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# Regio- and Stereoselective Epoxide Ring Opening Reactions of 4,5-Epoxy-2,3,4,5-tetrahydro-1-benzoxepines with Secondary Amines

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Abstract : cis-amino alcohols 1 were formed by regio- and stereoselective epoxide ring opening reactions of 4,5-epoxy-2,3,4,5-tetrahydro-1-benzoxepines 5 with secondary amines.

With our continued interest in the study of molecules which incorporates a 'Phenethylamino' group in a rigid frame work[1], the synthesis of cis- and trans-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols was carried out on account of their marked pharmacological effects[2]. Although the synthesis of trans-4-amino-2,3,4,5-tetrahydro-1-benzoxepin -5-ols was achieved stereoselectively in two steps from acetamido ketones, the corresponding cis-isomer was isolated by alkaline hydrolysis of cis-acetamido alcohol obtained by crystallization of a mixture of cis- and trans-acetamido alcohols[2]. A route for the stereoselective synthesis of cis-amino alcohols was therefore desired. The present paper discusses regio- and stereoselective synthesis of the regio-isomeric cis-amino alcohols 1 by epoxide ring opening of 4,5-epoxy-2,3,4,5-tetrahydro-1-benzoxepines with secondary amines.

A variety of β-hydroxylamine and their equivalents have been synthesised by reactions of epoxides with Nitrogen nucleophiles. The role of alumina[3] and acidic or basic zeolites[4,5] in regioselective oxirane opening reactions has already been demonstrated. The dramatic effects of metal salts on the regioselectivity of aminolysis of styrene oxide have recently been described[6]. Related work on the regioselective uncatalyzed ring opening of hetaryloxides with nitrogen nucleophiles has also been reported[7]. The use of lithium aluminium amides [Li Al$(NHR)_4$] for regioselective opening of aryl oxides has recently been published[8].

2,3-Dihydro-1-benzoxep-4-ene 6 needed as starting materials for the synthesis of epoxides (5) were obtained as oily liquids by $NaBH_4$ reduction of the corres-

TABLE. The Ratio of cis- and trans-amino alcohols (1 & 2) from Epoxides (5) with Secondary Amines

| Entry | Epoxide | Substrate (HN ) | Product[f] Ratio | | Yield (%) | M.p.[e] (°C) |
|---|---|---|---|---|---|---|
| | | | cis (1) J = 2Hz | trans (2) J = 8Hz | | |
| 1 | 5a | Pyrrolidine | 95 | 05 | 70 | oil |
| 2 | 5a | Piperidine | 95 | 05 | 65 | oil |
| 3 | 5a | $N^4$-methyl piperazine | 100 | 00 | 75 | oil |
| 4 | 5a | Morpholine | 92 | 08 | 65 | oil |
| 5 | 5b | Pyrrolidine | 93 | 07 | 60 | oil |
| 6 | 5b | Piperidine | 100 | 00 | 65 | oil |
| 7 | 5b | $N^4$-methyl piperazine | 90 | 10 | 75 | oil |
| 8 | 5b | Morpholine | 85 | 15 | 67 | oil |
| 9 | 5c | Pyrrolidine | 98 | 02 | 62 | oil |
| 10 | 5c | Piperidine | 100 | 00 | 72 | oil |
| 11 | 5c | $N^4$-methyl piperazine | 100 | 00 | 78 | oil |
| 12 | 5c | Morpholine | 100 | 00 | 68 | oil |
| 13 | 5d | Pyrrolidine | 75 | 25 | 73 | 110-112 |
| 14 | 5d | Piperidine | 90 | 10 | 55 | 105-108 |
| 15 | 5d | $N^4$-methyl piperazine | 95 | 05 | 60 | 92-94 |
| 16 | 5d | Morpholine | 100 | 00 | 69 | 104 |

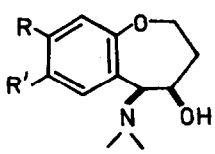
(e) Crystallized with benzene-hexane.

(f) Structure confirmed by I.R., $^1H$ NMR, MS and elemental (C,H,N) analysis.

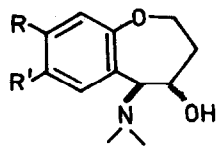
ponding 3,4-dihydro-1-(2H)-benzoxepin-5-ones[2,9] to 2,3,4,5-tetrahydro-1-benzoxepin-5-ols followed by their reaction with $PBr_3$-$CHCl_3$ at -10°C (84-91% yield)[10]. 4,5-Epoxy-2,3,4,5-tetrahydro-1-benzoxepines 5 were obtained by reaction of 6 with MCPBA in dry $CHCl_3$ and purified by column chromatography ($SiO_2$, $CHCl_3$; oil). Epoxide (5) on refluxing with secondary amines in methanol for 4 h gave cis-5-t-amino-2,3,4,5-tetrahydro-1-benzoxepin-4-ols 1 as the major product (Table).

The striking regio- and stereoselectivity in the ring opening reaction of epoxides (5) with secondary amines to form cis-amino alcohol (1) in which

the equatorial 5-H signal in $^1$H-NMR ($CDCl_3$) appeared at 4.8 δ ($J_{4a,5e}$ = 2Hz) can be explained by the endo attack of the nucleophilic nitrogen atom of secondary amines at the less hindered side of epoxides (5) (Fig.1) resulting in the formation of the thermodynamically favoured[2] cis-amino alcohol (1) having a twist-chair



1



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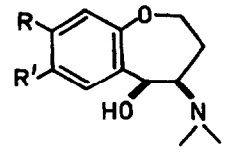

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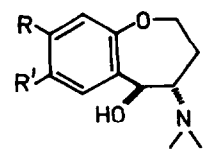

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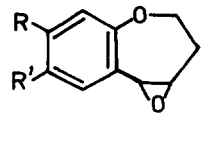

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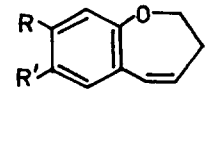

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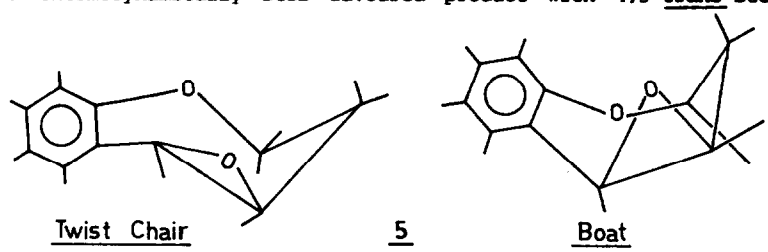
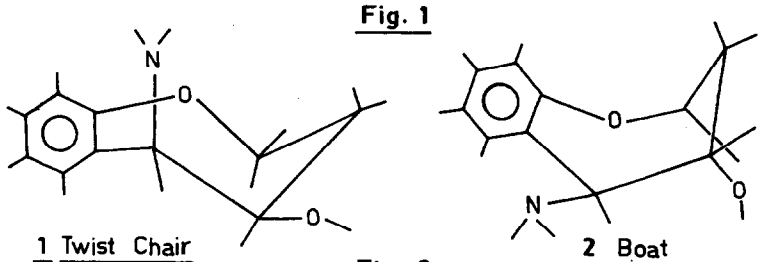
(a) R = R′ = H (b) R = H , R′ = Me
(c) R = H , R′ = OMe (d) R = R′ = Me

conformation with 4,5-cis-stereochemistry (Fig.2). The trans-amino alcohol (2), the thermodynamically less favoured product with 4,5-trans-stereochemistry



Twist Chair 5 Boat

Fig. 1



1 Twist Chair 2 Boat

Fig. 2

in a boat conformation (Fig.2) was formed as the minor product in some of the epoxide ring opening reactions (Entries 1,2,4,5,7-9,13-15).

The composition of trans-amino alcohol 2 was monitored by $^1$H-NMR. The 5-H signal in 2 appeared at 4.6-4.7 δ (d, $J_{4a,5a}$ = 8.00 Hz). The formation of isomeric trans-amino alcohol 4 was ruled out as no marked deshielding of the aromatic 6-H due to field effect of 5-OH group was observed in $^1$H-NMR[2].

The formation of any isomeric amino alcohol (3) was also ruled out by its independent synthesis from α-amino-ketones by LAH or $NaBH_4$ reduction[9,11].

Comparable oxirane ring opening reactions of epoxy benzopyrans with secondary amines but with trans opening have been reported.[12] The regioselectivity observed in these epoxide ring opening reactions[9] as well as in related examples[6,8] is due to expected inversion of configuration ($SN^2$) at the reacting carbon atom. Thus the conformations of benzoannelated oxepines[2,13] play crucial role in directing the attack of the nucleophile in epoxide opening reactions such that retention of configuration is observed.

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11. cis-4-Morpholino-7,8-Dimethyl-2,3,4,5-tetrahydro-1-benzoxepin-5-ols 3d (N = $N^4$-morpholino) had m.p. 121°C. It was different in its m.p.; m.m.p. & GLC with cis amino alcohol 1d (N = $N^4$-morpholino-, entry 16).
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