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REVISED ABSOLUTE CONFIGURATION OF DYSIDENIN AND ISODYSIDENIN

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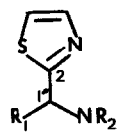
Summary: The absolute configuration of dysidenin and isodysidenin are revised.

Dysidenin and isodysidenin are two highly modified peptides isolated from the sponge Dysidea herbacea. The structure of dysidenin, without stereochemistry was established by the Roche group.[1] The x-ray structure of isodysidenin with absolute configuration was reported shortly thereafter by Tursch's group.[2] Subsequently, Tursch's group reported that dysidenin and isodysidenin were epimers at C-5 based on comparison of optical rotation data for acid hydrolysis products.[3] One product, thiazole 1 (isolated from both peptides) exhibited a very small positive rotation $[\alpha]_D$ + 0.65° and + 0.77°.[3] We felt this result warranted reinvestigation since our recent studies with the lissoclinum peptides indicated that 2-(1'-aminoalkyl)thiazoles racemize upon acid hydrolysis of the peptide.[4,5] We now report, based on a new method for determining the chirality of 2-(1'-aminoalkyl)thiazoles,[4] that the 2-(1'-aminoethyl)thiazole present in dysidenin and isodysidenin have identical stereochemistry but opposite to that reported previously. Thus, by inference dysidenin and isodysidenin have the opposite absolute configuration as previously reported and are structures 2 and 3, respectively.



a

1 R_1 = Me R_2 = DNB

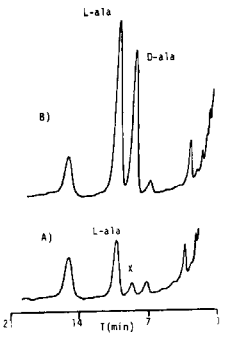
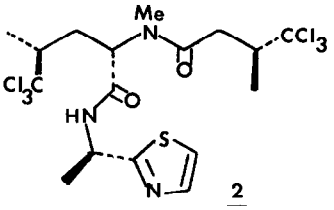
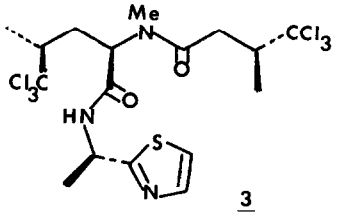


Figure 1. A) GC analysis of isodysidenin (treated with singlet oxygen) hydrolysis products as EE-TFA derivatives (column, SP-300; 110°). B) co-injection with D/L-alanine standard. X) this peak did not analyze for alanine by GC-MS.



2



3

Thiazole amino acids of the general formula a present in peptide structures undergo extensive racemization during acids hydrolysis.[4] Racemization is apparently initiated by protonation of the thiazole nitrogen followed by reversible loss of a proton from C-1'. However, chiral information can be retained by treating the peptide with $^1O_2$ prior to hydrolysis. Singlet oxygen adds in a 4+2 fashion to the thiazole disrupting the aromaticity of the ring. Hydrolysis cleaves the ring with expulsion of the side chain as an amino acid. The α-amino acid is then derivatised as the ethylester-N-trifluoroacetate and analyzed by chiral GC (see References 4 and 5 for complete experimental details). The product obtained from treatment of both dysidenin and isodysidenin with $^1O_2$ was L-alanine indicating that the thiazole has the S absolute configuration not the R configuration as reported by x-ray. Figure 1 depicts the analysis of isodysidenin. L-Alanine was identified by co-injection with standards and GC-EIMS.

Previously, Kishi revised the absolute configuration of gephyrotoxin,[6] which, had originally been assigned by x-ray.[7] Apparently the error did not result from misinterpretation of x-ray data but instead represents a statistical anomaly. It seems probable that the same is true for isodysidenin and suggests that other examples may be found.

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References

1. Kazlauskas, R.; Lidgard, R.O.; Wells, R.J.; Vetter, W. Tetrahedron Letters 1977, 3183-6.
2. Charles, C.; Braekman, J.C.; Daloze, D.; Tursch, B.; Karlsson, R. Tetrahedron Letters 1978, 1519-20.
3. Charles, C.; Braekman, J.C.; Daloze, D.; Tursch, B. Tetrahedron Letters 1980, 36, 2133-5.
4. Biskupiak, J.E.; Ireland, C.M. J. Org. Chem. 1983, 48, 2302-4.
5. Wasylyk, J.M.; Biskupiak, J.E.; Costello, C.E.; Ireland, C.M. J. Org. Chem. 1983, 48, 4445-9.
6. Fujimoto, R.; Kishi, Y. Tetrahedron Letters 1981, 22, 4197-8.
7. Daly, J.W.; Witkop, B.; Toyuyama, T.; Nishikawa, T.; Karle, I.L. Helv. Chim. Acta 1977, 60, 1128-1130.

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