SYNTHESIS OF 5-ALKYLTHIO-8-HYDROXYQUINOLINES

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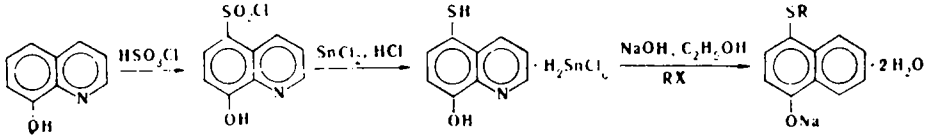
Introduction of the alkylthio group into position 5 of 8-mercaptoquinoline endows the chelate compounds of the resulting 5-alkylthio-8-mercaptoquinolines with very high solubility in inert organic solvents (by comparison with 8-mercaptoquinolinates) [1] as a result of the loosely packed crystal lattice (due to the steric interactions set up by the alkylthio group). Chelates of 8-hydroxyquinoline are at best poorly, or usually not extracted by nonpolar organic solvents, while extraction by slightly polar solvents (chloroform, dichloroethane) is slow and requires a very large excess of 8-hydroxyquinoline. Consequently, 8-hydroxyquinoline is used for the extractive concentration of microquantities of metals only.

We conjectured that the introduction of the alkylthio group into position 5 of 8-hydroxyquinoline would greatly enhance the solubility of the chelates in inert organic solvents, as in the case of 8-mercaptoquinoline, and would offer new possibilities for the use of this very thoroughly studied reagent. This conjecture has been confirmed. The chelates of 5-pentylthio-8-hydroxyquinoline are efficiently extracted by organic solvents of various types. The overwhelming majority of chelates cannot be extracted by aliphatic hydrocarbons, but 5-pentylthio-8-hydroxyquinolinates are extracted by these solvents (isooctane, ligroin, and kerosene). Calcium, strontium, and barium 8-hydroxyquinolinates are not extracted by inert organic solvents, such as chloroform, but their 5-pentylthio-8-hydroxyquinolinates are efficiently extracted.

Here we describe methods for the synthesis of 5-alkylthio-8-hydroxyquinolines and their sodium salts (Table 1). A five-stage route to 5-methylthio-8-hydroxyquinoline by the Skraup method from methylthioacetylacryl acetate has been described [2], but this can be used to prepare only the first member of the homologous series.

We have developed a method for preparing 5-alkylthio-8-hydroxyquinolines by the reactions



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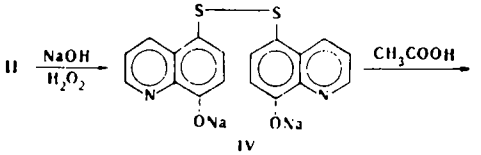
X = I, Br, III a R = CH_3, b R = C_2H_5; c R = C_3H_7; d R = C_4H_9; e R = C_5H_{11}; f R = C_6H_{13}; g R = C_8H_{17}; h R = C_9H_{19}

If purer 5-alkylthio-8-hydroxyquinolines uncontaminated by tin compounds are required, we recommend that the synthesis be carried out via 8,8'-dihydroxy-5,5'-diquinolyl disulfide (V):



IV

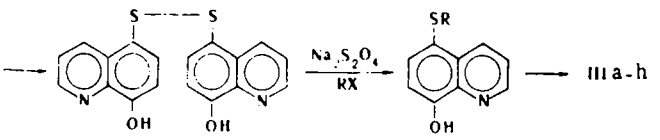


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TABLE 1. 5-Alkylthio-8-hydroxyquinolines

Compound	mp, °C	Found, %				Formula	Calculated, %				Yield, %	Sodium salt*	mp, °C
		C	H	N	S		C	H	N	S			
VIa	50—51	62,7	4,8	7,2	16,5	$C_{10}H_9NOS$	62,8	4,7	7,3	16,8	25	IIIa	>300†
VIb	54—55	64,4	5,3	6,5	15,8	$C_{11}H_{11}NOS$	64,4	5,4	6,8	15,6	28	IIIb	276—278
VIc	56—57	65,4	5,9	6,5	14,5	$C_{12}H_{13}NOS$	65,7	5,9	6,4	14,6	37	IIIc	268—270
VId	Oil	66,7	6,3	5,9	13,6	$C_{13}H_{15}NOS$	66,9	6,5	6,0	13,7	38	IIId	255—258
VIe	33—34	68,0	6,8	5,6	13,0	$C_{14}H_{17}NOS$	68,0	6,9	5,7	13,0	35	IIIe	253—254
VIf	50—51	68,7	7,1	5,3	12,3	$C_{15}H_{19}NOS$	69,0	7,3	5,4	12,3	15	IIIf	250—252
VIg	41—42	71,0	7,9	4,8	11,1	$C_{17}H_{23}NOS$	71,0	8,0	4,8	11,1	8	IIIg	246—248
VIh	55—56	71,1	9,4	4,6	10,4	$C_{18}H_{25}NOS$	71,3	9,3	4,6	10,6	10	IIIh	230—237

*The sodium salts of the 5-alkylthio-8-hydroxyquinolines (IIIa)-(IIIh) are the dihydrates and had satisfactory elemental analyses.

†With decomposition.

Decomposition of chlorostannate salt (II) with dilute NaOH solution forms a yellow solution of the disodium salt of 5-mercapto-8-hydroxyquinoline; this is easily oxidized to the disodium salt of 8,8'-dihydroxy-5,5'-diquinolyl disulfide (IV), which is also highly soluble in water.

When the alkaline solution resulting from the decomposition of chlorostannate salt (II) is neutralized, the tin compounds present in the solution react with 5-mercapto-8-hydroxyquinoline to form a complex. At pH 9-10 the disodium salt (IV) is partially hydrolyzed to disulfide (V), which is precipitated. Here tin compounds can also be precipitated as a result of hydrolysis and are practically impossible to remove. Consequently, we decompose chlorostannate salt (II) with 20% NaOH solution and on cooling oxidize the disodium salt of 5-mercapto-8-hydroxyquinoline that is now present in solution by adding exactly the calculated amount of hydrogen peroxide. With excess hydrogen peroxide oxidation proceeds further and the precipitate of disodium salt (IV) dissolves. At lower alkali concentrations (10% NaOH solution) disodium salt (IV) is not completely precipitated. In work with 16-18% alkali solution we also got a slightly lower yield of disodium salt of the disulfide (~40%) than with 20% NaOH (50-55% free disulfide based on 8-hydroxyquinoline). Increasing the alkali concentration above 20% is not advisable, since it causes difficulties in filtration. The literature method [3] of preparing disulfide (V) by thiocyanation of 8-hydroxyquinoline and saponification of the resulting 5-thiocyanato-8-hydroxyquinoline gives very low yields of the disulfide (4% based on 8-hydroxyquinoline).

Disulfide (V) can then be reduced to 5-mercapto-8-hydroxyquinoline by hypophosphorous acid in hydrochloric acid. However, 5-mercapto-8-hydroxyquinoline is very rapidly oxidized in alkaline medium and subsequent alkylation gives poor yields of the 5-alkylthio-8-hydroxyquinoline (VI), while 5-methylthio-8-hydroxyquinoline cannot be prepared in the pure form by this method. Consequently, we reduce disulfide (V) with sodium hydrosulfite in alkaline aqueous ethanol and add an alcoholic solution of the alkyl halide to the reaction mixture containing the reductant. At the end of alkylation the reaction mixture is neutralized and the 5-alkylthio-8-hydroxyquinoline (VI) is extracted with hexane. 5-Alkylthio-8-hydroxyquinolines can be prepared by neutralization with acetic acid of the aqueous suspension of the sodium salts followed by extraction with hexane. The free reagents and their sodium salts are relatively poorly soluble in water; the solubility diminishes as the number of carbon atoms in the alkyl group increases.

EXPERIMENTAL

8-Hydroxy-5-quinolinesulfonyl Chloride (I). 8-Hydroxyquinoline (7.5 g, 0.05 mole) was added in small portions with cooling and stirring to chlorosulfonic acid (50 ml, 0.8 mole). After all the 8-hydroxyquinoline had been added, stirring was continued until the evolution of hydrogen chloride ceased. Then the flask was stoppered and left to stand for 12 h. The reaction mixture was poured into ice (450-500 g) and then diluted with cold water to 700 ml. The precipitate was filtered off and washed with cold water (25 ml). The yield was 8 g (60%). The faintly yellowish compound had mp 265-267°C (from acetone). Found: Cl 14.4; N 5.8; S 12.8%. $C_9H_6ClNO_3S$. Calculated: Cl 14.6; N 5.8; S 13.2%.

Chlorostannate Salt of 5-Mercapto-8-hydroxyquinoline (II). Immediately after preparation the wet sulfonyl chloride without recrystallization was suspended with vigorous stirring in concentrated hydrochloric acid (45 ml) and poured into a previously prepared solution of stannous chloride dihydrate (35 g, 0.15 mole) in concentrated hydrochloric acid (40 ml). The reaction mixture was vigorously stirred and the undissolved lumps of the sulfonyl chloride were triturated with a glass rod for 5-10 min. The reaction mixture was left at room temperature for 1 h. The precipitated chlorostannate salt (II) was filtered off, washed with concentrated hydrochloric acid (20 ml), and carefully pressed. The wet product was used in the next stage.

Sodium Salt of 5-Pentylthio-8-hydroxyquinoline (IIIe). To a solution of sodium hydroxide (20 g, 0.5 mole) in water (100 ml) was added chlorostannate salt (II), prepared from 8-hydroxy quinoline (7.5 g, 0.05 mole). The mixture was stirred until the salt had completely dissolved. The solution was rapidly cooled to room temperature in an ice bath, ethanol (100 ml) was added and the solution was stirred. Pentyl bromide (7.5 ml, 0.06 mole) in ethanol (50 ml) was added and the solution was stirred and left at room temperature for 12 h. The reaction mixture was diluted with cold distilled water (300 ml) and left in a refrigerator for 1-2 h. The precipitate was filtered off and crystallized from moist acetone (40-50 ml acetone and 1 ml water) to give the sodium salt (IIIe) (5.3 g, 34% based on 8-hydroxyquinoline) as lustrous lemon-yellow platelets with mp 253-254°C. The other 5-alkylthio-8-hyxroxyquinolines were prepared in the same way (Table 1).

Disodium Salt (IV) and 8,8'-Dihydroxy-5,5'-diquinolyl Disulfide (V). The wet chlorostannate salt (II) prepared from 8-hydroxyquinoline (7.5 g, 0.05 mole) was dissolved with stirring in 20% NaOH solution (100 ml). The solution was cooled to room temperature and placed in an ice bath; 30% hydrogen peroxide (2 ml) was added and the solution was left for 1 h, being stirred from time to time. Disodium salt (IV) precipitated from the solution. The precipitate was filtered off and carefully pressed on a suction filter. The yellow disodium salt (IV) was crystallized from ethanol [6 g of disulfide (IV) was crystallized from 30 ml of ethanol]; in a humid atmosphere it gradually hydrolyzed to the free disulfide (V). Salt (IV) without recrystallization was dissolved in distilled water (300-350 ml). The solution was filtered and glacial acetic acid was added dropwise to pH 5-6. The resulting precipitate was filtered off, washed on the suction filter with distilled water, and dried to give disulfide (V) (5.0 g, 55% based on 8-hydroxyquinoline).

5-Ethylthio-8-hydroxyquinoline (VIb) and Its Sodium Salt (IIIb). To a solution of sodium hydroxide (7.0 g, 0.18 mole) in distilled water (60 ml) was added disulfide (V) (6.7 g, 0.02 mole). The reaction mixture was stirred until the disulfide had completely dissolved and then ethyl alcohol (200 ml) was added. The solution was filtered and a solution of sodium hydrosulfite ($Na_2S_2O_4 \cdot 2H_2O$; 0.5 g, 0.03 mole) in water (40 ml) was added. After 30 min ethyl bromide (3.3 ml, 0.04 mole) in ethyl alcohol (100 ml) was added and the mixture was stirred and left at room temperature for 12 h. It was then diluted with cold distilled water (400 ml), glacial acetic acid was added dropwise to pH 5-6, and the mixture was extracted with two portions of hexane (75 ml each). The extract was dried over anhydrous sodium sulfate, filtered, and evaporated in a stream of air at room temperature to give compound (VIb) (2.5 g) with mp 54-55°C. The synthetic 8-hydroxyquinoline (VIb) was treated with 20% sodium hydroxide solution (~1 ml) and the sodium salt was crystallized from acetone (30 ml) with added water (1 ml). The precipitate was filtered off to give the sodium salt (IIIb) [2.0 g, 20% based on disulfide (V)]. The other 5-alkylthio-8-hydroxyquinolines and their sodium salts were prepared in the same way.

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