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THE REACTION OF SULFUR WITH ORGANIC COMPOUNDS

VII. Catalytic Reaction Of Sulfur With Ring-Substituted Cumenes*

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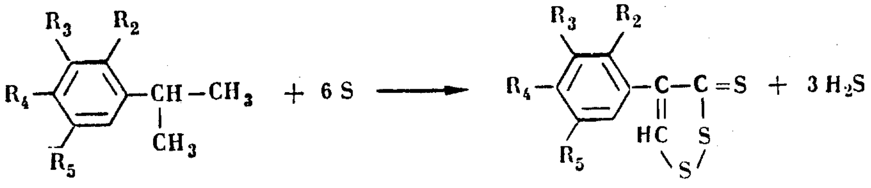
The most effective catalyst for thionation of cumenes to 4-aryl-1, 2-dithiol-3-thiones, have been proven to be sym-diphenylguanidine, mercury acetamide, mercaptobenzthiazole + ZnO. The way in which thionation of cumeme derivatives depends on the nature of the substituent in the aromatic ring is investigated. Eight derivatives (4 previously unknown) of 4-phenyl-1, 2-dithiol-3-thione, with a chlorine atom and an alkyl or alkoxy group in the benzene ring are synthesized and described.

The present paper continues a series, interrupted 15 years ago, dealing with the reaction of sulfur with organic compounds [1-11]. It is concerned with studying the catalytic reaction of elemental sulfur with nuclear-substituted isopropylbenzenes (cumenes) I, to give the corresponding 4-aryl-1,2-dithiol-3-thiones (II);



I II

R_2, R_3, R_4, R_5 = H, Cl, alkyl, alkoxy

1,2-dithiol-3-thione derivatives have been known for a long time [12-17], but the chemistry of these heterocyclic compounds was born in the 1940's, and systematic researches on 1,2-dithiol-3-thiones were begun practically simultaneously and independently in the USSR [4,5,7,9,10], Germany [18,19], France [20-22], and Great Britain [23]. Later such compounds were also found to occur naturally (in plants [24]).

The present growing interest in 1,2-thiol-3-thiones is not surprising, since they find practical application in a number of spheres [25-34], particularly in medicine (agents for stimulating working of the liver and gall bladder) [25-29]. 4-Aryl 1,2-dithiol-3-thione chlorination products possess fungicidal activity [30-33]. The 1,2-dithiol heterocyclic ring is part of the structure of some antibiotics (thiolutin, galomycin), for the synthesis of which, use is made of the corresponding derivatives of 1,2-dithiol-3-thione [34].

Table 1

Effect of catalyst (0.2 mole %) on yield of 4-(p-tolyl)-1,2-dithiol-3-thione (IV) in the Reaction of Sulfur with p-Cymene

Catalyst	Reaction time, hr	% Yield IV	
		Based on Sulfur taken	Based on reacted p-cymene
Sym.-diphenylguanidine	20	72.1	40.7
Mercury acetamide	20	69.5	40.5
Sodium salt of 8-mercaptoquinoline	20	64.4	37.5
Quinoline	20	62.7	33.6
Mercaptobenzothiazole + ZnO*	18	60.9	36.5
8-mercaptoquinoline (thiooxine)	12	60.1	32.3
Dimethylaniline	12	58.4	27.2
Thiourea	20	56.8	29.9
Molybdenum sulfide	20	56.7	26.4
N-morpholinobenzothiazole-2-sulfenamide (Sulfenamide M)	9	54.9	29.5
Benzothiazole disulfide	20	54.9	27.8
Mercaptobenzothiazole	20	52.7	36.7
Diethanolamine	20	43.8	23.5
N-diethylaminomethylenebenzothiazolethione-2 (BTMA)	20	42.9	21.4
N-cyclohexylbenzothiazole-2-sulfenamide (Sulfenamide Ts)	20	41.2	22.1

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* For previous papers see [1-6].

All this makes it necessary to seek the simplest and cheapest synthetic route to 1, 2-dithiol-3-thiones. Hitherto they have mainly been made by the action of sulfur on olefins [4, 5, 7, 9, 22, 35-37], or of phosphorus pentasulfide on β-ketocarboxylic acid esters [38, 39].

In 1955 it was shown that it was possible to prepare 4-p-alkyl-phenyl-1, 2-dithiol-3-thiones by the method given above, (R_2, R_3, R_5 = H, R_4 = alkyl), the action of elemental sulfur on p-alkylcumenes in the presence of basic catalysts (Na_2CO_3, NaOH, amines, and particularly di-o-tolylguanidine) [40-42].

It was of interest to work out a simple method of synthesizing 4-aryl-1, 2-dithiol-3-thiones of type II, with the aromatic ring containing not only p-alkyl groups, but also other substituents with various orientations with respect to the heterocyclic radical. At the same time it was desirable to study the effect of different catalysts on the course of the reaction of elemental sulfur with nuclear-substituted cumenes, and its relationship to the nature and positions of the substituents.

A large number of various classes of organic and inorganic compounds (diphenylguanidine, quinoline, diethanolamine, dimethylaniline, N-diethylaminomethylenebenzothiazolthione-2, thiourea, mercaptobenothiazole, benzothiazole disulfide, 8-mercaptoquinoline, and its sodium salt, N-cyclohexylbenzothiazole-2-sulfenamide, N-morpholinobenzothiazole-2-sulfenamide, mercury acetamide, many metal sulfides , aluminum chloride, boron trifluoride, ethyleneimine, iodine, etc.) have been investigated for catalytic action in the reaction of sulfur with cymene. The most effective of them are listed in Table 1.

The results obtained make it possible to recommend the following thionation catalysts for cumene derivatives (in order of decreasing activity): sym-diphenylguanidine, mercury acetamide, sodium salt of 8-mercaptoquinoline, and mercaptobenzothiazole. A number of catalysts cutting the sulfur-cymene reaction time (N-dimethylaniline, 8-mercaptoquinoline, and N-morpholinobenzothiazole-2sulfenamide) also cut the yield of 3-p-tolyl-1, 2-dithiol-3-thione (IV), as they promote side reactions.

It was further found that thionation of organic compounds, including substituted cumenes, proceeds most smoothly in a solvent not reacting with the sulfur under the reaction conditions, viz., temperatures up to 230°, and in the presence of a catalyst. Mesitylene can also be used as solvent in the case of high boiling starting compounds, making it possible to cut the refluxing temperature of the reaction mixture to that required.

Carrying out thionation of type I nuclear-substituted cumenes under optimum conditions (catalyst 0.2 mole % mercury acetamide), it proved possible to prepare a series of 4-aryl-1, 2-dithiol-3-thiones (II), which are given in Table 2 (4 previously unknown). When I had two substituents in the benzene ring, yields of II are generally lower. Starting substituted cumenes I with a substituent ortho to the isopropyl group, do not react with sulfur under the conditions used. Consequently it is not possible to prepare 4-aryl-1, 2-dithio-3-thiones from o-cymene, or from 2, 5-dichloro-2, 5-dimethyl- and 2, 5-dimethoxycumene. This limitation of the synthetic possibilities of the thionation reaction with nuclear-substituted cumenes is of definite practical interest, since it makes it possible to use mixtures of o- and p-isomers which are alkylates obtained from the appropriate aromatics for preparing the individual II compounds. For example, when cymene, chlorocumene, and methoxycumene, made by alkylating toluene, chlorobenzene, and anisole with isopropanol are thionated, they give the same II compounds as the products of alkylating the corresponding individual p-substituted cumenes.

Still, thymol methyl ether, with a methoxy group ortho to the $CH(CH_3)_2$ group, gives the corresponding 1, 2-dithiol-3-thione (VIII) with sulfur. It was not possible to prepare the II compounds using, under the stated conditions, 3, 4-dimethyl-, 3, 4-dimethoxy- and p-ethylcumene. Cumene itself reacts very slowly with sulfur: a 50 hr reaction in the presence of 0.2 mole % mercury acetamide giving only 15% 4-phenyl-1, 2-dithiol-3-thione (III).

Experimental

Starting materials

p-Cymene and cumene. C. p. materials are on sale. After distilling through a column, over sodium, they had the physical properties given in Table 3.

o-Cymene. A mixture of 100 g (0.6 mole) o-bromotoluene and 92 g (0.7 mole) isopropyl bromide was added dropwise to 30 g (1.3 g-at) thinly cut sodium metal covered with 150 ml dry ether. As the reaction was violent, cooling was used at first. The next day the precipitate of sodium bromide was filtered off, along with unreacted sodium, the ether distilled off from the filtrate, and the residue distilled through a column. The yield of o-cymene, bp 79-81° (15 mm), n_D^{20} 1.5003, was 32 g, or 41% on the starting o-bromotoluene.

p-Chlorocumene was prepared via the diazo-compound from p-cumidine [43].

Table 2

4-Aryl-1,2-dithiol-3-thiones (II, R_5 = H), and Preparation Conditions

Compound	II			Molar ratio I:S:$C_6H_3Cl_3$	Reaction Temperature °C	Reaction Time, hr	Mp, °C	External form of crystals	Formula	Found %			Calculated %			% yield (on the starting sulfur)
	R_2	R_3	R_4							C	H	S	C	H	S	
III*	H	H	H	1 : 1,5	156—158	50	120.5	Red needles	$C_9H_6S_3$	51.25	2.80	45,86	51.39	2.87	45.73	15
IV*	H	H	CH_3	1 : 1.5	181—187	20	119.5	Orange needles	$C_{10}H_8S_3$	53.88	3.73	42.39	53,53	2,59	42,87	70
V*	H	H	$C(CH_3)_3$	1 : 1.5	220—225	5	148.5	Yellow plates	$C_{13}H_{14}S_3$	58,93	5,34	36,28	58.60	5,29	36.10	60
VI**	H	H	Cl	1 : 1.5	195—198	10	93.5	Glistening orange plates	$C_9H_5S_3Cl$	44.36	2.34	39,28	44.16	2.06	39,29	67
VII*	H	H	CH_3O	1 : 1,5	204—206	10	152	Fluffy yellow needles	$C_{10}H_8OS_3$	50.33	2.28	39,90	49,96	3,35	40.02	68
VIII**	CH_3O	H	CH_3	1 : 6 : 2	214—216	8	153,2	Fluffy yellowish-orange needles	$C_{11}H_{10}OS_3$	52,00	4,29	37,60	51,93	3,96	37,81	40
IX**	H	H	C_2H_5O	1 : 2 : 0.15***	210—214	10	116	Fluffy yellow needles	$C_{11}H_{10}OS_3$	52,03	3,99	37,93	51.93	3,96	37,81	40
X**	H	Cl	Cl	1 : 6 : 2	217—220	8	159.5	Orange plates	$C_9H_4S_3Cl_2$	38.99	1.74	34,22	38,72	1.44	34.45	30

*The literature gives: III mp 122° [40]; IV mp 122.5° [40]; V mp 146° [40]; VII mp 152° [35].

**New compound

***Mesitylene

Thymol methyl ether. This was made by etherification of thymol with methyl iodide [44].

The basic method for preparing nuclear-substituted cumenes was alkylation of the appropriate benzene derivative, using the alcohols plus sulfuric or phosphoric acid. Two typical examples of alkylation are given below.

Alkylating chlorobenzene with isopropanol and sulfuric acid. 400 g (3.5 mole) chlorobenzene, 108 g (1.8 mole) isopropanol, and 900 ml 80% sulfuric acid were placed in a flask fitted with stirrer, reflux condenser, and thermometer. The mixture was intensively stirred, and heated for 6 hr at 70-80°. The upper layer was separated off, washed with sodium carbonate solution and then with water, dried over calcium chloride, and distilled through a column. The yield of chlorocumene bp 71-73° (10 mm), n_D^{20} 1.5140 was 198 g, or 68%, calculated on the reacted chlorobenzene. The p-chlorocumene made in this way contained a small amount of o-isomer.

p-Tertbutyl-, p-ethyl-, 3,3-dimethyl-, 2,5-dimethyl-, and 2,5-dichlorocumene are prepared similarly (Table 3).

Isopropanol-phosphoric acid alkylation of anisole. 260 g (2.4 mole) anisole, 90 g (1.5 mole) isopropanol, and 330 ml phosphoric acid (d 1.8) were placed in a flask fitted with stirrer and reflux condenser. The mixture was vigorously stirred and heated on a steam bath for 9 hr. The upper layer was then separated off, washed with water, dried over calcium chloride, and distilled through a column, to give 173 g, or a 70% yield calculated on the reacted anisole of p-methoxycumene (containing a small amount of the o-isomer), bp 78-80° (7 mm), n_D^{20} 1.5048.

This method was used to prepare p-ethoxy-, 3,4-dimethoxy-, and 2,5-dimethoxycumene (Table 3).

Method of synthesizing 4-aryl-1,2-dithiol-3-thiones (II). A mixture of 1 mole of substituted cumene, 1.5 g-at sulfur, and 0.002 mole mercury acetamide was refluxed until all the sulfur had reacted, then cooled to 0°, and kept there for a few hours. The crystals which separated were filtered off, washed, and recrystallized from 75% acetic acid. Two typical examples of the synthesis of compounds II are given below.

4-(p-Tolyl)-1,2-dithiol-3-thione (IV). 28 g (0.21 mole) p-cymene, 10 g (0.31 g-at) sulfur, and 0.1 g (0.0003 mole) mercury acetamide were refluxed together for 20 hr at 180-187°. Then the reactions products were cooled, and held at 0-5° for 2 hr, after which the crystals of IV which separated were filtered off, and washed with hexane-benzene (2:1). Yield of unpurified IV was 8.2 g (69.5% theoretical on the initial sulfur, or 40.5% on the cymene reacted). Recrystallized from 75% acetic acid, IV forms orange needle-shaped crystals, mp 119.5°.

4-(p-Tert-butylphenyl), 4-(p-chlorophenyl)-, and 4-(p-methoxyphenyl)-1,2-dithiol-3-thione (Table 2) were prepared similarly.

4-(3',4'-Dichlorophenyl)-1,2-dithiol-3-thione (X). 10 g (0.053 mole) 3,4-dichlorocumene, 29 g (0.064 mole) 1,2,4-trichlorobenzene, 10 g (0.31 g atom) sulfur, and 0.1 g (0.0003 mole) mercury acetamide were heated together at 217-220° for 7 hr. Crystals of X separated when the reaction product was cooled, they were filtered off and washed with hexane-benzene (2:1). Yield of impure X 4.6 g (30%, calculated on the starting sulfur). After recrystallizing from 75% acetic acid, X formed yellow plate-shaped crystals mp 157.5°.

4-(4'-Methyl-2'-methoxyphenyl)-and 4-(p-ethoxyphenyl)-1,2-dithiol-3-thione (Table 1) were prepared similarly.

Action of sulfur on 2,5-dichlorocumene. A mixture of 20 g (0.11 mole) 2,5-dichlorocumene, 6.5 g (0.2 g-at) sulfur, 0.1 g (0.0003 mole) mercury acetamide, and 2.5 ml mesitylene was heated at 189-190° for 40 hr. On working up the reaction mixture in the same way, 4.2 g (65%) of unreacted sulfur was recovered, and no 4-(2',5'-dichlorophenyl)-1,2-dithio-3-thione could be isolated from the residue.

The action of sulfur on o-cymene gave the same result.

Table 3

Nuclear-Substituted Cumenes (I) used as Starting Materials

I				Bp, °C (mm pressure)	n_D^{20}	% Yield
R_2	R_3	R_4	R_5			
H	H	H	H	152.4 (760)	1.4913	—
H	H	CH_3	H	177.2 (760)	1.4905	—
H	H	C_2H_5	H	78—80 (15)	1.4938	57
H	H	$C(CH_3)_3$	H	85—86 (5)	1.4917	55
H	H	CH_3O	H	78—80 (7)	1.5048	70*
H	H	C_2H_5O	H	90—92 (15)	1.4983	35
H	H	Cl	H	68—69 (7)	1.5115	77
H	H	Cl	H	71—73 (10)	1.5150	68*
H	CH_3	CH_3	H	76—78 (7)	1.5036	52
H	CH_3O	CH_3O	H	92—94 (5)	1.5140	77
H	Cl	Cl	H	118—120 (20)	1.5340	43
CH_3	H	H	H	80—81 (15)	1.5003	41
CH_3O	H	CH_3	H	88.5 (7)	1.5059	80
CH_3	H	H	CH_3	70—72 (7)	1.5011	53
CH_3O	H	H	CH_3O	105—107 (7)	1.5122	50
Cl	H	H	Cl	112—114 (20)	1.5323	39

*Alkylation product contains o-isomer.

Action of sulfur on p-ethylcumene. A mixture of 30 g (0.2 mole) p-ethylcumene, 10 g (0.31 g-at) sulfur, and 0.1 g (0.0003 mole) mercury acetamide was heated at 190°-195° for 5 hr. The reaction products were then kept for 24 hr at −5°, but no crystals separated, and after distilling off the unreacted p-ethylcumene only a dark red resin remained.

3,4-Dimethyl-, 2,5-dimethyl-, 3,4-dimethoxy- and 2,5-dimethoxy cumene reacted similarly with sulfur, giving resinous products.

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