NITROGEN BRIDGEHEAD COMPOUNDS PART 59[1]. NUCLEOPHILIC SUBSTITUTION REACTIONS OF 9-BROMO-6,7,8,9-TETRAHYDRO-4H-PYRIDO[1,2-a]PYRIMIDIN-4-ONES

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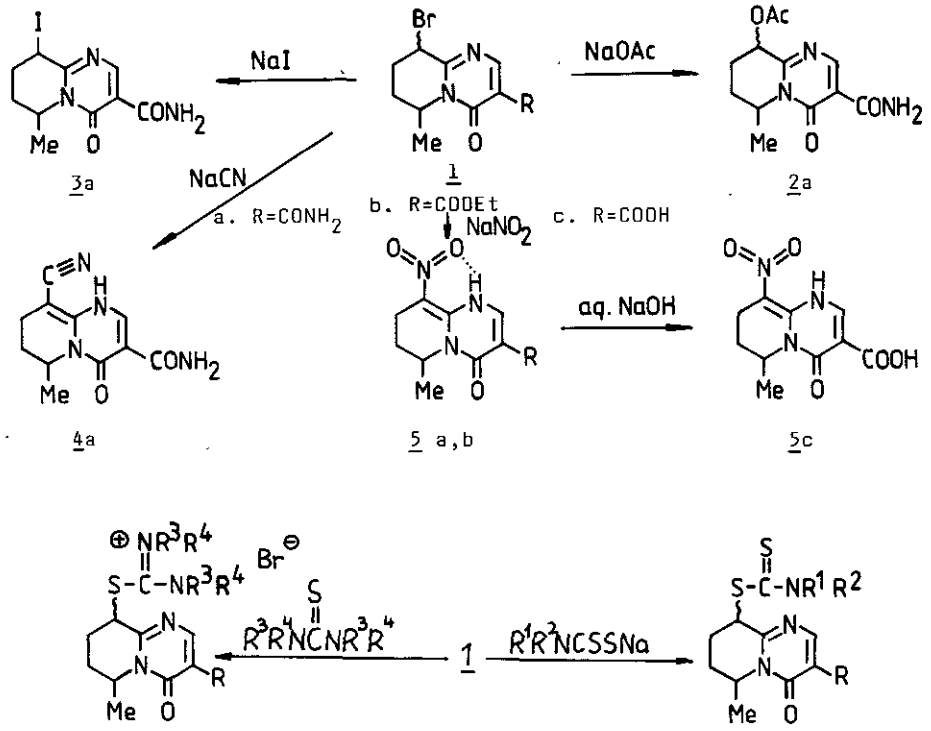
Abstract - Halogen replacement of 9-bromo-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-ones with C-, N-, O-, and S-nucleophiles can be readily accomplished.

During the course of our investigations concerning the isomerism and tautomerism of biologically active tetrahydropyrido[1,2-a]pyrimidin-4-ones we have prepared a great number of derivatives containing different groups in the position 9. These compounds could be prepared by electrophilic substitution reaction with aldehydes[2], halogen[3a,b], diazonium salts[3c,4], isocyanates[5], iminium chlorides[6] and nitrous acid[7] on the activated piperidine ring [8] and recently by nucleophilic substitution of the 9-bromine atom[3c,4b,7,9]. Since the halogen atom proved to be most reactive owing to the activating effect of the neighbouring pyrimidone ring, compound 1 readily reacted with simple nucleophiles to give compounds (2-5) (40-60%), as shown in Scheme 1.

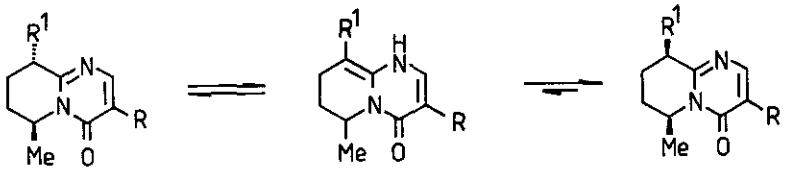
Bromine replacements were carried out in DMF (10 mmol of compound 1 + 15 mmol of NaX, t = 25°C, 1-6 h)[10]. Strong S-nucleophiles of carbamate and urea type, however, smoothly reacted with compounds 1 a,b,c even in acetone at room temperature resulting in the formation of dithiocarbamates (6,7) and isothiuronium salts (8-10) respectively[11] (Scheme 1).



8a	R^3, R^4=H	6a,c	R^1+R^2=$(CH_2CH_2)_2O$
9a,c	R^3=H, R^4+R^4=-CH_2CH_2-	7a,b,c	R^1+R^2=$(CH_2)_4$
10a,b,c	R^3, R^4=Me		

Scheme 1.

Earlier we have described[6] that 6-methyltetrahydropyrido[1,2-a]pyrimidin-4-ones substituted in the position 9 may exist in cis and trans isomer (A,C) and tautomer (B) forms (Scheme 2).



A — trans imine; B — enamine; C — cis imine

Scheme 2.

Enamine form (B) can be distinguished in ^{1}H NMR by the lack of H-9 signal, NH signal above 10 ppm (chelation), and doublet signal of H-2 (not always) while in ^{13}C NMR, by the sp^2 character of C-9. Imine forms (A,C) can be differentiated on the bases of the coupling constants between $H\text{-}9_{eq}$ or $H\text{-}9_{ax}$ and H-8 protons and the γ-gauche interaction of R substituent and C-7 atom in ^{13}C NMR. In case of R^1=$CONR_2$ and COOR we succeeded in identifying every species by NMR spectral analysis[8a]. Now having prepared new derivatives with different characteristic groups in the position 9 we wanted to gain more data about the imine-enamine tautomerism. According to ^{1}H NMR investigations the ratios of A-B-C forms are summarized in the table.

Isomer ratio and characteristic NMR data of compounds 1-7 and 10.

Comp.	B	A(trans)	C(cis)
	Enamine	Imine	
1a[x]	-	(82%), Me 1.28d	(18%), Me 1.42d
2a[+]	-	(93%), H_{eq}-9 5.66t	(7%), Me 1.38d
3a[+]	-	-	(100%), H_{ax}-9 3.80
4a[x]	(90%) Me 1.16d,NH 11,11	(A+B:10%),Me 1.21d	
5a[x]	(100%) Me 1.26d,NH 13.69s	-	-
5b[x]	(100%) Me 1.12d,NH 13.74s	-	-
5c[x]	(100%) Me 1.12d,NH 13.29	-	-
6a[+]	-	A(50%),C(50%),Me 1.45d,1.46d, H-2 8.88s	
7a[+]	-	A(50%),C(50%),Me 1.47d,1.48d, H-2 8.89s	
10a[+]	(20%) Me 1.17d,H-2 8.20s	(A+C:80%),Me 1.41d(50%),1.43d(30%),H-2 8.74s(80%)	
10b[+]	(50%) Me 1.13d,H-2 8.16s	(A+B:50%) H-2 8.54s (50%)	
10c[x]	(38%) Me 1.12d,H-2 7.97s	(A+C:62%),Me 1.32d(25%),1.33d(37%),H-2 8.65s(25%)	8.68s(37%)

Solvent: [x]DMSO-d_6 , [+]$CDCl_3$

The data of the table indicate that the A⇌B⇌C equilibria is remarkably affected by strongly electron withdrawing groups (NO_2, CN:predominant enamine structure) and strongly electron releasing groups (OAc,$SCSNR^1R^2$, I : exclusive imine form with different cis/trans ratio). Compounds 10, however, are characteristic examples of the simultaneous existence of the cis and trans isomers and the enamine tautomer as well.

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10. 1a,b,c, were prepared by the bromination of the corresponding 3-substituted 4-oxo-6-methyl-6,7,8,9-tetrahydro[1,2-a] pyrimidine with equimolar Br_2 in AcOH+NaOAc at 25-30°C[2,3b]. Trans: cis ratio=4:1 2a mp: 220°C, Y: 52 %, 3a mp 152-154°C, Y: 56 %, 4a mp 250°C, Y: 46 %, 5 mp 240-242°C Y: 61 % 5b mp 216-218°C, Y: 40 %, 5c mp 228°C, Y: 62 %.

11. 6a mp 198-200°C, Y: 75 %, 6c mp 158-160°C, Y: 70 %, 7a mp 220°C, Y: 69 % 7b mp 158-160°C, Y: 49 %, 7c mp 156°C, Y: 66 %, 8a mp 182-183°C, Y: 85 %, 9a mp 204-206°C, Y: 75 %, 9c mp 160-164°C, Y: 81 %, 10a mp 151-153°C, Y: 75 %, 10b mp 150-151°C, Y: 61 % 10c mp 156-157°C, Y: 80 %.

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