New Synthesis of Pyrido[2,3-*d*]pyrimidines. III. Nucleophilic Substitution on 4-Amino-2-halo and 2-Amino-4-halo-5,6-dihydropyrido[2,3-*d*]pyrimidin-7(8*H*)-ones

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As the third step of a new general synthesis of pyrido[2,3-*d*]pyrimidines, the substitution of the halogens by several nucleophiles has been carried out. Yields are between good and high in every case, even when 4-halogenated compounds have a neighbouring methyl group in C5.

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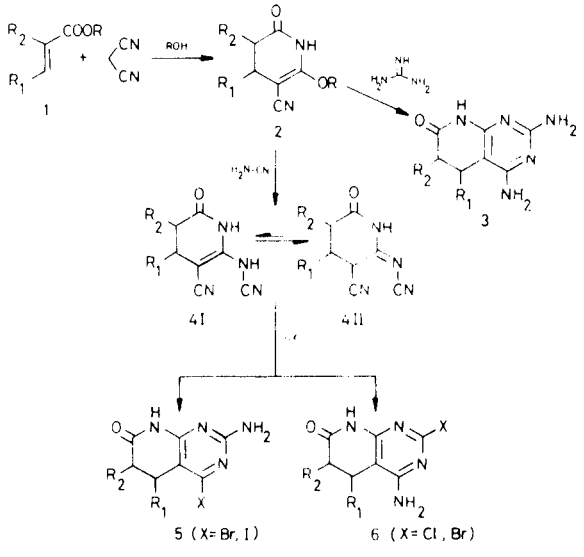
We have previously reported some steps of a new synthesis of pyrido[2,3-*d*]pyrimidines (Scheme 1), which begins with the preparation of 6-alkoxy-5-cyano-3,4-dihydro-2-pyridones **2** by a Michael reaction between propanedinitrile and an α,β-unsaturated ester [1]. The following step is the reaction of **2** with guanidine and cyanamide as nucleophiles [2]. The cyclization of 6-cyanamino-5-cyano-3,4-dihydro-2-pyridones **4** with hydrogen halides yields two isomers, **5** and **6**, depending, whenever tautomerism is possible, on the temperature and the hydrogen halide used [3].

Scheme 1



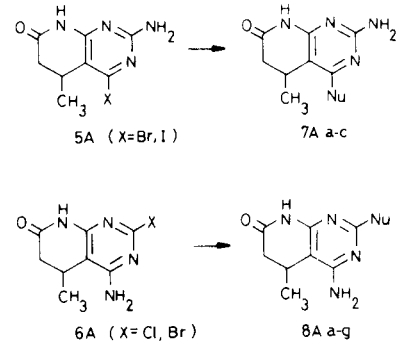
Both, **5** and **6**, are excellent substrates for nucleophilic substitution. Now we wish to report the results we have obtained using several bases.

First of all, we have studied the reaction in the case of **5A** and **6A** (R_1 = CH_3, R_2 = H) for all the available halogenated precursors (Scheme 2). Table I shows the results obtained.

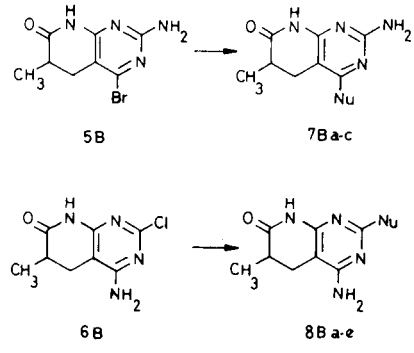
As a rule, all the yields are very good, independently of the starting material.

As all the halogens have been found to be excellent leaving groups, in the next substrates **5B** is always the brominated compound, because of its easier preparation, whereas **6B** is the chlorinated one, regioespecifically obtained on the cyclization of **4** with hydrogen chloride [3] (Scheme 3). Table II shows the results obtained in these two cases.

Scheme 2



Scheme 3



The synthesized products do not need any structure discussion, the structure of the halogenated compounds having been unequivocally established by both synthetic and spectroscopic evidences [3].

Table I

	X	Nu	Compound No.	Procedure	Yield, %	Time, hours	mp, °C	Molecular Formula	Analyses, % Calcd./Found C	H	N
		Methoxy	**7Aa**	A	90	92	298	$C_9H_{12}N_4O_2$	51.92	5.81	26.91
									51.94	5.88	27.06
	Br	Morpholino	**7Ab**	B	80	24	299	$C_{12}H_{17}N_5O_2$	54.74	6.51	26.60
									55.05	6.51	26.64
		Hydrazino	**7Ac**	D	90	0.5	264-265	$C_8H_{12}N_6O$	46.15	5.81	40.36
									46.19	5.89	40.46
5A											
		Methoxy	**7Aa**	A	80	100					
	I	Morpholino	**7Ab**	B	100	45					
		Hydrazino	**7Ac**	D	80	4					
		Methoxy	**8Aa**	A	77	100	203-204	$C_9H_{12}N_4O_2$	51.92	5.81	26.91
									52.02	6.12	26.64
		Morpholino	**8Ab**	B	85	24	248-250	$C_{12}H_{17}N_5O_2$	54.74	6.51	26.60
									54.94	6.44	26.68
		Hydrazino	**8Ac**	D	85	1	265-267	$C_8H_{12}N_6O$	46.15	5.81	40.36
									46.12	6.09	40.18
	Cl	Anilino	**8Ad**	C	83	100	262-263	$C_{14}H_{15}N_5O$	62.44	5.61	26.00
									62.66	5.63	26.10
		Cyclohexylamino	**8Ae**	C	75	72	297-298	$C_{14}H_{21}N_5O$	61.07	7.69	25.43
									60.77	7.87	25.14
		Piperidino	**8Af**	B	75	18	245-247	$C_{13}H_{19}N_5O$	59.75	7.33	26.80
									59.63	7.31	26.89
		Ethoxy	**8Ag**	A	60	70	168-170	$C_{10}H_{14}N_4O_2$	54.04	6.35	25.21
									53.96	6.38	25.13
6A											
		Methoxy	**8Aa**	A	100	76					
		Morpholino	**8Ab**	B	100	24					
		Hydrazino	**8Ac**	D	74	1.5					
	Br	Anilino	**8Ad**	C	80	80					
		Cyclohexylamino	**8Ae**	C	80	76					
		Piperidino	**8Af**	B	87	20					
		Ethoxy	**8Ag**	A	85	52					

Table II

	X	Nu	Compound No.	Procedure	Yield, %	Time, hours	mp, °C	Molecular Formula	Analyses, % Calcd./Found C	H	N
		Methoxy	**7Ba**	A	82	70	324-326	$C_9H_{12}N_4O_2$	51.92	5.81	26.91
									51.61	5.87	26.69
5B	Br	Morpholino	**7Bb**	B	78	48	318-320	$C_{12}H_{17}N_5O_2$	54.74	6.51	26.60
									54.77	6.60	26.59
		Hydrazino	**7Bc**	D	45	1	325-326	$C_8H_{12}N_6O$	46.15	5.81	40.36
									45.96	6.03	39.98
		Methoxy	**8Ba**	A	80	80	244-245	$C_9H_{12}N_4O_2$	51.92	5.81	26.91
									52.08	5.89	26.54
		Morpholino	**8Bb**	B	86	17	215-216	$C_{12}H_{17}N_5O_2$	54.74	6.51	26.60
									54.92	6.70	26.39
6B	Cl	Hydrazino	**8Bc**	D	65	1	316	$C_8H_{12}N_6O$	46.15	5.81	40.36
									46.24	5.75	40.65
		Anilino	**8Bd**	C	85	48	367	$C_{14}H_{15}N_5O$	62.44	5.61	26.00
									62.13	5.38	26.33
		Cyclohexylamino	**8Be**	C	78	70	288-289	$C_{14}H_{21}N_5O$	61.07	7.69	25.43
									60.90	7.80	25.43

EXPERIMENTAL

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. The Infrared spectra were recorded on a Perkin-Elmer 683 spectrophotometer as potassium bromide pellets.

General Procedures for the Preparation of Compounds **7** and **8**.

All the compounds were recrystallised from 96% aqueous ethanol. Spectral data are presented in Tables III and IV.

Table III

IR Spectral Data of Compounds **7a-c**, cm^{-1}

Compound No.	N-H	C=O	C=C and C=N
7Aa	3390, 3340, 3220	1675	1625, 1570
7Ab	3410, 3320, 3220	1690	1605, 1545
7Ac	3430, 3360, 3220 3220	1670	1620, 1570
7Ba	3370, 3360, 3220	1690	1622, 1565
7Bb	3450, 3330, 3225	1675	1620, 1555
7Bc	3430, 3330, 3225	1680	1625, 1580

Table IV

IR Spectral Data of Compounds **8a-g**, cm^{-1}

Compound No.	N-H	C=O	C=C and C=N
8Aa	3465, 3365, 3205	1685	1610, 1575
8Ab	3425, 3330, 3220 3140	1680	1610, 1560
8Ac	3460, 3310, 3290 3180	1675	1590, 1535
8Ad	3460, 3310, 3230 3180	1680	1585, 1570, 1540
8Ae	3490, 3310, 3260 3200, 3110	1680	1590, 1545
8Af	3470, 3340, 3210 3100	1670	1610, 1565
8Ag	3400, 3310, 3220 3150	1680	1610, 1565
8Ba	3450, 3355, 3215	1695	1615, 1575
8Bb	3410, 3320, 3295	1690	1615, 1605, 1555
8Bc	3410, 3320, 3230	1680	1580, 1535
8Bd	3465, 3310, 3250 3170	1685	1585, 1570, 1540
8Be	3465, 3360, 3285 3190, 3090	1695	1610, 1585, 1545

Procedure A.

A mixture of 0.004 mole of the appropriate halogenated compound, 0.02 mole of sodium alkoxide and 50 ml of anhydrous alcohol was refluxed while stirring for 70-120 hours. After cooling to room temperature, the solvent was evaporated *in vacuo* to dryness. The residue was dissolved in 10 ml of water and carefully neutralized to *p*H 7 with 6*N* hydrochloric acid. The precipitate was filtered off and dried *in vacuo* over phosphorus pentoxide.

Procedure B.

A mixture of 0.004 mole of the appropriate halogenated compound, 0.2 mole of the corresponding nucleophile and 25 ml of anhydrous methanol was refluxed while stirring for 17-48 hours. After cooling to room temperature, the solvent was evaporated *in vacuo* to dryness. The residue was treated with a little amount of methanol to give a solid which was filtered off and dried *in vacuo* over phosphorus pentoxide.

Procedure C.

A mixture of 0.004 mole of the appropriate halogenated compound, 0.2 mole of the corresponding nucleophile and 50 ml of anhydrous methanol was refluxed while stirring for 48-100 hours. After cooling to room temperature, the precipitate was filtered off, washed with methanol and dried *in vacuo* over phosphorus pentoxide.

Procedure D.

A mixture of 0.004 mole of the appropriate 4-halogenated compound **5** and 19 ml (0.4 mole) of 100% hydrazine hydrate was refluxed while stirring for 0.5 hours. After the reaction was completed, the solution was allowed to cool. The solid was filtered off, washed with water and dried *in vacuo* over phosphorus pentoxide.

A mixture of 0.004 mole of the appropriate 2-halogenated compound **6**, 19 ml (0.4 mole) of 100% hydrazine hydrate and 40 ml methanol was refluxed while stirring for 1 hour. After cooling to room temperature, the solid was filtered off and dried *in vacuo* over phosphorus pentoxide.

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