Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 4, No. 12, pp. 1453-1456, 1994

0960-894X/94 $7.00+0.00

0960-894X(94)00170-7

SYNTHESIS OF SULPHUR HETEROCYCLES AS HEPATOPROTECTANTS+: PART I

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Abstract: The synthesis and hepatoprotective activity of 1,3-dithiolanes **(2)**, 1,3-dithianes **(3)**, 2H-thiopyran-2-thione **(4)**, 1,3-dithiole-2-thione **(5)** and pyrazole **(6)** are described.

Introduction: Many herbal preparations whose efficacies have been known for a long time, yet are little understood, are claimed to be effective in hepatic diseases. Some synthetic and semisynthetic drugs, which include steroids, immuno-suppressants and antiviral agents, provide only symptomatic relief with risk of relapse and side effects. Hence the search for a safe synthetic hepatoprotectant continues. The effect of high concentrations of reactive species, such as superoxide (O_2^-), hydrogen peroxide and hydroxy radicals in biochemical reactions, has recently received great attention due to their cytotoxic nature causing ageing, arteriosclerosis, cataract, cancer and hepatitis[1]. Carbon tetrachloride, a known hepatotoxin, causes hepatic damage in experimental animals through superoxide-induced radical, $Cl_3COO^{\bullet}$. The concept of radical scavengers in designing hepatoprotectants was suggested by observing the properties of certain sulphur compounds, such as thioamides, thioethers and sulphur heterocycles, which could trap the superoxide generated in the system and themselves become transformed into the corresponding oxo analogs[2,3]. 1,1-Bis(ethylthio)ethane[4] and malotilate[5-8], known hepatoprotectants, presumably act through this mechanism. The latter, in phase II clinical trials, exhibited the side effects of dry skin and hair loss.

Taking malotilate as a template, several 5- and 6-membered sulphur heterocycles **(2-5)** were prepared and their hepatoprotective activity is reported in the present communication.

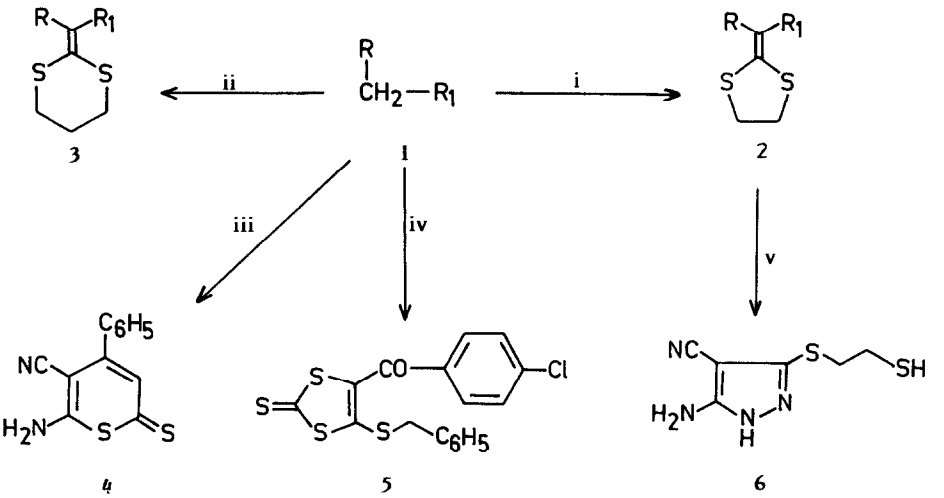
Synthesis: Cyclic ketene dithioacetals, 1,3-dithiolanes **(2)** and 1,3-dithianes **(3)** were prepared[9,10] by intramolecular substitution reactions of dipotassium dithiolate with dihaloalkanes. These heterocycles were susceptible to ambiphilic nucleophilic attack at the highly electrophilic carbon with ring opening followed by cyclization. (1,3-Dithiolane-2-ylidene) malononitrile (**2**,R,R_1=CN) for example, was reacted with hydrazine hydrate to give (5-amino-4-cyano-1H-pyrazol-3-yl)thioethylthiol **(6)**, providing a novel procedure for the synthesis of highly substituted pyrazoles. The IR spectrum of pyrazole **(6)** showed CN and NH frequencies at 2215 and 3200 cm^{-1} respectively. Reaction of

+CDRI Communication No.5210.

arylidene malononitrile with carbon disulphide in the presence of triethylamine in DMF provided 6-amino-5-cyano-4-phenyl-2H-thiopyran-2-thione **(4)** following the procedure of Gewald[12]. During the synthesis of S,S-benzyl ketene dithioacetal by reacting ethyl 4-chlorobenzoylmethylxanthate with carbon disulphide and benzyl bromide in the presence of NaH in DMF, an unexpected product was isolated and characterized as 4-benzylthio-5-(4-chlorobenzoyl)-1,3-dithiole-2-thione **(5)**[13] (Scheme 1).

Biological Activity: All the synthesised compounds listed in Table 1 were tested for their hepatoprotective activity against thioacetamide-induced hepatic damage in rats according to the procedure reported earlier[14]. The activity of the compounds was assessed on the basis of the % protection afforded in various levels of serum enzymes such as glutamate pyruvate transaminase (GPT), glutamate oxaloacetate transaminase (GOT), acid phosphatase (ACP), alkaline phosphatase (ALP) and glutamate dehydrogenase (GlDH). The results are presented in Table 1.

Scheme-1



Reagents/Conditions: i) $CS_2/K_2CO_3/(CH_2)_2Br_2$ /DMF, ii) $CS_2/K_2CO_3/(CH_2)_3Br_2$/DMF, iii) $Et_3N/CS_2/C_6H_5COCH_3$, iv) CS_2/NaH/$BrCH_2C_6H_5$/DMF/-10°C, v) N_2H_4/EtOH.

Table 1: Hepatoprotective activity of 1,3-dithiolanes **(2)** and 1,3-dithianes **(3)** against thioacetamide-induced toxicity in rats at 6 mg/kg dose (P.O. x 7 days). Values are the % protection afforded by the compounds.

	R	R_1	GOT	GPT	ACP	ALP	GlDH
2a	CN	$COOC_2H_5$	74**	73**	35	11	46
2b	$COCH_3$	$COCH_3$	67**	40	0	0	8
2c	$COCH_3$	$COOCH_3$	7	0	9	0	0
2d	C_6H_5CO	$COOC_2H_5$	0	0	29	0	0
2e	C_6H_5CO	CN	0	0	0	31	0
2f	$4\text{-}ClC_6H_4CO$	CN	0	0	0	0	0
2g	C_6H_5CO	C_6H_5CO	0	0	8	34	0
2h	$COOC_2H_5$	$COOC_2H_5$	0	0	39	0	2
2i	$COOCH(CH_3)_2$	$COOCH(CH_3)_2$	92**	77**	0	0	0
2j	$(C_2H_5)_2NC(S)S$	$4\text{-}ClC_6H_4CO$	46*	0	27	0	5
2k	$(C_2H_5)_2NC(S)S$	$4\text{-}CH_3C_6H_4CO$	56*	0	70*	0	93**
3a	CN	$COOC_2H_5$	84**	59*	0	76**	0
3b	$COCH_3$	$COCH_3$	27	0	0	67*	0
3c	$COCH_3$	$COOCH_3$	66**	0	0	14	68**
3d	C_6H_5CO	$COOC_2H_5$	35	45	7	0	23
3e	C_6H_5CO	CN	0	0	0	0	0
3f	$4\text{-}ClC_6H_4CO$	CN	63*	0	0	0	0
3g	$(C_2H_5)_2NC(S)S$	$4\text{-}ClC_6H_4CO$	85**	0	6	37	26
3h	$(C_2H_5)_2NC(S)S$	$4\text{-}BrC_6H_4CO$	38	0	20	0	0
4			41*	35	47*	30	47*
5			80**	39	4	3	15
6			0	0	9	0	0
	Silymarin (standard drug)		50.14*	47.25*	43.65*	47*	39.81

(**$P < 0.01$; *$P < 0.05$) as compared to toxin treated group.

Dihydromalotilate **(2i)**, a logical variant of malotilate, gave 92 and 77 percent protection of GOT and GPT levels respectively, while it failed to afford protection against loss of ACP, ALP and GlDH activity, the other important parameters. Reduction in protection may be attributed to the loss of planarity in dihydromalotilate. In an attempt to ascertain the effect of planarity, the ring size or substituents R,R_1 at position 2 in **2** and **3**, responsible for conferring the hepatoprotective activity, several 1,3-dithiolanes **(2)** and 1,3-dithianes **(3)** were prepared. A critical examination of structure-activity relationship in the given series revealed that the 5-membered ring size with R=CN and $R_1=COOC_2H_5$ substituents are essential requirements to potentiate the hepatoprotective activity. Compounds with R=aroyl and R_1=CN substituents displayed

drastic decrease in the measured activity. The most active compound, **2a**, gave protection in all the enzyme assays while **3a** exhibited better protection only for GPT and ALP. The other active compound **2i** offered excellent protection for GPT and GOT and was found ineffective for the other enzymes.

6-Amino-4-aryl-5-cyano-2H-thiopyranthione **(4)** demonstrated activity in all the enzyme parameters at a dose of 6 mg/kg (P.O. x 7 days) but compounds **5** and **6** did not exhibit any significant activity.

Acknowledgement: N. Haque and S.K. Singh are grateful to CSIR for the award of Senior Research Fellowship and Research Associateship while VJR and M. Nath are thankful to ICMR for financial support.

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    b) Male Sprague-Dawley rats (100-125 g) were caged separately in groups of 5 animals each. Group I consisted of normal animals. Group II animals were administered thioacetamide (200 mg/kg, P.O. x 1). Group III animals were fed the test compound daily at a dose level of 6 mg/kg (P.O. x 7 days). Thioacetamide was administered to them on day 7.

    Animal of all the groups were sacrificed 24 h after administration of the toxin and their blood collected. Serum enzyme parameters described in Table 1 were analysed according to standard procedures and the percent protection was calculated using the formula:

$$\frac{\text{(Toxin treated)} - \text{(Toxin + test compound treated)}}{\text{(Normal)} - \text{(Toxin treated)}} \times 100$$

(*Received in USA* 22 *October* 1993; *accepted* 2 *May* 1994)