[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Reaction of Gramine with Methyl Iodide. The Preparation and Properties of Gramine Methiodide

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The methylation of gramine with methyl iodide in alcoholic solution leads to a substance, previously regarded as gramine methiodide, which is shown to be a mixture consisting largely of 3,3'-bis-indolylmethyldimethylammonium iodide and tetramethylammonium iodide. Pure gramine methiodide is described for the first time. The use of gramine and its alkylation products as alkylating agents is discussed and certain anomalous observations which have appeared in the literature are accounted for. The cleavage of gramine with acetic anhydride is described.

The reaction of gramine (I) with methanolic potassium hydroxide in the presence of methyl iodide leads to 3-methoxymethylindole (II), while the use of ethanolic alkali and ethyl iodide leads to 3-ethoxymethylindole (III). These reactions have been interpreted[1] as proceeding by way of a hydrolytic cleavage of gramine to dimethylamine and 3-hydroxymethylindole, followed by methylation or ethylation of the latter by the alkyl halide. It appeared to us more likely that the 3-alkoxymethylindoles arose as a result of the attack of alkoxide ion on the gramine alkiodide formed by an initial alkylation of gramine. That the function of the alkyl halide used was not to alkylate an intermediate 3-hydroxymethylindole was readily demonstrated by carrying out the reactions

$$\text{Gramine} + \text{methanolic NaOCH}_3 + \text{C}_2\text{H}_5\text{I} \longrightarrow \text{3-methoxymethylindole (II)} \quad (1)$$

$$\text{Gramine} + \text{ethanolic NaOC}_2\text{H}_5 + \text{CH}_3\text{I} \longrightarrow \text{3-ethoxymethylindole (III)} \quad (2)$$

An attempt to clarify these reactions by preparing gramine methiodide (IV) and allowing it to react with sodium alkoxides led to the discovery that the substance which has heretofore been described as gramine methiodide is not this compound.

The alkylation of gramine with methyl iodide has been described many times.[2–7] The conflicts which are found in these papers regarding the properties of gramine methiodide appeared to be resolved when it was reported[7] that the compound exhibits a remarkable dimorphism, existing in low-melting (175°, 176–177°) and high-melting (over 300°) forms. It is worthy of note that in none of the articles mentioned were carbon–hydrogen analyses reported, and only one[3] gives the result of an analysis for iodine. The studies of Snyder and his co-workers[6] and of Albertson, Archer and Suter[8] presented a further anomaly in that alkylations with gramine methiodide appeared to require more vigorous conditions and to give poorer yields than similar alkylations carried out with gramine in the presence of an alkyl halide or sulfate.

Our samples of "gramine methiodide," prepared by methods described by previous investigators,[2–7] corresponded in their properties with the published descriptions of the m.p. 175–176° material. The quaternary salt formed readily and in excellent yield when gramine was treated with methyl iodide in alcoholic solutions. It was surprising to find that when this substance was added to an excess of methanolic sodium methoxide and dry nitrogen passed through the solution, trimethylamine was formed in very low yields or, in some cases, not at all. No trimethylamine was formed when the "gramine methiodide" used was that prepared with a slight excess of gramine over methyl iodide.

In a closer examination of this "gramine methiodide," the two "isomers" were separated.[7] The high-melting material was very water-soluble and showed no absorption in the ultraviolet; it proved to be tetramethylammonium iodide. The low-melting "isomer" was insoluble in water. It was found to have an ultraviolet absorption spectrum (Fig. 1) similar to that of gramine (Fig. 1) but to give analytical figures which agreed moderately well with those calculated for 3,3'-bis-indolylmethyldimethylammonium iodide (V). Upon further purification it had m.p. 171–171.5° and analyzed correctly for V.

These results clarified the observations made when the "gramine methiodide" was treated with sodium methoxide. The absence of trimethylamine and the presence of gramine itself among the products of this reaction, and the variability of the results with modifications in the conditions of the gramine-methyl iodide reaction suggested that the "gramine methiodide" was a mixture of tetramethylammonium iodide, V, and occasionally some authentic gramine methiodide. The formation of these compounds is represented by the reactions

$$\underset{\text{(I)}}{\text{RCH}_2\text{N(CH}_3)_2} + \text{CH}_3\text{I} \longrightarrow \underset{\text{(IV)}}{\text{RCH}_2\text{N}^+\text{(CH}_3)_3\,\text{I}^-}$$

$$\text{RCH}_2\text{N(CH}_3)_2 + \text{RCH}_2\text{N}^+\text{(CH}_3)_3\,\text{I}^- \longrightarrow \underset{\text{(V)}}{\text{(RCH}_2)_2\text{N}^+\text{(CH}_3)_2\,\text{I}^-} + \text{N(CH}_3)_3$$

$$\text{N(CH}_3)_3 + \text{CH}_3\text{I} \longrightarrow \text{N}^+\text{(CH}_3)_4\,\text{I}^-$$

$$(\text{R} = \text{3-indolyl})$$

It is clear that the relative proportions of the final products will depend upon the mode of addition and the relative amounts of the reagents. That V and tetramethylammonium iodide are formed in about equal amounts was found by their quantitative estimation; the amounts found indicate that little gramine methiodide is formed when the alkyla-

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(1) J. Madinaveitia, *J. Chem. Soc.*, 1927 (1937).

(2) H. V. Euler and H. Erdtmann, *Ann.*, **520**, 1 (1935).

(3) A. Orechoff and S. Norkima, *Ber.*, **68**, 436 (1935).

(4) T. Wielan and Chi Yi Hsing, *Ann.*, **526**, 188 (1936).

(5) H. Kühn and O. Stein, *Ber.*, **70**, 567 (1937).

(6) H. R. Snyder, C. W. Smith and J. M. Stewart, THIS JOURNAL, **66**, 200 (1944).

(7) C. H. Schramm, *ibid.*, **73**, 2961 (1951).

(8) N. F. Albertson, S. Archer and C. M. Suter, *ibid.*, **67**, 36 (1945).

tion is conducted in the manner previously[2-7] described.

The preparation of authentic gramine methiodide (IV) was readily accomplished by adding gramine slowly to a large excess of methyl iodide. Even under the conditions the initial product is not pure IV, but the small amounts of V and tetramethylammonium iodide which were present were easily removed. Pure IV is quite water-soluble, in contrast to V and the so-called "gramine methiodide" of m.p. 175–176°. The absorption spectrum of IV is shown in Fig. 1.

Gramine methiodide reacts readily with sodium methoxide in methanol at ordinary temperature to yield trimethylamine and 3-methoxymethylindole in excellent yields. When it was allowed to stand for a day with alcoholic potassium cyanide the liberation of trimethylamine was nearly quantitative and an excellent yield of 3-indoleacetic acid was isolated after hydrolysis of the resulting nitrile.

The foregoing observations clarify the experimental results described in earlier reports of the results of studies on gramine and its alkylation reactions. The differences in ease of reaction and yields of products reported by Archer, *et al.*,[8] who used gramine and methyl sulfate to alkylate sodioacetamidomalonic ester, and by Snyder, *et al.*,[6] who alkylated the same ester with the so-called "gramine methiodide," are now understandable.

It is clear that gramine methiodide (or methosulfate) formed *in situ*[8] undergoes rapid displacement of trimethylamine when attacked by a nucleophilic agent such as gramine or a sodiomalonic ester. The use of V instead of IV necessitates the use of vigorous conditions to utilize all of the indole residues since the first step in the reaction of V results in the liberation of gramine. Alkylations by means of gramine appear to be relatively slow reactions,[9] and it is probable that the occasionally inferior yields of products obtained when the impure V ("gramine methiodide") was used were the result of the incomplete utilization of half of the indole residues due either to the incomplete reaction or to losses during extended periods of reaction at elevated temperatures.

The work of Madinaveitia[1] has been cited by Goutarel, *et al.*,[10] as offering an analogy to the cleavage of cinchonamine to diacetylallocinchonamine by the action of acetic anhydride. The latter reaction appears to bear only a distant relationship to the displacement of trimethylamine from gramine methiodide, but resembles closely many other cleavages of trialkylamines by acid anhydrides and halides.[11] Gramine itself reacts with boiling acetic anhydride with the formation of N-acetyl-3-acetoxymethylindole (VI). The course of this reaction may involve an intermediate such as VII

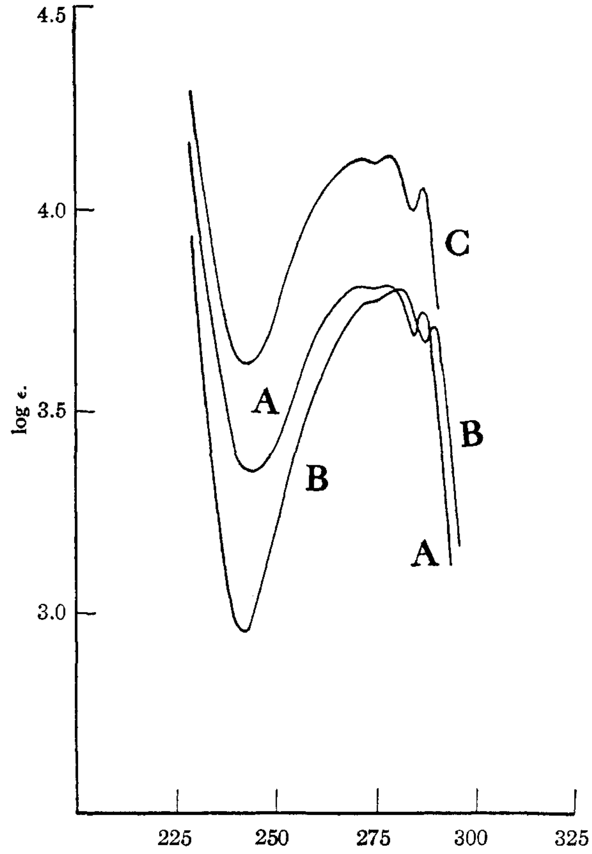
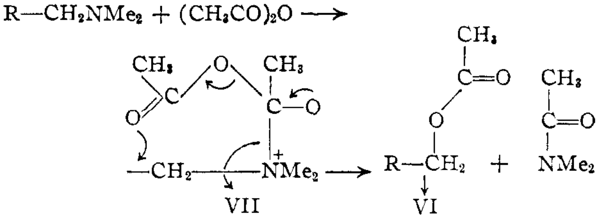


Fig. 1.—Absorption spectra in 95% ethanol of: A, gramine methiodide; B, gramine; C, 3,3'-bisindolylmethyldimethylammonium iodide.



(R = 3-indolyl)

The ultraviolet absorption spectra of VI and of N-acetylskatole are shown in Fig. 2; the infrared spectra are given in Fig. 3.

Experimental

3-Ethoxymethylindole from Gramine, Methyl Iodide and Sodium Ethoxide.—To a cooled solution of 0.35 g. of sodium in 15 ml. of absolute ethanol was added 1.0 g. (5.75 mM.) of gramine.[5] After the addition of 2.1 g. of methyl iodide a stream of dry nitrogen was passed through the solution and into a solution of standard hydrochloric acid. After 24 hours a back-titration of the acid showed that 0.97 mM. of a volatile amine had been collected. The reaction mixture contained 4.43 mM. of tetramethylammonium iodide. The volatile amine was identified as trimethylamine by means of its picrate (m.p. and mixed m.p. 224–225°). The total yield of trimethylamine was 94%. The alcoholic filtrate was poured into water, affording 4.4 mM. of 3-ethoxymethylindole, m.p. 63–64° (Madinaveitia[1] reported m.p. 93–94°, possibly a typographical error). *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.36; H, 7.49. Found: C, 75.11; H, 7.83.

When the experiment was carried out as described by Madinaveitia (using ethyl iodide), the same compound was obtained.

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[9] E. E. Howe, A. J. Zambito, H. R. Snyder and M. Tishler, THIS JOURNAL, **67**, 38 (1945).

[10] R. Goutarel, M. M. Janot, V. Prelog and W. I. Taylor, *Helv. Chim. Acta*, **33**, 150 (1950).

[11] *Cf.* for example, S. N. McGeoch and T. S. Stevens, *J. Chem. Soc.*, 1465 (1934); E. Späth and O. Hromatka, *Ber.*, **62**, 325 (1929); J. H. Gardner, N. R. Easton and J. R. Stevens, THIS JOURNAL, **70**, 2906 (1948); R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, *ibid.*, **71**, 2821 (1949).

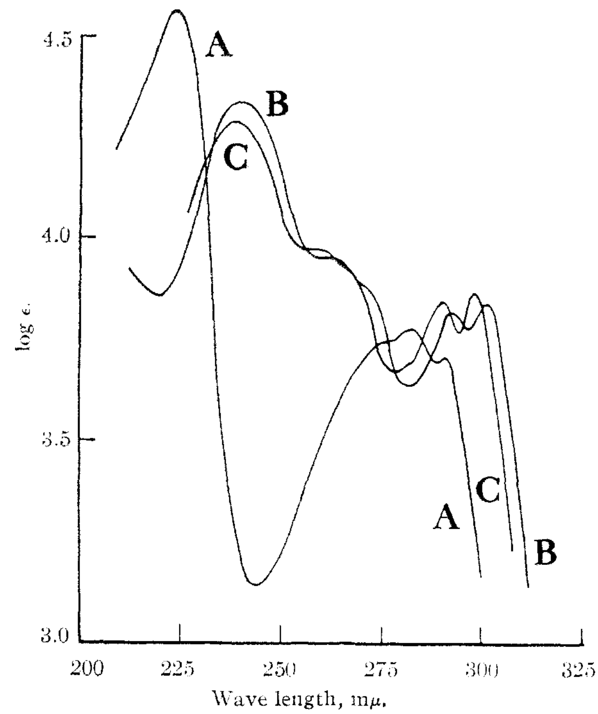

Fig. 2.—Ultraviolet absorption spectra in 95% ethanol of: A, skatole; B, N-acetylskatole; C, N-acetyl-3-acetoxymethylindole.

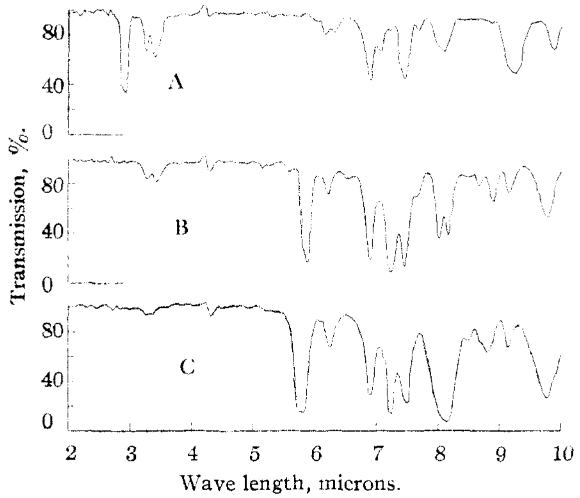

Fig. 3.—Infrared absorption spectra of: A, skatole; B, N-acetylskatole; C, N-acetyl-3-acetoxymethylindole.

3-Methoxymethylindole from Gramine, Sodium Methoxide and Ethyl Iodide.—This experiment was conducted in substantially the same way as that described above. Dimethylethylamine was identified as the picrate, m.p. 206–207°.[12] The 3-methoxymethylindole melted at 98–99° (reported,[1] 99–100°).

Methylation of Gramine with Methyl Iodide.—To a solution of 1.0 g. (5.75 mM.) of gramine in 7 ml. of absolute ethanol was added 0.81 g. (5.7 mM.) of methyl iodide. After one hour at 0–5°, the solid which had formed was collected, washed with ether and dried. It weighed 1.5 g. and melted at 170–171.5°.

A saturated solution of 0.5 g. of this product in hot methanol was allowed to cool without disturbance in an ice-bath. The crystals (90 mg.) which separated had a m.p. over 300°. Concentration of the filtrate afforded a second crop, which had m.p. 175–176° after recrystallization from methanol and a further recrystallization from ethanol (*cf.* ref. 7).

Anal. of cpd. m.p. 175–176°. Calcd. for gramine methiodide: C, 45.57; H, 5.42; I, 40.13. Calcd. for V: C, 54.12; H, 5.32; I, 29.98. Found: C, 55.69; H, 5.14; I, 29.42.

The tetramethylammonium iodide (m.p. over 300°) which separated in the first recrystallization, was recrystallized from methanol.

Anal. Calcd. for $C_4H_{12}NI$: C, 23.88; H, 6.02; I, 63.10. Found: C, 23.75; H, 6.30; I, 62.84.

3,3'-Bisindolylmethyldimethylammonium Iodide (V).—Purification of the 175–176° material described above by several recrystallizations from aqueous methanol yielded a compound which, after a further recrystallization from ethanol, melted at 171–171.5°.

Anal. Calcd. for $C_{20}H_{22}N_3I$: C, 55.69; H, 5.14. Found: C, 55.52; H, 5.40.

Composition of the Gramine Methylation Product.—A methylation of gramine (3.0 g.) with methyl iodide (2.45 g.) in absolute ethanol yielded 5.1 g. of product with m.p. 169–171°.

From 1.70 g. of this material were isolated 0.45 g. (2.25 mM.) of tetramethylammonium iodide and 0.80 g. (1.86 mM.) of incompletely purified V. The maximum possible amount of gramine methiodide (IV) present was estimated as 25%.

Reaction of the Gramine Methylation Product (M.p. 169–171°) **with Sodium Methoxide.**—To a solution of 1.20 g. of sodium in 20 ml. of methanol was added 1.0 g. (equivalent to 3.16 mM. of gramine) of the m.p. 169–171° quaternary salt mixture. Dry nitrogen was passed through the solution and into standard hydrochloric acid. After 24 hours the volatile amine collected amounted to 0.25 mM. (8%). It was identified as trimethylamine. From the reaction mixture was isolated 0.31 g. of tetramethylammonium iodide. The alcoholic filtrate yielded an impure mixture from which was isolated a small amount of gramine, m.p. 132–133°.[5]

When sodium ethoxide was used instead of sodium methoxide the yield of volatile amine was 9%.

Gramine Methiodide (IV).—Five grams of gramine was added slowly to 80 ml. of stirred methyl iodide. No appreciable heat evolution was observed. A viscous oil separated on the flask wall. After 12 hours at 5° the oil crystallized, and 9.0 g. of a crude solid was isolated. This was dissolved in 30 ml. of hot methanol and on cooling 0.32 g. of tetramethylammonium iodide separated. The addition of 300 ml. of dry benzene to the methanolic filtrate caused the separation of a white solid with m.p. 162–164°. This was treated with water, leaving undissolved 0.52 g. of V, m.p. 167–170°. The aqueous filtrate was concentrated to 10 ml. and allowed to cool. The crystalline precipitate (5.0 g.) was recrystallized from methanol–benzene. The pure product had m.p. 168–169°; admixture with V lowered the m.p. to 162–165°.

Anal. Calcd. for $C_{12}H_{17}N_2I$: C, 45.57; H, 5.42. Found: C, 45.70; H, 5.57.

Reaction of Gramine Methiodide with Sodium Alkoxides. (A) **Sodium Methoxide.**—To a solution of 1.0 g. of sodium in 20 ml. of methanol was added 1.0 g. (3.16 mM.) of gramine methiodide. A stream of nitrogen was passed through the solution and into standard acid. After 24 hours back-titration showed that 2.91 mM. of volatile amine had been evolved. The amine was converted into the picrate and was thus shown to be trimethylamine. The methanolic reaction mixture was poured into water and yielded 0.40 g. (2.48 mM., 79%) of 3-methoxymethylindole, m.p. 97–98°.

(B) **Sodium Ethoxide.**—The reaction of gramine methiodide with sodium ethoxide under the conditions used in (A) gave a 93% yield of trimethylamine and a 58% yield of 3-ethoxymethylindole.

3-Indoleacetic Acid.—To a solution of 0.5 g. (7.7 mM.) of potassium cyanide in 5 ml. of 60% aqueous ethanol was added 1.0 g. of gramine methiodide. The trimethylamine produced was swept into standard acid by means of a stream of nitrogen. After 24 hours 91% of the theoretical amount of trimethylamine was collected. To the alcohol solution was added 10 ml. of 20% aqueous potassium hydroxide and the mixture refluxed for 10 hours. After removal of the ethanol and acidification of the solution, 0.42 g. (76%) of 3-indoleacetic acid, m.p. 164.5–166.5°, was obtained.

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(12) K. Bowden and L. Marion, *Can. J. Chem.*, **29**, 1037 (1951).

N-Acetyl-3-acetoxymethylindole (VI).—A mixture of 5.0 g. of gramine, 50 ml. of redistilled acetic anhydride and 10 g. of dry sodium acetate was refluxed for 4 hours and poured into a mixture of ice and 5% sodium carbonate solution. After the excess acetic anhydride had decomposed the mixture was extracted with benzene. The dried and decolorized (Norite) benzene extract was evaporated and the oily residue dissolved in ethanol (60 ml.). After removal of about a gram of tarry material the ethanol solution was diluted with water (500 ml.) and cooled. The crystalline product (0.87 g., m.p. 87–89°) was recrystallized from ligroin from which it formed colorless needles, m.p. 90–90.5°.

Anal. Calcd. for $C_{13}H_{13}O_3N$: C, 67.52; H, 5.66. Found: C, 67.43; H, 5.80.

The infrared spectrum of VI (Fig. 3) showed no absorption in the region of 2.9 μ, and showed a two-banded absorption peak at about 5.9 μ, indicative of the two acyl carbonyl groups. The infrared spectrum of skatole (Fig. 3) shows the 2.9-μ band; and that of N-acetylskatole (Fig. 3) resembles that of VI except for a sharper 5.9-μ band.

N-Acetylskatole was prepared for comparison of its ultraviolet and infrared spectra with those of VI. This compound has been described by Oddo,[13] who prepared it by the action of acetyl chloride on indolylmagnesium bromide. A simpler method of preparation is as follows: A solution of 2.0 g. of skatole in 20 ml. of acetic anhydride was heated at 180–200° for 7 hours. The excess acetic anhydride was removed by distillation under reduced pressure and the black residue distilled with steam. The crystalline material in the cooled distillate had m.p. 63–66° and after two recrystallizations from aqueous ethanol afforded pure N-acetylskatole, m.p. 66–67°.[13] The spectra of this compound have been referred to above.

NOTE ADDED IN PROOF.—In an article which appeared after this paper had been accepted for publication, J. Thesing and F. Schülde [*Ber.*, **85**, 324 (1952)] described the use of gramine methosulfate for the preparation of 3-indolylacetonitrile, and referred to a preliminary announcement in which the preparation of gramine methiodide is accomplished *via* the methosulfate [C. Schöpf and J. Thesing, *Angew. Chem.*, **63**, 377 (1951)]. Although the details of the latter work have not been reported in detail, it appears that Schöpf and Thesing have reached conclusions in agreement with ours.

Acknowledgments.—The authors' thanks are due Mr. Wm. Netusil for the determination of the spectra and Mr. David Wilson for carbon–hydrogen analyses.

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[13] B. Oddo, *Gazz. chim. ital.*, **43**, II, 190 (1913); *C. A.*, **8**, 85 (1914).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF VANDERBILT UNIVERSITY]

Grignard Reagents of Sulfones. I. Preparation and Reactions of β-Phenyl-β-hydroxyethyl Phenyl Sulfone[1]

BY LAMAR FIELD

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The reaction of phenylsulfonylmethylmagnesium bromide with benzaldehyde yields β-phenyl-β-hydroxyethyl phenyl sulfone (I). The possible utility of compounds such as I for the synthesis of several classes of sulfones is suggested by the conversion of I in good yields to the corresponding keto, chloro, unsaturated and saturated sulfones.

α-Halomagnesium derivatives of sulfones undergo several reactions typical of Grignard reagents including acylation,[2–4] carbonation,[2,5] alkylation,[3] halogenolysis[2,6] and hydrolysis.[2,6] Previous interest in these sulfone derivatives which may be regarded as Grignard reagents of sulfones has apparently originated largely incidentally to other problems. A more direct study appeared to be worthwhile because of the possibility that the reactions of these compounds might provide unique and useful routes to a wide variety of classes of sulfones, many of which would otherwise be difficultly obtainable. Furthermore, the effect which the highly electronegative but relatively unreactive sulfonyl group might have upon the adjacent organometallic bond is of considerable theoretical interest.

Phenylsulfonylmethylmagnesium bromide was found to react with benzaldehyde to give the hydroxysulfone (I) in 90% yield. Intermediates such as I clearly provide attractive routes to several general classes of sulfones, especially unsaturated ones.[7] The reactions described in this paper were carried out to confirm this apparent utility. Studies of the generality of the addition reaction are now in progress.

$$C_6H_5SO_2CH_3 \xrightarrow[(2)\ C_6H_5CHO]{(1)\ C_2H_5MgBr} \underset{\text{I}}{C_6H_5SO_2CH_2CH(OH)C_6H_5}$$

The hydroxysulfone I is formed in a mildly exothermic reaction. It is stable in boiling water, possibly because of its insolubility, but upon treatment with potassium hydroxide[8] gives methyl phenyl sulfone and benzaldehyde. Further characterization of I is afforded by its oxidation to the corresponding ketone, ω-phenylsulfonylacetophenone (II), in 79% yield. Ashworth and Burkhardt[9] found that II is isomerized to phenyl α-phenylethyl sulfone by reduction using acidic conditions followed by reoxidation with chromic acid. In order to eliminate any possibility that a similar rearrangement had occurred in the present instance, II was catalytically reduced to a hydroxysulfone identical with I.

The formation of an unsaturated sulfone such as III by the condensation of benzaldehyde and an

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[1] Presented at the 121st Meeting of the American Chemical Society at Milwaukee, Wis., March 30–April 3, 1952.

[2] E. P. Kohler and H. A. Potter, THIS JOURNAL, **57**, 1316 (1935).

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

[4] E. P. Kohler and H. A. Potter, *ibid.*, **58**, 2166 (1936).

[5] H. Gilman and F. J. Webb, *ibid.*, **71**, 4062 (1949).

[6] W. M. Ziegler and R. Connor, *ibid.*, **62**, 2596 (1940).

[7] A referee directed our attention to a report of H. A. Potter at the Spring (1951) Meeting of the Midland Section of the A.C.S. in which, as Dr. Potter has kindly informed us, the addition of *p*-tolylsulfonylmethylmagnesium bromide to benzophenone and the dehydration of the product were described. Conversions of hydroxysulfones, somewhat similar to some presently described but seemingly used mainly for characterization, were recently reported by H. J. Backer, *et al.* [*Rec. trav. chim.*, **70**, 365 (1951)], and C. C. J. Culvenor, *et al.* [*J. Chem. Soc.*, 2198 (1949)].

[8] E. Rothstein, *ibid.*, 684 (1934).

[9] F. Ashworth and G. N. Burkhardt, *ibid.*, 1791 (1928).