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THE ACTION OF SULFUR UPON PARA-TOLUIDINE IN THE PRESENCE OF LITHARGE. THIO-PARA-TOLUIDINE, ITS CONSTITUTION AND SOME NEW DERIVATIVES

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Introductory

When *p*-toluidine and sulfur are heated together, various products are formed depending upon the proportions of initial materials, temperature and duration of the heating, presence or absence of such hydrogen sulfide absorbents as litharge, and other factors. The commercially important products are dehydrothio-*p*-toluidine and primuline, but one of the simplest is the "thio-*p*-toluidine" first isolated by Merz and Weith[1] from a melt obtained by heating *p*-toluidine with sulfur at 140° in the presence of litharge.

The literature concerning the structure of this latter compound is inconclusive and contradictory. Merz and Weith merely gave the molecular formula as $C_{14}H_{16}N_2S$. In fact, they even failed to state until 15 years later[2,3] which toluidine they used. Truhlar[4] investigated the compound quite extensively, at the request of Professor Merz, and prepared a large number of derivatives, but did not commit himself further regarding the constitution of the base than to write the formula as $(CH_3.C_6H_3.NH_2)_2S$ and to propose the name "amidothio-*p*-tolyl." Dahl and Co.[3,5] patented certain of the azo dyes obtainable from this amine, characterizing the base as "thio-*p*-toluidine (of melting point 103°)." Green,[6] however, adopted Formula II, but without citing any experimental proof in support thereof, and expressed the opinion that it was the antecedent substance from which both dehydrothio-*p*-toluidine and primuline were formed by further action of sulfur, since he had actually obtained[7,8] primuline from it in this way. Subsequently[9] he changed his views regarding the origin of the dehydrothio-*p*-toluidine and suggested a different explanation. In 1890, Purgotti[10] removed the amino groups through the diazo reaction and stated that he obtained a di-*o*-tolyl sulfide, from which he concluded that the Merz

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[1] Merz and Weith, *Ber.*, **4**, 393 (1871).

[2] Merz and Weith, *Ber.*, **19**, 1571, footnote (1886).

[3] Dahl and Co., Ger. pat. 34,299; *Friedlaender*, 1, 534 (1885).

[4] Truhlar, *Ber.*, **20**, 664 (1887).

[5] Dahl and Co., Brit. pat., 14,232 (1885).

[6] Green, *J. Chem. Soc.*, 55, 233 (1889).

[7] Ref. 6, p. 227.

[8] Green, *Ber.*, **22**, 968 (1889).

[9] Green, Thorpe's, "Dictionary of Applied Chemistry, Longmans and Co., 1913, vol. 4, p. 386.

[10] Purgotti, *Gazz. chim. ital.*, **20**, 31 (1890).

and Weith base should be represented by Formula III. Beilstein[11] gives the preference to Formula II.

Hence, it seemed to us worth while to study this problem somewhat more fully, so as to establish definitely the constitution of the Merz and Weith base and to determine under what conditions, if any, it could be converted into dehydrothio-*p*-toluidine. As set forth in what follows, we believe that we have solved the first of these two problems, but the work upon the second is unfinished and the report thereon must be deferred to a later communication.

The plan of attack involved the preparation of the base by the Merz and Weith method, examination of the product and comparison of the same with ditolyl sulfides synthesized in other ways.

In the repetition of the process of Merz and Weith, it was found far more satisfactory to isolate the products from the crude melt by a method which rested upon the assumption of a sufficient difference in basicity to permit their successive extraction from a benzene solution by a series of acids each stronger than its predecessor. In this way, *p*-toluidine, thio-*p*-toluidine and dithio-*p*-toluidine were isolated.

Purgotti[10] prepared di-*o*-tolyl sulfide (*o*-cresyl sulfide) from *o*-toluidine by the customary diazo-reaction, and described his product as an oil, boiling at 285°. Since the product he obtained by de-amination of the Merz and Weith base was similar in appearance and boiled at 284–286°, the two were regarded as identical, although he gave no analytical data or other criteria of purity or of identity. Both Zeiser[12] and Mauthner,[13] however, have since shown that pure di-*o*-tolyl sulfide is a solid, which melts at 64° and boils at 174° at 15 mm. pressure. Purgotti's product, therefore, must have been either very impure or something else. Mauthner prepared also the di-*m*-tolyl sulfide as a colorless oil, boiling at 174° at 12 mm. pressure, and the *o*-tolyl-*m*-tolyl sulfide as a colorless and odorless oil, boiling at 170° at 11 mm. pressure. There is thus but little difference in the boiling points of the three isomers and, as a means of identifying such isomers, it is consequently of little value.

On repeating Purgotti's experiment for the elimination of the amino groups from the Merz and Weith base, much difficulty was encountered in our efforts to get a product of unquestionable purity. Our lack of success here corresponded with that of Truhlar,[4] who found it impossible to replace the amino groups by halogen or cyanogen through the diazo reaction, although he did succeed in getting the phenol finally.

The sulfide obtained from the Merz and Weith base by de-amination

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[11] Beilstein, "Handbuch der Organischen Chemie," Leopold Voss, 3d ed., **1903**, II, 821, and Suppl., II, 483.

[12] Zeiser, *Ber.*, **28**, 1674 (1895).

[13] Mauthner, *Ber.*, **39**, 3595 (1906).

therefore was easily oxidized to the sulfone, forming colorless crystals melting sharply at 94°, and whose analysis gave figures agreeing closely with those calculated for a ditolyl sulfone. Di-*o*-tolyl sulfone has been reported[10] as melting at 134–135°, and the di-*p*-tolyl isomer[14,15] at 158°, but we failed to find in the literature any record of the di-*m*-tolyl sulfone. It is obvious, however, that Purgotti was in error in concluding that the sulfide obtained by de-aminating the Merz and Weith base was the di-*o*-tolyl compound, as he would have discovered very quickly himself had he carried his work one step farther and oxidized it to the sulfone.

It remained, then, to check the accuracy of the deduction that our sulfone melting at 94°, and its antecedent sulfide, were actually the *meta* compounds, and this was accomplished by synthesizing di-*m*-tolyl sulfide from *m*-iodotoluene and sodium *m*-thiocresylate. In this undertaking, it was found advantageous to prepare the necessary *m*-thiocresol from benzaldehyde-*m*-sulfo acid, rather than by the methods hitherto recorded in the literature. When this synthetic di-*m*-tolyl sulfide was oxidized, it yielded a sulfone identical in appearance with that obtained from the deaminated Merz and Weith base and which also melted sharply at 94°. An intimate mixture of the two melted at the same point.

Further, among the by-products of the thio-*p*-toluidine melt, there was found a yellowish-brown, waxy solid, which formed a beautifully crystalline acetyl derivative, melting at 213° (corr.). The analysis of this acetyl derivative showed that it contained carbon and hydrogen in the proportion present in a bis(acetaminotolyl) disulfide, $(CH_3CONH(CH_3)C_6H_3)_2S_2$. Jacobson and Ney[16] have described the diacetyl derivative of bis(2-amino-5-methylphenyl) disulfide (V) as crystallizing in similar form and as melting at 204–206°.

These facts seem to us to justify the conclusion that thio-*p*-toluidine should be represented by Formula II, and not by III. Of course, this does not exclude the possibility of III, or even IV, being formed also in the thio-*p*-toluidine melt, but we have uncovered no proof of their presence or of dehydrothio-*p*-toluidine. Nor have we encountered either *p*-amino dithiobenzoic acid, $H_2NC_6H_4CSSH$, or its *p*-toluidide, which Green[9] suggested as intermediate products in the conversion of *p*-toluidine into dehydrothio-*p*-toluidine. It is quite likely, on the other hand, that small amounts of stilbene derivatives are formed in this reaction, since Aronstein and van Nierop[17] found that on long (120 hours) boiling of toluene with sulfur, hydrogen sulfide was liberated and some stilbene produced,

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[14] Otto and Beckurts, *Ber.*, 11, 2068 (1878).

[15] Crafts, *Ber.*, **12**, 1177 (1879).

[16] Jacobson and Ney, *Ber.*, **22**, 908 (1889). See also Rassow and Reim, *J. prakt. Chem.*, [2] **93**, 216 (1916).

[17] Aronstein and van Nierop, *Rec. trav. chim.*, 21, 450 (1902).

and our own experiments have demonstrated the fact that sulfur acts much more vigorously upon toluene in the presence of litharge, or other hydrogen sulfide absorbents, likewise with formation of stilbene.

Our experiments then indicate that when *p*-toluidine is heated with sulfur, in the presence of litharge and at a temperature of 140–145°, the main course of the reaction is the formation first of the mercaptan (I). This, then, through the simultaneous oxidizing influence of sulfur and litharge, unites with unchanged *p*-toluidine to thio-*p*-toluidine (II), while small amounts (generally not over 5%) escape this reaction and are oxidized directly to the disulfide (V). In the absence of litharge, and at the higher temperatures employed (180–220°) for the manufacture of dehydrothio-*p*-toluidine and primuline, the mercaptan condenses with the methyl group of unchanged *p*-toluidine, instead of with its nuclear hydrogen, thus generating a compound which is more stable than thio-*p*-toluidine under these conditions of temperature. This deduction as to the course of the reaction by which dehydrothio-*p*-toluidine (VI) is formed from *p*-toluidine and sulfur, is in accord with the surmise of Friedlaender.[18] Conversely, Gattermann and Pfitzinger[19] have shown that when dehydrothio-*p*-toluidine is fused with potassium hydroxide, it is hydrolyzed to the mercaptan (I) and *p*-aminobenzoic acid. Schultz and Beyschlag[20] treated *m*-tolylene diamine with sulfur in boiling alcohol solution and obtained a bis(2,4-diamino-5-methylphenyl) polysulfide, proving that here also the sulfur entered *meta* to the methyl group and *ortho* to the amino.

We have tried in vain to convert thio-*p*-toluidine into dehydrothio-*p*-toluidine by the action of heat alone, and also in the presence of sulfur or of *p*-toluidine. These experiments are being continued since, as already mentioned, Green obtained primuline from thio-*p*-toluidine and sulfur. The explanation of this apparent discrepancy may lie in the fact that "primuline" is really the name not of a chemical individual but of a group of compounds of high molecular weight, produced from *p*-toluidine and sulfur at elevated temperatures, through elimination of varying amounts of hydrogen sulfide. The manner in which the *p*-toluidine residues combine, and the number of residues so uniting, differ considerably, but all have certain tinctorial properties in common. The constitution of most of them is still unknown.

Through its diacetyl derivative, thio-*p*-toluidine was oxidized to bis(2-acetamino-5-carboxyphenyl) sulfone, which was then de-acetylated (VII) and the product esterified. It is hoped that some of the esters so accessible may exhibit the local anesthetic properties characteristic of *p*-aminobenzoic esters (benzocaine, propaesin, cycloform, etc.), for the physio-

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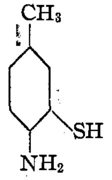
[18] Friedlaender, *Fortschritte Teerfarb.*, **7**, 481 (1905).

[19] Gattermann and Pfitzinger, *Ber.*, **22**, 1066 (1889).

[20] Schultz and Beyschlag, *Ber.*, **42**, 743 (1909).

logical effects of the sulfonals appear to depend mainly upon the alkyl groups present and not upon the sulfone bridges.

The disulfide (V) corresponding to thio-*p*-toluidine was discovered by Jacobson and Ney.[16] It is a homolog of the bis(2-aminophenyl) disulfide originally described by Hofmann[21] and recently put upon the market as a remedy for syphilis under the name of "Intramin." The isomeric disulfides from 2-amino-4-methylphenyl mercaptan[22] and 4-amino-2-methylphenyl mercaptan[23] are also known. It is a matter of some historical interest that the diacetyl derivative of dithio-*p*-toluidine (V) agrees closely in crystalline form, solubilities and melting point, with what Truhlar[4] thought was the diacetyl derivative of thio-*p*-toluidine itself. Our experiments have shown that when crude thio-*p*-toluidine, containing even very small amounts of the disulfide, is acetylated, it is the diacetyl derivative of the disulfide which separates immediately and not that of thio-*p*-toluidine. This would account for Truhlar's error, except for the fact that his analytical figures check for the mono- and not for the disulfide derivative.



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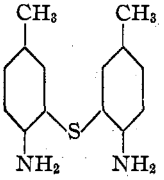

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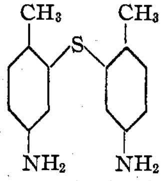

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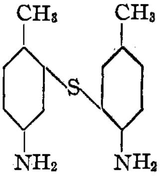

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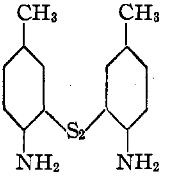

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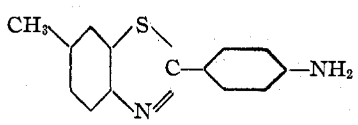

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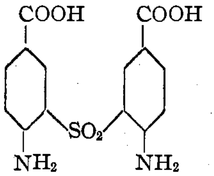

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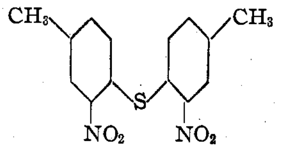

(VIII)

Experimental Part

Fusion of *p*-Toluidine and Sulfur, and Treatment of the Crude Melt.—The claim of the Dahl patent[3] that a yield of thio-*p*-toluidine amounting to about 60% of that

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[21] Hofmann, *Ber.*, **12**, 2363 (1879).

[22] *Ber.*, **42**, 4310 (1909).

[23] *Ber.*, **45**, 1496, 1501 (1912).

calculated can be obtained by the Merz and Weith process is not in agreement with our experience, for our yields of pure product (m. p., 103–104° corr.) were invariably far below that figure. We found it advisable, therefore, to modify the method somewhat, as explained in what follows.

A mixture of 1070 g. of *p*-toluidine (10 moles) and 320 g. of sulfur (10 equivalents) was melted in a suitable flask, and the temperature of the melt raised gradually to 140–145°, where it was maintained while litharge was added slowly in small amounts and with vigorous stirring, until further addition no longer caused effervescence or rise of temperature. Usually, this condition was attained after some 1600 g. of litharge had been added during 6 hours.

In most cases, the reaction proceeded quite smoothly with evolution of steam, but occasionally the flask boiled over without apparent cause. This was due neither to the rate of addition of the litharge, nor to any detectable impurity in the latter.

The presence of iron or nickel wool (sometimes partially oxidized), or substitution of other oxides or carbonates for the litharge, with the object of providing an absorbent for hydrogen sulfide which would not react as rapidly with free sulfur, failed to improve the yield of final product. With ferric or zinc oxide, no reaction occurred even at 165°. With lead carbonate, a reaction took place at 165–170°, but the higher temperature necessary offset any advantage which might have been inherent in this substitution.

It seemed not unlikely that the thio-*p*-toluidine as formed was attacked by the unchanged sulfur present and that the velocity of this decomposition was determined by the concentrations of thio-*p*-toluidine and of sulfur, and the temperature and duration of the heating. Under the conditions noted above, equilibrium appeared to have been reached when the amount of thio-*p*-toluidine present was such as to give a final yield of approximately 30% of that calculated from the *p*-toluidine actually consumed in the operation. In support of this assumption, it was found that an increase in the amount of sulfur used in the reaction resulted in no increase in the yield of thio-*p*-toluidine, but a decrease in the weight of *p*-toluidine recovered and the formation of more tarry by-products. Similarly, any considerable prolongation of the heating after the requisite amount of litharge had been added tended to diminish the yield.

Upon completion of the reaction, the melt was agitated with 3 to 4 liters of boiling 95% alcohol, some "Sil-o-Cel" added, and the mixture filtered hot, giving a dark brown filtrate. Addition of an alcoholic solution of oxalic acid to this filtrate precipitated the *p*-toluidine quantitatively as oxalate, free from sulfur compounds, and proved a rapid and convenient way of following the progress of the reaction in the smaller scale preliminary experiments. It was not the best way, however, of recovering the *p*-toluidine in the major runs, when it was desired to isolate also the other products of the reaction. The usual method of procedure was to distil the alcohol from this filtrate, take up the residue in benzene and extract the benzene solution with acids of increasing strength. Benzene was not used for the preliminary extraction of the melt, since it rendered the filtration from the lead sulfide sludge much more tedious and troublesome. The residue obtained by evaporating the alcohol from the filtrate mentioned, amounting to about 1080 g. generally (equivalent to 88% of the combined weight of initial *p*-toluidine plus half the sulfur), was poured into 1500 cc. of benzene.

Extraction of the benzene solution with aqueous solutions of different acids was carried out in a tall cylinder equipped with a mechanical stirrer and siphon, for this was found to be more satisfactory than the use of a large separatory funnel.

An unstable salt with one of the products of its hydrolysis constantly withdrawn into another phase should be almost completely hydrolyzed, while a more stable one, under identical conditions would remain but little affected. Hence, in the case of two immiscible solvents, such as benzene and water, in one of which the free base is the more soluble, and in the other the salt, it should be possible to extract a benzene solution of free bases with aqueous solutions of suitable acids, thus forming a series of salts of which only those of the stronger bases would be stable in the presence of the other phase and remain in the aqueous extract. Thus, by selection of the proper acids, of gradually increasing ionization constants, the attempt was made to extract the various bases seriatim. In the absence of exact quantitative data concerning the strength of the bases to be extracted, it was assumed that the order of basicity was probably *p*-toluidine > thio-*p*-toluidine > dithio-*p*-toluidine. The acids chosen were acetic (k = 0.000018), citric (k = 0.00081), tartaric (k = 0.00109), oxalic (k = 0.10), and sulfuric. These values for k are all at the uniform temperature of 25°. Dilute (15%) acetic acid failed to extract all of the *p*-toluidine. Dilute (15%) citric acid extracted practically all of the *p*-toluidine, with only traces of thio-*p*-toluidine. Tartaric acid likewise extracted the *p*-toluidine, but formed with it a more difficultly soluble salt and so was less satisfactory.

Successive extractions of the benzene solution were conducted, therefore, with 1 liter portions of dilute (15–20%) citric acid, and the temperature was kept at 25° to avoid separation of *p*-toluidine citrate, which is rather difficultly soluble at lower temperatures. The separated extracts were neutralized with ammonia, and *p*-toluidine was precipitated in small colorless crystals. Those obtained from the first extraction often showed a reddish tinge, due to traces of an impurity which possessed the properties of an indicator, giving a yellow solution with acids and a red one with bases. When further extraction with citric acid yielded on neutralization only a slight turbidity, the remaining citric acid was removed from the benzene layer by washing it once with water. Five or six extractions in this way with citric acid yielded 320 g. of pure *p*-toluidine.

The benzene layer was extracted next with a saturated aqueous solution of oxalic acid, also used in 1-liter portions. The yellow extracts were united and diluted with at least an equal volume of water, to provide for the rather low solubility of ammonium oxalate, and then neutralized with ammonia. The crude thio-*p*-toluidine thus precipitated was light yellow and fairly pure (m. p., about 100°), except that separated from the final extraction, which was apt to be colored a darker yellow from contamination by small amounts of the disulfide. Four or five extractions yielded 276 g. of crude thio-*p*-toluidine, equivalent to 32% of that calculated after allowing for the *p*-toluidine recovered. Since *p*-toluidine oxalate is but slightly soluble in water or the more common organic solvents, it was very easy to determine whether any *p*-toluidine had escaped the citric acid extraction.

During the final oxalic acid extractions, a heavy viscous tar separated in the extraction cylinder, thus giving a 3-phase system, composed of an upper benzene layer, an intermediate aqueous oxalic acid layer, and a lower one of tar. After siphoning off the oxalic layer, the benzene layer and tar were washed with water, the water was separated and the benzene layer decanted from the tar.

Extraction of the benzene layer was then resumed, using dilute (10%) sulfuric acid. Neutralization of the sulfuric acid extracts gave 40 g. of a yellow, waxy solid, which proved to be the crude disulfide (V). The yield of this never exceeded 5% of the weight of the *p*-toluidine entering into reaction. Some tar separated also in these extractions.

The extracted benzene solution was finally evaporated and the dark viscous residue boiled with concd. hydrochloric acid and filtered. When this hydrochloric acid extract was poured into water, a small amount of yellow solid precipitated, but it was not dehydrothio-*p*-toluidine (VI), for its alcoholic solution exhibited no fluorescence.

The tar separated during the oxalic acid extractions was digested with fresh benzene, in the presence of a 5% sodium hydroxide solution, to recover any organic bases present. The benzene layer was separated and the solvent driven off. There remained 35 g. of a heavy, greenish oil. The tar separating from the sulfuric acid extractions was treated similarly, and yielded 70 g. of a dark bluish oil. Neither acetyl nor benzoyl derivatives could be prepared from either of these oils. Addition of phenyl isocyanate to their benzene solutions precipitated amorphous solids, insoluble in the usual organic solvents, with the exception of nitrobenzene, from which they deposited in a greenish, pulverulent form.

Thio-*p*-toluidine (II).—The crude thio-*p*-toluidine, obtained as described above, was dissolved in hot dil. (10%) hydrochloric acid, and to this hot solution concd. hydrochloric acid was added until precipitation began. As the solution cooled, pale yellowish needles of the hydrochloride separated. These were dissolved in hot water, the solution was heated with animal charcoal, filtered, and ammonia added in excess to the filtrate. Thio-*p*-toluidine separated as a pale yellow powder, melting at 102–103°, sufficiently pure for most purposes. The yield was 80% of the crude substance. A single crystallization from dil. alcohol gave a pure product in lustrous, colorless scales; m. p., 103–104° (corr.). This melting point was not altered by further crystallization and agrees with that reported by other investigators.

The picrate, benzoyl derivative (m. p., 186°), and urethan (m. p., 113°), were also prepared and agreed entirely with Truhlar's description of them.

Diacetyl Derivative.—This was obtained by the action of acetic anhydride, or of acetyl chloride, upon the base. It crystallized from alcohol in large rhombic plates; m. p., 165° (corr.).

Analyses. Calc. for $C_{18}H_{20}O_2N_2S$: C, 65.85; H, 6.10; S, 9.76. Found: C, 65.76, 65.85; H, 5.91, 5.78; S, 9.46.

As noted in the introductory portion of this paper, this product is not the same as the one (m. p., 211°) which Truhlar believed to be the diacetyl derivative of thio-*p*-toluidine, nor have we been able to obtain his product from pure thio-*p*-toluidine, although many different methods of acetylation were applied.

Di-*m*-tolyl Sulfide.—Forty-one g. of thio-*p*-toluidin was dissolved in 200 cc. of alcohol, 28 cc. of concd. sulfuric acid added, and the mixture warmed until a clear solution resulted. This solution was stirred vigorously during preliminary cooling, so that whatever sulfate separated would be in a finely divided state. The mixture was then further cooled to 0–5°, and maintained at that temperature, with constant stirring, while a solution of 27.2 g. of sodium nitrite in 45 cc. of water was run in slowly. After all the nitrite had been added, the dark red solution was left at 0° for 3 hours. Four g. of copper powder was then added. A slow evolution of gas commenced immediately and the temperature of the solution gradually rose. After standing overnight at laboratory temperature, the solution was boiled for 2 hours under a reflux condenser and then distilled at 100°, to remove aldehyde, alcohol and water. The tarry residue was extracted with chloroform, the extracts dried over calcium chloride and fractionated under diminished pressure. Six and a half g. of a pale amber, highly refracting oil was thus secured, boiling at 197° (23 mm.), 200° (25 mm.), and 202° (28 mm.). Purgotti[10] reported the boiling point of the ditolyl sulfide obtained by him from thio-*p*-toluidine (by the action of nitrous acid and alcohol) as 284–286° at atmospheric pressure, but gave no further information concerning his process or product, other than the bald statement that its analysis (not given) and other properties (not specified) proved it to be the di-*o*-tolyl sulfide (*o*-cresyl sulfide), identical with that prepared by him from *o*-toluidine.

In order to secure a di-*m*-tolyl sulfide of high purity, benzaldehyde-*m*-sulfo acid was converted into the benzalchloride-*m*-sulfochloride, which was reduced to *m*-thiocresol, and the sodium salt of the latter then condensed with *m*-iodotoluene in the presence of copper powder. This process starts with readily accessible materials, is neither difficult nor laborious, and gives an excellent yield of water-clear thiocresol.

Of the methods utilized by other investigators, toluene-*m*-sulfochloride[24] is not so easily obtainable, while the employment of *m*-toluidine as initial material is expensive

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[24] Huebner and Post, *Ann.*, **169**, 51 (1873).

and involves some risk of explosion in the conversion of the diazonium salt to the thiocresol through the xanthogenate.[25]

Benzaldehyde-*m*-sulfo acid was made from benzaldehyde and fuming sulfuric acid, by the method of Wallach and Wuesten.[26] Fifty-five g. of the aldehyde yielded 85 g. of the sodium *m*-sulfonate. From the dry salt and phosphorus pentachloride[27] the crude benzalchloride-*m*-sulfochloride was obtained. This was reduced directly by zinc dust and dil. sulfuric acid at 0°, giving the *m*-thiocresol as a colorless, highly-refracting liquid, of extremely disagreeable odor; b. p., 195°; yield, 18 g. from 75 g. of the sodium *m*-sulfonate, or 40%.

One g. of metallic sodium was dissolved in 18 cc. of absolute alcohol, 5.7 g. of *m*-thiocresol added and the alcohol distilled. To the residual, colorless solid were added 0.2 g. of copper powder and 10.6 g. of *m*-iodo-toluene, and the whole was heated for several hours at 235–240°. When cold, the mixture was treated with alcohol, the alcoholic solution acidified with sulfuric acid, some zinc dust added, and steam blown through as long as it carried over any oily distillate. The residual sludge was extracted with ether, the ethereal solution dried over calcium chloride and distilled. Three g. of di-*m*-tolyl sulfide was thus obtained as a pale yellowish, highly-refracting oil; b. p., about 290°. This is essentially the method of Mauthner.[13]

Di-*m*-tolyl Sulfone.—The di-*m*-tolyl sulfide thus synthesized was suspended in boiling 40% acetic acid and oxidized carefully by gradual addition of 5 g. of powdered potassium permanganate. The sulfone as formed collected with the manganese oxide sludge, from which it was extracted by alcohol. On crystallization from the same solvent, it was obtained in colorless needles; m. p., 94°. Five g. of the sulfide yielded 3 g. of the sulfone.

Similar treatment of the ditolyl sulfide resulting from the de-amination of thio-*p*-toluidine gave a sulfone of the same appearance and melting point. An intimate mixture of the two also melted sharply at 94°. This sulfone from the thio-*p*-toluidine was analyzed.

Analyses. Calc. for $C_{14}H_{14}O_2S$: C, 68.29; H, 5.69. Found: C, 68.27, 68.19; H, 5.69, 5.51.

Bis(2-aceto-amino-5-methylphenyl) Sulfone, $(CH_3CONH(CH_3)C_6H_3)_2SO_2$.—Forty-four g. of thio-*p*-toluidine was acetylated with 45 cc. of acetic anhydride, and the reaction product poured into a solution of 300 cc. of glacial acetic acid in 400 cc. of water. The resulting solution was heated to boiling, and 48 g. of potassium permanganate dissolved in 250 cc. of hot water was added gradually in small amounts. The oxidation ensued rapidly and the solution was filtered hot from precipitated manganese oxides. Some of the sulfone crystallized from the filtrate as it cooled, and more was recovered therefrom by partially neutralizing the solution with ammonium hydroxide. From the precipitated manganese oxides also some was collected by extraction with alcohol. The total amount obtained was 35 g. It crystallized from alcohol in long prismatic needles; m. p., 225° (corr.).

Analyses. Calc. for $C_{18}H_{20}O_4N_2S$: C, 60.00; H, 5.55. Found: C, 60.37; H, 5.66.

Three g. of this sulfone was heated for several hours at 180° with 15 cc. of concd. sulfuric acid, and then for 30 minutes longer at 300°. The cooled solution was poured upon twice its volume of ice. A small amount of tar separated and was removed. By further dilution of the filtrate, 2 g. of yellow solid was precipitated, which proved to be the de-acetylated sulfone (m. p., 206°) described beyond. No toluidine sulfo acids were found among the products.

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[25] Bourgeois, *Rec. trav. chim.*, **18**, 449 (1899).

[26] Wallach and Wuesten, *Ber.*, **16**, 150 (1883).

[27] Ger. pat. 239,311; *Chem. Zentr.*, 1911, II, 1394.

Bis(2-amino-5-methylphenyl) Sulfone.—The diacetyl derivative was hydrolyzed by boiling it with dil. (15%) sulfuric acid until a clear solution resulted. This warm solution was poured with stirring into an excess of ammonium hydroxide solution. The amino sulfone separated as a yellow powder, and was crystallized from alcohol, when it appeared in yellow granular crystals, melting at 210° (corr.), practically insoluble in water or in dilute acids; yield, 6 g. from 8.5 g. of the diacetyl derivative.

Analyses. Calc. for $C_{14}H_{16}O_2N_2S$: C, 60.87; H, 5.80. Found: C, 61.17, 60.77; H, 6.32, 5.99.

Bis(2-aceto-amino-5-carboxyphenyl) Sulfone.—Ten and eight-tenths g. of finely pulverized diacetyl-thio-*p*-toluidine (m. p., 165°) was added to a solution containing 32 g. of potassium permanganate and 24 g. of magnesium sulfate in 750 cc. of water. The mixture was boiled under a reflux condenser until the color of the permanganate was discharged, when it was filtered hot and the hot filtrate acidified with sulfuric acid. Eight g. of the dicarboxylic acid separated as a fine, white precipitate, insoluble in the common neutral organic solvents. It was purified by washing it with hot alcohol and then with ether, and showed a melting point (with decomposition) above 360°.

Analyses. Calc. for $C_{18}H_{16}O_8N_2S$: C, 51.43; H, 3.86. Found: C, 50.56, 52.48; H, 3.83, 4.07.

Bis(2-amino-5-carboxyphenyl) Sulfone (VII).—The free amino acid was prepared from its diacetyl derivative by boiling the latter with dil. (10%) sodium hydroxide solution and precipitating the filtrate with dil. hydrochloric acid. It was difficultly soluble in the ordinary organic solvents and likewise melted above 360° with decomposition.

Methyl Ester.—As obtained from the acid, methyl alcohol and hydrogen chloride, it crystallized from alcohol in thin, square, colorless tablets with ridged diagonals; m. p., 234° (corr.).

Analyses. Calc. for $C_{16}H_{16}O_6N_2S$: C, 52.70; H, 4.40. Found: C, 52.85, 52.94; H, 4.49, 4.67.

Ethyl Ester.—This was obtained as yellowish, transparent prisms (from alcohol); m. p., 206° (corr.).

Analyses. Calc. for $C_{18}H_{20}O_6N_2S$: C, 55.10; H, 5.10. Found: C, 55.14; H, 5.09.

Structurally, these esters are composed of two benzocaine (anesthesine) molecules united by a sulfone (sulfuryl) bridge, and hence might be expected to exhibit some local anesthetic action. Unfortunately, the solubility of the methyl and ethyl esters was too low to cause any pronounced physiological effects, as indicated by preliminary tests, but the field is being explored further, in the hope of discovering more soluble derivatives of therapeutic value.

Bis(2-nitro-4-methylphenyl) Sulfide (VIII).—Forty g. of crystallized sodium sulfide, $Na_2S.9H_2O$, and 88 g. of 4-iodo-3-nitrotoluene were dissolved in 300 cc. of alcohol, and the dark brown solution boiled for 12 hours under a reflux condenser. The alcohol was distilled and the residue poured into water. On standing overnight, 27 g. of a dark red oil collected. This was washed repeatedly with dilute acid and with alkali. After several days, it solidified partially, yielding 4 g. of crystals. Re-crystallized from acetone, it appeared in large, dark red, short prisms, giving a yellow powder when crushed; m. p., 125–126° (corr.).

Analyses. Calc. for $C_{14}H_{12}O_4N_2S$: C, 55.26; H, 3.95. Found: C, 55.21, 55.36; H, 3.85, 3.40.

Bis(2-aceto-amino-5-methylphenyl) Disulfide.—Ten g. of the crude dithio-*p*-toluidine obtained from the sulfuric acid extraction of the *p*-toluidine sulfur melt as already described, was treated with 12 cc. of acetic anhydride. Rapid solution occurred, with evolution of considerable heat, and the entire mass soon congealed to a brown crystalline magma. This was washed with water, and then crystallized repeatedly from alcohol, giving bunches of small, snow-white, silky needles; m. p., 213° (corr.). At higher temperatures, it sublimed with decomposition.

Analyses. Calc. for $C_{18}H_{20}O_2N_2S_2$: C, 60.00; H, 5.55. Found: C, 60.12, 60.28; H, 5.54, 5.80.

This compound agrees in appearance, solubility and percentage composition, with the acetyl derivative obtained by Jacobson and Ney[16] from the corresponding amine, except that they gave the melting point as 204–206°.

Bis(2-amino-5-methylphenyl) Disulfide (Dithio-*p*-toluidine) (V).—The diacetyl derivative was hydrolyzed by boiling it with concd. hydrochloric acid, the amine hydrochloride precipitating. It was dissolved in water, the base liberated by the addition of excess of ammonium hydroxide and purified by crystallization from dil. alcohol. Long, greenish needles were obtained; m. p., 88.5° (corr.). Jacobson and Ney gave its melting point as 89°.

Truhlar states that when he treated his thio-*p*-toluidine with a slight excess of acetic anhydride, crystals of the acetyl derivative soon appeared which when washed with water and crystallized from alcohol separated quickly and copiously in bundles of snow-white silky needles, melting at 211°.

Judging from the resemblance in melting point and other properties that what Truhlar believed to be the diacetyl derivative of thio-*p*-toluidine was actually the disulfide derivative, we prepared some crude thio-*p*-toluidine by the Merz and Weith process and subjected it to acetylation as described by Truhlar. The crystals which separated first were removed and recrystallized from alcohol, yielding small, snow-white, silky needles, melting at 213°, identical with the disulfide derivative just mentioned, and giving the disulfide (m. p., 88.5°) on hydrolysis. This same crude thio-*p*-toluidine, after being freed from all disulfide, yielded only the diacetyl derivative (m. p., 165°) of thio-*p*-toluidine recorded above.

Summary

1. The structure of the thio-*p*-toluidine of Merz and Weith is proved to be bis(2-amino-5-methylphenyl) sulfide.
2. The course of the action of sulfur upon *p*-toluidine, in the presence of litharge and at 140–145°, is shown to lead first to the formation of 4-amino-3-mercapto-toluene, part of which oxidizes to the disulfide, while the major portion reacts with more *p*-toluidine, yielding thio-*p*-toluidine.
3. The acetyl derivative described by Truhlar as a thio-*p*-toluidine compound is probably the disulfide derivative.
4. Certain derivatives of di-*m*-tolyl sulfide are recorded, as well as a new synthesis of *m*-thiocresol.
5. New derivatives of thio-*p*-toluidine also have been prepared and studied.

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