Pak. j. sci. ind. res., vol. 38, no. 7, July 1995

SYNTHESIS OF NEW CYCLIC PYRAZOLONESULFONYL THIOANALOGES OF POSSIBLE PHARMACOLOGICAL ACTIVITY

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(Received July 24, 1994 ; revised March 15, 1995)

Condensation of benzenesulphonylthiourea derivatives **1** with halogeno esters in absolute ethanol afforded the corresponding iminoesters **2-4**, while in glacial acetic acid they yielded the thiazolidinone and the thiazinone derivatives **6** and **7**. Reaction of **4** with arylhydrazines afforded the thiadiazines **5**. Cyclization of **1** with α-bromoacetophenones yielded the thiazolines **8**.

Key words: Pyrazolonebenzene sulphonylurea, Thiazinone, Thiadiazine.

Introduction

A wide variety of pharmacological properties have been encountered with di- and trisubstituted pyrazoles [1-5]. On the other hand thiazole [6], thiazolidone [7] and thiazinone [8,9] derivatives are well known for their varied biological and pharmacological activities.

Therefore, it was felt interesting to synthesise heterocyclic systems containing two of these pharmacological moieties with the hope that they may be of pharmacological and/ or biological interest.

Experimental

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}HNMR spectra were recorded on a Varian EM 90 spectrometer. IR spectra were measured on a Unicam SP 1025 spectrophotometer using KBr pellets.

*p(3-Substituted pyrazolon-1-yl) benzenesulphonylimino ester derivatives (**2-4** ; Table 1).* A mixture of **1** (0.01 mol) and the appropriate halogeno ester (0.11 mol) in absolute ethanol (30 ml) was refluxed with stirring for 2.5 hr, concentrated and allowed to crystallise. The product was recrystallized from ethanol as needles.

*3-Subtituted 2-[p-(3-substitutedpyrazolon-1yl) benzenesulphonylimino]-4-oxothiazolidines(**6**; Table 1)* A solution of the appropriate thiourea derivative 1 (0.01 mol) in glacial acetic acid (20ml) was refluxed with ethyl bromoacetate (0.011 mol) and sodium acetate (0.2 mol, 2ml H2O) for 2h. The reaction mixture was then cooled, poured into ice cold water and the product which seperated out was recrystallized from ethanol - benzene mixture as needles.

3-Substituted 2-[p3-substituted pyrazolon-l-yl benzenesulphonylimino]-4-oxo-5, 6-dihydro-1, 3-thiazines (7; Table 1). A solution of (0.01 mol) in glacial acetic acid (20 ml) was refluxed with β-bromopropionate (0.01 mol) and sodium acetate (0.02 mol, 2ml H_2O) for 2 hr. The reaction mixture was then coold, poured into water and the precipitated thiazine was recrystallized from ethanol-benzene mixture as needles.

*3-Substituted 2-[p-(3-methylpyrazolon-1-yl) benzenesulphonylimino]-1,3,4-thiadiazine derivatives (**5**; Table 1).i* A solution of **4a** (R'=Ph) (0.01 mol) in ethanol (30 ml) was refluxed with the appropriate arylhydrazines (0.011 mol) for 3hr, concentrated and allowed to crystallize. The product r obtained was recrystallized from methanol as needles.

*3-Phenyl-2-[p-(3-substitutedpyrazolon-1-6 yl) benzenesulphonylimino] 1,3-thiazoline derivatives (**8**; Table 1).* A solution of the corresponding thiourea derivative **1**(0.01 mol) in absolute ethanol (20 ml) was refluxed with the appropriate α–bromoacetophenones (0.011 mol) for 3 hr. The product which separated out during heating was allowed to cool, filtered and recrystallized from glacial acetic acid in yellow needles.

*5-Benzal-4-thiazolidone derivatives (**9**; Table 1).* A solution of **6b** (R'=Ph) (0.05 mol) in absolute ethanol was refluxed with the appropriate aldehyde (0.051 mol) in presence of two drops of piperidine for 1.5hr, concentrated and allowed to cool. The benzal derivative which separated out r was recrystallized from methanol in needles.

Results and Discussion

Substituted p-(3-methylpyrazolon-1-yl) - and p-(3-phenylpyrazolon-1-yl) benzenesulphonylthiourea derivatives (**1**)were prepared by the treatment of corresponding p-sulphamylphenylpyrazolone derivatives with the appropriate isothiocyanate [8]. Condensation of thiourea derivatives (**1**) with ethyl bromoacetate, ethyl β - bromopropionate and ethyl 2-chloroacetoacetate in absolute ethanol yielded the

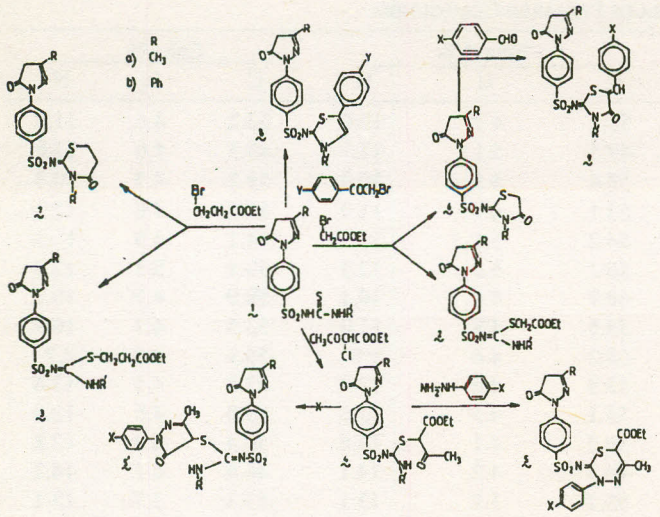
TABLE 1. CHARACTERIZATION DATA OF PREPARED COMPOUNDS.

Compound	R'	X or Y	Yield [%]	M.P. [°C]	Formula	Found % C	Found % H	Found % N	Calc. % C	Calc. % H	Calc. % N
2a/1	Ph		72	220	$C_{21}H_{22}N_4O_5S_2$	53.1	4.7	12.0	53.2	4.6	11.8
2a/2	Allyl		65	122	$C_{18}H_{22}N_4O_5S_2$	49.5	5.1	12.7	49.3	5.0	12.8
2b/1	Ph		70	190	$C_{26}H_{24}N_4O_5S_2$	58.4	4.5	10.3	58.2	4.5	10.4
2b/2	Allyl		66	107	$C_{23}H_{24}N_4O_5S_2$	55.1	4.7	11.0	55.2	4.8	11.2
3a/1	Ph		70	208	$C_{22}H_{24}N_4O_5S_2$	54.2	5.1	11.5	54.1	4.9	11.5
3a/2	Allyl		64	216	$C_{19}H_{24}N_4O_5S_2$	50.3	5.2	12.3	50.4	5.3	12.4
3b	Ph		72	275	$C_{27}H_{26}N_4O_5S_2$	60.1	4.8	10.1	58.9	4.7	10.2
4a	Ph		75	265	$C_{23}H_{24}N_4O_6S_2$	53.5	4.8	11.0	53.5	4.7	10.9
4b	Ph		70	171	$C_{28}H_{26}N_4O_6S_2$	58.2	4.6	9.8	58.1	4.5	9.7
5a/1		H	74	232	$C_{23}H_{23}N_3O_5S_2$	53.9	4.6	13.4	53.8	4.5	13.6
5a/2		MeO	70	164	$C_{24}H_{25}N_3O_6S_2$	53.1	4.5	13.0	53.0	4.6	12.9
5a/3		Cl	69	178	$C_{23}H_{22}ClN_5O_5S_2$	50.2	4.1	12.8	50.4	4.0	12.8
5a/4		SO_2NH_2	65	190	$C_{23}H_{24}N_6O_7S_3$	46.3	4.2	14.1	46.6	4.1	14.2
6a	Ph		68	186	$C_{19}H_{16}N_4O_4S_2$	53.2	3.8	13.1	53.3	3.7	13.1
6b	Ph		70	255	$C_{24}H_{18}N_4O_4S_2$	59.0	3.6	11.2	58.8	3.7	11.4
7a/1	Ph		67	162	$C_{20}H_{18}N_4O_4S_2$	54.3	3.9	12.6	54.3	4.1	12.7
7a/2	Ally		62	208	$C_{17}H_{18}N_4O_4S_2$	50.3	4.3	13.8	50.2	4.4	13.8
7b	Ph		68	194	$C_{25}H_{20}N_4O_4S_2$	59.6	3.9	11.0	59.5	4.0	11.1
8a/1	Ph	H	76	314	$C_{25}H_{20}N_4O_3S_2$	61.2	4.4	11.4	61.5	4.1	11.5
8a/2	Ph	Br	75	303	$C_{25}H_{19}BrN_4O_3S_2$	52.8	3.2	10.1	52.9	3.4	9.9
8a/3	Ph	Me	70	308	$C_{26}H_{22}N_4O_3S_2$	62.4	4.3	11.1	62.2	4.4	11.2
8a/4	Ph	Meo	72	280	$C_{26}H_{22}N_4O_4S_2$	60.4	4.3	11.0	60.2	4.2	10.8
8b/1	Ph	H	75	303	$C_{30}H_{22}N_4O_3S_2$	65.8	3.9	10.1	65.5	4.0	10.2
8b/2	Ph	Br	76	301	$C_{30}H_{21}BrN_4O_3S_2$	57.0	3.4	8.7	57.2	3.3	8.9
8b/3	Ph	Me	69	322	$C_{31}H_{24}N_4O_3S_2$	66.3	4.1	10.1	66.0	4.3	9.9
8b/4	Ph	MeO	70	306	$C_{31}H_{24}N_4O_4S_2$	64.2	4.2	9.7	64.1	4.1	9.7
9b/1	Ph	H	86	198	$C_{31}H_{22}N_4O_4S_2$	64.5	4.0	9.6	64.4	3.8	9.7
9b/2	Ph	Me	84	192	$C_{32}H_{24}N_4O_4S_2$	64.7	3.8	9.3	64.9	4.1	9.5

TABLE 2. ^{1}H NMR SPECTRAL DATA (δ/PPM)[a] OF COMPOUND (2-11)

Compound No.	R'	X or Y	CH_2 (s)	CH_3 (s)	Ester CH_2 (q, J = 7Hz)	Ester CH_3 (t, J = 7Hz)	NH_2 and/orArH(m)	Others
2a/1	Ph		3.8, 4.2	2.4	4.3	1.3	7.4 - 8.2	
2a/2	Allyl		3.5, 4.1	2.3	4.3[b]	1.2	7.6 - 8.0	5.5 (2H, m, CH = CH_2)
2b/1	Ph		3.6, 4.1		4.3	1.2	7.3 - 8.3	
3a/1	Ph		3.2 - 4.1[c]	2.4	4.3	1.3	7.4 - 8.1	
3b	Ph		3.3 - 4.3[c]		4.2	1.2	7.3 - 7.8	
4a	Ph		3.7	2.3, 2.7	4.4	1.3	7.7 - 8.3	6.6 (1H, s, CHCO)
4b	Ph		3.5	2.6	4.3	1.4	7.3 - 8.4	6.4 (1H, s, CHCO)
5a/1	Ph	H	3.6	2.3, 2.7	4.3	1.3	7.1 - 8.2	6.2 (1H, s, CHCO)
5a/2	Ph	MeO	3.5	2.2, 2.5	4.2	1.2	6.9 - 8.1	3.8 (s,OMe); 6.2 (1H,s,CHCO)
6a	Ph		3.4, 4.2	2.2			7.3 - 8.1	
6b	Ph		3.6, 4.4				7.2 - 8.3	
7a/1	Ph		3.4 - 4.2[c]	2.3			7.3 - 8.1	
7b	pH		3.3 - 4.2[c]				7.2 - 8.2	
8a/1	pH	H	3.5	2.4			7.1 - 8.4	
8a/4	pH	MeO	3.4	2.3			7.2 - 8.3	3.8 (s, OMe)
8b/2	pH	Br	3.4				7.5 - 8.4	
8b/4	pH	MeO	3.5				7.3 - 8.3	3.9 (s, OMe)
9b/1	pH	H	3.6				7.3 - 8.2	8.7 (s, CH=)
9b/2	pH	Me	3.5	2.4			7.2 - 8.3	8.8 (s, CH=)

a Solutions in DMSO - d_6 - $CDCl_3$ mixture. b m, 4H. c m, 6H ($3CH_2$).



corresponding esters (**2-4**). Their IR spectra revealed a carbonyl ester at 1722 - 1732 cm^{-1} as well as a pyrazolone carbonyl at 1705 - 1708 cm^{-1}. However, compounds (**4**) exhibited an additional ketonic carbonyl absorption at 1667 - 1669 cm^{-1}. The structure of the above esters was further supported from their ^{1}H NMR spectra (Table 2).

On the other hand, cyclization of (**1**) with ethyl bromoacetate and ethyl β-bromopropionate in acetic acid afforded the corresponding 4-oxothiazolidine (**6**) and 4-oxo-5,6-dihydrothiazine derivatives (**7**) respectively. The IR spectra of (**6**) and (**7**) showed two carbonyl absorptions at 1705 - 1712 cm^{-1} and 1720 - 1732 cm^{-1} for the pyrazolone and the cyclic ketone respectively. Their ^{1}H NMR was further supported the suggested structure. It lacked the signals of the ester group, and showed beside the aromatic protons, two CH_2 singlets at δ 3.4 - 3.6 and 4.2 - 4.4 for pyrazolone and thiazolidinone moieties in compounds (**6**).The thiazinone derivatives (**7**) showed one multiplet at δ 3.4 - 4.2 corresponding to the three CH_2 of both the pyrazolone and the thiazinone moieties.

Reaction of the ester derivative (4a, R' = Ph) with arylhydrazines afforded the thiadiazines derivatives (**5**) instead of the expected dipyrazolone derivative (**5**)'. The IR spectra of these compounds showed an ester carbonyl at 1725 - 1730 cm^{-1} as well as pyrazolone carbonyl at 1698 - 1702 cm^{-1}. The structure of the above thiadiazine derivatives was further confirmed from their ^{1}HNMR spectra which showed the ester protons as a triplet and quartet at δ 1.2 - 1.3 and 4.2 - 4.3 respectively.

Moreover, cyclization of (**1**) with α-bromoacetophenones derivatives yielded the corresponding thiazoline derivatives (**8**). Their IR spectra revealed a pyrazolon carbonyl at 1695 - 1708 cm^{-1} in addition to two bands at 1350 - 1340 cm^{-1} and 1156 - 1162 cm^{-1} indicative of the SO_2N group. The structure was further supported from their ^{1}H NMR spectra (Table 2).

It has been reported that the complex - CO-CH_2-S in the 4-thiazolidones exhibited general properties of an acid methylene grouping [9]. Thus, condensation of thiazolidone derivative (**6b**) with aromatic aldehydes in presence of few drops of piperidine afforded the corresponding 5-benzal-4-thiazolidones (**9**). Their ^{1}H NMR lacked the CH_2 singlet appeared in the parent thiazolidone derivative and showed a singlet of one proton intensity in the range of δ 8.7 - 8.8 for the CH = proton.

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