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EVIDENCE FOR THE INTERMEDIACY OF QUINONE-METHIDES IN THE REARRANGEMENT OF AMINOCHROMES TO 5,6-DIHYDROXYINDOLES

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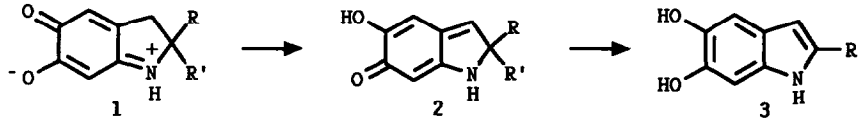
ABSTRACT: Oxidation of α-methyldopa methyl ester leads to the aminochrome **4**, which, at neutral pH, spontaneously rearranges to give a relatively stable quinone-methide identified as **5**. This provides the first evidence for the postulated intermediacy of quinone-methides in the conversion of aminochromes to 5,6-dihydroxyindoles.

It has long been known that enzymic or chemical oxidation of catecholamines results in the formation of orange-red 2,3-dihydroindole-5,6-quinone derivatives, collectively known as aminochromes.[1,2] Compounds of this class have received considerable attention in relation to their role in several biological processes, e.g. the oxidative metabolism of adrenaline[3] and the formation of tyrosine-melanin.[4] A distinguishing feature of the chemistry of aminochromes is their tendency to undergo rearrangement to 5,6-dihydroxyindoles.[3,5,6] The mechanism of this reaction is generally envisaged as depicted in the scheme.[1] However, no detailed kinetic study has been carried out in so far to support the proposed mechanism, nor the supposed quinone-methide intermediates **2** have ever been detected.



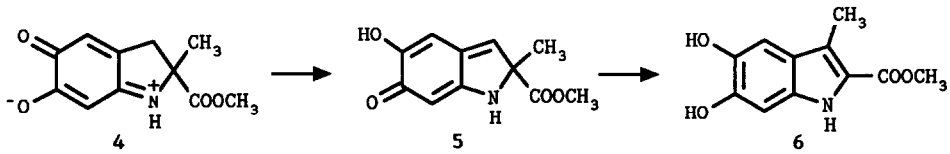
1 **2** **3**

a: R-CH_3, R'-COOH
b: R-H, R'-COOH
c: R-$COOCH_3$, R'-H

SCHEME

In connection with our studies of the chemistry of melanogenesis, we found that the aminochrome **1a**, generated by periodate or ferricyanide oxidation of α-methyldopa in aqueous buffered solution (pH 7) undergoes rearrangement with concomitant decarboxylation to give the expected 5,6-dihydroxy-2-methylindole (**3a**). To gain information on the mechanism of the reaction, we investigated the rearrangement behaviour of the related aminochrome **4**, in which decarboxylation is prevented. When allowed to stand at neutral pH, **4** was smoothly converted into a yellow, ethyl acetate extractable compound. This was isolated after column chromatography on polyamide, and was identified as the quinone-methide **5** on the basis of the

following evidence. The EI-MS displays the molecular ion at m/z 221, indicating an isomer of **4**. The UV spectrum (EtOH) shows absorption maxima at 221, 313 and 420 nm, consistent with a quinonoid chromophore. The ^{1}H-NMR spectrum shows, besides signals for two methyl groups, a singlet at δ 6.26 and two doublets at δ 5.56 and 6.89 ppm (J=1.1 Hz), attributable to the protons at 4, 3 and 7 position, respectively. These assignments were substantiated by the ^{13}C-NMR spectrum,[7] showing a carbonyl resonance at δ 179.58 ppm, and three doublets in the sp^2 region.



4 **5** **6**

Kinetic experiments showed that the conversion of **4** to **5** is first order with respect to **4**, the rate constant lying within the range of values found for the rearrangement of the aminochromes **1a-c** to the corresponding 5,6-dihydroxyindoles.[8] From this it can be inferred that the hydrogen shift from position 3 is the rate-determining step in the rearrangement of aminochromes, rather than a side-reaction. The quinone-methides of the type **2** are too unstable to be detected, for they rapidly undergo aromatization either by decarboxylation or by hydrogen shift from position 2. In the case of **5**, both processes are forbidden, which accounts for its relative stability. Interestingly, on addition of few drops of conc. HCl to an acetone solution of **5**, a rapid reaction takes place, leading to a colourless isomeric product ($C_{11}H_{11}NO_4$), identified as methyl 5,6-dihydroxy-3-methylindole-2-carboxylate (**6**), arising evidently from **5** *by* 1,2-methyl shift.

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References and notes.

1. Heacock, R.A.; *Adv.Heterocycl.Chem.*, **1965**, *5*, 205.
2. Sobotka, H.; Barsel, N.; Chanley, J.D.; *Fortschr.Chem.Org.Naturst.*, **1957**, *14*, 217.
3. Bu'Lock, J.D.; Harley-Mason, J.; *J.Chem.Soc.*, **1951**, 712.
4. Prota, G.; *Medicinal Research Reviews*, **1988**, *8*, 525.
5. Heacock, R.A.; Mattok, G.L.; *Can.J.Chem.*, **1963**, *41*, 139.
6. Austin, A.; Chanley, J.D.; Sobotka, H.; *J.Am.Chem.Soc.*, **1951**, *73*, 2395.
7. ^{13}C-NMR (acetone-d$_6$), δ (ppm): 179.58 (s), 171.10 (s), 163.95 (s), 152.19 (s), 139.17 (d), 134.03 (s), 96.81 (d), 91.65 (d), 74.47 (s), 53.38 (q), 22.33 (q).
8. Spectrophotometric measurements were carried out at 30°C, in 0.088 *M* phosphate buffer, pH 7.00. The first-order rate constants for the disappearance of aminochrome absorptions are as follows: **1a**, 0.0324; **1b**, 0.0508; **1c**, 0.27; **4**, 0.066 min^{-1}.

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