A NEW DITERPENE ACID FROM *SALVIA TOMENTOSA*

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ABSTRACT.—A new diterpene acid, 3-β-hydroxy-8,11,13(14),15-abietatetraen-18-oic acid, along with dehydroabietic acid, three triterpenes, namely, ursolic, oleanolic and crateagolic acids, and the steroidal glycoside sitosteryl 3-β-glucoside, were isolated from leaves of *S. tomentosa* Mill. All of the compounds were characterized by chemical and spectral methods.

Many diterpenoids are known from species of *Salvia* (Family Labiatae). For example, the diterpene carnosol was found in *S. officinalis* (1, 2) and *S. triloba* (3). Later ferruginol was obtained from *S. officinalis* (4). Both carnasol and ferruginol have the 8,11,13-abietatrien skeleton. Salvin, one of the antibacterial diterpenes from *S. officinalis*, is 11,12-dihydroxy-8,11,13(14)-abietatrien-20-oic acid (5). In addition, naphthaquinones, namely tanshinone I and II and cryptotanshinone, were isolated from *S. miltiorrhizza* (6, 7). Several diterpene quinones (8, 9) and diterpene alcohols (10, 11) were obtained from different *Salvia* species.

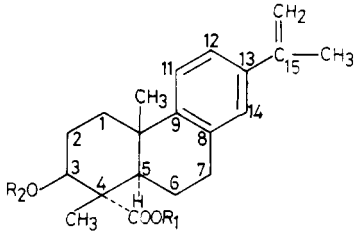
We report here the isolation and structure determination of a new diterpene acid and several known compounds including three triterpenes, a diterpene acid, and a steroidal glycoside from *Salvia tomentosa* collected in the Mediterranean section of Turkey. The new acid is of the abietane-type common for species of *Pinus* (12, 13), *Agathis* (14) and *Picea* (15) as well as *Salvia* (3–5).

Although the flavonoids in *S. tomentosa* were described previously (16), this is the first report of terpenoids from this species.

RESULTS AND DISCUSSION

A benzene extract of *S. tomentosa* was partitioned with water (16). The material from the aqueous part, when fractioned over silica gel, afforded a crude diterpene acid which, after crystallization from ethanol, was established to be 3-β-hydroxy-8,11,13(14),15-abietatetraen-18-oic acid (**1a**). The same extract also contained crateagolic acid as well as the known steroidal glycoside, sitosteryl 3-β-glucoside. Silica gel column chromatography of the material from the benzene fraction afforded three known compounds, namely, ursolic, oleanolic and dehydroabietic acids.

The ir of the new acid **1a** showed hydroxyl (3440 cm^{-1}) and carboxylic (1707 cm^{-1}) functions as well as unsaturation (1675, 1625 cm^{-1}) and a 1,2,4-trisubstituted aromatic ring (885, 828 cm^{-1}). The uv spectrum exhibited a strong absorption at 251 nm (ϵ 14000) in accord with the presence of α-methyl styrene group (17). Pmr of the new compound in C_5D_5N showed three methyl singlets at δ 1.29, 1.73, and 2.14 (broadened) for the C_{10}, C_4, and C_{15} groups, respectively. Signals for three aromatic protons appeared between δ 7.2 and 7.4, and a broad two-proton triplet at δ 2.9 was in agreement with a benzylic methylene group at C_7. Two broad proton singlets at δ 5.1 and 5.5 were assigned to the methylene group of an isopropenyl moiety. Jones oxidation of the acid gave a ketone (ir: 1725 cm^{-1} and uv: 250 nm) which established a secondary hydroxyl group in the natural

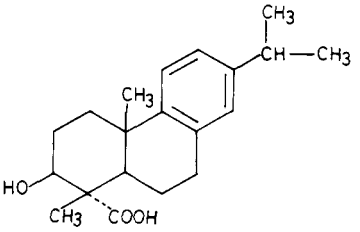


3β-ol-8,11,13(14),15-abietatetraen 18-oic acid

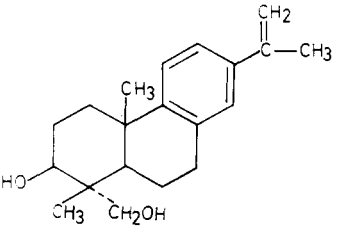
$R_1=R_2=H$, (1a)

$R_1=CH_3$; $R_2=H$, (1b)

$R_1=H$; $R_2=OCCH_3$, (1c)



3β-ol-8,11 13(14)-abietatrien 18-oic acid (2)

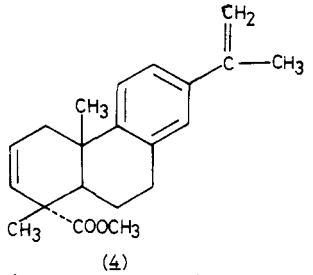


3β,4α-diol-8,11,13(14),15-abietatetraen (3)

product. This finding was further supported by a doublet for a proton on a carbon atom bearing a hydroxyl group at δ 4.7 in the pmr spectrum.

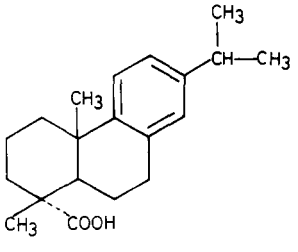
These spectral findings indicated that the new acid ($C_{20}H_{26}O_3$) differed from dehydroabietic acid (**5**, $C_{20}H_{28}O_2$), a compound with which it co-occurs, by the presence of one double bond and one hydroxyl group. Therefore, in order to establish a skeletal relationship, the new acid's methyl ester (**1b**) was converted to dehydroabietic acid methyl ester by dehydration with $POCl_3$ in pyridine at 5° for 16 hrs and then hydrogenation of the product at room temperature with Adam's catalyst. The final product was identified as dehydroabietic acid methyl ester by uv, ir, nmr and tlc; $[\alpha]^{30}$ +60 (in EtOH); literature value for dehydroabietic acid $[\alpha]_D$ +62° (EtOH) (18). Thus the abietane skeleton, including the stereochemistry at C_4, C_5 and C_{10}, was established for the new acid. Since an isopropenyl side chain was indicated by comparison of the pmr of the new acid and its hydrogenated product (a new six-proton doublet at δ 1.25, $J=6$ Hz), the only remaining structural problems concerned the location and stereochemistry of the hydroxyl group.

The proton on the carbon atom bearing the hydroxyl group exhibited coupling



(4)

2(3),8,11,13(14),15-abietapentaen 18-oic acid methyl ester



dehydroabietic acid (5)

with only two neighboring protons in accord with axial-equatorial ($J=6$ Hz) and axial-axial ($J=10$ Hz) coupling; this pattern requires a β-hydroxyl group at either position 1, 3 or 7. The assignment of the β-hydroxyl to C_3 is based on the following evidence. First, the ^{13}C nmr data (table 1) for the methyl ester of the new

TABLE 1. Comparison of ^{13}C nmr data for dehydroabietic acid and the methyl ester of new acid.

	Methyl ester (**1b**) of the new acid	Dehydroabietic acid (**5**)
C_1	36.9 t	37.9
C_2	30.2 t	18.5
C_3	75.6 d	36.5
C_4	53.7 s	47.4
C_5	45.5 d	44.5
C_6	21.3 t	21.7
C_7	27.3 t	29.2
C_8	134.6 s	134.4
C_9	148.1 s	146.1
C_{10}	36.5 s	36.8
C_{11}	124.4 d	123.9
C_{12}	123.3 d	123.7
C_{13}	143.1 s	145.4
C_{14}	126.2 d	126.7
C_{15}	138.7 s	33.4
C_{16}	111.9 t	23.9
C_{17}	21.7 q	23.9
C_{18}	177.8 s	185.5
C_{19}	10.7 q	16.1
C_{20}	25.1 q	25.1
OCH_3	52.2 q	

acid **1b**, when compared to those for dehydroabietic acid (**5**), indicated that C_3 and C_4 exhibited the expected α and β shifts of about 40–44 Hz and 7–10 Hz, respectively (C_3: δ 36.5 for **5** to 75.6 for **1b**; C_4: δ 47.4 for **5** to 53.7 for **1b**). Moreover, the signal for C_{10} in **1b** showed only an δ-effect (i.e., little or no shift) eliminating C_1 for the hydroxyl group. A small γ-shift (expected value: -3 to -4 Hz) was exhibited by C_1 (δ 37.9 in **5** versus 36.9 in **1b**). Furthermore, oxidation with MnO_2 in pyridine, both at room temperature and under reflux, did not yield a ketone, indicating that the hydroxyl grup is not benzylic and therefore not at C_7.

Finally, all the pmr (14, 15) and ^{13}C nmr (19) data for **1b** were in agreement with those published for similar compounds.

Pmr data of **1a** and **1b** in $CDCl_3$ versus pyridine confirmed the stereochemistry of the C_4 and C_{10} methyl groups relative to the C_4 carboxyl group since it is well established that the chemical shifts of methyl groups in terpenoids spatially near carbonyl or hydroxyl groups are highly affected by solvents (20–21). Moreover, it has also been shown that an ionized axial acid group at C_4 in abietic acid-type diterpene acids produces a deshielding effect of about 0.38 ppm on both the C_4 and C_{10} methyl groups, while the ionized equitorial acid moiety causes a large shift (0.25 ppm) only for the C_4–CH_3 (the C_{10}–CH_3 shifts only about 0.03 ppm). Since the new acid **1a** was not soluble in $CDCl_3$, the solvent shifts were determined by comparison of the spectrum of **1a** in d_5-pyridine with that of its methyl ester **1b** in $CDCl_3$, while **1b** was recorded in both solvents (table 2). Since only one methyl group for both **1a** and **1b** shifted, it must be the C_4-methyl group and therefore

the C_4-carboxyl in **1a** should have an equatorial (α) orientation as in dehydroabietic acid.

Ms degradation of **1b** gave fragments typical for the abietatetraen skeleton (23): M^+ at m/z 328 (27); ($M-CH_3$), 313 (0.5); ($M-H_2O$), 310 (1.0); ($M-H_2O-CH_3$), 295 (33); and ($M-H_2O-COOCH_3-CH_3$), 235 (54).

TABLE 2. Pyridine-induced pmr shifts of the methyl groups in **Ia** and **Ib**.

	$CDCl_3$	Pyr.	Δ	$CDCl_3$	Pyr.	Δ
	Ib	**Ia**	ppm	**Ib**	**Ib**	ppm
C_4-CH_3	1.29	1.73	0.44	1.29	1.56	0.27
C_{10}-CH_3	1.24	1.29	0.05	1.24	1.27	0.03

$LiAlH_4$ reduction of the new acid **1a** gave a primary alcohol **3** whose pmr spectrum showed a signal for the C_4-CH_3 group upfield at 0.95 ppm. An AB quartet ($J=11$ Hz) for the CH_2OH group, appeared in the spectrum of **3** at δ 3.74; acetylation shifted this quartet to 3.89 ppm.

The spectral and chemical transformations established structure **1a** for the new acid.

EXPERIMENTAL[1]

PLANT MATERIAL.—The plant material was collected from the Mediterranean section of Turkey (Antakya-old Antioch); a voucher is deposited in the Herbarium of the Faculty of Pharmacy, University of Istanbul (Voucher No. ISTE 35146). Air-dried leaves of the plant (1 kg) were extracted in a Soxhlet with light petrol and benzene; the latter extract was partitioned with water by the addition of 60% aqueous ethanol. After flavonoids were extracted from the aqueous layer with ether, the remaining aqueous layer afforded 15 g of a residue which was subjected to silica gel (0.063–0.2 mm) column (5 x 75 cm) separation. The column was eluted with a gradient of benzene and ethyl acetate beginning with benzene.

3-β-HYDROXY-8,11,13(14),15-ABIETATETRAEN-18-OIC ACID (**1a**).—When ethyl acetate reached 30% in the eluting solution, the fractions yielded 1 g of crude acid, which was crystallized from ethanol, mp 182–184° $[\alpha]^{30}D$ +86.6° (in EtOH). Found: C, 76.81; H, 8.24. $C_{20}H_{26}O_3$ requires: C, 76.43; H, 8.24. R_f 0.19 on silica gel plates using chloroform-ethanol (93:7). Uv, λ max (EtOH) 251 nm (ε 13800); ir (KBr) 3440 (OH), 3300, 3000 (C-H phenyl), 2920, 2880, 1707 (carboxyl), 1675, 1625, 1490 (phenyl), 1060 (C-O), 885 and 828 cm^{-1} (1,2,4-trisubstituted phenyl ring); pmr (C_5D_5N, TMS) 1.29 (s, C_{10}-CH_3), 1.73 (s, C_4-CH_3), 2.14 (brs, C_{15}-CH_3), 1.8 (2H, m), 2.2 (2H, m), 2.5 (2H, dd), 2.9 (2H, brt, benzylic CH_2), 4.7 (1H, dd, $J=6$ Hz, 10 Hz, H gem. to OH), 5.10 (1H, brs), 5.50 (1H, brs) (=CH_2), 7.2–7.4 (3H, phenyl protons); ms, M^+, 314 (100); ($M-15$), 299 (20); ($M-18$), 296 (12); ($M-H_2O-CH_3$), 281 (40) ($M-CH_3-COOH$), 254 (25); ($M-CH_3-H_2O-COOH$), 236 (60).

METHYL ESTER (**1b**) OF THE NEW ACID.—An ether solution of **1a** (250 mg) was treated with CH_2N_2 for 5 hrs; when the solution was evaporated to dryness, a glass-like material was obtained. Crystallization from ethanol yielded colorless crystals, mp 92–94°; uv (EtOH) λ max 251 (ε 14000); ir (KBr) 3250 (OH), 3070, 2970, 1720 (-COOMe), 1630, 1495, 1430, 1380, 890, 828 cm^{-1}; pmr ($CDCl_3$) 1.24 (s, C_{10}-CH_3), 1.29 (s, C_4-CH_3), 2.1 (d, $J=2$ Hz, C_{15}-CH_3), 1.87 (2H, t), 2.3 (2H, brd), 2.9 (2H, brt), 3.85 ($COOCH_3$), 4.05 (1H, t, $J=6$ Hz, H gem. to OH), 5.05 (1H, brs), 5.39 (1H, brs) (=CH_2), 7.2 (2H, $J=9$ Hz), 7.22 (1H, s) (phenyl protons); pmr (C_5D_5N) 1.27 (s, C_{10}-CH_3), 1.56 (s, C_4-CH_3), 2.16 (brs, C_{15}-CH_3), 3.7 ($COOCH_3$), 4.5 (1H, t) (H, gem. to OH), 5.15 (1H, brs), 5.50 (1H, brs) (=CH_2), 7.2–7.3 (3H, phenyl protons); ^{13}C nmr of **1b** ($CDCl_3$) 36.9 (t) C_1, 30.2 (t) C_2, 75.6 (d) C_3, 53.7 (s) C_4, 45.5 (d) C_5, 21.3 (t) C_6, 27.3 (t) C_7, 134.6 (s) C_8, 148.1 (s) C_9, 36.5 (s) C_{10}, 124.4 (d) C_{11}, 123.3 (d) C_{12}, 143.1 (s) C_{13}, 126.2 (d) C_{14}, 138.7 (s) C_{15}, 111.9 (t) C_{16}, 21.7 (q) C_{17}, 177.8 (s) C_{18}, 10.7 (q) C_{19}, 25.1 (q) C_{20}, 52.2 (q) C_{21}: ms, M^+, 328 (27);

[1]Spectra were recorded with the following instruments: uv, Varian Techtron model 635; ir, Perkin-Elmer 577 grating model; pmr, Varian HA-100 and Bruker spectrospin 200 MHz; ms, Dupont 21-491. Melting points were recorded in a Reichert microscope instrument and not corrected. The adsorbants for cc and tlc were from A. Merck.

(M–CH_3) 313 (0.5); (M–H_2O), 310 (1); (M–H_2O–CH_3), 295 (33); (M–H_2O–75), 235 (54), 197 (13), 183 (9), 91 (20), 83 (100), 71 (50), 43 (55).

ACETYLATION OF THE NEW ACID TO GIVE **1c**.—Twenty mg of **1a** was dissolved in pyridine and acetylated with acetic anhydride at room temperature (24 hrs); amorphous compound $[\alpha]^{30}D$ +66° (in EtOH); uv (EtOH) λ max 251 nm; ir (KBr) 3400 (sh), 3050, 2920, 2850, 1720 (acetyl), 1680, 1590, 1560, 1440, 1360, 1230 (C–O), 1020, 880, 820 cm^{-1}; pmr ($CDCl_3$) 1.25 (s, C_4–CH_3), 1.29 (s, C_{10}–CH_3), 2.00 (acetyl methyl), 2.12 (s, C_{15}–CH_3) 2.9 (2H, brt), 4.9 (t, H gem. to acetyl), 5.05 (1H, brs), 5.3 (1H, brs), 7.1–7.3 (3H, phenyl protons).

HYDROGENATION OF THE NEW ACID TO GIVE **2**.—Fifty mg of **1a** was hydrogenated in the presence of PtO_2/C (10%) in ethanol for 16 hrs. After removal of the catalyst, the solvent was evaporated *in vacuo*; the residue was crystallized from ethanol, mp 169–171°. Uv (EtOH) λ max 273 nm (ε 400); ir (KBr) 3400 (OH), 1695 (carboxyl), 1650, 1520, 1465, 1380, 1070, 1030, 890, 825 cm^{-1}; pmr ($CDCl_3$) 1.25 (6H, d, J=6 Hz, isopropyl group), 1.20 (s, C_4–CH_3), 1.27 (s, C_{10}–CH_3), 1.7 (2H, m), 2.9 (2H, t, J=6 Hz), 4.1 (1H, brt), 6.9–7.2 (3H, phenyl protons); pmr (C_5D_5N) 1.22 (6H, d, J=7 Hz, isopropyl group), 1.25 (s, C_4–CH_3), 1.72 (s, C_{10}–CH_3), 4.7 (1H, t).

REDUCTION OF **1a** TO ALCOHOL **3**.—When $LiAlH_4$ was added to a THF solution of 50 mg of **1a**, an alcohol **3** was formed as an amorphous material; uv (EtOH) λ max 251 nm; ir (KBr), 3400 (OH), 3050, 2920, 1620, 1600, 1560, 1450, 1370, 1080, 1070, 1030, 1010, 930, 880, 820 cm^{-1}; pmr ($CDCl_3$) 0.95 (s, C_4–CH_3), 1.24 (s, C_{10}–CH_3), 2.12 (d, J=1 Hz, C_{15}–CH_3), 2.3 (2H, dd), 2.9 (2H, t), and AB quartet centered at 3.74 for CH_2OH, J=11 Hz, 4.1 (1H, m, H gem. to OH), 5.05 (1H, brs), 5.32 (1H, brs), 7.2 (2H, d, J=9 Hz), 7.36 (1H, s).

ACETYLATION OF **3**.—Thirty mg of **3** was acetylated in the usual way, giving an amorphous product; uv λ max (EtOH) 251 nm; ir (KBr) 3050, 2980, 1730, 1725, 1650, 1580, 1450, 1255, 880, 820 cm^{-1}; pmr ($CDCl_3$) 0.92 (s, C_4–CH_3), 1.25 (s, C_{10}–CH_3), 1.98 (acetyl CH_3), 2.01 (acetyl CH_3), 2.12 (s, C_{15}–CH_3), AB quartet of CH_2OAc centered at 3.89 with J=12 Hz, 4.9 (1H, t), 5.05 (1H, brs), 5.32 (1H, brs), 7.2 (2H, d), 7.25 (1H, s).

OXIDATION OF THE NEW ACID.—Fifty mg of **1a** was dissolved in 2 ml of Me_2CO, then 2 ml of Jones reagent were added, and the solution was left at room temperature for 1.5 hrs. The solution was diluted with water and extracted with chloroform; upon evaporation, the chloroform layer afforded an amorphous material, uv λ max (EtOH) 250 nm; ir (KBr) 3250, 3000, 2960, 2880, 1725 (carbonyl), 1698 (carboxyl), 1650, 1570, 1480, 880, 825 cm^{-1}.

DEHYDRATION OF THE METHYL ESTER OF THE NEW ACID TO GIVE **4**.—Fifty mg of **1b** was dissolved in 1 ml pyridine, and then 0.1 ml $POCl_3$ was added. The mixture was stored in a refrigerator for 16 hr. The solution was poured onto ice and extracted with ether; the solvent was evaporated *in vacuo*. Uv λ max (EtOH) 250 nm, pmr ($CDCl_3$) 1.24, 1.30, 2.1 (methyl singlets for C_4, C_{10} and C_{15} groups), 2.9 (2H, benzylic CH_2), 3.7 (s, $COOCH_3$), 5.05 (1H, brs), 5.39 (1H, brs) (=CH_2), 5.2 (brm, 2H) (vinylic protons), 7.2–7.3 (3H, phenyl protons).

HYDROGENATION OF THE DEHYDRATED PRODUCT **4**.—Ten mg of **4** was dissolved in ethanol and 10 mg of PtO_2/C (10%) was added; the hydrogenation was carried out for 6 hr at room temperature. After removal of the catalyst, the solvent was evaporated *in vacuo*; the residue was cleaned by preparative tlc in benzene-chloroform (3:1). The band (R_f 0.4) was extracted with chloroform, the solvent was evaporated, and the product was crystallized from ethanol, mp 158°, uv λ max 275 (ε 560), 269 (ε 580), 260 (sh) nm; ir (KBr) 3400 (OH), 2950, 2920, 2850, 2600, 1726 ($COOCH_3$), 1500, 1450, 1280, 1200, 1120, 885, 820 cm^{-1}; pmr ($CDCl_3$, TMS) 1.20 (3H, s, C_{10}–CH_3), 1.23 (3H, s, C_4–CH_3), 1.27 (6H, d, isopropyl group), 2.9 (2H, brt, benzylic CH_2), 3.68 (3H, s, $COOCH_3$) 6.95–7.2 (3H, phenyl protons).

CRATAEGOLIC ACID.—The mp of crataegolic acid was 265°. When ethyl acetate reached 40% for the elution of the original silica gel column (see above), a known triterpenic acid, crataegolic acid, was obtained. Ir and pmr indicated a triterpenic acid; acetylation (mp 200–200°) showed the presence of two acetyl groups (ir, pmr and ms). The methyl ester of the acid was prepared (mp 215–217°) and found to be identical with an authentic sample (ir, pmr, ms and tlc). Therefore, the natural product was crataegolic acid.

SITOSTERYL 3-β-D-GLUCOSIDE.—Finally, ethyl acetate-acetone (8:2) elution of the column gave a steroidal glycoside, mp 305°; ir, pmr and ms indicated that the compound was sitosteryl 3-β-D-glucoside. Acetylation afforded a tetraacetate (mp 162°). Standard sample comparison (ir, pmr, tlc) for both the glycoside and the hydrolysis product established that the compound was sitosteryl 3-β-glucoside.

DEHYDROABIETIC ACID (**5**).—The remaining benzene part from the aqueous partitioning of the original extract (see above) was evaporated to dryness (20 g) and chromatographed over a silica gel column (4 x 60 cm). The column was eluted with a gradient of benzene and ethyl acetate, beginning with benzene. The benzene elutes yielded a single compound which was

crystallized from ethanol, mp 172–173°, R_f 0.48 on silica gel G plates with chloroform-ethanol (97:3) as the developing solvent; uv λ max (EtOH) 275 (ε 560), 269 (ε 560), 260 (sh) nm; ir (KBr) 3400 (OH), 3040, 2920, 2860, 2600, 1685 (carboxyl), 1500, 1450, 1280, 1200, 950, 885, 820 cm^{-1}; pmr ($CDCl_3$, TMS) 1.18 (3H, s, C_{10}-CH_3), 1.23 (3H, s, C_4-CH_3), 1.3 (6H, d, isopropyl group), 2.9 (2H, brt, benzylic CH_2), 6.95–7.2 (3H, aromatic protons). Standard sample comparison (ir, pmr, tlc) established that the compound was dehydroabietic acid.

DEHYDROABIETIC ACID METHYL ESTER.—Twenty mg of **5** dissolved in ether was treated with CH_2N_2 for 5 hrs; when the solution was evaporated to dryness, the residue gave (from ethanol) an oily semicrystalline product; λ max 275, 269, 260 (sh); ir (KBr) 3400 (OH), 2950, 2920, 2860, 1726 ($COOCH_3$) 1500, 1450, 1245, 1175, 1120, 880, 820, 815 cm^{-1}; pmr ($CDCl_3$, TMS) 1.20, 1.23 (C_4 and C_{10}-CH_3, 3H each, s); 1.27 (6 H, d, isopropyl group), 2.9 (2H, brt, benzylic CH_2), 3.68 (3H, s, $COOCH_3$), 6.85–7.20 (3H; phenyl protons); ms, M^+, 314; (M-CH_3), 299; (M-47), 267; (M-59), 255; (M-75), 239; (M-129), 185; (M-131), 183; (M-241), 173; (M-155), 159.

URSOLIC AND OLEANOLIC ACIDS.—When ethyl acetate reached 10% for the eluting solvent for the column which afforded dehydroabietic acid (see above), a mixture of triterpenic acids was obtained. The separation of the mixture was not effected by column or preparative tlc. Therefore, methyl esters were prepared with CH_2N_2 and subjected to gc analysis: 3% SE 30 on Chromosorb W, AW-DMCS 60, 60–80 mesh was used in a 3.2 m column. Two compounds with retention times of 7.67 and 8.57 were obtained. Comparison with standard acid methyl esters and integration of the peak areas established that the two peaks corresponded to 79.04% ursolic acid (rt 8.57) and 20.96% oleanolic acid (rt 7.67).

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