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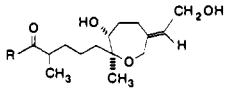
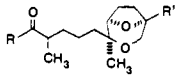
Zoapatanol and Montanol, Novel Oxepane Diterpenoids, from the Mexican Plant Zoapatle (*Montanoa tomentosa*)

Sir:

A tea prepared from the leaves of zoapatle (*Montanoa tomentosa*) has been used in Mexico for the past four centuries to induce menses and labor and terminate early pregnancy. Although there are many conflicting references[1] to the biological activity of zoapatle extracts, definitive studies leading to the isolation and identification of the biologically active component(s) of this plant have not yet been reported.[2,3] We describe herein our efforts that have culminated in the structural elucidation of two novel and biologically active oxepane diterpenoids, zoapatanol (**1**) and montanol (**2**).





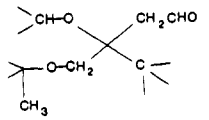
1 R = $(CH_3)_2C{=}CH{-}CH_2{-}$

2 R = $(CH_3)_2CH{-}C(CH_3){=}C(H){-}$

3 R = $(CH_3)_2C{=}CH{-}CH_2{-}$ R′ = CH_2CHO

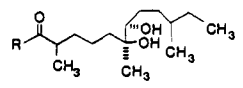
4 R = $(CH_3)_2C{=}CH{-}CH_2{-}$ R′ = $CH{=}CH_2$

Aqueous extraction of the leaves, followed by treatment with organic solvents, afforded a crude extract possessing contragestational activity.[4] Chromatography of this extract first on a silica gel column and then on a vinyl acetate copolymer column afforded **1** and **2** as oils.[5] Although **1** had an apparent M^+ of 320 by electron ionization–mass spectroscopy (EI-MS), it became clear from the preparation of a variety of derivatives that the true M^+ was 338 ($C_{20}H_{34}O_4$), which was confirmed by chemical ionization–mass spectroscopy (CI-MS). Twenty carbon atoms were observed by ^{13}C NMR and from examination of the chemical shifts and multiplicities in the ^{13}C NMR and by decoupling experiments in the ^1H NMR, the following were identified: $\delta^{CDCl_3}_{Me_4Si}$ 5.47 (t, J = 7 Hz, 1 H, >C=C*H*$CH_2C(=O)$-), 5.29 (t, J = 7 Hz, 1 H, >C=C*H*CH_2OH), 4.14 (d, J = 7 Hz, 2 H, >C=CHCH_2OH), 4.08 (s, 2 H, -$COCH_2C$=), 3.53 (d, d, J = 4, 8 Hz, 1 H, >C*H*OH), 3.12 (d, J = 7 Hz, 2 H, >C=CH$CH_2C(=O)$-), 1.75 and 1.62 (s, 3 H each, $(CH_3)_2C$=CH), 1.14 (s, 3 H, >$C(CH_3)OCH_2$-), and 1.08 (d, J = 7 Hz, 3 H, CH_3CH-). Treatment of **1** with MnO_2 in CH_2Cl_2 gave the saturated aldehyde **3**, presumably arising by intramolecular addition of a secondary alcohol to the initially formed product.[6] The assignment was supported by: M^+ 336, the absence of an OH in the IR, and the appearance of a triplet at δ 9.73 coupled to a doublet at δ 2.60 (J = 2 Hz) for a CH_2CHO group. In addition, the methylene at δ 4.08 was absent and replaced by an AB q at δ 3.29 and 3.76 (J = 11 Hz). These data were consistent with the following partial formula:

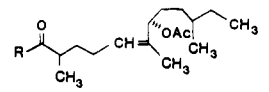


Analysis of the spectral data for the dehydrated product **4** obtained when **1** was treated with *p*-TsOH in benzene indicated that a similar type of intramolecular reaction had occurred; M^+ 320;[7] δ 3.29 and 3.75 (AB q, 2 H, J = 11 Hz, -OCH_2C-) and 5.0–6.2 (3 H, -$OCCH{=}CH_2$).

Hydrogenation (PtO_2, $NaNO_2$)[8] of **1** saturated both double bonds, whereas hydrogenation over Pd/C led to the uptake of 4 mol of H_2 and the isolation of a major product ($C_{20}H_{40}O_3$) in which both double bonds were saturated, hydrogenolysis of the two allylic oxygen bonds had occurred, and the secondary alcohol was still intact [δ 3.26 (m, 1 *H*, >C*H*OH)]. The vicinal nature of the diol in the hydrogenation product was substantiated by monoacetylation (Ac_2O, pyr, room temperature) followed by dehydration ($POCl_3$, pyr, room temperature) to an allylic acetate **6** [δ 1.59 (s, 3 H, CH_3C=), 5.1 (m, 1 H,



5 R = $(CH_3)_2CH{-}(CH_2)_2{-}$

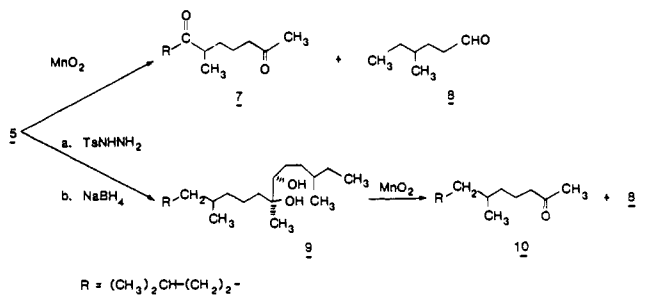


6 R = $(CH_3)_2CH{-}(CH_2)_2{-}$

=C*H*OAc)]. An unequivocal structure proof for **5** was obtained when MnO_2 cleavage[9] of **5** afforded the diketone **7** and aldehyde **8** (Scheme I). In addition to spectral data supporting their structures, both compounds were synthesized and their identities confirmed. The synthesis of **7** is outlined in Scheme II, while the known aldehyde **8**[10] was prepared by treatment of 4-methyl-1-hexene with 9-BBN followed by oxidation (CrO_3, pyr, CH_2Cl_2). These results, along with chemical, spectroscopic, and biogenetic considerations on a variety of derivatives,[11] led us to propose an oxepane derived structure **5** for the hydrogenation product.

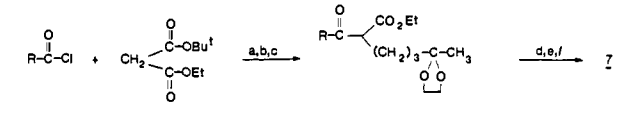
The same aldehyde **8** was obtained along with hexahydropseudoionone (**10**)[12] when **5** was converted to a tosylhydrazone and reduced with $NaBH_4$ to the deoxo-*vic*-glycol **9**

Scheme I



R = $(CH_3)_2CH{-}(CH_2)_2{-}$

Scheme II



R = $(CH_3)_2CH{-}(CH_2)_2{-}$

a. Mg, EtOH, ether; b. TsOH, Δ, PhH; c. NaH, DMF, $CH_3{-}C(O_2){-}(CH_2)_3{-}Cl$; d. MeI, DMF, NaH; e. NaOH, EtOH; f. TsOH, Δ, acetone

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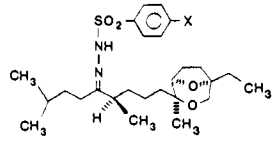
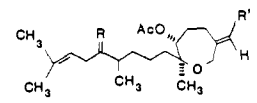


11 X = Br

12 X = CH_3



13 R = O R' = CH_2OAc

14 R = α-OH R' = CH_2OAc

15 R = α-OH R' = CH_2OH

16 R = α-OH R' = CHO

17 R = α-OH R' = CO_2Me

and then cleaved with MnO_2. At this time in our work, we obtained our first crystalline compounds, the hydrazones **11** and **12** derived from the hydrogenation (Pd/C) product of **4**. An X-ray analysis of **12** led to the assignment of the absolute configuration shown (2*S*,3*R*).[13] We were now confident in portraying zoapatanol as **1** based on the chemistry involved in the conversion of **1** to **12**. A point that still remained to be established, however, was the geometry of the hydroxyethylidine group at C-6. Acetylation (Ac_2O, pyr) of **1** afforded the diacetate **13**, which was reduced with $NaBH_4$ to the hydroxy compound **14**. Selective hydrolysis (K_2CO_3, H_2O, MeOH) of **14** afforded the primary alcohol **15**, which upon oxidation with MnO_2 gave the aldehyde **16**. Oxidation (NaCN, MnO_2, MeOH)[14] of **16** gave the desired carboxylic ester **17**. The NMR spectrum of **17** showed a signal at δ 4.17 for the 7-CH_2, while the corresponding signal in several related primary alcohols appeared at δ ~4.11. This difference in chemical shift was consistent with the 6*E* configuration, since a downfield shift of 0.4–0.6 ppm would be anticipated for a methylene group in close proximity (6*Z*) to the anisotropic ester carbonyl.[15] Since the method for converting **1** to **17** was stereoretentive at C-6, the structure of zoapatanol was now firmly established. The structure of montanol ($C_{21}H_{36}O_4$, **2**) was established by studies similar to those conducted with **1**.

Acknowledgment. The authors thank Edward Deegan, John Garner, Joe Grodsky, Robert Mallory, Roxanne Naldi, Deborah Rowand, Arvin Shroff, Yolanda Williams, and Benny Wong of Ortho Pharmaceutical Corporation for their contributions to this work.

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(13) The X-ray crystallographic study was carried out by Professor Eli Shefter, School of Pharmacy, SUNY—Buffalo. Compound **12** ($C_{27}H_{44}N_2O_4S$, mp 100–101 °C) crystallized as small monoclinic needles with *a* = 5.378 (7) Å, *b* = 18.973 (18) Å, *c* = 14.182 (17) Å; β = 102.68 (10)°; and space group $P2_1$ with two molecules in the unit cell. The refined structure gave an *R* value of 0.087 for the observed data.
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Preparation and Properties of Molybdenum- and Tungsten-Dinitrogen Complexes. 10.[1] Conversion of Ligating Dinitrogen into Hydrazine with Hydrazido(1−) Complexes as Intermediates

Sir:

The protonation reactions of ligating dinitrogen in molybdenum and tungsten complexes have been receiving much attention in relevance to nitrogen fixation. Previously Chatt and his co-workers[2] reported that the complexes *cis*-$[M(N_2)_2(PMe_2Ph)_4]$ or *trans*-$[M(N_2)_2(PPh_2Me)_4]$ (M = Mo or W) give, on treatment with sulfuric acid in methanol at room temperature and then base distillation for M = Mo, high yields of ammonia, together with a little hydrazine for M = W and a trace for M = Mo. The yield of ammonia is essentially 2 mol/metal atom for M = W, but only ~0.66 mol/metal atom for M = Mo.

We have recently found new protonation reactions which lead to the production of moderate yields of hydrazine in preference to ammonia from ligating dinitrogen in the tungsten complexes.[1] The reactions have now been applied to the molybdenum complexes. In a typical reaction, HCl gas was bubbled through a suspension of *cis*-$[Mo(N_2)_2(PMe_2Ph)_4]$ or $[MoX_2(NNH_2)(PMe_2Ph)_3]$ (X = Cl or Br) in 1,2-dimethoxyethane for several minutes at room temperature. After being stirred for ~20 h, the mixture was evaporated to dryness and the residue extracted with water. Potassium hydroxide solution (~40 wt %) was then added and the mixture distilled into dilute sulfuric acid. The yields of ammonia and hydrazine are given in Table I, which were determined by using indophenol and *p*-dimethylaminobenzaldehyde reagents, respectively. It is of great interest to note that the ligating dinitrogen on molybdenum is converted into hydrazine in moderate yields in these reactions and the nitrogen atom greater than one per molybdenum atom seems to be protonated to give hydrazine and ammonia. This is in sharp contrast to the protonation reactions reported by Chatt and his co-workers (vide supra).[2,3] They proposed the disproportionation of the N_2H_2 ligand at the hydrazido(2−) stage of reduction as in the equation $3N_2H_2 \rightarrow 2NH_3 + 2N_2$ in the case of the molybdenum dinitrogen complexes, which accounted for formation of only ~0.66 mol of NH_3/molybdenum atom. However, the results obtained here indicate that there is no substantial difference between the protonation reactions of the molybdenum- and tungsten-dinitrogen complexes, and the N_2H_2 ligand in both

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