Selenium Heterocycles XXVI. (1) Synthesis of Theino[3,4-*b*]benzofuran and Selenolo[3,4-*b*]benzofuran. Two Novel Heterocycles

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Starting from the readily available aryl 3-methyl-2-benzo[*b*]furyl ketones a series of 3-substituted thieno[3,4-*b*]benzofurans and 3-substituted selenolo[3,4-*b*]benzofurans were prepared in high yield. The parent compound, thieno[3,4-*b*]benzofuran was prepared through the reaction of thioacetamide with 2-chloromethyl-3-formylbenzo[*b*]furan in moderate yield.

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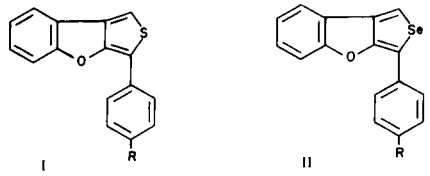
In continuation of the study on the chemistry of selenium heterocyclic compounds (2-6) and as a part of a program designed to expand the chemistry of benzofuran (7-8), it became necessary to synthesize substituted thieno-[3,4-*b*]benzofuran (I) and seleno[3,4-*b*]benzofuran (II) for biological evaluation.



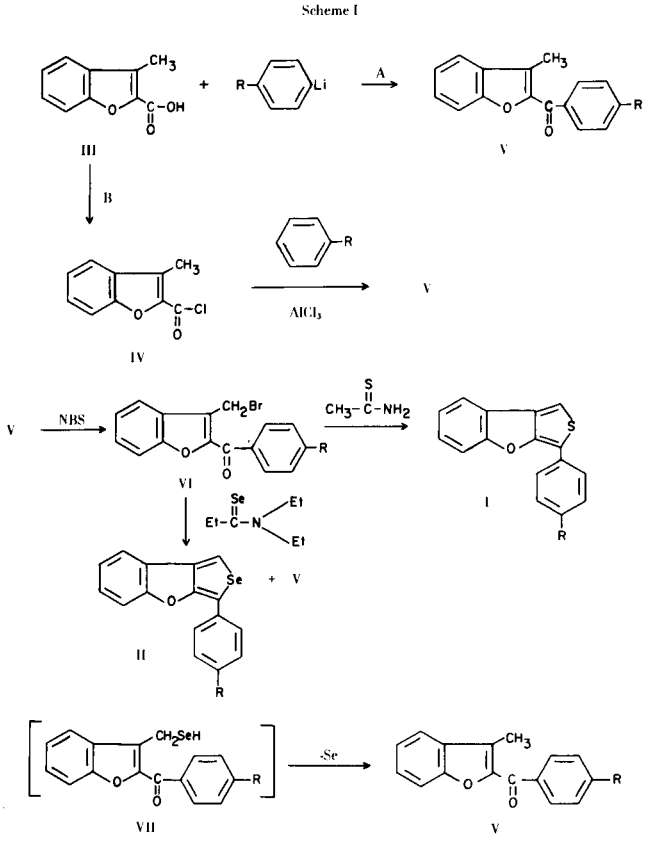
I II

The starting materials, aryl 3-methyl-2-benzo[*b*]furyl ketones (V) could be prepared either from the reaction of aryl lithium (9) with 3-methylcoumarilic acid (III) (10) or Friedel Crafts' reaction of 3-methylcoumarilyl chloride (IV) with aromatic hydrocarbons (11,12). Reaction of *N*-bromosuccinimide with compound V afforded aryl 3-bromomethyl-2-benzo[*b*]furyl ketones (VI) in good yield. Reaction of thioacetamide with the later, according to our procedure reported previously (6), gave the desired compound I. The reaction of *N*,*N*-diethylselenopropionamide (13) with compound VI afforded compound V in addition to the desired compound II. It is worthwhile to note that only debromination without the reduction of keot group was observed in all cases. Debromination probably occured through the intermediate VII. In fact, in all cases we observed the precipitation of selenium in the reaction mixture (See Scheme I).

The reaction of compound I (R = H) or II (R = H) with dimethyl acetylenedicarboxylates afforded 4-phenyl-2,3-dicarbomethoxydibenzofuran (VIII) in support of the structures I and II (Scheme II).

The nmr spectrum of compound II was also in agreement with the suggested structure. In the nmr spectrum of this compound the proton which is geminal to the selenium appears as a strong singlet and a weak doublet, centered around the singlet. This doublet is assigned to the splitting caused by the presence of the selenium isotope ^{77}Se with a natural abundance of 7.5%. The selenium splitting constant was found to be 44 cps. This splitting constant was identical with the one reported for

Scheme I



R = a) H, b) CH_3, c) OCH_3, d) SCH_3, e) Cl, f) Br.

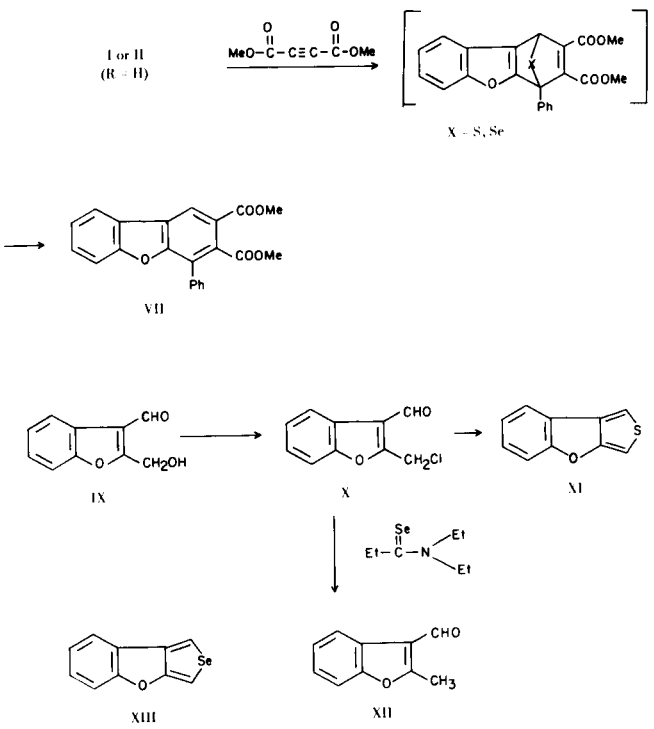
the fused selenophene (6).

The parent compound, thieno[3,4-*b*]benzofuran (XI), was synthesized from 2-hydroxymethyl-3-formylbenzo-[*b*]furan (IX) (7) as is shown in Scheme II.

Reaction of thionyl chloride with compound IX in ether gave 2-chloromethyl-3-formylbenzo[*b*]furan (X). Reaction of thioacetamide with compound X afforded the desired compound XI in 60% yield.

The selenium analog of X, namely selenolo[3,4-*b*]-benzofuran (XIII), could not be prepared through the reaction of different selenamides with X under different experimental conditions. In fact, in all cases 3-formyl-2-methylbenzo[*b*]furan (XII) (14) was isolated in high yield. It is interesting to note that in this case, as in the above cases, we did not observe the reduction of the

Scheme II



carbonyl group.

The structure of all compounds was confirmed by analytical and spectroscopic methods.

The physical constants of all compounds prepared are summarized in Tables I and II.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer model 267 spectrograph (potassium bromide discs). The nmr spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 eV.

p-Methoxyphenyl 3-Methyl-2-benzo[*b*]furyl Ketone (Vc).

Method A.

A stirring mixture of 3-methylcoumariryl chloride (IV, 1.945 g., 0.01 mole), anisole (1.08 g., 0.01 mole), and aluminium chloride (1.335 g., 0.01 mole) in 20 ml. of carbon disulfide was refluxed in water bath for 4 hours. After cooling, the complex was decomposed with ice-water and dilute hydrochloric acid. The organic layer was separated and the mother liquid was extracted with carbon disulfide once more. The combined organic solvent was washed with a saturated sodium bicarbonate solution in water. The organic layer was dried, filtered and evaporated, and the residue was crystallized from petroleum ether to give 2.13 g. (80%) of Vc (12), m.p. 85-86°; ir: 1640 cm^{-1} (carbonyl); nmr (deuteriochloroform): 8.06 (d, 2H, aromatic), 7.73-7.17 (m, 4H, aromatic), 6.90 (d, 2H, aromatic), 3.78 (s, 3H, OCH_3), and 2.57 ppm (s, 3H, CH_3).

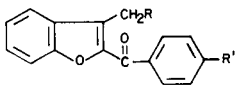
Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.69; H, 5.26. Found: C, 76.84; H, 5.08.

p-Chlorophenyl 3-Methyl-2-benzo[*b*]furyl Ketone (Ve).

Method B.

To a stirring solution of *p*-chlorophenyllithium, which was prepared from *p*-chlorobromobenzene (9.575 g., 0.05 mole) and *n*-butyl lithium (32 ml. of 10% solution in hexane, 0.05 mole) according to the literature (9), was added 3-methylcoumarilic acid (III, 1.76 g., 0.01 mole). The mixture was stirred overnight

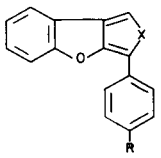
Table I



Compound	R	R'	Method	Yield (%)	M.p. °C (a)	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found
Va	H	H	A or B	80	51-52 (b)	$C_{16}H_{12}O_2$	81.36	81.23	5.08	5.26
Vb	H	CH_3	A	60	69-70	$C_{17}H_{14}O_2$	81.60	81.76	5.60	5.78
Vc	H	OCH_3	A	80	85-86	$C_{17}H_{14}O_3$	76.69	76.84	5.26	5.08
Vd	H	SCH_3	A	80	72-73	$C_{17}H_{14}O_2S$	72.34	72.19	4.96	4.78
Ve	H	Cl	B	40	102-103	$C_{16}H_{11}ClO_2$	70.98	70.79	4.07	4.21
Vf	H	Br	A	50	110-111	$C_{16}H_{11}BrO_2$	60.95	60.76	3.49	3.65
VIa	Br	H	-	90	79-80 (c)	$C_{16}H_{11}BrO_2$	60.95	61.07	3.49	3.68
VIb	Br	CH_3	-	50	114-115 (c)	$C_{17}H_{13}BrO_2$	62.01	61.84	3.95	4.25
VIc	Br	OCH_3	-	90	138-139 (c)	$C_{17}H_{13}BrO_3$	59.13	59.29	3.77	3.58
VId	Br	SCH_3	-	85	139-140 (c)	$C_{17}H_{13}BrO_2S$	56.51	56.32	3.60	3.56
VIe	Br	Cl	-	94	125-126 (c)	$C_{16}H_{10}BrClO_2$	54.94	54.77	2.86	2.99
VIf	Br	Br	-	93	133-134 (c)	$C_{16}H_{10}Br_2O_2$	48.73	48.92	2.54	2.72

(a) Unless otherwise mentioned, the compound was crystallized from petroleum ether. (b) Reference 11, m.p. 51-52°. (c) This compound was crystallized from ethyl acetate-petroleum ether.

Table II



Compound	R	X	Yield (%)	M.p. °C (a)	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found
Ia	H	S	80	109-110	$C_{16}H_{10}OS$	76.80	76.65	4.00	4.18
Ib	CH_3	S	85	112-113	$C_{17}H_{12}OS$	77.27	77.09	4.55	4.73
Ic	OCH_3	S	82	111-112	$C_{17}H_{12}O_2S$	72.86	72.65	4.29	4.18
Id	SCH_3	S	83	116-117	$C_{17}H_{12}OS_2$	68.92	68.99	4.05	3.87
Ie	Cl	S	35	129-130	$C_{16}H_9ClOS$	67.49	67.68	3.16	3.34
If	Br	S	70	132-133	$C_{16}H_9BrOS$	58.36	58.18	2.74	2.58
IIa	H	Se	70	119-120	$C_{16}H_{10}OSe$	64.65	64.83	3.37	3.18
IIb	CH_3	Se	68	106-107	$C_{17}H_{12}OSe$	65.59	65.74	3.86	3.99
IIc	OCH_3	Se	70	109-110	$C_{17}H_{12}O_2Se$	62.38	62.44	3.67	3.48
IId	SCH_3	Se	70	100-101	$C_{17}H_{12}OSSe$	59.47	59.28	3.50	3.66
IIe	Cl	Se	35	99-100	$C_{16}H_9ClOSe$	57.92	57.74	2.71	2.90
IIf	Br	Se	65	104-105	$C_{16}H_9BrOSe$	51.06	50.86	2.39	2.56

(a) All compounds were crystallized from ethanol.

under nitrogen at room temperature. Ice-water was added to the mixture followed by extraction with ether. The ether was dried, filtered and evaporated. The residue was purified by tlc (silica gel, chloroform-petroleum ether; 30:70) and the desired compound was crystallized from petroleum ether to give 2.16 g. (80%) of Ve, m.p. 102-103°; ir: 1650 cm^{-1} (ketone); nmr (deuteriochloroform): 8.10 (d, 2H, aromatic), 7.90-7.33 (m, 6H, aromatic), and 2.66 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{16}H_{11}ClO_2$: C, 70.98; H, 4.07. Found: C, 70.79; H, 4.21.

Other aryl 3-methyl-2-benzo[*b*]furyl ketones were prepared similarly by method A or B (See Table I); however, when compound Va or Vb was prepared by method A, benzene or toluene was used as a solvent, respectively.

p-Methoxyphenyl 3-Bromomethyl-2-benzo[*b*]furyl Ketone (VIc).

A mixture of Vc (2.66 g., 0.01 mole) and *N*-bromosuccinimide (1.96 g., 0.011 mole) in 30 ml. of carbon tetrachloride was irradiated with a 500 W (G.E. photospot) lamp while heating and stirring at reflux temperature for 4 hours. The reaction mixture was cooled and filtered. The solvent was evaporated and the residue was crystallized from ethyl acetate-petroleum ether to give 3.1 g. (90%) of VIc, m.p. 138-139°; ir: 1633 cm^{-1} (ketone); nmr (deuteriochloroform): 8.16 (d, 2H, aromatic), 7.66-7.40 (m, 4H, aromatic), 6.96 (d, 2H, aromatic), 5.03 (s, 2H, CH_2Br) and 3.93 ppm (s, 3H, OCH_3).

Anal. Calcd. for $C_{17}H_{13}BrO_3$: C, 59.13; H, 3.77. Found: C, 59.29; H, 3.58.

4-*p*-Methoxyphenylthieno[3,4-*b*]benzofuran (Ic).

A solution of VIc (345 mg., 1 mmole) and thioacetamide (82.5 mg., 1.1 mmoles) in 10 ml. of ethanol was refluxed for 7 hours. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform-petroleum ether, 1:1). The desired compound was crystallized from ethanol to give 230 mg. (82%) of Ic; m.p. 111-112°; nmr (deuteriochloroform): 7.70 (d, 2H, aromatic), 7.53-7.13 (m, 4H, aromatic), 7.10 (s, 1H, H_1), 6.90 (d, 2H, aromatic), and 3.81 ppm (s, 3H, OCH_3); ms m/e (%): 280 (M^+, 100), 266 (14), 265 (82), 237 (22), 165 (12), and 140 (12).

Anal. Calcd. for $C_{17}H_{12}O_2S$: C, 72.86; H, 4.29. Found: C, 72.65; H, 4.18.

Other 4-arylthieno[3,4-*b*]benzofurans were prepared similarly (See Table II).

4-*p*-Methoxyphenylselenolo[3,4-*b*]benzofuran (IIc).

A solution of VIc (345 mg., 1 mmole) and *N,N*-diethylselenopropionamide (211 mg., 1.1 mmoles) (13) in 10 ml. of ethanol was refluxed for 4 hours. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform-petroleum ether, 1:1). The fast moving fraction was crystallized from ethanol to give 229 mg. (70%) of IIc, m.p. 109-110°; nmr (deuteriochloroform): 7.73 [s, 1H, H_1; this hydrogen was split into a doublet with J = 44 Hz (^{77}Se coupling)], 7.66 (d, 2H, aromatic), 7.43-7.10 (m, 4H, aromatic), 6.90 (d, 2H, aromatic) and 3.77 ppm (s, 3H, OCH_3); ms m/e (%): 328 (M^+, 100), 326 (50), 313 (76), 311 (37), 285 (18), 205 (32), and 176 (23).

Anal. Calcd. for $C_{17}H_{12}O_2Se$: C, 62.38; H, 3.67. Found: C, 62.44; H, 3.48.

The slow moving fraction was crystallized from petroleum ether to give 53 mg. (20%) of Vc, m.p. 85-86°; mixed melting point with an authentic sample, 85-86°.

Other 4-arylselenolo[3,4-*b*]benzofurans were prepared similarly (See Table II).

4-Phenyl-2,3-dicarbomethoxydibenzofuran (VIII).

A solution of Ia (125 mg., 0.5 mmole) and dimethyl acetylenedicarboxylate (71 mg., 0.5 mmole) in 10 ml. of xylene was refluxed for 24 hours. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform) to give 54 mg. (30%) of VIII, m.p. 155° (ether); ir: 1730 cm^{-1} (ester); nmr (deuteriochloroform): 8.73 (s, 1H, H_1), 8.10-7.83 (m, 2H,

aromatic), 7.63-7.20 (m, 7H, aromatic), 3.96 (s, 3H, OCH_3) and 3.67 ppm (s, 3H, OCH_3).

Anal. Calcd. for $C_{22}H_{16}O_5$: C, 73.33; H, 4.44. Found: C, 73.52; H, 4.63.

Compound VIII was also obtained in 25% yield from the reaction of IIa and dimethyl acetylenedicarboxylates.

2-Chloromethyl-3-formylbenzo[*b*]furan (X).

To a solution of compound IX (518 mg., 3 mmoles) in 30 ml. of dry ether, 2 ml. of thionyl chloride was added. The mixture was allowed to stand overnight at room temperature. The solvent was evaporated and the residue was crystallized from ether to give 370 mg. (64%) of X, m.p. 93-94°; nmr (deuteriochloroform): 10.40 (s, 1H, HCO), 8.33-7.17 (m, 4H, aromatic) and 4.96 ppm (s, 2H, CH_2).

Anal. Calcd. for $C_{10}H_7ClO_2$: C, 61.70; H, 3.60. Found: C, 61.62; H, 3.51.

Thieno[3,4-*b*]benzofuran (XI).

A solution of X (194.5 mg., 1 mmole) and thioacetamide (82.5 mg., 1.1 mmoles) in 10 ml. of ethanol was refluxed for 4 hours. The solvent was evaporated and the residue was crystallized from petroleum ether to give 122 mg. (70%) of XI, m.p. 75-77°; nmr (deuteriochloroform): 8-7.66 (m, 1H, aromatic), 7.60-7.17 (m, 4H, aromatic) and 6.52 ppm (d, 1H, H_1, $J_{1,3}$ = 2.5 Hz); ms m/e (%): 174 (M^+, 15), 173 (100), 102 (22), 87 (16), and 32 (20).

Anal. Calcd. for $C_{10}H_6OS$: C, 68.97; H, 3.45. Found: C, 68.79; H, 3.36.

2-Methyl-3-Formylbenzo[*b*]furan (XII).

A solution of X (194.5 mg., 1 mmole) and *N,N*-diethylselenopropionamide (211 mg., 1.1 mmoles) in 10 ml. of ethanol was refluxed for 3 hours. The solvent was evaporated and the residue was purified by tlc (silica gel, chloroform-petroleum ether; 3:7). The desired compound was crystallized from ether to give 112 mg. (70%) of XII, m.p. 81-82° [lit. (14) m.p. 79°]; ir: 1670 cm^{-1} (C=O); nmr (deuteriochloroform): 10.23 (s, 1H, HCO), 8.40-8.17 (m, 1H, aromatic), 7.37-7.16 (m, 3H, aromatic) and 2.77 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_8O_2$: C, 75.00; H, 5.00. Found: C, 74.82; H, 5.18.

Acknowledgment.

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