

tions were collected ($n_D^{25} 1.6716-1.6493$). Fractions 1-3 contained principally unchanged starting material. The infrared spectrum of fraction 3 was identical to that of the starting material. Analysis of the ultraviolet spectra of V, 2-ethoxy-1,4-benzodithiane, and fraction 4 revealed that

fraction 4 had a composition¹⁸ corresponding to 57% V and 43% 2-ethoxy-1,4-benzodithiane. Thus, the yield of recovered V was 87% of the distillable liquid.

MINNEAPOLIS, MINN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

Side-chain Sulfonation of Phenylalkanoic Acids¹

BY WILLIAM E. TRUCE AND CECIL E. OLSON

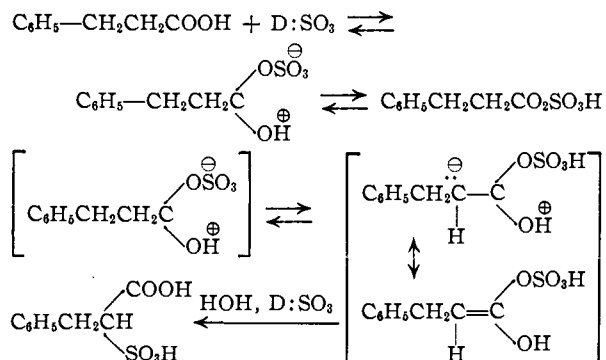
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Several ω -phenylalkanoic acids have been directly sulfonated to α -sulfo- ω -phenylalkanoic acids. ω -Phenylbutyric acid reacts abnormally, undergoing cyclization as well as sulfonation. α -Phenylbutyric acid can be sulfonated by this method, but only in poor yield. Diphenylacetic acid and α -cyclohexylphenylacetic acid do not react with dioxane sulfur trioxide under the conditions employed. A possible explanation for the unreactivity of these acids and a mechanism for the sulfonation reaction is suggested.

The direct sulfonation of phenylalkanoic acids has been reported to result in nuclear sulfonation only. Phenylacetic acid has been sulfonated with concentrated sulfuric acid,² chlorosulfonic acid³ and sulfur trioxide⁴ to give *o*- and *p*-sulfophenylacetic acids. Analogous results have been obtained with β -phenylpropionic acid.⁵

Recently, acetophenone has been sulfonated with dioxane sulfur trioxide to give ω -acetophenonesulfonic acid in good yield.⁶ In view of some structural similarity, it seemed of interest to employ this reagent with phenylalkanoic acids in the attempt to achieve side-chain sulfonation. This paper reports on the reaction of phenylalkanoic acids with dioxane sulfur trioxide leading to α -sulfo- ω -phenylalkanoic acids in good yield. Phenylacetic acid, β -phenylpropionic acid and ω -phenylcaproic acid were converted by this reagent to phenylsulfoacetic acid, β -phenyl- α -sulfopropionic acid and ω -phenyl- α -sulfoacaproic acid, respectively.

The mechanism for the side-chain sulfonation of phenylalkanoic acids with dioxane sulfur trioxide is probably related to the mechanisms proposed for the acid-catalyzed bromination⁷ and the sulfonation⁸ of ketones.



The first step involves polarization of the carboxyl group by coordination with sulfur trioxide. This is followed by the loss of an α -hydrogen to a sulfate ion, dioxane or other Lewis base, giving rise to an active enolate-type intermediate, which would be attacked by the reagent to give the product.

The fact that diphenylacetic acid did not react with dioxane sulfur trioxide can be explained on the basis of steric factors. In the Fisher-Hirschfelder molecular model of α -sulfo-diphenylacetic acid, before the sulfur trioxide group can be attached to the α -carbon, the two phenyl rings must be turned to specific positions. Even then, the entering group must be oriented in a certain manner before it can be connected. These special requirements in orientation of the two reacting groups would hinder the reaction.

To determine whether an electronic effect is also operative in determining the unreactivity of diphenylacetic acid, α -cyclohexylphenylacetic acid was considered. In this molecule a cyclohexyl group replaces a phenyl radical and results in greater steric hindrance at the α -carbon than in diphenylacetic acid. However, the electronic effect of the cyclohexyl group is such that the resulting intermediate would be even more susceptible to attack at the α -carbon by an electrophilic agent. α -Cyclohexylphenylacetic acid did not react with dioxane sulfur trioxide, the unchanged acid being recovered nearly quantitatively. These results demonstrate the importance of steric hindrance by phenyl and cyclohexyl substituents at the α -carbon in the sulfonation reaction.

Related results were obtained in the sulfonation of α -phenylbutyric acid. On the basis of Fisher-Hirschfelder models, this compound should be subject to nearly the same steric hindrance toward sulfonation as diphenylacetic acid, but would have the electron-supplying ethyl group in place of one of the phenyl groups. Treatment of this acid with dioxane sulfur trioxide gave sulfonation but in poor yield (14-20%). More than half of the unreacted acid was recovered in each reaction.

Sulfonation of γ -phenylbutyric acid with dioxane sulfur trioxide produced β -sulfo- α -tetralone and a small amount of γ -phenyl- α -sulfobutyric acid.

(1) Presented at the Atlantic City Meeting of the American Chemical Society, September 15, 1952.

(2) J. Hausman, German Patent 289,028; *Chem. Zentr.*, **87**, 194 (1916).

(3) J. Stewart, *J. Chem. Soc.*, **121**, 2555 (1922).

(4) J. Brust, *Rec. trav. chim.*, **47**, 153 (1928).

(5) J. B. Senderens and J. Abouenc, *Compt. rend.*, **186**, 1497 (1928).

(6) W. E. Truce and C. C. Alfieri, *This Journal*, **72**, 2740 (1950).

(7) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 96.

Excess aluminum chloride,⁸ phosphoric acid and phosphorus pentoxide,⁹ and polyphosphoric acid¹⁰ cause cyclization of γ -phenylbutyric acid. Evidently, dioxane sulfur trioxide (a strong Lewis acid) functions in the same manner. The cyclic ketone, α -tetralone, is then subject to attack by dioxane sulfur trioxide to give the product. The same product was obtained by treating α -tetralone with dioxane sulfur trioxide under the same conditions.

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Experimental

General Procedure for Sulfonation.—All sulfonation reactions were carried out in a 500-ml., three-neck, round-bottom flask equipped with a mechanically-driven, all-glass, sealed stirrer, a constant-pressure dropping funnel and a reflux condenser capped with a drying tube. To maintain a temperature below 10°, the reaction flask was submerged in an ice-water-bath. Where special equipment was used, a description of it will be found with the reaction procedure.

Sulfur trioxide (135.2 g., 1.69 moles) was distilled into 315.5 g. of dry ethylene chloride kept below 10°. Dioxane (150 g., 1.7 moles) was added to the well-stirred solution at a rate that did not raise the temperature above 10°. The resulting slurry was placed in glass-stoppered bottles, sealed and kept in a refrigerator until needed. The color and properties of the reagent did not change during the two months of storage.

Phenylacetic Acid.—Dioxane sulfur trioxide reagent containing 72.5 g. of sulfur trioxide (0.906 mole) in ethylene chloride was allowed to warm to room temperature. Phenylacetic acid (80 g., 0.588 mole) was added over the course of 30 minutes. The solids went into solution in a few minutes and the temperature climbed to 35°. The solution was stirred overnight and then poured into 500 ml. of cold water. The organic layer which was separated and washed several times with water yielded no phenylacetic acid. The aqueous washings were added to the water layer neutralized with sodium hydroxide and evaporated to dryness. The white residue was extracted several times with boiling 70% ethanol. The product obtained on concentrating and cooling the alcohol solution was recrystallized twice from 70% ethyl alcohol and dried at 90° (117 g., 96% yield of sodium sulfophenylacetate).

Anal. Calcd. for $C_8H_8O_2SN_2$: Na, 17.69. Found: Na, 17.91, 17.50.

Oxidation of the sodium salt with alkaline permanganate yielded benzoic acid (76%) whose m.p. (120–122°) was undepressed on admixture with an authentic sample.

Its *S-p*-chlorobenzylthiuronium salt, when dried at 78° (10 mm.) over phosphorus pentoxide, had m.p. 184–186°.

Anal. Calcd. for $C_{24}H_{20}O_5N_4Cl_2S_3$: C, 46.58; H, 4.24; N, 9.1. Found: C, 46.60; H, 4.20; N, 9.34.

The *S-p*-chlorobenzylthiuronium salt of an authentic sample of phenylsulfoacetic acid¹² melted at 184–186°. A mixture of the derivative and the corresponding derivative of the sulfonation product of phenylacetic acid melted at 184–185°.

β -Phenylpropionic Acid.— β -Phenylpropionic acid (17.3 g., 0.115 mole, m.p. 48°) was treated with dioxane sulfur trioxide reagent containing 10.0 g. (0.125 mole) of sulfur trioxide. Sodium β -phenyl- α -sulfopropionate (28.3 g., 89% of theory) was the only product isolated. A sample of the sulfonate was dried over phosphorus pentoxide at 78° (15 mm.).

Anal. Calcd. for $C_9H_8O_5SN_2$: Na, 16.79. Found: Na, 16.48, 16.60.

(8) W. E. Truce and C. E. Olson, *THIS JOURNAL*, **74**, 4721 (1952); W. L. Mosby, *ibid.*, **74**, 2564 (1952); R. T. Arnold, *et al.*, *ibid.*, **69**, 2322 (1947).

(9) A. J. Birch, R. Jaeger and R. Robinson, *J. Chem. Soc.*, 582 (1945).

(10) H. R. Snyder and F. X. Werber, *THIS JOURNAL*, **73**, 2956 (1950).

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(12) J. Papislky, *Jahresber. Forstchr. Chem.*, 856 (1880).

Its *S-p*-chlorobenzylthiuronium derivative had m.p. 176°.

Anal. Calcd. for $C_{23}H_{27}O_5Cl_2N_4S_3$: C, 47.53; H, 4.47. Found: C, 47.47; H, 4.46.

The *S-p*-chlorobenzylthiuronium salt of an authentic sample of β -phenyl- α -sulfopropionic acid¹³ had m.p. 176–177°. A mixed m.p. with the derivative of the sulfonation product of β -phenylpropionic acid was 176°.

γ -Phenylbutyric Acid.— γ -Phenylbutyric acid¹⁴ (20 g., 0.12 mole) was treated with dioxane sulfur trioxide reagent (0.13 mole of SO_3). From the organic layer was isolated 8.87 g. of unchanged γ -phenylbutyric acid. From the aqueous portion, two sulfonation products were obtained. A pale green solid, sodium α -tetralone- β -sulfonate, was isolated first from solution; yield 13.2 g. (78%). Its *S-p*-chlorobenzylthiuronium derivative had m.p. 85–87°.

Anal. Calcd. for $C_{18}H_{19}O_4N_2S_2Cl$: C, 50.6; H, 4.48. Found: C, 49.1; H, 4.59.

The sodium salt of γ -phenyl- α -sulfobutyric acid also was isolated on further concentration of the solution; yield 2.8 g. (13%). Its *S-p*-chlorobenzylthiuronium salt had m.p. 167–168°.

Anal. Calcd. for $C_{26}H_{30}O_5Cl_2N_4S_3$: C, 48.4; H, 4.68. Found: C, 47.2; H, 4.81.

Dioxane sulfur trioxide reagent (9.6 g., 0.12 mole of SO_3) was treated with 14.6 g. (0.1 mole) of α -tetralone. A tan product, sodium 1-tetralone-2-sulfonate, was isolated; yield 17.4 g. (70%). Its *S-p*-chlorobenzylthiuronium derivative melted at 85–87°, and a mixture of this product with the analogous derivative obtained by way of sulfonating γ -phenylbutyric acid melted at 84–86°.

β -Bromo- α -tetralone, prepared¹⁵ from 10.4 g. (0.065 mole) of bromine and 10.0 g. (0.068 mole) of α -tetralone, was dissolved in as little 50% ethanol as possible. Potassium pyrosulfite (4.44 g.) and 2.2 g. of potassium hydroxide were dissolved in 10–15 ml. of water, cooled and added to the alcoholic solution of β -bromo- α -tetralone. The solution was shaken vigorously and left for 18 hours. The resulting tan precipitate was filtered and dried. An *S-p*-chlorobenzylthiuronium salt was prepared in the usual manner; m.p. 86–88°. A mixture of this derivative and the one prepared from the sulfonation product of α -tetralone had m.p. 85–87°.

An authentic sample of γ -phenyl- α -sulfobutyric acid was prepared by the same procedure as described for β -phenyl- α -sulfopropionic acid.¹³ Its *S-p*-chlorobenzylthiuronium salt had m.p. 167–168°. A mixed melting point with the corresponding derivative of the sulfonation product of γ -phenylbutyric acid was 167–169°.

ω -Phenylcaproic Acid.—Ethyl ϵ -benzoylvalerate¹⁶ (101 g., 0.43 mole, b.p. 170° at 7 mm.) and 88 g. of potassium hydroxide in 550 ml. of triethylene glycol were heated at reflux temperature for two hours. The solution was cooled and 55 ml. of hydrazine hydrate (85%)¹⁷ was added. This mixture was refluxed for two hours. The water was drained from the reflux condenser and the temperature was kept at 190° for four hours. After the mixture had cooled, it was diluted with a liter of water and acidified with hydrochloric acid. A dark oil separated and was removed. The aqueous part was washed several times with ether and discarded. The washings and oil were combined and dried over drierite for two days. The product was distilled. A colorless fraction boiled at 175–180° at 9 mm. (lit.¹⁶ b.p. 190–194° at 25 mm.); neut. equiv., 194 (calcd., 192).

Dioxane sulfur trioxide reagent containing 12 g. (0.15 mole) of sulfur trioxide was treated with 15.5 g. (0.081 mole) of ω -phenylcaproic acid. A white solid, sodium α -sulfo- ω -phenylcaproate, was isolated. Its *S-p*-chlorobenzylthiuronium salt had m.p. 162–164°.

Anal. Calcd. for $C_{28}H_{34}O_5Cl_2N_4S_3$: C, 49.9; H, 5.08. Found: C, 50.3; H, 5.10.

An authentic sample of α -sulfo- ω -phenylcaproic acid was prepared using the method employed for α -sulfo- β -phenylpropionic acid.¹³ Its *S-p*-chlorobenzylthiuronium derivative had m.p. 162–164°. A mixture of this derivative and the analogous one from the sulfonation product of ω -phenylcaproic acid melted at 161–162°.

(13) C. H. K. Mulder, *Rec. trav. chim.*, **51**, 174 (1932).

(14) R. V. Christian, Jr., *THIS JOURNAL*, **74**, 1691 (1952).

(15) A. Wilds and J. Johnson, Jr., *ibid.*, **63**, 86 (1946).

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(17) Huang-Minlon, *THIS JOURNAL*, **68**, 2487 (1946).

10-Phenylundecanoic Acid.—10-Phenylundecanoic acid (50 g., 0.191 mole) was treated with 88.4 g. of dioxane sulfur trioxide reagent (0.25 mole of SO_3). A white waxy sulfonation product was obtained. The *S-p*-chlorobenzylthiuronium salt melted at 152° .

Anal. Calcd. for $\text{C}_{33}\text{H}_{44}\text{O}_5\text{Cl}_2\text{N}_4\text{S}_3$: C, 53.3; H, 5.96. Found: C, 52.96; H, 6.44.

Diphenylacetic Acid.—Treatment of diphenylacetic acid¹⁸ (14.2 g., 0.067 mole) with dioxane sulfur trioxide reagent (8.75 g., 0.11 mole of SO_3) gave no sulfonation product. Unchanged diphenylacetic acid was recovered; weight 10.8 g. (76% recovery).

α -Cyclohexylphenylacetic Acid.— α -Cyclohexylphenylacetone nitrile¹⁹ (51.3 g., 0.257 mole) was treated with 250 ml. of concentrated sulfuric acid (sp. gr. 1.84) in 300 ml. of water at reflux temperature for six hours. The solution was cooled and diluted with a liter of water. The organic layer

was separated, dried and upon cooling, it solidified; m.p. $145\text{--}149^\circ$. Recrystallization from petroleum ether gave 29.7 g. of α -cyclohexylphenylacetic acid (53.0%), m.p. $147\text{--}149^\circ$ (lit.²⁰ m.p. $148\text{--}149^\circ$).

Dioxane sulfur trioxide (0.2 mole of SO_3) and 29.7 g. (0.136 mole) of α -cyclohexylphenylacetic acid were combined and stirred for the usual time. No heat was evolved, and unreacted α -cyclohexylphenylacetic acid was recovered; 25.3 g. (86%). No sulfonation product was isolated.

α -Phenylbutyric Acid.— α -Phenylbutyric acid (41.2 g., 0.25 mole) was treated with dioxane sulfur trioxide (0.3 mole of SO_3). The sodium salt of the product was isolated; yield 10.1 g. (14.0%).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{Na}_2$: Na, 15.96. Found: Na, 16.15.

Its *S-p*-chlorobenzylthiuronium derivative had m.p. $155\text{--}157^\circ$.

(18) C. S. Marvel, F. Hager and E. Caudle, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 224.

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LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NOTRE DAME]

The Preparation of Some Acetylenic Primary Amines¹

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Secondary and tertiary ethynylcarbinyl chlorides, $\text{R}(\text{R}')\text{C}(\text{Cl})\text{—C}\equiv\text{CH}$, obtained from the corresponding carbinols, react with sodamide in liquid ammonia to produce primary amines, $\text{R}(\text{R}')\text{C}(\text{NH}_2)\text{—C}\equiv\text{CH}$. Eight compounds of this type were prepared. The method failed (in two cases) where one of the R groups was phenyl, yielding only polymeric material.

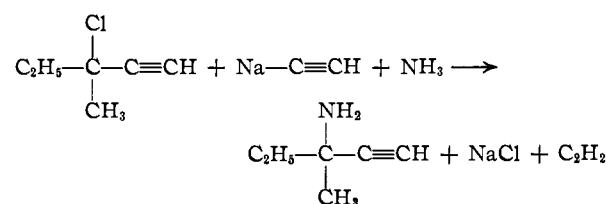
Dimethylethynylcarbinyl chloride, $(\text{CH}_3)_2\text{C}(\text{Cl})\text{—C}\equiv\text{CH}$, was recently shown³ to undergo a unique solvolysis in alkaline 80% ethyl alcohol to produce chiefly the corresponding ethyl ether. The reaction was found to obey second order kinetics and it was proposed that the dipolar ion $(\text{CH}_3)_2\overset{\oplus}{\text{C}}\text{—C}\equiv\overset{\ominus}{\text{C}}$ is an intermediate. One of the consequences of the suggested mechanism is that reaction with bases in other suitable media should likewise produce the solvolytic products. An especially good test of this idea is found in the reaction of dimethylethynylcarbinyl chloride with sodamide in liquid ammonia: according to our mechanism the amine should be produced, as indeed it is. The ordinary course of sodamide-ammonia reactions on aliphatic halides produces unsaturated hydrocarbons by HX elimination.⁴ We have found that many secondary and tertiary ethynylcarbinyl chlorides, $\text{R}(\text{R}')\text{C}(\text{Cl})\text{—C}\equiv\text{CH}$, react atypically to produce primary amines in reasonable yield. This we regard as good evidence for the detailed mechanism proposed previously.³ These ideas are further supported by the fact that sodium acetylide may be substituted for sodamide in the amine synthesis, showing that the reaction is not a simple nucleophilic displacement. When methylethylethynylcarbinyl chloride was added to sodium acetylide in liquid ammonia, evolution of acetylene occurred and the amine was produced in 52% yield.

(1) Paper LVIII on substituted acetylenes; previous paper, *J. Org. Chem.*, **16**, 1289 (1951).

(2) Eli Lilly Company Fellow, 1951-1953.

(3) G. F. Hennion and D. E. Maloney, *THIS JOURNAL*, **73**, 4735 (1951).

(4) F. W. Bergstrom and W. C. Fernelius, *Chem. Revs.*, **12**, 92 (1933); **20**, 433 (1937).



The acetylenic amine synthesis involves three steps: reaction of a carbonyl compound (aldehyde or ketone) with sodium acetylide, conversion of the carbinol so obtained to the chloride by treatment with hydrochloric acid or thionyl chloride, and ammonolysis with sodamide in liquid ammonia. These steps were applied successfully to *n*-butyraldehyde, *n*-heptaldehyde, acetone, methyl ethyl ketone, diethyl ketone, methyl *n*-propyl ketone, methyl *n*-amyl ketone and cyclohexanone. Benzaldehyde and propiophenone failed in the last step; the acetylenic chlorides derived from these compounds gave only tar by reaction with sodamide in liquid ammonia.

The acetylenic amines manifest the usual acetylenic properties and undergo the ordinary primary amine reactions. Each compound gave a copious curdy precipitate with ammoniacal silver nitrate solution, confirming the presence of the $\text{—C}\equiv\text{CH}$ group. They formed crystalline hydrochlorides and sulfates in the usual way and reacted with acetic anhydride, benzoyl chloride, benzenesulfonyl chloride, potassium cyanate, etc., in typical fashion. Every derivative responded to the silver nitrate test showing that the ethynyl radical does not interfere in the reactions of the amino group.

The amines are described in Table I and some assorted derivatives in Table II. Further work is in progress.