

L186.878

PATENT SPECIFICATION

NO DRAWINGS

L186.878



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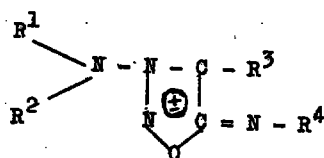
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COMPLETE SPECIFICATION

N-Acyl Sydnonimine Derivatives

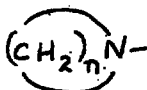
We, TAKEDA YAKUHIN KOGYO KABUSHIKI KAISHA (Takeda Chemical Industries Ltd.) of 54 4-chome, Jusonishino-cho, Higashiyodogawa-ku, Osaka, Japan, a body corporate organised under the laws of Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel N-acyl sydnonimine derivatives useful as medicines, and to the preparation thereof. In particular, the present invention relates to novel 3-disubstituted amino-N-acyl sydnonimine derivatives of the general formula (I) below and to acid salts thereof which have characteristic effects, e.g. as hypotensive drugs, coronary and peripheral vessel dilators;



(I),

wherein R^3 is a hydrogen atom or a lower alkyl group having one to five carbon atoms; R^4 is $-\text{NO}$, an $\text{R}^5\text{CO}-$ group derived from a carboxylic acid, a carbamic acid or a carbonic acid, R^5 being hydrogen or a radical containing one to nine carbon atoms, an $\text{R}^6\text{CO}-$ group derived from a naturally occurring amino acid, R^6COOH forming the amino acid or a N-acyl derivative thereof, or an R^7SO_2- group derived from a sulphonic acid, R^7 being a radical containing one to seven carbon atoms; and R^1 and R^2 are the same or different and represent a lower alkyl group having one to five carbon atoms, a lower alkenyl group having two to five carbon atoms or an aralkyl group having seven to nine carbon atoms, or R^1 and R^2 taken together with the adjacent N-atom represent morpholino, pipercolino, a



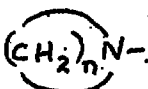
radical wherein n is 4, 5 or 6, or an

[Price 5s. 0d.]



30 In the formula (I), R^2 represents hydrogen or a lower alkyl group having one to five carbon atoms, such as methyl, ethyl, propyl, *n*-butyl, isobutyl and amyl, R^4 represents (1) the ON- group, (2) an R^5 CO- group derived from a carboxylic acid, a carbamic acid or a carbonic acid, wherein R^5 is hydrogen or a radical containing one to nine carbon atoms consisting of a lower alkyl group such as methyl, ethyl, 35 propyl, *n*-butyl, tert.-butyl or amyl, a lower haloalkyl group such as monochloromethyl, dichloromethyl, trichloromethyl, monofluoromethyl, difluoromethyl, trifluoromethyl, monochloroethyl, dichloroethyl or trifluorethyl, an aryloxy alkyl such as phenoxyethyl or phenoxyethyl, an aralkyl such as benzyl or phenylethyl, an aralkenyl group such as styryl, an alkanoyl alkyl group such as acetyl methyl or propionyl ethyl, 40 a lower alkoxy group such as methoxy, ethoxy, propoxy, *n*-butoxy, tert.-butoxy or t-amyl, an aralkyloxy group such as benzyloxy, a lower alkylamino group such as methylamino or ethylamino, an arylamino group such as phenylamino, a pyridyl group such as 2 - pyridyl, 3 - pyridyl or 4-pyridyl, (3) an R^6 CO- group derived from a naturally occurring amino acid, 45 wherein R^6 COOH forms the amino acid such as L-alanine, L-valine, L-leucine, L-serine, L-cysteine or L-phenylalanine or an N-acyl derivative thereof such as an N-carbobenzyloxy or an N-acetyl derivative, or (4) an R^7 SO₂- group derived from a sulphonic acid, wherein R^7 is a radical containing from one to seven carbon atoms consisting of a lower alkyl group such as methyl, ethyl, propyl, *n*-butyl, isobutyl or 50 amyl, an aryl group such as phenyl or tolyl, a haloaryl group such as *o*-chlorophenyl, *m*-chlorophenyl or *p*-chlorophenyl, an aminoaryl group such as *p*-amino phenyl or *p*-acetylaminophenyl, and R_1 and R_2 are the same or different and each represents a

lower alkyl group having from one to five carbon atoms, such as methyl, ethyl, propyl, isopropyl, *n*-butyl, tert.-butyl or amyl a lower alkenyl group having two to five carbon atoms such as vinyl, allyl or butenyl, or an aralkyl group having from seven to nine carbon atoms, such as benzyl, phenylethyl or phenylpropyl, and R¹ and R² may form together with the adjacent nitrogen atom a ring such as morpholino, pipercolino, a



radical wherein *n* is 4, 5 or 6, which is exemplified by piperidino, pyrrolidino or hexahydroazepinyl, an



radical wherein R is a lower alkyl group having one to five carbon atoms such as methyl, ethyl, propyl, isopropyl, *n*-butyl, tert.-butyl or amyl, or the group (III):



(III),

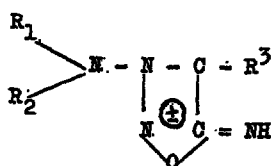
wherein R³ and R⁴ have respectively the same meanings as above.

The compounds of formula (I), which form salts with various acids, are exemplified as follows:

- | | | |
|----|--|----|
| 15 | 3-morpholino-N-formylsydnonimine, | 15 |
| | 3-morpholino-N-acetylsydnonimine, | |
| | 3-morpholino-N-propionylsydnonimine, | |
| 20 | 3-morpholino-N-monochloroacetylsydnonimine, | 20 |
| | 3-morpholino-N-dichloroacetylsydnonimine, | |
| | 3-morpholino-N-trichloroacetylsydnonimine, | |
| | 3-morpholino-N-trifluoroacetylsydnonimine, | |
| | 3-morpholino-N-phenoxyacetylsydnonimine, | |
| 25 | 3-morpholino-N-phenoxypropionylsydnonimine, | 25 |
| | 3-morpholino-N-phenylacetylsydnonimine, | |
| | 3-morpholino-N-phenylpropionylsydnonimine, | |
| | 3-morpholino-N-cinnamoylsydnonimine, | |
| | 3-morpholino-N-benzoylsydnonimine, | |
| 30 | 3-morpholino-N-methoxycarbonylsydnonimine, | 30 |
| | 3-morpholino-N-ethoxycarbonylsydnonimine, | |
| | 3-morpholino-N-propoxycarbonylsydnonimine, | |
| | 3-morpholino-N-benzoyloxycarbonylsydnonimine, | |
| | 3-morpholino-N-methylcarbamoylsydnonimine, | |
| 35 | 3-morpholino-N-ethylcarbamoylsydnonimine, | 35 |
| | 3-morpholino-N-phenylcarbamoylsydnonimine, | |
| | 3-morpholino-N-nicotinoylsydnonimine, | |
| | 3-morpholino-N-isonicotinoylsydnonimine, | |
| | 3-morpholino-4-methyl-N-benzoylsydnonimine, | |
| 40 | 3-morpholino-4-ethyl-N-benzoylsydnonimine, | 40 |
| | 3-dimethylamino-N-benzoylsydnonimine, | |
| | 3-dimethylamino-4-methyl-N-benzoylsydnonimine, | |
| | 3-morpholino-N-(N'-carbobenzyloxy alanyl)-sydnonimine, | |
| | 3-morpholino-N-methylsulphonylsydnonimine, | |
| 45 | 3-morpholino-N-phenylsulphonylsydnonimine, | 45 |

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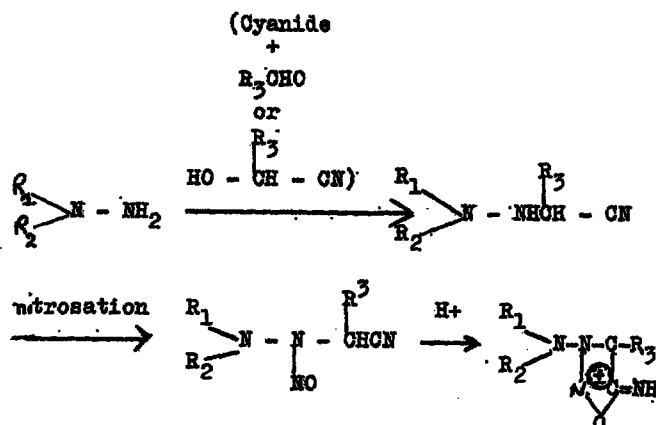
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The starting material of the formula (II) of the present invention is produced by a method described in U.S. Specification No. 3,312,690, the method being shown by the following equation:

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acid fluoride), the acid anhydride, acid ester, ketene or isocyanate, preferably with cooling, in the presence of an organic solvent such as water, in alcohol, pyridine, acetonitrile or ether, with the use of an acid eliminating agent such as an alkaline substance (e.g. sodium hydroxide, sodium bicarbonate or sodium carbonate) and an amine compound (e.g. triethyl amine or pyridine).

Thus, the desired N-acyl sydnonimine derivative is produced as a free base or an acid salt. When the desired compound is obtained as a free base, the compound may be converted into a pharmaceutically acceptable salt thereof such as a mineral acid salt (e.g. of hydrochloric, nitric, sulphuric or phosphoric acid), an organic acid salt (e.g. of formic, acetic, butyric, citric, ascorbic, salicylic or *p*-aminosalicylic acid).

The present N-acyl sydnonimine derivatives or their salts are preferably administered in the form of an aqueous solution containing about 1 milligram of N-acyl sydnonimine per milliliter of water and are generally administered *per os* but an injection may also be applied, the dose for an adult being selected from the range of from about 5 to about 100 milligrams per day.

For the purpose of giving those skilled in the art a better understanding of the invention, the following illustrative test and examples are now given.

In the following examples, parts are shown on a weight basis unless otherwise stated. Parts by weight bear the same relationship to parts by volume as do grams to milliliters.

Test for depressor response.

1) Anaesthetized cats with pyloric-ligated stomach.

The compounds of the present invention were administered to the stomach or duodenal of an anaesthetised cat with pyloric-ligated stomach through a tube previously put into the stomach or the duodenum. After the administration, the systolic and diastolic blood pressure of the cat was continuously registered with a haemodynamometer to calculate the percentage change of pressure drop. The results of the test are as follows.

TABLE I

Compound	Route of administration	Dose mg/kg	Percentage change of pressure drop syst./diast.				
			15 min.	30 min.	60 min.	120 min.	240 min.
3-morpholino-N-ethoxycarbonylsydnominine	G	2	-8/-5	-9/-6	-12/-7	-16/-11	-16/-11
	D	1	-33/-24	-35/-27	-30/-19	-19/-12	-7/-5
3-morpholino-N-benzoylsydnominine	G	1	-11/-10	-12/-11	-13/-14	-17/-13	-15/-9
	D	1	-10/0	-11/0	-12/0	-12/0	-10/0
Control 3-morpholinosydnominine	G	1	0/0	0/0	0/0	0/0	0/0
	D	1	-31/-30	-34/-35	-30/-29	-15/-12	-10/-9

N.B. G: Intra-gastric administration.

D: Intra-duodenal administration.

From the results of the test, it can be seen that the hitherto known sydnominine compound is absorbed only from the duodenum and is scarcely absorbed from the stomach while compounds of this invention are absorbed not only from the duodenum but also from the stomach in large amounts. This suggests that the compounds of this invention show their activities more rapidly than the control compound after oral administration.

2) Nembutalized dogs.

The compounds of the present invention were administered orally to a Nembutal-anaesthetized dog (5 kg.), and the blood pressure of the dog was continuously measured by a hemodynamometer and the changes in blood pressure before administration and at various intervals after the administration were calculated, the changes being described as fall of blood pressure in Table II.

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TABLE II

Compound	Fall of blood pressure mm/Hg.					
	10 min.	20 min.	30 min.	60 min.	120 min.	180 min.
1	-13	-18	-25	-40	-40	-31
2	-11	-22	-23	-20	-30	-22
Control 3	-10	-14	-18	-14	-12	-11

Compound (1) : 3-morpholino-N-ethoxycarbonylsydnnonimine.

Compound (2) : 3-morpholino-N-benzoylsydnnonimine

Control compound (3) : 3-morpholinosydnnonimine.

The compounds (1) and (2) of the present invention are more effective, and have a longer effective duration than the control compound (3) in lowering blood-pressure.

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Test for acute toxicity

The compounds of this invention were administered intraperitoneally to groups each consisting of 4 mice (male, 4 weeks old, ICR—JCL strain).

The treated mice were observed for 3 days to count the number of mice killed within that period and to measure the time taken until the mice finally died. The results are as follows.

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TABLE III

Compound	Number of killed mouse or mice Dose mg/Kg.			
	1000	500	250	125
3-morpholino-N-benzoylsydnnonimine	4 60 min.	0	0	0
3-morpholino-N-ethoxycarbonylsydnnonimine	0	0	0	0
3-morpholino-N-p-chlorobenzenesulphonylsydnnonimine	0	0	0	0
3-morpholino-N-nitrososydnnonimine	1 12 hrs.	0	0	0
3-morpholino-N-acetylsydnnonimine	4 15 min.	0	0	0
Control 3-morpholinosydnnonimine	4 10 min.	4 15 min.	1 40 min.	0

The compounds of this invention have a remarkably low toxicity in comparison with the control compound.

EXAMPLE 1

Twenty parts by weight of 3-morpholinosydnonimine hydrochloride suspended in a mixture of 200 parts by volume of acetic anhydride and 40 parts by volume of pyridine are agitated for 48 hours at room temperature, whereby precipitates are formed. The precipitates collected by filtration are recrystallised from about 700 parts by volume of ethanol to give 20.3 parts by weight (84%) of 3-morpholino-N-acetylsydnonimine hydrochloride having a melting point of 175° C. (with decomposition).

Analysis $C_9H_{15}N_4O_3Cl$

	C	H	N
Calculated	38.64	5.27	22.53
Found	38.77	5.26	22.23

EXAMPLE 2

5 parts by weight of benzoyl chloride are added dropwise with ice-cooling and agitation to 5 parts by weight of 3-morpholinosydnonimine hydrochloride suspended in 25 parts by volume of pyridine. The mixture is then agitated for 4 hours to give crude crystals. The crude crystals thus obtained are collected by filtration, washed with 75 parts by volume of water, and recrystallised from 500 parts by volume of absolute methanol to yield 5.5 parts by weight of 3-morpholino-N-benzoylsydnonimine having a melting point of 186° C. to 188° C.

5.5 parts by weight of the 3-morpholino-N-benzoylsydnonimine obtained are dissolved in methanolic hydrochloric acid, and the solvent is evaporated off under reduced pressure to give crude crystals. Recrystallisation of the crude crystals from methanol gives 6.0 parts by weight of 3-morpholino-N-benzoylsydnonimine hydrochloride having a melting point of 159° C. to 160° C. (with decomposition).

Analysis $C_{13}H_{15}N_4O_3Cl$

	C	H	N
Calculated	50.25	4.87	18.03
Found	50.35	4.78	17.99

EXAMPLE 3

1.2 parts by weight of *p*-chlorophenylsulphonyl chloride are added dropwise with ice-cooling and agitation to 1.0 part by weight of 3-morpholinosydnonimine hydrochloride suspended in 5 parts by volume of pyridine. The resulting mixture is agitated overnight at room temperature, whereby crystals are formed, and this is followed by the addition of 30 parts by volume of water. The mixture is subjected to filtration to leave 1.5 parts by weight of crude crystals which are recrystallised from about 200 parts by volume of ethanol to give 1.3 parts by weight (78%) of 3-morpholino-N-*p*-chlorophenylsulphonylsydnonimine melting at 178° C. to 179° C. (with decomposition).

Analysis $C_{12}H_{13}N_4O_4SCl$

	C	H	N
Calculated	41.80	3.80	16.25
Found	41.50	3.72	16.13

EXAMPLE 4

1.6 parts by volume of ethyl chloroformate are added dropwise with agitation to a suspension of 1.0 parts by weight of 3-morpholinosydnnonimine hydrochloride in 5 parts by volume of pyridine, and the mixture is agitated for a while to allow the reaction to take place. Pyridine is removed from the reaction mixture by evaporation, and the residue is dissolved in a small amount of water and extracted with chloroform several times. The extractant is dehydrated by adding anhydrous magnesium sulphate and subjected to filtration. Chloroform is removed from the filtrate by distillation to give crude crystals. Recrystallisation of the crude crystals from toluene gives 0.6 part by weight of 3-morpholino-N-carboethoxysydnnonimine having a melting point of 140° C. to 141° C. Yield: 51%.

Analysis $C_9H_{14}N_4O_4$

	C	H	N
Calculated	44.62	5.83	23.13
Found	44.57	5.85	23.19

EXAMPLE 5

0.9 part by weight of sodium bicarbonate is added with ice-cooling and agitation to 2.0 parts by weight of 3-morpholinosydnnonimine hydrochloride dissolved in 20 parts by volume of water. 5 minutes after, 1.2 parts by weight of phenyl isocyanate are added. The mixture is then agitated for 6 hours and kept standing overnight to give precipitates which are separated from the reaction mixture by filtration. The recovered precipitates are subjected to column chromatography to remove contaminating diphenylurea. Recrystallisation from methanol of the treated crude crystals gives 0.8 part by weight of 3-morpholino-N-phenylcarbamoysydnnonimine having a melting point of 162° C. (with decomposition).

The yield is 29%.

Analysis $C_{13}H_{18}N_5O_3$

	C	H	N
Calculated	53.97	5.23	24.21
Found	54.04	5.53	24.29

By the same procedure as above, precipitates are separated from the reaction mixture by filtration. The precipitates are dissolved in methanolic hydrochloric acid and methanol is distilled off from the solution. The residue is washed with acetone to remove contaminated diphenylurea so as to yield crude 3-morpholino-N-phenylcarbamoysydnnonimine hydrochloride. Recrystallisation of the crude compound from methanol gives crystals having a melting point of from 175° C. to 176° C. (with decomposition).

Analysis $C_{13}H_{18}N_5O_3Cl$

	C	H	N
Calculated	47.93	4.95	21.50
Found	47.86	4.96	21.57

EXAMPLE 6

0.4 part by weight of sodium nitrite in 15 parts by volume of water is added with ice-cooling and agitation to 1.0 part by weight of 3-morpholinosydnnonimine hydrochloride dissolved in 5 parts by volume of water. The mixture is agitated for 6 hours and further kept standing overnight to yield yellow precipitates which are recovered by filtration.

Recrystallisation of the precipitates gives 0.8 part by weight of yellow prisms of 3-morpholino-N-nitrososydnnonimine having a melting point of 130° C. (with decomposition).

The yield is 83%.

Analysis $C_6H_9N_5O_3$

	C	H	N
Calculated	36.18	4.55	35.16
Found	36.06	4.53	34.94

EXAMPLE 7

Two parts by weight of 3-morpholinosydnnonimine hydrochloride are dissolved in an excess amount of trifluoroacetic acid anhydride. After standing overnight, the mixture is concentrated to dryness under highly reduced pressure. The crude crystals produced are carefully recrystallised from ethanol to yield 2.3 parts by weight (89.5%) of pure 3-morpholino-N-trifluoroacetylsydnnonimine having a melting point of 167° C. to 168° C. (with decomposition).

Analysis $C_8H_9N_4F_3$

	C	H	N
Calculated	36.10	3.41	21.41
Found	36.22	3.72	21.69

EXAMPLE 8

1.3 parts by weight of sodium bicarbonate are added with ice-cooling and agitation to 3.0 parts by weight of 3-morpholinosydnnonimine hydrochloride suspended in 30 parts by volume of water and the mixture is further agitated for about 10 minutes. 3.0 parts by weight of *p*-nitrophenyl formate dissolved in 20 parts by volume of tetrahydrofuran are added dropwise with ice-cooling and agitation to the treated mixture. The resulting solution is further agitated for two hours, whereby the temperature of the reaction system is raised to room temperature. After tetrahydrofuran has been distilled off from the reaction mixture, *p*-nitrophenol and unreacted reagent are removed by extraction with ether, and then, from the treated reaction mixture, the desired compound is extracted several times with ethyl acetate.

After being dried, the extractant is subjected to distillation to remove the solvent and to leave crude crystals of 3-morpholino-N-formylsydnnonimine. The crude crystals are recrystallised from ethanol to yield 2.3 parts by weight (80%) of pure crystals having a melting point of 149° C. to 151° C. (with decomposition).

Analysis $C_7H_{10}N_4O_3$

	C	H	N
Calculated	42.42	5.09	28.27
Found	42.25	5.17	28.47

The desired compound may also be produced by the following process. 3.0 parts by weight of 3-morpholinosydnimine hydrochloride are dissolved in an excess amount of formic acid anhydride. After standing overnight, the mixture is condensed to dryness. The crude crystals obtained are recrystallised from ethanol to yield 2.5 parts by weight (87%) of 3-morpholino-N-formylsydnimine.

EXAMPLE 9

1.7 parts by weight of sodium bicarbonate are added with ice-cooling and agitation to 4.0 parts by weight of 3-morpholinosydnimine hydrochloride suspended in 40 parts by volume of water and the mixture is further agitated for about 10 minutes. 4.5 parts by weight of *p*-nitrophenyl monochloroacetate dissolved in 20 parts by volume of tetrahydrofuran are added dropwise with ice-cooling and agitation to the treated mixture. The resulting mixture is stirred for a further 2 hours, whereby the temperature of the reaction system is raised to room temperature. Tetrahydrofuran is distilled off from the reaction mixture, and water is added to the residue to separate out crude crystals. The crystals are washed with water and ether and are recrystallised from ether to yield 4.5 parts by weight (91%) of 3-morpholino-N-monochloroacetylsydnimine having a melting point of 105° C. to 107° C.

Analysis $C_8H_{11}N_4O_3Cl$

	C	H	N
Calculated	38.95	4.50	22.72
Found	39.07	4.56	22.61

EXAMPLE 10

4.0 parts by weight of 3-morpholinosydnimine hydrochloride are reacted in a similar manner to Example 9 with 5 parts by weight of *p*-nitrophenyl dichloroacetate to yield 5.0 parts by weight (89%) of 3-morpholino-N-dichloroacetylsydnimine having a melting point of 165° C. to 167° C. (with decomposition).

Analysis $C_8H_{10}N_4O_3Cl_2$

	C	H	N
Calculated	34.18	3.59	19.93
Found	34.46	3.52	19.91

EXAMPLE 11

3 parts by weight of trichloroacetyl chloride are added with ice-cooling and agitation to 3.1 parts by weight of 3-morpholinosydnimine hydrochloride suspended in 25 parts by volume of dry pyridine, and the resulting mixture is further agitated for 4 hours at a temperature of from 5° C. to 10° C.

The reaction mixture is cooled again with ice, and about 50 parts by volume of water are added to the treated mixture to separate out crude crystals. After recovery by filtration, the crystals are washed with water and recrystallised from ethanol to yield 4.5 parts by weight (95%) of crystals of 3-morpholino-N-trichloroacetylsydnimine having a melting point of 180° C. to 181.5° C. (with decomposition).

Analysis $C_8H_9N_4O_3Cl_3$

	C	H	N
Calculated	30.45	2.87	17.76
Found	30.25	2.74	17.90

EXAMPLE 12

5 3.0 parts by weight of 3-morpholinosydnnonimine hydrochloride are suspended in a mixture of 19.0 parts by weight of propionic acid anhydride and 4 parts by volume of pyridine, followed by stirring for about 20 hours at room temperature to precipitate out white crystals. The crystals collected by filtration are recrystallised from isopropanol to yield 3.2 parts by weight of 3-morpholino-N-propionylsydnnonimine hydrochloride having a melting point of 169° C. to 171° C. (with decomposition).

Analysis $C_9H_{15}N_4OI$

	C	H	N
Calculated	41.45	5.76	21.33
Found	41.42	5.78	21.23

EXAMPLE 13

10 1.7 parts by weight of phenyl propionyl chloride are added dropwise with ice-cooling and agitation to 2.0 parts by weight of 3-morpholinosydnnonimine hydrochloride suspended in 15 parts by volume of pyridine. After being left standing overnight, the pyridine is distilled off from the reaction mixture under reduced pressure, and the resulting oily substance is washed with ether to remove impurities.

15 Subsequently, the oily substance is subjected to silica gel column chromatography with the use of ethyl acetate as a solvent. Concentration of the eluate gives 0.5 part by weight of powdery product. This powdery product is recrystallised from methanol to yield 0.3 part by weight of needle crystals of 3-morpholino-N-phenyl propionylsydnnonimine having a melting point of 127° C. to 129° C.

Analysis $C_{15}H_{18}N_4O_3$

	C	H	N
Calculated	59.59	5.96	18.53
Found	59.46	6.02	18.15

EXAMPLE 14

25 2.5 parts by weight of cinnamoyl chloride are added with ice-cooling and agitation to 2.0 parts by weight of 3-morpholinosydnnonimine hydrochloride suspended in 15 parts by volume of pyridine. After the mixture has been left standing overnight, water is added thereto, pyridine hydrochloride is dissolved in the water and crystals are separated out. After recovery by filtration, the crystals are recrystallised from methanol to yield 2 parts by weight of flake crystals of 3-morpholino-N-cinnamoylsydnnonimine having a melting point of 184° C. to 187° C.

Analysis $C_{15}H_{16}N_4O_3$

	C	H	N
Calculated	59.99	5.37	18.66
Found	59.85	5.46	18.54

EXAMPLE 15

1.2 parts by weight of benzoyl chloride are added with ice-cooling and agitation to 1.0 part by weight of 3-dimethylaminosydnonimine hydrochloride suspended in 5 parts by volume of pyridine, and the mixture is agitated for a further 2 hours.

After being left standing overnight, 1.0 part by weight of benzoyl chloride is added to the mixture, followed by stirring.

The mixture is then subjected to distillation under reduced pressure at a temperature below 40° C. to remove the solvent. The resulting residue is dissolved in chloroform, and the chloroform layer is washed with water, dehydrated by magnesium sulphate and subjected to distillation to remove chloroform, whereby a brown oil substance is produced. The oily substance is then purified by means of silica gel chromatography (solvent: Ethyl acetate) to yield crude crystals. The recrystallisation of the crude crystals from ethanol gives 0.8 part by weight of 3-dimethylamino-N-benzoylsydnonimine having a melting point of 127° C. to 128° C.

Analysis $C_{11}H_{12}N_4O_2$

	C	H	N
Calculated	56.89	5.21	24.13
Found	56.81	5.20	24.31

EXAMPLE 16

1 part by weight of benzoyl chloride is added with ice-cooling and agitation to 1.0 part by weight of 3-dimethylamino-4-methylsydnonimine hydrochloride suspended in 3 parts by volume of pyridine followed by stirring for 4 hours. The mixture is subjected to distillation to remove pyridine, and the resulting residue is dissolved in ethyl acetate and decolorised by activated charcoal.

The treated solution is concentrated to precipitate out crude crystals. Recrystallisation of the crude crystals from methanol yields 0.1 part by weight of 3-dimethylamino-4-methyl-N-benzoylsydnonimine having a melting point of from 109° C. to 110° C.

Analysis $C_{11}H_{14}N_4O_2$

	C	H	N
Calculated	58.52	5.73	22.75
Found	58.60	5.85	22.74

EXAMPLE 17

1.0 part by weight of phenoxyacetyl chloride is added dropwise with ice-cooling and agitation to 1.0 part by weight of 3-morpholinosydnonimine hydrochloride suspended in 5 parts by volume of dry pyridine, followed by continued agitation for 10 hours. 0.6 part by weight of phenoxyacetyl chloride is further added to the mixture, followed by stirring for 8 hours. 50 parts by volume of water are added to the resulting mixture and the aqueous layer is separated from the oily layer by decantation. Crystals separated from the aqueous layer are collected by filtration and recrystallised from ethanol to yield 0.15 part by weight of 3-morpholino-N-phenoxy-sydnonimine.

On the other hand, the oily layer is dissolved in ethyl acetate and dried with magnesium sulphate. The solvent is distilled off from the solution to yield a brown oily residue. The residue is purified by means of silica gel column chromatography (solvent: ethyl acetate) to yield 0.2 part by weight of crystals.

Recrystallisation of the crystals from ethanol gives 0.5 part by weight of crystals of 3-morpholino-N-phenoxyacetylsydnonimine.

These crystals have a melting point of 149° C. to 151° C.

Analysis $C_{14}H_{16}N_4O_4$

	C	H	N
Calculated	55.26	5.30	18.41
Found	54.93	5.20	18.36

EXAMPLE 18

0.8 part by weight of sodium bicarbonate, and then 0.8 part by weight of carbobenzoxychloride are added with ice-cooling and agitation to 1.0 part by weight of 3-morpholinosydnonimine hydrochloride dissolved in a small amount of water. A small amount of methanol is added to the mixture which is then kept standing for a few hours to precipitate out crystals.

The solvent is distilled off from the filtrate under reduced pressure to separate crystals. Recrystallisation of the crystals from methanol gives 0.7 part by weight of 3-morpholino-N-carbobenzoxy-sydnonimine having a melting point of 115°C . to 116°C . as flake crystals.

Analysis $C_{14}H_{16}N_4O_4$

	C	H	N
Calculated	55.26	5.30	18.41
Found	55.39	5.29	19.10

EXAMPLE 19

0.4 part by weight of sodium bicarbonate, and then, dropwise, 0.4 part by weight of diketene are added with ice-cooling and agitation to 1.0 part by weight of 3-morpholinosydnonimine hydrochloride dissolved in a small amount of water.

After stirring further for about two hours, the mixture becomes cloudy and crystals are precipitated out. The crystals are collected by filtration and washed with water to yield 1.0 part by weight of crude crystals. These crude crystals are recrystallised from methanol to yield 0.6 part by weight of 3-morpholino-N-acetoacetylsydnonimine having a melting point of 110 — 113°C . as flake crystals.

Analysis $C_{10}H_{14}N_4O_4$

	C	H	N
Calculated	47.24	5.55	22.04
Found	47.30	5.33	21.25

EXAMPLE 20

A mixture of 2.7 parts by weight of N-carbobenzyloxy-L-alanine, 2.5 parts by weight of dicyclohexylcarbodiimide and 100 parts by volume of acetonitrile is stirred for two hours at room temperature. 2.0 parts by weight of 3-morpholinosydnonimine hydrochloride and 1.6 parts by weight of dry pyridine are added to the treated mixture, and the mixture is then stirred for about ten hours.

Separated precipitates comprising dicyclohexylurea and unreacted 3-morpholinosydnonimine hydrochloride are removed by filtration and the filtrate is concentrated under reduced pressure to obtain an oily substance. The oily substance is subjected to silica gel chromatography (silica gel column: $6 \times 10\text{ cm}$; solvent: ethyl acetate; volume of 1 fraction: 15 ml) and fraction numbers from 27 to 70, are combined together, followed by concentration under reduced pressure. The residue obtained is

recrystallised from a mixture of ethyl acetate and ethyl ether to yield 0.94 part by weight (24%) of 3-morpholino-N-(N'-carbobenzyloxy-L-alanyl)-sydnonimine having a melting point of 108° C.—110° C.

Analysis $C_{17}H_{21}N_5O_5$

	C	H	N
Calculated	54.39	5.64	18.66
Found	54.13	5.49	18.70

EXAMPLE 21

0.9 part by weight of sodium bicarbonate is added with ice-cooling and agitation to 2.0 parts by weight of 3-morpholinosydnonimine hydrochloride suspended in 20 parts by volume of water, and the mixture is further stirred for about ten minutes. 4 parts by weight of N-carobenzyloxy-L-alanyl-p-nitrophenyl ester in 10 parts by volume of tetrahydrofuran are then added with ice-cooling and agitation, and the mixture is further agitated for two hours, whereby the temperature of the reaction system is raised to room temperature. 1.0 part by weight of sodium bicarbonate is added to the reaction mixture and the mixture is extracted with ethyl acetate three times. The extractant is dried and the solvent is removed by concentration under reduced pressure. The separated oily substance is purified by means of silica gel column chromatography in a similar manner to Example 20 to yield 2.1 parts by weight (56%) of 3-morpholino-N-(N'-carbobenzyloxy-L-alanyl)sydnonimine having a melting point of 108° C.—110° C.

Analysis $C_{17}H_{21}N_5O_5$

	C	H	N
Calculated	54.39	5.64	18.66
Found	54.13	5.49	18.70

EXAMPLE 22

29.0 parts by volume of ethylchloroformate are added dropwise to a mixture of 0.67 part by weight of N-carbobenzoxy-L-alanine, 0.42 part by volume of triethylamine and 6 parts by volume of tetrahydrofuran with ice-cooling and agitation, and the mixture is then further stirred for about 15 minutes. A suspension prepared by reacting 0.6 part by weight of 3-morpholinosydnonimine hydrochloride with 0.26 part by weight of sodium bicarbonate in 6 parts by volume of water is then added dropwise with ice-cooling and agitation to the reaction mixture followed by agitation for one hour, whereby the temperature of the reaction system is raised to room temperature. The reaction mixture is extracted three times with ethyl acetate. The extractant is dried, and the solvent is distilled off under reduced pressure. The residue obtained is washed with ethyl ether, and then recrystallised from ethyl acetate-ethyl ether to give 0.86 part by weight (76%) of 3-morpholino-N-(N'-carbobenzoxy-L-alanyl)sydnonimine.

EXAMPLE 23

1.1 parts by weight of ethylchloroformate and 1.0 part by weight of triethylamine are added with cooling to 1.2 parts by weight of nicotinic acid suspended in 10 parts by volume of dry tetrahydrofuran. The precipitated crystals of triethylamine hydrochloride are removed by filtration to yield a mixed anhydride solution as the filtrate.

On the other hand, 0.8 part by weight of sodium bicarbamate is added with cooling to 2.0 parts by weight of 3-morpholinosydnonimine hydrochloride dissolved in a small amount of water and the filtrate obtained above is then added dropwise. The resulting solution is extracted with ethyl acetate. After the extractant is dried, the solvent is removed under reduced pressure to give crude crystals. Recrystallisation

of the crude crystals from methanol gives 0.3 part by weight of 3-morpholino-N-nicotinoylsydnnonimine having a melting point of 202° C. to 204° C.

Analysis $C_{12}H_{13}N_5O_3$

	C	H	N
Calculated	52.36	4.76	25.44
Found	52.08	4.70	25.80

EXAMPLE 24

5 3-morpholino-N-*p*-acetaminophenylsulphonylsydnnonimine having a melting point of 198° C.—199° C. (with decomposition) is obtained in the manner of Example 3. 5

Analysis $C_{14}H_{17}N_5O_5S$

	C	H	N
Calculated	45.77	4.66	19.06
Found	45.74	4.80	18.63

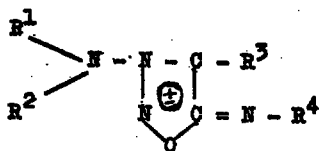
EXAMPLE 25

The following compounds are obtained in the manner of Example 6.

- 10 3-piperidino-N-nitrososydnnonimine m.p. 124° C. (with decomposition) 10
 3-dibutylamino-N-nitrososydnnonimine m.p. 53° C.
 3-dibenzylamino-4-methyl-N-nitrososydnnonimine m.p. 103—106° C. (with decomposition)
 15 3-pyrrolidino-N-nitrososydnnonimine m.p. 132—134° C. (with decomposition) 15
 3- α -pipecolino-N-nitrososydnnonimine m.p. 83—84° C. (with decomposition)
 3,3'-(1,4-piperazino-diyl)-N,N-dinitrosobis-sydnnonimine m.p. 168—169° C. (with decomposition)
 3-(N-methylpiperazino)-N-nitrososydnnonimine m.p. 132—133° C. (with decomposition)

20 WHAT WE CLAIM IS:—

1. An N-acyl sydnnonimine derivative of the formula



(I),

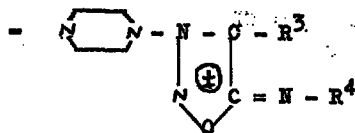
- 25 wherein R³ is a hydrogen atom or a lower alkyl group having one to five carbon atoms; R⁴ is —NO, an R⁵CO— group derived from a carboxylic acid, a carbamic acid or a carbonic acid, R⁵ being hydrogen or a radical containing one to nine carbon atoms, an R⁶CO— group derived from a naturally occurring amino acid, wherein R⁶COOH forms the amino acid or its N-acyl derivatives, or an R⁷SO₂— group derived from a sulphonic acid wherein R⁷ is a radical containing one to seven carbon atoms; and R¹ and R² are the same or different and each represent a lower alkyl group 30 having one to five carbon atoms, a lower alkenyl group having two to five carbon atoms, or an aralkyl group having seven to nine carbon atoms, or R¹ and R² taken together with the adjacent N-atom represent morpholino, pipecolino, a



radical wherein n is 4, 5 or 6, an



radical wherein R is an alkyl group having one to five carbon atoms, or the radical:



(III),

wherein R^3 and R^4 have the same meaning as above, or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein the group $\begin{array}{c} R^1 \\ >N- \\ R^2 \end{array}$ is morpholino.
3. 3-morpholino-N-benzoylsydnnonimine.
4. 3-morpholino-N-carboethoxysydnnonimine.
5. A method for producing a compound of the formula:



(I),

wherein R^3 is a hydrogen atom or a lower alkyl group having one to five carbon atoms, R^4 is an acyl group, R^1 and R^2 are the same or different and each represent a lower alkyl group having one to five carbon atoms, a lower alkenyl group having two to five carbon atoms, or an aralkyl group having seven to nine carbon atoms, or R^1 and R^2 taken together with the adjacent N-atom represent morpholino, pipercolino, a

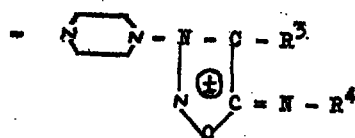


radical wherein n is 4, 5 or 6, an



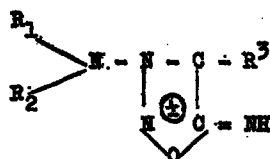
radical, wherein R is an alkyl group having one to five carbon atoms, or the radical:





(III),

wherein R^3 and R^4 have the same meaning as above, or a pharmaceutically acceptable salt thereof, wherein a compound of the formula:



(II),

5 in which R^1 , R^2 and R^3 having the same meaning as above is reacted with an appropriate acylating agent. 5

6. A compound as claimed in claim 1 substantially as herein described with reference to any of the specific examples.

10 7. A method as claimed in claim 5 substantially as herein described with reference to any of the specific examples. 10

8. Compounds as claimed in claim 1 when prepared by a method as claimed in claim 5 or 7.

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