Tetrahedron Vol. 41, No. 22, pp. 5159 to 5168, 1985
Printed in Great Britain.

0040-4020/85 $3.00+.00
© 1985 Pergamon Press Ltd.

STEREOCHEMICAL STUDIES 87[1]
SATURATED HETEROCYCLES 82[1]

SYNTHESIS AND STERIC STRUCTURE OF STEREOISOMERIC N-SUBSTITUTED TETRAHYDRO-1,3-OXAZINES FUSED WITH NORBORNANE OR NORBORNENE

FERENC FÜLÖP, GÉZA STÁJER and GÁBOR BERNÁTH*

Institute of Pharmaceutical Chemistry, University Medical School, P.O.B. 121, H-6701 Szeged, Hungary

and

PÁL SOHÁR

Spectroscopic Department, EGIS Pharmaceuticals, P.O.B. 100, H-1475 Budapest, Hungary

(*Received in UK* 17 *July* 1985)

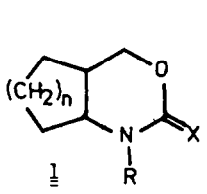
Abstract - diendo- and diexo-2-Methylamino and 2-benzylamino-3-hydroxymethylbicyclo[2.2.1]heptanes and the corresponding bicyclo[2.2.1]heptenes (5a-d, 7a-d) were synthesized from β-amino acid esters containing the norbornane or norbornene skeleton (3a-d). The aminoalcohols were converted to 5,8-methano-3,1-benzoxazines by reaction with formaldehyde. As established by ^1H and ^{13}C NMR spectroscopy, the predominant conformation is endo-boat (B) for the diexo, and exo-boat (E) for the diendo derivatives.

In earlier work we investigated the syntheses and structures of stereoisomeric 1,3-oxazines,[2-5] 1,3-oxazin-2-ones[6,7] and 1,3-oxazin-4-ones[8] fused with a cyclopentane, cyclohexane, cycloheptane or cyclooctane ring (1, 2). It was found that the 2-aryl-substituted compounds (X = ArH) were always formed stereospecifically.[4,8] The configuration of the new chirality centre appearing as a result of ring closure is determined by the predominant conformation of the product, since the C-2 substituent of the heteroring will be equatorial. NMR spectroscopic investigations of the tetrahydrooxazines[3,6,9] showed that the C-2 substituent did not essentially affect the predominant conformation of the product. In all cases examined in our experiments, it was found that cis-1,3-oxazines of type 2 and also 1,3-oxazin-2-ones and -4-ones had O-inside dominant conformations, i.e. the prevailing conformer contained the oxygen atom axial to the cycloalkane ring.

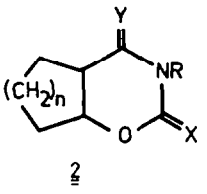
At the same time, in compounds 1, if R^1 = H the N-inside conformer is preferred, whereas if R^1 = Me or CH_2Ph the N-outside conformer is preferred, because the equatorial arrangement of the bulkier substituent is energetically favoured.[3]

In a continuation of this work, our aims were the synthesis and study of the steric structures of stereoisomeric 1,3-oxazines fused with the norbornane or norbornene structural moiety (8, 9).

During the past ten years there has been great interest in the conformational analysis of saturated heterocycles. A large number of papers have dealt with monocyclic 1,3-oxazines (see e.g.[10,11]), but relatively little has been published on the less readily accessible fused-skeleton analogues; the syntheses of and stereospecific studies on a few bicyclic fused-ring heterocycles have been reported.[12-14] Fused-skeleton 1,3-oxazole and thiazole derivatives have been pre-



1



2

cis or trans; n = 1, 2, 3, 4
X = H_2, O, ArH; Y = H_2, O; R = H, Me, Ph

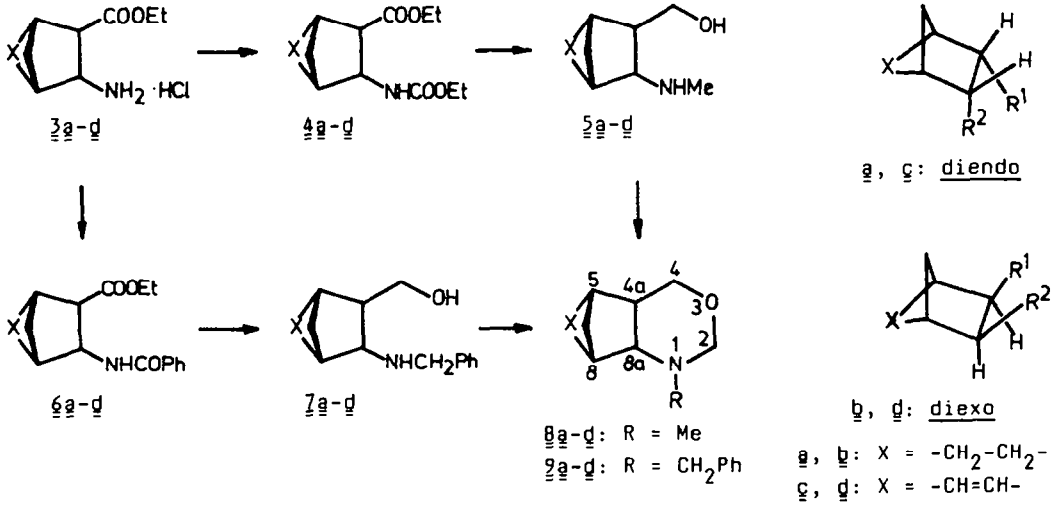
pared by the reaction of N-substituted trans-2-amino-1-cycloalkanols and trans-2-amino-1-cycloalkenethiols with formaldehyde. Unsubstituted 1,2-difunctional compounds gave polycyclic products with formaldehyde.[12] At the same time, N-unsubstituted trans-2-hydroxymethyl-1-cyclohexylamine and formaldehyde yielded the corresponding fused-skeleton 1,3-oxazine.[13,14]

Only a few 1,3-oxazine derivatives with a fused norbornane or norbornene skeleton have so far been reported. Spectroscopic evidence and preparative studies indicate that 4a,5,8,8a-tetrahydro-2-trichloromethyl-5,8-methano-4H-1,3-benzoxazin-4-one,[15,16] prepared from the cycloaddition of norbornane or norbornene with trichloroacetyl isocyanate, and 4a,5,8,8a-tetrahydro-2-phenyl-5,8-methano-4H-1,3-benzoxazine,[17] resulting from the cycloaddition of norbornane and the benzamidomethylium ion, have the diexo configuration.[16,18] diendo-5,8-Methanoperhydro-3,1-benzoxazine-2,4-dione was obtained by hydrolysis of the corresponding β-isocyanatocarboxylic acid trimethyl esters.[19]

We recently reported the syntheses[20,21] of and stereochemical studies[22] on some diexo- and diendo-2-aryltetrahydro-, 2-oxo- and 2-thioxohexahydro-5,8-methano-1,3- and 3,1-benzoxazines. diexo- and diendo-2-Aryltetrahydro-5,8-methano-3,1-benzoxazin-4-ones[23,24] were also prepared, from which the retro Diels-Alder reaction, under very mild conditions, gave the otherwise not readily available[25] 2-aryl-1,3-oxazin-6-ones.

Syntheses

The syntheses of the diendo (3a,c) and diexo (3d,b) β-amino acid esters containing the norbornane or norbornene skeleton have been described previously.[21,24] The N-methyl (5a-d) and N-benzyl-substituted (7a-d) 1,3-aminoalcohols were prepared by the synthesis used for the analogous compounds with a cyclohexane skeleton[5] (Scheme 1). This procedure gave the required 1,3-aminoalcohols 5a-d and 7a-d in good yield and as pure compounds.



Scheme 1

High yields were also obtained when the N-substituted 1,3-oxazines 8a-d and 9a-d were prepared by treatment of the appropriate aminoalcohols with aqueous formaldehyde. All products were oils, which were purified through the picrate salts. For spectroscopic studies, the bases were liberated from the picrates with aqueous potassium hydroxide solution.

Spectroscopic studies

The principles of the NMR spectroscopic configurational and conformational analyses of 5,6-dihydro-4H-oxazines containing a fused norbornane or norbornene skeleton have been described in detail earlier.[22] As merely slight modifications were introduced for the perhydrooxazine analogues, only the most essential points will be treated here.

Table 1. Characteristic IR bands (cm^{-1}) of compounds 8a-d and 9a-d in KBr discs

Compound	νC-O	γ(=CH)	$\gamma C_{Ar}H$	$\gamma C_{Ar}C_{Ar}$
8a	1124, 1111[a]	-		
8b	1109	-		
8c	1113	729		
8d	1107	716		
9a	1090	-	750	690
9b	1100	-	740	700
9c	1101	731	750	698
9d	1097	716	754	698

[a]Splitted bands

(1) Among the IR data (Table 1), definitive evidence of the structure is given by the intense band in the region 1124-1090 cm^{-1}, due to the νCO vibration of the oxazine ring, by the γ(=CH) band of the olefin group of norbornene between 716 and 731 cm^{-1}, and by the $\gamma C_{Ar}H$ and $\gamma C_{Ar}C_{Ar}$ bands in the ranges 740-755 and 690-700 cm^{-1}, respectively, characteristic of the phenyl group in the N-benzyl-substituted compounds 9a-d.

(2) As regards the ring anellation, the multiplicity of the proton resonance signal of H-8a is decisive (Table 2). As the C_8-H,C_{8a}-H dihedral angle for the diexo-anellated compounds b and d is about 90°, whereas for the diendo isomers a and c it is about 50°, in the former case the H-8a signal is a doublet due to the 4a,8a spin-spin interaction (the coupling constant being ~8 Hz), while for the diendo derivatives a doublet of doublets is found (coupling constants: ~9 and ~3.6 Hz); the vicinal coupling constant J(8,8a), <1 Hz for a dihedral angle of 90°, as follows from the Karplus relation,[26] does not give rise to significant splitting. The coupling constant J(4a,8a) is a little larger for the diendo isomers (similarly as for the dihydrooxazines) because the corresponding dihedral angle is nearer to 0°; in the diexo isomers this angle is higher, due to steric hindrance between the H-4'(a') H-5 and H-2'(a'),H-9(endo) atom pairs.

(3) Information about the conformation of the heteroring (Fig. 1) is obtained from the coupling constants J(4,4a) and J(4',4a). In the case of diexo-anellation there are three possible relatively stable conformations of the oxazine ring (A-C). In the twist-like conformation (A), C-2 stands out of the plane formed by the five nearly coplanar atoms of the heteroring, thereby coming near to C-9. In the two boat-like conformations, the angles are either each approximately 60°, or about 50° and 170°. The two boat conformations (B and C) differ in that C-4 and the nitrogen atom stand out from the plane constituted by C-2,C-4a,C-8a and the oxygen atom, in the exo direction (C) (the 4,4a and 4',4a dihedral angles each being 60°) or in the endo direction (B) (the 4,4a and 4',4a dihedral angles being 50° and 170°, respectively) relative to the norbornane or norbornene skeleton. However, the "exo-boat" arrangement is unfavoured because of the high steric

hindrance between the hydrogens in opposite positions at C-2 and C-9; therefore, only the twist (A) and "endo-boat" (B) conformations need be considered.

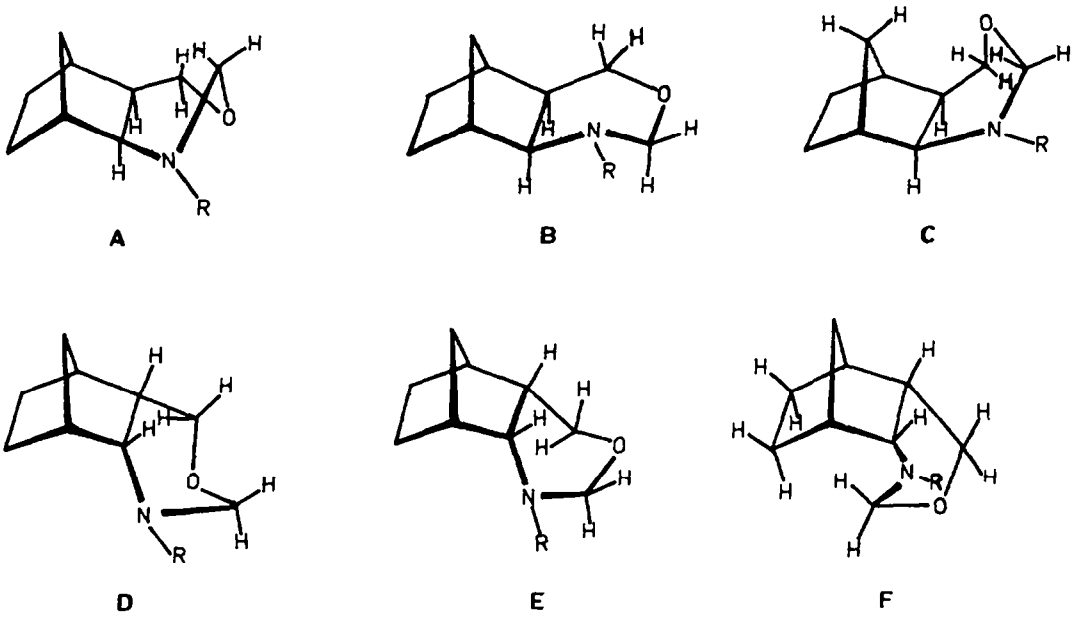


Figure 1

In the diendo-anellated skeleton, two relatively stable conformations are possible: a boat-like form in which the nitrogen atom and C-4 protrude, in the exo position (E), from the plane formed by C-2,C-4a,C-8a and the oxygen atom, the 4,4a and 4',4a dihedral angles being about 50° and 170°, respectively; the other conformation is twist (D), with dihedral angles of 90° and 30°. (The endo-boat conformation (F) is not stable due to the very high steric compression between the hydrogens attached to C-2 and to C-6 and C-7.)

As relatively large, but considerably different J(4,4a) and J(4',4a) values (<10 and ~7 Hz) were measured for all compounds, in view of the Karplus relation the probable conformations are endo-boat (B) for diexo compounds, and exo-boat (E) for the diendo analogues. The practically equal coupling constants correspond to identical dihedral angles.

The slightly smaller J(4,4a) and J(4',4a) values obtained for the analogous dihydrooxazine derivatives can be explained by the somewhat smaller dihedral angles (~40° and ~160°) characteristic of the analogous conformations;[22] hence, this difference can be regarded as additional evidence of the suggested conformations.

(4) In the 2-aryldihydrooxazines fused with the norbornene skeleton, an anomalous shift of the H-4 and H-4' signals was observed.[22] For these compounds, the rule generally holding for cyclohexanes and their hetero analogues,[27] viz. that the axial geminal methylene proton is always the more shielded, is no longer valid. In the present case the H-4' signal in the diendo series is shifted downfield by about 0.55 ppm relative to that of its quasi-equatorial counterpart H-4. This anomaly was also observed in the diexo-anellated norbornane series, though with a smaller shift difference (~0.25 ppm).[22] The anomaly was explained by the anisotropic effect of the 2-phenyl substitutent.[22] This explanation is substantiated by the absence of such an anomaly in the norbornene derivatives 8c,d

Table 2. ^{1}H NMR data (δ_{TMS} = 0 ppm) on compounds 8a-d and 9a-d in $CDCl_3$ at 250 MHz

Compound	H-2 2xd(2H)[a]	H-4 2xdd(2H)[b]	H-4a m(1H)	H-5 ~s(1H)[c]	H-6 (1H)[d]	H-7 (1H)[d]	H-9 (1H)[d]	H-8 ~s(1H)[c]	H-8a dd or d(1H)[e]	NCH$_{2,3}$ s or 2xd[f]	ArH m(5H)
8a	3.70 4.32	3.62 3.93	~2.02	2.10	1.2-1.4(4H),	1.55-1.65(1H),	1.9(1H)	2.35	~2.3	2.10	-
8b	3.74 4.28	3.62 d	~1.85[g]	~1.85[g]	1.05-1.3(3H),	1.5-1.65(2H),	~1.85(1H)[g]	2.35	2.07	2.16	-
8c	3.74 4.25	3.29 3.75	2.35	2.72	~6.15[c]		1.30, 1.52	3.07	2.63	2.18	-
8d	3.72 4.32	3.64 3.80	1.75	2.48	6.00	6.20	1.35, 1.92	2.96	1.96	2.25	-
9a	3.68 4.28	3.64 3.97	1.98	~2.18[g]	1.2-1.4(4H),	1.6-1.7(1H),	~2.1(1H)[g]	2.41	2.63	3.10 3.80	7.20-7.40
9b	3.81 4.25	3.67 3.70	~1.88[g]	~1.90[g]	1.1-1.3(3H),	1.5-1.6(2H),	2.08(1H)	~2.41[h]	~2.44[h]	3.21 3.91	7.20-7.40
9c	3.78 4.18	3.42 3.78	2.35	2.72	~6.20[c]		1.30, 1.50	3.07	2.98	3.29 3.97	7.25-7.35
9d	3.79 4.31	3.70 3.81	1.78	2.45	5.97	6.18	1.35, 2.12	2.95	2.35	3.28 3.93	7.20-7.40

[a] AB multiplet; J(A,B): 5.3 (8a-d) and 5.9 Hz (9a-d); [b] A and B part of an ABX multiplet (2H); J(A,B)≈J(A,X): 10.0-10.6, J(B,X): 7.0-8.2 Hz, for 8c,d and 9c,d. In the cases of 8a and 9a,b, due to a higher-order interaction, only the 1/2 J(A,X) + J(B,X) value is obtainable. The rudimental AB part of the ABX multiplet is a doublet in the spectrum of 8b, from which 1/2 J(A,X) + J(B,X) = 8.9 Hz, while J(A,B) cannot be deduced; [c] singlet-like broadened signal; [d] three overlapping multiplets of 4H, 1H and 1H (8a,9a) or 3H, 2H and 1H intensity (8b,9b) two dd, (8d,9d), J(6,7)≈ 5.7 Hz, J(5,6)≈J(7,8)≈ 3 Hz; [e] d, J(4a,8a)≈ 8 Hz (8b,d, 9b,d) or dd, J(4a,8a): 9.0, J(8,8a): 3.6 Hz (8a,c, 9a,c); [f] s of 3H intensity (8a-d) or AB multiplet (2H), J(A,B): 14.0 (9a,c) and 14.4 Hz (9b,d); [g,h] overlapping signals

and 9c,d; the shift relation of the 4-methylene hydrogen is normal ($\delta H_e > \delta H_a$).

In the norbornane compounds, similarly again to the 2-phenyldihydro derivatives, the chemical shift difference of the C-4 methylene protons is much smaller; accordingly, a first-order approximation of the ABX spin system formed by H-4, H-4' and H-4a is not justified. Hence, only the average of the coupling constants J(A,X) and J(B,X) can be obtained from the spectrum. In the case of 8b, the AB part of the ABX spectrum is reduced to a doublet, and thus the value of J(A,B) cannot be determined. The shift difference is also very small (0.1 ppm) in the spectrum of the benzyl analogue 9b, but the structure of the AB part indicates anomalous shielding of the geminal C-4 hydrogens. This is perfectly obvious in the case of the diendo analogues (8a, 9a), where the shift difference is considerably greater (0.31 and 0.32 ppm) and the splitting of the downfield double doublet is higher, indicating that this is due to the quasi-axial proton, whose H-4e counterpart is thus more shielded. It follows that the anomalous relation $\delta H_e < \delta H_a$ in the norbornane derivatives should be attributed to the anisotropy of the C_6-C_7 bond; however, this effect is much smaller, and also of opposite sign, than the corresponding influence of the C_6-C_7 double bond in norbornenes. A comparison of the data on 8c with those for the analogous 2-phenyldihydrooxazine (H-4e: 3.76; H-4a:4.32 ppm[22]) shows that the shielding of H-4(e) remains unchanged, but that the shielding of its counterpart, H-4(a), is reduced by more than 1 ppm, due to the effect of the coplanar aromatic ring.

(5) The endo hydrogens of norbornane are more shielded,[28] and it is therefore understandable that the H-4a and H-8a signals are upfield shifted in the spectra of 8b and 9b relative to the analogous signals of 8a and 9a. The much stronger analogous effect in the norbornene derivatives is due to the anisotropic effect of the double bond.

(6) The anisotropic effect of the heteroring is responsible for the upfield shift of the H-5 signal and for the downfield shifts of the H-6(exo) and H-9(endo) signals of the norbornanes and norbornenes, respectively, in the exo isomers, as compared with the endo counterparts [the signal of the H-7(exo) atom in norbornanes is, anyway, shifted downfield].

(7) The H-2, N-methyl and N-benzyl protons are not sensitive to anellation. The shift difference is very high both for the two diastereotopic H-2 protons and for the two chemically also nonequivalent benzyl methylene hydrogens (~0.55 and ~0.7 ppm).

(8) In the exo benzyl compounds (9b, 9d), H-8 and H-8a come under the shielding effect of the phenyl ring, and their signals show upfield shifts as compared with those of the endo counterparts.

(9) The steric compression shift[29] (increased shielding of the carbon atoms bearing sterically hindered groups) observed in the ^{13}C NMR spectra affords a number of data in support of the stereostructure.

In the series 9a-d, upfield shifts of the C-2 and C-4 signals are observed compared with those in the corresponding compounds 8a-d and, naturally, the methyl signal (38.2-39.4 ppm) is replaced by the downfield signal of the N-methylene carbon in the region 55.6-56.2 ppm. In the benzyl derivatives, the four lines of the aromatic carbon atoms can also be identified.

(10) In the diendo series the C-7 shifts, and in the norbornanes the C-6 shifts too, are considerably decreased. Independently of the degree of saturation of the alicyclic ring, there is steric hindrance between the N-substituent and the H-7 atom(s); however, the field effect on the C-6 signal can only be observed in the norbornanes, due to the hindrance between the H-6(endo) and H-4(a) atoms.

Table 3. ^{13}C NMR chemical shifts (δ_{TMS} = 0 ppm) for compounds 8a-d and 9a-d in $CDCl_3$ at 20 MHz

Compound	C-2	C-4	C-4a[a]	C-5[a]	C-6	C-7	C-8[a]	C-8a	C-9	NCH_n[b]	C-1'	C-2',6'	C-3',5'	C-4'
8a	84.3	63.0	40.2	39.7	23.3	21.7	38.4	63.9	37.6	38.9	-	-	-	-
8b	84.1	63.1	43.1	38.1	29.5	26.6	39.8	69.1	33.4	39.4	-	-	-	-
8c	83.7	64.3	45.4	44.3	134.4		46.7	64.6	39.9	38.3	-	-	-	-
8d	84.0	64.1	45.5	43.0	134.6	139.0	44.0	65.4	38.7	38.2	-	-	-	-
9a	81.6	61.7	40.1	39.8	23.0	21.7	42.9	63.7	37.3	55.8	138.0	128.1	128.5	126.8
9b	81.6	63.9	40.3	38.1	29.3	26.4	40.0	66.8	33.6	55.6	138.7	128.1	128.2	126.8
9c	81.5	62.8	46.8	44.8	134.7	135.0	46.3	65.3	39.7	56.2	138.4	128.1	128.4	126.9
9d	81.7	62.1	46.0	43.2	134.6	139.0	44.8	66.2	37.9	56.0	138.7	128.3[c]		126.9

[a] Assignments may be reversed; [b] n=3 (8a-d) or n=2 (9a-d); [c] two overlapping lines

(11) A field effect is shown by the C-9(endo) signal in the diexo series; this is significant only for the norbornanes (~4 ppm) as compared with the norbornenes (~1.5 ppm).

(12) Information about the saturation of the skeleton is obtained from the positions of the C-6 and C-7 signals: these methylene carbon signals of the norbornanes lie in the region 21.6-29.5 ppm; the corresponding olefin signals of the norbornene derivatives are found between 134.4 and 139.6 ppm.

(13) The β-effect[30] of the olefinic bond of norbornenes also increases the C-4a, C-5, C-8 and C-8a shifts by a few ppm, but in the exo isomers the C-8a shift is overcompensated by the steric compression shift due to the interaction of the H-7 and N-alkyl hydrogens. The diexo-diendo anellation is also reflected by the field effect (upfield shift) shown by the C-8a signals of the latter compounds. The steric compression shifts displayed by the C-4a, C-5 and C-8 signals appear in both anellation isomers, but the two latter atoms are a little more shielded in the diexo isomers, due to the greater strain in the skeleton.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded in 5 mm tubes at room temperature in $CDCl_3$ solution on a Bruker WM-250 FT or WP 80 SY FT spectrometer at 250.13 and 20.14 MHz, respectively, using the ^2H signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters for the ^1H and ^{13}C NMR spectra were as follows: sweep width, 5 kHz; pulse width, 1 and 3.5 μs (ca. 20° and 30° flip angle); aquisition time, 1.64 s; number of scans, 8 and 1-4K; computer memory, 16K. Complete proton noise decoupling (ca. 1.5 W) for the ^{13}C spectra and Lorentzian exponential multiplication for signal-to-noise enhancement were used (line width, 0.7 and 1.0 Hz).

The yields, physical properties and analytical data on the prepared compounds are given in Tables 4 and 5.

Ethyl 2-endo-ethoxycarbonylaminobicyclo[2.2.1]hept-5-ene-1-endo-carboxylate (4c)

Ethyl 2-endo-aminobicyclo[2.2.1]hept-5-ene-1-endo-carboxylate hydrochloride (3c) (2.18 g; 0.01 mol) was dissolved in water (15 ml), and $NaHCO_3$ (1.7 g; 0.02 mol) and ethyl chloroformate (1.3 g; 0.012 mol) were added. After stirring for 30 min, an oily phase separated which was extracted with chloroform (3x30 ml). On drying and evaporation of the combined extracts, an almost colourless oil was obtained.

Table 4. Physical and analytical data on the starting compounds 4-7[a]

Compound	M.p., °C	Yield, %	Found, % C	H	N	Formula	Calculated, % C	H	N
4c	oil[b]	b							
4d	73-75[c]	93	61.5	7.6	5.5	$C_{13}H_{19}NO_4$	61.6	7.6	5.5
5c	40-42[c]	60[d]	70.4	9.8	9.2	$C_9H_{15}NO$	70.5	9.9	9.1
5d[e]	163-165	84	57.1	8.6	7.3	$C_9H_{16}ClNO$	57.0	8.5	7.4
6a	68-70[c]	91	71.1	7.5	4.8	$C_{17}H_{21}NO_3$	71.0	7.4	4.9
6b	84-85[c]	75	70.9	7.4	5.0	$C_{17}H_{21}NO_3$	71.0	7.4	4.9
6c	58-59[c]	87	71.6	6.8	4.8	$C_{17}H_{19}NO_3$	71.6	6.7	4.9
6d	70-72[c]	92	71.5	6.8	5.0	$C_{17}H_{19}NO_3$	71.6	6.7	4.9
7a[e]	215-217	79	67.2	8.4	5.4	$C_{15}H_{22}ClNO$	67.3	8.3	5.2
7b	59-61[c]	84	78.0	9.1	6.2	$C_{15}H_{21}NO$	77.9	9.1	6.1
7c[e]	155-157	75	67.9	7.4	5.4	$C_{15}H_{20}ClNO$	67.8	7.6	5.3
7d[e]	158-161	87	67.6	7.7	5.4	$C_{15}H_{20}ClNO$	67.8	7.6	5.3

[a] Compounds 4a,b and 5a,b were described earlier[21]; [b] compound 4c was reduced without purification; [c] recrystallized from n-hexane; [d] overall yield of two steps; [e] hydrochloride salt, recrystallized from ethanol/ether

Table 5. Physical and analytical data on oxazinium picrates 8a-d and 9a-d

Compound	M.p., °C	Found, % C	H	N	Formula	Calculated, % C	H	N
8a	187-188	48.4	5.3	14.4	$C_{16}H_{20}N_4O_8$	48.5	5.1	14.1
8b	164-167	48.5	5.2	14.1				
8c	170-172	48.8	4.8	14.1	$C_{16}H_{18}N_4O_8$	48.7	4.6	14.2
8d	151-152	48.7	4.8	14.3				
9a	133-135	56.2	5.3	12.1	$C_{22}H_{24}N_4O_8$	55.9	5.1	11.9
9b	134-136	56.0	5.4	11.6				
9c	115-117	56.0	4.9	12.1	$C_{22}H_{22}N_4O_8$	56.2	4.7	11.9
9d	134-137	56.2	4.9	11.8				

[a] All compounds were recrystallized from ethanol/ether

Ethyl 2-endo-benzoylaminobicyclo[2.2.1]heptane-1-endo-carboxylate (6a)

Ethyl 2-endo-aminobicyclo[2.2.1]heptane-1-endo-carboxylate hydrochloride (3a) (2.2 g; 0.01 mol) was benzoylated by the Schotten-Baumann method. After separation and evaporation of the benzene layer, an almost white crystalline product was obtained.

2-endo-Benzylamino-3-endo-hydroxymethylbicyclo[2.2.1]heptane (7a)

$LiAlH_4$ (0.38 g; 0.01 mol) was suspended in THF (50 ml) and stirred for 10 min, and then 6a (1.27 g; 5 mmol) was added. After stirring and refluxing for 1 h (the end of the reduction was detected by TLC), the cooled mixture was decomposed with water (1 ml). The inorganic material was filtered off, and evaporation of the filtrate gave 7a.

3-Methyl-5,8-methano-rel-(4aR,5R,8R,8aR)-perhydro-3,1-benzoxazinium picrate (8a)

2-endo-Methylamino-3-endo-hydroxymethylbicyclo[2.2.1]heptane (5a) (0.58 g; 3 mmol) was stirred with 35% aqueous formaldehyde (5 ml) for 1 h. The mixture was then treated with 10% aqueous potassium hydroxide solution (10 ml) and extracted with ether (3x30 ml). The combined extracts were dried (Na_2SO_4), evaporated to 10 ml, and treated with a saturated ethereal solution of picric acid. After 1 h the picrate was filtered off.

References

1. Part 86/81, G. Stájer, A. E. Szabó, J. Pintye, G. Bernáth and P. Sohár, J. Chem. Soc. Perkin 1, Accepted for publication.
2. G. Bernáth, G. Stájer, A. E. Szabó, F. Fülöp and P. Sohár, Tetrahedron 41, 1353 (1985).
3. P. Sohár, L. Gera and G. Bernáth, Org. Magn. Reson. 14, 204 (1980).
4. G. Bernáth, F. Fülöp, A. Kálmán, Gy. Argay, P. Sohár and I. Pelczer, Tetrahedron 40, 3587 (1984).
5. F. Fülöp, G. Bernáth, Gy. Argay, A. Kálmán and P. Sohár, Tetrahedron 40, 2053 (1984).
6. P. Sohár and G. Bernáth, Org. Magn. Reson. 5, 159 (1973).
7. G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth, A. Kálmán, Gy. Argay and P. Sohár, Tetrahedron 39, 1829 (1983).
8. F. Fülöp, G. Bernáth, P. Sohár and I. Pelczer, J. Chem. Soc. Perkin 1, 2043 (1984).
9. P. Sohár, F. Fülöp and G. Bernáth, Org. Magn. Reson. 22, 527 (1984).
10. F. G. Riddell, The Conformational Analysis of Heterocyclic Compounds, Academic Press, London (1980).
11. A. R. Katritzky, V. J. Baker and F. M. S. B-Palma, J. Chem. Soc. Perkin 2, 1739 (1980).
12. P. M. R. Barkworth and T. A. Crabb, J. Chem. Soc. Perkin 2, 91 (1982); J. Chem. Soc. Perkin 1, 2777 (1982).
13. I. P. Boiko, O. I. Zhuk, Yu. F. Malina, Yu. Yu. Samitov and B. V. Unkovskii, Zh. Org. Khim. 11, 612 (1975).
14. O. S. Danilova, Yu. Yu. Samitov, S. P. Boiko, A. D. Yakusheva and B. V. Unkovskii, Zh. Org. Khim. 20, 2323 (1984).
15. A. J. Speziale and L. R. Smith, J. Org. Chem. 28, 1805 (1963).

16. L. R. Smith, A. J. Speziale and J. E. Fedder, J. Org. Chem. 34, 633 (1969).
17. R. R. Schmidt, Chem. Ber. 103, 3242 (1970).
18. B. Birne, C. A. Wilson and W. A. Agosta, Tetrahedron Letters 2189 (1976); S. S. Simons, J. Am. Chem. Soc. 96, 6492 (1974).
19. H. R. Kricheldorf, Makromol. Chem. 173, 13 (1973).
20. G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth and P. Sohár, J. Heterocycl. Chem. 20, 1181 (1983).
21. G. Stájer, A. E. Szabó, F. Fülöp, G. Bernáth and P. Sohár, J. Heterocycl. Chem. 21, 1373 (1984).
22. P. Sohár, G. Stájer and G. Bernáth, Org. Magn. Reson. 21, 512 (1983).
23. G. Stájer, A. E. Szabó, F. Fülöp and G. Bernáth, Synthesis 345 (1984).
24. G. Stájer, L. Mód, A. E. Szabó, F. Fülöp, G. Bernáth and P. Sohár, Tetrahedron 40, 2385 (1984).
25. I. Kato, N. Katagiri and Y. Yamamoto, Heterocycles 13, 1333 (1980).
26. M. Karplus, J. Chem. Phys. 30, 11 (1959); 33, 1842 (1960).
27. P. Sohár, Nuclear Magnetic Resonance Spectroscopy CRC Press, Boca Raton, Florida, 1983. Vol. II. pp. 25, 27.
28. E. Pretsch, I. Clerc, J. Seibl and W. Simon, Tabellen zur Strukturaufklärung organischer Verbindungen mit spektroskopischen Methoden. Springer Verlag, Berlin, 1976, p. H 190.
29. D. M. Grant and B. V. Cheney, J. Am. Chem. Soc. 89, 5315 (1967).
30. J. Mason, J. Chem. Soc. A. 1038 (1971).