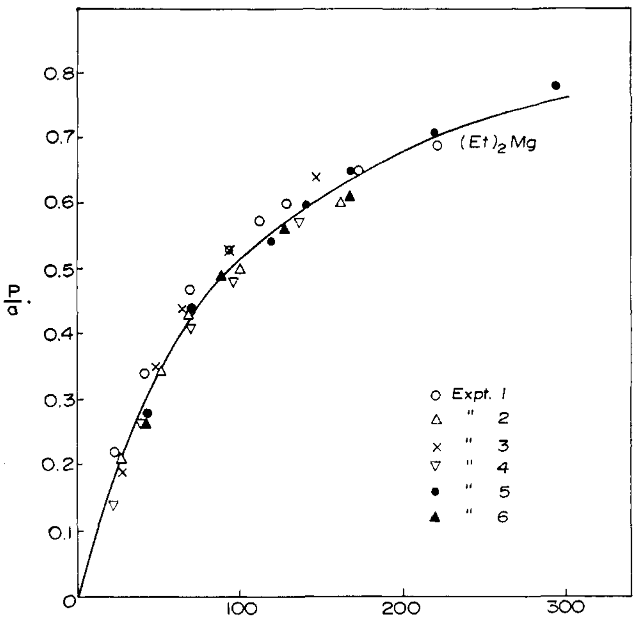

Fig. 1.—$P/a$ vs. $\theta$ for diethylmagnesium. Points, experimental. Curve, theoretical. Experiment numbers are those given in Table I.

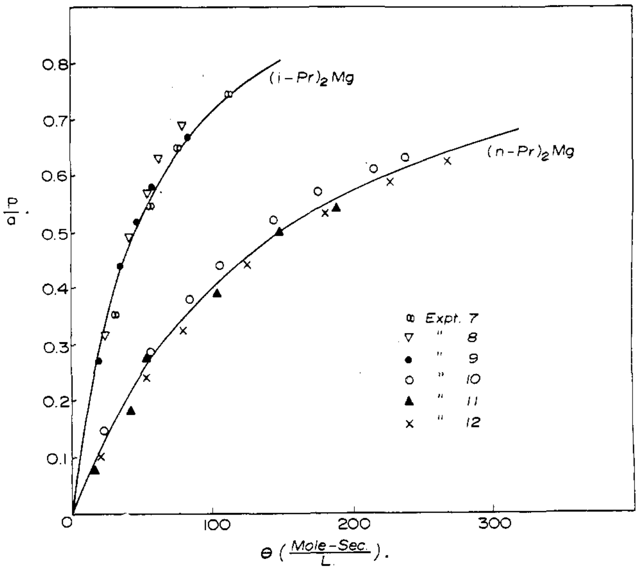

Fig. 2.—$P/a$ vs. $\theta$ for di-$n$-propylmagnesium and diisopropylmagnesium. Points, experimental. Curves, theoretical. Experiment numbers are those given in Table I.

curves given by equation 3 and with the values of $k_1$ and $k_2$ given in Table I are also shown in Fig. 1 and 2. There may be a small dependence on $a$ indicated, but in this respect the results are not conclusive. The results do show clearly that the order of reactivity is isopropyl > ethyl > $n$-propyl, in agreement with the order previously found for the corresponding Grignard reagents.[3] Also, it is clear that the reaction consists of at least two steps and that the first half of the alkyl groups are more reactive than the second half.

### Experimental

**Materials.**—1-Hexyne (Farchan) was passed over alumina and distilled [b.p. 68°, (745 mm.)].

TABLE I

INITIAL CONCENTRATIONS AND RATE CONSTANTS (33 ± 1°)

| Expt. | $R_2Mg$ | $a^a$ | $b^a$ | $k_1^b$ | $k_2^b$ |
|---|---|---|---|---|---|
| 1 | $Et_2Mg$ | 1.01 | 0.89 | $2.2 \times 10^{-2}$ | $3.0 \times 10^{-3}$ |
| 2 | $Et_2Mg$ | .57 | .52 | | |
| 3 | $Et_2Mg$ | .55 | .50 | | |
| 4 | $Et_2Mg$ | .46 | .41 | | |
| 5 | $Et_2Mg$ | .47 | .76 | | |
| 6 | $Et_2Mg$ | .17 | .76 | | |
| 7 | $(i\text{-Pr})_2Mg$ | .44 | .60 | $4.0 \times 10^{-2}$ | $8.0 \times 10^{-3}$ |
| 8 | $(i\text{-Pr})_2Mg$ | .55 | .50 | | |
| 9 | $(i\text{-Pr})_2Mg$ | .39 | .39 | | |
| 10 | $(n\text{-Pr})_2Mg$ | .88 | .74 | $1.3 \times 10^{-2}$ | $2.0 \times 10^{-3}$ |
| 11 | $(n\text{-Pr})_2Mg$ | .54 | .50 | | |
| 12 | $(n\text{-Pr})_2Mg$ | .70 | .65 | | |

[a] The value of $a$ is twice the initial molarity of $R_2Mg$ and $b$ is the initial molarity of 1-hexyne. [b] $k_1$ and $k_2$ are second-order constants expressed l × mole$^{-1}$ × sec.$^{-1}$.

The dialkylmagnesiums were prepared from the Grignard reagents by the addition of dioxane as described previously.[7] In all cases analysis showed that the resulting ethyl ether solution of dialkylmagnesium contained excess basic magnesium. In three separate preparations of diethylmagnesium the ratios of active dialkyl to total basic magnesium was 0.72, 0.73, and 0.77. The ratios of active dialkyl to total basic magnesium for the diisopropyl and the di-$n$-propyl were 0.85 and 0.90, respectively. Care was taken to keep moisture and oxygen from the starting materials and reagents. The alkyl bromides were freshly fractionally distilled; dioxane was fractionally distilled from sodium; the ether (Mallinckrodt, anhydrous, analytical reagent) was freshly opened and stored over sodium for several hours before use; the products were transfered under cover of prepurified nitrogen and stored in serum rubber capped bottles. Samples were removed by means of hypodermic syringes. All of the dialkylmagnesiums gave a negative bromide test with silver nitrate.

**Apparatus.**—The apparatus and method used to determine the rates by gas evolution were the same as those described in previous papers.[8,9] Special care was taken to prevent an increase in pressure within the apparatus when gas was evolving rapidly. This was a problem for reactions with a half-life of less than 4 min. An increase in pressure of 1 or 2 cm. was found to cause enough "hold up" of gaseous product (probably mostly in the condenser, which was charged with ice and alcohol or Dry Ice and acetone) to cause a significant decrease in the value obtained for $k_1$.

**Acknowledgment.**—This work was supported by the National Science Foundation.

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## 3-Mercaptopropionamidine and S-2-Amidinoethyl Thiosulfuric Acid[1]

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*Received December 10, 1962*

Recently reported[2,3] syntheses of S-substituted mercaptoamidine derivatives attest interest in aminoalkane-

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(1) This investigation was supported by the U. S. Army Research and Development Command under contract no. DA-49-193-MD-2028.

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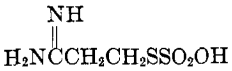
thiol analogs of this type as potential antiradiation drugs. This report concerns the conversion of 3-mercaptopropionitrile (I) in several steps to 3-mercaptopropionamidine hydrochloride (V) and S-2-amidinoethyl thiosulfuric acid (VI, inner salt).


$\mathrm{HSCH_2CH_2C({=}NH)NH_2{\cdot}HCl}$

V


$\mathrm{H_2NC({=}NH)CH_2CH_2SSO_2OH}$

VI

Protection of the mercapto group was achieved by the immediate iodine oxidation of freshly distilled I to 3,3′-dithiobispropionitrile (II). The conversion of II to 3,3′-dithiobispropionamidine dihydrochloride (IV) was effected *via* uncharacterized diethyl 3,3′-dithiobispropionimidate dihydrochloride (III). Contamination of IV by partially changed bisnitrile as detected by CN absorption in the infrared was minimized by a prolonged reaction time for the formation of III in chloroform, a better solvent for this conversion than *p*-dioxane. The use of these solvents was suggested by a previously described bisamidine synthesis in which a mixture of the two was helpful.[4] The structure of IV was evident in the close resemblance of its infrared absorption spectrum to that of acetamidine hydrochloride.

An investigation of conditions for the catalytic hydrogenolysis of IV in neutral aqueous solution at 50 p.s.i. revealed that catalyst poisoning could be overcome by the use of an amount of 30% palladium on charcoal equal to at least 50% of the disulfide weight. Hydrogenolysis of IV under these conditions thus afforded the thiol V in high yield but was completely retarded or extremely slow when only 40% by disulfide weight of catalyst was used. A similar hydrogenolysis of the dimethyl ester of L-cystine dihydrochloride has been reported.[5] Hydrogenolytic reactions of other disulfides have been carried out by the use of "sulfactive" cobalt[6] and molybdenum[7] sulfide catalysts at elevated temperatures and relatively high pressures.

Sulfite cleavage of IV gave a mixture of products from which the nitroprusside-negative internal thiosulfate VI was separated by extraction with N,N-dimethylformamide. The structure of VI was confirmed by an infrared absorption spectrum showing thiosulfate bands typical of salts of this type.[8] The N,N-dimethylformamide-insoluble fraction, which was strongly nitroprusside-positive, apparently consisted mainly of salts of 3-mercaptopropionamidine and its oxidized form with sodium bisulfite. Treatment of these salts with hydrochloric acid and subsequent *in vacuo* evaporation gave a residue containing sodium chloride from which IV was extracted by concentrated hydrochloric acid in low yield.

## Experimental[9]

**3,3′-Dithiobispropionitrile.**—Freshly prepared and distilled 3-mercaptopropionitrile[10] (12.5 g., 0.143 mole) in 50 ml. of ethanol was titrated with 1 *N* iodine–potassium iodide solution (143 ml.). The solution was decolorized with sodium thiosulfate and brought to pH 6 with 10 *N* sodium hydroxide. The product was extracted with chloroform (3 × 100 ml.), and the chloroform solution, washed with water (2 × 25 ml.) and dried over magnesium sulfate, was evaporated to dryness under reduced pressure. The residual oil, further dried *in vacuo* (oil pump) at 60° for 1 hr., quickly solidified to a hard, white, crystalline solid; yield of bisnitrile, 11.4 g. (92.5%); m.p. 49–51° (lit.[11] m.p. 48°). For analysis, a sample was recrystallized from ether as long, white needles with no change in melting point; $\tilde{\nu}_{\max}^{\mathrm{KBr}}$ in cm.$^{-1}$: 2250 (s, CN).

*Anal.* Calcd. for $\mathrm{C_6H_8N_2S_2}$: C, 41.83; H, 4.68; S, 37.22. Found: C, 42.08; H, 4.57; S, 37.5.

**3,3′-Dithiobispropionamidine Dihydrochloride.**—A cold (0°) solution of 3,3′-dithiobispropionitrile (2.18 g., 12.5 mmoles) in 10 ml. of chloroform containing 1.5 ml. (26 mmoles) of anhydrous ethanol was treated with anhydrous hydrogen chloride until 1.03 g. (28.0 mmoles) had been absorbed. This solution was refrigerated for 4 days. The solid that formed was collected by filtration under nitrogen, washed with ether (2 × 10 ml.), and dried *in vacuo* over phosphorus pentoxide and sodium hydroxide for 1 hr. The crude bisimidate dihydrochloride thus obtained was suspended in 15 ml. of anhydrous ethanol, and 5.2 ml. of a 9–10% solution of ammonia in ethanol was added. The resulting mixture was stirred at room temperature for 24 hr. The white solid was collected, washed with N,N-dimethylformamide (3 × 15 ml.) and then ethanol, and dried *in vacuo* over phosphorus pentoxide; yield of bisamidine dihydrochloride 2.21 g. (63%). Recrystallization of a small sample from ethanol gave white crystals for analysis; m.p. 182–183° dec.; $\tilde{\nu}_{\max}^{\mathrm{KBr}}$ in cm.$^{-1}$: 1705 (s), 1685 (s), 1510 (m), 715 (m-s, broad) $[\text{—}\mathrm{C(NH_2)({=}NH_2)^{\oplus}}]$.

*Anal.* Calcd. for $\mathrm{C_6H_{14}N_4S_2{\cdot}2HCl}$: C, 25.79; H, 5.77; S, 23.00. Found: C, 26.12; H, 5.78; S, 23.0.

**3-Mercaptopropionamidine Hydrochloride (V).**—A solution of 3,3′-dithiobispropionamidine dihydrochloride (1.40 g., 5.00 mmoles) in water (25 ml.) was hydrogenated at an initial pressure of 50 p.s.i. in a Parr apparatus over 700 mg. of 30% palladium on charcoal, hydrogen absorption being complete within 4 hr. The catalyst was removed by filtration under nitrogen, and the colorless filtrate was evaporated to dryness *in vacuo*. The residual oil was dissolved in ethanol and the filtered solution evaporated to dryness *in vacuo* without heating. The white crystalline residue, further dried *in vacuo* over phosphorus pentoxide, weighed 1.38 g., melted at *ca.* 100° dec., and assayed 89% as V by iodometric titration; $\tilde{\nu}_{\max}^{\mathrm{KBr}}$ in cm.$^{-1}$: 2540 (w, SH), 1680 (s), 1500 (m), 720 (s, broad) $[\text{—}\mathrm{C(NH_2)({=}NH_2)^{\oplus}}]$. (The somewhat low thiol content is attributed to oxidation of V during isolation and handling rather than incomplete hydrogenolysis.)

*Anal.* Calcd. for $\mathrm{C_3H_8N_2S{\cdot}HCl}$: C, 25.62; H, 6.45; N, 19.76; S, 22.80. Found: C, 25.80; H, 6.48; N, 19.92; S, 22.3.

**S-2-Amidinoethyl Thiosulfuric Acid (VI).**—To a mixture of 3,3′-dithiobispropionamidine dihydrochloride (2.32 g., 8.30 mmoles) and sodium acetate trihydrate (2.25 g., 16.6 mmoles) was added 12.5 ml. of a 10% solution of sulfur dioxide in water. The resulting clear solution was stored in a stoppered flask at room temperature for 10 days and then evaporated to dryness under reduced pressure. The gummy residue was triturated in ethanol (3 × 5 ml.) and the resulting white solid dried *in vacuo* over phosphorus pentoxide. The dried solid (3.02 g.) was extracted with N,N-dimethylformamide (5 × 25 ml.), leaving an insoluble residue (1.36 g., after being dried). The extract was evaporated to dryness *in vacuo*, and the oily residue was reevaporated three times after successive additions of ethanol. The resulting white crystalline residue was further dried *in vacuo* over phosphorus pentoxide; yield of VI, 1.66 g. (54%). For analysis, a small sample was recrystallized from methanol with Norit treatment; m.p. 148–150° dec.; $\tilde{\nu}_{\max}^{\mathrm{KBr}}$ in cm.$^{-1}$: 1685 (s), 1500 (m-w), 705 (m-s) $[\text{—}\mathrm{C(NH_2)({=}NH_2)^{\oplus}}]$, 1235 (s), 1165 (s), 1010 (s), 640 (m-s) $[\text{—}\mathrm{SO_3^{\ominus}}]$.

*Anal.* Calcd. for $\mathrm{C_3H_8N_2O_3S_2}$: C, 19.55; H, 4.37; N, 15.26; S, 34.80. Found: C, 19.76; H, 4.56; N, 15.31; S, 35.1.

**Acknowledgment.**—The authors are indebted to Mr. Carl R. Stringfellow, Jr., for technical assistance and to members of the Analytical Section of Southern Research Institute who performed the reported spectral and analytical determinations under the direction of Dr. W. J. Barrett.

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