

A CAUTIONARY NOTE ON THE USE OF COMMERCIAL (*R*)-MTPA-CL AND (*S*)-MTPA-CL IN DETERMINATION OF ABSOLUTE CONFIGURATION BY MOSHER ESTER ANALYSIS

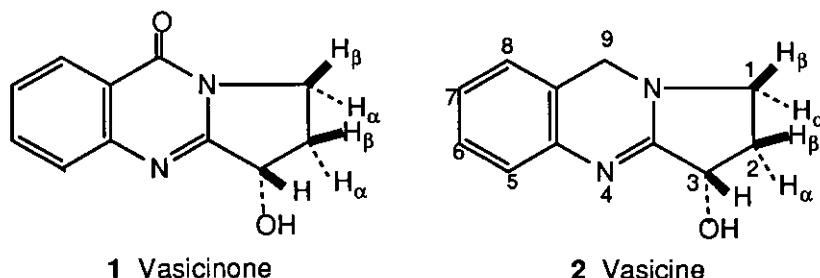
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Abstract – While the absolute configuration of a Mosher ester derivative (MTPAOR) is identical with that of the Mosher acid (MTPAOH) precursor, it is opposite that of the Mosher acid chloride (MTPA-Cl). Since (*R*)-MTPA-Cl and (*S*)-MTPA-Cl are now commercially available, incorrect conclusions may be drawn in deriving the absolute configuration, if this fact is overlooked. The absolute configuration of (-)-vasicinone (**1**) derived by Mosher ester analysis (*Tetrahedron Asymmetry*, 1996, 7, 25) has been revised as 3*S*. Mosher ester analysis of (-)-vasicine (**2**) confirmed a 3*S* configuration for this alkaloid.

Mosher's empirically derived technique of the use of MTPA [α -methoxy- α -(trifluoromethyl)-phenylacetic acid] esters is an important and less cumbersome technique for determination of the absolute configuration of stereogenic centers bearing hydroxyl groups.¹ The chiral alcohol is condensed with each of the enantiomers of the Mosher acid chloride to form the MTPA-ester. The *R*-MTPA is converted to the acid chloride which gives the acid chloride of the *S*-configuration (*S*-MTPA-Cl). The subsequently formed MTPA ester has an *R*-configuration, i.e. *R*-MTPA gives *S*-MTPA-Cl and *R*-MTPA ester (Cahn-Ingold-Prelog nomenclature rules²). The ¹H-NMR spectra of *R*-MTPA ester and the *S*-MTPA ester are then determined. The absolute configuration of the chiral center is then derived by comparison of the ¹H chemical shift differences ($\Delta\delta$ s) throughout the molecule of the Mosher esters.

The pyrrolo[2,1-*b*]quinazoline alkaloid (-)-vasicine from an Indian medicinal plant *Adhatoda vasica* was assigned a 3*R* absolute configuration on the basis of an X-Ray analysis of the hydrochloride.³ Our work on the X-Ray crystal structure of (+)-vasicine hydrobromide and the related alkaloid (+)-vasicinone hydrobromide showed a 3*S* absolute configuration based on the Flack parameter α and a consistent set of anomalous dispersion results.⁴ In order to determine the absolute configuration of (-)-vasicinone (**1**) by the Mosher ester derivatives, we prepared the enantiomers of the MTPA esters from the commercially procured (Aldrich) *R*-MTPA-Cl and *S*-MTPA-Cl.



Inadvertently, we assumed that the esters derived from these acid chlorides had the same *R*- and *S*-configurations. This led us to incorrect conclusions that the Mosher's empirical correlations are not valid in deriving the absolute configurations of the alkaloids vasicine, vasicinone, vacicinol and vasicinolone.^{4,5} In fact the $\Delta\delta$ chemical shifts support a 3*S* stereochemistry for these alkaloids. It is reassuring to note that revised 3*S* configuration of (-)-vasicinone has been confirmed by synthesis of (*S*)-(-) vasicinone.⁶ We prepared the correct *R*- and *S*- MTPA esters of (-)-vasicine (2) from the commercial MTPA-Cl taking in to consideration the CIP priority rules. The ¹H chemical shift values $\Delta\delta = (\delta_S - \delta_R)$ for H-2 α (-15 Hz), H-2 β (-7.5 Hz), H-1 α (0), H-1 β (-20 Hz), H-3 (+55 Hz) confirm that (-)-vasicine should have the 3*S* configuration.

The stereochemical nomenclature change has been pointed out in earlier literature.⁷ However, the priority interchange from MTPA to MTPA-Cl and to MTPA ester should not be overlooked since the enantiomeric acid chlorides are now commercially available.

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