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Tetrahedron
Tetrahedron 61 (2005) 4075–4080

New insight into the oxidative chemistry of noradrenaline: competitive *o*-quinone cyclisation and chain fission routes leading to an unusual 4-[bis-(1*H*-5,6-dihydroxyindol-2-yl)methyl]-1,2-dihydroxybenzene derivative

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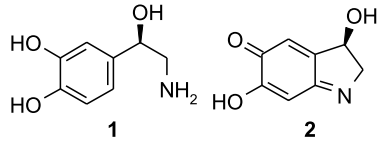
Received 29 November 2004; revised 25 January 2005; accepted 10 February 2005

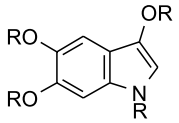
Abstract—Oxidation of 5×10^{-3} M noradrenaline in aqueous phosphate buffer, pH 7.4, with $K_3Fe(CN)_6$, $NaIO_4$ or Fe^{2+}/EDTA/H_2O_2 followed by extraction with ethyl acetate and acetylation with Ac_2O/Pyr led to a main reaction product which was isolated and identified as 4-[bis-(1*H*-5,6-diacetoxyindol-2-yl)methyl]-1,2-diacetoxybenzene, an unprecedented [bis-(indol-2-yl)methyl]-benzene derivative unsubstituted on the 3-position of the indole rings. This product was also obtained in 40% yield by reaction of 5,6-dihydroxyindole with 3,4-dihydroxybenzaldehyde. Other components of the oxidation mixture were 1-acetyl-3,5,6-triacetoxyindole, derived from noradrenolutin, and 5,6-diacetoxyindole, originating from cyclisation/dehydration of the *o*-quinone of noradrenaline, along with some 3,4-diacetoxybenzaldehyde. Inspection of the aqueous phase revealed the presence of 3,4-dihydroxymandelic acid and 3,4-dihydroxybenzaldehyde, derived from oxidative breakdown of the 2-amino-1-hydroxyethyl chain via a *p*-quinomethane intermediate. These results disclose new aspects of the oxidative chemistry of noradrenaline beyond the aminochrome stage and provide a route to novel [bis-(indol-2-yl)methyl]-benzene derivatives of potential pharmacological interest.

1. Introduction

The elucidation of the oxidative pathways of catecholamines involving the spontaneous cyclisation and/or tautomerism of their *o*-quinones has traditionally been an important goal in organic chemistry.[1–6] The biological significance of these reactions is that they appear to be the mechanism of formation of a series of reactive indolic species and/or quinomethane (quinone methide) intermediates involved in the synthesis of neuromelanin and related pigments,[7–9] in neuronal degeneration,[10–13] in the sclerotisation of insect cuticle,[14] and in the autoactivation of tyrosinase.[15] Catecholamine oxidation represents also a convenient entry to 5,6-dihydroxyindoles and related systems of biological and pharmacological relevance.[16,17]

Whereas several insights have been gained into the oxidative pathways of dopamine and adrenaline,[1–6,18,19] knowledge of the oxidative chemistry of noradrenaline (norepinephrine, **1**) has remained surprisingly scanty. This neurotransmitter is produced mainly in the *locus coeruleus*, one of the putative candidates for the brain's 'pleasure' centre implicated in physical and mental arousal and elevated mood.





3a R = H
3b R = CH_3CO

Oxidation of **1** leads to the formation of the unstable *o*-quinone. This undergoes cyclisation and oxidation to give noradrenochrome (**2**) via an indoline intermediate

Keywords: Noradrenaline; Noradrenolutin; Oxidation; Quinomethane; [Bis-(indol-2-yl)methyl]-benzene.
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0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.02.030

commonly referred to as leuconoradrenochrome.[20,21] The subsequent steps of the pathway are believed to involve isomerisation of **2** to a fluorescent indoxyl derivative, known as noradrenolutin (**3a**).[22] Whereas the analogous oxidation product of adrenaline, adrenolutin (3,5,6-trihydroxy-1-methylindole), was isolated and characterised as early as 1949,[23] compound **3a** has never been obtained by direct oxidation of **1**, and has become available only by a synthetic approach.[24] Apart from **2**, no other product of noradrenaline oxidation has so far been identified.

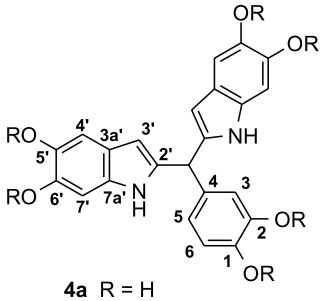
In an attempt to fill this gap, we have re-examined the oxidation of **1**, and have succeeded in isolating a major product whose spectral features are different from those of the known oxidation products of catecholamines. We report herein the isolation and structural characterisation of this new product and the elucidation of new aspects of the oxidative chemistry of **1**.

2. Results and discussion

In preliminary experiments, the oxidation of **1** (5×10^{-3} M) was investigated using a range of oxidising systems, including potassium ferricyanide, sodium periodate and the Fe^{2+}/EDTA/H_2O_2 system (Fenton reagent) in 0.1 M phosphate buffer, pH 7.4. In all cases, the reaction mixture became red in colour and then turned to purplish and dark brown. Ethyl acetate extraction, followed by acetylation with Ac_2O/Pyr to prevent oxidation of the phenolic components, afforded four main products (HPLC). When little sodium dithionite was added prior to extraction, to halt the reaction and prevent degradation of oxidisable species, a modest increase in the yield of extractable material was observed without, however, appreciable changes in product distribution. Accordingly, this precaution was included in all work-up procedures for preparative purposes.

The most abundant of the four products, which was relatively more retained on reverse phase, displayed in the ESI(+)-MS spectrum a pseudomolecular ion peak at *m/z* 671 ($[M+H]^+$), with peaks at 693 ($[M+Na]^+$) and 709 ($[M+K]^+$). The ^{1}H NMR spectrum displayed a broad singlet (2H) at δ 10.20 for N–H protons, three apparent singlets at δ 6.86, 7.14 and 7.28 (2H each), the signals (1H each) for an ABX spin system at δ 7.17 (d, $J=8.0$ Hz), 7.21 (d, $J=2.0$ Hz) and 7.31 (dd, $J=8.0$, 2.0 Hz), and a singlet (1H) at δ 5.91. The signals for six acetyl groups completed the ^{1}H NMR spectrum. The ^{1}H,^{1}H COSY spectrum revealed correlations between the signal at δ 10.20 and those at δ 6.86 and 7.14, ascribable to the H-3 and H-7 protons of a 5,6-diacetoxyindole system, respectively.[25]

The ^{13}C NMR spectrum showed the presence of fourteen signals in the sp^2 region between δ 144.0 and 105.9 and one signal at δ 40.7 correlating with the proton resonance at δ 5.91. This latter displayed multibond proton–carbon connectivities with several sp^2 carbons, including indolic ones, suggesting a methine group linking two indole rings and a disubstituted phenyl moiety. Overall, these data were consistent with the structure of the unusual 4-[bis-(1*H*-5,6-diacetoxyindol-2-yl)methyl]-1,2-diacetoxybenzene (**4b**). A complete assignment of the proton and carbon resonances, as deduced from ^{1}H,^{13}C HMQC and ^{1}H,^{13}C HMBC experiments, is reported in Table 1.



Consistent with the proposed formulation, a ROESY experiment revealed contacts of the methine singlet at δ 5.91 with the protons of the catechol moiety at δ 7.21 and

Table 1. NMR spectroscopic data of compound **4b** ($(CD_3)_2CO$)

	δ ^{13}C	δ ^{1}H (mult, *J* Hz)	^{1}H,^{1}H COSY	^{1}H,^{13}C HMBC
C–H	40.7	5.91 (bs)	6.86, 10.20	118.8, 120.3, 123.5, 124.1, 126.3, 127.1
C-1	142.0	—	—	—
C-2	144.0	—	—	—
C-3	124.1	7.21 (d, 2.0)	7.31	40.7, 142.0
C-4	127.1	—	—	—
C-5	123.5	7.31 (dd, 8.0, 2.0)	7.17, 7.21	40.7, 124.1, 142.0
C-6	124.1	7.17 (d, 8.0)	7.31	127.1, 144.0
C-2′	120.3	—	—	—
C-3′	126.3	6.86 (bs)	5.91, 7.14, 10.20	118.8, 127.1, 134.1
C-3a′	118.8	—	—	—
C-4′	105.9	7.28 (s)	7.14	126.3, 136.3, 138.6
C-5′	136.3	—	—	—
C-6′	138.6	—	—	—
C-7′	112.9	7.14 (s)	6.86, 7.28, 10.20	118.8, 134.1, 136.3, 138.6
C-7a′	134.1	—	—	—
N–*H*		10.20 (s)	5.91, 6.86, 7.14	—
COO*C*H_3	21.3	2.20 (s)	—	169.5
COO*C*H_3	21.3	2.24 (s)	—	169.8
*C*OOCH$_3$	169.5	—	—	—
*C*OOCH$_3$	169.8	—	—	—

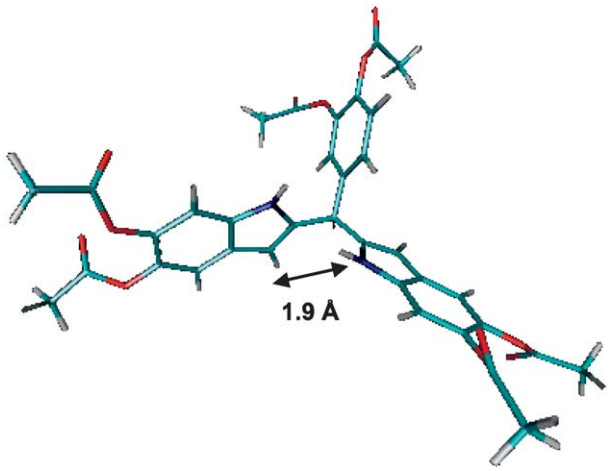
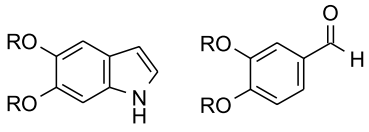


Figure 1. Energy minimised (MM+) structure of compound **4b**. Highlighted is the distance between the H-3 and the NH proton of two different indole units.

7.31 and between the N–H proton of one indole unit with the H-3 proton of the other indole unit. In accord with this conclusion, brief inspection of the geometry optimised structure of **4b** (MM+) indicated a low energy conformation in which the planes of the indole units form a dihedral angle of about 89° and the distance between the NH of one indole unit and the H-3 proton of the other one was 1.9 Å, that is, low enough to account for a well detectable contact (Fig. 1). In addition, a distinct cross peak in the ROESY spectrum between the signals at δ 6.86 and 7.28, the latter due to the indolic H-4 proton, provided further support to the 2-substitution of the indole rings, consistent with previous reports.[26,27] The alternative substitution through the 3-position, that is, with the $\delta = 6.86$ H being H-2 rather than H-3, is untenable on the basis of the observed through-space contacts and the chemical shift values reported in the literature for the H-2 protons of 5,6-dihydroxyindoles, which never fall at $\delta < 7.0$.[27–29]

Scrutiny of the parent structure **4a** shows that it conceivably arises by coupling of two 5,6-dihydroxyindole (**5a**) units through the 2-position with one molecule of 3,4-dihydroxybenzaldehyde (**6a**). This mechanism was supported by the identification of 5,6-diacetoxyindole (**5b**) and 3,4-diacetoxybenzaldehyde (**6b**) among the four main products obtained by oxidation of **1**, and was definitively secured by reaction of **5a** with **6a** in 0.1 M phosphate buffer at pH 7.4 under a vigorous stream of argon. After extraction and acetylation it was possible to isolate by PLC fractionation a product identical in all respects with **4b** (40% yield).



5a R = H
5b R = CH_3CO **6a** R = H
6b R = CH_3CO

In separate experiments, attempts were made to detect the [bis-(indol-2-yl)methyl]-benzene derivative **4a** in the oxidation mixture from **1** by direct HPLC analysis. To this aim, compound **4b** was deacetylated with 1 M NaOH under carefully controlled conditions ensuring rigorous exclusion of oxygen. As obtained, the compound was rapidly converted into a species exhibiting a reddish purple chromophore ($\lambda_{max} = 476$, 553 nm) denoting an oxidation product. This, however, proved to be too unstable to be isolated and characterised by spectroscopic techniques, despite several attempts.

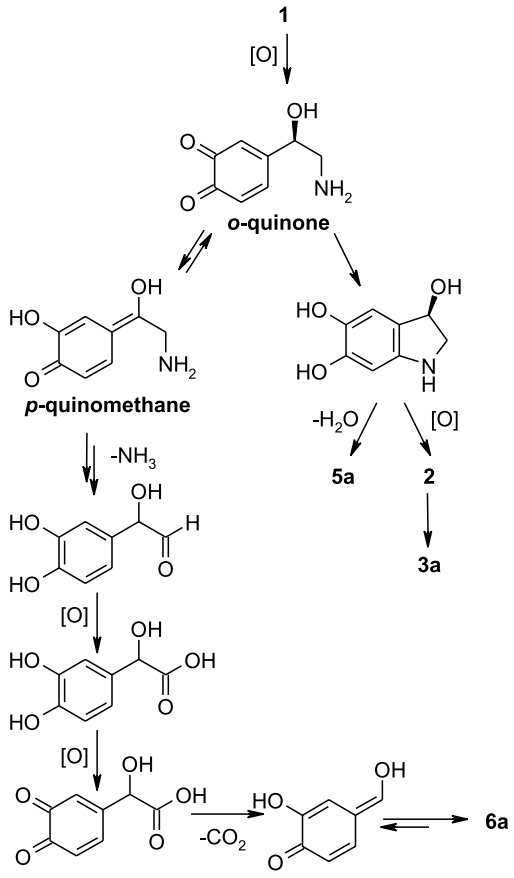
The fourth product isolated from the oxidation mixture of **1** was formulated as 1-acetyl-3,5,6-triacetoxyindole (**3b**). It exhibited a pseudomolecular ion peak ($[M+H]^+$) in the ESI(+)-MS spectrum at *m/z* 334, with ($[M+Na]^+$) and ($[M+K]^+$) peaks at *m/z* 356 and 372. The ^1H NMR spectrum showed three singlets (1H each) in the aromatic region, two of which shifted downfield at δ 7.87 and 8.28, and signals for four acetyl groups. The ^{13}C NMR spectrum consistently showed eight signals in the range between δ 141.0 and 111.4, besides the signals for four acetyl groups.

The overall yields of the isolated products **3b–6b** were less than 10% of the starting material. The remainder of the oxidation mixture was accounted for by significant amounts of insoluble dark polymeric materials together with a series of products all in very small amounts, which could not be isolated for spectroscopic characterisation. The poor mass balance was apparently due to the relative instability of the products which do not tend to accumulate in the reaction mixture but, as generated, are rapidly degraded to polymeric materials.

The formation of structure **4a** by oxidation of **1** was remarkable, since it incorporated the 5,6-dihydroxyindole system which is at a lower oxidation state compared to **2**. As mentioned earlier, the possibility that its incorporation into the structure of **4a** could be due to the reduction of **2** following treatment with dithionite[30] was ruled out by a careful analysis of the ethyl acetate extractable fraction obtained omitting treatment with dithionite. Under these conditions, acetylation of the extract gave a more complex mixture in which **4b** was clearly present, along with some **5b**, indicating the presence of **5a** in the crude mixture. On this basis, it is argued that **5a** is formed by dehydration of leuconoradrenochrome, a process that would favourably compete with the usual oxidative route to **2**. To the best of our knowledge, this is the first study demonstrating the direct formation of **5a** by oxidation of **1** under physiologically relevant conditions without a reductive step.[30]

The mechanism of formation of **6a** is likewise worthy of note, as it reflects the oxidative breakdown of the side chain of **1**. This would likely proceed through the intermediacy of 3,4-dihydroxymandelic acid, which had previously been proposed as the direct precursor of **6a** under oxidative conditions.[31,32] Consistent with this prediction, analysis of the oxidation mixture of **1** showed the presence of detectable amounts of 3,4-dihydroxymandelic acid. Moreover, when reacted under the above conditions, the acid was converted to **6a**.

On this basis, a possible mechanistic scheme for the oxidation of **1** is outlined in Scheme 1. Formation of 3,4-dihydroxymandelic acid from **1** would involve oxidation of the catecholamine to the *o*-quinone followed by rapid



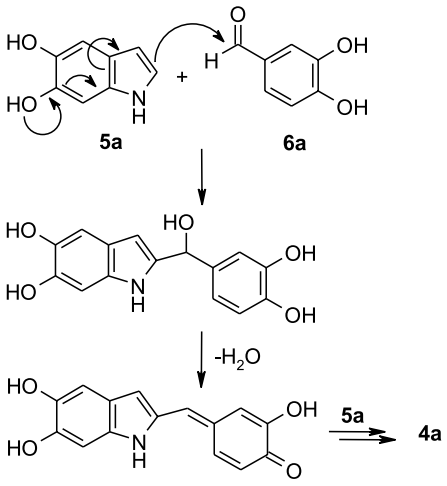
Scheme 1. Proposed mechanism of formation of compounds **3a**, **5a** and **6a** by oxidation of **1**.

tautomerism leading to a *p*-quinomethane intermediate and then to 3,4-dihydroxymandelic aldehyde, which would then be readily oxidised to the carboxylic acid. Quinomethane formation from catecholamine quinones is usually much slower than cyclisation and only occurs when the latter process is unfavourable.[33] This is consistent with the notion that *o*-quinone of **1** undergoes cyclisation at a relatively slower rate[34] and is therefore susceptible to tautomerism, a process favoured by the hydroxyl group enhancing the acidity of the β-proton.

As shown in Scheme 1, cyclisation and tautomerism of the *o*-quinone of **1** represent two competing routes leading to **5a** and **6a**, respectively. These latter, as confirmed by the synthetic experiment described before, would then concur to the formation of **4a** through coupling processes reminiscent of the reaction of indoles with the Ehrlich reagent (Scheme 2).[35]

The unusual regiochemical course of the coupling reaction would be dictated by frontier orbital interactions, as argued by the high HOMO coefficient on the C-2 position of **5a**,[36] due to the electron-releasing effect of the hydroxyl group on the 6-position of the indole ring.

In conclusion, the identification of a novel [bis-(indol-2-yl)methyl]-benzene derivative provides the first detailed insight into the oxidative pathway of **1** beyond the aminochrome stage and fills a gap in the chemistry of



Scheme 2. Proposed mechanism of formation of compound **4a**.

catecholamines. Other highlights of this study include the hitherto unrecognised conversion of **1** quinone to 3,4-dihydroxymandelic acid under non-enzymatic conditions; the isolation of **3a** as the acetylated derivative by direct oxidation of **1**; and the identification of **5a** among the products spontaneously formed by oxidation of **1** without reductive treatment of the mixture.

The chemistry described in this paper may also hint at practical routes to novel [bis-(indol-2-yl)methyl]-benzene compounds. [Bis-(indolyl)methyl]-benzene derivatives are the focus of increasing interest because of their biological activities, as exemplified by their antibacterial, anticarcinogenic, antiinflammatory and toxic properties.[37–39] Generally, these compounds are prepared by protic or Lewis acid catalysed condensations of indoles with aldehydes.[40–42] In all cases, however, [bis-(indol-3-yl)methyl]-benzene derivatives are obtained, unless the 3-position is substituted, for example, by an alkyl residue,[43] and no straightforward route to [bis-(indol-2-yl)methyl]-benzenes unsubstituted on the 3-position is available.

3. Experimental

3.1. General methods

ESI(+)-MS spectra were recorded with a Waters ZQ quadrupole mass spectrometer. High resolution EI-MS spectra were obtained at 70 eV and 230 °C using a Kratos MS 50 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using a Bruker WM 400 spectrometer. $^{1}H,^{1}H$ COSY, $^{1}H,^{13}C$ HMQC, $^{1}H,^{13}C$ HMBC, and ROESY experiments were run at 400 MHz using standard pulse programs from the Bruker library.

UV spectra were performed with a Beckmann DU 640 spectrophotometer. Analytical and preparative HPLC were carried out on a Gilson apparatus equipped with a UV detector set at 280 nm using a Sphereclone ODS (5 μm, 4.6×250 mm) or Econosil (10 μm, 22×250 mm) column, respectively. For analytical runs, 0.02 M acetic acid/acetonitrile 60:40 (v/v) was used as the eluant, at a flow rate of

1 mL/min. In preparative runs elution conditions were 0.02 M acetic acid/acetonitrile 50:50 (v/v), at a flow rate of 15 mL/min. TLC and PLC was carried out on silica gel plates (0.25 and 0.50 mm, respectively) from Merck. Noradrenaline hydrochloride was from Sigma and 3,4-dihydroxybenzaldehyde was from Fluka. 3,4-Dihydroxymandelic acid, hydrogen peroxide (30% solution in water), $NaIO_4$ and $K_3Fe(CN)_6$ were from Aldrich. 5,6-Dihydroxyindole was prepared as reported.[44] Molecular mechanics calculations were carried out with Hyperchem 6.01 package produced by Hypercube, Inc. (Waterloo, Ont., Canada) 2000.

3.2. Oxidation of noradrenaline (1)

A solution of **1** (60 mg, 0.29 mmol) in 0.1 M phosphate buffer, pH 7.4 (60 mL), was treated with $K_3Fe(CN)_6$ (97 mg, 0.29 mmol). After 5 min the reaction mixture was reduced with sodium dithionite (2 mg/mL), acidified to pH 5 with HCl, and extracted with ethyl acetate (2×30 mL). The organic layers were collected, dried over anhydrous sodium sulphate, evaporated under reduced pressure, and the residue was treated with acetic anhydride (0.500 mL) and pyridine (0.025 mL) overnight. The acetylated mixture was evaporated under reduced pressure and the residue was taken in ethyl acetate (5 mL) and subjected to HPLC analysis. Similar experiments were carried out by treating **1** (60 mg, 0.29 mmol) with $NaIO_4$ (63 mg, 0.29 mmol) or with $Fe(NH_4)_2(SO_4)_2\times 6H_2O$ (95 mg, 0.29 mmol), EDTA (90 mg, 0.29 mmol) and H_2O_2 (0.025 mL, 0.29 mmol). All the experiments were carried out also by omitting treatment with sodium dithionite.

3.3. Isolation of 1-acetyl-3,5,6-triacetoxyindole (3b), 4-[bis-(1*H*-5,6-diacetoxyindol-2-yl)methyl]-1,2-diacetoxybenzene (4b), 5,6-diacetoxyindole (5b) and 3,4-diacetoxybenzaldehyde (6b)

A solution of **1** (600 mg, 2.9 mmol) in 0.1 M phosphate buffer, pH 7.4 (600 mL), was treated with $NaIO_4$ (624 mg, 2.9 mmol). After 5 min, the reaction mixture was worked up as above. After acetylation, the mixture was subjected to preparative HPLC to give compounds **3b** (29 mg, 3% yield, $t_R=11.9$ min), **4b** (45 mg, 7% yield, $t_R=23.0$ min), **5b** (7 mg, 1% yield, $t_R=7.2$ min), and **6b** (7 mg, 1% yield, $t_R=6.8$ min). Purity of compounds **3b**–**6b** was at least 98% as determined by ^{1}H NMR.

Compound **3b**. FT-IR ($CHCl_3$) ν_{max} 1766, 1713, 1458, 1411, 1386, 1371, 1298; δ_H ($(CD_3)_2CO$), 2.30 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.37 (3H, s, CH_3), 2.67 (3H, s, CH_3), 7.39 (1H, s, H-4), 7.87 (1H, s, H-2), 8.28 (1H, s, H-7); δ_C ($(CD_3)_2CO$), 19.6 (2×CH_3), 19.8 (CH_3), 22.8 (CH_3), 111.4 (C-7), 111.7 (C-4), 115.9 (C-2), 121.6 (C-3a), 129.9 (C-7a), 133.6 (C-3), 139.4 (C-5), 141.0 (C-6), 167.6 (CH_3COO–), 168.0 (2×CH_3COO–), 168.9 (CH_3COO–); ESI(+)-MS: *m*/*z* 334 ($[M+H]^+$), 356 ($[M+Na]^+$), 372 ($[M+K]^+$); HREI-MS for $C_{16}H_{15}NO_7$: calcd 333.0848, found 333.0935.

Compound **4b**. UV λ_{max} 277, 286, 293 nm (CH_3OH); FT-IR ($CHCl_3$) ν_{max} 1766, 1602, 1505, 1469, 1371, 1329; δ_H ($(CD_3)_2CO$), see Table 1; δ_C ($(CD_3)_2CO$), see Table 1; ESI(+)-MS: *m*/*z* 671 ($[M+H]^+$), 693 ($[M+Na]^+$), 709 ($[M+K]^+$); HREI-MS for $C_{35}H_{30}N_2O_{12}$: calcd 670.1799, found 670.1823.

Compound **5b**. FT-IR ($CHCl_3$) ν_{max} 1765, 1509, 1468, 1371, 1325, 1304; δ_H (CD_3OD), 2.26 (6H, s, CH_3), 6.48 (1H, d $J=3.2$ Hz, H-3), 7.28 (1H, s, H-7), 7.36 (1H, s, H-4), 7.38 (1H, d $J=3.2$ Hz, H-2).[45]

Compound **6b**. FT-IR ($CHCl_3$) ν_{max} 1766, 1690, 1600, 1490, 1450, 1420, 1365, 1250; δ_H (CD_3OD), 2.26 (6H, s, CH_3), 7.44 (1H, d $J=8.0$ Hz, H-5), 7.77 (1H, d $J=2.0$ Hz, H-2), 7.84 (1H, dd $J=8.0$, 2.0 Hz, H-6), 9.94 (1H, s, CHO).[46]

3.4. Synthesis of 4-[bis-(1*H*-5,6-diacetoxyindol-2-yl)methyl]-1,2-diacetoxybenzene (4b)

Compound **5a** (100 mg, 0.67 mmol) was added to 0.1 M phosphate buffer, pH 7.4 (134 mL), previously purged with an argon stream, and treated with **6a** (464 mg, 3.4 mmol). After 24 h, the reaction mixture was acidified to pH 5 and worked up as above. After acetylation the residue was subjected to PLC (eluant chloroform/ethyl acetate 1:1 plus 1% acetic acid) to afford **4b** (90 mg, 40%, $R_f=0.37$).

Acknowledgements

This work was carried out in the frame of research programs on antitumor agents, sponsored by MIUR (PRIN 2003) and on the mechanisms of aging and photoaging (IFO 2003) sponsored by the Ministry of Health. We thank the 'Centro Interdipartimentale di Metodologie Chimico-Fisiche' (CIMCF, University of Naples Federico II) for NMR and mass facilities. We thank Mrs Silvana Corsani for technical assistance.

References and notes

1. Napolitano, A.; Pezzella, A.; Prota, G. *Chem. Res. Toxicol.* **1999**, *12*, 1090–1097.
2. Napolitano, A.; Pezzella, A.; Prota, G. *Tetrahedron Lett.* **1999**, *40*, 2833–2836.
3. Manini, P.; Panzella, L.; Napolitano, A.; d'Ischia, M. *Tetrahedron* **2003**, *59*, 2215–2221.
4. Napolitano, A.; Crescenzi, O.; Pezzella, A.; Prota, G. *J. Med. Chem.* **1995**, *38*, 917–922.
5. d'Ischia, M.; Palumbo, A.; Prota, G. *Tetrahedron* **1988**, *44*, 6441–6446.
6. Palumbo, A.; d'Ischia, M.; Misuraca, G.; Prota, G. *Biochim. Biophys. Acta* **1989**, *990*, 297–302.
7. Prota, G. *Melanins and Melanogenesis*; Academic: San Diego, 1992.
8. Double, K. L.; Zecca, L.; Costi, P.; Mauer, M.; Griesinger, C.; Ito, S.; Ben-Shachar, D.; Bringmann, G.; Fariello, R. G.; Riederer, P.; Gerlach, M. *J. Neurochem.* **2000**, *75*, 2583–2589.
9. Sugumaran, M. *Pigment Cell Res.* **2002**, *15*, 2–9.
10. Smythies, J.; De Iuliis, A.; Zanatta, L.; Galzigna, L. *Neurotox. Res.* **2002**, *4*, 77–81.
11. Pezzella, A.; d'Ischia, M.; Napolitano, A.; Misuraca, G.; Prota, G. *J. Med. Chem.* **1997**, *40*, 2211–2216.

12. Dryhurst, G. *Adv. Exp. Med. Biol.* **2001**, *500*, 373–396.
13. Segura-Aguilar, J.; Metodiewa, D.; Baez, S. *Neurotox. Res.* **2001**, *3*, 157–165.
14. Sugumaran, M.; Semensi, V.; Kalyanaraman, B.; Bruce, J. M.; Land, E. J. *J. Biol. Chem.* **1992**, *267*, 10355–10361.
15. Land, E. J.; Ramsden, C. A.; Riley, P. A. *Acc. Chem. Res.* **2003**, *36*, 300–308.
16. Land, E. J.; Ramsden, C. A.; Riley, P. A.; Yoganathan, G. *Pigment Cell Res.* **2003**, *16*, 397–406.
17. Wrona, M. Z.; Dryhurst, G. *Biochem. Pharmacol.* **1991**, *15*, 1145–1162.
18. Heacock, R. A. *Adv. Heterocycl. Chem.* **1965**, *5*, 205.
19. Palumbo, A.; Napolitano, A.; Barone, P.; d'Ischia, M. *Chem. Res. Toxicol.* **1999**, *12*, 1213–1222.
20. Jimenez, M.; Garcia-Canovas, F.; Garcia-Carmona, F.; Lozano, J. A.; Iborra, J. L. *Biochem. Pharmacol.* **1984**, *33*, 3689–3697.
21. Remiao, F.; Milhazes, N.; Borges, F.; Carvalho, F.; Bastos, M. L.; Lemos-Amado, F.; Domingues, P.; Ferrer-Correia, A. *Biomed. Chromatogr.* **2003**, *17*, 6–13.
22. Cohen, G.; Goldenberg, M. *J. Neurochem.* **1957**, *2*, 58–70.
23. Lund, A. *Acta Pharmacol. Toxicol.* **1949**, *5*, 1218.
24. Heacock, R. A.; Scott, B. D. *Experientia* **1961**, *XVII*, 347–348.
25. d'Ischia, M.; Prota, G. *Tetrahedron* **1987**, *43*, 431–434.
26. Corradini, M. G.; Napolitano, A.; Prota, G. *Tetrahedron* **1986**, *42*, 2083–2088.
27. d'Ischia, M.; Napolitano, A.; Tsiakas, K.; Prota, G. *Tetrahedron* **1990**, *46*, 5789–5796.
28. Kujala, T.; Klika, K.; Ovcharenko, V.; Loponen, J.; Vienila, M.; Pihlaja, K. *Z. Naturforsch.* **2001**, *56c*, 714–718.
29. Mee, S. P. H.; Lee, V.; Baldwin, J. E.; Cowley, A. *Tetrahedron* **2004**, *60*, 3695–3712.
30. Lim, M. I.; Patil, D. G. *Tetrahedron Lett.* **1987**, *28*, 3775–3778.
31. Martinez Ortiz, F.; Tudela Serrano, J.; Rodriguez Lopez, J. N.; Varon Castellanos, R.; Lozano Teruel, J. A.; Garcia-Canovas, F. *Biochim. Biophys. Acta* **1988**, *957*, 158–163.
32. Sugumaran, M. *Biochemistry* **1986**, *25*, 4489–4492.
33. Land, E. J.; Ramsden, C. A.; Riley, P. A.; Yoganathan, G. *Org. Biomol. Chem.* **2003**, *1*, 3120–3124.
34. Chavdarian, C. G.; Karashima, D.; Castagnoli, N., Jr. *J. Med. Chem.* **1978**, *21*, 548–554.
35. Sundberg, R. J. *The Chemistry of Indoles*; Academic: New York, 1970; pp 39–44.
36. Powell, B. J.; Baruah, T.; Bernstein, N.; Brake, K.; McKenzie, R. H.; Merdith, P.; Pederson, M. R. *J. Chem. Phys.* **2004**, *120*, 8608–8615.
37. Sanderson, J. T.; Slobbe, L.; Lansbergen, W. A.; Safe, S.; van der Berg, M. *Toxicol. Sci.* **2001**, *61*, 40–48.
38. Chintharlapalli, S.; Smith, R.; Samudio, I.; Zhang, W.; Safe, S. *Cancer Res.* **2004**, *64*, 5994–6001.
39. Qin, C.; Morrow, D.; Stewart, J.; Spencer, K.; Porter, W.; Smith, R., III; Phillips, T.; Abdelrahim, M.; Samudio, I.; Safe, S. *Mol. Cancer Ther.* **2004**, *3*, 247–260.
40. Feng, X. L.; Guan, C. J.; Zhao, C. X. *Synth. Commun.* **2004**, *34*, 487–492.
41. Nagarajan, R.; Perumal, P. T. *Synth. Commun.* **2002**, *32*, 105–109.
42. Pindur, U.; Mueller, J. *J. Heterocycl. Chem.* **1987**, *24*, 159–163.
43. Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, *44*, 1959–1961.
44. Benigni, J. D.; Minnis, R. L. *J. Heterocycl. Chem.* **1965**, *2*, 387–392.
45. Heacock, R. A.; Hutzinger, O.; Scott, B. D.; Daly, J. W.; Witkop, B. *J. Am. Chem. Soc.* **1963**, *85*, 1825–1831.
46. Corda, L.; Fadda, A. M.; Maccioni, A.; Maccioni, A. M.; Podda, G. *J. Heterocycl. Chem.* **1988**, *25*, 311–314.