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STEREOCHEMISTRY—60†

KINETIC CONTROL OF ASYMMETRIC INDUCTION DURING OXAZOLIDINE FORMATION FROM (−)-EPHEDRINE AND AROMATIC ALDEHYDES

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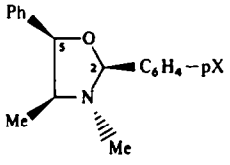
Abstract—Kinetically controlled oxazolidine formation was observed with aromatic aldehydes substituted by electron-withdrawing groups. The stereoselectivity is solvent dependent: non-stereoselective ring closure occurred in chloroform while a high diastereodifferentiation was observed in methanol. The first oxazolidine showing an unambiguous 2*R* configuration was synthesized from *p*-bromobenzaldehyde and (−)-ephedrine in alcohol medium. A mechanism involving a nucleophilic assistance by alcoholic solvents is suggested in order to clarify the differences in stereoselectivity.

Neelakantan's report[2,3] of remarkable diastereoselective oxazolidine formation from aldehydes and (−)-ephedrine has led to many uses of these chiral oxazolidines as intermediates in asymmetric transformations. Besides considerable controversy over the stereochemistry of the oxazolidines (*vide infra*), the reaction is concerned with two major areas: (i) the resolution of chiral aldehydes via crystalline diastereoisomeric oxazolidines;[4] (ii) asymmetric induction using the oxazolidine moiety as a chiral auxiliary.[5,6]

As implied above, Neelakantan's stereochemical assignments[2] were seriously disputed, although they were partly based upon an X-ray structural analysis.[3] It is now widely accepted[5,7-11] that the major isomer **1** presents the (*S*)-configuration at C-2, and the proportion of the (2*R*)-isomer **2** does not exceed 10% in the isolated products.



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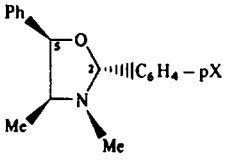

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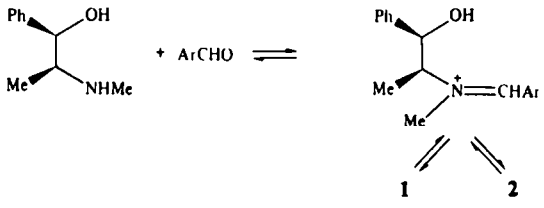
The high stereoselectivity observed during this cyclization still requires an explanation. The main problem is to determine whether the preponderance of the (2*S*)-isomer arises as a result of thermodynamic or kinetic control, particularly as it has been reported[12] that the (2*S*)-isomer derived from acetaldehyde is more stable than the (2*R*)-isomer.

Aldehydes react with ephedrine by a sequence of reversible steps; in fact, this mechanism was deduced from the well-known reverse reaction: oxazolidine hydrolysis[13] (Scheme 1). Therefore the stereodirecting



Scheme 1.

step is the intramolecular addition of the hydroxy group onto the iminium ion.

We report here that kinetic control of the diastereodifferentiation can operate when aromatic aldehydes are substituted by electron-withdrawing groups. Such substituents enhance the rate of the forward reaction, which formally involves two successive nucleophilic attacks at the benzylic carbon atom[14] and may also retard the reverse reaction, which is responsible for the unwanted equilibration (see Scheme 1).

RESULTS

Benzaldehyde and *p*-methoxybenzaldehyde reacted with (−)-ephedrine yielding the (2*S*)-isomers **1** as the major products (90%) whatever the reaction time employed (solvent: $CHCl_3$ or MeOH). However with *p*-cyano and *p*-nitrobenzaldehydes (solvent: $CHCl_3$, T = 0° or 20°) both isomers **1** and **2** appeared in a 50/50 ratio at the beginning (extent of reaction: 10%) and, as for benzaldehyde and *p*-methoxybenzaldehyde, isomers **1** were the major products (85%) at the end of the reaction.

Configurations were assigned by ^{1}H-NMR (Table 1): H on C-2 and on C-5 are more shielded[9a] by the aromatic ring substituents in isomers **1**.

When the condensation took place in methanol instead of chloroform, the observed steric course was completely different: only isomers **2** (with *p*-cyano and

† Previous part of this series, Ref. 1.

Table 1. ^{1}H-NMR data of oxazolidines deriving from (−)-ephedrine (solvent: $CDCl_3$)

X	Isomer	C-2-H[a]	C-5-H[b]
H	1	4.70	5.13
H	2	5.35	5.58
CN	1	4.58	5.15
CN	2	5.35	5.55
NO_2	1	4.82	5.22
NO_2	2	5.43	5.59
MeO	1	4.60	5.08
MeO	2	5.30	5.57
Br	1	4.64	5.12
Br	2	5.15	5.37

[a] Singlet.
[b] Doublet (1: J = 8 Hz; 2: J = 6 Hz).

p-nitrobenzaldehydes) showed up at the first stage of the reaction. As above, isomers **1** predominated in the final products.

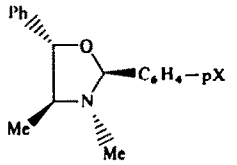
The above solvent effect prompted us to reinvestigate Neelakantan's disputed experiment:[2,3] condensation of (−)-ephedrine with *p*-bromobenzaldehyde in absolute *ethanol* was claimed to afford the (2*R*)-isomer **2**. Thus we repeated Neelakantan's work and observed that structure **1** (X = Br) should indeed be attributed to the resulting oxazolidine.[10] However isomer **2** (X = Br) could be isolated under carefully controlled conditions when the condensation took place in aqueous ethanol. These two isomers differ by their melting points, optical rotations (see experimental) and ^{1}H-NMR spectra (Table 1). The ^{13}C-NMR data (solvent: C_6D_6) also agreed with these assignments: the methyl groups on C-4 and N-3 respectively appeared at 8.9 and 33.1 ppm in isomer **2** (X = Br) whereas they appeared at 15.3 and 35.7 ppm in isomers **1** (X = H, CN, NO_2, OMe and Br); these shieldings bear out the *cis* relationship between the methyl groups.

Isomerization of the (2*R*)-oxazolidine **2** (X = Br) to the (2*S*)-compound **1** occurred in solution, giving rise to a thermodynamic mixture of both isomers (**1**/**2** = 87/13). It was already reported that the oxazolidine part of atisine is prone to isomerization in methanol without any added catalyst.[15] We noticed that this isomerization also occurred at room temperature in less polar solvents (benzene, dioxane), giving clear indication that the ring opening is unusually favoured.

These results therefore confirm that a (2*R*)-oxazolidine can be obtained in an alcoholic medium; nevertheless Neelakantan's experimental conditions were not the most appropriate and it is likely that this fortuitous result was due only to the lower solubility of the (2*R*)-compound compared to the (2*S*)-isomer; the single crystal which was then submitted to the X-ray analysis[3] was not representative of the dissolved material.[10]

The pure isomers **1** can be conveniently obtained from the thermodynamic mixtures, where they are contaminated by only minor amounts of **2**, by a single crystallization from boiling ethanol.

With the aim of strengthening the mechanistic interpretations (*vide infra*), (+)-pseudoephedrine and *p*-cyanobenzaldehyde were condensed together. In accordance with earlier results[9,11] only isomer **3** was isolated after reaction under the usual (thermodynamic) conditions. To follow the kinetic course of this condensation, the chemical evolution of $CDCl_3$ and CD_3OD solutions of the reactants was monitored by ^{1}H-NMR, in the preceding experiments. Here again isomers **3** and **4** appeared in a 50/50 ratio in $CHCl_3$ at the beginning of the reaction. A difference between the behaviour of (−)-ephedrine and (+)-pseudoephedrine was visible in MeOH: at the beginning of the reaction involving pseudoephedrine and *p*-cyanobenzaldehyde, isomers **3** and **4** appeared in a 75/25 (**3**/**4**) ratio (extent of reaction 10%) instead of a 0/100 ratio for the corresponding **1**/**2** pair.



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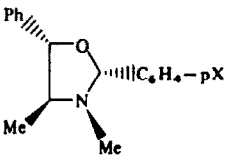

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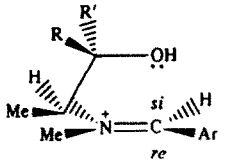
The ^{1}H-NMR features of isomers **3** and **4** agreed with previous results;[9a] the resonances of C-2-H (s) and C-5-H (d = 9 Hz and 6 Hz for **3** and **4** respectively) were at 4.97 (**3**)/5.50 (**4**) ppm and at 4.72 (**3**)/4.66 (**4**) ppm respectively.

DISCUSSION

The results described above clearly show that the observed diastereoselectivities so far reported were the result of thermodynamic control.

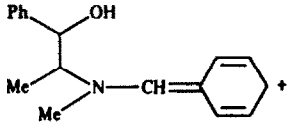
The absence of kinetic stereoselectivity in chloroform can be rationalized in the following way. Dreiding models show that, owing to the planarity of the prochiral sp^2 carbon, steric hindrance is nearly the same for the addition onto the *re* or onto the *si* diastereofaces of the iminium ion intermediate **5**. The same argument applies to the pseudoephedrine-derived intermediate **6**, which also leads to a nonstereoselective ring closure.



5 R = Ph, R' = H
6 R = H, R' = Ph

Most probably, intermediates **5** and **6** show an *E* configuration; however the same interpretation is also valid with *Z* double bond configurations.

Actually cyclization of such iminium ions is a disfavored *5-Endo-Trig* process, according to Baldwin's rules;[20] in the case of benzaldehydes, contribution of structure **7** would allow the favored *5-Exo-Trig* ring closure.



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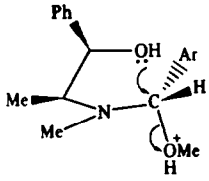
On the other hand, diastereodifferentiation occurred in methanol solution. The stereoselective ring closure leading to the kinetic product could be ascribed to nucleophilic participation of the solvent which adds without stereoselectivity onto the *re* and the *si* faces of the iminium intermediate **5** (the powerful electrophilicity of iminium ions is well documented);[16] the stereoisomeric adduct **8** arising from the addition onto the *si* diastereoface is better suited for cyclization as it exhibits fewer interactions between the aryl groups, as the reacting carbon atom is no longer planar in this intermediate.



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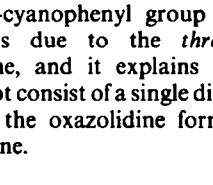
The monitoring of a dioxan solution of either isomer **1** or **2** (X = Br) by ultraviolet spectroscopy revealed the appearance of a band at 258 nm. This band was not produced in a similar ethanolic solution. The 258 nm absorption can be attributed to the iminium intermediate **5** as the iminium salt **9** (prepared according to standard procedures)[18] showed the same electronic transition.

$$HOCHPh—CHMe—\overset{+}{N}Me{=}CH—C_6H_4—p\text{-}Br \quad ClO_4^- \quad \mathbf{9}$$

This result gives strong evidence for solvent addition onto the intermediate iminium ion during formation or isomerization of oxazolidines in alcoholic medium. An analogous ring closure is well documented in the aldose acetal series.[17] The reaction is much slower in CD_3OD than in $CDCl_3$ (T = 20°); although this fact agrees with the above explanation, it could merely be due to the formation of the unreactive acetals in the alcoholic solvent.

In the methanol adduct intermediate **10** derived from pseudoephedrine, it would be pointed out that steric hindrance between aryl groups is still reduced (compared with the other intermediate resulting from methanol addition onto the *si* face of the iminium intermediate **6**) but there is here a 1,3 interaction between the *p*-cyanophenyl group and the methyl group. This is due to the *threo* structure of pseudoephedrine, and it explains why the kinetic product does not consist of a single diastereoisomer, as in the case of the oxazolidine formation from the *erythro*-ephedrine.



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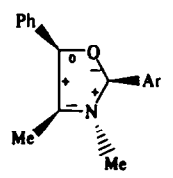
The greater thermodynamic stability of the (2*S*)-isomers **1** and **3** compared to the (2*R*)-isomers **2** and **4** respectively, can be understood by looking at the



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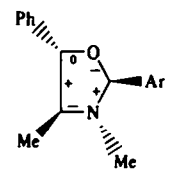

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Fig. 1. Structures of oxazolidines **1** and **3** (Ar = *p*-Br–C_6H_4) resulting from condensation of *p*-bromobenzaldehyde with ephedrine and pseudoephedrine respectively.

envelope conformations shown by their X-ray analysis.[7,10] The torsion angle notation[19] (Fig. 1) is indicative of equatorial geometries for every substituent in **1** and **3** but one: the C-5 phenyl group whose position is quasiequatorial in oxazolidine **3** (Ar = *p*-Br—C_6H_4) and quasiaxial in the isomer **1** (Ar = *p*-Br—C_6H_4). In both these cases the C-2 aromatic substituent takes an equatorial position.

Clearly the nature of the asymmetric induction during oxazolidine formation is solvent-dependent, and all the stereoselective cyclizations reported so far are thermodynamically controlled. It is hoped that these results will finally settle a long-standing controversy.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on Jeol C 60 HL and Jeol FX 90 Q spectrometers at 35°; chemical shifts are reported in ppm (δ). Corresponding resonances are given in the same order for all the oxazolidines mentioned above; unless otherwise stated, the J coupling constants (Hz) are the same as those shown by compound **1** (X = H). UV spectra were carried out on a Beckman DK-2A spectrophotometer. Optical rotations were determined with a Perkin Elmer 141 polarimeter (benzene solution). Satisfactory analytical data (±0.3% for C, H and N) were obtained for all new compounds indicated by a molecular formula.

Oxazolidine formation

The aromatic aldehyde (2.4 mmol) was allowed to react with (−)-ephedrine or (+)-pseudoephedrine (2.4 mmol) in $CDCl_3$ or CD_3OD (5 ml) with sufficient 5A molecular sieves to fill the whole solution. Aliquot samples were analyzed over a period of 48 hr. Removal of the solvent and crystallization from methanol gave pure isomers **1** and **3** in 70–80% yield.

2S,5R - *Diphenyl* - 3,4S - *dimethyloxazolidine* (**1**; X = H)—m.p. 68°. $[\alpha]_D^{20} = -50.5°$ (c 1.5). ^{1}H-NMR ($CDCl_3$) 0.75 (d, J = 7, C—CH_3), 2.16 (s, N—CH_3), 2.93 (m, C-4-H), 4.70 (s, C-2-H), 5.13 (d, J = 8, C-5-H). ^{13}C-NMR (C_6D_6) 15.3 (C-$\underline{C}H_3$), 35.7 (N-CH_3), 64.1 (C-4), 82.6 (C-5), 99.1 (C-2).

2S - p - *Cyanophenyl* - 5R - *phenyl* - 3,4S - *dimethyloxazolidine* (**1**; X = CN)—m.p. 112°. $[\alpha]_D^{20} = -37.3°$ (c 1.5). ^{1}H-NMR ($CDCl_3$) 0.76, 2.01, 3.01, 4.70, 5.13. ^{13}C-NMR (C_6D_6) 15.3, 35.7, 64.1, 82.9, 97.8. $C_{18}H_{18}N_2O$.

2S - p - *Nitrophenyl* - 5R - *phenyl* - 3,4S - *dimethyloxazolidine* (**1**; X = NO_2)—m.p. 100°. $[\alpha]_D^{20} = -31.9°$ (c 1.5). ^{1}H-NMR ($CDCl_3$) 0.76, 2.21, 3.00, 4.82, 5.22. ^{13}C-NMR (C_6D_6) 15.3, 35.7, 64.1, 82.9, 97.8. $C_{17}H_{18}N_2O_3$.

2S - p - *Bromophenyl* - 5R - *phenyl* - 3,4S - *dimethyloxazolidine* (**1**; X = Br)—m.p. 90°. $[\alpha]_D^{20} = -27.8°$ (c 1.5). ^{1}H-NMR ($CDCl_3$) 0.75, 2.14, 2.96, 4.64, 5.12. ^{13}C-NMR (C_6D_6) 15.3, 35.6, 64.1, 82.7, 98.2. $C_{17}H_{18}NOBr$.

2S - p - *Methoxyphenyl* - 5R - *phenyl* - 3,4S - *dimethyloxazolidine* (**1**; X = MeO)—m.p. 86°. $[\alpha]_D^{20} = -38.3°$ (c 1.5). ^{1}H-NMR ($CDCl_3$) 0.76, 2.13, 2.91, 4.60, 5.08. ^{13}C-NMR (C_6D_6) 15.3, 35.7, 54.8 (MeO), 64.1, 82.5, 98.9. $C_{18}H_{21}NO_2$.

2S-p-*Cyanophenyl*-5S-*phenyl*-3,4S-*dimethyloxazolidine* (**3**; X = CN)—m.p. 63° $[\alpha]_D^{20} = +72.3°$ (c 1.5). ^{1}H-NMR ($CDCl_3$) 1.18 (d, J = 6), 2.18, 2.60, 4.72 (d, J = 9), 4.97. ^{13}C-NMR 14.2, 34.9, 68.7, 86.7, 98.2. $C_{19}H_{18}N_2O$.

2R-p-*Bromophenyl*-5R-*phenyl*-3,4S-*dimethyloxazolidine* (**2**; X = Br)—*p*-Bromobenzaldehyde (0.44 g) and (−)-ephedrine (0.40 g) were dissolved in aqueous ethanol (5:95, 5 ml); a spontaneous crystallization soon occurred when the solution was kept at room temp and the pure oxazolidine (**2**; X = Br) was isolated (0.25 g) after 3.5 hr. M.p. 115°. $[\alpha]_D^{20} = -78.0°$ (c 1.5). ^{1}H-NMR ($CDCl_3$) 0.53, 1.94, 3.31, 5.15, 5.37. ^{13}C-NMR (C_6D_6) 8.9, 33.1, 61.3, 82.0, 94.6. $C_{17}H_{18}NOBr$.

p-*Bromobenzylidene*-N-*methyl*-N-[2-(1-*phenyl*-1-*hydroxy*)*propyl*]*ammonium perchlorate* (**9**)

10% Perchloric acid (3 ml) was added to the stirred oxazolidine **1** (X = Br) (1 g) in ether (17 ml). The white precipitate was washed with Et_2O and crystalized from Et_2O–MeCN. 1.2 g, m.p. 190–192°. UV (dioxane) 258 nm (10790). $C_{17}H_{19}NO_5ClBr$.

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