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THE TOTAL SYNTHESIS OF (-)-DIHYDROASZONALENIN AND THE STEREOCHEMISTRY OF ASZONALENIN

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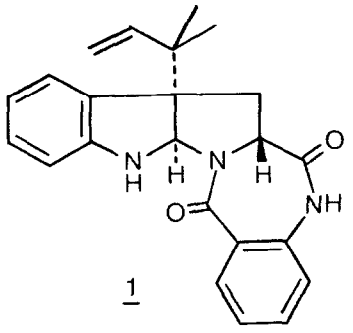
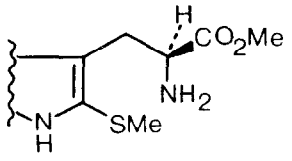
SUMMARY. The enantiomer of dihydroaszonalenin has been synthesised from *L*-tryptophan; aszonalenin 1 has been assigned the relative and absolute stereochemistry indicated.

Kimura *et al.* have described the isolation and structure of the mould metabolite aszonalenin but the stereochemistry of this compound was not determined.[1] We report below the total synthesis of the enantiomer of dihydroaszonalenin and the consequent assignment of the relative and absolute stereochemistry, shown in 1, to aszonalenin.



1



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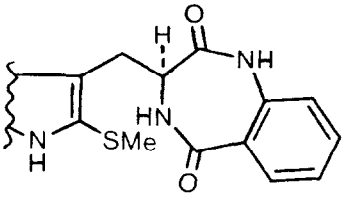
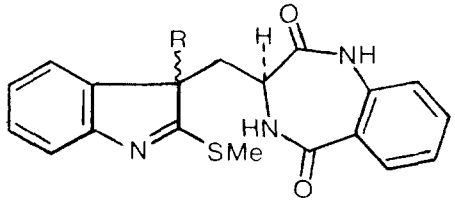


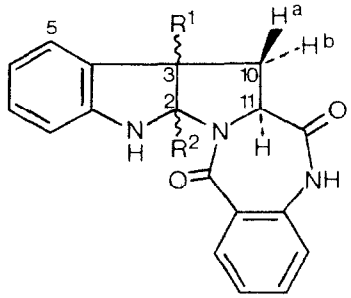
3

The tryptophan derivative 2 was prepared, in 65% yield, by the reaction of methanesulphenyl chloride with the hydrochloride salt of *L*-tryptophan methyl ester. Condensation of 2 with isatoic anhydride in pyridine gave the desired benzodiazepine 3, m.p. 155-159°, in 40% yield. The latter compound was then treated with 3,3-dimethylallyl bromide in acetone, at room temperature, to furnish the diastereoisomeric (1,1-dimethylallyl)indolenines 4a, m.p. 127-128°, $[\alpha]_D$ -24°, (42% yield), and 4b, m.p. 116-117°, $[\alpha]_D$ +187°, (19% yield), which presumably were formed *via* Claisen rearrangement of an intermediate sulphonium salt.[2,3] The stereochemical assignments follow from the work that is presented below.

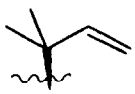
Desulphurization of 4a with Raney nickel in refluxing ethanol followed by hydrogenation over Adams' catalyst furnished the pentacycle 5a, m.p. 254-255°, $[\alpha]_D$ -50.2°. The 360 MHz ^{1}H-n.m.r. spectrum of the latter, in $CDCl_3$, showed *inter alia* the following significant resonances: δ 5.6 (1H, s, H-2),

4.0 (1H, dd, J 7.4 and 9.1 Hz, H-11), 3.5 (1H, dd, J 7.4 and 13.9 Hz, H-10a), 2.4 (1H, dd, J 9.1 and 13.9 Hz, H-10b), 0.97 and 0.99 (each 3H, s, quaternary methyls). Similar desulphurization-hydrogenation of 4b gave the pentacycle 5b, m.p. 125°, $[\alpha]_D$ +800°, δ ($CDCl_3$) 5.7 (1H, s, H-2), 4.1 (1H, dd, J 1.0 and 9.5 Hz, H-11), 3.1 (1H, d, J 13.4 Hz, H-10a), 2.6 (1H, dd, J 9.6 and 13.4 Hz, H-10b), 0.94 and 0.98 (each 3H, s, quaternary methyls). The stereochemical assignments follow principally from the results of N.O.E. difference spectra that were recorded at 360 MHz and which gave mutually consistent results for the two diastereoisomers. For example, irradiation of either quaternary methyl in 5a resulted in enhancement only of resonances due to protons 2 (7%), 5 (4%), and 10a (4%); the equivalent N.O.E. experiment on 5b resulted in enhancement of the resonances due to H-2 (5%), H-5 (3%), and H-10b (2%) alone.

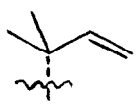




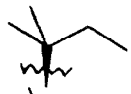
4 a; R =



b; R =

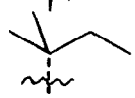


5 a; R^1 =



, R^2 =

b; R^1 =



, R^2 =

Authentic aszonalenin was hydrogenated over Adams' catalyst to yield the dihydro-derivative, m.p. 251°, which showed identical chromatographic and spectroscopic behaviour to compound 5a but surprisingly showed a mixed melting point depression with the latter and had $[\alpha]_D$ +59.7°. It is concluded that aszonalenin has the relative and absolute stereochemistry depicted in 1.

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References

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