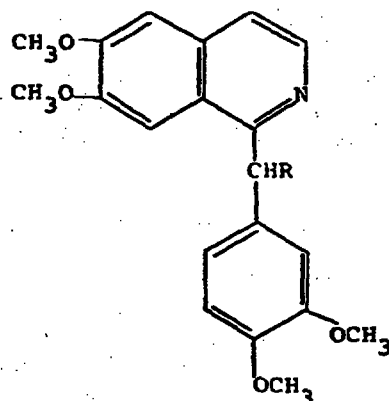


SPECIFICATION

Papaverine Carbanion

The invention relates to the carbanion of 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-isoquinoline (papaverine), a compound of ephemeral existence, and to the preparation of the same. This compound is interesting because its high reactivity opens up many possibilities for the synthesis of new compounds, particularly those of the formula:



in which R represents a straight chain, branched chain or cyclic, saturated or unsaturated hydrocarbon residue, optionally ω -substituted by an alkoxycarbonyl, hydroxy or alkylamino group, or a hydrocarbon chain bonded to the nitrogen atom of the isoquinoline ring to form, with that nitrogen atom and with the 1-C atom of the isoquinoline ring and with the α -C atom of the benzyl group, a fused ring structure.

When R stands for a negative charge⁻, the above formula represents the papaverine carbanion. According to this invention, this compound may be prepared by reacting on papaverine, in a basic solvent, a slight excess of a highly basic agent. The preferred highly basic agents are butyl lithium, a lithium alkyl amide, sodium amide or potassium amide. The preferred basic solvents are hexamethylphosphotriamide, tetrahydrofuran, dimethyl formamide or liquid ammonia.

(a) Liquid Ammonia/Sodamide Method

Into a 1 litre three-necked flask provided with stirring means and dry ice refrigeration means are successively introduced 300 ml of liquid ammonia, 0.1 g of ferric chloride acting as catalyst and 0.8 g (0.03 mole) of sodium (cf. Org Synthese Coll., Vol. 5, p. 523). The reacting mixture is stirred for 1 1/2 hours and there is then added, in small portions, 10 g (0.0295 mole) of papaverine. To complete the formation of the carbanion, the mixture is stirred for 2 hours. A red solution is obtained, for use as such in synthesis reactions, for instance those described in the Examples hereinbelow.

(b) Butyl Lithium/Hexamethylphosphotriamide Method

Into a 1 litre reactor, fitted with heating, cooling and stirring means, are poured 10 g (0.0295 mole) of papaverine and 100 ml of hexamethylphosphotriamide. Keeping the temperature at approximately 5°C, there is progressively added 18.5 ml (0.03 mole) of commercial butyl lithium in solution in hexane. After the addition is complete, stirring is continued for 1 hour at ambient temperature.

(c) Sodamide/Hexamethylphosphotriamide Method

Into the same apparatus as in method (b) above are poured 10 g (0.0295 mole) of papaverine and 30 ml hexamethylphosphotriamide. 1.2 g (0.03 mole) of sodamide are added gently under stirring; the mixture becomes red but there is no evolution of gases. The mixture is heated to 70—75°C, resulting in evolution of ammonia; stirring is continued for 3 hours until the gaseous evolution ends. The reaction mixture is cooled for use as such in synthesis reactions.

(d) Lithium Diisopropylamide/Tetrahydrofuran Method

In the same apparatus as in method (a) above, cooled by an ethanol/dry ice bath, are poured 400 ml of dry tetrahydrofuran. Lithium diisopropylamide is prepared in situ by adding dropwise at -30°C, 18.5 ml of butyl lithium (0.03 mole) dissolved in hexane; 4.2 ml (0.03 mole) of diisopropylamine are added and the mixture is stirred for 15 min at 10°C; after cooling at -40°C, 10 g (0.0295 mole) of papaverine (powder) are added and the mixture is stirred for 4 hours at -40°C.

(e) Potassium Amide/Dimethyl Formamide Method

In the same apparatus as in Example (b) above are poured 10 g (0.0295 mole) of papaverine and 35 ml of dimethyl formamide. 1.7 g (0.03 mole) of potassium amide are slowly added, under stirring.

After the end of the addition, stirring is maintained while the reacting mixture is warmed at 70°C for 3 hours and a half.

The reaction mixture is used as such, after cooling, for further syntheses.

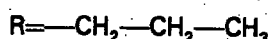
For characterization and identification of the carbanion, the oxidation reaction leading to 1-(3,4-dimethoxy-benzoyl)-6,7-dimethoxy-isoquinoline (papaveraldine) is used. Into the solution of the carbanion is bubbled for 2 1/2 hours a current of dry oxygen; then 200 ml of dry toluene is poured in and the ammonia is allowed to evaporate off. The solution is treated at ambient temperature with 200 ml of water and dried; m.p. 208°C (literature: 209—210°C).

The Examples which follow describe in detail the syntheses of various compounds starting from the carbanion by way of illustrating the usefulness thereof.

In these Examples, the thin layer chromatography (TLC) data was obtained using Merck F 254 plates; the NMR spectra were recorded on Perkin-Elmer R 24 (60 MHz) apparatus; and the IR spectra were recorded on Perkin-Elmer 257 apparatus. 'Merck' is a Trade Mark.

Example 1

15 1-[1-(3,4-dimethoxy-phenyl)-butyl]-6,7-dimethoxyisoquinoline



Method (i)

To a solution of the carbanion, obtained by the method (a) above, there is slowly added 5.8 g (0.048 mole) of propyl bromide. After stirring for 1 hour, 200 ml of dry toluene is added and the ammonia is allowed to evaporate off. At ambient temperature, 200 ml of water is added and the reaction mixture is filtered over celite. The toluene solution is then decanted, washed, dried over anhydrous sodium sulphate and concentrated. The oil obtained is chromatographed over a silica gel column (eluant dichloromethane) to give 8.4 g of crystals, m.p. 122°C. Yield 75%.

Method (ii)

Of course the title compound may also be prepared from the carbanion obtained by methods other than method (a) above. For instance, its preparation from the carbanion obtained by method (c) above is now given.

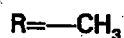
To a solution of the carbanion, obtained by the method (c), 5.8 g (0.048 mole) of propyl bromide are slowly added. After stirring overnight at room temperature, 200 ml of an 10% ammonium chloride aqueous solution are added and the mixture is extracted with benzene (2 x 100 ml). The benzene solutions were separated, washed with water, dried over anhydrous sodium sulphate and concentrated. The oil obtained is chromatographed over 150 g of silica gel (eluant dichloromethane) to give 6.9 g of crystals, m.p. 122°C. Yield 60%.

NMR (CDCl₃)

δppm: 8.45 (d, 1H, CH—N=); 7.15 (m, 6H, aromatic protons); 4.65 (t, 1H, CH—CH₂CH₂CH₃); 3.85 (m, 12H, OCH₃); 2.3 (m, 2H, CH—CH₂); 1.3 (m, 2H, —CH₂—CH₃); 1 (t, 3H, CH₃—CH₂).

Example 2

1-[1-(3,4-dimethoxy phenyl)-ethyl]-6,7-dimethoxyisoquinoline



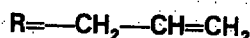
The title compound is prepared following the methods (i) and (ii) described in Example 1, but using methyl iodide as alkylating agent instead of propyl bromide. The product is obtained in 60% yield by method (i), in 70% yield by method (ii) and melts at 156°C.

NMR (CDCl₃)

δppm: 8.45 (d, 1H, CH—N=); 7.15 (m, 6H aromatic protons); 4.85 (q, 1H, CH—CH₃, J=7Hz); 3.85 (m, 12H, OCH₃); 1.85 (d, 3H, CH—CH₃, J=7 Hz).

Example 3

1-[1-(3,4-dimethoxy phenyl)-but-3-enyl]-6,7-dimethoxyisoquinoline



Following the method (i) described in Example 1, but using allyl bromide as alkylating agent in place of propyl bromide, the title compound (m.p. 112°C) is obtained in 70% yield.

δppm: 8.40 (d, 1H, CH—N=); 7.10 (m, 6H, aromatic protons); 5.75 (m, 1H, CH₂—CH=CH₂); 5.00 (m, 2H, CH=CH₂); 4.70 (t, 1H, >CH—CH₂—); 3.85 (m, 12H, OCH₃); 3.15 (m, 2H, >CH—CH₂—CH=).

Example 4**1-[1-(3,4-dimethoxy-phenyl)-heptyl]-6,7-dimethoxyisoquinoline**

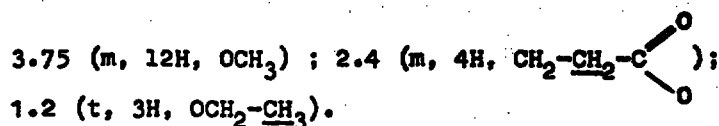
Operating as in method (ii) of Example 1, but substituting *n*-hexyl iodide for the propyl bromide, the title compound (m.p. 110°C) is obtained in 60% yield.

Example 5**1-[1-(3,4-dimethoxy-phenyl)-3-ethoxycarbonyl-propyl]-6,7-isoquinoline**

Using ethyl ω -bromo-propionate in place of propyl bromide, but otherwise following the method (i) described in Example 1, gives the title compound in 70% yield m.p. 115°C.

NMR (CCl₄)

δ ppm: 8.20 (d, 1H, CH—N=); 6.9 (m, 6H, aromatic protons); 4.65 (t, 1H, CH—CH₂); 4 (q, 2H, OCH₂—CH₃);



IR (KBr)

$\nu_{\text{cm}^{-1}}$: 1730 (C=O)

Example 6**1-[(1-(3,4-dimethoxy-phenyl)-4-hydroxy-butyl)-6,7-dimethoxy-isoquinoline**

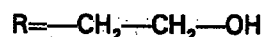
4.4 g (0.01 mole) of 1-[1-(3,4-dimethoxy-phenyl)-but-3-enyl]-6,7-dimethoxy-isoquinoline, prepared as described in Example 3, are refluxed for 2 hours in a suspension of 2 g of lithium aluminium hydride in tetrahydrofuran. Water is added to hydrolyse any excess reducing agent, and the water/alcohol mixture is then extracted with dichloromethane. The extracts are dried and the dichloromethane is evaporated off to give 3.5 g (yield 90%) of product, melting at 115°C.

IR (KBr)

$\nu_{\text{cm}^{-1}}$: 3350 (OH)

NMR (CDCl₃)

δ ppm: 8.30 (d, 1H, CH—N=); 7.05 (m, 6H, aromatic protons); 4.6 (t, 1H, CH); 3.8 (m, 12H, OCH₃); 3.6 (m, 2H, CH₂—OH); 2.75 (1H, OH); 2.35 (m, 2H, CH₂—CH₂—CH₂); 1.65 (m, 2H, CH—CH₂).

Example 7**1-[1-(3,4-dimethoxy-phenyl)-3-hydroxy-propyl]-6,7-dimethoxy-isoquinoline**

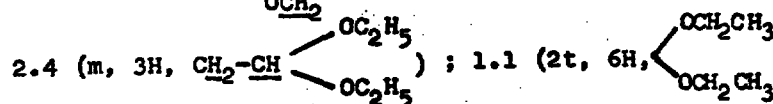
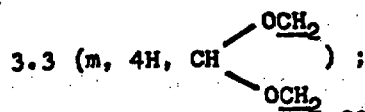
This compound is obtained by the following sequence of reactions.

A. Formation of the Acetal Intermediate: 1-[1-(3,4-dimethoxy-phenyl)-3,3-diethoxy-propyl]-6,7-dimethoxy-isoquinoline

To a solution containing 0.016 mole of the carbanion obtained by one of the methods described above there is slowly added 5.3 g (0.025 mole) of 2,2-diethoxy-ethyl bromide. After stirring for 1 hour, 200 ml of dry toluene is added and the ammonia is allowed to evaporate off. At ambient temperature, 200 ml of water is added and the whole is filtered over Celite. 'Celite is a Trade Mark'. The toluene solution is then decanted, washed, dried over anhydrous sodium sulphate and concentrated. The oil obtained (9.5 g) is hydrolysed without purification.

NMR (CCl₄)

δppm: 8.20 (d, 1H, CH=N=); 7 (m, 6H, aromatic protons); 4.25 (t, 1H, CH—CH₂); 3.75 (m, 12H, OCH₃);



B. Formation of the Aldehyde: 1-[1-(3,4-dimethoxy-phenyl)-3-oxo-propyl]-6,7-dimethoxy-isoquinoline

8.7 g (0.014 mole) of the compound prepared in A above are hydrolysed for 2 hours at 50°C in 200 ml of 2% hydrochloric acid solution. After strong alkalinisation, with Na₂CO₃, the mixture is

extracted 3 times by 50 ml of dichloromethane.

7.25 g of an oil are obtained: Yield 95%.

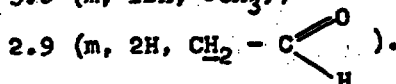
IR

νcm⁻¹: 2730, 1715 (CH=O)

NMR (CDCl₃)

δppm: 9.6 (s, 1H, CH=O); 8.35 (d, 1H, CH=N=); 7 (m, 6H, aromatic protons); 5.25 (t, 1H, CH);

3.8 (m, 12H, OCH₃);



C. Reduction of the Aldehyde

3.8 g (0.01 mole) of the compound prepared in B above are reduced by 1 g of sodium borohydride in 40 ml of methanol. After evaporation off of the solvent, water is added to hydrolyse any excess of the reducing agent and the whole is extracted with dichloromethane. The extracts are dried and the solvent evaporated off to give 3.4 g (yield 90%) of the product in a white meringue like form.

IR

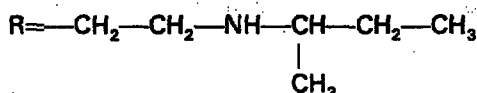
νcm⁻¹: 3250 (OH)

NMR (CDCl₃)

δppm: 8.3 (d, 1H, CH=N=); 7.05 (m, 6H, aromatic protons); 5 (t, 1H, CH—CH₂); 3.8 (m, 12H, OCH₃); 3.6 (m, 3H, CH₂—OH); 2.55 (m, 2H, CH₂—CH₂).

Example 8

1-[1-(3,4-dimethoxy-phenyl)-3-(1-methyl-propylamino)-propyl]-6,7-dimethoxy-isoquinoline



13 g of the aldehyde obtained as described in Example 7B above, 2.5 g of 1-methyl-propylamine and 120 ml of ethanol are stirred for 30 minutes over 1 g of molecular sieve at ambient temperature. The mixture is cooled to 0°C and 3 g of sodium borohydride is added. The mixture is stirred overnight at ambient temperature and worked-up as described in Example 7C to give 11.2 g of a yellow oil. This is dissolved in 100 ml of isopropanol and 25.4 ml of 1N hydrochloric acid (1 equivalent) are added to form the hydrochloride. The hydrochloride solution is concentrated to dryness and the residue is taken up in isopropanol and recrystallized therefrom to give 6.3 g of product. m.p. 246°C.

TLC (methanol/acetone/hydrochloric acid 90/10/4)

Rf=0.5 | spot

NMR (base) (CDCl₃)

δppm: 8.45 (d, 1H, =CH=N=); 7.3—7.5 (m, 2H, aromatic protons); 6.15—7 (m, 4H, aromatic protons); 4.85 (m, 1H, >CH—CH₂); 3.95 (s, 6H, OCH₃); 3.75 (s, 6H, OCH₃); 2.1—3 (m, 5H); 1.1—1.6 (m, 3H of which 1H is exchangeable NH); 0.7—1 (m, 6H).

Example 9

1-(3,4-dimethoxy-phenyl)-1,2,3,4-tetrahydro-9,10-dimethoxy-benzo(a) quinolizinium Chloride



terminating on the isoquinoline nitrogen atom.

The carbanion is treated with 1-bromo-3-iodopropane following the method (ii) described in Example 1. The oil obtained is refluxed in acetone and the quaternary ammonium salt is isolated in 80% yield, m.p. 220°C.

5	Elemental analysis $C_{23}H_{28}NO_4Cl \cdot H_2O$ (433.5)				5
	calc.	C% 63.6	H% 6.46	N% 3.23	
	found	62.9	6.43	2.93	

Example 10

1-(3,4-dimethoxy-phenyl)-8,9-dimethoxy-benzo(g) Indolizine



- 10 terminating on the isoquinoline nitrogen atom. 10
 7 g (0.0154 mole) of 1-[1-(3,4-dimethoxy-phenyl)-3,3-diethoxy-propyl]-6,7-dimethoxy-isoquinoline, prepared as described in Example 7A, are refluxed at 160°C for 16 hours in a mixture of 9 ml of dimethylformamide, 1.3 ml of 85% formic acid and 0.5 ml concentrated hydrochloric acid. After the reaction mixture has been concentrated under reduced pressure, it is made alkaline and extracted
 15 with benzene. 4 g of the title product are obtained, equivalent to a yield of 71.5%; m.p. 170°C. 15

NMR ($CDCl_3$)

δ ppm: 6.30—7.50 (m, 9H, aromatic protons); 3.40—3.80 (m, 12H, OCH_3).

Elemental analysis $C_{22}H_{21}NO_4$ (364)

20	calc.	C% 72.7	H% 5.78	N% 3.85	20
	found	72.60	5.97	3.82	

Example 11

1-[1-(3,4-dimethoxy-phenyl)-3-amino-propyl]-6,7-dimethoxy-isoquinoline



- 25 This compound can be prepared starting from the product of Example 7B (hereinafter called "the aldehyde") by three different routes. 25

a) Direct Route by Reductive Amination

- 12 g of the aldehyde are added to a cooled solution of 100 ml of ethanol saturated by ammonia and the mixture is put in a hydrogenation autoclave with 1 g of Raney nickel. Operation in under a pressure of 90 atmospheres. The solution is filtered and the solvent is evaporated off. The product is
 30 obtained in mediocre yield because the hydrogenation under pressure also affects the isoquinoline nucleus. The following two methods lead, on the other hand, to excellent yields. 30

b) Oxime Route

- 7.6 g (0.02 mole) of the aldehyde, 60 ml of water and 60 ml of ethanol are refluxed for 1 1/2 hours in a 250 ml flask with 2 g of soda and 4.2 g of hydroxylamine hydrochloride. The solvents are
 35 then evaporated off and the residue is taken up in dichloromethane and washed with water. 6.4 g (80% yield) of 1-[1-(3,4)-dimethoxy-phenyl]-3-hydroxyimino-propyl]-6,7-dimethoxy-isoquinoline is obtained. 35

NMR ($CDCl_3$)

δ ppm: 8.3 (d, 1H, $CH=N$); 7.05 (m, 7H, aromatic protons and $CH=N$); 4.9 (m, 1H, $CH-CH_2$); 3.8 (m, 13H, OCH_3 and OH); 3.05 (m, 2H, CH_2).

- 40 The reduction of this oxime by lithium aluminium hydride or its catalytic hydrogenation or its chemical reduction lead to the desired compound with good yields (85% to 95%). 40

NMR ($CDCl_3$)

δ ppm: 8.45 (d, 1H, $CH=N$); 7.1 (m, 6H, aromatic protons); 4.8 (t, 1H, $CH-CH_2$); 3.85 (m, 12H, OCH_3); 2.45 (m, 4H, CH_2CH_2-N); 1.5 (m, 2H, NH_2).

- 45 The dimaleate is formed in ethanol. m.p. 130°C. anhydrous content by titration: 98%. 45

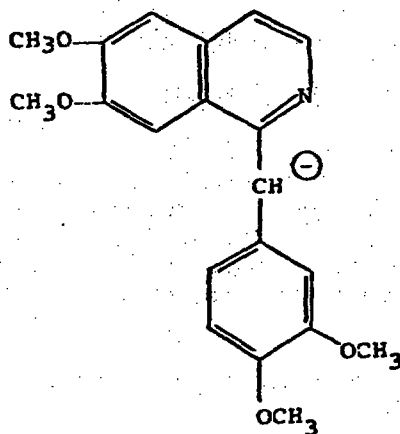
c) Debenzylation Route

- 1-[1-(3,4-dimethoxy-phenyl)-3-benzylamino-propyl]-6,7-dimethoxy-isoquinoline obtained as
 50 described in Example 6 of my British Patent Application No. 8,023,760 (filed herewith) is treated as follows: 50

In a hydrogenation flask there is put 5.1 g (0.01 mole) of the aforesaid compound in 150 ml of ethanol and 1 g of 10% palladium-on-charcoal. Hydrogenation is carried out at 50°C for 3 hours. The catalyst is filtered off and the solvent is evaporated off under reduced pressure. After alkalisation, 3.75 g (90% yield) of an oil is extracted with dichloromethane.

5 Claims

1. A carbanion of papaverine having the formula



in solution in a basic solvent.

2. A process for the preparation of the papaverine carbanion claimed in Claim 1, the process comprising reacting on papaverine, in a basic solvent, a slight excess of a highly basic agent.

3. A process according to Claim 2 wherein the highly basic agent is butyl lithium, a lithium alkyl amide, sodium amide or potassium amide.

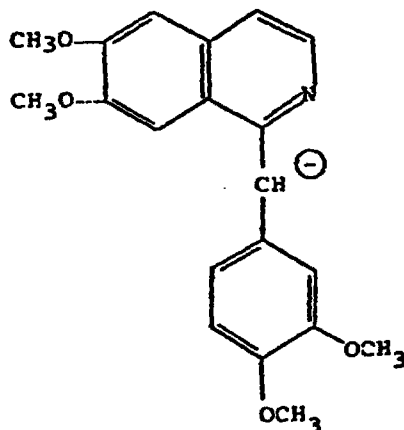
4. A process according to Claim 2 or Claim 3 wherein the basic solvent is hexamethylphosphotriamide, tetrahydrofuran, dimethyl formamide or liquid ammonia.

In a hydrogenation flask there is put 5.1 g (0.01 mole) of the aforesaid compound in 150 ml of ethanol and 1 g of 10% palladium-on-charcoal. Hydrogenation is carried out at 50°C for 3 hours. The catalyst is filtered off and the solvent is evaporated off under reduced pressure. After alkalisation, 3.75 g (90% yield) of an oil is extracted with dichloromethane.

5 Claims

1. A carbanion of papaverine having the formula

5



in solution in a basic solvent.

2. A process for the preparation of the papaverine carbanion claimed in Claim 1, the process comprising reacting on papaverine, in a basic solvent, a slight excess of a highly basic agent.

3. A process according to Claim 2 wherein the highly basic agent is butyl lithium, a lithium alkyl amide, sodium amide or potassium amide.

4. A process according to Claim 2 or Claim 3 wherein the basic solvent is hexamethylphosphotriamide, tetrahydrofuran, dimethyl formamide or liquid ammonia.

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