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Synthesis, Reactions and Stereochemistry of 3-Hydroxymethyl-2,3-dihydro-4*H*-1,3-benzoxazin-4-one and Some Perhydrogenated Derivatives[1]

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

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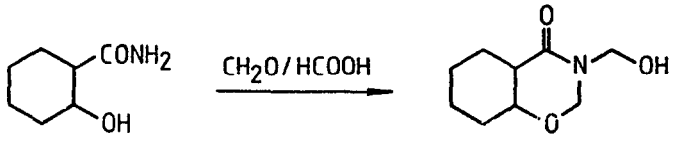
Abstract: *3-Hydroxymethyl-2,3-dihydro-4H-1,3-benzoxazin-4-one and a number of its perhydrogenated derivatives were prepared from the corresponding 2-hydroxycarboxamides by treatment with a formaldehyde/formic acid mixture. Thermal decomposition of the 3-hydroxymethyl derivatives led to the previously unknown parent compounds. With one exception (14), both in the N-unsubstituted (16-18) and in the N-substituted (7-15) cyclopentane- and cyclohexane-fused derivatives the oxazinone ring predominantly attains a single half-chair conformation.*

It was recently found[2] that refluxing of *cis*- and *trans*-2-hydroxycyclohexanecarboxamides **1** and **2** with a mixture of aqueous formaldehyde and formic acid led to a ring-closure reaction accompanied by hydroxymethylation, and gave rise to perhydrobenzoxazines **3** and **4**. Although the aromatic 2,3-dihydro-1,3-benzoxazin-4-ones[3] were synthesized at the beginning of this century, and a number of differently substituted derivatives have been prepared for both chemical[4,5] and pharmacological purposes,[6,7] 2,3-dihydro-1,3-benzoxazin-4-one itself and its *N*-hydroxymethyl derivative[8] have not been described previously.



cis : 1 trans : 2 cis : 3 trans : 4

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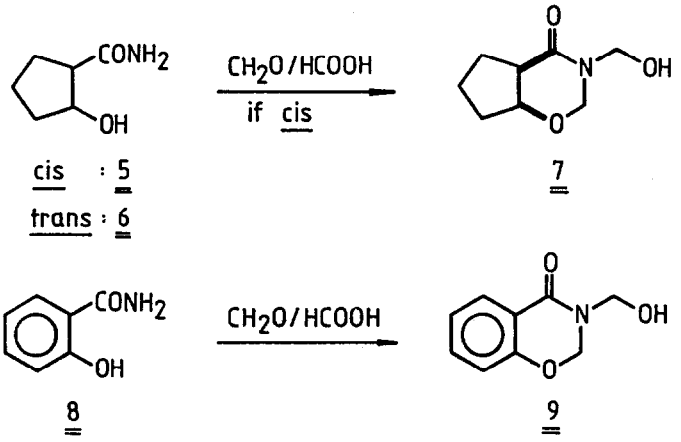
The aim of this study was to investigate the scope and limitations of application of the formaldehyde/formic acid reaction to *cis*- and *trans*-2-hydroxycyclopentanecarboxamides and salicylamide.

RESULTS AND DISCUSSION

When *cis*- and *trans*-2-hydroxycyclopentanecarboxamides[9] **5** and **6** were refluxed in an aqueous formaldehyde/formic acid mixture for 1 h, the former underwent the desired ring-closure and gave the hydroxymethylated product **7** (Scheme 1). Even after a 5 h reaction time, only the unreacted starting material **6** was recovered (in *ca* 70% yield) in the case of the *trans* isomer. The difference in the reactivities of the above *cis* and *trans* 1,2-disubstituted 1,3-bifunctional derivatives is known[10] and has been utilized, for example, in the separation of diastereomers.[11,12]



Scheme 1

When the above reaction (Scheme 1) was carried out with salicylamide **8**, a column chromatographic separation led to **9** in 45% yield. The ^{1}H NMR spectrum of the latter contained not only the four well-separated aromatic signals, but also the signals of 2x2 aliphatic hydrogens at relatively low field (Table 1). The differentiation between the C-2 and C-9 protons was based on the fact that the latter are coupled to the hydroxy proton, *i.e.* they show a broadened signal at 5.06 ppm.

On the addition of phenyl or *p*-chlorophenyl isocyanate to **3**, **4** and **7**, carbamoyloxy derivatives **10-13** were obtained. The ^{1}H NMR spectrum revealed that the cyclohexane-fused *cis* derivatives **3** gave mainly **10**, but also less than 10% of **14**.

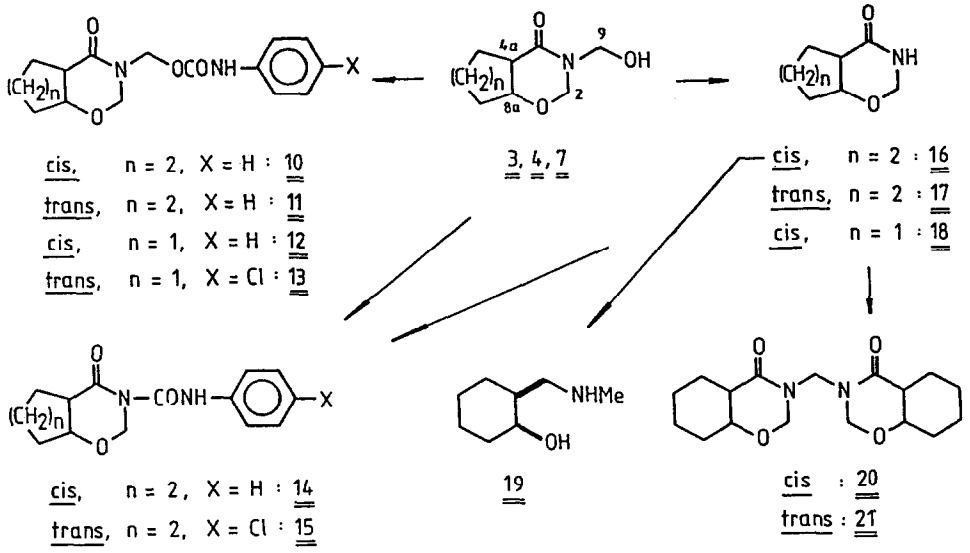
Compound **10** did not yield **14**. This was proved when **10** was subjected to prolonged heating both alone and together with phenyl isocyanate in benzene. The ^{1}H NMR spectra of the crude products gave no indication of the formation of **14**, and only unchanged **10** was recovered.

When hydroxymethyl derivative **3** was heated in toluene for 30 min, the product **16** (Scheme 2) was obtained in 84% yield. The parallel formation of **10** and **14** in the isocyanate addition can be explained by this route.

Similarly, the thermal decompositions of **4** and **7** (Scheme 2) resulted in **17** and **18**. Although a great number of cyclopentane-, cyclohexane- and cycloheptane-fused tetrahydro-1,3-oxazin-4-one derivatives have been prepared for pharmacological[13] and chemical/stereochemical[14-16] investigations, both the unsubstituted parent compounds and their aromatic analogues were previously not known.

Addition of the isocyanates to **16** and **17** resulted in ready formation of **14** (a side-product of Method C) and **15**, respectively (Scheme 2). The large downfield shift of the ^{1}H resonance of one of the

C-2 hydrogens ($\Delta\delta$ 0.8-0.9 ppm) in comparison with that of **16** or **17** clearly shows that *N*-substituted products were formed. *O*-Substitution and the resulting introduction of a C=N double bond in the ring does not cause a large downfield shift.[17]

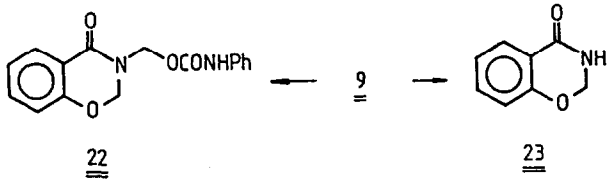


Scheme 2

Lithium aluminium hydride reduction of 2-substituted 1,3-oxazin-4-ones leads to *N*-substituted 1,3-aminoalcohols.[12] Similarly, **16** gave *cis*-2-(*N*-methylaminomethyl)cyclohexanol[18] (**19**) in good yield.

The ring-closure of **1** and **2** with formaldehyde could result in the formation of **16** and **17**. However, this reaction led to the formation of methylenebis(oxazinones) **20** and **21** in 30% and 69% yields, respectively.[14] In the reaction of **16** and **17** with paraformaldehyde in the presence of acid, the bisoxazinones **20** and **21** were obtained, but in rather low yields. In the formation of bis(oxazines) **20** and **21** from **1** and **2**, respectively, the presence of the parent derivatives **16** and **17** was not observed. In light of the low yields of the transformations of **16** to **20** and **17** to **21** and the above, it can be concluded that the formation of a methylene bridge between the two carboxamides precedes the ring-closure.

The addition of phenyl isocyanate to the aromatic derivative **9** gave **22**, while its thermal decomposition led to **23** (Table 1, Scheme 3).



Scheme 3

Stereochemistry of the products

The availability of the cyclohexane-fused parent compounds **16** and **17** allows a study of the effects of the N-3 substitutions on the predominant conformations. The NMR and X-ray diffraction results suggest that the most stable conformation for the hetero ring in the cyclohexane-fused oxazinones,[15,16,19] the

closely related dioxanones[20] and the 1-oxa-4-decalones[21] is a half-chair or a sofa-like structure where O-1 is out of the plane.

The vicinal coupling constants (Table 1) for the unsubstituted parent compounds **16-18** support the predominance of a half-chair conformation (Fig. 1) similarly to the C-2-substituted derivatives[15] and in agreement with the X-ray structure of **3**. The ring fusion of *trans* **17** is *diequatorial*, whereas the predominant conformation of the *cis* derivatives **16** and **18** is the *O-in* form. It is interesting to note that in all of these compounds one of the C-2 protons exhibits a relatively strong coupling to the *N*-H proton.

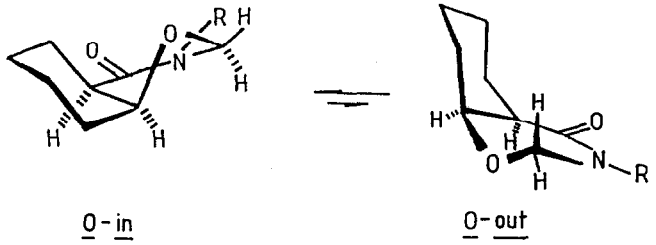


Fig. 1

Table 1. ^{1}H NMR Chemical Shifts (ppm) and Coupling Constants[a] (Hz) of the 1,3-Oxazinones Studied

No.	2-H	2-H'	9-H	9-H'	8a-H	4a-H	Aliphatic CH_2	ArH
3	4.98*d* -7.5	4.92*d* -7.5	4.88*d* -10.9	4.68*d* -10.9	3.96*m* (*eq*) Σ9.7	2.31 (*ax*) 3.0, 5.0, 11.5	1.3-2.0	-
4	5.03*d* -7.6	4.95*d* -7.6	4.88*d* -10.7	4.70*d* -10.7	3.44*dt* (*ax*) 4.1, 10.7, 10.8	2.33*m* (*ax*) not detected	1.1-2.2	-
7[b]	4.97*d* -8.3	4.84*d* -8.3	4.93*dd* -10.7, 7.3[c]	4.73*dd* -10.7, 7.9[c]	4.32*m* (*eq*) 2.0, 5.4, 5.4	2.59*m* (*ax*) 5.4, 9.2, 9.2	1.5-2.2	-
9	5.32*s*	5.32*s*	5.06*s*	5.06*s*	-	-	-	6.9-8.0[e]
10	5.08*d* -7.8	5.01*d* -7.8	5.52*d* -10.5	5.35*d* -10.5	3.98*m* (*eq*) 2.5, 3.4, 3.0	2.40*m* (*ax*) 3.4, 5.0, 11.1	1.3-1.9	7.0-7.4
11	5.08*d* -8.1	5.08*d* -8.1	5.49*d* -10.8	5.36*d* -10.8	3.45*dt* (*ax*) 4.2, 10.7, 10.7	2.18*dt* (*ax*) 4, 10.7, 11	1.1-2.2	7.0-7.4
12[b]	5.01*d* -8.8	4.99*d* -8.8	5.60*d* -10.7	5.30*d* -10.7	4.33*m* (*eq*) 2.1, 5.9, 6.0	2.66*dt* (*ax*) 5.9, 9.0, 9.0	1.5-2.2	7.0-7.4
13[b]	5.00*d* -9.0	4.98*d* -9.0	5.59*d* -10.5	5.29*d* -10.5	4.33*m* (*eq*) 2.4, 5.9, 5.9	2.66*dt* (*ax*) 5.9, 9.3, 9.3	1.5-2.2	7.2-7.4
14	5.76*d* -9.0	5.01*d* -9.0	-	-	4.03*m* (*eq*) 3.7, 3.7, 3.9	2.59*m* (*ax*) 3.7, 6.1, 9.5	1.2-2.0	7.1-7.5
15	5.55*d* -9.3	5.27*d* -9.3	-	-	3.48*dt* (*ax*) 3.9, 10.7, 10.7	2.45m (*ax*) 10.7, Σ26	1.2-2.2	7.3-7.5
16	4.89*d* -7.8	4.88*dd* -7.8, 2.5[d]	-	-	3.94*m* (*eq*) all≤3	2.33*m* (*ax*) 2x(≤4), 11	1.3-2.0	-
17	4.94*d* -7.3	4.88*dd* -7.3, 2.2[d]	-	-	3.42*dt* (*ax*) 4.4, 10.7, 10.7	2.33*dt* (*ax*) 3.4, 10.7, 11.2	1.1-2.2	-
18[b]	4.79*d* -8.5	4.77*dd* -8.5, 3.4[d]	-	-	4.28*t* (*eq*) 2.0, 5.8, 5.8	2.58*dt* (*ax*) 5.8, 8.85, 8.85	1.5-2.2	-
22	5.60*s*	5.60*s*	5.45*s*	5.45*s*	-	-	-	7.0-8.0
23	5.24*d* 3.3[d]		-	-	-	-	-	7.0-8.0

[a]Chemical shifts on the first line, coupling constants on the second line for each compound. [b]For easier comparison of the data, the same numbering is used for cyclopentane and cyclohexane derivatives (see Scheme 2). [c]Couplings to O-H. [d]Couplings to N-H. [e]7.93*dd*, 7.45*td*, 7.10*td*, 6.95*dd*.

The *N*-substituted derivatives display practically the same couplings (Table 1) and hence the same preferred conformations. Independently of their bulkiness, therefore, the *N*-3 substituents have no or only a very weak effect on the predominant conformation of the condensed 1,3-oxazin-4-ones. The diminished value of the large vicinal coupling constant $J_{4a\text{-}H,5\text{-}H}$ for **14** (Table 1), however, can be best explained by the presence of about 15% of the *O-out* conformation (9.5 Hz=0.84x10.7 Hz + 0.16x3.4 Hz).

X-ray structure determination of **3**

The X-ray structure of **3**, depicted in Fig. 2, clearly shows the *cis* function between the puckered six-membered rings. The corresponding fractional atomic coordinates are listed in Table 3. The carbocyclic ring, characterized by mean values of 1.524(7) Å and 111.8(11)°, assumes a chair conformation, with a mean endocyclic torsion angle of 53.6(34)°, whereas the hetero ring exhibits an almost perfect $^1H_6$ half-chair shape with O(1) and C(6) situated at distances of 0.393(1) and 0.406(1) Å, respectively, from the least-squares plane computed from the other four ring atoms. The corresponding puckering parameters[22], starting from O(1) through C(2), etc. in a clockwise direction, are as follows: Q=0.531(3) Å, Θ=47.5(3)° and Φ=330.1(4)°. The out-of-plane amplitudes of O(1) and C(6) and the puckering parameter Φ give a perfect fit to the plots of such amplitudes versus Φ in the range 315-360° that were inferred recently[23] from an analysis of a number of 1,3-oxazin-4-one structures. The atomic distances and bond angles pertaining to the 1,3-oxazin-4-one moiety agree well with the corresponding values observed in structures I, c-II and t-II discussed in Ref. 23. Additionally, it is worth noting that the difference between the distances C(sp^3)-O (Δ=0.037 Å) maintained by O(1) [C(6)-O(1)=1.436(2) *vs* C(2)-O(1)=1.399(2) Å], at least in this structure, seems to be significant. This phenomenon may be attributed to the ring puckering being especially pronounced along the longer C(sp^3)-O bond.

The molecules are held together by an infinite chain of hydrogen-bonds formed by the glide plane c(X,1/4,Z) along the c axis with the parameters:

	O···O	H···O	OH···O
O(3)-H(03)···O(2)[x,y-1/2,z-1/2]	2.702(3) Å	1.86(3) Å	177(2)°

EXPERIMENTAL

M.p.'s were determined with a Boetius micro melting point apparatus. ^1H NMR spectra were recorded on a JEOL GX 400 FT-NMR spectrometer in $CDCl_3$ solution at ambient temperature with TMS as internal standard. IR spectra were recorded in KBr pellets on a Unicam SP 200 spectrometer.

Method A: *3-Hydroxymethyl-cis-5,6-trimethylene-2,3,5,6-tetrahydro-4H-1,3-oxazin-4-one* (**7**). *cis*-2-Hydroxycyclopentanecarboxamide[9] **5** (0.65 g, 5 mmol) was refluxed with a formaldehyde (5 ml, 37% aq. solution)/formic acid (5 ml, 100%) mixture. After 1 h, the mixture was poured onto ice (50 g), neutralized with sodium carbonate and extracted with chloroform (3x30 ml). The combined organic layers were dried (Na_2SO_4) and evaporated, resulting in a colourless oil, which crystallized after trituration with ether (Table 2).

Method B: *3-Hydroxymethyl-2,3-dihydro-4H-1,3-benzoxazin-4-one* (**9**). Compound **9** was prepared according to Method A, starting from salicylamide. After extraction and evaporation, the oily residue was eluted through a silica gel column with benzene. The pure fractions detected by TLC were combined and evaporated, resulting in colourless crystalline **9** (Table 2).

Method C: *Isocyanate addition to hydroxymethyl derivatives* **3**, **4**, **7** *and* **9**. The *N*-hydroxymethyl derivative (1 mmol) was refluxed in benzene (10 ml) with 1.1 mmol of phenyl isocyanate or *p*-chlorophenyl isocyanate. After 1 h, the solvent was evaporated off and the residue was recrystallized. It was proved by ^{1}H NMR that, with **4** as starting compound, a 10:1 mixture of **10** and **14** was formed, from which **10** was obtained pure after two recrystallizations (Table 2).

Method D: *Thermal decomposition of N-hydroxymethyl derivatives* **3**, **4**, **7** *and* **9**. The *N*-hydroxymethyl derivative (1 mmol) was refluxed in toluene for 30 min. After evaporation and ethereal treatment, the crystalline parent compounds were obtained.

Method E: *Isocyanate addition to* **16** *and* **17**. The reaction was performed according to Method C with equivalent amounts of **16** or **17** and isocyanates (Table 2).

Method F: *Lithium aluminium hydride reduction of* **16**. Lithium aluminium hydride (114 mg, 3 mmol) was suspended in dry tetrahydrofuran (50 ml), and oxazinone **16** (155 mg, 1 mmol) was added with stirring.

Table 2. Physical and Analytical Data on the New Oxazinone Derivatives **7**, **9-18**, **22** and **23**

No.	Method	Yield %	Mp (°C) Solvent	Formula Mw	Calcd/Found (%) C	H	N
7	A	74	86-88	$C_8H_{13}NO_3$	56.12	7.65	8.18
			hexane	171.19	55.94	7.69	8.25
9	B	45	92-94	$C_9H_9NO_3$	60.33	5.06	7.82
			hexane	179.17	60.17	5.19	7.98
10	C	60	159-161	$C_{16}H_{20}N_2O_4$	63.14	6.62	9.21
			di-isopropyl ether	304.34	63.23	6.70	9.34
11	C	71	175-176	$C_{16}H_{20}N_2O_4$	63.14	6.62	9.21
			di-isopropyl ether	304.34	63.10	6.79	9.16
12	C	70	123-125	$C_{15}H_{18}N_2O_4$	62.05	6.25	9.65
			di-isopropyl ether	290.31	61.87	6.41	9.92
13	C	83	157-161	$C_{15}H_{17}ClN_2O_4$	55.47	5.28	8.63
			di-isopropyl ether	324.76	55.72	5.41	8.40
14	E	79	132-133	$C_{15}H_{18}N_2O_4$	62.05	6.25	9.65
			ethanol	290.31	61.91	6.37	9.41
15	E	76	180-182	$C_{15}H_{17}ClN_2O_4$	55.47	5.28	8.63
			ethanol	324.76	55.51	5.39	8.60
16	D	84	125-126	$C_8H_{13}NO_2$	61.91	8.44	9.03
			hexane	155.19	61.86	8.63	9.04
17	D	83	143-145	$C_8H_{13}NO_2$	61.91	8.44	9.03
			hexane	155.19	61.97	8.60	9.11
18	D	69	146-148	$C_7H_{11}NO_2$	59.55	7.86	9.92
			hexane	141.17	59.67	8.02	9.77
22	C	61	173-175	$C_{16}H_{14}N_2O_4$	64.42	4.73	9.39
			di-isopropyl ether: ethanol = 9:1	298.29	64.60	4.91	9.40
23	D	74	129-131	$C_8H_7NO_2$	64.42	4.73	9.39
			di-isopropyl ether	149.14	64.30	4.91	9.19

The mixture was stirred and refluxed for 2 h, then cooled with ice, and water (1 ml) in tetrahydrofuran (20 ml) was added dropwise. After stirring for 1 h at room temperature, the inorganic material was filtered off. The filtrate was dried (Na_2SO_4) and evaporated. Treatment of the oily residue with hexane resulted in aminoalcohol **19**: mp 81-83 °C, yield 59%; lit[18] mp 83-84 °C. Picrate salt mp 149-151 °C.

Formaldehyde reaction with parent compounds **16** *and* **17**. Compound **16** or **17** (155 mg, 1 mmol) was dissolved in 1,4-dioxane (10 ml), paraformaldehyde (60 mg, 2 mmol) and a few mg of concentrated sulphuric acid were added and the mixture was refluxed for 20 h. After evaporation off of the solvent, the oily residue was dissolved in 50 ml of ether with boiling. After drying and evaporation, products **20** and **21** were obtained in crystalline form.

20: mp 154-156 °C, yield 23%; lit[14] mp 156-157 °C.

21: mp 190-192 °C, yield 38%; lit[14] mp 192-193 °C.

Determination of X-ray crystal structure of **3**

Crystal data: $C_9H_{15}NO_3$. $M_r = 185.22$, monoclinic. $a = 12.775(2)$, $b = 6.577(1)$, $c = 11.377(3)$ Å. $\beta = 97.76(2)°$. $V = 947.2(6)$ Å^3, $Z = 4$, $D_x = 1.298$ gcm^{-3}, $F(000) = 400$, space group $P2_1/c$, $\mu = 0.91$ for MoK_α radiation ($\lambda = 0.71073$ Å). Dimensions of the crystal sample: 0.41 x 0.44 x 0.68 mm.

Table 3. Fractional Atomic Coordinates of Compound **3**. E.s.d.'s are given in parentheses

Atom	x/a	y/b	z/c
O(1)	0.2547(1)	0.1562(2)	0.4036(1)
O(2)	0.1323(1)	-0.2096(2)	0.6311(1)
O(3)	0.1024(1)	-0.4116(2)	0.3510(1)
N(3)	0.1287(1)	-0.0908(2)	0.4451(1)
C(4)	0.1629(1)	-0.0854(2)	0.5618(1)
C(2)	0.1603(2)	0.0579(2)	0.3600(1)
C(5)	0.2433(1)	0.0761(2)	0.6058(1)
C(6)	0.2446(1)	0.2477(2)	0.5161(1)
C(7)	0.3514(1)	-0.0269(2)	0.6352(2)
C(8)	0.4388(2)	0.1289(3)	0.6714(2)
C(9)	0.4412(1)	0.2879(3)	0.5741(2)
C(10)	0.3353(1)	0.3946(2)	0.5477(2)
C(11)	0.0535(1)	-0.2453(2)	0.3961(1)
H(2a)	0.178(2)	-0.016(4)	0.298(2)
H(2b)	0.104(2)	0.156(4)	0.337(2)
H(5)	0.221(2)	0.124(4)	0.678(2)
H(6)	0.173(2)	0.311(3)	0.510(2)
H(7a)	0.349(2)	-0.139(3)	0.701(2)
H(7b)	0.365(2)	-0.115(4)	0.561(2)
H(8a)	0.423(2)	0.198(4)	0.749(2)
H(8b)	0.508(2)	0.056(4)	0.699(2)
H(9a)	0.449(2)	0.228(4)	0.509(2)
H(9b)	0.500(2)	0.384(4)	0.605(2)
H(3)	0.114(2)	-0.372(4)	0.284(2)
H(10a)	0.322(2)	0.478(4)	0.608(2)
H(10b)	0.333(2)	0.494(4)	0.485(2)
H(11a)	0.007(2)	-0.177(4)	0.337(2)
H(11b)	0.017(2)	-0.290(4)	0.452(2)

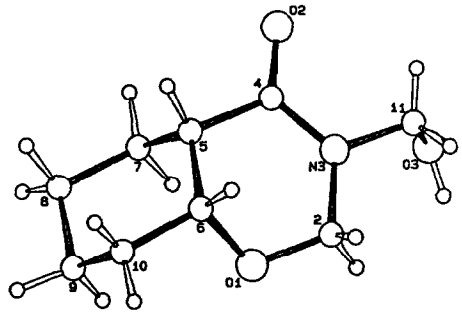


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Fig. 2

Intensities of 3266 unique reflections were collected on an Enraf-Nonius CAD-4 diffractometer equipped with a graphite monochromator in the range $1.0 < \theta < 32.5$ by ω-2θ scan. Cell constants were determined by least-squares refinement of 20 reflections. After data reduction, 2068 reflections with $I > 3\sigma(I)$ were taken as observed. Absorption correction was performed. The phase problems were solved by direct methods, using the SHELX 76 program.[24] The fractional coordinates of hydrogen atoms were located in a difference Fourier map (Table 2). The hydrogen positions were refined in isotropic mode together with the anisotropic treatment of the non-hydrogen atoms. Final values: $R = 0.046$, $R_w = 0.058$. The final difference Fourier map showed no significant peak: max. 0.25, min. -0.20 eÅ^{-3}. Scattering factors were taken from the SHELX 76 program.[24] Calculations were performed on an IBM 4341 computer.

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