

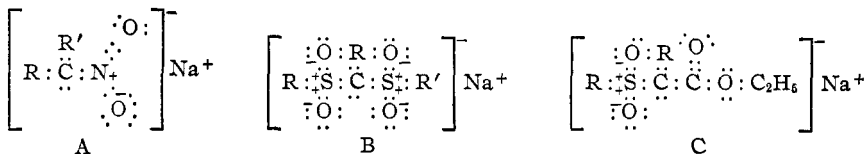
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]
THE ACTION OF SODIUM ETHYLATE ON LEVO-ETHYL- α -PHENYLSULFONEBUTYRATE

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RECEIVED JULY 5, 1932

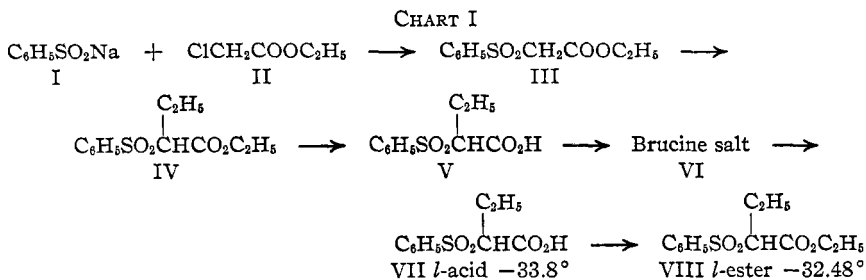
PUBLISHED NOVEMBER 5, 1932

Studies of the sodium and potassium salts of secondary aliphatic nitro compounds have shown that they can exist in an optically active state.¹ If the structure suggested for these salts is that shown in formula A, then



other types of salts with a similar constitution should likewise be capable of existing in optically active forms. Since a study of disulfones² indicated that they formed salts possessing the structure B, it seemed probable that an unsymmetrical disulfone of this structure should yield optically active sodium salts. The synthesis of compounds of this Type B is very difficult and no methods are available at present for the preparation of such a compound in an optically active condition. Pending the development of such methods, attention was turned to a closely related substance, ethyl- α -phenylsulfonebutyrate which has a carbethoxy group in place of one of the sulfone groups. This ester was prepared in the optically active state in order to determine whether it would yield optically active salts of Type C.

The condensation of sodium benzenesulfinate with chloroacetic ester yielded ethyl phenylsulfoneacetate, which was alkylated with ethyl iodide. Saponification and acidification gave racemic α -phenylsulfonebutyric acid. The latter was resolved by means of its brucine salt and the optically active acid obtained. The active ester was made from the acid through the acid chloride. The chart summarizes these reactions.

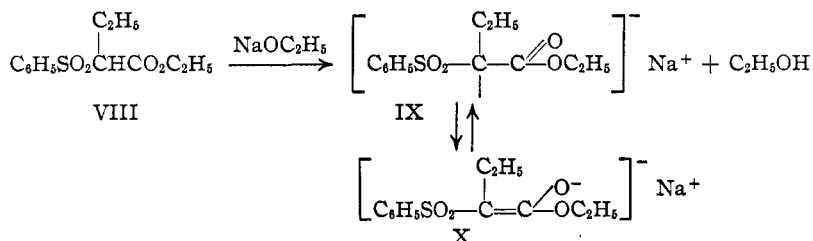


¹ Kuhn and Albrecht, *Ber.*, **60**, 1297 (1927); Shriner and Young, *THIS JOURNAL*, **52**, 3332 (1930).

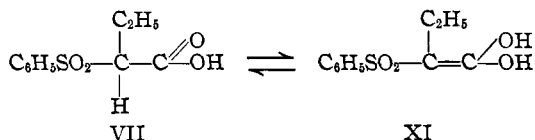
² Shriner, Struck and Jorison, *ibid.*, **52**, 2060 (1930).

When the active ester (VIII) was treated with one equivalent of sodium ethylate in absolute alcohol at -10° the solution of the sodium derivative of the ester was optically inactive although the solution was examined immediately.

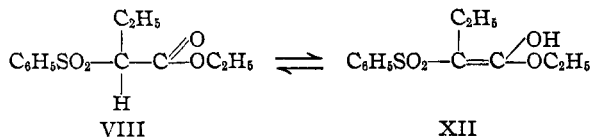
It was hoped that the active ion IX would have a life long enough for its existence to be detected but apparently a very rapid isomerization to the inactive form X occurred.



The rapid racemization of compounds with an asymmetric carbon atom carrying a hydrogen atom alpha to a keto or ester group in alkaline solutions³ is well known. In support of the above explanation for the rapid racemization of the sodium derivative, the half-life periods of the active ester (VIII) and active acid (VII) were determined. It was found that the half-life period of the ester was eighty hours at 27° and of the acid 1350 hours at 27° . The slower racemization of the free acid is usually attributed to the fact that the hydrogen ion from the carboxyl group represses the tendency for the hydrogen on the alpha carbon to shift to form the enolic structure XI.



However, in the case of the ester (VIII) no such repression can occur and hence the inactive enol (XII) is formed much more readily and especially so in the presence of alkaline reagents.



The possibility of enolization on the sulfone group has been discussed previously² and shown to be untenable. The above difference in rates of racemization of the active acid and ester is additional evidence that the

³ O. Rothe, *Ber.*, **47**, 843 (1914); McKenzie and Widdows, *J. Chem. Soc.*, 107, 702 (1915); *ibid.*, **113**, 210 (1918); *ibid.*, **115**, 602 (1919).

sulfone group is not directly involved, although it certainly contributes to the mobility of the α -hydrogen atom.

Moreover, in the resolution of the acid V only the salt composed of *l*-brucine-*l*-acid could be obtained. Even the mother liquor, after filtering the salt which crystallized, on evaporation yielded more of the same salt, indicating that the (*d*) acid was transformed into the (*l*) form under the influence of the brucine. All of these facts indicate the tautomeric character of this acid and ester and lend support to the explanation of the optical inactivity of the sodium derivative of the *l*-ethyl- α -phenylsulfonebutyrate.

Experimental

Sodium Benzenesulfinate.—This compound was prepared by a modification of the directions for the preparation of sodium *p*-toluenesulfinate.⁴ After the temperature of three liters of distilled water, placed in a large earthen jar, had been raised to 70° by the introduction of steam, the steam was turned off, and 315 g. (4.8 moles) of zinc dust was added. The temperature was now increased to 83°. Over a period of twenty minutes, 388 g. (2.15 moles) of benzenesulfonyl chloride was added in small portions with vigorous stirring. The stirring was continued for fifteen minutes. After further increasing the temperature to 90°, the steam was turned off, and 220 cc. of 12 normal sodium hydroxide solution was added to the hot solution. The solution was made strongly alkaline by the addition of sodium carbonate in 50-g. portions. The supernatant liquid was filtered and the residue extracted with one liter of water heated with steam as before. The combined filtrates were concentrated on the steam cone to a volume of 300 cc. After cooling and filtering, the precipitate was warmed with an additional 300 cc. of water, again cooled and filtered. The yield of crude sodium benzene sulfinate amounted to 334 g. or 94.6% of the theoretical.

Ethyl Phenylsulfoneacetate.—In a two-liter, three-necked, round-bottomed flask equipped with a stirrer, a condenser carrying a calcium chloride tube, and a dropping funnel, were placed 328 g. (2.0 moles) of the crude sodium benzenesulfinate and 1.25 liters of absolute alcohol. With stirring and slow refluxing, 306.3 g. (2.5 moles) of ethyl chloroacetate was added through the dropping funnel over a period of one hour. With continuous stirring, the solution was refluxed for eight hours, let stand overnight, and then refluxed for an additional two hours. One liter of alcohol was distilled and 800 cc. of water added. An oily layer separated. The oil was dissolved in ether and the aqueous solution extracted three times with this solvent. The combined ether extractions (including the solution containing the oil), amounting to about two liters, were washed and dried over anhydrous sodium sulfate. The dried solution was filtered through glass wool and the ether distilled. After removing the low boiling material under diminished pressure (water pump), the residue was distilled under vacuum (oil pump). The yield amounted to 215 g. of crude product, b. p. 175–205° at 5 mm. The oil readily crystallized to a solid mass, m. p. 40–43°. The low boiling fraction contained 83 g. of ethyl chloroacetate; the aqueous solution yielded 56 g. of crude sodium benzenesulfinate. The yield of crude product based on the ethyl chloroacetate used amounted to 51.8% of the theoretical.

Pure ethyl phenylsulfoneacetate may be obtained by one recrystallization from hot absolute alcohol, m. p. 42–43°. ^{5,6}

⁴ "Organic Syntheses," 1922, Vol. II, p. 80.

⁵ Michael and Comey, *Am. Chem. J.*, **5**, 116 (1883).

⁶ Otto, *J. prakt. Chem.*, [2] **30**, 343 (1884).

Ethyl α -Phenylsulfonebutyrate.⁷—In a three-necked, one-liter, round-bottomed flask equipped with a stirrer, dropping funnel, and condenser carrying a calcium chloride tube was placed 750 cc. of absolute alcohol (commercial). Twenty-one and six-tenths grams (0.94 mole) of metallic sodium cut in small pieces was added at such a rate as to cause the alcohol to reflux slowly. By stirring and refluxing 215 g. (0.94 mole) of phenylsulfoneacetic ester (m. p. 40–43°) was dissolved into the solution of sodium alcoholate. To the hot solution 146.6 g. (0.94 mole) of ethyl iodide was added slowly (one hour) through the dropping funnel. The solution after six hours of stirring and refluxing reacted neutral to moist litmus. After distilling 500 cc. of alcohol, the residue was poured over cracked ice, whereby crystallization of the oil occurred at once. The yield of crystals, filtered and dried on a clay plate, amounted to 212 g., m. p. 52–55°, or 88.1% of the quantity calculated from theory. (Another run, using pure (m. p. 42–43°) phenylsulfoneacetic ester resulted in a yield of 91.8%, m. p. 57–59°.) A pure product may be obtained by recrystallization several times from acetone and water, m. p. 62–63°. An extraction with low-boiling petroleum ether and subsequent removal of the solvent yields a beautiful white product, m. p. 63–64°.

α -Phenylsulfonebutyric Acid.⁸—In 700 cc. of 95% alcohol placed in a three-necked one-liter flask equipped with a stirrer and condenser, was dissolved 100 g. of potassium hydroxide. Crude (m. p. 52–55°) α -phenylsulfonebutyric ester, 212 g. (0.83 mole), was added and the resulting solution refluxed and stirred for ten minutes. The solution, diluted with an equal volume of cold water, was poured rapidly with stirring into 500 cc. of cold (an ice-salt mixture surrounded the beaker) concentrated hydrochloric acid. The solution was extracted four times with ether, the ether extractions—amounting to 1.5 liters—washed, and the ether distilled. The oily residue readily crystallized when treated with 300 cc. of water. The yield of crude product amounted to 188 g. or practically 100%; m. p. 115–117°. Dissolving in acetone, treating with norite, filtering and precipitating by the addition of water gave a pure product, m. p. 123–124°. The amount of pure acid obtained was 122.6 g.

Anal. Subs., 0.3211: 12.98 cc. of 0.1082 N NaOH. Calcd. for $C_{10}H_{12}O_4S$: neut. equiv., 228.2. Found: 228.6.

Brucine Salt of α -Phenylsulfonebutyric Acid.—A solution consisting of 85.9 g. (0.376 mole) of α -phenylsulfonebutyric acid and 148.2 g. (the equivalent amount) of brucine dissolved in 400 cc. of hot acetone was filtered and set aside to cool. Rapidly the solution turned to a semi-solid mass of crystals. The crystals, filtered and washed with 50 cc. of acetone, amounted to 197 g. By concentrating the filtrate and washing, a second crop of 24.5 g. was obtained. The combined yield was 221.5 g.; theoretical for complete precipitation, 234.1 g. The filtrate was acidified and the free acid extracted with ether. For the brucine salt recrystallized from acetone α_D^{25} –25.4° (in chloroform); α_D^{25} –17.05° (in acetone).

Anal. Subs., 0.5951: $BaSO_4$, 0.2287 g. Calcd. for $C_{33}H_{38}N_2O_8S$: S, 5.16. Found: S, 5.27.

Anal. (Micro Dumas). Subs., 3.612 mg.: 0.157 cc. gas, at 742 mm. and 27.5°. Calcd. for $C_{24}H_{28}N_2O_8S$: N, 4.50. Found: N, 4.82.

l- α -Phenylsulfonebutyric Acid.—Forty grams (0.064 mole) of the above brucine salt was covered with 300 cc. of water and 300 cc. of ether and 20 cc. of concentrated hydrochloric acid added with stirring. When all the salt had dissolved the aqueous layer was extracted twice with two portions of 200 cc. each of ether. After washing the combined ether extractions, the solvent was distilled on the steam cone to a volume

⁷ Michael and Palmer, *Am. Chem. J.*, **7**, 66 (1885–1886).

⁸ Troeger and Uhde, *J. prakt. Chem.*, [2] **59**, 322 (1899).

of 25 cc. The rest of the ether was removed under vacuum and the residue dried for twenty-four hours in a vacuum desiccator. The semi-solid was poured on a clay plate for crystallization (one week). The solid mass amounted to 5.07 g. or 34.7% of the theoretical. It softened at 60° and melted to a clear liquid at 105–107°; α_D^{27} –27.30° (in absolute alcohol).

Anal. Subs., 0.2406: 11.88 cc. of 0.0908 *N* NaOH. Calcd. for $C_{10}H_{12}O_4S$: neut. equiv. calcd., 228.2. Found: 223.1.

Anal. Subs., 0.4558: $BaSO_4$, 0.4745. Calcd. for $C_{10}H_{12}O_4S$: S, 14.06. Found: S, 14.30.

Ethyl *l*- α -Phenylsulfonebutyrate.—Eight grams of active acid was mixed with 15 cc. of thionyl chloride, whereby evolution of sulfur dioxide and hydrogen chloride occurred at once. After heating for twenty minutes in a water-bath just at the boiling point of the reagent, the oil had completely dissolved. The excess thionyl chloride was removed under vacuum and the residue treated with 15 cc. of absolute alcohol. After fifteen minutes the excess alcohol was removed by vacuum distillation. The residue, amounting to 6 g., was extracted several times with low boiling petroleum ether which dissolved the active ester. Evaporation of the ether left 2.8 g. of the ester which melted at 44–45° and had a rotation of –27.56°. Slow crystallization of the ester from petroleum ether gave a mass of beautiful colorless needles which melted at 44.5–45.5° and had α_D^{25} –32.48°.

Anal. (Micro). Subs., 4.605 mg.; $BaSO_4$, 4.28 mg. Calcd. for $C_{12}H_{16}O_4S$: S, 12.52. Found: S, 12.75.

Amide of α -Phenylsulfonebutyric Acid.—The acid chloride prepared as described above was dissolved in absolute ether and the solution saturated with ammonia. The precipitate of the amide and ammonium chloride was filtered. The amide was extracted by means of acetone and recrystallized twice from ethyl acetate. Colorless needles were obtained which melted at 169–170°. The amide was optically inactive.

Anal. Subs., 0.2845: $BaSO_4$, 0.2946. Calcd. for $C_{10}H_{13}O_3NS$: S, 14.12. Found: S, 14.22.

Sodium Salt of Ethyl *l*- α -Phenylsulfonebutyrate.—A solution consisting of 0.1803 g. (0.000704 mole) of ethyl *l*-phenylsulfonebutyrate dissolved in absolute alcohol was made up to a volume of 10 cc. and then cooled in an ice-salt mixture to –10°. The equivalent amount of sodium ethylate dissolved in absolute alcohol, 1.955 cc. containing 0.02450 g. per cc., was likewise cooled to –10°. The 1-dm. polariscope tube packed in ice and salt was given time to cool. The solutions were mixed rapidly, poured into the polariscope tube at –10° and readings taken within four minutes from the time of mixing the solutions. The solution was optically inactive. The experiment was repeated using more dilute solutions but no activity was ever observed.

Racemization of *l*- α -Phenylsulfonebutyric Acid and Ester.—The rate of racemization of an absolute alcoholic solution of the active acid was observed over a period of several weeks at 27°. The half-life period of the acid was 1350 hours.

The half-life period of the ester was found to be eighty hours at 27° and twenty-four hours at 47°.

Summary

The preparations of *l*- α -phenylsulfonebutyric acid and its ester are described. Treatment of the active ester with sodium ethylate yielded an inactive sodium derivative.

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