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AREOLAL, A THYMOL FROM *PIPTOTRIX AREOLARE*

J. D. HERNÁNDEZ, L. U. ROMÁN, J. RODRÍGUEZ M., J. ESPIÑEIRA* and P. JOSEPH-NATHAN*

Instituto de Investigaciones Químico-Biológicas, Universidad Michoacana de San Nicolás de Hidalgo, Morelia, Mich., 58240 México; *Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, P.O. Box 14-740, México, D.F., 07000 México

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Key Word Index—*Piptotrix areolare*; Compositae; Eupatoriae; roots; thymolaldehyde; structural determination.

Abstract—From the roots of *Piptotrix areolare*, a new natural thymol aldehyde, areolal, was obtained, and the structure elucidated by spectral analysis and chemical methods.

INTRODUCTION

The tribe Eupatorieae (Compositae) has been recognized as a source of several types of natural products [1, 2], which among others include *p*-hydroxyacetophenone and thymol derivatives [3], diterpenes [3, 4], chromenes [5] and sesquiterpenes [6–8]. In continuation of our phytochemical studies on Mexican Compositae, we report the isolation and characterization of a new thymol derivative from the roots of *Piptotrix areolare* (tribe Eupatorieae, subtribe Ageratinae) [9].

RESULTS AND DISCUSSION

The spectral data of the new compound led to structure 1. The ^{13}C NMR spectrum was very informative since it showed the presence of a cinnamate at 165.6 (COO), 116.6 (α-CH=), 145.3 (β-CH=), 133.6 (*ipso*), 127.7 (2 *ortho*), 128.5 (2 *meta*) and 130.1 (*para*), an isobutyrate at 174.4 (COO), 33.9 (CH) and 18.6 (2Me), an epoxide on quaternary and secondary carbons at 56.8 and 50.7, respectively, and an ester bearing methylene group at 65.9 ppm. The remaining signals are those of an aromatic aldehyde carbon at 190.2 and the six carbons of the benzene ring which appear at 137.2 (*s*, C-1), 122.9 (*d*, C-2), 149.1 (*s*, C-3), 135.2 (*s*, C-4), 129.6 (*d*, C-5) and 126.7 (*d*, C-6). The specific assignments of the signals in the ^{13}C NMR spectrum were made taking into account published data for cinnamate [10, 11], isobutyrate [12] and oxygen substituted *p*-cymene derivatives [13].

The structural fragments in areolal (1) are further evidence in the ^1H NMR spectrum which shows the isobutyrate at 2.90 (1H, heptet, J = 7 Hz) and 1.36 (6H, doublet, J = 7 Hz), the epoxide methylene signals as an AB system (J_{AB} = 5 Hz) at δ3.14 and 2.87, the oxygen bearing methylene group as a second AB system (J_{AB} = 12 Hz) at 4.73 and 4.40, the cinnamate double bond protons as a third AB system (J_{AB} = 16 Hz) at 7.65 and 6.37, the aldehyde singlet at 10.03 and the remaining eight aromatic protons overlap in the 7.3–7.6 region.

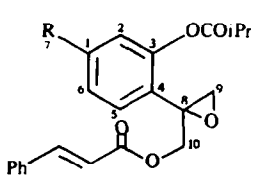
The above data clearly indicated that the structure of areolal corresponds to a thymol in which the aromatic methyl group has been oxidized to an aldehyde and the three carbons of the isopropyl moiety contain oxygen, two of them forming an epoxide, the third carbon an ester. The second ester is located at C-3 on the aromatic ring. That the isobutyrate group is at C-3 follows from the ^1H NMR chemical shifts of the signals at 2.90 and 1.36, in agreement with published shifts for aromatic isobutyrates [1, 14, 15] which are found in the 2.85–2.77 and 1.34–1.28 regions, in contrast to aliphatic isobutyrates reported in the 2.50–2.44 and 1.09–1.06 regions [1, 14, 16], respectively.

Furthermore, the ^1H NMR data of areolal (1) resemble those of a similar thymol derivation isolated from *Callilepsis laureola* [17], the only difference being the presence of a second isobutyrate instead of the cinnamate.

Other spectral data supporting the structure of areolal as 1, are given in the Experimental. It is worth mentioning that the sole chiral centre of 1 is racemic as evident from the lack of optical activity. This was further confirmed by use of the optical active shift reagent Eu(THC)$_3$, which produced signal splitting of the peaks attributed to the C-10 methylene protons.

Sodium borohydride reduction of areolal (1) afforded the alcohol 2 as evident from the presence of a new CH_2OH group providing a ^1H NMR singlet at 4.60 (2H) and 3.82 (1H) ppm, the latter disappearing upon addition of D_2O.

Acetylation of the primary alcohol 2 gave 3, which showed the acetate singlet at δ2.04 and the shift of the CH_2OAc to 5.06 (2H) ppm. Other spectral data of 2 and 3 are given in the Experimental.



1 R = CHO
2 R = CH_2OH
3 R = CH_2OAc

EXPERIMENTAL

Piptotrix areolare R. et K. was collected at Santa Bernardina, State of Michoacán, México in October, 1983. Voucher samples have been deposited at Departamento Botánico, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Mexico City where Prof. J. Rzedowski identified the material. Hexane extracts of the air-dried ground roots (1 kg) gave 7 g of a brown oil. It was chromatographed over silica gel (80 g), the fractions eluted with hexane–C_6H_6 (3:1) yielding 2 g of areolal (1) as a pale yellow oil showing $[\alpha]_D \pm 0°$ (*c* 2; $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2730, 1730, 1635, 1615; UV λ_{max}^{EtOH} nm: 215, 254, 280 (*e* 22200, 13900, 14900); ^1H NMR: see Results and Discussion; ^{13}C NMR: see Results and Discussion.

Reduction of areolal (1). A soln of 500 mg of 1 in 5 ml of MeOH was treated with 100 mg of $NaBH_4$ at room temp. during 30 min. The reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dried (Na_2SO_4), filtered and evapd to yield 300 mg of 2 as a colourless oil showing IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600, 3100, 1745, 1715, 1635, 1570, 1165; ^1H NMR ($CDCl_3$, 90 MHz): δ 7.63 and 6.30 (1H each, 2*d*, J = 16 Hz, cinnamoyl vinyls), 7.36 (7H, complex; cinnamoyl aromatics, H-5 and H-6), 7.03 (1H, *d*, J = 2 Hz, H-2), 4.60 (2H, *s*, H-7 and H-7'), 4.57 and 4.34 (1H each, J = 12 Hz, H-10 and H-10'), 3.82 (*br s*, OH), 3.07 and 2.80 (1H each, 2*d*, J = 5 Hz, H-9 and H-9'), 2.91 (1H, heptet, J = 7 Hz) and 1.30 (6H, *d*, J = 7 Hz, isobutyrate).

Acetylation of 2. A soln of 250 mg of 2 in 1 ml of pyridine was treated with 1 ml of Ac_2O. The reaction mixture was poured into ice-H_2O and extracted with EtOAc. The organic layer was washed with H_2O, dil. HCl, aq $NaHCO_3$, H_2O, dried (Na_2SO_4), filtered and evapd to yield 250 mg of 3 as a colourless oil that shows IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3100, 1750, 1720, 1635, 1575; ^1H NMR ($CDCl_3$, 90 MHz): δ 7.63 and 6.40 (1H each, 2*d*, J = 16 Hz, cinnamoyl vinyls), 7.34 (7H, complex, cinnamoyl aromatics, H-5 and H-6), 7.12 (1H, *d*, J = 2 Hz, H-2), 5.06 (2H, *s*, H-7 and H-7'), 4.66 and 4.40 (1H each, 2*d*, J = 12 Hz, H-10 and H-10'), 3.14 and 2.83 (1H each, 2*d*, J = 5 Hz, H-9 and H-9'), 2.91 (1H, heptet, J = 7 Hz) and 1.33 (6H, *d*, J = 7 Hz, isobutyrate).

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