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Antituberculosis Agents. Part II.† α-[5-(2-Furyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazide and Related Compounds

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α-[5-(2-Furyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazide, 4-allyl-1-{[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetyl}-thiosemicarbazide, and related compounds have been prepared. α-[5-(2-Furyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazide showed *in vitro* activity against *M. tuberculosis*.

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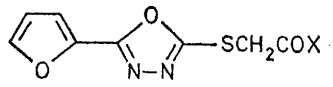
NUMEROUS oxadiazoles are known which possess biological activity. For example, 5-phenyl-1,3,4-oxadiazole-2-thiol is antitubercular [1] and 5-(3-pyridyl)-1,3,4-oxadiazole-2-thiol is both leprostatic and tuberculostatic,[2] while 2-(5-nitro-2-furyl)-1,3,4-oxadiazole and other related compounds are active against several pathogenic organisms.[3] Recently, it has been shown that 2-(4-amino-2-hydroxyphenyl)-Δ^2-1,3,4-oxadiazolin-5-one is tuberculostatic and has a favourable therapeutic index.[4]

In view of the bacteriostatic and particularly the tuberculostatic activity of 1,3,4-oxadiazoles, it was therefore considered worthwhile to synthesize α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio] acetohydrazide (1; X = $NHNH_2$), its acyl, arylidene, and alkylidene derivatives and other cognate compounds for antituberculosis examination.

The key intermediate, ethyl α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetate (1; X = OEt) was prepared by the base-catalysed cyclization of 2-furohydrazide with carbon disulphide giving 5-(2-furyl)-1,3,4-oxadiazole-2-thiol the sodio-derivative of which with ethyl bromoacetate gave the required ester. Hydrazine hydrate and ammonia, respectively, converted it into the acethydrazide (1; X = $NHNH_2$) and amide (1; X = NH_2). The structure of the hydrazide was confirmed by microanalysis, mass spectrum, and chemical properties. Thus, the thiosemicarbazide (1; X = $NHNHCSNHCH_2CH{:}CH_2$) was obtained with allyl isothiocyanate while aliphatic and aromatic aldehydes and ketones gave alkylidene and arylidene derivatives (1; X = $NHN{:}CRR'$) respectively (Table). Acetic anhydride gave

(1) 

the monoacetyl derivative (1; X = NHNHAc) rather than the diacetyl derivative. This was supported by analysis and mass spectrum. The product with L-arabinose has probably the cyclic arabinosyl rather than the open-chain hydrazone structure.[5] Hydrolysis of ethyl α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetate gave a sulphur-free product which showed strong absorption in the i.r. at about 1770 cm^{-1} characteristic of a 1,3,4-oxadiazolin-2(3*H*)-one.[6] Microanalysis and mass spectrum confirmed that it was 5-(2-furyl)-1,3,4-oxadiazolin-2(3*H*)-one [7] and from the i.r. spectrum it exists in this form rather than the tautomeric 5-(2-furyl)-2-hydroxy-1,3,4-oxadiazole at least in the solid state.[6] Under the experimental conditions the ultimate effect is nucleophilic replacement of the ethyl thioglycollate anion by hydroxide followed by a protrophic shift, rather than ester hydrolysis. The parent acid (1; X = OH) was prepared from monochloroacetic acid and 5-(2-furyl)-1,3,4-oxadiazole-2-thiol and the structure was confirmed by analysis and by i.r., n.m.r., and mass spectroscopy. In contrast, the analogous reaction between 4-hydroxy-2-mercapto-5,6-dimethylpyrimidine and monochloroacetic acid gives 2,4-dihydroxy-5,6-dimethylpyrimidine.[8]

The *in vitro* examination of α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazide against *M. tuberculosis* $H_{37}R_v$ in Peizer and Schecter medium showed activity comparable with Isoniazid.

EXPERIMENTAL

M.p.s are uncorrected and i.r. spectra were recorded on Nujol mulls using a Beckman IR4 or Perkin-Elmer 157 instrument. The n.m.r. spectrum was determined on a Perkin-Elmer R12 (60 MHz) and mass measurements on an A.E.I. MS9 instrument. The homogeneity of analytical samples was determined by t.l.c. on silica gel.

Ethyl α-[5-(2-Furyl)-1,3,4-oxadiazol-2-ylthio]acetate (1; X = OEt).—5-(2-Furyl)-1,3,4-oxadiazole-2-thiol (16·8 g) in water (100 ml) containing sodium carbonate (5·3 g) was evaporated to dryness and the residue was dissolved in dry ethanol (150 ml). Ethyl bromoacetate (16·7 g) was added to the mixture which was then vigorously shaken for 1 h and finally left overnight at room temperature. The solution was filtered and evaporated to dryness under reduced pressure and the residue was extracted with ether (250 ml) in a continuous extractor for 4 h. The extract was dried (Na_2SO_4) and the solvent removed to yield a solid. Recrystallization from methanol gave the *ester* (17·8 g) as prisms, m.p. 60—61·5° (Found: C, 47·1; H, 3·9; N, 11·6. $C_{10}H_{10}N_2O_4S$ requires C, 47·2; H, 4·0; N, 11·0%), $\nu_{max.}$ 1740 cm^{-1} (C=O).

α-[5-(2-Furyl)-1,3,4-oxadiazol-2-ylthio]acetamide (1; X = NH_2).—Ethyl α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetate (0·5 g) was dissolved in dry ethanol (15 ml) and a steady

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stream of dry ammonia bubbled through the mixture for 1 h. The crude product was filtered off, washed with cold water (5 ml), and dried. Recrystallization from methanol gave the *amide* (0·37 g) as prisms, m.p. 163—164° (Found: C, 42·6; H, 3·0; N, 18·9. $C_8H_7N_3O_3S$ requires C, 42·7; H, 3·1; N, 18·7%), $\nu_{max.}$ 1640 cm^{-1} (C=O).

2-ylthio]acetohydrazide (0·5 g) was added to acetic anhydride (5 ml), and the mixture was heated under reflux for 15 min and then left at 0° overnight. The solid was filtered off, washed with ether (20 ml), and dried. Recrystallization from methanol gave the *product* (0·51 g) as needles, m.p. 175—178° (Found: C, 43·0; H, 3·6; N,

TABLE

N'-Alkylidene-α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazides (1; X = NHN:CRR')

Derivatives :CRR'	M.p.	Solvent *	Yield (%)	Formula	Requires (%) C	H	N	Found (%) C	H	N	$\nu_{max.}$/cm^{-1} (C=O)
Benzylidene	162—163°	A	90·0	$C_{15}H_{12}N_4O_3S$	54·9	3·7	17·1	55·3	3·8	16·9	1665
Salicylylidene	184	A	90·0	$C_{15}H_{12}N_4O_4S$	52·3	3·5	16·3	52·3	3·6	16·1	1685
Cinnamylidene	181—182	B	87·0	$C_{17}H_{14}N_4O_3S$	57·6	4·0	15·8	57·4	3·8	15·5	1675
Veratrylidene	165—167	A	85·0	$C_{17}H_{16}N_4O_5S$	52·6	4·15	14·4	52·5	4·0	14·3	1680
Piperonylidene	228—229	C	80·0	$C_{16}H_{12}N_4O_5S$	51·6	3·25	15·05	51·3	3·3	14·8	1685
Vanillylidene	109—110	A + C	77·0	$C_{16}H_{14}N_4O_5S$	51·3	3·8	15·0	50·8	3·9	14·4	1680
α-Phenylethylidene	206—207	A	88·0	$C_{16}H_{14}N_4O_3S$	56·1	4·1	16·4	56·2	4·0	16·1	1665
p-Methoxybenzylidene	199—200	A	91·0	$C_{16}H_{14}N_4O_4S$	53·6	3·9	15·6	53·9	4·0	15·6	1670
2-Pyrrolylmethylidene	170—173	A	92·0	$C_{13}H_{11}N_5O_3S$	49·2	3·5	22·1	49·1	3·6	21·3	1665
2-Thenylidene	176—178	A	86·0	$C_{13}H_{10}N_4O_3S_2$	46·7	3·0	16·75	46·0	2·9	16·2	1665
Nicotinylidene	231—233 (decomp.)	A	81·0	$C_{14}H_{11}N_5O_3S$	51·1	3·4	21·3	50·6	3·4	20·9	1695
Isonicotinylidene	178—180	A	84·0	$C_{14}H_{11}N_5O_3S$	51·1	3·4	21·3	51·6	3·4	20·8	1700
Ethylidene	184—186	A	85·0	$C_{10}H_{10}N_4O_3S$	45·1	3·8	21·05	45·4	4·0	21·1	1680
Isopropylidene	193—194	A	90·0	$C_{11}H_{12}N_4O_3S$	47·1	4·3	20·0	46·95	4·1	19·9	1680
Propylidene	146—148	A	92·0	$C_{11}H_{12}N_4O_3S$	47·1	4·3	20·0	46·9	4·3	19·5	1670

* A = MeOH; B = EtOH; C = $CHCl_3$.

α-[5-(2-*Furyl*)-1,3,4-*oxadiazol*-2-*ylthio*]*acetohydrazide* (1; X = $NHNH_2$).—Ethyl α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetate (15 g) was dissolved in dry ethanol (75 ml), hydrazine hydrate (5·9 g) was added, and the mixture was heated under reflux for 5—10 min, cooled, concentrated, and left at 0°. The solid was filtered off, washed with cold water and sucked dry, and then washed with ether and dried *in vacuo*; it was crystallized thrice from methanol to give the *acetohydrazide* (12·9 g) as needles, m.p. 198—200°. (Found: C, 40·2; H, 3·3; N, 23·3%; *M*, 240. $C_8H_8N_4O_3S$ requires C, 40·0; H, 3·35; N, 23·3%; *M*, 240), $\nu_{max.}$ 1655 cm^{-1} (C=O).

α-[5-(2-*Furyl*)-1,3,4-*ozadiazol*-2-*ylthio*]*acetic Acid* (1; X = OH).—A mixture of 5-(2-furyl)-1,3,4-oxadiazole-2-thiol(1·0 g) and monochloroacetic acid (0·6 g) in water (40 ml) was heated under reflux for 8 h and then cooled and set aside. The crystalline solid was filtered off, washed with cold water, and sucked dry. Recrystallization from methanol yielded the *acid* (0·89 g) as fine needles, m.p. 194—195° (Found: C, 42·5; H, 2·8; N, 12·2%; *M*, 226. $C_8H_6N_2O_4S$ requires C, 42·5; H, 2·7; N, 12·4%; *M*, 226), $\nu_{max.}$ 2800w (CO_2H), 1710 cm^{-1} (C=O), τ (Me_2SO) solution) −1·0 (1H, s, CO_2H), 2·08 (1H, d, furyl 5-H), 2·60 (1H, d, furyl 3-H), 3·30 (1H, q, furyl 4-H), 5·60 (2H, s, CH_2).

4-*Allyl*-1-{[5-(2-*furyl*)-1,3,4-*oxadiazol*-2-*ylthio*]*acetyl*}*thiosemicarbazide* (1; X = $NHNHCSNHCH_2CH{:}CH_2$).—A mixture of α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazide (0·5 g) in acetonitrile (10 ml) and freshly distilled allyl isothiocyanate (0·21 g) was heated under reflux for 1 h, concentrated, and then left overnight at 0°. The solid was filtered off, washed with benzene, and dried. Recrystallization from methanol–benzene gave the *product* (0·38 g) as needles, m.p. 150—151° (Found: C, 42·4; H, 3·6; N, 20·7. $C_{12}H_{13}N_5O_3S_2$ requires C, 42·5; H, 3·9; N, 20·6%), $\nu_{max.}$ 1695 cm^{-1} (C=O).

N'-Acetyl-α-[5-(2-*furyl*)-1,3,4-*oxadiazol*-2-*ylthio*]*acetohydrazide* (1; X = NHNHAc).—α-[5-(2-Furyl)-1,3,4-oxadiazol-

19·75%; *M*, 282. $C_{10}H_{10}N_4O_4S$ requires C, 42·6; H, 3·6; N, 19·85%; *M*, 282).

N'-2-Furfurylidene-α-[5-(2-*furyl*)-1,3,4-*oxadiazol*-2-*ylthio*]-*acetohydrazide* (1; X = NHN:CH·C:CH·CH:CH·O).—Freshly distilled 2-furfural (0·2 g) and α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazide (0·5 g) in ethanol (25 ml) was heated under reflux for 1 h; the solid was filtered off, dried, and recrystallized from methanol to give the *furfurylidene derivative* (0·61 g) as needles, m.p. 166—168° (Found: C, 49·5; H, 3·1; N, 17·3. $C_{13}H_{10}N_4O_4S$ requires C, 49·1; H, 3·2; N, 17·6%), $\nu_{max.}$ 1665 cm^{-1} (C=O).

The other alkylidene and arylidene derivatives were similarly prepared (Table).

N'-L-Arabinosyl-α-[5-(2-*furyl*)-1,3,4-*oxadiazol*-2-*ylthio*]-*acetohydrazide*.—A mixture of α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetohydrazide (0·5 g) in methanol (10 ml) and L-arabinose (0·314 g) in methanol (20 ml) was heated under reflux for 45 min; the solution was then concentrated under reduced pressure and left overnight at 0°. The crystalline solid was filtered off, washed with cold water (10 ml), and sucked dry. Recrystallization from methanol gave the *product* (0·3 g), m.p. 181—184° (Found: C, 42·85; 42·75; H, 4·5, 4·65; N, 14·8. $C_{13}H_{16}N_4O_7S$ requires C, 41·9; H, 4·3; N, 15·0%) $\nu_{max.}$ 1680 cm^{-1} (C=O).

5-(2-*Furyl*)-1,3,4-*oxadiazol*-2(3H)-*one*.—Ethyl α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetate (0·5 g) was dissolved in 2N-sodium hydroxide (20 ml) and left overnight at room temperature; it was then acidified with 2N-hydrochloric acid and extracted into ether (75 ml). The ether layer was washed with water, dried, (Na_2SO_4), evaporated to dryness and the residue recrystallized from benzene–methanol to give the product (0·35 g) as needles, m.p. 108—110° (Found: C, 47·5; H, 2·7; N, 18·3%; *M*, 152. Calc. for $C_6H_4N_2O_3$ C, 47·4; H, 2·6; N, 18·4%; *M*, 152), $\nu_{max.}$ 1770 cm^{-1} (C=O).

[1/463 *Received, April* 1*st*, 1971]