# PMR SPECTRA AND STEREOCHEMISTRY OF CHIRAL 2-ARYL- AND 2-HETARYLOXAZOLIDINES-1,3

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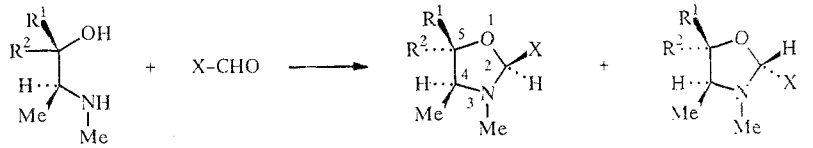
*PMR spectra of 2-aryl- and 2-hetaryloxazolidines-1,3 are studied. A PMR criterion is revealed according to which the absolute configuration of the $C_{(2)}$ atom of the oxazolidine ring can be assigned.*

Chiral substituted 1,3-oxazolidines are mainly prepared by reaction of optically active β-aminoalcohols (ephedrine and its analogs, serine ethers, threonine, etc.) with carbonyl compounds. They are widely used as intermediates in "chiral auxiliary" asymmetric reactions [1-4] and as synthons of biologically active compounds. Furthermore, optically active oxazolidines are convenient subjects for various physicochemical investigations.

The synthesis of oxazolidines from chiral β-aminoalcohols and aldehydes is highly selective. In most instances epimeric oxazolidines differing in absolute configuration at the $C_{(2)}$ atom are formed with an excess of one of them. The substituent on $C_{(2)}$ in the predominant isomer is oriented *cis* relative to both substituents in the 4 and 5 positions (starting with ephedrine) and *cis* relative to the substituent on $C_{(4)}$ (for the pseudoephedrine derivative). We proposed a PMR criterion for determining the absolute configuration of $C_{(2)}$. According to this criterion, a strong-field shift of the 5-H and 2-H signals corresponds to the (2*S*,4*S*,5*R*) diastereomer, Aa, for the ephedrine derivative and (2*S*,4*S*,5*S*), Ba, for the pseudoephedrine derivative.

The PMR spectra of the Aa+Ab and Ba+Bb isomers [(2*S*,4*S*,5*R*) Aa, (2*R*,4*S*,5*R*) Bb, (2*S*,4*S*,5*S*) Ba, (2*R*,4*S*,5*S*) Bb] of the 2-aryl- and 2-hetaryl-1,3-oxazolidines prepared by reaction of the corresponding aldehydes with ephedrine (series A) and pseudoephedrine (series B) are presented in Table 1.




1-9

X = phenyl (1), 4-dimethylaminophenyl (2), 4-nitrophenyl (3), 2-chlorophenyl (4), 2-pyridyl (5), 3-pyridyl (6), 2-thienyl (7), 2-furyl (8), 3,5-di-*tert*-butyl-4-hydroxyphenyl (9). $R^1$ = Ph, $R^2$ = H (A); $R^1$ = H, $R^2$ = Ph (B).

An analysis of the spectra revealed the following features. On going from the Aa to the Ab isomers, the 2-H, 5-H, and 4-H signals in all instances clearly shift to weak field. Furthermore, it turned out for all compounds except one of the 9 isomers that the spin—spin coupling constant (SSCC) $^3J_{(4,Me)}$ insignificantly increases and $^3J_{(4,5)}$ decreases from 8.22 (Aa) to 5.28 Hz (Ab).

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TABLE 1. PMR Spectra of 1-9

| Compound | Isomer | Chemical shifts, δ, ppm | | | | | | | SSCC, J, Hz | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 4-Me | N—Me | 2-H | 4-H | 5-H | Ph | H* | $J_1$** | $J_2$*** |
| 1 | Aa | 0,78 | 0,45 | 4,70 | 2,97 | 5,15 | 7,2...7,4 | | 8,2 | 6,4 |
| | Ab | 0,99 | | 5,33 | 3,65 | 5,58 | 7,2...7,4 | | 5,3 | 6,8 |
| | Ba | 1,28 | 0,19 | 4,96 | 3,53 | 4,77 | 7,2...7,4 | | 8,8 | 6,2 |
| 2 | Aa | 0,77 | 0,68 | 4,42 | 2,92 | 5,10 | 7,2...7,4 | | 8,2 | 6,5 |
| | Ab | — | | 5,27 | — | 5,56 | 7,2...7,4 | | 5,3 | — |
| | Ba | 1,23 | 0,15 | 4,87 | 2,50 | 4,74 | 7,2...7,4 | | 8,8 | 5,9 |
| 3 | Aa | 0,80 | 0,39 | 4,80 | 3,04 | 5,19 | 7,2...7,4 | | 8,2 | 6,5 |
| | Ab | — | | 5,39 | 6,39 | 5,56 | 7,2...7,4 | | 5,3 | — |
| | Ba | 1,22 | 0,29 | 5,06 | 2,61 | 4,77 | 7,2...7,4 | | 8,8 | 6,0 |
| 4 | Aa | 0,79 | 0,09 | 5,28 | 3,04 | 5,19 | 7,2...7,4 | | 8,2 | 4,4 |
| | Ab | 0,98 | | 5,90 | 3,32 | 5,56 | 7,2...7,4 | | 5,3 | 6,8 |
| | Ba | 1,23 | 0,80 | 5,56 | 2,59 | 4,76 | 7,2...7,4 | | 8,8 | 6,0 |
| 5 | Aa | 0,78 | 2,31 | 4,85 | 3,03 | 5,23 | 7,2...7,4 | 7,6...8,6 | 8,2 | 6,5 |
| | Ab | 0,73 | 2,34 | 5,43 | 3,72 | 5,62 | 7,2...7,4 | 7,6...8,6 | 5,3 | 6,7 |
| | Ba | 1,27 | 2,31 | 5,13 | 2,62 | 4,80 | 7,2...7,4 | 7,6...8,6 | 8,8 | 6,0 |
| | Bb | 0,91 | 2,36 | — | — | — | 7,2...7,4 | 7,6...8,6 | | |
| 6 | Aa | 0,79 | 2,20 | 4,75 | 3,01 | 5,17 | 7,2...7,4 | 7,8...8,9 | 8,2 | 6,5 |
| | Ab | 0,73 | 2,27 | 5,35 | 3,72 | 5,57 | 7,2...7,4 | 7,8...8,9 | 5,3 | — |
| | Ba | 1,21 | 2,19 | 4,49 | 2,57 | 4,75 | 7,2...7,4 | 7,8...8,9 | 8,8 | 6,0 |
| | Bb | 0,97 | 2,31 | — | — | — | 7,2...7,4 | 7,8...8,9 | | |
| 7 | Aa | 0,73 | 2,20 | 4,98 | 2,91 | 5,10 | 7,2...7,4 | 8,9...7,4 | 8,2 | — |
| | Ab | 0,75 | 2,28 | 5,63 | 3,38 | 5,46 | 7,2...7,4 | 8,9...7,4 | 5,3 | 6,5 |
| | Ba | 1,20 | 2,30 | 5,29 | 2,53 | 4,71 | 7,2...7,4 | 6,9...7,2 | 8,8 | — |
| | Bb | 1,17 | 2,34 | 5,82 | — | 4,16 | 7,2...7,4 | 6,9...7,2 | 8,2 | 6,0 |
| 8 | Aa | 0,74 | 2,22 | 4,80 | 2,90 | 5,12 | 7,2...7,5 | 6,2...6,5 | 7,9 | — |
| | Ab | 0,69 | 2,28 | 5,53 | 3,59 | 5,46 | 7,2...7,5 | 6,2...6,5 | 5,9 | 6,5 |
| | Ba | 1,21 | 2,31 | 5,08 | 2,50 | 4,73 | 7,2...7,5 | 6,2...6,5 | 8,8 | — |
| | Bb | 1,16 | 2,25 | 5,66 | 3,15 | 4,60 | 7,2...7,5 | 6,2...6,5 | 7,9 | 6,0 |
| | | | | | | | | *t*-Bu | | 6,2 |
| 9 | Aa | 0,83 | 2,45 | 4,62 | 2,78 | 4,74 | 7,2...7,4 | 1,5 | 4,2 | 6,4 |
| | Ab | 0,79 | 1,17 | 5,26 | 2,93 | 5,10 | 7,2...7,4 | 1,5 | 8,8 | 6,4 |
| | Ba | 1,23 | 2,20 | 4,89 | 2,50 | 4,72 | 7,2...7,4 | 1,5 | 8,8 | 6,2 |

*Heterocyclic

**$J_1 = {}^3J_{(4,5)}$

***$J_2 = {}^3J_{(4,Me)}$

Since the formation reaction of oxazolidines is highly selective, we could not in most instances detect the Bb isomer in the reaction mixture. The PMR data of Bb were obtained only for 7 and 8. The 2-H and 4-H signals shift to weak field ($\simeq 0.6$ ppm) and the 5-H to strong field ($\simeq 0.13$ ppm) on going from Ba to Bb.

A comparison of the Aa isomers with the Ba stereoisomers demonstrated that the PMR spectra of 1-9 are peculiar since the 5-H and 2-H signals switch places on going from Aa to Ba. Apparently the weak-field shift of 2-H in the Ba isomer is due to the deshielding effect of ring currents from the *cis* aromatic ring 5-Ph.

The practically identical SSCC $^3J_{(4,5)}$ in the Aa and Ba series suggests that the five-membered ring of these stereoisomers has an identical conformation. The x-ray structures of 2Ba, 5Ba, and 4Aa were solved [5] in order to investigate the conformation of the oxazolidines. Furthermore, the conformations of 2Ba and 5Ba were calculated. According to the x-ray structure analysis, the dihedral angle 4-H—$C_{(4)}$—$C_{(5)}$—5-H, which determines the ring conformation, differs by ~20° in crystalline 2Ba and 5Ba (142.337° for 2Ba and 161.335° for 5Ba). However, they are similar in the free state (119.748° for 2Ba and 128.713° for 5Ba). Moreover, the SSCC $^3J_{(4,5)}$ corresponding to these dihedral angles are similar for both

compounds. The SSCC agrees well with the dihedral angle found from the Williamson—Johnson curve [6]. The dihedral angles for compounds of the Aa and Ab series that were found in this manner suggest that the angle 4-H—$C_{(4)}$—$C_{(5)}$—5-H of Aa is about two times less than the analogous angle of Ab. This is consistent with a large distortion of the oxazolidine ring of Ab compared with Aa. The single exception is 9, which has the bulkiest aromatic substituent on $C_{(2)}$. It was found that $^3J_{(4,5)}$ of 9Aa (4.18 Hz) is almost two times less than that of 9Ab (8.22 Hz). Apparently steric interactions of the substituent on $C_{(2)}$ in 9Aa with the 4-$CH_3$ and 5-Ph groups significantly distort the ring (angle 4-H—$C_{(4)}$—$C_{(5)}$—5-H is $\sim 50 \pm 3°$). However, the same interactions of the substituent in the 2-position of 9Ab with the N—Me group flatten the five-membered ring (angle 4-H—$C_{(4)}$—$C_{(5)}$—5-H is $\sim 30 \pm 3°$). With respect to the Ba—Bb series, the comparative conformations of these isomers cannot be judged from the PMR spectra owing to a lack of data for the Bb isomer.

## LITERATURE CITED


1. I. Fleming and N. Kingdom, *J. Chem. Soc., Chem. Commun.*, 1177 (1987).
2. J. Berlan, Y. Besace, G. Pourcelot, and P. Cresson, *Tetrahedron*, **42**, 4757 (1986).
3. L. Colombo, C. Gennari, G. Poli, and C. Scolartico, *Tetrahedron Lett.*, **44**, 5459 (1985).
4. C. Agami, F. Meinier, and T. Rizk, *Synth. Commun.*, **17**, No. 3, 241 (1978).
5. S. Belyakow, F. Polyak, A. Mishnew, T. Dorofeeva, and G. Zelchan, *Z. Kristallogr.*, in press (1991).
6. K. L. Williamson and W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 4623 (1961).


# SYNTHESIS OF *N*-BENZYLOXYCARBONYL-*N*-METHYLAMINOACIDS FROM OXAZOLIDINE-5-ONE DERIVATIVES


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*Hydrogenolysis of 3-benzyloxycarbonyloxazolidine-5-one and 3-benzyloxycarbonyl-4-benzyloxazolidine-5-one by $Et_3SiH$ in the presence of $F_3CCO_2H$ is demonstrated to be a convenient method for preparing substituted N-methylaminoacids. In contrast with catalytic hydrogenation on Pd/C catalyst, the benzyloxycarbonyl is not removed and the methyl is not lost using this method.*


Natural antibiotics such as actinomycins, etamycins, enniamtins, and others containing the *N*-methylaminoacid residue are widely used for modifying biologically active peptides [1, 2]. Synthetic analogs of oxytocin and vasopressin [3], bradykinin [4], gramicidin [5], and other peptides also contain *N*-methylaminoacids. Heterocyclic derivatives of 1,3-oxazolidine-5-one and pyrroline-2-one [6] are synthesized using *N*-methylaminoacids.

Many synthetic methods for synthesizing *N*-methylaminoacids have been developed (see a previous monograph [7]). A promising method for preparing *N*-substituted-*N*-methylaminoacids is the hydrogenolysis of the corresponding derivatives of 5-oxazolidinones by $Et_3SiH$ in $F_3CCO_2H$ [8]. This method was used to synthesize *N*-methyl-*N*-(9-fluorenylmethyloxycarbonyl)aminoacids, mainly lysine derivatives.

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