

SPECIFICITY AND TRANSFORMATIONS OF THE TRISPORIC ACID SERIES OF FUNGAL SEX HORMONES

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(Received 30 November 1971)

Abstract—Chromatographic and spectroscopic characterizations and comparative bioassay data are given for trisporic acid A, the separate 9-*cis*- and 9-*trans*-isomers of trisporic acids B and C, and trisporol C, all obtained from 'mated' (*plus* and *minus*) cultures of *Blakeslea trispora*. All five acids show comparable levels of hormone activity on both the mating types of *Mucor mucedo*, whereas natural trisporol C more specifically affects a *plus* strain and the laboratory-derived methyl esters are *minus*-specific. Similarly *plus* and *minus* strains of *B. trispora* convert trisporol C and the esters into trisporic acids at different rates, and they effect different transformations of administered methyl ¹⁴C-trisporate C.

INTRODUCTION

HETEROTHALLIC fungi in the order Mucorales display a very simple form of sexuality and the processes involved are mediated by interdiffusing hormones, the situation being described in detail in a recent review.¹ The sexual designations *plus* and *minus* apply irrespective of species and are based upon the ability of two strains of opposite sex, growing in close proximity, mutually to elicit the first morphogenic step in the sex process, the production of zygothores (progametangia). Zygothores of opposite sex grow towards each other (zygotropism), but only if two zygothores are also of the same or of closely-related species are subsequent stages of the sexual cycle observed. Thus the sexual designation rests primarily on the process of zygothore induction. Morphological and simple biochemical differences between strains prove, in general, not to be linked to sexual type.

Zygothore induction is caused by the production of a series of hormones, the trisporic acids (structures I–III), which are characteristically produced (along with various come-tabolites) only by mixed cultures of *plus* and *minus* strains. Because of contradictions in the literature¹ it is important to establish whether or not any of these hormones act selectively upon one or other mating type (i.e. whether *plus* and *minus* differ in their hormone response system). The mechanism by which the strains collaboratively produce the hormones is also of crucial importance: i.e. do *plus* and *minus* strains differ in their actual or potential ability to carry out individual reaction steps in the biosynthetic sequence?

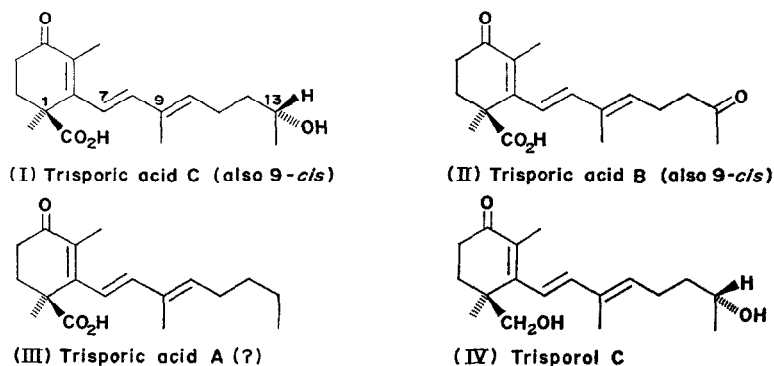
In this paper we give biological activity data for the main natural trisporic acids, having separated the principal stereoisomers. None of them is mating-type-specific. Some related substances are shown to have a degree of specificity for *plus* and *minus* *Mucor mucedo* (the preferred test organism). This apparent specificity is comparable to differences in the ability of *plus* and *minus* strains of *Blakeslea trispora* (the organism preferred for trisporic

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¹ H. VAN DEN ENDE and D. STEGWEE, *Bot. Rev.* **37**, 22 (1971).

acid production²) to convert substances into trisporic acids and to effect related transformations. The separation and characterization of trisporic acid stereoisomers and some co-metabolites are described, together with preparations of ¹⁴C-labelled substrates for the transformation studies.



In trisporic acid C (I) the *R*-configuration at C-13 has been established degradatively,^{3,4} and the *S*-configuration at C-1 (and its biosynthetic origin) follows from circular dichroism and biosynthetic data.⁵ Natural I comprises two geometric isomers, both 7-*trans*,^{3,6} as does natural trisporic acid B (II). Trisporic acid A, for which we suggest structure III, is a very minor metabolite and its stereochemistry is conjectural. The 9-*cis/trans* pairs are conveniently separated as the methyl esters, from which the free acids can be regenerated for bioassays. In these trienones the chromophore is perturbed by the non-conjugated substituents at C-1 (for example, reduction of I to the alcohol IV causes a hypsochromic shift of 15 nm) so that assignments of the stereochemistry about Δ^9 from UV spectra³ must be questioned. In synthetic racemic methyl 7-*trans*-9-*trans*-trisporate B, Edwards *et al.*⁷ showed that the chemical shift of the proton at C-8 could be used to assign the stereochemistry about Δ^9 correctly, and here we correlate such assignments with the chromatographic behaviour and the biological activity.

RESULTS AND DISCUSSION

Methyl Trisporate A

This is the least polar of the three (pairs of) methyl esters found in working-up² mated *B. trispora* acids; it occurs in very small proportions (< 2%), but our encountering it as a transformation product of methyl trisporate C, as described below, led us to attempt a structural assignment. The trienone chromophore is perturbed as in I and II (λ_{\max} 319 nm shifting by -24 nm on reduction with borohydride), but the mass spectrum, with $m^+/e = 304$, requires the O-free side-chain shown in structure III. In agreement with this are the observed fragmentations of the molecular ion and the fact that the mass spectrum is unchanged after attempted acetylation. Hence the ester of III is the 13-deoxy derivative; we

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³ T. RESCHKE, *Tetrahedron Letters* **39**, 3435, (1969).

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⁶ O. K. SEBEK and H. K. JAEGER, *Am. Chem. Soc. 148th Meeting*, Chicago (1964).

⁷ J. A. EDWARDS, V. SCHWARZ, J. FAJKOS, M. L. MADDOX and J. H. FRIED, *J. Chem. Soc. D, Chem. Commun.* 292 (1971).

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