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# FORMATION OF 1,3-PERHYDROBENZOXAZINES AND THEIR N-METHYL DERIVATIVES. A COMPARATIVE STUDY

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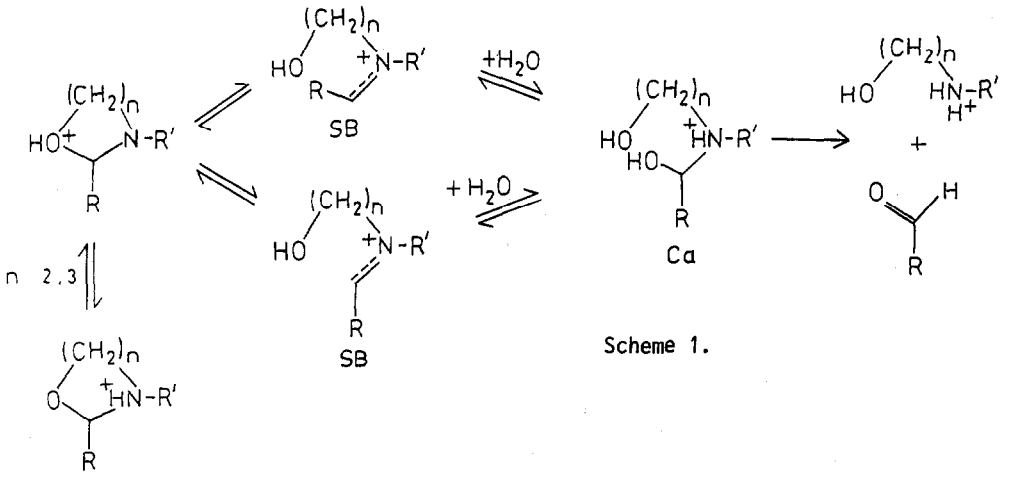
**Abstract:** The formation of perhydro-1,3-oxazine derivatives (3) through the cyclization reaction of *p*-nitrobenzaldehyde with *cis*- (1) and *trans*-2-aminomethyl-1-cyclohexanol (2) or with their N-methyl derivatives (1m and 2m) were studied by $^1$H NMR spectroscopy in $CDCl_3$. The reactions with 1 and 2 proceeded via open-chain intermediates whereas those with 1m and 2m showed no signs of these intermediates. The cyclization reactions of the N-methyl substituted cyclohexanols (1m and 2m) were much faster than those of the corresponding hydroxymethylcyclohexylamines studied earlier. The cyclization of 1 was kinetically controlled but in much lesser extent than the corresponding reaction with *cis*-2-hydroxymethyl-1-cyclohexylamine. These results confirmed that the cyclization reactions of *p*-nitrobenzaldehyde with 2-aminomethyl-1-cyclohexanols and their *N*-methyl derivatives parallel to those with 2-hydroxymethyl-1-cyclohexylamines and their *N*-methyl derivatives are not usually diastereospecific.

2-Substituted 3-alkyl- and 3-aryl-1,3-oxazolidines (Scheme 1, n=2) derived from aromatic and aliphatic carbonyl compounds[1] and 2-substituted 3-methyltetrahydro-1,3-oxazines[2] (Scheme 1, n=3) have been reported to hydrolyze into the starting materials via open-chain intermediates, very similar to the corresponding acyclic Schiff bases (Scheme 1, SB). To complement our studies on this type of reactions the formation of 3,1-oxazine derivatives (4) from *p*-nitrobenzaldehyde and 2-hydroxymethyl-1-cyclohexylamine (5 and 6, respectively) was also examined.[3] The reaction proceeds via open-chain intermediates although the formation of the *N*-methyl derivatives showed no sign of these intermediates, even in the presence of $CD_3COOD$.

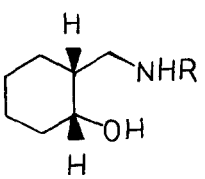
It has been argued that the cyclizations of alicyclic 1,3-aminoalcohols with aldehydes occur diastereospecifically.[4] However, according to a previous work these reactions are not usually diastereospecific, although in one case a remarkable kinetic control was detected in early stages of the equilibrium reaction.[3] In this report the formation of 1,3-oxazine derivatives (3) via the cyclization of *p*-nitrobenzaldehyde with *cis*- (1) and *trans*-2-aminomethyl-1-cyclohexanol (2) or with their *N*-methyl derivatives (1m and 2m, respectively) are described to understand better the role of the amino and hydroxy functions.



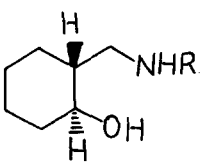
Scheme 1.

## RESULTS AND DISCUSSION

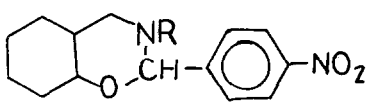
Figure 1 shows an example of the $^1H$ NMR spectra taken on the reaction of p-nitrobenzaldehyde and cis-2-amino-methyl-1-cyclohexanol (1) in $CDCl_3$ solution at 300 K. The NMR spectra revealed the presence of Schiff base intermediates in the formation of 2-p-nitrophenyl-1,3-perhydrobenzoxazines (3) from p-nitrobenzaldehyde and both cis- (1) and trans-2-amino-methyl-1-cyclohexanol (2). This is demonstrated in Fig. 2 by the time dependent $^1H$ NMR spectra of the aryl part of the spectra for the same reaction as in Fig. 1.



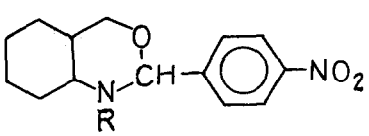
**1: R = H**
**1m: R = Me**



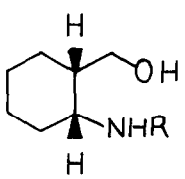
**2: R = H**
**2m: R = Me**



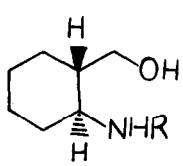
**3: R = H**
**3m: R = Me**



**4: R = H**
**4m: R = Me**



**5: R = H**
**5m: R = Me**



**6: R = H**
**6m: R = Me**

In the reaction of 1 with p-nitrobenzaldehyde the relative mole fraction

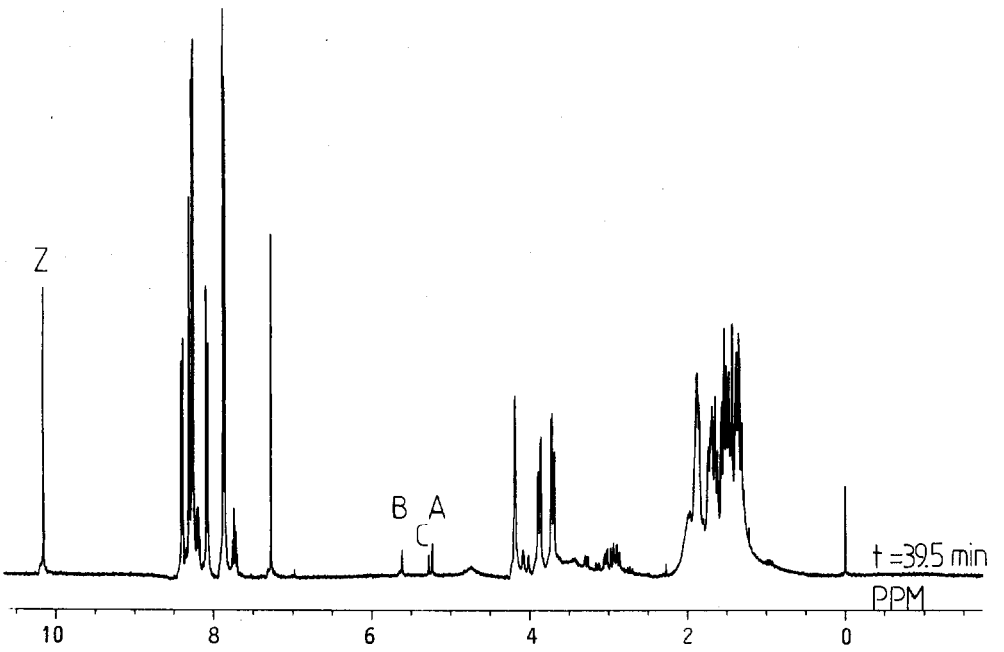



**Figure 1.** $^1$H NMR spectrum on the reaction mixture of cis-2-aminomethyl-1-cyclohexanol with p-nitrobenzaldehyde in $CDCl_3$ solution at 300 K. TMS as internal reference. A, C(2)-H of the $O_{in}$ ring form; B, C(2)-H of the O-out ring form; C, C(2)-H of the carbinolamine; Z, p-$NO_2C_6H_4CHO$.

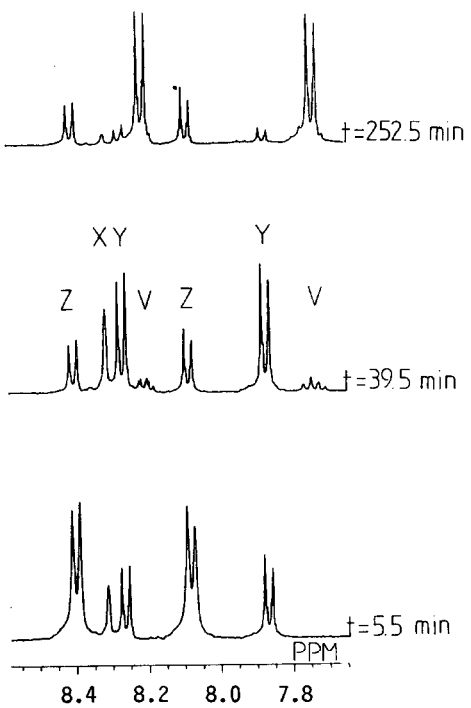
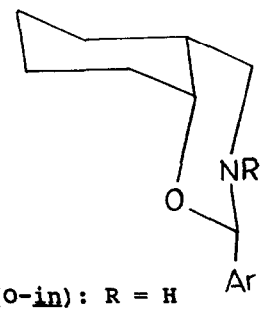
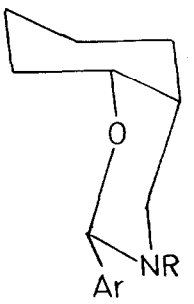



**Figure 2.** The time dependent $^1$H NMR spectra of the aryl protons for the reaction between cis-2-aminomethyl-1-cyclohexanol and p-nitrobenzaldehyde in $CDCl_3$ solution at 300 K. TMS as internal reference. V, ring forms; X, H-C=N-; Y, p$NO_2C_6H_4$C=N-; Z, p$NO_2C_6H_4CHO$.

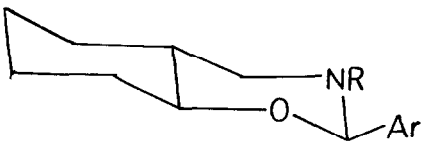
of the Schiff base intermediate reached its maximum almost at once after the initiation of the reaction but decreased then quickly. At the early stages of the reaction the two ring forms, 3c (O-in and O-out) were obtained with equal rates but the relative mole fraction of the less stable O-out form reached its maximum fairly quickly and began to decrease. After about 3 hours the amounts of the ring forms attained an equilibrium stage, the O-in/O-out ratio being 31±4. For this reaction a peak corresponding to the "C-2" proton of the corresponding carbinolamine (cf Ca in Scheme 1) could also be found at a concentration level comparable to that of the less stable ring epimer at equilibrium (Fig. 3).



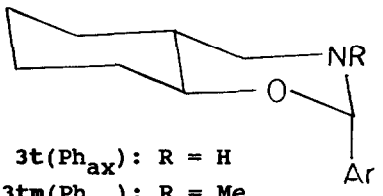

3c(O-in): R = H
3cm(O-in): R = Me




3c(O-out): R = H
3cm(O-out): R = Me




3t(2-Ph$_{eq}$): R = H
3tm(2-Ph$_{eq}$): R = Me




3t(Ph$_{ax}$): R = H
3tm(Ph$_{ax}$): R = Me

In the cyclization of trans-2-aminomethyl-1-cyclohexanol (2) with p-nitrobenzaldehyde no sign of carbinolamine could be found. Now the maximum of the relative mole fraction of the Schiff base intermediate was reached faster and remained somewhat lower than above (Fig. 3). The equilibrium between the 3t(2-Ph$_{eq}$) and 3t(2-Ph$_{ax}$) ring-forms was reached in ca. 3h (2-Ph$_{eq}$/2-Ph$_{ax}$ = 13±2) (Figure 4).

The hydrolytic decomposition of 2-substituted 3-methyl-1,3-oxazolidines[1a,b] and 2-substituted 3-methyltetrahydro-1,3-oxazines[2] in aqueous acid has been shown to occur via open chain Schiff base intermediates. In changing the media from water to chloroform and the reaction from decomposition to formation, respectively, no sign of the Schiff base intermediates could be detected in cyclization of the N-methyl derivatives

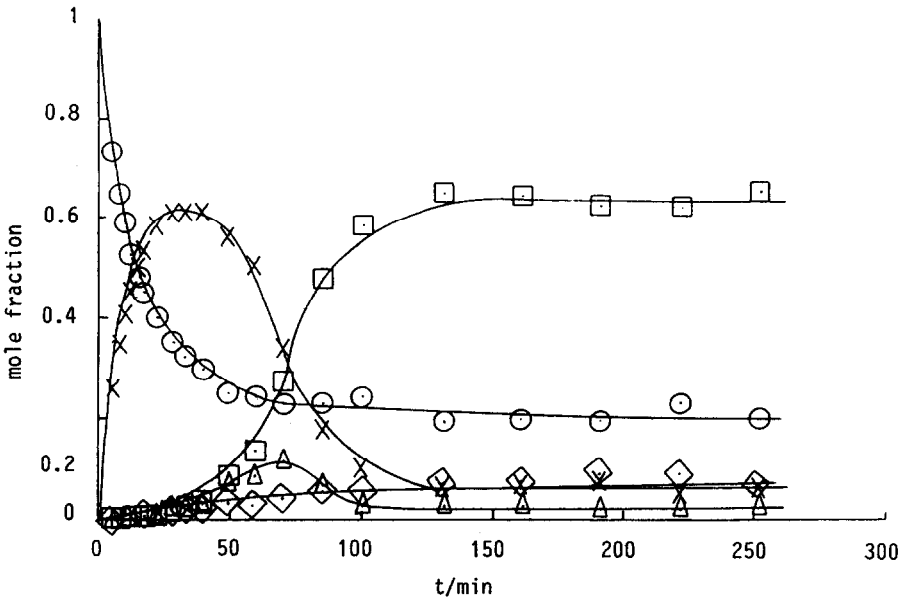



**Figure 3.** The relative mole fractions of the epimeric ring forms, the Schiff base intermediate and the aldehyde in the cyclization of p-nitrobenzaldehyde with cis-2-aminomethyl-1-cyclohexanol in $CDCl_3$ at 300 K against time: (□) O-in ring form; (△) O-out ring form; (X) Schiff base intermediate; (◇) carbinolamine and (0) aldehyde.

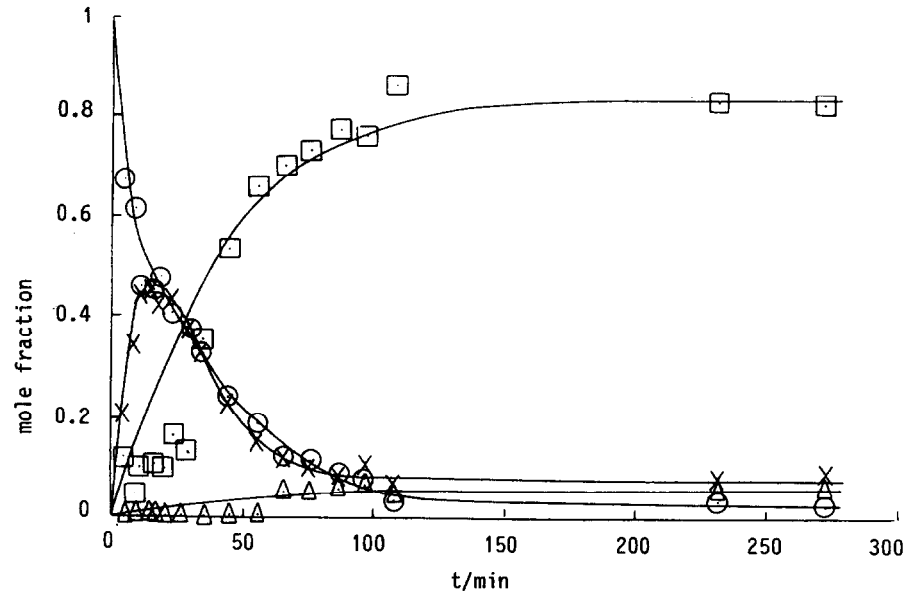



**Figure 4.** The relative mole fractions of the epimeric ring forms, the Schiff base intermediate and the aldehyde in the cyclization of p-nitrobenzaldehyde with trans-2-aminomethyl-1-cyclohexanol in $CDCl_3$ at 303 K against time: (□) $Ph_{eq}$-ring form; (△) $Ph_{ax}$-ring form; (X) Schiff base intermediate and (0) aldehyde.

of the cis- and trans-2-aminomethyl-1-cyclohexanol (**1m** and **2m**) even in the presence of added $CD_3COOD$, which in principle makes the protonation of the substrate possible.

For **1m** a 50% conversion to the **3cm**(O-in) form occurred in about 4h at 323 K in $CDCl_3$ solution and the relative mole fraction of the O-out ring form remained rather low throughout the whole reaction. An addition of $CD_3COOD$ made the reaction about 20 times faster. No sign of the carbinolamine could be found.

In the case of **2m** a peak corresponding to the formation of the carbinolamine could be located. Here a 50 % conversion to the **3tm**($2\text{-}Ph_{eq}$) ring form took place in about 10 h at 323 K. The addition of $CD_3COOD$ made the reaction about 25 times faster. Inspection of the cyclizations of p-nitrobenzaldehyde with cis- (1) and trans-2-aminomethyl-1-cyclohexanol (2) and with cis- (5) and trans-2-hydroxymethylcyclohexylamine (6)[3] showed that all of these reactions proceed via open-chain intermediates.

In the cyclization reaction of p-nitrobenzaldehyde with cis-2-hydroxymethyl-1-cyclohexylamine (5) the Schiff base intermediate is formed very quickly and also its subsequent decrease is fast since the kinetic control favours the less stable ring epimer which can be formed directly from the E(N-out) form of the open chain intermediate.[3] The final equilibration, however, is controlled by the E(N-in) conformation of the open chain intermediate.[3] In the reaction of p-nitrobenzaldehyde with cis-2-aminomethyl-1-cyclohexanol (1) the Schiff base intermediate (SB) was also formed quickly kinetic control being now, however, much less in favour of the less stable ring form since SB has now more conformational freedom and it is relatively more stable than above. Therefore in the reaction of p-nitrobenzaldehyde with cis-2-aminomethyl-1-cyclohexanol (1) the relative amounts of both ring forms are from the very beginning of the reaction more thermodynamically controlled than in the case of 5, i.e. the equilibration of the ring forms is controlled by the decomposition of SB, whereas the equilibration process itself is the main rate limiting step in the formation of **4** from 5.

The maximum of the relative mole fraction of SB for 1 and 5 was practically equal, but the latter reached it about two times faster than the former. For 5 the less stable ring epimer (N-out) was the predominant cyclization product at the early stages of the reaction because of a kinetic control.[3] The kinetic control could also be observed for the less stable ring epimer (O-out) of 1, although in much lesser amount.

The formation of carbinolamine was evident for the cyclizations of both **1** and **5**, although its concentration remained at such a low level that it did not influence the conlusions drawn in our previous discussion.[3] The equilibrium between the ring forms was in greater extent in favour of the more stable ring epimer for **1** than for **5** ($K = 31\pm4$ at 300 K and $13\pm1$ at 303 K, respectively).

No carbinolamine could be detected in the reactions of p-nitrobenzaldehyde with the trans-aminoalcohols, **2** and **6**. For **2** the maximum amount of the Schiff base intermediate (SB) was clearly higher than for **6** and the 2-$Ph_{ax}$-epimer of **2** exhibits somewhat less severe syn-axial interactions (by ca 3 kJ $mol^{-1}$) than that of **6** as shown by the equilibrium constants ($13 \pm 2$ and $45 \pm 10$ (Ref. 3) at 303 K, respectively). In the cyclization reactions of p-nitrobenzaldehyde with the N-methyl derivatives of both 2-hydroxymethylcyclohexylamines (**1m** and **2m**) and 2-aminomethyl-1-cyclohexanols[3] (**5m** and **6m**) no sign of SB could be detected even in the presence of $CD_3COOD$. The cyclization reaction of p-nitrobenzaldehyde with **1m** occurred about 45 times faster without added acid and about 30 times faster with the acid than that with **5m**. Furthermore the presence of carbinolamine could not be verified in the reactions with **1m** or **5m**, whereas in the reactions with **2m** and **6m** in acidic $CDCl_3$ it could be detected, although at a very low concentration level.

## Experimental

Materials The preparation[5,6] of 2-aminomethyl-1-cyclohexanols and their N-methyl derivatives and the characterization of 2-p-nitrophenyl-1,3-perhydrobenzoxazines[7-9] and their N-methyl derivatives[7] and the corresponding Schiff base intermediates[9] are described in previous studies.

Measurements The time dependent $^1H$ NMR spectra taken with 4 scans and 32K data points at intervals on the cyclization reaction of cis- and trans-2-aminomethyl-1-cyclohexanol and their N-methyl derivatives with p-nitrobenzaldehyde were recorded on a Jeol GX-400 FT-NMR spectrometer in $CDCl_3$ solutions (about 10 mg of both substrates per 0.8 ml) using TMS as internal standard.

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