

PATENT SPECIFICATION

NO DRAWINGS

1.016.514



Date of Application and filing Complete Specification: Oct. 2, 1962.

No. 37360/62.

Application made in Germany (No. B64319 IVd/12p) on Oct. 9, 1961.

Complete Specification Published: Jan. 12, 1966.

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Index at acceptance:—C2 C(1H1A2, 1H1A3, 1H1C3, 1M1A, 1M1C2, 2A3, 2A5, 2A14, 2C2, 2C7E, 2R16, 2R17); A5 B(1D, 1S, 31); C5 D(6B1, 6B2, 6B12E)

Int. Cl.:—C 07 c, d // A 61 k, C 11 d

COMPLETE SPECIFICATION

2-Aryl-Amino-1,3-Diazacyclopentenes

We, BOEHRINGER INGELHEIM G.M.B.H., a Body Corporate organised under the laws of Germany, of Ingelheim am Rhein, Germany, 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 is concerned with improvements in or relating to the preparation of substituted 2-aryl-amino-1,3-diazacyclopentenes.

Various methods have already been proposed for the preparation of 2-amino-1,3-diazacyclopentenes. For example, these compounds may be prepared from substituted 1,3-diazacyclopentenes, by introducing the basic group. Alternatively, the compounds may be prepared by condensing alkylene diamines with carbamic acid derivatives.

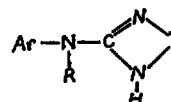
In U.S. Patent Specification No. 2,899,426 there is described a process for the preparation of 1,3-diazacycloalkenes in which isothiuronium salts are heated at temperatures of 20—140°C., preferably 60—80°C., in polar solvents containing hydroxyl groups, such as water or lower alcohols, with ethylene or propylene diamines. The mild conditions are necessary since the starting materials tend to decompose. The reaction time is stated to be from 15 minutes to 24 hours; however, in none of the examples is the reaction time shorter than 8 hours.

A re-working of the examples showed that these long reaction times are necessary for obtaining good yields. The progress of the reaction was observed by estimating the quantity of mercaptan liberated. On re-working Example II of said U.S. Specification it was found that only after 16 hours had reaction taken place between 90% of the reactants. After isolating the product, the yield of imidazoline hydroiodide was about 60% of theory. It will thus be seen that this

process does not lend itself readily for effecting the reaction on a technical scale.

It has now been found that substituted 2-phenyl - amino - 1,3 - diazacyclopentenes may be prepared from isothiuronium salts and alkylene diamines in very good yields if the reactants are heated to temperatures of 100—200°C. in the absence of a solvent. The reaction is generally substantially complete within a few minutes.

Accordingly the invention provides a process for the preparation of compounds of the general formula

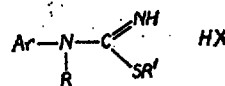


I

(in which R represents a hydrogen atom or a lower alkyl group;

Ar represents a phenyl group which is at least disubstituted, the substituents being halogen atoms and/or lower alkyl groups; and

Y represents an ethylene group either unsubstituted or substituted by a methyl group), and acid addition salts thereof in which an isothiuronium salt of the formula



II

(wherein R and Ar have the meanings given above, R¹ represents a lower alkyl group and X represents a chlorine, bromine or iodine atom) is heated at a temperature of 100 to 200°C for 10 to 120 minutes in the absence

of a solvent with an alkylene diamine of the formula



(in which Y has the meaning given above).

The term "lower alkyl" is used herein to designate alkyl groups containing from 1 to 4 carbon atoms.

Preferably, the reaction is effected at a temperature of 140 to 180°C.

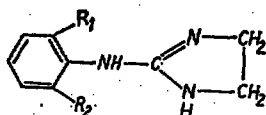
For example, the reaction may be effected by heating with stirring and under reflux the isothiuronium salt of formula II with an equimolar proportion or a slight excess of the alkylene diamine for 10—120 minutes. The reaction time and temperature will depend on the isothiuronium salt used. After the evolution of mercaptan is completed the reaction mixture is cooled and the product may be isolated as desired, for example by precipitation of the base and recrystallisation.

The preferred starting materials of formula II since they lead to compounds of especial pharmacological value are compounds in which at least one of the substituents is a methyl or ethyl group. The symbol R advantageously represents hydrogen and the alkylene diamine preferably used is ethylene diamine.

Where the compounds of formula I are obtained in salt form, the salts may be converted into the free bases or other acid addition salts with organic or inorganic acids, for example by reacting the free base with an appropriate acid.

It should be noted that when N - (2,6-diethyl - phenyl) - S - methyl - isothiuronium hydroiodide was boiled in amyl alcohol for 15 hours under reflux with ethylene diamine according to the process described in U.S. Patent Specification No. 2,899,426, no imidazoline could be isolated from the reaction products. When, however, the reactants were boiled without solvent for 2 hours at about 170°C, 2 - (2¹,6¹ - diethyl - phenyl) - amino - 1,3 - diazacyclopentene was obtained, after purification, in a yield of 50% of theory.

The invention further provides compounds of the general formula



IV

(wherein R₁ and R₂, which may be the same or different, each represents a halogen atom or an alkyl group containing 1 or 2 carbon atoms) and non-toxic acid addition salts thereof.

By the term "non-toxic acid addition salts" are meant salts the anionic portion of which gives rise to no substantial toxic effects in the doses employed.

Preferred acid-addition salts according to

the invention are salts formed with hydrohalic acids, particularly hydrochloric acid, sulphuric acid, phosphoric acid, tartaric acid and acetic acid.

The compounds of formula I and their acid-addition salts possess valuable vasoconstrictive and pilo-erecting properties. These compounds are thus particularly useful in medicine as decongestants in common cold preparations, and also in shaving preparations. The decongestant activity of compounds of formula IV is especially pronounced and of extended duration. Some of the compounds also have valuable hypotensive and sedative actions.

Particularly preferred compounds according to the invention, by virtue of their especially valuable vasoconstrictive properties are:—

2 - (2¹,6¹ - diethyl - phenyl) - amino - 1,3 - diazacyclopentene - (2),
2 - (2¹,6¹ - dichloro - phenyl) - amino - 1,3 - diazacyclopentene - (2),
2 - (2¹,6¹ - dimethyl - phenyl) - amino - 1,3 - diazacyclopentene - (2)

and

2 - (2¹ - chloro - 6¹ - methyl - phenyl) - amino - 1,3 - diazacyclopentene - (2).

The hypotensive action of the 2 - (2¹,6¹ - dichloro - phenyl) - amino - 1,3 - diazacyclopentene - (2) is quite outstanding and this compound also has relatively low toxicity coupled with good sedative action.

The decongestive activity of compounds of formula IV was compared with that of one of the most effective known decongestants, 2 - (4¹ - tert - butyl - 2¹,6¹ - dimethylbenzyl) - 2 - imidazoline hydrochloride, which is also known under the name xylometazoline hydrochloride. The compounds of formula IV have been observed to be more effective than this comparison substance.

1. Decongestant action on nasal mucous membranes

The experiments were carried out on dogs under morphine-chloralose-urethane narcosis, using the method of Ardaunet and Binet (Presse Medicale, 1929, pp. 1637—1639), the substances being administered intravenously. In an average of seven experiments on three animals each time, and with the same concentration of the compounds, 2 - (2¹,6¹ - diethyl - phenyl) - amino - 1,3 - diazacyclopentene - (2) was found to be 2.1 times, and 2 - (2¹,6¹ - dichloro - phenyl) - amino - 1,3 - diazacyclopentene - (2) 2.0 times more effective than the control substance xylometazoline.

2. Vasoconstrictory activity

The vasoconstrictory activity was examined on decerebrated cats using xylometazoline as control substance. The substances were injected intravenously into the animals and the blood pressure in the arteria carotis measured with a mercury manometer. In an average of eleven individual determina-

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tions and using the same concentrations of both substances, 2 - (2¹,6¹ - diethyl - phenyl)-amino - 1,3 - diazacyclopentene - (2) was observed to be 3.9 times more effective than xylometazoline.

3. Antihistamine action

The antihistamine action was examined on an isolated guinea pig rectum by the method of R. Magnus (Pflüger, Arch.ges.Physiol., vol. 102, p. 123 (1904)), the occurrence of histamine spasm on administration of the test substance being observed. As compared with Benadryl, the substance was a thousand times less effective and thus possesses no perceptible antihistamine action.

4. Local compatibility

a) The inhibition of the ciliar movement was tested on the gullet of a frog as a measure of the damage to the mucous membrane (method according to M. Kochmann, Naunyn-Schmiedeberg's Arch. Exper. Path. Pharmacol., vol. 150, p. 23 (1930)). The test and control substances were administered as a 0.1% solution and the inhibition calculated in per cent relative to a control period. Xylometazoline caused, in an average of 5 experiments, a 54% inhibition of the ciliar movement, whilst 2 - (2¹,6¹ - diethyl - phenyl) - amino - 1,3 - diazacyclopentene - (2) increased the ciliar movement by 17% so that the local compatibility of 2 - (2¹,6¹ - diethyl - phenyl)-amino - 1,3 - diazacyclopentene - (2) is better by 71% than that of xylometazoline.

b) The possibility of influencing the ciliar movement was tested on the guinea pig trachea according to the method of Scudi, Kimura and Reinhard (J.Pharm.Expt.Therap. vol. 102, p. 132 (1951)). 0.1% and 0.05% solutions of xylometazoline effected, in an average of five experiments, an absolute inhibition of the ciliar movement for a period of 50 minutes, whilst solutions of the same concentration of 2 - (2¹,6¹ - diethyl - phenyl)-amino - 1,3 - diazacyclopentene - (2) caused no inhibition of the ciliar movement.

The invention further provides compositions adapted for topical administration or for cosmetic purposes comprising a compound of formula I or an acid addition salt thereof when prepared by the process of the present invention or a compound of formula IV, whether or not prepared by the process of the present invention, in association with an inert carrier or excipient.

The preferred active ingredients in the compositions according to the invention are compounds of formula IV, advantageously the hydrochlorides of these compounds.

The expression "topical administration" includes administration to the interior of the nose, for example in the form of nasal drops, sprays or ointments. Thus the inert carrier may comprise demineralised water which has been buffered to a pH at which the composi-

tion is compatible with the mucous membranes of the nose, for example with citric acid and disodium hydrogen phosphate. The inert carrier may also comprise demineralised water and one or more suspending agents, for example hydroxyethyl cellulose. The inert carrier may also comprise an ointment base, for example petroleum jelly.

The compositions for administration into the nose advantageously also contain a germicide, for example phenyl mercury borate.

Since the compounds of formula I also possess pilo-erecting properties, the compositions according to the invention may also be presented as pre-shave preparations, in a form suitable for administration to the area of the skin to be shaved, for example as lotions, soaps or creams. In such compositions the inert carrier will be a conventional carrier used in the cosmetic art for such preparations. Thus, for example, the carrier may include one or more perfumes, preservatives, wetting agents, dispersing agents, soaps, detergents, thickening agents, suspending agents, humectants, powder bases, colouring agents or oils.

Since the active ingredients are water-soluble, the compositions may be prepared on an aqueous base and contain one or more of the above adjuvants.

The compositions according to the invention preferably contain 0.1 to 0.3% by weight of active ingredient.

For the better understanding of the invention the following Examples are given by way of illustration only:—

EXAMPLE 1.

2-(2¹,6¹-diethyl-anilino)-1,3-diazacyclopentene-(2)

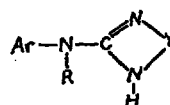
37.5 g. of the thiourea (m.pt. = 162—164°C.) produced from 2,6-diethyl-aniline and ammonium thiocyanate are heated for several hours under reflux with 29.4 g. of ethyl bromide in 50 ml. of methanol. The solvent is then removed *in vacuo* and the isothiuronium hydrobromide remaining as residue is heated for 1 to 2 hours at 150—170°C. with a small excess of ethylene diamine (120%). Ethyl mercaptan is liberated. After cooling, the reaction mixture is dissolved in water, filtered off from the oily residue, the filtrate purified over charcoal and made alkaline with 2N sodium hydroxide. The base thus precipitates out and is filtered off with suction and thoroughly washed with ice water. Yield: 50% of theory, m.pt. 155—157°C.; the hydrochloride melts at 209°C.

EXAMPLE 2.

2(2¹,6¹-diethyl-anilino)-4-methyl-1,3-diazacyclopentene-(2)

0.2 mol of the isothiuronium hydroiodide synthesised, according to Example 1, from 2,6-diethyl aniline, is heated with stirring at 130—160°C. for 1 to 2 hours with a small

- excess of propylene diamine-1,2. After cooling, water is added to the reaction mixture which is filtered and made alkaline with 5N sodium hydroxide, thus separating the base as an oil. For purification, it is dissolved in hydrochloric acid, re-precipitated by adding sodium hydroxide solution and treated with animal charcoal. The hydrochloride, prepared from the base, is strongly hygroscopic.
- 5
- 10 **EXAMPLE 3.**
2-(2,6-Dichloro-phenyl)-amino-1,3-diazacyclopentene-(2)
16.0 g. of the thiourea (m.pt. 149°C.) obtained from 2,6-dichloroaniline (prepared according to Org. Synth. III, 262-63) and ammonium thiocyanate are heated under reflux for 2½ hours with 16 g. of methyl iodide in 150 ml. of methanol. The solvent is taken off *in vacuo* and the isothiuronium hydro-
- iodide (22 g.; m.pt.=170°C.) remaining as residue heated for about 1 hour at 130 to 150°C. with stirring with a small excess of ethylene diamine (120%). Methyl mercaptan is liberated. The reaction mixture is then taken up in hot dilute acetic acid and the solution thus obtained made alkaline with 2N sodium hydroxide. The base which is thus precipitated is filtered off with suction, washed with water and dried. Yield: 4.0 g.; m.pt.=130°C.; hydrochloride: m.pt. 305°.
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- The following compounds of the formula



were also prepared.

Example No.	Ar	R	Y	Base M.pt. °C.	Hydrochloride M.pt. °C.	Prepared according to Example
4	2,4,6-trimethyl phenyl	H	—CH ₂ —CH ₂ —	156—157.5	117—121	1
5	2,4-dimethylphenyl	H	—CH ₂ —CH ₂ —	106	146	1
6	2,6-dimethylphenyl	H	—CH ₂ —CH ₂ —	143	202—205	1
7	2-methyl-4-ethyl phenyl	H	—CH ₂ —CH ₂ —	105—106	hygroscopic	1
8	2-chloro-6-methyl-phenyl	H	—CH ₂ —CH ₂ —	143—145	217—220	1
9	2,6-dimethyl-4-tert-butyl-phenyl	H	—CH ₂ —CH ₂ —	oil	160—163	1
10	2,4,6-triethyl-phenyl	H	—CH ₂ —CH ₂ —	133—137	240—243	1
11	2,6-diethylphenyl	CH ₃	—CH ₂ —CH ₂ —	oil	hygroscopic	1

Example 12 — Nasal drops**I. Containing 0.1% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2) hydrochloride.**

2-(2 ¹ ,6 ¹ -Diethylphenyl)-amino-1,3-diazacyclopentene-(2) hydrochloride	0.100 g.
Secondary sodium phosphate	3.610 g.
Citric acid	0.250 g.
Phenyl mercury borate	0.001 g.
Hydroxy-ethyl cellulose	0.700 g.
Demineralised water	to 100.000 ml.

II. Containing 0.2% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2) hydrochloride

2-(2 ¹ ,6 ¹ -Diethylphenyl)-amino-1,3-diazacyclopentene-(2) hydrochloride	0.200 g.
Secondary sodium phosphate	3.610 g.
Citric acid	0.250 g.
Phenyl mercury borate	0.001 g.
Hydroxy-ethyl cellulose	0.700 g.
Demineralised water	to 100.000 ml.

III. Containing 0.3% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2) hydrochloride

2-(2 ¹ ,6 ¹ -Diethylphenyl)-amino-1,3-diazacyclopentene-(2) hydrochloride	0.300 g.
Secondary sodium phosphate	3.610 g.
Citric acid	0.250 g.
Phenyl mercury borate	0.001 g.
Hydroxy-ethyl cellulose	0.700 g.
Demineralised water	to 100.000 ml.

Preparation.

Active substance, citric acid, secondary sodium phosphate and phenyl mercury borate (as 0.1%) solution are successively dissolved in half of the available quantity of water and

filtered clear. The hydroxy-ethyl cellulose is dissolved with stirring in the remaining quantity of water, the two solutions are combined and filtered.

Example 13 — Nasal sprays

I. Containing 0.1% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)

2-(2 ¹ ,6 ¹ -Diethylphenyl)-amino-1,3-diazacyclopentene-(2)	0.100 g.
Secondary sodium phosphate	3.610 g.
Citric acid	0.250 g.
Phenyl mercury borate	0.001 g.
Demineralised water	to 100.000 ml.

II. Containing 0.2% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)

2-(2 ¹ ,6 ¹ -Diethylphenyl)-amino-1,3-diazacyclopentene-(2)	0.200 g.
Secondary sodium phosphate	3.610 g.
Citric acid	0.250 g.
Phenyl mercury borate	0.001 g.
Demineralised as water	to 100.000 ml.

III. Containing 0.3% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)

2-(2 ¹ ,6 ¹ -Diethylphenyl)-amino-1,3-diazacyclopentene-(2)	0.300 g.
Secondary sodium phosphate	3.610 g.
Citric acid	0.250 g.
Phenyl mercury borate	0.001 g.
Demineralised water	to 100.000 ml.

Preparation

Active substance, citric acid, secondary sodium phosphate and phenyl mercury

borate (as 0.1% solution) are successively dissolved in the demineralised water and the solution filtered clear.

Example 14 — Nasal ointments

I. Containing 0.1% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)2-(2¹,6¹-diethylphenyl)-amino-1,3-diazacyclopentene-(2) 0.100 g.

Yellow petroleum jelly to 100.000 g.

II. Containing 0.2% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)2-(2¹,6¹-Diethylphenyl)-amino-1,3-diazacyclopentene-(2) 0.200 g.

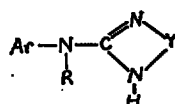
Yellow petroleum jelly to 100.000 g.

III. Containing 0.3% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)2-(2¹,6¹-Diethylphenyl)-amino-1,3-diazacyclopentene-(2) 0.300 g.

Yellow petroleum jelly to 100.000 g.

WHAT WE CLAIM IS:—

1. A process for the preparation of compounds of the general formula



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atom) is heated at a temperature of 100 to 200°C for 10 to 120 minutes in the absence of a solvent with an alkylene diamine of the formula



(in which Y has the meaning given above).

2. A process as claimed in claim 1 in which the reaction is effected at a temperature of 140 to 180°C. 25

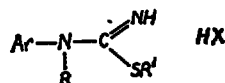
3. A process as claimed in claim 1 or claim 2 in which the molar ratio of alkylene diamine of formula III to isothiuronium salt of formula II is at least 1:1. 30

4. A process as claimed in claim 1 substantially as herein described.

(in which R represents a hydrogen atom or a lower alkyl group;

10 Ar represents a phenyl group which is at least disubstituted, the substituents being halogen atoms and/or lower alkyl groups; and

Y represents an ethylene group either unsubstituted or substituted by a methyl group), and acid addition salts thereof, in which an isothiuronium salt of the formula



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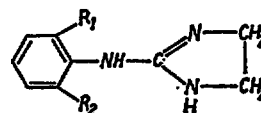
II

(wherein R and Ar have the meanings given above, R¹ represents a lower alkyl group and X represents a chlorine, bromine or iodine

5. A process as claimed in claim 1 substantially as herein described in any of Examples 1 to 11. 35

6. Compounds of the formula I (as defined in claim 1) when prepared by a process as claimed in any of claims 1 to 5.

7. Compounds of the general formula 40



IV

(wherein R₁ and R₂, which may be the same



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Example 14 — Nasal ointments

I. Containing 0.1% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)

2-(2¹,6¹-diethylphenyl)-amino-1,3-diazacyclopentene-(2) 0.100 g.

Yellow petroleum jelly to 100.000 g.

II. Containing 0.2% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)

2-(2¹,6¹-Diethylphenyl)-amino-1,3-diazacyclopentene-(2) 0.200 g.

Yellow petroleum jelly to 100.000 g.

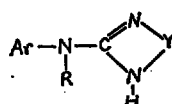
III. Containing 0.3% of 2-(2¹,6¹-diethyl-phenyl)-amino-1,3-diazacyclopentene-(2)

2-(2¹,6¹-Diethylphenyl)-amino-1,3-diazacyclopentene-(2) 0.300 g.

Yellow petroleum jelly to 100.000 g.

WHAT WE CLAIM IS:—

1. A process for the preparation of compounds of the general formula

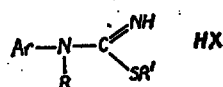


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I

(in which R represents a hydrogen atom or a lower alkyl group;

Ar represents a phenyl group which is at least disubstituted, the substituents being halogen atoms and/or lower alkyl groups; and
10 Y represents an ethylene group either unsubstituted or substituted by a methyl group), and acid addition salts thereof, in which an isothiuronium salt of the formula



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II

(wherein R and Ar have the meanings given above, R¹ represents a lower alkyl group and X represents a chlorine, bromine or iodine

atom) is heated at a temperature of 100 to 200°C for 10 to 120 minutes in the absence of a solvent with an alkylene diamine of the formula



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(in which Y has the meaning given above).

2. A process as claimed in claim 1 in which the reaction is effected at a temperature of 140 to 180°C.

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3. A process as claimed in claim 1 or claim 2 in which the molar ratio of alkylene diamine of formula III to isothiuronium salt of formula II is at least 1:1.

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4. A process as claimed in claim 1 substantially as herein described.

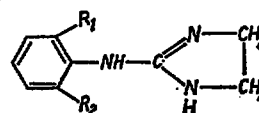
5. A process as claimed in claim 1 substantially as herein described in any of Examples 1 to 11.

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6. Compounds of the formula I (as defined in claim 1) when prepared by a process as claimed in any of claims 1 to 5.

7. Compounds of the general formula

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IV

(wherein R₁ and R₂, which may be the same

- or different, each represents a halogen atom or an alkyl group containing 1 or 2 carbon atoms) and non-toxic acid addition salts thereof.
- 5 8. 2 - (2¹,6¹ - Diethyl - phenyl) - amino-1,3 - diazacyclopentene - (2).
 9. 2 - (2¹,6¹ - Dichloro - phenyl) - amino-1,3 - diazacyclopentene - (2).
 10 10. 2 - (2¹,6¹ - Dimethyl - phenyl) - amino-1,3 - diazacyclopentene - (2).
 11. 2 - (2¹ - Chloro - 6¹ - methyl - phenyl) - amino - 1,3 - diazacyclopentene - (2).
 12. Compounds as claimed in any one of claims 6 to 11 in the form of hydrohalic acid, sulphuric acid, phosphoric acid, tartaric acid or acetic acid addition salts.
 15 13. Compounds as claimed in any one of claims 6 to 11 in the form of hydrochloride acid addition salt.
 20 14. Compositions adapted for topical administration or for cosmetic purposes comprising a compound as claimed in any one of claims 6 to 11 in association with an inert carrier or excipient.
 25 15. Compositions as claimed in claim 14 in the form of nasal drops, sprays or ointments.
 16. Compositions as claimed in claim 15 in which the carrier is demineralised water which has been buffered to a pH at which the composition is compatible with mucous membranes of the nose.
 30 17. Compositions as claimed in claim 15 or, claim 16 in which the carrier comprises one or more suspending agents. 35
 18. Compositions as claimed in claim 15 in which the carrier is an ointment base.
 19. Compositions as claimed in any one of claims 14 to 18 comprising a germicidal agent. 40
 20. Compositions as claimed in claim 19 in which said germicidal agent is phenyl mercury borate.
 21. Compositions as claimed in claim 14 in the form of lotions, creams or soaps. 45
 22. Compositions as claimed in claim 21 in which the carrier comprises one or more perfumes, preservatives, wetting agents, dispersing agents, humectants, powder bases, colouring agents or oils. 50
 23. Compositions as claimed in any one of claims 14 to 22 containing 0.1 to 0.3% by weight of a compound as claimed in any one of claims 6 to 13.
 24. Compositions as claimed in claim 14 55 substantially as herein described.
 25. Compositions as claimed in claim 14 substantially as herein described in any of Examples 12 to 14.

For the Applicants,
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