SYNTHESIS OF SULFUR AND SELENIUM ANALOGUES OF PSORALEN

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Abstract - *7H-Thieno[3,2-g][1]benzothiopyran-7-one (**1a**), 7H-selenopyrano[3,2-f][1]benzothiophen-7-one (**1b**), 2H-selenolo[3,2-g][1]benzothiopyran-2-one (**1c**), 7H-selenolo[3,2-g][1]benzoselenopyran-7-one (**1d**) have been synthesized.*

INTRODUCTION

Psoralens (derivatives of furo[3,2-*g*][*1*]benzopyran-7-one) are commonly used in the photochemotherapy (PUVA therapy) of vitiligo and psoriasis as well as reagents for the biophysical study of nucleic acids.[1,2] Several viruses[3] and tumor cells[4,5] have been photoinactivated by furocoumarins. Psoralens have been shown to intercalate nucleic acids and undergo photochemically induced [2+2] cycloadditions to adjacent pyrimidine bases to form a monoadduct or a cross-link.[6] Cross-link formation has been associated with mutagenic and carcinogenic properties of linear furocoumarins and thus shows undesired side-effects in the photochemotherapy.[7]

Among the different approaches which have been followed to obtain psoralens with superior photoreactivity one consists in the synthesis of hetero analogues of psoralen.

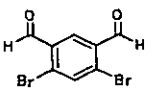
So far, some nitrogen[8-11] and sulphur[12] analogues have been described. Our intention is to investigate sulphur and selenium analogues of psoralen since their photochemical and photobiological behaviour would be expected

to be modified by replacing the oxygen heteroatoms by either sulphur or selenium. Light absorption by these analogues at 365 nm should be enhanced compared to psoralen since replacement of the oxygen atom in either benzofuran[13] and 2*H*-benzopyran-2-one[14] by other chalcogens present a bathochromic effect. Furthermore, the geometry and the enophilic character of hetero psoralens are expected to be modified compared to psoralen itself.

The photophysical properties of psoralens are well described[15] but to our knowledge, no study on behalf of the effect of a heavy atom (like selenium) on psoralen photoreactivity has been reported. We wish to report here the synthesis of the four possible hetero psoralens where sulphur and selenium replace the two intracyclic oxygen atoms of psoralen.

RESULTS AND DISCUSSION

4,6-Dibromoisophthalaldehyde[16] (**2**) is a very versatile starting material for the synthesis of all sulphur and selenium analogues of psoralen. It reacts with one equivalent of potassium ethanethiolate in DMF to yield 4-bromo-6-ethylthioisophthalaldehyde (**3a**). This aldehyde yields 2-ethoxycarbonyl-6-ethylthio-5-formylbenzo[*b*]thiophene (**5a1**) upon reaction with one equivalent of ethyl 2-mercaptoacetate in basic medium. Saponification of this ester (**5a1**) followed by decarboxylation of the corresponding acid (**5a2**) affords 6-ethylthio-5-formylbenzo[*b*]thiophene (**5a3**). This thioether (**5a3**) can easily be transformed into 5-(2-ethoxycarbonylvinyl)-6-ethylthiobenzo[*b*]thiophene (**6a1**) by a Wittig-Horner[17] reaction using triethyl phosphonoacetate and C-200 ($BaCO_3.0,8H_2O$) as catalyst. The ester function of this acrylic acid derivative (**6a1**) is hydrolysed to 5-(2-carboxyvinyl)-6-ethylthiobenzo[*b*]thiophene (**6a2**). Cyclization of **6a2** in polyphosphoric acid silyl ether (PPSE)[18] leads to 7*H*-thieno[3,2-*g*][*1*]benzothiopyran-7-one (**1a**).



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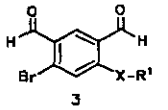

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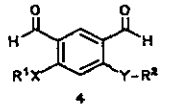
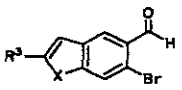


4

3a: X=S, R^1=C_2H_5
3c1: X=Se, R^1=CH_3
3c2: X=Se, R^1=$CH_2COOC_2H_5$

4a: X=S, Y=S, R^1=C_2H_5, R^2=C_2H_5
4c: X=Se, Y=Se, R^1=CH_3, R^2=C_2H_5
4d: X=Se, Y=Se, R^1=CH_3, R^2=CH_3



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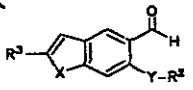
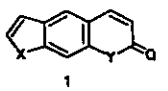


5

7a1: X=S, R^3=$COOC_2H_5$
7a2: X=S, R^3=COOH
7a3: X=S, R^3=H
7c1: X=Se, R^3=$COOC_2H_5$
7c2: X=Se, R^3=COOH
7c3: X=Se, R^3=H

5a1: X=S, Y=S, R^2=C_2H_5, R^3=$COOC_2H_5$
5a2: X=S, Y=S, R^2=C_2H_5, R^3=COOH
5a3: X=S, Y=S, R^2=C_2H_5, R^3=H
5b1: X=S, Y=Se, R^2=CH_3, R^3=$COOC_2H_5$
5b2: X=S, Y=Se, R^2=CH_3, R^3=COOH
5b3: X=S, Y=Se, R^2=CH_3, R^3=H
5c1: X=Se, Y=S, R^2=C_2H_5, R^3=$COOC_2H_5$
5c2: X=Se, Y=S, R^2=C_2H_5, R^3=COOH
5c3: X=Se, Y=S, R^2=C_2H_5, R^3=H
5d1: X=Se, Y=Se, R^2=CH_3, R^3=$COOC_2H_5$
5d2: X=Se, Y=Se, R^2=CH_3, R^3=COOH
5d3: X=Se, Y=Se, R^2=CH_3, R^3=H



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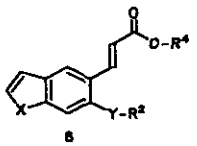

6

1a: X=S, Y=S
1b: X=S, Y=Se
1c: X=Se, Y=S
1d: X=Se, Y=Se

6a1: X=S, Y=S, R^2=C_2H_5, R^4=C_2H_5
6a2: X=S, Y=S, R^2=C_2H_5, R^4=H
6b1: X=S, Y=Se, R^2=CH_3, R^4=C_2H_5
6b2: X=S, Y=Se, R^2=CH_3, R^4=H
6c1: X=Se, Y=S, R^2=C_2H_5, R^4=C_2H_5
6c2: X=Se, Y=S, R^2=C_2H_5, R^4=H
6d1: X=Se, Y=Se, R^2=CH_3, R^4=C_2H_5
6d2: X=Se, Y=Se, R^2=CH_3, R^4=H

To synthesize 7*H*-selenopyrano[3,2-*f*][*1*]benzothiophen-7-one (**1b**), we first converted the 4,6-dibromoisophthalaldehyde (**2**) into 6-bromo-2-ethoxycarbonyl-5-formylbenzo[*b*]thiophene (**7a1**). Two further steps lead to 6-bromo-5-formylbenzo[*b*]thiophene (**7a3**). The bromine atom of 6-bromo-5-formylbenzo[*b*]thiophene (**7a3**) is substituted by methaneselenolate to afford 5-formyl-6-methylselenobenzo[*b*]thiophene (**5b3**). This aldehyde (**5b3**) is reacted with triethyl phosphonoacetate to yield 5-(2-ethoxycarbonylvinyl)-6-methylselenobenzo[*b*]thiophene (**6b1**). The latter is saponified to the corresponding acid (**6b2**) which upon cyclisation yields 7*H*-selenopyrano[3,2-*f*][*1*]benzothiophen-7-one (**1b**).

In order to obtain 2*H*-selenolo[3,2-*g*][*1*]benzothiopyran-2-one (**1c**), 4,6-dibromoisophthalaldehyde (**2**) is successively reacted with one equivalent of potassium ethanethiolate and one equivalent of potassium methaneselenolate affording 4-ethylthio-6-methylselenoisophthalaldehyde (**4c**). Inversion of the addition of these two reagents leads to a mixture containing principally 4,6-diethylthioisophthalaldehyde (**4a**). We then constructed 6-ethylthio-5-formylbenzo[*b*]selenophene (**5c3**) in the following way : 4-ethylthio-6-methylselenoisophthaladehyde (**4c**) is refluxed in ethyl bromoacetate and the selenoether obtained thus is cyclized to the benzo[*b*]selenophene derivative (**5c1**). This ester (**5c1**) is saponified and the resulting acid (**5c2**) is decarboxylated to 6-ethylthio-5-formylbenzo-[*b*]selenophene (**5c3**). We then followed the same reaction procedure as for the hetero psoralens described above: The aldehyde (**5c3**) is transformed into ester (**6c1**). Hydrolysis of this ester gives the acid (**6c2**) which is cyclized to the heterocycle (**1c**).

7*H*-Selenolo[3,2-*g*][*1*]benzoselenopyran-7-one (**1d**) is accessible through reaction of methaneselenolate with 2-ethoxycarbonyl-6-bromo-5-formylbenzo-[*b*]selenophene (**7c1**). This compound (**7c1**) is obtained by first reacting 4,6-dibromoisophthalaldehyde (**2**) with one equivalent of potassium methaneselenolate in acetonitrile to yield 69% of 4-bromo-6-methylseleno-

isophthalaldehyde (**3c1**). The same reaction in DMF leads to a mixture of 4,6-dimethylselenoisophthalaldehyde (**4d**), 4-bromo-6-methylselenoisophthalaldehyde (**3c1**) and 4,6-dibromoisophthalaldehyde (**2**).

The methylseleno ether (**3c1**) is subsequently refluxed in ethyl bromoacetate to afford the precyclic selenoether (**3c2**).

Selenophene ring closure is completed by potassium carbonate. The resulting 6-bromo-2-ethoxycarbonyl-5-formylbenzo[*b*]selenophene (**7c1**) is reacted with one equivalent of potassium methaneselenolate to yield 2-ethoxycarbonyl-5-formyl-6-methylselenobenzo[*b*]selenophene (**5d1**) by nucleophilic substitution of the bromine moiety. This ester is subsequently saponified and the resulting acid (**5d2**) is decarboxylated to 5-formyl-6-methylselenobenzo[*b*]selenophene (**5d3**).

We prepared the vinylogous ester (**6d1**) of the compound (**5d3**) via a Wittig-Horner reaction. This ester (**6d1**) is saponified to the corresponding acid (**6d2**) which is cyclised in PPSE to afford 7*H*-selenolo[3,2-*g*][*1*]benzoselenopyran-7-one (**1d**).

We later devised an improved method to obtain the heterocycle (**1a**). The bromine moiety of 6-bromo-5-formylbenzo[*b*]thiophene (**7a3**) could be substituted by ethanethiolate in refluxing DMF and lead to 6-ethylthio-5-formylbenzo[*b*]thiophene (**5a3**) in good yield (92%).

EXPERIMENTAL

Unless otherwise stated reactions were carried out in commercial pure grade solvents without further purification. Tetrahydrofuran was dried by distillation over sodium. Analytical grade dry K_2CO_3 was used. The standard isolation procedure consists in pouring the reaction medium in ice/water mixture, filtration of the precipitate, redissolution of the precipitate in CH_2Cl_2, washing with 1N $NaHCO_3$ solution, drying ($MgSO_4$) and evaporating the solvent under reduced pressure (12 mm Hg).

Melting points were determined with a Kofler hotplate melting point apparatus and are corrected. Nmr spectra were recorded on Varian T-60 or Brucker 400 AM spectrometers. The δ values for ^{1}H and ^{13}C are given in ppm using HMDSO (hexamethyldisiloxane) as internal standard. The ^{77}Se chemical shifts are relative to dimethyl selenide. Mass spectra were recorded on a Varian MAT 112 spectrometer operating at an ionisation potential of 70 eV. Isotopic distributions are in agreement with theory and only the most abundant isotopes (^{79}Br, ^{80}Se) are mentioned in the experimental section. Combustion analysis were performed by L'Institut de Pharmacie (Liege, Belgium).

4-Bromo-6-ethylthioisophthalaldehyde (3a): 2.6 ml of ethanethiol (2.18 g, 35.1 mmol) are added to a cooled (5°C) suspension of 5g of K_2CO_3 (36.2 mmol) in 200 ml DMF. 10 g of 4,6-dibromoisophthalaldehyde (2) (34.25 mmol) are added and the solution is stirred for 24 h at room temperature. The reaction medium is poured into water, the precipitate is filtered, dissolved in CH_2Cl_2, dried and the solvent evaporated. The residue is recrystallized from toluene/hexane. Yield 6.74 g (72%). mp 123°C; ^{1}H-nmr δ($CDCl_3$, 60 MHz): 10.2 (s, 1H), 10.1 (s, 1H), 8.2 (s, 1H), 7.5 (s, 1H), 3.0 (q, J = 7 Hz, 2H), 1.4 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 270 (M^+ ,98), 243 (100), 214 (51), 106 (87). Anal. Calcd for $C_{10}H_9O_2BrS$: C, 43.97; H, 3.32; S, 11.74. Found: C, 44.20; H, 3.34; S, 11.78.

2-Ethoxycarbonyl-6-ethylthio-5-formylbenzo[*b*]thiophene (5a1): 5 g of 4-bromo-6-ethylthioisophthalaldehyde (3a) (18.3 mmol) and 3.5 g of K_2CO_3 (26.0 mmol) are suspended in 60 ml of DMF. Ethyl mercaptoacetate (2.01 ml, 2.2 g , 18.3 mmol) is added and the reaction mixture is stirred at 20°C for 24 h. After standard isolation, the product is recrystallized from ethanol/toluene. Yield 4.37 g (81%). mp 104°C; ^{1}H-nmr δ($CDCl_3$, 60 MHz): 10.3 (s, 1H), 8.1 (s, 1H), 7.9 (s, 1H), 7.6 (s, 1H), 4.25 (q, J = 7

Hz, 2H), 2.9 (q, J = 7 Hz, 2H), 1.3 (m, 6H); EIms, m/z (relative intensity) 294 (M^+, 100), 279 (13), 265 (38), 238 (24). Anal. Calcd for $C_{14}H_{14}O_3S_2$: C, 57.12; H, 4.79; S, 21.78. Found: C, 57.29; H, 4.83; S, 22.05.

6-Bromo-2-ethoxycarbonyl-5-formylbenzo[*b*]thiophene (7a1): The same reaction procedure is followed as for **5a1**. Yield 86%, mp 150°C (ethanol/toluene); ^{1}H-nmr δ($CDCl_3$, 60 MHz): 10.4 (s, 1H), 8.35 (s, 1H), 8.1 (s, 1H), 8.0 (s, 1H), 4.35 (q, J = 7 Hz, 2H), 1.3 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 312 (M^+, 100), 283 (36), 267 (55). Anal. Calcd for $C_{12}H_9O_3BrS$: C, 46.02; H, 2.90; S, 10.24. Found: C, 46.19; H, 2.85; S, 10.37.

4-Ethylthio-6-methylselenoisophthalaldehyde (**4c**): 10 g of 4,6-dibromoisophthalaldehyde (**2**) (34.2 mmol) are suspended in 100 ml of DMF. 5 *g of* K_2CO_3 (36.2 mmol) are added and the mixture is cooled to 5°C. 2.6 ml of ethanethiol (2.18 g, 35.1 mmol) are added and the reaction temperature is allowed to raise to room temperature. After 24 *h*, the reaction mixture is cooled to 5°C and 2.15 ml of methaneselenol (3.44 g, 36.2 mmol) are added. This slurry is reacted another 8 h at room temperature. Standard isolation and recrystallization of the residue in toluene/heptane yields 7.48 g (76%) of **4c**. mp 152°C; ^{1}H-nmr δ($CDCl_3$, 60 MHz): 10.1 (s, 1H), 9.9 (s, 1H), 7.9 (s, 1H), 7.1 (s, 1H), 2.9 (q, J = 7 Hz, 2H), 2.2 (s, $J^{77}Se$-CH_3 = 14 Hz, 3H), 1.3 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 288 (M^+, 50), 273 (100), 260 (25), 216 (17). Anal. Calcd for $C_{11}H_{12}O_2SSe$: C, 46.00; H, 4.21; S, 11.16. Found: C, 46.12; H, 4.25; S, 10.96.

2-Ethoxycarbonyl-6-ethylthio-5-formylbenzo[*b*]selenophene (**5c1**): 4 g (13.9 mmol) of 4-ethylthio-6-methylselenoisophthalaldehyde (**4c**) are refluxed in 10 ml (90.2 mmol) of ethyl bromoacetate for 2 h and allowed to cool. The precipitate is then filtered and washed with petroleum ether (bp 40-60).

The obtained solid is suspended in 50 ml of DMF and 2 g (14.4 mmol) of K_2CO_3 are added. This mixture is stirred for 16 h at room temperature to complete selenophene ring-closure. Standard isolation and recrystallization of the residue in toluene/heptane yields 2.85 g (60%) of **5c1**. mp 122°C; ^{1}H-nmr δ($CDCl_3$, 60 MHz): 10.1 (s, 1H), 8.0 (s, 2H), 7.55 (s, 1H), 4.1 (q, J = 7 Hz, 2H), 2.75 (q, J = 7 Hz, 2H), 1.1 (t, J = 7 Hz, 6H); EIms, m/z (relative intensity) 342 (M^+, 100), 314 (49), 285 (37), 212 (34). Anal. Calcd for $C_{14}H_{14}O_3SSe$: C, 49.27; H, 4.14; S, 9.40. Found: C, 49.61; H, 4.10; S, 9.26.

4-Bromo-6-methylselenoisophthalaldehyde (**3c1**): 21 g of 4,6-dibromoisophthalaldehyde (**2**) (72 mmol) and 10.5 g (76,1 mmol) of K_2CO_3 are suspended in 150 ml of acetonitrile. This slurry is cooled to 5°C and 4.3 ml of methaneselenol (7.36 ml, 77 mmol) are added. After 24 h at room temperature, the mixture is poured into water, the precipitate is washed with water and then dissolved in 800 ml of hot toluene. The organic layer is decanted and evaporated under reduced pressure. The residue is recrystallized in approximately 200 ml of toluene. Yield 15 g (69%) of yellow crystals of mp 196°C; ^{1}H-nmr δ(DMSO, 60 MHz): 9.8 (s, 1H), 9.75 (s, 1H), 7.9 (s, 1H), 7.3 (s, 1H), 2.25 (s, 3H); EIms, m/z (relative intensity) 306 (M^+, 43), 291 (100), 277 (11), 263 (11), 235 (5), 212 (7), 183 (11), 156 (17). Anal. Calcd for $C_9H_7O_2BrSe$: C, 35.32; H, 2.31. Found: C, 35.29; H, 2.30.

6-Bromo-2-ethoxycarbonyl-5-formylbenzo[*b*]selenophene (**7c1**): Starting from 4-bromo-6-methylselenoisophthalaldehyde (**3c1**), the same reaction procedure is followed as for **5c1**. Yield 71%. mp 167°C (toluene/heptane); ^{1}H-nmr δ($CDCl_3$, 60 MHz): 10.1 (s, 1H), 8.1 (s, 1H), 8.0 (s, 1H), 7.9 (s, 1H), 4.25 (q, J = 7 Hz, 2H), 1.3 (t, J = 7 Hz, 2H); EIms, m/z (relative intensity) 360 (M^+, 100), 332 (23), 331 (29), 315 (68), 286 (20). Anal. Calcd for $C_{12}H_9O_3BrSe$: C, 40.03; H, 2.52. Found: C, 40.32; H, 2.51.

2-Ethoxycarbonyl-5-formyl-6-methylselenobenzo[*b*]selenophene (5d1): 6 g of 6-bromo-2-ethoxycarbonyl-5-formylbenzo[*b*]selenophene (**7c1**) (16.7 mmol) and 2.5 g (18.1 mmol) of K_2CO_3 are suspended in 60 ml of DMF and cooled to 5°C. 1.0 ml of methaneselenol (1.6 g, 16.7 mmol) is added and the reaction mixture is stirred for 8 h at room temperature. Standard isolation yields 5.05 g (81%) of **5d1**. mp 158°C (toluene/hexane); ^{1}H-nmr δ($CDCl_3$, 60 MHz): 10.0 (s, 1H), 8.15 (s, 1H), 8.1 (s, 1H), 7.75 (s, 1H), 4.3 (q, J = 7 Hz, 2H), 2.2 (s, 3H), 1.25 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 376 (M^+, 83), 361 (100), 333 (32), 303 (32). Anal. Calcd for $C_{13}H_{12}O_3Se_2$: C, 41.73; H, 3.21. Found: C, 41.98; H, 3.22.

Saponification reaction : All saponification reactions were carried out in the following way : one milliequivalent of ester is refluxed for 40 min in 3 ml of water/ethanol (5/7 v/v) containing two milliequivalents of KOH. After cooling, the mixture is washed once with ether, acidified with 6N HCl, filtered and the precipitate washed with water. The precipitate is air dried at 110°C. Yields are between 80 and 96%. The acids are used without further purification.

Decarboxylation reactions : General procedure : 10 mmol of the dried acid and 2 g of copper bronze are mixed with 25 ml of freshly distilled quinoline. The mixture is heated to 185°C until CO_2 evolution stops (5 to 25 min at 185°C). The reaction mixture is allowed to cool to 60°C and the copper bronze is filtered off and washed with $CHCl_3$. More $CHCl_3$ is added and the organic phase is washed several times with 2N HCl, once with 1 N $NaHCO_3$ and water. The organic layer is dried and the solvent is evaporated. The products are purified by column chromatography (silica gel/toluene).

6-Ethylthio-5-formylbenzo[*b*]thiophene (5a3): Yield 70 %. mp 86°C (toluene/hexane). ^{1}H-Nmr δ($CDCl_3$, 60 MHz): 10.2 (s, 1H), 8.0 (s, 1H), 7.6 (s, 1H), 7.2 (d, J = 6 Hz, 1H), 7.1 (d, J = 6 Hz, 1H), 2.7 (q, J = 7 Hz, 2H),

1.3 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 222 (M^+, 100), 207 (18), 194 (58), 190 (22), 165 (33). Anal. Calcd for $C_{11}H_{10}OS_2$: C, 59.43; H, 4.53; S, 28.85. Found: C, 59.71; H, 4.56; S, 28.50.

6-Bromo-5-formylbenzo[*b*]thiophene (7a3): Yield 73 %. mp 104°C (toluene/hexane); ^{1}H-nmr δ($CDCl_3$, 60 MHz): 10.0 (s, 1H), 8.15 (s, 1H), 7.8 (s, 1H), 7.3 (d, J = 6 Hz, 1H), 7.1 (d, J = 6 Hz, 1H), 7.0 (s, 1H); EIms, m/z (relative intensity) 240 (M^+, 100), 212 (26), 132 (40). Anal. Calcd for C_9H_5OBrS: C, 44.83; H, 2.09; S, 13.30. Found: C, 45.21; H, 2.28; S, 13.45.

6-Ethylthio-5-formylbenzo[*b*]selenophene (5c3): Yield 67 %. mp 70°C (toluene/hexane). ^{1}H-Nmr δ($CDCl_3$, 400 MHz): 10.4 (s, 1H), 8.15 (s, 1H), 7.9 (s, 1H), 7.9 (d, J = 5.9 Hz, 1H), 7.5 (d, J = 5.9 Hz, 1H), 2.9 (q, J = 7 Hz, 2H), 1.25 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 270 (M^+, 100), 241 (46), 212 (24), 180 (16), 167 (32).

5-Formyl-6-methylselenobenzo[*b*]selenophene (5d3): Yield 73 %. mp 62°C (toluene/pentane); ^{1}H-nmr δ($CDCl_3$, 60 MHz): 8.25 (d, J = 16 Hz, 1H), 8.0 (s, 1H), 7.9 (s, 1H), 7.9 (d, J = 5 Hz, 1H), 7.4 (d, J = 5 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 4.25 (q, J = 7 Hz, 2H), 2.25 (s, $J^{77}Se\text{-}CH_3$ = 12 Hz, 3H), 1.3 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 374 (M^+, 8), 329 (4), 286 (39), 279 (70), 250 (100), 234 (18), 206 (42).

5-Ethoxycarbonylvinyl-6-ethylthiobenzo[*b*]thiophene (6a1): 1.4 g of 6-ethylthio-5-formylbenzo[*b*]thiophene (7.36 mmol) are dissolved in 30 ml of dry THF. 930 mg of C-200 ($BaCO_3.0,8H_2O$) and 1.84 ml of triethyl phosphonoacetate (2.08 g, 9.27 mmol) are added. The reaction mixture is stirred vigorously while 0.176 ml of water are added. This mixture is then refluxed for 1 h. The reaction mixture is poured in 1N HCl, extracted with CH_2Cl_2 (60 ml), washed with water and dried. The solvent is evaporated and the product is chromatographied on a short silica gel column (toluene/heptane, 80/20) to eliminate the excess phosphonate.

Yield 2.02 g (94%). Yellow oil. ^{1}H-Nmr δ($CDCl_3$, 60 MHz): 8.35 (d, J = 16 Hz, 1H), 7.9 (s, H), 7.9 (d, J = 5 Hz, 1H), 7.2 (d, J = 5 Hz, 1H), 7.2 (s, 1H), 6.35 (d, J = 16 Hz, 1H), 4.2 (q, J = 7 Hz, 2H), 2.85 (q, J = 7 Hz, 2H), 1.25 (m, 6H); EIms, m/z (relative intensity) 292 (M^+, 39), 260 (5), 247 (5), 231 (54), 219 (25), 203 (35), 190 (81), 189 (100).

The same reaction procedure is used to obtain 5-ethoxycarbonylvinyl-6-methylselenobenzo[*b*]thiophene (**6b1**), 5-ethoxycarbonylvinyl-6-ethylthiobenzo[*b*]selenophene (**6c1**), and 5-ethoxycarbonylvinyl-6-methylselenobenzo[*b*]selenophene (**6d1**).

5-Ethoxycarbonylvinyl-6-methylselenobenzo[*b*]thiophene (**6b1**): Yield 92%. mp 58°C (pentane/toluene); ^{1}H-nmr δ($CDCl_3$, 60 MHz): 8.0 (d, J = 16 Hz, 1H), 7.7 (s, 1H), 7.1 (d, J = 5 Hz, 1H), 6.95 (d, J = 5 Hz, 1H), 6.1 (d, J = 16 Hz, 1H), 4.0 (q, J = 7 Hz, 2H), 2.1 (s, 3H), 1.1 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 326 (M^+, 23), 281 (4), 231 (36), 202 (36). Anal. Calcd for $C_{14}H_{14}O_2SSe$: C, 51.69; H, 4.34; S, 9.86. Found: C, 51.72; H, 4.29; S, 9.87.

5-Ethoxycarbonylvinyl-6-ethylthiobenzo[*b*]selenophene (**6c1**): Yield 93%. Yellow oil. ^{1}H-Nmr δ($CDCl_3$, 400 MHz): 8.35 (d, J = 16 Hz, 1H), 7.9 (s, 2H), 7.85 (d, J = 5 Hz, 1H), 7.5 (d, J = 5 Hz, 2H), 6.4 (d, J = 16 Hz, 1H), 4.2 (q, J = 7 Hz, 2H), 2.85 (q, J = 7 Hz, 2H), 1.25 (m, 6H); EIms, m/z (relative intensity) 340 (M^+, 56), 279 (65), 266 (25), 250 (33), 238 (100), 158 (55).

5-Ethoxycarbonylvinyl-6-methylselenobenzo[*b*]selenophene (**6d1**): Yield 90%. Yellow liquid. ^{1}H-Nmr δ($CDCl_3$, 60 MHz): 8.25 (d, J = 16 Hz, 1H), 8.0 (s, 1H), 7.9 (d, J = 5 Hz, 1H), 7.9 (s, 1H), 7.4 (d, J = 5 Hz, 1H), 6.35 (d, J = 16 Hz, 1H), 4.25 (q, J = 7 Hz, 2H), 2.25 (s, $J^{77}Se\text{-}CH_3$ = 12 Hz, 3H), 1.3 (t, J = 7 Hz, 3H); EIms, m/z (relative intensity) 374 (M^+, 8), 329 (4), 286 (39), 279 (70), 250 (100), 234 (18), 206 (42).

7*H*-Thieno[3,2-*g*][1]benzothiopyran-7-one (1a): Polyphosphoric acid silyl ester has been prepared by refluxing 3.3 g of P_4O_{10} with 6 ml of HMDSO in 14 ml of $CHCl_3$ for 1 h. Care must be taken that all P_4O_{10} is dissolved otherwise emulsion formation during the isolation process results in much lower yield. $CHCl_3$ is evaporated under reduced pressure and 165 mg of **6a2** are added. After dissolution of this acid the reaction medium is heated on an oil bath at 100°C for 24 h. After cooling, the reaction mixture is poured in $CHCl_3$, the organic phase is washed subsequently with 1N $NaHCO_3$ solution, water, dried and the solvent is evaporated. The product is purified by column chromatography (silica gel/toluene/$CHCl_3$ 90/10) and recrystallisation in ethanol. Yield 42%. mp 146°C; ^{1}H-nmr δ($CDCl_3$, 400 MHz): 8.0 (s, 1H), 7.9 (s, 1H), 7.75 (d, J = 10.6 Hz, 1H), 7.4 (d, J = 5.5 Hz, 1H), 7.35 (d, J = 5.5 Hz, 1H), 6.5 (d, J = 10.6 Hz, 1H); ^{13}C-nmr δ($CDCl_3$, 100 MHz): 188.7, 144.1, 141.8, 138.4, 131.1, 127.8, 126.2, 123.5, 123.1, 122.6, 118.8; EIms, m/z (relative intensity) 218 (M^+, 98), 190 (100), 158 (6), 146 (12), 145 (21). Anal. Calcd for $C_{11}H_6OS_2$: C, 60.52; H, 2.77; S, 29.38. Found: C, 59.85; H, 2.81; S, 28.46.

7*H*-Selenopyrano[3,2-*f*][1]benzothiophen-7-one (1b): PPSE is prepared as above. 150 mg of **6b2** are added and the mixture is heated at 120°C for 5 h. The same isolation procedure is used as for **1a**. Yield 44%. mp 158°C (ethanol); ^{1}H-Nmr δ($CDCl_3$, 400 MHz): 8.0 (s, 1H), 8.0 (s, 1H), 7.65 (d, J = 11.0 Hz, 1H), 7.4 (d, J = 5.5 Hz, 1H), 7.3 (d, J = 5.5 Hz, 1H), 6.15 (d, J = 11.0 Hz, 1H); ^{13}C-nmr δ($CDCl_3$, 100 MHz): 189.0, 146.1, 143.0, 139.3, 132.2, 129.0, 128.4, 124.6, 124.4, 123.6, 122.5; ^{77}Se-nmr δ($CDCl_3$): 623 ppm; EIms, m/z (relative intensity) 266 (M^+, 73), 238 (100), 158 (72). Anal. Calcd for $C_{11}H_6OSSe$: C, 49.82; H, 2.28; S, 12.09. Found: C, 49.42; H, 2.33; S, 12.48.

2*H*-Selenolo[3,2-*g*][1]benzothiopyran-2-one (1c): PPSE is prepared as above. Heating of 150 mg of **6c2** for 3 h at 150°C and isolation as above

yield 57% of **1c**. mp 178°C (ethanol); ^{1}H-nmr δ($CDCl_3$, 400 MHz): 8.0 (s, 1H), 8.0 (d, J = 6 Hz, 1H), 7.95 (s, 1H), 7.75 (d, J = 10.5 Hz, 1H), 7.6 (d, J = 6 Hz, 1H), 6.5 (d, J = 10.5 Hz, 1H); ^{13}C-nmr δ($CDCl_3$, 100 MHz): 185.2, 144.1, 143.6, 140.9, 132.4, 130.0, 127.7, 127.0, 123.2, 122.9, 122.0; ^{77}Se-nmr δ($CDCl_3$) 544 ppm; EIms, m/z (relative intensity) 266 (M^+, 90), 238 (100), 158 (84), 145 (55). Anal. Calcd for $C_{11}H_6OSSe$: C, 49.82; H, 2.28; S, 12.09. Found: C, 49.79; H, 2.27; S, 12.05.

7*H*-Selenolo[3,2-*g*][*1*]benzoselenopyran-7-one (**1d**): PPSE is prepared as indicated above. 100 mg of the acid (**6d2**) are added and the mixture is heated at 120°C for 22 h. Yield 34%. mp 189-190°C (ethanol); ^{1}H-nmr δ($CDCl_3$, 400 MHz): 8.1 (s, 1H), 8.05 (s, 1H), 7.8 (d, J = 5.9 Hz, 1H), 7.75 (d, J = 11 Hz, 1H), 7.6 (d, J = 5.9 Hz, 1H), 6.25 (d, J = 11 Hz, 1H); ^{13}C-nmr δ($CDCl_3$, 100 MHz): 189.07, 145.21, 143.95, 140.97, 131.85, 129.71, 129.55, 127.09, 124.90, 124.00, 122.78; ^{77}Se-nmr δ($CDCl_3$): 640, 542; EIms, m/z (relative intensity) 314 (M^+, 40), 286 (100), 206 (73). Anal. Calcd for $C_{11}H_6OSe_2$: C, 42.18; H, 2.09. Found: C, 42.18; H, 1.94.

ACKNOWLEDGEMENTS

We gratefully thank the "Metallurgie Hoboken Overpelt" (MHO-Belgium) for a generous gift of selenium.

We also thank the CREMAN for nmr spectra.

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Received, 28th January, 1992