[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

THE REACTIVITY OF DIBENZOSELENOPHENE[1]

NG. PH. BUU-HOÏ AND NG. HOÁN

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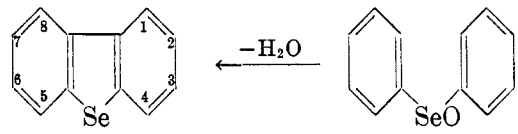
Dibenzoselenophene (I) was discovered in 1934 by Courtot and Motamedi (1), who obtained it by applying to phenyl selenoxide (II) the cyclodehydration reaction found by Schönberg for the synthesis of dibenzothiophene from phenyl sulfoxide and sodium amide (2). Later, Cullinane and associates (3) obtained



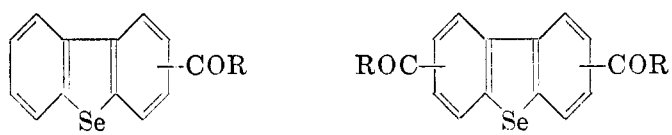
I II

dibenzoselenophene by heating either dibenzothiophene dioxide with selenium, or selenanthrene with copper bronze, and Behagel and Hofmann (4) prepared it both by a Pschorr reaction upon *o*-aminophenyl selenide, and by the treatment of *o*-biphenylselenium trichloride with potassium hydroxide. A convenient method has recently been described by McCullough, Campbell, and Gould (5), who converted *o*-aminobiphenyl to I by a three-step synthesis.

Up to now, knowledge of the chemistry of dibenzoselenophene has been very limited. Courtot and Motamedi (1) found that addition-compounds were readily obtained with two atoms of chlorine or bromine; these compounds, treated with sodium hydroxide, gave dibenzoselenophene oxide, a substance which was also obtained by McCullough and associates (5) from dibenzoselenophene and peracetic acid.

We have become interested in the reactivity of dibenzoselenophene for the purpose of comparison with that of its two more closely studied analogs: dibenzofuran and dibenzothiophene. Biologically, the outstanding toxicity of certain heterocyclic selenium compounds (6) toward the liver has been a further incentive for the synthesis of derivatives of I to be tested as potential liver-carcinogens.

Both dibenzofuran (7) and dibenzothiophene (8) are known to undergo Friedel-Crafts reactions with acid chlorides and anhydrides readily, to give mono- and di-ketones, in which molecules the acyl groups have entered chiefly positions 2 and 7, *para* to the heterocycle atom. It has now been found that dibenzoseleno-



III R = CH_3
IV R = CH_2CH_3

V R = CH_3
VI R = CH_2CH_3

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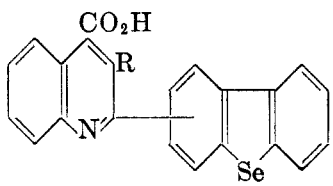
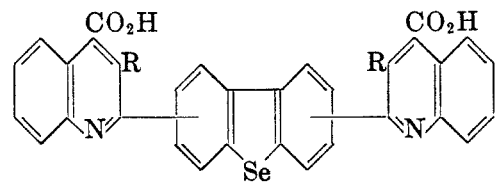
phene undergoes the Friedel-Crafts reaction in a similar way. Thus, acetylation yielded a mixture of a monoacetyldibenzoselenophene (III) and a diacetyldibenzoselenophene (V); similarly, propionylation resulted in a mixture of a monopropionyldibenzoselenophene (IV) and a dipropionylbenzoselenophene (VI). It should be mentioned that whereas in the acylations of dibenzofuran the ketones obtained showed sharp melting-points after a single recrystallization, in the case of dibenzothiophene (9) and especially of dibenzoselenophene, the ketones obtained were far more difficult to purify, and each appeared to be contaminated by at least one isomer. Since we have as yet been unable to obtain definite proofs of constitution for the new ketones prepared, no attempt will be made to assign any structure formulae to them, although, by analogy with the oxygen and sulfur series, acylation at the positions *para* to the selenium atom might be favored. If this is true, the presence of substantial amounts of isomers would mean that the quantitative difference between the orienting power of the heterocycle sulfur and selenium atoms on the one hand, and the biphenyl bond on the other, is less important than that between the heterocycle oxygen atom and the biphenyl bond. This was evidently the reason why phenacetylation of dibenzoselenophene gave but a non-crystalline monoketone, probably impure 3-phenacetyldibenzoselenophene, and a solid diketone which however melted over a wide range.

Atophan is known to produce yellow degeneration of the liver (10), and some atophan-like substances containing the dibenzoselenophene radical have therefore been prepared by the Pfitzinger reaction for testing as potential liver-poisons. Thus, 2-(x-dibenzoselenophene)-3-methylcinchoninic acid (VII) and 2-(x-dibenzoselenophene)-3-phenylcinchoninic acid (VIII) were obtained from isatin, and x-propionyl- and x-phenacetyl-dibenzoselenophene respectively. From two molecules of isatin and one of x,y-diacetyldibenzoselenophene, x,y-*bis*(4′-carboxyquinolyl)dibenzoselenophene (IX) was similarly obtained; from the mixture of isomeric diphenacetyldibenzoselenophenes, an analogous dicinchoninic acid (X) was also prepared. All these atophan-like substances were readily decar-

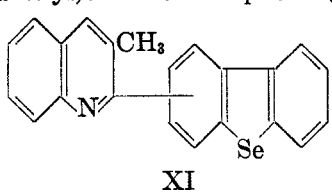


VII R = CH_3
VIII R = C_6H_5

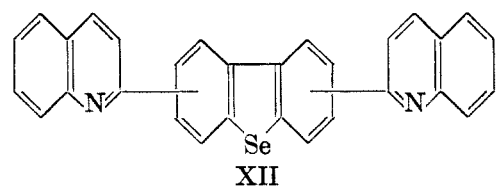


IX R = H
X R = C_6H_5

boxylated by heat to give the corresponding bases; thus were obtained for instance, x-(3′-methyl-2′-quinolyl)dibenzoselenophene (XI) and x,y-*bis*(2′-quinolyl)dibenzoselenophene (XII).

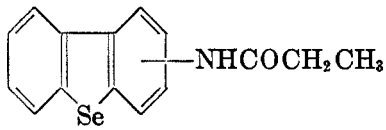


XI

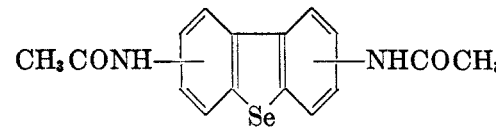


XII

Nitrogen-containing derivatives of dibenzoselenophene also synthesized for liver cancer research were x-propionylaminodibenzoselenophene (XIII) and x,y-*bis*-acetaminodibenzoselenophene (XIV), prepared by Beckmann rearrangement of x-propionyldibenzoselenophene oxime and x,y-diacetyldibenzoselenophene dioxime. These compounds are built on the same pattern as the strongly carcinogenic 2-acetoaminofluorene (11).



XIII



XIV

Preliminary biological examination has shown all the substances quoted in this paper to be highly toxic in mice.

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EXPERIMENTAL

Preparation of dibenzoselenophene. For the preparation of this compound, both the method of Courtot and Motamedi (1) and that of McCullough, Campbell, and Gould (5) were used; the latter is more convenient whenever *o*-aminobiphenyl is available.

Acetylation of dibenzoselenophene. (*a*) *With acetyl chloride.* To an ice-cooled solution of 23 g. of redistilled dibenzoselenophene and 9 g. of acetyl chloride in 150 ml. of dry carbon disulfide, 15 g. of finely powdered aluminum chloride was added in small portions with stirring, only a slight sign of reaction being observed. The mixture was kept at room temperature overnight, then poured into cold dilute hydrochloric acid. The carbon disulfide layer was washed with an aqueous solution of sodium carbonate, then with water, and dried over sodium sulfate. After removal of the solvent, the residue was vacuum-distilled, yielding 8 g. of a monoketone fraction, b.p. 265–270°/15 mm., and 10 g. of a diketone fraction, b.p. 280–300°/15 mm. Repeated recrystallization of the lower-boiling fraction from ethanol gave *x-acetyldibenzoselenophene* (III) as fine colorless needles, m.p. 134°, giving with sulfuric acid an orange-yellow coloration.

Anal. Calc'd for $C_{14}H_{10}OSe$: C, 61.5; H, 3.7.
Found: C, 61.4; H, 4.0.

Recrystallization from toluene of the higher-boiling portion yielded *x,y-diacetyldibenzoselenophene* (V) as fine colorless prisms, m.p. 213°, giving with sulfuric acid an orange coloration.

Anal. Calc'd for $C_{16}H_{12}O_2Se$: C, 61.0; H, 3.8.
Found: C, 60.8; H, 3.8.

(*b*) *With acetic anhydride.* The results were substantially the same as with acetyl chloride, except that the yield was lower and that two molecules of aluminum chloride were necessary. This experiment was performed in view of Bachmann and Cortes' observations (12) that acetyl chloride and acetic anhydride might bring about substitution at different positions in the phenanthrene series.

x,y-Bis-acetaminodibenzoselenophene (XIV). *x,y-Diacetyldibenzoselenophene dioxime* formed from a mixture of ethanol and benzene fine, pale yellowish prisms, m.p. 255°.

Anal. Calc'd for $C_{16}H_{14}N_2O_2Se$: C, 55.7; H, 4.1.
Found: C, 55.5; H, 4.2.

Beckmann rearrangement was effected by shaking a suspension of the dioxime in anhydrous ether with phosphorus pentachloride; the *diamide* (XIV) formed from ethanol fine colorless, sublimable needles, m.p. 314° (yield, 95%). The structure was proved by hydrolysis to acetic acid with hydrochloric acid.

Anal. Calc'd for $C_{16}H_{14}N_2O_2Se$: C, 55.6; H, 4.1; N, 8.1.
Found: C, 55.2; H, 4.2; N, 7.9.

Propionylation of dibenzoselenophene. The reaction was performed in the usual way with 11.5 g. of dibenzoselenophene, 6 g. of propionyl chloride, and 8 g. of aluminum chloride in 150 ml. of carbon disulfide. Yield, 8 g. of a monoketone portion, b.p. 260–270°/15 mm., and 2 g. of a diketone portion, b.p. 285–310°/15 mm. Repeated recrystallization of the former fraction gave *x-propionyldibenzoselenophene* as fine colorless prisms, m.p. 90°, giving with sulfuric acid an orange coloration.

Anal. Calc'd for $C_{15}H_{12}OSe$: C, 62.7; H, 4.2.
Found: C, 62.4; H, 4.2.

The higher-boiling fraction gave on recrystallization from a mixture of ethanol and benzene fine colorless needles, m.p. 154°, giving an orange coloration (H_2SO_4).

Anal. Calc'd for $C_{18}H_{16}O_2Se$: C, 63.0; H, 4.7.
Found: C, 62.9; H, 4.6.

x-Propionylaminodibenzoselenophene (XIII). *x-Propionyldibenzoselenophene oxime* formed from methanol or ligroin fine colorless prisms, m.p. 148°.

Anal. Calc'd for $C_{15}H_{13}NOSe$: C, 59.6; H, 4.3.
Found: C, 59.5; H, 4.6.

Beckmann rearrangement, performed as above in almost quantitative yield, gave *x-propionylaminodibenzoselenophene*, crystallizing from methanol or ligroin in fine colorless needles, m.p. 181°; hydrolysis with hydrochloric acid yielded propionic acid.

Anal. Calc'd for $C_{15}H_{13}NOSe$: C, 59.6; H, 4.3; N, 4.6.
Found: C, 59.4; H, 4.1; N, 4.5.

Phenacetylation of dibenzoselenophene. This was performed with 11.5 g. of dibenzoselenophene, 9 g. of phenacetyl chloride, and 8 g. of aluminum chloride in 150 ml. of carbon disulfide. The reaction product boiled over a wide range (about 285–300°/18 mm.), and did not solidify on prolonged storage in the refrigerator, but gave on twelve hours' reaction with isatin and potassium hydroxide in boiling ethanol, a cinchoninic acid (described below), proof that the starting compound was a monoketone. A small amount of a higher-boiling portion (above 310°/18 mm.) solidified partly on prolonged standing with ethanol, but no further purification could be effected. Nevertheless, the substance could be transformed into a dicinchoninic acid, proof that it was diketonic.

2-(x-Dibenzoselenophene)-3-methylcinchoninic acid (VII). A mixture of 1.5 g. of x-propionyldibenzoselenophene, 0.8 g. of isatin, and 0.8 g. of potassium hydroxide in 15 ml. of ethanol, was refluxed for 24 hours. After cooling, water was added, the neutral impurities were removed by ether-extraction, and the aqueous layer acidified with acetic acid. An almost quantitative yield was obtained of a *cinchoninic acid*, crystallizing from toluene or acetic acid in yellowish microscopic needles, m.p. 323°.

Anal. Calc'd for $C_{23}H_{15}NO_2Se$: C, 66.3; H, 3.6; N, 3.2.
Found: C, 66.0; H, 3.4; N, 3.4.

x-(3'-Methyl-2'-quinolyl)dibenzoselenophene (XI). Obtained by dry distillation of the foregoing acid in a high vacuum, it formed from ethanol fine colorless prisms, m.p. 134°, giving a blue coloration (H_2SO_4).

Anal. Calc'd for $C_{22}H_{15}NSe$: C, 70.9; H, 4.0.
Found: C, 70.7; H, 4.1.

The corresponding *hydrobromide* formed yellow prisms, melting with decomposition at about 272°; the *picrate* crystallized from ethanol as microscopic yellow needles, m.p. 233–234°.

2-(x-Dibenzoselenophene)-3-phenylcinchoninic acid (VIII) formed from acetic acid or toluene fine yellowish needles, softening at about 275° and melting at 292°.

Anal. Calc'd for $C_{28}H_{17}NO_2Se$: C, 70.3; H, 3.5; N, 2.9.
Found: C, 70.0; H, 3.4; N, 3.1.

The corresponding *quinoline* formed from ethanol fine colorless needles; it gave a *picrate* crystalling from ethanol in microscopic yellow prisms, m.p. 252° (decomp.), and a yellow *hydrobromide*, m.p. 206° (decomp.).

x,y-Bis(4'-carboxyquinolyl)dibenzoselenophene (IX) formed from toluene or acetic acid fine orange-yellow needles, softening above 315° and melting completely at 336°.

Anal. Calc'd for $C_{32}H_{18}N_2O_4Se$: N, 4.8; M.W. (acidimetric), 573.
Found: N, 4.5; M.W., 568.

x,y-Bis(2'-quinolyl)dibenzoselenophene (XII) formed from a mixture of ethanol and benzene fine pale yellow needles, m.p. 201°, giving an orange-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{30}H_{18}N_2Se$: C, 74.2; H, 3.7.
Found: C, 74.0; H, 4.0.

x,y-Bis(3'-phenyl-4'-carboxy-2'-quinolyl)dibenzoselenophene (X). This compound formed microscopic yellow needles, insoluble in the ordinary solvents, which did not melt even at 340°.

Anal. Calc'd for $C_{44}H_{26}N_2O_4Se$: N, 3.8, M.W. (acidimetric), 725.
Found: N, 3.5; M.W., 726.

SUMMARY

1. The behavior of dibenzoselenophene in Friedel-Crafts reactions with some acid chlorides has been investigated; dibenzoselenophene is shown to give readily both mono- and di-ketones.

2. Several nitrogen-containing derivatives of dibenzoselenophene have been prepared for biological testing as potential carcinogens of the liver.

PARIS V^e^, FRANCE

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