

3. These substances and chaulmoogrylacetic acid have been tested for bactericidal action against *B. leprae*.

4. A number of cyclopentane, cyclohexane and cinnamic acids and benzene derivatives have been tested for bacteriological effect on *B. leprae*.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

## THE MECHANISM OF REACTION BETWEEN THIONYLANILINE AND ORGANOMAGNESIUM HALIDES

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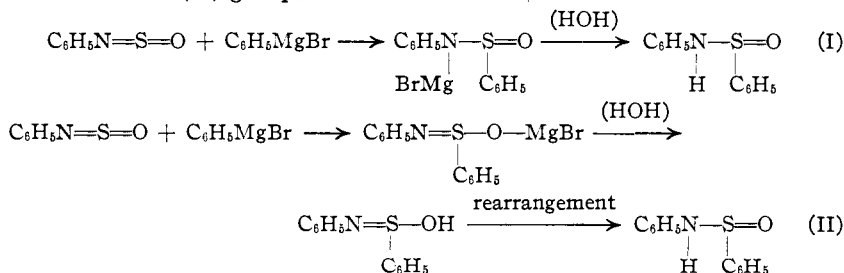
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### Introduction

Thionylamines ( $\text{RN}=\text{S}=\text{O}$ ) are related structurally to ketenes ( $\text{R}_2\text{C}=\text{C}=\text{O}$ ), isocyanates ( $\text{RN}=\text{C}=\text{O}$ ) and isothiocyanates ( $\text{RN}=\text{C}=\text{S}$ ). These different classes of compounds have a pair of terminal cumulated unsaturated groups and take part in a number of reactions in common. It has been proved that the ketenes,<sup>2</sup> isocyanates<sup>3</sup> and isothiocyanates<sup>3</sup> react under ordinary conditions with but one molecular proportion of  $\text{RMgX}$  compound. Addition is restricted exclusively to the terminal unsaturated group, the R of the  $\text{RMgX}$  compound attaching itself to carbon and the  $-\text{MgX}$  to oxygen and to sulfur, respectively.

When thionylaniline,  $\text{C}_6\text{H}_5\text{NSO}$ , the most representative of thionylamines, is treated with typical organomagnesium halides but one molecule of the latter adds under ordinary conditions and anilides of sulfinic acids result. These sulfinanilides may have resulted by either of two mechanisms, depending on whether addition took place at the  $-\text{N}=\text{S}-$  (I) or at the  $=\text{S}=\text{O}$  (II) group, as follows.



<sup>1</sup> This paper is an abstract of a thesis submitted by H. L. Morris in partial fulfillment of the requirements for the degree of Master of Science in Chemistry at Iowa State College in 1922. A preliminary account of the work was presented at the Birmingham, Alabama, meeting of the American Chemical Society, April 5-6, 1922 and abstracted in *Science*, **56**, 54 (1922).

<sup>2</sup> Gilman and Heckert, *THIS JOURNAL*, **42**, 1010 (1920).

<sup>3</sup> Gilman and Kinney, *ibid.*, **46**, 493 (1924).

A standard method for determining the mode of reaction is to treat the addition compound, prior to hydrolysis, with a so-called reliable<sup>4</sup> reagent which will replace the —MgBr group by another, in order to give a compound that lends itself to ready identification. Unfortunately, none of the compounds used for this purpose in earlier studies<sup>2,3</sup> succeeded in replacing the —MgX group. This indicated strongly that the —MgX group had attached itself to oxygen, because the study of isocyanates<sup>3</sup> showed that the —OMgX group was decidedly inert in the sense that the —MgX attached to oxygen would not undergo ordinary replacement reactions. Furthermore, advantage was taken of a recent extensive study<sup>5</sup> of new reagents for characterizing simpler —OMgX groups and none of these was found effective. Inasmuch as these reagents replace the —MgX group attached to nitrogen in a variety of compounds<sup>5</sup> and do not replace generally the —MgX attached to oxygen, it must be concluded that the —MgX group has added to oxygen and not to nitrogen. Accordingly, the mechanism of reaction is that of Scheme II.<sup>6</sup>

The amides of sulfinic acids are new compounds. Unsuccessful attempts have been made to prepare them from sulfinic anhydrides<sup>7</sup> and from the acid chlorides of sulfinic acids.<sup>8</sup> The identity of benzene-sulfinanilide<sup>9</sup> obtained from thionylaniline and phenylmagnesium bromide was confirmed, in part, by a mixed-melting-point determination with the same compound obtained by the slow addition of benzene-sulfinic chloride to a highly diluted cold ether solution of aniline. This anilide, as well as other amides, was prepared by v. Braun and Kaiser<sup>10</sup> in a related manner.

Recently, Sonn and Schmidt<sup>11</sup> reported on the preparation of sulfinani-

<sup>4</sup> Unpublished results of completed work have shown that the several reagents commonly used to replace the —MgX group do not lead to ambiguous results due to rearrangements. These studies have been made with groups, particularly the benzyl group, that are known to undergo rearrangement in some reactions of the Grignard reagent.

<sup>5</sup> Unpublished work.

<sup>6</sup> This conclusion, which admittedly is based on negative results, finds admirable confirmation in the electronic interpretation of terminal cumulated unsaturated groups as proposed by Carothers, *THIS JOURNAL*, **45**, 1734 (1923); **46**, 2226 (1924).

Aliphatic diazo compounds ( $R_2CN_2$ ) and diazo-imides ( $RN_2$ ), although having in one of their generally accepted formulas a pair of terminal cumulated unsaturated groups do not behave towards the Grignard reagent like the ketenes, isocyanates and thionylamines. Instead, addition takes place at the terminal nitrogen atom alone. Preliminary mention of this work with reference to an abstract is contained in Ref. 22 of a paper by Gilman and Pickens [*THIS JOURNAL*, **47**, 2406 (1925)].

<sup>7</sup> Knoevenagel and Polack, *Ber.*, **41**, 3323 (1908).

<sup>8</sup> Hilditch and Smiles, *Ber.*, **41**, 4113 (1908).

<sup>9</sup> Gilman and Morris, *Science*, **56**, 54 (1922). See Ref. 1 of this paper.

<sup>10</sup> v. Braun and Kaiser, *Ber.*, **56**, 549 (1923).

<sup>11</sup> Sonn and Schmidt, *Ber.*, **57**, 1355 (1924). The final publication of our work was withheld until the study of the —OMgX compounds (Ref. 5) had been completed in order to ascertain more definitely the mode of reaction.

lides from the reaction between thionylaniline and the Grignard reagent. Where the same Grignard reagents were used, the results are in complete agreement with ours. However, in some cases we obtained aniline salts of sulfonic acids ( $\text{RSO}_3\text{H}\cdot\text{C}_6\text{H}_5\text{NH}_2$ ) instead of the sulfinanilides. Several experiments showed that these salts were readily formed by the hydrolysis and oxidation, particularly in wet ether solution, of the sulfinanilides. It is possible to avoid the formation of the aniline sulfonates by rapidly working up the product of hydrolysis of thionylaniline and Grignard reagent.

### Experimental Part

Thionylaniline was prepared according to the method described by Michaelis.<sup>12</sup> A 10% increase in yield over that obtained by him is to be attributed in large part to the use of continuous stirring.

In the several experiments an emulsion of the thionylaniline in ether was added slowly to a well-stirred, cold solution of the Grignard reagent, of which about a 10% excess was generally used.<sup>13</sup> After the thionylaniline had been added, the mixture was refluxed for about one hour and then hydrolyzed by being poured slowly into an iced 5% solution of hydrochloric acid.<sup>14</sup> The solid reaction products were obtained in the customary manner from the dried ether solution.

**Reaction with Phenylmagnesium Bromide.**—From 35 g. or 0.25 mole of thionylaniline and a slight excess of phenylmagnesium bromide, there was obtained 28 g. or an 80% yield of benzene-sulfinanilide. When recrystallized from boiling ether it melted<sup>15</sup> at 115°.

<sup>12</sup> Michaelis, *Ann.*, **274**, 173 (1893); *Ber.*, **24**, 745 (1891).

<sup>13</sup> The yields of some Grignard reagents have been determined by Gilman and McCracken [*THIS JOURNAL*, **45**, 2462 (1923)]. In some later experiments the  $\text{RMgX}$  compound was added to the thionylaniline until a positive color test for an excess of the Grignard reagent was obtained [Gilman and Schulze, *ibid.*, **47**, 2002 (1925)]. In this way it was determined that about one molecular equivalent of  $\text{RMgX}$  compound was required. Unless the thionylaniline is freshly distilled, an excess of  $\text{RMgX}$  is necessary because of the hydrolysis of thionylaniline (see Ref. 12 of this paper) to aniline and sulfur dioxide, both of which react with  $\text{RMgX}$  compounds.

The protracted digestion of thionylaniline with an excess of phenylmagnesium bromide at about 100° gives apparently intractable oils. However, when the reaction is carried out with an excess of phenylmagnesium bromide at the boiling point of ether, benzene-sulfinanilide is obtained in good yields.

Phenylisocyanate and -isothiocyanate, when refluxed for several hours at about 100° with an excess of phenylmagnesium bromide, give a good yield of a yellow compound that melts at 143°. This compound has not as yet been identified, although it undergoes quantitative acid hydrolysis into aniline and phenylfluorene.

<sup>14</sup> Sonn and Schmidt (Ref. 11) hydrolyzed their reaction mixtures with ammoniacal ammonium chloride in order to avoid the extensive decomposition products they obtained when hydrolysis was effected by acids. In our work no marked decomposition was noticed when hydrolysis was carried out by the careful addition to iced dil. hydrochloric acid.

<sup>15</sup> The melting point reported by v. Braun and Kaiser (Ref. 10) is 112–114° and that

*Anal.* Calcd. for  $C_{12}H_{11}ONS$ : S, 14.74. Found: 14.96, 14.89.

When warmed for 30 minutes with very dilute sulfuric acid the sulfinanilide gave aniline and benzenesulfonic acid. V. Braun and Kaiser<sup>10</sup> reported deep-seated decomposition and no smooth hydrolysis when the sulfinanilide was heated with acids. They recommended hydrolysis by dil. alcoholic alkali solution and this, too, was found effective after we had first hydrolyzed the substance by acids.

The identity of benzene-sulfinanilide was further confirmed by a mixed-melting-point determination with the compound obtained by the reaction between benzenesulfonic chloride and aniline. This sulfinanilide was prepared by the slow addition of benzenesulfonic chloride in petroleum ether to a highly diluted, well stirred solution of aniline in ether, kept cold by a freezing mixture. The compound so obtained, after two recrystallizations from ether, melted sharply at  $116^{\circ}$ .<sup>15</sup>

**Attempted Replacement Reactions of the —OMgX Group.**—After the customary reaction between thionylaniline and phenylmagnesium bromide, most of the ether was replaced by toluene, an equivalent amount of triphenylchloromethane was added and the mixture refluxed at about  $100^{\circ}$  for two hours. On hydrolysis there was obtained a 62.5% yield of benzene-sulfinanilide in addition to some triphenylcarbinol that undoubtedly owed its formation to the hydrolysis of triphenylchloromethane.

In like manner, when the reaction mixture in ether was refluxed with an equivalent of diethyl sulfate, there was obtained subsequent to hydrolysis a 75% yield of benzene-sulfinanilide.

When the reaction mixture in ether was refluxed, prior to hydrolysis, with benzoic anhydride,<sup>16</sup> the following products were obtained after acid hydrolysis of the entire mixture: benzanilide, dibenzoylaniline,  $C_6H_5N(COC_6H_5)_2$ , aniline benzenesulfonate and an unidentified compound, m. p.  $160^{\circ}$ , that contained nitrogen but no sulfur. In another experiment, the ether was replaced largely by benzene prior to refluxing with benzoic anhydride and, in addition to a 30% yield of benzanilide, some benzene-sulfinanilide was obtained. Acetic anhydride under corresponding conditions gave largely the aniline-benzenesulfonate. When bromomethyl-ethyl ether,  $BrCH_2OC_2H_5$ , was used in an attempt to replace the —MgBr attached to oxygen, the largest part of the reaction mixture consisted of apparently intractable oils.

**Aniline-benzenesulfonate.**<sup>16</sup>—The aniline-benzenesulfonate previously described in connection with the benzoic and acetic anhydride experiments was identified by its neutralization equivalent (calcd.: 251; found: 254, 255.5) and by a mixed-melting-point determination with an authentic specimen.<sup>17</sup> It was possible to get needles melting at  $243^{\circ}$  by precipitation caused by the addition of ether to an alcoholic solution.

In the experiments involving the reaction between thionylaniline and phenylmagnesium bromide, it was observed that no aniline-benzenesulfonate was formed when benzene was used as a solvent. However, the salt appeared to form quite readily with ether as a solvent. This suggested the following qualitative experiments.

Benzene-sulfinanilide was allowed to stand in wet ether, anhydrous ether, a mixture of dry ether and dry benzene, and in dry benzene. The characteristic needles of aniline-benzenesulfonate began to form in the wet ether solution after a few hours; reported by Sonn and Schmidt (Ref. 11) is  $112$ – $113^{\circ}$ . The temperatures recorded in this paper are uncorrected. Benzene-sulfinanilide melts at  $110^{\circ}$  but a mixed-melting-point determination with benzene-sulfinanilide shows a depression.

<sup>15</sup> Work of F. Schulze.

<sup>17</sup> Gericke, *Ann.*, **100**, 207 (1856). Norton and Westenhoff, *Am. Chem. J.*, **10**, 129 (1888). Knight, *ibid.*, **19**, 151 (1897).

the dry ether and dry ether-benzene solutions yielded a smaller amount of the salt after several days; the dry benzene solution gave the salt after ten days. It is known that benzene-sulfinanilide is hydrolyzed readily by merely warming with water. What very probably happens is that the sulfinate is first hydrolyzed and subsequently the sulfinic acid is oxidized to sulfonic acid which then forms a salt with aniline. Possibly the ether may accelerate the hydrolysis by its greater miscibility with water, and also accelerate the oxidation by the intermediate formation of an ether peroxide.<sup>18</sup>

**Reaction with *p*-Tolylmagnesium Bromide.**—The reaction was carried out in a manner identical with that of phenylmagnesium bromide. However, the product was permitted to undergo hydrolysis and oxidation to aniline *p*-toluenesulfonate. It melted at 230° when precipitated from an alcoholic solution by the addition of ether. No depression was noted when a mixed-melting-point determination was made with an authentic specimen prepared according to Norton and Otten.<sup>19</sup>

**Reaction with *n*-Butylmagnesium Bromide.**—The product obtained after hydrolysis of material from the thionylaniline and *n*-butylmagnesium bromide experiment was allowed to stand in ether for a longer time than usual. It was best obtained in a pure state by adding ether to an ethyl acetate solution. After three recrystallizations it melted sharply at 159°. Solubility tests indicated that it was an aniline-sulfonate and not the *n*-butylsulfinanilide. Analysis confirmed its identity as aniline-*n*-butylsulfonate. The yield was 80%, starting with 0.25 mole of thionylaniline.

*Anal.* Calcd. for C<sub>13</sub>H<sub>17</sub>O<sub>3</sub>NS: C, 51.94; H, 7.36; N, 6.06; S, 13.85; H<sub>2</sub>O, 7.79. Found: C, 51.6, 51.6; H, 7.7, 7.7; N, 6.21, 6.55; S, 14.26, 14.29, 14.16; H<sub>2</sub>O, 7.69.

The loss of water was determined by heating at 105° for three hours. It is interesting that Norton and Westenhoff<sup>17</sup> observed no dehydration of aliphatic amine salts of benzenesulfonic acid when heated in a vacuum at 110°. The dehydration product of aniline-*n*-butylsulfonate is being investigated.

**Reaction with Benzylmagnesium Chloride.**<sup>16</sup>—Twenty-eight and a half g. or a 61.6% yield of benzyl sulfinanilide was obtained from 0.2 mole of thionylaniline and an excess of benzylmagnesium chloride. When crystallized from benzene it melts at 144–145°, which agrees with the melting point given by Sonn and Schmidt.<sup>11</sup> After standing overnight in wet ether the sulfinanilide is converted to white, flaky crystals that melt between 230° and 235° when crystallized from alcohol. This compound is soluble in water, slightly soluble in alcohol and insoluble in ether. Very probably it is aniline-benzylsulfonate, and like the other aniline sulfonates, owes its formation to the hydrolysis and oxidation of the sulfinanilide.

**Reaction with Cyclohexylmagnesium Bromide.**—The product obtained from the reaction between thionylaniline and cyclohexylmagnesium bromide was soluble in dry ether and in hot benzene, but insoluble in hot ethyl acetate. After two crystallizations from hot benzene it melted sharply at 214°. The yield of aniline-cyclohexylsulfonate was 75%, starting with 0.25 mole of thionylaniline.

*Anal.* Calcd. for C<sub>12</sub>H<sub>15</sub>O<sub>3</sub>NS: S, 12.45; H<sub>2</sub>O, 7.0. Found: S, 12.15, 12.33; H<sub>2</sub>O, 6.85.

The water was determined by drying for three hours at 105°.

### Summary

Thionylaniline adds one molecule of an RMgX compound at the S=O group to give sulfinanilides in good yields. The sulfinanilides undergo

<sup>18</sup> Gilman and Wood, *THIS JOURNAL*, **48**, 806 (1926). See, particularly, Ref. 9.

<sup>19</sup> Norton and Otten, *Am. Chem. J.*, **10**, 140 (1888).

ready hydrolysis and oxidation, particularly in wet ether solution, yielding aniline salts of the corresponding sulfonic acids.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

### OPTICALLY ACTIVE DIAZO COMPOUNDS III. A CRYSTALLINE, ALICYCLIC DIAZO ESTER

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Levene and La Forge<sup>2</sup> first discussed the possibility of an asymmetric aliphatic diazo group. They obtained a crystalline diazo compound that very probably contained such a group, but they could not demonstrate this, as the compound contained other asymmetric carbon atoms.

In 1918 Levene<sup>3</sup> assumed optically active diazo groups and a Walden inversion in the treatment of an aliphatic amino group with nitrous acid. Some years before, Potter<sup>4</sup> and one of us had observed a Walden inversion, involving the shift of a methyl group, on treatment of an alicyclic amino acid with nitrous acid.

In 1920 Marvel and Noyes<sup>5</sup> attempted unsuccessfully the preparation of an aliphatic diazo compound in which the only asymmetric carbon atom was the one attached to the diazo group.

Levene and Senior and Levene and Mikeska<sup>6</sup> had also been working on the problem and the latter obtained an active compound with a small rotatory power. In the latter paper they reaffirm their belief in the optical activity of the diazo group, based on the different products obtained by the action of nitrous acid on glucose-aminic and manosaminic esters. As they did not isolate the two isomeric diazo compounds, such a conclusion does not seem to be entirely valid.

Chiles and Noyes<sup>7</sup> obtained six optically active diazo compounds in which the asymmetric carbon atom was combined with the diazo group. Levene and Mikeska<sup>8</sup> have confirmed their work in part, but have found some differences.

In the discussion of Levene and in the earlier discussion by the senior

<sup>1</sup> Abstract from a thesis presented to the Graduate Faculty of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

<sup>2</sup> Levene and La Forge, *J. Biol. Chem.*, **21**, 347 (1915). Dr. Levene and the senior author of this paper discussed the possibility of such asymmetry in March, 1915.

<sup>3</sup> Levene, *J. Biol. Chem.*, **36**, 89 (1918).

<sup>4</sup> Noyes and Potter, *THIS JOURNAL*, **34**, 1067 (1912).

<sup>5</sup> Marvel and Noyes, *ibid.*, **42**, 2259 (1920).

<sup>6</sup> Levene and Mikeska, *J. Biol. Chem.*, **45**, 592 (1921); **52**, 485 (1922).

<sup>7</sup> Marvel with Noyes, *THIS JOURNAL*, **42**, 2259 (1920). Chiles and Noyes, *ibid.*, **44**, 1798 (1922).

<sup>8</sup> Levene and Mikeska, *J. Biol. Chem.*, **55**, 795 (1923).