Phytochemistry 1974 Vol 13 pp 2815 to 2818 Pergamon Press Printed in England

A NEW VALEPOTRIATE: 7-*EPI*-DEACETYLISOVALTRATE FROM *VALERIANA OFFICINALIS*

S. POPOV, N. HANDJIEVA and N. MAREKOV

Institute of Organic Chemistry, Bulgarian Academy of Sciences, Sofia 13, Bulgaria

(*Received* 22 *February* 1974)

Key Word Index—*Valeriana officinalis*, Valerianaceae; valepotriates, 7-*epi*-deacetylisovaltrate, didrovaltrate

Abstract—A new valepotriate (VII) has been isolated from *Valeriana officinalis* roots and its structure and stereochemistry determined Comparison with didrovaltrate is made and a correction of its C-1 configuration proposed

INTRODUCTION

A NUMBER of ester iridoids, named Valepotriates, have been previously isolated[1,2] from the roots of some Valeriana species. Valtrate (**1**) and didrovaltrate (**2**) are the principal compounds. Recently we isolated[3] from *V. officinalis* a number of new valepotriates, containing chlorine, namely valechlorine (**3**) and valeridine.

We now report on the isolation from *V. officinalis* of a further two new valepotriates

RESULTS AND DISCUSSION

Compound A_1 is a colourless oil with $[\alpha]_D^{20°}$ +35° (MeOH). Its UV spectrum (EtOH) is similar to that of valtrate (maxima at 212 nm and 254 nm) indicating the presence of the same chromophore (**4**). This similarity was also observed in its IR spectrum with maxima at 1770 cm^{-1} (ester at C-1), 1740 cm^{-1} (ester) 1610 and 1640 cm^{-1} (conjugated double bonds). The ester maximum at 1700 cm^{-1} was less intense than that in the spectrum of valtrate. Also the maximum at 1250 cm^{-1} (acetyl) was not present but a maximum at 3500 cm^{-1} (OH) was present. The absence of an acetyl group was confirmed by hydroxylaminolysis;[1] TLC of the product showed the presence only of the isovaleric acid hydroxamic derivative. In agreement with this A_1 afforded a product identical chromatographically with valtrate on mild acetylation.

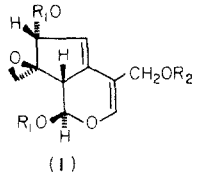
The NMR spectrum of A_1 was also similar to that of valtrate.[1] The characteristic one-proton singlet for the C-3 proton appears at δ6·55 and the one-proton doublet at δ5·8 is attributed to the proton at C-1. The one-proton doublet at δ5 65 may be assigned either to the proton at C-6 or C-7 (in valtrate these signals appear at δ5·34 and δ5·86 respectively). The C-11 protons appear at δ4·60 as a quartet, those at C-10 at δ2·80 (quartet) and those at C-9 at δ3·30 (doublet), similar to the corresponding protons of valtrate. The two isovaleryl residues are observed in the predicted region. The three-proton singlet at δ2·05 due

[1] THIES, P W (1968) *Tetrahedron* **24**, 313
[2] STAHL, E and SCHILD, W (1969) *Tetrahedron Letters* 1053
[3] POPOV, S, HANDJIEVA, N and MAREKOV, N (1973) *Compt Rend* **26**, 913

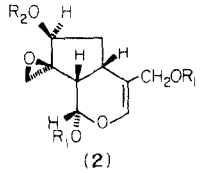
to an acetyl group is not present in agreement with the IR spectrum A new one-proton doublet however, is present at δ4·20 due to a proton adjacent to a hydroxyl group. This group cannot be at C-1, since the signal for this proton is the same as in valtrate Also, an IR band is present at 1770 cm^{-1} due to an ester carbonyl at C-1 Furthermore, it should be noted that valepotriates with a free hydroxyl group at C-1 are unstable. The C-11 methylene proton signals also coincide with those of valtrate, which shows that the C-11 hydroxyl group is acylated Therefore, the free hydroxyl group must be at C-7.

Consequently A_1 contains two isovaleryl groups at C-1 and C-11 as in isovaltrate (**5**). found in other *Valeriana* species[4] and at C-7 there is a hydroxyl group Therefore the structure of deacetylisovaltrate (**6**) can be assigned to A_1

The second product A_2 was isolated only in a very small amount sufficient only for IR and UV spectra which were similar to those of valtrate The ester bands at 1770 and 1740 cm^{-1} were the most intense. Acetylation resulted in a product with a lower R_f value compared to that of valtrate and giving the same colour with the benzidine reagent

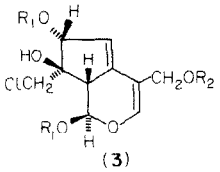


(1)

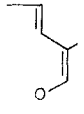


(2)

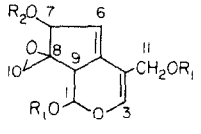
R_1 = $COCH_2CH(Me)_2$
R_2 = COMe



(3)

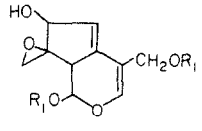


(4)

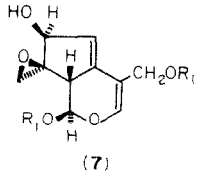


(5)

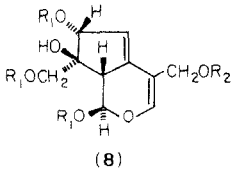
R_1 = $COCH_2CH(Me)_2$
R_2 = COMe



(6)

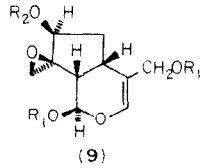


(7)



(8)

R_1 = $COCH_2CH(Me)_2$
R_2 = COCMe



(9)

Stereochemistry

The stereochemistry of valepotriates has been studied mainly by NMR spectroscopy[1] and in some cases by chemical transformations.[5] The valepotriates can be divided in two steric groups, valtrate and didrovaltrate. The first group includes valtrate (**1**), acevaltrate, valtrate isovaleroxyhydrin (**8**) and valechlorine (**3**), with an α-proton at C-1 and a β-proton

[4] Brit pat 1 195 666
[5] THIES P W (1970) *Tetrahedron Letters* 3087

at C-7. The didrovaltrate group includes didrovaltrate (**2**), homodidrovaltrate, deoxydodidrovaltrate and homodeoxydodidrovaltrate, with a β-proton at C-1 and an α-proton at C-7. Both groups have the same stereochemistry at C-8 and C-9.

The specific rotation of A_1 ($[\alpha]_D^{20°}$ +35° in MeOH) differs from that of valtrate ($[\alpha]_D^{20°}$ +172·7° in MeOH) and isovaltrate ($[\alpha]_D^{22°}$ +151° in MeOH). The stereochemistry of isovaltrate is unknown, but on account of the similarity observed in the NMR spectra and the specific rotations of the latter two compounds it can be assumed they possess identical configurations. Since the alcohols and their acetates have similar specific rotation values it can also be concluded that A_1 and valtrate differ from one another in their stereochemistry.

The coupling constant of the protons at C-1 and C-9 (J 1·9) is closely similar to that found for the valtrate steric group (10 cps). Therefore, the protons at C-1 and C-9 have a *trans*-diaxial configuration. The C-7 proton couples only with the C-6 proton (J 6·7 = 2 cps) The lack of any long-range coupling between the protons at C-7 and C-9 proves unambiguously their *trans* configuration, which is analogous to that observed in didrovaltrate (**2**).

The IR maximum at 3500 cm^{-1} (diluted solution in CCl_4) indicates the presence in A_1 of an internal hydrogen bond. This is possible if the C-7 hydroxyl group and the epoxy ring at C-8 are in a *cis* relationship.

The absolute configuration established for the proton at C-9 in all known iridoids is β. If we accept the same in A_1 the assigned stereochemistry (**2**) is absolute, i.e. 7-*epi*-deacetylisovaltrate. Stereochemically it is related to didrovaltrate (**2**) with the same position of the isovaleryl groups (at C-1 and C-11). If a biogenetic relationship between these two compounds can be suggested it will be at variance with the difference in C-1 stereochemistry. The β-configuration of the proton at C-1 in didrovaltrate is different to the configuration in all known iridoids, which calls its correctness in question. This configuration was established according to the Dreiding model for didrovaltrate and the use of the Karplus rule.[1] However, the dehydropyran ring in didrovaltrate can possess two half-chair conformations with different dihedral angles and consequently the calculated J value must also be different.

The epoxy ring in valtrate and didrovaltrate has the same stereochemistry.[1] Both compounds give hydrins, which possess a β-hydroxyl group and an α-CH_2X group. The interaction of the α-proton of valtrate at C-1 with CH_2X leads to a downfield shift of this proton. In valtrate and valtrate isovaleroxyhydrin (**8**) these signals appear at δ5·96 and δ6·15, respectively. In didrovaltrate and its isovaleroxyhydrin these signals appear at δ5·74 and δ6·20, i.e. a greater shift is apparent. This can be explained only by a *cis* relationship of CH_2X and the C-1 proton. Therefore, the C-1 proton has an α-configuration. Accordingly the configuration of the proton at C-1 in didrovaltrate must be corrected to (**9**). It now does not differ from the C-1 configuration of all other known iridoids.

EXPERIMENTAL

IR spectra were determined in $CHCl_3$ NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard TLC was performed on silica gel G Alumina (Woelm, Neutral) containing 10% H_2O was used for column chromatography

The total $CHCl_3$ extract of dry *Valeriana officinalis* L roots (1 kg) was chromatographed on an alumina column (1 2 kg) A mixture of petrol–Me_2CO–EtOAc (100 8 8) was used as eluent The first 1 litre of the eluate

contained valtrate, valechlorine and acevaltrate, the next 500 ml containing 800 mg valeridine (R_f = 0.20 using the same solvent). Prep. TLC of the crude valeridine using CH_2Cl_2–Me_2CO–EtOAc (100 : 2 : 2) gave valeridine as the main band (550 mg) followed by the bands of 7-*epi*-deacetylisovaltrate (A_1) (80 mg) and the compound A_2 (10 mg).