Synthesis and stereochemistry of stereoisomeric 1,2,3-oxathiazino[4,3-*a*]isoquinolines

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The ring-closures of homocalycotomine and its 1′- and 2′-methyl-substituted diastereomers **3**, **4** and **7**, **8** with thionyl chloride or with sulfuryl chloride led to 1,2,3-oxathiazino[4,3-*a*]isoquinoline derivatives **9–11** and **18**, **19** or to **15**, **17** and **22**, **23**, respectively. The relative configurations and the predominant conformations of the *cis*[1]–*trans*–*cis*[2] conformational equilibrium were studied by means of ^{1}H- and ^{13}C-NMR spectroscopy, with the application of DNOE, 2D HSC and 2D-COSY measurements. In good agreement with the liquid-phase results, the X-ray investigations revealed that **9** and **10** have the *cis*[1], while **18** has the *trans*-anellated stereostructure.

Introduction

Benzo[*a*]quinolizidines and their heteroanalogues, the angularly tetrahydroisoquinoline-fused saturated 1,3-heterocycles, have been thoroughly studied from both stereochemical and pharmacological aspects.[1–7] The hetero atoms, the substituents on the saturated rings and the configurations of the substituted carbon atoms have been demonstrated to exert pronounced effects on the conformation of these compounds.[7–9]

The possibility of synthesis, and especially enantioselective synthesis, and the properties, *e.g.* the conformational behaviour, of the 1,2,3-oxathiazine ring system[10–12] and some related heterocycles[13–17] are therefore of current interest. As a continuation of our systematic studies on the synthesis, stereochemistry and pharmacological acitivity of isoquinoline-fused 1,3-heterocycles,[5–8] our present aim was to prepare and investigate the stereostructures of the title compounds, a new ring system. In this paper, the synthesis, and determination of the stereostructure of 1,2,3-oxathiazino[4,3-*a*]isoquinoline derivatives will be discussed. The bioactivity testing of the substances is in progress.

Results and discussion

The 1-methyltetrahydroisoquinoline derivatives **3** and **4** were synthesized in two independent ways.[18] The 1′-methyl-substituted homocalycotomine **3** was prepared from the corresponding 1-ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline by C-1′ alkylation with methyl iodide, followed by reduction according to the literature.[19] Its diastereomer **4** was synthesized *via* a new method: formaldehyde addition to **1**, followed by sodium borohydride reduction and fractional crystallization resulted in a 51% overall yield of the diastereomerically pure amino alcohol **4** (Scheme 1). The relative configuration of **4** was proved by transforming amino alcohol **4** to the previously known azetoisoquinoline **5** with thionyl chloride,[19] followed by alkali treatment.

The 2′-methyl-substituted homocalycotomines **7** and **8** were prepared from the corresponding 1-isoquinolylacetone (Scheme 2).[8] The (1*R**,2′*R**) diastereomer **7** was obtained by sodium borohydride reduction of **6** at −5 °C. Compound **7** was readily converted to its (1*R**,2′*S**) counterpart **8** *via* epimerization. By using a protocol recently applied to the epimerization of enantiopure cyclic 1,2-amino alcohols,[20] a better result could be obtained than that of the earlier procedure.[8]

Homocalycotomine and amino alcohols **3, 4** and **7, 8** reacted readily with thionyl chloride in the presence of triethylamine. In the ring-closure reactions, *S*-4 epimeric oxathiazines **9**–**14** and **18**–**21** could be formed. Although TLC and the ^{1}H-NMR spectra of the crude products indicated 10–20% of the epimeric oxathiazines, after column chromatographic purification only the single isomers **9**–**11**, **18** and **19** containing the sulfoxide oxygen and H-11b in the *cis* position, were isolated (Scheme 3). These types of compounds are highly sensitive to nucleophilic attack.[14–17] Accordingly, in the purification process, the less stable minor diastereomers **12**–**14** and **20**, **21** were decomposed by the moisture present and gave the starting amino alcohols.

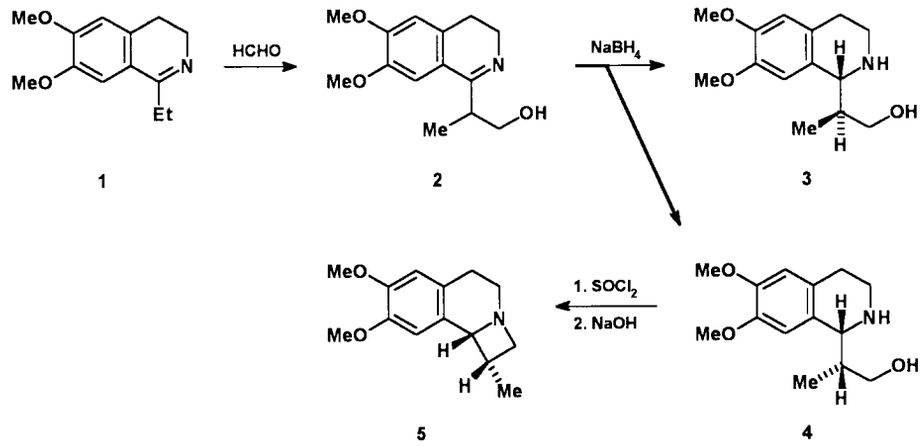
A number of different oxidation methods have been developed to prepare sulfones from sulfoxides (see *e.g.* refs. 10, 11, 14–17). We have prepared sulfones by a direct method from homocalycotomines. When they were reacted with sulfuryl chloride in the presence of triethylamine, the desired sulfones **15**, **17** and **22**, **23** were formed in 10–47% yields. Compound **16** was found to be unstable in the purification process.

Structure

The stereostructure of tetrahydroisoquinoline-fused six-membered saturated 1,3-heterocycles can be described by a conformational equilibrium of *cis*[1]–*trans*–*cis*[2] type (Fig. 1). In the *trans* structure, the B/C hetero rings are *trans*-anellated, with H-11b and the N-5 lone pair *trans-diaxial*. In the two other configurations, the hetero rings are *cis*-anellated, where in the *cis*[1] conformation C-1 is in the *inside* position, while in the *cis*[2] conformation C-1 is in the *outside* position (Fig. 1).

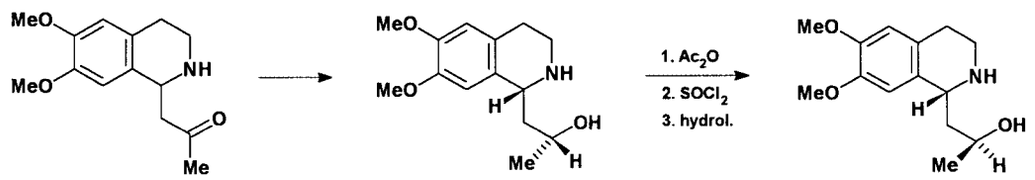
The characteristic ^{1}H- and ^{13}C-NMR spectral data are listed in Tables 1 and 2. Elucidation of the constitution of the new compounds is straightforward from these data and only the stereostructure needs further explanation.

Four problems are to be considered: (i) the *B*/*C* anellation; (ii) the preferred conformation in *cis*-*B*/*C* anellated structures (*cis*[1] or *cis*[2]); (iii) the orientation (*cis* or *trans* to H-11b) of the 1- or 2-methyl substituent (the C-1 or C-2 configuration) in the methyl-substituted derivatives; and (iv) the stereoposition of



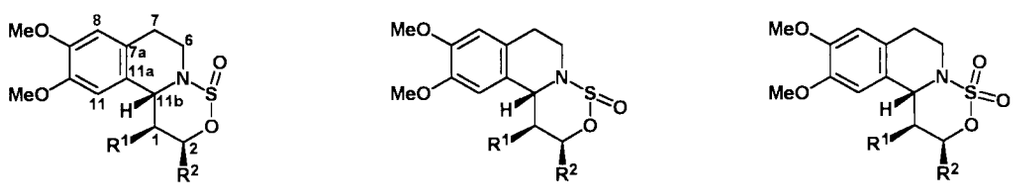
1 2 3 4 5

Scheme 1



6 7 8

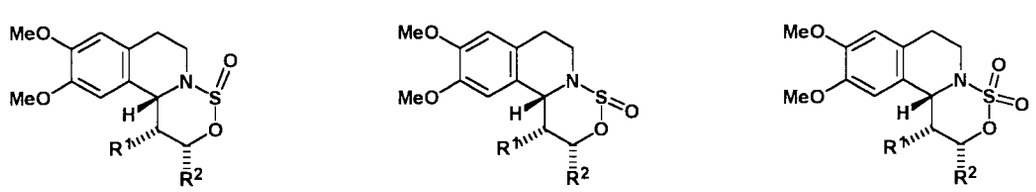
Scheme 2



9: $R^1 = R^2 = H$ **12**: $R^1 = R^2 = H$ **15**: $R^1 = R^2 = H$

10: $R^1 = Me$, $R^2 = H$ **13**: $R^1 = Me$, $R^2 = H$ **16**: $R^1 = Me$, $R^2 = H$

11: $R^1 = H$, $R^2 = Me$ **14**: $R^1 = H$, $R^2 = Me$ **17**: $R^1 = H$, $R^2 = Me$



18: $R^1 = Me$, $R^2 = H$ **20**: $R^1 = Me$, $R^2 = H$ **22**: $R^1 = Me$, $R^2 = H$

19: $R^1 = H$, $R^2 = Me$ **21**: $R^1 = H$, $R^2 = Me$ **23**: $R^1 = H$, $R^2 = Me$

Scheme 3 Relative configurations of **9**–**11**, **18** and **19**: 11b*R**,4*R**; **12**–**14**, **20** and **21**: 11b*R**,4*S**.

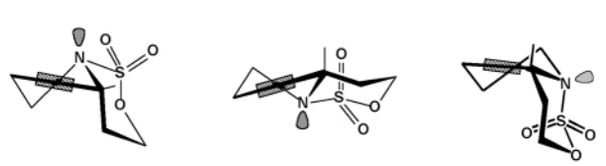


Fig. 1 Possible steric structures of 1,2,3-oxathiazino[4,3-*a*]isoquinoline-4,4-dioxides.

the S=O bond (or the lone pair on S), *i.e.* the S configuration in the sulfoxides.

To determine the stereostructures of our new compounds, it is reasonable to start with the sulfone **15**, because only the first two of the above problems arise in this case. The 12.4 Hz H-1,H-11b vicinal coupling in **15**, corresponding to a 1,3-*diaxial*-type interaction, excludes the chemically *ab ovo* improbable (sterically unfavourable) *cis*[2] structure, where this coupling would be much smaller, due to the 60° dihedral angle of the interacting hydrogens.[21] Consequently, only the *cis*[1] and *trans* structures as the preferred ones remain to be considered. (The high value of the *diaxial* coupling refers to a quasi-rigid system.)

Due to the two chiral centres (C-2 and C-11b) in the 2-methyl-substituted sulfone derivatives, two diastereomers **17** and **23** can exist, and both were synthesized. The *cis*[2] form is

Table 1 ^{1}H-NMR data[a] on compounds **9**–**11**, **15**, **17**–**19**, **22** and **23** in $CDCl_3$ solution at 500 MHz[b]

	CH_3[c] *d*(3H)	OCH_3(9,10) 2 × *s*(2 × 3H)		H-1[d] 1/2 × *m*(1H/2 × 1H)		H-2[e] 1/2 × *m*(1H/2 × 1H)		CH_2(6)[f] 1/2 × *m*(2H/2 × 1H)		CH_2(7)[g] 1/2*m*(2H/2 × 1H)		H-8,11[h] 2 × *s*(2 × 1H)		H-11b[i] *dd*(1H)
9	—	3.86	3.87	1.88	2.30	3.98	5.11	3.26	3.35	~2.9		6.60	6.56	5.06
10	0.95	3.83	3.85	2.35		3.75	4.61	3.45		2.84	3.01	6.62	6.59	4.83
11	1.74	3.86	3.87	2.10	2.32	4.50		3.20	3.36	2.87	2.91	6.60	6.57	5.07
15	—	3.85	3.86	1.83	2.26	4.50	4.88	3.32	3.80	2.77	3.05	6.62	6.51	5.10
17	1.78[j]	3.85	3.87	1.75[j]	2.38	4.90		3.40	3.73	2.80	3.00	6.62	6.47	5.14
18	0.94	3.85	3.86	2.25		3.84	5.23	2.82	3.38	2.64	3.00	6.56	6.57	5.07
19	1.34	3.88	3.89	~1.9		5.20		3.25	3.32	~2.9		6.61	6.58	5.05
22	0.97	3.84[j]	3.87	2.28		4.39	5.01	3.18	~3.85[j]	2.75	2.98	6.61	6.52	4.94
23	1.42	3.84	3.85	~1.9		~5.0[j]		3.25	3.76	2.75	3.03	6.60	6.50	~5.0[j]

[a] Chemical shifts in ppm (δ_{TMS} = 0 ppm) and coupling constants in Hz. [b] Assignments were supported by DNOE (**10**, **11**, **17**–**19** and **22**) and 2D-HSC (**10**, **17**, **18**, **22** and **23**), and for **17** and **19** also by 2D-COSY measurements. [c] *J*: 6.8 (**10**, **11** and **18**), 6.4 (**19** and **23**) and 7.1 (**17** and **22**). [d] Complex multiplet of 1H (**10**, **18** and **22**) or 2H intensity (**19** and **23**), for **9**, **11** and **15** upfield signal *td* (*J*: 14, 4, 4), downfield signal *dqa* (**9** and **15**, *J*: 13.5, 5.3) or *ddd* (**11**, *J*: 14.1, 10.3, 5.4 and **17,** *J*: 14.5, 12.0, 6.2). [e] Upfield signal *ddd* for **9** (*J*: 11.5, 4.7, 1.6), *dd* for **10** (*J*: 11.5, 4.5), **15** (*J*: 11.4, 4.9), **18** and **22** (*J*: 11.2, 1.2), downfield signal *ddd* for **9** (*J*: 13.1, 11.6, 2.5) and **15** (*J*: 11.5, 11.5, 2.5), *t* for **10** (*J*: 11.5) and *dd* for **18** and **22** (*J*: 11.5, 2.5), unresolved sextet (1H) for **11,** *m* (1H) for **17** and **19** (*J*: 5.6). [f] Two (**9**, **11** and **19**) or one (**10**) unresolved *m* (2 × 1H or 2H intensity), upfield signal *dt* (*J*: 11.6, 3.7,) for **15** and **23**, (*J*: 11.0, 4.0 for **17** and 11.0, 2.8 for **18**), *ddd* (*J*: 11.2, 9.6, 3.8 for **22**), downfield signal *ddd* (*J*: 11.8, 5.8, 2.6 for **15** and **23**, *J*: 11.0, 4.6, 2.3 for **18**); *td* (*J*: 11.8, 5.3) for **17**. [g] Unresolved *m* (2H) for **9**, **19**, upfield signal *td* (*J*: 16.0 ± 0.2, 3.2 ± 0.2 for **10**, **15** and **23**, 15.8, 4.2 for **22**, unresolved for **11** and **17**), ~*d* (*J*: ~15) for **18**, downfield signal *ddd* (*J*: 16.5, 11.2, 5.6 for **15** and **23**, *J*: 15.9, 10.1, 5.7 for **17**), unresolved *m* (**10** and **22**), *dt* (**18**), *td* (**11**). [h] Interchangeable assignments, except for **10**, **11**, **17**, **18**, **19** and **22**, for which combined DNOE and 2D-HSC measurements proved the given assignments. [i] *dd* (*J*: 12.2, 2.8) for **9** and **15**, *J*: 10.4, 4.2 (**11**), *J*: 11.8, 3.0 (**17**), *J*: 9.9, 5.0 (**19**), *d*, *J*: 10.7 (**10**), 2.3 (**22**), unresolved signal, half-width 5 Hz for **18**. [j] Overlapping signals.

Table 2 ^{13}C-NMR chemical shifts[a] of compounds **9**–**11**, **15**, **17**–**19**, **22** and **23**[b]

	CH_3	C-1	C-2	C-6	C-7	C-7a[c]	C-8	C-9[d]	C-10[d]	C-11	C-11a[c]	C-11b	OCH_3	
9	—	30.1	58.6	40.7	28.7	125.7	111.6	147.9	148.1	108.8	127.6	45.8	55.9	56.1
10	15.2	31.1	63.8	39.2	28.2	125.3	111.7	146.5	148.5	112.6	126.2	51.5	55.8	56.1
11	23.3	36.1	73.8	41.6	29.1	126.1	111.8	148.0	148.1	108.9	128.1	42.3	56.0	56.2
15	—	27.3	71.5	40.2	28.1	125.0	111.5	148.0	148.5	109.1	126.1	57.2	55.9	56.1
17	20.4	33.1	80.8	41.0	28.6	125.8	112.1	148.4	148.9	109.4	126.5	60.8	56.3	56.6
18	10.3	33.5	64.1	42.9	28.3	125.5	110.8	147.0	147.4	107.6	126.4	49.4	55.1	55.3
19	21.5	37.5	65.4	40.5	28.8	125.7	111.6	147.9	148.1	108.8	127.7	46.5	55.9	56.1
22	11.4	34.2	77.4	41.9	28.4	126.7	111.5	148.2	148.3	108.1	124.4	60.8	55.9	56.2
23	21.4	35.4	80.5	40.6	28.6	125.5	111.9	148.4	148.9	109.5	126.5	57.0	56.3	56.5

[a] In $CDCl_3$ solution at 500 MHz, δ_{TMS} = 0 ppm. [b] Assignments were supported by DEPT (except for **18**) and 2D-HSC (**10**, **17**, **18**, **22** and **23**) measurements. [c,d] Interchangeable assignments.

not possible in these compounds either. The H-1,H-11b couplings are 11.8 and 3.0 Hz for **17** and, though the values of these couplings cannot be determined in **23** because of signal overlap (H-2 and H-11b), no sign of a sterically crowded structure was observed. A change in the *B*/*C* ring anellation is not probable because of the similar C-6 chemical shifts (41.0 and 40.6 ppm). In the *cis*^{I} form, there is a strong steric interaction between the close-lying H-1*ax* and H-6*ax*, and the corresponding field effect (steric compression shift[22a,23]) must be manifested in an upfield shift of the C-6 signal.

The upfield shift of the C-1 and C-11b lines of **17** (by 2.3 and 3.4 ppm) as compared to its isomer **23** suggested the sterically more unfavourable structure of **17**, *i.e.* the *axial* orientation of the 2-methyl group in it. Accordingly, the chemical shifts of H-2 in **23** and of the methyl hydrogens in **17** are larger in consequence of the anisotropic neighbouring effect of the S=O bond in the 1,3-*diaxial* position.[22b]

It follows that **17** and **23** must have the 2*S**,11b*R** and 2*R**,11b*R** configurations, respectively, that is H-11b and the methyl group are in the *cis* (**17**) and *trans* (**23**) positions, respectively.

To decide between the *cis*^{I} and *trans* forms (*cis*- or *trans*-*B*/*C* anellation), we performed differential nuclear Overhauser effect (DNOE[22c,24]) measurements (Table 3), which proved the steric proximity of H-1*ax* and H-6*ax* and hence the *cis*^{I} structure involving *cis*-*B*/*C* anellation in **17**.

Disregarding the α and β effects[22d,25] of the methyl substitution (resulting in downfield shifts of the C-2 and C-1 signals for **17** and **23**, respectively, relative to **15**), no significant changes were observed for the ^{1}H- and ^{13}C-NMR chemical shifts of **15** as compared to **17** and **23** (except for the field effect on C-11b in **17**, mentioned above), and hence the stereohomogeneous character and *cis* anellation can be regarded as proved for all three compounds (Fig. 2).

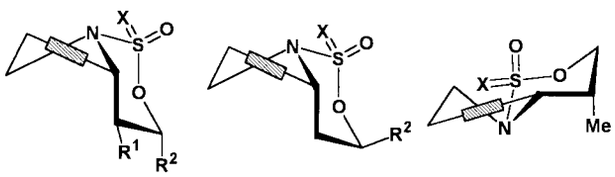
Table 3 NOE results relevant to the steric structure (nontrivial responses) for compounds **10**, **11**, **17**–**19** and **22**

Saturated signals	H-1*ax*	H-2*ax*	H-6*ax*	H-11b	CH_3
H-1*ax*			**10**, **11**, **17**		
H-2*ax*				**18**, **19**	
H-6*ax*	**10**, **11**, **17**			**11**, **18**, **22**	[**22**][a]
H-11b		**18**, **19**	**11**, **18**, **22**		**11**
CH_3[b]			[**22**][a]	**11**	

[a] [**22**]: The absence of these interactions excludes the *cis*-*B*/*C* anellation. [b] Position 2 (**11**) or position 1 (**22**).

The only 1-methyl-substituted sulfone formed from **4** has a H-1,H-11b coupling of 2.3 Hz. Consequently, the 1-methyl group must be *axial* in the preferred conformation. If so, the *cis*^{I} structure can be excluded because of the very strong steric hindrance which would then act between the methyl group and H-6*ax*. Hence, the *B*/*C* anellation and the mutual position of the methyl group and H-11b must be *trans*. The configurations are: 1*R**,11b*R** and the structure is **22** (Fig. 2).

This stereostructure is supported (i) by the strong field effect between the methyl group and the lone pairs on O-3 and N-5 in the 1,3-*diaxial* position, causing upfield shifts of the methyl carbon line relative to **17** and **23**; (ii) by the upfield shift of the



cis *trans*

9 (X = ⬭, R^1 = R^2 = H) **18** (X = ⬭)
15 (X = O, R^1 = R^2 =H) **22** (X = O)

10 (X = ⬭, R^1 = Me, R^2 = H) **11** (X = ⬭, R^2 = Me)
19 (X = ⬭, R^1 = H, R^2 = Me) **17** (X = O, R^2 = Me)
23 (X = O, R^1 = H, R^2 = Me)

Fig. 2 Steric structures of 1,2,3-oxathiazino[4,3-*a*]isoquinolines investigated.

signal of the methyl hydrogens (0.97 ppm, whereas for the other two sulfones 1.78 and 1.42 ppm were measured), this being a consequence of the anisotropy of the aromatic ring above its plane;[22e] (iii) by the downfield shift of the C-6 line (by 1.7 ppm in comparison with **15**) in the absence of the field effect present in the case of *cis*-*B*/*C* anellation; (iv) by DNOE results (*cf.* Table 3).

The chemical shifts of H-6*ax* and H-11b have practically the same value in the sulfone **15** and the sulfoxide **9**. The change in the H-2*ax* shift is also only moderate ($\Delta\delta$H-2*ax*: 0.23 ppm), but the shift differences for the H-2*eq* and H-6*eq* multiplets are very large (0.52 and 0.54 ppm). These observations prompted the conclusion that in **9** the S=O bond must be *axial*, *i.e. cis* to H-11b. The changes in the C-2 and C-11b shifts (the difference in the β effects of the SO and SO_2 groups) are significant and similar (12.9 and 11.4 ppm), and the C-6 shift is practically unchanged in **9**, suggesting an unaltered preferred (*cis*^{1}) conformation. The configurations in **9** are therefore 4*R**,11b*R** (Fig. 2), in accordance with the X-ray results (Fig. 3).

As concerns the isomeric sulfoxide pairs **10** and **18** and **11** and **19**, the very similar ^{1}H- and ^{13}C-NMR chemical shifts for the groups in positions 6 and 11b in **9** and **11** suggest analogous steric structures, *i.e.* dominance of the *cis*^{1} conformation in the conformational equilibrium and an *axial* S=O bond. The DNOE experiment confirmed the *cis*^{1} conformation (*cis*-*B*/*C* anellation) and the 1,3-*diaxial* position for the 2-methyl group and H-11b. The steric structure (Fig. 2) involving the 2*S**,4*R**,11b*R** configuration of **11** can be taken as proved. The high deshielding of the methyl hydrogens is noteworthy, due to the anisotropic effect of the S=O bond in the 1,3-*diaxial* orientation (*cf.* with compound **17**). It is to be noted, that a weak NOE between H-6*ax* and H-11b refers to a conformational equilibrium, where besides the *cis*^{1} the *trans* form is also present. Hence, in contrast to the other practically stereohomogeneous, quasi-rigid compounds **11** is a more flexible molecule.

The NOE results are consistent with an *equatorial* (*trans* to H-11b) 2-methyl group in **19**. The practically unchanged ^{1}H- and ^{13}C-NMR chemical shifts of the methylene groups in positions 1 and 6 for the pair of epimers **11** and **19** exclude a different ring anellation, which is therefore also *cis*^{1} in **19**.

Of course, the less crowded structure of **19** (Fig. 2), containing an *equatorial* 2-methyl group (the absence of the field effect due to the *axial* 2-methyl group in **11**), is revealed in the downfield shifts of the C-1 and C-11b lines relative to those in **11**. The deshielding effect of the S=O bond (in the 1,3-*diaxial* orientation: *cis* to H-11b) explains the large downfield shift (0.7 ppm) of the H-2 signal in **19**. The configurations are 2*R**,4*R**,11b*R** (Fig. 2).

The NOE measurements prove the *trans*-*B*/*C* anellation for **18**. This structure is supported by the downfield shift (by 3.7 ppm) of the C-6 line of **18** as compared to **10**, in the absence of steric hindrance between H-1*ax* and H-6*ax* in the *cis*^{1} form. The upfield shift of the methyl carbon line (10.3 ppm), similar to that for **22** (11.4 ppm), again suggests analogous steric structures. The irregular[22g] relation δH-2*ax* > δH-2*eq* is due to the anisotropic effect of the S=O bond on H-2*ax* and supports the *axial* position of this bond (*cf.* **19**). The 1-methyl group is *axial* and *trans* to H-11b, as shown by the small H-1,H-11b coupling (<5 Hz). This structure (1*S**,4*R**,11b*R**) is also confirmed by the X-ray diffraction results (Fig. 2 and 3).

The DNOE experiment with the isomeric counterpart **10** demonstrated the *cis*^{1} conformation and *axial* position of H-1. The latter fact and also the large (*diaxial* type) coupling constant of the H-1,H-11b interaction confirm the *cis* arrangement of H-11b with the *equatorial* 1-methyl group. X-ray measure-

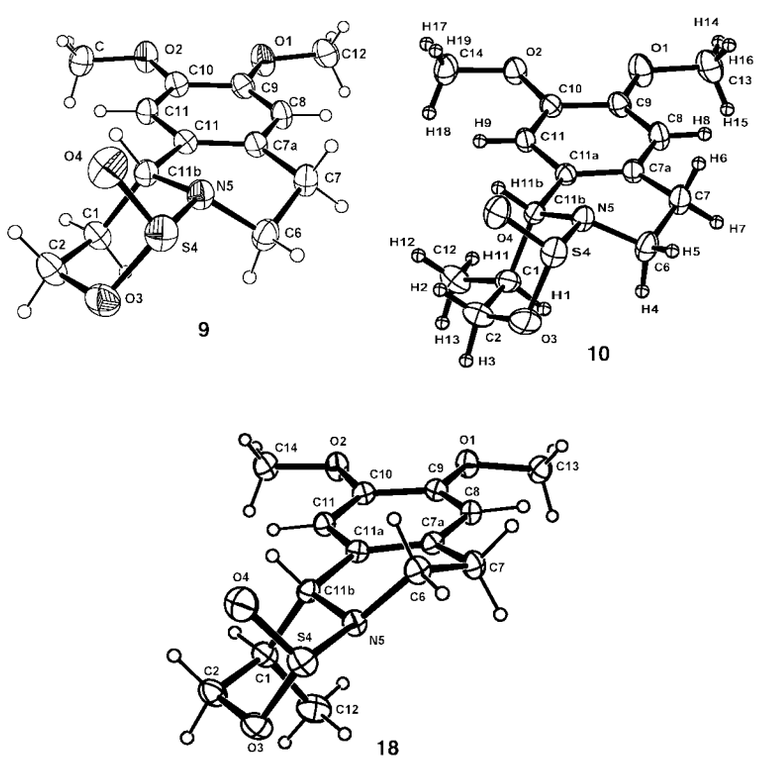


Fig. 3 Perspective views of **9**, **10** and **18**.

Table 4 Physical and analytical data on 1,2,3-oxathiazino[4,3-*a*]isoquinolines prepared

Compound	Yield (%)	Mp/°C	Found (%)			Formula (MW)	Requires (%)		
			C	H	N		C	H	N
9	30	118–119[a]	54.89	6.11	4.80	$C_{13}H_{17}NO_4S$ (283.35)	55.11	6.05	4.96
10	26	113–114[a]	56.35	6.27	4.54	$C_{14}H_{19}NO_4S$ (297.38)	56.55	6.44	4.71
11	29	79–81[b]	56.27	6.52	4.48	$C_{14}H_{19}NO_4S$ (297.38)	56.55	6.44	4.71
15	14	133–134[a]	51.85	5.70	4.62	$C_{13}H_{17}NO_5S$ (299.35)	52.16	5.72	4.68
17	30	130–133[a]	53.27	6.03	4.51	$C_{14}H_{19}NO_5S$ (313.38)	53.66	6.11	4.47
18	47	138–139[b]	56.23	6.20	4.81	$C_{14}H_{19}NO_4S$ (297.38)	56.55	6.44	4.71
19	10	93–97[a]	56.66	6.81	4.56	$C_{14}H_{19}NO_4S$ (297.38)	56.55	6.44	4.71
22	20	109–111[a]	53.79	6.34	4.60	$C_{14}H_{19}NO_5S$ (313.38)	53.66	6.11	4.47
23	19	126–127[b]	53.93	6.28	4.59	$C_{14}H_{19}NO_5S$ (313.38)	53.66	6.11	4.47

Solvent for recrystallization: [a] diisopropyl ether, [b] ethyl acetate–diisopropyl ether.

ments provided proof of the *axial* position of the S=O bond, and thus the configuration of **10** is 1*S**,4*R**,11b*R** (Fig. 2 and 3).

To support our conclusions concerning the stereostructures, it is convincing to compare the sulfone–sulfoxide counterparts. The larger β effect of the SO_2 group as compared to that of the SO group resulted in downfield shifts of the C-2 and C-11b lines for the pairs **11** and **17**, **18** and **22** and **19** and **23** by 7.0 and 11.3, 11.4 and 13.3, and 10.5 and 15.5 ppm, respectively. Thus, the same sign and the similar values of the shift differences for these three pairs support the analogous steric structures, the identical ring anellation of the pairs and the exclusively α-*axial* position of the S=O bond in the sulfoxides.

From the steric structures determined by NMR and X-ray measurements, all the prepared sulfones and sulfoxides can be concluded to be characterized by *cis*[1]-*B*/*C* anellation, with the exception of the two compounds, **18** and **22**, that contain a *trans* (to the H-11b) 1-methyl substituent. In these compounds, the strong steric hindrance between H-6*ax* and the 1-methyl group makes the *cis*-*B*/*C* anellation unfavourable and the molecules take the *trans* form by nitrogen inversion. The *cis*[2] structure would also be unfavourable in consequence of the strained molecular skeleton and the strong steric interaction of H-11 with the here *equatorial* 1-methyl group and H-2*ax*.

X-Ray data

Perspective views of the molecules **9**, **10** and **18** are shown in Fig. 3. It can be seen from Ortep drawings that the methoxy groups are in each case almost coplanar with the benzene ring. In **9** and **18**, C-6 is below, while N-5 is in the opposite position relative to the best plane of the isoquinoline moiety. The oxathiazine ring has an almost perfect chair conformation, oriented *cis*[1] to the isoquinoline ring. The distance of N-(5) from the S(4)–C(11b)–C(6) plane is −0.3887 and −0.3523 Å, respectively. In **10**, C-6 is above, while N-5 is in the opposite position relative to the best plane of the isoquinoline moiety and ring B now adopts a sofa-like conformation. The oxathiazine ring has an almost perfect chair conformation, oriented *trans* to the isoquinoline ring. The distance of N-(5) from the S(4)–C(11b)–C(6) plane is 0.403 Å.

Experimental

The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at room temperature on a Bruker DRX-500 FT-spectrometer at 500.13 (^{1}H) and 125.76 MHz (^{13}C), respectively, using the ^{2}H signal of the solvent as the lock and TMS as internal standard. 2D-COSY,[26a] NOE difference (DNOE)[22c,24] and two-dimensional heteronuclear shift correlation (2D-HSC) measurements[26b] were carried out with the standard software written for the Bruker DRX spectrometers. DEPT spectra[27] were run in a standard way,[28] using only the $\Theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up" and "down", respectively.

Melting points were determined with a Kofler apparatus and the values are not corrected. The physical and analytical data on the compounds prepared are listed in Table 4.

The homocalycotomine and amino alcohol **3** were prepared according to the literature.[19,29]

(1*R**,1′*R**)-1-(1′-Methyl-2′-hydroxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (4)

1-Ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (21.9 g, 0.1 mol) was added to a suspension of paraformaldehyde (6.0 g, 0.2 mol) in methanol (70 ml) with stirring. Freshly prepared sodium ethoxide was added dropwise to the suspension until a light-yellow, homogeneous solution was obtained (about 0.5 g sodium in 25 ml ethanol was needed). After stirring for 5 h at room temperature, 20% ethanolic hydrogen chloride (25 ml) was added with ice cooling. The separated 1-(1′-methyl-2′-hydroxyethyl)-6,7-dimethoxy-3,4-tetrahydroisoquinoline hydrochloride was filtered off (mp 177–181 °C). The hydrochloride obtained was basified with 10% sodium carbonate solution and extracted with chloroform. The base obtained was dissolved in methanol (150 ml), the solution was cooled with ice, and sodium borohydride (10.2 g, 0.3 mol) was added in small portions. Stirring was continued for 3 h at room temperature, the solution was then evaporated, and the residue was suspended in water (100 ml) and extracted with chloroform (3 × 100 ml). After drying and evaporation of the solvent, a 5:1 mixture of amino alcohols **4** and **3** was obtained. Fractional crystallization of the product from ethyl acetate resulted in the diastereomerically pure **4** in 51% overall yield, mp 137–139 °C, Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.02; H, 8.51; N, 5.43%.

(1*R**,2′*R**)-1-(2′-Hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7)

The hydrochloride of **6** (24.9 g, 0.1 mol) was suspended in methanol (200 ml). The suspension was stirred and cooled in an ice–salt bath. Sodium hydrogen carbonate (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 for a further 3 h and processed in the usual way. Fractional crystallization of the crude product, containing a *ca.* 6:1 mixture of diasteromers **7** and **8**, from ethyl acetate resulted in the diastereomerically pure **7**. Yield: 62%, mp 130–131 °C (the melting point of **7** was given erroneously earlier[8]).

(1*R**,2′*S**)-1-(2′-Hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (8)

To a stirred suspension of **7** (12.6 g, 50 mmol) in ethyl acetate (150 ml) cooled in an ice-bath and water (150 ml), sodium

carbonate (7.95 g, 75 mmol) was added. After dropwise addition of acetic anhydride (5.61 g, 55 mmol), the mixture was stirred at 0–5 °C for 1 h, and was then allowed to warm to room temperature over 1 h, and stirring was continued for an additional 1 h. The organic phase was separated off and the aqueous phase was extracted with ethyl acetate (3 × 100 ml). After drying and evaporation, the *N*-acetyl derivative of **7** was obtained (mp 141–143 °C) which was used further without purification. This material was dissolved in dry chloroform (30 ml) and the solution was added dropwise to ice-cooled, stirred thionyl chloride (15 ml) over 30 min. The reaction mixture was allowed to warm to room temperature over 1 h, stirred at room temperature for an additional 2 h, and then evaporated. To the residue, 10% HCl (170 ml) was added and the mixture was heated under reflux for 1 h. The cooled solution was washed with diethyl ether (2 × 50 ml) and made alkaline (20% NaOH) under cooling. After extraction with chloroform (4 × 100 ml), drying and evaporation, crude **8** was obtained, which was recrystallized from diisopropyl ether–ethyl acetate. Yield: 58%, mp 106–108 °C (the melting point of **8** was given erroneously earlier[8]).

General procedure for the preparation of 1,2,3-oxathiazino-[4,3-*a*]isoquinoline-4-oxides (9–11 and 18, 19)

To a solution of the corresponding homocalycotomine derivative (5 mmol) and triethylamine (1.42 ml, 10 mmol) in anhydrous dichloromethane (30 ml), cooled to −20 °C, a solution of thionyl chloride (0.38 ml, 5.2 mmol) in anhydrous dichloromethane (30 ml) was added at −20 °C, over a period of 10 min. The mixture was maintained at this temperature for 3 h, allowed to warm to room temperature and stirred for a further 48 h. The reaction mixture was washed with saturated sodium hydrogen carbonate (2 × 15 ml) and with water (2 × 15 ml), and dried (Na_2SO_4). After evaporation of the solvent, the crude oily product was purified by column chromatography, elution being performed with ethyl acetate.

General procedure for the preparation of 1,2,3-oxathiazino-[4,3-*a*]isoquinoline-4,4-dioxides (15, 17, 22 and 23)

To a solution of homocalycotomine derivative (5 mmol) and triethylamine (10 mmol) in anhydrous dichloromethane (30 ml), a solution of sulfuryl chloride (0.41 ml, 5.2 mmol) in anhydrous dichloromethane (30 ml) was added at −20 °C over a period of 10 min. The mixture was maintained at this temperature for 3 h, allowed to warm to room temperature and stirred for a further 48 h. The reaction mixture was washed with saturated sodium hydrogen carbonate (2 × 15 ml) and with water (2 × 15 ml), and dried (Na_2SO_4). After evaporation of the solvent, the crude oily product was purified by column chromatography, with elution with ethyl acetate.

X-Ray diffraction studies

All data were collected on a Rigaku AFC5S diffractometer with graphite-monochromated MoKα radiation ($\lambda = 0.71069$ Å). The lattice parameters were calculated by least-squares refinements of 25 reflections. The data were corrected for Lorentz and polarization effects.

The structures were solved by direct methods and refined by full-matrix least-squares techniques to $R = 0.036$ ($R_w = 0.039$) for **9**, $R = 0.035$ ($R_w = 0.044$) for **10** and $R = 0.033$ ($R_w = 0.044$) for **18**. The heavy atoms were refined anisotropically, and the H atoms with fixed isotropic temperature factors (1.2 times B_{eq} of the host atom). The methyl H-atoms were included in calculated positions. Neutral atomic scattering and dispersion factors were taken from *International Tables*.[30] All calculations were performed with TEXSAN[31] crystallographic software. The figures were drawn with ORTEP-II.[32] Atomic coordinates, and full lists of bond lengths and angles for **9**, **10** and **18** have been deposited at the Cambridge Crystallographic Data Centre.†

Crystal data for 9. $C_{13}H_{17}NO_4S$, $M_r = 283.35$, monoclinic, space group $P2_1/n$ (No. 14), lattice parameters: $a = 10.251(1)$, $b = 9.291(1)$, $c = 14.606(1)$ Å, $\beta = 104.33(1)°$, $Z = 4$, $V = 1347.8(3)$ Å^3. $D_c = 1.396$ g cm^{-3}, μ(MoKα) = 2.38 cm^{-1}, $F(000) = 600$, $T = 294$ K; colourless prisms, crystal dimensions 0.22 × 0.32 × 0.38 mm.

Crystal data for 10. $C_{14}H_{19}NO_4S$, $M_r = 297.38$, triclinic, space group $P\bar{1}$ (No. 2), lattice parameters: $a = 9.2390(6)$, $b = 10.0433(8)$, $c = 8,7398(6)$ Å, $\alpha = 96.680(7)$, $\beta = 112.886(6)$, $\gamma = 81.562(7)°$, $Z = 2$, $V = 737.5(1)$ Å^3, $D_c = 1.339$ g cm^{-3}, μ(MoKα) = 2.21 cm^{-1}, $F(000) = 316$, $T = 294$ K; colourless prisms, crystal dimensions 0.22 × 0.26 × 0.32 mm.

Crystal data for 18. $C_{14}H_{19}NO_4S$, $M_r = 297.38$, triclinic, space group $P\bar{1}$ (No. 2), lattice parameters: $a = 8.3082(6)$, $b = 12.308(1)$, $c = 7.5713(5)$ Å, $\alpha = 105.084(6)$, $\beta = 92.260(7)$, $\gamma = 104.576(7)°$, $Z = 2$, $V = 718.9(1)$ Å^3, $D_c = 1.374$ g cm^{-3}, μ(MoKα) = 2.26 cm^{-1}, $F(000) = 316$, $T = 294$ K; colourless prisms, crystal dimensions 0.22 × 0.34 × 0.38 mm.

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† CCDC reference number 188/203. See http://www.rsc.org/suppdata/p2/a9/a907236e for crystallographic files in .cif format.

References

1 J. W. Guiles and A. I. Meyers, *J. Org. Chem.*, 1991, **56**, 6873.
2 M. Sugiura, N. Takao, H. Fujiwara and Y. Sasaki, *Chem. Pharm. Bull.*, 1978, **26**, 2555.
3 M. Rubiralta, A. Diez and J. Bosch, *Heterocycles*, 1988, **27**, 1653.
4 P. Scheiber and P. Nemes, *Heterocycles*, 1995, **41**, 2189.
5 J. Kóbor, P. Sohár and F. Fülöp, *Tetrahedron*, 1994, **50**, 4873.
6 G. Bernáth, F. Fülöp *et al.*, *Hung. Pat. 209393*, *Chem. Abstr.*, 1993, **119**, 225960.
7 F. Fülöp, G. Bernáth, M. S. El-Gharib, J. Kóbor, P. Sohár, I. Pelczer, G. Argay and A. Kálmán, *Chem. Ber.*, 1990, **123**, 803.
8 P. Sohár, L. Lázár, F. Fülöp, G. Bernáth and J. Kóbor, *Tetrahedron*, 1992, **48**, 4937.
9 B. E. Maryanoff, D. F. McComsey, R. R. Inners, M. S. Mutter, G. P. Wooden, S. L. Mayo and R. A. Olofson, *J. Am. Chem. Soc.*, 1989, **111**, 2487.
10 T. Viljanen, K. Pihlaja and F. Fülöp, *Acta Chem. Scand.*, 1996, **50**, 1036.
11 Z. Zubovics, L. Toldy, A. Varró, G. Rablóczky, P. Dvortsák, G. Jerkovich and É. Tomori, *Eur. J. Med. Chem.*, 1986, **21**, 370.
12 R. J. Goodridge, T. W. Hambley and D. D. Ridley, *Aust. J. Chem.*, 1986, **39**, 591.
13 V. K. Aggarwal, J. M. Worrall, H. Adams, R. Alexander and B. F. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1997, 21.
14 G. Lowe and M. A. Reed, *Tetrahedron: Asymmetry*, 1990, **1**, 885.
15 D. Alker, K. J. Doyle, L. M. Harwood and A. McGregor, *Tetrahedron: Asymmetry*, 1990, **1**, 877.
16 J. E. Baldwin, A. C. Spivey and C. J. Schofield, *Tetrahedron: Asymmetry*, 1990, **1**, 881.
17 H. S. H. Gautun and P. H. J. Carlsen, *Tetrahedron: Asymmetry*, 1995, **6**, 1667.
18 The compounds studied were racemates. In Scheme 1 and the Figures, C-1 (for **3**, **4** and **7**, **8**) or C-11b (for **9**–**23**) is drawn *R**.
19 J. Kóbor, F. Fülöp, G. Bernáth and P. Sohár, *Tetrahedron*, 1986, **43**, 1887.
20 S. E. Schaus, J. F. Larrow and E. N. Jacobsen, *J. Org. Chem.*, 1997, **62**, 4197.
21 M. J. Karplus, *Chem. Phys.*, 1959, **30**, 11; 1960, **33**, 1842.
22 P. Sohár, *Nuclear Magnetic Resonance Spectroscopy*, CRC Press, Boca Raton, FL, 1983, (*a*) **2**, 154–155; (*b*) **1**, 34; (*c*) **1**, 196–197; (*d*) **2**, 152–154; (*e*) **1**, 35–38; (*f*) **2**, 166; (*g*) **2**, 27.
23 D. M. Grant and B. V. Cheney, *J. Am. Chem. Soc.*, 1967, **89**, 5315.

24 J. K. M. Sanders and J. D. Mersch, *Prog. Nucl. Magn. Reson.*, 1982, **15**, 353, and references cited therein.
25 J. Mason, *J. Chem. Soc.*, 1971, 1038.
26 R. R. Ernst, G. Bodenhausen and A. Wokaun, *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Clarendon Press, Oxford, UK, 1987, (*a*) pp. 400–426; (*b*) pp. 471–479.
27 D. T. Pegg, D. M. Doddrell and M. R. Bendall, *J. Chem. Phys.*, 1982, **77**, 2745.
28 M. R. Bendall, D. M. Doddrell, D. T. Pegg and W. E. Hull, *High Resolution Multipulse NMR Spectrum Editing and DEPT*, Bruker, Karlsruhe, 1982.
29 J. Kóbor, F. Fülöp and G. Bernáth, *Heterocycles*, 1986, **24**, 2227.
30 *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham, UK, 1974, Vol. IV.
31 *teXsan for Windows: Single Crystal Structure Analysis Software*, Version 1.01. Molecular Structure Corporation, 3200 Research Forest Drive, The Woodlands, TX 77381, 1997.
32 C. K. Johnson, *ORTEP-II, Report ORNL-5138*, Oak Ridge National Laboratory, Oak Ridge, TN, 1976.

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