was heated briefly to effect solution and allowed to stand for several days. After addition of 26 ml. of water, four crops of crystals were obtained at −15° as follows: (a) 100 mg., m.p 130–144°; (b) 50 mg., m.p. 136–150°; (c) 100 mg., m.p. 110–160°; and (d) 60 mg., m.p. 160–180°. Recrystallization of fractions a and b from acetone gave a colorless solid, m.p. 135–185°, which showed two spots (t.l.c.)[19] at R_f 0.7 and 0.8.

Anal. Calcd. for $C_9H_{12}N_4O_3$ (VI, R = H): C, 48.21; H, 5.39. Calcd. for $C_{11}H_{14}N_4O_4$ (VI, R = Ac): C, 49.62; H, 5.30. Found (on different preparations): C, 48.01, 48.70; H, 5.52, 5.30.

Recrystallization of d from acetone gave a colorless solid, m.p. 182–185°; $\lambda_{max}^{95\%\ EtOH}$ 232 with shoulder at 264 mμ; $\lambda_{max}^{95\%\ EtOH}$ (pH 1) 278 and 232 mμ; λ_{max}^{KBr} 3.0–3.6 (broad), 3.16, 3.36, 5.80, and 6.05 μ; R_f (t.l.c.)[19] 0.8. This compound was presumed to be VI (R = Ac).

Other similar preparations of oximino ester VI gave variable yields of an apparently homogeneous product which by t.l.c. showed a single spot at R_f 0.7. After recrystallization from 95% ethanol the colorless solid had m.p. 148–149°; $\lambda_{max}^{95\%\ EtOH}$ 295 mμ (ε 4300) and 226 mμ (ε 20,000); $\lambda_{max}^{95\%\ EtOH}$ (pH 1) 301 and 220 mμ; λ_{max}^{KBr} 2.9–3.0 (broad), 3.01, 3.12, 3.61 (broad), 5.80, and 6.15 μ; n.m.r. (measured in hexadeuterioacetone) absorptions at τ 8.78 (triplet, J = 7 c.p.s.), 7.98 (multiplet), 6.10, 5.82 (quartet, J = 7 c.p.s.), 3.98, 3.55 (doublet, J = 5 c.p.s.), and 1.92 (doublet, J = 5 c.p.s.) with relative areas of 3:2:2:2:1:1:1. Addition of a singlet drop of deuterium oxide to the acetone solution caused immediate disappearance of the absorption at τ 3.98. This product was assumed to be VI (R = H).

β-(2-Aminopyrimidin-4-yl)alanine Hydrochloride.—The α-oximino ester VI was converted to *dl*-lathyrine by procedures similar to those described[22] previously. VIa–VIb mixture (100 mg.) was heated under reflux for 10 min. with 1 ml. of 1 *N* sodium hydroxide. After addition of 0.6 ml. of glacial acetic acid to the hot solution, colorless crystals slowly formed. The solid material was filtered and washed two times with water to afford 72 mg. of VII, m.p. 195–198° dec.; $\lambda_{max}^{95\%\ EtOH}$ (pH 1) 360 mμ (ε 300), 301 mμ (ε 5000), and 220 mμ (ε 27,000); λ_{max}^{KBr} 3.0–3.4 (broad), 3.54, 5.96, and 6.16 μ; R_f 0.65 (t.l.c. using 15:5:6 butanone–propionic acid–water).

To a solution containing 454 mg. (1.8 mmoles) of stannous chloride dihydrate in 2.2 ml. of concentrated hydrochloric acid was added 161 mg. (0.8 mmole) of VII. After standing several days, the reaction mixture was diluted with 25 ml. of water and saturated with hydrogen sulfide. The yellow precipitate formed was separated by filtration, and the filtrate was concentrated by lyophilization at 0° and 1 mm. to 151 mg. of a pale yellow solid, dec. >140°. The chromatographic behavior of this product was identical with that of natural lathyrine. The characteristic red color upon ninhydrin treatment was obtained, and identical R_f values were observed in the following solvent systems: 12:3:5 butanol–acetic acid–water (R_f 0.27, Whatman No. 1), 3:1 propanol–water (R_f 0.31, Whatman No. 1), 4:1 phenol–water containing 0.5% ammonia (R_f 0.53, silica gel G), and 15:5:6 butanone–propionic acid–water (R_f 0.23, silica gel G). The major peak observed during column chromatography (using a 50-cm. Amberlite IR-120 resin as absorbent, 0.38 *N* sodium citrate buffer at pH 4.26 as eluent, at 30–50°, in conjunction with a Beckman Spinco Model 120 amino acid analyzer) emerged at 6 hr., 12 min., with the optical density at 440 mμ 2.5 times greater than that at 570 mμ. An equimolar mixture of synthetic and natural lathyrine emerged from the column as a single symmetrical peak, with a D_{440}/D_{570} ratio of 2.5.

A portion (78 mg.) of lyophilized material was dissolved in 1 ml. of water, and acetone was added to a faint turbidity. Upon standing at −15°, 28 mg. of white solid (first crop) was obtained. After three recrystallizations (acetone–water) and drying (56°, 1 mm.), 8 mg. of colorless solid, dec. >165°, was obtained. This material had $\lambda_{max}^{pH\ 1}$ 298 and 222 mμ; $\lambda_{max}^{pH\ 13}$ 292 and 226 mμ; λ_{max}^{KBr} 2.9, 3.07, 2.9–4.4 (broad), 5.88, 6.11, and 6.29 μ.

Anal. Calcd. for $C_7H_{11}ClN_4O_2 \cdot 0.5H_2O$: C, 36.93; H, 5.31; Cl, 15.57; N, 24.62. Found: C, 37.66; H, 5.32; Cl, 15.44; N, 24.35.

When a drop of hydrochloric acid and additional acetone were added to the mother liquor from the first crystallization, 23.9 mg. of colorless needles, $[\alpha]^{27}D$ 0.0° (*c* 1.7, water) was obtained. This material, in contrast to that obtained in the first crop, possessed an infrared spectrum identical with that of natural lathyrine hydrochloride. This variation in infrared spectra is attributed to differences in crystal form.

Constituents of *Iva* Species. IV. Structure of Pseudoivalin, a New Guaianolide[1,2]

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Two new guaianolides, pseudoivalin and dihydropseudoivalin, have been isolated from the nonpolar sesquiterpene lactone fraction of a variety of *Iva microcephala* Nutt. Their structures are shown to be **2** and **3**. The stereochemistry **22** is postulated.

In an earlier paper[1] we described the isolation and structure determination of microcephalin (**1**), a polar sesquiterpene lactone constituent of a variety of *Iva microcephala* Nutt. collected in Taylor County, Florida.[3] We now deal with the nonpolar fraction which consists of two new sesquiterpene lactones, pseudoivalin (**2**) and its dihydro derivative **3**.

The two nonpolar constituents of *Iva microcephala* were difficult to separate. In fact the mixture, m.p 130–132°, had properties reminiscent of ivalin, m.p. 131–132°,[4] although it was finally resolved into a solid component (**2**), $C_{15}H_{20}O_3$, m.p. 122–123°, which was named pseudoivalin, and a liquid (**3**), $C_{15}H_{22}O_3$.[5]

The physical properties of pseudoivalin, $[\alpha]D$ −145°, high-intensity ultraviolet absorption at 210 mμ, infrared bands at 1760 and 1660 cm.$^{-1}$, suggested the presence of an exocyclic methylene group conjugated with a lactone function also found in other constituents of *Iva* species.[1,4,6] The presence of a second, perhaps tetrasubstituted double bond was inferred from a weak absorption near 1630 cm.$^{-1}$ in the infrared spectrum which also revealed the presence of a hydroxyl group. The latter was probably tertiary since it could not be acetylated with pyridine–acetic anhydride, although more vigorous conditions resulted in the formation of an acetate **4**.

The functional groups postulated on the basis of the spectroscopic properties were confirmed in the following way. Epoxidation of **2** and **4** resulted in the formation of two epoxides (**5** and **6**) whose ultraviolet (211 mμ, ε 7400) and infrared spectra (for **5**: 3700, 3500, 1770,

(1) Previous paper: W. Herz, G. Högenauer, and A. Romo de Vivar, *J. Org. Chem.*, **28**, 1700 (1964). In this paper the species yielding microcephalin was incorrectly attributed. The correct name is *Iva microcephala* Nutt.

(2) Supported in part by a grant from the United States Public Health Service (GM-05814).

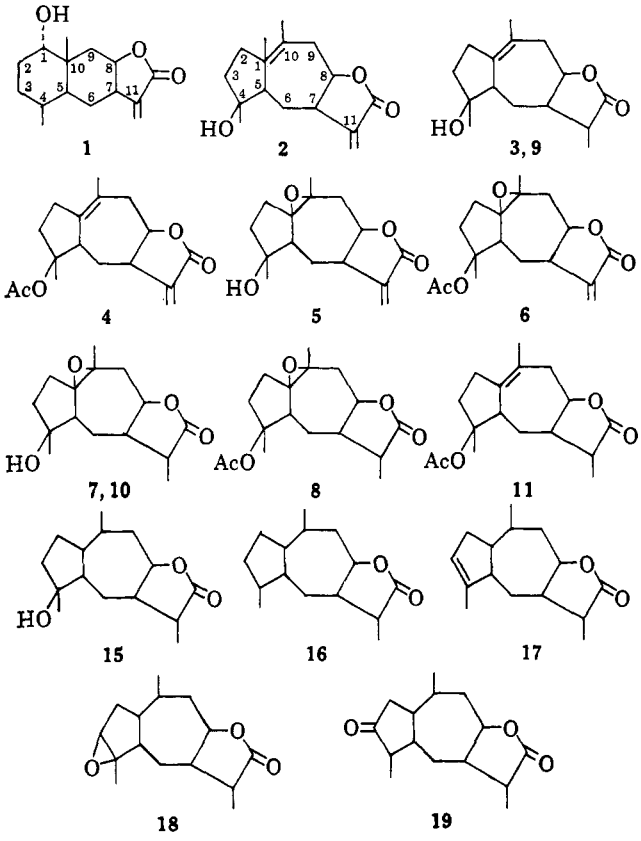
(3) Material collected to the north and west of Tallahassee furnished ivalin consistently[1] and never any microcephalin or pseudoivalin.

(4) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

(5) That the mixture of solid **2** and liquid **3** melted at a temperature higher than that of the pure solid was an additional factor complicating analysis of the extract.

(6) W. Herz and N. Viswanathan, *J. Org. Chem.*, **29**, 1022 (1964).

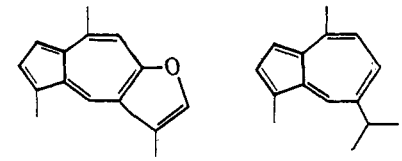
CHART I



1660 cm.$^{-1}$; for **6**: 1770, 1745, and 1660 cm.$^{-1}$) still indicated the presence of a conjugated exocyclic methylene group. Hydrogenation of **5** and **6** led to **7** and **8** whose ultraviolet and infrared spectra indicated that the conjugated double bond had been saturated. Ozonolysis of **2**, **4**, and **5** resulted in the liberation of formaldehyde; **7** or **8** were inert.

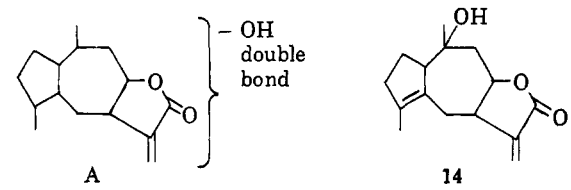
Pseudoivalin itself furnished two epimeric unconjugated dihydro derivatives **3** and **9** depending on the method of reduction. Catalytic hydrogenation yielded a substance **3** identical in all respects with the oily material isolated directly from the plant. Chemical reduction resulted in a substance **9** possessing the more stable configuration α to the lactone carbonyl since treatment with base converted **3** to **9**. The unconjugated double bond had remained unaffected by both methods of reduction since **3** and **9** could be converted to epoxides **7** and **10**, the former being epimerizable to the latter. Similarly, sodium amalgam reduction of **4** generated a dihydro derivative **11**.

The functional groups thus shown to be present (two double bonds, hydroxyl and lactone) in conjunction with the empirical formula required that pseudoivalin be bicyclic. A clue to the carbon skeleton was provided by the observation that various attempts to dehydrate pseudoivalin which, incidentally, did not result in the isolation of well-characterized products, were accompanied by the formation of highly colored bluish green solutions. This suggested that pseudoivalin was an azulenogen and indeed pyrolysis of pseudoivalin led to linderazulene (**12**); reduction and dehydrogenation led to a mixture of guaiazulene (**13**) and linderazulene in relatively respectable yields. As a working hypothesis, partial formula A was therefore adopted where lactone



ring closure to C-6 is necessitated by the isolation of linderazulene.

Consideration of the n.m.r. spectra of pseudoivalin and its derivatives (Table I) supported formula A and allowed expansion to **2** or **14**. Pseudoivalin and its

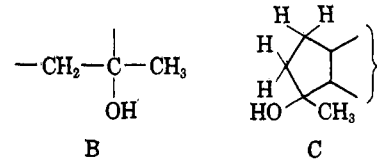


acetate **3** exhibited the typical low-field doublets of the exocyclic methylene group; these disappeared on reduction and were replaced by a methyl doublet at 1.18 p.p.m. No other vinyl proton was in evidence which confirmed that the unconjugated double bond was tetrasubstituted. One of these substituents was a methyl group, its presence betrayed by a narrowly split doublet at 1.57 p.p.m. which moved to higher field on epoxidation.

A third low-field proton, immovable near 4.6 p.p.m., had to be ascribed to the lactonic hydrogen at C-8. The absence of a fourth immediately signified the tertiary nature of the hydroxyl group. If this were attached to a ring junction, *i.e.*, C-1 or C-5, no place remains for the tertiary methyl group which is responsible for a singlet near 1.1 p.p.m. Hence the tertiary hydroxyl group is attached to a carbon atom also bearing a methyl group, which limits the possibilities to **2** or **14**.

To confirm these formulas it was necessary to demonstrate the presence of a five-membered ring, to decide between them to locate the double bond. This was accomplished in the following manner.

Catalytic hydrogenation of the tetrasubstituted double bond was difficult but could be achieved readily with ruthenium dioxide at elevated temperature and pressure. The n.m.r. spectrum of the resultant tetrahydropseudoivalin (**15**) exhibited the expected methyl singlet and two methyl doublet signals. Prolonged exposure to high pressure and temperature led mainly to the crystalline desoxy derivative **16** which was also accessible by hydrogenation of **17**, prepared from **15** by treatment with methanesulfonyl chloride–pyridine. The n.m.r. spectrum of **17** had one vinyl methyl and one vinyl proton singlet, the latter only slightly broadened by spin coupling to H-2, thus confirming the presence of the grouping B in pseudoivalin.



The unsaturated lactone **17** was converted to the epoxide **18** and the latter rearranged with boron trifluoride in the usual manner. The end product **19** was

TABLE I[a]

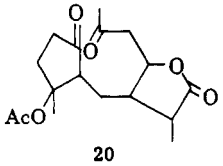
N.M.R. SPECTRA OF PSEUDOIVALIN AND ITS DERIVATIVES

Compd.	H-8	H-13	C-4 CH_3	C-10 CH_3	C-11 CH_3	Misc.
2	4.6 c	6.02 d (3) 5.45 d (3)	1.00	1.57 d (1)	...	...
3	4.65 c	...	1.08	1.65	1.18 d (7)	...
4	4.63 c	6.08 d (3) 5.45 d (3)	1.21	1.60 br	...	1.94[b]
5	4.80 t	6.29 d (3) 5.62 d (3)	1.10	1.25	...	...
6	4.72 m	6.21 d (3) 5.62 d (3)	1.27	1.42	...	2.01[b]
7	4.6 c	...	1.24	1.30	1.18 d (6)	...
9	4.6 c	...	1.00	1.66	1.25 d (5)	...
10	4.62 c	...	1.19	1.28	1.22 d (6)	...
11	4.7 c	...	1.27	1.67 br	1.32 d (7)	2.03[b]
15	4.5 c	...	1.30	0.97	1.12 d (7)	2.8 m[c]
16	4.61 c	...	0.93 d (7)	0.93 d (7)	1.08 d (7)	2.84 q[c]
17	4.5 c	...	1.75	1.15 d (6)	1.25 d (6)	5.3 br[d]
18	4.58 c	...	1.43	0.92 d (7)	1.22 d (7)	2.86 q,[c] 3.3 br[d]
19	4.51 c	...	1.01 d (7)[e]	0.99 d (7)[e]	1.12 d (7)	

[a] Values are given in p.p.m. relative to tetramethylsilane as internal standard. All signals in first two columns correspond to one proton, all signals in last four, to three unless otherwise specified. Singlets are unmarked, multiplets are described as follows: d, doublet; t, triplet; q, quartet; br, somewhat broadened singlet; c, complex signal whose center is given; m, multiplet of uncertain multiplicity. Numbers in parentheses denote coupling constants in c.p.s. [b] Acetate. [c] H-11 partially superimposed on other absorption. [d] H-3. [e] Assignment arbitrary.

clearly a cyclopentanone (infrared bands at 1775 and 1750 cm.$^{-1}$) which had an α-methylene group (positive Zimmerman test). Partial formula C for pseudoivalin established in this fashion coupled with the experimental results cited previously left **2** as the sole structure compatible with the evidence.

We record in the following the results of an additional transformation which was intended to shed light on the structure of pseudoivalin. Ozonolysis of **11** followed by reductive work-up afforded the acetoxydiketo lactone **20** (infrared bands at 1780, 1750 double strength, and 1740 cm.$^{-1}$), which was clearly a methyl ketone (positive iodoform test, n.m.r. signal at 2.22 p.p.m.). The alternative structure **14** being considered at this juncture would have led to a methyl ketone as well, but it was anticipated that the presence of a cyclopentanone carbonyl in a ketone **20** derived from **2** would permit facile differentiation between the two possibilities. In the event, while **20** did indeed exhibit a new infrared band at 1750 cm.$^{-1}$, the abnormally high frequency of the methyl ketone function at 1740 cm.$^{-1}$ tended to becloud the issue.



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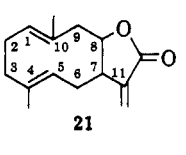

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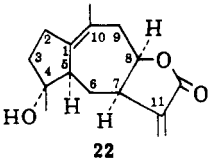


22

The new variety of *Iva microcephala* Nutt. provides the first example of a plant which generates simultaneously eudesmanolides and guaianolides. Microcephalin (**1**) and pseudoivalin (**2**) can be envisaged as having been formed from the same germacranolide (**21**) by two different modes of oxidative cyclization. The stereochemistry of microcephalin is exactly that predicted by the Markovnikov-oriented cyclization involving C-10 and C-5[7] except for the orientation of the C-1 hydroxyl which is axial instead of equatorial, a transformation which may have occurred subsequently.

The stereochemistry of pseudoivalin, produced by an anti-Markovnikov-oriented cyclization involving C-1 and C-5 is therefore postulated as depicted in **22**. However the C-1–C-10 orientation of the double bond requires its precursor to have an axial hydroxyl at C-10 unless it is formed from the microcephalin precursor (**1**, but equatorial –OH) by rearrangement followed by migration of the double bond. That derivatives of pseudoivalin on bimolecular dehydration eliminate toward C-3 rather than toward C-5 is in accord with the suggested configuration at C-4.

(7) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959).

Experimental[8]

Pseudoivalin (2) and Dihydropseudoivalin (3).—The extraction of *Iva microcephala* Nutt. collected in Taylor County, Florida, and its separation into polar and nonpolar fractions by chromatography has been described previously.[1] The material eluted with benzene–chloroform and chloroform contained about 70% pseudoivalin and 30% dihydropseudoivalin (no other spot appeared on the thin layer chromatogram), but it was not possible to separate these quantitatively. Chromatography of 20 g. of the mixture over 600 g. of silica gel (solvent and eluent 1:1 benzene–ether) gave the following results (composition controlled by thin layer chromatography, 200-ml. fractions): fractions 1–6, yellow oils in small amount; fraction 7, small amount of impure pseudoivalin; fractions 8–17, combination and recrystallization from acetone–pentane furnished 10.25 g. of pseudoivalin, m.p. 121–123° (one spot); the mother liquors contained 7.5 g. of oily mixture; fractions 18–21, 0.5 g. of mixture (solid); fractions 22–37, 1 g. of oil rich in dihydropseudoivalin. The more polar fractions of several chromatograms were combined, 17 g., and rechromatographed over 600 g. of silica gel, solvent and eluent benzene–ether (1:1). Fractions 1–3 were oils; fractions 4–6 yielded 0.8 g. of pseudoivalin; fraction 7, 1.9 g. of pseudoivalin (80% pure); fraction 8, small amount of **3** (75% pure); fraction 9, small amount of **3** (90% pure); fractions 10–15, 5 g. of dihydropseudoivalin (pure by t.l.c.).

(8) Melting points are uncorrected. Analyses by Dr. F. Pascher, Bonn, Germany. Infrared Spectra were run in chloroform unless otherwise specified, ultraviolet spectra in 95% ethanol, rotations in chloroform. N.m.r. spectra were run on an A-60 n.m.r. spectrometer in deuteriochloroform with tetramethylsilane serving as internal standard.

Pseudoivalin melted at 122–123°, $[\alpha]_D$ −145° (*c* 1.00), high intensity absorption but no λ_{max} above 210 mμ; infrared bands at 3650, 3500, 1760 (γ-lactone), 1660 (conjugated double bond), and 1630 cm.$^{-1}$ (weak, isolated double bond).

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; O, 19.33. Found: C, 72.70; H, 8.36; O, 19.01.

Chromatographically pure dihydropseudoivalin had no ultraviolet absorption; infrared bands at 3650, 3500, and 1760 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 71.82; H, 8.61; O, 19.89.

Dehydrogenation of Pseudoivalin.—A solution of 1 g. of pseudoivalin in 70 ml. of ethylmorpholine containing 0.4 g. of lithium aluminum hydride was refluxed for 24 hr., diluted cautiously with water, acidified with dilute sulfuric acid, and extracted with ether. The washed and dried ether extract furnished a gum which could not be induced to crystallize. The triol was mixed with 0.2 g. of 30% palladium charcoal and heated at 310–320° for about 5 min. (evolution of blue vapors). The cooled mixture was extracted with hexane and the extract was chromatographed over alumina. A fast-moving blue zone, yield 16 mg., was converted to the trinitrobenzene complex, m.p. 143–144°, which was slightly lower than that of authentic guaiazulene trinitrobenzene complex, m.p. 150°. However, the mixture melting point was undepressed and the visible and ultraviolet spectrum of the freed azulene was superimposable on that of guaiazulene. A slower moving violet zone, 35 mg., was identified as linderazulene, trinitrobenzene complex m.p. 159°, authentic sample m.p. 153–157°, m.m.p. 153–157°, ultraviolet and visible spectrum of the freed azulene superimposable on that of linderazulene. Because of the slight discrepancy in melting points, the sample was analyzed.

Anal. Calcd. for $C_{21}H_{17}N_3O_7$: C, 59.57; H, 4.05; N, 9.93. Found: C, 59.58; H, 3.82; N, 9.76.

Linderazulene was also obtained in somewhat better yield (8%) on pyrolysis of a sample of pseudoivalin.

Acetylpseudoivalin (4).—A mixture of 0.2 g. of pseudoivalin, 8 ml. of acetic anhydride, and 0.2 g. of sodium acetate was refluxed for 2 hr., cooled, diluted with water, and extracted with ether. The organic layer was washed, dried, and evaporated, and the residue was recrystallized from ether–pentane; yield 0.115 g.; m.p. 167–169°; $[\alpha]_D$ −180° (*c* 1.00); infrared bands at 1770 (γ-lactone), 1740 (ester), 1665, and 1630 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64; O, 22.04. Found: C, 70.69; H, 7.65; O, 21.93.

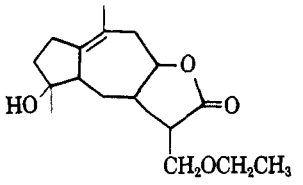
11-Epidihydropseudoivalin (9).—A solution of 1 g. of **2** in 70 ml. of ethanol was treated with 25 g. of 3% sodium amalgam and stirred over a period of 2.5 hr. Sufficient acetic acid was added periodically to maintain acidic conditions. The solution was concentrated, diluted with water, and the residue, 0.71 g., m.p. 128–131°, was recrystallized from ether–pentane. The analytical sample melted at 137–139°, $[\alpha]_D$ −90° (*c* 1.00), infrared band at 1770 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 71.98; H, 8.78; O, 19.57.

This substance was also prepared by epimerization of dihydropseudoivalin. A methanolic solution of 0.459 g. of **3** was mixed with sodium methoxide prepared from 0.2 g. of sodium, refluxed for 1 hr., cooled, diluted with water, acidified with acetic acid, and extracted with chloroform. The organic layer was concentrated, the residue was crystallized on rubbing with ether, yielding 0.195 g., m.p. 140–142°; the infrared spectrum was superimposable on that of **9**, mixture melting point undepressed.

When the sodium amalgam reduction of 1 g. of pseudoivalin was carried out in the absence of added acetic acid, acidification, concentration to dryness, extraction with acetone, evaporation of the acetone extract, and chromatography of the residual gum over alumina furnished in the benzene eluate, after recrystallization from benzene–pentane, 0.49 g. of **23**[9]: m.p. 80–81°; infrared bands at 1770 (γ-lactone) and 1620 cm.$^{-1}$ (unconjugated double bond); n.m.r. signals at 4.68 (complex triplet, H-8), 3.75 d, (**3**, 2 protons, H-11), 3.539 (**7**, 2 protons, methylene of ethoxy group), 1.65 br (C-10 methyl), 1.19 t (methyl of ethoxy group), and 1.01 (C-4 methyl). The compound was transformed into a brown gum on standing.

Anal. Calcd. for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90; O, 21.74. Found: C, 69.04; H, 8.68; O, 21.89.



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Treatment of pseudoivalin or **9** with formic acid in attempts at preparation of anhydro derivatives resulted in the formation of highly colored solutions which furnished mixtures of azulenes on chromatography. Treatment with bromine resulted in immediate development of a blue color. Ozonolysis of **3** and **9** and reductive work-up gave complex mixtures (at least four products were detected by thin layer chromatography). Osmylation gave gums which resisted purification after attempted cleavage with periodic acid. Catalytic hydrogenation of **3** and **9** (platinum oxide in ethanol or acetic acid) resulted in recovery of starting material.

1,10-Epoxypseudoivalin (5).—A solution of 2 g. of *m*-chloroperbenzoic acid in 30 ml. of chloroform was added gradually to 2.7 g. of pseudoivalin in 40 ml. of chloroform and refluxed for 3 hr., cooled, washed with dilute sodium bicarbonate and water, dried, and evaporated. The residue was recrystallized from ether–pentane; m.p. 165°; yield 2.14 g.; $[\alpha]_D$ −20° (*c* 1.00); λ_{max} 211 mμ (ε 7400); infrared bands at 3700, 3500, 1770, and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.50; H, 7.36; O, 24.39.

Acetyl-1,10-epoxypseudoivalin (6).—Epoxidation of 0.5 g. of **4** with 0.4 g. of *m*-chloroperbenzoic acid in the same manner furnished 0.38 g. of **4** after recrystallization from acetone–pentane; m.p. 166–167°; $[\alpha]_D$ −34.8° (*c* 1.00); infrared bands at 1770, 1745, and 1660 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 66.93; H, 7.23; O, 25.99.

1,10-Epoxydihydropseudoivalin (7).—A solution of 0.2 g. of 1,10-epoxypseudoivalin (**5**) in 20 ml. of ethanol was reduced with 0.05 g. of palladium on calcium carbonate at atmospheric pressure; hydrogen uptake 21 ml. (calcd. 20 ml.). The solution was evaporated *in vacuo* and the residue was recrystallized from acetone–hexane; m.p. 165–166°; yield 0.12 g.; $[\alpha]_D$ −56° (*c* 1.00); infrared bands at 3650, 3500, and 1770 cm.$^{-1}$.

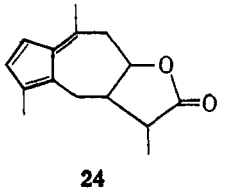
Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.56; H, 8.19; O, 24.23.

The same substance was prepared in 50% yield by epoxidation of dihydropseudoivalin (**3**) with *m*-chloroperbenzoic acid.

1,10-Epoxy-11-epidihydropseudoivalin (10).—A solution of 0.1 g. of *m*-chloroperbenzoic acid in 2 ml. of chloroform was added to 0.15 g. of **9** in 3 ml. of chloroform, refluxed for 3 hr., washed with dilute sodium bicarbonate solution, dried, and evaporated. The residue was recrystallized from acetone–hexane; yield 0.07 g.; m.p. 179–180°; $[\alpha]_D$ −10° (*c* 1.00); infrared bands at 3700, 3500, and 1770 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.52; H, 8.38; O, 24.01.

This substance was also prepared by refluxing 0.25 g. of **7** for 1 hr. with sodium methoxide prepared from 0.1 g. of sodium in 10 ml. of methanol. Dilution of the mixture with water and extraction with ether furnished, from the organic layer, a small amount of orange needles: m.p. 162–164°; infrared bands at 1750, 1630, 1560 and 1525 cm.$^{-1}$ (perhaps **24**). Insufficient material was available for an analysis. The aqueous layer on acidification and extraction with chloroform yielded 0.075 g. of **10**.



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(9) The formation of such ethers under the influence of alcoholic base has been observed previously.[10]

(10) G. H. Kulkarni, A. Paul, A. S. Rao, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, **12**, 178 (1961); W. Herz, K. Ueda, and S. Inayama, *ibid.*, **19**, 483 (1963); E. Dominguez and J. Romo, *ibid.*, **19**, 1415 (1963); L. Dolejs and V. Herout, *Collection Czech. Chem. Commun.*, **27**, 2654 (1962).

Acetyl-1,10-epoxydihydropseudoivalin (8).—A solution of 1 g. of **6** in 50 ml. of ethanol was hydrogenated with 0.15 g. of palladium on calcium carbonate at atmospheric pressure. The solution was evaporated at reduced pressure and the residue was recrystallized from ether–pentane; yield 0.52 g.; m.p. 129–130°; $[\alpha]D$ −40° (*c* 1.00); infrared bands at 1770 and 1745 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85; O, 25.94. Found: C, 66.46; H, 7.48; O, 26.26.

Attempts to open the epoxide ring with BF_3 resulted in highly colored solutions and gums. Treatment with dilute sulfuric acid in the cold furnished in one instance a 10% yield of an alcohol, m.p. 198–199°, whose infrared spectrum (carbonyl bands at 1770 and 1740 cm.$^{-1}$) suggested that it might be the desired glycol.

Acetyl-11-epidihydropseudoivalin (11).—A solution of 1 g. of acetylpseudoivalin (**4**) in 70 ml. of ethanol was reduced with 25 g. of 3% sodium amalgam with stirring and gradual addition of acetic acid to keep the mixture neutral. After 3 hr., the solution was worked up in the usual way. The product was recrystallized from ether–pentane; yield 0.55 g.; m.p. 154–156°; infrared bands at 1775 and 1740 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; O, 21.90. Found: C, 70.12; H, 8.44; O, 21.71.

An attempt to oxidize this substance with chromic acid–acetic acid or *t*-butyl chromate resulted in quantitative recovery of starting material. Attempts to reduce **11** catalytically (platinum oxide–acetic acid) failed. Selenium dioxide in acetic acid or ethanol resulted in gums which on chromatography furnished only small amounts of crystalline solids melting over a wide range. Reoxidation of the gums with chromic acid and chromatography furnished a small amount of a crystalline substance, m.p. 224° after two recrystallizations from ether, positive Zimmerman test, infrared bands at 1770 (double strength, γ-lactone and ester) and 1745 cm.$^{-1}$ (cyclopentanone). There was insufficient material for analysis.

Tetrahydropseudoivalin (15).—A solution of 1.5 g. of pseudoivalin in 75 ml. of ethanol was hydrogenated with 0.3 g. of ruthenium dioxide at 1900 p.s.i. and 80°. After 9 hr., the filtered solution was evaporated at reduced pressure and the solid was recrystallized from ether–pentane; m.p. 157–159°; $[\alpha]^{21}D$ +15° (*c* 1.00); infrared bands at 3700 (weak) and 1770 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.24; H, 9.49; O, 19.25.

This substance could be prepared most conveniently by direct hydrogenation of the pseudoivalin–dihydropseudoivalin mixture obtained from the first chromatogram of the crude sesquiterpene lactone fraction. A solution of 12.33 g. of the mixture in 75 ml. of ethanol was hydrogenated with 2.5 g. of ruthenium dioxide at 1900 p.s.i. and 80° for 9 hr., filtered, evaporated to dryness, dissolved in benzene, and passed through a small column of alumina. The eluate was concentrated at reduced pressure and the residue recrystallized from acetone–petroleum ether; yield 6.3 g. (51%), m.p. 149–152°. The material from the mother liquors, 4.8 g., was used for subsequent hydrogenations.

Anhydrotetrahydropseudoivalin (17).—A mixture of 0.2 g. of **15**, 2 ml. of pyridine, and 1 ml. of methanesulfonyl chloride was kept in the refrigerator overnight, poured over ice–water, and extracted with chloroform; the organic layer was washed, dried, and evaporated. The residue crystallized on standing and was recrystallized from pentane; m.p. 75°–76°; yield 0.12 g.; $[\alpha]^{25}D$ +14.5° (*c* 1.00); infrared bands at 1770 and 1650 (weak) cm.$^{-1}$; n.m.r. signals at 5.3 br (half-width 6 c.p.s., H-3), 4.5 c (H-8), 1.75 (C-4 methyl), 1.25 (**6**), and 1.15 (**6**, C-10 and C-11 methyls).

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46; O, 13.66. Found: C, 76.85; H, 9.30; O, 13.65.

In a somewhat larger subsequent run, the yield of **17** from 4 g. of **15** was 2.74 g. (68%), m.p. 76–78°.

Dihydroanhydrotetrahydropseudoivalin (16).—Catalytic hydrogenation of 0.144 g. of **17** in ethanol with 0.05 g. of platinum oxide at 3 atm., filtration, evaporation of the filtrate, and recrystallization from dilute ethanol furnished 0.1 g. of the crystalline guaianolide **16**, m.p. 107°, $[\alpha]^{21}D$ −7.9° (*c* 1.62), infrared band at 1770 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24; O, 13.54. Found: C, 76.53; H, 9.75; O, 13.44.

This substance was first encountered when a ruthenium dioxide catalyzed high-pressure reduction of pseudoivalin–dihydropseudoivalin mixture was prolonged for 16 hr. The usual work-up gave a gum which was taken up in benzene and chromatographed. Fractions 2–6 (benzene) solidified and were recrystallized from acetone, petroleum ether, and dilute ethanol; yield of **16**: 3.9 g.; m.p. 107°. Later fractions, eluted with chloroform and ether, furnished 4 g. of solid which on recrystallization afforded 2.0 g. of **15**, m.p. 157.

Epoxyanhydrotetrahydropseudoivalin (18).—A solution of 1.2 g. of **17** in 40 ml. of dry chloroform was refluxed with 1.2 g. of *m*-chloroperbenzoic acid overnight and worked up in the usual manner. The residue was recrystallized from acetone–petroleum ether, yield 0.8 g., m.p. 150°, infrared bands at 1775 (γ-lactone).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 71.58; H, 8.75; O, 19.62.

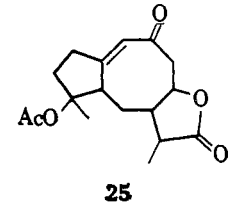
Isomerization of the Epoxide 18.—A solution of 0.1 g. of the preceding substance in 5 ml. of benzene was allowed to stand with 0.1 ml. of boron trifluoride etherate. After 15 min., the benzene layer was washed with sodium bicarbonate solution and water and then dried and evaporated. The residue was recrystallized from acetone–isopropyl ether; yield of **19**, 0.035 g.; m.p. 145°; $[\alpha]^{21}D$ −78.8° (*c* 1.02); infrared bands at 1775 (γ-lactone) and 1750 cm.$^{-1}$ (cyclopentanone). For analysis, the substance was recrystallized from anhydrous ether and sublimed in a high vacuum; O.R.D. curve (*c* 0.04, CH_3OH), $[\alpha]_{589}$ −65°, $[\alpha]_{314}$ −1923°, $[\alpha]_{274}$ +1764°, $[\alpha]_{260}$ +1484° (last reading).

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 72.01; H, 8.60; O, 19.42.

Ozonolysis of 11.—A solution of 0.3 g. of **11** in 20 ml. of methanol was ozonized at −72°. The solution was transferred to a hydrogenator, reduced catalytically (palladium charcoal), filtered, and concentrated, and the residue (**20**) was recrystallized from ether; yield 0.15 g.; m.p. 117–119°. On recrystallization from chloroform–ether the melting point suddenly rose to 151–153°, a value which was observed subsequently; $[\alpha]^{21}D$ −94.8° (*c* 0.989); infrared bands at 1780 (γ-lactone), 1750 (double strength), and 1740 cm.$^{-1}$; n.m.r. signals at 5.1 m (H-8), 2.22 (methyl ketone), 2.02 (acetate), 1.45 (C-4 methyl), and 1.25 d (**7**, C-11 methyl). The substance gave a positive Zimmerman test.

Anal. Calcd. for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46; O, 29.59. Found: C, 62.43; H, 7.35; O, 29.93.

Treatment of **20** with sodium methoxide at reflux temperature in an attempt to induce an intramolecular aldol cyclization resulted in formation of an acidic fraction which could not be purified satisfactorily. Treatment with *p*-toluenesulfonic acid and chloroform furnished a noncrystallizable gum, b.p. 150° (0.2 mm.), bath, whose properties were compatible with **25**; infrared bands at 1780 (γ-lactone), 1730 (acetate), 1695 (conjugated ketone), and 1645 cm.$^{-1}$ (strong, conjugated double bond); λ_{max} 235 and 302 mμ (ε 8300 and 116). The substance could not be induced to form a dinitrophenylhydrazone.



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