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Aminoxyl Radicals from *N*-Phenyl-1-(2-oxo-1-azacycloalkyl)-methanesulfonamides

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Summary. The synthesis and reaction with two oxidation agents is described for *N*-phenyl-1-(2-oxo-1-azacycloalkyl)methanesulfonamides. Their oxidation was carried out using $RO_2\cdot$ radicals and 3-chloroperbenzoic acid. In both cases, the EPR spectra of corresponding aminoxyl radicals were recorded. Their simulation confirmed that the $-SO_2-$ group in the neighbourhood of the $-NO^{\bullet}-$ fragment does not prevent the interaction of the unpaired electron with the methylene protons and the nitrogen atom of the heterocyclic ring.

Keywords. Aminoxyl radicals; EPR; Sulfonamides.

Introduction

Substituted *N*-phenyl-1-(2-oxo-1-azacycloalkyl)methanesulfonamides constitute a group of compounds, which can be considered as potential candidates for the therapy of neurodegenerative diseases. Their action is based on the strengthening of the cognitive function. The presence of a secondary amino group in the molecule represents the structural factor, which implies a tendency towards oxidation either with peroxyradicals or peroxyacids. As a result, the formation of corresponding arylsulfonaminoxyl radicals is expected in both oxidation reactions, where the first one characteristically proceeds by a radical [1], the second one by a nonradical mechanism [2]. Generally, the ability of studied compounds to form aminoxyl radicals can be regarded as a measure of their readiness to scavenge various reactive oxygen species (ROS), taking part in origin of many serious diseases like diabetes, cancer, or *Alzheimer* disease.

Until now, only a limited number of EPR data characterizing this type of aminoxyl radicals is available. Therefore, new information on the spin density

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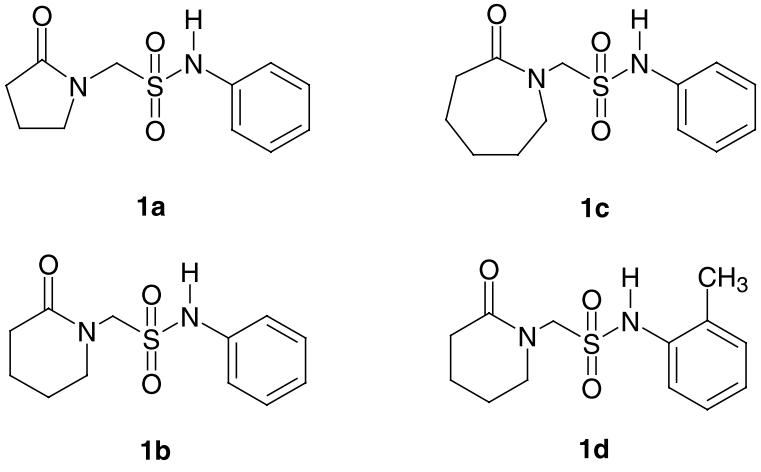
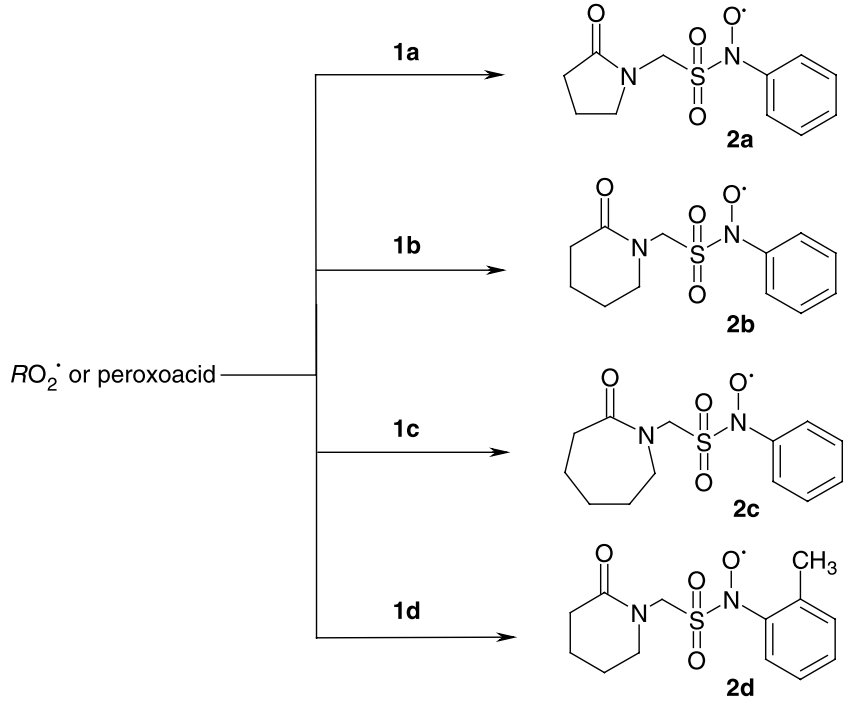
distribution should be extracted from the detailed analysis of the experimental EPR spectra.

Results and Discussion

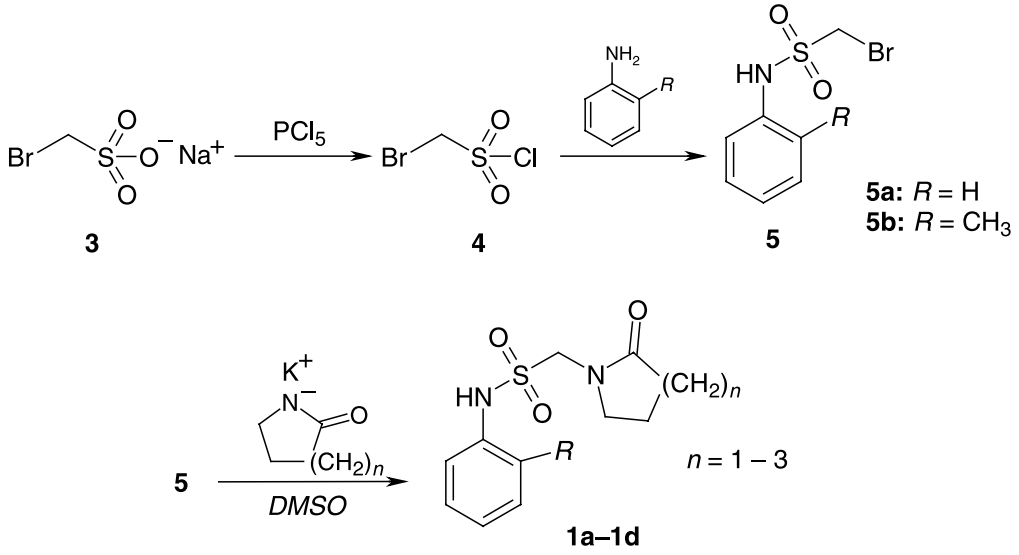
Within the present EPR study compounds **1a**–**1d** (Formulae) prepared according to Scheme 2 were investigated. As a source of peroxy radicals, $(CH_3)_3COO^{\bullet}$ radicals prepared by the decomposition of *t*-butylhydroperoxide on the surface of PbO_2



Formulae



Scheme 1



Scheme 2

were employed [3]. Simultaneously, 3-chloroperbenzoic acid was utilized as an oxidation agent in benzene solution for the generation of aminoxyl radicals from **1a**–**1d**. Application of both procedures proved the formation of the corresponding aminoxyl radicals **2a**–**2d** (Scheme 1).

The quality of the EPR spectra enabling their unambiguous interpretation using spectral simulation was substantially better with aminoxyls prepared by oxidation using 3-chloroperbenzoic acid. Also the achieved concentration of aminoxyls was higher in this case. In Fig. 1 experimental and simulated EPR spectrum of the aminoxyl radical **2a** is shown. In Table 1 the splitting constants obtained by simulation are presented.

From the values in Table 1 it follows that the $-SO_2-$ group in the neighbourhood of the $-NO^{\bullet}-$ fragment does not prevent the distribution of the spin density to the $-CH_2-X$ moiety (X = heterocyclic ring). The spin density is considerably transferred to this group, what can be documented by the splitting constants of the methylene protons in **2a**–**2d**. The $a_H(CH_2)$ splittings in the region 0.4–0.5 mT are about 0.2 mT lower than those found in substituted aromatic aminoxyls $Ph-NO^{\bullet}-CH_2-Ph$, prepared by spin-trapping of benzyl radicals [4]. Another phenomenon observed with **2a**–**2d** is the steric effect originating from carbonyl group of the heterocyclic part of the molecule, which becomes evident by its extension from a 5-membered (**2a**) to a 7-membered (**2c**) ring. While in **2a**, **2b**, and **2d** the methylene protons are fully equivalent, in **2c** containing the 7-membered ring the partial unequivalency of the methylene protons ($1 \times a_H = 0.49$ mT, $1 \times a_H = 0.43$ mT) has to be accounted for in a simulation of the experimental EPR spectrum. A steric effect appears also in aminoxyl **2d** where the presence of the methyl group in *ortho* position of the phenyl ring leads, in comparison with unsubstituted aminoxyls **2a**–**2c**, to a decrease of the splitting constants in *ortho* and *para* position accompanied by an increase of the $a_N(NO)$ value. This can be reproduced as a consequence of the reduced extent of conjugation between the $-NO^{\bullet}-$ group

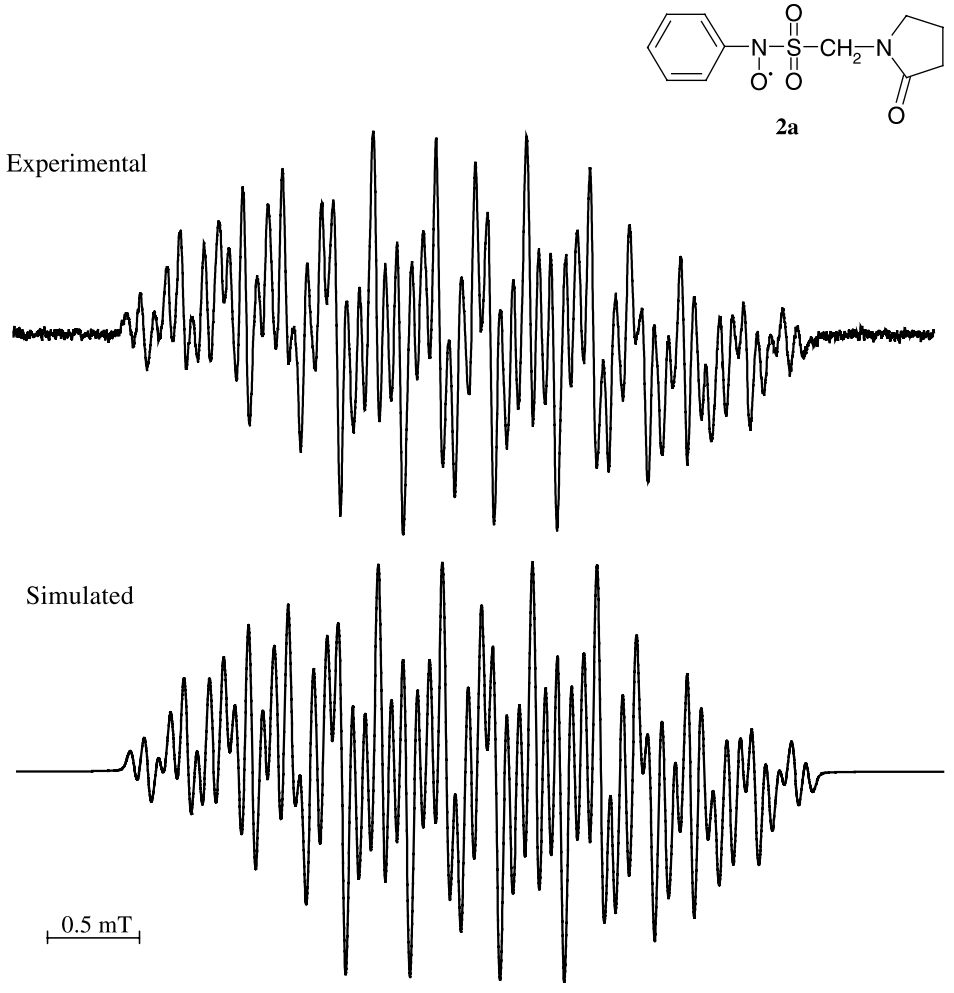


Fig. 1. Experimental and simulated EPR spectrum of the aminoxyl radical **2a** in benzene solution

Table 1. EPR parameters of aminoxyl radicals **2a**–**2d** in benzene solution ($g \cong 2.0055$)

Radical	a_N(NO) / mT	a_H(o, p) / mT	a_H(m) / mT	a_H(CH_2) / mT	a_N(het) / mT
2a	1.030	0.265	0.090	0.430	0.350
2b	1.035	0.260 (2H) 0.290 (1H)	0.090	0.475	0.280
2b[a]	1.062	0.260 (2H) 0.290 (1H)	0.090	0.510	0.280
2c	1.035	0.260 (2H) 0.295 (1H)	0.098	0.430 (1H) 0.460 (1H)	0.293
2d	1.145	0.170 (2H) 0.180 (1H)	0.080	0.480	0.431

[a] In $CHCl_3$ solution

and the phenyl ring, which results in the decline of spin density in the aromatic part of the molecule. Similar effects have been reported in the case of different mono *ortho* substituted diphenylaminoxyls, where the decrease of conjugation in an *ortho* substituted phenyl ring leads to the considerably asymmetrical distribution of spin density [5].

The stability of aminoxyl radicals **2a**–**2d** characterized by the life-time of more than 10 min, can be attributed not only to the presence of the $-SO_2-$ group in the neighbourhood of the $-NO^{\bullet}-$ fragment, but the effect of the heterocyclic ring must also be taken into account. This statement is supported by the fact that similar experiments, aiming at the generation of aminoxyl radicals from bromo substituted analogues **5** were unsuccessful. On the other side, replacing the $-SO_2-$ group by the –CO– group in structure **1**, no aminoxyl radicals were observed using both oxidation methods.

To summarize, the oxidation of *N*-phenyl-1-(2-oxo-1-azacycloalkyl)methanesulfonamides **1a**–**1d** with *t-Bu*$O_2^{\bullet}$ radicals and 3-chloroperbenzoic acid affords the stable aminoxyl radicals **2a**–**2d**. Their EPR parameters, confirmed by simulation, point out the specific property of $-SO_2-$ group. Relatively high splitting constants $a_H(CH_2)$, comparable with those in benzyl phenyl aminoxyl radicals $Ph-NO^{\bullet}-CH_2-Ph$, document the effective transfer of spin density to $-CH_2-X$ moiety (X = heterocyclic ring), *i.e.* $-SO_2-$ group does not significantly isolate the $-NO^{\bullet}-$ fragment from methylene protons and N atom of heterocyclic ring. The steric effects, stemming either from the *ortho* substitution in phenyl ring or from the size of heterocyclic ring were also observed.

Experimental

The *N*-phenyl-1-(2-oxo-1-azacycloalkyl)methanesulfonamides **1a**–**1d** were synthesized according to the procedure described below. All other chemicals, including benzene, $CHCl_3$, and oxidation agents (*t*-butylhydroperoxide, PbO_2, 3-chlorperbenzoic acid) were commercially available (Fluka). ^1H and ^{13}C NMR spectra were measured on the 200 MHz FT-NMR spectrometer Varian Gemini 2000 (Varian, Palo Alto, CA, U.S.A.), and melting points were determined on the *Boetius* apparatus PHMK-05 (Rapido, Radebeul, Germany). EPR spectra were recorded with a SpectraNova (E-I-A Warenhandels GmbH) spectrometer. The processing and simulation of experimental EPR spectra were performed using WINEPR and SimFonia programs (Bruker).

*N-Phenyl-1-(2-oxoazacycloalkyl)sulfonamides **1a–1d***

The appropriate lactame (4 mmol, pyrrolidin-2-one, piperidin-2-one, or azepan-2-one) was added to a suspension of 0.9 g finely powdered KOH (16 mmol) in 3 cm^3 *DMSO*. After 5 min stirring, 1 mmol of the appropriate *N*-phenyl-1-bromomethanesulfonamide **5** was portionwise added and the stirring at room temperature was continued for additional 3 h. Then, the reaction mixture was acidified with 12% aqu acetic acid and stored with cooling, until a white precipitate appeared. This product was filtered off, washed with H_2O, and dried *in vacuo*.

N-Phenyl-1-(2-oxopyrrolidin-1-yl)methanesulfonamide (**1a**, $C_{11}H_{14}N_2O_3S$)

Yield 40% (100 mg); mp 151–153°C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.26–7.15$ (m, 2H, *m*-arom) 6.80–6.72 (m, 3H, *o*-+*p*-arom) 4.76 (d, $J = 6.0$ Hz, SO_2CH_2) 4.38 (s, NH) 3.40 (t, $J = 7.0$ Hz, 5-CH_2pyrr) 2.38 (t, $J = 8.0$ Hz, 3-CH_2pyrr) 2.03–1.92 (m, 4-CH_2pyrr) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 175.41$, 145.69, 129.41, 118.63, 113.26, 51.91, 45.92, 31.15, 17.77 ppm.

N-Phenyl-1-(2-oxopiperidin-1-yl)methanesulfonamide (**1b**, $C_{12}H_{16}N_2O_3S$)
Yield 31% (78 mg); mp 124–125°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.26$–7.15 (m, 2H, *m*-arom) 6.79–6.72 (m, 3H, *o*-+*p*-arom) 4.85 (d, $J = 5.0$ Hz, SO_2CH_2) 4.56 (s, NH) 3.33 (t, $J = 6.0$ Hz, 6-CH_2pip) 2.38 (t, $J = 5.5$ Hz, 3-CH_2pip) 1.77–1.71 (m, 4 + 5-CH_2pip) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 166.65$, 137.96, 129.32, 124.76, 120.65, 55.62, 47.38, 38.91, 33.45, 19.22 ppm.

N-Phenyl-1-(2-oxoazepan-1-yl)methanesulfonamide (**1c**, $C_{13}H_{18}N_2O_3S$)
Yield 63% (178 mg); mp 146–147°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.26$–7.15 (m, 2H, *m*-arom) 6.79–6.70 (m, 3H, *o*-+*p*-arom) 4.82 (s, SO_2CH_2) 4.55 (s, NH) 3.37 (t, $J = 5.0$ Hz, 7-CH_2azep) 2.50 (t, $J = 6.0$ Hz, 3-CH_2azep) 1.64–1.47 (m, 4 + 5 + 6-CH_2azep) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 146.13$, 129.35, 118.66, 114.01, 57.56, 48.36, 37.56, 29.90, 28.48, 23.31 ppm.

N-(2-Methylphenyl)-1-(2-oxopiperidin-1-yl)methanesulfonamide (**1d**, $C_{13}H_{18}N_2O_3S$)
Yield 45% (127 mg); mp 135–138°C; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.35$–7.18 (m, 4H, arom), 4.85 (d, $J = 5.0$ Hz, SO_2CH_2) 4.57 (s, NH) 3.33 (t, $J = 6.0$ Hz, 6-CH_2pip) 2.38 (t, $J = 5.5$ Hz, 3-CH_2pip) 2.32 (s, CH_3) 1.77–1.71 (m, 4 + 5-CH_2pip) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 166.65$, 137.96, 129.32, 126.15, 124.76, 120.65, 119.42, 55.62, 47.38, 38.91, 33.45, 19.22, 17.75 ppm.

Bromomethanesulfonyl chloride (**4**)
Sodium bromomethanesulfonate (**3**, 19.7 g, 0.1 mol), prepared according to Ref. [6] was mixed with 21.9 g PCl_5 (0.105 mol). A spontaneous exothermal reaction immediately started and after its finishing (10–15 min), the reaction mixture was heated 45 min at 130–140°C and additional 30 min at 70°C. The reaction product was obtained by distillation at reduced pressure, bp 93–95°C/2.7 kPa (Ref. [7] 87–89°C/2.0 kPa), yield 79% (15.3 g); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 5.11$ (s, CH_2) ppm.

N-Phenyl-1-bromomethanesulfonamides ***5***
Bromomethanesulfonyl chloride (**4**, 3.9 g, 0.02 mol) dissolved in 10 cm^3 toluene were dropwise added to a stirred solution of 0.04 mol aniline or 2-methylaniline during 15 min. The resulting reaction mixture was refluxed for 5 h, then cooled, and the precipitate of anilinium chloride was filtered off. The filtrate was extracted with 3% aqu HCl and H_2O and then the desired **5** was extracted into 3% NaOH solution. The alkaline H_2O extract was acidified with HCl to $pH = 1$ and the precipitated product was isolated by filtration.

N-Phenyl-1-bromomethanesulfonamide (**5a**, $C_7H_8NO_2SBr$)
Yield 50% (1.4 g); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 10.34$ (s, NH) 7.38–7.13 (m, 5H, arom) 4.90 (s, CH_2) ppm; ^{13}C NMR (50 MHz, *DMSO*-d_6): $\delta = 137.17$, 129.13, 124.26, 120.38, 41.28 ppm.

N-(2-Methylphenyl)-1-bromomethanesulfonamide (**5b**, $C_8H_{10}NO_2SBr$)
Yield 38% (2.0 g); ^{1}H NMR (200 MHz, *DMSO*-d_6): $\delta = 9.65$ (s, NH) 7.33–7.16 (m, 4H, arom) 4.88 (s, CH_2) 2.33 (s, CH_3) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 134.73$, 134.46, 130.67, 126.72, 126.41, 42.42, 17.99 ppm.

Oxidation of ***1*** *with t-BuOOH/PbO_2*
Sulfonamides **1** were dissolved in a 0.01 *M* benzene solution of *t-Bu*OOH in a molar ratio **1**/*t-Bu*OOH = 1/1. In 2 cm^3 of this solution 10 mg PbO_2 were suspended and stirred for 1 min. After the sedimentation of solid PbO_2, 0.5 cm^3 of the liquid phase were transferred into an EPR tube ($\phi = 5$ mm), bubbled with N_2, and measured.

*Oxidation of **1** with 3-Chloroperbenzoic Acid*
A 0.01 *M* benzene solution of **1** (1 cm^3) was mixed with the same volume of a 0.01 *M* benzene solution of 3-chloroperbenzoic acid and stirred for 1 min. 0.5 cm^3 of the reaction mixture were placed into an EPR tube, bubbled with N_2, and measured.

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