Nitrogen Bridgehead Compounds. Part X (1). ^1H and ^{13}C Nmr Study of Pyrido[1,2-*a*]pyrimidines

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By ^1H nmr, the predominance of the conformer with a quasi-axial 6-methyl group was established for the pyrido[1,2-*a*]pyrimidines I-III. The ^{13}C nmr spectra of I-III were completely assigned. The conjugative effect of substitution at C-3 on ^1H and ^{13}C chemical shifts of the C-9 methylene group parallels its effect on reactivity.

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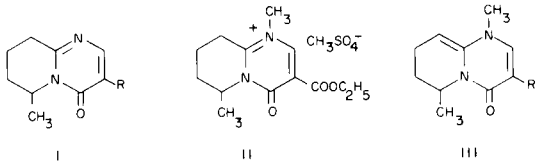
In recent years we prepared several pyrido[1,2-*a*]pyrimidines (2-6), and studied in detail their reactivity (2-6) and pharmacological activity (8-10). Some representatives were subjected to quantum chemical (11,12), x-ray (13-17), uv (18), ir (19), ms (20,21) and chromatographic (22) investigations. In this paper the ^1H and ^{13}C nmr spectra and the conformation of three types (I-III) of pyrido[1,2-*a*]pyrimidines are discussed, of which II is a potent analgesic (Rimazolium); IIIg is its active metabolite.



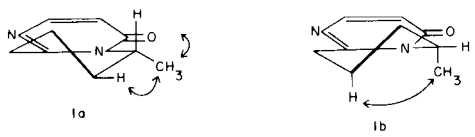
I II III

R

a: H
b: CH_3
c: $CH_2COOC_2H_5$
d: C_6H_5
e: CN
f: $CONH_2$
g: COOH
h: $COOC_2H_5$

Conformation.

It was demonstrated by X-ray diffraction (13-17) that in pyridopyrimidines of types I-III, the pyrimidine ring is nearly planar, whereas the tetrahydropyridine ring assumes a pair of half-chair conformations (**1a** and **1b**)



1a 1b

which interconvert by ring inversion. If the tetrahydropyridine ring is unsubstituted, ring inversion is fast at room temperature. The same was found with some tricyclic analogues, in which the fast inversion of the tetrahydropyrimidine ring entails an approximate averaging of quasi-axial and quasi-equatorial methylene protons (23). Accordingly, conformers **1a** and **1b** can also be expected to be analogous to the 6-methyl analogues I-III. However, due to different energy contents, conformer populations should be different. In **1a** the C(6)-methyl and carbonyl groups are almost co-planar, thus involving an unfavourable interaction, *i.e.*, A 1,3-type allylic strain (24,25). *peri*-Interaction between the C(7)-hydrogen (equatorial) and the methyl group (equatorial) is also unfavourable, although less so. In similar molecules such strains were estimated (26) to amount to 7.7 and 1 kcal. mole^{-1}, respectively. No such interactions are associated with conformer **1b**, but this involves a 1,3-diaxial methyl-hydrogen interaction.

Investigating a series of cyclic amides containing a similar moiety, Nagarajan, *et al.*, demonstrated that the dominant conformer is the one containing an axial methyl group, *i.e.*, the steric interaction between the quasi-equatorial methyl group with the oxygen atom of a neighbouring amide group is very unfavourable (26-30).

An X-ray analysis of Ih, II, and IIIg, carried out in parallel (13-17), showed that in the solid phase the C(6)-methyl group is disposed quasiaxially. Since this finding has no direct relevance to the conformational situation in solution, the ^1H nmr spectra of I-III at 100 MHz in deuteriochloroform (*cf.* Table 1) were examined. A characteristic feature of the rather similar spectra is the high shift of the multiplet representing C(6)-H. Common to the spectra of Ia-h are the essentially identical shifts for C(7)-H_2 and C(8)-H_2, whereas compared with the situation in Ia-d, C(9)-H_2 is shifted downfield by 0.1-0.2 ppm in the derivatives Ie-h having a carboxyl function at C(3). This observation is in agreement with our previous findings which show that electrophilic substitutions can be done, *i.e.* with bromine (2,3), at position 9 of the tetrahydropyridopyrimidines. It should be noted, however,

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Table 1

^{1}H Chemical Shifts (Intensity)

Compound No.	CH_3-C(6)	H-C(6)	H_2-C(7,8)	H_2-C(9)	H-C(2)	R-C(3)	δ TMS = 0 ppm NCH_3	$CH_3SO_4^-$
Ia	1.41 (3)	4.96 (1)	1.85-2.25 (4)	3.00 (2)	7.76 (1)	6.28 (1)		
Ib	1.39 (3)	4.93 (1)	1.85-2.25 (4)	2.97 (2)	7.63 (1)	2.06 (3)		
Ic	1.41 (3)	4.98 (1)	1.85-2.25 (4)	3.00 (2)	7.72 (1)	1.33 (2), 4.23 (2), 3.51 (2)		
Id	1.39 (3)	4.99 (1)	1.75-2.25 (4)	2.97 (2)	7.94 (3)	7.20-7.45 (3), 7.55-7.70 (2)		
Ie	1.44 (3)	4.93 (1)	1.85-2.25 (4)	3.13 (2)	8.23 (1)			
If	1.44 (3)	5.02 (1)	1.85-2.25 (4)	3.10 (2)	8.78 (1)	6.48 (1), 8.80 (1)		
Ig	1.50 (3)	5.03 (1)	1.85-2.25 (4)	3.20 (2)	8.66 (1)	12.4 (1)		
Ih	1.43 (3)	5.05 (1)	1.85-2.25 (4)	3.10 (2)	8.46 (1)	1.43 (3), 4.40 (2)		
II	1.43 (3)	4.98 (1)	1.85-2.25 (4)	3.35 (2)	8.30 (1)	1.40 (3), 4.37 (2)	3.91 (3), 3.46 (3)	
IIIf	1.37 (3)	5.01 (1)	1.55-1.90 (2) 2.05-2.40 (2)	4.08 (1)	7.96 (1)	5.95 (1), 8.67 (1)	3.43 (3)	
IIIg	1.33 (3)	4.97 (1)	1.55-1.95 (2) 2.10-2.45 (2)	4.34 (1)	8.00 (1)	13.28 (1)	3.32 (3)	

that the inaccuracy associated with the determination of the chemical shift of this methylene group (given in Table 1 as the center of the unresolved multiplet of about 30 Hz width) as well as the small variation of the chemical shifts does not permit a prediction of the reactivity of the C(9) methylene group on the basis of its chemical shift.

In case of the derivatives If and IIIf, which contain an amide group at C(3), an intramolecular hydrogen bond is established between the C(4)=O group and one of the amide-NH groups. As a consequence, the chemical shift of the chelated NH is 2.3 and 2.7 ppm higher, compared with the other amide-NH.

The signals for C(9)-H in the spectrum of IIIf and IIIg appear, as expected (31), at relatively high field at 4.08 and 4.32 ppm, respectively. This effect is due to conjugation with N(1) and N(5) associated with the C(9)-C(10) double bond. The signals appear as a doublet of doublets (couplings with C(8)-methylene protons, 5 and 3 Hz).

The conformations **Ia** and **Ib** for compounds I-III were also supported by double resonance experiments. The signal multiplet for C(6)-H, coming, as already mentioned, at relatively low field, collapses to a triplet on irradiation of the adjacent methyl group. The value of the coupling constants ($J_{6e,7e} = J_{6e,7a} = 3$ Hz) indicates the quasi-equatorial orientation of C(6)-H, placing the methyl group in the quasi-axial position. This means that in solution, conformer **Ib** predominates and considering the anisotropic effect of the neighbouring C(4)=O group (32), this also qives a rationale for the relatively high and low shifts for C(6)-H (equatorial) and C(6)-CH_3 (axial), respectively. This is true since the above mentioned proton falls into the deshielding region of the shielding cone of the carbonyl group, while the methyl group is reaching into the region causing an upfield shift. A similar phenomenon was described by Bohlmann, *et al.* (33), in a report on *Lupinus* alkaloids which contain a similar moiety. In the case of II, IIIf and IIIg, $J_{6e,7e}$ and $J_{6e,7a}$ was found also to be 3 Hz, *i.e.* neither quaternerization nor the introduction of an additional sp^2 carbon atom by means of the C(9)-C(10) double bond brought about a change in conformation.

^{13}C Nmr Studies.

^{13}C Nmr signals of compounds I-III were assigned by taking both noise decoupled and off-resonance spectra. Known additivity rules and correlation tables (31) permitted the unambiguous assignment of all signals except for the closely spaced signals representing the pairs C(4), C(10), and C(7), C(9), *cf.*, Table 2. In order to be able to assign the signals for C(4) and C(10), the proton-coupled spectrum of Ia was recorded. Results of Vögeli, *et al.*, with compounds containing a similar conjugated lactam moiety (34) suggested a vicinal coupling constant of 10-12 Hz between C(4) and C(2)-H, whereas coupling to C(6)-H was expected to be 2-4 Hz. Geminal coupling between C(4) and C(3)-H may be smaller ($\leq$ 1.5 Hz) (34). Accordingly, the C(4) signal should be a doublet of a doublet, while C(10) is expected to give a complex multiplet due to vicinal coupling with four protons [C(2)-H, C(6)-H, C(8)-H (axial) and C(8)-H (equatorial)] and geminal coupling to the C(9)-methylene protons. In the proton coupled spectrum of Ia, signals at 161.5 and 159.9 ppm must represent C(4) and C(10). Of these, the first is in fact a doublet of doublets ($^3J_{C(4)\text{-}H,C)2} = 11.0$ and $^3J_{C(4)\text{-}H,C(6)} = 2.5$ Hz) and must be assigned therefore to C(4) (*cf.* Table 3). Geminal coupling with C(3)-H ($\leq$ 1.5 Hz) only causes line broadening. The other signal (at 159.9 ppm) is a broad mulitplet showing that it originates from C(10).

Selective decoupling aided the assignment of the signals for C(7) and C(9). As pointed out before (*cf.* Table 1) the signal for the C(9) methylene protons appear

Table 2

^{13}C Chemical Shifts

	Ia	Ib	Ic	Id	Ie	If	Ig	Ih	II	IIIf	IIIg
									δ TMS = 0 ppm		
C(2)	152.2	149.3	149.0	148.0	157.5	157.4	156.8	157.6	151.1	150.9	152.4
C(3)	112.3	121.2	117.1	122.2	112.9	114.2	110.0	113.8	113.6	96.8	92.8
C(4)	161.5	162.6	159.6	158.7	163.5	164.0	163.3	164.0 (a)	160.9	160.5	162.9
C(6)	47.4	47.6	47.2	48.5	48.7	48.0	49.3	48.0	43.3	44.2	44.9
C(7)	27.9	28.3	27.7	27.7	27.2	27.8	27.2	27.9	25.7	24.9	24.6
C(8)	15.3	15.3	15.0	14.9	14.5	14.7	14.3	14.8	13.2	17.2	17.1
C(9)	31.1	30.9	30.7	30.7	31.3	31.4	31.4	31.5	28.3	81.3	85.0
C(10)	159.9	157.2	156.7	156.7	156.8	161.5	162.2 (a)	158.2	154.4	136.4	135.3
CH_3-C(6)	19.0	19.2	18.8	18.8	18.6	19.0	18.8	19.0	18.2	16.0	16.0
R-C(3)		13.4	32.8	132.4	98.3	165.7	162.4 (a)	164.5 (a)	168.0	166.5	165.0
			168.5	126.8				60.8	62.2		
			60.2	126.6				14.3	14.1		
			14.3	126.2							
NCH_3									51.6 (a)	40.3	40.9
CH_3SO_4									54.0 (a)		

(a) The assignments may be reversed.

Table 3

^1H-^{13}C Coupling Constants in Hz for Ia

^1J	C(2), H	C(3), H	C(6), H	C(7), H	C(8), H	C(9), H
	177.0	169.1	145.3	129.4	129.4	127.0
^2J	C(4), C(3)-H					
	≤ 1.5					
^3J	C(4), C(2)-H					
	2.4					

separately at 3.00 ppm. On irradiating these protons, the triplet at 31.1 ppm in the ^{13}C spectrum became a singlet, whereas the multiplicity of the signal at 27.9 ppm did not change, indicating that the lower field signal can be associated with C(9). Comparing the spectra of Ia-d with those of Ie-h, a small but significant increase of chemical shift can be observed with the compounds with an acid function at C(3). This also indicates that owing to extended conjugation substitution at C(3) has an influence on the charge density and by this on the reactivity at C(9).

EXPERIMENTAL

^1H nmr spectra were recorded on a Jeol-Ps-100 spectrometer in CW mode. The ^{13}C nmr spectra were obtained at natural abundance in the pulsed Fourier transform mode at 22.63 MHz using a Bruker WH-90 spectrometer. The proton-coupled spectrum of Ia was recorded on a Jeol-FX-100 spectrometer at 25.1 MHz. The samples were run at a concentration of about 0.5-1.0*M* in deuteriochloroform with tetramethylsilane as internal standard. The accuracy of the chemical shifts is about ± 0.05 ppm. The assignment of the signals were supported with spectra obtained under ^1H off-resonance irradiation conditions.

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