[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SWARTHMORE COLLEGE]

SOME KNOEVENAGEL REACTIONS WITH ETHYLSULFONYLACETIC ACID

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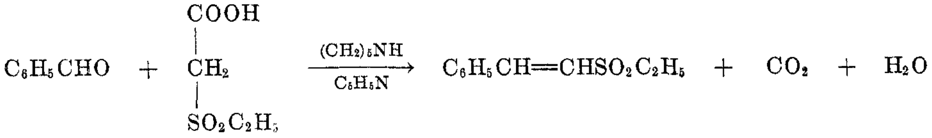
Knoevenagel-type reactions leading to α,β-unsaturated sulfones have been carried out with several arylsulfonylacetic acids (1, 2) and with sulfonyldiacetic acid (3, 4), but no examples involving simple alkylsulfonylacetic acids of the type RSO_2CH_2COOH have been reported.[1] In the course of attempts to synthesize certain α,β-unsaturated sulfones containing the $C_2H_5SO_2CH{=}CH$— moiety, we have had occasion to investigate the behavior of ethylsulfonylacetic acid with benzaldehyde and with phenylacetaldehyde under Knoevenagel reaction conditions and have obtained the results described in the present communication.

Treatment of ethylsulfonylacetic acid (I) with benzaldehyde in pyridine solution in the presence of a small amount of piperidine provided low yields of the expected product, ethyl styryl sulfone (II). Attempts to improve the yield in this reaction by variations in the nature of the solvent, nature and amount of catalyst, and duration of heating were unsuccessful. The presence of relatively large amounts of unreacted benzaldehyde even after prolonged refluxing suggests that a considerable proportion of the ethylsulfonylacetic acid underwent direct decarboxylation to ethyl methyl sulfone. The structure of the unsaturated sulfone was confirmed by hydrogenation to ethyl phenethyl sulfone and by comparison of the ultraviolet absorption spectrum (Fig. 1) with those of appropriate styryl compounds.



$$C_6H_5CHO + \underset{SO_2C_2H_5}{\overset{COOH}{CH_2}} \xrightarrow[C_5H_5N]{(CH_2)_5NH} C_6H_5CH{=}CHSO_2C_2H_5 + CO_2 + H_2O$$

I II

Condensation between I and phenylacetaldehyde was brought about by refluxing in glacial acetic acid in the presence of an equivalent amount of piperidine. In this case, however, the only isolable product proved to be the β,γ-unsaturated sulfone IV resulting from the isomerization of the initially formed Knoevenagel condensation product (III). This behavior is analogous to that of malonic acid, which on condensation with phenylacetaldehyde affords styrylacetic acid instead of the expected γ-phenylcrotonic acid (5). The structure of IV was established unequivocally by reduction to ethyl 3-phenylpropyl sulfone, by ozonolysis to benzaldehyde (identified as the 2,4-dinitrophenylhydrazone), by

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[1] Ethyl n-butylsulfonylacetate has been condensed with several aldehydes to produce unsaturated carbethoxy sulfones, but attempts to hydrolyze and decarboxylate these products have resulted only in a reversal of the original condensation reaction (1).

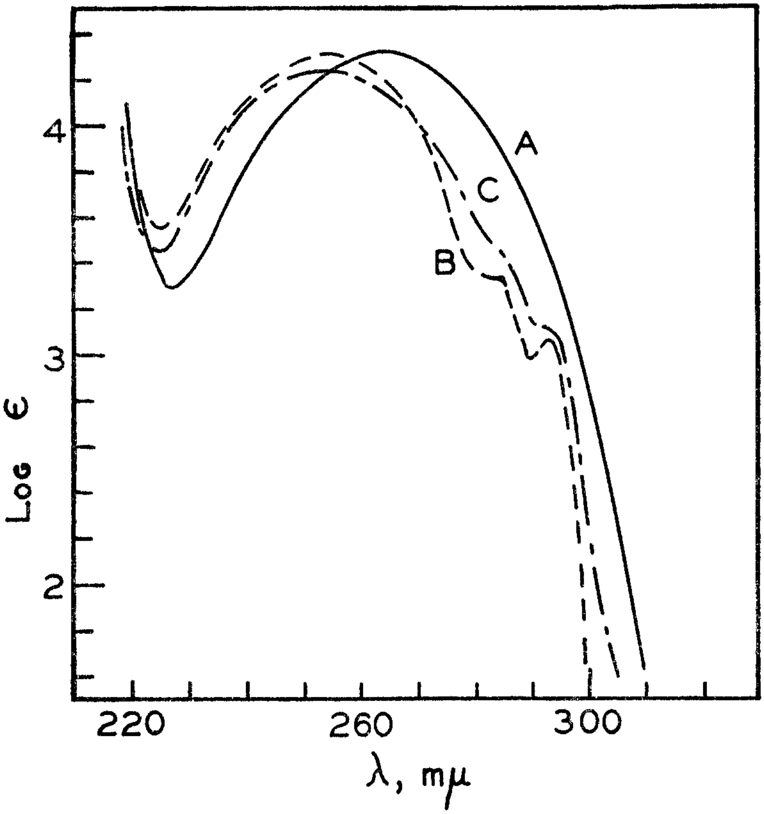

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA IN ETHANOL: A, $C_6H_5CH{=}CHSO_2C_2H_5$; B $C_6H_5CH{=}CHCH_2SO_2C_2H_5$; C, $C_6H_5CH{=}CHCH_2SC_2H_5$.

synthesis from cinnamyl ethyl sulfide, and by comparison of the ultraviolet absorption spectrum (Fig. 1) with those of typical styrene hydrocarbons.

$$C_6H_5CH_2CHO + \text{I} \xrightarrow[\text{AcOH}]{(CH_2)_5NH} \underset{\text{III}}{[C_6H_5CH_2CH{=}CHSO_2C_2H_5]} + CO_2 + H_2O$$

$$\downarrow$$

$$\underset{\text{IV}}{C_6H_5CH{=}CHCH_2SO_2C_2H_5}$$

The absorption spectrum of IV in ethanol was unaffected by the presence of sodium ethoxide, indicating that this β,γ-unsaturated sulfone has little or no tendency to tautomerize to the α,β-unsaturated isomer. All efforts to prepare the latter compound (III) were unsuccessful, including a series of attempts to dehydrate the β-hydroxysulfone VI produced in the following series of reactions:

$$C_6H_5CH_2COCH_2Cl + C_2H_5SO_2Na \longrightarrow \underset{\text{V}}{C_6H_5CH_2COCH_2SO_2C_2H_5}$$

$$\xrightarrow[\text{Pt}]{H_2} \underset{\text{VI}}{C_6H_5CH_2CHOHCH_2SO_2C_2H_5}$$

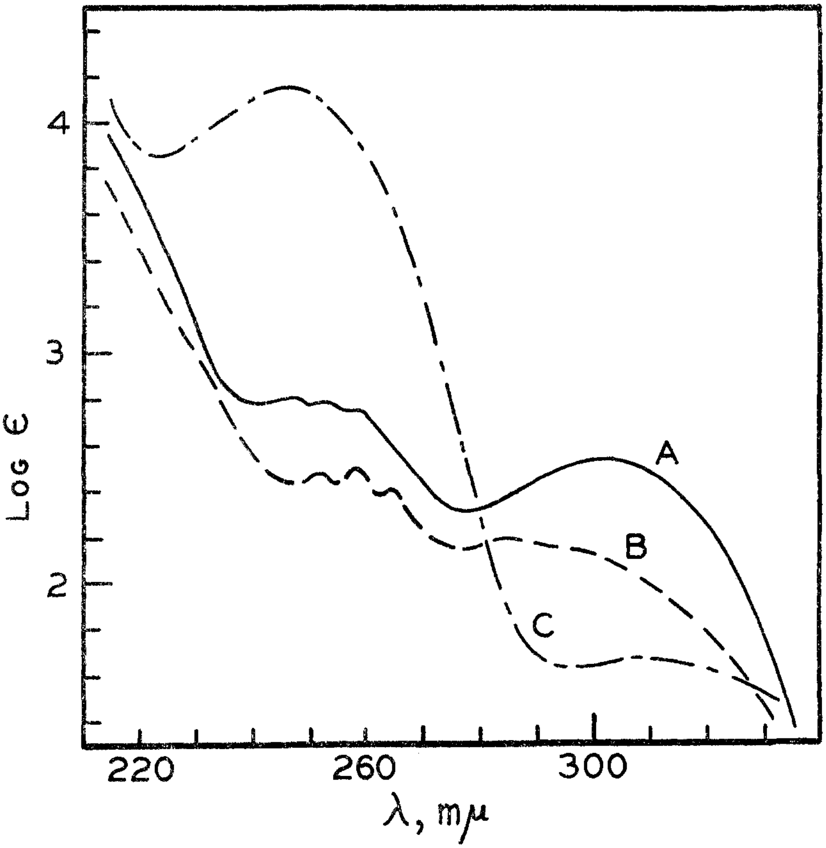

FIG. 2. ULTRAVIOLET ABSORPTION SPECTRA: A, $C_6H_5CH_2COCH_2SC_2H_5$ in ethanol; B, $C_6H_5CH_2COCH_2SO_2C_2H_5$ in ethanol; C, $C_6H_5CH_2COCH_2SO_2C_2H_5$ in 0.01 *N* ethanolic sodium ethoxide.

Although a variety of dehydrating agents and conditions were employed, only unchanged VI or intractable tars were obtained in these experiments. The properties and methods of preparation of a number of new organic sulfur compounds which were synthesized in the course of this work are described in the experimental section.

EXPERIMENTAL[2]

Ethyl styryl sulfone (II). A mixture of 7.6 g. (0.050 mole) of ethylsulfonylacetic acid (6), 6.0 g. (0.056 mole) of benzaldehyde, 25 ml. of anhydrous pyridine, and 3 drops of piperidine was heated on the steam-bath for 6 hours and then was refluxed for 8 hours, after which it was cooled and poured into a mixture of 40 ml. of concentrated hydrochloric acid and 60 g. of ice. The aqueous suspension was extracted several times with chloroform, and the combined extracts were washed with saturated sodium bisulfite solution until free of benzaldehyde and were dried over magnesium sulfate. After removal of the chloroform on the steam-bath, an oily residue was obtained which yielded a waxy solid on trituration with water.

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[2] Microanalyses are by the Clark Microanalytical Laboratory, Urbana, Illinois.

This product was collected, dried on a porous plate, and recrystallized from a mixture of benzene and petroleum ether (b.p. 35–60°) to give 1.2 g. (12%) of colorless crystals, m.p. 66–67°.

Anal. Calc'd for $C_{10}H_{12}O_2S$: C, 61.2; H, 6.2.
Found: C, 60.9; H, 6.1.

Ethyl phenethyl sulfone. A solution of 0.36 g. of II in 20 ml. of glacial acetic acid was hydrogenated in the presence of 0.3 g. of a 10% palladium-charcoal catalyst at 3 atmospheres pressure for 1 hour. After removal of the catalyst, the solution was evaporated to about one-third of its original volume and diluted with water. The resultant precipitate was collected, washed with water, and dried; yield 0.30 g. (83%) of almost colorless solid, m.p. 76–77°. Recrystallization from benzene-petroleum ether gave colorless crystals melting at 79–80°.

Anal. Calc'd for $C_{10}H_{14}O_2S$: C, 60.6; H, 7.1.
Found: C, 60.8; H, 7.0.

The same compound was obtained when ethyl phenethyl sulfide (7) (1.66 g., 0.010 mole) was oxidized with 30% hydrogen peroxide (2.5 ml., 0.022 mole) in glacial acetic acid (10 ml.) in the usual way. Concentration of the reaction mixture to a small volume followed by dilution with water provided a quantitative yield (2.0 g.) of colorless solid, m.p. 79–80°, which showed no depression on admixture with the hydrogenation product described above.

Cinnamyl ethyl sulfone (IV). A mixture of 3.04 g. (0.020 mole) of ethylsulfonylacetic acid (6), 2.40 g. (0.020 mole) of freshly distilled phenylacetaldehyde, 1.70 g. (0.020 mole) of piperidine, and 5 ml. of glacial acetic acid was refluxed for 1 hour and allowed to stand overnight. The reaction mixture was filtered to remove a small amount of crystalline precipitate, and the filtrate was concentrated under reduced pressure. The oily residue was taken up in 10 ml. of chloroform and the solution was washed with water and with saturated sodium bisulfite solution and then was dried over magnesium sulfate. Removal of the chloroform under reduced pressure left a viscous red oil which gradually crystallized to a tacky solid. Recrystallization of this material from benzene-petroleum ether provided 0.78 g. (19%) of pale yellow crystals which melted at 87–92°. Repeated recrystallization from aqueous ethanol raised the m.p. to 100–101°.

Anal. Calc'd for $C_{11}H_{14}O_2S$: C, 62.8; H, 6.7.
Found: C, 62.7; H, 6.5.

The same compound was produced when a solution of 17.8 g. (0.10 mole) of cinnamyl ethyl sulfide (for preparation see below) in 50 ml. of glacial acetic acid and 50 ml. of acetic anhydride was treated with 25 ml. (0.22 mole) of 30% hydrogen peroxide at 10–15° and allowed to stand at room temperature for 12 days. Removal of the solvent under reduced pressure and dilution of the semicrystalline residue with water afforded 15.8 g. (75%) of colorless waxy ctystals, m.p. *ca.* 70–85° after drying on a porous plate. Recrystallization from aqueous ethanol gave 9.5 g. (45%) of colorless leaflets which melted at 98–100° and showed no m.p. depression when mixed with the Knoevenagel condensation product described above.

Treatment of IV (0.50 g.) with bromine (0.40 g.) in chloroform (2.0 ml.) gave, after removal of the solvent and recrystallization of the waxy residue from benzene, 0.28 g. of *2,3-dibromo-3-phenylpropyl ethyl sulfone* as colorless needles, m.p. 125–126°.

Anal. Calc'd for $C_{11}H_{14}Br_2O_2S$: C, 35.7; H, 3.8.
Found: C, 35.8; H, 3.9.

Ozonolysis of IV in the presence of 2,4-dinitrophenylhydrazine (8) gave an orange microcrystalline solid which melted at 236–237° after recrystallization from ethanol and which failed to depress the m.p. of authentic benzaldehyde 2,4-dinitrophenylhydrazone (m.p. 236–237°).

Ethyl 3-phenylpropyl sulfone. A solution of 0.45 g. of IV in 50 ml. of absolute ethanol was hydrogenated in the presence of 0.05 g. of Adams' platinum oxide catalyst at 3 atmospheres pressure for 7 hours. Removal of the catalyst and evaporation of the solvent provided 0.43

g. (93%) of light brown crystals, m.p. 43–48°. Recrystallization from petroleum ether gave colorless silky needles which melted at 47–48°.

Anal. Calc'd for $C_{11}H_{16}O_2S$: C, 62.2; H, 7.6.

Found: C, 62.6; H, 7.5.

The same compound was obtained when a mixture of 3.98 g. (0.020 mole) of 3-bromopropylbenzene, 3.48 g. (0.030 mole) of sodium ethanesulfinate, and 20 ml. of absolute ethanol was refluxed for 10 hours and then filtered, concentrated to a small volume by distillation, and diluted with water. The precipitated solid was collected, washed with water, and dried to give 3.41 g. (80%) of crude product melting at 40–44°. Recrystallization from petroleum ether raised the m.p. to 47–48°. This material showed no m.p. depression when mixed with the sulfone obtained by hydrogenation of IV as described above.

Cinnamyl ethyl sulfide. To a cold solution of 8.7 g. (0.38 g.-atom) of sodium in 150 ml. of absolute ethanol there was added 23.6 g. (0.38 mole) of ethanethiol, followed by 58.0 g. (0.38 mole) of cinnamyl chloride (9) added dropwise at such a rate as to cause the mixture to reflux gently. The mixture then was refluxed for another 15 minutes (total reaction time *ca.* 30 minutes), after which it was cooled, filtered, and concentrated to a small volume by distillation. The residual oil was diluted with water, the layers were separated, and the aqueous layer was extracted several times with ether. The combined oil layer and ether extracts were washed with water, dried over magnesium sulfate, and evaporated on the steam-bath. Distillation of the residue under reduced pressure yielded 58.9 g. (87%) of a pale yellow oil, b.p. 115–130° at 5 mm. On redistillation most of this material (47.6 g.) was obtained as a colorless oil boiling at 123–126° at 5 mm.

Anal. Calc'd for $C_{11}H_{14}S$: C, 74.1; H, 7.9.

Found: C, 74.2; H, 8.1.

Benzyl ethylthiomethyl ketone. Ethanethiol (5.0 g., 0.080 mole) was added to a solution of 1.8 g. (0.080 g.-atom) of sodium in 90 ml. of absolute ethanol and the mixture was cooled in an ice-bath while 13.6 g. (0.080 mole) of benzyl chloromethyl ketone[3] was run in dropwise over a 10-minute period. After standing in the ice-bath with occasional agitation for another 20 minutes, the mixture was filtered and concentrated to a small volume by distillation. Dilution of the residue with water caused the separation of an oil phase, which was removed, and the aqueous phase was extracted several times with ether. The combined oil phase and ether extracts were dried over magnesium sulfate and distilled to yield 13.4 g. (86%) of a pale yellow oil, b.p. 134–138° at 5 mm. Redistillation of a portion of this material provided an analytical sample with b.p. 124° at 2 mm.

Anal. Calc'd for $C_{11}H_{14}OS$: C, 68.0; H, 7.3.

Found: C, 68.0; H, 7.0.

α-(Ethylthiomethyl)phenethyl alcohol. A mixture of 19.4 g. (0.10 mole) of benzyl ethylthiomethyl ketone, 61.2 g. (0.30 mole) of aluminum isopropoxide, and 400 ml. of isopropyl alcohol was distilled slowly through a 12-inch Vigreux column at such a rate as to provide 340 ml. of distillate after 6 hours. The residue was treated with a mixture of 110 ml. of concentrated hydrochloric acid and 300 g. of ice, and the resultant aqueous suspension was extracted with ether. The combined ether extracts were washed with aqueous sodium bicarbonate and dried over magnesium sulfate. After removal of the ether, the residual oil was distilled under reduced pressure to give 13.1 g. (67%) of a colorless oil, b.p. 126–132° at 2–3 mm.

Anal. Calc'd for $C_{11}H_{16}OS$: C, 67.3; H, 8.2.

Found: C, 67.8; H, 8.2.

Benzyl ethylsulfonylmethyl ketone (V). A mixture of 15.1 g. (0.090 mole) of benzyl chloromethyl ketone,[3] 15 g. (0.13 mole) of sodium ethanesulfinate, and 100 ml. of absolute ethanol was refluxed for 6 hours, after which it was cooled and diluted with 300 ml. of water. The

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[3] Prepared in 90% yield (b.p. 138–140° at 20 mm.; 116–118° at 6 mm.) by the method of McPhee and Klingsberg (10).

resultant precipitate was collected, washed with water, and dried to give 16.9 g. (84%) of yellow leaflets, m.p. 67–71° with previous sintering. Decolorization with Nuchar and recrystallization from methanol provided colorless leaflets which melted at 74–75°.

Anal. Calc'd for $C_{11}H_{14}O_3S$: C, 58.4; H, 6.2.
Found: C, 58.5; H, 6.3.

α-(Ethylsulfonylmethyl)phenethyl alcohol (VI). A suspension of 2.00 g. of V in 50 ml. of absolute ethanol was hydrogenated in the presence of 0.1 g. of Adams' platinum oxide catalyst and 1 ml. of 0.1 *M* ferrous ammonium sulfate at 60° and three atmospheres pressure for 2 hours. After removal of the catalyst and evaporation of the ethanol under reduced pressure, the semicrystalline residue was diluted with 100 ml. of water and the resultant suspension was extracted with five 10-ml. portions of chloroform. The combined chloroform extracts were washed with three 10-ml. portions of 10% sodium hydroxide solution and finally with water. Acidification of the combined alkaline extracts with hydrochloric acid precipitated 0.90 g. (45% recovery) of unchanged V, which melted at 72–74° after one recrystallization from methanol and showed no m.p. depression on admixture with V. Evaporation of the dried chloroform solution provided 0.98 g. (49%) of a pale yellow crystalline solid, m.p. 67–72°. Recrystallization of this product from benzene-petroleum ether gave colorless crystals which melted at 72–73° and showed a marked m.p. depression on admixture with V.

Anal. Calc'd for $C_{11}H_{16}O_3S$: C, 57.9; H, 7.1.
Found: C, 58.0; H, 7.1.

Ultraviolet absorption spectra. The ultraviolet absorption spectra were determined with a Beckman Model DU spectrophotometer, readings being made at intervals of 5 mμ or less (1 mμ in the vicinity of absorption maxima) with a nominal band width of approximately 1 mμ. The wavelengths and logarithms of the molar extinction coefficients at the absorption maxima and at prominent inflection points are listed in Table I.

TABLE I

ULTRAVIOLET ABSORPTION DATA

Compound	Solvent[a]	Maxima[b]	
		λ (mμ)	log ε
$C_6H_5CH{=}CHSO_2C_2H_5$	EtOH	264	4.32
$C_6H_5CH{=}CHCH_2SO_2C_2H_5$	EtOH[c]	255	4.31
		(283)	3.34
		293	3.06
$C_6H_5CH{=}CHCH_2SC_2H_5$	EtOH	254	4.24
		(292)	3.12
$C_6H_5CH_2COCH_2SC_2H_5$	EtOH	248	2.81
		252	2.80
		302	2.54
$C_6H_5CH_2COCH_2SO_2C_2H_5$	EtOH	252	2.48
		258	2.50
		264	2.42
		286	2.19
$C_6H_5CH_2COCH_2SO_2C_2H_5$	NaOEt	246	4.16
		308	1.66

[a] EtOH designates absolute ethanol; NaOEt designates 0.01 *N* sodium ethoxide in absolute ethanol. [b] Wavelengths in parentheses refer to inflection points. [c] Identical results were obtained with this compound in 0.01 *N* alcoholic sodium ethoxide.

SUMMARY

Ethylsulfonylacetic acid has been condensed with benzaldehyde and with phenylacetaldehyde under Knoevenagel reaction conditions to give ethyl styryl sulfone and cinnamyl ethyl sulfone, respectively. The latter compound is presumably produced by isomerization of the initially formed ethyl 3-phenylpropenyl sulfone. The properties and methods of preparation of a number of new organic sulfur compounds are described.

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