Nitrogen Bridgehead Compounds, Part 31 (1). ^{1}H and ^{13}C NMR Study of Tetra- and Octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones

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Conformational analysis of some tetra- and octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones **1-3** by ^{1}H and ^{13}C nmr revealed that the 9-methyl-6,7,8,9-tetrahydro derivative exists mainly in the conformation containing the methyl group in a quasi-axial orientation. Of the 1,2,3,4,5,6,7,8-octahydro compounds, the 9-methyl derivative **3e** contains the methyl group in a guasi-axial position, while that in the 7-methyl and the 8-methyl derivatives **3c,d** is in the equatorial position, and the 6-methyl derivative **3b** is a mixture of the two conformers.

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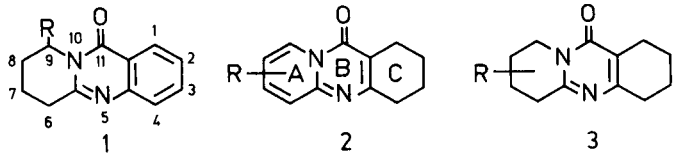
11*H*-Pyrido[2,1-*b*]quinazolin-11-ones have recently acquired much interest as antiallergic compounds (2). Their derivatives saturated in the **A** ring, **1** and **3**, are convenient intermediates for rutecarpine alkaloids (3). Compound **1a** is a natural product, a constituent of the *Mackinlaya* species (4).

In the present paper we report a ^{1}H and ^{13}C nmr investigation of the 6,7,8,9-tetrahydro- and 1,2,3,4-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones, compounds **1a,e** and **2a-e**, and respectively, and the 1,2,3,4,5,6,7,8-octahydro derivatives **3a-e**.



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Synthesis of the 11*H*-pyrido[2,1-*b*]quinazolin-11-ones **1-3**.

Compounds **1a** (4,5), **2a,e** (6) and **3a,e** (6) were prepared by the previously reported routes.

Compound **1e** was obtained by the reaction of anthranilic acid and 6-methoxy-3,4,5,6-tetrahydropyridine in benz-

Table 1

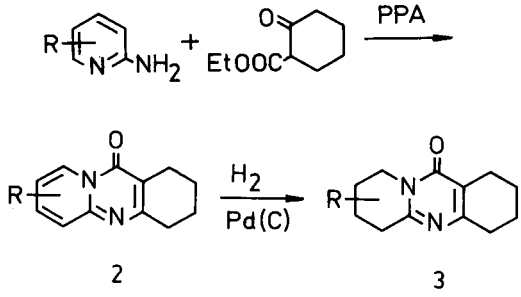
Melting Points, Yields and Analytical Data for Compounds **1e**, **2b-d** and **3d-b**.

Compound No.	Position of Methyl	Mp °C	Yield %	Molecular Formula	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1e	9	117-118	73	$C_{13}H_{14}N_2O$	72.87	6.59	13.07	73.01	6.50	13.20
		265 dec		$C_{13}H_{14}N_2O\cdot HCl$	62.28	6.03	11.17	62.15	5.95	11.42
2b	6	105-106	50	$C_{13}H_{14}N_2O$	72.87	6.59	13.07	72.92	6.32	12.91
		214-215		$C_{13}H_{14}N_2O\cdot HCl$	62.28	6.03	11.17	62.44	6.11	11.18
2c	7	90-92	50	$C_{13}H_{14}N_2O$	72.87	6.59	13.07	72.68	6.70	13.21
		240		$C_{13}H_{14}N_2O\cdot HCl$	62.28	6.03	11.17	62.29	6.00	11.20
2d	8	118	67	$C_{13}H_{14}N_2O$	72.87	6.59	13.07	73.17	6.82	13.15
		240		$C_{13}H_{14}N_2O\cdot HCl$	62.28	6.03	11.17	62.51	6.18	11.08
3b	6	100-101	85	$C_{13}H_{18}N_2O$	71.53	8.31	12.83	71.25	8.03	12.80
3c	7	108-109	98	$C_{13}H_{18}N_2O$	71.53	8.31	12.83	71.28	8.45	12.66
3d	8	116-117	87	$C_{13}H_{18}N_2O$	71.53	8.31	12.83	71.37	8.30	12.88

Table 2

^{1}H Chemical Shifts (Intensity) and Coupling Constants (Hz) of 11*H*-Pyrido[2,1-*b*]quinazolin-11-ones (**1-3**) in Deuteriochloroform δ_{TMS} = 0 ppm

Compound	R	H-1	H-2,3 and 4	H-6	H-7	H-8	H-9	Me
1a	H	8.25 d (1) $J_{1,2}$ = 7.7	7.20-7.90 m (3)	3.00 t (2) $J_{6,7}$ = 6.8	1.70-2.25 m (4)		4.08 t (2) $J_{8,9}$ = 7.0	—
1e	9-Me	8.25 d (1) $J_{1,2}$ = 7.7	7.25-7.85 m (3)	2.85-3.20 m (2)	1.75-2.30 m (4)		5.11 m (1) $J_{8,9}$ = 3.0 $J_{H9,Me}$ = 6.7	1.39 d (3)
		H-1 and H-4	H-2 and H-3					
2a	H	2.40-3.05 m (4)	1.60-2.10 m (4)	7.55 AB q (2) $J_{6,7}$ = 9.0; $^4J_{6,8}$ = 2.4; $^5J_{6,9}$ = 1.3;		7.02 ddd (1) $J_{7,8}$ = 6.0; $^4J_{7,9}$ = 1.3;	8.95 dt (1) $J_{8,9}$ = 7.3	—
2b	6-Me	2.55-3.00 m (4)	1.60-2.05 m (4)	—	7.40 dd (1) $J_{7,8}$= 7.0;	6.90 t (1) $^4J_{7,9}$ = 1.0;	8.82 dd (1) $J_{8,9}$ = 7.0	2.50 s (3)
2c	7-Me	2.50-3.00 m (4)	1.55-2.05 m (4)	7.26 m (1) $^4J_{6,8}$ = 1.9;	—	6.83 dd (1) $J_{8,9}$ = 7.5;	8.87 d (1) $^4J_{6,Me}$ = 0.8	2.40 d (3)
2d	8-Me	2.50-3.00 m (4)	1.60-2.05 m (4)	7.45 d (2) $^5J_{6,9}$ = 1.3;		$^4J_{7,9}$ = 1.3;	8.75 sx (1) $^4J_{9,Me}$ = 1.3	2.42 d (3)
2e	9-Me	2.40-2.90 m (4)	1.55-2.00 m (4)	7.30 AB q (2) $J_{6,7}$ = 8.5;		6.60 ddd (1) $J_{7,8}$ = 5.2; $^4J_{6,8}$ = 3.0;	— $^4J_{8,Me}$ = 0.7	3.05 d (3)
3a	H	2.30-2.80 m (4)	1.60-2.00 m (4)	2.90 t (2)	1.80-2.20 m (4) $J_{6,7}$ = 6.0; $J_{8,9}$ = 6.1		3.98 t (2)	—
3b	6-Me	2.30-2.75 m (4)	1.60-2.00 m (4)	2.88 sx (1)	1.80-2.25 m (4) $J_{6,Me}$ = $J_{6,7a}$ = $J_{6,7e}$ = 6.9		3.60-4.25 m (2)	1.39 d (3)
3c	7-Me	2.30-2.75 m (4)	1.60-2.00 m (4)	eq 3.00 ddd (1) ax 2.60 ddd (1)	1.40-2.30 m (3)		eq 4.25 ddd (1) ax 3.67 ddd (1)	1.13 d (3)
	$J_{6e,6a}$ = 17.2;	$J_{6e,7a}$ = 4.8;	$J_{8e,9a}$ = 5.2;	$J_{8a,9a}$ = 10.6	$J_{8a,9e}$ = 5.6;	$J_{8e,9e}$ = 3.7;	$J_{9e,9a}$ = 14.6;	$J_{7a,Me}$ = 6.4
3d	8-Me	2.30-2.75 m (4)	1.60-2.00 m (4)	2.75-3.10 m (2) $J_{8a,9e}$ = 4.8;	1.75-2.25 m (3) $J_{8a,9a}$ = 9.8;		eq 4.34 dd (1) ax 3.19 dd (1) $J_{9e,9a}$ = 14.3; $J_{8a,Me}$ = 6.4	1.16 d (3)
3e	9-Me	2.30-2.75 m (4)	1.60-2.00 m (4)	2.70-3.05 m (2)	1.75-2.10 m (4) $J_{8e,9e}$ = $J_{8a,9e}$ = 3.0;		eq 4.95 m (1) $J_{9e,Me}$ = 6.4	1.35 d (3)



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ene. Compounds **2b-d** were prepared by the condensation of 2-aminopyridines and ethyl 2-cyclohexanonecarboxylate in polyphosphoric acid, and compounds **3b-d** by the catalytic hydrogenation of compounds **2b-d** (see Table 1).

Conformational Analysis of the 11*H*-Pyrido[2,1-*b*]quinazolin-11-ones **1-3**.

The ^{1}H nmr data on compounds **1-3** are compiled in Table 2, and the ^{13}C nmr data in Table 3. Earlier work in this field covered only the ^{1}H nmr characteristics of **1a** (4,7) **2a** (6) and **3a** (6).

In compounds **1-3** the pyrimidine ring **B** must be planar, since it consists of four sp^2 hybridized C atoms and an amide group with a quasi-double bond. For the tetrahydro rings (**A** in 1; **C** in 2; **A** and **C** in **3**) the energetically favoured half-chair conformations must be considered.

The above structures were supported by X-ray analysis of the hydrobromide of **3a** (8) and of the tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidines (9). The latter are analogues of compounds **1-3** as concerns the structure of rings **A** and **B**. The sp^2 character of the bridgehead nitrogen atom in the tetrahydropyrido[1,2-*a*]pyrimidin-4-ones is supported by the pyramidality parameter of less then 3° (9).

The ^{1}H nmr spectra of compounds **2** and **3** exhibit time-averaged signals for the methylene protons of the **C** ring (1.55-2.10 ppm for the C(2)H$_2$ and C(3)H$_2$ protons; 2.30-3.05 for the C(1)H$_2$ and C(4)H$_2$ protons). This indicates that at room temperature the **C** ring undergoes fast interconversion between the two half-chair conformations.

In the spectra of the unsubstituted derivatives **1a** and

Table 3

^{13}Chemical Shifts of 11*H*-Pyrido[2,1-*b*]quinazolin-11-ones (**1-3**) Deuteriochloroform (δ = 0 ppm)

Compound	R	C-1 (a)	C-2 (a)	C-3 (a)	C-4	C-4a	C-5a	C-6	C-7	C-8	C-9	C-11	C-11a	Me
1a	H	133.9	126.4 (b)	126.3 (b)	125.8 (b)	147.3	154.7	31.9	19.3	22.0	42.2	161.8	120.3	—
1e	9-Me	134.0	126.6 (b)	126.2 (b)	125.8 (b)	147.3	154.3	31.4	15.5	28.3	47.5	161.7	120.6	19.3
2a	H	23.0	22.1	22.4	32.5	157.7	148.2	125.6	134.3	114.2	126.6 (c)	161.9	113.2	—
2b	6-Me	23.2	22.2	22.5	32.8	158.2	147.9	134.1	132.8	113.6	124.8	161.2	112.8	18.0
2c	7-Me	22.5	21.7	22.0	32.1	156.9	147.7	123.0	145.4	116.3	125.3 (c)	161.3	111.4	20.7
2d	8-Me	23.0	22.0	22.3	32.3	157.2	147.0	123.6	137.0	123.9	124.8	161.0	112.6	17.6
2e	9-Me	23.0	22.3	22.4	31.9	159.6	150.4	124.7	133.1	116.8	142.8	161.4	114.7	24.6
3a	H	22.4	22.1	22.4	31.4	158.5	155.5	31.4	19.8	22.0 (a)	42.3	162.2	118.2	—
3b	6-Me	22.3	21.7	22.3	31.3	158.4 (b)	158.8 (b)	34.5	27.4	19.8	42.1	162.1	117.7	19.3
3c	7-Me	21.9	21.6	21.9	30.9	157.9	154.9	39.2	25.6	29.7	41.8	161.6	117.7	20.7
3d	8-Me	22.2	21.9	22.2	31.3	158.3	155.0	31.0	28.0	27.5	48.6	161.9	117.9	18.9
3e	9-Me	22.3	22.0	22.3	31.4	158.4	155.0	30.8	15.4	28.2	47.2	161.7	118.4	19.1

(a) The assignments for **2** and **3** may be reversed. (b) The assignments may be reversed. (c) Supported by selective irradiation.

Table 4

Substituent Chemical Shift of Methyl Group in 11*H*-Pyrido[2,1-*b*]quinazolin-11-ones **1e** and **3b-e**

Compound	Position of Methyl Group	at C-6	at C-7	at C-8	at C-9
3b	6-Me	+3.1 (a)	+7.6 (b)	−2.2 (c)	−0.2 (d)
3c	7-Me	+7.8 (b)	+5.8 (a)	+7.7 (b)	−0.5 (c)
3d	8-Me	−0.4 (c)	+8.2 (b)	+5.5 (a)	+6.3 (d)
3e	9-Me	−0.6 (d)	−4.4 (c)	+6.2 (b)	+4.9 (a)
1e	9-Me	−0.5 (d)	−3.8 (c)	+6.3 (b)	+5.3 (a)

(a) α Effect. (b) β Effect. (c) γ Effect. (d) δ Effect.

3a a similar averaging of the methylene protons was observed for the **A** ring.

Introduction of a methyl substituent into position 7, 8 or 9 of the **A** ring resulted in the predominance of one of the two half-chair conformers.

In the 9-methyl substituted derivatives **1e** and **3e** the conformer containing the 9-Me group in the quasi-axial position becomes predominant, as a consequence of the allylic strain (10) arising between the methyl and the C(11)=O groups. The quasi-equatorial position of the 9-H proton is shown by its downfield shift, due to the anisotropic effect of the adjacent carbonyl group, and by its triplet splitting of 3 Hz in response to irradiation of the methyl group.

Further support for the quasi-axial disposition of the 9-methyl group was provided by the ^{13}C nmr spectra of **1e** and **3e**, where unfield shifts of about 4 ppm were found for the C(7) atom as compared with the unsubstituted derivatives **1a** and **3a**. Shifts of such an extent are in good agreement with the γ gauche effect of axial methyl groups (11).

In the 7-and 8-methyloctahydro derivatives **3c** and **3d** the conformer containing the equatorial methyl group predominates. Because of the overlapping of the 7-H, 8-H_2 and 6-H_{ax} signals in the 7-methyl compound **3c**, the coupling constants for H-7 could not be determined. In the 8-methyl derivative **3d** the value of the coupling constant of 8-H and 9-H_{ax} (9.8 Hz) suggested the antiperiplanar disposition of these protons and the equatorial orientiation of the methyl group. In the ^{13}C nmr spectra of compounds **3c,d** the C atoms the γ-position to the 7- or 8-methyl groups, C-9 and C-6, are shifted upfield by 0.4 and 0.5 ppm, respectively, indicating the equatorial position of the methyl groups.

A Dreiding model of the 6-methyl substituted compound **3b** shows that there is only a slight difference between the conformers containing the methyl group in a guasi-axial or in a guasi-equatorial orientation.

The intermediate values of the upfield shift of the C(8) atom, 2.2 ppm (see Table 4), and of the coupling constant, $J_{6H,7H}$ = 6.9 Hz, suggest that **3e** is a mixture of the two conformers.

EXPERIMENTAL

Melting points are uncorrected. The nmr spectra were recorded on a Brucker WP-80 Ft spectrometer in deuteriochloroform, with tetramethylsilane as internal standard. The ^{13}C nmr spectra were obtained with noise decoupling in saturated solution in 5 mm tubes at 20.115 MHz. The assignment of the signals was supported by [H^1] SFORD experiments.

6-Methyl-2-methoxy-3,4,5,6-tetrahydropyridine.

6-Methyl-2-oxo-3,4,5,6-tetrahydropyridine (50 mmoles) was reacted with dimethyl sulfate (50 mmoles) at 100° for 2.5 hours. After cooling to 20°, the reaction mixture was diluted with water (3 ml), and ether (20 ml) was added. The *p*H of the aqueous layer was adjusted to 8 with aqueous potassium hydroxide (60 mmoles in 8 ml water) under cooling. The phases were separated and the aqueous layer was extracted with ether (2

× 10 ml). The combined ethereal layers were dried (potassium hydroxide) and evaporated. The residue was distilled *in vacuo* (6 mm Hg) to yield 5.2 g (83%) of the imino ether bp $_6$ = 59-60°.

Anal. Calcd. for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 66.46; H, 10.20; N, 10.97%.

9-Methyl-6,7,8,9-tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-one (**1e**).

2-Methoxy-6-methyl-3,4,5,6-tetrahydropyridine (10 mmoles) was reacted with anthranilic acid (10 mmoles) in refluxing benzene (20 ml) for 3 hours. The solution was evaporated *in vacuo*, and the residue was dissolved in chloroform (12 ml). The chloroform solution was extracted with 3% sodium hydroxide (2 × 2 ml) and then with water (1 × 2 ml), dried sodium sulfate), evaporated and recrystallized from a mixture of acetone and benzene (see Table 1).

1,2,3,4-Tetrahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones (**2b-d**).

2-Aminopyridines (10 mmoles) and ethyl 2-cyclohexanone carboxylate (10 mmoles) were reacted in PPA (10 g, Fluka) at 110-112° for 2 hours. The reaction mixture was poured into water (50 ml) and the *p*H was adjusted to 7-8 with 10% sodium hydroxide. The aqueous phase was extracted with chloroform (3×50 ml). The combined organic layers were dried (sodium sulfate) and evaporated, the dark residue was dissolved in ethanol (5 ml) and the ethanolic solution was saturated with dry hydrogen chloride gas under cooling. The precipitated hydrochloride of the pyridoquinazoline **2b-d** was filtered off and recrystallized from ethanol. The base was liberated in the usual way and recrystallized from ethanol (see Table 1).

1,2,3,4,6,7,8,9-Octahydro-11*H*-pyrido[2,1-*b*]quinazolin-11-ones (**3b-d**).

Compounds **2b-d** (5 mmoles) were hydrogenated over a 10% Pd/C catalyst (0.5 g) in ethanol (25 ml). The catalyst was filtered off, the filtrate was evaporated and the residue was recrystallized from ethyl acetate (see Table 1).

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