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<p>(54) Title: SYDNONE IMINE DERIVATIVES, INTERMEDIATES THEREFORE AND METHODS OF PREPARATION</p>		
<p>(57) Abstract</p> <p>The disclosed [2-(substituted amino)-2-phenyl-ethyl] nitrosoamin] acetonitrile derivatives and the ring closed oxadiazolium salts thereof as well as their pharmaceutically acceptable acid addition salts are antihypertensive agents useful in the treatment of hypertension and serve as intermediates in the production of 3-[2-(dimethylamino)-2-phenylethyl]-N-[(phenylamino)-carbonyl]sydnone imine derivatives which are useful central nervous system stimulants.</p>		

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SYDNONE IMINE DERIVATIVES, INTERMEDIATES THEREFORE AND  
METHODS OF PREPARATIONBackground of the Invention

After the discovery of the central nervous system stimulatory properties of 3-(1-methyl-2-phenylethyl)-  
5 N-(phenylcarbamoyl)sydnone imine (Sydnocarb; U.S.S.R. 329,890 and Offenlegungsschrift 2,028,880) various analogues have been reported. U.S.S.R. 222,370 and Offenlegungsschrift 2,738,022 disclose sydnone imines which contain phenyl, 1- or 2-phenylethyl and the phenyliso-  
10 propyl groups in 3-position as well as N-meta- and para-chlorophenyl and N-phenyl carbamoyl groups. Variations of 3-benzyl sydnonimines are disclosed in U.S. 3,277,108. Other variously substituted 3-aralkyl sydnonimines are disclosed by Olovyanishinkiva et al., Khim. Geterotsikl  
15 Soedin, 2 170-175 (1978) and 9 1198-1203 (1975).

Sydnocarb is conventionally produced by cyanomethylation of amphetamine followed by nitrosation and ring closure with a mineral acid yielding sydnophen as an acid halide salt which is reacted with phenylisocyanate  
20 under mildly basic conditions to introduce the N-phenylcarbamoyl group. As an asymmetric compound, amphetamine may be employed as the initial reactant as the racemic d,l-mixture or as the pure d- or l-isomer to yield racemic or optically active sydnophen and ultimately sydnocarb.  
25

Yashunskii et al., J. Med. Chem., 14 1013-1015 (1971) disclose the marked CNS-stimulatory effect of 3-(1-methyl-2-phenylethyl) sydnonimine (Sydnophen). The relative activities of a large number of alkyl, aryl  
30 and aralkylsydnonimines are presented in Table 1 on page 1014. Most of them, including compound XVIII (2-hydroxy-1-methyl-2-phenylethyl-sydnonimine), were essentially inactive central nervous system stimulants relative to compound XIII (Sydnophen), demonstrating the  
35 criticality of the structure of the 3-substituent in

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the Sydnocarb series of compounds as far as CNS stim-  
ulatory activity is concerned. Thus, although the  
activity profile of Sydnocarb is not identical to that  
of amphetamine, or for that matter Sydnophen, CNS stim-  
5 ulatory activity is a common property of the initial  
reactant amphetamine, the intermediate Sydnophen and  
the final product Sydnocarb.

Although Sydnocarb and its derivatives disclosed  
in the literature forms salts with various organic and  
10 inorganic acids, such salts are not appreciably water  
soluble and when stirred in water, the complex or adduct  
salt is broken up to reisolate the neutral mesoionic  
sydnone imine substrate.

The metabolites of Sydnocarb have been studied by  
15 several groups. L.E. Kholodov and E.T. Lilin, Mater.  
Resp. Rasshir. Konf. Farmacol. Gruz. 2nd 1977, 84-5  
report finding hydroxylation of Sydnocarb at the beta  
carbon of the phenylisopropyl substituent and at the  
phenyl ring of the phenylcarbamoyl group, hydrolytic  
20 cleavage of the phenylcarbamoyl group and ring opening  
of the heterocyclic nucleus. They report that the psycho-  
stimulating activity of Sydnocarb is a property of that  
compound and not its metabolites. Polgar et al. Acta.  
Pharm. Hung., 48, Suppl. 23-24 (1978) and Xenobiotica  
25 9, No. 8, 511-520 (1979) report several hydroxylated  
metabolites and conjugates of hydroxylated Sydnocarb.

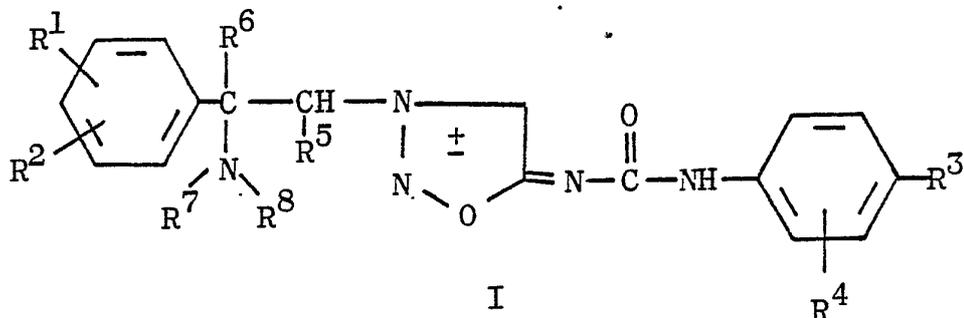
It has been suggested by Kikuchi et al. Jap. J.  
Pharmac. 20 23-43 (1970) that sydnonimines containing  
an amine in 3-position produce hypotension while syd-  
30 nonimines containing an alkyl, cycloalkyl or dialkyl-  
aminoalkyl group in 3-position produce hypertension.

### Description of the Invention

In accordance with this invention there is provided  
a group of central nervous system (CNS) stimulants which  
35 are 3-(2-amino-2-phenylethyl)-N-[(phenylamino)carbonyl]-  
sydnonimines optionally substituted in either or both



phenyl rings, of the formula:



in which

$R^1$  and  $R^2$  are, independently, hydrogen, alkyl  
of 1 to 6 carbon atoms, alkoxy of 1 to 6  
5 carbon atoms, halo, perfluoroalkyl of 1 to  
3 carbon atoms, nitro, alkanoyl of 2 to 4  
carbon atoms, or alkoxy carbonyl of 2 to 4  
carbon atoms;

$R^3$  is hydrogen, halo, nitro or alkanoyl of 2 to 4  
10 carbon atoms;

$R^4$  is hydrogen, halo, nitro or perfluoroalkyl of  
1 to 3 carbon atoms;

$R^5$  and  $R^6$  are, independently, hydrogen or methyl  
and

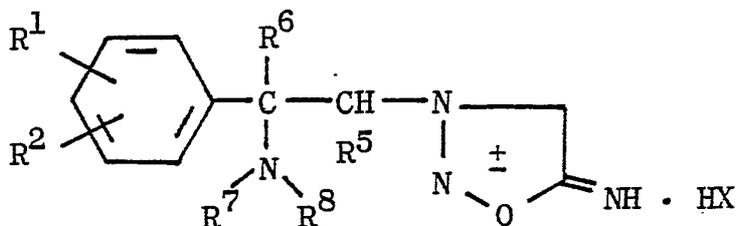
15  $R^7$  and  $R^8$  are, independently, alkyl of 1 to 4 car-  
bon atoms, or when taken with the nitrogen  
atom to which they are attached, form a pip-  
eridinyl, pyrrolidinyl, morpholinyl, N-alkyl  
piperazinyl in which the alkyl group contain  
20 from 1 to 6 carbon atoms or N-phenylpiper-  
azinyl group;

or a non-toxic acid addition salt thereof.

In addition, there is provided a group of 5-amino-  
3-[2-(substituted amino)-2-phenylethyl]nitrosoamino]-  
25 acetonitrile derivatives which are intermediates useful  
in the production of the CNS stimulants disclosed in  
the preceding paragraph, which intermediates

are, in their own right, antihypertensive agents useful in the treatment of hypertension.

The oxadiazolium salts of this invention are represented by the following structural formula:



II

5 in which

$R^1$  and  $R^2$  are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 3 carbon atoms, nitro, alkanoyl of 2 to 4 carbon atoms, or alkoxy carbonyl of 2 to 4 carbon atoms;

10

$R^5$  and  $R^6$  are, independently, hydrogen or methyl;

$R^7$  and  $R^8$  are, independently, alkyl of 1 to 4 carbon atoms, or when taken with the nitrogen

atom to which they are attached, form a piperidinyll, pyrrolidinyl, morpholinyl, N-alkyl

15

piperazinyl in which the alkyl group contains from 1 to 6 carbon atoms or N-phenylpiperazinyl group;

and

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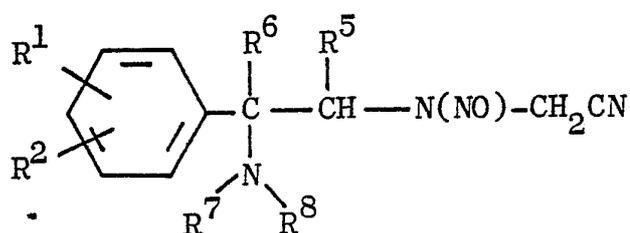
X is the anion of a strong acid having a pKa below 2.

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The oxadiazolium salts of this invention revert to the corresponding nitroso-nitrile precursor via a pH dependent ring opening. Ring opening occurs rapidly under basic conditions and slower in mild acid, in essence demonstrating the reverse of the ring closing accomplished with strong acids. The nitroso-nitriles are,

both intermediates for the antihypertensive oxadiazolium salts and active antihypertensive agents in their own right.

Thus, in accordance with this invention there is also provided a group of nitroso-nitriles useful as antihypertensive agents and in the production of oxadiazolium antihypertensive salts, of the formula:



III

in which

$\text{R}^1$  and  $\text{R}^2$  are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 3 carbon atoms, nitro, alkanoyl of 2 to 4 carbon atoms, or alkoxy carbonyl of 2 to 4 carbon atoms;

$\text{R}^5$  and  $\text{R}^6$  are, independently, hydrogen or methyl;

$\text{R}^7$  and  $\text{R}^8$  are, independently, alkyl of 1 to 4 carbon atoms, or when taken with the nitrogen atom to which they are attached, form a piperidinyl, pyrrolidinyl, morpholinyl, N-alkyl piperazinyl in which the alkyl group contains from 1 to 6 carbon atoms or N-phenylpiperazinyl group;

or a pharmaceutically acceptable salt thereof.

In the preceding structural formulae, it is generally preferred that the halo substituent be chlorine, bromine or fluorine although iodine is acceptable.

Likewise, it is preferred that the alkyl and alkoxy substituents be relatively small, the methyl, ethyl, propyl, isopropyl, methoxy, ethoxy, propoxy and isopropoxy groups being preferred.

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The pharmaceutically acceptable acid addition salts of the compounds of formulae II and III are conventionally produced by the method and from any of the acids disclosed in U.S. 3,277,108, which exhibit a pKa below 2. The salt is preferably that formed during cyclization of the nitrosonitrile, such as with hydrochloric, hydrobromic, sulfuric, phosphoric, methane sulfonic, p-toluene sulfonic acid, and the like. The anion can subsequently be replaced with a desired anion of ion exchange chromatography following conventional procedures. The salts of the compounds of formulae I may be produced with milder acids such as acetic, propionic, oxalic, succinic, maleic, fumaric acid, and the like, as well as with the strong acids previously mentioned in connection with the compounds of formulae II and III. The salts formed with the aminic bases of this invention are generally water soluble, dissociating sufficiently to dissolve in aqueous medium to provide a homogeneous solution. Thus, the compounds of this invention may be formulated for administration in aqueous vehicle for practical dosing to reduce blood pressure in patients unable to receive treatment orally.

The compounds of this invention contain one chiral center when  $R^5$  is hydrogen and two chiral centers when  $R^5$  is methyl. Thus, depending upon the identity of the substituent  $R^5$ , there is obtained either one or two racemic mixtures of product. The epimers and optical isomers are readily separable by standard techniques well known to the chemist. By selection of the desired starting material, the product can be limited to a single racemic mixture of isomers.

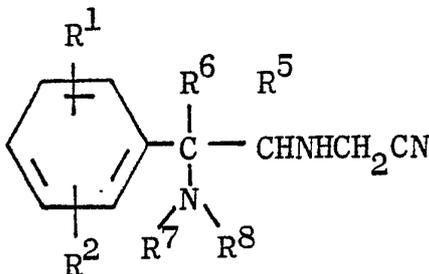
The oxadiazolium salts and the nitroso-nitriles of this invention are prepared by conventional techniques employed in the preparation of sydnonimines.

The starting materials are either known or preparable by routine synthetic methods. Thus, a properly substituted 2-tertiary amino-2-phenylethyl amine is

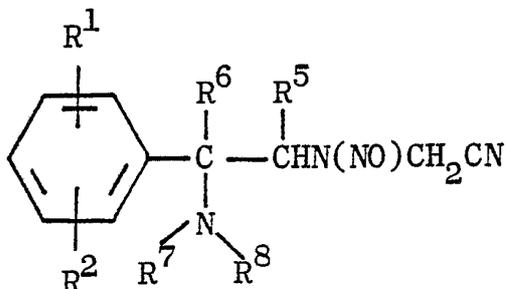


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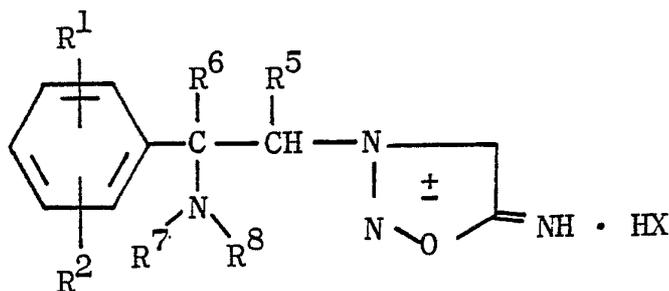
cyanomethylated with a reactant  $XCH_2CN$  where X may be -OH, -Br, -Cl, tosyl, and the like to form the intermediate-



5 which is nitrosated with an excess of  $NaNO_2$  in aqueous HCl to yield the nitroso-nitrile-

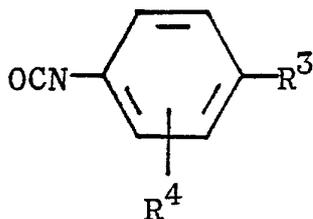


which is then reacted with excess strong acid to form the oxadiazolium salt-



10 The compounds of formula I are produced from either the nitroso-nitrile of formula III or the oxadiazolium salt of formula II by reaction with an isocyanate-

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in the presence of an organic amine base such as triethylamine, 4-dimethylaminopyridine, and the like, following the procedure disclosed in Offenlegungsschrift 2,738,022. In theory, the base selected must be sufficiently alkaline to neutralize the oxadiazolium salt (including the aminic salt) which permits ring opening and reformation of the nitroso-nitrile which in turn undergoes nucleophilic addition of the isocyanate.

The following example illustrates the preparation of d,l-[[2-(dimethylamino)-2-phenylethyl]nitrosoamino]acetonitrile and its use as an intermediate in the production of d,l-5-amino-3-[2-(dimethylamino)-2-phenylethyl]-1,2,3-oxadiazolium chloride.

#### Example 1

dl-5-Amino-3-[2-(dimethylamino)-2-phenylethyl]-1,2,3-oxadiazolium chloride

Dissolve dl-2-dimethylamino-2-phenylethylamine, dihydrochloride (4.74 g.) in water (50 ml.), stir and cool with an ice-bath. Add 37% aqueous formaldehyde solution (2.0 ml.), stir for 10 minutes, then drip in a solution of potassium cyanide (1.30 g.) in water (20 ml.). Stir the cold solution for 1 hour, then cool further to 0° C. (ice-salt bath). Drip in a solution of sodium nitrite (1.4 g.) in water (15 ml.) followed by 5N aqueous HCl (8 ml.). Stir, then again drip in a solution of sodium nitrite (1.4 g.) in water (15 ml.) and continue stirring for 3 hours, allowing the reaction to warm to room temperature. Drip in 5N aqueous

sodium hydroxide solution until a pH of 10 is attained. Quickly extract with diethyl ether, then dry and evaporate the solvent in vacuo. Pump dry, then treat the oil in diethyl ether with decolorizing carbon, filter and evaporate, then pump to obtain dl-[[2-(dimethylamino)-2-phenylethyl]nitrosoamino]acetonitrile as an oil (about 3 g.). To characterize this product dissolve a sample (313 mg.) in methylene chloride, treat with 5N isopropanolic-HCl (1 ml.), then evaporate the solvent in vacuo. Crystallize the residue from acetone, filter to obtain the hydrochloride salt (210 mg.); m.p. 164-166° C.

Analysis for:  $C_{12}H_{16}N_4O \cdot HCl$   
Calculated: C, 53.63; H, 6.38; N, 20.85%  
Found: C, 53.51; H, 6.34; N, 21.31%

Dissolve [[2-(dimethylamino)-2-phenylethyl]nitrosoamino]acetonitrile (4.43 g.) in methylene chloride, add excess 5N isopropanolic-HCl (8 ml.) and let stand overnight. Filter to obtain 1.86 g. of the crude title product, m.p. 150° C (dec).

Combine the product of several runs (3.34 g.), dissolve in 70% aqueous ethanol, treat with decolorizing carbon, filter and dilute the filtrate with isopropanol. Evaporate the solvents in vacuo, cover the remaining glassy material with methylene chloride and let stand to crystallize. Filter to obtain 2.62 g. of the title product as the hydrochloride hydrate, m.p. 157-158° C (dec).

Analysis for:  $C_{12}H_{17}ClN_4O \cdot HCl \cdot 1.5H_2O$   
Calculated: C, 43.38; H, 6.37; N, 16.86%  
Found: C, 43.66; H, 5.85; N, 17.49%

The antihypertensive activity of d,l-5-amino-3-(2-(dimethylamino)-2-phenylethyl)-1,2,3-oxadiazolium chloride, hydrochloride, which compound is representative in its activity of the compounds of formulae II and III, was established by orally administering the compound to a group of unanesthetized, spontaneously

hypertensive rats while indirectly measuring their systolic blood pressure employing a Decker Caudal Plethysmograph. A decrease of 51 mmHg blood pressure was found at 1.5 hours after oral administration of 50 mg/kg of compound and a decrease of 40 mmHg at 1.5 and 4 hours at 25 mg/kg was demonstrated.

Thus, the antihypertensive agents of formulae II and III are useful in treatment of hypertension and as such they may be administered to a patient suffering from hypertension, orally or parenterally, in an amount of from about 25 to 50 mg/kg or more, based upon the test results, in single or divided doses. The dosage regimen and route of administration may be varied by the attending physician to achieve the desired response depending upon the condition of the patient relative to age, severity of hypertensive state, etc.

The following examples illustrate, without limitation, the process for directly producing the compounds of formula I. Where the intermediate cyanomethylated product of the phenethyl amine and the N-nitroso derivative thereof are isolated as oils, no attempt was made to obtain the purified intermediate. The activity counts presented at the end of each example represent the difference from control based upon the test procedure disclosed, infra. dl-Sydnocarb demonstrated a difference from control of 939 activity counts at 10 mg/kg., p.o.

#### Example 2

dl-N-Nitroso-N-[2-(dimethylamino)-2-phenylethyl]amino  
acetonitrile hydrochloride

Dissolve dl-2-dimethylamino-2-phenylethylamine, dihydrochloride (4.74 g.) in water (50 ml.), stir and cool with an ice-bath. Add 37% aqueous formaldehyde solution (2.0 ml.), stir for 10 minutes, then drip in



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a solution of potassium cyanide (1.30 g.) in water (20 ml.). Stir the cold solution for 1 hour, then cool further to 0° C. (ice-salt bath). Drip in a solution of sodium nitrite (1.4 g.) in water (15 ml.) followed by 5N aqueous HCl (8 ml.). Stir, then again drip in a solution of sodium nitrite (1.4 g.) in water (15 ml.) and continue stirring for 3 hours, allowing the reaction to warm to room temperature. Drip in 5N aqueous sodium hydroxide solution until a pH of 10 is attained. Quickly extract with diethyl ether, then dry and evaporate the solvent in vacuo. Pump dry, then treat the oil in diethyl ether with decolorizing carbon, filter and evaporate, then pump to obtain the free-base of the title product as an oil (about 3 g.). To characterize this product dissolve a sample (313 mg.) in methylene chloride, treat with 5N isopropanolic-HCl (1 ml.), then evaporate the solvent in vacuo. Crystallize the residue from acetone, filter to obtain the title product (210 mg.); m.p. 164-166° C.

Analysis for:  $C_{12}H_{16}N_4O \cdot HCl$   
Calculated: C, 53.63; H, 6.38; N, 20.85%  
Found: C, 53.51; H, 6.34; N, 21.31%

The crude, oily free-base of the product obtained above is sufficiently pure for subsequent reactions.

25

Example 3

dl-3-[2-(Dimethylamino)-2-phenylethyl]-N-[(phenylamino)-carbonyl]sydnone imine, dihydrochloride

Stir the oily free base, dl-N-nitroso-N-[2-(dimethylamino)-2-phenylethyl]amino acetonitrile (10.2 g.) with toluene (150 ml.), add phenylisocyanate (5.75 g.) followed by triethylamine (4.44 g.) and heat the mixture at 55° C. for 4 hours. Cool and let stand at room temperature. Evaporate the solvent in vacuo and pump to obtain an oil. Treat the oil in ethyl acetate with



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decolorizing carbon, filter, then treat the filtrate with 5N isopropanolic-HCl (20 ml.). Evaporate the solvent in vacuo without the application of heat, triturate the gum with isopropanol containing a little methylene chloride to initiate crystallization. Let stand, then filter to obtain 16.7 g. of the crude title product; m.p. 139-143° C. (dec). Dissolve the solid in methylene chloride containing a little methanol, treat with decolorizing carbon, filter and evaporate the solvents in vacuo. Cover the oil with acetonitrile, then scratch and triturate to fully crystallize and filter to obtain 8.0 g. of the pure title product as a partial hydrate; m.p. 149-151° C. (dec).

Analysis for:  $C_{19}H_{21}N_5O_2 \cdot 2HCl \cdot 1/3H_2O$   
 15 Calculated: C, 53.03; H, 5.54; N, 16.28%  
Found: C, 53.17; H, 5.42; N, 16.41%  
Activity Counts: 859 at 10 mg/kg.

#### Example 4

20 dl-3-(2-Dimethylamino-2-phenylethyl)-N-[(4-chlorophenyl-amino)carbonyl]sydnone imine, dihydrochloride

The title compound is prepared following the procedure of Example 2 with the exception that p-chlorophenylisocyanate is employed as the reactant rather than phenylisocyanate, m.p. 150-153° C.

25 Analysis for:  $C_{19}H_{20}N_5O_2Cl \cdot 2HCl \cdot 1.5H_2O$   
Calculated: C, 46.97; H, 5.19; N, 14.42  
Found: C, 46.62; H, 4.86; N, 14.18  
Activity Counts: 1329 at 10 mg/kg and 431 at 1 mg/kg.

30 The activity profile of the compounds of formula I is similar to that of amphetamine in some aspects while being devoid of other activities of amphetamine. For example, like amphetamine the compounds of this invention increase motor activity. However, the compounds of this invention are much less toxic than amphetamine

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providing a slower onset of activity (which indicates less euphoria and abuse potential).

The compounds of formula I were shown to possess central nervous system stimulant activity by subject-  
5 ing them to the following standard test procedure:

Male mice weighing 17 to 25 gms. are injected orally with drug solubilized or suspended in 1% Tween<sup>®</sup> 80. Control animals are injected with 1% Tween<sup>®</sup> 80.

10 Six Columbus Instrument Company activity chambers are employed. Three mice given identical treatment are placed in each chamber for all tests. During each run, control animals (1% Tween<sup>®</sup> only) occupy 3 chambers; the other 3 chambers measure activity of  
15 drug treated animals. For each dose of a given drug the experiment is run two times in a counterbalanced design so that each specific activity chamber records the activity of control animals during one run, and the activity of drug animals on the other run. Thus  
20 at each dose level 18 mice are used in the drug group and 18 mice in the control group.

Activity counts are recorded every ten minutes for a period of 2 hours. The data are analyzed using Students "t" test comparing the means of the control and  
25 drug groups for each 10 minute period. The drug treated group is compared graphically with the control group in regard to duration of action and dose response at peak drug activity.

As central nervous system stimulants with unique  
30 activity profiles, the compounds of formula I are useful in the treatment of anergic disorders (such as sleepiness and fatigue) including related types of depression and narcolepsy. Based upon the potency of the compounds of formula I in use in mice, the dose con-  
35 templated for use in the 70 kilogram human would vary from about 35-700 milligrams administered orally once



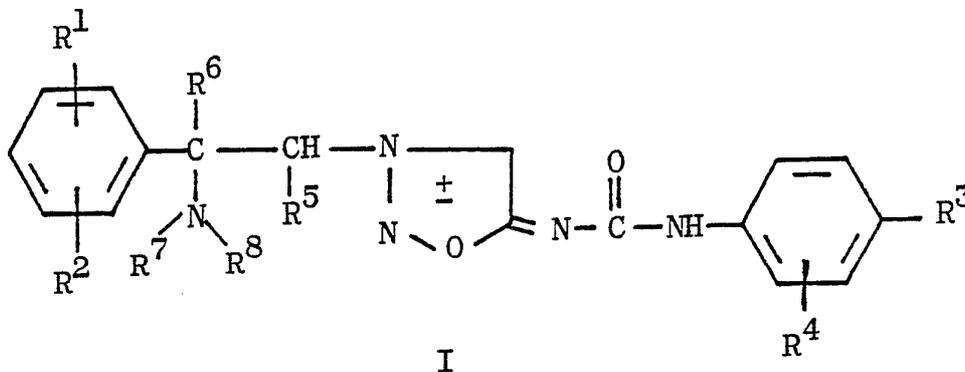
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or twice per day under the guidance of a physician. Of course, the dosage regimen as well as the route of administration, oral or parenteral, will vary with the condition of the patient relative to age, severity of  
5 depression, etc.



WHAT IS CLAIMED IS:

1. A compound of the formula:



in which

5  $R^1$  and  $R^2$  are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 3 carbon atoms, nitro, alkanoyl of 2 to 4 carbon atoms or alkoxycarbonyl of 2 to 4 carbon atoms;

10  $R^3$  is hydrogen, halo, nitro or alkanoyl of 2 to 4 carbon atoms;

$R^4$  is hydrogen, halo, nitro or perfluoroalkyl of 1 to 3 carbon atoms;

$R^5$  and  $R^6$  are, independently, hydrogen or methyl;

and

15  $R^7$  and  $R^8$  are, independently, alkyl of 1 to 4 carbon atoms, or when taken with the nitrogen atom to which they are attached form a piperidinyl, pyrrolidinyl, morpholinyl, N-alkyl piperazinyl in which the alkyl group contains

20 from 1 to 6 carbon atoms or N-phenylpiperazinyl group;

or a non-toxic acid addition salt thereof.

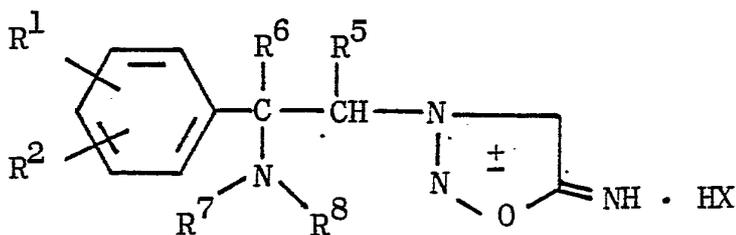
25 2. A compound of Claim 1 which is dl-3-(2-dimethylamino-2-phenylethyl)-N-[(phenylamino)carbonyl]sydnone imine or a non-toxic acid addition salt thereof.

3. A compound of Claim 1 which is d or l-3-(2-dimethylamino-2-phenylethyl)-N-[(phenylamino)carbonyl]-sydnone imine or a non-toxic acid addition salt thereof.

4. A compound of Claim 1 which is dl-3-(2-dimethyl-  
5 amino-2-phenylethyl)-N-[(4-chlorophenylamino)carbonyl]-sydnone imine or a non-toxic acid addition salt thereof.

5. A compound of Claim 1 which is d or l-3-(2-di-  
10 methylamino-2-phenylethyl)-N-[(4-chlorophenylamino)car-  
bonyl]sydnone imine or a non-toxic acid addition salt  
thereof.

6. A compound of the formula



II

in which

15  $R^1$  and  $R^2$  are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 3 carbon atoms, nitro, alkanoyl of 2 to 4 carbon atoms, or alkoxy carbonyl of 2 to 4 carbon atoms;

$R^5$  and  $R^6$  are, independently, hydrogen or methyl;

20  $R^7$  and  $R^8$  are, independently, alkyl of 1 to 4 carbon atoms, or when taken with the nitrogen atom to which they are attached, for a piperidiny, pyrrolidiny, morpholinyl, N-alkyl piperazinyl in which the alkyl group contains from 1 to 6 carbon atoms or N-phenylpiperazinyl group;

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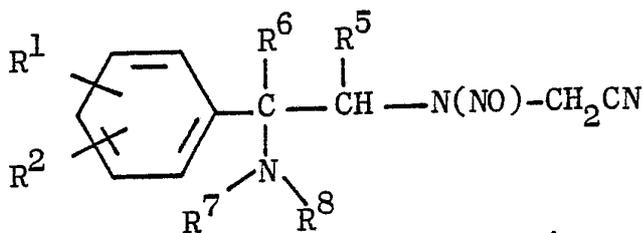
and

X is the anion of a strong acid having a pKa below 2;

5 or a pharmaceutically acceptable acid addition salt thereof.

7. A compound of Claim 6 which is 5-amino-3-[2-(dimethylamino)-2-phenylethyl]-1,2,3-oxadiazolium chloride or a pharmaceutically acceptable acid addition salt thereof.

10 8. A compound of the formula:



in which

15  $\text{R}^1$  and  $\text{R}^2$  are, independently, hydrogen, alkyl of 1 to 6 carbon atoms, alkoxy of 1 to 6 carbon atoms, halo, perfluoroalkyl of 1 to 5 carbon atoms, nitro, alkanoyl of 2 to 4 carbon atoms, or alkoxycarbonyl of 2 to 4 carbon atoms;

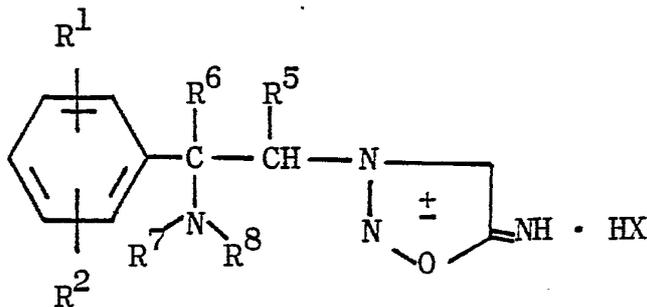
$\text{R}^5$  and  $\text{R}^6$  are, independently, hydrogen or methyl;

20  $\text{R}^7$  and  $\text{R}^8$  are, independently, alkyl of 1 to 4 carbon atoms, or when taken with the nitrogen atom to which they are attached, form a piperidinyl, pyrrolidinyl, morpholinyl, N-alkyl piperazinyl in which the alkyl group contains from 1 to 6 carbon atoms or N-phenylpiperazinyl group;

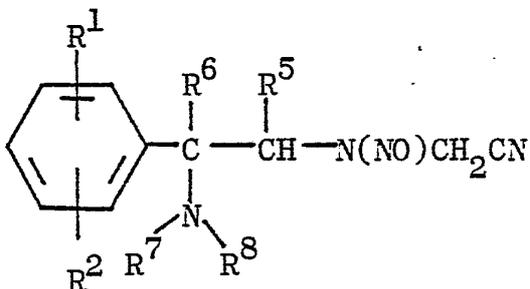
25 or a pharmaceutically acceptable salt thereof.

9. The compound of Claim 8 which is d,l-[[2-(dimethylamino)-2-phenylethyl]nitrosoamino]acetonitrile or a pharmaceutically acceptable acid addition salt thereof.

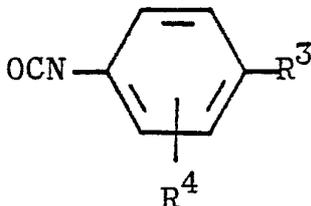
10. A process for the production of a compound of Claim 1 which comprises reacting an oxadiazolium salt of the formula:



or a nitroso-nitrile of the formula:



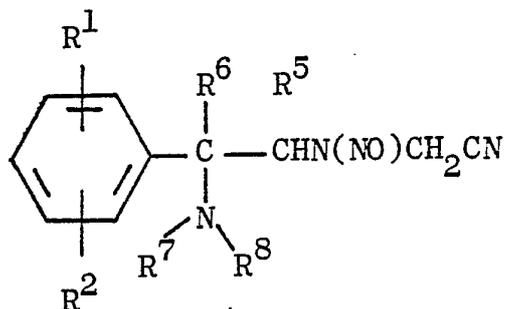
with an isocyanate of the formula:



in the presence of an organic amine base.

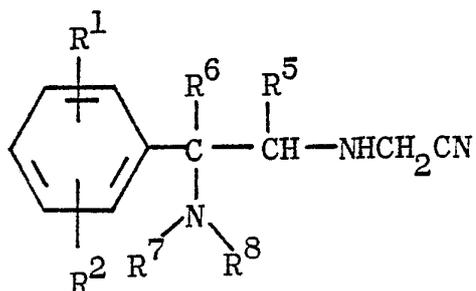
10 11. A process for the production of an oxadiazolium salt of Claim 6 which comprises treating a nitroso-nitrile of the formula:





wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$  and  $\text{R}^8$  are defined in Claim 6 with excess strong acid.

12. A process for the production of a nitroso-nitrile of Claim 8 which comprises nitrosating a compound  
5 of the formula:



wherein  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$  and  $\text{R}^8$  are defined in Claim 8.

# INTERNATIONAL SEARCH REPORT

International Application No **PCT/US81/01205**

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (if several classification symbols apply, indicate all) <sup>3</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int. Cl. <sup>3</sup> C07C, 111/00; C07D 271/04, 295/14, 413/06 US CL. 544/138, 163, 367, 394, 398, 399; 546/209; 230; 548/125; (cont'd)		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>4</sup>		
Classification System	Classification Symbols	
US	544/138, 163, 367, 394, 398, 399; 546/209, 230; 548/125; 260/326.41, 326.5J, 326.5L, 465D, 465E	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>5</sup>		
Chemical Abstracts - Sydnoneimine - Acetonitrile		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <sup>14</sup>		
Category *	Citation of Document, <sup>16</sup> with indication, where appropriate, of the relevant passages <sup>17</sup>	Relevant to Claim No. <sup>18</sup>
X, P	US, A, 4,245,100, Published 13 January 1981, Kholodov et al.	1-10
X	DE, A, 2,738,022 Published 06 January 1978, Cholodov et al.	1-10
X	US, A, 3,277,108 Published 04 October 1966, Daeniker.	10-12
X	US, A, 3,312,690 Published 04 April 1967, Masuda et al.	11-12
A	N, Japanese Journal of Pharmacology, Volume 20, Issued 1970, Kenzo Kikuchi et al, 'Cardiovascular Action of Mesoionic Compounds, 3-Substituted Sydnonimines', Pages 23-43.	6-7
<p>* Special categories of cited documents: <sup>15</sup></p> <p>"A" document defining the general state of the art</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document cited for special reason other than those referred to in the other categories</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but on or after the priority date claimed</p> <p>"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search <sup>2</sup>		Date of Mailing of this International Search Report <sup>2</sup>
23 November 1981		02 DEC 1981
International Searching Authority <sup>1</sup>		Signature of Authorized Officer <sup>20</sup>
ISA/US		Robert W. Ramsuer RR/Ramsuer

## FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

## I. CLASSIFICATION OF SUBJECT MATTER (CONTINUED)

US CL. 260/326.41, 326.5J, 326.5L, 465D, 465E

V.  OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE <sup>10</sup>

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1.  Claim numbers \_\_\_\_\_, because they relate to subject matter <sup>12</sup> not required to be searched by this Authority, namely:
2.  Claim numbers \_\_\_\_\_, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out <sup>13</sup>, specifically:

VI.  OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING <sup>11</sup>

This International Searching Authority found multiple inventions in this international application as follows:

- |                 |               |
|-----------------|---------------|
| I. Claims 1-5   | V. Claim 10   |
| II. Claims 6-7  | VI. Claim 11  |
| III. Claims 8-9 | VII. Claim 12 |
| IV. Claim 10    |               |

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

## Remark on Protest

- The additional search fees were accompanied by applicant's protest.
- No protest accompanied the payment of additional search fees.