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Organic Disulfides and Related Substances. IV. Thiolsulfonates and Disulfides Containing 2-Aminoethyl Moieties[1]

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Thiolsulfonates, unsymmetrical disulfides and related substances are described which contain 2-aminoethyl moieties and are of physiological interest, particularly as potential anti-radiation drugs. The thiolsulfonates were prepared by oxidizing thiols or disulfides with hydrogen peroxide; several other oxidants were unsatisfactory. Solid unsymmetrical disulfides containing aryl and alkyl moieties were obtained by reaction of the thiolsulfonates with thiols, a route hitherto little used. Evidence of several kinds showed that these products were unsymmetrical and were not simply mixtures of symmetrical disulfides. Preliminary studies of disproportionation revealed that the solid disulfides are far more stable than their solutions, that an acylated aminodisulfide is more stable than the hydrochloride, and that *p*-nitrophenyl and *t*-butyl groups confer greater stability than does *p*-tolyl.

Organic sulfur compounds, especially thiols, disulfides and similar substances, represent the most generally active class of compounds yet discovered for protection against the lethal effects of ionizing radiation.[3] Of these, the most important contain a 2-aminoethylthio moiety, $-\mathrm{N}(\mathrm{CH_2})_2\mathrm{S}-$, and include cysteine, 2-aminoethanethiol, 2-aminoethyl disulfide and S-2-aminoethylisothiouronium bromide hydrobromide (AET).[3] This paper reports an attempt to find more active compounds among thiolsulfonates (RSO_2SR) and unsymmetrical disulfides ($RSSR'$) which contain a 2-aminoethylthio moiety. Various ancillary features of the chemistry of both classes also are discussed, especially relative to disproportionation of the disulfides.

It has been suggested that a prime requirement for protection against damaging radiation is the capability of certain agents for formation of a disulfide linkage involving a thiol grouping of the agent and those of proteins.[3] Both thiolsulfonates and unsymmetrical disulfides afford good prospects for formation of such disulfide linkages and accordingly for useful physiological activity, especially as radioprotective agents.

One of the most attractive syntheses of unsymmetrical disulfides, although it has been little used or studied, is through reaction of a thiol with a thiolsulfonate,[4] as shown by the equation

$$\mathrm{RSH} + \mathrm{R'SSO_2R'}$$

II, $R' = \mathrm{AcNH(CH_2)_2}$
V, $R' = \mathrm{Cl^-H_3N^+(CH_2)_2}$

$$\downarrow$$

$$\mathrm{RSSR'} + \mathrm{R'SO_2H}$$

I, $R,R' = \mathrm{AcNH(CH_2)_2}$
III, $R = p\text{-}\mathrm{CH_3C_6H_4}$, $R' = \mathrm{AcNH(CH_2)_2}$
IV, $R = p\text{-}\mathrm{O_2NC_6H_4}$, $R' = \mathrm{AcNH(CH_2)_2}$
VI, $R = t\text{-}\mathrm{C_4H_9}$, $R' = \mathrm{Cl^-NH_3^+(CH_2)_2}$
VII, $R = p\text{-}\mathrm{CH_3C_6H_4}$, $R' = \mathrm{Cl^-NH_3^+(CH_2)_2}$

By this means, a 2-aminoethyl group could be introduced into the disulfide $RSSR'$ either as R of the thiol RSH or as R' of the thiolsulfonate $R'SO_2SR'$. In all instances reported here, the amino group was masked, either by an acetyl group or as its hydrochloride, because of the lability of free 2-aminoethyl 2-aminoethanethiolsulfonate[5] and because at elevated *p*H thiols react with thiolsulfonates to produce two symmetrical disulfides rather than one unsymmetrical disulfide.[4] The unsymmetrical disulfides obtained were stable solids which could be purified by recrystallization.

2-Acetamidoethanethiol[6] could not be oxidized practicably to the corresponding disulfide I with air alone[6] or with iodine, nor could I be converted effectively to thiolsulfonate II with nitric acid, perbenzoic acid, chromium trioxide or chlorine.[7] Hydrogen peroxide in acetic acid–acetic anhydride with I gave 2-acetamidoethanesulfonic acid, which reportedly decomposes spontaneously[8] but actually proved reasonably stable in boiling ethanol (although somewhat unstable on long storage); this acid also was prepared from the thiol and was converted to its 2-mercaptoethylamine salt, which had seemed a potential radioprotective agent but was impracticably hygroscopic.

Oxidation of 2-acetamidoethanethiol or its disulfide I with aqueous hydrogen peroxide gave thiolsulfonate II in excellent yield, which reacted rapidly with thiols. Thus, II with 2-acetamidoethanethiol gave the disulfide I, substantiating the structure of II; *p*-toluenethiol and *p*-nitrobenzenethiol gave disulfides III and IV, and 1,2-ethanedithiol gave 1,2 - bis - (2 - acetamidoethyldithio) - ethane. Evidence for the structure of disulfide III was afforded by its alternative formation from 2-acetamidoethanethiol and *p*-tolyl *p*-toluenethiolsulfonate.[9] *t*-Butyl mercaptan, α-monothiolglycerol and diethyl α-mercaptosuccinate gave oils with II which were not studied further (spectra and solubilities were consistent for unsymmetrical disulfides). The product from diethyl α-mercaptosuccinate slowly deposited I, presumably by disproportionation.

(1) Research supported by the U. S. Army Medical Research and Development Command (Contract No. DA-49-193-MD-2030). For Paper III, see L. Field, C. B. Hoelzel, J. M. Locke and J. E. Lawson, *J. Am. Chem. Soc.*, **83**, 1256 (1961).

(2) On study leave from The College of Technology, Liverpool, England.

(3) A. Pihl and L. Eldjarn, *Pharmacol. Revs.*, **10**, 437 (1958), and references there cited.

(4) *Cf.* "Methoden der Organischen Chemie (Houben-Weyl)," E. Müller, Ed., Vol. 9, 4th ed., G. Thieme Verlag, Stuttgart, 1955, p. 72 (A. Schöberl and A. Wagner).

(5) D. Cavallini, C. De Marco and B. Mondovi, *Giorn. biochim.*, **2**, 338 (1953); *C. A.*, **49**, 13897 (1955).

(6) R. Kuhn and G. Quadbeck, *Chem. Ber.*, **84**, 844 (1951).

(7) I. B. Douglass and B. S. Farah, *J. Org. Chem.*, **24**, 973 (1959).

(8) M. Teroaka, *Z. physiol. Chem.*, **145**, 238 (1925); *C. A.*, **19**, 2808 (1925).

(9) Prepared by extending the route of Douglass and Farah[7] to the aromatic disulfide, *p*-tolyl disulfide.

The thiolsulfonate salt V was prepared like II, by oxidizing 2-aminoethanethiol hydrochloride with hydrogen peroxide.[10] Unsymmetrical disulfides VI and VII were prepared from V with *t*-butyl mercaptan or *p*-toluenethiol.

Considerable evidence shows that the unsymmetrical disulfides are homogeneous compounds and not eutectic mixtures or molecular compounds of symmetrical disulfides: (1) One of the symmetrical disulfides (*t*-butyl disulfide) corresponding to the *t*-butyl salt VI is an evil smelling liquid, but VI is odorless and solid. (2) If the unsymmetrical disulfides were mixtures, dissolution of VI in water or of IV in alcohol either ought to liberate the insoluble *t*-butyl or *p*-nitrophenyl disulfide or, conversely, these symmetrical disulfides should codissolve with 2-aminoethyl disulfide dihydrochloride or I, respectively; neither phenomenon occurred. Similar considerations apply for VII. (3) Fractional extraction[11] of the tolyl amide III between ether and water placed 96% of III in the first two ether layers; had compound I been present, much would have been expected in the water. For the salts VI and VII, distribution between water and ether in their preparation showed absence of the symmetrical disulfides (the symmetrical aminodisulfide salt is soluble in water and insoluble in ether; the converse is true for the other possible symmetrical disulfides). (4) A melting point–composition diagram for *p*-tolyl disulfide and I showed no m.p. (all broad in range) corresponding to the sharp m.p. of III; the mixtures and III were completely dissimilar in melting behavior. (5) Infrared spectra of the unsymmetrical disulfides have some similarity to superimpositions of those of the symmetrical disulfides. Differences are readily apparent, however; new absorptions occur and also, in some instances, absorptions of the symmetrical compounds are absent.[12]

It is well known that unsymmetrical disulfides disproportionate to equilibrium mixtures of unsymmetrical and symmetrical disulfides.

$$2RSSR' \rightleftharpoons RSSR + R'SSR'$$

Indeed, the possibility of such behavior provided the principal reason for seeking the assurances given above that the unsymmetrical disulfides were not mixtures.

Disproportionation may proceed spontaneously, or may be caused by heat, ultraviolet radiation, alkali or thiolate ions. The equilibrium may be approached from either direction and, for primary aliphatic disulfides, the ratio RSSR:R'SSR':RSSR' approaches the statistical distribution 1:1:2.[13,14]

(10) Conversion of the disulfide to V with this oxidant was described by W. G. Christiansen and M. A. Dolliver (U. S. Patent 2,242,236; *C. A.*, **35**, 5647 (1941)), although V was considered a disulfoxide, RSOSOR.

(11) M. T. Bush and P. M. Densen, *Anal. Chem.*, **20**, 121 (1948).

(12) The following absorptions (in cm.$^{-1}$; w, weak; m, medium) in the spectra of I or of 2-aminoethyl disulfide dihydrochloride (as appropriate) are absent in those of the unsymmetrical disulfides: 1,2-bis-(2-acetamidoethyldithio)-ethane, 980w and 820w; III, 980w; IV, 980w and 770w; VI, 1095m and 820m; VII, 1020m and 775m.

(13) L. Haraldson, C. J. Olander, S. Sunner and E. Varde, *Acta Chem. Scand.*, **14**, 1509 (1960).

(14) D. T. McAllan, T. V. Cullum, R. A. Dean and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).

The crystalline unsymmetrical disulfides reported here show several properties which commend them for disproportionation studies. They are readily recrystallized to high purity and, as solids, are stable to storage and reasonably so to heating. Thus, the *t*-butyl and tolyl salts VI and VII were rather stable at 104–160°; VII seemed stable at 136° (m.p.) −190° on a microscope slide. Both VI and VII decomposed rapidly above 190°, however, and *t*-butyl disulfide resulted in high yield from VI. The m.p. of 1,2-bis-(2-acetamidoethyldithio)-ethane (134.5–135.5°) was essentially that of a resolidified melt.

In solution, the unsymmetrical disulfides showed much greater tendency toward disproportionation.[15] The tolyl salt VII in water was 46% disproportionated after 36 hr., 68% after 2.75 hr. at 104°, and virtually quantitatively after brief irradiation; its free base was 10% disproportionated after 90 min. The tolyl amide III was 11% disproportionated after irradiation. The *t*-butyl salt VI in water gave negligible *t*-butyl disulfide after 20 hr. at 104°, and was only 7% disproportionated after irradiation. The nitro compound IV gave negligible *p*-nitrophenyl disulfide after longer irradiation. Pertinently, Parker and Kharasch found a number of unsymmetrical disulfides (*e.g.*, ethyl phenyl disulfide and ethyl 2,4-dinitrophenyl disulfide) to be stable in hot alcohol or acetone and toward irradiation.[16]

Although these studies of disproportionation are intended only as a preliminary survey, several conclusions seem sufficiently warranted to deserve mention: (1) The unsymmetrical disulfides are much more stable in the solid than in the dissolved state. This fact is of considerable interest, since it may forecast a general tendency of special significance for biologically important disulfides. (2) Unsymmetrical disulfides containing the amine hydrochloride group seem less stable than their counterparts containing an acetamido group, and those containing the *p*-tolyl group seem less stable than those containing the *p*-nitrophenyl or the *t*-butyl group.

Those of the compounds described which seem promising as anti-radiation drugs are being tested in this respect, and also for general biological activity, by the Department of Radiobiology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

Experimental[17]

2-Acetamidoethyl Disulfide (I).—Iodine (177.8 g.) in benzene (4 l.) was slowly added to 2-acetamidoethanethiol (162.3 g.) in benzene (500 ml.)–pyridine (111 g.). The mixture then was stirred 1 hr. The solid product (422 g.) was separated and stirred with chloroform (1 l.). The solution was filtered and evaporated. A solution of the residue in

(15) Solvents were chosen so that one of the two possible symmetrical disulfides which resulted would be sparingly soluble, thus permitting easy separation and estimation. Normal considerations of equilibria doubtless do not obtain.

(16) A. J. Parker and N. Kharasch, *J. Am. Chem. Soc.*, **82**, 3071 (1960).

(17) Melting points are corrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained using a Perkin–Elmer model 137 Infracord spectrophotometer with films of liquids or Nujol mulls of solids. Moist extracts usually were dried using anhydrous magnesium sulfate and, after filtration, were evaporated under reduced pressure for recovery of products.

chloroform was filtered, evaporated to 200 ml., and chilled. The product contained iodide, and a solution of 44 g. in chloroform was washed with aqueous potassium bicarbonate (which was extracted ten times with chloroform), dried and evaporated. Recrystallization gave 31.7 g. (46%) of I, m.p. 92–93° (reported[6] 87°); very soluble in water and chloroform, sparingly so in ether, benzene, and petroleum ether (*Anal.* Calcd. for $C_8H_{16}N_2O_2S_2$: C, 40.65; H, 6.82. Found: C, 40.93; H, 6.81).

2-Acetamidoethanesulfonic Acid.—Hydrogen peroxide (81 ml. of 10 molar) was added to 2-acetamidoethanethiol (20.8 g.)[6] in 300 ml. of 1:1 acetic acid–acetic anhydride at 3–6° during 3 hr. After 3 days at *ca.* 25°, evaporation gave a glass which was triturated with acetone (100 ml.). The resulting solid (24 g.), recrystallized from ethanol–ether, gave 8.9 g. (31%) of 2-acetamidoethanesulfonic acid, m.p. 194–196°, and a second crop upon addition of more ether of 4.9 g. (17%), m.p. 192–196°. Heating for 43 hr. in 95% ethanol at the reflux temperature and evaporation did not change the m.p. (194–196°); after 2 mo. at *ca.* 25°, an odor of acetic acid had appeared, and the m.p. was 189–215° (mainly 189–193°).

Anal. Calcd. for $C_4H_9NO_4S$: C, 28.74; H, 5.43; N, 8.38; S, 19.18; neut. equiv., 167. Found: C, 28.84; H, 5.78; N, 8.34; S, 19.22; neut. equiv., 167.

For preparation of the salt of the sulfonic acid, a hot solution of 2.94 g. of 2-aminoethanethiol in absolute ethanol (10 ml.) was added to 3.18 g. of the acid in 225 ml. of absolute ethanol. The clear solution was evaporated below 40° to a semi-solid which was washed with hot benzene. Chilling of the resulting oil at 4° for 7 days gave an extremely hygroscopic white solid, necessitating use of a dry-box in all subsequent exposures. Trituration with three 30-ml. portions of 2-propanol and then three recrystallizations from 2-propanol gave 1.7 g. (37%) of hygroscopic crystals, m.p. 110–165° dec., which liquefied within seconds after exposure.

Anal. Calcd. for $C_8H_{16}N_2O_4S_2$: N, 11.47; S, 26.25. Found: N, 11.24; S, 26.20.

2-Acetamidoethyl 2-Acetamidoethanethiolsulfonate (II).—Hydrogen peroxide (50 ml. of 10.5 *M*) was added to a stirred solution of 2-acetamidoethanethiol (122 g.) in water (375 ml., containing a crystal of potassium iodide) with ice cooling during 30 min. A 10-ml. aliquot of the solution then gave 2.85 g. of the disulfide I, m.p. 89–91.5° (m.p. 92–93° after recrystallization; identified by its infrared spectrum). More hydrogen peroxide (100 ml.) was added and the mixture was allowed to stand for 20 hr. Evaporation and recrystallization (1-butanol) gave 116.5 g. (87%) of the thiolsulfonate II, m.p. 95–96°; the infrared spectrum was similar to that of the disulfide I, except for the presence of strong bands at 1335, 1135 and 1050 cm.$^{-1}$.

The same product (identical infrared spectra) was obtained in poor yield by oxidation of I with perbenzoic acid in chloroform at −35°. It was purified for analysis by recrystallization to a constant m.p. of 95–96° (chloroform–ether, carbon tetrachloride, benzene and benzene–ether).

Anal. Calcd. for $C_8H_{16}N_2O_4S_2$: C, 35.80; H, 6.01; N, 10.44; S, 23.90. Found: C, 35.84; H, 6.04; N, 10.35; S, 23.71.

2-Aminoethyl 2-Aminoethanethiolsulfonate Dihydrochloride (V).—By means of the procedure used for II, based on one applied to the disulfide dihydrochloride by Christiansen and Dolliver,[10] 2-aminoethanethiol hydrochloride (57.0 g.) was oxidized with hydrogen peroxide (72 ml. of 10.5 *M*). Crystallization from glacial acetic acid (300 ml.) gave 59.2 g. (93%) of V as white needles with a constant m.p. of 165–166° (reported[10] 166°) (*Anal.* Calcd. for $C_4H_{14}Cl_2N_2O_2S_2$: N, 10.89. Found: N, 10.80).

The salt V was converted, for structural evidence, to its diacetyl derivative II by heating 4.5 g. with 7 g. of acetic anhydride and 10 ml. of pyridine. Water was added, the mixture was evaporated, and the residue was taken up in chloroform–water. The solution was neutralized, and a chloroform extract was dried and evaporated. A chloroform solution of the resulting oil was adjusted to turbidity with ether and chilled; yield 0.4 g. (9%), m.p. 77–80°. Recrystallization gave II with m.p. 92–93° (mixture m.p. 92–95°; identical infrared spectrum).

Reaction of Thiolsulfonate II with Thiols. (a) With 2-Acetamido-ethanethiol.—2-Acetamidoethanethiol (0.60 g.) was added to 1.34 g. of II in 95% ethanol (5 ml.). After 10 min., 1 g. of potassium hydroxide in water was added. Six chloroform extracts were combined, dried and evaporated; yield of 2-acetamidoethyl disulfide (I), 0.93 g. (79%), m.p. and mixture m.p. with I prepared by oxidation, 91–92°.

(b) **With Ethanedithiol.**—Ethanedithiol (3.13 g.) in ethanol (10 ml.) was added to II (17.9 g.) in ethanol (60 ml.). After 2 hours, the mixture was chilled. The solid product was collected and washed with ethanol; yield of 1,2-bis-(2-acetamidoethyldithio)-ethane, 10 g. (92%), m.p. 133.5–135°. After recrystallization to constant m.p. from ethanol, the m.p. was 134.5–135.5°; white plates, sparingly soluble in water or cold ethanol; a cooled melt remelted at 132–134°.

Anal. Calcd. for $C_{10}H_{20}N_2O_2S_4$: C, 36.56; H, 6.14; N, 8.54; S, 39.04. Found: C, 36.71; H, 6.14; N, 8.70; S, 39.39.

(c) **With *p*-Toluenethiol.**—*p*-Toluenethiol (6.95 g.) in 28 ml. of ethanol was added to a stirred solution of II (15.0 g.) in 90 ml. of ethanol. After 4 days,[18] the solvent was evaporated. An ether extract of the product was washed with cold dilute aqueous sodium hydroxide and saturated brine, then dried and evaporated. Trituration with pentane gave 12.13 g. (90%) of 2-(*p*-tolyldithio)-1-acetamidoethane (III), m.p. 63–65°. Recrystallization from benzene (25 ml.)–pentane (35 ml.) gave III (10.8 g., 80%) with m.p. 64–65.5°, which was identical (mixture m.p., infrared spectrum) with III prepared by the alternative route below:

A suspension of 2-acetamidoethanethiol (1.57 g.) and *p*-tolyl *p*-toluenethiolsulfonate (4.0 g.)[9] in absolute ethanol was stored for 4 weeks (for convenience; *cf.* ref. 18) and evaporated. The yellow oil was treated as before; yield of III, 2.3 g. (73%), m.p. 45–51°. Recrystallization from pentane–benzene and methanol gave III with a constant m.p. of 64–65.5°.

Anal. Calcd. for $C_{11}H_{15}NOS_2$: C, 54.73; H, 6.26; N, 5.80; S, 26.57. Found: C, 54.79; H, 6.08; N, 5.60; S, 26.47.

(d) **With *p*-Nitrothiophenol.**—*p*-Nitrothiophenol (4.0 g.) in ethanol (30 ml.) was added to II (10.9 g.) in ethanol (30 ml.). After 6 hr., evaporation gave a residue which was taken up in chloroform–water and neutralized with potassium bicarbonate (10 g.). Chloroform extracts were dried and evaporated to an oil which crystallized on scratching under ether. Recrystallization to constant m.p. (ether) gave 1-(*p*-nitrophenyldithio)-2-acetamidoethane (IV, 4.8 g., 68%) as pale yellow microneedles, m.p. 81.5–82°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S_2$: C, 44.10; H, 4.44; N, 10.29; S, 23.55. Found: C, 44.26; H, 4.26; N, 10.40; S, 23.75.

Reaction of Thiolsulfonate V with Thiols. (a) With *t*-Butyl Mercaptan.—*t*-Butyl mercaptan (9.0 g.) in ethanol was added to V (25.7 g.) in water (20 ml.). The solution was kept at *ca.* 25° for 1 hr., chilled overnight, and filtered. The insoluble precipitate (2.75 g.) was shown by m.p. (325° dec.) and infrared spectrum to be taurine (presumably formed by oxidation or disproportionation of 2-aminoethanesulfinic acid hydrochloride). The filtrate was evaporated and the residue taken up in water and ether and neutralized with potassium bicarbonate (30 g.). The ether layer was washed with water and extracted with 8.5 ml. of 12 *N* hydrochloric acid in water. The acid extract and a water wash were evaporated. Two recrystallizations of the resulting 2-(*t*-butyldithio)-ethylamine hydrochloride (VI) from 2-propanol–hexane gave 13.5 g. (67%) of VI as white crystalline powder. The VI changed to an apparently different solid at *ca.* 195° and liquid separated; no further change occurred until the solid melted sharply at 213–214° dec. (2-aminoethyl disulfide dihydrochloride melts at 214°).

Anal. Calcd. for $C_6H_{16}ClNS_2$: C, 35.71; H, 7.99; N, 6.94; Cl, 17.57; neut. equiv., 202. Found: C, 35.78; H, 7.85; N, 6.91; Cl, 17.87; neut. equiv., 205.

(b) **With *p*-Toluenethiol.**—*p*-Toluenethiol (6.2 g.) and V (12.9 g.) were stirred in ethanol (80 ml.)–water (30 ml.) for

(18) For convenience only. Reaction seemed complete after a few min. Thus, titration with 0.1 *N* alkali using brom phenol blue[19] gave results indicating presence of 67% of the expected amount of sulfinic acid after 5 min., 65% after 40 min., and 23% after 4 days. The decrease in acidity may have resulted from disproportionation according to the equation[20] $3RSO_2H \rightarrow RSO_3H + RSSO_2R + H_2O$.

(19) D. Barnard and E. R. Cole, *Anal. Chim. Acta*, **20**, 540 (1959).

(20) See ref. 4, p. 331.

24 hr. Evaporation below 30° resulted in 1.07 g. of *p*-toluenethiol in the distillate. The residue was dissolved in water and extracted with ether; the ether removed 0.5 g. more of the thiol. The aqueous layer then was shaken with ether[21] while an iced aqueous solution of potassium hydroxide (9.5 g.) was added. The water layer was extracted thrice more with ether; each ether layer was backwashed rapidly with water and at once shaken with 5 ml. of 12 *N* hydrochloric acid in water. Finally, the combined ether extracts were washed with water; evaporation gave *p*-tolyl disulfide (1.15 g.). Upon partial evaporation of the acid extracts, crystallization occurred. Filtration separated 2-(*p*-tolyldithio)-ethylamine hydrochloride (VII) as colorless plates; yield 5.0 g., 75% (allowing for recovery of the thiol and *p*-tolyl disulfide; the actual conversion was 42%), m.p. 136–137°. Heating of the melt to 190° resulted in separation into two liquid layers.

Anal. Calcd. for $C_9H_{14}ClNS_2$: C, 45.84; H, 5.98; Cl, 15.04; S, 27.20; neut. equiv., 236. Found: C, 45.58; H, 6.20; Cl, 14.91; S, 27.08; neut. equiv., 232.

Evidence for Homogeneity of III.—By the usual procedure of multiple fractional extraction,[11] III (1.4982 g.) in water-saturated ether was extracted with six portions of ether-saturated water. Each aqueous phase was contacted in sequence with five ether layers. The first ether layer contained 1.3348 g., and the second, 0.1063 g. (total recovery, 96%). In view of the solubilities of I mentioned above, III therefore is very unlikely to be a mixture of I and *p*-tolyl disulfide such as could afford the excellent analysis for III.

In the m.p.–composition studies, five mixtures of I and *p*-tolyl disulfide (mole fraction, 0.2–0.8), all melted over broad ranges (42–49°) between the extremes of *ca.* 45° and 93° for the pure substances.

Disproportionation of Unsymmetrical Disulfides.—The symmetrical disulfides isolated were identified by their infrared spectra. The "% disproportionated" was calcd. as (100 × 2 × moles of either symmetrical disulfide isolated)/(moles of unsymmetrical disulfide used).

(a) **Of 2-(*t*-Butyldithio)-ethylamine Hydrochloride (VI).**—(1) A sintered glass funnel containing VI was heated at 104° for 17 hr. The product was washed with cold pentane and dried; recovery 99.9%. Heating was continued for 1.5 hr. at 150–160°; recovery 99.7%. The infrared spectrum in both instances was unchanged. At 210°, VI darkened and partially liquefied; clogging of the filter prevented the usual washing. When VI(0.2468 g.) was heated in a slow nitrogen stream, no change was apparent in 10 min. at 190°, but at 205–210° after 1 hr. *t*-butyl disulfide (0.0836 g.) was trapped; % disproportionated, at least 77. (2) A solution of VI (0.3 g.) in water (9 ml.) heated in a sealed ampoule at 104° for 20 hr. and cooled showed no separation of insoluble material. (3) A solution of VI (0.1285 g.) in water (10 ml.) was irradiated in a silica cell 3-4 in. from a 250-watt mercury vapor-lamp (General Electric Co., Uviarc UA-2). In 10 min., the clear solution clouded. After 45 min., extraction with ether and evaporation left 0.1244 g. of solid; % disproportionated,[7] (assuming the loss in wt. represented *t*-butyl disulfide, the only ether-extractable product).

(b) **Of 2-(*p*-Tolyldithio)-ethylamine Hydrochloride (VII).**—(1) Solid VII (0.0907 g.) was unchanged (wt., appearance) after 2.75 hr. at 104° and gave only slight cloudiness upon dissolution in water, indicating negligible disproportionation. (2) A solution of VII (0.0874 g.) in water (10 ml.) was heated for 2.75 hr. (ampoule) at 104°. Ether extracted 0.0303 g. of *p*-tolyl disulfide; % disproportionated, 68 (the water layer gave 0.0560 g. of presumed mixture). (3) After 36 hr. of normal exposure to light at 25°, 0.0905 g. of VII in water (2 ml.) deposited 0.0214 g. of *p*-tolyl disulfide; % disproportionated, 46. When 0.0870 g. of VII in 10 ml. of water was irradiated with ultraviolet light as above, insoluble material quickly separated; after 45 min. 0.0447 g. of *p*-tolyl disulfide was extracted with ether; % disproportionated, 98 (the water layer contained 0.0426 g. of solid, largely 2-aminoethyl disulfide dihydrochloride from its infrared spectrum).

(c) **Of 2-(*p*-Tolyldithio)-ethylamine.**—A solution of the hydrochloride VII (0.2291 g.) in aqueous ethanol (32 ml., 1:1) neutralized to *p*H 10.5 with potassium hydroxide was kept at 25° for 90 minutes, acidified with dilute hydrochloric acid and extracted with ether. The ether extract afforded *p*-tolyl disulfide (0.0115 g.); % disproportionated, 10.

(d) **Of 2-(*p*-Nitrophenyldithio)-1-acetamidoethane (IV).**—Ultraviolet irradiation as above of 0.3 g. of IV in ethanol (10 ml.) for 80 min. at 0° resulted in no precipitate of *p*-nitrophenyl disulfide, even after the solution was seeded and chilled for 2 days in the dark. Since the solubility of *p*-nitrophenyl disulfide in ethanol proved to be *ca.* 0.02% at *ca.* 25°, evidently less than 1% disproportionation occurred.

(e) **Of 2-(*p*-Tolyldithio)-1-acetamidoethane (III).**—A solution of III (0.1252 g.) in 10 ml. of ether was irradiated as above for 45 min. The cloudy solution (initially clear) was seeded with I and chilled overnight. A deposit of 0.0065 g. of I resulted, m.p. 88°; % disproportionated, *ca.* 11 (the solubility of I in ether at 0°, while not determined quantitatively, is such as to preclude the possibility that any significant amount of I remained in solution).

(21) If the aqueous solution is not shaken with solvent when alkali is added a high yield of *p*-tolyl disulfide and little or none of the disulfide VII result.

[CONTRIBUTION FROM THE GORGAS LABORATOEY, ROHM & HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION, HUNTSVILLE, ALA.]

Small Ring Heterocyclic Nitrosoamines[1]

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N-Nitroso-3-nitrocarbazole, a mild nitrosating reagent, converts N-methylaniline to N-nitrosomethylaniline in benzene solution. This reagent reacts with aziridine under similar conditions to yield ethylene and nitrous oxide, products which may arise from decomposition of N-nitrosoaziridine (I). Previous observations concerning the stability of N-nitrosoazetidine (II) have been verified and the structure characterized by its n.m.r. spectrum. The effect of temperature on the n.m.r. spectrum of N-nitrosoazetidine is compared with that of N-nitrosodimethylamine, and the differences attributed to ring strain. Oxidation of N-nitrosoazetidine with peroxytrifluoroacetic acid gives N-nitroazetidine. Differences in the ultraviolet spectra of N-nitroazetidine and di-*n*-propylnitramine are rationalized in terms of ring strain.

Cyclic nitrosoamines, where a nitrogen atom is part of a small ring system, have received little attention. N-Nitrosoaziridine (I) has been postulated as an intermediate in solution but has not been isolated.[2] N-Nitrosoazetidine (II) has been

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reported but has not been characterized com-

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(2) H. Euler, *Chem. Zentr.*, **74, II,** 1165 (1903).