

PATENT SPECIFICATION

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(54) NITROGEN CONTAINING ISOPRENOID COMPOUNDS

(71) We, PIERREL S.P.A., an Italian body corporate, existing under the laws of the Italian Republic of Via Turati 30, Milan, Italy, 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:—

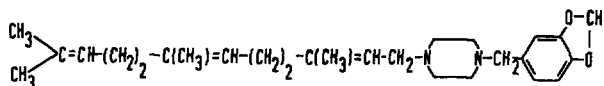
The present invention relates to novel nitrogen containing isoprenoid compounds which display remarkable pharmacodynamic activity.

The compounds of the present invention show a poor toxicity and a remarkable activity as inhibitors of the gastric secretion; also the anti-ulcer action is very good.

Moreover, they show also a spasmolytic action of the papaverinic type, and an analgesic-anti-inflammatory activity.

It must also be noted that these products exhibit anti-secretive and anti-ulcer activity in absence of anti-cholinergic properties, proving therefore very interesting from the therapeutic viewpoint.

The compounds of the present invention are represented by the following formula



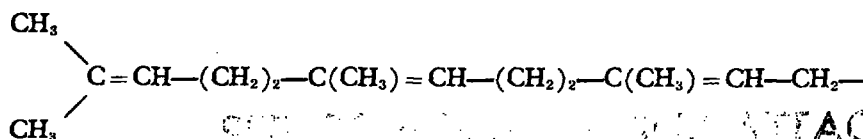
wherein the presence of three double carbon-carbon bonds makes possible the existence of geometric isomers with the following possibilities:

- the sole configuration trans C₂—C₃, trans C₆—C₇;
- the sole configuration cis C₂—C₃, trans C₆—C₇;
- a mixture of the two mentioned geometric isomers of triene;
- the sole configuration cis C₂—C₃, cis C₆—C₇;
- the sole configuration trans C₂—C₃, cis C₆—C₇;
- a mixture of the two just-mentioned geometric isomers of triene;
- a mixture of the four specified geometric isomers of triene.

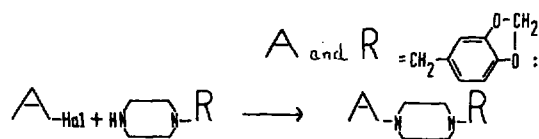
The compounds of the present invention (sole isomer or mixture of various isomers, as explained before) are available in the form of free bases or in the form of pharmacologically acceptable non-toxic acid addition salts thereof.

The compounds of the present invention can be prepared by employing various processes and methods already known in the art, some of which can be summarized as follows:

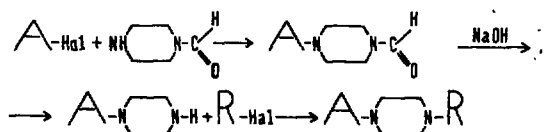
1) A suitable acyclic isoprenoid halide is reacted with a monosubstituted piperazine according to the following scheme, wherein the group



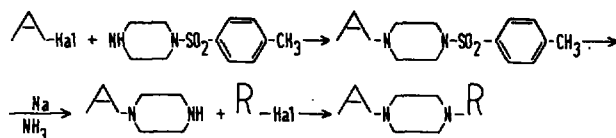
is conventionally indicated as



2) A suitable acyclic isoprenoid halide is reacted with piperazine-carboxaldehyde and, after alkaline hydrolysis, the resulting 1-acyclic isoprenoidpiperazine is reacted with a suitable R-halide wherein R has the meaning stated above, according to the following scheme:



3) A suitable acyclic isoprenoid halide is reacted with p-tosylpiperazine and the resulting sulphonamide is reacted with Na in liquid ammonia to give a secondary amine which, by treatment with a R-halide (R has the meaning stated above) gives the desired product, according to the following scheme:



The products of the present invention show, as mentioned above, a remarkable interesting pharmacological activity as it appears from the following description, wherein

i.p. = intraperitoneally
i.d. = intraduodenally
i.v. = intravenously
p.o. = per os
L.D.₅₀ = Lethal dose 50
E.D.₅₀ = Effective dose 50

The acute toxicity on male mice of the tested products was found to be very low and such as not to hinder clinical experimentation. The approximate L.D.₅₀ values are reported in the table. Behaviour investigation proved no particular symptomatology at low dosages, whereas at very high dosages, or at the dosages which caused the death of animals, the tested products caused slight convulsions.

With regard to the effects on the isolated organs (segments of Guinea pig ileum) no one of the tested products possesses a remarkable antagonist action to acetylcholine or histamine. In fact, an inhibiting action was evidenced only with concentrations at least 100 times higher than the ones proper to obtain an approximate E.D.₅₀ with the control substances (atropine sulphate 0,006 γ/ml.; diphenhydramine 0,007 γ/ml.).

On the contrary, the products evidenced a spasmolytic action of the papaverinic type, inhibiting the spasm induced by BaCl₂. In this case the concentrations which resulted active, are in the same range as evidenced for the specific antagonist (papaverine 1—10 γ/ml.).

When administered in cats narcotized with chloralose (80 mg./Kg. i.v.b.w.), even at high dosages (100 mg./Kg. i.d.b.w.), none of the tested products caused remarkable variations on the blood pressure or on breathing. The tested products showed a remarkable activity in inhibiting the gastric secretion on the 4 hrs. Shay test in the rat.

The approximate E.D.₅₀ by i.d. route are reported in the Table. Moreover, the products displayed significant anti-ulcer properties in the various experimental condi-

tions in rat at dosages between 50 and 200 mg./Kg. i.p. (reserpine ulcer, immobilization ulcer, phenylbutazone ulcer and Shay ulcerogenic test).

The products displayed also analgesic and anti-inflammatory actions and the active doses proved to be from 50 to 200 mg./Kg. p.o. With regard to the anti-cholinergic activity, said products were completely inactive up to doses of 200 mg./Kg. i.p. in the oxotremorine test in the mouse, as well as in the chromodacryorrhea test in the rat.

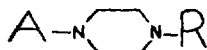
In the same tests, under the same experimental conditions, atropine sulphate resulted to be highly active already at doses of 0.5—1 mg./Kg. i.p. b.w.

Moreover, other conventional pharmacological tests were utilized during the investigations, but they are not reported because no conclusive results have been achieved.

From the table, the products showing the highest toxicity are 2,2'-bipyridine and atropine-sulphate, whereas the products according to the present invention (indicated as:



show a very low toxicity by oral route. On the contrary, the most active product is atropine-sulphate, whereas 2,2'-bipyridine and



show a very close activity level.

It is known, however, that atropine-sulphate, at the active dose, shows marked undesired effects of anticholinergic type (e.g. mydriasis). The action of the products according to the present invention remains practically unchanged when administering the products as such, as well as when administering their pharmacologically acceptable non toxic acid addition salts.

Accordingly therefore the present invention provides a therapeutic composition comprising as the active ingredient one of the compounds of the invention together with a pharmaceutically acceptable carrier.

Comparative values of Acute Toxicity and Gastric Antisecretory Activity (Shay test) of invention compounds $A-N\text{---}\text{C}_6\text{H}_4\text{---}N\text{---}R$
 Atropine Sulphate, 2,2'-Bipyridine.

Compounds	Acute Toxicity in Mice LD ₅₀ (mg./Kg.)		Inhibition of Gastric Secretion in Rats	
	i.p.	p.o.	Volume ED ₅₀ (mg./Kg. i.d.)	Free acid output ED ₅₀ (mg./Kg. i.d.)
1) $A-N\text{---}\text{C}_6\text{H}_4\text{---}N\text{---}R$				
a) trans C ₂ -C ₃ , trans C ₆ -C ₇	300		14	9
b) cis C ₂ -C ₃ , trans C ₆ -C ₇	600		26	15
c) mixture of a) + b)	400	2000	20	14
d) cis C ₂ -C ₃ , cis C ₆ -C ₇	500		26	15
e) trans C ₂ -C ₃ , cis C ₆ -C ₇	250		10	6
f) mixture of d) + e)	350	2000	20	13
g) mixture of a) + b) + d) + e)	400	2000	16	9
2) Atropine Sulphate	200	800	2,5 - 5	2,5
3) 2,2'-Bipyridine	250	330	10	10

The following non-limitative Examples illustrate the products and processes of the present invention.

EXAMPLE I.

*N*¹-piperonyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(four isomers mixture)

A solution of 45 mmoles of 1-bromo-3,7,11-trimethyl-2,6,10-dodecatriene (obtained from synthetic farnesol, commercially available and containing four isomers) in 10 ml. of benzene was added dropwise at 0°C to a stirred solution of 45 mmoles of piperonylpiperazine in 60 ml. of benzene containing 5 g. of triethylamine. The mixture was stirred for 2 hours and then the precipitated triethylammonium bromide was filtered off.

The benzene solution was washed first with water and then with K₂CO₃ solution and finally dried (K₂CO₃).

Removal of benzene under reduced pressure gave a crude oily residue which was dissolved in acetone and treated at 5–8°C with a slight excess of 37% HCl solution. The precipitated hydrochloride was filtered, washed with acetone and with absolute ethanol. The corresponding base was purified on a silica gel column and the purity of all fractions was checked by thin layer chromatography and gas liquid chromatography. Thin layer chromatography on silica gel gave three spots in the solvent system ethyl-acetate-petrol ether 1:1.

Gas liquid chromatography showed three peaks indicating the presence of four possible isomers.

Pure product was a colourless oil: the NMR showed the following signals in δ:
1.55–1.80 (m, 12H, CH₃—C=), 1.95–2.20 (m, 8H, CH₂—C=),
2.48 (s, 8H, CH₂—N), 3.00 (d, 2H, J = 7 cps, N—CH₂—C=),
3.41 (s, 2H, CH₂—arom), 4.90–5.50 (m, 3H, CH=C),
5.91 (s, 2H, O—CH₂—O), 6.75–6.90 (3H, arom).

EXAMPLE II.

*N*¹-piperonyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(four isomers mixture)

The title compound is prepared condensing 45 mmoles of piperonyl chloride with 45 mmoles of 3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine following the procedure described in Example I.

*N*¹-formyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(four isomers mixture)

The procedure of Example I was carried out with 45 mmoles of formylpiperazine instead of piperonylpiperazine. The oily residue obtained by evaporation of the benzene solution was chromatographed on silica gel column (elution with chloroform-methanol) to afford the pure base. The NMR showed the following signals in δ:
1.55–1.85 (m, 12H, CH₃—C=), 1.95–2.20 (m, 8H, CH₂—C=),
2.30–2.60 (m, 4H, CH₂—N), 3.00 (d, 2H, J = cps, N—CH₂—C=),
3.26–3.70 (m, 4H, CH₂—N—CO—), 4.95–5.45 (m, 3H, CH=C),
8.00 (s, 1H, —CHO).

3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(four isomers mixture)

A solution of 47.09 mmoles of the *N*¹-formyl derivative in 50 ml. ethanol was refluxed for 20 hours with 7.5 g. of NaOH in 50 ml. water and then the ethanol was evaporated in vacuo. An ethylether extract of the reaction mixture was washed with water, dried (Na₂SO₄) and concentrated to an oil, a solution of which was purified on silica gel column.

Structure was confirmed by analyses.

The NMR showed the following signals in δ:
1.55–1.80 (m, 12H, CH₃—C=), 1.95–2.20 (m, 8H, CH₂—C=),
2.30–2.60 (m, 4H, CH₂—N), 2.42 (s, 1H, N—H),
2.80–3.10 (m, 6H, CH₂—N), 4.95–5.50 (m, 3H, CH=C).

*N*¹-tosyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(four isomers mixture)

To a cold solution (0°C) of 21.6 mmoles of tosylpiperazine in 8 ml. of absolute ethanol containing 1.2 g. of anhydrous KOH, 23.8 mmoles of 1-bromo-3,7,11-trimethyl-

2,6,10-dodecatriene were added dropwise under stirring. The mixture was stirred for 1 hour at room temperature and filtered to remove KBr.

Concentration of the solution gave a crude oily residue which was treated with 5% KOH, extracted with methylene dichloride, washed with water and dried (K_2CO_3). Evaporation to dryness in vacuo gave an oil which was chromatographed on silica gel using ethylacetate-petrol ether as eluants.

Ir (neat) 1345 (ν_{as} SO_2) and 1160 cm^{-1} (ν_s SO_2).

3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(four isomers mixture)

A solution of 4.9 mmoles of the tosyl derivative in 10 ml. of toluene was slowly added to 100 ml. of liquid ammonia and the resulting suspension was treated with about 250 mg. (10.9 mg.-atoms) of sodium in small portions until a deep blue colour persisted for 15 min. Then 1.0 g. of ammonium chloride was added in one portion and the blue colour was immediately discharged. The mixture was stirred for additional 10 min. and then 100 ml. of toluene were added dropwise allowing ammonia to evaporate over a 2 hours period. The organic solution was washed with water, dried (K_2CO_3) and concentrated under reduced pressure.

Purification by chromatography over silica gel (chloroform-methanol eluants) afforded the pure base.

For NMR signals see above.

EXAMPLE III.

N'-piperonyl-N'-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(cis C_2-C_3 , trans C_6-C_7)

10.5 ml. of anhydrous pyridine are added to a solution of 100 g. (0.45 moles) of commercially available pure trans-nerolidol in 300 ml. petroleum ether and then, under stirring and maintaining the temperature between -5 and $-10^\circ C$, a solution of 53 g. (0.2 moles) of PBr_3 in 70 ml. petroleum ether are added thereto.

When the addition is completed, stirring is maintained for 2 hours at $-2-0^\circ C$, then the solution is washed first with water-ice up to neutrality, and then with cold saturated $NaHCO_3$ solution. After drying on Na_2SO_4 and then on anhydrous K_2CO_3 , the solvent is eliminated and the remaining oil is treated with 100 ml. benzene. The so obtained solution (1-bromo-3,7,11-trimethyl-2,6,10-dodecatriene) is added under stirring at $0^\circ C$ to a solution of 99 g. (0.45 moles) of N-piperonylpiperazine dissolved in 600 ml. of benzene containing 50 g. of triethylamine.

When the addition is completed, stirring is maintained for 2 hours then the precipitated triethylammonium bromide is filtered off and the solution is washed first with water and then with K_2CO_3 solution and finally dried.

Afterwards, the solvent is evaporated under vacuum and the oily residue is dissolved in acetone and treated with a slight excess of 37% aqueous HCl, maintaining the temperature below $+10^\circ C$. The precipitated hydrochloride is filtered, washed with acetone and with absolute ethanol.

The corresponding base is the expected mixture of the two isomers cis C_2-C_3 , trans C_6-C_7 and trans C_2-C_3 , trans C_6-C_7 .

Chromatography of 15 g. of the product on 3 Kg. Silica gel (160 $\times$ 9.5 cm. column), using 25% benzene in ethylacetate as eluant, resulted in complete separation of the two isomers.

The first eluted product is the pure cis C_2-C_3 , trans C_6-C_7 isomer.

Thin layer chromatography on silica gel gave one spot in the system benzene-ethylacetate 25:75.

Gas liquid chromatography showed only one peak on OV 17—5% on Chromosorb G AW-DMCS 80—100 mesh, 6 m. length, 1.6 mm. inlet diameter. "Chromosorb" is a registered Trade Mark.

EXAMPLE IV.

N'-piperonyl-N'-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(trans C_2-C_3 , trans C_6-C_7)

After separation of the pure isomer cis C_2-C_3 , trans C_6-C_7 of Example III, some fractions are obtained which contain the isomer mixture. At the end, the pure isomer trans C_2-C_3 , trans C_6-C_7 is eluted.

Thin layer chromatography on silica gel gave one spot in the system benzene-ethylacetate 25:75.

Gas liquid chromatography showed only one peak.

EXAMPLE V.

*N*¹-piperonyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(cis C₂—C₃, cis C₆—C₇)

5 The procedure of Example III is carried out with 0.45 moles of cis-nerolidol (from commercially available mixture of cis and trans-nerolidols; the separation was achieved on 5% silver nitrate impregnated silica gel column with benzene-ethylacetate 70:30 as eluant). The obtained base is the expected mixture of the two isomers cis C₂—C₃, cis C₆—C₇, and trans C₂—C₃, cis C₆—C₇. 5

10 After chromatography as in Example III, the first eluted product is the pure cis C₂—C₃, cis C₆—C₇ isomer, as showed by thin layer chromatography and gas liquid chromatography. 10

EXAMPLE VI.

*N*¹-piperonyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(trans C₂—C₃, cis C₆—C₇)

15 After separation of the pure isomer cis C₂—C₃, cis C₆—C₇ of Example V, some fractions are obtained which contain the isomer mixture. At the end, the pure isomer trans C₂—C₃, cis C₆—C₇ is eluted. 15

Thin layer chromatography on silica gel gave one spot in the system benzene-ethylacetate 25:75.

20 Gas liquid chromatography showed only one peak. 20

EXAMPLE VII.

Preparation of 1000 tablets, each containing 50 mg. of the active substance.

25	<i>N</i> ¹ -piperonyl- <i>N</i> ⁴ -3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine	g. 50	
	Colloidal silicic acid	g. 150	25
	Starch	g. 150	
	Lactose	g. 40	
	Talc	g. 8	
	Magnesium Stearate	g. 2	

30 *Procedure.*

The active substance is dissolved in ethanol and the resulting solution is adsorbed by colloidal silicic acid using a suitable mixer.

The mixture is dried in stove under vacuum at 40°C.

35 Starch, lactose and the half of the lubricants are added to the dried mixture which, after accurate mixing, is compressed in slugs which are afterwards granulated. The remaining quantity of lubricants is added to the obtained granulate and the mixture is then compressed into tablets of 400 mg., each containing 50 mg. of active substance. 35

EXAMPLE VIII.

Preparation of enteric-coated tablets.

40 The ingredients and the procedures described in Example VII are used. At the end, the tablets are covered with a cellulose acetophthalate-film. 40

EXAMPLE IX.

Preparation of 1000 tablets of soft-gelatine capsules, each containing 50 mg of active substance.

45	<i>N</i> ¹ -piperonyl- <i>N</i> ⁴ -3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine	g. 50	
	Vegetable oil	g. 70	45

Procedure

50 The active substance and the vegetable oil are homogeneously mixed proceeding thereafter to the preparation of Scherer type capsules. Each capsule contains 50 mg. of active substance. 50

EXAMPLE X.

Gastro-resistant soft-gelatine capsules.

The same ingredients and procedures of Example IX are used. The capsules, at the end, undergo a treatment with formalin in order to obtain gastro-resistance.

55 **WHAT WE CLAIM IS:—**

1. *N*¹-piperonyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine and pharmaceutically acceptable acid addition salts thereof and the geometric isomers thereof. 55



* C L H S *

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EXAMPLE V.

*N*¹-piperonyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(cis C₂—C₃, cis C₆—C₇)

The procedure of Example III is carried out with 0.45 moles of cis-nerolidol (from commercially available mixture of cis and trans-nerolidols; the separation was achieved on 5% silver nitrate impregnated silica gel column with benzene-ethylacetate 70:30 as eluant). The obtained base is the expected mixture of the two isomers cis C₂—C₃, cis C₆—C₇ and trans C₂—C₃, cis C₆—C₇.

After chromatography as in Example III, the first eluted product is the pure cis C₂—C₃, cis C₆—C₇ isomer, as showed by thin layer chromatography and gas liquid chromatography.

EXAMPLE VI.

*N*¹-piperonyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.
(trans C₂—C₃, cis C₆—C₇)

After separation of the pure isomer cis C₂—C₃, cis C₆—C₇ of Example V, some fractions are obtained which contain the isomer mixture. At the end, the pure isomer trans C₂—C₃, cis C₆—C₇ is eluted.

Thin layer chromatography on silica gel gave one spot in the system benzene-ethylacetate 25:75.

Gas liquid chromatography showed only one peak.

EXAMPLE VII.

Preparation of 1000 tablets, each containing 50 mg. of the active substance.

<i>N</i> ¹ -piperonyl- <i>N</i> ⁴ -3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine	g. 50
Colloidal silicic acid	g. 150
Starch	g. 150
Lactose	g. 40
Talc	g. 8
Magnesium Stearate	g. 2

Procedure.

The active substance is dissolved in ethanol and the resulting solution is adsorbed by colloidal silicic acid using a suitable mixer.

The mixture is dried in stove under vacuum at 40°C.

Starch, lactose and the half of the lubricants are added to the dried mixture which, after accurate mixing, is compressed in slugs which are afterwards granulated. The remaining quantity of lubricants is added to the obtained granulate and the mixture is then compressed into tablets of 400 mg., each containing 50 mg. of active substance.

EXAMPLE VIII.

Preparation of enteric-coated tablets.

The ingredients and the procedures described in Example VII are used. At the end, the tablets are covered with a cellulose acetophthalate-film.

EXAMPLE IX.

Preparation of 1000 tablets of soft-gelatine capsules, each containing 50 mg of active substance.

<i>N</i> ¹ -piperonyl- <i>N</i> ⁴ -3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine	g. 50
Vegetable oil	g. 70

Procedure

The active substance and the vegetable oil are homogeneously mixed proceeding thereafter to the preparation of Scherer type capsules. Each capsule contains 50 mg. of active substance.

EXAMPLE X.

Gastro-resistant soft-gelatine capsules.

The same ingredients and procedures of Example IX are used. The capsules, at the end, undergo a treatment with formalin in order to obtain gastro-resistance.

WHAT WE CLAIM IS:—

1. *N*¹-piperonyl-*N*⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine and pharmaceutically acceptable acid addition salts thereof and the geometric isomers thereof.



2. A compound according to claim 1 wherein the pharmaceutically acceptable acid addition salt is the hydrochloride.

3. N¹-piperonyl-N⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine.

4. N¹-piperonyl-N⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine hydrochloride.

5. A compound according to claim 1 and consisting of the isomer trans C₂—C₃, trans C₆—C₇.

6. A compound according to claim 1 and consisting of the isomer cis C₂—C₃, trans C₆—C₇.

7. A compound according to claim 1 and consisting of the isomer cis C₂—C₃, cis C₆—C₇.

8. A compound according to claim 1 and consisting of the isomer trans C₂—C₃, cis C₆—C₇.

9. A compound according to claim 1 and consisting of a mixture of the isomers as claimed in claims 5 and 6.

10. A compound according to claim 1 and consisting of a mixture of the isomers as claimed in claims 6 and 7.

11. A compound according to claim 1 and consisting of a mixture of all of the isomers as claimed in any of claims 5 to 8.

12. A process for the preparation of a compound as claimed in claim 1 which comprises reacting a 1-halo-3,7,11-trimethyl-2,6,10-dodecatriene with piperonylpiperazine.

13. A process for the preparation of a compound as claimed in claim 1 which comprises reacting a 1-halo 3,7,11-trimethyl-2,6,10-dodecatriene with piperazine carboxaldehyde, subjecting the resulting N¹-formyl-N⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine to alkaline hydrolysis to form 3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine and then reacting the latter compound with a piperonyl halide.

14. A process for the preparation of a compound as claimed in claim 1 which comprises reacting a 1-halo 3,7,11-trimethyl-2,6,10-dodecatriene with tosyl piperazine, reacting the resulting N¹-tosyl-N⁴-3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine with sodium in liquid ammonia to form 3,7,11-trimethyl-2,6,10-dodecatrienylpiperazine and then reacting the latter compound with a piperonyl halide.

15. A process as claimed in any of claims 12 to 14 wherein the 1-halo-3,7,11-trimethyl-2,6,10-dodecatriene is 1-bromo-3,7,11-trimethyl-2,6,10-dodecatriene.

16. A process as claimed in claim 13 or 14 wherein the piperonyl halide used is piperonyl chloride.

17. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 1 to 4 together with a pharmaceutically acceptable carrier.

18. A therapeutic composition comprising as the active ingredient a compound as claimed in any of claims 5 to 11 together with a pharmaceutically acceptable carrier.

19. A process for the preparation of a compound as claimed in claim 1 or claim 3 substantially as herein described with reference to Example I.

20. A process for the preparation of a compound as claimed in claim 1 substantially as herein described with reference to Examples II to VI.

21. A therapeutic composition comprising as the active ingredient a compound as claimed in claim 1 substantially as herein described with reference to Examples VII to X.

22. A process for the preparation of a compound as claimed in any of claims 1 to 11 substantially as herein described with reference to Examples I to VI.

23. A compound as claimed in any of claims 1 to 11 when prepared by a process as claimed in any of claims 12 to 16, 19, 20 or 22.

24. A therapeutic composition comprising as active ingredient a compound as claimed in any of claims 1 to 11 or 23 together with a pharmaceutically acceptable carrier.

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