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THE ABSOLUTE CONFIGURATION OF NORTRYPTOQUIVALINE

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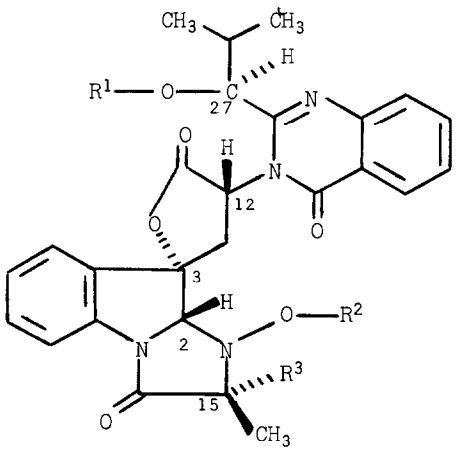
The tryptoquivalines are an unusual series of metabolites recently isolated from two different fungal species: *Aspergillus clavatus*[1] and *Aspergillus fumigatus*[2]. Altogether 14 different naturally occurring tryptoquivalines have been reported, some of which including tryptoquivaline 1 itself have toxic and tremorgenic properties.



1	R^1	=	$\overset{O}{\overset{\|}{C}}-CH_3$	R^2	=	H	R^3	= CH_3
2	R^1	=	H	R^2	=	$\overset{O}{\overset{\|}{C}}-CH_3$	R^3	= H
3	R^1	=	$\overset{O}{\overset{\|}{C}}-CH_3$	R^2	=	H	R^3	= H

Initial structural work using spectroscopic, chemical and X-ray diffraction experiments established the structure and relative stereochemistry of this series of compounds. Degradation work by Yamazaki *et al*[2a,b] established that in tryptoquivaline D 2, C15 possessed an *S* configuration. However, the absolute stereochemistry of the tryptoquivalines was not known because the original X-ray work was done on a derivative of tryptoquivaline which did not possess a center of asymmetry at C15[1a]. In order to establish the absolute configuration of the whole series of tryptoquivalines as well as to unambiguously show the existence of the spiro-γ-lactone a single crystal X-ray diffraction experiment was performed on nortryptoquivaline 3.

Crystals of nortryptoquivaline 3 ($C_{28}H_{28}N_4O_7$) formed as large prisms from methylene chloride/hexane mixtures[3]. Preliminary X-ray experiments indicated that the space group was either $P4_12_12$ or $P4_32_12$; subsequent calculations revealed that $P4_32_12$ was correct with a = 10.343(2), c = 49.366(6) Å and Z = 8 for a calculated density of 1.34 g/cc. Of the 2182 unique reflections measured with $2\theta \leq 114^\circ$ (λ=1.5418 Å), 1977 (91%) were considered observed ($I \geq 3\sigma_I$). Corrections were made for background, Lorentz and polarization effects. A multisolution tangent formula approach was used to find initial positions for 32 of the 39 nonhydrogen atoms[4]. The remainder of the atoms and thermal parameters were found using Fourier difference techniques and least-squares refinements[5] by minimizing $\Sigma\omega(|F_o|-|F_c|)^2$ where $\omega = (1/\sigma_{F_o})^2$. The final unweighted R factor is .054 for the 1977 observed reflections using anisotropic temperature factors for the nonhydrogen atoms and fixed isotropic temperature factors for the hydrogen atoms[6]. Bond distances and angles are reasonable and there are no abnormally short intermolecular contacts. Figure 1 contains a perspective drawing of nortryptoquivaline 3 with the correct absolute stereochemistry *(vide infra)*[7].

The absolute configuration of C15 of tryptoquivaline D 2 has been established to be *S* consistent with hypothesis that L-alanine is incorporated in the molecule[2b,c]. A number of chemical, spectroscopic and chiroptical experiments have shown that except for epimerization at C12 the corresponding centers of asymmetry in the tryptoquivalines are identical[1,2,8]. Consequently, the present work in conjunction with the above information establishes that the absolute configuration of nortryptoquivaline 3 as well as the rest of the tryptoquivalines is as shown in Figure 1; i.e. C2-*S*, C3-*S*, C12-*R*, C15-*S* and C27-*S*. The absolute configuration shown in Figure 1 is opposite that drawn in previous reports[1,2]. In addition the present crystal structure analysis confirms the presence of the spiro-γ-lactone functionality. In the solid state one intramolecular hydrogen bond exists involving O33, H33 and O35 with dimensions: O33-H33 .99 Å; H33-O35 1.76 Å; O33-O35 2.73 Å; and O33-H33-O35 165°.

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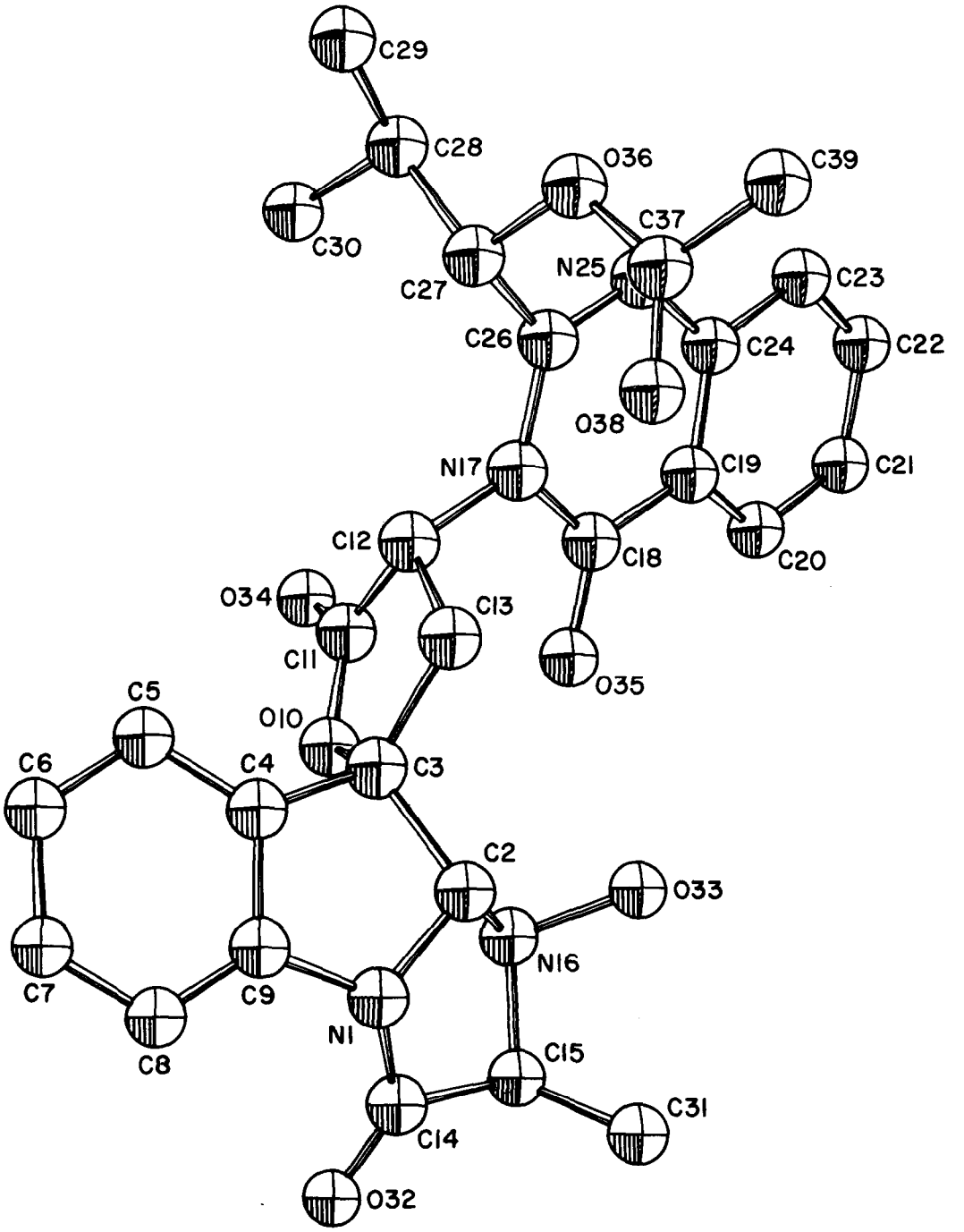

FIGURE 1: A perspective drawing of nortryptoquivaline 3

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3. Nortryptoquivaline $\frac{3}{2}$ was isolated as described in reference *1b*; the author wishes to thank G. Büchi and K. Luk for providing a sample.

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