Anodic Methoxylation of Isatin

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Anodic methoxylation of isatin was investigated. The product formed contained a unique 3a,7a-dihydroindole ring system. 3a,7a-Dihydro-(Z)-3a,7a-dimethoxyisatin was isolated and characterized with a variety of spectroscopic methods.

Introduction

Isatin, which is the substrate for industrial synthesis of the most popular fabric dye, the indigo, has been subject to electrolytic reduction under a variety of experimental conditions \cite{1,2}. Polargraphic behavior of isatin and a variety of isatin derivatives has been described in many of papers \cite{3–6}. However, most of those reports were devoted to cathodic phenomena.

Here we report the electrochemical synthesis of an unusual indole ring system formed anodically during the electrolysis of methanolic isatine solutions. This procedure results in the formation of 3a,7a-dihydro-3a,7a-dimethoxyisatin, a stable compound with saturated double bond between two partner rings of the indole nucleus.

Results and Discussion

Isatin is unstable in alkaline medium. Therefore, the electrolysis of isatin solutions should be performed under acidic conditions. Among a number of methanolic electrolyte compositions tested, sodium acetate/acetic acid-supplemented medium proved to be the most effective. To avoid cathodic reduction of isatin, electrolysis was performed in a diaphragm-equipped cell. The oxidation potential of isatin is higher than that of acetate. Therefore, isatin oxidation was investigated by a kinetic approach, that is, by studying product formation dependence on current density (Fig. 1). The strongly fluorescent main product of the electrolysis is less polar than isatin, and is easily separated by liquid chromatography. Elemental and mass spectroscopy analyses indicated to the addition of two methoxyl groups to isatin molecule. UV-absorption spectra (Fig. 2) showed similarity between isatin and the reaction product in the 220–320 nm range. However, the product spectrum lacked the longwave band at 420 nm (orange colour) which is characteristic of isatin and indicates π-electron conjugation between the benzene ring and \(\sigma\)-carbonyl system. In contrast to isatin, the isolated oxidation product showed strong fluorescence with the emission maximum at 380 nm in water, and 362 nm in methanol (Fig. 3).

One may conclude from the above experimental data that the oxidation results in the addition of two methoxy groups, and saturation of the double bond between the benzene and pyrrole rings according to the Scheme 1.

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme1.png}
\end{center}

Scheme 1. Mechanism of anodic methoxylation of isatin.

The detailed structure of the electrolysis product has been confirmed by NMR spectroscopy. Assignments for proton and carbon chemical shifts of isatin and 3a,7a-dihydro-(Z)-3a,7a-dimethoxyisatin (Table I) and coupling constants (Table II) in DMSO-\(d_6\) agree with data published for isatin \cite{7,8}. The signal sequence in order of

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Fig. 1. Formation of 3a,7a-dihydro-(Z)-3a,7a-dimethoxyisatin during the electrolysis of isatin at different current densities in methanol/acetic acid/sodium acetate; 0.02 A/cm$^2$ (O) carbon electrodes, 0.02 A/cm$^2$ (o) (Pt), 0.04 A/cm$^2$ (A) (Pt); and in methanolic 0.1 M LiClO$_4$, 0.02 A/cm$^2$ (+) (Pt).

Fig. 2. Ultraviolet absorption spectra of isatin (solid) and 3a,7a-dihydro-(Z)-3a,7a-dimethoxyisatin (dashed) in pH 7.

Fig. 3. Fluorescence emission spectra of 3a,7a-dihydro-(Z)-3a,7a-dimethoxyisatin in unbuffered water (1) and in methanol (2).
increasing chemical shift for the carbons of homocyclic ring: \( C(7) < C(5) < C(4) < C(6) \) remains unchanged after methoxylation like in the series of isatin derivatives reported earlier [8], although the deshielding effect of methoxy groups on \( C(4) \) and \( C(7) \) causes significant downfield shifts (\( \sim 6 \) ppm) of these signals, which is accompanied by shielding of other carbons, especially of \( C(3) \) and \( C(7a) \).

NOE measurements (see data Experimental) demonstrated that both methoxy groups were situated on the same side of the 3a,7a-dihydro-3a,7a-dimethoxyisatin molecule. The 3a and 7a carbons are tetragonal in the product, which indicates that oxidation results in a change from planar (indole) to a non-planar (dihydroindole) structure. The NOE spectra suggest the plane of pyrrole ring in the oxidation product is slanted and a little tortuous with respect to the approximated plane of the six-carbon ring, that is, the N(1)-H is rather \textit{trans} to the methoxy groups. Moreover, the six-carbon ring is not planar, but the \( C(5)-H \) and \( C(6)-H \) are positioned a little \textit{cis} to the methoxy groups. Exact conformation of the methoxyls cannot be established because they rotate around \( C(3a)-O \) and \( C(7a)-O \) bonds quickly compared with the NMR measurements’ time scale. Two methoxy groups have to be situated at the same site of the molecule. This change of the geometry in the molecule causes the former invisible \( ^4J(C(3)-H) \) coupling constants and quite different transoid and cisoid \( ^3J(C(3)-H) \) coupling constants average now \( \sim 4.2 \) Hz (Table II); similar but weaker effect can be seen for the carbon \( C(7) \).

Stable 3a,7a-dihydroindole structure is a rare case in indole chemistry. There is only one report in the literature showing an indole derivative with saturated 3a,7a-double bond being an unstable intermediate in the synthesis of indolecarboxylic acids [9]. The structure of the 3a,7a-\textit{trans}-substituted molecule with saturated double bond suggests a strong sterical hindrance, and may be expected highly unstable. However, the introduction of both methoxyls in \textit{cis} position may be explained by a particular adsorption of isatin onto anodic surface.

The specific modification of the 3a,7a double bond may be related to the electron-pulling effect of carbonyl groups at the pyrrole nucleus. How-
ever, we did not observe anodic methoxylation using phtalimide (which could be considered a structural isomer of isatin) in the same reaction conditions.

Anodically formed methoxy radical is a highly reactive species. There are many reports showing electrochemical bis-methoxylation of a C=C bond or aromatic ring. Methoxylation of methylated benzenes results in methoxy-substitution of both benzene core and side chain. The products of the core substitution are 1,4-cyclo-hexadienes [10]. Cis- and trans-3,6-dimethylcyclohexa-1,4-dienes obtained by electrochemical methoxylation of p-xylene were completely separated [11]. Anodic oxidation of 4-methoxybenzo[b]thiophen in methanolic solution gives benzo[b]thiophen-4,7-quinone bisacetals with excellent yield [12]. Electrolysis of methanolic sodium methoxylate containing cyclohexa-1,3-diene yields 3,4- and 3,6-dimethoxycyclohexene, whereas cyclohexane yields dimethoxymethylcyclopentane [13]. Styrene reacts with anodically formed methoxy radicals to give, among other products, styrene glycol dimethyl ether with a 16–22% yield [14,15]. Electrolysis of methanolic sodium methoxylate containing cyclohexa-1,3-diene yields 3,4- and 3,6-dimethoxycyclohexene, whereas cyclohexane yields dimethoxymethylcyclopentane [13]. Styrene reacts with anodically formed methoxy radicals to give, among other products, styrene glycol dimethyl ether with a 16–22% yield [14,15]. Electrolysis of cis- and trans-stilbenes results in formation of both meso- and dl-hydrobenzoindimethyl ethers with different yields depending on the starting compound [16,17]. Interestingly, electrolysis of methanolic norbornene solution does not provide the expected vic-dimethoxylated derivative, but a variety of other dimethoxylated products is formed [17]. There is also a report showing efficient dimethoxylation of C(15)=C(16) bond in porphyrine-like compound, a bilindione [18].

In a present study, electrochemical methoxylation of isatin resulted in exclusive formation of one of the expected stereoisomers. Indole ring is a core structure in numerous alkaloids. While it is difficult to predict whether the stereospecific modification of the indole core described here will take place in other indole derivatives, we expect it may open a new avenue in indole chemistry.

Experimental

Electrolysers were run in a divided cell apparatus equipped with two 3 cm² platinum electrodes and a porous glass membrane. Analytical TLC was performed on pre-coated silica gel 60 F254 (Merck). Melting points (uncorr.) were measured on a Boetius microscope hot stage. HPLC was performed on a Shimazu LC 6A instrument (UV detector, λ=254 nm) with a C18 column (4.6 x 255 mm) (Beckmann) (water-MeOH). Kinetic measurements were normalized. Mass spectra (70 eV) were obtained with a model AMD-60 (In- tectra) spectrometer. UV spectra were recorded on Kontron Uvikon 940 spectrophotometer. IR spectra were measured on a Perkin-Elmer 2000 apparatus. Fluorescence spectra were obtained with a Spex (USA) Fluoromax spectrofluorimeter. The fluorescence quantum yield for 3a,7a-dihydro-(Z)-3a,7a-dimethoxyisatin has been calculated as 52% (±5) in reference to quinine (ϕ=0.55). 1H and 13C-NMR and NOE spectra were measured with Varian UNITYplus 500 MHz spectrometer.

3a,7a-dihydro-(Z)-3a,7a-dimethoxyisatin: The anolyte consisted of methanol (25 ml), acetic acid (2 ml), anh. sodium acetate (2 g), and isatin (450 mg, 3 mmol). The catholyte was of the same composition except isatin. The electrolysis was performed for 5 hours at a constant current density (0.02A/cm²). Following the electrolysis, the anolyte was evaporated to dryness and mixed into 30 ml of water. The mixture was extracted with ethyl acetate (3 x 40 ml). The extracts were adsorbed on a silica gel and deposited onto a silica gel column (3.5 x 25 cm). The column was eluted with chloroform, and the eluent fractions containing fluorescent product were evaporated to dryness and crystallized from ethyl acetate/petroleum ether to give white prisms (220 mg, 35%). M.p. 54.5 °C. TLC (CHCl3): Rf=0.8. MS: m/z (%) = 209 (56), 177 (69), 146 (100). IR (KBr): 1306, 1322, 1433, 1459, 1538, 1597, 1691, 1741, 3300 cm⁻¹.

Analysis for C10H11NO4 (209.20)
Calc C 57.41 H 5.30 N 6.70%
Found C 57.36 H 5.35 N 6.64%

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