

The present invention relates to new 2-amino-4-morpholino-6-propyl-1,3,5-triazines, to their non-toxic pharmaceutically acceptable acid-addition salts, and to processes for preparing them. It also concerns therapeutic compositions containing the aforementioned compounds.

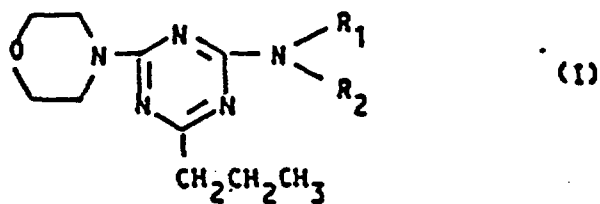
According to Japanese Patent Application 69688/74, 2-amino-1,3,5-triazines substituted in the 4 position by an amino group, by an amino group mono- or disubstituted by an alkyl, alkenyl, cycloalkyl, aryl or aralkyl radical, or by a nitrogen-containing heterocyclic radical, or in the 6 position by an alkyl, aryl or aralkyl radical are already known. In particular, the preparation of 2-amino-4-morpholino-6-propyl-1,3,5-triazine is described there. According to this patent application, these compounds have the property of increasing the secretion of corticosteroids, and in particular of glucocorticoids.

In another connection, K. Wakabayashi Ko et al., (Yuki Gosei Kagaku Kyokai Shi, 28, (1970), 252-260; Chem. Abstr., 72, (1970), 100653v) have synthesized 2-alkyl-4,6-bis(alkylamino)-1,3,5-triazines in which the radical in the 2 position contains 1 to 17 carbon atoms and can also represent the trichloromethyl, tribromomethyl or 2-chloroethyl group, while the radicals in the 4 and 6 positions are identical and can be substituted by a hydroxyl group or represent a nitrogen-containing heterocyclic radical, such as the piperidino or morpholino radical. A representative compound of this family is 2-methyl-4,6-dimorpholino-1,3,5-triazine. These compounds are studied for their herbicidal activity as well as for their property of inhibiting the conversion of ammonia to nitrate. However, no mention is made there of pharmacological properties.

New 2-amino-4-morpholino-6-propyl-1,3,5-triazines have now been found, which have valuable pharmaceutical properties and in particular the property of potentiating

the central and peripheral cholinergic effects caused by a cholinomimetic agent such as, for example, oxotremorine, whereas these compounds have no cholinergic effect of their own. Moreover, it has been found also that these compounds have the advantageous property of attenuating the effects resulting from cholinergic hypofunction induced by a cholinergic antagonist such as, for example, scopolamine. The cholinergic system is greatly involved in the phenomena of memorisation and learning. Thus, for example, the administration to young subjects of an anticholinergic agent such as scopolamine causes memory deficiencies to appear, resembling those observed in elderly subjects. Conversely, cholinergic agents, such as physostigmine, are capable of combating the amnesia resulting from the administration of anticholinergic agents (S.D. Glick et al., Behavioral Biology, 7, (1972), 245-254; U. Schindler et al. Drug Develop. Res. 4, (1984), 567-576). In addition, it is at present well established that one of the characteristics most frequently associated with the dementias is precisely a deterioration of the cholinergic system (Cellular and molecular basis of cholinergic function. Ed. M.J. Dowdall and J.N. Hawthorne, 1987, Chapter 99: article by A. Nordberg et al.). For this reason, these compounds can be used for the treatment of cognitive and behavioural disorders associated with age and with the demential syndromes. In particular, they are used in the treatment of the disorders associated with Alzheimer's disease, with the senile dementias of the Alzheimer type, and with all evolutive cognitive pathology (C.G. Gottfries Psychopharmacology, 86, (1985), 245-252; C.G. Gottfries, Neurobiology of Ageing, 4, (1983), 261-271).

More particularly, the present invention relates to new 2-amino-4-morpholino-6-propyl-1,3,5-triazines of the general formula



in which

- R_1 represents a hydrogen atom or an alkyl, phenylalkyl or acetyl radical,
- R_2 represents a hydroxyl group, a hydroxyalkyl, alkoxyalkyl, dialkylamino, phenylhydroxyalkyl, (hydroxycycloalkyl)alkyl, alkanoyloxyalkyl, benzoyloxyalkyl, phenylacetyloxyalkyl or aminocarbonyloxyalkyl radical, a COR_3 group in which R_3 represents an alkyl, phenyl, halogenophenyl, alkylphenyl, alkoxyphenyl, phenylalkyl or phenoxy radical, or a $CONR_4R_5$ group in which R_4 and R_5 represent hydrogen or an alkyl radical, or

R_1 and R_2 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino radical substituted by a hydroxyalkyl radical, the alkyl, alkoxy and alkanoyloxy radicals having 1 to 4 carbon atoms, and the cycloalkyl radicals having 4 to 6 carbon atoms,

with the proviso that when R_1 represents the acetyl radical, R_2 represents an acetoxyalkyl radical, as well as their non-toxic pharmaceutically acceptable acid-addition salts.

As examples of hydroxyalkyl radicals, the 2-hydroxyethyl, 3-hydroxypropyl, 2-hydroxypropyl, 2-hydroxybutyl, 1-(hydroxymethyl)propyl, 2,3-dihydroxypropyl, 2-hydroxy-1,1-bis(hydroxymethyl)ethyl radicals etc. will be mentioned.

As an example of a phenylhydroxyalkyl radical, the 2-hydroxy-1-(hydroxymethyl)-2-phenylethyl radical etc. will be mentioned.

As an example of a (hydroxycycloalkyl)alkyl radical, the (1-hydroxycyclohexyl)methyl radical etc. will be mentioned.

As examples of alkanoyloxyalkyl radicals, the 2-(acetoxy)ethyl, 2-(isobutyryloxy)ethyl radicals etc. will be mentioned.

As examples of pyrrolidino or piperidino radicals substituted by a hydroxyalkyl radical, the 2-hydroxymethyl-pyrrolidino, 2-hydroxymethyl-piperidino radicals etc. will be mentioned.

The preferred compounds of the present invention are the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which

R_1 represents a hydrogen atom or an alkyl radical,

R_2 represents a hydroxyl group, a hydroxyalkyl, alkoxyalkyl, dialkylamino or alkanoyloxyalkyl radical or a COR_3 group in which R_3 represents a phenyl radical that is unsubstituted or substituted by a halogen atom or an alkyl or alkoxy radical, the alkyl, alkoxy and alkanoyloxy radicals having 1 to 4 carbon atoms,

as well as their non-toxic pharmaceutically acceptable acid-addition salts.

The especially preferred compounds according to the invention are:

- 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol,
- 2-(hydroxyamino)-4-morpholino-6-propyl-1,3,5-triazine,

- 2-[(2-methoxyethyl)amino]-4-morpholino-6-propyl-1,3,5-triazine,
- (S)-3-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]-2-propanol,
- (R)-3-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]-2-propanol,
- 2-(2,2-dimethylhydrazino)-4-morpholino-6-propyl-1,3,5-triazine,
- the hydrochloride of N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)benzamide
- the hydrochloride of N-methyl-N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)benzamide,
- 2-[[2-(acetoxymethyl)amino]-4-morpholino-6-propyl-1,3,5-triazine.

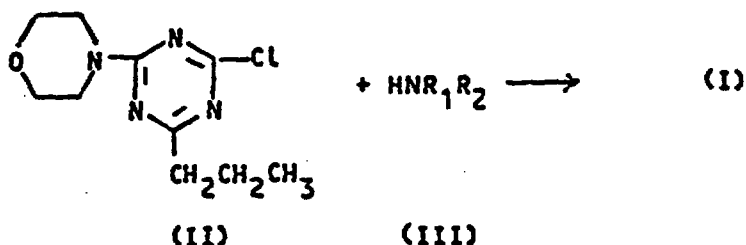
The present invention also concerns the non-toxic pharmaceutically acceptable acid-addition salts of the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of formula I. Examples of pharmaceutically acceptable acids that can be cited are the mineral acids such as hydrochloric, hydrobromic, sulphuric, nitric and phosphoric acids etc., and the organic acids such as acetic, citric, tartaric, benzoic, salicylic, maleic acids etc.

When the molecule contains an asymmetric carbon atom, the compounds of formula I can be in the form either of a racemic mixture or of one or other enantiomer. These various forms are also within the scope of the present invention.

The 2-amino-4-morpholino-6-propyl-1,3,5-triazines in accordance with the present invention can be prepared by one or other of the following processes:

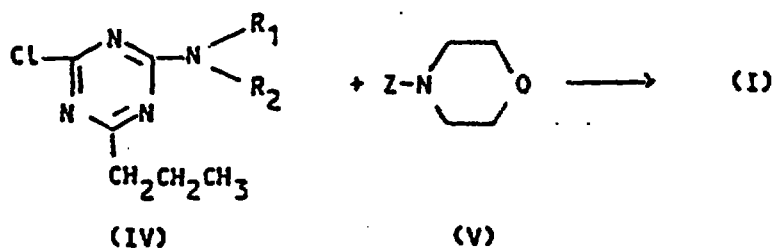
- (a) When, in formula I, R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents a hydroxyl

group or a hydroxyalkyl, alkoxyalkyl, dialkylamino, phenylhydroxyalkyl or (hydroxycycloalkyl)alkyl radical, or R_1 and R_2 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino radical substituted by a hydroxyalkyl radical, 2-chloro-4-morpholino-6-propyl-1,3,5-triazine of formula II is reacted with an amine of formula HNR_1R_2 (III) according to the equation:



in these formulae, R_1 and R_2 have the meaning given above.

- (b) When, in formula I, R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents a hydroxyl group or a hydroxyalkyl, alkoxyalkyl, dialkylamino, phenylhydroxyalkyl or (hydroxy-cycloalkyl)alkyl radical, or R_1 and R_2 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino radical substituted by a hydroxyalkyl radical, a 2-amino-4-chloro-6-propyl-1,3,5-triazine of formula IV is reacted with a morpholine of formula V according to the equation:



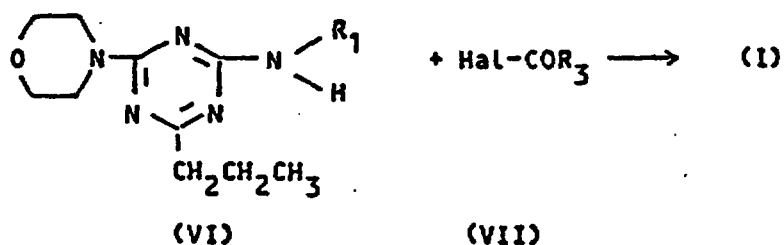
In these formulae, R_1 and R_2 have the meaning given above and Z represents a hydrogen atom or a methyl radical.

Processes (a) and (b) above are carried out at elevated temperature, generally at the boiling point of the solvent used, and in presence of a base. The solvent in which these reactions are carried out is either the amine itself, used in excess, or an inert organic solvent, preferably dioxane, and in the latter case the base used is an inorganic or organic base other than the amine used in the reaction, for example triethylamine.

The 2-chloro-4-morpholino-6-propyl-1,3,5-triazine (II) used as starting material is already known (T. Tsujikawa et al., *Yakugaku Zasshi*, 95, (1975), 512-520)

The starting compounds of formula IV are prepared according to the conventional methods by reacting 2,4-dichloro-6-propyl-1,3,5-triazine with an amine of formula HNR_1R_2 (III) in which R_1 and R_2 have the meaning given above.

- (c) When, in formula I, R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents the COR_3 group in which R_3 is an alkyl, phenyl, halogenophenyl, alkylphenyl, alkoxyphenyl, phenylalkyl or phenoxy radical, the alkyl and alkoxy radicals having 1 to 4 carbon atoms, a 2-amino-4-morpholino-6-propyl-1,3,5-triazine of formula VI is reacted in equimolar proportions with an R_3 carbonyl halide of formula VII according to the equation



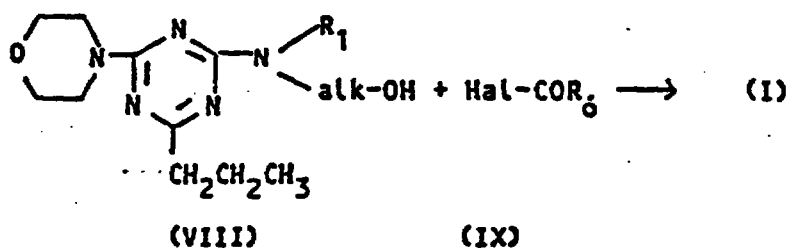
In these formulae R_1 and R_3 have the meaning given above and Hal represents a halogen atom, preferably a chlorine

atom.

This reaction, which is known per se, is generally carried out in an organic solvent such as, for example, dichloromethane, dichloroethane or pyridine, at a temperature between ambient temperature and the boiling point of the solvent and in presence of an acid acceptor such as a tertiary organic base (e.g. triethylamine or pyridine) or an inorganic base.

The starting compounds of formula VI can be prepared by one or other of the two processes (a) or (b) described previously.

- (d) When, in formula I, R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents an alkanoyloxyalkyl, benzoyloxyalkyl or phenylacetyloxyalkyl radical, the alkyl and alkanoyl radicals having 1 to 4 carbon atoms, a (4-morpholino-6-propyl-1,3,5-triazin-2-yl)aminoalkanol of formula VIII is reacted in equimolar proportions with an R_6 carbonyl halide of formula IX, according to the equation



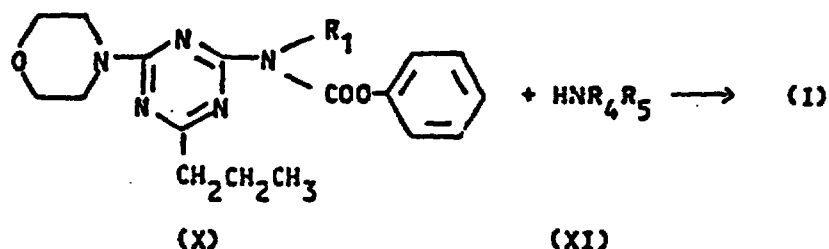
In these formulae, R_1 has the meaning given above, alk represents a C_1 - C_4 alkylene radical, R_6 represents a C_1 - C_4 alkyl, phenyl or benzyl radical and Hal represents a halogen atom, preferably a chlorine atom.

This reaction, which is known per se, is generally carried out in an organic solvent such as, for example, dichloromethane, dichloroethane or pyridine, at a temperature of between 0°C and 25°C and in presence of an acid acceptor such as a tertiary organic base (e.g.

triethylamine or pyridine) or an inorganic base.

The starting compounds of formula VIII can be prepared according to one or other of the two processes (a) or (b) described previously.

- (e) When, in formula I, R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 a CONR_4R_5 group in which R_4 and R_5 represent hydrogen or an alkyl radical, the alkyl radicals having 1 to 4 carbon atoms, a phenyl (4-morpholino-6-propyl-1,3,5-triazin-2-yl)carbamate of formula X is reacted with a nitrogen compound of formula HNR_4R_5 (XI), according to the equation

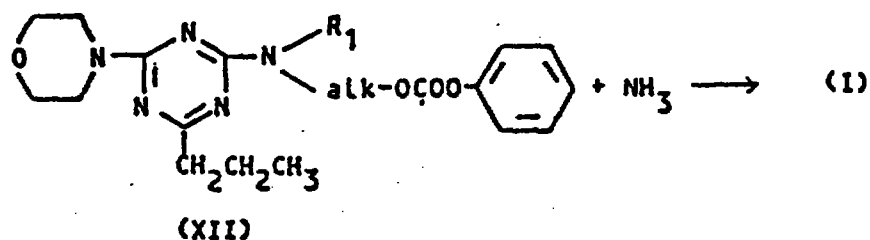


In these formulae, R_1 , R_4 and R_5 have the meaning given above. This reaction is generally carried out in an inert solvent such as dichloromethane and at a temperature between -45°C and $+25^\circ\text{C}$.

The starting compounds of formula X can be prepared according to the process (c) above, by reacting a 2-amino-4-morpholino-6-propyl-1,3,5-triazine of formula VI, in which R_1 has the meaning given above, with an R_2 carbonyl halide of formula VII in which R_2 represents a phenoxy radical and Hal represents a halogen atom, preferably a chlorine atom.

- (f) When, in formula I, R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 an aminocarbonyloxyalkyl radical, the alkyl radicals having

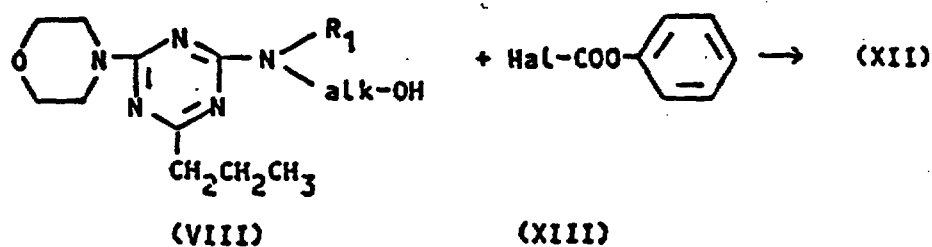
1 to 4 carbon atoms, ammonia is reacted with a 2-morpholino-4-(phenoxy-carbonyloxyalkylamino)-6-propyl-1,3,5-triazine of formula XII, according to the equation



In these formulae, R_1 has the meaning given above and alk represents a C_1 - C_4 alkylene radical.

This reaction is generally carried out in an inert solvent such as dichloromethane and at a temperature of between -35°C and -45°C .

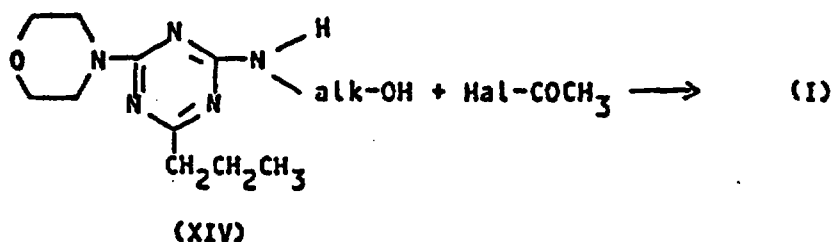
The starting compounds of formula XII can be prepared according to the process (d) above, by reacting a (4-morpholino-6-propyl-1,3,5-triazin-2-yl)aminoalcanol of formula VIII with a phenyl halogenoformate of formula XIII according to the equation



In these formulae, R_1 has the meaning given above, alk represents a C_1 - C_4 alkylene radical and Hal a halogen atom, preferably a chlorine atom.

- (g) When, in formula I, R_1 represents the acetyl radical and R_2 an acetoxyalkyl radical whose alkyl radical has 1 to 4 carbon atoms, at least two moles of an acetyl halide, preferably acetyl chloride, are reacted with one

mole of a
(4-morpholino-6-propyl-1,3,5-triazin-2-yl)aminoalcanol of
formula XIV according to the equation



In these formulae, alk represents a C₁-C₄ alkylene radical and Hal a halogen atom, preferably a chlorine atom. This reaction is carried out in an inert solvent such as dichloromethane, at a temperature between ambient temperature and the reflux temperature of the solvent, and in presence of a base such as triethylamine.

The starting compounds of formula XIV can be prepared according to one or other of the two processes (a) or (b) described previously.

The non-toxic pharmaceutically acceptable acid-addition salts can be prepared from the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of formula I by methods known per se.

The examples which follow illustrate the present invention without limiting it.

Example 1. Preparation according to process (a).
2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol
(compound 1).

145.5 g (0.6 mole) of 2-chloro-4-morpholino-6-propyl-1,3,5-triazine are dissolved in 600 ml of dioxane. To this solution there is introduced, dropwise and with good agitation, over about 80 minutes, a solution of 444 g (7.28

moles) of 2-aminoethanol in 600 ml of dioxane. The reaction mixture is then heated under reflux for 7 hours. The mixture is cooled, the hydrochloride of 2-aminoethanol which has formed is allowed to settle, and the dioxane removed at reduced pressure. The residue obtained is dissolved in 5 litres of diethyl ether. This solution is washed with water and the wash water reextracted with dichloromethane. The organic phases are combined and dried over magnesium sulphate. The solvent is removed at reduced pressure. The solid residue obtained is recrystallized from a 50:50 (v/v) ethyl acetate/petroleum ether mixture. 139.8 g of 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol are obtained.

Yield: 88%. m.pt. 95-99°C.

Analysis for $C_{12}H_{21}N_5O_2$ in %:

calculated:	C 53.91	H 7.92	N 26.20
found:	54.30	8.10	26.13

The 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol can appear in two different crystalline forms according to whether the product has been crystallized from methanol (m.pt. 97-99°C) or from toluene (m.pt. 89-90°C).

The compounds of formula I assembled in Table I are prepared in the same way:

TABLE I

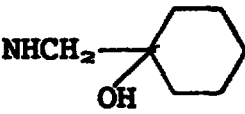
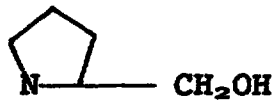
2-R-4-morpholino-6-propyl-1,3,5-triazines

<u>Com- pound</u>	<u>Substituent R</u>	<u>Mol (1)</u>	<u>Yield (%)</u>	<u>m.pt. (°C)</u>	<u>Analyses</u>	
					<u>calc. %</u>	<u>found %</u>
2	NHOH	1.1(2)	51.6	93-94	C 55.68 H 8.20 N 32.24	55.70 8.19 32.19
3	NHCH ₂ CH ₂ CH ₂ OH	2	86.6	95-96	C 55.51 H 8.18 N 24.91	55.02 8.26 24.42
4	NH(CH ₂) ₃ CH ₂ OH	2	74.6	79-80	C 56.95 H 8.47 N 23.73	56.95 8.61 23.42
5	$\begin{array}{c} \text{OH} \\ \\ \text{NHCH}_2-\text{CH}-\text{CH}_3 \end{array}$	3	90.0	104-105	C 55.52 H 8.19 N 24.91	55.50 8.00 23.48
6	$\begin{array}{c} \text{OH} \\ \\ \text{NHCH}_2-\text{CH}-\text{C}_2\text{H}_5 \end{array}$	1(3)	22.0	56-57	C 56.95 H 8.47 N 23.73	56.76 8.37 23.50
7	$\begin{array}{c} \text{C}_2\text{H}_5 \\ \\ \text{NH}-\text{CH}-\text{CH}_2\text{OH} \end{array}$	2	75.4	90-91	C 56.95 H 8.47 N 23.73	56.92 8.40 23.60
8	NH-C(CH ₃) ₂ -CH ₂ OH	2	32.2	85-86	C 56.95 H 8.47 N 23.73	57.87 8.12 24.24
9	N(CH ₃)-CH ₂ CH ₂ OH	2	62.6	32-33	C 55.51 H 8.19 N 24.91	55.48 8.30 24.86

TABLE I (continued)

<u>Com- pound</u>	<u>Substituent R</u>	<u>Mol (1)</u>	<u>Yield (%)</u>	<u>m.pt. (°C)</u>	<u>Analyses</u>	
					<u>calc. %</u>	<u>found %</u>
10	NHCH ₂ CH ₂ OCH ₃	2	42.7	44-45	C 55.52 H 8.19 N 24.91	55.60 8.20 24.99
11	NHCH ₂ CHOHCH ₂ OH	2	68.7	119-120	C 52.52 H 7.74 N 23.57	52.69 7.76 23.60
12	NH-C(CH ₂ OH) ₃	2	61.0	110-111	C 51.37 H 7.64 N 21.41	50.94 7.53 21.16
13	NH-C(CH ₂ OH) ₂ -CH ₃	2	48.0	121-122	C 54.02 H 8.04 N 22.5	54.13 8.00 22.2
14	N(CH ₂ C ₆ H ₅)C ₂ H ₄ OH	2	50	57-58	C 63.86 H 7.56 N 19.6	64.60 7.76 19.8
15	NHCH(CH ₂ OH)- CHOHC ₆ H ₅	2	63	107-108	C 61.13 H 7.24 N 18.77	62.00 7.45 18.92
16(4)	NHCH ₂ CHOHCH ₃	2	38	97-98	C 55.52 H 8.19 N 24.91	56.30 8.42 24.70
17(5)	NHCH ₂ CHOHCH ₃	2	49	94-95	C 55.52 H 8.19 N 24.91	55.64 8.13 24.73

TABLE I (concluded)

Com- pound	Substituent R	Mol (1)	Yield (%)	m.pt. (°C)	Analyses	
					calc. %	found %
18		2	63	75-76	C 60.90 H 8.66 N 20.99	59.83 8.73 20.48
19(6)	 CH ₂ OH	2	47	134-136	C 52.40 H 7.57 N 20.38	52.48 7.40 19.83
20	NHN(CH ₃) ₂	2	63.6	105-106	C 54.14 H 8.97 N 31.58	54.39 8.81 31.65

- (1) number of moles of amine per mole of starting material
 (2) in presence of 2 moles of triethylamine
 (3) in presence of 1 mole of triethylamine
 (4) S-configuration enantiomer; $[\alpha]_D^{25} = +15.3$ (C=1, methanol)
 (5) R-configuration enantiomer; $[\alpha]_D^{25} = -16.1$ (C=1, methanol)
 (6) hydrochloride

The 2-chloro-4-morpholino-6-propyl-1,3,5-triazine used as starting material for the synthesis of the compounds cited in this example has been prepared by the method described by T. Tsujikawa et al. (Yakugaku Zasshi, 95, (1975), 512-520) from 2,4-dichloro-6-propyl-1,3,5-triazine. The latter compound has been prepared by the method of R. Hirt et al., (Helv. Chim. Acta, 33, (1950), 1365-69).

Example 2. Preparation according to process (b).

a) Obtaining the starting material, 2-[(4-chloro-6-propyl-1,3,5-triazin-2-yl)amino]ethanol.

At ambient temperature, 24.4 g (0.4 mole) of 2-aminoethanol dissolved in 100 ml of dioxane are added

dropwise to a solution of 38.4 g (0.2 mole) of 2,4-dichloro-6-propyl-1,3,5-triazine in 100 ml of dioxane. After the addition, the agitation is continued for one night. The 2-aminoethanol hydrochloride is filtered off and the filtrate evaporated at reduced pressure. The residue obtained is recrystallized from a 50:50 (v/v) ethyl acetate/hexane mixture. 41.5 g of 2-[(4-chloro-6-propyl-1,3,5-triazin-2-yl)amino]ethanol are obtained. Yield: 96%. M.pt.: 87-88°C.

Analysis for $C_8H_{13}ClN_4O$ in %

calculated:	C 44.34	H 6.00	N 25.88	Cl 16.40
found:	44.42	H 6.17	25.69	16.52

b) Preparation of 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol.

- Variant 1.

10.83 g (0.05 mole) of 2-[(4-chloro-6-propyl-1,3,5-triazin-2-yl)amino]ethanol and 8.7 g (0.10 mole) of morpholine are mixed in 150 ml of dioxane. The temperature of the mixture rises spontaneously to 41 °C. The mixture is then heated under reflux for 30 minutes and then cooled, and the morpholine hydrochloride which has formed filtered off. The filtrate is evaporated, and the residue recrystallized from a 50:50 (v/v) ethyl acetate/hexane mixture. 11.8 g of 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol are obtained.

Yield: 88.4 %. M.pt.: 93-94°C.

The product recrystallized from methanol melts at 97-98°C and is identical with compound 1 prepared in example 1.

- Variant 2.

10.83 g (0.05 mole) of 2-[(4-chloro-6-propyl-1,3,5-triazin-2-yl)amino]ethanol and 15.15 g (0.15 mole) of N-methylmorpholine are mixed in 100 ml of dioxane. The mixture is heated under reflux for 20 hours and then cooled and the dioxane removed at reduced pressure.

The residue is dissolved in 200 ml of ethyl acetate. The solution is twice washed with 50 ml water, dried over sodium sulphate, and concentrated. The product crystallizes during the evaporation. 9.23 g of 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol, identical with the product obtained above, are obtained.

Example 3. Preparation according to process (c).

a) Obtaining the starting 2-amino-4-morpholino-6-propyl-1,3,5-triazines.

1. 2-amino-4-morpholino-6-propyl-1,3,5-triazine (hydrochloride).

This product is described by S. Murai et al. in Japanese Patent Application 69.688/74 (Chem. Abstr. 81, (1974), 136188x). It can be prepared in the following way.

87 g (1 mole) of morpholine and 8.6 g (0.05 mole) of 2-amino-4-chloro-6-propyl-1,3,5-triazine are mixed. The temperature of the mixture rises spontaneously to 54 °C. The mixture is then heated under reflux for 5 hours. The reaction mixture is evaporated at reduced pressure and the residue obtained redissolved in ethyl acetate. The solution is washed three times with water, and then dried over sodium sulphate. The solvent is removed at reduced pressure and the residue crystallized from hexane. 9.1 g of 2-amino-4-morpholino-6-propyl-1,3,5-triazine are obtained.

Yield: 82%. M.pt.: 127-128°C.

Hydrochloride: m.pt.: 210-211°C (isopropanol/ether).

Analysis for $C_{10}H_{17}N_5O.HCl$ in %

calcd.:	C 46.24	H 6.94	N 26.97	Cl ⁻ 13.68
found:	46.21	6.90	26.78	13.61

The 2-amino-4-chloro-6-propyl-1,3,5-triazine used as starting material in this step was prepared according

to the method of S. Murai et al., (Japanese Patent Application 69.688/74).

2. 2-(methylamino)-4-morpholino-6-propyl-1,3,5-triazine (hydrochloride).

To a solution containing 5.6 g (0.03 mole) of 2-chloro-4-(methylamino)-6-propyl-1,3,5-triazine in 50 ml dioxane, a solution containing 8.7 g (0.1 mole) of morpholine in 50 ml of dioxane is added. The mixture is heated under reflux for 5 hours. It is then cooled and the morpholine hydrochloride formed filtered off. The solvent is removed at reduced pressure and the residue taken up in chloroform. The organic phase is water-washed and dried over sodium sulphate. The solvent is evaporated and the residue recrystallized from ethyl acetate. 5.3 g of 2-(methylamino)-4-morpholino-6-propyl-1,3,5-triazine are obtained.

Yield: 74%. M.pt.: 131-133°C.

The product obtained is dissolved in hot isopropanol. To this solution there is added the equivalent quantity of hydrochloric acid in solution in diethyl ether. The hydrochloride crystallizes by cooling. The product is filtered off, washed with diethyl ether and dried.

Yield: 75%. M.pt.: 177-178°C

Analysis for $C_{11}H_{19}N_5O.HCl$ in %

calcd.:	C 48.26	H 7.31	N 25.59	Cl ⁻ 12.97
found:	48.38	7.40	25.57	12.64

The 2-chloro-4-(methylamino)-6-propyl-1,3,5-triazine used as starting material in this step has been prepared by the method of T. Tsujikawa et al. (Yakugaku Zasshi, 95, (1975), 512-520).

b) Preparation of the 2-amino-4-morpholino-6-propyl-1,3,5-triazines.

1. N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)acetamide (compound 21).

At ambient temperature, 4 g (0.05 mole) of acetyl chloride are added dropwise to a solution of 11.2 g (0.05 mole) of 2-amino-4-morpholino-6-propyl-1,3,5-triazine in 100 ml of anhydrous pyridine. The mixture is agitated for 6 hours and then allowed to stand for 48 hours. The pyridine hydrochloride is filtered off and the filtrate evaporated at reduced pressure. The residue obtained is taken up once in toluene, which is evaporated again. Then the residue is taken up in dichloromethane and the solution water-washed and dried over sodium sulphate. The residue obtained after evaporation of the solvent is purified by chromatography on silica (eluant: 90:10 (v/v) dichloromethane/methanol) and the product finally crystallized from ethyl acetate. 5.75 g of N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)acetamide are obtained.

Yield: 43.4%. M.pt.: 141-2°C (Compound 21a)

Hydrochloride: M.pt.: 145-146°C (isopropanol/ether). (Compound 21b).

Analysis for $C_{12}H_{19}N_5O_2 \cdot HCl$ in %

calcd.:	C 47.76	H 6.63	N 23.22	Cl ⁻ 11.77
found:	47.78	6.73	22.80	11.62

2. N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)benzamide (hydrochloride) (compound 22).

To a solution of 11.2 g (0.05 mole) of 2-amino-4-morpholino-6-propyl-1,3,5-triazine in 200 ml of dichloroethane, there are added successively at ambient temperature a solution of 7.7 g (0.055 mole) of benzoyl chloride in 50 ml of dichloroethane and a solution of 5.5 g (0.055 mole) of triethylamine in 50 ml of dichloroethane. The mixture is heated under reflux for

6 hours and then cooled to ambient temperature. It is then washed successively with water, with an aqueous sodium bicarbonate solution, and then once more with water. The organic phase is dried over sodium sulphate and the solvent evaporated at reduced pressure. The residue obtained is chromatographed on silica (eluant: 95:5 (v/v) dichloromethane/ethanol) and then finally recrystallized from a 50:50 (v/v) diethyl ether/hexane mixture. The product forms a hydrochloride in the diethyl ether. There is thus obtained 12.1 g of the hydrochloride of

N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)benzamide.

Yield: 66.5%. M.pt.: 197-198°C

Analysis for $C_{17}H_{21}N_5O_2 \cdot HCl$ in %

calcd.:	C 56.12	H 6.05	N 19.26	Cl ⁻ 9.77
found:	56.30	6.50	19.16	9.54

The compounds assembled in Table II have been prepared, as indicated, either by the method of example 3b)1 or by the method of example 3b)2 above.

TABLE II

2-R-4-morpholino-6-propyl-1,3,5-triazines

<u>Com- pound</u>	<u>Substituent R</u>	<u>Method</u>	<u>Yield (%)</u>	<u>M.pt. (°C)</u>	<u>Analyses</u>	
					<u>calc. %</u>	<u>found %</u>
23	NHCOCH ₂ C ₆ H ₅	3b.1	51.3	110-113	C 63.34 H 6.74 N 20.52	63.18 6.85 20.55
24	NHCOCH(CH ₃) ₂	3b.1	34.3	141	C 57.34 H 7.85 N 23.89	56.84 7.84 23.70
25a	N(CH ₃)COCH ₃	3b.1	34.8	60-61	C 55.91 H 7.53 N 25.09	56.02 7.57 25.05
25b (1b)	N(CH ₃)COCH ₃	3b.1	75.5	104-105	C 49.44 H 6.97 N 22.19	48.78 7.01 22.43
26	N(CH ₃)COCH(CH ₃) ₂	3b.1	38.5	36-37	C 58.62 H 8.16 N 22.80	58.78 8.33 22.62
27 (1)	N(CH ₃)COC ₆ H ₅	3b.2	46.5	122	C 57.22 H 6.36 N 18.54	56.78 6.40 18.28
28	NH-COOC ₆ H ₅	3b.2	24.8	154-155	C 59.48 H 6.12 N 20.41	 6.32 20.31
29 (1)	NH-COC ₆ H ₄ -pCl	3b.2	66	205-206	C 51.27 H 5.31 N 17.58	51.19 5.34 17.49

TABLE II (concluded)

<u>Com- pound</u>	<u>Substituent R</u>	<u>Method</u>	<u>Yield (%)</u>	<u>M.pt. (°C)</u>	<u>Analyses</u>	
					<u>calc. %</u>	<u>found %</u>
30	N(CH ₃)COC ₆ H ₄ -pCl	3b.2	72	96-97	C 57.52 H 5.90 N 18.63	58.07 6.17 18.65
31 (1)	NHCOC ₆ H ₄ -pOCH ₃	3b.2	33	199	C 54.89 H 6.14 N 17.78	54.83 6.17 17.80
32 (1)	N(CH ₃)COC ₆ H ₄ - pOCH ₃	3b.2	56	120	C 55.94 H 6.42 N 17.17	53.4 6.48 17.22
33 (1)	NHCOC ₆ H ₄ -pCH ₃	3b.2	53	188	C 57.21 H 6.40 N 18.53	57.45 6.42 18.73
34 (1)	N(CH ₃)COC ₆ H ₄ - pCH ₃	3b.2	74	99	C 58.23 H 6.69 N 17.87	58.08 6.73 18.11
35	N(CH ₃)COC ₆ H ₃ - (3,4-di-OCH ₃)	3b.2	70	73	C 59.84 H 6.78 N 17.44	60.12 7.09 17.45
36	NHCOC ₆ H ₃ - (3,4-di-CH ₃)	3b.2	45	232	C 58.23 H 6.69 N 17.87	58.42 6.65 17.72
(1)	hydrochloride					

Example 4. Preparation according to process (d).

1. 2-[[2-(acetoxy)ethyl]amino]-4-morpholino-6-propyl-1,3,5-triazine (compound 37).

To a solution of 13.4 g (0.05 mole) of 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol (compound 1 prepared in example 1) in 200 ml of dichloromethane there are added simultaneously, between 0°C and 5°C, 4.3 g (0.055 mole) of acetyl chloride dissolved in 50 ml of dichloromethane and 5.5 g (0.055 mole) of triethylamine in solution in 50 ml of dichloromethane. The addition of these two reactants is so controlled that in the reaction medium the acid chloride is always in excess in relation to the triethylamine. The agitation of the mixture is continued for one hour at 5°C and then for 12 hours at ambient temperature. The reaction mixture is washed successively with an aqueous sodium bicarbonate solution and with water. The mixture is dried over sodium sulphate and the solvent evaporated under reduced pressure. The residue crystallizes in a 1:2 toluene/hexane mixture. The product obtained is first purified by chromatography on silica (eluant: 95:5 (v/v) dichloromethane/ethanol) and then finally crystallized from a 1:1 toluene/hexane mixture. 9.3 g of 2-[[2-(acetoxy)ethyl]amino]-4-morpholino-6-propyl-1,3,5-triazine are obtained.

Yield: 60%. M.pt.: 94-95°C

Analysis for $C_{14}H_{23}N_5O_3$ in %

calculated:	C 54.37	H 7.44	N 22.65
found:	54.98	7.69	22.62

The compounds assembled in Table III are prepared in the same way.

TABLE III

2-R-4-morpholino-6-propyl-1,3,5-triazines

<u>Com- pound</u>	<u>Substituent R</u>	<u>Yield (%)</u>	<u>M.pt. (°C)</u>	<u>Analyses</u>	
				<u>calc. %</u>	<u>found %</u>
38	NH(CH ₂) ₂ O-COCH(CH ₃) ₂	59.3	54-55	C 56.97	56.86
				H 8.01	8.04
				N 20.77	20.74
39	NH(CH ₂) ₂ O-COC ₆ H ₅	67.4	98-99	C 61.46	61.52
				H 6.74	6.75
				N 18.87	18.91
40	NH(CH ₂) ₂ O-COCH ₂ C ₆ H ₅	63.4	63-64	C 62.34	62.45
				H 7.01	7.07
				N 18.18	18.15

Example 5. Preparation according to process (e).

N,N-dimethyl-N'-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)urea (compound 41).

A stream of gaseous dimethylamine is passed at a temperature of 20°C for 3 hours into a solution of 5 g (0.0145 mole) of phenyl (4-morpholino-6-propyl-1,3,5-triazin-2-yl)carbamate (compound 28 prepared in example 3) in 100 ml of anhydrous dichloromethane. The mixture is then left to stand for 12 hours. It is washed successively with a dilute solution of sodium hydroxide and with water. The organic phase is dried over sodium sulphate, and the solvent evaporated at reduced pressure. The residue obtained crystallizes in a 50:50 (v/v) ethyl acetate/hexane mixture. 1.7 g of N,N-dimethyl-N'-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)urea are obtained.

Yield: 39.9%. M.pt.: 110-111°C

Analysis for C₁₃H₂₂N₆O₂ in %

calculated:	C 53.06	H 7.48	N 28.57
found:	53.20	7.69	28.67

Example 6. Preparation according to process (f).

2-[[2-[(aminocarbonyl)oxy]ethyl]amino]-4-morpholino-6-propyl-1,3,5-triazine (compound 42).

To one litre of liquid ammonia there are introduced 19.4 g (0.05 mole) of 2-morpholino-4-[[2-[(phenoxy carbonyl)oxy]ethyl]amino]-6-propyl-1,3,5-triazine dissolved in 100 ml of anhydrous dichloromethane. Stirring is continued at a temperature of between -35°C and -45°C for 7 hours. The ammonia is then evaporated and the organic phase washed successively with an aqueous sodium bicarbonate solution and with water. The product is dried over sodium sulphate and the solvent evaporated off under reduced pressure. The residue obtained crystallizes in a 50:50 (v/v) ethyl acetate/hexane mixture. 15.1 g of 2-[[2-[(aminocarbonyl)oxy]ethyl]amino]-4-morpholino-6-propyl-1,3,5-triazine are obtained.

Yield: 97.4%. M.pt.: 139-140°C

Analysis for $C_{13}H_{22}N_6O_3$ in %

calculated: C 50.32 H 7.09

found: 50.39 7.15

The 2-morpholino-4-[[2-[(phenoxy carbonyl)oxy]ethyl]amino]-6-propyl-1,3,5-triazine used as starting material in this example has been prepared by the process of example 4 from 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol and phenyl chloroformate.

Yield: 85%. M.pt.: 83-84°C.

Analysis for $C_{19}H_{25}N_5O_4$ in %

calculated: C 58.91 H 6.46 N 18.0

found: 58.99 6.60 18.1

Example 7. Preparation according to process (g).

N-[2-(acetoxy)ethyl]-N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)acetamide (compound 43).

To a suspension of 13.4 g (0.05 mole) of 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol (compound 1 prepared in example 1) in 250 ml of dichloroethane,

maintained at a temperature near 20°C, there are added a solution of 11.8 g (0.15 mole) of acetyl chloride in 50 ml of dichloroethane and a solution of 15 g (0.15 mole) of triethylamine in 50 ml of dichloroethane. This addition is made as follows: first, half of the acid chloride is introduced and the mixture allowed to react for 15 minutes, then half of the triethylamine is introduced; then the remainder of the acetyl chloride is introduced, reaction is allowed to occur for a further 15 minutes, the mixture is heated to 55°C and finally the remainder of the triethylamine is introduced. The mixture obtained is heated under reflux for 7 hours. It is then allowed to stand for one night at ordinary temperature. It is washed successively with an aqueous sodium bicarbonate solution and with water. The product is dried over sodium sulphate and filtered in presence of norite. After evaporating the solvent under reduced pressure, the residue obtained is purified by chromatography on silica (eluant: 95:5 (v/v) dichloromethane/ethanol). The product obtained crystallizes in the cold from hexane. 6.35 g of N-[2-(acetoxy)ethyl]-N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)acetamide are obtained.

Yield: 36.2%. M.pt.: 49-50°C.

Analysis for $C_{16}H_{25}N_5O_4$ in %

calculated:	C 54.70	H 7.12	N 19.94
found:	55.22	7.22	20.0

As indicated above, the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of formula I, as well as their non-toxic pharmaceutically acceptable acid-addition salts, have the property of correcting the effects of a hypofunction of the cholinergic system. This advantageous property is demonstrated by a series of pharmacological tests by which it is shown that the compounds in accordance with the present invention show certain effects similar to those of well known cholinergic compounds such as oxotremorine, arecoline or physostigmine, or else counteract the effect of a

cholinergic antagonist such as scopolamine.

The compounds of the present invention have been subjected to pharmacological tests whose results are reproduced below.

1. Potentiation of the cholinergic effects of oxotremorine.

The purpose of this test (R.C. Rathbun et al., *Psychopharmacologia*, 4, (1963), 114-125) is to show that the compounds in accordance with the invention potentiate the central and peripheral cholinergic effects caused by the administration to the mouse of a low dose of oxotremorine.

The degree of peripheral cholinergic activation is measured by the salivatory effect quantified by the following marking system:

- score 0: the saliva does not exceed that secreted by a normal mouse;
- score 1: a little saliva is found around the teeth;
- score 2: the saliva appears as a narrow strip around the mouth;
- score 4: the saliva wets an area under the chin;
- score 6: the saliva flows from the mouth, for example onto the forelegs.

The intermediate scores are not used, and the saliva is removed after each observation.

The degree of central cholinergic activation is measured by the tremogenic effect quantified by the following marking system:

- score 0: no tremors;
- score 1: periodic and slight occasional tremors;
- score 2: slight and moderate tremors, often repeated;
- score 4: pronounced tremors, but interrupted by periods of stillness;
- score 6: very pronounced and almost continuous tremors.

Male NMRI mice (20 to 25 g) are divided into four groups of five animals: that is to say one control group and three treated groups. The compound to be tested is administered intraperitoneally (to the three treated groups) 20 minutes before the administration of oxotremorine, at a different dose for each of the treated groups. The oxotremorine is administered intraperitoneally to the treated groups and the control group at a dose of 0.05 mg/kg, in solution in 10 ml/kg of isotonic solution. This dose corresponds approximately to the minimum dose of oxotremorine which causes tremors and salivation.

After the administration of the oxotremorine, the animals are individually placed in small cages and observed at regular intervals of 5 minutes until the cholinergic effects have completely disappeared.

For each of the groups, the individual scores recorded in each period of observation are summed; this enables a curve to be constructed, characteristic for each group, showing the sum of the scores as a function of time.

The average values of the areas under the curves obtained for each of the treated groups are compared with the average value of the area under the curve corresponding to the control group and are subjected to a statistical analysis by the Mann-Whitney method. From this comparison, a "minimum active dose" can be determined. This "minimum active dose" is the minimum dose of a compound necessary for still observing a potentiation of the salivatory or tremogenic effect of oxotremorine or, in other words, for obtaining a greater area than the area under the curve obtained for the control group.

The results obtained in this test showed that the compounds of the invention potentiate the salivatory effect of oxotremorine at a minimum dose of between 7.7 and 107 mg/kg, and potentiate the tremogenic effect at a minimum dose between 8 and 112 mg/kg.

Moreover, the minimum active doses do not show any

cholinergic effects of their own and are far removed from the lethal doses determined in the Irwin test.

In addition, this test has demonstrated that certain compounds in accordance with the invention, administered at the minimum active dose, have effects of longer duration than those of the methyl ester of 1,2,5,6-tetrahydro-1-methyl-3-pyridinecarboxylic acid (arecoline), which is a well known cholinergic compound.

Thus the compounds of the invention show a potentiation of the salivatory and tremogenic effects of oxotremorine twenty minutes after having been administered in the minimum active dose, whereas under the same conditions arecoline gives no potentiation.

2. Inhibition of the hyperactivity induced by scopolamine.

An animal placed for the first time in a new environment shows an intense exploratory activity in this new environment. The progressive diminution and final disappearance of this exploratory activity, or in other words, the habituation to the new environment, can be considered as an elementary form of learning. This elementary form of learning is sensitive to the influence of drugs which facilitate or slow down learning (A. Platel et al., *Psychopharmacology*, 78, (1982), 346-352). Thus, for example scopolamine, a compound which causes disorders of memory, induces exploratory hyperactivity in the rat placed in a new environment; this phenomenon is linked with the central anticholinergic activity of this compound (W.J. Stewart et al., *Psychopharmacologia*, 44, (1975), 291-295). On the other hand, a cholinergic agonist such as physostigmine counteracts the hyperactivity induced by scopolamine.

In the test described below, the compounds of the invention are administered, according to their solubility, either in the isotonic solution or in an appropriate vehicle (usually a citrate buffer at pH 5). This test establishes that the

activity of the compounds of the invention is comparable with that of physostigmine.

It is based on the one hand on the original technique described by A. Platel (loc. cit.) and on the other hand by the method of automating the recording of the measurements described by H.J. Tauger et al. (J. Neuroscience Methods, 10, (1984), 237-245).

In this test, male Sprague-Dawley SPF rats (Specific Pathogen Free; 160 to 200 g) are used. During the week preceding the experiment, these animals are kept in normal conditions in groups of 15 animals in standard grid cages, and food and drink are freely accessible.

At the start of the experiment, the rats are divided into 4 homogeneous groups of 10 animals and are acclimatized for one hour to the place of the experiment. Each group of animals is then subjected to a specified treatment:

- group 1 receives two simultaneous intraperitoneal injections of isotonic solution or of the vehicle used;
- group 2 receives one intraperitoneal injection of isotonic solution or of the vehicle used and one intraperitoneal injection of 0.5 mg/kg of scopolamine in solution;
- group 3 receives one intraperitoneal injection of the compound to be tested in solution in an appropriate vehicle and one intraperitoneal injection of isotonic solution or of the vehicle used;
- group 4 receives one intraperitoneal injection of the compound to be tested and one intraperitoneal injection of 0.5 mg/kg of scopolamine.

Thirty minutes after this treatment, the four groups of animals are tested simultaneously. To this end, each group

is distributed in a square enclosure (100 x 100 cm) consisting of a grid floor and a vertical wall 50 cm high. Each of these enclosures contains 16 zones, comprising 4 zones in the corners, 4 central zones and 8 peripheral zones. Furthermore, each enclosure is equipped with 2 rows of infra-red cells arranged 2 cm above the floor in order to record the horizontal movements of the animals and 2 other rows of infra-red cells arranged at a height of 10 cm above the floor for recording the vertical movements. These infra-red cells are connected to a microprocessor which permits the determination of the average distances covered (in cm) by a group of animals, the average number of times they straighten up, and the distribution of the horizontal movements in the various central, peripheral and corner zones, expressed as the average residence time in these various zones.

Each compound tested is studied at at least three different doses, from which the minimum active dose which inhibits the hyperactivity induced by intraperitoneal administration of 0.5 mg/kg of scopolamine is determined.

A comparison is then made either between the values obtained in group 2, treated only with scopolamine, and those obtained in group 4, treated simultaneously with scopolamine and with the compound to be tested; or between the values obtained in group 4 and those obtained in group 3, treated only with the compound to be tested. The control group 1 serves as control for the action of the scopolamine administered to group 2. The observed differences are evaluated statistically in all cases by the Mann-Whitney method.

The results obtained in this test showed that the compounds of the invention have a good inhibitory activity on the hyperactivity induced by scopolamine. The minimum active doses determined for these compounds are between 1 and 89 mg/kg. But, unlike physostigmine, which is inactive when administered more than 15 minutes before making the

measurements, the compounds according to the invention still have an inhibitory activity when administered 30 minutes before making the measurements. Their activity is therefore of longer duration than that of physostigmine.

3. Inhibition of the effects of scopolamine on the electroencephalogram (EEG).

The administration of scopolamine to man or animal induces mnemonic disorders comparable with those which appear in the course of normal or pathological ageing. In patients suffering from senile dementia of Alzheimer's type, an improvement of mnemonic disorders has been obtained by administration of physostigmine, a compound which inhibits acetylcholinesterase.

Scopolamine, administered intraperitoneally to rats at a dose of 0.5 mg/kg, induces changes in the EEG spectrum, which take the form of an increase of the intensity of the 8 Hz band, a reduction of the intensity of the bands from 20.8 to 40 Hz, and an increase of the total intensity of the EEG spectrum. Physostigmine counteracts these changes. The objective of this test is to show, by the method of quantitative analysis of the electroencephalogram, that the compounds of the invention have the property of neutralizing the effects that scopolamine exerts on the EEG spectrum (P. Etevenon - Electroencephalography on the computer. Quantitative and statistical analysis. Copedith, Paris, 1978).

In this test, male albino Sprague-Dawley SPF rats (160 to 200 g) are used.

When the animals are aged 3 months, 5 cortical electrodes are permanently implanted, aseptically and under general anaesthesia: a neutral electrode, a left and a right frontal electrode, and a left and a right occipital electrode. (P. Etevenon, loc. cit.).

The test is carried out when the animals are aged about 15

months. In the interim, the animals are kept in individual cages; they receive water and food ad libitum and are subjected to a regular daily cycle including a period of darkness between 6 p.m. and 6 a.m. At the same time the animals are progressively habituated to the cages of the soundproof cabin which they will later occupy for the recording of the electroencephalograms, as well as to the experimental conditions, by the intraperitoneal administration of a placebo.

The products are administered immediately before the EEG is recorded.

The rats are divided into groups of 8 animals and 16 EEG spectra are recorded in 5 seconds (two EEG spectra per animal). The spectra obtained are then analysed by computer (fast Fourier transform), which enables the average of the 16 measurements carried out to be determined for each group and the total intensity of the EEG spectrum and the distribution of this intensity (in %) in the different frequency bands to be determined for each animal. This operation (recording of the spectra) is repeated 9 times (total duration: 121 minutes).

The effect of the compound studied is deduced from the statistical comparison of the results obtained for the different groups of animals, to which there have been administered the compound to be tested, scopolamine and a placebo respectively.

Table IV below shows, for some compounds of the invention administered intraperitoneally at the dose indicated in mg/kg, the percentage reduction of the intensity increase of the 6.4 to 9.6 Hz band (mean 8 Hz) caused by the intraperitoneal administration of 0.5 mg/kg of scopolamine.

TABLE IV

Inhibition of the effects of scopolamine on
the 6.4 to 9.6 Hz band of the EEG

<u>Compound</u>	<u>Dose (mg/kg)</u>	<u>Inhibition (%)</u>
1	5.3	52
7	29.5	50
9	8.8	53.3
20	2.7	66.7
21a	2.7	100
22	3.6	66.7
25a	0.88	46.7
26	3.1	55.6
27	12	93.8
37	9.9	53.3
43	11.2	77.8
physostigmine	0.4	76.8

The results show that the compounds of the invention, like physostigmine, inhibit the effects which scopolamine exerts on the electroencephalogram. It is seen that this inhibition reaches and even exceeds 50% at relatively low doses, very far from toxic doses, which is not the case for physostigmine.

4. Multiple-trial passive avoidance.

The compounds of the present invention have been studied in order to reveal on the one hand their property of assisting learning, expressed by the reduction in the number of trials necessary for reaching a predetermined criterion, and on the other hand their property of counteracting amnesia caused by the administration of scopolamine. To this end, the method of multiple-trial passive avoidance has been used. This method is well known for evaluating the effects that a product exerts on memory and learning (A. Fine et al., Proc. Natl. Acad. Sci. USA, 82, (1985),

5227-5230).

The test is carried out on male Sprague-Dawley rats (160-200 g), which are kept during the experiment in standard cages. The apparatus used is a square transparent cage, of 35 cm side and 25 cm height, fitted with a floor consisting of an electrifiable grid. An insulating rubber mat (10 x 17 cm) is placed on the floor in one of the corners of the cage.

To assess whether a compound is able to assist learning, the following test is carried out.

Each animal is placed on the rubber mat, and the time that the animal takes to decide to leave this position to explore the cage is noted. After 20 seconds of exploration, the animal receives an electric shock (duration, 3 seconds) in the paws, causing a flight reaction. The rat is immediately taken from the apparatus and replaced in its original cage. This experiment is repeated until the animal stays for at least 180 seconds on the rubber mat to avoid the electric shock. The learning is expressed by the average number of trials necessary to reach a time of stay on the mat of 180 seconds.

A time of stay of 180 seconds on the rubber mat is considered to be the maximum performance in avoiding the electric shock which has to be achieved by the animal. The rats which stay on the mat for this length of time have acquired the avoidance reflex and are replaced in their original cage without receiving an electric shock.

To assess whether a compound is able to assist mnemonic retention over a period of time, the following experiment is carried out. Each animal is subjected to four tests at times of 0, 4, 24 and 28 hours. In the first test (time 0), the animal is placed on the rubber mat, and the time the animal takes to decide to leave this position to explore the cage is noted. After 20 seconds of exploration, the rat receives an electric shock (duration 3 seconds) in the paws, causing a flight reaction. The rat

is immediately withdrawn from the apparatus and replaced in its original cage. During the three subsequent tests (times: 4, 24 and 28 hours), the animal is replaced on the mat, and the time it takes to leave this position is noted. As soon as the four paws of the animal rest on the grid, it receives an electric shock and is immediately withdrawn from the apparatus.

At the start of the experiment, the rats are divided into 4 homogeneous groups of 15 animals. Thirty minutes after each test, each group of animals is subjected to a specified treatment:

- group 1 receives an intraperitoneal injection of isotonic solution;
- group 2 receives an intraperitoneal injection of the compound to be tested;
- group 3 receives an intraperitoneal injection of 0.5 mg of scopolamine; and
- group 4 receives an intraperitoneal injection of 0.5 mg of scopolamine and simultaneously an intraperitoneal injection of the compound to be tested.

Groups 1 and 2 are used in the first experiment and groups 3 and 4 in the second experiment.

The results obtained in this test with the compounds of the invention are reproduced in Table V. This table indicates the compound subjected to the test (column 1) and the dose administered intraperitoneally, expressed in mg/kg (column 2).

Columns 3 and 4 give the results obtained in the test used to evaluate learning. The figures indicate the average number of trials necessary for a control animal (group 1) or an animal treated by the compound (group 2) to learn to stay for 180 seconds on the rubber mat to avoid the electric shock. The results have been analysed by the Student test. Columns 5 to 12 give the results obtained in the experiment used to evaluate mnemonic retention. The figures in columns 5 to 8 represent the average times

of stay observed at 0, 4, 24 and 28 hours for the animals of group 3, treated only with scopolamine; and in columns 9 to 12 are found the corresponding figures for the animals of group 4, treated simultaneously by scopolamine and by the compound studied (at the dose indicated in the second column). The favourable influence of a compound in counteracting amnesia induced by scopolamine is demonstrated by the increase of the time of stay on the mat at each observation. The differences observed are analysed statistically by the Mann-Whitney method.

TABLE V

Com- pound	Dose (mg/kg)	Learning: average number of trials		Mnemic retention: time of stay (in seconds)							
				Group 3				Group 4			
		Group 1	Group 2	0	4	24	28	0	4	24	28
1	5.35	2.27	1.53	1.27	13.3	24.2	26.3	2.7	44.8	61.3	102.7
7	29.54	2.67	2.57	1.0	1.5	3.3	4.0	1.3	7.3	22.5	52.1
9	8.72	2.27	2.0	1.4	2.3	3.3	5.7	3.3	67.9	62.7	160.3
10	28.14	2.87	2.07	1.8	4.5	2.3	4.5	5.5	15.7	31.1	34.1
20	2.66	1.93	1.53	1.1	2.5	4.6	5.5	2.7	55.3	57.7	87.9
21a	2.65	1.60	1.53	2.4	9.7	9.1	33.9	3.4	60.4	74.6	102.4
22	3.64	2.20	1.0	1.7	11.1	20.3	12.8	2.8	70.9	82.8	137.6
25a	0.89	2.07	2.07	2.1	3.0	7.7	3.3	1.7	8.1	34.7	44.5
27	3.78	2.20	1.13	1.9	8.9	31.6	54.1	11.3	88.6	111.5	133.5
37	9.6	2.0	1.3	1.0	2.5	4.5	5.8	2.9	24.0	44.4	49.9
41	9.12	2.53	1.33	1.0	3.7	7.0	7.7	1.3	15.8	27.3	66.3
PS*	0.4	2.60	2.30	1.7	1.4	6.9	21.3	1.9	17.8	56.2	53.4

* PS = physostigmine

From this table it is apparent that:

- the compounds of the invention assist learning of the avoidance reflex: the average number of trials necessary to attain the predetermined criterion (maximum time of stay on the mat of 180 seconds) is less high for the treated animals (column 4) than for the control animals (column 3);
- the amnesic effect of scopolamine is very marked: it can be seen that the times of stay of the animals of group 3 (columns 5 to 8) are clearly less than the 180 seconds achieved by the controls after an average number of trials (column 3); and that, under these conditions, the favourable influence of the compounds of the invention in counteracting the amnesic effect of scopolamine is very clear: the animals of group 4, treated simultaneously by scopolamine and by a compound of the invention, have times of stay, at each observation, considerably higher than the animals of group 3 treated with scopolamine alone (compare the results of column 5 with those of column 9, 6 with 10, etc.).
- physostigmine exerts a favourable effect against the amnesic effect of scopolamine, similar to that of the compounds of the invention, but at a dose giving secondary effects and very close to the toxic dose, which is not the case for the compounds of the invention.

5. Toxicity.

The toxicity of the compounds of the invention has been determined on the male NMRI mouse by means of the Irwin test (S. Irwin, *Psychopharmacologia*, 13, (1968), 222-257). Progressive doses of the compound to be tested are administered intraperitoneally to groups of three mice until the lethal dose (i.e. the dose causing the death of two animals in three in 48 hours) is reached. In Table VI below, the lethal dose observed for the compounds of the invention is given. It emerges from this

table that the compounds of the invention have a very low toxicity, unlike physostigmine.

TABLE VI

Compound	Lethal dose (mg/kg)	Compound	Lethal dose (mg/kg)
1	802	23	> 1024
2	718	24	880
3	844	25a	838
4	886	25b	947
5	563	26	922
6	886	27	1133
7	886	28	> 1030
8	886	29	398
9	844	30	1125
10	844	31	511
11	892	32	1222
12	982	33	1132
13	934	34	1174
14	> 1073	35	401
15	1121	36	1174
16	844	37	928
17	844	38	> 1012
18	1007	39	> 1114
19	1031	40	1157
20	799	41	294
21a	996	42	> 931
21b	905	43	351
22	1091	physostigmine	0.82

6. Posology and administration.

The pharmaceutical compositions containing the compounds of the invention can be administered orally, parenterally or rectally. The pharmaceutical compositions which can be used for oral administration can be solids or liquids, for example in the form of tablets (coated or non-coated),

pills, dragees, gelatine capsules, solutions, syrups and the like. Likewise, the compositions which can be used for parenteral administration are the pharmaceutical forms known for this type of administration, for example, aqueous or oily solutions, suspensions or emulsions.

For rectal administration, the compositions containing the compounds of the invention usually take the form of suppositories.

The pharmaceutical forms, such as injectable solutions, injectable suspensions, tablets, drops, suppositories and the like are prepared according to the methods currently used by pharmacists. The pharmaceutical forms also comprise compositions which enable the active product to be delivered progressively. The compounds of the invention are mixed with a solid or liquid vehicle which is non-toxic and pharmaceutically acceptable, and optionally with a dispersant, a disintegrating agent, a stabilizer and the like. Sweetening agents, colouring agents and the like may also be added if appropriate. The percentage of active compound in the pharmaceutical compositions can vary within very wide limits, according to the patient and the mode of administration, and in particular according to the frequency of administration.

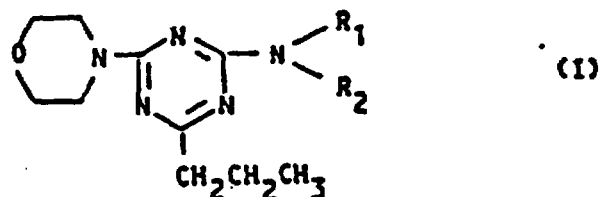
As regards the daily dosage, this can vary within an wide range of unit doses, for example from 0.1 to 2 g of active compound, according to the mode of administration. Thus, for example, it can be 0.25 to 0.75 g, preferably 0.5 g, one to three times per day, if the compound is administered in tablet form.

A formulation for tablets is quoted below as a non-limiting example of a composition containing a compound of formula I that can be administered orally:

Compound 1	250 mg
Methylcellulose (Methocel K4M)	200 mg
Dry lactose	154 mg
Aerosil	5 mg
Anhydrous citric acid	60 mg
Talc	11 mg
Magnesium stearate	20 mg

CLAIMS for the Contracting States: AT, BE, CH, DE, FR, GB, IT,
LI, LU, NL, SE

1. 2-amino-4-morpholino-6-propyl-1,3,5-triazines, their optical isomers and their racemic mixtures, of the general formula



in which

R_1 represents a hydrogen atom or an alkyl, phenylalkyl or acetyl radical,

R_2 represents a hydroxyl group, a hydroxyalkyl, alkoxyalkyl, dialkylamino, phenylhydroxyalkyl, (hydroxycycloalkyl)alkyl, alkanoyloxyalkyl, benzoyloxyalkyl, phenylacetyloxyalkyl or aminocarbonyloxyalkyl radical, a COR_3 group in which R_3 represents an alkyl, phenyl, halogenophenyl, alkylphenyl, alkoxyphenyl, phenylalkyl or phenoxy radical, or a $CONR_4R_5$ group in which R_4 and R_5 represent hydrogen or an alkyl radical, or

R_1 and R_2 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino radical substituted by a hydroxyalkyl radical, the alkyl, alkoxy and alkanoyloxy radicals having 1 to 4 carbon atoms, and the cycloalkyl radicals having 4 to 6 carbon atoms,

with the proviso that when R_1 represents the acetyl radical, R_2 represents an acetoxymethyl radical, as well as their non-toxic pharmaceutically acceptable acid-addition salts.

2. 2-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]ethanol and its non-toxic pharmaceutically acceptable



acid-addition salts according to claim 1.

3. 2-(hydroxyamino)-4-morpholino-6-propyl-1,3,5-triazine and its non-toxic pharmaceutically acceptable acid-addition salts according to claim 1.

4. 2-[(2-methoxyethyl)amino]-4-morpholino-6-propyl-1,3,5-triazine and its non-toxic pharmaceutically acceptable acid-addition salts according to claim 1.

5. (S)-3-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]-2-propanol and its non-toxic pharmaceutically acceptable acid-addition salts according to claim 1.

6. (R)-3-[(4-morpholino-6-propyl-1,3,5-triazin-2-yl)amino]-2-propanol and its non-toxic pharmaceutically acceptable acid-addition salts according to claim 1.

7. 2-(2,2-dimethylhydrazino)-4-morpholino-6-propyl-1,3,5-triazine and its non-toxic pharmaceutically acceptable acid-addition salts according to claim 1.

8. N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)benzamide and its non-toxic pharmaceutically acceptable acid-addition salts according to claim 1.

9. N-methyl-N-(4-morpholino-6-propyl-1,3,5-triazin-2-yl)benzamide and its non-toxic pharmaceutically acceptable acid-addition salts according to claim 1.

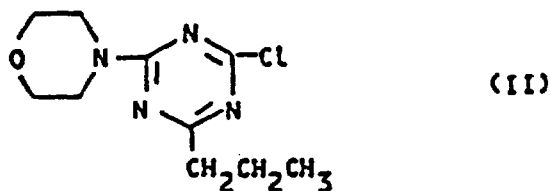
10. 2-[[2-(acetoxy)ethyl]amino]-4-morpholino-6-propyl-1,3,5-triazine and its non-toxic pharmaceutically acceptable acid-addition salts according to claim 1.

11. A process for preparation of 2-amino-4-morpholino-6-propyl-1,3,5-triazines and of their salts as defined in claim

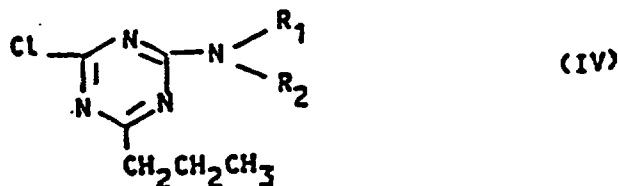


1, characterized in that

- a) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents a hydroxyl group or a hydroxyalkyl, alkoxyalkyl, dialkylamino, phenylhydroxyalkyl or (hydroxycycloalkyl)alkyl radical, or R_1 and R_2 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino radical substituted by a hydroxyalkyl radical, the alkyl and alkoxy radicals having 1 to 4 carbon atoms and the cycloalkyl radicals having 4 to 6 carbon atoms, 2-chloro-4-morpholino-6-propyl-1,3,5-triazine of formula



is reacted with an amine of formula HNR_1R_2 (III) in which R_1 and R_2 have the meaning given above, or a 2-amino-4-chloro-6-propyl-1,3,5-triazine of formula

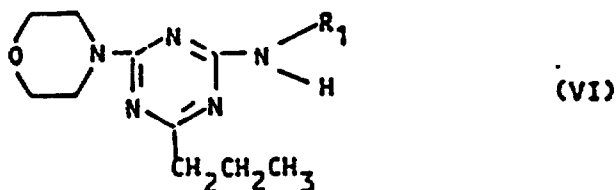


in which R_1 and R_2 have the meaning given above is reacted with a morpholine of formula



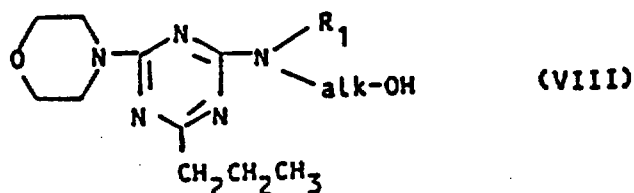
in which Z represents a hydrogen atom or a methyl radical; or

- b) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents a COR_3 group in which R_3 represents an alkyl, phenyl, halogenophenyl, alkylphenyl, alkoxyphenyl, phenylalkyl or phenoxy radical, the alkyl and alkoxy radicals having 1 to 4 carbon atoms, a 2-amino-4-morpholino-6-propyl-1,3,5-triazine of formula



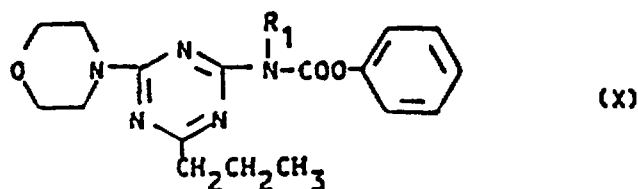
in which R_1 has the meaning given above is reacted in equimolar proportions with an R_3 carbonyl halide of formula $HalCOR_3$ (VII) in which R_3 has the meaning given above and Hal is a halogen atom; or

- c) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents an alkanoyloxyalkyl, benzoyloxyalkyl or phenylacetyloxyalkyl radical, the alkyl and alkanoyl radicals having 1 to 4 carbon atoms, a (4-morpholino-6-propyl-1,3,5-triazin-2-yl)aminoalkanol of formula



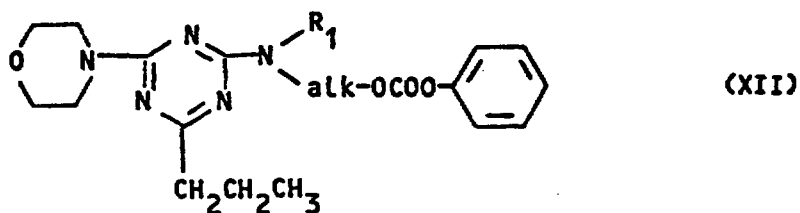
in which R_1 has the meaning given above and alk represents an alkylene radical having 1 to 4 carbon atoms, is reacted in equimolar proportions with an R_6 carbonyl halide of formula HalCOR_6 (IX), in which R_6 represents an alkyl radical having 1 to 4 carbon atoms, phenyl or benzyl, and Hal is a halogen atom; or

- d) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents a CONR_4R_5 group in which R_4 and R_5 represent hydrogen or an alkyl radical, the alkyl radicals having 1 to 4 carbon atoms, a phenyl (4-morpholino-6-propyl-1,3,5-triazin-2-yl)carbamate of formula



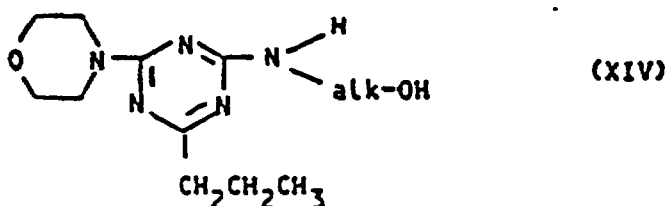
in which R_1 has the meaning given above is reacted with a nitrogen compound of formula HNR_4R_5 (XI) in which R_4 and R_5 have the meaning given above; or

- e) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents an aminocarbonyloxyalkyl radical, the alkyl radicals having 1 to 4 carbon atoms, ammonia is reacted with a 2-morpholino-4-(phenoxy carbonyloxyalkylamino)-6-propyl-1,3,5-triazine of formula



in which R_1 has the meaning given above and alk represents an alkylene radical having 1 to 4 carbon atoms; or

- f) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents the acetyl radical and R_2 an acetoxymethyl radical whose alkyl radical has 1 to 4 carbon atoms, at least two moles of an acetyl halide are reacted with one mole of a (4-morpholino-6-propyl-1,3,5-triazin-2-yl)aminoalkanol of formula



in which alk represents an alkylene radical having 1 to 4 carbon atoms; and

- g) in that optionally the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of formula I thus obtained are converted to their non-toxic pharmaceutically acceptable acid-addition salts.

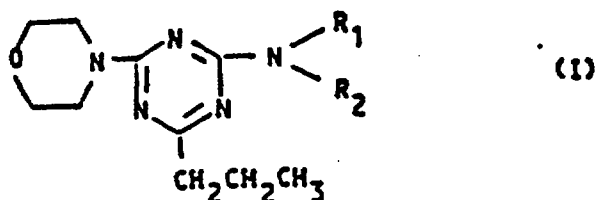
12. 2-amino-4-morpholino-6-propyl-1,3,5-triazines according to any one of claims 1 to 10 or one of their non-toxic pharmaceutically acceptable acid-addition salts for use in the treatment of cognitive and behavioural disorders associated with age and with demential syndromes.

13. Therapeutic compositions containing a therapeutically effective quantity of a 2-amino-4-morpholino-6-propyl-1,3,5-triazine according to any one of claims 1 to 10 or of one of its non-toxic pharmaceutically acceptable acid-addition salts in association with solid or liquid pharmaceutical excipients.



CLAIMS for the Contracting States: ES, GR

A process for preparation of 2-amino-4-morpholino-6-propyl-1,3,5-triazines, their optical isomers and their racemic mixtures, of the general formula



in which

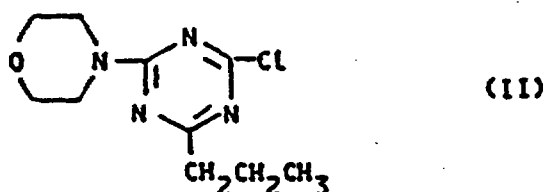
- R_1 represents a hydrogen atom or an alkyl, phenylalkyl or acetyl radical,
- R_2 represents a hydroxyl group, a hydroxyalkyl, alkoxyalkyl, dialkylamino, phenylhydroxyalkyl, (hydroxycycloalkyl)alkyl, alkanoyloxyalkyl, benzoyloxyalkyl, phenylacetyloxyalkyl or aminocarbonyloxyalkyl radical, a COR_3 group in which R_3 represents an alkyl, phenyl, halogenophenyl, alkylphenyl, alkoxyphenyl, phenylalkyl or phenoxy radical, or a $CONR_4R_5$ group in which R_4 and R_5 represent hydrogen or an alkyl radical, or
- R_1 and R_2 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino radical substituted by a hydroxyalkyl radical, the alkyl, alkoxy and alkanoyloxy radicals having 1 to 4 carbon atoms, and the cycloalkyl radicals having 4 to 6 carbon atoms,

with the proviso that when R_1 represents the acetyl radical, R_2 represents an acetoxyalkyl radical, as well as their non-toxic pharmaceutically acceptable acid-addition salts, characterized in that:

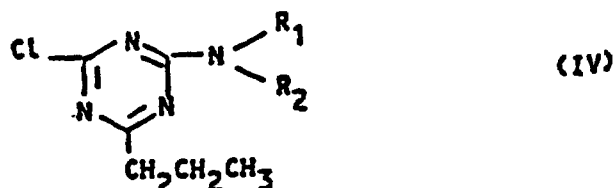
- a) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2



represents a hydroxyl group or a hydroxyalkyl, alkoxyalkyl, dialkylamino, phenylhydroxyalkyl or (hydroxycycloalkyl)alkyl radical, or R_1 and R_2 together with the nitrogen atom to which they are attached form a pyrrolidino or piperidino radical substituted by a hydroxyalkyl radical, the alkyl and alkoxy radicals having 1 to 4 carbon atoms and the cycloalkyl radicals having 4 to 6 carbon atoms, 2-chloro-4-morpholino-6-propyl-1,3,5-triazine of formula



is reacted with an amine of formula HNR_1R_2 (III) in which R_1 and R_2 have the meaning given above, or a 2-amino-4-chloro-6-propyl-1,3,5-triazine of formula



in which R_1 and R_2 have the meaning given above is reacted with a morpholine of formula

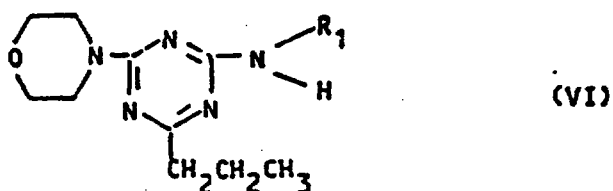


in which Z represents a hydrogen atom or a methyl radical; or

- b) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents a COR_3 group in which R_3 represents an alkyl,

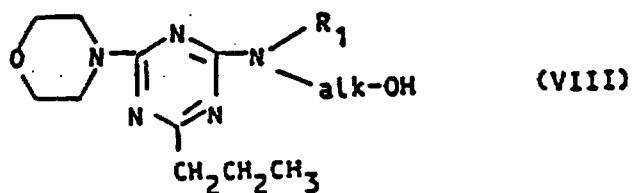


phenyl, halogenophenyl, alkylphenyl, alkoxyphenyl, phenylalkyl or phenoxy radical, the alkyl and alkoxy radicals having 1 to 4 carbon atoms, a 2-amino-4-morpholino-6-propyl-1,3,5-triazine of formula



in which R_1 has the meaning given above is reacted in equimolar proportions with an R_3 carbonyl halide of formula HalCOR_3 (VII) in which R_3 has the meaning given above and Hal is a halogen atom; or

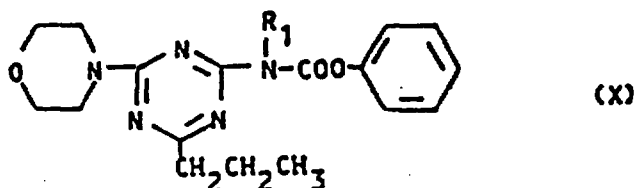
- c) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents an alkanoyloxyalkyl, benzoyloxyalkyl or phenylacetyloxyalkyl radical, the alkyl and alkanoyl radicals having 1 to 4 carbon atoms, a (4-morpholino-6-propyl-1,3,5-triazin-2-yl)aminoalkanol of formula



in which R_1 has the meaning given above and alk represents an alkylene radical having 1 to 4 carbon atoms, is reacted in equimolar proportions with an R_6 carbonyl halide of formula HalCOR_6 (IX), in which R_6 represents an alkyl radical having 1 to 4 carbon atoms, phenyl or benzyl, and Hal is a halogen atom; or

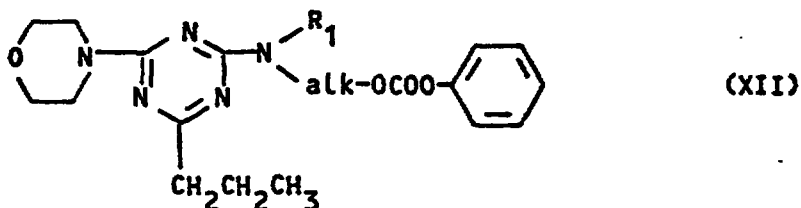


- d) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents a CONR_4R_5 group in which R_4 and R_5 represent hydrogen or an alkyl radical, the alkyl radicals having 1 to 4 carbon atoms, a phenyl (4-morpholino-6-propyl-1,3,5-triazin-2-yl)carbamate of formula



in which R_1 has the meaning given above is reacted with a nitrogen compound of formula HNR_4R_5 (XI) in which R_4 and R_5 have the meaning given above; or

- e) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents a hydrogen atom or an alkyl or phenylalkyl radical and R_2 represents an aminocarbonyloxyalkyl radical, the alkyl radicals having 1 to 4 carbon atoms, ammonia is reacted with a 2-morpholino-4-(phenoxy carbonyloxyalkylamino)-6-propyl-1,3,5-triazine of formula

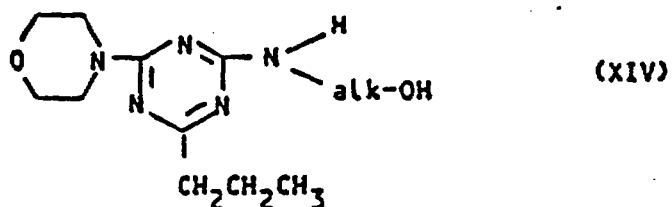


in which R_1 has the meaning given above and alk represents an alkylene radical having 1 to 4 carbon atoms; or

- f) to prepare the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of general formula I in which R_1 represents the



acetyl radical and R_2 an acetoxylalkyl radical whose alkyl radical has 1 to 4 carbon atoms, at least two moles of an acetyl halide are reacted with one mole of a (4-morpholino-6-propyl-1,3,5-triazin-2-yl)aminoalkanol of formula



in which alk represents an alkylene radical having 1 to 4 carbon atoms; and

- g) in that optionally the 2-amino-4-morpholino-6-propyl-1,3,5-triazines of formula I thus obtained are converted to their non-toxic pharmaceutically acceptable acid-addition salts.

