Synthesis and Properties of a Selenium-bridged Bisquinolone

Werner Löwe* and Robert Schmidt

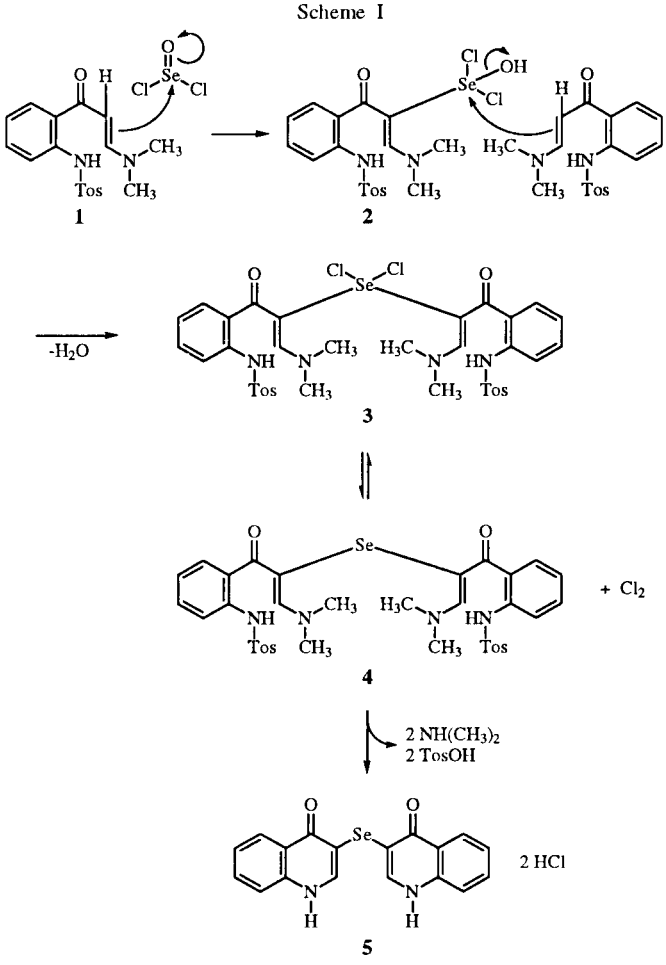
Institut für Pharmazie der Freien Universität Berlin
Königin-Luise-Str. 2+4, D-14195 Berlin, Germany
Received August 30, 1993

The preparation of the selenium-bridged bisquinolone **5** has been investigated. Compound **5** was methylated giving the *N*-methyl derivative **6**. Compound **5** and phosphorus oxychloride yielded 4-chloroquinoline **8** which was converted to novel selenium heterocycles **7, 11** and **12** and the 4-phenoxy product **9**.

J. Heterocyclic Chem., **32**, 271 (1995).

This work describes a new method for preparation of organoselenium compounds whereby electrophilic selenium oxychloride is first caused to react with the tosylated enaminone **1** [1] of the 2-aminophenylethanone type. This gives the intermediate **2** after selenium oxychloride attaches to the enamine's electron-rich β-C atom. A second enaminone reacts with **2**, thereby eliminating water and resulting in the formation of the open-ringed dichloro product **3**, which is in equilibrium with the selenide **4** and chlorine. **4** then gives the selenium- bridged bisquinolone **5** after dimethylamine elimination and detosylation (Scheme I).

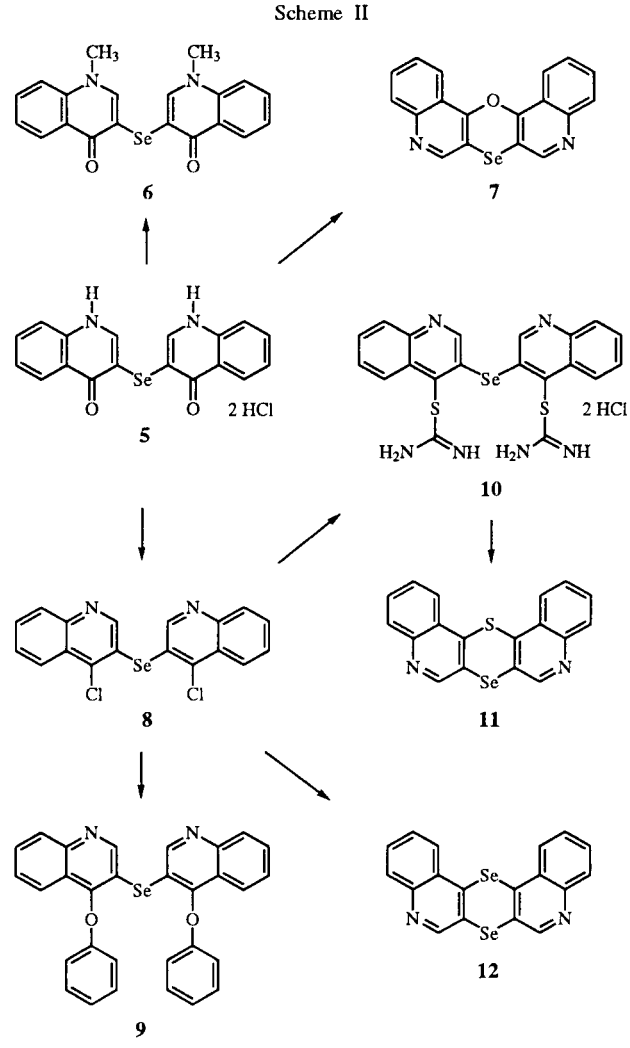
Scheme I



The fact that **5** has an H-2 singlet at 8.10 ppm and that the NH proton (exchangeable with deuterium oxide) occurs at 12.45 ppm provides evidence of ring closure. The mass spectrum shows a mole peak with characteristic isotopic patterns, and the results of elemental analysis proved that the compound **5** is present as dihydrochloride.

Since the synthetic potential of the selenobisquinolone **5** is great, a closer study of its reaction behaviour would seem worthwile (Scheme II).

Scheme II



Conceiveably, alkylation of **5** with iodomethane could yield various products; the methylation of nitrogen, oxygen or selenium could occur. However, according to the observations of Hayakara *et al.* [2], only the *N*-alkyl product **6** arises. Heating **5** with acetic anhydride does not yield an *O*-acetyl derivative, but rather leads to ring closure and the formation of the heterocyclic compound 1,4-oxaseleno[3,2-*c*:5,6-*c'*]bisquinoline (**7**) after dehydration has taken place [3].

In order to achieve chlorination, **5** was heated to boiling with phosphorous oxychloride, as described by Surrey and Hammer [4], thus giving the 4-chloroquinoline derivative **8**. Substitution of the 4-chloro atom of compound **8** with phenolate occurs in the presence of an excess of phenol in a melting reaction, thus forming the compound 3,3'-selenobis(4-phenoxyquinoline) (**9**).

The isothiuronium salt **10** arises when the compound **8** is heated with thiourea [6]. By heating the compound **10** for one hour above the decomposition point at 220°, the new heterocyclic compound 1,4-thiaselenino-[3,2-*c*:5,6-*c'*]-bisquinoline (**11**) can arise after a dicyandiamide and hydrogen sulfide molecule, respectively, have been eliminated. However, the conversion reaction of the compound **8** with selenourea proceeds in a different manner. In the latter reaction, the new heterocyclic compound 1,4-diselenino-[3,2-*c*:5,6-*c'*]bisquinoline (**12**) is formed immediately, and no isoselenuronium salt arises as the intermediate product.

EXPERIMENTAL

General Methods.

Melting points were determinated on a Linström apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 297 spectrometer. The ^{1}H-nmr spectra were recorded on a Bruker AC 300 spectrometer. Mass spectra were obtained on a Finnegan MAT Bremen CH-7A spectrometer and Finnigan MAT Bremen CH-5 DF. Elemental analyses were performed by the Institute für Pharmazie Analytical Service Laboratory.

3,3'-Selenobis(1,4-dihydroquinolin-4-one) Dihydrochloride (**5**).

Selenium oxychloride (500 mg, 3.0 mmoles) was added to a stirred solution of **1** (1 g, 2.9 mmoles) [1] in absolute acetonitrile (30 ml) and stirring continued at room temperature for 18 hours. Evaporation of the solvent gave crude **5** that was washed with chloroform (20 ml). Recrystallization of the residue from ethanol/petroleum ether (5:2) gave colorless crystals (460 mg, 72%); mp >300°; ir (potassium bromide): 3000, 1630, 1610, 1570 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.43-7.75 (m, 6H, 2H-6, 2H-7, 2H-8), 8.10 (s, 2H, 2H-2), 8.17 (d, 2H, J = 8.1 Hz, 2H-5), 12.45 (s, 2H, 2 NH); ms: m/z 368 (^{80}Se, M$^{+\bullet}$).

Anal. Calcd. for $C_{18}H_{14}Cl_2N_2O_2Se$: C, 49.12; H, 3.21; N, 6.36. Found: C, 49.42; H, 3.24; N, 6.44.

3,3-Selenobis(1-methyl-1,4-dihydroquinolin-4-one) (**6**).

Potassium carbonate (500 mg) and methyl iodide (1 g, 7.0 mmoles) were added to a vigorously stirred suspension of **5** (100 mg, 0.23 mmole) in absolute DMF (20 ml). The mixture was refluxed for 2 hours.

The solvent was evaporated and 10% aqueous sodium thiosulfate (10 ml) was added to the residue and the mixture heated under reflux for 3 minutes. Then the solution was allowed to cool. The crude product **6** was recrystallized from ethanol (45 mg, 47%); mp 313°; ir (potassium bromide): 3030, 2930, 1620, 1600 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.37 (s, 6H, 2 CH_3), 7.43-7.80 (m, 6H, 2H-6, 2H-7, 2H-8), 8.05 (s, 2H, 2H-2), 8.21 (d, 2H, J = 6.9 Hz, 2H-5); ms: m/z 396 (^{80}Se, M$^{+\bullet}$).

Anal. Calcd. for $C_{20}H_{16}N_2O_2Se\bullet H_2O$: C, 58.12; H, 4.39; N, 6.77. Found: C, 58.39; H, 4.35; N, 6.76.

1,4-Oxaselenino[3,2-*c*:5,6-*c'*]bisquinoline (**7**).

A solution of **5** (100 mg, 0.22 mmole) in acetic anhydride (3 ml) was refluxed for 3 hours. After cooling to 25°, the precipitate was collected and recrystallized from ethanol to give **7** (16 mg, 20%) as colorless plates; mp 183-184°; ir (potassium bromide): 3060, 1620, 1500, 1350, 1230, 1080 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.78-7.88 (m, 4H, H-2, H-3, H-11, H-12), 8.05 (d, 2H, J = 8.4 Hz, H-1, H-13), 8.54 (d, 2H, J = 7.8 Hz, H-4, H-10), 8.87 (s, 2H, H-6, H-8); ms: m/z 350 (^{80}Se, M$^{+\bullet}$).

Anal. Calcd. for $C_{18}H_{10}N_2OSe\bullet H_2O$: C, 58.86; H, 3.29; N, 7.62. Found: C, 58.70; H, 2.66; N, 7.61.

3,3'-Selenobis(4-chloroquinoline) (**8**).

Compound **5** (1 g, 2.3 mmoles) and phosphorus oxychloride (30 g, 196 mmoles) were heated at 120° for 45 minutes and heating continued at 150° for 1 hour. The reaction mixture was poured into ice-water. After that 14% aqueous sodium hydroxide (500 ml) was added to neutralise the mixture, followed by elution with chloroform (2 x 25 ml). The organic phase was washed with water, dried (magnesium sulfate) and evaporated under reduced pressure to afford a residue which was recrystallized from ethanol to give **8** (650 mg, 71%) as colorless needles, mp 142; ir (potassium bromide): 3060, 1610, 1550, 1330 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.84 (t, 2H, J = 7.1 Hz, 2H-7), 7.93 (t, 2H, J = 7.6 Hz, 2H-6), 8.10 (d, 2H, J = 8.3 Hz, 2H-8), 8.25 (d, 2H, J = 8.3, 2H-5), 8.76 (s, 2H, 2H-2); ms: m/z 404 (^{35}Cl, ^{80}Se, M$^{+\bullet}$).

Anal. Calcd. for $C_{18}H_{10}Cl_2N_2Se$: C, 53.49; H, 2.49; N, 6.93. Found: C, 53.50; H, 2.29; N, 6.93.

3,3'-Selenobis(4-phenoxyquinoline) (**9**).

A mixture of **8** (180 mg, 0.45 mmole) and phenole (220 mg, 2.3 mmoles) was melted at 125° for 1 hour. The residue formed by cooling was dissolved in ether (120 ml). The organic layer was washed with 10% aqueous potassium hydroxide (20 ml) and dried over sodium sulfate. Evaporation of the solvent gave **9** as a crystalline product (160 mg, 67%). Recrystallization from ethanol gave colorless needles, mp 172°; ir (potassium bromide): 3060, 1610, 1480, 1375 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.77 (d, 4H, J = 7.8 Hz, 2H-2', 2H-6'), 7.02 (t, 2H, J = 7.3 Hz, 2H-4'), 7.24 (t, 4H, J = 7.9 Hz, 2H-3', 2H-5'), 7.61 (t, 2H, J = 7.6 Hz, 2H-7), 7.76-7.85 (m, 4H, 2H-6, 2H-8), 8.11 (d, 2H, J = 8.4 Hz, 2H-5), 8.83 (s, 2H, 2H-2); ms: m/z 520 (^{80}Se, M$^{+\bullet}$).

Anal. Calcd. for $C_{30}H_{20}N_2O_2Se\bullet 1/2H_2O$: C, 68.18; H, 4.00; N, 5.30. Found: C, 68.11; H, 3.73; N, 5.13.

3,3'-Selenobis(quinolin-4-yl-isothiuronium) Dichloride (**10**).

To a suspension of **8** (300 mg, 0.74 mmoles) in ethanol (20 ml) was added thiourea (200 mg, 2.6 mmoles). The mixture was

stirred and heated under reflux for 5 minutes. The resulting yellow precipitate was filtered, washed with ethanol (3 x 20 ml) and dried in air to give analytically pure compound **10** as a yellow powder (290 mg, 73%); mp 123-125° dec; ir (potassium bromide): 3500, 2700, 1650, 1550, 1480 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.24 (s, br, 8H, $\overset{+}{N}H_2$, NH_2), 7.93-7.81 (m, 4H, 2H-6, 2H-7), 8.13 (d, 2H, J = 7.8 Hz, 2H-8), 8.72 (d, 2H, J = 8.1 Hz, 2H-5), 9.16 (s, 2H, 2H-2); +FAB-ms: m/z 485 (^{80}Se, MH^+).

Anal. Calcd. for $C_{20}H_{18}Cl_2N_6S_2Se \cdot 2H_2O$: C, 40.55; H, 3.06; N, 14,18. Found: C, 40.72; H, 3.05; N, 14.10.

1,4-Thiaselenino[3,2-*c*:5,6-*c'*]bisquinoline (**11**).

Compound **10** (200 mg, 0.36 mmole) was heated without any solvent at 220° for 1 hour. The solid was recrystallized from ethanol to give **11** as beige crystals (20 mg, 15%), mp 258°; ir (potassium bromide): 3050, 1550, 1485 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 7.79-7.91 (m, 4H, H-2, H-3, H-11, H-12), 8.12 (d, 2H, J = 8.2 Hz, H-1, H-13), 8.65 (d, 2H, J = 7.8 Hz, H-4, H-10), 9.13 (s, 2H, H-6, H-8); ms: m/z 366 (^{80}Se, $M^{+\bullet}$).

Anal. Calcd. for $C_{18}H_{10}N_2SSe \cdot 1/2H_2O$: C, 57.75; H, 2.69; N, 7.48. Found: C, 57.40; H, 2.52; N, 7.46.

1,4-Diselenino[3,2-*c*:5,6-*c'*]bisquinoline (**12**).

Selenourea (200 mg, 2.6 mmoles) was added to a suspension of **8** (300 mg, 0.74 mmole) in ethanol (20 ml). The mixture was heated under reflux for 10 minutes. The resulting precipitate was removed by filtration and recrystallized from ethanol to give **12** (37 mg, 15%) as colorless needles; mp 279°; ir (potassium bromide): 3045, 1545, 1485 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 7.78 (t, 2H, J = 7.1 Hz, H-3), 7.77 (t, 2H, J = 7.6 Hz, H-2, H-12), 8.13 (d, 2H, J = 8.2 Hz, H-1, H-13), 8.47 (d, 2H, J = 7.5 Hz, H-4, H-10), 9.06 (s, 2H, H-6, H-8); ms: m/z 415 (^{80}Se, $M^{+\bullet}$).

Anal. Calcd. for $C_{18}H_{10}N_2Se_2$: C, 52.44; H, 2.45; N, 6.80. Found: C, 52.06; H, 2.27; N, 6.97.

REFERENCES AND NOTES

[1] A. Kietzmann, Diss., FU Berlin 1986.

[2] I. Hayakawa, N. Suzuki, K. Suzuki and Y. Tanaka, *Chem. Pharm. Bull.*, **32**, 4914 (1984).

[3] R. Gompper, H. Euchner and H. Kast, *Liebigs Ann. Chem.*, **675**, 151 (1964).

[4] A. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **68**, 1532 (1946).

[5] A. Surrey and R. Cutler, *J. Am. Chem. Soc.*, **73**, 2623 (1951).

[6] E. Rosenhauer, H. Hoffmann and W. Heuser, *Ber.*, **62**, 2730 (1929).