Synthesis of Thienothiepinofurans and Thiepinodifurans Novel Synthesis of Heterocyclic Thiolactones and 3-Furyl Ketones

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The synthesis of thienothiepinofurans and thiepinodifurans is described. The displacement reaction between lithium furan-2-thiolate and 2-bromomethyl-substituted thiophenes and furans gave the expected thioether. The cyclization of thioether with polyphosphoric acid (PPA) in xylene gave thiepinone derivatives and heterocyclic thiolactones. The formation of the latter compounds can be explained in terms of a cyclization *via* the sulfur atom. The desulfuration with Raney nickel gave 3-furyl ketones in good yields.

Derivatives of the tricyclic system containing in the central ring a sulfide sulfur atom as heteroatom, such as derivatives of phenothiazine, dibenzo[*b,e*]thiepine, and dibenzo[*b,f*]thiepine, represent one of the most important groups of potential psychotropic and neurotropic drugs [1, 2]. Doubly annellated thiepinones and their heterocyclic analogues have been shown to possess significant activity as antidepressants, antihistamines, and antiinflammatory agents [1—5].

The successful introduction of thiepinodithiophenes [3, 4] which are synthetically useful and biologically interesting compounds has stimulated efforts to discover novel structures with improved biological efficacy. Thus the parent thiepinodithiophene skeleton *I* has been modified and novel tricyclic thienothiepinofurans *II—IV* and thiepinodifurans *V*, *VI* prepared (Scheme 1). These derivatives were prepared by reaction of the lithium 2-furanthiolate [6] which was treated with 2-bromomethyl esters *VII—XI* to give the thioether *IIb—VIb* in 66—80 % yield. The ester group was then hydrolyzed by treatment with KOH in methanol, and the free acid condensed with polyphosphoric acid (82 % P_2O_5 equivalent) in xylene [7] at 100 °C to afford derivatives *II—VI* in 17—34 % yield. In addition, novel heterocyclic thiolactones *IIa—VIa* were obtained as a result of a cyclization at the sulfur atom.

2-Furylsulfides *IIc—VIc* are in most instances readily hydrolyzed under mildly acidic conditions to benzyl thiols, which in turn cyclize to thiolactones. Such reaction pathway has not been observed in the synthesis of thiepinodithiophenes [3, 4]. The desulfuration of selected thiepinones *V, VI* was accomplished by simply heating them with W4 Raney nickel in ethanol — a procedure that gave good yields of the corresponding 3-furyl ketones *Vd, VId.*

Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds.

EXPERIMENTAL

Melting points were determined with a Kofler hot-stage apparatus. NMR spectra were recorded with a Tesla spectrometer, model BS 476 C (80 MHz) using tetramethylsilane as internal standard.

Compounds *VII—XI* were prepared by *N*-bromosuccinimide (NBSI) bromination of the corresponding methyl derivatives [8—11].

Thioethers *IIb—VIb*

To freshly distilled furan (1.7 g; 0.025 mol) in anhydrous diethyl ether (300 cm^3) 12.5 cm^3 of butyllithium (1.6 M hexane solution, 0.02 mol) was added under argon atmosphere and the resulting suspension was stirred at room temperature for 20 min. Treatment of the furyllithium thus prepared with finely powdered sulfur (0.6 g) at 4 °C (exothermic reaction) over 5 min resulted in a quick formation of lithium 2-furanthiolate. Subsequently, a solution of alkyl halides *VII—XI* (0.02 mol) in anhydrous diethyl ether or dimethyl sulfoxide was added at 4 °C, the mixture refluxed for 4—5 h and allowed to reach room temperature. Saturated ammonium chloride solution was added and the mixture extracted with diethyl ether. The solvent was removed and the residue purified by column chromatography (Silica gel Merck 60, eluted with the toluene—ethyl acetate mixture).

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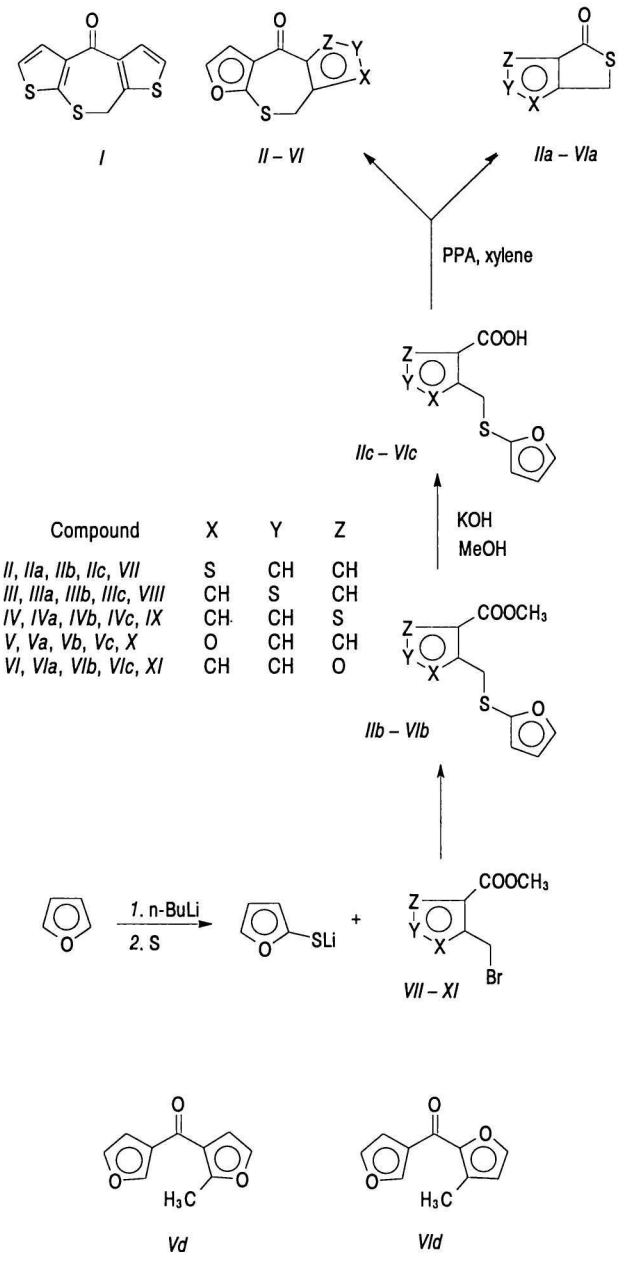

Compound	X	Y	Z
II, IIa, IIb, IIc, VII	S	CH	CH
III, IIIa, IIIb, IIIc, VIII	CH	S	CH
IV, IVa, IVb, IVc, IX	CH	CH	S
V, Va, Vb, Vc, X	O	CH	CH
VI, VIa, VIb, VIc, XI	CH	CH	O

Scheme 1

Physicochemical data of derivatives *IIb—VIb* are given in Table 1.

Saponification of Thioethers *IIb—VIb*

Saponification of *IIb—VIb* (0.015 mol) to *IIc—VIc* was carried out by heating of *IIb—VIb* for 2 h with 50 cm^3 of 2 M-KOH (50 % aqueous methanol). The solvent was removed *in vacuo*, the residue dissolved in water and extracted with 2 × 100 cm^3 of diethyl ether. The aqueous layer was acidified by adding 1M-HCl and again extracted with either diethyl ether or dichloromethane. After removal of the solvent, crude *IIc—VIc* was used directly for cyclization.

Thienothiepinofurans *II—IV*; Thiepinodifurans *V, VI* and Heterocyclic Thiolactones *IIa—VIa*

To the crude acids *IIc—VIc* 10 g of polyphosphoric acid and 25 cm^3 of anhydrous xylene were added and the stirred solution was heated to 95—100 °C for 4 h [4]. Stirring was continued at 100 °C for further 3 h, and the mixture was diluted with ice water (40 cm^3). The organic layer was decanted and the aqueous layer extracted with 3 × 20 cm^3 of dichloromethane. The combined organic layers were washed with water and dried with sodium sulfate. The solvent was evaporated and the crude product purified by column chromatography on silica gel, using benzene and chloroform as eluants. Physicochemical data are given in Tables 2 and 3.

Difuryl Ketones *Vd* and *VId*

W-4 RaNi (prepared from 20 g of nickel-aluminum alloy) was added in a solution of *V* or *VI* (0.01 mol) in 50 cm^3 of absolute ethanol and the mixture was refluxed for 12 h. After filtration of the catalyst and evaporation of solvent, the crude product was purified by chromatography on silica gel (column eluted with benzene : chloroform) to give 55—59 % of *Vd,*

Table 1. Characterization of 2-Furyl Sulfides

Compound	Formula	Yield/%	M.p./°C	^{1}H NMR, δ_i							
				H_5Fu	H_4Fu	H_3Fu	CH_2	CH-X	CH-Y	CH-Z	CH_3
IIb	$C_{11}H_{10}O_3S_2$	79	Oil*	7.55	6.40	6.40	4.53		7.10	7.44	3.84
IIc	$C_{10}H_8O_3S_2$	88	132—134								
IIIb	$C_{11}H_{10}O_3S_2$	67	Oil*	7.50	6.33	6.33	4.27	6.81		8.11	3.88
IIIc	$C_{10}H_8O_3S_2$	87	119—122								
IVb	$C_{11}H_{10}O_3S_2$	66	Oil*	7.54	6.29	6.29	4.36	6.80	7.32		3.85
IVc	$C_{10}H_8O_3S_2$	91	136—138								
Vb	$C_{11}H_{10}O_4S$	72	Oil*	7.50	6.34	6.34	4.85		6.66	7.30	3.83
Vc	$C_{10}H_8O_4S$	87	110—117								
VIb	$C_{11}H_{10}O_4S$	80	Oil*	7.47	6.37	6.37	4.15	6.37	7.44		3.85
VIc	$C_{10}H_8O_4S$	87	110—112								

*Purified by column chromatography (silica gel Merck 60).

Table 2. Characterization of Thienothiepinofurans and Thiepinodifurans

Compound	Formula	Yield/%	M.p./°C	^{1}H NMR, δ_i							
				H_4Fu	H_5Fu	$J_{4,5}$	CH_2	CH-X	CH-Y	CH-Z	J/Hz
II	$C_{10}H_6O_2S_2$	27	147—150	7.45	7.02	1.8	4.15		6.97	7.57	5.2
III	$C_{10}H_6O_2S_2$	18	149—151	7.35	6.85	1.8	4.09	7.07		8.17	3.4
IV	$C_{10}H_6O_2S_2$	34	157—158	7.42	7.08	1.8	4.27	7.02	7.60		5.4
V	$C_{10}H_6O_3S$	32	155—157	7.37	7.02	1.8	4.18		6.97	7.29	1.8
VI	$C_{10}H_6O_2S_2$	17	163—167	7.38	7.03	1.8	4.19	6.90		7.31	1.8

Table 3. Characterization of Furo- and Thienocondensed Thiolactones

Compound	Yield/%	M.p./°C	$M^{\bullet+}$	^{1}H NMR, δ_i				
				CH-X	CH-Y	CH-Z	CH_2	J/Hz
IIa	30	114—117	156		7.19	7.48	4.45	5.4
IIIa	30	87—90	156	7.10		7.75	4.28	2.5
IVa	35	77—80	156	7.12	7.92		4.37	5.4
Va	33	65—67	140		6.58	7.57	4.26	2.0
VIa	41	95—97	140	6.53	7.76		4.08	1.9

VId as an oil. Mass spectrum (M^+ 176), ^{1}H NMR spectrum (80 MHz, $CDCl_3$), δ_i: *Vd*: 6.60, 7.25 (d, each 1H, J = 1.9 Hz), 7.9, 6.7 (each 1H, furan), 2.57 (s, 3H); *VId*: 6.40, 7.50 (d, each 1H, J = 1.9 Hz), 7.87, 7.35, 6.65 (each 1H, furan), 2.55 (s, 3H).

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