results must be interpreted with caution. The results for the three pairs of dioxetanes agree with one another (despite the size of the error) and *qualitatively* agree with the predicted ΔE_a based on the diradical model.

The data for the *cis*-dioxetanes clearly show that 3,4 steric interactions in *cis*-dialkyl-1,2-dioxetanes are of minor importance. This is not unexpected in view of the results[12] from a study of 3,3-diethyl-1,2-dioxetane (7). The E_a for 7 was found to be 1.5 kcal/mol higher than that of 3,3-dimethyl-1,2-dioxetane with little or no effect on $\Delta S^{\ddagger}$. The ΔE_a for the formal replacement of 3,3-dimethyl groups by 3,3-diethyl groups was large enough to account for the increased E_a of tetraethyl-1,2-dioxetane as compared to that of tetramethyl-1,2-dioxetane. Those results[12] suggested that a major substituent effect on alkyldioxetane thermolysis was due to 3,3 steric interactions as opposed to 3,4 steric interactions.

Experimental Section

All solvents were of reagent grade. ^{1}H NMR spectra were recorded on a Varian 360L spectrometer. GC studies were performed on a Varian 920 gas chromatograph with a 6 ft × 0.25 in. SE-30 on Chromosorb W column (helium flow rate 60 mL/min). 9,10-Diphenylanthracene (Aldrich) was used without further purification. 9,10-Dibromoanthracene (Aldrich) was recrystallized from xylenes (Aldrich) before use. The alkenes were available commercially. *cis*-3,4-Diethyl-1,2-dioxetane (**3**)[9c] has been previously reported.

Dioxetane Synthesis. The following procedure for the synthesis of *trans*-3,4-diethyl-1,2-dioxetane (**2**) was employed for the preparation of all dioxetanes. A 74-mmol sample of *trans*-3-hexene was converted to the bromo hydroperoxide by the standard method of Kopecky.[13] The bromo hydroperoxide, an oil (**Caution!**), was placed in 10 mL of CCl_4 with rapid magnetic stirring (cooled by an ice bath). KOH (5 g) in 20 mL of cold distilled (deionized) H_2O was added dropwise (15 min) to the bromo hydroperoxide solution in the dark. The bright yellow CCl_4 layer was separated, dried over $MgSO_4$, and filtered. The dioxetanes were partially purified by low-temperature vacuum distillation.

Additional purification was accomplished by column chromatography using a jacketed 1-cm-column at −60 °C packed with 20 g of silica gel containing 1% Na_2EDTA (pentane). The dioxetane in CCl_4 was placed on the column and washed with 50 mL of pentane, followed by successive 50-mL portions of a 5% methylene chloride/pentane step gradient. Fractions were assayed for dioxetane by placing a small portion in a concentrated DBA solution in the chemiluminescence apparatus. The solvent from fractions containing dioxetane was removed under reduced pressure and the NMR spectra taken. The ^{1}H NMR spectrum of the dioxetane in CCl_4 showed the dioxetane to be approximately 90% pure. ^{1}H NMR (CCl_4) for **1**: δ 0.9 (t, J = 7 Hz, 6 H), 1.9 (m, 4 H), 5.15 (br t, J = 5 Hz, 2 H). For **2**: δ 0.9 (t, J = 7 Hz, 6 H), 1.9 (m, 4 H), 4.90 (br t, J = 4 Hz, 2 H). For **3**: δ 0.9 (t, J = 7 H, 6 H), 1–2 (br m, 6 H), 5.25 (br t, J = 5 Hz, 2 H). For **4**: δ 0.9 (t, J = 7 Hz, 6 H), 1–2 (br m, 6 H), 5.0 (br t, J = 4 Hz, 2 H). For **5**: δ 0.9 (t, 6 H), 1–2 (br m, 8 H), 5.20 (br t, J = 5 Hz, 2 H). For **6**: δ 0.9 (t, 6 H), 1–2 (br m, 8 H), 5.00 (br t, J = 4 Hz, 2 H). The concentrations of the dioxetane solutions were determined by the method of Wilson and Schaap.[10c] The dioxetane solutions (CCl_4) were stored at −30 °C.

Product Studies. The following general procedure was employed. An approximately 0.2 M solution of the dioxetane in CCl_4 was heated at 60 °C in a sealed NMR tube until the yellow color disappeared. In all cases, the corresponding aldehyde was detected in high yield by NMR spectroscopy. The reaction mixture was also checked by VPC analysis.

Kinetic Studies. The chemiluminescence monitoring system is essentially identical with that described previously by Wilson.[8] The temperature of the cell (±0.2 °C) was monitored by using a YSI Model 42SC with a Series 400 probe before and after each run. The cell was jacketed and the temperature maintained by using a Haake constant-temperature circulating bath. The cell was pretreated with a concentrated aqueous Na_2EDTA solution. Kinetic runs were carried out in benzene or in xylenes (mixture of isomers) as the solvent. The initial dioxetane concentrations were kept low ($\sim 10^{-4}$ M) in order to avoid induced decomposition of the dioxetane. Runs carried out without added fluorescer and with low concentrations ($\sim 10^{-3}$ M) of DPA or DBA were of the first order for at least 3 half-lives and showed essentially no dependence on the type or amount of added fluorescer.

Yields of Excited States. The chemiluminescence monitoring apparatus was calibrated by taking the yield of excited triplet from tetramethyl-1,2-dioxetane, determined by the DBA method,[8] as 0.30 at 45 °C. All experiments were carried out at 45 °C with a constant concentration of dioxetane. The yields of excited carbonyl products were calculated by a method which has been discussed in detail.[2,8]

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Registry No. 1, 73353-62-5; 2, 83929-08-2; 3, 83929-09-3; 4, 83929-10-6; 5, 83929-11-7; 6, 83929-12-8.

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Electrochemical Reduction in the Synthesis of Catechol-Derived Peptides as Potential Metal Chelators and Enzyme Inhibitors

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There has been considerable recent interest in the synthesis[1] of new metal-binding agents, especially catechol based, both as models for related microbial natural products[2] (e.g., the iron-binding enterobactins) and for potential medical use in man.[3] In addition, the catecholamines are important in neurochemistry. Dopamine β-hydroxylase (EC 1.14.2.1) plays an important role in the dynamics of neurotransmission as it catalyses the last step in the biosynthesis of noradrenaline.[4] In view of a recent report of powerful inhibition of this enzyme by bleomycin, a strongly metal-binding glycopeptide antitumor antibiotic,[5] we considered that catechol peptides might bind strongly to dopamine β-hydroxylase by virtue of their extended peptide backbone. We now report a synthetic route to a catechol dipeptide which involves a useful, preparative, electrochemical reduction step, successful where several other reductive procedures failed.

Results and Discussion

N^{α}-Benzoyl-DL-(2,3-dihydroxyphenyl)alanylglycine (**8**) was synthesized by the route shown in Scheme I.

The azlactone **2** was formed by condensation[6] of *N*-benzoylglycine with **1**. Conversion of **2** to the free amino acid **3** followed by N-protection as a variety of derivatives (e.g., Cbz, trifluoroacetyl), even in the presence of borate,

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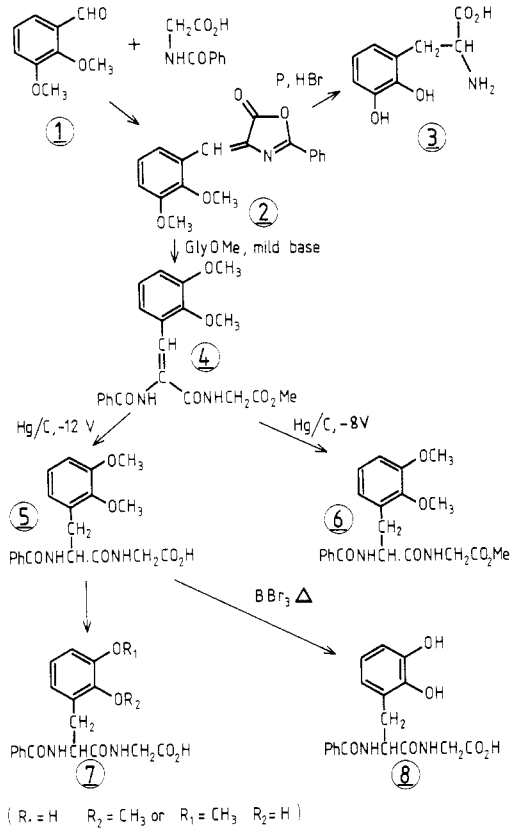
Scheme I



to protect the catechol, was discounted early as a synthetic means to 8 because of oxidation and crystallization problems. Compound 2 was reacted directly with glycine methyl ester in excess to overcome such problems. Derivative 4 was resistant to the usual reductive procedures (e.g., to H_2–Pt/CH_3CO_2H, H_2–Pd/CH_3CO_2H, $LiAlH_4$, $NaBH_4$/pyridine, dithionite, Sn/HCl). The use of Na/liquid NH_3 led to the desired reduction but with concomitant ring reduction. Successful selective reduction was achieved electrochemically by using a variant of the method described by Horner and Neumann.[7] Depending on the voltage conditions chosen, either the methyl ester 6 or the free acid form 5 could be isolated in good yields. Demethylation of 5 by using BBr_3 in excess[8] resulted in the formation of a monomethoxy derivative (7) at lower temperatures, but reflux conditions (in CH_2Cl_2) were necessary to obtain the fully demethylated product 8. Reid and Gebhardtsbauer[6] converted 2 by hydrolysis and Raney nickel reduction to *N*-benzoyl-2,3-dimethoxy-DL-phenylalanine. Assignment of the methyl group to the 2- or 3-position in 7 is difficult, but on the basis of chemical precedent for somewhat analogous systems,[9] 7 is likely to be the 3-methoxy species. An attempt to debenzoylate 5 electrochemically as described for other *N*-benzoyl peptides[7] by using a higher voltage etc. failed in this case and for *N*-benzoyl-2,3-dimethoxy-DL-phenylalanine.

Experimental Section

Melting points (uncorrected) were determined with a melting point microscope (Reichart). The NMR spectra were recorded on a Varian A-60 instrument (^1H) or a Bruker WP 805 Y FT spectrometer (^1H, ^{13}C) at 80 MHz for ^1H NMR and 20.15 MHz for ^{13}C NMR with Me_4Si as an external standard. Evaporations were accomplished in vacuo with a Büchi Rotovapor-RE at ≤55 °C. Elemental analyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Manchester. Electron impact (EI) mass spectra (50 eV) were performed on a AEI MS 12 with a VG Micromass 2S8 control unit. Optical rotations were performed by using a Perkin-Elmer 241 automatic polarimeter at 5890 Å and 30 °C.

Conditions for Electrochemical Reduction. Preparation-scale reductions were carried out in a electrochemical cell prepared as described by Horner and Neumann,[7] with 0.01 M substrate and 0.86 M tetramethylammonium chloride in methanol as the electrolyte, a carbon anode, an Hg pool cathode (area 4.9 cm^3), and water as the anolyte solution.

4-(2,3-Dimethoxybenzylidene)-2-phenyl-5-oxazolone (2). This was prepared according to a literature procedure: mp 169–170 °C (lit.[6] mp 166.5 °C); ^1H NMR ($CDCl_3$) δ 3.9 (s, 6 H, OCH_3), 7.7 (s, 1 H, CH=C), 7.0–7.5, 8.1–8.5 (m, 8 H, Ar H). Anal. Calcd for $C_{18}H_{15}NO_4$ (mol wt 309.3): C, 69.9; H, 4.9; N, 4.5. Found: C, 70.1; H, 4.8; N, 4.3.

N^{α}-Benzoyl-2,3-dimethoxydehydrophenylalanylglycine Methyl Ester (4). To a stirred solution of 5 g (0.02 mol) of 2 in 100 mL of dioxane was added 4.03 g (0.032 mol) of glycine methyl ester hydrochloride dissolved in 20 mL of 2.4 M $NaHCO_3$ adjusted to pH 9.5. After 2 h at 50 °C and 12 h at room temperature, the mixture was extracted with $CHCl_3$, washed with 1 M HCl and H_2O, dried ($MgSO_4$), filtered, and evaporated, with the residue being recrystallized from $CHCl_3/Et_2O$ to give 4: 3.8g (41.6%); mp 158–159 °C; ^1H NMR (CD_3CN) δ 3.7 (s, 3 H, CO_2CH_3), 3.8 (d, 6 H, 2 OCH_3), 3.95 (d, 2 H, CH_2), 6.9–7.9 (m, 9 H, CH=C, Ar H); ^{13}C NMR ($CDCl_3$) δ 30.9, 41.7, 52.1, 55.7, 61.8, 112.9, 122.3, 124.7, 127.7, 128.2, 128.7, 131.6, 132.1, 133.2, 146.2, 153.1, 165.8, 166.2, 170.6; mass spectrum, *m/e* 398. Anal. Calcd for $C_{21}H_{22}N_2O_6$ (mol wt 398.4): C, 63.3; H, 5.6; N, 7.0. Found: C, 63.1; H, 5.5; N, 6.9.

N^{α}-Benzoyl-DL-(2,3-dimethoxyphenyl)alanylglycine Methyl Ester (6). A 0.35-g (0.8 mmol) sample of 4 dissolved in the electrolyte (16 mL) was reduced at a mercury cathode potential of −8 V for 20 h. The reaction mixture was then shaken with H_2O/EtOAc, the organic layer was separated, washed with H_2O, dried ($MgSO_4$), filtered, and evaporated, and the oily redisue was treated with a mixture of EtOAc/$C_6H_5CH_3/Et_2O$ to give 6: 0.27 g (78.3%); mp 127–128 °C; ^1H NMR ($CDCl_3$) δ 3.3 (m, 2 H, CH_2), 3.7 (s, 3 H, CO_2CH_3), 3.9 (m, 8 H, CH_2, 2 OCH_3), 4.8 (m, 1 H, CH), 6.9–7.7 (m, 8 H, Ar H); mass spectrum, *m/e* 400. Anal. Calcd for $C_{21}H_{24}N_2O_6$ (mol wt 400.4): C, 63.0; H, 6.0; N, 7.0. Found: C, 62.9; H, 6.0; N, 6.7.

N^{α}-Benzoyl-DL-(2,3-dimethoxyphenyl)alanylglycine (5). A 2.5-g (0.0063 mol) sample of 4 dissolved in the electrolyte (50 mL) was reduced at a mercury cathode potential of −12 V for 20 h. The reaction mixture was worked up as above, with the residue being recrystallized from EtOH/EtOAc to give 4: 1.48 g (61.0%), mp 159–160 °C; ^1H NMR (CD_3CN) δ 3.9 (m, 10 H, 2 CH_2, 2 OCH_3), 4.7 (m, 1 H, CH), 7.0–7.8 (m, 8 H, Ar H). Anal. Calcd for $C_{20}H_{22}N_2O_6$ (mol wt 386.4): C, 62.2; H, 5.7; N, 7.3. Found: C, 61.8; H, 6.0; N, 7.1.

N^{α}-Benzoyl-DL-(3-hydroxy-2-methoxyphenyl)alanylglycine (7). To a stirred solution of 0.5 g (1.3 mmol) of 5 suspended in 15 mL of CH_2Cl_2 precooled to −70 °C was added 0.4 mL of 2 M BBr_3 in CH_2Cl_2, and the solution was stirred at room temperature overnight. Water was then added, the solution was extracted with $CHCl_3$, and the organic layer was separated, washed with H_2O, dried (Na_2SO_4), filtered, and evaporated, with the residue being recrystallized from EtOAc/EtOH to give 7: 0.29 g (62.5%); mp 180–182 °C; ^1H NMR (CD_3CN) δ 4.1 (m, 7 H, 2 CH_2, OCH_3), 4.5 (m, 1 H, CH), 6.9–7.8 (m, 8 H, Ar H); ^{13}C NMR (CD_3CN/D_2O) δ 32.9, 41.7, 56.5, 61.2, 113.0, 123.9, 125.2, 128.2, 129.6, 132.2, 132.8, 134.8, 148.3, 153.8, 168.5, 171.9, 173.2. Anal. Calcd for $C_{19}H_{20}N_2O_6$ (mol wt 372.4): C, 61.3; H, 5.4; N, 7.5. Found: C, 61.3; H, 5.6; N, 7.1.

N^{α}-Benzoyl-DL-(2,3-dihydroxyphenyl)alanylglycine (8). To a stirred solution of 0.5 g (1.3 mmol) 5 in 15 mL of CH_2Cl_2 was added 1.5 mL of 2 M BBr_3 in CH_2Cl_2, and the solution was refluxed for 1 h. Water was then added, the solution was extracted with EtOAc, and the organic layer was washed with saturated NaCl, dried (Na_2SO_4), filtered, and evaporated, with the residue

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being recrystallized from $CHCl_3/CH_3OH/C_6H_6$ to give 8: 0.12 g (25.9%); mp 194–195 °C; ^1H NMR (CD_3CN/D_2O) δ 3.2 (m, 2 H, CH_2), 3.95 (s, 2 H, CH_2), 4.85 (m, 1 H, CH), 6.7–7.8 (m, 8 H, Ar H); ^{13}C NMR (CD_3CN/D_2O) δ 37.1, 46.0, 60.1, 119.4, 125.3, 127.5, 129.5, 132.4, 133.9, 137.3, 138.5, 148.1, 149.7, 173.4, 176.9, 178.1. Anal. Calcd for $C_{18}H_{18}N_2O_6$ (mol wt 358.3): C, 60.3; H, 5.1; N, 7.8. Found: C, 60.7; H, 5.4; N, 7.5.

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Registry No. 1, 86-51-1; 2, 43087-79-2; 4, 83949-20-6; DL-5, 83949-21-7; DL-6, 83949-22-8; DL-7, 83949-23-9; DL-8, 83949-24-0; $HO_2CCH_2NHCOPh$, 495-69-2; GlyOMe·HCl, 5680-79-5; EC 1.14.2.1, 9013-38-1.

Efficient Synthesis of Non-K-Region *trans*-Dihydro Diols of Polycyclic Aromatic Hydrocarbons from *o*-Quinones and Catechols

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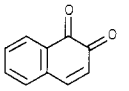
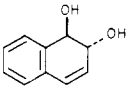
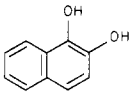
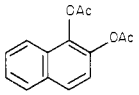
Non-K-region[1] dihydro diols of polycyclic aromatic hydrocarbons (PAH), generated by the epoxide hydrolase mediated hydration of metabolically formed arene oxides, play an important role in the metabolism of PAH.[2-7] They are precursors of dihydro diol epoxides, some of which are considered to be ultimate carcinogenic metabolites of PAH.[8-10]

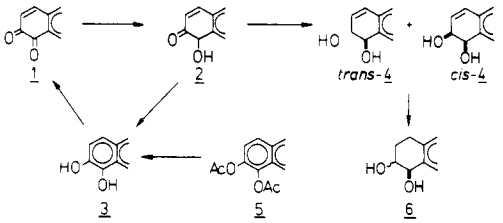
The two currently used methods for the synthesis of *trans*-dihydro diols are (a) the introduction of the *trans*-diol structure into a suitable dihydroarene by the Prévost reaction, followed by generation of the olefinic bond in the *trans*-dihydro diol either by dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone or by bromination–dehydrobromination, or (b) the reduction of a suitable *o*-quinone with complex metal hydrides. Non-K-region *trans*-dihydro diols have been prepared in most cases by pathway a[11-14] while pathway b has been almost exclusively used for the synthesis of K-region *trans*-dihydro diols.[15,16]

Table I. Reaction of 1,2-Naphthoquinone, 1,2-Dihydroxynaphthalene, and 1,2-Diacetoxynaphthalene with Sodium Borohydride

entry	starting matl	reaction conditions[a]	end product	yield, %
1	 1a	air, 48 h	 4a	80
2	1a	air, 5 min	 3a	82
3	1a	argon, 24 h	3a	82
4	3a	air, 48 h	4a	78
5	 5a	air, 18 h	4a	75

[a] Detailed reaction conditions are given in the Experimental Section.

Scheme I



In many instances, the application of pathway b for the synthesis of non-K-region dihydro diols would be desirable, either because of difficulties encountered when introducing the olefinic bond in the *trans*-dihydro diol or because the non-K-region *o*-quinone needed for pathway b can be prepared more conveniently than the dihydroarene needed for pathway a.

Attempts to reduce non-K-region *o*-quinones with lithium aluminum hydride started in 1950 when Booth et al.[17] successfully converted the 1,2-quinones of naphthalene and anthracene to the corresponding *trans*-dihydro diols in 46% and 25% yields, respectively. Application of this method to the synthesis of dihydro diols of other PAH, however, proved to be less successful as yields of 1–5% in the case of the non-K-region dihydro diols of phenanthrene[18] and of 15% in the case of *trans*-3,4-dihydroxy-3,4-dihydro-7-methylbenz[*a*]anthracene[19] illustrate. Recently it was reported that non-K-region *o*-quinones can be more efficiently reduced to dihydro diols with lithium aluminum hydride by improvements of the experimental conditions.[20-22] The yields of *trans*-dihydro diols according to these studies[20,21] vary between 0 and 61%.

The use of sodium borohydride for the reduction of non-K-region *o*-quinones of PAH to dihydro diols met with no success; this is illustrated by the 1.2% yield of *trans*-1,2-dihydroxy-1,2-dihydronaphthalene from 1,2-naphtho-

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