Organic Disulfides and Related Substances. XXIII. Unsymmetrical Carbonyl Disulfides and Cognate Compounds[1a-c]

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Thioalkylation of thiocarboxylic acids by thiolsulfonates was found to provide a convenient synthesis of representative unsymmetrical carbonyl disulfides, RC(O)SSR′, in yields of 52–100%; one product, 2-acetamidoethyl acetyl disulfide (**3**), was quite effective as an antiradiation drug. Homogeneity of the products was established chromatographically and typical structures were confirmed by independent synthesis using benzenesulfenyl chloride, by hydrolysis, and by acylation of aromatic amines (to an extent dependent on the basicity of the amine). In resistance toward thermally induced disproportionation to the symmetrical disulfides, typical alkyl and aryl compounds did not vary greatly, but there was some tendency toward stabilization by aryl moieties. Attempts are summarized to extend the thioalkylation reaction to preparation of thiocarbonyl and imido disulfides by reaction, respectively, of dithiocarboxylic acids and of thioamides with thiolsulfonates; these were unpromising, at least in several instances, apparently because of instability of the thiocarbonyl or imido disulfides themselves.

Earlier papers described the synthesis of various unsymmetrical disulfides by reaction of thiolsulfonates with thiols according to a known, though previously little used, reaction.[2] This paper reports extension of the method to the use of thiocarboxylic acids in synthesis of disulfides of the general structure RC(O)SSR′ (eq 1).

$$\underset{\text{R} = \text{CH}_3 \text{ or } \text{C}_6\text{H}_5}{\text{RC(O)SH}} + \underset{\begin{matrix}1,\ \text{R}' = \text{AcNH(CH}_2)_2 \\ 2,\ \text{R}' = \text{C}_6\text{H}_5\end{matrix}}{\text{R}'\text{SO}_2\text{SR}'} \longrightarrow \underset{\begin{matrix}\mathbf{3},\ \text{R} = \text{CH}_3;\ \text{R}' = \text{AcNH(CH}_2)_2 \\ \mathbf{4},\ \text{R} = \text{C}_6\text{H}_5;\ \text{R}' = \text{AcNH(CH}_2)_2 \\ \mathbf{5},\ \text{R} = \text{CH}_3;\ \text{R}' = \text{C}_6\text{H}_5 \\ \mathbf{6},\ \text{R} = \text{C}_6\text{H}_5;\ \text{R}' = \text{C}_6\text{H}_5\end{matrix}}{\text{RC(O)SSR}'} + \text{R}'\text{SO}_2\text{H} \quad (1)$$

Results are shown in Table I (under procedure A). The combination of alkyl and aryl groups chosen to be present in the products (**3**–**6**) suggests that the reaction is general. Carbonyl disulfides have been previously prepared by reaction of a thiocarboxylic acid with a sulfenyl chloride[3] or an alkyl thiolsulfate,[4] and by reaction of acyl sulfenyl chlorides with thiols.[5] The yields of 52–100% for **3**–**6** suggest that eq 1 is a useful and convenient alternative to these methods.

Reaction of 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (**1**) with thioacetic acid and thiobenzoic acid gave 2-acetamidoethyl acetyl disulfide (**3**) and 2-acetamidoethyl benzoyl disulfide (**4**), respectively (90–100%, Table I), when an equivalent of triethylamine was used as catalyst in chloroform. With water as the solvent and sodium hydroxide as the base, however, **3** and **4** were obtained both in lower purity and lower yields (46–48%), probably because of hydrolysis of the products to the carboxylic acid salt and 2-acetamidoethyl hydrodisulfide, $\text{AcNH(CH}_2)_2\text{SSH}$. Attempted synthesis of 2-aminoethyl acetyl disulfide hydrochloride by reaction of 2-aminoethyl 2-aminoethanethiolsulfonate dihydrochloride under conditions like those described for **3** gave only the disproportionation product cystamine dihydrochloride (80%) in one experiment and its acylated derivative in another (*i.e.*, N,N′-diacetylcystamine, 23% yield).

Reaction of phenyl benzenethiolsulfonate (**2**) with thioacetic and thiobenzoic acid in chloroform, with triethylamine as base catalyst, gave phenyl acetyl disulfide (**5**) and phenyl benzoyl disulfide (**6**) (66%, 52%, Table I).

Independent syntheses of the phenyl acetyl and benzoyl disulfides (**5** and **6**), achieved by reaction of benzenesulfenyl chloride with thioacetic and thiobenzoic acids, confirmed the structures assigned to them (the infrared spectra of products from procedures A and B in Table I were identical). Disulfides **5** and **6** have been obtained previously by the use of acetylsulfenyl or benzoylsulfenyl chloride.[5b] Procedure B, with benzenesulfenyl chloride, is a modification of one used with trichloromethanesulfenyl chloride.[3] Disulfides **5** and **6** were obtained in somewhat lower yields than with the thiolsulfonates in procedure A.

Homogeneity of disulfides **3**–**6** was demonstrated using column chromatography, thin layer chromatography, or gas–liquid partition chromatography, thus confirming that none of these products was merely a mixture of the two symmetrical disulfides. Furthermore, the infrared spectra of disulfides **3**–**6** showed absorptions absent in the symmetrical disulfides as well as loss of absorptions present in the symmetrical disulfides.[6]

Hydrolysis of 2-acetamidoethyl benzoyl disulfide (**4**) with alkali to benzoic acid (46%) further confirmed the structure of **4**, as well as the suggestion that hydrolysis may account for the low yields of disulfides **3** and **4** when they are prepared in an aqueous medium.

Cleavage of phenyl acetyl disulfide (**5**) with various aromatic amines to form acetanilides (eq 2) also was

$$\underset{\mathbf{5}}{\text{CH}_3\text{C(O)SSC}_6\text{H}_5} + \text{ArNH}_2 \longrightarrow \text{CH}_3\text{C(O)NHAr} + \text{C}_6\text{H}_5\text{SSH} \quad (2)$$

investigated, both because of the physiological connotation and because of the relation to attempted synthesis of an unsymmetrical trisulfide by thioalkylation of the

(1) (a) Paper XXII: M. Bellas, D. L. Tuleen, and L. Field, *J. Org. Chem.*, **32**, 2591 (1967). (b) this investigation was supported by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. (c) Abstracted from part of the Ph.D. dissertation of J. D. B., Vanderbilt University, June 1966. (d) National Science Foundation Summer Fellowship for Graduate Teaching Assistants, 1964; Du Pont Postgraduate Teaching Assistant, 1964–1965.

(2) *Cf.* ref 1a, L. Field, T. F. Parsons, and D. E. Pearson, *J. Org. Chem.*, **31**, 3550 (1966), and earlier papers in this series.

(3) R. S. Hawley and A. R. Kittleson, U. S. Patent 2,553,777 (1951); *Chem. Abstr.*, **45**, 7742 (1951).

(4) B. Milligan, B. Saville, and J. M. Swan, *J. Chem. Soc.*, 4850 (1961).

(5) (a) P. Raoul and J. Vialle, *Bull. Soc. Chim. France*, 1670 (1959); (b) H. Böhme and M. Clement, *Ann.*, **576**, 61 (1952).

(6) A general characteristic of unsymmetrical disulfides which supports their identity (*cf.* earlier papers in this series).

TABLE I

SYNTHESIS OF UNSYMMETRICAL CARBONYL DISULFIDES

$$RC(O)SH + R'SY \longrightarrow RC(O)SSR' + HY^{a}$$

Compd	R	R′	Procedure[a]	Product Yield, %	Product Bp or mp (°C), or $n^{25}D$	Purified Bp or mp (°C) or $n^{25}D$	Anal. Calcd (found), % Carbon	Hydrogen	Nitrogen	Sulfur
3	CH_3	$AcNH(CH_2)_2$	A[b]	100	1.5452	139–139.5 (5 μ) 1.5452	37.28 (37.17)	5.72 (5.89)	7.22 (7.08)	33.08 (32.92)
4	C_6H_5	$AcNH(CH_2)_2$	A[c,d]	90	58–61	62–63	51.75 (51.81)	5.13 (5.06)	5.49 (5.58)	25.09 (24.96)
5	CH_3	C_6H_5	A[e]	66	75–114 (500 μ)	77–79 (5 μ) 1.6102	52.14 (52.33)	4.38 (4.40)		
			B[f]	54		77–82 (25 μ) 1.6102				
6	C_6H_5	C_6H_5	A	52	51–52	52–53[g]				
			B	35	45–48	52–53[g]				

[a] Procedure A where Y = $R'SO_2$; B where Y = Cl. [b] When water and 1 equiv of 0.1 *N* sodium hydroxide were used, **3** was isolated by extraction with methylene chloride. The extract was washed with 5% aqueous bicarbonate solution and water, dried, and evaporated to leave disulfide **3** in 63% yield. Purification gave **3** in 46% yield ($n^{25}D$ 1.5478). [c] Water was used instead of brine in the isolation of **4**. Trituration of the residue, left after evaporation of the chloroform, with absolute ether (Dry Ice cooling) gave crystalline **4**; recrystallization from 1:1 acetone–pentane gave **4** of constant mp 62–63°. [d] Reaction in water, as described for **3** in *b*, gave **4** (mp 61–62°) in 48% yield. [e] Anhydrous ether was the reaction solvent. Disulfide **5** was isolated by washing the reaction mixture with 1 *N* hydrochloric acid, 5% bicarbonate, and water (to neutrality) and evaporating the dried ether layer. Distillation, first simple, then through a 1 × 20 cm Vigreux column, gave the phenyl acetyl disulfide (**5**) reported in Table I (lit.[5b] bp 146–148 (11 mm)). [f] Hexane was the reaction solvent. Disulfide **5** was isolated by evaporation of the reaction mixture and distillation (1 × 20 cm Vigreux column) of the residue. [g] Lit.[5b] mp 52–53°.

TABLE II

THERMAL STABILITIES OF CARBONYL DISULFIDES, RC(O)SSR′[a]

Compd	R	R′	Hr	Disproportionation, %,[b] based on $[RC(O)S]_2$	Disproportionation, %,[b] based on R′SSR′	Disproportionation, %,[b] based on RC(O)SSR′ recovered	Disproportionation, %,[b] Average
3	CH_3	$AcNH(CH_2)_2$	24	18[c]	25	22	22
			48		32		32
4	C_6H_5	$AcNH(CH_2)_2$	24	12	10	13	12
			48		18		18
5	CH_3	C_6H_5	24			4[d]	4
			48			30[d]	30
6	C_6H_5	C_6H_5	24			0	0
			48			0	0

[a] Determined in anhydrous dioxane at 100° in the dark. [b] Calculated using the following equations based on the disproportionation reaction (eq 3), and on the products or starting material isolated: % disproportionation = 2 (mmoles of $[RC(O)S]_2$ or R′SSR′) (100)/(mmoles RC(O)SSR′) = 100 − % RC(O)SSR′ recovered. "Average % disproportionation" is the numerical average of the other values reported. [c] Determined by weight loss. [d] Determined by gas–liquid partition chromatography.

resulting phenyl hydrodisulfide.[7] The extent of cleavage of disulfide **5**, as determined by the yields of acetanilides, paralleled the basicity of the amines (p-$CH_3OC_6H_4NH_2$ > $C_6H_5NH_2$ ≫ p-$O_2NC_6H_4NH_2$; *cf.* Table III, Experimental Section).

Thermal disproportionation of disulfides **3–6** to the symmetrical disulfides (eq 3) was investigated by heating solutions in dioxane at 100° for 24 and 48 hr.

$$\underset{\textbf{3–6}}{2RC(O)SSR'} \longrightarrow [RC(O)S]_2 + R'SSR' \qquad (3)$$

Results of these experiments (Table II) indicate that the stabilities of most of these disulfides do not vary greatly. The trend noted, however, was that an aromatic group as either R or R′ in the general formulation RC(O)SSR′ stabilizes the disulfide toward thermally induced disproportionation. Thus the most stable disulfide was phenyl benzoyl disulfide (**6**), in which both R and R′ are aromatic. This result is in interesting contrast to unsymmetrical disulfides containing only alkyl and aryl combinations, where the effect of aryl groups is to decrease the resistance to disproportionation.[2] Unfortunately, the fact that disproportionation of **3–6** could not be studied in water or ethanol, used in our previous studies, precludes further comparison with results reported earlier in this series.[2]

The acetamidoethyl disulfides **3** and **4** also were of interest as antiradiation drugs, since the thiolsulfonate **1** is effective in reducing harmful effects of ionizing radiation.[8a] 2-Acetamidoethyl acetyl disulfide (**3**) gave "good" protection (on a scale of good, fair, slight, or inactive) when tested at a dose level of less than 50 mg/kg in mice.[8b] 2-Acetamidoethyl benzoyl disulfide (**4**) was inactive at the same dose level. Most of the disulfides **3–6** also proved to have significant activity in controlling the growth of bacteria or fungi.[8c]

Attempts to extend the reaction of eq 1 to synthesis of imido disulfides and thiocarbonyl disulfides by thioalkylation of thioamides and dithiocarboxylic acids, respectively, with thiolsulfonates were unpromising.[9a]

(7) J. D. Buckman and L. Field, *J. Org. Chem.*, **32**, 454 (1967).

(8) (a) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964). (b) Private communication from Drs. T. R. Sweeney and D. P. Jacobus, Walter Reed Army Institute of Research, Washington, D. C. For details of testing and the scale of activity, see ref 8a; pH 5.1, CMC/Tw vehicle (The compound was suspended in a physiological saline solution containing 0.2% methylcellulose (4000 centipoises) and 0.4% Tween 180). (c) J. D. Buckman, B. S. Johnson, and L. Field, *Can. J. Microbiol.*, **12**, 1263 (1966).

(9) (a) For details see J. D. Buckman, Ph.D. Dissertation, Vanderbilt University, 1966. (b) F. Fischer and R. Gottfried, *Z. Chem.*, **6**, 146 (1966); *Chem. Abstr.*, **65**, 5392 (1966), which also leads one to earlier work.

We have since learned that Fischer and Gottfried have been able to synthesize specialized examples of these structures by thioalkylating a dithiobenzoate or thiobenzamide with trichloromethylsulfenyl chloride.[9b]

In an effort to achieve the reaction formulated in eq 4, with 1 equiv of sodium ethoxide as a base catalyst, reaction of *p*-tolyl *p*-toluenethiolsulfonate (**7**) with thioacetamide in ethanol resulted in isolation of unchanged **7** (90%) or of *p*-tolyl disulfide (82–100%)

$$CH_3C(S)NH_2 + \underset{7}{C_7H_7SO_2SC_7H_7} \longrightarrow \underset{8}{CH_3C(NH)SSC_7H_7} + C_7H_7SO_2H \quad (4)$$

with reaction periods of 15 sec or 3–15 min, respectively (the reaction was quenched by adding hydrochloric acid in the hope of preserving **8** as its hydrochloride). With attempted catalysis of reaction 4 by boron trifluoride, a quite complex reaction occurred which produced only large amounts of sulfur and some *p*-toluenethiol. Under neutral conditions in ether, the desired imido disulfide **8** was suspected as the reaction product, but its hydrochloride did not survive recrystallization. In neutral alcohol, reaction of thiolsulfonate **7** with thioacetamide led to the formation of *p*-tolyl trisulfide (**9**,[7] 54%). The trisulfide **9** may have arisen through ethanolysis of the desired disulfide **8** and subsequent thioalkylation of the resulting hydrodisulfide (eq 5).

$$\underset{8}{CH_3C(NH)SSC_7H_7} + C_2H_5OH \longrightarrow CH_3(NH)OC_2H_5 + C_7H_7SSH \quad (5a)$$

$$C_7H_7SSH \xrightarrow{7} C_7H_7SO_2H + \underset{9}{(C_7H_7S)_2S} \quad (5b)$$

Thiocarbonyl disulfides, except for the widely studied 1,2-dithiole-3-thiones[10] and the trichloromethyl compounds of Fischer and Gottfried,[9b] apparently are a novel class of compounds. Their preparation was investigated by attempting reaction of the acetamido thiolsulfonate **1** with dithioacetic and dithiobenzoic acids (eq 6). In neither instance could the pure unsymmetrical thiocarbonyl disulfide **10** or **11** be isolated by column chromatography or by techniques that were successful in the isolation of the corresponding carbonyl disulfides; distillation could not be used for purification because of extensive decomposition even at quite low pressures. It appeared that the crude disulfides **10** and **11** may have been formed in yields of perhaps 30–70%, but that attempted purification resulted only in material having a carbon composition about 2% too high.[9a]

$$RCS_2H + \mathbf{1} \longrightarrow RC(S)SS(CH_2)_2NHAc + AcNH(CH_2)_2SO_2H \quad (6)$$

10, R = CH_3
11, R = C_6H_5

Experimental Section[11]

Preparation of Unsymmetrical Carbonyl Disulfides.—General procedures can be exemplified by the preparation of 2-acetamidoethyl acetyl disulfide (**3**) and phenyl benzoyl disulfide (**6**). Any significant variations from these procedures are reported in Table I.

Procedure A. Reaction of Thiocarboxylic Acids with Thiolsulfonates.—For the preparation of **3**, triethylamine (5.00 g, 49 mmoles) was added (15 min) to a stirred solution of 4.18 g (55 mmoles) of thioacetic acid[12] and 13.4 g (50 mmoles) of thiolsulfonate **1**[7] in 50 ml of chloroform. The mixture was stirred 15 min more and was washed with eight 10-ml portions of saturated brine. It was then dried, and evaporated to afford 9.65 g (100%) of disulfide **3**, as a light yellow oil. This oil was extracted into dry ether by rubbing with three 50-ml portions, solid was separated by filtration, and the ether was evaporated. Residue was dried (1 mm, 4 hr) to leave 6.07 g (63%) of 2-acetamidoethyl acetyl disulfide (**3**).

The analytical sample of **3** was obtained by short-path distillation (bp 139–139.5° (0.005 mm), 10% recovery), but this material was identical in infrared spectrum and refractive index with that reported above. The above purification procedure was used because, of the materials recovered after washing with brine, the thiolsulfonate **1** and N,N′-diacetylcystamine are ether insoluble while the unsymmetrical disulfide is ether soluble. The drying of the product should have removed any acetyl disulfide (lit.[13] bp 40–47° (1.5 mm)).

Procedure B. Reaction of Thiocarboxylic Acids and Benzenesulfenyl Chloride.[14]—For the preparation of **6**, benzenesulfenyl chloride[15] (66.4 mmoles) in 50 ml of petroleum ether was added over 30 min to a stirred solution of 8.86 g (64.2 mmoles) of thiobenzoic acid in petroleum ether (50 ml) at 5–10°. The reaction mixture was chilled to −50° with Dry Ice, and the insoluble material then was removed by filtration and dried overnight to give 12.8 g (81%) of a tan semisolid (*ca.* mp 25°). This material was extracted into five 50-ml portions of hexane at room temperature. The hexane extracts were evaporated to leave 5.55 g (35%) of disulfide **6**, mp 45–48°.

Cleavage of Unsymmetrical Carbonyl Disulfides. A. With Amines.—Phenyl acetyl disulfide (**5**, 1.84 g, 10 mmoles) was dissolved (to volume) in 10 ml of anhydrous ether. One milliliter of this solution was transferred to tubes containing a solution of 1 mmole of the appropriate amine (*cf.* Table III) in 4 ml of ether and the mixtures were allowed to stand at room temperature (time periods given in Table III). The acetamides were isolated by adding an equal volume of pentane to the reaction mixture and chilling (Dry Ice) to cause crystallization. *p*-Nitroacetanilide was isolated after extracting unchanged amine from the reaction mixture with 0.45 *N* hydrochloric acid until the extracts were colorless and then evaporating the dried ether phase and triturating the resulting residue with hexane. Attempted titration of the filtrate from isolation of the acetamides with 0.1 *N*

TABLE III

CLEAVAGE OF PHENYL ACETYL DISULFIDE (**5**) WITH AMINES

		Acetamide			
Amine	Time	Wt, mg	Yield, %[a]	Mp, °C	Lit. mp, °C
Aniline	20 hr	73.8	55	113–114	114
p-Anisidine	20 hr	119.7	72	127–128	127
p-Nitroaniline	96 days	19.6	11	185–190[b]	215

[a] Based on eq 2. [b] Not purified.

Gas–liquid partition chromatography (glpc) was performed on an F & M Model 720 gas chromatograph (detection and injection temperatures, 250°; flow rate of helium carrier gas, 60 cc/min; bridge current, 150 ma; column, 30-cm 5% silicone gum rubber on Chromosorb P).

Thin layer chromatography (tlc) usually was done on a layer of Woelm Silica Gel G (thickness of 250 μ) with acetone for development and with location of spots by exposure to iodine vapor in a closed vessel for 30 min. The R_f* reported in certain instances is an average of three determinations of the distance moved by a compound relative to the distance moved by *p*-tolyl disulfide; the variation was less than ±0.02. It was found important that the developing tank be completely wrapped in aluminum foil to exclude ambient light; otherwise, spots appeared corresponding to the symmetrical disulfides.

(10) P. S. Landis, *Chem. Rev.*, **65**, 237 (1965).

(11) Melting points are corrected and boiling points are uncorrected. Elemental analyses were done by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Moist extracts were dried using anhydrous magnesium sulfate; solvents were removed at *ca.* 25 mm using a rotating-flask evaporator.

(12) Distilled commercial material, bp 87–89.5°, $n^{25}D$ 1.4584, iodine titer 91%.

(13) E. L. Jenner and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **83**, 1911 (1961).

(14) Modified from the procedure for the reaction of trichloromethanesulfenyl chloride with thio acids given in ref 3.

(15) From chlorination of phenyl disulfide (7.24 g) in petroleum ether (50 ml) with 2.36 g of chlorine at 0 to −5°.

TABLE IV
HOMOGENEITY OF DISULFIDES 3 AND 4

RC(O)SSR′	R_f* [a]	[RC(O)S]$_2$ or R′SSR′
	0.93	$[CH_3C(O)S]_2$
$CH_3C(O)SS(CH_2)_2NHAc$ (3)	0.72	
	0.30	$[AcNH(CH_2)_2S]_2$
$C_6H_5C(O)SS(CH_2)_2NHAc$ (4)	0.91	
	1.00	$[C_6H_5C(O)S]_2$

[a] Reference 11.

iodine resulted in indecisive end points and consumption in excess of 100% of theory.

B. Hydrolysis.—A solution of 0.758 g of 2-acetamidoethyl benzoyl disulfide (4) and 0.37 g of potassium hydroxide in 10 ml of water was heated on a steam bath for 30 min. The basic solution was acidified to pH 2 and extracted with benzene. The benzene was evaporated and the residue washed with boiling water. Chilling of the aqueous washes gave 0.161 g of benzoic acid (44%): infrared spectrum identical with that of authentic material; mp and mmp 120–121°.

Homogeneity of Unsymmetrical Carbonyl Disulfides.—Column chromatography of 0.25 g of phenyl benzoyl disulfide (6) on 7.0 g of Woelm Silica Gel G (activity I) with hexane–ether (50:1) resulted in elution of only one material, disulfide 6 with unchanged physical properties (100% recovery). Glpc analysis of 2 μl of phenyl acetyl disulfide (5) with an oven temperature of 185°, and attenuation of 16 demonstrated disulfide 5 to be a single component with a retention time of 176 sec; phenyl disulfide and acetyl disulfide had retention times of 565 and 60 sec, respectively. Tlc was used to demonstrate the homogeneity of disulfides 3 and 4 with the results shown in Table IV.

Disproportionation of Carbonyl Disulfides.—Thermal stabilities of disulfides 3–6 were determined by the general procedure below, the % disproportionation being determined either by large-scale isolation (3, 4, and 6) or by glpc analysis of the reaction products (5).

A. By Large-Scale Isolation.—The disulfide (1.00 mmole) was dissolved in 10 ml of dioxane[16] in a glass ampoule. The solution was frozen (0°), and the tube was purged with nitrogen and sealed. The tube then was wrapped with aluminum foil and heated at 100° for the period stated (Table II), after which the contents were freeze dried to constant weight (24–48 hr).[17]

Disproportionation products were separated as described below for the various disulfides and were dried to constant weight. The results of these experiments are given in Table II. Materials for which values are given in Table II were identified by infrared spectra, melting points and mixture melting points, and/or tlc R_f (*vs.* an authentic sample).

With 2-acetamidoethyl acetyl disulfide (3), the dried product was washed with 5 ml of anhydrous ether at 0° to separate 3 from the insoluble N,N′-diacetylcystamine; acetyl disulfide was assumed to be the weight lost in the original evaporation and was not characterized. With 2-acetamidoethyl benzoyl disulfide (4), the product was washed with 10 ml of methanol–water (3:7) to separate disulfide 4 and N,N′-diacetylcystamine from the insoluble benzoyl disulfide; the residue from evaporation of the filtrate was washed with 2 ml of water at 0° to separate the N,N′-diacetylcystamine from the disulfide 4; all three products then were identified by their spectra and tlc R_f. With phenyl benzoyl disulfide (6), the product was chromatographed on a 0.5 × 10 cm column of 7.0 g of Woelm Silica Gel G (activity 1) with 25 ml of hexane–ether (10:1); disulfide 6 was recovered (100%) unchanged from the hexane–ether effluent, less than 0.5% of the original weight being eluted by hexane alone (which would have displaced any phenyl disulfide).

B. Disproportionation of 5 by Gas–Liquid Partition Chromatography.—Glpc was performed as usual (oven temperature, 175°).[11] Retention times for the various components were as follows: dioxane, 11–20 sec; 1,2,4-trichlorobenzene, 55 sec; phenyl acetyl disulfide (5), 190 sec.

Disulfide 5 (0.1838 g) and 0.1678 g of trichlorobenzene were dissolved to volume in 10 ml of dioxane and a 3-ml aliquot was heated in a sealed tube at 100° as usual. The contents of this tube were chromatographed. The per cent disproportionation was taken as the ratio of the change in area[18] of the peak for disulfide 5 from its area in a sample of the original solution (which had been kept frozen) to the original area, times 100.

Registry No.—3, 10048-01-8; 4, 10048-03-0; 5, 5813-74-1; 6, 5718-98-9.

(16) Purified according to the procedure of K. Hess and H. Frahm, as described by L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 285.

(17) If not analyzed immediately, the mixture was kept (frozen) at −5°.

(18) Area was the average of three determinations with a planimeter, corrected for slight differences reflected by the trichlorobenzene standard.

Variations in the Stereochemistry of Sulfone Desulfuration[1]

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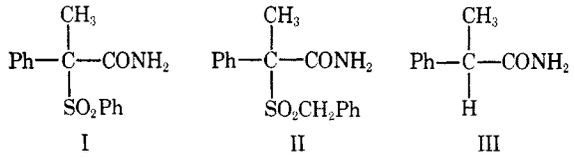
2-Phenyl-2-phenylsulfonylpropanoamide (I) is desulfurated by Raney nickel with predominant inversion of configuration in ethanol solvent and with predominant retention in acetone solvent. Variable ratios of inversion to retention are noted after pretreating the Raney nickel catalyst with different solvents. 2-Phenyl-2-benzylsulfonylpropanoamide (II) is desulfurated with predominant retention of configuration in both ethanol and acetone solvent, but the extent of retention again varies with the pretreatment of the nickel catalyst. Benzyl sulfones (such as II and dibenzyl sulfone) undergo Raney nickel desulfuration markedly more rapidly than phenyl sulfones (such as I and diphenyl sulfone) in ethanol and react more slowly in benzene solvent than in ethanol. Tentative explanations of these results are suggested.

In 1952, initiating studies on the stereochemical consequences of Raney nickel catalyzed hydrogenolyses of various functional groups, we undertook experiments involving the desulfuration of the enantiomers of 2-phenyl-2-phenylsulfonylpropanoamide (I).[2] When (−)-I was heated with W-2 Raney nickel[3] in refluxing ethanol, *R*-(−)-hydratropamide (*R*-(−)-III)[4] was produced of about 50% optical homogeneity. Similarly (+)-I yielded *S*-(+)-III with analogous stereoselectivity. On the basis of the application of Freudenberg's "displacement rule"[5] to a limited series of derivatives related to (−)-I and *R*-(−)-III, it was tentatively



(1) (a) This constitutes communication XVII in the series "The Stereochemistry of Raney Nickel Action;" (b) for XVI, see W. A. Bonner and R. A. Grimm, *J. Org. Chem.*, **32**, (1967).

(2) W. A. Bonner, *J. Am. Chem. Soc.*, **74**, 1034 (1952).

(3) R. Mozingo, *Org. Syn.*, **21**, 15 (1941).

(4) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., New York, 1962, pp 89, 93.

(5) K. Freudenberg, "Stereochemie," F. Deuticke, Leipzig, 1933, p 695 ff.