Pergamon

Tetrahedron Letters, Vol. 37, No. 24, pp. 4241-4242, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00806-4

The First Characterisation of a Transient 5,6-Indolequinone.

Alessandra Napolitano, Alessandro Pezzella, Marco d'Ischia and Giuseppe Prota*

Department of Organic and Biological Chemistry, University of Naples Federico II,
Via Mezzocannone 16, I-80134 Naples, Italy.

Abstract: Oxidation of 5,6-dihydroxy-2,3-dimethylindole (**1**) with $NaIO_4$ or *o*-chloranil afforded a yellow transient intermediate with λ_{max} around 360 nm which was identified as the hitherto unknown 2,3-dimethyl-5,6-indolequinone (**2**) by straightforward ^{1}H-NMR analysis.

Among naturally occurring heterocyclic quinones, the 5,6-indolequinones have attracted keen interest because of their putative involvement in the biosynthesis of melanins, the most prominent pigments in man and non-human mammals.[1] Yet, all attempts towards a structural characterisation of these compounds have been frustrated by their inherent instability, which is reminiscent of that of 2,3-naphthoquinones.[2] In fact, even the existence of 5,6-indolequinones as independent intermediates in the enzymatic or chemical oxidation of 5,6-dihydroxyindoles to melanin has remained more a matter of surmise than of unambiguous experimental proof, in spite of the claimed detection of the parent quinone by pulse radiolytic techniques.[3]

In pursuing a direct approach to 5,6-indolequinone, we focused our attention on the oxidation of 5,6-dihydroxy-2,3-dimethylindole (**1**) as a potentially viable route to the target system. The rationale was that protection of the reactive positions on the pyrrole moiety and the inductive involvement of the electron donating alkyl substituents would confer to the postulated quinone a sufficient stabilisation for chemical analysis. Such an expectation was corroborated by an early observation[4] showing that on oxidation **1** is converted to a yellow intermediate which persists for some time before changing into a melanin-like pigment.

Indeed, when **1** was treated with a stoichiometric amount of $NaIO_4$ in phosphate buffer pH 7.0, or methanolic *o*-chloranil, a transient chromophoric phase with a maximum at 361 nm and a shoulder at 380 nm soon developed, which survived for some minutes before flattening out. HPLC analysis of the oxidation mixtures during the yellow phase showed the complete disappearance of the starting indole, which could be regenerated by prompt reduction with sodium borohydride, but no definite peak attributable to oxidation products. To get insight into the nature of the yellow intermediate, the oxidation of **1** (10 mg/ml) was conducted in methanol-d_4 and was monitored by ^{1}H-NMR at 400 MHz (Figure). After addition of *o*-chloranil to the tube, the resonances of **1** (spectrum A) rapidly disappeared and were replaced by a new set of signals (spectrum B) whose chemical shifts and integrated areas were indicative of the expected 2,3-dimethyl-5,6-indolequinone (**2**). In particular, the singlets at δ 5.47 and 6.26 (1H each) matched fairly well with those of aminochrome-like structures[5] with an amine or a related nitrogen substituent on the 4-position of an

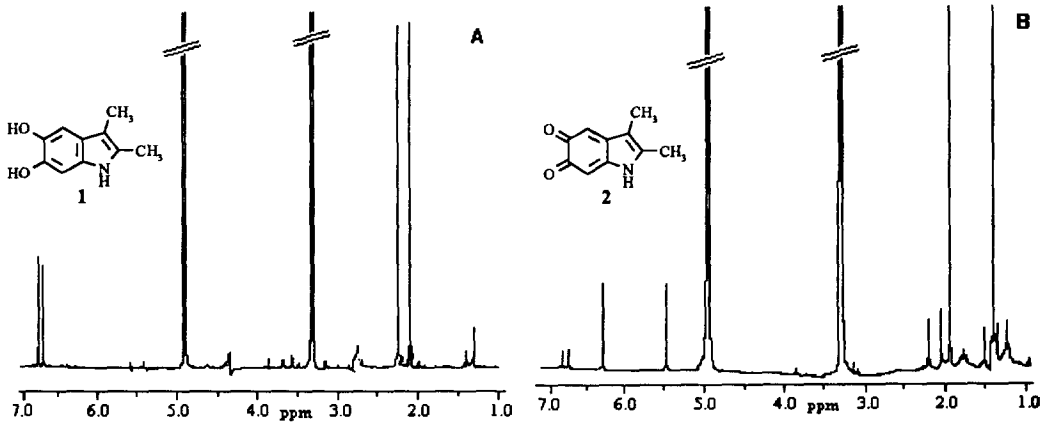

Figure. ^{1}H NMR (400 MHz, methanol-d_4) spectrum of **1** (A) and **2** (B) as generated by *o*-chloranil oxidation.

o-quinone ring. The upfield shift of the methyl groups at δ 1.47 and 2.02 was also suggestive of an indole system in which the aromaticity of the pyrrole moiety was disrupted. The estimated half life of **2** under such conditions was about 5 minutes, which precluded acquisition of a meaningful ^{13}C-NMR spectrum (with DEPT modality). Although **2** seemed on the verge of being isolable, it rapidly polymerised when subjected to chromatography and/or upon concentration, even in the cold and with absolute exclusion of oxygen, which thwarted all efforts towards a more complete characterisation.

Besides filling an important gap in the chemistry of heterocyclic compounds, the present study represents the first successful attempt to characterise one of the most elusive melanogenic intermediates, and provides the basis for a novel interpretation of the origin of the melanin chromophore and its light absorption properties.

ACKNOWLEDGEMENTS

This work was supported by grants from M.U.R.S.T., C.N.R. and the Lawrence M. Gelb Research Foundation (Stamford, CT, USA).

REFERENCES AND NOTES

1. Prota, G. *Fortschr. Chem. Org. Naturst.* **1995**, *64*, 94-148.
2. Horak, V.; Foster, F. V.; de Levie, R.; Jones, J. W.; Svoronos, P. *Tetrahedron Lett.* **1981**, *22*, 3577-3578.
3. Lambert, C.; Chacon, J.N.; Chedekel, M.R.; Land, E. J.; Riley, P. A.; Thompson, A.; Truscott, G. T. *Biochim. Biophys. Acta* **1989**, *993*, 12-20.
4. Beer, R. J. S.; Broadhurst, T.; Robertson, A. *J. Chem. Soc.* **1954**, 1947-1953.
5. For typical proton spectra of aminochrome-type structures see: d' Ischia, M.; Palumbo, A.; Prota, G. *Tetrahedron*, **1988**, *44*, 6441-6446. Napolitano, A.; d'Ischia, M.; Costantini, C.; Prota, G. *Tetrahedron*, **1992**, *48*, 8515-8522.

(*Received in UK* 3 *April* 1996; *accepted* 26 *April* 1996)