

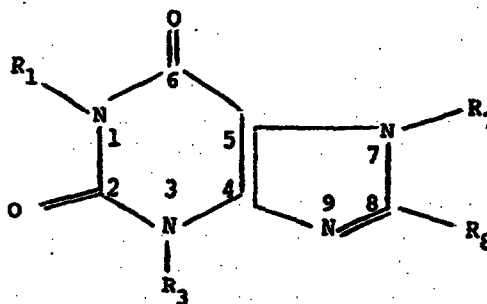
SPECIFICATION

A process for the preparation of 1,3,7-trialkyl xanthines and 1-isopropyl 1-isobutyl-3,7-dimethyl xanthine as medicaments

This invention relates to a process for the preparation of 1,3,7-trialkyl xanthines and to 1-isopropyl-3,7-dimethyl xanthine as a medicament.

More particularly the invention relates to a process for the preparation of 1,3,7-trialkyl xanthines, i.e. to xanthines completely substituted on the nitrogen atoms, by the N-alkylation of xanthines by phase transfer catalysis.

The xanthines correspond to the following formula:



One method of obtaining completely substituted xanthines is to alkylate the nitrogen atoms in the 1,3, or 7 position of the xanthine ($R_1=R_3=R_7=H$, $R_8=H$ or $\neq H$ for the C-alkylated xanthines) of xanthines partly substituted in this 1,3 or 7 position. In addition, alkylation is often the last step in a total synthesis of alkyl xanthines because it is the most economical and easy way of introducing a substituent into the

1 or 7 position.

The most common examples emanate from the alkylation of theophylline ($R_1=R_3=CH_3$, $R_7=H$, $R_8=H$) and theobromine ($R_1=H$, $R_3=R_7=CH_3$, $R_8=H$) which are natural products.

Normally, xanthine, C-alkylated xanthines and xanthines partly substituted on the nitrogen atom, among which theobromine has the least affinity for alkylation of the dimethyl xanthines ($R_8=H$), are alkylated either in an aqueous solution of an alkaline base or in an organic solvent after conversion into an alkali metal (K or Na) salt or of another metal (for example Ag or Pb) by a suitable alkylating agent $R-X$. X represents any suitable nucleophilic group, such as sulphonate, preferably sulphate or halide (chloride or bromide).

This reaction system has the disadvantage of being heterogeneous, in other words the reactants are present in two different phases, on the one hand aqueous or solid for the xanthine in question and, on the other hand, organic for the alkylating agent. This disadvantage is reflected in often poor yields for drastic conditions (pressure, temperature) and long reaction times.

This problem may be solved by using an adequate mutual solvent, such as dimethyl formamide (DMF), dimethyl sulphoxide (DMSO) or hexamethyl phosphotriamide (HMPT). However, these solvents have the disadvantage of being expensive and difficult to recover (low volatility).

So far as these questions of synthesis are concerned, useful information may be found in the Article by K. H. Klinger in *Chemiker zeitung* 96 (8), 424 (1972).

Phase transfer catalysis enables these difficulties to be overcome. The reaction velocity is increased by the addition of a catalytic quantity of an agent which transfers the water-soluble reactant to the organic phase and which thus enables a homogeneous reaction to take place. In addition solvation phenomena are prevented and the reactivity of the xanthine is greater.

The present invention provides a process for the preparation of a 1,3,7-trialkyl xanthine which comprises reacting a xanthine with an alkylating agent in the presence of a phase transfer catalyst and an excess of an alkali metal hydroxide. In the context of the invention, the term "a xanthine" is to be understood to designate xanthine itself, a C-alkylated xanthine or a xanthine partly substituted in the 1,3, or 7 position.

The alkyl radical R in the alkylating agent which generally has the formula RX is understood to be a straight-chain or branched-chain, optionally substituted alkyl radical. In the context of the invention, the term "substituted alkyl" is to be understood to comprise hydrocarbonyl radicals such as benzyl or alkyl.

Fuller information on the subject of phase transfer catalysis may be found in the Article by G. W. Gokel and W. P. Weber in *J. Chem. Educ.* 55, 350 (1978).

The reactions are easy to carry out on a experimental scale. The product is readily isolated by separation and evaporation of the organic phase. The yields are often very good. If necessary, the catalyst may be recovered.

The reaction may be carried out by liquid-liquid phase transfer or by solid-liquid phase transfer, depending primarily on the starting group X. The first variant is preferred where for example $X = OSO_3R$, whilst the second variant is preferred where $X = Cl$ or Br in particular. The alkylating agent $R-X$ preferably used in a molar excess of from 50 to 100% in relation to the xanthine, depending on the

number of groups to be alkylated. Crown ethers on the one hand and quaternary ammonium and phosphonium salts on the other hand are the chosen phase transfer catalysts. Whenever the conditions permit, it is preferred to use catalysts belonging to the second category by virtue of their more reasonable price. Of these second-category catalysts, the most effective appear to be the largest and the most symmetrical cations. For example, it is possible to use tetrabutyl ammonium hydrogen sulphate (TBA), which is preferred by virtue of its effectiveness, its reasonable price, the fact that it is easy to handle and the ease with which it can be separated from the product formed. Other suitable catalysts include hexadecyl tributyl phosphonium bromide (HDTBP) or the methyl trialkyl ammonium chlorides known commercially as Aliquat 336 (Registered Trade Mark) or Adogen 464.

The catalyst is generally used in a molar concentration of from 10 to 50% and preferably from 10 to 20% based on the xanthine.

The presence of a solvent is not essential because the alkylating agent $R-X$ may take its place. Otherwise, the solvents normally used are chlorinated solvents for the reactions involving two liquid phases, such as for example methylene chloride or *o*-dichlorobenzene, and any other aprotic solvent for the solid-liquid reactions, for example toluene, tetrahydrofuran (THF) or acetonitrile.

For the liquid-liquid reactions, the starting xanthine is dissolved in water in the presence of an excess of an alkali metal hydroxide. For the solid-liquid reactions, it is reacted as such, accompanied by an excess of a solid alkali metal hydroxide, generally NaOH or KOH.

The alkyl radical R to be introduced into the xanthine nucleus may be any alkyl radical and the Table presented by J. H. Lister on page 224 of the book entitled "Fused pyrimidines, Part II: Purines" by D. J. Buron (Wiley, 1971) gives some idea of the wide range of possible radicals R . What is more, the reaction by phase transfer catalysis makes it possible to introduce radicals which, hitherto, it has not been possible to introduce by the conventional methods mentioned at the beginning of this specification.

It is possible in this way to obtain new derivatives, more particularly:

-1-isopropyl-3,7-dimethyl xanthine ($R_1=i$ -propyl, $R_3=R_7=CH_3$, $R_9=H$) and its C-alkylated derivatives ($R_9 \neq H$), -1-(1'-theobrominyl)-methyl-3,7-dimethyl xanthine ($R_1=(1'$ -theobrominyl)-methyl, $R_3=R_7=CH_3$, $R_9=H$), or (1,1-ditheobrominyl)-methane and its C-alkylated derivatives ($R_9 \neq H$).

Other new derivatives include in particular:

1-(*p*-*t*-butyl)-benzyl-3,7-dimethyl xanthine ($R_1=(p$ -*t*-butyl)-benzyl, $R_3=R_7=CH_3$, $R_9=H$), and its C-alkylated derivatives.

the series of 1,7-dialkyl-3-methyl xanthines ($R_1 \neq H$, $R_3=CH_3$, $R_7 \neq H$) with the exception of 1,7-diethyl- and 1,7-dibenzyl-3-methyl xanthines, and the C-alkylated derivatives of this series ($R_9=H$), 1,7-diallyl-3-methyl xanthine.

The reaction temperatures are selected in dependence upon the reactivity of $R-X$ and upon the type of solvent used, if any. They are generally in the range from 20 to 100°C., for example 40°C where CH_2Cl_2 is used, at reflux where THF (66°C) or acetonitrile (80°C) is used and between 80 and 100°C where toluene and *o*-dichlorobenzene are used.

The reaction time is variable. It depends upon the temperature, upon the reactivity of $R-X$ and upon the reactivity of the xanthine or, more exactly, upon that of the sites to be alkylated on the nucleus. It may be between 2 and 3 hours for reactive substrates and as long as a few days for a group of slow-reacting reactants, such as for example isopropyl bromide with theobromine. Generally, it amounts to between 5 and 20 hours for substrates of medium reactivity.

The crude yields (i.e. based on crude products) are often quantitative. They are of the order of 50% where the isopropyl radical is reacted with theobromine. This radical, it will be recalled, cannot be introduced by conventional methods.

The known pharmacological properties of xanthines are their stimulating effect on the central nervous system, their spasmolytic activity and their diuretic activity.

Behavioural studies on rats have unexpectedly shown that, in contrast to the psychostimulating xanthines used for therapeutic purposes, such as for example caffeine or theophylline, 1-isopropyl-3,7-dimethyl xanthine and 1-isobutyl-3,7-dimethyl xanthine have a sedative effect comparable with that of a standard neuroleptic, such as chlorpromazine and haloperidol.

Accordingly, the present invention also relates to a pharmaceutical composition containing 1-isopropyl-3,7-dimethyl xanthine in combination with an inert pharmaceutically acceptable carrier or support. The pharmaceutical composition contains an active quantity for the neuroleptic effect of the active material.

The medicaments according to the invention may be made up in various pharmaceutical forms containing the usual excipients or vehicles, such as tablets, capsules, suppositories, solutions, suspensions, and may be administered orally, sublingually, rectally, subcutaneously, intramuscularly, intravenously or by inhalation, in daily doses of from 0.02 to 0.2 g.

These compounds have an acute toxicity in mice of from 200 to 300 mg/kg when administered orally and from 100 to 200 mg/kg when administered intraperitoneally.

The invention is illustrated by the following Examples:

EXAMPLES 1 TO 24

Reaction

Method A: liquid-liquid

- 5 Into a 200 ml reactor equipped with a magnetic stirrer and a condenser are introduced 40 mMoles of xanthine and then, for each site to be alkylated, 1.3 equivalents of solid NaOH and 0.1 or 0.2 equivalent of tetrabutyl ammonium hydrogen sulphate (TBA). After dilution with 40 ml of water, the stirrer is switched on. 40 ml of the organic solvent selected containing 1.5 equivalents of alkylating agent for each site to be alkylated are then added. Stirring is carried out in such a way as to obtain thorough mixing of the two liquid phases. If necessary, the mixture is heated.

10 Method B: solid-liquid

- 10 The reactor used is the same as for Method A, being completed by a drying tube. 40 mMoles of xanthine are introduced, followed by the addition for each site to be alkylated of 1.3 equivalents of solid NaOH reduced to a fine powder, 0.1 or 0.2 equivalent of tetrabutyl ammonium hydrogen sulphate (TBA) and 1.5 equivalents of alkylating agent. The mixture is diluted in 40 ml of the organic solvent selected, after which the stirrer is switched on to ensure thorough mixing of the two phases. The mixture is heated to the boiling point of the solvent, but at most to 100°C (temperature of the bath).

Separation and purification

- 20 On completion of the reaction, the reaction mixture is transferred to a separation funnel, the organic phase is separated, the aqueous phase is extracted with CH_2Cl_2 (Method A); or (Method B) 20 to 30 ml of water are added, the mixture is transferred to a separation funnel, if necessary the organic phase is separated or the aqueous phase is extracted with CH_2Cl_2 , followed by extraction with the same solvent.

- 25 The organic extracts are combined and evaporated to dryness. The residue is dissolved in 3 N HCl, washed with petroleum ether (3×10 ml), neutralised with solid K_2CO_3 to pH 10—11 and the aqueous medium is extracted with CH_2Cl_2 . After drying over Na_2SO_4 , the solvent is evaporated to dryness.

The crude product thus obtained is generally fairly pure and substantially colourless.

It may be purified by one or two crystallisations, generally in the presence of active carbon, from water, alcohol or a water/alcohol mixture.

The details are given in the Tables following the text of Example 25.

30 EXAMPLE 25

Preparation of (1,1'-ditheobrominyl)-methane:

This compound emanates from the substitution by two theobromine residues of the two Cl atoms in CH_2Cl_2 .

- 35 Into a 400 ml capacity extractor for solvents heavier than water is introduced a solution containing 9.01 g (50 mMoles) of theobromine, 16.98 g (50 mMoles) of TBA, 4.40 g (110 mMoles) of NaOH and 100 ml of H_2O . This is followed by continuous extraction with boiling CH_2Cl_2 (400 ml) for 24 hours. After cooling, the precipitate formed is filtered:

7.57 g are obtained. The filtrate is concentrated to a small volume: 0.35 g of additional precipitate is obtained.

- 40 The total crude yield amounts to 7.90 g (85%). the product may be recrystallised from DMF. M.p. >360°C. The structure is verified by ^1H -NMR (CF_3COOD).

From 3-methyl xanthine ($\text{R}_1=\text{R}_7=\text{H}$, $\text{R}_3=\text{CH}_3$, $\text{R}_8=\text{H}$)

Examples	R in R_1 and R_7	Method	Equivalent of catalyst	X
1	allyl	B	0.4	Br
2	pentyl	B	0.4	Cl

Examples /cont.	Solvent	Temperature in °C	Time in h	Crude yield in %
1	toluene	100	20	80
2	toluene	100	15	90

From theobromine ($R_1=H$, $R_3=R_7=CH_3$, $R_8=H$)

Examples	R in R_1	Method	Equivalent of catalyst	X
3	methyl ¹⁴ C	A	0.2	OSO ₃ Me
4	ethyl	A	0.2	OSO ₃ Et
5	"	B	0.4	Cl
6	propyl	B	0.1	Br
7	"	B	0.1	Br
8	butyl	B	0.1	Br
9	pentyl	B	0.1	Br
10	hexyl	B	0.2	Br
11	"	B	0.2	Cl

Examples /cont.	Solvent	Temperature in °C	Time in h	Crude yield in %
3	CH ₂ Cl ₂	30	20	100
4	CH ₂ Cl ₂	40	20	100
5	toluene	80	20	60
6	toluene	80	20	95
7	—	70	20	100
8	toluene	100	15	100
9	toluene	100	15	100
10	toluene	100	24	90
11	toluene	100	7	95

From theobromine ($R_1=H$, $R_3=R_7=CH_3$, $R_8=H$) (continuation)

Examples	R in R_1	Method	Equivalent of catalyst	X
12	isopropyl	B	0.2	Br
13	isobutyl	B	0.2	Br
14	allyl	B	0.1	Br
15	benzyl	B	0.1	Cl
16	"	B	0.1	Cl
17	p-t-butyl-benzyl	B	0.1	Cl

Examples /cont.	Solvent	Temperature in °C	Time in h.	Crude yield in %
12	CH ₃ CN	80	48	45
13	toluene	100	48	60
14	THF	66	3	100
15	toluene	100	10	100
16	THF	66	10	95
17	THF	66	3	80

From theophylline ($R_1=R_3=CH_3$; $R_7=H$, $R_8=H$)

Examples	R in R ₇	Method	Equivalent of catalyst	X
18	methyl ¹⁴ C	A	0.2	OSO ₃ Me
19	ethyl	A	0.1	OSO ₃ Et
20	butyl	B	0.2	Br
21	"	A	0.1	Br
22	hexyl	B	0.2	Br

Examples /cont.	Solvent	Temperature in °C	Time in h	Crude yield in %
18	CH ₂ Cl ₂	15	20	90
19	CH ₂ Cl ₂	20	7	90
20	toluene	100	4	95
21	CH ₂ Cl ₂	40	50	85
22	toluene	100	3	90

From paraxanthine ($R_1=R_7=CH_3$, $R_3=H$, $R_8=H$)

Examples	R in R ₃	Method	Equivalent of catalyst	X
23	methyl ¹⁴ C	A	0.2	OSO ₃ Me
24	ethyl	A	0.1	OSO ₃ Et
Examples /cont.	Solvent	Temperature in °C	Time in h	Crude yield in %

23	CH ₂ Cl ₂	10	20	80
24	CH ₂ Cl ₂	5	20	80

Remarks:

In Example 7, the alkylating agent (propyl bromide) acts as solvent.

The xanthines obtained, which are completely substituted on the nitrogen, were verified by the melting point M.p. and their ^1H -NMR spectrum (CDCl_3) or ^{13}C -NMR spectrum (CDCl_3).

- 5 M.p. of the new products: 1,7-diallyl-3-methyl xanthine (Example 1): M.p. = 57—58°C 5
- 1,7-dipentyl-3-methyl xanthine (Example 2): M.p. = 45—46°C.
- 1-isopropyl-3,7-dimethyl xanthine (Example 12): M.p. = 155—157°C (after crystallisation from water containing active carbon).
- 10 1-(p-t-butyl)-benzyl-3,7-dimethyl xanthine (Example 17): M.p. = 143—144°C. 10

Examples 3, 18 and 23 allow the preparation of trimethyl xanthines or caffeines variously marked to ^{14}C which are very useful for metabolism studies for example.

EXAMPLE 26

- 15 1-isopropyl and 1-isobutyl-3,7-dimethyl xanthine were the subject of a behavioural study on rats as a function of the anxiety induced by a new environment. Rats show their anxiety by rising up on their two rear paws, whilst their movements express locomotive activity. 15

Method

- 20 An anxiety state is induced by confronting "naive" male Sprague-Dawley rats (Iffa-Credo, France) weighing from 260 to 300 g with a new environment in the form of cages of Macrolon (30 x 25 cm) which are situated in a sound-proofed and air-conditioned chamber 22°C/50% relative humidity). 20

- The number of rearings and movements is determined automatically from infra-red photoelectric cells which only emit electrical pulses for the complete movements of the animal and not for static movements, like those of the head and tail, for reasons of reproducibility. These photoelectric cells sweep the cages at two different levels so as to distinguish the rearings from the movements. The number of rearings and movements is countered by the two groups of photoelectric cells, memorised and then printed out according to a pre-established programme. 25

- The compound under test is orally administered in solution by oesophageal intubation, the reference administration being formed by 6 ml/kg of distilled water, 30 minutes before the animals are placed in the cages. The number of rearings and movements is determined during the 15 minutes following encagement in relation to the effect produced by the reference administration. 30

Evaluation of the results

Table 1 below showed the development of the effects of the tested substances on the number of displacements and rearings in dependence upon the doses administered expressed as a percentage of the displacements and rearings counted for the reference administration.

TABLE 1

Substance	Dose administered mg/kg oral	Movements % of the reference administration	Rearings % of the reference administration
1-isobutyl-3,7- dimethyl xanthine	7.5	107	95
	10	87	74
	12.5	82	72
	15	64	56
	17.5	55	46
	20	49	35
1-isopropyl-3,7- dimethyl xanthine	10	92	89
	20	81	80
	30	85	64
	40	56	36
	50	42	24
chlorpromazine	5	109	105
	7.5	80	90
	10	62	70
haloperidol	0.16	104	120
	0.31	73	73
	0.63	63	57
	0.94	52	51
	1.25	43	40
	1.56	37	29
	2.5	6	5
chlordiazepoxide	5	85	85
	7.5	85	72
	10	69	57
	12.5	58	44

From the preceding data, the regression lines for the movements and rearings are established by the method described by Saubrie, P. J. Pharmacol (Paris) 2 (1971) 457—472, the equation of these regression lines corresponding to the average expressed in % of the performances of the controls in dependence upon the product of multiplication by 10 of the logarithm of the doses (only the doses which do not reduce the motive activity by more than 75% are considered).

The gradients of the regression lines corresponding to the movements and to the rearings are compared by recording on the abscissa (d) of a system of orthogonal axes the value of the gradient of the line representing the movements and, on the ordinate (r), the value of the gradient of the line representing the rearings. These values demonstrate the effect-dose relation for a given substance.

The ratio of the gradient of the movements to that of the rearings is also determined, enabling the specificity of the effect of a given substance on the anxiety state to be judged.

The results obtained are set out in Table II below:

TABLE II

Substance	Movements regression line	gradient $\neq 0$	Rearings regression line
1-isobutyl-3,7-dimethylxanthine	$y = -138.7 \times + 367.5$	$P < 0.001$	$y = -135.9 \times + 350.7$
		gradient $\neq 0$	Comparison of the gradients (d/r)
		$P < 0.001$	N.S.
1-isopropyl-3,7-dimethylxanthine	$y = -48.32 \times + 186.5$	$P < 0.05$	$y = -69.75 \times + 225$
		$P < 0.05$	$P < 0.05$ ($d/r < 1$)
chlorpromazine	$y = -84.58 \times + 238.6$	$P < 0.05$	$y = 067.11 \times + 211.6$
		$P < 0.05$	N.S.
haloperidol	$y = -51.99 \times + 100.9$	$P < 0.01$	$y = -59.2 \times + 103.9$
		$P < 0.01$	N.S.
chlordiazepoxide	$y = -66.72 \times + 202.4$	$P < 0.01$	$y = -108.3 \times + 273.2$
		$P < 0.01$	$P < 0.01$ ($d/r < 1$)
theophylline	$y = 40.54 \times + 61.83$	$P < 0.001$	$y = -9.63 \times + 119$
		N.S.	$P < 0.001$ ($d/r > 1$)

Legend:

— comparison of the gradients is carried out by the "t" test to the probabilities P 0.05, P 0.01 and P 0.001.

— N.S. means that the gradient is not significantly different from 0 or that the ratio between the gradients of the movements and the rearings is not significantly different from 1.

Conclusions

The effect of a substance is determined by its localisation in relation to the line $d = r$ of gradient =

- 5 1. The substances situated on this line have a similar effect on the rearings and movements. The substances for which the absolute value of the gradient of the rearings is significantly higher than that of the movements have a specific effect on anxiety. 5

10 Table II above shows: that 1-isobutyl-3,7-dimethyl xanthine has an action profile similar to the neuroleptics chlorpromazine and haloperidol, i.e. it is non-specific sedative; that 1-isopropyl-3,7-dimethyl xanthine has a slightly anxiolytic sedative effect of the type developed by chlordiazepoxide; that theophylline is a psychostimulant and does not have any effect on anxiety. 10

**CLAIMS**

1. A process for the preparation of a 1,3,7-trialkyl xanthine which comprises reacting a xanthine with an alkylating agent in the presence of a phase transfer catalyst and an excess of an alkali metal hydroxide.
- 5 2. A process as claimed in Claim 1, wherein the starting xanthine is xanthine, a C-alkylated xanthine or a xanthine partly substituted in the 1-,3- or 7-position. 5
3. A process for the preparation of a 1,3,7-trialkyl xanthine substantially as described with reference to any of the examples.
- 10 4. A 1,3,7-trialkyl xanthine when prepared by a process as claimed in any of claims 1 to 3. 10
5. 1-isopropyl-3,7-dimethyl xanthine.
6. A pharmaceutical composition containing 1-isopropyl-3,7-dimethyl xanthine in combination with an inert pharmaceutically acceptable carrier or support.