CHEMICAL EXAMINATION OF MEDICINAL PLANTS

A

THESIS

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By

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A C K N O W L E D G M E N T

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(Miss) S.N. Shanbhag.

N. C. L.
P O O N A
September 1966.

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INTRODUCTION

India, due to her geographic position and the resulting climatic pattern, is endowed with an abundance of diversified flora which includes, amongst others, plants of medicinal value. The history of the medicinal use of plants in India can be traced to the remote past. The earliest mention of this is found in the Rig Veda, perhaps the oldest repository of human knowledge, having been composed between 4500 and 1600 BC.[1] During the centuries that have gone by, the materia medica of the indigenous systems of medicine has become extensive and heterogeneous and at present more than 2,000 drugs of vegetable origin have been enlisted,[1] quite a number of these being known both to eastern and western medicine. However, very little work of scientific value was done on these till the beginning of this century and still, there are many drugs which grow mature and eventually die without being put to any practical use whatsoever for a lack of their proper investigation. It is much likely that a large number of these growing in India may possess properties and actions similar to the often expensive imported remedies and would form excellent substitutes.

From amongst the medicinal plants that have thus far been studied and chemically investigated, many

examples[2] can be cited of the relationship which seems to exist between the botanical classification and the chemical and physiological characters, some of these being, the presence of powerful bitter and purgative principles in the wild members of Cucurbitaceae, alkaloids with similar physiological properties in the members of the genus chinchona, the toxic substance andromedotoxin in many members of Ericaceae, glycosidal alkaloid solanine in many solanums, raphides of calcium oxalate in a number of species of Araceae, saponins in several plants of Caryophyllaceae etc. They show that in many of the families and genera these characteristics show a marked degree of correlation. There is, however, an element of disturbance[2] in this pattern, in that, the climate, soil, method of cultivation etc. have a profound effect on the chemical composition and hence the physiological characteristics of plants. It is for this reason that some of the closely related plants differ in their physiological properties.

The roots of Nardostachys jatamansi (Fam. Valerianaceae) have been known to possess a number of medicinal properties.[1,3] In the indigenous medicine, they are described as aromatic, antiseptic, diuretic, antispasmodic, tonic, carminative, nerve sedative, nerve stimulant and a substitute for official valerian. The

essential oil from the roots is reported to be antiseptic, disinfectant, antispasmodic etc. and has also been of use as an ingredient in perfumery.

Very little is known about the composition of this oil. G.R. Chowdhari et al[4,5] isolated a crystalline acid, named as jatamanshic acid from this oil and established its structure. Govindachari et al isolated a sesquiterpene ketone jatamansone[6] (valeranone) and proposed a structure[7] for it, which was later modified by Šorm and coworkers[8] with respect to the position of the carbonyl group, the absolute stereochemistry of this ketone being established more recently.[9] The sesquiterpene hydrocarbons β-maaliene and calarene have been isolated by Buchi and coworkers[10] from the oil extracted from the Chinese variety.

Considering the importance of roots of Nardostachys jatamansi in the indigenous medicine, and as investigations carried out so far on this have only been of a preliminary nature, critical study of the same was thought to be desirable.

Two types of Nardostachys jatamansi roots, dark-brown variety and greyish-brown variety, have been collected and their chemical composition is being studied by us.

The latter variety was found to be rich in coumarin compounds. However, occurrence of coumarins in valerianaceous plants is unusual from chemotaxonomic point of view.

Because of this its botanical identity was re-examined* and it was found to be an umbelliferous plant, Selinum vaginatum C.B. Clarke.

Roots of Selinum vaginatum are also medicinally active.[11] In the indigenous medicine, they have been mainly used as nervine sedative. Analgesic and hypotensive properties are also attributed to them. Very little is known about the chemical constituents of these roots. Handa et al[12] identified in 1963 the presence of many monoterpenes in the oil obtained from dry distillation of roots and no further work is reported on the same until we took up the investigation. As mentioned earlier, we could isolate coumarins in large amounts from the 'concrete' obtained by the solvent extraction of these roots.

As this thesis will deal only with coumarin compounds, a brief introduction of the same is being given here. An exhaustive survey of the literature on coumarins is avoided for the sake of brevity and especially since a large number of monographs and reviews[13-18] have appeared from time to time. However, appropriate references are made to relevant literature in the body of the thesis wherever it is found necessary to illustrate and emphasise a particular point.

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* We are grateful to Prof. R. Hegnauer and Prof. K.E.Schulte for their interest and help in this identification.

Coumarins, which are 5,6-benzo-α-pyrone derivatives, have been found to be widely distributed in the plant kingdom. They occur in all parts[13] from roots to flowers and fruits. Coumarin itself (5,6-benzo-α-pyrone) which is a parent member of this series, was first isolated by Vogel in 1820, from the plant Coumarona odorata, and was named after the common name 'coumarona' of the same plant. Particularly, the plants belonging to the natural orders of Orchidaceae, Leguminosae, Rutaceae, Umbelliferae and Labiatae are rich sources of naturally occurring coumarins[14] though they occur less abundantly in some other families. More recently, a few complex coumarins such as aflatoxins[19] have been found as metabolic products of bacteria and fungi. Only few coumarins have been isolated from animal sources, one of the examples being the yellow pigments isolated by Lederer from castoreum.[20] It is quite interesting to note that except for coumarin and dicoumarol all other naturally occurring coumarins bear an oxygen substituent at 7 position.[13] Simple hydroxy or methoxy compounds, as well as coumarin itself occur widely in many different families, but, as the complexity of the compound increases, they seem to be more and more restricted with respect to the familial occurrence.[13]

Although the naturally occurring coumarins is a large and important group of plant products, it is doubtful whether the full range of their physiological actions has been appreciated by most of the investigators.[13] However, many naturally occurring coumarins find an important place in modern medicine because of their physiological activities. Dicoumarol which is 3,3'-methylene-bis-(4-hydroxy-coumarin), enjoys extensive usage in the treatment of thrombosis and as antagonist of Vitamin K; the anticoagulant property of this compound being first recognised by Link et al.[21] while working on spoiled sweet clover hay. The furocoumarins pscralene, imperatorin, bergapten and xanthotoxin have been found to be very potent in the restoration of melanine depleted skin, and therefore they find use in the treatment of leucoderma.[22] In 1957 Bickoff et al isolated an estrogenic coumarin named as coumestrol,[23,24] while working on ladinoclover (Trifolium repens). Further, some coumarins have been found to possess good antibacterial activity. Possibly, the antibiotic, novobiocin[25-27] isolated as a fungal metabolite of Streptomyces niveus is the most important coumarin-type antibacterial agent and because of the excellent antibacterial spectrum, chiefly against gram-positive organisms and Proteus vulgaris it is widely accepted in medicine.[13] Pyranocoumarins, samidin, visnadin, dihydrosamidin, pteryxin and suksdorfin[28,65-68] are well known for their vasodilatory activity.

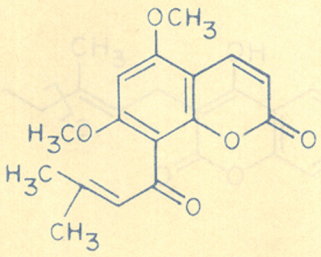
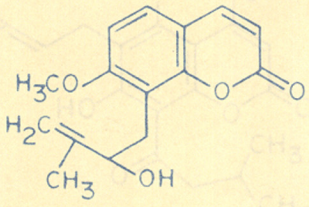
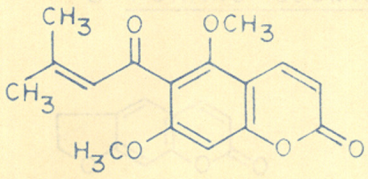
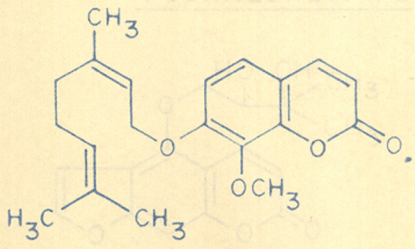
Coumarins are isolated from dried and pulvurized plant material by successive extraction with solvents of increasing polarity in the conventional type of apparatus. Eventhough coumarins are quite insoluble in petroleum ether, the other constituents, present in the oil, tend to impart a solubilizing effect on them, as a consequence of which, a number of coumarins have been isolated from petroleum ether extracts of different plant materials. The petroleum ether extraction is omitted sometimes and is replaced by a direct extraction with the more polar solvent diethyl ether. Following the extraction with petroleum ether and/or ether a solvent of still higher polarity such as methanol or ethanol is used as the menstruum, which often isolates coumarin glycosides.[13]

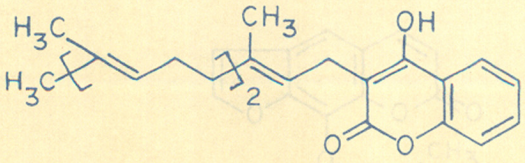
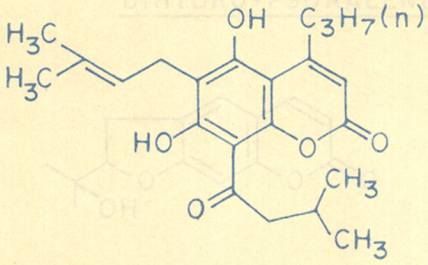
Purification of the crude coumarin fractions and separation into individual coumarins can be conveniently carried out by the usual techniques such as fractional crystallisation, column chromatography, preparative layer chromatography etc., out of which, the column chromatographic technique is extensively used. Deactivated alumina, which has been proved to be an effective adsorbent,[29] is widely employed for this purpose, but, in some cases silica gel G[30,31] or formamide impregnated cellulose powder[32] is found to be a better adsorbent. Thin layer chromatography has been extensively utilised for demonstrating the homogeneity of unknown and known coumarins and frequently for detection purposes.[13]

Infrared and ultraviolet spectral analyses have found their place in the structural characterisation of coumarins. In the ultraviolet region coumarin itself absorbs at λmax. 274 and 312 mμ (log ε 4.1 and 3.5 respectively), the variation from this pattern being attributed to the pronounced effect of substituents and their location.[33] In the infrared spectra of these compounds the characteristic bands for the α-pyrone moiety are found, as a rule, in the region 1715-45 cm^{-1} together with that of conjugated double bond at about 1625-1640 cm^{-1},[13] Proton magnetic resonance (PMR) spectra are also extensively used in the structural identification of coumarins. In some cases the structural argument has been based entirely on this technique as it would have been difficult or impossible to do it chemically.[34,35,54,69] The use of mass spectrometry in the structural studies of these compounds has not yet been exploited much, but, in some cases it has been used to determine the exact molecular weights.[35] Recently investigations[36,37] on the behaviour of coumarins on electron impact may prove to be helpful for further studies in this field. X-ray crystallographic technique has also been used in determination of exact molecular weights of some complex coumarins, such as novobiocin.[25]

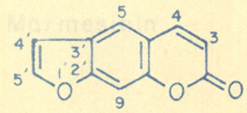
Table I depicts some naturally occurring coumarins. However, an exhaustive list is avoided for the sake of brevity.

TABLE - 1 SOME NATURALLY OCCURRING COUMARINS

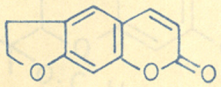
NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE
	A. SIMPLE COUMARINS		
Gabralactone		Roots of *Angelica glabra* Makino [Fam. Umbelliferae]	38, 39
Auraptenol		*Citrus aurantium* Linn, subspecies Amara Linn [Fam. Rutaceae]	40
Angelicone		Roots of *Angelica shishindo* *Angelica ursina* [Fam. Umbelliferae]	41
Collinin		Bark of *Flindersia collina*, Bail [Fam. Rutaceae]	42

NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE
Ferulenol		Latex of *Ferula Communis* Linn. [Fam. Umbelliferae]	43, 44
Mammein		Fruits of *Mammea americana* Linn. [Fam. Guttiferae]	45, 46, 47

B. FURANO-COUMARINS

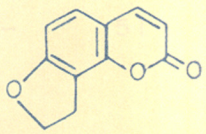


Psoralene



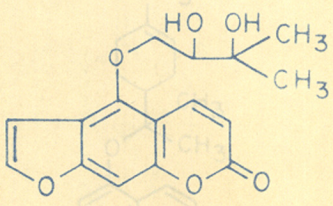
Dihydro-psoralene

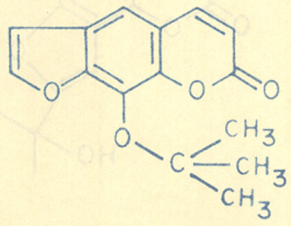
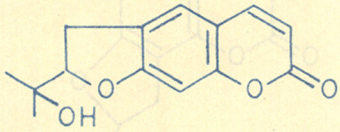
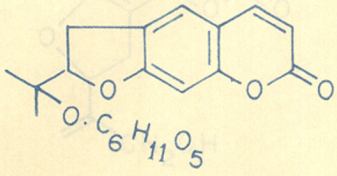
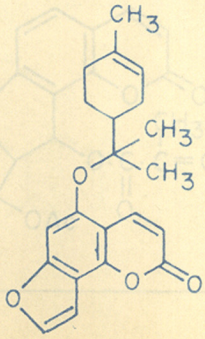
Angelicin

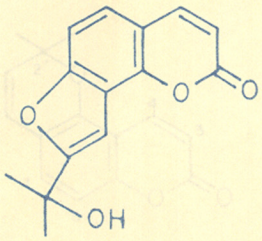
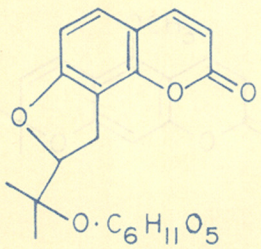
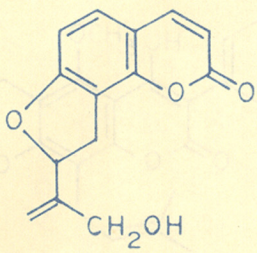
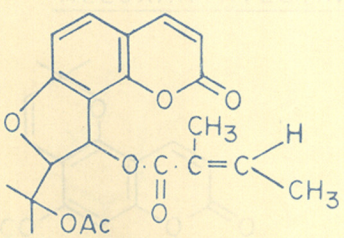


Dihydro-angelicin

PSORALENE TYPE

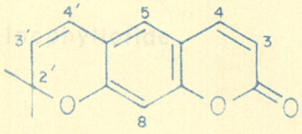
Aviprin		Roots of *Prangos pabularia* Lindl. [Fam. Umbelliferae]	48

NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE
Prangein		Roots of Prangos pabularia Lindl. [Fam. Umbelliferae]	49
	DIHYDRO-PSORALENE TYPE		
Marmesin		Bark of Aegle marmelos Correa [Fam. Rutaceae]	50
Marmesinin		Fruits of Ammi majus L. [Fam. Umbelliferae]	51
	ANGELICIN TYPE		
Archangelin		Roots of Angelica archangelica Linn [Fam. Umbelliferae]	52

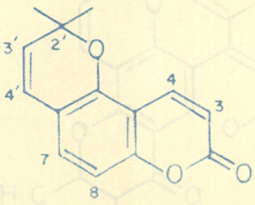
NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE
Oroselol		Roots of Athamanta oreoselinum L. [Fam. Umbelliferae]	53
	DIHYDRO-ANGELICIN TYPE		
Columbianin		Roots of Lomatium columbianum [Fam. Umbelliferae]	54
Discophoridin		Leaves of Valleia discophora. F. Muell [Fam. Goodeniaceae]	55
Edultin		Roots of Angelica edulis. Miyabe [Fam. Umbelliferae]	56

NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE

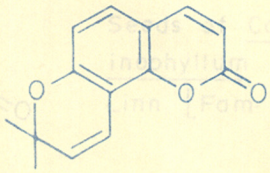
C. CHROMENO-α-PYRONES



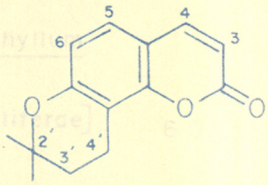
Xanthyletin



alloXanthyletin



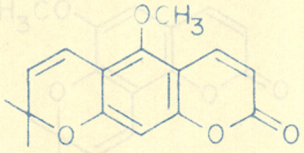
Seselin



Dihydro-seselin

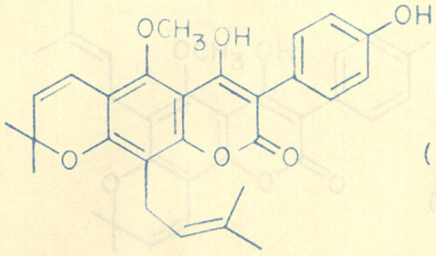
XANTHYLETIN TYPE

Xanthoxyletin



Bark of Zanthoxylum americanum Mill [Fam. Rutaceae] — 57

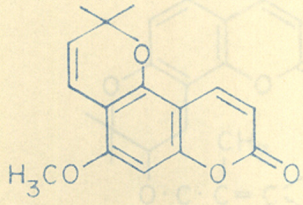
Lonchocarpic acid



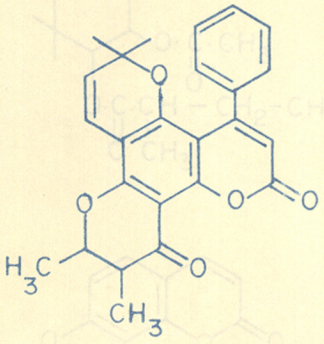
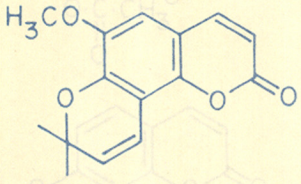
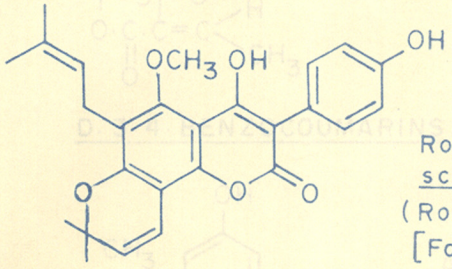
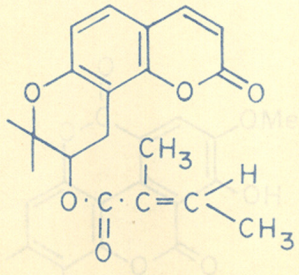
Roots of Derris scandens (Roxb.) Benth [Fam. Leguminosae] — 58

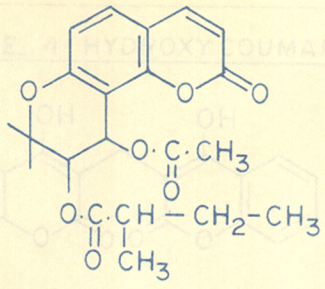
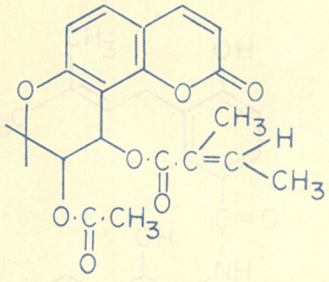
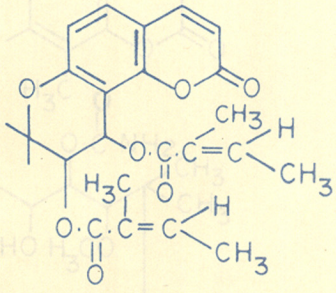
ALLOXANTHYLETIN TYPE

alloXanthoxyletin

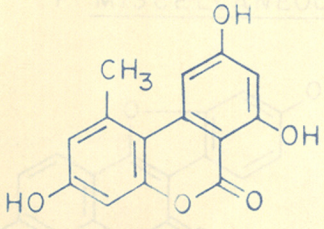
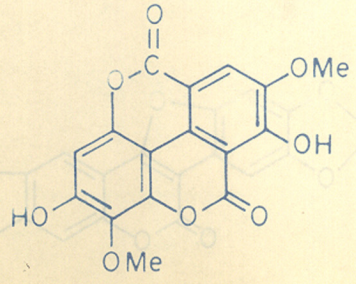


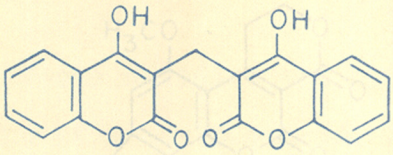
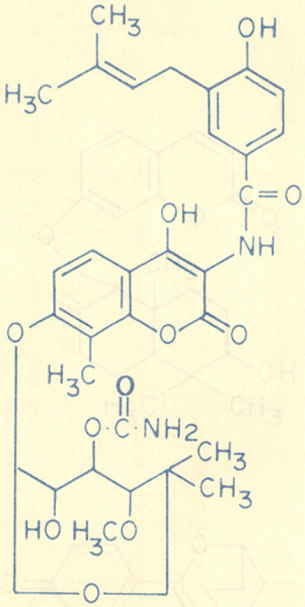
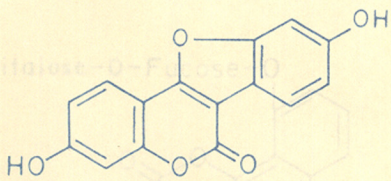
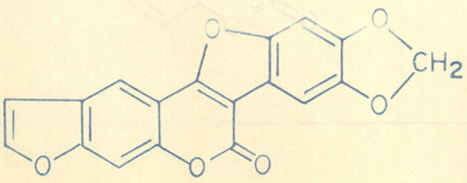
Bark of Zanthoxylum americanum (Mill) [Fam. Rutaceae] — 59

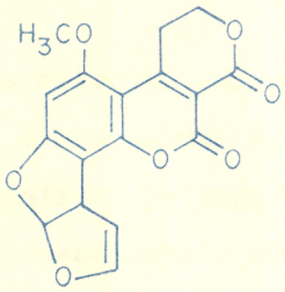
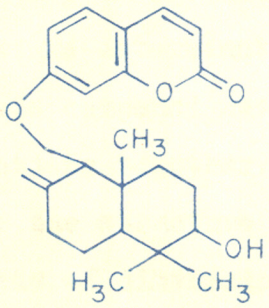
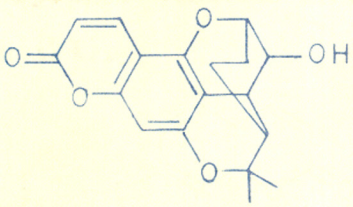
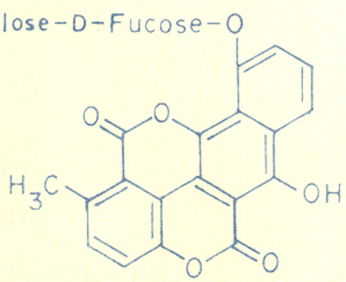
NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE
Inophyllolide		Seeds of Calophyllum inophyllum Linn [Fam. Guttiferae]	60
	SESELIN TYPE		
Braylin		Bark of Flindersia brayleyana F. Muell [Fam. Rutaceae]	61
Scandenin		Roots of Derris scandens. (Roxb.) Benth [Fam. Leguminosae]	62
	DIHYDRO-SESELIN TYPE		
Jatamansin (Selinidin)		Roots of Selinum vaginatum C.B. Clarke [Fam. Umbelliferae]	63 64

NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE
Visnadin		Seeds of Ammi visnaga L [Fam. Umbelliferae]	65 66
Pteryxin		Roots of Pteryxia terbinthina (Hook) [Fam. Umbelliferae]	67 68
Anamelin		Roots of Angelica anomala. Lall [Fam. Umbelliferae]	69

D. 3·4· BENZOCOUMARINS

Alternariol		Alternaria tenuis [Fam. Dematiaceae]	70
Dimethyl ether of ellagic acid		Roots of Euphorbia formosana. [Fam. Euphorbiaceae]	20

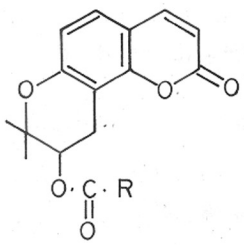
NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE
E. 4-HYDROXY COUMARINS			
Dicoumarol		Leaves of *Melilotus alba*; *Melilotus officinalis*. [Fam. Leguminosae.]	21
Novobiocin		*Streptomyces niveus*	25 26
F. MISCELLANEOUS TYPES			
Coumestrol		*Trifolium repens* Linn [Fam. Leguminosae]	23 24
Erosnin		Seeds of *Pachyrrhizus erosus* Urban [Fam. Leguminosae]	71 72

NAME OF COUMARIN	STRUCTURE	SOURCE	REFERENCE
Aflatoxin G		Aspergillus flavus Link Ex. Fries [Fam. Moniliaceae]	35 19
Farnesiferol A		Latex of Ferula asafoetida [Fam: Umbelliferae]	73
Bruceol		Leaves of Eriostemon brucei (F. Muell) [Fam. Rutaceae]	74
Chartreusin		Streptomyces arten	75

PRESENT INVESTIGATION

This thesis embodies the work on structural characterisation of a new coumarin, named as jatamansin, isolated from the roots of Selinum vaginatum* C.B. Clarke, and on syntheses of vasodilatory drugs (±)-cis-dihydrosamidin, (±)-cis-vinadin and (±)-cis-suksdorfin.

The first chapter of this thesis deals with the isolation and structure determination of jatamansin (I). The structure of this compound was elucidated with the help of chemical degradations together with spectral studies. Further support for the structure of jatamansin (I) was obtained by synthesis of dihydrojatamansin (II) starting from jatamansinol (III) and also by conversion of jatamansinol into known compounds seselin (IV), dihydroseselin (V) and jatamansinone (VI).



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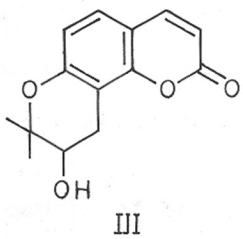

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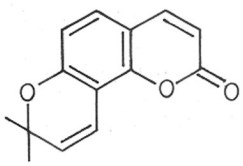
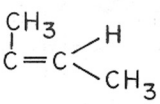
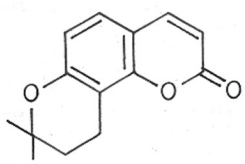


I R = 

II R = $-CH(CH_3)-CH_2-CH_3$



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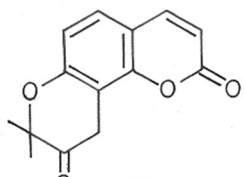

VI

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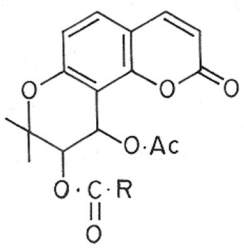
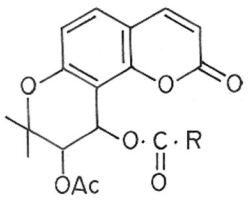
* As these roots were originally mistaken for those of Nardostachys jatamansi, D.C., the new coumarin was named as jatamansin.

As mentioned earlier, naturally occurring pyrano coumarins samidin (VIIa), dihydrosamidin (VIIb), visnadin (VIIc), pteryxin (VIIIa) and suksdorfin (VIIIb) have been known to possess a strong vasodilatory activity. Since they are closely related with jatamansin, and except that of (±)-trans-samidin the synthesis of none of these compounds was reported in the literature, it was felt desirable to synthesise some of these compounds.



VII



VIII

a. R = $-HC=C\begin{matrix}CH_3\\CH_3\end{matrix}$

b. R = $-CH_2-CH\begin{matrix}CH_3\\CH_3\end{matrix}$

c. R = $-CH(CH_3)-CH_2-CH_3$

a. R = $-C(H_3C)=C\begin{matrix}H\\CH_3\end{matrix}$

b. R = $-CH_2-CH\begin{matrix}CH_3\\CH_3\end{matrix}$

The second chapter of the thesis includes the syntheses of (±)-cis-dihydrosamidin (VIIb) and (±)-cis-visnadin (VIIc), the ketone jatamansinone (VI, 3'-keto-3',4'-dihydroseselin), which has been synthesised by earlier workers starting from 7-hydroxy-coumarin (umbelliferone) being used

as a starting material for this purpose. Direct synthesis of visnadin from dihydrojatamansin was also attempted, but without success.

The work on conversion of jatamansinone into (±)-cis-suksdorfin is described in the third chapter. This series of reactions includes two types of interesting rearrangements, the mechanisms of which have been discussed. Efforts in the direction of synthesis of (±)-cis-dihydropteryxin have also been dealt with in this chapter. It is interesting to note that during these preparations we have come across many new compounds, which have been fully characterised.

General remark

Numbering of structures, figures, tables and references in each chapter refers to that particular chapter only.

REFERENCES

1. R.N. Chopra, S.L. Nayar and I.C. Chopra, Glossary of Indian Medicinal Plants, p. iv and 173, C.S.I.R., New Delhi (1956).
2. R.N. Chopra, I.C. Chopra, K.L. Handa and L.D. Kapur, Indigenous drugs of India (2nd Ed.), p.42, V.N.Dhur, Calcutta (1958).
3. K.M. Nadkarni and A.K. Nadkarni, Indian Materia Medica, Vol.I (3rd Ed.), p.840, Popular book depot, Bombay(1954).
4. G.R. Chaudhari, V.N. Sharma and S. Siddiqui, J.Sci.Ind.Research (India), 10B, 48 (1951).
5. G.R. Chaudhari, M.M. Dhar, Nitya Anand and M.L. Dhar, J.Sci.Ind.Research(India), 17B, 159 (1958).
6. T.R. Govindachari, S. Rajdurai and B.R.Pai, Chem.Ber., 91, 908 (1958).
7. T.R. Govindachari, B.R.Pai, K.K.Purushothaman and S. Rajdurai, Tetrahedron 12, 105 (1961); and with C. Djerassi, Tetrahedron Letters, 6, 226 (1961).
8. L.J. Krepinsky, M.Romanuk, V.Herout and F. Sorm, Coll.Czech.Chem Comm., 27, 2638 (1962); and with E. Hohne, Ibid., 28, 3122 (1963).

9. a) H. Hikino, Y. Hikino, Y.Takeshita, K.Meguro and T. Takemoto, Chem.Pharm.Bull.(Japan), 11,1207(1963).
b) K.S. Kulkarni, S.K. Paknikar and S.C. Bhattacharyya, Tetrahedron, 20, 1289 (1964).

10. G. Büchi, F.Greuter and T. Tokoroyana, Tetrahedron Letters, 18, 827 (1962).

11. Y.K. Satin and L.D. Kapoor, Perf. & Ess.Oil Rec., 54 (7), 437 (1963).

12. K.L. Handa, M.C. Nigam and M.L. Sharma, Riechstoffe and Aromen, 13, 181 (1963).

13. T.O. Soine, J.Pharm.Sci., 53 (3), 231 (1964).

14. E. Spath, Ber., 70A, 83 (1937).

15. S.M. Sethna and N.M. Shah, Chem.Rev., 36,1 (1945).

16. L. Reppel, Pharmazie, 9, 278 (1954).

17. F.M. Dean, Fortschr. Chem.Org.Naturstoffe, 9,225(1962).

18. F.M. Dean, Naturally occurring oxgen ring compounds, p. 176, Butterworth, London (1963).

19. P.C. Spensley, Endeavour, 22, 75 (1963).

20. E. Lederer, J.Chem.Soc., 2115 (1949).

21. (a) M.A. Stahman, C.R. Huebner and K.P.Link, J.Biol.Chem., 138,513(1941).
(b) H.A. Campbell and K.P. Link, Ibid., 138, 21 (1941).

22. M.D. Schulzberger and A.B. Lerner, J.Amer.Med.Assoc., 167, 2677 (1958).

23. E.M. Bickoff, A.N. Booth, R.L. Layman, A.L.Livingston, C.R. Thompson and F. Deeds, Science, 126, 969 (1957).

24. (a) E.M. Bickoff, R.L. Layman, A.L.Livingston and A.N. Booth, J.Amer.Chem.Soc., 80, 3969 (1958).
(b) O.H. Emerson and E.M. Bickoff, ibid., 80,4381(1958).

25. (a) H. Hoeksema, J.L. Johnson and J.W. Hinman, J.Amer.Chem.Soc., 77, 6710 (1955).
(b) E.A. Kaczka, C.H.Shunk, J.W.Richters, F.J.Wolf, M.M. Gasser and K. Folkers, Ibid., 78, 4125(1956).

26. (a) J.W. Hinman, E.L. Caron and H.Hoeksema, J.Amer.Chem Soc., 79,3789(1957);
(b) C.H. Stammer, E. Walton, A.N. Wilson, R.W. Walker, N.R. Trenner, F.W. Holly and K. Folkers, Ibid, 80,137(1958).

27. K. Okumura, J.Pharm.Soc. Japan, 80, 525(1960); ibid., 81, 1482 (1961).

28. E. Smith, L.A. Pucci and W.G. Bywater, Science, 115, 520 (1952).

29. S. Sengupta, Naturally occurring oxygen heterocycles, Ph.D. thesis, University of Calcutta (1963).

30. B.E. Nielsen and J. Lemmich, Acta.Chem.Scand., 18, 932 (1964); ibid., 19, 601 (1965).

31. W.L. Stanley and S.H. Vannier, J.Amer.Chem.Soc., 79, 3488 (1957).

32. A. Chatterjee, P.K. Bose and S.K. Saha, Arch.Pharm., 295 (4), 248 (1962).

33. D.P. Chakraborty and S.K. Chakraborti, Trans.Bose Res. Inst., 24 (1), 15 (1961).

34. H.R. Arthur and W.D. Ollis, J.Chem.Soc., 3910(1963).

35. T. Asao, G. Büchi, M.M.Abdel-Kader, S.B. Chang, L. Wich and G.N. Wogan, J.Amer.Chem.Soc., 85,1706(1963).

36. C.S. Barnes and J.L. Occolowitz, Austal.J.Chem. 17, 975 (1964).

37. N.S. Wuljson, V.I. Zaretskii and V.G. Zyakoon Isv.Akad.Nauk. SSSR.Ser.Khim., 2215 (1963).

38. K. Hata, J.Pharm.Soc.(Japan), 76, 666 (1956).

39. T. Koriyone and K. Hata, J.Pharm.Soc.(Japan), 76, 649 (1956).

40. W.L. Stanley, A.C. Waiss, R.E. Lundin and S.H.Varnier, Tetrahedron, 21, 89 (1965).

41. M. Fujita and T. Furuya, J.Pharm.Soc.(Japan), 76,538(1956).

42. F.A.L. Anet, F.R.Blanks and G.K. Hughes, Austral.J.Sci. Res.(A) 2, 127 (1949).

43. S. Carboni, Bull.Soc.Ital.Biol.Sper., 16, 544 (1941); ibid., 16, 546 (1941).

44. S. Carboni, V. Melaguzzi and A. Marsili, Tetrahedron Letters, 38, 2783 (1964).

45. N.P. Morris and C. Pagan, J.Amer.Chem.Soc., 75,1489(1953).

46. C. Djerassi, E.L. Eisenbraun, B.Gilbert, A.I. Lemin, S.P. Marfey and M.P. Morris, J.Amer.Chem.Soc., 80,3686(1958).

47. C. Djerassi, E.J. Eisenbraun, R.A. Finnegan and B. Gilbert, Tetrahedron Letters, 1, 10 (1959).

48. B.K. Gupta, B.K. Wali, Vishwapaul and K.L. Handa, Ind.J.Chem., 2, 465 (1964).

49. G.V. Pigulevsrikii and G.A. Kuznetsora, Zhur.obschei, Khim., 23, 1237 (1953).

50. a) A. Chatterjee and S.S. Mitra, J.Amer.Chem.Soc., 71, 606 (1949).

b) M. Nakajima, J.Oda and H.Furumi, Agric.Biol.Chem., 27, 695 (1963).

51. a) N. Starkowsky, J.Org.Chem., 23, 1818 (1958)

b) E.A. Abu-mustafa and M.B.E. Fayez, J.Org.Chem., 26, 161 (1961).

52. A. Chatterjee and S. Sengupta, Tetrahedron Letters, 29, 1961 (1964).

53. a) O. Halpern, P.Weser and H. Schmid, Helv.Chim.Acta, 40, 758 (1957).

b) H. Mitsuhasi and T. Itoh, Chem.Pharm.Bull.(Japan), 10, 514 (1962).

54. R.E. Willette and T.O. Soine, J.Pharm.Sci., 53(3), 275 (1964).

55. W. Bottomley, Austral.J.Chem., 16, 143 (1963).

56. H. Mitsuhashi and J. Itoh, Chem.Pharm.Bull.(Japan), 10, 170 (1961); ibid., 10, 511 (1962).

57. J.C. Bell, J.Chem.Soc., 627 (1936).

58. (a) A. Pilter and A.P. Johnson, Tetrahedron Letters, 39, 2817 (1964)

(b) V.V. Sreerama Murti, N.N. Subba Rao and T.R.Seshadri, Proc.Ind.Acad.Sci., A 27, 111 (1948).

59. A. Robertson and T.S. Subramaniam, J.Chem.Soc.,1545(1937).

60. J. Polonsky, Bull.Soc.Chim.France, 24, 1079 (1957).

61. F.A. Anet and G.K. Hughes, Austral.J.Sci.Res. A2, 608 (1949).

62. A. Pelter and P. Stainton, Tetrahedron Letters, 19, 1209 (1964).

63. S.N. Shanbhag, C.K. Mesta, M.L. Maheshwari, S.K. Paknikar and S.C. Bhattacharyya, Tetrahedron, 20, 2605 (1964).

64. T.R. Seshadri, M.S. Sood, K.L. Handa and Vishwapaul, Tetrahedron Letters, 45, 3367 (1964).

65. (a) W. Beneze, O. Halpern and H. Schmid, Experientia, 12, 137 (1956).
(b) E. Smith, N. Hosansky, W.G. Bywater and E.E.Van Tamelen, J.Amer.Chem.Soc., 79, 3534 (1957).

66. H.D. Schroeder, W. Beneze, O. Halpern and H. Schmid, Chem. Ber., 92, 2338 (1959).

67. R.E. Willette and T.O. Soine, J.Pharm.Sci., 51 (2), 149 (1962).

68. T.G. Call and E.B. Fischer, Northwest Sci., 32, 96 (1958).

69. K. Hata, M.Kozawa, Y.Ikeshiro, Chem.Pharm.Bull(Japan), 14 (1), 94 (1966).

70. H. Raistrich, C.E. Stickings and R.Thomas, Biochem.J. 55, 421 (1953).

71. L.B. Norton and R. Hansberry, J.Amer.Chem.Soc., 67, 1609 (1945).

72. J. Eisenbeiss and H. Schmid, Helv.Chem.Acta, 42, 61 (1959).

73. L. Caglotti, H.Naef, D. Arigoni and O. Jeger, Helv.Chim.Acta, 41, 2278 (1958); ibid., 42, 2557 (1959).

74. A.M. Duffield, P.R. Jefferies, E.N. Maslen and A.I.M. Rae, Tetrahedron, 19, 593 (1963).

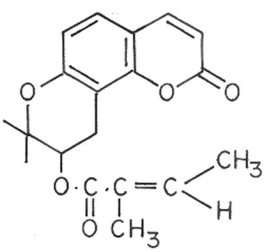
75. W. Eisenbuth, O.A. Stamm and H. Schmid, Helv.Chim.Acta, 47, 1476 (1964).

CHAPTER I

ISOLATION AND STRUCTURE DETERMINATION OF JATAMANSIN

SUMMARY

Roots of the plant Selinum vaginatum C.B. Clarke were extracted with petroleum ether (40-60°) under controlled conditions and from the extractive a new compound, named as jatamansin, has been isolated in high yield by simple refrigeration. Jatamansin is a coumarin and from study of its chemical degradations coupled with infrared, ultraviolet and PMR spectra, structure I has been assigned to it.

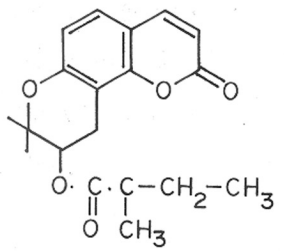


I

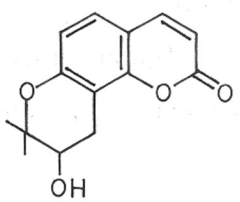
Support for this structure was obtained by conversion of jatamansin into the chromene seselin (XI) and the ketone jatamansinone (XIV), structures of which have been fully established by previous workers.

Seselin was prepared from the alcohol jatamansinol (IX, obtained by alkaline hydrolysis of jatamansin) through simple heating of its tosylate in 2:4:6-collidine. Seselin, thus prepared, was hydrogenated to the known compound dihydroseselin (XII). The ketone jatamansinone (XIV) was

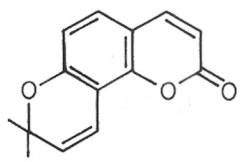
obtained by oxidation of jatamansinol (IX) with Jones' reagent. The properties of these compounds are in full agreement with those reported in the literature. Further, dihydroseselin, thus prepared, was found to be identical in all respects with that prepared from authentic osthol (XIII) by treatment of red phosphorous and hydrobromic acid (demethylation accompanied by ring closure).



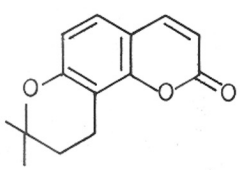
VIII



IX



X



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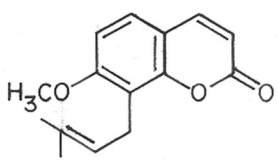
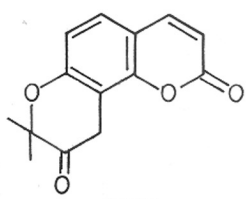


XIII



XIV

The structure assigned to jatamansin was confirmed by synthesising dihydrojatamansin (VIII) by the condensation of jatamansinol (IX) with ∝-methyl-butyryl chloride.

Since the synthesis of jatamansinone (XIV) from 7-hydroxy-coumarin (umbelliferone) and the conversion of jatamansinone to jatamansinol (IX) have been achieved by earlier workers, the above conversion of jatamansinol to dihydrojatamansin can be considered as a total synthesis of dihydrojatamansin.

*Selinum vaginatum** C.B. Clarke (Fam. Umbelliferae) is a perennial, glabrous herb[1] of about 1-1 1/2 m height with finely grooved hollow stems, roots abruptly tapering from the middle and the upper portion of the subterranean stems being covered by long leaf bases. The plant is commonly found throughout the Western Himalayas, extending from Kashmir to Kumaon at altitudes of about 6000-12000 ft.

Some medicinal properties[1] have been attributed to the roots which include hypotensive, sedative and analgesic actions. In the indigenous medicine they are mainly used as nervine sedative. The roots with their sweet, musky odour are also used as incense.

Very little is known about the chemical composition of these roots. By dry distillation of roots, Handa *et al.*[2] in 1963 obtained an oil, in which, they identified the presence of α-pinene, limonene, camphene, phellandrene, α-thujene, fenchyl alcohol and terpeniol. No further work was reported on the same until we took up the investigation. We could isolate coumarins in large amounts from the extractive obtained by the solvent extraction of the roots.

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* Hindi: Boot-keshi.

The powdered roots, on extraction with petroleum ether (40-60°) at room temperature (25-30°) and removal of solvent at controlled temperature (bath, 40 ± 2°) under vacuum, yielded a liquid extractive (9.7%). Simple refrigeration of this extractive at 0° separated a crystalline compound (8% of the extractive) in an almost pure state which was further purified by crystallisation from a large volume of petroleum ether and its homogeneity was proved by TLC. This is found to be a new compound and has been named as jatamansin.

The present chapter deals with the elucidation of structure of jatamansin.

Jatamansin is a highly crystalline optically active compound, m.p. 97-98°, $(\alpha)_D^{25}$ - 24.06° (c, 5.1). It analysed for $C_{19}H_{20}O_5$ and the molecular weight values 321 and 326 (calculated 328.37), obtained by the Rast method agreed with the formula. This molecular weight was also confirmed by mass spectral studies of jatamansin and its derivatives.

From the infrared spectrum (Fig.2) which included the characteristic peaks at 1724 (conjugated δ-lactone), 1610, 1490 and 846 cm^{-1} (aromatic), it was surmised to be an aromatic conjugated δ-lactone. The ultraviolet

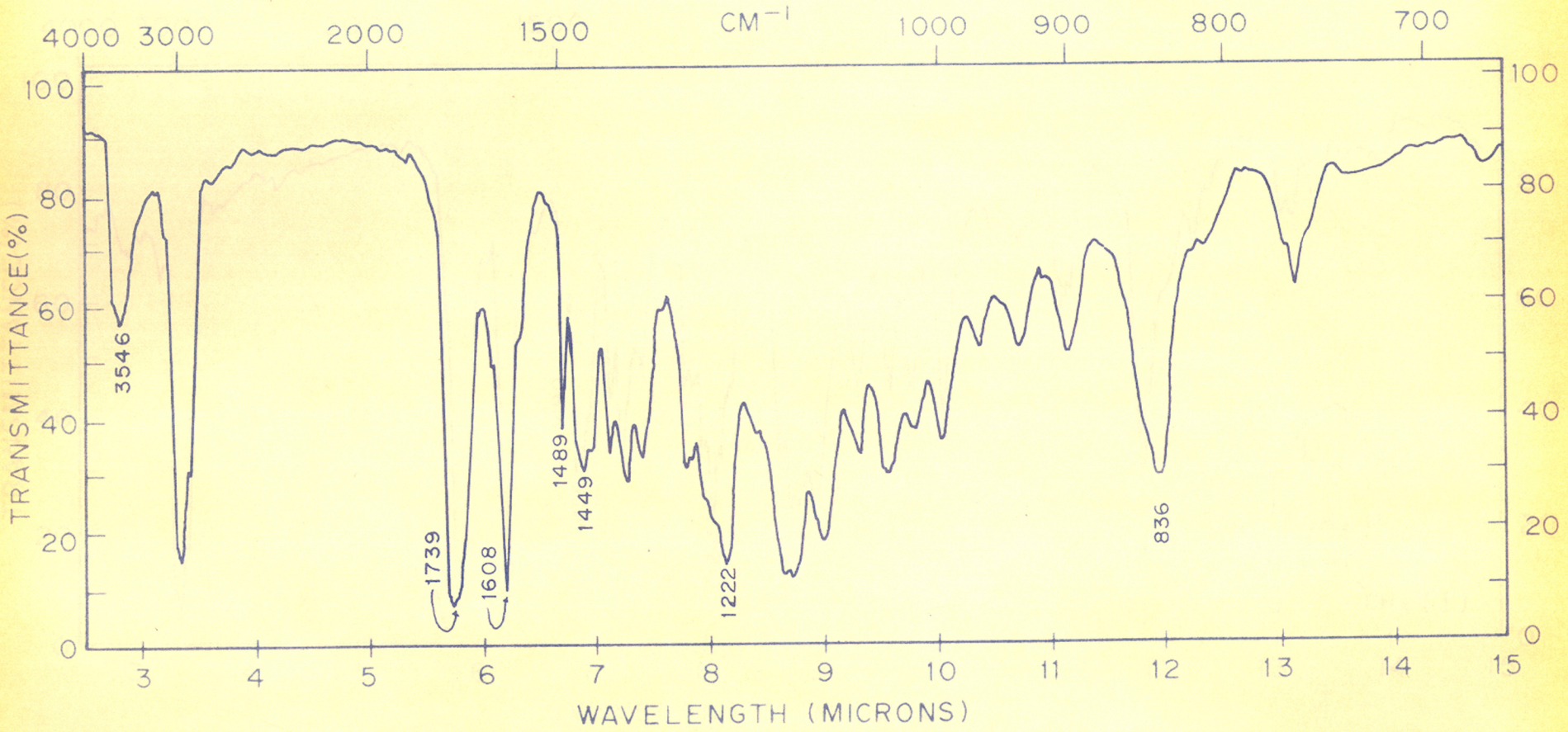


FIG. 1. IR SPECTRUM OF EXTRACTIVE FROM THE ROOTS OF SELINUM VAGINATUM

C. B. CLARKE.

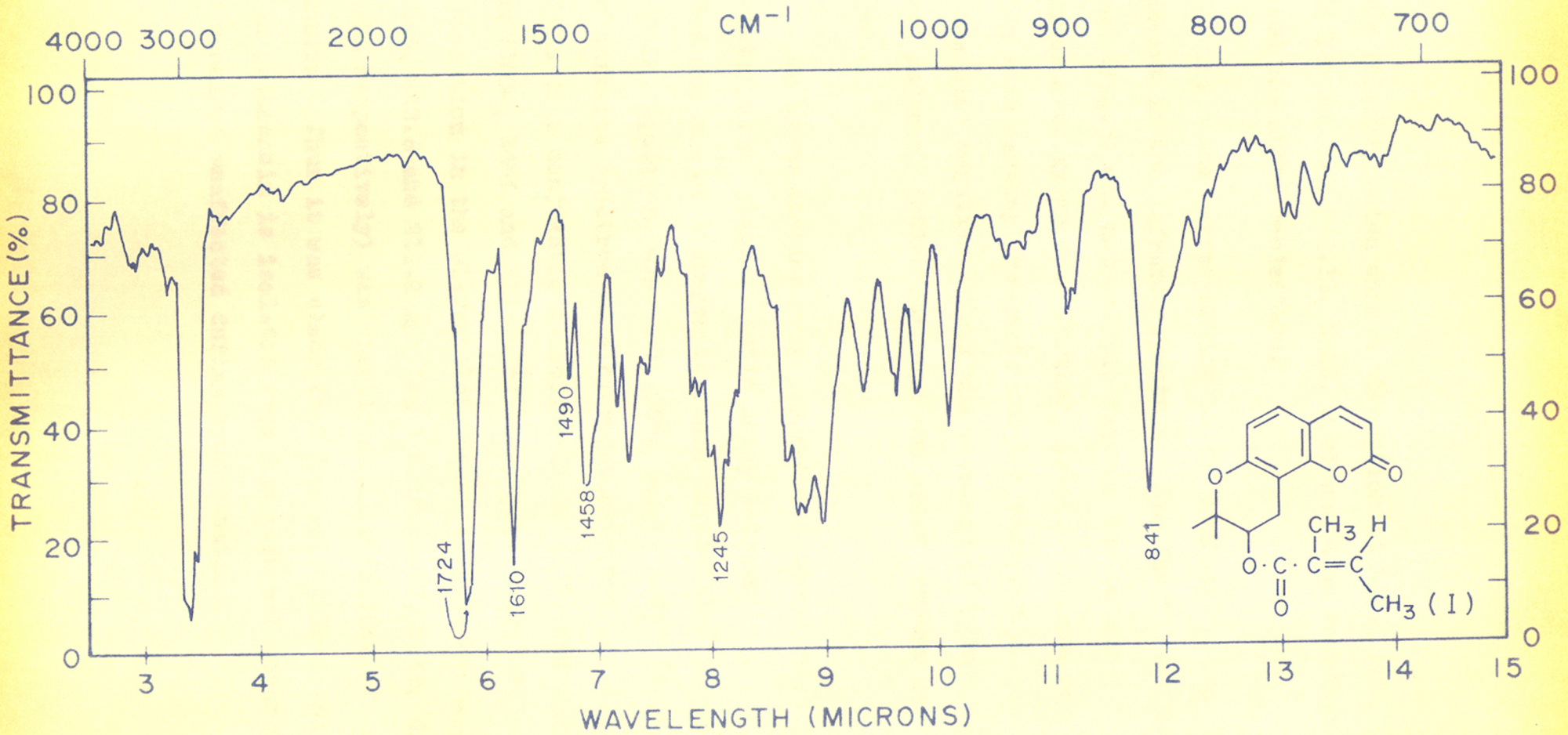


FIG. 2. IR SPECTRUM OF JATAMANSIN (I).

spectrum (Fig.3), which showed absorption at $\lambda_{max.}$ 326, 256, 246 and 220 mμ (log ε 4.13, 3.38, 3.47 and 4.30 respectively), supported the above conjecture.

The bands corresponding to the hydroxyl group were absent in the infrared spectrum. Similarly the PMR spectrum (Fig.5) did not exhibit signals due to any acetoxy or methoxy group. Further, jatamansin gave no reaction with carbonyl reagents and the test for an epoxy[3] group was also negative. Thus the presence of hydroxyl, acetoxy, methoxy, active carbonyl and epoxy groups was excluded.

On hydrogenation over pre-reduced Adams' platinum oxide catalyst in glacial acetic acid, jatamansin (I) absorbed one mol of hydrogen to yield crystalline dihydro-jatamansin, $C_{19}H_{22}O_5$, m.p. 107-108°, $(\alpha)_D$ + 5.06° (c, 6.11). In the infrared spectrum of dihydrojatamansin (Fig. 4), the bands due to a conjugated δ-lactone (1724 cm^{-1}) and aromatic system (1600, 1484 and 833 cm^{-1}) still persisted. Further, its absorption in the ultraviolet region (Fig.3; $\lambda_{max.}$ 326, 256, 246, 223.5 and 211.8 mμ; log ε 4.13, 3.47, 3.49, 4.16 and 4.24 respectively) was exactly similar to that of jatamansin. Thus it was clear that the reducible double bond in jatamansin is isolated from the main chromophore which remained unaffected during hydrogenation.

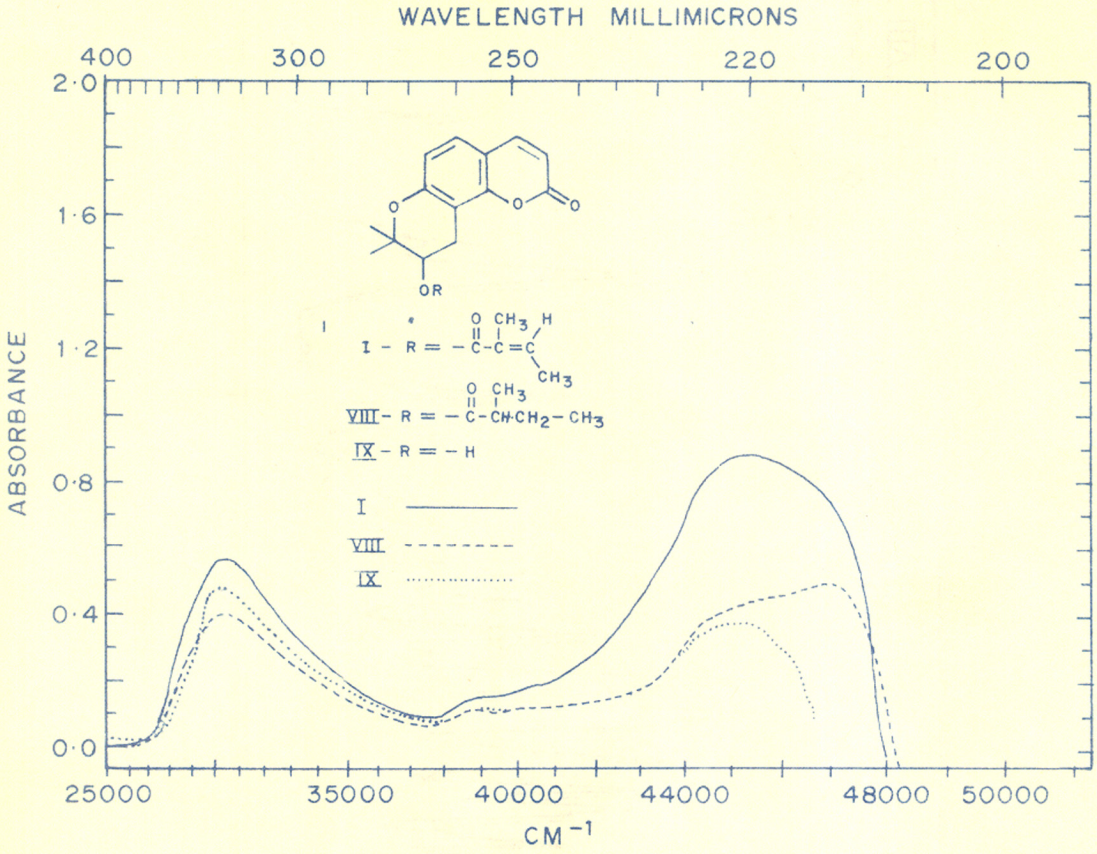


FIG. 3. UV SPECTRA OF JATAMANSIN (I), DIHYDROJATAMASIN (VIII) AND JATAMANSINOL (IX).

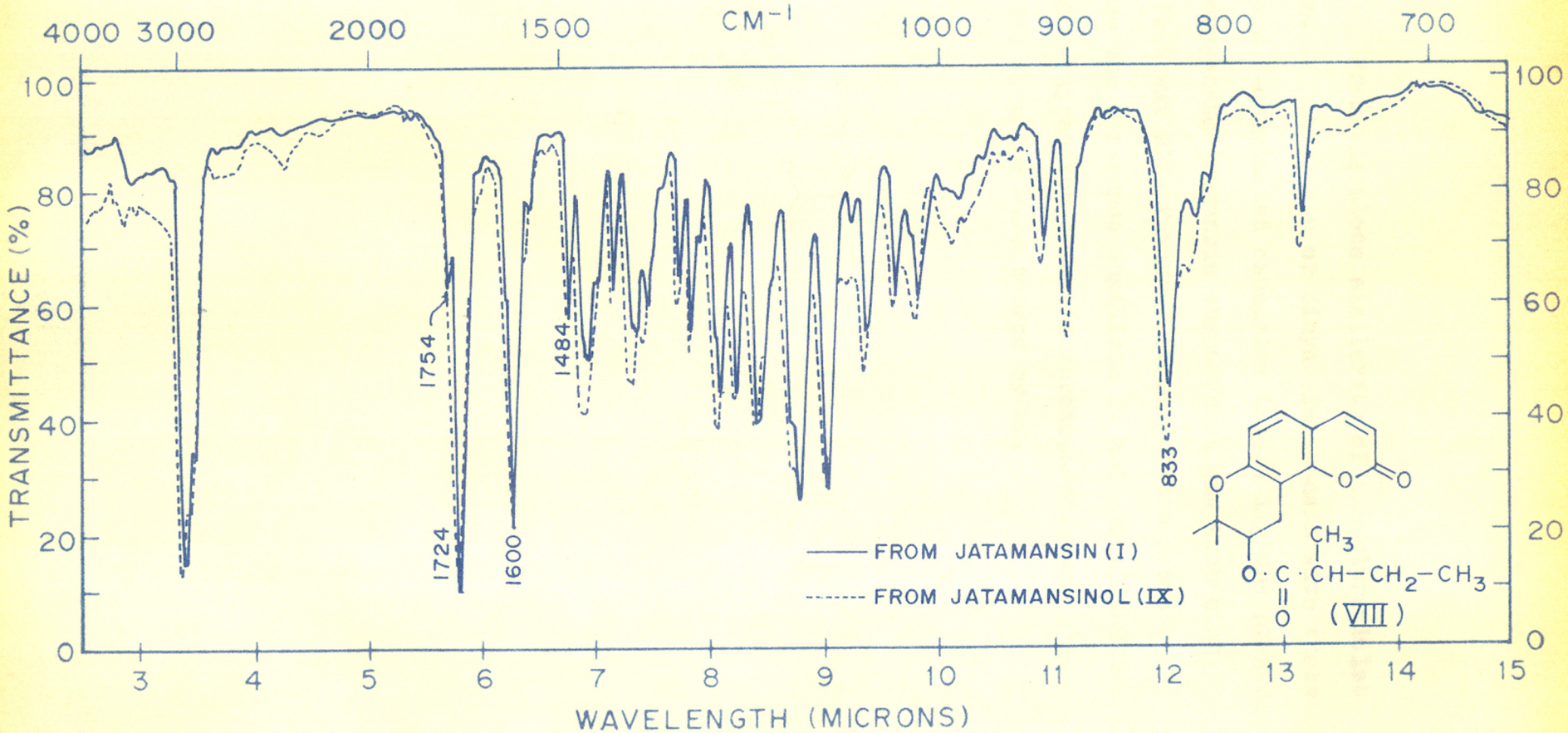
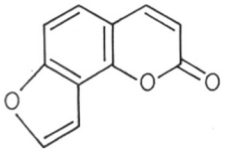
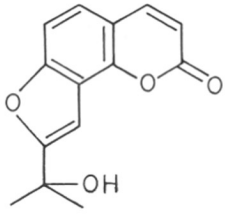


FIG. 4. IR SPECTRUM OF DIHYDROJATAMANSIN (VIII).

From the close similarity of the ultraviolet spectra of jatamansin or dihydrojatamansin with those of known 7-oxygenated coumarins (Table 1), the presence of 7-oxygenated coumarin chromophore was suspected. This fact was also favoured on biogenetic grounds because the compounds angelicin II and oroselol III, having 7-oxygenated coumarin chromophore, were also isolated from the same source by us.

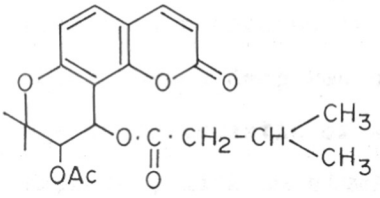
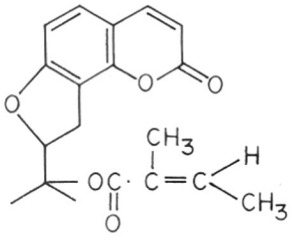
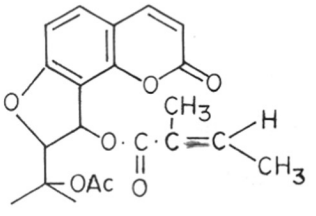


II



III

TABLE I - ULTRAVIOLET ABSORPTIONS OF 7-OXYGENATED COUMARIN CROMOPHORE.

Compound	$\lambda_{max.}$	log ε	Reference
	323	4.07	4
	255	3.46	
	245	3.52	
	219	4.05	
Suksdorfin			
	327	4.19	5
	261	3.59	
	250	3.56	
	219	4.35	
Columbianadin			
	323	4.16	6
	259	3.37	
	249	3.48	
	219	4.21	
Edultin			

Confirmation of the above conjecture was obtained by lithium aluminium hydride reduction of jatamansin and colour reactions described below.

Jatamansin and its derivatives gave yellow colouration on warming with alcoholic alkali[7] and gave violet fluorescence on adding conc. sulphuric acid[8] which turned deep red on warming. These colour tests are characteristic of a coumarin ring. Further, as expected, lithium aluminium hydride reduction product of jatamansin gave a positive test for phenolic hydroxyl group (which was absent in jatamansin). Thus, the presence of coumarin ring in jatamansin was conclusively proved.

Evidences for the nature of the remaining carbon skeleton and oxygen atoms were obtained as follows.

The PMR spectrum of jatamansin (Fig.5) depicted a six proton singlet at 82.8 cps assignable to two quarternary methyl groups (gemdimethyl) and a multiplet located around 114 cps (6 H) due to two methyl groups on an olefinic linkage, whereas in the PMR spectrum of dihydrojatamansin (Fig.6) two tertiary methyl groups at 79.2 cps were still discernible, however, it did not display the signal corresponding to the methyl groups on double bond, but showed instead a doublet at 67.2 cps

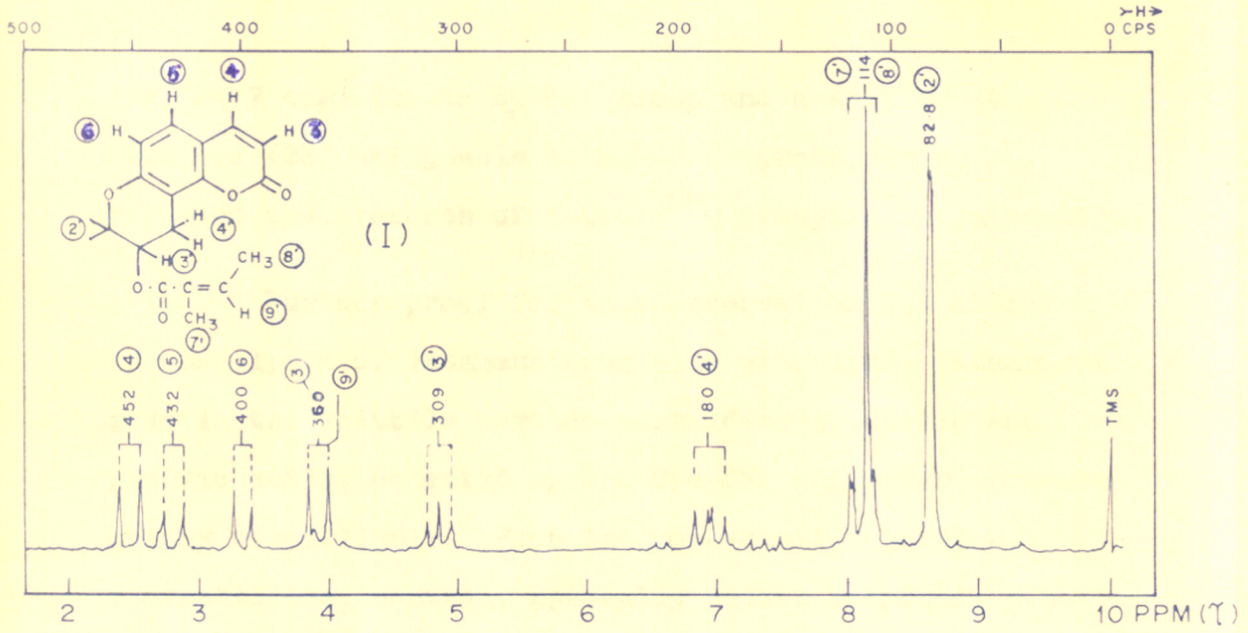


FIG. 5. PMR SPECTRUM OF JATAMANSIN (I).

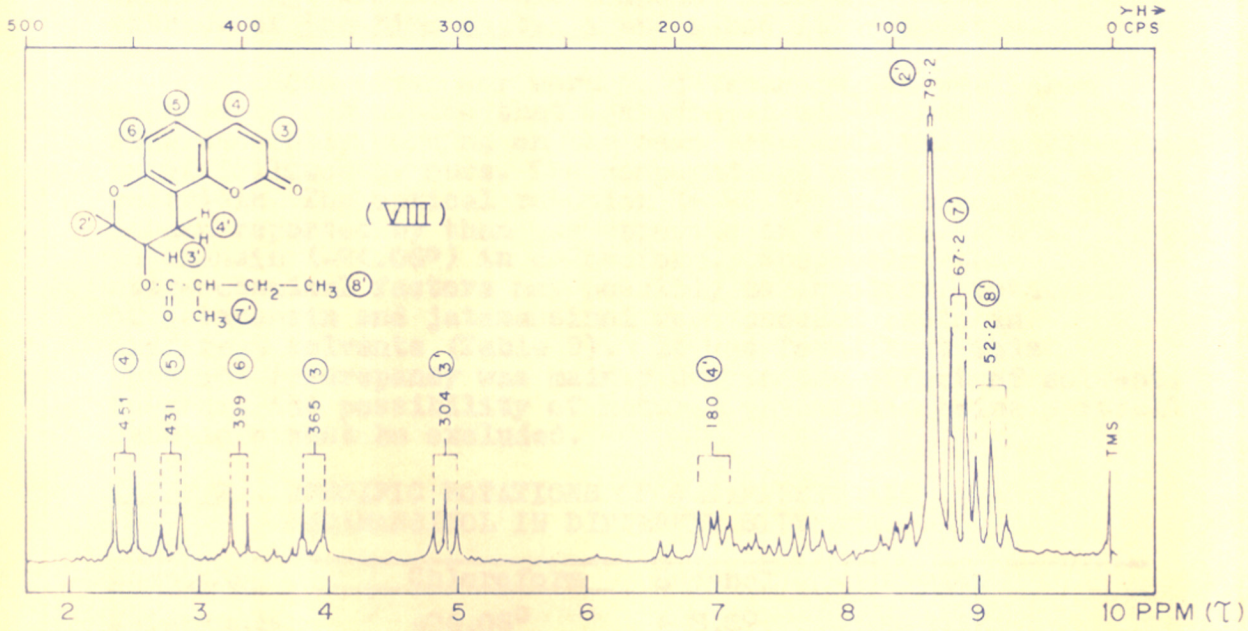


FIG. 6. PMR SPECTRUM OF DIHYDROJATAMANSIN (VIII).

(3H, J= 7 cps) due to H_3C-CH< group and a triplet at 52.2 cps (3H) assignable to H_3C-CH_2- group, which revealed the presence of H-C=C<(CH3 / H_3C) grouping in jatamansin.

Further proof for this observation was obtained by ozonolysis of jatamansin. On mild ozonolysis jatamansin gave in the volatile portion acetaldehyde, acetic and pyruvic acids, detected by the 2:4-DNP and paper chromatography respectively. From the non-volatile portion, a crystalline, neutral, optically active compound, m.p. 183-84°; $(\alpha)_D^{28}$ + 7.6° (c, 5.8), named as jatamansinol* was isolated. It analysed for $C_{14}H_{14}O_4$. In the infrared

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*We subsequently noticed that almost simultaneously Soine et al[9] isolated this compound from the petroleum ether extract of Lomatium nuttalli and named it as lomatin.

Soon after our work on jatamansin was published it came to our notice that Seshadri et al.[10] had also been simultaneously working on the same compound, their publication being followed by ours. The compound was named by them as selinidin. The optical rotation (+ 20.3°) of selenidin in dioxan reported by them was opposite in sign to that of jatamansin (-24.06°) in chloroform. Suspecting that stereochemical factors may possibly be involved, rotations of jatamansin and jatamansinol were checked again in different solvents (Table 2). It was found that this apparent discrepancy was mainly due to the effect of solvent. However, the possibility of natural jatamansin being partially racemic cannot be excluded.

TABLE 2 - SPECIFIC ROTATIONS OF JATAMANSIN AND JATAMANSINOL IN DIFFERENT SOLVENTS.

Compound	Chloroform	Ethanol	Dioxan
Jatamansin	-24.06°	+ 8.6°	+ 1.5°
Selinidin	-	-	+ 20.3°
Jatamansinol	+ 7.6°	+ 56.9°	+ 35.56°
Lomatin	-	+ 74.8°	-
Selinetin[10]	-	-	+ 17.2°

spectrum (Fig.7) it exhibited bands corresponding to the hydroxyl group (3623 cm^{-1}). It also depicted the presence of a coumarin ring (1721, 1618, 1499 and 833 cm^{-1}). Other bands of diagnostic importance in the infrared spectrum consisted of a doublet at 1387 and 1368 cm^{-1}, typical of a gemdimethyl group. Jatamansinol did not show any test for phenol. Further, the ultraviolet spectrum of jatamansinol (Fig.3; λmax. 329, 256, 246 and 216 mμ; log ϵmax. 4.06, 3.36, 3.41 and 4.01 respectively) was exactly similar to that of jatamansin, which indicated that the main chromophore in jatamansin remained unaffected during ozonolysis also. Jatamansinol, on treatment with p-toluenesulphonyl chloride in pyridine, gave a crystalline monotosylate, $C_{21}H_{20}O_6S$, m.p. 158-59°. On acetylation with acetic anhydride in pyridine it formed a crystalline monoacetate, $C_{16}H_{16}O_6$, m.p. 137-38°, showing the presence of only one hydroxyl group in it.

In the PMR spectrum of jatamansinol (Fig.8) gemdimethyl group (85.2 cps , 6H) was still discernible however, it did not display signals corresponding to other methyl groups present in jatamansin, evidently the grouping $H-C(H_3C)=C<CH_3$ which accounted for the formation of acetaldehyde and acetic acid was removed during ozonolysis. Molecular formulae of jatamansin ($C_{19}H_{20}O_5$) and jatamansinol ($C_{14}H_{14}O_4$) indicated the loss of a C_5

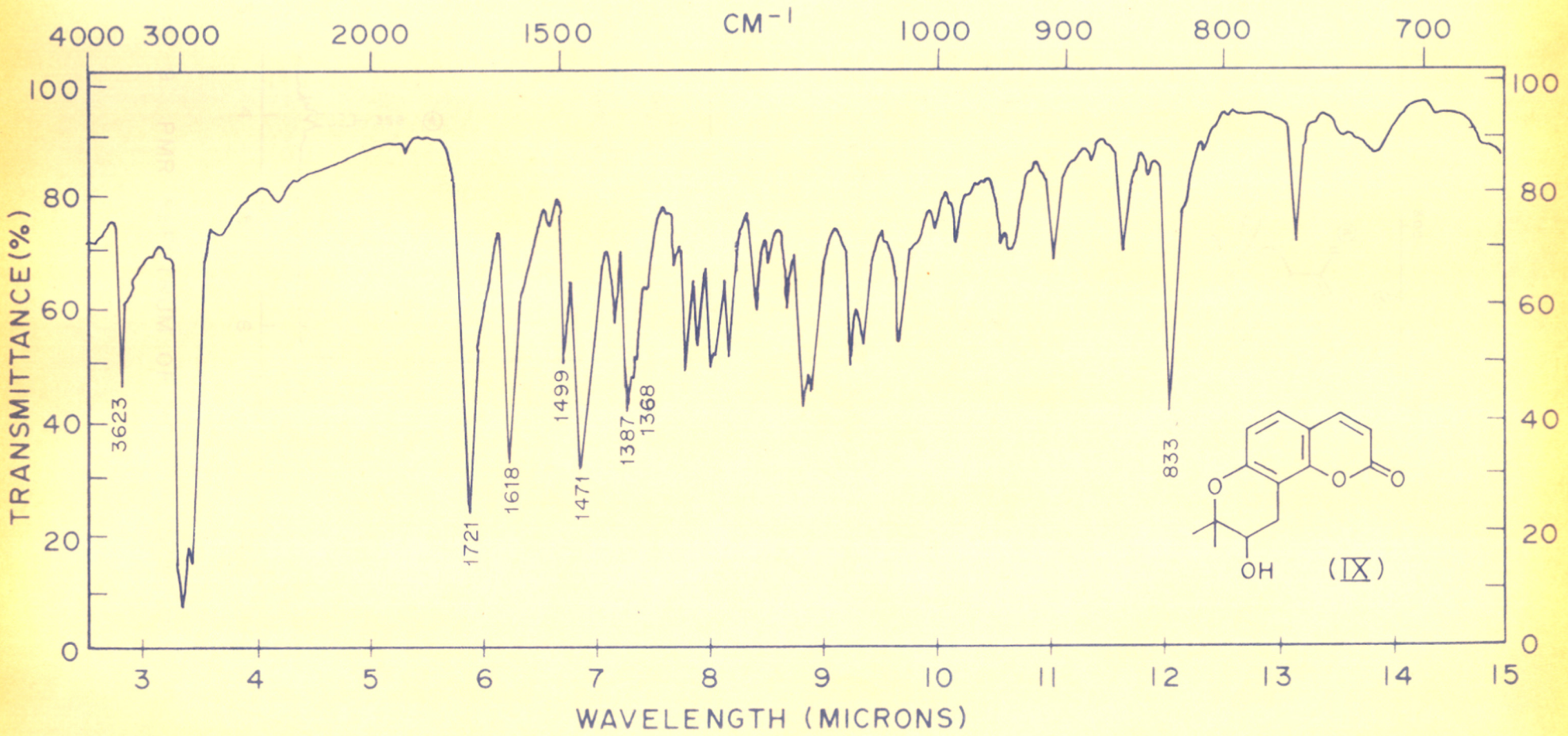


FIG. 7. IR SPECTRUM OF JATAMANSINOL (IX).

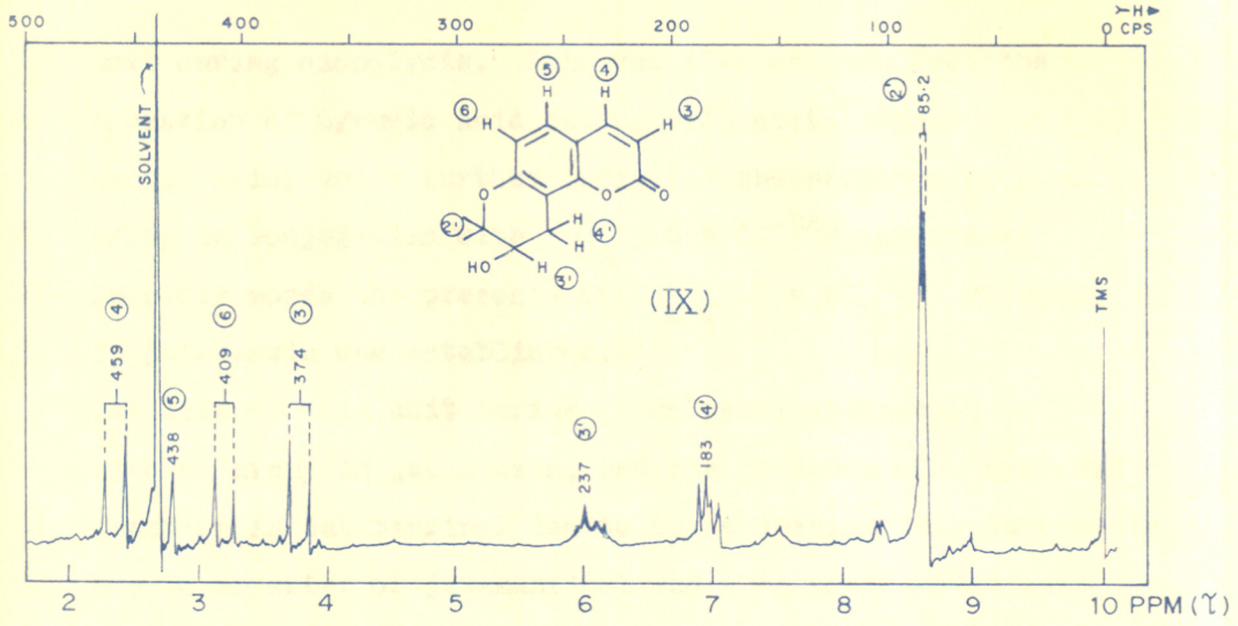


FIG. 8. PMR SPECTRUM OF JATAMANSINOL (IX).

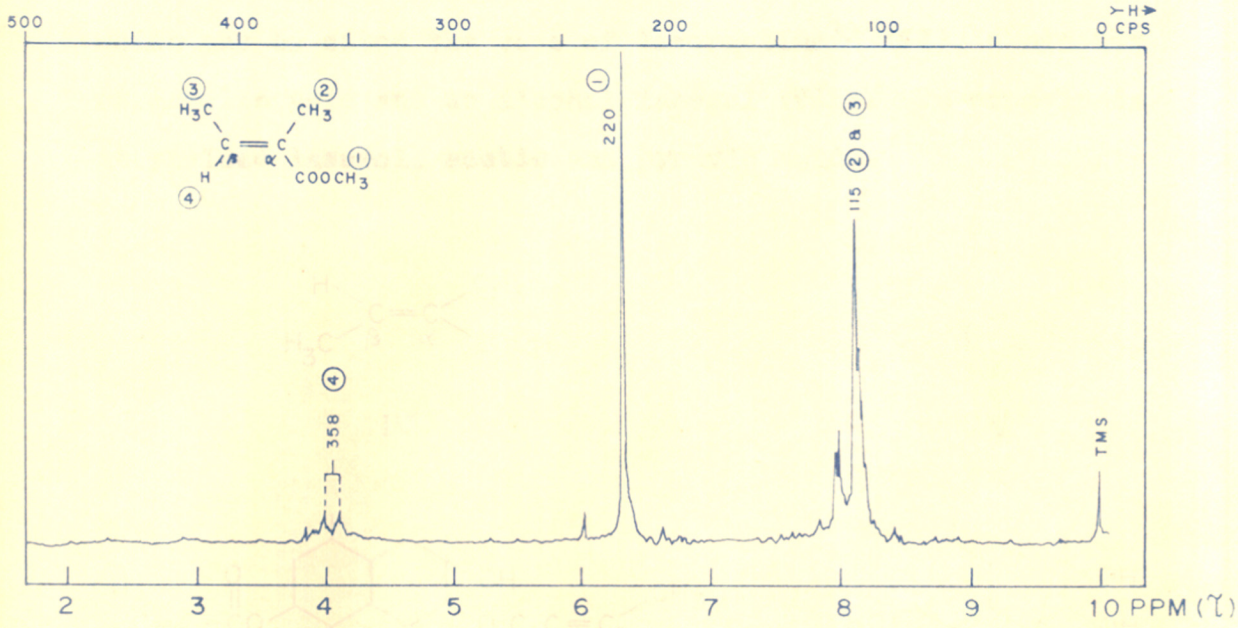
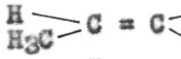
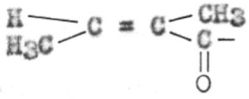
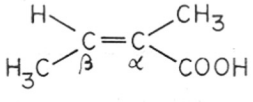


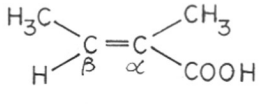
FIG. 9. PMR SPECTRUM OF METHYLANGELATE.

unit during ozonolysis. This was also evident from the formation of pyruvic acid (along with acetaldehyde and acetic acid) which further indicated the presence of >C=O group in conjugation with  grouping; in other words the presence of  grouping in jatamansin was established.

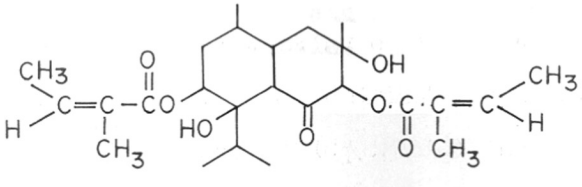
The loss of this unit during ozonolysis, absence of an alcohol group in jatamansin, and the presence of a hydroxyl function in jatamansinol led to the suspicion that jatamansin may be an ester of jatamansinol and a C_5 unsaturated acid (angelic, IV or tiglic, V). This conjecture was also supported by the fact that angelate and tiglate esters have been reported[11] to give on ozonolysis corresponding alcohols, acetaldehyde, acetic and pyruvic acids, as an example of which may be cited the case of laserpetine[11] (VI), a diester of angelic acid and an alcohol laserol (VII). On ozonolysis it yielded laserol, acetic and pyruvic acids.



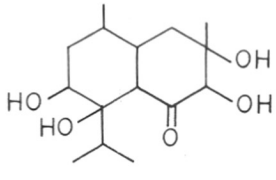
IV



V



VI



VII

The conclusions drawn from the results of ozonolysis were fully corroborated by hydrolysis experiments. Dihydrojatamansin, on hydrolysis with 5% methanolic potassium hydroxide at room temperature, yielded jatamansinol and an acid $C_5H_{10}O_2$. The latter was identified as ∝-methylbutyric acid by comparison with an authentic sample on GLC and through formation of p-bromophenacyl ester, m.p.52-53°. This fact conclusively proved that dihydrojatamansin is an ester of jatamansinol and ∝-methylbutyric acid, further confirmation of which was sought by condensation of jatamansinol with ∝-methylbutyric acid. Jatamansinol, on refluxing with ∝-methylbutyryl chloride in benzene solution, yielded dihydrojatamansin* identical in all respects with that prepared from hydrogenation of jatamansin.

Jatamansin, on mild hydrolysis, furnished jatamansinol and a C_5 unsaturated acid, m.p. 43-45° (with the characteristic infrared absorption bands at: 2800-2600, 938 cm^{-1} due to -COOH group and 1695, 1645 cm^{-1} assignable

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* Since the synthesis[12] of jatamansinone (XIV) from 7-hydroxy-coumarin (umbelliferone) and conversion[4] of jatamansinone to jatamansinol has been achieved by earlier workers, the conversion of jatamansinol to dihydrojatamansin can be considered as a total synthesis of dihydrojatamansin.

to -C=C-C=O entity; and ultraviolet absorption[13] at λmax. 216 mμ, log ε 3.69), which as expected, on hydrogenation+ over pre-reduced Adams' platinum oxide catalyst in methanol, absorbed one mole of hydrogen to yield α-methylbutyric acid. It was proved to be angelic acid (IV) from its m.p. 43-45° (tiglic acid, V, melts at 62-64°) and PMR spectrum. The vinyl proton of an angelate has been reported[14] to give a signal at 358.8 cps (multiplet) and that of a tiglate at 394.2 cps (multiplet). The PMR spectrum of methyl ester of acid isolated from jatamansin (Fig. 9) showed a signal at 358 cps (multiplet) due to vinyl proton and in jatamansin also it appeared around 360.0 cps. From these observations it was clear that jatamansin is an angelic ester of the alcohol jatamansinol.

Thus all the foregoing evidences reveal the presence of a 7-oxygenated coumarin ring, angelate ester side chain and gemdimethyl group in jatamansin, which accounts for 17 carbon atoms out of the 19 and all 5 oxygens. By the analogy with various other naturally occurring coumarins the remaining 2 carbon atoms, the oxygen atom at 7 position and the gemdimethyl group were believed to be present in the form of a tetrahydropyran

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+ This observation also supported that the unsaturated acid may either be angelic (IV) or tiglic (V) acid.

or a tetrahydrofuran ring fused at 7:8 (Fig.10, A and B) or 6:7 positions (Fig.10, C and D) of the coumarin moiety. The four possible structures may be written for jatamansin skeleton as shown in Fig. 10. One of these with an angelic ester side chain attached at the appropriate position will represent the structure of jatamansin.

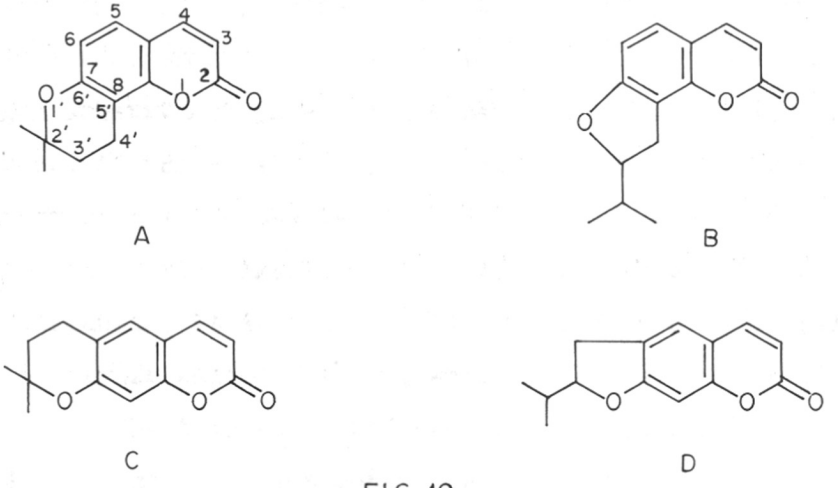

FIG. 10

A decision in favour of the 2'2'-dimethyl tetrahydropyrano (6', 5', 7, 8) coumarin skeleton (Fig.10, A) could be made by a critical study of the PMR spectra of jatamansin and its derivatives which further depicted structure I for jatamansin. As can be seen from Fig. 5, jatamansin showed a pair of doublets forming an AB system at 452 and 366 cps (1H each, J=9 cps) which could be assigned respectively to the protons at 4 and 3 positions

of the δ-lactone ring by comparison with known coumarin compounds, such as discophoridin,[15] where the corresponding doublets occurred at 456 and 372 cps. The position of other doublets (due to protons at 5 and 6 positions) in the aromatic region and their splitting (432 and 400 cps, 1H each, J=9 cps) were typical of the signals from ortho-protons in a 1,2,3,4-substituted benzene ring.* It is known[16] that aromatic protons which are not adjacent to an oxygen substituent give signals between 444 and 438 cps, whereas, if there is an adjacent oxygen atom, the signal is shifted upfield to the region 408-402 cps. From the positions of the signals of two aromatic protons (at 5 and 6) in jatamansin, it is evident that the one at 6 (400 cps) has an oxygen adjacent to it, while the other at 5 (432 cps) has not. The triplet at 309 cps (1H) was assigned to proton at 3' and the multiplet centred around 180 cps (2H) was ascribed to benzylic protons at 4'. As mentioned earlier the multiplet located around 114 cps (6H) was due to α- and β methyl groups of angelic ester side chain and a strong singlet at 82.8 cps (6H) was assignable to gemdimethyl group at 2'. The absorption due to β-proton of angelic ester side chain (360 cps) was merged with one of the absorptions of doublet due to proton at 3, but the integration curve clearly showed the presence of two protons in that region. Finally in the

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* In view of this the possibility of the skeletons, Fig. 10, C & D was excluded.

PMR spectrum of jatamansinol (Fig. 8) the signal due to 3' proton (237 cps) was shifted upfield by 72 cps than that of jatamansin (309 cps). It is well known[17] that in the case of primary hydroxyl group, the signal due to protons on a carbon atom bearing a hydroxyl group shifts downfield by about 30 cps after acetylation, whereas, in the case of secondary hydroxyl group this shift is about 60-70 cps. Therefore the presence of secondary hydroxyl group* in jatamansinol was evident.

Thus the chemical degradations (Fig. 11) coupled with spectral studies enabled Structures I, VIII and IX to be assigned respectively to jatamansin, dihydrojatamansin and jatamansinol.

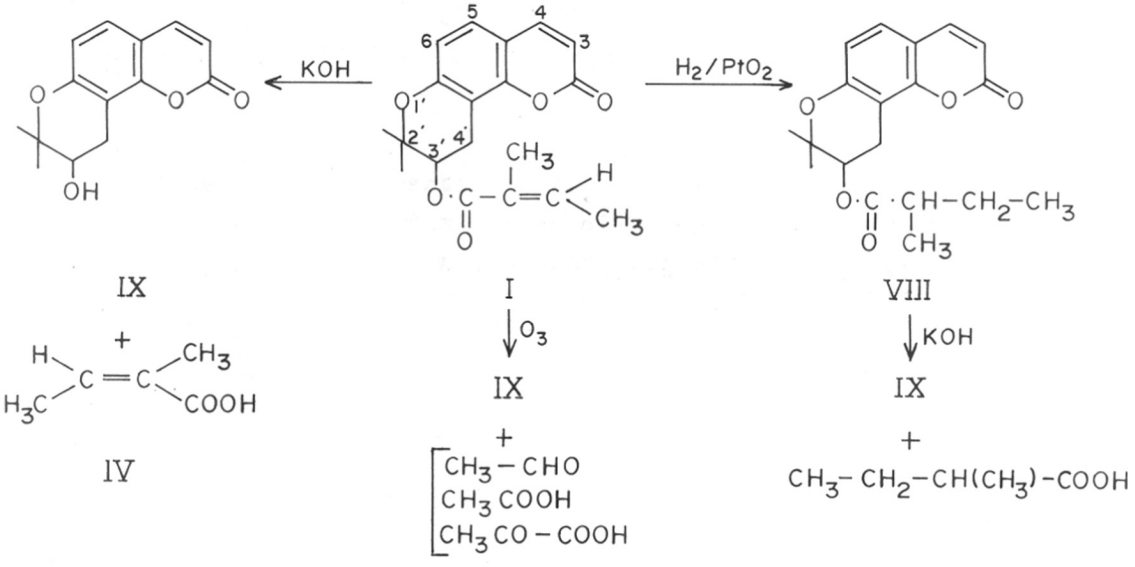
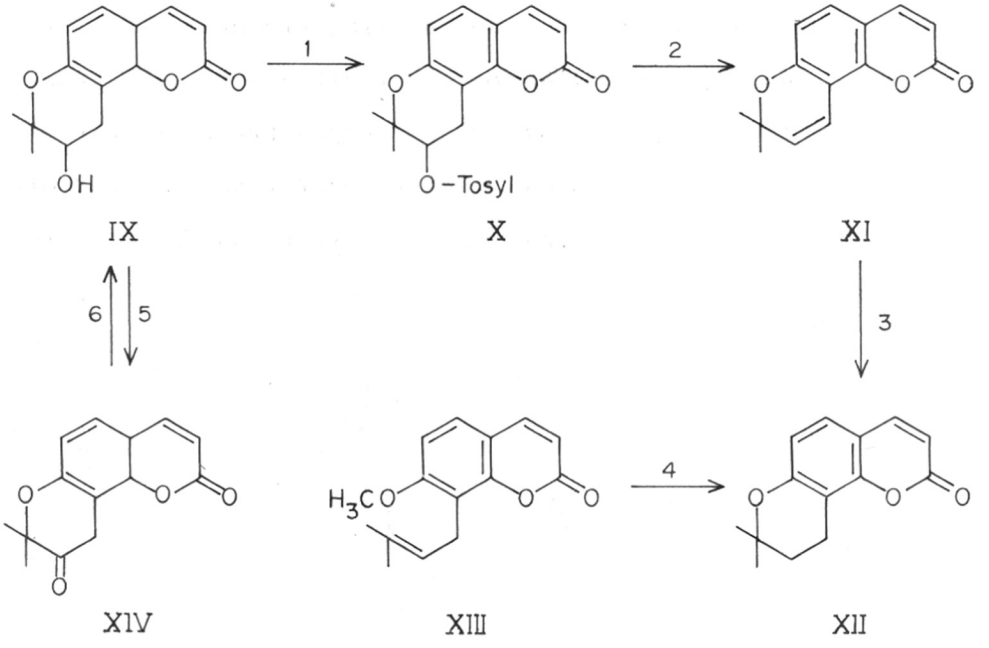


FIG. 11

* In view of the presence of secondary hydroxyl group and two benzylic protons in jatamansin, the possibility of the skeleton Fig. 10B was excluded.

Further chemical support in favour of the structure (I) of jatamansin was obtained by the correlations schematically depicted in Fig. 12.



Reactions: (1) Condensation with p-toluene sulphonyl chloride.
(2) Detosylation by refluxing in 2:4:6 collidine.
(3) Hydrogenation over PtO_2 catalyst in HAc.
(4) Demethylation accompanied by ring closure by red P & HBr.
(5) Oxidation with Jones' reagent in acetone.
(6) Reduction with $NaBH_4$ in methanol.

FIG. 12

Tosylate of jatamansinol (X) on heating with 2:4:6-collidine furnished an optically inactive chromene, m.p. 119-120°, identified as seselin (XI)[18] from the melting point and ultraviolet spectrum[19] (Fig. 17) in which it showed the presence of extended conjugation (λmax. 330, 294, 284 and 218 mμ; log ε 4.07, 4.05, 4.04 and 4.42 respectively). The structure of this chromene was fully corroborated by its PMR spectrum (Fig.15). A pair of doublets at 452 and 366 (1H each, J=9 cps) was assigned to protons at 4 and 3 respectively and another pair of doublets at 430 and 397 cps (1H each, J=9 cps) to the ortho protons at 5 and 6 respectively. The third pair of doublets at 413 and 341 cps (1 H each, J = 10 cps) is very much characteristic of two cis hydrogens (4& and 3' respectively) on a double bond conjugated with an aromatic ring[20] (chromene system). The last pair of doublets was absent in the PMR spectrum of jatamansinol (IX, Fig. 8), but instead of that a triplet at 237 cps (1H, due to one proton at 3') and a multiplet centred at 183 cps (2H, due to benzylic proton at 4') were present which disappeared in that of seselin (XI) due to formation of double bond between 3' and 4' carbon atoms. Lastly the PMR spectrum of XI also depicted a strong signal at 88.8 cps (6H) due to the gemdimethyl group at 2'.

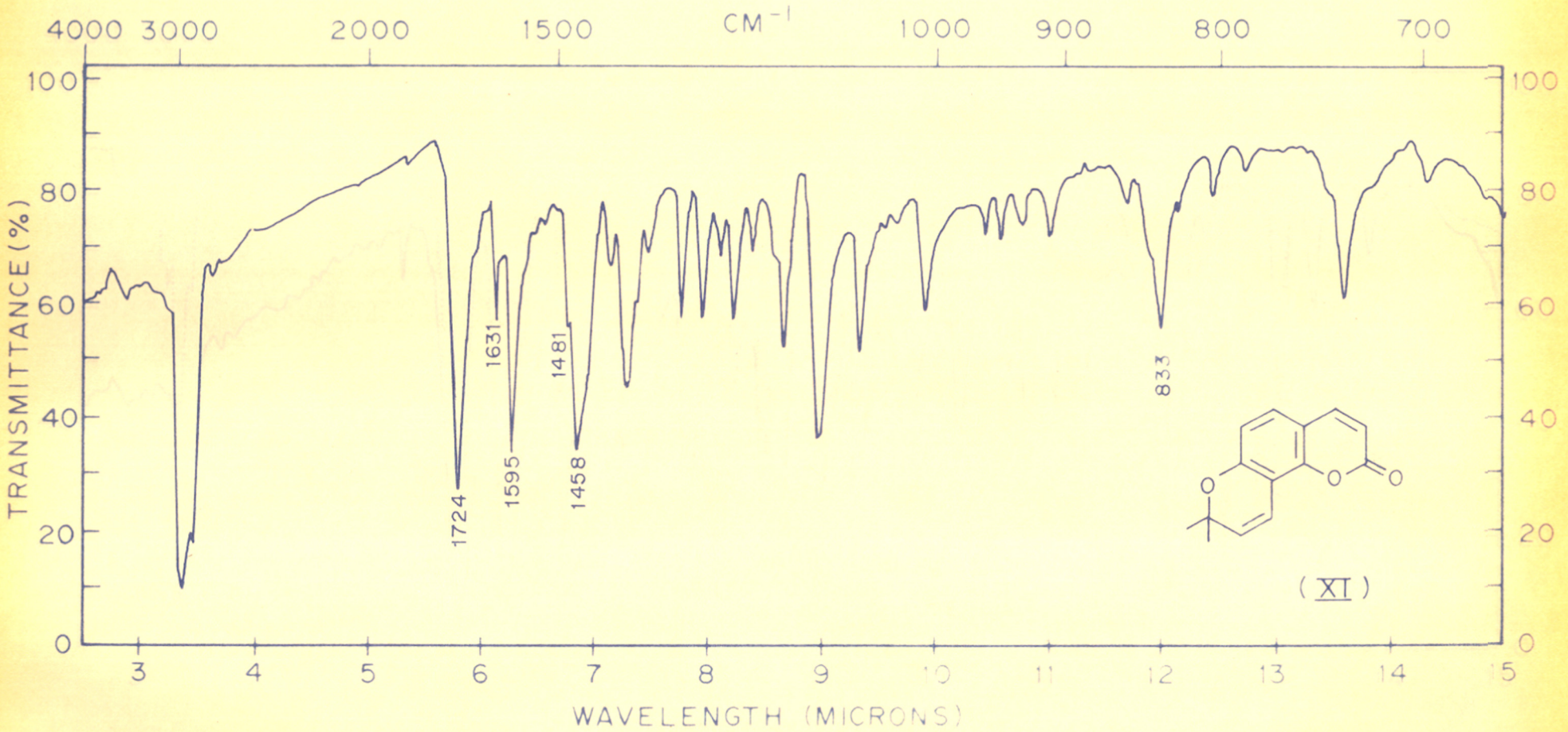


FIG. 13. IR SPECTRUM OF SESELIN (XI).

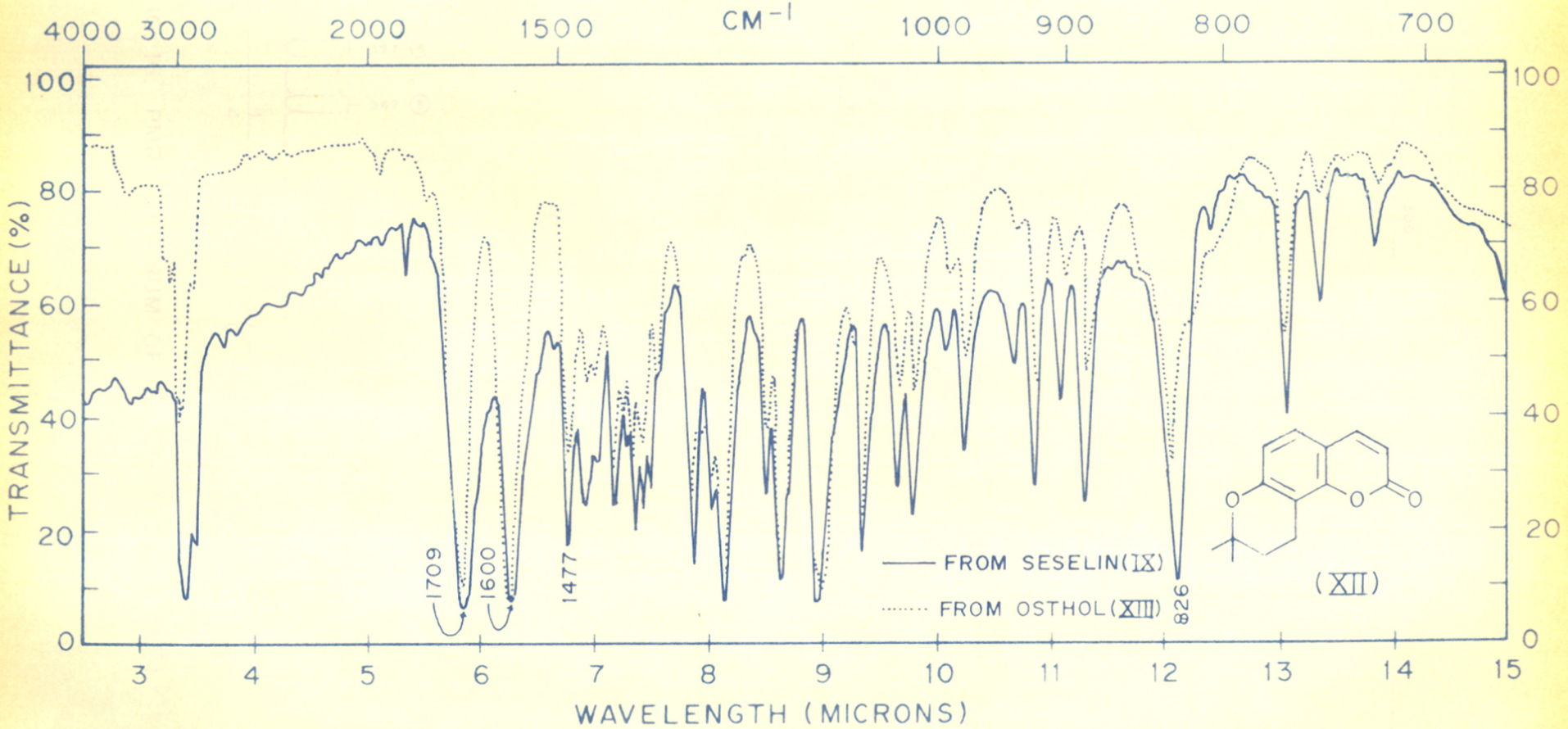
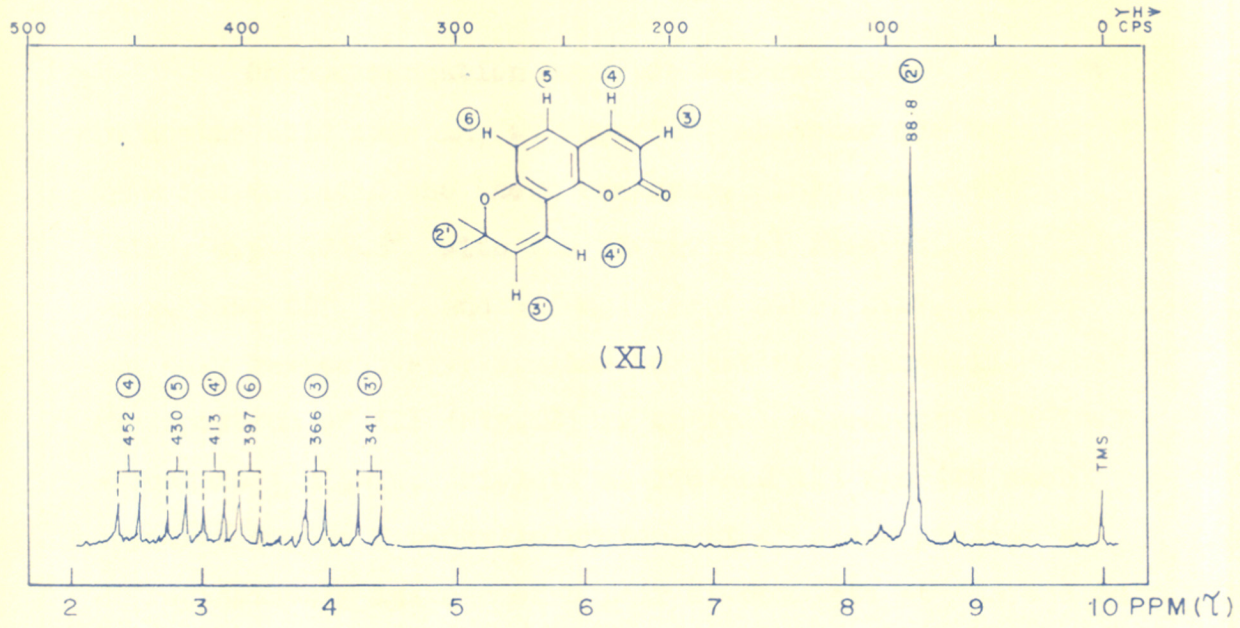
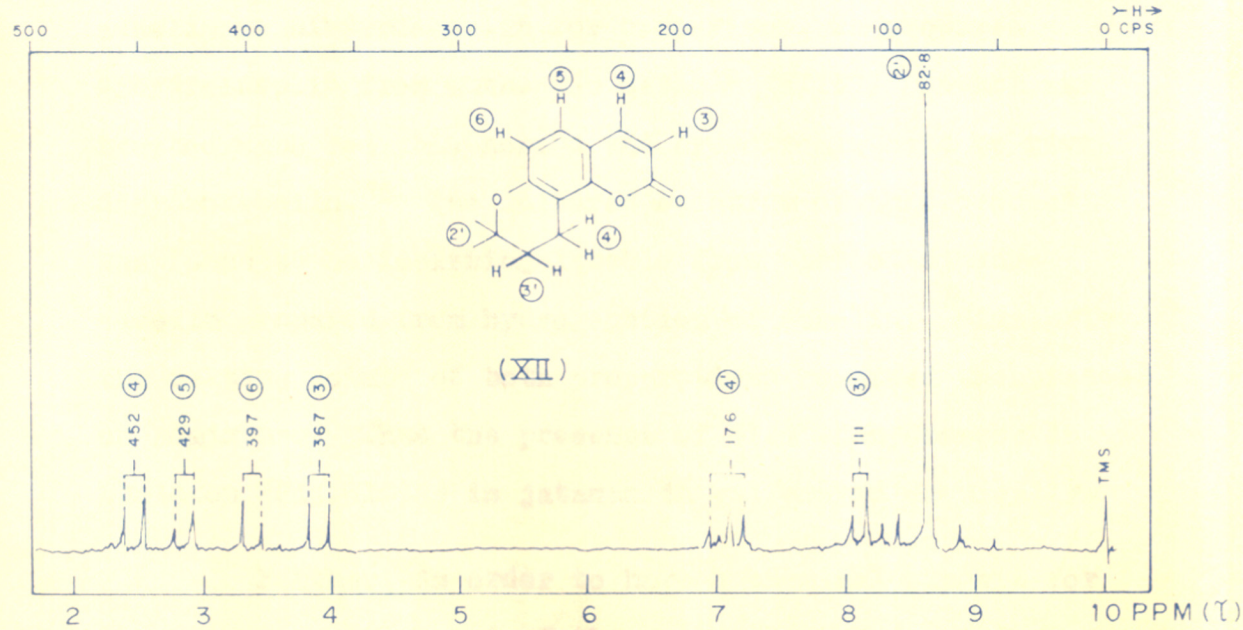


FIG. 14. IR SPECTRUM OF DIHYDROSESELIN (XII).



(XI)

FIG. 15. PMR SPECTRUM OF SESELIN (XI).



(XII)

FIG. 16. PMR SPECTRUM OF DIHYDROSESELIN (XII).

On hydrogenation over pre-reduced Adams' catalyst in acetic acid seselin, as expected, absorbed one mole of hydrogen to yield the known compound, dihydroseselin[21] (XII), m.p. 104-5°, with the ultraviolet absorption (Fig.17, λmax. 329, 255, 246 and 213 mμ; log ε 4.09, 3.37, 3.41 and 4.17 respectively) similar to that of jatamansin. The PMR spectrum of XII (Fig.16) is in full agreement with its structure (in this, triplets at 176 and 111 cps (2H each) appeared due to 2 benzylic protons at 4' and 2 protons at 3' respectively instead of a pair of doublets at 413 and 341 cps due to olefinic protons at 4' and 3' present in that of seselin).

As we could not get an authentic sample either of seselin or dihydroseselin for comparison, we prepared dihydroseselin from authentic osthol* (XIII). Osthol was treated with red phosphorous and hydrobromic acid to give dihydroseselin.[22] The infrared spectrum of this product was found to be indistinguishable from that of dihydroseselin prepared from hydrogenation of seselin. Similarly the melting points of both preparations remained undepressed on admixture. Thus the presence of 3',4'-dihydroseselin skeleton (Fig. 10 A) in jatamansin was proved chemically.

Further, in order to have a chemical support for the point of attachment of the ester side chain at 3' carbon atom, the alcohol jatamansinol (IX) was oxidised with

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* We are thankful to Dr.(Mrs) A. Chatterjee for supplying the sample of osthol.

Jones' reagent[23] which afforded the ketocompound, $C_{14}H_{12}O_4$, m.p. 157-58°, named as jatamansinone. It was found to be identical with the known compound[12,24] (3'-keto-3',4'-dihydroseselin) by comparison of the melting point and ultraviolet spectrum (Fig. 17, λmax. 321, 256, 248 and 218 mμ; log ε 4.12, 3.5, 3.54 and 4.15 respectively). In the PMR spectrum of jatamansinone (Fig. 18), as expected, signals due to the proton at 3' (present in that of jatamansinol) disappeared and the absorption due to protons at 4' position was shifted to a much lower field (223 cps, singlet) than that of jatamansinol (183 cps, multiplet). This may be ascribed to the diamagnetic anisotropy of the adjacent carbonyl group. Jatamansinone (XIV) was reduced with sodium borohydride to yield racemic jatamansinol,[4] m.p. 162-66°, the spectral characteristics of which were identical in all respects with those of an active jatamansinol obtained by hydrolysis or ozonolysis of jatamansin. The formation of jatamansinone confirmed the presence of an ester side chain at 3' position in jatamansin (I). Thus the structure of jatamansin was unambiguously established.

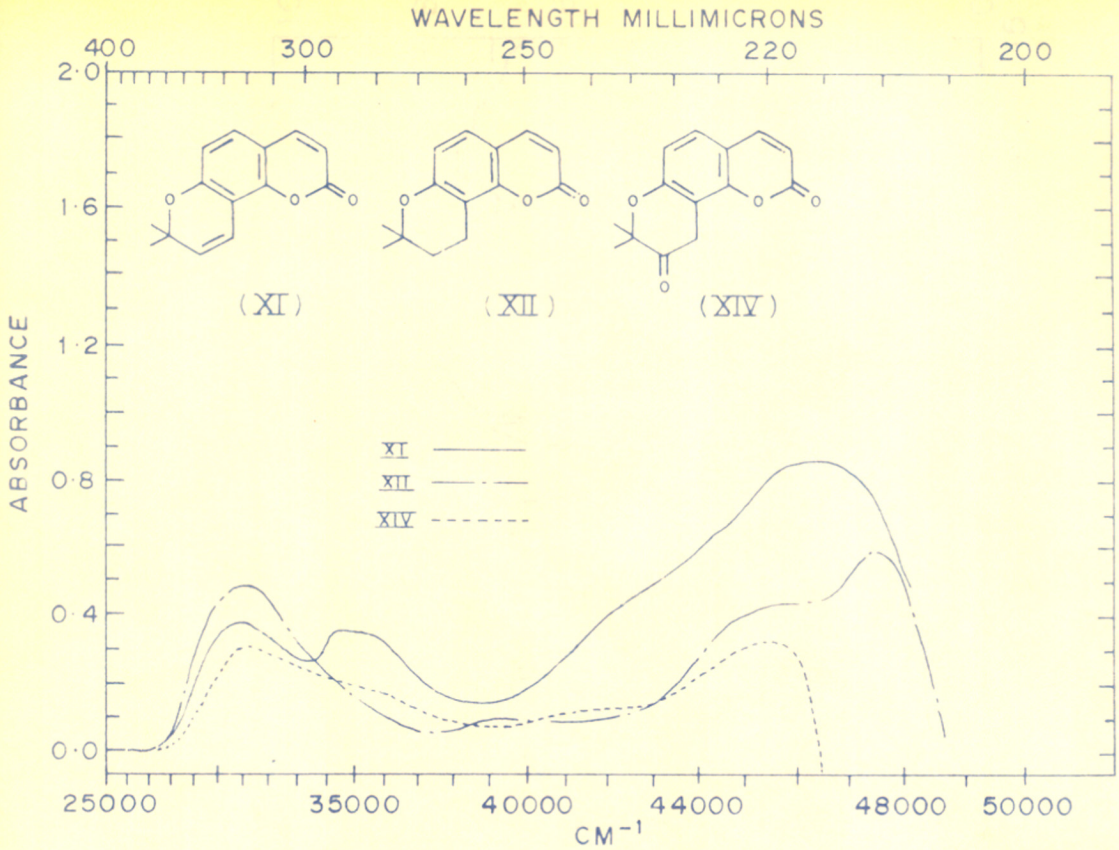

FIG. 17. UV SPECTRA OF SESELIN (XI), DIHYDROSESELIN (XII) AND JATAMANSINONE (XIV).

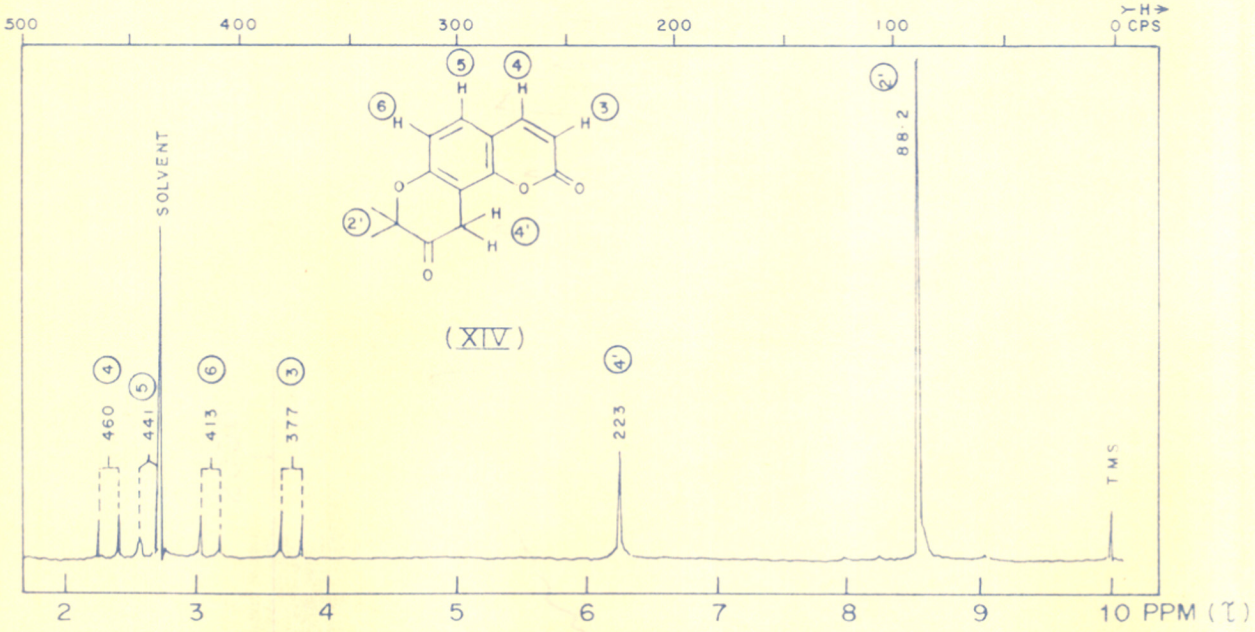

FIG. 18. PMR SPECTRUM OF JATAMANSINONE (XIV).

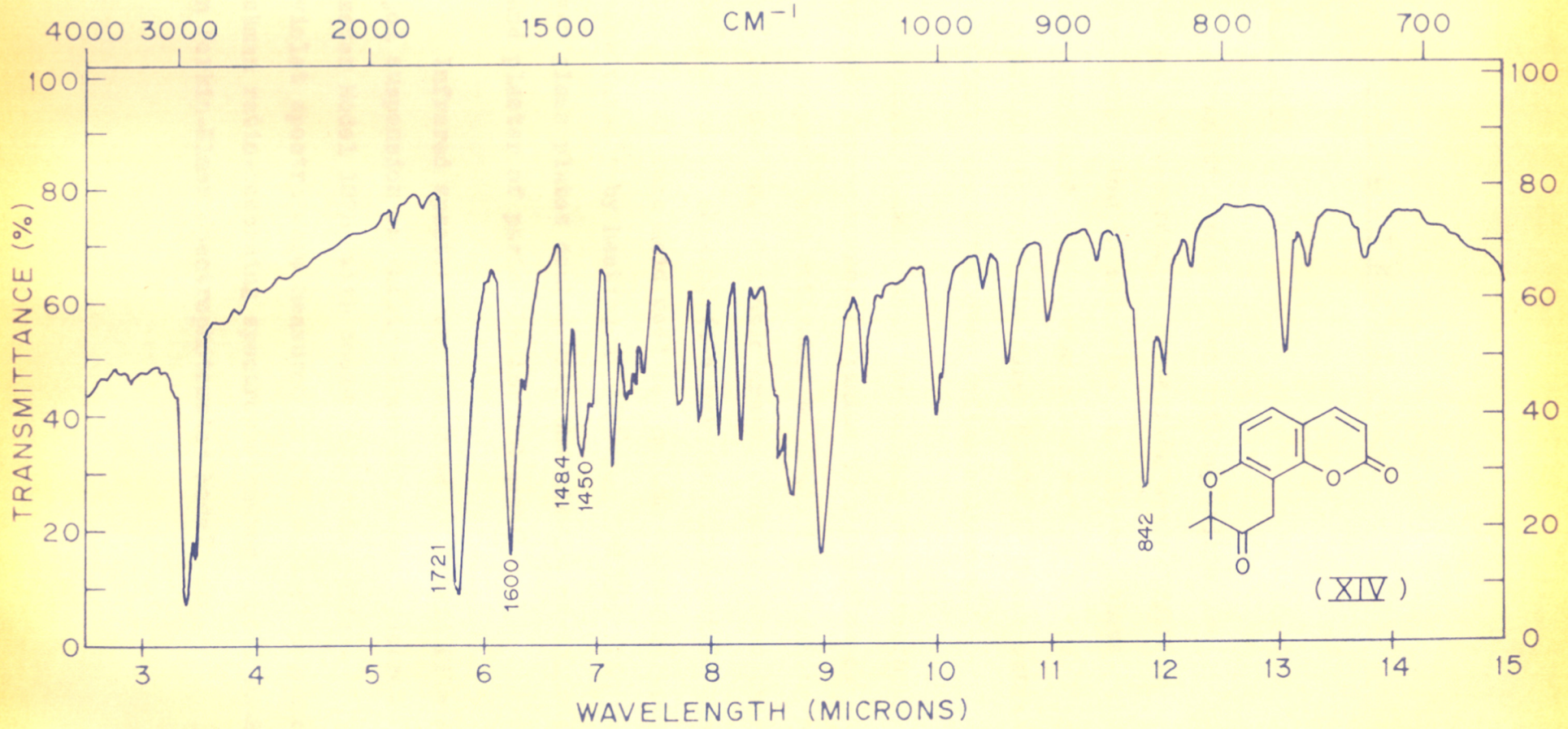

FIG. 19. IR SPECTRUM OF JATAMANSINONE (XIV).

EXPERIMENTAL

GENERAL REMARKS

All melting points and boiling points are uncorrected and recorded on centegrade scale. Optical rotations were taken in chloroform solutions unless otherwise mentioned. Petroleum ether refers to the fraction boiling between the range 60-80°. Ether extracts after washings were dried over sodium sulphate.

Neutral alumina used for column chromatography was prepared from commercial alumina by the method of Evans and Shoppe[25] and activated to grade I by heating at 450-460° for 6-8 hr. Suitable grades were prepared therefrom by mechanical shaking (4-6 hr) with appropriate amounts of water.[26] Silicic acid used for column chromatography was deactivated[27] by heating at 450° for 1/2 hr. TLC was run over glass plates coated with the mixture of silicic acid and plaster of paris (85:15; 200 mesh).

Infrared spectra were recorded as liquid film or in nujol suspension on Perkin-Elmer Infracord Spectrophotometer Model 137B, with sodium chloride optics. Ultraviolet spectra were measured in 95% ethanol solution on Beckman ratio-recording spectrophotometer, Model DK-2 and on Perkin-Elmer Spectrophotometer Model 350.

PMR spectra were taken on 10-20% solutions in carbon tetrachloride, dueterochloroform, acetone or pyridine. on a Varian Associates A-60 spectrometer with tetramethyl silane as the internal standard and chemical shifts were measured in cps units. GLC analyses were carried out using hydrogen under pressure as the carrier gas on modified Griffin GLC apparatus, MK IIA with polyester column.

Extraction of the roots of Selinum vaginatum (C.B.Clarke*)

The powdered roots (74.9 kg) were added to petroleum ether (40-60°; 170 lit.) and were stirred mechanically for about 4 hr. at room temperature. The extract was first filtered through cloth and the plant pulp squeezed thoroughly to press out the maximum amount of solvent. The extract was then filtered through filter paper. The residual pulp was subjected to two more similar extractions but using only 140 lit. of petroleum ether each time. The combined filtrate were poured into a double jacketed stainless steel vessel fitted with adequate condensers and connection for vacuum. The jacket temperature of the above vessel was maintained at 40 ± 2° and the solvent removed

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* obtained from Jammu & Kashmir.

under reduced pressure. Traces of suspended matter were removed by filtration under vacuum. The extractive thus obtained (7.28 kg; 9.7%) had the following properties; colour: light brown; n_D^{27} 1.5254; $(\alpha)_D^{30}$ - 10.36° (c, 1.15); acid number 6.5; ester number 104.8 and alcohol number 78.52.

Ultraviolet spectrum: $\lambda_{max.}$ 326, 256, 246 and 220 mμ ($\epsilon_{1\ cm.}^{1\%}$ 240.1, 142.9, 163.3 and 678.8 respectively).

Infrared spectrum (Fig.1), bands at: 3425, 2941, 1739, 1608, 1488, 1449, 1370, 1282, 1222, 1143, 1111, 1060, 1047, 1020, 995, 960, 934, 892, 936 and 760 cm^{-1}.

Jatamansin (I)

The extractive after refrigeration for several days deposited crystals of jatamansin (580g) which were filtered out, washed and crystallised (thrice) from a large volume of petroleum ether to give colourless crystals, m.p. 97-98°; $(\alpha)_D^{25}$ - 24.06° (c, 5.1).

Infrared spectrum (Fig.2), bands at: 1724, 1610, 1490, 1458, 1404, 1383, 1348, 1245, 1147, 1119, 1075, 1042, 1022, 994, 900, 847, 769 and 751 cm^{-1}.

Ultraviolet and PMR spectra (described in the theoretical part).

Analysis

Found: C, 69.55; H, 6.22.
$C_{19}H_{20}O_5$ requires: C, 69.50; H, 6.14%.

Dihydrojatamansin (VIII)

Jatamansin (4 g) was hydrogenated at room temperature (28°) and pressure (710 mm) in glacial acetic acid (200 ml) over pre-reduced Adams' platinum oxide catalyst (0.200 g). The hydrogen uptake came to a close after absorption of 305 ml of hydrogen (calculated for one double bond, 316 ml) during 4 hr. The catalyst was then filtered and the solvent was removed in vacuum to furnish a residue (3.90 g) which on crystallisation from petroleum ether afforded dihydrojatamansin in colourless needles, m.p. 107-108°; $(\alpha)_D^{27}$ + 5.06° (c,6.11).

Ultraviolet spectrum (described in the theoretical part).

Infrared spectrum (Fig.4), bands at: 1734, 1600, 1484, 1403, 1364, 1346, 1292, 1279, 1241, 1218, 1190, 1146, 1111, 1070, 1042, 1020, 917, 900, 833 and 760 cm^{-1}.

PMR spectrum (Fig.6 in CCl_4): A pair of doublets at 451 and 365 cps (1H each, J = 9 cps, due to protons at 4 and 3 respectively); another pair of doublets at 431 and 399 cps (1H each, J = 8 cps, due to protons at 5 and 6 respectively); triplet at 304 cps (1H, due to proton at 3'); a multiplet centred at 180 cps (2H, due to benzylic protons at 4'); strong singlet at 79.2 cps (6H, due to gemdimethyl group at 2'); a doublet at 67.2 cps (3H, J = 7 cps, due to

$HC-CH<_{3}$ grouping) and a triplet at 52.2 cps (3H, due to CH_3-CH_2-grouping).

Analysis

Found: C, 69.4; H, 7.00.

$C_{19}H_{20}O_5$ requires: C, 69.07; H, 6.71%.

Ozonolysis of jatamansin

A slow stream of ozonised oxygen was passed through a solution of jatamansin (3.6 g) in carbon tetrachloride (50 ml) for 5 hr at 0°. The reaction mixture after removal of solvent in vacuum was diluted with water (30 ml) and subjected to steam distillation.

Volatile products of ozonolysis (acetaldehyde, acetic and pyruvic acids)

Distillate obtained as above was neutralised with sodium bicarbonate and again subjected to steam distillation. The distillate, thus obtained, was converted into its crystalline 2,4-dinitrophenyl-hydrazone (0.20 g), m.p.147-48°, by the usual procedure and identified as the 2,4 -DNP of acetaldehyde by mixed melting point with an authentic sample which remained undepressed.

Analysis

Found: C, 42.90; H, 3.66; N, 25.04.

$C_8H_8O_4N_4$ requires: C, 42.86; H, 3.60; N, 24.99%.

The non-volatile portion of second steam distillation containing sodium salts of acids was concentrated and subjected to paper chromatography[28] using n-butanol-aq. ammonia as a developing solvent. It showed the presence of acetic and pyruvic acids by comparison with authentic samples.

Non-volatile product of ozonolysis (jatamansinol, IX).

The non-volatile portion left after the first steam distillation was extracted with ether and worked up in the usual manner to give a residue (2.7 g) which showed the presence of two spots on TLC and was subjected to column chromatography over neutral alumina (gr. III).

CHROMATOGRAM

Wt. of compound 2.7 g.
Wt. of Al_2O_3 (Neu. III) 75.0 g.

Fr.	Eluent	Ratio by volume	Volume of eluate (ml)	Wt. of fraction. (g)	Remarks
1	Pet.ether	100%	300	-	-
2	Pet.ether-benzene	50:50	300x3	0.600	unreacted jatamansin.
3	Benzene	100%	300	0.020	rejected
4	Benzene-ether	50:50	300x5	1.900	jatamansinol
5	Ether	100%	300x2	0.005	rejected.

Fraction 4 containing jatamansinol (IX) was crystallised from benzene and ethanol to give colourless needles, m.p. 183-84°; $(\alpha)_D^{28}$ + 7.6° (c, 5.8).

Ultraviolet spectrum: (described in the theoretical part).

Infrared spectrum (Fig.7), bands at: 3623, 1721, 1618, 1499, 1471, 1408, 1387, 1368, 1297, 1256, 1235, 1198, 1160, 1140, 1130, 1088, 1075, 1041, 989, 943, 911, 862, 833 and 762 cm^{-1}.

PMR spectrum (Fig.8; in $CDCl_3$): a pair of doublets at 459 and 374 cps (1H each, due to protons at 4 and 3 respectively); another pair of doublets at 438 and 409 cps (1H each, J = 9 cps, due to protons at 5 and 6 respectively); a broad signal at 237 cps (1H due to one proton at 3'); a multiplet at 183 cps (2H, due to two benzylic protons at 4'); and a strong doublet at 85.2 cps (6H, due to gemdimethyl group at 2').

Analysis

Found: C, 68.26; H, 5.63.

$C_{14}H_{14}O_4$ requires: C, 68.28; H, 5.73%.

Jatamansinol acetate

Acetic anhydride (5 ml) was added to a solution of jatamansinol (0.790 g) in pyridine (10 ml) and the mixture kept overnight at room temperature. The product

was diluted with excess of water and extracted with ether. Ether extract was washed with dilute hydrochloric acid, water, sodium bicarbonate solution, then water, dried and the solvent removed to furnish a residue (0.820 g) which on crystallisation from pet.ether-benzene mixture gave colourless needles of jatamansinol acetate, m.p. 137-38°, $(\alpha)_D^{30}$ - 6.79° (c, 5.33).

Ultraviolet spectrum: $\lambda_{max.}$ 327, 256, 246 and 216 mμ (log ε 4.17, 3.51, 3.56 and 4.15 respectively).

Infrared spectrum, bands at: 1733, 1111, 1099, 1064, 1053, 1001, 992, 930, 909, 893, 840, 821, 806, 772, 760 and 685 cm^{-1}.

PMR spectrum (in CCl_4): a pair of doublets at 455 and 368 cps (1H each, J = 9 cps, due to protons at 4 and 3 respectively); another pair of doublets at 434 and 402 cps (1H each, due to protons at 5 and 6 respectively); triplets at 368 cps (1H, due to the 3' proton) and 183 cps (2H, due to benzylic protons at 4') and strong singlets at 123 cps (3H, due to $-\overset{\overset{O}{\|}}{C}-CH_3$ group) and 81 cps (6H, due to gemdimethyl group at 2').

Analysis

Found: C, 66.97; H, 5.97; $-CO.CH_3$, 15.25.

$C_{16}H_{16}O_6$ requires: C, 66.66; H, 5.59; $-CO.CH_3$, 14.93%.

Jatamansinol tosylate (X)

p-Toluene-sulphonyl chloride (2.0 g) was added to a solution of jatamansinol (1.93 g) in pyridine (20 ml) and the mixture kept at room temperature for 24 hr. The product was worked up in the usual manner to give a residue (3.0 g) which on crystallisation from methanol yielded colourless needles of jatamansinol tosylate, m.p. 158-59°.

Infrared spectrum: bands at 1727, 1610, 1488, 1406, 1353, 1323, 1282, 1250, 1215, 1190, 1176, 1151, 1136, 1112, 1074, 1035, 1017, 982, 947, 917, 833, 840, 781, 759, 738 and 697 cm^{-1}.

Analysis

Found: C, 62.67; H, 5.02.

$C_{21}H_{20}O_6S$ requires: C, 62.99; H, 5.04%.

Alkaline hydrolysis of dihydrojatamansin (VIII)

Methanolic potassium hydroxide (5%; 50 ml) was added to a solution of dihydrojatamansin (3.0 g) in methanol (30 ml) and the resulting solution was allowed to stand at room temperature for about 24 hr. The reaction mixture after removal of excess of solvent under vacuum was diluted with water, acidified with dilute sulphuric acid

and extracted with ether. The ether extract was washed with sodium bicarbonate solution to separate the acidic portion.

Acidic portion (∝-methylbutyric acid). The sodium bicarbonate washings were combined and acidified with dilute sulphuric acid, and the resulting solution was extracted repeatedly with ether. The ether extract was dried and the solvent removed to give an oily residue (0.8 g) which was distilled at 115-120° (bath)/90 mm. It was found to be identical with ∝-methylbutyric acid on GLC.

Infrared spectrum, bands at: 2900 – 2600 (v.broad), 1724, 1480, 1408, 1379, 1333, 1292, 1227, 1161, 1111, 1087, 1015, 971, 950, 885, 826, 781 and 741 cm^{-1}.

p-Bromophenacyl-(∝-methyl)-butyrate: The above acid (0.10 g) was esterified with p-bromophenacyl bromide (0.30 g) in the usual manner to furnish p-bromo-phenacyl ester (0.22 g). It was crystallised from aqueous methanol to give colourless plates, m.p. 52-53° which remained undepressed on admixture with authentic p-bromophenacyl-(∝-methyl)-butyrate.

Analysis

Found: Br, 36.13.

$C_{13}H_{15}O_3Br$ requires: Br, 36.57%.

Neutral portion (jatamansinol, IX). The ether extract containing the neutral product of hydrolysis of dihydrojatamansin was washed with water, dried and the solvent removed to furnish a residue (2.0 g) which was crystallised from benzene to yield colourless needles of jatamansinol, m.p. 183-84°, $(\alpha)_D^{28}$ + 9.5° (c, 4.8). Melting point remained undepressed on admixture with the sample obtained from ozonolysis.

Infrared spectra of both samples were completely superimposable.

Analysis

Found: C, 68.39; H, 5.83.

$C_{14}H_{14}O_4$ requires: C, 68.28; H, 5.73%.

Hydrolysis of jatamansin

Jatamansin (5.0 g) in methanol (50 ml) was hydrolysed with methanolic potassium hydroxide (5%; 80 ml) by the procedure described earlier. The reaction mixture after removal of excess of solvent and acidification was extracted with ether. The ether extract was washed well with sodium bicarbonate solution to separate the acidic portion.

Acidic portion(angelic acid, IV). The sodium bicarbonate washings of the ethereal solution were combined

and acidified with dilute sulphuric acid. The resulting solution was extracted thoroughly with ether. The ether extract was dried and solvent removed to give an oily residue (1.3 g) which was distilled at 135-40° (bath)/58 mm. The distillate on cooling in a refrigerator gave colourless crystals, m.p. 43-45°, identical with that reported for angelic acid (IV).

Ultraviolet spectrum: $\lambda_{max.}$ 216mμ (log ε 3.69).

Infrared spectrum, bands at: 2800-2600 (v.broad), 1695, 1645, 1460, 1418, 1379, 1346, 1282, 1185, 1163, 1085, 1044, 1018, 938, 854, 792 and 739 cm^{-1}.

Methyl angelate: To a solution of above acid (0.25 g) in ether (4 ml) was added an ethereal solution of diazomethane (in lots) at room temperature till light yellow colour persisted. After about 5 minutes excess of diazomethane was destroyed by addition of few drops of glacial acetic acid. The solution was then diluted with ether (20 ml), washed with water, sodium bicarbonate solution, followed by water, dried, and the solvent was removed to yield an oily residue (0.23 g) of methyl angelate which was distilled at 135-40° (bath)/713 mm.

Infrared spectrum, bands at: 2950, 1718, 1639, 1449, 1429, 1372, 1360, 1266, 1255, 1232, 1189, 1149, 1018, 990, 917, 893, 847, 758 and 735 cm^{-1}.

PMR spectrum (Fig.9, in CCl_4): multiplets centred around 358 cps (1H, vinyl proton) and 115 cps (6H, due to 2 methyl groups on double bond); and a strong singlet at 220 cps (3H, due to $-C(=O).OCH_3$ group).

Analysis

Found: C, 63.01; H, 8.70.

$C_6H_{10}O_2$ requires: C, 63.13; H, 8.83%.

Neutral portion (jatamansinol, IX). The ethereal extract containing the neutral portion of hydrolysis of jatamansin was worked up in the usual manner and the resulting product (3.3 g) was crystallised from benzene to give colourless needles of jatamansinol, identical in all respects (m.p. mixed m.p., rotation, infrared and ultraviolet spectra) with that obtained from ozonolysis of jatamansin.

Hydrogenation of angelic acid (IV)

Angelic acid (0.1 g) was hydrogenated at room temperature (30°) and pressure (713 mm) in methanol (10 ml) over pre-reduced Adams' platinum oxide catalyst (0.010 g). The hydrogen uptake came to a close after absorption of 25 ml of hydrogen (calculated for 1 double bond, 26 ml). The product was worked up in the usual manner to give a residue (0.10 g) which was distilled at 15-20° (bath)/80 mm.

This product was shown to be identical with ∝-methylbutyric acid by comparison with authentic sample on GLC and through the preparation of p-bromophenacyl ester, m.p. 52-53°, which remained undepressed on admixture with an authentic p-bromophenacyl-(∝-methyl)-butyrate.

Preparation of dihydrojatamansin by condensation of jatamansinol with ∝-methylbutyryl chloride

A suspension of jatamansinol (IX, 930 mg) in dry benzene (25 ml) was added to ∝-methylbutyryl chloride (460 mg, prepared through usual procedure by the action of thionyl chloride on ∝-methylbutyric acid). The mixture, protected by calcium chloride guard tube was refluxed on a steam bath for 24 hr., the course of reaction being followed by TLC. The reaction mixture was then cooled, diluted with benzene (50 ml), washed with water, sodium bicarbonate solution, water and dried overnight. The solvent was removed to afford a residue (1.2 g) which was purified by passing through neutral alumina (Grade II; 25 g, elution with 300 ml benzene) and by crystallisation from petroleum ether to give colourless needles of dihydrojatamansin, m.p. 107-108°; $(\alpha)_D^{28}$ + 9.5° (c, 4.1). Its melting point remained undepressed on admixture with the sample obtained from hydrogenation of jatamansin. Infrared, ultraviolet and PMR spectra of both samples are identical.

Analysis

Found: C, 69.21; H, 6.89.

$C_{19}H_{20}O_5$ requires: C, 69.07; H, 6.71%.

Seselin (XI)

Jatamansinol tosylate (X; 1.35 g) was heated[30] with 2:4:6-collidine (8 ml) for 6 hr. in an oil bath at 180-90°. The reaction mixture was worked up in the usual manner and the product (0.75 g) was purified by passing through neutral alumina (grade III; 25 g ,elution with 800 ml of petroleum ether)and crystallised from petroleum ether to give colourless crystals of seselin, m.p. 119-20°, $(\alpha)_D^{30} \pm 0°$ (c, 7.67).

Ultraviolet and PMR spectra: (described in the theoretical part).

Infrared spectrum (Fig.13), bands at: 1724, 1631, 1595, 1480, 1401, 1370, 1287, 1258, 1235, 1217, 1193, 1153, 1114, 1074, 1009, 909, 833, 803 and 734 cm^{-1}.

Analysis

Found: C, 74.12; H, 5.55.

$C_{14}H_{12}O_3$ requires: C, 73.67; H, 5.30%.

Dihydroseselin (XII)

Seselin (0.50 g) in glacial acetic acid (25 ml) was stirred in hydrogen atmosphere at room temperature (25°) and pressure (713 mm) in the presence of pre-reduced Adams'

platinum oxide catalyst (50 mg). Absorption of hydrogen equivalent to one mol was over in 3 hr., after which there was no further absorption. The product was worked up in the usual manner to give a residue (0.450 g) which on crystallisation from petroleum ether and aqueous methanol afforded colourless crystals of dihydroseselin, m.p.104-105°, $(\alpha)_D^{28} \pm 0°$ (c, 4.9).

Ultraviolet spectrum: (described in the theoretical part).

Infrared spectrum (Fig.14), bands at: 1709, 1600, 1477, 1418, 1393, 1361, 1267, 1232, 1176, 1161, 1117, 1071, 1036, 1021, 978, 936, 923, 903, 885, 826, 766, 749 and 722 cm^{-1}.

PMR spectrum (Fig.16, in CCl_4): a pair of doublets at 452 and 367 cps (1H each, due to protons at 4 and 3 respectively); another pair of doublets at 428 and 397 cps (1H each, due to 5 and 6 protons respectively); triplets at 176 cps (2H, due to benzylic protons at 4') and at 111 cps (2H, due to two protons at 3'), and a strong singlet at 82.8 cps (due to gemdimethyl group at 2').

Analysis

Found: C, 73.21; H, 5.99.

$C_{14}H_{14}O_3$ requires: C, 73.02; H, 6.13%.

Dihydroseselin (XII) from authentic osthol (XIII)

Osthol (0.10 g), red phosphorous (0.05 g) and hydrobromic acid (6 ml, d 1.49) were heated under reflux for 1 hr. The reaction mixture was then diluted with water and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, followed by water, dried and then solvent removed to give a residue (0.090 g). It was purified by passing through neutral alumina (grade III; 5 g), elution with 200 ml of petroleum ether, and repeatedly crystallised from petroleum ether-ether mixture to give colourless crystals of dihydroseselin (0.035 g), m.p. 103-105°, which remained undepressed on admixture with the sample obtained from hydrogenation of seselin.

Ultraviolet, infrared and PMR spectra of both preparations are identical in all respects.

Analysis

Found: C, 72.90; H, 6.03.

$C_{14}H_{14}O_3$ requires: C, 73.02; H, 6.13%.

Jatamansinone (XIV)

Jatamansinol (IX; 1.3 g) was dissolved in acetone (25 ml) in a 100 ml three-necked flask fitted with a thermometer, dropping funnel and mechanical stirrer. The solution was cooled in an ice salt mixture. Jones' reagent (2.6 ml) was added slowly with stirring (1/2 hr.). The solution was

stirred for 5 minutes more. The excess of reagent was then destroyed by addition of methanol until the mixture became green. The solvents were removed and the residue was diluted with water and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution followed by water, dried and the solvent removed to give a residue (1.23 g) which on TLC showed the presence of at least three components. It was subjected to column chromatography over silicic acid.

CHROMATOGRAM

Wt. of compound 1.23 g.
wt. of silicic acid 31 g.

Fr.	Eluent	Ratio by volume	Volume of eluate (ml)	Wt. of fraction (g)	Remarks
1	Pet.ether	100%	150	-	
2	Pet.ether-benzene	50:50	150	-	
3	Benzene	100%	150x2	0.020	jatamansinone
4	Benzene-ether	95:5	150x5	0.550	jatamansinone
5	" "	85:15	150x3	0.030	not identified
6	" "	50:50	150x3	0.600	jatamansinol.
7	Ether	100%	150	0.004	-

Fraction 4 was crystallised from ethyl acetate to afford jatamansinone in colourless prisms, m.p.157-58°, $(\alpha)_D^{30} \pm 0^\circ$ (c, 2.7).

Ultraviolet spectrum (Fig.17): $\lambda_{max.}$ 321, 256, 248 and 218 mμ (log ε 4.12, 3.50, 3.54 and 4.12 respectively).

Infrared spectrum (Fig.19), bands at: 1721, 1600, 1570, 1484, 1430, 1395, 1379, 1366, 1357, 1342, 1289, 1263, 1235, 1205, 1159, 1144, 1111, 1066, 999, 939, 909, 843, 832 and 763 cm^{-1}.

PMR spectrum (Fig.18, in CCl_4): a pair of doublets at 460 and 377 cps (1H each, due to protons at 4 and 3 respectively); second pair of doublets at 441 and 413 cps (1H each, due to protons at 5 and 6 respectively); and singlets at 223 cps (2H, due to benzylic protons at 4') and 88.2 cps (6H, due to gemdimethyl group at 2').

Analysis

Found: C, 68.89; H, 4.83.

$C_{14}H_{12}O_3$ requires: C, 68.84; H, 4.95%.

REFERENCES

1. Y.K. Sarin and L.D. Kapoor, Perf. & Ess.Oil Rec., 54 (7), 437 (1963).
2. K.L. Handa, M.C. Nigam and M.L. Sharma, Riechstoffe and Aromen, 7, 181 (1963).
3. H. Bohme and E. Schneider, Ber., 72, 780 (1939).
4. R.E. Willette and T.O. Soine, J.Pharm.Sci., 51(2), 149 (1962).
5. R.E. Willette and T.O. Soine, J.Pharm.Sci., 53(3), 275 (1964).
6. H. Mitsuhashi and T. Itoh, Chem.Pharm.Bull(Japan), 10 (6), 511 (1962).
7. C.R. Ghoshal, S. Sen Gupta and A. Chatterji, Chem. Ind., 1430 (1963).
8. J.C. Bell and A. Robertson, J.Chem.Soc., 1829(1936).
9. T.O. Soine and F.H. Jawad, J.Pharm.Sci., 53(8), 990 (1964).
10. T.R. Seshadri, M.S. Sood, K.L. Handa and Vishwapaul, Tetrahedron Letters, 45, 3367 (1964).
11. (a) M. Holub, V.Herout and F.Sorm, Collection, 23, 1280 (1958);
    (b) E. Spath and F. Gandini-Kezstler, Monatsh, 83, 1301 (1952).
12. H.D. Schroeder, W. Bencze, O . Halpern and H.Schmid, Chem.Ber., 92, 2338(1959).

13. E. Bueding, J.Biol.Chem., 202, 505 (1953).

14. L.M. Jackman and R.H. Wiley, J.Chem.Soc.,2886(1960).

15. W. Bottomley, Austral.J.Chem., 16,143(1963).

16. J.B. Bredenberg and J.N. Schoolery, Tetrahedron Letters, 9, 285 (1961).

17. L.M. Jackman, Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, p.55, Pergamon Press, New York, N.Y. (1959).

18. E. Spath, P.K. Bose, J.Matzke and N.C. Guha, Ber., 72, 821 (1939).

19. D.P. Chakraborty and K. Chakraborti, Trans.Bose Res. Inst.(India), 24 (1), 15 (1961).

20. (a) B.F. Burrows, W.D. Ollis and L.M. Jackman, Proc.Chem.Soc., 177 (1960).
(b) L. Chrombie and J.W. Lown, J.Chem.Soc., 775(1962).

21. W. Bottomley and D.E. White, Aust.J.Sci.Res., A4, 112 (1951).

22. E. Spath, K.Eiter and T. Meinhard, Chem.Ber., 75B, 623 (1942).

23. K. Bowden, J.W. Heilborn, E.R.H. Jones and B.C.L. Weedon, J.Chem.Soc., 39 (1946).

24. (a) Manefa Pharmaceutical Co.Inc., C.A. 60 (3), 2932 (1964);
(b) E. Smith, N. Hosansty, W.G.Bywater and E. van Tamelen, J.Amer.Chem.Soc., 79, 3534(1957).

25. D.D. Evans and C.W. Shoppe, J.Chem.Soc., 543(1963).

26. a) H. Brockmann and H. Schodder, Chem.Ber., 74, 73 (1941).

b) H. Brockmann and F.J. McQuillin, J.Chem.Soc., 2423 (1955).

c) E. Lederer and M. Lederer, Chromatography, p.26, Elsevier, N.Y. (1957).

27. S.M. Siegel, Experientia, 16 , 358 (1960).

28. F. Brown and L.P. Hall, Nature, 66,166 (1950).

29. R.E. Willette and T.O. Soine, J.Pharm.Sci., 53(3), 275(1964).

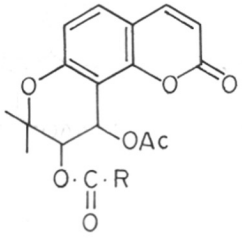
30. R. Henderson and R. Hodges, Tetrahedron 11,226(1960).

CHAPTER II

SYNTHESES OF DIHYDROSAMIDIN AND VISNADIN

SUMMARY

The coumarins dihydrosamidin (IIb) and visnadin (IIc) isolated from the extracts of Ammi visnaga L. have been known to possess a strong vasodilatory activity. As the syntheses of these compounds were not reported in literature, it was thought worthwhile to attempt them.



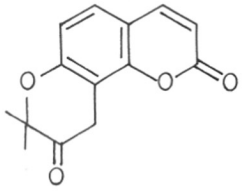
II

b. R = $-CH_2-CH(CH_3)_2$

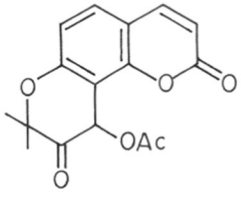
c. R = $-CH(CH_3)-CH_2-CH_3$

For this purpose, jatamansinone (IX), which was obtained from jatamansin (Chapter I, p. 19) by hydrolysis followed by chromic acid oxidation, was employed as the starting material. It was treated with lead tetraacetate in acetic acid to yield the ketoacetate X. The latter was subsequently converted into (±) -cis-4'-acetyl-khellactone (XI) by the action of sodium borohydride.

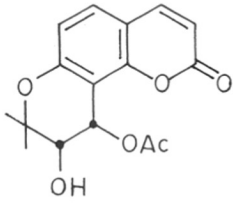
The cis-orientation of the 3' and 4' substituents in (±) -4'-acetyl-khellactone (XI), thus prepared, was shown by converting it to the diacetate XVII and showing the identity of the latter with authentic (±)-cis-diacetyl-khellactone, obtained by osmium tetroxide oxidation of seselin (XV), followed by acetylation of the resulting (±)-cis-khellactone (XVI).



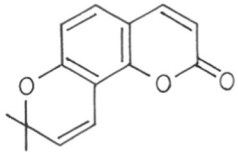
IX



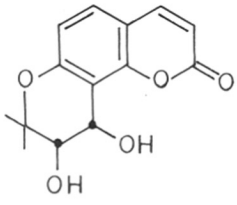
X



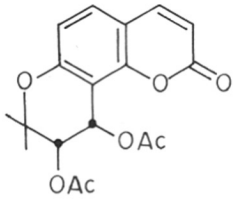
XI



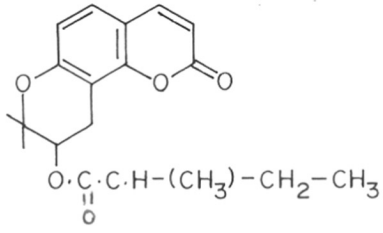
XV



XVI



XVII

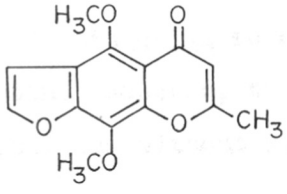


XVIII

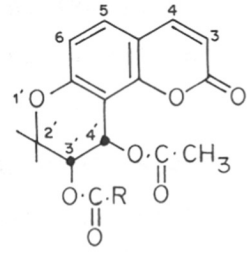
(±)-cis-4'-Acetyl-khellactone (XI) was then converted into (±)-cis-dihydrosamidin and (±)-cis-visnadin by condensation with appropriate acid chlorides.

A direct synthesis of visnadin from dihydro-jatamansin (XVIII) was tried but without success.

The plant Ammi visnaga L (bishop's weed) has been used[1] in Egypt for centuries as a home remedy and spasmolytic. A discovery of the coronary vasodilatory activity of khellin,[1] a crystalline furochromone (I), isolated from the ethereal extract of the seeds of the same attracted much attention. The fact that the seeds contain vasodilatory substances other than khellin has been shown by Samaan,[2] whose 'visnagan' fraction (extractive remaining behind after removal of the crystalline material) evidenced considerable activity, from which by using refined chromatographic techniques Smith et al.[3] later on could isolate three strongly vasodilatory active coumarins, samidin (IIa), dihydrosamidin(IIb) and visnadin (IIc).*



I



II

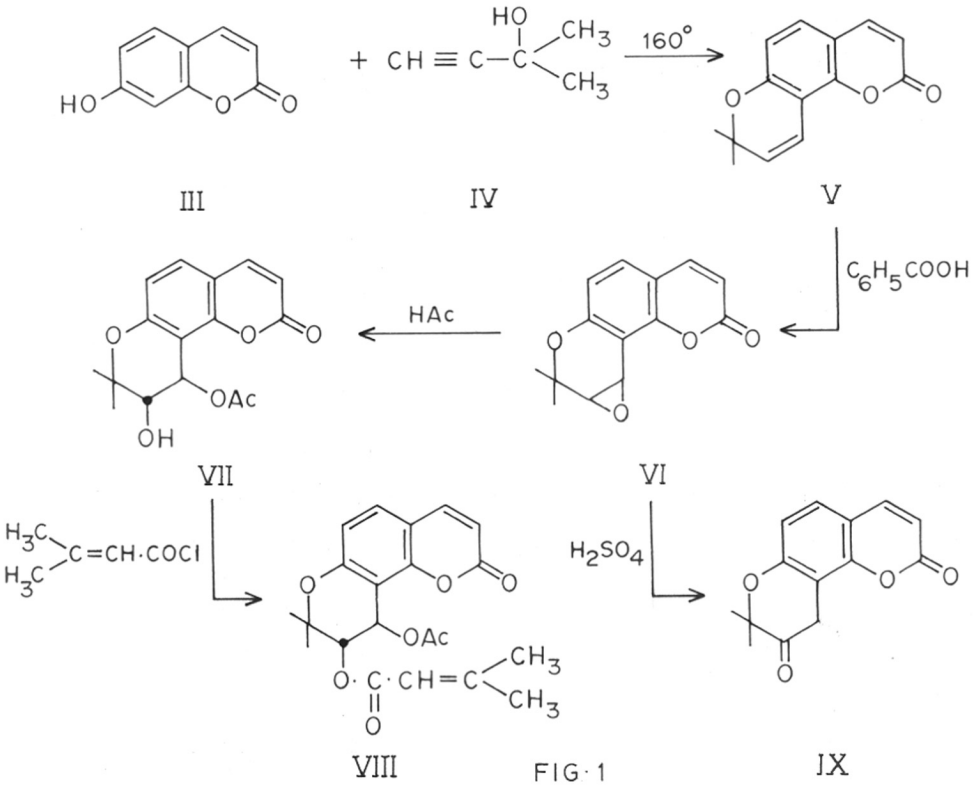
a. R = $-CH=C(CH_3)_2$

b. R = $-CH_2-CH(CH_3)_2$

c. R = $-CH(CH_3)-CH_2-CH_3$

* Since these vasodilatory agents are closely related with jatamansin (Chapter I, p. 19) it was thought to be desirable to work on these.

The structures of samidin, dihydrosamidin and visnadin have been established by Smith *et al*.[4] in 1957. Schmid *et al*[5] in 1959 reported the possible stereochemistry (both 3' and 4' substituents being in the cis-configuration) of these products (II), along with the synthesis of (±) -trans-samidin from 7-hydroxy coumarin (III, umbelliferone). The reactions used by them in this synthesis are schematically depicted in Fig.1. They condensed umbelliferone (III) with 2-methyl-2'-hydroxy-but-3-yne (IV) by heating at 160° in O-dichlorobenzene to give seselin (V), which was converted into epoxide (VI) by the action of perbenzoic acid. Seselin epoxide was treated with acetic acid under reflux to give (±)-trans-4'-acetyl-khellactone (VII); the latter being finally converted into (±) -trans-samidin (VIII) by acylation with β,β'-dimethylacrylic acid chloride. Thus Schmid *et al* successfully synthesised (±)-trans-samidin. However, their attempt to synthesise the cis product was without success.



FIG·1

Present chapter describes successful syntheses of (±)-cis-dihydrosamidin and (±)-cis-visnadin carried out by us from jatamansinone* (IX), which was obtained from jatamansin by hydrolysis followed by chromic acid oxidation. Fig. 2 schematically shows the reactions used during this conversion.

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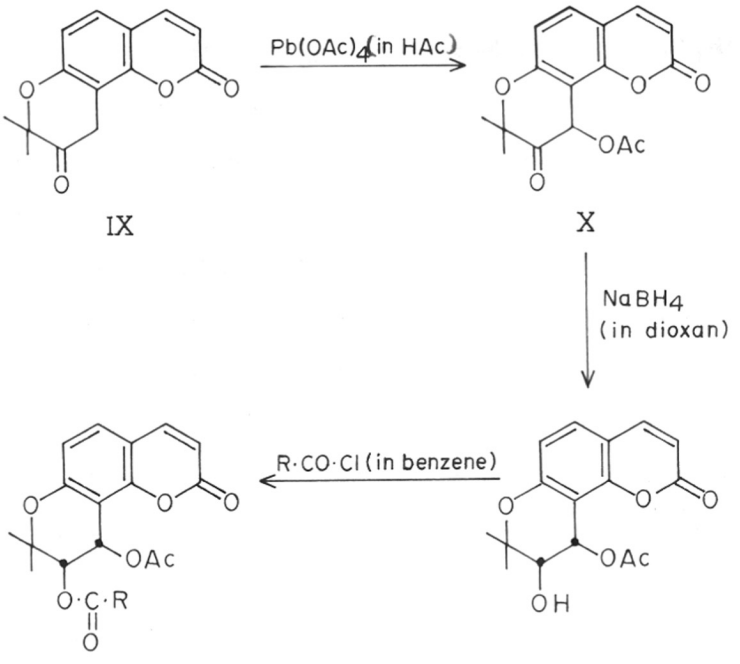
* Synthesis of this ketone starting from 7-hydroxy-coumarin was also reported by Schmid et al.[5] alongwith the synthesis of (±)-trans-samidin (Fig.1).



a. $R = -CH_2-CH(CH_3)_2$

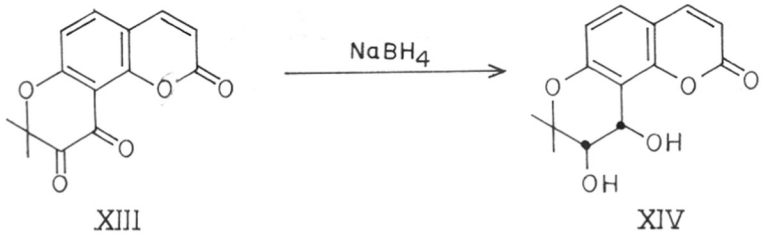
b. $R = -CH(CH_3)-CH_2-CH_3$

FIG·2

To introduce an acetoxy group in the 4' position, jatamansinone (IX) was treated with lead tetraacetate in acetic acid under reflux for 1/2 hr.[6] However, the product on TLC showed the presence of atleast five components. With a view to obtain better yields of the ketoacetate X, many conditions of reaction time and temperature were tried. Finally oxidation at the room temperature in an atmosphere of nitrogen for 1 hr. was found to give the best results (45-50% yield).

The ketoacetate X [(±)-3'-keto-4'-acetoxy-3',4'-dihydroseselin] is a new compound, the structure of which was fully corroborated by its infrared, ultraviolet and PMR spectra. In the infrared spectrum (Fig.3) it showed a characteristic strong absorption band at 1250 cm^{-1} due to acetate group, along with those of a coumarin ring (1739, 1613, 1460 and 843 cm^{-1}) and its ultraviolet absorption (Fig. 4; having λmax. at 324, 261, 248 and 213 mμ; log ε 4.11, 3.55, 3.59 and 4.13 respectively) was very similar to that of its precursor (IX). Further, in its PMR spectrum (Fig.5), as expected, the singlet at 223 cps (2H), due to two benzylic protons at 4' present in that of jatamansinone (Chapter 1, Fig.18) disappeared, but instead of that, a singlet at 392 cps (1H) due to proton at 4' along with a strong signal at 138 cps (3H, singlet, due to $-CO-CH_3$ group) appeared, the rest of the absorption signals being essentially similar to that of jatamansinone.

Since it was already known that sodium borohydride reduction of the diketone XIII, gave cis-khellactone (XIV)[5] it was decided to carry out the same reaction on keto-acetate X in order to obtain the desired cis-acetyl-khellactone (XI).



XIII XIV

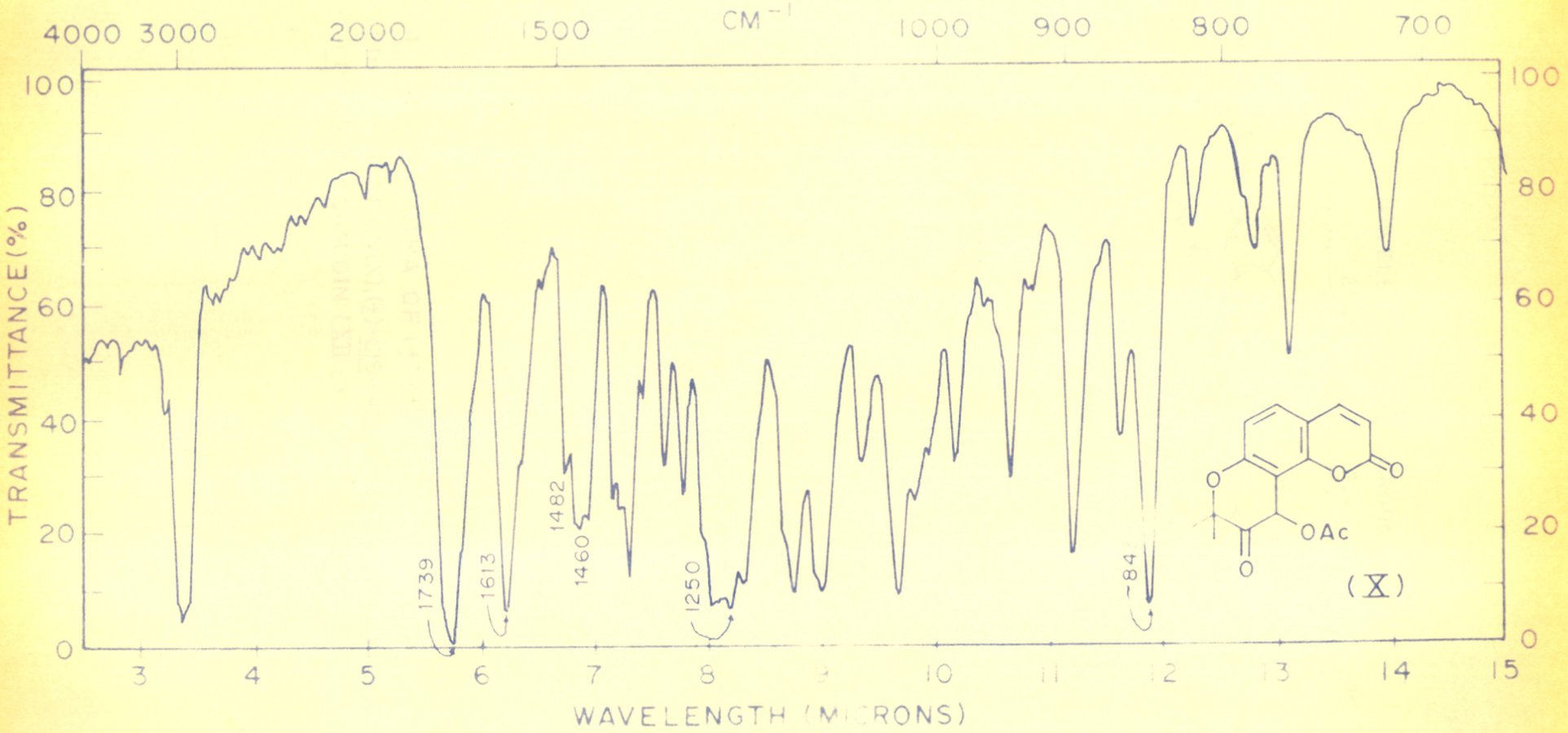


FIG. 3. IR SPECTRUM OF (±)-3'-KETO-4'-ACETOXY-3',4'-DIHYDROSESELIN (X).

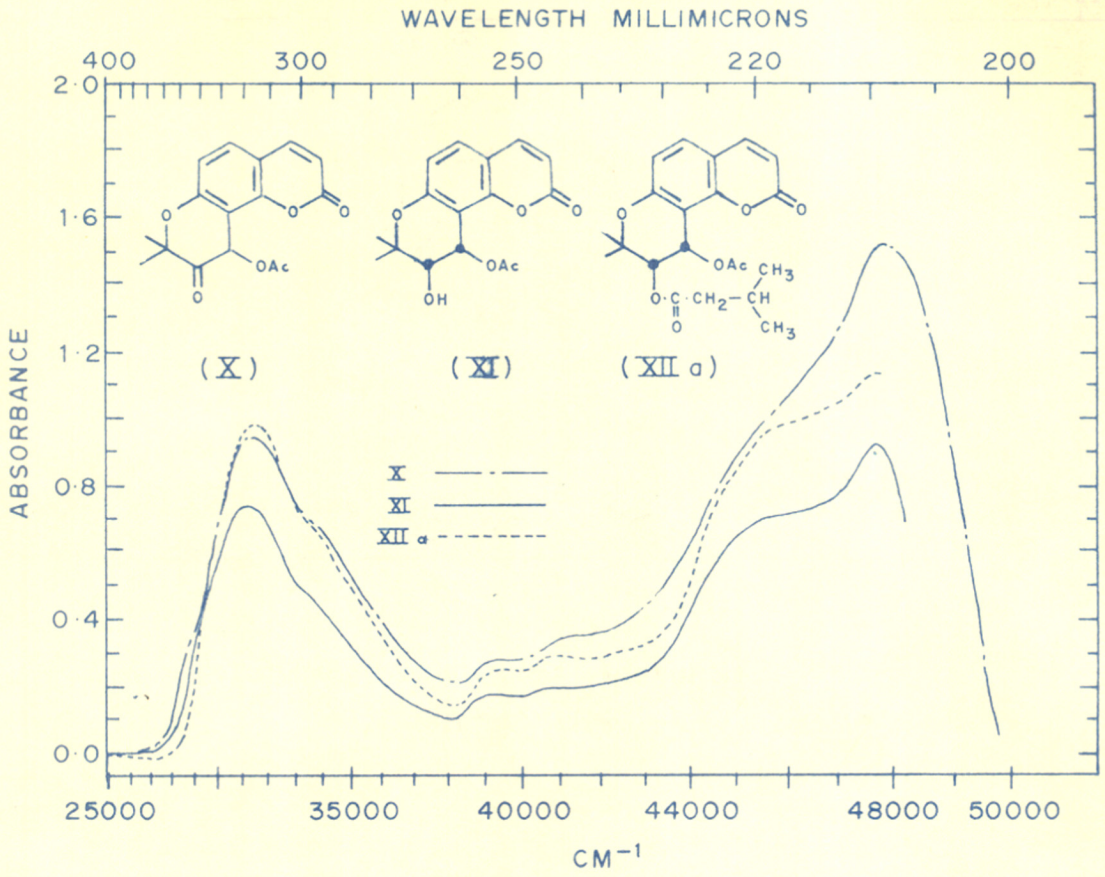


FIG. 4. UV SPECTRA OF (±)-3'-KETO-4'-ACETOXY-3',4'-DIHYDROSESELIN(X),(±)-CIS-4'-ACETYL-KHELLACTONE (XI), AND (±)-CIS-DIHYROSAMIDIN (XII a).

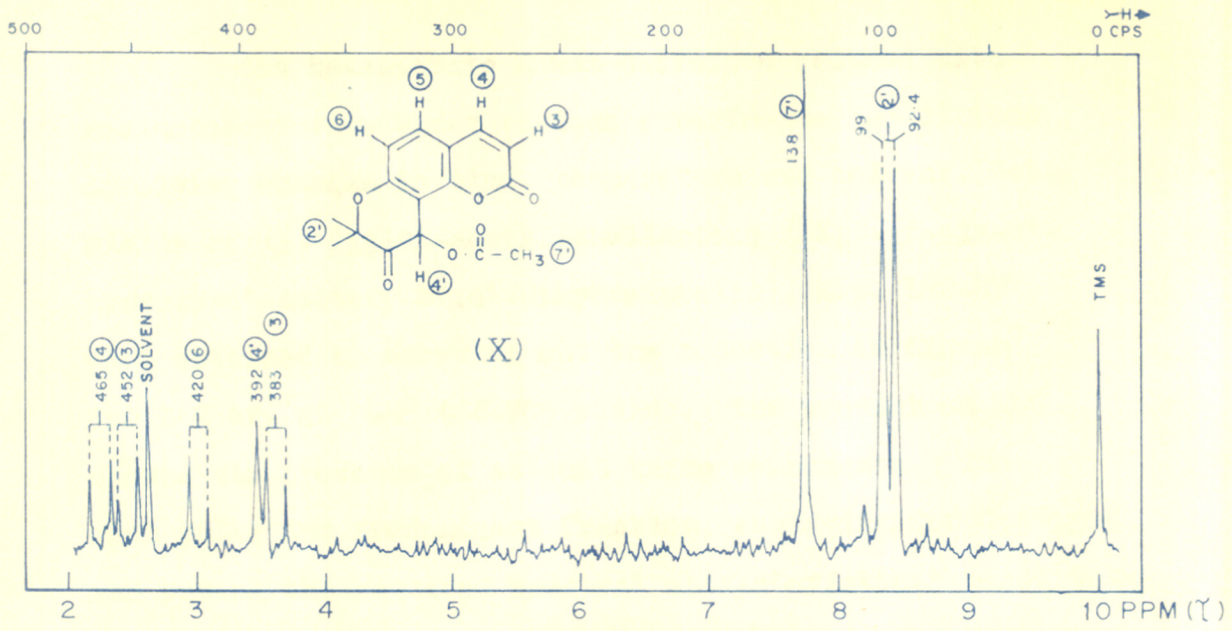


FIG. 5. PMR SPECTRUM OF (±)-3'-KETO-4'-ACETOXY-3',4'--DIHYDROSESELIN (X).

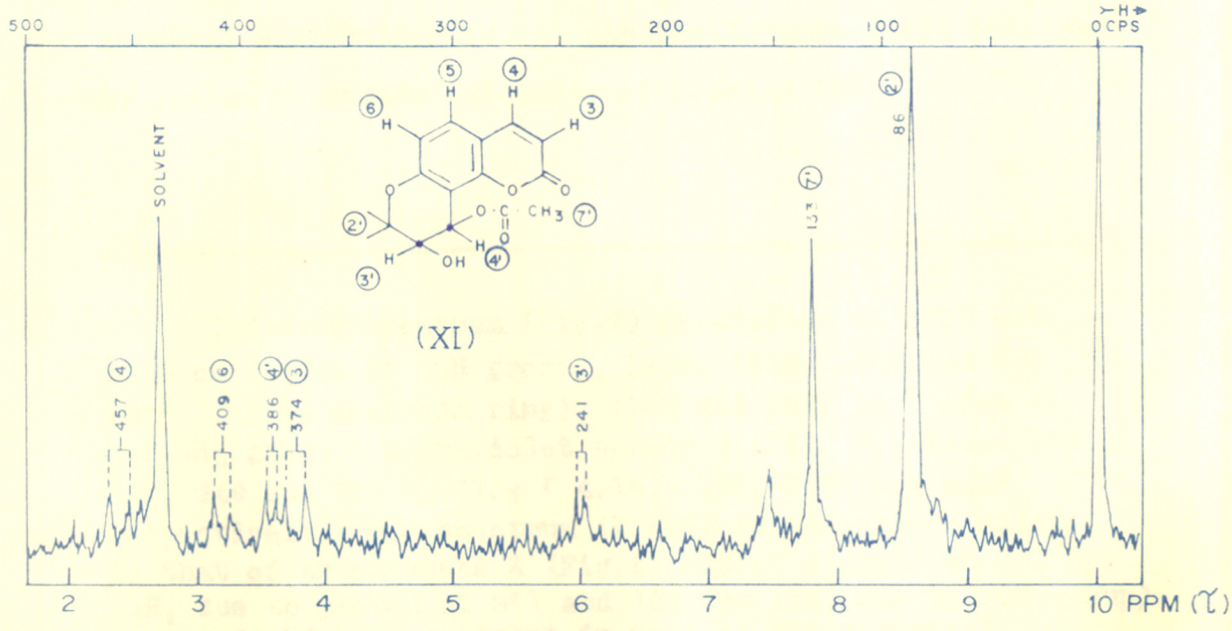


FIG. 6. PMR SPECTRUM OF (±)-CIS-4'-ACETYL-KHELLACTONE (XI).

The ketoacetate X was therefore reduced with sodiumborohydride under various experimental conditions involving changes in time, temperature and solvent. Better yields of (±)-cis-4'-acetyl-khellactone [XI, (±)-cis-3'-hydroxy-4'-acetoxy-3',4'-dihydroseselin], m.p. 182-83°, were obtained by carrying out the reduction in dioxan[7] for 1/2 hr. at 2-5° (65-70% yield). The product on TLC showed the presence of atleast three components. The most polar and predominant fraction, analysing for $C_{16}H_{16}O_6$ and having the required spectral characteristics* constituted the required reaction product and was used in the next step. The second fraction, m.p. 158-60° which analysed for $C_{14}H_{14}O_5$ was identified as (±)-cis-khellactone by comparison (melting point, mixed melting point, infrared and ultraviolet spectra) with authentic (±)-cis-khellactone (XVI) obtained by osmium tetroxide oxidation of seselin (XV).[5]

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* Infrared spectrum (Fig.7) absorption at 3509 and 1020 cm^{-1} (due to -OH group), 1709, 1613, 1460 and 933 cm^{-1} (due to coumarin ring), 1748 and 1227 cm^{-1} (due to $-O-\overset{O}{\overset{\|}{C}}-CH_3$ group); ultraviolet spectrum (Fig. 4), λmax. 324, 261, 249 and 215 mμ (log ε 4.14, 3.52, 3.57 and 4.17 respectively); PMR spectrum (Fig.6) essentially similar to that of ketoacetate X (Fig.5) except signals at 241 cps (1H, due to proton at 3') and 154 cps (1H, due to -OH group) appeared which were absent in that of ketoacetate X.

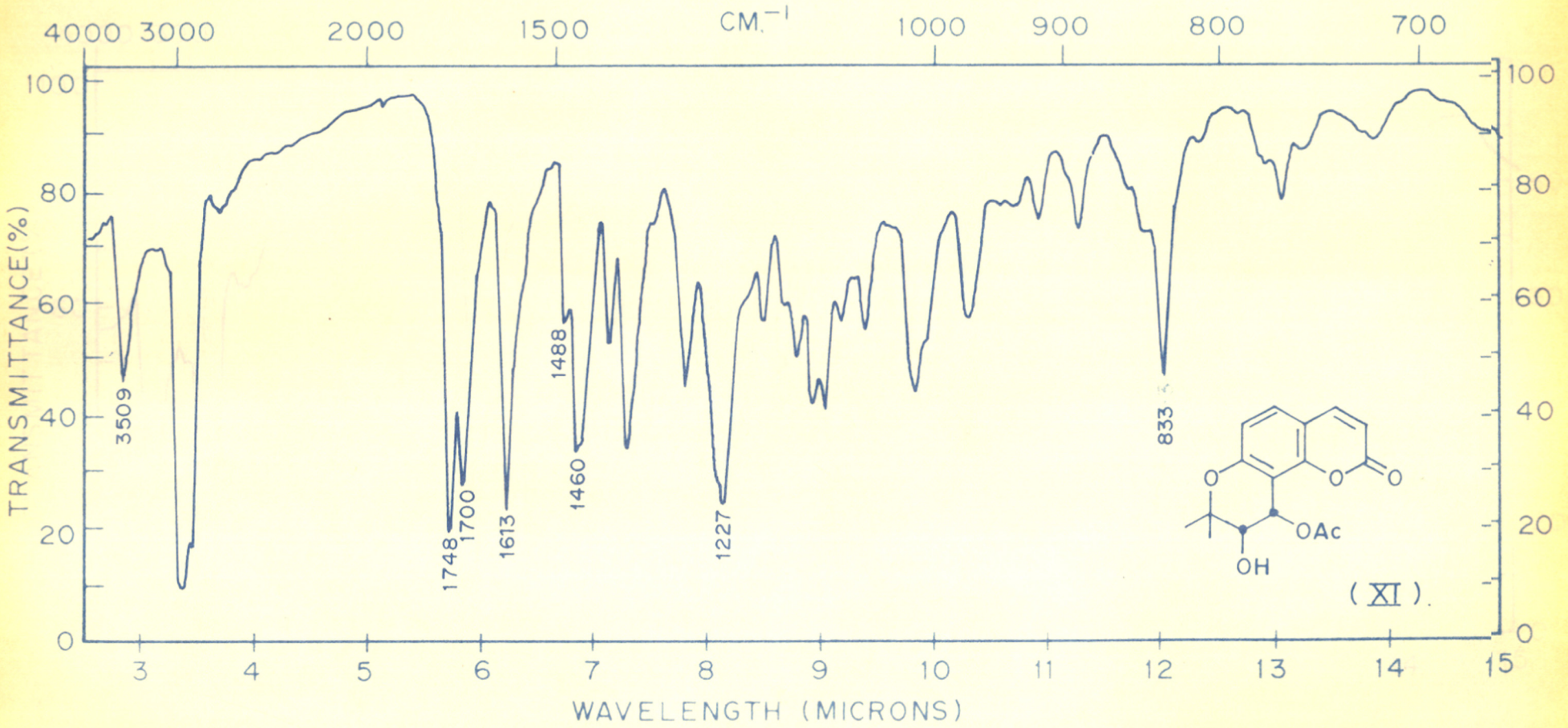


FIG. 7. IR SPECTRUM OF (±)-CIS-4'-ACETYL-KHELLACTONE (XI).

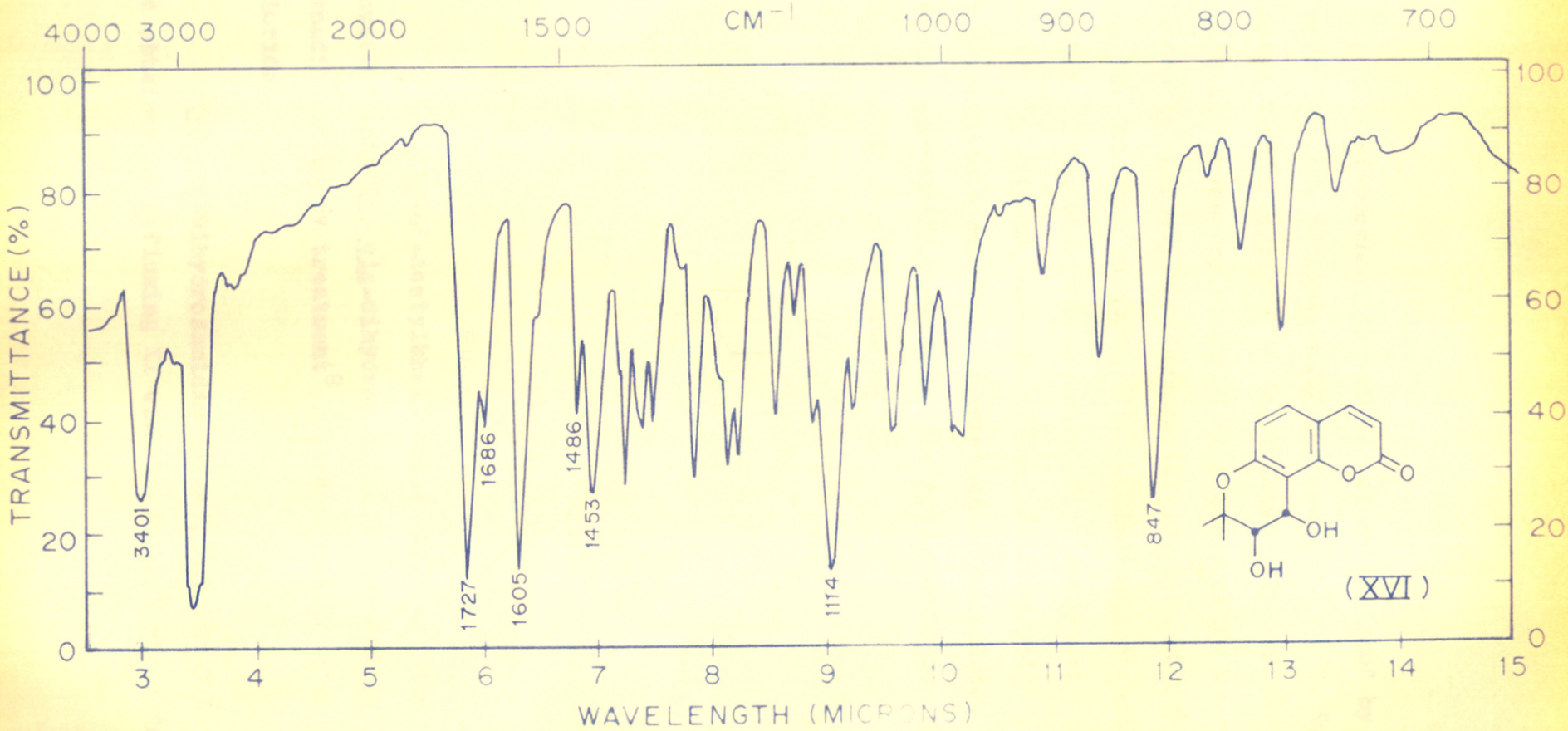
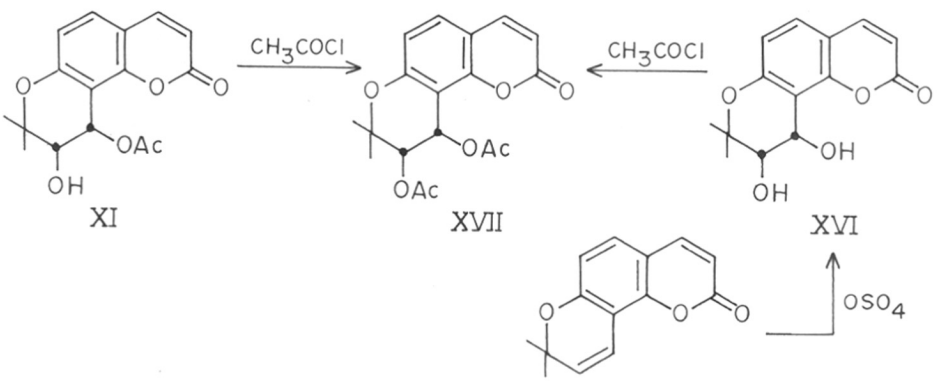


FIG. 8. IR SPECTRUM OF (±)-CIS-KHELLACTONE (XVI).

The stereochemistry of XI was established by the correlations, schematically represented in Fig. 9. (±)4'-Acetyl-khellactone(XI) was acetylated with acetyl chloride in benzene solution at room temperature to yield the (±)-diacetylkhellactone (XVII), m.p.160-62°, having its infrared spectrum (Fig.10) indistinguishable from that of the diacetate obtained from acetylation of authentic (±)-cis-khellactone (XVI). Melting point of both preparations remained undepressed on admixture. Thus this correlation confirmed the cis-orientation of both 3' and 4' substituents in XI.



XI XVII XVI

XV

FIG. 9

(±)-cis-4'-Acetylkhellactone (XI) was then converted into (±)-cis-dihydrosamidin (XIIa) and (±)-cis-visnadin (XIIb) by treatment[8] with appropriate acid chlorides.

(±)-cis-Dihydrosamidin (XIIa), m.p.125-27° was obtained by refluxing XI with isovaleryl chloride in

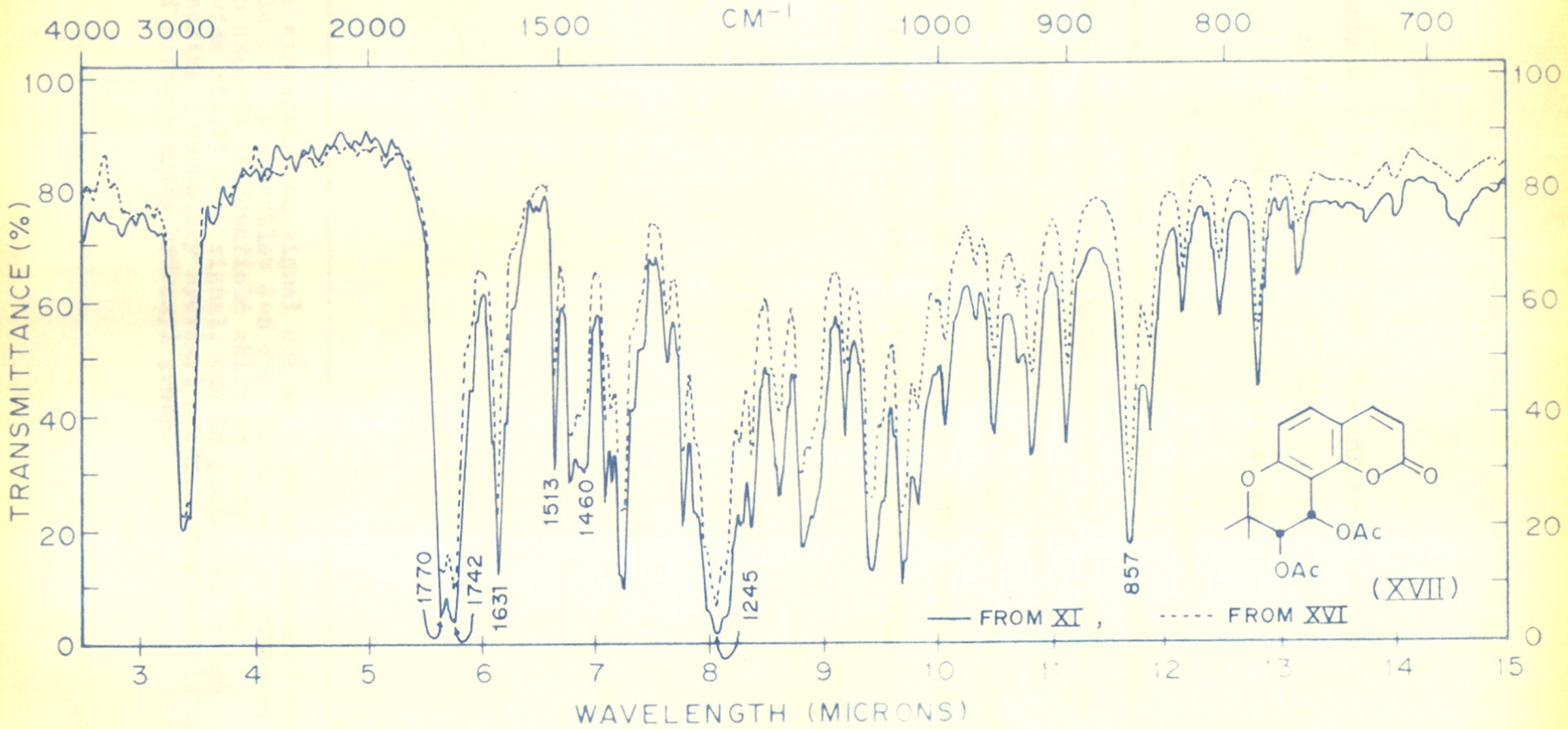
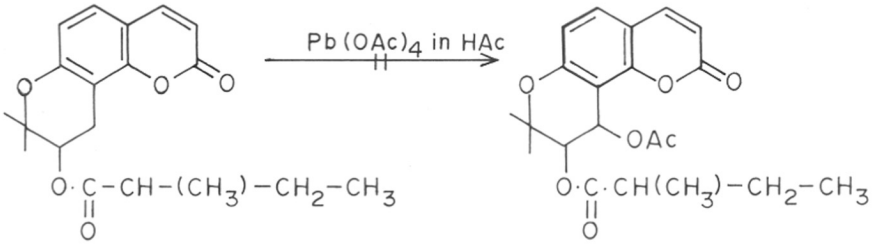


FIG. 10. IR SPECTRUM OF (±)-CIS-3',4'-DIACETYL-KHELLACTONE (XVII).

benzene solution for 24 hr. The infrared (Fig.11), ultraviolet (Fig.4) and PMR* (Fig.12) spectra of XIIa are in full agreement with its structure.

(±)-cis-Visnadin (XIIb), m.p.150-52°, was prepared by similar condensation of XI with α-methyl-butyryl chloride. The difference in melting point of (±)-cis-visnadin (XIIb), thus prepared, and that of natural visnadin[4] (IIc) m.p. 85-88°, is very conspicuous. But, the structure of XIIb has been fully corroborated by its infrared (Fig. 14), ultraviolet and PMR (Fig.13) spectra.



XVIII XII b

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* As expected, the signal due to 3′ proton appeared at 314 cps (1H, doublet J=5 cps) which may be cited as an example of downfield shift of about 73 cps (vide Fig.6) of a signal, due to proton on carbon bearing a secondary hydroxyl group, after acetylation of corresponding hydroxyl group.

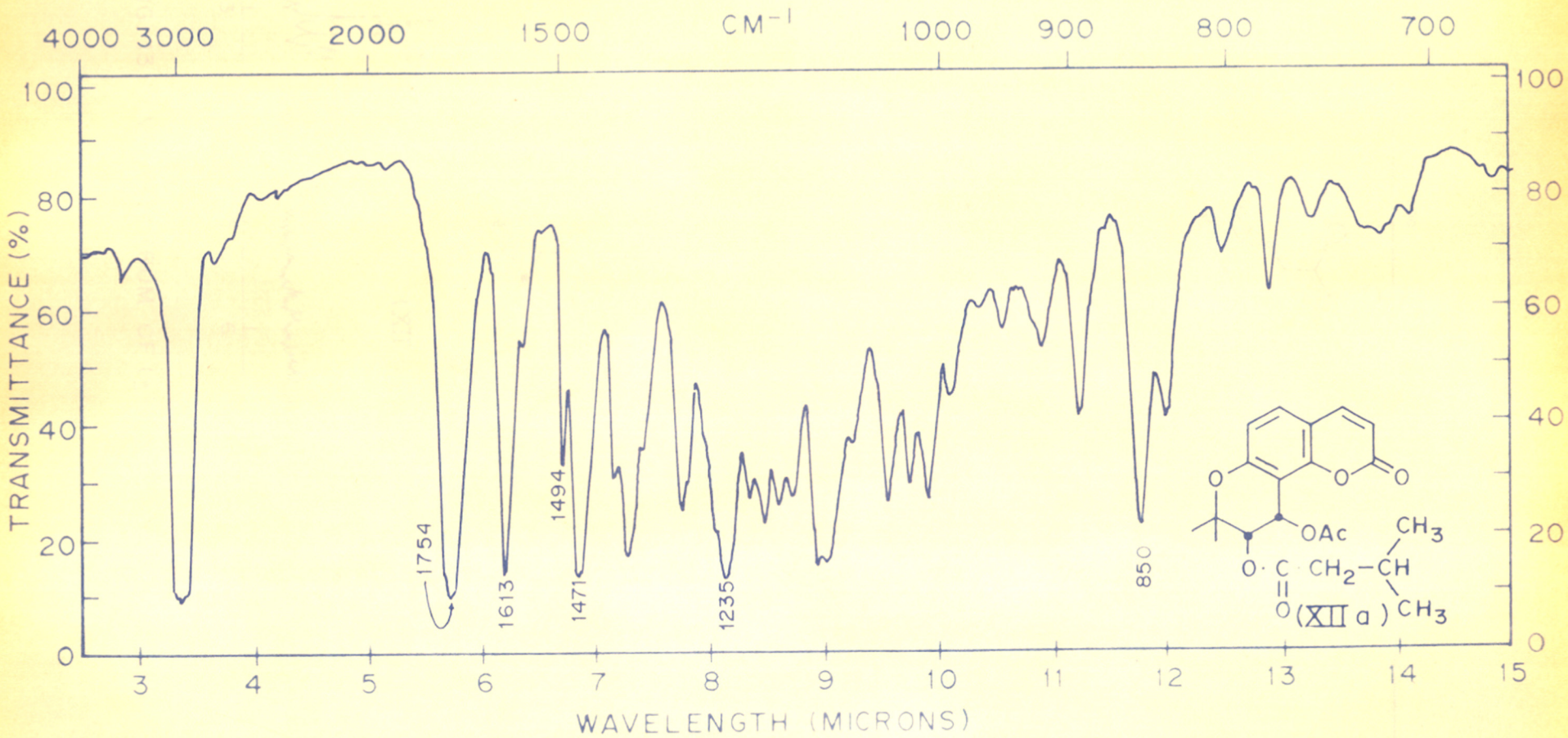


FIG. 11. IR SPECTRUM OF (±)-CIS-DIHYDRO-SAMIDIN (XII a).

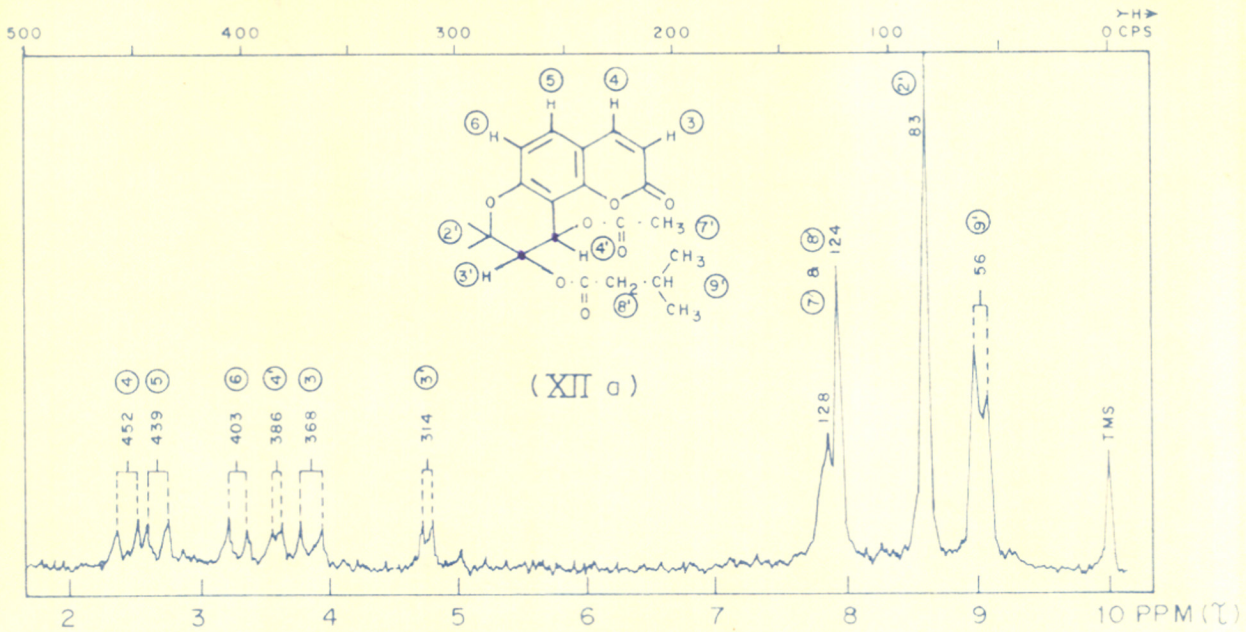


FIG. 12. PMR SPECTRUM OF (±)-CIS-DIHYDRO-SAMIDIN (XII a)

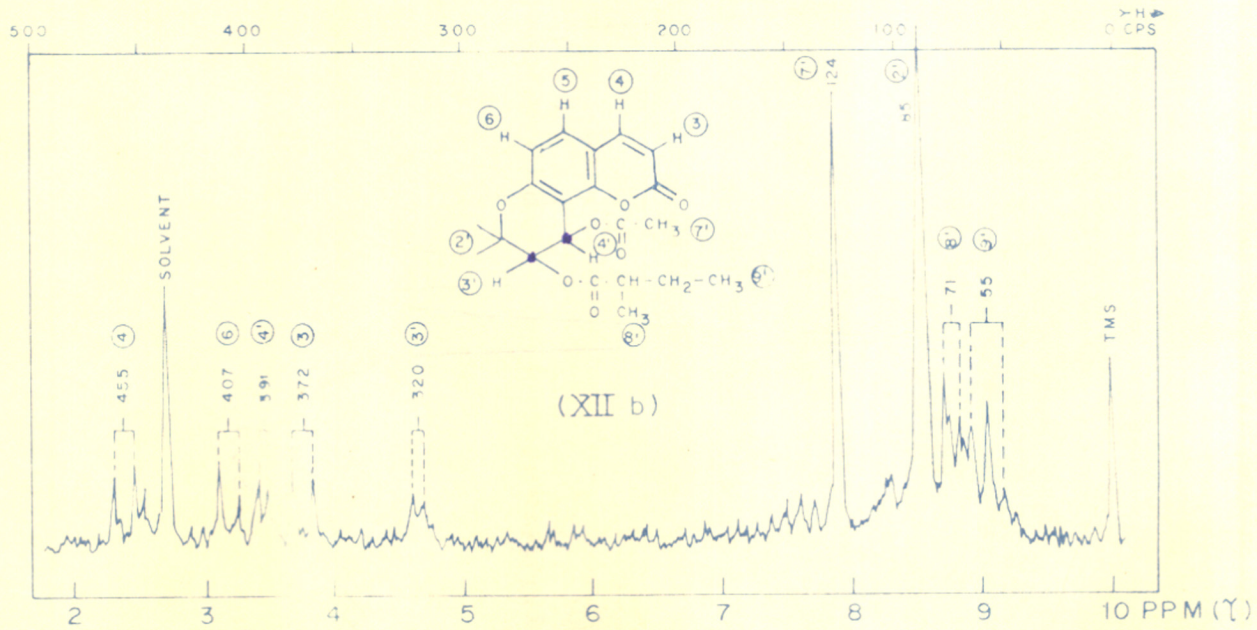


FIG. 13. PMR SPECTRUM OF (±)-CIS-VISNADIN (XII b)

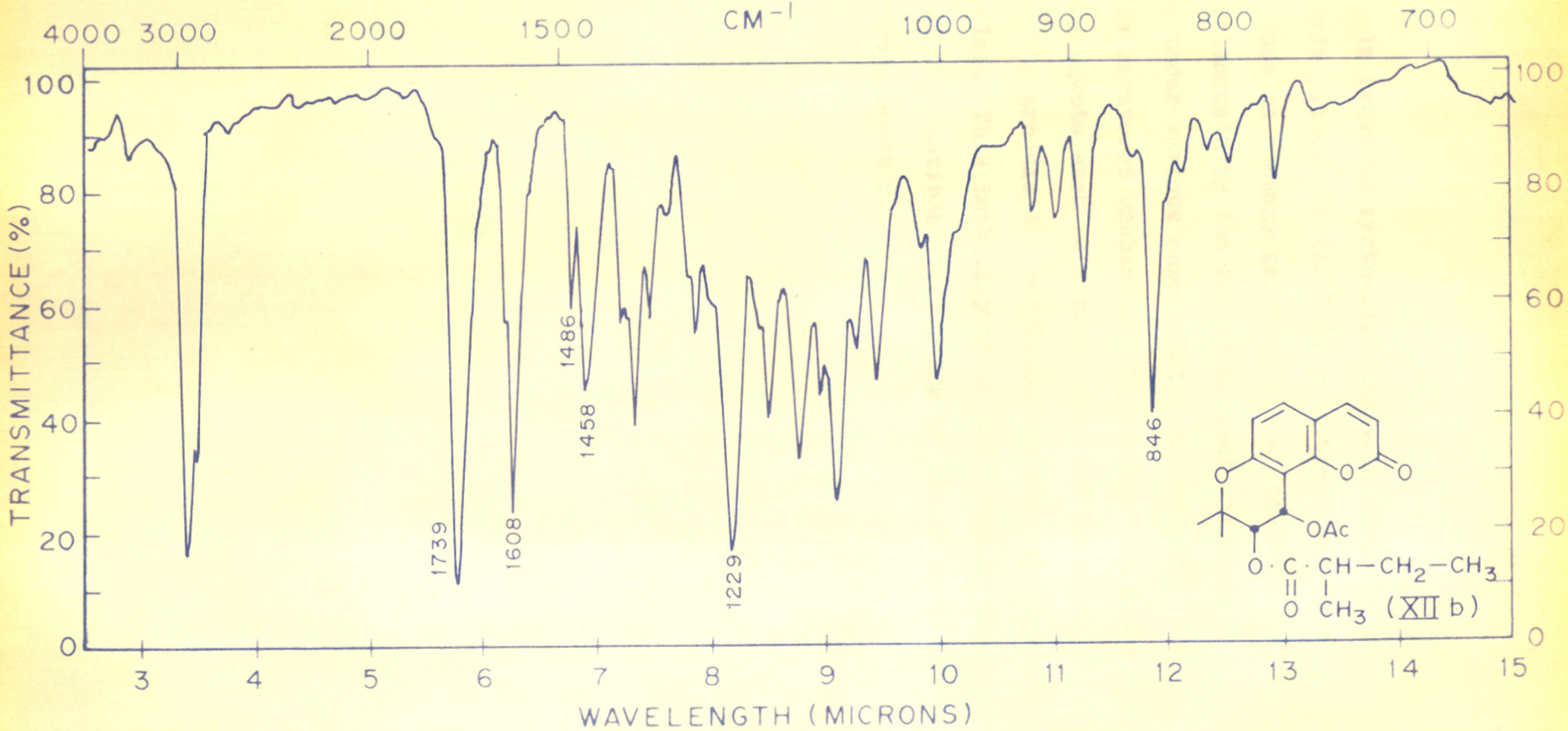


FIG. 14. IR SPECTRUM OF (±)-CIS-VISNADIN (XII b).

In order to synthesise visnadin directly from dihydrojatamansin (XVIII), an attempt was made to introduce an acetoxy group in the 4' position of dihydrojatamansin by the action of lead tetraacetate. However, under various experimental conditions[6,9,10] XVIII was recovered unchanged. Oxidation with other oxidising agents such as chromic acid and selenium dioxide[11] to produce the corresponding hydroxyl compound also failed. This inability is probably due to the steric effect of the flexible overlapping of the ester side chain in dihydrojatamansin.

EXPERIMENTAL

For general remarks vide Chapter I, p.39.

(±)-3'-Keto-4'-acetoxy-3',4'-dihydroseselin (X)

Lead tetraacetate (9.4 g) was added to a solution of jatamansinone (X, 4.94 g) in acetic acid (120 ml) and the mixture stirred at room temperature in an atmosphere of nitrogen for 1 hr. The product was added to excess of water and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, again water, dried and the solvent removed to furnish a residue (4.4 g). It showed the presence of atleast four components on TLC and was subjected to column chromatography over silicic acid.

CHROMATOGRAM

Wt. of compound 4.4 g.
Wt. of silicic acid 110 g.

Fr.	Solvent	Ratio by volume	Volume of eluate (ml)	Wt. of fraction. (g)	Remarks
1	Pet.ether	100%	300	-	
2	Pet.ether-benzene	50:50	300	-	
3	Benzene	100%	300x3	0.85	Jatamansinone
4	Benzene-ether	97.3	300x2	0.55	mixture of jatamansinone & ketoacetate X.
5	"	92.8	300x5	2.12	Ketoacetate I.
6	"	85.15	300	0.21	
7	"	50.50	300	0.53	Compound m.p.225-28° (not characterised)
8	Ether	100%	300	0.11	

Fraction 5 containing the ketoacetate X was crystallised twice from benzene to give colourless crystals, m.p. 180-82°, $(\alpha)_D^{28} \pm 0°$.

Ultraviolet spectrum: (described in the theoretical part). Infrared spectrum (Fig.3), bands at: 1739, 1613, 1482, 1460, 1370, 1316, 1289, 1250, 1143, 1111, 1073, 1036, 985, 938, 893, 862, 843, 769 and 716 cm^{-1}.

PMR spectrum (Fig.5, in $CDCl_3$): doublets at 465, 452, 420 and 383 cps (1H each, J = 8.9 cps), due to protons at 4,5,6 and 3 respectively) and singlets at 392 cps (1H due to 4' proton), 138 cps (3H, due to -O-C(=O)-CH_3 group), 99 and 92.4 cps (6H, due to gemdimethyl group at 2').

Analysis

Found: C, 63.63; H, 4.94.

$C_{16}H_{14}O_6$ requires: C, 63.57; H, 4.60%.

(±) -cis-4'-Acetyl-khellactone (XI)

To a cooled (2-5°) and stirred solution of the ketoacetate (X, 1.3 g) in aqueous dioxan (80%; 50 ml) a solution of sodium borohydride (0.23 g) in aqueous dioxan (10 ml) was added during a period of 5 minutes. The mixture was stirred further for 25 minutes at the same temperature. It was then made slightly acidic (pH 4-5) with 1N sulphuric acid. The solvent was removed under suction at 40-45°

and the residue was extracted with ether. The ether extract was washed with water, sodium bicarbonate solution, then water, dried and the solvent removed to give a residue (1.30 g). It showed 3 spots on TLC and was subjected to column chromatography over silicic acid.

CHROMATOGRAM

Wt. of compound 1.30 g.
Wt.of silicic acid 33.0 g.

Fr.	Solvent	Ratio by volume	Volume of eluate (ml)	Wt. of fraction (g)	Remarks
1	Pet.ether	100%	250	-	
2	Pet.ether-benzene	50:50	250	-	
3	Benzene	100%	250	-	
4	Benzene-ether	90:10	250	0.02	
5	" "	70:30	250x4	0.88	(±)cis-4'-Acetyl khellactone [XI]
6	" "	50:50	250x2	0.20	(±)-cis-khellactone [XVI]
7	" "	25:75	250x2	0.10	Compound, m.p. 186-88° (not identified)
8	Ether	100%	250	0.03	

Fraction 5 containing (±)-cis-4'-acetyl-khellactone was purified by crystallisation (twice) from benzene to furnish colourless crystals, m.p. 182-84°; $(\alpha)_D^{30} \pm 0°$. Ultraviolet spectrum: (described in the theoretical part). Infrared spectrum (Fig.7): bands at 3509, 1748, 1709, 1613, 1460, 1370, 1282, 1227, 1111, 1020, 971, 889, 833 and 766 cm^{-1}.

PMR spectrum (Fig.6, in $CDCl_3$): doublets at 457, 409 and 374 cps (1H each, J = 9-10 cps, due to protons at 4, 6 and 3 respectively, absorption due to proton at 5 being merged in solvent absorption); 386 and 241 cps (1H each, J = 5 cps, due to 4' and 3' protons respectively); and singlets at 154 (1H), 133 (3H) and 86 (6H) cps (due to -OH, -C.C-CH_3 and gemdimethyl groups respectively).

Analysis

Found: C, 62.95; H, 5.36.

$C_{16}H_{16}O_6$ requires: C, 63.15; H, 5.30%.

(±)-cis-Khellactone (XVI)

Fraction 6 containing (±)-cis-khellactone was purified by crystallisation from benzene to furnish colourless crystals, m.p. 158-60°, which remained undepressed on admixture with authentic cis-khellactone. Infrared (Fig.8) and ultraviolet spectra of both samples were superimposable.

Analysis

Found: C, 64.33; H, 5.65.

$C_{14}H_{14}O_5$ requires: C, 64.11; H, 5.38%.

(±)-cis-Khellactone (XVI) by osmium-tetroxide oxidation[12] of seselin (XV)

Osmium tetroxide (0.41 g) in dry purified dioxan (5 ml) was added to seselin (0.22 g) in the same solvent (5 ml). The solution was left at room temperature for 4 days and then saturated with hydrogen sulphide. The back precipitate was filtered off and dioxan solution was evaporated to dryness under reduced pressure. The crude product (0.31 g) was crystallised from benzene to give colourless crystals of XVI m.p. 159-61°. Ultraviolet spectrum: λ_{max}. 325, 258, 246, 219 and 213 mμ (log ε 4.14, 3.45, 3.48, 4.10 and 4.13 respectively). Infrared spectrum (Fig. 10); bands at 3390, 1728, 1686, 1616, 1492, 1461, 1398, 1369, 1352, 1289, 1242, 1225, 1180, 1160, 1138, 1114, 1091, 1050, 1021, 1006, 999, 930, 890, 855, 822, 802, 780 and 752 cm^{-1}.

Analysis

Found: C, 64.03; H, 5.53.

$C_{14}H_{14}O_5$ requires: C, 64.11; H, 5.38%.

Acetylation of (±)-cis-khellactone (XVI)

Acetyl chloride (0.40 g) was added to a solution of the (±)-cis-khellactone (0.096 g) in benzene (20 ml)

and the mixture was kept at room temperature for 3 days. The course of reaction was followed by TLC on silicic acid. The reaction mixture was diluted with benzene (20 ml), washed with water, sodium bicarbonate solution, then water, dried overnight and the solvent was removed. The product (0.11 g) showing traces of impurities on TLC was purified by preparative layer chromatography [which was run over silicic acid plates (20 x 20 cm) by usual procedure using ethyl acetate-benzene (1:1) as developing solvent], and then through crystallisation from petroleum ether-benzene to give colourless needles, of (±) -cis-3',4'-diacetyl-khellactone (XVII), m.p. 161-63°. Ultraviolet spectrum: λ_{max}. 322, 296, 256, 245 and 219 mμ (log ε 4.14, 3.94, 3.53, 3.60 and 4.15 respectively). Infrared spectrum (Fig.10): bands at 2941, 2899, 1764, 1742, 1631, 1508, 1477, 1412, 1389, 1312, 1287, 1245, 1195, 1163, 1136, 1087, 1063, 1031, 1013, 994, 952, 923, 899, 856, 843, 823, 800, 781 and 759 cm^{-1}.

Analysis

Found: C, 62.52; H, 5.32.

$C_{18}H_{18}O_7$ requires: C, 62.42; H, 5.24%.

Acetylation of (±)-cis-4'-acetyl-khellactone (XI)

(±)-cis-4'-Acetylkhellactone (0.10 g) in benzene (15 ml) was acetylated with acetyl chloride (0.35 g) by the procedure described earlier. The product (0.11 g) showing

traces of impurities on TLC was purified by preparative layer chromatography and by crystallisation from petroleum ether-benzene mixture to give colourless needles of XVII, m.p. and mixed m.p. with authentic cis-3',4'-diacetyl-khellactone, prepared as above, 160-62°. Infrared and ultraviolet spectra of both preparations were identical.

Analysis

Found: C, 62.57; H, 5.34.

$C_{18}H_{18}O_7$ requires: C, 62.42; H, 5.24%.

(±)-cis-Dihydrosamidin (XIIa)

Isovaleryl chloride (0.138 g) in dry benzene (2 ml) was added to a suspension of (±)-cis-monoacetyl-khellactone (XI, 0.134 g) in dry benzene (10 ml). The reaction mixture protected by a $CaCl_2$ guard tube was refluxed on a steam bath for 28 hr. The course of reaction was followed by TLC on silicic acid. The reaction mixture was cooled, diluted with benzene (30 ml), washed with water, sodium bicarbonate solution, then water, dried and the solvent removed to afford a residue (0.160 g) which was chromatographed over silicic acid.

CHROMATOGRAM

Wt. of compound 0.16 g.
Wt. of silicic acid 4.0 g.

Fr.	Solvent	Ratio by volume	Volume of eluate (ml)	Wt. of fr. (g)	Remarks
1	Pet.ether	100%	100	-	
2	Pet.ether-benzene	50:50	100	0.030	Rejected
3	Benzene	100%	100	0.020	
4	Benzene-ether	93:7	100x4	1.40	(±)-cis-dihydrosamidin(XIIa)
5	Ether	100%	100X2	0.020 g.	Rejected.

Fraction 4 containing (±)-cis-dihydrosamidin was crystallised from pet.ether to give colourless needles, m.p. 125-27°, $(\alpha)_D^{28} \pm 0^\circ$ (c, 1.5). Ultraviolet spectrum (Fig.4): λ_{max}. 324, 260, 249 and 216 mμ (log ε 4.17, 3.57, 3.65 and 4.19 respectively). Infrared spectrum (Fig. 11): bands at 1754, 1613, 1494, 1471, 1410, 1379, 1299, 1235, 1190, 1124, 1053, 1030, 1010, 920, 893, 851, 836 and 774 cm^{-1}.

PMR spectrum (Fig.12, in CCl_4): doublets at 452, 439, 403, 368 cps (1H each, J = 8-9 cps, due to protons at 4, 5, 6 and 3 respectively), 386 and 314 cps (1H each, J = 5 cps, due to protons at 4' and 3' respectively);

singlets at 128, 124 cps (5H, due to -C.CH_3 and -C-CH_2- group) and 83 cps (6H, due to gemdimethyl group at 2'); and a doublet at 56 cps (6H, J = 6 cps, due to -CH$<^{CH_3}_{CH_3}$ group).

Analysis

Found: C, 64.86; H, 6.26.

$C_{21}H_{24}O_7$ requires: C, 64.95; H, 6.23%.

(±)-cis-Visnadin (XIIb)

(±)-cis-4'-Acetyl-khellactone (XI, 0.15 g) was esterified with ∝-methyl-butyryl chloride (0.130 g) by following the procedure described earlier. The reaction product (0.18 g) was chromatographed on silicic acid (6 g). Benzene-ether mixture (93.7) eluted the ester (0.15 g), which on crystallisations from pet.ether afforded (±)-cis-visnadin, m.p. 150-52°. Ultraviolet spectrum: λmax. 324, 261, 249 and 215 mμ. log ε 4.15, 3.55, 3.62 and 4.19 respectively.

Infrared spectrum (Fig.14): bands at 1739, 1608, 1486, 1458, 1372, 1348, 1277, 1229, 1181, 1147, 1103, 1062, 1007, 926, 909, 892, 846 and 775 cm^{-1}.

PMR spectrum (Fig.13): doublets at 455, 440, 407, 372 cps (1H each, J = 8-9 cps, due to protons at 4,5,6 and 3 respectively), 391, and 320 cps (1H each, J=5 cps, due to protons at 4' and 3' respectively); singlets at 124 cps

(3H, due to -O.C(=O)-CH_3 group at 4') and 85 cps (6H, due to gemdimethyl group at 2'); a doublet at 71 cps (3H, J = 7 cps, due to CH_3-CH< grouping) and a triplet at 55 cps (3H, due to CH_3-CH_2- grouping).

Analysis

Found: C, 65.16; H, 6.44.

$C_{21}H_{24}O_7$ requires: C, 64.95; H, 6.23%.

REFERENCES

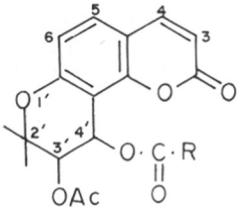
1. C.P. Huttrer and E. Dale, Chem.Revs., 48,543(1951).
2. K. Samman, Quart.J.Pharm.Pharmacol., 4, 14 (1931); 6, 12 (1933); 18, 83 (1945).
3. (a) E. Smith, L.A. Pucci and W.G. Bywater, Science, 115, 520 (1952).
   (b) E. Smith, N. Hosansky and W.G. Bywater, Abstracts of the Medicinal Division, 24N, 126th Meeting of the American Chemical Society, New York, Sept. 1954.
4. E. Smith, N. Hosansky , W.G. Bywater and E.E. van Tamelen, J.Amer.Chem.Soc., 79, 3534 (1957).
5. H.D. Schroeder, W. Bencze, O. Halpern and H.Schmid, Chem.Ber., 92, 2338 (1959).
6. W.S. Johnson, A.D. Kemp, R. Pappo, J.Ackerman and W.E. Johns, J.Amer.Chem.Soc., 78, 6312(1956).
7. (a) E. Elisberg, H.Vanderhaeghe and T.F.Gallagher, J.Amer.Chem.Soc., 74, 2814 (1952).
   (b) A. Hunger and T. Riechstein, Chem.Ber., 85,635(1952).
8. R.E. Willette and T.O. Soine, J.Pharm.Soc., 53 (3), 275 (1964).
9. L.F. Fieser and R. Stevenson, J.Amer.Chem.Soc., 76, 1728 (1954).
10. G.W.K. Cavill and D.H. Solomon, J.Chem.Soc., 3942(1954).
11. K.B. Wiberg and S.D. Nielsen, J.Org.Chem., 29,3353(1964)
12. D.H.R. Barton and Dov Elad, J.Chem.Soc.,2085(1956).

CHAPTER III

SYNTHESIS OF SUKSDORFIN

SUMMARY

The vasodilatory drug (±)-cis-suksdorfin (Ib) has been synthesised starting from jatamansinone (II).

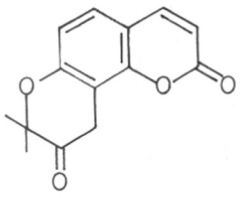


I

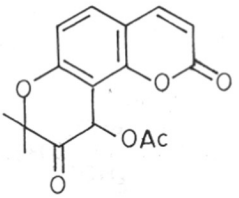
b. R = $-CH_2-CH(CH_3)_2$

c. R = $-CH-(CH_3)-CH_2-CH_3$

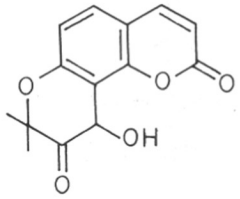
Jatamansinone (II) was converted into the keto-acetate III by treatment with lead tetraacetate. The ketoacetate III was hydrolysed with alkali in order to obtain the ketoalcohol IV. However, instead of the desired material a rearranged product having a tertiary hydroxyl group and no keto function was obtained (Elucidation of the structure of this compound will be taken up at a future date). Alternatively, III was hydrolysed with acid under controlled conditions which yielded the ketoalcohol VIII. Evidently, during acid hydrolysis IV has rearranged to VIII, the mechanism of which has been discussed.



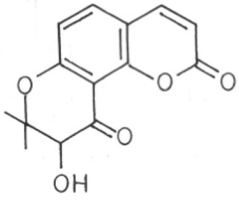
II



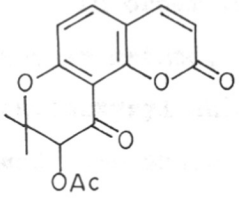
III



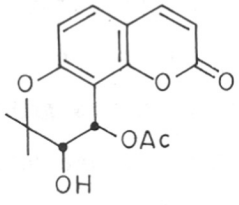
IV



VIII



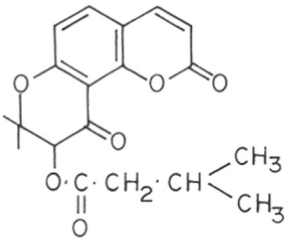
IX



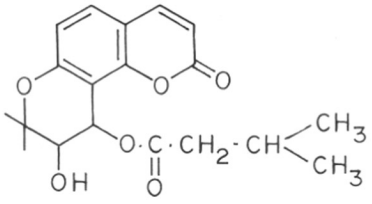
XI

Keto-alcohol VIII was acetylated to yield the ketoacetate IX. It was then reduced with sodium borohydride and the product was found to be identical with (±) -cis-4'-acetyl-khellactone (XI). Thus during sodium borohydride reduction of IX, there was one more rearrangement, the migration of acyl group from 3' to 4' position. The reaction mechanism of this has also been discussed.

In view of the above rearrangements (±)-cis-suksdorfin has been prepared from the ketoalcohol VIII, by condensing the same with isovaleryl chloride, reducing the resulting ester XVI with sodium borohydride and then acetylating the alcohol XVII (obtained through acyl migration) with acetyl chloride.

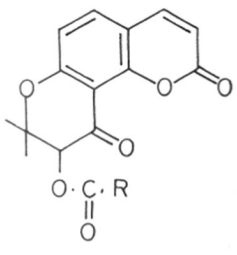


XVI

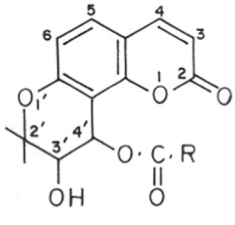


XVII

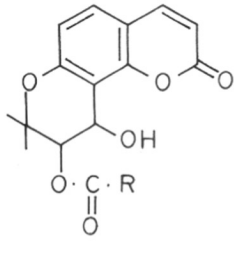
In order to prepare (±)-cis-dihydropteryxin (Ic) by similar method, the ketoalcohol VIII was condensed with α-methylbutyryl chloride and the resulting ester XIX was reduced with sodium borohydride. In this case, however, there was no acyl migration and the product was found to be 3'-α-methylbutyryl-khellactone(XXI), instead of the desired 4'-α-methylbutyryl-khellactone(XX). This was further confirmed by acetylation of XXI which yielded (±) -cis-visnadin(XXII). Thus it has not been possible for us to synthesise dihydropteryxin at present and the problem is receiving our further attention.



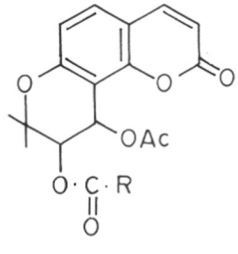
XIX



XX



XXI

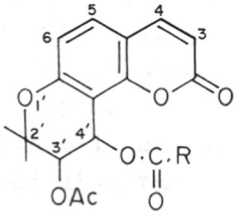


XXII

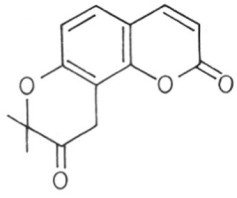
R = −CH−(CH$_3$)−CH$_2$−CH$_3$

Syntheses of dihydrosamidin and visnadin have been detailed in the second chapter. Present chapter describes successful synthesis of (±) -cis-suksdorfin(Ib) from jatamansinone (II) carried out by us.

The coumarins pteryxin (Ia) and suksdorfin (Ib), which have been known to possess a strong vasodilatory activity, were first isolated by Call et al.[1,2] in 1956 from the plants Pteryxia terebinthina(Hook) and Lomatium suksdorfii (Wats.) respectively. Structures of these compounds have been established by Soine et al.[3] in 1962. However, syntheses of these products have not been attempted by earlier workers and therefore it was thought to be desirable to achieve the same.



I

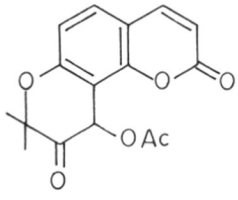


II

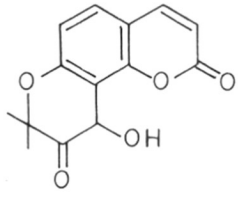
a. R = $-C(CH_3)=CH-CH_3$

b. R = $-CH_2-CH(CH_3)_2$

c. R = $-CH(CH_3)-CH_2-CH_3$



III

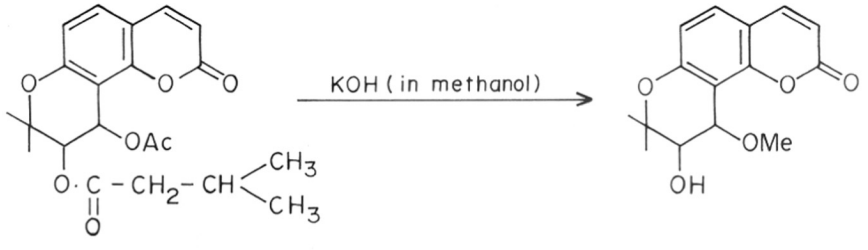


IV

As a prelude to the syntheses of these vasodilatory drugs (I), the keto-acetate III [(±)-3'-keto-4'-acetoxy-3',4'-dihydroseselin] which has been obtained from jatamansinone (II; 3'-keto-3',4'-dihydroseselin) by lead tetraacetate oxidation (vide Chapter II, p. 66) was saponified with aqueous alkali* in nitrogen atmosphere with a view to obtain the keto-alcohol IV;[(±)-3'-keto-4'-hydroxy-3',4'-dihydroseselin], but instead of this, an isomerised product, $C_{14}H_{12}O_5$, m.p. 196-200° (V) was obtained. It showed an extended conjugation[4] in the ultraviolet region (Fig. 4),

---

* The use of alcoholic solvents during these hydrolysis experiments was avoided, as it has been reported[3,5] that 3',4'-diacyl-khellactone (samidin, visnadin, pteryxin, suksdorfin etc) give 4'-alkyl-khellactone on hydrolysis in alcoholic solutions by incorporation of a solvent molecule on an oxygen atom at 4' position. For example, dihydrosamidin (VI) on hydrolysis in methanolic potassium hydroxide yielded 4'-methyl-khellactone (VII).



VI VII

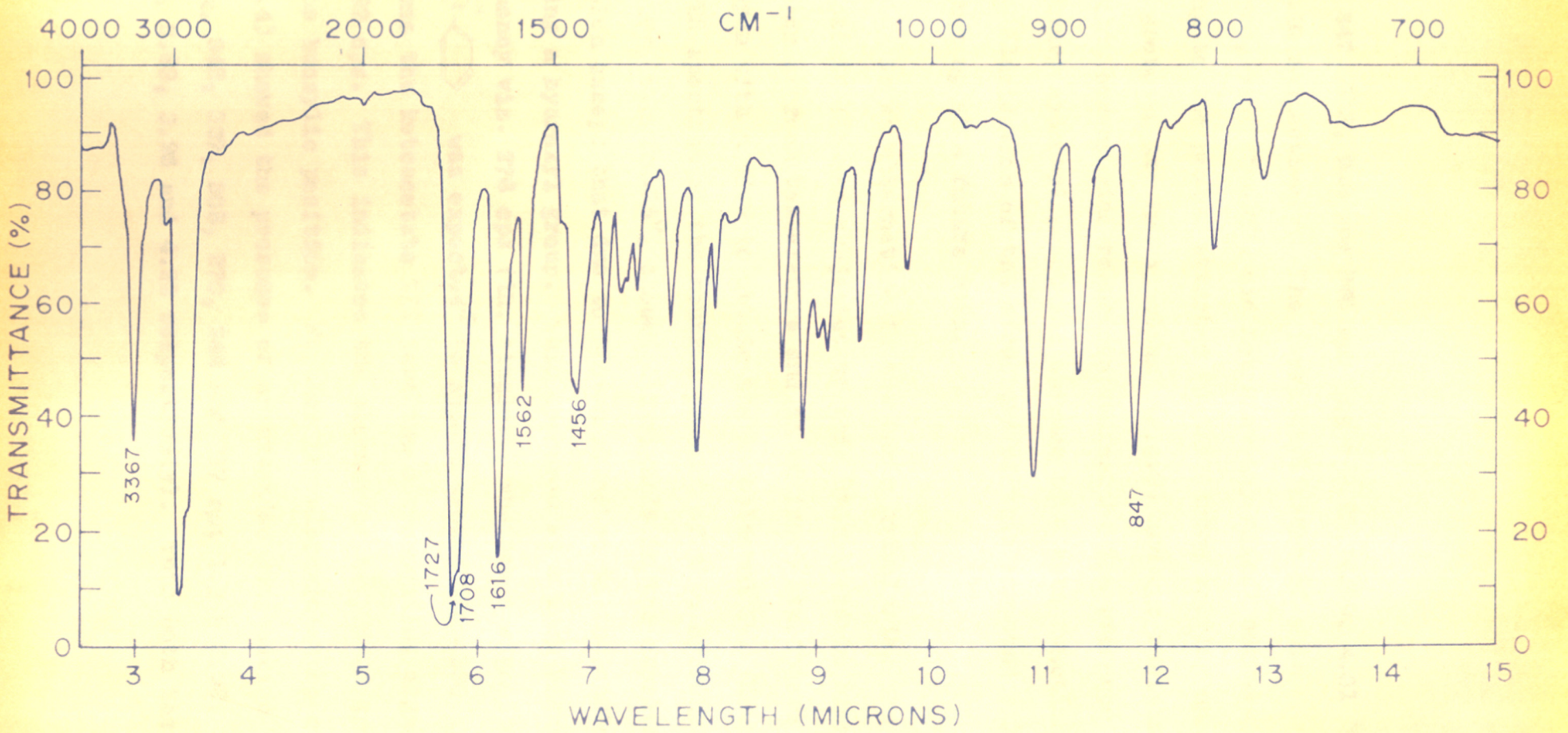
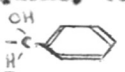


FIG. 1. IR SPECTRUM OF COMPOUND V.

$\lambda_{max.}$ 347, 312, 268 and 260 mμ, log ε 3.93, 4.09, 4.01 and 4.10 respectively. The isovaleryl ester of this compound, m.p. 156-58°, did not show any signal corresponding to the proton attached to the carbon bearing an ester group in its PMR spectrum[5] (Fig.2) and was resistant to sodium borohydride reduction indicating the presence of a tertiary hydroxyl group and absence of a keto function in V. Elucidation of the structure of this compound will be taken up at a future date.

As an alternative to the basic hydrolysis, the ketoacetate III was subjected to acid hydrolysis in dioxan solution at room temperature and in an inert atmosphere of nitrogen with a view to obtain the ketoalcohol IV. However, the PMR spectrum of the neutral product of this hydrolysis, $C_{14}H_{12}O_5$, m.p.212-16°, showed all signals in the expected position except that due to proton attached to the carbon bearing a hydroxyl group. This appeared at a much higher frequency viz. 276 cps (1H, singlet); whereas a signal due to  was expected[5] to appear around 320 - 330 cps because the ketoacetate III gave the corresponding signal at 392 cps. This indicated the absence of a >CH-OH group in the benzylic position. Further its ultraviolet spectrum (Fig.4) showed the presence of an extended conjugation ($\lambda_{max.}$ 348, 337, 308, 270, 242 and 217 mμ; log ε 3.92, 3.95, 3.97, 3.83, 3.96 and 4.22 respectively). Thus both the

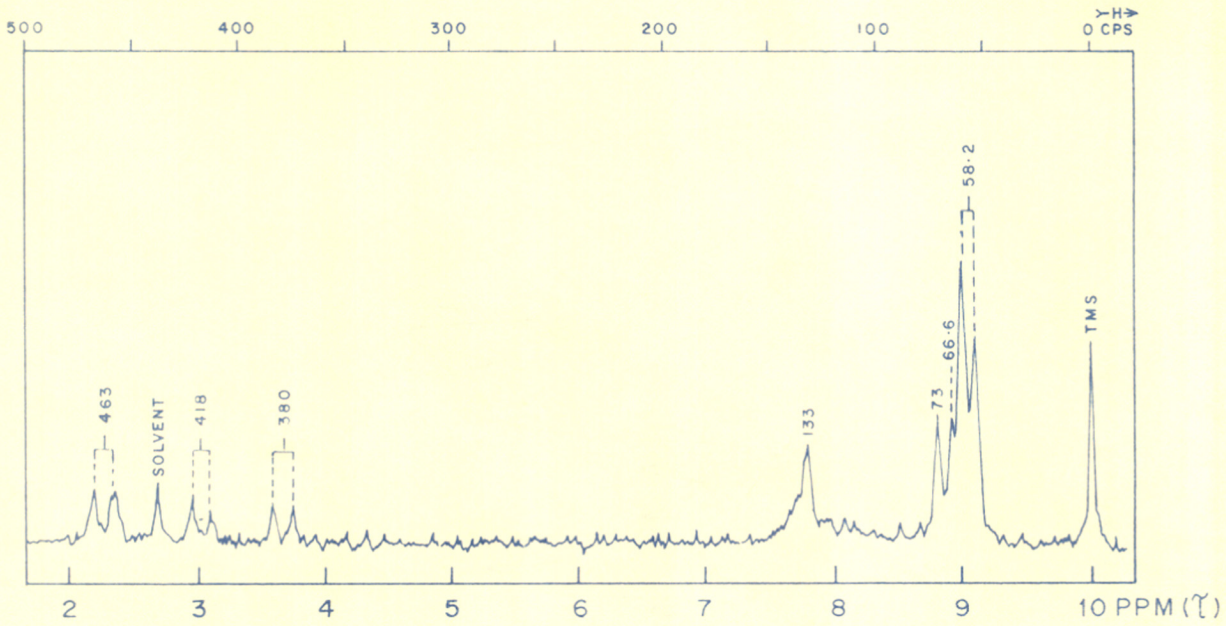


FIG. 2. PMR SPECTRUM OF ISOVALERYL ESTER OF V.

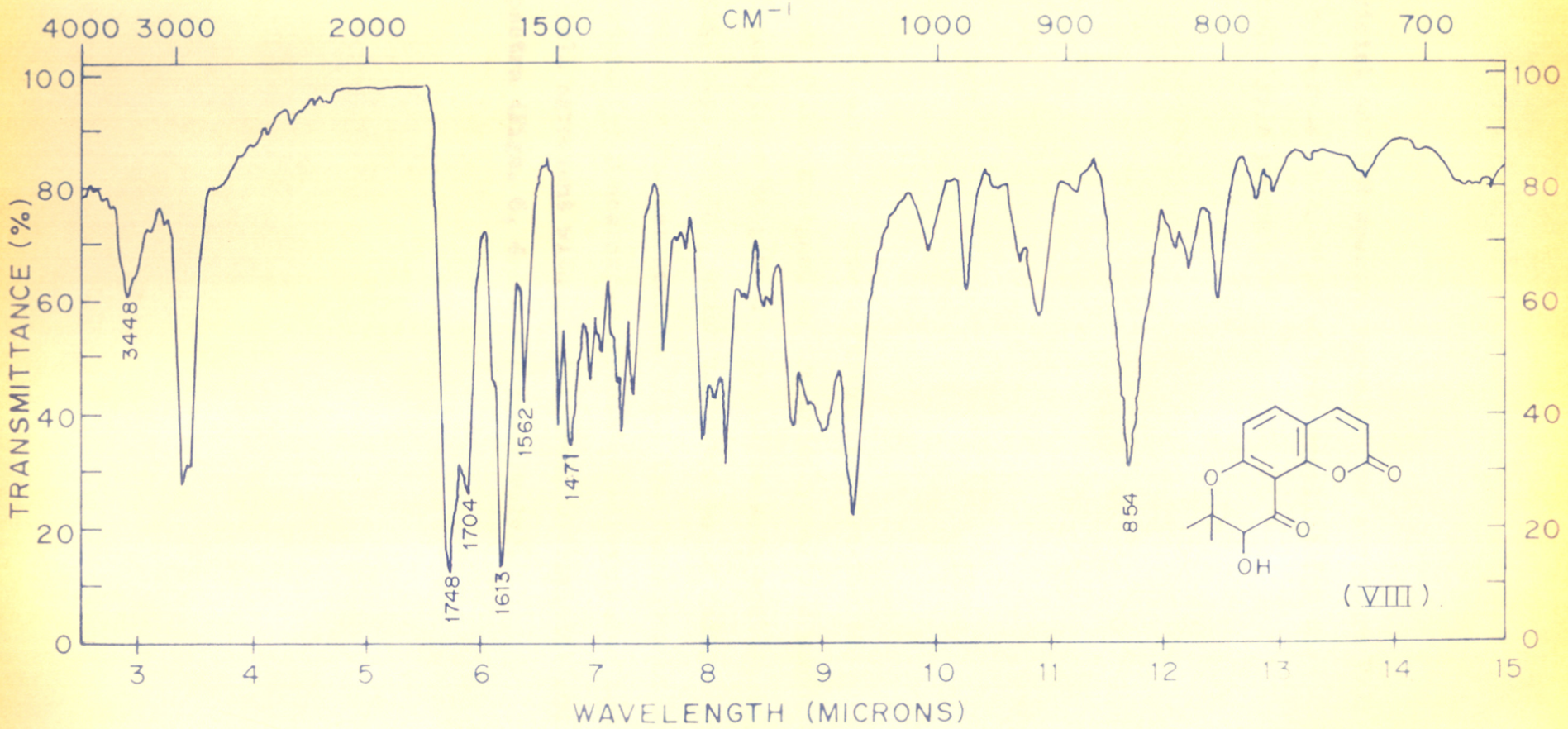
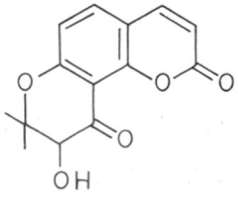
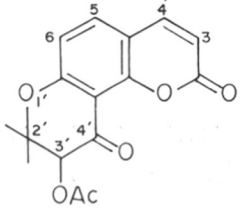


FIG. 3. IR SPECTRUM OF (±)-3'-HYDROXY-4'-KETO-3',4'-DIHYDROSESELIN (VIII).

ultraviolet and PMR spectra revealed the structure VIII [(±)-3-hydroxy-4'-keto-3',4'-dihydroseselin] for the acid hydrolysis product.



VIII



IX

In order to have a further support for the structure (VIII) assigned to the acid hydrolysis product, it was acetylated to give a crystalline keto-acetate IX, $C_{16}H_{16}O_6$, m.p. 154-56°, which was found to be quite different from the ketoacetate III. The structure of the ketoacetate IX [(±)-3-acetoxy-4'-keto-3',4'-dihydroseselin] is in full agreement with its infrared, ultraviolet and PMR spectra (Figs. 6, 4 and 5 respectively).

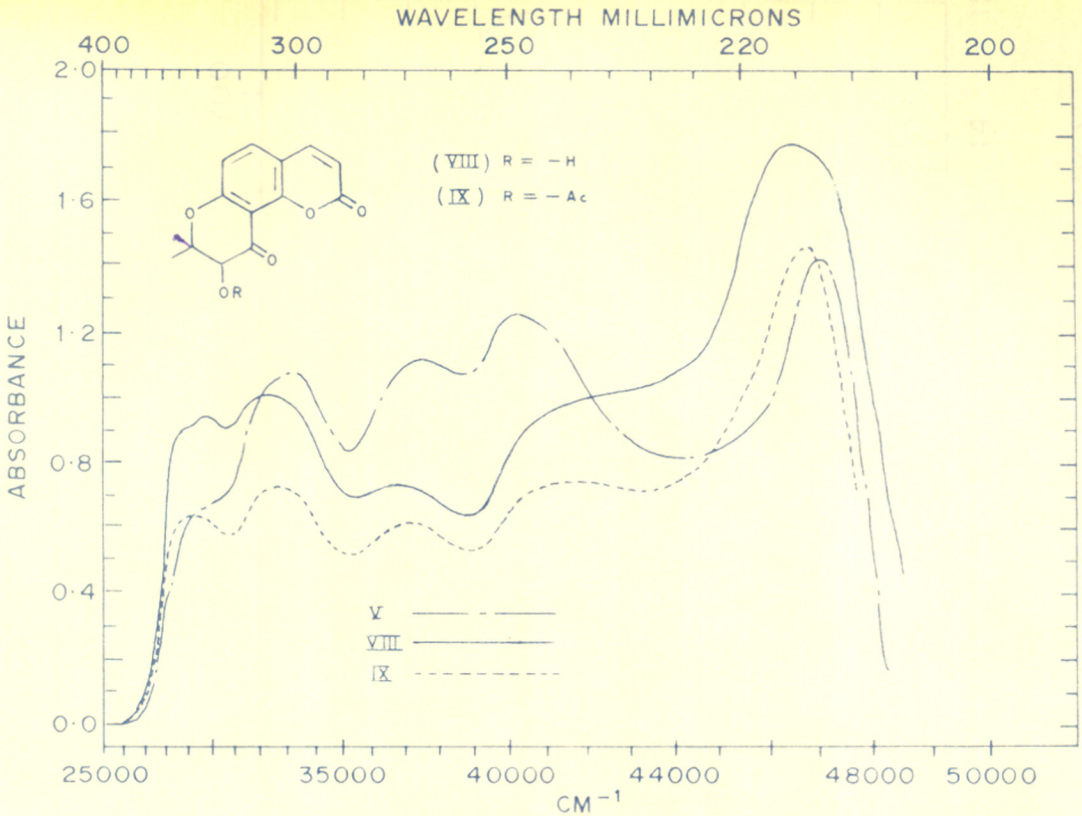


FIG. 4. UV SPECTRA OF COMPOUND V, (±)-3'-HYDROXY-4'-KETO-3',4'-DIHYDROSESELIN (VIII), (±)-3'-ACETOXY-4'-KETO-3',4'-DIHYDROSESELIN (IX).

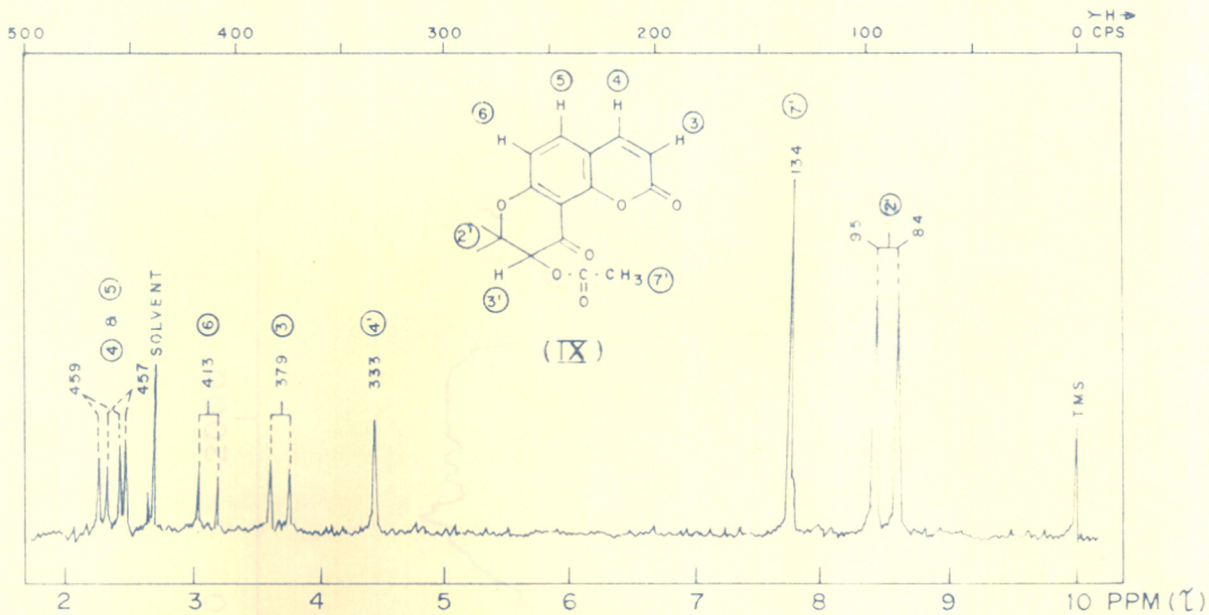


FIG. 5. PMR SPECTRUM OF (±)-3'-ACETOXY-4'-KETO-3',4'-DIHYDROSESELIN (IX).

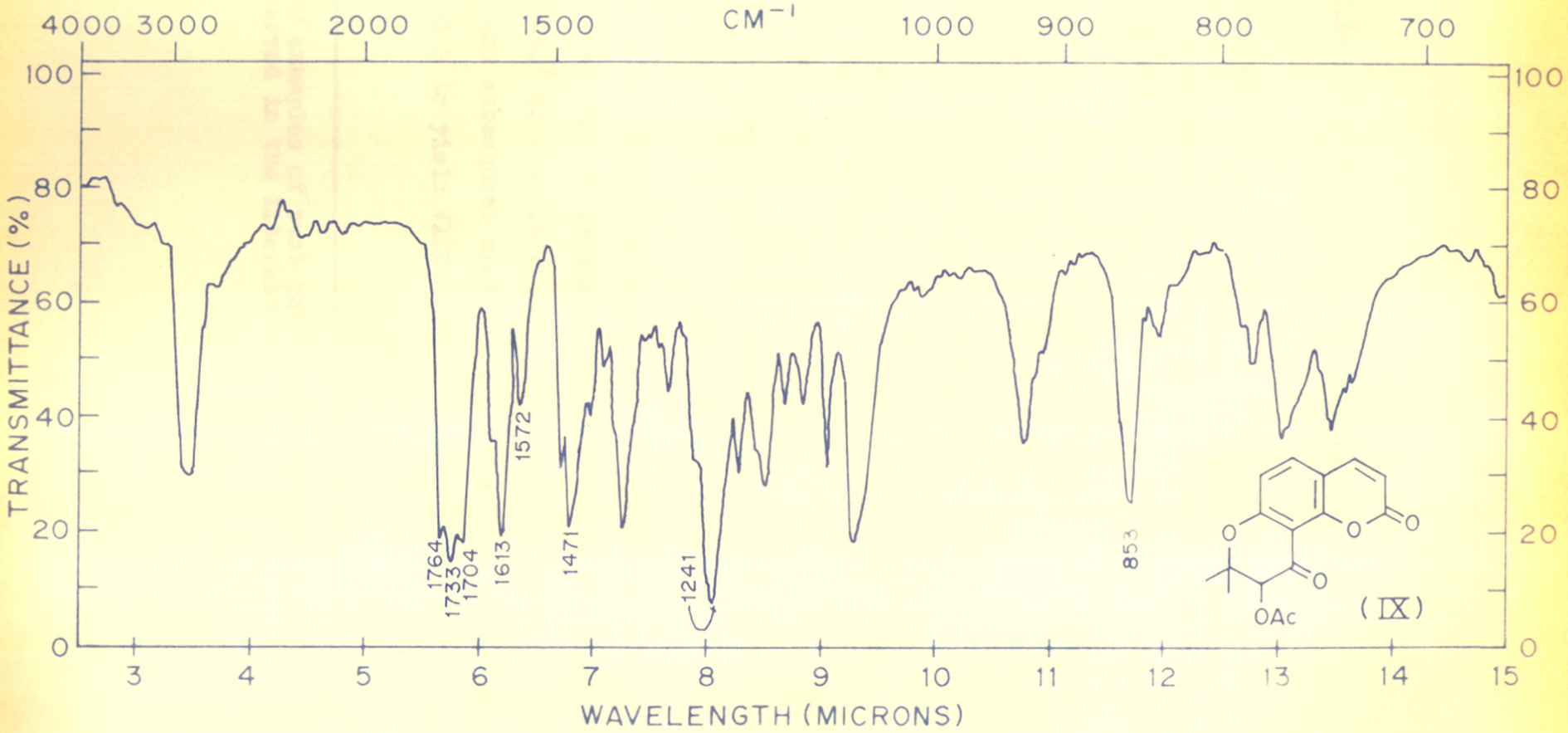


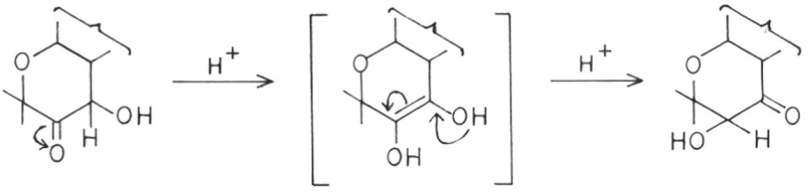
FIG. 6. IR SPECTRUM OF (±)-3'-ACETOXY-4'-KETO-3',4'-DIHYDROSESELIN (IX).

TABLE I. COMPARISON OF PHYSICAL CONSTANTS OF KETOACETATE III AND KETOACETATE IX

	Property	Ketoacetate III	Ketoacetate IX
1.	Melting point	180-82°	154-56°
2.	Ultraviolet spectrum ($\lambda_{max.}$ in Mμ(log ε))	324(4.11),261(3.55) 249(3.58) and 213 (4.13)	348(3.96), 336(3.98), 305(4.03), 266(3.96), 240(4.04) and 215(4.11).
3.	PMR spectrum (Signal (in cps) due to proton attached to carbon bearing -OH group)	392	333

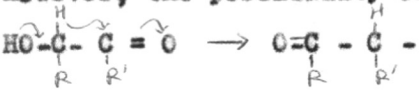
Evidently, during acid hydrolysis the keto alcohol IV has rearranged* to the ketoalcohol VIII, the probable mechanism[7] of this rearrangement being the rapid enolisation of IV and subsequent proton migration of the resulting enediol X to yield VIII.

* Many examples of such rearrangements have been observed in the literature.[7]



IV X VIII

However, the possibility of one step proton migration

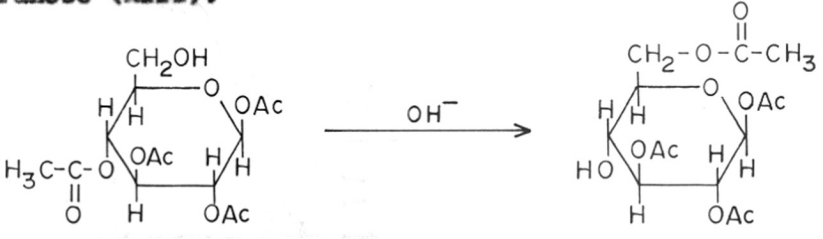


cannot be excluded.

In addition to the above rearrangement it was also observed that, both the ketoacetate III and keto-acetate IX on reduction with sodium borohydride in dioxan gave identical (±)-cis-4'-acetyl-khellactone (XI, Fig.7 & 8; also vide Chapter II, p. 68) thereby indicating the occurrence of one more rearrangement namely the migration of acyl group* from the 3' carbon atom to 4' during sodium borohydride reduction of the keto acetate IX.

---

* Many examples of such acyl migrations in basic medium have been observed[8] in carbohydrate chemistry. It is interesting to note that Helferich and Klein[9] observed that in the case of 1,2,3,4-tetra-o-acetyl-β-D-gluco-pyranose (XII) simple soft glass container catalysed the transfer of an acyl group from the forth carbon atom to the sixth yielding 1,2,3,6-tetra-o-acetyl-β-D-gluco-pyranose (XIII).



XII XIII

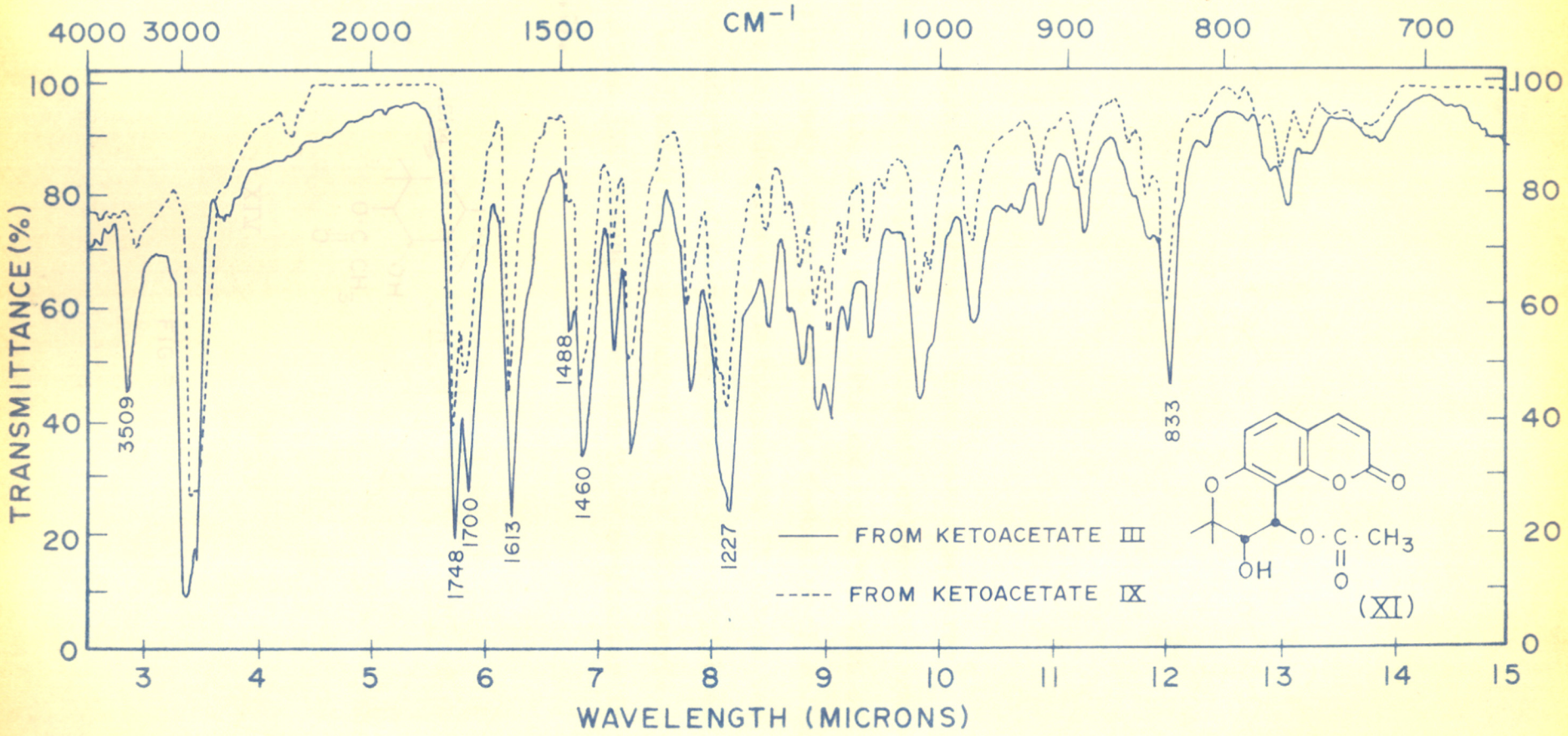
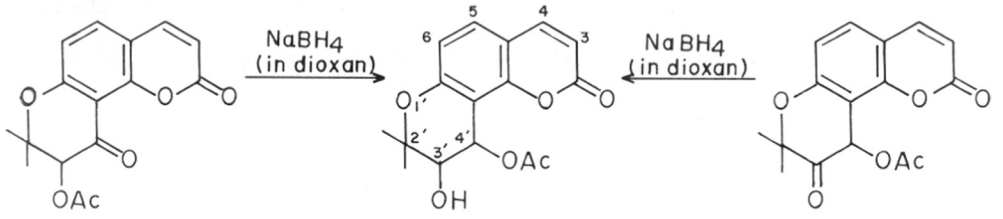


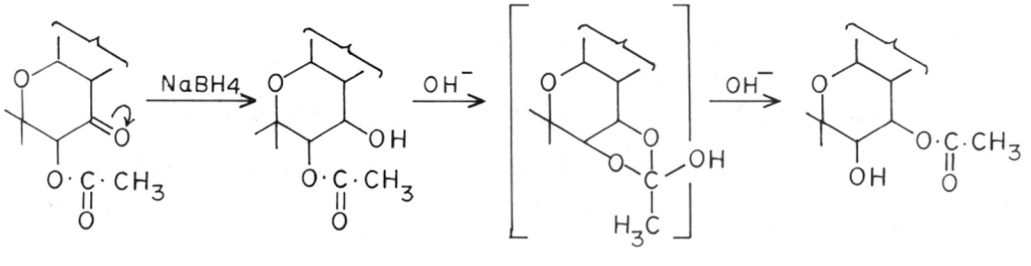
FIG. 5 IR SPECTRUM OF (±)-CIS-4'-ACETYL-KHELLACTONE (XI).



IX XI III

FIG·7

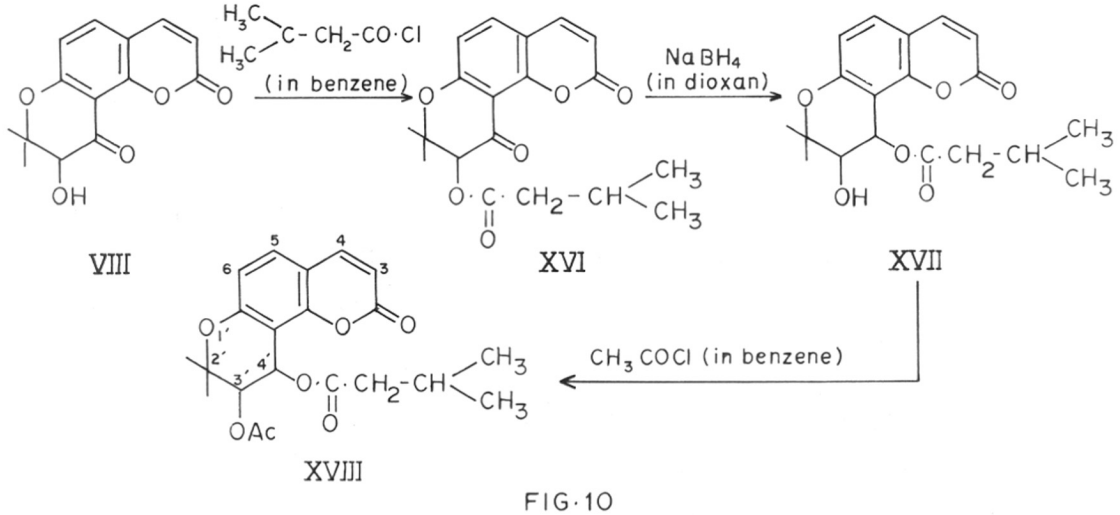
Such acyl migrations have been considered[8] to take place through an intermediate orthoester formation rather than the actual hydrolysis and recombination of the wandering group. Thus, the probable mechanism of sodium borohydride reduction of the ketoacetate IX may be the initial reduction of keto group to give 3'-acetyl-khellactone (XIV) which then rearranges to (±) -4'-acetyl-khellactone (XI) through an intermediate orthoester XV (Fig.9).



IX XIV XV XI

FIG·9

In view of the above rearrangements, the keto-alcohol VIII has been converted into (±) cis-suksdorfin (XVIII) through series of reactions depicted in Fig. 10.



FIG·10

The ketoalcohol VIII was refluxed with isovaleryl chloride in benzene solution in an inert nitrogen atmosphere to yield a keto-ester XVI [(±)-3'-isovaleryloxy-4'-keto-3',4'-dihydroseselin], $C_{19}H_{20}O_6$, m.p.122-24°. Infrared, ultraviolet and PMR spectra (Figs. 11, 12 and 13 respectively) of this compound are in complete agreement with its structure.

The keto-ester XVI was then reduced with sodium borohydride in dioxan solution at the temperature of 2-5° for 1/2 hr. This afforded an alcohol XVII; through reduction of keto group followed by acyl migration. The structure of

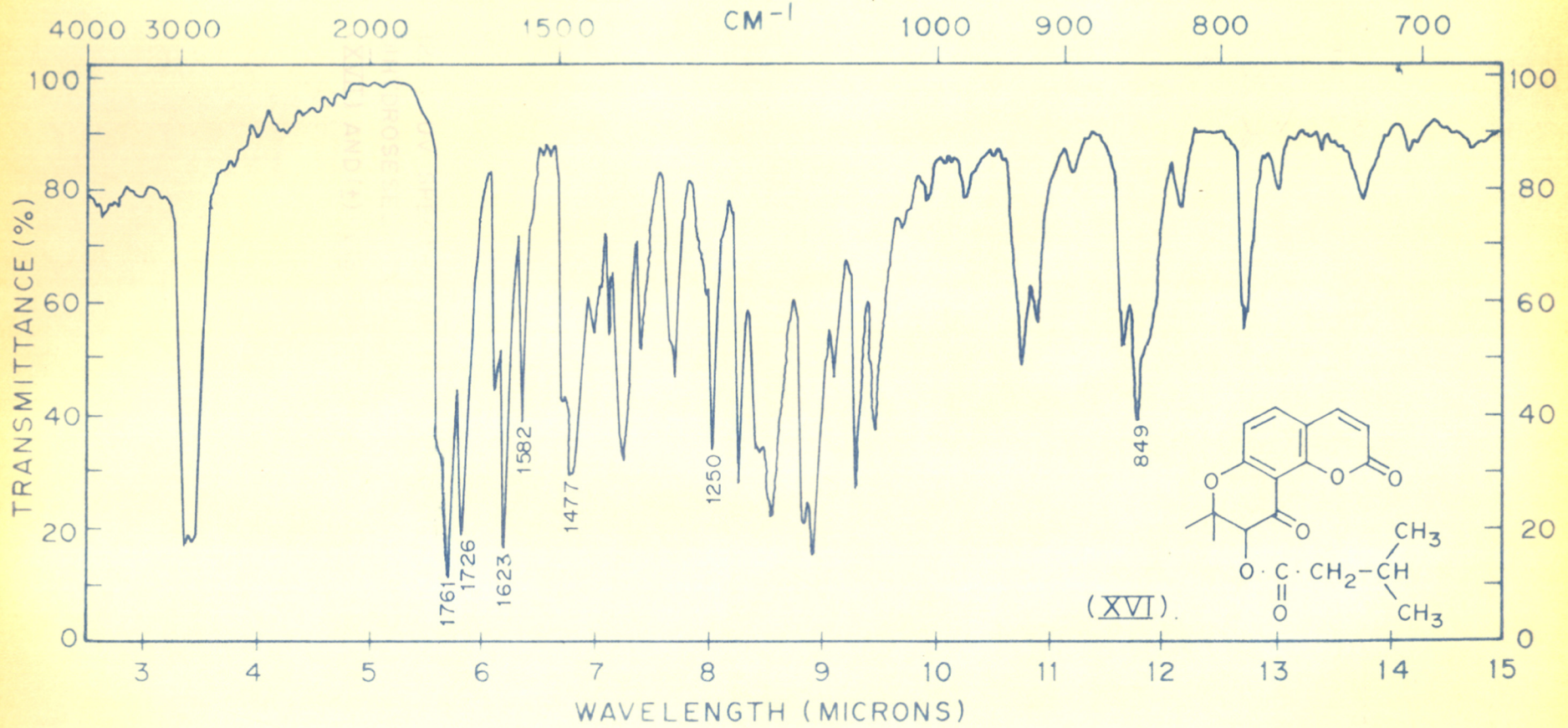


FIG. 11. IR SPECTRUM OF (±)-3'-ISOVALERYLOXY-4'-KETO--3',4'-DIHYDROSESELIN (XVI).

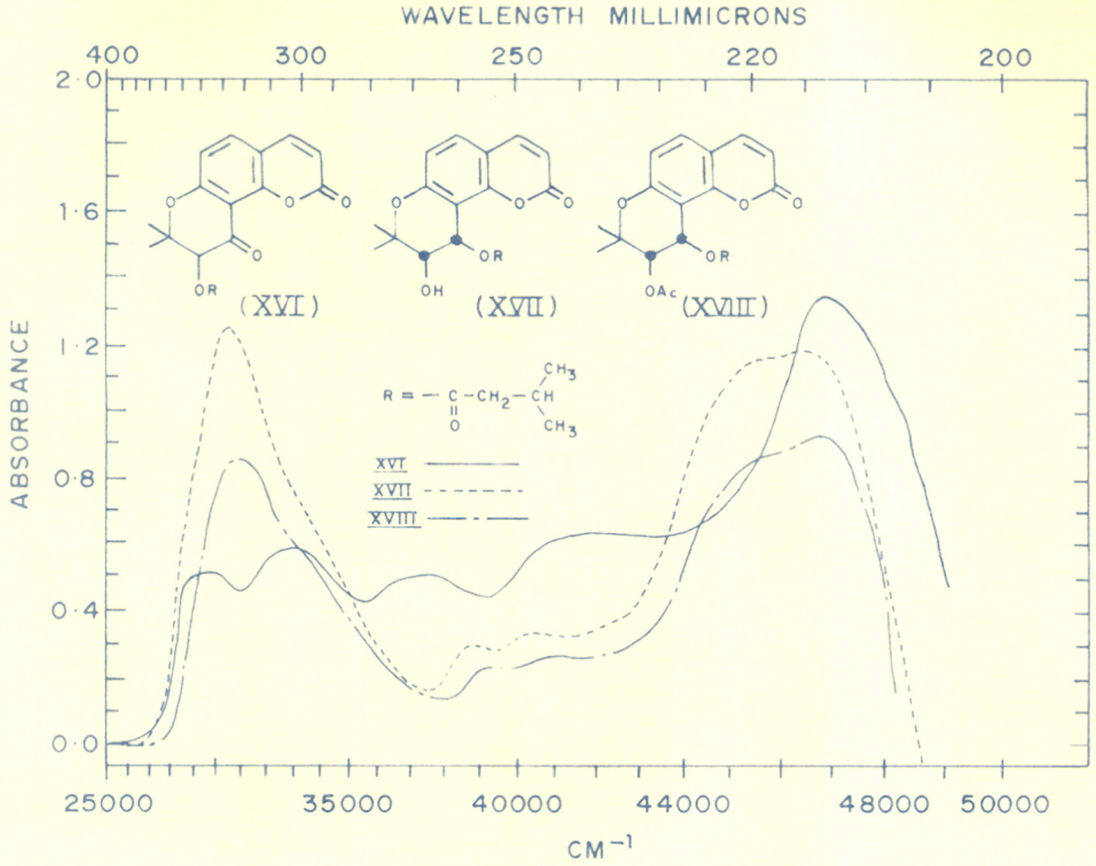


FIG. 12. UV SPECTRA OF (±)-3'-ISOVALERYLOXY-4'-KETO-3'-4'-DIHYDROSESELIN (XVI), (±)-CIS-4'-ISOVALERYL-KHELLACTONE (XVII) AND (±)-CIS SUKSDORFIN (XVIII).

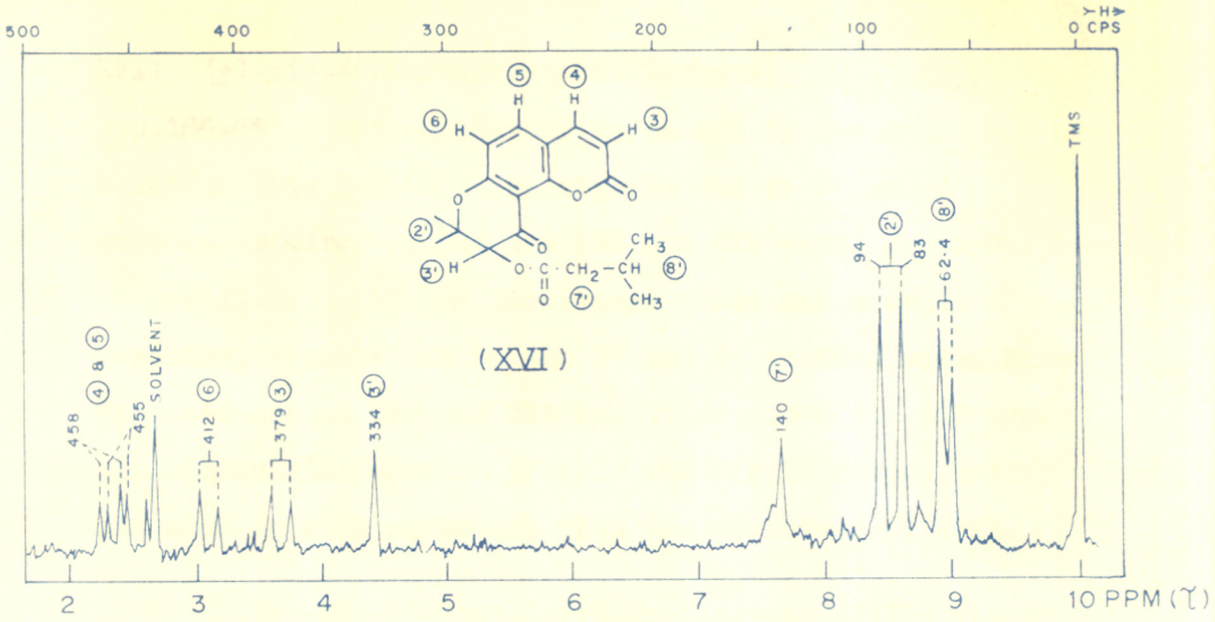


FIG. 13. PMR SPECTRUM OF (±)-3'-ISOVALERYLOXY-4'-KETO-3'-4'-DIHYDROSESELIN (XVI).

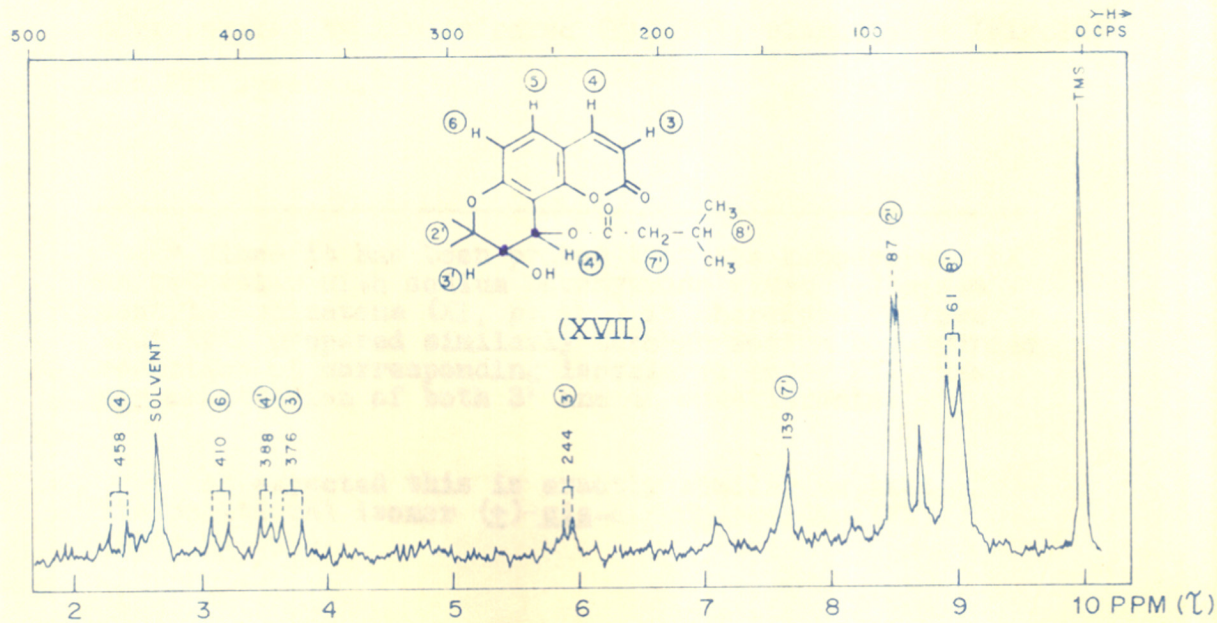


FIG. 14. PMR SPECTRUM OF (±)-CIS-4'-ISOVALERYL-KHELLACTONE (XVII)

XVII [(±)-cis-4'-isovaleryl-khellactone]*, $C_{19}H_{22}O_6$, m.p.166-68° , was completely borne out by its PMR spectrum (Fig.14) in which signals due to 3' and 4' protons appeared at 244 and 388 cps (1H each, J = 6 cps) respectively . If the isovaleryl group had been at 3' position, signals due to the 3' and 4' protons would have appeared around 299 and 313 cps (vide p. 96). Infrared and ultraviolet spectra (Fig.15 and Fig.12 respectively) are also in full agreement with the structure of XVII.

(±)-cis-4'-Isovaleryl-khellactone (XVII) was then converted into (±) -cis-suksdorfin (XVIII) by acetylation with acetyl chloride. The structure of (±) cis-suksdorfin, thus prepared, $C_{21}H_{24}O_7$, m.p. 134-36°, has been fully corroborated by its infrared (Fig.16), ultraviolet (Fig.12) and PMR spectra.+

---

* Since it has been proved that the ketoacetate IX on reduction with sodium borohydride gives (±) cis-4'-acetyl-khellactone (XI, p. 91) it therefore follows that XVII prepared similarly through sodium borohydride reduction of corresponding isovaleryl ester XVI, has cis orientation of both 3' and 4' substituents.

+ As expected this is exactly similar to that of its positional isomer (±)-cis-dihydrosamidin (VI) (vide p. 69).

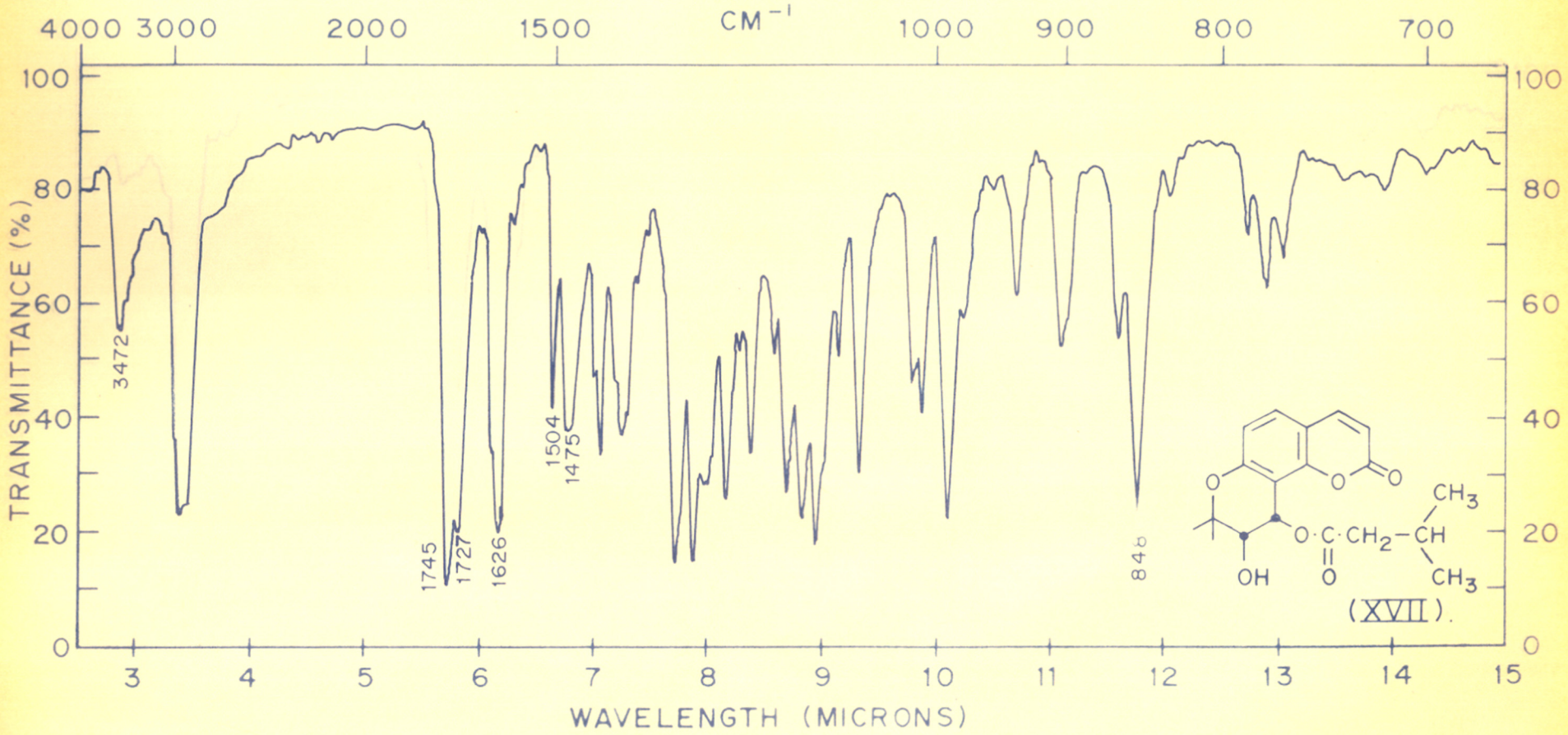


FIG. 15. IR SPECTRUM OF (±)-CIS-4'-ISOVALERYL-KHELLACTONE (XVII).

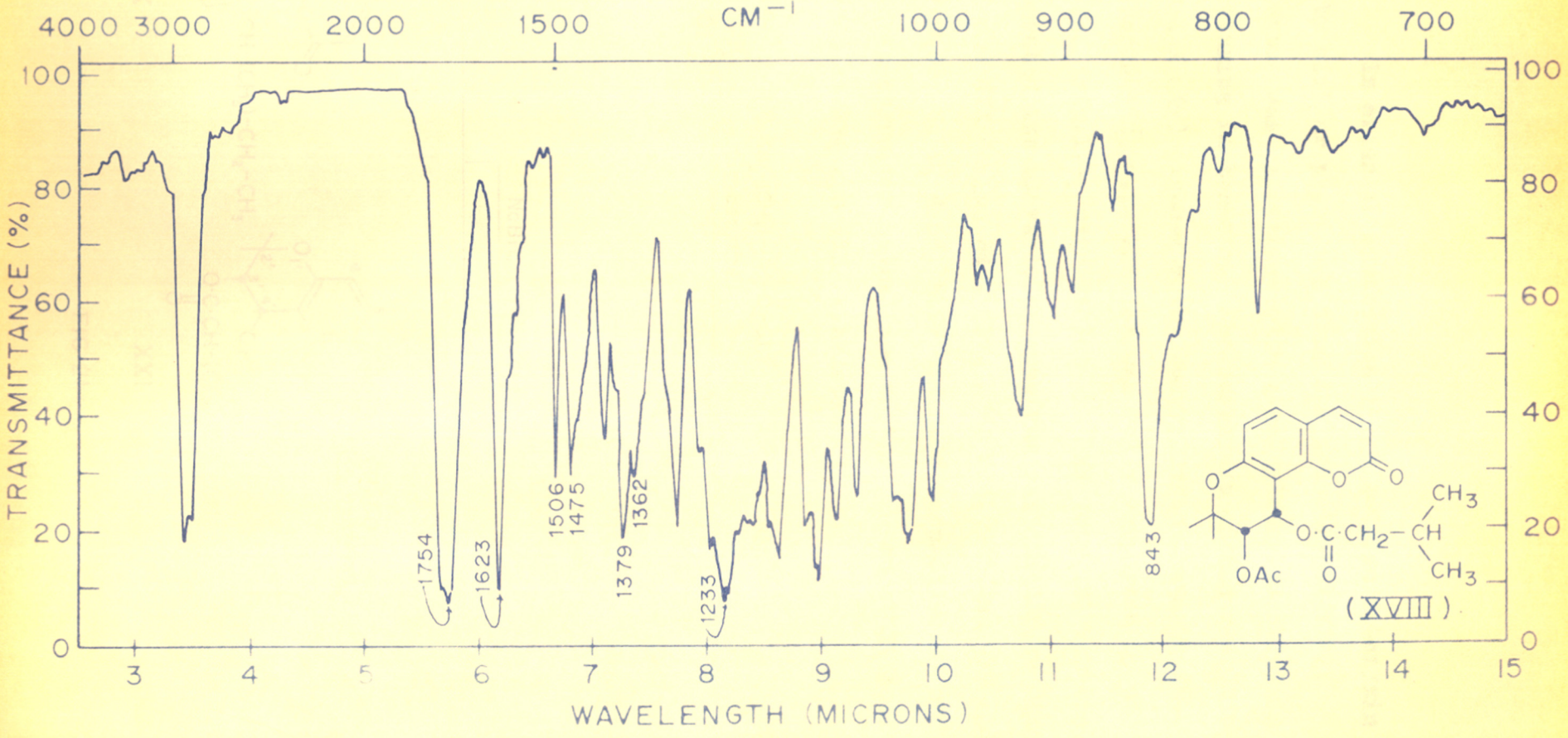
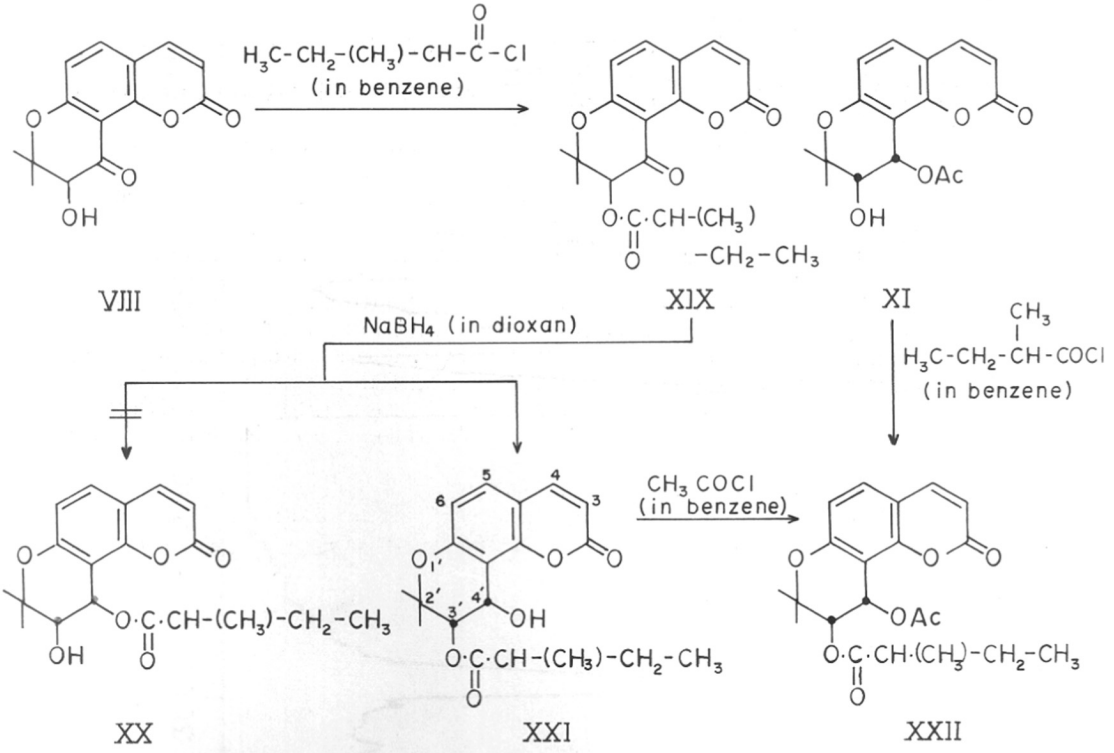


FIG. 16. IR SPECTRUM OF (±)-CIS-SUKSDORFIN (XVIII).

In order to synthesise (±)-cis-dihydropteryxin (Ic) by similar procedure from the ketoalcohol VIII, the latter was esterified with α-methylbutyryl chloride by refluxing in benzene. The structure of the resulting ester XIX [(±)-cis-3′-α-methylbutyryloxy-4′-keto-3′,4′-dihydroseselin], m.p. 116-18°, was fully supported by its infrared (Fig.17), ultraviolet and PMR (Fig.18) spectra. As expected its ultraviolet spectrum was similar to that of IX and XVI (λ_{max}. 349, 337, 304, 266, 240 and 217 mμ; log ε 3.98, 3.99, 4.04, 3.97 and 4.06 respectively) and in PMR spectrum the signal due to the proton at 3′ position appeared at 334 cps (1H, singlet).



FIG·21

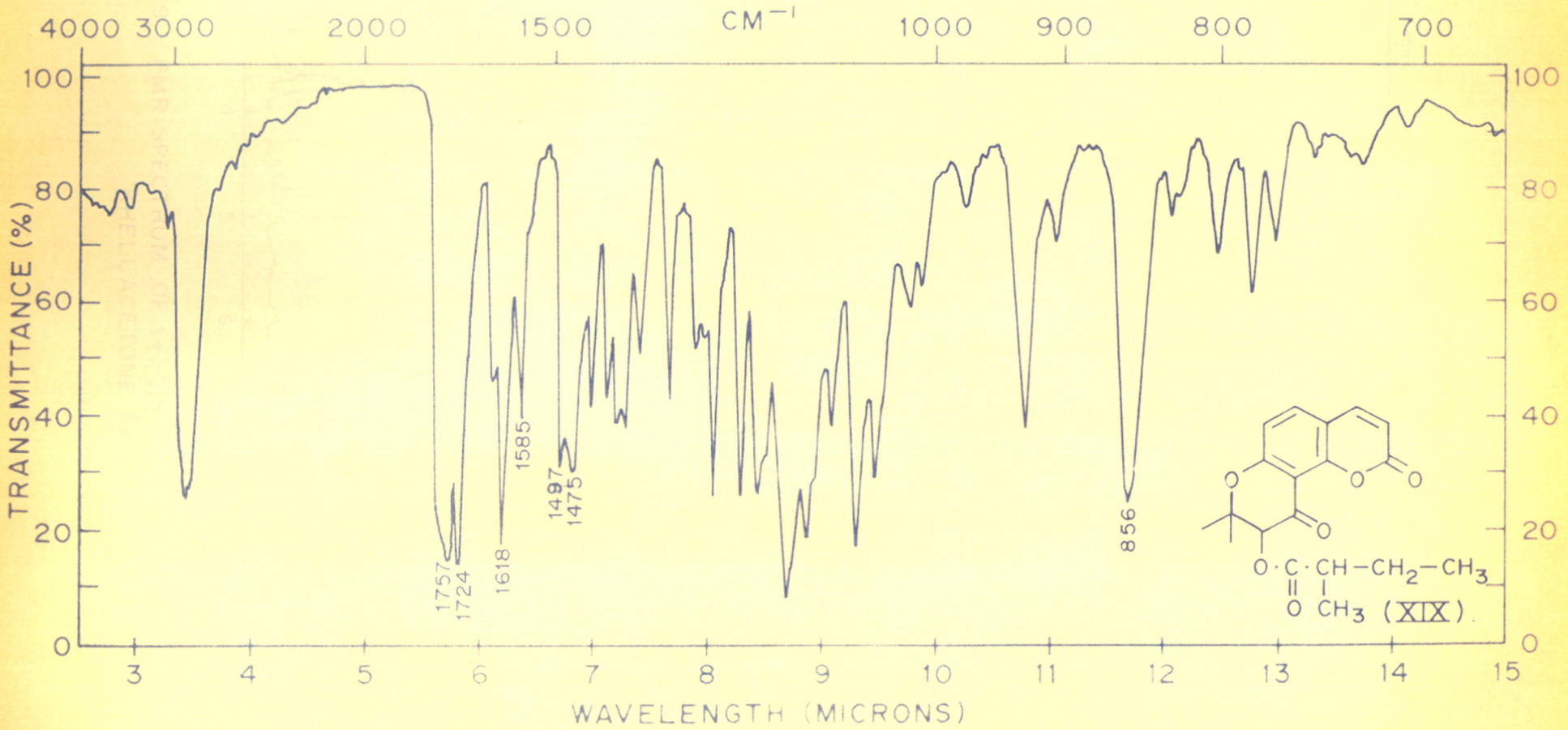


FIG. 17. IR SPECTRUM OF (±)-3'-α-METHYLBUTYRYLOXY-4'-KETO--3',4'-DIHYDROSESELIN (XIX)

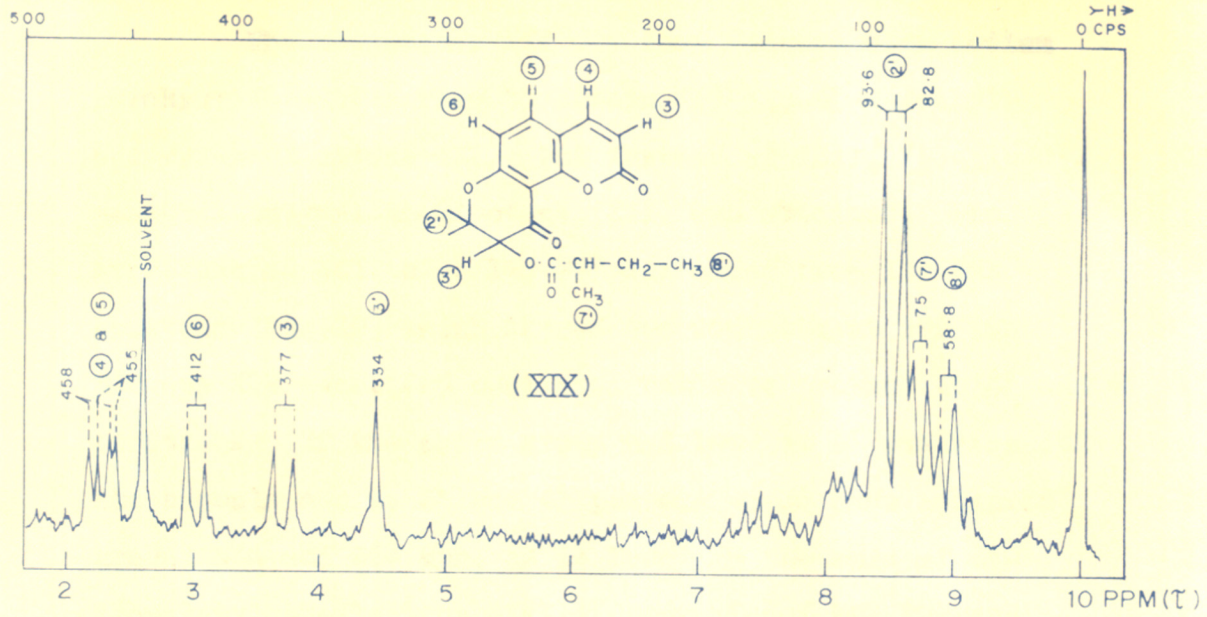


FIG. 18. PMR SPECTRUM OF (±)-3'-α-METHYL-BUTYRYLOXY--4'-KETO-3',4'-DIHYDROSESELIN (XIX).

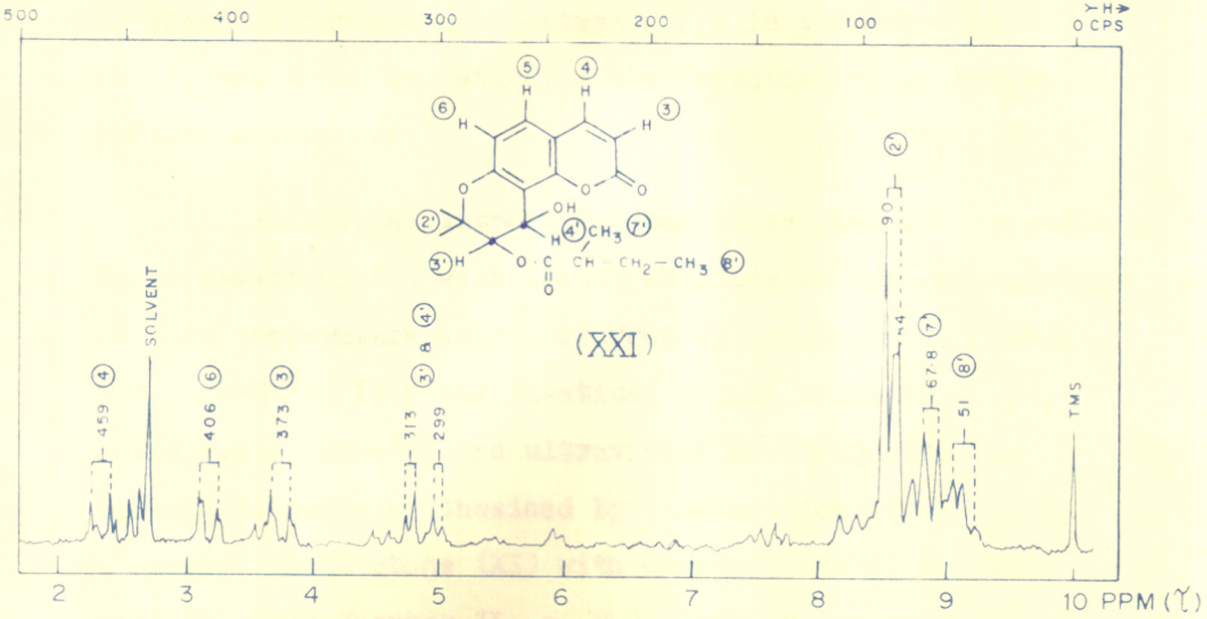


FIG. 19. PMR SPECTRUM OF (±)-CIS-3'-α-METHYLBUTYRYL-KHELLACETONE (XXI).

The keto-ester XIX was then reduced with sodium borohydride with a view to obtain (±)-cis-4'-∝-methyl-butyryl-khellactone (XX), but instead of this, (±)-cis-3'-∝-methyl-butyryl-khellactone (XXI) was obtained. The structure of XXI, m.p. 176-78° was clear from its PMR spectrum (Fig.19) which showed two doublets at 299 and 313 cps (1H each, J=6 cps) assignable to protons at 3' and 4' positions. If the ester group had been at 4' position (IX) the signals due to 3' and 4' protons would have appeared around 244 and 388 cps, as is found in the case of 4'-isovaleryl khellactone (XVII). Infrared (Fig.20) and ultraviolet spectra of XXI are in full agreement with its structure. Evidently, there was no acyl migration during the sodium borohydride reduction of XIX. This may be due to steric hindrance of ∝-methyl group in the ester side chain, which may be retarding the formation of an intermediate orthoester.[8]

Additional support for the above fact was obtained by treatment of XXI with acetyl chloride in benzene solution at room temperature which afforded (±)-cis-visnadin (XXII), m.p. 152-54°. This was identical in all respects (m.p., mixed m.p., infrared and ultraviolet spectra) with the (±)-cis-visnadin synthesised by condensation of (±)-cis-4'-acetyl-khellactone (XI) with ∝-methylbutyryl chloride (Fig.21, vide Chapter II, p. 70). Thus it has not been possible for us to synthesise dihydropteryxin at present, but the problem is receiving our further attention.

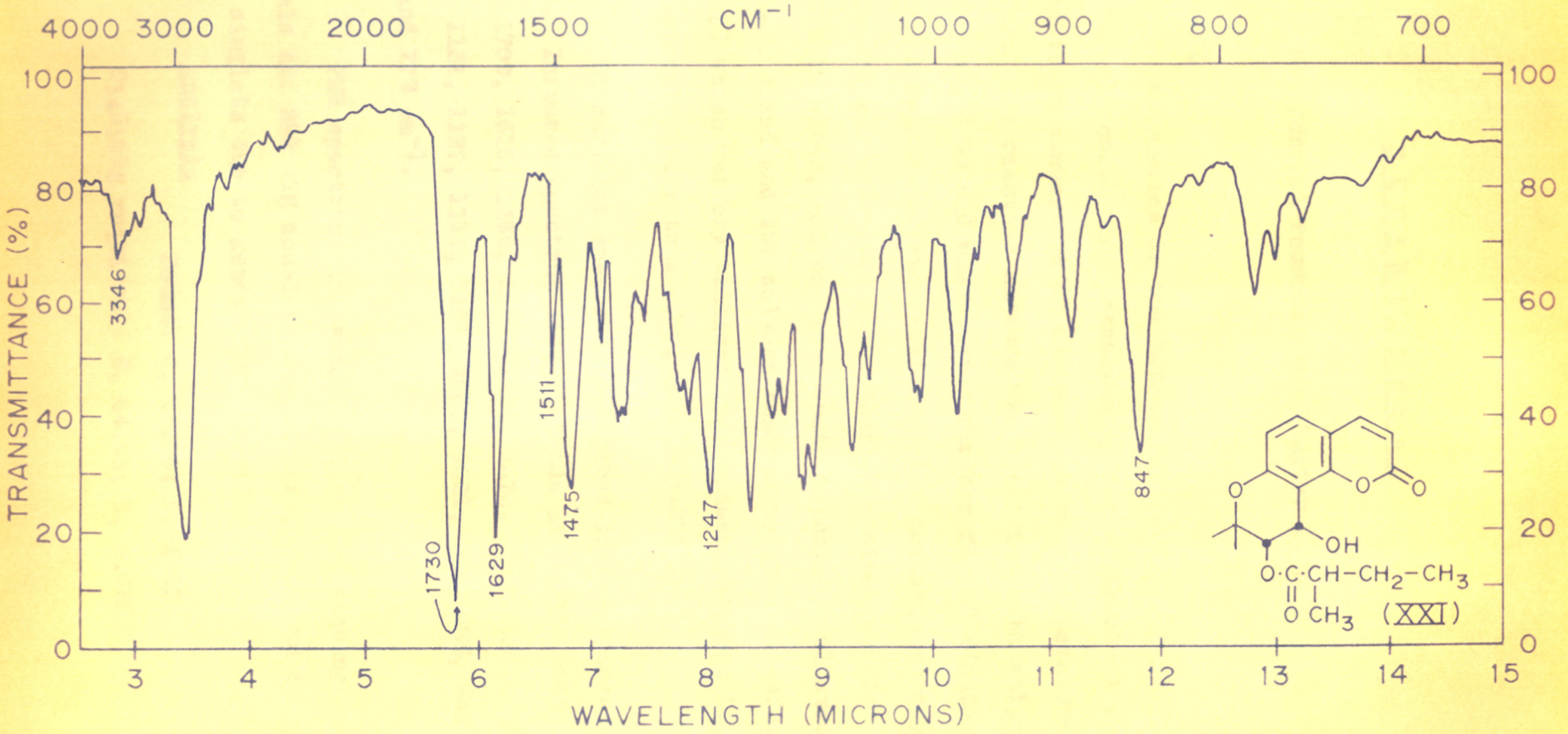


FIG. 20. IR SPECTRUM OF (±)-CIS-3'-α-METHYLBUTYRYL-KHELLACTONE (XXI).

EXPERIMENTAL

For general remarks vide Chapter I, p. 39 .

Compound V

A suspension of the ketoacetate III (2.05 g) in water (60 ml) containing potassium hydroxide (3.30 g) was stirred in an atmosphere of nitrogen at room temperature for 4 hr. The reaction mixture was acidified with sulphuric acid (25 ml; 4 N) and was stirred further for 45 minutes for ensuring complete relactonization of the coumarin moiety. The product was extracted with ether; the ether extract washed with water, sodium bicarbonate solution, followed by water, dried and the solvent removed to give a residue (0.61 g) which was crystallised from benzene-acetone to give colourless crystals of V, m.p. 196-200°.

Ultraviolet spectrum: (described in the theoretical part). Infrared spectrum (Fig.1): bands at 3367, 2967, 2899, 1727, 1709, 1616, 1562, 1456, 1404, 1376, 1348, 1299, 1259, 1235, 1151, 1127, 1111, 1101, 1066, 1021, 917, 885, 847, 800 and 772 cm^{-1}.

PMR spectrum (in pyridine, after D_2O exchange) signals at: 382 (1H doublet, J = 10 cps), 75.6 and 69 cps (6H, singlets due to gemdimethyl group)

Analysis

Found: C, 65.00; H, 5.16.

$C_{14}H_{12}O_5$ requires: C, 64.61; H, 4.65%.

Isovaleryl ester of compound V

Isovaleryl chloride (0.30 g) in dry benzene (10 ml) was added to a suspension of the [illegible] compound V (0.51 g) in dry benzene (80 ml). The mixture protected by $CaCl_2$ guard tube was refluxed on a steam bath under an atmosphere of nitrogen for 50 hr. The course of reaction was followed by TLC on silicic acid. The reaction mixture was cooled diluted with benzene, washed with sodium bicarbonate solution, then water, dried overnight and the solvent removed to afford a residue (0.65 g) which was chromatographed over silicic acid.

CHROMATOGRAM

Wt. of compound 0.65 g.
Wt. of silicic acid 16.0 g.

Fr.	Solvent	Ratio by volume	Volume of eluate	Wt. of fraction (g)	Remarks
1	Pet.ether	100%	300	-	
2	Pet.ether-benzene	50:50	300	0.030	Rejected
3	Benzene	100%	300	0.010	
4	Benzene-ether	90:10	300X4	0.580	Isovaleryl ester of V
5	Ether	100%	300	0.020	Rejected

Fraction 4 containing isovaleryl ester of V was crystallised from petroleum ether-benzene to afford colourless needles, m.p. 155-57°, $(\alpha)_D \pm 0^\circ$ (c, 4.1). Ultraviolet spectrum: $\lambda_{max.}$ 345, 308, 268 and 250 mμ (log ε 3.81, 4.03, 4.05 and 4.09 respectively). Infrared spectrum: bands at 1754, 1639, 1590, 1493, 1405, 1399, 1353, 1311, 1264, 1252, 1244, 1176, 1157, 1157, 1136, 1081, 1070, 1043, 969, 923, 891, 869, 853, 830, 787 and 729 cm^{-1}. PMR spectrum (Fig.2 in $CDCl_3$) doublets at 463 cps (2H, J=10 cps), 418 cps (1H, J = 8 cps) and 380 cps (1H, J = 9 cps); singlets at 133 cps (2H, due to $-C(=O)-CH_2-$ group), 73 and 66 cps (6H, gemdimethyl group); and a doublet at 58.2 cps (6H, J=6 cps, due to $-CH<^{CH_3}_{CH_3}$ group).

Analysis

Found: C, 66.03; H, 5.74.

$C_{19}H_{20}O_6$ requires: C, 66.27; H, 5.85%.

(±) -3'-Hydroxy-4'-keto-3',4'-dihydroseselin (VIII)

Hydrochloric acid (2 ml conc. acid + 6 ml water) was added to a solution of the ketoacetate III (3.9 g) in dioxan (140 ml) and the mixture stirred at room temperature under an atmosphere of nitrogen for 24 hr. The solvent was flashed off under reduced pressure at room temperature and the product was extracted with large excess of ether. The ether extract was washed with water, sodium

bicarbonate solution, followed by water, dried and the solvent removed to give a residue (3.2 g) which on crystallisation from benzene yielded pale yellow needles of the keto alcohol VIII, m.p. 212-16°.

Ultraviolet spectrum(described in the theoretical part). Infrared spectrum (Fig.3): bands at 3448, 2941, 1748, 1708, 1613, 1562, 1497, 1471, 1437, 1381, 1361, 1316, 1258, 1242, 1227, 1176, 1143, 1124, 1111, 1079, 1010, 975, 930, 917, 958, 819, 800, 781, 771 and 724 cm^{-1}.

PMR spectrum (in pyridine and acetone, after D_2O exchange): doublets at 461 and 459 cps (2H, J = 10 cps, due to protons at 4 and 5), 410 and 376 cps (1H each, J = 9 cps, due to protons at 6 and 3 respectively) and singlets at 276 cps (1H, due to proton at 3'), 95 and 84 cps (6H, due to gemdimethyl group at 2').

Analysis

Found: C, 65.02; H, 4.85.

$C_{14}H_{12}O_5$ requires: C, 64.61; H, 4.65%.

(±)3'-Acetoxy-4'-keto-3',4'-dihydroseselin(IX)

Acetyl chloride (0.15 g) was added to a solution of the ketoalcohol VIII (0.10 g) in benzene (30 ml) and the mixture was kept at room temperature for 3 days. The reaction product was worked up in the usual manner to

furnish a residue (0.11 g), which was subjected to preparative layer chromatography on silicic acid [carried out in the usual manner using benzene-ethyl acetate (1:1) as a developing solvent] and then was crystallised from benzene to afford colourless needles, m.p. 154-56°. Ultraviolet spectrum (described earlier). Infrared spectrum (Fig.6): bands at 1764, 1733, 1704, 1613, 1572, 1490, 1471, 1433, 1408, 1374, 1302, 1241, 1205, 1176, 1149, 1130, 1106, 1075, 925, 853, 837, 784, 769 and 743 cm^{-1}.

PMR spectrum (Fig.5): doublets at 459 and 457 cps (2H J = 10 cps, due to protons at 4 and 5), 413 and 379 cps (1H each, J = 9 cps, due to protons at 6 and 3 respectively) and singlets at 333 cps (1H due to proton at 3'), 134 cps (3H, due to $-O-\overset{\overset{O}{\|}}{C}-CH_3$ group), 95 and 84 cps (6H, due to gemdimethyl group at 2').

Analysis

Found: C, 63.05; H, 5.26.

$C_{16}H_{16}O_6$ requires: C, 63.15; H, 5.30%.

Sodium borohydride reduction of the ketoacetate IX

To a cooled (2-5°) stirred solution of the ketoacetate IX (94 mg) in aqueous dioxan (80%; 5 ml) a solution of sodium borohydride (18 mg) in aqueous dioxan (1 ml) was added during a period of 5 minutes and the resulting

mixture was stirred for a further period of 25 minutes at the same temperature. The product was made slightly acidic (pH 4.5) and worked up in the usual manner to give a residue (90 mg) which was purified by preparative layer chromatography and through crystallisation from benzene to furnish colourless crystals of (±) -cis-4'-acetyl-khellactone (XI), m.p. 183-86°, which remained undepressed on admixture with an authentic sample obtained by sodium borohydride reduction of the keto acetate III (vide Chapter II, p. 73). Infrared (Fig.8), ultraviolet and PMR spectra of both the samples were identical.

Analysis

Found: C, 62.96; H, 5.28.

$C_{16}H_{16}O_6$ requires: C, 63.15; H, 5.30%.

(±)-3'-Isovaleryloxy-4'-keto-3',4'-dihydroseselin(XVI)

The ketoalcohol VIII (0.66 g, in benzene (90 ml) was esterified with isovaleryl chloride (0.50 g) by usual procedure. The reaction product was chromatographed on silica gel (22 g). Benzene ether mixture (95:5, 600 ml) eluted crude ester (0.750 g) which on crystallisation from petroleum ether-benzene mixture afforded colourless needles of XVI, m.p.122-24°.

Ultraviolet spectrum (Fig.12): $\lambda_{max.}$ 348, 337, 307, 268, 243 and 218 mμ (log ε 3.99, 4.01, 4.05, 3.99, 4.06 and 4.12 respectively).

Infrared spectrum (Fig.11): bands at 1754, 1718, 1608, 1575, 1471, 1439, 1385, 1351, 1304, 1285, 1250, 1215, 1190, 1176, 1136, 1124, 1110, 1078, 1059, 918, 850, 787 and 728 cm^{-1}.

PMR spectrum (Fig.13 in $CDCl_3$): doublets at 458 and 455 cps (2H, J = 10 cps, due to protons at 4 and 5), 412 and 379 cps (1 H each, J = 9 cps, due to protons at 6 and 3 respectively), singlets at 334 cps (1H, due to proton at 3') 140 cps (2H, due to $-\overset{\overset{O}{\|}}{C}-CH_2-$group); 94 and 72 cps (6H, due to gemdimethyl group at 2') and a doublet at 62.4 cps (6H, J= 6 cps, due to $-CH\lessdot^{CH_3}_{CH_3}$ group).

Analysis

Found: C, 66.74; H, 5.99.

$C_{19}H_{20}O_6$ requires: C, 66.27; H, 5.85%.

(±) -cis-4'-Isovaleryl-khellactone (XVII)

The ketoester XVI (0.270 g) in aqueous dioxan (80%; 15 ml) was reduced with sodium borohydride (0.051 g) by the procedure described earlier. The product (0.26 g) was purified by column chromatography over silicic acid.

CHROMATOGRAM

Wt. of compound 0.26 g.
Wt. of silicic acid 7.0 g.

Fr.	Solvent	Ratio by volume	Volume of eluate (ml)	Wt. of fraction (g)	Remarks
1	Pet.ether	100%	200	-	-
2	Pet.ether-benzene	50:50	200	-	-
3	Benzene	100%	200	0.005	Rejected
4	Benzene:ether	93:7	200x2	0.010	
5	Benzene:ether	75.25	200x3	0.196	(+)cis-4' isovaleryl khellactone
6	Benzene:ether	50:50	200x2	0.030	
7	Ether	100%	200	0.010	Rejected

Fraction 5 containing (+)-cis-4'-isovaleryl-khellactone (XVII) was crystallised from ether to give colourless crystals, m.p.165-68°, Ultraviolet spectrum (Fig.12) $\lambda_{max.}$ 326, 258, 248 and 214 mμ (log ε 4.11, 3.47, 3.50 and 4.08 respectively).

Infrared spectrum (Fig.15): bands at 3472, 1745, 1721, 1626, 1504, 1475, 1418, 1379, 1295, 1269, 1250, 1225, 1192, 1168, 1153, 1133, 1117, 1693, 1072, 1020, 1012, 990,

938, 960, 862, 848, 785, 775 and 767 cm^{-1}.

PMR spectrum (Fig.14, in $CDCl_3$, after D_2O exchange): doublets at 458, 443, 410 and 376 cps (1H each, J= 9.10 cps due to protons at 4,5,6 and 3 respectively), 388 and 244 cps (1H each J = 5 cps due to protons at 4' and 3' respectively); singelet at 139 cps (2H, due to $-\overset{\overset{O}{\|}}{C}-CH_2-$group) and doublets at 87 cps (6H, due to gemdimethyl group at 2') and 61 cps (6H, J = 6 cps, due to $-CH<\begin{matrix}CH_3\\CH_3\end{matrix}$ group).

Analysis

Found: C, 65.55; H, 6.54.

$C_{19}H_{22}O_6$ requires: C, 65.88; H, 6.40%.

(±)-cis-Suksdorfin (XVIII)

(±)-cis-4'-Isovaleryl-khellactone (XVII, 0.105 g) in benzene(10 ml) was acetylated with acetyl chloride (0.150 g) by usual procedure. The product (0.122 g) was subjected to column chromatography over silicic acid benzene-ether mixture (95: 5, 250 ml) eluted (±)-cis-suksdorfin which was crystallised from ethanol-water and petroleum ether to give colourless crystals, m.p. 134-36°. Ultraviolet spectrum (Fig.12); λmax. 324, 299, 256, 245, and 213 mμ (log ε 4.10, 3.90, 3.52, 3.58 and 4.13 respectively).

Infrared spectrum (Fig.16): bands at 1754, 1623, 1606, 1475, 1410, 1382, 1297, 1233, 1163, 1119, 1099,

1076, 1027, 1005, 956, 934, 909, 895, 869, 843, 826, 816, and 781 cm^{-1}.

PMR spectrum (in CCl_4) doublets at 453, 439, 400 and 370 cps (1H each, J = 8-9 cps, due to protons at 4,5,6 and 3 respectively), 387 and 314 cps (1H each, J=5 cps, due to protons at 4' and 3' respectively); singlets at 131, 124 cps (6H, due to -C(=O)-CH_2- and -C(=O)-CH_3 groups), 85.2 cps (6H, due to gemdimethyl group at 2') and a doublet at 59 cps (6H, J= 6 cps, due to -CH$<^{CH_3}_{CH_3}$ group).

Analysis

Found: C, 64.78; H, 6.11.

$C_{21}H_{24}O_7$ requires: C, 64.95; H, 6.23%.

(±)-3'-α-Methylbutyryloxy-4'-keto-3',4'-dihydroroseselin (XIX)

The keto alcohol VIII (0.82 g) in benzene (120 ml) was esterified with α-methylbutyryl chloride (0.61 g) by the usual procedure. The reaction product (1.01 g) was chromatographed over silicic acid (26 g); benzene-ether mixture (95:5; 900 ml) eluted the ester (XIX, 0.98 g) which on crystallisation from petroleum ether-benzene afforded colourless needles, m.p. 116-18°.

Ultraviolet spectrum (in ~~CDCl3~~): λ_{max}. 349, 337, 304, 266 and 240 mμ (log ε 3.98, 3.99, 4.04, 3.97 and 4.06 respectively).

Infrared spectrum (Fig.17): bands at 1757, 1724, 1618, 1585, 1497, 1475, 1439, 1410, 1395, 1381, 1353, 1314,

1271, 1248, 1214,1190, 1153, 1133, 1105, 1075, 1058, 1027, 1016, 978, 928, 906, 856, 830, 803, 784, 771, 751, 727 and 708cm^{-1}.

PMR spectrum (Fig.18, in $CDCl_3$): signals at 458, 455 cps (1H each, doublets J = 10 cps, due to protons at 4 and 5), 412 and 377 cps (1H each, doublets J = 9 cps, due to protons at 6 and 3 respectively), 333 cps (1H singlet, due to proton at 3'), 93.6 and 82.8 cps (3H each, singlets, due to gemdimethyl group at 2'), 75 cps(3H, doublet, J = 7 cps, due to CH_3-CH< grouping) and 58.8 cps (3H, triplet, due to CH_3-CH_2- grouping).

Analysis

Found: C, 66.28; H, 5.78.

$C_{19}H_{20}O_6$ requires: C, 66.27; H, 5.85%.

(±)-cis-3'-α-Methylbutyryl-khellactone (XXI)

The ketoester XIX (0.44 g) in aqueous dioxan (80%; 25 ml) was reduced with sodium borohydride (0.084 g) by the procedure described earlier. The product (0.43 g) was chromatographed over silicic acid (12 g). Benzene-ether mixture (75:25, 500 ml) eluted XXI which was crystallised from ether to give colourless crystals, m.p. 176-78°.

Ultraviolet spectrum: $\lambda_{max.}$ 324, 258, 246, 219, and 213 mμ (log ε 4.09, 3.47, 3.50, 4.06 and 4.09 respectively). Infrared spectrum (Fig.20): bands at 3546, 2959, 2907, 1730, 1629, 1511, 1475, 1416, 1389, 1379, 1344, 1294, 1279, 1247,

1193, 1170, 1157, 1133, 1119, 1079, 1062, 1020,1012, 980, 936, 893, 847, 781, 769 and 756 cm^{-1}.

PMR spectrum (Fig.19, in CDCl3): doublets at 459 406 and 373 cps (1H each, J = 8-9 cps due to protons at 4,6 and 3 respectively, the absorption due to proton at 5 being merged into solvent absorption), 313 and 299 cps (1H each, J=5 cps, due to protons at 4' and 3'); singlets at 90 and 84 cps (6H, due to gemdimethyl group at 2'); a doublet at 67.8 cps (3H, J = 7 cps, due to CH_3-CH<-group), and a triplet at 51 cps (3H, due to CH_3-CH_2-group).

Analysis

Found: C, 65.98; H, 6.52.

$C_{19}H_{22}O_6$ requires: C, 65.88; H, 6.40%.

Acetylation of (±)-cis-3-α-methylbutyryl-khellactone (XXI)

The alcohol ester XXI (0.16 g) in benzene (15 ml) was acetylated with acetyl chloride (0.20 g) by usual procedure. The product was chromatographed over silicic acid (6 g). Benzene-ether mixture (95:5, 250 ml) eluted (±)-cis-visnadin (XXII; 0.17 g) which was crystallised from ethanol-water and petroleum ether to give colourless needles, m.p. and mixed m.p. with (±)-cis-visnadin, prepared earlier by condensation of (±)-cis-4'-acetyl-khellactone (X) with α-methyl-butyryl chloride (vide Chapter II, p.80), 151-53°. Infrared, ultraviolet and PMR spectra of both the samples were identical.

Analysis

Found: C, 65.05; H, 6.40.

$C_{21}H_{24}O_7$ requires: C, 64.95; H, 6.23%.

REFERENCES

1. T.G. Call, Ph.D. thesis, University of Minnesota, 1956.
2. T.G. Call and J. Green, Proc.Montana Acad.Sci., 16, 49 (1956).
3. R.E. Willette and T.O. Soine, J.Pharm.Sci., 51 (2), 149 (1962).
4. D.P. Chakraborty and S.K. Chakraborti, Trans.Bose Res.Inst., 24 (1), 15 (1961).
5. L.M. Jackman, Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, p. 55, Pergamon Press, New York, N.Y. (1959).
6. E. Smith, N. Hosansky, W.G. Bywater and E.E. van Tamelen, J.Amer.Chem.Soc., 79, 3534 (1957).
7. J.W. Baker, Tautomerism, p. 285, George Routledge, London (1934).
8. W. Pigman, The Carbohydrates, p. 147, Academic Press, New York, N.Y. (1957).
9. B. Helferich and W. Klein, Ann., 450, 219 (1926); ibid., 455, 173 (1927).