Stereospecific Synthesis of *N*-(1-Phenylethyl)-2,4,5-triphenyloxazolidines

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Treatment of the diastereoisomeric *N*-(1-phenylethyl)-1,2-diphenyl-2-aminoethanols with benzaldehyde yields stereospecifically *N*-(1-phenylethyl)-2,4,5-triphenyloxazolidines with four chiral centers. The configurations of these oxazolidines are established through their ring-opening reactions with methylmagnesium iodide and subsequent oxidation with lead tetracetate.

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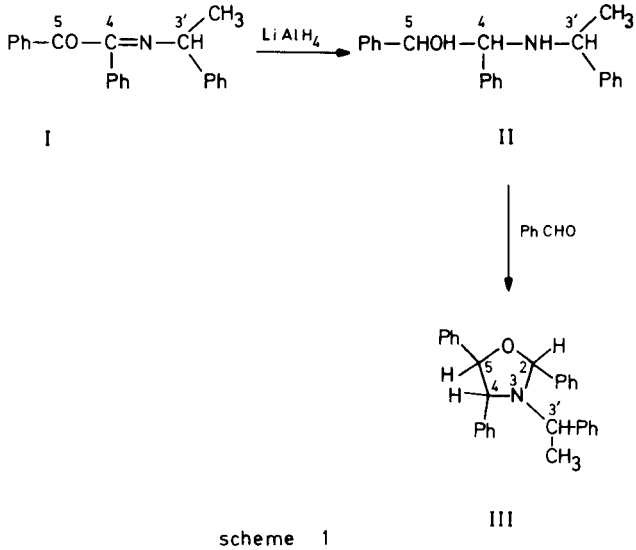
Introduction.

A method for the stereoselective synthesis of β-aminoalcohols having three chiral centers through reduction of the related benzylmonoimines has been previously reported (1). These aminoalcohols have been condensed with benzaldehyde by a well known reaction (2). In this way a stereospecific synthesis of oxazolidines having four resolved chiral centers has been achieved. The process for the case in which all aryl groups are phenyl (3) is summarized in Scheme 1.



I II III

scheme 1

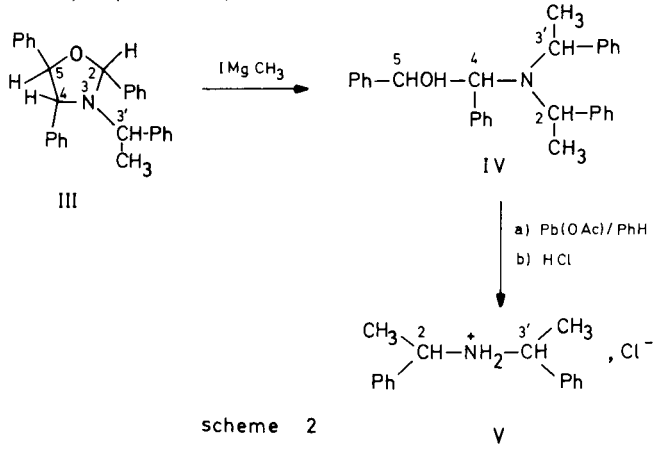
It has been conclusively shown (4) that the configurations of carbon atoms 4 and 5 are retained in going from the aminoalcohol to the oxazolidine. Another important feature is that formation of chiral center 2 of the oxazolidine ring, one of the two possible stereoisomers is obtained predominantly. This quite general result is consistent with the mechanism of the process as proposed by Beckett (4c).

In the present paper the stereochemistry of the ring closure reaction of II to III is discussed. The absolute configurations of oxazolidines are established via their reactions with methylmagnesium iodide.

Results.

Synthesis of II and assignment of its configuration have been reported previously (1b). Starting with 3′*R*-I, two major aminoalcohols (5*R*, 4*R*, 3′*R*)-II, **1**, and (5*S*, 4*S*, 3′*R*)-II, **2**, were isolated, together with two minor products to which configurations (5*R*, 4*S*, 3′*R*)-II, **3**, and (5*S*, 4*R*, 3′*R*)-II, **4**, were assigned. Independent synthesis of these minor aminoalcohols through opening of *trans*-stilbene oxide with (±)-1-phenylethylamine confirmed the proposed assignment (5). As an additional test the imine 3′*S*-I was reduced and the major aminoalcohols (5*S*, 4*S*, 3′*S*)-II and (5*S*, 4*R*, 3′*S*)-II were isolated. The results obtained from these aminoalcohols were "enantiomeric" to those obtained when starting with 3′*R*-I.

Aminoalcohols **1**, **2**, **3** and **4** were treated with benzaldehyde. In the obtained oxazolidines **5**, **6**, **7** and **8** only the configurations of C-2 remains to be known. Then III were treated with methylmagnesium iodide (4a) and the resulting tertiary ethanolamines (6), IV, were subjected to degradation with lead tetracetate (7) to yield a secondary amine, V (Scheme 2).



III IV V

scheme 2

Table I

Configuration of C-2 in the Oxazolidine Ring

II	III	IV				V			
Compound	Compound	Compound	^{1}H-NMR (a)	Mp	$[\alpha]_{578}^{25}$	Compound	$[\alpha]_{589}^{25}$ (EtOH)	Configuration 2-3	$[\alpha]_{589}^{25}$ lit (7)
1	**5**	(b)							
2	**6**	**9**	δ 4.91 (d, J = 10 Hz, H-*a*); 4.05 (d, J = 10 Hz, H-*b*) 4.36 (q, J = 7.0 Hz, H-*c*); 1.58 (d, J = 7.0 Hz, CH_3); 4.0 (OH, overlapped)	174-173°	+ 160.5 (EtOH)	**10**	+ 71.08	RR	+ 73.42
3	**7** (c)	**11** (d)	δ 4.9 (H-*a*); 3.7 (H-*b*); $J_{a,b}$ = 3.0 Hz; 1.6 (CH_3)				+ 65.14 (e)	RR	+ 73.42
		12 (d)	δ 4.6 (H-*a*); 4.1 (H-*b*); $J_{a,b}$ = 3.0 Hz; 1.3 (CH_3)					RS	0
		13	δ 4.66 (dd, J = 3.0 Hz, H-*a*); 4.06 (d, J = 3.0 Hz, H-*b*); 4.23 (q, J = 7.0 Hz, H-*c*); 1.53 (d, J = 7.0 Hz, CH_3); 2.0 (d, J = 2 Hz, OH).	146-147°	+ 72.25 (acetone)	**10**	+ 72.04	RR	+ 73.42
4	**8** (f)	**14** (g)	d 1.80 (d, J = 2 Hz, OH)					RS (h)	0

(a) 60 MHz. (b) Compound **5** was recovered unaltered even when forcing the reactions conditions (boiling THF for 20 hours). (c) Compound **7** yields a mixture of compounds IV in the approximate ratio **11**:**12** ≈ 5:1. (d) Signals were read on the spectrum of the mixture. (e) Rotatory power of the reaction mixture. (f) Compound **8** yields a mixture of compounds IV in the approximate ratio 1:1. (g) Product was not isolated, see experimental. (h) By exclusion, taking into account the configuration of **13**.

Since the configuration of C-3′ is known a comparison of the rotatory power of V with that reported in the litterature (8) allows assignment of configuration to the 1-phenylethyl residue formed by ring opening and consequently to the oxazolidine C-2.

The results of this whole process are summarized in Table I.

Discussion.

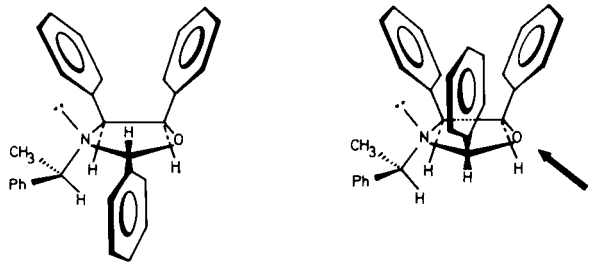
The configuration assignment to C-2 is based on the generally accepted assumption that the first step in the reaction of oxazolidines with Grignard reagents is the coordination of the organometallic to the ring oxygen atom (4a). According to this, oxazolidine **6**, obtained from (5*S*, 4*S*, 3′*R*)-II should have the 2*R* configuration since in that case the conformation (9) shown in Scheme 3 will allow easy coordination of the Grignard reagent to the unhindered top side of the ring. The complete stereoselectivity observed for the reaction of **6** with methylmagnesium iodide is thus accounted for.

The lack of reactivity of **5** obtained from (5*R*, 4*R*, 3′*R*)-II could not be accounted for if a 2*S* configuration was present, since then a practically unhindered face available for attack would allow an easy reaction (Scheme 3). On the contrary, the alternating arrangement of bulky groups for the 2*R*-**5** oxazolidine would hinder both faces of the ring and prevents coordination.

On this basis configuration (2*R*, 4*R* 5*R*, 3′*R*) is assigned to **5** and (2*R*, 4*S*, 5*S*, 3′*R*) to **6**.

scheme 3

Assignment of configuration to **7** and **8** is less clear-cut. Oxazolidine **7** originated from (5*R*, 4*S*, 3′*R*)-II. The reactive conformations for a 2*R*-**7** and 2*S*-**7** are shown in Scheme 4. The latter would have the botton face very accesible to the reagents attack. The stereochemical result



2R-7 2S-7

scheme 4

would be the formation of only one tertiary aminoalcohol. The formation of two alcoholamines **11** and **12** can only be accounted for by assuming a 2*R* configuration for **7**. In fact in the reactive conformation of 2*R*-**7** shown in Scheme 4 neither side of the ring is highly hindered. The sequence O, C-5, C-4 on the bottom face and the sequence O, C-2, N on the top face limit slightly hindered zones available for reagent's attack. It is on this basis that the configuration (2*R*, 4*S*, 5*R*, 3′*R*) is assigned to **7**.

A similar analysis applies to **8** which originates from (5*S*, 4*R*, 3′*R*)-II. As 2*R*-**8** and 2*S*-**8**, and obviously their reactive conformations, are enantiomeric with 2*S*-**7** and 2*R*-**7** as far as the oxazolidine ring is concerned the configuration (2*S*, 4*R*, 5*S*, 3′*R*) is derived for **8**.

The foregoing analysis is based on the assumption that only unhindered faces of the oxazolidines ring are easily attacked by the organometallic reagent. These unhindered faces have always a three atom sequence in which oxygen is always included an which has no bulky groups attached to the side of attack.

The relative degree of stereoselectivity obtained in the ring opening reactions of **7** and **8** cannot be accounted for as yet.

EXPERIMENTAL

Synthesis of *N*-(1-phenylethyl)-2,4,5-triphenyloxazolidines (III).

They were obtained by reaction of the isomeric aminoalcohols II with benzaldehyde. A 15% excess of the latter was used. Reaction temperature was maintained at 160-170°. ^{1}H-nmr spectra of the crude reaction products showed the presence of only oxazolidine, benzaldehyde and benzoic acid.

(2*R*, 4*R*, 5*R*, 3′*R*)-III (**5**).

This was prepared from aminoalcohol **1** (810 mg, 2.55 mmoles) by heating for nine hours. The crude reaction product was chromatographed on a silica gel (24 g) column using benzene as eluant. The head fraction was pure oxazolidine (795 mg). The clear oil could not be crystallized, yield 77%. ^{1}H nmr (deuteriochloroform) δ 1.23 (d, J = 7.0 Hz, CH_3); 3.73 (d, J = 8.0 Hz, Ph-C*H*-N); 3.90 (q, J = 7.0 Hz, Me-C*H*-Ph); 4.73 (d, J = 8.0 Hz, Ph-C*H*-O); 5.56 (s, N-C*H*Ph-O); 6.60-7.60 (aromatic). $[\alpha]^{25}_{546}$ + 15.96 (acetone, 2.50 g/100 cc).

Anal. Calcd. for $C_{29}H_{27}NO$: C, 85.88; H, 6.71; N, 3.45. Found: C, 86.01; H, 6.73; N, 3.41.

Enantiomeric Oxazolidine (2*S*, 4*S*, 5*S*, 3′*S*)-III.

This compound had $[\alpha]^{25}_{546}$ - 16.44 (acetone, 2.50 g/100 cc).

(2*R*, 4*S*, 5*S*, 3′*R*)-III (**6**).

This compound was prepared from aminoalcohol, **2**, (1480 mg, 4.67) mmoles) during 9 hours. The crude reaction mixture was diluted with ethanol and a white solid precipitated. Two recrystallizations from ethanol yielded pure oxazolidine (1470 mg), mp 82-83°, yield, 77%. ^{1}H nmr (deuteriochloroform): δ 1.12 (d, J = 7.0 Hz, CH_3); 3.85 (d, J = 8.0 Hz, PhC*H*-N); 3.96 (q, J = 7.0 Hz, PhC*H*-Me); 4.80 (d, J = 8.0 Hz, Ph-C*H*-O); 5.53 (s, N-C*H*Ph-O); 6.87-7.76 (aromatic); $[\alpha]^{25}_{546}$ - 47.23 (acetone, 0.42 g/100 cc).

Anal. Found: C, 85.86; H, 6.70; N, 3.49.

Enantiomeric Oxazolidine (2*S*, 4*R*, 5*R*, 3′*S*)-III.

This compound had $[\alpha]^{25}_{546}$ + 47.45 (acetone, 2.66 g/100 cc).

(2*R*, 4*S*, 5*R*, 3′*R*)-III (**7**).

This compound was obtained from the aminoalcohol **3** (1200 mg, 3.78 mmoles) by heating for 12 hours. From the crude reaction mixture after dilution with ethanol a white solid precipitated. Recrystallization from ethanol yielded pure oxazolidine (1196 mg), mp 109-110°, yield, 78%; ^{1}H nmr (deuteriochloroform): δ 1.20 (d, J = 7.0 Hz, CH_3); 4.03 (q, J = 7.0 Hz, PhC*H*-Me); 4.50 (d, J = 8.0 Hz, PhC*H*-N); 5.23 (d, J = 8.0 Hz, Ph-C*H*-O); 5.33 (s, N-C*H*Ph-O); 6.87-7.76 (aromatic); $[a]^{25}_{546}$ - 93.43 (acetone, 0.18 g/100 cc).

Anal. Found: C, 85.71; H, 6.69; N, 3.50.

(2*S*, 4*R*, 5*S*, 3′*R*)-III (**8**).

This compound was prepared from aminoalcohol **4** (700 mg, 2.21 mmoles) by heating for 5 hours. From the crude reaction mixture by dilution with ethanol a white precipitate was obtained. Recrystallization from ethanol yielded the pure oxazolidine (715 mg), mp 100-101°. yield 85%; ^{1}H nmr (deuteriochloroform): δ 1.13 (d, J = 7.0 Hz, CH_3); 4.07 (q, J = 7.0 Hz, PhC*H*-Me); 4.43 (d, J = 8.0 Hz, PhC*H*-N); 5.13 (d, J = 8.0 Hz, Ph-C*H*-O); 5.50 (s, N-C*H*Ph-O); 6.83-7.60 (aromatic); $[a]^{25}_{546}$ - 51.09 (acetone).

Anal. Found: C, 85.80; H, 6.86; N, 3.56.

Reaction of Oxazolidines with Methylmagnesium Iodide.

The reactions were carried out in the molar ratio oxazolidine: MeMgI ~ 1:4 in ether for 10 hours. After hydrolysis (ammonium chloride), extraction with ether and drying (magnesium sulfide), the crude reaction mixture was separated and analyzed.

Ring Opening Reaction of **6**.

From oxazolidine **6** (1000 mg, 2.40 mmoles) **9** was obtained (900 mg). It was crystallized from ethanol, yield 87%. See Table I for ^{1}H nmr and other properties.

Anal. Calcd. for $C_{30}H_{31}NO$: C, 85.64; H, 7.65; N, 3.69. Found: C, 85.50; H, 7.36; N, 3.32.

The enantiomeric aminoalcohol had $[\alpha]^{28}_{589}$ - 159.9 (acetone, 0.33 g /100 cc).

Ring Opening Reaction of **7**.

From **7** (600 mg, 1.48 mmoles) 620 mg of crude reaction product separated. The ^{1}H nmr spectra showed the presence of the two possible isomeric aminoalchols. Differentiating signals taken for analysis were read directly from the spectrum of the mixture and are collected in Table I. All isolation attempts of the major isomer either by crystallization or by column chromatography failed. On heating partial decomposition of the reaction mass with progressive darkening and production of ben-

zaldehyde was detected.

Ring Opening Reaction of **8**.

From **8** (600 mg, 1.48 mmoles) 500 mg of crude reaction product was obtained. The ^1H nmr analysis showed the apparent presence of only one isomer except for the doubling of the coupled signals of the hydroxy proton in a ratio of 1:1. Treatment of the crude reaction product with ethanol yielded **13** (200 mg). Mother liquors were enriched in **14**. Progressive darkening and production of benzaldehyde was also observed. Attempts to isolate **14** either by crystallization or by chromatography failed and increased the decomposition of the product. Spectral and other data are given in Table I.

Anal. Calcd. for **13** Found: C, 85.61; H, 7.68; N, 3.81.

Reaction of *N,N*-bis (1-phenylethyl)-1,2-diphenyl-2-aminoethanols, IV, with Lead Tetracetate.

Compound IV was added to a lead tetracetate suspension in anhydrous benzene with cooling in an ice-bath. A molar ratio of 1:1 was used. The reaction mass was then heated at 50-60° for 5 hours. Lead acetate which was filtered off, anhydrous hydrogen chloride was passed through the resulting benzene solution and the hydrochloride salt which formed was filtered and crystallized several times from ethanol-ether (1:20) until a constant rotatory power were obtained.

Reaction of **9** with Lead Tetracetate.

From **9** (600 mg, 1.42 mmoles), hydrochloride **10** (180 mg, 48.5% yield) was obtained.

The enantiomeric hydrochloride had $[\alpha]_{578}^{28}$ - 73.42 (ethanol, 0.33 g/100 cc).

Reaction of the Mixture **11** + **12** with Lead Tetracetate.

From the mixture (450 mg, 1.11 mmoles) after two recrystallizations a mixture of hydrochlorides (163 mg, 58% yield) was obtained.

Reaction of **13** with Lead Tetracetate.

From **13** (200 mg, 0.47 mmoles) the hydrochloride (63.5 mg. 51% yield) was obtained with constant rotatory power.

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