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Synthesis and Conformational Analysis of Stereoisomeric 1- and 2-Methyl-2*H*,4*H*-1,6,7,11b-tetrahydro-1,3-oxazino[4,3-*a*]isoquinolines[1]

Pál Sohár

Spectroscopic Department, EGIS Pharmaceuticals, POB 100, H-1475 Budapest, Hungary,

László Lázár, Ferenc Fülöp and Gábor Bernáth*

Institute of Pharmaceutical Chemistry, Albert Szent-Györgyi Medical University, POB 121, H-6701 Szeged, Hungary,

and

Jenő Kóbor

Chemical Department, Pedagogical Training College, H-6720 Szeged, Hungary

Dedicated to Professor Gábor Fodor on the occasion of his 75th birthday

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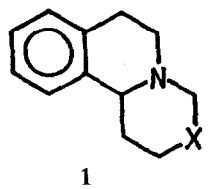
Abstract - Starting from diastereomerically pure 1-(β-hydroxyethyl)-1'-methyl- or 2'-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (3a,b and 5a,b), 4-unsubstituted, 4-p-nitrophenyl- and 4-oxo-1- or 2-methyl-9,10-dimethoxy-2H,4H-1,6,7,11b-tetrahydro-1,3-oxazino[4,3-a]isoquinoline diastereomers (a and b) 6-9, 12 and 13 were prepared. The relative configurations and the predominant conformations were determined by ^1H and ^{13}C NMR spectroscopy, use also being made of DR, DEPT, DNOE and 2D-HSC measurements.

INTRODUCTION



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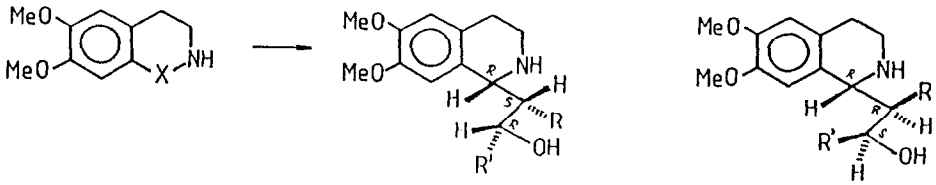
Benzo[*a*]quinolizidines, *i.e.* tetrahydroisoquinoline derivatives angularly condensed with the cyclohexane ring (**1**, X=CH_2), are well-studied compounds from both pharmacological and stereochemical points of view.[2-4] Much less attention has been paid to the corresponding 1,3-heterocycles of type **1**. Of these compounds, only the medicinally noteworthy pyrimido[6,1-*a*]isoquinolines have been studied. 2-Mesitylimino-3-methyl-9,10-dimethoxy-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one (*Trequinsin*) is an antihypertensive drug.[5]

A few 1-hydroxymethyl-9,10-dialkoxy-2*H*,4*H*-1,6,7,11b-tetrahydro-1,3-oxazino[4,3-*a*]isoquinolines were earlier synthesized in our laboratory.[6] NMR and X-ray diffraction measurements revealed that, depending on the configuration of the 1-hydroxymethyl group and the 4-substituent, the *trans* or the *cis*-**B** conformation was favoured.

In the present work, we have studied the influence of 1- or 2-methyl substituents on the conformation, comparing the spectra of diastereomeric pairs. A further aim was to investigate the effects of 4-substituents. Therefore, besides the 4-unsubstituted derivatives, 4-*p*-nitrophenyl and 4-oxo compounds too were prepared.

RESULTS AND DISCUSSION

The C-1' epimeric aminoalcohols **3a,b** were synthesized from 1-ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2**) by C-1 alkylation with methyl iodide, followed by reduction with sodium borohydride and lithium aluminium hydride (LAH); fractional crystallization of the product then gave **3a** (m.p. 132-134 °C) and **3b** (m.p. 117-119 °C)[7,8] (Scheme 1).



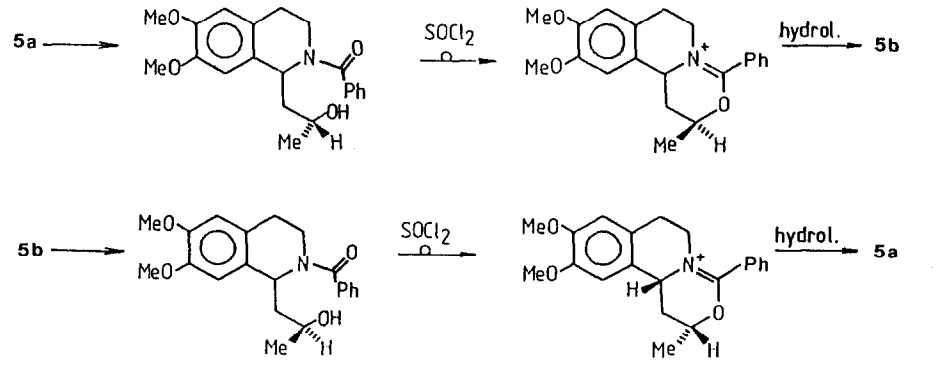
2 (X: C=CHCOOEt) $\xrightarrow[\text{3. LAH, 4. Fract. cryst.}]{\text{1. MeI, 2. NaBH}_4}$ **3a** (R: Me, R': H) + **3b** (R: Me, R': H)

4 (X: $CHCH_2Ac$) $\xrightarrow[\text{2. Fract. cryst.}]{\text{1. NaBH}_4}$ **5a** (R: H, R': Me) + **5b** (R: H, R': Me)

Scheme 1

The synthesis of the C-2' epimeric aminoalcohols **5a,b** is also shown in Scheme 1. Compound **4** was prepared from 3,4-dihydroisoquinoline by condensation with ethyl acetoacetate.[9] Reduction with sodium borohydride gave a mixture of the aminoalcohols **5a,b**; fractional crystallization furnished **5a**, having the $1R^*, 2'R^*$ configuration. When the reduction was conducted at 30-40 °C, the main product was **5a**, whereas below -5 °C chiefly the diastereomer **5b** was obtained.

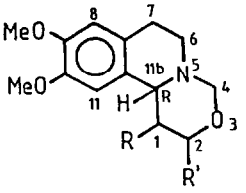
It is known that 1,2- and 1,3-aminoalcohols, whose hydroxy group is attached to an asymmetric carbon atom, can be converted by inversion into the other epimer;[11-13] we therefore attempted this interconversion of compounds **5a** and **5b**. Benzoylation of **5a** and **5b** and subsequent inversion, elicited with thionyl chloride, gave the dihydrooxazines; without isolation, the hydrolysis of these compounds furnished the C-2' epimeric pairs (Scheme 2).



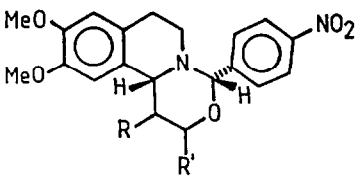
Scheme 2

Treatment of the aminoalcohols **3a,b** and **5a,b** with formaldehyde gave the pairs of oxazinoisoquinolines **6a,b-7a,b**; with *p*-nitrobenzaldehyde, **8a,b-9a,b** were obtained. In the cases of the 4-(*p*-nitrophenyl) derivatives **8a,b** and **9a,b**, formation of the pairs of C-4 epimers is possible. The NMR spectra described below indicated that the reaction gives only the diastereomer in which H-11b and H-4 are in the *cis* position (Scheme 3).

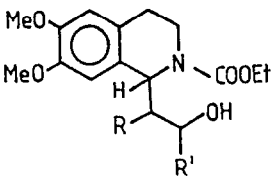
The 4-oxo derivatives **12a,b** and **13a,b** were synthesized in two different ways; either the urethanes **10a,b** and **11a,b**, prepared from the aminoalcohols with ethyl chloroformate, were reacted with sodium methoxide, or the aminoalcohols were treated with phosgene.



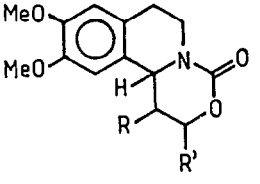
6a,b (R = Me, R' = H)
7a,b (R = H, R' = Me)



8a,b (R = Me, R' = H)
9a,b (R = H, R' = Me)



10a,b (R = Me, R' = H)
11a,b (R = H R' = Me)



12a,b (R = Me, R' = H)
13a,b (R = H, R' = Me)

a, b: R^*, R^* or R^*, S^* diastereomers

Scheme 3

STRUCTURE

The ^1H and ^{13}C NMR data on the **a** and **b** epimers of **6-9**, **12** and **13** are listed in Tables 1 and 2. As these data unequivocally prove the constitutions, the following discussion is focussed on the steric structures.

In **6b**, H-1 and H-11b are certainly *trans-diaxial*, as revealed by their coupling of 10.4 Hz.[16] For this reason, structures containing *cis*-annelated hetero rings and C-1 *quasi-equatorial* to the isoquinoline skeleton (*cis*-**A** and *trans*-**A**, Fig. 1*) cannot come into consideration; in these structures the dihedral angles would be about 40° and 80°, respectively, corresponding to a much smaller splitting. Compared with the isomer **6a**, in **6b** there is a considerable steric hindrance between C-1 and C-6, as indicated by the upfield shift of their C-NMR lines (steric compression shift[17]) by 2.7 and 3.0 ppm (*cf.* Table 2).

On the other hand, in isomer **6a** a field effect is observed on the C-11 and methyl carbon lines, the upfield shifts being 4.1 and 2.0 ppm, respectively; hence, in **6a** the methyl group and the aromatic H-11 are in sterically less favoured positions. It follows that the isomer **6b** has steric structure **B**, *i.e.* the hetero

**cis* and *trans* refer to the steric position of H-11b and the methyl substituent (Pos 1 or 2) relative to the oxazine ring. Structures with *cis* or *trans* annelated hetero ring are denoted A and B, or C, respectively.

rings are *cis*-annelated, C-1 is *quasi-axial* relative to the isoquinoline ring, and the 1-methyl group is attached to the oxazine ring in the *equatorial* direction (Fig. 1).

The H-11b signal of the isomer **6a** is a barely split doublet, with J(H-1,H-11b) < 2 Hz. Accordingly, the *cis* position of these hydrogens is beyond doubt. However, if skeletal structure **B** is presumed, the *cis* arrangement of H-1 and H-11b is impossible for steric reasons: owing to the interaction between the 1-methyl group and H-6*ax*.

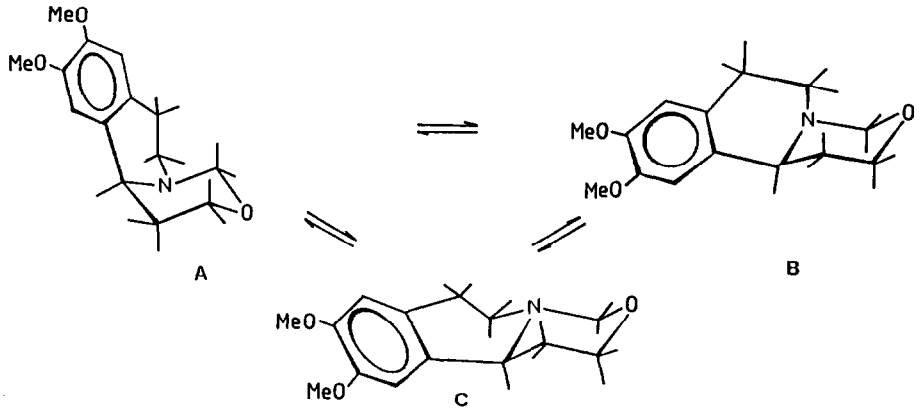


Fig. 1.

Structure **A**, which is the least favoured one above, can be excluded on the basis of the fact that the carbon shifts indicate a relatively unstrained skeleton.

Therefore, the preference of the *trans*-annelated **C**-structure (Fig. 1) can be suggested, in which the methyl group is *axial*, accounting for the field effect observed for the methyl carbon line. The upfield shift of the C-11 line is then a consequence of the interaction between H-11 and H-1.

The similar stereostructures of the 4-(*p*-nitrophenyl)-substituted analogues **8a** and **8b** and their counterparts **6a** and **6b** unequivocally follow from their very similar spectral data, allowance being made for the expectable substituent effects. The chemical shifts of eleven of the fifteen carbon signals for **6a** and **8a** differ by less than 0.4 ppm, and for ten signals of the isomeric **6b** and **8b** the difference is ≤ 0.6 ppm. The most significant difference is observed, of course, in the shift of the C-4 signal; the α-effect[18,19a] of the substituent is revealed by the downfield shifts of 8.3 (**8a**) and 5.7 ppm (**8b**) as compared with the 4-unsubstituted analogues **6a,b**. In the case of **6b**, the difference is smaller, owing to the opposite field effect. The latter overcompensates the ß-effect[20] of the substituent, to a slight extent in **8a**, and considerably in **8b**; as a result, the C-6 signal shows an upfield shift of 1.1 ppm and 6.5 ppm, respectively, on 4-substitution.

The analogous steric structures are also indicated by the nearly identical shifts of the H-4 signals effected by the substitution (downfield shifts of 0.81 ppm for **8a**, and 0.96 ppm for **8b**), and also by the similarly low, or considerably higher, shift differences for the 2-methylene hydrogens in the pairs **6a-8a** (0.15 and 0 ppm) and **6b-8b** (0.62 and 0.63 ppm). The vicinal couplings in the latter pairs (11.3 and 4.5 Hz, and 11.5 and 4.8 Hz, respectively) provide further confirmation of the identical steric structures.

Thus, the **C** structure of **8a** and the **B** form of **8b** are very probable. This assumption is supported by the DNOE spectra[19b,21] of **8a,b**. The DNOE spectrum of **8a** proves the *cis*-1,3-*diaxial* arrangement of H-4 and H-11b in this compound, as saturation of either of their signals increases the intensity of the other. The *trans*-1,2-*diaxial* arrangement of H-11b and the 1-methyl group is evidenced by the absence of a NOE between them. The DNOE measurements also clarified some dubious assignments, *e.g.* the close singlets of H-8 and H-11 in **8a**.

The DNOE spectra of **8b** clearly proves that H-4 and H-11b are in the *cis*-1,3-*diaxial* position in this compound too; this definitely excludes the structures of type **A**.

In the spectra of the isomer pair **7a,b**, the H-11b and H-2 multiplets appear as signals of coalesced lines, from which the coupling constants cannot be discerned. Therefore, the *cis* or *trans* arrangement of H-11b and the 2-methyl group had to be established by DNOE measurements. Compound **7a** has a more crowded structure than **7b**, as shown by the upfield shift of the C-1,2,4,11b signals: 3.8, 4.9, 7.7 and 5.4 ppm, respectively. Accordingly, from the aspect of H-11b and the 2-methyl group, the *trans* and/or *trans*-annelated steric structure (**C**) is evidently probable for **7b**. The structures *cis*-**C** and *cis*-**B** can be excluded, since there is no NOE between the 2-methyl group and H-4*ax* to indicate steric proximity. On the basis of the NOE appearing between H-11b and H-4*ax*, the *cis*-**A** and *trans*-**A** structures can also be rejected, which are likewise improbable for steric reasons. Finally, the *trans*-**B** steric structure cannot be considered either, since the ^{13}C NMR data show that the C-1 shift is 6.5 ppm larger than that for **6b** with structure **B**, and this difference cannot be attributed to the C-1 → C-2 positional change of the methyl group; the difference between the α- and ß-effects would be expected to cause a downfield shift of only about 2.6 ppm.[19c] Hence, the *trans*-**C** structure of **7b** in which the 2-methyl group is *equatorial* (Fig. 1) can be considered proved.

The analogous structure of the 4-aryl derivative **9b** is evident for the same reasons as in the case of the pair **6b-8b**; the ^{1}H and ^{13}CNMR chemical shift differences are very close to those measured for **7b-9b**. For example: $\Delta\delta$ C-4 = +5.7 (**8b-6b**) and +5.8 ppm (**9b-7b**); $\Delta\delta$ C-6 = -6.3 and -5.9 ppm; and $\Delta\delta$ H-4 = 0.96 and 0.94 ppm.

The analogous steric structures are also evident for the pair **7a-9a**, as the shift difference for ten carbon lines is ≤ 0.5 ppm. Significant differences can be observed only for the C-4 and C-6 signals, which is expected owing to the 4-substitution. However, while the $\Delta\delta$ C values for the pairs **6a-8a** and **6b-8b** are different (*e.g.* the C-4 downfield shift is larger and the C-6 upfield shift is considerably smaller for the first pair), the $\Delta\delta$ C values obtained for the pair **7a-9a** are the same as for **7b-9b** within 0.6 ppm, and the signs are the same without exception. This suggests that, in contrast with the pairs **6a-6b** and **8a-8b**, the skeletal structures of the pairs **7a,b** and **9a,b** do not differ; **7a** and **9a** also have a *trans*-annelated (**C**) skeleton, *i.e.* the *cis*-**C** structure where the 2-methyl group and H-11b are in the *cis*-1,3-*diaxial* position. In accordance, a comparison of the ^{13}C NMR data on the pair **7a,b** shows that the field effect of the *axial* 2-methyl group gives rise to the upfield shifts of the C-11b, C-2 and C-4 lines of **7a** by 5.4, 4.9 and 7.7 ppm. These field effects are very similar for **9a**: 5.1, 4.6 and 7.6 ppm, further supporting their analogous steric structures.

A smaller field effect (3.8 ppm for both isomer pairs) is also found on the C-1 line.

As evidence of the unchanged skeletal structure, no marked field effect was observed for the C-6 and C-7 lines, the shift differences of these lines for the pairs **7a-9a** and **7b-9b** being ≤ 0.7 ppm.

Irradiation of the methyl signal of **7a** elicited the appearance of the H-4*ax* doublet at 4.30 ppm in the DNOE spectrum, in accordance with the *cis*-**C** structure, where the 2-methyl group and H-4*ax* are 1,3-*diaxial*. The forms *cis*-**B** and *trans*-**B** are impossible on the basis of the NOE results, as there is no NOE between H-1*ax* and H-6*ax*; their distance in these structures is about 1.7 Å, and consequently a strong DNOE signal should mutually appear. Similarly, the DNOE measurements also exclude structures **A**, as there is no interaction between H-4*ax* and H-7*ax*. The correct assignments of the ^{1}H NMR signals of the methylene hydrogen pairs at positions 1, 6 and 7 were proved by the heteronuclear shift correlation (2D-HSC) spectra.

From the foregoing, it follows that:

(1) the 4-aryl substituent does not influence the steric structures, and it is in each case in the *equatorial* position, *i.e.* in the *trans* arrangement relative to H-11b;

(2) to avoid the strong steric hindrance between the *cis*-arranged 1-methyl substituent and H-11b (their minimal distance being about 1.2 Å for the *trans*-annelated skeleton), the molecules take the *cis*-**B** structure by nitrogen inversion.

The conformational relations are drastically changed in the 4-oxo compounds **12a,b**. The planar sp^2 nitrogen at the annelation site greatly increases the flexibility of the annelation, and structures of type **A** and **B** are impossible; here, N-5 is no longer a centre of asymmetry.

A comparison of the spectra of the pair **12a,b** reveals considerable differences for the vicinal coupling constants of the 2-methylene hydrogens and for the chemical shift of the methyl carbon signal. The upfield shift observed for the methyl carbon line in **12a**, as compared with **12b**, is indicative of a much less favourable steric position of the methyl group in **12a**. Consequently, H-1 and H-11b are *cis*-arranged in **12a**. The H-1,H-2*ax* and H-1,H-2*eq* couplings, both being smaller than 2 Hz, indicate a sofa-like preferred conformation of the oxazinone ring, where C-2 is not coplanar with the five other atoms of the oxazine ring, and lies on the same side of this plane as H-11b (Fig. 2, **D**). The dihedral angles of the 2-hydrogens are about 60°; thus, the measured small vicinal couplings are consistent with the theoretically expected values.[16] The dihedral angle of *ca.* 20° for the interaction H-1,H-11b and the observed coupling constant of 3.8 Hz are also in good agreement with the suggested steric structure; further evidence is provided by the field effect on the methyl carbon line, since in the postulated stereostructure a strong steric hindrance is expected between H-11 and the 1-methyl group, their distance being ca. 0.8 Å.

The large downfield shift (4.68 ppm) of the H-6*eq* signal is noteworthy as compared with that of its *axial* counterpart (ca. 2.9 ppm); this can be explained by the anisotropic effect[19d] of the coplanar carbonyl group. The correctness of the assignments was confirmed by double resonance measurements.

As the vicinal couplings of the 2-hydrogens in **12b** are 7.6 and 3.7 Hz, the unchanged skeletal structure, i.e. the preference of the same conformer, can be proposed; the corresponding dihedral angles are about 180° and 60°. The *quasi-equatorial* 1-methyl group is in a sterically favoured position, and thus the absence of a field effect for this ^{13}C NMR signal is in agreement with expectation.

The H-1*ax* signal of the 2-methyl analogue **13b** is a double triplet, whose coupling constants (13.7, 11.5 and 11.5 Hz) are indicative of two dihedral angles of about 180°. Hence, the dominant conformation is unchanged as compared with **12a,b** and the 2-methyl group is *equatorial* and *trans*-arranged with H-11b. In accordance, the DNOE measurements showed the steric nearness of H-11b and H-2, approaching the *cis*-1,3-*diaxial* arrangement. The correct assignments of the signals were supported by the 2D-HSC spectra.

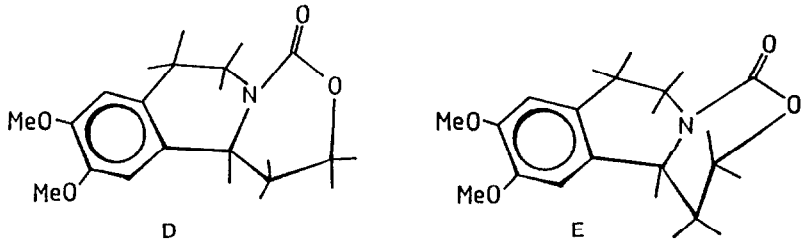


Fig. 2

The more crowded steric structure of the isomer **13a** (the *cis* arrangement of H-11b and the 2-methyl group) is evident from the upfield shifts of the methyl carbon line and the C-1,2,11,11b signals (1.2, 3.3, 1.0, 0.9 and 2.6 ppm). It remains only to be decided whether the dominant conformation is the same as in the analogues **12a,b** and **13b**, which requires the *axial* position of the methyl group, or whether it is the other relatively stable form that prevails in the conformational equilibrium, where the 2-methyl group is *equatorial* and the oxazine ring assumes a half-chair conformation, with C-2 in the out-of-plane position, situated opposite to H-11b (Fig. 2, **E**).

Table 1. ^{1}H NMR data on the epimeric pairs **a-b** of compounds **6-9**, **12** and **13** in $CDCl_3$ solution at 250.14 MHz[a]

Com-pound	CH_3 *d*[b](3H)	H-11b (1H)[c]	CH_2(7) NCH_2(6) 1-4*m*'s(4H)	CH(Me) *m*(1H)	CH_2(1)/OCH_2(2) (2x1H or 2H)[d]	CH_2/CH(4) 2x*d*/*s*(2/1H)[e]	OCH_3 2x*s*(2x3H)	H-8,11 2x*s*(2x1H)
6a	0.97	~ 3.6	~ 2.45, ~2.65, ~3.0[f]	2.15	3.85[g] 4.05[h]	3.98[h] 4.54	3.84 3.85[g]	6.57 6.59
6b	0.88	3.62[g]	~ 2.8, ~3.0,[f] ~3.6[g]	~ 2.2	3.33 3.95	4.61	3.83 3.85	6.55 6.63
7a	1.47[g]	~ 4.2[h]	2.7- 3.0[i] 3.40	~ 4.2[h]	1.55[g] 2.30	4.30 4.80	3.85	6.49 6.60
7b	1.22	3.97	2.65-3.0[i] ~3.3	~ 3.75	1.68	4.54 4.63	3.84	6.52 6.60
8a	1.10	~ 3.85[g]	~ 2.2,~ 2.5,[f]~2.8	~ 2.3	4.09	4.09	3.85[g] 3.87[g]	6.56[j] 6.65[j]
8b	0.98	~ 3.85[g]	~ 2.5,~2.65,~2.8, ~3.1	~ 2.3	3.58 4.21	5.57	3.85[g] 3.87[g]	6.62[h]
9a	1.58[g]	4.43	2.3-3.0[h]	4.56[k]	~1.55[g] 2.3-3.0[h]	5.77	3.84 3.88	6.56 6.60
9b	1.35	4.00	~ 2.75	4.25	~ 1.8	5.48	3.84 3.87	6.60[g]
12a	0.77	4.94	~ 2.6,[g] ~2.9,[f] 4.68	~ 2.6[g]	4.19 4.52	-	3.87 3.88	6.63 6.65
12b	1.34	~ 4.35[g]	~ 2.7, ~3.05,[f] 4.35[g]	~ 2.45	3.96 4.12	-	3.87	6.68 6.72
13a	1.48	4.75	~ 2.65, ~3.0,[f]~4.6	4.45[l]	~2.3	-	3.87	6.59 6.65
13b	1.42	4.74	~ 2.6,[g] ~3.0,[f] 4.55	~ 4.5	1.75 2.6[g]	-	3.87	6.61 6.63

[a] Chemical shifts in δ (δ TMS = 0 ppm), coupling constants in Hz. Assigments were proved by 2D-HSC measurements (**6a,b**, **7a,b** and **13b**) and by DNOE (**7a,b**, **8a,b** and **13b**) or DR spectra (**12a** and **13a**). Signals of the 4-aryl substituent (*A* and *B* part of an *AA'BB'* spin system, 2x~*d*, 2x2H): H-2', 6': 7.72±0.02: H-3',5': 8.22±0.02; *J*: 8.8±0.2. Characteristic IR frequencies (cm^{-1}, in KBr discs): ν C=O: 1681 (**12a**), 1691 and 1670 (split bands, **12b**), 1674 (**13a**) and 1678 (**13b**), $\nu_{as}NO_2$, ν_sNO_2 and ν C-N(O_2) bands of **8a,b** and **9a,b**: 1516±1, 1340±5, 855±1. [b] *J*: 6.9 (**6a**, **7a**, **8a**, **9a**, **12a,b**), 6.5 (**6b**, **8b**, **13a**), 6.2 (**7b**, **9b**, **13b**); [c] *d*, *J*: <2 (**6a**), 10.4 (**6b**), 3.8 (**12a**), *dd*, *J*: ~10 and ~5 (**7b**), 12.4 and 3.2 (**9a**), 11.4 and 5.1 (**13b**), *t*, *J*: 7.5 (**13a**), unresolved *m* (signal width~30 Hz) for **9b**; [d] Upfield signal: H*ax*, *t*, *J*: 11.2 (**6b**), 11.5 (**8b**), *d*, *J*: 10.7 (**12a**), *dd*, *J*: 10.9 and 7.6 (**12b**), *dt*, *J*: 13.7, 11.5 and 11.5 (**13b**); downfield signal: H*eq*, *dd*, *J*: 11.4 and 4.5 (**6b**), 11.5 and 4.8 (**8b**), 10.9 and 3.7 (**12b**), *dt*, *J*: ~14, ~14 and ~6 (**7a**), *d*, *J*: 10.7 (**12a**); the two signals are overlapped for **7b**, **8a**, **9b** and **13a**; [e] *AB*-type spin system: 2x*d*(2x1H), *J*(*A*,*B*): 8.1 (**6a**), 10.2 (**7a,b**), *s*(2H) for **6b**, *s*(1H) for **8a,b** and **9a,b**; [f/i] Intensity: 2H/3H; [g/h] Overlapping signals; [j] δH-11 > δH-8 (proved by DNOE spectrum); [k] ~*qi*, *J*: ~7; [l] *sx*, *J*: ~6.5.

Table 2. ^{13}C NMR chemical shifts of the epimers **a-b** of compounds **6-9**, **12** and **13** in $CDCl_3$ solution at 62.89 MHz[a]

Compound	C-1	C-2	C-4	C-6	C-7	C-7a	C-8	C-9,10		C-11	C-11a	C-11b	OCH_3(9,10)		CH_3
6a	33.1	74.0	87.6	46.4	28.8	127.6[b]	111.7	147.6	147.7	108.0	128.0[b]	63.7	55.8	56.1	12.9
6b	30.4	73.8	86.2	43.4	28.9	126.3	111.8	146.1	148.0	112.1	128.0	63.5	55.7	56.0	14.9
7a	33.1	68.4	78.4	43.6	28.7	126.2	111.7	147.3	147.6	108.9	129.9	52.0	55.8	56.0	17.2
7b	36.9	73.3	86.1	43.7	29.4	126.2	112.0	147.6	147.9	109.5	130.3	57.4	56.0	56.2	21.9
8a	33.0	73.8	95.9	45.3	28.8	126.7	111.6	147.0[c]	147.8[b]	108.1	129.0[d]	64.7	55.9	56.3	12.7
8b	29.4[b]	74.4	91.9	36.9	28.6[b]	127.9[e]	111.9	146.3[f]	147.5	112.1	128.0[e]	65.8	55.8	56.1	14.6
9a	32.0	69.4	84.3	37.4	28.9	126.5	111.7	146.9[b]	147.6[b]	109.1	130.2	54.1	55.9	56.2	17.7
9b	35.8	74.0	91.9	37.8	29.0	126.2	111.6	147.4[b]	147.8[b]	109.1	130.0	59.2	55.9	56.1	21.8
12a	31.6	70.4	152.3	41.0	28.1	125.3[b]	111.2	147.4[e]	147.8[e]	107.8	127.6[b]	57.5	55.5	55.8	9.8
12b	32.4	69.1	153.7	43.9	28.1	127.6[b]	111.9	147.4	148.3	108.1	128.7[b]	60.3	55.9	56.2	16.3
13a	34.3	70.5	153.0	42.6	28.1	127.5[b]	111.9	147.7	148.0	107.8	127.6[b]	51.2	55.8	56.1	19.8
13b	37.6	71.5	153.3	42.1	28.1	127.0[b]	111.9	148.0[c]	148.0[c]	108.3	127.8[b]	53.8	55.9	56.2	21.0

[a] Assignments were proved by DEPT (**9b** and **12b**) or 2D-HSC measurements (**6a,b**, **7a,b** and **13b**). Further signals: lines of the aromatic carbons of the 4-aryl group in **8a,b** and **9a,b**: C-1: 147.0,[c] 146.2,[f] 147.4,[b] 146.5[b]; C-2',6': 129.0,[d] 127.5, 128.0, 127.9, C-3',5': 123.8, 123.2, 123.4, 123.4, C-4: 148.4,[b] 148.3,[f] 147.8,[b] 147.6;[b] [b,e,f] Interchangeable assignments; [c,d] Two overlapping lines.

The observed coupling constants indicate that the former case is probable; the preferred conformation is unchanged, and the *axial* 2-methyl group is *cis*-arranged to H-11b. This is based on the following evidence:

(1) The vicinal couplings of H-11b with the 1-methylene hydrogens are about the same as those in **13b**; the H-11b signal is a triplet with a split of 7.5 Hz. In the proposed structure, the corresponding dihedral angles are 20° and 140°, which suggest splittings of about the same magnitude. In the other conformer, one of the dihedral angles would be about 90°, and thus no splitting could be expected.

(2) The vicinal couplings of H-2 are similar to those of the 1-methylene hydrogens and the H-2,CH_3 interaction; the H-4 signal is a sextet split by 6.5 Hz. If the methyl group were in the *equatorial* position, the H(1)-C-C-H(2) dihedral angles would be ca. 180° and 60°, and thus one of these couplings should be larger.

As a conclusion, it can be said that the preferred conformations of **12a,b** and **13a,b** are changed neither by the 1- or 2-position of the methyl group, nor by its *cis* or *trans* arrangement to H-11b.

EXPERIMENTAL

The NMR spectra were recorded in $CDCl_3$ solution in 5 or 10 mm tubes, at room temperature, on Bruker WM-250 (^1H and ^{13}C) or WP-80-SY (^{13}C) FT-spectrometers controlled by an Aspect 2000 computer at 250.13 (^1H) and 62.89 or 20.14 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: spectral width 5 and 16 or 5 kHz, pulse width 1 (^1H) and 7.0 or 3.5 (^{13}C) μs (ca. 20° and ca. 90° flip angle, respectively), acquisition time 1.64 and 0.40 or 1.64 s, number of scans 16 (^1H) and 0.5-1 K (^{13}C), computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (line width: 0.7 and 1.0 or 2.0 Hz), and for ^{13}C NMR spectra complete proton noise decoupling (ca. 0.5 or 3.5 W) was applied.

Conventional CW irradiation of ca. 0.15 W was used in the DR experiments.

The "DNOE MULT.AU" standard Bruker microprogram to generate NOE was used with a selective pre-irradiation time of 5 μs and a decoupling power (CW mode) of ca. 30-40 mW; number of scans 32-512; relaxation delay 0.15 s; dummy scans 2, pulse width 5.0 μs (90°) and 16 K data points for ca. 2 kHz spectral width. A line broadening of 1.0 Hz was applied to diminish residual dispersion signals in the difference spectra.

DEPT[22] spectra were run in a standard way,[23] using only the $\theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively; typical acquisition data were: number of scans 128-512, relaxation delay for protons 3 μs, 90° pulse widths 17.5 and 43 μs for ^{13}C and ^1H, respectively. The estimated value for J(C,H) resulted in a 3.7 ms delay for polarization.

The 2D-HSC spectra[24] were obtained by using the standard BRUKER pulse program "XHCORRD.AU". The number of data points was 4 K in the ^{13}C domain, and 64-256 increments were used to give better than 5 Hz/points digital resolution in the ^1H domain; 256 transients were obtained with a relaxation delay of 3 μs. All C-H correlations were found by using a value of J(C,H) = 135 Hz for calculation of the delay.

Melting points were determined on a Kofler apparatus and are uncorrected.

Compounds **3a,b** and **4** were prepared according to known methods[7-9]. The physical and analytical data on the oxazine diastereomers **a** and **b** of **6-9**, **12** and **13** are listed in Table 3.

(1*R**,2*R**)-1-(2'-Hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5a**)

The base liberated from the hydrochloride of **4** (24.9 g; 0.1 mol) was dissolved in methanol (150 ml). Sodium borohydride (15.1 g; 0.4 mol) was added to the solution in small portions, with stirring, at

30-40 °C internal temperature. The reaction mixture was stirred for 3 h at room temperature. It was then evaporated to dryness. The residue was dissolved in water (200 ml); the solution was cooled in ice-water and acidified with conc. hydrochloric acid, then made alkaline with conc. sodium hydroxide solution, and extracted with chloroform (4x100 ml). After drying (Na_2SO_4), evaporation of the solvent left an oil which crystallized on rubbing with diethyl ether. The crystals were isolated by filtration and twice recrystallized from ethyl acetate to yield the diastereomer **5a**; m.p. 115-116 °C; yield: 40%; formula (m.w.): $C_{14}H_{21}NO_3$ (251.32). Analysis (required/found): C, 66.90/66.73; H, 8.42/8.60; N, 5.57/5.66%.

(1*R**,2'*S**)-1-(2'-Hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5b**)

The hydrochloride of **4** (24.9 g; 0.1 mol) was suspended in methanol (200 ml). The suspension was stirred and cooled in ice-water. Sodium hydrogencarbonate (8.4 g; 0.1 mol), and then small portions of sodium borohydride (15.1 g; 0.4 mol) were added, the temperature of the mixture being maintained below -5 °C. Stirring was continued until the mixture warmed up to room temperature (about 5 h). It was then stirred further for 3 h and processed in the usual way. Rubbing of the oily residue with diethyl ether gave a crystalline product that was filtered off and twice recrystallized from ethyl acetate. The compound had m.p. 130-131 °C; yield: 62%. Analysis (required/found): C, 66.90/66.71; H, 8.42/8.31; N, 5.57/5.66%.

General procedure - Isomerization of **5a** and **5b** via the *N*-benzoyl derivatives

The benzoyl derivatives were prepared from **5a** and **5b**, respectively, by means of Schotten-Baumann acylation. The product (25 g; 0.07 mol) was dissolved in dry chloroform (500 ml). The solution was stirred and chilled in a bath of common salt and crushed ice to 0 °C, and thionyl chloride (20 ml; 0.27 mol) was then added dropwise. The mixture was slowly warmed to room temperature (1 h) and was further stirred for 2.5 h, and finally the solvent was evaporated. The oily residue was taken up in 10% hydrochloric acid (500 ml), and refluxed for 3 h. After cooling, the solution was shaken with diethyl ether (2x200 ml); it was then made alkaline with 10% sodium hydroxide solution and extracted with chloroform (4x150 ml). The oil obtained after drying (Na_2SO_4) and evaporation of the solvent was rubbed with diethyl ether to give a crystalline product that was filtered off and recrystallized from ethyl acetate.

The compound resulting from **5a** was found to be identical with its diastereomer **5b**, the yield being 59%.

When starting from **5b**, the above procedure gave the aminoalcohol diastereomer **5a** in a yield of 54%.

(1*S**,11b*R**)- and (1*R**,11b*R**)-9,10-Dimethoxy-1-methyl-1,6,7,11b-tetrahydro-2*H*,4*H*[1,3]oxazino[4,3-*a*] isoquinolines (**6a,b**)

The aminoalcohol **3a** or **3b** (1.01 g; 4 mmol) was added to a mixture of 36% formaldehyde (10 ml) and water (10 ml). The suspension was stirred at room temperature for 20 min. The crystalline product was isolated by filtration and washed with water.

(2*R**,11b*R**)- and (2*S**,11b*R**)-9,10-Dimethoxy-2-methyl-1,6,7,11b-tetrahydro-2*H*,4*H*[1,3]-oxazino[4,3-*a*] isoquinolines (**7a,b**)

The aminoalcohol **5a** or **5b** (1.01 g; 4 mmol) was dissolved in ethanol (10 ml), and 36% formaldehyde (0.5 ml) was added to the solution. The mixture was allowed to stand at room temperature for 1 h. It was then poured into water (100 ml) and extracted with chloroform (4x25 ml). After drying (Na_2SO_4) and evaporation of the solvent, the residual oil crystallized on rubbing with diethyl ether.

General procedure - Synthesis of 4-(*p*-nitrophenyl)-substituted oxazinoisoquinolines (**8a,b** and **9a,b**)

The aminoalcohol **3a,b**; **5a,b** (1.01 g; 4 mmol) and *p*-nitrobenzaldehyde (0.60 g; 4 mmol) were refluxed in benzene (30 ml) for 10-15 h. The progress of the reaction was monitored by TLC. The solvent was evaporated, and the residual oil was rubbed with ether to give a crystalline product.

General procedure - Synthesis of urethanes (**10a,b; 11a,b**)

A reaction mixture was made from the respective aminoalcohol **3a,b**; **5a,b** (2.51 g; 0.01 mol), sodium hydrogencarbonate (0.84 g; 0.01 mol), water (30 ml) and ethyl chloroformate (0.96 ml; 0.01 mol). It was stirred for 1 h at room temperature, and then extracted with ethyl acetate (4x25 ml). Drying of the extract and subsequent evaporation of the solvent left an oily material that became crystalline on rubbing with a mixture of hexane and ether.

10a: M.p. 94-98 °C (diisopropyl ether); yield: 70%. Analysis for $C_{17}H_{25}NO_5$ (323.28) (required/found): C, 63.14/63.05; H, 7.79/7.84; N, 4.33/4.26%.

10b: M.p. 73-76 °C (diisopropyl ether); yield: 64%. Analysis (required/found): C, 63.14/63.00; H, 7.79/8.03; N, 4.33/4.37%.

11a: M.p. 85-87 °C (hexane); yield: 56%. Analysis (required/found): C, 63.14/63.22; H, 7.79/7.76; N, 4.33/4.56%.

11b: M.p. 138-140 °C (diisopropyl ether); yield: 60%. Analysis (required/found): C, 63.14/63.42; H, 7.79/7.85; N, 4.33/4.49%.

Table 3. Physical and analytical data on oxazinoisoquinolines **6a,b-13a,b**

Com-pound	Mp (°C)	Yield (%)	Found C	H	N
6,7	$C_{15}H_{21}NO_3$[a]	263.33[b]	68.41[c]	8.04[c]	5.32[c]
6a	112-116[d]	45	68.23	7.73	5.36
6b	113-115[d]	50	68.70	8.32	5.24
7a	96-98[e]	65	68.61	8.23	5.38
7b	99-100[d]	50	68.40	8.09	5.28
8,9	$C_{21}H_{24}N_2O_5$[a]	384.42[b]	65.61[c]	6.29[c]	7.29[c]
8a	186-188[f]	47	65.91	6.55	7.34
8b	207-210[g]	52	65.95	6.29	7.60
9a	148-151[g]	35	65.63	6.48	6.92
9b	179-181[g]	48	65.84	6.45	7.30
12,13	$C_{15}H_{19}NO_4$[a]	277.31[b]	64.96[c]	6.91[c]	5.05[c]
12a	143-147[g]	22	65.06	6.59	5.13
12b	120-123[g]	20	64.73	6.80	5.22
13a	157-159[f]	32	65.10	7.18	4.96
13b	105-108[e]	30	65.22	6.85	5.08

[a,b,c] Formula, molecular weight and calculated analytical data for the groups of four isomers.
[d]Hexane. [e]Diisopropyl ether. [f]EtOAc. [g]Diisopropyl ether-EtOAc.

General procedure - Synthesis of oxazinoisoquinolin-4-ones (**12a,b; 13a**)

The urethane **10a,b**; **11a** (2.0 g; 6.2 mmol) was thoroughly mixed with sodium methoxide (0.2 g; 3.7 mmol), and the mixture was maintained for 45 min at 130 °C. The melt was extracted with hot ethyl acetate (5x50 ml); the combined and filtered extract was dried (Na_2SO_4) and the solvent was evaporated. The oily residue crystallized on rubbing with diethyl ether.

(2*S**,11b*R**)-9,10-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-2*H*,4*H*[1,3]oxazino[4,3-*a*]isoquinolin-4-one **13b**

The aminoalcohol **5b** (0.60 g; 2.4 mmol) in dry benzene (10 ml) was mixed with triethylamine (0.49 g; 0.67 ml; 4.8 mmol), and a 20% solution of phosgene in toluene (1.2 ml; 2.4 mmol) was added. The mixture was allowed to stand for 2 h at ambient temperature. Ethyl acetate (50 ml) was added, and the organic phase was washed by shaking with 2N hydrochloric acid (30 ml) and then with water (2x30 ml). After drying and evaporation of the solvents, the remaining oil became crystalline on rubbing with diethyl ether.

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