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Pyridopyrimidines. Part-VII. Synthesis and Antibacterial Activity of 4-Iminopyrido[2,3-*d*]pyrimidin-2(1*H*)-thiones, 2-Thioxopyrido[2,3-*d*]pyrimidin-4(3*H*)-ones and related Compounds

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2-Amino-3-cyano-4-(4-chlorophenyl)-6-phenylpyridine (1) and 2-amino-3-carboxamido-4-(4-chlorophenyl)-6-phenylpyridine (3) when reacted with various isothiocyanates, 4-imino-3-substituted-5-(4-chlorophenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-thiones (2) and 2-thioxo-3-substituted-5-(4-chlorophenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones (4) were obtained respectively. 4 on methylation afforded the 2-methylmercapto derivatives (5) which on reaction with morpholine/piperidine yielded 2-*N*-(morpholino/piperidino)-3 substituted-5-(4-chlorophenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones (6). Some of the compounds have been tested for antibacterial activity.

SEVERAL-2-substituted-aminopyrido[2,3-*d*]pyrimidin-4-ones analogs of pipamidic acid have been patented as antibacterial agents[1,2]. Therefore, it was thought, in continuation of our interest in pyridopyrimidines[3-5] to describe the synthesis and reaction of 4-iminopyrido[2,3-*d*]-pyrimidin-2(1*H*)-thiones and 2 thioxopyrido[2,3-*d*]pyrimidin-4(3*H*)-ones. Some of the compounds were screened for their antibacterial activity.

4-Imino-3-substituted-5-(4-chlorophenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-2(1*H*)-thiones (2) and 2-thioxo-3-substituted-5-(4-chlorophenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones (4) were synthesised by treating 2-amino-3-cyanopyridine[6] (1) and 2-amino-3-carboxamidopyridine[6] (3) with various isothiocyanates respectively. 4 were methylated with dimethylsulphate to get 2-methylmercapto-3-substituted-5-(4-chlorophenyl)-7-phenylpyrido-[2,3-*d*]pyrimidin-4(3*H*)-ones (5), which when refluxed with morpholine/piperidine, gave 2-*N*-(morpholino/piperidino)-3-substituted-5-(4-chlorophenyl)-7-phenylpurido[2,3-*d*]pyrimidin-4(3*H*)-ones (6) in good yields (Table 1).

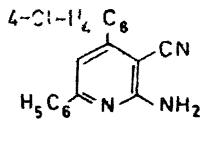
Ir spectra of 2 exhibited bands at 3 100 (NH), 1 570 – 1 550, 1 360 – 1 330 (NH – C=S) and 1 200 cm^{-1} (C=S). The absence of absorption around 2 250 – 2 210 cm^{-1} (C≡N) indicated the completion of reaction. 4 showed bands at 3 100 (NH), 1730 – 1 695 (C=O), 1 580 – 1 565, 1 375 (NH – C=S) and 1 200 cm^{-1} (C=S). In the case of 5, no characteristic absorptions for NH and C=S were found, instead a band around 880 cm^{-1} (SCH_3) was found. This band possessed by SCH_3 group was not found in the spectra of 6. The pmr spectra of 2a exhibited aromatic signals at δ 7.05 – 8.10 while signals for

TABLE 1 – PHYSICAL DATA OF COMPOUNDS 2, 4, 5 AND 6*

Compd no.	R	Yield %	M.p. °C	Mol. formula
2a	C_6H_5	65	310	$C_{25}H_{17}ClN_4S$
2b	$CH_2-C_6H_5$	67	302 – 3	$C_{26}H_{19}ClN_4S$
2c	*o* $CH_3-C_6H_4$	56	286 – 88	$C_{26}H_{19}ClN_4S$
2d	*m*-$CH_3-C_6H_4$	58	264 – 65	$C_{26}H_{19}ClN_4S$
2e	*p*-$CH_3-C_6H_4$	9	290 – 92	$C_{26}H_{19}ClN_4S$
2f	*o*-$OCH_3-C_6H_4$	68	272 – 74	$C_{26}H_{19}ClN_4OS$
2g	*m*-$OCH_3-C_6H_4$	66	297 – 98	$C_{26}H_{19}ClN_4OS$
2h	*p*-$OCH_3-C_6H_4$	64	280	$C_{26}H_{19}Cl_2N_4S$
2i	*m*-$Cl-C_6H_4$	58	235	$C_{25}H_{16}ClN_4OS$
4a	*n*-C_4H_9	46	354 – 55	$C_{25}H_{20}ClN_4OS$
4b	C_6H_5	52	357	$C_{25}H_{16}ClN_4OS$
4c	*o*-$CH_3-C_6H_4$	62	358 – 60	$C_{26}H_{18}ClN_4OS$
4d	*m*-$CH_3-C_6H_4$	55	367	$C_{26}H_{18}ClN_4OS$
4e	*p*-$CH_3-C_6H_4$	57	361 – 62	$C_{26}H_{18}ClN_4OS$
4f	*o*-$OCH_3-C_6H_4$	43	363 – 64	$C_{26}H_{18}ClN_4O_2S$
4g	*m*-$OCH_3-C_6H_4$	51	348 – 50	$C_{26}H_{18}ClN_4OS$
4h	C_6H_{11}	38	364	$C_{25}H_{22}ClN_4OS$
5a	*n*-C_4H_9	91	317	$C_{24}H_{22}ClN_4OS$
5b	C_6H_5	80	312 – 14	$C_{26}H_{18}ClN_4OS$
5c	*o*-$CH_3-C_6H_4$	90	304 – 05	$C_{27}H_{20}ClN_4OS$
5d	*m*-$CH_3-C_6H_4$	90	296	$C_{27}H_{20}ClN_4OS$
5e	*p*-$CH_3-C_6H_4$	85	289 – 90	$C_{27}H_{20}ClN_4O_2S$
5f	*o*-$OCH_3-C_6H_4$	76	293 – 94	$C_{27}H_{20}ClN_4O_2S$
5g	*p*-$OCH_3-C_6H_4$	78	300 – 01	$C_{27}H_{20}$ (X=O)
6a	C_6H_5	60	346 – 48	$C_{30}H_{28}ClN_4O_2$
6b	*p*-$CH_3-C_6H_4$	65	312 – 13	$C_{30}H_{28}ClN_4O_2$
6c	*p*-$OCH_3-C_6H_4$	84	339 – 40	$C_{30}H_{28}$ (X=CH)
6d	C_6H_5	57	360 – 61	$C_{29}H_{28}ClN_4O$
6e	*p*-$CH_3-C_6H_4$	68	342 – 44	$C_{30}H_{28}ClN_4O_2$
6f	*p*-$OCH_3-C_6H_4$	59	359 – 60	$C_{30}H_{28}ClN_4O_3$

*All compounds gave satisfactory C, H and N analyses.

imino protons were found little downfield (δ 8.5) **2b** showed characteristic SCH_3 protons at δ 2.75 along with aromatic protons (δ 7.15–8.12).



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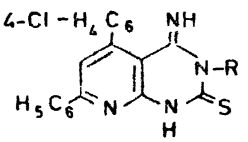

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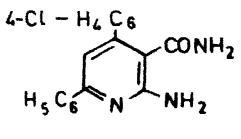

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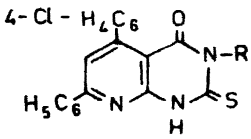

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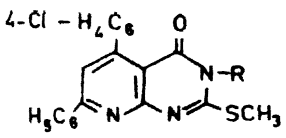

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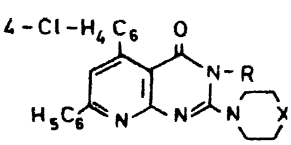

(6)

R = n-C_4H_9, C_6H_5, $CH_2C_6H_5$, 2-CH_3-C_6H_4, 3-CH_3-C_6H_4, 4-CH_3-C_6H_4, 2-OCH_3-C_6H_4, 4-OCH_3-C_6H_4, 3-Cl-C_6H_4, C_6H_{11}

X = CH, O

Scheme 1

Antibacterial activity : The antibacterial activity of some of the compounds **2a, c, e, h ; 4b–h ; 5b, c, e–g ; 6a–d, f** were tested against *S. aureus, B. subtilis, E coli* and *S. typhi* by cup plate method[7] using nutrient agar as medium. The compounds were used at a concentration of 5 mg ml^{-1} in absolute ethanol and 0 05 ml was used in each cup. Compounds **2e, h ; 4b–d, f–h ; 5b, c, e–g ;** and **6a–d, f** showed antibacterial activity against all organisms tested (Table 2). It has been interesting to note that amino functionality at position-2 in compounds **6** enhanced antibacterial activity.

TABLE 2 – ANTIBACTERIAL ACTIVITY DATA OF COMPOUNDS

Compd. no.	Zone of inhibition in mm after 48 h			
	S. a	*B. s*	*E c*	*S. t*
2a	10.5	9.0	Nil	11.0
2c	9.5	Nil	10 5	10.0
2e	10 0	11.0	10.5	12.0
2h	9 0	9.5	10.0	11.5
4a	11.0	11 0	Nil	Nil
4b	10.0	12.0	12.0	9.0
4c	12.0	13.0	12.0	10 0
4d	10.0	10.0	10.0	10.0
4e	11.0	11.0	Nil	12.0
4f	12.0	12.0	10.0	10.0
4g	11.0	10.0	10.0	10.0
4h	12.5	11 0	9 0	9.0
5b	11.0	10.0	9.0	9.0
5c	10.0	9.0	10.0	11.5
5e	11.0	10 0	Nil	9.0
5f	11.0	10.5	9 5	10.0
5g	9.0	11.0	9.0	10.0
6a	11.0	13.0	12.0	11.5
6b	11.0	12 5	10.0	13.0
6c	12.0	11.0	10 5	13.0
6d	11.5	12 0	13 0	10.5
6f	11 0	10 0	11 0	12.0

**S a = S. aureus, B.s = B. subtilis, E.c = E coli, S.t = S. typhi.*

Experimental

Melting points are uncorrected. Ir spectra (KBr) were run on a Perkin-Elmer 377 spectrophotometer and pmr spectra (60 MHz) on a Perkin-Elmer R 12 B spectrometer using TMS as internal standard. Tlc was carried out on silica gel-G plates using benzene–methanol (80 : 20) mixture as irrigant and spots were developed with iodine vapours.

*4-Imino-3-substituted-5-(4-chlorophenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones* (**2**) *:* A mixture of 2-amino-3-cyano-4-(4-chlorophenyl)-6-phenylpyridine (0 01 mol), appropriate isothiocyanate (0.01 mol), dioxane (15.00 ml) and pyridine (2.00 ml) was refluxed for 20–22 h. The reaction mixture on cooling was added to crushed ice and the resulting solid was washed with water, dried and crystallised from glacial acetic acid.

*2-Thioxo-3-substituted-5-(4-chlorophenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones* (**4**) *:* A mixture of 2-amino-3-carboxamido-4-(4-chlorophenyl)-6-phenylpyridine (0.01 mol), appropriate isothiocyanate (0.01 mol) and diphenyl ether (30.0 ml) was refluxed for 7 h. The reaction mixture was kept overnight at room temperature and the resulting solid was washed with cold ethanol, dried and crystallised from DMF/EtOH mixture.

*2-Methylmercapto-3-substituted-5-(4-chlorophenyl)7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones* (**5**) *:* Compound **4** (0.005 mol) was dissolved in a mixture of ethanol (20 00 ml) and NaOH (0 01 mol). To the resulting clear solution, was added dimethyl sulphate (0.005 mol) with constant stirring. The reaction mixture on cooling was added to crushed ice and the resulting solid was washed successively with water, sodium bicarbonate solution (5%, w/v) and water, dried and crystallised from DMF–ethanol mixture.

*2-N(Morpholino/piperidine)-3-substituted-5-(4-chlorophenyl)-7-phenylpyrido[2,3-*d*]pyrimidin-4(3*H*)-ones* (**6**) *:* Compound **5** (0.005 mol) was refluxed in morpholine/piperidine (10.00 ml) for 16 h. The reaction mixture on cooling was added to crushed ice and the resulting solid was washed with water, dried and crystallised from DMF–ethanol mixture.

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