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ASTROCASINE: A NEW EUPHORBIACEAE ALKALOID

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An alkaloid representing a new type of carbon skeleton has been isolated from Astrocasia phyllantoides, a shrub of the Euphorbiaceae family. We have named it astrocasine and propose structure I on the following evidence.

Astrocasine, m.p. 171-172°, $[\alpha]_D^{24}$ -270° (ethanol), was assigned the formula $C_{20}H_{26}N_2O$ (1). The empirical formula was confirmed by high resolution mass spectrometry with a molecular ion peak at m/e 310.2044 (2) (Calcd. mass with C = 12.000, 310.2045). The base forms a monoperchlorate, $C_{20}H_{27}N_2O_5Cl$, m.p. 149-151°, and a monomethiodide, $C_{21}H_{29}N_2OI$, m.p. 227-228°. The presence of one N-CH_3 and absence of C-CH_3, O-CH_3 or N-acetyl groups in astrocasine was shown by microanalysis and confirmed by n.m.r.

The infrared ($\nu_{max}^{CCl_4}$ 1645, 1610, 1597, 1570 cm.$^{-1}$), ultraviolet ($\lambda_{max}^{ethanol}$ 263 mμ, log ε 4.09) and n.m.r. (3) spectra (4 aromatic H, δ7.31 - 7.49; 2 olefinic H as 2 doublets centered at δ7.08 and 6.43, J = 12 cps) of astrocasine fit best a nearly planar cis-cinnamoyl (4) N-dialkylated lactam structure.

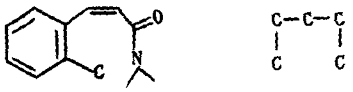
The double bond was reduced easily at room temperature and atmospheric pressure in the presence of Pd/C and the resulting dihydroastrocasine exhibits the characteristic UV spectrum of a simple aromatic system ($\lambda_{max}^{ethanol}$ 262 mμ, log ε 2.44 and 271 mμ log ε 2.29) whereas the infrared absorption is that of an N-dialkylated lactam (1628 cm.$^{-1}$ with shoulder at 1651 cm.$^{-1}$). Dihydroastrocasine, $C_{20}H_{28}N_2O$, m.p. 121-122°, $[\alpha]_D^{24}$ +235° (ethanol), gives a methiodide, $C_{21}H_{31}N_2OI$, m.p. 278-280°d.

Astrocasine was reduced rapidly with lithium aluminum hydride in ether, at room temperature, forming an oily oxygen-free base, desoxyastrocasine. This gave a hydrated dihydrochloride, $C_{20}H_{30}N_2Cl_2.H_2O$, m.p. 220°d, λ_{max}^{EtOH} 244 mμ (log ε 3.94). The oily desoxybase also formed a diperchlorate, $C_{20}H_{30}N_2O_8Cl_2$, m.p. 221-223°. The n.m.r. spectrum of desoxyastrocasine shows one olefinic proton as a doublet centered at δ 6.94 (J = 10 cps). The other olefinic proton is now split into a pair of triplets centered at δ 6.27 and 6.10 (J = 6.5 cps). The newly formed methylene group between the double bond and the nitrogen atom appears as a pair of doublets centered at δ 3.05 and δ 3.01 (J = 6.5 cps).

Catalytic reduction (Pd/C in ethanol) of desoxyastrocasine or treatment of dihydroastrocasine with lithium aluminum hydride in refluxing tetrahydrofuran gave an oily base, $[\alpha]_D^{24}$ +82°, $C_{20}H_{30}N_2$, dihydrated dipicrate, $C_{20}H_{30}N_2.C_6H_3H_3O_7.2\ H_2O$, diperchlorate, $C_{20}H_{32}N_2O_4Cl_2$, m.p. 278-280° and dimethiodide, $C_{29}H_{36}N_2I_2$, m.p. 270°d.

The infrared spectra of astrocasine and its reduction products are consistent with an o-disubstituted aromatic ring. This conclusion was substantiated by the isolation of phthalic acid from the oxidation of the alkaloid with potassium permanganate in water at room temperature.

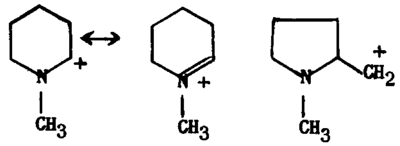
Phthalonic, oxalic, malonic, succinic and glutaric acids were also isolated in this oxidation. Therefore astrocasine has the partial structure:



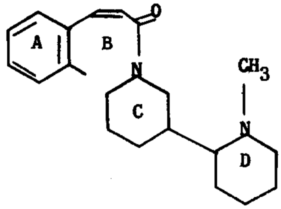
Hofmann degradation of astrocasine methiodide produced only unchanged alkaloid. However, the reaction proceeded smoothly with dihydroastrocasine methiodide under the same conditions yielding an oily methine base (Calcd. m/e for $C_{21}H_{30}N_2O$: 326.2358. Found m/e: 326.2352) whose n.m.r. spectrum shows 2 olefinic protons in a broad band at δ 5.5. The infrared spectrum of the methine suggests that the double bond is trans-disubstituted since a strong band is present at 972 cm.$^{-1}$ and disappears upon hydrogenation.

When this methine (V) was oxidized with osmium tetroxide-sodium metaperiodate in tetrahydrofuran, a neutral aldehyde $C_{15}H_{17}NO_2$ was obtained as an oil, $\nu^{CCl_4}_{max}$ 2720, 1736 cm.$^{-1}$, 2,4-dinitrophenylhydrazone, $C_{21}H_{21}O_5N_5$, m.p. 190° d.

The type of substitution on the double bond of the methine and the loss of the basic $-N(CH_3)_2$ moiety together with four other carbons upon oxidation can be accounted for by the presence of either an α-N-methyl-piperidine or an α-N-methylpyrollidine ring in the alkaloid. The most intense fragment, m/e 98.0968 (2), (Calcd. for $C_6H_{12}N$: 98.0969) observed in the mass spectra of both the alkaloid and its dihydro derivative may be attributed to the resonance stabilized N-methylpiperidyl cation rather than to the N-methylpyrollidylmethyl cation.

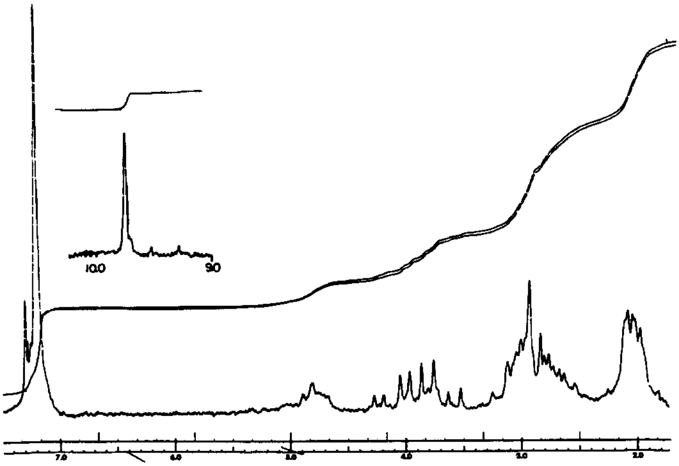


Biogenetic considerations and analogy with the known alkaloid orensine VIII (5) (an N-trans-cinnamoyltetrahydroanabasine which can be resolved into d- and l-adenocarpine) led us to the following partial structure for astrocasine:



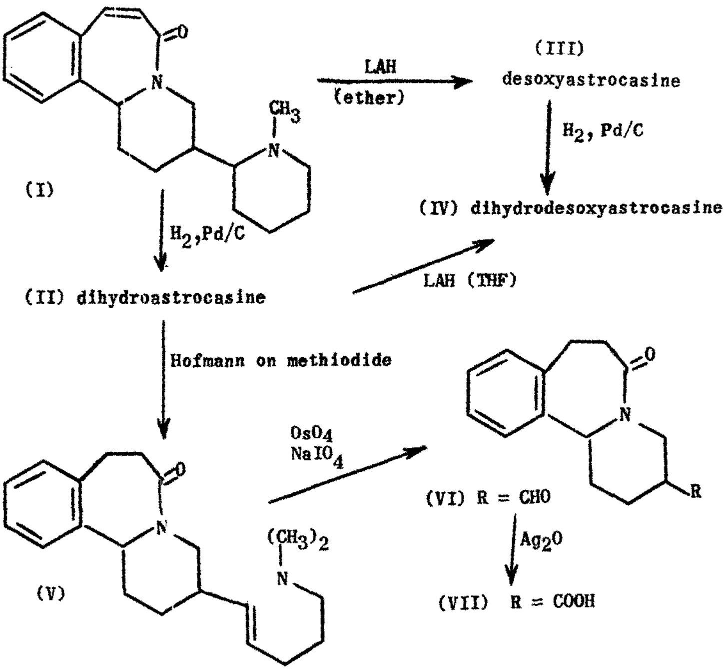
Ring closure alpha to the nitrogen of ring C results in structure I for astrocasine and VI for the Hofmann-derived aldehyde. All the features of the n.m.r. spectrum of the aldehyde are best explained by this structure (fig. 1). One aldehydic proton appeared as a sharp signal at δ9.75, at first suggesting that the neighboring carbon was fully substituted; but when the scale was expanded the signal was resolved as a doublet (J = 0.8 cps). The 4 aromatic protons give rise to a signal at δ7.2; a broad triplet at about 4.80 may be assigned to the lone benzylamido proton and the very sharply defined peaks between δ4.3 and 3.5 (2H) form a typical AB pattern of an ABX system and may be assigned to the non-equivalent methylene protons next to the lactam nitrogen. The next group of peaks (δ3.3 to 2.5) is a distinctive A_2B_2 or AA'BB' system arising from the 2 methylene groups between the aromatic ring and the carbonyl carbon. It integrated for 5H showing that the methine proton next to the aldehyde group (X of the ABX system) absorbs between these frequencies. The remaining 4 protons appear between δ 2.3 - 1.7, a value consistent with structure VI.

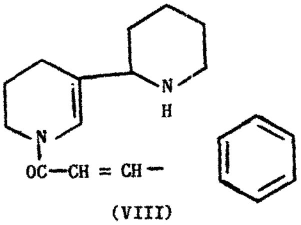
FIG. 1

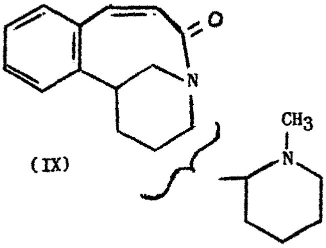


Atom bridged isomers such as IX might also be accomodated by the observed n.m.r. spectrum but are eliminated by consideration of the ultraviolet and infrared spectra as well as the chemical properties of the original alkaloid.

The aldehyde was oxidized with silver oxide to an acid (VII), $C_{15}H_{17}NO_3$, m.p. 225-229°. Mass spectrometry confirmed the empirical formula; its fragmentation was in accord with the proposed structure


(I)
LAH
(ether)
(III)
desoxyastrocasine
H2, Pd/C
(IV) dihydrodesoxyastrocasine
H2,Pd/C
(II) dihydroastrocasine
LAH (THF)
Hofmann on methiodide
OsO4
NaIO4
(V)
(VI) R = CHO
Ag2O
(VII) R = COOH


(VIII)


(IX)

and will be reported in the full paper along with stereochemical considerations of the parent alkaloid.

REFERENCES

1. All the compounds reported gave satisfactory elemental analyses.

2. We are indebted to Dr. Martin Eliott of Associated Electronic Industries, Manchester, England, for this measurement.

3. The n.m.r. spectra were taken in deuterochloroform with tetramethylsilane as internal standard on a Varian A-60 spectrometer.

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