Tetrahedron Letters, Vol. 22, No.18, pp 1715 - 1718, 1981 0040-4039/81/181718-04$02.00/0
Printed in Great Britain

CHEMICAL EXAMINATION OF NEPETA HINDOSTANA (ROTH) HAINES THE STRUCTURE OF NEPETICIN

Viqar Uddin Ahmad* and Shaheen Bano
HEJ Postgraduate Institute of Chemistry,
University of Karachi, Karachi-32/Pakistan.

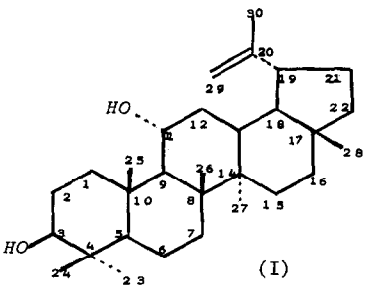
Wolfgang Voelter and W.Fuchs
Institut fur Organische Chemie, der Universitat,
Tubingen, 74 Tubingen, Auf der Morgenstelle 18,
Federal Republic of Germany.

Summary: The structure of nepeticin, a new triterpenoid isolated from Nepeta hindostana, has been determined.

Nepeta hindostana (Roth) Haines (N.O. Labiatae) is an important medicinal plant of the Indo-Pak subcontinent. It is known in the indigenous system of medicine as Badrangboya and is used to cure fever, as cardiac tonic and in sore throat.[1] Its extract is reported to lower blood cholesterol level in animals.[2]

Earlier investigators have reported the occurrence of following substances in this plant: stigmasterol, oleanolic acid, essential oils,[3] triacontane, β-sitosterol, a waxy ester, a triterpenoid alcohol named as nepetol,[4] a flavone glycoside nepitrin (nepetin glucoside),[5] flavone aglycones dinatin (hispidulin), nepetin (6-methoxyluteolin), 6-hydroxyluteolin, 7,4-O-dimethylscutellarein[6] and the sequiterpene alcohols nehipetol and nehipediol.[7]

A reinvestigation of the chemical constituents of Nepeta hindostana (Roth) Haines has led to the isolation of a new triterpenoid provisionally named as nepeticin. It crystallises from methanol as colourless needles, m.p. 215°, $[\alpha]_D^{30}$ + 22.5 (c=1, chloroform). The molecular formula, according to the high resolution mass determination of the molecular peak, is $C_{30}H_{50}O_2$. On the basis of spectroscopic and chemical studies described below, the structure of nepeticin is proposed as lup-20(29)-ene-3β,11α-diol(I).



(I)

The u.v. spectrum in methanol shows only end absorption at 208 nm. In the i.r. spectrum ($CHCl_3$) a broad hydroxyl absorption appears at 3460 cm^{-1} but no bands in the carbonyl region are visible. The bands at 1640 cm^{-1} and 885 cm^{-1} are due to the isopropenyl double bond. The n.m.r. spectrum (250 MHz) is typical of lup-20(29)-enes[8] indicating that nepeticin is a member of this class of

triterpene. The methyl singlets were present at δ 0.78, 0.79, 0.96, 0.98, 1.03 ($2xCH_3$) and 1.68 (broad s, C(20)-Me). The triplet-like signal of C(3)-α proton is centered at δ 3.2 (J=7.5 Hz). Thus from the position and shape of this signal as well as from the biogenetic point of view, it was concluded that one hydroxyl group is present as 3β. The C-11 proton signal is a hextet centered at δ 3.93 showing two diaxial (J=10.5 Hz) and one axial equatorial (J=5Hz) spin spin couplings. This clearly indicates that the second hydroxyl group is in α position. The olefinic protons of the isopropenyl group appear as two doublets at δ 4.59 and δ 4.72 (J=2.2 Hz).

The mass spectrum of nepeticin shows important peaks at m/e 442 (M^+), 427 (M^+-CH_3), 424 (M^+-H_2O), 406 (M^+-2H_2O), 391 ($M^+-CH_3-2xH_2O$), 255,237,231,216,189,175. The last two peaks show that rings D and E are not substituted[11] (Chart 1).

On acetylation with acetic anhydride and pyridine,a diacetate (m.p. 186°) was formed. This indicates that nepeticin contains two hydroxyl groups, one of which is 3β and the position of the second one remains to be established. Nepeticin cannot be oxidised with periodic acid indicating that the second hydroxyl group is not present at C-2. On stirring nepeticin in acetone, containing two drops of conc. sulphuric acid, no acetonide is formed but nepeticin is partly dehydrated to dehydronepeticin (m.p. 198°). The mass spectrum of this compound (M^+ at m/e 424) indicates that only one hydroxyl group has been eliminated as water. Its n.m.r. spectrum shows only one additional olefinic proton signal as a triplet at δ 5.26 while the signal due to 3α H is present as a broad multiplet at δ 3.2. This indicates that the other hydroxyl group, which is eliminated during the acid-catalysed dehydration, must be present at one of the following positions:5,6,9,11, 12,13,18,19,21. On Jones oxidation, a diketone (M^+ at m/e 438, m.p. 164°) was formed which does not show the u.v. absorption of 1, 3-diketones as recorded for lup-20(29)-ene-1,3-dione.[10] It showed a strong peak at 1700 cm^{-1} in the i.r. spectrum, but no peaks due to cyclopentanones or aldehydes indicating that both hydroxyl groups are secondary and the second hydroxyl group is not present in ring E. Thus the position of the second hydroxyl group is restricted to 6,11 or 12.

The melting point, mass and n.m.r. spectral data of nepeticindione closely resemble those of lup-20(29)-ene-3,11-dione (lit.[12] m.p. 262° decomp.). It may be noted here that the presence of the second hydroxyl group at C-6 would be expected to give rise to a peak at m/e 223 observed in loranthol,[13] and a deshielding of the C-23 methyl to δ 1.26 as observed in dihydrorigidinol.[14] These peaks were not observed in the mass and n.m.r. spectrum respectively of nepeticin, indicating that the second hydroxyl group is in C-11 α position. Thus nepeticin has the structure lup-20(29)-ene-3β,11α-diol.

The proposed structure is supported by the ^{13}C-nmr data of nepeticin (see Table I). The assignments were made on the basis of the known ^{13}C chemical shifts of lupeol and related compounds[14,15] as well as the observed multiplicities in the off-resonance spectrum of nepeticin. It may be noted that the compounds containing the lup-20(30)-ene skeleton generally show a peak at about 20.9 ppm for C-11 which is shifted to 70.46 ppm in nepeticin due to the presence of a hydroxyl group at this carbon atom.

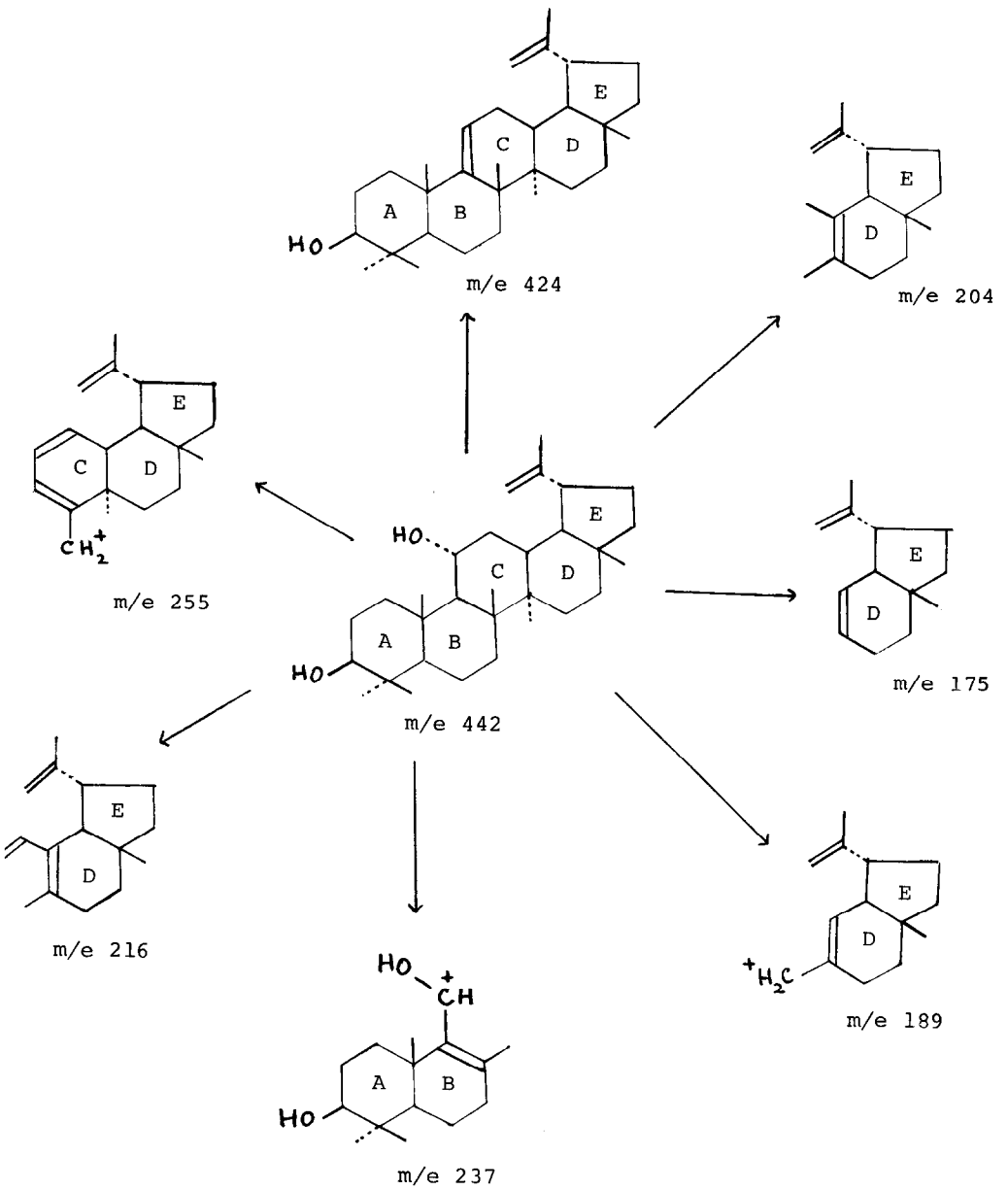


CHART - I

ACKNOWLEDGEMENT

To express their sincere thanks to Dr. E.L.Ghisalberti for the U.V., I.R., and ^{1}H-NMR spectra of lup-20(29) ene-3,11-dione.

The supply of plant material by the Hamdard Foundation is gratefully acknowledged. Thanks are also due to Pakistan Science Foundation for a financial award.

REFERENCES

1. *R.N.Chopra, S.L.Nayar, I.C.Chopra, Glossary of Indian Medicinal Plants, Council of Scientific and Industrial Research, New Delhi (1956), 0.175.*
2. *Hakim Mohammad Said (Editor), Hamdard Pharmacopoeia of Estern Medicine, Hamdard Foundation Karachi (1969) p.446.*
3. *K.W.Gopinath, C.Prakash, A.R.Kidwai, J.Sci.Ind.Res. (India) 21B, 404 (1962).*
4. *U.A.Siddiqui and A.M.Ahsan, Pak.J.Sci.Ind.Res., 10 (1) I (1967).*
5. *R.Krishnaswamy, T.R.Seshadri, P.J.Tahir, Indian J.Chem. 8 (12), 1074 (1970).*
6. *T.R.Seshadri and P.Sharma, Indian J.Chem. 11 (4), 338 (1973).*
7. *J.K.Pyrek, B.E. Marian, C.K.Atal and R.S. Sharma, Acad.Soc.Warsaw 50 (11) 1931 (1976).*
8. *J.M.Lehn and G.Ourisson, Bull.Soc.Chim.Fr. 1962, 1137.*
9. *A.K. Ganguly, T.R.Govindachlari, P.A.Mohammad, A.D.Rahimtulla and N.Viswanathan, Tetrahedron 22, 1513 (1966).*
10. *E.L.Ghisalberti, P.R.Jeffries and M.A.Sefton, Phytochem. 12, 1125 (1973).*
11. *Atta-ur-Rahman, Mohammad Ataullah Khan, Noorul Haq Khan, Phytochemistry, 12 3004 (1973).*
12. *M.Marta, F.D.Monache and G.B.Marini-Bettolo, Gazz.Chim.Ital. 109, 61 (1979).*
13. *E.Wenkert, G.V.Baddeley, I.R.Burfitt and L.N.Moreno, Org.Mag.Res. 11 (7) 337 (1978).*
14. *M.Sholichin, K.Yamasaki R.Kasai, and O.Tanaka,Chem.Pharm.Bull 28(3), 1006 (1980).*

TABLE - I

^{13}C-nmr chemical shifts in ppm of nepeticin (I) in $CDCl_3$. (TMS 0.00 ppm). 66237 scans.

Carbon No.	Chemical shift	Carbon No.	Chemical shift
C-1	39.03	C-16	35.51
C-2	27.50	C-17	43.01
C-3	78.59	C-18	47.73
C-4	39.43	C-19	47.73
C-5	55.62	C-20	150.20
C-6	18.11	C-21	29.88
C-7	35.33	C-22	39.88
C-8	41.07	C-23	28.29
C-9	55.74	C-24	15.55
C-10	37.72	C-25	16.14
C-11	70.46	C-26	17.26
C-12	27.72	C-27	14.53
C-13	37.72	C-28	18.11
C-14	42.61	C-29	109.79
C-15	27.50	C-30	19.42

(Received in UK 20 February 1981)