DIMERIZATION OF 2-HYDROXYBENZINDOLEQUINONES

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It is shown that the decarboxylation of 2-hydroxybenz[f]indolequinone-3-carboxylic acids and the demethylation of 2-methoxybenz[f]indolequinone are accompanied by oxidative dimerization and lead to the 3,3'-dimers of 2-hydroxybenz[f]indolequinones.

According to [1], ethyl N-methyl-2-hydroxybenz[f]indolequinone-3-carboxylate (I) is converted to 2-hydroxybenzindolequinone (II) (2-hydroxy-1-methylbenz[f]indole-4,9-dione) when it is heated in sodium hydroxide solution. By way of analogy, the same structure was assigned to the products of hydrolysis and decarboxylation in acetic acid of N-unsubstituted, N-alkyl, and aryl analogs of I [2]. In a more detailed study we established that the compounds formed actually have dimeric structures. Evidence for this was provided by the mass-spectrometric determination of the molecular mass of the product (III) and of the products of its reductive acetylation (IV) and methylation (V, VI). Two potential differences, each of which corresponds to the molecular mass of N-methyl-2-hydroxybenzindolequinone, are observed during the potentiometric titration of dimer III with alkali. The PMR spectra of hexaacetate IV and methyl derivatives V and VI do not contain signals of β-pyrrole protons, which indicates fusion of the 2-hydroxybenzindolequinone residues at the 3,3' positions. Dimer III is regenerated by alkaline hydrolysis of hexaacetate IV in the presence of air oxygen and in the hydrolysis of methylated compounds V and VI in a mixture of hydrobromic and acetic acids.

The dimeric products are more deeply colored than the starting esters. Thus the absorption maximum in the visible region of the spectrum of dimer III is shifted bathochromically 128 nm as compared with the maximum in the spectrum of ester I. The reason for this difference becomes understandable when the structures and properties of the isomeric methyl derivatives obtained by treatment of dimer III with dimethyl sulfate in diglyme in the presence of ethyldiisopropylamine are analyzed. With respect to its electronic spectrum, one of the isomers (V), which was isolated in 53% yield, is similar to ester I and its O-methyl derivative (VII) (Fig. 1), and its IR spectrum contains bands of vibrations only of quinone carbonyl groups at 1665 cm^{-1}; its PMR spectrum contains signals of methyl groups of two types, and this provides a basis for the assignment of the symmetrical 3,3'-bis(2-methoxy-1-methylbenz[f]indole-4,9-dione) formula to it. The electronic spectrum of the second isomer (VI), which was isolated in lower yield (10%), is similar to the spectrum of dimer III (Fig. 2), and its IR spectrum contains the band of a lactam CO group at 1715 cm^{-1} in addition to bands of quinone carbonyl groups at 1660 cm^{-1}; its PMR spectrum contains signals of methyl groups of at least three types. These data indicate an unsymmetrical structure resembling the electronic structure of dimer III. Since the ability to undergo conversion to dimer III during acid hydrolysis excludes the probability of C-methylation, the only possible unsymmetrical structure common to dimer III and its O,O'-dimethyl derivative VI is a structure in which a 9-hydroxy- or 9-methoxybenz[f]indole-2,4-dione residue is joined to a 2-hydroxy- or 2-methoxybenz[f]indole-4,9-dione residue, respectively, in the 3,3' positions (see the scheme below). The factor that stabilizes the unsymmetrical tautomeric structure of the dimers is evidently the formation of an intramolecular hydrogen bond between the hydroxy group of one ring and the lactam CO group of the other. The existence of an intramolecular hydrogen bond explains the absence of the band of a lactam CO group at 1710-1715 cm^{-1} as a consequence of its shift to the lower-frequency region and superimposition on the band of the quinone CO groups. It should be noted that intramolecular hydrogen bonding with the participation of the oxygen atom of the carbethoxy group is responsible for the existence of ester I in the hydroxy form, as evidenced by the above-noted similarity in the electronic spectra of ester I and O-methyl derivatives V and VII, as well as the shift of the band of the carbonyl absorption of the ester group in ester I to 1686 cm^{-1} (this band is found at 1735 cm^{-1} in the spectrum of methoxy derivative VII).

One must ascribe the presence of a quinone grouping and a 2-hydroxy group to the structural peculiarities responsible for the dimerization, since neither 2-hydroxyindole-3-carboxylic acid [3] nor 2-methoxy-1-

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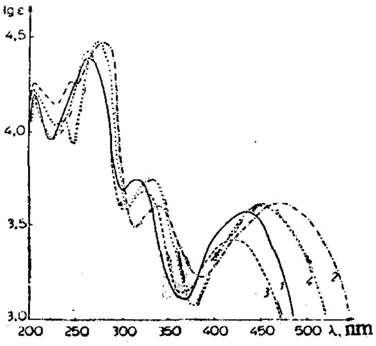


Fig. 1

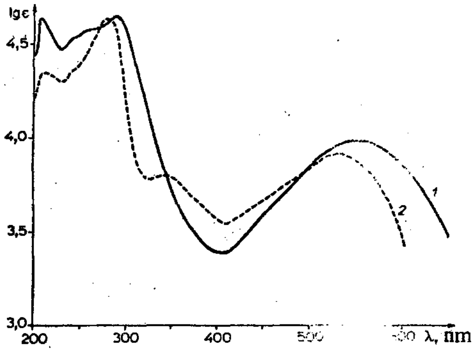


Fig. 2

Fig. 1. Electronic spectra in ethanol: 1) 3-carbethoxy-2-hydroxy-1-methylbenz[f]indole-4,9-dione (I); 2) 3,3'-bis(2-methoxy-1-methylbenz[f]indole-4,9-dione) (V); 3) 3-carbethoxy-2-methoxy-1-methylbenz[f]indole-4,9-dione (VII); 4) 2-methoxy-1-methylbenz[f]indole-4,9-dione (IX) (in the case of IV, log ε/2 values are plotted along the axis of ordinates).

Fig. 2. Electronic spectra in ethanol: 1) 3,3'-bis(2-hydroxy-1-methylbenz[f]indole-4,9-dione) (III); 2) 3-(9-methoxy-1-methyl-2,4-dihydrobenz[f]indole]2,4-dion-3-yl)-2-methoxy-1-methylbenz[f]indole-4,9-dione (VI).

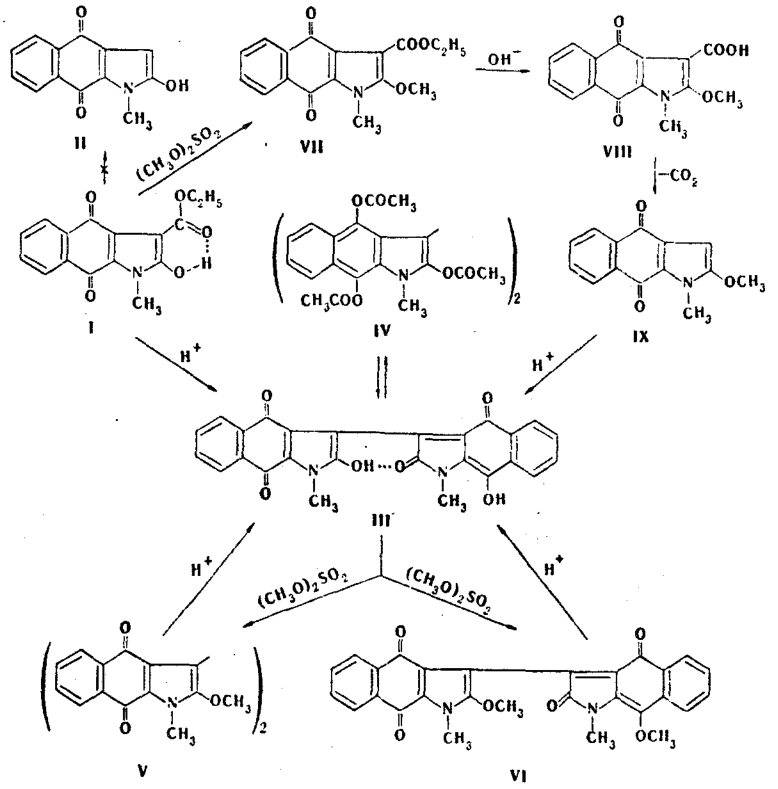
TABLE 1. 3,3'-Bis(2-hydroxy-1-R-benz[f]indole-4,9-diones)*

R	mp, °C (solvent)	IR spectrum, cm^{-1}			Found, %			Empirical formula (molecular mass)	Calc., %			Yield, %
		quinone ν_{CO}	lactam ν_{CO}	ν_{OH}	C	H	N		C	H	N	
H†	>360 (DMF)	1640	1710	3270	67,9	2,9	6,9	$C_{24}H_{12}N_2O_6$ (424,36)	68,0	2,9	6,6	97
i-C_3H_7	257 (CH$_3$COOH)	1635	1700	3220	70,3	5,0	5,5	$C_{30}H_{24}N_2O_6$ (508,52)	70,8	4,8	5,5	90
n-$C_{11}H_{25}$	193 (CH$_3$COOH)	1663	1720	3200	75,6	8,1	4,0	$C_{48}H_{60}N_2O_6$ (760,98)	75,9	7,9	3,7	84
C_6H_5	293 (CHCl$_3$)	1650	1700	3200	74,5	3,5	4,6	$C_{36}H_{20}N_2O_6$ (576,54)	75,0	3,5	4,9	80

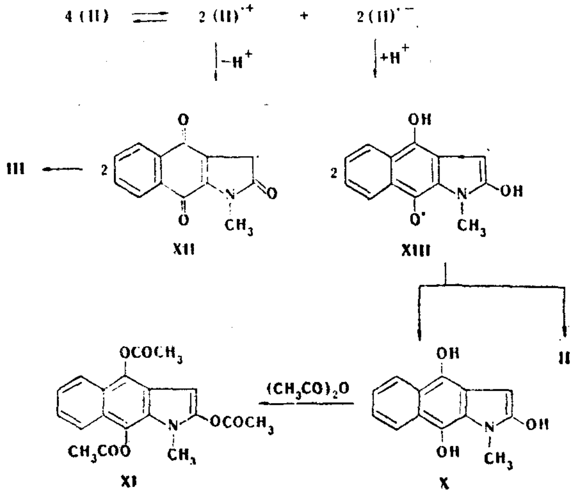
*Also see [2].

† Found: M$^+$ 424.

methylbenz[f]indolequinone-3-carboxylic acid (VIII), obtained from ester VII by alkaline hydrolysis, undergoes dimerization during decarboxylation. When acid VIII is refluxed in quinoline in the presence of copper acetate, it is converted to monomeric 2-methoxybenzindolequinone (IX), the electronic spectrum of which is similar to the spectra of O-methyl derivatives V and VII (Fig. 1); the PMR spectrum of IX contains the signal of a β-pyrrole proton at 6.02 ppm. However, during an attempt to convert 2-methoxybenzindolequinone IX to 2-hydroxy derivative II by cleavage of the methoxy group by heating with hydrobromic acid we found that dimer III is formed even in the absence of air. Thus the observed oxidative dimerization is not directly associated with the decarboxylation reaction but rather is peculiar to 2-hydroxybenzindolequinone II and other N-substituted compounds, regardless of the method of preparation. Since dimerization does not require an external oxidizing agent, a portion of the 2-hydroxybenzindolequinone or the resulting dimer should act in this capacity. In order to ascertain which of these variants is actually realized, we carried out the reaction by heating ester I in acetic acid without access to air and, after separation of dimer III (65%), treated the filtrate with acetic anhydride with pyridine and isolated 2,4,9-triacetoxy-1-methylbenz[f]indole (XI) (20%). A portion of 2-hydroxybenzindolequinone II, which is reduced to hydroquinone X, consequently acts as the oxidizing agent. The first step in the reaction is evidently transfer of an electron from one molecule of the hydroxybenzindolequinone to another with the development of cation and anion radicals, which subsequently undergo, respectively, deprotonation and protonation to give neutral radicals (XII), which recombine to give dimer III, and semiquinones (for example, XIII), which undergo disproportionation to quinone II and hydroquinone X.



This sequence of steps should lead to two-thirds conversion of hydroxybenzindolequinone to the dimer and one-third conversion to hydroquinone X; this is in agreement with the experimental data. The absence of dimerization in the case of 2-methoxy derivative IX is evidently explained by the impossibility of deprotonation of the cation radical during electron transfer because of the absence of an acidic hydrogen atom.



EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The electronic spectra were recorded with a Specord UV-vis spectrophotometer. The mass spectra were recorded with a Varian CH-6 spectrometer at an ionizing voltage of 70 eV. The PMR spectra of the compounds were recorded with Tesla BS-467 and Jeol C-60 spectrometers (60 MHz) with tetramethylsilane as the internal standard.

3,3'-Bis(2-hydroxy-1-methylbenz[f]indole-4,9-dione) (III). A) A mixture of 29.7 g (0.1 mole) of ester I and 250 ml of glacial acetic acid was refluxed for 3 h, after which it was cooled, and the precipitated dimer III was removed by filtration. The product was washed thoroughly with methanol and hexane and dried to give 18.5 g (82%) of fine violet crystals, which did not melt when they were heated to 360°C. IR spectrum: 1650 (quinone CO), 1708 (lactam CO, shoulder), and 3200 cm^{-1} (OH, broad band). Found: C 68.9; H 3.5; N 6.2%; M^+ 452. $C_{26}H_{16}N_2O_6$. Calculated: C 69.0; H 3.6; N 6.2%; M 452.4. A compound with an identical IR spectrum was obtained by hydrolysis and decarboxylation of ester I in alkaline media by the method in [1].

Analogs of dimer III, the properties of which are presented in Table 1, were obtained in the same way.

B) A mixture of 29.7 g (0.1 mole) of ester I and 250 ml of glacial acetic acid, which had been previously refluxed thoroughly and cooled in a stream of nitrogen, was refluxed for 3 h in a stream of nitrogen, after which it was cooled to 15°C. The precipitated dimer III [15 g (65%)] was rapidly removed by filtration, 3 g of zinc dust was added to the filtrate to prevent oxidation, and the mixture was heated to the boiling point and treated with 20 ml of acetic anhydride and 10 ml of pyridine and refluxed for 20 min. It was then cooled and poured into 300 ml of water, and the precipitated 2,4,9-triacetoxy-1-methylbenz[f]indole (XI) was removed by filtration, washed with methanol, and recrystallized from chloroform to give 7.1 g (20%) of colorless acicular crystals with mp 220-222°C (dec.). IR spectrum: 1732 and 1767 cm^{-1} (CO). Mass spectrum: m/e 313 ($M^+ - CH_2CO$). PMR spectrum (in $CDCl_3$): 2.42 (3H, s, CH_3CO), 2.48 (3H, s, CH_3CO), 3.40 (3H, s, CH_3CO or CH_3N), 3.50 (3H, s, CH_3N or CH_3CO), and 7.60 ppm (5H, m, 3-H, 5-H, 6-H, 7-H, and 8-H). Found: C 64.6; H 5.0; N 4.2%. $C_{19}H_{17}NO_6$. Calculated: C 64.3; H 4.8; N 4.0%.

C) A mixture of 0.05 g of methoxy derivative IX, 1 ml of glacial acetic acid, and 1 ml of freshly distilled (over stannous chloride) 48% hydrobromic acid was placed in an ampul, and the ampul was evacuated to a residual pressure of 10^{-7} mm (mercury column) and sealed. It was then heated at 110°C for 3 h, during which precipitation of violet dimer III was observed. The ampul was then cooled and opened, and the precipitate was removed by filtration [the yield was 0.028 g (60%)]. Another ~0.01 g of quinone III precipitated from the filtrate when it was allowed to stand in the air. According to its IR spectrum, the product was identical to the samples obtained in methods A and B.

3,3'-Bis(2-methoxy-1-methylbenz[f]indole-4,9-dione) (V) and 3-(9-Methoxy-2,4-dihydrobenz[f]indole-2,4-dion-3-yl)-2-methoxy-1-methylbenz[f]indole-4,9-dione (VI). A mixture of 5 g (11.7 mmole) of quinone III, 8.9 g (70.5 mmole) of dimethyl sulfate, 9.1 g of ethyldiisopropylamine, and 100 ml of absolute diglyme was stirred at 120-130°C for 4 h, after which it was cooled to 10°C, and the precipitated methoxy derivative V was separated. The solution was poured into 500 ml of water, and the resulting precipitate was removed by filtration, dried, and chromatographed on aluminum oxide; elution with chloroform gave, successively, methoxy derivatives V and VI.

Compound V [2.82 g (53%)] was obtained as orange acicular crystals with mp 331°C (from methanol). IR spectrum: 1665 cm^{-1} (quinone CO). PMR spectrum (in $CDCl_3$): 3.88 (3H, s, OCH_3), 4.00 (3H, s, NCH_3), and 7.35 ppm (4H, m, 5-H, 6-H, 7-H, and 8-H). Found: C 69.9; H 4.1; N 5.8%; M^+ 480. $C_{28}H_{20}N_2O_6$. Calculated: C 70.0; H 4.2; N 5.8%; M 480.4.

Compound VI [0.55 g (10.2%)] was obtained as fine violet crystals with mp 279-280°C (from chloroform–methanol). IR spectrum: 1660 (quinone CO) and 1715 cm^{-1} (lactam CO). PMR spectrum (in $CDCl_3$): 3.60 (3H, s, NCH_3), 3.86 (3H, s, OCH_3), 3.98 (6H, s, OCH_3, NCH_3), and 7.52 ppm (8H, m, aromatic protons). Found: C 69.7; H 4.2; N 5.6%; M^+ 480. $C_{28}H_{20}N_2O_6$. Calculated: C 70.0; H 4.2; N 5.8%; M 480.4.

Compounds V and VI were formed in approximately the same yields in the case of methylation under the same conditions of the corresponding N-unsubstituted dimer (see above) with doubled amounts of dimethyl sulfate and ethyldiisopropylamine.

Starting dimer III was recovered (90-95%) when methoxy derivative V or VI was refluxed with a mixture of hydrobromic and acetic acids (1 : 1 by volume).

3,3'-Bis(2,4,9-triacetoxy-1-methylbenz[f]indole) (IV). A mixture of 1 g (2.2 mmole) of quinone III and 25 ml of acetic acid was heated to the boiling point, 3 g of zinc dust was added in portions in the course of 40 min, and the mixture was refluxed for 20 min. Acetic anhydride (10 ml) and 10 ml of pyridine were added, and the mixture was refluxed for 30 min. It was then cooled and diluted with water, and the precipitate was recrystallized from acetic acid to give 0.91 g (58.7%) of fine colorless crystals with mp 285°C (decomp.). IR spectrum: 1732 and 1775 cm^{-1} (CO). PMR spectrum (in DMSO, fragment): 3.58 (6H, s, CH_3CO or CH_3N), 3.63 (6H, s, CH_3N or CH_3CO), and 7.71 ppm (8H, m, aromatic protons). Found: C 64.4; H 4.5; N 3.9%; M^+ 708. $C_{38}H_{32}N_2O_{12}$. Calculated: C 64.4; H 4.6; N 4.0%; M 708.

Dimer III, which was identified from its IR spectrum, was formed in quantitative yield when hexaacetate IV was refluxed with a 20% solution of potassium hydroxide for 1 h with simultaneous passage of air into the reaction mixture and the mixture was subsequently acidified.

3-Carbethoxy-2-methoxy-1-methylbenz[f]indole-4,9-dione (VII). A solution of 29.9 g (0.1 mole) of ester I and 12.9 g (0.1 mole) of ethyldiisopropylamine in 250 ml of absolute THF was heated to the boiling point with stirring, 12.6 g (0.1 mole) of dimethyl sulfate was added dropwise, and the mixture was refluxed for 1 h. It was then cooled, evaporated in vacuo to a minimal volume, and treated with 30 ml of methanol. The resulting precipitate was removed by filtration, washed thoroughly with water, methanol, and hexane, and recrystallized from alcohol to give 30.9 g (98.7%) of long orange needles with mp 112-113°C. IR spectrum: 1670 (quinone CO) and 1735 cm^{-1} (ester CO). PMR spectrum (in $CDCl_3$): 1.20 (3H, t, $C-CH_3$), 3.31 (3H, s, NCH_3 or OCH_3), 3.55 (3H, s, OCH_3 or NCH_3), 3.75 (2H, q, OCH_2), and 6.73 ppm (4H, m, 5-H, 6-H, 7-H, 8-H). Found: C 65.1; H 4.8; N 4.5%. $C_{17}H_{15}NO_5$. Calculated: C 65.2; H 4.8; N 4.5%.

3-Carboxy-3-methoxy-1-methylbenz[f]indole-4,9-dione (VIII). A mixture of 15.7 g (0.05 mole) of VII, 75 ml of alcohol, and 75 ml of a 40% solution of potassium hydroxide was refluxed for 20 min, after which it was cooled, and the precipitated potassium salt of acid VIII was removed by filtration, washed with alcohol, and dissolved in 3 liters of hot water. Hydrochloric acid (25 ml) was added to the filtered hot solution, and the precipitate was removed by filtration, washed thoroughly with water, dried, and recrystallized from alcohol to give 12.3 g (78.5%) of pale-yellow crystals with mp 234-236°C (decomp.). IR spectrum: 1664 (quinone CO), 1735 (carboxyl CO), and 3440 cm^{-1} (OH). Found: C 63.7; H 4.2; N 4.8%. $C_{15}H_{11}NO_5$. Calculated: C 63.7; H 3.9; N 4.9%.

2-Methoxy-1-methylbenz[f]indole-4,9-dione (IX). A mixture of 4.8 g (16.8 mmole) of acid VIII, 0.1 g of cupric acetate, and 25 ml of quinoline was refluxed for 20 min in a nitrogen atmosphere, after which it was cooled and poured into 200 ml of 4 N hydrochloric acid. The resulting precipitate was removed by filtration, dried, and treated with boiling chloroform. The resulting solution of quinone IX in chloroform was filtered to remove dimer III [1.1 g (29%), identified from its IR spectrum], and the filtrate was filtered through a layer of aluminum oxide. The filtrate was then subjected to vacuum evaporation, and the residue was recrystallized from alcohol to give 2.28 g (57%) of orange needles with mp 220-221°C. IR spectrum: 1647 and 1668 cm^{-1} (quinone CO). PMR spectrum (in $CDCl_3$): 3.86 (3H, s, OCH_3), 4.00 (3H, s, NCH_3), 6.02 (1H, s, 3-H), and 7.92 ppm (4H, m, 5-H, 6-H, 7-H, and 8-H). Found: C 69.9; H 4.7; N 5.7%; M^+ 241. $C_{14}H_{11}NO_3$. Calculated: C 69.9; H 4.6; N 5.8%; M 241.

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