A New Synthesis of Selenoureas and Selenothiocarbamic Esters from Thioureas

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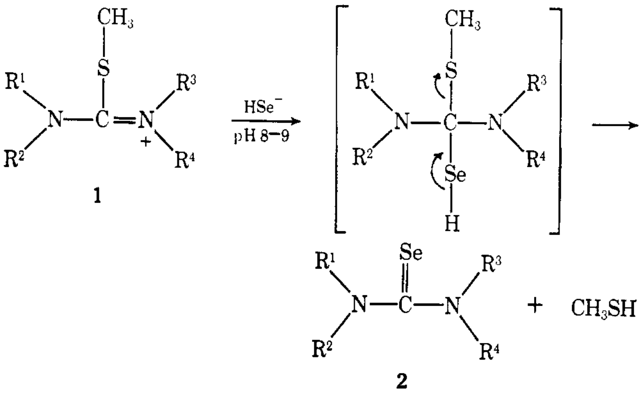
Selenoureas having either aliphatic or aromatic substituents were prepared by displacement of the thiomethyl moiety from S-methylthiopseudoureas by hydroselenide ion. The reaction, performed at pH 8–9, is general for all degrees of nitrogen substitution and gives yields in the range of 60–70%. At lower pH (*ca.* 5–6) displacement of an amino moiety by hydroselenide ion in several thiopseudoureas was observed to give selenothiocarbamates, a previously unreported class of compounds.

Selenium analogs of ureas can be synthesized by several methods. For example, selenourea[2] and mono-[3] and 1,1-disubstituted[4] selenoureas have been prepared by the reaction of hydrogen selenide with cyanamides, while the reaction of hydrogen selenide with carbodiimides has resulted in the formation of mono-[4] and 1,3-disubstituted[4,5] selenoureas. The reaction of isoselenocyanates[6–9] with ammonia or amines has led to the preparation of mono-,[6,7a] 1,3-di-,[6,7] and trisubstituted[8] selenoureas, while the action of amines on carbon diselenide has given 1,3-di-[10] and trisubstituted[11] selenoureas. Many of the procedures cited above have limited synthetic applicability because of the poor yields obtained, and, it should be noted, no single procedure lends itself readily to the preparation of all types of selenoureas. We report here a new synthesis of selenoureas which can give good yields of these compounds without regard to the nature or degree of their substitution.

In the course of the investigation of the behavior of S-methyl derivatives of various thioureas toward alkali, it was found[12] that the S-methyl derivatives of all but trisubstituted thioureas give methyl mercaptan and, presumably, the corresponding urea when subjected to this treatment. Subsequent work[13] with sulfide ion as the nucleophile showed that the thiomethyl moiety could be displaced from all S-methylthiopseudoureas, including those which are trisubstituted, to regenerate the original thiourea.

The success of the above reaction led to the trial of hydroselenide ion as the attacking nucleophile on S-methylthiopseudoureas possessing a variety of N-substitution patterns. It was found that selenoureas could be prepared in good yield, for the most part, from all thiopseudoureas regardless of the degree or nature of N substitution (*cf.* Table I). Especially noteworthy was the preparation of the difficultly attainable 1,1,3,3-tetramethyl-2-selenourea,[14,15] 3-selenosemicarbazide, and 1-phenyl-3-selenosemicarbazide. The previously unknown 2-seleno-4-thiobiuret (**4**) was synthesized from 2-methyl-2,4-dithiopseudobiuret hydriodide (**3**).



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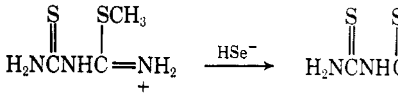

$$H_2N\overset{S}{\overset{\|}{C}}NH\overset{SCH_3}{\overset{|}{C}}{=}\underset{+}{NH_2} \xrightarrow{HSe^-} H_2N\overset{S}{\overset{\|}{C}}NH\overset{Se}{\overset{\|}{C}}NH_2$$

3 4

The selenoureas thus prepared were relatively stable if stored in the dry state in the absence of air and light, and could be recrystallized from chloroform–hexane or ethanol. Heating the selenoureas in water and, in some instances, ethanol caused slight decomposition of the selenoureas.

Hydrogen selenide was generated from aluminum selenide by addition of dilute sulfuric acid in a manner described by Bennett and Zingaro.[16] Their procedure was modified in that no external heat was applied to the exothermic reaction. The *in situ* generation of hydrogen selenide by addition of aluminum selenide to an aqueous solution of the S-methylthiopseudourea was tried. While it was possible to obtain the desired selenourea, the difficulties encountered in separating the product from the inorganic by-products (mainly aluminum hydroxide) negated whatever advantage was gained by this technique.

The reaction of an S-methylthiopseudourea with sodium hydroselenide was run in the pH range of 8–9. A solution of sodium hydroselenide, prepared by the addition of hydrogen selenide gas to an aqueous–ethanolic solution of sodium bicarbonate, was combined with an ethanolic solution of the S-methylthiopseu-

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(2) (a) A. Verneuil, *Ann. Chim.* (Paris), [6] **9**, 294 (1886); (b) H. J. Backer and H. Bose, *Rec. Trav. Chim. Pays-Bas*, **62**, 580 (1943); (c) L. C. King and R. J. Hlavacek, *J. Amer. Chem. Soc.*, **73**, 1864 (1951).

(3) (a) H. Stolte, *Ber.*, **19**, 1577 (1886); (b) H. Schmidt, *ibid.*, **54B**, 2067 (1921); (c) J. Haginiwa, *Yakugaku Zasshi*, **69**, 565 (1949); *Chem. Abstr.*, **44**, 4465*f* (1950).

(4) R. A. Zingaro, F. C. Bennett, Jr., and G. W. Hammar, *J. Org. Chem.*, **18**, 292 (1953).

(5) F. Zetzsche and H. Pinske, *Ber.*, **74**, 1022 (1941).

(6) E. Bulka and K.-D. Ahlers, *Z. Chem.*, **3**, 387 (1963).

(7) (a) E. Bulka, K.-D. Ahlers, and E. Tucek, *Chem. Ber.*, **100**, 1459 (1967); (b) C. Hasan and R. F. Hunter, *J. Chem. Soc.*, 1762 (1935).

(8) I. B. Douglass, *J. Amer. Chem. Soc.*, **59**, 740 (1937).

(9) M. Lipp, F. Dallacker, and I. M. zu Köcker, *Monatsh. Chem.*, **90**, 41 (1959).

(10) (a) H. G. Grimm and H. Metzger, *Ber.*, **69B**, 1356 (1936); (b) J. S. Warner, *J. Org. Chem.*, **28**, 1642 (1963).

(11) J. S. Warner and T. F. Page, Jr., *ibid.*, **31**, 606 (1966).

(12) D. L. Klayman and R. J. Shine, *Anal. Chim. Acta*, **41**, 408 (1968).

(13) D. L. Klayman and R. J. Shine, unpublished results.

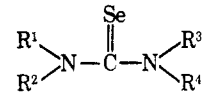
(14) K. A. Jensen, G. Felbert, and B. Kägi, *Acta Chem. Scand.*, **20**, 281 (1966).

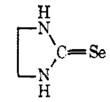
(15) D. L. Klayman and R. J. Shine, *Chem. Commun.*, 372 (1968).

(16) F. Bennett and R. Zingaro, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 359.

TABLE I

SELENOUREAS

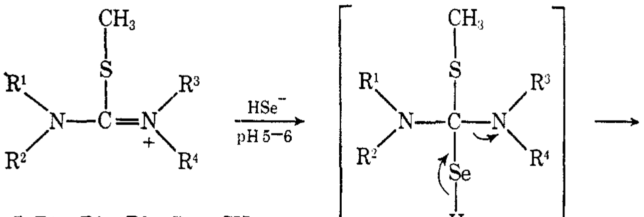


R¹	R²	R³	R⁴	Registry no.	Mp, °C	Lit. mp, °C	% yield	Recrystn solvent	Analysis, % Calcd N	Calcd Se	Found N	Found Se
H	H	H	H		223–225 dec	198[a]	80	H_2O	22.77	64.19	22.74	64.39
C_2H_5	H	H	H		123–125 dec	125[b]	74	$CHCl_3$–hexane	18.54	52.27	18.52	52.35
C_6H_5	H	H	H		190–192 dec	191–192[c]	79	$CHCl_3$–hexane	14.07	39.66	14.07	39.55
C_6H_5	C_6H_5	H	H	21347-28-4	205–207 dec		80	$CHCl_3$–hexane	10.18	28.69	10.22	28.74
C_6H_5	H	C_6H_5	H		178–182 dec	190–192 dec[d]	51	EtOH	10.18	28.69	9.93	28.81
CH_3	CH_3	C_6H_5	H		108–110		80	$CHCl_3$–hexane	12.33	34.76	11.86	34.71
CH_3	CH_3	CH_3	CH_3		79–81	78–79[e]	72	Hexane	15.64	44.08	15.92	44.36
NH_2	H	H	H		189–191 dec	180 dec[f]	67	EtOH	30.44	57.20	30.22	56.79
C_6H_5NH	H	H	H	21347-29-5	195–197		47	CH_2Cl_2	19.62	36.87	19.57	36.91
$C(=S)NH_2$	H	H	H	21347-30-8	185–188 dec		22	[g]	23.08	43.36[h]	22.86	42.78
					230–232 dec	234–236 dec[d]	71	EtOH	19.05	53.70	18.96	53.94

[a] R. E. Dunbar and E. P. Painter, *J. Amer. Chem. Soc.*, **69**, 1833 (1947); also reported mp 200° dec,[2a] mp 213° dec,[b] and mp 232° [J. F. Giudicelli, J. Menin, and H. Najer, *Bull. Chim. Soc. Fr.*, 1099 (1968)]. [b] Reference 3b. [c] J. F. Giudicelli, J. Menin, and H. Najer, *Bull. Chim. Soc. Fr.*, 1099 (1968); also reported mp 176–178° dec[4] and 182° dec [H. Stolte, *Ber.*, **19**, 2351 (1886)]. [d] Reference 10b. [e] Reference 12. [f] R. Huls and M. Renson, *Bull. Chim. Soc. Belges*, **65**, 511 (1956). [g] Because of difficulty in recrystallizing this material, the analytical sample was prepared by washing with methylene chloride and carbon disulfide. [h] Sulfur analysis: calcd, 17.61; found, 17.52.

dourea hydriodide. The pH of the solution was then immediately adjusted to 8–9 by the addition of sodium bicarbonate.

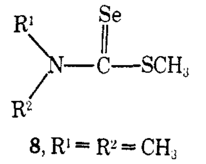
In the course of investigating optimal conditions for the formation of 1,1,3,3-tetramethyl-2-selenourea, it was found that, if the reaction was performed at pH 5–6, **5** gave N,N,S-trimethylselenothiocarbamate (**8**) instead of the desired selenourea. The elimination of the dimethylamino moiety rather than the thiomethyl group accounts for the formation of **8**. Protonation of the amino group at lower pH appears to favor its elimination over the elimination of methyl mercaptan. The reaction of hydroselenide ion with 1,1,2-trimethyl-3-phenyl-2-thiopseudourea hydriodide (**6**) and 1-phenyl-2-methyl-2-thiopseudourea hydriodide (**7**) led to the selenothiocarbamic ester, N-phenyl-S-methylselenothiocarbamate (**9**). To our knowledge, this represents the first reported synthesis of selenothiocarbamic esters.



5, $R^1 = R^2 = R^3 = R^4 = CH_3$

6, $R^1 = C_6H_5$; $R^2 = H$; $R^3 = R^4 = CH_3$

7, $R^1 = C_6H_5$; $R^2 = R^3 = R^4 = H$



8, $R^1 = R^2 = CH_3$

9, $R^1 = C_6H_5$; $R^2 = H$

An indication of the presence of a selenocarbony group was achieved by adding a few drops of 3% hydrogen peroxide to several milligrams of a selenourea dissolved in a small volume of methanol. Red elemental selenium precipitated from the solution within 30 sec; however, in some instances, heating the test mixture on a steam bath for 15 sec was required. No elemental selenium was obtained on treatment of 2-imidazolineselenone with hydrogen peroxide solution, necessitating the use of the sodium fusion method of King and Hlavacek.[20] Of the two selenothiocarbamic esters prepared, only **8** reacted positively with the peroxide solution.

Ammoniacal silver nitrate reacted with all of the selenoureas but 2-imidazolineselenone to give a black precipitate of silver selenide. In contrast, the analogous trisubstituted thioureas and 1,1,3,3-tetramethyl-2-thiourea failed to react with this reagent to give silver sulfide.[12] The selenothiocarbamic esters did not give silver selenide with ammoniacal silver nitrate.

Experimental Section[17]

2-Methyl-2-thiopseudourea Hydriodides.—An ethanol solution of a thiourea was heated under reflux for 0.5–1.0 hr with 1.1 equiv of methyl iodide. Evaporation of the solvent under reduced pressure gave the 2-methyl-2-thiopseudourea hydriodide which generally could be purified by recrystallization from ethanol–ether.

2-Methyl-2,4-dithiopseudobiuret Hydriodide.—To 20.3 g (0.15 mol) of dithiobiuret suspended in 75 ml of acetonitrile was added 35.5 g (0.25 mol) of methyl iodide and the mixture was heated under reflux for 40 min. The resultant solution was concentrated and cooled, giving white crystals (34.1 g, 82%) of 2-methyl-2,4-dithiopseudobiuret hydriodide, mp 150–152° (recrystallized from acetonitrile).

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[17] Melting points were determined a on Fisher-Johns melting point apparatus and are uncorrected. Microanalyses were performed by Mr. Joseph F. Alicino, Metuchen, N. J. 08840. Infrared spectra were determined on a Beckman IR-5 or Perkin-Elmer 221 spectrophotometer as KBr pellets. Nmr spectra were run on a Varian A-60 spectrometer using TMS as the internal standard.

Anal. Calcd for $C_3H_8IN_3S_2$: C, 13.00; H, 2.91; I, 45.79; N, 15.16; S, 23.14. Found: C, 12.78; H, 2.77; I, 45.81; N, 15.28; S, 23.47.

Selenoureas.—Hydrogen selenide, generated by adding 50 ml of 6 *N* sulfuric acid to 11.5 g of powdered aluminum selenide[18] (90% purity), was passed slowly into a solution of 8.25 g (0.10 mol) of sodium bicarbonate[19] in 250 ml of water and 100 ml of ethanol maintained at 0°. The resulting clear red solution contained about 0.10 mol of sodium hydroselenide.

To a solution of 0.05 mol of a 2-methylthiopseudourea hydriodide in 50 ml of ethanol was added 350 ml of the sodium hydroselenide solution described above, containing an additional 0.05 mol of sodium bicarbonate.[19] The combined clear red solution, which had a pH in the 8–9 range, was permitted to stand at room temperature for approximately 20 hr. Any crystals which formed were collected and combined with subsequent crops. Nitrogen gas was then passed through the filtrate, which was treated with 15 ml of glacial acetic acid, to dispel methyl mercaptan and hydrogen selenide. Any elemental Se which formed was removed by filtration and the solution was concentrated at reduced pressure to about 70–100 ml and allowed to stand at 0° until crystals formed. The selenourea was collected and the combined crops were recrystallized from chloroform–hexane or ethanol. The selenoureas are white or off-white compounds which usually turn pink or gray when allowed to stand in the air. The selenoureas were characterized by elemental analyses and, where possible, by comparison of the melting points and infrared spectra with literature values. The new selenoureas, in addition to giving the correct elemental analyses, also showed the infrared bands predicted by the work of Jensen and Nielsen.[20]

1,1-Dimethyl-3-phenyl-2-selenourea.—To a solution of 16.2 g (0.05 mol) of 1,1,2-trimethyl-3-phenyl-2-thiopseudourea hydriodide in 50 ml of ethanol was added 350 ml of the sodium hydrogen selenide solution (containing about 0.10 mol) whose preparation is described above. Immediately, a solution containing 4.2 g (0.05 mol) of sodium bicarbonate in 50 ml of water was added to the above mixture. The resulting clear red solution, which had a pH of 8, was allowed to stand at room temperature for 20 hr. Nitrogen gas was then passed through the solution while it was made slightly acidic by addition of 15 ml of glacial acetic acid. After filtration of the elemental selenium which had formed, the filtrate was evaporated to about 70 ml. The oil which had separated slowly crystallized on cooling giving 9.4 g (80%) of 1,1-dimethyl-3-phenyl-2-selenourea, mp 106–108°. Recrystallization from chloroform–hexane gave pale yellow crystals: mp 108–110°; ir 6.28, 6.50, 6.70, 7.16, 7.63, 8.80, 12.0, 13.25 and 14.50 μ.

Anal. Calcd for $C_9H_{12}N_2Se$: N, 12.33; Se, 34.76. Found: N, 11.86; Se, 34.71.

N,N,S-Trimethylselenothiocarbamate (**8**).—A solution of 11.0 g (0.04 mol) of 1,1,2,3,3-pentamethyl-2-thiopseudourea iodide in 50 ml of ethanol was added to 280 ml of the sodium hydroselenide solution (containing about 0.08 mol of sodium hydroselenide). Glacial acetic acid (4.8 g, 0.08 mol) was immediately added to bring the pH to about 5–6. The resultant turbid red mixture was allowed to stand at room temperature for 21 hr. Excess hydrogen selenide was dispelled by passing nitrogen through the mixture and any black elemental selenium present was removed by filtration. Rose-colored crystals which formed in the filtrate were collected and dried giving 4.8 g (66%) of product, mp 66–68°. Recrystallization from hexane gave white crystals: mp 67–69°; ir 6.73, 7.28, 8.06, 8.70, 9.47, and 11.0 μ. Hindered rotation about the C–N bond has been observed in the 60-MHz nmr spectrum of **8**. At 0° in $CDCl_3$ absorption occurs at δ 2.72 (3 H, s), 3.38 (3 H, s) and 3.70 (3 H, s). The two N-methyl peaks coalesce around 52°.

Anal. Calcd for C_4H_9NSSe: C, 26.36; H, 4.98; N, 7.69; S, 17.60; Se, 43.35. Found: C, 26.25; H, 4.77; N, 7.64; S, 17.88; Se, 42.86.

N-Phenyl-S-methylselenothiocarbamate (**9**).—1,1,2-Trimethyl-3-phenyl-2-thiopseudourea hydriodide (16.2 g, 0.05 mol) was converted into N-phenyl-S-methylselenothiocarbamate (5.5 g, 48% yield) utilizing the above procedure. The analytical sample was prepared by recrystallization of the compound from chloroform–hexane as yellow crystals: mp 90–93°; ir 6.30, 6.68, 6.93, 7.10, 7.47, 10.10, 10.58, 11.09, 13.25, and 14.50 μ; nmr ($CDCl_3$) δ 2.80 (3 H, s), 7.78 (5 H, s), and 11.5 (1 H, broad).

Anal. Calcd for C_8H_9NSSe: N, 6.09; S, 13.93; Se, 34.30. Found: N, 5.96; S, 13.64; Se, 34.49.

The identical product, **9**, mp 90–93°, was obtained (3.5 g, 31%) in the same manner from 14.7 g (0.05 mol) of 1-phenyl-2-methyl-2-thiopseudourea hydriodide. The infrared spectrum and nmr spectrum of the selenothiocarbamate was identical with that of the product whose preparation is described above.

Anal. Calcd for C_8H_9NSSe: N, 6.09; S, 13.93; Se, 34.30. Found: N, 6.05; S, 14.12; Se, 33.69.

Registry No.—**3**, 21347-31-9; **8**, 21347-33-1; **9**, 21347-34-2; 1,1-dimethyl-3-phenylselenourea, 21347-32-0.

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(18) Aluminum selenide, supplied commercially as very hard lumps, was finely pulverized in a ball mill immediately prior to use.

(19) Higher yields were achieved when sodium carbonate was used in place of sodium bicarbonate in the synthesis of selenourea and 1-ethyl-2-selenourea.

(20) K. A. Jensen and P. H. Nielsen, *Acta Chem. Scand.*, **20**, 597 (1966).