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SYNTHESIS OF HEXAHYDROPOLYANDROCARPIDINE (A REVISED STRUCTURE)[1]

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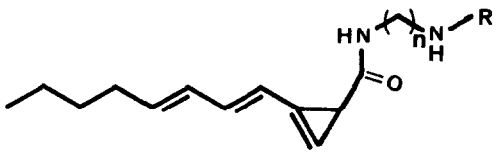
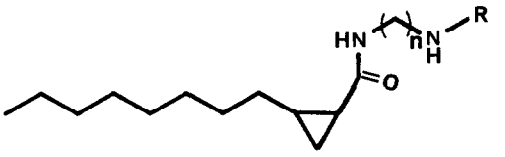
Abstract: The structures previously assigned hexahydropolyandrocarpidines I and II have been revised and hexahydropolyandrocarpidine I [1-(5-guanidinopentyl)-5-octyl-2-pyrrolidinone] has been synthesized.

In 1978 we reported on two compounds from a Polyandrocarpa sp. (compound tunicate) collected at Bahia de Los Angeles in Baja California.[2] These compounds, which we named polyandrocarpidines I and II, have modest antimicrobial and L1210 inhibitory activity and marginal antiviral activity. We have recently concluded that structures 1a, 1b and 2a, 2b, which we earlier assigned[2] to polyandrocarpidines and hexahydropolyandrocarpidines, and 3a,b and 4a,b to their respective 4,6-dimethylpyrimidyl (DMP) derivatives, are incorrect and have assigned structures 5a and 5b to hexahydropolyandrocarpidines I and II and 6a and 6b to their DMP derivatives instead.[1] At the same meeting where our assignment of 5a,b was reported, Carté and Faulkner reassigned the structures of the polyandrocarpidines themselves as 7a-d, based on ozonolysis and ^{1}H NMR evidence, and their work has now appeared.[3]

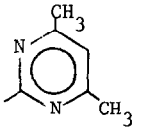
Structures 1a and 1b assigned earlier to the polyandrocarpidines were based on mass spectrometric identification of a C_8 alkyl group (octadienyl and octyl) and an ω-dimethylpyrimidyl-



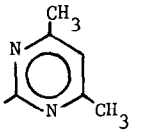
1a, n = 5; 1b, n = 4; R = —C(=NH)NH$_2$



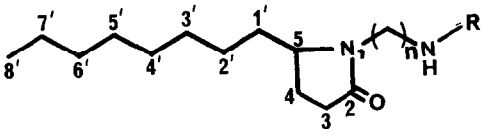
2a, n = 5; 2b, n = 4; R = —C(=NH)NH$_2$



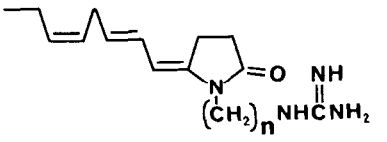
3a, n = 5; 3b, n = 4; R =



4a, n = 5; 4b, n = 4; R =

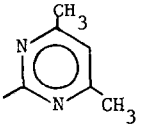


5a, n = 5; 5b, n = 4; R = —C(=NH)NH$_2$



7a, n = 5; 7b, n = 4

7c, n = 5; 7d, n = 4; $\Delta^{2',3'}$ cis



6a, n = 5; 6b, n = 4; R =

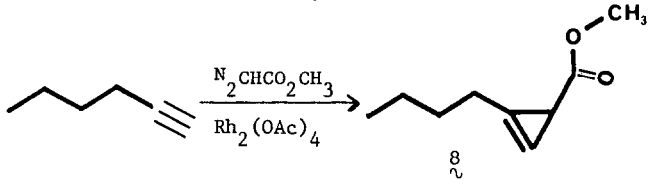
aminoalkyl group, $H_2NC(=NH)NH(CH_2)_n-$ (n = 4 or 5), in the DMP derivatives of the polyandrocarpidines (assigned structures 3a and 3b) and their hydrogenated derivatives (assigned structures 4a and 4b). The remaining portion of the polyandrocarpidines, C_4H_3NO, was assigned[2] as a substituted cyclopropenecarboxamido group, $-\underline{C=CH}\underline{C}HCONH$, partly from high resolution mass spectrometric data on the DMP derivative of hexahydropolyandrocarpidine, partly by analogy to the guanidinylated structure of the acarnidines we had previously assigned,[4] e.g.

$$CH_3(CH_2CH=CH)_2CH_2CH_2CH=CHCH_2CH_2CON[(CH_2)_3NHCOCH=C(CH_3)_2](CH_2)_5NHC(=NH)NH_2$$

for 14:3-acarnidine, and partly by negative inference (lack of allene absorption).

The cyclopropenoid structures we originally assigned were sufficiently novel that we synthesized the compounds (cis and trans isomers) having the structure 2a assigned hexahydropolyandrocarpidine I and noted that the DMP derivative (4a) of one of the two stereoisomeric synthetic cyclopropanes had the same GC retention time on an OV-17 column as the derivative of the hydrogenated natural product and coeluted, apparently confirming the structure.[5] In addition, hexahydropolyandrocarpidine (a mixture of I and II) and synthetic 2a and 2b all had similar antimicrobial activity.[6]

Recently, however, we have synthesized the cyclopropenecarboxylate 8 by the route shown[7] as a model for the proposed structures (1a,b) of the polyandrocarpidines. To our chagrin, the ^{13}C and ^{1}H NMR chemical shifts of the =CH— group in the cyclopropene 8 (δ 94.4 and 6.4) were somewhat different from those of polyandrocarpidine I (δ 103.2 and 5.5) and the ^{13}C chemical shift for the quaternary cyclopropene carbon was dramatically different (δ 115.7 for 8 vs. 141 for polyandrocarpidine I), requiring rejection of structure 1a,b. Another compelling argument against structure 1a was the observation that, while the dimethylpyrimidines from hexahydropolyandrocarpidine I and synthetic 4a appear, as noted, as a single GC peak on coinjection on OV-17,[5] and have the same mass spectral peaks, on closer examination the relative intensities of the mass spectral peaks due to loss of portions of the n-octyl group (M - CH_3 to M - C_8H_{15}) differ, being much stronger for the DMP derivative from the hydrogenated natural product.



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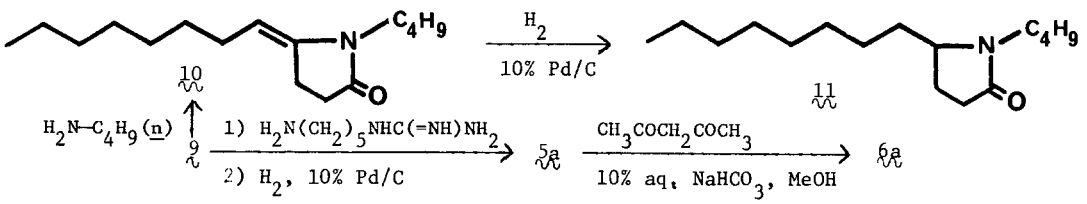
These discrepancies between the previously proposed structure and our recent observations of properties for synthetic models can be satisfactorily explained by revised structures 5a and 5b for hexahydropolyandrocarpidines I and II, since cleavage in the n-octyl group of their DMP derivatives (6a,b) would be enhanced by the adjacent nitrogen.[8] According to this proposal, polyandrocarpidines I and II would be $\Delta^{4,5}$ or $\Delta^{5,1'}$ enamides related to 5a,b, resulting from the addition of the amide nitrogen to a γ-keto group in the acyl unit. An enamide structure would explain the low-field off-resonance singlet (δ 141) and high-field doublet (δ 103) in the olefinic region of the ^{13}C NMR spectrum of the polyandrocarpidines.[9,10]

To prepare a model compound methyl 4-oxododecanoate (9, n-$C_8H_{17}COCH_2CH_2COOCH_3$), synthesized by a standard route,[11] was condensed with n-butylamine to give 10, whose ^{13}C NMR spectrum contained off-resonance singlet and doublet signals for the enamide at δ 139.9 and 100.7,

respectively (cf. polyandrocarpidine above), and whose EI mass spectrum contained as a base peak m/z 166, arising from allylic cleavage and locating the alkene bond as $\Delta^{5,1'}$. Hydrogenation of 10 gave 11, whose mass spectrometric fragmentation pattern in the M - CH_3 to M - C_8H_{17} region mirrored that of the DMP derivative of hexahydropolyandrocarpidine. To prepare hexahydropolyandrocarpidine itself the keto ester 9 was condensed with 1-amino-5-guanidinopentane and reduction of the product gave 5a, whose DMP derivative (6a) had GC retention times on both OV-17 and Tabsorb as well as gas chromatographic mass spectra (Fig. 1) identical to those of the DMP derivative of hexahydropolyandrocarpidine I. The structures of the hexahydropolyandrocarpidines are, thus, established now as 5a and 5b.



The positions of the double bonds in polyandrocarpidine itself can be argued to be $\Delta^{5,1';2',3';5',6'}$ with some reservations, as follows. The UV spectrum (λ_{max} 275 nm) would agree with that expected for a dienamide[12,13] but not a trienamide, locating a 4'-methylene group. The third alkene linkage is then assigned as $\Delta^{5',6'}$ (rather than $\Delta^{6',7'}$) from the ^{1}H NMR triplet for the terminal methyl group at 0.99 ppm.[6] The arguments previously advanced[2,6] for the location of the double bonds are invalid since the enamide nature of polyandrocarpidine invalidates the previous UV interpretation of a triene unit and since formation of the DMP derivative in base, with possible rearrangement of the alkene linkage, invalidates the previous interpretation of the mass spectrum of the DMP derivative of polyandrocarpidine. Although no sample of the natural product remained for our reinvestigation, the studies of Carté and Faulkner[3] on chromatographically separated samples provide convincing arguments for the location and stereochemistry of the alkene linkages as depicted in 7a-d.

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References and Notes

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3. B. Carté and D. J. Faulkner, 4th IUPAC International Symposium on Marine Natural Products, Tenerife, Spain, July 26-30, 1982; Tetrahedron Lett. 23, 3863 (1982).
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5. We have more recently shown that one stereoisomer of 4a also has the same GC retention time as the DMP derivative of hexahydropolyandrocarpidine I, and coelutes, on a Tabsorb column.
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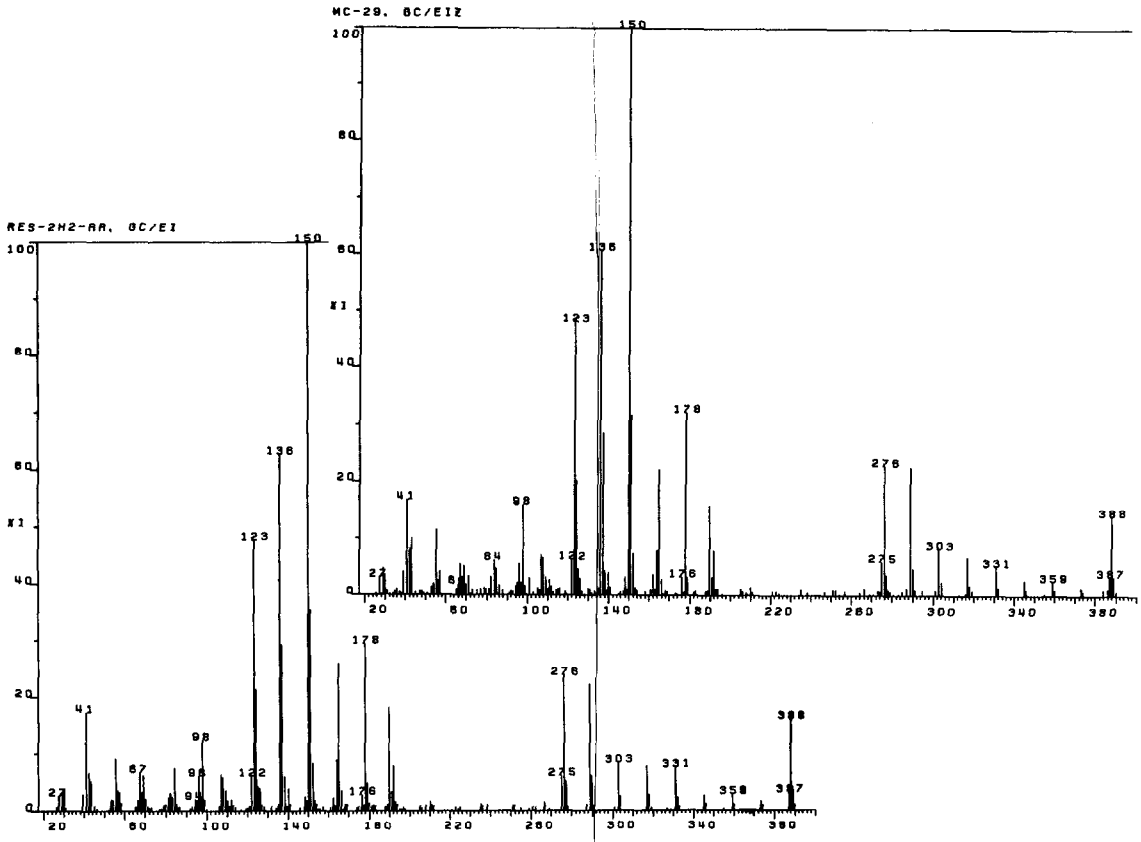

Fig. 1. Gas chromatographic mass spectra (EI, 70 eV) of the DMP derivative of hexahydropolyandrocarpidine (lower left) and of synthetic 6a (upper right).

8. Cf. e.g., N-(n-hexyl)acetamide (EPA/NIH Mass Spectral Data Base, Vol. 1, S. R. Heller and G. W. A. Milne, eds., U.S. Govt. Printing Office, Washington, D.C., 1978, p. 386).
9. For example, the 1' and 2' vinyl carbons of N-vinylpyrrolidone appear at 129.2 and 93.8 ppm, respectively (L. F. Johnson and W. C. Jankowski, Carbon-13 NMR Spectra, Wiley-Interscience, New York, 1972, Spectrum 173).
10. The newly proposed enamide structures would explain an earlier observation made during an unsuccessful attempt to isolate 2-octylcyclopropanecarboxylic acid.[6] Hydrolysis carried out on "hexahydropolyandrocarpidine" followed by methylation gave, in very low yield, the same keto ester (9) used in the synthesis of 10 and 5a (see text), which was identified by its GC/MS fragmentation pattern. It is now presumed that the small amount of this keto ester obtained was the hydrolysis-methylation product of partially hydrogenated polyandrocarpidine, an enamide. Hexahydropolyandrocarpidine itself (5a,b) cannot, of course, hydrolyze easily and the products would be nonvolatile.
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