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ALKALOIDS OF ASTROCASIA PHYLLANTHOIDES II. ASTROPHYLLINE

H. A. Lloyd
Laboratory of Metabolism, National Heart Institute
Bethesda, Maryland

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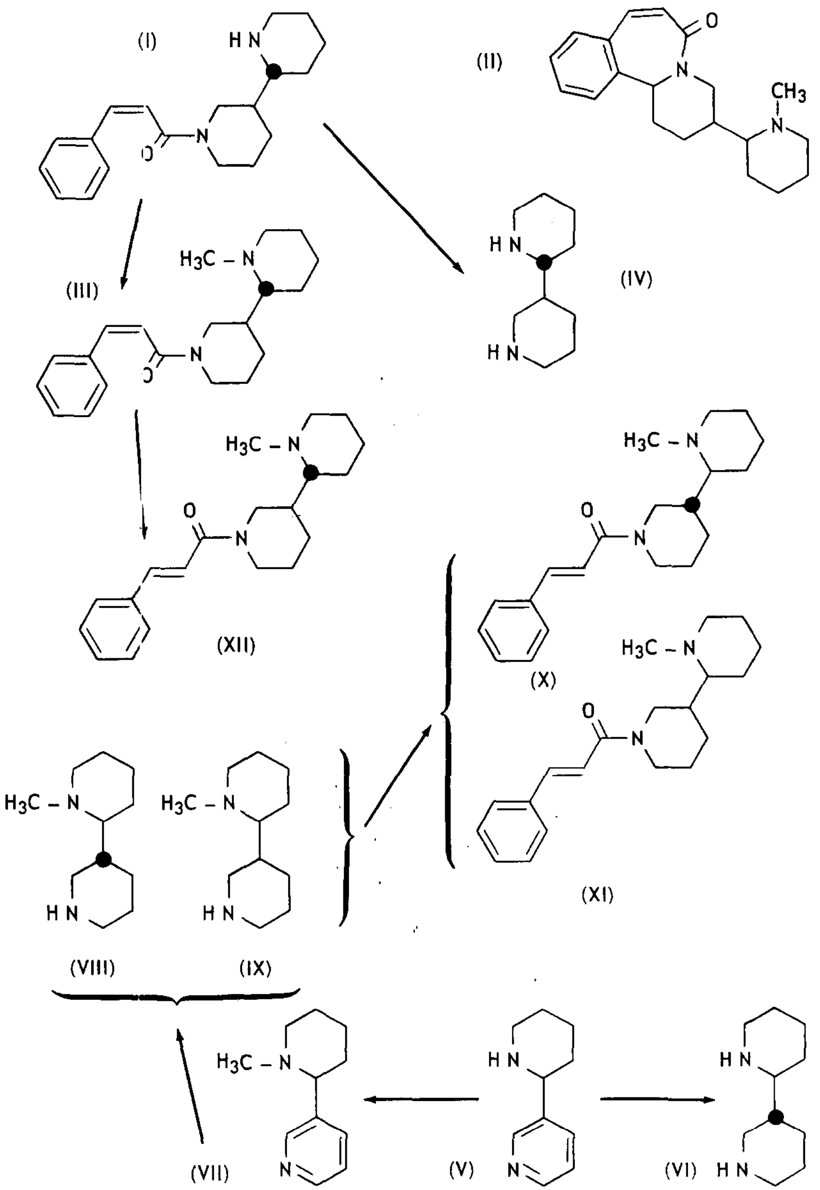
A new alkaloid, astrophylline, has been isolated from *Astrocasia phyllanthoides*. Its structure (I), an N-*cis*-cinnamoyl α, β dipiperidyl, lends support to the structure proposed recently (1) for another alkaloid of the same plant, astrocasine (II), and suggests a biogenetic relationship between the two alkaloids. Evidence for the structure and absolute configuration of astrophylline is presented below.

The free base (I), $C_{19}H_{26}N_2O$ (2), $[\alpha]_D$ +23°, was obtained as a viscous oil, b.p. 115°/.001mm., and purified through its perchlorate $C_{19}H_{27}N_2O_5Cl$, m.p. 172-174°. The empirical formula was confirmed by high resolution mass spectrometry with a molecular ion peak at m/e 298.201 (Calcd. mass with C = 12.000, 298.204) and also by analyses on a monopicrate $C_{25}H_{29}N_5O_8$, m.p. 146-148°d.

The basic nitrogen of astrophylline is secondary (positive Simon test (3), broad infrared band at 3350 cm.$^{-1}$) and an N-methyl derivative (III) was easily prepared with formic acid-formaldehyde ($C_{20}H_{28}N_2O$, oil, $[\alpha]_D$ +92°, λ_{max} 254 mμ, log ε 4.05, perchlorate $C_{20}H_{29}N_2O_5Cl$, m.p. 152-154°). The presence of a monosubstituted benzene ring was shown by n.m.r. (5 aromatic protons) and confirmed by permanganate oxidation of the alkaloid to benzoic acid. The infrared (ν_{max} 1645, 1620, 1580 cm.$^{-1}$), ultraviolet (λ_{max} 254 mμ, log ε 4.05) and n.m.r. spectra (2 olefinic protons as 2 doublets centered at


(I)
(II)
(III)
(IV)
(XII)
(X)
(XI)
(VIII)
(IX)
(VII)
(V)
(VI)

δ6.64 and δ6.01, J = 12 cps.) also suggested a cis-cinnamoyl disubstituted amide system (4).

Hydrolysis of astrophylline in 6N HCl at 120° for 12 hours proceeded quantitatively to give trans-cinnamic acid and a base (IV), $C_{10}H_{20}N_2$, m.p. 67-68°, $[\alpha]_D$ +5°, which was identified as (+)α,β dipiperidyl (5) (dihydrochloride, m.p, 360° d., $[\alpha]_D$ +6°; dipicrate, m.p. 213-215°; dibenzoate, m.p. 152-154°, $[\alpha]_D$ +179°). The n.m.r. spectrum of the base and the infrared spectra of the base and its derivatives were identical to that of an authentic sample of (-)α,β dipiperidyl (VI) prepared by catalytic hydrogenation of (-)anabasine (V) (6).

Although trans-cinnamic acid was obtained in the hydrolysis, the cis-cinnamoyl system is present in the original alkaloid as shown by the ultraviolet absorption and the typical n,m,r. spectrum of the base. Astrophylline was converted to a trans-isomer by heating it in a sealed tube at 220° for 12 hours. No starting material was recovered after this treatment and an oily base having approximately twice the retention time of astrophylline on vapor phase chromatography (7) was obtained. It had the same empirical formula as astrophylline (mass spectrometry), ultraviolet absorption at λ_{max} 281 mμ, log ε 4.30, and the 2 olefinic doublets in the n,m,r. spectrum were now centered at δ7.56 and δ6.95 (J = 16 cps.). Similarly N-methylastrophylline, heated at 250°, yielded trans-N-methylastrophylline (XII), $C_{20}H_{28}N_2O$, m.p. 92-94°, $[\alpha]_D$ +99°, λ_{max} 281 mμ, log ε 4.30.

It remained to determine which of the 2 nitrogen atoms of the alkaloid is attached to the cinnamoyl group. For this purpose the N-methyldipiperidyl obtained by hydrolysis of N-methylastrophylline was compared to a synthetic N-methyldipiperidyl prepared by catalytic hydrogenation (PtO_2 in HCl, at atmospheric pressure) of (-)N-methylanabasine (VII). Unfortunately, VII gave an equimolecular mixture of the 2 possible epimers VIII and IX, in contrast to (-)anabasine (V) which yields only one isomer (VI) under the same conditions (6). Separation of the isomers was unsuccessful, but the mixture, upon reaction with cinnamoyl chloride, yielded the 2 corresponding N-trans-cinnamoyl-N'-methyldipiperidyls X and XI which were separated by chromatography on alumina. One of the bases $C_{20}H_{28}N_2O$, m.p. 93-94°, $[\alpha]_D$ -102°, was the enantiomorph of trans-N-methylastrophylline (XII) with identical infrared, ultraviolet and n.m.r. spectra and a mirror image O.R.D. curve.

This evidence establishes the structure of astrophylline. Furthermore since the absolute configuration of (+)α,β dipiperidyl is known (8), it also establishes the absolute configuration of the alkaloid as N-cis-cinnamoyl-3(S)-[2'(R)-piperidyl]-piperidine.

References

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