PATENT SPECIFICATION (11) 1 563 745

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(21) Application No. 25326/77 (22) Filed 16 Jun. 1977 (19)

(31) Convention Application No. 51/073789 (32) Filed 24 Jun. 1976 in

(33) Japan (JP)

(44) Complete Specification Published 26 Mar. 1980

(51) INT. CL.[3] C07D 221/26
A61K 31/435

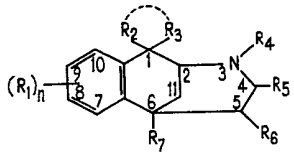
(52) Index at Acceptance
C2C 1173 1174 1175 1504 1531 1539
1672 200 211 213 214 215 220
221 225 226 227 22Y 246 247 250
251 253 255 25Y 29X 29Y 302 305
30Y 311 313 31Y 337 338 340 34Y
351 355 364 365 366 368 36Y 37X
386 388 43X 491 509 50Y 623 624
628 634 637 644 658 65X 662 665
672 678 67X 697 70Y 774 776 77X
77Y 802 80Y AA BE BL KA UL WE
WL ZF ZH ZL

(54) METHANOBENZAZOCINE DERIVATIVES AND PROCESS FOR PREPARING THE SAME

(71) We, CHUGAI SEIYAKU KABUSHIKI KAISHA, a Japanese body corporate of No. 5-1, 5-chome, Ukima, Kita-ku, Tokyo, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:-

This invention relates to methanobenzazocine derivatives.

The invention provides benzazocine derivatives represented by the formula



(I)

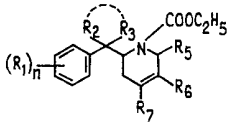
wherein R_1 is hydrogen, halogen, hydroxyl, acyloxyl, C_1 to C_4 alkyl, C_1 to C_4 alkoxy or methylenedioxy; n is an integer of from 1 to 4; R_2 and R_3 are independently C_1 to C_4 alkyl or are bonded to each other directly or through oxygen to represent an alicyclic or heterocyclic ring containing 3 to 6 members; R_4 is hydrogen, C_1 to C_6 alkyl which may have a substituent selected from cycloalkyl, phenyl or benzoyl optionally having one or more substituents, or C_1 to C_6 alkenyl which may have phenyl as a substituent; R_5 and R_6 are independently hydrogen or C_1 to C_4 alkyl; and R_7 is C_1 to C_4 alkyl or phenyl.

The invention also provides salts of such derivatives.

Each of the derivatives represented by Formyula (I) and the salts thereof is novel and has high analgesic action and therefore it is useful for use in drugs. Thus, the invention also provides pharmaceutical compositions which comprise either a derivative of the invention or a salt thereof, in association with a pharmacologically acceptable carrier.

The compound represented by Formula (I) may be prepared, for example, by

(a) hydrolyzing a compound represented by the formula



(II)

wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined above under an alkaline condition to remove its ethoxycarbonyl radical and cyclizing the hydrolisate by the action of a mineral acid, or

(b) making a mineral acid act on a compound represented by Formula (II) to have hydrolisis and cyclization take place simultaneously thereby giving a compound (III) represented by Formula (I) wherein R_4 is hydrogen.

(c) Furthermore, the compound (III) may be prepared by making boron trifluoride etherate act on a compound represented by Formula (II) in the absence of a solvent to give a compound (IV) represented by Formula (I) wherein R_4 is $COOC_2H_5$ in a substantially quantitative amount and then making hydrogen bromide in acetic acid act on the compound (IV) whereby the hydrolisis can be easily effected to give the compound (III).

The compound (III) may be reacted with an alkyl or alkenyl halide to give various compounds represented by Formula (I)

(e) The compound represented by Formula (I) may be prepared by hydrolizing the compound of Formula (II) to remove it ethoxycarbonyl radical and then alkylating and cyclizing the hydrolyzed compound.

In effecting the procedure (a), the hydrolysis of the compound of Formula (II) may be carried out in the presence of a strong base such as sodium hydroxide, potassium hydroxide or the like in a dipolar solvent such as ethylene glycol, diethylene glycol, dipropylene glycol or the like at a temperature of from 100°C to the boiling point of the solvent used for 1-5 hours. The cyclization may be carried out by refluxing the reactant in an aqueous solution of a mineral acid such as hydrogen bromide, hydrogen iodide, phosphoric acid or polyphosphoric acid with or without an organic acid such as acetic acid or propionic acid for 1-15 hours.

In the procedure (b), the cyclization may be carried out in the same manner as in (a).

In effecting the procedure (c), the substantially quantitative cyclization may be carried out by heating a compound of Formula (II) at a temperature of from room temperature to the boiling point of the solvent to be used, more preferably from 50 to 100°C for 1-5 hours in the presence of a boron halide such as boron trifluoride etherate, boron trifluoride, boron trichloride or boron tribromide with or without using a solvent such as benzene, toluene or methylene chloride.

For the compound of Formula (II) wherein $(R_1)_n$ is methylenedioxy, the cyclization may be preferably effected by using a cyclization accelerator such as *p*-toluene sulfonic acid in an inert solvent such as benzene or toluene. The compound (IV) obtained according to the procedure (c) may, of course, be hydrolized as in the procedure (a) to give the compound (III).

In order to prepare a compound represented by Formula (I) wherein R_4 is not hydrogen from the compound (III) wherein R_4 is hydrogen, the following procedure (d), (f) or (g) is used.

(d) The reactant is reacted with a halide represented by the formula

$$R'_4X$$

wherein R'_4 is the same as R_4 except that it is not hydrogen and X in halogen is aprotic dipolar solvent such as dimethylformamide or dimethyl sulfoxide in the presence of an alkaline substance such as potassium carbonate, sodium bicarbonate or sodium hydroxide at a temperature of from room temperature to the boiling point of the solvent to be used, preferably 100-150°C for 1-6 hours while stirring.

(f) The reactant is reacted with a carboxylic acid of the formula

$$R'½COOH$$

wherein R'_4 is as defined above or its reactive derivative such as acid halide or mixed acid anhydride under the conditions for a conventional amide-formation reaction and then the resulting corresponding N-acyl compound is reduced in a conventional manner.

(g) The reactant is reacted with an aldehyde represented by the formula

$$R'_4CHO$$

wherein R'_4 is as defined above in an organic solvent such as methanol, ethanol, chloroform or acetic acid at room temperature or at an elevated temperature on a water bath and then reduced with a metal hydride such as sodium borohydride or sodium borocyanohydride.

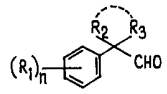
Furthermore, in order to prepare the compound represented by the formula (I), without forming the compound (III) as an intermediate, the procedure (e) may be used. This procedure may be effected by reacting the hydrolyzed compound produced by the procedure (a) with a halide in the same manner as in the procedure (d) and cyclyzing the resulting compound as in the procedure (a).

In order to obtain the compound represented by the formula (I) wherein R_4 is CH_3, it may be prepared in situ by the procedure (h), namely, by suspending or dissolving a metal

hydride such as lithium laminium hydride, sodium alminium hydride or sodium bismethoxyethoxy aluminium hydride in an inert solvent such as ethyl ether, tetrahydrofuran, benzene or toluene and adding dropwise the compound (IV) to the suspension or solution to react it at a temperature of from −10°C to the boiling point of a solvent used, preferably room temperature to 100°C, for 10 minutes to several hours to give the compound of Formula (I) wherein R_4 is CH_3.

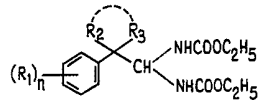
Alternatively, the compound of Formula (I) wherein R_4 is methyl may be prepared by the procedure (i), namely, by treating the compound of Formula (II) instead of the compound (IV) to convert its N-ethoxycarbonyl radical to N-methyl radical and then cyclizing the N-methyl compound to give the compound of Formula (I) wherein R_4 is methyl.

The compound of formula (II) which is also novel can be prepared, for example, by refluxing a compound represented by the formula



(V)

wherein R_1, R_2, R_3 and n are as defined above with urethane in an inert solvent such as benzene or toluene in the presence of a catalytic amount of acid such as boron trifluoride etherate or *p*-toluene sulfonic acid to give the compound represented by the formula



(VI)

wherein R_1, R_2, R_3 and n are as defined above, adding dropwise a butadiene derivative solution represented by the formula

$$R_5 - CH = \overset{R_6}{\underset{|}{C}} - \overset{R_7}{\underset{|}{C}} = CH_2 \qquad \text{(VII)}$$

wherein R_5, R_6 and R_7 are as defined above to a solution of the compound (VI) in an inert solvent such as benzene or toluene while mildly refluxing and after the completion of the addition, heating the mixture to reflux.

The resulting object compound (I) according to this invention has asymmetric carbon atoms and is present as racemate. However, the racemate can be easily subjected to optical resolution in a conventional manner with the use of a natural acid such as quinic acid, tartaric acid, malic acid, camphoric acid, camphorsulfonic acid or mandelic acid.

The compound (I) can be converted to its mineral acid addition salt such as hydrochloride, sulfate, hydrobromide or phosphate or its organic acid addition salt such as malonate, lactate, malate or acetate.

Each of the compounds represented by Formula (I) is novel and has an excellent analgesic action resembling that of morphine. Further, since it produces no or only a minor degree of levallorphan antagonism and physical dependence, it is very useful for use in drugs.

The present invention will be further illustrated by the following Experiments and Examples, but they are given for illustrative purposes only and are not to be construed as limiting the scope of this invention.

Experiment 1

Analgesic Activities

The compounds of this invention, each of which was used in the form of hydrochloride or lactate, or morphine.HCl (a comparative standard drug) were subcutaneously administered to male mice of ddY strain, 4 weeks old (10 mice/dosage level) and 45 min later, the analgesic activity was determined by the following methods. Each drug was administered at three different dosage levels.

(1) *Acetic Acid Writhing Method* (Koster, R. *et al.*, Fed. Proc., *18*, 412, 1959)

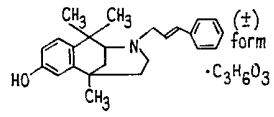
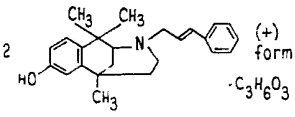
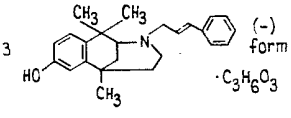
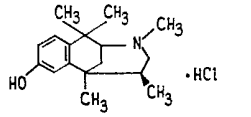
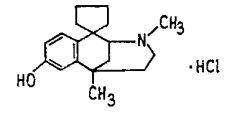
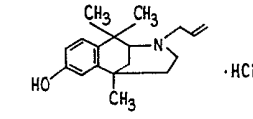
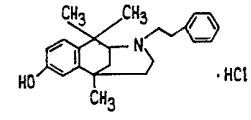
Each mouse was intraperitoneally administered with 0.6% acetic acid saline solution and 5 min later the number of writhing syndromes occurring was counted for 5 min.

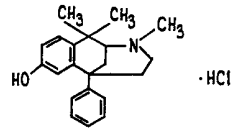
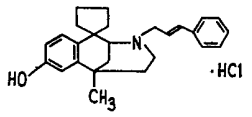
The dose of test drug that decreased the number of writhing syndromes to half that of control mice was calculated graphically and defined as ED (effective dose).

(2) *Haffner Method* (Green, A.F. *et al.*, Brit. J. Pharmcol. *6*, 572, 1951)
The base of mouse's tail was pressed by a dull edged bakelite bar and the pressure loaded on the tail that made the mouse squeak was measured by a mercurymanometer.
The dose of test drug that increased the squeaking pressure to twice that of control mice was calculated graphically and defined as ED (effective dose).

(3) *Hot Plate Method* (Takagi, K. *et al.*, Yakugaku Zasshi (in Japanese), *77*, 871, 1957)
Drug-administered mice were placed on a hot plate of 55°C and the time until they jumped was measured individually.
The dose of test drug that increased the time to jump to twice that of control mice was calculated graphically and defined as ED (effective dose).
Results obtained are shown in Table 1.

Table 1

TEST COMPOUNDS	ACETIC ACID METHOD	HAFFNER METHOD	HOT PLATE METHOD
1  (±) form $\cdot C_3H_6O_3$	1·1	1·1	1·2
2  (+) form $\cdot C_3H_6O_3$	–	–	9·0
3  (-) form $\cdot C_3H_6O_3$	0·6	0·6	0·8
4.  $\cdot$HCl	10·5	9·1	8·2
5.  $\cdot$HCl	1·8	1·8	2·1
6.  $\cdot$HCl	7·1	4·5	6·0
7.  $\cdot$HCl	10·5	10·0	15·1

8.		7·3	8·8	11·5
9.		2·5	2·7	4·0
10.	Pentazocine · $C_3H_6O_3$	20·0	7·0	9·6
11.	Morphine · HCl	0·6	0·6	0·8

Remarks: the figures show ED (mg/kg; subcutaneous injection)

Experiment 2
Levallorphan Antagonism and Physical Dependence

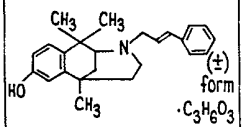
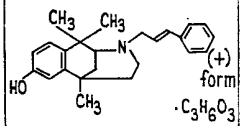
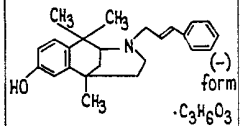
(1) *Levallorphan Antagonism* (Blumberg, H. *et al.*, Proc. Soc. Exp. Biol. Med., *123*, 755, 1966)

Male mice of ddY strain, 4 weeks old, were used. The compounds of this invention, each of which was used in the form of loctate, or morphine·HCl were subcutaneously administered to mice. Thirty minutes later, the mice were injected subcutaneously with 10 mg/kg of levellorphan. Antagonism by levallorphan to analgesic effect of test compounds was then determined by acetic acid writhing method 15 min after injection with levallorphan.

(2) *Physical Dependence* (Lorenzetti O.J. *et al.*, Arch. Int. Pharmacodyn., *183*, 391, 1970; Hosoya, H. *et al.*, Folia Pharmcol. Jap., *53*, 120p, 1957; Hosoya, H. *et al.*, Yakuri to Chiryo (in Japanese), *2*, 1235, 1974)

Male rats of Sprague Dawlay strain, 5 weeks old, were used. The compounds of this invention or morphine·HCl were subcutaneously administered twice a day for 3 weeks. The administration was started on Thursday, but was withdrawn every Sunday. The daily dose of the test compound was increased weekly (i.e. 20 mg/kg/day for the 1st week, 40 mg/kg/day for the 2nd week and 60 mg/kg/day for the 3rd week). The physical dependence was evaluated in terms of the decrease in the body weight on the day following the day of withdrawal (Sunday) and in terms of the decrease in the body weight induced by 10 mg/kg of levallorphan on the day following the final administration of the test compound.

Results obtained are shown in Table 2.

TEST COMPOUNDS	LEVALLORPHAN ANTAGONISM FOR MOUSE (ACETIC ACID METHOD)	CONTINUOUS ADMINISTRATION (3 WEEKS) FOR RATS	
		WEIGHT REDUCTION BY DISCONTINUOUS ADMINISTRATION	WEIGHT REDUCTION BY LEVALLORPHAN ANTAGONISM
 (±) form $\cdot C_3H_6O_3$	++	+	++
 (+) form $\cdot C_3H_6O_3$	−	−	−
 (−) form $\cdot C_3H_6O_3$	+	−	+
Morphino· HCl	+++	+++	+++

Remarks: The symbol (−) shows no effect.
The symbols (+), (++) and (+++) show the degree of effect in an increasing order.

Example 1

(1) 2-(4-Methoxyphenyl)-2-methylpropanal-1 (70g) and urethane (73g) were dissolved in benzene (500 ml), and after the addition of 1 ml of boron trifluoride etherate, the mixture was refluxed for 5 hours with a reflux condenser equipped with a water separater. After cooling, the reaction mixture was washed several times with water and then two times with a saturated sodium bicarbonate aqueous solution and dried over potassium carbonate. After removal of benzene, the residue was recrystallized from chloroformhexane to obtain 108 g of 1,1-bis(ethoxycarbamino)-2-(4-methoxyphenyl)-2-methylpropane as colorless needles. (m.p.: 127-128°C)

Analysis:
Calcd. for $C_{17}H_{26}O_5N_2$: C, 60.34;H, 7.74; N, 8.28 (%)
Found : C, 60.13; H, 7.85; N, 8.34 (%)

(2) The resulting 1,1-bis(ethoxycarbamino)-2-(4-methoxy-phenyl)-2-methylpropane (67.2 g) and boron trifluoride etherate (30 ml) were dissolved in dried benzene (500 ml). Isoprene (15 g) dissolved in 50 ml of dried benzene was added dropwise to the solution over one hour while mildly refluxing and the mixture was refluxed for 3 hours while stirring. After cooling, the reaction mixture was washed several times with water and then washed two times with a saturated sodium bicarbonate aqueous solution and dried over potassium carbonate. After removal of benzene, the residue was further distilled under reduced pressure to obtain 49 g of 1-ethoxycarbonyl-1,2,3,6-tetrahydro-2-[1-(4-methoxyphenyl)-1-methylethyl]-4-methylpyridine as a light yellow syrup. (b.p.: 158-160°C/0.5 mmHg)

Analysis:
Calcd. for $C_{19}H_{27}O_3N$: C. 71.89; H, 8.57; N, 4.41 (%)
Found : C, 71.95; H, 8.85; N, 4.60 (%)

(3) 1-Ethoxycarbonyl-1,2,3,6-tetrahydro-2-[1-(4-methoxyphenyl)-1-methylethyl]-4-methylpyridine (3.17 g) dissolved in 10 ml of dried tetrahydrofuran was added dropwise to a suspension of 0.9 g of lithium aluminium hydride in 5 ml of dried tetrahydrofuran while stirring under cooling with ice and then the mixture was refluxed for 30 minutes. After cooling, water-containing ether (150 ml) and then 10 ml of a 30% sodium hydroxide aqueous solution was added dropwise to the mixture while stirring under cooling with ice. An diethyl ether-tetrahydrofuran layer was decanted and combined with the diethyl ether

portions with which the remaining matter had been washed. The combined liquid was dried over potassium carbonate, stripped of the solvent and distilled under reduced pressure to obtain 2.1 g of 1,2,3,6-tetrahydro-2-[1-(4-methoxyphenyl)-1-methylethyl]-1,4-dimethylpyridine as a colorless viscous mass. (b.p.: 115-117°C/0.4 mmHg)

Analysis:

Calcd. for $C_{17}H_{25}ON$: C, 78.71; H, 9.72; N, 5.40 (%)

Found : C, 78.81; H, 10.14; N, 5.45 (%)

(4) A mixture of 2.6 g of 1,2,3,6-tetrahydro-2-[1-(4-methoxyphenyl)-1-methylethyl]-1,4-dimethylpyridine, 30 ml of 47% hydrobromic acid and 10 ml of acetic acid was refluxed for 12 hours while stirring. After cooling, the reaction mixture was made alkaline with concentrated ammonia water under cooling and then extracted with chloroform. The extract was washed with water, dried over sodium sulfate, stripped of chloroform, and recrystallized from chloroform-hexane to obtain 2.0 g of 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,3,6-tetramethyl-3-benzazocine as pale orange cubes. (m.p.: 182-184°C)

Analysis:

Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71 (%)

Found : C, 78.44; H, 9.49; N, 5.61 (%)

(5) The resulting product in the form of free base was dissolved in diethyl ether and to the solution was added a saturated hydrogen chloride in diethyl ether to render the precipitation in the form of its hydrochloride. The precipitated crystals were recovered by the filtration and then recrystallized from methanol-ethyl ether to obtain reddish brown prisms. (m.p.: 270-272°C)

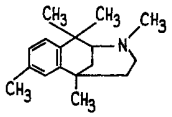
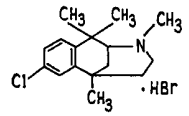
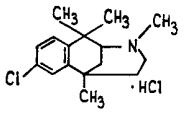
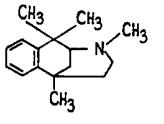
Analysis:

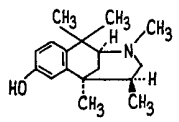
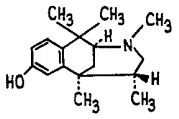
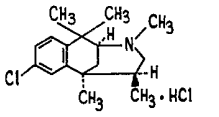
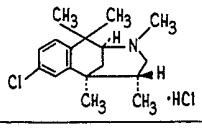
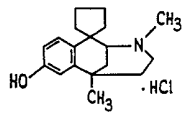
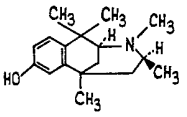
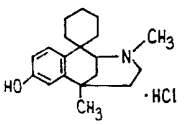
Calcd. for $C_{16}H_{24}ONCl$: C, 68.19; H, 8.58; N, 4.97 (%)

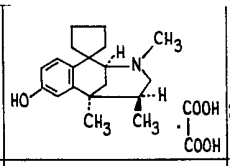
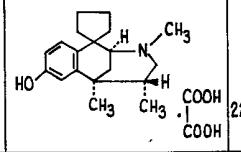
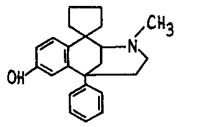
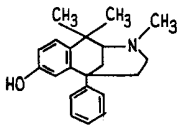
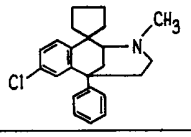
Found : C, 67.89; H, 8.73; N, 4.94 (%)

The following compounds shown in Table 3 were prepared in a manner similar to that described above.

Table 3

NO.	COMPOUNDS	APPEARANCE MELTING POINT (°C) OR BOILING POINT (°C/mmHg)	ANALYSIS: CALCD.: C(%); H(%); N(%) FOUND: C(%); H(%); N(%)
1.		COLOURLESS SYRUP 103 - 105/0.4	$C_{17}H_{25}N$ 83.89 10.35 5.76 83.80 10.21 5.73
2.	COMPOUND 1 (HYDROCHLORIDE)	COLOURLESS NEEDLES ABOVE 260 (SUBLIMABLE)	$C_{17}H_{26}NCl$ 72.96 9.36 5.01 73.00 9.40 5.00
3.		COLOURLESS PRISMS 253 - 254	$C_{16}H_{22}NCl \cdot HBr$ 55.75 6.73 4.06 55.56 6.74 3.80
4.		COLOURLESS PRISMS ABOVE 250 (SUBLIMABLE)	$C_{16}H_{23}NCl_2$ 64.00 7.72 4.66 63.85 7.70 4.60
5.		PALE YELLOW SYRUP 100 - 102/0.8	$C_{16}H_{23}N$ 83.78 10.11 6.11 83.81 10.32 6.05

6	COMPOUND 5 (HYDROCHLORIDE) MONOHYDRATE	COLOURLESS PLATES ABOVE 250 (SUBLIMABLE)	$C_{16}H_{24}NCl \cdot H_2O$ 67·70 9·23 4·93 67·90 9·49 5·21
7.		PALE RED NEEDLES 187 – 189	$C_{17}H_{25}ON$ 78·71 9·72 5·40 78·83 9·96 5·51
8.	COMPOUND 7 (OXALATE)	YELLOW GRANULES ABOVE 250 (SUBLIMABLE)	$C_{19}H_{27}O_5N$ 65·31 7·79 4·01 65·24 8·07 4·06
9.		PALE BROWN GRANULES 147 – 148	$C_{17}H_{25}ON$ 78·71 9·72 5·40 78·75 9·86 5·40
10.	COMPOUND 9 (OXALATE)	PALE BROWN GRANULES 228(DECOMPOSITION)	$C_{19}H_{27}O_5N$ 65·31 7·79 4·01 65·33 7·99 4·14
11.		COLOURLESS GRANULES 247(DECOMPOSITION)	$C_{17}H_{25}NCl_2 \cdot 1/2H_2O$ 63·15 8·11 4·33 63·10 8·13 4·35
12.		COLOURLESS NEEDLES ABOVE 230 (SUBLIMABLE)	$C_{17}H_{25}NCl_2$ 64·96 8·02 4·46 64·69 8·04 4·40
13.		PALE RED GRANULES 253(DECOMPOSITION)	$C_{18}H_{26}ONCl$ 70·22 8·51 4·55 69·99 8·55 4·45
14.		COLOURLESS PRISMS 164 – 165	$C_{17}H_{25}ON$ 78·71 9·72 5·40 78·79 9·69 5·43
15.	COMPOUND 14 (OXALATE)	COLOURLESS GRANULES 233(DECOMPOSITION)	$C_{19}H_{27}O_5N$ 65·31 7·79 4·01 65·18 7·74 3·96
16		PALE GREEN PRISMS 285(DECOMPOSITION)	$C_{19}H_{28}ONCl$ 70·90 8·77 4·35 70·69 8·90 4·41

17.		COLOURLESS PRISMS 243 (DECOMPOSITION)	$C_{21}H_{29}O_5N$ 67·18 7·79 3·73 67·15 8·01 3·75
18.		PALE BROWN GRANULES 223 (DECOMPOSITION)	$C_{21}H_{29}O_5N$ 67·18 7·79 3·73 67·05 8·00 3·78
19.		PALE BROWN GRANULES 112 (DECOMPOSITION)	$C_{23}H_{27}ON$ 82·84 8·16 4·20 82·80 8·15 4·15
20.	COMPOUND 19 (HYDROCHLORIDE)	PALE RED PRISMS 283 - 286	$C_{23}H_{28}ONCl$ 74·68 7·63 3·79 74·43 7·78 3·75
21.	COMPOUND 19 (OXALATE)	PALE BROWN GRANULES ABOVE 250 (SUBLIMABLE)	$C_{25}H_{29}O_5N$ 70·90 6·90 3·31 70·71 6·85 3·14
22.		COLOURLESS NEEDLES 210 - 212	$C_{21}H_{25}ON$ 82·04 8·20 4·56 82·00 8·15 4·59
23.	COMPOUND 22 (HYDROCHLORIDE)	COLOURLESS NEEDLES 282 (DECOMPOSITION)	$C_{21}H_{26}ONCl$ 73·34 7·62 4·07 73·31 7·71 3·97
24.		COLOURLESS NEEDLES 254 - 256	$C_{23}H_{27}NCl_2$ 71·13 7·01 3·61 71·01 7·16 3·60

Example 2

A mixture of 1-ethoxycarbonyl-1,2,3,6-tetrahydro-2-[1-(4-chlorophenyl)-1-methylethyl]-4-methylpyridine (14.5 g), sodium hydroxide (15 g) and diethylene glycol (150 ml) was refluxed for 5 hours. After cooling, water was added to the reaction mixture and the resulting mixture was extracted with benzene. The extract was washed with water and dried over potassium carbonate. After removal of benzene, the residue was distilled under reduced pressure to obtain 10.7 g of a colorless viscous mass of 2-[1-(4-chlorophenyl)-1-methylethyl]-1,2,3,6-tetrahydro-4-methylpyridine. (m.p.: 136-138°C/0.6 mmHg)

The product (6.5 g) was dissolved in 40 ml of 47% hydrobromic acid and refluxed for 10 hours. After cooling, the reaction mixture was alkalized with concentrated ammonia water and extracted with benzene. The extract was dried over potassium carbonate and distilled to remove benzene. The residue was fed into a silica gel column chromatograph and eluted with chloroform-methanol (100:1). The solvent was distilled off from the eluant to obtain 3.3 g of 8-chloro-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6-trimethyl-3-benzazocine as a colorless viscous mass.

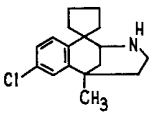
The product was treated as in Example 1-(5) to give the corresponding hydrochloride as

colorless needles having a melting point above 250°C (sublimable) as colorless needles.

Analysis:
Calcd. for $C_{15}H_{21}NCl_2$: C, 62.94; H, 7.39; N, 4.89 (%)
Found : C, 62.68; H, 7.27; N, 5.04 (%)

The following two compounds were prepared in the same manner as above.

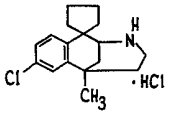
(i)



Colorless syrup
b.p. 140-143°C/0.5 mmHg
Analysis: for $C_{17}H_{22}NCl$

	C	H	N
Calcd.:	74.03	8.04	5.08 (%)
Found ;	73.84	8.23	4.97 (%)

(ii)



Colorless needles
m.p. above 280°C (sublimable)
Analysis: for $C_{17}H_{23}NCl_2$

	C	H	N
Calcd.:	65.38	7.42	4.49 (%)
Found :	65.52	7.57	4.47 (%)

Example 3

A mixture of 1-ethoxycarbonyl-1,2,3,6-tetrahydro-4-methyl-2-[1-methyl-1-(4-methylphenyl)ethyl] pyridine (4.2 g) and 40 ml of 47% hydrobromic acid was refluxed for 10 hours while stirring. After cooling, the mixture was made alkaline with a 10% sodium hydroxide aqueous solution and extracted with benzene. The extract was dried over potassium carbonate and benzene was distilled off. The residue was distilled under reduced pressure to give 3.0 g of 1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6,8-tetramethyl-3-benzazocine as colorless oil. (b.p.: 107-109°C/0.3 mmHg)

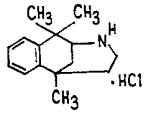
Analysis:
Calcd. for $C_{16}H_{23}N$: C, 83.73; H, 10.11; N, 6.11 (%)
Found : C, 83.55; H, 10.11; N, 6.00 (%)

The product was treated as in Example 1-(5) to obtain the corresponding hydrochloride having a melting point above 250°C (sublimable) as colorless prisms.

Analysis:
Calcd. for $C_{16}H_{24}NCl$: C, 72.29; H, 9.10; N, 5.27 (%)
Found : C, 72.46; H, 9.11; N, 5.02 (%)

The following two compounds were prepared in the same manner as above.

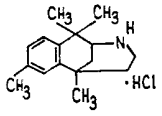
(i)



Colorless fine needles
m.p. above 290°C (sublimable)
Analysis: for $C_{15}H_{22}NCl$

	C	H	N
Calcd.:	71.55	8.81	5.56 (%)
Found :	71.30	8.65	5.22 (%)

(ii)



Pale brown prisms
m.p. above 250°C (sublimable)
Analysis: for $C_{16}H_{24}NCl$

	C	H	N
Calcd.;	72.29	9.10	5.27 (%)
Found :	72.46	9.11	5.02 (%)

Example 4

(1) A mixture of 1-ethoxycarbonyl-1,2,3,6-tetrahydro-2-[1-(4-methoxyphenyl)-1-methylethyl]-4-methylpyridine (6.34 g) and boron trifluoride etherate (10 ml) was maintained at a temperature ranging from 70 to 80°C for 4 hours while stirring. After cooling, ice-water was added to the reaction mixture and then the mixture was extracted with benzene. The extract was washed three times with water and then two times with a saturated sodium bicarbonate aqueous solution and dried over potassium carbonate. After removal of benzene, the residue was further distilled under reduced pressure to obtain 6 g of 3-ethoxycarbonyl-1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-1,1,6-trimethyl-3-

benzazocine as a pale yellow syrup. (b.p.: 162-164°C/0.7 mmHg)

Analysis:

Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57; N, 4.41 (%)

Found : C, 72.12; H, 8.64; N, 4.51 (%)

(2) A mixture of the resulting product, 3-ethoxycarbonyl-1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-1,1,6-trimethyl-3-benzazocine (30 g), 47% hydrobromic acid (80 ml) and acetic acid (80 ml) was refluxed for 2 hours while stirring. After cooling, the reaction mixture was made alkaline with a concentrated ammonia water while cooling with ice and the resulting precipitate was recovered by the filtration, dried with air and recrystallized from methanol to obtain 16.3 g of 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine as colorless granules. (m.p.: 255-257°C)

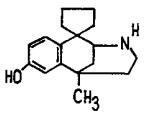
Analysis:

Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05 (%)

Found : C, 77.62; H, 9.15; N, 6.15 (%)

The following compounds were prepared in the same manner as above.

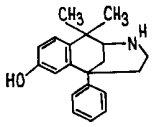
(i)



Colorless granules
m.p. 254-256°C
Analysis: for $C_{17}H_{23}ON$

	C	H	N
Calcd.:	79.33	9.01	5.44 (%)
Found :	79.30	9.15	5.30 (%)

(ii)



Colorless granules
m.p. 257-259°C
Analysis: for $C_{20}H_{23}ON$

	C	H	N
Calcd.:	81.87	7.90	4.77 (%)
Found :	81.78	7.82	4.80 (%)

Example 5

(1) A mixture of 1(1-ethoxycarbonyl-1,2,3,6-tetrahydro-4-methylpyridine-2-yl)-1-(4-chlorophenyl) cyclopentane (6.8 g) and 47% hydrobromic acid (60 ml) was heated to reflux for 10 hours while stirring. After cooling, the reaction mixture was made alkaline with a 10% sodium hydroxide aqueous solution and extracted with benzene. The extract was dried over potassium carbonate and distilled to remove benzene. The residue was further distilled under reduced pressure to obtain 4.1 g of 8-chloro-1,2,3,4,5,6-hexahydro-2,6-methano-6-methyl-3-benzazocine-1-spiro-1'-cyclopentane as colorless oil.
(b.p.: 140-143°C/0.5 mmHg)

Analysis:

Calcd. for $C_{17}H_{22}NCl$: C, 74.03; H, 8.04; N, 5.08 (%)

Found : C, 73.84; H, 8.13; N, 4.97 (%)

The resulting product was treated as in Example 1-(5) to obtain the corresponding hydrochloride as colorless fine needles having a melting point above 270°C and being sublimable (after recrystallization from methanol-diethyl ether).

Analysis:

Calcd. for $C_{17}H_{23}NCl$: C, 65.38; H, 7.42; N, 4.49 (%)

Found : C, 65.62; H, 7.57; N, 4.47 (%)

(2) The resulting product, 8-chloro-1,2,3,4,5,6-hexahydro-2,6-methano-6-methyl-3-benzazocine-1-spiro-1'-cyclopentane (4 g) was dissolved in 40 ml of methanol and to the solution was added 5 ml of 37% aqueous formaldehyde and then 0.7 g of sodium borohydride was slowly added under cooling with ice while stirring. After further stirring the mixture at room temperature for one hour, the solvent was distilled off from the mixture and the residue, after adding water, was extracted with benzene. The extract was dried over potassium carbonate and distilled to remove benzene to obtain 4.1 g of 8-chloro-1,2,3,4,5,6-hexahydro-2,6-methano-3,6-dimethyl-3-benzazocine-1-spiro-1'-cyclopentane as colorless oil. The product was further treated as in Example 1-(5) to obtain the corresponding hydrochloride as colorless fine needles having a melting point above 270°C and being sublimable after recrystallization from methanolethyl ether.

Analysis:

Calcd. for $C_{18}H_{25}NCl_2$: C, 66.25; H, 7.72; N, 4.29 (%)

Found : C, 66.46; H, 7.74; N, 4.38 (%)

Example 6

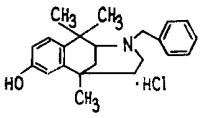
A mixture of 1,2,3,6-tetrahydro-2-[1-(4-methoxyphenyl)-1-methyethyl]-4-methylpyridine (2.9 g), pentyl iodide (2.34 g), potassium carbonate (3 g) and dimethylformamide (20 ml) was heated to reflux for 4 hours while stirring. After cooling and adding water, the reaction product was extracted with benzene. The extract was washed twice with water, dried over potassium carbonate and distilled to remove benzene to obtain 2.8 g of 1,2,3,6-tetrahydro-1-pentyl-2-[1-(4-methoxyphenyl)-1-methylethyl]-4-methylpyridine as a viscous mass. To the mass was added 20 ml of 47% hydrobromic acid and the mixture was heated to reflux for 10 hours while stirring, after cooling, made alkaline with a concentrated ammonia water under cooling and extracted with chloroform. The extract was dried over sodium sulfate and distilled to remove chloroform. The residue was fed to a column chromatograph on silica gel and eluated with chloroform. Chloroform was distilled off from the elute to obtain 2.2 g of 1,2,3,4,5,6-hexahydro-8-hydroxy-3-pentyl-2,6-methano-1,1,6-trimethyl-3-benzazocine as a viscous mass. The product was treated as in Example 1-(5) to obtain the corresponding hydrochloride as colorless fine needles having a melting point above 230°C (sublimable) after the recrystallization from methanolethyl ether.

Analysis:

Calcd. for $C_{20}H_{32}ONCl$: C, 71.08; H, 9.54; N, 4.14 (%)
Found : C, 69.95; H, 9.58; N, 4.36 (%)

The following compounds were prepared in a manner similar to that described above.

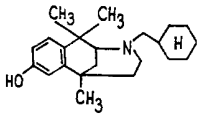
(i)



Pale brown granules
m.p. 257-260°C
Analysis: for $C_{22}H_{28}ONCl$

	C	H	N
Calcd.:	73.83	7.89	3.91 (%)
Found :	73.92	8.00	4.05 (%)

(ii)



Pale brown needles
m.p. above 250°C
Analysis: for $C_{22}H_{33}ON \cdot CHCl_2$

	C	H	N
Calcd.:	61.98	7.66	3.13 (%)
Found :	62.02	7.89	3.41 (%)

Example 7

A mixture of 2.5 g of 1-ethoxycarbonyl-1,2,3,6-tetrahydro-2-[1-methyl-1-(3,4,5-trimethoxyphenyl)ethyl]-4-methylpyridine, 1.4 g of para-toluene sulfonic acid hydrate and 50 ml of dried benzene was heated to reflux for 2 hours while stirring and, after cooling, washed twice with water and once with a saturated sodium bicarbonate aqueous solution and then dried over potassium carbonate. Benzene was distilled off from the reaction mixture to obtain 2.5 g of 3-ethoxycarbonyl-1,2,3,4,5,6-hexahydro-2,6-methano-7,8,9-trimethoxy-1,1,6-trimethyl-3-benzazocine. The product was dissolved in 20 ml of tetrahydrofuran and the solution was added dropwise to a suspension of 0.8 g of lithium aluminium hydride in 5 ml of tetrahydrofuran while stirring under cooling with ice, followed by refluxing for 30 minutes. After cooling, to the mixture was added 100 ml of ethyl ether containing water while stirring under cooling with ice to decompose excess lithium aluminium hydride and then was added a 10% sodium hydroxide aqueous solution. The supernatant was recovered by the decantation and combined with the remaining residue after it had been washed with diethyl ether. The mixture was dried over potassium carbonate and distilled to remove the solvent to obtain 2.0 g of viscous mass. The mass was purified through column chromatograph on silica gel and then recrystallized from diethyl ether to obtain 1 g of 1,2,3,4,5,6-hexahydro-2,6-methano-7,8,9-trimethoxy-1,1,3,6-tetramethyl-3-benzazocine as colorless needles. (m.p.: 68-70°C)

Analysis:

Calcd. for $C_{19}H_{29}O_3N$: C, 71.44; H, 9.15; N, 4.39)%)
Found : C, 71.58; H, 9.24; N, 4.30 (%)

The product obtained above was treated as in Example 1-(5) to obtain the corresponding hydrochloride as colorless silky needles.
(m.p.: 265-267°C, (foaming upon melting)

Analysis:

Calcd. for $C_{19}H_{30}O_3NCl$: C, 64.12; H, 8.50; N, 3.94 (%)
Found : C, 64.00; H, 8.50; N, 3.82 (%)

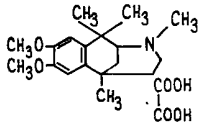
Example 8

A mixture of 5.0 g of 1-(1-ethoxycarbonyl-1,2,3,6-tetrahydro-4-methylpyridine-2-yl)-1-(4-methoxyphenyl)cyclopropane and 11 ml of boron trifluoride etherate was heated to 70°C for 3.5 hours while stirring and, after cooling, extracted with benzene. The extract was washed three times with ice-water and then twice with a saturated sodium bicarbonate aqueous solution, dried over potassium carbonate and distilled to remove benzene to obtain 4.2 g of residue. The residue was treated as in Example 7 by the use of 1.2 g of lithium aluminium hydride to obtain 1.8 g of 1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-3,6-dimethyl-3-benzazocine-1-spiro-1'-cyclopropane. The produce was treated as in Example 1-(5) to obtain the corresponding hydrochloride as pale brown needles. (m.p.: 266-268°C)

Analysis:
Calcd. for $C_{11}H_{24}ONCl$: C, 69.49; H, 8.23; N, 4.77 (%)
Found : C, 69.30; H, 8.14; N, 4.65 (%)

The following compounds were prepared in the manner disclosed above.

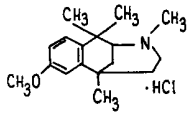
(i)



Colorless granules
m.p. 240-242°C (foaming upon melting)
Analysis: for $C_{20}H_{29}O_6N$

	C	H	N
Calcd.:	63.30	7.70	3.69 (%)
Found :	63.16	7.72	3.82 (%)

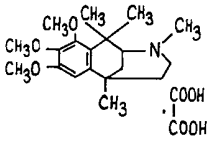
(ii)



Colorless prisms
m.p. 251-253°C
Analysis: for $C_{17}H_{26}ONCl$

	C	H	N
Calcd.:	69.01	8.86	4.73 (%)
Found :	69.12	9.02	4.60 (%)

(iii)



Colorless needles
m.p. 265°C (decomposition)
Analysis: for $C_{21}H_{31}O_7N$

	C	H	N
Calcd.:	61.59	7.63	3.42 (%)
Found :	61.38	7.62	3.43 (%)

Example 9

(1) 4-(1-Ethoxycarbonyl-1,2,3,6-tetrahydro-4-methylpyridine-2-yl)-4-(4-methoxyphenyl)-tetrahydropyran (4.2 g) was treated as in Example 8 to obtain 3.4 g of 1,2,3,4,5,6-hexahydro-2,6-methano-8-methoxy-3,6-dimethyl-3-benzazocine-1-spiro-4'-tetrahydropyran as colorless prisms. (m.p.: 149-150°C; after recrystallization from methanol)

Analysis:
Calcd. for $C_{19}H_{27}O_2N$: C, 75.71; H, 9.03; N, 4.65 (%)
Found : C, 75.68; H, 9.22; N, 4.80 (%)

(2) The product in the form of a base was dissolved in ethyl ether and to the solution was added a saturated solution of oxalic acid in ethyl ether to form precipitates. The precipitates were recrystallized from methanol-ethyl ether to obtain the corresponding oxalate as colorless plates. (m.p.: 253°C (decomposition))

Analysis:
Calcd. for $C_{21}H_{29}O_6N$: C, 64.43; H, 7.47; N, 3.58 (%)
Found : C, 64.62; H, 7.63; N, 3.79 (%)

(3) A mixture of the product obtained in (1) above (1 g) and pyridine hydrochloride (20 g) was refluxed on a bath having a temperature of 200°C for 30 minutes while stirring. After cooling, water was added to the reaction mixture and then the mixture was made alkaline with ammonia and extracted with benzene. The extract was thoroughly washed with water, dried over potassium carbonate and distilled to remove benzene. Ethanol and toluene were added to the residue and distilled to remove pyridine with the added solvents. The residue was purified through a column chromatograph on silica gel to obtain 0.5 g of 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-3,6-dimethyl-3-benzazocine-1-spiro-4'-tetrahydropyran as a glassy mass. The product was treated as in (2) above to obtain the corresponding oxalate as pale brown needles.
(m.p.: 247°C (decomposition))

Analysis:
Calcd. for $C_{20}H_{27}O_6N$: C, 63.64; H, 7.21; N, 3.71 (%)
Found ; C, 63.65; H, 7.43; N, 3.68 (%)

Example 10

1-Ethoxycarbonyl-1,2,3,6-tetrahydro-2-[1-methyl-1-(3,4-methylene-dioxyphenyl)ethyl]-4-methylpyridine (2.9 g) was cyclized and reduced by the use of 2.0 g *p*-toluenesulfonic acid monohydrate, 55 ml of dried benzene and 0.7 g of lithium aluminium hydride as in Example 7 and recrystallized from chloroform-hexane to obtain 1,2,3,4,5,6-hexahydro-2,6-methano-1,1,3,6-tetramethyl-8,9-methylenedioxy-3-benzazocine as colorless needles. (m.p. 156-158°C)

Analysis:
Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12 (%)
Found : C, 74.85; H, 8.43; N, 5.09 (%)

The resulting product was treated as in Example 1-(5) to obtain the corresponding hydrochloride monohydrate. (m.p.: 264-266°C)

Analysis:
Calcd. for $C_{17}H_{24}O_2NCl$: C, 62.28; H, 7.99; N, 4.27 (%)
Found ; C, 62.36; H, 7.86; N, 4.11 (%)

Example 11

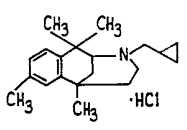
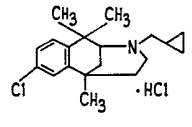
A mixture of 1 g of 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine, 0.66 g of cinnamyl chloride, 0.3 g of sodium iodide, 1 g of potassium carbonate and 20 ml of dimethylformamide was refluxed for 3 hours while stirring and, after cooling and adding water, extracted with benzene. The extract was washed twice with water, dried over potassium carbonate and distilled to remove benzene. The residue was fed to a column chromatograph on silica gel and the fraction eluted by a solvent of chloroform or chloroform-methanol (100:1) was collected. By distillating off the solvent from the fraction, 1.3 g of reddish brown viscous mass was obtained. A small amount of diethyl ether was added to the mass and the mixture was allowed to stand to deposit crystals. The crystals were recovered by filtration and recrystallized from chloroform-hexane to obtain 3-cinnamyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3,benzazocine as pale yellow plates. (m.p.: 86-88°C)

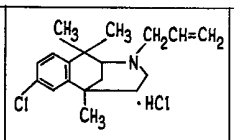
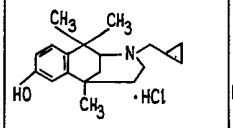
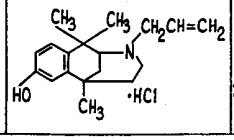
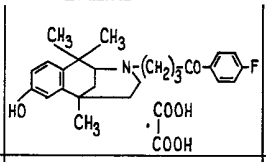
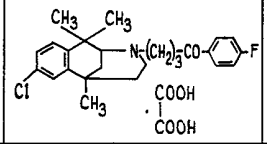
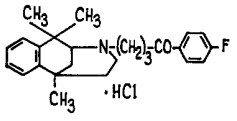
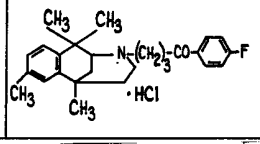
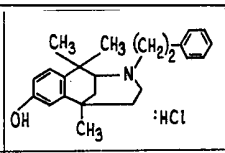
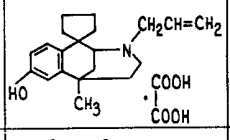
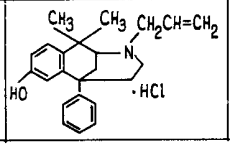
Analysis:
Calcd. for $C_{24}H_{29}ON$: C, 82-95; H, 8.41; N, 4.03 (%)
Found : C, 82.81; H, 8.53; N, 4.00 (%)

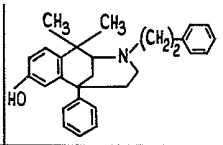
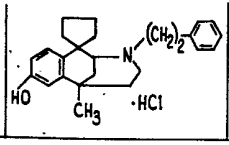
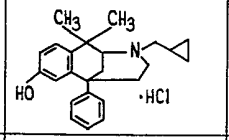
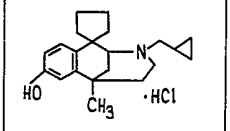
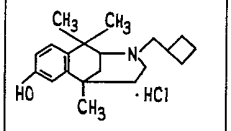
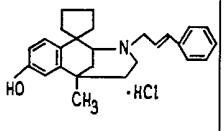
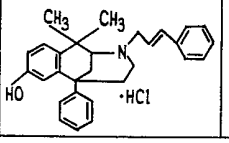
The product in the form of free base was dissolved in methanol followed by adding a saturated hydrogen chloride solution in ethyl ether. The deposited crystals were recovered by the filtration and recrystallized from methanol-ether to obtain the corresponding hydrochloride as pale yellow needles.
(m.p.: 188°C (decomposition))

Analysis
Calcd. for $C_{24}H_{30}ONCl \cdot 1/2H_2O$: C, 73.35; H, 7.95; N, 3.56 (%)
Found : C, 73.40; H, 7.93; N, 3.60 (%)

The following compounds shown in Table 4 were prepared in the same manner as above.

NO.	COMPOUNDS	APPEARANCE MELTING POINT (°C) OR BOILING POINT (°C/mmHg)	ANALYSIS.: CALCD.: C(%); H(%); N(%) FOUND: C(%); H(%); N(%)
1.		COLOURLESS PLATES ABOVE 230 (SUBLIMABLE)	$C_{20}H_{30}NCl$ 75·09 9·45 4·38 74·99 9·40 4·53
2.		COLOURLESS NEEDLES ABOVE 230 (SUBLIMABLE)	$C_{19}H_{27}NCl_2$ 67·05 8·00 4·11 66·89 8·04 4·27

3.		COLOURLESS NEEDLES ABOVE 230 (SUBLIMABLE)	$C_{18}H_{25}NCl_2$ 66·25 7·72 4·29 66·41 7·87 4·06
4.		COLOURLESS GRANULES 197(DECOMPOSITION)	$C_{19}H_{28}ONCl \cdot H_2O$ 67·14 8·90 4·12 67·40 9·10 4·18
5.		COLOURLESS LEAVES 237(DECOMPOSITION)	$C_{18}H_{26}ONCl$ 70·22 8·51 4·55 70·01 8·45 4·63
6.		PALE YELLOW PRISMS 120 (DECOMPOSITION)	$C_{27}H_{32}O_6NF$ 66·79 6·64 2·88 67·00 6·70 2·99
7.		COLOURLESS GRANULES 214 (DECOMPOSITION)	$C_{27}H_{31}O_5NFCl$ 64·34 6·20 2·78 64·26 6·18 2·89
8.	COMPOUND 7 (HYDROCHLORIDE)	COLOURLESS PRISMS 196 - 198	$C_{25}H_{30}ONFCl_2$ 66·66 6·71 3·11 66·86 6·50 3·34
9.		COLOURLESS GRANULES 223 - 225	$C_{25}H_{31}ONFCl$ 72·18 7·51 3·37 72·23 7·61 3·53
10.		COLOURLESS NEEDLES 201 - 203	$C_{26}H_{32}NOFCl$ 72·62 7·74 3·26 72·65 7·72 3·47
11.		COLOURLESS PLATES 233 - 253	$C_{23}H_{30}ONCl$ 74·27 8·13 3·76 74·25 8·13 3·72
12.		PALE BROWN PRISMS 205 (DECOMPOSITION)	$C_{22}H_{29}O_5N$ 68·19 7·54 3·62 68·28 7·60 3·58
13.		COLOURLESS NEEDLES 210 (CHANGED TO RED)	$C_{23}H_{28}ONCl$ 74·68 7·63 3·79 74·47 7·65 3·79

14.		COLOURLESS NEEDLES 117 - 119	$C_{28}H_{31}ON \cdot 1/4CHCl_3$ 79·48 7·38 3·08 79·40 7·40 3·00
15.	COMPOUND 14 (HYDROCHLORIDE)	COLOURLESS PLATES 205 (DECOMPOSITION)	$C_{28}H_{32}ONCl \cdot H_2O$ 74·40 7·58 3·10 74·43 7·51 3·22
16.		COLOURLESS NEEDLES 256 - 258	$C_{25}H_{32}ONCl$ 75·45 8·10 3·52 75·28 8·24 3·64
17.		PALE BROWN NEEDLES 278 - 281	$C_{24}H_{29}ON \cdot HCl$ 75·08 7·88 3·65 74·92 8·00 3·69
18.		COLOURLESS PLATES 276 - 278	$C_{21}H_{30}ONCl$ 72·49 8·69 4·03 72·70 8·90 4·16
19.		COLOURLESS PRISMS 253 - 255	$C_{20}H_{30}ONCl \cdot H_2O$ 67·87 9·11 3·95 67·69 9·23 3·92
20.		COLOURLESS PRISMS 247 (DECOMPOSITION)	$C_{26}H_{32}ONCl \cdot 1/2H_2O$ 74·53 7·94 3·34 74·71 7·93 3·19
21.		PALE BROWN PRISMS 269 - 272	$C_{29}H_{32}ONCl$ 78·09 7·23 3·14 77·97 7·39 3·18

Example 12

A mixture of 9.5 g of 1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,3,6-tetramethyl-3-benzazocine which is the product of Example 1-(4) and 40 ml of acetic anhydride was held at 80°C for 4 hours and then distilled under reduced pressure on a bath having a temperature of 50°C to remove acetic anhydride and acetic acid. The residue was extracted with benzene and the extract was washed several times with a sodium bicarbonate aqueous solution and dried over sodium sulfate. The distillation off of benzene from the extract gave 8.9 g of 8-acetoxy-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,3,6-tetramethyl-3-benzazocine as a viscous mass. The product was treated as in Example 9-(2) and recrystallized from acetone-diethyl ether to obtain the corresponding oxalate as colorless granules. (m.p.: 161°C(decomposition))

Analysis:
Calcd. for $C_{20}H_{27}O_6N$: C, 63.64; H, 7.21; N, 3.71)%)
Found : C, 63.48; H, 7.16; N, 3.62 (%)

Example 13

(1) 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine

(17.32 g) and 14.4 g of D-(−)-quinic acid were dissolved in 150 ml of 70% aqueous ethanol at an elevated temperature and the solution was allowed to stand at room temperature to deposit colorless fine crystals. The crystals were recovered by filtration, washed with a small amount of ethanol and recrystallized from 90% aqueous ethanol to obtain 12.5 g of prisms having a melting point of from 250-252°C. The crystals (11.5 g) was dissolved in 100 ml of 50% aqueous ethanol and the solution was made alkaline with concentrated ammonia water and allowed to stand in a refrigerator overnight to deposit crystals. The crystals were recovered by filtration and recrystallized from methanolchloroform to obtain 6.0 g of (−)-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine as colorless prisms having a melting point above 290°C.

Analysis:
Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05 (%)
Found : C, 77.69; H, 9.14; N, 6.25 (%)

$[\alpha]_D^{20} = -30.6°$ (C=1, methanol)

(2) The filtrate in the last step of (1) above was allowed to stand in a refrigerator overnight to deposit colorless cubes. The crystals were separated out by filtration and recrystallized from ethanol to obtain 9.8 g of colorless granules. (m.p.: 236-238°C) The crystals were dissolved in 100 ml of 50% aqueous ethanol and the solution was made alkaline with concentrated ammonia water and allowed to stand in a refrigerator overnight to deposit crystals. The crystals were separated out by filtration, and recrystallized from methanol-chloroform to obtain 4.5 g of (+)-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine as colorless prisms. (having a melting point above 290°C)

Analysis:
Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05 (%)
Found : C, 77.82; H, 9.23; N, 6.24 (%)

$[\alpha]_D^{20} = +30.5°$ (C=1, methanol)

(3) A mixture of 2.31 g of (−)-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine (the product according to (1) above), 1.53 g of cinnamyl chloride, 0.5 g of sodium iodide, 2.0 g of potassium carbonate and 50 ml of dimethyl formamide was heated to reflux for 2 hours. After cooling, ice water was added to the reaction mixture and then extracted with benzene. The extract was washed twice with benzene, dried over potassium carbonate and distilled to remove benzene. The residue was dissolved in ethanol and to the solution was added HCL-ethanol to deposit crystals. The crystals were recovered by filtration and recrystallized from methanol-ethanol to obtain 2.8 g of (−)-3-cinnamyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine hydrochloride as colorless needles. (m.p.: 237-239°C)

Analysis:
Calcd. for $C_{24}H_{30}ONCL$: C, 75.07; H, 7.87; N, 3.65; Cl, 9.23 (%)
Found : C, 75.16; H, 7.94; N, 3.82; Cl, 9.22 (%)

$[\alpha]_D^{20} = -30.2°$ (C=1, methanol)

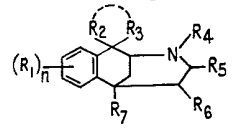
(4) The product of (2), (+) -1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine (2.31 g) and cinnamyl chloride (1,53 g) were treated as in (3) above to obtain 2.9 g of (+) -3-cinnamyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine hydrochloride as colorless needles. (m.p.: 237-239°C)

Analysis:
Calcd. for $C_{24}H_{30}ONCL$: C, 7507; H, 7.87; N, 3.65; Cl, 9.23 (%)
Found : C, 75.26; H, 8.17; N, 3.88; Cl, 9.29 (%)

$[\alpha]_D^{20} = +29.8°$ (c=1, methanol)

WHAT WE CLAIM IS:-

1. A methanobenzazocine derivative represented by the formula



wherein R_1 is hydrogen, halogen, hydroxyl, acyloxyl, C_1 to C_4 alkyl, C_1 to C_4 alkoxy or methylenedioxy; n is an integer of from 1 to 4; R_2 and R_3 are independently C_1 to C_4 alkyl or are bonded to each other directly or through oxygen to represent an alicyclic or heterocyclic ring containing 3 to 6 members; R_4 is hydrogen, C_1 to C_6 alkyl which may have a substituent selected from cycloalkyl, phenyl or benzoyl optionally having one or more substituents; or C_1 to C_6 alkenyl which may have phenyl as a substituent; R_5 and R_6 are independently hydrogen or C_1 to C_4 alkyl; and R_7 is C_1 to C_4 alkyl or phenyl.

2. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-1,1,3,6-tetramethyl-3-benzazocine.
3. 1,2,3,4,5,6-Hexahydro-2,6-methano-1,1,3,6,8-pentamethyl-3-benzazocine.
4. 8-Chloro-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,3,6-tetramethyl-3-benzazocine.
5. 1,2,3,4,5,6-Hexahydro-2,6-methano-1,1,3,6-tetramethyl-3-benzazocine.
6. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-1,1,3,5,6-pentamethyk-3-benzazocine.
7. 8-Chloro-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,3,5,6-pentamethyl-3-benzazocine.
8. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,6-dimethyl-3-benzazocine-1-spiro-1'-cyclopentane.
9. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-1,1,3,4,6-pentamethyl-3-benzazocine.
10. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,6-dimethyl-3-benzazocine-1-spiro-1'-cyclopropane.
11. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,5,6-trimethyl-3-benzazocine-1-spiro-1'-cyclopentane.
12. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3-methyl-6-phenyl-3-benzazocine-1-spiro-1'-cyclopentane.
13. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-1,1,3-trimethyl-6-phenyl-3-benzazocine.
14. 8-Chloro-1,2,3,4,5,6-hexahydro-2,6-methano-3-methyl-6-phenyl-3-benzazocine-1-spiro-1'-cyclopentane.
15. 8-Chloro-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6-trimethyl-3-benzazocine.
16. 8-Chloro-1,2,3,4,5,6-hexahydro-2,6-methano-6-methyl-3-benzazocine-1-spiro-1'-cyclopentane.
17. 1,2,3,4,5,6-Hexahydro--2,6-methano-1,1,6,8-tetramethyl-3-benzazocine.
18. 1,2,3,4,5,6-Hexahydro-2,6-methano-1,1,6-trimethyl-3-benzazocine.
19. 1,2,3,4,5,6-Hexahydro-2,6-methano-1,1,6,8-tetramethyl-3-benzazocine.
20. 1,2,3,4,5,6-Hexahydro--8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine.
21. 1,2,3,4,5,6-Hexahydro--8-hydroxy-2,6-methano-6-methyl-3-benzazocine-1-spiro-1'-cyclopentane.
22. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-1,1-dimethyl-6-phenyl-3-benzazocine.
23. 8-Chloro-1,2,3,4,5,6-hexahydro-2,6-methano-6-methyl-3-benzazocine-1-spiro-1'-cyclopentane.
24. 8-Chloro-1,2,3,4,5,6-hexahydro-2,6-methano-3,6-dimethyl-3-benzazocine-1-spiro-1'-cyclopentane.
25. 1,2,3,4,5,6-Hexahydro-8-hydroxy-3-pentyl-2,6-methano-1,1,6-trimethyl-3-benzazocine.
26. 3-Benzyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine.
27. 3-Cyclohexylmethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine.
28. 1,2,3,4,5,6-Hexahydro-2,6-methano-7,8,9-trimethyoxy-1,1,3,6-tetramethyl-3-benzazocine.
29. 1,2,3,4,5,6-Hexahydro-2,6-methano-8-methoxy-3,6-dimethyl-3-benzazocine-1-spiro-1'-cyclopropane.
30. 8,9-Dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,3,6-tetramethyl-3-benzazocine.
31. 1,2,3,4,5,6-Hexahydro-2,6-methano-8-methoxy-1,1,3,6-tetramethyl-3-benzazocine.
32. 1,2,3,4,5,6-Hexahydro-2,6-methano-8,9,10-trimethoxy-1,1,3,6-tetramethyl-3-benzazocine.
33. 1,2,3,4,5,6-Hexahydro-2,6-methano-8-methoxy-3,6-dimethyl-3-benzazocine-1-spiro-4'-tetrahydropyran.
34. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-3,6-dimethyl-3-benzazocine-1-spiro-4'-tetrahydropyran.
35. 1,2,3,4,5,6-Hexahydro-2,6-methano-1,1,3,6-tetramethyl-8,9-methylenedioxy-3-benzazocine.
36. 3-Cinnamyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-

benzazocine.

37. 3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6,8-tetramethyl-3-benzazocine.

38. 8-Chloro-3-cyclopropylmethyl-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6-trimethyl-3-benzazocine.

39. 3-Allyl-8-chloro-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6-trimethyl-3-benzazocine.

40. 3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine.

41. 3-Allyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine.

42. 3-[4'-(4"-Fluorophenyl)-4'-oxobutyl]-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine.

43. 8-Chloro-3-[4'-(4"-fluorophenyl)-4'-oxobutyl]-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6-trimethyl-3-benzazocine.

44. 3-[4'-(4"-Fluorophenyl)-4'-oxobutyl]-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6-trimethyl-3-benzazocine.

45. 3-[4'-(4"-Fluorophenyl)-4'-oxobutyl]-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,6,8-tetramethyl-3-benzazocine.

46. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-phenethyl-3-benzazocine.

47. 3-Allyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6-methyl-3-benzazocine-1-spiro-1'-cyclopentane.

48. 3-Allyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1-dimethyl-6-phenyl-3-benzazocine.

49. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-1,1-dimethyl-3-phenethyl-6-phenyl-3-benzazocine.

50. 1,2,3,4,5,6-Hexahydro-8-hydroxy-2,6-methano-6-methyl-3-phenethyl-3-benzazocine-1-spiro-1'-cyclopentane.

51. 3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1-dimethyl-6-phenyl-3-benzazocine.

52. 3-Cyclopropylmethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-6-methyl-3-benzazocine-1-spiro-1'-cyclopentane.

53. 3-Cyclobutymethyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1,6-trimethyl-3-benzazocine.

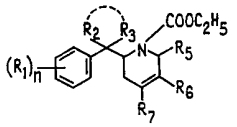
54. 3-Cinnamyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-6-methyl-3-benzazocine-1-spiro-1'-cyclopentane.

55. 3-Cinnamyl-1,2,3,4,5,6-hexahydro-8-hydroxy-2,6-methano-1,1-dimethyl-6-phenyl-3-benzazocine.

56. 8-Acetoxy-1,2,3,4,5,6-hexahydro-2,6-methano-1,1,3,6-tetramethyl-3-benzazocine.

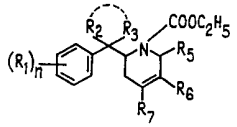
57. A process for preparing a methanobenzazocine derivative as claimed in claim 1, which comprises carrying out a procedure selected from:

(a) hydrolizing under an alkaline condition a compound represented by the formula



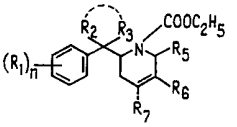
wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1, and then subjecting the hydrolysate to the action of a mineral acid;

(b) subjecting a compound represented by the formula



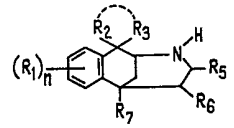
wherein R_1, R_2, R_3, R_5. R_6, R_7 and n are as defined in claim 1 to the action of mineral acid;

(c) reacting a compound by the formula



wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1 with a boron halide and optionally hydrolyzing the reaction product;

(d) reacting a compound represented by the formula

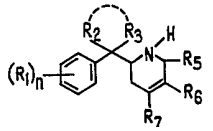


wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1 with a compound represented by the formula

R'_4X

wherein R'_4 is the same as R_4 as defined in claim 1 except that it is not hydrogen and X is halogen;

(e) reacting a compound represented by the formula

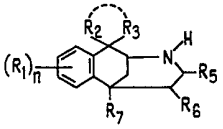


wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1 with a compound represented by the formula

R'_4X

where R'_4 is as defined above and X is a halogen and then cyclizing the reaction product by the action of a mineral acid;

(f) reacting a compound represented by the formula

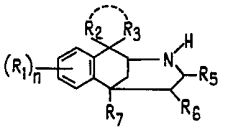


wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1 with a carboxylic acid of the formula

R'_4COOH

wherein R'_4 is as defined above or its reactive derivative and reducing the resulting N-acyl compound;

(g) reacting a compound represented by the formula

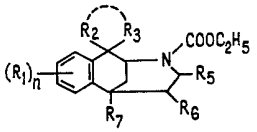


wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1 with an aldehyde represented by the formula

R'_4CHO

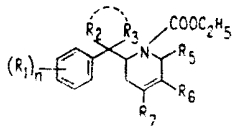
wherein R'_4 is as defined above and reducing the resulting compound;

(h) reacting a compound represented by the formula



wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1 with a metal hydride; and

(i) reacting a compound represented by the formula



wherein R_1, R_2, R_3, R_5, R_6, R_7 and n are as defined in claim 1 with a metal hydride and cyclizing the reaction product by the action of a mineral acid.

58. A process for preparing a methanobenzazocine derivative as claimed in claim 1, substantially as described in any one of the preparations set out in any one of the foregoing Examples.

59. A methanobenzazocine derivative whenever produced by the process claimed in claim 57 or 58.

60. A salt of a methanobenzazocine derivative as claimed in any of claims 1 to 56 and 59.

61. A pharmaceutical composition which comprises either a methanobenzazocine derivative as claimed in any one of claims 1 to 56 and 59 or a salt as claimed in claim 60, in association with a pharmacologically acceptable carrier.

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Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1980.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.