ATISENOL, A NEW *ENT*-ATISENE DITERPENOID LACTONE FROM *ACONITUM HETEROPHYLLUM*

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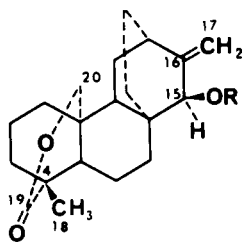
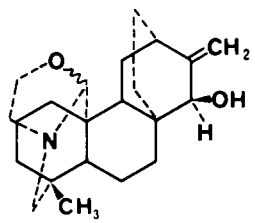
The roots of *Aconitum heterophyllum* Wall have been used extensively in native Indian medicine for the treatment of diarrhea, dysentery, cough, dyspepsia and chronic enteritis. Whether these reputed pharmacological properties are derived from the alkaloidal content or other constituents is not known. A detailed study of the basic components of the roots of *A. heterophyllum* had led to the isolation and structure elucidation of twelve new diterpenoid alkaloids (1,2). During the isolation of some known alkaloids from the "weak-base" fraction, we isolated a new diterpenoid lactone, atisenol (**1**), which is closely related in structure to the major alkaloid of this plant, atisine (**2**).



1 R=H Atisenol
3 R=Ac



2 Atisine

A solution of 630 mg. of the "weak base" fraction in toluene was chromatographed over 5 g of silica gel; 15 ml. fractions were collected. Fractions 8–12, when combined and crystallized from hexane-acetone, afforded 32 mg of needles of atisinol, $C_{20}H_{28}O_3$, (ms, elemental analysis) mp 161–163° (corrected), $[\alpha]^{24}-23.8°$ (c 0.53, $CHCl_3$), which showed ir absorption at 3490 (hydroxyl), 1710 (six-membered lactone), and 894 (exocyclic double bond) cm^{-1}. The mass spectrum exhibited the following fragmentation pattern: m/e 316(33), 298(12), 270(8), 258(37), 233(25), 187(35), and 84(100%). The 90 MHz ^1H nmr spectrum of atisenol in $CDCl_3$ revealed the existence of a sharp singlet at δ 1.21 for the C(4)-CH_3 group, a two-proton broad singlet at δ 2.22 for the O-CH_2-C(10) group, a triplet at 3.70 for the C(15)-α-proton, and a multiplet at δ 5.20 for the exocyclic double bond. The ^{13}C nmr spectrum of atisenol in $CDCl_3$ exhibited the following signals: 176.7 [C(19)], 155.6 [C(16)], 110.3 [C(17)], 76.5 [C(15)], 74.7 [C(20)], 49.6 [C(5)], 42.7 [C(4)], 40.2 [C(1)], 40.0 [C(9)], 37.5 [C(3)], 37.3 [C(8)], 36.0 [C(10)], 31.0 [C(12)], 29.7 [C(17)], 28.9 [C(18)], 27.3 [C(11)], 26.4 [C(13)], 23.3 [C(14)], 20.5 [C(6)] and 20.0 [C(2)] ppm, which indicated the presence of a lactone group, a methyl group at C(4), a secondary hydroxyl group, an exocyclic double bond, and other characteristic features of the atisene-type skeleton (3,4).

Treatment of atisenol with acetic anhydride in pyridine at room temperature yielded the monoacetate **3**, mp 142–144° (corrected), $[\alpha]^{24}D-41°$ (c 1.5, CH_2Cl_2), which showed the presence of the acetate and lactone (1740 and 1730 cm^{-1}) groups and the absence of a hydroxyl group. The presence of a 6-membered lactone

ring was deduced from the absence of a 5-membered lactone absorption at 1750 cm^{-1} in the ir spectrum of atisenol. The lactone was assumed to be present between C(19) and C(20) because of the absence of a signal in the 11–14 ppm range of the ^{13}C nmr spectrum, which is typical of a diterpene containing the C(20) angular methyl group (4). The position of the lactone carbonyl group at C(19) was based on the downfield value of the C(4)-CH_3 group (5) in the ^1H nmr spectrum of atisenol. The stereochemistry of the hydroxyl group at C(15) was determined by comparison with the ^{13}C nmr shifts of the C(15)-OH group-containing compounds (3) and by acetylation of the parent compound. The ^{13}C nmr spectrum of the monoacetate **3** indicated an upfield shift of the exocyclic double bond carbons (150.2 and 111.4 ppm) relative to the original compound. Based on the above results, structure **1** was assigned to atisenol. This assignment was confirmed subsequently by a single- crystal X-ray analysis of atisenol (figure 1).

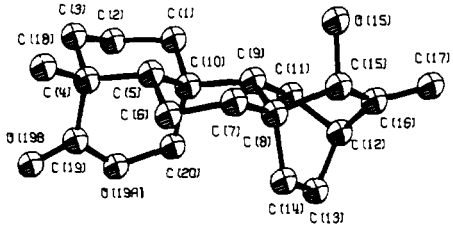
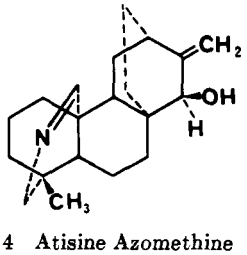


FIGURE 1. ORTEP Drawing of Atisenol (**1**).

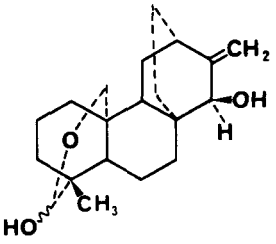
A clear crystal of atisenol of approximate dimensions 0.6 x 0.5 x 0.3 mm. was mounted on a glass fiber. Preliminary examination and data collection were performed on an Enraf-Nonius CAD–4 diffractometer with CuKα radiation ($\lambda = 1.5418$Å). The crystal belonged to the monoclinic space group $P2_1$ with two molecules in the unit cell, $a = 7.0415(5)$, $b = 12.6728(8)$, $c = 9.7283(8)$Å, $\beta = 103.328(7)°$, and $d_{calcd.} = 1.24$g cm^{-3}. All unique data with $\theta \leq 75°$ were measured by an ω-2θ scan technique with scan widths of $(1.0+0.14 \tan\theta)°$. Three intensity control reflections, measured every two hours, showed an approximate 10% fluctuation during data collection. The data were corrected for Lorentz and polarization effects before conversion to structure factors and E's. Of the 1813 reflections measured, 1643 were judged observed on the basis of counting statistics ($I \geq 3$ (I)).

All non-hydrogen atoms were located by means of direct methods (6) and hydrogens were subsequently located on difference syntheses (7). Non-hydrogen atoms were refined anisotropically, and hydrogens were refined isotropically by a blocked least-squares program where the quantity minimized was $w(|F_o|-|F_c|)^2$ and the weight, $w = 0.35+|F|+0.07F^2$, was chosen to give negligible variation in $w(F)^2$ over the range of $|F|$ and sin θ (F). Three reflections with low θ values were excluded from refinement because of secondary extinction problems. The final R factor for the remaining observed reflections was 0.043 and $R_w = 0.060$. A final difference map was essentially featureless with no peaks greater than 0.20e$Å^{-3}$.

Interestingly, atisenol was isolated from the "weak-base" fraction, and, therefore, we thought that atisenol might have been formed as an artifact during the isolation from atisine (**2**) or atisine azomethine (**4**). Furthermore, atisine azomethine can be easily



4 Atisine Azomethine



5

oxidized (8) with nitrous acid to give compound **5**, which under mild oxidizing conditions, could lead to atisenol. To test this speculation, we attempted air-oxidation of atisine and atisine azomethine to atisenol under various isolation conditions using polar solvents such as acetone and ethanol in the presence of silica gel and alumina. Since in each experiment we failed to obtain atisenol, we conclude that atisenol is not formed as an artifact during the isolation. Thus atisenol is the first neutral compound isolated from *Aconitum* species which is related to the C_{20}-diterpenoid alkaloids.

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