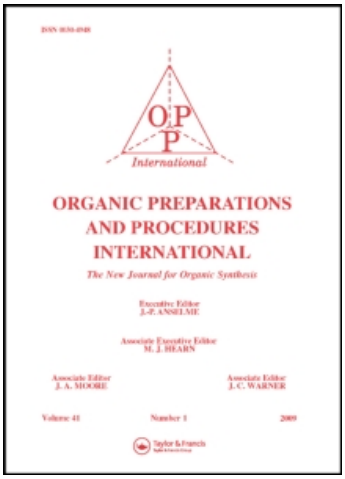
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

SYNTHESIS AND SPECTRAL DATA OF SOME NEW N-NITROSO-N-PHENYLHYDROXYLAMINE (CUPFERRON) DERIVATIVES

Alexandru T. Balaban[ab]; Robert E. Garfield[c]; Melanie J. Lesko[b]; William A. Seitz[b]
[a] Organic Chemistry Department, Polytechnic University Bucharest, Bucharest, ROMANIA [b] Department of Marine Sciences, Texas A & M University at Galveston, Galveston, TX, USA [c] Medical Branch, Reproductive Sciences, University of Texas, Galveston, TX, USA

To cite this Article Balaban, Alexandru T. , Garfield, Robert E. , Lesko, Melanie J. and Seitz, William A.(1998) 'SYNTHESIS AND SPECTRAL DATA OF SOME NEW N-NITROSO-N-PHENYLHYDROXYLAMINE (CUPFERRON) DERIVATIVES', Organic Preparations and Procedures International, 30: 4, 439 — 446
To link to this Article: DOI: 10.1080/00304949809355306
URL: http://dx.doi.org/10.1080/00304949809355306

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

ORGANIC PREPARATIONS AND PROCEDURES INT., 30 (4), 439-446 (1998)

SYNTHESIS AND SPECTRAL DATA OF SOME NEW N-NITROSO-N-PHENYLHYDROXYLAMINE (CUPFERRON) DERIVATIVES

Alexandru T. Balaban*,[†,†††] Robert E. Garfield,[††] Melanie J. Lesko[†††] and William A. Seitz[†††]

[†]*Polytechnic University Bucharest, Organic Chemistry Department Bucharest, ROMANIA*

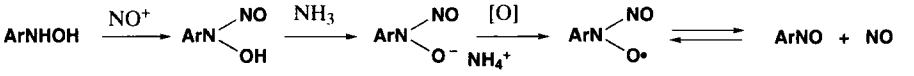
[††]*University of Texas Medical Branch, Reproductive Sciences Ob/Gyn 301 University Blvd., Galveston, TX 77555-1062, USA*

[†††]*Texas A & M University at Galveston, Department of Marine Sciences Galveston, TX 77553-1675, USA*

Downloaded At: 07:58 27 January 2011

Over the past ten years, nitric oxide (NO) has been shown to play a remarkable role in the biology of mammals. As a neuronal mediator which is continuously synthesized by the endothelial nitric oxide synthase (NOS), NO is responsible for vasodilation and its deficiency leads to hypertension. Large amounts of nitric oxide are found in the brain, where it is produced by the neuronal NOS. These two constitutive NOS isoforms produce low amounts of NO, but much larger amounts are released by a third inducible isoform which is present in macrophages and plays a beneficial role in killing invading microorganisms, but may become lethal in shock. Although when coming in contact with oxygen the stable free radical NO reacts rapidly yielding the toxic NO_2, this reaction is much slower at very low concentrations of NO because it is second order in NO; for its bronchodilatory effect, NO can therefore be inhaled by newborn infants or patients with pulmonary problems, admixed with air or oxygen, at NO concentrations of less than 100 ppm. Several books on NO have been recently published,[1-5] and in 1992 the journal *Science* advertised NO as "the molecule of the year".

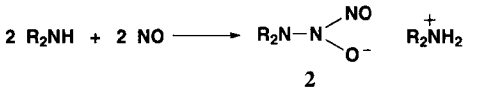
This paper describes cupferron derivatives **1**, most of which are novel, prepared as possible donors of nitric oxide. They have been shown to generate NO under the the conditions of chemiluminiscence reaction with ozone, and to cause muscular relaxation with tissues. By analogy with literature data,[6] it was inferred that, due to their ability to act *in vivo* as nitric oxide donors, these compounds in addition to promoting vasodilation, may accelerate the healing of wounds and burns.



1

© 1998 by Organic Preparations and Procedures Inc.

The reaction between amines (especially secondary amines) and NO was studied in the 1960s by Drago and coworkers,[7] and more recently by Keefer and associates.[8] Two equivalents of NO and one equivalent of amine afford salts of *amino-NONO-ates* **2** (1-substituted diazen-1-ium-1,2-diolates) which were shown by Keefer and coworkers to be able to donate NO in biological systems. X-Ray structure determinations indicated a *cisoid* conformation of the NONO-ate moiety.[8d]



2

The goal of the present study was to explore derivatives of the commercially available cupferron (the ammonium salt of N-nitroso-N-phenylhydroxylamine), which may be termed *arene-NONO-ates* **1** *(1-aryldiazen-1-ium-1,2-diolates),* by analogy with the preceding compounds.[8h] Their advantage over amino-NONO-ates lies in the wider possibilities of varying electronic and/or steric effects by substitution in the phenyl ring, or its replacement by polycyclic or heterocyclic aromatic rings. The ammonium salt α-naphthyl-NONO-ate is commercially available under the name *neocupferron.* Moreover, the risk of leaving carcinogenic residues after donation of NO is probably minimized by comparison with some amino-NONO-ates which may generate carcinogenic N-nitrosoamines.

In a recent patent, Keefer *et al.* included, in addition to the amino-NONO-ates that had been reviewed, cupferron and some derivatives as potential hypotensive agents.[8c] In reviews, Keefer et al.[8a,b] indicated that when the NONO group is attached to a carbon atom as in the parent N-aryl-N-nitroso-hydroxylamine (cupferron), it is stable under protonating conditions, implying that unlike amino-NONO-ates which release NO readily, cupferron and its derivatives would act more sluggishly. Our tests showed, however, that this is not true for *ortho*-substituted derivatives.

Several methods have been published for the preparation of N-nitroso-N-phenylhydroxylamine (named N-hydroxy-N-nitrosobenzeneamine in *Chemical Abstracts*), its derivatives and its salts; a few had been reviewed in two older monographs.[9]

1. Formal α-addition of the elements of nitrous acid to arylnitrenes putatively generated from anthranil to give N-nitroso-N-(*o*-formylphenyl)hydroxylamine.[10]

2. Nitrosation of N-arylhydroxylamine (*see below*).

3. Reaction of two equivalents of NO with aryl radicals formed by reduction of diazonium salts in the presence of Cu(II) and Fe(II) cations.[11]

4. Spin trapping of NO by nitrosoarenes followed by reduction of the resulting N-aryl-N-nitrosonitroxides.[12,13]

5. Reaction of aryl Grignard reagents with two equivalents of NO.[14]

6. Reaction of hyponitrous acid salts with nitroarenes or nitrosoarenes.[15]

Very few theoretical studies on cupferron analogs are available.[16]

The preparation of N-phenylhydroxylamine by reduction of nitrobenzene with zinc, and its nitrosation with alkyl nitrites in the presence of gaseous ammonia leading to cupferron is described in

Downloaded At: 07:58 27 January 2011

TABLE 1. Yields and mps (dec.) of Ammonium Salts of N-Aryl-N-nitrosohydroxylamine **1**

No.	Aryl	Formula[a]	Yield[b] (%)	mp (°C)	%N Calcd	%N Found
1	Phenyl	$C_6H_9N_3O_2$	81	154	-	-
2	Phenyl[a]	$C_6H_5N_2NaO_2$	66	-	-	-
3	1-Naphthyl	$C_{10}H_{11}N_3O_2$	70	110	-	-
4	1-Naphthyl[a]	$C_{10}H_8N_2NaO_2$	75	-	-	-
5	2-Methylphenyl	$C_7H_{11}N_3O_2$	66	110	24.84	24.38
6	3-Methylphenyl	$C_7H_{11}N_3O_2$	75	131	24.84	24.66
7	4-Methylphenyl	$C_7H_{11}N_3O_2$	80	151	24.84	24.78
8	2,3-Dimethylphenyl	$C_8H_{13}N_3O_2$	60	116	22.94	22.65
9	2-Methoxyphenyl	$C_7H_{11}N_3O_3$	25	112	22.69	22.38
10	4-Methoxyphenyl	$C_7H_{11}N_3O_3$	40	136	22.69	22.56
11	2-Ethylphenyl	$C_8H_{13}N_3O_2$	20	82	22.94	22.59
12	4-Ethylphenyl	$C_8H_{13}N_3O_2$	35	112	22.94	22.79
13	2-Isopropylphenyl	$C_9H_{15}N_3O_2$	22	92	21.30	21.05
14	2-Fluorophenyl	$C_6H_8FN_3O_2$	58	104	24.26	24.18
15	4-Fluorophenyl	$C_6H_8FN_3O_2$	66	151	24.26	24.36
16	2,4-Difluorophenyl	$C_6H_7F_2N_3O_2$	44	113	21.98	21.66
17	2,5-Difluorophenyl	$C_6H_7F_2N_3O_2$	51	125	21.98	21.79
18	2-Chlorophenyl	$C_6H_8ClN_3O_2$	52	102	22.16	22.06
19	3-Chlorophenyl	$C_6H_8ClN_3O_2$	79	154	22.16	22.08
20	4-Chlorophenyl	$C_6H_8ClN_3O_2$	84	150	22.16	22.04
21	2,3-Dichlorophenyl	$C_6H_7Cl_2N_3O_2$	60	118	18.76	18.68
22	2,4-Dichlorophenyl	$C_6H_7Cl_2N_3O_2$	64	119	18.76	18.58
23	2,5-Dichlorophenyl	$C_6H_7Cl_2N_3O_2$	44	93	18.76	18.50
24	2-Bromophenyl	$C_6H_8BrN_3O_2$	49	100	17.95	17.43
25	4-Bromophenyl	$C_6H_8BrN_3O_2$	69	153	17.95	17.88
26	5-Fluoro-2-methylphenyl	$C_7H_{10}FN_3O_2$	33	114	22.45	22.40
27	4-Fluoro-2-methylphenyl	$C_7H_{10}FN_3O_2$	39	113	22.45	22.33
28	5-Chloro-2-methylphenyl	$C_7H_{10}ClN_3O_2$	47	124	20.64	20.55
29	3-Chloro-2-methylphenyl	$C_7H_{10}ClN_3O_2$	41	127	20.64	20.58
30	3-Acetylphenyl	$C_8H_{11}N_3O_3$	59	149	21.31	21.22
31	4-Acetylphenyl	$C_8H_{11}N_3O_3$	66	154	21.31	21.23
32	4-Hydroxyphenyl	$C_6H_9N_3O_3$	38	151	24.55	24.30
33	3-Methylolphenyl	$C_7H_{11}N_3O_3$	55	138	22.69	22.49
34	4-Acetylaminophenyl	$C_8H_{12}N_4O_3$	77	272	26.40	26.20

a) As sodium salt. b) The yield for sodium salts refers to the conversion from ammonium salts *via* exchange with cation exchange resins.

Downloaded At: 07:58 27 January 2011

Organic Syntheses.[17] Analogous procedures were employed in the present study with slight modifications in order to avoid the isolation of the unstable crystalline N-arylhydroxylamines, and using mixed solvent systems during the reduction step. Ion exchange columns were used for the conversion of the ammonium salts into sodium salts which may be more appropriate for clinical internal use.

The simplest approach consists in reducing an aromatic or heteroaromatic nitro derivative to the corresponding arylhydroxylamine, either electrochemically or with zinc powder and ammonium chloride in water or aqueous lower alcohols. The arylhydroxylamine was extracted with ethyl ether or another non-polar solvent, and after drying was converted into the crystalline cupferron analog by treatment with gaseous ammonia and an alkyl nitrite. Unlike the previously described procedure,[17] isolation of the solid unstable arylhydroxylamine was avoided. Finally, an alkali metal cation could be exchanged for the ammonium cation by means of an ion exchange column. This method was used for preparing a variety of compounds **1**, where the Ar group was phenyl, or substituted phenyl: 2-, 3-, or 4-methyl; 2,3-dimethyl; 2-, 3-, or 4-ethyl; 2-isopropyl; 2-, or 4-methoxy; 4-hydroxy; 2-, or 4-fluoro; 2,4- or 2,5-difluoro; 4-, or 5-fluoro-2-methyl; 2-, 3-, or 4-chloro; 2,3-, 2,4-, or 2,5-dichloro; 3-, or 5-chloro-2-methyl; 4-bromo; 3-, or 4-acetyl; 3-methylol; 4-acetylamino; 1-naphthyl. Electron-donating substituents (e. g. methoxy, ethoxy, hydroxy, dimethylamino or diethylamino) render the arylhydroxylamine and its salts sensitive to air oxidation converting them into deeper colored products (azo or azoxy derivatives);[18] thus they must be processed rapidly at lower temperatures under inert atmosphere, and stored in the freezer. Compounds with dialkylamino substituents should be considered as vinylogues to Drago's and Keefer's NONO-ates prepared from nitric oxide and secondary amines.[7,8] With other substituents on the aromatic ring, the dry crystalline products are stable at room temperature and can be stored for a very long time in the freezer.

Downloaded At: 07:58 27 January 2011

Table 1 displays the N-aryl-N-nitrosohydroxylamine derivatives that were prepared. All compounds melt with darkening and decomposition, evolving gases vigorously. In agreement with earlier observations, compounds with electron-donating groups such as hydroxy or methoxy tend to be less stable on storage, and have to be stored in the freezer. The same approach failed to allow us to obtain systems with other highly electron-donating groups such as amino. Some compounds in Table 1 (1-3, 6, 7, 18-20, 25 and 32) were described previously. All new compounds gave acceptable results in elemental analyses for nitrogen; due to hygroscopicity (especially for sodium salts), the errors for carbon and hydrogen analyses were sometimes above the normal limits.

Infrared absorption spectra indicated the presence of water of crystallization in some instances. This was the case of the *ortho*-methyl derivative, and of a few other compounds with other *ortho*-groups. Otherwise, the IR spectra did not have unusual features. The characteristic strong bands of these compounds appear in the following ranges: 1215-1225, 1265-1280, 1320-1345, 1400-1405, 1480-1505 and 1590-1605 cm^{-1}. The bond stretching vibrations of the ammonium cation appear also as medium strong bands. ^{1}H-NMR and ^{13}C-NMR Spectra of selected cupferron derivatives (Tables 2 and 3) confirmed the structures of all new compounds. X-ray Structure determinations were carried out for cupferron, its *ortho*-methyl and *ortho*-chloro derivatives, and will be published separately.[19] The

planar NONO group has dihedral angles of 18, 53, and 64°, respectively, relative to the aryl groups of these three compounds.

TABLE 2. ^{1}H NMR Spectra of Selected Compounds **1** in DMSO-d_6 (δ, ppm)

Cmpd	Aromatic hydrogens [a]					NH_4	CH_2	CH_3
1	2	3	4	5	6			
H	7.91d (7.4)	7.38t (7.4)	7.27t (7.4)	7.38t (7.4)	7.91d (7.4)	7.75br	-	-
2-Me	-	7.27d (8.0)	7.24t (8.0)	7.26t (8.0)	7.38d (8.0)	6.38br	-	2.28s
4-Me	7.78d (8.5)	7.21d (8.5)	-	7.21d (8.5)	7.28d (8.5)	7.35br	-	-
2-Et	-	7.31d (8.5)	7.23t (8.5)	7.31t (8.5)	7.32d (8.5)	6.15br	2.65q (7.5)	1.11t (7.5)
4-Et	7.82d (8.5)	7.22d (8.5)	-	7.22d (8.5)	7.82d (8.5)	7.87br	2.61q (7.4)	1.18t (7.4)
3-Cl	7.88s	-	7.26d (8.0)	7.35t (8.0)	7.83d (8.0)	7.23br	-	-
2-F	-	7.33m (9.1) [11.4]	7.36m (9.1, 9.1) [4.4]	7.26m (9.1, 9.1) [3.3]	7.71m (9.1) [8.6]	7.70br	-	-
2,5-F_2	- (9.9) [5.0, 10.2]	7.35m (3.5, 9.9) [3.5, 7.4]	7.15m	-	7.56m (3.5) [6.0, 9.2]	7.75br		
4-F,2-Me	7.15m (2.8) [9.7]	-	7.07m (2.8, 8.7) [8.7]	7.38m (8.7) [5.6]	4.91br	2.27s		

a) Coupling constants *J* (Hz) are in parentheses for H-H and in brackets for H-F.

Under the conditions of chemiluminiscence reaction with ozone, all cupferron derivatives were shown to yield NO. On aortic rings, all compounds exerted relaxation; the *ortho*-substituted ones also indicated that they were causing a more pronounced relaxing action on smooth muscle strips (rat or human uterine strips *in vitro*) than the other ones. The use of such cupferron derivatives (particularly *ortho*-substituted ones) as nitric oxide donors has been patented recently.[20] The biological activity data are presented in the patent.

EXPERIMENTAL SECTION

Commercial nitro compounds were obtained from Aldrich and used as received. Infrared spectra were recorded with an FT-IR instrument, and NMR spectra were determined on a 300 MHz Varian Gemini instrument. Mps were obtained in capillaries on a MEL-TEMP apparatus.

Downloaded At: 07:58 27 January 2011

TABLE 3. ^{13}C NMR Spectra of Selected Compounds in DMSO-d_6 (δ, ppm) [a]

Subst. in **1**	C-1	C-2	C-3	C-4	C-5	C-6	CH_2	CH_3
H	144.2	118.2	128.7	129.6	128.7	118.2	-	-
2-Me	144.4	132.1	131.1	126.3	128.1	124.5	-	18.5
4-Me	141.8	118.3	129.1	136.5	129.1	118.3	-	20.6
2-Et	144.1	138.1	129.4	126.2	128.2	124.8	24.4	15.2
4-Et	142.7	118.4	127.9	142.1	127.9	118.4	27.8	15.6
3-Cl	145.3	117.5	132.8	125.6	129.5	116.2	-	-
2-F	132.9 (10.8)	154.4 (250.8)	116.9 (20.7)	128.7 (7.4)	124.6 (3.7)	124.8 (0)	-	-
2,5-F_2	133.6 (12.6) (10.6)	150.6 (274.6) (2.8)	118.3 (24.4) (9.3)	114.5 (7.7) (24.1)	157.9 (2.4) (240.5)	110.7 (0) (27.7)	-	-
4-F,2-Me	124.4 (2.8)	136.1 (8.3)	114.4 (22.4)	162.1 (242.5)	118.5 (22.5)	127.4 (9.1)	-	19.7 (0)

a) Coupling constants between ^{13}C and ^{19}F (in Hz) are in parentheses.

Downloaded At: 07:58 27 January 2011

N-Nitrosoarylhydroxylamine Salts. General Procedure.- The nitro derivative (0.1 mole) was stirred with 500 mL of an aqueous (or 30% ethanol-aqueous) solution of ammonium chloride (11.0 g, 0.2 mole). When the nitro derivative was solid with melting point above 85° or had a very low water solubility, 30% percent aqueous ethanol was used, and the initial temperature was raised to 60-70°. Zinc powder (0.2 mole) was added gradually under vigorous mechanical stirring so as to maintain the temperature around 70° due to the exothermicity of the reaction. After 60-90 minutes, the mixture was cooled below 35° and filtered with suction. The solid residue was thoroughly washed with three or four 60 mL portions of diethyl ether; the wash ether was saved and used for extracting the filtrate each time.[21] The combined ethereal extracts were dried over sodium sulfate, and cooled under 0° in an ice-salt mixture. A vigorous stream of gaseous ammonia was bubbled into the ethereal solution, and after 5-10 minutes, a slight excess (0.15 mol) of *n*-butyl nitrite was added in small portions during 15 minutes maintaining the cooling and the stream of NH_3. The cupferron analog (ammonium salt) precipitated. If it separated as a liquid, crystallization was induced by scratching with a glass rod. The product was collected after being kept at 0° for 1-2 hrs, and washed thoroughly with diethyl ether. Overall yields varied between 20 and 85% (Table 1).

The optional conversion into sodium salts was performed as follows. A column (2 cm diameter) packed with 100 g of cation exchange resin which had been soaked in a saturated aqueous solution of sodium hydrogen carbonate for 24 hrs and then rinsed with distilled water, was used for exchanging ammonium with sodium cations: a saturated solution of the cupferron analog (1-2 g) in water or in 50% aqueous ethanol was passed through the column; elution was performed with the same solvent. The eluates were combined and the solvent was removed by using a rotary evaporator

under vacuum (1 Torr) at 30-40°, or by freeze-drying techniques for some of the heat-sensitive compounds with electron-donating substituents. The yield was in the range 50-80 % (Table 1).

Acknowledgment.- We acknowledge assistance from the Advanced Technology Transfer of the State of Texas, and from the Welch Foundation of Houston, Texas.

REFERENCES

1. L. Ignarro and F. Murad (Eds.), *Nitric Oxide. Biochemistry, Molecular Biology, and Therapeutic Implications,* Advances in Pharmacology vol. 34, Academic Press, San Diego, 1995.

2. S. R. Vincent, in *Nitric Oxide in the Nervous System,* (Ed. S. R. Vincent), Academic Press, New York, 1995, p. 83.

3. J. S. Stamler and M. Feelisch, in *Methods in Nitric Oxide Research* (Eds. M. Feelisch and J. Stamler), Wiley, New York, 1996.

4. J. S. Beckman, in *Nitric Oxide. Principles and Actions* (Ed. J. Lancaster Jr.), Academic Press, New York, 1996; B. Mayer, in *Nitric Oxide in the Nervous System* (Ed. S. R. Vincent), Academic Press, London, 1995, p. 21.

5. Y. A. Henry, in *Nitric Oxide Research from Chemistry to Biology: EPR Spectroscopy of Nitrosylated Compounds,* (Ed. J. A. Henry, A. Guissani and B. Ducastel), Chapman and Hall, New York and Landes Bioscience, Austin, TX, 1996, p. 3.

6. M. R. Schäffer, U. Tantry, S. S. Gross, H. L. Wasserkrug and A. Barbul, *J. Surgical Res.,* **63**, 237 (1996); G.-B. Yi, M. A. Khan and G. B. Richter-Addo, *Inorg. Chem.,* **39**, 5703 (1995).

7. a) R. S. Drago and F. E. Paulik, *J. Am. Chem. Soc.,* **82**, 96 (1960); b) R. S. Drago and B. R. Karstetter, *ibid.,* **83**, 1819 (1961);c) R. S. Drago, R. O. Ragsdale and D. P. Eyman, *ibid.,* **83**, 4337 (1961); d) R. S. Drago, *in Free Radicals in Inorganic Chemistry,* Advances in Chemistry Series No. 36, Amer. Chem. Soc., Washington, D.C., 1962, p. 143; d) R. Longhi, R. O. Ragsdale and R. S. Drago, *Inorg. Chem.,* **1**, 768 (1962); f) R. O. Ragsdale, B. R. Karstetter and R. S. Drago, *ibid.,* **4**, 420 (1965).

8. a) T. J. Hansen, A. F. Croisy and L. K. Keefer, in: *N-Nitroso Compounds: Occurrence and Biological Effects* (Eds. H. Bartsch, I. K. O'Neill, M. Castegnaro and M. Okada), IARC Publication No. 41, International Agency for Research on Cancer, Lyon, p. 21; b) L. K. Keefer, D. Christodolou, T. M. Dunams, J. A. Hrabie, C. M. Maragos, J. E. Saavedra and D. A. Wink, in *Nitrosamines and Related N-Nitroso Compounds: Chemistry and Biochemistry* (Eds. R. N. Loeppky and C. J. Michedja), A.C.S. Symp. Series No. 553, Amer Chem Soc., Washington, D.C., p. 136 (1994); c) L. K. Keefer, D. A. Wink, T. M. Dunams and J. A. Hrabie, U.S. Pat. 5,212,204 (May 18, 1993); *Chem. Abstr.,* **113**, 145344 (1990) for Pat. Appl. 423,279 (March 1, 1990); d) J. E. Saavedra, T. M. Dunams, J. L. Flippen-Anderson and L. K. Keefer, *J. Org. Chem.* **57**, 6134 (1992); e) S. T. Hanson, T. C. Hutsell, L. K. Keefer, D. L. Mooradian and D. J. Smith, *Adv. Pharmacol.,* **34**, 383 (1995); f) D. L. Mooradian, T. C. Hutsell and L. K. Keefer, *J. Cardiovasc. Pharmacol.,* **25**, 674 (1995); g) J. E. Saavedra, G. J. Southan, K. M. Davies, A. Lundell, C.

Downloaded At: 07:58 27 January 2011

Markou, S. R. Hanson, C. Adrie, W. E. Horford, W. M. Zapol and L. K. Keefer, *J. Med. Chem.*, **39**, 4361 (1996); h) L. K. Keefer, R. W. Nims, K. M. Davies and D. A. Wink, *Methods in Enzymology,* **268**, 281 (1996).

9. A. T. Pilipenko, L. L. Shevchenko and O. S. Zulfigarev, *Kupferron,* Nauka, Moscow, 1988 (in Russian); G. F. Smith, *Cupferron and Neo-Cupferron,* G. F. Smith Chem. Co., Columbus, Ohio, 1938.

10. E. Bamberger, *Ber.,* **42**, 1689 (1909).

11. F. Minisci and R. Galli, *Chim. Ind. (Milano),* **46**, 423 (1964).

12. a) A. T. Balaban, N. Negoita and I. Pascaru, *Rev. Roum. Chim.,* **16**, 721 (1971); b) A. T. Balaban and N. Negoita, *ibid.,* **17**, 1227 (1972); c) A. T. Balaban, N. Negoita and R. Baican, *J. Magn. Reson.* **9**, 1 (1973); d) M. T. Caproiu, N. Negoita and A. T. Balaban, *Tetrahedron Lett.,* 1825 (1977); e) A. T. Balaban, E. U. Würthwein and P. R. Schleyer, *Tetrahedron,* **43**, 405 (1987).

13. H. Iida, T. Sato, H. Kawamoto, K. Takahashi and K. Yamada, *Nippon Kagaku Kaishi* 1003 (1978); *Chem. Abstr.,* **89**, 179627 (1978).

14. J. Sand and F. Singer, *Ann.,* **329**, 190 (1903).

15. E. M. Y. Quinga, T. Bieker, M. P. Dziobak and G. D. Mendenhall, *J. Org. Chem.,* **54**, 2769 (1989).

16. D. K. Taylor, I. Bytheway, D. H. R. Barton, C. A. Bayse and M. H. Hall, *J. Org. Chem.,* **60**, 435 (1995).

17. C. S. Marvel and O. Kamm, *Org. Synth. Coll. Vol. 1*, p. 445, 1941.

18. J. R. Hwu, C. S. Yau, S. Tsay and T. Ho, *Tetrahedron Lett.,* **38**, 9001 (1997).

19. E. Czerwinski, R. E. Garfield, W. A. Seitz and A. T. Balaban, *To be published.*

20. R. E. Garfield, A. T. Balaban, W. A. Seitz, D. J. Klein and M. Lesko, U. S. Pat. 5,698,738 (Dec. 16, 1997); Internat. Pat. Applic. PCT/US/96/0694 (May 15, 1996).

21. O. Kamm and C. S. Marvel, *Org. Synth. Coll. Vol. 1*, p. 177, 1941.

(Received August 13, 1997; in final form May 27, 1998)

Downloaded At: 07:58 27 January 2011