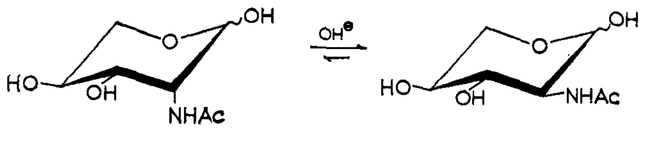

I II

codistillation with ethanol and toluene, and the remaining sirup was dissolved in ethanol, whereupon 2-acetamido-2-deoxy-α-L-xylose crystallized (first nuclei were obtained by cellulose-column chromatography); yield 0.40 g. (40%). Recrystallization from ethanol gave pure material; yield 0.33 g.; m.p. 194–195° dec.; $[\alpha]^{19}\text{D}$ −58, initial, extrapolated, → −7.1°, 4 hr., equil. (*c* 0.5, water); $\lambda_{\max}^{\text{KBr}}$ 3.00 (OH), 6.10, 6.50 (NHAc), 12.90, 10.90, and 10.66 μ; X-ray powder diffraction data[17]: 8.98 vw, 6.86 vs (2), 5.09 s (3), 4.67 w, 4.27 vs (1), 3.95 m, 3.80 m, 3.51 m, 3.44 vw, 3.36 vw, 3.17 vw, 3.10 m; Morgan-Elson[14] reaction (+).

*Anal.* Calcd. for $C_7H_{13}NO_5$: C, 43.97; H, 6.85; N, 7.33. Found: C, 44.34; H, 7.15; N, 7.59.

The D enantiomorph has been reported[4] to have m.p. 186–189° dec., [α]D +56 → +9°. The X-ray powder diffraction pattern of the D enantiomorph was found to be identical with that recorded herein for the L-enantiomorph.

Paper chromatography of the residual mother liquors on borate-treated paper[12] with a 6:4:3 butanol–pyridine–water system, gave two principal zones, $R_x$ value[16] 0.72 and 1.00 in the intensity ratio, determined densitometrically, of 3 to 2, together with proportions of slower moving components. The zone $R_x$ 0.72 corresponded to starting material (I); the faster zone corresponded to the product (II). 2-Acetamido-2-deoxy-D-xylose[4] was indistinguishable from its enantiomorph on paper chromatograms. A further yield of (sirupy) 2-acetamido-2-deoxy-L-xylose (II) was obtainable by isolative paper chromatography, to raise the total yield to 62%. The two epimers were not separable on untreated Whatman No. 1 paper.

**2-Amino-2-deoxy-α-L-xylose Hydrochloride.**—A solution of 2-acetamido-2-deoxy-α-L-xylose (123 mg.) in 2 *N* hydrochloric acid (50 ml.) was heated for 2 hr. at 100°. The solution then was evaporated, and traces of acid were removed by codistillation with 2-propanol and ethanol. The residue was crystallized from ethanol–acetone; yield 80 mg. (68%), m.p. 164–168° dec. Recrystallization was effected, with little loss, from ethanol–acetone–ether; m.p. 165–169° dec.; $[\alpha]^{23}\text{D}$ −78, initial, extrapolated, → −46.4 ± 0.5°, 3 hr., equil. (*c* 0.5, water); $\lambda_{\max}^{\text{KBr}}$ 3.0–3.3 (OH, $NH_3^+$), 6.25, 6.61 ($NH_3^+$), 10.98, 11.30, and 13.25 μ; X-ray powder diffraction data[17]: 8.01 m, 6.03 s, 4.54 s (2), 4.37 s (3), 4.06 s, 3.41 s (1), 3.23 s, 3.06 w, 2.95 w, 2.78 w, 2.69 w, 2.61 m, 2.51 m, 2.37 m, 2.33 m, 2.26 m, 2.21 s; Elson–Morgan[15] reaction (+).

*Anal.* Calcd. for $C_5H_{12}ClNO_4$: Cl, 19.10. Found: Cl, 18.76.

For 2-amino-2-deoxy-α-D-xylose hydrochloride, Wolfrom and Anno[4] report m.p. 160–165° dec.; [α]D +80, initial, extrapolated → +40° (*c* 0.8, water, final).

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[17] Interplanar spacing, Å., Cu Kα radiation. Relative intensity estimated visually: s, strong; m, medium; w, weak; v, very. First three strongest lines are numbered (1, strongest).

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# Mercaptan–Disulfide Interchange Reactions. II. Some Equilibrium Constants[1]

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Equilibrium constants have been determined for the interchange reactions between two organic disulfides and/or between a mercaptan and a disulfide for the following cases: *n*-hexyl–phenyl, *n*-hexyl–β-hydroxyethyl, *n*-hexyl–(β-diethylamino)ethyl, *n*-propyl–*sec*-butyl, and *n*-butyl–*t*-butyl. The constants differ from the statistically predicted values by a factor of two or less, except for the reactions of phenyl mercaptan with hexyl phenyl disulfide and of *t*-butyl mercaptan with *n*-butyl *t*-butyl disulfide, which have smaller constants. These data and others indicate that the interchange reactions are not sensitive to the effect of substituent groups, except ones that interfere sterically.

Mercaptans and organic disulfides can react with one another in appropriate conditions. Such reactions occur in diverse chemical systems and may have consequences of considerable importance; examples may be found in petroleum,[3] polysulfide rubber,[4] and living organisms.[5] In organic chemistry, reactions which proceed to a measurable equilibrium state are comparatively rare, and the mercaptan–disulfide interchange reactions to be described are interesting from this point of view also. The present paper will be concerned with some general aspects of the problem and with reactions taking place in an organic medium. Paper III of this series, which follows,[6] will consider reactions of water-soluble compounds in buffered aqueous medium.

The reaction of two symmetrical disulfides to give the unsymmetrical, or "mixed," disulfide may be represented by eq. 1a. Unsymmetrical disulfides also may

$$\text{RSSR} + \text{R'SSR'} \rightleftarrows 2\text{RSSR'} \qquad (1a)$$

result from the reaction of RSSR with a mercaptan, according to eq. 2a. The reaction may then proceed further, according to eq. 3a.

$$\text{RSSR} + \text{R'SH} \rightleftarrows \text{RSSR'} + \text{RSH} \qquad (2a)$$

$$\text{RSSR'} + \text{R'SH} \rightleftarrows \text{R'SSR'} + \text{RSH} \qquad (3a)$$

The corresponding equilibrium expressions are

$$K_1 = (\text{RSSR'})^2/(\text{RSSR})(\text{R'SSR'}) \qquad (1b)$$

$$K_2 = (\text{RSSR'})(\text{RSH})/(\text{RSSR})(\text{R'SH}) \qquad (2b)$$

$$K_3 = (\text{R'SSR'})(\text{RSH})/(\text{RSSR'})(\text{R'SH}) \qquad (3b)$$

where the quantities in parentheses are the activities of the respective chemical species. The product $K_2K_3$ measures the equilibrium constant for reaction 4a.

$$\text{RSSR} + 2\text{R'SH} \rightleftarrows \text{R'SSR'} + 2\text{RSH} \qquad (4a)$$

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[1] (a) Paper I: G. Gorin, G. Dougherty, and A. V. Tobolsky, *J. Am. Chem. Soc.*, **71**, 3551 (1949); (b) presented in part at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept., 1962.

[2] To whom inquiries concerning this paper should be sent.

[3] E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., New York, N. Y., 1958, pp. 16–18.

[4] E. M. Fettes and J. S. Jorczak in "Polymer Processes," C. E. Schildknecht, Ed., Interscience Publishers, New York, N. Y., 1956, pp. 475–498.

[5] R. Cecil and J. R. McPhee, *Advan. Protein Chem.*, **14**, 296 (1959).

[6] H. A. Smith, G. Doughty, and G. Gorin, *J. Org. Chem.*, **29**, 1485 (1964).

$$K_4 = K_2K_3 = (R'SSR')(RSH)^2/(RSSR)(R'SH)^2 \qquad (4b)$$

Finally, it should be obvious that this relation obtains.

$$K_1 = K_2/K_3 \qquad (5)$$

If the distribution of R and R′ groups were determined by probability, a mixture originally containing equimolar amounts of RSSR and R′SSR′ would contain, at equilibrium, twice as much RSSR′ as either remaining symmetrical disulfide; *i.e.*, $K_1$ would equal 4. Similarly, a mixture originally containing 1 mole of RSSR and 2 moles of R′SH would give, at equilibrium, the following amounts: RSSR and R′SSR′, 0.25 mole each; RSSR′, 0.50 mole; RSH and R′SH, 1 mole each; *i.e.*, $K_2$ would equal 2, $K_3$ 0.5, $K_4$ 1. The aim of the present investigation was to determine the actual values of the constants for some mercaptans and disulfides and to correlate the deviations from the statistically predicted behavior with chemical constitution.

Two investigations of this problem had been conducted before the present work (excluding studies conducted in buffered aqueous medium, to be discussed in paper III[6]) by Birch, Cullum, and Dean[7] and by Haraldson, *et al.*[8] Their results will be considered in the Discussion section. It might be stated at this point that these studies were restricted to the determination of $K_1$ and that the results showed only small divergences from the statistical value, except in the cases involving *t*-butyl groups. In the present work, phenyl and substituted ethyl compounds were examined, to see whether more marked effects would be encountered. Values of $K_1$ and of $K_2K_3$ were determined independently, thus making possible an internal check on the validity of the data.

## Experimental

**Materials.**—1-Hexanethiol, 1-butanethiol, 2-methyl-2-propanethiol, 2-mercaptoethanol, *n*-butyl disulfide, *n*-propyl disulfide, hexadecane (practical grade), and 1-octanol were obtained from Eastman Organic Chemicals, Rochester 3, N. Y.; benzenethiol, 1-propanethiol, benzyl ether (practical grade), and 2,2,4-trimethylpentane from Matheson Coleman and Bell, Cincinnati 12, Ohio; phenyl disulfide and *sec*-butyl disulfide from Columbia Organic Chemicals Co., Columbia, S. C.; bis(2-hydroxyethyl) disulfide from Aldrich Chemical Co., Milwaukee 10, Wis.; octadecane and tetradecane from Humphrey-Wilkenson, Inc., North Haven, Conn.; lithium aluminum hydride from Metal Hydrides, Inc., Beverly, Mass.; sodium methoxide (purified) from Fisher Scientific Co., St. Louis, Mo. 2-(Diethylamino)-ethanethiol hydrochloride was a gift from Evans Chemetics, Waterloo, N. Y. Except when otherwise designated, these substances were of the highest quality available and were used without further purification. *t*-Butyl disulfide (practical grade) from Eastman Organic Chemicals was redistilled under reduced pressure.

To prepare *n*-hexyl disulfide, iodine was added with shaking to 59.1 g. of hexanethiol in 200 ml. each of chloroform and 0.05 *M* sodium hydroxide to a slight excess. The chloroform layer was washed with 5% aqueous sodium bicarbonate and 0.1 *M* sodium thiosulfate to remove hydrogen iodide and iodine; then the solvent was removed under reduced pressure and the residue was distilled at 0.3-mm. pressure; 44.5 g. (76%) of disulfide was obtained, boiling at 108–110°. The physical properties of a center fraction collected at 109° were $n^{25}{}_D$ 1.6756; $d^{25}$ 0.9052; absorbance maximum in 95% ethanol at 255 mμ, molar absorbancy coefficient 410.

*sec*-Butyl mercaptan was prepared by placing 6.6 g. of lithium aluminum hydride and 250 ml of dry ether in a 500-ml. three-necked flask fitted with a dropping funnel, a reflux condenser, and a mechanical stirrer, and adding 41 g. of *sec*-butyl disulfide dropwise in the course of 1 hr. The reaction mixture was refluxed 40 min., cooled in an ice bath, treated with water to decompose excess hydride, and acidified with 100 ml. of 15% sulfuric acid. After stirring for 24 hr., the mixture was extracted with ether, the ether layer was washed with water and dried, the solvent was removed under reduced pressure, and the residue was distilled. A 20-g. fraction of *sec*-butyl mercaptan, boiling at 83°, was collected for use.

(2-Diethylamino)ethanethiol was prepared by dissolving 48 g. of the hydrochloride salt in 200 ml. of air-free ethanol, adding 11 g. of sodium hydroxide in 150 ml. of ethanol, removing the precipitated sodium chloride by filtration, and distilling the filtrate under nitrogen at reduced pressure; a 15-g. fraction, boiling at 62° and 15 mm., was taken for use. Bis(2-diethylaminoethyl) disulfide was prepared by dissolving 26 g. of (2-diethylamino)-ethanethiol hydrochloride and 12 g. of sodium hydroxide in 200 ml. of methanol, passing air through the solution for 24 hr., removing the sodium chloride by filtration and the solvent by evaporation under reduced pressure, again filtering, and distilling the filtrate under reduced pressure; a 5.8-g. fraction boiling at 115–120° and 0.4 mm. was taken for use.

All the mercaptans, disulfides, and marker compounds gave a single peak on gas phase chromatography as described below.

**Gas Chromatographic Procedure.**—The gas chromatograph used was an Aerograph Model A-300. The SE-30 silicone columns were prepared from commercial materials or purchased ready made; the Carbowax column was purchased (Wilkens Instruments and Research Co., Walnut Creek, Calif.). Helium was the carrier gas. A thermal-conductivity detector was used. Samples were injected into the chromatograph with a 10-μl. Hamilton syringe. A 1-mv. Brown Electronik recorder (Minneapolis-Honeywell Corp., Philadelphia, Pa.) was employed. Areas under the recorder tracings were measured with an Ott compensating planimeter, Type 30 (Frederick Post Co., Chicago, Ill.), set at the scale 1 vernier unit = 4 mm.².

**Disulfide Interchange Reactions.**—The procedure employed for *n*-hexyl–phenyl disulfide will be described in detail. Other pairs of disulfides were handled similarly.

To calibrate the gas chromatographic analysis, known amounts of each disulfide were dissolved in ethanol, and benzyl ether was added as a "marker." Conditions were then established, by which the mixture would give well-defined and separated peaks on the recorder tracing (see Table I, p. 1482). Calibration constants were determined from the relation: $k = WA_m/W_mA$ where $W$ and $W_m$ are the weight of component and of marker, respectively, and $A$ and $A_m$ the corresponding areas.

For the equilibrium experiments, solutions were prepared in ethanol containing each of the disulfides at 0.15–0.25 *M* concentration. Sodium hydroxide, 0.01 g., was added as a catalyst (for all other disulfide pairs, the same quantity of sodium methoxide was used), and, in some cases, 0.02 g. of the *n*-alkyl mercaptan. The reaction mixture was kept in a water bath at 25 ± 0.1° and aliquot samples were taken for analysis at appropriate times. The samples were neutralized with concentrated hydrochloric acid using pH-paper indicator. They were then subjected to gas chromatography.

The tracings obtained from the reaction mixtures comprised a peak located midway between the symmetrical disulfide peaks, which could be ascribed to the mixed disulfide. It was assumed that the calibration constant for this compound would be the mean of the values for the symmetrical disulfides. In most cases, a marker compound was added after the reaction mixture had been made acidic, and the amounts of disulfides present could be calculated from the relation given above. However, the marker could be omitted, since only the relative amounts of the components need be known for calculating the equilibrium constant; the required data can be obtained by multiplying the peak areas by the calibration constants.

**Hexyl–Phenyl Mercaptan–Disulfide Interchange Reactions.**—To calibrate the gas chromatographic analysis, mixtures containing known amounts of *n*-hexyl mercaptan, phenyl mercaptan, and marker, decane, were prepared in ethanol solvent and subjected to analysis (see Table I, p. 1482). Some calibration experiments were also done with mixtures of mercaptans and disulfides; in this case, the column temperature was maintained at the lower value

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[7] S. F. Birch, T. V. Cullum, and R. A. Dean, *J. Inst. Petrol.*, **39**, 206 (1953).

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

TABLE I

CONDITIONS FOR GAS CHROMATOGRAPHY

| Compound | Calibrtd. $k$ | Marker | Column temp., °C. | Column | Flow rate, ml./min. |
|---|---|---|---|---|---|
| *n*-Hexyl disulfide | 0.98 ± 0.04 | Benzyl ether | 200 | 0.25 in. × 8 ft. Al<br>5% SE-30<br>60–80 Chromosorb-W | 90 |
| Phenyl disulfide | 1.18 ± 0.07 | | | | |
| Mixed disulfide | (1.08)[a] | | | | |
| *n*-Hexyl mercaptan | 1.05 ± 0.02 | Decane | 100 | | |
| Phenyl mercaptan | 1.21 ± 0.02 | | | | |
| *n*-Hexyl disulfide | 1.06 ± 0.03 | Octadecane | 180 | 0.25 in. × 5.5 ft. Al<br>5% SE-30<br>60–80 Chromosorb-W | 90 |
| $(HOCH_2CH_2S)_2$ | 1.69 [illegible] 0.04 | | | | |
| Mixed disulfide | (1.38)[a] | | | | |
| *n*-Hexyl mercaptan | 1.08 ± 0.02 | Decane | 80 | | |
| $HOCH_2CH_2SH$ | 2.54 ± 0.39 | | | | |
| *n*-Hexyl disulfide | 1.26 ± 0.05 | Hexadecane | 180 | 0.25 in. × 5 ft. Al<br>5% Carbowax 20-M<br>60–80 Chromosorb-HMDS | 90 |
| $(Et_2NCH_2CH_2S)_2$ | 1.54 ± 0.03 | | | | |
| Mixed disulfide | (1.40)[a] | | | | |
| *n*-Hexyl mercaptan | 0.89 ± 0.02 | Tetradecane | 100 | | |
| $Et_2NCH_2CH_2SH$ | 1.12 ± 0.06 | | | | |
| *n*-Propyl disulfide | 1.09 ± 0.02 | Octanol | 150 | 0.25 in. × 8 ft. Al<br>10% SE-30<br>60–80 Chromosorb-W | 50 |
| *sec*-Butyl disulfide | 1.20 ± 0.02 | | | | |
| Mixed disulfide | (1.15)[a] | | | | |
| *n*-Propyl mercaptan | 1.03 ± 0.05 | Isooctane | 75 | | |
| *sec*-Butyl mercaptan | 1.04 ± 0.05 | | | | |
| *n*-Butyl disulfide | 1.12 ± 0.04 | Dodecane | 160 | 0.25 in. × 8 ft. stainless steel<br>10% SE-30<br>60–80 Chromosorb-W | 50 |
| *t*-Butyl disulfide | 1.28 ± 0.02 | | | | |
| Mixed disulfide | (1.20)[a] | | | | |
| *n*-Butyl mercaptan | 1.03 ± 0.04 | Toluene | 80 | | |
| *t*-Butyl mercaptan | 1.06 ± 0.03 | | | | |

[a] Estimated.

specified until the mercaptans had emerged, and then the temperature was raised as quickly as possible by manual control of the heater.

Some reaction mixtures were made up with hexyl mercaptan and phenyl disulfide, others with phenyl mercaptan and hexyl disulfide, each at concentrations of 0.2–0.4 *M*. Sodium hydroxide was added in the amount of 0.01 g./10 ml. The mixture was kept at 25° and aliquot samples were taken for analysis at appropriate intervals. The catalyst was neutralized as described in the preceding section.

**Other Mercaptan–Disulfide Interchange Reactions.**—The procedure for all other mercaptan–disulfide systems except butyl was the same as described in the preceding section, except that sodium methoxide was used instead of sodium hydroxide.

With the *n*-butyl *t*-butyl compounds, 2 mmoles of disulfide and 2–3 mmoles of mercaptan were mixed with 0.2 mmole of sodium methoxide and 1.2 ml. of ethanol, which gave a homogeneous solution. Ampoules of 0.4-ml. capacity with a long capillary neck were made by drawing 10 × 75 mm. Pyrex test tubes in the flame. The reaction mixture was transferred into these ampoules by placing them, neck downwards, in the mixture, reducing the pressure above momentarily, and then restoring atmospheric pressure; the necks were then sealed The ampoules were placed in an aluminum heating block, the temperature of which was maintained at 60 ± 0.5° by a heater, thermoregulator, and relay.

The composition of the mixtures originally containing *n*-butyl disulfide and *t*-butyl mercaptan changed perceptibly for about 30 days; to ensure equilibrium, the mixtures were kept for another 70 days and then analyzed. After 100 days, the composition of the mixtures initially containing *t*-butyl disulfide and *n*-butyl mercaptan was still changing, and the experiments were not continued.

**Oxidation of Butyl Mercaptan Mixtures.**—Measured amounts of *n*-butyl and *t*-butyl mercaptan (usually, 5.0 mmoles each) were dissolved in 100 ml. of 1 *M* sodium hydroxide. Freshly prepared potassium ferricyanide solution, 20% by weight, was added with constant stirring until the yellow color of ferricyanide did not fade on standing. The oxidation was effected at room temperature. The reaction mixture was acidified with 8 ml. of concentrated hydrochloric acid and extracted with 10 ml. of ether. The organic layer was separated and dried over calcium chloride, and the ether was evaporated. The residue was taken up in methanol and analyzed by gas chromatography. No mercaptan peaks were observed.

## Results

Gas chromatography effected in the conditions summarized by Table I permitted the separation of the mercaptans and disulfides mentioned therein. Four or five calibration experiments were conducted for each compound, and the average deviation from the mean value of the calibration constant indicates the degree of reproducibility obtained in the peak areas.

As has been stated, each mercaptan and disulfide used as a reagent in this investigation gave a single peak on gas chromatography. When mixtures of symmetrical disulfides or of a disulfide and a mercaptan were made up in ethanol and analyzed soon thereafter, the number of peaks corresponded to the number of components added, indicating that no interchange had taken place before or during the analysis.

As a matter of fact, little or no reaction took place in any case, even after several days, unless a catalyst were added. In the mercaptan–disulfide interchange reactions, sodium methoxide was the usual catalyst, and equilibrium was attained in 2–4 days, except with the *t*-butyl compounds. In the reaction of *n*-butyl disulfide with *t*-butyl mercaptan, 30–60 days at 60° were required to attain equilibrium, while in the case of *t*-butyl disulfide and *n*-butyl mercaptan, reaction was not complete even after 100 days.

The disulfide interchanges came to equilibrium in 2–5 days if conducted in the presence of sodium methoxide and *n*-alkyl mercaptan as catalyst (note that the experiments did not include *t*-butyl disulfide, which doubtless would take very long). In the most rapidly reacting system, hexyl–phenyl, equilibrium was attained with sodium hydroxide alone, in about 4 days; in the presence of *n*-hexyl mercaptan, equilibrium was established in a matter of hours.

Table II summarizes the values of the constants obtained. These are indexed in accordance with equations (1–5), where RSSR represents the *n*-alkyl disulfide (propyl, butyl, or hexyl), and R'SH the "nonnormal" mercaptan (phenyl, substituted ethyl, *sec*- or *t*-butyl). Actually, the mercaptan–disulfide interchange reactions were conducted with both possible pairs of starting materials, *e.g.*, hexyl disulfide and phenyl mercaptan as well as phenyl disulfide and hexyl mercaptan, and strict adherence to the scheme represented by the equations (1–5) would lead to different constants depending on which mercaptan and disulfide was used. However, all the values reported in Table II and elsewhere in the paper refer to the equilibrium expressions written as specified above.

TABLE II

EQUILIBRIUM CONSTANTS

| System | $K_1$ | $K_2$[a] | $K_3$[a] | $K_4$ | $K_2/K_3$ |
|---|---|---|---|---|---|
| R = *n*-hexyl | 8.5 | 1.02 | 0.14 | | |
| R' = phenyl | 8.2 | 1.03 | 0.14 | | |
| | 8.0 | 1.16* | 0.15* | | |
| | 7.7 | 1.15* | 0.15* | | |
| | 8.1 | 1.09 | 0.15 | 0.16 | 7.3 |
| R = *n*-hexyl | 4.9 | 1.1 | 0.21 | | |
| R' = $HOCH_2CH_2$ | 5.1 | 1.3* | 0.30* | | |
| | 4.9 | 0.95* | 0.25* | | |
| | 5.0 | 1.1 | 0.25 | 0.28 | 4.4 |
| R = *n*-hexyl | 5.08 | 1.31 | 0.25 | | |
| R' = $Et_2NCH_2CH_2$ | (5.85) | 1.30 | 0.29 | | |
| | 4.98 | 1.26* | 0.19* | | |
| | 5.08 | | | | |
| | 5.05 | 1.29 | 0.24 | 0.31 | 5.4 |
| R = *n*-propyl | 4.55 | 2.17 | 0.51 | | |
| R' = *sec*-butyl | 4.21 | 1.95 | 0.46 | | |
| | 4.36 | 1.87* | 0.47* | | |
| | 4.60 | 2.12* | 0.54* | | |
| | | 1.91* | 0.45* | | |
| | 4.43 | 2.00 | 0.49 | 0.98 | 4.1 |
| R = *n*-butyl | | 3.64 | 0.175 | | |
| R' = *t*-butyl | | 3.20 | 0.154 | | |
| | | 3.55 | 0.160 | | |
| | | 3.18 | 0.150 | | |
| | | 3.39[b] | 0.160[b] | | 21 |

[a] The unstarred values were determined in mixtures originally containing RSSR and R'SH; the starred values with R'SSR' + RSH. [b] At 60°.

When equimolar mixtures of *n*-butyl and *t*-butyl disulfides in 1 *M* sodium hydroxide were oxidized with potassium ferricyanide, the product contained *n*-butyl disulfide, *t*-butyl disulfide, and the mixed disulfide in the ratio 1:0.88:1.7. These ratios are quite different from those obtaining at equilibrium (1:1:5).

## Discussion

Although the existence of mixed disulfides was reported as early as 1886 and several were prepared subsequently,[9] it was believed by some that they were intrinsically less stable than symmetrical disulfides. In 1952–1953, McAllan, Birch, and co-workers[7,10] reported clear evidence that this is not the case for alkyl disulfides; if two disulfides, or a disulfide and a mercaptan, are mixed and allowed to come to equilibrium, the mixed disulfide is formed, often to the extent expected from probability considerations. Birch, *et al.*,[7] prepared several mixed disulfides by equilibrating two symmetrical disulfides or a disulfide and a mercaptan in ethanol solution containing a little water and sodium hydroxide. After neutralizing the base, the relative amounts of mixed and symmetrical disulfides were determined by distillation. While results of only moderate precision could be expected by this method, the presence of mixed disulfide at equilibrium was clearly demonstrated, the ratio unsymmetrical–symmetrical being 2 to 1 for methyl–ethyl, ethyl–*n*-butyl, ethyl–isobutyl; 5 to 1 for methyl–*t*-butyl; 6 to 1 for ethyl–*t*-butyl; 4 to 1 for octyl–*t*-butyl; and 3 to 1 for methyl–phenyl. Birch, *et al.*, also prepared some mixed disulfides by oxidizing mixtures of two mercaptans with hydrogen peroxide, iodine, or potassium ferricyanide; in two cases, methyl–ethyl and ethyl–*n*-butyl, the same results were obtained by oxidation and by base-catalyzed equilibration.

Haraldson, *et al.*,[8] studied the interchange reaction between pairs of disulfides and analyzed the products by gas chromatography. The values of the equilibrium constant $K_1$ at 25° were 5.6 for methyl–ethyl, 4.1 for ethyl–isopropyl, and 24.5 for ethyl–*t*-butyl. Essentially the same values were found at 60°, showing that the heat of reaction is very small or zero.

Since the interchange reactions are rather slow, even in the presence of catalyst, it is desirable to check the attainment of equilibrium in more than one way. Haraldson, *et al.*,[8] accomplished this by preparing the mixed disulfides, and using these compounds, as well as mixtures of two symmetrical disulfides, as the starting material in the equilibrium experiments. In all but one of the mercaptan–disulfide reactions studied in the present work, the attainment of equilibrium was checked by conducting the experiments with both the possible combinations of mercaptan and disulfide. As far as the disulfide interchange reactions are concerned, the validity of $K_1$ can be checked by comparison with the values of $K_2/K_3$ (eq. 5); the data are consistent within their limits of precision.

With the *n*-butyl–*t*-butyl compounds, only one type of equilibrium experiment was performed, starting with *n*-butyl disulfide and *t*-butyl mercaptan. This system came to equilibrium in 30–60 days at 60°, and measurements were made after 100 days. The equilibrium constant $K_1$ calculated from the experimentally determined values of $K_2$ and $K_3$ is quite similar to the value found experimentally for the ethyl–*t*-butyl system by Haraldson, *et al.*[8] (these workers, as well as Fava, *et al.*,[11] also noted the very slow rate of reaction for *t*-butyl compounds). The thermodynamic instability of *t*-butyl disulfide has been attributed[8] to the steric interference with the rotation of the alkyl groups.

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(9) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. III, Chemical Publishing Co., New York, N. Y., 1960, pp. 362, 406–411.

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

(11) A. Fava, A. Iliceto, and E. Camera, *ibid.*, **79**, 833 (1957).

Oxidation of an equilibrium mixture of *n*- and *t*-butyl mercaptans did not give a product containing the disulfides in the equilibrium ratio. There is no reason to expect that they should, since the nature of the products must be determined by the relative rate of reaction. The fact that Birch, *et al.*,[7] obtained the same product by oxidation and base-catalyzed equilibration in two cases may well be a coincidence.

The propyl–*sec*-butyl system gives a value of $K_1$ essentially identical with that predicted on the basis of probability. This falls in line with the values found by other investigators for *n*- and isoalkyl compounds. The present work shows, furthermore, that $K_2$ and $K_3$ separately conform to the statistical values.

Substitution of diethylamino or hydroxo groups for hydrogen reduce $K_1$ and $K_2$ each by a factor of about two; *i.e.*, the substituted disulfides are slightly better oxidizing agents than the *n*-alkyl disulfides; $K_1$, however, conforms closely to the statistical value. Phenyl disulfide is a still better oxidizing agent, and, in addition, the mixed disulfide is relatively favored. All in all, the deviations from statistical behavior must be regarded as small, and, in view of the variety of compounds examined, it is concluded that the effect is a general one. *In the absence of steric or extraneous* chemical effects,[6] therefore, it may be expected that mercaptan–disulfide interchange reactions will conform closely to the distribution predicted on the basis of probability.

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# Mercaptan–Disulfide Interchange Reactions.[1] III. Reaction of Cysteine with 4,4′-Dithiobis(benzenesulfonic acid)

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Sodium 4,4′-dithiobisbenzenesulfonate ($Na_2BSSB$) has been prepared from sulfanilic acid. The ultraviolet absorption spectra have been determined for BSSB, the mixed disulfide formed from it upon reaction with cysteine (BSSR), 4-mercaptobenzenesulfonate (BSH), and its mercaptide ion ($BS^-$). The ionization constant of BSH is $10^{-5.7}$. The following equilibrium constants have been measured: [(BSSR)(BSH)]/[(BSSB)(RSH)] = 1.2 and [(RSSR)(BSH)]/[(BSSR)(RSH)] = 1.0 at 25°. The ionization of BSH tends to drive the reaction of cysteine with BSSB toward completion at pH values above 6.5. Some measurements of reaction rate are reported.

Cysteine and some of its derivatives are involved in many important physiological processes: for example, enzymic catalysis,[2] protein aggregation,[3] and cell division.[4] A measure of protection against ionizing radiation is afforded by cysteine and a few congeners, and it has been suggested that the radioprotective action involves the formation of mixed disulfides with protein molecules.[5] Some measurements of equilibria have been made for mercaptan–disulfide interchange reactions involving these compounds; these data will be considered briefly in the Discussion section. The experimental results are limited and in some cases uncertain. The present investigation was undertaken because further study of the problem seemed desirable.

The reaction of cysteine with 4,4′-dithiobisbenzenesulfonate can be measured with comparative ease because the 4-mercaptobenzenesulfonate formed in the reaction ionizes to give a mercaptide anion that has a characteristic absorption peak in the ultraviolet and can be determined spectrophotometrically. The ionization of 4-mercaptobenzenesulfonate and the employment of a buffered medium introduce additional considerations, however. The interchange reactions may be represented by the equations

$$\mathrm{BSSB + RSH \rightleftarrows BSSR + BS^- + H^+} \qquad (1)$$

$$\mathrm{BSSR + RSH \rightleftarrows RSSR + BS^- + H^+} \qquad (2)$$

where BSSB is the doubly charged anion, 4,4′-dithiobisbenzenesulfonate; RSH is cysteine; BSH is 4-mercaptobenzenesulfonate; $BS^-$ is the corresponding mercaptide anion, 4-sulfidobenzenesulfonate (since the sulfonic acid groups are completely ionized in all the conditions of interest, the charges resulting from their ionizations are not indicated).

The ionization constant expression for BSH

$$K_i = [(\mathrm{BS^-})(\mathrm{H^+})]/(\mathrm{BSH}) \qquad (3)$$

relates the equilibrium-constant expressions for eq. 1 and 2 to those given in paper II,[1] which are written for unionized compounds.

$$K_2' = [(\mathrm{BSSR})(\mathrm{BS^-})(\mathrm{H^+})]/[(\mathrm{BSSB})(\mathrm{RSH})] = K_2K_i \qquad (4)$$

$$K_3' = [(\mathrm{RSSR})(\mathrm{BS^-})(\mathrm{H^+})]/[(\mathrm{BSSR})(\mathrm{RSH})] = K_3K_i \qquad (5)$$

$$K_4 = K_2'K_3' = [(\mathrm{RSSR})(\mathrm{BS^-})^2(\mathrm{H^+})^2]/[(\mathrm{BSSB})(\mathrm{RSH})^2] = K_2K_3K_i^2 \qquad (6)$$

## Experimental

**Materials.**—Cysteine hydrochloride monohydrate was an "A" grade product of the California Corporation for Biochemical Research, Los Angeles 63, Calif. Cystine and oxidized glutathione were products of Schwarz Laboratories, Mt. Vernon, N. Y.;

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[1] See preceding paper: G. Dalman, J. McDermed, and G. Gorin, *J. Org. Chem.*, **29**, 1480 (1964).

[2] P. D. Boyer, "The Enzymes," Vol. I, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1959, p. 511.

[3] E. V. Jensen, *Science*, **130**, 1319 (1959).

[4] D. Mazia, "Sulfur in Proteins," R. Benesch, *et al.*, Ed., Academic Press, Inc., New York, N. Y., 1959, p. 357.

[5] L. Eldjarn and A. Pihl, "Mechanisms in Radiobiology," Vol. II, M. Errera and A. Forssberg, Ed., Academic Press, Inc., New York, N. Y., 1960, p. 231.