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Oxidation of *N*-substituted dopamine derivatives: irreversible formation of a spirocyclic product

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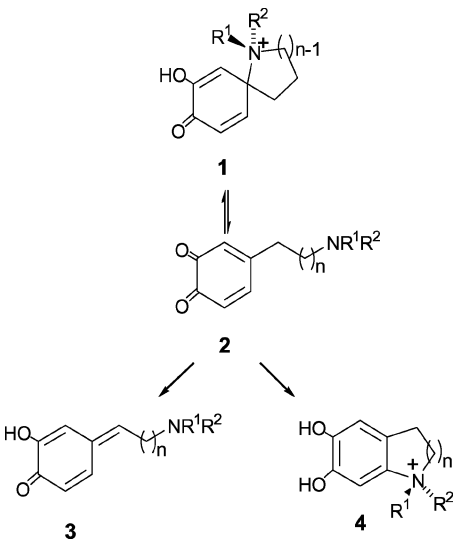
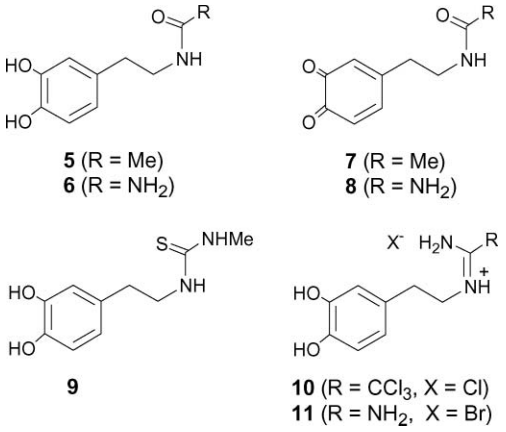
Oxidation of amide, urea and guanidinium derivatives of dopamine gives relatively stable *ortho*-quinones whereas oxidation of corresponding thioamide and amidinium derivatives rapidly and quantitatively gives novel bicyclic and spirocyclic products formed *via* the corresponding *ortho*-quinone.

Using a combination of tyrosinase oximetry, pulse radiolysis and chemical oxidation we have studied the transformations of a variety of novel *ortho*-quinone amines **2**, formed by chemical or enzymatic oxidation of the corresponding catechols.[1] These studies have shown that the final product can vary considerably depending upon the structure of the catechol precursor and the lifetimes of intermediate species (Scheme 1).[2–6] Oxidation of higher homologues of dopamine gives transient spirocyclic products **1** ($n = 1, 2$) but these kinetic products rapidly re-open leading to the thermodynamically more stable *para*-quinomethanes **3** or the benzoheterocycles **4**. In this communication we report the irreversible formation of a novel and stable spirocyclic product by oxidation of an amidine derivative of dopamine.



Scheme 1

In vertebrates, tyrosinase oxidation of dopa leads to formation of the melanin pigments.[7–9] In insects, oxidation of *N*-acetyldopamine **5** (NADA) leads to enzyme-assisted isomerisation of the *ortho*-quinone **7** to the corresponding *para*-quinomethane, which is a reactive intermediate involved in the sclerotization of insect cuticle.[10] In the search for a dopamine derivative related to NADA **5** that may either give the isomeric quinomethane (*cf.* **3**) without enzyme assistance or act as a prototype tyrosinase-activated prodrug[11] by cyclising to form a readily hydrolysable intermediate (*cf.* **4**), we have studied a series of closely related derivatives, including compounds **6** and **9**–**11**. These derivatives were selected to give a wide variation of



5 (R = Me)
6 (R = NH_2)

7 (R = Me)
8 (R = NH_2)

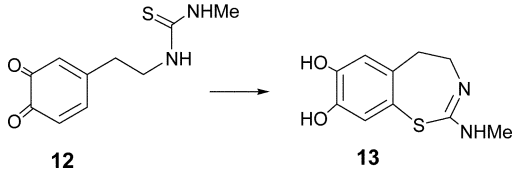
9

10 (R = CCl_3, X = Cl)
11 (R = NH_2, X = Br)

pK_a and nucleophilicity of the side-chain functional group. The catechols **5**[12] and **10**[13] were prepared by literature methods. The catechols **6**, **9** and **11** were prepared by demethylation (aq. 48% HBr at 90 °C) of the corresponding dimethyl ethers[14–16] and were purified and fully characterised before oxidation.

Oxidation of the catechols **5** (amide p$K_a \approx -1$) and **6** (urea p$K_a \approx +1$) in $CDCl_3/CH_3OH$ solution using DDQ (1 equiv.) resulted in rapid formation of the *ortho*-quinones **7** and **8** (3 aromatic H, δ 6.2–7.2). These products are relatively stable and slowly decompose over two days to give complex mixtures, including some unreacted quinone. Similar behaviour was observed in aqueous solution using pulse radiolytic or tyrosinase oxidation.

In contrast, oxidation (DDQ) of the thiourea **9** (thiourea p$K_a \approx -1$) resulted in rapid quantitative formation of a product that was not the *ortho*-quinone **12** since only two protons were observed in the aromatic region of the ^{1}H NMR spectrum. This product was isolated as the hydrochloride salt (mp 227–228 °C), after recrystallisation from ethanolic HCl, and was identified as the 8,9-dihydro-5-thia-7-aza-benzocycloheptene **13** [δ 3.07 (2H, t, J 6.0 Hz), 3.13 (3H, s), 3.69 (2H, t, J 6.0 Hz), 6.59 (1H, s), 6.66 (1H, s), 31.3 (CH_2), 32.4 (NCH_3), 46.8 (NCH_2), 115.1 (C), 118.6 (CH), 119.8 (CH), 133.4 (C), 146.2 (C), 149.3 (C), 167.3 (C)].This heterocycle has a UV spectrum (λ_{max} 287 nm) identical



12 **13**

to the product formed by tyrosinase oxidation of catechol **9**, and pulse radiolysis showed that product **13** is formed ($k = 1.8$ s^{-1} at pH 8) from the *ortho*-quinone **12** (λ_{max} 380 nm).

When the amidine **10** (amidine p$K_a \approx$ 11–12) was oxidised (1 equiv. DDQ) an NMR spectrum was obtained that appeared to be consistent with quantitative formation of the *ortho*-quinone. However, this product was remarkably more stable

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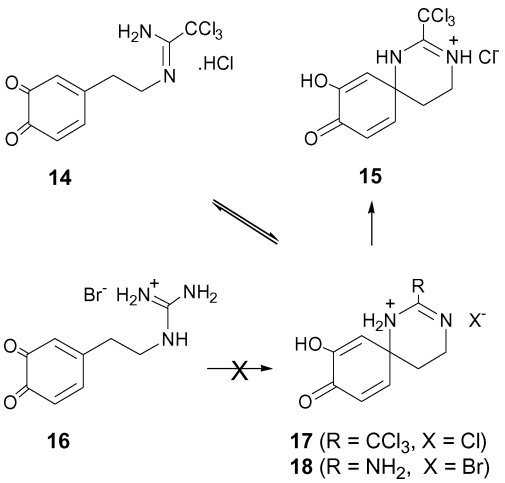
than the *ortho*-quinones **7** and **8** and the ^{1}H NMR spectrum was unchanged after several days. This product was isolated as colourless crystals, mp 144 °C (decomp.) [M^+ (cation) m/z 294.9802 (^{35}Cl) = $C_{10}H_{10}N_2O_2Cl_3$]. Closer inspection of the ^{1}H and ^{13}C NMR spectra revealed this product to have the spirocyclic structure **15**. In particular, the ^{1}H NMR spectrum shows two signals due to the methylene protons (δ 2.20 and 3.85). The signal at δ 3.85 (t) is entirely consistent with the NCH_2 function. The signal at δ 2.20 is too high field to be a benzylic signal (δ 2.75 in **10**) but is entirely consistent with a spirocyclic CH_2 attached to a quaternary carbon. Furthermore, this signal appears as a quartet due to the non-equivalence of the methylene protons. The structural assignment **15** is further supported by the ^{13}C NMR spectrum which shows signals at δ 29.1 and 38.5, due to the methylene carbons, and a signal a δ 55.3, due to the spiro carbon atom. All other aspects of the NMR spectra support the hexadienone structure **15** [δ 5.95 (1H, d, J 3 Hz), 6.35 (1H, d, J 10 Hz), 7.00 (1H, dd, J 3 and 10 Hz), 87.9 (CCl_3), 115.1, 128.8, 147.5, 149.4 (4C, diene C), 159.0 (N=C–N), and 182.0 (C=O)]. The UV spectrum [λ_{max} (0.1 M phosphate buffer: pH 7.4) 220, 244 (ε 7415) and 320sh (ε 1440) nm] is entirely consistent with the dienone structure and comparable to those observed for the transient species **1** (λ_{max} 250 nm).[3,5]

In contrast to the amidine **10**, DDQ oxidation of the guanidine **11** (p$K_a \approx 13$) gave a ^{1}H NMR spectrum [δ 6.50 (1H, s), 6.57 (1H, d, J 7 Hz), 7.30 (1H, d, J 7 Hz)] very similar to those of the amide **5** and the urea **6**, and which is clearly due to the *ortho*-quinone **16**. There was no evidence of cyclisation to the spiro derivative **18**. This observation suggests that it is the equilibrating amidine free base **14** that cyclises ($k \approx 2.5 \times 10^2$ s^{-1} at pH 8) and that the guanidinium cation is too weak an acid to be able to cyclise *via* the free base. If the initial amidine cyclisation product is the 1-proto cation **17**, this will rapidly equilibrate to the resonance stablised 3-proto cation **15** (Scheme 2). Since the transformation **17** to **15** is irreversible this may account for the stability of the spirocyclic species **15**. In the case of the amine spirocycles **1** any free amine formed can readily reprotonate the nitrogen atom, enabling facile reversal of the cyclisation.



Scheme 2

When the NMR solution of the bromide **16** was monitored after four hours it was found to contain an approximately equimolar mixture of the *ortho*-quinone **16** and its catechol precursor **11**. The regeneration of the catechol **11** is consistent with the bromide ion reducing ($2Br^- \rightarrow Br_2^{\bullet -} \rightarrow Br_2$) the *ortho*-quinone (Q) to the semi-quinone ($Q^{\bullet -}$) followed by rapid disproportionation ($2Q^{\bullet -} \rightarrow Q + Q^{2-}$).

In conclusion, relatively simple but unexplored derivatives of dopamine quinone show an interesting variety of reaction modes. The *ortho*-quinone **14** provides an unusual example of formation of a stable spiro-cyclic product (**15**), which are often kinetic[3,5] but not thermodynamic products of quinone amine cyclisations. None of the derivatives studied showed evidence of rapid *para*-quinomethane formation assisted by the neighbouring functional group.[4] The lack of cyclisation of the urea **8** suggests that ureas, carbamates and related species are unlikely to function as prodrugs activated by tyrosinase to form hydrolysable species of the type **4** ($R^1 = H$, $R^2 = CO.R$).[11]

Acknowledgements

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