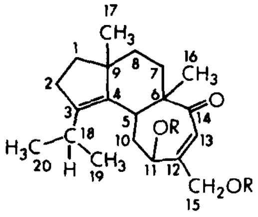
Tetrahedron Letters No. 19, pp 1917 - 1920, 1972. Pergamon Press. Printed in Great Britain.

METABOLITES OF CYATHUS HELENAE. CYATHIN A_3 AND ALLOCYATHIN B_3, MEMBERS OF A NEW GROUP OF DITERPENOIDS.

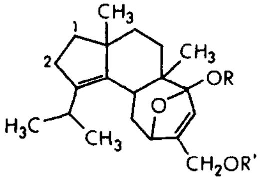
By W. A. Ayer and H. Taube
Chemistry Department, University of Alberta,
Edmonton 7, Canada

(Received in USA 9 February 1972; received in UK for publication 5 April, 1972)

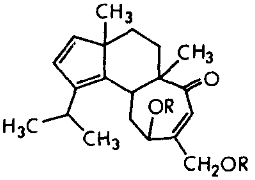
We have recently reported the isolation, separation, and preliminary characterization of a mixture of antibiotic substances produced by the bird's nest fungus Cyathus helenae Brodie (1). We now report evidence which allows us to assign structure 1 to cyathin A_3 and structure 4 to allocyathin B_3[†].



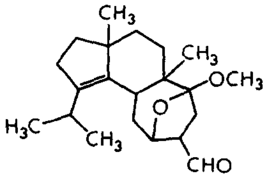
1a R=H
2a R=Ac



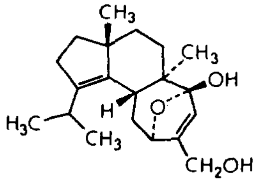
1b R=R'=H
2b R=Me, R'=H
3b R=Me, R'=Ac
4b R=R'=H (1,2-dehydro)
5b R=Me, R'=H (1,2-dehydro)



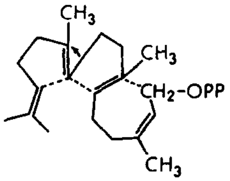
4a R=H
5a R=Ac



6



7



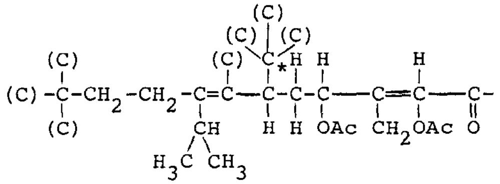
8

[†] The substance previously called cyathin A3 and assigned formula $C_{20}H_{30}O_3$ has now been shown to be a mixture of a major component, $C_{20}H_{30}O_3$ (cyathin A_3), and a minor component, $C_{20}H_{28}O_3$ (allocyathin B_3, not previously reported), separable by chromatography over silver nitrate-silica gel. Molecular formulas of all new compounds reported were determined by high resolution mass spectrometry.

Cyathin A_3, m.p. 148-150°, $[\alpha]_D$ -160° (MeOH), exists in solution in equilibrium between the tautomeric forms 1a and 1b. The infrared spectra of cyathin A_3, both in solution ($CHCl_3$) and in the solid phase (KBr), show in the carbonyl region only a weak, broad absorption band centered around 1650 cm^{-1}. However, acetylation (acetic anhydride-pyridine) gives the keto diacetyl derivative 2a, $\gamma_{max}^{CCl_4}$ 1750, 1685 cm^{-1}, whereas treatment with methanol-HCl gives the ketal 2b, which shows no carbonyl absorption. The acetyl compound 2a shows uv absorption charactersitic of an α,β-unsaturated ketone (λ_{max} 323 nm (ε 7000), λ_{max} 323 nm (ε 130) (isooctane)) whereas the ketal 2b shows only end absorption. The n.m.r. spectrum of 2a and appropriate decoupling revealed all the protons of the isolated system $-CH{=}C(CH_2OAc)CH(OAc){-}CH_2{-}\overset{*}{C}H-$. The methine proton on the starred carbon (C-5) appears to be in an allylic position (δ 2.80) as does the methine proton of an isopropyl group ($\underline{CH}(CH_3)_2$, δ 2.81). Two quaternary methyls were also apparent (δ 1.07, 1.00). The n.m.r. spectra of the methyl ketals show that the primary hydroxyl is not involved in ketal formation.

Allocyathin B_3, m.p. 143-144°, $[\alpha]_D$ -250° (MeOH), is 1,2-dehydrocyathin A_3 (correlation described below) and exists in solution as the tautomeric pair 4a$\rightleftarrows$4b. Diacetylallocyathin B_3 (5a) shows a complex uv spectrum (λ_{max} 225 nm (ε 16000), λ_{sh} 250 nm (ε 9700)) containing a diene chromophore superimposed on the α,β-unsaturated carbonyl chromophore. The methyl ketal 5b shows only the diene chromophore, λ_{max} 256 nm (ε 4200) (isooctane). The n.m.r. spectrum of 5a (see Figure) is similar to that of 2a but in addition shows an AB quartet, J = 5 Hz, corresponding to two olefinic protons (δ 6.29 and 6.23). This double bond cannot be conjugated to that of the α,β-unsaturated ketone system and thus, in order to complete the diene system, allocyathin B_3 must contain a fully substituted double bond. By inference, cyathin A_3 must also contain this tetrasubstituted double bond, and if one attributes the low chemical shifts noted for isopropyl methine and the C-5 proton to their being allylic to this double bond, partial structure A results for diacetylcyathin A_3[††].

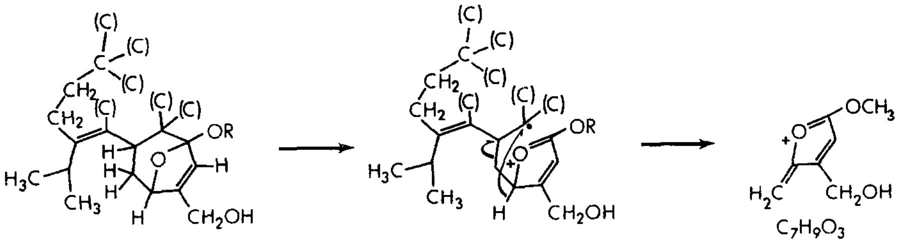
[††] Alternate part structures in which the isopropyl group is located on the other end of the tetrasubstituted double bond cannot be excluded at this point.



$$(C)-\overset{\overset{\textstyle (C)}{|}}{\underset{\underset{\textstyle (C)}{|}}{C}}-CH_2-CH_2-\underset{\underset{\underset{\textstyle H_3C\;\;CH_3}{\textstyle CH}}{|}}{C}=\overset{\overset{\textstyle (C)}{|}}{C}-\overset{\overset{\textstyle (C)_3\overset{*}{C}}{|}}{\underset{\underset{\textstyle H}{|}}{C}}-\overset{\overset{\textstyle H}{|}}{\underset{\underset{\textstyle H}{|}}{C}}-\overset{\overset{\textstyle H}{|}}{\underset{\underset{\textstyle OAc}{|}}{C}}-\underset{\underset{\textstyle CH_2}{|}}{C}=\overset{\overset{\textstyle H}{|}}{\underset{\underset{\textstyle OAc}{|}}{C}}-\underset{\underset{\textstyle O}{\|}}{C}-$$

A

The mass spectra of the ketals 2b and 4b are both dominated by an intense peak at m/e 141, shown to correspond to the ion $C_7H_9O_3$. This was taken as an indication that the carbonyl carbon in A is linked directly to the starred carbon in A, i.e., contained in a seven-membered ring. The genesis of the ion $C_7H_9O_3$ is then as shown in the Scheme, in which the partial structure (ketal form) has been expanded to B to accomodate this feature.



B

SCHEME

Part structure B (R = H) contains 22 carbons, two of which must be quaternary methyl groups, and two must be duplications. Since the compounds must be tricarbocyclic, and since the disubstituted double bond in allocyathin B_3 appears to be in a five-membered ring ($J_{1,2}$ = 5 Hz (2), uv spectrum consistent with a 1,2-disubstituted cyclopentadiene (3)), structures 1 and 4 follow as a logical[§] solution to the structural problem. The complete analysis of the n.m.r. spectrum of 5a is shown in the Figure.

Cyathin A_3 and al ocyathin B_3 were correlated in the following manner. When a methanol solution of cyathin A_3 methyl ketal (2b) is stirred for 10 minutes in a hydrogen atmosphere in the presence of 5% palladium-charcoal, it is in large part isomerized (4) to the aldehyde 6, m.p. 115-117°, $[\alpha]_D$ -30° (isooctane), $\lambda_{max}^{CCl_4}$ 2710, 1725 cm^{-1}, δ 9.64 (CHO, d, J = 2 Hz). Treatment of allocyathin B_3

[§] Structures containing a cyclopropane ring, for which there is no evidence, or highly strained anti-Bredt double bonds, were ignored. This latter requirement may only be met if the isopropyl group is located as in part structure A.

methyl ketal (5b) under these conditions causes this same isomerization to occur concurrent with hydrogenation of the C-1, C-2 double bond, leading to aldehyde 6, identical with that obtained from cyathin A_3.

The constitution of cyathin A_3 ($1a \rightleftarrows 1b$) described herein has now been independently confirmed by an x-ray crystallographic study (5), which shows that crystalline cyathin A_3 exists in the hemiketal form 1b. This latter study also discloses the complete relative stereochemistry of cyathin A_3 as that shown in 7. Since the reactions leading to aldehyde 6 should not affect any of the asymmetric centers, this also establishes the stereochemistry of allocyathin B_3.

Geranylgeranyl pyrophosphate (8) is regarded as the natural precursor of the diterpenoids (6). The carbon skeleton of the cyathins may be derived by cyclization (dotted lines) and rearrangement (arrow) of 8. To the best of our knowledge, this carbon skeleton has not been encountered previously.

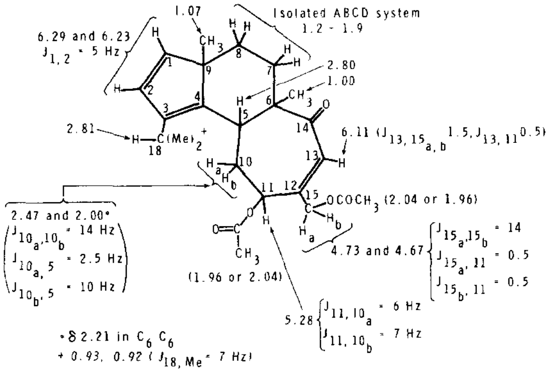


FIGURE. PMR Spectrum of Diacetylallocyathin B_3 (δ values, J in Hz, $CDCl_3$ solution)

References

1. A. D. Allbutt, W. A. Ayer, H. J. Brodie, B. N. Johri, and H. Taube, Canad. J. Microbiol., 17, 1401 (1971).
2. O. L. Chapman, J. Am. Chem. Soc., 85, 2014 (1963).
3. S. McLean and P. Haynes, Tetrahedron, 21, 2313, 2343 (1965).
4. P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals", Academic Press, New York, 1967, p. 439.
5. M. J. Bennett and R. M. Tuggle, personal communication.
6. cf. D. Arigoni, Pure Appl. Chem., 17, 331 (1968).