Reaction of Nitriles under Acidic Conditions. Part VI. Synthesis of Condensed 4-Chloro- and 4-Aminopyrimidines from *ortho*-Aminonitriles

C. J. Shishoo*, M. B. Devani, V. S. Bhadti [1a],
K. S. Jain and S. Ananthan [1b]

Department of Pharmaceutical Chemistry, L. M. College of Pharmacy,
Ahmedabad 380 009, India

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Condensation of a nitrile with benzene, furan and thiophene *ortho*-aminonitriles in the presence of dry hydrogen chloride yields condensed 4-chloropyrimidines, condensed 4-aminopyrimidines or a mixture of the two condensed pyrimidines in varying proportions depending upon the nature of the nitrile and the substrate, *ortho*-aminonitrile.

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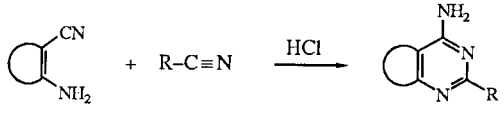
We have been investigating the hydrogen chloride catalysed reaction of nitriles with *o*-aminocarbonyl compounds as a useful route to synthesize fused pyrimidines [2,3]. In this reaction the use of *o*-aminonitrile, **1**, as the substrate generally results in the formation of 4-aminopyrimidine, **3**, as the product. However, this is not true in all



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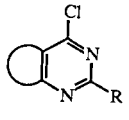
the cases. In some of our reactions the product formed was 4-chloropyrimidine, **4**, instead of the 4-aminopyrimidine, **3**.



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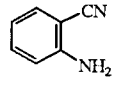
Our preliminary studies [4] indicated that the nature of the nitrile plays an important role in determining the course of the reaction. For example, nitriles, such as acetonitrile, yielded exclusively fused 4-aminopyrimidines, **3**, while chloroacetonitrile lead to the formation of fused 4-chloropyrimidines, **4**. Since the electron withdrawing nature of chlorine in chloroacetonitrile appeared to influence the course of the reaction, an attempt was made to investigate the product distribution in the reactions of a series of substituted acetonitriles, arylcyanides and other nitriles possessing various electron withdrawing functions.

The readily accessible anthranilonitrile, **5**, thiophene *o*-aminonitriles, **6a**, **6b** and furan *o*-aminonitrile, **7**, were selected as substrates. The condensation between these substrates and variously substituted nitriles was conducted in dioxane, under carefully controlled conditions employing anhydrous hydrogen chloride gas as the catalyst.



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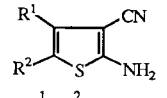
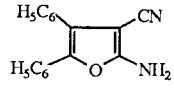


6a, R^1, R^2 = $-(CH_2)_4-$
6b, R^1 = R^2 = CH_3



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A perusal of the results (Table I) indicates that acetonitrile, phenylacetonitrile and benzonitrile when reacted with *o*-aminonitriles, **5**, **6a** and **7**, yielded exclusively the condensed 4-aminopyrimidines, **8b-14b**. Similarly, nitriles like alkyl thiocyanates and dialkylcyanamides when reacted with the thiophene *o*-aminonitriles, **6a** and **6b**, resulted in the formation of the fused 4-aminopyrimidines, **15b-18b**.

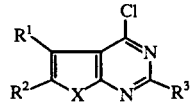
On the other hand, nitriles such as chloro and dichloroacetonitriles when reacted with the *o*-aminonitriles, **5**, **6a**, **6b** and **7**, result in the formation of the 4-chloropyrimidines, **19a-25a**, exclusively. However, nitriles possessing electron withdrawing groups such as cyanoformates, cyanoacetates, aryloxy-, arylthio-, and arylsulfonylacetonitriles, and also arylacetonitriles bearing electronegative groups on the benzene ring, yielded mixture of 4-chloro and 4-aminopyrimidines, in varying proportions.

The nature of the substrate, *o*-aminonitriles, also affects the course of the reaction as is brought out by the comparison of the product distribution in the reaction of thiophene *o*-aminonitrile, **6a**, and furan *o*-aminonitrile, **7**, with phenylsulfonylacetonitrile. Formation of the 4-chlorothienopyrimidine, **39a**, was nearly twice (35%) than that of 4-chlorofuranopyrimidine, **40a** (15%). Also, the reaction of furan *o*-aminonitrile, **7**, with ethyl cyanoformate and anthranilonitrile, **5**, with phenoxyacetonitrile resulted in the formation of 4-aminopyrimidines, **31b** and **35b**, respectively, as the sole reaction products. The same nitriles when reacted with substrate, **6a**, however, yielded a mixture of the corresponding 4-chloro and 4-aminopyrimidines, **30a,b** and **36a,b**, respectively.

An examination of the overall results obtained with the substituted acetonitriles employed appears to substantiate

Table I

Physical and Analytical Data of Condensed 4-Chloro and 4-Aminopyrimidines



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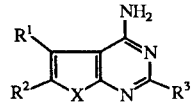

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Compound No.	R^1	R^2	X	R^3	MP °C	% Yield	Recrystallization solvent [c]	Molecular Formula	Mol. Wt.	Microanalysis Calcd./Found %C	%H
8b	H	H	CH=CH	CH_3	227-229 [e]	63	CH-EA	$C_9H_9N_3$	159.18	67.90 68.28	5.70 5.93
9b	$-(CH_2)_4$		S	CH_3	224-225 [f]	50	B	$C_{11}H_{13}N_3S$	219.30	60.42 60.30	5.98 6.25
10b	C_6H_5	C_6H_5	O	CH_3	253-255 [g]	68	B	$C_{19}H_{15}N_3O$	301.33	75.73 75.80	5.02 5.01
11b	H	H	CH=CH	$C_6H_5CH_2$	252-254 [d]	40	CH-EA	$C_{15}H_{13}N_3$	235.28	76.57 76.51	5.57 5.76
12b	$-(CH_2)_4-$		S	$C_6H_5CH_2$	193-195	43	B	$C_{17}H_{17}N_3S$	295.39	69.12 69.27	5.80 5.86
13b	$-(CH_2)_4-$		S	C_6H_5	195-197 [h]	47	B	$C_{16}H_{15}N_3S$	281.37	68.30 67.96	5.37 5.49
14b	C_6H_5	C_6H_5	O	C_6H_5	234-236	47	B-M	$C_{24}H_{17}N_3O$	363.40	79.32 79.32	4.72 4.96
15b	$-(CH_2)_4-$		S	CH_3S	210-212	84	I	$C_{11}H_{13}N_3S_2$	251.36	52.56 52.50	5.21 5.02
16b	CH_3	CH_3	S	CH_3S	248-249	66	I	$C_9H_{11}N_3S_2$	225.33	47.97 48.18	4.92 5.00
17b	$-(CH_2)_4-$		S	morpholino	338-340	40	C-H	$C_{14}H_{18}N_4OS$	290.38	57.90 57.92	6.25 6.30
18b	CH_3	CH_3	S	morpholino	176-178	35	B-H	$C_{12}H_{16}N_4OS$	264.34	54.52 54.13	6.10 6.20
19a	H	H	CH=CH	$ClCH_2$	100-102 [i]	85	H	$C_9H_6Cl_2N_2$	213.06	50.73 50.30	2.84 2.66
20a	$-(CH_2)_4-$		S	$ClCH_2$	98-100 [j]	69	H	$C_{11}H_{10}Cl_2N_2S$	273.17	48.36 48.30	3.69 3.70
21a	CH_3	CH_3	S	$ClCH_2$	144-145 [k]	73	H	$C_9H_8Cl_2N_2S$	247.16	43.74 43.58	3.26 3.17
22a	C_6H_5	C_6H_5	O	$ClCH_2$	120-122 [l]	58	H	$C_{19}H_{12}Cl_2N_2O$	355.21	64.24 64.00	3.41 3.67
23a	H	H	CH=CH	Cl_2CH	135-137 [m]	87	H	$C_9H_5Cl_3N_2$	247.50	43.67 43.93	2.04 2.15
24a	$-(CH_2)_4-$		S	Cl_2CH	118-120 [n]	78	H	$C_{11}H_9Cl_3N_2S$	307.64	42.94 43.30	2.95 3.16
25a	CH_3	CH_3	S	Cl_2CH	152-154	80	H	$C_9H_7Cl_3N_2S$	281.60	38.38 38.68	2.51 2.79
26b	C_6H_5	C_6H_5	O	Cl_2CH	214-216	55	B-H	$C_{19}H_{13}Cl_2N_3O$	370.22	61.64 61.87	3.54 4.00
27b	$-(CH_2)_4-$		S	Cl_3C	231-233 [d]	50	E	$C_{11}H_{10}Cl_3N_3S\bullet$ $1/2C_2H_5OH$	345.69	41.69 41.75	3.79 3.57

Table 1 continued

Compound No.	R^1	R^2	X	R^3	MP °C	% Yield	Recrystallization solvent [c]	Molecular Formula	Mol. Wt.	Microanalysis Calcd./Found %C	%H
28a	$-(CH_2)_4-$		S	$CH_2CO_2C_2H_5$	57-60	26	H	$C_{14}H_{15}ClN_2O_2S$	310.79	54.10 54.09	4.86 4.90
28b	$-(CH_2)_4-$		S	$CH_2CO_2C_2H_5$	170-171	35	B	$C_{14}H_{17}N_3O_2S$	291.36	57.71 57.35	5.88 5.87
29a	C_6H_5	C_6H_5	O	$CH_2CO_2C_2H_5$	115-116	39	H	$C_{22}H_{17}ClN_2O_3$	392.82	67.26 67.54	4.36 4.60
29b	C_6H_5	C_6H_5	O	$CH_2CO_2C_2H_5$	175-176	41	B-H	$C_{22}H_{19}N_3O_3$	373.39	70.76 71.09	5.13 5.26
30a	$-(CH_2)_4-$		S	$CO_2C_2H_5$	139-141	25	H	$C_{13}H_{13}ClN_2O_2S$	296.77	52.61 52.33	4.42 4.61
30b	$-(CH_2)_4-$		S	$CO_2C_2H_5$	254-256	45	E	$C_{13}H_{15}N_3O_2S$	277.34	56.30 56.38	5.45 5.65
31b	C_6H_5	C_6H_5	O	$CO_2C_2H_5$	270-272	35	B-H	$C_{21}H_{17}N_3O_3$	359.37	70.18 70.29	4.77 4.95
32a	$-(CH_2)_4-$		S	$4\text{-}NO_2C_6H_4CH_2$	180-185	42	B-H	$C_{17}H_{14}ClN_3O_2S$	359.84	56.74 56.77	3.92 4.08
32b	$-(CH_2)_4-$		S	$4\text{-}NO_2C_6H_4CH_2$	320-322	44	DS-E	$C_{17}H_{16}N_4O_2S$	340.39	59.81 59.96	4.74 5.03
33a	C_6H_5	C_6H_5	O	$4\text{-}NO_2C_6H_4CH_2$	142-144	34	B-H	$C_{25}H_{16}ClN_3O_3$	441.85	67.96 68.15	3.65 4.00
33b	C_6H_5	C_6H_5	O	$4\text{-}NO_2C_6H_4CH_2$	156-158	35	B-H	$C_{25}H_{18}N_4O_3$	422.42	71.08 71.13	4.30 4.60
34a	$-(CH_2)_4-$		S	$4\text{-}NO_2C_6H_4$	235-237	43	H	$C_{16}H_{12}ClN_3O_2S$	345.79	55.57 55.91	3.50 3.70
34b	$-(CH_2)_4-$		S	$4\text{-}NO_2C_6H_4$	256-258	28	DS-E	$C_{16}H_{14}N_4O_2S$, $1/2H_2O$	335.38	57.29 57.01	4.51 4.31
35b	H	H	CH=CH	$C_6H_5OCH_2$	225-227	40	E	$C_{15}H_{13}N_3O$	251.28	71.69 71.61	5.22 5.29
36a	$-(CH_2)_4-$		S	$C_6H_5OCH_2$	70-72	15	H	$C_{17}H_{15}ClN_2OS$	330.82	61.72 61.64	4.57 4.77
36b	$-(CH_2)_4-$		S	$C_6H_5OCH_2$	205-207	42	E	$C_{17}H_{17}N_3OS$	311.39	65.57 65.79	5.50 5.80
37a	$-(CH_2)_4-$		S	$C_6H_5SCH_2$	82-84	11	H	$C_{17}H_{15}ClN_2S_2$	346.89	58.86 59.07	4.36 4.48
37b	$-(CH_2)_4-$		S	$C_6H_5SCH_2$	167-169	49	E	$C_{17}H_{17}N_3S_2$	327.46	62.35 62.52	5.23 5.56
38a	C_6H_5	C_6H_5	O	$C_6H_5SCH_2$	72-74	32	H	$C_{25}H_{17}Cl_2N_2OS$	428.92	70.01 70.36	3.99 4.20
38b	C_6H_5	C_6H_5	O	$C_6H_5SCH_2$	180-181	35	B-H	$C_{25}H_{19}N_3OS$	409.49	73.32 73.01	4.68 4.34
39a	$-(CH_2)_4-$		S	$C_6H_5SO_2CH_2$	155-157	35	B-H	$C_{17}H_{15}ClN_2O_2S_2$	378.89	53.89 53.85	3.99 3.61
39b	$-(CH_2)_4-$		S	$C_6H_5SO_2CH_2$	219-222	45	E	$C_{17}H_{17}N_3O_2S_2$	359.46	56.80 57.05	4.77 5.05
40a	C_6H_5	C_6H_5	O	$C_6H_5SO_2CH_2$	185-187	15	B-H	$C_{25}H_{17}ClN_2O_3S$	460.92	65.14 64.98	3.72 4.13

Table 1 continued

Compound No.	R^1	R^2	X	R^3	MP °C	% Yield	Recrystallization solvent [c]	Molecular Formula	Mol. Wt.	Microanalysis Calcd./Found %C	%H
40b	C_6H_5	C_6H_5	O	$C_6H_5SO_2CH_2$	212-215	35	E	$C_{25}H_{19}N_3O_3S$, C_2H_5OH	487.56	66.51 66.85	5.17 5.09
41a	$-(CH_2)_4-$		S	4-$ClC_6H_4SO_2$-CH_2	156-158	29	B-H	$C_{17}H_{16}Cl_2N_2O_2S_2$	413.33	49.40 49.63	3.41 3.73
41b	$-(CH_2)_4-$		S	4-$ClC_6H_4SO_2$-CH_2	265-267	56	D-E	$C_{17}H_{16}ClN_3O_2S_2$	393.90	51.84 51.81	4.09 4.12
42b	$-(CH_2)_4-$		S	2-C_5H_4N	249-251	40	B-M	$C_{15}H_{14}N_4S$	282.35	63.80 63.86	4.99 4.72
43a	$-(CH_2)_4-$		S	3-C_5H_4N	146-148	13	B-H	$C_{15}H_{12}ClN_3S$	301.78	59.70 59.46	4.01 4.42
43b	$-(CH_2)_4-$		S	3-C_5H_4N	206-208	35	B-M	$C_{15}H_{14}N_4S$	282.35	63.80 63.94	4.99 5.28
44a	$-(CH_2)_4-$		S	4-C_5H_4N	152-155	10	B-H	$C_{15}H_{12}ClN_3S$	301.78	59.70 59.75	4.01 4.21
44b	$-(CH_2)_4-$		S	4-C_5H_4N	240-242	48	B-M	$C_{15}H_{14}N_4S$	282.35	63.80 64.09	4.99 5.32

[c] B = Benzene, C = Chloroform, CH = Cyclohexane, D = Dimethylformamide, DS = Dimethylsulfoxide, E = Ethanol, EA = Ethyl acetate, H = *n*-Hexane (60-80°), I = 2-Propanol, M = Methanol. [d] = decomposes. [e] = Reported mp 228-229° [22]. [f] Reported mp 224-225° [2] . [g] Reported mp 253-255° [2]. [h] Reported mp 195-197° [2]. [i] Reported mp 95-96° [23]. [j] Reported mp 98-100° [4]. [k] Reported mp 144-145° [4]. [l] Reported mp 120-122° [4]. [m] reported mp 135-137° [4]. [n] Reported mp 118-120° [4].

the expectation that the electron withdrawing ability of the substituent on the C≡N group of the nitrile does affect the course of the reaction. As a case in point, yields of the 4-chlorothienopyrimidine, **39a**, were almost three times (35%) in the reaction of, **6a**, with phenylsulfonylacetonitrile as compared to the reaction of **6a**, with phenylthioacetonitrile which yielded only 11% of the corresponding 4-chlorothienopyrimidine, **37a**. The higher yields of 4-chloropyrimidines with phenylsulfonylacetonitrile compared to the phenylthioacetonitrile can be attributed to the greater electron withdrawing ability of the phenylsulfonyl group of the former nitrile.

Although the same trend is discernible in the reaction with other nitriles employed, a few exceptions were noted. The product distribution in the condensation of phenylthio- and phenylsulfonylacetonitrile with furan *o*-aminonitrile, **7**, illustrates this point. Formation of 4-chlorofuranopyrimidine, **38a**, in the reaction of furan *o*-aminonitrile, **7**, with phenylthioacetonitrile was twice (32%) than that of, **40a** (15%), obtained through its reaction with phenylsulfonylacetonitrite. Also unexpected was the exclusive formation of the 4-aminopyrimidines, **26b**, and **27b**, in the reaction of dichloroacetonitrile and trichloroacetonitrile with substrates, **7**, and **6a**, respectively.

The possibility of a formation of 4-chloropyrimidines, **4**, from 4-aminopyrimidines, **3**, under the reaction conditions employed for the condensation has been excluded by pass-

Scheme I

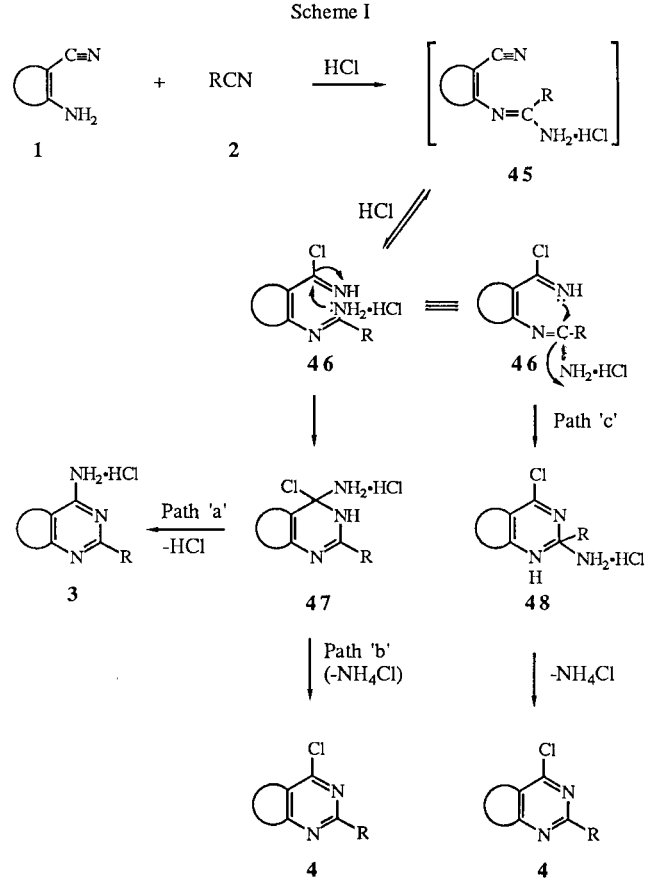

Table II

Spectral Data for 4-Chloro and 4-Aminopyrimidines

Compound	IR (cm^{-1})	MS: m/e	^{1}H-NMR [a]
8b	3510, 3380 (NH)	—	—
9b	3450, 3300 (NH)	219 (M^+), 204, 191	—
10b	3460, 3300 (NH)	301 (M^+), 300, 260, 259, 258, 231, 216, 189, 178, 155	—
11b	3460 (NH)	235, (M^+), 144, 119, 118, 117	—
12b	3300, 3100 (NH)	—	—
13b	3400, 3275 (NH)	—	—
14b	3480 (NH)	—	—
15b	3520, 3300 (NH)	251 (M^+)	—
16b	3520, 3290 (NH)	—	—
17b	3480 (NH)	290 (M^+), 264, 261, 248, 236, 220, 205, 192, 151, 130, 117, 109, 91	—
18b	3480, 3300 (NH)	264, (M^+), 233, 219, 207, 206, 179, 178, 165, 151, 146, 137, 117	—
19a	1600, 1540,1260, 1210, 1020	—	
20a	1560, 1520, 1250, 1200, 1130	276, 274, (M+2), 272 (M^+), 246, 244, 239, 237, 211, 209, 187	—
21a	1560, 1535, 1480, 1290, 1160	250, 248, (M+2), 246 (M^+), 231, 213, 211	—
22a	1640, 1600, 1540, 1260, 1215, 1170	356 (M+2), 354 (M^+)	
23a	1600, 1560, 1265, 1245, 1225, 1165	250, 248 (M+2), 246 (M^+), 213, 211, 184, 176, 163, 150, 129, 114, 102	—
24a	1520, 1260, 1200, 1130, 1010	310, 308 (M+2), 306 (M^+), 273, 271, 245, 243, 210, 208, 181, 169, 159, 147	—
25a	1540, 1520, 1220, 1145, 1045	—	—
26b	3480, 3300 (NH)	371 (M+2), 369 (M^+), 334, 298, 260, 216, 189, 105	—
27b	3510, 3310, 3210 (NH)	323 (M+2), 321 (M^+), 286, 285, 284, 256, 243, 231, 223, 189, 161, 143, 134, 129, 117, 108	—
28a	1740 (C = O)	312, (M+2), 310 (M^+), 284, 282, 267, 265, 258, 256, 240, 239, 238, 237, 212, 203, 202, 201	—
28b	3480, 3280, 3160 (NH), 1740 (C = O)	291, (M^+), 263, 246, 219, 217, 202, 189, 179, 177, 163, 150, 134, 123, 108, 77	—
29a	1735 (C = O)	394 (M+2), 392 (M^+), 382, 379, 347, 335, 333, 321, 319, 306, 284, 281, 279, 255, 244, 217, 210, 201, 189, 177, 165, 105, 99, 97, 95	—
29b	3400, 3300 (NH), 1740 (C = O)	—	δ 1.1-1.5 (3H, t, $COOCH_2CH_3$), 3.9 (2H, s, $CH_2COOCH_2CH_3$) 4.1-4.4 (2H, q, $COOCH_2CH_3$), 5.3 (2H, s, NH_2 deuterium oxide exchangeable), 7.3-7.8 (10H, m, aryl-*H*)
30a	1740 (C = O)	298 (M+2), 296 (M^+), 268, 251, 240, 224, 196, 189, 161, 151, 147, 134, 133, 116	—
30b	3480, 3280, 3160 (NH), 1740 (C=O)	—	—
31b	3475, 3250 (NH), 1725 (C = O)	331, 317, 297, 281, 273, 272, 110, 107, 94, 77	δ 2.2-2.4 (3H, t, $COOCH_2CH_3$), 2.7-3.0 (2H, q, $COOCH_2CH_3$), 5.6-5.75 (2H, s, NH_2), 6.75-7.25 (10H, m, aryl-*H*)

Table II continued

Compound	IR (cm^{-1})	MS: m/e	^{1}H-NMR [a]
32a	1650, 1580, 1520, 1530		
		361 (M+2), 359 (M^+), 344, 342, 258, 256, 240. 239, 238, 202, 196, 171, 160, 150, 149, 136, 128, 111, 105, 97, 77	—
32b	3420 (NH)	340, (M^+), 339, 326, 313, 312, 295, 294, 287, 253, 239, 227, 197, 183, 179, 177, 155, 136, 117	—
33a	1600, 1520, 1345, 1250	—	—
33b	3460, 3300, 3150 (NH)	422 (M^+), 421, 405, 392, 376, 339, 311, 298, 297, 271, 269, 178, 162, 132, 116	δ 4.3 (2H, s, *CH_2*), 5.1 (2H, s, *NH_2*, deuterium oxide exchangeable), 7.4-7.8 (10H, m, aryl-*H* at 5 and 6) 8.2-8.5 (4H, m, aryl -*H*)
34a	1600, 1520, 1490, 1430, 1350, 1200	—	—
34b	3480, 3280, 3150 (NH)	—	—
35b	3440 (NH)	—	—
36a	1600, 1590, 1250	332 (M+2), 330 (M^+), 239, 237, 211, 209, 201, 198, 196, 178, 134, 86, 84	—
36b	3490, 3280 (NH)	311, (M^+), 218, 201, 191, 190, 189, 177, 176, 163, 160, 150, 135, 134, 118, 116	—
37a	1580, 1560, 1530, 1265, 1200	348 (M+2), 346 (M^+), 239, 237, 224, 209, 201, 176, 134	—
37b	3400, 3300, 3200 (NH)	327 (M^+), 312, 294, 265, 250, 219, 218, 205, 201, 191, 190, 189, 177, 176, 160, 150, 149	—
38a	1590, 1460, 1360	—	—
38b	3420, 3280, 3120 (NH)	—	—
39a	1590, 1540, 1480, 1300	380 (M+2), 378 (M^+), 317, 315, 239, 237, 231, 219	—
39b	3510, 3320, 3180 (NH)	359 (M^+), 314, 312, 296, 295, 294, 293, 280, 266, 237, 218, 217, 201, 191, 172, 163, 150, 105, 78	δ 1.5-1.8 (4H, m, CH_2 at 6 and 7), 2.5-3.0 (4H, m, CH_2 at 5 and 8), 4.7 (2H, s, CH_2 at 2), 7.0-7.2 (2H, m, *NH_2*, deuterium oxide exchangeable), 7.3-7.8 (5H,m, aryl-*H*)
40a	1650, 1560, 1520, 1230	462 (M+2), 460 (M^+), 398, 396, 319, 279, 255, 244, 216, 189, 165, 141, 127	—
40b	3480, 3320, (NH)	—	—
41a	1650, 1550, 1460, 1340	415, (M+2), 413 (M^+), 412, 350, 348, 239, 237, 211, 209, 202, 201, 198, 176, 174, 169, 161, 159, 146, 134, 113, 111	—
41b	3460, 3300, 3160 (NH)	395, (M+2), 393 (M^+), 350, 348, 331, 330, 329, 328, 239, 237, 219, 201, 191, 189, 177, 175, 163, 113, 111	δ 1.6-1.8 (4H, m, CH_2 at 6 and 7), 2.5-2.8 (4H, m, CH_2 at 5 and 8), 4.4 (2H, s, CH_2 at 2), 6.5 (2H, s, *NH_2*, deuterium oxide exchangeable), 7.4-8.0 (4H, m, aryl-*H*)
42b	3480, 3280, 3190 (NH)	—	—
43a	1600, 1500, 1450, 1360, 1200	303, (M+2), 301, (M^+), 275, 273, 266, 260, 249, 238	—
43b	3500, 3280 (NH)	282 (M^+), 281, 267, 254, 108, 105, 94, 78	δ 1.7-1.9 (4H, m, CH_2 at 6 and 7), 2.5-2.9 (4H, m, CH_2 at 5 and 8), 6.3 (2H, s, NH_2, deuterium oxide exchangeable), 7.5-9.5 (4H, m, aryl-*H*)

44a	1600, 1560, 1460, 1380	303 (M+2), 301 (M^+), 274, 272, 268, 238	—
44b	3520, 3320 (NH)	—	—

[a] The ^1H nmr spectra were taken in deuteriochloroform, except for compounds **31b** and **41b**, which were taken in DMSO-d_6.

ing excess of dry hydrogen chloride gas through the solution of the 4-aminopyrimidine in dioxane; workup of the reaction mixture yielded the unreacted starting material. Therefore, the chloro- and aminopyrimidine formation occurs probably by different reaction pathways. It appears reasonable to assume that under the reaction conditions employed, the C≡N groups of both the substrate and the reactant are activated by protonation or by the formation of hydrogen chloride adducts. The initial condensation between the two components or their activated forms might be expected to result in the formation of amidine hydrochloride, **45**, or its hydrochloride adduct, **46**.

All our attempts to demonstrate the formation of such amidine intermediates by their isolation under carefully controlled conditions did not meet with success. Only fused pyrimidines could be isolated. However, amidine intermediates have been isolated in the condensations of certain thiophene *o*-aminoamides with nitriles [5] and in the reaction of pyrrole *o*-aminonitrile with cyanamide under acidic conditions [6].

Assuming that the imidoyl chloride derivative, **46**, is the common intermediate, the formation of 4-aminopyrimidines, **3**, can take place by path 'a' from the cyclic adduct, **47**, and that of 4-chloropyrimidines by path 'b' or 'c'. In the pathway 'c' it is likely that the presence of an electron withdrawing 'R' group would increase the electrophilic nature of the amidine carbon and thereby facilitate the cyclization of the intermediate, **46**, to 4-chloropyrimidines, **4** (Scheme I).

The condensed 4-amino- and 4-chloropyrimidines synthesized are pale yellow to colorless crystalline compounds. While the condensed 4-chloropyrimidines are low melting solids, highly soluble in almost all organic solvents except *n*-hexane, the 4-amino analogs exhibit only a moderate solubility in solvents like benzene, chloroform and ethanol. In general, the 4-aminopyrimidines exhibit higher melting points compared to their corresponding 4-chloro analogs.

The ir spectra of these condensed 4-aminopyrimidines reveal at least two strong absorption bands around 3500-3200 cm^{-1} due to asymmetric and symmetric N-H stretching. The 2-carbethoxymethyl and 2-carbethoxypyrimidines, **28-30a,b** and **31b**, are characterized by strong C=O stretching absorption at around 1740 cm^{-1} (Table II).

The nmr spectra of the 4-aminopyrimidines exhibit a singlet corresponding to two NH-protons in the region δ 5-7 exchangeable with deuterium-oxide.

In general, all the 4-aminopyrimidines except, **31b**, exhibit prominent molecular ion peak (M^+) in the mass spectra. In most of the cases the molecular ion peak is also the base peak. All the 4-chloropyrimidines are characterized by intense M+2 peaks, apart from prominent M^+ peaks. Almost all the 4-chloropyrimidines exhibit prominent M^+-35 and $(M+2)^+$-35 peaks in their mass spectra due to the loss of $Cl^·$ radicals from these ions.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The uv absorption spectra were determined using a Beckman model 24 Spectrophotometer. The ir spectra were recorded in nujol mulls or potassium bromide on a Perkin Elmer 337 Grating Spectrophotometer. The ^1H nmr spectra were taken on a Varian A-60 Spectrophotometer using tetramethylsilane as the internal standard. The mass spectra were obtained on a Varian Atlas CH-7 Spectrophotometer at 70 eV ionizing beam using direct insertion probe.

For the preparation of quinazolines, commercially available anthranilonitrile (Fluka), **5**, was used as the starting material, while the *o*-aminonitriles, **6a**, **6b** [7] and **7** [8] were prepared by literature methods.

Of the nitriles employed, acetonitrile, phenylacetonitrile, benzonitrile, ethyl cyanoacetate and the 2-cyano-, 3-cyano and 4-cyanopyridines (Fluka), were available commercially. Other nitriles namely, chloroacetonitrile [9], dichloroacetonitrile [10], trichloroacetonitrile [11], cyanomorpholine [12], methyl thiocyanate [13], ethylcyanoformate [14], 4-nitrobenzylcyanide [15], 4-nitrobenzonitrile [16], phenoxyacetonitrile [17], phenylthioacetonitrile [18], phenylsulfonylacetonitrile [18] and 4-chlorophenylsulfonylacetonitrile [19] were prepared by literature methods.

I. Reaction of *o*-Aminonitriles, **5**, **6a** and **7**, with Various Nitriles to Yield 4-Aminopyrimidines, **8b-18b**, **26b**, **27b**, **31b**, **35b** and **42b**, Exclusively.

General Procedure.

A stream of dry hydrogen chloride gas was bubbled through an ice-cold mixture of *o*-aminonitrile (0.01 mole) and the appropriate nitrile (0.011 mole) in 30 ml of dioxane for 6 hours. The reaction mixture was allowed to stand at room temperature for 12 hours, poured into ice-water and the mixture and basified with 10% ammonium hydroxide solution. The solid obtained was filtered, washed with water, dried and crystallized from a suitable solvent.

With aromatic nitriles the yields of the products were improv-

ed by heating the reaction mixture on a water bath for a few hours before diluting with ice-water mixture. In case of a reaction with acetonitrile, excess of it was used as the solvent.

II. Reaction of *o*-Aminonitriles, **5**, **6a**, **6b** and **7**, with Chloro and Dichloroacetonitrile to Yield 4-Chloropyrimidines, **19a-25a**, Exclusively.

General Procedure.

The *o*-aminonitriles, **5**, **6a**, **6b** and **7** were reacted with chloroacetonitrile and dichloroacetonitrile as described in procedure I. However, the reaction mixture was neutralized with saturated sodium bicarbonate solution. The solid which separated was filtered, washed with water and dried. The crude product was crystallized from *n*-hexane in all cases.

III. Unambiguous Synthesis of 4-Chloro-2-chloromethyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine (**20a**).

A mixture of 5.25 g (0.02 mole) 2-chloromethyl-5,6,7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidin-4(3*H*)-one [20] and 50 ml of phosphoros oxychloride was heated to a gentle reflux for 12 hours. Phosphoros oxychloride was removed by distillation under reduced pressure. The residue was poured into ice-water and neutralized with a saturated solution of sodium bicarbonate. The solid obtained was filtered, washed with water and dried. Recrystallization from *n*-hexane afforded 3.0 g (55%) of pale yellow crystalline product mp 98-100°. The compound was found identical (mmp, tlc, ir) with compound, **20a**, prepared by the reaction of **6a**, with chloroacetonitrile described in general procedure II.

IV. Reaction of *o*-Aminonitriles, **6a** and **7**, with Various Nitriles to Yield a Mixture of 4-Chloro and 4-Aminopyrimidines, **28a,b-30a,b**, **32a,b-34a,b**, **36a,b-41a,b**, **43a,b** and **44a,b**.

General Procedure.

The *o*-aminonitrile (0.01 mole) was reacted with an appropriate nitrile (0.011 mole) in 30 ml dioxane as described in procedure I. The reaction mixture was poured into ice-water. The solid obtained was filtered, washed successively with water, saturated sodium bicarbonate solution and water and dried. The crude product was purified by elution with benzene on a column of neutral alumina. Appropriate fractions were combined and evaporated. The residue on recrystallization from either *n*-hexane or a mixture of benzene-*n*-hexane afforded pure 4-chloropyrimidines, **28a-30a**, **32a-34a**, **36a-41a**, **43a** and **44a**.

The acidic mother liquor obtained after the filtration of the 4-chloropyrimidine was neutralized with saturated sodium bicarbonate solution. The solid obtained was filtered, washed with water and dried. Recrystallization from suitable solvents yielded pure 4-aminopyrimidines **28b-30b**, **32b-34b**, **36b-41b**, **43b** and **44b**.

V. Reaction of 4-Amino-2-chloromethyl-5,6,7,8-tetrahydrobenzo-[*b*]thienopyrimidine with Dry Hydrogen Chloride Gas - An Attempt to Investigate the Possible Formation of 4-Chloropyrimidines from 4-Aminopyrimidines.

A stream of dry hydrogen chloride gas was passed into an ice-cold solution of 2.5 g (0.01 mole) of 4-amino-2-chloromethyl-5,6,-7,8-tetrahydrobenzo[*b*]thieno[2,3-*d*]pyrimidine [21], in dioxane, for 6 hours. The reaction mixture, after allowing to stand at room temperature for 12 hours, was poured into ice-water and neutralized with a saturated solution of sodium bicarbonate. The solid obtained was filtered, washed with water and dried. Recrystallization from ethanol yielded 2.2 g of colorless crystals, mp 173-175°, identical (mmp, tlc, ir) with the starting material.

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[1a] Present Address: Department of Medicinal Chemistry, College of Pharmacy, Athens, Georgia, 30602, USA.

[1b] Present Address: Southern Research Institute, Birmingham, Alabama, 35255-5305, USA.

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