Stereochemistry and ^{13}C NMR Investigation of 9-Halotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (1)

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It was shown that the halogen atom occupies the quasi-axial position in the predominant conformer of the 9-halo derivatives of tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. When R^3 = Me, the conformational equilibrium is determined by the latter substituent which is always quasi-axial. The effects of the methyl group and the halogen atoms on the ^{13}C chemical shifts (SCS values) were used for the identification of *cis* and *trans* isomers. Interesting non additivity of substituent effects was found in derivatives bearing quasi-axial substituents at C-6 and C-9: and this was caused by the ring flattening.

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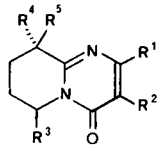
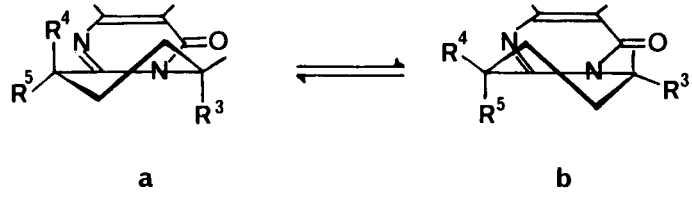
Previously we have reported on the halogenation at the C-9 atom of 6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones (2). The 9-halo derivatives are important starting materials for the synthesis of the antiallergic 9-amino- and 9-hydrazonopyridopyrimidines (3). In the present paper, the stereochemistry and ^{13}C nmr study of 9-halo derivatives **1-16** are described.

SCHEME 1



	R^1	R^2	R^3	R^4	R^5
1	H	COOH	H	H	H
2	H	COOH	Me	H	H
3	H	COOH	H	Cl	H
4	H	COOH	Me	Cl	H
5	H	COOH	Me	H	Cl
6	H	COOH	H	Br	H
7	H	COOH	Me	Br	H
8	H	COOH	Me	H	Br
9	Ph	Br	Me	Br	H
10	Ph	Br	Me	H	Br
11	H	COOH	H	Cl	Cl
12	H	COOH	Me	Cl	Cl
13	H	COOH	H	Br	Br
14	H	COOH	Me	Br	Br
15	H	COOH	Me	Br	Me
16	H	COOH	Me	Me	Br

The pyrimidine ring of 6,7,8,9-tetrahydropyrido[1,2-*a*]-pyrimidin-4-ones is nearly coplanar (4), while the fused tetrahydropyridine ring can exist in the form of two half-chair conformations **a** and **b**. These can be interconverted by ring inversion and this process requires a relatively small activation energy (5).



a **b**

Figure 1. Conformations of C—6 and C—9 substituted tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

When R^3 = Me and R^4 and R^5 are identical, the conformational equilibrium **a** ⇌ **b** is strongly shifted to the side of **a** as supported by the small coupling constants $J_{H\text{-}6,H_e\text{-}7} \sim J_{H\text{-}6,H_a\text{-}7}$ appearing in the ^1H nmr spectra (2,5). Namely, the conformer **b** is very unfavourable because of the *peri* effect and the allylic strain occurring as a consequence of the quasi-equatorial position of the Me-6 group (5,6).

Further support for determination of steric position of the Me-6 group was obtained from the ^{13}C nmr studies. The ^{13}C chemical shifts of compounds **1-16** and the assignments are given in Table 1.

The assignment of the signals appearing with identical multiplicity in the off-resonance spectrum are based on the assignment of the starting materials of the halogena-

Table 1

^{13}C Chemical Shifts (δ TMS = 0) of Compounds **1-16** in Deuteriochloroform

C	2	3	4	6	7	8	9	9a	COOH	Me-6
1	159.0	111.4	164.4 (a)	43.9	21.3	18.5	32.3	164.2 (a)	165.0	—
2	156.8	110.0	163.3	49.0	27.2	14.3	31.4	162.2	162.4	18.8
3	158.9	113.0	163.9	43.6	16.4	27.7	54.5	161.0	163.3	—
4	158.8	113.2	163.7	50.3	22.7	24.1	55.1	161.0	163.5	19.1
5	158.5	113.2	163.9	50.5	26.4	25.7	54.5	161.8	163.5	20.0
6	158.8	112.5	164.2	43.6	17.2	27.9	44.5	162.0	163.5	—
7	158.7	112.7	163.5	50.1	23.3	24.4	45.3	161.8	163.5	19.6
8	158.7	112.7	163.5	50.4	26.6	26.8	43.4	161.8	163.5	19.6
9 (b)	154.3	110.0	159.3	49.5	23.5	25.0	46.2	158.5	—	19.4
10 (b)	155.0	110.0	159.1	50.0	26.6	27.3	44.6	158.8	—	19.9
11	158.6	113.4	163.5	44.6	18.7	41.7	81.5	160.3	162.9	—
12	158.2	113.5	163.0	50.7	25.1	38.0	81.5	160.1	162.9	18.9
13	158.7	112.7	163.2	44.1	19.3	44.8	55.0	161.4	162.9	—
14	158.7	113.2	162.9	50.6	26.3	40.7	55.1	161.2	163.0	19.3
15 (c)	158.5	112.4	163.7	50.3	24.9	33.4	59.7	164.2	163.6	19.8
16 (d)	158.3	112.4	163.7	51.1	26.9	35.3	57.5	164.2	163.6	17.7

(a) Values may be interchanged pairwise. (b) Ph-2 137.0, 129.0, 129.6, 127.8. (c) Me-9 31.3. (d) Me-9 32.3.

Table 2

SCS of Me-C(6) Substituents in Compounds **2, 4, 7, 12** and **14** (a)

	α	β	γ gauche	δ
2 (1)	5.1	5.9	−4.2	−0.9
4 (3)	6.7	6.3	−3.6	0.6
7 (6)	6.5	6.1	−3.5	0.8
12 (11)	6.1	6.4	−3.7	0.0
14 (13)	6.5	7.0	−4.1	0.1

(a) In ppm; positive values correspond to downfield and negative upfield SCS.

tion described previously (5), in addition to known additivity rules (7).

The characteristic α, β, γ and δ substituent effects (SCS) of the Me-6 group were determined by comparison of the pairs of C-6, C-7, C-8 and C-9 chemical shifts of the individual R^3 = H (**1, 3, 6, 11** and **13**) as well as R^3 = Me (**2, 4, 7, 12** and **14**) derivatives. These data are summarized in Table 2. For a better survey, the serial numbers of both compounds used for calculation of the SCS values are given in the first column of the Table 2.

It can be seen from Table 2 that an upfield shift of about 4 ppm appears at the C-8 signal caused by the Me-6 substituent, proving its quasi-axial position in the above compounds, *i.e.* the conformer **a** is predominant.

When the substituent at the C-9 atom is quasi-axial, than an unfavourable γ_{gauche} steric interaction occurs with the 7-methylene group, while a similarly unfavourable allylic strain appears with the C=N bond when this substituent is in quasi-equatorial position (6,8). We have previously found with analogous C-9-carbamoyl derivatives that the quasi-equatorial arrangement is favoured (6). The ^1H nmr studies indicated however, that the halogen atom in the 9-halo derivatives **3** and **6** occupied a quasi-axial position (2). All these become understandable when considering that the quasi-equatorial position of the 9-halogen atom is further destabilized by the unfavourable dipole-dipole interaction between the 9-halogen and C=N bonds in contrast to a favourable orbital interaction occurs when the halogen is axial (2,9,10).

Table 3

SCS of Hal-C(9) Substituents in **3-8, 11-14** (a)

ax-Hal		α	β	γ gauche	δ
Cl	**3 (1)**	22.2	9.8	−4.9	−0.3
Cl	**4 (2)**	23.7	9.8	−4.5	1.3
Cl	**12 (5)**	27.0	12.3	−1.3	0.2
Br	**6 (1)**	12.2	9.4	−4.1	−0.3
Br	**7 (2)**	13.9	10.1	−3.9	1.1
Br	**14 (8)**	11.7	13.9	−0.3	0.2
eq-Hal				γ anti	
Cl	**5 (2)**	23.1	11.4	−0.8	1.5
Br	**8 (2)**	12.0	12.5	−0.6	1.4
Cl	**11 (3)**	27.0	14.0	2.3	1.0
Cl	**12 (4)**	26.4	13.9	2.4	0.4
Br	**13 (6)**	10.5	16.9	2.1	0.5
Br	**14 (7)**	9.8	16.3	3.0	0.5

(a) In ppm; positive values correspond to downfield and negative to upfield SCS.

If R^3 = Me and only one of R^4 or R^5 substituents is halogen, *e.g.* in compounds **4, 5, 7, 8, 9** and **10**, then *cis* and *trans* isomers appear. It has previously been indicated

that the conformational equilibrium **a** ⇌ **b** is substantially determined by the Me-6 substituent thus, the elucidation of isomerism is limited to the determination of the steric position of the 9-substituent. When C-9 is monosubstituted, the chemical shift and multiplicity of signal H-9 make possible an unambiguous differentiation between the isomers (2). This is not possible, however, with the isomeric pairs of **15** and **16**. The ^{13}C nmr studies afforded the opportunity of determining the structures in this case too. Comparing the chemical shifts of the appropriate isomeric pairs, it turns out that the chemical shifts of C-9 are smaller in all *cis* isomers, while those of C-8 and C-7 are always smaller in the *trans* isomers. The signals of C-7 show the most significant differences which are due to the difference of γ_{gauche} and γ_{anti} effects of the halogen substituents (11-13). The substituent effects of the halogen atom (SCS values) on the C-9, C-8, C-7 and C-6 signals are summarized in Table 3.

The diamagnetic shifts of 4-5 ppm, found at the C-7 signals of compounds **3, 4, 6** and **7** prove that the halogen atom is quasi-axial. In case of **5** and **8** small upfield shifts of 0.8 and 0.6 ppm at the C-7 signal were observed corresponding to a γ_{anti} effect that means the halogen atom is quasi-equatorial. Consequently in the *trans/cis* isomeric pairs of **9** and **10** the bromine atom is quasi-axial in the former isomer, while it is quasi-equatorial in the latter one.

It is known that the presence of 1,3-diaxial hydrogen atoms at C-α and C-γ has a shielding effect. When the hydrogen atom attached to the C-α carbon atom is replaced by another atom or group, then a 2-5 ppm paramagnetic alteration of the γ_{anti} effect of the hetero substituents occurs (13,14). In full agreement with these facts, about 3 ppm paramagnetic alteration of the γ_{anti} effect of Cl and Br atoms was observed in the derivatives **11-14** disubstituted at C-9, as compared to the monosubstituted compounds **5-8**. The study of the chemical shift and multiplicity of the H-9 signal, which had previously (2) been proved very suitable for identification of the structure of the isomers **15** and **16**, could not of course be used. Neither the ^1H chemical shifts of the Me-9 signals gave possibility for the elucidation of the above problem, being proved to be nearly identical (δ = 2.33 and 2.26, respectively). The difference is similarly small in the appropriate ^{13}C chemical shifts (δ = 31.3 and 32.3, respectively) which can be explained with a γ_{gauche} steric interaction between the 7-methylene group and the Me-9 group if it is quasi-axial, and with the N-1 atom when this group is quasi-equatorial. Consequently, the general experience, that $\delta_{Me\text{-}ax} < \delta_{Me\text{-}eq}$, could not be used. After all, the problem could be solved by considering the γ_{anti} effects of the Br atom and the Me group.

The γ_{gauche} effects of the Br atom and Me group were found to be nearly identical (see Table 2 and 3, respectively) thus it could be expected that the difference in the C-7 chemical shifts of compounds **15** and **16**, respectively, arose from the different γ_{anti} effects of the above substituents. For estimation of these effects, the values found in 2-bromo-2-methyladamantene were accepted *i.e.* +2.9 ppm γ_{anti} effect for the Me group and +4.5 ppm for the Br atom (15). According to these data, the chemical shifts of C-7 is higher in that 6-methyl-9-bromotetrahydropyrimidine where the Br atom is quasi-equatorial and the Me group is quasi-axial **16**.

Table 4

Differences (Δ) of SCS of Quasi-axial Hal-C(9) Substituents (a)

ax-Hal		Δα	Δβ	Δγ	Δδ
Cl	**3 (4)**	1.5	0.0	0.4	1.6
Br	**6 (7)**	1.7	0.7	0.2	1.4
Cl	**4 (12)**	3.3	2.5	3.2	−1.1
Br	**7 (14)**	−2.2	3.8	3.6	−0.9

(a) Positive values correspond a paramagnetic and negative values a diamagnetic alteration of SCS.

Characteristic differences appear in the substituent effects of the quasi-axial 9-halogen atom, depending on the number of substituents on the tetrahydropyridine ring. Table 4 shows the alterations of the α, β, γ and δ SCS values of Cl and Br atoms, caused by the R^3 = H → Me replacement. It is obvious from these data that the alteration, *i.e.* the non additivity at the disubstituted derivatives **4** and **7** is most pronounced on the signal of atoms bearing the substituent.

In the case of both di- or trisubstituted compounds **12** and **14** a reduced upfield shift of the γ_{gauche} effect of the quasi-axial halogen atom was observed. At compounds **12** and **14** the γ_{gauche} effects were found to be only −1.4 and −0.3 ppm, respectively. The effect of the Me group causing diamagnetic shift at C-8 similarly decreases with a quasi-axial halogen atom is attached to the C-9 atom. In our opinion, these phenomena are due to the deformation of the tetrahydropyridine ring bearing two substituents in axial position. By ring flattening it can achieve a more favourable steric arrangement resulting in the outward turning of the substituents. This explanation is further supported by the systematic differences found at the Me-6 signals in the ^1H nmr spectra, namely the chemical shifts are always higher in the *trans* isomers. The chemical shifts measured are as follows: **4** 1.43/**5** 1.57; **7** 1.42/**8** 1.62; **9** 1.37/**10** 1.58 as well as **15** 1.41/**16** 1.59. A study of the molecular model showed that, on outward displacement, the Me-6 group reached such a position relative to C(4)=O carbonyl group that its diamagentic effect became even more pronounced. An analogous phenomenon was observed at the appropriate 9-carbamoyl derivatives (6). This led to the conclusion that the deformation caused by

similar type of diaxial substitution in the piperidine ring of tetrahydropyridopyrimidines can be regarded a general phenomenon.

EXPERIMENTAL

The ^{13}C nmr spectra were recorded in deuteriochloroform in the FT mode (16 K data points for the FID) at ambient temperature with internal deuterium lock using a JEOL FX-100 spectrometer (25 MHz). The chemical shifts were determined on δ-scale using tetramethylsilane (δ_{TMS} = 0 ppm) as internal standard. They can be reproduced in repeated experiments within an error limit of 0.1 ppm. Typical acquisition parameters were as follows: pulse width 12 μseconds (tip angle 30°), repetition time 1.5 seconds, spectral width 5000 Hz.

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