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Reactions of Hydroxyethylamino-1,4-benzoquinones with 2,4,6-Trimethylbenzonitrile Oxide, II [1]*

Manfred Schubert-Zsilavecz[1,2,*], Dagmar Gusterhuber[1], and Werner Likussar[2]

[1] Institut für Pharmazeutische Chemie, Universität Graz, Schubertstraße 1, A-8010 Graz, Austria
[2] Lehrstuhl für Organische Chemie, Universität Ulm, Albert-Einstein-Allee 11, D-89081 Ulm, Bundesrepublik Deutschland

Summary. 3,4,9a,9b-Tetrahydro-2*H*-1,2-oxazolo[5,4-h]1,4-benzoxazin-6(6a*H*)-ons **5a–c** were obtained by the reaction of hydroxyethylamino-1,4-benzoquinones **2a–c** with nitrile oxide **3**. The structures of the cycloadducts were elucidated NMR techniques including inverse longe-range $^{13}C,^{1}H$-experiments and homonuclear NOE difference spectroscopy.

Keywords. Hydroxyethylamino-1,4-quinones; Nitrile oxide; 1,2-Oxazolines, 4,5-fused; 1,3-Dipolar cycloadditions.

Über die Reaktion von Hydroxyethylamino-1,4-benzochinonen mit 2,4,6-Trimethylbenzonitriloxid, 2. Mitt. [1]

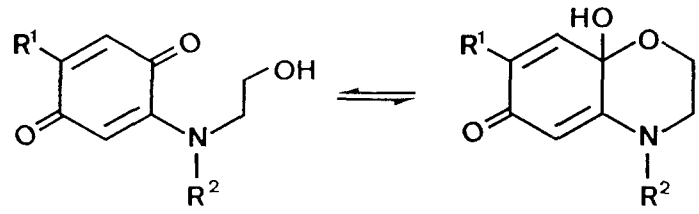
Zusammenfassung. Bei der Reaktion von Hydroxyethylamino-1,4-benzochinonen **2a–c** mit dem Nitriloxid **3** werden 3,4,9a,9b-Tetrahydro-2*H*-1,2-oxazolo[5,4-h]1,4-benzoxazin-6(6a*H*)-one **5** erhalten. Deren Strukturen wurden NMR-spektroskopisch – unter Einbeziehung inverser long-range $^{13}C,^{1}H$-Experimente und NOE-Differenz-Spektroskopie – aufgeklärt.

Introduction

The reactivity of 1,4-benzoquinones in [3 + 2] cycloadditions with aromatic nitrile oxide is well documented by the reaction of several substituted quinone derivatives (e.g. tetrachloro-, tetramethoxy-, 2,6-dichloro-, 2-methyl-, 2,6-dimethyl- and 2,5,6-trimethyl-*p*-benzoquinone). Depending on the number, pattern, combination and nature of the substituents of the quinones, isoxazoline (C=C adducts) or spiro-[1,4,2]dioxazole (C=O adducts) derivatives were obtained in these reactions [2]. Isoxazoles and related derivatives are basic units of many compounds most of which possess biological [3] or pharmaceutical [4] interest.

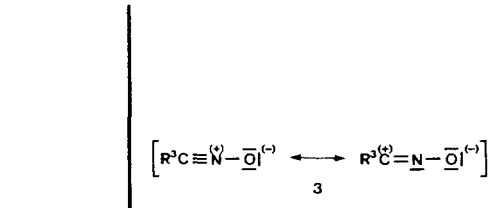
As part of our ongoing interest in the synthetic application of the reactions of quinones with 1,3-dipoles, we have begun to investigate the cycloaddition reactions

* Dedicated to Prof. Dr. R. Ott on the occasion of his 70th birthday

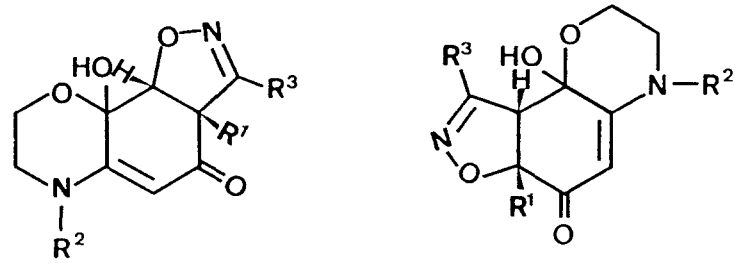


1: R^1 = -H

2: R^1 = $-CH_3$



3



4 5

1, 4	R^1	R^2	R^3
a	-H	$-CH_3$	Mesityl
b	-H	$-CH_2-C_6H_5$	Mesityl
c	-H	$-CH_2-CH_2-OH$	Mesityl

2, 5	R^1	R^2	R^3
a	$-CH_3$	$-CH_3$	Mesityl
b	$-CH_3$	$-CH_2-C_6H_5$	Mesityl
c	$-CH_3$	$-CH_2-CH_2-OH$	Mesityl

of aromatic nitrile oxides with monosubstituted 2-hydroxyethylamino-1,4-benzoquinones.

Monosubstituted quinones **1a–c** and 2,4,6-trimethylbenzonitrile oxide (*TMBNO*) **3** react with a high regioselectivity to give the cycloadducts **4** [1]. We now

report the results of our studies on the site- and regioselectivity in the reaction of *TMBNO* **3** with hydroxyethylamino-1,4-benzoquinones **2a–c** with a methyl-substituted C=C double bond.

Results and Discussion

The reactions of **2a–c** with the dipole **3** were carried out in refluxing methanol solution and lead to cycloadducts **5a–c** in low yields. In each case one regioisomer **5** was isolated. The characteristic feature of the mass spectra of the adducts **5a–c**, which furthermore confirm 1:1 adducts, is that weak molecular ion peaks appear, whereas the dominant peaks correspond to retro Diels–Alder cycloaddition fragments (**5a**: $m/z = 155$, $m/z = 127$, $m/z = 202$). It should be noted that the elimination of carbon dioxide from the molecular ion peaks appears as a key step in the fragmentation of C=C-adducts.

The modes the isoxazoline and cyclohexene moiety are fused were readily elucidated by means of HMBC-experiments [5] (Heteronuclear Multiple-Bond Connectivity: ^{1}H detected C,H-correlation, optimized for small coupling constants) and homonuclear NOE difference spectroscopy. In the HMBC spectrum of **5a** the signal of the angular proton H-9a shows crosspeaks versus five quarternary ^{13}C NMR signals at $\delta = 87.86$ (C-6a), 91.64 (C-5), 158.18 (C-9), 162.01 (C-4a), 192.60 (C-6) and versus the angular methyl group at $\delta = 22.91$, corresponding to an angular methyl group. The NOE difference spectra of **5a** and **5b** resulting from irradiation of the angular proton show through-space connectivities due to H-9a/angular CH_3, H-9a/mesityl *o*-methyl and H-9a/C-9b-OH, thus indicating the junction of isoxazoline and cyclohexene ring to be *cis*. Furthermore the site of oxygen-atom attachment of the nitrile oxide must be at carbon atom C-6 of the quinone.

Inspection of all data, particularly the NMR-spectra, leads to the conclusion that the LUMO (nitrile oxide)/HOMO (quinone) interaction is the governing factor in the cycloaddition reaction of *TMBNO* **3** to hydroxyethylamino-1,4-benzoquinones **1–2**. Contrary to the reactions of benzoquinones **1** the direction of addition is altered in the cycloaddition reactions of toluquinones **2**.

Experimental

Melting points were determined on a Tottolli melting point apparatus (Büchi) and are uncorrected. The IR spectra were recorded on a Perkin-Elmer-Gitterspektrophotometer 225. UV/VIS-spectra were obtained with a Shimadzu-UV-160 A UV/VIS Recording Spectrophotometer. The NMR spectra were recorded on a Bruker AMX-500 and on a Bruker AM-200 spectrometer. HMQC: phase-sensitive using TPPI, BIRD sequence, GARP-decoupled (^{13}C-decoupling: 60 ms). HMBC: phase-sensitive using TPPI, delay to achieve longe-range couplings: 71 ms ($J_{C,H} = 7$ Hz). Mass spectra were recorded with a Varian-Mat-312-Spectrometer with an ionisation energy of 70 eV. Thin-layer chromatography was performed on precoated plates of silica gel 60 F_{254} plates (Merck).

Starting Materials

2-Hydroxyethylamino-1,4-toluquinones **2a–c** were prepared using the method of König and Letsch [6]. 2,4,6-Trimethylbenzonitrile oxide **3** was formed according to literature by oxidation of 2,4,6-trimethylbenzaldoxime [7].

General Procedure for the Reaction of Quinones **2a–c** *with the Nitrile Oxide* **3**

A solution (50 ml) containing 6 mmol of the quinone **2** and 9 mmol of **3** in 50 ml methanol was heated at reflux for 50 h. Removal of the solvent left an oily residue, which crystallized on stirring with ethyl acetate (**5a**, **5b**) or chloroform (**5c**). The crude adducts **5** were recrystallized from a mixture of ethyl acetate and ethanol.

9b-Hydroxy-4,6a-dimethyl-9-(2,4,6-trimethylphenyl)-3,4,9a,9b-tetrahydro-2H-1,2-oxazolo[5,4-h]1,4-benzoxazin-6(6aH)-one (**5a**)

Yield 20%, m.p. 208–209 °C. UV/VIS (MeOH): λ_{max} (log ε) = 308.0 (4.70). IR (KBr): $\bar{\nu} = 1610\,cm^{-1}$ (C=O). ^{1}H-NMR (*DMSO-d*$_6$): δ = 6.75 (d, 2H, *m*-mesityl), 5.10 (s, 1H, 5-H), 4.07 (s, 1H, 9a-H), 4.02 (m, 1H, 2-$H_{ps.ax}$), 3.16 (m, 1H, 2-$H_{ps.eq}$), 2.88 (m, 1H, 3-$H_{ps.ax}$), 2.78 (s, 3H, NCH_3), 2.67 (m, 1H, 3-$H_{ps.eq}$), 2.14, 2.13 (each s, 3H, mesityl *o*-methyl), 1.97 (s, 3H, mesityl *p*-methyl), 1.63 (s, 3H, C-6a-CH3). ^{13}C-NMR (*DMSO-d*$_6$): δ = 192.00 (C-6), 162.01 (C-4a), 159.18 (C-9), 139.49, 138.38, 137.21 (mesityl C-2, C-4, C-6), 129.30 (mesityl C-3), 128.23 (mesityl C-1), 97.46 (C-5), 91.64 (C-9b), 87.86 (C-6a), 65.05 (C-9a), 57.20 (C-2), 48.82 (C-3), 39.39 (NCH_3), 22.91 (C-6a-CH3), 21.23, 21.01, 20.50 (mesityl CH_3). MS (70 eV): *m/z* (%) = 356 (8.5) [M^+], 328 (7.0), 202 (37.0), 155 (8.4), 127 (100), 82 (19.9). $C_{20}H_{24}N_2O_4$ (356.4). Calcd. C 67.40, H 6.79, N 7.86; found C 67.42, H 7.00, N 7.83.

4-Benzyl-9b-hydroxy-6a-methyl-9-(2,4,6-trimethylphenyl)-3,4,9a,9b-tetrahydro-2H-1,2-oxazolo[5,4-h]1,4-benzoxazin-6(6aH)-one (**5b**)

Yield 21%, m.p. 218–220 °C. UV/VIS (MeOH): λ_{max} (log ε) = 246 (4.06), 309 (4.48). IR (KBr): $\bar{\nu} = 1608\,cm^{-1}$ (C=O). ^{1}H-NMR (*DMSO-d*$_6$): δ = 7.41–7.25 (m, 5H, Aryl), 6.87 (d, 2H, *m*-mesityl), 5.09 (s, 1H, 5-H), 4.39 (dd, 2H, $CH_2C_6H_5$), 4.18 (s, 1H, H-9a), 4.06 (m, 1H, 2-$H_{ps.ax}$), 3.14 (m, 1H, 2-$H_{ps.eq}$), 2.74 (m, 2H, $H_{ps.ax}$, 3-$H_{ps.eq}$), 2.23, 2.20 (each s, 3H, mesityl *o*-methyl), 2.03 (s, 3H, Mesityl *p*-methyl), 1.62 (s, 3H, C-6a-CH_3). ^{13}C-NMR (*DMSO-d*$_6$): δ = 188.11 (C-6), 158.66 (C-9), 156.63 (C-4a), 137.16, 136.31, 135.74, 135.22 (mesityl C-2, C-4, C-6, phenyl C-1), 128.58, 127.91, 127.36, 127.18, 126.86 (mesityl C-3 and C-5, phenyl C-2/6, C-3/5, C-4), 96.18 (C-5), 90.60 (C-9b), 85.94 (C-6a), 63.49 (C-9a), 56.29 (C-2), 53.65 ($NCH_2C_6H_5$), 46.02 (C-3), 22.33 (C-6a-CH_3), 20.60, 20.20, 19.68 (mesityl CH_3). MS (70 eV): *m/z* (%): 432 (1.2) [M^+], 404 (4.22), 389 (2.0), 256 (2.9), 231 (36.7), 202 (33.0), 91 (100). $C_{26}H_{28}N_2O_4$ (432.5). Calcd. C 72.20, H 6.53, N 6.48; found C 72.27, H 6.69, N 6.54.

9b-Hydroxy-4-(2-hydroxyethyl)-6a-methyl-9-(2,4,6-trimethylphenyl)-3,4,9a,9b-tetrahydro-2H-1,2-oxazolo[5,4-h]1,4-benzoxazin-6(6aH)-one (**3c**)

Yield 27%, m.p. 232.5–234 °C. UV/VIS (MeOH): λ_{max} (log ε) = 377.5 (2.60), 310.5 (4.36), 247.5 (4.41). IR (KBr): $\bar{\nu} = 1614\,cm^{-1}$ (C=O). ^{1}H-NMR (*DMSO-d*$_6$): δ = 7.18 (s, 1H, OH), 6.84 (d, 2H, *m*-mesityl), 5.12 (s, 1H, 5-H), 4.82 (t, 1H, alkyl-OH), 4.12 (s, 1H, 9b-H), 3.97 (m, 1H, 2-$H_{ps.ax}$), 3.54 (m, 2H, CH_2OH), 3.32 (m, 1H, 2-$H_{ps.eq}$), 3.11 (m, 3H, NCH_2CH_2OH, H-3$_{ps.ax}$). 2.68 (m, 1H, 3-$H_{ps.eq}$), 2.22, 2.18 (each s, 3H, mesityl *o*-methyl), 2.03 (s, 3H, mesityl *p*-methyl), 1.61 (s, 3H, C-6b-CH_3). ^{13}C-NMR (*DMSO-d*$_6$): δ = 187.91 (C-4), 158.54 (C-4a or C-9), 156.76 (C-9 or C-4a), 137.15, 136.28, 135.79 (mesityl C-2, C-4, C-6), 127.92 (mesityl C-3/5), 127.26 (mesityl C-1), 95.26 (C-5), 90.42 (C-9b), 85.95 (C-6a), 63.43 (C-9a), 57.05 (C-2), 56.17 (NCH_2CH_2OH), 53.02 (NCH_2CH_2OH), 46.48 (C-3), 22.47 (C-6a-CH_3), 19.58, 20.25, 20.67 (mesityl CH_3). $C_{21}H_{26}N_2O_5$ (386.5). Calcd. C 65.27, H 6.78, N 7.25; found C 65.16, H 6.81, N 7.24.

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