60 (s, 1H, C<u>H</u>=O), 8.35 (d, 1H, C<u>H</u>-N=), 7.00 (m, 6H, aromatic), 5.25 (t, 1H, C<u>H</u>-CH_2), 3.80(4s, 12H, O$C\underline{H}_3$), 2.90 (m, 2H, $C\underline{H}_2$-CHO).

1-[1-(3,4-Dimethoxyphenyl)-3-hydroxypropyl]-6,7-dimethoxyisoquinoline (9) :

The compound 8 (3.8g, 0.01 mole) prepared in B above are reduced by 1 g of sodium borohydride in 40 ml of methanol. After evaporation of the solvent, water is added to hydrolyze any excess of the reducing agent and the whole is extracted with dichloromethane. The extracts are dried and the solvent evaporated to give 3.4 g (yield 90%) of the product in a white meringue like form. IR: 3250 (OH) cm^{-1}. ^1H NMR: 8.30 (d, 1H, C<u>H</u>-N=), 7.05 (m, 6H, aromatic), 5.00 (t, 1H, C<u>H</u>-CH_2), 3.80 (4s, 12H, OC<u>H</u>$_3$), 3.60 (m, 3H, C<u>H</u>$_2$-O<u>H</u>), 2.55 (m, 2H, C<u>H</u>$_2$-CH_2).

1-(3,4-Dimethoxyphenyl)-1,2,3,4-tetrahydro-9,10-dimethoxybenzo [a]-quinolizinium chloride (3) :

The carbanion 1 is treated with 1-chloro-3-iodo-propane; the oil obtained is refluxed 0.5 h in butanone and the quaternary ammonium salt is isolated. Yield 80%. mp 220°C. Anal. Calcd. for $C_{23}H_{26}NO_4Cl.H_2O$: C, 63.60; H, 6.46; N, 3.23. Found: C, 62.90, H. 6.43; N, 2.93%.

8,9-Dimethoxy-1-(3,4-dimethoxyphenyl)-pyrrolo[2,1-a]-isoquinoline (6) :

1-[1-(3,4-Dimethoxyphenyl)-3,3-diethoxypropyl]-6,7-dimethoxyisoquinoline (7 g, 0.015 mole) is refluxed at 160°C for 16 h in a mixture of 9 ml of DMF, 1.3 ml of 85% formic acid and 0.5 ml of concentrated hydrochloric acid. After evaporation under reduced pressure, the mixture is made alkaline and extracted with benzene; 4 g is obtained. Yield 71%. mp 170°C. ^1H NMR: 7.50-6.30 (m, 9H, aromatic), 3.80-3.40 (3s, 12H, OC<u>H</u>$_3$).

9,10-Dimethoxy-1-(3,4-dimethoxyphenyl)-benzo [a]-quinolizidine (4) :

The compound 3 (0.26 g, 0.6 mmole) in 10 ml of ethanol is cooled by an ice bath; 0.26 g (6.9 mmole) of sodium borohydride is in portions added. After stirring for 1 h at room temperature, removal of the solvent gave an oil which is extracted by methylene chloride after alkalization by bicarbonate solution: Yield 98% oil. ^1H NMR: 7.40-6.30 (m, 5H, aromatic), 3.80-3.70 (3s,12H, OC<u>H</u>$_3$), 3.20-1.30 (m, 12H, C<u>H</u>$_2$).

9,10-Dimethoxy-1-(3,4-dimethoxyphenyl)-2,3-dihydro-3-hydroxybenzo[a]-indolizinium perchlorate (7) :

8 (17.5 mmole) is treated by HCl 2% and stirred for 1 h 5 at 50°C. After cooling the aqueous layer is washed with benzene and concentrated under vacuo; the residue is dissolved in methylene chloride. After being dried on magnesium sulfate, the solvent was evaporated to leave a solid. Yield 3.5 g (48%). Exchange in water/methylene chloride with lithium perchlorate gave the perchlorate salt: mp 202°C. IR (νOH): 3370 cm^{-1}; ^1H NMR (DMSO-d_6): 8.45 (d, 1H, C<u>H</u>-N), 8.30 (m, 1H, OH), 8.12 (d, 1H, C<u>H</u>=C), 7.65-6.95 (m, 5H, aromatic), 6.60 (t, 1H, NC<u>H</u>OH), 5.35 (t, 1H, C<u>H</u>CH_3), 3.80 (4s,12H, O<u>CH</u>$_3$). 3.25 (m, 2H, C<u>H</u>$_2$-CHOH).

Papaveraldine:

To a stirred solution of papaverine carbanion 1 (*from 0.03 mole of papaverine*) oxygen is bubbled; after 10 min the mixture is decolorated; oxygen is bubbled 2 h more. 250 ml of toluene is added and ammonia is allowed to escape; addition of 200 ml of water gave a solid; Yield 6.5 g. Evaporation of the toluene layer gave an additionnal papaveraldine crop: Yield 3.0 g. The solid is recrystallized in ethanol: Yield 7 g (66%); mp 204°C.[4] ^1H NMR: 8.15 (m, 1H, aromatic), 7.5~6.5 (m, 6H, aromatic), 3.80 (2s,12H, O<u>CH</u>$_3$).

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