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O²-ARYLATED OR O²-GLYCOSYLATED 1-SUBSTITUTED DIAZEN-1-IUM-1,2-DIOLATES AND O²-SUBSTITUTED 1-[(2-CARBOXYLATO)PYRROLIDIN-1-YL] DIAZEN-1-IUM-1,2-DIOLATES

This application claim benefit to provisional application No. 60/026,816 Sep. 27, 1996 which claims benefit of 60/045,917 May 7, 1997 which claims benefit of 60/051,696 Jul. 3, 1997.

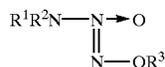
TECHNICAL FIELD OF THE INVENTION

The present invention relates to O²-aryl 1-substituted diazen-1-ium-1,2-diolates (O²-aryl diazeniumdiolates) O²-glycosylated 1-substituted diazeniumdiolates, and O²-substituted 1-[(2-carboxylato)pyrrolidin-1-yl] diazeniumdiolates, compositions comprising such diazeniumdiolates, methods of using such diazeniumdiolates, and methods of preparing O²-aryl diazeniumdiolates.

BACKGROUND OF THE INVENTION

Nitric oxide (NO) has been implicated in a wide variety of bioregulatory processes, and compounds, which contain nitric oxide or are capable of releasing nitric oxide, have been identified as useful in regulating these processes. Many classes of nitric oxide-containing and/or -releasing adducts are known in the art, such as glyceryl trinitrate and nitroprusside (reviewed in U.S. Pat. No. 5,405,919 (Keefer et al.), including limitations of their use in biological applications). The limited utility of such compounds has, in part, given rise to the development of another class of nitric oxide-generating compounds, diazeniumdiolates, which are especially useful biologically.

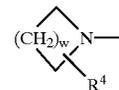
Diazeniumdiolates include compounds containing an N₂O₂⁻ functional group and are structurally and functionally distinct from nitrosamines (see, e.g., Reilly, U.S. Pat. No. 3,153,094). The known diazeniumdiolates are disclosed in recently issued patents. U.S. Pat. Nos. 5,039,705 (Keefer et al.) and 5,208,233 (Keefer et al.) disclose secondary amine-nitric oxide adducts and salts thereof. U.S. Pat. Nos. 5,155,137 (Keefer et al.) and 5,250,550 (Keefer et al.) disclose complexes of nitric oxide and polyamines. U.S. Pat. No. 5,389,675 (Christodoulou et al.) discloses mixed ligand metal complexes of nitric oxide-nucleophile adducts and U.S. Pat. Nos. 5,525,357 (Keefer et al.) and 5,405,919 (Keefer et al.) disclose polymer-bound nitric oxide/nucleophile adduct compositions. U.S. Pat. Nos. 4,954,526 (Keefer et al.; the '526 patent) and 5,212,204 (Keefer et al.) disclose the use of ionic diazeniumdiolates as cardiovascular agents. In addition, the '526 patent discloses O²-substituted and metal-bound diazeniumdiolates. Keefer et al., U.S. Pat. No. 5,366,997 ('997), discloses diazeniumdiolates having the formula:



in which the O²-oxygen of the N₂O₂⁻ group is bonded to the functional group R³. When the R³ group is cleaved from the O²-oxygen, NO can be released spontaneously.

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Although Keefer et al. ('997) discloses that (i) R¹ and R², together with the nitrogen atom to which they are bonded, can form a pyrrolidinyl, piperazino or other heterocyclic group, (ii) R³ is a C₁₋₁₂ straight-chain or C₃₋₁₂ branched-chain alkyl, optionally olefinic and/or substituted with hydroxy, halo, acyloxy or alkoxy, a C₁₋₁₂ unsubstituted/substituted acyl, sulfonyl, carboxamido, sulfinyl, sulfenyl, a carbonate derivative or a carbamate derivative, and (iii) the pyrrolidinyl group can have the structure:



wherein w=4, and R⁴=hydrogen, a C₁₋₈ straight or branched chain alkyl, a C₃₋₆ cycloalkyl, or a substituted or an unsubstituted aryl, Keefer et al. ('997) does not disclose that R³ is an aryl or a substituted aryl or that the pyrrolidino group can be substituted with a substituted or unsubstituted carboxyl group (see, also, Example 1 of U.S. Pat. No. 5,632,981) at position 2. Similarly, Keefer et al. ('997) does not disclose O²-glycosylation of diazeniumdiolates.

Heretofore it was not known that O²-aryl substitutions of the diazeniumdiolates was possible. Further, chemical studies of previously disclosed diazeniumdiolates led to the conclusion that they are generally at least as stable at high pH as they are at low pH, and that, unlike certain other classes of "nitrovasodilator" drugs, their rates of NO release are not affected by the presence of nucleophilic thiols.

Thus, there remains a need for such classes of diazeniumdiolates, which offer advantages over other currently available diazeniumdiolates. In this regard, the O²-aryl substituted diazeniumdiolates are advantageous in that they can release NO spontaneously under alkaline conditions or after nucleophilic attack. O²-Aryl substituted diazeniumdiolates also can release NO spontaneously after a combination of oxidative or electrophilic activation and nucleophilic attack.

It is, therefore, a principal object of the present invention to provide a nitric oxide/nucleophile adduct in which the O²-oxygen of the N₂O₂⁻ group is derivatized with an aryl or substituted aryl group to protect the diazeniumdiolate against the spontaneous release of NO. It is another object of the invention to provide a novel class of diazeniumdiolates, which resists releasing nitric oxide in neutral or acidic solutions, but releases NO on nucleophilic attack or on increasing the pH. It is still another object of the present invention to provide O²-glycosylated 1-substituted diazen-1-ium-1,2-diolates and O²-substituted 1-[(2-carboxylato)pyrrolidin-1-yl]diazen-1-ium-1,2-diolates. It is a further object of the present invention to provide compositions comprising such compounds, including compositions comprising a nitric oxide/nucleophile adduct comprising a novel targeting moiety. It is a related object to provide O²-aryl substituted diazeniumdiolates, which are amenable to biological tissue-targeting strategies, which offer greater flexibility and specificity for targeting NO release. It is a still further object of the present invention to provide methods of using such compounds. These and other objects of the present invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.