(51) International Patent Classification 5:
C07C 245/24, A61K 31/00
A61K 31/395, C07D 207/50
C07D 211/98, 241/54, 265/30
C07D 205/00

(11) International Publication Number: WO 93/07114

(43) International Publication Date: 15 April 1993 (15.04.93)

(21) International Application Number: PCT/US92/08078

(22) International Filing Date: 23 September 1992 (23.09.92)

(30) Priority data:
764,908 24 September 1991 (24.09.91) US

(71) Applicant: THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Box OTT, Bethesda, MD 20892-9902 (US).

(72) Inventors: KEEFER, Larry, Kay; 7016 River Road, Bethesda, MD 20817 (US). DUNAMS, Tambra, Marie; 1541 Melton Drive, Florence, AL 35630 (US). SAAVEDRA, Joseph, Euclid; 7189 Brown's Lane, Thurmond, MD 21708 (US).


Published
With international search report.

(54) Title: OXYGEN SUBSTITUTED DERIVATIVES OF NUCLEOPHILE-NITRIC OXIDE ADDUCTS AS NITRIC OXIDE DONOR PRODRUGS

(57) Abstract

There are disclosed cardiovascularly active compounds possessing antihypertensive properties, and pharmaceutical compositions containing these agents and a method of treating cardiovascular disorders with the compounds. The active components of the pharmaceutical compositions are compounds of formula (I) wherein R₁ and R₂ are independently chosen from straight chain and branched chain alkyl and olefinic groups, which may be unsubstituted or substituted; or R₁ and R₂ together with the nitrogen atom they are bonded to form a heterocyclic group; and R₃ is a pharmaceutically acceptable organic group selected from alkyl and olefinic groups which may be unsubstituted or substituted, acyl, a sulfonyl, sulfanyl, sulfonyl, carbonate, or carbamate derivative; or R₃ is a group of the formula: (CH₂)nONN(O)NR₁R₂, wherein n is 2-8, and R₁ and R₂ are as described above. Novel compounds are disclosed wherein at least one of R₁, R₂ and R₃ is an olefinic group or heteroatom-substituted straight or branched chain alkyl or olefinic group. Novel methods of synthesizing the compounds are also disclosed.

IN VITRO VASORELAXANT EFFECTS

\[
\text{R}_1\text{R}_2\text{N}=\text{N}+\text{O}
\]

\[
\text{N}+\text{OR}_3
\]

(1)
<table>
<thead>
<tr>
<th>Code</th>
<th>Country</th>
<th>Code</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>Austria</td>
<td>CA</td>
<td>Canada</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
<td>CG</td>
<td>Central African Republic</td>
</tr>
<tr>
<td>BR</td>
<td>Barbados</td>
<td>CI</td>
<td>Côte d'Ivoire</td>
</tr>
<tr>
<td>BE</td>
<td>Belgium</td>
<td>CM</td>
<td>Cameroon</td>
</tr>
<tr>
<td>BF</td>
<td>Burkina Faso</td>
<td>CS</td>
<td>Czechoslovakia</td>
</tr>
<tr>
<td>BG</td>
<td>Bulgaria</td>
<td>CZ</td>
<td>Czech Republic</td>
</tr>
<tr>
<td>BJ</td>
<td>Benin</td>
<td>DE</td>
<td>Germany</td>
</tr>
<tr>
<td>BR</td>
<td>Brazil</td>
<td>DK</td>
<td>Denmark</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
<td>ES</td>
<td>Spain</td>
</tr>
<tr>
<td>FR</td>
<td>France</td>
<td>FI</td>
<td>Finland</td>
</tr>
<tr>
<td>GA</td>
<td>Gabon</td>
<td>GB</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>GN</td>
<td>Guinea</td>
<td>GR</td>
<td>Greece</td>
</tr>
<tr>
<td>HU</td>
<td>Hungary</td>
<td>IE</td>
<td>Ireland</td>
</tr>
<tr>
<td>IT</td>
<td>Italy</td>
<td>JP</td>
<td>Japan</td>
</tr>
<tr>
<td>KP</td>
<td>Democratic People's Republic of Korea</td>
<td>MR</td>
<td>Mauritania</td>
</tr>
<tr>
<td>MR</td>
<td>Mauritania</td>
<td>MW</td>
<td>Malawi</td>
</tr>
<tr>
<td>NL</td>
<td>Netherlands</td>
<td>NO</td>
<td>Norway</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
<td>PL</td>
<td>Poland</td>
</tr>
<tr>
<td>PT</td>
<td>Portugal</td>
<td>RO</td>
<td>Romania</td>
</tr>
<tr>
<td>RU</td>
<td>Russian Federation</td>
<td>SD</td>
<td>Sudan</td>
</tr>
<tr>
<td>SK</td>
<td>Slovakia</td>
<td>SN</td>
<td>Senegal</td>
</tr>
<tr>
<td>SU</td>
<td>Soviet Union</td>
<td>TD</td>
<td>Chad</td>
</tr>
<tr>
<td>TG</td>
<td>Togo</td>
<td>UA</td>
<td>Ukraine</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
<td>VN</td>
<td>Viet Nam</td>
</tr>
<tr>
<td>VN</td>
<td>Viet Nam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FIELD OF THE INVENTION

The present invention generally relates to the treatment of patients suffering from cardiovascular disorders requiring a lowering of the blood pressure. Certain novel compounds and pharmaceutical compositions which release nitric oxide on in vivo activation are utilized in the method.

BACKGROUND OF THE INVENTION

Endothelium-derived relaxing factor (EDRF) is a labile humoral agent which is part of a cascade of interacting agents involved in the relaxation of vascular smooth muscle. EDRF is thus important in the control of vascular resistance to blood flow and in the control of blood pressure. Some vasodilators act by causing EDRF to be released from endothelial cells. (See Furchgott, Ann. Rev. Pharmacol. Toxicol. 24, 175-197, 1984.) Recently, Palmer et al. have presented evidence suggesting that EDRF is identical to the simple molecule, nitric oxide, NO (Nature 317, 524-526, 1987), though there remains controversy on this point. It has been hypothesized for years that many nitrovasodilators that mimic the effect of EDRF, like glyceryl trinitrate, amyl nitrite, NaNO₂, and sodium nitroprusside (SNP), do so by virtue of their conversion to a common moiety, namely NO, which is also a vasodilator. (See Kruszyna et al., Tox. & Appl. Pharmacol. 91, 429-438, 1987; Ignarro, FASEB J. 2, 31-36, 1989; Ignarro et al., J. Pharmacol. Exper. Therapeutics 218 (3), 739-749, 1981.)

Some of the compounds suitable for use in the method of the present invention are previously described in scientific literature. However, there is no suggestion in the prior art that any of the disclosed compounds are antihypertensive; indeed there is no suggestion in the prior art that they have any pharmaceutical use. Four compounds are described in Reilly, U.S. Patent 3,153,094, and in Longhi and Drago, Inorg. Chem. 2, 85-88, 1963, and

Related inventions (to the present invention) are described in U.S. patent applications SN 07/316,958, filed 2/28/89 (now U.S. Patent No. 4,954,526), SN 07/409,552, filed 9/15/89 (now U.S. Patent No. 5,039,705), SN 07/423,279, filed 10/18/89, SN 07/585,793, filed 9/20/90, SN 07/743,892, filed 8/12/91, SN 07/764,906, filed 9/24/91, SN 07/764,908, filed 9/24/91, SN 07/858,885, filed 3/27/92, SN 07/867,759, filed 4/13/92, and SN 07/935,565 filed 8/24/92 each of which is incorporated herein by reference.

**SUMMARY OF THE INVENTION**

It has now been discovered that a class of compounds of the structure:

\[
R_1R_2N-N=O
\]

\[
\text{N-OR}_3
\]

wherein \(R_1\) to \(R_3\) are organic moieties defined below, are long-acting cardiovascular agents and thus are useful for treating cardiovascular disorders in which lowering the blood pressure has a beneficial result. It is believed that these compounds function by metabolic cleavage of the \(R_3\) group to produce an anion that releases NO in the blood after administration to a mammal; however, the invention should not be limited by this hypothesis.

**BRIEF DESCRIPTION OF THE DRAWING**

The present invention will become more fully understood from the detailed description given here and below and the accompanying drawing which is given by way of illustration only, and thus is not limitative of the present invention, and wherein:
Figure 1 - shows the dose response curve for Et₂N-N(O)NOEt, which was obtained by testing the compound via a standard isolated vascular ring preparation.

**DETAILED DESCRIPTION OF THE INVENTION**

The present invention provides for pharmaceutical compositions comprising a compound of formula I,

\[
R_1R_2N-N=O \\
\mid \\
N-OR_3
\]

wherein \( R_1 \) and \( R_2 \) are independently chosen from \( C_{1-12} \) straight chain alkyl, \( C_{1-12} \) alkoxy or acyloxy substituted straight chain alkyl, \( C_{2-12} \) hydroxy or halo substituted straight chain alkyl, \( C_{3-12} \) branched chain alkyl, \( C_{3-12} \) hydroxy, halo, alkoxy, or acyloxy substituted branched chain alkyl, \( C_{3-12} \) straight chain olefinic and \( C_{3-12} \) branched chain olefinic which are unsubstituted or substituted with hydroxy, alkoxy, acyloxy, halo or benzyl, or \( R_1 \) and \( R_2 \) together with the nitrogen atom to which they are bonded form a heterocyclic ring selected from the group consisting of:

\[
\begin{align*}
\text{(CH}_2)_w \text{N} \rightarrow \text{N} \\
\text{R}_4 \\
\text{(CH}_2)_y \\
\text{N} \rightarrow \text{N}
\end{align*}
\]

and

\[
\text{N(CH}_2\text{CH}_2\text{O})_z - \text{CH}_3\text{CH}_2
\]

wherein

- \( w \) is 1 to 12, \( y \) is 1 or 2, \( z \) is 1 to 5, \( R_4 \) is hydrogen, \( C_{1-8} \) straight chain alkyl, \( C_{3-8} \) branched chain alkyl, \( C_{3-8} \) cycloalkyl, unsubstituted or substituted aryl, such as phenyl, tolyl or the like, and \( R_5 \) is hydrogen, \( C_{1-6} \) straight chain alkyl or \( C_{3-6} \) branched chain alkyl; and \( R_3 \)
is a group selected from C₁₋₁₂ straight chain and C₃₋₁₂ branched chain alkyl which are unsubstituted or substituted by hydroxy, halo, acyloxy or alkoxy, C₂₋₁₂ straight chain or C₃₋₁₂ branched chain olefinic which are unsubstituted or substituted by halo, alkoxy, acyloxy or hydroxy, C₁₋₁₂ unsubstituted or substituted acyl, a sulfonyl, sulfinyl, sulfinyl, or carbonate derivative, and a carbamate derivative, as for example, carboxamido; or R₃ is a group of the formula -(CH₂)ₙ-ON=N(O)NR₁R₂, wherein n is an integer of 2-8, and R₁ and R₂ are as defined above; with the proviso that R₁, R₂ and R₃ do not contain a halo or a hydroxy substituent attached to a nitrogen or an oxygen atom; and a pharmaceutically acceptable carrier. By straight chain alkyl is meant the non-branched methyl, ethyl, n-propyl, n-butyl, n-decyl, and similar groups. By branched chain alkyl is meant groups like 3-methylopentyl, 2-ethylbutyl, etc.

The compounds of Formula I are long-acting cardiovascular antihypertensives. They are useful for lowering the blood pressure and treating any cardiovascular disorder in which a lowering of the blood pressure has a beneficial effect. As such, the invention also provides an effective method of lowering the blood pressure in a patient in need thereof by administering a pharmaceutical composition containing an effective amount of a compound of Formula I to the patient in need thereof.

Many of the compounds of Formula I, including, for example, wherein R₁, R₂ or R₃ are a heteroatom-substituted (e.g., hydroxy, halo, alkoxy, or acyloxy substituted) straight or branched chain alkyl, or an olefinic group, are novel.

The methods of synthesis of the Formula I compounds are in many cases similar to those disclosed by Reilly, U.S. Patent 3,153,094. Other Examples are best obtained by N-derivatization of the 0-alkylated primary amine complexes (Formula I, R₁=H*R₂) disclosed in U.S. Patent 4,954,526. In addition, novel synthesis methods are
provided herein. The following Experimental Section and the Examples therein illustrate some of the procedures which may be utilized to prepare compounds encompassed hereby. The following Examples, however, are not limiting to the present invention.

EXPERIMENTAL

Proton NMR spectra were recorded using a Varian XL-200 Spectrometer. Spectra were obtained in deuteriochloroform. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane. Low and high resolution mass spectral (MS) measurements were carried out on a VG-Micromass Model 7070 Mass Spectrometer. The IR spectra were obtained on a Perkin-Elmer 467 spectrophotometer. Gas chromatographic analyses were carried out on a Shimadzu Model 4BM gas chromatograph equipped with a Hewlett-Packard 18652A A/D converter coupled to the recorder of a flame ionization detector. A 10% Carbowax 20M (+2% KOH) on 80/100 Gaschrom Q glass column was used unless otherwise specified. Ultraviolet (uv) spectra were run as ethanolic or aqueous solutions on a Beckman UV spectrophotometer unless specified otherwise. Elemental analyses were done at Galbraith Laboratories Inc. (Knoxville, Tennessee), and at Atlantic Microbe (Norcross, Georgia).

EXAMPLE 1

1-n-PROPOXY-2-OXO-3,3-DIETHYL-1-TRIAZENE

\[
\text{[(C}_2\text{H}_5\text{)N}_2\text{O}_2\text{C}_3\text{H}_7\text{]} \]

A partial solution of 1.55 g (0.01 mol) of 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt (i.e., 3,3-diethyl-1,2-dioxotriazene, mono sodium salt) in 10 ml of anhydrous N,N-dimethylformamide (DMF) was treated with 1.46 ml (0.015 mol) of n-propyl iodide at 25°C. Within 5 minutes of stirring a homogeneous solution resulted, which gradually formed a precipitate (NaI) upon further
reaction. The reaction mixture was stirred at room
5 temperature overnight. To this was added 20 ml of
distilled water, and the product was extracted into ether
and dried over sodium sulfate. Gas liquid
chromatographic (GLC) analysis of the solution gave the
following relative composition: 43% DMF, 1%
nitrosodiethylamine, and 56% 1-n-propoxy-2-oxo-3,3-
diethyl-1-triazene. The solution was filtered through a
pad of magnesium sulfate, and the solvent was removed on
a rotary evaporator. The residual oil was fractionally
distilled under vacuum to give 601 mg (33%) of pure
product: bp 70-72°C at 0.5 mmHg; NMR, δ 0.972 (t, 3H),
1.093 (t, 6H), 1.7945 (m, 2H), 3.079 (q, 4H), 4.235 (t, 2H);
IR(film) 2980, 2945, 2885, 1505, 1384, 1230, 1143, 1066,
10 1005, 841 cm⁻¹; uv, λ_max (ε), 237 (8,049); MS, m/z (%),
176 (M⁺, 1), 145 (1), 132 (1), 103 (100), 102 (16), 87
15 (4), 75 (38), 58 (3), 57 (6), 56 (13), 47 (12), 44 (32),
43 (62), 42 (22), 41 (27).
Exact mass: calculated for C₇H₁₅N₃O₂, 176.1499; found for
MH⁺, 176.1410.
Analysis: C, H, N. Calculated for C₇H₁₅N₃O₂: C, 48.00;
10 H, 9.71; N, 24.00. Found: C, 47.80; H, 9.39; N, 23.54.

\[ \text{Et}_2\text{NN(NO)O}^+\text{Na}^+ + \text{n-PrI} \xrightarrow{\text{DMF, 25°C}} \text{Et}_2\text{NN(O)NO(n-Pr)} \]

EXAMPLE 2

1-METHOXY-2-OXO-3,3-DIETHYL-1-TRIAZENE

\[
[(\text{C}_2\text{H}_5)_2\text{NN}_2\text{O}_2\text{CH}_3]\]

To a solution of 2.24 g (0.014 mol) of 2,2-diethyl-1-
nitroso-1-oxyhydrazine sodium salt in 14 ml of absolute
methanol was slowly added 1.99 ml (0.021 mol) of dimethyl
sulfate. The reaction was distinctly exothermic, and the
resulting solution was stirred at 25°C for 72 hours. The
methanol was evaporated in vacuo; the residue was taken
up in 20 ml of distilled water and extracted with
dichloromethane. The organic layer was separated, dried
over sodium sulfate and filtered through a layer of magnesium sulfate. The solvent was removed on a rotary evaporator and the residual oil was vacuum distilled to give 469 mg (23%) of 1-methoxy-2-oxo-3,3-diethyl-1-triazene: bp 44°C at 0.7 mmHg; NMR, δ 1.101 (t, 6H), 3.102 (q, 4H), 4.058 (s, 3H); IR (film) 2989, 2945, 2875, 1500, 1450, 1383, 1230, 1143, 1058, 1000, 935, 840 cm⁻¹; uv, \( \lambda_{\text{max}} (\epsilon) \), 234 nm (7,945); MS, m/z (%), 147 (M⁺,3), 103(6), 102(100), 87(27), 86(2), 85(5), 84(4), 74(3), 71(3), 58(4), 57(32), 56(33), 54(92), 42(44), 41(8).

Exact mass: calculated for C₅H₁₄N₃O₂, 148.1086; found for MH⁺, 148.1109.

Analysis: C, H, N. Calculated for C₅H₁₃N₃O₂:
C, 40.82; H, 8.84; N, 28.57. Found: C, 40.81; H, 8.86; N, 28.62.

\[
\text{Et₂NN(NO)O⁻Na⁺ + Me₂SO₄} \xrightarrow{\text{MeOH, 25°C}} \text{Et₂NN(O)NMe}
\]

EXAMPLE 3

1-(2-HYDROXYPROPOXY)-2-OKO-3,3-DIETHYL-1-TRIAZENE

To a slurry of 4.2 g (0.027 mol) of 2,2-diethyl-1-nitroso-1-oxyhydratine sodium salt in anhydrous tetrahydrofuran was added 2.1 ml (0.03 mol) of propylene oxide. The slurry was stirred at reflux for 20 hours. The reaction was treated with 20 ml of distilled water and the tetrahydrofuran was removed on a rotary evaporator. The aqueous layer was extracted with dichloromethane, dried over sodium sulfate, filtered through a pad of magnesium sulfate and evaporated in vacuo. The residual oil was vacuum distilled to give 298 mg (6%) of product: bp 140°C at 0.7 mmHg. As an alternative, a more efficient purification procedure than vacuum distillation was developed. The product was chromatographed on dry packed Activity III silica gel, eluted with 2:1 dichloromethane:ethyl acetate, and recovered from the
eluate by evaporating the solvent: NMR, δ 1.100 (t, 6H), 1.2205 (d, 3H), 3.122 (q, 4H), 4.103–4.264 (3H, m); IR (film), 3430, 2990, 2960, 2880, 1500, 1454, 1370, 1230, 1058, 1010, 952, 845 cm⁻¹; uv, λ_max (ε), 236 (7,204); MS, m/z (%), 192 (MH⁺, 7), 132 (8), 164 (14), 103 (100), 102 (66), 86 (22), 84 (34), 75 (53), 59 (53), 58 (11), 57 (16), 56 (26), 49 (52), 47 (15), 45 (69), 44 (75), 43 (23), 42 (44), 41 (39).

Exact mass: calculated for C₇H₁₈N₃O₃, 192.1348; found for MH⁺, 192.1417.

\[
\text{Et₂NN(NO)O}^- \text{Na}^+ + \text{Me-CH-CH₂} \xrightarrow{\text{THF, reflux}} \text{Et₂NN(O)NOCH₂CHOHCH₃}
\]

**EXAMPLE 4**

**1-ETHOXY-2-OXO-3,3-DIETHYL-1-TRIAZENE**

\([(C₂H₅)₂NN₂O₂C₂H₅]\)

To a solution of 19.26 g (0.124 mol) 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt in 100 ml of freshly distilled (from Mg) methanol was added 31 g (0.2 mol) of diethyl sulfate dropwise, with stirring. The resulting heterogeneous mixture was stirred for 18 hours at 25°C. The reaction mixture was evaporated in vacuo and the residual blend was extracted with dichloromethane. The organic layer was washed with aqueous sodium hydroxide solution, dried over sodium sulfate and filtered through a layer of magnesium sulfate. The solvent was removed on a rotary evaporator and the residue was vacuum distilled to give 8.9 g (45%) of a pale yellow product: bp 52°C at 0.7 mmHg; NMR, δ 1.097 (t, 6H), 1.39 (t, 3H), 3.086 (q, 4H), 4.34 (q, 2H); IR (film) 2985, 2940, 2905, 1510, 1450, 1390, 1230, 1200, 1060, 1010, 925, 830 cm⁻¹; uv, λ_max (ε) 235 nm (6717); MS, m/z (%), 162 (MH⁺, 100), 161 (M⁺, 7), 145 (30), 131 (16), 127 (12), 103 (34), 99 (3), 73 (21), 72 (96), 44 (44).

\[
\text{Et₂NN(NO)O}^- \text{Na}^+ + \text{Et₂SO₄} \xrightarrow{25°C} \text{Et₂NN(O)NOEt}
\]
EXAMPLE 5

1-ALLYLOXY-2-OXO-3,3-DIETHYL-1-TRIAZENE

\[ \text{[(C}_2\text{H}_5)_2\text{NN}_2\text{O}_2\text{CH}_2\text{CH}=\text{CH}_2] \]

A solution of 2.48 g (0.016 mol) of 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt in anhydrous \( N,N \)-di-methylformamide (DMF) was cooled to 0°C. To the solution was added 1.73 ml (0.02 mol) of allyl bromide dropwise; the solution was allowed to warm up gradually to room temperature and stirred overnight under nitrogen. The reaction mixture was dissolved in 75 ml of water and extracted with ether. The organic layer was dried over sodium sulfate and filtered through a layer of magnesium sulfate; the solvent was removed on a rotary evaporator. The residual oil was vacuum distilled to give 1.01 g (36%) of product: bp 76-79°C at 0.6 mmHg; IR(film) 3090, 2985, 2910, 2880, 1510, 1450, 1385, 1235, 1060, 1020, 1000, 940, 845 cm\(^{-1}\); uv, \( \lambda_{\text{max}} \) (\( \varepsilon \)), 243 (8,868); NMR, \( \delta \) 1.091 (t, 6H), 3.094 (q, 4H), 4.734 (t, 1H), 4.764 (t, 1H), 5.333 (m, 2H), 6.024 (m, 1H); MS, m/z (%), 174 (MH\(^+\), 3), 157(2), 143(40), 132(26), 103(25), 102(100), 99(2), 98(30), 87(16), 85(9), 75(5), 57(20), 56(36), 44(82), 42(83).

Exact mass: calculated for C\(_7\)H\(_{15}\)N\(_2\)O\(_2\), 173.1164; found for M\(^+\), 173.1135.

\[ \text{Et}_2\text{NN(NO)}\text{O}^-\text{Na}^+ + \text{CH}_2=\text{CHCH}_2\text{Br} \xrightarrow{\text{DMF, } 25^\circ\text{C}} \text{Et}_2\text{NN(O)NOCH}_2\text{CH}=\text{CH}_2 \]

EXAMPLE 6

1-(METHOXYMETHYLENEOXY)-2-OXO-3,3-DIETHYL-1-TRIAZENE

\[ \text{[(C}_2\text{H}_5)_2\text{NN}_2\text{O}_2\text{CH}_2\text{OCH}_3] \]

To a slurry of 3.5 g (0.023 mol) of 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt in 40 ml of anhydrous THF was added 3 g of anhydrous sodium carbonate. The well-stirred mixture was cooled to 0°C followed by the dropwise addition of chloromethylmethylether. The ice-bath was removed and the reaction mixture was stirred at room temperature under argon for 72 h. The solvent was removed on a rotary evaporator to give 1.89 g of an amber...
liquid. The crude product was vacuum distilled to give 1.68 g (41%) of 1-(methoxymethyleneoxy)-2-oxo-3,3-
diethyl-1-triazene: bp 67-68°C at 1.2 mmHg; NMR, δ 1.113
(t, 6H), 3.1645 (q, 4H), 3.498 (s, 3H), 5.262 (s, 2H);
IR(film) 2985, 2940, 1515, 1440, 1380, 1235, 1165, 970
cm⁻¹, uv (MeOH), λmax(ε), 227 (6,511); MS, m/z (%), 147
(M⁺-30, 5), 117 (M⁺-60, 100), 102 (48), 97 (10), 89 (7),
87 (15), 86 (42), 73 (14), 72 (21), 71 (20), 70 (13), 61
(13), 58 (63), 57 (72), 56 (99).

Analysis: C, H, N. Calculated for C₆H₁₃N₃O₃: C, 40.68; H,
8.47; N, 23.73. Found: C, 40.69; H, 8.65; N, 23.90.

\[ \text{Et}_2\text{NN(}\text{NO})\text{O}^-\text{Na}^+ + \text{ClCH}_2\text{OCH}_3 \rightarrow \text{Et}_2\text{NN(}\text{O})\text{NOCH}_2\text{OCH}_3 \]

EXAMPLE 7

1-(2-HYDROXYETHOXY)-2-OKO-3,3-DIETHYL-1-TRIAZENE

(C₂H₅)₂N₂O₂CH₂CH₂OH

To a slurry of 1.51 g (0.0097 mol) of 2,2-diethyl-1-
nitroso-1-oxyhydrazine sodium salt in 20 ml of anhydrous
THF was added 1.42 ml (0.02 mol) of freshly distilled 2-
bromoethanol. The reaction mixture was heated at reflux,
under nitrogen overnight. The mixture was allowed to
cool to room temperature, and the solvent was removed on
a rotary evaporator. The residue was chromatographed on
silica gel and eluted with 1:1 dichloromethane:ethyl
acetate. The fractions were analyzed by GLC using 3% OV-
17 as the stationary phase. The solutions containing the
product were combined and evaporated in vacuo to give 160
mg of product: IR (film) 3445, 2990, 2950, 2880, 1505,
1455, 1285, 1065, 1015, 890 cm⁻¹; NMR (CDCl₃), δ 1.105
(t, 6H), 3.127 (q, 4H), 3.920 (m, 2H), 4.391 (m, 2H); MS, m/z
(%), 178 (MH⁺, 3), 147 (1), 132 (9), 118 (2), 104 (5),
103 (100), 102 (56), 87 (10), 75 (6), 76 (3), 75 (29), 73
(3), 73 (6), 71 (14), 57 (14), 56 (20), 55 (5).

Exact mass: calculated for C₆H₁₆N₃O₃, 178.1191;
found for MH⁺, 178.1188.
$$\text{Et}_2\text{NN(NO)}\text{O}^-\text{Na}^+ + \text{BrCH}_2\text{CH}_2\text{OH} \rightarrow \text{Et}_2\text{NN(O)}\text{NOCH}_2\text{CH}_2\text{OH}$$

**EXAMPLE 8**

1-(2-Bromoethoxy)-2-oxo-3,3-diethyl-1-triazene

$$(\text{C}_2\text{H}_5)_2\text{NN}_2\text{O}_2\text{CH}_2\text{CH}_2\text{Br}$$

A partial solution of 2.7 g (17.4 mmol) of 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt in 17 ml of DMF was cooled to 0°C under a stream of nitrogen. A solution of 1.4 ml of 1,2-dibromoethane in anhydrous THF was added dropwise. Once addition was complete, the ice bath was removed, and the resulting mixture was stirred at 25°C overnight. To the reaction mixture was added 200 ml of water and the product was extracted with ether. The organic layer was separated and washed with water. The solution was dried over sodium sulfate and filtered through a layer of magnesium sulfate. Evaporation of the solvent gave 2.1 g of crude product. The product was chromatographed through silica gel and eluted with dichloromethane to give 706 mg of pure 1-(2-bromoethoxy)-2-oxo-3,3-diethyl-1-triazene: IR (film) 2980, 2965, 2880, 1510, 1500, 1450, 1383, 1241, 1235, 1070, 1005 cm$^{-1}$; NMR, $\delta$ 1.104 (t, 6H), 3.124 (q, 4H), 3.582 (t, 2H), 4.522 (m, 2H); UV, $\lambda_{\text{max}}$(e), 233 (8,977); MS, m/z (%), 242 (MH$^+$, $^{81}\text{Br}$, 8), 240 (MH$^+$, $^{79}\text{Br}$, 9), 224 (4), 223 (4), 211 (37), 209 (36), 132 (41), 109 (56), 107 (56), 101 (64), 102 (100), 84 (32), 72 (32), 56 (36).

Exact mass: calculated for $\text{C}_6\text{H}_{14}^{81}\text{BrN}_3\text{O}_2$, 242.0327, and for $\text{C}_6\text{H}_{14}^{79}\text{BrN}_3\text{O}_2$, 240.0347; found for MH$^+$, 242.0356 and 240.0417.
EXAMPLE 9

SYNTHESIS OF FORMULA I COMPOUNDS BY N-SUBSTITUTION
OF 1-ALKOXY-2-OXO-3-ALKYL-1-TRIAZENES

Synthesis of starting material, 1-methoxy-2-oxo-3-
isopropyl-1-triazene (i-PrNHN\(_2\)O\(_2\)Me).

A solution of 9.2 g (0.065 mol) of 2-isopropyl-1-
nitroso-1-oxhydrazine sodium salt in 65 ml of anhydrous
methanol was cooled to 0°C. To the cold solution was
added 5 ml (0.07 mol) of freshly distilled dimethyl
sulfate, and the mixture was stirred in the cold for 1
hour. The ice bath was removed and the resulting
solution was stirred at 25°C overnight. The solvent was
removed on a rotary evaporator; the residue was taken up
in dichloromethane and washed with 5% aqueous sodium
hydroxide solution. The organic layer was dried over
sodium sulfate and filtered through a pad of magnesium
sulfate; the solvent was removed in vacuo. The residual
oil crystallized on standing at 0°C and was
recrystallized from ether to give 3.64 g (42%) of 1-
methoxy-2-oxo-3-isopropyl-1-triazene: mp 29-30°C; IR
(film), 3245, 2982, 2950, 1570, 1468, 1390, 1275, 1205,
1605, 1012, 830 cm\(^{-1}\); uv (H\(_2\)O), \(\lambda_{max}\)(\(\epsilon\)), 242 nm (6,495);
NMR, \(\delta\) 1.184 (d, 6H), 3.93 (m, 1H), 3.977 (s, 3H), 5.90
(b, 1H); MS, m/z (%), 133 (M\(^+\), 6), 132 (11), 118 (32), 102
(18), 88 (42), 87 (7), 86 (10), 85 (8), 73 (6), 61 (9),
60 (5), 57 (12), 56 (17), 49 (21), 47 (20), 45 (32), 44
(7), 43 (100).

Exact mass: calculated for C\(_4\)H\(_{11}\)N\(_3\)O\(_2\), 133.0851; found for
M\(^+\), 133.0859.

\[
\text{i-PrNHN(NO)O}^-\text{Na}^+ + \text{Me}_2\text{SO}_4 \xrightarrow{0^\circ \text{ to } 25^\circ\text{C}} \text{i-PrNHN(O)NMe}
\]
EXAMPLE 9A

1-METHOXY-2-OXO-3-ISOPROPYL-3-METHYL-1-TRIAZENE

(CH₃)₂CHN(CH₃)N₂O₂CH₃

To a solution of 200 mg (1.5 mmol) of the 1-methoxy-2-oxo-3-isopropyl-1-triazene prepared above in 1.5 ml of anhydrous THF and 0.5 ml of N,N-dimethylformamide (DMF) was added 200 mg of finely powdered sodium hydroxide.

The resulting mixture was stirred at room temperature for 15 minutes, then treated with 0.187 ml (3 mmol) of methyl iodide and stirred for 12 hours at 25°C under nitrogen.

To the reaction mixture was added 10 ml of water and the product was extracted with ether. The solution was dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified on silica gel using 5:1 dichloromethane:ethyl acetate as the eluant.

Fractions were monitored by gas chromatographic analysis on a 3% OV-210 packed glass column. The fractions containing the product were combined and concentrated. The residual oil was vacuum distilled to give a 60% yield of 1-methoxy-2-oxo-3-isopropyl-3-methyl-1-triazene: bp 52°C at 1 mmHg; IR (film), 2980, 2940, 2880, 1500, 1450, 1370, 1250, 1060, 1001, 940, 738 cm⁻¹; UV (H₂O), λ_max (ε), 236 (6,391); NMR, δ 1.126 (d, 6H), 2.840 (s, 3H), 3.861 (m, 1H), 4.028 (s, 3H); MS, m/z (%), 147 (M⁺, 3), 132 (32), 102 (47), 97 (11), 95 (8), 91 (7), 88 (3), 87 (14), 85 (24), 71 (70), 70 (9), 69 (19), 68 (4), 67 (8), 60 (12), 57 (51), 56 (36), 55 (32), 49 (13), 45 (27), 43 (100), 42 (34).

Exact mass: calculated for C₈H₁₃N₃O₂, 147.1007; found for M⁺, 147.0982.
EXAMPLE 9B

1-METHOXY-2-OXO-3-ISOPROPYL-3-ALLYL-1-TRIAZENE

(CH₃)₂CHN(CH₂-CH=CH₂)N₂O₂CH₃

To a solution of 399 mg (3 mmol) of 1-methoxy-2-oxo-3-
5
isopropyl-1-triazene in 20 ml of anhydrous THF was added
1 g of powdered sodium hydroxide. To the stirred mixture
was added 433 µl (5 mmol) of allyl bromide; the mixture
was heated at reflux under nitrogen for 2 hours. The
mixture was evaporated to dryness, and the residue was
extracted with dichloromethane. The extract was washed
10
with aqueous sodium bisulfite, dried over sodium sulfate,
and filtered through a layer of magnesium sulfate.
Evaporation of the solvent gave 454 mg of a brown oil.
The oil was chromatographed through silica gel and eluted
15
with 5:1 dichloromethane:ethyl acetate to give 345 mg of
an orange oil. This oil was further purified by
fractional vacuum distillation to give 180 mg of pure 1-
methoxy-2-oxo-3-isopropyl-3-allyl-1-triazene as a pale
yellow oil: bp 74°C at 1.9 mmHg; IR (film) 3085, 2982,
20
2942, 1502, 1460, 1445, 1390, 1238, 1065, 1006, 942 cm⁻¹;
NMR, δ 1.162 (d, 6H), 3.474 (septet, 1H), 3.646 (d, 2H),
4.027 (s, 3H), 5.204 (m, 2H), 5.832 (m, 1H).

\[
\begin{align*}
\text{i-PrHNN(O)NMe} & \quad \xrightarrow{\text{CH₂-CH₂Br \quad NaOH}} \quad \text{i-PrN(CH₂-CH=CH₂)N(O)NMe} \\
\end{align*}
\]

EXAMPLE 10

1-METHOXY-2-OXO-3-METHYL-3-(2-HYDROXYPROPYL)-1-TRIAZENE

CH₃CHOHCH₂N(CH₃)N₂O₂CH₃

A solution of 10 g (0.112 mol) of N-methyl-N-(2-
30
hydroxypropyl)amine in 10 ml of triethylamine and 20 ml
of petroleum ether was placed in a Parr bottle. The
solution was cooled to -80°C and evacuated, then charged
with 60 psi of nitric oxide. After 72 hours the pressure
was released, and the reaction mixture was flushed with
nitrogen. To the mixture was added 20 ml of 25% sodium
methoxide in methanol. The mixture was stirred for 10
minutes and the petroleum ether was removed on a rotary evaporator. The residue was taken up in 75 ml of methanol and cooled at 0°C, followed by the dropwise addition of 10 ml of dimethyl sulfate. The mixture was concentrated on a rotary evaporator, and the residue was treated with 50 ml of 10% NaOH. The solution was extracted with dichloromethane, dried over sodium sulfate, and filtered through a layer of magnesium sulfate. Evaporation of the solvent gave 1.47 g of crude product. The crude material was chromatographed on silica gel and eluted with 2:1 dichloromethane:ethyl acetate to give 1.2 g of product: NMR, δ 1.199 (d, 3H), 1.922 (m, 1H), 3.015 (s, 3H), 3.303 (m, 2H), 3.969 (m, 1H), 4.033 (s, 3H); IR (film), 3450, 2980, 2945, 1595, 1450, 1340, 1230, 1060, 978, 860, 770 cm⁻¹; uv (H₂O), λₘₐₓ(e), 237 nm (5,759).

\[
\text{MeCHOHCH₂NHMe } \xrightarrow{1.\text{NO, NaOH}} \text{MeCHOHCH₂N(Me)N(O)NMe}_2
\]

**EXAMPLE 11**

Utilizing the procedure set forth in Example 1, and substituting one of the following compounds for 2,2-diethyl-1-nitroso-1-oxhydrazine sodium salt:

a.)

![Diagram a](image)

b.)

![Diagram b](image)

c.)

![Diagram c](image)
there are obtained, respectively:

a.) \[
\begin{align*}
\text{N} & \rightarrow \text{O} \\
\text{N} & \rightarrow \text{O} (\text{CH}_2 \text{CH}_2 \text{CH}_3)
\end{align*}
\]

b.) \[
\begin{align*}
\text{N} & \rightarrow \text{O} \\
\text{N} & \rightarrow \text{O} (\text{CH}_2 \text{CH}_2 \text{CH}_3)
\end{align*}
\]

c.) \[
\begin{align*}
\text{O} & \rightarrow \text{O} \\
\text{N} & \rightarrow \text{O} (\text{CH}_2 \text{CH}_2 \text{CH}_3)
\end{align*}
\]

**EXAMPLE 12**

Utilizing the procedures set forth in Example 1, and substituting the following compound for 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt:

\[
\begin{align*}
\text{N} & \rightarrow \text{O} \\
\text{N} & \rightarrow \text{O} \text{Na}^+
\end{align*}
\]

there is obtained the corresponding n-propyl ether compound, which is thereafter subjected to a base hydrolysis reaction, whereby there is obtained the following compound of Formula I.

\[
\begin{align*}
\text{N} & \rightarrow \text{O} \\
\text{N} & \rightarrow \text{O} (\text{CH}_2 \text{CH}_2 \text{CH}_3)
\end{align*}
\]
EXAMPLE 13

1,3-BIS(3,3-DIETHYL-2-OXO-1-TRIAZEN-1-YLOXY)PROPANE
(C₂H₅)₂NN₂O₂CH₂CH₂CH₂O₂N₂N(C₂H₅)₂

A partial solution of 1.947 g (0.0126 mol) of 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt in 12 ml of anhydrous N,N-dimethylformamide was cooled to 0°C. A solution of 713 µl (0.006 mol) of 1,3-diiodopropylene in 12 ml of THF was added dropwise over a period of 30 minutes. The ice bath was removed and the resulting reaction mixture was stirred at 25°C under argon overnight. To the reaction mixture was added 50 ml of distilled water and then it was extracted with ether. The ether layer was washed with sodium bisulfite solution, dried over sodium sulfate and filtered through a layer of magnesium sulfate. Evaporation of the solvent in vacuo gave 1.16 g of crude product. Purification was carried out by column chromatography on silica-gel; 5:1 methylene chloride:ethyl acetate was used as the eluant. The fractions containing the desired product were combined and evaporated in vacuo to give 966 mg (26%) of 1,3-bis(3,3-diethyl-2-oxo-1-triazene-1-yloxy)propene: NMR, δ 1.086 (t, 12H), 2.241 (q, 2H), 3.101 (q, 8H), 4.385 (t, 4H); IR (film), 2980, 2945, 1510, 1459, 1384, 1240, 1065, 1008 cm⁻¹; uv (H₂O), λmax (ε), 235 (14,066).

Et₂NN(NO)O⁻Na⁺ + I(CH₂)₃I → Et₂NN(O)NO(CH₂)₃ONN(O)NET₂

EXAMPLE 14

1,2-BIS(3,3-DIETHYL-2-OXO-1-TRIAZEN-1-YLOXY)ETHANE
(C₂H₅)₂NN₂O₂CH₂CH₂O₂N₂N(C₂H₅)₂

Step 1: A partial solution of 2.7 g (17.4 mmol) of 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt in 17 ml of DMF was cooled to 0°C under a stream of nitrogen. A solution of 1.4 ml of 1,2-dibromoethane in anhydrous THF was added dropwise. Once addition was complete, the ice bath was removed, and the resulting mixture was stirred...
at 25°C overnight. To the reaction mixture was added 200 ml of water and the product was extracted with ether. The organic layer was separated and washed with water. The solution was dried over sodium sulfate and filtered through a layer of magnesium sulfate. Evaporation of the solvent gave 2.1 g of crude product. The product was chromatographed through silica gel and eluted with dichloromethane to give 706 mg of pure 1-(2-bromoethoxy)-2-oxo-3,3-diethyl-1-triazene: IR (film), 2980, 2965, 2880, 1510, 1500, 1450, 1383, 1241, 1235, 1070, 1005 cm⁻¹; NMR (CDCl₃), δ 1.104 (t, 6H), 3.124 (q, 4H), 3.582 (t, 2H), 4.522 (m, 2H); uv, λₘₐₓ(ε), 233 (8,977); MS, m/z (%), 242 (MH⁺, ⁸¹Br, 8), 240 (MH⁺, ⁷⁹Br, 9), 224 (4), 223 (4), 211 (37), 209 (36), 132 (41), 109 (56), 107 (56), 101 (64), 102 (100), 84 (32), 72 (32), 56 (36).

Exact mass: calculated for C₆H₁₄⁸¹BrN₃O₂, 242.0327, and for C₆H₁₄⁷⁹BrN₃O₂, 240.0347; found for MH⁺, 242.0356 and 240.0417.

Step 2: To a solution of 1.27 g (8.2 mmol) of 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt in 5 ml of DMF was added a solution of 425 mg (1.7 mmol) of 1-(2-bromoethoxy)-2-oxo-3,3-diethyl-1-triazene in 5 ml of THF, and the resulting solution was stirred at 25°C overnight. To the reaction mixture was added 100 ml of distilled water, and the product was extracted in pentane. The organic layer was dried over sodium sulfate and filtered through a layer of magnesium sulfate and the solvent was removed on a rotary evaporator to give 476 mg of crude product. The crude material was purified on dry-packed silica gel Activity III, eluted with 5:1 dichloromethane:ethyl acetate to give pure 1,2-bis(3,3-diethyl-2-oxo-1-triazen-1-yloxy)ethane: NMR, δ 1.095 (t, 12H), 3.113 (q, 8H), 4.50 (s, 4H); uv, H₂O, λₘₐₓ (ε), 232 (15,083); MS/, m/z (%), 292 (0.4), 132 (15), 103 (30), 102 (100), 87 (7), 86 (2), 85 (5), 75 (5), 74 (2), 72
(11), 71 (4), 70 (2), 58 (7), 57 (17), 56 (20), 47 (2), 45 (7), 44 (87), 43 (6), 42 (25).

Exact mass: calculated for $\text{C}_{10}\text{H}_{24}\text{N}_{6}\text{O}_{4}$, 292.1854; found for $M^+$, 292.1911.

**Step 1**  
\[ \text{Et}_2\text{NN(NO)}\text{O}^-\text{Na}^+ + \text{BrCH}_2\text{CH}_2\text{Br} \rightarrow \text{Et}_2\text{NN(O)NOCH}_2\text{CH}_2\text{Br} \]

**Step 2**  
\[ \text{Et}_2\text{NN(O)NOCH}_2\text{CH}_2\text{Br} + \text{Et}_2\text{NN(NO)}\text{O}^-\text{Na}^+ \rightarrow \text{Et}_2\text{NN(O)NOCH}_2\text{CH}_2\text{ONN(O)NEt}_2 \]

**EXAMPLE 15**

**1-VINYLOXY-2-OXO-3,3-DIETHYL-1-TRIAZENE**  
$(\text{C}_2\text{H}_5)_2\text{NN}_2\text{O}_2\text{CH}=\text{CH}_2$

A solution of 100 mg of 1-(2-bromoethoxy)-2-oxo-3,3-diethyl-1-triazene (Example 14, step 1) in 5 ml of anhydrous THF was heated at reflux for 24 hours with 200 mg of powdered sodium hydroxide. The solution was filtered and the solvent was evaporated to give 66 mg of product: IR (film), 3080, 2985, 2940, 2880, 1640, 1518, 1500, 1442, 1388, 1245, 1170, 1145, 1016, 950, 860 cm$^{-1}$; NMR, 1.130 (t, 6H), 3.219 (q, 4H), 4.437 (q, 1H), 4.898 (q, 1H), 6.9075 (q, 1H).

\[ \text{NaOH}, \text{reflux} \rightarrow \text{Et}_2\text{NN(O)NOCH}_2\text{CH}_2 \]

**EXAMPLE 16**

**1-DIMETHYLAMINOSULFONYLOXY-2-OXO-3,3-DIETHYL-1-TRIAZENE**  
$[(\text{C}_2\text{H}_5)_2\text{NN}_2\text{O}_2\text{SO}_2\text{NMe}_2]$  

A slurry of 2.54 g (0.0164 mol) of 2,2-diethyl-1-nitroso-1-oxyhydrazine sodium salt in 20 ml of anhydrous tetrahydrofuran was cooled to 0°C. To this was added 1.72 ml (0.016 mol) of dimethyl sulfamoyl chloride. The mixture was stirred at room temperature for 24 h and filtered. The filtrate was washed with 10% aqueous

**SUBSTITUTE SHEET**
sodium hydroxide, dried over sodium sulfate and evaporated under reduced pressure to give 2.1 g of a product mixture. The crude product was purified on silica gel and eluted with dichloromethane:

\[ \text{NMR } \delta \text{ 1.20 (t, 6H), 3.03 (s, 6H), 3.52 (q, 4H); uv, } \lambda \text{ max (e), 260 nm (7,306) and 217 nm (7,713); IR(film) 2985, 2940, 1460, 1390, 1250, 1185, 1159, 985, 960, 940, 860, 750 cm}^{-1}. \text{ Analysis: C, H, N. Calculated for } C_6H_{16}N_4O_4S: C, 30.00%; H, 6.66%; N, 23.33%. \text{ Found: C, 30.09%; H, 6.72%; N, 23.30%}. \]

\[ \text{Et}_2\text{NN(NO)}\text{O}^-\text{Na}^+ + \text{ClSO}_2\text{NMe}_2 \rightarrow \text{Et}_2\text{NN(O)NOSO}_2\text{NMe}_2 \]

**NOVEL SYNTHESIS PROCESSES**

In preparing some of the Formula (I) compounds of the above Examples, there were used novel synthesis processes. The following comments are provided in order to fully disclose these novel synthesis processes. In the first and second novel synthesis processes described below, compounds of Formula (I) wherein \( R_1 \) and \( R_2 \) are not identical can be prepared. The above Examples 9A and 10 illustrate the two methods. In the third novel synthesis method disclosed below compounds of Formula (I) wherein \( R_3 \) is a group of the formula \(-(\text{CH}_2)_n\text{O(NO)NNR}_1\text{R}_2\) are prepared. The third process is illustrated in the above Example 14.

**FIRST NOVEL SYNTHESIS PROCESS**

\[
\begin{align*}
R_1\text{NN(O)NOR}_3 + R_2X & \xrightarrow{\text{base}} R_1R_2\text{NN(O)NOR}_3 \\
\text{(e.g., NaOH or the like)} & \quad (\text{e.g., NaOH or the like})
\end{align*}
\]

In the above reaction scheme \( R_1, R_2 \) and \( R_3 \) are as defined in Formula I, and \( X \) is the leaving group for the electrophile \( R_2 \) (e.g., halo). The reaction is allowed to take place in an appropriate solvent (e.g., 3:1 anhydrous THF:DMF, or the like) at about room temperature (about 25°C).
SECOND NOVEL SYNTHESIS PROCESS

A solution of an unsymmetrical secondary amine of the formula \( R_1R_2NH \) in an appropriate solvent (e.g., petroleum ether) is charged with nitric oxide (at about 60 psi and at about -80°C). The unstable complex that precipitates out of solution is not isolated, but instead is treated with sodium methoxide in methanol (or a like compound in an appropriate solvent). This is followed by reacting with an appropriate electrophile at about 0°C. There is obtained a compound of formula I wherein \( R_1 \) and \( R_2 \) are not identical and \( R_3 \) is an alkyl moiety.

THIRD NOVEL SYNTHESIS PROCESS

A process for preparing a compound of Formula (I) wherein \( R_3 = -(CH_2)_nONN(O)NR_2 \) wherein \( n \) is an integer of from 2 to 8 and \( R_1 \) and \( R_2 \) are as defined in Formula I. In the process, a compound of the Formula \( R_1R_2N(NO)NO^-M^+ \) (wherein \( M^+ \) is an alkali metal ion) is slurried in an appropriate solvent (e.g., THF) and treated at about 0°C with a bifunctional electrophile of the Formula \( X(CH_2)_nX \), wherein \( X \) is halo or another leaving group. Thereafter, the temperature is allowed to rise to about room temperature (about 25°C).

PHARMACOCOLOGICAL TESTING

Effects of Drugs on Mean Arterial Pressure (MAP) and Aortic Diameter

The effects of the compounds of Formula I on the MAP of male Sprague-Dawley rats were measured using a pressure transducer connected to the left carotid artery via a catheter containing heparinized saline. The MAP was recorded on a Grass Recorder. The rat was anesthetized with nembutal at an initial dose of 35 mg/kg and recurrent smaller injections as needed. The test substance was dissolved in 0.9% sodium chloride and injected at the doses shown below into the rat via a
catheter in the left jugular vein. The effects on the MAP are recorded in Table I.
TABLE I

Hypotensive Effects of 1-Alk oxy-2-oxo-3,3-dialkyl-1-triazenes

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (μmol/kg)</th>
<th>Initial</th>
<th>Minimum</th>
<th>Final</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et₂N-N-O</td>
<td>40</td>
<td>84</td>
<td>49</td>
<td>56</td>
<td>(at 69 min)</td>
</tr>
<tr>
<td>N-O(n-Pr)</td>
<td>35</td>
<td>108</td>
<td>54</td>
<td>91</td>
<td>(at 47 min)</td>
</tr>
<tr>
<td>Et₂N-N-O</td>
<td>45</td>
<td>102</td>
<td>56</td>
<td>84</td>
<td>(at 35 min)</td>
</tr>
<tr>
<td>N-OMe</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et₂N-N-O</td>
<td>28</td>
<td>108</td>
<td>85</td>
<td></td>
<td>(lasted at least 1 hour)</td>
</tr>
<tr>
<td>N-OEt</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the tests of Table I, SNP (i.e., sodium nitroprusside) was used as a control. It is a known, clinically useful vasodilator, but it had a much shorter duration of action than the compounds of Table I. The results show that the compounds of Table I are long-acting antihypertensive agents, decreasing the blood pressure significantly for a prolonged period.

In contrast to the data of Table I, two other rats also received i.v. doses of Et₂NN(O)NOMe and/or Et₂NN(O)NOEt but the doses of the drugs produced no effect on their MAP. Though these rats gave indications of compromised responsiveness (for example, one animal had experienced a severe ischemic episode earlier in the test day resulting from an accidental penetration of the lungs during a gavage experiment), it was decided to

---

1 The ethoxy derivative was tested in a male Wistar Kyoto rat that had not been anesthetized. The drug was administered by intravenous bolus after dissolution in 5% dextrose. The pressure transducer was connected to the right carotid artery and the MAP was recorded on a Grass Model 2800 8-channel recorder.

2 Time post-injection is indicated in parentheses.
confirm the inherent activity of Et$_2$NN(O)NOEt as a vasorelaxant by testing it via a standard isolated vascular ring preparation. Thoracic aortic rings from New Zealand White rabbits were suspended in pH 7.4 buffer at 37°C and a 10-g preload was applied to each. After equilibration for 2 hours, the rings were preconstricted with norepinephrine. By measuring the grams of relaxation induced by adding the Et$_2$NN(O)NOEt to the organ baths at successively increasing concentrations from 10$^{-9}$ to 10$^{-3}$ M, a dose-response curve was constructed for the compound (see Figure 1). All three rings studied showed significant vasorelaxation at concentrations of 10$^{-7}$ to 10$^{-3}$ M. We conclude that the compound does indeed exert a reproducible and reliable vasorelaxant effect useful in the treatment of hypertension.

In an in vivo test with rabbits, the acetal derivative synthesized in Example 6 above was also proven active. The compound (11.4 mg) was dissolved in 1.0 ml of phosphate buffered saline and 0.9 ml was injected intravenously into a 6.5 pound New Zealand White rabbit. Hemodynamic data were collected in the rabbit using a procedure similar to that employed in the rat studies of Table I. At this dose of 20 µmol/kg, the blood pressure behaved as indicated in Table II, with MAP falling very rapidly to a low plateau and staying down until the experiment was terminated 15 minutes after injection.

<table>
<thead>
<tr>
<th>Time following injection</th>
<th>Systolic pressure (mm)</th>
<th>Diastolic pressure (mm)</th>
<th>MAP (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (baseline values)</td>
<td>90</td>
<td>50</td>
<td>66</td>
</tr>
<tr>
<td>1 min</td>
<td>70</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>10 min</td>
<td>68</td>
<td>20</td>
<td>32</td>
</tr>
<tr>
<td>15 min</td>
<td>70</td>
<td>25</td>
<td>36</td>
</tr>
</tbody>
</table>
The compounds of this invention are useful in a method of treating any cardiovascular disorder that will respond favorably to a decrease in blood pressure. These disorders include chronic hypertension, hypertensive crisis, acute congestive heart failure, angina, acute myocardial infarction, left ventricular failure, cerebrovascular insufficiency, and intracranial hemorrhage. It is thought that these long-acting drugs may be advantageously administered orally for treatment of chronic disorders.

**PHARMACEUTICAL COMPOSITIONS**

The pharmaceutical compositions of the invention are comprised of an effective amount of a compound of formula I and a pharmaceutical carrier therefor. The carrier can be any of those conventionally used and is limited only by physicochemical considerations such as stability and solubility. For intravenous administration, the carrier will be a sterile aqueous carrier and may contain solubilizing agents, buffers, preservatives, antioxidants, chelating agents, and agents to control the tonicity, such as dextrose or sodium chloride. The requirements for effective pharmaceutical carriers for injectable compositions are well known by one of ordinary skill in this art. (See "Pharmaceutics and Pharmacy Practice", J. B. Lippincott Company, Philadelphia, 1982, edited by Banker and Chalmers, pages 238-250, which are incorporated by reference; also see ASHP "Handbook on Injectable Drugs", 4th edition, by Trissel, pages 622-630, which lists commercially available intravenous infusion solutions; these pages are incorporated by reference.) The compounds may also be formulated as inclusion complexes, such as, for example, cycloexextrin inclusion complexes, or the compounds may be carried within liposomes. Preferred pharmaceutical carriers for injection are phosphate buffered saline, 5% dextrose, and sterile water. Oral administration may also be by
standard methods well known to those with ordinary skill in the art, such as capsules, tablets or ingestible liquids utilizing excipients generally used for such purposes (e.g., cornstarch, microcrystalline cellulose, PVP, lactose, stearic acid, purified water U.S.P., and the like).

When the compounds of the present invention are administered to a patient in need thereof, it is thought that a suitable dosage for lowering blood pressure in a patient is from about 0.01 to 100 mg/kg (preferably about 0.1 to 50 mg/kg) of the patient's body weight, regardless of the route of administration or the exact cardiovascular disorder encountered. Administration of such dosages from one to eight times daily (preferably one to four times daily) is contemplated. In order to provide such dosages of the Formula I compounds, it is considered advantageous that solid or liquid unit dosage forms containing about 0.01 to 30 mg (preferably 0.1 to 15 mg) of one of the Formula I compounds be administered to a patient in need thereof from 1 to 8 times daily (preferably from one to four times daily).

The invention being thus described, it will be obvious that the same may be varied in many ways. Such variations are not to be regarded as a departure from the spirit and scope of the invention, and all such modifications as would be obvious to one skilled in the art are intended to be included within the scope of the following claims.
What is claimed is:

Claim 1. A pharmaceutical composition, comprising:
an effective amount of a compound of the formula:

\[ R_1 R_2 N-N-O \]
\[ \text{N-OR}_3 \]

wherein:
R₁ and R₂ are the same or different and are selected from
the group consisting of:
C₁₋₁₂ straight chain alkyl,
C₁₋₁₂ alkoxy or acyloxy substituted straight chain alkyl,
C₂₋₁₂ hydroxy or halo substituted straight chain alkyl,
C₃₋₁₂ branched chain alkyl,
C₃₋₁₂ hydroxy, halo, alkoxy or acyloxy substituted
branched chain alkyl,
C₃₋₁₂ straight chain olefinic,
C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted
straight chain olefinic,
C₃₋₁₂ branched chain olefinic,
C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;
or
R₁ and R₂ join together with the nitrogen atom to which
they are bonded to form a heterocyclic ring selected from
the group consisting of:

\[ (\text{CH}_2)_w \]
\[ R_4 \]
\[ \text{N-} \]
\[ \text{N-} \]
\[ \text{N(CH}_2\text{CH}_2\text{O})_z \]
\[ \text{CH}_3\text{CH}_2 \]

wherein w is 1 to 12, y is 1 or 2, z is 1 to 5, R₄ is
hydrogen, C₁₋₈ straight chain alkyl, C₃₋₈ branched chain
alkyl, C₃₋₈ cycloalkyl, unsubstituted or substituted aryl, and R₅ is hydrogen, C₁₋₆ straight chain alkyl or C₃₋₆ branched chain alkyl;
R₃ is selected from the group consisting of
C₁₋₁₂ straight chain alkyl,
C₁₋₁₂ straight chain alkyl substituted by hydroxy,
halo, alkoxy or acyloxy,
C₃₋₁₂ branched chain alkyl,
C₃₋₁₂ branched chain alkyl substituted by hydroxy,
alkoxy, acyloxy or halo,
C₂₋₁₂ straight chain olefinic,
C₂₋₁₂ straight chain olefinic substituted by hydroxy,
alkoxy, acyloxy or halo,
C₃₋₁₂ branched chain olefinic,
C₃₋₁₂ branched chain olefinic substituted by hydroxy,
alkoxy, acyloxy or halo,
C₁₋₁₂ acyl, a sulfonyl, sulfinyl, sulfenyl, carbonate, or carbamate derivative; or
R₃ is a group of the Formula -(CH₂)ₓ-ONN(O)NR₁R₂, wherein
n is an integer of 2-8, and R₁ and R₂ are as defined above;
with the proviso that R₁, R₂ and R₃ do not contain a halo
or a hydroxy substituent α to an oxygen or a nitrogen atom; and
a pharmaceutically acceptable carrier therefor.

Claim 2. A pharmaceutical composition as recited in
claim 1, wherein said composition is an injectable
composition, and said pharmaceutically acceptable carrier
is sterile.

Claim 3. A pharmaceutical composition as recited in
claim 1, wherein said composition is in the form of a
tablet, capsule or an ingestible liquid.
Claim 4. A pharmaceutical composition as recited in claim 1, wherein the composition comprises from about 0.01 to 30 mg of the compound of Formula I.

Claim 5. A pharmaceutical composition as recited in claim 1, wherein:
R₁ and R₂ are the same or different and are selected from the group consisting of:
C₁⁻¹₂ straight chain alkyl,
C₁⁻¹₂ alkoxy or acyloxy substituted straight chain alkyl,
C₂⁻¹₂ hydroxy or halo substituted straight chain alkyl,
C₃⁻¹₂ branched chain alkyl,
C₃⁻¹₂ hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl,
C₃⁻¹₂ straight chain olefinic,
C₃⁻¹₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic,
C₃⁻¹₂ branched chain olefinic, and
C₃⁻¹₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;
and
R₃ is selected from the group consisting of:
C₁⁻¹₂ straight chain alkyl,
C₁⁻¹₂ straight chain alkyl substituted by hydroxy, halo, alkoxy or acyloxy,
C₃⁻¹₂ branched chain alkyl,
C₃⁻¹₂ branched chain alkyl substituted by hydroxy, alkoxy, acyloxy or halo,
C₂⁻¹₂ straight chain olefinic,
C₂⁻¹₂ straight chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo,
C₃⁻¹₂ branched chain olefinic,
C₃⁻¹₂ branched chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo,
C₁⁻¹₂ acyl, a sulfonyl, sulfinyl, sulfenyl, carbonate, or carbamate derivative; or
with the proviso that $R_1$, $R_2$ and $R_3$ do not contain a halo or hydroxy substituent $\alpha$ to an oxygen or a nitrogen atom.

Claim 6. A pharmaceutical composition as recited in claim 1, wherein $R_1$ and $R_2$ join together with the nitrogen atom to which they are bonded to form a heterocyclic ring selected from the group consisting of:

\[
\begin{align*}
\text{(CH$_3$)$_w$} & \quad \text{N}^- \\
\text{(CH$_3$)$_y$} & \quad \text{N}^- \\
\end{align*}
\]

wherein $w$ is 1 to 12, $y$ is 1 or 2, $z$ is 1 to 5, $R_4$ is hydrogen, $C_{1-8}$ straight chain alkyl, $C_{3-8}$ branched chain alkyl, $C_{3-8}$ cycloalkyl, unsubstituted or substituted aryl, and $R_5$ is hydrogen, $C_{1-6}$ straight chain alkyl or $C_{3-6}$ branched chain alkyl.

Claim 7. A pharmaceutical composition as recited in claim 6, wherein said composition is an injectable composition, and said pharmaceutically acceptable carrier is sterile.

Claim 8. A pharmaceutical composition as recited in claim 1, wherein said Formula I compound is:

1-n-propoxy-2-oxo-3,3-diethyl-1-triazene,
1-methoxy-2-oxo-3,3-diethyl-1-triazene,
1-(2-hydroxypropoxy)-2-oxo-3,3-diethyl-1-triazene,
1-ethoxy-2-oxo-3,3-diethyl-1-triazene,
1-allyloxy-2-oxo-3,3-diethyl-1-triazene,
1-(2-bromoethoxy)-2-oxo-3,3-diethyl-1-triazene,
1-(methoxymethyleneoxy)-2-oxo-3,3-diethyl-1-triazene,
1-(2-hydroxyethoxy)-2-oxo-3,3-diethyl-1-triazene,
1-methoxy-2-oxo-3-isopropyl-3-methyl-1-triazene,
1-methoxy-2-oxo-3-isopropyl-3-allyl-1-triazene,
1-methoxy-2-oxo-3-methyl-3-(2-hydroxypropyl)-1-triazene,
1,3-bis(3,3-diethyl-2-oxo-1-triazen-1-yloxy)propane,
1,2-bis(3,3-diethyl-2-oxo-1-triazen-1-yloxy)ethane,
1-vinyl oxy-2-oxo-3,3-diethyl-1-triazene, or
1-dimethylaminosulfonyloxy-2-oxo-3,3-diethyl-1-triazene.

Claim 9. A pharmaceutical composition as recited in
claim 5, wherein said Formula I compound is:
1-n-propoxy-2-oxo-3,3-diethyl-1-triazene,
1-methoxy-2-oxo-3,3-diethyl-1-triazene,
1-(2-hydroxypropoxy)-2-oxo-3,3-diethyl-1-triazene,
1-ethoxy-2-oxo-3,3-diethyl-1-triazene,
1-allyloxy-2-oxo-3,3-diethyl-1-triazene,
1-(2-bromoethoxy)-2-oxo-3,3-diethyl-1-triazene,
1-(methoxymethyleneoxy)-2-oxo-3,3-diethyl-1-triazene,
1-(2-hydroxyethoxy)-2-oxo-3,3-diethyl-1-triazene,
1-methoxy-2-oxo-3-isopropyl-3-methyl-1-triazene,
1-methoxy-2-oxo-3-isopropyl-3-allyl-1-triazene,
1-methoxy-2-oxo-3-methyl-3-(2-hydroxypropyl)-1-triazene,
1,3-bis(3,3-diethyl-2-oxo-1-triazen-1-yloxy)propane,
1,2-bis(3,3-diethyl-2-oxo-1-triazen-1-yloxy)ethane,
1-vinyl oxy-2-oxo-3,3-diethyl-1-triazene, or
1-dimethylaminosulfonyloxy-2-oxo-3,3-diethyl-1-triazene.

Claim 10. A method for treating cardiovascular disorders
in a patient in need thereof, wherein said disorders may
be treated by lowering the patient's blood pressure, the
method comprising:
administering to the patient in need thereof, a blood
pressure lowering effective amount of a compound of the
formula:

\[ R_1 R_2 N-N-O \]
\[ \quad \parallel \quad N-OR_3 \]

wherein:
\( R_1 \) and \( R_2 \) are the same or different and are selected from
the group consisting of:
$C_{1-12}$ straight chain alkyl,
$C_{1-12}$ alkoxy or acyloxy substituted straight chain alkyl,
$C_{2-12}$ hydroxy or halo substituted straight chain alkyl,
$C_{3-12}$ branched chain alkyl,
$C_{3-12}$ hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl,
$C_{3-12}$ straight chain olefinic,
$C_{3-12}$ hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic,
$C_{3-12}$ branched chain olefinic,
and
$C_{3-12}$ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;
or
$R_1$ and $R_2$ join together with the nitrogen atom to which they are bonded to form a heterocyclic ring selected from the group consisting of:

\[
\text{and}
\]

wherein $w$ is 1 to 12, $y$ is 1 or 2, $z$ is 1 to 5, $R_4$ is hydrogen, $C_{1-8}$ straight chain alkyl, $C_{3-8}$ branched chain alkyl, $C_{3-8}$ cycloalkyl, unsubstituted or substituted aryl, and $R_5$ is hydrogen, $C_{1-6}$ straight chain alkyl or $C_{3-6}$ branched chain alkyl; and

$R_3$ is selected from the group consisting of

$C_{1-12}$ straight chain alkyl,
$C_{1-12}$ straight chain alkyl substituted by hydroxy, halo, alkoxy or acyloxy,
$C_{3-12}$ branched chain alkyl,
$C_{3-12}$ branched chain alkyl substituted by hydroxy, alkoxy, acyloxy or halo,
$C_{2-12}$ straight chain olefinic,
C2-12 straight chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo,
C3-12 branched chain olefinic,
C3-12 branched chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo,
C1-12 acyl, a sulfonyl, sulfinyl, sulfenyl, carbonate, or carbamate derivative; or
R3 is a group of the formula -(CH2)nONN(O)NR1R2, wherein n is an integer of 2-8, and R1 and R2 are as defined above;
with the proviso that R1, R2 and R3 do not contain a halo or a hydroxy substituent α to an oxygen or a nitrogen atom; and
a pharmaceutically acceptable carrier therefor.

Claim 11. The method of claim 10, wherein the cardiovascular disorder treated is chronic hypertension, hypertensive crisis, acute congestive heart failure, angina, acute myocardial infarction, left ventricular failure, cerebrovascular insufficiency and intracranial hemorrhage.

Claim 12. The method of claim 10, wherein the cardiovascular disorder is chronic hypertension, hypertensive crisis, acute congestive heart failure or acute myocardial infarction.

Claim 13. The method of claim 10, wherein:
R1 and R2 are the same or different and are selected from the group consisting of:
C1-12 straight chain alkyl,
C1-12 alkoxy or acyloxy substituted straight chain alkyl,
C2-12 hydroxy or halo substituted straight chain alkyl,
C3-12 branched chain alkyl,
C3-12 hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl,
C3-12 straight chain olefinic,
C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic,
C₃₋₁₂ branched chain olefinic, and
C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;
and
R₃ is selected from the group consisting of
C₁₋₁₂ straight chain alkyl,
C₁₋₁₂ straight chain alkyl substituted by hydroxy,
halo, alkoxy or acyloxy,
C₃₋₁₂ branched chain alkyl,
C₃₋₁₂ branched chain alkyl substituted by hydroxy,
alkoxy, acyloxy or halo,
C₂₋₁₂ straight chain olefinic,
C₂₋₁₂ straight chain olefinic substituted by hydroxy,
alkoxy, acyloxy or halo,
C₃₋₁₂ branched chain olefinic,
C₃₋₁₂ branched chain olefinic substituted by hydroxy,
alkoxy, acyloxy or halo,
C₁₋₁₂ acyl, a sulfonyl, sulfinyl, sulfenyl, carbonate, or carbamate derivative; of
with the proviso that R₁, R₂ and R₃ do not contain a halo or a hydroxy substituent α to an oxygen or a nitrogen atom.

Claim 14. The method of claim 10, wherein:
R₁ and R₂ join together with the nitrogen atom to which they are bonded to form a heterocyclic ring selected from the group consisting of:
wherein w is 1 to 12, y is 1 or 2, z is 1 to 5, R₄ is hydrogen, C₁₋₈ straight chain alkyl, C₃₋₈ branched chain alkyl, C₃₋₈ cycloalkyl, unsubstituted or substituted aryl, and R₅ is hydrogen, C₁₋₆ straight chain alkyl or C₃₋₆ branched chain alkyl.

Claim 15. The method of claim 10, wherein said Formula I compound is:
1-n-propanoyl-2-oxo-3,3-diethyl-1-triazene,
1-methoxy-2-oxo-3,3-diethyl-1-triazene,
1-(2-hydroxypropoxy)-2-oxo-3,3-diethyl-1-triazene,
1-ethoxy-2-oxo-3,3-diethyl-1-triazene,
1-allyloxy-2-oxo-3,3-diethyl-1-triazene,
1-(2-bromoethoxy)-2-oxo-3,3-diethyl-1-triazene,
1-(methoxymethyleneoxy)-2-oxo-3,3-diethyl-1-triazene,
1-(2-hydroxyethoxy)-2-oxo-3,3-diethyl-1-triazene,
1-methoxy-2-oxo-3-isopropyl-3-methyl-1-triazene,
1-methoxy-2-oxo-3-isopropyl-3-allyl-1-triazene,
1-methoxy-2-oxo-3-methyl-3-(2-hydroxypropyl)-1-triazene,
1,3-bis(3,3-diethyl-2-oxo-1-triazen-1-yloxy)propane,
1,2-bis(3,3-diethyl-2-oxo-1-triazen-1-yloxy)ethane,
1-vinylloxy-2-oxo-3,3-diethyl-1-triazene, or
1-dimethylamino-sulfonyloxy-2-oxo-3,3-diethyl-1-triazene.

Claim 16. A method of treating hypertension in a patient in need thereof, said method comprising:
administering to the patient a blood pressure lowering effective amount of a compound of the formula:

\[ \text{R}_1\text{R}_2\text{N-N-O} \]
\[ \text{N-OR}_3 \]

wherein:
R₁ and R₂ are the same or different and are selected from the group consisting of:
C₁₋₁₂ straight chain alkyl,
C₁₋₁₂ alkoxy or acyloxy substituted straight chain alkyl,
C₂₋₁₂ hydroxy or halo substituted straight chain alkyl,
C₃₋₁₂ branched chain alkyl,
C₃₋₁₂ hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl,
C₃₋₁₂ straight chain olefinic,
C₃₋₁₂ branched chain olefinic,
C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic,
and
C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;
or
R₁ and R₂ join together with the nitrogen atom to which they are bonded to form a heterocyclic ring selected from the group consisting of:

![Chemical Structure Diagram]

wherein w is 1 to 12, y is 1 or 2, z is 1 to 5, R₄ is hydrogen, C₁₋₈ straight chain alkyl, C₃₋₈ branched chain alkyl, C₃₋₈ cycloalkyl, unsubstituted or substituted aryl, and R₅ is hydrogen, C₁₋₆ straight chain alkyl or C₃₋₆ branched chain alkyl; and

R₃ is selected from the group consisting of
C₁₋₁₂ straight chain alkyl,
C₁₋₁₂ straight chain alkyl substituted by hydroxy, halo, alkoxy or acyloxy,
C₃₋₁₂ branched chain alkyl,
C₃₋₁₂ branched chain alkyl substituted by hydroxy, alkoxy, acyloxy or halo,
C₂₋₁₂ straight chain olefinic,
C₂₋₁₂ straight chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo,
C₃₋₁₂ branched chain olefinic,
C₃₋₁₂ branched chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo,
C₁₋₁₂ acyl, a sulfonyl, sulfinyl, sulfenyl, carbonate, or carbamate derivative; or
R₃ is a group of the formula -(CH₂)ₙONN(O)NR₁R₂, wherein n is an integer of 2-8, and R₁ and R₂ are as defined above; with the proviso that R₁, R₂ and R₃ do not contain a halo or a hydroxy substituent α to an oxygen or a nitrogen atom; and
a pharmaceutically acceptable carrier therefor.

Claim 17. The method of claim 16, wherein:
R₁ and R₂ are the same or different and are selected from the group consisting of:
C₁₋₁₂ straight chain alkyl,
C₁₋₁₂ alkoxy or acyloxy substituted straight chain alkyl,
C₂₋₁₂ hydroxy or halo substituted straight chain alkyl,
C₃₋₁₂ branched chain alkyl,
C₃₋₁₂ hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl,
C₃₋₁₂ straight chain olefinic,
C₃₋₁₂ branched chain olefinic,
C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic,
and
C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;
and
R₃ is selected from the group consisting of
C₁₋₁₂ straight chain alkyl,
C₁₋₁₂ straight chain alkyl substituted by hydroxy, halo, alkoxy or acyloxy,
C₃₋₁₂ branched chain alkyl,
C₃₋₁₂ branched chain alkyl substituted by hydroxy, alkoxy, acyloxy or halo,
C₂₋₁₂ straight chain olefinic,
C₂₋₁₂ straight chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo,
C₃₋₁₂ branched chain olefinic,
C₃₋₁₂ branched chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo,
C₁₋₁₂ acyl, a sulfonyl, sulfinyl, sulfenyl, carbonate, or carbamate derivative; or
with the proviso that R₁, R₂ and R₃ do not contain a halo or a hydroxy substituent α to an oxygen or a nitrogen atom.

Claim 18. The method of claim 16, wherein said Formula I compound is:
1-n-propoxy-2-oxo-3,3-diethyl-1-triazene,
1-methoxy-2-oxo-3,3-diethyl-1-triazene,
1-(2-hydroxypropoxy)-2-oxo-3,3-diethyl-1-triazene,
1-ethoxy-2-oxo-3,3-diethyl-1-triazene,
1-allyloxy-2-oxo-3,3-diethyl-1-triazene,
1-(2-bromoethoxy)-2-oxo-3,3-diethyl-1-triazene,
1-(methoxymethyleneoxy)-2-oxo-3,3-diethyl-1-triazene,
1-(2-hydroxyethoxy)-2-oxo-3,3-diethyl-1-triazene,
1-methoxy-2-oxo-3-isopropyl-3-methyl-1-triazene,
1-methoxy-2-oxo-3-isopropyl-3-allyl-1-triazene,
1-methoxy-2-oxo-3-methyl-3-(2-hydroxypropyl)-1-triazene,
1,3-bis(3,3-diethyl-2-oxo-1-triazene-1-yloxy)propane,
1,2-bis(3,3-diethyl-2-oxo-1-triazene-1-yloxy)ethane,
1-vinylloxy-2-oxo-3,3-diethyl-1-triazene, or
1-dimethylaminosulfonyloxy-2-oxo-3,3-diethyl-1-triazene.

Claim 19. A compound having the Formula:

\[
\begin{array}{c}
\text{R}_1\text{R}_2\text{N-N-O} \\
| \\
\text{N-OR}_3
\end{array}
\]

wherein:
R₁ and R₂ are the same or different and are selected from the group consisting of:
C₁₋₁₂ straight chain alkyl,
\[ \text{C}_{1-12} \text{ alkoxy or acyloxy substituted straight chain alkyl,} \\
\text{C}_{2-12} \text{ hydroxy or halo substituted straight chain alkyl,} \\
\text{C}_{3-12} \text{ branched chain alkyl,} \\
\text{C}_{3-12} \text{ hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl,} \\
\text{C}_{3-12} \text{ straight chain olefinic,} \\
\text{C}_{3-12} \text{ branched chain olefinic,} \\
\text{C}_{3-12} \text{ hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic,} \\
\text{and} \\
\text{C}_{3-12} \text{ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;} \\
or \\
\text{R}_1 \text{ and } \text{R}_2 \text{ join together with the nitrogen atom to which they are bonded to form a heterocyclic ring selected from the group consisting of:} \\
\begin{align*}
\text{(CH}_{2}\text{)}_w & \text{ N}^- \\
\text{R}_4 & \text{ N}^- \\
\text{(CH}_{2}\text{)}_y & \text{ and } \text{N}(\text{CH}_{3}\text{CH}_2\text{O})_2 \text{CH}_2\text{CH}_2
\end{align*}
\]

wherein \( w \) is 1 to 12, \( y \) is 1 or 2, \( z \) is 1 to 5, \( R_4 \) is hydrogen, \text{C}_{1-8} \text{ straight chain alkyl, } \text{C}_{3-8} \text{ branched chain alkyl, } \text{C}_{3-8} \text{ cycloalkyl, unsubstituted or substituted aryl,} \\
\text{and } \text{R}_5 \text{ is hydrogen, } \text{C}_{1-6} \text{ straight chain alkyl or } \text{C}_{3-6} \text{ branched chain alkyl; and} \\
\text{R}_3 \text{ is selected from the group consisting of} \\
\text{C}_{1-12} \text{ straight chain alkyl,} \\
\text{C}_{1-12} \text{ straight chain alkyl substituted by hydroxy,} \\
\text{halo, alkoxy or acyloxy,} \\
\text{C}_{3-12} \text{ branched chain alkyl,} \\
\text{C}_{3-12} \text{ branched chain alkyl substituted by hydroxy, alkoxy, acyloxy or halo,} \\
\text{C}_{2-12} \text{ straight chain olefinic,}
C$_{2-12}$ straight chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo, C$_{3-12}$ branched chain olefinic, C$_{3-12}$ branched chain olefinic substituted by hydroxy, alkoxy, acyloxy or halo, C$_{1-12}$ acyl, a sulfonyl, sulfinyl, sulfenyl, carbonate, or carbamate derivative; or R$_{3}$ is a group of the Formula -(CH$_{2}$)$_{n}$ONN(O)NR$_{1}$R$_{2}$ wherein n is an integer of 2-8, and R$_{1}$ and R$_{2}$ are as defined above; with the proviso that at least one of R$_{1}$, R$_{2}$ and R$_{3}$ is an olefinic group or heteroatom-substituted straight or branched chain alkyl group or olefinic group, as recited above; and with the further proviso that R$_{1}$, R$_{2}$ and R$_{3}$ do not contain a halo or hydroxy substituent a to an oxygen or a nitrogen atom.

Claim 20. A compound as recited in claim 19, wherein R$_{1}$ and R$_{2}$ are the same or different and are selected from the group consisting of:

C$_{1-12}$ straight chain alkyl, C$_{1-12}$ alkoxy or acyloxy substituted straight chain alkyl, C$_{2-12}$ hydroxy or halo substituted straight chain alkyl, C$_{3-12}$ branched chain alkyl, C$_{3-12}$ hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl, C$_{3-12}$ straight chain olefinic, C$_{3-12}$ branched chain olefinic, C$_{3-12}$ hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic, and C$_{3-12}$ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic.
Claim 21. A process for preparing a compound of the formula

\[
R_1R_2N-N-O
\]

\[
\downarrow
\]

\[
N-OR_3
\]

wherein:

R₁ and R₂ are the same or different and are selected from the group consisting of:
- C₁₋₁₂ straight chain alkyl,
- C₁₋₁₂ alkoxy or acyloxy substituted straight chain alkyl,
- C₂₋₁₂ hydroxy or halo substituted straight chain alkyl,
- C₃₋₁₂ branched chain alkyl,
- C₃₋₁₂ hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl,
- C₃₋₁₂ straight chain olefinic,
- C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic,
- C₃₋₁₂ branched chain olefinic,
- C₃₋₁₂ hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;

or

R₁ and R₂ join together with the nitrogen atom to which they are bonded to form a heterocyclic ring selected from the group consisting of:

\[
\begin{align*}
\text{and } & \quad N(CH₂CH₂O)₂ \\
\text{and } & \quad CH₂CH₂
\end{align*}
\]

wherein w is 1 to 12, y is 1 or 2, z is 1 to 5, R₄ is hydrogen, C₁₋₈ straight chain alkyl, C₃₋₈ branched chain alkyl, C₃₋₈ cycloalkyl, unsubstituted or substituted aryl,
and R5 is hydrogen, C1-6 straight chain alkyl or C3-6 branched chain alkyl; and
R3 is selected from the group consisting of
C1-12 straight chain alkyl,
C1-12 straight chain alkyl substituted by hydroxy,
halo, alkoxy or acyloxy,
C3-12 branched chain alkyl,
C3-12 branched chain alkyl substituted by hydroxy,
alkoxy, acyloxy or halo,
C2-12 straight chain olefinic,
C2-12 straight chain olefinic substituted by hydroxy,
alkoxy, acyloxy or halo,
C3-12 branched chain olefinic,
C3-12 branched chain olefinic substituted by hydroxy,
alkoxy, acyloxy or halo,
C1-12 acyl, a sulfonyl, sulfinyl, sulfenyl, carbonate, or carbamate derivative; or
R3 is a group of the Formula -(CH2)nONN(O)NR1R2, wherein n
is an integer of 2-8, and R1 and R2 are as defined above;
with the proviso that R1, R2 and R3 do not contain a halo
or a hydroxy substituent α to an oxygen or a nitrogen atom;
the process comprising:
reacting a compound of the Formula R1NHN(O)NOR3, wherein
R1 and R3 are as defined above, with a compound of the
Formula R2X in the presence of a base, wherein R2 is as
defined above and X is the leaving group of an
electrophile.

Claim 22. A process for preparing a compound of the
formula

\[
 \begin{array}{c}
 R_1R_2N-N-O \\
 \quad N-OR_3
 \end{array}
\]

wherein:
R1 and R2 are the same or different and are selected from
the group consisting of:
C\textsubscript{1-12} straight chain alkyl,
C\textsubscript{1-12} alkoxy or acyloxy substituted straight chain alkyl,
C\textsubscript{2-12} hydroxy or halo substituted straight chain alkyl,
C\textsubscript{3-12} branched chain alkyl,
5 C\textsubscript{3-12} hydroxy, halo, alkoxy or acyloxy substituted branched chain alkyl,
C\textsubscript{3-12} straight chain olefinic,
C\textsubscript{3-12} hydroxy, alkoxy, acyloxy, halo or benzyl substituted straight chain olefinic,
10 C\textsubscript{3-12} branched chain olefinic,
and
C\textsubscript{3-12} hydroxy, alkoxy, acyloxy, halo or benzyl substituted branched chain olefinic;
or
15 R\textsubscript{1} and R\textsubscript{2} join together with the nitrogen atom to which they are bonded to form a heterocyclic ring selected from the group consisting of:

wherein w is 1 to 12, y is 1 or 2, z is 1 to 5, R\textsubscript{4} is hydrogen, C\textsubscript{1-8} straight chain alkyl, C\textsubscript{3-8} branched chain alkyl, C\textsubscript{3-8} cycloalkyl, unsubstituted or substituted aryl, and R\textsubscript{5} is hydrogen, C\textsubscript{1-6} straight chain alkyl or C\textsubscript{3-6} branched chain alkyl; and
R\textsubscript{3} is a group of the Formula -(CH\textsubscript{2})\textsubscript{n}ONN(O)NR\textsubscript{1}R\textsubscript{2}, wherein n is an integer of 2-8, and R\textsubscript{1} and R\textsubscript{2} are as defined above;
25 with the proviso that R\textsubscript{1}, R\textsubscript{2} and R\textsubscript{3} do not contain a halo or a hydroxy substituent \& to an oxygen or a nitrogen atom;
the process comprising:
reacting a compound of the Formula R\textsubscript{1}R\textsubscript{2}NN(O)NO\textsuperscript{-} M\textsuperscript{+},
wherein M\textsuperscript{+} is an alkali metal ion and R\textsubscript{1} and R\textsubscript{2} are as
defined above, with a bifunctional electrophile of the 
Formula X(CH₂)ₙX, wherein X is a leaving group of an 
electrophile and n is as defined above.
IN VITRO VASORELAXANT EFFECTS

FIG. #1
INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/08078

I. CLASSIFICATION OF SUBJECT MATTER

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Classification Symbols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int.Cl. 5</td>
<td>CO7C; A61K; CO7D</td>
</tr>
</tbody>
</table>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 CO7C245/24; A61K31/00; A61K31/395; C07D207/50
CO7D211/98; C07D241/54; C07D265/30; C07D205/00

II. FIELDS SEARCHED

Minimum Documentation Searched

<table>
<thead>
<tr>
<th>Classification System</th>
<th>Classification Symbols</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int.Cl. 5</td>
<td>CO7C; A61K; CO7D</td>
</tr>
</tbody>
</table>

Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, 11 with indication, where appropriate, of the relevant passages 12</th>
<th>Relevant to Claim No.13</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>US, A, 3 153 094 (REILLY) 13 October 1964 columns 11 and 18</td>
<td>1-22</td>
</tr>
<tr>
<td>A</td>
<td>WO, A, 9 105 551 (WINK) 2 May 1991 formula (I)</td>
<td>1-22</td>
</tr>
<tr>
<td>A</td>
<td>US, A, 5 039 705 (KEEFER) 13 August 1991 formula (I)</td>
<td>1-22</td>
</tr>
<tr>
<td>X</td>
<td>US, A, 4 954 526 (KEEFER) 4 September 1990 claim 1</td>
<td>1-22</td>
</tr>
</tbody>
</table>

IV. CERTIFICATION

Date of the Actual Completion of the International Search

2 10 FEBRUARY 1993

International Searching Authority

EUROPEAN PATENT OFFICE

Date of Mailing of this International Search Report

10-02-93

Signature of Authorized Officer

GETTINS M.P.

Form PCT/ISA/210 (second sheet) (January 1985)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
</tr>
</thead>
</table>
This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDF file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 10/02/93

<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-A-3153094</td>
<td></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA-A- 2070388</td>
<td>19-04-91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO-A- 9104022</td>
<td>04-04-91</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU-A- 5192290</td>
<td>26-09-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP-T- 4505317</td>
<td>17-09-92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO-A- 9009785</td>
<td>07-09-90</td>
</tr>
</tbody>
</table>

For more details about this annex: see Official Journal of the European Patent Office, No. 12/82.