under reflux for 2 hr. After 12 hr at 25° the supernatant was decanted and concentrated *in vacuo* at 25° to give **1** (100 mg).

Stability of N-Nitroso-N-phenylaspartic Anhydride.—The compound, refluxed in C_6H_6 alone (2 hr), was essentially unchanged with respect to sydnone.

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N-Substituted Derivatives of 2-Aminoethanethiol and 2-Hydrazinoethanethiol[1]

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A study was made of the effect on radioprotective action of many variations in nitrogen substitution of 2-aminoethanethiol. Direct alkylation of primary amines with ethylene sulfide (generated *in situ*) provided many of the analogs. Other derivatives were obtained by debenzylation of N-[2-(benzylthio)ethyl]alkylamines. These benzylthio ethers were prepared by (1) reduction ($LiAlH_4$) of amides obtained from either (benzylthio)-acetyl chloride or 2-(benzylthio)ethylamine, and (2) alkylation of 2,2,2-trifluoroacetamides with benzyl 2-chloroethyl sulfide. Alkylation of 1,2-bis(trifluoroacetyl)-1-alkylhydrazines using benzyl 2-chloroethyl sulfide afforded substituted 2-hydrazinoethanethiols. None of the compounds was superior to 2-aminoethanethiol in protecting against radiation damage. Antibacterial activity was found for some compounds against *Streptococcus pyogenes*, *Staphylococcus aureus*, and *Mycobacterium tuberculosis*.

Derivatives and analogs of 2-aminoethanethiol are still the most promising antiradiation agents available. Many structural variations incorporating a variety of synthetic methods have been reported.[2] Considering the mechanisms of protective action postulated[3] for active agents, it seemed likely that increased activity could result from changes in drug transport properties and/or selective absorption by tissues most vulnerable to radiation damage. Accordingly, mercaptoethyl analogs of drugs which are known to be transported and selectively absorbed *in vivo* were synthesized (Table I). Analogs were prepared from norephedrine, amphetamine, 1-phenylcyclohexylamine, some *o*-alkoxyphenoxyalkylamines, *trans*-2-phenylcyclopropylamine, norepinephrine, and (α-methylphenethyl)hydrazine. Additionally, mercaptoethylamines possessing cyclopropyl and cyclobutyl groups and derivatives of hydrazine were prepared.

Mercaptoethylamine derivatives which could be distilled using ordinary techniques were obtained by the use of ethyl 2-mercaptoethyl carbonate, which was introduced for this purpose by Reynolds and coworkers.[4,5] Although aldehydes are incompatible with mercaptans, the mercaptoethyl derivative of aminoacetaldehyde diethyl acetal was isolated. This provided a 2-alkylaminoethanethiol bearing a potential aldehyde function.

Other compounds were obtained from 2-amino-1-alkanols which were prepared conveniently by reduction of esters of DL-α-amino acids using lithium aluminum hydride.[2f,6] Metal hydride reductions of the methyl esters of glutamic acid and tyrosine on a preparative scale afforded very low yields of products. Such reductions have given some amino alcohol on a small scale,[6b-d] although the preparation of tyrosinol from tyrosine apparently is not reproducible.[6f] Catalytic hydrogenation of tyrosine methyl ester using a rhodium catalyst effected dehydration and reduction of the aromatic ring to give a derivative of cyclohexane. An attempt to prepare 2-amino-1,5-pentanediol from DL-glutamic acid by high-pressure catalytic hydrogenation using a rhenium catalyst resulted in isolation of only the lactam, 5-(hydroxymethyl)-2-pyrrolidinone, in about 48% yield. In a few instances in which the product was difficult to distil satisfactorily, the excess amine was distilled using an oil diffusion pump and the product was isolated from the undistilled residue. In two cases the mercaptan was separated from excess amine by precipitating the lead mercaptide. Recrystallization from aqueous alcohol effected purification of the lead salts.

Some of the pharmacologically active amines we wished to use were either in short supply or could not be distilled, and it was necessary to develop other procedures for these examples. In one variation used to prepare substituted 2-(benzylthio)ethylamines (Table II), amines were acylated with (benzylthio)acetyl chloride to give simple amides. Reduction of the amides using $LiAlH_4$ in ether or tetrahydrofuran as illustrated in Scheme I, method A, provided secondary amines with no detectable cleavage of the thio ether. The substituted 2-(benzylthio)ethylamines generally were purified as hydrochloride salts. Sodium–liquid

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(2) (a) For a summary of earlier syntheses see R. J. Wineman, M. H. Gollis, J. C. James, and A. M. Pomponi, *J. Org. Chem.*, **27**, 4222 (1962), and D. Rosenthal, G. Brandrup, K. H. Davis, Jr., and M. E. Wall, *ibid.*, **30**, 3689 (1965); (b) L. Bauer and B. K. Ghosh, *ibid.*, **30**, 4298 (1965); (c) A. F. Ferris, O. L. Salerni, and B. A. Schutz, *J. Med. Chem.*, **9**, 391 (1966); (d) G. R. Handrick and E. R. Atkinson, *ibid.*, **9**, 558 (1966); (e) O. L. Salerni and R. N. Clark, *ibid.*, **9**, 778 (1966); (f) J. R. Piper, C. R. Stringfellow, Jr., and T. P. Johnston, *ibid.*, **9**, 911 (1966).

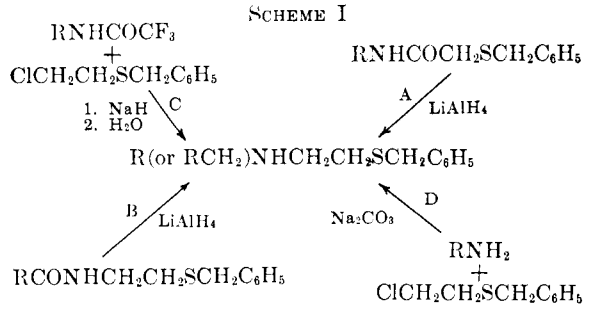
(3) Z. M. Bacq, "Chemical Protection Against Ionizing Radiation," Charles C Thomas, Publisher, Springfield, Ill., 1965, Chapter 19.

(4) D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5125 (1961).

(5) Ethylene sulfide is now available from Aldrich Chemical Co. and can be handled easily.

(6) (a) K. S. Topchiev, *Dokl. Akad. Nauk SSSR*, **63**, 147 (1948); *Chem. Abstr.*, **43**, 2579 (1949); (b) P. Karrer, P. Portmann, and M. Suter, *Helv. Chim. Acta*, **31**, 1617 (1948); (c) P. Karrer and P. Portmann, *ibid.*, **31**, 2088 (1948); (d) A. Dornow, G. Messwarb, and H. Frey, *Chem. Ber.*, **83**, 445 (1950); (e) G. R. Handrick, E. R. Atkinson, F. E. Granchelli, and R. J. Bruni, *J. Med. Chem.*, **8**, 762 (1965); (f) H. Gershon and R. Rodin, *ibid.*, **8**, 864 (1965).

SCHEME I



ammonia reduction,[7] with some caution to avoid air oxidation during work-up, gave N-substituted 2-aminoethanethiols which could be purified as hydrochloride salts without prior distillation of the free bases. DL-Valine methyl ester, acylated with (benzylthio)acetyl chloride, afforded directly an amino alcohol on reduction of the amide ester with $LiAlH_4$. Debenzylation gave the thiol **6**.

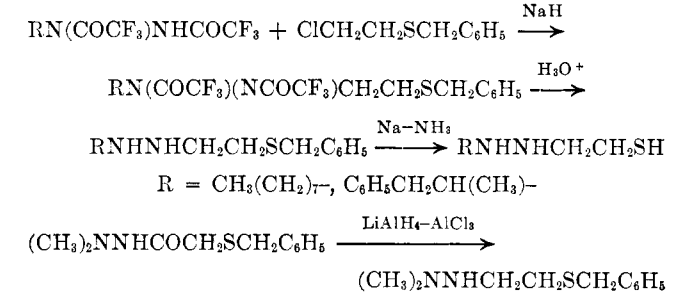
Reductions using $LiAlH_4$ generally gave reasonable yields of secondary amines. However, some of the substituted amides were unstable to the vigorous conditions necessary to reduce the amide carbonyl group. Reduction of 2-(benzylthio)-N-cyclopropylacetamide in refluxing THF for 40 hr resulted in opening of the cyclopropane ring and some cleavage of the benzyl sulfide. Thio ethers have been reported to be stable to $LiAlH_4$,[8] a characteristic substantiated by our work; however, this example illustrates that under extreme conditions cleavage can occur. The opening of a cyclopropane ring under these conditions has been reported by other workers.[9] $LiAlH_4$ also cleaved another amide, 2-(benzylthio)acetohydroxamic acid methyl ester (amide of methoxyamine); 2-(benzylthio)ethylamine was the only product isolated.

Another method allowed use of available carboxylic acids and their derivatives as starting materials. 2-(Benzylthio)ethylamine[10] is readily available as an intermediate and can be acylated by any of several methods. Reduction of the resulting amides again provided N-substituted 2-(benzylthio)ethylamines (Scheme I, method B). N,N'-(Dithiodiethylene)bis-(2,2,2-trifluoroethylamine) [disulfide of 2-(2,2,2-trifluoroethylamino)ethanethiol] was prepared in 37% yield (crude, 79%) as the dihydrochloride salt, using trifluoroacetic anhydride as the acylating agent. Prolonged handling of the thiol in an attempt to prepare a homogeneous crystalline product resulted in complete conversion to the disulfide during the purification step.

Alkylation of amines using benzyl 2-chloroethyl sulfide was introduced by Cavallini and Ravenna[11] (Scheme I, method D). However, excess amine is necessary for a practical route to monoalkylation products, thereby complicating work-up procedures. We sought optimum yields based on the amine for expensive amines such as cyclopropylamine, particularly if the corresponding 2-(benzylthio)acetamides would decompose on reduction. Alkylation of N-substituted 2,2,2-trifluoroacetamides as shown in Scheme I (method C) by benzyl 2-chloroethyl sulfide in an inert solvent and in the presence of sodium hydride proved useful. Acidic hydrolysis of the amide and debenzylation of the resulting amino compound with sodium in liquid ammonia gave the desired product. Debenzylations using sodium in liquid ammonia generally proceeded smoothly, but a pure product was not obtained by debenzylation of *trans*-N-2-(benzylthio)ethyl-2-phenylcyclopropylamine (**54**).

A convenient method for obtaining mercaptoethyl derivatives of hydrazines was not available to us. Only oligomers were isolated on reaction of ethylene sulfide with alkylhydrazines.[4] Alkylation of the bis-trifluoroacetyl derivatives of hydrazines using benzyl 2-chloroethyl sulfide in the presence of sodium hydride proceeded in excellent yield (Scheme II). Hydrolysis following alkylation unambiguously gave 1,2-bissubstituted hydrazines. Carbobenzoxy groups were used by Zeller *et al.*,[12] in a related reaction. The S-benzyl group was removed in this case also using sodium in liquid ammonia and the 2-(2-substituted hydrazino)-ethanethiol was distilled. The mercaptoethyl derivative of 1,1-dimethylhydrazine was obtained by reduction of the 1,1-dimethylhydrazide of (benzylthio)-acetic acid using $LiAlH_4$–$AlCl_3$. Difficulties attending the reduction of hydrazides have been elaborated by Hinman.[13] The free thiol was liberated in the manner described for other hydrazines given above.

SCHEME II



Biological Activity.—The aminoethanethiols were tested for antiradiation activity at Walter Reed Army Institute of Research.[14] Most of the compounds were found to be inactive. Slight protection (7–15% survival) was observed for some of the compounds. Compound **39** at 30 mg/kg afforded 94 and 20% survival (30 days) in two different tests when administered 15 min preirradiation. Administration of **39** 30 min preirradiation resulted in 40% survival.

Several compounds displayed antibacterial activity in *in vitro* test systems.[15] Against *Streptococcus pyogenes* complete inhibition of growth was obtained at 20

(7) (a) J. Baddiley and E. M. Thain, *J. Chem. Soc.*, 800 (1952); (b) F. I. Carroll, J. D. White, and M. E. Wall, *J. Org. Chem.*, **28**, 1236 (1963).

(8) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p 838.

(9) C. Kaiser, A. Burger, L. Zirngibl, C. S. Davis, and C. L. Zirkle, *J. Org. Chem.*, **27**, 768 (1962).

(10) (a) D. B. Reisner, *J. Am. Chem. Soc.*, **78**, 5102 (1956); (b) S. H. Chu and H. G. Mautner, *J. Org. Chem.*, **26**, 4498 (1961); (c) T. P. Johnston and A. Gallagher, *ibid.*, **28**, 1305 (1963); (d) F. I. Carroll, H. M. Dickson, and M. E. Wall, *ibid.*, **30**, 33 (1965).

(11) G. Cavallini and F. Ravenna, *Farmaco, Ed. Sci.*, **12**, 151 (1957); *Chem. Abstr.*, **51**, 11245 (1957).

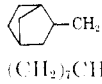
(12) P. Zeller, H. Gutmann, B. Hegedüs, A. Kaiser, A. Langemann, and M. Müller, *Experientia*, **19**, 129 (1963).

(13) R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 1645, 2463 (1965).

(14) For a description of the test method see L. Field, A. Ferretti, R. R. Crenshaw, and T. C. Owen, *J. Med. Chem.*, **7**, 39 (1964).

(15) For the general test procedures (*in vitro* and *in vivo*) see M. W. Fisher, M. C. Manning, L. A. Gagliardi, M. R. Gaetz, and A. L. Erlandson in "Antibiotics Annual 1959–1960," Antibiotica, Inc., New York, N. Y., 1960, pp 293–303.

TABLE I

No.	R	Method[a]	Yield,[b] % Base	Yield,[b] % HCl salt[c]	Bp, °C (mm) (base)	Mp, °C (HCl salt)	Formula	Analyses[d]
	N-Substituted 2-Aminoethanethiols, $RNHCH_2CH_2SH$							
1	$(CH_2)_2CH$ $\quad\quad O$	F[e]	31	18	95–100 (40)	142–144	$C_5H_{11}NS\cdot HCl$	C, H, N, SH
2	$CH_2CH_2CH_2CHCH_2$	E[f]	75	25	92–98 (0.2)	188–193	$C_7H_{15}NOS\cdot HCl$	C, H, N, SH
3	$(CH_2)_3CHCH_2$	F[g]	30	30	35–38 (0.02)	237–240	$C_7H_{15}NS\cdot HCl$	C, H, N, SH
4	$C_2H_5O(CH_2)_3$	E[h]	76	56	60 (0.2)	108–110	$C_7H_{15}NOS\cdot HCl$	C, H, N, SH
5	$CH_3(CH_2)_2CH(CH_2OH)$	E[i]	69	58	71–76 (0.1)	45–51	$C_7H_{17}NOS\cdot HCl$	C, H, N, SH
6	$(CH_3)_2CHCH(CH_2OH)$	F	...	29	...	90–96	$C_7H_{17}NOS\cdot HCl$	C, H, N, SH
7	$CH_3(CH_2)_3CH(CH_2OH)$	E[j]	50	40	73–83 (0.1)	47–52	$C_8H_{19}NOS\cdot HCl$	C, H, N, S, SH
8	$(C_2H_5O)_2CHCH_2$	E	45	...	74 (0.2)	...	$C_8H_{19}NO_2S$	C, H, N, SH
9	$(C_2H_5O)_2CHCH_2$	...	...	38	...	95–97	$C_8H_{19}NO_2S\cdot HCl$	C, H, N, SH
10	$(CH_3)_2CHCH_2CH(CH_3)$	E[k]	39	29	86–87 (45)	155–157	$C_8H_{19}NS\cdot HCl$	C, H, N, SH
11	$(CH_2)_6CH$	E[k]	27	7	...	193–196	$C_8H_{19}NS\cdot HCl$	C, H, N, S, SH
12	$(CH_2)_5CHCH_2$	F[l]	...	17	...	231–232	$C_8H_{19}NS\cdot HCl$	C, H, N, SH
13	$CH_3(CH_2)_2CH(OH)C(CH_3)_2$	E[l]	23	...	71–77 (0.2)	75–77[m]	$C_9H_{21}NOS$	C, H, N; SH[n]
14	CH_3N  $N(CH_2)_2$	E[k]	73	34	88–90 (0.1)	274–278[o]	$C_{10}H_{27}N_3S\cdot 3HCl$	C, H, Cl, N, SH
15		E	71	21	89 (0.1)	267–268	$C_{10}H_{19}NS\cdot HCl$	C, H, Cl, S; SH[p]
16	$(CH_2)_7CH$	E[k]	65	54	94–100 (0.7)	237–240	$C_{10}H_{21}NS\cdot HCl$	C, H, N, SH
17	$(CH_2)_4CH(CH_2)_3$	F[q]	...	73	...	201–203	$C_{10}H_{21}NS\cdot HCl$	C, H, N, SH
18	$(CH_3)_2CHCH_2C(CH_3)_2CH_2$	E[r]	68	15	115–118 (10)	192–195	$C_{10}H_{23}NS\cdot HCl$	C, H, N, SH
19	$CH_3(CH_2)_5CH(CH_2OH)$	E[s]	50	28	105–120 (1.4)	63–65	$C_{10}H_{23}NOS\cdot HCl$	C, H, N, SH
20	$C_6H_5CH(OH)CH(CH_3)$	E[t]	17	8	120–125 (0.7)	165–167	$C_{11}H_{17}NOS\cdot HCl$	C, H, N; SH[n]
21	$C_6H_5OCH_2CH(OH)CH_2$	E[r]	...	9	...	112–115	$C_{11}H_{17}NO_2S\cdot HCl$	C, H, N, SH
22	$C_6H_5(CH_2)_3$	E	65	43	86–94 (0.1)[u]	120–123	$C_{11}H_{17}NS\cdot HCl$	C, H, Cl, N; SH[v]
23	$C_6H_5CH(CH_2CH_3)$	E	77	20	78–85 (0.1)	138–140	$C_{11}H_{17}NS\cdot HCl$	C, H, Cl, N, S; SH[w]
24	$C_6H_5CH_2CH(CH_3)$	E[x]	87	46	77–79 (0.1)	174.5–175	$C_{11}H_{17}NS\cdot HCl$	C, H, Cl, N, SH
25	$(CH_2)_5CHCH_2CH(CH_2OH)$	F	...	29	...	98–99	$C_{11}H_{23}NOS\cdot HCl$	C, H, N, SH
26	$(CH_2)_5N(CH_2)_4$	E[a,s]	41	24	92–99 (0.1)	207–209	$C_{11}H_{24}N_2S\cdot 2HCl$	C, H, N, SH
27	$CH_3(CH_2)_3O(CH_2)_2O(CH_2)_3$	E[r]	60	23	65–70 (0.01)	*bb*	$C_{11}H_{25}NO_2S\cdot HCl$	C, H, N; SH[cc]

[a] E, $RNH_2 + C_2H_5OCO_2C_2H_4SH$, see ref 3; F, $RNHCH_2CH_2SCH_2C_6H_5 + Na\text{–}NH_3$. [b] For method A yields are based on ethyl 2-mercaptoethyl carbonate; for method B yields are based on the intermediate S-benzyl compound shown in footnote *a*. Yields of HCl salts have the same basis as the distilled free amines, and therefore are lower than the free amines. [c] Generally recrystallized from EtOH–Et_2O. [d] Thiol (SH) values were determined by iodine titration. Most values were within ±0.4% of calculated values; however, greater tolerance was allowed for the thiol values because of the nature of the assay. [e] From N-[2-(benzylthio)ethyl]-N-cyclopropyl-2,2,2-trifluoroacetamide. After the ammonia had evaporated the basic mixture (aqueous) was stirred for 3 hr at 25°. Hydrolysis was continued by warming a solution in MeOH-concentrated HCl for 1.5 hr; **1** has nmr peaks (D_2O) at δ 3.4 (t, 3, CH_2S), 2.8 (m, 3, $CHNCH_2$), and 0.9 ppm (m, 4, $(CH_2)_2N$). [f] Primary amine from Commercial Solvents Corp. [g] Intermediate N-[2-(benzylthio)-ethyl]cyclobutanecarboxamide, mp 60–67°. *Anal.* ($C_{14}H_{19}NOS$) C, H, N. The corresponding N-[2-(benzylthio)ethyl]cyclobutanemethylamine was obtained as an oily free base in 92% crude yield. See Experimental Section for debenzylation procedure; the free base was liberated and distilled before conversion to a salt for purification. [h] Primary amine from American Cyanamid Co. [i] From DL-2-amino-1-pentanol. [j] From DL-2-amino-1-hexanol: H. Adkins and A. A. Pavlic, *J. Am. Chem. Soc.*, **69**, 3039 (1947). [k] Primary amine from Aldrich Chemical Co. [l] Intermediate N-[2-(benzylthio)ethyl]cyclohexanecarboxamide was crude, mp 76–79°; reduction by $LiAlH_4$ gave N-[2-(benzylthio)ethyl]cyclohexanemethylamine in 79% yield, bp 130–131° (0.04 mm). [m] Free base. [n] SH: calcd, 17.29; found, 17.84. [o] The trihydrochloride salt was recrystallized from EtOH–H_2O. [p] SH: calcd, 14.91; found, 15.68. [q] Intermediate N-[2-(benzylthio)ethyl]cyclopentanepropionamide resisted both crystallization and distillation; reduction by $LiAlH_4$ gave N-(2-(benzylthio)ethyl]cyclopentanepropylamine in 96% yield, bp 130–135° (0.05 mm). [r] Primary amine from Union Carbide and

μg/ml for **11**, **18**, **19**, **25**, **33**, and **34**; at 10 μg/ml for **17**; at 5 μg/ml for **37–39**; and at 0.6 μg/ml for **40**. Against *Mycobacterium tuberculosis* complete inhibition of growth was obtained at 20 μg/ml for **15**, **17–19**, **22–24**, **28**, **33**, **38**, and **40**; at 10 μg/ml for **37**; and at 5 μg/ml for **39**. Against *Staphylococcus aureus* complete inhibition of growth was obtained at 20 μg/ml for **18**, **37**, and **39**; at 10 μg/ml for **38** and **57**; and at 2.5 μg/ml for **40**. Compound **18** given orally[15] at 25 mg/kg to mice infected with *S. aureus* had about one-third the effectiveness of sulfadiazine given orally at 100 mg/kg. Similarly, **40** given subcutaneously[15] at 12.5 mg/kg to mice infected with *S. pyogenes* had about one-third the effectiveness of sulfadiazine given orally at 100 mg/kg.

Experimental Section[16]

2-{[2-(Benzylthio)ethyl]amino}-3-(*o*-methoxyphenoxy)-2-propanol Hydrochloride (57). Method A.—Reaction between 33.8 g (0.17 mole) of *1-amino-3-(o-methoxyphenoxy)-2-propanol*[17] and 34.3 g (0.17 mole) of (benzylthio)acetyl chloride[18] in 1 l. of CH_2Cl_2 containing 18.9 g of Et_3N gave on work-up (washing, drying, and concentrating the solution) 48 g of viscous oil. The crude 2-(benzylthio)-N-[2-hydroxy-3-(*o*-methoxyphenoxy)propyl]acetamide was reduced without further purification.

A solution of 39.9 g (0.11 mole) of the oily amide in 400 ml of Et_2O was added to a mixture of 34 g (0.85 mole) of $LiAlH_4$ in 200 ml of Et_2O. The mixture was stirred and heated under reflux for 68 hr, and decomposed by the successive addition of 34 ml of H_2O, 34 ml of 15% NaOH, and 100 ml of H_2O. Filtration followed by the addition of dry HCl to the filtrate gave 12.5 g (29%) of **57**, mp 118–120°.

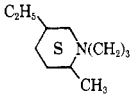
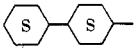
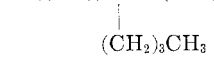
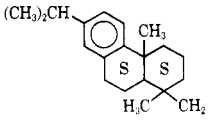
Reduction of 2-(Benzylthio)-N-cyclopropylacetamide. N-[2-(Benzylthio)ethyl]propylamine (51) and N,N′-(Dithiodiethylene)-

(16) Melting points were determined using a Thomas–Hoover melting point apparatus. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

(17) C. D. Lunsford, R. P. Mays, J. A. Richman, Jr., and R. S. Murphey, *J. Am. Chem. Soc.*, **82**, 1166 (1960).

(18) R. Lesser and A. Mehrländer, *Ber.*, **56B**, 1642 (1923).

TABLE I (*Continued*)

No.	R	Method[a]	Yield,[b] % Base	HCl salt[c]	Bp, °C (mm) (base)	Mp, °C (HCl salt)	Formula	Analyses[d]
28	$[(CH_3)_2CHCH_2]_2CH$	E	72	14	60–61 (0.2)	139–144	$C_{11}H_{25}NS\cdot HCl$	C, H, Cl, N, S; SH[dd]
29	$(C_2H_5)_2N(CH_2)_2O(CH_2)_3$	E[ee]	74	51	94–96 (0.2)	124–126	$C_{11}H_{26}N_2OS\cdot 2HCl$	C, H, Cl, N, SH
30	$[CH_3(CH_2)_2]_2N(CH_2)_3$	E[k]	91	43	80–87 (0.3)	173–174	$C_{11}H_{26}N_2S\cdot 2HCl$	C, H, Cl, N, S, SH
31	$3,4\text{-}(CH_3O)_2C_6H_3(CH_2)_2$	E[k]	...	8[ff]	*gg*	137–140	$C_{12}H_{19}NO_2S\cdot HCl$	C, H, Cl, N, S, SH
32	$2\text{-}C_2H_5OC_6H_4O(CH_2)_2$	E[hh]	84	44	133–136 (0.2)	102–103	$C_{12}H_{19}NO_2S\cdot HCl$	C, H, Cl, N; SH[ii]
33	$C_6H_5(CH_2)_4$	E	57	30	103 (0.5)	102–108	$C_{12}H_{19}NS\cdot HCl$	C, H, Cl, N, SH
34	$2\text{-}C_2H_5OC_6H_4O(CH_2)_3$	E[jj]	40	9.4	136–142 (0.03)	79–82	$C_{13}H_{21}NO_2S\cdot HCl$	C, H, N, SH
35		E[r]	32	29	100 (0.1)	204–205	$C_{13}H_{28}N_2S\cdot 2HCl$	C, H, Cl, N, SH
36	$(CH_2)_5C(C_6H_5)$	E[kk]	50	36	125–130 (0.6)	209–211	$C_{14}H_{21}NS\cdot HCl$	C, H, Cl, N, SH
37		E[ll]	63	36	124 (0.1)	244–247	$C_{14}H_{27}NS\cdot HCl$	C, H, Cl, N, S, SH
38	$(CH_2)_{11}CH$	E[k]	72	55	103–105 (0.3)	184–186	$C_{14}H_{29}NS\cdot HCl$	C, H, Cl, N, SH
39	$(CH_2)_5CH(CH_2)_6$	F	...	48	...	212–214	$C_{14}H_{29}NS\cdot HCl$	C, H, N, SH
40	$CH_3(CH_2)_9N(CH_3)(CH_2)_3$	E	60	13	145 (0.2)	184–185	$C_{16}H_{36}N_2S\cdot 2HCl$	C, H, Cl, N, S; SH[mm]
41	$CH_3(CH_2)_{11}O(CH_2)_3$	E[nn]	44	23	155–156 (0.1)	224–226	$C_{17}H_{37}NOS\cdot HCl$	C, H, Cl, N, S; SH[oo]
42		E[nn]	30	24	120–125 (0.1)	*pp*	$C_{17}H_{37}NOS\cdot HCl$	C, H, N, SH
43		E[qq]	...	23	...	243–246	$C_{22}H_{35}NS\cdot HCl$	C, H, Cl, N, SH
	Hydrazines, $RNHCH_2CH_2SH$[rr]							
44	$(CH_3)_2N$	F	77	...	63–64 (20)	...	$C_4H_{12}N_2S$	C, H, N
45	$(CH_3)_2N$	F	...	...	...	50–55	$C_4H_{12}N_2S\cdot C_6H_8O_7$[ss]	C, H, N, S
46	$CH_3(CH_2)_7NH$	F[tt]	...	4	...	90–100	$C_{10}H_{24}N_2S\cdot HCl$	C, H, S; N[uu]
47	$C_6H_5CH_2CH(CH_3)NH$	F[vv]	...	52	...	*ww*	$C_{11}H_{16}N_2S\cdot HCl$	C, H, Cl, N

Carbon Corp. [e] From DL-2-aminooctanol: O. Vogl and M. Pöhm, *Monatsh. Chem.*, **84**, 1097 (1953). [f] From DL-norephedrine. [u] SH: calcd, 13.35; found, 12.92. [v] Primary amine: H. R. Ing and W. E. Ormerod, *J. Pharm. Pharmacol.*, **4**, 21 (1952). The thiol was separated as the lead salt from excess starting amine; see preparation of **43** in the Experimental Section. [w] Free base.[2c] [z] SH: calcd, 14.26; found, 14.69. [y] SH: calcd, 14.26; found, 15.14. [z] From D-amphetamine. [aa] Primary amine: F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, C. Weisel, and W. Yanko, *J. Am. Chem. Soc.*, **66**, 725 (1944). [bb] Semisolid. [cc] SH: calcd, 12.16; found, 11.60. [dd] SH: calcd, 13.79; found, 14.89. [ee] Primary amine from Tennessee Eastman Chemical Co. [ff] A 4% yield of the corresponding disulfide dihydrochloride also was obtained, mp 211–213°. *Anal.* ($C_{24}H_{38}NO_4S_2\cdot 2HCl$) C, H, Cl, S. [gg] Not distilled; from pot residue after distillation of starting amine. [hh] 2-(*o*-Ethoxyphenoxy)ethylamine was supplied by Dr. R. W. Fleming, Parke, Davis and Co. [ii] SH: calcd, 11.90; found, 12.33. [jj] 3-(*o*-Ethoxyphenoxy)propionitrile was catalytically (Raney Co) hydrogenated to 3-(*o*-ethoxyphenoxy)propylamine, bp 110–118° (1 mm). *Anal.* ($C_{11}H_{17}NO_2$) C, H. [kk] Primary amine: Parke, Davis and Company, British Patent 853,775 (1960); *Chem. Abstr.*, **55**, 13383 (1961). [ll] Primary amine from Dow Chemical Co. [mm] SH: calcd, 9.15; found, 8.00 [nn] Primary amine from Chemical Intermediates and Research Laboratories, Inc. [oo] SH: the sample was insoluble and gave a cloudy end point. [pp] One equivalent of 1 *N* HCl was added to freshly distilled free base and the solution was evaporated to dryness to obtain the semisolid product. [qq] Primary amine, Rosin Amine D from Hercules Powder Co. [rr] Iodine titrations of hydrazines gave erratic results. [ss] Monocitrate salt prepared in 62% yield in MeOH from the thiol and an equivalent of citric acid; recrystallized from MeOH–Et_2O. [tt] After cleaving the benzyl group the product was extracted into Et_2O and crude product was precipitated by dry HCl. [uu] N: calcd, 11.63; found, 11.19. [vv] See *tt* for modification of method F. [ww] Amorphous solid.

bispropylamine Dihydrochloride.—Reduction of 88 g (0.4 mole) of 2-(benzylthio)-N-cyclopropylacetamide (Table II, footnote *f*) with 17 g (0.45 mole) of $LiAlH_4$ was allowed to continue for 40 hr in 500 ml of refluxing THF. Work-up as for **57** gave 45 g of crude HCl salt. Recrystallization from EtOH–Et_2O gave 15 g of salt, mp 140–144°. Another recrystallization gave N-[2-(benzylthio)-ethyl]propylamine hydrochloride (**51**): mp 144–146°; nmr (DMSO-d_6), δ 9.4 (m, 2, $^+NH_2$), 7.35 (s, 5, C_6H_5), 3.75 (s, 2, $C_6H_5CH_2$), 2.8 (m, 6, $SCH_2CH_2NCH_2$), 1.6 (m, 2, CCH_2C), and 0.95 ppm (t, 3, J = 6 Hz, CH_3). The inorganic salt cake was continuously extracted with Et_2O for 20 hr. The Et_2O extract was washed with saturated NaCl solution, dried ($MgSO_4$), and treated with dry HCl to give a solid. Recrystallization of the solid from EtOH–Et_2O resulted in 15 g of white powder, mp 117–180°, and a small second crop, mp 235–244°. Recrystallization of the second crop from EtOH gave the disulfide, mp 258–262° dec.

Anal. ($C_{10}H_{24}N_2S_2\cdot 2HCl$) C, H, Cl, N, S, SH.

DL-2-{[2-(Benzylthio)ethyl]amino}-3-methyl-1-butanol.—Methyl DL-2-[2-(benzylthio)acetamido]-3-methylbutyrate was prepared as a crude oil (117 g, 85%) from 85 g (0.5 mole) of DL-valine methyl ester hydrochloride and 100 g (0.5 mole) of (benzylthio)acetyl chloride (see preparation of **57**). Reduction of the N-acylvaline methyl ester was achieved by treating the oil successively in refluxing Et_2O with 3–17-g portions of $LiAlH_4$ a-total of 50 g, 1.3 moles, of $LiAlH_4$ and 5 days at reflux tempera) ture). Distillation of the crude product resulted in 31 g (30%) of amino alcohol, bp 130–135° (0.05 mm). The structure was verified by conversion to DL-2-[(2-mercaptoethyl)amino]-3-methyl-1-butanol hydrochloride (**6**) by the method used for **39**.

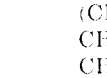
Reduction of 2-(Benzylthio)acetohydroxamic Acid Methyl Ester.—Reaction of 100 g (1.2 moles) of methoxyamine hydrochloride with 240 g (1.2 moles) of (benzylthio)acetyl chloride (see preparation of **57**) resulted in 178 g of crude oily 2-(benzylthio)-acetohydroxamic acid methyl ester. Reduction of 100 g (0.47 mole) of the amide in 1450 ml of Et_2O and 50 ml of THF with 21.6 g (0.57 mole) of $LiAlH_4$ was allowed to proceed for 2.5 days at reflux temperature. Crude product was distilled to give 18 g (33%) of 2-(benzylthio)ethylamine, bp 82–85° (0.1 mm) [lit.[10a] bp 100° (0.8 mm)] and an ir spectrum identical with that of an authentic sample.

N-[2-(Benzylthio)ethyl]cyclohexanehexylamine Hydrochloride (58). Method B.—A solution of 122 g (0.35 mole) of N-[2-(benzylthio)ethyl]cyclohexanehexanamide (Table II, footnote

TABLE II

N-[(2-BENZYLTHIO)ETHYL]ALKYLAMINES

$RNHCH_2CH_2SCH_2C_6H_5 \cdot HCl$

No.	R	Method[a]	Yield, %	Mp, °C	Formula	Analyses
48	CF_3CH_2	B[b]	71	176–177.5	$C_{11}H_{14}F_3NS \cdot HCl$	C, H, N, S
49	CH_3CH_2	B,[c] C	58	169–171	$C_{11}H_{17}NS \cdot HCl$	C, H, N, S
50	$(CH_3)_2N$	A[d]	81[e]	80–85 (0.5)[e]	$C_{11}H_{18}N_2S$	C, H, N
51	$CH_3(CH_2)_2$	[f]		144–146	$C_{12}H_{19}NS \cdot HCl$	C, H, N
52	$CH_3(CH_2)_7$	A[g]	20	194–196.5	$C_{17}H_{29}NS \cdot HCl$	C, H, Cl, N, S
53	$CH_3(CH_2)_7NH$	C	49	92–95	$C_{17}H_{30}N_2S \cdot HCl$	C, H, N
54		C	38	142–143	$C_{15}H_{21}NS \cdot HCl$	C, H, N
55	$C_6H_5CH_2CH(CH_3)NH$	C[h]	30	99–102	$C_{13}H_{24}N_2S \cdot HCl$	C, H, N
56	$(CH_2)_5CHCH_2CH(CH_2OH)$	D	29	111–114	$C_{18}H_{29}NOS \cdot HCl$	C, H, N, S
57	$2\text{-}CH_3OC_6H_4OCH_2CH(OH)CH_2$	A	29	118–120	$C_{19}H_{25}NO_3S \cdot HCl$	C, H, N
58	$(CH_2)_5CH(CH_2)_6$	B[i]	73	175–177	$C_{21}H_{35}NS \cdot HCl$	C, H, N

[a] A, $RNHCOCH_2SCH_2C_6H_5 + LiAlH_4$; B, $RCONHCH_2CH_2SCH_2C_6H_5 + LiAlH_4$; C, $RNHCOCF_3 + C_6H_5CH_2SCH_2CH_2Cl \xrightarrow{NaH}$ $RN(COCF_3)CH_2CH_2SCH_2C_6H_5 \xrightarrow{H_2O} RNHCH_2CH_2SCH_2C_6H_5$; D, $RNH_2 + ClCH_2CH_2SCH_2C_6H_5 + Na_2CO_3$. [b] Intermediate N-[2-(benzylthio)ethyl]-2,2,2-trifluoroacetamide, bp 100° (0.05 mm). Treatment of **48** with sodium in liquid ammonia gave only N,N'-(dithiodiethylene)bis-2,2,2-trifluoroethylamine dihydrochloride, mp 251–253° dec. *Anal.* ($C_8H_{14}F_6N_2S_2 \cdot 2HCl$) C, H, N, SH. [c] Intermediate N-[2-(benzylthio)ethyl]acetamide, bp 150–160° (0.03 mm). [d] (Benzylthio)acetic acid 2,2-dimethylhydrazide was obtained from (benzylthio)acetyl chloride and 1,1-dimethylhydrazine in 80% yield; mp 55–56° from C_6H_6–hexane. *Anal.* ($C_{11}H_{16}N_2OS$) C, H, N. Reduction of the amide was effected in THF. [e] Yield and boiling point are for free base. [f] $C_6H_5CH_2SCH_2CONHCH(CH_2)_2 + LiAlH_4$. 2-(Benzylthio)-N-cyclopropylacetamide (mp 53–56°) was prepared in 84% yield from cyclopropylamine and (benzylthio)-acetyl chloride. *Anal.* ($C_{12}H_{15}NOS$) C, H, N. [g] Intermediate 2-(benzylthio)-N-octylacetamide was obtained in 52% yield, bp 160–170° (0.2 mm). *Anal.* ($C_{17}H_{27}NOS$) H, N; C: calcd, 69.56; found, 69.13. [h] Acylation of DL-(α-methylphenethyl)hydrazine (Catron[R], Lakeside Laboratories) by trifluoroacetic anhydride resulted in a 63% yield of liquid DL-1-(α-methylphenethyl)-1,2-bis(trifluoroacetyl)hydrazine, bp 88–90° (0.05 mm). *Anal.* ($C_{13}H_{12}F_6N_2O_2$) C, H, N. [i] N-[2-(Benzylthio)ethyl]cyclohexanehexamide (mp 59–60°) was prepared in 88% yield from cyclohexanehexanoyl chloride [J. S. Mihina and R. M. Herbst, *J. Org. Chem.*, **15**, 1082 (1950)] and 2-(benzylthio)ethylamine. *Anal.* ($C_{12}H_{33}NOS$) C, H.

h) in 500 ml of Et_2O was added in a slow stream to a mixture containing 13.5 g (0.35 mole) of $LiAlH_4$ in 1 l. of Et_2O. The mixture was stirred and heated under reflux for 48 hr and stirred at 25° for 24 hr. Product was isolated as in the preparation of **54** to give 118 g (91%) of crude material, mp 170–175°. Recrystallization of a 10-g portion from EtOH–Et_2O gave 8 g of **58**, mp 175–177°.

2-[(6-Cyclohexylhexyl)amino]ethanethiol Hydrochloride (39). Method F.—To *ca.* 1.2 l. of refluxing liquid NH_3 were added 11.8 g (0.32 mole) of **58** and then 24 g of Na pellets over a period of 1 hr. The mixture became yellow-brown before turning dark. The NH_3 was allowed to evaporate and the flask was evacuated and then flushed with N_2. Crushed ice, 300 ml of H_2O, and 100 ml of concentrated HCl were added to the dry cake. The water-insoluble precipitate was washed with H_2O and Et_2O. The product was recrystallized from EtOH–Et_2O to give 53 g of product, mp 205–212°. Another 12 g of solid (mp 210–212°) was recovered from the filtrate. The 53-g crop was dissolved in warm EtOH; the solution was cooled and filtered to give 3.5 g of solid disulfide, mp 245–250°. Ether was added to the filtrate to give 38 g (42%) of **39**, mp 212–214°.

***trans*-N-[2-(Benzylthio)ethyl]-2-phenylcyclopropylamine Hydrochloride (54). Method C.**—A solution of 63 g (*ca.* 0.27 mole) of crude *trans*-2,2,2-trifluoro-N-(2-phenylcyclopropyl)acetamide[19] in 300 ml of toluene was added to a slurry of 6.9 g (13 g of 53% oil dispersion) of NaH in 200 ml of toluene. The addition of 60 ml of THF was required to effect a single liquid phase. The mixture was stirred for *ca.* 4 hr at 25° before adding 51 g (0.27 mole) of benzyl 2-chloroethyl sulfide. The mixture was gently refluxed for 16 hr, cooled, and decomposed with H_2O. The organic layer was separated, washed (H_2O), dried, and concentrated. A solution of the oily residue in 600 ml of MeOH containing 50 ml of concentrated HCl was refluxed for 16 hr. Concentration of the solution to a small volume resulted in separation of 23 g of white solid, mp 135–140°. The filtrate was diluted with 400 ml of MeOH and 50 ml of concentrated HCl, and the mixture was refluxed for 40 hr to give an additional 11 g of product (32% yield). Recrystallization of a small sample from EtOH gave **54**, mp 142–143°.

N-Cyclopropyl-2,2,2-trifluoroacetamide.—To 200 g of trifluoroacetic anhydride was added cautiously at about −70° 40 g (0.7 mole) of cyclopropylamine. The mixture was allowed to warm to 25° and to stand at this temperature for 16 hr. Concentration of the solution at reduced pressure gave an oil which was taken up in Et_2O, and the resulting solution was washed with H_2O, saturated $NaHCO_3$, and saturated NaCl. The Et_2O solution was dried and concentrated to give 76 g of oil which was crystallized from hexane–cyclohexane–Et_2O to give 24 g (20%) of the amide, mp 38–41°.

Anal. ($C_5H_6F_3NO$) C, H, N.

2-(Cyclopropylamino)ethanethiol Hydrochloride (1).—Alkylation of 55 g (0.36 mole) of N-cyclopropyl-2,2,2-trifluoroacetamide using 67 g (0.36 mole) of benzyl 2-chloroethyl sulfide as in the preparation of **54** gave 84 g (80%) of N-[2-(benzylthio)ethyl]-N-cyclopropyl-2,2,2-trifluoroacetamide: mp 130–135° (0.01 mm); nmr ($CDCl_3$), δ 7.34 (s, 5, C_6H_5), 3.74 (s, 2, $C_6H_5CH_2$), 3.60 (t, 2, J = 7 Hz, SCH_2CH_2), 2.7 (m, 1, NC*H*), 2.62 (t, 2, J = 7 Hz, CH_2N), and 0.83 ppm [m, 4, $(CH_2)_2C$]. Conversion to **1** was by the method used to prepare **39**.

1-[2-(Benzylthio)ethyl]-2-octylhydrazine (53).—1-Octyl-1,2-bis(trifluoroacetyl)hydrazine was prepared in 70% yield from octylhydrazine[20] and trifluoroacetic anhydride; bp 165° (20 mm), 115–123° (0.7 mm).

Alkylation of 73 g (0.2 mole) of 1-octyl-1,2-bis(trifluoroacetyl)-hydrazine using 40 g (0.2 mole) of benzyl 2-chloroethyl sulfide was accomplished as described for the preparation of **54**. Hydrolysis in the refluxing MeOH–HCl was continued for 48 hr. Crude solid product was recrystallized from EtOH–Et_2O to give 28 g (39%) of **53**, mp 92–95°. An additional 7 g (10%) of **53** was obtained by further hydrolysis of material obtained from the crystallization liquor.

DL-2-[2-(Benzylthio)ethylamino]-3-cyclohexyl-1-propanol Hydrochloride (56). Method D.—A solution of 189 g (0.82 mole) of methyl DL-tyrosinate hydrochloride in 1 l. of MeOH containing 10 g of 10% Rh–C was treated for 43 hr at 25° under H_2 at about 3 atm. The oily product (193 g), obtained after removal of catalyst and solvent and after conversion to the free base, was treated in Et_2O with 49 g (1.3 moles) of $LiAlH_4$ to reduce the ester group. This process gave 50 g (*ca.* 35%) of a clear yellow oil which was characterized by ir spectrum as an amino alcohol, presumably β-aminocyclohexanepropanol.[21] A mixture of the amino alcohol, 28 g (0.15 mole) of benzyl 2-chloroethyl sulfide,

(19) Preparation of this amide and its alkylation by methyl iodide are given in ref 9.

(20) O. Westphal, *Ber.*, **74**, 759 (1941).

(21) J. N. Ashley and M. Davis, *J. Chem. Soc.*, 63 (1952).

8.5 g (0.08 mole) of Na_2CO_3, and 150 ml of absolute EtOH was refluxed for 2.5 hr. The hot supernatant solution was decanted from inorganic salts and concentrated. The oily residue was acidified by addition of 50 ml of 6 *N* HCl and to this mixture was added Et_2O; the solid which separated amounted to 17 g (29%), mp 108–112°, uv maxima (MeOH) at 260 mμ (ε 260) and 267 mμ (ε 171). The aqueous filtrate was concentrated to dryness and the residue was treated with MeOH and Et_2O to give a second solid which was devoid of uv absorption for phenyl, 18 g, mp 175–185°. A portion of the 17-g crop was recrystallized three times from EtOH–Et_2O to give pure **56**: mp 111–114°; nmr ($CDCl_3$), δ 8.9 (m, 2, $^+NH_2$), 7.36 (s, 5, C_6H_5), 4.63 (m, 1, *OH*), 3.80 (s, 2, $C_6H_5CH_2S$), 3.80 (m, 2, CH_2O), 3.00 (m, 5, SCH_2CH_2NCH), and 1.3 ppm (m, 13, $C_6H_{11}CH_2$).

[(2-Mercaptoethyl)amino]acetaldehyde Diethyl Acetal (8). Method E.—A solution of 80 g (0.62 mole) of aminoacetaldehyde diethyl acetal and 250 ml of toluene was dried by azeotropically distilling H_2O with the use of a Dean–Stark trap. To the refluxing solution was added slowly 31.5 g (0.21 mole) of ethyl 2-mercaptoethyl carbonate using techniques previously described.[4] The mixture was stirred and refluxed for 14 hr, and then distilled to give forerun of aminoacetaldehyde diethyl acetal, and 18.5 g (45%) of **8**, bp 74° (0.2 mm).

A solution of 5 g (0.026 mole) of **8** in dry Et_2O was treated with dry HCl to obtain 5 g (84%) of **9**, mp 95–97°.

2-{[(1,2,3,4,4a,9,10,10a-Octahydro-7-isopropyl-1,4a-dimethyl-1-phenanthryl)methyl]amino}ethanethiol Hydrochloride (43).—A reaction employing 45 g (0.16 mole) of commercial Rosin Amine D[22] and 8 g (0.05 mole) of ethyl 2-mercaptoethyl carbonate was carried out as described above for **8**. The toluene was evaporated and the residue was taken up in *ca.* 500 ml of EtOH. A solution of 9.9 g (0.026 mole) of lead acetate trihydrate in 50 ml of H_2O was added dropwise with stirring. Decantation of the solvent left a gummy solid which was crystallized from 65 ml of heptane to give 15 g of solid. Recrystallization from EtOH–H_2O gave 10 g of the lead salt (mp 112–116°) which was then dissolved in 500 ml of C_6H_6 and the solution was saturated with H_2S. The C_6H_6 solution was separated and concentrated, and the residue was dissolved in Et_2O. The HCl salt, formed by the addition of dry HCl, was recrystallized from EtOH–Et_2O to give 4.6 g (23%) of **43**, mp 243–246°.

2,2,2-Trifluoro-N-(2-mercaptoethyl)-N-octylacetamide.—To 70 g of trifluoroacetic anhydride was slowly added at *ca.* −50° with stirring 15 g (0.08 mole) of 2-(octylamino)ethanethiol.[23] The mixture was allowed to stir at 25° for 4 hr. Excess anhydride was removed at reduced pressure and a solution of the residue in MeOH was stored at 25° for 3.5 hr. The MeOH was evaporated and dilute $NaHCO_3$ was added to the residue. The slurry was extracted with Et_2O and the extract was washed successively with H_2O, saturated NaCl, dilute HCl, and again with saturated NaCl. The Et_2O solution was dried ($MgSO_4$) and concentrated to give 22 g of crude oil. Distillation resulted in 2 g of forerun and 15 g (66%) of product, bp 77–78° (0.05 mm).

Anal. ($C_{12}H_{22}F_3NOS$) C, H, N, SH.

5-(Hydroxymethyl)-2-pyrrolidinone.—A solution of 147 g (1.0 mole) of L-glutamic acid in 400 ml of H_2O containing 10 g of charcoal and 1 ml of aqueous perrhennic acid (1.5 g of Re/ml) was hydrogenated for 5 days at 200° under H_2 at about 300 atm. The mixture was filtered and the filtrate was concentrated and distilled to give 55.5 g (48%) of 5-(hydroxymethyl)-2-pyrrolidinone as a viscous liquid: bp 153–160° (0.25 mm) [lit.[24] bp 185–187° (4 mm)]; nmr ($CDCl_3$), δ 7.5 (m, 1, *NH*), 4.6 (m, 1, *OH*), 3.6 (m, 3, $CHCH_2O$), and 2.1 ppm (m, 4, CH_2CH_2).

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(22) For a description of the primary amine see W. J. Gottstein and L. C. Cheney, *J. Org. Chem.*, **30**, 2072 (1965). It has not been established whether the product was contaminated with derivatives of dihydroabietylamine and tetrahydroabietylamine.

(23) Supplied by Dr. T. R. Sweeney.

(24) J. C. Sauer and H. Adkins, *J. Am. Chem. Soc.*, **60**, 402 (1938).

Molecular Orbital Methods in the Study of Cholinesterase Inhibitors

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It has been suggested that the ability of 3-hydroxyphenyltrimethylammonium derivatives (3-HPTA) to inhibit acetylcholinesterase competitively depends on the strength of the hydrogen bond between the 3-hydroxy group of these derivatives and the esteratic site of AChE. However, the results of previous simple Hückel calculations did not appear to be related to the observed inhibition constants. Using very empirical molecular orbital (MO) methods, we have calculated some σ and π properties of these derivatives and have obtained a correlation which is consistent with a hydrogen-bonding interaction between the 3-hydroxy group of these compounds and the AChE receptor site.

In recent years there has been a pronounced trend toward the application of molecular orbital (MO) methods to questions of pharmacological interest. Successful correlations of drug activity with one or more of the indices derived by these procedures have been reported for hallucinogens[2] and other neurotropic drugs,[3] for batericides[4] and bacteriostats,[5] for antidiuretics,[6] and, most notably, for cholinergic substances.[7–13]

Interestingly, the inhibition potency of 3-hydroxyphenyltrimethylammonium (3-HPTA) derivatives

(1) Trainee, National Institutes of Health Training Grant 2T1-GM-484.

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