SYNTHESIS OF SOME NEW HETEROCYCLIC COMPOUNDS BASED ON THIOPYRANE-2-THIONE AS ANTIMICROBIAL AGENTS

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Some new derivatives containing both thiopyrane-2-thione (*I*) and β-lactams, thiazolidinones, triazoles, sulfonamides and tricyclic compound have been previously prepared[1-3]. Here we attempted to use the compound *I*, for synthesis of new heterocycles.

EXPERIMENTAL

All melting points are uncorrected. Elemental analyses were performed on Perkin–Elmer 240 E analyzer. IR spectra (given in cm^{-1}) were recorded on Pye–Unicam SP 200 G in KBr pellet. ^1H NMR spectra (given in δ ppm) were recorded on 90 MHz Varian NMR spectrometer using TMS as internal standard. Physicochemical data are given in Table I.

Schiff's Bases *IIa – IIg*; General Procedure

A mixture of *I* (0.01 mol) and the appropriate aldehyde (0.015 mol) in absolute ethanol (50 ml) was heated under reflux for 2 h in the presence of piperidine (2 drops). The reaction mixture was concentrated and allowed to cool. The separated crystalline solids were filtered and recrystallized from ethanol to give *IIa – IIg*. Typical bands in IR spectra: 2 220 – 2 200 (C≡N), 1 330 – 1 300 (C=S), 1 630 – 1 615 (CH=N). ^1H NMR ($(CD_3)_2SO$): 2.55 – 1.20 m, 8 H (cyclohexane ring); 8.8 – 8.5 s, 1 H (N=CH); 7.45 m, 5 H (aromatic protons) for compound *IIa* and 2.6 – 1.3 m, 8 H (cyclohexane ring); 8.7 – 8.3 s, 1 H (N=CH); 7.5 m, 4 H (aromatic protons); 5.9 s, 1 H (OH group – D_2O exchangable) for compound *IIf*.

Substituted Monocyclic β-Lactams *IIIa – IIIg*; General Procedure

To a solution of the Schiff base (*IIa – IIg*; 0.002 mol) in dry benzene (10 ml) containing triethylamine (0.004 mol) chloroacetyl chloride (0.004 mol) was added dropwise at room temperature. The reaction mixture was shaken for 6 h and then kept at room temperature for a further 36 h. The precipitated triethylamine hydrochloride was filtered off and the filtrate evaporated to dryness under vacuum. The precipitated product was crystallized from benzene. Typical bands in IR spectra: 2 200 (C≡N), 1 320 – 1 300 (C=S),

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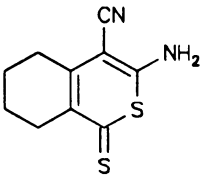
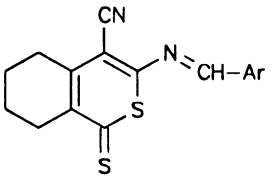


I



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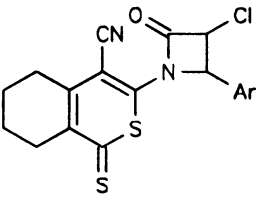

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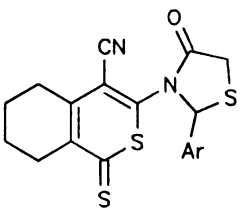

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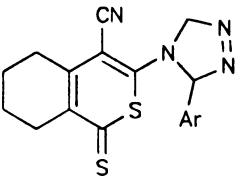
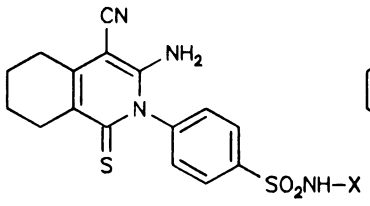
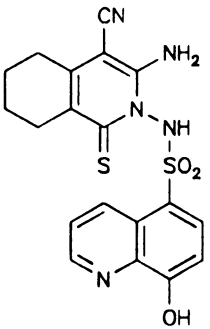


V

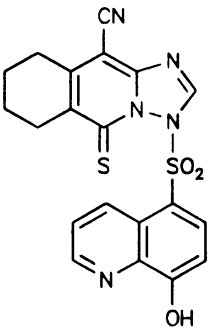
II – V	Ar
a	C_6H_5
b	4-$NO_2C_6H_4$
c	4-$CH_3OC_6H_4$
d	4-$CH_3C_6H_4$
e	4-ClC_6H_4
f	4-HOC_6H_4
g	2-furyl



VI



VII



VIII

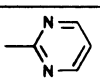
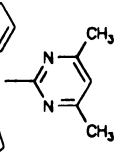
VI	X	*VI*	X
a	H	*d*	
b	$COCH_3$	*e*	
c	$-C(=NH)NH_2$	*f*	

TABLE I
Physico-chemical data of compounds *II – VIII*

Compound	M. p., °C Yield, %	Formula (M. w.)	Calculated/Found			
			% C	% H	% N	% S
IIa	240 63	$C_{17}H_{14}N_2S_2$ (310.4)	65.77 65.90	4.55 4.46	9.02 9.11	20.66 20.74
IIb	220 78	$C_{17}H_{13}O_2N_3S_2$ (355.4)	57.45 57.38	3.69 3.51	11.82 11.52	18.04 18.16
IIc	230 72	$C_{18}H_{16}ON_2S_2$ (340.5)	63.50 63.37	4.74 4.82	8.23 8.32	18.84 18.76
IId	262 65	$C_{18}H_{16}N_2S_2$ (324.5)	66.63 66.54	4.97 5.02	8.63 8.71	19.76 19.67
IIe	255 71	$C_{17}H_{13}N_2S_2Cl$ (344.9)	59.21 59.30	3.80 3.91	8.12 8.02	18.59 18.68
IIf	245 69	$C_{17}H_{14}ON_2S_2$ (326.4)	62.55 62.65	4.32 4.39	8.58 8.67	19.64 19.53
IIg	270 72	$C_{15}H_{12}ON_2S_2$ (300.4)	59.98 59.87	4.03 4.10	9.33 9.41	21.36 21.45
IIIa	192 56	$C_{19}H_{15}ON_2S_2Cl$ (386.9)	58.98 58.85	3.91 4.01	7.24 7.33	16.57 16.64
IIIb	215 48	$C_{19}H_{14}O_3N_3S_2Cl$ (431.9)	52.84 52.81	3.27 3.26	9.73 9.58	14.85 14.31
IIIc	222 66	$C_{20}H_{17}O_2N_2S_2Cl$ (417.0)	57.61 57.49	4.11 4.20	6.72 6.80	15.38 15.45
IIId	210 59	$C_{20}H_{17}ON_2S_2Cl$ (401.0)	59.91 60.01	4.27 4.36	6.99 7.06	15.99 16.04
IIIe	173 60	$C_{19}H_{14}ON_2S_2Cl_2$ (421.4)	54.16 54.27	3.35 3.44	6.65 6.73	15.22 15.28
IIIf	182 56	$C_{19}H_{15}O_2N_2S_2Cl$ (402.9)	56.64 56.87	3.75 4.00	6.95 7.36	15.92 15.64
IIIg	232 59	$C_{17}H_{13}O_2N_2S_2Cl$ (376.9)	54.18 54.29	3.48 3.55	7.43 7.52	17.02 17.08
IVa	232 63	$C_{19}H_{16}ON_2S_3$ (384.5)	59.35 59.44	4.19 4.25	7.28 7.36	25.01 25.07
IVb	192 69	$C_{19}H_{15}O_3N_3S_3$ (429.5)	53.13 53.04	3.52 3.46	9.78 10.31	22.39 22.48
IVc	205 53	$C_{20}H_{18}O_2N_2S_3$ (414.6)	57.95 57.80	4.38 4.45	6.76 6.83	23.20 23.27
IVd	242 58	$C_{20}H_{18}ON_2S_3$ (398.6)	60.27 60.14	4.55 4.46	7.03 7.13	24.13 24.22

TABLE I
(*Continued*)

Compound	M. p., °C Yield, %	Formula (M. w.)	Calculated/Found			
			% C	% H	% N	% S
IVe	230 66	$C_{19}H_{15}ON_2S_3Cl$ (419.0)	94.47 94.33	3.61 3.69	6.69 6.78	22.69 22.61
IVf	225 65	$C_{19}H_{16}O_2N_2S_3$ (400.5)	56.98 56.87	4.02 4.10	6.99 7.03	24.02 24.11
IVg	252 68	$C_{17}H_{11}O_2N_2S_3$ (374.5)	54.52 54.43	3.77 3.70	7.48 7.38	25.68 25.77
Va	190 68	$C_{18}H_{16}N_4S_2$ (352.5)	61.34 61.25	4.58 4.65	15.90 15.98	18.19 18.28
Vb	225 77	$C_{18}H_{15}O_2N_5S_2$ (379.5)	56.97 56.86	3.98 4.03	18.46 18.37	16.90 16.81
Vc	178 65	$C_{19}H_{18}ON_4S_2$ (382.5)	59.66 59.58	4.74 4.83	14.65 14.72	16.77 16.69
Vd	168 68	$C_{19}H_{18}N_4S_2$ (366.5)	62.27 62.33	4.95 5.02	15.29 15.21	17.50 17.39
Ve	169 59	$C_{18}H_{15}N_4S_2Cl$ (368.9)	56.88 55.94	3.93 4.22	14.48 15.02	16.57 17.46
Vf	182 68	$C_{18}H_{16}ON_4S_2$ (368.5)	58.67 58.79	4.39 4.45	15.20 15.33	17.40 17.51
Vg	250 75	$C_{16}H_{11}ON_4S_2$ (342.4)	56.12 56.22	4.12 4.21	16.36 16.24	18.73 18.60
VIa	220 77	$C_{16}H_{16}O_2N_4S_2$ (360.5)	53.31 53.22	4.47 4.56	15.55 15.69	17.79 17.90
VIb	270 69	$C_{18}H_{18}O_3N_4S_2$ (402.5)	53.71 53.61	4.51 4.59	13.92 13.80	15.93 15.82
VIc	248 65	$C_{17}H_{18}O_2N_6S_2$ (402.5)	50.73 50.85	4.51 4.40	20.89 20.77	15.93 15.81
VId	255 75	$C_{20}H_{18}O_2N_6S_2$ (438.5	54.78 54.92	4.14 4.23	19.17 19.27	14.62 14.48
VIe	238 78	$C_{22}H_{22}O_2N_6S_2$ (466.6)	56.63 56.74	4.75 4.84	18.02 18.14	13.74 13.62
VIf	245 73	$C_{19}H_{17}O_2N_5S_3$ (443.6)	51.45 51.57	3.86 3.77	15.79 15.90	21.68 21.77
VII	240 69	$C_{19}H_{17}O_3N_5S_2$ (427.5)	53.38 53.49	4.01 4.10	16.39 16.48	15.00 15.11
VIII	212 65	$C_{20}H_{15}O_3N_5S_2$ (437.5)	54.90 54.81	3.46 3.53	16.01 16.11	14.66 14.51

1 760 – 1 720 (C=O). ^{1}H NMR ($(CD_3)_2SO$): 2.6 – 1.25 m, 8 H (cyclohexane ring); 6.7 – 6.9 s, 1 H (N–CHPh); 6.6 – 6.4 s, 1 H (CH–Cl of β-lactam ring).

Substituted Thiazolidinones *IVa – IVg*; General Procedure

A mixture of the Schiff base (*IIa – IIg*, 0.002 mol) in dry benzene (10 ml) and mercaptoacetic acid (0.002 mol) was heated under reflux for 20 h. The solvent was evaporated and the solid product thiazolidinone was washed repeatedly with a 1 : 1 mixture of benzene–petroleum ether. The product was crystallized from ethanol. Typical bands in IR spectra: 2 220 – 2 210 (C≡N); 1 330 – 1 310 (C=S); 1 685 – 1 645 (C=O, thiazolidinone ring). ^{1}H NMR: 2.55 – 1.35 m, 8 H (cyclohexane ring); 6.85 s, 1 H (CH–Ph); 4.20 s, 2 H (CH_2, thiazolidinone ring) for compound *IVa* and 2.6 – 1.45 m, 8 H (cyclohexane ring); 7.60 – 6.95 m, 3 H (furyl ring); 6.76 s, 1 H (CH–Ph); 4.40 s, 2 H (CH_2 thiazolidinone ring) for compound *IVg*.

Substituted 1,2,3-Δ^2-Triazolines *Va – Vg*; General Procedure

A mixture of the Schiff base (*IIa – IIg*, 0.002 mol) in dry dioxane (10 ml) was treated with an excess of cold dry ethereal diazomethane solution (20 ml). The reaction mixture was kept at –10 °C for 15 days during which fresh amounts of ethereal diazomethane solution were added. The products were filtered, washed with ether and crystallized from ethanol. Typical bands in IR spectra: 2 220 – 2 210 (C≡N); 1 330 – 1 300 (C=S); 1 570 – 1 530 (–N=N–, triazole ring). ^{1}H NMR ($CDCl_3$): 2.50 – 1.30 m, 8 H (cyclohexane ring); 6.70 s, 1 H (CH–Ph); 3.80 s, 2 H (CH_2, triazole ring) for compound *Va* and 2.60 – 1.45 m, 8 H (cyclohexane ring); 6.90 s, 1 H (CH–Ph); 3.95 s, 2 H (CH_2, triazole ring) for compound *Ve*.

2-Amino-3-cyano-1-substituted-4,5,6,7-tetrahydro-8-thiocyclohexane[c]pyridine *VIa – VIf* and *VII*; General Procedure

A mixture of *I* (0.002 mol) and the selected sulfonamide derivatives (0.002 mol) in pyridine (15 ml) was heated under reflux for 4 h. A syrupy mass obtained on distilling off the excess of pyridine was poured into crushed ice containing 5 ml of concentrated hydrochloric acid. The separated solid was filtered, washed with cold water and recrystallized from ethanol. 8-Quinolinol-5-sulfonylhydrazide applied in the same procedure afforded compound *VII*. Physical and analytical data are listed in Table I. Typical bands in IR spectra: 2 220 – 2 200 (C≡N); 3 250, 3 150 (NH_2); 3 100 (NH); 1 370 – 1 320 (SO_2, asym.); 1 160 – 1 145 (SO_2, sym.), 1 330 – 1 300 (C=S). ^{1}H NMR ($CDCl_3$): 2.60 – 1.40 m, 8 H (cyclohexane ring); 8.20 – 7.45 s, 2 H (NH_2); 4.5 – 4.3 s, 1 H (NH); 9.20 – 8.92 s, 1 H (OH).

Ring Closure of *VII* with Formic Acid

A mixture of compound *VII* (0.002 mol) and formic acid (10 ml) was refluxed for 9 h. The reaction mixture was cooled, poured into water and the solid product was collected. Solution of this product in ethanol (30 ml) was treated with anhydrous potassium carbonate (1 g) and heated under reflux for 5 h, cooled and poured into cold water. The solid product was collected and recrystallized from ethanol to give 10-cyano-5,6,7,8,9-pentahydro-3-[5-sulfonyl-8-quinolinol]-5-thioxocyclohexa[*d*]-1,2,4-triazolo[1,5-*a*]pyridine (*VIII*). The IR spectrum: 2 200 (C≡N); 1 360 – 1 320 (SO_2, asym.); 1 160 – 1 140 (SO_2, sym.), 1 340 – 1 300 (C=S); bands characteristic for NH_2 were not present.

Screening for Antibacterial Activity

The biological screening was studied by the ususal cup-plate agar diffusion technique[1], 1% dimethylformamide solutions of these compounds were prepared. The antibacterial activities of the compounds *I – VIII* hae been screened in vitro against seven Gram positive and Gram negative bacteria (*Bacillus cereus*,

Serratia sp., *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Micrococus roseus* and *Staphylococus aureus*). The antibacterial activity of all synthesized compounds showed variable activities (inhibition zones ranged from 5 – 60 mm) against all bacteria tested. Schiff's bases (*IIc*, *IIg*), β-lactams (*IIIc*, *IIId*) and triazoles (*Va*, *Ve*) showed mild and strong effects (inhibition zones 10 – 40 mm) against all bacteria used. On the other hand, the majority of thiazolidinones (*IVa* – *IVg*) were higher active than β-lactams (*IIIa* – *IIIg*) and triazoles (*Va* – *Vg*) against the bacteria under investigation.

Interestingly, all of the synthesized compounds exhibited a pronounced antibacterial activities against *Bacillus subtilis* and *Staphylococus aureus*.

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