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

3-AMINODIBENZOSELENOPHENE AND ITS DERIVATIVES[1]

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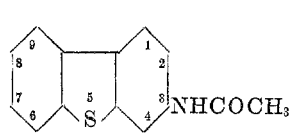
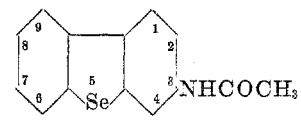
In a previous paper (1) the nitration of dibenzoselenophene was shown to take place in the 2-position. It was also demonstrated that iso-*pi*-electronic (2) dibenzothiophene and dibenzoselenophene were closely isospectral as were their iso-*pi*-electronic 2-substituted derivatives. Since it was desirable to prepare analogs of the carcinogenic 3-acetylaminodibenzothiophene I (3), such as the iso-*pi*-electronic 3-acetylaminodibenzoselenophene (II), it was necessary to introduce a nitro group in the 3-position. The procedure for the nitration of di-



I



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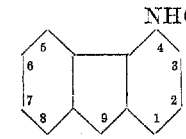

III

benzoselenophene-5-oxide was patterned after the analogous nitration of dibenzothiophene-5-oxide (4). If a nitro group were substituted in the 1-position, the spectrum of the derived acetylamino derivative would show a definite steric effect as compared to the curve for 3-acetylaminodibenzothiophene. This has been shown to be true for the analogous 4-acetylaminofluorene (III), as compared to its 2-isomer (5). Such a steric effect is absent in the acetylaminodibenzoselenophene under consideration, Fig. 1.

The substituent could not be in the 2-position for the absorption spectrum, Fig. 2, and physical properties (1) of 2-acetylaminodibenzoselenophene have been shown to be entirely different from those of the new isomer. Substitution in the 4-position should give an absorption spectrum similar to the spectra of dibenzoselenophene, 2-aminodibenzoselenophene, and 2-acetylaminodibenzoselenophene, Fig. 2. For in the 2- and 4-positions the free electrons on the nitrogen would interact mainly with the *pi* electrons of the adjacent benzene ring. The consequent transverse polarization would not have too great an effect on the topology of the curves. However, the spectra of the new dibenzoselenophene compounds are entirely different from the spectrum of dibenzoselenophene, Fig. 2. This is consistent with the fact that the amine prepared from the nitrodibenzoselenophene-5-oxide is isospectral with the known 3-aminodibenzothiophene, Fig. 3. In the same way the acetylaminodibenzoselenophene is isospectral and, on the basis of the facts presented, iso-*pi*-electronic to the known 3-acetylaminodibenzothiophene, Fig. 1, (4). The inescapable conclusion is that nitration of dibenzoselenophene-5-oxide gives the 3-nitro derivative.

Comparison of the 5-oxides of dibenzothiophene and dibenzoselenophene

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shows that these derivatives are not closely isospectral although points of resemblance can be noted for the lower energy bands, Fig. 4. This is probably because the dibenzoselenophene derivative may be present mainly as the 5,5-

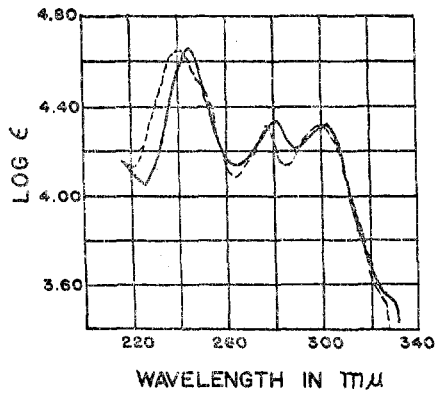

FIG. 1. 3-ACETYLAMINODIBENZOSELENOPHENE (————) AND 3-ACETYLAMINODIBENZOTHIOPHENE (- - -) in 95% ethanol

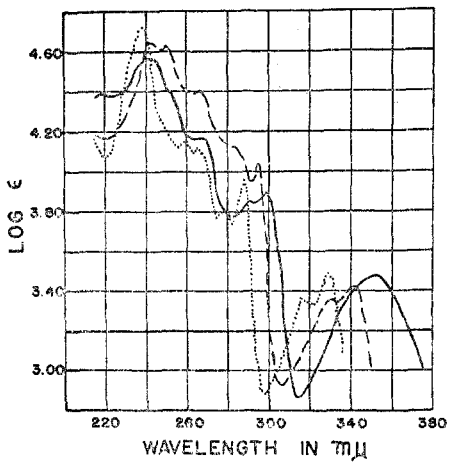

FIG. 2. DIBENZOSELENOPHENE (.....), 2-AMINODIBENZOSELENOPHENE (————), AND 2-ACETYLAMINODIBENZOSELENOPHENE (- - -) in 95% ethanol

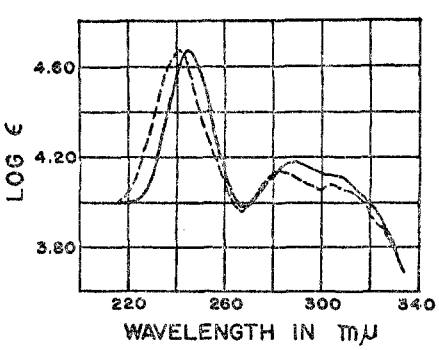

FIG. 3. 3-AMINODIBENZOSELENOPHENE (————) AND 3-AMINODIBENZOTHIOPHENE (- - -) in 95% ethanol

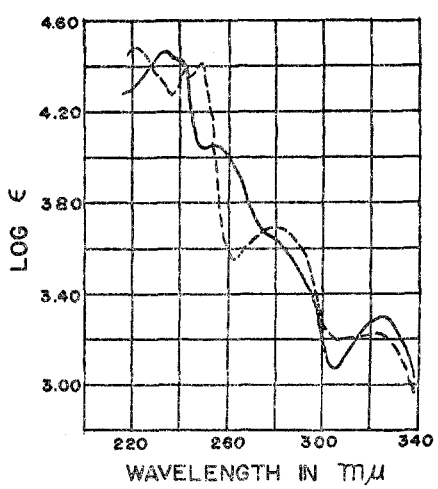

FIG. 4. DIBENZOSELENOPHENE-5-OXIDE (————) AND DIBENZOTHIOPHENE-5-OXIDE (- - -) in 95% ethanol

dihydroxide in aqueous solutions while the sulfur analog is present mostly as the 5-oxide. This fits in with the fact that no 5,5-disubstituted dibenzothiophene derivatives are known, although a 5,5-dichlorodibenzothiophene has been postu-

lated as an intermediate in the preparation of dibenzothiophene-5-oxide (4). Because of steric factors the larger selenium group can expand its outer shell of eight electrons to ten more readily than can a sulfur group. For example, 5,5-dichlorodibenzoselenophene and 5,5-dibromodibenzoselenophene have been prepared (6). Consistent with this is the solubility of dibenzoselenophene-5-oxide and its 3-nitro derivative and the insolubility of the sulfur analogs in boiling water. In Fig. 5, the spectra of 3-trifluoroacetylaminodibenzoselenophene and 3-nitrodibenzoselenophene-5-oxide are shown. The main difference between the spectra of 3-trifluoroacetyl- and 3-acetyl-aminodibenzoselenophene is the presence of shoulders at 220 and 270 mμ in the spectrum of the fluorine compound. The substitution of a 3-nitro group into dibenzoselenophene-5-oxide causes a profound change in absorption spectrum, Fig. 5.

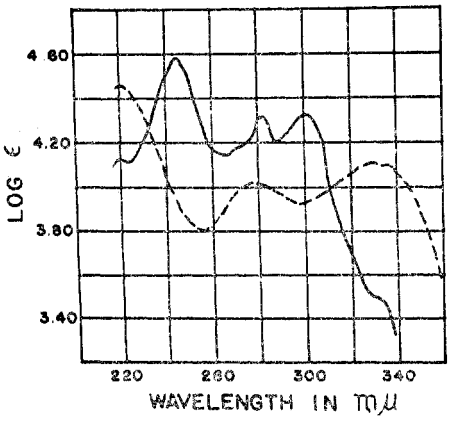

FIG. 5. 3-TRIFLUOROACETYLAMINODIBENZOSELENOPHENE (————) AND 3-NITRODIBENZOSELENOPHENE-5-OXIDE (– – –) in 95% ethanol

Carbamates have shown interesting biological properties. Many of them are powerful mitotic poisons, *e.g.*, N-2-fluorenylurethan (7). Others, such as urethan (8, 9, 10) and methylene and ethylidene diurethans (11) induce pulmonary tumors in mice. Urethan, N-phenyl-, N,N-dipropyl-, and N,N-dibutyl-urethan have shown leukopenic activity (12). Urethan has been found to be of value in the treatment of leukemia (13, 14) and carcinoma (15). Consequently, because of the possible interesting properties they may have, the following new urethan derivatives have been synthesized: β-fluoroethyl N-3-dibenzoselenyl carbamate, ethyl N-3-dibenzoselenyl carbamate, and ethyl N-3-dibenzoselenyl thiolcarbamate. β-Fluoroethyl N-3-dibenzoselenyl carbamate and 3-fluoroacetylaminodibenzoselenophene will probably form fluoroacetic acid when metabolized. As fluoroacetic acid is a powerful convulsant poison, probably because of its interference with the Krebs cycle (16, 17, 18), these two derivatives should prove to be of interest in cancer chemotherapy and biological studies. The toxicity of selenium compounds is well known. In the 3-acylaminodibenzoselenophenes, we have potential carcinogens containing a selenium atom. Thus, on this basis also, these compounds are worthy of cancer therapeutic and biological study.

EXPERIMENTAL[2]

3-Nitrodibenzoselenophene-5-oxide. Dibenzoselenophene-5-oxide (19) (3 g.) in an ice-cold mixture of 6.5 ml. of glacial acetic acid and 6.5 ml. of concentrated sulfuric acid was treated with 6.0 ml. of fuming nitric acid (*d.* 1.5) at 0–10°. After four hours it was poured into 50 ml. of ice-water and allowed to stand overnight. A yield of 2.85 g. (80%) of yellow product melting at 178–188° was obtained. When crystallized twice from water it gave light yellow needles, m.p. 211–212°.

Anal. Calc'd for $C_{12}H_7NO_3Se$: C, 49.32; H, 2.40.
Found: C, 49.08; H, 2.76.

3-Aminodibenzoselenophene. To 2.92 g. of crude 3-nitrodibenzoselenophene-5-oxide in 20 ml. of hot glacial acetic acid there was carefully added a warm solution of 20 g. of stannous chloride in 16 ml. of concentrated hydrochloric acid. The mixture was refluxed for one half hour and then allowed to stand overnight. An aqueous solution of sodium hydroxide was added dropwise to a stirred suspension of the tin complex (3.5 g. yield) in cold water until the mixture was definitely alkaline. The precipitate was crystallized from heptane to yield 1.0 g. (41%) of colorless crystals, m.p. 132–133°.

Anal. Calc'd for $C_{12}H_9NSe$: N, 5.69. Found: N, 5.52.

3-Acetylaminodibenzoselenophene. A warm solution of 2.46 g. of 3-aminodibenzoselenophene in 10 ml. of benzene was acetylated with acetic anhydride. Filtration gave 2.8 g. (97%) of product, m.p. 190–194°. Crystallization from xylene gave colorless microcrystals, m.p. 194–195°.

Anal. Calc'd for $C_{14}H_{11}NOSe$: C, 58.33; H, 3.82.
Found: C, 58.57; H, 3.92.

Fluoroacetyl chloride. This compound was prepared using the procedure of Brown (20) to give approximately a 90% yield of colorless product, b.p. 71–73°/760 mm. Lit. b.p. 71.5–73.0°/760 mm. (21).

3-Fluoroacetylaminodibenzoselenophene. A solution of 0.5 g. of 3-aminodibenzoselenophene in 2 ml. of benzene and 0.2 ml. of pyridine was reacted with 0.2 ml. of fluoroacetyl chloride. Crystallization from heptane gave 0.57 g. (92%) of colorless needles, m.p. 156–157°.

Anal. Calc'd for $C_{14}H_{10}FNOSe$: C, 54.90; H, 3.27.
Found: C, 54.72; H, 3.16.

3-Trifluoroacetylaminodibenzoselenophene. To a warm solution of 0.5 g. of 3-aminodibenzoselenophene in 5 ml. of benzene there was added 0.3 ml. of trifluoroacetic anhydride.[3] Crystallization from heptane gave 0.66 g. (95%) of small colorless needles, m.p. 185–185.5°.

Anal. Calc'd for $C_{14}H_8F_3NOSe$: C, 49.12; H, 2.34.
Found: C, 48.95; H, 2.26.

3-Trichloroacetylaminodibenzoselenophene. The same procedure was followed as for the preparation of the fluoroacetylaminodibenzoselenophene except that 0.24 ml. of trichloroacetyl chloride was used. Crystallization from heptane gave 0.71 g. (90%) of colorless needles, m.p. 168°.

Anal. Calc'd for $C_{14}H_8Cl_3NOSe$: Cl, 27.2. Found: Cl, 26.5.

Ethyl N-3-dibenzoselenyl carbamate. (*a*) 3-Aminodibenzoselenophene (2.5 g.) in pyridine was reacted with ethyl chlorocarbonate by the standard procedure. Crystallization from heptane gave 3.0 g. (94%) of colorless needles, m.p. 119–120°.

(*b*) The dried tin complex from the reduction of 2.92 g. of crude 3-nitrodibenzoselenophene-5-oxide in 25 ml. of pyridine was treated with one ml. of ethyl chlorocarbonate and the cold mixture was stirred a half hour. It was then poured into 100 ml. of ice-cold, 25% sulfuric acid. Crystallization from heptane gave 1.41 g. (43%) of colorless needles, m.p., 118.5–119.5°. The remainder of the carbamates could also be prepared in a similar fashion. This reaction between an active acyl compound and an aromatic amine tin complex in

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[2] Melting points are not corrected.

[3] Minnesota Mining and Manufacturing Co., St. Paul 6, Minn.

pyridine has been used to prepare many acylamino compounds (22) and thus is a synthetic shortcut of value.

Anal. Calc'd for $C_{15}H_{13}NO_2Se$: C, 56.60; H, 4.09.
Found: C, 56.68; H, 4.13.

β-Fluoroethyl N-3-dibenzoselenyl carbamate. The same procedure was followed as for the preparation of the preceding carbamate except that β-fluoroethyl chlorocarbonate (23, 24) was used. Crystallization from heptane gave 3.1 g. (92%) of colorless needles, m.p. 120–120.5°.

Anal. Calc'd for $C_{15}H_{12}FNO_2Se$: C, 53.57; H, 3.57.
Found: C, 53.41; H, 3.76.

Ethyl N-3-dibenzoselenyl thiolcarbamate. The same procedure was followed as for the preparation of the preceding carbamates, except that ethyl chlorothiolcarbonate (25) was used. Crystallization from heptane gave a 95% yield of colorless needles, m.p. 138–139°.

Anal. Calc'd for $C_{15}H_{13}NOSSe$: C, 53.89; H, 3.89.
Found: C, 53.72; H, 4.02.

SUMMARY

1. The nitration of dibenzoselenophene-5-oxide has been shown to take place in the 3-position.

2. The ultraviolet absorption spectra of 3-acetylaminodibenzoselenophene, 3-acetylaminodibenzothiophene, 3-aminodibenzoselenophene, 3-aminodibenzothiophene, 3-trifluoroacetylaminodibenzoselenophene, 3-nitrodibenzoselenophene-5-oxide, dibenzoselenophene, dibenzoselenophene-5-oxide, dibenzothiophene-5-oxide, 2-aminodibenzoselenophene, and 2-acetylaminodibenzoselenophene have been compared and discussed.

3. The following new compounds have been prepared for cancer research—3-nitrodibenzoselenophene-5-oxide, 3-aminodibenzoselenophene, 3-acetylaminodibenzoselenophene, 3-fluoroacetylaminodibenzoselenophene, 3-trifluoroacetylaminodibenzoselenophene, 3-trichloroacetylaminodibenzoselenophene, ethyl N-3-dibenzoselenylcarbamate, β-fluoroethyl N-3-dibenzoselenylcarbamate, and ethyl N-3-dibenzoselenylthiolcarbamate.

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