6-HYDROXYINDOLE DERIVATIVES FROM BENZOQUINONIMINES

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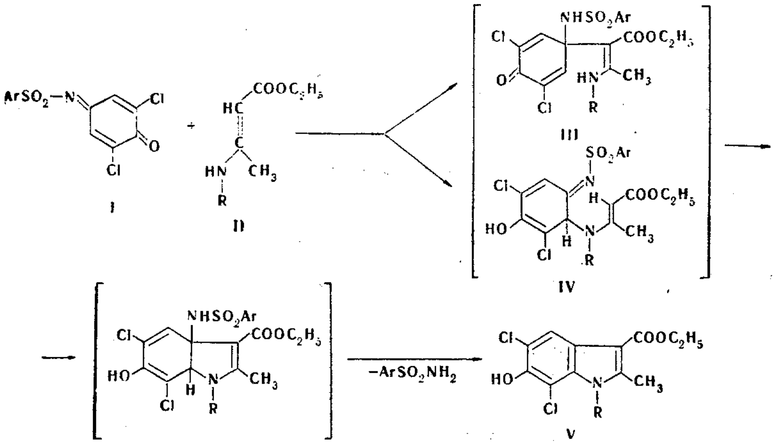
The reaction of N-arylsulfonyl-2,6-dichloro-1,4-benzoquinonimines with 3-alkylaminocrotonates proceeds with displacement of the arylsulfonyl group and formation of a substituted 6-hydroxyindole.

The reaction of quinones with aminocrotonate esters (the Nenitzescu indole synthesis), which usually leads to 5-hydroxyindoles, may give 6-hydroxy isomers if the hydrogen atom is replaced by an aryl group [1, 2]. The change in the orientation of ring formation is apparently associated both with electronic and steric factors.

We have previously shown [3] that N-arylsulfonyl-1,4-benzoquinonimines react with N-alkyl-3-aminocrotonates to give noncyclic addition products; however, depending on the conditions, cyclization leads to benzofuran derivatives, i.e., it proceeds with loss of an alkylamine, or, in the case of N-aryl-3-aminocrotonates, it gives N-arylindole derivatives [4]. In both cases, addition takes place as nucleophilic attack of the β-carbon atom of the enamine component in the β position with respect to the ketimine group of the quinonime (i.e., adjacent to the oxo group).

In the present research we investigated a similar reaction of N-aryl-sulfonyl-2,6-dichloro-1,4-benzoquinonimines (I), in which the α positions relative to the oxo group are occupied by chlorine atoms. We found that this reaction proceeds with displacement of the arylsulfonyl residue and the formation of a substituted 6-hydroxyindole (V). Steric factors hinder attack at the C-2 and C-6 atoms, and the carbon atom of the C=N bond, i.e., the C-4 atom of the quinonimines, apparently therefore reacts with the β-carbon atom of the N-alkyl-3-aminocrotonate (IIa) to give intermediate III.



I a $Ar=C_6H_5$ b $Ar=p\text{-}CH_3C_6H_4$; II V a $R=CH_3$; b $R=C_2H_5$

In view of the effect of the arylsulfonyl grouping and the chlorine atoms, nucleophilic attack at the C-3 atom to give intermediates IV is less likely. Nevertheless, in both cases closing of a five-membered ring and elimination of an arenesulfonamide, which was isolated and identified in a number of experiments, lead to V.

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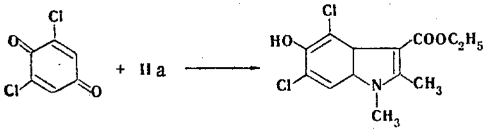
One might also have assumed that the reaction proceeds with the formation of a 5-hydroxyindole (VI) via the usual scheme of the Nenitzescu synthesis rather than via a 6-hydroxyindole. However, VI, obtained by reaction of 2,6-dichloroquinone with aminocrotonate IIa, proved to be identical to Va, which is formed from quinonimine Ia and IIa.



VI

The IR spectra of the synthesized substituted 6-hydroxyindoles V contain absorption bands of stretching vibrations at 3450 (OH), 1700 (C=O), and 1280 (C—O—C) cm^{-1}, and the absorption bands of NH and NO_2 groups of sulfonamides are absent.

A singlet of only one aromatic proton (4-H) at 7.62 ppm is observed in the PMR spectrum of 6-hydroxyindole Va. In the mass spectrum the molecular ion peak with m/e 302 (51.5%) and a peak with m/e 300 (100%), which corresponds to the intensity ratio of the isotopic composition (primarily the chlorine atoms), are the maximum peaks in the mass spectrum. Subsequent fragmentation with splitting out of an ethyl or ethoxy group to give ions with m/e 273 (27.3%) and 271 (48.5%) or 257 (21%) and 255 (36%) is characteristic for esters of heterocyclic acids [5].

EXPERIMENTAL METHOD

The PMR spectra of acetone solutions of the compounds were recorded by V. A. Budylin with an RS-60 spectrometer with hexamethyldisiloxane as the internal standard. The mass spectra were obtained by P. A. Sharbatyan with an MKh-1303 mass spectrometer with a system for introduction of the substances directly into the ionization region at 100°, 20 and 50 eV, and an emission current of 150 μA. The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer with KBr, NaCl, and LiF prisms. Thin-layer chromatography on LS_{250} 5/40 silica gel (elution with chloroform) was used to evaluate the individuality of the compounds obtained; the chromatograms were developed in iodine vapors or with UV light.

1,2-Dimethyl-3-carbethoxy-5,7-dichloro-6-hydroxyindole (Va). A solution of 1.45 g (0.011 mole) of ethyl N-methyl-3-aminocrotonate (IIa) in 10 ml of acetone was added at room temperature with mechanical stirring to a suspension of 3.16 g (0.01 mole) of N-phenylsulfonyl-2,6-dichloro-1,4-benzoquinonimine (Ia) in 50 ml of acetone. The deep blue-green color that developed as the reagents were mixed very rapidly changed to red-violet and then to red. After 10 min, the solution was filtered, and the acetone was evaporated from the filtrate in a stream of air. Methanol (20 ml) was added to the dark red oil, and the resulting precipitate was removed by filtration and washed on the filter with methanol to give 0.9 g (30%) of colorless crystals with mp 137-137.5° (from methanol). The product was very slightly soluble in petroleum ether, slightly soluble in benzene and ether, somewhat more soluble in methanol, and quite soluble in acetone. Found: C 52.0; H 4.6; Cl 23.2; N 4.6%. $C_{13}H_{13}Cl_2NO_3$. Calculated: C 51.7; H 4.3; Cl 23.5; N 4.6%.

1-Ethyl-2-methyl-3-carbethoxy-5,7-dichloro-6-hydroxyindole (Vb). A solution of 3.5 g (0.022 mole) of N-ethyl-3-aminocrotonate (IIb) in 50 ml of acetone was added at room temperature with mechanical stirring to a suspension of 6.32 g (0.02 mole) of quinonimine Ia in 100 ml of acetone. The solution immediately took on a deep blue-green color that rapidly changed to red-violet and then to dark red. A qualitative reaction for the starting quinonimine [6] (indophenol reaction with 1-naphthol in alkaline media) gave a negative result after a few minutes. The acetone was evaporated in a stream of air, the residual oil was treated with a small amount of methanol, and the resulting crystals were removed by filtration and washed on the filter with methanol to give 0.8 g of product. Concentration of the filtrate gave an additional 0.5 g of Vb. The overall yield of pinkish needles (from benzene—petroleum ether), with mp 142°, was 1.3 g (20%). Vacuum sublimation gave colorless crystals with mp 142.5°. The product was very slightly soluble in petroleum ether, more soluble in benzene, and quite soluble in acetone. Found: Cl 22.2; N 4.5%. $C_{14}H_{15}Cl_2NO_3$. Calculated: Cl 22.3; N 4.5%.

1,2-Dimethyl-3-carbethoxy-4,6-dichloro-5-hydroxyindole (VI). A solution of 1.45 g (0.011 mole) of aminocrotonate IIa in 10 ml of acetone was added to 1.77 g (0.01 mole) of 2,6-dichloro-p-quinone in 30 ml of acetone, and the mixture was allowed to stand overnight. The acetone was evaporated, and the residue was treated with methanol to give 0.45 g (15%) of colorless crystals with mp 148-149° (from methanol).

The yields could be raised somewhat by concentration of the filtrate. Found: Cl 23.5; N 4.5%. $C_{13}H_{13}Cl_2NO_3$. Calculated: Cl 23.5; N 4.6%. A melting-point depression was observed for a mixture of this product with hydroxyindole Va. The substances also differed with respect to chromatography on aluminum oxide and their IR spectra.

N-(p-Tolylsulfonyl)-2,6-dichloro-4-aminophenol. A stream of dry hydrogen chloride was passed through a solution of 52 g (0.176 mole) of N-(p-tolylsulfonyl)-2-chloro-1,4-benzoquinonimine [7] in 250 ml of chloroform until the solution became colorless. The resulting precipitate was removed by filtration, washed with chloroform, and air dried to give 42 g (72%) of colorless crystals (from toluene) with mp 170-171°. Found: Cl 21.4%. $C_{13}H_{11}NO_3S$. Calculated: Cl 21.4%.

N-(p-Tolylsulfonyl)-2,6-dichloro-1,4-benzoquinonimine (Ib). A 225-ml sample of HNO_3 (sp. gr. 1.29) was added to 40 g of the substituted aminophenol obtained in the preceding experiment, and the mixture was stirred for 5 min. The solid material was then removed by filtration, washed successively with water and methanol, and air dried to give 18 g (45%) of shiny yellow crystals (from glacial acetic acid) with mp 140-141°. Found: C 47.0; H 2.6; Cl 21.4%. $C_{13}H_9Cl_2NO_3S$. Calculated: C 47.4; H 2.74; Cl 21.5%.

A solution of 0.8 g (5 mmole) of IIa in 5 ml of acetone was added to a solution of 1.65 g (5 mmole) of quinonimine Ib in 25 ml of acetone, and the mixture was allowed to stand overnight. The acetone was evaporated, and the residue was treated with benzene and worked up to give 0.3 g (35%) of a white crystalline substance. No melting-point depression was observed for a mixture of this product with p-toluenesulfonamide. The product gave a negative qualitative test for chlorine and a positive test for sulfur. We were unable to isolate 6-hydroxyindole Va from the oily residue.

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