Reductive Phenolic Coupling: A Novel Intramolecular Capture of a Nitro-Intermediate Generated Through Reduction of a Nitrobenzophenone.

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<u>Abstract</u>: Zinc ethanol reduction of 2'-nitro-2,6-dimethoxy-4-hydroxybenzophenone gives the amine together with a spiro-hydroxylamine - the result of a novel reductive phenolic coupling process.

Reduction of nitroarenes normally gives the corresponding anilines purportedly through intermediates such as the nitroso- and hydroxylamino-compounds.¹ Other reactions can occur if electron acceptor groups such as carbonyl or cyano are proximate to the nitro functionality under reduction. In such circumstances capture of one of the intermediates can take place as in formation of 2,1-benzisoxazolone from ethyl o-nitro-benzoate² and 3-aminoanthranil from o-nitrobenzonitrile,³ both of which involve capture of the intermediate hydroxylamine.



Reduction of the o-nitrobenzophenone⁴ (1; R=NO₂) with zinc acetic acid, stannous chloride, or palladised charcoal and hydrazine hydrate predictably gave the corresponding amine (1; R=NH₂). When zinc, ethanol, water and ammonium chloride⁴ was used as the reducing agent the amine (1; R=NH₂) was only a minor product the major one being a yellow, sparingly soluble crystalline solid $C_{15}H_{13}NO_5$. This was not the corresponding benzisoxazolone [2; Ar = C₆H₂(OMe₂)OH] since it showed carbonyl absorption at 1727 and 1648 cm⁻¹ and -OH or -NH absorption at 3178 cm⁻¹ in the infrared region. In the ¹H-nmr spectrum the methoxy protons (6H) appeared as a singlet at $\delta 3.51$; a singlet at $\delta 5.62$ suggested the presence of two equivalent olefinic protons. The downfield resonance at $\delta 10.03$ which was exchangeable confirmed the presence of -NH or -OH. Its UV spectrum in methanol showed λ_{max} 211, 238 and 294 nm similar to those of the known spirodienones geodin⁵ and geodoxin.⁶

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Treatment of a methanolic solution of the yellow product with alkali gave 2,6-dimethoxybenzoquinone. This chemical and spectroscopic evidence is consistent with either of the spirodienones (3) or (4).

The hydroxylamine structure (3) was favoured because the product gave a bright red colour, on treatment with alkaline 2,3,5-triphenyl tetrazolium chloride⁷ and because there was evidence for the loss of OH (M-17) in the mass spectrum⁸ and OD (M-18) in that of the deuterated analogue.



Further structural evidence in favour of the hydroxylamine structure was adduced from the intense signals which were detected when a solution of the product in benzene was oxidised in the cavity of an esr spectrometer. The observed spectrum was interpreted in terms of the nitroxide (5). Its main nitrogen splitting $a_N = 9.65G$, "ortho" proton 3.16(2H) and "meta" proton 1.04G (2H) splittings are fully consistent with the nitroxide structure (5) [cf. (6) which has $a_N = 9.3$, $a_H = 3.1$ (2H), $a_H = 1.0G$ (2H)]⁹. The unusual features of the spectrum of (5) are the small long range splitting of 0.6G (2H) which is due to the two dienone protons and the linewidth alternation effect which distorts the intensities of some of the lines.



The correctness of the structural assignment based on these chemical and spectroscopic results has been confirmed by X-ray crystallographic analysis (see footnote and Fig. 1). The crystallographic results not only show the expected connectivity but are of sufficient quality to confirm the aromatic nature of the ring C(8), C(9) ... C(13) and the presence of the C(1)-C(6) and C(3)-C(4) double bonds.

The most likely route to the spirohydroxylamine is via the nitroso intermediate (1; R=NO) which is captured by nucleophilic adduction of the electron rich aryl ring to the nitroso group before it can be reduced further to the corresponding hydroxylamine (3). This represents a rare example of reductive phenolic coupling in contrast to the many examples of oxidative phenolic coupling.



Figure 1 Drawing of the molecule showing the crystallographic atom numbering scheme and bond distances accurate (1 × e.s.d.) to ± 0.01Å. C, N and O are differentiated by the increasing radii of the circles used to represent them.

2'-Nitro-2,6-dimethoxy-4-hydroxybenzophenone (1; $R=NO_2$; 250 mg) was dissolved in ethanol (20 ml) containing water (2 ml) and ammonium chloride (250 mg). Zinc dust (250 mg) was added in ten portions over two hours to the stirred mixture and the stirring continued overnight (17 hours). The mixture was warmed for five minutes on a steam bath and filtered; the residue washed with additional hot ethanol (3 × 10 ml) and the combined filtrates evaporated to give a solid residue. Extraction of this residue with hot ethyl acetate gave, after evaporation a solid (143 mg) which partly dissolved in chloroform to give 2'-amino-2.6-dimethoxy-4-hydroxybenzophenone* (1; $R=NH_2$; 45 mg). mp 210-212°.

The insoluble material was boiled with ethanol (50 ml) containing some ethyl acetate (5 ml) and filtered hot, the filtrate was concentrated under reduced pressure whence deposition of yellow crystals occurred. The spirodienone* (3; 65 mg) had mp. 270-274°, λ_{max} MeOH 211 nm (log ϵ 4.29), 238 (4.56) and 294 (4.09) $\nu^{\text{KBr}}_{\text{max}}$ 3178 cm⁻¹, 1727 cm⁻¹ and 1648 cm⁻¹. ¹H_{nmr} (DMSO-d₆) δ 10.03 (1H, s, D₂O exch.) 7.67-6.94 (4H, complex, Δr -H), 5.62 (2H, s, 3 and 5-H), 3.51 (6H, s, 2 × OCH₃). m/z 287 (30%) 271(20), 270(8), 258(6), 256(5), 242(64), 241(26), 240(100), 199(25),

^{*} Satisfactory analyses (C, H and accurate mass measurement) were obtained for these new compounds.

169(20). After D_2O exchange m/z 288 (40%), 287(20), 272(6), 271(8), 270(8), 258(4), 243(24), 242(100, 241(29), 240(19), 199(18), 169(15).

E.s.r. spectra were measured on a Varian E 104A spectrometer.

Footnote

Crystallographic data for $C_{15}H_{13}NO_5$: triclinic, space group P_1 (No. 2); a = 7.35(1), b = 8.84(2), c = 10.93(2)Å, $\alpha = 93.9(2)$, $\beta = 92.8(1)$, $\gamma = 111.0(1)^\circ$; V = 660(3)Å³; Z = 2; F = 287.274; Dx = 1.445 g cm⁻³; F(000) = 300 e⁻; MoKa radiation; μ (MoKa) = 1.03 cm⁻¹; yellow crystal 0.1 × 0.2 × 0.4 mm; 859 observed reflections [I > 4 σ (I)] with 0 < 2 θ < 50° and 0(-13, -16) < h(k,1) < 11(13,16). Structure solved by direct methods (MULTAN80)¹⁰ and Fourier techniques and refined¹¹ by block diagonal least squares minimising $\Sigma M\Delta^2$ (F) with unit weights to R = 0.075. Relatively high R and limited amount of data due to poor diffraction of the sample crystal. H not determined and all non-H refined with anisotropic displacement parameters (191 parameters in all). Atomic coordinates and thermal vibration parameters have been deposited at the Cambridge Crystallographic Data Centre.

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