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2-Substituted Hexahydroacylanthranils: Synthesis and Selective Reactions with Amines[#]

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Summary. In contrast to their aromatic analogues, the corresponding saturated diamides **5–9** are formed exclusively when hexahydro-3,1,4-benzoxazinones (**3**, **4**) are reacted with amines. The cyclodehydration reaction of the diamides **5–9** cannot be carried out at arbitrarily high temperatures.

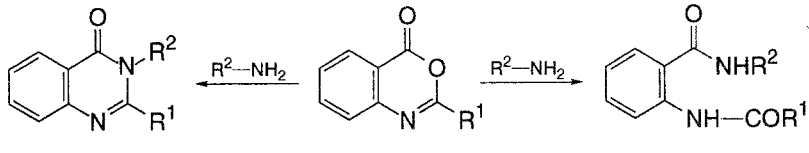
Keywords. Hexahydroacylanthranils; Hexahydrobenzoxazinones; Stereochemistry; Ring-opening reaction.

2-Substituierte Hexahydroacylanthranile: Synthese und selektive Reaktionen mit Aminen

Zusammenfassung. Im Gegensatz zu den aromatischen Analoga bilden sich bei der Reaktion von Hexahydro-3,1,4-benzoxazinonen (**3**, **4**) mit Aminen ausschließlich die entsprechenden gesättigten Diamide **5–9**. Die Cyclodehydrierungsreaktion der Diamide **5–9** kann nicht bei beliebig hoher Temperatur durchgeführt werden.

Introduction

It is well known that 2,3-disubstituted 4(3*H*)-quinazolinones can be prepared from the reaction of benzoxazinones with primary amines [1–3]. According to literature data [4–11], benzoxazinones react with amines to give either quinazolinones **I** (attack at position 2) or 2-acylaminobenzoic acid amides **II** (attack at position 4) (Scheme 1).



I II

Scheme 1

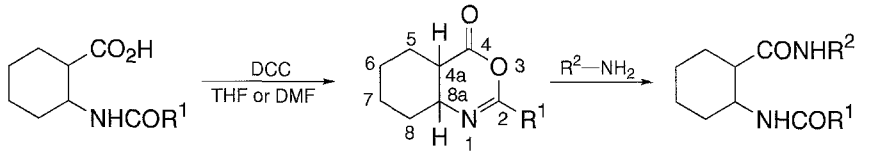
[#] Saturated Heterocycles, Part 217. Part 216: L. Simon, S. G. Talpas, F. Fülöp, G. Bernáth, G. Argay, A. Kálmán, P. Sohár (1995) J Heterocyclic Chem **32**: 161

Accordingly, it seemed reasonable to study the reaction of hydrogenated *N*-acylanthranils, *e.g. cis*- and *trans*-2-methyl- and 2-phenyl-4a,5,6,7,8,8a-hexahydro-3,1,4-benzoxazinones (**3**, **4**), and to investigate the reaction of amines as a function of the configuration of the benzoxazinones and the effects upon the selectivity of the substituents at position 2.

Results and Discussion

The starting materials (*cis*- and *trans*-2-amino-1-cyclohexanecarboxylic acids) were synthesized according to Ref. [12]. From these compounds, *N*-acetyl-*cis*- and -*trans*-2-amino-1-cyclohexanecarboxylic acids (**1a**, **1b**; [13]) and *N*-benzoyl-*cis*- and *trans*-2-amino-1-cyclohexanecarboxylic acids (**2a**, **2b**; [14]) were prepared as published earlier [13].

Although 2-phenyl-*cis*- and *trans*-4a,5,6,7,8,8a-hexahydro-3,1,4-benzoxazinones (**4a**, **4b**) have been synthesized from **2a** and **2b** by reaction with thionyl chloride [15], the synthesis of 2-methyl-*cis*- and *trans*-4a,5,6,7,8,8a-hexahydro-3,1,4-benzoxazinones has not yet been published. We have elaborated a convenient method for the preparation of *cis*- and *trans*-2-methyl- and -2-phenyl-4a,5,6,7,8,8a-hexahydro-3,1,4-benzoxazinones (**3**, **4**) from **1** and **2** [15] (Scheme 2).



1, 2

		R^1
1a	*cis*	Me
1b	*trans*	Me
2a	*cis*	Ph
2b	*trans*	Ph

3, 4

		R^1
3a	*cis*	Me
3b	*trans*	Me
4a	*cis*	Ph
4b	*trans*	Ph

5–9

		R^1	R^2
5a	*cis*	Me	*n*-Bu
5b	*trans*	Me	*n*-Bu
6a	*cis*	Me	Ph
6b	*trans*	Me	Ph
7a	*cis*	Me	*p*-Cl-C_6H_4
7b	*trans*	Me	*p*-Cl-C_6H_4
8a	*cis*	Ph	Ph
8b	*trans*	Ph	Ph
9a	*cis*	Ph	$PhCH_2$
9b	*trans*	Ph	$PhCH_2$

Scheme 2

The stereoisomeric *N*-acetyl amino acids **1a** and **1b** were allowed to react at room temperature with equimolar amounts of 1,3-dicyclohexylcarbodiimide (*DCC*) in tetrahydrofuran (*THF*). Compounds **3a** (83%) and **3b** (87%) were isolated. The corresponding 2-phenyl derivatives (**4a**, **4b**) could be prepared by the same method in dimethylformamide (*DMF*) (78% and 92% Table 1).

The ^{1}H NMR spectra of the hexahydrobenzoxazinones **3** and **4** exhibit the appropriate resonances for the particular groups as shown in Table 2. The anellation of the two six-membered rings is evident from the coupling constants between the protons attached to C-5 and C-6. In case of the *trans*

Table 1. Physical and analytical data for compounds **3** and **4**

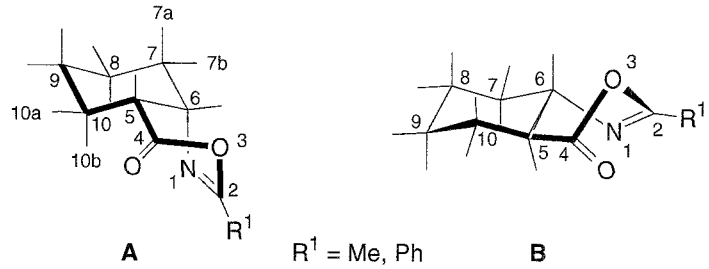
	Yield[a] (%)	m.p. or b.p. (°C)	Formula (mol. mass)	Analysis (%) C calcd. (found)	H calcd. (found)	N calcd. (found)
3a	83	77–79/2.5 torr	$C_9H_{13}NO_2$ (167.2)	64.64 (64.71)	7.83 (7.73)	8.37 (8.11)
3b	87	90–93/2.5 torr	$C_9H_{13}NO_2$ (167.2)	64.64 (64.52)	7.83 (7.68)	8.37 (8.33)
4a	78	74[b]	$C_{14}H_{15}NO_2$ (229.3)	73.33 (73.17)	6.59 (6.62)	6.11 (6.05)
4b	92	98–101[b]	$C_{14}H_{15}NO_2$ (229.3)	73.33 (73.40)	6.59 (6.11)	6.11 (6.21)

[a] Yield of isolated product; [b] Ref. [15]; m.p. (**4a**): 75–76 °C, m.p. (**4b**): 97 °C

Table 2. ^{1}H NMR data ($CDCl_3$, 400 MHz) of compounds **3** and **4**

	δ (ppm) 5-H	6-H	Me or Ph	J (Hz)				
3a	2.76	3.62	2.09	$J_{5,6} \approx J_{6,7a}$	$\approx J_{6,7b} = 2.9$	$J_{5,10a} = 7.3$	$J_{5,10b} = 3.0$	
3b	2.96	3.41	2.10	$J_{5,6} = 9.2$	$J_{6,7a} = 9.2$	$J_{6,7b} = 3.1$	$J_{5,10a} = 9.0$	$J_{5,10b} = 3.1$
4a	3.12	4.40	7.2–7.76	$J_{5,6} = 3.2$	$J_{5,10a} = 9.5$	$J_{5,10b} = 3.2$		
4b	3.81	4.05	7.38–7.90	$J_{5,6} = 9.1$	$J_{6,7a} = 9.1$	$J_{6,7b} = 3.1$	$J_{5,10a} = 9.1$	$J_{5,10b} = 3.0$

compounds **3b** and **4b**, the carbonyl group and the nitrogen atom are oriented equatorially; therefore, the axial protons H-5 and H-6 have a coupling constant of about 9 Hz (Scheme 3, **B**). In the *cis* compounds **3a** and **4a**, an axial nitrogen atom is accompanied by an equatorial carbonyl group. H-6 shows three small couplings ($J \approx 3$ Hz), whereas H-5 displays a diaxial coupling ($J \approx 9$ Hz).



Scheme 3

The 2-methylhexahydrobenzoxazinones **3a** and **3b** were reacted with *n*-butylamine, aniline, and *p*-chloroaniline in etheral solution. N-Substituted *cis*- and *trans*-2-acetylamino-1-cyclohexanecarboxamides (**5–9**) were produced exclusively

Table 3. Physical and analytical data of compounds **5–9**

	Yield (%)	m.p. (°C)	Literature m.p. (°C)	Formula (mol. mass)	Analysis (%) C calcd. (found)	H calcd. (found)	N calcd. (found)
5a	92	136	133–135 [13]	$C_{13}H_{24}O_2N_2$ (240.3)	64.95 (64.83)	10.06 (9.97)	11.65 (11.35)
5b	85	221	218–222 [13]	$C_{13}H_{24}O_2N_2$ (240.3)	64.95 (64.78)	10.06 (9.83)	11.65 (11.51)
6a	97	212–213	211–213 [13]	$C_{15}H_{20}O_2N_2$ (260.3)	69.22 (69.01)	7.75 (7.48)	10.75 (10.53)
6b	92	270	266–268 [13]	$C_{15}H_{20}O_2N_2$ (260.3)	69.22 (69.10)	7.75 (7.51)	10.75 (10.81)
7a	94	235	234–236 [13]	$C_{15}H_{19}O_2N_2Cl$ (294.7)	61.12 (61.30)	6.50 (6.44)	9.50 (9.10)
7b	87	284–286	283–285 [13]	$C_{15}H_{19}O_2N_2Cl$ (294.7)	61.12 (61.04)	6.50 (6.39)	9.50 (9.37)
8a	96	125	123–124 [15]	$C_{20}H_{22}O_2N_2$ (322.40)	74.50 (74.12)	6.87 (6.57)	8.68 (8.51)
8b	99	300–304	301–303 [15]	$C_{20}H_{22}O_2N_2$ (322.40)	74.50 (74.28)	6.87 (6.60)	8.68 (8.47)
9a	92	141–144	142–143 [15]	$C_{21}H_{24}O_2N_2$ (336.43)	74.97 (74.88)	7.19 (7.08)	8.32 (8.11)
9b	90	287–290	287–289 [15]	$C_{21}H_{24}O_2N_2$ (336.43)	74.97 (74.71)	7.19 (6.97)	8.32 (8.20)

by a ring-opening reaction. The reactions could be followed visually, and it could be observed that the precipitation of the diamides **5a**, **6a**, and **7a** from etheral solutions of *cis*-hexahydrobenzoxazinone compounds is considerably faster than that of the corresponding *trans* isomers **5b**, **6b**, and **7b**. The diamides formed were identical with the diamides which were obtained by the *Grimmel* reaction as published earlier [13].

When the hexahydrobenzoxazinones **4a** and **4b** were reacted with aniline or benzylamine in *THF* or benzene at room temperature, compounds **8** and **9** were formed exclusively. This is in contrast to the results obtained with aromatic analogues. The results of these experiments are summarized in Table 3. The structures of the compounds were identical with those published previously [15]. The formation of the corresponding amidine salts could not be observed.

Heating compounds **5–9** in xylene at 138–140 °C or in diglyme (diethylene glycol dimethyl ether) at 162 °C for several hours left the compounds unchanged. The same results could be obtained when they were refluxed in xylene in the presence of strong dehydrating agents (phosphorus pentoxide, polyphosporic acid, or acetic anhydride) for 12–18 hours.

Experimental

Melting points: Kofler melting point instrument, uncorrected; microanalyses: CHN analyzer Laboratorni Pristroje Praha; ^{1}H NMR: Bruker AM 400 (400 MHz) spectrometer (δ, internal *TMS*). Starting

compounds: N-acetyl-*cis*- and -*trans*-2-amino-1-cyclohexanecarboxylic acids (**1a**, **1b**) and N-benzoyl-*cis*- and -*trans*-2-amino-1-cyclohexanecarboxylic acids (**2a**, **2b**) were prepared *via* literature procedures [13, 14].

General procedure for the preparation of 2-substituted cis- and trans-4a,5,6,7,8a-hexahydro-3,1,4-benzoxazinones (**3**, **4**)

Cis- or *trans*-2-N-acyl-1-cyclohexanecarboxylic acids (**1**, **2**; 0.02 mol) and 1,3-dicyclohexylcarbodiimide (0.02 mol) were dissolved in anhydrous *THF* (5 ml) or *DMF* (12 ml). The reaction mixtures were kept at room temperature for 24 h. The precipitated 1,3-dicyclohexylurea was removed by filtration. The solvent was evaporated under reduced pressure to give a dark yellow oily product. The crude products of **3a** and **3b** were purified by distillation under reduced pressure. The crude products of **4a** and **4b** were recrystallized from diethyl ether. Yields and physical data of the products are summarized in Table 1.

General procedure for the reaction of amines with 2-substituted hexahydrobenzoxazinones (**5**–**9**)

A solution of an amine (1 mmol) in *THF* (5 ml), diethyl ether (8 ml), or benzene (5 ml) was added dropwise to a solution of an equivalent amount of the 2-substituted hexahydrobenzoxazinones **3**, **4** in *THF* (2 ml), diethyl ether (8 ml), or benzene (5 ml) and kept at room temperature. The products **5**–**9** were precipitated completely at room temperature (12–24 h) and collected by filtration. The filtrates were evaporated under reduced pressure; the residues (5–8%) turned out to be unchanged starting material. Yields and melting points of the products are summarized in Table 2.

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