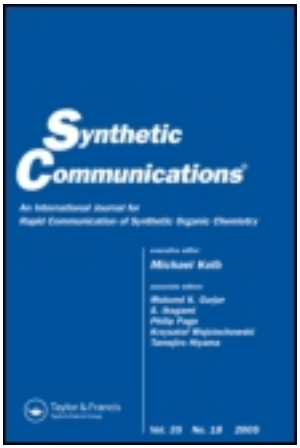

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Preparation of 1-Arylideneamino- and 1-Alkylideneamino-3-phenoxyprop N-Oxides—A New Type of Nitrones

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Preparation of 1-Arylideneamino- and 1-Alkylideneamino-3-phenoxypropan-2-ol *N*-Oxides—A New Type of Nitrones

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Abstract: The reaction of phenylglycidyl ether with hydroxylamine was evaluated, and the prepared 1-hydroxyamino-3-phenoxypropan-2-ol was used for the

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1-arylideneamino- and 1-alkylideneamino-3-phenoxypropan-2-ol N-oxides syntheses. The title nitrones were tested as antioxidants in biological systems.

Keywords: Free radical scavengers, nitrones, oxidative stress

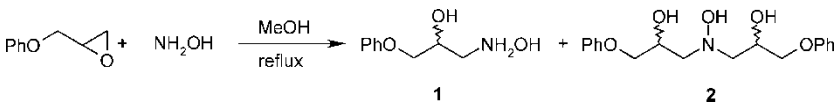
In the search for new biologically active free-radical scavengers and antioxidants, we concerned ourselves with compounds capable of dissolving in aqueous media. According to our expectations, some alcohols possessing a nitrone moiety, for example, β-hydroxynitrones, might exhibit the desired properties.

To prepare these compounds, we decided to use β-hydroxy-N-substituted hydroxylamines as the substrates and to react them with aldehydes. Opening of the appropriate oxirane derivative with the hydroxylamine base was considered as the simplest method for preparing these substrates. In this research we used the reaction of phenylglycidyl ether with hydroxylamine as described almost half a century ago.[1,2] According to the authors,[1] the sole product of the reaction, obtained by them in the yield of 95%, has to be 1-hydroxyamino-3-phenoxypropan-2-ol (**1**). Following the literature procedure, we repeated the reaction several times and found that the yield and the melting point of the crude reaction product were close to the literature[1] data, but the ^{1}H NMR spectrum was much too complicated for such a simple molecule. The TLC analysis showed at least five substances present: two in large amounts and three other in traces. After separation by means of silica-gel column chromatography and recrystallization, the two main products were identified as the expected monosubstituted hydroxylamine derivative **1** (45–50% yield) and its symmetrical N,N-disubstituted analog (**2**) formed according to Scheme 1.

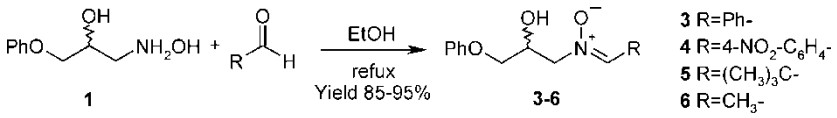
The structures of both compounds were confirmed by IR, MS, ^{1}H NMR, and ^{13}C NMR spectra, and C,H,N elemental analyses.

Pure 1-(hydroxyamino)-3-phenoxypropan-2-ol (**1**) refluxed in an ethanol solution with an equimolar amount of an aromatic aldehyde gave the corresponding 1-arylideneamino-3-phenoxypropan-2-ol N-oxides (**3–4**) according to Scheme 2.

The reaction also proceeded well with aliphatic aldehydes to yield the corresponding 1-(alkylideneamino)-3-phenoxypropan-2-ol N-oxides (**5,6**). All of the prepared nitrones (**3–6**) are crystalline compounds, which, upon concentration of the reaction mixture, separate almost pure. The yields of



Scheme 1.



Scheme 2.

the nitrones were high, ranging up to 95% of the theory, and their structures were confirmed by IR, ^{1}H NMR, and ^{13}C NMR spectra, as well as by CHN elemental analyses. Analysis of the NMR spectra allowed us to confirm that the compounds exist as single isomers with E configuration on the C=N double bond[3–6] and to rule out the cyclic 1,3-oxadiazolidine structure suggested by Kliegel.[7]

The antioxidant activity of the β-hydroxynitrones was examined by determination of the index of lipid peroxidation.[8] The oxidative stress was induced in vitro in the Sparque–Dawley rat's cerebral cortex homogenate by Fenton's reaction with $FeCl_2$ and L(+)-ascorbic acid solutions. In vivo experiments were preformed using 2-VO model (two vessel occlusion) on gerbils (*Merinos unquiculatus*). In both methods concentrations of thiobarbituric acid reactive substances (TBARS), including malondialdehyde (MDA), were spectrometrically recorded as an index of lipid peroxidation. The IC_{50} values obtained by regression analysis showed the activity of compound **6** is close to that exhibited by known antioxidants, for example, Carvedilol and Trolox.

The chemical and biological properties of the β-hydroxynitrones, as well as the extention of this reaction to other hydroxyaminoalcohols, are under investigation in our laboratories.

EXPERIMENTAL

Preparation of 1-(hydroxyamino)-3-phenoxypropan-2-ol (1): Sodium (6.90 g, 0.3 mol) was dissolved in methanol (200 mL) and the solution was added dropwise to a solution of hydroxylamine hydrochloride (20.85 g, 0.3 mol) in methanol (200 mL). The resulting NaCl was filtered off and the solution of hydroxylamine was treated with 15 g (0.1 mol) of phenylglycidyl ether. The mixture was refluxed for 2.5 h and, upon cooling to room temperature, the inorganic solid was removed, and the solvent was evaporated under reduced pressure. The residue was recrystallized twice from 2-propanol to yield 8.97 g (49%) of **1** as a colorless solid. $M_p = 111.5–112.5^\circ$C. ^{1}H NMR (DMSO-d_6) δ: 2.78 (dd; 1H$_a$; CH$_a$H$_b$N; $J_{gem} = 12.8$ Hz; $J_1 = 6.8$ Hz); 2.86 (dd; 1H$_b$; CH$_a$H$_b$N; $J_2 = 5.2$ Hz); 3.85 (dd; 1H$_c$; OCH$_c$H$_d$; $J_{gem} = 9.6$ Hz; $J_3 = 6.2$ Hz); 3.97 (dd; 1H$_d$; OCH$_c$H$_d$; $J_4 = 3.6$ Hz); 4.00 (m; 1H; CH); 4.94 (d; 1H; OH; $J_3 = 4.8$ Hz); 5.68 (s; 1H; OH); 6.88–6.92 (m; 3H; Ph); 7.24–7.28 (m; 3H; Ph + NH); ^{13}C NMR (DMSO-d_6) δ: 56.75; 66.06; 70.74;

114.41; 120.38; 129.44; 158.73; IR (Nujol mull; cm^{-1}) 3400; 3350; 1595; 1495; 1455; 1250; 1045; 745; 690. Anal. calcd. for $C_9H_{13}NO_3$: C, 59.00%; H, 7.15%; N, 7.65%. Found: C, 58.90%; H, 7.07%; N, 7.60%. The residual liquor after separation of **1** was evaporated, chromatographed on silica-gel column with 98 : 2 v/v chloroform/methanol and recrystallized from 2 : 3 v/v cyclohexane/diethyl ether to give **2** (30%) as a colorless solid. Mp = 89–92°C; ^{1}H NMR ($CDCl_3$) δ: 2.90–3.04 (m; 4H; 2 × CH_2N); 3.93–4.04 (m; 4H; 2 × CH_2O); 4.34–4.43 (m; 2H; 2 × CH); 6.78–6.90 (m; 4H; Ph); 6.93–6.97 (m; 2H; Ph); 7.23–7.27 (m; 4H; Ph); ^{13}C NMR ($CDCl_3$) δ: 63.30; 63.44; 67.46; 68.09; 69.91; 70.02; 114.56; 121.13; 129.48; 158.47; IR (Nujol mull; cm^{-1}). Anal. calcd. for $C_{18}H_{23}NO_5$: C, 64.85%; H, 6.95%; N, 4.20%. Found: C, 64.95%; H, 6.97%; N, 4.27%.

General method of 1-(arylideneamino)- and 1-(alkylideneamino)-3-phenoxypropan-2-ol N-oxides (3–6) preparation: Hydroxylamine derivative **1** (1.0 g; 5.45 mmol) was refluxed for 1.5 h. with an equimolar amount of the appropriate aldehyde in 50 mL of ethanol. After evaporation of approximately 20 mL of the solvent, the formed crystals were separated and recrystallized from ethanol to give nitrones **3** or **4**, or from 3 : 7 v/v benzene/hexane to give nitrones **5** or **6**.

(*E*)-1-(benzylideneamino)-3-phenoxypropan-2-ol N-oxide (3): Mp = 146.5–148.0°C; ^{1}H NMR ($CDCl_3$) δ: 3.97 (dd; $1H_a$; J_{gem} = 9.6 Hz; J = 7.2 Hz; $-CH_aH_bN=$); 4.14 (dd; $1H_b$; J = 4.8 Hz; $-CH_aH_bN=$); 4.17 (dd; $1H_c$; J_{gem} = 12.4 Hz; J = 7.2 Hz; $-OCH_cH_d-$); 4.28 (dd; $1H_d$; J = 2.6 Hz; $-OCH_cH_d-$); 4.56 (m; 1H; CH); 5.18 (d; 1H; J = 5.2 Hz; OH); 6.91 (m; 2H; Ph); 6.98 (m; 1H; Ph); 7.29 (m; 2H; Ph); 7.41 (s; 1H; H_α); 7.43 (m; 3H; Ph); 8.19 (m; 2H; Ph); ^{13}C NMR ($CDCl_3$) δ: 67.37; 68.39; 68.44; 114.46; 121.33; 128.57; 129.07; 129.57; 129.64; 131.09; 136.90; 158.16; IR (Nujol mull; cm^{-1}) 3220 (νOH); 1600 (νC=N); 1100 (νNO); MS (ES; MeOH): 272.1 (M + 1); 294.1 (M + 23); calcd.: 271.314. Anal. calcd. for $C_{16}H_{17}NO_3$: C, 70.83%; H, 6.32%; N, 5.16%. Found: C, 70.59%; H, 6.34%; N, 5,19%.

(*E*)-1-(4-nitrobenzylideneamino)-3-phenoxypropan-2-ol N-oxide (4): Mp = 151.5–152.5°C; ^{1}H NMR ($CDCl_3$) δ: 4.01 (dd; $1H_a$; J_{gem} = 9.6 Hz; J = 7.2 Hz; $-CH_aH_bN=$); 4.16 (dd; $1H_b$; J = 4.8 Hz; $-CH_aH_bN=$); 4.25 (dd; 1Hc; J_{gem} = 12.4 Hz; J = 7.2 Hz; $-OCH_cH_d-$); 4.32 (d; 1H; J = 5.2 Hz; OH); 4.34 (dd; $1H_d$; J = 3.0 Hz; $-OCH_cH_d-$); 4.60 (m; 1H; CH); 6.91 (m; 2H; Ar); 6.99 (m; 1H; Ar); 7.30 (m; 2H; Ar); 7.56 (s; 1H; H_α); 8.26 (m; 2H; Ar); 8.37 (m; 2H; Ar); ^{13}C NMR (CDCl3) δ: 68.31; 68.41; 68.60; 114.45; 121.59; 123.81; 129.32; 129.67; 134.57; 135.26; 148.25; 158.04; IR (Nujol mull; cm^{-1}) 3450 (νOH); 1650 (νC=N); 1515 (ν_{asym} NO_2); 1345 (ν_{sym} NO_2). Anal. calcd. for $C_{16}H_{16}N_2O_5$: C, 60.74%; H, 5.11%; N, 8.86%. Found: C, 60.76%; H, 5.20%; N, 8.80%.

(*E*)-1-(2,2-dimethylpropylideneamino)-3-phenoxypropan-2-ol N-oxide (5): Mp = 86.5–88.5°C; ^{1}H NMR ($CDCl_3$) δ: 0.93 (s; 9H; 3 × CH_3); 2.98 (dd; $1H_a$; J_{gem} = 12.7 Hz; J = 10.7 Hz; $-CHaH_bN=$); 3.41 (dd; 1Hb;

J = 4.7 Hz; $-CH_aH_bN=$); 4.10 (dd; 1Hc; J_{gem} = 10.4 Hz; J = 4.8 Hz; $-OCH_cH_d-$); 4.16 (dd; $1H_d$; J = 4.8 Hz; $-OCHcH_d-$); 4.50–4.55 (m; 2H; CH + OH); 6.43 (s; 1H; H_α); 6.91–6.96 (m; 3H; Ph); 7.26–7.31 (m; 2H; Ph); ^{13}C NMR ($CDCl_3$) δ: 25.28; 34.54; 60.77; 67.86; 74.03; 110.65; 114.54; 120.98; 129.44; 158.70; IR (Nujol mull; cm^{-1}) 3240 (νOH); 1630 (νC=N); 1110 (νNO); MS (ES; MeOH): 252.1 (M + 1); 274.1 (M + 23); calcd. 251.324. Anal. calcd. for $C_{14}H_{21}NO_3$: C, 66.91%; H, 8.42%; N, 5.57%. Found: C, 66.81%; H, 8.63%; N, 5.35%.

(*E*)-1-(ethylideneamino)-3-phenoxypropan-2-ol N-oxide (6): Mp = 105.5–107.0°C; ^{1}H NMR ($CDCl_3$) δ: 2.07 (d; 3H; J = 6 Hz; CH_3); 3,90 (dd; $1H_a$; J_{gem} = 9.6 Hz; J = 7.8 Hz; $-CH_aH_bN=$); 3.99 (dd; $1H_c$; J_{gem} = 12.5 Hz; J = 7 Hz; $-OCH_cH_d-$); 4.12 (m; $1H_b + 1H_d$); 4.44 (m; 1H; CH); 5.54 (d; 1H; J = 3.6 Hz; OH); 6.85 (q; 1H; J = 5.8 Hz; H_α); 6.87–6.91 (m; 2H; Ph); 6.97 (m; 1H; Ph); 7.26–7.31 (m; 2H; Ph); ^{13}C NMR ($CDCl_3$) δ: 12.61; 65.54; 68.00; 68.27; 114.38; 121.29; 129.56; 137.87; 158.15; IR (Nujol mull; cm^{-1}); MS (ES; MeOH): 210.1 (M + 1); 232.1 (M + 23); calcd. 209.243. Anal. calcd. for $C_{11}H_{15}NO_3$: C, 63.14%; H 7.23%; N, 6.69%. Found: C, 62.58%; H, 7.51%; N, 6.47%.

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