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Synthesis and Stereochemical Study of cis- and trans-1-(3'-Substituted-propyl)benzo[a]quinolizidine

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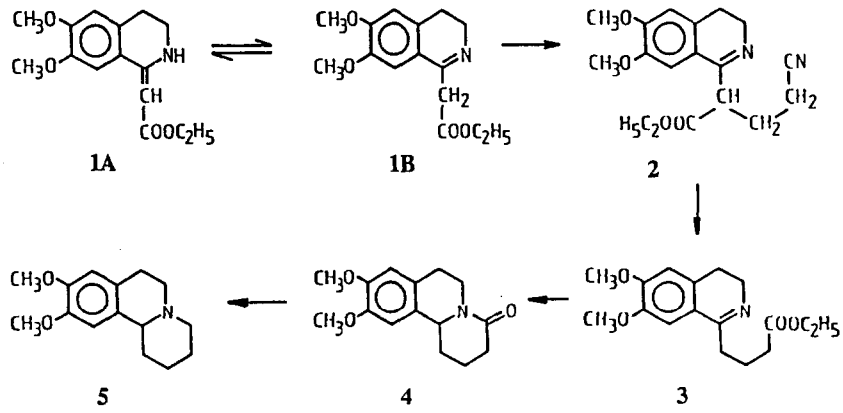
Abstract - From 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline with methyl or ethyl acrylate or with acrylonitrile, via Michael addition products, cis- and trans-1-(3'-substituted-propyl)benzo[a]quinolizidinones and quinolizidines were prepared. The relative configurations and the predominant conformations were determined by means of ^1H and ^{13}C NMR spectroscopy, with the application of DR, DNOE and 2D HSC measurements.

We earlier studied the nucleophilic reactivity of 1-ethoxycarbonylmethylene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1**), including the reaction with acrylonitrile. Our chemical and spectroscopic investigations demonstrated that a 1-(3'-ethoxycarbonylpropyl)-3,4-dihydroisoquinoline derivative (**3**) was formed from the monoacrylonitrile adduct **2** on acidic hydrolysis followed by esterification. Alkaline treatment of the reduction product obtained from **3** gave a benzo[*a*]quinolizinone derivative (**4**), the structure of which was proved by its spectroscopic data and by its reductive transformation (LAH) to the corresponding known benzo[*a*]quinolizidine derivative **5** (Scheme 1).[1]



Scheme 1

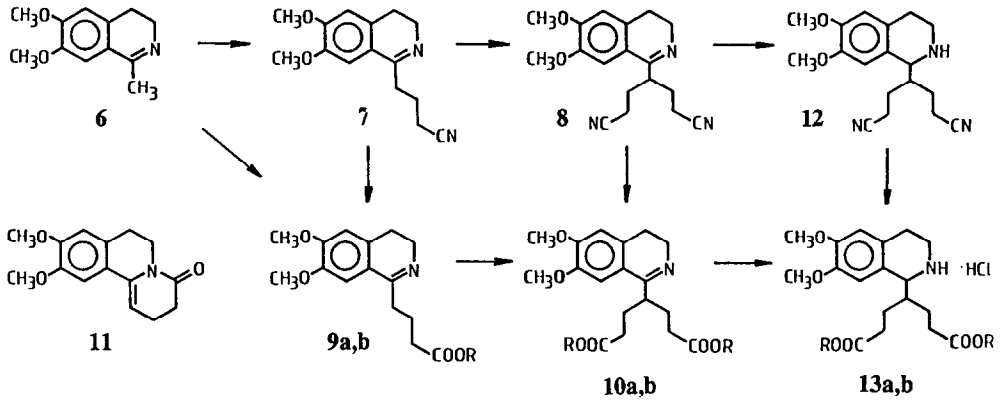
As a continuation of the earlier studies we recently investigated the nucleophilic reactivity of the methyl group in 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**6**).[2] Because of the pharmacological[3-7] and stereochemical interest[8-15] of benzo[*a*]quinolizidine derivatives, we have now studied the reactions

of **6** with acrylonitrile and acrylic esters and some transformations of the addition products. We discuss here the steric structure determination and the conformational analysis of the products.

Results and discussion

The earlier literature claimed that the reactions of **6** with acrylic derivatives were unsuccessful,[16] but in accordance with recent data,[17,18] we have found that **6** forms adducts with both acrylonitrile and acrylic esters.

With the reactants in 1:1 molar ratio, a mixture of the mono and double acrylonitrile (**7** and **8**) or acrylic ester (**9a,b** and **10a,b**) adducts was formed, which also contained unchanged starting material (**6**). When 1.5 equivalents of acrylic derivative was used, the reaction product contained the mono and double adducts (**7** and **8**, or **9a,b** and **10a,b**) without any trace of compound **6**. The components of these mixtures were separated by fractional crystallization. In the cases of ethyl and methyl acrylate, benzo[*a*]-quinolizidin-4-one (**11**) was also isolated from the reaction mixture as a side-product, which was poorly soluble in ether. Its formation could be explained by an intramolecular cyclocondensation, which occurred via the enamine tautomeric form presumed for the acrylic ester monoadducts. With two or more equivalents of acrylonitrile or acrylic ester, the double adducts (**8** or **10a,b**) were formed as sole products. The monoadducts could be transformed to the double adducts through the use of one or more equivalents of acrylonitrile (**7** **8**) or acrylic ester (**9a,b** **10a,b**).



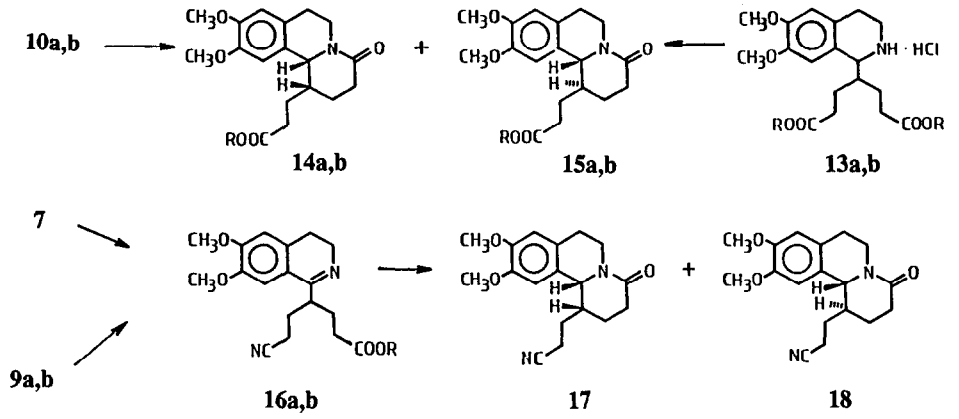
R = CH_3: **a**, R = C_2H_5: **b**

Scheme 2

The nucleophilic reactivity of the methylene group adjacent to the carbon atom in position 1 of the isoquinoline ring was utilized for transformation of the monoadducts to mixed acrylic ester-acrylonitrile adducts. Due to the stronger electrophilic character of acrylonitrile, the reactions **9a,b** **16a,b** occurred faster and with higher yields than for **7** **16a,b**. The structures of the monoadducts were proved by chemical correlation (**7** **9a,b**) and by their transformation to benzo[*a*]quinolizidine derivatives (**9a,b** **5**), while the structures of the other adducts were confirmed by their transformations into each other (Schemes 2 and 3).

The temperature, solvent and time dependences of the reactions were also studied. The best yields were achieved by using methanol or a mixture of benzene and methanol as solvent. The optimal

reaction time in the case of acrylonitrile was 3-4 hrs at the boiling point of the solution, or 40-50 hrs at room temperature. For acrylic ester additions, it was 22-24 hrs at 70 °C, 40-48 hrs at 50 °C and 7-8 days at room temperature. The yields were 85-95%. Increase of the duration of the reactions resulted in lower yields due to decomposition.

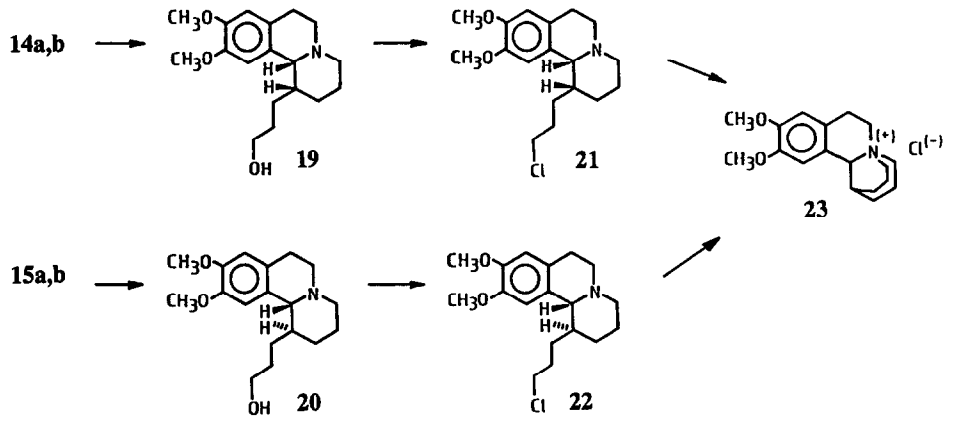


R = CH_3: **a**, R = C_2H_5: **b**

Scheme 3

Both mono and double adducts could easily be hydrogenated. Sodium borohydride reduction of the acrylonitrile adducts and also the catalytic hydrogenation of the hydrochlorides of the acrylic ester adducts (**9a,b** and **10a,b**) gave the corresponding tetrahydroisoquinoline derivatives. In the latter cases, basification of the solutions led to intramolecular carboxamide formation from the δ-amino esters, which resulted in benzo[*a*]quinolizidin-4-one derivatives (**4** and **14a,b**). The same tricylic lactams could also be obtained in a one-step reaction, on sodium borohydride reduction of the corresponding acrylic ester adducts. The above transformation was reported just as our experiments finished, but the authors[18] made no mention of the isolation and steric structure determination of the possible stereoisomers. The catalytic reduction followed by alkaline cyclization, in the cases of the acrylic ester double adducts (**10a,b**), and also the sodium borohydride reduction of the mixed (acrylonitrile-acrylic ester) double adducts (**16a,b**), were accompanied by the appearance of a new chiral centre, while in the sodium borohydride reduction of the acrylic ester double adducts, two chiral centres were formed "*quasi*-simultaneously". The reaction products could consist of two diastereomeric racemates. The racemic benzo[*a*]quinolizidine diastereomers (**14a,b**, **15a,b**, **17** and **18**) were isolated from the reaction mixtures by means of fractional crystallization. The degree of stereoselectivity could be deduced during the preparative work-up. In the case of the double acrylic ester adducts, when the chirality centres are formed successively, the diastereomeric ratio was 5:1, whereas it was 8:1 for the "*quasi*-simultaneous" formation in the sodium borohydride reduction. The diastereomeric ratio changed to 1:3 in the sodium borohydride reduction of the mixed double adduct, which already had a chirality centre. The ratios were probably due to the direction of the hydride attack, which, in the reduction of **16**, is opposite to the hydrogen on C-1'. However, the reduction of **10** does not result in a new C-1' chirality centre, *i.e.* the ratio of the products **14** and **15** is determined only by the rates of their formation.

The LAH reduction of lactams **14a,b** and **15a,b** yielded the 1-(3'-hydroxypropyl)-benzo[*a*]-quinolizidine diastereomers (**19** and **20**), the hydrochlorides of which were converted with thionyl chloride to the corresponding 1-(3'-chloropropyl)benzo[*a*]quinolizidine hydrochlorides (**21** and **22**). As expected, the alkaline treatment of both diastereomers resulted in the same tetracyclic quaternary salt (**23**) by intramolecular cycloquaternization, due to the disappearance of one of the chirality centres during the reaction (Scheme 4).



Scheme 4

It is noteworthy that in the case of the *cis* isomer, 1-(3'-chloropropyl)benzo[*a*]quinolizidine (**21**) could be liberated and isolated from its hydrochloride, but only the salt **23** was obtained under similar conditions in the case of the *trans* diastereomer **22**, owing to the rapid cycloquaternization. Formation of the tetracycle **23** confirmed the assumed structures and configurations of its intermediates.

Structure determinations

The conformational relations of the benzo[*a*]quinolizidine skeleton have been very thoroughly studied for a long time, resulting in a great number of publications, *e.g.*[8-15]. Our prepared compounds could exist in three predominant conformations (Fig. 1) due to the nitrogen or the heteroring inversion.[15] However, a planar nitrogen permits free pseudorotation, which causes increased conformational flexibility.[11] The conformational relations of the prepared compounds discussed in this paper were studied by means of IR, ^1H and ^{13}C NMR spectroscopy (Tables 1 and 2). There are characteristic differences in the spectra of the *cis-trans* isomer pairs of the piperidone derivatives, suggesting that these molecules have predominant conformations despite the greater flexibility:

a) the chemical shift of H-11b in the *cis* compound is higher by *ca* 0.5 ppm;

b) the coupling constant *J*(H-1, H-11b) is 3.1±0.1 Hz for the *cis* and 4.9±0.2 Hz for the *trans* isomer;

c) the signal of one of the NCH_2 hydrogens (H-6_{eq}) is separated in downfield position, and by *ca* 0.5 ppm further downfield shift was observed for the *cis* isomers;

d) the C-1 line is downfield shifted by 2-3 ppm, while the lines of C-6, C-11 and especially C-7 in the spectra of the *cis* isomers are upfield shifted relative to the corresponding lines of the *trans*-

counterparts (by *ca* 3.5, 3.0 and 8.0 ppm, respectively)

The differences corresponding to b) and d) unambiguously prove the *cis* or *trans* configurations (the smaller coupling constant corresponds to a dihedral angle of *ca* 60°,[19] the upfield shifts of the carbon lines are a consequence of the steric compression shift,[20] *i.e.* a more crowded structure, for the *cis* isomers), while the differences according to a) and c) suggest the conformation.[5] The predominant conformation of the *cis* isomer could probably be characterized by an approximate *twist* tetrahydropyridine and a *boat* piperidone ring (C-6,7 and C-3,11b are in the out-of-plane positions), the *axial* H-7 and the *quasiaxial* side-chain in position 1, and H-11b$_{ax}$ and H-3$_{ax}$ are in steric proximity, while H-6$_{eq}$ and the carbonyl group, and likewise H-11b and the benzene ring are nearly coplanar (Fig. 2).

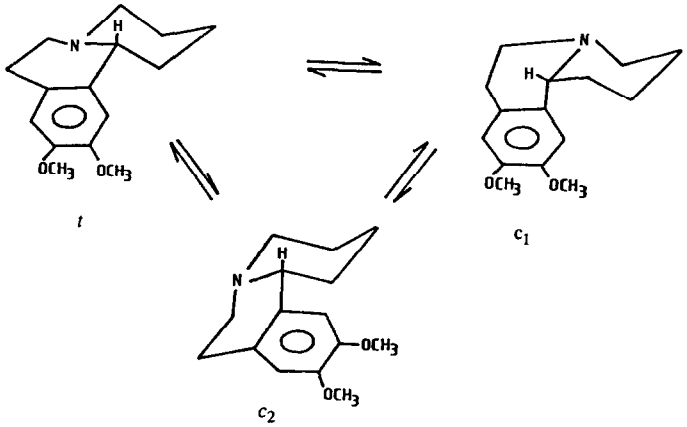


Figure 1

The large upfield shift of the C-7 line is due to the interaction between H-7$_{ax}$ and the side-chain. The downfield shifts of H-6$_{eq}$ and H-11b could be explained by the anisotropic effect of the carbonyl group or the benzene ring,[21a] respectively.

Consequently, the *trans* isomers have a different preferred conformation. The molecules with *cis* configuration alter their conformation to avoid the steric hindrance between H-11 and the side-chain. In the *trans* isomers, this is indicated by an upfield shift of the C-1 line [cf. d)], owing to the interaction between H-1 and H-11. The value (~5 Hz) of *J*(H-1,H-11b) also proves the different conformation from that of the *cis* compounds, because in the event of the same conformation the dihedral angle of *ca* 180° would be expected to cause a much greater splitting (> 10 Hz).[15]

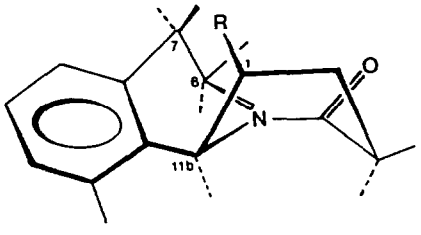


Figure 2

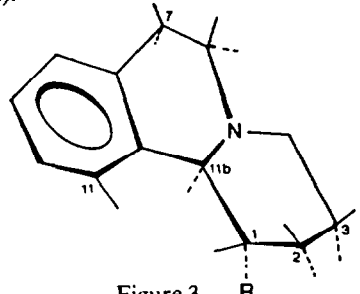


Figure 3

Table 1. Characteristic IR frequencies (cm^{-1}, in KBr discs) and ^1H NMR chemical shifts ($\delta_{TMS} = 0$ ppm) in $CDCl_3$ solution at 250 MHz for compounds **14a,b**, **15a,b** **17-23**

Compound	νC=O νC≡N[b]	Amide-I νOH[c]	OCH_3 *s*(3H)	ArH *s*(1H)	H11b *d/s*[d]	CH(1) *m*(1H)	CH_2 (2)	CH_2 (3)	CH_2 (4)	CH_2 (6) 2x*m*(2x1H) or *m*(2H)[f]	CH_2 (7)	CH_2 (α)	CH_2 (β)	CH_2 (γ)[e]
14a	1731	1634	3.87 3.88	6.61 6.64	4.83	2.4	1.35	2.6[g]	-	2.75 4.95[h]	2.5 2.6[g]	2.2	1.95 2.05	3.6
14b[i]	1732	1635	3.87 3.88	6.61 6.64	4.83	2.4	1.35	2.5[g]	-	2.75 4.95[h]	2.5[g] 2.6	2.15	1.95 2.05	4.05
15a	1738	1627	3.87 3.91	6.68 6.86	4.32	2.5	1.65 1.9	2.25 2.55	-	3.0 4.4[h]	2.7 3.1	2.4	1.85 2.15	3.71
15b[i]	1734	1626	3.87 3.90	6.68 6.86	4.33	2.5[g]	1.65 1.85	2.5[g]	-	3.05[j] 4.4[h]	2.7 3.05[j]	2.4[g]	1.85 2.12	4.16
17	2241	1634	3.87 3.88	6.63 6.68	4.90	2.55[g]	1.4	2.45 2.55[g]	-	2.7 4.95[h]	2.55[g] 2.65	2.2[j]	1.95 2.2[j]	-
18	2245	1622	3.87 3.89	6.68 6.76	4.36	2.55[g]	1.65 1.9[j]	2.4	-	3.05[k] 4.45[h]	2.72 3.05[k]	2.55[g]	1.9[j] 2.12	-
19	-	3375[l]	3.38 3.85	6.55 6.63	3.24	2.2	1.5[m] 1.85	1.5[m]	2.28 2.95	2.4 2.85	2.5 3.05	3.52	1.05 1.5[m]	1.5[m] 1.9
20	-	3536	3.83 3.84	6.56 6.64	3.65	2.0	1.25 1.75	1.55	2.77	2.85[g] 3.28	2.7 2.85[g]	3.57	1.4[j] 1.65[k]	1.4[j] 1.65[k]
21	-	-	3.38 3.85	6.56 6.63	3.24	2.2	1.6 1.8[g]	1.5[j] 1.8	2.3 2.9	2.4 2.8	2.5 3.0	3.4	1.15 1.5[j]	1.5[j] 1.9
21.HCl	-	-	3.84 3.86	6.61	4.44	2.65	1.9[g] 2.05[j]	1.85 2.45	3.05 3.7	3.2 3.6	2.75 3.9	3.5	1.5 2.05[j]	1.62 1.9[j]
22.HCl	-	-	3.85 3.86	6.65 6.67	4.24	2.1	1.45 1.9[g]	1.7[j] 1.9[g]	3.5[k]	3.4[k] 3.7	3.1 3.4[k]	3.55[k]	1.7[j] 1.9[g]	1.7[j] 1.9[g]
23	-	-	3.86 3.88	6.67 6.71	5.04	2.9	2.1 2.4[g]	1.7[j] 2.4[g]	4.3[k]	4.0 4.3[k]	3.05 3.25	3.48 4.0	1.7[j]	2.0 2.5

[a]Assignments were proved by 2D-HSC for **22**. HCl and DNOE and 2D-HSD measurements for **14a** **15a**, **17**, **18**, **20**, **21**, **21**.HCl and **23**. [b]Ester band (**14a,b** and **15a,b**), nitrile band (**17**, **18**). [c]Amide-I band (**14-18**), νOH hydroxy band (**19**, **20**). [d]Doublet for **14a,b**, **15a,b** **17**, **18**, **20** and **22**.HCl, *J*: 3.2 (**14a**, **16**), 3.0 (**14b**), 5.1 (**15a**), 4.8 (**15b**, **18**), 6.2 (**20**) and 5.8 Hz (**22**.HCl), singlet for **19** , **21**, **21**.HCl, **23**; [e]OCH_3, *s*(3H) for **14a**, **15a**; OCH_2, *qa* (2H) for **14b**, **15b**, Pos. 2' for **23**. [f]From these unresolved overlapping multiplets, the chemical shifts are determined only with limited accuracy. Accordingly they are given rounded off (± 0.05 ppm). [g,i,k]Overlapping multiplets. [h]Double doublet, H-6*eq*. [i]CH_3, *t* (*J*: 7.2 Hz): 1.20 (**14b**), 1.28 (**15b**). [l]Broad maximum. [m]Overlapping multiplets, also in overlap with the OH signal (total intensity: 6H).

Table 2. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) of compounds **14a,b**, **15a,b** and **17-23** in $CDCl_3$ solution at 62.89 MHz[a]

Com-pound	C-1	C-2	C-3	C-4	C-6	C-7	C-7a,11a		C-8	C-9,10		C-11	C-11b	$CH_2(\alpha)$ side	$CH_2(\beta)$ chain
14a	37.5	20.1	27.8[b]	169.5	38.7	28.7[b]	128.6	126.6	112.0	148.2	148.5	109.5	60.6	31.5	23.2
14b	37.2	19.8	27.5[b]	169.3	38.4	28.4[b]	128.3	126.3	111.7	147.8	148.2	109.2	60.3	31.4	22.8
15a	30.6	22.0	28.7	169.1	41.9	27.2[c]	128.7	128.5	111.4	147.0	147.7	107.5	59.9	34.3	27.2[c]
15b	31.9	22.9	29.5	169.5	42.5	28.1[c]	129.3	129.5	112.6	147.9	148.7	109.0	60.7[b]	35.5	28.1[c]
17	37.2	20.8	27.4[b]	169.0	38.4	28.4[b]	128.1	125.8	111.8	148.0	148.4	108.8	59.8	14.9	22.8
18	34.3	21.9	28.6	168.6	42.0	27.4	128.8	127.8[d]	111.9	147.2	148.9	107.6	59.5	14.5	27.6
19	37.1	31.2	20.6	57.5	52.9	29.0	128.9	129.1	111.8	147.2	147.4	107.7	67.4	63.0	21.8
20	34.0	26.9	19.8	50.3	46.7	25.5	126.5	128.4[d]	111.4	146.2	147.3	110.6	62.1	62.3	28.4
21	36.7	27.4	20.5	57.3	52.7	29.0	128.0	128.8	111.2	147.0	147.3	107.6	67.1	44.7	23.0
21.HCl	34.2	24.3	17.5	56.0	52.3	25.0	121.1	124.3	111.1	147.9	148.4	106.7	66.3	43.6	21.2
22.HCl	35.2	25.4	17.7	50.2	45.5	23.7	121.6	122.8	111.2	147.4	149.1	110.5	62.0	44.4	28.6[b]
23	28.1	27.6	19.8[c]	64.5	60.6	23.2	120.4	122.5	111.4	148.6	149.0	107.4	66.3	50.5[e]	19.8[c]

[a]Measuring frequency: 20.14 MH for **14a,b 15b** and **16**. Assignments were proved by 2D-HSC (for **14a**, **15a**, **17**, **18**, **20**, **21**, **21**.HCl, **22**.HCl, **23** and DEPT measurements (**21**, **21**.HCl, **22**.HCl, **23**). Further signals: OCH_3 (Pos. 9, 10), two lines between 55.3 and 56.6 ppm; Ester group; OCH_3: 51.4 (**14a**), 51.0 (**15a**), CH_3: 13.9 (**14b**), 14.3 (**15b**), OCH_2: 59.9 (**14b**), 60.5[b] (**15b**); C=O: 173.3 (**14a**), 172.6 (**14b**), 173.0 (**15a,b**) C≡N: 118.8 (**17**), 118.6 (**18**), γCH_2 (side chain, C-2' for **23**): 27.5 (**19**), 30.0 (**20**), 31.2 (**21**), 29.7 (**21**.HCl), 29.3[b] (**22**.HCl), 20.9 (**23**). [b]Interchangeable assignments. [c]Two overlapping lines, C-3,3' for **22**. [d]Assignments to C-11a was proved by INEPT measurement. [e]C-4'.

Therefore, the preferrence can be suggested of a *trans* isomer conformation in which the piperidone ring is in *sofa* form, having C-2 in out-of-plane position, and the *B* ring has a nearly *boat* shape, with C-7 and C-11b as out-of-plane atoms. In this structure, the dihedral angle of the carbonyl and C-H-6_{eq} is *ca* 30° (H-6_{eq} is not coplanar with the amide carbonyl), the H-11b . . . H-1 distance is *ca* 1.5 Å (this means significant steric hindrance), and the side-chain and H-3_{ax} are in 1,3-*diaxial* positions (Fig. 3). The C-H-11b bond is approximately perpendicular to the benzene ring (the angle formed by the bond and the plane of the benzene ring is *ca* 110°).

19-22 containing a piperidine ring are more rigid systems and expected to have homogeneous conformations. This is confirmed by the summed differences of the carbon chemical shifts, which is much greater for the counterparts **19-20** or **21-22** (45.2 and 36.6 ppm, respectively) than for the piperidinone analogues (the average of the summed differences being about 27 ppm for the pairs **14a-15a**, **14b-15b** and **17-18**). For the *cis* piperidone compounds, the sum of the carbon chemical shifts is smaller, as expected,[21b] than that of the *trans* counterparts, whereas for the piperidine analogues, the ^{13}C NMR data indicate the more crowded structure of the *trans* isomers.

The c_1 and c_2 conformations of the *cis* isomers cannot come into consideration because of the strong steric hindrance between the side-chain in position 1 and either H-11 (for the c_1 conformation) or H-6_{ax} (for the c_2 conformation) their minimal distance being about 0.5 . However, for the *trans* isomers, a *t* conformation would cause a very strong steric hindrance between the side-chain and H-11. Therefore, the *cis* isomers **19** and **21** have the preferred conformation characterized by the *trans* ring annelation, which was also proved by X-ray diffraction studies on the hydrochloride of **19**,[22] while for **20** and **22**, the *t* conformation is not possible. The c_1 or c_2 conformation of **20** had to be determined by differential nuclear Overhauser effect experiments.[21c,23]

The dominance of the c_1 conformation was unambiguously proved by the strong NOE between H-1 and H-11 (irradiatiation of the ^1H NMR lines of these hydrogens resulted in a mutual increase in intensity[24]). The NOE-s expected for c_2 conformation are absent, *e.g.* the saturation of H-11 not influenced the signal intensity of the methylene hydrogens in the side-chain, and a similar negative effect was observed on saturation of H-1 at the signal of the H-6_{ax}, which has a close arrangement with H-1 in the c_2 conformation.

The side-chain homologue, 1-hydroxymethyl-substituted oxazine analogues of isomers **19-20**, which contain oxygen in position 3, were investigated earlier.[15] Similarly to **19**, the *t* conformation was preferred for the *cis* isomer, but the *trans* counterpart had a c_2 predominant conformation according to NOESY experiments. This is in perfect accordance with the differences in the comparable carbon chemical shifts, confirming the conclusions on conformations in both our earlier and present papers.

A comparison of the ^{13}C NMR data on the *trans* oxazine homologue and the piperidine analogue revealed that C-1 and C-7 are in less favourable steric positions in the latter compound according to the c_1 structure (4.4 and 3.9 ppm upfield shift, respectively), while in the oxazine with a c_2 steric structure, the more hindered position of C-2 and C-4 is demonstrated by the steric compression shifts (2.6 and 3.5 ppm, respectively). Although, the chemical shifts of C-2 and C-4 are not directly comparable, owing to the difference in the group at position 3 (CH_2 or O), the characteristically different shift differences for the *cis-trans* pairs, even with opposite signs for C-2 (-1.3 and 1.6 ppm for the oxazines, and 4.3 and 7.2 ppm for **20**), undoubtedly prove the difference in steric structure of the analogues, and elegantly support

the much less favourable steric positions of C-2 and C-4 in the structure c_1 relative to those in the c_2 form.

Following the oxazinoisoquinolines, the piperidine analogues discussed in this paper provide a further example for the occurrence of two different conformations. Additionally, all three possible relatively stable conformers (*t*, c_1 and c_2) are present in these two related groups of compounds. No similar examples were found in the literature.

The c_1 conformation of the *trans* compounds explains the spontaneous cyclization of base **22** to tetracycle **23**, in contrast with the *cis* counterpart **21**, which is stable even in basic form. The sterically less favourable of the two piperidine rings (*i.e.* which is perpendicular to the tetrahydroisoquinoline skeleton) in tetracycle **23** is present in the isomer **22**, and the bridgehead *N*-5 is available for the side-chain to build the other ring. In the *cis* isomer with *t* conformation, an unfavourable change in conformation of the side-chain (*S-trans S-cis* to the flat, tricyclic skeleton) is necessary for ring closure. Since, the tetracycle formation needs a c_2 c_1 or c_2 *t* conformational change, the spontaneous **22** **23** transformation can be regarded as further evidence of the preferred c_1 conformation of **22**.

Experimental

Melting points were determined on a Boetius apparatus and are uncorrected. The physical and analytical data on the prepared compounds are listed in Table 3.

IR spectra were run in KBr discs on a Bruker IFS-113v FT-spectrometer equipped with an Aspect 2000 computer and a vacuum optical system.

The NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes, on Bruker WM-250 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, respectively, using the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measurement parameters were as follows: spectral width 5 and 15 or 5 kHz, pulse width 1 (^1H) and 7.0 or 3.5 (^{13}C) μs (20° and 30° flip angle), acquisition time 1.64 and 0.40 or 1.64 s, number of scans 16 (^1H) and 2-8 K (^{13}C), computer memory 16 and 32 or 16 K. Complete proton noise decoupling (1.5 or 3.0 W, ^{13}C) and Lorentzian exponential multiplication for signal-to-noise enhancement were used, line width 0.7 (^1H) and 1.0 or 2.0 (^{13}C).

The standard Bruker microprogram "DNOEMULT.AU" to generate NOE was used with a selective pre-irradiation time of 5 s and a decoupling power (CW mode) of ca 30-40 mW; number of scans 64-256, dummy scans 4-8, pulse width 5.0 μs (90°) and 16 K data points for ca 3 kHz spectral width. A line broadening of 1.0 Hz was applied to diminish residual dispersion signals in the difference spectra.

DEPT[25] spectra were run in a standard way,[26] using only the θ = 135° pulse to separate CH/CH_3 and CH_2 lines phased up and down, respectively. Typical acquisition data were: number of scans 128-12 K, relaxation delay for protons 3 s, 90° pulse widths 10.8 and 22.8 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[27] were obtained by using the standard BRUKER pulse program "2XHCORRD.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/point digital resolution in the ^1H domain; 256 transients were obtained with a relaxation delay of 3 s. All C-H correlations were found by using a value of J(C,H) = 135 Hz for

calculation of the delay.

*Reaction of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**6**) with acrylonitrile*

Method A - A solution of compound **6** (20.5 g, 0.1 mol) and acrylonitrile (5.3 g, 0.1 mol) in benzene (80 ml) was refluxed for 4 hrs. After evaporation, the residue was treated with ether. Fractional crystallization of the crude crystalline product gave **7** (yield: 24%) besides unchanged **6**.

Method B - The reaction was carried out according to Method A, but using 2 equivalents of acrylonitrile (10.6 g, 0.2 mol). Fractional crystallization of the crude product resulted in **7** (yield: 23%) and **8** (yield 33%).

Method C - A solution of **6** (20.5 g, 0.1 mol) and acrylonitrile (21.0 g, 0.4 mol) in benzene (80 ml) was refluxed for 5 hrs. The solution was evaporated and the residue was crystallized from methanol to give **8** (yield: 95%).

*Reduction of dihydroisoquinoline derivatives **7** and **8***

Method D - Dihydroisoquinoline **7** or **8** (0.05 mol) was dissolved in methanol (200 ml), the solution was cooled in ice-water, with stirring, and sodium borohydride (0.15 mol) was added in small portions during 40 min. The stirring was continued for 1 hr at room temperature, the solution was then evaporated, and the residue was dissolved in water (100 ml) and extracted with benzene (3 x 80 ml). Drying and evaporation of the organic phase gave the isoquinoline derivative **12** as a crystalline product.

*Reaction of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline (**6**) with acrylic ester*

Method E - A solution of compound **6** (62 g, 0.3 mol) and ethyl or methyl acrylate (0.8 mol) in benzene (200 ml) was refluxed for 20 hrs. After evaporation, the product (**10a** or **10b**) was isolated as the hydrochloride. Yield: 85-95%.

Method F - A solution of **6** (12 g, 0.06 mol) and ethyl acrylate (10 g, 0.1 mol) in benzene (50 ml) was refluxed for 25 hrs. After evaporation, the residue was converted to the hydrochloride. Fractional crystallization of the crude product resulted in the double adduct **10b** (yield: 42%) and the monoadduct **9b** (yield 21%).

Method G - To a solution of **6** (41 g, 0.2 mol) in methanol-benzene 1:1 ratio (300 ml), ethyl or methyl acrylate (0.27 mol) was added and the mixture was kept at room temperature for 6-7 days (or at 50-55 °C for 2 days). The solution was evaporated and the residue was fractionally crystallized from ether. Besides the monoadduct **9a** or **9b** (yield: 72-75%), the same tricyclic lactam derivative (**11**) was isolated in both cases (yield: 5-10%). (The yield of the lactam was higher in the reaction involving methyl acrylate.)

The yields of the adducts **9a** and **9b** were almost the same when the reactions were carried out in methanol. In ethanol the process was slower, with a lower yield, but increase of either the reaction time or the amount of the acrylate led to higher yields of the double adduct **10a** or **10b**.

By reaction of the monoadduct **9a** or **9b** with a further amount of acrylate (refluxing in benzene for 20-25 hrs), the double adduct **10a** or **10b**, respectively, was obtained.

Table 3. Physical data on compounds **7-23**

Compound	Mp (°C) Solvent	Method	Yield %	Formula Mw	Analysis C (%) Calcd.	C (%) Found	H (%) Calcd.	H (%) Found	N (%) Calcd.	N (%) Found
7[a]	81-83 ether	A B	24 23	$C_{15}H_{18}N_2O_2$ 258.31	69.74	70.21	7.02	6.71	10.89	11.31
8[b]	108-109 methanol	B C	33 95	$C_{18}H_{21}N_3O_2$ 311.37	69.45	69.58	6.76	6.89	13.50	13.14
9a	54-56 ether	G	75	$C_{16}H_{21}NO_4$ 291.34	65.95	65.56	7.26	7.42	4.80	4.42
9b[c]	72-74 ether	F G	21 75	$C_{17}H_{23}NO_4$ 305.37	66.85	66.71	7.59	7.40	4.88	4.77
10a[d]	62 ether	E H	85 80	$C_{20}H_{27}NO_6$ 377.20	63.64	63.46	7.20	7.10	3.71	3.42
10b[e]	147-150 acetone	E F H	90 42 85	$C_{22}H_{32}ClNO_6$ 441.92	59.78	59.46	7.29	7.41	3.17	3.01
11	176-178 benzene	G	10	$C_{15}H_{17}NO_3$ 259.29	69.47	69.40	6.10	6.41	5.40	5.28
12	118-120 benzene	D	76	$C_{18}H_{23}N_3O_2$ 313.39	68.98	68.92	7.39	7.65	13.41	13.15
13a	192-194 methanol	I	95	$C_{20}H_{30}ClNO_6$ 415.91	57.75	57.42	7.27	7.38	3.36	3.48
13b[f]	145-146 ethanol	I	94	$C_{22}H_{34}ClNO_6$ 443.93	59.51	59.42	7.71	7.35	3.15	3.40
14a[g]	152-154 benzene	M N	71	$C_{19}H_{25}NO_5$ 347.40	65.68	65.85	7.25	7.62	4.03	3.75
14b[g]	110-112 ether	M N	76	$C_{20}H_{27}NO_5$ 361.42	66.46	66.47	7.52	7.78	3.87	3.82
15a	101-103 benzene	M N	21	$C_{19}H_{25}NO_5$ 347.40	65.68	65.41	7.25	7.63	4.03	4.42
15b	94-96 ether	M N	12	$C_{20}H_{27}NO_5$ 361.42	66.46	67.02	7.52	7.43	3.87	3.66
16a[h]	97-98 benzene	K L	90 12	$C_{19}H_{24}N_2O_4$ 344.40	66.25	66.45	7.02	7.28	8.31	8.57
16b	84-86 benzene	K	94	$C_{20}H_{26}N_2O_4$ 358.42	67.01	67.36	7.30	7.82	7.81	8.12
17	155-157 benzene	M	28	$C_{18}H_{22}N_2O_3$ 314.37	68.76	69.14	7.05	7.37	8.91	8.19
18	92-94 benzene	M	60	$C_{18}H_{22}N_2O_3$ 314.37	68.76	68.74	7.05	7.59	8.91	8.66
19[i]	113 ether	O	96	$C_{18}H_{27}NO_3$ 305.40	70.78	70.18	8.90	8.65	4.58	4.26
20[j]	100-102 ether	O	85	$C_{18}H_{27}NO_3$ 305.40	70.78	70.26	8.90	8.49	4.58	4.35
21[k]	84-86 ether	P	85	$C_{18}H_{26}ClNO_2$ 325.85	66.75	66.45	8.04	7.84	4.32	4.52
22[l]	222-224 methanol-ether	P	80	$C_{18}H_{27}Cl_2NO_2$ 360.32	59.99	59.76	7.55	7.40	3.88	3.71
23	268-270 ethanol-ether	R	70	$C_{18}H_{26}ClNO_2$ 323.85	66.75	66.54	8.04	8.21	4.32	4.39

[a]Mp of HCl salt: 166-168 °C. [b]Mp of HCl salt: 169-170 °C. [c]Mp of HCl salt: 126-128 °C; Mp of MeI quaternary salt: 172 °C. [d]Mp of HCl salt: 146-148 °C. [e]The crystallization of **12b** failed; data are given for HCl salt salt. [f]After melting, the substance solidifies and melts at 164 °C. [g]R = H, mp: 214-216 °C (EtOH). [h]Mp of HCl salt: 156-158 °C. [i]Mp of HCl salt: 182-184 °C. [j]Mp of HCl salt: 212-214 °C. [k]Mp of HCl salt 183-184 °C. [l]Analytical data are given for HCl salt salt.

*Preparation of 1-bis(2'-alkoxycarbonylethyl)methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (***10a** *or* **10b***) by hydrolysis of the bis(2'-cyanoethyl) compound (***8***)*

Method H - Compound **8** (21.8 g, 0.07 mol) was added to 12% aqueous hydrochloric acid (200 ml) and the solution was refluxed for 6 hrs. After evaporation, the residue was dissolved in ethanol or methanol (150 ml) and the solution was kept at room temperature for 2 days. The precipitated ammonium chloride was removed by filtration and the solution was evaporated. The residue crystallized on treatment with acetone to give **10a** or **10b**. Yield: 80-85%.

Reduction of dihydroisoquinolines **9a**, **9b**, **10a** *and* **10b**

Method I - The hydrochloride of dihydroisoquinoline **9a**, **9b**, **10a** or **10b** (0.02 mol) was dissolved in ethanol or methanol (100 ml) and reduced in a hydrogen atmosphere under normal conditions in the presence of a platinum catalyst (prehydrogenated PtO_2, 0.1 g). After the calculated amount of hydrogen had been absorbed (1.5-2 hrs), the catalyst was removed by filtration. Evaporation of the reaction mixture gave the tetrahydroisoquinoline hydrochloride **13a** or **13b**. Yield: 94%.

Hydrolysis of **12** according to Method H gave the same product as in Method I.

*1-(1'-Cyanoethyl-3'-alkoxycarbonylpropyl)-6,7-dimethoxy-3,4-dihydroisoquinolines (***16a** *or* **16b***)*

Method K - A solution of ester **9a** or **9b** (0.05 mol) and acrylonitrile (0.1 mol) in methanol (60 ml) was refluxed for 20 hrs. The orange reaction mixture was evaporated and the residue was crystallized from a benzene-ether mixture to give **16a** or **16b**. Yield: 90-95%.

Method L - In the "reverse" synthesis of the title compounds, a solution of **7** and methyl acrylate in methanol was refluxed for 56 hrs, but **16a** was isolated (from its mixture with a large amount of decomposition products) in only 10-15% yield.

Preparation of hexahydrobenzo[a]quinolizine derivatives **4**, **14**, **15**, **17** *and* **18** *from dihydroisoquinolines* **9**, **10** *and* **16**

Method M - To a solution of dihydroisoquinoline base **9**, **10** or **16** (0.05 mol) in methanol or ethanol (150-200 ml), sodium borohydride (5 g, 0.15 mol) was added in small portions with stirring and mild cooling. Stirring was continued for 30 min at room temperature. The reaction mixture was then evaporated, ice-cold water (100 ml) was added to the residue, and the solution was extracted with chloroform (3 x 50 ml). After drying, the chloroform was evaporated off, and the residue was dissolved in benzene (150 ml) and the solution was boiled for 30 min. On fractional crystallization of the reaction products obtained from **10** or **16**, racemates **14**, **15** or **17**, **18**, respectively were isolated. After reduction of **10**, acidification (acetic acid) of the aqueous solution remaining after chloroform extraction gave carboxylic acid derivative **14** (R = H, mp.: 216-218 °C /ethanol/). On dissolution in ethanolic hydrochloric acid, this was transformed to **13b** by opening of the lactam ring.

Method N - An aqueous solution of tetrahydroisoquinoline hydrochloride **9** or **13** was basified and extracted with benzene. After drying and evaporation, the residue was crystallized. The product **4**, **14** or **15** was identical to that prepared according to Method M.

*1-(3'-Hydroxypropyl)-1,2,3,4,6,7-hexahydrobenzo[a]quinolizines (**19**, **20**)*

Method O - To a stirred suspension of $LiALH_4$ (3.8 g, 0.1 mol) in dry THF (200 ml), benzoquinolizinone derivative **14** or **15** (0.03 mol) was added during 30 min. After stirring at 50-60 °C for 3 hrs, the cooled reaction mixture was worked up in the usual way, and the product was crystallized from ether.

Transformation of **19** *and* **20** *to benzoquinolizines* **21** *and* **22**. *Hydroxy → chloro exchange*

Method P - Thionyl chloride (5 ml) was added to **19** or **20** (3.4 g, 0.01 mol) under ice cooling. The reaction mixture was kept at 50 °C for 30 min, then evaporated under reduced pressure. The evaporation was repeated a few times after addition of benzene. The residue crystallized on scratching in acetone to give **21** or **22**.

Transformation of **21** *and* **22** *to tetracyclic salt* **23**

Method R - To hydrochloride **21** or **22** (0.72 g, 2 mmol), a methanolic solution of sodium hydroxide (0.08 g, 2 mmol) was added, and the reaction mixture was refluxed for 4 hrs. After evaporation, ethanol was added to the solid residue to dissolve the organic substances. Compound **23** crystallized out from the filtered and concentrated ethanolic solution. On heating in a glass capillary, base **21** melts at 83 °C, then solidifies and melts again only at 268-270 °C.

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