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STEREOCHEMICAL STUDIES, 145. SATURATED HETEROCYCLES, 152. PREPARATION AND CONFORMATIONAL ANALYSIS OF STEREOISOMERIC 1,6,7,11b-TETRAHYDRO-2H[1,3]OXAZINO[4,3-a]ISOQUINOLIN-4-ONE DERIVATIVES

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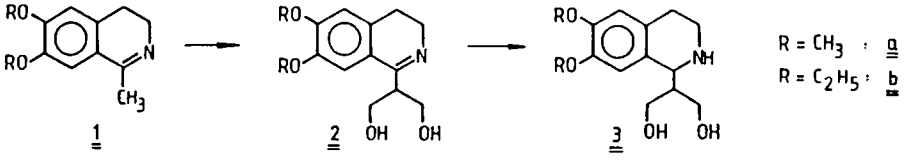
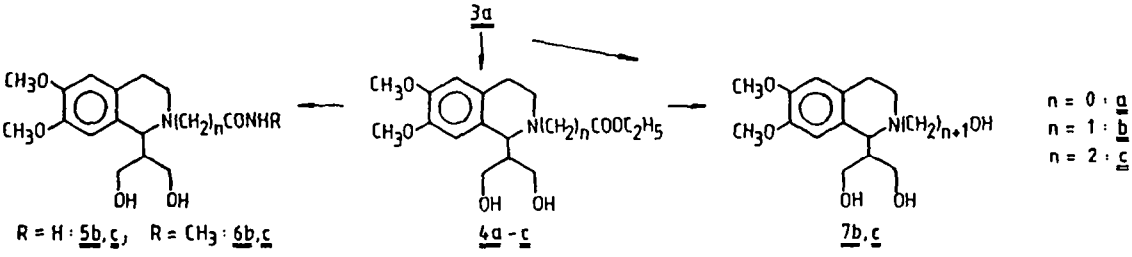
Abstract - Starting from 1-[bis(hydroxymethyl)-methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **3a**, trifunctional 1,2,3,4-tetrahydroisoquinolines were synthetized. From the N-ethoxycarbonyl derivative of **3a**, (r-11b,c-1)-1-hydroxymethyl- (**8**) and (r-11b,t-1)-1-chloromethyl-9,10-dimethoxy-1,6,7,11b-tetrahydro-2H[1,3]oxazino[4,3-a]isoquinolin-4-one (**9**) were formed in unexpected reactions. High-resolution NMR revealed that the tetrahydroisoquinoline-fused C-1 epimer oxazinone derivatives **8** and **9** have different conformations in solution. The first X-ray diffraction evidence of the presence of two different conformations of oxazinoisoquinolines **8** and **9** in the solid state is provided.

A simple synthesis of 1-[bis(hydroxymethyl)-methyl]-6,7-dialkoxy-1,2,3,4-tetrahydroisoquinolines **3a,b** was recently[2] developed. In the base-catalysed reaction of 1-methyl-6,7-dialkoxy-3,4-dihydroisoquinolines **1** with 2 mol of formaldehyde, the 1-[bis(hydroxymethyl)-methyl]-3,4-dihydroisoquinolines **2a,b** were obtained, and, on reduction with sodium borohydride or by catalytic reduction, these furnished the trifunctional isoquinoline 1,3-aminoalcohols **3a,b**. Compounds **3a,b** are readily available, versatile, inexpensive starting materials for the synthesis of substances of interest from both chemical and pharmacological points of view.[3-6] In this paper, some transformations of aminoalcohol **3a** are described.



Results and discussion

Compound **3a** reacted with ethyl chloroformate to give the corresponding urethane **4a**. The N-ethoxycarbonylmethyl derivative **4b** was obtained from aminoalcohol **3a** with ethyl bromoacetate. The ethoxycarbonyl ethyl derivative **4c** was formed from aminoalcohol **3a** by ethyl acrylate addition (Schemes 1 and 2).



Scheme 1

The reduction of esters **4b** and **4c** with lithium aluminium hydride yielded the corresponding hydroxyalkyl derivatives **7b** and **7c**. Similar reduction of urethane **4a**, as anticipated,[7] resulted in the N-methyl derivative **10**.

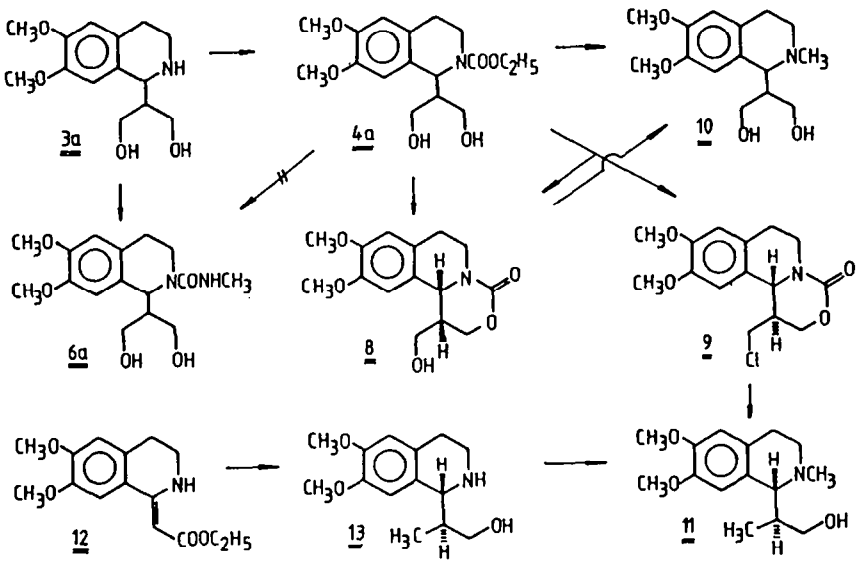
The N-hydroxyethyl derivative **7b** was synthetized directly from **3a** too, by addition of ethylene oxide. This reaction could be carried out under milder conditions than those described[8] for the similar addition of ethylene oxide to 1-phenyl-1,2,3,4-tetrahydroisoquinoline (24 h, 75 °C, in an autoclave).

On treatment with ammonia or methylamine, compounds **4a-c** yielded the expected amides **5** and **6** only in the reactions of esters **4b** and **4c**. Treatment of urethane **4a** with methylamine did not furnish urea derivative **6a**. Compound **6a** was prepared in another way: from aminoalcohol **3a** by methyl isocyanate addition. Treatment of urethane **4a** with either ammonia or methylamine yielded the same unexpected oxazino[4,3-a]isoquinoline derivative **8**.

Besides the ^{1}H NMR spectroscopic evidence, the structure of oxazine **8** was confirmed chemically. Melting of ester **4a** with sodium methylate similarly afforded **8**. Reduction of oxazine **8** with lithium aluminium hydride led to the corresponding N-methyl-substituted tetrahydroisoquinoline **10** through ring-opening. This reaction is also characteristic of 1,3-oxazines.[9]

In 1,3-oxazino[4,3-a]isoquinoline syntheses, mainly 1,3-difunctional isoquinolines are used.[10-17] The other well-known method is the cycloaddition of ketenes to 3,4-dihydroisoquinolines.[18-21] In a recent paper, the synthesis of an oxazolo[4,3-a]isoquinolin-3-one derivative is described[22], starting from an N-ethoxycarbonylisoquinoline derivative, using alcoholic potassium hydroxide. However, when this type of cyclization was attempted for ester **4a** in the present case, only the starting aminoalcohol **3a** could be isolated.

Thionyl chloride treatment of urethane **4a** resulted in a mixture of oxazines **8** and **9**. The attempted OH→Cl exchange of oxazine **8** failed to give compound **9**, even on refluxing for 3 h in thionyl chloride.



Scheme 2

The relative configuration of oxazine **9** was proved not only by the NMR and X-ray evidence, but also by preparative means. Erythro-1-[1'-(hydroxymethyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **13** was prepared from the 1-ethoxycarbonylmethylene derivative **12** by the known method[4]: C-alkylation with methyl iodide and subsequent catalytic and lithium aluminium hydride reduction. Aminoalcohol **13** reacted with ethyl chloroformate (similarly as in reaction **3a** → **4a**) to yield the corresponding urethane, which on lithium aluminium hydride reduction gave the N-methyl derivative **11**. The lithium aluminium hydride reduction of oxazine **9** (similarly as in reaction **8** → **10**) gave the same N-methyl compound **11** as was formed from the erythro-aminoalcohol **13**. These chemical reactions did not affect the asymmetric carbon atoms of compounds **13** and **9**, so oxazine **9** has the (r-11b,t-1) configuration.

^{1}H NMR spectroscopic investigations on oxazinoisoquinolines **8** and **9**

250 MHz ^{1}H 1D and 2D NMR studies allowed a complete analysis of the spectra and determination of the full set of coupling constants. The data listed in Table 1 lead to the only configuration corresponding to the spectroscopic results and the favoured conformation of the oxazinoisoquinoline ring system.

From the spectra of compounds **8** and **9**, it is obvious that only one of the possible diastereomers is formed under the given reaction conditions. The most important coupling, which gives information about the connection of the two saturated rings, is $J_{1,11b}$, which has typical axial-equatorial values 4.4 and 3.0 Hz, respectively. The nuclear Overhauser effects (NOE) found between

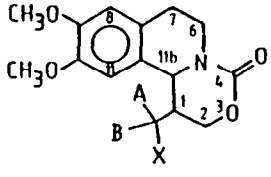
protons H_{11b},H_6 and H_{11b},H_2, respectively, in **8** show that all these protons are axial and that they are close to each other (1,3-diaxial connection). This means that, similarly as from the X-ray results on compound **8**, the two saturated rings are trans-annelated to each other, the hydroxymethyl axial, and H_1 is equatorial.

The lack of a NOE between protons H_{11b},H_2 shows that the hetero ring is connected to the tetrahydroisoquinoline moiety. The coupling constants in **8** and **9** differ only slightly, indicating that the saturated rings have similar conformations. In both cases the CH_2X group is axial and C_1 is equatorial. The difference in the saturated ring annelation is that the CO group attached to the nitrogen is quasi-equatorial in **8** (cis connection of the two hetero rings), while in **9** it is quasi-axial (trans connections of the two hetero rings). Because of the lack of a proton at the annelation position, the sets of coupling constants are very similar.

These results are supported by the fact that couplings $J_{1,2ax}$ and $J_{1,2eq}$ do not have trans-diaxial values (>10 Hz). The saturated heterocycle of the isoquinoline part of the molecule is twisted, because $J_{6eq,7eq}$ has a small value, suggesting a 90° dihedral angle between these atoms. The anisotropic shielding effect of the carbonyl group on H_{6eq} in **9** and the NOE effect prove the inversion of the nitrogen.

Table 1. Chemical shifts (ppm) and coupling constants (Hz) for compounds **8** and **9**[a]

	H_1	H_{2a}	H_{2e}	H_{6a}	H_{6e}	H_{7a}	H_{7e}	H_{11b}	H_A	H_B	X	H_8	H_{11}	^9Me	^{10}Me
δ(ppm)	2.58 2.71	4.65 4.27	4.41 4.14	2.59 2.62	2.82 3.10	4.63 4.55	2.91 3.02	5.08 4.66	3.26 3.88	3.52 3.83	2.71 —	6.64 6.66	6.61 6.67	3.86 3.88	3.87 3.88
H_1		4.4 4.2	1.7 3.0					4.4 3.0	4.4 3.7	5.9 3.8					
H_{2a}	4.4 4.2		-11.0 -11.4					~1 1.0							
H_{2e}	1.7 3.0	-11.0 -11.4													
H_{6a}					-12.0 -11.8	10.7	2.4 2.8								
H_{6e}				-12.0 -11.8		0 0	3.9 4.8								
H_{7a}				10.7	0 0		-11.1 -11.9								
H_{7e}				2.4 2.8	3.9 4.8	-11.1 -11.9									
H_{11b}	4.4 3.0	~1 1.0													
H_A	4.4 3.7									-10.8 -11.5	5.1				
H_B	5.9 6.8								-10.8 -11.5		5.5				
X									5.1 —	5.5 —					



[a]Upper trace compound **8**, lower trace compound **9**.

X-ray analysis of **8** and **9**

The perspective views of the X-ray structures (Figure 1) computed from the atomic coordinates listed for **8** and **9** in Table 2 show the principal differences in their conformations and configurations. The C-1 epimers are characterized by the different chirality of C(1) with respect to the permanent chiral centre C(11B), chosen deliberately in both drawings with R configuration. Accordingly, the CH_2OH group of **8** assumes the α-axial position, whereas the CH_2Cl moiety is bound β-axially. The B/C rings fused along the C(11B)-N(5) bond exhibit further conformational differences.

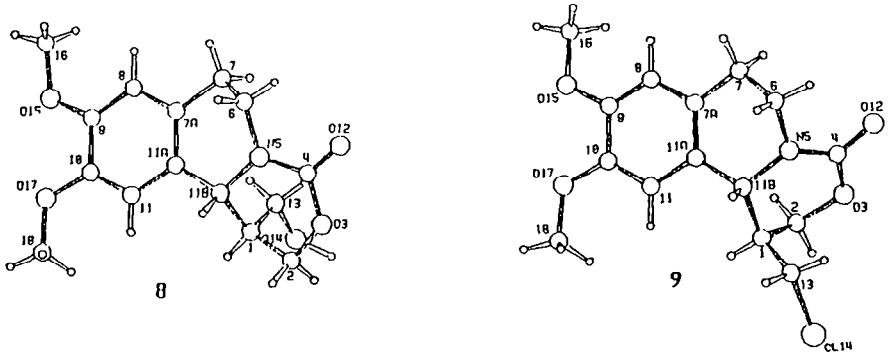


Figure 1. Perspective view of the molecular structures of **8** and **9** with atomic numbering. The bare numbers are for carbon atoms unless indicated otherwise. The hydrogen atoms are shown but not labelled.

The 1,3-oxazine (C) ring conformation, assuming a transition state between an envelope (^1E), skew-boat ($^1S_{11B}$) and half-chair ($^1H_{11B}$) in **8**, is shifted towards an almost perfect half-chair ($^2H_1$) in **9**. This motion is accompanied by simultaneous pseudorotation in the tetrahydropyridine (B) ring, which represents a shift from a distorted envelope shape with C(6) in the flap towards an also nearly perfect half-chair ($^5H_6$). In the course of these pseudorotations, the fairly planar N(5) gains some pyramidality[26] (χ_N = -0.06→→0.23 rad). The corresponding pseudorotation can be expressed by the following puckering parameters[27], the ring numbering starting from O(3) towards C(4) and from N(5) towards C(6), respectively.

	Ring C			Ring B	
	8	**9**		**8**	**9**
Q	0.525(3)	0.498(3) Å	Q	0.487(3)	0.522(3) Å
φ	223.3(4)	90.6(4)°	φ	71.8(3)	26.9(4)°
θ	55.6(3)	128.6(3)°	θ	61.4(3)	52.5(3)°

The molecules of **8** are bound together by centre of symmetry-related hydrogen-bond pairs, thereby forming dimer associates. The parameters of these hydrogen-bonds are:

		O ····· O	H····· O	OH····· H
O(14)-H····· O(12)	2-x,1-y,1-z	2.745(2)°	1.712(2)°	172.6(2)°

Experimental

The ^1H NMR spectra were measured in $COCl_3$ solution at room temperature on a Bruker AC 250 SY spectrometer, with TMS as internal standard. The magnetic field was locked on the deuterium signal of the solvent. The 2D measurements (COSY and NOESY) were carried out with the standard software written for the Aspect 3000 computer of the spectrometer. Size of the matrix: 2K x 512 W; spectral width: 2748 Hz; scans 32, experiments 512.

The spectral data on compounds **4-7**, **10** and **11** are in accordance with the structures given in the Schemes.

Melting points were determined on a Boetius micro melting point hot stage.

1-[bis(Hydroxymethyl)-methyl]-2-ethoxycarbonyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4a**). **Method A**

Compound **3a** (8.02 g, 0.03 mol) was suspended in a solution of $NaHCO_3$ (2.51 g, 0.03 mol) in water (30 ml), and ethyl chloroformate (3.26 g, 0.03 mol) was added. The mixture was stirred at room temperature for 1 h, and then extracted with EtOAc. After drying and evaporation, **4a** was obtained as crystals.

1-[bis(Hydroxymethyl)-methyl]-2-(ethoxycarbonylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4b**). **Method B**

To a suspension of K_2CO_3 (12.44 g, 0.09 mol) in abs. acetone (50 ml), compound **3a** (8.02 g, 0.03 mol) and ethyl bromoacetate (5.01 g, 0.03 mol) were added. After stirring for 4 h at room temperature, the inorganic salts were filtered off and washed with abs. acetone, and the filtrate was evaporated. Compound **4b** was obtained as an oil, which was converted to the hydrochloride with ethanolic HCl.

1-[bis(Hydroxymethyl)-methyl]-2-(β-ethoxycarbonylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**4c**). **Method C**

Compound **3a** (8.02 g, 0.03 mol) was refluxed for 4 h with ethyl acrylate (3.00 g, 0.03 mol) in methanol (50 ml). After evaporation, compound **4c** was obtained as an oil, which was converted into its derivatives **5c**, **6c** and **7c** without purification.

1-[bis(Hydroxymethyl)-methyl]-2-(aminocarbonylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5b**). **Method D**

Compound **4b** (1.06 g, 3 mmol) was dissolved in methanol containing 20% ammonia (25 ml), and the mixture was left to stand at room temperature for 2 weeks. The solution was then evaporated, and amide **5b** was obtained as an oil, which was converted to the hydrochloride with ethanolic HCl.

1-[bis(Hydroxymethyl)-methyl]-2-(β-aminocarbonylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**5c**).

Compound **5c** was prepared from ester **4c** by Method D.

1-[bis(Hydroxymethyl)-methyl]-2-methylcarbamoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6a**). **Method E**

Methyl isocyanate (0.40 g, 7 mmol) was added to compound **3a** (1.87 g, 7 mmol) in benzene (25 ml). After stirring and refluxing for 2 h, the mixture was evaporated and urea derivative **6a** was obtained as crystals.

1-[bis(Hydroxymethyl)-methyl]-2-[(methylaminocarbonyl)-methyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6b**).

Compound **6b** was prepared from ester **4b** with methanol containing 20% methylamine by Method D.

1-[bis(Hydroxymethyl)-methyl]-2-[β-(methylaminocarbonyl)-ethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**6c**).

Compound **6c** was prepared from ester **4c** with methanol containing 20% methylamine by Method D.

(r-11b,c-1)-1-Hydroxymethyl-9,10-dimethoxy-1,6,7,11b-tetrahydro-2H[1,3]oxazino-[4,3-a]isoquinolin-4-one (**8**).

Compound **8** was prepared from urea derivative **4a** by Method D, using methanolic ammonia or methylamine solution. After evaporation of the reaction mixture, oxazine **8** was obtained as crystals.

Method F

Compound **4a** (3.39 g, 0.01 mol) was heated with sodium methylate (0.1 g) at 130 °C for 30 minutes. Hot EtOAc was added to the mixture and the sodium methylate was filtered off. The filtrate was dried and evaporated, and crystalline oxazine **8** was obtained.

Reaction of **4a** with ethanolic KOH. **Method G**

Compound **4a** (1.70 g, 5 mmol) was refluxed in 10% ethanolic potassium hydroxide solution (30 ml) for 1 h. Following evaporation, the residue was dissolved in water and extracted with $CHCl_3$. After drying and evaporation, aminoalcohol **3a** was obtained as crystals.

(r-11b,t-1)-1-Chloromethyl-9,10-dimethoxy-1,6,7,11b-tetrahydro-2H[1,3]oxazino-[4,3-a]isoquinolin-4-one (**9**). **Method H**

Compound **4a** (5.35 g, 15.8 mmol) was refluxed in thionyl chloride (10 ml) for 30 minutes. After evaporation of the mixture, a brown oil was obtained, which was crystallized by the addition of ethanol and ether. On recrystallization from EtOAc, only compound **8** (0.3 g) crystallized out. The mother liquor was evaporated and the residue was recrystallized from EtOH, when pure oxazine **9** was obtained.

1-[bis(Hydroxymethyl)-methyl]-2-(β-hydroxyethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**7b**). **Method I**

$LiAlH_4$ (0.76 g, 0.02 mol) was suspended in abs. THF (100 ml), and compound **4b** (2.34 g, 6 mmol) was added. After stirring for 15 minutes at room temperature, the mixture was decomposed with 1.5 ml water under ice cooling. After stirring for 1 h, the inorganic material was filtered off, and the filtrate was dried (Na_2SO_4) and evaporated. Compound **7b** was obtained as an oil, which was converted to the hydrochloride with ethanolic HCl.

Method J

Compound **3a** (2.67 g, 0.01 mol) was dissolved in methanol (40 ml), and ethylene oxide (0.66 g, 0.015 mol) was added. After standing for 24 h at room temperature, the mixture was evaporated. Compound **7b** was obtained as an oil, which was converted to the hydrochloride with ethanolic HCl.

1-[bis(Hydroxymethyl)-methyl]-2-(γ-hydroxypropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**7c**)

Compound **7c** was prepared by $LiAlH_4$ reduction of ester **4c**, as described in Method I.

1-[bis(Hydroxymethyl)-methyl]-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**10**)

Compound **10** was prepared from urea derivative **4a** by $LiAlH_4$ reduction, as described in method I. The mixture was stirred and refluxed for 3 h. Product **10** was obtained as an oil, which was converted to the hydrochloride with ethanolic HCl.

Compound **10** was also prepared from oxazine **8** by $LiAlH_4$ reduction, as described in Method I. The mixture was stirred under reflux for 1 h.

Erythro-1-[1'-(Hydroxymethyl)-ethyl]-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**11**)

From aminoalcohol 13

Compound 13 was converted into its N-ethoxycarbonyl derivative by method A, in 45% yield. Mp: 73-76 °C (diisopropyl ether), $C_{17}H_{25}NO_5$ (calcd/found) C 63.14/63.10, H 7.79/8.03, N 4.33/4.37%.

The product of the above reaction was reduced wih $LiAlH_4$, as described in Method I. The mixture was stirred and refluxed for 1 h. Compound 11 was obtained as an oil, which was converted to the hydrochloride with ethanolic HCl.

From oxazine 9

Oxazine 9 was reduced with $LiAlH_4$ by Method I. The mixture was stirred and refluxed for 2 h. Compound 11 was formed as an oil, which was converted to the hydrochloride with ethanolic HCl.

The products obtained by these two methods were identical.

Table 2. Physical and analytical data on prepared tetrahydroisoquinolines 4-11

Compound	Yield (%) (Method)	M.p. (°C) (Solvent)	Formula (M.W.)	Analysis, Calculated/Found (%) C	H	N
4a	75 (A)	114-117 (EtOAc)	$C_{17}H_{25}NO_6$ (339.38)	60.16/60.57	7.43/7.02	4.13/4.20
4b[a]	79 (B)	178-181 (EtOH-ether)	$C_{18}H_{28}ClNO_6$ (389.86)	55.45/55.42	7.24/7.25	3.59/4.20
5b[a]	65 (D)[b]	213-217 (96% EtOH-ether)	$C_{16}H_{25}ClN_2O_5$ (360.84)	53.25/52.87	6.98/7.19	7.77/7.31
5c[a]	60 (D)	212-217 (EtOH-ether)	$C_{17}H_{27}ClN_2O_5$ (374.87)	54.46/54.43	7.26/7.22	7.47/7.15
6a	72 (E)	176-179 (EtOH)	$C_{16}H_{24}N_2O_5$ (324.37)	59.24/59.68	7.45/7.27	8.63/8.42
6b[a]	68 (D)	211-213 (EtOH-ether)	$C_{17}H_{27}ClN_2O_5$ (374.87)	54.46/54.19	7.26/7.61	7.47/7.26
6c	64 (D)[b]	147-148 (EtOH)	$C_{18}H_{28}N_2O_5$ (352.42)	61.34/61.73	8.00/7.79	7.95/7.80
7b[a]	74 (I) 80 (J)	219-221 (EtOH-ether)	$C_{16}H_{26}ClNO_5$ (347.84)	55.24/55.48	7.54/7.68	4.03/4.29
7c	65 (I)[b]	138-140 (EtOAc)	$C_{17}H_{27}NO_5$ (325.40)	62.74/62.31	8.37/8.24	4.31/4.23
8	45 (D) 30 (F) 5 (H)	188-192 (EtOAc)	$C_{15}H_{19}NO_5$ (293.31)	61.42/61.68	6.52/6.73	4.78/4.86
9	15 (H)	155-157 (EtOH)	$C_{15}H_{18}ClNO_4$ (311.76)	57.78/58.05	5.82/5.93	4.49/4.68
10[a]	35 (I)[c] 28 (I)[d]	199-201 (EtOH-ether)	$C_{15}H_{24}ClNO_4$ (317.81)	56.68/56.48	7.61/7.43	4.41/4.23
11[a]	55 (I)[f] 32 (A,I)[b,e]	199-202 (EtOH-ether)	$C_{15}H_{24}ClNO_3$ (301.81)	59.69/59.32	8.01/8.31	4.64/4.58

[a]Hydrochloride. [b]Overall yield. [c]From 4a. [d]From 8. [e]From 13. [f]From 9.

Crystal structure determination of 8

Crystal data: $C_{15}H_{19}NO_5$, M = 293.31, monoclinic, a = 11.148(2), b = 9.104(1), c = 14.763(2) Å, β = 106.33(1)°, V = 1437.7(7) Å^3 (by least squares refinement on diffractometer angles for 25 automatically centred reflexions), space group

$P2_1/n$ (No 14) from systematic absences as h + l = 2n + l in h0l and k = 2n + l in 0k0 reflexions. Z = 4, D_x = 1.36 g cm^{-3}, F(000) = 624, u(Cu-$K_{\bar{\alpha}}$, λ = 1.54184 Å) = 8.1 cm^{-1}. Crystal dimensions: 0.25 x 0.30 x 0.70 mm^3.

Data collection was carried out with a CAD-4 diffractometer in the range $1.5<\theta<75.0^{\circ}$ with $\omega/2\theta$ scan using graphite monochromated Cu-$K_{\bar{\alpha}}$ radiation. Three standard reflexions (270, $\bar{7}$ 2 10, $\bar{2}$ 0 12) were monitored every hour and showed no detectable deviation. 2961 unique, non-zero and independent observations were recorded, of which 2640 with $I \geq 3.0\sigma(I)$ were used for structure analysis and refinement. The structure was solved by MULTAN,[28] using 257 $E \geq 1.73$ normalized the $\Sigma w(\Delta F)^2$. Final R = 0.048, wR = 0.049, R_{tot} = 0.054, S = 0.76. In the last cycle of refinement, the largest shift-error was 0.065, while the highest peak in the final difference Fourier map was 0.22 e.$Å^3$.

Table 3. Fractional atomic coordinates for compounds **8** and **9** with their e.s.d.'s in parentheses.

	8				**9**		
Atom	x/a	y/b	z/c	Atom	x/a	y/b	z/c
C(1)	0.8517(1)	0.4891(2)	0.2955(1)	C(1)	0.1186(3)	0.6211(1)	0.5808(1)
C(2)	0.8514(2)	0.6007(3)	0.3716(1)	C(2)	0.3079(4)	0.5906(1)	0.5366(1)
O(3)	0.9765(1)	0.6433(2)	0.4242(1)	O(3)	0.4893(2)	0.6004(1)	0.5947(1)
C(4)	1.0770(2)	0.6220(2)	0.3921(1)	C(4)	0.5182(3)	0.6808(2)	0.6355(1)
N(5)	1.0611(1)	0.5720(2)	0.3042(1)	N(5)	0.3568(2)	0.7379(1)	0.6384(1)
C(6)	1.1707(2)	0.5451(2)	0.2708(1)	C(6)	0.3949(3)	0.8326(1)	0.6622(1)
C(7)	1.1614(2)	0.3944(2)	0.2264(1)	C(7)	0.3974(3)	0.8889(1)	0.5806(1)
C(7a)	1.0412(1)	0.3796(2)	0.1489(1)	C(7a)	0.2160(3)	0.8650(1)	0.5184(1)
C(8)	1.0332(2)	0.2912(2)	0.0692(1)	C(8)	0.1680(3)	0.9231(1)	0.4489(1)
C(9)	0.9242(2)	0.2817(2)	-0.0023(1)	C(9)	0.0026(3)	0.9081(1)	0.3920(1)
C10)	0.8197(1)	0.3643(2)	0.0024(1)	C(10)	-0.1309(3)	0.8345(1)	0.4061(1)
C(11)	0.8267(1)	0.4512(2)	0.0802(1)	C(11)	-0.0826(3)	0.7757(1)	0.4738(1)
C(11a)	0.9372(1)	0.4578(2)	0.1545(1)	C(11a)	0.0936(3)	0.7887(1)	0.5294(1)
C(11b)	0.9353(1)	0.5516(2)	0.2388(1)	C(11b)	0.1437(3)	0.7217(1)	0.6032(1)
O(12)	1.1794(1)	0.6508(2)	0.4470(1)	O(12)	0.6881(2)	0.6979(1)	0.6686(1)
C(13)	0.8926(2)	0.3376(2)	0.3342(1)	C(13)	0.0817(3)	0.5673(1)	0.6623(1)
O(14)	0.8033(1)	0.2670(2)	0.3708(1)	Cl(14)	0.0455(1)	0.44835(4)	0.63940(4)
O(15)	0.9079(1)	0.1981(1)	-0.0821(1)	O(15)	-0.0516(2)	0.9613(1)	0.3217(1)
C(16)	1.0155(2)	0.1298(3)	-0.0959(1)	C(16)	0.0969(4)	1.0266(1)	0.2970(1)
O(17)	0.7166(1)	0.3538(2)	-0.0746(1)	O(17)	-0.2986(2)	0.8277(1)	0.3491(1)
C(18)	0.6144(2)	0.4474(3)	-0.0752(2)	C(18)	-0.4432(3)	0.7574(1)	0.3618(1)

At the end of the least-squares treatment of the non-hydrogen atoms with isotropic temperature factors, an empirical absorption correction was performed through the use of program DIFABS.[29] Relative transmission coefficients ranged from 0.633 to 1.313, with an average value of 0.984. At this stage, the positions of hydrogen atoms bound to carbons were generated from assumed geometries, while H(O14) was located in a difference Fourier map. The hydrogen positions were not refined, but only added to structure factor calculations with mean isotropic temperature factors ($B_{iH} = B_{iX}+1$ in $Å^2$, where X = C or O). Atomic scattering factors were taken from Cromer and Waber.[30] Program system applied: Enraf-Nonius Structure Determination Package, with local modification adapted to a PDP-11/34 minicomputer.

Crystal structure determination of **9**

Crystal data: $C_{15}H_{18}ClNO_4$, M = 311.76, monoclinic, a = 6.477(1), b = 14.646(1), c = 15.531(1) Å, β = 93.38(1)°, V = 1470.6(4) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflexions) space group $P2_1/n$ (No. 14) from systematic absences as h + l = 2n + 1 in h0l and k = 2n + 1 in 0k0 reflexions, Z = 4, D = 1.41 g cm^{-3}, F(000) = 656, μ(Cu-K$_\alpha$, λ = 1.54184 Å) = 24.6 cm^{-1}.

Data collection, structure determination and refinement were basically similar as for **8**. Of 3069 unique reflexions, 2768 were taken as observed with $I > 3.0\sigma(I)$. MULTAN 82; minimum and maximum relative transmission coefficients: 0.778 and 1.338, with an average value of 0.979. The H positions were refined in isotropic mode. Full matrix refinement. Final R = 0.049, R_w = 0.044, R_{tot} = 0.053, S = 0.72. The highest peak in the final difference Fourier map was 0.26(4) e.Å^{-3}, (Δ/σ)max 0.026.

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REFERENCES

1. Parts 144/151. Stájer, G.; Szőke-Molnár, Zs.; Bernáth, G.; Sohár, P. Tetrahedron, accepted for publication.
2. Kóbor, J.; Fülöp, F.; Bernáth, G. Heterocycles, **24**, 2227 (1986).
3. Bernáth, G.; Kóbor, J.; Fülöp, F.; Sohár, P.; Argay, Gy.; Kálmán, A. Tetrahedron, **42**, 5139 (1986).
4. Kóbor, J.; Fülöp, F.; Bernáth, G.; Sohár, P. Tetrahedron, **43**, 1887 (1987).
5. Bernáth, G.; Kóbor, J.; Fülöp, F.; Sohár, P.; Perjési, P.; Ezer, E.; Hajós, Gy.; Pálosi, É.; Dénes, L.; Szporny, L. Ger. Pat. DE 3,439,131 Chem. Abstr. **103**, 160523 (1985).
6. Bernáth, G.; Kóbor, J.; Fülöp, F.; Sohajda, A.; Kálmán, A.; Ezer, E.; Hajós, Gy.; Pálosi, É.; Dénes, L.; Szporny, L. Ger. Pat. DE 3,510,526 Chem. Abstr. **104**, 109667 (1986).
7. Hajós, A. Complex Hydrides, Akadémia, Budapest, Hungary, 1979, p. 99.
8. Vlaeminck, F.; De Cock, E.; Tourwé, D.; Van Binst, G. Heterocycles, **15**, 1213 (1981).
9. Fülöp, F.; Bernáth, G. Synthesis, **1981**, 628.
10. Openshaw, H. T.; Whittaker, N. J. Chem. Soc., **1963**, 1449.
11. Schneider, W.; Schilken, K. Arch. Pharm., **299**, 997 (1966).
12. Crabb, T. A.; Newton, R. F. Tetrahedron Letters, **1971**, 3361.
13. Crabb, T. A.; Mitchell, J. S. Org. Magn. Reson., **8**, 258 (1976).
14. Crabb, T. A.; Mitchell, J. S.; Newton, R. F. J. Chem. Soc. Perkin 2, **1977**, 370.
15. Harsányi, K.; Kiss, P.; Korbonits, D. J. Heterocyclic Chem., **10**, 435 (1973).
16. Fülöp, F.; El-Gharib, M. S.; Sohajda, A.; Bernáth, G.; Kóbor, J.; Dombi, Gy. Heterocycles, **20**, 1325 (1983).
17. Kano, S.; Yuasa, Y.; Shibuya, S. Synth. Comm., **15**, 883 (1985).
18. Pratt, R. N.; Taylor, G. A. J. Chem. Soc. (C), **1967**, 1569.
19. Huisgen, R.; Davis, B. A.; Morikawa, M. Angew. Chem., **80**, 802 (1968); Angew. Chem. Int. Ed. Engl., **7**, 826 (1968).
20. Martin, J. S.; Brannock, K. C.; Burrpitt, R. D.; Gott, P. G.; Hoyle, V. A. J. Org. Chem., **36**, 2211 (1971).
21. Taylor, G. A. J. Chem. Soc. Perkin 1, **1975**, 1001.
22. Czarnocki, Y.; MacLean, D. B.; Szarek, W. A. Can. J. Chem., **64**, 2005 (1986).
26. Dunitz, J. D.; Winkler, F. K. Acta Crystallogr., **B31**, 251 (1975).
27. Cremer, D.; Pople, J. A. J. Am. Chem. Soc., **97**, 1354 (1975).
28. Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J.-P.; Woolfson, M. M. MULTAN 82, A System of Computer Programs of Automatic Solution of Crystal Structures from X-ray Diffraction Data, 1982, University of York, England and Louvain, Belgium.
29. Walker, N.; Stuart, D. Acta Crystallogr., **A39**, 158 (1983).
30. Cromer, D. T.; Waber, J. T. in International Tables for X-ray Crystallography. The Kynoch Press, Birmingham, 1974, Vol. IV. Table 2628.