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Studies on Biologically Active Heterocycles. Part-III. Synthesis and Antibacterial Activity of some 2-Aryl/Aralkyl-3-substituted-4-thiazolidinones†

M. M. DUTTA, B. N. GOSWAMI and J. C. S. KATAKY*

Regional Research Laboratory, Jorhat-785 006

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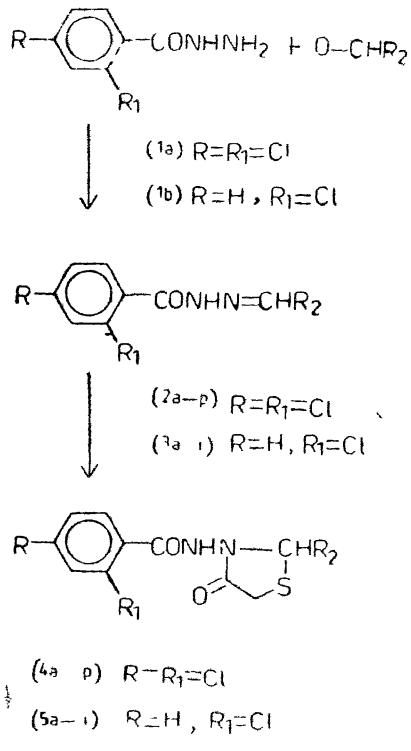
A series of new 2-aryl/aralkyl-3-[2,4-dichlorobenzamido]-4-thiazolidinones and 2-aryl/aralkyl-3-[2-chlorobenzamido]-4-thiazolidinones have been synthesised by condensation of the respective hydrazones with mercaptoacetic acid. The hydrazones have been prepared by condensing different aromatic and aliphatic aldehydes with the corresponding acylhydrazides. All the compounds were screened for their antibacterial activity.

IN continuation of our work[1] and in view of the biological activities associated with hydrazones and 4-thiazolidinones[2-4], we report here the synthesis of some hydrazones and 4-thiazolidinones possessing a 2,4-dichlorophenyl/2-chlorophenyl moiety at 3-position with the objective of screening for their antibacterial activities. The synthesis route of the title compounds **2a – p** **3a – i** and **4a – p**, **5a – i** is presented in Scheme 1.



Scheme 1

1-(2,4-Dichlorobenzoyl)-(**1a**) and (2-chlorobenzoyl)hydrazine (**1b**) were obtained[5] by refluxing the corresponding ethyl esters and hydrazine hydrate (99%) in ethanol. Condensation of **1** with appropriate alkyl, aryl and aralkyl aldehydes yielded the corresponding hydrazones[8] (**2a – p**, **3a – i**), which on condensation with mercaptoacetic acid afforded 4-thiazolidinones[6] (**4a – p**, **5a – i**).

The compounds were characterised by elemental analysis, ir, ^{1}H nmr and mass spectra. The hydrazones (**2a – p**, **3a – i**) showed ir bands at 3 190 – 3 160 (NH), 1 675 – 1 650 (CONH) and 1 615 – 1 580 cm^{-1} (C=N), whereas 4-thiazolidinones (**4a – p**, **5a – i**) showed at 3 250 – 3 150 (NH), 1 670 – 1 625 (C=O), 1 575 – 1 585 (N – CO) and 1 300 – 1 290 cm^{-1} (C – S – C). ^{1}H nmr spectra of the hydrazones (**2a – p**, **3a – i**) showed peaks at δ 10.2 – 10.6 (CONH) and 8.2 – 8.4 (–CH=N–), whereas the 4-thiazolidinones (**4a – p**, **5a – i**) showed characteristic peaks at δ 3.4 – 3.6 (CH_2).

Antibacterial activity : The compounds were screened for antibacterial activity against *Bacillus cereus t.*, *E. coli* and *B. megatarium* OMB1552 applying the agar plate diffusion technique[7] at a concentration of 50 μg ml^{-1} in acetone and incubated for 24 h at 37°. The results show that compounds **2o**, **3b**, **4i** and **4o** were active (zone of inhibition = 7 – 9 mm), **2a**, **2b**, **2i**, **3c**, **3g**, **4b** and **5b – i** moderately active (4 – 6 mm), **2d**, **2l**, **3f**, **4d**, **4j – m** and **4p** less active (1 – 3 mm) against *B. cereus* ; compounds **2o** and **4o** were much active (10 – 12 mm), **5c**, **5e** and **5h** active (4 – 6 mm), **2f**, **2i**, **2k – m**, **3b**, **3c**, **4a**, **4b**, **4h**, **4i**, **4k – m**, **5a**, **5f**, **5g** and **5i** moderately active (4 – 6 mm), **2a**, **2b**, **2f**, **2g**, **2m**, **3a**, **3e**, **3f**, **3i**, **4d**, **4f**, **4g**, **4n**, **5b** and **5d** less active (1 – 3 mm) against *E. coli* ; compounds **2o**, **4o** and **5c** were much active (10 – 12 mm), **2a**, **2i**, **3b**, **3c**, **4d**, **4i**, **5d**, **5e** and **5g – i** active (7 – 9 mm), **2b**, **2d**,

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3f, 3g, 3i, 4b, 4g, 4k – m, 5a, 5b and **5f** were active (4 – 6 mm), **2f, 2j – n, 3e, 4a, 4h, 4j** and **4n** are less active against *B. megatarium* ; and the rest of the compounds were inactive.

Experimental

Melting points were determined in a Büchi oil-heated apparatus in open capillaries and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 237B spectrophotometer and ^{1}H nmr spectra (60 MHz) on a Varian T-60 spectrometer with TMS as internal standard.

2,4-Dichloro/2-chlorobenzhydrazide (**1**) was prepared[5] from ethyl 2,4-dichloro-2-chlorobenzoate, 62 – 64%.

1-(2,4-Dichloro-2-chlorobenzoyl)hydrazones (**2a – p, 3a – i**). *General procedure*[8] : To a hot ethanolic solution of the hydrazide (**1** ; 0.01 mol), a solution of the corresponding aldehyde (0.01 mol) in ethanol (10 ml) was added dropwise and the reaction mixture was refluxed for 2 – 3 h. On cooling the resulting solid was recrystallised from ethanol to yield the hydrazones (**2a – p, 3a – i**) ; ν_{max} (KBr) 3 190 – 3 160 (NH), 1 675 – 1 650 (CONH) and 1 615 – 1 580 cm^{-1} (C=N) ; δ (CDCl$_3$/DMSO-d$_6$) 10.2 – 10 6 (s, CONH), 8 2 – 8.4 (s, CH=N) and 7.0 – 7.4 (m, ArH).

TABLE 1—PHYSICAL DATA OF COMPOUNDS*

Compd no.	R^2	Yield %	M.p °C	Mol. formula
2a	C_6H_5	86	150	$C_{14}H_{11}ON_2Cl$
2b	CH=CH-C_6H_5	68	165	$C_{16}H_{13}ON_2Cl$
2c	CH=CH.C_6H_4 N$(CH_3)_2$ (*p*)	63	173	$C_{19}H_{18}ON_3Cl$
2d	$C_6H_4(OCH_3)$ (*p*)	84	126	$C_{15}H_{13}O_2N_2Cl$
2e	CH=CHCH$_3$	50	201	$C_{11}H_{11}ON_2Cl$
2f	CH_2CH_3	57	136	$C_{10}H_{11}ON_2Cl$
2g	2-Furfuryl	75	149	$C_{12}H_9O_2N_2Cl$
2h	$CH_2CH(CH_3)$-$(CH_2)_2CH$ = $C(CH_3)_2$	62	80	$C_{16}H_{21}ON_2Cl$
2i	$C_6H_4(OH)$(*o*)	87	147	$C_{14}H_{11}O_2N_2Cl$
2j	$CH(CH_3)_2$	62	82	$C_{11}H_{13}ON_2Cl$
2k	$CH_2CH_2CH_3$	76	130	$C_{11}H_{13}ON_2Cl$
2l	$C_6H_3(OCH_3)$-(OH)(*m p*)	79	208	$C_{15}H_{13}O_3N_2Cl$
2m	$CH_2(CH_2)_2CH_3$	65	123	$C_{12}H_{15}ON_2Cl$
2n	$C_6H_3(OH)_2$ (*o m*)	67	196	$C_{14}H_{12}O_3N_2Cl$
2o	1-β-Naphthyl	87	239	$C_{18}H_{13}ON_2Cl$
2p	C_6H_4-N-$(CH_3)_2$(*p*)	74	145	$C_{16}H_{16}ON_3Cl$
3a	$C_6H_4(OCH_3)$(*p*)	94	170	$C_{15}H_{12}O_2N_2Cl_2$
3b	$C_6H_4N(CH_3)_2$(*p*)	92	214	$C_{16}H_{15}ON_3Cl_2$
3c	$C_6H_3(OH)_2$ (*o,p*)	93	235	$C_{14}H_{10}O_3N_2Cl_2$
3d	$CH_3(CH_2)_2CH_3$	92	139	$C_{13}H_{15}Cl_2N_2O$
3e	$CH_2CH_2CH_3$	89	133	$C_{11}H_{11}Cl_2N_2O$
3f	2-Furfuryl	90	202	$C_{12}H_9O_2N_2Cl_2$
3g	CH=CHCH$_3$	87	197	$C_{11}H_{10}ON_2Cl_2$
3h	C_6H_5	88	170	$C_{14}H_{10}ON_2Cl_2$
3i	$C_6H_4(OH)$(*o*)	82	145	$C_{14}H_{10}O_2N_2Cl_2$
4a	C_6H_5	78	120	$C_{16}H_{15}ClN_2O_2S$
4b	CH=CH-C_6H_5	76	127	$C_{18}H_{15}ClN_2O_2S$
4c	CH=CH-C_6H_4-N$(CH_3)_2$(*p*)	80	139	$C_{20}H_{20}ClN_3O_2S$
4d	$C_6H_4(OCH_3)$(*p*)	82	141	$C_{17}H_{15}ClN_2O_3S$
4e	CH=CHCH$_3$	77	151	$C_{13}H_{13}ClN_2O_2S$
4f	CH_2CH_3	84	105	$C_{12}H_{13}ClN_2O_2S$
4g	2-Furfuryl	76	134	$C_{14}H_{11}ClN_2O_3S$
4h	Citronellyl	68	68	$C_{19}H_{25}ClN_2O_2S$
4i	$C_6H_4(OH)$(*o*)	85	152	$C_{16}H_{13}ClN_2O_3S$
4j	$CH(CH_3)_2$	65	67	$C_{13}H_{15}ClN_2O_2S$
4k	$CH_2CH_2CH_3$	73	101	$C_{13}H_{15}ClN_2O_2S$
4l	$C_6H_3(OCH_3)$-(OH)(*m,p*)	76	212	$C_{17}H_{15}ClN_2O_4S$
4m	$CH_2(CH_2)_2CH_3$	75	103	$C_{14}H_{17}ClN_2O_2S$
4n	$C_6H_3(OH)_2$(*o m*)	85	171	$C_{16}H_{13}ClN_2O_4S$
4o	1-β-Naphthyl	82	242	$C_{20}H_{15}ClN_2O_2S$
4p	$C_6H_4N(CH_3)_2$(*p*)	81	105	$C_{18}H_{18}ClN_3O_2S$
5a	$C_6H_4(NCH_3)_2$(*p*)	78	148	$C_{18}H_{17}Cl_2N_3O_2S$
5b	$C_6H_4(OCH_3)$(*p*)	80	176	$C_{17}H_{14}Cl_2N_2O_3S$
5c	$C_6H_3(OH)_2$(*o,p*)	72	212	$C_{16}H_{12}Cl_2N_2O_4S$
5d	$CH_3(CH_2)_2CH_3$	82	122	$C_{14}H_{17}Cl_2N_2O_2S$
5e	$CH_2CH_2CH_3$	62	102	$C_{13}H_{15}Cl_2N_2O_2S$
5f	2-Furfuryl	81	183	$C_{14}H_{10}Cl_2N_2O_3S$
5g	CH=CHCH$_3$	50	148	$C_{13}H_{12}Cl_2N_2O_2S$
5h	C_6H_5	70	175	$C_{16}H_{12}Cl_2N_2O_2S$
5i	C_6H_4OH(*o*)	68	156	$C_{16}H_{12}Cl_2N_2O_3S$

*All compounds gave satisfactory C and N analyses.

2-Alkyl/aryl/aralkyl-3-(2,4-dichloro/2-chlorobenzamido)-4-thiazolidinones (**4a – p, 5a – i**). *General procedure*[6] : A mixture of the hydrazone (**2** and **3** ; 0.01 mol) and mercaptoacetic acid (0.012 mol) was refluxed in dry benzene (100 ml) for 10 h in Dean and Stark water separator. Excess benzene was then removed and the usual workup gave the 4-thiazolidinones (**4a – p, 5a – i**) which were crystallised from ethanol ; ν_{max} (KBr) 3 250 – 3 150 (NH), 1 670 – 1 625 (C=O), 1 585 – 1 575 (N – CO) and 1 300 – 1 290 cm^{-1} (C – S – C) ; δ (CDCl$_3$/DMSO-d$_6$) 3.4 – 3.6 (s, CH_2).

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