Recrystallization of VII from acetic acid caused rearrangement and appearance of the 7-deuterio compound. Harris, *et al.*,[14] reported that this reaction does not take place in molten I at 180°.

(14) R. K. Harris, *et al.*, *J. Chem. Soc.*, 197 (1963).

The Synthesis of Aminoethyl-Substituted Selenium Compounds

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Selenium analogs of sulfur-containing pharmacologically active compounds have received attention owing to their interesting biological properties. Though organoselenium compounds tend to exhibit chemical instability and marked toxicity to animals, a number of potentially useful therapeutic agents have been prepared and studied.[1] The sulfur-containing compound, cysteamine (2-aminoethanethiol), and its derivatives possessing the aminoethyl moiety, such as cystamine [bis(2-aminoethyl) disulfide] and 2-aminoethanethiosulfuric acid, have been demonstrated to be good antiradiation agents.[2] Selenocystine and selenomethionine were reported[3] recently to show antiradiation activity *in vitro* superior to cystine and methionine, respectively. Several aminoethylselenium compounds were, therefore, synthesized for evaluation as potential radioprotective drugs and for comparison with their sulfur analogs.

2-Aminoethaneselenosulfuric acid (I), first prepared

$$H_2NCH_2CH_2SeSO_3H$$
I

by Günther and Mautner,[4] was found to be a valuable precursor for most of the selenium compounds made. An alternative method for its synthesis consisted of combining potassium selenosulfate and ethylenimine in aqueous solution, followed by the gradual acidification of the solution until pH 6 was attained.

$$SeSO_3^{-2} + \underset{\diagdown\,\diagup}{CH_2—CH_2}\overset{N^+H_2}{} \longrightarrow H_2NCH_2CH_2SeSO_3^-$$

Aqueous solutions of I are unstable above 60° resulting in the slow formation of sulfur dioxide. When an aqueous solution of I was heated under reflux for 62 hr. until sulfur dioxide was no longer evolved, the product isolated in quantitative yield was selenocystamine [II, bis(2-aminoethyl) diselenide] hydrosulfate.[5] The formation of these compounds may be accounted for by the mechanism shown below. The nucleophilic attack of a water molecule on the sulfur atom of I (written here in its zwitterionic form) gen-

$$\overset{H}{HO}\!: + \overset{O^-}{\underset{|}{SO_2}}SeCH_2CH_2NH_3^+ \longrightarrow H_3\overset{+}{N}CH_2CH_2Se^- + H_2SO_4$$

$$H_3\overset{+}{N}CH_2CH_2Se^- + \overset{SO_3^-}{\underset{|}{Se}}CH_2CH_2NH_3^+ \longrightarrow (H_3\overset{+}{N}CH_2CH_2Se—)_2 + SO_3^{-2}$$

$$H_2SO_4 + SO_3^{-2} \longrightarrow SO_2 + SO_4^{-2} + H_2O$$

erates the selenide ion and sulfuric acid. A similar step has been proposed[6] for the acid hydrolysis of a Bunte salt (alkyl or aryl thiosulfate). The selenide ion then attacks another molecule of I, the displacement now occurring at the selenium atom. This is comparable with the reaction of a mercaptide with a Bunte salt to form a disulfide. The diprotonated selenocystamine thus formed reacts with the sulfate ion to give the observed product.

When I was heated for 5 hr. without solvent at 105–110°, no sulfur dioxide was detected and the melting point of the compound was unchanged. Pyrolysis of the compound at 145–150° resulted in the formation of sulfur dioxide, which was detectable for 2.5 hr., and a high yield of II hydrosulfate.

The sulfur–sulfur bond in organic thiosulfates is attacked by various nucleophiles and it was anticipated that these ionic species would also be effective toward the selenium–sulfur bond in selenosulfates. Footner and Smiles[7] reported that the cyanide displacement on sulfur in a Bunte salt gives the corresponding thiocyanate and sulfite ion. The action of cyanide on the sodium salts of 2-aminoethanethiosulfuric acids in aqueous solution results in the formation of 2-aminothiazolines.[8] Similarly, the cyanide displacement performed on sodium 2-aminoethaneselenosulfate produced, in addition to sulfite ion, 2-aminoselenazoline. The latter was isolated as the

$$CN^- + \overset{SO_3^-}{\underset{|}{Se}}CH_2CH_2NH_2 \longrightarrow$$

$$SO_3^{-2} + [H_2NCH_2CH_2SeCN] \longrightarrow \begin{array}{l} H_2C—CH_2 \\ \quad | \quad\quad | \\ \quad Se \quad\; N \\ \quad\diagdown\; \| \\ \quad\quad C \\ \quad\quad | \\ \quad\quad NH_2 \end{array}$$

hydrobromide salt, inasmuch as the free base is an unstable oil which polymerizes rapidly.

Unsymmetrical amino disulfides are formed when mercaptides are allowed to react with amino Bunte salts.[9] When the sodium mercaptide of 1-decanethiol was added to a methanol solution of sodium 2-aminoethaneselenosulfate at about 0°, sodium sulfite precipitated instantaneously with the mercaptan undetectable within 2 min. In addition to the main product,

(1) For a review article, see D. Dingwall, *J. Pharm. Pharmacol.*, **14**, 765 (1962).

(2) J. F. Thomson, "Radiation Protection in Mammals," Reinhold Publishing Corp., New York, N. Y., 1962.

(3) F. Shimazu and A. L. Tappel, *Radiation Res.*, **23**, 210 (1964).

(4) W. H. H. Günther and H. G. Mautner, *J. Med. Chem.*, **7**, 229 (1964).

(5) When the analogous sulfur compound, 2-aminoethanethiosulfuric acid, was heated under reflux in aqueous solution for 70 hr., there was no detectable evolution of sulfur dioxide. A small amount of sulfate was found in solution and 92% of the 2-aminoethanethiosulfuric acid was recovered unchanged.

(6) B. Milligan and J. M. Swan, *J. Chem. Soc.*, 2172 (1962); J. L. Kice, *J. Org. Chem.*, **28**, 957 (1963).

(7) H. B. Footner and S. Smiles, *J. Chem. Soc.*, **127**, 2887 (1925).

(8) D. L. Klayman, unpublished results.

(9) D. L. Klayman, J. D. White, and T. R. Sweeney, *J. Org. Chem.*, **29**, 3737 (1964).

$$n\text{-}C_{10}H_{21}S^- + SeCH_2CH_2NH_2(SO_3^-) \longrightarrow n\text{-}C_{10}H_{21}SSeCH_2CH_2NH_2 + SO_3^{-2}$$

1-amino-3-selena-4-thiatetradecane, the reaction mixture contained *n*-decyl disulfide and II. The latter two materials were formed by the disproportionation of the selenosulfide, a type of compound observed by Bergson and Norström[10] to undergo this transformation. The product was more stable, however, as the hydrochloride salt.

Compound II was readily obtained from I by treatment of the latter with 10% sodium hydroxide solution at room temperature followed by extraction of the yellow solution with chloroform. This procedure is considerably easier than the Coblentz[11] synthesis of this compound.

Reduction of II with sodium borohydride in aqueous solution gave selenocysteamine (2-aminoethaneselenol) which was converted to the hydrochloride salt. The free base was made earlier by Günther and Mautner[4] in this manner; however, they used the selenol in a subsequent synthetic step without isolating it. Selenocysteamine hydrochloride is a white, crystalline material which is readily air oxidized to II dihydrochloride.

Oxidation of II as either the free base or the dihydrochloride with excess hydrogen peroxide stopped at the seleninic acid stage to give selenohypotaurine (2-aminoethaneseleninic acid). Cystamine, in contrast, when subjected to the identical reaction conditions did not give hypotaurine (2-aminoethanesulfinic acid) but taurine. Attempts to oxidize selenohypotaurine with 30% hydrogen peroxide at room temperature for 3 days failed to give selenotaurine. Also, treatment of II with a large excess of 10% hydrogen peroxide at 90° for 4.5 hr. gave only the seleninic acid. Recently, Caldwell and Tappel[12] observed that oxidation of selenocystine with excess hydrogen peroxide gave selenocysteineseleninic acid, alanine, and metallic selenium while similar treatment of cystine gave a mixture which included the sulfonic acid, cysteic acid. McCollough and Gould[13] obtained seleninic acids from aromatic diselenides using a threefold excess of hydrogen peroxide.

Two further attempts were made to prepare selenotaurine. 2-Bromoethylamine hydrobromide was allowed to react with 1 equiv. of sodium selenite in aqueous solution. The product decomposed rapidly on isolation releasing elemental selenium. The ring opening of ethylenimine with aqueous selenous acid also failed to give a stable, isolable product. Pichat, *et al.*,[14] reported similar difficulties in obtaining selenotaurine.

Experimental[15]

2-Aminoethaneselenosulfuric Acid (I).—Potassium sulfite[16] (15.8 g., 0.1 mole) was dissolved in 16 ml. of water by heating and stirring for 20 min. under a nitrogen atmosphere. To this solution was added 8.69 g. (0.11 mole) of powdered selenium and *ca.* 10 mg. of sodium lauryl sulfate. The vigorously stirred solution was heated near the reflux temperature for 1 hr., permitted to cool to room temperature, and suction filtered to remove the unreacted selenium (3.44 g., 0.044 mole). The selenium was washed with several small portions of water and the washings were combined with the bulk of the potassium selenosulfate[17] solution. Ethylenimine (4.3 g., 0.1 mole) was dissolved in the ice-cooled, stirred selenosulfate solution which was followed by the dropwise addition of approximately 200 ml. of a 1 *N* sulfuric acid solution at such a rate that the elemental selenium which separated momentarily redissolved before the succeeding drop was added. When the pH of the solution reached 6, the sulfuric acid addition was stopped and the solution was evaporated to dryness under reduced pressure at about 50° using a rotary evaporator. The residue was extracted with two 75-ml. portions of boiling 80% ethanol. The combined extracts, on cooling, gave 11.7 g. of I contaminated with potassium sulfate and taurine.[18] Further recrystallization of the finely powdered product from water at 50° gave 10.45 g. (77.6% yield based on reacted selenium) of I as hard, colorless crystals which darkened at 148°, m.p. 152–154° dec., lit.[4] m.p. 196°, also reported to resolidify and then decompose at 270°.[19]

Anal. Calcd. for $C_2H_7NO_3SSe$: C, 11.77; H, 3.46; N, 6.86; Se, 38.68. Found: C, 12.04; H, 3.62; N, 6.88; Se, 38.82.

I was also made by the reaction of potassium selenosulfate and 2-chloroethylamine hydrochloride using essentially the method of Günther and Mautner.[4] The product darkened at *ca.* 148° and melted at 154–157° dec.[20]

Hydrolysis of I.—A solution of 2.04 g. (0.01 mole) of I in 10 ml. of water was heated under reflux for 62 hr. until the evolution of sulfur dioxide was no longer detectable using filter paper spotted with dilute potassium permanganate solution. The solution of selenocystamine (II) hydrosulfate was evaporated to dryness under reduced pressure to give 1.72 g. (100% yield) of the yellow, crystalline product, m.p. 273–275° dec. Recrystallization twice from water–ethanol raised the melting point to 288° dec.

Anal. Calcd. for $C_4H_{14}N_2O_4SSe_2$: C, 13.96; H, 4.10; N, 8.14; Se, 45.88. Found: C, 14.11; H, 4.19; N, 8.09; Se, 46.08.

Pyrolysis of I.—A test tube containing 1.45 g. (7.1 mmoles) of I which had been finely powdered was suspended in an oil bath maintained at 145–150°. The powder was stirred periodically with the thermometer used to determine its temperature. The evolution of sulfur dioxide began in about 15 min. and continued for about 2.5 hr. The pale yellow residue consisting of II hydrosulfate, m.p. 268–270° dec., weighed 1.27 g. (101%) indicating the presence of a slight amount of starting material. The product was recrystallized from water–ethanol bringing the melting point up to 270–273° dec.

2-Aminoselenazoline Hydrobromide.—To a solution of 2.04 g. (0.01 mole) of I and 0.40 g. (0.01 mole) of sodium hydroxide in 15 ml. of water was added 0.55 g. (0.011 mole) of sodium cyanide and 40 ml. of chloroform. The entire mixture was vigorously agitated with a Vibromixer for 2.5 hr. The chloroform phase was then separated, filtered to remove any polymer which may have formed, and shaken with 6 ml. of 24% hydrobromic acid. The two layers were evaporated together under reduced pressure and the residue was treated twice with water and taken down to dryness each time. The solid thus obtained was recrystallized from

(10) G. Bergson and G. Norström, *Arkiv Kemi*, **17**, 569 (1961).

(11) V. Coblentz, *Ber.*, **24**, 2131 (1891).

(12) K. A. Caldwell and A. L. Tappel, *Biochemistry*, **3**, 1643 (1964).

(13) J. D. McCullough and E. S. Gould, *J. Am. Chem. Soc.*, **71**, 674 (1949).

(14) L. Pichat, M. Herbert, and M. Thiers, *Tetrahedron*, **12**, 1 (1961).

(15) Melting points are uncorrected and were determined on a Fisher-Johns melting point apparatus. Microanalyses were performed by Mr. Joseph Alicino, Metuchen, N. J. Infrared spectra were determined on a Beckman IR-5 spectrophotometer.

(16) It is important to use a good grade of potassium sulfite which has not been subjected to air oxidation. The presence of sulfate will diminish the yield of potassium selenosulfate.

(17) The preparation of potassium selenosulfate is based on the procedure of T. S. Price and L. M. Jones [*J. Chem. Soc.*, **95**, 1729 (1909)].

(18) Taurine was formed by the ring opening of ethylenimine with unreacted sulfite and was identified by its characteristic bands at 10.4 (s), 11.8 (s), and 13.5 μ (broad).

(19) A sample of compound I prepared by us and 2-aminoethanethiosulfuric acid have been compared polarographically. See W. Stricks and R. G. Mueller, *Anal. Chem.*, **36**, 40 (1964).

(20) A sample of compound I kindly provided by Dr. W. H. H. Günther had an infrared spectrum identical with our products made by the two methods mentioned. The melting point of his sample, determined on a Fisher-Johns apparatus, was 152–155° dec. The melting points of Dr. Günther's sample and our analytical samples determined in a capillary tube using an Electrothermal melting point block and one made by the Scientific Glass Co., Inc. were 20–40° higher. In view of the fact that the decomposition of I was shown to occur at 145° and possibly lower, the technique used to ascertain the melting point of compound I and the rate of heating will influence its decomposition point.

ethanol and charcoaled to give 1.20 g. (52.2%) of product as thin white needles, m.p. 170–172°. Further recrystallization twice from ethanol increased the melting point to 173° (lit.[21] m.p. 170°); λ_{max}^{KBr} 6.1 μ (C=N).

1-Amino-3-selena-4-thiatetradecane Hydrochloride.—Sodium hydroxide (1.20 g., 0.03 mole) was dissolved with stirring in 30 ml. of methanol through which nitrogen was slowly bubbled. Then 4.08 g. (0.02 mole) of finely powdered I was added with stirring. When solution was complete, the temperature of the reaction mixture was lowered to near 0° by external cooling and 1.72 g. (0.01 mole) of freshly distilled 1-decanethiol was added in one portion. Sodium sulfite immediately precipitated from solution, and, when an aliquot of the reaction mixture was centrifuged, the supernatant liquid reacted negatively to sodium nitroprusside indicating complete uptake of the mercaptan. The reaction mixture was filtered with the aid of Celite and the filtrate, still maintained near 0°, was acidified with ethanolic hydrogen chloride. The sodium chloride and unreacted I which precipitated were filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was recrystallized from isopropyl alcohol to give 1.15 g. (34.6% yield) of product as pale yellow, waxy crystals, m.p. 107–108°.

Anal. Calcd. for $C_{12}H_{28}ClNSSe$: C, 43.30; H, 8.48; N, 4.21; Se, 23.72. Found: C, 43.43; H, 8.23; N, 4.45; Se, 24.50.

Selenocystamine (II).—Compound I (10.2 g., 0.05 mole) was dissolved in 50 ml. of 10% aqueous sodium hydroxide and permitted to remain at room temperature for 2 hr. The yellow solution was then extracted with three 30-ml. portions of chloroform and the combined extracts were dried with anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator under reduced pressure giving a moderately viscous, yellow-orange oil as a residue; yield, 3.14 g. (51.1%). About 80% of the product could be vacuum distilled (0.1 mm.) using a Hickman still before the onset of decomposition.[22]

The dihydrochloride (yellow crystals from methanol) softened at 179° and melted at 186–188° (lit. m.p. 188°,[11] 177–179° dec.[23]).

The picrate (from ethanol) melted at 179–181° (lit.[11] m.p. 178°).

Selenocysteamine (2-Aminoethaneselenol) Hydrochloride.—To a solution of 0.615 g. (0.025 mole) of II in 5 ml. of water into which nitrogen was slowly bubbled was added 0.052 g. (0.014 mole) of sodium borohydride in 5 ml. of water. The yellow color of II was dispelled after about 22 min. At the end of 0.75 hr. the solvent was removed on a rotary evaporator at reduced pressure at 50° to give a white residue. (Atmospheric pressure was restored to the evaporator system by allowing nitrogen, rather than air, to enter.) The residue was acidified with *ca.* 30 ml. of ice-cooled ethanolic hydrogen chloride. The mixture was agitated for 0.5 hr. under nitrogen to dissolve the selenocysteamine hydrochloride and was then filtered. The filtrate was taken down to dryness under reduced pressure to give 0.64 g. (80.0%) of the product as white, slightly hygroscopic crystals, m.p. 108–110°. Titration of 0.1699 g. of the compound with 10.70 ml. of 0.0965 *N* iodine solution indicated a purity of 97.5%.

Anal. Calcd. for C_2H_8ClNSe: C, 14.96; H, 5.02; N, 8.73; Se, 49.19. Found: C, 15.11; H, 4.91; N, 8.77; Se, 49.60.

Selenohypotaurine (2-Aminoethaneseleninic Acid).—To an ice-cooled solution of 2.46 g. (0.01 mole) of II in 5 ml. of water was added 5.0 ml. of 30% hydrogen peroxide in small portions over 1 hr. with stirring. The solution, which turned from yellow to colorless, was stirred an additional hour at room temperature. Isopropyl alcohol was added to the solution until the appearance of cloudiness and it was then cooled. Selenohypotaurine, which separated as white needles, 2.56 g. (82.1% yield), darkened at *ca.* 125° and melted at 150–151° dec. (lit.[14] m.p. 150–152° dec.). Further recrystallization from water–ethanol gave a sample which darkened at *ca.* 135° and melted at 155–156° dec.

Cystamine[24] (1.52 g., 0.01 mole), if oxidized in the manner described above, gave 1.72 g. (68.8% yield) of taurine, which darkened at *ca.* 280°, m.p.[25] 325° dec. The infrared spectrum was identical with that of an authentic sample of taurine.

If 0.01 mole of the dihydrochloride of either II or cystamine was used as the starting material in the above procedure, it was dissolved in 4 ml. of water and 1 ml. of 28% ammonia solution. Selenohypotaurine and taurine were obtained in 66.3 and 60.2% yields, respectively.

(21) W. Baringer, *Ber.*, **23**, 1003 (1890).

(22) It was found that cystamine could similarly be distilled despite a report to the contrary [J. von Braun, A. Bahn, and H. Munch, *Ber.*, **62**, 2766 (1929)].

(23) W. H. H. Gunther and H. G. Mautner, *J. Am. Chem. Soc.*, **82**, 2762 (1960).

(24) For an earlier report of the peroxide oxidation of cystamine dihydrochloride to taurine, see A. Schöberl, *Z. physiol. Chem.*, **216**, 193 (1933).

(25) The melting point was determined on an Electrothermal melting point apparatus.

2-Benzhydryl-7,7,8,8-tetracyanoquinodimethan

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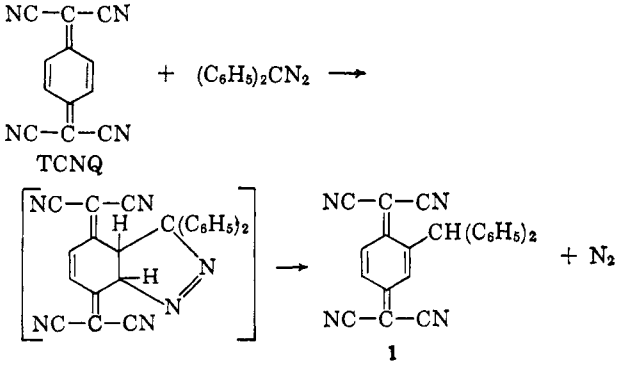
The remarkable electrical properties of salts of the anion radical of 7,7,8,8-tetracyanoquinodimethan (TCNQ)[1] have prompted investigations of related systems. Direct substitution on the ring of TCNQ proved difficult because nucleophiles generally displaced cyano groups (by an addition–elimination mechanism),[2] free radicals usually added across the 7 and 8 carbon atoms to give aromatic systems,[3] and TCNQ was inert to most electrophilic reagents. This paper describes the behavior of TCNQ with diazoalkanes. The properties of 2-benzhydryl-7,7,8,8-tetracyanoquinodimethan (1), in which the quinodimethan system is nonplanar, are contrasted with those of TCNQ.

Diphenyldiazomethane and TCNQ in acetone, acetonitrile, or tetrahydrofuran react slowly at 60 to 80° to release nitrogen and form 1 in 58% yield. The reaction occurred considerably more rapidly than the unassisted thermal decomposition of the diazoalkane. The rate of reaction as well as the absence of products of reaction of diphenylmethylene with the solvents[4] suggest that the reaction occurs by way of electrophilic attack of the diazo compound on TCNQ.



1

Diphenyldiazomethane apparently reacts similarly with *p*-benzoquinone,[5] but the intermediate enolizes to give the aromatic system 2.

(1) L. R. Melby, R. J. Harder, W. R. Hertler, W. Mahler, R. E. Benson, and W. E. Mochel, *J. Am. Chem. Soc.*, **84**, 3374 (1962).

(2) W. R. Hertler, H. D. Hartzler, D. S. Acker, and R. E. Benson, *ibid.*, **84**, 3387 (1962).

(3) D. S. Acker and W. R. Hertler, *ibid.*, **84**, 3370 (1962).

(4) W. Kirmse, L. Horner, and H. Hoffmann, *Ann.*, **614**, 19 (1958).

(5) H. von Pechmann, *Ber.*, **28**, 885 (1895).