[CONTRIBUTION FROM THE CANCER RESEARCH LABORATORY, UNIVERSITY OF FLORIDA]

# Structure of 2,1,3-Benzoselenadiazole and Its Derivatives. I. Ultraviolet-Visible Absorption Spectra[1]

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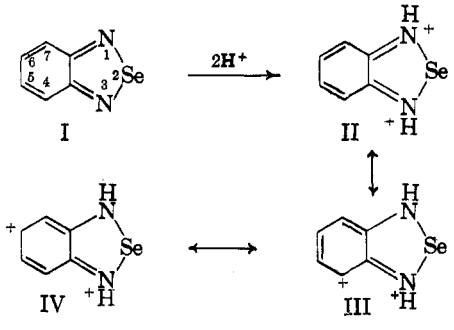
Approximately eighteen new derivatives of 2,1,3-benzoselenadiazole have been prepared. The effect of electronegative and electropositive substituents on the ultraviolet absorption spectrum of this ring system has been investigated and discussed. The $N_2Se$ grouping was found to be electron attracting.

In the preparation of derivatives of 2,1,3-benzoselenadiazole or piaselenole[4] (I) as possible purine antimetabolites for cancer chemotherapy studies, the structure of the ring system was investigated. X-ray crystallographic study of compound I, 2,1,3-benzothiadiazole, and benzofurazan has shown that these compounds in the solid state have the *ortho*-quinone structure.[5–7]

I forms a dicationic salt, II, in concentrated sulfuric acid which has the cationic reasonating structures, III and IV, contributing to the resonance hybrid. III is a much higher energy structure than IV because of the adjacent positive charges. Consequently there is a higher electron density in the 4- and 7- positions of II and nitration or sulfonation would be expected to attack these positions:

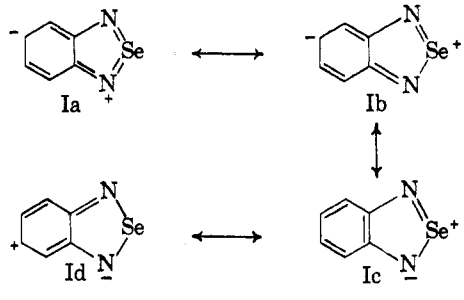


This line of reasoning would also be expected to hold for the nitration in sulfuric acid of benzofurazan, 2,1,3-benzothiadiazole, 1,2,3-benzothiadiazole, and 1,2,3-benzoselenodiazole.

The nitrations of benzofurazan[8] and 1,2,3-benzothiadiazole[9] have been reported as taking place in the 4- position. The nitration of I in sulfuric acid gave a nitro derivative, m.p. 220–221°, which is obviously the 4-nitro derivative for it is different spectrally from 5-nitro compound m.p. 223–224°, Table I.

The spectra of I and 2,1,3-benzothiadiazole are closely similar except that the spectrum of the selenium compound shows a red shift as compared to its sulfur analog, Tables I and II. This is also apparent for the 4-nitro derivatives. This phenomenon has been found previously in the spectra of analogous sulfur and selenium heterocyclic compounds.[10,11]

Some of the contributing structures to the excited state of I are:



As the structures Ia and Ib would involve either the high energy $\diagup\!\overset{+}{N}\!\diagdown$ (strained because allene type bonds are linear) or a positive charge on the selenium atom (in preference to the more electropositive nitrogen atoms), these structures would be expected to be of high energy. This fits in with the fact that I shows only a weak bathochromic shift on substitution with electronegative groups. The band found at 329–349 mμ in all derivatives of I shows a slight bathochromic shift with electron acceptor groups and a weak hypsochromic shift with the amino and methoxy substituents. This band may be associated with structures such as Ia or, most likely, Ib. An electron acceptor substituent, such as the nitro group, would accept the negative charge more readily and thus would cause a slight bathochromic shift in the spectrum. Res-

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(3) Taken in part from the Dissertation to be submitted by Albert Carr in partial fulfillment of the requirements for the Doctor of Philosophy Degree at the University of Florida.

(4) Origin of this name has been discussed by Hinsberg, *Ber.*, **22**, 862 (1889).

(5) Luzzati, *Acta Cryst.*, **4**, 193 (1951).

(6) Luzzati, *Compt. rend.*, **226**, 738 (1948).

(7) Luzzati, *Compt. rend.*, **227**, 210 (1948).

(8) Drost, *Ann.*, **307**, 49 (1899).

(9) Efros and Levit, *Zhur. Obshchei Khim.*, **23**, 1552 (1953); *Chem. Abstr.*, **48**, 12091 (1954).

(10) Sawicki, *J. Am. Chem. Soc.*, **77**, 957 (1955).

(11) Sawicki, *J. Org. Chem.*, **19**, 1163 (1954).

TABLE I

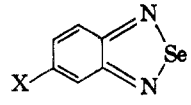
ULTRAVIOLET-VISIBLE ABSORPTION SPECTRAL DATA IN 95% ETHANOL

| Compound | $\lambda_{max}$ (log $\epsilon$) | | |
|---|---|---|---|
| 2,1,3-Benzothiadiazole | 221–222 (4.16) | 304 (4.14)<br>310 (4.14) | 330[a] (3.39) |
| 4-Nitro-2,1,3-benzothiadiazole | | 244–254 (3.61)<br>314 (4.11) | |
| 4-Nitro-I | | 268–274 (3.57)<br>337–340 (4.19) | |
| 5-Nitro-I | 230 (3.71) | 274 (4.02)<br>342 (4.21) | |
| 5-Methylsulfonyl-I | 244 (3.84) | 334 (4.27) | 358 (3.58) |
| 5-Chloro-I | 238 (3.62) | 337 (4.22) | 360 (3.58) |
| 4-Phenyl-I | 251 (4.12) | 332 (4.20)<br>340 (4.25) | 373 (3.62) |
| 4-Amino-I | 242 (4.14) | 328–332 (4.04) | 458–466 (3.28) |

[a] Underlined values are inflections. The inflections at 330, 358, and 360 mμ are very weak. See Fig. 1.

TABLE II

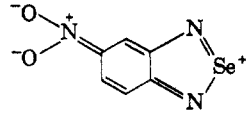
EFFECT OF 5-SUBSTITUTED ELECTRON-DONOR GROUPS ON THE ABSORPTION SPECTRUM OF 2,1,3-BENZOSELENADIAZOLE[a]



| X | $\lambda_{max}$ in mμ (log $\epsilon$) | | |
|---|---|---|---|
| H | 230–233 (3.66) | 331 (4.22) | 360[b] (3.32) |
| $CH_3$ | 230 (3.7) | 334 (4.24) | 365 (3.4) |
| $OCH_3$ | 236 (3.69) | 329 (4.04) | 358 (3.88) |
| $C_6H_5$ | 230 (4.09)<br>253 (4.34) | 346 (4.24) | 370 (3.94) |
| 4-$C_6H_4$-$C_6H_5$ | 240 (4.02)<br>273 (4.47) | 349 (4.26) | 373 (4.13) |
| $SCH_3$ | 246 (4.19) | 340 (3.94) | 390 (3.99) |
| $NH_2$ | 236 (4.25)<br>265 (3.65) | 324 (3.94) | 426 (3.80) |
| $N(CH_3)_2$ | 242 (4.26)<br>246 (4.25)<br>270 (3.75) | 326 (3.88) | 446–452 (3.83) |

[a] In 95% ethanol. [b] Underlined values are shoulders, except for the first two compounds wherein the values at 360 and 365 mμ are very weak inflections.

onance of the following type would be involved:



From the data in Tables I and II and the spectra in Figs. 1 and 2 it is evident that an electron acceptor substituent has only a weak effect on the absorption spectrum of I, while an electron donor group has a relatively strong effect dependent upon the electron donor strength of the substituent.

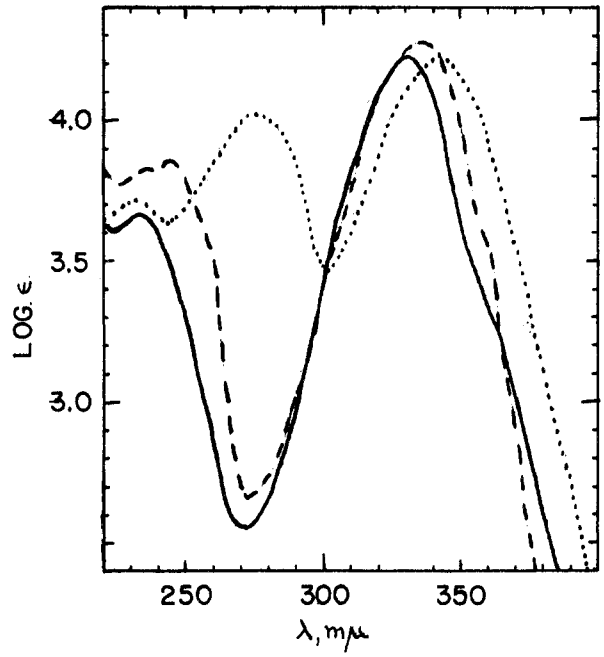



FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA IN 95% ETHANOL: 2,1,3-Benzoselenadiazole (———); 5-methylsulfonyl-2,1,3-benzoselenadiazole (– – – –); 5-nitro-2,1,3-benzoselenadiazole (. . . . . ).

In a structure such as Id the substitution of increasingly stronger electron donor groups in the benzene ring should cause a progressive decrease in the energy of the structure for the more basic substituents would accept the positive charge much more readily. This structure must be of fairly low energy in these derivatives, for in 5-substituted I there is a strong increasing shift in the spectra toward the visible with the following substituents —H < $CH_3$ < $OCH_3$ < $C_6H_5$ < $p$-$C_6H_4$—$C_6H_5$ < $SCH_3$ < $NH_2$ < $N(CH_3)_2$, Table II. This same order can be seen for *para*-substituted nitrobenzene derivatives, *e.g.*, substituent (log $\lambda_{max}$ in

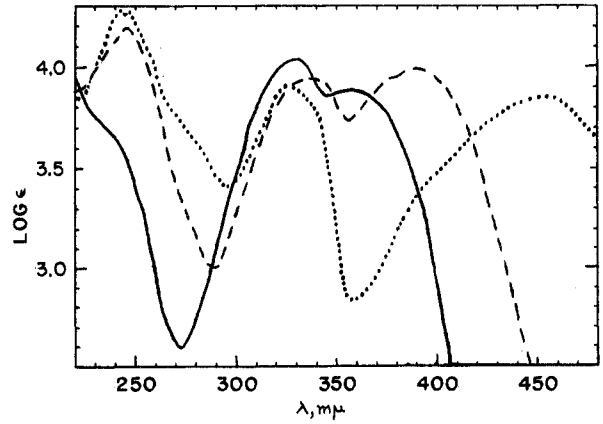



FIG. 2. ULTRAVIOLET VISIBLE ABSORPTION SPECTRA IN 95% ETHANOL: 5-Methoxy-2,1,3-benzoselenadiazole (———); 5-methylthio-2,1,3-benzoselenadiazole (– – – –); 5-dimethylamino-2,1,3-benzoselenadiazole.

(12) The spectra of all these compounds are given in alcohol except for the $CH_3$ derivative which was determined in water containing a small amount of methanol.

mμ)[12]—H(260)[13] < $CH_3$ (285)[14] < $OCH_3$ (305)[18] < $C_6H_5$ (306)[15] < $SCH_3$ (340)[16] < $NH_2$ (375)[17] < $NMe_2$ (390)[17]. Note that these nitrobenzene compounds absorb at a shorter wave length than the analogous I derivatives.

In *para*-substituted triphenylmethane dyes the same order has been found for the substituents in respect to the effect on basicity and visible absorption spectra.[18] In the few 4-substituted derivatives of I examined the same relationship is seen for the unsubstituted, phenyl and amino derivatives, Tables I and II.

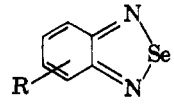
The relation between the long wave-length bands in alcohol of *p*-nitroaniline, $\lambda_{max}$ 375, log ε 4.19 and *o*-nitroaniline,[19] $\lambda_{max}$ 403–404, log ε 3.72, 4-aminoazobenzene, $\lambda_{max}$ 384–386, log ε 4.39 and 2-aminoazobenzene,[20] $\lambda_{max}$ 410, log ε 3.83 is similar to that of 5-amino-I, $\lambda_{max}$ 426, log ε 3.80 and 4-amino-I, $\lambda_{max}$ 458-466, log ε 3.28.

The long wave-length band of *o*-nitroaniline is approximately 380 mμ in hexane and 405 mμ in methanol while *p*-nitroaniline has its long wave-length band at approximately 320 mμ in hexane and 375 mμ in methanol.[21] 4-Amino-2,1,3-benzoselendiazole has $\lambda_{max}$ at 320, 328, 334, and 437 mμ in heptane and 242, 329, 336, and 462 mμ in 95% ethanol while the 5-amino compound has $\lambda_{max}$ at 322, 328, 334, and 392 mμ in heptane and 236, 324, and 426 mμ in 95% ethanol. Just as in the nitroanilines there is a red shift of the long wave-length band in alcohol as compared to the band in the less polar hydrocarbon solvent. In the spectra of 4- and 5-amino-I in heptane there is more fine structure than in alcohol.

Derivatives of I are usually prepared by the reaction between an aromatic orthodiamine and selenous acid in aqueous or alcoholic solution.[4,22] 4-Phenyl-, 5-chloro-, 5-methoxy-, and 4-nitro-I were prepared in this fashion, Table III.

TABLE III

MONOSUBSTITUTED DERIVATIVES




| R | M.P., °C. | Yield, % | Formula | Analyses Calcd. N | Analyses Found N |
|---|---|---|---|---|---|
| 4-$CH_3CONH$ | 177–178 | 80 | $C_8H_7N_3OSe$ | 17.5 | 17.6 |
| 4-$CH_2FCONH$ | 135–136 | 75 | $C_8H_6FN_3OSe$ | 16.3 | 16.4 |
| 4-$CHF_2CONH$ | 145–146 | 75 | $C_8H_5F_2N_3OSe$ | 15.2 | 15.2 |
| 4-$CF_3CONH$ | 140–141 | 95 | $C_8H_4F_3N_3OSe$ | 14.3 | 14.4 |
| 4-$C_2F_5CONH$ | 152 | 60 | $C_9H_4F_5N_3OSe$ | 12.2 | 12.0 |
| 4-$C_3F_7CONH$ | 129–131 | 50 | $C_{10}H_4F_7N_3OSe$ | 10.7 | 10.7 |
| 4-$C_2H_5OCONH$ | 89–90 | 80 | $C_9H_9N_3O_2Se$ | 15.5 | 15.7 |
| 4-$C_6H_5$ | 103–104 | 85 | $C_{12}H_8N_2Se$ | 10.8 | 10.9 |
| 5-$CH_3CONH$ | 268–270 | 90 | $C_8H_7N_3OSe$ | 17.5 | 17.2 |
| 5-$CHF_2CONH$ | 193–194 | 90 | $C_8H_5F_2N_3OSe$ | 15.2 | 15.0 |
| 5-$CF_3CONH$ | 234–235 | 95 | $C_8H_4F_3N_3OSe$ | 14.3 | 14.1 |
| 5-$C_2H_5OCONH$ | 179–180 | 55 | $C_9H_9N_3O_2Se$ | 15.6 | 15.4 |
| 5-Cl | 118–119 | 90 | $C_6H_3ClN_2Se$ | 12.9 | 12.7 |
| 5-$CH_3O$ | 110–111 | 80 | $C_7H_6N_2OSe$[a] | 13.1 | 13.3 |
| 5-$NO_2$ | 223–224 | 90 | $C_6H_3N_3O_2Se$ | 18.4 | 18.3 |

[a] Calcd.: C, 39.4; H, 2.81. Found: C, 39.5; H, 2.74.

5-Methylthio- and 5-methylsulfonyl-I were prepared by the following reaction sequence: aniline → *p*-thiocyanoaniline → *p*-thiocyanoacetanilide → 2-nitro-4-thiocyanoacetanilide[23] → 2-nitro-4-methylthioaniline → 4-methylthio-1,2,phenylenediamine → 5-methylthio-I → 5-methylsulfonyl-I.

Reduction of 4-nitro-I gave 1,2,3-triaminobenzene dihydrochloride which was reacted with selenous acid in water to give 4-amino-I. This compound and 5-amino-I were found to react readily with acyl chlorides and acid anhydrides to give beautifully crystalline acylamino derivatives, Table III. The powerful effect of an N-acyl group on the biological activity of an amine has been recently shown. 2-Aminofluorene, 2-acetylamino-

(13) Ungnade and Ortega, *J. Org. Chem.*, **17**, 1475 (1952).
(14) Doub and Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).
(15) Mangini and Passerini, *Gazz. chim. ital.*, **84**, 606 (1954).
(16) Mangini and Passerini, *J. Chem. Soc.*, 1168 (1952).
(17) Kumler, *J. Am. Chem. Soc.*, **68**, 1184 (1946).
(18) Deno, Jaruzelski, and Schriesheim, *J. Org. Chem.*, **19**, 155 (1954).
(19) Schroeder, Wilcox, Trueblood, and Dekker, *Anal. Chem.*, **23**, 1740 (1951).
(20) Approximate values from the spectral curve. Martynoff, *Compt. rend.*, **235**, 54 (1952).
(21) Dede and Rosenberg, *Ber.*, **67**, 147 (1934). Values taken from spectral curves.
(22) Hinsberg, *Ber.*, **22**, 2895 (1889).
(23) Challenger and Peters, *J. Chem. Soc.*, 1364 (1928).

fluorene, and 2-trifluoroacetylaminofluorene are cancer producing chemicals in the rat with the latter compound the most potent,[24] while 2-*p*-toluenesulfonylaminofluorene is non-carcinogenic.[25] This was the reason for the preparation of the acylamino-I derivatives.

## EXPERIMENTAL[26]

*General procedure for the preparation of acylamino-2,1,3-benzoselenadiazole derivatives*, Table III. To a solution of amino-I in benzene was added an equivalent of the acid anhydride or an acyl halide such as fluoroacetyl chloride or ethyl chlorocarbonate. An equivalent amount of pyridine was added and the mixture was refluxed 15 min. Excess water was added and the benzene was evaporated. The residue was crystallized from the appropriate solvent.

*4-Nitro-2,1,3-benzoselenadiazole.* A mixture of 1 ml. of nitric acid (*d* 1.4) and 2 ml. of sulfuric acid (*d* 1.84) was added to a solution of 1.83 g. of I in 4 ml. of sulfuric acid at 0–10°. The solution was allowed to stand 30 min. at room temperature and then poured into excess ice water. A quantitative yield of yellow product, m.p. 210–214°, was obtained. Crystallization from alcohol, methyl cellosolve, or xylene gave a 90–95% yield of crystals, m.p. 219–221°. Two crystallizations from methyl cellosolve gave an analytical sample, m.p. 220–221°. The compound in dimethylformamide solution gave a red color with 10% tetraethylammonium hydroxide.

*Anal.* Calcd. for $C_6H_3N_3O_2Se$: N, 18.4. Found: N, 18.4.

*4-Amino-2,1,3-benzoselenadiazole.* A mixture of 2.28 g. of 4-nitro-I and 8 g. of zinc dust in 70 ml. of water and 20 ml. of concentrated hydrochloric acid was refluxed vigorously for 30 min. The mixture was filtered hot and the residue was washed with a few ml. of hot water. An equal volume of concentrated hydrochloric acid was added. The solution was cooled and filtered. The crystals of triaminobenzene dihydrochloride (1.85 g., 79%) were washed with 20 ml. of dilute hydrochloric acid (concentrated aqueous hydrochloric acid diluted 1:3 with water) and dissolved in a minimum amount of water. This solution was neutralized with potassium acetate and reacted at 0–5° with 1.1 g. of selenous acid in 2 ml. of water. The mixture was filtered within a few min. The reddish brown crystals (1.4 g., 78%) melted at 154–158°. Crystallization from heptane gave orange needles, m.p. 159.5–160.5°. The amine in dimethylformamide solution gave a red color with *p*-nitrobenzenediazonium tetrafluoroborate. Upon the addition of a few drops of 10% aqueous tetraethyl ammonium hydroxide a dark blue color, $\lambda_{max}$ 620 mμ, was obtained. The 5-amino isomer gave a dark blue-violet color, $\lambda_{max}$ 580 mμ, upon reaction with the diazonium salt and tetraethylammonium hydroxide.

*Anal.* Calcd. for $C_6H_5N_3Se$: N, 21.2. Found: N, 20.8.

*5-Dimethylamino-2,1,3-benzoselenadiazole.* Twenty-one g. of finely powdered 3,4-dinitro-N,N-dimethylaniline[27] was gradually added to a stirred solution of 210 g. of stannous chloride in 210 ml. of concentrated hydrochloric acid at 0–5°. The mixture was stirred for 2 hr. at 50° and allowed to stand overnight at room temperature. It was then cooled and filtered to give approximately 15 g. of 4-dimethylamino-1,2-diaminobenzene dihydrochloride. This salt was dissolved in a minimum amount of water, neutralized with potassium carbonate, and filtered. A concentrated aqueous solution of 9.4 g. of selenous acid was added to the filtrate. Crystallization from heptane or hexane gave 4.5 g. (20%) of orange crystals, m.p. 107–109°.

*Anal.* Calcd. for $C_8H_9N_3Se$: N, 18.6. Found: N, 18.8.

*4-Methylthio-2-nitroaniline.* Twenty-five g. of 2-nitro-4-thiocyanoacetanilide[23] was dissolved in a solution of 24 g. of potassium hydroxide in 350 ml. of methanol at room temperature. Seven and a half ml. of methyl iodide was added and the mixture was allowed to stand overnight at 10–20°. Excess water was added and the precipitate was crystallized from water to give 17.5 g. (91%) of red needles, m.p. 75°. Crystallization from hexane gave red plates.

*Anal.* Calcd. for $C_7H_8N_2O_2S$: N, 15.2. Found: N, 15.1.

*5-Methylthio-2,1,3-benzoselenadiazole.* A solution of 90 g. of stannous chloride in 50 ml. of concentrated hydrochloric acid was added to a suspension of 18 g. of 4-methylthio-2-nitroaniline suspended in 50 ml. of concentrated hydrochloric acid. Following the exothermic reaction the mixture was cooled, filtered, and washed with aqueous hydrochloric acid (concentrated hydrochloric acid, 1; water, 1). Twelve g. of the diamine salt was obtained. It can be crystallized nicely from aqueous hydrochloric acid. The salt was suspended in a small volume of water; the mixture was made alkaline with sodium hydroxide, and filtered. The residue was extracted with boiling methanol and treated with an aqueous solution of 12.9 g. of selenous acid. Most of the methanol was evaporated and excess water was added. Crystallization from hexane gave 16 g. (70%) of yellow crystals, m.p. 99–100°.

*Anal.* Calcd. for $C_7H_6N_2SSe$: C, 36.7; H, 2.61; N, 12.4. Found: C, 36.9; H, 2.77; N, 12.3.

*5-Methylsulfonyl-2,1,3-benzoselenadiazole.* To a solution of 0.92 g. of 5-methylthio-2,1,3-benzoselenadiazole in 4 ml. of hot acetic acid was added 1 ml. of 30% hydrogen peroxide. The solution was warmed for 15 min. and 0.2 ml. of 30% hydrogen peroxide was added. Following an additional reflux period of 30 min., 4 ml. of water was added. The solution was allowed to cool and filtered. Crystallization from xylene or methyl cellosolve gave 0.93 g. (90%) of pale yellow crystals, m.p. 206°.

*Anal.* Calcd. for $C_7H_6N_2O_2SSe$: C, 32.2; H, 2.29; N, 10.7. Found: C, 32.3; H, 2.38; N, 10.8.

*4-Phenyl-2,1,3-benzoselenadiazole.* A hot solution of 1.3 g. of selenous acid in 5 ml. of water was added to a hot solution of 1.84 g. of 2,3-diaminobiphenyl in 10 ml. of alcohol. The solution was allowed to cool and was filtered. Crystallization from heptane gave 2.2 g. (85%) of yellow plates, m.p. 103–104°. The compound dissolved in sulfuric acid with a blue-violet color.

*5-Chloro-, 5-methoxy-, and 5-nitro-2,1,3-benzoselenadiazole* were prepared by reaction of the appropriate *o*-diamine with selenous acid by essentially the same procedure as used for the 4-phenyl derivative. Physical constants for all these compounds are given in Table III.

GAINESVILLE, FLA.

(24) Morris, *J. Natl. Cancer Inst.*, **15**, 1535 (1955).

(25) Ray and Argus, *Cancer Research*, **11**, 783 (1951).

(26) Melting points are uncorrected. Analyses are by Peninsular Chem Research, Inc., Gainesville, Fla.

(27) Romburgh, *Rec. trav. chim.*, **6**, 251 (1887).