Tetrahedron. Vol. 26, pp. 5235–5238. Pergamon Press 1970 Printed in Great Britain

ANTITUBERCULOSIS AGENTS—I

α-[5-(2-FURYL)-1,2,4-TRIAZOL-3-YLTHIO] ACETHYDRAZIDE AND RELATED COMPOUNDS

I. MIR and M. T. SIDDIQUI

Drugs Research Division, P.C.S.I.R. Laboratories, Peshawar

A. COMRIE

School of Pharmaceutical Sciences, University of Strathclyde, Glasgow

(*Received in the UK* 15 *June* 1970; *Accepted for publication* 15 *July* 1970)

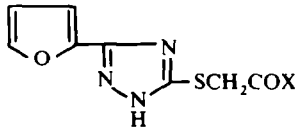
Abstract—α-[5-(2-Furyl)-1,2,4-triazol-3-ylthio] acethydrazide, δ-Allyl-α-[5-(2-furyl)-1,2,4-triazol-3-ythio-acet] thiosemicarbazide, α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acethydroxamic acid and other related compounds have been prepared α-15-(2-furyl)-1,2,4-triazol-3-ylthiol acethydrazide has significant activity against *Myco. tuberculosis*.

MEDNE *et al.*[1] investigated a number of 3-amino-1,2,4-triazol derivatives *in vivo* against *Mycobacterium tuberculosis* and *Mycobacterium bovis* strains and found that the tuberculotherapeutic activity of these compounds was the function of their basicity and the active H atoms in the triazole ring. Jeney and Zsolnai[2] in similar investigations were unable to correlate the structure-activity relationship. Matsuda and Hirao[3] prepared 3-amino-,3,5-dimethyl-, 3-methylthio-5-phenyl-4 [(5-nitro-furfurylidene) amino] -1,2,4-triazoles and other related compounds and found them active against Gram-positive and Gram-negative organisms. Recently Burch[4] synthesised a series of 1,5-disubstituted 3-(5-nitro-2-furyl)-1,2,4-triazoles by ring closure of an N-alkanoylamido-5-nitro-2-furamidine by means of phosphorous oxychloride/glacial acetic acid and claimed them to be highly bacteriostatic.

DISCUSSION

In the present work, it was decided to synthesise α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acethydrazide (1, X = $NHNH_2$) and its acyl, arylidene and alkylidene derivatives and other related compounds for pharmacological evaluation. With a view to achieve such a system, 2-furoyl chloride was condensed with thiosemicarbazide hydrochloride in dry pyridine to yield 2-furoyl thiosemicarbazide, which was cyclised according to the method of Mndzhoian *et al*[5] to give 5-(2-furyl)-1,2,4-triazol-3-thiol. Treatment of the sodio derivative of the thiol with ethyl bromoacetate in dry ethanol yielded ethyl-α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acetate (1, X = OEt) which reacted with either water, ammonia, hydroxylamine or hydrazine to yield respectively the acid (I, X = OH), the amide (I, X = NH_2), the hydroxamic acid (I, X = NHOH) and the hydrazide (I, X = $NHNH_2$). The hydrazide crystallised as trihydrate. The structure was supported by microanalysis and mass spectrum (M^+; *m/e* 239). The hydrazide formed a thiosemicarbazide (I, X = $NHNHCSNHCH_2CH:CH_2$), arylidene, alkylidene (Table 1), acyl and sugar derivatives (Experimental). Mass spectral measurements of vanillylidene, pipronylidene, nicotinylidene, salicylidene

and benzylidene derivatives showed M^+ at *m/e* 373, 371, 328, 343 and 327 respectively. The reaction of formaldehyde with the hydrazide gave the methylidene derivative and not the trimer, although the corresponding reaction with INAH gives a trimer.[6] This was indicated by the mass spectrum of methylidene derivative which gave M^+ at *m/e* 251 and there was no indication of a trimer. The purity of the analytical samples was checked by TLC (silica gel).



I

Bacteriological results. Dr. A. H. Saeed, M.B.B.S., T.D.D. (Wales), F.C.C.P. (University of Vienna), T. B. Sanatorium, Quetta, has kindly carried out the *in vitro* examination of α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acethydrazide against *Mycobacterium tuberculosis* strains $H_{37}R_v$ and Academia in Peizer and Schecter medium. The compound showed significant activity compared with isoniazid.

EXPERIMENTAL

M.Ps are uncorrected. IR spectra were recorded on nujol mulls using Beckman IR4 spectrophotometer. Mass measurements were carried out on the MS9 mass spectrometer.

Ethyl-α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acetate (1, X = OEt). 5-(2-Furyl)-1,2,4-triazole-3-thiol (16·7 g, 0·1 mole) was dissolved in water (100 ml) containing $NaHCO_3$ (8·4 g, 0·1 mole) and the soln evaporated to dryness. The residue was dissolved in dry EtOH (150 ml) and ethyl bromoacetate (16·54 g, 0·09 mole) added and the mixture vigorously shaken till a faint smell of ethyl bromoacetate remained. The soln was filtered, evaporated to dryness under vacuum and the residue extracted with ether (200 ml) in a continuous extractor for 3 hrs and dried (Na_2SO_4), and then ether removed to yield a crystalline solid. Recrystallisation from benzene–MeOH gave the product (16·25 g) as colourless needles, m.p. 112–114°. (Found: C, 47·6; H, 4·1; N, 16·6; $C_{10}H_{11}N_3O_3S$ requires: C, 47·4; H, 4·4; N, 16·6%); ν_{max} 1735 cm^{-1} (C=O).

α-[5-(2-Furyl)-1,2,4-triazol-3-ylthio] acetamide (1, X = NH_2). Ethyl-α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acetate (0·5 g, 0·002 mole) was dissolved in dry EtOH (20 ml) and a steady stream of dry ammonia gas passed through for 1 hr. The crude product was filtered off, washed with cold water (5 ml) and dried. Recrystallisation from benzene–EtOH mixture gave the product (0·4 g) as needles, m.p. 194–196°. (Found: C, 42·9; H, 3·5; N, 25·1, (M^+ *m/e* 253); $C_8H_8N_4O_2S$ requires: C, 42·85; H, 3·6; N, 24·99%); (M^+ *m/e* 253); ν_{max} 1659 cm^{-1} (C=O).

α-[5-(2-Furyl)-1,2,4-triazol-3-ylthio] acethydrazide (1, X = $NHNH_2$). Ethyl-α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acetate (12·6 g, 0·05 mole) was dissolved in dry EtOH (75 ml) and hydrazine hydrate (4 g, 0·1 mole) added and the mixture refluxed for 1 hr. The solvent was removed under vacuum to give a white viscous oil which slowly crystallised at 0°. The solid was filtered off, washed with cold water and sucked dry. It was then washed with ether and dried *in vacuo*, and twice crystallised from MeOH–water to give the acethydrazide (10·55 g) as prisms, m.p. 59–60° as trihydrate. (Found: C, 32·2; H, 5·2; N, 23·55 (M^+ *m/e* 239). $C_8H_9N_5O_2S \cdot 3H_2O$ requires: C, 32·8; H, 5·1; N, 23·9%); (M^+ *m/e* 239), ν_{max} 1672 cm^{-1} (C=O).

α-[5-(2-Furyl)-1,2,4-triazol-3-ylthio] acetic acid (1, X = OH). Ethyl-α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acetate (0·5 g, 0·002 mole) was dissolved in 2N NaOH (20 ml) and the soln set aside at room temp overnight. The resulting soln was made acidic with 2N HCl. The ppt was filtered off, washed with cold water (25 ml) and dried *in vacuo*. Recrystallisation from water–EtOH gave the product (0·4 g) as colourless needles, m.p. 240–243°. (Found: C, 42·75; H, 3·0; N, 18·7. $C_8H_7N_3O_3S$ requires: C, 42·7; H, 3·1; N, 18·7%) ν_{max} 1715 cm^{-1} (C=O).

δ-Allyl-α-[-5-(2-furyl)-1,2,4-triazol-3-ylthioacet] thiosemicarbazide (1, X = $NHNHCSNHCH_2CH:CH_2$).

TABLE 1. N′-ALKYLIDENE-α-[5-(2-FURYL)-1,2,4-TRIAZOL-3-YLTHIO]ACETHYDRAZIDES
(I,X = NH.N:CR′R″)

Derivatives :CR′R″	M.P	Recrystin solvent[a]	Yield %	Formula	Calc %			Found %			ν_{max}(C=O) cm^{-1}
					C	H	N	C	H	N	
Benzylidene	154–156	B + C	83·0	$C_{15}H_{13}N_5O_2S$	55·0	4·0	21·4	54·8	4·0	21·0	1680
Salicylidene	183–184	B + C	83·7	$C_{15}H_{13}N_5O_3S$	52·5	3·8	20·4	52·7	3·7	20·6	1662
Cinnamylidene	164–166	A	87·0	$C_{17}H_{15}N_5O_2S$	57·8	4·3	19·8	57·7	4·4	19·7	1660
Veratrylidene	197–199	A	87·5	$C_{17}H_{17}N_5O_4S$	52·7	4·4	18·1	52·2	4·3	18·2	1658
Piperonylidene[b]	134	A + C	82·0	$C_{16}H_{13}N_5O_4S \cdot \frac{1}{2}H_2O$	50·5	3·7	18·4	50·2	3·4	17·9	1675
Vanillylidene[c]	109–112	A + C	80·0	$C_{16}H_{15}N_5O_4S \cdot 2H_2O$	46·9	4·65	17·1	47·0	4·2	16·8	1671
α-Phenylethylidene	183–184	A	78·0	$C_{16}H_{15}N_5O_2S$	56·3	4·4	20·5	55·9	4·0	20·9	1674
Furfurylidene	154–156	A	90·0	$C_{13}H_{11}N_5O_3S$	49·2	3·5	22·1	48·85	3·5	21·5	1681
2-Pyrrylmethylidene	239–241 (decomp.)	B	87·0	$C_{13}H_{12}N_6O_2S$	49·35	3·8	26·6	49·2	3·7	26·6	1645
Thenylidene	193–194	A	88·5	$C_{13}H_{11}N_5O_2S_2$	46·8	3·3	21·0	47·3	3·2	20·7	1678
Nicotinylidene[d]	134–138	A + C	78·0	$C_{14}H_{12}N_6O_2S \cdot 1\frac{1}{2}H_2O$	47·3	4·2	23·7	47·1	3·8	23·9	1680
Isonicotinylidene	222–224	A	81·0	$C_{14}H_{12}N_6O_2S$	51·2	3·7	25·6	50·8	3·6	25·1	1670
Methylidene	137–140	B	68·0	$C_9H_9N_5O_2S$	43·0	3·6	27·8	42·9	3·9	27·5	1670
Ethylidene	189–190	A	91·5	$C_{10}H_{11}N_5O_2S$	45·3	4·2	26·4	45·6	4·2	26·0	1648
Isopropylidene	178–179	B + C	80·0	$C_{11}H_{13}N_5O_2S$	47·3	4·7	25·1	47·5	4·5	25·1	1656
Propylidene	155–156	A	89·0	$C_{11}H_{13}N_5O_2S$	47·3	4·7	25·1	47·3	4·6	25·0	1641

[a] A = MeOH; B = EtOH; C = C_6H_6.
[b] hemihydrate.
[c] dihydrate.
[d] $1\frac{1}{2}$ H_2O.

A mixture of α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acethydrazide (0·5 g, 0·002 mole) and allyl isothiocyanate (5 ml) was heated on a water-bath for 5 min, excess of the allyl isothiocyanate removed under vacuum, benzene (10 ml) added and then the mixture left at room temp for 2 days. The crystalline solid was filtered off, washed with cold benzene (10 ml), and dried. Recrystallisation from benzene–MeOH gave the product (0·3 g) as prisms, m.p. 127–130°. (Found: C, 42·4; H, 4·3; N, 24·7. $C_{12}H_{14}N_6O_2S_2$ requires: C, 42·6; H, 4·2; N, 24·8%), ν_{max} 1677 cm^{-1} (C=O).

α-[5-(2-*Furyl*)-1,2,4-*triazol*-3-*ylthio*] *acethydroxamic acid* (1, X = NHOH). A mixture of ethyl-α-[5-(2-furyl)-1.2.4- triazol-3-ylthio] acetate (1 g, 0·004 mole), hydroxylamine hydrochloride (0·3 g, 0·0043 mole) and NaOMe (0·215 g) in dry MeOH was refluxed for 1 hr. The mixture was cooled, solid filtered off, washed with ether (10 ml) and dried. Recrystallisation from benzene–MeOH mixture gave the product (0·7 g) as colourless needles, m.p. 158*–161°. (Found: C, 39·9; H, 3·36; N, 23·3. $C_8H_8N_4O_3S$ requires: C, 39·99; H, 3·35; N, 23·3%); ν_{max} 1660 (C=O), 3220 (OH) cm^{-1}.

N'N' *Diacetyl*-N-[5-(2-*furyl*)-1,2,4-*triazol*-3-*ylthioacetyl*] *hydrazine* (1, X = NHN $(COCH_3)$. α-[5-(2-Furyl)-1,2,4-triazol-3-ylthio] acethydrazide (0·5 g, 0·002 mole) was added to Ac_2O anhydride (5 ml), and the mixture warmed and left at room temp overnight. The crystalline solid was filtered off, washed with ether (20 ml) and dried. Recrystallisation from benzene–MeOH gave the product (0·5 g) as needles, m.p. 124*–127°. (Found: C, 44·6, H, 4·2; N, 21·7 $C_{12}H_{13}N_5O_4S$ requires: C, 44·6; H, 4·05; N, 21·7%); ν_{max} 1665 (C=O), 1692 and 1710 $(COCH_3)$ cm^{-1}.

N'-*Furfurylidene*-α[5-(2-*furyl*)-1,2,4-*triazol*-3-*ylthio*] *acethydrazide*. A mixture of freshly distilled 2-furfural (0·2 g, 0·002 mole) and α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acethydrazide (0·5 g, 0·002 mole) in EtOH (25 ml) was shaken vigorously for 3 hr and then left at 0° overnight. The solid separating was washed with ether (20 ml) and recrystallised from MeOH to give the *furfurylidene derivative* (0·6 g) as fine needles, m.p. 154–156°. (Found: C, 48·85; H, 3·5; N, 21·5. $C_{13}H_{11}N_5O_3S$ requires: C, 49·2; H, 3·2; N, 22·1%); ν_{max} 1681 cm^{-1} (C=O). All other alkylidene and arylidene derivatives were prepared in a similar manner.

L(+) *Arabihose hydrazone of* α-[5-(2-*furyl*)-1,2,4-*triazol*-3-*ylthio*] *acethydrazide*. A mixture of α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acethydrazide (0·5 g, 0·002 mole) in MeOH (5 ml) and L(+) arabinose (0·314 g, 0·002 mole) in MeOH (20 ml) was vigorously shaken for 3 hr, concentrated under reduced press and left at 0° overnight. The crystalline solid was filtered off, washed with cold water (10 ml) and sucked dry. Recrystallisation from MeOH gave the product (0·311 g) as white crystalline solid, m.p. 189–191°, dec. (Found: C, 42·0; H, 4·4; N, 18·7. $C_{13}H_{17}N_5O_6S$ requires: C, 42·04; H, 4·61; N, 18·86%). D(+) Mannose hydrazone was prepared in a similar manner. Recrystallisation from MeOH gave the product (yield 70%), m.p. 204–205°, dec. (Found: C, 41·70; H, 4·50; N, 17·60; $C_{14}H_{19}N_5O_7S$ requires: C, 41·88; H, 4·77; N, 17·44%).

REFERENCES

[1] K. Medne, V. Grinsteins and G. Cipens, *Latvigas PSR Zinatnu Akad. Vestis* **7**, 85 (1961); *Chem. Abstr.* **56**, 13506[f] (1962)

[2] E. Jeney and T. Zsolnai, *Zentr. Bakteriol. Parasitenk. Abt. I Orig.* **177**, 215 (1960); *Chem. Abstr.* **54**, 21498[h] (1960)

[3] T. Matsuda and I. Hirao, *Nippon Kagaku Zasshi* **86** (11), 1195 (1965); *Chem. Abstr.* **65**, 12598[b] (1966)

[4] H. A. Burch, *U.S.Patent* No. 3, 277, 110 (1966); *Chem. Abstr.* **66**, 37930[f] (1967)

[5] A. L. Mndzhoian, *Synthesis of Heterocyclic Compounds* Vols 1 & 2. Chapman & Hall, London (1959)

[6] H. H. Fox, *J. Org. Chem.* **23**, 468 (1958)

* Foams.