[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF VANDERBILT UNIVERSITY]

# Grignard Reagents of Sulfones. III. Preparation and Properties[1]

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The powdery solid isolated after replacing one hydrogen atom of methyl phenyl sulfone using methylmagnesium iodide appears to be mainly unsolvated phenylsulfonylmethylmagnesium iodide (II). The product II is thermostable and, since it does not disproportionate in ether, may be useful for studying RMgX reactions in the absence of $R_2Mg$ and $MgX_2$. The product obtained after replacement of two hydrogen atoms reacted with only one mole of benzaldehyde. Attempted further replacement of hydrogen resulted in considerable reduction to thiophenol. Iodomethyl phenyl sulfone was converted to its Grignard reagent by magnesium (ethyl bromide also was required), but significant practical conversions could not be obtained with vinylogous halides, with 2-haloethyl aryl sulfones or with 1,1-dimethyl-4-halobutyl aryl sulfones; possible explanations for the refractory character of these halosulfones are considered.

Grignard reagents of sulfones which are typified by the structure $RSO_2CR'R''MgX$ add to carbonyl compounds[1b,2] and also undergo other useful reactions[3] characteristic of more familiar types of Grignard reagents. As a preliminary to further use of Grignard reagents of sulfones in synthesis and in examination of the influence of the sulfonyl group upon the organometallic bond, a more detailed study of their preparation and properties was desirable. This paper reports such a study.

*n*-Butyl ether and methylmagnesium iodide seemed best suited to a gasometric study of the conversion of methyl phenyl sulfone (I) to its Grignard reagent; the reaction was slower than with benzene–ether and ethylmagnesium bromide, which usually have been used[4] in preparing the Grignard reagent of I.[5] The reaction, at first, was not forced beyond a methane evolution of 81%, in order to obviate reduction of I. Removal of starting materials left solid in an amount equivalent to a 77% yield of II (although the formulation of the product as $[C_6H_5SO_2CH_2]MgI$ has the advantage of making no implication as to bonding, that shown by II is used because it is satisfactory at present and is simpler).

$$\begin{tikzcd}
\underset{\text{I}}{C_6H_5SO_2CH_3} + CH_3MgI \arrow[r] & \underset{\text{II}}{C_6H_5SO_2CH_2MgI} + CH_4 \arrow[d, "CH_3MgI\ \text{(excess)}"] \\
\underset{\text{III}}{C_6H_5SO_2CH_2CH(OH)C_6H_5} & C_6H_5SO_2CH(MgI)_2 + CH_4 \arrow[l, "C_6H_5CHO"']
\end{tikzcd}$$

This product was a white powder which was virtually insoluble in several common solvents for Grignard reagents; dioxane and pyridine caused discoloration, probably because of complex formation. Analyses for basic magnesium, halogen and the phenylsulfonylmethyl radical suggest that the product consisted of unit amounts of the phenylsulfonylmethyl and iodomagnesium radicals and is best regarded as being mainly II rather than, for example, a dialkylmagnesium compound; for convenience, therefore, the product will be referred to hereafter as II.

The product was shown to have the activity as a Grignard reagent expected of II by conversion with benzaldehyde to $\beta$-phenyl-$\beta$-hydroxyethyl phenyl sulfone (III). Evidently II is not subject to the disproportionation common to soluble Grignard reagents, because washing with large volumes of ether did not affect its composition. This characteristic, probably a consequence of insolubility in ether, suggests that the use of II may provide a novel and useful means for studying RMgX reactions in the absence of the $R_2Mg$ and $MgX_2$ which accompany soluble Grignard reagents because of disproportionation equilibria.

In order to ascertain both the thermal stability of II and the extent of its solvation with ether, it was heated at 100° (0.6 mm.) for 17 hours. Hydrolysis then gave I in 78% yield, thus demonstrating good thermal stability. The loss of weight upon heating was far less than calculated for even a monoetherate and indicates that II is unsolvated; the solid di-(bromomagnesium) derivative of diphenylsulfonylmethane evidently shows a similar failure to undergo solvation.[6]

The reaction of I with ethylmagnesium bromide in benzene–ether[4] gave a solid which was mainly phenylsulfonylmethylmagnesium bromide (IV). This, like II, was not affected by an ether wash, lost less weight upon being heated than an etherate should, and was thermally stable.

When compound I was heated with a large excess of methylmagnesium iodide for 3.5 hours, 108% of two molar equivalents of gas was evolved. Presumably, therefore, two hydrogen atoms were replaced. Nevertheless, after addition of benzaldehyde the only solid isolated was the monoadduct III (in 17% yield as the benzoate). This experience is not without precedent, however, since Kohler and Tishler[6] were able to effect acylation or alkylation involving only one of two bromomagnesium residues attached to the diphenylsulfonylmethylene radical. An effort to characterize the bis-Grignard reagent from I by halogenolysis resulted only in diphenyl disulfide; since thiophenol was not detected in the first experiment, it seems likely that reduction did not occur during the metalation of the sulfone, and that this disulfide was formed in

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[1] (a) Presented in part at the 125th Meeting of the American Chemical Society, Kansas City, Mo., March, 1954; Abstracts of Papers, p. 9 N; (b) Paper II, L. Field and J. W. McFarland, THIS JOURNAL, **75**, 5582 (1953).

[2] W. E. Truce and K. R. Buser, *ibid.*, **76**, 3577 (1954); H. Potter, *ibid.*, **76**, 5472 (1954).

[3] For leading references, see ref. 4; see also H. Gilman, L. F. Cason and H. G. Brooks, Jr., *ibid.*, **75**, 3760 (1953), and H. E. Faith, U. S. Patent 2,656,362 (1953) [*C. A.*, **48**, 10775 (1954)].

[4] L. Field, THIS JOURNAL, **74**, 3919 (1952).

[5] The use of methylmagnesium iodide is presumably one significant cause of the decreased rate; see J. H. Wotiz, C. A. Hollingsworth and R. Dessy, *ibid.*, **77**, 103 (1955).

[6] E. P. Kohler and M. Tishler, *ibid.*, **57**, 217 (1935).

some less obvious way than by oxidation of thiophenol produced during the metalation.

Heating of I with excess methylmagnesium iodide until gas evolution ceased resulted in 85% of three molar equivalents of gas. A low recovery of I and a considerable consumption of methylmagnesium iodide in processes other than gas formation, however, pointed to the occurrence of considerable reduction. Isolation of thiophenol (25%, as the disulfide) confirmed this inference. Since the gas evolved probably originated partly in oxidation processes, therefore, conclusions seem unjustified as to the replacement of all three hydrogen atoms of the methyl group of I. The fact that the thiophenol was formed by reductive action of excess methylmagnesium iodide rather than from thermal decomposition of II is evident from the stability of II when alone and from the consumption of the methylmagnesium iodide. Reduction of I has been observed previously in boiling xylene.[7]

An examination of methods which promised direct conversion of haloalkylsulfones to the corresponding Grignard reagents was of both theoretical and practical interest. A variety of such sulfones were accordingly subjected to various conditions which normally result in conversion of other halides to Grignard reagents.

The halogen atom of an α-bromo sulfone is inert in metathetical reactions, but does react in several instances in which another reagent can be oxidized.[8] Nevertheless, iodomethyl phenyl sulfone (V) did not react with magnesium. Notwithstanding, since bromomethyl *p*-tolyl sulfone and phenylmagnesium bromide yield a solid presumed to be *p*-tolylsulfonylmethylmagnesium bromide on the basis of its hydrolysis to methyl *p*-tolyl sulfone,[8] "entrainment" conversion of V as used for refractory halides[9] seemed feasible. After treatment of two equivalents of magnesium with V and ethyl bromide, the benzaldehyde adduct III was obtained in 58% yield, thus establishing that a Grignard reagent of V can indeed be formed in this way.

In marked contrast to the halogen atom of an α-halosulfone, that of its vinylog is quite reactive in metathetical reactions, presumably because of remoteness from the steric blocking influence of the sulfonyl group.[10,11] Since the inertness of V toward magnesium might stem from a blocking effect of the sulfonyl group, treatment of its vinylogs with magnesium was desirable.

3-*p*-Tolylsulfonylprop-2-en-1-ol (VI) was converted to the chloro compound VIII.[10] Confirmation that neither VI nor VIII was an allylic isomer was provided by their partial reduction to VII. It is interesting that the chlorine atom of VIII was apparently hydrogenolyzed to about the same extent that the double bond was reduced in a competing reaction. Thus, the reduction of VIII, stopped after absorption of one molar equivalent of hydrogen, gave VII in 45% yield and resulted in 46% of one molar equivalent of hydrogen chloride. The remaining half of the hydrogen, therefore, evidently reduced VIII directly to the 3-chloropropyl sulfone which resisted hydrogenolysis.

$$\begin{tikzcd}
\underset{\text{VI}}{C_7H_7SO_2CH{=}CHCH_2OH} \arrow[r, "PCl_5"] \arrow[dr, "H_2(Pd)"'] & \underset{\text{VIII}}{C_7H_7SO_2CH{=}CHCH_2Cl} \arrow[d, "H_2(Pd)"] \\
& \underset{\text{VII}}{C_7H_7SO_2CH{=}CHCH_3}
\end{tikzcd}$$

The chlorosulfone VIII, as well as the analogous iodosulfone IX,[10] failed to react significantly with magnesium. Attempts to obtain the Grignard reagent of VIII or IX by entrainment or halogen–metal interchange were also unpromising because of the intervention of an addition reaction. Thus, although the product (unidentified) from the facile reaction of VIII with ethylmagnesium bromide contained no halogen, it was saturated and probably resulted from halogen–metal interchange complicated by addition to the olefinic linkage; nitration of this product gave a pure but also unidentified solid.[12]

In view of the inactivity of both the α-halosulfone and its vinylogs toward magnesium, the behavior of 2-haloethyl sulfones became of interest, since these generally manifest a reactivity typical of alkyl halides.[13] 2-Chloroethyl phenylsulfone (X) was prepared from ethylene chlorobromide and sodium benzenesulfinate; excess dihalide and conditions of fairly high dilution, achieved by slow extraction of the sulfinate into the reaction mixture, considerably improved the yield of X at the expense of the by-product, 1,2-di-(phenylsulfonyl)-ethane. In the reaction of X with magnesium, elimination or a migration of –MgCl to the α-carbon would not have been unexpected, but the lack of any reaction whatever was rather surprising. 2-Iodoethyl *p*-tolyl sulfone (XI) behaved similarly in ether and gave only tars in *n*-butyl ether.

Gas evolution occurred when magnesium was treated with both ethyl bromide and X or XI, and only unsaturated tars and starting material were isolated. When benzaldehyde was added, however, XI was isolated only in traces indicating that it may have been trapped as a Grignard reagent. In the reaction of XI, therefore, ethylmagnesium bromide presumably effects both replacement of α-hydrogen and an elimination reaction.

A 1,1-dimethyl-4-halobutyl aryl sulfone such as XII or XIII has no α-hydrogen atom which could interfere with a normal Grignard reaction of the halogen. Furthermore, the remoteness of the halogen atom should be sufficient to preclude both elimination reactions and steric or electronic influences of the sulfonyl group. The reactivity of XII and XIII toward magnesium consequently should have an important bearing on the question of the reactivity of halosulfones generally.

Preparation of XII, by alkylation as shown in the equation, led to a product containing a trace of im-

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[7] D. T. Gibson, *J. prakt. Chem.*, [2] **142**, 218 (1935).

[8] W. M. Ziegler and R. Connor, THIS JOURNAL, **62**, 2596 (1940).

[9] V. Grignard, *Compt. rend.*, **198**, 625 (1934).

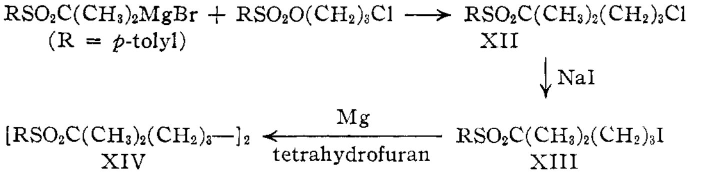
[10] C. C. J. Culvenor, W. Davies and W. E. Savige, *J. Chem. Soc.*, 2198 (1949).

[11] F. G. Bordwell and G. D. Cooper, THIS JOURNAL, **73**, 5184 (1951).

[12] There had seemed a reasonable prospect that reaction of the chlorine atom of VIII would take precedence over the competing addition reaction of a Grignard reagent, which reportedly adds only slowly to an unsaturated sulfone [E. P. Kohler and H. Potter, THIS JOURNAL, **57**, 1316 (1935)].

[13] C. M. Suter, "The Organic Chemistry of Sulfur," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 689.

purity which could not be removed, but metathesis of XII yielded the pure iodide XIII. Neither XII nor XIII reacted with magnesium in ether. It is noteworthy that XII reacted negligibly even with lithium, although the recovered metal reacted satisfactorily with *n*-butyl chloride. Use of XIII in solvents other than ether resulted either in no reaction, in decomposition or in coupling (XIII in tetrahydrofuran gave the presumed coupling product XIV in fair yield). XIII gave unpromising results also when entrainment was attempted.



$$\begin{tikzcd}
\underset{(R = p\text{-tolyl})}{RSO_2C(CH_3)_2MgBr + RSO_2O(CH_2)_3Cl} \arrow[r] & \underset{XII}{RSO_2C(CH_3)_2(CH_2)_3Cl} \arrow[d, "NaI"] \\
\underset{XIV}{[RSO_2C(CH_3)_2(CH_2)_3-]_2} & \underset{XIII}{RSO_2C(CH_3)_2(CH_2)_3I} \arrow[l, "Mg"', "\text{tetrahydrofuran}"]
\end{tikzcd}$$

It is, of course, entirely possible that alteration of the numerous variables involved in heterogeneous reactions of the kinds attempted might effect conversion of halosulfones to Grignard reagents. Nevertheless, there seems little doubt that the halosulfones studied showed marked reluctance toward reaction with magnesium under the usual conditions convenient in synthesis. Similar refractory character has been reported for other halosulfones[14a] and for halosulfonates[14b]; electronic influences may play a role in certain of these instances.

The observations outlined above can be connected in a tentative way. Both the insolubility and lack of solvation of II and IV are explained if coördination of the sulfonyl group of each molecule with the halomagnesium moiety of another effects intermolecular association into insoluble polymeric aggregates. The insolubility of the resulting aggregate should favor association of this kind, instead of with ether in the usual way. The fact that a coprecipitate formed when ether solutions of ethylmagnesium bromide and diphenyl sulfone were mixed supports the suggestion that such association may be possible (although the precipitate also conceivably could be a consequence of a "salting-out" process); earlier observations also support the possibility of complex formation.[1b]

Formation of small amounts of an insoluble aggregate on the metal might easily prevent further reaction of a halosulfone without resulting in a visible film, since it is probable that only a relatively few active points,[9,15] in the metal need be blocked (readily apparent films were noted only in a very few instances with the halosulfones). A halide which can readily form a soluble solvated Grignard reagent, however, should still be capable of attacking the metal at remaining or incompletely blocked active centers, although the reaction should be sluggish until its progression has resulted in an increase of surface reactivity[15]; magnesium recovered from attempted reactions with VIII, IX, XI and XIII did indeed react satisfactorily with halides such as ethyl bromide, although these reactions seemed more sluggish than with fresh metal.

An alternative explanation of the inactivity is not without appeal: if the sulfone group does indeed have the coördinating capability suggested, perhaps it can be adsorbed at an active center of the metal surface in preference to the halogen atom of its own molecule, so that no reaction would occur upon any adsorption. Such adsorption, presumably being reversible, need not prevent reaction of ethyl bromide which could react effectively whenever adsorbed and could then pass into solution as a solvated Grignard reagent.

In substantiation of the foregoing discussion, it seems more than coincidental that ethers,[16] tertiary amines[16] and pyridine[17] form addition compounds with Grignard reagents, and that certain halogen derivatives of alkyl and aryl ethers or amines and of pyridine react difficultly or not at all with magnesium alone.[18] Refractory character toward magnesium presumably would vary with such features of halides as their coördinating capabilities and the solubilities of their Grignard reagents.

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## Experimental[19]

**Reactions of Methyl Phenyl Sulfone (I) and Grignard Reagents. (a) Replacement of One Hydrogen Atom.**—A 2.56 *M* solution of methylmagnesium iodide in *n*-butyl ether prepared essentially by the method of Shriner[20] was centrifuged for 3 hours and assayed gasometrically. I[4] (44.9 mmoles) and 150 ml. of *n*-butyl ether were placed in a three-necked flask containing a mercury-sealed stirrer, and equipped with a dropping funnel and a condenser (containing a thermometer), both connected through drying tubes to a Dry Ice trap, in turn connected to a gas buret. The apparatus was flushed with nitrogen, and the mixture heated until solution occurred (71°). The Grignard solution (50.5 mmoles, measured by weight) was then added. After a stirring period of 4.5 hours at 71–74°, gas evolution was quite slow. About one-half of the evolved gas appeared during the first half-hour; total evolution, 815 ml. (81% of one molar equivalent). The supernatant solution gave a positive color test.[21] The resulting suspension, including solid dislodged from the flask walls, was pumped under nitrogen into a centrifuge bottle, and was followed with a benzene wash. The mixture was centrifuged, and the supernatant liquid decanted under nitrogen. The solid was washed with two 175-ml. portions of benzene and 200 ml. of ether by centrifugation and decantation under nitrogen, and then dried for 0.5 hour each at 30 mm. and at 0.2 mm.; weight, 10.8 g. Further drying for 39 hours at 2 mm. over concd. sulfuric acid, for removal of ether, reduced the weight only to 10.6 g. (77% of phenylsulfonylmethylmagnesium iodide (II)).

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[14] (a) W. E. Truce and M. F. Amos, THIS JOURNAL, **73**, 3013 (1951); (b) D. C. Morrison, *ibid.*, **74**, 3431 (1952); H. Gilman and N. J. Beaber, *ibid.*, **45**, 839 (1923).

[15] M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Non-metallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 61–62.

[16] F. Runge, "Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft G.m.b.H., Stuttgart, 1944 (lithoprinted by Edwards Brothers, Ann Arbor, Mich., 1945), p. 189 ff.

[17] A. C. Cope, THIS JOURNAL, **60**, 2215 (1938).

[18] Reference 16, pp. 214–217.

[19] Melting points are corrected, and boiling points are uncorrected. Moist extracts were dried using anhydrous magnesium sulfate, and solvents removed by distillation under reduced pressure. Materials and apparatus used directly with Grignard reagents were well dried. Analyses are by Clark Microanalytical Laboratory, Urbana, Ill., and Micro-Tech Laboratories, Skokie, Ill.

[20] R. L. Shriner, "Quantitative Analysis of Organic Compounds," 3rd ed., Edwards Brothers Inc., Ann Arbor, Mich., 1948, p. 58.

[21] The Michler ketone test of Gilman, *et al.*, for RMgX, according to L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath and Co., New York, N. Y., 1941, p. 408.

The product II was a highly hygroscopic, free-flowing white powder, m.p. 194° (dec., slight previous sintering; sealed tube immersed at 185°, and heated at 1–2°/min.) A strong green color test[21] was obtained with an ether suspension of II, but only after gentle boiling for 10 minutes. Qualitative experiments showed II to be virtually insoluble in boiling ether, benzene, toluene and *n*-butyl ether; dioxane[22] caused a red-brown coloration and swelling, but very little solution at the b.p.; pyridine gave rise to a heating effect and coloration—the solid seemed slightly soluble at 30° and more so at the b.p. A recent observation by Mr. J. R. Holsten of this Laboratory indicates that compounds similar to II may dissolve in tetrahydrofuran.

The product II (3.5998 g.) was slowly added to ice-water. Basic magnesium was determined by adding excess 0.4 *N* nitric acid and titrating with sodium hydroxide and methyl orange. Methyl phenyl sulfone (I) was extracted with chloroform and dried to constant weight (1.8746 g., m.p. and mixture m.p. 83–86.5°). The aqueous layer was then extracted with benzene, and iodide determined using silver nitrate–nitric acid.[23] *Anal.* Calcd. for $C_7H_7IMgO_2S$ (II): $C_6H_5SO_2CH_2$–, 51; I, 41; basic Mg, 8. Found: $C_6H_5SO_2CH_2$–, 52; I, 35; basic Mg, 9.

The product II (6.2 g.) was shaken twice with 200 ml. of ether for 1.5 hours, and the ether decanted under nitrogen after centrifugation. The solid, dried briefly under reduced pressure, lost no further weight when dried at 2 mm. pressure over concentrated sulfuric acid for 11 hours; recovery, 5.8 g. (94%), m.p. 191–193° dec. *Anal.* Found: $C_6H_5SO_2CH_2$–, 50; I, 35; basic Mg, 10.

In determining the thermal stability and possible solvation of II, 1.2473 g. of the rewashed II was heated (without noticeable change) at 100° and 0.6 mm. over phosphorus pentoxide for 17 hours; wt. loss, 0.0553 g. (4%; calcd. for II monoetherate, 19%). The product then reacted vigorously with water–ice, and acidification gave I, amounting after recrystallization to 0.475 g. (75%, assuming the sample to have been pure II), m.p. and mixture m.p. 84–87.5°.

For characterization, 2.224 g. of rewashed II was suspended in ether–benzene, and allowed to react with 0.97 g. of benzaldehyde[24] as previously described.[4] Four recrystallizations from carbon tetrachloride gave 0.8552 g. (45%) of β-phenyl-β-hydroxyethyl phenyl sulfone (III), m.p. 88–93°, which after further recrystallization had m.p. and mixture[4] m.p. 92–94°.

Addition of I (47.1 mmoles) in 80 ml. of benzene to 70.6 mmoles of 3.1 *M* ethereal ethylmagnesium bromide resulted in gas evolution, which amounted within 15 minutes to 57% of one molar equivalent and then seemed complete; further evolution of only 9% occurred upon heating at 71° for 8 minutes. Since the volumes were measured at 26°, partial solution of the gas probably is a cause of the apparently low volume. The product, washed with three 150-ml. portions of ether and dried, was a free-flowing white solid, weight 13.0 g. (107% of the weight expected for phenylsulfonylmethylmagnesium bromide (IV)). IV was added to water (vigorous reaction) and analyzed as before. *Anal.* Calcd. for $C_7H_7BrMgO_2S$ (IV): $C_6H_5SO_2CH_2$–, 60; Br, 31; basic Mg, 9. Found: $C_6H_5SO_2CH_2$–, 48; Br, 30; basic Mg, 9. IV was recovered in 90% yield after further washing of 6 g. with three 150-ml. portions of ether. *Anal.* Found: $C_6H_5SO_2CH_2$–, 48; Br, 30; basic Mg, 10. This material when heated at 110–160° (2 mm.) for 4 hours lost 6% in weight (calcd. for IV etherate, 22%). Thermal stability of IV was demonstrated by heating 4.77 g. in toluene under reflux for 2.3 hours and acidifying; yield of I, 2.15 g. (75%), m.p. 73–87°, undepressed by authentic I.

(b) **Replacement of Two Hydrogen Atoms.**—A solution of 25.6 mmoles of I in 100 ml. of *n*-butyl ether was prepared in the apparatus described, and 154 mmoles of 2.4 *M* methylmagnesium iodide was added with stirring and heating at 73–76°, which were then continued for 3.5 hours before cooling to room temperature; gas evolution, 1236 ml. (108% of two molar equivalents). Benzaldehyde[24] (170 mmoles) in benzene was added, and the mixture stirred overnight and acidified. A benzene extract was washed with dilute alkali (which then contained no thiophenol) and water, and was then dried. Removal of solvent and washing with petroleum ether yielded 7.0 g. of sirup which could not be crystallized.

Chromium trioxide oxidation[4] of part of the sirup yielded only benzoic acid. After Oppenauer oxidation only a little III was isolated and a small amount of a sulfur-free 2,4-dinitrophenylhydrazone obtained. Treatment of 0.931 g. of the sirup with benzoyl chloride and pyridine[4] gave the benzoate of III, which after recrystallization amounted to 0.215 g. (over-all yield from I, 17%), m.p. and mixture[4] m.p. 144.5–145.5°, unchanged by further recrystallization.

In a similar replacement (methane evolution, 100% of 2 molar equivalents), bromine in benzene was added at 10°, and the mixture was stirred and briefly heated. After hydrolysis the only solid isolated was diphenyl disulfide (14%), m.p. and mixture m.p. after recrystallization, 59.5–60.5°.

(c) **Reaction Until Cessation of Gas Evolution.**—A solution of 12.8 mmoles of I in 50 ml. of *n*-butyl ether was prepared at 70° in the apparatus described, 77.0 mmoles of 3.1 *M* methylmagnesium iodide in *n*-butyl ether was added, and the mixture stirred with heating at 62–72°. After about 23.5 hours, 729 ml. of gas had been evolved (85% of three molar equivalents), none of which appeared during the last hour; the first one-third of the total amount appeared after about 1.5 hours, the second after about 4 hours more, and the last after a still further period of about 17 hours. Separation of a solid cake above the solution probably limited reaction to some extent.

Hydrolysis of the cooled mixture resulted in 472 ml. of methane. A benzene extract of the acidified mixture was washed with aqueous sodium hydroxide and water. Removal of solvent from the organic layer gave I, which after purification amounted to 0.554 g. (28% recovery), m.p. and mixture m.p. 85–88°. The alkaline layer was washed with ether, acidified and extracted with benzene. The extract was treated with iodine (2 g.) and then aqueous sodium thiosulfate; yield of diphenyl disulfide, 0.352 g. (25%), m.p. (after recrystallization) and mixture m.p., 59–60.5°. When the above conditions were used but the I omitted, only 9 ml. of gas was evolved and gasometric analysis showed survival of 96% of the methylmagnesium iodide.

**Preparation of Halosulfones.** (a) **Iodomethyl Phenyl Sulfone (V).**—This sulfone was prepared in 70% yield by heating anhydrous sodium benzenesulfinate (40 g.) with methylene iodide (72 g.) in ethanol under reflux for 41 hours,[25] removing solvent, triturating with water–sodium bisulfite–petroleum ether, and recrystallizing from aqueous ethanol. The m.p. of 58.5–59° was unchanged by recrystallization from ethanol, but rose after a period of drying to 64–64.5°; m.p. reported,[26] 64.5°. *Anal.* Calcd. for $C_7H_7IO_2S$: I, 44.99. Found: I, 44.86.

(b) **3-Chloro-1-*p*-tolylsulfonyl-1-propene (VIII).**—The structure of 3-*p*-tolylsulfonylprop-2-en-1-ol[10] (VI, m.p. 123–124°) was confirmed by shaking 500 ml. of dioxane and 10 g. of palladium catalyst[27] until hydrogen absorption was negligible and then reducing 48.4 g. of VI until 5780 ml. of hydrogen had been absorbed (40 minutes; 113% of one molar equivalent). The solution was filtered, solvent was removed and water added, and the product then recrystallized from ethanol, 1:2 benzene–petroleum ether, and methanol; yield of 1-(*p*-tolylsulfonyl)-1-propene (VII), 18.2 g. (41%), m.p. 97–100°. Further recrystallization gave VII with a constant m.p. of 101–102° which did not depress the m.p. of authentic VII,[1b] but also was not depressed by VI.

*Anal.* Calcd. for $C_{10}H_{12}O_2S$: C, 61.19; H, 6.17. Found: C, 61.12; H, 6.23.

Structure VII was confirmed by further reduction (ethanol) of the product, which ceased after absorption of 93% of one molar equivalent of hydrogen; yield of *n*-propyl *p*-tolyl sulfone, 96% (m.p. 49.5–52°; constant m.p. after recrystallization, 51.5–52.5°).

The halosulfone VIII was prepared[10] from VI and recrystallized from 3:1 carbon tetrachloride–petroleum ether; yield 93%, m.p. 57.5–58.5°. Reduction of VIII in purified dioxane,[22] with palladium catalyst[27] was stopped after

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[22] Reference 21, p. 369.

[23] W. W. Scott, "Standard Methods of Chemical Analysis," N. H. Furman, Ed., Vol. I, 5th ed., D. Van Nostrand Co., New York, N. Y., 1939, p. 451.

[24] Reference 21, p. 224.

[25] A procedure based on one of R. Otto, *Ber.*, **21**, 652 (1888).

[26] A. Michael and G. M. Palmer, *Am. Chem. J.*, **6**, 253 (1885).

[27] E. R. Alexander and A. C. Cope, *Org. Syntheses*, **26**, 32 (1946).

absorption of 102% of one molar equivalent of hydrogen. After filtration and addition of water, titration showed the presence of 46% of one molar equivalent of hydrogen chloride. Recrystallization gave VII in 45% yield, m.p. 97–100.5°, which after further recrystallization had m.p. (constant) and mixture[1b] m.p. 100–101°.

(c) **3-Iodo-1-*p*-tolylsulfonyl-1-propene (IX).**—This was obtained,[10] after four recrystallizations from carbon tetrachloride alone and containing petroleum ether in 72% yield, constant m.p. 72–74°. It absorbed no hydrogen whatever under the conditions used with VIII. After further recrystallization from ethanol the m.p. was 72.5–73.5°; IX still could not be reduced and immediately halted a reduction of cyclohexene.

(d) **2-Chloroethyl Phenyl Sulfone (X).**—X was prepared by extracting 43.4 g. of finely ground anhydrous sodium benzenesulfinate, using a Soxhlet extractor, into 190 g. of ethylene chlorobromide[28] in 400 ml. of refluxing ethanol during 4 hours. Reflux was continued for 12 hours more. Solvent was then removed and 250 ml. of water with 150 ml. of benzene added. Insoluble solid was removed and combined with a further amount obtained by chilling the benzene layer; yield of 1,2-di-(phenylsulfonyl)-ethane, 9.14 g. (22%), m.p. 177.5–184°, undepressed by authentic material.[29] Removal of solvent from the dried benzene layer left greasy solid which was triturated with cold petroleum ether and dissolved in carbon tetrachloride. Seeding and chilling resulted in 23.1 g. (43%) of X, m.p. 50–53°. Recrystallization from isopropyl and ethyl alcohol removed further traces of the disulfone, but this was separated best by taking advantage of its insolubility in an ether solution of X. After recrystallization to constant m.p., X had m.p. 54–55°, reported[30] 55°.

*Anal.* Calcd. for $C_8H_9ClO_2S$: C, 46.94; H, 4.43. Found: C, 46.81; H, 4.30.

The reaction of equimolar amounts of sulfinate and chlorobromide by simple mixture in refluxing ethanol gave 48% of the disulfone and only 10% of X, m.p. 50–52.5°.

(e) **2-Iodoethyl *p*-Tolyl Sulfone (XI).**—Pulverized iodine (35 g.) was mixed well during 15 minutes into 2-hydroxyethyl *p*-tolyl sulfone[31] (34.9 g.) and red phosphorus (31 g.). The mixture was stirred for 22 hours and then at 120–130° for 5 hours. Benzene extracts were poured into ice-water washed with 5% aqueous sodium hydroxide and water, and dried. Removal of solvent and recrystallization from alcohol and carbon tetrachloride gave 28.5 g. (53%) of XI as colorless prisms, m.p. 100–101° (unchanged by recrystallization from methanol), reported[32] m.p. 100°.

*Anal.* Calcd. for $C_9H_{11}IO_2S$: C, 34.85; H, 3.58. Found: C, 35.02; H, 3.77.

(f) **1,1-Dimethyl-4-chlorobutyl *p*-Tolyl Sulfone (XII).**—In a modified general procedure,[33] $\gamma$-chloro-*n*-propyl *p*-toluenesulfonate (77.0 g., $n^{25}$D 1.5214) was added during 10 minutes to the $\alpha$-(*p*-tolylsulfonyl)-isopropylmagnesium bromide prepared[1b] in 250 ml. of benzene from isopropyl *p*-tolyl sulfone (25.1 g.) and 3.99 *N* ethereal ethylmagnesium bromide (37 ml.). The mixture was stirred for 3 hours, heated (1.5 hours) to reflux temperature, and there maintained for 18 hours; it was then chilled and acidified. Removal of solvent from a water-washed and dried benzene extract left 56.4 g. of oil which was heated with 21 g. of lithium chloride[34] in refluxing acetone for 17 hours to destroy unreacted ester. Acetone was largely removed, water was added, and a benzene extract washed with water, dried and concentrated to 31.4 g. of oil, which solidified at −5°. Trituration with cold 1:1 water–ethanol and recrystallizations from 2-propanol and aqueous methanol gave 13.0 g. (38%) of XII, m.p. 78.5–80°; 11% of isopropyl *p*-tolyl sulfone was isolated from the mother liquors. Four recrystallizations from ethanol gave XII with constant m.p. 80–80.5° (depressed to 53–59° by isopropyl *p*-tolyl sulfone).

*Anal.* Calcd. for $C_{13}H_{19}ClO_2S$: C, 56.82; H, 6.97; Cl, 12.90; S, 11.67; mol. wt., 275. Found: C, 56.02[35]; H, 6.73; Cl, 13.09; S, 11.92; mol. wt. (Rast, camphor), 251, 271.

(g) **1,1-Dimethyl-4-iodobutyl *p*-Tolyl Sulfone (XIII).**—XII (7.90 g.) and sodium iodide (17.2 g.) were heated in 65 ml. of refluxing acetone for 46 hours. Acetone was removed, water added, and a benzene extract washed with aqueous sodium bisulfite and water. Removal of solvent after drying left 10.00 g. (95%) of XIII, m.p. 93–94.5°. Recrystallization from methanol (9.63 g., 91%, m.p. 94–95.5°), ethanol and 10:1 carbon tetrachloride–petroleum ether gave XIII of constant m.p. 94.5–95° as colorless crystals which became pale yellow-orange after several months.

*Anal.* Calcd. for $C_{13}H_{19}O_2SI$: C, 42.63; H, 5.23; I, 34.65. Found: C, 42.71; H, 5.26; I, 35.22.

**Metalation Studies with Halosulfones.**—The chlorosulfones VIII (up to 7-fold excess), X and XII (equivalent amounts) were used in *ca.* 0.5–2 *M* ethereal solutions with magnesium turnings and iodine and/or considerable amounts of iodinated magnesium catalyst.[36] Since saturated ethereal solutions of the less soluble iodosulfones V, IX, XI and XIII were unreactive, IX, XI and XIII were also used in benzene–ether (*ca.* 0.3–0.8 *M;* 0.25–1 part of benzene). Stirring and refluxing under nitrogen were frequently continued for 40–52 hours. In no instance was there a promising conversion to a Grignard reagent. In representative trials where decomposition did not occur, yields of basic magnesium (by titration[37]) were insignificant and recoveries of sulfone and metal were 90–100%. Recovered metal was usually bright or only slightly dull and not appreciably coated or attacked. Magnesium used with VIII and XIII reacted satisfactorily with ethyl bromide used in the same molar amount and concentration as the halosulfone and, despite an oily film, metal used with IX and XI gave similar results; in all of these instances the reaction seemed sluggish, however. Magnesium (0.5 m. atom) remained bright and was only slightly attacked by XIII (4.7 mmoles) with iodine in 6 ml. of refluxing 1:1 ether–benzene during 16 hours; when ethyl bromide (4.7 mmoles) was added, however, reaction began easily and the metal was soon consumed without external heating.

When XII (6.6 mmoles) was stirred under reflux with lithium (14.0 m. atoms) in ether (6.5 ml.) for 2 hours, it was recovered in 84% yield; the lithium (89% recovery) was completely consumed upon heating for 1 hour with *n*-butyl chloride (6.6 mmole) in ether (8 ml.).

XI is stable in boiling *n*-butyl ether (11 hours), but reacted when magnesium was present although only tars were isolated. A sharp stainless steel stirrer (1400 r.p.m.)[38] was used with XIII and iodine in various other solvents. Reaction seemed inappreciable in anisole at 25 or 80°; at 155° reaction occurred but with much decomposition, and only unsaturated tars were isolated. Reflux for 11 hours in 1,2-dimethoxyethane[38] was followed by nearly quantitative recoveries (the metal was attacked subsequently by ethyl bromide).

A mixture of XIII (510.5 mg.), magnesium (29.4 mg.) and iodine in tetrahydrofuran (1.75 ml.) was heated briefly and then stirred for 18 hours at 26°; the metal had been attacked but much remained. Further attack occurred upon stirring under reflux but ceased well before the end of a 9-hour heating period. Recovered metal (4.4 mg.) was bright. Hydrolysis (titration[37] indicated basic magnesium in 59% yield) gave a precipitate which was recrystallized from carbon tetrachloride–petroleum ether, methanol and ethanol; yield 118.2 mg. (35% of presumed 1,8-bis-(*p*-tolylsulfonyl)-1,1,8,8-tetramethyloctane (XIV)), m.p. 144.5–146°. Further crystallization gave material of constant m.p. 145–145.5° which neither contained halogen nor decolorized aqueous potassium permanganate.

*Anal.* Calcd. for $C_{26}H_{38}O_4S_2$: C, 65.24; H, 8.00; mol.

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(28) Kindly supplied by Westvaco Chemical Division, Food Machinery and Chemical Corp., New York, N. Y.

(29) R. Otto, *Ber.*, **13**, 1279 (1880).

(30) A. H. Ford-Moore, R. A. Peters and R. W. Wakelin, *J. Chem. Soc.*, 1754 (1949).

(31) C. C. J. Culvenor, W. Davies and N. S. Heath, *ibid.*, 278 (1949).

(32) R. Otto and H. Damköhler, *J. prakt. Chem.*, [2] **30**, 321 (1884) [*J. Chem. Soc., Abstracts*, **48**, 537 (1885)].

(33) S. S. Rossander and C. S. Marvel, THIS JOURNAL, **50**, 1491 (1928).

(34) L. Field and J. R. Holsten, *ibid.*, **77**, 1286 (1955).

(35) C % unchanged after passage through alumina and recrystallization from carbon tetrachloride–petroleum ether; m.p. 80.5–81°.

(36) Prepared according to H. Gilman and R. H. Kirby, *Rec. trav. chim.*, **54**, 577 (1935), and reactivated before use by heating until iodine vapor was evident.

(37) Reference 21, p. 407.

(38) H. L. Cohen and G. F. Wright, *J. Org. Chem.*, **18**, 432 (1953).

wt., 479. Found: C, 65.45; H, 7.65; mol. wt. 268, 283 (Rast, camphor), 400 (ebullioscopic, butanone).

**"Entrainment" Reactions Involving Halosulfones, Magnesium and Ethyl Bromide.**—About one-seventh of a solution of 17.7 mmoles of V and 18.0 mmoles of ethyl bromide in 35 ml. of ether was added to 35.4 m. atoms of magnesium and 0.1 g. of catalyst.[36] After reaction began, the remaining solution was added with stirring during 40 minutes. Considerable white precipitate appeared, which slowly became gummy. The mixture was stirred for 2 hours and heated under reflux for 15 minutes. Benzaldehyde[24] (37.4 mmoles) in 15 ml. of ether was added, and the product isolated and recrystallized[4]; yield of III, 2.72 g. (59%), m.p. 91.5–95°. Further recrystallization gave III with m.p. (constant) and mixture[4] m.p. of 93–94°.

The ether solution from the reaction of ethyl bromide and VIII (7.7 mmoles each) with magnesium (15.4 m. atoms) gave no color test[21] and 8.2 m. atoms of metal was recovered, thus indicating that VIII reacted with ethylmagnesium bromide formed rather than with magnesium. In order to confirm the probability of an addition reaction, ethereal ethylmagnesium bromide (70.4 mmoles) was added to VIII (12.96 g., 56.2 mmoles) in 100 ml. of ether during 0.75 hour at about −15°. A gum appeared and the clear solution gave a negative color test.[21] The mixture was stirred at 5° for 2 hours and then at 25°. Since negligible gas was evolved, the reaction evidently involved no "active" hydrogen atoms. A benzene extract of the acidified product contained negligible amounts of *p*-toluenesulfinic acid; hence cleavage of VIII was insignificant. The sirup (12.42 g.) obtained from the extract was shaken with 5% aqueous potassium permanganate until decolorization ceased (145 ml.). The saturated residue (8.1 g.) upon distillation at 98–100° (0.01 mm.) yielded 3.80 g. of colorless oil, $n^{25}_{D}$ 1.5308–1.5311, which contained no chlorine. *Anal.* C, 64.49; H, 7.70; S, 11.47; nitro derivative[39] (547.9 mg., m.p. 63–64°, from 667.3 mg.), constant m.p. 65.5–66°. *Anal.* C, 53.61, 53.46; H, 5.45, 5.72; N, 5.16; mol. wt., 186, 191 (Rast in camphor), 433, 482 (ebullioscopic, in butanone). A similar reaction probably also occurred with IX but the product was intractable.

Reaction of X and ethyl bromide (11.7 mmoles each) with magnesium (23.6 m. atoms) and 0.2 g. of catalyst[36] yielded oil from which only 21% of X was recovered; the residue decolorized aqueous potassium permanganate. Similarly, reaction of XI (9.6 mmoles) and ethyl bromide (10.4 mmoles) with magnesium (19.5 m. atoms) and catalyst[36] yielded XI (26%) and a little halogen-free unsaturated material, m.p. 62–64° (probably vinyl *p*-tolyl sulfone); in a similar experiment at least 50% of one molar equivalent of gas was evolved and, after addition of benzaldehyde, the only isolable materials were traces of XI and *p*-toluenesulfinic acid, and 85% of the magnesium taken in excess of ethyl bromide. XIII reacted with ethyl bromide and magnesium (7 hours in refluxing ether) but, although titration[37] indicated basic magnesium in 35% yield (a negative color test[21] indicated negligible ethylmagnesium bromide), recovery of 81% of metal in excess of ethyl bromide and evidence for several organic products suggest that side reactions probably greatly exceeded any useful conversion to a Grignard reagent.[40]

**Precipitation of Diphenyl Sulfone by Ethylmagnesium Bromide.**—When 3.3 mmoles of 3.43 *N* ethereal ethylmagnesium bromide was added to 6.5 mmoles of dry diphenyl sulfone in 100 ml. of ether, a flocculent precipitate appeared which soon became gummy. Centrifugation, washing under nitrogen with two 25-ml. portions of benzene, and drying to constant weight resulted in 219.8 mg. of gummy solid, which upon titration[37] evolved gas and proved equivalent to 1.1 mmoles of basic magnesium. Filtration of the chilled solution then yielded 51.5 mg. of diphenyl sulfone, m.p. 124–128° (undepressed by authentic material). A duplicate experiment, except for omission of the sulfone, resulted only in 10.1 mg. of precipitate (probably in consequence of slight hydrolysis during manipulation).

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[39] V. N. Ipatieff and B. S. Friedman, THIS JOURNAL, **61**, 684 (1939).

[40] It is worth noting that the activity of V and the inactivity of X, XI and XIII in entrainment conversions support the suggestion that reactivity of a halogen atom with Grignard reagents may be expected if the hydrogen atom which it replaces is "active" toward Grignard reagents (ref. 15, p. 1062).

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[CONTRIBUTION FROM THE SCHOOL OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

# 2-Phenylselenosemicarbazide and Related Compounds. Dipole Moment and Spectroscopic Measurements on Analogous Ureides, Thioureides, and Selenoureides[1,2]

BY HENRY G. MAUTNER[3] AND W. D. KUMLER

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2-Phenylselenosemicarbazide, its sulfur and oxygen analogs, and a series of their *para*-substituted benzaldehyde derivatives were synthesized. The dipole moments, infrared and ultraviolet spectra of some analogous carbamyl, thiocarbamyl and selenocarbamyl compounds were investigated. Evidence is cited that the contribution of the form with a separation of charge is greatest in the selenocarbonyl, less in the thiocarbonyl and least in the carbonyl group.

Since 1946, when Domagk[4] first reported the antitubercular activity of *p*-acetamidobenzaldehyde thiosemicarbazone, large numbers of thiosemicarbazones were synthesized and tested.[5–7] Among these, highest antitubercular action was found to reside in a series of *para*-substituted benzaldehyde derivatives and somewhat lower but still considerable *in vitro* activity in thiosemicarbazide itself.[8] More recently it was found that thiosemicarbazide and thiosemicarbazones also possess some ability to inhibit the growth of fungi.[9,10]

Replacement of sulfur by oxygen resulted in complete or partial loss of both the antitubercular and the antifungal action of these compounds.[10,11]

Since it has been stated that thiosemicarbazones exert their antimicrobial action by forming copper chelates,[10,12,13] the lower effectiveness of semicar-

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[1] The material reported here represents part of a thesis submitted by Henry G. Mautner in partial fulfillment of the requirements for the Ph.D. degree in pharmaceutical chemistry.

[2] This paper was presented before the Division of Medicinal Chemistry at the 127th Meeting of the American Chemical Society, Cincinnati, Ohio, March–April, 1955.

[3] Fellow of the American Foundation for Pharmaceutical Education 1954–1955.

[4] G. Domagk, *et al.*, *Naturwissenschaften*, **33**, 315 (1946).

[5] R. Donovick, *et al.*, *J. Bact.*, **59**, 603 (1950).

[6] R. Donovick, *et al.*, *ibid.*, **59**, 667 (1950).

[7] E. Hoggarth, *et al.*, *Brit. J. Pharmacol.*, **4**, 248 (1949).

[8] J. P. Jouin and Buu-Hoi, *Ann. inst. Pasteur.*, **72**, 580 (1946).

[9] C. W. Johnson, J. W. Joyner and R. P. Perry, *Antibiotics & Chemotherapy*, **2**, 636 (1952).

[10] H. W. Gausman, *et al.*, *Botan. Gaz.*, **114**, 292 (1953).

[11] D. Hamre, J. Bernstein and R. Donovick, *J. Bact.*, **59**, 679 (1950).

[12] E. Carl and P. Marquardt, *Z. Naturforsch.*, **4B**, 280 (1949).

[13] K. Liebermeister, *ibid.*, **5B**, 79 (1950).