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Formation of *para*-quinomethanes *via* 4-aminobutylcatechol oxidation and *ortho*-quinone tautomerism

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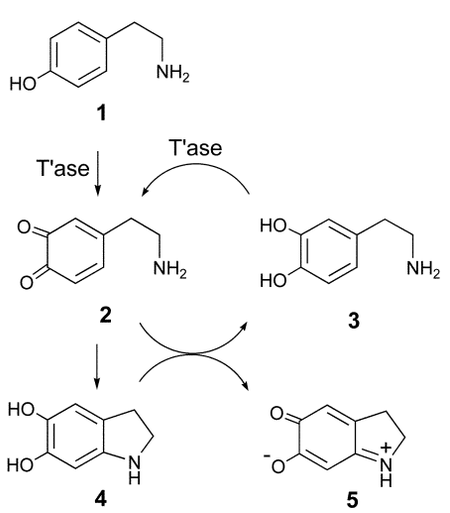
Enzymatic and chemical oxidation of 4-(4-*N*,*N*-dialkylaminobutyl)catechols leads to formation of 1,1-dialkylpyrrolidinium salts in good yield. It is proposed that these products are formed by tautomerism of the initially formed *ortho*-quinones to *para*-quinomethanes. The corresponding secondary amines do not form *para*-quinomethanes but cyclise giving tetrahydro-1*H*-benzo[*b*]azepine-7,8-diones. The failure of the dialkylaminobutyl derivatives to cyclise to bicyclic betaines, in a manner analogous to lower homologues and monoalkylaminobutyl derivatives, is attributed to steric hindrance. This proposal is supported by evidence that the sterically hindered *N*-*tert*-butylaminobutyl derivative, in contrast to other secondary amines, does not cyclise but gives a *para*-quinomethane-derived product. Based on pulse radiolysis and spectrophotometric evidence, *para*-quinomethane formation appears to be much slower than cyclisation and only occurs when cyclisation is unfavourable. The *ortho*-quinones formed from 5-aminopentylcatechols neither cyclise nor tautomerise suggesting that the chain length in these derivatives is too long for both cyclisation and intramolecular deprotonation.

Introduction

As part of a study of the mechanism of catechol formation by the enzyme tyrosinase we have investigated the chemistry of *ortho*-quinone amines using a combination of enzymatic, pulse radiolytic and chemical methods.[1] Tyrosinase, an important enzyme in early stages of the biosynthesis of melanin pigments,[2] oxidizes both phenols and catechols to *ortho*-quinones. This is exemplified in Scheme 1 by the oxidation of tyramine **1** and dopamine **3**. Formation of catechol amines, *e.g.* **3**, in the tyrosinase oxidation of phenolamines, *e.g.* **1**, occurs mainly by a non-enzymatic indirect redox exchange mechanism between the *ortho*-quinone **2**, and its cyclisation product **4**. For tyramine oxidation (Scheme 1) this gives a dopachrome **5** and dopamine **3**, which is then further oxidized by tyrosinase.



Scheme 1

In order to investigate details of the tyrosinase oxidation mechanism we have studied the oxidation of the tertiary amines **6**. These amines give the dihydroindol-1-ium-5-olates **7** which cannot undergo redox exchange with their precursors. In a similar manner the higher homologues **8** give the tetrahydroquinolin-1-ium-6-olates **9**. We have previously described the betaines **7** and **9** and associated mechanistic studies.[3,4] When oxidized either chemically or enzymatically the tertiary amines **10** show interesting differences to the lower homologues **6** and **8**. In particular we have reported preliminary evidence that the initially formed *ortho*-quinones tautomerise to *para*-quinomethanes.[5] In this paper we describe chemical and enzymatic studies of the oxidation of 4-(4-dialkylaminobutyl)catechols **10** and chemical oxidation of the secondary amines **18**. The results of tyrosinase oximetry and pulse radiolysis studies on the secondary amines **18** have been described elsewhere.[6]

Results and discussion

When the catechol **10a** was oxidized in $CHCl_3$/MeOH using dianisyltellurium oxide (DAT)[7] a solid product was isolated in good yield (83%). Spectroscopic evidence clearly showed that this was not the tetrahydrobenzo[*b*]azepin-1-ium-7-olate **11a**. In particular the ^{1}H NMR spectrum showed three aromatic protons indicating that cyclisation on to the aromatic ring had not occurred. This oxidation product was found to be the pyrrolidinium hydroxide **12a** and this structure was fully supported by spectroscopic data. A low field pseudo-triplet at δ_H 4.60 corresponds to the methine proton at position 2 of the heterocyclic ring and the signals due to the *N*-ethyl substituents are non-equivalent (triplets at δ_H 0.99 and 1.25) due to the proximity of the asymmetric carbon atom at position 2. The six protons of the three methylene groups directly bonded to the pyrrolidinium nitrogen all give signals in the region δ 2.7–3.5 consistent with the adjacent positive charge. The UV spectrum in phosphate buffer (pH 7.4) [λ_{max}/nm (ε/M^{-1} cm^{-1}) 242 (3600), 251sh (1250), 286 (2700) and 310sh (650)] was also consistent with structure **12a**. Using a similar procedure the amines **10b**,**c** gave the salts **12b**,**c** in good yield. The product **12c** was obtained as a mixture of diastereoisomers: in the ^{1}H NMR spectrum the methyl triplets of the *n*-propyl substituents (δ_H 0.69 and 0.80) occurred in the ratio 1 : 2 and two *N*-methyl singlets (δ_H 2.45 and 2.75) were observed with intensities in the same ratio.

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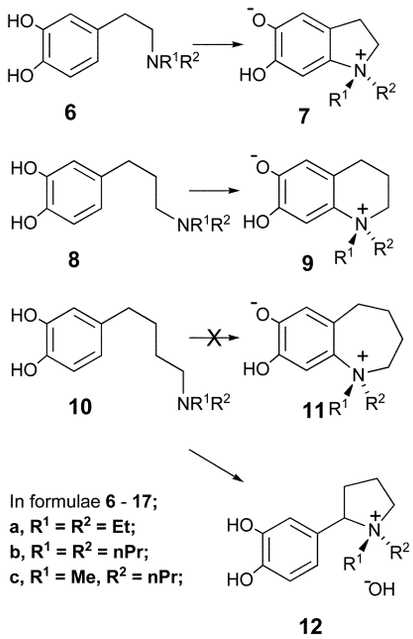
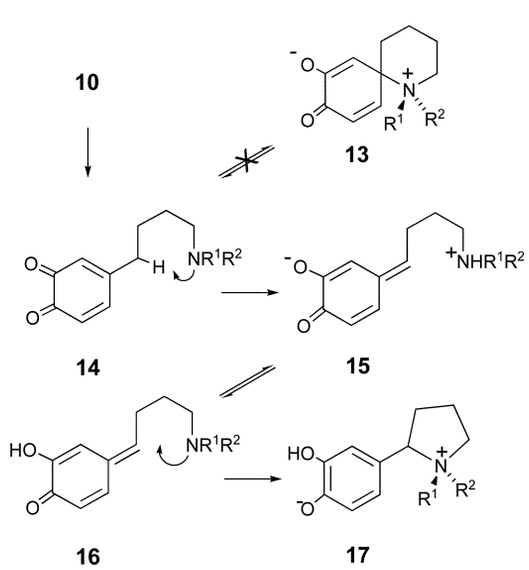
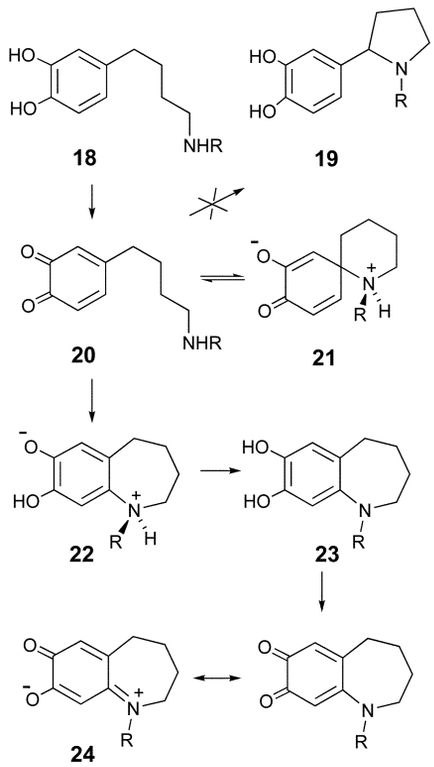


We propose that the salts **12** are formed *via* the mechanism shown in Scheme 2. When the *ortho*-quinone **14a** (λ_{max} 400 nm) was generated from the catechol **10a** in a pulse radiolysis experiment it was found to be relatively stable with a life-time of at least several seconds. It did not undergo spirocyclisation to give the spirobetaine **13a**. Since the secondary amine **20a** (Scheme 3) does undergo 6-*exo*-*trig* spirocyclisation[6] we attribute the absence of cyclisation of the tertiary amines **14** to a steric effect. In this context it should be noted that we have shown that the *ortho*-quinone formed by oxidation of the lower homologue tertiary amine **8a** also undergoes initial spirocyclisation,[3] presumably because 5-*exo*-*trig* cyclisation is more favourable. Because nucleophilic cyclisations of the amines **14** are unfavourable, these amines instead react as a base and deprotonate at the 1-position of the butyl chain, through a favourable six-membered transition state, to give the zwitterions **15** which equilibrate with the *para*-quinomethanes **16**. The reactive *para*-quinomethane intermediate then undergoes 5-*exo*-*trig* cyclisation to give a betaine **17**, which subsequently reacts with water to give the isolated products **12**. It should be noted that in contrast to the lower homologues, *para*-quinomethane formation takes place because (i) alternative modes of reaction (*i.e.* cyclisation) are not favourable and (ii) the chain length is favourable for deprotonation. It is clear from the



Scheme 2



Scheme 3

stability of the *ortho*-quinone **14a** on the pulse radiolysis timescale that deprotonation is a much slower reaction than the cyclisation reactions of the lower homologues and secondary amines.

In accord with the above observations, the tertiary amine **10a** was rapidly oxidised by tyrosinase with an oxygen utilization stoichiometry of 0.5 and oxidation was complete within three minutes. Initially there was a rise in absorbance at λ_{max} 400 nm consistent with formation of the *ortho*-quinone **14a**. This absorbance peaked after 30 seconds and began to decay with concomitant generation of a product with an absorbance at λ_{max} 282 nm (isosbestic points at 265 and 350 nm). There was a close correspondence between the apparent rate of decay of the intermediate *ortho*-quinone and formation of the final product. The absorption spectrum of the final product was identical to that of an authentic synthetic sample of the salt **12a** in buffer at the same pH (7.4). This result suggests that the *ortho*-quinone **14a** undergoes the same transformation (Scheme 2) when generated either enzymatically or chemically. In the case of the enzymatic reaction the base catalysed deprotonation may be due to the medium (intermolecular), which may also facilitate tautomerism.

The observation of the intermediate *ortho*-quinone prior to final product formation during tyrosinase oxidation of the catechol amine **10a** is significant. In the tyrosinase catalysed oxidation of the lower homologue **8a** rapid oxidation with oxygen utilization stoichiometry of 0.5 also occurred but no *ortho*-quinone absorbance was observed. Instead, a spectrum corresponding to the betaines **9a** was rapidly generated. These two observations are consistent with the pulse radiolysis evidence that tautomerisation to a *para*-quinomethane **16** is relatively slow and much slower than intramolecular cyclisation of *ortho*-quinone amines of lower homologues to give betaines **7** and **9**.

In principle the mode of reaction shown in Scheme 2 is an attractive route to novel pyrrolidines **19** and we therefore investigated the extension of this approach to secondary

amines. The secondary 4-(4-alkylaminobutyl)catechols **18a**–**c** and **25** were prepared by standard methods and oxidized using DAT in $CHCl_3$–MeOH solution. In the case of the amines **18a**–**c** a purple colour developed and the only products isolated (50–60% yield) were the tetrahydrobenzo[*b*]azepine-7,8-diones **24a**–**c**. These products are analogous to the dopachromes (*e.g.* **5**) formed by oxidation of dopamine derivatives. The ^{1}H NMR of compound **24a** showed only two aromatic protons (δ 5.50 and 6.15) which were uncoupled indicating that cyclisation onto the 5 position of the aromatic ring had occurred. All other aspects of the structure **24a** were confirmed by ^{1}H and ^{13}C NMR spectroscopy. As expected, this purple product **24a** showed an absorption at 518 nm (EtOH) in the visible spectrum.

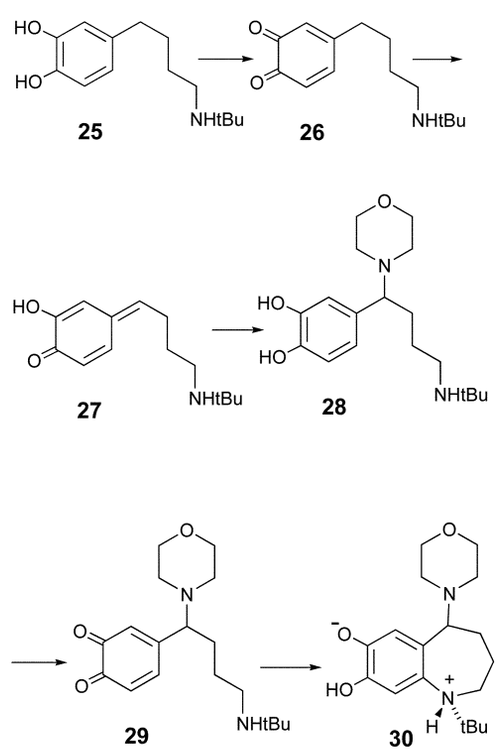
We propose the mechanism shown in Scheme 3 to account for the formation of the "aminochromes" **24**. 7-*Exo*-*trig* cyclisation of the initially formed *ortho*-quinones **20** gives the betaines **22** which tautomerise to the catechols **23**. A second oxidation then occurs to give the isolated products **24**. Since the use of one or two equivalents of oxidising agent (DAT) makes little difference to the outcome of the reaction, we believe that the reactive, electron-rich aminocatechols **23** are probably oxidised by aerial oxygen, partially during work up. Some product **24** may also be formed by redox exchange with the *ortho*-quinone precursor **20**.

Pulse radiolysis studies[6] have shown that the *ortho*-quinone **20a** is in equilibrium with the spirobetaine **21a**. We have considered the possibility that the spirobetaines **21** rearrange directly to the isomeric betaines **22**. However, modeling studies of the kinetics of pulse radiolytic studies of catechols **18** do not support a mechanism in which the spirobetaine leads directly to the seven-membered ring (*i.e.* **21** → **22**).[6]

In our studies of the oxidation of the catechols **18** we have detected no evidence of *para*-quinomethane formation either as products isolated or as products detected when reactions were monitored by ^{1}H NMR spectroscopy. These secondary amines **18** clearly behave differently to the tertiary amines **10**. We conclude that cyclisation is less favoured for the tertiary amines **10** for steric reasons and consequently the much slower proton abstraction and *para*-quinomethane formation occurs (Scheme 2).

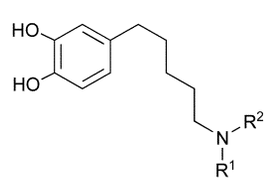
A significant difference in behaviour was observed when a sterically hindered secondary amine was investigated. Oxidation of the *tert*-butyl derivative **25** using DAT did not give the aminochrome **24** (R = *t*-Bu) and no purple colouration was observed. However, no pyrrolidine **19** (R = *t*-Bu) was detected either and this contrasts with our observations when the same substrate was oxidised by tyrosinase.[6] We attribute this difference to the more complex aqueous enzyme medium (pH 7.4) facilitating faster intermolecular deprotonation. When the reaction was monitored by ^{1}H NMR spectroscopy evidence of a mixture of *ortho*-quinone and *para*-quinomethane products was observed. Firm evidence of *para*-quinomethane formation was obtained when the oxidation was carried out in the presence of morpholine. Thus, oxidation of a solution of the catechol amine **25** in the presence of morpholine gave the betaine derivative **30** in 20% isolated yield. The structure of compound **30** was assigned on the basis of its ^{1}H NMR and mass spectra. Two singlets at δ 6.85 and 6.99 are characteristic of a 1,2,4,5-tetrasubstituted aromatic ring and a triplet at δ 5.26 is assigned to the single benzylic proton at position 5. A second triplet at δ 3.66 is assigned to the methylene protons at position 2 of the azepine ring. This chemical shift suggests that it must be directly bonded to a quaternary nitrogen and on this basis we have eliminated the isomeric catechol amine structure (*cf.* **23**). The preferred betaine structure of this product in organic solvents may account for its resistance to oxidation during work-up. The mass spectrum (FAB) showed a strong protonated molecular ion (MH^+ *m*/*z* 321) and the only significant fragment ion corresponded to loss of *t*-Bu (*m*/*z* 263).

The *N*-morpholino substituent in product **30** is clearly introduced by the reaction of morpholine with the *para*-quinomethane **27**, formed by base catalysed tautomerism of the *ortho*-quinone **26** (Scheme 4). The morpholine may assist by acting as a base catalyst as well as nucleophile. As in the case of the tertiary amines **14** (Scheme 2) steric hindrance must inhibit cyclisation of the *ortho*-quinone. The product **28** is then further oxidised to the *ortho*-quinone **29** which does cyclise, presumably slowly and because alternative pathways do not favourably compete, to give the betaine **30**. The *ortho*-quinone **29** could in principle undergo alternative reactions including *para*-quinomethane formation but no other products were identified although the low yield of product **30** does suggest that other pathways compete. The transformation **25** ⟶ **30** is of no synthetic value but it does underline the role of steric hindrance in favouring slower *para*-quinomethane formation (Schemes 2 and 4).



Scheme 4

DAT oxidation of the 4-(5-aminopentyl)catechols **31** and **32** gave the *ortho*-quinones, which could be detected in solution by ^{1}H NMR spectroscopy. However, no products were detected or isolated and there was no evidence of cyclisation. We conclude that the chain length [$(CH_2)_5$] in these derivatives is too long for either nucleophilic cyclisation or intramolecular deprotonation to occur.



31; $R^1 = R^2 =$ nPr
32; $R^1 =$ nPr, $R^2 = H$

Conclusion

In conclusion we have shown that the *ortho*-quinones formed by oxidation of 4-(4-*N*,*N*-dialkylaminobutyl)catechols do not cyclise to bicyclic betaines in a manner analogous to lower homologues[3] but instead tautomerise to *para*-quinomethanes.

This process, probably mediated by intramolecular deprotonation, is relatively slow and only occurs when alternative cyclisation pathways are unfavourable and chain length is optimal. We propose that cyclisation of these tertiary amines does not occur due to steric hindrance and this is supported by the observation that 4-*N*-monoalkylaminobutyl derivatives, with the exception of the sterically hindered *tert*-butyl derivative, do cyclise.

Experimental

Melting points were determined using a Reichert Kofler Block apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer with only major absorbances being quoted. Unless otherwise stated IR spectra were measured as KBr discs. UV-visible spectra were determined using a Carey 1C instrument. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperatures using a Brucker Avance DPX 300 MHz. Elemental analyses were determined either using a Perkin-Elmer 240 CHN Elemental Analyser or by SACS, University of North London. Mass spectra were determined by the EPSRC National Mass Spectrometry Service Centre at Cardiff. In addition to elemental analysis and HRMS, the purity and homogeneity of products were confirmed by NMR spectroscopy and chromatography. Flash chromatography was performed using silica gel (Janssen Chimica) 0.035–0.07 mm. All solvents were pre-distilled and dried appropriately prior to use. Concentration and evaporation refer to the removal of volatile materials under reduced pressure on a Büchi Rotovapor. Substances stated to be identical were so with respect to mps, mixed mps and IR spectra.

The pulse radiolytic oxidation of catechol amine **10a** and the simultaneous oximetric and spectrophotometric measurements of tyrosinase-catalysed oxidation on catechol amines **8a** and **10a** were made using the apparatus and methods previously described.[3,4] The preparation of compound **8a** has been described previously.[3]

Preparation of 1,1-dialkyl-pyrrolidinium hydroxides 12

4-(4-*N*,*N*-Dialkylaminobutyl)catechols **10** were prepared as hydrobromide salts from 4-(3,4-dimethoxyphenyl)butyric acid (purchased from Sigma-Aldrich) by conversion to the appropriate amide ($SOCl_2$), reduction ($LiAlH_4$) and demethylation (48% aq. HBr) using literature methods.[8,9] In each case the free amine was prepared by treating the hydrobromide with excess saturated aqueous sodium bicarbonate, extraction into $CHCl_3$, drying and evaporation. Structure and purity were confirmed by ^{1}H NMR and tlc, and batches of the free amines were used without further purification.

2-(3,4-Dihydroxyphenyl)-1,1-diethylpyrrolidinium hydroxide 12a. To a stirred solution of 4-(4-diethylaminobutyl)catechol **10a** [δ_H ($CDCl_3$) 1.06 (t, *J* 7.3 Hz, 6H, 2 × CH_2CH_3), 1.54 (m, 4H, 2 × CH_2), 2.46 (t, *J* 7.0 Hz, 2H, $ArCH_2$), 2.55 (t, *J* 7.3 Hz, 2H, CH_2CH_2N), 2.65 (q, *J* 7.3 Hz, 4H, 2 × CH_2CH_3), 6.47 (dd, *J* 8.0 and 2.0 Hz, 1H, aromatic *H*), 6.57 (d, *J* 2.0 Hz, 1H, aromatic *H*), 6.68 (d, *J* 8.0 Hz, 1H, aromatic *H*) and 7.75 (br s, 2H, 2 × O*H*)] (0.5 g, 0.002 mol) in $CHCl_3$–MeOH (9 : 1, 50 cm^3) under a nitrogen atmosphere was added dropwise (15 min) dianisyltellurium oxide (0.75 g, 0.002 mol) in $CHCl_3$–MeOH (9 : 1, 20 cm^3). The resulting red solution was then stirred at ambient temperature (30 min). The reaction mixture was partitioned with water (50 cm^3) and the organic phase was separated and washed with water (2 × 30 cm^3). The combined aqueous layers were then washed with $CHCl_3$ and the water was removed under reduced pressure to yield compound **12a** (0.44 g, 83%), reddish brown solid, mp 118–120 °C (Found: C, 66.15; H, 9.40; N, 5.42. $C_{14}H_{23}NO_3$ requires C, 66.37; H, 9.15; N, 5.53%); ν_{max}/cm^{-1} (KBr) 3415, 2970, 1595, 1507, 1470, 1281 and 1140; λ_{max}/nm (ε/M^{-1} cm^{-1}, 0.1 M phosphate buffer, pH 7.4): 242 (3600), 251sh (1250), 286 (2700) and 310sh (650); δ_H (D_2O) 0.99 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 1.25 (t, *J* 7.0 Hz, 3H, CH_2CH_3), 2.00 (m, 2H, ring CH_2), 2.23 (m, 2H, ring CH_2), 2.69 (m, 2H, 2 × $NCH_aH_bCH_3$), 2.95 (m, 1H, $NCH_aH_bCH_3$), 3.20 (m, 1H, $NCH_aH_bCH_3$), 3.27 (t, *J* 7 Hz, 2H, NCH_2CH_2), 4.60 (t, 1H, $NCHCH_2$), 6.5–6.7 (m, 3H, 3 × aromatic *H*); HRMS (FAB) Found: M–OH$^-$, *m*/*z* 236.1642; Calc. for $C_{14}H_{22}NO_2$; 236.1650.

In a similar manner the following salts were prepared from the amine **10b** (thick yellow oil; 80%) [δ_H (d_4-MeOH) 0.76 (t, *J* 7.1 Hz, 6H, 2 × CH_2CH_3), 1.37 (m, 8H, 4 × CH_2), 2.35 (m, 8H, 4 × CH_2), 6.35 (d, *J* 7.6 Hz, 1H, aromatic *H*), 6.50 (s, 1H, aromatic *H*) and 6.55 (d, *J* 7.6 Hz, 1H, aromatic *H*)] and amine **10c** (thick yellow oil; 82%) [δ_H ($CDCl_3$) 0.79 (t, *J* 7.3 Hz, 3H, CH_2CH_3), 1.44 (m, 6H, 3 × CH_2), 2.21 (s, 3H, NCH_3), 2.36 (m, 6H, 3 × CH_2), 6.38 (d, *J* 8.0 Hz, 1H, aromatic *H*), 6.49 (s, 1H, aromatic *H*), 6.59 (d, *J* 8.0 Hz, 1H, aromatic *H*) and 7.19 (br s, 2H, 2 × O*H*)].

2-(3,4-Dihydroxyphenyl)-1,1-di-*n*-propylpyrrolidinium hydroxide 12b. Yield: 0.42 g (79%), reddish brown solid, mp 110–112 °C; ν_{max}/cm^{-1} (KBr) 3410, 2965, 1595, 1507, 1475, 1279 and 1136; δ_H (D_2O) 0.62 (t, *J* 7.2 Hz, 3H, CH_2CH_3), 0.82 (t, *J* 7.2 Hz, 3H, CH_2CH_3), 1.2–1.7 (m, 4H, 2 × $CH_2CH_aH_bCH_3$), 2.14 (m, 2H, ring CH_2), 2.37 (m, 2H, ring CH_2), 2.64, 2.75, 3.02 and 3.15 (4 × dt, 4H, 2 × $NCH_aH_bCH_2CH_3$), 3.45 (t, *J* 7.3 Hz, 2H, NCH_2CH_2), 4.65 (t, 1H, $NCHCH_2$), 6.8–6.9 (m, 3H, 3 × aromatic *H*); δ_C (D_2O) 12.7 (q), 18.8 (t), 18.9 (t), 19.4 (t), 22.4 (t), 59.5 (t), 62.8 (t), 63.0 (t), 80.7 (d), 118.7 (d), 120.2 (d), 124.7 (s), 125.6 (d), 148.0 (s), 150.1 (s); HRMS (FAB) Found: M–OH$^-$, *m*/*z* 264.1963; Calc. for $C_{16}H_{26}NO_2$; 264.1964.

2-(3,4-Dihydroxyphenyl)-1-*n*-propyl-1-methylpyrrolidinium hydroxide 12c. Yield: 0.38 g (72%), reddish brown solid, mp 116–119 °C; ν_{max}/cm^{-1} (KBr) 3410, 2966, 1594, 1507, 1471, 1279 and 1139; δ_H (D_2O) 0.69 and 0.80 (integration 1 : 2) (2t, *J* 7.2 Hz, 3H, non-equiv. CH_2CH_3), 1.35–1.7 (br m, 2H, $CH_2CH_aH_b$-CH_3), 2.15 (m, 2H, ring CH_2), 2.45 and 2.75 (integration 2 : 1) (2 × s, 3H, non-equiv. NCH_3), 2.0–3.7 (overlapping br m, 6H, 2 × ring CH_2 + $NCH_aCH_bCH_2CH_3$), 4.35 (dd, 1H, NCH-CH_aH_b), 6.6–6.8 (m, 3H, 3 × aromatic *H*); HRMS (FAB) Found: M–OH$^-$, *m*/*z* 236.1654; Calc. for $C_{14}H_{22}NO_2$; 236.1651.

Preparation of 1-alkyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-7,8-diones 24

4-(4-*N*-Alkylaminobutyl)catechols were prepared from 4-(3,4-dimethoxyphenyl) butyric acid using literature methods.[8,9]

1-*n*-Propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-7,8-dione 24a. To a stirred solution of 4-(4-*n*-propylaminobutyl)catechol hydrobromide **18a** [δ_H (d_6-DMSO) 0.90 (t, *J* 7.6 Hz, 3H, CH_2CH_3), 1.55 (br m, 6H, 3 × CH_2), 2.42 (t, *J* 5.5 Hz, 2H, $ArCH_2$), 2.80 (br m, 4H, 2 × CH_2N), 6.43 (dd, *J* 8.0 and 2.0 Hz, 1H, aromatic *H*), 6.57 (d, *J* 2.0 Hz, 1H, aromatic *H*), 6.63 (d, *J* 8.0 Hz, 1H, aromatic *H*), 8.28 (br s, 2H, NH_2), 8.68 (s, 1H, O*H*) and 8.72 (s, 1H, O*H*)] (0.3 g, 0.001 mol) and DBU (0.15 g, 0.001 mol) in $CHCl_3$–MeOH (9 : 1, 30 cm^3) under a nitrogen atmosphere was added dropwise (15 min) dianisyltellurium oxide (0.35 g, 0.001 mol) in $CHCl_3$–MeOH (9 : 1, 15 cm^3). The purple solution was stirred at ambient temperature (1 h) and the solvent evaporated under reduced pressure. The resulting thick purple oil was dissolved in CH_2Cl_2 (30 cm^3), washed with H_2O (30 cm^3) and dried ($MgSO_4$). Evaporation gave a purple oil that was purified by flash chromatography using $CHCl_3$ as eluent (to remove dianisyltellurium) and then $CHCl_3$–MeOH (9 : 1) to give compound **24a** (121 mg, 55%) purple solid, mp 80–81 °C; ν_{max}/cm^{-1} (KBr) 2925, 1593, 1502, 1262, 1102 and 800; λ_{max}/nm (ε/M^{-1} cm^{-1}, EtOH): 315 (8370) and 518 (3620); λ_{max}/nm (ε/M^{-1} cm^{-1}, aq. buffer, pH 8.0): 320 (9600) and 529

(2800); δ_H ($CDCl_3$) 0.90 (t, *J* 7.4 Hz, 3H, CH_2CH_3), 1.5–1.9 (m, 6H, 3 × CH_2), 2.63 (t, *J* 5.5 Hz, 2H, $=CCH_2CH_2$), 3.25 (t, *J* 7.9 Hz, 2H, NCH_2), 3.52 (t, *J* 4.0 Hz, 2H, NCH_2), 5.59 (s, 1H, C*H*=C), 6.15 (s, 1H, C*H*=C); δ_C ($CDCl_3$) 11.3 (q), 19.5 (t), 22.9 (t), 25.4 (t), 33.1 (t), 52.0 (t), 57.1 (t), 102.0 (d), 130.5 (d), 150.2 (s), 159.0 (s), 175.5 (s), 182.9 (s); HRMS (FAB) Found: [M + H] *m*/*z* 220.1335; Calc. for $C_{13}H_{18}NO_2$: 220.1337.

In a similar manner the following derivatives were prepared from the hydrobromide salts of the amines **18b** [δ_H (d_6-DMSO) 1.19 (d, *J* 6.5 Hz, 6H, $CH(CH_3)_2$), 1.53 (br m, 4H, 2 × CH_2), 2.39 (t, *J* 7.0 Hz, 2H, $ArCH_2$), 2.83 (m, 2H, CH_2N), 3.32 (m, 1H, C*H*N), 6.41 (dd, *J* 8.0 and 2.0 Hz, 1H, aromatic *H*), 6.56 (d, *J* 2.0 Hz, 1H, aromatic *H*), 6.62 (d, *J* 8.0 Hz, 1H, aromatic *H*) and 8.40 (br s, 2H, 2 × O*H*)] and **18c** [δ_H (d_6-DMSO) 1.3–1.6 (br m, 4H, 2 × CH_2), 2.30 (t, *J* 7.0 Hz, 2H, $ArCH_2$), 2.95 (m, 2H, CH_2N), 4.04 (t, *J* 17.4 Hz, 2H, CF_2CH_2N), 6.31 (dd, *J* 8.0 and 2.0 Hz, 1H, aromatic *H*), 6.45 (d, *J* 2.0 Hz, 1H, aromatic *H*), 6.52 (d, *J* 8.0 Hz, 1H, aromatic *H*) and 9.35 (br s, 2H, 2 × O*H*)].

1-iso-Propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-7,8-dione 24b. Yield: 125 mg (57%), purple semi-solid, mp ill-defined; ν_{max}/cm^{-1} (KBr) 2921, 2853, 1578, 1512, 1459, 1256, 1096, 1034 and 801; λ_{max}/nm (ε/M^{-1} cm^{-1}, EtOH): 320 (8100) and 520 (3400); δ_H ($CDCl_3$) 1.23 (d, *J* 6.6 Hz, 6H, $CH(CH_3)_2$), 1.6–1.9 (m, 4H, 2 × CH_2), 2.60 (t, *J* 5.1 Hz, 2H, $=CCH_2CH_2$), 3.37 (t, *J* 5.3 Hz, 2H, NCH_2), 3.98 (sept, *J* 6.6 Hz, 1H, NC*H*), 5.68 (s, 1H, C*H*=C), 6.15 (s, 1H, C*H*=C); HRMS (FAB) Found: [2M + H] *m*/*z* 438.2522; Calc. for $C_{26}H_{35}N_2O_4$: 438.2519.

1-(2,2,3,3,3-Pentafluoro-*n*-propyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-7,8-dione 24c. Yield: 82 mg (51%), purple gum; ν_{max}/cm^{-1} (KBr) 2920, 1580, 1520, 1459, 1259, 1092 and 801; δ_H ($CDCl_3$) 1.82 (m, 4H, 2 × CH_2), 2.62 (t, *J* 5.5 Hz, 2H, $=CCH_2CH_2$), 3.58 (t, *J* 5.0 Hz, 2H, NCH_2), 3.93 (t, *J* 14.6 Hz, 2H, NCH_2CF_2), 5.70 (s, 1H, C*H*=C), 6.18 (s, 1H, C*H*=C).

1-*tert*-Butyl-5-morpholin-4-yl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepine-7,8-diol 30

To a stirred solution of 4-(4-*tert*-butylaminobutyl)catechol hydrobromide [δ_H (d_6-DMSO) 1.25 (s, 9H, $C(CH_3)_3$), 1.56 (m, 4H, 2 × CH_2), 2.42 (t, *J* 5.5 Hz, 2H, $ArCH_2$), 2.82 (m, 2H, CH_2N), 6.43 (d, *J* 8.0 Hz, 1H, aromatic *H*), 6.57 (s, 1H, aromatic *H*), 6.63 (d, *J* 8.0 Hz, 1H, aromatic *H*) and 8.36 (br s, 2H, 2 × O*H*)] (0.5 g, 0.0016 mol) and morpholine (0.27 g, 0.0032 mol) in $CHCl_3$–MeOH (9 : 1, 50 cm^3) under a nitrogen atmosphere was added dropwise (15 min) dianisyltellurium oxide (0.56 g, 0.0016 mol) in $CHCl_3$–MeOH (9 : 1, 20 cm^3). The mixture was stirred at ambient temperature (24 h) and the solvent evaporated under reduced pressure. The resulting material was dissolved in CH_2Cl_2 (30 cm^3) and filtered (to remove morpholine hydrobromide). Evaporation gave a solid that was purified by flash chromatography using $CHCl_3$ as eluent (to remove dianisyltellurium), then $CHCl_3$–MeOH (19 : 1 followed by 9 : 1) and finally MeOH to give a brown solid. This was recrystallised from CH_2Cl_2 and identified as compound **30** (100 mg, 20%) buff solid, mp 238–240 °C; ν_{max}/cm^{-1} (KBr) 3250, 3144, 2960, 1606, 1525, 1450, 1379, 1289, 1193, 1106, 930 and 889; δ_H (d_4-MeOH) 1.37 (s, 9H, $C(CH_3)_3$), 2.1–2.55 (m, 6H, 3 × CH_2), 2.85 (m, 4H, 2 × CH_2), 3.66 (t, *J* 7.5 Hz, 2H, NCH_2), 3.90 (m, 4H, 2 × CH_2), 5.26 (t, *J* 8.0 Hz, 1H, NC*H*), 6.84 (s, 1H, aromatic C*H*) and 6.99 (s, 1H, aromatic C*H*); HRMS (FAB) Found: [M + H] *m*/*z* 321.2184; Calc. for $C_{18}H_{29}N_2O_3$: 321.2178.

4-(4-Aminopentyl)catechols

The amines **31** and **32** were prepared from 5-(3,4-dimethoxyphenyl)pentanoic acid[10] *via* formation of the appropriate amides using the method of Hölzel and Spiteller.[11] Amide reduction using $LiAlH_4$ gave the corresponding amines and the unprotected catechol amines were prepared as their hydrobromide salts by heating with 48% aq. HBr. This procedure gave hydrobromide **31** (1.06 g, 91%) gum (Found: C, 56.80; H, 8.42. $C_{17}H_{30}BrNO_2$ requires C, 56.67; H, 8.39%); ν_{max}/cm^{-1} ($CHCl_3$) 3400, 2971, 2932, 1500, 1458 and 1269; δ_H (d_6-DMSO) 0.95 (t, *J* 7.2 Hz, 6H, 2 × CH_2CH_3), 1.33 (m, 2H, CH_2), 1.57 (m, 2H, CH_2), 1.71 (m, 6H, 3 × CH_2), 2.45 (t, 7.3 Hz, 2H, $ArCH_2$), 2.60 (s, 1H, N*H*), 3.00 (m, 6H, 3 × NCH_2), 6.48 (d, *J* 8.0 Hz, 1H, aromatic H), 6.50 (s, 1H, aromatic H), 6.70 (d, *J* 8.0 Hz, 1H, aromatic H), 9.45 (br s, 2H, 2 × O*H*) and hydrobromide **32** (0.62 g, 52%) sticky brown solid (Found: C, 52.65; H, 7.83. $C_{14}H_{24}BrNO_2$ requires C, 52.84; H, 7.60%); ν_{max}/cm^{-1} ($CHCl_3$) 3250, 2970, 2935, 1507, 1452 and 1271; δ_H (d_6-DMSO) 1.03 (t, *J* 7.4 Hz, 3H, CH_2CH_3), 1.41 (m, 2H, CH_2), 1.55–1.8 (br m, 6H, 3 × CH_2), 2.52 (t, 7.4 Hz, 2H, $ArCH_2$), 2.64 (br s, 2H, NH_2), 2.95 (m, 4H, 2 × NCH_2), 6.55 (dd, *J* 8.0 and 2.0 Hz, 1H, aromatic H), 6.68 (d, *J* 2 Hz, 1H, aromatic H), 6.75 (d, *J* 8.0 Hz, 1H, aromatic H), 9.40 (br s, 2H, 2 × O*H*). The free bases were obtained by treatment with saturated aq. $NaHCO_3$ and extraction into $CHCl_3$ and ^1H NMR studies of the amines and their DAT oxidation products were carried out using this material.

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