J. Indian Chem. Soc.,
Vol. LIX, May 1982, pp. 678-680

Studies on Acetamide Derivatives : Preparation and Antimicrobial Activity of 2-α-Arylaminoacetamido/α-Carbamoyl benzylamino/Arylcarbamoylmethylamino-5-*o*-Nitrophenyl/Benzoylaminomethyl-1,3,4-Thiadiazole

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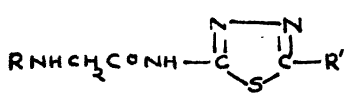
Manuscript received 19 March 1981, accepted 2 February 1982

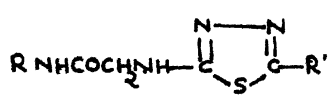
Some new 1,3,4-thiadiazoles having acetamide sidechain at two position have been prepared. The products were screened for antimicrobial activity.

ACETAMIDE derivatives have been found to possess antiarrhythmic[1], antimetastatic[2], psychoneurosis[3], schistosomicidal[4], fungicidal[5], herbicidal[6], pesticidal[7] activities. 1,3,4-Thiadiazole derivatives have been found to possess herbicidal[8], radioprotective[9], antitumor[10], diuretic[11], bacteriostatic[12], cytostatic[13] activities.

With a view to prepare better therapeutic agent, we undertook the preparation of 2-amino-5-*o*-nitrophenyl- and 2-amino-5-benzoylaminomethyl-1,3,4-thiadiazoles by the cyclisation of *o*-nitrophenyl-3-thiosemicarbazide[14] and benzoylaminomethyl-3-thiosemicarbazide. The products were (i) chloroacetylated and condensed with different amines to give compounds of type (I), (ii) condensed with chloroacetylated amines to give compounds of type (II), and (iii) condensed with different aldehydecynohydrin and treated with conc. H_2SO_4 to give compounds of the type (III).



(I)



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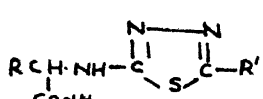

(III)

where R=Aryl ; R'=*o*-Nitrophenyl/Benzoylaminomethyl

The products were screened for antimicrobial activity.

Experimental

Preparation of 2-amino-5-o-nitrophenyl/benzoylaminomethyl-1,3,4-thiadiazole : o-Nitrophenyl-3-thiosemicarbazide or benzoylaminomethyl-3-thiosemicarbazide (20 g) was treated with conc. H_2SO_4 and poured into cold water and product was isolated ; *o*-nitrophenyl derivative, yield 66% ; m.p. 233°, reported[14] 234° ; benzoylaminomethyl derivative, yield 70% ; m.p ; 216°. Found : C, 51.25 ; H, 4.26 ; N, 23.90 ; S, 13.65. $C_{10}H_{10}N_4OS$ requires C, 51.28 ; H, 4.27 ; N, 23.93 ; S, 13.67%.

Chloroacetylation of 2-amino-5-o-nitrophenyl/benzoylaminomethyl-1,3,4-thiadiazole and different amines : The chloroacetylation of 2-amino-5-*o*-nitrophenyl/benzoylaminomethyl-1,3,4-thiadiazole and different amines were carried out[15,16]. 2-Chloroacetyl-5-*o*-nitrophenyl derivative, yield 64% ; m.p. 210°. Found : C, 40.0 ; H, 2.31 ; N, 18.70 ; S, 10.68. $C_{10}H_7N_4O_3SCl$ requires C, 40.10 ; H, 2.34 ; N, 18.72 ; S 10.70%. 2-Chloroacetyl 5-benzoylaminomethyl derivative, yield 66% ; m.p. 202°. Found : C, 46.25 ; H, 3.50 ; N, 17.99 ; S, 10.25. $C_{12}H_{11}N_4O_2SCl$ requires C, 46.30 ; H, 3.53 ; N, 18.00 ; S 10.28%. All chloroacetylated aromatic amines gave correct N analysis.

Preparation of 2-α-arylaminoacetamido-5-o-nitrophenyl/benzoylaminomethyl-1,3,4-thiadiazole[17] : 2-Chloroacetylamino-5-*o*-nitrophenyl/benzoylaminomethyl-1,3,4-thiadiazole (0.1 *M*) was refluxed with different amines (0.12 *M*) in ethanol for 6 hr and product isolated. The physical constants are recorded in Table 1.

Preparation of α-carbamoylbenzylamino-5-o-nitrophenyl/benzoylaminomethyl-1,3,4-thiadiazole : 2-Amino-5-*o*-nitrophenyl/benzoylaminomethyl-1,3,4-thiadiazole (0.1 *M*) was refluxed with different chloroacetylated amines (0.1 *M*) in ethanol for 8 hr and product isolated. The physical constants are recorded in Table 2.

TABLE 1—PREPARATION OF 2-α-ARYLAMINOACETAMIDO-5-*o*-NITROPHENYL/BENZOYLAMINOMETHYL-2,3,6-THIADIAZOLE

Sl. No.	R	R′	m.p. °C	Yield %	Diameter of zone of inhibition in mm	
					S. aureus 24 hr	*E. coli* 24 hr
1.	Phenyl	*o*-Nitrophenyl	140	48	15	14
2.	*o*-Nitrophenyl	,,	80	50	10	—
3.	*m*-Nitrophenyl	,,	90	52	17	5
4.	*p*-Nitrophenyl	,,	138	54	12	—
5.	*o*-Tolyl	,,	80	55	12	—
6.	*m*-Tolyl	,,	75	47	13	—
7.	*p*-Tolyl	,,	108	59	8	—
8.	*m*-Hydroxyphenyl	,,	105	53	12	2
9.	*p*-Hydroxyphenyl	,,	117	52	17	2
10.	2,5-Dichlorophenyl	,,	340D	55	10	2
11.	Phenyl	Benzoylaminomethyl	120D	56	19	4
12.	*o*-Nitrophenyl	,,	68	59	16	5
13.	*m*-Nitrophenyl	,,	100	60	7	11
14.	*p*-Nitrophenyl	,,	160	57	8	2
15.	*o*-Tolyl	,,	100	61	11	2
16.	*m*-Tolyl	,,	130	64	5	—
17.	*p*-Tolyl	,,	200D	65	5	—
18.	*o*-Anisyl	,,	310	50	5	—
19.	*p*-Anisyl	,,	284	57	8	4
20.	*p*-Chlorophenyl	,,	274	59	16	—
21.	Cyclohexyl	,,	120	60	10	—

All compounds gave consistent nitrogen analysis.

TABLE 2—PREPARATION OF 2-α-CARBAMOYLBENZYLAMINO-5-*o*-NITROPHENYL/BENZOYLAMINOMETHYL-2,3,4-THIADIAZOLE

Sl. No.	R	R′	m.p. °C	Yield %	Diameter of zone of inhibition in mm	
					S. aureus 24 hr	*E. coli* 24 hr
1.	Phenyl	*o*-Nitrophenyl	100	50	16	4
2.	*o*-Nitrophenyl	,,	190	52	12	6
3.	*m*-Nitrophenyl	,,	205	54	15	4
4.	*p*-Nitrophenyl	,,	200	55	14	6
5.	*o*-Chlorophenyl	,,	205	57	16	—
6.	*p*-Chlorophenyl	,,	133	53	10	—
7.	*o*-Anisyl	,,	105	54	10	—
8.	*o*-Tolyl	,,	190	60	10	—
9.	3,5-Dichlorophenyl	,,	175	59	14	9
10.	2-Naphthyl	,,	180	61	13	12
11.	Phenyl	Benzoylaminomethyl	140	63	8	10
12.	*o*-Nitrophenyl	,,	50	60	8	—
13.	*m*-Nitrophenyl	,,	142	57	8	—
14.	*p*-Nitrophenyl	,,	175	65	7	2
15.	*o*-Tolyl	,,	275	68	9	—
16.	*m*-Tolyl	,,	86	69	10	—
17.	*o*-Anisyl	,,	180	63	12	—
18.	*p*-Anisyl	,,	160	61	15	—
19.	*p*-Chlorophenyl	,,	143	62	17	6
20.	2-Naphthyl	,,	195	64	10	9

All compounds gave consistent nitrogen analysis.

Preparation of arylcarbamoylmethylamino-5-o-nitrophenyl/benzoylaminomethyl-1,3,4-thiadiazole : The nitriles were prepared[18] which on further treatment with conc. H_2SO_4 at 0° gave corresponding amides.

The physical constants are recorded in (Table 3).

TABLE 3—PREPARATION OF α-(5-*o*-NITROPHENYL/BENZOYLAMINOMETHYL-1,3,4-THIADIAZOL-2-YLAMINO)-ARYLACETONITRILES

Sl. No.	R	R′	m.p. °C	Yield %	Diameter of zone of inhibition in mm	
					S. aureus 24 hr	*E. coli* 24 hr
1.	Phenyl	*o*-Nitrophenyl	205	50	7	—
2.	*m*-Nitrophenyl	,,	190	48	10	—
3.	Cinnamyl	,,	165	55	10	—
4.	2-Hydroxyphenyl	,,	240	56	8	—
5.	3-Bromo-2-hydroxyphenyl	,,	285	59	8	—
6.	3,5-Dibromo-2-hydroxyphenyl	,,	185	60	15	—
7.	4-Hydroxy-3-methoxyphenyl	,,	225	61	12	—
8.	5-Bromo-4-hydroxy-3-methoxyphenyl	,,	230	63	10	4
9.	*p*-Anisyl	,,	200D	64	12	—
10.	Furfuryl	*o*-Nitrophenyl	320D	66	—	11
11.	Phenyl	Benzoylaminophenyl	100	50	10	—
12.	*m*-Nitrophenyl	,,	110	55	9	—
13.	Cinnamyl	,,	90	53	16	—
14.	2-Hydroxyphenyl	,,	180	54	8	—
15.	3-Bromo-2-hydroxyphenyl	,,	200	59	18	—
16.	3-5-Dibromo-2-hydroxyphenyl	,,	240	57	8	6
17.	4-Hydroxy-3-methoxyphenyl	,,	165	56	6	9
18.	5-Bromo-4-hydroxy-3-methoxyphenyl	,,	280	60	5	10
19.	*p*-Anisyl	,,	175	59	15	—
20.	Furfuryl	,,	199	58	8	—

All compounds gave consistent nitrogen analysis.

Antibacterial activity : The products were screened for antibacterial activity by cup-plate method[19], using DMF as solvent, at a concentration of 10 mg/ml. It was observed that all the compounds were moderately active against *S. aureus* but not against *E. coli* (recorded in the tables).

TABLE 4—PREPARATION OF 2-ARYLCARBAMOYLMETHYLAMINO-5-*o*-NITROPHENYL/BENZOYLAMINOMETHYL-1,3,4-THIADIAZOLE

Sl. No.	R	R′	m.p. °C	Yield %	Diameter of zone of inhibition in mm	
					S. aureus	*E. coli*
1.	Phenyl	*o*-Nitrophenyl	300D	47	10	—
2.	3-Nitrophenyl	,,	170	45	8	—
3.	Cinnamyl	,,	not melt	48	9	—
4.	2-Hydroxyphenyl	,,	not melt	50	11	—
5.	3-Bromo-2-hydroxyphenyl	,,	105	55	12	—
6.	3,5-Dibromo-2-hydroxyphenyl	,,	235	57	15	4

(Table 4 Contd.)

7.	4-Hydroxy-3-methoxyphenyl	„	197	59	17	—
8.	5-Bromo-4-hydroxy-3-methoxyphenyl	„	215	60	10	4
9.	*p*-Anisyl	„	250	61	9	4
10.	Furfuryl	„	280	63	8	2
11.	Phenyl	Benzoyl-amino-methyl	125	50	10	2
12.	3-Nitrophenyl	„	150	51	12	2
13.	Cinnamyl	„	195	53	14	5
14.	2-Hydroxyphenyl	„	205	55	14	—
15.	3-Bromo-2-hydroxyphenyl	„	275D	57	10	—
16.	3,5-Dibromo-2-hydroxyphenyl	„	300	59	11	—
17.	4-Hydroxy-3-methoxyphenyl	„	235D	60	12	—
18.	5-Bromo-4-hydroxy-3-methoxyphenyl	„	265D	61	8	—
19.	*p*-Anisyl	„	189	52	7	8
20.	Furfuryl	„	225D	53	10	9

All compounds gave consistent nitrogen analysis.

Acknowledgement

The authors are thankful to Bhavnagar University for providing a research scholarship to one of them (V. H. S.).

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