After cooling to room temperature, 50 ml. of dry 1,2-dimethoxyethane was injected through a side arm closed by a rubber serum cap, followed by 2.61 ml. (25 mmoles) of *n*-butylamine dissolved in 20 ml. of 1,2-dimethoxyethane. The mixture was stirred magnetically for 1 hr. Carbon monoxide was then admitted to a pressure of 1.4 atm. After 1 hr., the temperature was increased to 65°. Decreases in pressure were noted, and the pressure was maintained at approximately 1.4 atm. by addition of CO. Samples of the reaction mixture were withdrawn periodically and analyzed by vapor phase chromatography and infrared spectroscopy. The presence of *n*-butyl isocyanate was detected after 1.75 hr. at 65°, and successive samples were shown to contain increasing amounts of this material. Solids in the reaction flask became progressively blacker, indicating reduction of $PdCl_2$ to metal.

After 48 hr. the mixture was cooled to room temperature. Analysis of a sample withdrawn at that time showed that the liquid phase contained 2 vol. % of *n*-butyl isocyanate, constituting a yield of 49.2 mole % (based on amine).

The mixture was then treated with excess *n*-butylamine and stirred for 0.5 hr. Infrared analysis confirmed the conversion of isocyanate present to di-*n*-butylurea. The mixture was filtered and the solids were washed with 1,2-dimethoxyethane. The solvent was stripped under vacuum from the combined filtrate and washings. The residue was dissolved in ether, extracted with aqueous NaCN, dried over $MgSO_4$, filtered, and stripped. The solid residue (2.59 g.) was recrystallized from ethanol–ether, yielding 2.34 g. of white crystals shown to be identical in melting point and infrared spectrum with an authentic sample of di-*n*-butylurea. The total yield of urea (based on $PdCl_2$) was 54.4 mole %.

Phenyl Isocyanate. Procedure A.—The procedure used was essentially that employed in the preparation of *n*-butyl isocyanate. After the addition of 2.27 ml. (25 mmoles) of aniline in 20 ml. of 1,2-dimethoxyethane, the mixture was stirred at an initial CO pressure of 1.1 atm. After 1.5 hr. at room temperature, the presence of phenyl isocyanate was detected by infrared spectroscopy. The mixture was then stirred at 65° for 24 hr. and at 80° for 96 hr. During this time, reduction of $PdCl_2$ was again observed and the presence of increasing amounts of phenyl isocyanate was noted. Carbon monoxide was absorbed continuously during the reaction period, and the pressure was maintained at 1.4 atm. by periodic additions of CO. Final vapor phase chromatographic analysis of the liquid phase showed a phenyl isocyanate content of 2.1 vol. %, constituting a 53.4 mole % yield.

Treatment of the mixture with excess aniline followed by the same procedure as before led to the isolation of 3.7 g. of solid which, when recrystallized from ethanol yielded 2.67 g. (50.2 mole % based on $PdCl_2$) of diphenylurea, identical with authentic material.

Procedure B.—To a 250-ml. flask fitted with a dropping funnel, a Vibromix stirrer, a gas inlet, and a reflux condenser, were added 4.43 g. (25 mmoles) of $PdCl_2$ and 5.89 g. (41 mmoles) of Na_2HPO_4. Dry nitrogen was passed through the flask for 16 hr. after which 60 ml. of dry 1,2-dimethoxyethane was added. Agitation of the mixture was then begun and the nitrogen flow was replaced with CO at a rate of 17,000 cc./hr. The solvent was brought to reflux and 2.27 ml. (25 mmoles) of aniline in 40 ml. of 1,2-dimethoxyethane was added dropwise over a period of 3 hr. Carbon monoxide flow and temperature were maintained for an additional 18 hr. Solids in the flask assumed a black coloration during this time, and analysis of periodic samples indicated the presence of phenyl isocyanate. After the addition of sufficient 1,2-dimethoxyethane to restore the liquid volume to its original level, the mixture was shown to contain 1.8 vol. % of phenyl isocyanate by vapor phase chromatographic analysis, constituting a yield of 68.0 mole %.

Toluene 2,4-Diisocyanate.—The procedure followed was essentially procedure B used for phenyl isocyanate. The reaction was carried out in 100 ml. of 1,2-dimethoxyethane, and the mixture was agitated under nitrogen for 24 hr. and under CO for 24 hr. prior to the dropwise addition of 1.80 g. (15 mmoles) of toluene-2,4-diamine (recrystallized four times from benzene) in 100 ml. of 1,2-dimethoxyethane (this solution having been flushed with nitrogen for 48 hr.) over a period of 2 hr. Formation of metallic palladium was observed during the latter period. Agitation was continued for an additional 0.5 hr. at which time vapor phase chromatographic analysis indicated a yield of 9.6 mole % of toluene 2,4-diisocyanate (based on the diamine).

Acknowledgment.—The authors wish to thank Dr. H. Güllemann and Mr. P. Taylor for assistance with portions of the experimental work.

Organic Disulfides and Related Substances. XV. Attempted Syntheses of Mercapto Disulfides[1]

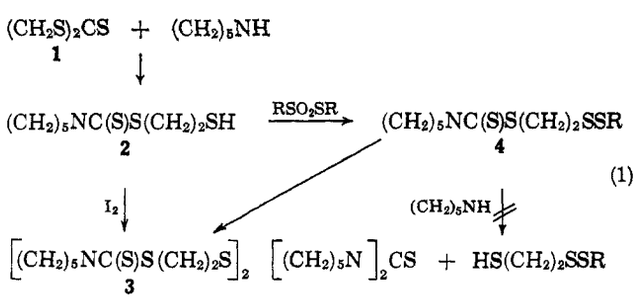
LAMAR FIELD AND H. K. KIM

Department of Chemistry, Vanderbilt University, Nashville, Tennessee

Received September 7, 1965

To our knowledge, only one mercapto disulfide actually has been isolated,[2] although some others either have been identified in solution or suggested to be present. Since mercapto disulfides contain two mutually reactive groups, more information on their characteristics would be of much interest, even though thiol–disulfide interchange reactions[3] presumably would lead to polymer in the absence of careful handling. This paper reports results worthy of record obtained during two approaches to synthesis of mercapto disulfides, which were unsuccessful although based on reasonable analogies.

As shown by eq 1, one approach depended upon cleavage of ethylene trithiocarbonate (**1**) with piperidine, followed by thioalkylation of the resulting thiol (**2**) to give the disulfide **4**, with the final step to be cleavage of the thiocarbamoyl moiety of **4** with piperidine.



(1)

R = $(CH_2)_2NHAc$

Reactions of ethylene trithiocarbonate with secondary amines have been studied before. Delaby and co-workers believed their first products to be thiols (as in eq 1);[4] they later identified these as disulfides but were able to obtain thiols under modified conditions.[5] Durden and co-workers obtained only disulfides,[6] and Johnston and co-workers obtained neither

(1) 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. Paper XIV: T. F. Parsons, J. D. Buckman, D. E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965).

(2) P. C. Ray and S. K. Mitra, *J. Indian Chem. Soc.*, **6**, 865 (1929).

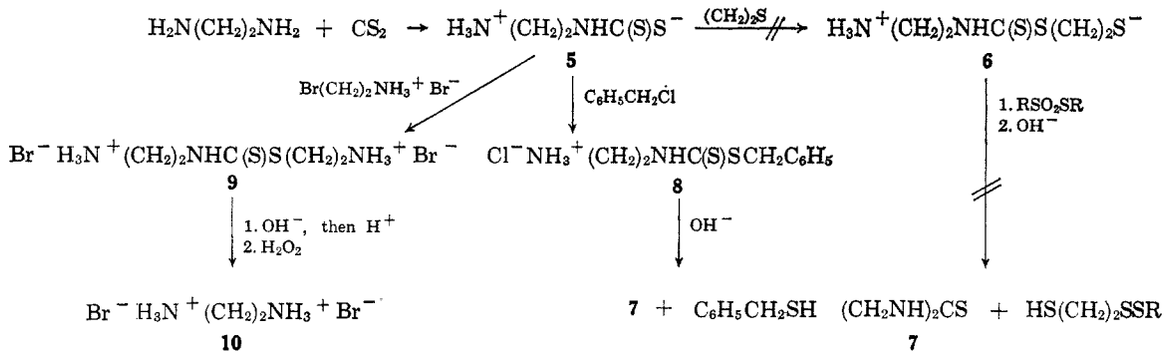
(3) *Cf.*, for example, E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., New York, N. Y., 1960, p 373.

(4) R. Delaby, P. Piganiol, and C. Warolin, *Compt. Rend.*, **230**, 1671 (1950).

(5) R. Delaby, C. Warolin, P. Chabrier, and P. Piganiol, *ibid.*, **232**, 1676 (1951).

(6) J. A. Durden, Jr., H. A. Stansbury, Jr., and W. H. Catlette, *J. Am. Chem. Soc.*, **82**, 3082 (1960).

CHART I



thiols nor disulfides but a third type of product,[7a] which was found also by Mayer and Schaefer (as well as disulfides).[7b] With piperidine, under nitrogen, we found that ring cleavage of **1** gave the thiol **2** in 66% yield as malodorous oil easily oxidizable in air. The structure of the thiol **2** was evidenced by infrared spectrum (SH), iodometric titration, and oxidation to the disulfide **3** in 94% yield. The disulfide **3** differed in melting point from that of the Durden group[6] but agreed with that reported by Mayer and Schaefer and that for the thiol by the Delaby group;[4] it had satisfactory infrared (no SH) and nmr spectra, as well as appropriate analyses and molecular weight.

Further evidence for the structure of thiol **2** was afforded by its thioalkylation (eq 1) to give the desired unsymmetrical disulfide (**4**) in 98% yield. Unfortunately, conditions were not found which then would permit removing the thiocarbamoyl group of **4** (*cf.* eq 1) without destruction of the mercapto disulfide sought. For example, piperidine did not react with **4** in benzene in 23 hr at room temperature or in 3 hr under reflux (no thiol present by infrared spectrum or by a nitroprusside test), and only **3** resulted after 5 months at room temperature (61% yield).

The second approach (Chart I) was to involve cleavage of thiirane with the salt **5** to give the thiolate ion **6**. Thioalkylation of **6** was to be followed by neutralization, which hopefully would result in loss of the protecting group to form 2-imidazolidinethione (**7**) accompanied by liberation of a mercapto disulfide.

In conformity with its formulation as a salt,[8] we found that **5** is too sparingly soluble in ordinary solvents for effective alkylation but that in dimethylformamide (DMF) a model reaction with benzyl chloride gave alkylation to form **8** in 65% yield. As hoped, neutralization of the benzyl derivative **8** produced the thioamide **7** (100% yield) and liberated α-toluenethiol (44–78% yield).

We feel that alkylation of the salt **5**, followed simply by neutralization to pH 7–8 in this way, will provide a useful means of converting suitable halides to thiols which would be sensitive to the more vigorous conditions required in the usual syntheses of thiols. The halide must be quite reactive, however. Thus attempted reaction of the salt **5** with bromobenzene resulted only in conversion of **5** to the thioamide **7** (100%), and with *n*-butyl bromide only the ethylenediamine salt **10** could be isolated (40%); in neither instance was there indication of the desired type of reaction. Synthetic difficulties may arise in the liberation of thiol sometimes, as well as in the alkylation. For example, as Chart I shows, although the reactive halide, 2-bromoethylamine hydrobromide, alkylated the salt **5** at room temperature to form **9** (88% yield), neutralization of **9** followed by acidification and oxidation gave no cystamine salt; instead, the wrong amino group of **9** evidently participated in cyclization, since the only product isolated was the ethylenediamine salt **10**. It is worth adding, however, that compounds similar to **8** and **9** might be pharmacologically useful because of the prospect of liberation of thiol under physiological conditions.

This projected synthesis of mercapto disulfides was abandoned because of the lack of promise in efforts to convert the salt **5** to the next intermediate (**6**) with thiirane. The thiirane presumably polymerized, because after its reaction with salt **5** addition of benzyl chloride gave only the benzyl derivative of **5** (*i.e.*, **8**) with no indications of a benzyl derivative of **6**.

In tests for activity as antiradiation drugs, **3**, **4**, and **8** were inactive; tests are incomplete for **9**.[9]

Experimental Section[10]

2-Mercaptoethyl 1-Piperidinocarbodithioate (2) and Dithiodiethylene 1-Piperidinocarbodithioate (3).—A solution of 20.0 g of ethylene trithiocarbonate (**1**) in 200 ml of absolute alcohol was warmed at 40–50°, and 12.5 g of piperidine (previously dried over potassium hydroxide and distilled) was added. The reaction mixture was stirred for 3 hr at 40–50° under nitrogen. After the mixture had been cooled to room temperature and filtered to remove solid (2.3 g), solvent was removed. The residue (26 g, 80% of **2**) was dissolved in a minimum of ether (100 ml) and was dried over anhydrous magnesium sulfate. After removal of solvent, the clear yellow malodorous viscous oil gave 97% of the iodometric titer expected for **2**; the yield was

(7) (a) T. P. Johnston, C. R. Stringfellow, Jr., and A. Gallagher, *J. Org. Chem.*, **27**, 4068 (1962); (b) R. Mayer and K. Schaefer, *J. Prakt. Chem.*, **26**, 279 (1964).

(8) A. Ya. Yakubovich and V. A. Klimova, *J. Gen. Chem. USSR*, **9**, 1777 (1939); *Chem. Abstr.*, **34**, 3685 (1940).

(9) We are indebted for these tests to Drs. T. R. Sweeney, D. P. Jacobus, and P. Coad of the Walter Reed Army Institute of Research, Washington, D. C. For general procedures used, see L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(10) Melting points are corrected. Decomposition points were determined by immersion about 10° below the decomposition point and then heating so that the temperature rose *ca.* 2–3°/min. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Infrared spectra were obtained using a Perkin-Elmer Model 137B or Beckman Model IR 10 spectrophotometer with films of liquids, and Nujol mulls or KBr pellets of solids; abbreviations are s (strong), m (medium), w (weak), and br (broad). Nmr spectra were obtained with a Varian A-60 spectrometer, using tetramethylsilane as an internal standard; we are indebted to the National Science Foundation for a major grant toward purchase of this instrument. Evaporation of solvents usually was done under reduced pressure, using a rotary evaporator.

21.5 g (66%). The infrared spectrum showed absorption for SH at 2551 cm^{-1} (w) and for -NC(=S)- at 1481 cm^{-1} (s).[11]

The crude thiol (19.3 g) in 300 ml of ethyl ether was oxidized to **3** with 80 ml of 1 *N* aqueous iodine–potassium iodide solution to an iodine-color end point. Yellow precipitate was collected and washed with ether and then with *n*-hexane. A solution of the crude **3** in hot acetone (500 ml) was decolorized with charcoal, diluted with 300 ml of *n*-hexane, and chilled, giving a yield of **3** as fine needles of 18.0 g (94%): mp 112–113°; lit. mp 111° (at first believed to be thiol **2**—*cf.* discussion),[4,5] 104–105°,[6] and 112–114°.[7b]

Anal. Calcd for $C_{16}H_{28}N_2S_6$: C, 43.59; H, 6.40; S, 43.65; mol wt, 441. Found: C, 43.55; H, 6.41; S, 43.44; mol wt, 450.

Strong infrared bands were found at 2940, 1470, 1430, 1278, 1240, 1230, 1120, 1110, 1000, 970, 890, and 850 cm^{-1}. The nmr spectrum (CS_2) showed an unresolved multiplet centered at τ 8.3 (12H, β,γ ring), one multiplet in each of the regions of τ 6.8–7.2 and 6.2–6.7 in the integral ratio 4:4 (two different CH_2– units), and a broad singlet centered at τ 6.0 (8H, α ring).

(2-Acetamidoethyl)dithioethyl 1-Piperidinocarbodithioate (4).—Freshly prepared **2** (44.3 g) in 200 ml of ethanol was added to a stirred solution of 2-acetamidoethyl 2-acetamidoethanethiolsulfonate (50.0 g)[12] in 200 ml of ethanol, and stirring was continued for 2 hr. After evaporation of solvent, the viscous residue was thoroughly washed by rubbing and shaking with water (1 l.) and then was kept at 0° for 2 days. After trituration with *n*-hexane (500 ml) containing ether (50 ml) until all yellow color was discharged, 80 g of wet product resulted (mp 49–51°). Recrystallization to constant melting point of still-wet **4** from ethyl acetate by addition of *n*-hexane (1:1) gave 62.0 g (98%) of **4**, mp 67–69°.

Anal. Calcd for $C_{12}H_{22}N_2OS_4$: C, 42.57; H, 6.55; N, 8.28; S, 37.88. Found: C, 42.44; H, 6.28; N, 8.41; S, 37.62.

The infrared spectrum (KBr pellet) showed complete absence of -SH and new absorption bands at 3340 (m, $-NHC(O)CH_3$), 1650 (s, amide I), and 1530 (s, amide II) cm^{-1}. The nmr spectrum (CS_2) showed an unresolved multiplet centered at τ 8.3 (6H, β,γ ring), a sharp N-acetyl singlet at τ 8.12 (3H), one multiplet in each of the regions τ 6.9–7.4 and 6.3–6.8 in the integral ratio 4:4, a broad singlet at τ 6.0 (4H, α ring), and an extremely broad NH singlet at τ 2.9 (1H).

S-Benzyl 2-Aminoethyldithiocarbamate Hydrochloride (8).—Carbon disulfide (7.61 g, redistilled, bp 46°) in 12.5 ml of dimethylformamide (DMF) was added slowly with chilling to 6.01 g of ethylenediamine (redistilled, bp 116–117°) in 12.5 ml of DMF, the temperature being kept below 25°. Stirring was continued at room temperature for 1 hr. Without isolation of the salt **5**, 6.33 g of benzyl chloride was added slowly so that the temperature did not rise above 40°. A creamy white suspension resulted immediately. The reaction mixture then was heated at 65–70° until the odor of benzyl chloride had disappeared (2 hr). As much as possible of the DMF was removed below 50° under reduced pressure, and the viscous residue thus obtained was triturated with absolute alcohol–ether (60 ml, 1:5). Filtration gave 8.50 g (65%) of **8**, mp 177–185°. Recrystallization from ethanol–water (3:1) gave 6.0 g (46%) of **8** as a fine white solid having mp 201–203° dec.

Anal. Calcd for $C_{10}H_{15}ClN_2S_2$: C, 45.69; H, 5.75; Cl, 13.49; N, 10.67; S, 24.40. Found: C, 45.62; H, 5.77; Cl, 13.57; N, 10.80; S, 24.28.

The infrared spectrum showed strong bands (KBr pellet) at 3200, 3020–2450 (br), 1515, 1453, 1400, 1370, 1310, 1170, 1065, 1025, 970, 922, 775, 710, and 690 cm^{-1}.

Cyclication of 8 with Formation of α-Toluenethiol.—A solution of 6.57 g of **8** prepared in 150 ml of hot water was cooled, and a solution of 1.40 g of potassium hydroxide in 15 ml of water was added (pH 7–8). A creamy appearance resulted immediately, but after a stirring period of 5 min more, clear solution resulted with an oil floating. Stirring was continued at room temperature for 1 hr. Then the mixture was extracted three times with 50 ml of ether, which was dried over anhydrous magnesium sulfate. An aliquot of one-fourth of the extract consumed 27.78 ml of 0.1 *N* iodine–potassium iodide solution (corresponding to a yield of 44% of α-toluenethiol); benzyl disulfide, isolated after the titration and recrystallized, amounted to 0.50 g (corresponding to 65% yield of α-toluenethiol over-all).

When 2 equiv of potassium hydroxide were used, benzyl disulfide was directly obtained in 78% yield without iodine oxidation.

Evaporation of the aqueous layer from both experiments almost to dryness and recrystallization of the precipitate from ethanol–water (6:1) gave in each instance 2.55 g (100%) of 2-imidazolidinethione (**7**), mp and mmp 195–197° (infrared spectrum identical with that of authentic sample).[6]

S-2-Aminoethyl 2-Aminoethyldithiocarbamate Dihydrobromide (9).—2-Bromoethylamine hydrobromide (10.3 g) in 12.5 ml of DMF was slowly added (10 min) to the salt **5** prepared exactly as described above, the temperature meanwhile being kept below 25°. A creamy white suspension resulted. Stirring was continued overnight and the DMF was then removed under reduced pressure below 50°. The oily residue was triturated with 25 ml of absolute alcohol and kept at *ca.* 0° overnight. Filtration gave 15.0 g (88%) of **9** as white solid, mp 199–202° dec. The **9** was recrystallized from ethanol–water (2:1): yield, 10.4 g (61%); mp 215–217° dec.

Anal. Calcd for $C_5H_{15}Br_2N_3S_2$: C, 17.60; H, 4.43; Br, 46.85; N, 12.32; S, 18.80. Found: C, 17.80; H, 4.53; Br, 46.70; N, 12.35; S, 18.86.

The infrared spectrum showed strong bands (KBr pellet) at 3435 (br), 2900–2000 (br), 1550, 1510, 1480, 1460, 1385, 1330, 1310, 1265, 1155, 1050, 1025, 935, 880, 845, and 820 cm^{-1}.

When the reaction of 2-bromoethylamine hydrobromide with **5** was carried out at 75°, the only product which could be isolated was an ethylenediamine salt, obtained finally as its picrate in *ca.* 62% yield.

Cyclization of 9.—A solution of **9** (6.8 g) in 50 ml of warm water was prepared and then was cooled. Upon addition of sodium hydroxide (1.60 g) in water (16 ml), the pH rose to 10 and turbidity increased as addition of base proceeded. Stirring was continued for 1 hr and the mixture then was acidified with concentrated hydrochloric acid (pH 2), after which 3 ml of 8.34 *M* hydrogen peroxide was added until a positive starch–iodide test resulted. After 1 hr of stirring, 0.6 g of precipitate (sulfur?) which had deposited was removed by filtration. The aqueous solution was evaporated to a viscous residue, which was extracted with water by centrifugation. The combined extracts were evaporated, and the resulting oil was triturated with absolute ethanol–ether; the mixed ethylenediamine salts (**10**, plus the hydrochloride) weighed 3.5 g: mp above 300°; picrate mp and mmp 230–235° dec (lit.[13] picrate mp 233–235° dec). No cystamine salt could be isolated despite considerable effort.

(11) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd ed, John Wiley and Sons, Inc., New York, N. Y., 1958, p 357.

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

(13) S. Gabriel and J. Weiner, *Ber.*, **21**, 2670 (1888).

Organic Disulfides and Related Substances. XVI. Synthesis of Bisthiolsulfonates[1a-d]

LAMAR FIELD AND WILLIAM B. LACEFIELD[1e]

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203

Received September 7, 1965

Synthesis of a number of bisthiolsulfonates has been reported, but essentially the same general reac-

(1) (a) For paper XV in the series, see L. Field and H. K. Kim, *J. Org. Chem.*, **31**, 597 (1966). (b) This investigation was supported in part by the U. S. Army Medical Research and Development Command, Department of the Army, under Research Contract No. DA-49-193-MD-2030. (c) We thank Drs. D. P. Jacobus, T. R. Sweeney, and P. Coad for evaluation of antiradiation-drug activity; this was done at the Walter Reed Army Institute of Research, Washington, D. C., by procedures described by Field, *et al.*[2] Tests for antitumor activity were kindly provided by the Cancer Chemotherapy National Service Center, Bethesda, Md. (d) Abstracted from part of the Ph.D. Dissertation of W. B. L., Vanderbilt University, Aug. 1965. (e) W. B. L. is indebted to the U. S. Department of Health, Education, and Welfare for an National Defense Education Act Fellowship, 1961–1964.

(2) L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).