

PATENT SPECIFICATION

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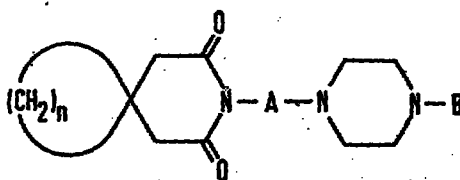
(54) HETEROCYCLIC AZASPIROALKANEDIONES

(71) We, BRISTOL-MYERS COMPANY, a Corporation of the State of Delaware, United States of America, of 345 Park Avenue, New York, State of New York, 10022, 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:—

The present invention relates to N-(heterocyclic)-piperazinylalkyl derivatives of azaspiroalkanediones, non-toxic pharmaceutically acceptable acid addition salts thereof and to a process for the preparation of such derivatives and salts.

The compounds of the invention have potent and specific tranquilizing action and anti-emetic properties.

In accordance with the invention there is provided a compound having the formula



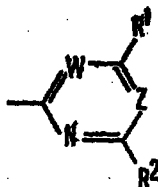
Formula I

wherein

n is 4 or 5;

A is a divalent straight or branched alkylene chain of 2 to 6 carbon atoms inclusive and connects the nitrogen atoms as shown through at least 2 carbon atoms;

B is 2-imidazolyl or a heterocyclic ring represented by



wherein

Z is CH, nitrogen, C—NO₂, C-alkyl(C₁—C₆)sulfonamido, or C—OH;

W is CH, nitrogen, or C-alkanoyl(C₁—C₆)amino;

R¹ and R² are independently either hydrogen, nitro, lower alkyl of from 1 to 4 carbon

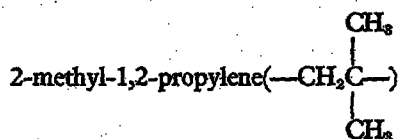
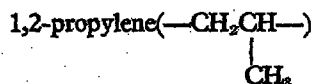
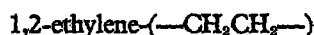
atoms inclusive, lower alkoxy of from 1 to 4 carbon atoms inclusive, hydroxy, amino, alkylthio of 1 to 4 carbon atoms inclusive, halogen, trifluoromethyl, alkanoylamino of 1 to 6 carbon atoms inclusive, or alkylsulfonamido of 1 to 6 carbon atoms inclusive.

and the non-toxic pharmaceutically acceptable acid addition salts thereof.

By the term "lower alkyl" as employed herein it meant straight or branched chain alkyl radicals including methyl, ethyl, propyl, isopropyl, 1-butyl, 1-methylpropyl, 2-methylpropyl and *tert*-butyl. Similarly, the alkyl fragment of the alkylthio substituent refers to straight or branched chain radicals described above. Straight or the branched chain alkanes of 1 to 6 carbon atoms inclusive comprise the alkane radical of alkanamido and alkanesulfonamido groupings.

The term "heteroarocyclic" as used herein, refers to substituents comprised of nitrogen, carbon and hydrogen which, when taken together form a heteroaromatic system.

The symbol —A— above, which connects the spiro-glutarimide and the N-(heteroarocyclic)piperazine represents a divalent alkylene chain of 2 to 6 carbon atoms inclusive. Said alkylene chain can be straight- or branched-chain hydrocarbon grouping in which the ring connecting bonds are on different carbon atoms such as



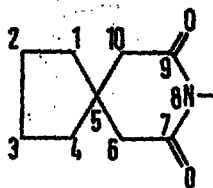
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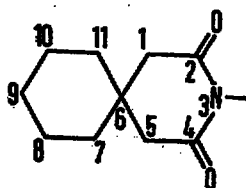
The term "non-toxic pharmaceutically acceptable acid addition salts" as used herein refers to a combination of compounds of the present invention with relatively non-toxic inorganic or organic acids. Illustrative of the variety of acids which may be used are sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, methane-sulfonic, benzenesulfonic, *para*-toluenesulfonic, acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, and cinnamic acids.

Conversion of the compounds of the present invention to pharmaceutically acceptable acid addition salts is accomplished by admixture of these compounds with substantially one chemical equivalent of a suitable acid. Generally the reactions are carried out in an inert solvent. Suitable solvents are, for example, ethanol, benzene, ethyl acetate, ether and halogenated hydrocarbons.

Illustrative of the nomenclature employed herein for the naming of the compounds of this invention are partial structures corresponding to the substituted glutarimide portions of Formula I are shown below with the positions numbered.



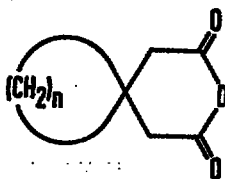
8-Azaspiro [4.5] decane-7,9-dione
Formula I, =4



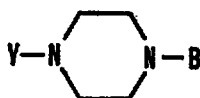
3-Azaspiro [5.5] undecane-2,4 dione
Formula I, $n=5$

Compounds of Formula I which are particularly preferred embodiments of the present invention are those wherein "n" is 4, the divalent alkylene chain " $-A-$ " is a chain of 4 carbon atoms and the heteroaracyclic "B" substituent is a 2-pyridyl or a 2-pyrimidyl group having R^1 and R^2 substituents with the meanings hereinbefore stated. Represented of these compounds are the individually preferred compounds 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione and 8-[4-[4-(2-pyridyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]-decane-7,9-dione.

The invention also provides a process for the preparation of compounds having the above Formula I or the non-toxic pharmaceutically acceptable acid addition salt thereof, which process comprises reacting a compound having the formula



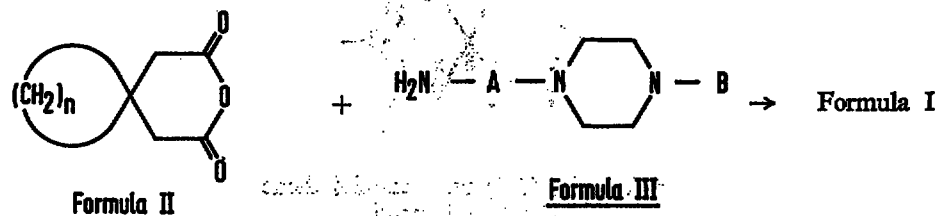
where n is 4 or 5 and D is oxygen or the group $N-A-X$ or $N-M$, wherein X is a reactive ester group and M is an alkali metal; with a compound having the formula



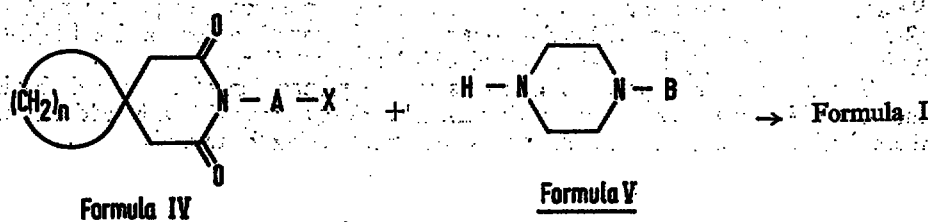
wherein B is as defined above and Y is hydrogen or the group H_2N-A- or $X-A-$, wherein A and X are as defined above except that when D is oxygen, Y is the group H_2N-A- , when D is the group $N-A-X$, Y is hydrogen, and when D is the group $N-M$, Y is the group $X-A-$.

The general embodiments of the process of the present invention are schematically illustrated below and labelled Method A, Method B and Method C. The use of a particular process method to produce compounds in accordance with the invention is dictated to a large extent by conditions which will be apparent to those skilled in the art. In practice, the selection of the method used for the preparation of any particular compound is principally determined by the commercial availability of the necessary intermediates and/or by the ease which available compounds can be converted to desired intermediates.

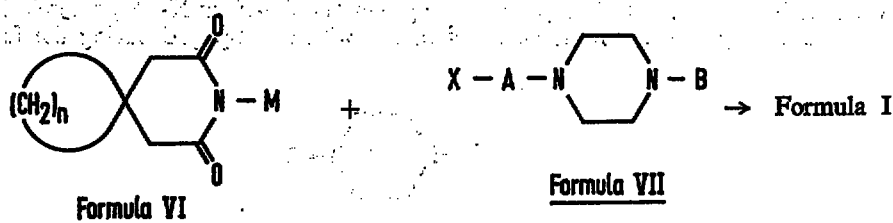
METHOD A



METHOD B



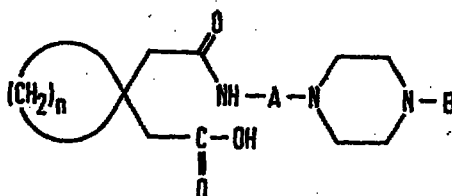
METHOD C



In the foregoing reaction schemes, the symbols n , $-\text{A}-$, and B have the same meanings as previously defined relative to formula I. The symbol X refers to the acid residue of a reactive ester grouping such as a chloride, bromide, iodide, sulfate, phosphate, tosylate or mesylate. M comprises an alkali metal salt of the substituted glutarimide and is preferably sodium or potassium.

Method A is carried out by reacting a spiro-substituted glutaric anhydride of formula II with the 1-(ω -aminoalkyl)-4-(heterocyclic)piperazines of Formula III to provide products of Formula I. Preferably, the reaction is carried out at elevated temperatures in an inert organic solvent. By the term "inert organic solvent", as referred to herein is meant any protic or aprotic solvent or diluent which does not enter into the reaction to any substantial degree. Pyridine is the preferred solvent. Temperatures of 100°C to 200°C are preferred to facilitate completion of the reaction. The duration of the reaction is critical only to the extent of providing maximum

yields and reaction periods of from 16 hr. to as much as 11 days are preferred. The lengthy reaction periods are necessary in some instances to obtain complete conversion of glutaric acid half-amides of Formula L below which are initially formed when an anhydride of Formula II is combined with an amine of formula III.



Formula L

The glutaric acid half-amides of formula L may also be transformed into formula I products by heating in boiling acetic anhydride. This is a well known standard organic procedure for ring closure useful in the formation of cyclic imides.

Method B is carried out under reaction conditions amply described in literature wherein tertiary amines are formed by alkylation of a secondary amine with an alkyl halide, sulfate, phosphate, tosylate or mesylate. The Formula IV and Formula V intermediates are preferably reacted in an inert liquid reaction medium at temperatures of from 60°C. to 200°C. In the presence of a base suitable for use as an acid binding agent. Sodium carbonate is a particularly preferred acid binding agent but other inorganic and tertiary organic bases may be employed including other alkali and alkaline earth metal carbonates, bicarbonates or hydrides and tertiary amines. Reaction periods ranging from 2 hrs. to 4 days are preferred in order to obtain satisfactory yields of the present compounds. A particularly preferred reaction medium is n-butanol but any inert reaction medium is generally applicable to use in this reaction. To a large extent, the duration of the reaction period depends upon the temperature and reaction medium selected. By way of illustration, alkylation is facilitated and the reaction period is appreciably shortened if dimethylformamide is employed as the reaction medium compared to a medium which is a solvent such as benzene.

In Method C, the spiroglutarimide metal salt depicted by Formula VI is reacted with substituted piperazines of Formula VII. Standard laboratory procedures are employed in carrying out the reaction such as those described for the alkylation step of the Gabriel synthesis — S. Gabriel, Ber. 20, 2224 (1887).

For example, the reactants are combined in an inert reaction medium at temperatures ranging from 25°C. to 200°C. Preferred reaction media for carrying out the reaction are dimethylformamide, acetone, benzene, n-butanol and ethanol.

With respect to the reactants for Methods A, B and C, many of them, including 3,3-tetramethyleneglutaric anhydride, (formula II, n=4) are known compounds which are readily available from commercial sources. Others, which are not commercially available, can be prepared in accordance with standard synthetic procedures which are known to those skilled in the art.

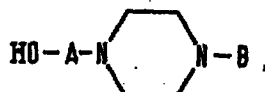
Preparation of N-(heterocyclic)piperazines of formula V have been described by K. L. Howard et al. in J. Org. Chem., 18, 1484 (1953). Their procedures are applicable to the preparation of other N-(heterocyclic)-piperazine intermediates not specifically disclosed but which are required for the preparation of compounds embraced by Formula I.

The 1-(ω-aminoalkyl)-4-heterocyclic)piperazine of formula III are obtained according to methods described in United States Patent 3,398,151 by alkylation of N-(heterocyclic)piperazines of formula V with haloalkylnitriles to provide 1-(ω-cyanoalkyl)-4-(heterocyclic)piperazine intermediates which are subsequently reduced to the formula III substituted piperazines. Reduction of the cyano intermediate may be carried out catalytically, preferably with W-6 Raney Nickel catalyst under high pressure, or alternatively with hydrazine and W-6 Raney Nickel.

The intermediate azospirodecane and undecanediones of formula IV having the —A—X group attached to the nitrogen atom are prepared according to procedures described in United States Patent 3,398,151. Reaction of the glutaric anhydrides of formula II with an alkanolamine of the formula H₂N—A—OH are carried out under conditions similar to those described hereinabove for Method A. The resulting intermediate glutarimide has the structure shown for formula IV wherein X is OH. Esteri-

fication of this material is accomplished by conventional techniques well known to the art to provide the intermediate of formula IV. Preferably, thionyl chloride is reacted with the alcohol precursor of formula IV ($X=OH$) to provide the intermediate wherein X is chlorine. Conventional techniques which are adequately described in the literature are employed to provide the bromides, iodides, phosphates, sulfates, tosylates and mesylates corresponding to formula IV.

The piperazine reactant of formula VII having the $X-A$ grouping attached to the nitrogen atom is prepared according to standard organic procedures. By way of example, reaction of the piperazines of formula V with alkanol halides of the formula $HO-A-X$ provides intermediate of formula VIII.



Formula VIII

This intermediate is then esterified according to conventional techniques well known to the art to provide the formula VII reactants. For instance, thionyl chloride acting upon the compounds of formula VIII provides the formula VII intermediate in which X is chlorine.

In a similar fashion, bromides and iodides may be prepared. Phosphates, sulfates, tosylates and mesylates corresponding to formula VII are obtained with conventional laboratory techniques.

The present invention relates to azaspirodecanedione and azaspiroundecanedione derivatives as hereinabove described by formula I. In United States Patent 3,398,158 reference is also made to derivatives of azaspirodecanediones and azaspiroundecanediones which have a number of pharmacological activities including tranquilizing action. In the present case, it has been discovered that N-(heterocyclic)piperazine alkyl derivatives of azaspirodecanediones and azaspiroundecanediones are highly active and specific tranquilizing agents and in addition also exhibit anti-emetic properties. The present compounds are improved tranquilizing agents compared to the azaspirodecanediones and azaspiroundecanediones of United States Patent 3,398,151, in that tranquilizing activity is more potent and specific.

With respect to side effects such as sedative and alpha-adrenergic blockade which are exhibited by a number of prominent tranquilizing agents the present compounds are unique in that such adverse reaction is substantially diminished or practically non-existent. By way of illustration, 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride has only about 1/400 th. the alpha-adrenergic blocking activity of the well known tranquilizer, chlorpromazine.

Tranquilizing properties of the compounds of this invention can be demonstrated in rats by a shuttle box technique described by J. R. Albert and L. E. Allen in the Pharmacologist 4,152 (1962). This test is designed to differentiate tranquilizing agents from non-specific central nervous system depressants such as sedatives and hypnotics. Tranquilizing effects are observed when the compounds of the present invention are administered intraperitoneally to the rat in dosage ranging from 1.5 to 180 mg./kg. of body weight.

The tranquilizing action of the compounds of the present invention can be demonstrated in Rhesus monkeys by observing general behavioral effects. Intramuscular administration of present compounds to the monkey in dosages ranging from 2 to 16 mg./kg. of body weight affords tranquilizing effects similar to those produced by chlorpromazine.

The compounds of the present invention are relatively non-toxic compounds. For example, the intraperitoneal 50% lethality dose of 8-[4]-[4-(2-pyrimidinyl)-1-piperazinyl] butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride is 146 mg./kg. of body weight in the mouse.

Systemic administration of the compounds of the present invention to mammals in dosages ranging from 0.01 to 40 mg./kg. of body weight per day induce effective tranquilizing responses in the mammalian recipient. Oral, parenteral and rectal routes are preferred forms of systemic administration. Forms of parenteral administration include intramuscular, intravenous and subcutaneous administration. Those skilled in the art will recognize that the dosage of the compounds of the present invention will vary with the form and mode of administration and in some instances with the particular compound chosen.

Generally, it will be found that when a compound of the present invention is

administered orally, a larger quantity of the active agent is required to produce the same effect as a smaller quantity thereof which is given parenterally. It is generally preferred to administer the compounds of this invention at a concentration level that will produce effective tranquilizing effects without causing any harmful or deleterious side effects.

For pharmaceutical purposes, the compounds of Formula I may be administered to mammals in the form of free bases or in the form of non-toxic acid addition salts. In the free base form, the compounds are relatively insoluble in water but are soluble in most organic solvents such as lower alkyl alcohols, esters, acetones and chloroform. The present compounds in the form of their acid addition salts are, in general, soluble in water and methanol but relatively insoluble in solvents such as benzene, ether and petroleum ether. In either the free base or the acid addition salt form, the compounds of Formula I may be compounded and formulated into pharmaceutical compositions and unit dosage form suitable for systemic administration. Such compositions may comprise a compound of Formula I or a non-toxic pharmaceutically acceptable acid addition salt thereof and an inert carrier e.g. an organic or inorganic solid or liquid which is pharmaceutically acceptable.

Pharmaceutical compositions considered within the scope of this invention may take the form of tablets, powders, granules, capsules, suspensions, solutions, suppositories, elixirs and ointments. Unit dosages ranging from 1 to 500 mg. may be employed. Suitable carriers comprise both solids and liquids such as corn starch, lactose, calcium phosphate, stearic acid, polyethylene glycol, water sesame seed oil, peanut oil and propylene glycol.

Following is a description by way of example of the preparation of compounds in accordance with the invention.

METHOD A.

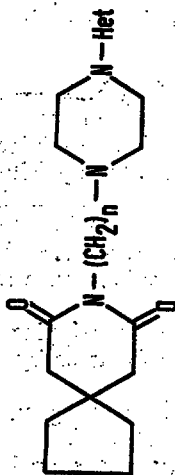
Procedure 1. — Condensation with Substituted Glutaric Anhydride. — A mixture of 0.1 mole of the substituted glutaric anhydride (Formula II), 0.1 mole of 1-(ω -aminoalkyl)-4-heterocyclicpiperazine (Formula III), and 300 ml. of pyridine is refluxed until imide formation is complete. The degree of reaction is readily followed by taking an aliquot portion of the reaction mixture, removing the solvent and obtaining the infrared absorption spectrum of the residue. When reaction is complete, the spectrum exhibits typical infrared imide bands at 1700 and 1710 cm^{-1} , whereas if incomplete, the infrared spectrum contains amide and carboxyl absorption bands at 1680, 1760 and 3300 cm^{-1} .

The azaspiroalkanedione product purified is the free base by stripping off the pyridine solvent and crystallizing the residue from a suitable solvent or by vacuum distillation thereof.

Suitable acid addition salts of the product are prepared by treating an ethanol solution of the free base with an equi-molar amount of the appropriate acid.

Examples of representative compounds of the present invention prepared according to Procedure 1 are indicated in Table I.

TABLE I
8-[4-(N-HETEROARCYCLIC)-1-PIPERAZINYLALKYL]-8-AZASPIRO[4.5]DECANE-7,9-DIONE PRODUCTS



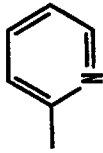
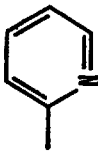
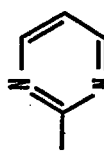
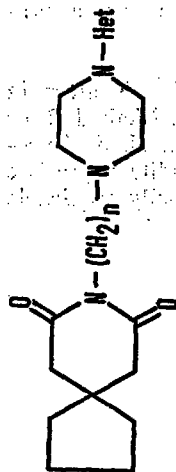
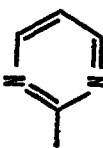
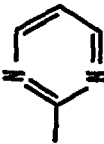
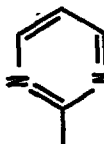
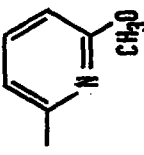
Example No.	Product		Base		Hydrochloride			Analyses	
	Method	n	Het.	B.P., °C. (mm Hg)	Percent Yield	M.P. °C.	Crystn. Solvent		Formula
1	A	2		—	—	208.5—209.5	ethanol	C ₂₀ H ₂₈ N ₄ O ₂ ·HCl	C 61.11 H 7.25 N 14.26 Cl 8.81
2	A	4		255—260 (0.1)	76	172—173.5	2-butanone	C ₂₂ H ₃₂ N ₄ O ₂ ·HCl	C 63.01 H 7.89 N 13.55 Cl 8.29
3	A	2		230—250 (0.1)	90	206—207	absolute ethanol	C ₁₉ H ₂₇ N ₄ O ₂ ·HCl	C 58.00 H 7.23 N 17.75 Cl 9.03

TABLE I (Cont'd)

8-[4-(N-HETEROARCYCLIC)-1-PIPERAZINYLALKYL]-8-AZASPIRO[4.5]DECANE-7,9-DIONE PRODUCTS



Example No.	Product		Base		Hydrochloride				
	Method	n	Het.	B.P., °C. (mm Hg)	Percent Yield	M.P. °C.	Crystn. Solvent	Formula	Analyses
4	B	3		—	—	214—215	absolute ethanol-ether	C ₂₀ H ₂₈ N ₆ O ₂ .HCl	C 59.06 H 7.30 N 17.24
5	A	4		240—265 (0.1)	67	201.5—202.5	absolute ethanol	C ₂₁ H ₃₁ N ₆ O ₂ .HCl	C 60.29 H 7.41 N 16.60 Cl 8.48
6	A	5		260—275 (0.07)	52	188.5—190.5	methanol-ethyl acetate	C ₂₂ H ₃₃ N ₆ O ₂ .HCl	C 60.44 H 7.93 N 16.01
7	B	3		260—270 (0.2)	59	233.5—234.5	ethanol	C ₂₂ H ₃₃ N ₆ O ₂ .HCl	C 60.72 H 7.73 N 13.01 Cl 7.98

METHOD B.

Procedure 2. — Alkylation of N-(heterocyclic)-piperazines. — A mixture of 4.9 g. (0.02 mole) of 8-[3-chloro-1-propyl]-8-azaspiro[4.5]decane-7,9-dione, 3.3 g. (0.02 mole) prepared in the manner of United States Patent 3,398,151, N-(2-pyrimidinyl)piperazine, and 2.2 g. (0.02 mole) of sodium carbonate in 75 ml. of n-butanol is refluxed for three days and filtered. The filtrate is concentrated *in vacuo* and the residue taken up in 100 ml. of benzene. Addition of 4.0 ml. of 5.0 N. ethanolic hydrogen chloride to the benzene solution of the free base provides the product 8-[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]-8-azaspiro[4.5]decane-7,9-dione as a hydrochloride salt which is collected and crystallized from absolute ethanol-ether, yield 3.4 g., m.p. 214—215°C. (corr.).

Examples of representative products of this invention and physical properties thereof prepared according to Method B are listed in Table I.

METHOD C.

Procedure 3. — Alkylation of Azaspiroalkaneimides. — A solution of 0.1 mole of 3,3-tetramethyleneglutarimide in methanol (150 ml.) is treated with 0.1 mole of sodium methoxide. The solvent is removed *in vacuo* to provide a residue consisting of the sodium salt of 3,3-tetramethyleneglutarimide which without further purification is combined with 0.1 mole of 1-(2-chlorobutyl)-4-(pyrimidinyl)piperazine in 150 ml. of n-butanol. The mixture is refluxed for a period of time of sufficient duration to provide approximately 0.1 mole of precipitated sodium chloride as a by-product. Isolation of the product by standard laboratory procedures provide 8-[3-[4-(2-pyrimidinyl)-1-piperazinyl]propyl]-8-azaspiro[4.5]decane-7,9-dione which is also a product of Procedure 2.

Examples 8—28.

Additional exemplification of compounds of the present invention is given in Table II along with the mode of preparation according to Method A, Method B, or Method C and the appropriate intermediates. Although only a single method of preparation is indicated for each example, one skilled in the art can readily appreciate that any of the Methods A, B and C hereinabove described are equally applicable to the preparation of the compounds of the present invention.

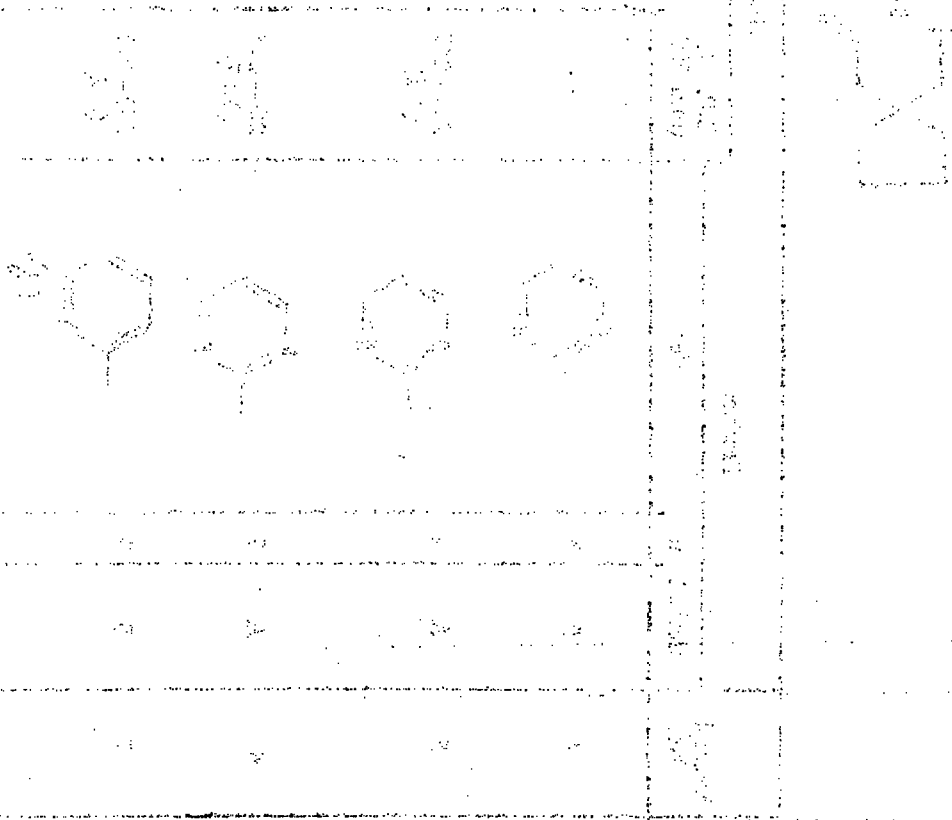
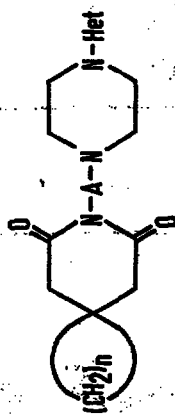


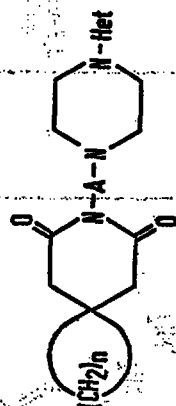
TABLE II
Additions N-(HETEROARCYCLIC)PIPERAZINYLALKYLASPIROALKANEDIONES



Example No.	Product		Method	Starting Materials
	n	Het.		
8	5 —(CH ₂) ₄ —		A	3,3-pentamethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[2-(pyrimidinyl)]piperazine
9	5 —(CH ₂) ₄ —		A	3,3-pentamethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[4-(2,6-diaminopyrimidinyl)]piperazine
10	4 —(CH ₂) ₄ —		A	3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[4-(2-amino-6-methylpyrimidinyl)]piperazine

TABLE II Cont'd

Additions N-(HETEROARCYCLIC)PIPERAZINYALKYLASPIROALKANEDIONES



Example No.	Product		Method	Starting Materials
	n	A		
11	4	—(CH ₂) ₄ —	A	3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[2-(4,6-dimethoxypyrimidinyl)]piperazine
12*	4	—(CH ₂) ₄ —	A	3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[2-(4,6-dimethylpyrimidinyl)]piperazine
13	4	—(CH ₂) ₄ —	A	3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[4-(2-methylthio)pyrimidinyl]]piperazine

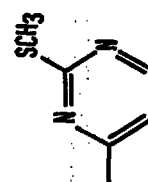
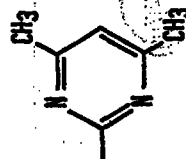
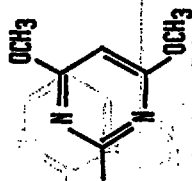
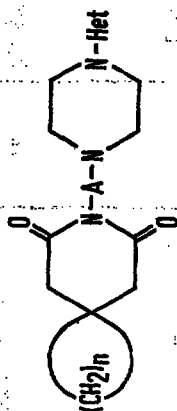


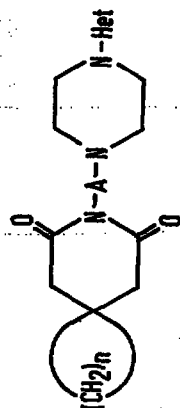
TABLE II Cont'd
Additional N-(HETEROARCYCLIC)PIPERAZINYLALKYL AZASPIROALKANEDIONES



Example No.	Product		Method	Starting Materials
	n	A	Het.	
14	4	—(CH ₂) ₄ —		3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[2-(4,6-dichloropyrimidinyl)]piperazine
15	4	—(CH ₂) ₄ —		3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[4-(2-chloropyrimidinyl)]piperazine
16	4	—(CH ₂) ₄ —		8-(4-chlorobutyl)-8-azaspiro[4.5]decane-7,9-dione and 1-[4-(2-nitro-6-methylpyrimidinyl)]piperazine

TABLE II Cont'd

Additional N-(HETEROARCYCLIC)PIPERAZINYLALKYLASPIROALKANEDIONES



Example No.	Product		Method	Starting Materials
	n	A		
17	4	$-(CH_2)_4-$	A	3,3-tetramethyleneglutamic anhydride and 1-(4-aminobutyl)-4-[4-(2-methanesulfonamido-6-methylpyrimidinyl)]piperazine
18	5	$-(CH_2)_5-$	C	3,3-pentamethyleneglutaramide and 1-(2-chloroethyl)-4-[2-(5-nitropyrimidinyl)]piperazine
19	5	$-(CH_2)_5-$	A	3,3-pentamethyleneglutamic anhydride and 1-(6-amino-hexyl)-4-[2-(5- <i>n</i> -butanesulfonamidopyrimidinyl)]piperazine

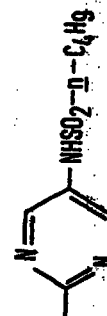
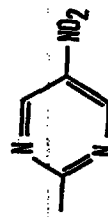
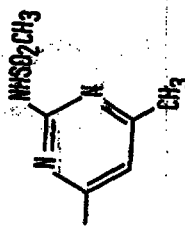
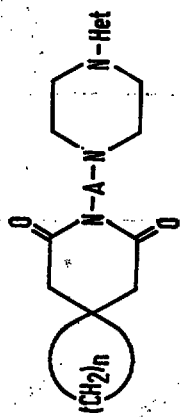


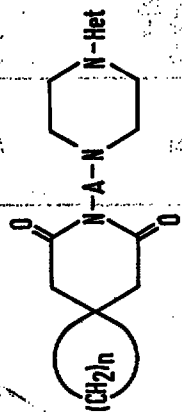
TABLE II Cont'd
Additional N-(HETEROACYCLIC)PIPERAZINYLALKYL AZASPIROALKANEDIONES



Example No.	Product		Method	Starting Materials
	n	A	Het.	
20	4	—(CH ₂) ₄ —		3,3-tetramethyleneglutarimide and 1-(4-chloroethyl)-4-[4-tert.-butylpyrimidinyl]piperazine
21	4	—(CH ₂) ₄ —		8-(4-chlorobutyl)-8-azaspiro[4.5]decane-3,9-dione and 1-[2-(4-tert.-butylpyrimidinyl)]piperazine
22	4	—(CH ₂) ₄ —		8-(4-chlorobutyl)-8-azaspiro[4.5]decane-3,9-dione and 1-[2-(6-trifluoromethylpyridinyl)]piperazine

TABLE II Cont'd

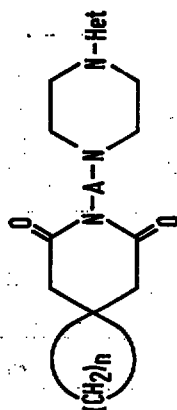
Additions N-(HETEROARCYCLIC)PIPERAZINYLALKYLASPIROALKANEDIONES



Example No.	Product		Method	Starting Material
	n	Het.		
23	4		A	3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[2-(1,3,5-triazinyl)]piperazine
24	4		C	3,3-tetramethyleneglutarimide and 1-(2-chloroethyl)-4-[2-(4-nitro-1,3,5-triazinyl)]piperazine
25	4		A	3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[2-(3-propionylamidopyridinyl)]piperazine

TABLE II Cont'd

Additions N-(HETEROARCYCLIC)PIPERAZINYLALKYL AZASPIROALKANEDIONES



Example No.	Product		Method	Starting Material
	A	Het.		
26	4 —(CH ₂) ₄ —		A	3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[4-(2,6-dimethanesulfonamidopyrimidinyl)]piperazine
27	4 —(CH ₂) ₄ —		A	3,3-tetramethyleneglutaric anhydride and 1-(4-aminobutyl)-4-[2-(4-hydroxypyrimidinyl)]piperazine
28	5 —(CH ₂) ₄ —		A	3,3-pentamethyleneglutaric anhydride and 1-(4-aminobutyl)-4-(2-pyridinyl)piperazine

* 8-[4-[4-(4,6-dimethyl-2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride, m.p. 216.5—217.5°C. (corr.) crystallized from absolute ethanol-anhydrous ether. Analysis — Calcd. for C₂₃H₃₈ClN₆O₂: C, 61.38; H, 8.06; N, 15.56. Found: C, 61.26; H, 8.10; N, 15.53.

Procedure 4. — 1-(3-Cyanopropyl)-4-(2-pyrimidinyl)piperazine. — A mixture of 1-(2-pyrimidinyl)piperazine (6.0 g., 0.04 mole), 4.6 g. (0.044 mole) of 3-chloropropionitrile and sodium carbonate (4.24 g., 0.04 mole) in 50 ml. of n-butanol is gently refluxed for 16 hours. The reaction mixture is concentrated *in vacuo* and the residual oil dissolved in about 100 ml. of cyclohexane. On standing a white crystalline material separates which is crystallized from cyclohexane to provide 6.5 g. (yield 70%) of the cyano intermediate, m.p. 56.6–58°C. Representative examples of cyano intermediates useful in Procedure 5 along with information relative to the preparation thereof according to Procedure 4 are listed in Table III.

5

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TABLE III

1-(*ω*-CYANOALKYL)-4-(HETEROARCYCLIC)PIPERAZINES

Intermediate No.	Het.	n	Yield	B.P., °C. (mm Hg)	M.P., °C. (Crystn. Solv.)	Formula	Analysis		
							C	H	N
1		1	82	163–165 (0.08)	—	$\text{C}_{11}\text{H}_{14}\text{N}_4$	—	—	—
2		3	92	185–205 (0.02)	47–49 (cyclohexane)	$\text{C}_{19}\text{H}_{18}\text{N}_4$	—	—	—

TABLE III (Cont'd)
1-(*o*-CYANOALKYL)-4-(HETEROARCYCLIC)PIPERAZINES



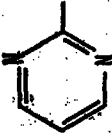
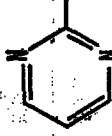
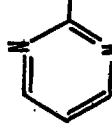
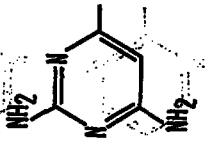
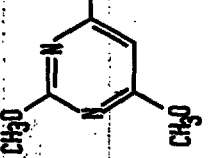
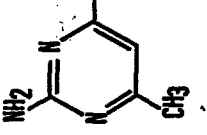
Intermediate No.	Het	n	Yield	B.P., °C. (mm Hg)	M.P., °C. (Crystn. Solv.)	Formula	Analysis		
							C	H	N
3		1	80	—	98—100 (cyclohexane)	C ₁₀ H ₁₃ N ₅	59.12	6.62	34.77
4		3	70	—	56—58 (cyclohexane)	C ₁₃ H ₁₇ N ₅	62.04	7.31	30.08
5		4	80	—	77—88 (cyclohexane)	C ₁₃ H ₁₉ N ₅	63.49	7.62	28.41

TABLE III (Contd.)
1-(*o*-CYANOALKYL)-4-(HETEROARCYCLIC)PIPERAZINES

Intermediate No.	Het.	n	Yield	B.P., °C. (mm Hg)	M.P. °C. (Crystn. Solv.)	Formula	Analysis		
							C	H	N
6		3	87	—	191—192 (methanol)	$C_{13}H_{19}N_7$	55.07	7.28	37.84
7		3	46	220—235 (0.1)	—	$C_{11}H_{21}N_5O_2$	56.90	7.01	23.41
8		3	100 (Crude)	245 (0.15)	109—110 (ethyl acetate-Skilysolve F)	$C_{13}H_{20}N_6$	59.94	7.66	32.48

Procedure 5. — 1-(4-Aminobutyl)-4-(2-pyrimidinyl)piperazine. — A. A solution of 11.5 g. (0.05 mole) of 1-(3-cyanopropyl)-4-(2-pyrimidinyl)piperazine in 150 ml. of absolute ethanol is saturated with ammonia. W-6 Raney Nickel catalyst is added and the mixture hydrogenated under 1200 p.s.i. When the hydrogenation is completed the mixture is filtered and the residual oil distilled under reduced pressure to provide 8.2 g. (70%) of 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine.

Reduction of cyano intermediates of Procedure 4 in the manner described for Procedure 5 or alternatively by reduction with hydrazine and Raney Nickel provide the amino intermediates of Formula III. The following procedure is illustrative of hydrazine and Raney Nickel reductions.

B. Hydrazine hydrate (85% (640 ml) is added dropwise to 4-[-(2-pyrimidinyl)-1-piperazinyl]butyronitrile (189.8 g., 0.82 mole), Raney Nickel (190 g. — wet with water, activated by washing with 2-propanol) and 2-propanol (1.4 liter) in 2 hours at reflux. The reaction mixture is stirred for 5 minutes, filtered, concentrated *in vacuo* and the residual material distilled to yield 168.2 g. (87%) of 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine, b.p. 143—6°C. at 0.1 mm (N_D^{20} 1.5582).

Procedure 6. — Solution for Parenteral Injection. — The azaspiroalkanedione compounds of the present invention may be formulated for parenteral administration according to the following example. A sterile solution suitable for intravenous injection is prepared by dissolving 21.9 g. of 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride in 2 liters of water for injection, USP. The solution is adjusted to pH 4.2 with 0.1 N-sodium hydroxide. After adjusting the pH, the solution is sterilized by passage through a bacteriological filter and 10 ml. glass ampoules aseptically filled in order to provide 10 mg. of active ingredient per ampoule.

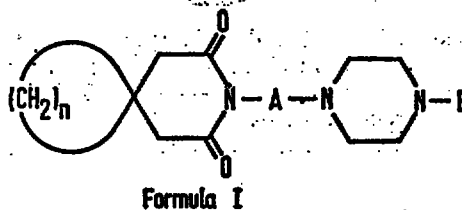
Procedure 7. — Tablets. — The azaspiroalkanedione compounds of the present invention may be compounded into tablets in accord with the following example.

Material	Amount
8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride	54.8 g.
Magnesium Stearate	1.3 g.
Corn starch	12.4 g.
Corn starch pregelatinized	1.3 g.
Lactose	180.2 g.

The foregoing materials are blended in a twin-shell blender and then granulated and pressed into tablets weighing 250 mg. each. Each tablet contains 50 mg. of active ingredient.

WHAT WE CLAIM IS:—

1. A compound having the formula

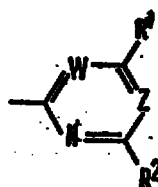


wherein

n is 4 or 5;

A is a divalent straight or branched alkylene chain of 2 to 6 carbon atoms inclusive and connects the nitrogen atoms as shown through at least 2 carbon atoms;

B is 2-imidazolyl or a heteroarocyclic ring represented by



Procedure 5. — 1-(4-Aminobutyl)-4-(2-pyrimidinyl)piperazine. — A. A solution of 11.5 g. (0.05 mole) of 1-(3-cyanopropyl)-4-(2-pyrimidinyl)piperazine in 150 ml. of absolute ethanol is saturated with ammonia. W-6 Raney Nickel catalyst is added and the mixture hydrogenated under 1200 p.s.i. When the hydrogenation is completed the mixture is filtered and the residual oil distilled under reduced pressure to provide 8.2 g. (70%) of 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine.

Reduction of cyano intermediates of Procedure 4 in the manner described for Procedure 5 or alternatively by reduction with hydrazine and Raney Nickel provide the amino intermediates of Formula III. The following procedure is illustrative of hydrazine and Raney Nickel reductions.

B. Hydrazine hydrate (85% (640 ml) is added dropwise to 4-[-(2-pyrimidinyl)-1-piperazinyl]butyronitrile (189.8 g., 0.82 mole), Raney Nickel (190 g. — wet with water, activated by washing with 2-propanol) and 2-propanol (1.4 liter) in 2 hours at reflux. The reaction mixture is stirred for 5 minutes, filtered, concentrated *in vacuo* and the residual material distilled to yield 168.2 g. (87%) of 1-(4-aminobutyl)-4-(2-pyrimidinyl)piperazine, b.p. 143—6°C. at 0.1 mm (N_D^{20} 1.5582).

Procedure 6. — *Solution for Parenteral Injection.* — The azaspiroalkanedione compounds of the present invention may be formulated for parenteral administration according to the following example. A sterile solution suitable for intravenous injection is prepared by dissolving 21.9 g. of 8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride in 2 liters of water for injection, USP. The solution is adjusted to pH 4.2 with 0.1 N-sodium hydroxide. After adjusting the pH, the solution is sterilized by passage through a bacteriological filter and 10 ml. glass ampoules aseptically filled in order to provide 10 mg. of active ingredient per ampoule.

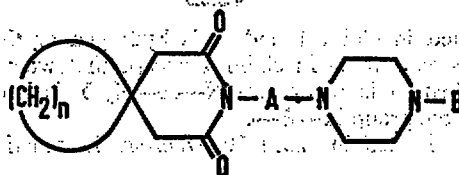
Procedure 7. — *Tablets.* — The azaspiroalkanedione compounds of the present invention may be compounded into tablets in accord with the following example.

Material	Amount
8-[4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl]-8-azaspiro[4.5]decane-7,9-dione hydrochloride	54.8 g.
Magnesium Stearate	1.3 g.
Corn starch	12.4 g.
Corn starch pregelatinized	1.3 g.
Lactose	180.2 g.

The foregoing materials are blended in a twin-shell blender and then granulated and pressed into tablets weighing 250 mg. each. Each tablet contains 50 mg. of active ingredient.

WHAT WE CLAIM IS:—

1. A compound having the formula



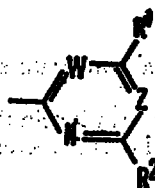
Formula I

wherein

n is 4 or 5;

A is a divalent straight or branched alkylene chain of 2 to 6 carbon atoms inclusive and connects the nitrogen atoms as shown through at least 2 carbon atoms;

B is 2-imidazolyl or a heterocyclic ring represented by



wherein

Z is CH₃, nitrogen, C—NO₂, C-alkyl(C₁—C₆)sulfonamido, or C—OH;

W is CH₃, nitrogen, or C-alkanoyl(C₁—C₆)amino;

5 R¹ and R² are independently either hydrogen, nitro, lower alkyl of from 1 to 4 carbon atoms inclusive, lower alkoxy of from 1 to 4 carbon atoms inclusive, hydroxy, amino, alkylthio of 1 to 4 carbon atoms inclusive, halogen, trifluoromethyl, alkanoylamino of 1 to 6 carbon atoms inclusive, or alkylsulfonamido of 1 to 6 carbon atoms inclusive.

2. 8-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl)-8-azaspiro(4.5)decane-7,9-dione.

10 3. 8-(4-(4-(2-pyrimidinyl)-1-piperazinyl)butyl)-8-azaspiro(4.5)decane-7,9-dione hydrochloride.

4. 8-(4-(4-(2-pyridyl)-1-piperazinyl)-butyl)-8-azaspiro(4.5)decane-7,9-dione.

5. 8-(4-(4-(2-pyridyl)-1-piperazinyl)-butyl)-8-azaspiro(4.5)decane-7,9-dione hydrochloride.

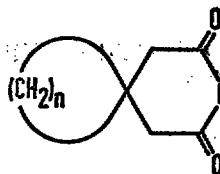
15 6. A non-toxic pharmaceutically acceptable acid addition salt of a compound as claimed in any one of claims 1, 2 or 4.

7. A salt as claimed in claim 6 with sulfuric, phosphoric, hydrochloric, hydrobromic or hydroiodic acid.

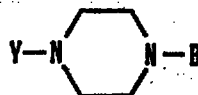
20 8. A salt as claimed in claim 6 with sulfamic, methanesulfonic, benzenesulfonic, *para*-toluenesulfonic, acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, or cinnamic acid.

9. A compound as claimed in claim 1 or a non-toxic pharmaceutically acceptable acid addition salt thereof substantially as hereinbefore described with reference to any one of Procedures 1 to 3.

25 10. A process for the preparation of compounds having the Formula I defined in claim 1 or the non-toxic pharmaceutically acceptable acid addition salts thereof, which process comprises reacting a compound having the formula

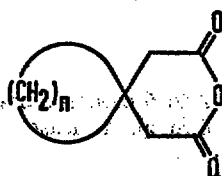


30 wherein n is 4 or 5 and D is oxygen or the group N—A—X or N—M, wherein X is a reactive ester group and M is an alkali metal; with a compound having the formula



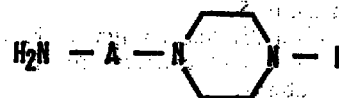
35 wherein B is as defined in claim 1 and Y is hydrogen or the group H₂N—A— or X—A— wherein A is as defined in claim 1 except that when D is oxygen, Y is the group H₂H—A—, when D is the group N—A—X, Y is hydrogen, and when D is the group N—M, Y is the group X—A—.

11. A process as claimed in claim 10, wherein the reaction is between the compounds



Formula II

and



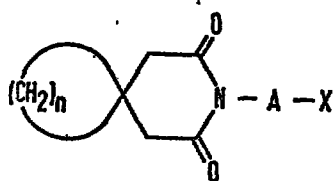
Formula III

40 and the reaction is carried out at a temperature of from 100°C to 200°C in the presence of an inert organic solvent.

12. A process as claimed in claim 11, wherein the solvent is pyridine.

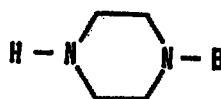
13. A process as claimed in claim 10, wherein the reaction is between the compounds





Formula IV

and

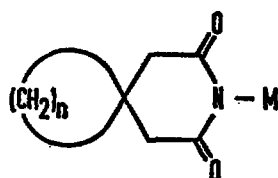


Formula V

, and the reaction is carried out at a temperature of from 60°C to 200°C in an inert reaction medium and in the presence of a base suitable for use as an acid binding agent.

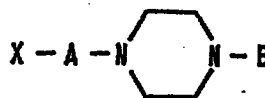
- 5 14. A process as claimed in claim 13, wherein the reaction medium is n-butanol.
 15. A process as claimed in claim 13 or claim 14, wherein the base is sodium carbonate.
 16. A process as claimed in claim 10, wherein the reaction is between the compounds

5



Formula VI

and



Formula VII

, and the reaction is carried out at a temperature of from 25°C to 200°C in an inert reaction medium.

17. A process as claimed in claim 16, wherein the reaction medium is dimethylformamide, acetone, benzene, n-butanol or ethanol.
 18. A process as claimed in claim 10 and substantially as hereinbefore described specifically.
 19. A process as claimed in claim 10 and substantially as hereinbefore described with reference to any one of Procedures 1 to 3.
 20. A compound of the Formula I defined in claim 1 or a non-toxic pharmaceutically acceptable salt thereof when prepared by a process as claimed in any one of claims 10 to 19.
 21. A pharmaceutical composition, which composition comprises a compound as claimed in any one of claims 1, 2, 4, 9 or 20 or a salt as claimed in any one of claims 3, 5 to 9 or 20 and an inert carrier.
 22. A pharmaceutical composition in dosage unit form suitable for systemic administration to a mammalian host, which composition comprises a compound as claimed in any one of claims 1, 2, 4, 9 or 20 or a salt as claimed in any one of claims 3, 5 to 9 or 20 in an amount to provide an effective daily dose of from 0.01 to 40 mg./kg. of body weight of said host and an inert carrier.
 23. A composition as claimed in claim 21 and substantially as hereinbefore described with reference to Procedure 6 or Procedure 7.
 24. A method of eliciting a tranquilizing effect in a non-human mammalian host, which method comprises administering systemically to said host a dose of from 0.01 to 40 mg./kg. of body weight of said host of a compound as claimed in any one of claims 1, 2, 4, 9 or 20 or a salt as claimed in any one of claims 3, 5 to 9 or 20.

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Agents for the Applicants.

