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Keefer et al.

[45] **Date of Patent:** Nov. 22, 1994[54] **OXYGEN SUBSTITUTED DERIVATIVES OF NUCLEOPHILE-NITRIC OXIDE ADDUCTS AS NITRIC OXIDE DONOR PRODRUGS**[75] **Inventors:** Larry K. Keefer, Bethesda, Md.;  
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represented by the Secretary of the  
Department of Health and Human  
Services, Washington, D.C.[21] **Appl. No.:** 950,637[22] **Filed:** Sep. 23, 1992**Related U.S. Application Data**[63] Continuation-in-part of Ser. No. 764,908, Sep. 24, 1991,  
abandoned.[51] **Int. Cl.<sup>5</sup>** ..... A61K 31/13; A61K 31/535;  
A61K 31/445; C07C 243/04[52] **U.S. Cl.** ..... 514/611; 514/238.2;  
514/255; 514/315; 514/426; 514/601; 514/929;  
544/164; 544/382; 546/244; 548/557; 564/81;  
564/113[58] **Field of Search** ..... 564/113, 81; 514/611,  
514/929, 238.2, 315, 426, 255, 601; 544/164,  
382; 546/244; 548/557[56] **References Cited****U.S. PATENT DOCUMENTS**

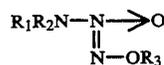
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*Primary Examiner*—Peter O. O'Sullivan  
*Attorney, Agent, or Firm*—Leydig, Voit & Mayer, Ltd.[57] **ABSTRACT**There are disclosed cardiovascularly active compounds  
possessing antihypertensive properties, and pharmaceu-  
tical compositions containing these agents and a method  
of treating cardiovascular disorders with the com-  
pounds. The active components of the pharmaceutical  
compositions are compounds of formula Iwherein R<sub>1</sub> and R<sub>2</sub> are independently chosen from  
straight chain and branched chain alkyl and olefinic  
groups, which may be unsubstituted or substituted; or  
R<sub>1</sub> and R<sub>2</sub> together with the nitrogen atom they are  
bonded to form a heterocyclic group; and R<sub>3</sub> is a phar-  
maceutically acceptable organic group selected from  
alkyl and olefinic groups which may be unsubstituted or  
substituted, acyl, a sulfonyl, sulfinyl, sulfenyl, carbon-  
ate, or carbamate derivative; or R<sub>3</sub> is a group of the  
formula—(CH<sub>2</sub>)<sub>n</sub>ONN(O)NR<sub>1</sub>R<sub>2</sub>, wherein n is 2-8, and  
R<sub>1</sub> and R<sub>2</sub> are as described above. Novel compounds are  
disclosed wherein at least one of R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> is an  
olefinic group or heteroatom-substituted straight or  
branched chain alkyl or olefinic group. Novel methods  
of synthesizing the compounds are also disclosed.**25 Claims, 1 Drawing Sheet**