Acknowledgments. The skillful assistance of Messrs. Edmund G. Andrews, Werner H. Kappeler, and Frank W. Rusek is greatly appreciated.

Registry No.—**6,** 7469-40-1; **8** HCl, 54308-10-0; **10,** 54308-11-1; **11,** 7498-87-5; **13** HCl, 54308-12-2; **14,** 14944-26-4; **16** HCl, 54308-13-3; **17,** 14578-68-8; **17** oxime, 50845-35-7; **17** phenylhydrazone, 54308-14-4; **18,** 52789-19-2; **19,** 54308-15-5; **19** HCl, 52371-38-7; **20,** 54308-16-6; **20** HCl, 52371-37-6; (1*S*,4*R*)-**20** *N*-acetyl-L-tyrosine salt, 52795-05-8; (1*S*,4*R*)-**20** HCl, 52760-48-2; (1*R*,4*S*)-**20** D-(−)-mandelate, 52795-03-6; (1*R*,4*S*)-**20** HCl, 52760-47-1; **21,** 54308-17-7; **23** HCl, 52371-39-8; **24,** 52371-40-1; **24** HCl, 54308-18-8; **25** HCl, 52371-31-0; **26** HCl, 52371-32-1; **27** HCl, 54308-19-9; **28** HCl, 54308-20-2; **29** HCl, 54308-21-3; **30** HCl, 54308-22-4; **31** HCl, 54308-23-5; **32** HCl, 54308-24-6; **33** HCl, 54308-25-7; **34** HCl, 54308-26-8; **35** HCl, 54308-27-9; **36** HCl, 54308-28-0; **37,** 34910-81-1; **38,** 54308-29-1; **39,** 54308-30-4; **40** HCl, 54308-31-5; **41,** 54308-32-6; **43** (R = H), 54308-33-7; **45** HCl, 54308-34-8; **46,** 54308-35-9; **47,** 54308-37-1; **48,** 54308-36-0; **48** HCl, 54308-38-2; **49,** 54308-39-3; **50,** 54308-40-6; **51,** 54308-41-7; **53,** 54308-42-8; **54,** 591-31-1; **55,** 54308-43-9; **56,** 54308-44-0; **57** HBF_4 adduct, 54308-46-2; **58,** 13719-61-4; **59,** 54308-47-3; **60,** 54308-48-4; **62,** 54308-49-5; **63,** 54308-50-8; **64,** 54308-51-9; **65,** 54308-52-0; **66,** 54308-53-1; **67** HCl, 54308-54-2; **68** HCl, 54308-55-3; **69,** 54308-56-4; **70,** 54308-57-5; **71** HCl, 54308-58-6; **72** HCl, 54308-59-7; mercuric nitrate, 10045-94-0; methyl iodide, 74-88-4; hydroxylamine hydrochloride, 5470-11-1; phenylhydrazine, 100-63-0; isopropylamine, 75-31-0; 4-phenyl-3,4-dihydro-1(2*H*)-naphthalenone isopropyl ketimine, 54308-60-0; 1-methylpiperazine, 109-01-3; *sec*-butyl cinnamate, 7726-62-7; 5-chloro-2-methoxybenzyl chloride, 7035-11-2; 1,3-propanedithiol, 109-80-8; boron trifluoride, 7637-07-2; *N*-acetyl-L-tyrosine, 537-55-3; ethylamine, 75-04-7; cyclopropylamine, 765-30-0; 1,4-dibromobutane, 110-52-1; bromobenzene, 108-86-1; D-(−)-mandelic acid, 611-71-2.

References and Notes

(1) R. Sarges, J. R. Tretter, S. S. Tenen, and A. Weissman, *J. Med. Chem.*, **16,** 1003 (1973).
(2) R. Weiss and K. Woldich, *Monatsh. Chem.*, **46,** 455 (1925).
(3) H. M. Crawford, *J. Am. Chem. Soc.*, **61,** 608 (1939).
(4) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70,** 4045 (1948).
(5) D. Chow, J. H. Robson, and G. F. Wright, *Can. J. Chem.*, **43,** 312 (1965).
(6) S. N. Ege and K. W. Sherk, *J. Am. Chem. Soc.*, **75,** 354 (1953).
(7) W. S. Johnson and H. J. Glenn, *J. Am. Chem. Soc.*, **71,** 1092 (1949).
(8) 2,4-Diphenylbutanoic acid was prepared by the method of W. G. Kenyon et al., *J. Org. Chem.*, **28,** 3108 (1963); **30,** 2937 (1965).
(9) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32,** 3246 (1967).
(10) J. H. Billman and A. C. Diesing, *J. Org. Chem.*, **22,** 1068 (1957).
(11) S. Wawzonek and J. Kozlkowski, *J. Am. Chem. Soc.*, **76,** 1641 (1954).
(12) R. Sarges, B. K. Koe, and A. Weissman, *J. Pharmacol. Exp. Ther.*, **191,** 393 (1974).
(13) R. Beugelmans, C. Kan, and J. Le Men, *Bull. Soc. Chim. Fr.*, 1306 (1963); S. S. Rawalay and H. Schechter, *J. Org. Chem.*, **32,** 3129 (1967).
(14) A. W. Huffman, *J. Org. Chem.*, **24,** 1759 (1959).
(15) A. S. Hussey and R. R. Herr, *J. Org. Chem.*, **24,** 843 (1959).
(16) J. K. Stille and R. A. Newsom, *J. Org. Chem.*, **26,** 1375 (1961).
(17) J. Munch-Petersen, *Acta Chem. Scand.*, **12,** 967 (1958); M. Kawana and S. Emoto, *Bull. Chem. Soc. Jpn.*, **39,** 910 (1966).
(18) H. E. Faith, M. E. Bahler, and H. J. Florestano, *J. Am. Chem. Soc.*, **77,** 543 (1955).
(19) W. S. Johnson, J. W. Petersen, and W. P. Schneider, *J. Am. Chem. Soc.*, **69,** 74 (1947); W. S. Johnson and M. W. Miller, ibid., **72,** 511 (1950).
(20) R. H. Wiley and N. R. Smith, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 731.
(21) D. Seebach, *Synthesis*, 17 (1969).
(22) In our hands, the procedure of D. Ginsburg, *J. Am. Chem. Soc.*, **73,** 702 (1951), treatment of *p*-methoxybenzaldehyde with *tert*-butyl hypochlorite, which is claimed to lead exclusively to 2-chloro-5-methoxybenzaldehyde, resulted in a mixture of isomers which could be separated only with difficulty. Consequently, we synthesized this compound by a more laborious route from 2-chloro-5-hydroxytoluene.[23]
(23) T. Inoi, P. Gericke, and W. J. Horton, *J. Org. Chem.*, **27,** 4597 (1962); 4-chloro-3-methylanisole was prepared by the method of A. Bhati, *J. Chem. Soc.*, 730 (1963).
(24) A. Bhati, *Tetrahedron*, **18,** 1519 (1962); we prepared this material by a slightly different route and found mp 70–71° after recrystallization from ether (lit. mp 39–41°).
(25) W. Treibs, G. Franke, G. Leichsenring, and H. Röder, *Chem. Ber.*, **86,** 616 (1953).
(26) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Wiley, New York, N.Y., 1967, p 446.
(27) H. W. Voigtländer and W. Rosenberg, *Arch. Pharm. (Weinheim)*, **292,** 632 (1959).
(28) R. Pfleger and K. Waldmann, *Chem. Ber.*, **90,** 2395 (1957).
(29) D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31,** 4303 (1966).
(30) L. A. Walter, W. K. Chang, J. Kenney, and I. Douvan, *J. Med. Chem.*, **17,** 459 (1974).

Novel Synthesis of Aminoethanethiols[1]

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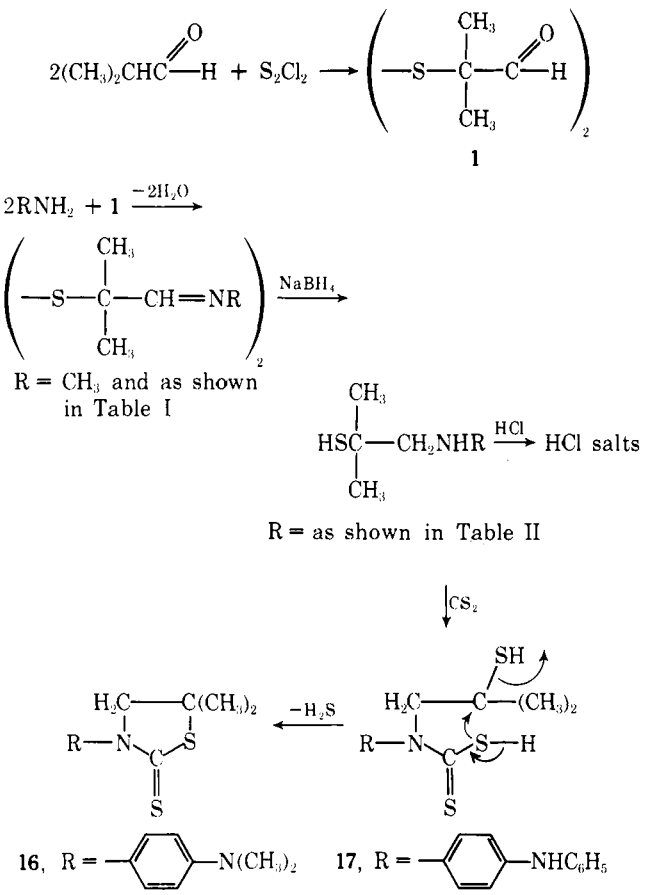
The reaction of α,α'-dithiodiisobutyraldehyde (**1**) with primary aromatic or aliphatic amines afforded novel Schiff bases (**2–8**). The reduction of these Schiff bases with sodium borohydride furnished a novel synthesis of 1,1-dimethyl 2-substituted aminoethanethiols (**9–15**). Two of the aminoethanethiols (**13** and **14**) were further characterized by the reaction with carbon disulfide to give the corresponding 3-substituted 5,5-dimethyl-2-thiazolidinethione (**16** and **17**).

Aminoethanethiols are among the most effective radiation-protective compounds known.[2,3] 2-Aminoethanethiols have been synthesized by the addition of aromatic or aliphatic amines to episulfides or episulfide precursors.[4] However, this method requires high temperatures in sealed tubes and gives low yields because of further mercaptoethylation on sulfur or nitrogen to give bis products or polymers. The addition of excess amine has been successfully used to repress these side reactions[4,5a] but also requires separation of the excess amine from the product. Recently, Luhowy and Meneghini[6] reported that the mercaptoethylation of primary aliphatic amines can be carried out at room temperature with equimolar amounts of episulfide and amine in aqueous media containing amine–silver ion complex.

We wish to report a novel synthesis for 1,1-dimethyl 2-substituted aminoethanethiols. The key intermediate, α,α-dithiodiisobutyraldehyde[7] (**1**), was prepared by the reaction of isobutyraldehyde with sulfur monochloride. The reaction of **1** with primary aromatic or aliphatic amines in refluxing heptane containing a catalytic amount of *p*-toluenesulfonic acid or in methyl alcohol at 25–30° gave the Schiff bases **2–8** in yields of 82–99%. Reduction of these products with sodium borohydride in refluxing ethanol furnished the aminoethanethiols (**9–15**) in good yields. The structures of the Schiff bases and aminoethanethiols were

Scheme I



consistent with their NMR and mass spectra. Two of the aminoethanethiols, **13** and **14**, were further characterized by the reaction with carbon disulfide to give the corresponding 3-substituted 5,5-dimethyl-2-thiazolidinethione (**16** and **17**) (Scheme I).

It is worthy to note that we obtained the same product, 1,1-dimethyl-2-methylaminoethanethiol hydrochloride (**15a**), which was previously reported by Luhowy and Meneghini.[6] A mixture melting point of the two samples[8] was not depressed and the NMR spectra of the two were identical.

The advantages afforded by this novel method are (1) it eliminates the synthesis of episulfides, which are difficult to prepare and in some cases unstable when stored under ordinary conditions,[5b] and (2) a simple, efficient method is now available for the synthesis of 1,1-dimethyl- (and possibly higher 1, 1-dialkyl-) 2-aminoethanethiols.

Proposed mass spectral fragmentation routes for **2, 9,** and **16** are depicted in Schemes II–IV, respectively.[9]

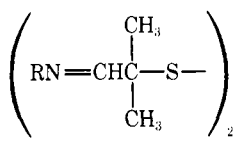
Experimental Section

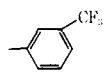
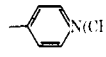
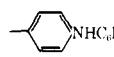
NMR spectra were obtained with a Varian A-60 NMR spectrometer. The chemical shifts are reported in δ, using tetramethylsilane as reference. All melting points were taken upon a Fisher-Johns block and are uncorrected. The mass spectra of **2, 7, 9, 16,** and **17** were determined with a Varian MAT CH-7 mass spectrometer operating at an ionizing potential of 70 eV using the direct insertion probe technique with a source temperature of 250°.

α,α′-Dithiodiisobutyraldehyde (1). A modified procedure reported by Niederhauser[7] was employed. To a stirred solution containing 578 g (8.0 mol) of isobutyraldehyde in 920 g of carbon tetrachloride, 540 g (4.0 mol) of 98% sulfur monochloride was added dropwise at 40–50° in 4 hr. Hydrogen chloride was copiously liberated and occasional cooling was necessary during the addition period. The stirred solution was held at 30–40° for an additional pe-

Table I

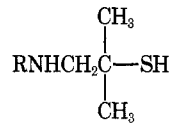
***N,N′*-[1,1′-Dithiobis(1,1-dimethyl-1-ethanyl-2-ylidene)]bis(methylamine) or (Substituted Anilines)[e]**

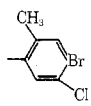
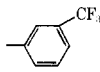
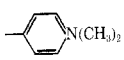
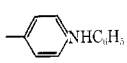


Compd	Method	R	Mp, °C	% yield (crude)	Nmr, δ, ppm, $CDCl_3$–TMS	Empirical formula
2[f]	I	$-C_6H_5$	108–109[a]	95	1.5 [s, 12, 2-C(CH3)2] 6.9–7.5 (m, 10, 2-ArH) 7.6 (s, 2, 2-CH=N)	$C_{20}H_{24}N_2S_2$
3	I		90–91[a]	99	1.4 [s, 12, 2-C(CH3)2][b] 6.8–7.5 (m, 8, 2-ArH) 7.6 (s, 2, 2-CH=N)	$C_{20}H_{22}Cl_2N_2S_2$
4	I		109–111[a]	96	1.5 [s, 12, 2-C(CH3)2] 2.2 (s, 6, 2-ArCH3) 6.8 (s, 2, 2-CH=N) 7.5 (d, 4, 2-ArH)	$C_{22}H_{24}Br_2Cl_2N_2S_2$
5	I		*c*	95	1.5 [s, 12, 2-C(CH3)2] 6.7–7.2 (m, 8, 2-ArH) 7.6 (s, 2, 2-CH=N)	$C_{22}H_{22}F_6N_2S_2$
6	II		133–134[a]	88	1.5 [s, 12, 2-SC(CH3)2] 3.0 [s, 12, 2-N(CH3)2] 6.6–7.4 (m, 8, 2-ArH) 7.7 (s, 2, 2-CH=N)	$C_{24}H_{34}N_4S_2$
7[g]	II		97–98[d]	97	1.5 [s, 12, 2-C(CH3)2] 5.7 (br, s, 2, 2-NH) 6.9–7.5 (m, 18, 2-2ArH) 7.7 (s, 2, 2-CH=N)	$C_{32}H_{34}N_4S_2$

[a] Recrystallization from isopropyl alcohol. [b] Solvent DMSO-d_6. [c] Dark amber, viscous liquid, decomposes on distillation in vacuo (0.30 mm). [d] Recrystallization from ethyl alcohol. [e] Satisfactory analytical data (±0.4% for C, H, N, and S) were reported for all compounds (2–7). Ed. [f] Mass spectrum *m/e* (rel intensity) (probe temperature 60°) 147 (63.3), 146 (81.1), 145 (20.3), 144 (34.7), 132 (22.5), 131 (25.2), 130 (33.0), 104 (43.2), 77 (100), 51 (39.0). [g] Mass spectrum *m/e* (rel intensity) (probe temperature 240°) 238 (100), 237 (20.4), 236 (87.1), 235 (53.8), 221 (20.4), 195 (53.5), 168 (42.0), 167 (77.1), 144 (32.6), 77 (25.2).

Table II
1,1-Dimethyl 2-Substituted Aminoethanethiols and Hydrochloride Salts[e]



Compd	R	Mp or bp, °C	% yield (crude)	Nmr, δ, ppm ($CDCl_3$–TMS)	Empirical formula
9[f]	$-C_6H_5$	$n^{25}D$ 1.6047[a]	81	1.3 [s, 7, $C(CH_3)_2$ + SH] 3.1 (s, 2, CH_2) 3.7 (br s, 1, NH) 6.4–7.3 (m, 5, ArH)	$C_{10}H_{15}NS$
9a		153–155[b]	89		$C_{10}H_{15}NS \cdot HCl$
10		$n^{25}D$ 1.6059[a]	89	1.3 [s, 7, $C(CH_3)_2$ + SH] 3.0 (s, 2, CH_2) 3.8 (br s, 1, NH) 6.3–7.2 (m, 4, ArH)	$C_{10}H_{14}ClNS$
10a		133–135[b]	85		$C_{10}H_{14}ClNS \cdot HCl$
11		a	87	1.4 [s, 7, $C(CH_3)_2$ + SH] 2.1 (s, 3, $ArCH_3$) 3.1 (s, 2, CH_2) 3.9 (br s, 1, NH) 6.5–6.8 (m, 1, ArH) 7.2 (s, 1, ArH)	$C_{11}H_{15}BrClNS$
11a		168–170	50		$C_{11}H_{15}BrClNS \cdot HCl$
12		a	82	1.3 [s, 7, $C(CH_3)_2$ + SH] 3.1 (s, 2, CH_2) 4.1 (br s, 1, NH) 6.5–7.4 (m, 4, ArH)	$C_{11}H_{14}F_3NS$
12a		104–105[b]	81		$C_{11}H_{14}F_3NS \cdot HCl$
13		82–83[c]	98	1.4 [s, 7, $C(CH_3)_2$ + SH] 2.8 [s, 6, $N(CH_3)_2$] 3.1 (s, 2, CH_2) 3.5 (br s, 1, NH) 6.7 (s, 4, ArH)	$C_{12}H_{20}N_2S$
14		a	90	1.4 [s, 7, $C(CH_3)_2$ + SH] 3.1 (s, 2, CH_2) 3.8 (br s, 1, $NHCH_2$) 5.3 (br s, 1, ArNHAr) 6.4–7.4 (m, 9, 2-ArH)	$C_{16}H_{20}N_2S$
15	$-CH_3$	bp 113–114/(0.75 mm) $n^{25}D$ 1.5142	88	1.1 (br s, 1, SH) 1.3 [s, 6, $C(CH_3)_2$] 2.5 (s, 3, NCH_3) 2.6 (s, 2, CH_2)	$C_5H_{13}NS$
15a		222–224[d]	90	1.4 [s, 7, $C(CH_3)_2$ + SH] 2.7 (s, 3, NCH_3) 3.1 (s, 2, CH_2)	$C_5H_{13}NS \cdot HCl$

[a] Amber viscous liquid, decomposes on distillation in vacuo (0.25 mm). [b] Recrystallization from ethyl alcohol–diethyl ether. [c] Recrystallization from heptane. [d] Recrystallization from methyl alcohol. [e] Satisfactory analytical data (±0.4% for C, H, N, and S) were reported for all compounds except **9a** and **11a** (only N and S reported). [f] Mass spectrum *m/e* (rel intensity) (probe temperature 25°) 181 (6.5), 106 (100), 93 (23.4), 79 (8.6), 77 (22.3), 66 (12.7), 65 (9.3), 51 (11.4), 41 (10.6), 39 (13.5).

riod of 48 hr while a current of nitrogen was passed through it in order to remove the hydrogen chloride. The solution was distilled and an 80% yield of product, by 100–110° (1 mm), was obtained: NMR ($CDCl_3$) δ 1.40 [s, 12, 2-$C(CH_3)_2$], 9.09 (s, 2, 2-CHO).

***N,N'*-[1,1'-Dithiobis(1,1-dimethyl-1-ethanyl-2-ylidene)] Bis Substituted Anilines. Method I (2–5).** A stirred mixture containing 51.6 g (0.25 mol) of **1**, 1 g of *p*-toluenesulfonic acid, 200 ml of heptane, and 0.5 mol of the appropriate primary aromatic amine was heated at reflux (82–105°) for 1.5 hr. During this period, by means of a Dean-Stark condenser, 9 ml of water and 100 ml of heptane were removed. For **2–4**, the stirred mixture was cooled to 0° and held at 0–5° for 1 hr. The solids were collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 25–30°. For **5**, the reaction mixture was filtered to remove the catalyst and the heptane was removed in vacuo at a maximum temperature of 80–90° (1–2 mm). The data are summarized in Table I.

Method II (6 and 7). To a stirred solution containing 0.2 mol of *N,N*-dimethyl-*p*-phenylenediamine or *N*-phenyl-*p*-phenylenediamine in 75 ml of methyl alcohol, 20.6 g (0.1 mol) of **1** was added in one portion. An exothermic reaction set in, causing a temperature rise of approximately 10°. The reaction mixture was stirred at 25–30° for 24 hr. The solids were collected by filtration and air dried at 25–30°. The data are summarized in Table I.

***N,N'*-[1,1'-Dithiobis(1,1-dimethyl-1-ethanyl-2-ylidene)]-bis(methylamine) (8).** To a stirred solution containing 101 g (1.3 mol) of 40% aqueous methylamine in 200 ml of methyl alcohol, 82.4 g (0.4 mol) of **1** was added dropwise at 25–35° in 0.5 hr. The reaction mixture was stirred at 25–30° for 4 days. After the addition of 300 ml of water and 500 ml of ethyl ether, stirring was continued for 0.5 hr. The separated ether layer was washed with water until the washings were neutral to litmus and dried over sodium sulfate. The ether was removed in vacuo at a maximum temperature of 70° (1–2 mm). The crude product, $n^{25}D$ 1.5225, was obtained in 82% yield. The crude product was distilled and a 60% yield of **8**, bp 86–87° (0.15 mm), $n^{25}D$ 1.5220, was obtained: NMR

($CDCl_3$) δ 1.3 [s, 12, 2-SC(CH_3)$_2$], 3.2 (s, 6, 2-NCH_3), 7.4 (s, 2, 2-CH=N).

Anal. Calcd for $C_{10}H_{20}N_2S_2$: C, 51.68; H, 8.67; N, 12.05; S, 27.59; mol wt, 232.4. Found: C, 51.76; H, 8.86; N, 11.73; S, 27.69; mol wt, 232 ($CHCl_3$).

1,1-Dimethyl 2-Substituted Aminoethanethiols (9–15). To a stirred solution containing 0.2 mol of **2, 3, 4, 5, 6, 7,** or **8** in 500 ml of ethanol at 60°, a solution containing 23.4 g (0.6 mol) of sodium borohydride in 600 ml of ethanol was added slowly at 65–70° over a 1-hr period. The stirred reaction mixture was heated at reflux for 1 hr and then allowed to cool to 30°. The reaction mixture was added to 2000 g of ice water and stirred at 0–10° for 1 hr. For **13,** the precipitate was collected by filtration, washed with water until the washings were neutral to litmus, and air dried at 25–30°. For the remainder, the viscous liquids were extracted by the addition of 1 l. of ethyl ether and filtered to remove any impurities. The separated ether layer was washed with water until the washings were neutral to litmus and dried over sodium sulfate. The ether was removed in vacuo at maximum temperature at 80–90° (1–2 mm). The data are summarized in Table II.

Hydrochloride Salts (9a–12a and 15a). To a stirred solution containing **9–12** or **15** in 300 ml of ethyl ether, hydrogen chloride gas was bubbled through the solution at 0–10° over a 0.5-hr period. The precipitate was collected by filtration, washed with 200 ml of ethyl ether, and air dried at 50°. The data are summarized in Table II.

3-[*p*-(Dimethylamino)phenyl]-5,5-dimethyl-2-thiazolidinethione (16) and 3-(*p*-Anilinophenyl)-5,5-dimethyl-2-thiazolidinethione (17). A stirred slurry containing 0.15 mol of **13** or **14,** 9.8 g (0.15 mol) of 85% potassium hydroxide, 22.8 g (0.3 mol) of carbon disulfide, and 50 ml of ethanol was heated at reflux for 24 hr. After the stirred reaction mixture was cooled to 0°, the precipitate was collected by filtration, washed successively with 25 ml of ethanol and 300 ml of water, and air dried at 25–30°. The crude **16,** mp 142–146°, and **17,** mp 165–166°, were obtained in yields of 75 and 99%, respectively. After recrystallization from ethyl acetate and toluene, respectively, **16** and **17** melted at 157–158 and 166–167°, respectively: NMR ($CDCl_3$) of **16,** δ 1.60 [s, 6, -C(CH_3)$_2$], 2.92 [s, 6, -N(CH_3)$_2$], 4.08 (s, 2, NCH_2C), 6.50–7.30 (m, 4, ArH), and **17,** δ 1.60 [s, 6, -C(CH_3)$_2$], 4.10 (s, 2, NCH_2C), 5.90 (br s, 1, -NH), 6.90–7.50 (m, 9, 2 ArH); mass spectrum *m/e* (rel intensity) of **16,** probe temperature 125°, 266 (86.8), 190 (39.1), 178 (16.7), 152 (26.8), 147 (100), 145 (31.5), 135 (22.4), 120 (21.7), 77 (22.5), and 42 (32.6), and **17,** probe temperature 200°, 314 (100), 238 (32.8), 226 (17.3), 200 (14.3) 195 (52.1), 183 (12.5), 168 (26.9), 167 (44.9), 77 (17.5), and 65 (10.1).

Anal. Calcd for $C_{13}H_{18}N_2S_2$ (**16**): C, 58.61; H, 6.81; N, 10.51; S, 24.07; mol wt, 266.4. Found: C, 58.82; H, 6.79; N, 10.46; S, 24.16; mol wt, 265 ($CHCl_3$). Calcd for $C_{17}H_{18}N_2S_2$ (**17**): C, 64.93; H, 5.77; N, 8.91; S, 20.39. Found: C, 64.80; H, 5.66; N, 8.83; S, 20.60.

Registry No.—**1,** 15581-80-3; **2,** 54410-19-4; **3,** 54410-20-7; **4,** 54410-21-8; **5,** 54410-22-9; **6,** 54410-23-0; **7,** 54410-24-1; **8,** 54410-25-2; **9,** 54410-26-3; **9a,** 54410-27-4; **10,** 54410-28-5; **10a,** 54410-29-6; **11,** 54410-30-9; **11a,** 54410-31-0; **12,** 54446-52-5; **12a,** 54410-32-1; **13,** 54410-33-2; **14,** 54410-34-3; **15,** 54410-35-4; **15a,** 39981-47-0; **16,** 54410-36-5; **17,** 54410-37-6; isobutyraldehyde, 78-84-2; sulfur chloride, 10025-67-9; *N,N*-dimethyl-*p*-phenylenediamine, 99-98-9; *N*-phenyl-*p*-phenylenediamine, 101-54-2; methylamine, 74-89-5; *m*-trifluoromethylaniline, 98-16-8; aniline, 62-53-3; *p*-chloroaniline, 106-47-8; 4-bromo-5-chloro-2-methylaniline, 30273-47-3.

Supplementary Material Available. Mass spectral fragmentation routes for **2, 9,** and **16** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-1224.

References and Notes

(1) Presented at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975.
(2) (a) A. Herve and Z. M. Bacq, *C. R. Soc. Biol.*, **143,** 881 (1949); (b) H. M. Patt, E. B. Tyree, R. L. Straube, and D. E. Smith, *Science,* **110,** 213 (1949).
(3) Z. M. Bacq, "Chemical Protection against Ionizing Radiation", Charles C. Thomas, Springfield, Ill., 1965, p 12.
(4) D. D. Reynolds and D. L. Johnson, *Mech. React. Sulfur Compd.*, **5,** 103 (1970).
(5) (a) R. J. Wineman, H. H. Gollis, J. C. James, and A. M. Pomponi, *J. Org. Chem.*, **27,** 4222 (1962); (b) H. R. Snyder, J. M. Stewart, and J. B. Ziegler, *J. Am. Chem. Soc.*, **69,** 2672 (1947); (c) N. S. Isaacs, *Can. J. Chem.*, **44,** 395 (1966); (d) E. Tobler, *Ind. Eng. Chem., Prod. Res. Dev.*, **8,** 415 (1969).
(6) R. Luhowy and F. Meneghini, *J. Org. Chem.*, **38,** 2405 (1973).
(7) W. D. Niederhauser, U. S. Patent 2,580,695 (1952).
(8) **15a** prepared by their method kindly furnished by F. Meneghini.
(9) See paragraph at end of paper regarding supplementary material.

Preparation of Protected Peptide Intermediates for a Synthesis of the Ovine Pituitary Growth Hormone Sequence 96–135

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The preparation of seven protected peptides (tri- to dodecapeptides) which span the sequence of the "active core" region 96–135 of ovine pituitary growth hormone is described. These peptides were synthesized through modified solid-phase techniques, i.e., use of *p*-alkoxybenzyl alcohol resin and hydroxymethyl resin or successive applications of both solid-phase and conventional procedures. The purity of all peptides was carefully ascertained.

The biochemical studies of Li and others[1–6] have led to the conclusion that an intact molecule of pituitary growth hormone is not essential for the manifestation of its biological activities. Indeed, an "active core" was isolated from tryptic digest of bovine growth hormone by Sonenberg et al.[4] and its amino acid sequence delineated.[7] The compound was reported to possess 20–30% of the activity[4,8] of the intact hormone both by the tibia test[9] and the body weight gain test.[10] Moreover, the species specificity appeared to become less stringent. The bovine core peptide exhibited activity in man whereas the intact bovine growth hormone did not. Comparison of the core fragment with the amino acid sequence of bovine growth hormone[11–13] revealed its identity with the sequence region 96–133 (Chart I). In a recent communication Li et al.[14] have described a solid-phase synthesis of the corresponding region of human growth hormone (i.e., sequence 95–136) and showed that the product stimulated the growth of rat tibia. Li and Yam-