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OXIDATION OF THE 2-HYDROXYBENZINDOLEQUINONE DIMER

EXPANSION OF THE QUINONE RING TO AN OXEPINE RING*

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One of the quinone rings of the 3,3' dimer of 2-hydroxybenzindolequinone undergoes expansion to an oxepine ring during oxidation with nitric acid. A benzisatinquinone structure was previously erroneously assigned to this compound. The structure was proved by spectral methods and stepwise degradation to be the monomeric 2-hydroxybenzindolequinone derivative. The possible oxidation pathways are discussed.

We have shown [2] that the 3,3' dimer (III) rather than 2-hydroxybenzindolequinone (II), as assumed in [3], is formed in the decarboxylation of 2-hydroxybenzindolequinone-3-carboxylic acid (I). A benzisatinquinone structure (IV) was assigned in [3] and later in [4] to the product of decarboxylation of I and subsequent oxidation with nitric acid in sulfuric acid. We have established that this substance is actually a dimeric quinone-lactone (V).
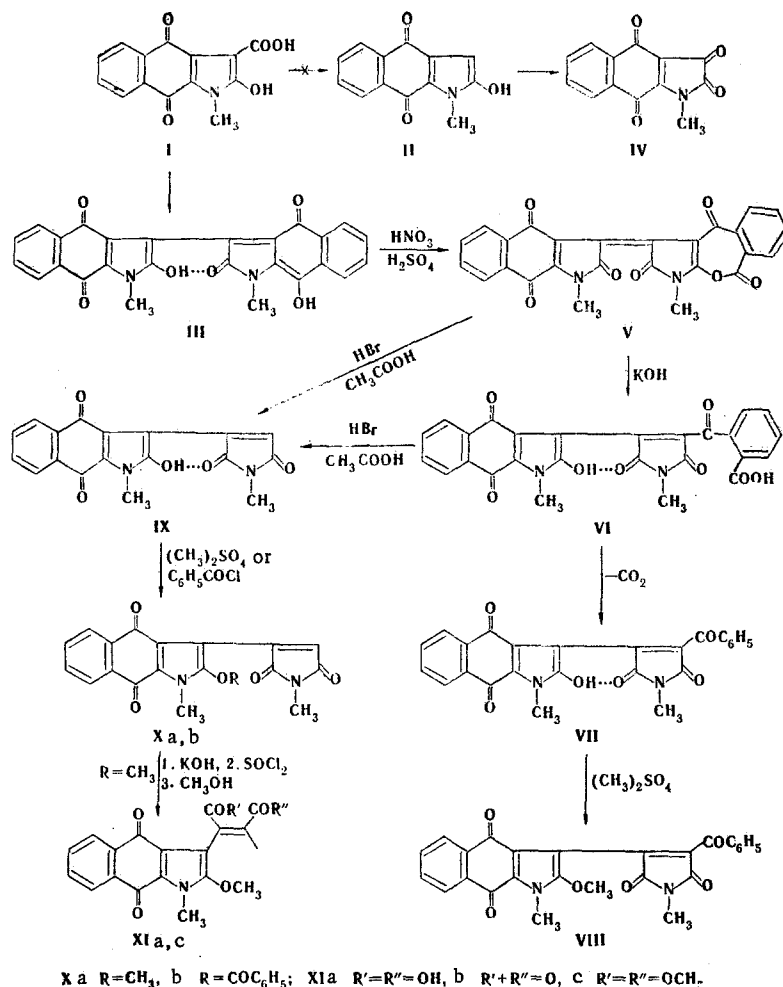
The mass spectrum of lactone V and of the corresponding nitrogen-unsubstituted compound and the results of elementary analysis show that the oxidation proceeds with retention of the dimeric structure as a result of splitting out of two hydrogen atoms from the III molecule and the addition of one oxygen atom.

Under the influence of an aqueous solution of potassium hydroxide lactone V is hydrolyzed to an acid (VI), treatment of which with dehydrating agents (sulfuric acid, acetic anhydride) does not result in the reversible formation of lactone V. Potentiometric titration of acid VI with a solution of tetramethylammonium hydroxide in dimethyl sulfoxide (DMSO) reveals the presence of two acidic groups (pK_a 3.5 and 12.9). When the first acidic group is neutralized, the color of the solution changes from red to blue, and this indicates the presence of an enol grouping conjugated with the quinone carbonyl groups. The formation of blue anions is also observed for other 2-hydroxybenzindolequinone derivatives [4]. The second acidic group is a carboxy group and is eliminated by heating to 200-220°C to give an enol (VII). Its structure is confirmed by its PMR spectrum, which contains signals of two N-methyl groups, and nine aromatic protons and the signal of an enol proton at 8.48 ppm. Methylation of enol VII with dimethyl sulfate gives a methoxy derivative (VIII), the PMR spectrum of which does not contain a signal at 8.48 ppm but does contain a signal of a methoxy group.

Both lactone V and its hydrolysis product (VI) are cleaved to give phthalic acid and an enol (IX) when they are refluxed in a mixture of hydrobromic and acetic acids. The PMR spectra of the methoxy and benzoxy derivatives of the latter (Xa,b) contain signals of four aromatic protons, two N-methyl groups, and a vinyl proton; in addition, the spectrum of Xa contains the signal of the protons of a methoxy group, while the spectrum of Xb contains the signal of the protons of another phenyl ring.

When methoxy derivative Xa is heated with a solution of potassium hydroxide, the N-methylmaleinimide ring is hydrolytically cleaved to give a dicarboxylic acid (XIa), the carboxy groups in which are evidently cis-oriented, since it is converted to an anhydride (XIb) during crystallization. The structure of acid XIa is confirmed by its mass spectrum, the PMR spectrum of its dimethyl ester (XIc) (signals of a vinyl proton, four methyl groups, and four aromatic protons), and its IR spectrum (ν_{CO} bands of quinone and ester groupings at 1667 and 1733 cm^{-1}). As expected, the electronic spectrum of diester XIc is similar to the spectrum of 2-methoxy-3-carbethoxybenzindolequinone [2] (see Fig. 1).

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*See [1] for our preliminary communication.

X a R=CH₃, b R=COC₆H₅; XIa R'=R''=OH, b R'+R''=O, c R'=R''=OCH₃

It follows from the data presented above that one of the quinone rings undergoes expansion to an oxepine ring in the oxidation of dimer III with nitric acid in sulfuric acid. The inability of acid VI to undergo lactonization (see above) indicates that an inclusion reaction rather than oxidative cleavage of the ring bond with subsequent recyclization occurs in this case. As far as we can judge, this is the first example of the conversion of a cyclic ketone to a lactone under the influence of nitric acid rather than peracids as in the Baeyer—Villiger reaction [5].

By oxidation of dimer III with nitric acid in acetic acid we were able to isolate an unstable colorless compound (XII), which is dehydrated to lactone V by the action of acids or by heating. The absence of absorption in the visible region of the spectrum, which distinguishes XII from benzindolequinone derivatives [2] (Fig. 1), indicates disruption of the conjugation of both nitrogen atoms with the quinone groupings and compels us to assign the 9a,9'a-diol structure XII to the compound. The IR spectrum of diol XII contains an intense band of vibrations of an OH group.

One may imagine that the conversion of diol XII to oxepine V begins with detachment of a hydroxide anion under the influence of the acid with the generation of a conjugated carbonium ion (XIII), in the delocalization of the positive charge in which the second ring of the benzindolequinone participates. Ring expansion proceeds as a result of a sigmatropic rearrangement in the carbonium ion during intramolecular nucleophilic attack by the hydroxy group on the carbonyl carbon atom (see XIII). The possibility that diol XII, which is converted to lactone V via a similar pathway, is initially formed also in the oxidation of dimer III in sulfuric acid is not excluded.

One could have assumed that the formation of diol XII from dimer III proceeds via oxidation to a diquinone (XIV) with subsequent nucleophilic addition of the elements of water (to give XV) and oxidation. The oxidation of dimer III with lead tetraacetate actually results in the formation of an unstable yellow compound, which upon reduction is converted almost quantitatively to dimer III and is evidently diquinone XIV. However, neither
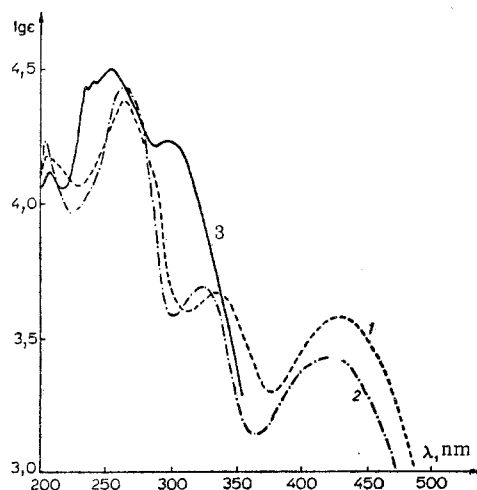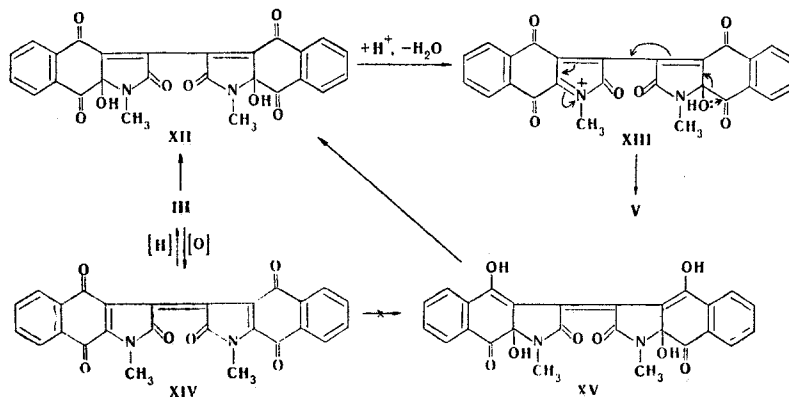
Fig. 1. Electronic spectra: 1) 1-methyl-2-methoxy-3-(cis-1,2-dicarbomethoxyvinyl)benz[f]indole-4,9-dione (XIc) in ethanol; 2) 1-methyl-2-methoxy-3-carbethoxy-benz[f]indole-4,9-dione in ethanol; 3) 3,3'-bis(1-methyl-9a-hydroxy-2,4,9-9a-tetrahydrobenz[f]indolyl) (XII) in acetonitrile.

diol XII nor lactone V is formed by the action of nitric acid on a solution of this compound in acetic acid, and diquinone XIV consequently is not an intermediate in the conversion of dimer III to diol XII.

The oxidation of dimer III with nitric acid in acetic acid occurs only when traces of nitrous acid are present. The addition of urea completely inhibits the reaction. According to [6], the oxidation of enolized ketones with nitric acid includes a step involving attack by the nitrosonium cation at the double bond of the enol and leads to α-hydroxy ketones. It is likely that in the case of dimer III the reaction evolves as a result of attack by the nitrosonium cation in the 9a position at the double bond of the ring that has a fixed enol grouping [2].

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The electronic spectra were recorded with a Specord UV-vis spectrophotometer. The mass spectra were obtained with a Varian CH-6 spectrometer at an ionizing voltage of 70 eV. The PMR spectra were obtained with Tesla BS-467 and Jeol C-60 spectrometers with tetramethylsilane as the internal standard. The pK_a values of acid VI were determined by potentiometric titration by the method in [7].

3-(1-Methyl-2,4,9-trioxo-2,3,4,9-tetrahydrobenz[f]indolid-3-ene)-1-methyl-2,4,9-trioxo-2,3,4,9-tetrahydrobenz[e]pyrrolo[2,3-b]oxepine (V). A 38-g (84 mmole) sample of dimer III was dissolved with stirring in 400 ml of 96% sulfuric acid, after which 16 g (0.165 mole) of 65% nitric acid was added dropwise in the course of an hour at no higher than 5°C. The reaction mixture was then poured into 4 liters of water, and the precipitated lactone V was removed by filtration, washed with water until the wash waters had pH 7, dried in vacuo at room temperature, and dissolved in chloroform. The chloroform solution was filtered through a layer of silica gel, the filtrate was concentrated to a small volume, and the concentrate was diluted with ethyl acetate. Work-up gave 35.3 g (90%) of a product with mp 272-274°C (dec.). IR spectrum: 1680 (quinone CO), 1725 (lactam CO), and 1788 cm^{-1} (lactone CO). PMR spectrum (in CDCl$_3$): 3.20 (3H, s, NCH$_3$), 3.35 (3H, s, NCH$_3$), and 7.95 ppm (8H, m, aromatic protons). Electronic spectrum (in acetonitrile), λ_{max} (log ε): 226 (4.56), 255 (4.43), 310

TABLE 1. 3-(1-R-2,4,9-Trioxo-2,3,4,9-tetrahydrobenz[f]indolid-3-ene)-1-R-2,4,9-trioxo-2,3,4,9-tetrahydrobenzo[e]pyrrolo[2,3-b]oxepines

| R | mp, °C (solvent) | IR Spectrum, ν_{co}, cm^{-1} | | | Found, % | | | Empirical formula | Calc., % | | | Yield, % |
		quinone	lactam	lactone	C	H	N		C	H	N	
H	>360 (dioxane)	1677	1735	1790	65,7	2,2	6,3	$C_{24}H_{10}N_2O_7$*	65,8	2,3	6,4	90
CH(CH$_3$)$_2$	267—269 (chloroform)	1665	1720	1770	69,1	4,1	5,0	$C_{30}H_{22}N_2O_7$	69,0	4,2	5,4	90
n-C$_{12}$H$_{25}$	84—87 (hexane)	1670	1713	1770	74,0	7,3	3,3	$C_{48}H_{58}N_2O_7$	74,4	7,5	3,6	62
C$_6$H$_5$	240 (dec., chloroform)	1681	1732	1783	73,1	2,7	4,4	$C_{36}H_{18}N_2O_7$	73,2	3,1	4,7	60

*Found (by mass spectrometry): M 438. Calculated: M 438.3.

(inflection, 3.99), and 520 nm (3.45). Found: C 66.9; H 3.0; N 6.0%; M$^+$ (by mass spectrometry) 466. $C_{26}H_{14}N_2O_7$. Calculated: C 67.0; H 3.0; N 6.0%; M 466.4.

The properties of the other similarly obtained [4] lactones are presented in Table 1. The lactones are orange (the unsubstituted compound) or crimson-red acicular crystals that fluoresce with red light both in the solid state and in solutions in aprotic solvents when they are irradiated with UV light.

3,3'-Bis(9a-hydroxy-1-methyl-2,4,9-trioxo-2,4,9,9a-tetrahydrobenz[f]indolyl) (XII). A 1.6-g (16.5 mmole) sample of 65% nitric acid was added dropwise with stirring to a suspension of 3.8 g (8.4 mmole) of dimer III in 25 ml of glacial acetic acid. After 30-40 min, violet-black dimer III dissolved, and a colorless precipitate of XII formed. The latter was removed by filtration, washed thoroughly with hexane, and dissolved in acetone. The acetone solution was cooled to −78°C, and hexane was added dropwise until crystallization began. Compound XII was separated, washed thoroughly with hexane, and dried in vacuo at room temperature in the dark to give 2.6 g (64%) of white acicular crystals with a pinkish tint (due to the presence of traces of lactone V). When this product was heated to 60-70°C it was converted quantitatively to lactone V. See Fig. 1 for the electronic spectrum of XII. IR spectrum: 1713 (CO), 1730 (CO), 3140 cm^{-1} (OH, broad band). Found: C 64.2; H 3.6; N 5.5%. $C_{26}H_{16}N_2O_8$. Calculated: C 64.4; H 3.3; N 5.8%. When 0.1 g of urea was added to a suspension of dimer III prior to the addition of nitric acid, dimer III remained unchanged after 2 h.

Oxidation of Dimer III with Lead Tetraacetate. A 1.11-g (2.5 mmole) sample of lead tetraacetate was added to a suspension of 0.5 g (1.1 mmole) of dimer III in 10 ml of glacial acetic acid, and the mixture was shaken for 6 h. The black-violet dimer III dissolved to give a yellow solution. The formation of diol XII or lactone V was not observed when 3.5 ml (5.0 mmole) of 65% nitric acid was added to the solution and the precipitated lead nitrate was separated after the mixture had stood for 5 h. Zinc dust (3 g) was added to the solution after oxidation with lead tetraacetate, and the mixture was stirred at 20°C for 1 h. It was then poured into water, and the violet precipitate of dimer III was removed by filtration. The yield was 0.46 g (92%). The product was identified from its IR spectrum.

Conversion of XII to Lactone V. A) A mixture of 5 g (10.3 mmole) of XII with 100 ml of absolute toluene was refluxed with simultaneous azeotropic distillation and protection of the distillate from air moisture. Titration of the distillate (~25 ml) with the Fischer reagent established the presence of 0.15 g (80.7%) of water. The precipitated lactone V was removed by filtration and recrystallized to give 4.5 g (93%) of product.

B) Boron trifluoride etherate (2 ml) was added to a suspension of 1 g (2.06 mmole) of XII in 10 ml of glacial acetic acid, and the mixture was heated at 45-50°C for 30 min. It was then poured into water, and the precipitated lactone V was removed and recrystallized. The yield was 0.8 g (83%).

C) A 1-g (2.06 mmole) sample of XII was dissolved in 10 ml of 96% sulfuric acid at 0°C, and the solution was stirred for 5 min. It was then poured into 100 ml of water, and the precipitated lactone V was removed by filtration. The yield was 0.96 g (99%). Lactone V was identified in experiments A-C from the IR spectra of the products.

3-[1-Methyl-4-(2-carboxybenzoyl)-2,5-dioxo-Δ^3-pyrrolin-3-yl]-1-methyl-2-hydroxybenz[f]indole-4,9-dione (VI). A 6.1-g (12.6 mmole) sample of lactone V was added with stirring to a solution of 4 g of potassium hydroxide in 250 ml of water, and the blue solution was filtered. The filtrate was acidified to pH 1 with hydrochloric acid, and the precipitated VI was removed by filtration, washed with methanol, dried, and chromatographed on silica gel [elution with chloroform−acetate−acetic acid (10:10:1)]. The eluate was evaporated to dryness, and the residue was crystallized from a mixture of tetrahydrofuran (THF) and methanol to give 2.28 g (36%) of red crystals of VI with mp 232°C [the product solidified at 235°C and was converted to VII (see below)]. IR spectrum: 1660 (quinone CO), 1690, 1727, 1730, 1785, 1802 (CO), and 3450 cm^{-1} (OH, broad band). Found: C 64.8; H 3.6; N 5.6%. $C_{26}H_{16}N_2O_8$. Calculated: C 64.4; H 3.3; N 5.8%.

3-(1-Methyl-4-benzoyl-2,5-dioxo-Δ^3-pyrrolin-3-yl)-1-methyl-2-hydroxybenz[f]indole-4,9-dione (VII). A 2-g (4.13 mmole) sample of VI was heated at 240-250°C for 10-15 min, after which the reaction product was dissolved in chloroform and chromatographed on silica gel [elution with chloroform−ethyl acetate (3:1)] to give 1.4 g (77%) of enol VII. The product was obtained as red needles (from chloroform−ethyl acetate) and was soluble in aqueous solutions of bases; acidification of the resulting blue solutions regenerated VII. The product did not fluoresce either in the solid state or in solution and had mp 306-308°C. IR spectrum (in CDCl$_3$): 2.76 (3H, s, NCH$_3$), 3.93 (3H, s, NCH$_3$), 7.95 (9H, m, aromatic protons), and 8.48 ppm (1H, s, OH). Found: C 68.1; H 3.5; N 6.5%; M$^+$ (by mass spectroscopy) 440. $C_{25}H_{16}N_2O_6$. Calculated: C 68.2; H 3.6; N 6.4%; M 440.4.

3-(1-Methyl-4-benzoyl-2,5-dioxo-Δ^3-pyrrolin-3-yl)-1-methyl-2-methoxybenz[f]indole-4,9-dione (VIII). A 1-g (2.27 mmole) sample of VII was dissolved in 30 ml of absolute THF, 1.30 g (10 mmole) of dimethyl sulfate and 1.29 g (10 mmole) of ethyldiisopropylamine were added, and the mixture was refluxed for 2 h. It was then cooled and poured into 100 ml of 1 N NCl, and the precipitate was removed by filtration and recrystallized from chloroform−acetone to give 0.82 g (79.5%) of small yellow plates with mp 318-319°C. IR spectrum: 1670 (quinone CO), 1728, and 1795 cm^{-1} (CO). PMR spectrum (in CDCl$_3$): 2.71 (3H, s, NCH$_3$), 3.93 (3H, s, NCH$_3$), 4.05 (3H, s, OCH$_3$), and 8.00 ppm (9H, m, aromatic protons). Found: C 68.1; H 4.0; N 5.8%; M$^+$ (by mass spectroscopy) 454. $C_{26}H_{18}N_2O_6$. Calculated: C 68.5; H 4.0; N 6.2%; M 454.4.

3-(1-Methyl-2,5-dioxo-Δ^3-pyrrolin-3-yl)-1-methyl-2-hydroxybenz[f]indole-4,9-dione (IX). A) A mixture of 9.32 g (20 mmole) of lactone V, 50 ml of acetic acid, and 50 ml of 48% hydrobromic acid was refluxed for 8 h, after which the precipitated IX was removed by filtration, washed successively with methanol and hexane, and dried to give red-brown crystals that were only slightly soluble in organic solvents. The yield of product with mp 252-255°C (from THF, with decomposition) was 4.7 g (70%). IR spectrum: 1650 (quinone CO), 1682, 1751 (CO), and 3400 cm^{-1} (OH, broad band). Found: C 64.7; H 3.8; N 8.0%; M$^+$ (by mass spectroscopy) 336. $C_{18}H_{12}N_2O_5$. Calculated: C 64.3; H 3.6; N 8.3%; M 336.3. The filtrate after separation of IX was evaporated to a small volume, and the resulting precipitate was removed by filtration, dried, and sublimed at 140-150°C to give 1.1 g (40%) of phthalic anhydride, which was identified from its melting point and IR spectrum.

B) A mixture of 0.48 g (1 mmole) of VI, 2 ml of acetic acid, and 2 ml of 48% hydrobromic acid was refluxed for 2 h, and the precipitated IX was removed by filtration, washed with methanol, and dried to give 0.25 g (74%) of a product that was identical to the product obtained in experiment A according to its IR spectrum.

3-(1-Methyl-2,5-dioxo-Δ^3-pyrrolin-3-yl)-1-methyl-2-methoxybenz[f]indole-4,9-dione (Xa). The methylation of IX was carried out as in the case of VI, and the yield of methoxy derivative Xa was 97.5%. The yellow lamellar crystals had mp 246-249°C (chloroform−methanol). IR spectrum: 1655 (quinone CO), 1715, and 1780 cm^{-1} (CO). PMR spectrum (in CDCl$_3$): 3.10 (3H, s, NCH$_3$), 3.94 (6H, broad s, NCH$_3$ and OCH$_3$), 6.75 (1H, s, =CH−CO), and 7.88 ppm (4H, m, 5, 6, 7, 8-H). Found: C 64.7; H 4.0; N 7.8%; M$^+$ (by mass spectroscopy) 350. $C_{19}H_{14}N_2O_5$. Calculated: C 65.0; H 4.0; N 8.0%; M 350.3. A dibromo derivative with mp 156-158°C (from chloroform−methanol) was obtained by the action of bromine on a solution of Xa in chloroform. Found: Br 30.0%. $C_{19}H_{14}Br_2N_2O_5$. Calculated: Br 31.4%.

3-(1-Methyl-2,5-dioxo-Δ^3-pyrrolin-3-yl)-1-methyl-2-benzoxybenz[f]indole-4,9-dione (Xb). A 0.2 g sample of benzoyl chloride and 0.2 ml of pyridine were added to a suspension of 0.34 g (1 mmole) of IX in 10 ml of absolute THF, and the mixture was stirred for 1-2 min. It was then poured into 50 ml of 2 N hydrochloric acid, and the resulting precipitate was removed by filtration and recrystallized from alcohol to give 0.42 g (92.5%) of pale-yellow needles with mp 189-190°C. IR spectrum: 1671 (quinone CO), 1720 (lactam CO), and 1773 cm^{-1} (ester CO). PMR spectrum (in CDCl$_3$): 2.97 (3H, s, NCH$_3$), 3.97 (3H, s, NCH$_3$), 6.97 (1H, s, =CH−CO), 7.67 (5H, m, COC$_6$H$_5$), and 8.13 ppm (4H, m, 5, 6, 7, 8-H). Found: C 68.0; H 3.8; N 6.2%; M$^+$ (by mass spectroscopy) 440. $C_{26}H_{16}N_2O_6$. Calculated: C 68.2; H 3.6; N 6.4%; M 440.4.

1-Methyl-3-(cis-1,2-dicarboxyvinyl)-2-methoxybenz[f]indole-4,9-dione (XIa) and Its Anhydride (XIb). A mixture of 7.0 g (20 mmole) of Xa and 100 ml of a 10% solution of potassium hydroxide was heated until all

of the solid had dissolved (20–30 min), after which the solution was cooled and acidified with hydrochloric acid, and the precipitated acid XIa was removed by filtration and dried. Recrystallization from acetic acid converted the product to anhydride XIb [5.6 g (83%)]. The yellow crystals had mp 219–221°C (dec.). IR spectrum: 1650, 1668 (quinone CO); 1718, 1785, and 1850 cm^{-1} (anhydride CO). PMR spectrum (in CF_3COOH): 3.98 (3H, s, NCH_3), 4.08 (3H, s, OCH_3), 7.25 (1H, s, $=CH-CO$), and 7.88 ppm (4H, m, 5, 6, 7, 8-H). Found: C 64.4; H 3.3; N 3.8%; M^+ (by mass spectroscopy) 337. $C_{18}H_{11}NO_6$. Calculated: C 64.1; H 3.3; N 4.2%; M 337.3.

1-Methyl-3-(cis-1,2-dicarbomethoxyvinyl)-2-methoxybenz[f]indole-4,9-dione (XIc). A mixture of 5 g (14.8 mmole) of XIb, 25 ml of thionyl chloride, and 0.2 ml of dimethylformamide (DMF) was refluxed for 2 h, after which it was evaporated to dryness in vacuo. Absolute methanol (20 ml) was added with cooling to the residue, and the mixture was refluxed for 1 h. It was then cooled, and the precipitated diester XIc was recrystallized from chloroform–methanol to give 5.2 g (91.5%) of pale-yellow needles with mp 161–162°C. IR spectrum: 1667 (quinone CO) and 1733 cm^{-1} (ester CO). PMR spectrum (in CF_3COOH): 4.00 (3H, s, NCH_3), 4.03 (3H, s, OCH_3), 4.07 (6H, broad s, $2OCH_3$), 6.88 (1H, s, $=CH-CO$), and 7.95 ppm (4H, m, 5, 6, 7, 8-H). Found: C 62.9; H 4.3; N 3.9%; M^+ (by mass spectrometry) 383. $C_{20}H_{15}NO_7$. Calculated: C 62.7; H 4.4; N 3.7%; M 383.3.

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REACTIONS OF 4-METHYL(CHLORO)SULFONYL-2,3,5,6-TETRABROMOPYRIDINES WITH NUCLEOPHILIC REAGENTS

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UDC 547.822.1.5.6'828

The $MeSO_2$ group is replaced in the reaction of 4-methylsulfonyltetrabromopyridine with small nucleophiles, whereas the Br atom in the 2 position is replaced in the reaction with bulky nucleophiles. Depending on the temperature conditions and the ratio of the reacting substances, 4-chlorosulfonyltetrabromopyridine reacts with primary amines to give either the corresponding amides or amines. It was established that the corresponding amines are formed when tetrabromopyridinesulfonic acid ω-hydroxyalkylamides are heated with triethylamine.

According to kinetic data, in nucleophilic substitution reactions the methylsulfonyl groups in nitrogen heterocycles are substituted considerably more rapidly than the halogen atoms [1], and hetaryl methyl sulfones are therefore valuable intermediates for all sorts of chemical transformations.

From this point of view it seemed of interest to study the reactions of 4-methylsulfonyl-2,3,5,6-tetrabromopyridine (I) with some nucleophilic reagents.

The presence of the strong electron-acceptor CH_3SO_2 group in I should activate the adjacent bromine atoms, and attack on the carbon atoms in the 2, 3, and 4 positions in sulfone I is therefore theoretically possible, depending on the nature of the nucleophile.

It was established that the CH_3SO_2 group is replaced exclusively in all cases when sulfone is heated even with excess ammonia, methylamine, sodium hydroxide, and sodium methoxide, and 4-amino, 4-methylamino, 4-hydroxy-, and 4-methoxy-2,3,5,6-tetrabromopyridine (IIa-d), respectively, are formed.