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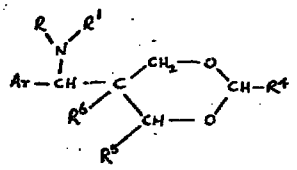
(72) Inventor RICHARD NOLAN BOOHER

(54) *M*-DIOXANE-5-METHYLAMINE ANALGESICS

(71) We, ELI LILLY AND COMPANY, a corporation of the State of Indiana, United States of America, having a principal place of business at 307 East McCarty Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to m-dioxane-5-methylamines and to processes for the preparation thereof and to their pharmaceutically acceptable acid-addition salts.

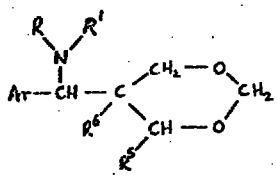
The invention provides a compound of formula (I):



(I)

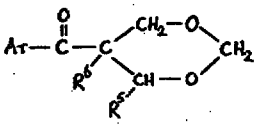
wherein R is hydrogen or methyl;
R^1 is methyl; or
R and R^1, when taken together with the nitrogen to which they are attached, are aziridino, pyrrolidino or piperidino;
R^4 is hydrogen, methyl, ethyl or phenyl;
R^5 and R^6 are hydrogen or one of R^5 and R^6 is methyl, with the limitations that, when R^6 is methyl, R and R^1 are other than aziridino, pyrrolidino or piperidino, and, when one of R^5 and R^6 is methyl, R^4 is hydrogen;
Ar is phenyl, halophenyl, methoxyphenyl, methylphenyl, trifluoromethylphenyl, hydroxyphenyl, acetoxyphenyl, benzyloxyphenyl provided that when Ar is substituted phenyl, the m-position is not occupied, or 3-pyridyl;
and the pharmaceutically acceptable acid-addition salts thereof.

The invention further provides a process for preparing a compound of formula (VII):



(VII)

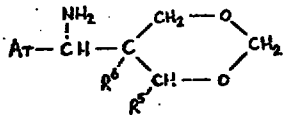
wherein R, R^1, R^5, R^6 and Ar are as defined above, which process comprises reacting a compound of formula (VIII):



(VIII)

in the presence of hydrogen with:

(A) hydroxylamine to provide a compound of formula (IX):



(IX)

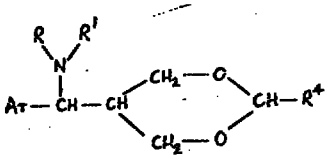
and

(1) reacting the compound of formula IX with formaldehyde and formic acid to yield the corresponding α-dimethylamino compound which is, if desired, demethylated to the α-methylamino comound; or

(2) reacting the compound of Formula IX with benzaldehyde to yield the corresponding Schiff base which is then reduced catalytically to the corresponding α-benzylamine, which α-benzylamine is methylated with methyl halide to yield the corresponding α-methyl-α'-benzylamine, which α-methyl-α'-benzylamine is reductively debenzylated to the corresponding α-methylamine; or

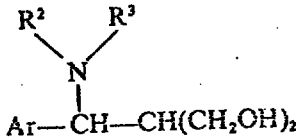
(B) with an amine of the formula RR^1NH when R^6 is H and wherein R and R^1 are as defined above.

In addition, the invention provides a process for preparing a compound of formula (III):



(III)

wherein R, R^1, R^4 and Ar are as defined above,
which process comprises reacting a compound of formula (IV)



(IV)

wherein R^2 is hydrogen, methyl or benzyl; R^3 is methyl or benzyl; and Ar is as defined above; with an aldehyde of formula (V):

R^4CHO (V)

wherein R^4 is as defined above, in the presence of borontrifluoride and when one of R^2 and R^3 is benzyl, reductively debenzylating and methylating; or when both of R^2 and R^3 are benzyl, removing both benzyl groups and methylating at least one of R^2 and R^3.

Further, the process of the invention includes the preparation of the compound of the formula IV, by reacting a di-lower-alkyl-benzalmalonate with an amine of formula (VI)

$$R^2R^3NH \qquad (VI)$$

to form a dialkyl (α-substituted amino) benzylmalonate which is reduced to yield the desired compound of formula IV. This process is claimed *per se* in copending Application No. 29003/76. Compounds of Formula IV above wherein R^2 and R^3 are methyl or when taken together the nitrogen to which they are attached are aziridino, pyrrolidino or piperidino and Ar is as defined above are claimed *per se* in copending Application No. 29003/76 (Serial No. 1,455,998).

The amines of the present invention are named as recommended by Chemical Abstracts [The Naming and Indexing of Chemical Compounds, section 259]. Cyclic compounds in which the amino group is separated from the ring (dioxane) by an aliphatic chain are named by the use of a conjunctive name, for example, m-dioxane-5-methylamine. The Greek letter α is used to indicate the position next to the amino group.

The term halophenyl refers to phenyl substituted by halogen such as 2-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl and 4-fluorophenyl. Methylphenyl refers to phenyl substituted by methyl such as 2-methylphenyl, 3-methylphenyl, 4-methylphenyl. Trifluoromethylphenyl refers to phenyl substituted by trifluoromethyl such as 2-trifluoromethylphenyl and 4-trifluoromethylphenyl. Methoxyphenyl refers to pehnyl substituted by methoxy such as 4-methoxyphenyl. Hydroxyphenyl refers to phenyl substituted by hydroxy such as 4-hydroxyphenyl and their derivatives such as 4-acetoxyphenyl and 4-benzyloxyphenyl.

The pharmaceutically-acceptable acid-addition salts are those salts formed from acids which do not increase the toxicity of the compound as a whole toward warm-blooded animals. Otherwise the identity of the salt-forming moiety is not critical, although in some instances a given anion may exhibit special advantages, such as ready solubility, ease of crystallization, and the like. Representative and suitable acids include the mineral acids such as hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, nitric, and carboxylic acids such as acetic, citric, maleic, and tartaric acids.

The compounds of formula I, wherein R^4 is hydrogen, and R^5, R^6 and Ar are as defined above, are prepared from 5-benzoyl-*m*-dioxanes which are obtained by the reaction of acetophenones, propionphenones or phenylpropenyl ketones with formaldehyde or formaldehyde polymer in the presence of boron trifluoride. [(a) Terade, *Nippon Kugaku Zasshi., 81,* 612 (1960); *Chem. Abstr.* 56, 1446h (1962), (b) British Patent 1,148,247 *Chem. Abstr., 71,* 6139u (1969), (c) Wesslen, *Acta. Chem. Scand., 23,* 1033 (1969)]. The 5-benzoyl-*m*-dioxanes are reacted with amines to yield derivatives which are reduced catalytically to provide instant compounds.

For example, the compounds of Formula I, wherein R^4 and R^6 are hydrogen, R^5 is hydrogen or methyl and Ar is as defined above, are prepared by reacting an amine, RR^1NH, with either 5-benzoyl-*m*-dioxanes or 5-benzoyl-4-methyl-*m*-dioxanes to provide enamine derivatives which are reduced catalytically with 5 percent palladium-on-carbon. The reaction sequence is illustrated below in Scheme I, route a.

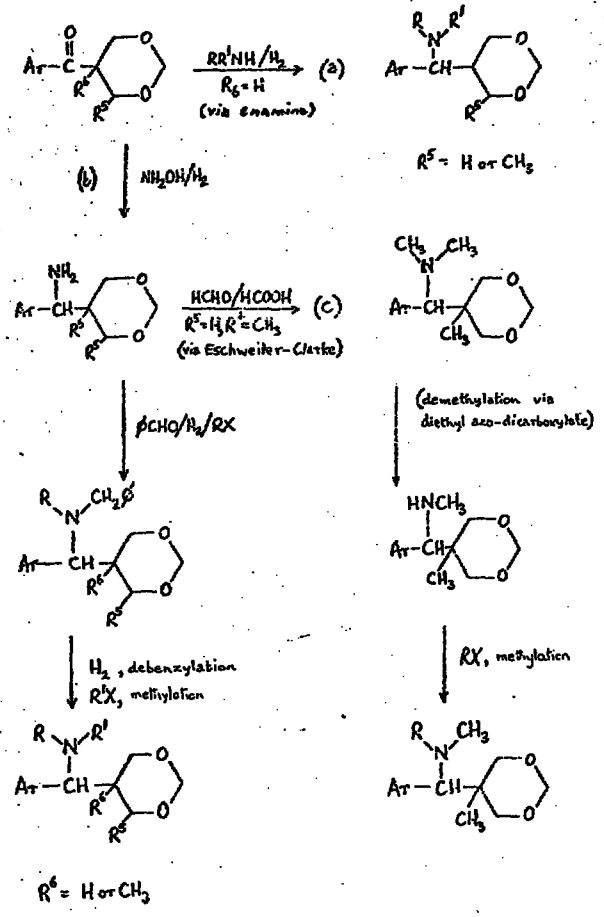
The compounds of formula I, wherein R, R^1 and R^6 are methyl, R^4 is hydrogen and Ar is as defined above, are prepared by reacting 5-benzoyl-5-methyl-*m*-dioxanes with hydroxylamine. The resultant 5-benzoyl-5-methyl-*m*-dioxane oxime derivatives are reduced in the presence of a hydrogenation catalyst to afford the corresponding α-aryl-5-methyl-*m*-5-methylamines. The α-aryl-5 - methyl - *m*-dioxane-5-methylamines are reacted with formaldehyde and formic acid under Eschweiler-Clarke conditions to yield the α-aryl-N,N,5-trimethyl-*m*-dioxane-5-methylamines of formula I. The reaction sequence is illustrated below in Scheme I, route c.

In addition compounds of formula I, wherein R, R^1 and R^6 are methyl, and Ar is as defined above, can be prepared by the demethylation of the α-aryl-N,N,5-trimethyl-*m*-dioxane-5-methylamines with diethyl azodicarboxylate. The resultant α-

aryl-N,5-dimethyl-*m*-dioxane-5-methylamines are methylated with methyl halides to provide the compounds of formula I. The reaction sequence is illustrated in Scheme I, route c.

In general the compounds of formula I, wherein R and R^1 are the same or different groups, R^4 is hydrogen and R^5, R^6 and Ar are as defined above are prepared by reacting the appropriate 5-benzoyl-*m*-dioxanes with hydroxylamine to yield the corresponding oximes. The oxime derivatives are reduced catalytically to provide the *α*-aryl-*m*-dioxane-5-methylamine analog of Formula I. The *α*-aryl-*m*-dioxane-5-methylamines are condensed with benzaldehyde to form Schiff base derivatives. The Schiff bases are reduced catalytically to provide the benzylamine analogs of Formula I, wherein R is hydrogen and R^1 is benzyl. The resultant benzylamine derivatives are methylated with methylhalides to yield the corresponding methylbenzyl amine analogs of Formula I, wherein R is methyl and R^1 is benzyl. The methylbenzyl derivatives are reductively debenzylated to provide the methylamino compounds of Formula I, wherein R is methyl and R^1 is hydrogen. The methylamino compounds are methylated with methylhalides to yield the compounds of Formula I wherein R and R^1 are methyl, R^4 is hydrogen, and R^5 and R^6 are hydrogen or methyl. The reaction sequence is illustrated in Scheme I, route b.

Scheme I. Preparation via 5-benzoyl-m-dioxanes.



The reductive debenzylation of the methylbenzylamine analogs of formula I is conveniently carried out [R. B. Wagner and H. D. Zook, "Synthetic Organic Synthesis," John Wiley, New York, N.Y., 1965, p. 665] in an amphiprotic solvent such as, for example, 95 percent ethanol under hydrogen pressures of from 15 to 16 pounds per square inch (psi) using a catalyst such as palladium-on-carbon or platinum to obtain the compounds of formula I wherein R is methyl and R^1 is hydrogen. The resultant debenzylated compound is methylated with a methyl halide, R^1X, by conventional methods to provide the compounds of formula I, wherein R and R^1 are methyl.

In an embodiment of the present invention, a compound of formula I, wherein R^4 and R^6 are hydrogen and R^5 is methyl, is prepared from 5-benzoyl-4-methyl-*m*-dioxane. Molar equivalents of phenylpropenyl ketone and s-trioxane are refluxed in chloroform in the presence of boron trifluoride etherate. The reaction mixture is decomposed by pouring it into a mixture of ice and saturated sodium bicarbonate. The resultant melt is extracted with ether. The ether extract is washed, dried and is evaoprated to an oil. The oil is distilled to provide 5-benzoyl-4-methyl-*m*-dioxane. 5-Benzoyl-4-methyl-*m*-dioxane and excess dimethylamine are reacted in benzene in the presence of titanium tetrachloride. After the reaction is completed, titanium dioxide is filtered off and the filtrate is evaporated to provide the crude enamine. The enamine is taken up in ethanol and hydrogenated at 15 to 60 psi with 5 percent palladium-on-carbon. The compound is isolated by acid-base extraction and purified by chromatography on silica gel using ethyl acetate-benzene as eluant. The salt is prepared by treating an ethereal solution of the free base with gaseous hydrogen chloride to provide pure N,N,4-trimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride after recrystallization from methanol ethyl acetate.

In an additional embodiment of the present invention, a compound of formula I, wherein R^4 and R^5 are hydrogen and R^6 is methyl, is prepared from 5-benzoyl-5-methyl-m-dioxane. Propiophenone and paraformaldehyde are reacted in the presence of boron trifluoride etherate to provide 5-benzoyl-5-methyl-*m*-dioxane. 5-Benzoyl-5-methyl-*m*-dioxane is reacted with hydroxylamine in ethanol to afford 5-benzoyl-5-methyl-*m*-dioxane oxime. The oxime is reduced with lithium aluminum hydride in tetrahydrofuran to provide 5-methyl-α-phenyl-*m*-dioxane-5-methylamine after isolation by acid-base extraction. The amine is reacted with formaldehyde and formic acid under Eschweiler-Clarke conditions to provide N,N,5-trimethyl-α-phenyl-*m*-dioxane-5-methylamine which is isolated as the hydrochloride salt.

The second process for the preparation of compounds of Formula I wherein R^5 and R^6 are hydrogen is described in Scheme II below.

Scheme II. *m*-Dioxane-5-methylamine preparation.

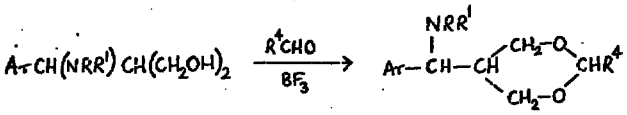
(A) Preparation of diethyl α-aminobenzylmalonates via Michael addition

$$ArCH{=}C(CO_2C_2H_5)_2 \xrightarrow{RR^1NH} ArCH(NRR^1)CH(CO_2C_2H_5)_2$$

(B) Preparation of 1,3-propanediols via reduction

$$ArCH(NRR^1)CH(CO_2C_2H_5)_2 \xrightarrow{\text{reduction}} ArCH(NRR^1)CH(CH_2OH)$$

(C) Preparation of *m*-dioxane-5-methylamines via aldehyde condensation



(III)

In a preferred embodiment of this invention, molar equivalents of benzaldehyde and diethylmalonate and a catalytic amount of piperidine are refluxed in benzene with azeotropic distillation of water for a period determined by the amount of water removed by azeotropic distillation. The reaction mixture is cooled, poured into water, and the aqueous mixture is extracted with ether. The ether extract is washed successively with saturated sodium bicarbonate solution and water. The extract is dried and the ether is evaporated in vacuo to a residual oil. The oil is distilled to provide diethyl benzalmalonate. Diethyl benzalmalonate and anhydrous dimethylamine are reacted in ether overnight at room temperature. The reaction mixture is evaporated in vacuo to yield crude diethyl [α-(dimethylamino)benzyl]malonate. The crude diethyl [α-(dimethylamino)benzyl]malonate in benzene is added to two molar equivalents of sodium bis(2-methoxyethoxy)-aluminum hydride in benzene in the cold. The reaction mixture is stirred overnight allowing the temperature to rise to room temperature. The reaction mixture is decomposed by stirring it into a mixture of ice and dilute sodium hydroxide solution. The resultant melt is extracted with ether and the extract is washed, dried and is evaporated in vacuo to an oil. The oil is taken up in ethyl acetate and petroleum ether is added. The mixture is concentrated by boiling on the steam bath. The mixture is cooled and petroleum ether is added to the point of incipient turbidity. Further cooling induces crystallization of 2-(α-dimethylamino)benzyl-1,3-propanediol. 2-(α-Dimethylamino)benzyl-1,3-propanediol and a 1.5 molar equivalent of paraformaldehyde are refluxed in acetonitrile with 3 molar

equivalents of boron trifluoride etherate for several hours. The cooled reaction mixture is poured into a saturated solution of sodium bicarbonate and the aqueous mixture is extracted with ether. The ether extract is washed, dried and is evaporated to an oil. The hydrochloride salt is prepared by treating an ethereal solution of the oil with gaseous hydrogen chloride to provide N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride.

It will be noted that the compounds represented by Formula I possess at least one asymmetric carbon atom, that of the methylamine. Accordingly, two different forms of each compound are possible, those consisting of an enantiomeric pair which can be resolved into dextro- and levorotatory isomers. When substitution occurs in an unsymmetrical position of the *m*-dioxane ring such as the 4-position, then the two additional asymmetric carbons are present. In such a situation eight different forms of each compound are possible. The optical resolution of such mixtures provides the analgesically active pure enantiomers. The resolution of an analgesic compound with three asymmetric centers is a major task which involves the separation of four diastereoisomeric pairs. While it is preferable to employ the pure isomers as analgesics, the racemic mixtures are useful for the purpose mentioned herein in accordance with their analgesic content. All the compounds of the present invention demonstrate analgesic activity as racemic mixtures. It will be understood by those skilled in the art that in such mixtures, pharmacological activity frequently resides to a greater degree or entirely, in one of the stereosiomeric forms.

In a further preferred embodiment, *dl*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine is resolved to provide the analgesically active *l*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine by use of dibenzoyl-*l*-tartaric acid monohydrate. *dl*-N,N-Dimethyl-α-phenyl-*m*-dioxane-5-methylamine in ethyl acetate solution is treated with a one half molar equivalent of dibenzoyl-*l*-tartaric acid monohydrate in ethyl acetate solution. Immediately the salt oils out of solution. Crystallization is effected by adding methanol and warming on the steam bath. Crystallization is completed by standing overnight. The tartrate salt is collected and recrystallized from ethyl acetate with the minimum amount of methanol needed for solution. The crystalline salt is collected and the crystallization is repeated to provide pure *l*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine dibenzoyl-*l*-tartaric acid salt. The *l*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine dibenzoyl-*l*-tartaric acid salt is suspended in distilled water and basified with ammonium hydroxide solution. The basic mixture is extracted with ether. The ether extract is washed, dried and evaporated to a solid residue. The solid *l*-amine is taken up in ether and treated with gaseous hydrogen chloride to provide pure *l*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride after recrystallization from methanol-ethyl acetate.

Analgesic activity for representative compounds was determined with two standard animal techniques. The mouse writhing assay used was a modification of the method wherein frequency of writhing [Hendershot and Sorsaith, *J. Pharm. Exp. Ther. 125*, 237 (1959)] is observed after intra peritoneal administration of 0.6 percent acetic acid [Koster et al., *Fed. Proc. Expt. Biol. 18*, 412 (1959)]. The mice were Cox standard males weighing 20—22 gm. The number of writhes was determined for each of five mice during the period 5—15 minutes after acetic acid treatment. The percent inhibition due to drug treatment was determined by comparison with control mice.

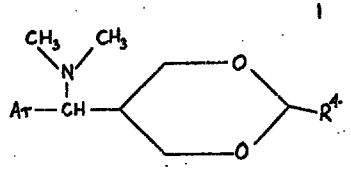
The other analgesic method was the rat tail jerk assay described by Robbins, *J. Amer. Pharm. Assoc. Sci. Ed., 44*, 497 (1955). The rats were Sprague-Dawley females weighing 70—90 g. Briefly, the tail was held on a temperature controlled tail rest near a nichrome resistance wire through which a current could flow. A switch used to start the flow of the current to heat the wire simultaneously started a timer. When a jerk of the tail was detected by the operator, the switch was released and the latency of the response was recorded as the "reaction time." The tail was placed near the hot wire stimulus for a maximum duration of 30 seconds. Twenty rats were tested as a group in a randomized order. At least five rats were used for each treatment and each rat was dosed and tested only once.

Table I below gives the results of testing representative compounds as analgesics by the above processes. The first four columns in table I describe the particular compound tested. The next eight columns give the mouse writhing results and the rat tail jerk results both by oral and subcutaneous administration. The columns headed PT ("Peak Analgesic Time") give the time in minutes after dosing at which the maximum analgesic responses are measured. The columns

headed "ED_{50} (mg./kg.)" give the doses (ED_{50}) in milligrams per kilogram (mg./kg.) of body weight that produces a significant peak analgesic effect in 50 percent of test animals.

TABLE 1

In Vivo Analgesic Activity of m-dioxane-5-methylamines



salt

Formula				Mouse Writhing				Rat Tail Jerk			
				Subcutaneous		Oral		Subcutaneous		Oral	
Form	Ar	R^4	Salt	PT* (min.)	ED_{50} (mg./kg.)	PT (min.)	ED_{50} (mg./kg.)	PT (min.)	ED_{50} (mg./kg.)	PT (min.)	ED_{50} (mg./kg.)
dl	C_6H_5	H	HCl	15	15	45	28	15	4.5	15	27
l	C_6H_5	H	HCl	15	6	15	16	15	7.0	15	10 to 20
dl	4-CH_3—C_6H_4	H	Maleate	30	20	45	110	30	8.0	45	60
dl	C_6H_5	CH_3	**	15	3.6	15	19	20	2.8	15	12
dl	C_6H_5	C_2H_5	**	75	19	75	23	15	3.4	15	21
dl	3-pyridyl	H	2HCl	30	10	30	25	15	7.0	15	7.0

* PT is the peak analgesic time in minutes

** Free base tested

Other compounds have a comparable analgesic activity although the dose required to produce analgesic activity varies from compound to compound. In addition, the time of peak analgesic action will vary somewhat from compound to compound. Many of the compounds are short acting, an advantage when pain is likely to be of short duration; however, 2-ethyl-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine is long acting in mice. The compounds of the invention are relatively non-toxic in that their analgesic effect dose is low compared to the dose at which their toxic signs appear. In some of the compounds tolerance develops slowly and physical dependence is minimal.

Since the compounds are effective analgesically by the oral route, this route of administration is preferred. The compounds of the invention can be administered at a non-toxic dose between about 1 and 20 mg./kg. of body weight as a single dose or as multiple doses until the desired therapeutic result is achieved. For oral administration, the compound may be placed in empty telescoping gelatine capsules, either with or without conventional pharmaceutical extending media. The compounds can also be mixed with various excipients, binders, etc., and compressed into tablets. Additionally, it is also possible to administer the compounds orally in a suspension or in aqueous solutions of their acid-addition salts.

Illustrative of the *m*-dioxane-5-methylamines which are provided are the following:

α-(4-acetoxyphenyl)-N,N-dimethyl-*m*-dioxane-5-methylamine,
α-(4-benzyloxyphenyl)-N,N-dimethyl-*m*-dioxane-5-methylamine,
N,N-dimethyl-α-(4-chlorophenyl)-*m*-dioxane-5-methylamine,
N,N-dimethyl-α-(2,4-dichlorophenyl)-*m*-dioxane-5-methylamine,
N,N-dimethyl-α,2-diphenyl-*m*-dioxane-5-methylamine,
N,N-dimethyl-α-(4-trifluoromethylphenyl)-*m*-dioxane-5-methylamine,
N,N-dimethyl-α-(4-fluorophenyl)-*m*-dioxane-5-methylamine,
N,N-dimethyl-α-(4-hydroxyphenyl)-*m*-dioxane-5-methylamine,
N,N-dimethyl-2-isopropyl-α-phenyl-*m*-dioxane-5-methylamine,
1-[α-(*m*-dioxan-5-yl)benzyl]aziridine,
1-[α-(*m*-dioxan-5-yl)-(4-chlorobenzyl)]piperidine,
1-[α-(*m*-dioxan-5-yl)benzyl]pyrrolidine,
N,N-dimethyl-2-ethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine.
N,N-dimethyl-2-phenyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine,
1-[α-(*m*-dioxan-5-yl)-(3-pyridyl)methyl]aziridine,
N-methyl-α-phenyl-*m*-dioxane-5-methylamine,
N-methyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine,
N,N,4-trimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine,
N,N,5-trimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine,
1-[α-(*m*-dioxan-5-yl)-(3-pyridyl)methyl]aziridine,
1-[α-(*m*-dioxan-5-yl)-(3-pyridyl)methyl]piperidine,
1-α-(*m*-dioxan-5-yl)-(3-pyridyl)methyl]pyrrolidine,
N,N-dimethyl-2-phenyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine,
1-[α-(2-ethyl-*m*-dioxan-5-yl)benzyl]aziridine,
1-[α-(2-ethyl-*m*-dioxan-5-yl)-(3-pyridyl)methyl]pyrrolidine,
and the pharmaceutically-acceptable acid-addition salts thereof.

Example 1.

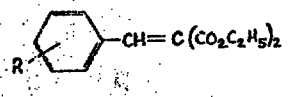
Preparation of Diethyl benzalmalonates

Diethyl benzalmalonate.- Two moles, 212 g., of benzaldehyde, 320 g. (2.0 moles) of diethyl malonate and 10 ml. of piperidine were refluxed in 400 ml. of benzene. The theoretical amount of water was collected in a Dean-Stark trap by azeotropic distillation in about 7 hours. The reaction mixture was poured into water after cooling. The aqueous mixture was extracted with ether and the extract was washed successively with saturated sodium bisulfite solution, water, saturated sodium bicarbonate solution and finally water. The extraction was dried over anhydrous magnesium sulfate and the ether was evaporated to an oil. The oil was distilled and the fraction, bp 140°C. (0.1 mm), was collected to yield 343 g. of diethyl benzalmalonate.

The following substituted diethyl benzalmalonates were prepared according using the procedure of example 1 with the appropriate aldehyde:

TABLE 2

Diethyl Benzalmalonates



		Analysis					
		Calculated			Found		
R	bp, C° (mm.)	C	H	Cl	C	H	Cl
2-CH_3	142 (0.7)	68.68;	6.92		68.79;	7.10	
4-CH_3O	162 (0.7)	64.73;	6.52		64.60;	6.49	
2-Cl	142 (0.7)	59.26;	5.68		59.48;	5.39	
4-Cl	144 (0.7)	59.26;	5.68		59.53;	5.77	
2,4-Cl_2	132 (0.05)	53.01;	4.45	22.36	50.47;	4.21	21.6
4-F	152 (0.05)						
4-ϕCH_2O	210–222 (0.10)						

Example 2.

Preparation of Diethyl (α-substitutedamino)benzylmalonates

Diethyl (α-dimethylamino)benzylmalonate.- One hundred grams (2.2 moles) of anhydrous dimethylamine was dissolved in 200 ml. of ether and the mixture was cooled to 0°C. in an ice bath. Diethyl benzalmalonate, 200 g. (0.81 mole), in ether was added dropwise at a rapid rate to the cooled, stirred reaction mixture. The mixture was stirred at room temperature for 12 hours. The reaction mixture was evaporated in vacuo to give 240 g. of diethyl (α-dimethylamino)benzylmalonate.

In general the diethyl (α-dimethylamino)benzylmalonates were not purified prior to their use because of their instability. They were characterized by nuclear magnetic resonance spectrum (NMR). The following intermediates were prepared according to the method of Example 2:

diethyl α-dimethylamino-(2-methylbenzyl)malonate
diethyl α-dimethylamino-(2-chlorobenzyl)malonate
diethyl α-dimethylamino-(4-chlorobenzyl)malonate
diethyl α-dimethylamino-(2,4-dichlorobenzyl)malonate
diethyl α-dimethylamino-(4-methoxybenzyl)malonate
diethyl α-dimethylamino-(4-benzyloxybenzyl)malonate
diethyl α-dimethylamino-(4-hydroxybenzyl)malonate
diethyl α-dimethylamino-(4-acetoxybenzyl)malonate
diethyl α-dimethylamino-(4-fluorobenzyl)malonate
diethyl α-aziridino)benzylmalonate
diethyl (α-pyrrolidino)benzylmalonate
diethyl (α-piperidino)benzylmalonate

Example 3.

Preparation of 2-(α-substitutedamino)benzyl-1,3-propanediols

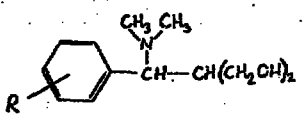
2-(α-Dimethylamino)benzyl-1,3-propanediol.- Sodium bis(2-methoxyethoxy)aluminum hydride, 450 ml. (1.6 mole), as a 70 percent solution in benzene, was dissolved in 200 ml. of dry benzene. The mixture was cooled in an ice bath. Diethyl (α-dimethylamino)benzylmalonate, 240 g. (0.81 mole), dissolved in 320 ml. of benzene, was added dropwise to the cold reaction mixture with stirring. The mixture was stirred for about 12 hours, allowing the temperature to rise to room

temperature. The reaction mixture was stirred into a mixture of ice and dilute sodium hydroxide solution. The resultant melt was extracted twice with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated in vacuo. The residual oil was taken up in 100 ml of ethyl acetate and diluted with 500 ml. of petroleum ether. The solution was concentrated by evaporation on the steam bath, and more petroleum ether was added to incipient turbidity. The mixture was cooled to induce crystallization. Eighty-five grams of 2-(α-dimethylamino)benzyl-1,3-propanediol, mp about 79—80°C., was obtained.

The following 1,3-propanediols were prepared by the method of Example 3:

TABLE 3

1,3-propanediols



		Analysis					
		Calculated			Found		
R	mp, °C.	C	H	N	C	H	N
2-CH_3	(oil)						
4-CH_3O	102	65.25;	8.85;	5.85	65.46;	9.09;	5.69
2-Cl	(oil)						
4-Cl	120	59.13;	7.44;	5.75	59.14;	7.20;	6.03
4-F	85						
2,4-Cl_2	(oil)						
4-ϕCH_2O	176						

Example 4.

Preparation of N,N-Dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride

2-(α-Dimethylamino)benzyl-1,3-propanediol, 137 g. (0.66 mole), and 300 g. (10.0 mole) of paraformaldehyde were added to 1000 ml. of acetonitrile. Boron trifluoride etherate, 500 ml, 560 g. (3.96 mole), was added dropwise to the stirred reaction mixture, and the mixture was refluxed for two hours. The cooled reaction mixture was poured into a saturated solution of sodium bicarbonate and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to an oil residue. The hydrochloride salt was prepared by treating an ethereal solution of the oil with gaseous hydrogen chloride. The yield was 97 g. of N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride, mp about 172°C. after recrystallization from methanol-ethyl acetate.

Analysis: Calcd. for $C_{13}H_{19}NO_2 \cdot HCl$: C, 60.58; H, 7.82; N, 5.43
Found: C, 60.78; H, 8.03; N, 5.40

Example 5.

Alternative preparation of N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride

(A) 5-Benzoyl-*m*-dioxane.- Sixty grams (0.5 mole) of acetophenone and 150 g. (5.0 mole) of paraformaldehyde were added to 500 ml. of acetonitrile. Boron tri-

fluoride etherate, 213 g. (1.5 mole), was added dropwise to the stirred reaction mixture. The mixture reached reflux temperature by the time one-half of the boron trifluoride etherate had been added. The addition was completed and the reaction mixture was refluxed for two hours. The cooled reaction mixture was stirred into a mixture of ice, water and saturated sodium bicarbonate solution. The resultant melt was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated in vacuo to an oil. The oil was distilled and the fraction bp 115—120°C. (0.5 mm.) was collected to yield 40 g. of 5-benzoyl-*m*-dioxane which was characterized by NMR.

(B) N,N-Dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride.- Titanium tetrachloride, 2.75 ml., 4.75 g. (0.025 mole), in 50 ml. of benzene, was added dropwise under nitrogen to 9.5 g (0.05 mole) of 5-benzyl-*m*-dioxane and 20 ml. of anhydrous dimethylamine in 200 ml. of benzene cooled in an ice bath with stirring. After coming to room temperature, the reaction mixture was refluxed for about 5 hours. The cooled reaction mixture was filtered and the filtrate was evaporated in vacuo to an oil. The oil was taken up in 200 ml. of ethanol and hydrogenated at 50 psi with 0.5 g. of 5 percent palladium-on-carbon for six hours. The catalyst was filtered and the filtrate was evaporated in vacuo to an oil which was taken up in ether. The ether phase was extracted with dilute hydrochloric acid and washed with water. The aqueous wash and the acid extract were combined and basified with ammonium hydroxide. The basic solution was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated in vacuo to yield 6 g. of oil. The oil was taken up in ether and treated with gaseous hydrogen chloride. The salt was collected and recrystallized from methanol-ethyl acetate to yield 3.0 g. of N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride, mp about 172°C.

Analysis: Calc. for $C_{13}H_{19}NO_2HCl$ C, 60.58; H, 7.82; N, 5.43
Found: C, 60.83; H, 7.90; N, 5.58

Example 6.

Resolution of *dl*-N,N-Dimethyl-α-phenyl-*m*-dioxane-5-methylamine

(A) Preparation of dibenzoyl-*l*-tartaric acid salt.- *dl*-N,N-Dimethyl-α-phenyl-*m*-dioxane-5-methylamine, 1106.5 (5.0 mole), was dissolved in 4 liters of ethyl acetate. Dibenzoyl-*l*-tartaric acid monohydrate, 940.8 g. (2.5 mole), was dissolved in 4 liters of ethyl acetate by warming. The warm tartaric acid solution was added to the amine solution and immediately an oil formed. Methanol, 300 ml., was added to the mixture and crystallization of the oil was effected by warming on the steam bath. The crystallization was completed by standing overnight. The salt was collected and recrystallized from 5 l. of ethyl acetate with the minimum amount of methanol needed for solution. The crystalline salt was collected and the crystallization was again repeated to yield 548 g. of *l*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine dibenzoyl-*l*-tartaric acid salt, mp about 132—133°C., $[\alpha]_D^{25}$ + 61.40° (c = 1, ethanol).

(B) *l*-N,N-Dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride.

l - N,N - Dimethyl - α - phenyl - *m* - dioxane - 5 - methylamine dibenzoyl - *l* - tartaric acid salt, 543 g., was suspended in distilled water and basified with ammonium hydroxide. The basic mixture was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to a solid residue. The solid, 210 g., was taken up in ether and treated with gaseous hydrogen chloride. The salt was collected and recrystallized from methanol-ethyl acetate to yield 156 g. of *l*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride, mp about 202—203°C. $[\alpha]_{275}^{27°}$ –92.6 (c = 51.825 mg./5 ml., water).

Analysis: Calcd for $C_{13}H_{19}NO_2HCl$ C, 60.58; H, 7.82; N, 5.43; Cl, 13.75
Found: C, 60.83; H, 7.58; N, 5.51; Cl, 13.67

Similarly, the following compounds were prepared:

l - N,N - dimethyl - α - (4 - methylphenyl) - *m* - dioxane - 5 - methylamine hydrochloride

l - N,N,2 - trimethyl - α - phenyl - *m* - dioxane - 5 - methylamine hydrochloride

l - N,N - dimethyl - 2 - ethyl - α - phenyl - *m* - dioxane - 5 - methylamine hydrochloride

Example 7.

Preparation of N,N-Dimethyl-α-(4-methylphenyl)-*m*-dioxane-5-methylamine maleate

(A) Diethyl (4-methylbenzal)malonate.- Following the method of Example 1 one hundred grams (0.83 mole) of *p*-tolualdehyde, 133 g. (0.83 mole) of diethylmalonate and 5 ml. of piperidine, were reacted in benzene. The yield of diethyl (4-methylbenzal)malonate, bp 140°C. (0.7 mm), was 89 g.

Analysis: Calc. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92
Found: C, 68.94; H, 7.08

(B) Diethyl α-dimethylamino-(4-methylbenzyl)malonate.- Following the methods of Example 2 twenty grams of diethyl (4-methylbenzal)malonate and 100 ml. of anhydrous dimethylamine were reacted in ether to provide 22 g. of diethyl α-dimethylamino-4-methylbenzylmalonate as an oil.

(C) 2-[α-Dimethylamino-(4-methylbenzyl)]-1,3-propanediol.- Diethyl α-dimethylamino-(4-methylbenzyl)malonate, 22 g. (0.77 mole), in 100 ml. of benzene, was added dropwise to a solution of 28 ml. (0.2 mole) of sodium bis (2-methoxyethoxy)aluminum hydride as a 70% solution in benzene, in 100 ml. of benzene cooled in an ice bath. After the addition, the reaction mixture was allowed to come to room temperature, and then it was refluxed for 2 hours. The cooled reaction mixture was decomposed with dilute sodium hydroxide solution. The phases were separated and the benzene layer was washed with water. The benzene phase was extracted with dilute hydrochloric acid and washed with water. Six grams of neutral oil was obtained from the benzene phase. The acidic aqueous extract was basified with ammonium hydroxide and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and was evaporated to a residual solid. The solid was recrystallized from ethyl acetate-hexane to yield 2.7 g. of 2-(α-dimethylamino-4-methylbenzyl)-1,3-propanediol, mp about 125°C.

Analysis: Calc. for $C_{13}H_{21}NO_2$: C, 69.92, H, 9.48, N, 6.27
Found: C, 70.08, H, 9.55, N, 6.05

(D) N,N-Dimethyl-α-(4-methylphenyl)-*m*-dioxane-5-methylamine maleate.- Following the method of Example 4, 2-(α-dimethylamino-4-methylbenzyl)-1,3-propanediol, 2 g., and 10 g. of paraformaldehyde, in 50 ml. of acetonitrile, were treated with 3 ml. of boron trifluoride etherate. Extraction of the spent reaction mixture yielded the 2.0 g. of oil. The maleate salt was prepared by treating the 2.0 g. of oil with 1 g. of maleic acid in ethyl acetate solution. Recrystallization of the salt from methanol-ethyl acetate yielded 1.5 g. N,N-dimethyl-α-(4-methylphenyl)-*m*-dioxane-5-methylamine maleate, mp about 138°C.

Analysis: Calc. for $C_{14}H_{21}NO_2C_4H_4O_4$: C, 61.52; H, 7.17; N, 3.99
Found: C, 61.60; H, 7.38; N, 3.80

Example 8.

Preparation of N,N-Dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine dihydrochloride

(A) Diethyl (3-pyridyl)methylenemalonate.- One hundred grams (0.935 mole) of 3-pyridinecarboxaldehyde, 150 g. (0.935 mole) of diethyl malonate and 5 ml. of piperidine were refluxed for 16 hours in 200 ml. of benzene with azeotropic distillation of 17 ml. of water. The cooled reaction was poured into water and the benzene phase was separated. The benzene layer was washed successively with saturated sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate and evaporated in vacuo. The oil residue was distilled to yield 180 g. of diethyl (3-pyridyl)methylene malonate, bp 143°C. (0.10 mm), which was characterized by NMR.

(B) Diethyl α-dimethylamino-(3-pyridyl)methylmalonate.- Following the method of Example 2, fifty grams of diethyl (3-pyridyl)methylenemalonate and 200 ml.of anhydrous dimethylamine were reacted in 200 ml. of ether to yield 56 g. of diethyl α-dimethylamino-(3-pyridyl)methylmalonate which was characterized by NMR.

(C) 2-[α-Dimethylamino-(3-pyridyl)methyl]-1,3-propanediol.- Nineteen grams (0.5 mole) of lithium aluminum hydride was covered by 200 ml. of dry tetrahydrofuran (THF). Sixty nine grams (0.24 mole) of diethyl α-dimethylamino-(3-pyridyl)methylmalonate, dissolved in 300 ml. of dry THF, was added dropwise to the hydride slurry cooled in an icebath. The stirred reaction mixture was allowed to come to room temperature overnight. The mixture was decomposed by the addition of saturated sodium acetate solution and the volume was

concentrated to 1/3 the original volume by evaporation in vacuo. The concentrated mixture was acidified with dilute hydrochloric acid and extracted with ether. The acidic aqueous phase was basified with dilute sodium hydroxide. The basic mixture was extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to yield 40 g. of 2-[α-dimethylamino-(3-pyridyl)methyl]-1,3-propanediol which was characterized by NMR.

(D) N,N-Dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine dihdyrochloride.- Following the method of Example 4, seven grams of 2-[α-dimethylamino-(3-pyridyl)methyl]-1,3-propanediol, 30 g. of paraformaldehyde and 50 ml. of boron trifluoride etherate were reacted in 100 ml. of acetonitrile to yield 6 g. of the free base. The salt was prepared by treating an etheral solution of the base with gaseous hydrogen chloride to yield 1.0 g. of N,N-dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine dihydrochloride, mp about 196°C., after recrystallization from methanol-ethyl acetate.

Analysis: Calc. for $C_{12}H_{18}N_2O_2 2HCl$: C, 48.82; H, 6.83; N, 9.49
Found: C, 48.65; H, 6.79; N, 9.60

Example 9.

Alternative preparation of N,N-dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine dihydrochloride

2-[α-Dimethylamine-(3-pyridyl)methyl]-1,3-propanediol, 10.5 g. (0.05 mole), 10 g. of trioxane, and 21 g. (0.11 mole) of *p*-toluenesulfonic acid were refluxed overnight in 200 ml. of chloroform in a flask fitted with a Soxhlet extractor containing 3A molecular sieve in the thimble. The cooled reaction mixture was washed twice with water. The aqueous solution was basified with ammonium hydroxide and extracted with chloroform. The chloroform extract was washed with water, dried over anhydrous magnesium sulfate and was evaporated to yield 6 g. of the free base. The salt was prepared to yield 1.0 g. of N,N-dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine dihydrochloride, mp about 195°C., after recrystallization from methanol-ethyl acetate.

Example 10.

Preparation of N,N,2-Trimethyl-α-phenyl-*m*-dioxane-5-methylamine

2-(α-Dimethylamino)benzyl-1,3-propanediol, 2.5 g. (0.012 mole), was dissolved in 25 ml. of acetonitrile. Water, 7.68 g. (0.48 mole), 10 ml. of acetaldehyde and 3.01 ml. (0.024 mol) of boron trifluoride etherate were added to the reaction mixture and the mixture was allowed to stir overnight. The reaction mixture was heated on the steam bath for 1 hour. The cooled mixture was poured into ammonium hydroxide and the basic mixture was extracted with ether. The ether extract was washed with water, dried over magnesium sulfate and evaporated to a solid residue. The solid was recrystallized from hexane to yield 0.44 g. of N,N,2-trimethyl-α-phenyl-*m*-dioxane-5-methylamine, mp about 140—143°C.

Analysis: Calc. for $C_{14}H_{21}NO_2$: C, 71.46; H, 9.00; N, 5.85
Found: C, 71.22; H, 8.92; N, 5.68

Examples 11 and 12.

The following compounds were prepared according to the method of Example 10 from 2-(α-dimethylamino)benzyl-1,3-propanediol and the appropriate aldehyde:

N,N-dimethyl-2-ethyl-α-phenyl-*m*-dioxane-5-methylamine, mp 95—98°C.

Analysis: Calc. for $C_{15}H_{23}NO_2$: C 72.25; H, 9.30; N, 5.62
Found: C, 72.49; H, 9.60; N, 5.69

N,N-dimethyl-α,2-diphenyl-*m*-dioxane-5-methylamine, mp, 105—108°C.

Analysis: Calc. for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71
Found: C, 76.91; H, 7.82; N, 4.45

Example 13.

Preparation of N,N,4-Trimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride

(A) 5-Benzoyl-4-methyl-*m*-dioxane.- Phenylpropenyl ketone, 30 g. (0.2 mole), and 18 g. (0.20 mole) of s-trioxane, were refluxed in 300 ml. of chloroform. Boron trifluoride etherate, 20 ml., was added to the reaction mixture. Immediately an exothermic reaction occurred and heating was discontinued until the initial

reaction had subsided. Subsequently, refluxing was resumed for about 15 minutes. The reaction mixture was poured onto a mixture of ice and saturated sodium bicarbonate solution. The resultant melt was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to an oil. The oil was distilled and the fraction, bp, 100—110°C. (0.50 mm.), was collected to yield 16 g. of 5-benzoyl-4-methyl-m-dioxane which was characterized by NMR.

(B) N,N,4-Trimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride.- To a stirred solution of 16 g. (0.08 mole) of 5-benzoyl-4-methyl-m-dioxane, and 40 ml. of anhydrous dimethylamine in 200 ml. of benzene cooled in an ice bath was added a solution of 7.6 g. (0.04 mole) of titanium tetrachloride in 50 ml. of benzene. The stirred solution was cooled at about 0°C. for 1 hour. The reaction mixture was allowed to come to room temperature overnight. The reaction mixture was diluted with ethanol and filtered to remove titanium dioxide. The filtrate was evaporated, the residual oil was taken up in 100 ml. of ethanol and hydrogenated at 60 psi with 0.5 g. of 5% palladium-on-carbon catalyst. After the catalyst was filtered and the filtrate evaporated, the residual oil was taken up in dilute hydrochloric acid. The acidic solution was extracted with ether and the extracts were discarded. The acidic solution was basified with ammonium hydroxide solution and the basic solution was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to yield 6 g. of oil. The oil was chromatographed on a silica gel column using 370 ml. of ethyl acetate-benzene gradient (1:4). One gram of N,N,4-trimethyl-α-phenyl-m-dioxane-5-methylamine was collected in the last 180 ml. of eluate. The salt was prepared by treating an ethereal solution of the free base with gaseous hydrogen chloride. The yield of N,N,4-trimethyl-α-phenyl-m-dioxane-5-methylamine hydrochloride, mp about 213°C., was 0.7 g. after recrystallization from methanol-ethyl acetate.

Analysis: Calc. for $C_{14}H_{21}NO_2HCl$: C, 61.87; H, 8.16; N, 5.15
Found: C, 61.63; H, 8.13; N, 5.25

Example 14.
Preparation of N,N,5-Trimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride

(A) 5-Benzoyl-5-methyl-*m*-dioxane.- Paraformaldehyde, 9 g. (0.30 mole) was dissolved in 100 ml. of acetonitrile by warming and 13.4 g. (0.10 mole) of propiophenone was added to the mixture. The mixture was cooled in an ice bath and 15 g. (0.10 mole) of boron trifluoride etherate was added dropwise at about 0°C. The solution became turbid. The turbid mixture was clarified by boiling for about 15 minutes on the steam bath. The boiled solution was stirred into a mixture of ice and saturated sodium bicarbonate solution. The amber layer which separated from the aqueous melt was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated in vacuo to give 17 g. of oil. The oil was distilled and the fraction, bp 120—130°C. (0.40 mm.), was collected. The redistilled fraction, bp 118—122°C. (0.40 mm.) was crystallized. The yield of 5-benzoyl-5-methyl-m-dioxane, mp about 84°C., was 2.1 g. after recrystallization from acetone-hexane.

Analysis: Calc. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84
Found: C, 70.08; H, 6.62

(B) 5-Benzoyl-5-methyl-*m*-dioxane oxime.- Two grams of 5-Benzoyl-5-methyl-*m*-dioxane and 2 g. of hydroxylamine hydrochloride in 10 ml. of ethanol and 10 ml. of pyridine were refluxed for 3 hours. The mixture was evaporated to dryness in vacuo and the residue was treated with 10 ml. of water. The oxime was collected and recrystallized from aqueous ethanol to yield 1.5 g. of 5-benzoyl-5-methyl-*m*-dioxane oxime, mp about 144°C.

Analysis: Calc. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83
Found: C, 65.36; H, 6.93

(C) 5-Methyl-α-phenyl-*m*-dioxane-5-methylamine.- Lithium aluminum hydride, 1.37 g. (0.036 mole), was covered with 100 ml. of dry tetrahydrofuran (THF). 5-Benzoyl-5-methyl-*m*-dioxane oxime, 4.0 g. (0.018 mole), was dissolved in 50 ml. of THF and added dropwise to the stirred hydride suspension. The stirred mixture was refluxed for 1 hour and then cooled. The mixture was decomposed with saturated ammonium chloride solution and the aqueous phase was decanted. The residue was treated twice with ether. The ether was evaporated and the residue was again taken up in ether. The hydrochloride salt was prepared by

treatment of the ethereal solution with gaseous hydrogen chloride. The salt was dissolved in water and the aqueous phase was extracted with ether. The ether extract was washed with water. The aqueous phase and the water washes were combined and basified with ammonium hydroxide. The basic solution was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and treated with gaseous hydrogen chloride to provide the salt of the product. The yield of 5-methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride, mp about 235°C. with decomposition, was 2.26 g. after recrystallization from methanol-ethyl acetate.

Analysis: Calc. for $C_{12}H_{17}NO_2HCl$: C, 59.13; H, 7.44
Found: C, 59.07; H, 7.56

(D) N,N,5-Trimethyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride.- Five grams of 5-methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride was converted to the free base by dissolving the salt in water, basifying with ammonium hydroxide and extracting the basic solution with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to provide the free base as an oil. The oil was taken up in 25 ml. of cold 90% formic acid. Twenty-five milliliters of 38% aqueous formaldehyde was added to the cold reaction mixture and the mixture was heated on the steam bath for about 12 hours. The reaction mixture was poured onto a mixture of ice and water and basified with dilute sodium hydroxide. The basic aqueous solution was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate, and evaporated to an oil. The salt was prepared by treating an ethereal solution of the oil with gaseous hydrogen chloride. The yield of N,N,5-trimethyl-α-phenyl-m-dioxane-5-methylamine hydrochloride, mp about 195°C., was 3.0 g. after recrystallization from methanol-ethyl acetate.

Analysis: Calc. for $C_{14}H_{21}NO_2HCl$: C, 61.87; H, 8.16; N, 5.15
Found: C, 61.74; H, 8.41; N, 4.98

Example 15.

Preparation of N-methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride

(A) 2-(α-N-Methylbenzylamino)benzyl-1,3-propanediol.- Two hundred grams (0.808 mole) of diethyl benzalmalonate and 89 g. (0.808 mole) of N-methylbenzylamine were allowed to stand overnight at room temperature. The resultant crude diethyl α-(N-methylbenzylamino)benzylmalonate was added dropwise to 560 ml. (2.0 mole) of sodium bis(2-methoxyethoxy)aluminum hydride as a 70% solution in benzene, in dry benzene and stirred overnight. The reaction mixture was poured into cold dilute sodium hydroxide solution. The basic solution was extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated to a residual oil. The yield was 233 g. of 2-(α-N-methylbenzylamino)benzyl-1,3-propanediol which was characterized by NMR.

(B) N-Benzyl-N-methyl-α-phenyl-*m*-dioxane-5-methylamine.- One hundred and twenty grams 2-(α-N-methylbenzylamino)benzyl-1,3-propanediol, 100 g. of paraformaldehyde and 200 ml. of boron trifluoride etherate were refluxed overnight in 500 ml. of acetonitrile. The reaction mixture was poured into ammonium hydroxide solution, and subsequent isolation provided 84 g. of free base as an oil. The salt was prepared to yield 25 g. of N-benzyl-N-methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride, mp about 193—195°C., which was characterized by NMR.

(C) N-Methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride.- Eighteen grams of N-benzyl-N-methyl-α-phenyl-*m*-dioxane-5-methylamine was hydrogenated at 60 psi in 80 ml. of ethanol with 0.9 g. of 5% palladium-on-carbon catalyst at 35°C. for 1 1/4 hours. The catalyst was filtered and the filtrate was evaporated to a residual oil. The oil was taken up in ether and the ethereal solution was treated with gaseous hydrogen chloride to yield 3.7 g. of N-methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride, mp about 155—157°C., after crystallization from methanol-ethyl acetate.

Analysis: Calc. for $C_{12}H_{17}NO_2HCl$: C, 59.13; H, 7.44; N, 5.75; Cl, 14.55
Found: C, 53.91; H, 7.43; N, 5.82; Cl, 14.82

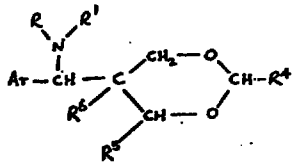
(D) Alternative preparation of N-methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride.- N,N-Dimethyl-α-phenyl-*m*-dioxane-5-methylamine, 5.5 g. (0.025 mole), and 4.5 g (0.025 mole) of diethyl azodicarboxylate were allowed to stand overnight in 100 ml. of benzene. The reaction mixture was evaporated in vacuo

and 50 ml. of saturated ammonium chloride was added to the residue. Enough ethanol was added to obtain a homogeneous solution and the mixture was heated on the steam bath for 5 hours. The cooled mixture was extracted with ether. The aqueous phase was basified with ammonium hydroxide and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated in vacuo to an oil. The oil was chromatographed over silica gel using ethyl acetate-benzene (1:4) as eluant. About 3 g. of starting material was eluted first. Continued elution with ethyl acetate gave 2 g. of oil. The salt was prepared by treating an ethereal solution of the oil with gaseous hydrogen chloride to yield 1.1 g of N-methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride, mp about 183—4°C., after recrystallization from methanol-ethyl acetate.

Analysis: Calcd. for $C_{12}H_{17}NO_2HCl$: C, 59.13; H, 7.44; N, 5.75
Found: C, 58.90; H, 7.51; N, 5.64

WHAT WE CLAIM IS:—

1. A compound of formula (I):



(I)

wherein R is hydrogen or methyl;
R^1 is methyl; or
R and R^1, when taken together, with the nitrogen to which they are attached, are aziridino, pyrrolidino or piperidino;
R^4 is hydrogen methyl, ethyl or phenyl;
R^5 and R^6 are hydrogen or one of R^5 and R^6 is methyl, with the limitations that, when R^5 is methyl, R and R^1 are other than aziridino, pyrrolidino or piperidino, and, when one of R^5 and R^6 is methyl, R^4 is hydrogen;
Ar is phenyl, halophenyl, methoxyphenyl, methylphenyl, trifluoromethylphenyl, hydroxyphenyl, acetoxyphenyl, benzyloxyphenyl, provided that when Ar is substituted phenyl the m-position is not occupied or 3-pyridyl;
and the pharmaceutically acceptable acid-addition salts thereof.

2. The compound of Claim 1, which is N,N-dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1, in which R^5 is hydrogen and Ar is phenyl, halophenyl, methoxyphenyl, methylphenyl, trifluorophenyl, hydroxyphenyl, acetoxyphenyl or benzyloxyphenyl.

4. The compound of Claim 3, which is the *l*-enantiomer.

5. The compound of Claim 3, which is the N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 3, which is N,N-dimethyl-α-(4-methylphenyl)-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 3 which is N,N,2-trimethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 3 which is N,N-dimethyl-2-ethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

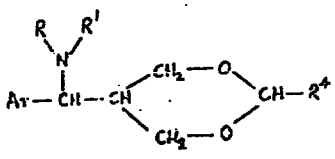
9. The compound of Claim 4 which is *l*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

10. The compound of Claim 4 which is *l*-N,N-dimethyl-α-(4-methylphenyl)-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

11. The compound of Claim 4 which is *l*-N,N,2-trimethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

12. The compound of Claim 4 which is *l*-N,N-dimethyl-2-ethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

13. A process for preparing a compound of formula (III)



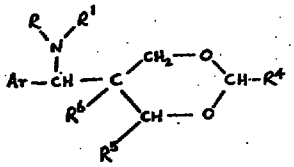
(III)

and 50 ml. of saturated ammonium chloride was added to the residue. Enough ethanol was added to obtain a homogeneous solution and the mixture was heated on the steam bath for 5 hours. The cooled mixture was extracted with ether. The aqueous phase was basified with ammonium hydroxide and extracted with ether. The ether extract was washed with water, dried over anhydrous magnesium sulfate and evaporated in vacuo to an oil. The oil was chromatographed over silica gel using ethyl acetate-benzene (1:4) as eluant. About 3 g. of starting material was eluted first. Continued elution with ethyl acetate gave 2 g. of oil. The salt was prepared by treating an ethereal solution of the oil with gaseous hydrogen chloride to yield 1.1 g of N-methyl-α-phenyl-*m*-dioxane-5-methylamine hydrochloride, mp about 183—4°C., after recrystallization from methanol-ethyl acetate.

Analysis: Calcd. for $C_{12}H_{17}NO_2HCl$: C, 59.13; H, 7.44; N, 5.75
Found: C, 58.90; H, 7.51; N, 5.64

WHAT WE CLAIM IS:—

1. A compound of formula (I):



(I)

wherein R is hydrogen or methyl;
R^1 is methyl; or
R and R^1, when taken together, with the nitrogen to which they are attached, are aziridino, pyrrolidino or piperidino;
R^4 is hydrogen methyl, ethyl or phenyl;
R^5 and R^6 are hydrogen or one of R^5 and R^6 is methyl, with the limitations that, when R^6 is methyl, R and R^1 are other than aziridino, pyrrolidino or piperidino, and, when one of R^5 and R^6 is methyl, R^4 is hydrogen;
Ar is phenyl, halophenyl, methoxyphenyl, methylphenyl, trifluoromethylphenyl, hydroxyphenyl, acetoxyphenyl, benzyloxyphenyl, provided that when Ar is substituted phenyl the m-position is not occupied or 3-pyridyl;
and the pharmaceutically acceptable acid-addition salts thereof.

2. The compound of Claim 1, which is N,N-dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 1, in which R^5 is hydrogen and Ar is phenyl, halophenyl, methoxyphenyl, methylphenyl, trifluorophenyl, hydroxyphenyl, acetoxyphenyl or benzyloxyphenyl.

4. The compound of Claim 3, which is the *l*-enantiomer.

5. The compound of Claim 3, which is the N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 3, which is N,N-dimethyl-α-(4-methylphenyl)-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

7. The compound of Claim 3 which is N,N,2-trimethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 3 which is N,N-dimethyl-2-ethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

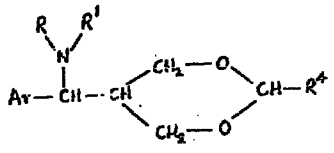
9. The compound of Claim 4 which is *l*-N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

10. The compound of Claim 4 which is *l*-N,N-dimethyl-α-(4-methylphenyl)-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

11. The compound of Claim 4 which is *l*-N,N,2-trimethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

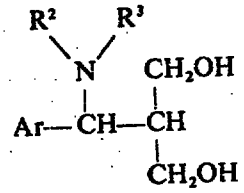
12. The compound of Claim 4 which is *l*-N,N-dimethyl-2-ethyl-α-phenyl-*m*-dioxane-5-methylamine or a pharmaceutically acceptable salt thereof.

13. A process for preparing a compound of formula (III)



(III)

wherein R, R^1, R^4 and Ar are as defined in Claim 1, which process comprises reacting a compound of formula (IV)



(IV)

wherein R^2 is hydrogen, methyl or benzyl;
R^3 is methyl or benzyl; and
Ar is as defined above;
with an aldehyde of formula (V)

$$R^4CHO \qquad (V)$$

wherein R^4 is as defined above, in the presence of borontrifluoride; and when one of R^2 and R^3 is benzyl, reductively debenzylating and methylating; or when both of R^2 and R^3 are benzyl, removing both groups and methylating at least one of R^2 and R^3.

14. A process as in claim 13 for the preparation of N,N-dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine which comprises reacting 2-[α-dimethylamino-(3-pyridyl)-methyl]-1,3-propanediol with paraformaldehyde in the presence of boron trifluoride etherate.

15. A process as in claim 13 for the preparation of N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine which comprises reacting 2-(α-dimethylamino)benzyl-1,3-propanediol with paraformaldehyde in the presence of boron trifluoride etherate.

16. A process as in claim 13 for the preparation of N,N-dimethyl-α-(4-methylphenyl)-*m*-dioxane-5-methylamine which comprises reacting 2-(α-dimethylamino-4-methylbenzyl)-1,3-propanediol with paraformaldehyde in the presence of boron trifluoride etherate.

17. A process as in claim 13 for the preparation of N,N-dimethyl-α-(3-pyridyl)-*m*-dioxane-5-methylamine which comprises reaction 2-[α-dimethylamino-(3-pyridyl)-methyl]-1,3-propanediol with trioxane in the presence of *p*-toluenesulfonic acid and chloroform.

18. A process as in claim 13 for the preparation of N,N,2-trimethyl-α-phenyl-*m*-dioxane-5-methylamine which comprises reacting 2-(α-dimethylamino)benzyl-1,3-propanediol with acetaldehyde in the presence of boron trifluoride etherate.

19. A process as in claim 13 for the preparation of N,N-dimethyl-2-ethyl-α-phenyl-*m*-dioxane-5-methylamine which comprises reacting 2-(α-dimethylamino)benzyl-1,3-propanediol with propionaldehyde in the presence of boron trifluoride etherate.

20. A process as in claim 13 for the preparation of N,N-dimethyl-α,2-diphenyl-*m*-dioxane-5-methylamine which comprises reacting 2-(α-dimethylamine)benzyl-1,3-propanediol with benzaldehyde in the presence of borontrifluoride etherate.

21. A process as in claim 13 for the preparation of N-methyl-α-phenyl-*m*-dioxane-5-methylamine which comprises reacting 2-(α-N-methylbenzylamino)-benzyl-1,3-propanediol with paraformaldehyde in the presence of boron trifluoride etherate to form N-benzyl-N-methyl-α-phenyl-*m*-dioxane-5-methylamine and debenzylating to obtain the desired product.

22. A process according to claim 13 wherein the compound of Formula (IV) is prepared by reacting a di-lower-alkyl-benzalmalonate with an amine of formula (VI):

$$R^2R^3NH \qquad (VI)$$

to form a dialkyl (α-substituted amino) benzylmalonate which is reduced to yield the desired compound of formula IV.

23. A process as in claim 22 in which the dialkyl (α-substituted amino) benzylmalonate is a diethyl (α-substituted amino)substituted-benzylmalonate and is formed by reacting a diethylbenzalmalonate with a substituted amine wherein the a substituted amino group is selected from the group consisting of dimethylamino, aziridino, pyrrolidino, and piperidino groups and the substituted benzyl group is

selected from the group consisting of benzyl, 2-methylbenzyl, 2-chlorobenzyl, 4-chlorobenzyl, 2,4-dichlorobenzyl, 4-methoxybenzyl, 4-benzyloxybenzyl, 4-hydroxybenzyl, 4-acetoxybenzyl and 4-fluorobenzyl.

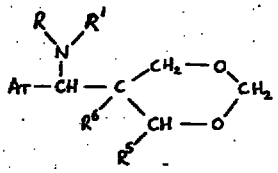
24. A process as in claim 22 in which the compound of formula (IV) is a 2-(α-dimethylamino) R^7-substituted-benzyl-1,3-propanediol prepared by reacting diethyl (α-dimethylamino) R^7-substituted benzylmalonate with sodium bis(2-methoxyethoxy)aluminum hydride in benzene wherein R^7 is hydrogen, 2-methyl, 4-methoxy, 2-chloro, 4-chloro, 4-fluoro, 2,4-dichloro, or 4-benzyloxy.

25. A process as in claim 16 in which the 2-(α-dimethylamino-4-methylbenzyl)-1,3-propanediol is prepared by reacting diethylmalonate with p-tolualdehyde in the presence of benzene and piperidine, reacting the resultant diethyl (4-methylbenzal)malonate with anhydrous dimethylamine in the presence of ether, and reacting the resultant diethyl α-dimethylamino-4-methylbenzylmalonate with sodium bis(2-methoxyethoxy)aluminum hydride in the presence of benzene.

26. A process as in claim 13 in which the 2-[α-dimethylamino-(3-pyridyl)-methyl]-1,3-propanediol is prepared by reacting diethyl malonate with 3-pyridinecarboxaldehyde in the presence of benzene and piperidine, reacting the resultant diethyl (3-pyridyl)methylene malonate with anhydrous dimethylamine in the presence of ether, and reacting the resultant diethyl α-dimethylamino-(3-pyridyl)methylmalonate with lithium aluminum hydride in the presence of dry tetrahydrofuran.

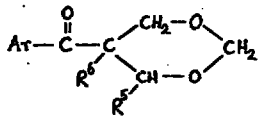
27. A process as in claim 21 in which the 2-(α-N-methylbenzylamino)benzyl-1,3-propanediol is prepared by reacting diethyl benzalmalonate with N-methylbenzylamine and reacting the resultant diethyl α-(N-methylbenzylamino)benzylmalonate with sodium bis(2-methoxyethoxy)aluminumhydride in the presence of benzene.

28. A process for preparing a compound of formula (VII):



(VII)

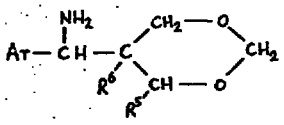
wherein R, R^1, R^5, R^6 and Ar are as defined in Claim 1, which process comprises reacting a compound of formula (VIII):



(VIII)

in the presence of hydrogen with

(A) hydroxylamine to provide a compound of formula (IX):



(IX)

and (1) reacting the compound of Formula IX with formaldehyde and formic acid to yield the corresponding α-dimethylamino compound; which is, if desired, demethylated to the α-methylamine compound or (2) reacting the compound of formula IX with benzaldehyde to yield the corresponding Schiff base which is then reduced catalytically to the corresponding α-benzylamine, which α-benzylamine is methylated with a methyl halide to yield the corresponding α-methyl-α'-benzylamine, which α-methyl-α'-benzylamine is reductively debenzylated to the corresponding α-methylamine; or

(B) with an amine of the formula RR^1NH when R^6 is H and wherein R and R^1 are as defined above.

29. A process as in claim 28 wherein the α-monomethyl amine compound of Formula I produced by the reductive debenzylation of the α-methyl-α'-benzyl amine compound is further alkylated with a methyl halide.

30. A process as in claim 29 wherein the methyl halide is methyl bromide.

31. A process as in claim 28 for the preparation of N,N-dimethyl-α-phenyl-*m*-dioxane-5-methylamine which comprises reacting acetophenone with paraformaldehyde in the presence of acetonitrile to form 5-benzoyl-*m*-dioxane and, reacting the 5-benzoyl-m-dioxane with anhydrous dimethylamine in the presence of titanium tetrachloride and benzene.

32. A process as in claim 28 for the preparation of N,N,4-trimethyl-α-phenyl-*m*-dioxane-5-methylamine which comprises reacting phenylpropenyl ketone with s-trioxane in the presence of chloroform and boron trifluoride etherate to form 5-benzoyl-4-methyl-*m*-dioxane, the reacting the resultant compound with dimethylamine in the presence of benzene and titanium tetrachloride.

33. A process as in claim 28 for the preparation of N,N,5-trimethyl-α-phenyl - *m* - dioxane - 5 - methylamine which comprises reacting propiophenone with paraformaldehyde in the presence of acetonitrile and boron trifluoride etherate to form 5-benzoyl-5-methyl-*m*-dioxane, reacting the resulting compound with hydroxylamine in the presence of ethanol and pyridine to form 5 - benzoyl - 5 - methyl - *m* - dioxane oxime, reacting the resulting oxime with lithium aluminum hydride in the presence of tetrahydrofuran to form 5-methyl-α-phenyl-*m*-dioxane-5-methylamine and reacting the resulting methylamine with formaldehyde and formic acid.

34. Process for preparing a compound of formula I or its pharmaceutically acceptable salts substantially as herein described with particular reference to any of Examples 4 to 15.

35. Compounds of formula I, whenever prepared by the process claimed in any one of Claims 13 to 21 and 28 to 34.

36. Pharmaceutical composition comprising as an active ingredient a compound as claimed in any one of Claims 1 to 12 and 35 in association with a pharmaceutically acceptable carrier therefor.

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