Registry No.—Benzophenone pentamethylenehydrazone, 13134-20-8; benzophenonimine hydrochloride, 5319-67-59; N-benzyl-N-methylpiperidinium chloride, 13127-28-1; 2,2′-binaphthyl, 612-78-2; *p,p′*-dimethoxybenzophenone, 90-96-0; *p,p′*-dichlorobenzophenone, 90-98-2; *p*-chloro-*p′*-methylbenzophenone, 5395-79-9; *p*-chloro-*p′*-methylbenzophenone oxime, 13134-28-6; acet-*p*-toluidide, 103-89-9; N-aminopiperidine, 2213-43-6; benzophenone, 119-61-9; *p*-chlorobenzaldehyde pentamethylenehydrazone, 13134-29-7.

Organic Disulfides and Related Substances. XXII. Substituted Benzyl 2-(*n*-Decylamino)ethyl Disulfide Hydrochlorides. A Possible Neighboring-Group Effect Involving Sulfur[1a,b]

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Unsymmetrical disulfides of structure **2** have been synthesized; for their purification, chromatography on specially prepared acidic alumina was necessary. Thermally induced disproportionation of these disulfides appears to be kinetically first order. The relative disproportionation rates are correlated by the Hammett σ^-, ρ relationship; $\rho = 1.1$. These data and other evidence are interpreted in terms of disulfide cleavage which involves stabilization of an incipient benzylthiolate anion by the phenyl ring and, in addition, anchimeric assistance to the cleavage by the neighboring amino group; the possible influence of similar factors on the stability of biochemically important disulfide linkages seems worth considering. Although the symmetrical disulfides are soluble in 95% ethanol, disproportionation proceeds virtually to completion and cannot be significantly reversed.

In a previous paper, we reported synthesis and disproportionation of a series of *para*-substituted 2-(aryldithio)ethylamine hydrochlorides (**1**).[2] Studies of

$$\underset{\textbf{1}}{p\text{-}XC_6H_4SS(CH_2)_2NH_3{}^+Cl^-}$$

disproportionation now have been extended to a series of *meta*- and *para*-substituted benzyl 2-(*n*-decylamino)ethyl disulfide hydrochlorides (**2**) The preparation and investigation of the benzyl derivatives had a threefold purpose: (a) to learn whether any correlations with the previous aryldithio series (**1**) could be found; (b) to examine the possibility of anchimeric assistance by the benzene ring; and (c) to see what effect, if any, the long side chain would have on the antiradiation activity of these compounds (it was thought that the long side chain might facilitate passage of the molecule through membrane barriers).

The compounds were prepared essentially as were those of series **1**,[2] but by reaction of an arylmethanethiol with 2-(*n*-decylamino)ethyl 2-(*n*-decylamino)ethanethiolsulfonate dihydrochloride, as is shown in eq 1.[3]

$$\begin{aligned}&m\text{- or } p\text{-}XC_6H_4CH_2SH\ +\\ &\quad Cl^-\ n\text{-}C_{10}H_{21}NH_2{}^+(CH_2)_2SO_2S(CH_2)_2NH_2{}^+\text{-}n\text{-}C_{10}H_{21}\ Cl^- \longrightarrow\\ &\qquad n\text{-}C_{10}H_{21}NH_2{}^+(CH_2)_2SO_2H\ Cl^-\ +\\ &\qquad\quad m\text{- or } p\text{-}XC_6H_4CH_2SS(CH_2)_2NH_2{}^+\text{-}n\text{-}C_{10}H_{21}\ Cl^- \qquad (1)\end{aligned}$$

2, X = substituent
3, X = H
4, X = p-CH_3
5, X = p-CH_3O
6, X = p-Cl
7, X = p-NO_2
8, X = p-CN
9, X = m-NO_2
10, X = m-CN

In preparing disulfides of structure **1**, we isolated the unsymmetrical disulfide by extracting unchanged thiol, making the reaction mixture alkaline, extracting the free base into an organic solvent, and reconverting it to the salt by treatment with HCl.[2] This procedure failed with disulfides of structure **2** owing to gel formation Good results were obtained, however, by chromatographing the crude reaction mixture on acid-washed alumina and eluting with chloroform. It is noteworthy that first trials using this procedure sometimes gave erratic results, which we attribute to excessively basic alumina This problem was resolved by treating the alumina in chloroform with HCl. Preparative results are shown in Table I. As before,[2] the products were well-defined crystalline compounds with sharp melting points and all showed only one spot on thin layer chromatography. In contrast to the aryldithio series (**1**), the compounds were insoluble in water but readily soluble in chloroform and dioxane; two (**7**, **10**) even showed some degree of solubility in ether, a property utilized to follow their disproportionation.

In order to study thermal disproportionations, ethanolic solutions of the disulfides were heated at 100° in sealed ampoules protected from light by aluminum foil. We reported evidence for the aryldithio series (**1**) that the disproportionation is largely heterolytic under these conditions.[2] The kinetics of disproportionation of the benzyl disulfides (**2**) were followed by determining the amount formed of the symmetrical disulfide **11** or **12** (eq 2).

$$\textbf{2} \longrightarrow {}^1/_2\underset{\textbf{11}}{(m\text{- or } p\text{-}XC_6H_4CH_2S\text{-})_2} + {}^1/_2\underset{\textbf{12}}{(Cl^-\ n\text{-}C_{10}H_{21}NH_2{}^+CH_2CH_2S\text{-})_2} \qquad (2)$$

All of the symmetrical benzyl disulfides (**11**) were soluble in ether and some of them in hexane, while most of the hydrochlorides of type **2** or **12** were insoluble in these solvents. However, the *p*-nitro (**7**) and *m*-cyano (**10**) derivatives were somewhat soluble in ether, and hexane could not be used because their corresponding symmetrical benzyl disulfides (**11**)

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[1] (a) 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. (b) Paper XXI: J. D. Buckman, M. Bellas, H. K. Kim, and L. Field, *J. Org. Chem.*, **32**, 1626 (1967). (c) To whom correspondence should be addressed.

[2] L. Field, T. F. Parsons, and D. E. Pearson, *J. Org. Chem.*, **31**, 3550 (1966).

[3] Some of the arylmethanethiols were obtained by reaction of the corresponding benzyl halides with thiourea. Hydrolysis of the benzylthiuronium salts to the thiols was achieved by brief treatment with aqueous sodium hydroxide, acidification, and extraction. This procedure avoids the prolonged boiling often used, which is likely to lead to more by-products (see Experimental Section).

TABLE I

SYNTHESIS OF SUBSTITUTED BENZYL 2-(*n*-DECYLAMINO)ETHYL DISULFIDE HYDROCHLORIDES

$XC_6H_4CH_2SS(CH_2)_2NH_2{}^+$-$n$-$C_{10}H_{21}\ Cl^-$

Product no.	X	Mp, °C	Yield,[a] %	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
3	H	145–146[b]	66	$C_{19}H_{34}ClNS_2$	60.68	9.10	3.72	17.06	60.99	9.15	3.76	17.11
4	*p*-CH_3	160–161	65	$C_{20}H_{36}ClNS_2$	61.57	9.30	3.59	16.44	61.29	9.28	3.61	16.21
5	*p*-OCH_3	144–145	62	$C_{20}H_{36}ClNOS_2$	59.15	8.94	3.45	15.80	58.74	8.97	3.44	15.57
6	*p*-Cl	141–142	61	$C_{19}H_{33}Cl_2NS_2$	55.59	8.10	3.41	15.61	55.76	8.15	3.59	15.54
7	*p*-NO_2	103–104	30	$C_{19}H_{33}ClN_2O_2S_2$	54.19	7.90	6.65	15.23	54.04	7.95	6.59	15.41
8	*p*-CN	122–123	65	$C_{20}H_{33}ClN_2S_2$	59.89	8.29	6.99	15.99	60.23	8.39	6.82	16.23
9	*m*-NO_2	133–134	50	$C_{19}H_{33}ClN_2O_2S_2$	54.19	7.90	6.65	15.23	54.11	7.83	6.48	15.44
10	*m*-CN	108–109	15	$C_{20}H_{33}ClN_2S_2\cdot 0.5H_2O$[c]	58.59	8.35	6.83	15.65	58.95	8.64	6.64	15.42

[a] After crystallization from a suitable solvent. [b] From acetone or aqueous ethanol. However, when **3** was crystallized from dioxane it had mp 152–153°. The infrared spectrum in chloroform showed the two products were identical, and so the forms presumably are isomorphic. It is noteworthy that a mixture melting point of the two forms was depressed to 137°. [c] Water of crystallization, determined by drying to constant weight at 65° (0.2 mm), 0.59.

TABLE II

THERMALLY INDUCED DISPROPORTIONATION OF DISULFIDES OF TYPE 2 AT 100°

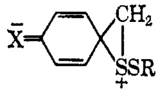
Product No.	X	Disproportionation, % after hr indicated 3	7	13	17	22	45	66	95	120	140	235	300	405	501	*k*, sec^{-1}	$t_{1/2}$, hr
3	H					4				22			39	52	58	4.9×10^{-7}	390
4	*p*-CH_3					6			8				35	41	48	3.6×10^{-7}	530
5	*p*-CH_3O					5			9				32		48	3.6×10^{-7}	530
6	*p*-Cl					13	16		34[a]		50	58				1.1×10^{-6}	170
7	*p*-NO_2	19	31	48	58	70										1.5×10^{-5}	13
8	*p*-CN	24	45	66	75	85				91[b]						2.3×10^{-5}	8
9	*m*-NO_2		12			30	46	66	83							4.8×10^{-6}	40
10	*m*-CN		6			19	34	47	60							2.7×10^{-6}	71

[a] This experiment was repeated at concentrations of 0.43, 2.4, and 5.4 mmoles in 10 ml; the disproportionation % was 30, 29, and 37, respectively. [b] Pure material purified by chromatography on alumina (crude yield, 103%).

were insoluble. In these instances, washing with ether and benzene removed **2** and **11** and the kinetics then were followed by estimation of **12**. In all instances, the reliability of the extraction procedures was first tested by showing that the composition of artificially prepared mixtures of the three possible disulfides (**2**, **11**, and **12**) could be verified by the separation within 5%. Results are listed in Table II. They may not always be within the accuracy of ±5% mentioned in the Experimental Section, however, because the reaction was sensitive to impurities. Despite careful purification of disulfides, cleaning of vials, and redistilling of solvent, therefore, results conceivably may reflect occasional unrecognized effects caused by trace impurities.

Plots of the results in Figure 1 show that disproportionations apparently were first order, as was found previously with the aryldithio series (**1**).[2] Apart from theoretical implications discussed below, the results unquestionably show a useful practical correlation of disproportionation rates with electronic influence in the *meta* and *para* positions; for example, one can now predict that electron-withdrawing substituents such as nitro and cyano will accelerate disproportionation significantly in systems of structure **2**.

Figure 2 extends these relationships more quantitatively and shows a correlation of log k/k_0 with Hammett σ^{-}[4] values. These results, and particularly the fact that correlations of *p*-nitro and *p*-cyano values are considerably better with σ^- than with σ, suggest a resonance involvement of the type shown in canonical form **13**. In the aryldithio series (**1**), a similar effect with the *p*-nitro derivative was noticed and the suggestion was made that resonance of the kind shown by structure **14** might be responsible.[2] The neighboring-group effect represented in structure **13** is not unreasonable; many reactions of sulfides have been rationalized in terms of similar contributors.[5] Also, it is of interest that a related neighboring-group effect, although with electrophilic interaction of sulfur, has been postulated to explain the formation of thiophenes upon treatment of arylalkyl disulfides with iodine.[6]



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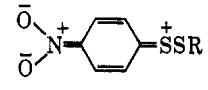

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It is interesting to place the disulfides of structure **2** in context with earlier work. The unsymmetrical benzyl disulfide **3** had a half-life at 100° of 390 hr, considerably larger than the aryl disulfide **1** (X = H; 8.7 hr at 89°).[2] Indeed, the benzyldithio series was done at 100° rather than at 68–89° as done previously because of its characteristically slower rate. As one might expect, the benzyl series also is somewhat less responsive to effects of substituents (ρ = 1.1, as compared with 1.9 for the aryldithio series).[2] We had hoped to evaluate activation parameters by carrying out disproportionations at various temperatures, but the experimental results were such that it was not possible to determine reliable values. In comparison with an earlier ranking of a number of classes of disulfides determined at 100° in ambient light,[7] even the most

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(4) K. B. Wiberg, "Physical Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1964, p 411.

(5) K.-D. Gundermann, *Angew. Chem.*, **75**, 1194 (1963).

(6) E. Campaigne and B. G. Heaton, *J. Org. Chem.*, **29**, 2372 (1964).

(7) L. Field, A. Ferretti, and T. C. Owen, *ibid.*, **29**, 2378 (1964).

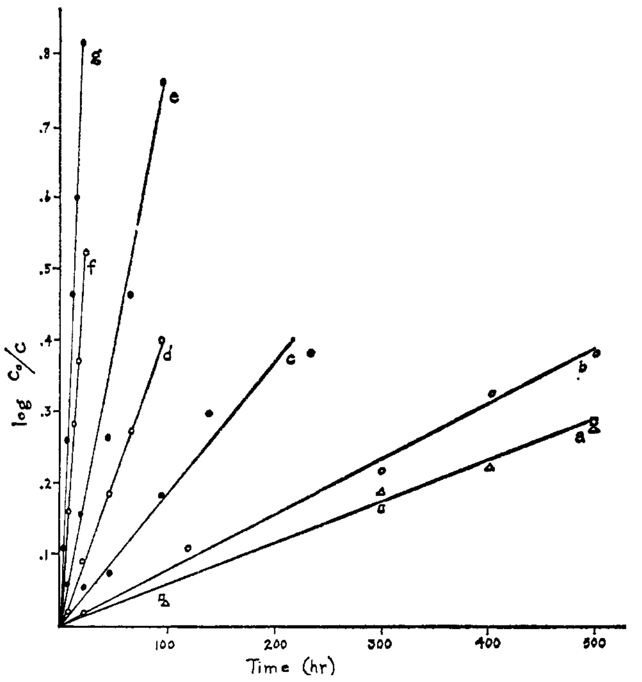

Figure 1.—First-order rate plot for the disproportionation in 95% ethanol of $XC_6H_4CH_2SS(CH_2)_2NH_2^+$-$n$-$C_{10}H_{21}Cl^-$, where X is a, Δ, p-CH_3 (**4**) and □, p-CH_3O (**5**); b, H (**3**); c, p-Cl (**6**); d, m-CN (**10**); e, m-NO_2 (**9**); f, p-NO_2 (**7**); g, p-CN (**8**).

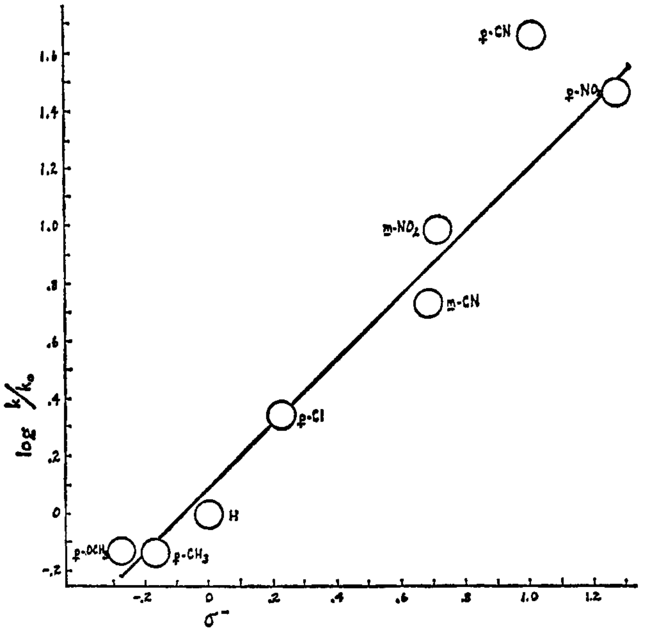

Figure 2.—Correlation of log k/k_0 at 100° with Hammett σ^- constants for the disproportionation of $XC_6H_4CH_2SS(CH_2)_2$-NH_2^+-n-$C_{10}H_{21}Cl^-$ (X as shown on plot).

reactive of the benzylthio series (*i.e.*, **7**, **8**) seem to resist disproportionation as do aliphatic bisdisulfide hydrochlorides, one of the more stable classes we have studied, suggesting that the benzyl class (**2**) also is one of the more stable.

An important difference exists between this series and the aryldithio series (**1**). Cleavage of an unsymmetrical disulfide has generally been considered to be a reversible process leading to an equilibrium mixture.[8,9] In our previous paper, we were under the impression that the insolubility of the phenyl disulfide in the reaction medium (water) prevented reversibility and was responsible for forcing the disproportionation to completion;[2] the reaction was later shown to be nonreversible for the phenyldithio compound (**1**, X = H) and the disproportionation was found to be a clean reaction with only the three possible disulfides being detectable in the reaction mixture.[9] In contrast, in the benzyldithio series (**2**) starting materials and products are all very soluble in warm ethanol. Nevertheless the reaction still goes essentially to completion. Heating of the p-cyano derivative (**8**) for 120 hr gave p-cyanobenzyl disulfide in 103% crude yield, which when purified on alumina gave pure p-cyanobenzyl disulfide in 91% yield. Essential irreversiblity also was demonstrated by approaching the reaction from the product side. When typical amounts of p-chlorobenzyl disulfide and n-decylaminoethyl disulfide dihydrochloride were heated for 95 hr, *i.e.*, under conditions for 34% disproportionation of **6** (Table II), only starting materials were recovered; these were positively identified by mixture melting point, infrared spectrum, and thin layer chromatography and only a minute trace of the unsymmetrical product **6** could be discerned. We agree with a referee that the results suggest involvement of a large equilibrium constant.

We sought evidence as to whether the reaction of eq 2 was inter- or intramolecular in nature because of its bearing on the possibility of neighboring-group rather than intermolecular effects. When the p-chloro compound **6** was heated for 95 hr over about a tenfold variation in concentration, the per cent disproportionation varied only from 29 to 37% (see Table II), indicating the reaction to be intramolecular. We suggest that the reactions of Scheme I mechanistically rationalize the facts now known, although possibly in an oversimplified way. According to Scheme I, (a) the unsymmetrical disulfide hydrochloride (**2**) can be considered in equilibrium with its free base (**15**) and (b) this free base (**15**) then undergoes disproportionation into ions **16** and **17**. The assumption that **15** would disproportionate seems reasonable since these free amines are known to be unstable.[2] Furthermore, in the aryldithio series (**1**), addition of hydrochloric acid reduced the rate of disproportionation[2] and indeed the decreasing order of stability in general is amides > hydrochlorides >> bases.[7] Careful neutralization of **6** and heating of the resulting free base for 1 hr under the usual conditions and reacidification gave 58% of p-chlorobenzyl disulfide; in contrast, the salt **6** disproportionated only to the extent of 13% after 22 hr (Table II). (c) Thiolate anion **16** then rapidly attacks the original disulfide **2** to give the symmetrical benzyl disulfide (**11**) and the aminothiolate anion **18**. This attack would be expected since the reaction of the aryldithio species (**1**) is catalyzed by a thiol.[2] (d) By repeating this type of process, **18** attacks **2** to give the symmetrical decylamino disulfide **12** and thereby regenerate **16**. (e) Cation **17**, because of its quaternary saltlike nature, is assumed to be internally stabilized and thus to have a reduced tendency for reaction with solvent or **2**, but would react rapidly with **18** (when its concentration suffices) and then with HCl formed earlier to give **12**. Therefore, the concentration of **16**

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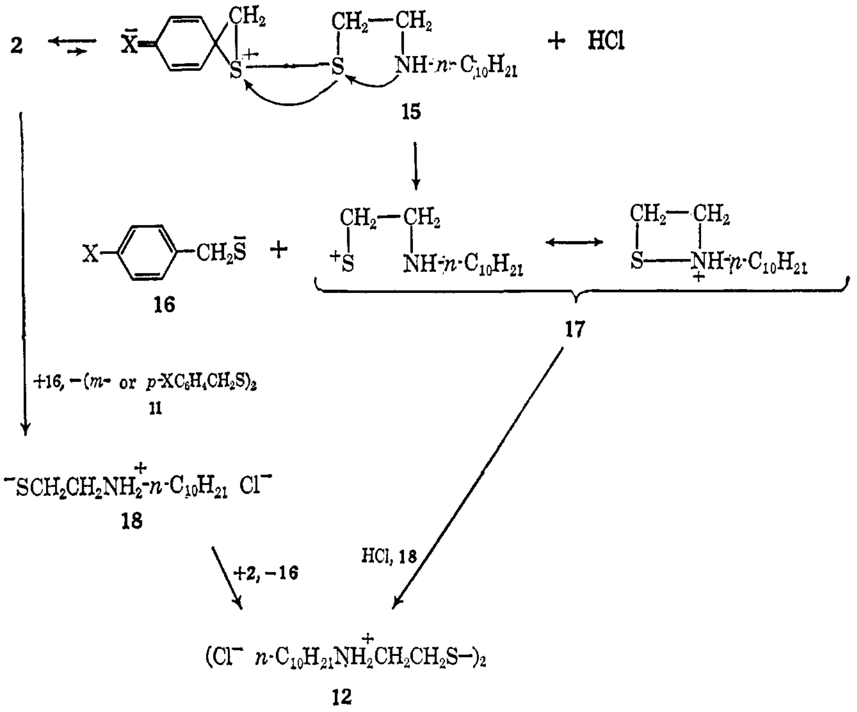
(8) *Cf.* E. Emmet Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., Inc., New York, N. Y., 1960, p 367.

(9) L. Field and H. K. Kim, *J. Med. Chem.*, **9**, 397 (1966); see ref 7 therein for leading references.

SCHEME I



may be considered to remain constant, although its rate of formation might be considered as the rate-determining step. (f) It is reasonable to assume the back reactions of **16** with **2** to regenerate **16** and of **18** with **2** to regenerate **18** occur, but they are not apparent in the study.

Disulfides **4**, **5**, and **6** were inactive and **3** was only slightly active, but **8** was active in protecting mice against the lethal effects of ionizing radiation.[10] Results on the other compounds are pending.

Experimental Section[11]

Preparation of Thiols.—*p*-Methyl-, *p*-methoxy-, and *p*-chlorophenylmethanethiols and phenylmethanethiol were commercial products. The *m*- and *p*-nitro- and -cyanophenylmethanethiols were prepared from the corresponding benzyl chlorides and thiourea. This procedure is exemplified by the preparation of *p*-cyanophenylmethanethiol.

p-Cyanobenzyl chloride (15.2 g, 0.100 mole) and thiourea (7.60 g, 0.100 mole) were dissolved in warm ethanol (70 ml) and the solution was heated under reflux for 1 hr. Evaporation of the solution and washing of the residue with ethyl acetate gave 21.0 g (92%) of the thiuronium salt. The crude salt (20 g) then was dissolved in water (1 l.) and sodium hydroxide solution (10%) was slowly added with rapid stirring at room temperature until the solution remained clear and alkaline to litmus after stirring for 2 min (during this addition, nitrogen was bubbled into the solution to prevent disulfide formation). Concentrated hydrochloric acid then was immediately added with rapid stirring until the reaction mixture was barely acidic. The cloudy solution then was extracted with ether and the ether extract was dried over anhydrous magnesium sulfate and evaporated. The residue of 11.4 g (80%, over-all) had mp 34° (lit.[12] mp 37°). The infrared spectrum (liquid film) showed bands at 2570 (SH) and 2230 cm^{-1} (CN). In all instances the crude thiols were used without further purification.

General Procedure for Preparing Unsymmetrical Disulfides (2).—The procedure is exemplified by the reaction of phenylmethanethiol with 2-(*n*-decylamino)ethyl 2-(*n*-decylamino)-ethanethiolsulfonate dihydrochloride. Care was necessary in working with several of the decylaminoethyl compounds to prevent skin rash (rubber gloves, hood). The decylaminoethyl thiolsulfonate dihydrochloride (13.4 g, 24.9 mmoles)[13] was dissolved in a boiling mixture of 1:1 ethanol-methylene chloride (500 ml) and the solution then was cooled to room temperature. Phenylmethanethiol (3.10 g, 25 mmoles) was added dropwise during about 2 min with rapid stirring. The reaction mixture was stirred 3 hr more and then was chilled overnight at 10°. Filtration gave some of the thiolsulfonate used as starting material (2.5 g; yields are based on thiolsulfonate taken first). The filtrate was evaporated and the residue chromatographed on an alumina column (Merck acid-washed, 24 mm × 300 mm) with chloroform, the first 500 ml being collected (*ca.* 5 l. with **7**).[14] Evaporation of the chloroform gave a pasty residue further purified by trituration with ether, collecting, and thoroughly washing the residue with ether. Crystallization from dioxane gave needles having mp 150–152° (**3**, 6.20 g, 66%). However, crystallization from aqueous ethanol or acetone gave plates of mp 145–146°. Infrared spectra of each product in chloroform showed the two products were identical. Thin layer chromatography (of **3** with mp 145–146°) in chloroform–95% ethanol (98:2) showed only one spot on exposure to iodine vapor in a desiccator. All compounds (**3**–**10**) showed only single spots in thin layer chromatography and all had absorption characteristic of amine salts (2000–2900 cm^{-1}), of the appropriately substituted aromatic moiety, and of the ring substituents.

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[10] Results furnished through the kindness of Drs. D. P. Jacobus and T. R. Sweeney of the Walter Reed Army Institute of Research. Details of procedures and meanings of activity ratings are given by L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

[11] Melting points are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained using a Perkin-Elmer Model 137B or Beckman IR-10 spectrophotometer with liquids neat and with solids in Nujol mulls or KBr pellets. All thin layer chromatographic separations were carried out using sheets of Eastman Chromagram Type K 301 R (silica gel) with solvents as follows: (a) 95% ethanol–chloroform (2:98) for products **3**–**10**; (b) 95% ethanol–chloroform (10:90) for **12**; (c) benzene for symmetrical benzyl disulfides (**11**). In all instances in which thin layer use is reported as a criterion of identity, the R_f value of the spot was essentially identical with that of simultaneously run authentic material. Evaporations of solvents usually were done under reduced pressure using a rotary evaporator.

[12] C. Barkenbus, E. B. Friedman, and R. K. Flege, *J. Am. Chem. Soc.*, **49**, 2549 (1927).

[13] This compound was kindly provided by Dr. Thomas R. Sweeney of the Walter Reed Army Institute of Research; prepared by the procedure of L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

[14] In preparing the column, it is necessary to pass HCl gas into a vigorously stirred chloroform slurry of the alumina for 0.5 min before use and then to use the HCl-saturated chloroform for packing the column; otherwise the results may be erratic.

Disproportionation of Unsymmetrical Disulfides (2).—Except for slight variations in procedures of isolation, the following method was used for all unsymmetrical disulfides. Approximately 1 mmole of the unsymmetrical disulfide was accurately weighed and added to 10 ml of redistilled 95% ethanol in a carefully cleaned 10-ml vial. The vial was sealed, protected from light with aluminum foil, and kept at 100° for the appropriate time.[15] After being cooled, the reaction mixture was evaporated and the residue was thoroughly washed with *n*-hexane (except for the p-NO$_2$ (**7**) and *m*-CN (**10**) derivatives discussed below). Evaporation of the hexane usually gave a pure sample of the symmetrial benzyl disulfide (**11**), which was characterized in typical instances by mixture melting point, infrared spectrum, and thin layer chromatography (single spots in all instances) with benzene as eluent. In the case of the *p*-cyano derivative, it was necessary to purify the product by washing with a little petroleum ether (bp 30–50°). "Disproportionation, %" in Table II was calculated as (millimoles of symmetrial disulfide formed × 2 × 100)/(millimoles of unsymmetrical disulfide used).[16]

For the *m*-CN (**10**) and p-NO$_2$ (**7**) derivatives, it was convenient to follow the disproportionations by estimating the amount of 2-(*n*-decylamino)ethyl disulfide dihydrochloride (**12**) formed. Thus in these instances the residue from evaporation of the reaction mixture was first washed thoroughly with ether (200 ml) and then with benzene (20 ml) leaving the pure *n*-decylaminoethyl disulfide dihydrochloride, identified by its superimposable infrared spectrum with those of authentic samples and thin layer chromatography (10:90 ethanol–chloroform). With each of the components **3–10**, the validity of each separation procedure was checked by mixing known amounts of reactant and products; results were usually within 5% of the known composition.

Rate constants (k) were obtained by plotting log C_0/C *vs.* time (Figure 1), where C_0 is the initial concentration of *ca.* 1 mmole and C is the concentration at time t (deduced by subtraction of "disproportionation, %" from Table II) and then multiplying the slope by 2.303. Half-lives (Table II) were calculated from the equation $t_{1/2} = 0.693/k$.

Experiments on the Nature of the Disproportionation Reaction. A. Extent of Completion.—*p*-Cyanobenzyl 2-(*n*-decylamino)ethyl disulfide hydrochloride (**8**, 0.4036 g, 1.004 mmoles) was dissolved in 95% ethanol (10 ml) in a vial protected from light and was heated for 120 hr at 100° in the usual manner. The reaction mixture was evaporated at room temperature and the residue was thoroughly rubbed and washed with warm dry ether (200 ml). The solid was separated by filtration and was washed with a little benzene (5 ml), dried, and weighed: yield of **12**, 0.2428 g (95%), mp 265° dec. It was shown to be pure **12** by its superimposable infrared spectrum and by using thin layer chromatography with ethanol–chloroform (10:90) as eluting solvent. The ether filtrate was evaporated to give 0.1537 g (103%) of *p*-cyanobenzyl disulfide. Thin layer chromatography using benzene as eluent showed this material to be nearly pure. Purification was effected by chromatography on Merck acid-washed alumina using benzene–chloroform (90:10) for elution. The product, 0.1352 g (91%), had mp 146–147° and mmp 146–147° (lit.[12] mp 148°). It was further identified by its superimposable infrared spectrum. It showed only one spot using thin layer chromatography, which had an R_f value identical with that of an authentic sample.

B. Extent of Reversibility.—A solution of *p*-chlorobenzyl disulfide (0.1576 g, 0.500 mmole) and 2-(*n*-decylamino)ethyl disulfide dihydrochloride (**12**, 0.2529 g, 0.500 mmole) in 10 ml of 95% ethanol was heated for 95 hr at 100°. The reaction mixture was cooled and the contents were evaporated at room temperature. The residue was rubbed well with *n*-hexane (250 ml) and solid was separated by filtration. Evaporation of the filtrate gave pure *p*-chlorobenzyl disulfide (0.1575 g, 100% recovery), which was identified by mixture melting point, infrared spectrum, and thin layer chromatography using benzene for elution. The residue, 0.2526 g (100%), had an infrared spectrum identical with that of pure **12**. Thin layer chromatography (10:90 of 95% ethanol–chloroform) showed the product to be almost pure and revealed only a barely discernible trace of the unsymmetrical disulfide (**6**); the only strong spot had an R_f value identical with that of the symmetrical disulfide **12**.

C. Disproportionation of a Disulfide Free Base.—*p*-Chlorobenzyl 2-(*n*-decylamino)ethyl disulfide hydrochloride (**6**, 0.4111 g, 1.00 mmole) was dissolved in 95% ethanol (9 ml) plus ethanolic sodium ethoxide (1 ml, containing 1.00 mmole of sodium ethoxide). The solution was heated in a sealed vial protected from light for 1 hr at 100°. The reaction mixture was cooled and acidified with HCl gas and then was evaporated to dryness. Extraction of the residue with hexane and evaporation of the hexane extract gave 0.0908 g (58% disproportionation) of *p*-chlorobenzyl disulfide, identified by mixture melting point, infrared spectrum, and thin layer chromatography (only one spot) using benzene for elution.

Registry No.—**3**, 13116-74-0; **4**, 13116-75-1; **5**, 13116-76-2; **6**, 13116-77-3; **7**, 13116-78-4; **8**, 13116-79-5; **9**, 13135-40-5; **10**, 13116-80-8; **12**, 13116-81-9.

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[15] It was noticed that, after completion of an experiment, removing the aluminum foil and briefly rewarming the vial on the water bath redissolved any reactant and product which had precipitated; it is on this type of observation that the statement of homogeneity during the reaction is based (see Discussion).

[16] L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Am. Chem. Soc.*, **83**, 4414 (1961).

Reduction of Difluoronitroacetate Esters. The Preparation and Properties of 2,2,2-Difluoronitroethanol and the Novel Formation of Hemiacetals by Reduction

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Alkyl and benzyl difluoronitroacetates are reduced primarily to hemiacetals by sodium borohydride in anhydrous solvents. In aqueous solvents, 2,2,2-difluoronitroethanol is the only product. Esterification and condensation reactions of difluoronitroethanol are described.

The reduction of aldehydes, ketones, and esters with complex metal hydrides is a well-known method for providing a wide variety of alcohols.[1] However, to obtain a nitro alcohol by reduction of a nitro carbonyl compound, selective reduction is necessary in order to retain the nitro group. Under certain conditions, sodium borohydride and even lithium aluminum hydride can be used to reduce the carbonyl groups preferentially in compounds which also contain nitro groups three and four carbons removed from the reduction site, but no examples have been reported for reduction of a carbonyl group α to the carbon–nitro group. For example, Feuer[2] reduced methyl 4-nitropentanoate and 4,4-dinitropentanoate esters to the corresponding nitro alcohols with lithium aluminum hydride in ether at −60° and Shechter[3] obtained nitro alcohols from nitro ketones at 20° by the action of sodium borohydride in methanol solution. In each of

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[1] N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956.

[2] H. Feuer and T. J. Kucera, *J. Am. Chem. Soc.*, **77**, 5740 (1955).

[3] H. Shechter, D. E. Ley, and L. Zeldin, *ibid.*, **74**, 3664 (1952).