Synthesis of a Selenium Analogue of Ellipticine: 5,11-dimethyl[1]benzoselenolo[2,3-*g*]isoquinoline

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A selenium analogue of the anti-cancer agent ellipticine (**2**; 5,11-dimethyl[1]benzoselenolo[2,3-*g*]isoquinoline) has been synthesized in eight steps, with an overall yield of 12%. The key intermediate is 1,4-dimethyldibenzoselenole **4** which has been obtained through an electrophilic cyclization of the corresponding selenide **5d**. The synthesis of **5d** was realized through a careful adaptation of the methods used in the synthesis of biaryls.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Ellipticinium acetate (9-hydroxy-2-methylellipticinium acetate) (**1**) is used as an antitumour drug.[1] Following our efforts to synthesize selenium analogues of natural[2–4] and biologically[5,6] active molecules, we have designed a synthesis for the preparation of the unknown selenoellipticine **2**. To our knowledge little is known about the pharmacological activity of oxygen and sulfur analogues[7–9] of ellipticine.

Results and discussion

Among the numerous syntheses of ellipticine derivatives[10–14] which can be adapted to organoselenium chemistry, the most attractive one,[15] based on *ortho*-lithiation reactions did not produce satisfactory results. So, sequential treatment of *N,N*-diethylisonicotinamide with *n*-butyllithium, 2-bromo-3-formylbenzo[*b*]selenole[16] and *n*-butyllithium resulted only in the self-condensation product of the starting amide.[17] By analogy with indole chemistry,[18] exploratory condensation of 2-lithiobenzo[*b*]thiophene with 3,4-pyridinedicarboxylic anhydride gave a mixture of two keto acids from which we were able to isolate the interesting isomer, the 4-(benzo[*b*]thiophene-2-carbonyl)nicotinic acid (**3**). Unfortunately we did not succeed in cyclizing the latter compound to the required tetracyclic quinone. Therefore we considered the 1,4-dimethyldibenzoselenole **4** as a possible intermediate to the target molecule **2**. Methods involving the synthesis of **4** through direct introduction of selenium onto organolithium or mercury(II) derivatives obtained from 2,5-dimethylbiphenyl[19–22] were unsatisfactory. The selenide **5d** was thus considered to be the most convenient precursor of **4** (Scheme 1). It has previously been obtained (20% yield) by coupling[23] 2-bromoselenoanisole[24] with 2,5-dimethylphenylboronic acid[25] or 2-methylselenobenzenediazonium tetrafluoroborate[24] with *p*-xylene.[26] Nevertheless, improved results were observed by introducing the selenium atom onto an appropriately substituted biphenyl. Thus selenide **5d** is available (50% yield) from the 2-lithio derivative of 2-bromo-2′,5′-dimethylbiphenyl (**5a**) [*n*-BuLi, $(CH_3Se)_2$]. We have found that the best method is the reduction of 2-nitro-2′,5′-dimethylbiphenyl (**5b**). A 90% yield was obtained through the boronic acid coupling technique[23] and condensation of the corresponding diazonium tetrafluoroborate with dimethyldiselenide.[24] The cyclization of selenides of type **5d** is well documented[1] and is always realized through intermediary selenenyl halides.

Nevertheless, by-products arising from side halogenation of the arene[1] often result when this method is used. We therefore applied a cyclization method using concentrated sulfuric acid as described by Japanese workers in the case of the synthesis of selenanthrene.[27] Surprisingly, a 65% yield of pure heterocycle **4** was obtained. The following conversion of dibenzoselenophene derivative **4** to selenoellipticine **2** is essentially an adaptation of the methodology developed for the construction of the oxygen and sulfur analogues of ellipticine.[7–9] Formylation (Cl_2CHOCH_3, $SnCl_4$) of compound **4** produces the aldehyde **6**, whose structure was firmly established by ^1H NMR spectroscopy. Indeed it is well known that in phenanthrene and its isosteres, the methyl group in position 1 is always deshielded.[7,8,28–30] Additive increments of the formyl group on the 1-methyl of **6** verify the assignment. Moreover an NOE effect clearly proves the positioning of both formyl and 1-methyl groups. Indeed, irradiation of the more deshielded methyl (CH_3 in position 1)

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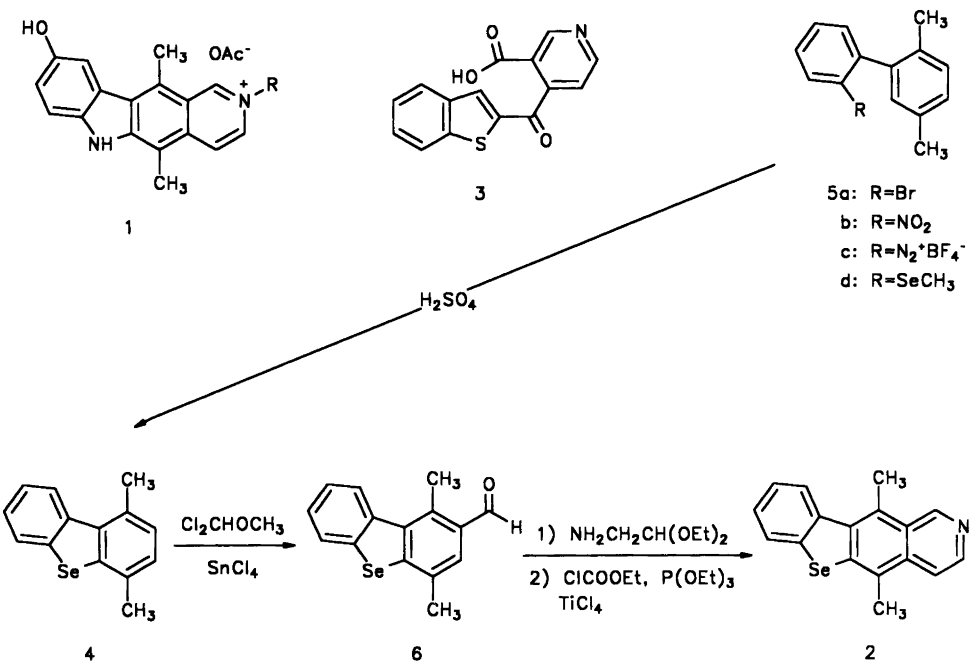

Scheme 1.

causes a decrease of the integration of both 9-H (78%) and CHO (50%). Moreover, decoupling of the methyl at higher field (CH_3 in position 4) leads to the decrease of the 3-H integration (95%). Condensation of the aldehyde **6** with aminoacetaldehyde diethylacetal affords the intermediate imine which was cyclized following an improved Pomeranz–Fritsch reaction.[31]

The target molecule **2** has been fully characterized by ^1H, ^{13}C and ^{77}Se NMR spectroscopy, mass spectrometry and elemental analysis.

Experimental

Solvents (C.P.) and products were from Janssen Chimica. All isolated products were pure on TLC (at least two elution systems). The usual work-up consisted of pouring the reaction mixture into dilute HCl, extraction, washing with a base if necessary, drying and removal of the solvent(s) under vacuum. Recrystallizations were carried out in E40 (light petroleum b.p. 40–60°C); E60 (light petroleum b.p. 60–80°C); T (toluene); TA (toluene–ethanol); AA (ethanol, acetic acid); A.EtOAc (ethanol–ethyl acetate); Ace (acetone). Chromatographic separations were performed on SiO_2 (Macherey Nagel 81533). Melting points (uncorrected) are given in °C. Elemental analyses are given in %. IR spectra (KBr 1%) are in cm^{-1}. ^1H NMR shifts ($CDCl_3$) are in ppm (δ) or Hz (*J*) and were determined at 400 MHz (unless otherwise stated). ^{13}C NMR shifts (100 MHz, $CDCl_3$) (broad-band decoupling) are in ppm (δ) with respect to hexamethyldisiloxane (HMDSO). ^{13}C values were attributed on the basis of values of 1-benzoselenole derivatives.[32] ^{77}Se NMR shifts (76 MHz, $CDCl_3$) are given in ppm (δ) with respect to CH_3SeCH_3 as an external standard. They were compared with ^{77}Se of 1-benzoselenole at 526 ppm.[33] Low resolution mass spectra are given in *m/z* for the most abundant natural isotopes (^{80}Se, ^{79}Br). ^1H and ^{13}C were attributed by comparison with dibenzoselenole[32] and its chalcogen analogues.[7,8,34–36]

2,5-Dimethylphenylboronic acid (m.p. 165°C) was obtained (80% yield) from 2-bromo-*p*-xylene and by analogy with a described method.[25] Condensation[26] of *o*-bromobenzenediazonium tetrafluoroborate with *p*-xylene produced a 60% yield of 2-bromo-2′,5′-dimethylbiphenyl (**5a**). This was Kugelrohr distilled and used in the next reaction, after verifying the purity and M^+ by GC–MS. The nitro derivative **5b** was synthesized (90% yield) from *o*-bromonitrobenzene and 2,5-dimethylphenylboronic acid.[23] It was purified by rapid distillation (b.p. 160°C/1 mmHg) (purity and M^+ verified by GC–MS). Its reduction (CH_3OH, Pd/C 10%, H_2 50 psi) gave 2-amino-2′,5′-dimethylbiphenyl, purified by means of acid–base treatment (90% yield) (purity and M^+ verified by GC–MS), which was transformed into its diazonium tetrafluoroborate **5c**.[24]

2-Methylseleno-2′,5′-dimethylbiphenyl (**5d**). (a) The bromobiphenyl **5a** (5.82 g, 22.3 mmol) was dissolved in 80 ml of dry THF and added under argon to 0.312 g (44.6 mmol) of Li. Stirring was maintained until complete dissolution occurred and 5.7 g (2.9 ml, 30 mmol) of $(CH_3Se)_2$ were added dropwise. The mixture was left overnight at room temperature. After the usual work-up the selenide was purified by LC (silica, eluent cyclohexane–toluene 9:1). It was isolated (3.1 g, 50% yield) as

yellowish crystals (m.p. 60°C). ^{1}H NMR: 2.08 (s, CH_3), 2.32 (s, CH_3), 2.19 (s, $SeCH_3$, J ^{77}Se–CH_3 = 15), 7.24–7.61 (m, 7 ArH). ^{77}Se NMR: 187.2 ppm (C_6H_5–$SeCH_3$: 203).[37] MS: 276 (M^+).

(b) The tetrafluoroborate **5c** (5.9 g, 20 mmol) was treated[24] with $(CH_3Se)_2$ (7.5 g, 3.8 ml, 40 mmol). After the usual work-up and chromatography, a compound was obtained (3.85 g, 70% yield) which was identical with **5d** described above.

1,4-Dimethyldibenzoselenole (**4**). The selenide **5d** (2.5 g, 9.1 mmol) was dissolved gradually in 50 ml of conc. H_2SO_4. The solution was stirred for 20 h at room temperature with exclusion of moisture. The mixture was then poured dropwise into 250 ml of water containing 300 mg of Zn powder. The mixture was then refluxed for 3 h. After the usual extraction and work-up, the residue was chromatographed (SiO_2, cyclohexane). The heterocycle **4** was obtained (1.53 g, 65% yield) as yellowish crystals (m.p. 46°C). Dibenzoselenole was synthesized in the same way (60% yield) and was identical with an authentic sample.

^{1}H NMR: *dibenzoselenole*: 7.28–7.32 (m, 2-H, 3-H, 7-H, 8-H), 7.74–7.78 (m, 4-H, 6-H), 7.96–8.02 (m, 1-H, 9-H).

^{1}H NMR: *1,4-dimethyldibenzoselenole*: 2.38 (s, 4-CH_3), 2.71 (s, 1-CH_3), 6.95 (m, 8-H), 7.03 (m, 7-H), 7.23 (m, 3-H), 7.32 (m, 2-H), 7.78 (dd, 6-H, J_{6-7} = 8.8, J_{6-8} = 1), 8.24 (dd, 9-H, J_{8-9} = 8.2, J_{7-9} = 1).

^{13}C NMR: *dibenzoselenole*:[36] (some values may be reversed): 124.7 (C-4, C-6), 125.9 (C-1, C-9), 126.1 (C-2, C-8), 126.8 (C-3, C-7), 138.2 (C-9a, C-9b), 139.2 (C-4a, C-5a).

^{13}C NMR: *1,4-dimethyldibenzoselenole*: 22.2 (4-CH_3), 22.9 (1-CH_3), 124.4, 125.5, 125.8, 125.9, 125.95, 126.5 (C-2, -3, -6, -7, -8, -9), 131.9, 133.2 (C-1, C-4), 136, 139.2, 140.2, 141.2 (C-4a, -5a, -9a, -9b). Owing to an NOE effect during total decoupling, the intensity of 1-CH_3 is smaller than that of 4-CH_3.

^{77}Se NMR: *dibenzoselenole*: 451, *1,4-dimethyldibenzoselenole*: 427. MS: 260 (M^+). Anal. $C_{14}H_{12}Se$: C, H.

2-Formyl-1,4-dimethyldibenzoselenole (**6**). To a cold solution (0°C) of 1,4-dimethyldibenzoselenole (**4**) (1.23 g, 4.7 mmol) in CH_2Cl_2 (20 ml), was added anhydrous $SnCl_4$ (1 ml). The temperature was kept at 0°C for 90 min whereupon dichloromethyl methyl ether (0.87 g, 0.68 ml, 7.53 mmol) was added in 10 ml of CH_2Cl_2. After an hour of stirring at 0°C and the usual work-up, a white solid was obtained. After chromatography (SiO_2, hexane then toluene) and recrystallization in hexane, the aldehyde **6** was isolated (0.87 g, 65% yield) as white flakes (m.p. 95°C). ^{1}H NMR: 2.42 (s, 4-CH_3), 2.98 (s, 1-CH_3), 7.37 (dd, 7-H, J_{6-7} = 7.8, J_{7-8} = 7.2), 7.42 (dd, 8-H, J_{8-9} = 8.2, J_{6-8} = 1.2), 7.55 (s, 3-H), 7.87 (d, 6-H), 8.36 (d, 9-H), 10.4 (s, CHO). ^{13}C NMR: 16.4 (4-CH_3), 22.1 (1-CH_3), 132.35, 132.4, 136.8, 137.2, 139.45 (C-1, C-4, C-5a, C-9a, C-9b), 148.5 (C-4a), 192.1 (C=O) (note that here again 1-CH_3 is smaller than 4-CH_3). ^{77}Se NMR: 447. MS: 288 (M^+). IR: $\nu_{C=O}$ 1695 cm^{-1}. Anal. $C_{15}H_{12}OSe$: C, H.

Selenoellipticine (**2**). The aldehyde **6** (1 g, 3.48 mmol) was dissolved in 50 ml of dry toluene and refluxed (Dean–Stark) with 0.46 g (0.5 ml, 3.5 mmol) of aminoacetaldehyde diethylacetal. The solvent was then removed under vacuum and the intermediate imine was isolated (m.p. 90°C from hexane). ^{1}H NMR: 1.19 (t, 2 × CH_3), 2.48 (s, 4-CH_3), 2.93 (s, 1-CH_3), 3.56 and 3.74 (q, 2 × CH_2), 3.82 (d, CH_2N–), 4.83 (t, CH), 7.33 (d, 7-H, J_{6-7} = 6.8), 7.4 (d, 8-H, J_{8-9} = 7.4), 7.71 (s, 3-H), 7.9 (d, 6-H), 8.4 (d, 9-H), 8.79 (s, CH=N). ^{13}C NMR: 15.3 (CH_2CH_3), 17.1 (1-CH_3), 22.2 (4-CH_3), 62.5 (CH_2CH_3), 65 (CH_2N), 102.1 (CH), 124.6, 125.7, 126.1, 127.1 (C-3, C-6, C-7, C-8, C-9), 132.1, 132.7, 133.3 (C-2, C-1, C-9b), 139.5 (C-4), 136.7, 140.1, 144.2 (C-9a, C-4a, C-5a), 162.9 (C=N). ^{77}Se NMR: 434. IR: $\nu_{C=N}$ = 1630 cm^{-1}. MS: 443. Anal. $C_{21}H_{25}NO_2Se$: C, H, N.

The crude imine was dissolved in 30 ml of dry THF. Ethyl chloroformate (0.38 g, 0.34 ml, 3.48 mmol) was then added with stirring at 0°C. After 15 min, triethyl phosphite (0.70 g, 0.72 ml, 4.2 mmol) was introduced at −10°C. Stirring was maintained for 1 h at 0°C and then overnight at room temperature. Volatiles were removed twice with toluene. The oily residue was taken up in 30 ml of dry CH_2Cl_2, treated with $TiCl_4$ (4.0 g, 2.35 ml, 21 mmol) and refluxed for 24 h. The mixture was basified at 0°C. The solid TiO_2 was washed with 20 ml EtOH and then with 100 ml of CH_2Cl_2. After the usual work-up, the solid residue was chromatographied (SiO_2, toluene–isopropyl alcohol; 8:2). Selenoellipticine (0.7 g, 65% yield) was obtained as pale-yellow microcrystals of m.p. 150°C.

^{1}H NMR: 2.39 (s, 5-CH_3), 2.79 (s, 11-CH_3), 7.3–7.4 (m, 7-H, 9-H), 7.45 (d, 4-H), 7.70–7.71 (m, 8-H), 8.06–8.07 (m, 10-H), 8.40 (d, 3-H, J_{3-4} = 5.7), 9.44 (s, 1-H). ^{13}C NMR: 15.9 (11-CH_3), 19.0 (5-CH_3), 115.3 (C-5), 125.9 (C-11a), 124.6, 124.62, 125.9, 127.7 (C-4, -7, -8, -10) interchangeable, 130.8 (C-10b), 131.6 (C-4a), 135.2 (C-10a), 138.7 (C-11), 139.2 (C-5a), 141.6 (C-3), 143.1 (C-6a), 150.0 (C-1). Peaks were attributed on the basis of, on the one hand our results for the compounds **4** and **6**, and on the other, of recent work on ellipticine itself.[28] ^{77}Se NMR: 431. Anal. $C_{17}H_{13}NSe$: C, H, N. MS: 311 (M^+).

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