[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

The Stereochemistry of Raney Nickel Action. IV. The Optical Course of Sulfoxide Desulfuration

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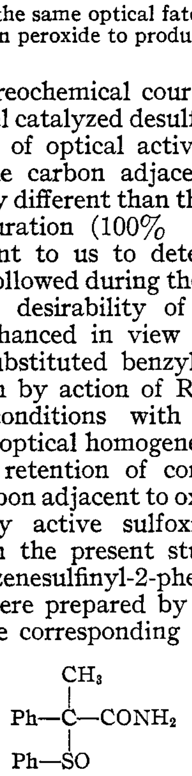
To obtain information as to the stereochemical fate of an asymmetric carbon atom adjacent to a sulfoxide grouping during reductive desulfuration, enantiomorphic 2-benzenesulfinyl-2-phenylpropionamides have been synthesized and subjected to reductive desulfuration with Raney nickel in ethanol. In each case the 2-phenylpropionamide obtained proved to be completely racemic, suggesting a free radical mechanism similar to that previously postulated as prevailing during sulfide desulfuration. Impure diastereomeric sulfoxides related to the crystalline enantiomorphs above were also obtained, and found to undergo the same optical fate during desulfuration. Evidence is presented that the mole for mole reaction of sulfides with hydrogen peroxide to produce sulfoxides follows a simple second order rate law.

Since the stereochemical course followed during the Raney nickel catalyzed desulfuration of sulfones (90% retention of optical activity with apparent inversion at the carbon adjacent to sulfur) was found[1] markedly different than that followed during sulfide desulfuration (100% racemization), it seemed pertinent to us to determine the stereochemical path followed during the desulfuration of a sulfoxide. The desirability of such information was further enhanced in view of the recent discovery[2] that substituted benzyl alcohols undergo dehydroxylation by action of Raney nickel under desulfurizing conditions with almost complete preservation of optical homogeneity and with what appears to be retention of configuration at the asymmetric carbon adjacent to oxygen.

The optically active sulfoxides subjected to desulfuration in the present study were enantiomorphic 2-benzenesulfinyl-2-phenylpropionamides, ± I. These were prepared by room temperature oxidation of the corresponding 2-phenyl-2-phenylmercaptopropionamides with one mole of hydrogen peroxide in acetic acid. The oxidations in question were followed polarimetrically, and the reaction order determined. Within experimental error the peroxide oxidation followed second order kinetics and the two enantiomorphs were oxidized at identical rates. No attempt was made to confirm the second order rate constants on varying the concentrations of reactants.


I

$$\begin{array}{c} CH_3 \\ | \\ Ph-C-CONH_2 \\ | \\ Ph-SO \end{array}$$

Because of the asymmetry of the sulfoxide grouping, a mixture of diastereomeric sulfoxides should be produced on oxidation of each of the enantiomorphic sulfides corresponding to I. For example, the (+)-sulfide should produce a (+)$_c$–(+)$_s$- and a (+)$_c$–(−)$_s$-sulfoxide. Indeed, such diastereomeric sulfoxides have been obtained[3] both in crystalline form from a single sulfide in the case of the lower homolog, 2-phenylmercaptophenylacetic acid. In the present case only the most strongly rotatory sulfoxide, *e.g.*, the (+)$_c$–(+)$_s$-diastereomer, was isolated in crystalline form. Evidence for the second diastereomer, *e.g.*, the (+)$_c$–(−)$_s$-form, was obtained in the fact that the mother liquors from the higher rotating forms produced on evaporation sirups of substantially lower rotatory power. These sirups in turn underwent desulfuration with the same optical consequences observed for the crystalline diastereomers.

When either the crystalline, high-rotating enantiomorphic sulfoxides or their sirupy diasteromeric by-products were desulfurized with Raney nickel in refluxing ethanol, the 2-phenylpropionamides produced were found to be completely racemic. Sulfoxide desulfuration thus follows the stereochemical path noted for sulfides rather than that of sulfones, and the reaction would appear to proceed mechanistically through the free radical intermediates previously postulated[1,4] for sulfides.

Experimental

2-Benzenesulfonyl-2-phenylpropionamide.—One gram of 2-phenyl-2-phenylmercaptopropionamide[1] was dissolved in acetic acid (8 ml.) and the mixture treated with 30% hydrogen peroxide (4 ml.). After 30 minutes on the steam-bath an additional 4 ml. of hydrogen peroxide was added, and heating continued an additional 30 minutes. The mixture was cooled, thrown into salt water and the gummy solid extracted into ether. The extract was washed with water, 5% sodium hydroxide solution, and again with water, dried (sodium sulfate), filtered and the solvent distilled. There remained a white solid which was recrystallized from a mixture of acetone and ligroin. The 0.5 g. of white prisms resulting, m.p. 207.5–208°, were unchanged in m.p. on further recrystallization from acetone.

Anal. Calcd. for $C_{15}H_{15}O_3NS$: C, 62.30; H, 5.23; N, 4.84. Found: C, 62.40, 62.49; H, 5.20, 5.23; N, 4.94.

2-Benzenesulfinyl-2-phenylpropionamide.—2-Phenyl-2-phenylmercaptopropionamide (1.5 g.) was dissolved in acetic acid (10 ml.) and the mixture treated with 30.6% hydrogen peroxide (0.65 g., 1 mole). The oxidation mixture was permitted to stand for 42 hours at room temperature, then thrown into water. The product was isolated by ether extraction as above. A 0.6-g. portion of the product, m.p. 141°, crystallized from the ether solution. The remainder, 0.25 g. (total yield 53%), m.p. 134–135°, was obtained on evaporation of the ether. The first crop was recrystallized from a 1:5 mixture of acetone and ligroin to give the pure product, m.p. 142°, unchanged on further recrystallization.

Anal. Calcd. for $C_{15}H_{15}O_2NS$: C, 65.90; H, 5.54; N, 5.13. Found: C, 65.93, 66.03; H, 5.47, 5.52; N, 5.25.

Enantiomorphic 2-Phenyl-2-phenylmercaptopropionic Acids.—2-Phenyl-2-phenylmercaptopropionic acid was resolved as previously described[1] by recrystallization of the (+)- and (−)-1-phenylethylammonium salts from dilute ethanol. The enantiomorphic acids used in the present study had the following values: (+)-enantiomorph, $[\alpha]^{25}D$

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[1] W. A. Bonner, THIS JOURNAL, **74**, 1033, 1034 (1952).

[2] W. A. Bonner, J. A. Zderic and G. A. Casaletto, *ibid.*, **74**, 5086 (1952).

[3] W. Piechulek and J. Suzko, *Bull. intern. acad. polonaise, Classe Sci. math. nat.*, A, 455 (1934); [*C. A.*, **29**, 2933 (1935)].

[4] H. Hauptmann and B. Wladislaw, THIS JOURNAL, **72**, 707, 711 (1950).

+ 159.0° (c 1.06, ethanol); (−)-enantiomorph, m.p. 84–87°.

Enantiomorphic 2-Phenyl-2-phenylmercaptopropionamides.—These were prepared *via* the acid chlorides from the above acids in the manner described before.[1] (+)-2-Phenyl-2-phenylmercaptopropionamide had m.p. 102–102.5° and $[\alpha]^{25}D$ +110° (c 0.827, ethanol). The (−)-antipode had m.p. 103–104° and $[\alpha]^{25}D$ −112.8° (c 1.063, ethanol).

$(+)_c$-$(+)_s$-2-Benzenesulfinyl-2-phenylpropionamide.—(+)-2-Phenyl-2-phenylmercaptopropionamide (1.00 g.) was dissolved in acetic acid (10 ml.), and the mixture treated with 30.6% hydrogen peroxide (0.44 g., 1 mole). The oxidation mixture was placed in an all-glass, jacketed polarimeter tube (2 dm.) and 25° water circulated through the jacket from a thermostat. The oxidation progress was followed by periodic polarimetric observation. The data in this experiment are presented graphically in the top curve of Fig. 1. The second order rate constants applying to each point in the curve were calculated from the polarimetric readings in the manner previously described,[5] taking the value R_0 as 8.5° and the value R_e as 35.0° from the complete mutarotation curve. During the first 180 minutes of reaction the average second order rate constant value was 0.0381 ± 0.0019 liter/mole minute. During the remainder of the reaction the thermostat temperature inadvertently rose, and the rate constant values slowly increased. At the end of 32 hours the reaction mixture was diluted with water, and the product isolated as before. Evaporation of the ether solution left 0.40 g. of the amber sirup which slowly crystallized. This was recrystallized from a mixture of acetone and ligroin to give a fine white powder, m.p. 116–117°. Another recrystallization gave 0.12 g. of product having m.p. 120° and $[\alpha]^{20}D$ +187.0° (c 0.256, acetone). Due to the small amount of material at hand and the need of its use in desulfuration experiments, no attempt was made to obtain an optically pure sample.

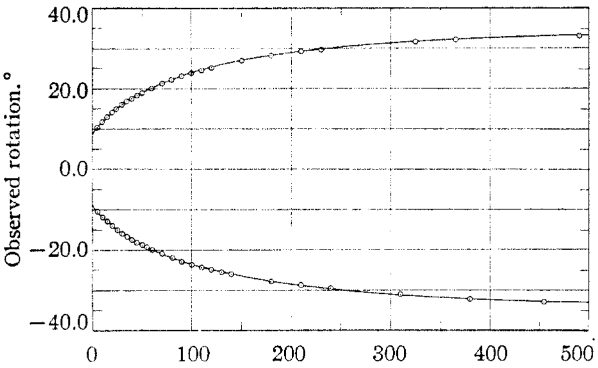

Fig. 1.—Mutarotation on oxidation of 2-phenyl-2-phenylmercaptopropionamides (0.366 M) with 30% hydrogen peroxide (0.366 M) in acetic acid: top curve, (+)-enantiomorph; bottom curve, (−)-enantiomorph.

Anal. Calcd. for $C_{15}H_{15}C_2NS$: C, 65.90; H, 5.54; N, 5.13. Found; C, 65.99; H, 5.60; N, 5.04.

The mother liquors from the above recrystallizations were evaporated to dryness to yield 0.22 g. of an amber sirup, $[\alpha]^{20}D$ +55.5° (c 0.45, acetone). It appears that the $(+)_c$-$(+)_s$-sulfoxide has been obtained as the crystalline material and the $(+)_c$-$(-)_s$-sulfoxide is present in the sirupy material recovered from the mother liquors.

$(-)_c$-$(-)_s$-2-Benzenesulfinyl-2-phenylpropionamide.—(−)-2-Phenyl-2-phenylmercaptopropionamide (2.50 g.) in acetic acid (25 ml.) containing 30.6% hydrogen peroxide (1.10 g., 2% excess) was placed in a 2-dm. polarimeter tube as before, thermostated at 25°, and the mutarotation followed during oxidation. The data are presented in the bottom curve of Fig. 1. Using values of R_0 = −8.5° and R_e = −35.3° the second order rate constants were calculated as before for each point on the curve. During the first 140 minutes of reaction these had an average value of 0.0347 ± 0.0009 liter/mole minute. Again thermostat difficulties due to increasing room temperature caused a rate increase in the latter stages of the reaction. The crude product, isolated as before, consisted of 1.22 g. of white solid. Two recrystallizations gave from a mixture of acetone and ligroin 0.60 g., m.p. 120°, $[\alpha]^{25}D$ −203° (c 0.537, acetone). This was apparently very nearly optically pure, since an additional recrystallization gave a product of m.p. 120° and $[\alpha]^{25}D$ −207° (c 0.43, acetone).

Anal. Calcd. for $C_{15}H_{15}O_2NS$: C, 65.90; H, 5.54; N, 5.13; S, 11.72. Found: C, 65.90; H, 5.68; N, 5.28; S, 11.50.

The mother liquors from the first recrystallization were evaporated to dryness to produce 0.43 g. of impure $(-)_c$-$(+)_s$-sulfoxide, $[\alpha]^{25}D$ −53.2° (c 0.997, acetone).

Desulfuration of 2-Benzenesulfinyl-2-phenylpropionamides.—The racemic 2-benzenesulfinyl-2-phenylpropionamide above (0.30 g.) was dissolved in absolute ethanol (25 ml.) and the mixture refluxed for 3.5 hours with *ca.* 4 g. of freshly prepared Raney nickel.[6] The catalyst was filtered (Celite) and the cake rinsed with hot solvent. Evaporation of the solvent from the filtrate led to 0.17 g. (100%) of sirup which rapidly crystallized. Recrystallization from a mixture of benzene (0.5 ml.) and ligroin (9 ml.) produced 0.10 g. of 2-phenylpropionamide, m.p. 92.5–93.5°; mixed m.p. with an authentic sample of identical m.p. was 92.5–93.5°.

An identical procedure was used in the desulfuration of both of the crystalline and both of the sirupy optically active 2-benzenesulfinyl-2-phenylpropionamides described above. The results in each case were identical, namely, the isolation in good yield of a pure sample of 2-phenylpropionamide which, after a single recrystallization, proved totally void of optical activity. In all four instances the sulfoxide desulfuration thus occurred with complete racemization.

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[5] W. A. Bonner and J. E. Kahn, THIS JOURNAL, **73**, 2245 (1951).

[6] R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).