

NITROGEN BRIDGEHEAD COMPOUNDS PART 59¹. NUCLEOPHILIC SUBSTITUTION
REACTIONS OF 9-BROMO-6,7,8,9-TETRAHYDRO-4H-PYRIDO[1,2-a]PYRIMIDIN-
4-ONES

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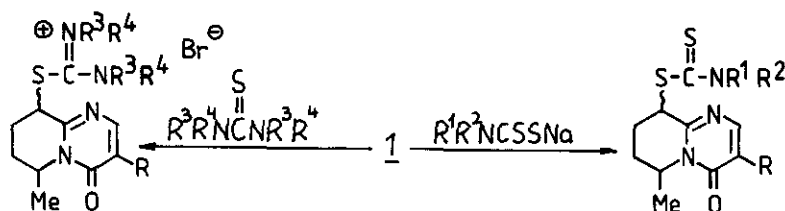
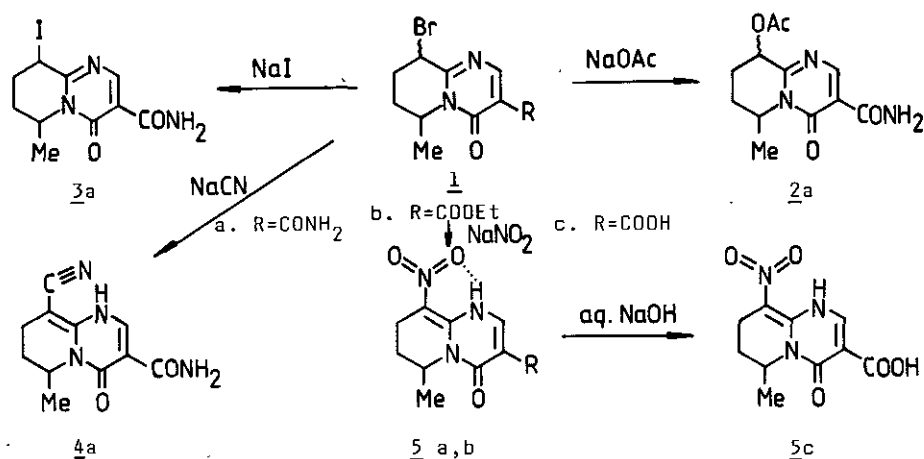
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Abstract - Halogen replacement of 9-bromo-6,7,8,9-tetrahydro-
4H-pyrido[1,2-a]pyrimidin-4-ones with C-, N-, O-, and S-nucleo-
philes can be readily accomplished.

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
aldehydes², halogen^{3a,b}, diazonium salts^{3c,4}, isocyanates⁵, iminium chlorides⁶
and nitrous acid⁷ on the activated piperidine ring⁸ and recently by nucleo-
philic 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) respectively¹¹ (Scheme 1).



8a $R^3, R^4 = H$

9a,c $R^3 = H, R^4 + R^4 = -CH_2CH_2-$

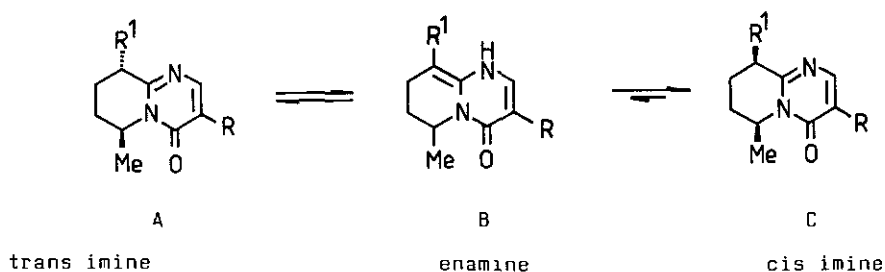
10a,b,c $R^3, R^4 = Me$

6a,c $R^1 + R^2 = (CH_2CH_2)_2O$

7a,b,c $R^1 + R^2 = (CH_2)_4$

Scheme 1.

Earlier we have described⁶ 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).



Scheme 2.

Enamine form (B) can be distinguished in ^1H 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-9_{eq} or H-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 $\text{R}^1=\text{CONR}_2$ 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 ^1H 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	
<u>1a</u> ^x	-	(82%), Me 1.28d	(18%), Me 1.42d
<u>2a</u> ⁺	-	(93%), H _{eq} -9 5.66t	(7%), Me 1.38d
<u>3a</u> ⁺	-	-	(100%), H _{ax} -9 3.80
<u>4a</u> ^x	(90%) Me 1.16d, NH 11.11	(A+B:10%), Me 1.21d	
<u>5a</u> ^x	(100%) Me 1.26d, NH 13.69s	-	-
<u>5b</u> ^x	(100%) Me 1.12d, NH 13.74s	-	-
<u>5c</u> ^x	(100%) Me 1.12d, NH 13.29	-	-
<u>6a</u> ⁺	-	A(50%), C(50%), Me 1.45d, 1.46d, H-2 8.88s	
<u>7a</u> ⁺	-	A(50%), C(50%), Me 1.47d, 1.48d, H-2 8.89s	
<u>10a</u> ⁺	(20%) Me 1.17d, H-2 8.20s	(A+C:80%), Me 1.41d(50%), 1.43d(30%), H-2 8.74s(80%)	
<u>10b</u> ⁺	(50%) Me 1.13d, H-2 8.16s	(A+B:50%)	H-2 8.54s (50%)
<u>10c</u> ^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: ^xDMSO-d₆, ⁺CDCl₃

The data of the table indicate that the $A \rightleftharpoons B \rightleftharpoons C$ 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 Br₂ 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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