siline.—An ethereal solution containing 0.015 mole of N-methyl-2,2′-dilithiodi-*p*-tolylamine was treated with 4.55 g. (0.015 mole) of dibenzyldichlorosilane[12] in 50 ml. of ether. After the customary reaction procedures and work-up, recrystallization from petroleum ether (b.p. 60–70°) gave 2.67 g. (43%) of colorless crystals, m.p. 123–125°. An additional recrystallization raised the melting point to 124–125.5°.

Anal. Calcd. for $C_{29}H_{29}NSi$: Si, 6.69. Found: Si, 6.87, 6.82.

Reaction of N-Methyl-2,2′-dilithiodi-*p*-tolylamine and *sym*-Tetraphenyldisilane.—N-Methyl-2,2′-dilithiodi-*p*-tolylamine, prepared from 5.75 g. (0.015 mole) of N-methyl-2,2′-dibromodi-*p*-tolylamine and 0.03 mole of *n*-butyllithium, was added to 5.55 g. (0.015 mole) of *sym*-tetraphenyldisilane[13] in 100 ml. of ether, and the reaction mixture stirred at room temperature for 24 hr. Toluene was added, the ether removed by distillation, and the resulting solution refluxed for 12 hr. before Color Test I[11] was negative. After hydrolysis and the usual work-up, the reaction products were chromatographed over alumina with petroleum ether (b.p. 60–70°). The first fractions gave only traces of oils; however, further elution with the same solvent gave a colorless solid which was recrystallized from petroleum ether to give 3.38 g. (58%) of colorless crystals, m.p. 160–165°. An additional recrystallization raised the melting point to 163–165°. This material was identified as 2,5,8-trimethyl-10,10-diphenyl-5,10-dihydrophenazasiline by mixed melting point and by comparison of the infrared spectra. Elution with other solvents gave oils which could not be further purified or identified.

Reaction of N-Methyl-2,2′-dilithiodi-*p*-tolylamine and Triphenylchlorosilane.—An ethereal solution containing 0.03 mole of N-methyl-2,2′-dilithiodi-*p*-tolylamine, prepared by halogen-metal interconversion as described above, was treated with 17.7 g. (0.06 mole) of triphenylchlorosilane in 150 ml. of ether. The reaction mixture was stirred 24 hr. at room temperature, 50 ml. of toluene was added, and then the ether removed by distillation. After heating the toluene suspension at reflux for 4 hr., Color Test I[11] was negative. The reaction mixture was hydrolyzed with water, ether was added, and the resulting solid material was removed by filtration. After washing with ether, the solid was recrystallized from a 1:1 mixture of benzene and petroleum ether (b.p. 60–70°) to give 5.36 g. of colorless needles, m.p. 236–240°. A portion was recrystallized from ethyl acetate to give needles, m.p. 237.5–239°, which was identified as tetraphenylsilane by mixed melting point and by comparison of the infrared spectra.

The combined organic layer and ether washings were dried and evaporated. The residue was chromatographed over alumina. Elution with petroleum ether (b.p. 60–70°), followed by three recrystallizations from absolute ethanol, gave 1.09 g. (6%) of *n*-butyltriphenylsilane, m.p. 86–88°, identified by mixed melting point. Further elution with petroleum ether gave a colorless solid, which was recrystallized two times from ethyl acetate to give 0.28 g. of tetraphenylsilane, m.p. 235–238°.

After continued elution with petroleum ether and then with cyclohexane, there was obtained a colorless solid, which resisted purification by recrystallization. This solid material was subsequently rechromatographed over alumina. Using petroleum ether as the eluent, there was obtained a trace of solid which was recrystallized from ethyl acetate to give 0.17 g. of tetraphenylsilane. This is a total yield of 5.81 g. (58%, based on one half of the silicon). Further elution with petroleum ether and then with cyclohexane gave a colorless solid. This material was recrystallized three times from petroleum ether to give 4.93 g. (42%) of colorless crystals, m.p. 161–165°. A portion was recrystallized from the same solvent raising the melting point to 163–165°. The material was identified as 2,5,8-trimethyl-10,10-diphenyl-5,10-dihydrophenazasiline by mixed melting point and by comparison of the infrared spectra.

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(13) H. Gilman and W. Steudel, *Chem. Ind.* (London), 1094 (1959).

Potential Antiradiation Agents. II. Selenium Analogs of 2-Aminoethylisothiouronium Hydrobromide and Related Compounds[1–3]

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The selenium analogs of 2-aminoethylisothiouronium salts, 2-aminothiazoline, and 2-thioethylguanidine have been prepared.

In view of the considerable effectiveness of aminoethyl mercaptan (cysteamine) and of 2-aminoethylisothiouronium salts (AET) in protecting animals against the effects of ionizing radiation,[4] efforts have been made to prepare even more active analogs of these compounds.

This problem can be approached in several ways: (1) through attachment of the 2-mercaptoethylamino grouping to molecules potentially capable of carrying it to sites where protection is needed;

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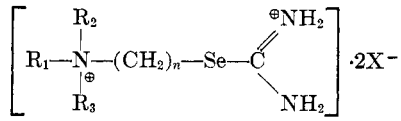
(2) Part of this material was presented before the Medicinal Chemistry Section of the American Chemical Society Meeting, Washington, D.C., March, 1962, 28-N.
(3) S. H. Chu and H. G. Mautner, *J. Org. Chem.*, **26**, 4998 (1961); Part I of this series.
(4) For a review of this field the reader is referred to A. Pihl and L. Eldjarn, *Pharmacol. Rev.*, **10**, 437 (1958).

TABLE I

AMINOALKYLISOSELENOURONIUM SALTS



R_1	R_2	R_3	n	X	M.p., °C.	Reaction time, hr.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Yield, %
H	H	H	2	Br	200–204	0.75	10.98	11.30	3.38	3.40	12.81	12.94	67
H	H	H	3	Br	123	1	14.04	14.16	3.83	3.88	12.28	12.42	69
H	H	CH_3	2	Br	158–161	1	14.04	14.34	3.83	3.95	12.28	12.34	81
H	CH_3	CH_3	2	Cl	170–172	4	22.48	22.58	5.66	5.59	15.73	15.59	44
H	C_2H_5	C_2H_5	2	Cl	206–208	3	28.48	28.79	6.48	6.58	14.23	14.14	50

nucleic acid bases[3] and sugars[5] have been used as such "carriers"; (2) through attachment of slowly hydrolyzable groups to the sulfur of cysteamine to form compounds capable of acting as depots of the radioprotective mercaptan,[3] which might otherwise lose activity on being oxidized to the disulfide form; (3) through the preparation of double-armed and triple-armed analogs of cysteamine[6]; (4) through replacement of the sulfur of radioprotective thiols by selenium.

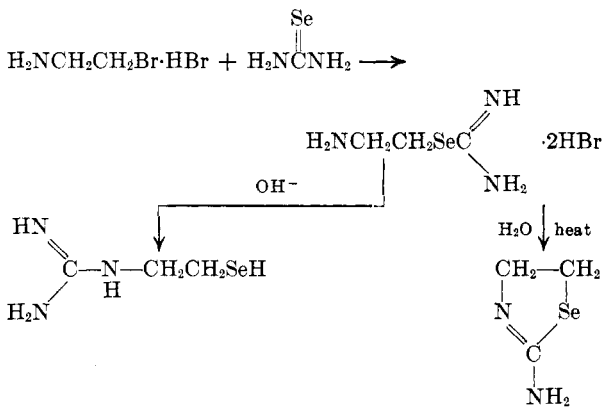
Sulfur has been considered to be essential to the radioprotective action of cysteamine analogs. Its substitution by alkyl groups[4] or its replacement by oxygen[7] leads to loss of such activity; however, it has been shown that the selenium analog of cysteamine[8] can shield mice against radiation.[9]

The atomic radii of sulfur and of selenium are so similar that sulfur and selenium analogs may be assumed to have the same ability of fit receptor sites. In terms of electron distribution and of chemical reactivity, however, sulfur and selenium compounds are rather different.[10–13]

In resonating systems the carbon-selenium bond is more highly polarized than is the carbon-sulfur bond; the latter, in turn, is more highly polarized than the carbon-oxygen bond. These differences in polarization greatly affect the reactivities of isologous oxygen, sulfur, and selenium compounds; for instance, selenoacyl compounds will transfer their acyl groups much more rapidly than the analogous thioacyl compounds.[14]

The antiradiation activity of 2-aminoethylisothiouronium bromide hydrobromide (AET) has been attributed to the ability of this compound to undergo a transformamidination reaction that, through a cyclic intermediate, converts it to 2-mercaptoethylguanidine (MEG).[15,16] Accordingly, the selenium analogs of these compounds were prepared, with a view to the formation of potential antiradiation agents and as model compounds for kinetic studies.

The following reaction sequence was used for the preparation of the selenium compounds



The selenium analog of AET was prepared by the reaction of selenourea with 2-bromoethylamine hydrobromide. Treatment of the selenouronium salt with sodium hydroxide yielded 2-selenoethylguanidine which was isolated as the flavianate salt. The reaction of 2-aminoethylisoselenouronium hydrobromide with boiling water resulted in the formation of 2-aminoselenazoline. The latter compound had been prepared previously by the addition of potassium selenocyanate to 2-bromoethylamine.[17]

Through the reaction of 2-methylaminoethyl, 2-dimethylaminoethyl, and 2-diethylaminoethyl halides with selenourea the corresponding 2-alkylaminoethyl selenouronium salts were obtained. Similarly, 3-aminopropylisoselenouronium hydrobromide was synthesized.

Several of the compounds described have been submitted to the Walter Reed Army Institute of Research for biological testing.

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(10) H. G. Mautner and W. D. Kumler, *J. Am. Chem. Soc.*, **78**, 97 (1956).
(11) H. G. Mautner, *ibid.*, **78**, 5292 (1956).
(12) H. G. Mautner and E. M. Clayton, *ibid.*, **81**, 6270 (1959).
(13) A. J. Parker, *J. Chem. Soc.*, 4398 (1961).
(14) H. G. Mautner and W. H. H. Günther, *J. Am. Chem. Soc.*, **83**, 3342 (1961).
(15) J. X. Khym, R. Shapira, and D. G. Doherty, *ibid.*, **79**, 5663 (1957).
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(17) W. Baringer, *Ber.*, **23**, 1003 (1890).

Experimental[18]

2-Aminoethylisoselenouronium Bromide Hydrobromide.—A solution of 5.78 g. (0.0282 mole) of 2-bromoethylamine hydrobromide and of 3.50 g. (0.0282 mole) of selenourea in 170 ml. of isopropyl alcohol was heated to reflux under a nitrogen atmosphere for 45 min. After cooling the product was removed by filtration. Recrystallization from a 10:1 mixture of ethanol and ethyl acetate yielded 6.20 g. (67%) of product melting at 200–204°.

The isoselenouronium salts shown in Table I were prepared in analogous fashion.

2-Selenoethylguanidine Flavianate.—A solution of 0.25 g. (0.00076 mole) of 2-aminoethylisoselenouronium bromide hydrobromide in 6.5 ml. of 0.2 *N* sodium hydroxide (pH 7.0–7.2) was left to stand at room temperature for 15 min. Addition of 1.0 ml. of 1 *M* aqueous flavianic acid resulted in the formation of a yellow precipitate which was washed successively with ice-cold water, ethanol, and ethyl acetate. Recrystallization from ethyl alcohol gave rise to a yield of 0.25 g. (68%) of material decomposing at 164°.

Anal. Calcd. for $C_{13}H_{15}N_5O_8Se$: C, 32.57; H, 3.12; N, 14.58. Found: C, 33.04; H, 3.26; N, 14.69.

2-Aminoselenazoline Hydrobromide.—A solution of 0.5 g. (0.0015 mole) of 2-aminoethylisoselenouronium bromide hydrobromide in 25 ml. of water was heated to reflux for 45 min. and then evaporated to dryness under reduced pressure. The residue was recrystallized twice from a 5:2 ethanol–ethyl acetate mixture to give a yield of 0.35 g. (70%) of product melting at 170–171°. A mixed melting point with an authentic sample[17] showed no depression.

(18) All melting points are uncorrected. Analyses were carried out at Midwest Microlab, Inc., Indianapolis, Indiana.

Synthesis and Anticholinergic Activity of Ester Derivatives of Substituted 3-Pyrrolidinols

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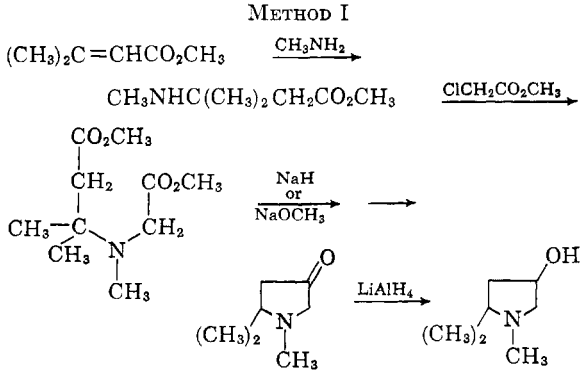
The preparation and preliminary pharmacological evaluation of eighteen ester derivatives of 3-pyrrolidinols are described.

A previous publication[1] recorded some ester derivatives of 2-substituted piperidines together with preliminary pharmacological data. In a similar fashion this paper reports esters of 3-pyrrolidinols[2] (Table I).

The N-alkyl-3-pyrrolidinols used were substituted monomethyl and dimethyl at positions 2, 4, and 5 and tetramethylene at 2 (Table II). The 3-pyrrolidinols other than 1,4,4-trimethyl-3-pyrrolidinol were prepared by lithium aluminum hydride reduction of the corresponding 3-keto compounds. The latter were formed *via* Dieckmann ring closure essentially according to the procedure of Leonard.[3]

The diesters used to prepare the dimethylpyrrolidinols and 1,5,5-trimethyl-3-pyrrolidinol were synthesized by the procedure illustrated below.

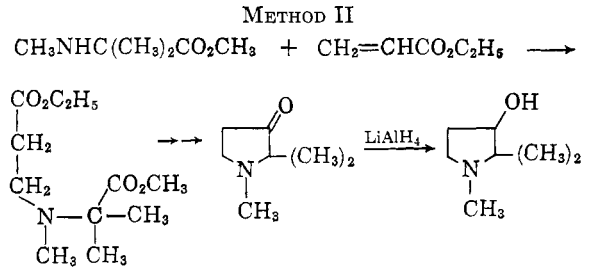
METHOD I



The method did not provide a synthetic route for the diester intermediates required for the 1,2,2- and 1,4,4-trimethyl-3-pyrrolidinols.

1,2,2-Trimethyl-3-pyrrolidinol and the corresponding spiro analog were prepared by the following scheme:

METHOD II



The methyl α-methylaminoisobutyrate was prepared essentially according to the procedure of Leonard and Barthel.[4]

1,4,4-Trimethyl-3-pyrrolidinol was prepared by an entirely different approach. α-Hydroxy-β,β-dimethyl-γ-butyrolactone[5] was converted to the

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(2) Since this work was completed, three publications related to it have appeared: (a) R. E. Bowman, J. F. Cavalla, and J. Davoll, British Patent 821,436; [*Chem. Abstr.*, **56**, 2427 (1962)]. (b) B. V. Franko and C. D. Lunsford, *J. Med. Pharm. Chem.*, **2**, 523 (1960). (c) J. F. Cavalla, *et. al.*, *ibid.*, **4**, 1 (1961).

(3) N. J. Leonard, *et al.*, *J. Am. Chem. Soc.*, **73**, 2371 (1951).

(4) N. J. Leonard and E. Barthel, Jr., *ibid.*, **72**, 3632 (1950).

(5) J. W. Lynn, U.S. Patent 2,863,878; [*Chem. Abstr.*, **53**, 7019 (1959)].