Conformational Analysis of Stereoisomeric Dodecahydropyrido[2,1-*b*]-quinazolin-11-ones [1,2]

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The structures and conformations of dodecahydropyrido[2,1-*b*]quinazolin-11-one diastereoisomers, prepared from the corresponding decahydro-derivatives by hydrogenation, have been established by ^{13}C and ^{1}H n.m.r. spectroscopy. Evidence has been found that the situations of the hydrogen atoms attached to the angular C-4a, C-11a, and C-5a correspond to the α,β,α; α,α,α; and α,α,β configurations. In the *cis* α,α,α product the conformational equilibrium is shifted towards that conformer in which N-5 is axial with respect to ring *A*, whereas in the α,α,β product the C=O group assumes the axial position. The configuration of the lone pair of N-5 has been determined as well.

Significant pharmacological activity has been found in numerous compounds containing the pyrido[1,2-*a*]pyrimidin-4-one structural unit.[3] Thus, stereochemical investigation of these compounds has become of particular importance. We recently reported n.m.r. (^{1}H, ^{13}C, and ^{15}N) investigations of perhydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones,[2] and now describe ^{13}C and ^{1}H n.m.r. structural investigations of the tricyclic analogues, dodecahydropyrido[2,1-*b*]quinazolin-11-ones.

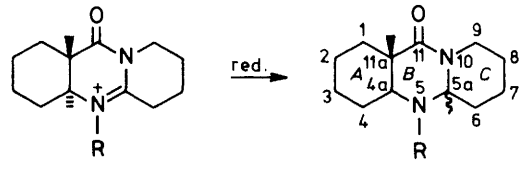
By studying the reduction of *trans*- (1) and *cis*-decahydropyrido[2,1-*b*]quinazolin-11-ones (2) and their quaternary salts (1a) and (2a) prepared with dimethyl sulphate, we have established that the formation of unsubstituted tricycles and 6-methylperhydropyrido[2,1-*b*]quinazolines is stereospecific for the *trans*- and stereoselective for the *cis*-derivatives.[1]

In the reduction of compounds (1) and (2), besides the two existing chiral centres C-4a and C-11a, a new one is formed at C-5a. Thus, in the case of dodecahydropyrido[2,1-*b*]quinazolin-11-ones one would in principle expect four diastereoisomers; despite this, only three have been found.[1] Although the compounds investigated by us were racemates, we show in the structural formulae only that enantiomer in which the configuration at C-4a is *S* (see Scheme and Figure 1). The configurations of the diastereoisomers are defined here by denoting the relative configurations at C-4a, C-11a, and C-5a (always in this order) by α and β. Compounds (3) and (7) can then be described as α,β,α; (4) and (8) as α,β,β; (5) and (9) as α,α,α; and (6) and (10) as α,α,β.

The stereostructures of the individual compounds and the conformers which can be interconverted by ring inversion of the *cis*-*A*/*B*-ring-fused derivatives are shown in Figure 1.

In consideration of the conformations, only the most stable chair conformations of the piperidine and cyclohexane rings were taken into account. In the pyrimidin-4-one ring the sofa conformation seems to be the preferred one, in which five atoms are nearly coplanar and only C-4a sticks out from the plane. In principle a twisted boat conformer is also possible, but this is less preferred owing to the eclipsed configuration. Nevertheless, its contribution to a sofa–boat equilibrium cannot be ruled out (Figure 2). It should be noted that in the α,β,α; α,α,α-1; and α,α,α-2 structures the boat conformation is not feasible, owing to the presence of adjoining rings.

Comparison of the *trans*-*A*/*B*-ring-fused α,β,α and α,β,β structures with Dreiding models indicates that no pronounced



	R	4a-H	11a-H	5a-H
(1)		α	β	
(1a)	Me	α	β	
(2)		α	α	
(2a)	Me	α	α	
(3)	H	α	β	α
(4)	H	α	β	β
(5)	H	α	α	α
(6)	H	α	α	β
(7)	Me	α	β	α
(8)	Me	α	β	β
(9)	Me	α	α	α
(10)	Me	α	α	β

Scheme

disadvantageous non-bonding interaction takes place. The α,β,β structure may have slightly higher energy, because 4a-H and 6-H_{ax} may be brought into close proximity. It is important that the reduction of (1) and (1a) yielded only one product in each case, revealed by *X*-ray diffraction to be α,β,α.[1]

It is a general experience with *cis*-*A*/*B*-ring-fused conformers that small heteroatoms, in our case N-5, prefer an *endo*-orientation, *i.e.* axial.[4] Thus, in compounds (2) and (5), our earlier ^{1}H n.m.r. measurements demonstrated that the conformational equilibrium α,α,α-1 ⇌ α,α,α-2 is shifted to-

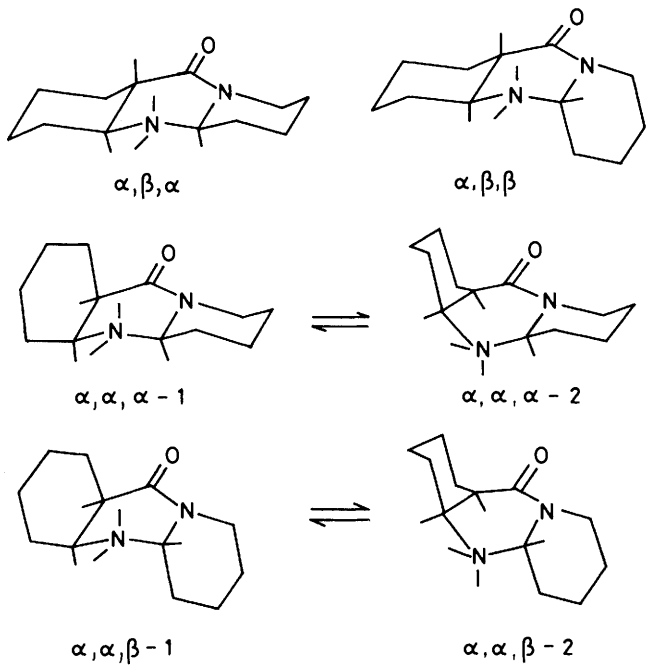


Figure 1. Stereostructures and conformations of dodecahydropyrido[2,1-*b*]quinazolin-11-ones

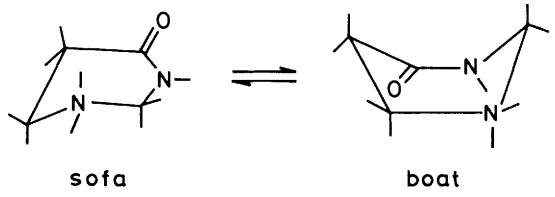


Figure 2. Conformations of the pyrimidinone ring in dodecahydropyrido[2,1-*b*]quinazolin-11-ones

wards the former conformers.[5] This was deduced from the fact that the 4a-H signal shows splittings of 3.5 and 4 Hz.[5] The ^{1}H n.m.r. spectra of the *N*-Me derivatives (7), (9), and (10) are even more complex than those of the corresponding *N*-H compounds; apart from the *N*-Me and 9-H_{eq} signals, only the 5a-H signal appears distinct from the skeleton-proton signals. The characteristic ^{1}H n.m.r. data are collected in Table 1.

The coupling constants measured for the 5a-H signal render it possible to investigate the sofa–boat conformational equilibrium of the pyrimidin-4-one ring. It is clear from molecular models that the torsion angles between the 5a-H and the C-6 methylene protons in the boat conformers are 30 and 150°, respectively. The measured coupling constants of 2.5 and *ca.* 10 Hz rule out this conformer, but they fit in well with the angles of *ca.* 60 and 180° in the sofa conformer.

In the six-membered ring the inversion of the nitrogen atom requires only a low activation energy.[6] Accordingly, in our investigations at room temperature it was necessary in all cases to consider or to investigate whether the preferred position of the substituent R on N-5 is axial or equatorial. Whereas the equatorial position has been shown to be preferred in *N*-alkylpiperidines,[7] there have long been contradictory opinions concerning the *N*-H *ax*/*eq* conformational equilibrium.[8,9] Recent investigations, however, have unequivocally proved that in solution the equatorial position of the *N*-H is preferred.[10] We have found that the *N*-H in compounds (3) and (5) in the solid phase is axial.[1] In the ^{1}H n.m.r. spectra

Table 1. ^{1}H Chemical shifts (p.p.m.) and coupling constants (Hz) of compounds (3), (5)—(7), (9), and (10)

	9-H_{eq}	5a-H	$J_{5a\text{-}H,6\text{-}H_2}$		*N*-Me
(3)	4.71	4.16	9.6	2.5	
(5)	4.72	4.13	10.0	2.5	
(6)	4.70	4.16	10.0	2.5	
(7)	4.77	3.66	10.0	2.5	2.32
(9)	4.75	3.42	10.0	2.5	2.28
(10)	4.77	3.88	10.0	2.5	2.45

$J_{NH,4a\text{-}H}$ values would provide a means of direct determination of the configuration of the *N*-H. The rapid *N*-H exchange, however, usually makes this approach impracticable. In carefully purified $CDCl_3$ solution, only in compound (5) was it feasible to measure $J_{NH.4a\text{-}H}$; the coupling constant of 9 Hz in this case proves that, even in solution, the *N*-H occupies the axial position.

It is known that when the lone pair of a nitrogen atom and the hydrogen atom attached to an adjacent carbon atom are in the antiperiplanar configuration, the chemical shift of the hydrogen atom is about 0.5 p.p.m. to high field of that for the *gauche* configuration.[11] Accordingly, on protonation of the nitrogen atom the increase in the chemical shift is greater, *ca.* 1 p.p.m. for the antiperiplanar configuration, than for the *gauche* configuration where it amounts only to about 0.5 p.p.m.[12] In view of these facts, only the 4a-H signal is worth investigation, for it follows from the sofa conformation of the pyrimidin-4-ones ring that an arrangement close to the *trans*-antiperiplanar configuration can be realized exclusively in this case. The torsion angles between 5a-H and the lone pair of N-5 in the *gauche* and antiperiplanar configuration are around 30 and 150°, and consequently the use of the above-mentioned rules is not possible.

In the compounds investigated we expected to observe the 4a-H signals separately only in certain cases; the chemical shift of 4a-H is determined not merely by the position relative to the lone pair, but by other factors too, *e.g.* the mode of the *A*/*B* ring fusion, *cis* or *trans*. We therefore attempted to utilize 'protonation shifts.' The 4a-H signals became distinctly observable on addition of trifluoroacetic acid to $CDCl_3$ solutions of compounds (3), (5), (6), (7), (9), and (10). This made possible an approximate determination of the protonation shifts even for those compounds where exact measurement of the 4a-H chemical shifts was not possible due to overlapping with other signals. Thus, in the *trans*-*A*/*B*-ring-fused products (3) and (7), the protonation shift is greater than 0.9 p.p.m., indicating that the configuration of the nitrogen atom is identical in the two cases, *i.e.* the equatorial position is preferred for the *N*-H as well as for the *N*-Me. We have found opposite configurations, however, for N-5 in the α,α,α compounds with *N*-Me (9) and *N*-H (5). The protonation shift is about 1 p.p.m. for the former, and 0.59 p.p.m. for the latter. The substantially lower value for compound (5) is in good agreement with the axial position of the *N*-H, for which evidence has been given by the coupling constant. These protonation shifts additionally support the view that the conformational equilibrium in compounds (5) and (9) favours the α,α,α-1 form.

^{13}C N.m.r. measurements provided further evidence for the deduced structures, and also made it possible to determine the structures of the α,α,β products (6) and (10). The characteristic chemical shifts of compounds (3)—(10), the assignments, and (where possible) the $^1J_{CH}$ for the angular carbon atoms and the adjoining hydrogens are listed in Table 2.

In the signal assignment we utilized broad-band decoupled

Table 2. ^{13}C Chemical shifts (p.p.m.) and $^{1}J_{CH}$ values (Hz) of compounds (1)—(3), (5)—(7), (9), and (10)

	(1)	(2)	(3)	(5)	(6)	(7)	(9)	(10)
C-1	25.3	23.6	26.1	25.7	23.1	25.5	26.0	23.0
C-2	25.1	23.2	25.8	24.9	25.1	24.9	25.6	22.5
C-3	25.1	22.8	25.2	19.9	25.7	24.9	19.8	24.4
C-4	34.4	29.3	33.3	29.6	28.3	32.7	28.4	26.3
C-4a	56.5	53.1	55.1	48.4	49.8	60.9	55.6	59.3
C-5a	153.2	153.1	71.2	70.8	68.6	78.2	78.8	74.6
C-6	31.9	31.8	33.9	33.7	33.9	30.6	33.4	31.3
C-7	20.8	20.7	23.7	23.5	24.2	23.6	23.7	23.5
C-8	22.9	22.9	25.1	24.9	25.1	24.9	24.9	25.0
C-9	41.0	40.9	40.3	39.8	40.2	41.7	41.0	41.8
C-11	172.2	172.4	169.8	171.6	171.5	169.6	171.1	169.3
C-11a	42.9	40.9	48.7	43.7	40.9	44.4	44.4	41.5
N-*Me*						34.4	37.2	38.2
$^{1}J_{4a,4a\text{-}H}$		141.6	129	137		130	130	138
$^{1}J_{5a,5a\text{-}H}$			149.5	150		141	139	142
$^{1}J_{11a,11a\text{-}H}$		127	126	125		128	128	128

and proton-coupled spectra and established additivity rules.[13]

In the starting compounds (1) and (2) the ^{13}C chemical shifts of tetrahydropyrido[1,2-*a*]pyrimidin-4-ones served as the basis for comparison.[14] The chemical shifts of the carbon atoms in ring *C* are nearly the same, while in (2) the signals of ring *A* display a significant upfield shift, indicating *cis*-fusion between rings *A* and *B*.

In the assignments for the dodecahydropyrido[2,1-*b*]-quinazolin-11-ones (3)—(10), our earlier assignments for octahydropyrido[1,2-*a*]pyrimidin-4-ones [2] and the ^{13}C data for perhydroacridine and its *N*-methyl derivative [15] were used for comparison. The spectra of the three diastereoisomers reveal *γ-gauche* steric effects between the oxygen atom of the amide group and the 1-methylene and 9-methylene groups. The extents of the steric interactions are nearly the same in all three stereoisomers, and thus the chemical shifts of C-9 are very close to each other. The greatest interaction of the oxygen atom with the 1-methylene group was found in the structure α,α,β-2: the distance between them is the shortest here, resulting in decreases in chemical shifts to 3.0 and 2.5 p.p.m. in (6) and (10), respectively. In compounds (5) and (9) with the α,α,α-1 structure, however, the chemical shifts of C-1 are not significantly different from those in (3) and (7). This stems from the fact that in the α,α,α-1 structure, although the disance between the 1-methylene group and the oxygen atom is considerably greater than that in the α,β,α structure owing to the *cis-A/B*-ring fusion, N-5 enters into a *γ-gauche* interaction. Additionally, being axial with respect to ring *A*, N-5 gives rise to a shielding of *ca.* 5 p.p.m. at C-3, indicating that in (5) and (9) the α,α,α-1 conformer predominates.

The α,α,β-2 structure of compounds (6) and (10) is supported by the upfield shift in the C-11a signals (2.8 and 2.9 p.p.m., respectively); this is due to the fact that the substituent (C=O) attached to this carbon atom is axial. Consequently, the chemical shifts of C-2 and C-4 are lower. The greater shielding observed for the signal of C-4 is in part a consequence of the *γ-gauche* arrangement of C-4 and C-5a. This results in the characteristic decrease in the chemical shift of C-5a in compounds (6) and (10).

An important feature of structural investigations of nitrogen heterocycles is always the determination of the configuration of the nitrogen atom. For establishment of the orientation of the lone pair of the nitrogen atom, measurement of $^{1}J_{CH}$ for the adjacent carbon atom has proved to be very useful, as the coupling constant in the antiperiplanar arrangement is 6—10 Hz lower than in the synclinal configuration.[16] In the different stereoisomers of *D*-homo-12-oxo-8-azasteroids containing the same structural unit, for *C/D*-ring fusion, coupling constants of 130—132 and 138—140 Hz have been found, respectively.[17] Taking these into consideration, the values of 129—130 Hz for $^{1}J_{4a,4a\text{-}H}$ in compounds (3), (7), and (9) indicate the antiperiplanar configuration of 4a-H and the lone pair, whereas the coupling constants of 137—138 Hz measured for (5) and (10) point to their *gauche* configuration. The coupling constants of 137 and 130 Hz measured for the *N*-H (5) and *N*-Me (9) derivatives with α,α,α-1 structure are in agreement with our earlier observation that the configurations at N-5 in the two molecules are opposite.

Experimental

The ^{1}H and ^{13}C n.m.r. spectra were recorded for solutions in $CDCl_3$ in the pulsed Fourier transform mode (16 K data points for the FID) at 99.6 and 25.0 MHz, at ambient temperature, with internal deuterium lock, using a JEOL FX-100 spectrometer. The chemical shifts were determined on the δ scale, using tetramethylsilane as internal standard. In repeated experiments, ^{13}C n.m.r. shifts were reproduced within an error limit of 0.1 p.p.m.

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Received 17*th May* 1982; *Paper* 2/808