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Sulfostyrils. IV. Reactions of 4-Keto-3,4-dihydrosulfostyril.

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The ketone group in 4-keto-3,4-dihydrosulfostyril (I) displays anomalous properties. Its reactions are described; in some reactions it behaved normally, in others it proved quite inert. Attempted oximination of I led to extrusion of the sulfone group with formation of isatin derivatives. Compound I was converted to a tetracyclic indole derivative.

In previous papers in this series (1–3) we described the synthesis and reactions of sulfostyril and dihydrosulfostyril, parent members of a new heterocyclic class of compounds. The critical intermediate in the synthesis of sulfostyril was 4-keto-3,4-dihydrosulfostyril (I). In this paper we describe reactions of this interesting intermediate.

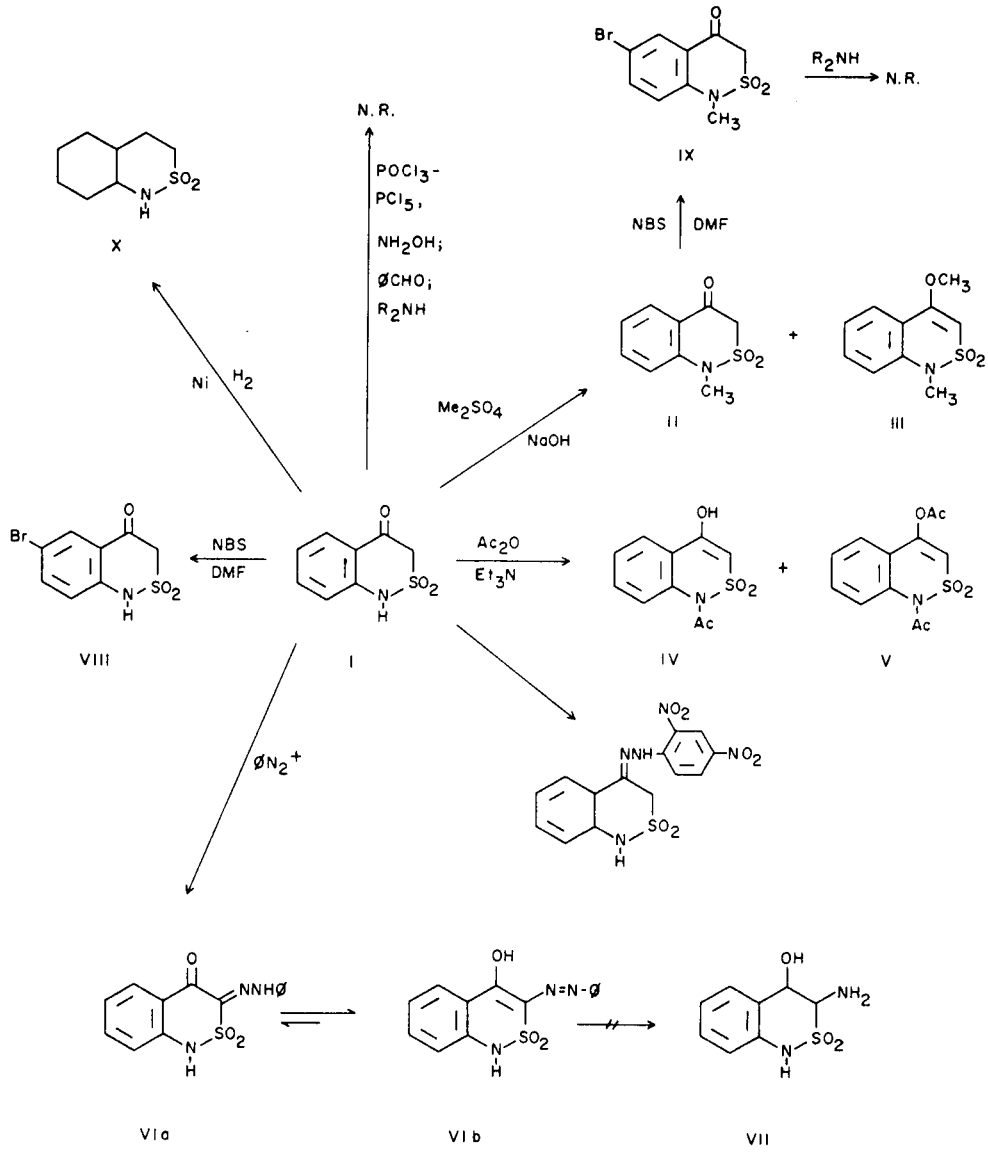
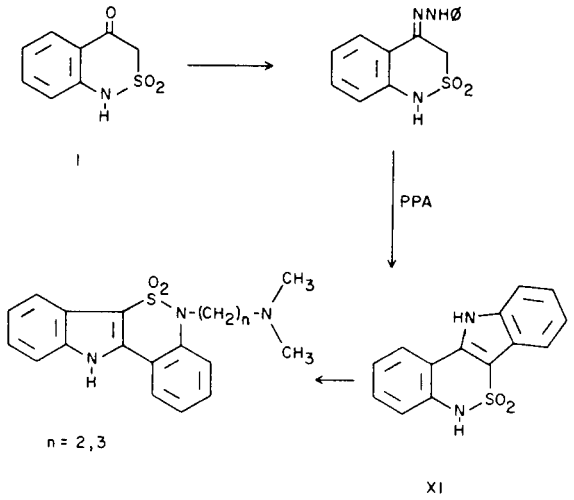


Figure I. Reactions of 4-Keto-3,4-dihydrosulfostyril.

The reactions of I are summarized in Figure I.

Compound I displayed many normal carbonyl properties such as absorption in the infrared at 5.95 μ and formation of tosyl- and 2,4-dinitrophenylhydrazones; nevertheless, it failed to form oximes or semicarbazones under the usual conditions, did not form enamines with secondary



XI

amines, did not undergo condensation with aldehydes, and could not be reduced by ordinary catalytic means. Reduction of I employing more vigorous conditions (2000 p.s.i. and 110°) gave the perhydro derivative, X.

Although I did not show any evidence of enolic character, as indicated by its infrared absorption (normal carbonyl, no hydroxyl) and lack of positive ferric chloride test, evidence of the tautomeric nature of the carbonyl was the finding that on alkylation or acylation of I, the *N*-alkyl (II) and *N*-acyl (IV) products were accompanied by *O*-alkylation (3) and *O*-acylation (V). The *N*-acyl derivative (IV) exists in the enol form (based on infrared).

Compound I failed to react with phosphorus pentachloride-phosphorus oxychloride. This was surprising since both ketones and enols react with this reagent. Compound I condensed readily with benzenediazonium chloride. The product appears to exist in the azo form, VIb, since the infrared no longer shows a carbonyl absorption. Attempts to catalytically reduce VI with platinum, palladium, or nickel in alcohol or acetic acid with the purpose of preparing 3-amino-4-hydroxydihydrosulfostyril (VII), failed. Only tarry products were isolated even when the reductions were carried out in the presence of acetic anhydride.

When I or the *N*-methyl derivative (II) was brominated with *N*-bromosuccinimide in dimethylformamide, monobromo derivatives were obtained (VIII, IX), assigned the 6-bromo position by analogy with the bromination results described earlier (1–3) and the fact that the bromo compounds did not react with alcoholic silver nitrate.

When the phenylhydrazone of I was treated with hydrogen chloride under the usual Fischer indole synthesis conditions (4), hydrolysis of the hydrazone resulted with liberation of 4-keto-3,4-dihydrosulfostyril. However, when polyphosphoric acid was used a tetracyclic indole (XI) was obtained.

The indole could be alkylated on the sultam nitrogen with dimethylaminoethyl- or propylhalides, employing sodium hydride in dimethylsulforixde.

A particularly unexpected reaction of I was observed on treatment with nitrous acid. This reaction was carried out for the purpose of obtaining the oxime, XII, to serve as an alternate route to the amino alcohol, VII. The only product isolated was isatin-β-oxime, XV (5). The *N*-methyl derivative (II) treated in a similar fashion, gave *N*-methylisatin-β-oxime (6).

A possible mechanism (Fig. II) involves extrusion of sulfur dioxide, either via direct displacement on the α-carbon by the sulfonamide nitrogen, or through the intermediacy of a sulfene (XIII) to give isatin-α-oxime (XIV) and then trans-oximination to give the isolated product isatin-β-oxime (XV).

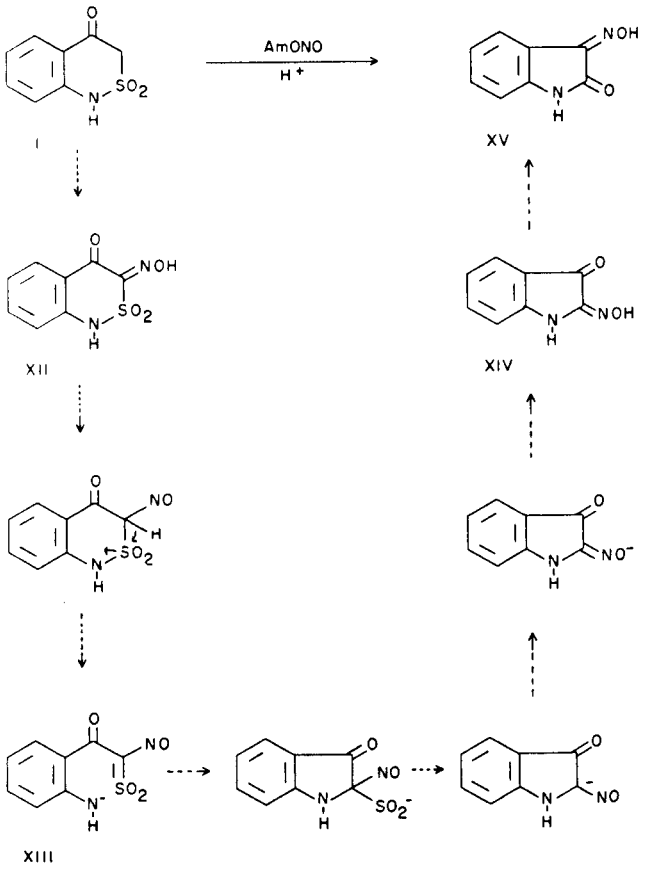


Figure II. Reaction of 4-Keto-3,4-dihydrosulfostyril with Nitrous Acid.

EXPERIMENTAL (8)

Perhydrosulfostyril (X).

A 5.0 g. sample of 4-keto-3,4-dihydrosulfostyril was hydrogenated using palladium-on-carbon as catalyst in acetic acid solvent. The hydrogenation was carried out at 2000 psi and 110° for four hours. The catalyst was filtered and the filtrate evaporated to give a solid which was recrystallized from water to give 1.5 g., m.p. 140–146°. A sample recrystallized again from water melted 146.5–148°.

Anal. Calcd. for $C_8H_{15}NO_2S$: C, 50.80; H, 7.99; N, 7.40. Found: C, 51.11; H, 7.96; N, 7.12.

N-Methyl-4-methoxysulfostyril (III).

4-Keto-3,4-dihydrosulfostyril (20 g.), was suspended in water and dissolved by the addition of 10% sodium hydroxide. To this solution was then added 35 ml. of dimethylsulfate. The resulting mixture was stirred and heated on the steam bath; at about 45° an exothermic reaction occurred. The *p*H began to drop and sufficient 10% sodium hydroxide was added dropwise to maintain the *p*H at 7–8°. The reaction was continued until the solution remained permanently basic. The mixture was chilled and the brown oil crystallized. The aqueous solution was decanted and used for the isolation of the monomethyl derivative as described below. The gummy brown solid was recrystallized from ether to give 1.6 g. of the dimethyl derivative, m.p. 155–156°. The nmr spectrum (deuteriochloroform) showed signals at δ values (ppm) of 3.5 (3H singlet, CH_3-N), 3.9 (3H singlet, CH_3-O), 6.18 (1H singlet, -CH=C), and 7–8 (multiplet, aromatic). In the infrared there was no absorption at 3.1 or 5.95 μ.

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22. Found: C, 53.81; H, 4.92; N, 6.01.

N-Methyl-4-keto-3,4-dihydrosulfostyril (II).

The aqueous layer from the above reaction was acidified and a yellow precipitate formed and was filtered, 14.9 g., m.p. 100-110°. The material was chromatographed on alumina, using benzene as solvent, giving 14.0 g. of the product, m.p. 122–123° (λ max 5.95 μ; no peak at 3.0 μ). This material can be recrystallized from ether; the melting point remains unchanged. The nmr spectrum (deuteriochloroform) showed signals at δ values (ppm) of 3.47 (3H singlet, CH_3-N), 4.35 (2H singlet -SO_2CH_2CO-), and 7.2–8.3 (multiplet, aromatic).

Anal. Calcd. for $C_9H_9NO_3S$: C, 51.17; H, 4.29; N, 6.63. Found: C, 51.17; H, 4.44; N, 6.59.

1-Acetyl-4-hydroxysulfostyril (IV).

4-Ketodihydrosulfostyril (5.0 g., 0.0254 moles) was dissolved in 100 ml. of tetrahydrofuran. To this was added 7.8 g. (0.0762 mole) of acetic anhydride and 20.5 g. (0.203 mole) of triethylamine. The reaction became slightly exothermic and the solution turned from colorless to pale yellow and then to red. The red solution was heated at reflux for 3 hours and then concentrated *in vacuo*. The resulting oil was stirred with water and a gum separated which appeared to consist mostly of starting material. The aqueous layer was decanted and acidified with concentrated hydrochloric acid to give an orange gum which soon crystallized to a white solid, 4.3 g., m.p. 130–160°. This solid was recrystallized from ethyl acetate giving 1.34 g. of product, m.p. 198.5–200°. The infrared of this material showed no ketone or ester carbonyl and only an amide absorption (6.2 μ).

Anal. Calcd. for $C_{10}H_9NO_4S$: C, 50.20; H, 3.79; N, 5.85. Found: C, 50.35; H, 3.74; N, 5.66.

1-Acetyl-4-acetoxysulfostyril (V).

From the filtrates of the preceding reaction, on concentration, was obtained 2.1 g. of solid, m.p. 129–135°. This was recrystallized from isopropyl ether to give 1.2 g. white solid, m.p. 136–138°. The infrared (in chloroform) showed ester (5.8 and 8.1 μ) and amide (6.25 μ) absorptions.

Anal. Calcd. for $C_{12}H_{11}NO_5S$: C, 51.24; H, 3.94; N, 4.98. Found: C, 51.71; H, 4.07; N, 4.88.

4-Hydroxy-3-phenylazosulfostyril (VIb).

A solution of 7.0 g. of sodium nitrite in 20 ml. of water was added to a solution containing 9.3 g. of aniline in 110 ml. of water and 33.3 ml. of concentrated hydrochloric acid cooled to 5°. This cold solution of benzenediazonium chloride was added dropwise to a solution of 19.9 g. of 4-keto-3,4-dihydrosulfostyril in 400 ml. of ethanol, 100 ml. of water and 34 g. of anhydrous sodium acetate which had been cooled to 10°. After about half of the diazonium solution had been added, an orange solid began to separate. After the addition was complete, the mixture was stirred for one hour at room temperature then cooled and filtered to give 30.3 g. of solid, m.p. 235° (d). Recrystallization of a sample for analysis, from acetone, gave m.p. 235° (d).

Anal. Calcd. for $C_{14}H_{11}N_3O_3S$: C, 55.80; H, 3.68; N, 13.95. Found: C, 55.92; H, 3.75; N, 13.67.

1-Methyl-4-keto-6-bromo-3,4-dihydrosulfostyril (IX).

4-Keto-1-methyl-3,4-dihydrosulfostyril (5.0 g., 0.0237 mole) and 4.2 g. (0.0237 mole) of *N*-bromosuccinimide were mixed together and then added to 15 ml. of dimethylformamide. The orange solution was heated on a steam bath for ½ hour then most of the solvent was removed, *in vacuo*, and the residue was treated with water to give a green solid, 8.6 g. m.p. 110–135°. The solid was dissolved in benzene and passed through a short column of alumina. The eluate, on evaporation, gave 3.8 g. of pale yellow solid m.p. 152–159°. This was recrystallized several times from cyclohexane to give the product, m.p. 160–163°.

Anal. Calcd. for $C_9H_8BrNO_3S$: C, 37.26; H, 2.78; N, 4.83; Br, 27.5; S, 11.05. Found: C, 38.57; H, 3.09; N, 4.55; Br, 27.6; S, 11.39.

4-Keto-3,4-dihydrosulfostyril Phenylhydrazone.

4-Ketodihydrosulfostyril (50 g., 0.254 mole) was dissolved in 625 ml. of hot ethanol, and to this solution was added 54.9 g. (0.51 mole) of phenylhydrazine and 12.5 ml. of glacial acetic acid. The mixture was heated at reflux for 30 minutes; after 15 minutes a yellow solid formed. The mixture was cooled and filtered, and the product was rinsed with isopropyl ether (47.5 g.), m.p. 246–249.5°.

Anal. Calcd. for $C_{14}H_{13}N_3O_2S$: C, 58.51; H, 4.56; N, 14.62. Found: C, 58.49; H, 4.70; N, 14.30.

5,11-Dihydro-6,6-dioxy[2,1]benzothiazino[4,3-*b*]indole (XI).

A suspension of 33 g. of the above hydrazone in a large excess of polyphosphoric acid was heated on a steam bath, with occasional stirring, until the yellow paste turned light brown (approximately 20 minutes). The mixture was heated for an additional 15 minutes and then poured into ice water and the solution was made strongly basic with 40% sodium hydroxide. The solution was filtered to remove insoluble materials and the filtrate, on acidification with concentrated hydrochloric acid, deposited 20.5 g. of white solid, m.p. 333–338°. A sample recrystallized from acetone-water melted at 350–352°.

Anal. Calcd. for $C_{14}H_{10}N_2O_2S$: C, 62.20; H, 3.73; N, 10.36. Found: C, 62.44; H, 4.05; N, 10.22.

5-(β-Dimethylaminoethyl)-6,6-dioxy[2,1]benzothiazino[4,3-*b*]indole Hydrochloride.

The above indole (10.8 g., 0.04 mole), dissolved in 100 ml. of dry dimethylsulfoxide, was converted to the sodium salt by the addition of 2.0 g. of a 55% dispersion of sodium hydride in mineral oil (0.046 mole). To this was added a benzene solution containing 0.05 mole of dimethylaminoethyl chloride and the resulting suspension was refluxed for 24 hours. The mixture was filtered to remove sodium chloride, the filtrate was concentrated to remove the benzene, and the remaining solution was poured into 300 ml. of water. The resulting cloudy solution was extracted with ether, and the ether extracts were dried and concentrated giving 8.5 g. of solid, m.p. 212–215°. The solid was suspended in water and dilute hydrochloric acid was added. The solid first dissolved,and then a new precipitate separated. The mixture was heated until the solid dissolved and then cooled and the product filtered, m.p. 282–284°.

Anal. Calcd. for $C_{18}H_{20}ClN_3O_2S$: C, 57.21; H, 5.34; N, 11.12. Found: C, 56.98; H, 5.62; N, 11.16.

5-(γ-Dimethylaminopropyl)-6,6-dioxy[2,1]benzothiazino[4,3-*b*]-indole Hydrochloride.

By the same procedure described above, 11.6 g. of the indole was converted to the dimethylaminopropyl derivative. The free base was obtained as a yellow oil, 5.6 g. This was converted to the hydrochloride with ethereal hydrogen chloride, and recrystallized from boiling ethanol, 1.4 g., m.p. 257–260°.

Anal. Calcd. for $C_{19}H_{22}ClN_3O_2S$: C, 58.23; H, 5.66; N, 10.72. Found: C, 58.02; H, 5.82; N, 10.68.

Isatin-β-oxime (XV).

Concentrated hydrochloric acid, 20 ml., was added to a solution of 10 g. of 4-ketodihydrosulfostyril in 60 ml. of methylcellosolve. Butyl nitrite (5 ml.) was added, and the solution turned yellow as the temperature rose to 35°. The solution was cooled to 25° then an additional 5 ml. of butyl nitrite was added and the solution was poured into 500 ml. of water and a cloudy solution resulted containing a small amount of black oil. The supernatant liquid was decanted away and allowed to stand. A yellow precipitate formed, was filtered (5.3 g.), then recrystallized from ethanol-water to give a product, 2.0 g., m.p. 235°. The compound was found to be identical with an authentic sample of isatin-β-oxime prepared by the literature method (5).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.2; H, 3.70; N, 17.3. Found: C, 59.08; H, 3.88; N, 17.02.

N-Methylisatin-β-oxime.

N-Methyl-4-ketodihydrosulfostyril (3.55 g., 0.0168 mole) was treated with butyl nitrite under the same conditions as described above. After hydrolysis with water, the aqueous solution was extracted with methylene chloride, dried, and concentrated to give 4.2 g. of an oil. On stirring with ether a solid separated, 1.1 g., which proved to be starting 4-ketosulfostyril. Evaporation of the filtrate gave a gum which was dissolved in sodium hydroxide and reprecipitated on acidification with hydrochloric acid. Recrystallization of the resulting orange solid from hot water gave *N*-methylisatin-β-oxime, m.p. 183–187° (lit. (6) m.p. 180–183°).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.56; N, 15.91. Found: C, 61.26; H, 4.62; N, 15.96.

4-Keto-3,4-dihydrosulfostyril *p*-Toluenesulfonylhydrazone.

A solution of 4-ketodihydrosulfostyril (10 g., 0.0507 mole), 10.4 g. of *p*-toluenesulfonylphenylhydrazine, and 0.1 ml. of concentrated hydrochloric acid in 105 ml. ethanol was heated at reflux for 3 hours. On cooling, the small amount of high melting solid which precipitated was filtered and discarded. The filtrate was diluted with water, and the resulting solid was recrystallized from ethanol-water, giving 14.1 g. of product, m.p. 213–214°.

Anal. Calcd. for $C_{15}H_{15}N_3O_4S_2 \cdot \frac{1}{2}H_2O$: C, 48.1; H, 4.31; N, 11.25. Found: C, 48.3; H, 4.30; N, 11.19.

The 2,4-dinitrophenylhydrazine was prepared in a similar manner, m.p. 276–277° (from ethanol-ethyl acetate).

Anal. Calcd. for $C_{14}H_{11}N_5O_6S$: C, 44.56; H, 2.94; N, 18.56. Found: C, 44.79; H, 3.16; N, 18.22.

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(8) All melting points are corrected. Analyses were performed by the Analytical Department of these laboratories.

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