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STUDIES ON VERSICOLIN, A NEW ANTIFUNGAL ANTIBIOTIC FROM ASPERGILLUS VERSICOLOR. I. STRUCTURE OF VERSICOLIN

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In our earlier communications (1,2) we have reported about the isolation and purification of versicolin. We wish to report here a structure for versicolin based on physico-chemical evidences.

Versicolin, m.p. 125-126°C is an optically inactive, acidic compound having the molecular formula $C_7H_8O_3$. The homogeneity of the compound has been established by paper chromatography (p.p.c.) and thin layer chromatography (t.l.c.) over silica gel (2). Versicolin is susceptible to oxidation when exposed to atmosphere. In presence of acid or alkali it shows colour changes resembling patulin (3). The presence of functional groups like, unsaturation, enolic hydroxyl, carbonyl and a reducing aldehyde has previously been confirmed by characteristic colour reactions (2).

The UV absorption spectra of versicolin (2) have the following peaks : λ_{max}^{EtOH} 222 mμ, log ε 4.4 (unsaturated aldehyde), 256 mμ, log ε 3.9 (unsaturated CO group), 390 mμ, log ε 2.6 and 520 mμ, log ε 2.2. In presence of acid or alkali the peaks suffer strong bathochromic shift : $\lambda_{max}^{0.1N\ NaOH}$ 288 mμ, log ε 3.66 and $\lambda_{max}^{0.1N\ HCl}$ 285 mμ, log ε 3.37 characteristic of tautomeric enol function. The infrared absorption spectrum of versicolin (2) had the following peaks : ν_{max}^{nujol} 3345 (enolic OH), 1640 (C=C conjugation) and 1150 cm^{-1} (ether linkage). A band in the 1754 cm^{-1} region which is attributable to lactone ring of α-pyrones (5) is, however, absent in the case of versicolin. The characteristic band in the region 1720-1740 cm^{-1} for aldehyde is also absent in the IR spectra.

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All these observations are further rationalized by the NMR spectra (6) as shown in Fig. 1. It showed the signals at δ 2.08 (3H, s, C-3-CH_3), δ 3.1 (1H, s, C-3-H or 1H, s, C-4-OH), δ 6.18 and δ 6.52 (2H, q, C-5-H and C-6-H, J = 8 cps) and at δ 7.3 (2H, m, C-2-H and C-2=C$\begin{matrix}H\\OH\end{matrix}$)

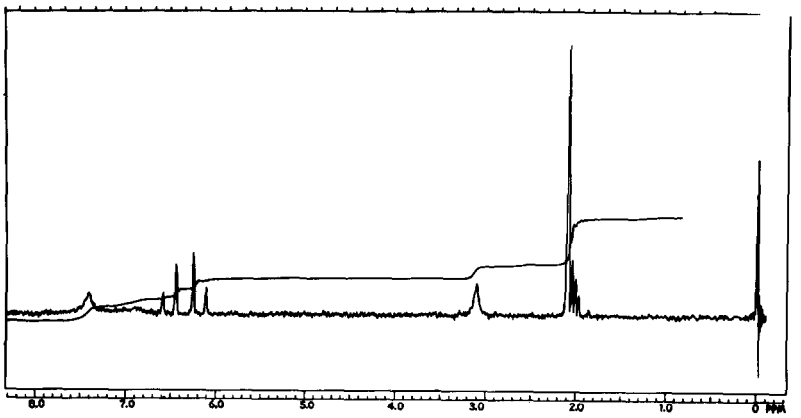
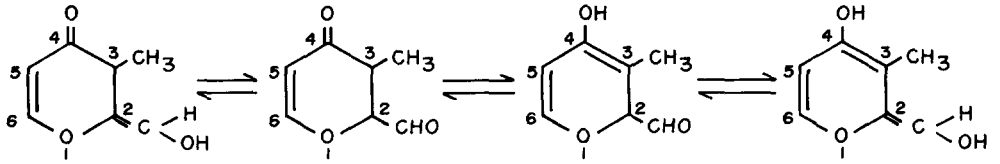


FIG.1. NMR spectrum of versicolin.

Versicolin on reduction with Zn/HOAc afforded a diacetate, $C_{11}H_{18}O_5$, m.p. 95°C. This compound does not respond to ferric chloride colour reaction and does not reduce Fehling's solution thereby indicating that the carbonyl chromophores present in versicolin have undergone reduction and subsequent acetylation. This observation was supported from the IR spectrum of the compound which exhibited broad bands at 1740 cm^{-1} and 1176 cm^{-1} attributable for acetate groups. It is interesting to mention that the diacetate had no antifungal activity.

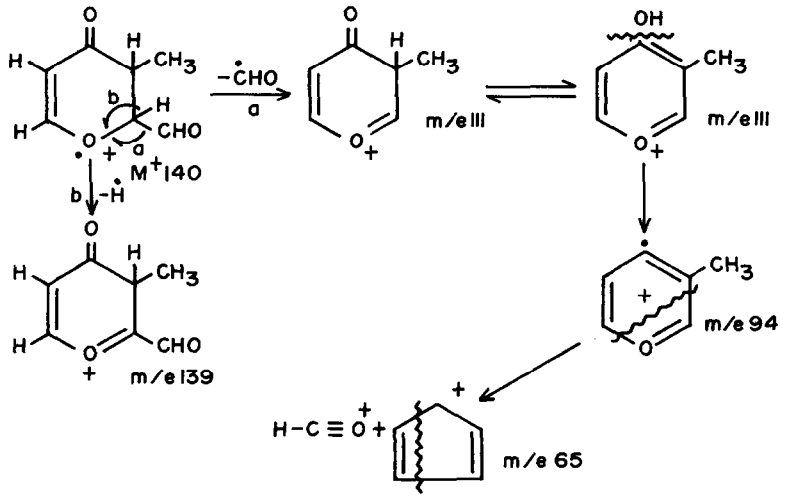
Correlating the above physico-chemical data, a 2:3-dihydro-3-methyl-2-aldehyde-γ-pyrone structure for versicolin may be proposed (structures I, II, III and IV).



I II III IV

The structure IV explains the reactions of aldehyde, absence of absorption peak for aldehyde in the IR spectra, weak absorption in the visible range because of extended conjugation, the sharp singlet at δ 2.08 (3H, s, C-3-C$\underline{H}_3$) and also the proton signal at δ 7.3 (2H, m, C-2-$\underline{H}$ and C-2=C$\begin{matrix}\underline{H}\\ OH\end{matrix}$) in the NMR spectra.

The above structure for versicolin received further support from a detailed analysis of its mass spectrum. It exhibited a molecular ion peak at m/e 140, and other important peaks were observed at m/e 139, 111, 94, 65 and 39. The genesis of the above peaks could best be explained by the following mechanistic rationale :



The proposed structure of versicolin explains its antifungal properties as exhibited by patulin (3) and kojic acid (7).

Versicolin is an hitherto undescribed fungal metabolite of γ-pyrone derivative having highly specific antifungal activity (2) and fairly low toxicity.

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6. NMR spectra were recorded at 60 Mc. in $CD_3CO\ CD_3$ solution, chemical shifts are expressed in δ (ppm) down field from TMS as internal standard, coupling constants in cps. The abbreviations are as follows : s, singlet; d, doublet; q, quartet and m, multiplet.
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