B. α -Oxime IIa.—The Beckmann rearrangement of 127 mg. of the α -oxime IIa, $[\alpha]_D + 0.29^\circ$ (ethanol), by the above procedure yielded 101 mg. of VIa, m.p. 99–106° (80%). Recrystallization from petroleum ether gave pure lactam VIa, m.p. 104.5– 106°; ν 3418 and 1655 (strong) cm.⁻¹; $[\alpha]^{26}_D$ -35.7° (c 1.90, water); lit.⁹ m.p. 105–106°, $[\alpha]_D$ -36.1° (c 25.6, water). None of the β -lactam VIb was isolated.

Another preparation of VI using 587 mg. of IIa, $[\alpha]^{25}D - 10.5^{\circ}$ (c 3.17, cyclohexane), gave 71% of VIa and 4.6% of VIb, m.p. 58-69°, $[\alpha]D - 23.6^{\circ}$ (c 0.905, water); lit.^g m.p. 68-69°, $[\alpha]D - 22.2^{\circ}$ (c 5.28, water).

O.R.D. of VIa in ethanol (c 0.26): $[\phi]_{695} - 19.6^{\circ}$, $[\phi]_{589} - 48.9^{\circ}$, $[\phi]_{295-285} - 500^{\circ}$ to -515° (fine structure), and $[\phi]_{252} - 886^{\circ}$.

C. β -Oxime IIb.—The Beckmann rearrangement of the β -oxime IIb (441 mg., $[\alpha]_D - 81^\circ$) was carried out as described for the oxime mixture and yielded 384 mg. (87%) of the lactams. The β -oxime was much more labile and produced a mixture of lactams which after fractional crystallization from petroleum ether yielded 82 mg. of the α -lactam, m.p. 90–103°, and 200 mg. of β -lactam, m.p. 60–77°. Purification of 104 mg. of β -lactam by chromatography on florisil and elution with 50% chloroform-petroleum ether produced 14 mg. of reasonably pure VIb, m.p. 61–66°, and 80 mg. of material melting 56–80° which was resistant to further purification.

Another rearrangement of 40 mg. of β -oxime gave 29 mg. of β -lactam, m.p. 55-72°, and 3 mg. of α -lactam, m.p. 96-105°.

Recrystallization of the β -lactam gave a fraction melting 61–65°; ν 3420 and 1655 (strong) cm.⁻¹; $[\alpha]D - 22.9^{\circ}$ (c 0.335, water). The infrared spectra of the α - and β -lactams have small but easily recognizable differences. The carbonyl band at 1655 cm.⁻¹ is evident in both compounds but the α -lactam has bands at 1340, 1170, and 1125 cm.⁻¹ which are much weaker or not present in the β -lactam, and absorption bands at 1385, 1312, and 1115 cm.⁻¹ are shown by the β - but not by the α -lactam.

O.R.D. of VIb in ethanol (c, 0.68): $[\phi]_{595} - 33.7^{\circ}$, $[\phi]_{589} - 48.6^{\circ}$, and $[\phi]_{254} - 319^{\circ}$.

D. Camphor Oxime (IV).—The base-catalyzed rearrangement, as described in A, of camphor oxime (IV) gave a mixture of products of the cleavage reaction.¹⁰ No solid material except unreacted oxime was recovered, and the oily nitrile ($\nu_{\rm film}$ 2260 cm.⁻¹) was not investigated further.

E. Menthone Oxime (V).—Menthone oxime (330 mg.) was rearranged by the procedure described in A to give 300 mg. (91%) of product which was fractionally crystallized from petroleum ether yielding 95 mg. of iso-*l*-menthone oxime (VII), m.p. 120–122°; ν_{mull} 3290 and 1670 cm.⁻¹; $[\alpha]_D - 51.0^\circ$ (ethanol); lit.¹⁷ m.p. 119–120°, $[\alpha]_D - 52.25^\circ$ (c 24, alcohol).

O.R.D. in ethanol (c 0.8): $[\phi]_{695} - 78.3^{\circ}$, $[\phi]_{589} - 97.3^{\circ}$, and $[\phi]_{250} - 2310^{\circ}$.

(17) O. Wallach and F. E. Tuttle, Ann., 277, 156 (1893).

The Synthesis of Some Compounds Related to 3-Amino-1-propanethiol¹

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A number of aminothiols derived from 3-amino-1-propanethiol have been prepared for studies on rate of oxidation of thiols to disulfides, hydrogen bonding in thiols, and for testing for radiation-protective properties. A convenient experimental procedure for the electrolytic reduction of disulfides to thiols is described. Treatment of 4-benzylmercapto-2-methyl-2-butanol (E) with benzonitrile and boron trifluoride gives 2-phenyl-4,4-dimethyl-5,6-dihydro-1,3-thiazine (G); this is reduced by aluminum amalgam to a mixture of the tetrahydrothiazine K and the dimeric reduction product L, whose structures are established by physical and chemical evidence. The tetrahydrothiazine is readily hydrolyzed to form 3-methyl-3-amino-1-butanethiol.

The present paper describes the synthesis of a number of aminothiols derived from 3-amino-1-propanethiol (A); these were required for studies on the kinetics of

$\underset{A}{\mathrm{H_2NCH_2CH_2SH}}$

oxidation of thiols to disulfides,² for studies on hydrogen bonding in thiols,³ and for evaluation as radiation protective agents. The compounds prepared included primary, secondary, and tertiary amines derived from 4-amino-2-butanethiol (B) and from the higher homologs C and D.

Details on the compounds made are given in Table I. Compounds B and C were prepared by the addition of benzyl mercaptan to crotonaldehyde (for B) or to mesityl oxide (for C); the β -benzylmercaptocarbonyl compound was then converted to the oxime, and the oxime group was reduced by lithium aluminum hydride

(3) (a) L. D. Colebrook and D. S. Tarbell, Proc. Natl. Acad. Sci. U. S.,
 47, 993 (1961); L. D. Colebrook, unpublished work.

to the primary amine (B-1 or C-1).⁴ The secondary amine was prepared by formylation, either by formic acid or by chloral,⁵ followed by reduction of the formyl group to methyl by lithium aluminum hydride.⁶ The tertiary amines.⁷ The benzyl group was removed from the sulfur by reductive cleavage with sodium-liquid ammonia⁸; the aminothiol obtained was usually contaminated by the corresponding disulfide, formed by air oxidation during the work-up.

It was found that disulfides were conveniently converted to the corresponding thiols by electrolytic reduction in aqueous hydrochloric acid.⁹

The preparation of D-1 involved some unexpected reactions. Methyl β -benzylmercaptopropionate¹⁰ was converted to the tertiary alcohol E, and this was sub-

(4) The general scheme is that of J. R. Catch, A. H. Cook, A. R. Graham, and I Heilbron, J. Chem. Soc., 1609 (1946).

(5) F. F. Blicke and C. J. Lu, J. Am. Chem. Soc., 74, 3933 (1952).

(6) J. Ehrlich, ibid., 70, 2286 (1948); K. E. Hamlin and A. W. Weston,

ibid., **71**, 2210 (1949). (7) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *ibid.*, **55**, 4571 (1933).

(8) R. H. Sifferd and V. du Vigneaud, J. Biol. Chem., 108, 753 (1935).

(9) L. Smith and B. Sjöberg, *Ber.*, **69**, 678 (1936); there do not seem to be detailed procedures described for this reduction, and our method is therefore given in full. Electrolytic reduction of a disulfide at a copper cathode is described by K. Schimmelschidt, H. Hoffmann, and E. Mundlos, *ibid.*, **96**, 38 (1963).

(10) C. D. Hurd and L. L. Gershbein, J. Am. Chem. Soc., 69, 2328 (1947).

⁽¹⁾ Supported by Contract DA-49-193-MD-2031 of the Surgeon General's Office.

^{(2) (}a) Cf. D. S. Tarbell, in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, Inc., New York, N. Y., 1961, p. 97. For leading references to recent work on this problem, see C. G. Overberger and J. J. Ferraro, J. Org. Chem., 27, 3539 (1962); T. J. Wallace and A. Schriesheim, *ibid.*, 27, 1514 (1962); D. G. Large, H. N. Rydon, and J. A. Schofield, J. Chem. Soc., 1752 (1961); T. J. Wallace, J. M. Miller, H. Probner, and A. Schriesheim, Proc. Chem. Soc., 384 (1962). (b) I. Pascal and D. S. Tarbell, J. Am. Chem. Soc., 79, 6015 (1957).

				TABLE I					
							-Hydrogen, %		M.p. or b.p.
Compd.	\mathbf{R}_1	R2	Rs	Formula	Caled.	Found	Calcd.	Found	(mm.), °C.
			A. Aminoth	HOL DERIVATIVES, 1	R_1 NCH ₂ C	H_2CHCH_3			
]			
					\mathbf{R}_2	\mathbf{SR}_3			
B-1	н	Н	Н	$C_4H_{12}CINS^a$	33.91	34.14	8.54	8.70	140-142
	H	H	b	$\mathrm{C_8H_{22}Cl_2N_2S_2}$	34.16	34.21	7.91	8.03	199 - 200
B-2	CH_3	H	$CH_2C_6H_5$	$C_{12}H_{19}NS$	68.87	68.64	9.15	9.15	157 (0.7)
	CH_3	н	$CH_2C_6H_5$	${ m C}_{22}{ m H}_{27}{ m N}_5{ m O}_5{ m S}^c$	55.80	56.07	5.75	5.69	167 - 168
B-3	CH_3	CH_3	$CH_2C_6H_5$	$C_{13}H_{21}NS$	69.92	69.84	9,48	9.24	142(0.1)
	CH.	CH_3	$CH_2C_6H_5$	$C_{23}H_{29}N_5O_5S^d$	56.66	56.64	6.00	6.19	152.5 - 154
		-	B. Aminothio	L DERIVATIVES, R1-	-NCH(CH _a	$CH_2C(CH_3)$)2		
				, -			,-		
					\mathbf{R}_2	SR_3			
C-1	Н	Н	$CH_2C_6H_5$	$\mathrm{C}_{13}\mathrm{H}_{22}\mathrm{ClnS}^{e}$	60.09	60.37	8.53	8.59	131
C-2	н	н	Н	$C_6H_{16}CINS'$	42.46	42.51	9.50	9.42	172 - 173
C-3	CH_3	CH_3	$CH_2C_6H_5$	$\mathrm{C}_{25}\mathrm{H}_{33}\mathrm{N}_5\mathrm{O}_5\mathrm{S}^g$	58.20	58.18	6,41	6.36	131 - 132
C-4	CH_3	CH_3	Н	$C_8H_{20}CINS^h$	48.60	48.41	10.19	10.17	124 - 125
C-5	CH_3	н	$CH_2C_6H_5$	$C_{24}H_{31}N_5O_5S^i$	57.50	57.24	6.24	6.24	156.5 - 157

^a Calcd. for hydrochloride: N, 9.89; S, 22.63. Found: N, 9.66; S, 22.80. ^b Calcd. for disulfide dihydrochloride: N, 9.96. Found: N, 9.66. ^c Picrolonate salt. ^d Picrolonate salt. ^e Hydrochloride. ^f Calcd.: N, 8.25; S, 18.85. Found: N, 8.00; S, 19.16. ^e Picrolonate salt. ^h Calcd. for hydrochloride: S, 16.18. Found: S, 16.27. ⁱ Calcd. for picrolonate salt: N, 7.09. Found: N, 6.79.

jected to the Ritter reaction conditions¹¹; the action of sulfuric acid-benzonitrile on the alcohol E or on the unsaturated compound F formed 2-phenyl-4,4-dimethyl-5,6-dihydro-1,3-thiazine (G). This product obviously resulted from debenzylation of the sulfide, probably through attack by the nitrilium ion H on the sulfide, with expulsion of the benzyl carbonium ion.





(11) J. J. Ritter and P. P. Minieri, J. Am. Chem. Soc., 70, 4045 (1948);
 J. J. Ritter and J. Kalish, *ibid.*, 70, 4048 (1948).

This view of the reaction was supported by the observation that I, the S-methyl analog of E, did *not* yield a heterocycle under Ritter conditions, but gave instead the expected formamide J; the methyl group would not

$$\begin{array}{ccc} H_{\$}SCH_{2}CH_{2}C(CH_{\$})_{2} & CH_{\$}SCH_{2}CH_{2}C(CH_{3}) \\ & & \\ OH & & \\ I & H-C \\ -NH \end{array}$$

be displaced as the carbonium ion as readily as the benzyl group.

Meyers¹² has obtained the thiazine G and related compounds by application of Ritter conditions to the free thiol corresponding to E, $HSCH_2CH_2C(CH_3)_2$ -OH.^{13,14}

We found that boron trifluoride etherate was a better catalyst for the formation of the thiazine G than sulfuric acid; the former gave a 75% yield of G, and, in addition, dibenzyl sulfide and N-benzylbenzamide were isolated and identified from the boron fluoride reaction. With sulfuric acid as catalyst, the yield of thiazine was 55%starting with the tertiary alcohol, but only 15% starting with the unsaturated compound F; the latter yielded much material which appeared to be polymeric.

Hydrolysis of the thiazine G with concentrated hydrochloric acid in a sealed tube at 200° yielded the dihydrochloride-disulfide corresponding to D-1 in variable yield,¹⁵ but the reaction could not be made useful. Treatment of G with aluminum bromide in chlorobenzene¹⁶ followed by addition of water was unsuccessful as a method of hydrolysis.

It appeared that the tetrahydrothiazine K should hydrolyze more readily than the dihydro compound G, and it was found eventually that the reduction of G to

(12) A. I. Meyers, J. Org. Chem., 25, 1147 (1960).

(13) Formation of heterocycles in the Ritter reaction is reported by E. J. Tillmans and J. J. Ritter [*ibid.*, **22**, 839 (1957)] and A. I. Meyers and J. J. Ritter [*ibid.*, **23**, 1918 (1958)].

(14) Syntheses in the dihydro-1,3-thiazine series have recently been reported, in connection with the cephalosporin-C problem, by D. M. Green, et al. [J. Chem. Soc., 766 (1964)] and G. C. Barrett, et al. [ibid., 788 (1964)].
(15) G. Pinkus [Ber., 26, 1077(1894)] reported that a lower homolog of

G hydrolyzed slowly under similar drastic acid conditions.

(16) Cf. D. P. Harnish and D. S. Tarbell, J. Am. Chem. Soc., 70, 4123 (1948).

K could be brought about by aluminum amalgam; in addition to K, there was formed a variable amount of a crystalline dimer L. The total yield of the two reduction products was around 80%. The structure of K,



which could be separated from starting material by preparative v.p.c., was shown by analysis, formation of a picrate, m.p. 198.5–199.5°, n.m.r. spectrum, and by its hydrolysis under mild acidic conditions to give the aminothiol D-1 (in 69% yield) and benzaldehyde (identified by a solid derivative). The aminothiol D-1 prepared as above was identical with the aminothiol obtained by electrolytic reduction of the disulfide prepared by drastic acid hydrolysis of the dihydrothiazine G. Treatment of the tetrahydrothiazine K with sodium-liquid ammonia gave the N-benzylaminothiol D-2, whose structure was evident from its analysis, a positive nitroprusside test for the thiol group, and its n.m.r. spectrum.

The dimer L, m.p. $129-131^{\circ}$, differed little from K in elemental analysis and ultraviolet absorption; it was converted by dilute acid hydrolysis to benzil (identified by mixture melting point), benzaldehyde, benzoic acid, and the aminothiol D-1. The dimer apparently disproportionated readily to the dihydrothiazine G and the tetrahydro compound K, accounting for the benzaldehyde and benzoic acid.

The n.m.r. spectrum of L substantiated the structure, and is given in Table II because it contains elements of general interest.

TABLE II N.M.R. BANDS OF 2,2'-BIS(2-PHENYL-4,4-DIMETHYLTETRA-UNDED 1.3 THATING) (L)

	HIDK0-1,0-1HIA		
Assignment	Chemical shift, $ au$	Multiplicity	Area ratios
–CH₃	9.58	Singlet	6
$-CH_3$	8.81	Singlet	6
$-CH_{2}$ -	8.55	Triplet	4
$S-CH_2-$	7.37	$\mathbf{Triplet}$	4
N–Hª	6.77	$\mathbf{Singlet}$	2
Phenyl	2.97	$\mathbf{Multiplet}$	10

^a Completely exchangeable in deuterium oxide.

The striking feature of the n.m.r. spectrum of the dimer L was the chemical shift of the two methyl singlets. One methyl singlet was normal for a methyl group in a gem-dimethyl grouping. The other methyl singlet was shifted upfield. This was consistent with the dimer structure, because the methyl groups would be expected to be very different in chemical environment. One was normal, while the other was forced into a drastic 1,3-interaction with the bulky phenyl group, as shown below. The thiazine rings may exist in boat forms, but there will still be differences between the two methyls of the gem-dimethyl groups; one of them will be close to the nitrogen or sulfur. Such chemical



shifts caused by enforced proximity of methyl groups to aromatic π -electron systems are well known.¹⁷ The broad singlet at τ 6.77 was completely exchangeable by shaking with deuterium oxide, indicating that the peak represented two NH protons rather than a deshielded C-H proton pair. The direction of dimerization was thus indicated because only a carbon-carbon dimerization would give two N-H protons; it is, of course, confirmed by the isolation of benzil.

The mass spectrum of the dimer L showed no parent peak at m/e = 412, but was consistent with a cracking pattern composed of the disproportionation products, 2-phenyl-4,4-dimethyl-5,6-dihydro-1,3-thiazine (G) and 2-phenyl-4,4-dimethyltetrahydro-1,3-thiazine (K). The thermally stable dihydro compound showed a strong parent peak at m/e = 205 while the tetrahydrothiazine parent peak was very small, in accord with the expected stabilities of these compounds. The remainder of the cracking pattern was reasonable for fragments derived from the two disproportionation products. The dimer L was found to disproportionate to a mixture of the dihydro and tetrahydrothiazines G and K during refluxing for 7 days in tetrahydrofuran.

Preparation of the aminothiol D-1 from the dihydrothiazine G by aluminum amalgam reduction followed by acid hydrolysis was practical without separation of the monomeric and dimeric reduction products; the yield of aminothiol was variable, because of the variation in yield of the two reduction products. The decomposition of the dimer during hydrolysis yielded the tetrahydrothiazine, which was hydrolyzed to aminothiol, and the dihydrothiazine could be recycled.

Thus, reduction of a 2-phenyl-5,6-dihydro-1,3-thiazine system can yield a γ -aminothiol or an N-benzyl derivative; this may be a general method of synthesis of γ -aminothiols.

The application of Ritter reaction conditions to the disulfide M gave the amino disulfide; a small amount of the dihydrothiazine G was also formed. In formation of G, the disulfide linkage may be cleaved heterolytically by protonation followed by attack of nitrilium ion on the thiol group, or by direct attack of the nitrilium ion during the Ritter reaction.¹⁸



The purity of the thiols in general was determined by analyzing for free thiol by the N-ethylmaleimide (NEM) procedure.¹⁹

(19) J. D. Gregory, J. Am. Chem. Soc., 77, 3922 (1955); for a modification, see J. Broekshuysen, Anal. Chim. Acta, 19, 542 (1958).

⁽¹⁷⁾ D. J. Wilson, V. Boekelheide, and R. W. Friggin, Jr., J. Am. Chem. Soc., **82**, 6302 (1960); V. Boekelheide and J. B. Phillips, *ibid.*, **85**, 1545 (1963).

⁽¹⁸⁾ For discussion of the heterolytic cleavage of the disulfide linkage, see A. J. Parker and N. Kharasch, *Chem. Rev.*, **59**, 590 (1959).

Experimental²⁰

3-Aminobutyl Benzyl Sulfide.—A solution of β -benzylthiobutyraldehyde oxime⁴ (27.9 g.) in 45 ml. of dry ether was dropped slowly into a vigorously stirred suspension of lithium aluminum hydride (10.2 g.) in 60 ml. of dry ether. After the addition was completed, the mixture was refluxed for 20 hr. and the excess hydride was decomposed with saturated sodium sulfate solution. The inorganic material was filtered off, the solid cake was washed with ether, the combined ether solutions were dried, the solvent was removed, and the residue was distilled; the product (18.5 g., 70%, b.p. 122° at 0.5 mm.) was converted to the hydrochloride, which melted at 122–123°; the reported value of the hydrochlorride prepared by aluminum amalgam reduction of the oxime⁴ is 123°.

4-Amino-2-butanethiol and the Disulfide (B-1).—3-Aminobutyl benzyl sulfide (9.75 g.) in 250 ml. of liquid ammonia was reduced by addition of small pieces of sodium until a blue color persisted. Ammonium chloride was added to discharge the color, the ammonia was evaporated, the residue was taken up in the water, and the aqueous solution was extracted with ether. The ether layer contained 1,2-diphenylethane, and was discarded. The aqueous solution was brought to a pH of 9.5, and was extracted continuously with ether for 3 days. From the ether extract was obtained by distillation in a short-path still 2.65 g. (51%) of material, m.p. 46-50°, which was very hygroscopic and was rapidly oxidized by air. It gave a strong nitroprusside test, and was converted to the aminothiol B-1 by electrolytic reduction as below. The hydrochloride melted at 140-142°, after crystallization from ethanol-ether.

The short-path distillation also gave 0.5 g. (9.5%) of the disulfide (bath temperature 150° at 0.1 mm.); this was converted to the dihydrochloride, which melted, after crystallization, at $199-200^{\circ}$.

2-(4-Amino-2-methyl)butyl Benzyl Sulfide (C-1).—Mesityl oxide, benzyl mercaptan, and piperidine gave a 60% yield of 2-methyl-2-benzylmercapto-4-pentanone; this was converted to the oxime, and 30 g. of the crude oxime was reduced as above with lithium aluminum hydride to the amine, isolated as the hydrochloride, m.p. 131° .

4-Amino-2-methyl-2-butanethiol (C-2). The sulfide C-1 (11 g.) was reduced by adding sodium to a well-stirred solution in 200 ml. of liquid ammonia until a blue color persisted. Excess sodium was decomposed with a little ethanol, and the ammonia was removed under reduced pressure. The residue was dissolved in a little dry methanol and a solution of hydrogen chloride in dry methanol was added; the solution was filtered to remove ammonium chloride, the filtrate was diluted with an excess of ethyl acetate, and the aminothiol hydrochloride was collected by filtration. The salt melted, after two crystallizations from methanol-ethyl acetate, at 172-173°. The yield was 7.5 g. (88%).

2-(4-Methylamino-2-methyl)butyl Benzyl Sulfide (C-5).— Anhydrous chloral (26 g.) was added dropwise to the amine C-1 (40 g.) and the mixture was stirred for 12 hr. and refluxed for 30 min. The product was taken up in ether, washed three times with 10% aqueous hydrochloric acid and dried, and the solvent was removed. The crude product (35 g.) was added in portions to a suspension of lithium aluminum hydride in ether, and the mixture was refluxed for 6 hr. Work-up in the usual way gave 22 g. of amine; the picrolonate melted at 157° and the hydrochloride melted at 124-125°.

Electrolytic Reduction of Disulfides .--- All compounds, whether isolated as the disulfide or as the mercaptan, were subjected to electrolytic reduction prior to titration with NEM. The cell consisted of a 250-ml. titration beaker with a mercury pool at the bottom to serve as the cathode. Electrical contact with the pool was made through 0.5 cm. of platinum wire $(0.0165 \times 10^{-3} \text{ in.})$ diameter) sealed in the end of a 3-mm. diameter, soft-glass tube filled with mercury. Wire from the electrical source was pushed down the open end of the tube until contact with the mercury was made. A similar glass tube was made for the anode, except that the platinum wire extending from the end of the tube was 4.5 cm. long. The extra length was needed to reduce the amount of heat evolved during electrolysis. The anode was surrounded by a porous cup to prevent chlorine gas from mixing with the compound undergoing reduction; the cup was held in place by means of a string attached through a hole drilled at the top of the

cup. The porous cup was an extraction thimble (12-mm. diameter, 90 mm. long) made out of alundum (RA 360, medium porosity), obtained from the Scientific Glass Apparatus Co., Inc., Bloomfield, N. J.

The aminothiol (2-5 g.) was dissolved in about 50 ml. of 1 N hydrochloric acid (prepared with demineralized water), and the resulting solution was poured into the titration beaker containing the mercury pool. The cathode was lowered into the solution until the platinum wire tip was below the surface of the mercury pool. The anode, surrounded by the porous cup, was placed in the solution about 1 to 2 cm. above the mercury pool cathode. The cup was filled with pure 1 N hydrochloric acid. The entire electrolytic cell was placed in an ice bath. The electrical source, a battery charger equipped with an ammeter, was connected, and the current was adjusted to 1 to 2 amp. The reaction was allowed to proceed for 10 min. beyond the time calculated by Faraday's law for the reduction of the disulfide.

After the reaction, the solution was transferred to a round-bottom flask; the solvent was removed by a rotary evaporator. The residue was dried in a drying pistol *in vacuo* at the temperature of refluxing acetone.

The fact that no side reactions occurred in this reduction procedure was checked by carrying out a reduction on an analytically pure sample of aminodisulfide; the aminothiol isolated, as the hydrochloride, was analytically pure.

2-Methyl-4-benzylmercapto-2-butanol (E).—Methyl 3-benzylmercaptopropionate¹⁰ (210 g., 1.0 mole) was added dropwise with stirring to 2.2 moles of methylmagnesium bromide in ether with cooling in an ice bath. The cooling was discontinued and the reaction mixture was stirred overnight. Excess saturated ammonium chloride solution was added dropwise with cooling. The solution was stirred for 30 min. and the ether layer was decanted. Four additional 250-ml. extracts were made and combined. The organic layer was dried and the solvent was evaporated; the oil remaining was distilled quickly using a short column, yielding 180 g. (86%) of a colorless oil, b.p. 107-109° (0.15 mm.); infrared showed aliphatic hydroxyl at 3305, a monosubstituted benzene ring at 760 and 700, and gem-dimethyl groups at 1371 and 1363 cm.⁻¹.

Anal. Calcd. for $C_{12}H_{18}OS$: C, 68.63; H, 8.64. Found: C, 68.72; H, 8.61.

2-Methyl-4-benzylmercapto-2-butene (F).—2-Methyl-4-benzylmercapto-2-butanol (2.1 g.) was added dropwise to 1.25 g. of powdered, fused potassium bisulfate at 200°; the pressure was maintained at 100–150 mm. The stillhead temperature varied between 90–120°. After the addition was completed, the pressure was reduced to 10 mm. and the distillation was continued until no more liquid condensed.

The distillate was dissolved in 25 ml. of ether and the organic layer was separated and dried; the ether was removed and the residue was distilled bulb-to-bulb, 140° (bath temperature) at 10 mm., yielding 0.86 g. (45%) of olefin.

The infrared spectrum revealed an olefin stretching vibration at 1667 cm.⁻¹, and an olefin CH out-of-plane deformation vibration at 835 cm.⁻¹. The n.m.r. spectrum showed one vinyl proton as a triplet at τ 4.84.

Anal. Calcd. for $C_{12}H_{16}S$: C, 75.06; H, 8.40. Found: C, 74.64; H, 8.47.

2-Phenyl-4-dimethyl-5,6-dihydro-1,3-thiazine (G). A. From 2-Methyl-4-benzylmercapto-2-butene Using Sulfuric Acid Catalyst.—A solution of 2-methyl-4-benzylmercapto-2-butene (9.6 g.), benzonitrile (25 ml.), and glacial acetic acid (7 ml.) was cooled to 0°. Sulfuric acid (7 ml.) in glacial acetic acid (6 ml.) was added dropwise at $0-5^{\circ}$. The reaction was quite exothermic and the solution became dark. The solution was stirred for 2 hr., then poured on excess ice and water; the aqueous solution was extracted with chloroform. Sodium hydroxide (40%) was added until the aqueous solution was strongly basic. Methylene chloride extraction of the basic solution yielded a dark, viscous oil on evaporation. Distillation of this oil gave 1.57 g. (15%), b.p. $118-123^{\circ}$ (1 mm.), of a yellow oil. This material yielded a crystalline picrate, m.p. 140-142°, identical in melting point and mixture melting point with the picrate form from method B and C

B. From 2-Methyl-4-benzylmercapto-2-butanol Using Sulfuric Acid Catalyst.—A solution of 2-methyl-4-benzylmercapto-2-butanol (10.5 g.), benzonitrile (25 ml.), and glacial acetic acid (7 ml.) was cooled to 0° . Sulfuric acid (7 ml.) in glacial acetic acid (6 ml.) was added dropwise at $0-5^{\circ}$; after stirring for 2 hr. at $0-5^{\circ}$, the solution was allowed to stand overnight.

⁽²⁰⁾ Microanalyses are by V. Landeryou of these laboratories and by Micro-Tech Laboratories. We are indebted to Dr. L. D. Colebrook for the n.m.r. spectra, taken on a Zarian HR-4300-B instrument.

The resulting dark solution was poured on excess ice and water. The aqueous solution was extracted several times with chloroform, then made basic cautiously with 40% sodium hydroxide. Two methylene chloride extractions of the basic solution yielded a dark oil on evaporation of solvent. This oil was distilled yielding 5.64 g.(55%), b.p. $119-122^{\circ}$ (1 mm.), of a light yellow oil. This material was identical in all respects with the material synthesized by Meyers.¹² It gave a cyrstalline picrate, m.p. $140-141.5^{\circ}$ (lit.¹² m.p. $141-142^{\circ}$). Its ultraviolet spectrum showed λ_{max} 232 m μ (ϵ 11,720) in 95% ethanol.

Sulfate salt, m.p. 223-224° dec. (ethanol-ether).

Anal. Calcd. for $C_{12}H_{17}NO_4S_2$: C, 47.56; H, 5.66. Found: C, 47.49; H, 5.69.

Methiodide, m.p. 228-230° (ethanol-ethyl acetate).

Anal. Calcd. for C₁₃H₁₈INS: C, 44.99; H, 5.23. Found: C, 44.75; H, 5.23.

Hydriodide, m.p. 231-233° (water).

Anal. Caled. for $C_{12}H_{16}INS$: C, 43.28; H, 4.84. Found: C, 43.36; H, 4.81.

C. From 2-Methyl-4-benzylmercapto-2-butanol Using Boron Trifluoride Catalyst.—A solution of 2-methyl-4-benzylmercapto-2-butanol (21.0 g.), benzonitrile (20.0 g.), boron trifluoride etherate (20 ml.), and dry ether (100 ml.) was allowed to stand for 3-7 days. Dilute hydrochloric acid was added, which dissolved a precipitated material. The ether solution was extracted three more times with acid. The aqueous extracts were neutralized with sodium carbonate, then extracted several times with chloroform. The chloroform solution was dried, evaporated, and the residue was distilled, yielding 15.3 g. (75%) of light yellow liquid, b.p. 119-122° (1 mm.). This material was identical in infrared spectrum and v.p.c. retention time (Ucon Polar, 185°) with the material made *via* the sulfuric acid procedure.

The original precipitated material could be filtered off and recrystallized several times from water, giving a white fluoroborate salt, m.p. 183–185°, which gave a positive boron flame test.

Anal. Calcd. for $C_{12}H_{16}BF_4NS$: C, 49.19; H, 5.50; N, 4.78; S, 10.94. Found: C, 49.23; H, 5.70; N, 4.75; S, 10.75.

The neutral fraction from above was analyzed directly by v.p.c. (4 ft. Apiezon M on chromosorb, 200°) showing 10% dibenzyl sulfide and 8% N-benzylbenzamide. The components were isolated by preparative v.p.c., crystallized on standing, and were identified by mixture melting point with authentic samples of dibenzyl sulfide and N-benzylbenzamide.²¹

4,4'-Dithiobis(2-methyl-2-butylamine) Dihydrochloride.—A solution of dihydrothiazine (G, 1.0 g.) was heated with 20 ml. of concentrated hydrochloric acid in a sealed tube at 210° for 4.5 hr. The resultant precipitate of benzoic acid was filtered and the filtrate was extracted with ether, then chloroform. The hydrochloride of the starting material was soluble in chloroform and could be recovered. The aqueous layer was decolorized with charcoal and then evaporated, leaving a viscous oil that solidified on standing. The solid was refluxed in methanol to dissolve it, ethyl acetate was added to the cloud point, and on cooling with ice, crystals appeared. Several recrystallization from methanol-ethyl acetate in like manner gave 0.35 g. of 4,4'-dithiobis(2-methyl-2-aminobutane) dihydrochloride, m.p. 285-287°. Infrared showed gem-dimethyl at 1379 and 1351 and NH₃+ at 1600 cm. ⁻¹, ultraviolet spectrum λ_{max} 246 m μ (ϵ 381). The n.m.r. spectrum was in accord with the proposed structure.

Anal. Calcd. for $C_{10}H_{26}Cl_2N_2S_2$: C, 38.87; H, 8.48. Found: C, 38.58; H, 8.57.

This reaction proved very erratic. In many cases only ammonium chloride was obtained from the aqueous solution. A preliminary assay of disulfide was possible by ultraviolet spectroscopy at 246 m μ . A good qualitative estimate of the reaction could be obtained by ascending paper chromatography using Whatman No. 1 and butanol-acetic acid-water, 4:1:5 (disulfide, $R_{\rm f}$ 0.67; ammonium chloride, $R_{\rm f}$ 0.17). Iodine vapor was used to develop the spots.

Nascent Hydrogen Reductions of 2-Phenyl-4,4-dimethyl-5,6dihydro-1,3-thiazine. A. Using Sodium and Amyl Alcohol.— To dihydrothiazine G (1.0 g.), dissolved in 50 ml. of amyl alcohol, was added sodium (3.0 g.) in small pieces. After all the sodium had dissolved, the solution was cooled and added slowly to an excess of dilute hydrochloric acid. The acid solution was evaporated to dryness. The residual solid was extracted with hot isopropyl alcohol; the residue was recrystallized from a variety of

(21) E. Beckmann, Ber., 23, 3334 (1890),

solvents and solvent combinations, but did not yield sharp-melting material.

Paper chromatography of impure material using Whatman No. 1 paper and saturated butanol (or butanol-water-acetic acid) showed spots corresponding to hydrochlorides of dihydrothiazine G, tetrahydrothiazine K, aminothiol D-1, and its disulfide.

B. Using Zinc and Acid.—Dihydrothiazine G (1.0 g.) was dissolved in 50 ml. of glacial acetic acid and 5 g. of acid-washed granular zinc was added. With vigorous stirring, concentrated hydrochloric acid was added at a rate of 0.5 ml./min. until all the zinc was dissolved. The solution was stirred overnight, and the solution was evaporated to dryness under high vacuum.

The residual solid was recrystallized from isopropyl alcohol, npropyl alcohol, methanol-ethyl acetate, and absolute ethanol. The best melting point obtained was $210-221^{\circ}$.

Paper chromatography, as described in method A, indicated hydrochlorides of the dihydrothiazine, tetrahydrothiazine, aminothiol, and its disulfide.

C. Aluminum Amalgam Reduction of 2-Phenyl-4,4-dimethyl-5,6-dihydro-1,3-thiazine (G). Preparation of 2-Phenyl-4,4-dimethyltetrahydro-1,3-thiazine (K) and 2,2'-Bis(2-phenyl-4,4-dimethyltetrahydro-1,3-thiazinyl (L).—Aluminum foil (4.0 g.) was amalgamated according to Vogel.²² Tetrahydrofuran (50 ml.) was added together with dihydrothiazine G (2.05 g.). Water (28.0 ml.) was added dropwise with a vigorous evolution of gas. The resulting solution was refluxed gently for 3 hr., then filtered through Celite and washed well with tetrahydrofuran. The filtrate was evaporated to dryness. Upon addition of methanol to the colorless oil, crystallization occurred; the crystals were filtered and washed with methanol. The filtrate labeled A was saved and worked up to yield tetrahydrothiazine K.

The crystals from above, m.p. 116–119°, were recrystallized from ether-methanol, yielding white crystals of 2,2′-bis(2-phenyl-4,4-dimethyltetrahydro-1,3-thiazinyl), m.p. 129–131°. Infrared showed N-H at 3309 and 3255 cm.⁻¹. The ultraviolet spectrum had λ_{max} 211 m μ (ϵ 11,240), in 95% ethanol; in 95% ethanol containing one drop of concentrated hydrochloric acid, λ_{max} 212 m μ (ϵ 24,300) and 258 m μ (ϵ 12,720).

Anal. Calcd. for $C_{24}H_{32}N_2S_2$: C, 69.96; H, 7.83. Found: C, 69.69; H, 7.67.

A dihydrochloride was formed from the above material in ether by adding dry gaseous hydrogen chloride. The resulting solid was recrystallized from methanol-ethyl acetate giving white prisms, m.p. 192-194°.

Anal. Calcd. for $C_{24}H_{34}Cl_2N_2S_2$: C, 59.43; H, 7.07. Found: C, 59.21; H, 6.94.

The methanolic filtrate labeled A from the original reaction mixture was evaporated *in vacuo*. The residue was distilled bulb-to-bulb, b.p. 150° (bath, 0.25 mm.) yielding 830 mg. of a colorless oil. Vapor phase chromatography (Ucon Polar column, 185°) showed that this material contained 15% dihydrothiazine. Preparative v.p.c. was used to collect the other component, which was shown to be 2-phenyl-4,4-dimethyltetrahydro-1,3-thiazine. The infrared showed N-H at 3225 and a monosubstituted benzene ring at 750 and 690 cm.⁻¹. The ultraviolet spectrum had λ_{max} 214 m μ (ϵ 5200) in 95% ethanol; in acid λ_{max} 214 m μ (ϵ 12,200) and 257 m μ (ϵ 6270).

Anal. Calcd. for $C_{12}H_{17}NS$: C, 69.62; H, 8.28; N, 6.77. Found: C, 69.66; H, 8.22; N, 7.15.

A picrate was formed in saturated 95% ethanolic picric acid, m.p. $198.5-199.5^{\circ}$ (67% yield), recrystallized from benzene.

Anal. Calcd. for $C_{18}H_{20}N_4O_7S$: C, 49.58; H, 4.62. Found: C, 49.61; H, 4.77.

Ultraviolet spectrum had λ_{max} 232 m μ (ϵ 7360) and 337 m μ (ϵ 7910).

The reaction mixture could be separated by careful chromatography on neutral grade I alumina, packed using petroleum ether. The dimer was eluted first using carbon tetrachloride. Dihydrothiazine was eluted with benzene while tetrahydrothiazine was eluted with ether.

3-Methyl-3-aminobutanethiol Hydrochloride (D-1).—2-Phenyl-4,4-dimethyltetrahydro-1,3-thiazine (100 mg.) was refluxed in 50 ml. of dilute hydrochloric acid overnight. The solution slowly deposited a dark oil having the characteristic smell of benzaldehyde. On cooling, the dark oil was extracted with chloroform. V.p.c. analysis of the chloroform extract indicated

⁽²²⁾ A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., John Wiley and Sons. Inc., New York, N. Y., 1957, p. 198.

that benzaldehyde was the main volatile product by comparison of retention time with a known sample.

The aqueous phase was taken to dryness. Recrystallization from methanol-ethyl acetate gave 52 mg. (69%) of a solid, m.p. 281-283°. This material showed gem-dimethyl peaks in the infrared, gave a positive thiol test with nitroprusside, and showed no absorption in the ultraviolet. A titration with N-ethylmaleimide indicated 92% thiol present.

Anal. Calcd. for $C_{6}H_{14}$ ClNS: C, 38.62; H, 9.07. Found: C, 38.85; H, 8.78.

3-Methyl-3-benzylaminobutanethiol Hydrochloride.—A solution of tetrahydrothiazine (2.0 g.) in 25 ml. of liquid ammonia was treated (with stirring) with pieces of freshly cut sodium until the blue color persisted for 10 min. The ammonia was evaporated on a steam bath while methanol was added slowly. The methanol was evaporated until the ammonia smell could not be detected. Anhydrous hydrogen chloride was added, with cooling, and the precipitated sodium chloride was filtered off. The filtrate was evaporated to dryness and extracted several times with hot, anhydrous ether. The residual, straw-colored oil crystallized on standing. It was recrystallized from chloroform-petroleum ether yielding white plates, m.p. 131-132°. Its infrared spectrum revealed the gem-dimethyl group at 1390 and 1375 and an aromatic ring at 692 and 750 cm.⁻¹. A positive thiol test was obtained using sodium nitroprusside. The n.m.r. spectrum was in complete agreement with the proposed structure.

Anal. Calcd. for $C_{12}\dot{H}_{20}$ ClNS: C, 58.66; H, 8.14. Found: C, 58.71; H, 7.98.

High Temperature Mass Spectral Analysis of 2,2'-Bis(phenyl-4,4-dimethyltetrahydro-1,3-thiazinyl).—A sample of dimer was placed in the heated inlet system (230°) of a 60° sector-type mass spectrograph, utilizing magnetic scanning with an ionizing potential of 70 e.v.

The cracking pattern indicated no dimer m/e peak at 412, but rather a pattern in keeping with C-12 fragments. The strongest and highest m/e peak, at 205, corresponded to dihydrothiazine.²³

Hydrolysis of 2,2'-Bis(2-phenyl-4,4-dimethyltetrahydro-1,3thiazinyl) (L).—Dimer L (2.06 g.) was heated at 100° with 50 ml. of concentrated hydrochloric acid for 3 hr. On cooling, the crystalline solid was filtered off and air dried. Recrystallization from ethanol gave a yellow solid, m.p. 96–97°. A mixture melting point with authentic benzil gave no depression.

The hydrolysis filtrate was heated for 24 hr., cooled, and extracted with ether. After continuous extraction with chloroform for 24 hr., the aqueous phase was taken to dryness and the residue was recrystallized from methanol-ethyl acetate, giving 0.29 g. (22%) of a white crystalline material, 3-methyl-3-amino-1-butanethiol hydrochloride, m.p. 281-283° dec. This material gave a positive nitroprusside test, while its infrared and ultraviolet spectra were in agreement with samples obtained in other ways.

The chloroform layer from the continuous extraction was evaporated. The residual, oily solid was basified with ammonia and extracted with methylene chloride. The methylene chloride residue, on evaporation, yielded 0.84 g. (41%) of a dark liquid. This liquid was shown to be dihydrothiazine by its characteristic infrared spectrum and comparison with an authentic sample. A picrate melted at 140–141° in good agreement with the literature¹² value.

The ether layer from the hydrolysis product was analyzed by v.p.c., infrared, and ultraviolet spectroscopy. It smelled strongly of benzaldehyde. The presence of benzoic acid, benzaldehyde, and benzil was indicated.

Thermal Decomposition of 2,2'-Bis(2-phenyl-4,4-dimethyltetrahydro-1,3-thiazinyl).—The dimer L (250 mg.) was refluxed in 25 ml. of purified tetrahydrofuran for 7 days; the solvent was evaporated, leaving a dark oil (245 mg.). Infrared examination indicated the presence of dihydrothiazine and some benzaldehyde. Vapor phase chromatographic analysis of the dark oil showed a considerable amount of dihydrothiazine, but only traces of the

 $(23)\,$ We are indebted to Dr. Glenn Happ of the Eastman Kodak Co. for these observations.

tetrahydro product. Collection of a sample and infrared examination and comparison with a known sample proved the structure of the dihydrothiazine. Quantitative analysis using v.p.c. (internal standard method) indicated $58 \pm 10\%$ of theory (based on a disproportionation reaction).

Preparation of Aminothiol D-1 Directly from Dihydrothiazine G.—To dihydrothiazine (10.0 g.) in freshly distilled tetrahydrofuran was added aluminum amalgam (20 g.) and enough solvent to cover the amalgam by several inches. Water was added dropwise at $15-25^{\circ}$ with cooling until the amalgam was consumed. The dark slurry was filtered through filter aid and washed well with solvent. The combined filtrates were evaporated, leaving a dark, viscous oil.

This oil was dissolved in 200 ml. of 10% hydrochloric acid and the solution was refluxed gently for 24 hr. The solution was cooled, filtered, and the filtrate was extracted five times with 100ml. portions of ether. The aqueous layer was evaporated to dryness. The residue was extracted continuously with chloroform for 24 hr. The chloroform extracts were worked up to yield dihydrothiazine, which was distilled and recycled.

The aqueous residue was dissolved in methanol, decolorized, and recrystallized from methanol-ethyl acetate, yielding 1.1-3.2 g. of aminothiol hydrochloride, m.p. 281-283°. This material was identical in all respects with material made by other methods.

4,4'-Dithiobis(2-methyl-2-butylamine). Ritter Reaction on 4,4'-Dithiobis(2-methyl-2-butanol).-4,4' - Dithiobis(2-methyl-2butanol) (2.60 g.), dissolved in concentrated sulfuric acid (5 ml.) and chloroform (25 ml.), was cooled to 0° and potassium cyanide (10.0 g.) was added portionwise with external cooling. The mixture was stirred overnight at 0-15°. After the addition of 200 ml. of water (dropwise, with cooling), solid potassium carbonate was added in small portions until the solution was basic. Extraction with methylene chloride yielded 0.09 g. of an oil. This oil was subjected to preparative v.p.c. using a Ucon Polar column. The main component was collected and appeared to be the corresponding dihydrothiazine (B, hydrogen instead of phenyl), based on the infrared absorption at 1381 and 1364, and the $C=N^{24}$ at 1645 cm.⁻¹. The aqueous phase from the extraction was evaporated overnight on a steam cone. The oily solid residue was extracted with hot n-propyl alcohol. The propanol extracts were combined and the propanol was removed by high vacuum distillation using minimum heat, leaving 1.2 g. of residual oil.

The residual viscous yellow oil had gem-dimethyl absorption at 1380 and 1360, amide N-H at 3245, and amide carbonyl at 1677 cm.⁻¹. The ultraviolet spectrum had λ_{max} 245 m μ (ϵ 340). This oil could not be induced to crystallize from a variety of solvents, nor could it be molecularly distilled. It was used directly in the hydrolysis reaction.

The residual yellow oil (1.00 g.) was dissolved in 100 ml. of 1 N sodium hydroxide and stirred at room temperature for 7 days while air was continuously bubbled through the solution. The solution was made strongly acid with dilute hydrochloric acid and evaporated to dryness using high-vacuum heat. The residual dark, semicrystalline solid was extracted with hot n-butyl alcohol. The butanol was distilled off and the remaining material was recrystallized from methanol-ethyl acetate. After 5 crystallizations, 253 mg. of aminothiol disulfide dihydrochloride, m.p. 285-287°, was obtained. The yields were variable. In some cases colored material was obtained which could not be crystallized to a sharp-melting compound.

This material was identical in infrared and ultraviolet spectra with authentic disulfide. Ascending paper chromatographic R_t values were identical.

When benzonitrile was substituted for potassium cyanide in the preceding example, the identical work-up procedure yielded very small amounts of an oil which was isolated by preparative v.p.c. and identified as 2-phenyl-4,4-dimethyl-5,6-dihydro-1,3thiazine by comparison of v.p.c. retention times and infrared comparison with an authentic sample.

(24) Cf. A. I. Meyers, J. Org. Chem., 26, 218 (1961), and ref. 14, above, for infrared data on 5,6-dihydro-1.3-thiazines.