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THE CYBRODINS: NEW SECO-ILLUDALANES FROM THE BIRD'S NEST FUNGUS CYATHUS BULLERI BRODIE.[1]

William A. Ayer* and Robert H. McCaskill
Department of Chemistry, University of Alberta, Edmonton, Alberta,
Canada T6G 2G2

Abstract: The structures of the seco-illudalane sesquiterpenoids cybrodol (2), isocybrodol (3), cybrodic acid (6), cybrodal (4), and trisnorcybrodolide (5), are presented. These are the first seco-illudalanes to be reported.

Some time ago we reported the isolation and structure determination of the degraded eudesmane-type sesquiterpenoid cybullol (1) from Cyathus bulleri (Brodie strain 6620, ATCC 38347)[2]. At that time we also reported the isolation of small amounts of a $C_{15}H_{28}O_3$ triol whose structure was not determined. In pursuit of further quantities of this triol we have examined the metabolites of a different strain of C. bulleri (Brodie strain 6680a, ATCC 38351), which we find does not produce cybullol (1) or the $C_{15}H_{28}O_3$ triol but which instead elaborates a series of sesquiterpenoids that represent a new class of seco-illudalane compounds, herein called cybrodins.

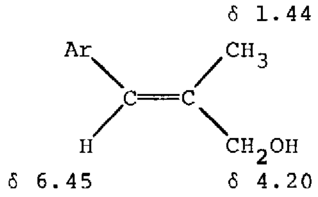
Fermentation of the above strain of C. bulleri in a yeast-malt extract liquid medium followed by extraction (EtOAc), separation into neutral and acidic fractions, and chromatography (Sephadex LH-20, then silica gel) gave as the neutral components cybrodol (2, major component), isocybrodol (3), cybrodal (4) and trisnorcybrodolide (5). The acidic fraction yielded cybrodic acid (6).

Cybrodol (2), $C_{15}H_{22}O_3$, obtained as an oil[3], shows hydroxyl and aromatic, but no carbonyl, absorption in the ir. The proton-decoupled ^{13}C nmr spectrum reveals 8 sp^2 carbons (six singlets (δ 134.9, 135.0, 135.8, 136.1, 137.9, 140.0), and two doublets (δ 123.9, 127.8)). Signals at δ 7.05 (aromatic proton) and δ 6.40 (olefinic proton) confirm the presence of a penta-substituted benzene and a trisubstituted olefin. Aromatic methyls appear at δ 2.38 and δ 2.16 and an olefinic methyl at δ 1.44. Methylene groups at δ 4.48, δ 4.20 and δ 3.74 in the ^1H nmr spectrum are accompanied by three methylene signals in the oxygenated sp^3 carbon region (δ 61.8, 63.3, 67.9) of the ^{13}C nmr spectrum. Acetylation of cybrodol (2) provides a triacetyl derivative 2a in which these methylene signals (proton spectrum) are each shifted downfield by about 0.45 ppm, confirming that cybrodol contains three primary alcohol groups. The signal at δ 4.48 suggests a benzylic alcohol, and that at δ 4.20, which is coupled to the olefinic proton, an allylic alcohol. The triplet at δ 3.74 is one half of an A_2X_2 system, the other half appearing at δ 3.0. The shifts of these latter signals, together with the diagnostic loss of 31 mass units in the mass spectrum, are consistent with the β-phenethyl alcohol grouping. Since the vinyl methyl and the allylic methylene show very small couplings to the olefinic proton, the grouping $—CH{=}C(CH_3)CH_2OH$ is indicated, and the structural problem reduces to arranging this latter group, two methyl groups, a hydroxymethyl group, and a β-hydroxyethyl group on the benzene ring. Biogenetic precedent favored an illudalane[4] skeleton 7 cleaved at *a* or *b*. Pteroside A has structure 8[5], but no *seco*-illudalanes have been reported.

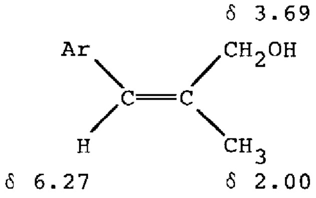
Decoupling and NOE experiments showed that the aromatic methyl at δ 2.38 in cybrodol is *ortho* to the aromatic hydrogen. Ozonolysis of triacetylcybrodol (2a) followed by oxidative workup provided the acid 9, the ^1H nmr spectrum of which lacked absorption for the vinylic methyl and allylic alcohol functions. The aromatic methyl which is not *ortho* to the aromatic hydrogen is considerably deshielded (to δ 2.62) in acid 9, suggesting this methyl is *ortho* to the newly introduced carboxyl group. Treatment of 9 with camphorsulfonic acid in methanol-benzene gave the phthalide 5, identical with trisnorcybrodolide isolated from *C. bulleri*. The unambiguous total synthesis of trisnorcybrodolide (5) reported in the accompanying paper firmly establishes the structure and thus also that of cybrodol (2), except for the stereochemistry about the double bond in the latter.

Isocybrodol (3)[3], mp 102-103°, which also readily forms a triacetyl derivative (3a), shows very similar spectral properties to cybrodol, except for the chemical shifts of the olefinic substituents. These are compared below:

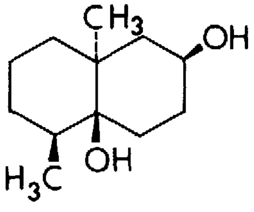
cybrodol,



; isocybrodol,



Ozonolysis of isocybrodol and lactonization provides trisnorcybrodolide (5), showing that it differs from cybrodol only in the stereochemistry about the double bond. Examination of space-filling models reveals that it is impossible for the olefinic group, flanked on both sides by substituents, to achieve coplanarity with the aromatic ring. Indeed, neither cybrodol nor isocybrodol show styrene-type uv spectra[6]. The high-field position of the vinylic methyl group in cybrodol, and its rather low-field position in isocybrodol can be explained if in the former the methyl is in the shielding region of the aromatic ring (i.e., A in 10) and in the latter in the deshielding region (i.e., B in 10)[7]. The hydroxymethyl signals show the same trend. On this basis cybrodol is assigned structure 2, isocybrodol structure 3.



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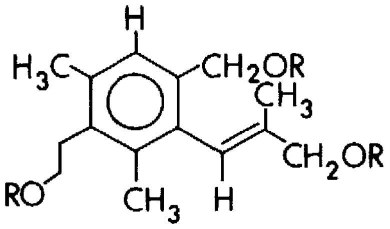
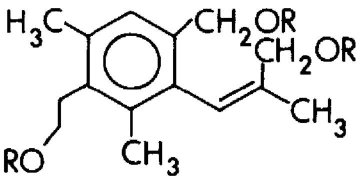
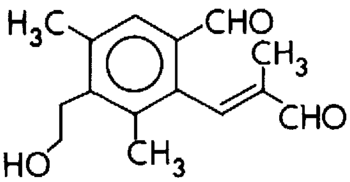


2 R=H
2a R=Ac



3 R=H
3a R=Ac



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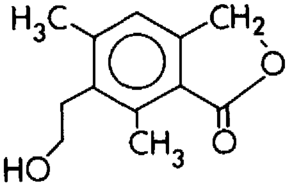

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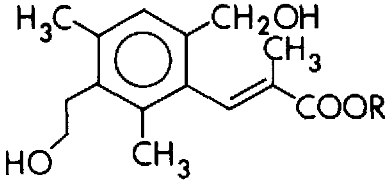
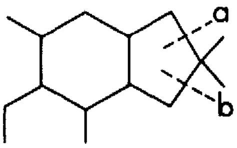


6 R=H
6b R=CH_3



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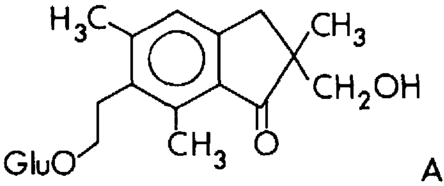

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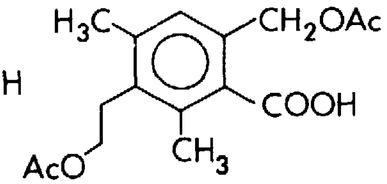

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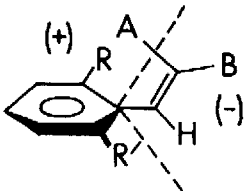

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Cybrodic acid (6), mp 176-178°, readily forms a methyl ester 6a, which on LAH reduction affords cybrodol (2). The ^1H nmr spectrum of cybrodic acid is similar to cybrodol except that the allylic alcohol signal is missing and the olefinic proton (δ 7.65) and the vinyl methyl (δ 1.60) are both deshielded. The substantial downfield shift of the olefinic proton is consistent with its being β and cis to the carboxyl group. The ultraviolet spectrum of methyl cybrodate (6b) (λ_{max} 215 (18,000), 258 nm (4300)) is a composite of an acrylate chromophore and a benzene chromophore and not that of a cinnamate (λ_{max} ~275 nm (~20,000))[8], in agreement with the earlier stereochemical deductions.

Cybrodal (**4**), obtained as an oil[3], shows carbonyl (1690 cm^{-1}) and hydroxyl absorption in the ir, and two aldehyde signals (δ 9.92, 9.75) in the ^1H nmr spectrum. Reduction with LAH provided cybrodol (**2**). Oxidation of cybrodol (**2**) with manganese dioxide gave cybrodal (**4**).

Trisnorcybrodolide (**5**), mp 189-191°; ir 3460, 1732 cm^{-1}, has a simple and characteristic ^1H nmr spectrum showing two aromatic methyls (δ 2.49, 2.73), a single aromatic proton (δ 7.11), a β-hydroxyethyl group (triplets at δ 3.79 and 3.06) and the lactone methylene (δ 5.15). The synthesis of trisnorcybrodolide (**5**) is described in the following communication[9].

The cybrodins **2**, **3**, **4**, and **6** represent the first *seco*-illudalanes (cleavage *a* in **7**) to be reported[10].

References and Notes

1. Part 13 in the series Metabolites of Bird's Nest Fungi. For part 12 see W.A. Ayer, S.P. Lee, and T.T. Nakashima. Canad. J. Chem. **57**, 3338 (1979).
2. W.A. Ayer and M.G. Paice. Canad. J. Chem. **54**, 910 (1976).
3. Because of the small quantities of material available, most molecular formulas have been established by high resolution mass spectrometry. Eventual correlation with compounds of established molecular formula validates the deductions made in this manner.
4. For a summary of sesquiterpenoid skeletons see R.W. Mills and T. Money, in "Terpenoids and Steroids," Vol. 4, ed. K.H. Overton (Specialist Periodical Reports), The Chemical Society, London. 1974. pp 78-81.
5. H. Hikino, T. Takahashi and T. Takemoto. Chem. Pharm. Bull. **20**, 210 (1972).
6. Cybrodol, λ_{max} (MeOH): 210 (6,800), 272 nm (sh, $\varepsilon \approx 320$). Isocybrodol, λ_{max} (MeOH): 210 (6,200), 270 nm (sh, $\varepsilon \approx 350$).
7. L.M. Jackman and S. Sternhell. Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, 2nd Ed. Pergamon Press, Oxford. 1969. pp 94-98.
8. A.I. Scott. Interpretation of the ultraviolet spectra of natural products. Pergamon Press, Oxford. 1964. p 122.
9. W.A. Ayer and R.H. McCaskill. Tetrahedron Letters, following paper.
10. We wish to thank the Natural Sciences and Engineering Research Council Canada for financial support in the form of a research grant (W.A.A.) and a scholarship (R.H.M.).

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