Stereochemistry of Ephedrine- and Pseudo-ephedrine-derived Oxazolidines and of Their *N*-Borane Adducts Determined by Nuclear Overhauser Effect Difference Spectroscopy

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Nuclear Overhauser effect difference spectra of 1,3-oxazolidines derived from ephedrine and pseudo-ephedrine and of their *N*-borane adducts allow the configuration at C(2) and N to be assigned.

The highly stereoselective condensations of aldehydes with ephedrines[1,2] are of considerable interest since the oxazolidines thus obtained may play an important role as chiral intermediates for a number of asymmetric transformations.[3] However, the configuration at C(2) of pseudo-ephedrine-derived 1,3-oxazolidines has not been determined, while there is currently controversy over that of the ephedrine-derived 1,3-oxazolidines.[1,2,4,5]

Considering the structure of the 1,3-oxazolidines (**1**) and (**2**) and of their *N*-borane adducts (**3**)—(**5**), nuclear Overhauser effect (n.O.e.) measurements[6] should allow the configuration at C(2) to be assigned unambiguously. For this purpose n.O.e. difference spectra† were obtained with saturation of the ^{1}H resonances of the NCH$_3$ group [(**1a**, **b**), (**2a**, **b**);

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† 200 MHz ^{1}H N.m.r. spectra were recorded on a Bruker WP 200 spectrometer, using a flip angle of *ca.* 25° and an acquisition time of 4.6 s. A saturation time of 10 s with an r.f. power setting of 40L (Low power irradiation) was used to allow the n.O.e. to build up. In view of the various competing contributions to the relaxation of the unique protons H(2,4,5) in addition to dipole–dipole interactions, quantitative measurements of the n.O.e.s have not been attempted. Throughout this paper appreciable or significant n.O.e.s indicate enhancements in the range 6—12% while small n.O.e.s indicate enhancements of $<6\%$.

(**3a, b**), (**4a, b**); (**5a, b**)], of the C(2)CH_3 group [(**1a**), (**2a**), (**3a**), (**4a**), (**5a**)], and of the NBH_3 group‡ [(**3a, b**), (**4a, b**), (**5a, b**)]. This enabled a search to be made for the n.O.e. of the unique protons H(2) and H(4,5). In the 1,3-oxazolidines (**1a, b**) and (**2a, b**)§ the saturation of the NCH_3-protons gave appreciable n.O.e.s only for H(2) and H(4) and there was a small n.O.e. for H(5) in (**1a**) and (**1b**). Similarly, the saturation of the C(2)CH_3-protons in (**1a**) causes an n.O.e. only for H(2) while in (**2a**) a small n.O.e. was detected for H(5). This is convincing evidence for the *cis*-position of the C(4)Me group and the C(2)Me or C(2)Ph group in (**1a**), (**2a**) and (**1b**), (**2b**) respectively, as shown in the structural formulae.

In order to obtain further proof the diastereoisomeric N-BH_3 adducts of these 1,3-oxazolidines were prepared.¶ The fixing of the configuration at nitrogen by borane co-ordination[7] provides a simple model in which the configuration at C(2), N, and C(4) can be assessed using n.O.e. measurements.

Saturation of the NCH_3 protons in (**3a, b**) and (**4a, b**) gave small n.O.e.s only for H(5) in (**4a**) and (**4b**), whereas in (**5a**) and (**5b**) appreciable n.O.e.s were detected for H(2,4). This was confirmed by saturation of the BH_3-protons which led to significant n.O.e.s for H(2,4) in (**3a, b**) and (**4a, b**), and to small n.O.e.s for H(5) in (**3a**) and (**3b**); consequently, there is only a small n.O.e. for H(5) in (**5a**) and (**5b**). The n.O.e. difference spectra are clearly in accord with the structures shown. This finding is also in complete agreement with other ^1H, ^{13}C, and ^{11}B n.m.r. parameters. This shows that the configuration at C(2) in these oxazolidine *N*-borane adducts can be correlated directly with that of the free oxazolidines.

In conclusion, the C(2)-substituent in the most stable isomer of the 1,3-oxazolidines prepared from ephedrine, pseudo-ephedrine, and aldehydes is in the *cis*-position relative to the C(4)-methyl group.[1,5] N.O.e. difference spectroscopy appears to be a reliable method to settle the question of the configuration at C(2) in cases of ambiguity.

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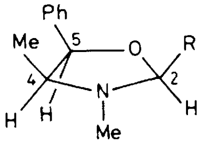
‡ This was achieved by simultaneous ^{11}B-decoupling.

§ Compounds (**1a**) and (**2a**) were prepared by direct reaction of acetaldehyde with the amino-alcohol in methylene chloride; after 30 min, the mixture was dried with Na_2SO_4, filtered, and evaporated *in vacuo*. Compounds (**1b**) and (**2b**) were prepared as reported,[2] by azeotropic distillation with benzene in a Dean–Stark column; after 2 h the solvent was removed *in vacuo* and the residue recrystallized from ethanol. The ^1H n.m.r. spectra of compounds (**1a,b**) and (**2a,b**) correspond to those in refs. 1 and 2.

¶ Addition of BH_3 (from borane–tetrahydrofuran solution, BH_3–THF) to the 1,3-oxazolidines under consideration produces a pair of diastereoisomeric (*N*-epimeric) compounds.[8] One compound of each pair was stable [(**3a, b**) and (**4a, b**)] while the other adducts (**5**) were isolated only for the pseudo-ephedrine oxazolidines (**5a,b**). The latter compounds slowly isomerize in solution and were converted quantitatively into (**4a, b**) when treated with excess of BH_3–THF. Full experimental details and spectroscopic and analytical data will be published in a full paper.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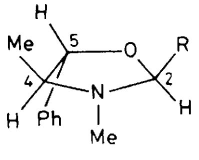
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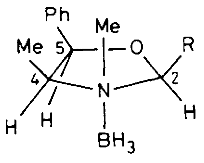
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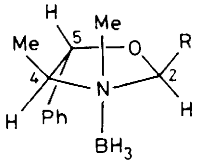
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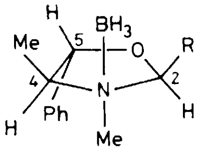
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a; R = Me
b; R = Ph

F. S. thanks Conacyt (Mexico) for a Graduate Scholarship and B. W. acknowledges support from the D.F.G. and the Fonds der Chemischen Industrie.

Received, 13th June 1983; Com. 784

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