Preparation of Diastereomeric 5,8-Methanobenzoxazino[2,1-*b*]- and [2,3-*b*]-1,3-benzoxazin-4-ones by Reaction of Norbornane/ene-condensed Dihydro-1,3-oxazines with Salicyl Chloride [1]

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Received November 1, 1990

Norbornane and norbornene-condensed dihydro-1,3-oxazines **1-6** were converted with salicyl chloride to 5,8-methanobenzoxazino[2,1-*b*]- and -[2,3-*b*]-1,3-benzoxazin-4-ones **7-12**. The addition takes place to the C=N bond: after acylation, the intermediate is stabilized through cyclization to the aryl-substituted carbon by hydrogen chloride elimination. Diastereomers containing the oxazine rings in isomeric positions could be isolated in two cases. This is the first example of the isolation of diastereomers in such a salicyl chloride reaction. In contrast with earlier findings with reactions of related systems, no addition to the C=C bond could be observed. The steric structures of the compounds were elucidated by ir, ^{1}H- and ^{13}C-nmr spectroscopy.

J. Heterocyclic Chem., **28**, 753 (1991).

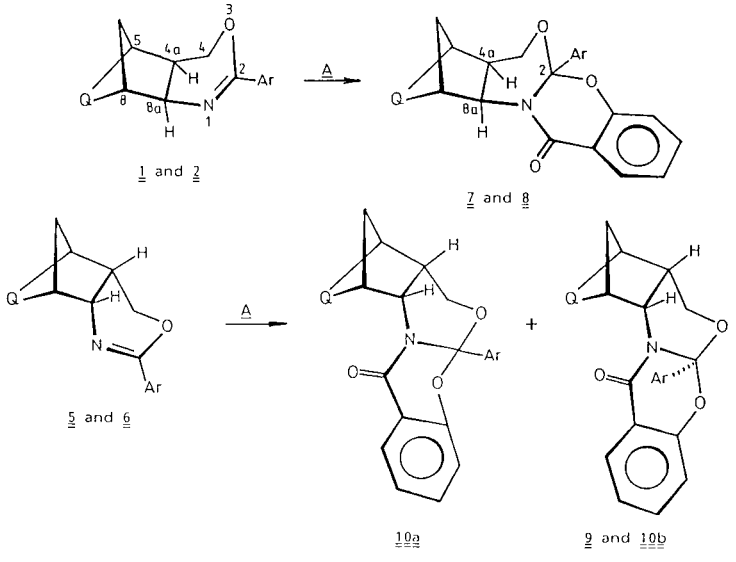
We earlier studied the [3 + 2] cycloadditions of norbornane- and norbornene-condensed dihydro-1,3-oxazines resulting in tetracyclic saturated heterocycles [2]. From the norbornene derivatives containing both C=C and C=N bonds, isoxazoline regioisomers were unexpectedly formed by the addition of nitrile oxide (benzonitrile and acetonitrile oxide) to the olefinic site [3,4]. The uncommon higher reactivity of the C=C bond than that of the C=N bond could be rationalized in terms of the strain in the bicycle; the hyperconjugative interaction between the bridged methylene hydrogens and the π-electrons was also considered to be a contributing factor [5]. The space requirement of the new hetero ring also makes a contribution, as supported by the cycloaddition of the azetidinone-condensed starting norbornenedihydro-1,3-oxazines [6]. The azetidinone ring was formed with chloroacetyl chlorides [7,8], which acylated the nitrogen of the heterodipolar C=N bond, with subsequent cyclization to β-lactams in the presence of TEA.

In the present work, the salicyl chloride reaction was applied for conversion of the norbornane/ene/dihydro-1,3-oxazines **1-6** to higher condensed heterocycles.

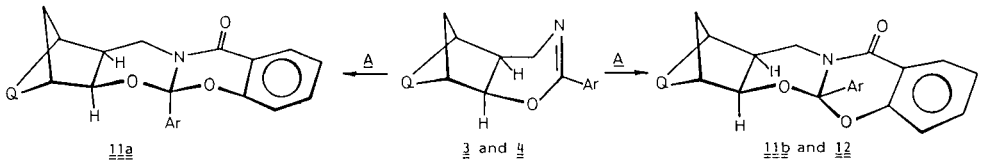
Results.

With salicyl chloride [9] (**A**), compounds **1-6** [2] furnish the methylene-bridged 3,1-benzoxazino[2,1-*b*]- **7-10** and 1,3-benzoxazino[2,3-*b*]benzoxazin-4-ones **11** and **12** (Schemes 1 and 2). It is presumed the **A** acylates the

Scheme 1



Scheme 2



3 and 11: Q = CH_2CH_2; 4 and 12: Q = CH=CH; Ar = $C_6H_4CH_3$-4; A: 2-HOC_6H_4COCl

nucleophilic nitrogen and, in the second step, the *ortho*-hydroxy group of the iminium ion intermediate stabilized by the oxazine oxygen cyclizes to the aryl-substituted carbon atom with the elimination of hydrogen chloride, which results in the new heterocycle.

In the reaction, the oxygen can attack from two directions. Hence, a mixture of two isomers **a** and **b** is formed, which could be separated in two cases, **10** and **11**. To our knowledge, this is the first example of the isolation of diastereomers in such a salicyl chloride reaction.

The isomers of the pairs **10a,b** and **11a,b** differ in the mutual positions of the two hetero rings, and hence in the steric positions of the aryl groups. In **10a** the *exo p*-tolyl group is situated relatively near to the two annelation hydrogens of the oxazine ring, while in **10b** the *endo* aryl group and the norbornene moiety are close to each other. In compound **11a** the aryl group is in the *endo* position, and in **11b** and *exo* position.

From the reaction products of **1-6** and chloroacetyl chloride/TEA, we earlier isolated azetidinone geometric isomers differing to the mutual positions of the two hetero rings [7,8].

A similar salicyl chloride reaction has already been applied to heterocyclic systems containing a C=N bond, *e.g.*, benzotriazoles, benzoxazoles and 3,4-dihydroisoquinolines [10], and the reagent has also been used for the structural development of carbonlines, isoquinolines [9,11] and benzothiazines [12]. In the present case, however, the partly saturated structure of the dihydro-1,3-oxazines **1**, **2**, **5** and **6** provides a possibility for the formation of isomeric condensed compounds.

According to Kametani *et al.* [11], the possibility can not be ruled out that in the first step salicyl chloride is converted into oxoketene by the intramolecular elimination of hydrogen chloride, and the oxoketene then reacts by cycloaddition.

As the mechanism suggested above and that of the [3+2] cycloadditions are different in principle, a preferred reaction on the C=C bond is not expectable at all.

Structure.

Spectral data on the new compounds are listed in Tables 1 and 2. (For easy comparison of analogous spectral data, all compounds are numbered as in Scheme 1).

Determination of the C-2 configuration is performed by comparison of the nmr data on the two isomers. In the

Table 1

IR and ^{1}H-NMR Spectral Data of Compounds 7-12 [a,b]

Compound	CH_3	H-4		H-4a	H-5	H-8	H-8a	H-6	H-7	H-9	
	s (3H)	d (1H) [c] dd	dd (1H) [d]	m (1H)	s (1H)	s (1H)	d/dd (1H) [e]	2 x dd/m	(2/4H) [f]	2 x d (2 x 1H) [g]	
7	2.22 [h]	4.00	4.39	1.98	2.22 [h]	2.60	4.65	1.1 -	1.7	0.92	
8	2.23	4.08	4.48	1.98	2.75	3.20	4.62	6.28	6.35	1.25	1.81
9	2.21	4.00	4.48	2.35 [h]		2.70	4.85	1.2 -	1.8 [i]	1.37 [i]	1.6 [i]
10a	2.23	3.78	4.00	2.70	2.84	4.30 [h]	4.27 [h]	6.04	6.15	1.40	1.62
10b	2.22	3.92	4.39	2.74	2.91	3.38	5.21	5.48	5.98	1.50	
11a	2.28	3.12	4.66	1.90	2.05	2.44	3.22		0.8 - 2.1		
11b	2.26	2.68	4.82	2.15	2.06	2.45	4.31		1.5 - 1.9		
12	2.25	2.70	4.92	2.12	2.65	3.02	4.26	5.98	6.27	1.52	1.92

Further signals, ArH (2 x 2H): 7.05 ± 0.05 and 7.33 ± 0.09 [j] (AA'BB'-type m, J = 8.2 ± 0.2). Condensed ring, H-3: 7.82 ± 0.03 dd (1H), H-4: 6.93 ± 0.03 dt (1H), H-5: 7.26 ± 0.06 [j] dt (1H), H-6: 6.82 ± 0.08 dd (1H). [a] Chemical shifts in ppm; δTMS coupling constants in Hz; solvent: deuteriochloroform at 250 MHz. [b] IR (potasium bromide, cm^{-1}), ν C=O: 1660-1675. [c] J = 12.0 ± 0.2 **7-9**, 11.0 **10a**, dd (J = 13.3, 11.3) for **11a** and t (J = 12.2 Hz) for **11b**, **12**. [d] J = 11.8 and 4.2 **7**, 12.0 and 4.4 **8**, 12.2 and 5.2 **9**, 10.9 and 6.8 **10a**, 12.3 and 5.1 **10b**, 13.3 and 8.3 **11a**, 12.6 and 7.6 **11b**, 12.6 and 7.3 **12**. [e] d for **7**, **11a,b** and **12** (J = 9.6, 6.6, 6.3 and 6.3), dd for **8** (J = 9.4 and 1.0), **9** (12.6 and 2.5), **10a** (12.1 and 3.5) and **10b** (10.6 and 3.6). [f] 2 x dd (2 x 1H) for **8**, **10a,b** and **12** (J = 5.7 and 3.0 ± 0.2) four m's (4H) also overlap to some extent with the AB-spectrum of the 9-methylene protons for **7**, **9** and **11a,b**. [g] One **7** or both d's **11a,b** overlap with the H 6,7 signals, s (2H) for **10b**, J = 10.4 **7**, 9.2 **8**, 10.0 **9**, **12** and 9.0 Hz **10a**. [h,i] Overlapping signals. [j] Overlapping signals in case of **10a,b**.

Table 2
^{13}C-NMR Data of Compounds 7-12 [a]

	7	8	9	10a	10b	11a	11b	12
C-2	108.3	108.2	108.3	108.3	107.8	106.6		107.8
C-4	64.0	63.8	61.7	64.5	61.9	40.2	37.7	39.8
C-4a	41.5	35.6	38.7	40.6	36.4	42.0	45.6	41.0
C-5	41.6	47.0	41.5	47.9	48.2	40.8	38.4	43.0
C-6	29.6	140.6	24.5	135.9 [b]	135.5 [b]	27.8	29.0	141.1
C-7	27.0	136.9	23.2	135.4 [b]	134.6 [b]	25.2	23.9	132.6
C-8	42.1	47.2	42.7	43.8	50.0	41.2	41.6	47.4
C-8a	56.0	52.5	54.0	55.5	54.4	78.4	77.0	73.6
C-9	35.3	44.6	35.5	46.7	46.6	33.5	33.3	43.1
CH_3	20.9	21.0	21.0	21.1	21.1	21.2	21.2	21.1
C=O	163.7	164.1	165.0	164.9	164.9	161.5	161.3	161.1

Aromatic carbon lines, Ar group: C-1': 136.0 ± 0.8, C-2',6': 126.8 ± 0.8, C-3,5: 128.8 ± 0.4, C-4: 139.5 ± 0.4, condensed ring: C-1: 154.7 ± 0.3, C-2: 119.0 ± 0.6, C-3: 128.0 ± 0.2, C-4: 122.3 ± 0.5, C-5: 134.2 ± 0.1, C-6: 116.8 ± 0.2 ppm. [a] In deuteriochloroform solution at 62.89 MHz; δTMS = 0 ppm, measuring frequency 20.14 MHz for **9** and **12**. The assignments were provided by DEPT experiments for compounds **10a**, **11a,b** and **12**. [b] Reversed assignments may also be possible.

diexo series, the H-8a chemical shift data are most different for isomers **11a-11b**, with a 1.1 ppm higher shielding in the case of **11a**. Smaller shifts in the same direction can also be observed for H-4a and H-4(*eq*) (Δδ: 0.25 and 0.16 ppm) in **11a**. The anisotropic effect of the parallel aryl group is responsible [13a] for the upfield shifts of the H-8a and H-4a signals in **11a**, while the downfield shift of H-4(*eq*) in compound **11b** can be explained by the analogous, but opposite effect of the coplanar carbonyl group [13b].

The crowded structure of **11b** is indicated by the upfield shifts of the C-4,5,7,8a and C-2',6' (aryl) signals (steric compression shift [14]). In **11a**, the opposite shift difference of the C-4a,6 lines is due to the steric hindrance between the 2-aryl group and H-4a.

All this holds only for a given conformation of the flexible hetero rings. However, the magnitudes of the coupling constants between the 4-methylene hydrogens and the neighbouring H-4a (~12.5 and ~7.5 Hz) define the conformation [15]: the oxazine ring has a *boat*-like structure, in which H-4'(*ax*) and H-4a are in *trans*-diaxial positions.

The analogous *exo*-aryl-substituted structure of the norbornene derivative **12** is plausible on the basis of the similar H-4,4',8a chemical shifts.

The conformation of isomers **7** and **8** is different from that of **11a,b**; this can be seen from the much smaller H-4(*eq*), H-4a and H-4'(*ax*), H-4a couplings (<1 and ~4 Hz). Hence, for both (*exo* and *endo*-aryl) C-2 configurations the form compatible with the coupling constants could be selected from the two relatively stable conformers on the basis of molecular models (in these the dihedral angles involving C-4a-H and C-4*eq*'-H or C-4'*ax*'-H are ~60°, while one of them is ~180° in the configurations excluded). In an *exo*-aryl (2*R**) configuration, this means a *twist* conformation for the oxazine ring (see Scheme 1). In this structure H-8a and the carbonyl bond are coplanar, and the *endo* H-9 lies in the anisotropic shielding cone of the 2-aryl group.

In the 2-*endo*-aryl configuration and conformation corresponding to a HC_4-$C_{4a}H$ dihedral angle of 60°, the H-8a-(C_8) and C=O bonds are not coplanar and the anisotropy of the aryl group can be expected on the H-4'(*ax*) signal above all (and to a lesser extent on those of H-4a and H-8a).

Both the upfield shift of the H-9(*endo*) doublet and the strong opposite shift of the H-8a signal (which is a consequence of the anisotropy of the aryl and carbonyl groups) prove the *exo*-aryl configuration (in the spectra of **7** and **8**, the upfield signals are at 0.92 and 1.25 ppm and the downfield signals are at 4.65 and 4.62 ppm, while for the starting compounds **1** and **2** the corresponding data are ~1.4 and ~3.4 ppm).

As concerns the *diendo*-annelated **9** and **10a-10b**, a comparison of the spectroscopic data on the latter isomeric pair likewise facilities determination of the C-2 configuration.

One of the vicinal coupling constants of the 4-methylene hydrogens is high (~11.5 Hz), which suggests a dihedral angle of ~180°. In the conformation derived from this (which corresponds to a *sofa* oxazine ring with an out-of-plane oxygen), the shielding effect of the aryl group yields the upfield shift of the H-6, 7, 8 signals in the case of the *endo*-2-aryl (2*S**) isomer. The skeleton is strained and the steric hindrance between the bicyclic ring and the oxazine moiety is significant.

The *exo*-2-aryl (2*R**) structure is sterically more favourable, in which the shielding effect of the aryl group is mostly manifested around H-8a. The carbonyl group is situated close the H-8 and is approximately coplanar with

it. The oxazine ring has a similar form, as can be seen in Scheme 1.

On the above basis, the considerable upfield shifts (0.92, 0.56 and 0.17 ppm) of the H-8a doublet and the H-6,7 double doublets for **10b** and the high (0.94 ppm) upfield shift of the H-8 signal for **10a** as compared with the corresponding shifts of the isomer prove the *exo*-aryl (2*R**) configuration in **10a** and the *endo*-aryl (2*S**) configuration in **10b**. These structures are supported by the upfield shifts of the C-4,4a,8a lines for **10b**, due to the strained skeleton (field (effect). The interaction between the carbonyl group and H-8 leads to a considerable (6.2 ppm) upfield shift of the C-8 line of **10a**.

The analogous spectral parameters (**e.g.** the downfield shifted H-8a signal and the upfield shifted C-4 line) indicated the same steric structures for **9** and **10b**, *i.e.* the 2*S** configuration. The identical conformation of the hetero rings in unambiguous from the chemical shifts and coupling constants of the 4-methylene group. The H-8 shift is similar to that for the starting compound **2** [16] (as in the case of **10b**), while the close-lying carbonyl group causes a large downfield shift (cf. the 4.30 ppm shift of **10a** and the 3.25 ppm signal of **1**), which leads further support to the presumed structures.

Table 3

Physical and Analytical Data on Compounds 7-12

Compound	Mp °C	Yield %	Molecular Formula	Analyses % Calcd./Found C	H	N
7 [a]	198-200	31	$C_{23}H_{23}NO_3$	76.43	6.41	3.88
				76.56	6.60	4.10
8 [b]	178-180	30	$C_{23}H_{21}NO_3$	76.86	5.89	3.90
				77.03	6.08	3.76
9 [a]	219-221	40	$C_{23}H_{23}NO_3$	76.43	6.41	3.88
				76.39	6.48	3.94
10a [b]	163-165	33	$C_{23}H_{21}NO_3$	76.86	5.89	3.90
				77.09	5.97	3.97
10b [b]	202-204	27	$C_{23}H_{21}NO_3$	76.86	5.89	3.90
				76.89	5.76	3.63
11a [b]	192-194	26	$C_{23}H_{23}NO_3$	76.43	6.41	3.88
				76.19	6.32	4.03
11b [b]	178-180	33	$C_{23}H_{23}NO_3$	76.43	6.41	3.88
				76.20	6.26	4.01
12 [c]	204-206	39	$C_{23}H_{21}NO_3$	76.86	5.89	3.90
				76.83	5.82	4.05

[a] From ethanol petroleum ether. [b] From ethanol. [c] From benzene–petroleum ether.

EXPERIMENTAL

The ^{1}H- and ^{13}C-nmr spectra were recorded at room temperature in deuteriochloroform solution, in 5 (^{1}H) and 5 or 10 (^{13}C) ml nmr tubes, on Bruker WM-250 (^{1}H, ^{13}C) or WP-80SY (^{13}C) FT spectrometers controlled by ASPECT 2000 computers at 250.13 (^{1}H) and 63.89 or 20.14 (^{13}C) MHz, using the deuterium signal of the solvent as the lock and TMS as internal standard.

2*r*-*p*-Tolyl-5,8-methano-4a*t*,5*t*,6,7,8*t*,8a*t*-hexahydro-3,1-benzoxazino[2,1-*b*]-1,3-benzoxazin-4-one **7**, 2*r*-*p*-tolyl-5,8-methano-4a*t*,-5*t*,8*t*,8a*t*-tetrahydro-3,1-benzoxazino[2,1-*b*]-1,3-benzoxazin-4-one **8**, 2*r*-*p*-tolyl-5,8-methano-4a*c*,5*t*,6,7,8*t*,8a*c*-hexahydro-3,1-benzoxazino[2,1-*b*]-1,3-benzoxazin-4-one **9** and 2*r*-*p*-tolyl-5,8-methano-4a*t*,5*t*,8*t*,8a*t*-tetrahydro-1,3-benzoxazino[2,3-*b*]-1,3-benzoxazin-4-one **12**.

Dihydro-1,3-oxazines **1**, **2**, **4** or **5** (0.5 g, 2 mmoles) and salicyl chloride [9] (0.35 g, 2.2 mmoles) were reacted in dry benzene (20 ml) at rt. After standing for 20 minutes (hydrogen chloride gas evolution), the mixture was refluxed for 2 hours. The solvent was evaporated off and the residue was transferred onto an alumina column (Alumina Woelm B, neutral) and eluted with benzene. The residue of the eluate was crystallized.

2*r*-*p*-Tolyl-5,8-methano-4a*c*,5*t*,8*t*,8a*c*-tetrahydro-3,1-benzoxazino-[2,1-*b*]-1,3-benzoxazin-4-one **10a** and 2*r*-*p*-Tolyl-5,8-methano-4a*t*,-5*t*,6,7,8*t*,8a*t*-hexahydro-1,3-benzoxazino[2,3-*b*]-1,3-benzoxazin-4-one **11b**.

A mixture of dihydro-1,3-oxazine **3** or **6** (0.5 g, 2 mmoles) and salicyl chloride (0.35 g, 2.2 mmoles) was left to stand in benzene (20 ml) at rt overnight. After filtration, the filtrate was evaporated and residue was chromatographed as above.

2*r*-*p*-Tolyl-5,8-methano-4a*t*,5*c*,8*c*,8a*t*-tetrahydro-3,1-benzoxazino[2,1-*b*]-1,3-benzoxazin-4-one **10b** and 2*r*-*p*-Tolyl-5,8-methano-4a*c*,5*c*,6,7,8*c*,8a*c*-hexahydro-1,3-benzoxazino[2,3-*b*]-1,3-benzoxazin-4-one **11a**.

Dihydro-1,3-oxazine **3** or **6** (0.5 g, 2 mmoles) was reacted as above at rt for 3 days. After chromatography and evaporation, the residue was crystallized.

Data on the compounds prepared are listed in Table 3.

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