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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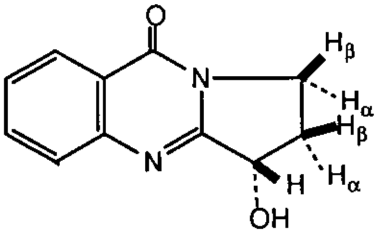
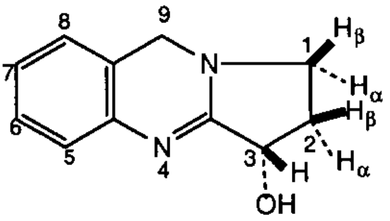
Abstract – While the absolute configuration of a Mosher ester derivative (MTPAOR) is identical with that of the Mosher acid (MTPAOH) precursor, it is opposite that of the Mosher acid chloride (MTPA-Cl). Since *(R)*-MTPA-Cl and *(S)*-MTPA-Cl are now commercially available, incorrect conclusions may be 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 alkloid.

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-Prelong nomenclature rules[2]). The ^{1}H-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 ^{1}H chemical shift differences (Δδs) 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.



1 Vasicinone



2 Vasicine

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 conideration the CIP priority rules. The ^{1}H chemical shift values $\Delta\delta = (\delta S\text{-}\delta R)$ for H-2α (-15 Hz), H-2β (-7.5 Hz), H-1α (0), H-1β (-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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