

STRUCTURES OF SATURATED AZETO[1,2-*a*][3,1]- AND AZETO-[2,1-*b*][1,3]BENZOXAZINES PREPARED BY ADDITION OF CHLOROACETYL CHLORIDES TO CYCLOHEXANE-CONDENSED DIHYDROOXAZINES¹

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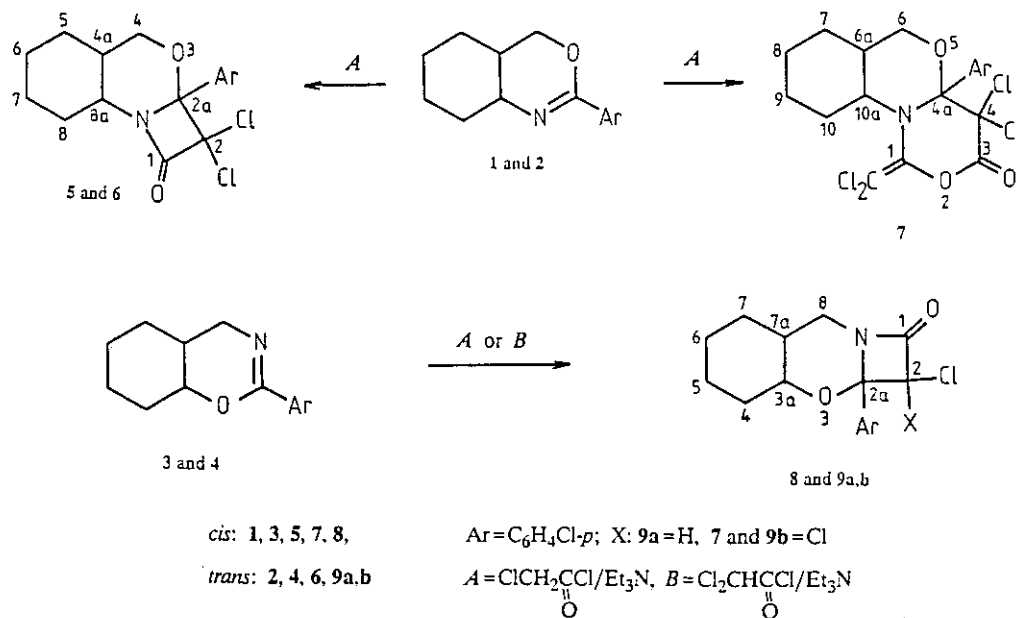
Abstract — Saturated *cis* and *trans* 3,1- and 1,3-benzoxazines (**1-4**) reacted with chloroacetyl chlorides to yield azeto[1,2-*a*][3,1]- and [2,1-*b*][1,3]benzoxazines (**5**, **6**, **8**, **9a,b**). In one case, the addition took place with partial *cis*→*trans* inversion of the starting compound. Adduct (**7**), containing two condensed 1,3-oxazine rings, was also isolated. The stereostructures of the new compounds were proved by ¹H- and ¹³C-nmr spectroscopy, with NOE measurement data. The reaction mechanism is discussed.

Azetidinone-condensed derivatives were earlier prepared from aryl substituted *diexo*- and *diendo*-norbornane- and norbornenedihydro-1,3-oxazines and chloroacetyl chlorides/triethylamine (TEA). Diastereomers differing in the position of the aryl group were formed.^{2,3} Since the acid chloride and TEA yield *in situ* ketene, the reaction can also be regarded as a [2+2] cycloaddition.

The current paper reports further examples of these reactions. The experiments were initiated by the expectable differences for the analogous reactions of the cyclohexane *cis*- and *trans*-condensed dihydro-1,3-oxazines in comparison with the rigid norbornane analogues. In the ring anellation, we observed one change which was not expected and observed for the norbornene derivatives.

PREPARATION AND MECHANISM

The 3,1- and 1,3-benzoxazines⁴ (1-4), prepared from the *cis*- and *trans*-2-hydroxymethylcyclohexylamines and the stereoisomeric 2-aminomethylcyclohexanols with *p*-chlorobenzimidates, were boiled in benzene with dichloroacetyl chloride or chloroacetyl chloride in the presence of TEA. After working up and separation by column chromatography, the octahydroazeto[1,2-*a*][3,1]benzoxazine (5) was isolated from the reaction of 1 and dichloroacetyl chloride. In 5, the *cis* anellation of the six-membered rings was unaltered in comparison with the starting benzoxazine. The *trans* isomer (6) was formed in equimolar amount and could be isolated in stereohomogeneous form. On working up by column chromatography, the third product, tetrahydro-1,3-oxazine[3,4-*a*][3,1]benzoxazine (7), formed in the addition to 1 of two moles of dichloroacetyl chloride, was also isolated (Scheme).



Scheme

From the reaction of *trans*-hexahydro-3,1-benzoxazine (2) with dichloroacetyl chloride, only one compound (6) could be isolated, but another substance [(the diastereomer (5))] was also detected by tlc.

The ratio of compounds (6) and (5) was risen up to 4:1 by crystallization, but we were unable to prepare it in stereohomogeneous form. From the reaction of dichloroacetyl chloride with *cis*-hexahydro-1,3-benzoxazine (3), containing the oxygen and nitrogen heteroatoms in the reversed positions relative to those in 1, one linearly condensed azetidinones (8) was isolated. The *trans* isomer (4) and chloro- or dichloroacetyl chloride also each yielded one linearly condensed azetidinones (9a,b).

For the mechanism of the reactions, we assume that the nitrogen is acylated by the chloroacetyl chloride in the first step, and the iminium salt is then stabilized by azetidinone ring formation. Besides electrocyclization, the [2+2] cycloaddition of the ketene formed *in situ* from the acetyl chloride with TEA is postulated in the literature.^{5,6} The formation of 7 can also be explained by the addition of ketene. The tricyclic nitrogen bridgehead saturated methylene-bridged 1,3-oxazino[2,3-*b*]-[1,3]benzoxazine, similar to 7, was isolated from the analogous reaction of the *diexo*-norbornane-condensed dihydro-1,3-oxazine and chloroacetyl chloride/TEA.³

STRUCTURES — SPECTROSCOPIC INVESTIGATIONS

The most important ir, ¹H and ¹³C-nmr data on 5-9 are listed in Tables 1 and 2. For azetidinone (5), the ~5 Hz signal width shows that H-8a is *equatorial*. From this, the unaltered *cis* anellation of the six-membered rings and the chair conformation follow, with the nitrogen *axial* and the 4-methylene group in *equatorial* position.⁷

Table 1. Characteristic ir frequencies and ¹H-nmr data for compounds(5-9)^a

Compound	ν C=O band ^b	CH ₂ +CCHC(cyclohexane) <i>m</i> 's (9H)	OCH ₂ /NCH ₂ 2 <i>xxdd</i> (2x1H) ^c	NCH/OCH <i>m</i> (1H) ^d	ArH (Pos. 2a/4a) <i>s/m</i> (4H)
5	1778	1.20-2.00	2.45 ^e	3.72 3.86	3.66 ~7.50 ^f
6	1795	0.90-1.90	2.26 ^e	3.74 ^g 3.98	3.44 7.42 ^h 7.48 ^h
7	1810	0.70-1.70	2.35 ⁱ	3.84 4.02 ^g	3.50 ~7.40 ^j 7.55 ^k 7.75 ^k
8	1817	1.10-1.60	~2.00 ^j	2.83 4.14	4.28 7.43
9a	1775	0.90-1.80	~2.20 ^l	~3.30 ~3.40	3.70 7.38 ^h 7.44 ^h
9b	1819	0.90-1.90	~2.20 ^l	~3.35 ~3.45	3.75 7.41

^aIn CDCl₃ solution at 250 MHz. Chemical shifts δ , δ SiMe₄=0 ppm and coupling constants in Hz; ^bIn KBr discs (cm⁻¹); ^cAB part of an ABX spin system, for 9a,b near to the A₂X limiting case. *J*: 12.0, 2.5 and 1.5 Hz (5), 11.4, 10.4 and 4.2 Hz (6), 12.5, 11.5 and 4.4 Hz (7), 13.5, 9.3 and 2.6 Hz (8); ^dSignal of coalesced lines with half width of ~5 (5) and 8 Hz (8) *dt*, *J*: 12.3, 12.3 and 3.6 (6), 12.6, 4.6 and 4.6 (7), unresolved *dt* (9a,b); ^eH-8eq (1H), ~d (*J*: ~15 Hz); ^fBroad signal; ^gCoalesced to a *t*-like signal; ^hA or B part of an AA'BB' spin system, *J*(A,B): 8.8 Hz; ⁱ*dt* with coalesced lines; ^j/Intensity: 2H/1H; ^k*dd* (1H).

The *cis* positions of H-8a and the 2a-aryl group relative to the oxazine ring were proved *via* DNOE (differential nuclear Overhauser effect): saturation of the H-8a signal was accompanied by an increase in the intensity of the broad signal of the aromatic hydrogens, which proves the nearness of H-8a and the aryl group. The reverse experiment was also successful: on irradiation of the aromatic ^1H -nmr signal, the signal of H-8a became more intense. The magnitude of the coupling between the 4-methylene hydrogens and H-4a (1,5 and 2.5 Hz) suggests a preference for the twist conformation of the oxazine ring in which C-4 and C-4a are in out-of-plane situations on opposite sides of the plane of the other four atoms in the oxazine ring (Figure 1).

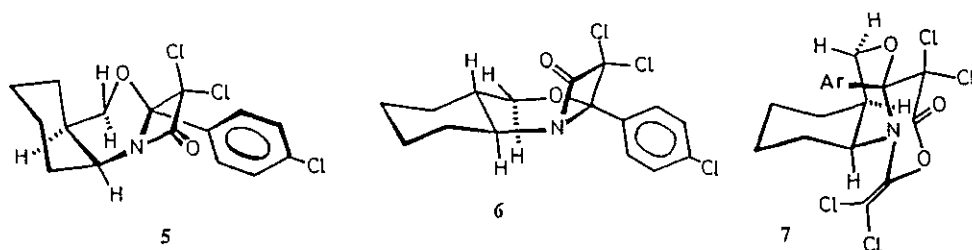


Figure 1

Rotation of the aryl ring is hindered by the interaction of H-4_{ax}, H-8a and one of the chlorine atoms at room temperature, and therefore the H-2',6' and C-2',3',5',6' nmr signals are broadened.

For 6, the more than 2 ppm average downfield shift of the cyclohexane carbon lines^{8a} in comparison with the *cis*-anellated isomer (5) and the distances between the lines of the H-8a double triplet show the *trans* anellation of the two six-membered rings. The 12.3 Hz triplet splitting proves two *diaxial* interactions, and hence the *axial* positions of H-8a and H-4a (Figure 1).

The structure of 7 follows from the ^{13}C -nmr spectrum, in which two additional lines of quaternary carbons appear. The large shielding difference (43.3 ppm) originates from the large substituent effects with opposite signs of the heteroatoms on the α and β olefin carbons.^{8b} The addition is not accompanied by a *cis*→*trans* change in the anellation, as proved by the double triplet splittings of H-10a (12.6 and twice 4.6 Hz). These indicate *axial* H-10 and *equatorial* H-6a. In accordance, the signal of the latter is a double quintet (due to the 6a,6_{ax} *diaxial* and the 6a,6_{eq}, 6a,7_{eq}, 6a,7_{ax} and 6a,10a couplings which correspond to the ~60° dihedral angles).

Examination of the steric structures in which Ar-4a and H-10a are *cis* or *trans*, and the cases when the two hetero rings are in the *trans* or the two possible *cis* positions for the diadduct (7), suggests the

structure in Figure 1. Here, the three six-membered rings have chair conformations, the cyclohexane is *cis*-, and the heterorings are *trans*-anellated, and the 4a-aryl group and the anellation hydrogens have a *trans* 4a*R**,6a*S**,10a*S**, 10b(N)*S** configuration. In accordance with this structure, the 4a-aryl group is hindered, as proved by the separation of the C-2',6' and C-3',5' line pairs, and by the DNOE results, which exclude the close situation of the 4a-aryl group and H-6a and H-10a.

For the linearly *cis*-condensed cyclohexaneazetidinone (**8**), the H-3a signal width (~5 Hz) proves the structure which contains an *axial* oxygen (*O-in* conformation). This is in accordance with our earlier experience that the bicyclic 1,3-oxazine isomers always prefer the *O-in* form, while the condensed *N*-unsubstituted 3,1-oxazines exhibit *N-in* and the *N*-substituted derivatives *N-out* preferred conformations, *i.e.* the NR group is *equatorial* in the latter case.^{7,9,10} From this point of view, the angularly condensed **5** is irregular, which can be explained by the different steric structures of the bi- and tricyclic molecules. In the two six-membered moieties of the linearly condensed tricycles and the bicycles, the steric relations are not essentially different, and hence the rule for the latter will be valid for the tricyclic compounds (**8**) and (**9**).

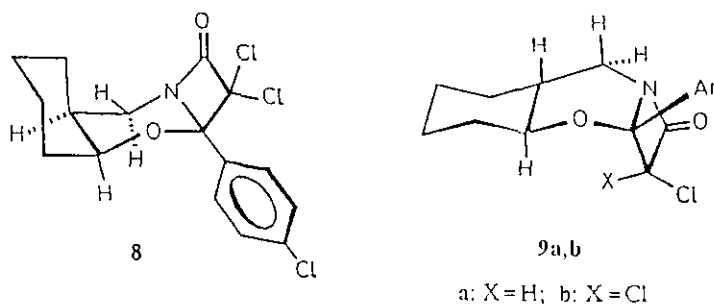


Figure 2

From the *axial* position of the oxygen, the full steric structure of the azetidinone (**8**) follows (Figure 2), because the six-membered hetero ring is not flexible (and could move only with a simultaneous *cis*→*trans* change in the cyclohexane anellation) and the *trans*-aryl structure relative to H-3a,7a is out of the question for steric reasons.

Table 2. ^{13}C -Nmr chemical shifts for compounds (5-9)^a

Com- pound	CH_2 in carbocycle				CCHC	NCH OCH	OCH ₂ NCH ₂	NCO	CCl ₂ CCl	C=O	C=1'	C-2',6'	C-3',5'	C-4'
5	21.4	24.6	24.7	27.1	36.2	51.9	69.3	92.3	?	160.3	131.8	~129 ^b	~129 ^b	136.8
6	24.4	24.8	27.6	32.6	37.4	57.0	69.6	91.8	90.0	167.0	135.7 ^c	~128.7	~128.4	136.1 ^c
7d	21.9	27.1	28.0	29.5	34.6	64.6	66.5	148.8 ^c	84.6	159.5	137.2	129.5	132.9	132.2
8	20.3	24.5	28.4	29.8	34.1	71.1	42.1	92.4	90.8	163.5	135.4	127.9	128.7	134.2
9a	24.1	24.8	30.0	32.5	36.8	76.4	43.1	89.1	67.9	164.6	135.8	128.1 ^c	128.4 ^c	135.0
9b	24.1	25.0	30.5	31.8	38.0	76.1	42.8	92.7	90.9	163.2	135.2 ^c	128.0	128.6	135.5 ^c

^aIn CDCl_3 solution; for compound (9) in $\text{DMSO}-d_6$; δ $\text{SiMe}_4 = 0$ ppm; at 63 MHz. ^bBroad signal due to hindered rotation of the aromatic ring; ^cInterchangeable assignments; ^dAssignments were proved by DEPT measurements; ^eC = CCl_2 group.

From the *trans* isomer (4), both the dichloroazetidinone (9b) and the monochloro derivative (9a) were prepared. The unchanged *trans* anellation of the six-membered rings and the analogous stereostructure of 9a and 9b follow from the ~30 Hz signal width of the H-3a double triplet. For the two compounds, the ^1H - and ^{13}C -nmr signals are practically identical, except for those which are influenced by the 2-substituent. This is further proof of the similar structures.

For 9b, the *trans* positions of the aryl group and H-3a are suggested by the lack of detectable mutual Overhauser effects. At the same time, the saturation of the aryl signal causes an intense H-8 α x signal in DNOE spectrum. In a *cis* H-3a, aryl(2a) configuration, H-8 α x is in a less favourable situation relative to the aryl group for NOE than H-3a. Additional proof of structure (9) (Figure 2) is the lack of a strong NOE between H-3a and H-8 α x. (In a *cis*-aryl configuration, H-3a and H-8 α x would be in a 1,3-*diaxial* position, which would favour NOE.)

The steric position of H-2 must also be clarified in 9a. As a mutual and strong NOE was observed between the H-2 and H-3a signals, these hydrogens are close, *i.e.* in a *cis* position on the same side of the molecular skeleton (for 9a the relative configuration is 2*R**, 2a*R**, 3a*R**, 7a*S**).

The results show that the fixed norbornane-condensed structure is favourable for the formation of diastereomers, because no inversions were experienced at the anellation carbons. For the norbornane dipolarophiles, therefore several isomeric pairs could be isolated from or detected in the reaction mixtures.^{2,3} Similarly, more diastereomers were isolated from the reactions of the norbornane-condensed dihydro-1,3-oxazines and salicyl chloride.¹¹

The *cis*→*trans* isomerization of the cyclohexane-condensed six-membered heterocycles containing two heteroatoms takes place readily in acidic or basic medium or on heating.^{12,13} Thus, the *cis*-*trans*

inversion is not surprising during the reaction **1**→**6** when the reaction mixture containing chloroacetyl chloride and TEA is boiled. Splitting of the C-N bond and subsequent re-attack of the carbenium ion on the nitrogen can be postulated as a mechanism. We earlier observed *cis*→*trans* epimerization for the intramolecular transacylation of cyclohexane-condensed azetidinones.¹⁴ Recently, however, we unexpectedly experienced a reverse *trans*→*cis* isomerization in the thermal cyclization of the *cis*-ethoxycarbonylcyclohexylureas.¹⁵

EXPERIMENTAL

Melting points are uncorrected.

Ir spectra were run in KBr discs on a Bruker IFS-113v vacuum optic FT-spectrometer controlled by an Aspect 2000 computer. The nmr spectra were recorded in CDCl₃ or DMSO-*d*₆ solution in 5 or 10 mm tubes at room temperature, on a Bruker WM 250 FT spectrometer controlled by an Aspect 2000 computer at 250.13 (¹H) and 62.89 MHz (¹³C), with the deuterium signal of the solvent as the lock and TMS as internal standard. The most important measuring parameters were as follows: spectrum width 5 and 15 kHz, pulse width 1 and 5 μs (~20° and ~30° flip angle), acquisition time 1.64 and 1.02 s, number of scans 16 or 32 (¹H) and 0.1-2 K (¹³C), computer memory 16 K. Lorentzian exponential multiplication for signal-to-noise enhancement (line broadening: 0.7 and 1.0 Hz) was applied.

DNOE experiments were performed with the standard Bruker microprogram 12.5 in the Aspect 2000 Pulse Programmer. Gated decoupling to generate NOE was used with a delay time of 30 s and a decoupling power of ca. 40 mW; number of scans 32; relaxation delay 0.1 s; dummy scans 2.

2,2-Dichloro-2*ar-p*-chlorophenyl-2,2a,4ac,5,6,7,8,8ac-octahydro-1*H*,4*H*-azeto[1,2-*a*][3,1]benzoxazin-1-one (5), 2,2-dichloro-2*ar-p*-chlorophenyl-2,2a,4*af*,5,6,7,8,8ac-octahydro-1*H*,4*H*-azeto[1,2-*a*][3,1]benzoxazin-1-one (6) and 4,4-dichloro-1-dichloromethenyl-4*ar-p*-chlorophenyl-3,4,6ac,7,8,9,10,10ac-octahydro-1*H*,6*H*-[1,3]oxazino[3,4-*a*][3,1]benzoxazin-3-one (7)

To a cooled (10 °C) solution of *cis*- (**1**) or *trans*-2-*p*-chlorophenyl-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazines⁵ (**2**) (2.5 g; 0.01 mol) in dry benzene (10 ml), dichloroacetyl chloride (1.47 g; 0.01 mol) in benzene (5 ml) was added dropwise, followed by TEA (1.0 g; 0.01 mol) in dry benzene (10 ml) dropwise

with stirring. The mixture was heated at 60 °C (30 min) and, after cooling, the solid was removed by filtration. The residue obtained on evaporation of the filtrate was applied to a silica gel column and eluted with petroleum ether-benzene (1:1 mixture), then benzene and EtOAc, with tlc monitoring. Compound (7) appeared in the first fractions, while the azetidinones (5) and (6) were obtained as the residues of the benzene and EtOAc fractions, respectively. Several crystallizations from benzene yielded the pure derivatives (5, 6 and 7). (Data are listed in Table 3.)

Table 3. Physical and analytical data on compounds (5-8 and 9a,b)

Compound	mp °C	Yield %	Molecular formula	Analysis					
				C	Found % H	N	Required % C	H	N
5	204-206	28	C ₁₆ H ₁₆ NO ₂ Cl ₃	53.14	4.30	3.95	53.28	4.47	3.88
6	187-190	55	C ₁₆ H ₁₆ NO ₂ Cl ₃	53.20	4.53	4.01	53.28	4.47	3.88
7	186-188	20	C ₁₈ H ₁₆ NO ₂ Cl ₅	45.61	3.25	3.17	45.84	3.42	2.97
8	180-183	68	C ₁₆ H ₁₆ NO ₂ Cl ₃	53.40	4.54	3.63	53.28	4.47	3.88
9a	109-110	65	C ₁₆ H ₁₇ NO ₂ Cl ₂	59.10	5.37	4.12	58.91	5.25	4.29
9b	146-148	67	C ₁₆ H ₁₆ NO ₂ Cl ₃	53.02	4.27	3.97	53.28	4.47	3.88

2,2-Dichloro-2*ar-p*-chlorophenyl-2,2a,3ac,4,5,6,7,7*at*-octahydro-1*H*,4*H*-azeto[2,1-*b*][1,3]benzoxazin-1-one (8), 2*r*-chloro-2ac-*p*-chlorophenyl-2,2a,3ac,4,5,6,7,7*at*-octahydro-1*H*,4*H*-azeto[2,1-*b*][1,3]benzoxazin-1-one (9a) and 2,2-dichloro-2*ar-p*-chlorophenyl-2,2a,3ac,4,5,6,7,7*at*-octahydro-1*H*,4*H*-azeto[2,1-*b*][1,3]benzoxazin-1-one (9b)

To a cooled (10 °C) solution of *cis*- (3) or *trans*-2-*p*-chlorophenyl-4a5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazines⁵ (4) (2.5 g; 0.01 mol) in dry benzene (10 ml), dichloroacetyl chloride or chloroacetyl chloride (1.47 g or 1.33 g; 0.01 mmol) in benzene (5 ml) was added dropwise, followed by TEA (1.0 g; 0.01 mol) in dry benzene (10 ml) dropwise with stirring. The reaction was completed, and the products were worked up, purified by column chromatography and crystallized as above. (Data are listed in Table 3.)

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