Progress in The Chemistry of Cyclopeptide Alkaloids Containing a Styrylamine Unit*

A.H.SHAH AND V.B.PANDAY+
Department of Chemistry, Gomal University, D.I.Khan, Pakistan
+Department of Medicinal Chemistry, Institute of Medical Sciences, B.H.U., Varanasi 221005 India

(Received 12th July, 1984, Revised 5th September, 1984)

The cyclopeptide alkaloids are polyamide plant bases composed of amino acid residues in common and highly modified forms. All so far known cyclopeptide alkaloids with the exception of lasiodineA [1] are cyclic, containing 13-, 14-, and 15-membered ring systems.

In 1963 a French group for the first time isolated and then gave the correct formulae of three 14-membered cyclopeptide alkaloids namely adouetine-X,-Y and -Z [2]. Derivatives of the 13-membered ring type were first isolated by Zbiral et al.[3], though the supposed structures have later to be revised. The correct formulae for 13- and 15-membered cyclopeptide alkaloids were first determined by R.Tschesche et al[4-6] in 1973-74. The major contributions in this field have been made by the groups working in Bonn and Paris, while others have done some important contributions.

Cyclopeptide alkaloids are particularly common in the plants of family Rhamnaceae and occasionally they are found in the plants of Sterculiaceae, Pandaceae, Urticaceae, Rubiaceae and Hymenocardiaceae; however, the distribution in the plant kingdom was not carefully investigated. The yield of total alkaloids from dried plant material mostly varies from 0.01 to 0.1%. The compounds are present in the leaves and bark and occur in most cases as complexed mixtures difficult to separate [7].

The isolation of alkaloids from ground plant material is generally achieved by the usual procedures. A simplified method is the extraction with a mixture of benzene: methanol: ammonia (100:1:1). From the combined benzene extract the rough bases are separated by shaking with 5% citric acid. The troublesome emulsions are largely avoided by this method. The isolation of the pure alkaloids is usually achieved by repeated chromatography on silica gel columns or plates with different solvent systems. Because of very little difference in the R_f values separation is tedious and sometimes even not possible [6]. In some cases such as isolation of sativanine-F[8], HPLC has been helpful. For identification of the isolated compound alongwith IR, UV, NMR mass spectrometry is the methods of choice and more informative [9].

Classification

The cyclopeptide alkaloids incorporate an alkoxy styrylamine unit as an integral part of 13-, 14-, or 15-membered heterocyclic rings. The size of the ring has been adopted as the basis for the classification of members of this group of natural products.

In 13-membered cyclopeptide alkaloids 2-methoxy-5-hydroxy styrylamine unit is bound to an α-amino acid and a β-hydroxy-α-amino acid forming

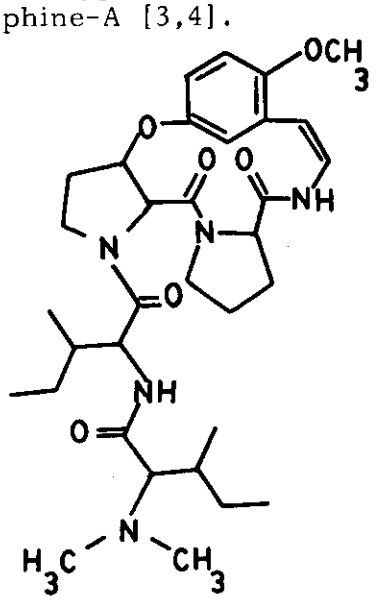
+ Dedicated to our kind teacher Late Professor Dr.Rudolf Tschesche.

Table -I

ZIZYPHINE-A TYPE

Name	Ring bound amino acid	Inter-mediate amino acid	Basic end amino acid	Molecular formula	MW	mp (°C)	$[\alpha]_D$	Refs.
Zizyphine-F	Pro	Ile	Dimethyl Ile	$C_{32}H_{47}N_5O_6$	597	235	-277°	15
Jubanine-A	Ile	Phe	Dimethyl Phe	$C_{40}H_{49}N_5O_6$	695	105-10	-326°	16
Jubanine-B	Phe	Phe	Dimethyl Phe	$C_{43}H_{47}N_5O_6$	729	97-100	-218°	16
Nummularine-H	Ile	Phe	Methyl Phe	$C_{39}H_{47}N_5O_6$	681	196	-343°	17
Sativanine-C	Ile	Val	Methyl Ala	$C_{29}H_{43}N_5O_6$	557	113-14	-	8
Sativanine-D	Ile	Val	Dimethyl Ala^{++}	$C_{30}H_{43}N_5O_6$	569	119-21	-	8
Sativanine-E	Leu	-	Dimethyl Trp	$C_{33}H_{41}N_5O_5$	587	127-28	-99°	8
Sativanine-F	Phe	Val	N-Formyl Val	$C_{34}H_{43}N_5O_7$	633	278-79	-	8
Sativanine-G	Ile	-	Dimethyl Ile	$C_{28}H_{42}N_4O_5$	514	92	-	18
Nummularine-N	Phe	Val	Dimethyl Gly	$C_{32}H_{41}N_5O_6$	591	243-45	-	19

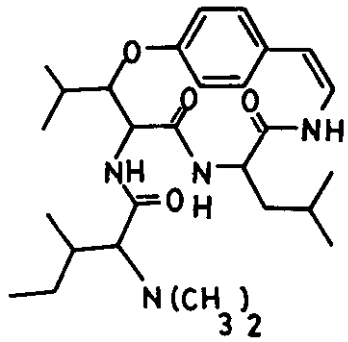
a ring. A typical example of this type is zizyphine-A [3,4].



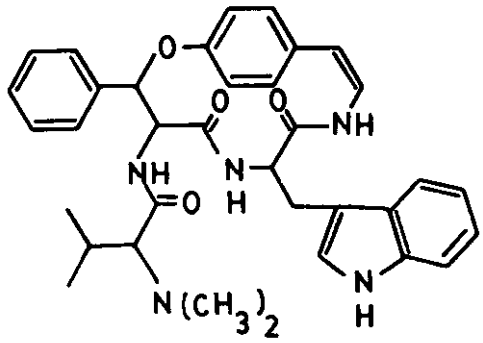
ZIZYPHINE-A-

The alkaloids containing 14-membered ring are the largest group. The ring system contains an α-amino acid, a β-hydroxy-α-amino acid and a β-hydroxy styrylamine unit. It can be subdivided into three subgroups depending on the β-hydroxy amino acid participating on the ring formation; namely β-hydroxyleucine (frangulanine-type), β-hydroxy phenylalanine (integerrine-type), and trans-3 -hydroxyproline (amphibine-B-type).

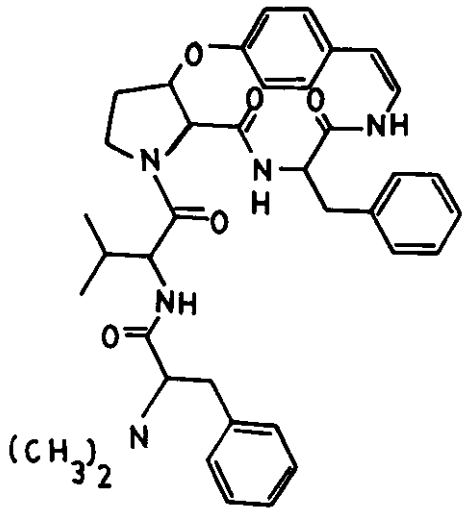
The 15-membered ring system consists of a 5-(N-methyl or N,N-dimethyl alaninyl)-4-methoxy or 2,4-dimethoxy -α-styrylamine unit and two amino acids (leucine, isoleucine or phenylalanine). The ring here is closed by direct substitution of the aromatic nucleus of the styrylamine by an amino



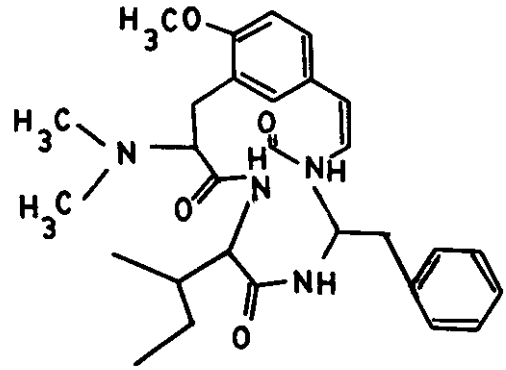
FRANGULANINE[10]



INTEGERRINE[11]



AMPHIBINE[12]



MUCRONINE-A

acid instead of usual ether linkage. Twelve representatives of this group have so far been isolated from different Zizyphus varieties. Mucronine-A [6a,13] is a typical representative of this class.

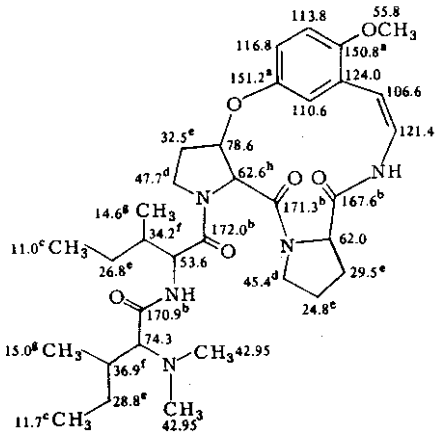
Since the previous review of the subject under discussion by Warnhoff (1970) [14] and Tschesche and Kaußmann (1974) [7], many new cyclopeptide alkaloids have been isolated and their structures established. The purpose of the present review is to give physical constants and structures of these alkaloids so as to provide an easy reference source for known alkaloids.

Since 1974 there have been many other valuable contributions in this field:

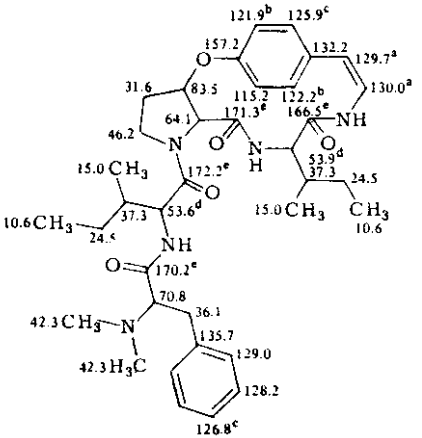
In his article R.Tschesche (1976) [29] gave general assesment of the cyclopeptide alkaloids containing a styrylamine unit.

R.Tschesche and U.Henke [30] reported the gas chromatographic determination of trimethylsilyl derivatives of various tyramines and established the method for the determination of styrylamine unit. This method is applicable to the hydrolysate of cyclopeptide alkaloids to know the exact arrangement of styrylamine units in them.

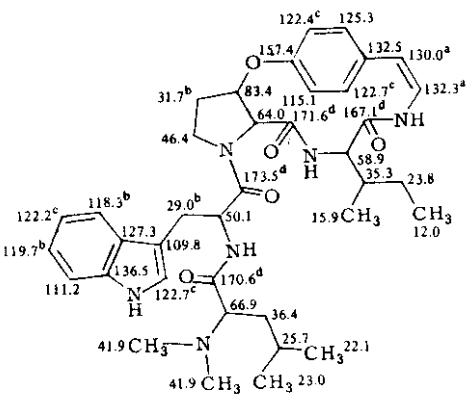
The constitution and conformation of the cyclopeptide alkaloid, mauritine-A were determined by X-ray diffraction methods [31,32]. All amino acids belong to L-series, 3-hydroxyproline has tran-configration. As indi-



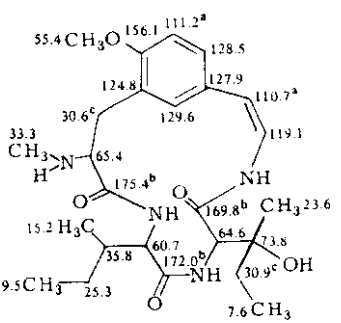
Zizyphine-A



Amphibine-D



Amphibine-E



Zizyphine-D

Table -II

FRANGULANINE TYPE

Name	Ring bound amino acid	Intermediate amino acid	Basic end amino acid	Molecular formula	MW	mp (°C)	$[\alpha]_D$	Refs.
Scutianine-I$^+$	Phe-Ser	-	Cinnamic acid	$C_{32}H_{33}N_3O_5$	539	232-34	+203°	20
Scutianine-J	Phe	-	Dimethyl Ile	$C_{31}H_{42}N_4O_4$	534	255-56	-210°	20
Nummularine-K	Leu	-	Dimethyl Trp	$C_{33}H_{43}N_5O_4$	573	237-39	-45°	17
Scutianine-F	Phe	Pro	Methyl Phe	$C_{38}N_{45}N_5O_5$	651	208	-132°	21
Scutianine-G	D-β-Phe-Ser	-	Dimethyl Phe	$C_{34}H_{40}N_4O_5$	584	162	-212°	22
Pubescine-A	Leu	-	Dimethyl Val	$C_{27}H_{42}N_4O_4$	486	247-50	-230°	23
Scutianine-H	β-Phe-Ser	-	Dimethyl Ile	$C_{31}H_{42}N_4O_5$	550	242-43	-233°	24
Melonovine-A	Leu	-	Dimethyl Val	$C_{27}H_{42}N_4O_4$	486	295	-285°	25
Melonovine-B	Tyr	-	Dimethyl Val	$C_{30}H_{40}N_4O_5$	536	200-6	-	25

cated by the UV spectrum, the 14-membered ring system is considerably strained.

The cyclopeptide alkaloids have shown photophosphorylation inhibitor activity in spinach chloroplasts [33], an observation which may be related to their function in plants in which they are produced.

PMR and ^{13}C-NMR spectroscopic studies gave further information about the confirmation of cyclopeptide alkaloids. Mainly 14-membered alkaloids remained the subject of these studies [24,34-37]. Anyhow, in one paper the ^{13}C-NMR spectra of variety of cyclopeptide alkaloids has been analysed with particular emphasis on the relationship between the size of the large ring and the chemical shift of the aromatic and vinylic carbon atoms [37]. The four alkaloids investigated were the 13-membered zizyphine-A [3,4], the 14-membered amphibine-D and amphibine-E [12,38] and 15-membered zizyphine-D [39]. The ^{13}C-NMR spectra of the four alkaloids clearly indicate that the 13- and 15-membered macrocycles allow conjugation of the styryl enamide π-electron system, while the strained 14-membered macrocycles evidence only isolated double bond and benzennoid spectroscopic behaviour.

In 1978 H.Rapoport [40] published the synthesis of several 14-membered para-bridged ring system of the cyclopeptide alkaloids via an active ester cyclization. Later on in 1981 the synthesis of several cyclopeptide alkaloids have been reported [41-44].

Nummularine-G isolated from Ziz-

Table -III

INTEGERRINE TYPE

Name	Ring bound amino acid	Inter-mediate amino acid	Basic end amino acid	Molecular formula	MW	mp (°C)	$[\alpha]_D$	Refs.
Crenatine-A	Phe	-	Dimethyl Leu	$C_{34}H_{40}N_4O_4$	568	223	-293°	26
Nummularine-D	Leu	-	Methyl Ile	$C_{30}H_{40}N_4O_4$	520	265-68	-186°	27
Nummularine-E	Leu	-	Dimethyl Thr	$C_{29}H_{38}N_4O_5$	522	278-79	-12°	27
Nummularine-G	Leu	-	Dimethyl Leu++	$C_{31}H_{40}N_4O_4$	532	174-75	-133°	17
Aralionine-C	Phe-Ser	-	Dimethyl Ile	$C_{34}H_{40}N_4O_5$	584	95-97	-17°	21
Sativanine-A	Val	-	Dimethyl Ile	$C_{30}H_{40}N_4O_4$	520	82°	-	28
Sativanine-B	Val	-	Dimethyl Leu/ Ile++	$C_{30}H_{38}N_4O_4$	518	amorph.	-	28
Nummularine-M	Ile	-	Dimethyl Ile	$C_{31}H_{42}N_4O_4$	534	263-65	-46.7°	19

Table -IV

AMPHIBINE-B TYPE

Name	Ring bound amino acid	Inter-mediate amino acid	Basic end amino acid	Molecular formula	MW	mp (°C)	$[\alpha]_D$	Refs.
Zizyphine-G	Pro	-	Ile	$C_{24}H_{32}N_4O_4$	440	130	-185°	15
Nummularine-F	Ile	-	Dimethyl Gly	$C_{23}H_{32}N_4O_4$	428	120	-204°	27
Hysodricanine-A	Pro	Phe	Dimethyl Ile	$C_{35}H_{45}N_5O_5$	615	93-96	-215°	21
Mauritine-H	Phe	Leu	Dimethyl Ala	$C_{33}H_{43}N_5O_5$	589	212-15	-169°	21

+ Probably an artifact.

++ Forming an additional ring.

phus nummularia is the first 14-membered cyclopeptide alkaloid which contains an additional ring in the side chain [17]. From Zizyphus sativa, the first naturally occuring N-formyl cyclopeptide alkaloid sativanine-F [8], and first 13-membered cyclopeptide alkaloid (sativanine-D) containing an additional ring in the side chain have been isolated [8].

References:

1. J.Marchand, M.Pais, X.Manseur, and F.X.Jarreau, *Tetrahedron*, **25**,*937 (1969)*.
2. a) M.Pais, J.Marchand, F.X. Jarreau and R.Goutarel, *Ann.Pharm.Fr.*, **21**, *139 (1963)*. b) M.Pais, J.Marchand, F.X. Jarreau and R.Goutarel, *Bull.Soc.Chim.Fr.*, *1145 (1968)*.
3. E.L.Zbiral, E.L.Menard and J.M. Muller, *Helv.Chim.Acta.* **48**, *404 (1965)*.
4. R.Tschesche, E.U.Kaussmann and G.Eckhardt, *Tet.Lett.*, *2577 (1973)*.
5. R.Tschesche, S.T.David, J. Uhlendorf and H.W.Fehlhaber, *Liebigs Ann.Chem.*, **789**, *195 (1972)*.
6. a) R.Tschesche, S.T.David, R. Zerbes, G.Eckhardt and E.U. Kaussmann, *Liebigs Ann.Chem.*, *1915 (1974)*. b) B.K.Cassels, G.Eckhardt, E. U.Kaussmann and R.Tschesche, *Tetrahedron*, **30**, *2461 (1974)*.
7. R.Tschesche and E.U.Kaussmann, The Alkaloids, R.H.F. Manske, Academic Press,New York,Vol.XV (1975).
8. a) A.H.Shah., Ph.D. Dissertation, Institute of Organic Chemistry and Biochemistry, Bonn University, (1982). b) A.H.Shah, V.B.Pandey, G. Eckhardt and R.Tschesche, Erster Gesamtkongress der Pharmazeutischen Wissenschaften,Munchen, 155 (17-20 April, 1983). c)A.H.Shah, V.B.Pandey, G. Eckhardt and R.Tschesche, *Phytochemistry*, **23**,*931 (1984)*.
9. H.W.Fehlhaber, *Z.Analyt.Chem.*, **235**, *91 (1968)*.
10. R.Tschesche, H.Last and H.W Fehlhaber, *Chem.Ber.*, **100**, *3937 (1967)*.
11. R.Tschesche, E.Frohberg and H.-W.Fehlhaber, *Tet.Lett.*, *1311 (1968)*.
12. R.Tschesche, E.U.Kaussman and H.-W.Fehlhaber, *Chem.Ber.*, **105**, *3094 (1972)*.
13. H.-W.Fehlhaber, J.Uhlendorf, S.T.David and R.Tschesche, *Liebigs Ann.Chem.*, **759**, *195 (1972)*.
14. E.W.Warnhoff, *Fortschr.Chem.Org.Naturst.*, **28**, *162 (1970)*.
15. R.Tschesche, I. Khokhar, Ch. Spilles, G.Eckhardt, B.K.Cassels, *Tet.Lett.*, *2941, (1974)*.
16. R.Tschesche, I. Khokhar, H.Wilhelm and G.Eckhardrt, *Phytochemistry*, **15**, *541 (1976)*.
17. R.Tschesche, M.Elgamal and G. Eckhardt, *Chem.Ber.*, **110**, *2649 (1977)*.
18. A.H.Shah, V.B.Pandey, J.P. Singh, K.N.Singh and G.Eckhardt, *Phytochemistry*, **23**,*2120 (1984)*.
19. V.B.Pandey, J.P.Singh, K.K. Seth, A.H.Shah and G.Eckhardt, *Phytochemistry*, **23**,*2118 (1984)*.
20. M.G.Sierra, O.A.Mascaretti, V. M.Merkuza, E.L.Tosti, E.Ruveda and C.J.Chang, *Phytochemistry*, **13**, *2865 (1974)*.
21. R.Tschesche, D.Hillebrand, H. Wilhelm, E.Ammermann and G.Eckhardt, *Phytochemistry*, **16**, *1025 (1977)*.
22. R.Tschesche and D.Hillebrand, *Phytochemistry*, **16**,*1817 (1978)*.
23. R.Tschesche, D.Hillebrand and I.R.C.Bick, *Phytochemistry*, **19**,*1000 (1980)*.
24. A.F.Morel, R.v.Fossen, F.A.Reis and E.A.Ruveda.

Phytochemistry, **18**,473 (1979).
25. G.J.Kapadia, Y.N.Shukla, J.F. Morton and H.-A.Lloyd, *Phytochemistry*, **16**,1431 (1977).
26. M.Silva, D.S.Bhakuni, P.G. Sammes, M.Pais and F.X.Jarreau, *Phytochemistry*, **13**,861 (1974).
27. R.Tschesche, M.Elgamal, G.A. Miana and G.Eckhardt, *Tetrahedron*, **31**,2944 (1975).
28. R.Tschesche, A.H.Shah and G. Eckhardt, *Phytochemistry*, **18**,702 (1979).
29. R.Tschesche, *Heterocycles*, **4**, 107 (1976).
30. R.Tschesche and U.Henke, *J.Chromatogr.*, **120**,477 (1976).
31. A.Kirfel and G.Will, *Kristallogr.*, **142**,368 (1975).
32. A.Kirfel, G.Will, R.Tschesche and H.Wilhelm, *Z.Naturforsch.*, **31b**,279 (1976).
33. R.A.Ravizzini, C.S.Andreo and R.H.Vallejos, *Plant Cell Physiol.*, **18**,701 (1977).
34. E.Haslinger, *Tetrahedron*, **34**,685 (1978).
35. E.Haslinger, *Monatsh.Chem.*, **109**,523 (1978).
36. M.Pais, F.-X.Jarreau, M.G.Sierra, O.A.Mascaretti, E.A.Ruveda, C.-J.Chang, E.W.Hagaman and E.Wenkert, *Phytochemistry*, **18**,1869 (1979).
37. D.H.Hindenlang, M.Shamma, G. A.Miana, A.H.Shah and B.K. Cassels. *Liebigs Ann.Chem.* 447 (1980).
38. R.Tschesche, H.Wilhelm and H.-W.Fehlhaber. *Tet.Lett.*, 2609 (1972).
39. B.K.Cassels, G.Eckhardt, E.U. Kaussmann and R.Tschesche, *Tetrahedron*, **30**,2461 (1974).
40. J.C.Lagarias, R.A.Houghten and H.Rapoport. *J.Am.Chem.Soc.*, **100**(26), 8202 (1978).
41. U.Schmidt, A.Lieberknecht, H. Bokens, H.Griesser, *Angew.Chem.*, **93**,1121 (1981).
42. U.Schmidt, A.Lieberknecht, H. Griesser and J.Hausler, *Angew.Chem.*, **93**,272 (1981).
43. U.Schmidt, H.Bokens, A.Lieberknecht, H.Griesser. *Tet.Lett.*, 4949 (1981).
44. M.M. Joullie, Personal communication,(1981/82).