Tetrahedron Vol. 44, No. 10, pp. 2993 to 2996, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + .00

STEREOCHEMICAL STUDIES, 142. SATURATED HETEROCYCLES, 148[1]

ONE-POT SYNTHESIS OF PARTIALLY SATURATED TETRACYCLIC BENZOXAZINES; SCOPE AND LIMITATIONS

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(*Received in UK* 4 *March* 1988)

Abstract - The partly saturated 1,3-benzoxazino[3,4-a][3,1]benzoxazine (3) and 1,3-benzoxazino[3,2-c][1,3]benzoxazines (6a-c) were prepared in one-pot syntheses from trans-2-hydroxymethylcyclohexylamine (2) and trans-2-aminomethylcyclohexanol (5) via ring-chain tautomeric mixtures. ^{1}H nmr spectroscopic characterization of the products 6a-c, including the assignment of the resulting diastereomers is presented.

The differently saturated 1,3-oxazines are an important family of heterocycles from both chemical and pharmacological points of view.[2,3] A characteristic feature of tetrahydro-1,3-oxazines is the ring-chain tautomerism,[4,5] which has been studied since 1942.[6] In the fifties and early sixties mostly qualitative,[7] but later quantitative studies were published. It has recently been reported[4] that the tautomerism of 2-aryl-substituted 1,3-oxazines can be described by a simple equation: $\log K_X = (0.76 \pm 0.04)\sigma^+ + \log K_H$, where K_X = [ring]/[chain] and σ^+ = Hammett constant.

The knowledge of the tautomerism of oxazines can be utilized in different chemical transformations of oxazines, e.g. the N-substitution of 1,3-aminoalcohols[10-12] to obtain products which are not easily available by other methods, making use of their facile reduction with sodium borohydride. The present paper describes the synthesis of several tetracyclic ring systems containing two 1,3-oxazine moieties. The reactions of the cis and trans isomers are compared, and the stereochemistry of the products is reported.

RESULTS AND DISCUSSION

A facile one-pot synthesis of a new 6,11-dioxa-8-aza-D-homosteroid ring system 3 was recently described.[13] By the treatment of trans-2-hydroxymethylcyclohexylamine[14] 2 with salicylaldehyde, followed by formaldehyde, 3 was obtained in good yield. Surprisingly, when the cis counterpart, aminoalcohol 1, was reacted under similar conditions, no tetracyclic product was formed, but transimination[15,16] took place and salicylaldehyde was recovered nearly quantitatively.

Similarly, starting from structurally isomeric 2-aminomethylcyclohexanols (4, 5), the cis isomer 4 failed to give tetracyclic products with different aldehydes, whereas the trans aminoalcohol 5 furnished 1,3-benzoxazino[3,2-c][1,3]benzoxazines 6a-c, a new ring system. ^{1}H nmr measurements showed the separated tetracycles 6a-c to be stereohomogeneous. The products are not stable: in solution, even at room

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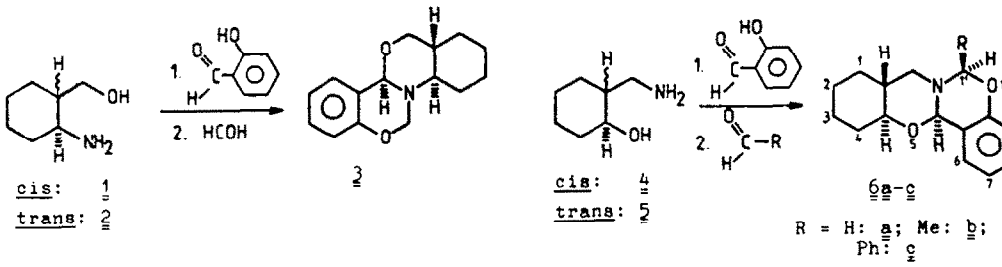
temperature, similarly as with the related condensed-skeleton 1,3-oxazines,[13,17] epimerization takes place in position 5a, and if R ≠ H in position 11, resulting in two and four diastereomers, respectively.

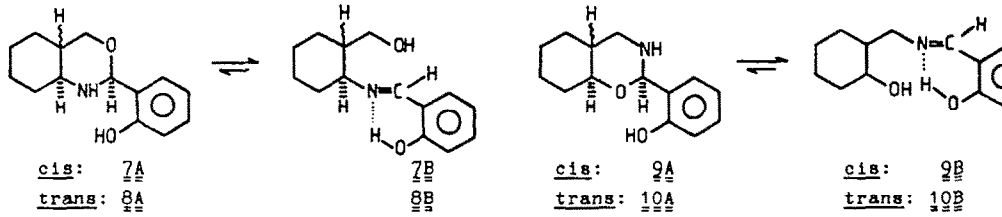


Scheme 1

Assignments could in most cases be made readily on the basis of characteristic chemical shifts and mutual coupling constants. The only exception was 6c, where the closely positioned singlets of H-5a and H-11 were assigned unambiguously through NOEDS experiments,[18] which revealed at the same time the relative configurations for C(4a), C(5a) and C(11). Intense NOE was detected (besides others) between H-4a and H-5a, and between H-11 and H-5a, which are consequently pairwise in 1,3-diaxial positions, according to the diastereomer depicted in Scheme 1.

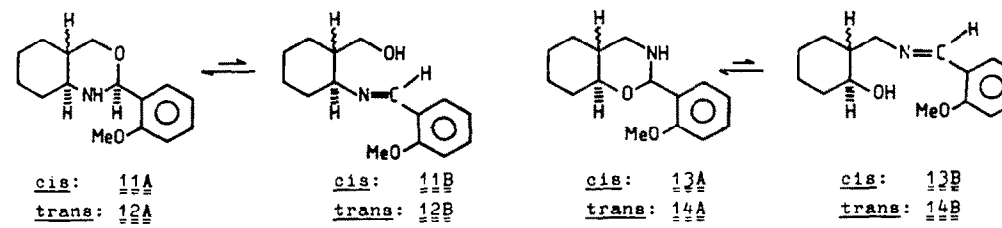
With regard to the substituent effects[19] and anisotropic shielding effect of the 11-phenyl substituent, and to the similar chemical shifts and coupling constants for the three tetracyclic derivatives, one can very probable assume them to be the same diastereomers.

In the reaction of aminoalcohol 2 and salicylaldehyde,[13] the intermediates were not isolated.



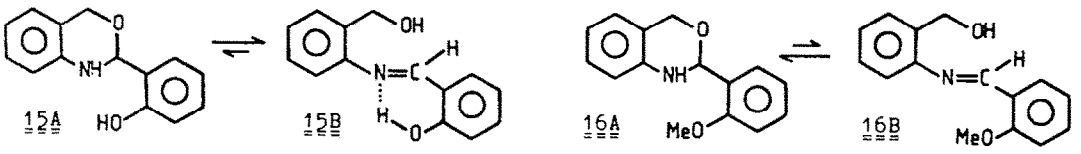
Scheme 2

^{1}H nmr measurements revealed that, when cis- and trans-2-hydroxymethylcyclohexylamine (2) or cis- and trans-2-aminomethylcyclohexanol (5) were reacted with salicylaldehyde, ring-chain tautomeric mixtures were formed. Determination of the tautomeric ratios was based on the integrals of the ring H-2 signal and the corresponding methine line in the ^{1}H nmr spectra of the open forms. In the mixtures 7-10, independently of the configuration, the open forms B predominate in deuterochloroform (Table 1), in spite of the fact that in chloroform solution the predominance of the ring forms is anticipated. The open forms are stabilized by a strong intramolecular hydrogen-bond.[20-22]



Scheme 3

The stabilization effect of the phenolic hydroxy group on the open-chain form was supported by the synthesis of the analogous o-methoxy derivative. If anisaldehyde was used instead of salicylaldehyde (11-14), the tautomeric ratios changed dramatically and the ring forms became preferred (Table 1).



Scheme 4

The experimental results led us to consider that the formation of tetracycles is successful if the end-product crystallizes out from the reaction mixture, resulting in a shift of the tautomeric equilibrium towards the ring-closed form. This is suggested by the fact that the yield of the reaction depends on the water content of the solvent. In the preparation of 3 and 6a,b, the yield increased in parallel with the water content. In the case of the cis derivatives with an excess of aldehyde, transimination took place, and salicylaldehyde could be recovered quantitatively.

EXPERIMENTAL

M.p.s were determined on a Boetius micro melting point apparatus and are uncorrected. The ^{1}H nmr recordings were run on a Bruker WM-250 spectrometer (250.13 MHz), in $CDCl_3$ solution at ambient temperature, using TMS as internal standard. Spectra were recorded immediately after dissolution of the samples in the case of tetracycles 6a-c, while establishment of the equilibrium state was allowed for compounds 7-16.

cis- and trans-2-Hydroxymethylcyclohexylamine (1, 2) and cis- and trans-2-aminomethylcyclohexanol (4, 5) were prepared as described earlier.*

General one-pot procedure for preparation of tetracycles 3 and 6a-c

Aminoalcohol 2 or 5 (5 mmol) and salicylaldehyde (5 mmol) were dissolved together in 10 ml of EtOH and were left to stand for 30 min. Then, under stirring, aqueous formaldehyde (10 ml), or acetaldehyde (2 ml) in water (8 ml), or 5 mmol benzaldehyde was added. After 30 min (in the case of 6c after a few days), product 3 or 6a-c crystallized from the reaction mixture. The physical and analytical data are listed in Table 2.

The most important and characteristic ^{1}H nmr data (chemical shifts in ppm, multiplicity and, in brackets, the coupling constants in Hz) are as follows:

6a: H-4a, 3.42 td (10.4, 10.4, 4.0); H-5a, 5.17 s; H-11, 5.05 d (7.0), 4.55 d (7.0); H-13, 3.06 dd (13.6, 4.3), 2.90 t (13.6, 13.6).

6b: H-4a, 3.24 td (10.3, 10.3, 6.2); H-5a, 4.86 s; H-11, 4.51 q (5.7); H-13, 3.12 dd (10.5, 3.8), 2.01 t (10.5).

6c: H-4a, 3.26 td (10.2, 10.2, 3.9); H-5a, 5.04 s; H-11, 5.26 s; H-13, 2.43 dd (10.6, 3.8), 1.82 t (10.6).

Table 1. Characteristic data on tautomeric mixtures 7-16

No.	Ring form(%)	δ2-H (ring)	δ=CH (open)
7	5.9	5.95	8.42
8	9.9	5.29	8.37
9	1.4	5.22	8.30
10	2.8	5.22	8.30
11	76.5	5.40	8.65
12	92.2	5.50	8.74
13	56.9	5.46	8.60
14	56.0	5.51	8.61
15	7.5	5.96	8.63
16	89.6	5.92	9.00

Isolation of intermediates, and preparation of their o-methoxy derivatives

Aminoalcohol 1, 2, 4 or 5 or o-aminobenzyl alcohol (5 mmol) and equivalent salicylaldehyde or o-anisaldehyde were dissolved together in 10 ml of EtOH and were left to stand for 30 min. The solvent was evaporated off and the products (7, 12, 15, 16) were crystallized. If an oily product (8-11, 13, 14) was formed, the evaporation was repeated after addition of benzene. Products were dried in a vacuum desiccator, and were then analysed by ^{1}H nmr spectroscopy.

Attempted cyclization of 7, 9 and 15 with formaldehyde

Compound 7, 9 or 15 was dissolved in 10 ml of ethanol and aqueous formaldehyde (10 ml) was added. After 2 hours, the reaction mixture, having

a strong salicylaldehyde odour, was weakly acidified with aqueous HCl and salicylaldehyde was extracted with ether. After evaporation of the ether, the residue was practically pure salicylaldehyde in nearly quantitative amount.

Table 2. Physical and analytical data on prepared compounds 3, 6-16

Compound	M.p. (°C)	Yield (%)	Found (%) C	H	N	Formula (M.W.)	Calculated (%) C	H	N
3	113-114[a,b]	69				$C_{15}H_{19}NO_2$(245.31)			
6a	106-109[a]	65	73.19	7.52	5.65	$C_{15}H_{19}NO_2$(245.31)	73.44	7.81	5.71
6b	128-136[a]	63	74.21	7.89	5.23	$C_{16}H_{21}NO_2$(259.34)	74.10	8.16	5.40
6c	180-184[a]	60	78.63	7.20	4.47	$C_{21}H_{23}NO_2$(321.40)	78.47	7.21	4.36
7	60-62	87	72.14	8.14	6.11				
8	c		71.79	8.39	5.90	$C_{14}H_{19}NO_2$(233.30)	72.07	8.21	6.00
9	c		72.04	8.44	5.86				
10	c		72.20	8.28	6.23				
11	c		72.96	8.66	5.75				
12	93-95[a]	84	72.93	8.81	5.61	$C_{15}H_{21}NO_2$(247.33)	72.84	8.56	5.66
13	c		72.61	8.74	5.78				
14	c		73.04	8.73	5.75				
15	124-125[a,d]	89				$C_{14}H_{13}NO_2$(227.25)			
16	84-85[a,e]	92				$C_{15}H_{15}NO_2$(241.28)			

[a] Crystallized from n-hexane. [b] Lit.[13] m.p. 112-114 °C. [c] Yellow viscous oil; the yield is quantitative. Lit.[23] m.p. 124-125 °C. Lit.[23] m.p. 84-85 °C.

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