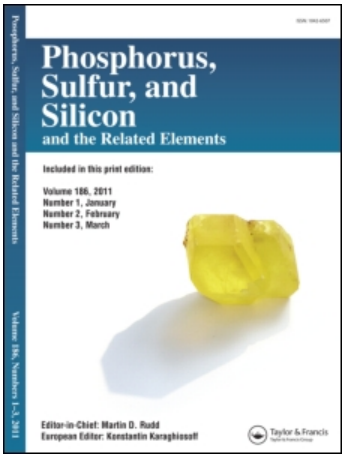

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STUDIES OF THE BEHAVIOR OF 2(3H)-FURANTHIONE AND THIONOPYRROLINE DERIVATIVES TOWARD SOME NITROGEN NUCLEOPHILES

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STUDIES OF THE BEHAVIOR OF 2(3H)-FURANTHIONE AND THIONOPYRROLINE DERIVATIVES TOWARD SOME NITROGEN NUCLEOPHILES

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The conversion of 2(3H)-furanthiones **3** and thiopyrrolines **4** into heterocyclic systems of synthetic and biological importamce viz. Thioacrylic acid hydrazide **5**, thiopyridazinone **7**, thioacrylamide **8**, and N-benzylthiopyrroline **9** derivatives were reported for the first time.

Keywords: 2(3H)-Furanone; Furanthione; Thionopyrroline; β-aroylpropionic; Thiopyrida zinones; Acrylamides; Lawesson's reagent

The furan ring system[1] is found in many naturally occurring compounds either as the fully unsaturated structure or in a reduced or partially reduced form. The majority of naturally occurring compounds which contain a fully unsaturated furan ring are terpenoid in haracter as for example rose oil. 2(3H)-furanones **1** represent an important class of furan derivatives. In connection with our synthetic[2] approach to the 5-aryl-3-furfurylidene-2-(3H)-furanones **1** and studies of the behavior of the hetero ring towards the action of semicarbazide in different media both acid and base catalyzed. The biological activity of the synthetic products was tested against bacteria and yeast strains. These preliminary results showed promising activity. The important compounds like 5-aryl-3-furfurylidene-2(3H)-furanones **1** have been previously prepared[3] by condensing furfural with β-aroylpropionic acid in sodium acetate-acetic anhydride mixture under Perkin conditions.

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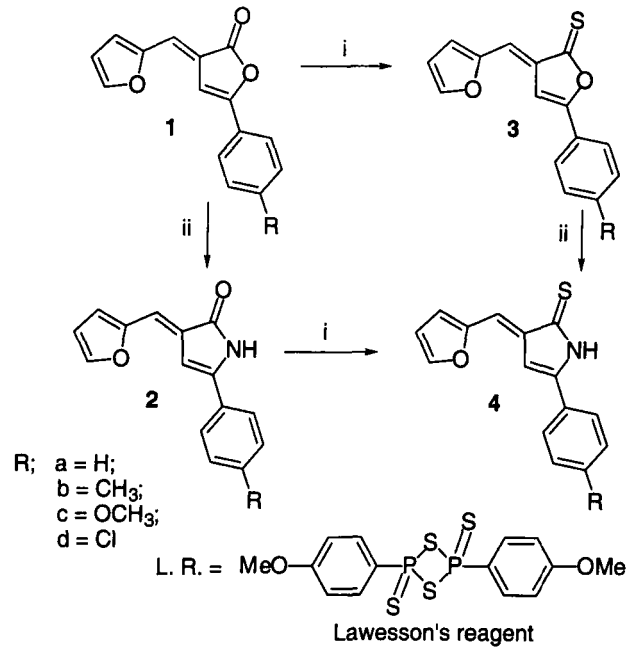
It was recently reported[4,5,6] that 5-methylfuran-2-carboxaldehyde and 5-methyl thiophene-2-carboxaldehyde condensed with 3-aroylpropionic acids under Perkin conditions yielding the *E-lactones* as the only product. There was no detectable amount of the *Z-isomers* by ^{1}H NMR. The conversion of these 2-(3H)-furanones into the corresponding oxopyrrolines was effected[7] by the action of gaseous ammonia in ethanol. Parallel studies concerning the synthesis and biological activity of the thio-lactone have shown that they show valuable effects on the growth of plants.[8,9] The use of furanone and furanthione derivatives for the preventation or treatment of autoimmune diseases have been proven.[10]

This reported biological importance of furanones and their thiono-derivatives prompted us to try the conversion of 2-(3H)-furanones **1** into their thiono-derivatives. The behaviour of the resulting furanthiones towards some nitrogen nucleophiles, viz. ammonia, hydrazine and benzylamine was also studied.

The reaction of the furanones **1** with Lawesson's reagent[11,12] was tried in nonpolar solvent thiophene free benzene. When 5-aryl-3-furfurylidene-2(3H)-furanones **1** are allowed to react with Lawesson's reagent[13,14,15] in refluxing dry benzene under a nitrogen atmosphere, the corresponding thiono-compounds 5-aryl-3-furfurylidene-furan-2-thiones **3** are formed, as shown in (Scheme 1). In a previous investigation 2-aryl-4-furfurylidene-5-oxo-2-pyrrolines **2** were prepared by the reaction of 5-aryl-3-furylidene-2(3H)-furanones **1** with gaseous ammonia in ethanol. Thiation of 5-oxo-2-pyrrolines **2** following the same previous method for thiation leads to the formation of the corresponding compounds of 2-aryl-4-furfurylidene-5-thione-2-pyrrolines **4** in 55–70% yield, spot tests confirmed the presence of the C=S group.

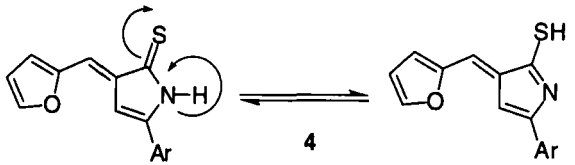
The infrared spectra of the compound **3** derivatives as shown in (Table I) Shows the disappearance of υC=O in the lactone ring and the appearance of υC=S at 1200 cm^{-1} characteristic of the five membered thio-lactone ring. Mass spectra of these derivatives show the presence of high relative abundance at fragment ions 177 and 110 for the thiolactone ring bearing furan nucleus as a side chain ($M.^+$-C_6H_4R) and thiofuranone ring ($M.^+$-144) respectively. Similarity of the infrared spectra of these compounds as shown (table I) which are also similar to those of 3-arylidene-5-aryl-2,3-dihydrofuran-2-thiones.[16] These compounds were shown by direct comparison (m.p and mixed m.p) to be identical with the authentic products obtained by the action of P_2S_5 in dryxylene on 2-(3H)-furanones **1**



(i) dissolve in dry benzene/ L.R. (ii) dissolve in Ethanol/ passing ammonia gas

SCHEME 1

The infrared spectra of the compound **4** derivatives as shown in (Table I) show the disappearance of υC=O of the lactam ring and the appearance of υC=S at 1450–1500 cm^{-1}, characteristic of the five membered thiolactam ring stretching frequency, as well as a broad band at 3130–3155 cm^{-1}, characteristic of the NH group and a broad band at 2560–2570 cm^{-1}, characteristic of the SH group indicating the existence of the thioenol form. The existence of tautomeric forms of **4** was also confirmed by spot tests which revealed the presence of the both C=S and -SH groups.



Ar; a = C_6H_5-; b = C_6H_4-CH_3 (P-); c = C_6H_4-OCH_3(p-); d = C_6H_4-

TABLE I Infrared (IR) and Mass (M/z) spectral data of compounds **3a-9d**

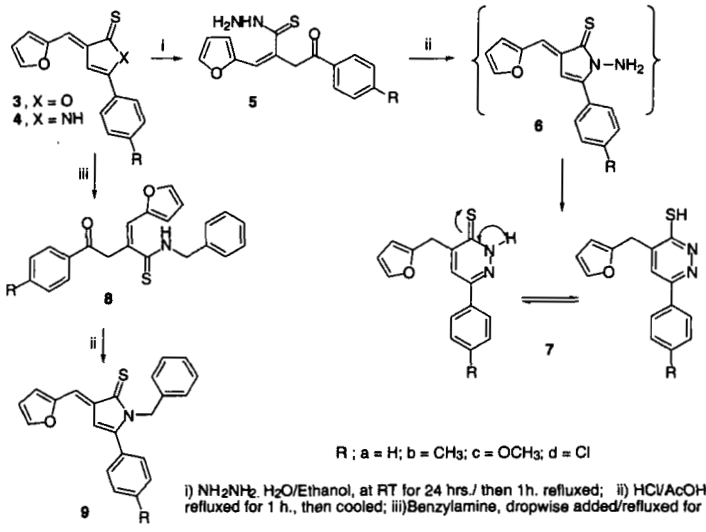
Alkyl group	*Infraredbands (IR)(cm−1)*			*Mass spectra data M/z of [M·+] and fragment ions with relative abandance %*
	$\upsilon_{C=S}$	υ_{-NH}	υ_{-SH}	
H	1160			[M·+, 258(8)], 210(20), 187(30), 177(70), 133(50), 110(80), 77(4), 67(3), 66(3), 38(2),
CH_3	1155			[M·+, 268(5)], 224(10), 177(60), 133(45), 110(75), 91(5), 77(5), 67(6), 65(4),
OCH_3	1150			[M·+, 284(12)], 269(25), 240(8), 217(6), 177(80), 110(90), 107(10), 100(9), 77(5), 69(2
Cl	1200			[M·+, 289(15)], 288(7), 244(30), 221(45), 177(65), 111(5), 110(90), 66(3).
H	1480	3130	2560	[M·+ 253 (7)], 252(3), 219(9), 209(20), 176(30), 109(70), 77(4),67(3).
CH_3	1480	3140	2565	[M.+, 267(5)], 266(5), 233(8), 176(60), 109(75), 91(5),77(5), 67(6), 65(4).
OCH_3	1480	3150	2565	[M·+, 283(12)], 282(7), 269(25), 252(5), 239(8), 176(80), 109(90), 107(10), 92(9), 65(<
Cl	1500	3155	2570	[M.+, 288(7)], 287(15), 286(10), 176(65), 112(80), 109(90), 67(<3).
H	1480	3100		[M·+, 286(5)], 269(12), 255(9), 211(60), 209(50), 181(80), 77(4).
CH_3	1481	3120		[M·+, 300(5)], 283(5), 269(12), 255(9), 223(70), 195(70), 91(5).
OCH_3	1482	3150		[M.+, 316(12)], 299(7), 285(25), 241(5), 239(8), 211(65), 109(90), 107(10), 92(9), 65(<
Cl	1520	3150		[M·+, 322(5)], 321(7), 303(15), 299(15), 285(10), 245(60), 243(55), 215(30), 214 (20), 112(80), 109(90), 67(<3).
H	1490	3110		[M·+, 268(5)], 251(12), 237(9), 193(60), 191(50), 181(80), 77(<4).
CH_3	1491	3130		[M·+, 282(5)], 265(5), 251(12), 207(9), 205(70), 177(70), 91(5).

Alkyl group	*Infraredbands (IR)(cm−1)*			*Mass spectra data M/z of [M·+] and fragment ions with relative abandance %*
	$\upsilon_{C=S}$	υ_{-NH}	υ_{-SH}	
OCH_3	1492	3130		[M.+, 298(12)], 281(7), 267(25), 223(5), 221(8), 193(50), 109(90), 107(10), 92(9), 65(<
Cl	1530	3140		[M·+, 303(15)], 302(7), 299(15), 286(10), 272(60), 228(55), 226(30), 198(20), 111(5), 112(80), 109(90), 67(<3).
H	1480	3100 – 3130		[M·+, 361(5)], 255(12), 256(90), 211(60), 150(50), 106(80), 77(4).
CH_3	1481	3100 – 3120		[M·+, 375(5)], 271(5), 269(90), 225(9), 150(70), 106(70), 91(5).
OCH_3	1482	3080 – 3130		[M·+, 391(12)], 285(80), 287(75), 241(5), 150(8), 106(65), 65(2).
Cl	1490	3100 – 3140		[M.+, 396(4)], 395(15), 321(7), 290(75), 246(10), 150(60), 106(55), 67(3).
H	1520	3100 – 3120		[M·+, 343(5)], 266(12), 222(9), 211(60), 150(50), 106(80), 77(4), 67(3).
CH_3	1521	3100 – 3130		[M·+, 357(5)], 280(5), 236(12), 106(70), 91(9), 67(70), 65(5).
OCH_3	1522	3080 – 3130		[M·+, 373(20)], 296(7), 252(25), 107(8), 92(65), 67(20), 65(2).
Cl	1540	3100 – 3150		[M·+, 378(15)], 301(7), 357(15), 246(10), 112(60), 106(5), 67(3).

Similarity of the electronic spectra of these compounds (cf., Table I), which are also similar to the a series of (2,6-dimethylphenyl)carboxythioamides.[17] Mass spectra of the compound **4** derivatives (cf., Table I) indicate the presence of high relative abundance at fragment ions ($M.^+$-77) and ($M.^+$-144) respectively. These compounds were shown by direct comparison (m.p and mixed m.p) to be identical with the products obtained by the action of P_2S_5 in dry xylene on the oxopyrrolines **2**. The same derivatives **4** were obtained via another route which involves passing ammonia gas into a solution of furanthiones **3** in ethanol. Identity of the products in each case was confirmed by direct comparison (m.p. and mixed m.p) and was also confirmed by spot tests which revealed the presence of the both C=S and -SH groups.

The title compounds (**3** and **4**) were allowed to react with hydrazine hydrate in ethanol, ring opening occurs with the formation of α-aracyl-β-(2-furyl)thioacrylic acid hydrazides **5**, as shown in (Scheme 2). The infrared spectra (**IR**) of these products (cf., Table I) show an absorption band at 3100–3150 cm^{-1} (broad band) characteristic of the NH group and an absorption band at 1480–1530 cm^{-1} for υC=S, characteristic of the amide thiocarbonyl group. Mass spectra of these derivatives (cf., Table I) reveal the presence of high relative abundance at fragment ions ($M.^+$-$NHNH_2$) and ($M.^+$- C_6H_4R) respectively. On refluxing the thiohydrazides **5** in HCl/AcOH mixture, cyclisation occurs leading to the formation of the corresponding 3(2H)-thiopyridazinones, namely 6-aryl-4-furylmethyl-3(2H)-thiopyridazinones or their tautomers **7**. The infrared spectra of these products (cf. Table I) show an absorption band at 3100–3150 cm^{-1} (broad band) characteristic of the NH group and an absorption band at 1490–1530 cm^{-1} for υC=S, characteristic of the amide thiocarbonyl group. Mass spectra of these derivatives (cf., Table I) show the presence of high relative abundance at fragment ions ($M.^+$-C_4H_3O) and ($M.^+$-Ar) respectively. Similarity of the infrared spectra of these compounds (cf., Table I), which are also similar to those of pyridazinone derivatives.[18,19,20,21]

The alternative mode of ring closure, attack by the other nitrogen would lead to the formation of the corresponding N-aminothiopyrrolines **6** as intermediate. But these N-aminothiopyrrolines are not formed, and the thiopyridazinones **7** are the only isolable products obtained from this reaction. We beleive that the N-aminothiopyrrolines **6** are unstable under the



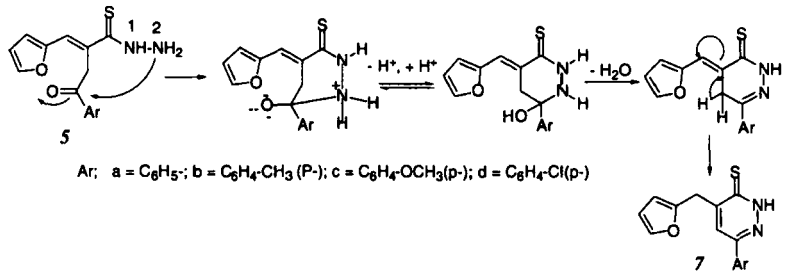
SCHEME 2

reaction conditions, and if formed they might undergo ring expansion yielding the corresponding thiopyridazinones **7**. This behaviour is in accordance with the reported[22] rearrangements of N-aminophthalimides in acid medium to the corresponding phthalaz-1,4-diones.

The previous ring opening was carried out using the reaction of benzylamine with 5-aryl-3-furfurylidene-2-thiofuranones **3**, to give the corresponding thioamides **8**, as shown in (Scheme 2). The infrared spectra of these products (cf. Table I) show an absorption band at 3000–3150 cm^{-1} (broad band) characteristic of the NH group and an absorption band at 1480–1500 cm^{-1} for υC=S, characteristic of the amide thiocarbonyl group. Mass spectra of these derivatives (cf., Table I) reveal the presence of high relitave abundance at fragment ions ($M.^{+}$-106) and ($M.^{+}$-150) respectively. Similarity of the infrared spectra of these compounds (cf. Table I), which are also similar to those of α-aracyl-β(2-furyl)-N-benzylacrylamides.[23,24] These products were shown by direct comparison (m.p and mixed m.p) to be identical with the products obtained by the action of benzylamine on 2-aryl-4-furfurylidene--5-thiono-2-pyrrolines **4**. On refluxing the thioacryl amides **8** in HCl/AcOH mixtures, cyclisation

occurs leading to the formation of the corresponding thiono-2-pyrrolines, namely 2-aryl-4-furfurylidene-N-benzyl-5-thiono-2-pyrrolines **9**. The infrared spectra of these products (cf. Table I) show an absorption band at 1480–1500 cm^{-1} for υC=S, characteristic of the amide thiocarbonyl group. Mass spectra of these derivatives (cf. Table I) indicate the presence of high relative a bundance at fragment ions (Ar^+) and ($M.^+$-C_6H_4R) respectively. The infrared spectra of these compounds (cf. Table I) shown similarity and are in accordance with the reported[25] infrared spectra of the 2-phenyl-4-furfurylidene-N-benzyl-5-oxo-2-pyrrolines.

The existence of tautomeric forms of **7** was confirmed by spot tests which revealed the presence of the both C=S and -SH groups. The formation of the thiopyridazinones **7** can be represented by the following (Scheme 3).



SCHEME 3

EXPERIMENTAL SECTION

Melting points (Thomas Hoover Capillary melting point apparatus), were determined on a Bristoline hot-stage microscope and are uncorrected. All reactions involving Lawesson's reagent requiring anydrous conditions were carried out in oven-dried glassware under an atmosphere of nitrogen. Dry peteroleum ether (90–100) or (100–120) was stirred with concentrated sulfuric acid for 1 week, washed (H_2O), dried ($MgSO_4$), and distilled (over CaH_2). Dry ethanol was distilled from calcium hydride and stored over 4 A molecular sieves. The Iodine-Azide test was utilized for evolution of nitrogen bubbles which indicated the presence of C=S group and =C-SH group.

TABLE II Elemental analysis of compounds **3a-9d**

Alkyl group	*m.p °C*	*Yield %*	*Solvent of crysta*	*M.F* *M.w*	*Analysis [Calcd/found]* *C*	*H*	*N*	
H	153–154	55 %	Pet.	$C_{15}H_{10}SO_2$ (254)	70.86/71.20	3.93/4.19		12.59
CH_3	140–142	60 %	Ether	$C_{16}H_{12}SO_2$ (268)	71.64/71.20	4.47/4.10		11.94
OCH_3	130–132	60 %	(90–100)	$C_{16}H_{12}SO_3$ (284)	67.60/68.32	4.22/4.56		11.26
Cl	176–178	60 %		$C_{15}H_9ClSO_2$ (288.5)	62.39/61.34	3.11/3.42		11.09
H	145–148	60 %	Pet.	$C_{15}H_{11}NSO$ (253)	71.14/71.25	4.34/4.32	5.53/5.40	12.64
CH_3	270–272	55 %	Ether	$C_{16}H_{13}NSO$ (267)	71.91/71.52	4.86/4.64	5.24/5.11	11.98
OCH_3	278–280	55 %	(90–100)	$C_{16}H_{13}NSO_2$ (286)	67.84/68.12	4.22/4.65	4.94/5.22	11.30
Cl	210–212	70 %		$C_{15}H_{11}ClNSO$ (288.5)	62.60/62.10	3.47/4.19	4.86/4.98	11.13
H	135–136	75 %	Ethanol	$C_{15}H_{14}SN_2O_2$ (286)	62.93/62.10	4.89/5.12	9.79/9.20	11.18
CH_3	173–175	70 %		$C_{16}H_{16}SN_2O_2$ (300)	64.00/63.92	5.33/4.98	9.33/9.76	10.66
OCH_3	110–112	65 %		$C_{16}H_{16}SN_2O_3$ (316)	60.75/59.19	5.06/5.12	8.86/9.15	10.12
Cl	215–217	75 %		$C_{15}H_{13}ClSN_2O_2$ (320.5)	56.15/57.14	4.05/4.14	8.73/9.13	9.08
H	160–162	60 %	Ethanol	$C_{15}H_{12}SN_2O$ (278)	67.16/67.22	4.47/5.13	10.44/10.98	11.94
CH_3	182–183	60 %		$C_{16}H_{14}SN_2O$ (282)	68.08/69.19	4.96/4.35	9.92/9.10	11.34
OCH_3	173–175	55 %		$C_{16}H_{14}SN_2O_2$ (298)	64.42/65.15	4.69/4.45	9.39/9.22	11.32

Alkyl group	*m.p °C*	*Yield %*	*Solvent of crysta*	*M.F* *M.w*	*Analysis [Calcd/found]* *C*	*H*	*N*	*S*
Cl	205–206	55 %		$C_{15}H_{13}ClSN_2O$ (302.5)	59.50/60.25	3.63/4.22	9.25/9.55	11.57/
H	157–158	60 %	Ethanol	$C_{22}H_{19}SNO_2$ (361)	73.13/73.28	5.26/4.98	3.87/3.19	8.86/
CH_3	175–177	60 %		$C_{23}H_{21}SNO_2$ (375)	73.60/73.05	5.60/5.16	3.73/3.86	8.53/
OCH_3	180–182	60 %		$C_{23}H_{21}SNO_3$ (391)	70.58/71.12	5.37/5.44	3.58/4.14	8.18/
Cl	165–167	65 %		$C_{22}H_{18}ClSNO_2$ (395.5)	66.75/66.10	4.55/4.89	3.53/3.78	8.09/
H	102–104	60 %	Ethanol	$C_{22}H_{17}SNO$ (343)	76.96/76.81	4.95/4.16	4.08/4.41	9.32/
CH_3	158–160	60 %		$C_{23}H_{19}SNO$ (357)	77.31/77.13	5.32/5.13	3.92/3.29	8.96/
OCH_3	167–168	60 %		$C_{23}H_{19}SNO_2$ (373)	73.99/73.24	5.09/5.12	3.75/3.91	8.57/
Cl	143–145	65 %		$C_{22}H_{16}ClSNO$ (377.5)	69.93/69.98	4.23/4.71	3.70/3.96	8.47/

Infrared **IR** spectra listed as recorded "neat" refer to a thin film of material on NaCl disks. Infrared spectra were recorded on a MIDAC Prospect spectrometer. Peaks of the IR spectrum are reported in $cm.^{-1}$ **Elemental analyses** were performed by M-H-W Laboratories (Phoenix, AZ) and Central Lab. of Ain Shams University, Cairo, Egypt. Low resolution mass spectroscopy (LREI) was performed under the indicated conditions (EI) and data presented in the following format; M/z (relative intensity %) with the exception of the parent ion and readily assignable high-mass fragments.

5-Aryl-3-furfurylidene-2-thiofuranones 3.; Method (A)

In three-necked flask fitted with a rubber septum, thermometer, magnetic stirring bar, and reflux condenser equiped with a nitrogen bubbler 2-(3H)-furanones **1** (2 mmole), and Lawssen's reagent (10 mmole) were suspended in dry benzene (10 mL). The reaction mixture was heated under reflux with stirring for 2 hours., and then cooled to room temperature. The solvent was removed with the aid a rotary evaporator and the resulting yellow slurry was distilled under reduced pressure. The yellow solid obtained was recrystallised from a suitable solvent as shown in (Table II).

2-Aryl-4-furfurylidene-5-thiono-2-pyrrolines 4

Was prepared from a) The *action of Lawssen's reagent on the oxopyrrolines 2*; Following the previous procedure **(method A)**. *b) The action of ammonia gas on the 2-(3H)-furanthiones 3*; In a three-necked flask fitted with a reflux condenser a stirring bar and gas inlet tube, was put a suspension of 2-(3H)-furanthiones **3** (2 mmole) in absolute ethanol (10 mL). The reaction mixture was refluxed in a water bath while a stream of ammonia gas was allowed to pass into the solution. The color of the reaction mixture changed from yellow to dark red after 1 hour then the solution was concentrated under reduced pressure to afford orange crystal in 55–70 % yield. The orange solid obtained was recrystallised from a suitable solvent as shown in (Table II).

α-Aracycl-β-(2-furyl)thioacrylic acid hydrazides 5

To suspension of the 2-(3H)-furanthiones **3** (2 mmole) in absolute ethanol (10 mL), was added hydrazine hydrate. The reaction mixture was allowed

to stand at room temperature with occasional shaking from time to time and was left overnight. The residue was montered by tlc and shown to be unchanged furanthiones **3**. The reaction mixture was refluxed for 1 h., cooled, and then concentration gave a colorless solid which separated out and was filtered off and recrystallised from a suitable solvent to give colorless crystals in 65–75 % yield, as shown in (Table II). Following the same procedure described above, products were obtained from the action of hydrazine hydrate on the thionopyrrolines **4**.

4-furylmethyl-6-aryl-3(2H)thiopyridazinones 7.; Method (B)

A mixture of α-Aracycl-β-(2-furyl)thioacrylic acid hydrazides **5** (2 mmole) and HCl/AcOH mixture (5 mL) in 1:1 ratio were refluxed for 1 h. During the refluxing the solution turned orange in color. On cooling an orange solid separated out and was filtered off, washed with warm water and finally recrystallised from a suitable solvent (cf. Table II).

α-Aracycl-β-(2-furyl)-N-benzylthioacrylamide 8

To a solution of the furanthione **3** (1 mmole) in dry benzene (10 mL), benzylamine (2 mmole) was added dropwise with continuous shaking. The reaction mixture was heated under reflux for 1 hour during which time the color of the furanthione **3** disappeared completely. On cooling, a colorless solid separated out which was filtered off and recrystallised from a suitable solvent to afford compound **8** in 60 % yield, (cf. Table II). Following the same experimental procedure described above the same product was obtained from the action of benzylamine on the thiopyrrolines **2**.

2-Aryl 4-furfurylidene-N-benzyl-5-thiono-2-pyrrolines 9

Pale red crystals were obtained in 60 % yield following the previous procedure described in **(method B)** They were recrystalized from a suitable solvent as shown in (Table II).

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