Azidobenzenes. The amines[8] were converted to the corresponding azides using procedure A or B of Smith and Brown[9] with the following modifications: When procedure B was employed, sodium nitrite was used in place of amyl nitrite. Furthermore, in each case, the azide was isolated from the aqueous mixture by extraction with a suitable solvent. The extracts were washed with water and carbonate solution, dried and evaporated at reduced pressure at 40–45°. All the azides were purified by chromatography on Woelm alumina, activity grade one (wt. ratio 10:1).

2-Isopropylazidobenzene (I) was formed in 68% yield by procedure B. The crude product was extracted with petroleum ether (b.p. 30–60°) and chromatographed in the same solvent.

Anal. Calcd. for $C_9H_{11}N_3$: C, 67.05; H, 6.88; N, 26.07. Found: C, 67.01; H, 6.75; N, 26.28.

2-Butylazidobenzene (II) was prepared, using procedure B, in 62% yield. The product was extracted with petroleum ether and chromatographed in this solvent.

Anal. Calcd. for $C_{10}H_{13}N_3$: C, 68.58; H, 7.48; N, 23.98. Found: C, 68.52; H, 7.36; N, 24.21.

o-Azidobenzyl alcohol (III) was obtained in 73% yield using procedure A. The product was extracted with benzene and purified by sublimation (60°/1 mm.); m.p. 52–53°.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.18. Found: C, 56.60; H, 4.81; N, 27.98.

2,6-Dimethylazidobenzene (IV) was obtained in 62% yield by procedure A. The crude product was extracted with petroleum ether and chromatographed.

Anal. Calcd. for $C_8H_9N_3$: C, 65.28; H, 6.16; N, 28.55. Found: C, 65.51; H, 6.42; N, 28.50.

2-(Trifluoromethyl)azidobenzene (V) was prepared in 68% yield using procedure B and was extracted with petroleum ether and chromatographed with this solvent.

Anal. Calcd. for $C_7H_4N_3F_3$: C, 44.93; H, 2.15; N, 22.46. Found: C, 45.10; H, 2.11; N, 22.42.

Azidobenzene (VI) was prepared in 90% yield using procedure A. The crude product was extracted with petroleum ether and chromatographed with the same solvent. Its infrared spectrum (neat) showed absorption characteristic of the N_3 group at 4.70–4.75 μ.[10]

Pyrolysis of the azides. The azides were vaporized at ambient temperatures and reduced pressure (0.1–0.3 mm.) in a stream of nitrogen. (The nitrogen was introduced by means of a fine capillary tube, and in the case of the liquid azides was bubbled through the liquid.) The vapors passed through a 3″ section of 15 mm. tubing packed with 1/8″ pyrex helices and maintained at 350–360° by means of an externally heated coil of nichrome wire. The products from the reactions were trapped in a cold finger at Dry Ice temperatures.

2-Isopropylazidobenzene (I, 235 mg.) gave 130 mg. of a liquid mixture which was separated by vapor phase chromatography[11] into two fractions. The major product (104 mg. 55%) was shown to be dihydroskatole by a comparison of its infrared spectrum (neat) with that of an authentic sample. The minor product could not be identified.

2-Butylazidobenzene (II, 1.15 g.) on pyrolysis gave 850 mg. of a pale yellow liquid having an infrared spectrum (neat) and ultraviolet spectrum in neutral (λ_{max} 293 mμ) and acidic (λ_{max} 249 mμ) ethanol consistent with that for an *o*-aminobenzene derivative.[12] This mixture was heated for 15 hr. at 200–210° with 60 mg. of 10% palladized carbon. The resulting mixture was taken up in ether and separated into neutral (427 mg.) and basic (246 mg.) fractions. The basic material was not 2-methylquinoline as shown by a comparison of its infrared spectrum with that of an authentic sample. The neutral product (2-ethylindole) was chromatographed on 15 g. of Merck acid-washed alumina in benzene. The colorless crystals thus obtained were recrystallized from petroleum ether and had a m.p. of 44–45° (lit.[13] m.p. 43°).

o-Azidobenzyl alcohol (III, 366 mg.) when pyrolyzed gave 130 mg. (65%) of a yellowish oil having an infrared spectrum (neat) consistent with that for *o*-aminobenzaldehyde (N—H: 2.85 μ, 2.95 μ; CO—H: 3.65 μ; and C = O: 6.0 μ). The phenylhydrazone derivative of this material had a m.p. of 223–224°. The reported m.p. of *o*-aminobenzaldehyde phenylhydrazone is 222°.[14]

2,6-Dimethylazidobenzene (IV, 289 mg.) when pyrolyzed formed an amorphous solid (154 mg.) having an infrared spectrum (carbon tetrachloride) exhibiting N-H absorption.

2-(Trifluoromethyl)azidobenzene (V, 353 mg.) formed a solid which when sublimed (60°/0.1 mm.) yielded 240 mg. (80%) of 2,2′-bis(trifluoromethyl)azobenzene (XVII). This material was recrystallized readily from methanol; m.p. 129–130°; the electronic absorption spectrum in cyclohexane exhibited three maxima and two shoulders, λ in mμ(ε): 230 (13,500); 307 (18,000); 318 (19,600); 330 (16,700); 453 (274).

Azidobenzene (VI, 411 mg.) yielded a dark oil which on sublimation (80°/0.3 mm.) gave 225 mg. (72%) of an orange solid of m.p. 65–67°. This material was shown to be azobenzene by a comparison of its melting point, mixed melting point and infrared spectrum (carbon tetrachloride solution) with that of an authentic sample.

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[8] Aniline, 2,6-dimethylaniline, and 2-(trifluoromethyl)-aniline are available commercially. The preparation of *o*-aminobenzyl alcohol has been described by A. Reissert and K. Crämer [*Ber.*, **61**, 2558 (1928)] and that of 2-isopropylaniline by G. Smolinsky (*J. Am. Chem. Soc.*, **83**, 2489 (1961)).

[9] P. A. S. Smith and B. B. Brown, *J. Am. Chem. Soc.*, **73**, 2438 (1951).

[10] E. Lieber, C. N. R. Rao, T. S. Chao and C. W. W. Hoffman, *Anal. Chem.*, **29**, 9161 (1957).

[11] A. Beckman GC-2 gas chromatograph having a 10′ column packed with Uconpolar on Fluoropak was used. A temperature of 210° and pressure of 30 p.s.i. gave good separation.

[12] T. Masamune, *J. Am. Chem. Soc.*, **79**, 4418 (1957).

[13] A. Verley and J. Beduivé, *Bull. soc. chim. France*, [4] **37**, 190 (1925).

[14] J. Eliasberg and P. Friedlander, *Ber.*, **25**, 1753 (1892).

2-Mercapto-2-phenylethylamine[1,2]

Walter C. McCarthy and Beng-Thong Ho

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In recent years there has been much interest in mercaptoethylamine and related compounds that contain mercapto and amino groups on

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[2] Presented before the Division of Medicinal Chemistry at the 138th Meeting of the American Chemical Society, N. Y., September 1960.

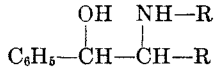
TABLE I

Addition of Thioacetic Acid to β-Nitrostyrene

Run	Time	Temp.	Catalyst	Solvent	M.P. After Recrystallization	Yield, %
1	0.5 hr.	100	None	None	122.5–125	12.7
2	2 hr.	100	None	None	122–124.5	12.4
3	0.5 hr.	100	n-$(C_4H_9)_3N$	None	120–123	8.9
4	Overnight	25	n-$(C_4H_9)_3N$	95% C_2H_5OH	121–123.5[a]	27.6[a]
5	Overnight	25	n-$(C_4H_9)_3N$	Benzene	124–126.5[a]	87[a]

[a] Not recrystallized.

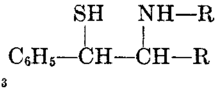
adjacent carbon atoms, as radiation protective agents. A number of widely used pharmaceutical agents contain hydroxy and amino groups on adjacent carbon atoms. We feel that mercapto analogs of these substances are a fertile field for investigation as antiradiation compounds, because they possess a structural moiety associated with high radiation protective activity, and because the parent hydroxy compounds are known to be absorbed and transported to many important widely distributed tissue sites in the body. As both epinephrine and serotonin have been demonstrated to possess radiation protective activity, we decided to initiate our studies with, the synthesis of mercapto analogs of sympathomimetic amines. The first studies reported herewith involve the mercapto analogs (IIa, IIb) of phenylethanolamine (Ia) and ephedrine (Ib).



$C_6H_5-\overset{OH}{CH}-\overset{NH-R}{CH}-R$

I

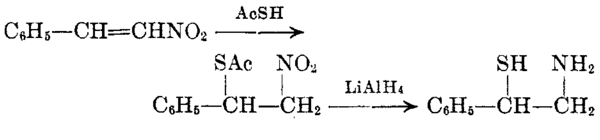
a. R = H
b. R = CH_3



$C_6H_5-\overset{SH}{CH}-\overset{NH-R}{CH}-R$

II

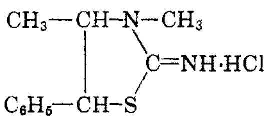
Thioacetic acid was found to add across the carbon-carbon double bond of β-nitrostyrene to produce 1-phenyl-1-acetthio-2-nitroethane. This compound was reduced with lithium aluminum hydride to 2-mercapto-2-phenylethylamine (IIa).



$$C_6H_5-CH{=}CHNO_2 \xrightarrow{AcSH} C_6H_5-\overset{SAc}{CH}-\overset{NO_2}{CH_2} \xrightarrow{LiAlH_4} C_6H_5-\overset{SH}{CH}-\overset{NH_2}{CH_2}$$

As is often the case with polyfunctional compounds, prolonged refluxing with a large excess of lithium aluminum hydride was required to effect this reduction.

An attempt was made to convert ephedrine (Ib) to its mercapto analog (IIb) by the classical procedure involving replacement of the alcohol group by chloride, followed by reaction with thiourea to form the corresponding isothiuronium salt, which could be hydrolyzed with base to the mercaptan. The intermediate isothiuronium salt split out ammonium chloride and cyclized to 3,4-dimethyl-5-phenyl-2-iminothiazolidine hydrochloride (III). This substance was hydrolyzed with aqueous sodium hydroxide; neither the free base, IIb, nor its hydrochloride salt could be crystallized, but a solid reineckate was obtained.



III

Because of the low yield and slow reaction of chlorodeoxypseudoephedrine hydrochloride with thiourea in alcohol solution, we studied the use of dimethyl sulfoxide as the solvent for this reaction, following recent reports of the advantageous use of this solvent in promoting high yields and increasing the rate of reactions of alkyl halides with sodium cyanide.[3] Under the conditions which we used, dimethyl sulfoxide was not a satisfactory solvent for the reaction with thiourea. The yield was poor and elemental sulfur was formed in a side reaction.

EXPERIMENTAL[4]

1-Phenyl-1-acetthio-2-nitroethane. Twenty-seven grams (0.181 mole) of β-nitrostyrene[5] was dissolved in 30 ml. of benzene by warming. After cooling to room temperature, 13.8 g. (0.181 mole) of thioacetic acid and 5 drops of tri-*n*-butylamine were added. An exothermic reaction occurred, and the solution turned green, then brown. After standing overnight, the white crystals were collected by suction filtration and washed with cold alcohol; yield, 35.5 g. (87%), m.p. 124–126.5°. After recrystallization from 95% ethanol, there was obtained 33.9 g. of white crystals, m.p. 125–127°. The analytical sample was obtained *via* two further recrystallizations from ethanol to give white needles, m.p. 124.5–125.5°.

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[3] R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960); L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 877 (1960).

[4] All melting points are uncorrected.

[5] D. E. Worall, *Org. Syntheses*, **Coll. Vol. I**, 413 (1941).

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.27; H, 4.92; N, 6.22; S, 14.24. Found: C, 53.47; H, 5.33; N, 6.15; S, 14.35.

Several sets of experimental conditions were tried to determine the procedure most appropriate for this compound. These are shown in Table I.

2-Mercapto-2-phenylethylamine (IIa). Anhydrous ether (1100 ml.) and 33.5 g. (0.8 mole) of lithium aluminum hydride were introduced into a 2-l. three-necked flask fitted with a sealed stirrer and a reflux condenser protected with a drying tube. The mixture was refluxed for 3 hr. Then the reflux condenser was replaced with a Soxhlet extractor containing a thimble packed with 45.2 g. (0.2 mole) of 1-phenyl-1-acetthio-2-nitroethane. The condenser of the Soxhlet extractor was also protected with a drying tube. Continuous extraction was carried out for 260 hr.; at the end of this time, 0.98 g. of the thio ester remained in the thimble. The reaction complex and unchanged lithium aluminum hydride were then hydrolyzed by the addition of 58 ml. of water introduced dropwise. Concentrated hydrochloric acid was added dropwise in the amount (66.3 ml., 0.8 mole) sufficient to form the salt with the lithium ion present but not with the alumina. Careful attention to the neutralization of the reaction mixture was found necessary, in order to extract the amphoteric mercaptoamine product with organic solvents. The mixture was filtered through an asbestos mat and the alumina precipitate was washed with several portions of ether. After evaporation of the filtrate to dryness, there remained 9.5 g. of pale yellow solid. Two recrystallizations from 95% ethanol gave 3.4 g. of white solid, m.p. 94–97°. The alumina residue above was placed in a Soxhlet extractor and extracted with ether for 50 hr. Evaporation of this extract gave an additional 14.9 g. of crude product. After one recrystallization from 95% ethanol three was obtained 9.0 g. of white solid, m.p. 95.5–97.5°; total yield 12.4 g. (41%). A sample, after further recrystallization from ethanol and vacuum sublimation, showed a m.p. of 97.5–98.5°. The mercaptan group was determined by oxidation to disulfide,[6] titrating samples iodometrically.

Anal. Calcd. for $C_8H_{11}NS$: Equiv. wt., 153.25. Found: 153, 149, 147.

Elemental quantitative analyses, as well as an infrared absorption peak at 1630 cm.$^{-1}$, indicated the presence of a small amount of bound carbon dioxide in all samples.

2-Mercapto-2-phenylethylamine hydrochloride. Dry hydrogen chloride was bubbled through an ether solution of the sublimed amine. The crude hydrochloride was collected in 98% yield by centrifugation, m.p. 160–161.5°. After two recrystallizations from isopropyl alcohol, the m.p. was 160.5–161.5°.

Anal. Calcd. for $C_8H_{12}ClNS$: C, 50.65; H, 6.38; Cl, 18.69; N, 7.38; S, 16.90. Found: C, 50.78; H, 6.15; Cl, 18.59; N, 7.25; S, 16.87.

Chlorodeoxypseudoephedrine hydrochloride.[7] This was prepared by reaction of l-ephedrine hydrochloride with thionyl chloride in chloroform, and recrystallized from ethyl alcohol, m.p. 196–197°, $[\alpha]_D^{25} + 119°$ (*C*, 1 water). Emde[7] reported a m.p. of 201°, $[\alpha]_D^{20} + 117°$.

3,4-Dimethyl-5-phenyl-2-iminothiazolidine hydrochloride (III). A mixture of 44 g. (0.2 mole) of chlorodeoxypseudoephedrine hydrochloride and 30.5 g. (0.4 mole) of thiourea in 500 ml. of absolute ethyl alcohol was heated under reflux for 88 hr. Upon cooling to room temperature, a white solid separated and was collected by filtration. This substance weighed 5.5 g., did not melt up to 300°, but started subliming at 140°. It was identified as ammonium chloride because of the ammonia odor evolved upon adding it to a cold sodium hydroxide solution and the white precipitate formed upon adding it to an acidified silver nitrate solution. The filtrate from the reaction mixture was evaporated to a gummy mass weighing 70.5 g. This was taken up in 200 ml. of ice cold 5% sodium hydroxide solution and extracted five times with ether. The ether extract was dried over sodium sulfate, saturated with hydrogen chloride gas, and evaporated to dryness to obtain 46 g. of a gummy solid. Two recrystallizations from isopropyl alcohol gave 19.4 g. (40%) of white crystals melting at 245–247°. Another recrystallization from isopropyl alcohol left 12.3 g. (25%) of product, m.p. 246–247°.

Anal. Calcd. for $C_{11}H_{15}ClN_2S$: C, 54.42; H, 6.23; Cl, 14.60; N, 11.54; S, 13.21. Found: C, 54.62; H, 6.23; Cl, 14.46; N, 11.33; S, 12.99.

From a similar run involving 5.5 g. of chlorodeoxypseudoephedrine hydrochloride, 2.1 g. of thiourea, and 50 ml. of dimethyl sulfoxide, stirred at 40° for 32 hr., and then evaporated under reduced pressure at 85°, there was isolated 0.5 g. of ammonium chloride, 0.2 g. of sulfur, and 0.4 g. of cyclized product, m.p. 244–245°.

Mercaptodeoxyephedrine reineckate. 3,4-Dimethyl-5-phenyl-2-iminothiazolidine hydrochloride was hydrolyzed by refluxing for 24 hr. in 5% aqueous sodium hydroxide. The solution was neutralized, then extracted with ether. The ether solution was dried over sodium sulfate, and hydrogen chloride was passed into it. An oil separated which could not be crystallized, nor could the free base be crystallized, but treatment with a solution of reinecke salt gave a pink precipitate of the reineckate, m.p. 123–125°.

Anal. Calcd. for $C_{14}H_{22}CrN_7S_5$: C, 33.58; H, 4.43. Found: C, 33.99; H, 4.37.

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Alkylation Reactions in Dimethyl Sulfoxide[1]

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In the course of other work it became necessary to prepare dimethylmalononitrile and 3,3-dimethyl-2,4-pentanedione. Although both of these compounds have been described the yields are either poor or unspecified.[3,4] We have found that in the usual solvents, *e.g.*, alcohol or benzene, the reaction of methyl iodide with 2,4-pentanedione pro-

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(6) S. Siggia, *Quantitative Organic Analysis via Functional Groups*, J. Wiley and Sons, Inc., New York, 1949, p. 85.

(7) H. Emde, *Helv. Chim. Acta*, 12, 384 (1929).

(1) The author is grateful to Prof. C. S. Marvel for a postdoctoral appointment under a National Science Foundation Grant, G5906.

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(3)(a) Dimethylmalononitrile is prepared in about 30% yield by alkylation of the disilver or disodium salt of malononitrile with methyl iodide; B. C. Hesse, *Am. Chem. J.*, 18, 723 (1896). (b) Treatment of the diamide of dimethylmalonic acid with phosphorus pentoxide also affords dimethylmalononitrile, G. Errera and E. Berté, *Gazz. chim. ital.*, II, 26, 220 (1896). Both methods are general.

(4)(a) Alkylation of the sodium salt of 3-methyl-2,4-pentanedione with methyl iodide at 120–130° in a sealed tube for thirty-five hours gives 3,3-dimethyl-2,4-pentanedione, A. Combes and C. Combes, *Bull. soc. chim., France* [3], 7, 783 (1892). (b) Acylation of methyl isopropyl ketone with acetic anhydride and boron trifluoride gives 3,3-dimethyl-2,4-pentanedione in 28% yield; C. R. Hauser and J. T. Adams, *J. Am. Chem. Soc.*, 66, 345 (1944).