In conclusion, I wish to express my sincere thanks to Professors H. S. Taylor and L. W. Jones for their invaluable suggestions in this research.

Summary

1. Vanadium pentoxide induces the oxidation of furfural and pyromucic acid with chlorates to give fumaric acid as the principal product.

2. Osmium tetroxide also induces the oxidation of furfural and pyromucic acid with chlorates to give mesotartaric acid as the principal product and oxalic acid as the by-product.

3. The mechanism of the reaction has been worked out and maleic acid aldehyde has been isolated as the intermediate product.

4. An acid having the empirical formula $C_5H_4O_6$ has also been isolated.

PRINCETON, NEW JERSEY

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY, NO. 548]

RESEARCHES ON SELENIUM ORGANIC COMPOUNDS. VII. THE SYNTHESIS OF 2-PHENYL-, 2-FURYL- AND 2-THIENYL-BENZOSELENAZOLES, OF 2-PHENYL-BENZOSELENAZOLE-4'-ARSONIC ACID AND OF OTHER BENZOSELENAZOLES[1]

BY MARSTON TAYLOR BOGERT AND ARTHUR STULL[2]

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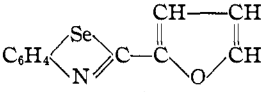
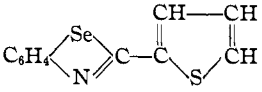
Nitro-, amino- and hydroxy-phenyl-benzoselenazoles have been synthesized by methods entirely analogous to those developed in these Laboratories for the corresponding benzothiazoles, by condensing the zinc *o*-aminoselenophenolate with the appropriate aldehyde or acid halide. As was expected, these compounds proved rather more difficult to prepare and less stable than their sulfur analogs.

Perhaps the most remarkable result of these syntheses is the persistence of the "Rosenkoerper" odor of 2-phenyl-benzothiazole even when the thiazole sulfur is replaced by selenium and the phenyl by a furyl or thienyl group. The odor of the dry compounds at ordinary temperature is faint, but when heated or in solution is of pronounced geranium or tea-rose type.

Further, these furyl (I) and thienyl (II) derivatives present new and interesting combinations of dissimilar heterocyclic systems, which offer



(I)



(II)

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[1] That portion of this paper which deals with the arsonic acid was presented at the Washington Meeting of the National Academy of Sciences, April 26, 1926. The other syntheses were reported to the Division of Organic Chemistry of the American Chemical Society, at the Philadelphia Meeting, September 8, 1926.

[2] Research Assistant, Columbia University, for the academic year 1925–1926.

opportunities of determining differences in the behavior of the cycles when attacked by various reagents.

Through the courtesy of Dr. Francis Carter Wood, Director of the Crocker Institute of Cancer Research, the sodium salt of the arsonic acid was tested, by intravenous injection, on mice and rats. It proved to be quite toxic to the host and without curative action on tumor growths in these animals. For healthy mice weighing 14–18 g. the lethal dose was 0.00025 g. and for rats of 40–50 g. the maximum tolerated dose was 0.00075 g. Its action upon various pathogenic microörganisms also will be investigated.

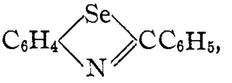
Experimental Part

***o*-Nitrophenyl Diselenide,** $(O_2NC_6H_4)_2Se_2$.—The method of Bogert and Andersen[3] was varied in several particulars, and the following process was found to give the best results.

A mixture of 25 g. of sodium selenide in 250–300 cc. of 95% alcohol was refluxed until a clear solution was obtained, when 16 g. of finely pulverized metallic selenium[4] was added and the refluxing continued for half an hour longer. This dark reddish-brown solution was gradually stirred into a warm solution of 50 g. of commercial *o*-nitrochlorobenzene in 100 cc. of alcohol and the mixture was refluxed for two to three hours additional. The use of a slight excess of sodium diselenide was found advantageous. As the hot solution cooled, the nitrophenyl diselenide separated. It was removed, washed thoroughly with water and with alcohol, and then formed a greenish-brown microcrystalline solid; yield, 37 g., or 57%. Recrystallized from glacial acetic acid to the constant melting point of 209° (corr.), it appeared as a pale brownish microcrystalline solid, readily soluble in benzene. Bogert and Andersen reported a melting point of 206.2–206.5° (corr.) for their product; Bauer,[5] who prepared it by a different method, found 209°.

***o*-Aminoselenophenol,** $H_2NC_6H_4SeH$.—From the nitrophenyl diselenide, the zinc salt of the aminoselenophenol was obtained by the method of Bogert and Andersen.[3] When a carefully purified nitro diselenide was used, the yield of zinc salt was 81%; with a crude diselenide, 55%. The product in the latter case also was found suitable for further syntheses.

As it separates first, the pure zinc salt is practically colorless, but it rapidly turns yellow and then brown in the light. Our observation in this matter is therefore at variance with that of Bauer,[5] who prepared the salt in another way and reported that it was stable in the air.

2-Phenyl-benzoselenazole,  $C_6H_4{<}^{Se}_{N}{>}CC_6H_5$, was synthesized from the zinc salt of *o*-aminoselenophenol and benzoyl chloride, as described by

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[3] Bogert and Andersen, *Proc. Nat. Acad. Sci.*, **11**, 217 (1925).

[4] The selenium used in this investigation was supplied by the Baltimore Copper Smelting and Rolling Co., through the courtesy of E. W. Rouse, Jr., General Superintendent, for whose assistance we are most grateful.—M. T. B.

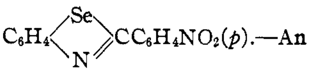
[5] Bauer, *Ber.*, **46**, 92 (1913).

Bauer[5] and modified by Bogert and Andersen;[3] pale, straw-colored needles, m. p. 117.5° (corr.), in agreement with the literature[3,5,6]; yield, 70%.

Anal. Calcd. for $C_{13}H_9NSe$: C, 60.14; H, 3.48; Se, 30.67. Found: C, 61.51, 62.71; H, 3.28, 3.76; Se, 30.38.

NITRO-, AMINO-, AND HYDROXY-BENZOSELENAZOLES

Derivative	Yield, %	M. p. (corr.), °C.	Se calcd., %	Se found, %	C and H, %
2-*m*-nitro	67	148	26.12	25.91	
2-*p*-nitro	71	211	26.12	...	Calcd.: C, 51.45; H, 2.64. Found: C, 51.88, 51.78; H, 3.08, 2.73
2-*o*-amino	..	142.5	28.98	28.80	
2-*m*-amino	77	159.5	28.98	28.87	
2-*p*-amino	98	156	28.98	28.54	
2-*o*-hydroxy	23	131	28.88	28.60	
2-*p*-hydroxy	46	223	28.88	28.36	

2-(*p*-Nitrophenyl)-benzoselenazole, 

$C_6H_4\langle{}^{Se}_{N}\rangle CC_6H_4NO_2(p)$.—An intimate mixture of finely pulverized zinc *o*-aminoselenophenolate (1 mole) and *p*-nitrobenzoyl chloride (2 moles) was fused for an hour at 100°. The reaction began at about the melting point of the chloride (71–73°). The cooled melt was pulverized, washed with water to remove zinc salts and with sodium carbonate to eliminate any *p*-nitrobenzoyl chloride or *p*-nitrobenzoic acid. Sodium hydroxide solution is not suitable, since it dissolves some of the selenazole also. The crude yellow product was decolorized and crystallized from glacial acetic acid until the melting point remained constant at 211° (corr.). The crystals, when finally washed with a little alcohol and dried at 100°, appeared in minute, pale yellow, lustrous, short needles.

2-(*m*-Nitrophenyl)-benzoselenazole was prepared in the same way as the *p*-nitro isomer, and the reaction began as soon as the *m*-nitrobenzoyl chloride melted (about 35°). The crude product was crystallized from glacial acetic acid by adding three volumes of water to the hot solution, and was then recrystallized from 95% alcohol until the melting point remained constant at 148° (corr.). Further crystallizations from glacial acetic acid, ethyl acetate, acetone or benzene failed to change this melting point. In appearance, the pure compound resembled its *p*-nitro isomer, except that it was much paler in color.

2-(*o*-Nitrophenyl)-benzoselenazole.—Attempts to get this isomer pure have proved futile so far, but a crude product was obtained which yielded the pure *o*-aminophenylbenzoselenazole upon reduction.

When zinc *o*-aminoselenophenolate and *o*-nitrobenzoyl chloride were brought together, even at temperatures near 0°, an explosion occurred with separation of carbon and zinc oxide. This is entirely similar to the experience of Smidth[7] on bringing together the same chloride with the zinc *o*-aminothiophenolate.

When the zinc salt and nitrobenzoyl chloride were allowed to interact in glacial acetic acid solution, a yellow, gummy product separated which, after washing with water and with sodium carbonate, still contained zinc in apparent chemical combination. All attempts to isolate from this any pure compounds failed. It was therefore reduced

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[6] Fromm and Martin, *Ann.*, **401**, 178 (1913). Bogert and Chen, THIS JOURNAL, **44**, 2355 (1922).

[7] Smidth, *Dissertation*, Columbia University, **1925**, p. 31.

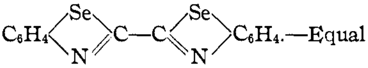
directly, by tin and dil. hydrochloric acid, to the **2-(*o*-aminophenyl)-benzoselenazole,** in much the same way as described for the following *m*- and *p*-amino isomers. Recrystallized from 75% alcohol to the constant melting point of 142.5° (corr.), it formed minute, pale greenish-yellow, lustrous scales, whose alcoholic solution exhibited no fluorescence; yield, 1.5 g. from 4 g. of the crude initial material.

2-(*m*-Aminophenyl)-benzoselenazole.—A mixture of 2 g. of the corresponding nitro derivative, 10 cc. of concd. hydrochloric acid, 90 cc. of water and 10 g. of granulated tin was boiled for three hours. Complete solution of the nitro derivative ensued within less than two hours. The hot filtrate from the excess of tin was stirred gradually into an excess of 4*N* sodium hydroxide solution, which precipitated the amine. After this alkali mixture had been kept warm for several hours, it was cooled and filtered. The crude amine was decolorized and crystallized from 50% alcohol, when it appeared in pale yellow, glassy needles, which dissolved in alcohol without fluorescence.

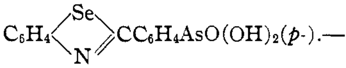
2-(*p*-Aminophenyl)-benzoselenazole was prepared in the same way as the *m*-amino isomer, and resembled it closely, except that the crystals were paler in color and their alcoholic solution exhibited a light violet fluorescence.

2-(*o*-Hydroxyphenyl)-benzoselenazole.—When a mixture of 1 g. of zinc *o*-aminoselenophenolate, 1 g. (an excess) of salicyl aldehyde and 125 cc. of glacial acetic acid was boiled for an hour, a clear, dark brown solution resulted. When left overnight at laboratory temperature, this solution deposited a small amount of zinc acetate and some metallic selenium. The filtrate from this deposit was diluted with three volumes of water, the curdy, brown precipitate separated and crystallized repeatedly from 50% alcohol; yield (after first crystallization from alcohol), 23%. The pure product formed fine, transparent needles of pale yellowish tinge, soluble in sodium hydroxide but not in sodium carbonate solution, and which gave no color reaction with ferric chloride either in aqueous or in alcoholic solution.

2-(*p*-Hydroxyphenyl)-benzoselenazole, produced similarly from the *p*-hydroxybenzaldehyde, using 0.6 g. of the aldehyde per gram of the zinc salt, formed larger and practically colorless, glassy needles, but in other respects resembled its *o*-isomer; yield, after one crystallization from alcohol, 46%.

2,2′-*bis*-Benzoselenazolyl,  $C_6H_4\langle{}^{Se}_{N}\rangle C{-}C\langle{}^{Se}_{N}\rangle C_6H_4$.—Equal molecular proportions of zinc *o*-aminoselenophenolate and oxalyl chloride were heated under a reflux condenser for 30 minutes at 70–80°. The cooled and pulverized product was warmed with an excess of *N* sodium hydroxide solution, and the insoluble material was heated in a porcelain dish. A sublimate was obtained which crystallized from toluene in colorless, glistening scales, m. p. 314° (uncorr.), which gradually turned brownish on standing in the light and air.

Anal. Calcd. for $C_{14}H_8N_2Se_2$: Se, 43.70. Found: Se, 43.74.

2-Phenyl-benzoselenazole-4′-arsonic Acid,  $C_6H_4\langle{}^{Se}_{N}\rangle CC_6H_4AsO(OH)_2(p\text{-})$.—To a suspension of 1 g. of 2-(*p*-aminophenyl)-benzoselenazole in 20 cc. of 2 *N* hydrochloric acid and 30 cc. of water, cooled to 0°, there was added slowly 0.5 g. of sodium nitrite dissolved in 10 cc. of water. The resulting solution, containing some suspended diazonium salt, was added to an ice-cold solution prepared from 5 g. of potassium arsenite, 50 cc. of water, 12 cc. of *N* sodium carbonate solution and 1 to 2 g. of copper bronze powder. The mixture was shaken from time to time, and tested periodically with litmus to make sure of its alkalinity. After standing for an hour at room temperature, it was heated at 100° until all frothing ceased (1 to 2 hours). During this heating, a slight odor was noted resembling that of 2-phenyl-benzoselenazole, The alkaline mixture was filtered warm and the insoluble material was washed with a little warm sodium carbonate solution. The combined greenish filtrate and washings were acidified with concd. hydrochloric acid, the pale yellow, flocculent precipitate was removed, washed thoroughly with water and dried at 100°. Recrystallized from 50% alcohol, it formed microscopic, pale yellow scales, which melted with decomposition above 360°; yield, 27%. It dissolved readily in alcohol, but slightly in water, chloroform or acetone, and was practically insoluble in ethyl acetate or carbon disulfide. In alkali hydroxide or carbonate solution, it was easily soluble and was reprecipitated when these solutions were acidified.

Anal. Calcd. for $C_{13}H_{10}O_3NAsSe$: C, 40.82; H, 2.61; Se, 20.72; As, 19.61. Found: C, 42.62; H, 3.05; Se, 20.41; As, 17.80.

As these figures demonstrate, the analysis was a troublesome one, because of the particular elements present and the small amount of product isolated. Arsenic was determined as follows.

The substance was digested in a Kjeldahl flask with a small amount of concd. sulfuric acid and with additions of concd. nitric acid from time to time, to assist in the oxidation of the arsenic to arsenate. When the oxidation was complete, the colorless solution was diluted, made slightly ammoniacal, magnesia mixture added, then the whole was made strongly ammoniacal and left overnight. The precipitated magnesium arsenate was washed, dried and converted into pyro-arsenate.

A blank run in exactly the same way with 2-phenyl-benzoselenazole showed that no selenium was thrown down by magnesia mixture.

Monosodium Salt—When the free arsonic acid and the calculated amount of 10% sodium hydroxide solution were brought together in absolute alcohol solution, the monosodium salt separated immediately as a fine, white solid, which was removed, washed thoroughly with absolute alcohol and dried; yield, practically that calculated. It is believed to be the first water-soluble organic selenium arsenic compound ever prepared.

2-(α-Furyl)-benzoselenazole (Formula I).—A mixture of one mole of zinc *o*-aminoselenophenolate with two moles of pyromucyl chloride was heated at 100° for 30 minutes, the cooled and pulverized melt extracted with *N* sodium hydroxide solution, to remove excess of acid chloride, and the residue decolorized and crystallized from 50% alcohol until the melting point remained constant at 133° (corr.). The compound formed colorless, glistening scales, with the characteristic agreeable odor of 2-phenylbenzothiazole ("Rosenkoerper"); yield, 83%.

Anal. Calcd. for $C_{11}H_7ONSe$: C, 53.18; H, 2.82; Se, 31.90. Found: C, 54.20; H, 2.97; Se, 31.51.

2-(α-Thienyl)-benzoselenazole (Formula II), was prepared from the zinc *o*-aminoselenophenolate and α-thienyl chloride in much the same way as the α-furyl derivative just described. Decolorized and crystallized from 95% alcohol to the constant melting point of 114.5°, it was obtained in well-formed, glassy, lustrous prisms, of a pale greenish-yellow color, and with the same odor as the α-furyl derivative; yield, 60%. From 50% alcohol, it crystallized in smaller, practically colorless needles, of the same melting point. It is believed that this is the only organic compound known which contains both unoxidized sulfur and unoxidized selenium in its molecule and yet has an *agreeable* odor.

Anal. Calcd. for $C_{11}H_7NSSe$: C, 49.99; H, 2.64; Se, 29.97. Found: C, 51.64; H, 2.86; Se, 30.15.

Analysis of Benzoselenazoles

So much difficulty was encountered in getting satisfactory carbon determinations in the combustion of these selenazoles, that in the case of many of the new products selenium was determined instead.

Bauer[8] tested the methods of Frerichs,[9] Becker and Meyer[10] and Michaelis,[11] and found the latter the most satisfactory. It has the disadvantage, however, of requiring the use of sealed tubes.

We found that the following process gave very good results.

The sample (0.2–0.3 g.) was heated carefully in a small Kjeldahl flask with the minimum amount (8–10 cc.) of concd. sulfuric acid until a clear, colorless solution was obtained (4–7 hours). The cold acid solution was rinsed into a beaker, diluted to about 200 cc. and neutralized with concd. ammonium hydroxide solution. An excess (50–60 cc.) of concd. hydrochloric acid was added, the solution heated to boiling and saturated with sulfur dioxide. The selenium separated at first in the red, colloidal form but soon turned gray and precipitated. After standing overnight, the selenium was filtered out on a Gooch crucible, washed with water until free from chloride ion, then with a little alcohol, dried at 105°, and weighed as metallic selenium.

Summary

1. Zinc *o*-aminoselenophenolate yields the corresponding 2-nitro- or 2-hydroxyphenyl-benzoselenazoles when condensed with the proper nitro- or hydroxybenzaldehydes; with oxalyl chloride it gives the *bis*-benzoselenazolyl, and with pyromucyl and α-thienyl chlorides the α-furyl- and α-thienyl-benzoselenazoles, both of the latter possessing very *agreeable* odors.

2. From the nitro derivatives, the corresponding amines were obtained by reduction, and an arsonic acid from the 2-(*p*-aminophenyl) derivative by means of the Bart reaction.

3. The sodium salt of the arsonic acid was found to be without curative value when tested upon mouse tumors.

NEW YORK, N. Y.

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[8] Bauer, *Ber.*, **48**, 507 (1915).

[9] Frerichs, *Arch. Pharm.*, **240**, 656 (1902). See also Price and Jones, *J. Chem. Soc.*, **95**, 1735 (1909). Vanino and Schinner, *J. prakt. Chem.*, [2] **91**, 123 (1915).

[10] Becker and Meyer, *Ber.*, **37**, 2551 (1903).

[11] Michaelis, *Ber.*, **30**, 2827 (1897). Michaelis and Langenkamp, *Ann.*, **404**, 27 (1914).