Tetrahedron Letters, Vol.22, No.28, pp 2685 - 2688, 1981
Printed in Great Britain

0040-4039/81/282685-04$02.00/0

THE STRUCTURE OF VEPRISINIUM SALT

J. Foyere Ayafor, B.L. Sondengam and B.T. Ngadjui
Department of Organic Chemistry, University of Yaounde, Yaounde, Cameroon.

Summary : The structure of a new quaternary dihydrofuroquinoline alkaloid, veprisinium salt, isolated from Vepris louisii and possessing antibacterial activity, has been determined from spectroscopic and chemical data and confirmed by partial synthesis.

There has been considerable interest in the dihydrofuroquinoline alkaloids of the Rutaceae. Of particular significance is the work of Grundon and collaborators on the determination of the absolute configuration of these alkaloids by asymmetric synthesis[1-3] and that of Rideau et al[4] on the biological activity of some members of this group. We report herein the isolation and structure determination of a new antibacterial quaternary dihydrofuroquinoline designated as veprisinium salt from the trunk bark of Vepris louisii G. Gilbert (Rutaceae).

The aqueous methanolic extract after extraction with chloroform was acidified to pH 2 (5%HCl) and treated with a solution of Mayer's reagent[5]. The precipitated alkaloidal complex was converted to the alkaloid hydrochlorides mixture with Amberlite IRA 400 in the chloride form. Purification of the quaternary salts by Si gel column chromatography afforded veprisinium chloride 1 as an amorphous powder (0.2% dry weight) $(\alpha)_D^{21}$-14.2° (MeOH). 1 was further characterised as the iodide, (needles from MeOH-ether), m.p. 126-127°, $(\alpha)_D^{21}$-12.2° (MeOH), and the perchlorate, m.p. 171-172° (needles from MeOH-ether), $(\alpha)_D^{21}$-11.8° (MeOH). Elemental analysis for the iodide and perchlorate of veprisinium 1 agreed with the empirical formula $C_{18}H_{24}NO_5$ for the cation.

The i.r. spectrum of veprisinium perchlorate 1 had absorptions at νmax 3495, 1630, 1600, 1500 and 800 cm^{-1} indicating the presence of a hydroxyl,

an $=\overset{+}{N}$-Me and an aromatic system. The u.v. spectrum, λ_{max}^{MeOH} (εmax) : 205 (24,700), 222 (46,700), 255 (49,500) and 327 nm (15,400), was very similar to that of O-methylhydroxyluninium chloride 2[6]. The ^{1}HNMR spectrum of 1 (perchlorate) in DMSO-d_6 was well-resolved and showed signals for two geminal methyl groups attached to an oxygen-bearing carbon atom (δ 1.20 and 1.33), three methoxyl groups represented by singlets at δ 3.87, 3.91 and 4.2, an $=\overset{+}{N}$-Me group (δ 4.45), an isolated -CH-CH_2-moiety represented by a two proton doublet (J8Hz) at δ 3.90 coupled to a one-proton triplet (J8Hz) at δ 5.20 and two ortho-coupled aromatic protons (δ 7.98 and 7.60 (1H doublets, J9Hz)). The chemical shift, δ 7.98, of the down-field doublet indicated that one of the aromatic protons was at C-5[6]. Finally, a one-proton sharp singlet at δ 4.98 which disappeared on deuteriation was assigned to an OH group. Lack of splitting of this signal eliminated the possibility of the isomeric dihydropyrano structure 3 for veprisinium salt. The above spectral data suggested structure 1, 2-(1-hydroxy-1-methylethyl)-4,7,8-trimethoxy-9-methyl-2,3-dihydrofuro [2,3-b] quinolinium for veprisinium salt.

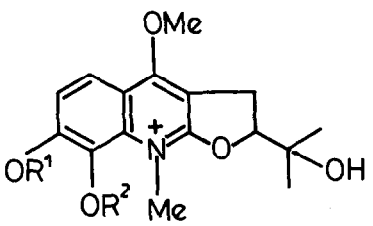
Structure 1 was readily confirmed by partial synthesis. N-methylpreskimmianine 4[7] in ter-butyl alcohol containing concentrated sulphuric acid was stirred with meta-chloroperbenzoic acid at 25° following the synthesis of O-methylbalfourodinium salt by Clarke and Grundon[8]. Work-up in the usual manner followed by treatment of the resulting persulphate with perchloric acid afforded the racemic veprisinium perchlorate almost quantitatively, m.p. 201-203° (needles from MeOH-Ether), whose i.r. spectrum was superimposable on that of the natural product.

The structure 1 was further confirmed by chemical reactions. Dequaternisation of the iodide with anhydrous pyridine at 80°[9] gave the laevorotatory 4-quinolone 5, (prisms from EtOAc), m.p. 173-175° $(\alpha)_D^{21}$-56.6° (MeOH), m/e 319 (M^+) and other prominent ion fragments at m/e 304, 286, 276, 248 and 232. The i.r., u.v. and ^{1}HNMR spectra were consistent with structure 5. Treatment of veprisinium perchlorate 1 with 2N NaOH on the other hand yielded a dextrorotatory 2-quinolone 6, m.p. 127-128°, $(\alpha)_D^{21}$+19.5° ($CHCl_3$) identical (u.v., ms, ^{1}Hnmr, i.r.) with racemate 6, m.p. 114-116° prepared by oxidation of N-methylpreskimmianine 4 with meta-chloroperbenzoic acid followed by extraction with NaOH (2N)[10].

The CD spectrum of veprisinium chloride 1 in EtOH with $(\theta)_{304}$ + 11,070, (θ_{252} + 12,900 and $(\theta)_{216}$ - 32,000 has the same sign with that of (S)-O-methylhydroxyluninium chloride 2[6] and thus shows that 1 has the absolute configuration S. Though this assignment is supported by the signs of rotation

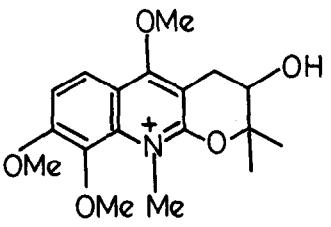
of the two degradation products of 1, viz : the 4-quinolone 5 and the 2-quinolone 6 (compare with the signs of rotation of the corresponding quinolones obtained from (R)-platidesminium salt[11]), a more direct determination by asymmetric synthesis is desirable for confirmation. The assigned S configuration however does not agree with the proposed general stereochemical correlation of aromatic hemiterpenoids[12].

Veprisinium chloride exhibited growth inhibitory activity against staphilococcus aureus at 200µg using the biodisc method but was totally inactive against Escherichia coli.

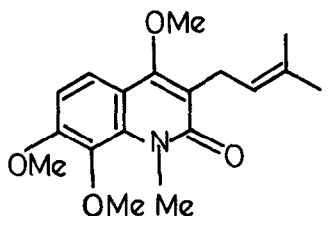


1. $R^1 = R^2 = Me$

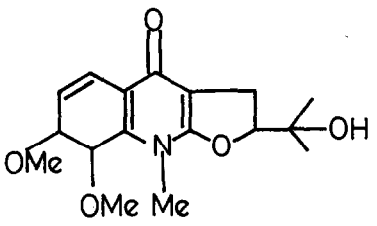
2. $R^1 + R^2 = CH_2$



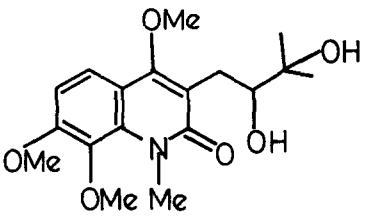
3



4



5



6

Acknowledgement : The authors are grateful to Professor Ola Sköld, Department of Pharmaceutical Microbiology, University of Uppsala for antibacterial tests, Dr. Peter Ekman, Department of Pharmaceutical Biochemistry for the CD curve of 1 and the International Foundation for Science, Stockholm for a research grant (N°443) to J.F.A.

REFERENCES

1. M.F. Grundon and S.A. Surgenor, J.C.S. Chem. Comm., 624 (1978).
2. J.F. Collins and M.F. Grundon, J.C.S. Perkin I, 161 (1973).
3. M.F. Grundon, (1979), the Alkaloids (Edited by R.H.F. Manske and R.G.A. Rodrigo), Vol. XVII, page 105, Academic Press.
4. M. Rideau, C. Verchère, P. Hibon, J-C. Chenieux, P. Maupas and C. Viel, Phytochemistry, 18, 155 (1979).
5. W. Jordan and P.J. Scheuer, J. Chrom., 19, 175 (1965).
6. L.A. Mitscher, M.S. Bathala, G.W. Clark and J.L. Beal, Lloydia, 38, 109 (1975).
7. J.F. Ayafor, B.L. Sondengam and B.T. Ngadjui, Tetrahedron Letters, 21, 3293 (1980).
8. E.A. Clarke and M.F. Grundon, J. Chem. Soc., 4196 (1964).
9. R.A. Corral and O.O. Orazi, Tetrahedron, 21, 909 (1965).
10. R.M. Bowman, J.F. Collins and M.F. Grundon, J.C.S. Perkin I, 626 (1973)
11. D.R. Boyd and M.F. Grundon, J.C.S. Perkin I, 556 (1970).
12. M.F. Grundon and I.S. Mc Coll, Phytochemistry, 14, 143 (1975).

(Received in UK 15 April 1981)