THE STRUCTURES OF BONVALOTINE, BONVALOL AND BONVALONE, THREE NEW C_{19}-DITERPENOID ALKALOIDS

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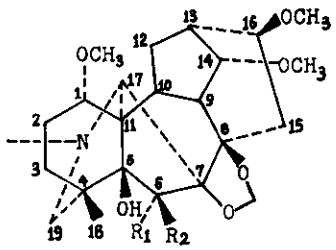
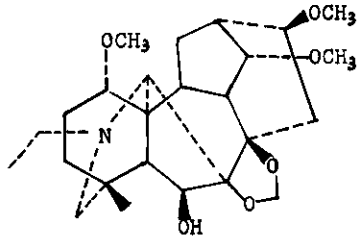
Abstract - Chemical investigation of the roots of Delphinium bonvalotii Franch results in the isolation of bonvalotine (1), bonvalol (2) and bonvalone (3), three new lycoctonine-type alkaloids with unique C(5)-OH substitution.

In this communication we report the structure elucidation of three new C_{19}-diterpenoid alkaloids, designated as bonvalotine (1), bonvalol (2) and bonvalone (3), isolated from the roots of Delphinium bonvalotii Franch[2], which is used as a folk medicine in China, claimed to be analgesic, anti-inflammatory, and anti-rheumatic.





1 R_1= H, R_2 = OAc Bonvalotine

2 R_1= H, R_2 = OH Bonvalol

3 R_1, R_2= O Bonvalone

5 R_1= OAc, R_2 = H

4 Delpheline

Bonvalotine, $C_{26}H_{39}NO_8$ (M^+ 493.2634, calc. 493.2665), mp 218-220°C, $[\alpha]_D^{32}$ -35.7° (c 0.6, $CHCl_3$). Infrared absorption (KBr) showed the presence of a hydroxyl group at 3600 and an ester group at 1738 and 1230 cm^{-1}. ^1H nmr spectrum of bonvalotine in $CDCl_3$ indicated the presence of a C-CH_3 at δ0.76 (3H, s), an acetyl group at δ2.16 (3H., s), an N-CH_3 at δ2.51 (3H, s), and three methoxyl groups (each 3H, s)

at δ3.28, 3.34 and 3.44. The spectrum also showed a one-proton triplet (J ≃ 5 Hz) centered at δ3.70 characteristic to CH_3O-C(14)-β-H, a two-proton singlet at δ4.94 for C(7)-O-CH_2-O-C(8), and a one-proton singlet at δ5.43 for AcO-C(6)-H. MS of bonvalotine gave 462 (M^+-31) as the base peak, which indicated the presence of C(1)-α-OCH_3[3a,b]. The third methoxyl group was assigned to C(16) position based on the biogenetic considerations of naturally occurring C_{19}-diterpenoid alkaloids[3a]. We noticed that the C(6) hydrogen showed a sharp singlet in the ^1H nmr, differring from that of the corresponding hydrogen of those structurally related compounds such as tatsiensine[4] and dictyocarpine[5], in which C(6) hydrogen exhibited a broad singlet or a doublet with small J values. This hinted that C(5) of bonvalotine, a lycoctonine-type molecule, was a quaternary carbon with an oxygenated substituent, presumably a hydroxyl group. We have experienced that the hydroxyl group in bonvalotine failed to be acetylated by acetic anhydride in the presence of pyridine, p-toluenesulfonic acid or p-dimethylaminopyridine[6], demonstrating that the particular hydroxyl group was a tertiary alcohol and highly hindered, and again it could reasonably be situated at C(5) position. This postulation was confirmed subsquently by the finding that the hydrolyzed alkamine of bonvalotine, upon oxidation with periodate, afforded a seco product (M^+ 449) which showed in IR the presence of two carbonyl groups (1725 and 1705 cm^{-1}) and in ^1H nmr an aldehyde, a singlet at δ9.69, and meanwhile, the singlet at δ4.11 for C(6)-H found in the alkamine disappeared. The assignment of the hydroxyl group to C(5) was further supported by the chemical shift values of ^{13}C nmr spectrum of the alkamine when comparison was made with that of delpheline (4)[4], an analogous compound without a C(5)-OH substituent (Table 1). It revealed that an α-effect of the hydroxyl group on C(5) caused a down-field shift of 21.2 ppm, β-effect on C(4) of 4.6, on C(6) of 3.6, and on C(11) of 3.4 ppm, and γ-effect on C(1) of -6.7, on C(3) of -5.4, and on C(18) of -4.3 ppm. Bonvalotine demonstrated an NOE enhancement of 17% on C(6)-H at δ5.43 when C(4)-CH_3 at δ0.76 was saturated, whereas no NOE was observed on its C(6)-epimer (5) prepared from bonvalotine in 4 steps. Molecular model showed that C(6)-α-H is more proximate to C(4)-CH_3 than C(6)-β-H, hence the acetyloxy group at C(6) of bonvalotine must be β-orientated. Based on the above spectral analyses, structure 1 was assigned for bonvalotine. Consequently, this structure (1) was confirmed by X-ray analysis[7].

Bonvalol, $C_{24}H_{37}NO_7$, M^+ 451, mp 165-166°C, $[\alpha]_D^{32}$-26.3° (c 0.4, $CHCl_3$). IR (KBr), 3540, 3480, 3420 cm^{-1} (OH). MS, m/z 420 (M^+-31, base). ^1H nmr ($CDCl_3$), δ0.80 (3H,

TABLE 1. Carbon-13 Chemical Shifts and Assignments for Bonvalotine (1), Bonvalol (2), Bonvalone (3), and Delpheline (4)[a]

	(1)	(2)	(3)	(4)
C(1)	76.7 d	76.4 d	82.2 d	83.1
C(2)	27.0 t	26.8 t	26.9 t	26.9
C(3)	31.5 t	31.5 t	32.4 t	36.9
C(4)	38.5 s	38.5 s	38.6 s	33.9
C(5)	77.1 s	76.7 s	81.7 s	55.5
C(6)	83.2 d	82.9 d	217.6 s	79.3
C(7)	91.2 s	91.7 s	88.9 s	92.8
C(8)	83.2 s	84.0 s	82.9 s	84.6
C(9)	40.2 d	40.4 d	41.9 d	47.9
C(10)	39.9 d	40.4 d	40.3 d	40.3
C(11)	54.0 s	53.8 s	49.8 s	50.4
C(12)	27.5 t	27.6 t	27.3 t	28.1
C(13)	38.1 d	37.3 d	38.2 d	37.9
C(14)	81.4 d	81.8 d	81.2 d	81.9
C(15)	33.9 t	33.4 t	33.2 t	33.5
C(16)	81.8 d	82.1 d	81.7 d	82.9
C(17)	64.7 d	64.1 d	64.1 d	63.7
C(18)	21.1 q	21.0 q	19.6 q	25.3
C(19)	61.6 t	62.0 t	61.7 t	57.3
$N-CH_3$	43.6 q	43.6 q	43.2 q	-
$N-CH_2$	-	-	-	50.2
CH_3	-	-	-	13.9
C(1)'	55.7 q	55.9 q	56.1 q	56.2
C(14)'	57.6 q	57.6 q	57.9 q	57.8
C(16)'	56.1 q	56.2 q	56.4 q	56.8
$O-CH_2-O$	93.6 t	93.0 t	95.4 t	92.8
C(6)-O-C=O	169.0 s	-	-	-
CH_3	21.5 q	-	-	-

a. Chemical shifts in ppm downfield from TMS. The solvent is $CDCl_3$.

s, C(4)-CH_3), 2.47 (3H, s, N-CH_3), 3.04, 4.04 (each 1H, s, exchangeable with D_2O, OH), 3.27, 3.33, 3.43 (each 3H, s, 3×OCH_3), 3.70 (1H, t, J = 4.8 Hz, C(14)-β-H), 4.11 (1H, d, J = 1.5 Hz, changed into s after addition of D_2O, HO-C(6)-α-H), 5.06, 5.15 (each 1H, s, C(7)-O-CH_2-O-C(8)). This base was shown to be identical with the hydrolyzed alkamine of bonvalotine (1) in all respects including R_f, ir, ^1H nmr, and mmp. The structure 2 was thus assigned for bonvalol.

Bonvalone, $C_{24}H_{35}NO_7$, M^+ 449, mp 235-236°C, $[\alpha]_D^{32}$ -89.3° (c 0.3, $CHCl_3$). IR (KBr), 3400 (OH) and 1750 cm^{-1} (cyclopentanone). MS, m/z 418 (M^+-31, base). ^1H nmr ($CDCl_3$), δ0.80 (3H, s, C(4)-CH_3), 2.46 (1H, s, exchangeable with D_2O, OH), 2.52 (3H, s, N-CH_3), 3.35, 3.39, 3.42 (each 3H, s, 3×OCH_3), 3.69 (1H, t, J = 4.8 Hz, C(14)-β-H), 5.12, 5.54 (each 1H, br s, C(7)-O-CH_2-O-C(8)). This compound was demonstrated to be identical (R_f, ir, ^1H nmr, and mmp) with the oxidation (CrO_3/pyridine) product (M^+ 449) of bonvalol (2). Hence, structure 3 was assigned for bonvalone.

The ^{13}C nmr chemical shifts of bonvalotine, bonvalol and bonvalone (Table 1) are in satisfactory agreement with the assigned structures 1, 2, and 3 when compared with that of delpheline (4).

These three bases are the first examples of C_{19}-diterpenoid alkaloid featured with an oxygenated substituent at the C(5) position.

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