

1.197.313

PATENT SPECIFICATION

NO DRAWINGS

1.197.313



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COMPLETE SPECIFICATION

Dioxolan Substituted Compounds

We, CUTTER LABORATORIES INC., a corporation organised and existing under the laws of the State of Delaware, U.S.A., and having a place of business at Fourth and Parker Streets, Berkeley, State of California, 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:—

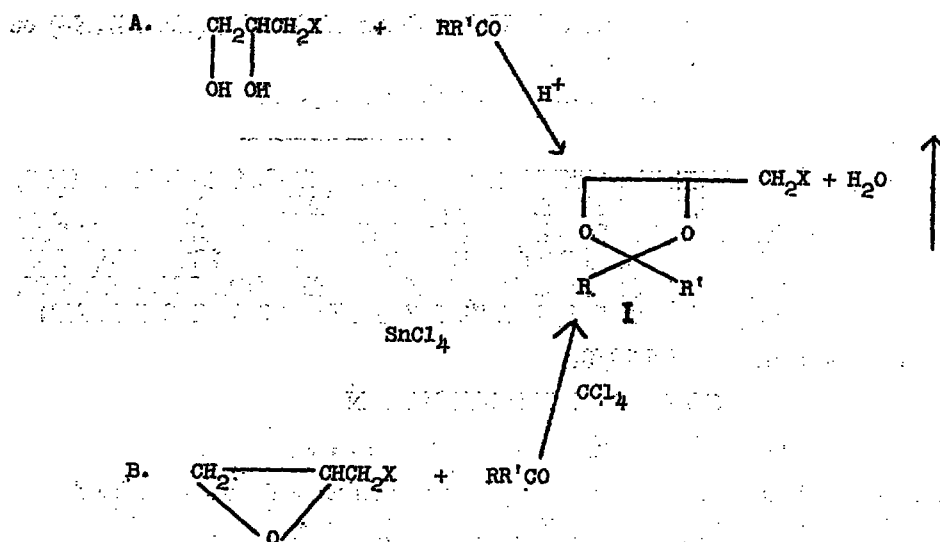
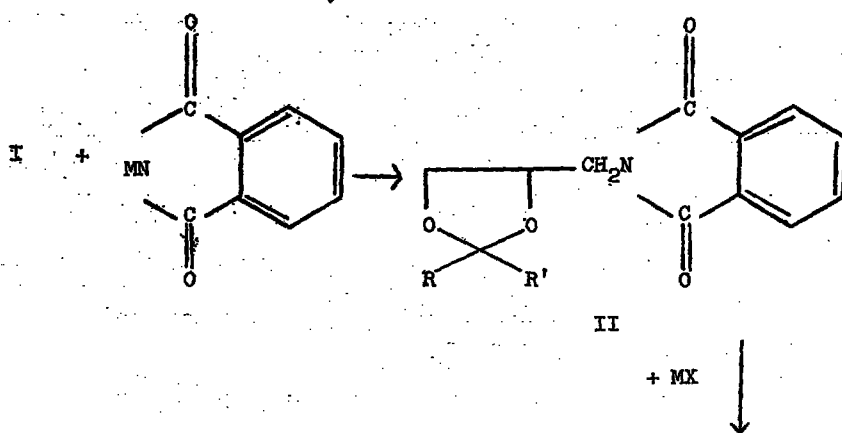
This invention relates to novel dioxolane substituted compounds, to their manufacture and to pharmaceutical compositions containing them.

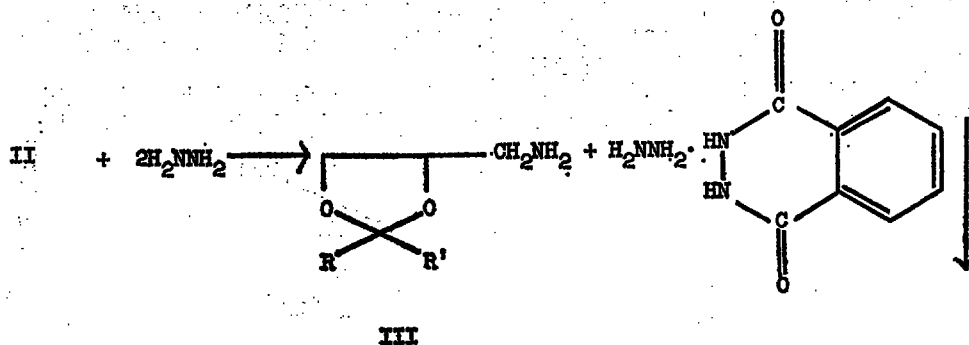
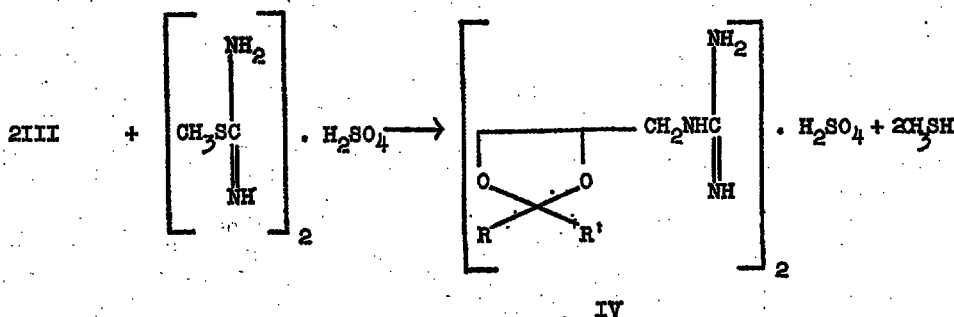
A compound according to the invention is a 1,3-dioxolane substituted at the 4-position by the group —A—B, where A is a C_{1-8} -alkylene group and B is a guanidino group or an N-substituted guanidino group, and pharmaceutically acceptable acid addition salts thereof. Compounds according to the invention have anti-hypertensive activity. Pharmaceutical compositions according to the invention accordingly comprise one of the compounds together with a pharmaceutically acceptable carrier.

Substituted guanidine having anti-hypertensive activity are known in the art. Examples of these are coumaranyl and indanyl substituted guanidines (U.S. 3,153,057), benzodioxanyl guanidines, (Augstein and Green, Nature, 201, 628, (1964), and benzo-1,3-dioxolyl-2-guanidines (U.S. 3,149,129).

The compounds according to the invention can be made most satisfactorily by reacting a 1,3-dioxolan-4-yl substituted C_{1-8} -alkylamine with a 2-alkyl or 2-arylthiopseudourea.

The following reaction scheme demonstrates schematically suitable methods for making the compounds of the invention.

STEP I.STEP II.

STEP III.STEP IV.

wherein X is a halogen other than fluorine preferably chlorine, M is an alkali metal, preferably sodium; and R and R' are each hydrogen or a substituent as defined hereinbelow.

5 In Step I, virtually any non-reactive acidic substance can be used as catalyst. See F. F. Blicke and E. L. Schumann J. Am. Chem. Soc. 76, 1226 [1954]. Toluene-sulfonic acid is preferred. Any inert solvent, e.g., benzene, pentane or preferably toluene, which provides an azeotropic distillation mixture with water and which phase separates in the Dean-Stark trap can be used. Step I A is preferred over Step I B. 10 In Step I B, neutral inert solvents are used, e.g., CCl_4 or other chlorinated hydrocarbon.

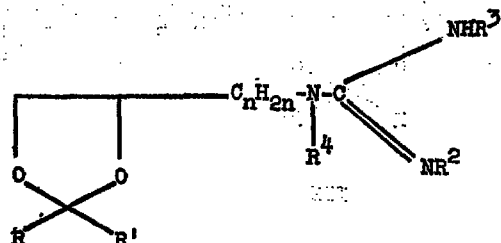
15 In Step II, dry solvents should be used; N,N-Dialkyl acid amides, e.g., dimethyl formamide and dimethyl acetamide, appear to catalyze the reaction. Alkanols, e.g., ethanol, are also useful solvents. Sodium is the preferred metallo salt of the phthalimide, although other salts such as the more readily available potassium phthalimide may also be used. 15

20 In Step III, aqueous, hydrated or anhydrous hydrazine can be used. 95 percent ethanol is a useful solvent although any inert solvent for Intermediate II can be used. At least one mole and preferably two moles of hydrazine per mole of the substituted phthalimide is preferably employed. Hydrolysis in alcoholic alkali-metal hydroxide is effective but gives lower yields than hydrazine. If desired product [III] can readily be converted to a secondary alkyl substituted amine by methods commonly employed in the art prior to proceeding with Step IV. 20

25 Step IV is the preferred method of producing the final products of this invention. Possible variations are the use of other 2-alkyl thiopseudoureas or 2-alkyl-2-thiopseudoureas such as benzyl thiopseudourea [U.S. 3,027,370]; ammonia to promote the reaction [Fielding et al, Brit. J. Pharmacol. 24, 395 [1965]]; an acid addition salt of the amine [III] and a thiopseudourea base; use of mono- or disubstituted. 25

[e.g., with alkyl] thiopseudoureas of the type described by McKay et al., J. Med. Chem. 6, 592 (1963); 2-methylthio-imidazole (Short et al., J. Med. Chem. 6, 283 (1963); and the use of 3,5-dimethyl-1-guanylpurazole, (Can. J. Biochem. Physiol. 38, 493 (1960); Scott et al., J. Am. Chem. Soc. 75, 4053 (1953); cyanamide (Braun, J. Am. Chem. Soc. 55, 1291 (1933) or guanidine base and tosylate esters thereof (Monroe, Chem. and Ind. 43, 1806 (1964).

The following is a description of preferred compounds of this invention which have pharmacological activity and which are exemplified by the following formula:



wherein n is an integer from 1 to 8, preferably 1 to 4 and most preferably 1, R², R³ and R⁴ are hydrogen or alkyl of 1 to 8 carbon atoms, preferably of 1 to 4 carbon atoms, e.g. methyl or ethyl, or R² and R³ together may be a C₂-C₈ alkylene chain, and R and R' have a collective molecular weight less than 300 and are each hydrogen, C₁₋₈ alkyl, preferably ethyl or isopropyl, hydroxy-C₁₋₈-alkyl, halo-C₁₋₈-alkyl and C₁₋₈-alkoxy-C₁₋₈-alkyl or a cyclic substituent containing up to three rings and which is a carbocyclic aromatic ring system of the benzene or naphthalene ring series, a carbocyclic ring system of the cycloalkyl or unsaturated cycloalkyl series or a carbocyclic ring system of the arylalkyl, aryloxyalkyl or cycloalkylalkyl series, or R and R' together with the 2-position carbon atom of the dioxolane ring form a spirocyclic carbocyclic or heterocyclic ring system.

The term "carbocyclic" means cyclic systems all of whose ring members are carbon atoms. Spirocyclic carbocyclic ring systems can be monocyclic or polycyclic, but preferably comprise no more than a total of 3 rings, and may be saturated or unsaturated. Thus they may be cycloalkyl ring systems, e.g., of the cyclohexane and cycloheptane series, and unsaturated cycloalkyl ring systems, e.g., of the cyclohexene and cycloheptadiene series such as 10,11-dihydro-5H-dibenzo(a,d)cycloheptene and cycloheptatriene series such as 5H-dibenzo(a,d)cycloheptene. The carbocyclic ring of each 2-position substituent can be attached directly to the 2-position carbon atom or via lower-alkylene or lower-alkyleneoxy bridge to form a carbocyclic ring system of, for example, the aralkyl, aryloxyalkyl, and cycloalkylalkyl series, e.g., benzyl, o-chlorobenzyl, phenethyl, diphenylmethyl, phenoxyethyl, p-tolylbutyl, phenyl, cyclohexylmethyl and cyclopentylpropyl. Any aromatic rings present may be of the benzene or naphthalene series. The term "heterocyclic ring" means cyclic systems corresponding to the carbocyclic systems discussed above but containing one or more heteroatoms, e.g., nitrogen, sulfur or oxygen, in the ring. Typical examples of such ring systems are those having a thiophene, pyridine, piperidine, xanthene, thioxanthene, pyrimidine, morpholine or pyrrolidine ring. Especially preferred are compounds containing a spirocyclic ring system wherein the 2-position carbon atom of the dioxolane ring is a carbon atom of a cycloalkyl ring substituent. The term "lower", e.g., when used in "lower-alkyl", means containing up to eight carbon atoms, inclusive.

The pharmacological activity of compounds of this invention is thought to be the result of the novel molecular combination of 1,3-dioxolane with guanidine via a lower-alkylene group. Naturally the manifestation of this activity varies in degree and character from compound to compound.

Because novelty and utility of the compounds are the result of the molecular combination of the 1,3-dioxolane structure joined by an alkylene bridge with the guanidine structure, embraced within the scope of the compounds having this structural combination are those having one or more, usually not more than four and preferably not more than three, simple substituents on the R and R' substituents. Those which can be on a carbon atom thereof include halo, e.g., chloro and fluoro, C₁₋₈-alkyl including methyl, ethyl, propyl and octyl, trifluoromethyl, trichloromethyl, C₁₋₈-alkoxy including methoxy and ethoxy, aryloxy and aralkoxy including benzyloxy and phenoxy, hydroxy, carboxy, nitro, a sulphonic acid group, acetamido, aryl including phenyl

and aralkyl including benzyl. The terminal amino nitrogen atoms of the guanidine group can bear hydrogen atoms or less preferably, can be mono- or di-substituted, e.g., with C₁₋₄-alkenyl, C₁₋₄-alkyl including methyl, ethyl, propyl, butyl, octyl, hydroxyalkyl, e.g., hydroxyethyl, hydroxyalkylene-oxyalkyl, e.g., hydroxyethyleneoxyethyl, aminoalkyl, e.g., dimethylaminoethyl, diethylaminoethyl, pyrrolidylethyl, piperidylethyl, morpholino-ethyl and the corresponding γ - and ω -amino-substituted propyl, butyl, etc. Preferably, so that the activity and characteristic structure is predominantly that a 1,3-dioxolan-4-yl-alkyl-guanidine, the sum of the molecular weight of these substituents is less than the sum of the molecular weights of the dioxolane and its 2-position substituents, e.g., less than 200 and more preferably less than 150, so that the resulting compound has a total molecular weight of less than 500, preferably less than 400.

Preferred classes of compounds within this invention are the 1,3-dioxolan-4-yl-lower-alkyl-guanidines meeting one or more of the following requirements: (a) other than the 2- and 4-positions of the dioxolane ring the compound is unsubstituted; (b) other than the guanidine nitrogen atoms and the dioxolane ring oxygen atoms, the compounds contain carbon and hydrogen only; (c) the lower-alkylene bridging group is methylene; (d) the valences of the 2-position dioxolane carbon atom are satisfied by non-aromatic hydrocarbon substituents, e.g., lower-alkyl, or more preferably by a single spiro carbocyclic ring which bears at most a single substituent which is preferably non-aromatic; (e) the compounds are in their acid addition salt form, preferably as their hydrochloride or sulfate.

The compounds of this invention possess asymmetric carbon atoms. They can thus exist as a mixture of its optical isomers or by conventional separation techniques, in the form of an optical isomer substantially free from the other isomers.

The pharmacological activity of compounds of the invention renders them useful in modifying body functions in laboratory test animals and other mammals by a modification of nerve impulses, e.g., the sympathetic nervous system. This activity manifests itself in laboratory tests utilized to detect sympathetic nervous system blocking activity, i.e., one or more of carotid occlusion, nictitating membrane and norepinephrine depletion tests.

In the Carotid Occlusion Test, a dog is anesthetized with 20 mg./Kg. of thiopental and maintained with 60 mg./Kg. of chloralose by IV injection. The femoral artery and vein are catheterized and the common carotid arteries are isolated for bilateral clamping. After determining the control arterial pressor response to 30 seconds of carotid occlusion, the test compound is administered and the response is again measured. The dose which produces approximately a 40 percent inhibition of the pressor response is used for potency comparison with other drugs.

In the Nictitating Membrane Test, a cat is anesthetized with Dialurethane (0.9 cc./Kg I. P.), with the femoral artery and vein catheterized. The nictitating membrane is drawn out and attached to a thread fastened to a force-displacement transducer. The pre-ganglionic nerve to the superior cervical ganglion is isolated for stimulation by supra maximal electrical shock. After determining the control response to pre-ganglionic stimulation, the drug is administered by intravenous injection and the dose which produces at least a 10 percent reduction in response is used for potency comparison with other test drugs.

In the Norepinephrine Depletion Test, albino guinea pigs weighing 200 to 300 g. are treated with the drug in three test groups, i.e., control 5 mg./Kg. I. P., and 10 mg./Kg. I. P., and then sacrificed after 15 to 18 hours. Quickly the hearts were removed, flushed with saline, placed in a vial and frozen in a dry ice-acetone bath. The hearts are individually analyzed for norepinephrine by the method of J. R. Crout, J. Pharmacol. 132, 269 (1961) and the level of depletion below control levels compared with other test drugs.

The compounds of this invention manifest fewer of the undesirable side effects of other known guanidyl anti-hypertensive agents, e.g., diarrhoea.

When the compositions of this invention are used as pharmaceuticals, they can be administered orally in the form of pills, tablets, capsules, e.g., in admixture with talc, starch, milk sugar, or other inert, i.e., non-toxic or pharmacologically acceptable pharmaceutical carrier, or in the form of aqueous solutions, suspension, encapsulated suspensions, gells, elixirs, aqueous alcoholic solutions, e.g., in admixture with sugar or other sweetening agent, flavorings, colorants, thickeners, and other conventional pharmaceutical excipients. When injected subcutaneously, intravenously or intramuscularly, usually the latter, they can be administered, e.g., as an aqueous or peanut oil solution or suspension using excipients and carriers conventional for this mode

of administration. The best route of administration and the best dosage will be apparent from the laboratory tests for activity and toxicity of the selected compound conventionally undertaken as part of the development phase of a pharmaceutical.

In the following preparations and examples, which are illustrative of the process and products of this invention, temperatures are in degrees centigrade.

STEP I

Preparation 1(a): 2-Chloromethyl-1,4-dioxaspiro[4,5]decane.

The preparations of this intermediate compound are illustrative of the methods used to make each of the corresponding first step intermediates leading to the guanidines described in the Examples. The first procedure is preferred.

Procedure A

In a reflux distillation apparatus (See F. F. Blicke and E. L. Schumann, J. Am. Chem. Soc. 76, 1226 (1954)) equipped with a Dean-Stark trap was placed 442 g. of 3-chloro-1,2-propanediol and 4 g. of *p*-toluene sulfonic acid and 1300 ml. of toluene. After reflux had been established, 392 g. of cyclohexanone was added dropwise during a period of 30 minutes. The mixture was then refluxed for 6 hours until water ceased to accumulate in the trap. A total of 68 ml. of water was collected. The solution was cooled and the pH adjusted to neutrality with sodium methylate and filtered. The filtrate was distilled, removing the toluene first and then 2-chloromethyl-1,4-dioxaspiro[4,5]decane, N_D^{25} 1.4754, at 112–116°/14.5 mm.

Procedure B

Using the method of F. F. Blicke and F. E. Anderson, J. Am. Chem. Soc. 74, 1735 (1952), this reaction is generally applicable to this group of intermediates. In a reaction flask equipped with a large stirrer, ice bath, dropping funnel, and protected from moisture by drying tubes, was placed 200 g. of cyclohexanone, 200 g. of epichlorohydrin, and 500 ml. of anhydrous carbon tetrachloride. When the solution had cooled to 10°, 67 g. of stannic chloride was added dropwise over a period of 2.5 hours with stirring. After another hour of stirring at room temperature, 69.8 g. of potassium hydroxide in 300 ml. of water was added at a temperature of 5 to 10°. After standing some hours, the aqueous phase was decanted and extracted with ether. The combined carbon tetrachloride and ether solutions were dried over anhydrous potassium carbonate and distilled. The portion boiling at 118 to 124°/15 mm., N_D^{25} 1.4750, was used.

Analysis:

Calculated for $C_9H_{15}ClO_2$:

Cl, 18.6

Found: Cl, 18.06

STEP II

Preparation 1(b): 2-Phthalimidomethyl-1,4-dioxaspiro[4.5]decane

The preparation of this phthalimido derivative is illustrative of the general procedure which was satisfactory for all such intermediates. See J. H. Billman and R. Vincent Cash, J. Am. Chem. Soc. 75, 2500 (1953).

A 9.1 g. portion of sodium hydride (52.3 percent in mineral oil suspension) was slurried with about 80 ml. of anhydrous dimethyl formamide, and then 29.4 g. of phthalimide was transferred gradually to the reaction mixture from an attached flask connected by tubing to form a closed system. After an additional period of about one hour at temperatures varying up to 70°, 38.1 g. of 2-chloromethyl-1,4-dioxaspiro[4.5]decane was added together with 0.5 g. of sodium iodide (optional) in 20 ml. of dry dimethylformamide, and the mixture was heated at reflux for 5 hours and then filtered hot leaving 10.8 g. of sodium chloride on the filter. Reaction is practically complete after 2 hours at reflux. Reaction at 125° appears to require at least 24 hours for a similar yield. The filtrate was evaporated at reduced pressure on the steam bath to an oily residue which was diluted with 200 ml. of benzene and filtered. The filtrate was washed once with 100 ml. of 1 percent aqueous sodium hydroxide and 3 times with 300 ml. of water. The benzene was removed at reduced pressure on the steam bath and the residue triturated with petroleum ether, whereupon it crystallized to give 2-(phthalimido-methyl)-1,4-dioxaspiro[4.5]decane, melting at 87–90°. Crystallization may also be induced with isopropanol.

This compound was also made by a similar procedure but using commercial potassium phthalimide reagent in place of the sodium phthalimide used in the procedure described above. 102 Grams of 2-chloromethyl-1,4-dioxaspiro[4.5]decane,

121 g. of potassium phthalimide, 6 g. of potassium iodide, and 500 ml. of anhydrous dimethyl formamide were mixed and refluxed gently for approximately 16 hours with the reflux condenser closed by a calcium chloride drying tube. The solution was filtered hot, and 48.1 g. of potassium chloride was recovered. The filtrate was diluted with 500 ml. of water which precipitated an oil. The aqueous portion was extracted twice with 250 ml. portions of chloroform which were combined and mixed with the oily precipitate. This chloroform extract was then washed with water, dried with magnesium sulfate, and evaporated to an oil which crystallized when triturated with isopropanol. The crude product was recrystallized from ethanol and the crystals washed with 50 ml. of 8 percent aqueous sodium hydroxide, followed by a wash with 50 ml. of water, and then dried to give 2-(phthalimido-methyl)-1,4-dioxaspiro[4.5]-decane, melting at 91–92°.

Analysis:

Calculated for $C_{17}H_{19}NO_4$:

C, 68.03; H, 6.38

Found: C, 68.20; H, 6.52.

STEP III

Preparation 1 (c): 1,4-Dioxaspiro[4.5]dec-2-yl-methylamine Sulfate.

20.3 Grams of 2-phthalimidomethyl-1,4-dioxaspiro[4.5]decane and 4.5 ml. of hydrazine (95 percent anhydrous) were heated at reflux in 300 ml. of ethanol with vigorous stirring for one hour. The cooled slurry was diluted with 200 ml. of dry ether, filtered, and the precipitate was washed twice with 100 ml. portions of ether. The combined filtrates and washes were evaporated to 100 ml. of residue and diluted with 100 ml. of fresh ether and refiltered. The filtrate was evaporated to an oily residue which was dissolved in 10 ml. water and adjusted to pH 6.0 with 50 percent sulfuric acid. A precipitate formed and was filtered, washed with ether, and dried to give 1,4-dioxaspiro[4.5]-dec-2-yl-methylamine sulfate, melting at 237.5–239.5°.

Analysis:

Calculated for $(C_{17}H_{17}NO_2)_2 \cdot H_2SO_4$:

C, 49.07; H, 8.24; N, 6.36; S, 7.28

Found: C, 48.75; H, 8.37; N, 6.32; S, 6.98.

The oily residue is usually of suitable purity and is in the desired free base form for use in the Step IV reaction, and therefore can be used as such. For further purification when necessary the amines can be distilled or converted to sulfate salts or both.

The following table gives the melting point and/or boiling point of the intermediates prepared by the above procedures and used to prepare the compounds of the examples having the same number which follow it. The amine intermediates (III) also possess useful pharmacological activity, especially analgesic activity and barbiturate potentiation activity.

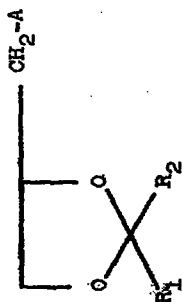


TABLE I

A

	Step I	Step II	Step III
			-NH ₂
	R₁ R₂	m.p. (°C)	m.p. salt (°C) (b.p. mm base)
1	R₁ R₂	114°/14.5	234—236 (H ₂ SO ₄)
2	R₁ R₂	143—4°/12	225—227 (H ₂ SO ₄)

TABLE I continued

A

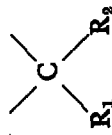
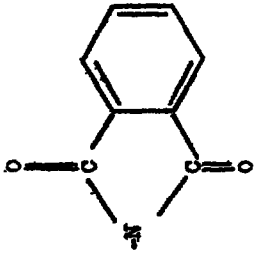
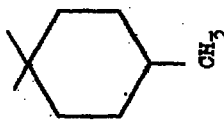
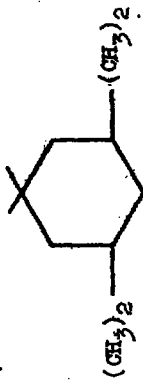
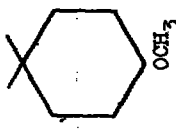
	Step I	Step II	Step III
			-NH ₂
	R ₁	R ₂	m.p. salt (°C) (b.p. mm base)
3		122—130°/12	246—247 (H ₂ SO ₄) (91—110/0.6)
4		137—140°/12	90—92
5		—	248—249 dec. (H ₂ SO ₄)

TABLE I continued

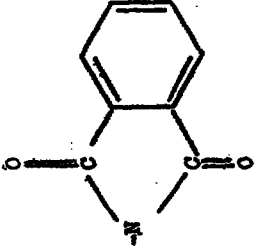
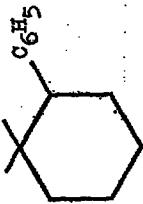
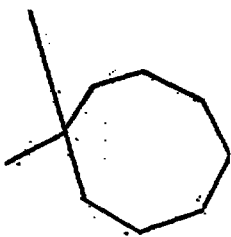
A		Step I	Step II	Step III
	$\begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} \begin{array}{l} \text{R}_1 \\ \text{R}_2 \end{array}$	—Cl		—NH ₂
	$\begin{array}{cc} \text{R}_1 & \text{R}_2 \end{array}$	b.p. (°C)/mm	m.p. (°C)	m.p. sol _s (°C) (b.p. mm base)
6		109—120°/0.1	80—90	203—205 dec. (H ₂ SO ₄)
7		120—125°/12	93—95	232 (H ₂ SO ₄)
8		145°/13	—	230—231 (H ₂ SO ₄) (80—84°/0.1)

TABLE I continued

A

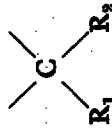
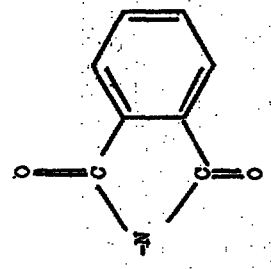
	Step I	Step II	Step III
			
	b.p. (°C)/mm	m.p. (°C)	m.p. salt (°C) (b.p. mm base)
9	114°/0.9 (m.p. 49—51°)	—	—
10	99—100°/11	96—99	234—235 dec. (H ₂ SO ₄) (65—70°/0.15)

TABLE I—continued

11	H	H	—	73—75	171.5 (HCl) (70—75/17)
12	CH ₃	CH ₃	45—50°/12	—	(60—65/12)
13	C ₂ H ₅	C ₂ H ₅	75—80°/12	44—46	221—223 (H ₂ SO ₄) (89—90/12)
14	i-C ₃ H ₇	i-C ₃ H ₇	107—112°/19	—	188—190 dec. (HCl)
15	n-C ₃ H ₇	n-C ₃ H ₇	105°/12	—	(105—123/12)
16	C ₆ H ₅	C ₆ H ₅	m.p. 52—54	129—130	230 (HCl)
17	cyclohexyl	cyclohexyl	119—122°/0.5	—	—

STEP IV

Example 1: (1,4-Dioxaspiro[4.5]dec-2-yl-methyl)guanidine Sulfate

A mixture of 10.5 g. of 1,4-dioxaspiro[4.5]dec-2-yl-methylamine and 8.6 g. of 2-methyl-2-thiopseudourea sulfate in 40 ml. of water was heated on the steam bath for 4 hours during which 2.0 g. of methylmercaptan was collected in a dry ice bath connected to the reaction flask through a water cooled reflux condenser. The reaction mixture was then evaporated at 15 mm. pressure to a solid residue which was then dissolved in 80 ml. of 50/50 methanol-ethanol. The solution was filtered and evaporated to approximately 50 ml. volume and allowed to cool and crystallize, giving a crop melting at 213.5 to 215° of (1,4-dioxaspiro[4.5]dec-2-yl-methyl)-guanidine sulfate.

Analysis:

Calculated for (C₁₀H₁₄N₂O₂)₂ · H₂SO₄:

C, 45.79; H, 7.69; N, 16.02; S, 6.11

Found: C, 45.97; H, 7.99; N, 15.76; S, 6.14

Another preparation which incorporated ammonia in the final crystallization step gave a product with a higher melting point of 225—227° C but a slightly poorer analysis. A sample of this material, when recrystallized from water, resulted apparently in the formation of another crystal form, melting at 243—245° dec. This appears

to be the stable form since recrystallization from methanol-ethanol did not alter the melting point.

This compound, in addition to pronounced anti-hypertensive activity, stimulates growth of the male accessory reproductive organs.

The compound of Example 1 is a potent sympathetic nerve ending blocker and depletes norepinephrine from the stores. Its anti-hypertensive properties have been demonstrated in renal hypertensive dogs. It appears superior to guanethidine or guanoxan in the following respects. First, it is well tolerated in large doses and does not induce diarrhea in any of the species in which it was tested. Both guanethidine and guanoxan produce diarrhea. Second, both the compound of Example 1 and guanoxan cross the blood brain barrier and have been shown to deplete hypothalamic norepinephrine. Guanethidine does not penetrate the brain. Depletion of hypothalamic norepinephrine may contribute to the anti-hypertensive activity of the compound. Third, both the compound of Example 1 and guanoxan decrease the total catecholamine content of the adrenal gland. Guanethidine is devoid of this property. This is an additional characteristic which suggests that the compound of Example 1 may be superior to guanethidine as an antihypertensive agent.

Example 2: (6-Chloro-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine Sulfate.

Following the procedure of Example 1, 31 g. of 6-chloro-1,4-dioxaspiro[4.5]dec-2-yl-methylamine, 23 g. of 2-methyl-2-thiopseudourea sulfate, and 75 ml. of water were heated for 2 hours and then evaporated at reduced pressure and the residue was recrystallized from methanol twice to give (6-chloro-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine sulfate, melting at 232—234°.

Analysis:

Calculated for $(C_{10}H_{16}ClN_3O_2)_2 \cdot H_2SO_4$:

C, 40.47; H, 6.45; N, 14.16

Found: C, 40.32; H, 6.59; N, 14.31

This compound possesses uterotrophic activity in addition to marked anti-hypertensive activity.

Example 3: (8-Methyl-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine Sulfate.

In 30 ml. of water were dissolved 11.5 g. of 8-methyl-1,4-dioxaspiro[4.5]dec-2-yl-methylamine sulfate, 6.8 g. of 2-methyl-2-thiopseudourea sulfate, and 2.0 g. of sodium hydroxide. The solution was heated for 4.5 hours on the steam bath and was then evaporated at reduced pressure to a solid. This was dissolved in 90 ml. of an equal parts mixture of methanol-ethanol-water. The solution was filtered and then evaporated to about 2/3 volume and then allowed to stand. Three successive crops of crystals were obtained at room temperature and at +2°. These were combined and recrystallized from 17 percent water in methanol to give (8-methyl-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine sulfate melting at 259°.

Analysis:

Calculated for $(C_{11}H_{20}N_3O_2)_2 \cdot H_2SO_4$:

C, 47.81; H, 8.02; N, 15.21

Found: C, 47.91; H, 8.10; N, 14.96

This compound possesses anti-hypertensive activity.

Example 4: (7,7,9,9-Tetramethyl-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine Sulfate:

Following the procedure of Example 1, 34 g. of 7,7,9,9-tetramethyl-1,4-dioxaspiro[4.5]dec-2-yl-methylamine and 23 g. of 2-methyl-2-thiopseudourea sulfate were dissolved in 50 ml. of water and reacted for 2 hours. The product melted at 254—256° after one recrystallization from methanol.

Analysis:

Calculated for $(C_{14}H_{27}N_3O_2)_2 \cdot H_2SO_4$:

C, 52.81; H, 8.86; N, 13.20

Found: C, 52.81; H, 8.63; N, 13.11

This compound possesses anti-hypertensive activity.

Example 5: (8-Methoxy-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine Sulfate.

By the procedure of Example 1, 37.6 g. of 8-methoxy-1,4-dioxaspiro[4.5]dec-

2-yl-methylamine was reacted with 23 g. of 2-methyl-2-thiopseudourea sulfate. The recrystallization of the product from isopropanol was very slow. A second and third crops were obtained by dilution of the mother liquor with ether. The crops were combined and recrystallized from isopropanol and then from methanol. The impure product was then dissolved in aqueous alkali at pH 11. The solution was then washed with ether and finally readjusted to pH 7.4 with sulphuric acid. The water was removed at reduced pressure and the residue was recrystallized from ethanol by ether dilution to give (8-methoxy-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine sulfate melting at 216—218.

Analysis:

Calculated for $(C_{11}H_{21}N_3O_3)_2 \cdot H_2SO_4$:

C, 45.19; H, 7.59; N, 14.37

Found: C, 44.96; H, 7.73; N, 14.51.

This compound possesses anti-hypertensive activity.

Example 6: (6-Phenyl-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine Sulfate.

Following the procedure of Example 1, 39 g. of 6-phenyl-1,4-dioxaspiro[4.5]-dec-2-yl-methylamine was reacted with 23 g. of 2-methyl-2-thiopseudourea sulfate to give a crystalline residue after removal of the reaction solvent at reduced pressure. The residue was washed with concentrated aqueous potassium bicarbonate and then triturated first with ether and then with ether-ethanol to give (6-phenyl-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine sulfate, melting at 244—245° dec.

Analysis:

Calculated for $(C_{16}H_{23}N_3O_3)_2 \cdot H_2SO_4$:

C, 56.79; H, 7.15; N, 12.42; S, 4.74

Found: C, 53.01; H, 7.23; N, 12.37; S, 4.51

This compound possesses anti-hypertensive activity.

Example 7: (1,4-Dioxaspiro[4.6]undec-2-yl-methyl)guanidine Sulfate.

By the procedure described in Example 1, 28 g. of 1,4-dioxaspiro[4.6]-undec-2-yl-methylamine was reacted with 20 g. of 2-methyl-2-thiopseudo-urea sulfate in 50 ml. of water for approximately 2 hours during which a heavy precipitate formed. It was separated and recrystallized from methanol twice to give (1,4-dioxaspiro[4.6]-undec-2-yl-methyl)guanidine sulfate, m.p. 255-256°.

Analysis:

Calculated for $(C_{11}H_{21}N_3O_3)_2 \cdot H_2SO_4$:

C, 47.81; H, 8.02; N, 15.21; S, 5.80

Found: C, 47.85; H, 8.01; N, 16.02; S, 5.71

This compound, in addition to strong anti-hypertensive activity, blocks the cardiac-conditioning response and has anti-inflammatory activity by the limb volume test.

Example 8: (1,4-Dioxaspiro[4.7]dodec-2-yl-methyl)guanidine Sulfate.

Following the procedure of Example 1, 32 g. of 1,4-dioxaspiro[4.7]-dodec-2-yl-methylamine, 23 g. of 2-methyl-2-thiopseudourea sulfate, and 75 ml. of water were heated for 1.5 hours and then allowed to stand overnight when a heavy precipitate formed and was filtered off. It was recrystallized from methanol, to give (1,4-dioxaspiro[4.7]dodec-2-yl-methyl)guanidine sulfate, melting at 260—261°.

Analysis:

Calculated for $(C_{12}H_{23}N_3O_3)_2 \cdot H_2SO_4$:

C, 49.64; H, 8.33; N, 14.47

Found: C, 49.41; H, 8.12; N, 14.61

This compound possesses anti-inflammatory activity in addition to anti-hypertensive activity.

Example 9: [Spiro(1,3-dioxolane-2,2'-indan)-4-yl-methyl]guanidine Sulfate.

According to the procedure of Example 1, 20 g. of spiro(1,3-dioxolane-2,2'-indan)-4-yl-methylamine, 14 g. of 2-methyl-2-thiopseudourea sulfate, and 65 ml. of water were heated on the steam bath and upon cooling a heavy precipitate formed which was filtered from the mother liquor and recrystallized from 200 ml. of ethanol to give [spiro(1,3-dioxolane-2,2'-indan)-4-ylmethyl]-guanidine sulfate, melting at 234—235°.

Analysis:

Calculated for $(C_{13}H_{17}N_3O_2)_2 \cdot H_2SO_4$:

C, 52.69; H, 6.12; N, 14.18

Found: C, 52.50; H, 6.06; N, 14.29

This compound possesses anti-hypertensive activity.

Example 10: (1,4-Dioxaspiro[4,4]nonan-2-yl-methyl)guanidine Sulfate.

Following the procedure of Example 1, 35 g. of 1,4-dioxaspiro[4,4]-nonane-2-methylamine and 21 g. of 2-methyl-2-thiopseudourea sulfate were reacted in 30 ml. of water. Evaporation at reduced pressure and re-evaporation after adding propanol to the residue gave an amorphous product which crystallized when stirred with 50 ml. of ethanol. The mixture was diluted with 200 ml. of dry ether and filtered. The crude product was recrystallized from ethanol and then from methanol to give (1,4-dioxaspiro[4,4]nonan-2-yl-methyl)-guanidine sulfate, melting at 205° dec.

Analysis:

Calculated for $(C_8H_{11}N_3O_2)_2 \cdot H_2SO_4$:

C, 42.97; H, 7.01; N, 16.92; S, 6.45

Found: C, 43.64; H, 7.15; N, 16.86; S, 6.54

This compound possesses anti-hypertensive activity.

Example 11: (1,3-Dioxolan-4-yl-methyl)guanidine Sulfate.

Using the procedure of Example 1, 15.3 g. of 1,3-dioxolan-4-yl-methylamine was reacted with 13.9 g. of 2-methyl-2-thiopseudourea sulfate. The reaction mixture was evaporated at reduced pressure on the steam bath to a colorless amorphous semi-solid. It was dissolved in 170 ml. of methanol and re-evaporated to an amorphous solid at high vacuum. This material was titrated with anhydrous ether to give an amorphous solid which was pulverized and triturated with fresh anhydrous ether to give a white powder which softened at approximately 60° and melted at 100° with decomposition.

Analysis:

Calculated for $(C_5H_9N_3O_2)_2 \cdot H_2SO_4$:

C, 30.92; H, 6.23; N, 21.64

Found: C, 30.7; H, 6.0; N, 20.8

This compound, in addition to anti-hypertensive activity, is a lipase inhibitor.

Example 12: (2,2-Dimethyl-1,3-dioxolan-4-yl-methyl)guanidine Sulfate.

By the procedure of Example 1, 29.5 g. of 2,2-dimethyl-1,3-dioxolan-4-yl-methylamine was reacted with 21 g. of 2-methyl-2-thiopseudourea sulfate. The crude product was recrystallized twice from propanol without prior treatment with ether. It was finally recrystallized from 95 percent ethanol to give (2,2-dimethyl-1,3-dioxolan-4-yl-methyl)guanidine sulfate, melting at 181°.

Analysis:

Calculated for $(C_7H_{13}N_3O_2)_2 \cdot H_2SO_4$:

C, 37.83; H, 7.26; N, 18.91

Found: C, 37.84; H, 7.20; N, 18.66

This compound possesses anti-hypertensive activity.

Example 13: (2,2-Diethyl-1,3-dioxolan-4-yl-methyl)guanidine Sulfate.

Following the procedure of Example 1, 20 g. of 2,2-diethyl-1,3-dioxolan-4-yl-methylamine and 14 g. of 2-methyl-2-thiopseudourea sulfate were reacted in 25 ml. of water. The product precipitated as a crystalline solid upon cooling the reaction

mixture and was filtered. It was recrystallized from ethanol to give (2,2-diethyl-1,3-dioxolan-4-yl-methyl)guanidine sulfate, melting at 229—231°.

Analysis:

Calculated for $(C_8H_{18}N_3O_2)_2 \cdot H_2SO_4$:

C, 43.19; H, 7.65; N, 16.79

Found: C, 43.19; H, 7.61; N, 16.62

This compound possesses anti-hypertensive activity.

Example 14: (2,2-Diisopropyl-1,3-dioxolan-4-yl-methyl)guanidine Hydrochloride.

A mixture of 5.2 g. of 2,2-diisopropyl-1,3-dioxolan-4-yl-methylamine and 4.0 g. of 2-methyl-2-thiopseudourea hydrochloride in 25 ml. of water was heated on the steam bath for one hour. Then the solvent was evaporated at reduced pressure and the residue was dissolved in 25 ml. of hot isopropanol and the solution was re-evaporated to a residue at reduced pressure. The residue was again dissolved in isopropanol and set aside at +2° for 3 days and a precipitate of 0.8 g. was filtered off. The filtrate was concentrated partially and allowed to stand for several days when it became crystalline. The mass was washed with hot ethyl acetate, filtered, and dried to give crystals melting at 143—145°, of (2,2-diisopropyl-1,3-dioxolan-4-yl-methyl)guanidine hydrochloride.

Analysis:

Calculated for $C_{11}H_{23}N_3O_2 \cdot HCl$:

C, 49.71; H, 9.10; N, 15.81

Found: C, 49.42; H, 9.34; N, 15.49

This compound possesses anti-hypertensive activity.

Example 15: (2,2-Dipropyl-1,3-dioxolan-4-yl-methyl)guanidine Sulfate.

By the procedure of Example 1, 17.4 g. of 2,2-dipropyl-1,3-dioxolan-4-yl-methylamine and 20.8 g. of 2-methyl-2-thiopseudourea sulfate in 30 ml. of water were reacted for 3 hours and the volatile material was then removed at reduced pressure. The residue was treated with 50 ml. of ethanol and re-evaporated to a heavy sirup which was dissolved in 100 ml. hot isopropanol, filtered, and diluted with about 200 ml. of ethyl acetate to give a crystalline precipitate. This crop was recrystallized from 30 ml. of water to give (2,2-dipropyl-1,3-dioxolan-4-yl-methyl)guanidine sulfate melting at 175—178°.

Analysis:

Calculated for $(C_{11}H_{23}N_3O_2)_2 \cdot H_2SO_4$:

C, 47.46; H, 8.69; N, 15.10

Found: C, 47.16; H, 8.35; N, 15.18

This compound possesses anti-hypertensive activity.

Example 16: (2,2-Diphenyl-1,3-dioxolan-4-yl-methyl)guanidine Sulfate.

9.1 Grams of 2,2-diphenyl-1,3-dioxolan-4-yl-methylamine hydrochloride was suspended in 20 ml. of 10 percent aqueous sodium hydroxide and extracted with two 40 ml. portions of ether. The combined extracts were dried and evaporated to an oil which was treated with 4.8 g. of 2-methyl-2-thiopseudourea sulfate as described in Example 1 for a period of 2 hours. The reaction mixture was evaporated at reduced pressure to a white solid which was then recrystallized from approximately 250 ml. of 50/50 ethanol-water 3 times to give (2,2-diphenyl-1,3-dioxolan-4-yl-methyl)guanidine sulfate, m.p. 229°.

Analysis:

Calculated for $C_{17}H_{15}N_3O_2 \cdot HCl$:

C, 58.94; H, 5.82; N, 12.13

Found: C, 59.00; H, 6.08; N, 12.20

This compound, in addition to mild anti-hypertensive activity, has anti-inflammatory activity, is a lipase inhibitor and decreases post-prandial lipemia of rats.

Example 17: (2,2-Dicyclohexyl-1,3-dioxolan-4-yl-methyl)guanidine Hydrochloride.

A solution of 27 g. of 2,2-dicyclohexyl-1,3-dioxolan-4-yl-methyl-amine in 40 ml. of ethanol was mixed with 13 g. of 2-methyl-2-thiopseudourea hydrochloride dissolved in 60 ml. of ethanol in a flask connected by a closed system through a water-cooled reflux condenser to a dry ice trap. The flask was then heated on the steam bath to reflux for 3 hours during which time 2.5 g. of methylmercaptan was collected. The reaction mixture was then diluted with 75 ml. of ether. Two liquid phases formed and the aqueous phase, a heavy syrup, was separated. It was diluted with water and washed with fresh ether and then allowed to stand at +2° for two days when a precipitate was separated. It was recrystallized from 25 ml. of water and then from methanol-ethyl-acetate to give (2,2-dicyclohexyl-1,3-dioxolan-4-yl-methyl)-guanidine hydrochloride, melting at 86—90°.

Analysis:Calculated for $C_{17}H_{31}N_3O_2 \cdot HCl$:

C, 58.85; H, 9.59; N, 12.11

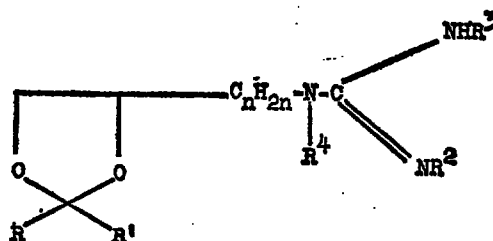
Found: C, 57.4; H, 9.4; N, 12.09

This compound possesses lipase inhibiting as well as anti-hypertensive activity.

WHAT WE CLAIM IS:—

1. A 1,3-dioxolane substituted at the 4-position by the group —A—B, where A is a C_{1-8} alkylene group and B is a guanidino group or an N-substituted guanidino group, and pharmaceutically acceptable acid addition salts thereof.

2. A compound according to claim 1 and having the formula:—



wherein n is an integer from 1 to 8; R^2 , R^3 and R^4 each are hydrogen or C_{1-8} -alkyl, and additionally R^2 and R^3 together may be C_{2-8} alkylene, and R and R' have a collective molecular weight less than 300 and are each hydrogen, C_{1-8} -alkyl, hydroxy- C_{1-8} -alkyl, halo- C_{1-8} -alkyl, C_{1-8} -alkoxy- C_{1-8} -alkyl or a cyclic substituent containing up to 3 rings and which is a carbocyclic aromatic ring system of the benzene or naphthalene series, a carbocyclic ring system of the cycloalkyl or unsaturated cycloalkyl series or a carbocyclic ring system of the aralkyl, aryloxyalkyl or cycloalkylalkyl series, or R and R' together with the 2-position carbon atom of the dioxolane ring form a spirocyclic carbocyclic or heterocyclic ring system.

3. A compound according to claim 2 wherein n is an integer from 1 to 4; R^2 , R^3 and R^4 each are hydrogen or C_{1-8} -alkyl; R and R' have a collective molecular weight less than 300 and are each hydrogen, C_{1-8} -alkyl, hydroxy- C_{1-8} -alkyl, halo- C_{1-8} -alkyl, C_{1-8} -alkoxy- C_{1-8} -alkyl or a cyclic substituent containing up to 3 rings and which is a carbocyclic ring system of the benzene or naphthalene series, of the cyclohexane, cycloheptane, cyclohexene, cycloheptadiene or cycloheptatriene series or of the aralkyl, aryloxyalkyl or cycloalkylalkyl series or R and R' together with the 2-position carbon atom of the dioxolane ring form a spirocyclic carbocyclic ring system.

4. A compound according to claim 2 or claim 3 in which R^2 , R^3 and R^4 are each hydrogen.

5. A compound according to any of claims 2 to 4 in which R is C_{1-8} -alkyl.

6. A compound according to any of claims 2 to 4 in which R is phenyl.

7. A compound according to claim 5 in which R' is C_{1-8} -alkyl.

8. A compound according to any of claims 2 to 6 in which R and R' together with the 2-position carbon atom of the dioxolane ring form a carbocyclic spirocyclic ring of 5 to 8 carbon atoms.

9. A compound according to any of claims 2 to 8 in which n is 1.

Example 17: (2,2-Dicyclohexyl-1,3-dioxolan-4-yl-methyl)guanidine Hydrochloride.

A solution of 27 g. of 2,2-dicyclohexyl-1,3-dioxolan-4-yl-methyl-amine in 40 ml. of ethanol was mixed with 13 g. of 2-methyl-2-thiopseudourea hydrochloride dissolved in 60 ml. of ethanol in a flask connected by a closed system through a water-cooled reflux condenser to a dry ice trap. The flask was then heated on the steam bath to reflux for 3 hours during which time 2.5 g. of methylmercaptan was collected. The reaction mixture was then diluted with 75 ml. of ether. Two liquid phases formed and the aqueous phase, a heavy syrup, was separated. It was diluted with water and washed with fresh ether and then allowed to stand at +2° for two days when a precipitate was separated. It was recrystallized from 25 ml. of water and then from methanol-ethyl-acetate to give (2,2-dicyclohexyl-1,3-dioxolan-4-yl-methyl)-guanidine hydrochloride, melting at 86—90°.

Analysis:Calculated for $C_{17}H_{31}N_5O_2 \cdot HCl$:

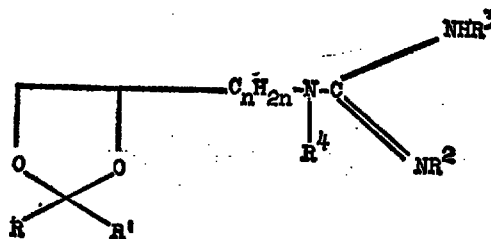
C, 58.85; H, 9.59; N, 12.11

Found: C, 57.4; H, 9.4; N, 12.09

This compound possesses lipase inhibiting as well as anti-hypertensive activity.

WHAT WE CLAIM IS:—

1. A 1,3-dioxolane substituted at the 4-position by the group —A—B, where A is a C_{1-8} alkylene group and B is a guanidino group or an N-substituted guanidino group, and pharmaceutically acceptable acid addition salts thereof.
2. A compound according to claim 1 and having the formula:—



wherein n is an integer from 1 to 8; R^2 , R^3 and R^4 each are hydrogen or C_{1-8} -alkyl, and additionally R^2 and R^3 together may be C_{2-8} alkylene, and R and R' have a collective molecular weight less than 300 and are each hydrogen, C_{1-8} -alkyl, hydroxy- C_{1-8} -alkyl, halo- C_{1-8} -alkyl, C_{1-8} -alkoxy- C_{1-8} -alkyl or a cyclic substituent containing up to 3 rings and which is a carbocyclic aromatic ring system of the benzene or naphthalene series, a carbocyclic ring system of the cycloalkyl or unsaturated cycloalkyl series or a carbocyclic ring system of the aralkyl, aryloxyalkyl or cycloalkylalkyl series, or R and R' together with the 2-position carbon atom of the dioxolane ring form a spirocyclic carbocyclic or heterocyclic ring system.

3. A compound according to claim 2 wherein n is an integer from 1 to 4; R^2 , R^3 and R^4 each are hydrogen or C_{1-8} -alkyl; R and R' have a collective molecular weight less than 300 and are each hydrogen, C_{1-8} -alkyl, hydroxy- C_{1-8} -alkyl, halo- C_{1-8} -alkyl, C_{1-8} -alkoxy- C_{1-8} -alkyl or a cyclic substituent containing up to 3 rings and which is a carbocyclic ring system of the benzene or naphthalene series, of the cyclohexane, cycloheptane, cyclohexene, cycloheptadiene or cycloheptatriene series or of the aralkyl, aryloxyalkyl or cycloalkylalkyl series or R and R' together with the 2-position carbon atom of the dioxolane ring form a spirocyclic carbocyclic ring system.

4. A compound according to claim 2 or claim 3 in which R^2 , R^3 and R^4 are each hydrogen.

5. A compound according to any of claims 2 to 4 in which R is C_{1-8} -alkyl.

6. A compound according to any of claims 2 to 4 in which R is phenyl.

7. A compound according to claim 5 in which R' is C_{1-8} -alkyl.

8. A compound according to any of claims 2 to 6 in which R and R' together with the 2-position carbon atom of the dioxolane ring form a carbocyclic spirocyclic ring of 5 to 8 carbon atoms.

9. A compound according to any of claims 2 to 8 in which n is 1.



10. (1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine and pharmaceutically acceptable acid addition salts thereof.

11. (6-chloro-1,4-dioxaspiro[4.5]dec-2-yl-methyl)guanidine and pharmaceutically acceptable acid addition salts thereof.

12. (1,4-dioxaspiro[4.6]undec-2-yl-methyl)guanidine and pharmaceutically acceptable acid addition salts thereof.

13. A compound according to claim 1 substantially as herein described with reference to any of the examples.

14. A process for the preparation of a compound according to any preceding claim comprising reacting a 1,3-dioxolan-4-yl substituted C_{1-8} -alkylamine and a 2-alkyl or aralkyl thiopseudourea.

15. A process according to claim 14 including the preliminary step of converting the halo group of a 1,3-dioxolan-4-yl- C_{1-8} -alkyl halide to an amino group by reaction with a metallo salt of phthalimide and subsequent hydrolysis.

16. A process according to claim 15 in which the hydrolysis is a hydrazinolysis carried out by the use of hydrazine.

17. A process according to claim 14 substantially as herein described with reference to any of the Examples.

18. A compound according to claim 1 obtained by a process according to any of claims 14 to 17.

19. A pharmaceutical composition comprising a compound according to any of claims 1 to 13 and a pharmaceutically acceptable carrier.

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