acid derivatives have been prepared in our laboratories. Six of these (the ethyl isopropyl, ethyl allyl, ethyl *n*-butyl, ethyl isoamyl, ethyl phenyl and allyl *s*-butyl thiobarbituric acids) are included in the list given by Tabern and Volwiler, and since their properties agree substantially with those already described, they need not be repeated here.

The synthesis of these compounds follows a single pattern, and one example will illustrate the method.

Ethyl *n*-Propyl Thiobarbituric Acid.—In a 1-liter, 3-necked round-bottomed flask, equipped with a mechanical stirrer and reflux condenser, is placed 276 ml. of anhydrous ethanol, and in it is dissolved 13.8 g. (0.6 mole) of metallic sodium. 24 3 g. (0.32 mole) of thiourea is added, while stirring. With continued stirring, 46 g. (0.2 mole) of ethyl *n*-propyl malonic ester is added quickly. Stirring is continued and the mixture is gently heated to incipient refluxing over a period of six to seven hours. After standing overnight the reaction mixture is concentrated on a steam-bath to about 150 ml. and diluted with 75 ml. of water. Concentrated hydrochloric acid is now added until the mixture is strongly acid to litmus paper, whereupon the desired ethyl *n*-propyl thiobarbituric acid precipitates out. The crystals, after drying and recrystallizing from toluene, melt at 174–174.5° (uncorr.).

By substituting an equimolar amount of the appropriate malonic ester in the above reaction, other desired 5,5-disubstituted thiobarbituric acids have been obtained. In general the yield is somewhat higher than that obtained for the oxygen analogs.

The thiobarbituric acid derivatives are listed in Table I.

The intermediate dialkyl malonic esters have all been described in the literature. They were purchased where possible, or synthesized by well-known procedures. Of the esters synthesized, it may be said that in general the yields are satisfactory, except when a second alkyl group is being introduced into secondary-alkylmalonic ester.

Summary

Twenty 5,5-disubstituted thiobarbituric acids have been prepared and their chemical characteristics determined. Of these, six have recently been described by others. The method of preparation corresponds to that used for the oxygen analogs, but the yields are generally somewhat higher. A pharmacological study of these compounds has been completed and will be presented elsewhere.

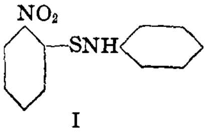
GLENOLDEN, PENNA. RECEIVED MARCH 7, 1936

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

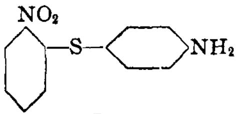
The Molecular Rearrangement of Sulfenanilides.[1] III

BY MAURICE L. MOORE[2] AND TREAT B. JOHNSON

In previous communications[3] from this Laboratory, the authors have discussed the rearrangement of certain aromatic sulfenanilide compounds of Type I. They have shown that on heating these alone or in the presence of an excess of the corresponding amine, they undergo rearrangement to *p*-aminophenyl sulfides II, whereas by digestion in alcoholic sodium hydroxide solution they give the corresponding *o*-mercaptodiphenylamines III. We have now extended the study of these molecular rearrangements to other compounds of similar structure, and in this paper we shall discuss the results of some new experiments in which we have accomplished molecular rearrangements under the influence of heat.



I



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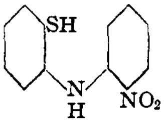

III

In addition to the compounds of Type I, previously studied by the authors, many others examined give the same type of change upon heating. Thus, 2,4-nitrochlorobenzene-sulfenanilide, prepared by the action of 2,4-nitrochlorobenzene-sulfenyl chloride upon aniline, gave 2,4-nitrochlorophenyl-4′-aminophenyl sulfide when heated at a temperature of 150–160° or when heated with an excess of aniline at a temperature of 180–190°. The corresponding *o*-toluidide underwent

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[1] In our previous papers we have observed the nomenclature of the earlier workers in related fields in naming these sulfur compounds, but we have noticed that the abstractors for the *Chemical Abstracts* prefer and have applied another nomenclature. In order to be consistent and to maintain uniformity of spelling, in our Journals, we are, therefore, now following their system, as indicated in the Abstracts of our previous papers, and also in the last edition of "Organic Syntheses," Vol. XV, 1935, p. 45.

[2] A. Homer Smith Research Fellow in Organic Chemistry, 1935–1936.

[3] Moore and Johnson, THIS JOURNAL, **57**, 1517, 2234 (1935); see also *Science*, **81**, 643 (1935).

a similar rearrangement, giving the isomeric *p*-aminophenyl sulfide. 2-Nitrobenzene-sulfen-*o*-chloroanilide and 4-nitrobenzene-sulfen-*o*-chloroanilide were prepared by the action of the nitrobenzene-sulfenyl chloride on *o*-chloroaniline and both have been rearranged successfully to the corresponding sulfides by heating.

It is now quite apparent from our studies that the -S-NH- linkage between aromatic nuclei is very susceptible to a change of structure by application of heat, forming aminophenyl sulfides II and that the transformation involved is universal to compounds of Type I. Substituents in either benzene nucleus of the sulfenanilide I do not seem to have any influence in affecting a successful molecular rearrangement as long as there is at least a para or an ortho position open in the aromatic nucleus. Rearrangement, however, to the para position predominates. If this position is occupied then an ortho substituted sulfide is formed.

In the case of the methylene type of rearrangement studied by Cohn and Fischer[4] it has been shown that the anilide group in the molecule can be displaced by another aromatic amine which will then undergo rearrangement when digested in an acid solution of the amine hydrochloride. For example, when *p*-aminobenzyl-anilide IV is digested on the steam-bath with a hydrochloric acid solution of *o*-toluidine, diamino-phenyl-tolyl-methane V is formed in excellent yield. This displacement of amine and subsequent rearrangement is explained upon the basis of the following intermediate reactions

$$\mathrm{NH_2C_6H_4{-}CH_2{-}NHC_6H_5} \xrightarrow[\text{hydrolysis}]{\text{Acid}} \underset{\text{IV}}{\mathrm{NH_2C_6H_4CH_2OH}} + \mathrm{C_6H_5NH_2}$$

$$\mathrm{NH_2C_6H_4CH_2OH} + \mathrm{NH_2C_6H_4CH_3}(o) \xrightarrow{\text{Acid}} \underset{\text{V}}{\mathrm{NH_2C_6H_4CH_2C_6H_3(CH_3)NH_2}}$$

In continuing the study of the rearrangement of sulfenanilides I, it was our prediction that these compounds would likewise suffer displacement of the anilide group in the molecule with subsequent rearrangement when heated in the presence of an excess of certain amines. This assumption has been confirmed. For example, when 2-nitrobenzene-sulfenanilide I was heated at a temperature of 180–190° with an excess of *o*-toluidine, 2-nitrophenyl-3′-methyl-4′-aminophenyl sulfide was formed. 2-Nitrobenzene-sulfen-*o*-toluidide and the corresponding *p*-toluidide also responded to similar reactions when treated with different aromatic amines. Aniline, *o*-toluidine and *p*-toluidine are able to displace each other from the respective sulfenanilide molecule.

Notwithstanding this similarity in chemical behavior of the two different types of compounds when they interact with amines, it does not seem plausible to explain our sulfenanilide reactions upon the theoretical basis of the mechanism suggested above and involving first an hydrolysis. When compounds of Type I are heated in acid solution the amine radical is removed and a disulfide is formed smoothly. No rearrangement takes place in an acidic, aqueous or alcoholic medium. Heating with an amine alone leads to a normal rearrangement forming a sulfide in good yield. In an alkaline solution the sulfenanilide I is unstable and undergoes a diphenylamine rearrangement III. These results seem to preclude any initial hydrolysis of I taking place in the displacement and subsequent rearrangement reaction although there must be some dissociation of the sulfenanilide molecule I before an intramolecular change can take place.

We have also found that the amine, *o*-chloroaniline, will not displace the anilide group in sulfenanilide compounds I although a normal rearrangement does take place upon heating. Thus, if 2-nitrobenzene-sulfenanilide I is heated at 180–190° with an excess of *o*-chloroaniline rearrangement takes place with formation of the sulfide II. Under similar conditions the corresponding sulfen-*o*- and *p*-toluidides undergo a similar rearrangement without being displaced from the molecule by the *o*-chloroaniline. It was found, however, that the *o*-chloroanilide group, when present in the sulfenanilide molecule, is easily displaced by other amines. For example, 2-nitrobenzene-sulfen-*o*-chloroanilide gave the sulfide II when heated at a temperature of 180–190° in the presence of an excess of aniline. Similar transformations were accomplished by heating the *o*-chloroanilide with *o*- and *p*-toluidine. In all three cases the *o*-chloroaniline group was displaced smoothly. These results indicate that the reactivity of the aromatic amines used determines whether there is a displacement of the group already present in the sulfenanilide molecule before a rearrangement takes place.

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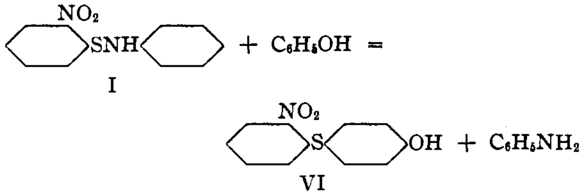
[4] Cohn and Fischer, *Ber.*, **33**, 2586 (1900).

An attempt was made to prepare directly aromatic sulfide phenols VI by heating compounds of the sulfenanilide type I with an excess of a phenol



but without success. The phenol served merely as a solvent and the final result under such experimental conditions is a normal rearrangement of the sulfenanilide I to its isomeric aminophenyl sulfide II.

Experimental Part

2,4-Nitrochlorobenzene-sulfenanilide.—The 2,4-nitrochlorobenzene-sulfenyl chloride used here was prepared by allowing chlorine gas to react with di-(2,4-nitrochlorophenyl) disulfide[5] according to the method of Zincke.[6] 2,4-Nitrochlorobenzene-sulfenyl chloride (25 g.) dissolved in anhydrous ether (500 ml.) was allowed to react with aniline (23 g.) dissolved in ether (50 ml.). The aniline solution was added slowly through a reflux condenser to the 2,4-nitrochlorobenzene-sulfenyl chloride solution. A precipitate of aniline hydrochloride immediately formed and sufficient heat was evolved to boil the ether. After standing for one hour the aniline hydrochloride was then removed by filtration and the ether expelled by distillation when the sulfenanilide crystallized as an orange-yellow solid; yield 33 g. It crystallized from alcohol, m. p. 102° and was soluble in the ordinary organic solvents but insoluble in dilute hydrochloric acid.

Anal. Calcd. for $C_{12}H_9O_2N_2SCl$: N, 9.98; S, 11.41; Cl, 12.66. Found: N, 9.82, 9.97; S, 11.15, 11.25; Cl, 12.46, 12.63.

2,4-Nitrochlorobenzene-sulfen-*o*-toluidide.—From 2,4-nitrochlorobenzene-sulfenyl chloride (25 g.) and *o*-toluidine (24 g.); yield 28 g. It crystallized from alcohol as bright glistening orange-red platelets; m. p. 127°.

Anal. Calcd. for $C_{13}H_{11}O_2N_2SCl$: N, 9.51; S, 10.87; Cl, 12.06. Found: N, 9.54, 9.67; S, 10.47, 10.70; Cl, 12.02, 12.14.

2-Nitrobenzene-sulfen-*o*-chloroanilide.—From 2-nitrobenzene-sulfenyl chloride (25 g.) as previously prepared[7] and *o*-chloroaniline (32 g.). This reaction proceeded much slower than expected and the *o*-chloroaniline hydrochloride did not settle out completely until after the ether solution had stood for at least two hours; yield 33 g. It crystallized from alcohol in bright yellow crystals melting at 130°. The compound is only slightly soluble in alcohol but is easily soluble in the ordinary organic solvents.

Anal. Calcd. for $C_{12}H_9O_2N_2SCl$: N, 9.98; S, 11.41; Cl, 12.66. Found: N, 10.11, 10.14; S, 11.62, 11.48; Cl, 12.95, 12.80.

4-Nitrobenzene-sulfen-*o*-chloroanilide.—*p,p'*-Dinitrodiphenyl disulfide[8] (25 g.) was suspended in ice-cold anhydrous chloroform (250 ml.) and treated with chlorine gas until all the solid was dissolved. The excess of chlorine gas was then removed by distillation of the chloroform under reduced pressure to a volume of 150 ml. and then made up to a volume of 400 ml. with anhydrous ether. This solution of 2-nitrobenzene-sulfenyl chloride was subsequently treated with *o*-chloroaniline (32 g.) dissolved in ether (100 ml.) when the sulfenanilide above was obtained in a yield of 23 g. of crude material. This was contaminated with 4,4'-dinitrodiphenyl disulfide and after final purification by washing with ether the yield was reduced to 8 g. This was recrystallized from alcohol, m. p. 99–101°. It is immediately converted to 4,4'-dinitrodiphenyl disulfide by treatment with dilute hydrochloric acid.

Anal. Calcd. for $C_{12}H_9O_2N_2SCl$: N, 9.98; S, 11.41; Cl, 12.66. Found: N, 9.84, 10.06; S, 11.20, 11.31; Cl, 12.51, 12.40.

Rearrangements by Heating. 2,4-Nitrochlorophenyl-4'-aminophenyl Sulfide.—From 2,4-nitrochlorobenzene sulfenanilide (10 g.) when heated for six hours at 150–160°, according to our previous procedure.[4] Recrystallization from alcohol gave a product crystallizing as bright, glistening yellow plates, m. p. 127–129°. The sulfide was easily soluble in the ordinary organic solvents, and the hydrochloride was difficultly soluble in water. The hydrochloride was obtained in crystalline form by dissolving the free base in ether solution and slowly adding concentrated hydrochloric acid, m. p. 215–225°.

Anal. Calcd. for $C_{12}H_9O_2N_2SCl$: N, 9.98; S, 11.41; Cl, 12.66. Found: N, 9.96, 9.89; S, 11.30, 11.14; Cl, 12.90, 12.79.

The sulfide was obtained with better results by heating the sulfenanilide (10 g.) with an excess of aniline (20 ml.) at 180–190° for six hours. The mixture was worked up according to the previous procedure and 5 g. of material obtained. It was purified by crystallizing from alcohol after decolorizing with norite, m. p. 129°.

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[5] This compound was prepared by the procedure given for *o,o'*-dinitrodiphenyl disulfide as described by Bogert and Still, "Organic Syntheses," John Wiley & Sons, Inc., New York, 1928, Vol. VIII, p. 64.

[6] Zincke, *Ann.*, **416**, 111 (1918).

[7] Moore and Johnson, THIS JOURNAL, **57**, 1517 (1935).

[8] This compound was prepared by the procedure given for *o,o'*-dinitrodiphenyl disulfide[4] as used by Foss, Dunning and Jenkins [THIS JOURNAL, **56**, 1978 (1934)]. The results of this procedure are very unsatisfactory due to the formation of many by-products during the reaction. Fromm and Wittmann [*Ber.*, **41**, 2264 (1908)] have studied the conditions of this reaction in some detail. They have reported the isolation of 4,4'-dinitrodiphenyl sulfide, m. p. 154°, 4,4'-nitroaminodiphenyl sulfide, m. p. 142°, and the dinitrophenyl ether of azophenyl-*p*-dimercaptan, m. p. 164°, as well as the desired compound, 4,4'-dinitrodiphenyl disulfide, m. p. 181°. The Russian workers Voraghtzow and Krihov [*J. Gen. Chem.* (U. S. S. R.), 2939 (1932)] have isolated and identified two isomers of the disulfide present in the mixture, *i. e.*, $(NO_2C_6H_4)_2S{:}S$, m. p. 134° and the symmetrical compound, m. p. 181°. In our results following the above procedure we have isolated all of the above substances in varying quantities but have found the largest quantity present to be the dinitrodiphenyl sulfide. We have separated 60–75 g. of the desired disulfide, m. p. 181°, from 200 g. of the reaction product (m. p. 120–130°) by treatment with boiling benzene. All of the above materials will dissolve in the benzene except the symmetrical disulfide. This is obtained in fair purity, m. p. 172–179°, in this one step but the yield is relatively low. Further separation of the desired material from the soluble mixture involves considerable time and effort.

TABLE I

In these first eight experiments it is shown that the excess of amine present could displace the anilide group in the sulfenanilide molecule followed by rearrangement to give an "aminophenyl sulfide" when heated at 180–190°. In experiments 9, 10 and 11 it is shown that *o*-chloroaniline is not able to displace the anilide group in the sulfenanilide but that a normal rearrangement takes place without the *o*-chloroaniline taking part in the change.

	Sulfenanilide	Amine	Sulfide	M. p., °C.	Yield, %
1	2-Nitrobenzene-sulfenanilide[6]	*o*-Toluidine	2-Nitrophenyl-3′-methyl-4′-	101–103	60
2	2-Nitrobenzene-sulfenanilide	*p*-Toluidine	2-Nitrophenyl-5′-methyl-2′-	105–107	55
3	2-Nitrobenzene-sulfen-*o*-toluidide	Aniline	2-Nitrophenyl-3′-	103–105	65
4	2-Nitrobenzene-sulfen-*o*-toluidide	*p*-Toluidine	2-Nitrophenyl-5′-methyl-2′-	105–107	60
5	2-Nitrobenzene-sulfen-*p*-toluidide	Aniline	2-Nitrophenyl-4′-	103–105	70
6	2-Nitrobenzene-sulfen-*p*-toluidide	*o*-Toluidine	2-Nitrophenyl-3′-methyl-4′-	101–103	60
7	2-Nitrobenzene-sulfen-*o*-chloroanilide	*o*-Toluidine	2-Nitrophenyl-3′-methyl-4′-	101–103	40
8	2-Nitrobenzene-sulfen-*o*-chloroanilide	*p*-Toluidine	2-Nitrophenyl-5′-methyl-2′-	105–107	35
9	2-Nitrobenzene-sulfenanilide	*o*-Chloroaniline	2-Nitrophenyl-4′-	105–106	70
10	2-Nitrobenzene-sulfen-*o*-toluidide	*o*-Chloroaniline	2-Nitrophenyl-3′-methyl-4′-	101–103	70
11	2-Nitrobenzene-sulfen-*p*-toluidide	*o*-Chloroaniline	2-Nitrophenyl-5′-methyl-2′-	105–107	60

2,4-Nitrochlorophenyl-3′-methyl-4′-aminophenyl Sulfide.—From 2,4-nitrochlorobenzene-sulfen-*o*-toluidide (10 g.) when heated with *o*-toluidine (15 ml.) in a yield of 6 g. Purification from alcohol after digesting with norite gave bright yellow prisms, m. p. 113–115°. A portion of the aminophenyl sulfide readily dissolved in ether and upon the addition of concentrated hydrochloric acid, gave a colorless precipitate of the hydrochloride, m. p. 216–220°.

Anal. Calcd. for $C_{13}H_{33}O_2N_2SCl$: N, 9.51; S, 10.87; Cl, 12.06. Found: N, 9.41, 9.36; S, 10.94, 10.80; Cl, 12.06, 12.20.

4-Nitrophenyl-3′-chloro-4′-aminophenyl Sulfide.—From the 4-nitrobenzene-sulfen-*o*-chloroanilide (m. p. 99–101°) when heated with boiling *o*-chloroaniline. The material was purified by dissolving in a mixture of ether–petroleum ether, boiling with norite and slowly evaporating. Yellow crystals were obtained, m. p. 127–129°. The free base was readily soluble in ether and gave a colorless crystalline hydrochloride.

Anal. Calcd. for $C_{12}H_9O_2N_2SCl$: N, 9.98. Found: N, 10.37, 10.11.

Rearrangement of Sulfenanilides by Heating in the Presence of an Excess of Aromatic Amines.—Our general procedure was to place 5 g. of the sulfenanilide in 10 ml. of the aromatic amine and heat on an oil-bath at a temperature of 180–190° for four hours. The reaction fluid was then poured into dilute hydrochloric acid solution with vigorous stirring and cooled in an ice-bath. The solid hydrochloride of the rearrangement product was filtered off and dissolved in alcohol. This solution was then neutralized with 5% sodium hydroxide solution, decolorized by boiling several times with norite, and the free aminophenyl sulfide separated by crystallization after cooling in an ice-bath. The reaction product in each case was identified by mixed melting points with the known amino sulfides. The results are tabulated in Table I.

Reaction in Acidic Alcoholic Solution.—2-Nitrobenzene-sulfenanilide I (5 g.) was dissolved in alcohol (25 ml.) and gently refluxed after concentrated hydrochloric acid (3 ml.) was added. If the refluxing was discontinued at the end of fifteen minutes the sulfenanilide was recovered whereas if the refluxing was continued for some time, *o,o*′-dinitrodiphenyl disulfide began to be formed and at the end of about two hours all the sulfenanilide had been converted into the insoluble disulfide, m. p. 193–195°.

Summary

1. A study of the rearrangement of the sulfenanilide type of compounds to their isomeric aminophenyl sulfides has been continued, and several new applications have been made of the rearrangement.

2. These rearrangements are influenced by the presence of other aromatic amines. The anilide group is replaceable when the sulfenanilide is warmed with another amine giving the corresponding aminophenyl sulfide.

3. The amine, *o*-chloroaniline, fails to respond in this replacement reaction. On the other hand its rearrangement is possible when it occurs in sulfenanilide combinations.

4. All sulfenanilides are decomposed by action of acids with formation of organic disulfides and an amine.

NEW HAVEN, CONN.

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