Synthesis of α-[5-(2-,3-, and 4-Pyridyl)-1,3,4-oxadiazol-2- ylthio]acethydrazides and Related Compounds.

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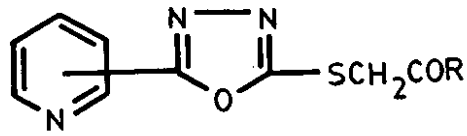
Summary: Potentially biologically active 2,5-disubstituted oxadiazoles have been prepared with a view to testing them against 1NH-resistant strains of Mycobacterium tuberculosis.

In the earlier papers [1-4], we reported the syntheses of α-[5-(2-furyl)-1,2,4-4-triazol-3-ylthio] acethydrazide,4-allyl-1-[{5-(2-furyl)1,2,4-triazol-3-ylthio]}acetyl]thiosemicarbazide, α-[5-(2-furyl)-1,2,4-triazol-3-ylthio] acethydroxamic acid, α-[5-(2-furyl)1,2,4-triazol-3-ylthio]acetamide, α−[5-(2-furyl)-1,3,4-oxadiazol-2-ythio] acethydrazide, 4-allyl-1-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio[acetyl] thiosemicarbazide, α-[5-(2-furyl)-1,3,4-oxadiazol-2-ylthio]acetamide, α-[5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-ylthio]acethydrazide, 4-allyl-1-[5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-ylthio]acetyl] thio-semicarbazide, α-[5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-ylthio] acetamide and related compounds. Some of these compounds have been found to exhibit significant activity against *M.tuberculosis* strains $H_{37}R_v$ and Academic in Peizer and Schectar medium compared with isoniazide.

Although some of the above compounds have been found to possess marked antitubercular activity, they proved inactive against INH- resistant strains of *M.tuberculosis*. Since incorporation of the nitro group into the ring confers enhanced antibacterial activity it was considered worthwhile to synthesize α-[5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-ylthio]acethydrazide and related compounds for bacteriological examination. When these compounds were tested, they were found to be less active than the corresponding compounds unsubstituted in the furan ring. The reduced activity of these nitro-compounds has been attributed to their unfavourable lipid-water partition coefficients. It seemed likely that the replacement of the nitrofuran ring in α-[5-(5-nitro-2-furyl)-1,3,4-oxadiazol-2-ylthio]acethydrazide and related compounds with a pyridine ring would improve the lipid- water partition coefficient of these compounds, and hence their anti-tubercular activity.Furthermore, a number of pyridyl-1,3,4- oxadiazol-2-thiols have been prepared and shown to be both leprostatic and tuberculostatic [5]. Hence it was considered worthwhile to sythesize α-[5-(2-,3-, and 4-pyridyl)-1,3,4-oxadiazol-2-ylthio]acethydrazides, thiosemi- carbazides and some salicylidene derivatives for testing against INH resistant strains of *M.tuberculosis*, $H_{37}R_v$ and Academia. With a view to synthesizing these compounds, the intermediate pyridyl-1,3,4-oxadiazol-2-thiols were prepared according to the method of Wilder Smith *et al.* [5]. The thiols were converted into their sodio-derivatives which on treatment with ethyl bromoacetate, yielded the corresponding esters. The esters reacted with dry hydrazine to give the corresponding hydrazides. The thiosemicarbazides were prepared by treating the respective hydrazides with allyl isothiocyanate in acetonitrile. The salicylidene derivatives were prepared by condensing the hydrazides with salicylaldehyde in dry ethanol and the structures confirmed by micro-analysis, mass spectra, IR, and chemical studies.



(I)

Experimental

IR spectra (KBr discs) were determined on a Beckman IR_4 instrument and mass spectra on an

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A.C.J.Ms-9 instrument. The purity of analytical samples was determined by TLC on silica gel.

Ethyl-α-[5-(Pyridyl)-1,3,4-oxadiazol-2-ylthio]acetate (I; R = OEt).

5-(4-pyridyl)-1,3,4-oxadiazol-2-thiol (8.95 g) was dissolved in water containing sodium bicarbonate (4.2 g), and the solution filtered and evaporated *in vacuo*. The residue was treated with ethyl bromoacetate (8.35 g) in dry ethanol, and the mixture stirred for 1 h, and evaporated *in vacuo* to give a solid which was crystallized to yield *the product* (11.4g) mp 87-88° (hexane- benzene). IR 1735 (C=O), 1580, 1490 (pyridine), 1026, 740 cm (oxadiazole); mass m/z 265 M^+. Aanal.Calc. for $C_{11}H_{11}N_3O_2S$: C, 49.81; H, 4.15; N, 15.85. Found: C 49.79; H, 4.10; N, 15.79%.

Ethyl-α-[5-(3-Pyridyl)-1,3,4-oxadiazol-2-ylthio] acetate (I; R = OEt).

Similarly, 5-(3-pyridyl)-1,3,4-exadiazol-2-thiol (8.9g) and ethyl bromoacetate (8.35 g) gave *the product* (11.5 g) mp 65-66° 750 cm^{-1} (oxadiazole). Anal.Calc. for $C_{11}H_{11}N_3O_3S$: C, 49.81; H, 4.15; N, 15.85. Found: C, 49.80, H, 41.09; N, 15.75%.

Ethyl-α-[5-(2-pyridyl)-1,3,4-oxadiazol-2-ylthio] acetate (I;R=OEt).

Similarly, 5-(2-pyridyl)-1,3,4-oxadiazol-2-thiol (8.95%) and ethyl bromoacetate (8.35%) gave the product (12.1g) mp 43-45° (hexane-benzene). IR: 1745 (C=O) 1595, (pyridine), 1035, 760 cm^{-1} (oxadiazole) Anal.Calc.for $C_{11}H_{11}O_3S$: C, 49.81; H, 4.15; N, 15.85. Found: C, 49.77; H, 4.08; N, 15.68%.

α-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio] acethydrazide(I:R=NHNH₂).

Ethyl-α-[5-(4-pyridyl)1,3,4-oxadiazol-2-ylthio] acetate (16.9g) was dissolved in dry ethanol at 0°, dry hydrazine (2.0 g) added, and the mixture stirred at 0°for 2 h. The resulting solid was washed with dry ethanol and ether, filtered and crysallized to give the product (9.0g) mp 178-180° (DMF-H_2O). IR; 1675 ($CONHNH_2$), 1590, 1470 (pyridine), 1020, 730 cm^{-1} (oxadiazole); mass m/z 251 M^+. Anal.Calc. for $C_9H_9N_5O_2S$; C, 43.02; H, 3.58: N, 27.88. Found: C, 43.0; H, 3.50; N, 27.80%.

α-[5-(3-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acethydrazide (I;R=NHNH₂)

Similarly, ethyl-α-[5-(3-pyridyl)-1,3,4-oxadiazol-2-ylthio] acetate (10.6g) and dry hydrazine (2.2g) gave the product (7.94) mp 160-162° (methanol). IR; 1680 ($CONHNH_2$), 1592, 1490 (pyridine), 1035, 725 cm^{-1} (oxadiazole). Anal.Calc. for $C_9H_9N_5O_2S$: C, 43.02, H: 3.58, N, 27.87 Found: C, 42.99; H, 3.52; N, 27.82%.

α-[5-(2-Pyridyl)-1,3,4-oxadiazol-2-ylthio] acethydrazide (I;R=NHNH₂).

Similarly, ethyl-α-[5-(2-pyridyl)-1,3,4-oxadiazol-2-yhlthio] acetate (10.6 g) and dry hydrazine (2.2 g) gave the product (6.13 g) mp 168-170° (methanol). IR: 1682 ($COHNHN_2$) 1501, 1490 (pyridine), 1038, 742 cm^{-1} (oxadiazole). Anal. Calc. for $C_9H_9N_5O_2S$: C, 43.02; H, 3.68; N, 27.87. Found: C, 42.95; H, 3.51; N, 27.67%.

4-Allyl-1-[5-(4-pyridyl)-1,3,4-oxadiazol-2- ylthio] acetyl]thiosemicarbazide (I;R = NHNHCSNHCH₂CH=CH₂).

α-[5-(4-Pyridyl)-1,3,4-oxadiazol-2-ylthio]acet hydrazide (0.5 g) was treated with freshly distilled allyl isothiocyanate (1 ml) in acetonitrile and the mixture refluxed for 2 h. The solvent was removed in vacuo, the residue washed with dry ether, filtered, and crystallized to give the product, (0.58 g) mp 155-157° (benzene-methanol). IR: 17500 (C=O), 1585, 1475 (pyridine) 1030, 1745 cm^{-1} (oxadiazole). Anal.Calc. for $C_{13}H_{14}N_6O_2S_2$; C 44.57; H, 4.00; N, 23.98. Found: C, 44.51: H, 3.95; N, 23.90%.

4-Allyl-1-[5-(3-pyridyl)-1,3,4-oxadiazol-2-ylhio] acetyl] thiosemicarbazide (I;R = NHNHCSNHCH₂CH₂).

Similarly, α-[5-(3-pyridyl)-1,3,4-oxadiazol-2-ylthio] acethydrazide (0.5 g) and allyl isothiocyanate (1 gm) gave the product (0.5 g)_ mp 159-160° (benzene-methanol). IR; 1700 ($CONHNH_2$), 1601, 1495 (pyridine), 1037, 725 cm^{-1} (oxadiazole). Anal.Calc. for $C_{13}H_{14}N_6O_2S_2$: C, 44.57; H, 4.00; N, 23.98. Found C, 44.49; H, 3.91; N, 23.88%.

4-Allyl-1-[5-(2-pyridyl)-1,3,4-oxadiazol-2-ylthio] acetyl]thiosemi-carbazide (;.R = NHNHCSNHCH$_3$ = CH$_2$).

Similarly, α-[5-(2-pyridyl)1,3,4-oxadiazol-2-ylthio] acetyhdrazide (0.5 g) and allyl isothiocyanate (1 gm) gave the product (0.488) mp 160-162° (benzene-methanol). IR: 1707 (CONHNH$_2$), 1600, 1498 (pyridine), 1031, 750 cm^{-1} (oxadiazole) Anal.Calc. for $C_{13}H_{14}N_6O_2S_2$: C, 44.57, H, 4.00; N, 23.98. Found: C 44.50; H, 3.93; N, 23.79%.

N-Salicylidene-α-[5-(pyridyl)-1,3,4-oxadiazol-2- ylthio]acethydrazide I;R = NHN = CH-C$_6$H$_6$(OH)

α-[5-(4-pyridyl)-1,3,4-oxadiazol-2-ylthio]acet hydrazide (0.5 g) was condensed with salicylaldehyde (0.244 g) in dry ethanol on a boiling water bath for 30 min, and then set aside at room temperature for 3 h. The solid was filtered, washed with cold dry ether and crystallized to give the product (0.53 g) mp 190-191° (DMF-H$_2$O) IR: 1685 (C=O), 1590, 1480, 1470 (pyridine), 1035, 750, cm^{-1} (oxadiazole). Anal.Calc. for $C_{16}H_{13}N_5O_3S$: C, 54.03; H, 3.66; N, 19.71. Found: C, 54.0, H, 3.59; N, 19.62%.

N-Salicylidene−α-[5-(3-pyridyl)-1,3,4-oxadiazol-2-ylthio] acethydrazide (I;R = NHN = CH-C$_6$H$_4$(OH)

Similarly, α-[5-(3-pyridyl)-1,3,4-oxadiazol-2-ylthio] acethydrazide (0.244 g) and salicylaldehyde (0.244 g) gave the product (0.524 g) mp 180-185° (methanol). IR; 1670 (V=O), 1601, 1599, 1495, 1480 (pyridine and benzene) 1032, 760, cm^{-1} (oxadiazole) Anal.Calc.for $C_{16}H_{13}N_5O_3S$: C, 54.08; H, 3.66; N, 19.71. Found: C, 54.00; H, 3.59; N, 19.6%.

N-Salicylidene-α-[5-(2-pyridyl)-1,3,4-oxadiazol-2yl-thio] acethydrazide (I.R = NHN=CHC$_6$H$_4$(OH).

Similary, α-[5-2-pyridyl)-1,3,4-oxadiazol-2-ylthio] acethydrazide (0.5 g) and salicylaldehyde (0.244g) gave the product (0.5 g) mp 208-211° (methanol). IR: 1680 (C=O) 1600, 1595, 1485 (pyridine and benzene) and 1038, 770 cm-1 (exadiazole). Anal.Calc. for $C_{16}H_{13}N_5O_3S$: C, 54.08, H, 3.66; N, 19.71; Found: C, 54.02 H, 3.58, N, 19.59%.

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