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SYNTHETIC ANALOGUES OF CRYPTOSPORIOPSIN: THE ACTION OF HYPOCHLORITE ON m-CRESOL

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The formulation I (R_1=OH, R_2=Cl) was recently advanced, on the basis of chemical evidence, for cryptosporiopsin (1), an antifungal metabolite produced by a species of Cryptosporiopsis (2). The structure was subsequently amended to I (R_1=Cl, R_2=OH) as a result of further chemical investigation (3). This was prompted by the independent X-ray studies of McGahren et al. on a metabolite isolated from Sporormia affinis Sacc., Bomm and Rouss, which was assigned the structure and absolute configuration I (R_1=β-Cl, R_2=α-OH) (4), and which proved to be identical with cryptosporiopsin (3).

Hypochlorite degradation of a suitably substituted phenol appeared to us to offer the most attractive synthetic approach to this interesting richly functionalized system. The action of alkaline hypochlorite on phenol (5) has been shown to give rise to the hydroxy acid II (R=H), possibly through Favorskii-type ring contraction of an intermediate such as III (6, c.f. 7). Assuming a mechanistic scheme of the type proposed for the phenol degradation (6,7), several structures are possible a priori for the rearrangement product of a meta-alkyl-substituted phenol.

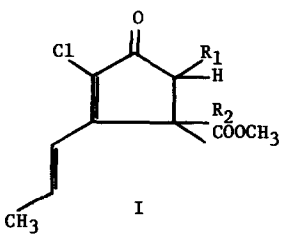
We have investigated the reaction of m-cresol with alkaline hypochlorite, and in this communication describe the transformation of the product into the racemic cryptosporiopsin analogue IV, whose structure was proven independently of its precursors (8). Accordingly the structure II ($R=CH_3$) can be advanced as the most plausible formulation for the rearrangement product of m-cresol with alkaline hypochlorite.

Treatment of an alkaline solution of m-cresol with chlorine, under conditions based on those described in the earlier work on phenol (5,6,7), gave rise to a 5.4% yield of the crystalline hydroxy acid II ($R=CH_3$) m.p. 166-171°, (optimization of yields was not attempted at this stage).

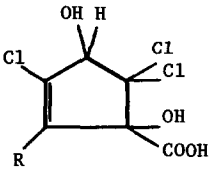
Sodium amalgam reduction of II ($R=CH_3$) effected replacement of one of the chlorines in the gem dichloro grouping by hydrogen (c.f. (5)) giving rise to V (R=H), m.p. 200-203° in 65% yield. The methyl ester of the latter, V ($R=CH_3$), m.p. 172.5-173.5° was obtained by reaction with diazomethane.

Oxidation of V ($R=CH_3$) to IV, m.p. 91-95°, was effected smoothly under the action of Jones' reagent in acetone. IV displays a UV chromophore, λ_{max}(EtOH) 242.5 mμ (ε 11700), strikingly similar to that of dihydrocryptosporiopsin (1,3), and IR absorption (CCl_4) at 3500, 1757, 1747 and 1663 cm^{-1}. The NMR spectrum ($CDCl_3$) of IV shows three-proton singlets at 7.91 and 6.17τ for the allylic methyl and the ester methyl protons respectively. A one-proton singlet at 5.51τ disappears on deuterium exchange and corresponds to the hydroxyl hydrogen, and a similar signal at 5.44τ represents the proton on C-3. In the spectrum

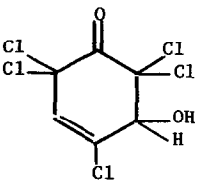
of the acetate, the signal for this proton is shifted downfield to 4.86τ. This behavior, analogous to that displayed by cryptosporiopsin (3) demonstrates that the relative stereochemistry of the asymmetric centres is as portrayed in IV (9).



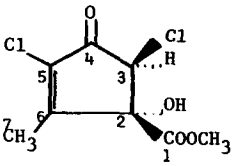
I



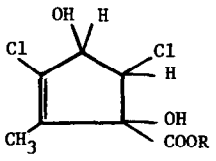
II



III



IV



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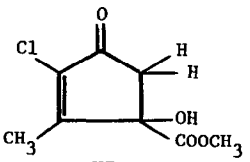
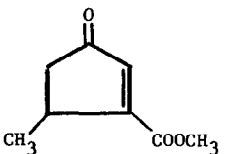
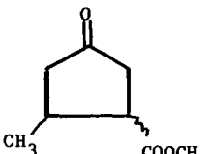


VI



VII



VIII

Evidence, relating to the environment of the chlorine on C-3 was forthcoming from the zinc-methanol reduction of IV. (c.f. (3)). The salient spectral feature displayed by the product VI, is a two-proton AB quartet, centred at 7.16τ, ($|J_{AB}|$=18Hz) attributable to the geminal hydrogens on C-3. Thus the zinc-labile chlorine of IV is located on a secondary carbon, flanked by fully substituted carbon atoms.

Additional reduction studies provided convincing evidence for the skeletal structure of IV. Hydrogenation of the latter in 95% ethanol with Pd/C afforded the ene-dione-type keto ester VII, which could be reduced with zinc and acetic acid to the epimer mixture VIII. These results, for which analogies are found in the cryptosporiopsin series (1,3), will be discussed in detail in a subsequent report.

These transformations rigorously establish the structure of IV, and demonstrate that ring contraction of a meta-alkyl-substituted phenol through the agency of alkaline hypochlorite provides a useful synthetic route to compounds in the cryptosporiopsin series. Extensions to the present work are currently under investigation.

REFERENCES AND FOOTNOTES

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8. All compounds prepared gave satisfactory analytical results by microanalysis and/or mass spectrometry.
9. A referee has drawn our attention to the observation of a similar anisotropic effect by Takada et al (Chem. Communications 538 (1967)).