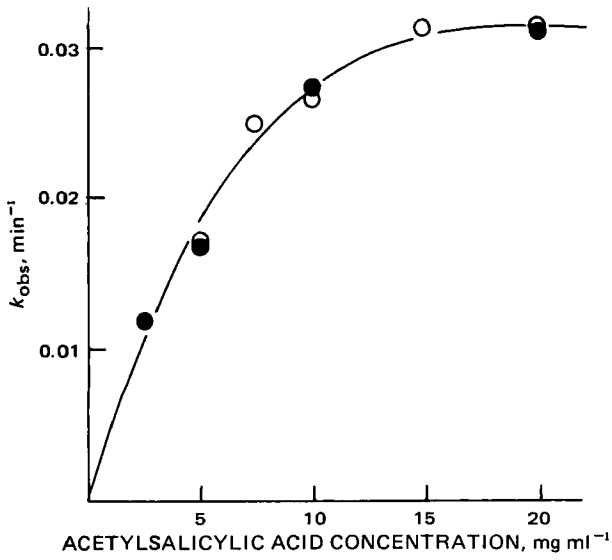

Figure 1—*Plot of observed first-order rate constants for formation of salicylic acid (●) and mixed acetylsalicylic acetic anhydride (○) at 60° in benzene solutions of acetylsalicylic acid as a function of the initial concentration of acetylsalicylic acid.*

presence of a metastable intermediate in the reactions and of a change in the rate-determining step with increasing concentrations of I; *i.e.*, the formation of the intermediate becomes rate limiting at the higher concentrations of I.

We interpret these results to mean that I, through an intramolecular addition of the carboxyl group to the ester carbonyl moiety, is converted into the mixed salicylic acetic anhydride (II), which then either returns to I or reacts at the anhydride moiety with the carboxyl group of a second molecule of I to produce III and IV (with attack on the acetyl carbonyl moiety of the anhydride) or to produce V (with attack on the salicyloyl carbonyl moiety) which, in turn, rearranges into VI (like II to I, Scheme I). Admittedly, other pathways can be imagined to lead to the formation of III, IV, and VI (*e.g.*, a reaction between two molecules of II), but it seems inevitable to postulate an intermediate formation of a mixed salicylic acetic anhydride (II). The *para*-substituted analog of I, *p*-acetoxybenzoic acid, completely fails to undergo any degradation in the present conditions.

A catalysis of all reactions shown in Scheme I was observed by triethylamine and also by benzene-insoluble materials such as magnesium hydroxide and magnesium carbonate. This finding apparently suggests that the ionized acetylsalicylate undergoes reactions *via* the anhydride II in nonhydroxylic solvents. A similar suggestion was advanced previously (17, 18).

The observations described may possibly contribute to an understanding of the mechanism of catalysis of reactions of I and related compounds in aqueous as well as in nonaqueous solutions [*cf.*, the recent paper by Kömives *et al.* (19) on aminolysis of I in acetonitrile]. Since preliminary experiments indicated that similar transformations of I can occur in the solid state at elevated temperatures, the results may become of relevance for the assessment of the stability of I formulations. This assessment has so far mostly been based on the conviction that IV and acetic acid are the only products of degradation (20).

As far as allergy to I is concerned, the formation of even small amounts of the immunogenic acetylsalicylsalicylic acid and acetylsalicylic anhydride should be avoided (21, 22). On the basis of the ready ability of the mixed acetylsalicylic acetic anhydride to salicyloylate amino groups as described here, this compound may most likely be as immunogenic as acetylsalicylsalicylic acid and acetylsalicylic anhydride.

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Two New Diterpenes from *Stemodia maritima* L.

Keyphrases □ Diterpenes—isolated from aboveground portion of *Stemodia maritima*, PMR, IR, mass, and circular dichroism spectral identification □ *Stemodia maritima*—aboveground portion extracted, diterpenes isolated and identified □ Maritimol—isolated from *Stemodia maritima*, PMR, IR, mass, and circular dichroism spectral identification □ Stemodinol—isolated from *Stemodia maritima*, PMR, IR, mass, and circular dichroism spectral identification

To the Editor:

An investigation of the aboveground portion of

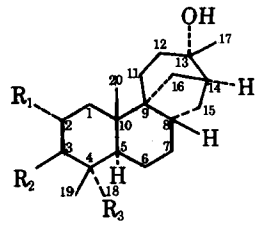
Stemodia maritima L. (Scrophulariaceae)[1] resulted in the isolation and identification of two new diterpenes containing an unusual tetracyclic skeleton. These new diterpenes have been named maritimol and stemodinol, and Structures I*a* and I*b* have been assigned to them, respectively.

Percolation of the dried, powdered, aboveground portion with petroleum ether (bp 40–60°) yielded a dark-green percolate. Concentration of the percolate yielded a yellowish-green precipitate, which was filtered and chromatographed over silica gel. Elution was initiated with *n*-hexane followed by increasing amounts of benzene in *n*-hexane, benzene, increasing amounts of chloroform in benzene, chloroform, and, finally, increasing amounts of methanol in chloroform. Elution with 3% methanol in chloroform yielded the two new diterpenes, which were obtained pure by crystallization.

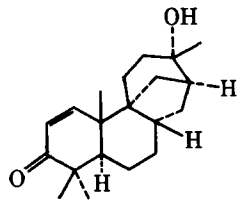
While this study was in progress, a report appeared concerning the isolation and identification of stemodin (I*c*) and stemodinone (I*d*) from the leaves of *S. maritima* (1). The structures for these diterpenes containing the novel stemodane ring system were solved through a single-crystal X-ray analysis of stemodinone (1). These two diterpenes were also identified in this study[2].

Maritimol (I*a*) had a melting point of 169–170° (isopropyl ether) and $[\alpha]_D^{25}$ +3.7° (c 0.93, pyridine). It exhibited a parent ion peak at *m/e* 306.255, corresponding to the formula $C_{20}H_{34}O_2$ (calculated *m/e* 306.256), which was also supported by elemental analysis. The IR spectrum had an absorption at ν_{max} (KBr) 3340 cm^{-1}; the proton magnetic resonance (PMR) spectrum[3] indicated four methyl singlets at δ 0.86, 0.96, 1.03, and 1.11 and another signal at δ 3.20 (dd, 1H, J = 11, 5 Hz). This last signal shifted to δ 4.41 (dd, 1H, J = 11, 5 Hz) in the monoacetate (I*e*)[4], mp 152–153° (ethanol); $[\alpha]_D^{25}$ +12.0° (c 0.60, chloroform); IR: ν_{max} (KBr) 3570 and 1725 cm^{-1}; PMR: δ 0.90, 0.91, 0.98, 1.11, and 2.05 (s, 3H each).

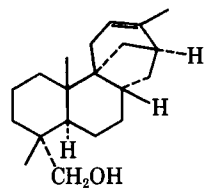
Oxidation of maritimol with Jones reagent gave the ketone (I*f*)[4], mp 117–118° (ether); $[\alpha]_D^{25}$ −37.0° (c 0.80, chloroform); IR: ν_{max} ($CHCl_3$) 3620 and 1705 cm^{-1}; PMR: δ 1.10 and 1.13 (s, 6H each). The circular dichroism spectrum[5] of I*f* showed a negative Cotton effect, $[\theta]_{296}$ − 3225. These data suggest that maritimol (I*a*) is isomeric with stemodin (I*c*). Reduction of I*f* under Huang-Minlon (2) conditions produced the known desoxy derivative (I*g*)[6], which confirmed the stemodane ring system.



I*a*: R_1 = H, R_2 = OH, R_3 = CH_3
I*b*: R_1 = R_2 = H, R_3 = CH_2OH
I*c*: R_1 = OH, R_2 = H, R_3 = CH_3
I*d*: R_1 = =O, R_2 = H, R_3 = CH_3
I*e*: R_1 = H, R_2 = $OCOCH_3$, R_3 = CH_3
I*f*: R_1 = H, R_2 = =O, R_3 = CH_3
I*g*: R_1 = R_2 = H, R_3 = CH_3
I*h*: R_1 = Br, R_2 = =O, R_3 = CH_3
I*i*: R_1 = R_2 = H, R_3 = CH_2OCOCH_3
I*j*: R_1 = R_2 = H, R_3 = CHO



II



III

The secondary hydroxyl group could be located at C-1, C-3, C-11, or C-12 based on the PMR data. Treatment of I*f* with trimethylphenylammonium tribromide (3) yielded the monobromo derivative, I*h*, mp 99–100° dec. (ether); IR: ν_{max} ($CHCl_3$) 3620 and 1725 cm^{-1}. The presence of one bromine atom was confirmed by observing the peaks at *m/e* 384 (10%) and 382 (10%) in the mass spectrum. The PMR spectrum showed signals for four methyl groups and two double doublets (1H each) centered at δ 2.60 (J = 12, 5.5 Hz) and 4.90 (J = 13, 5.5 Hz), which form the *MX* portion of an *AMX* pattern, with the *A* portion being hidden under the methylene envelope (4).

Dehydrobromination of I*h*, using lithium carbonate and lithium bromide in dimethylformamide (3), yielded the α,β-unsaturated ketone II[7]; IR: ν_{max} ($CHCl_3$) 3620 and 1660 cm^{-1}; UV: λ_{max} (CH_3OH) 230 nm (ϵ 8200), signals for four methyl groups and two doublets (1H each) at δ 7.06 (J = 9.5 Hz) and 5.80 (J = 9.5 Hz). These data are consistent only with placement of the secondary hydroxyl at C-1 or C-3. Position C-1 was eliminated by applying the octant rule (5). The predicted sign of the Cotton effect for a ketone at C-1 would be positive; at C-3, it would be negative. The observed sign for I*f* is negative, and thus the ketone (and, hence, the hydroxyl) can be placed at C-3. Since one coupling constant for the C-3 proton is large (J = 11 Hz), this proton is placed axial

[1] The plant material was obtained from the Caribbean island of Curacao, where it is used for the treatment of venereal disease. The plant was identified, collected, and provided to us by Dr. Julia Morton; a voucher specimen was deposited in the Herbarium of the Department of Pharmacognosy, University of Mississippi.

[2] Stemodin [$C_{20}H_{34}O_2$ (*m/e* 306.254, calculated *m/e* 306.256; the formula was also supported by elemental analysis), mp 195–196°, $[\alpha]_D^{25}$ −2.8° (c 1.03, pyridine)] had physical and spectral properties in agreement with those reported previously (1). The acetate of stemodin was also prepared, and the data agreed with those previously reported (1). Stemodinone [$C_{20}H_{34}O_2$ (*m/e* 304.238, calculated *m/e* 304.240; the formula was also supported by elemental analysis), mp 212–213°, $[\alpha]_D^{25}$ +13.1° (c 0.90, chloroform)] had physical and spectral properties as reported previously (1). It was also prepared by Jones oxidation of stemodin (1).

[3] The PMR data for all compounds were obtained at 60 MHz using deuterochloroform and tetramethylsilane as the internal standard.

[4] The formula was supported by high-resolution mass spectral and/or elemental analyses.

[5] The circular dichroism measurements were performed on a Jasco model J-40 automatic recording spectropolarimeter using methanol as the solvent.

[6] Compound I*g* was prepared from stemodinone as described previously (1). The physical and spectral properties of I*g*[4] were in agreement with those reported previously. Compound I*g* was identical in all respects (melting point, mixed melting point, TLC, IR, and NMR) to the Huang-Minlon reduction product obtained from I*f* and I*j*.

[7] Compound II could not be obtained in crystalline form but was one spot on TLC; the formula $C_{20}H_{30}O_2$ was confirmed by high-resolution mass spectrometry.

and the hydroxyl can be equatorial. Thus, maritimol (I*a*) is stemodane-3β,13α-diol[8].

Stemodinol (I*b*) had a melting point of 182–183° (chloroform–*n*-hexane) and $[\alpha]_D^{25}$ +13.8° (c 1.01, pyridine). It exhibited a parent ion peak at *m/e* 306.256, corresponding to the formula $C_{20}H_{34}O_2$ (calculated *m/e* 306.256), which was also supported by elemental analysis. The IR spectrum had absorptions at ν_{max} ($CHCl_3$) 3620 and 3340 cm^{-1}. The PMR spectrum indicated the presence of three methyl singlets at δ 0.70, 0.90, and 1.11 and a pair of doublets forming an *AB* quartet at δ_A 3.37 (J = 10 Hz) and δ_B 2.85 (J = 10 Hz). The pair shifted to δ_A 3.77 (J = 11 Hz) and δ_B 3.62 (J = 11 Hz) in the monoacetate[4] (I*i*), mp 81–83° (ethanol–water); $[\alpha]_D^{25}$ +17.5° (c 0.40, chloroform); IR: ν_{max} (KBr) 3410 and 1735 cm^{-1}; PMR: δ 0.83, 0.95, 1.13, and 2.05 (s, 3H each).

Oxidation of I*b* with chromium trioxide–pyridine produced the aldehyde (I*j*)[4], mp 145–146°; IR: ν_{max} ($CHCl_3$) 3620 and 1730 cm^{-1}; PMR: δ 0.90, 1.03, 1.15 (s, 3H each), and 9.20 (s, 1H). These data suggest that stemodinol (I*b*) is also isomeric with stemodin (I*c*) and that I*b* contains a primary alcohol. Reduction of I*j* under Huang-Minlon conditions (2) gave the known desoxy derivative, I*g*[6]. Thus, stemodinol contains the same carbon skeleton as stemodin. The primary alcohol could be located at any one of four positions (C-17, C-18, C-19, or C-20).

The failure of I*b* to form an acetonide with cupric sulfate and acetone[9] and the formation of III by treatment of I*b* with 1% HCl in acetone eliminated C-17 as a possible location of the primary alcohol group. The dehydrated product, III[10], had ν_{max} ($CHCl_3$) 3640 and 3470 cm^{-1}; PMR: δ 0.78, 1.01 (s, 3H each), 1.65 (d, 3H, J = 1.5 Hz), 4.95 (1H, broad), and the *AB* quartet δ_A 3.34 (J = 10 Hz) and δ_B 3.10 (J = 10 Hz).

The location of the primary alcohol at C-18[11] is based on PMR data. The center of the *AB* quartet for hydroxymethyl groups and their corresponding acetates has been related to their positions at C-18 and C-19 (8). The *AB* quartet for I*b* and its acetate I*e* is centered at 197 and 222 Hz, respectively, consistent with placement of the primary alcohol at C-18. Additional evidence for this placement can be found by observing both the chemical shift and long-range coupling of the aldehydic proton in positions C-18 and C-19 (9). If the aldehyde were at C-19, the signal for the aldehydic proton would appear near δ 9.70 as a doublet (J = 1–2 Hz) (8) rather than as a singlet near δ 9.20 as in I*j*. Based on this evidence, the structure proposed for stemodinol (I*b*) is stemodane-13α,18-diol[8].

[8] The numbering used is that for the hypothetical hydrocarbon, stemodane, as proposed by the authors in Ref. 1. This differs from the numbering proposed for aphidicolane, a hydrocarbon differing in stereochemistry only at C-9, C-13, and C-14 (6).

[9] Compound I*b*, cupric sulfate, and acetone were stirred at room temperature for 3 days and only starting material was recovered.

[10] Compound III could not be obtained in crystalline form but was one spot on TLC; the formula $C_{20}H_{32}O$ was confirmed by high-resolution mass spectrometry.

[11] Although C-20 was also a possibility, it was ruled out on biogenetic grounds since there are no known examples of diterpenes with a primary alcohol at this position. Numerous examples occur with hydroxyl at C-18 or C-19 (7).

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