SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL OXADIAZOLE AND ARYLACETAMIDE DERIVATIVES.

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ABSTRACT : 1,3,4-Oxadiazoles of the type ***2a-o*** have been prepared by the condensation of p-acetamidophenoxyacetyl hydrazide ***1*** with different aromatic acids. The same hydrazide ***1*** on treatment with aromatic acid chlorides afforded substituted arylacetamides of the type ***3a-o***. The structure of the compounds synthesised have been assigned using elemental analyses, IR and PMR spectral studies. The pharmacological profile of the compounds synthesised is described. Some of the synthesised compounds showed moderate ***in vitro*** antimycobacterial activity against a strain of ***Mycobacterium tuberculosis H37 Rv***.

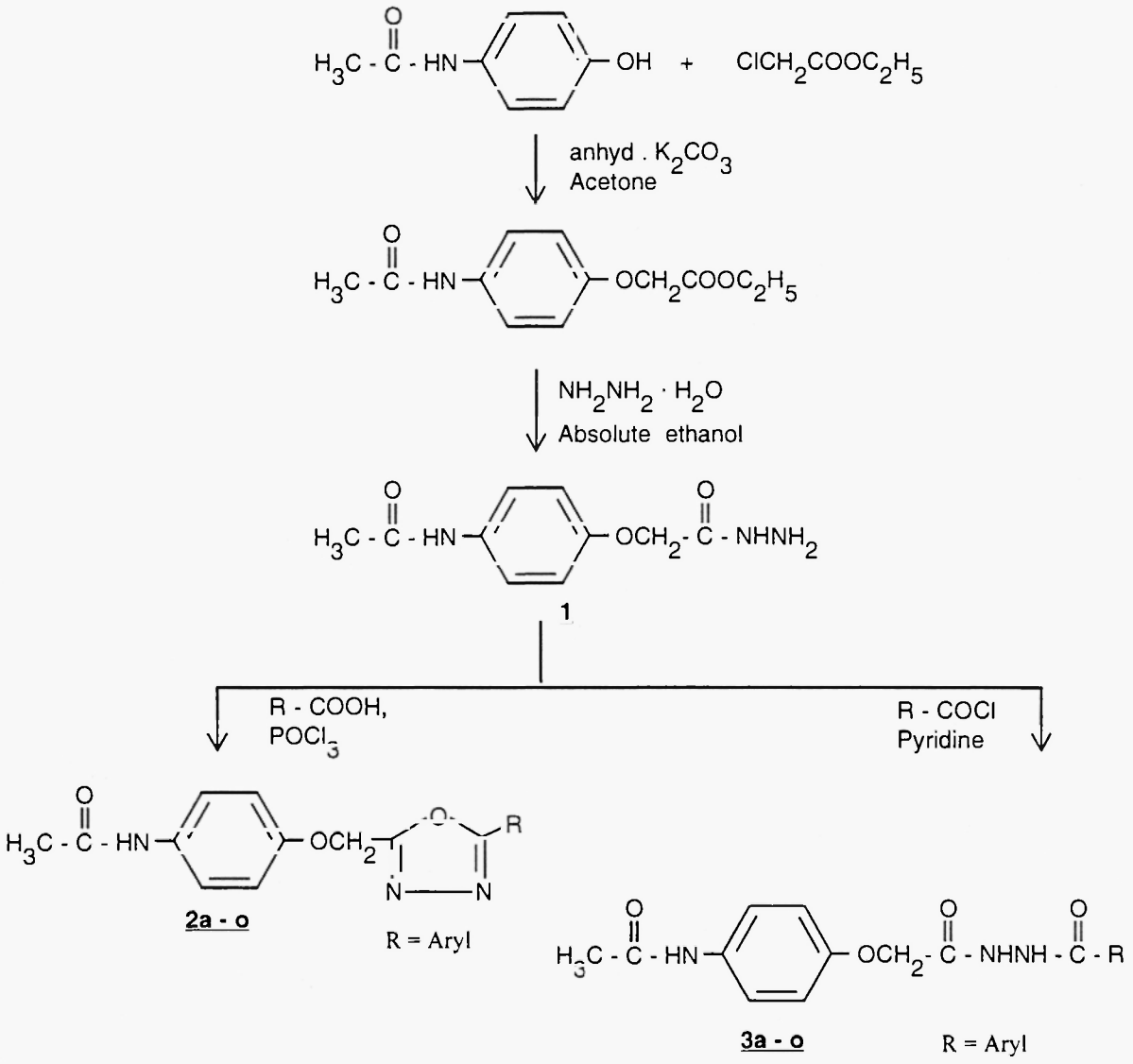
INTRODUCTION

In the past years, considerable evidence has been accumulated to demonstrate the efficacy of 1,3,4-oxadiazole (1-4) and arylacetamide (5-9) derivatives as biologically active compounds. Moreover, acetaminophen and some of its derivatives are useful for aspirin allergic individuals (10). The newer and less hepatotoxic agents may be developed bearing paracetamol moiety. Led by these considerations and by our interest in therapeutically active compounds, it appeared of interest to synthesise some novel oxadiazole and arylacetamide derivatives and assess their pharmacological profile.

The reaction of p-acetamidophenol with ethyl chloroacetate in the presence of dry acetone and anhyd. K_2CO_3 gave the desired ethyl p-acetamidophenoxy acetate which was converted into p-acetamidophenoxyacetyl hydrazide ***1*** by treatment with a slight excess of hydrazine hydrate in absolute ethanol under reflux. The hydrazide ***1*** on cyclisation with various aromatic acids in presence of $POCl_3$ afforded corresponding 2-p-acetamido phenoxymethyl-5-aryl-1,3,4-oxadiazoles ***2a-o***. The same hydrazide ***1*** was treated with different aromatic acid chlorides in presence of pyridine to yield corresponding N^1-aroyl, N^2-p-acetamidophenoxyacyl hydrazines ***3a-o*** (scheme).

The structure of the compounds synthesised have been assessed on the basis of elemental analyses, IR, and PMR spectral data. The compounds were evaluated for their antimicrobial screening against Gram +ve, Gram -ve bacterial and fungal strain. Some of the compounds were evaluated for their ***in vitro*** antimycobacterial activity towards a strain of ***Mycobacterium tuberculosis H37 Rv***.

SCHEME


anhyd . K2CO3
Acetone
NH2NH2 · H2O
Absolute ethanol
1
R - COOH,
POCl3
R - COCl
Pyridine
2a - o
R = Aryl
3a - o
R = Aryl

RESULTS AND DISCUSSION

The antimycobacterial activity of the tested compounds ***2a-o, 3a-o*** against ***Mycobacterium tuberculosis H37 Rv*** is shown in Table - 2.

The primary results suggest that oxadiazole and arylacetamide derivatives were poorly active with respect to the antimycobacterial screening except ***3e*** which showed 70% inhibition.

From Table - 2 it can be concluded that all the compounds have displayed maximum activity against ***E.coli.*** The compounds ***2m, 3b, 3c, 3d, 3q*** were highly active against ***B. megaterium***. The compounds ***3n*** showed highest activity against ***B. subtilis***, and the compounds ***2a, 2d, 3n*** were significantly active against ***A. awamori***. Moreover, compounds ***2c*** and ***2g*** have been selected for their agrochemical and pharmaceutical screening by Du Pont Agricultural Products, U.S.A. and MERCK Pharmaceuticals U.S.A. respectively.

IN VITRO EVALUATION OF PHARMACOLOGICAL STUDIES

The antimycobacterial activity of the compounds were carried out at Tuberculosis Antimicrobial Accquisition and Co-ordinating Facility (TAACF) U.S.A. Primary screening of the compounds for antimycobacterial activity have been conducted at 12.5 µg/ml against ***Mycobacterium tuberculosis H37 Rv*** in BACTEC 12 B medium using BACTEC 460 radiometric system.

The antimicrobial activity was assayed by using cup-plate agar diffusion method (11) by measuring inhibition zones in mm. All the compounds were screened ***in vitro*** for their antimicrobial activity such as ***Bacillus megaterium, Escherichia coli, Bacillus subtilis, Pseudomonas fluorescens*** and fungi such as ***Aspergillus awamori*** at a concentration of 50 µg. Known antibiotics like Chloramphenicol, Ampicillin, Norfloxacin and Griseofulvin were used for comparison purpose.

EXPERIMENTAL

All the recorded melting points were determined in open capillaries and are uncorrected. Infrared spectra (KBr) were recorded on a Shimadzu 435 - IR Spectrophotometer, ^{1}H-PMR spectra on Bruker AC 300F using TMS as an internal standard.

Preparation of ρ-Acetamidophenoxyacetyl hydrazide.

A mixture of ethyl ρ-acetamidophenylacetate (2.37 gm,0.01 mol) and hydrazine hydrate (2.0 ml, 0.04 mol) in absolute ethanol was refluxed for 5 hrs. The solution was then poured onto crushed ice, filtered and the resulting solid was crystallised from ethanol.***1***; yield : 65%, M.P. 190^{o}C, Calcd. for $C_{10}H_{13}N_3O_3$: C 53.81, H 5.82, N18.83%. Found : C 53.50, H 5.85,

N 18.90% IR υ max(KBr) : 3300 (N-H), 1680 (C=O of -NHCOCH$_3$), 1665 (C=O), 1600 (C=C) cm^{-1} ; ^{1}H-PMR δ ppm (TFA) : 2.54 (s, 3H, -COCH$_3$), 4.90 (s, 2H, -OCH$_2$), 7.12-7.38 (s, 4H, Ar-H).

Preparation of 2-ρ-Acetamidophenoxymethyl-5-ρ-methylphenyl-1,3,4-oxadizoles *2a-o* .

A mixture of ρ-acetamidophenoxyacetyl hydrazide (*1* , 0.01 mol), aromatic acid (0.01mol) and $POCl_3$ (10 ml) was refluxed for 5 hrs at 120^{o}C in oil bath. The contents were poured onto crushed ice and neutralised with 10% sodium bicarbonate solution. The product was isolated and crystallised from ethanol.*2i* : yield : 55%, M.P. 137^{o}C, Calcd for $C_{18}H_{17}N_3O_3$: C 66.87, H 5.26, N 13.00% Found : C 66.71; H 5.14, N 13.20% ; IR υ max (KBr) : 3320 (N-H), 1680 (C=O of -NHCOCH$_3$), 1600 (C=C) cm^{-1}; ^{1}H-PMR δ ppm (TFA) : 2.16 (s, 3H, -CH$_3$), 2.36 (s, 3H, -COCH$_3$), 4.78(s, 2H, -OCH$_2$), 6.95-7.38 (s, 9H, Ar-H), 8.36 (s, 1H, -N-H).

Other members of *2* were similarly prepared and their physical data are given in Table - 1.

Preparation of N^1-ρ-methoxybenzoyl, N^2-ρ-acetamidophenoxyacyl hydrazines *3a-o*.

A mixture of (*1*,0.01 mol) and aroylchloride (0.01 mol) and pyridine (5 ml) was refluxed in oil bath for 5 hrs at 120 ^{o}C. The contents were poured onto crushed ice and neutralised with HCl. The product was isolated and crystallised from ethanol. *3g* ; yield ; 54%, M.P. 119^{o}C, Calcd. for $C_{18}H_{19}N_3O_5$: C 60.50, H 5.32, N 11.76%. Found : C, 60.38; H 5.25, N 11.69% IR υ max(KBr) : 3320 (N-H), 1700 (C=O aryl acetamide), 1680 (C=O of -NHCOCH$_3$), 1670 (C=O), 1600 (C=C) cm^{-1}; ^{1}H-PMR δ ppm (TFA) : 2.41 (s, 3H, -COCH$_3$), 3.93 (s, 3H, -OCH$_3$), 4.85(s, 2H, -OCH$_2$), 6.9 (s, 9H, Ar-H), 8.8 (s, 3H, -N-H).

Other members of *3* were similarly prepared and their physical data are given in Table - 1.

Table - 2 : Antimicrobial data (inhibition zone = 18-24 mm) and Antitubercular data (% inhibition > 40%) of some selected compounds which exhibited highest activity.

Standard antibiotics	B.mega	B.subtilis	E.coli	A.awamori	Mycobacterium tuberculosis H37 Rv % inhi.
Chloramphenicol, 21-28 mm Ampicillin 15-25 mm Norfloxacin 24-30 mm Griseofulvin 15-26 mm	*2m, 3b, 3c, 3d, 3g, 3n, 3o*	*3n*	*2a, 2b, 2d, 2e, 2f, 2g, 2h, 2j, 2k, 2l, 2m, 2n, 2o, 3a, 3b, 3c, 3d, 3e, 3f, 3g, 3i, 3k, 3l, 3m, 3o*	*2a, 2d, 3n,*	*2h.3c,3e*

Table - 1 : Physical constants of the compounds *2a - o*, *3a - o* .

compd.	R	Yield (%)	M.P. (°C)	Molecular Formula	% of N Found	% of N Calcd
2a	4-Br-C_6H_4-	58	190	$C_{17}H_{14}N_3O_3Br$	10.90	10.82
2b	2-Cl-C_6H_4-	61	212	$C_{17}H_{14}N_3O_3Cl$	12.15	12.22
2c	4-Cl-C_6H_4-	62	218	$C_{17}H_{14}N_3O_3Cl$	12.13	12.22
2d	2-OH-C_6H_4-	57	320	$C_{17}H_{15}N_3O_4$	12.85	12.92
2e	2-OCH_3-C_6H_4-	55	125	$C_{18}H_{17}N_3O_4$	12.45	12.38
2f	3-OCH_3-C_6H_4-	56	155	$C_{18}H_{17}N_3O_4$	12.43	12.38
2g	4-OCH_3-C_6H_4-	58	145	$C_{18}H_{17}N_3O_4$	12.48	12.38
2h	2-$CH_3C_6H_4$-	51	120	$C_{18}H_{17}N_3O_3$	13.05	13.00
2i	3-CH_3-C_6H_4-	56	132	$C_{18}H_{17}N_3O_3$	13.10	13.00
2j	4-CH_3-C_6H_4-	55	137	$C_{18}H_{17}N_3O_3$	12.95	13.00
2k	3-NO_2-C_6H_4-	54	122	$C_{17}H_{14}N_4O_5$	15.85	15.81
2l	4-NO_2-C_6H_4-	56	136	$C_{17}H_{14}N_4O_5$	15.90	15.81
2m	C_6H_5-OCH_2-	50	250	$C_{18}H_{17}N_3O_4$	12.45	12.38
2n	C_6H_5-	52	230	$C_{17}H_{15}N_3O_3$	12.86	12.92
2o	C_6H_5-C_2H_2-	53	140	$C_{19}H_{17}N_3O_3$	13.49	13.59
3a	C_6H_5-CH_2-	50	105	$C_{18}H_{17}N_3O_4$	12.45	12.38
3b	4-Br-C_6H_4-	53	223	$C_{17}H_{16}N_3O_4Br$	10.28	10.34
3c	2-Cl-C_6H_4-	57	118	$C_{17}H_{16}N_3O_4Cl$	11.68	11.61
3d	4-Cl-C_6H_4-	55	176	$C_{17}H_{16}N_3O_4Cl$	11.72	11.61
3e	2-OH-C_6H_4-	50	150	$C_{17}H_{17}N_3O_5$	12.37	12.29
3f	3,4-$(OCH_3)_2$-C_6H_3-	52	58	$C_{19}H_{21}N_3O_6$	10.76	10.85
3g	2-OCH_3-C_6H_4-	53	115	$C_{18}H_{19}N_3O_5$	11.84	11.76
3h	4-OCH_3-C_6H_4-	54	119	$C_{18}H_{19}N_3O_5$	11.87	11.76
3i	2-CH_3-C_6H_4-	51	103	$C_{18}H_{19}N_3O_4$	12.39	12.31
3j	3-CH_3-C_6H_4-	50	108	$C_{18}H_{19}N_3O_4$	12.38	12.31
3k	4-CH_3-C_6H_4-	53	128	$C_{18}H_{19}N_3O_4$	12.37	12.31
3l	3-NO_2-C_6H_4-	54	>320	$C_{17}H_{16}N_4O_6$	15.12	15.05
3m	4-NO_2-C_6H_4-	56	260	$C_{17}H_{16}N_4O_6$	15.13	15.05
3n	C_6H_5-	52	195	$C_{17}H_{17}N_3O_4$	12.90	12.84
3o	C_6H_5-C_2H_2-	53	105	$C_{19}H_{19}N_3O_4$	11.95	11.89

Elemental analyses for N were found to be satisfactory (± 0.4% of the calculated values).

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