Tetrahedron Letters No. 1, pp 89 - 92, 1972. Pergamon Press. Printed in Great Britain.

CATHARANTHUS ALKALOIDS. XXVII.

CATHANNEINE, A NEW ALKALOID FROM CATHARANTHUS LANCEUS

G.H. Aynilian, M. Tin-Wa and N. R. Farnsworth

Department of Pharmacognosy and Pharmacology, College of Pharmacy,

University of Illinois at the Medical Center, Chicago, Illinois 60612

and

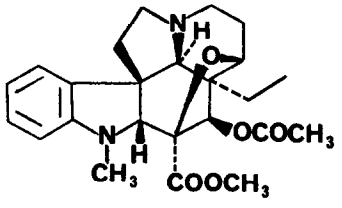
M. Gorman

Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, Indiana 46206

(Received in USA 19 October 1971; received in UK for publication 6 December 1971)

Cathanneine(I), $C_{24}H_{30}N_2O_5$, a dihydroindole alkaloid, has recently been reported isolated from the leaves of *Catharanthus lanceus* (Boj. ex. A. DC.) Pich. (1). Data have been accumulated to indicate that this new alkaloid contains a cyclic ether moiety. Mallett *et al.* (2) have reported on the isolation of several metabolites, including desacetyldihydrovindoline ether, after a vindoline substrate was incubated with a growing culture of *Streptomyces cinnamonensis*. Recently, Battersby and Gibson reported on a dihydrovindoline ether derivative obtained from the oxidation of vindoline with chromium trioxide and pyridine (3).

After analyzing the accumulated data, structure I was proposed for cathanneine. At this stage, the stereochemical implications are tentative, and will be discussed in a later paper.



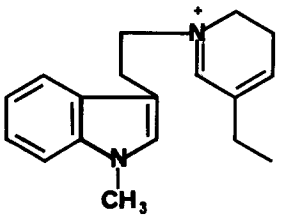
Cathanneine(I)

An examination of the ultraviolet spectrum of I showed it to be a dihydroindole derivative, with λ_{max} being at 208nm, 255nm and 308nm (1). The infrared spectrum of I in KBr showed 3 bands at 1740(s), 1250(m) and 1170(w) cm^{-1}, which tentatively were assigned to ester, carbomethoxy and acetate functions respectively. A band at 1600(s) cm^{-1} was assigned to the indoline moiety, while two bands at 1500(s) and 1460(s) cm^{-1}, together with a strong band at 740 cm^{-1}, gave evidence for an aromatic moiety with four adjacent protons. The absence of bands above the 2900 cm^{-1} region suggested the absence of -NH and -OH groups.

An NMR spectrum of I was analyzed in comparison with vindoline* and vindorosine (4,5). Four aromatic protons formed a multiplet centered at 6.83δ, with the protons at C-2, C-4, and C-19 showing unsplit peaks having chemical shifts of 3.81, 5.32 and 3.58δ. The latter was deshielded more than the corresponding proton in vindoline (2.66δ) due to the ether bridge.

The ether proton at C-6, having a chemical shift of 4.08δ, was split by the 2 nonequivalent protons at C-7 into 2 doublets. Protons of the methylene portion of the C-ethyl group were found as a multiplet centered at 1.39δ (J = 7.0 Hz). A symmetrical methyl triplet was found at a high field 0.78δ (J = 7.0 Hz). The C-7 and C-11 protons were found as a multiplet in the region of 2.12-2.67δ, whereas the protons next to the N on C-8 and C-10 were shifted to 2.67-3.08δ, and appeared as a multiplet. The $N\text{-}CH_3$, $-COOCH_3$ and $-OCOCH_3$ appeared as three proton singlets at 2.80, 3.68 and 1.94δ respectively. The mass spectrum of cathanneine exhibited all the intense peaks of aspidospermine-type alkaloids (6). Its characteristic peaks when compared with dihydrovindorosine were at the same masses except m/e 267 and m/e 123, which were shifted lower by 1 m/e due to the cleavage of the ether bridge.

A molecular ion M^+ of 426 was observed in the mass spectrum of cathanneine, followed by the less abundant *ion i*, m/e 367 (loss of carbomethoxy group). The base peak, *ion a* at m/e 267, with a metastable peak at m/e 167.3 was formed by a retro-Diels-Alder type reaction, followed by cleavage of the ether bridge, which resulted in expulsion of the neutral olefinic group.

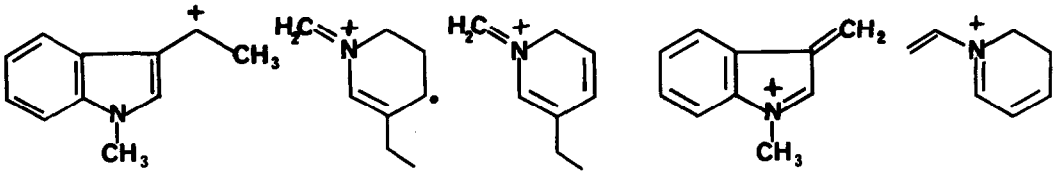


ion a m/e 267

Further fragmentation of *ion a* gave rise to *ion b*, with a metastable peak at m/e 93.5, and *ions c-f*.

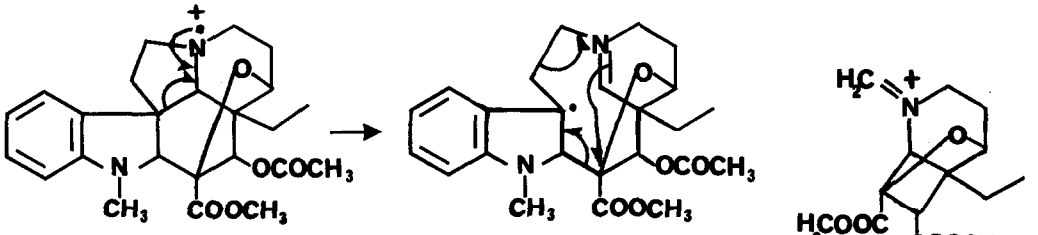
---

*Spectrum recorded using a Bruker HFX-5, 90 MHz instrument in $CDCl_3$ with tetramethylsilane as internal standard. Values δ TMS = 0.



ion b m/e 158 *ion c* m/e 123 *ion d* m/e 122 *ion e* m/e 144 *ion f* m/e 108

Another mechanism which seemed to be operating along with that leading to *ion a* was that involving cleavage of the C 12-19 bond and the formation of *ion g*. (7).



M^+ 426 *ion g* m/e 282

High resolution measurements (Table I) of these ions are in agreement with the fragmentation hypothesis.

Table I. High Resolution Measurements of Cathanneine

Formula	Observed m/e	Calculated m/e
$C_{24}H_{30}N_2O_5$	426.21457	426.21484
$C_{22}H_{27}N_2O_3$	367.20217	367.20227
$C_{14}H_{20}N_1O_5$	282.13415	282.13410
$C_{18}H_{23}N_2$	267.18612	267.18559
$C_{11}H_{12}N_1$	158.09688	158.09697
$C_{10}H_{10}N_1$	144.08132	144.07981
$C_8H_{13}N_1$	123.10480	123.10273
$C_8H_{12}N_1$	122.09697	122.09658
$C_7H_{10}N_1$	108.08132	108.08128

The possibility of a carbinolamine moiety in the structure, involving an ether linkage at C-8, C-10 or C-19 was ruled out when Cathanneine remained unchanged after treatment with sodium borohydride and silica gel G. Furthermore, the appearance of 2 doublets, instead of a multiplet at 4.08δ, and the very high strain if the ether linkage was attached at C-7, suggested that it was attached at C-6.

Acknowledgements.- This study was supported by research grant CA-12230 from the National Cancer Institute, Bethesda, Maryland, 20014. We wish to thank Dr. Thomas Glonek for supplying the 90 MHz NMR measurements.

REFERENCES

1. G.H. Aynilian, N. R. Farnsworth, R. L. Lyon and H. H. S. Fong, *J. Pharm. Sci.*, in press.
2. G.E. Mallett, D. S. Fukuda and M. Gorman. *Lloydia*, 27:334-339. (1964)
3. A. R. Battersby and K. H. Gibson, *J. Chem. Soc. D.*, 1971:902-903.
4. M. Gorman, N. Neuss and K. Biemann. *J. Am. Chem. Soc.*, 84:1058-1059 (1962).
5. B.K. Moza and J. Trojánek. *Collection Czech. Chem. Commun.*, 28:1427-1432 (1963).
6. K. Biemann, M. Friedmann-Spiteller and G. Spiteller. *J. Am. Chem. Soc.*, 85:631-638 (1963).
7. H. Budzikiewicz, C. Djerassi and D.H. Williams. *Structure Elucidation of Natural Products by Mass Spectrometry*. Holden-Day, Inc., Vol. I. p. 101 (1964).