Constituents of *Iva* Species. III. Structure of Microcephalin, A New Sesquiterpene Lactone[1,2]

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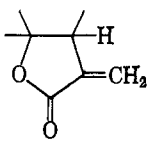
The structure of microcephalin, a sesquiterpene lactone from a variety of *Iva microcephala* Less., has been shown to be **2**.

A systematic search for sesquiterpene lactones in the genus *Iva* has been undertaken to delineate more fully disputed connections between genera related to *Ambrosia* and *Parthenium*[3] and to investigate a possible parallelism between their morphology and chemistry.

In a previous paper[4] we reported the isolation and structure determination of ivalin (**1**) from *Iva microcephala* Less. Collections of this species from the west and north of Tallahassee have given reproducible chemical results,[5] but material collected from the east and southeast frequently furnished little or no ivalin and relatively large amounts of other compounds.[4] The present article deals with the polar substance referred to earlier[4] which has been isolated reproducibly from collections of *Iva microcephala* made in Taylor County, Florida, and which we have named microcephalin. Work is in progress on the less polar constituents.

Microcephalin (**2**), m.p. 206–208°, $[\alpha]^{23}D$ +75°, had the formula $C_{15}H_{22}O_4$. It contained at least one hydroxyl group (infrared band at 3400 cm.$^{-1}$) and one double bond (band at 1660 cm.$^{-1}$) which was conjugated with a γ-lactone function (infrared band at 1760 cm.$^{-1}$) as demonstrated by the ultraviolet absorption at 212 mμ (ϵ 7200). The nature of the double bond was more clearly defined by ozonolysis. This resulted in liberation of formaldehyde and the formation of the enolic α-ketobutyrolactone **3**. Hence microcephalin contains partial structure A.



A

The exocyclic methylene group was saturated by catalytic reduction to dihydromicrocephalin (**4**), infrared bands at 3500 and 1760 cm.$^{-1}$, no ultraviolet absorption, which was oxidized to a dehydroderivative **5**. Since the infrared spectrum of **5** had a new carbonyl frequency at 1720 cm.$^{-1}$ (cyclohexanone), while retaining hydroxyl absorption at 3500 cm.$^{-1}$, the third oxygen atom of microcephalin is part of a secondary hydroxyl, the fourth being presumably incorporated in a tertiary hydroxyl group. A second route to **5** proceeded by way of oxidation of **2** to dehydromicrocephalin (**6**; infrared bands at 3620, 3530, 1765, 1715, and 1665 cm.$^{-1}$) and subsequent catalytic reduction.

Conversion of **5** to the ethylene thioketal was accompanied by dehydration, an observation which lent substance to the suspicion that a tertiary hydroxyl group was present. Desulfurization of the product and simultaneous saturation of the newly formed double bond resulted in formation of tetrahydroalantolactone (**7**) identical in all respects with an authentic sample. This established the carbon skeleton of microcephalin as that of the sesquiterpene lactones previously isolated from *Iva* species.

Since **5** and **6** gave a positive Zimmerman test, the secondary hydroxyl group of microcephalin had to be located in ring A. The tertiary hydroxyl group was attached to C-4 because the n.m.r. spectrum of **5** exhibited *two* methyl singlets at 1.38 and 1.20 and only one methyl doublet at 1.23 p.p.m., but had no low-field proton other than H_8 (triplet of doublets at 4.52 p.p.m.).[6] Now **2**, **3**, **4**, and **5** did not react with periodic acid or lead tetraacetate which limited the locus of the secondary hydroxyl group to C-1 or C-2. The conversion to tetrahydroalantolactone therefore also defines the absolute stereochemistry of microcephalin at C-5, C-7, C-8, and C-10.

Reaction of dihydromicrocephalin (**4**) with methanesulfonyl chloride afforded an unsaturated mesylate (**8**). The presence of an exocyclic methylene group in the latter was demonstrated by the n.m.r. spectrum (two narrowly split signals, J = 1 c.p.s., at 4.71 and 4.58 p.p.m., and only *one* methyl singlet at 0.88 in addition to the methyl doublet at 1.27 and the mesylate singlet at 3.04 p.p.m.) and by ozonolysis to the norketone mesylate **9**. Compound **8** was different from the previously unreported mesylate (**10b**) of dihydroivalin (**10a**), but, since the epimeric C-2 mesylate (β-hydroxyl) was unknown, the latter formulation was not necessarily excluded at this state.

Treatment of **8** with lutidine afforded an unconjugated diene (**11**) which again differed from the conjugated diene **12** (λ_{max} 230 mμ) obtained by similar treatment of **10b**. The n.m.r. spectrum of **11** had certain features of interest, H_1 and H_2 exhibiting the same chemical shift and no spin-coupling to the two protons at H_3 which appeared as a slightly broadened singlet at 3.00 p.p.m. That no rearrangement had occurred during the various elimination reactions was shown by catalytic hydrogenation which transformed **11** and **12** into **7**.

All signs thus pointed to C-1 as the attachment of the secondary hydroxyl group, particularly since the optical rotatory dispersion curve of **5** exhibited the

(1) Previous paper: W. Herz and N. Viswanathan, *J. Org. Chem.*, **28**, 1022 (1964).

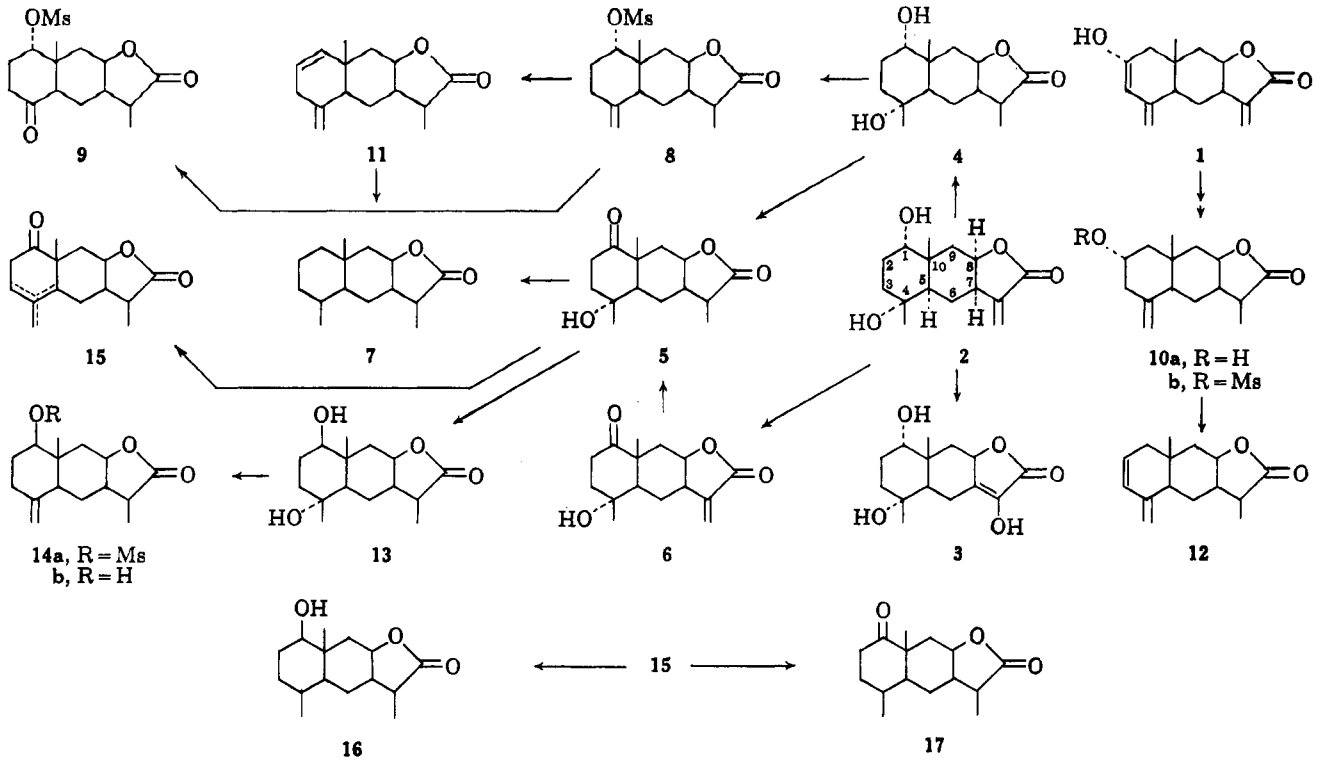
(2) Supported in part by grants from the U. S. Public Health Service (GM-05814) and the National Science Foundation (GP-1962).

(3) For a discussion of the taxonomic problem, see W. Herz and G. Högenauer, *J. Org. Chem.*, **26**, 5011 (1961).

(4) W. Herz and G. Högenauer, *ibid.*, **27**, 905 (1962).

(5) Unpublished work with S. Rajappa and L. R. Tether.

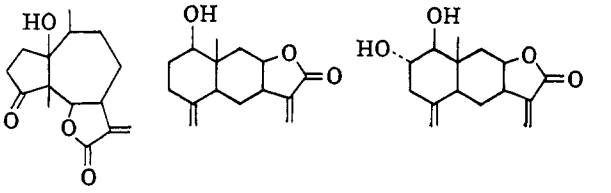
(6) In the n.m.r. spectrum of **6** the methyl doublet is replaced by the two characteristic narrowly split (J = 1 c.p.s.) doublets of the conjugated methylene group at 6.08 and 5.55 p.p.m.



positive Cotton effect of *trans*-9-methyl-1-decalones[7] of appropriate absolute configuration (a = +13). This was confirmed as follows. Sodium borohydride reduction of **5** resulted in the formation of a dihydroxylactone (**13**) epimeric with **4**. Since the newly introduced hydroxyl group is undoubtedly equatorial (rearside attack), it must be axial in **4** and therefore in 2.[8] Treatment of **13** with methanesulfonylchloride afforded an unsaturated mesylate identical in all respects with the mesylate (**14a**) of dihydroasperilin (**14b**) of established structure and stereochemistry.[1] Dehydration of **5** with formic acid furnished a mixture **15** containing mainly the $\Delta^{4,5}$-isomer which on catalytic hydrogenation (α-attack) led to a mixture of tetrahydroasperilin (**16**) and dehydrotetrahydroasperilin (**17**).

The secondary hydroxyl group of microcephalin is therefore attached to C-1 and, since **8** differs from **14a**, axial and α. The stereochemistry at C-4 (hydroxyl equatorial and α) follows from the direction taken by bimolecular elimination.[9]

An interesting fact emerges from this and previously published[1,3,4,10,11] results. All thoroughly characterized sesquiterpene lactones from *Ambrosia* and *Parthenium* species have been biogenetically "abnormal" pseudoguaianolides[12] such as coronopilin (**18**)[3] and parthenin.[10] On the other hand, all *Iva* species which we have investigated hitherto elaborated only "normally" constituted eudesmanolides such as ivalin (**1**),[4] asperilin (**19**)[1], and ivasperin (**20**),[1] although morphological criteria justifiably place *Iva* closer to *Ambrosia* than *Ambrosia* is to *Parthenium*. Future work may reveal whether this is a generally applicable criterion for differentiating between these genera.



Experimental[15]

Extraction of *Iva microcephala* Less.—*Iva microcephala* was collected in Taylor County, Florida, near State Road 51 in late September, 1961, when in the flowering state. Dried leaves and flowerheads were stripped and extracted in the usual fashion and yielded 420 g. of gum from 9 lb. 12 oz. of leaves and flowerheads. This was dissolved in 800 ml. of chloroform and chromatographed over 5 kg. of alumina (Alcoa F-20). Benzene–chloroform (1:1) eluted most of the less polar substances. The elution was completed by thorough washing with chloroform; the total yield of crude material was 218 g. (thin-layer chromatography showed this to be a mixture). Chloroform–methanol (9:1) eluted microcephalin; the yield of once-recrystallized material was 35 g.

Extraction of leaves and flowerheads collected in the same general vicinity in early October, 1962 and 1963, did not duplicate the yield of nonpolar material from the earlier collection. Thus

(7) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956); C. Djerassi and W. Klyne, *J. Chem. Soc.*, 4929 (1962).

(8) Although the yield of pure crystalline **13** was less than 50%, thin-layer chromatography of the mother liquors showed the presence of only small amounts of **4**.

(9) D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 44 (1956).

(10) W. Herz, H. Watanabe, M. Miyazaki, and Y. Kishida, *J. Am. Chem. Soc.*, **84**, 2601 (1962).

(11) M. Suchy, V. Herout, and F. Sorm, *Collection Czech. Chem. Commun.*, **28**, 2257 (1963).

(12) We are adopting this term, suggested by Dr. V. Herout, for lactones derived from 1a,4-dimethyl-7-isopropyldecahydroazulenes, a group which also includes tenulin,[13] helenalin,[14] and their congeners.

(13) W. Herz, W. A. Rohde, K. Rabindran, P. Jayaraman, and H. Viswanathan, *J. Am. Chem. Soc.*, **84**, 3857 (1962).

(14) W. Herz, A. Romo de Vivar, J. Romo, and N. Viswanathan, *ibid.*, **85**, 19 (1963).

(15) Melting points are uncorrected. Analyses were by Dr. F. Pascher, Bonn, Germany. Ultraviolet spectra were determined in 96% ethanol; infrared spectra and rotations were in chloroform unless otherwise specified. N.m.r. spectra were run in deuteriochloroform on a Varian A-60 spectrometer purchased with the aid of a grant from the National Science Foundation. Frequencies are given in parts per million with tetramethylsilane serving as the internal standard. t, d = triplet of doublets.

200 g. of gum, when chromatographed over 1.8 kg. of alumina, furnished only 29 g. of nonpolar substances and 19.6 g. of microcephalin.

Microcephalin (2).—The material eluted with chloroform–methanol was recrystallized from ethyl acetate or acetone, m.p. 206–208°; infrared bands at 3400, 1760, and 1660 cm.$^{-1}$; λ_{max} 212 mμ (ε 7200); $[\alpha]^{23}D$ +75° (*c* 1.31). It was insoluble in the solvents ordinarily used for n.m.r. spectroscopy.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.36; H, 8.18; O, 24.21.

Acetylation did not furnish crystalline material, but the infrared spectrum (bands at 3500, 1765, 1740, and 1650 cm.$^{-1}$) indicated that the reaction had proceeded with esterification of the secondary hydroxyl group.

Ozonolysis of Microcephalin.—A solution of 1 g. of microcephalin in 100 ml. of methanol was ozonized at −70° in the usual way. Steam distillation of the ozonide into a saturated solution of dimedone, followed by steam distillation of the dimedone solution resulted, on cooling, in the precipitation of only 0.1 g. (9%) of the formaldehyde derivative. The solution containing the decomposed ozonide was evaporated *in vacuo* and the viscous residue was triturated with ethanol, yielding 0.27 g. of crystalline **3** which gave a positive ferric chloride test. Two recrystallizations from ethanol furnished the analytical sample, m.p. 169–170° dec.

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.67; H, 7.51; O, 29.82. Found: C, 62.84; H, 7.80; O, 29.70.

When the ozonolysis was carried out in chloroform solution, the yield of formaldehyde dimedone derivative rose to 46%, but **3** could not be isolated.

Dihydromicrocephalin (4).—A solution of 0.5 g. of microcephalin in 50 ml. of ethanol was hydrogenated at atmospheric pressure with 0.05 g. of 5% palladium–charcoal at 23°; observed hydrogen uptake was 41.8 ml., calculated for one double bond, 45.1 ml. Evaporation of the solution followed by recrystallization from acetone or ethanol–ether furnished 0.28 g. of **7**, m.p. 208–208° (depression on admixture of microcephalin), infrared bands at 3500 and 1700 cm.$^{-1}$, $[\alpha]^{26}D$ +9° (*c* 3.6, ethanol). In subsequent runs, the yield of recrystallized material averaged 80%.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02; O, 23.96. Found: C, 66.78; H, 8.85; O, 23.96.

Dehydromicrocephalin (6).—A solution of 0.27 g. of **2** in 5 ml. of acetic acid was mixed with 0.13 g. of chromic oxide in 20 ml. of acetic acid and allowed to stand in the refrigerator for 2 hr. Excess oxidizing agent was destroyed by adding a few drops of methanol, the solution was concentrated *in vacuo*, and the residue was extracted with hot benzene several times. The hot benzene extract was centrifuged, and evaporated; the colorless residue was recrystallized from benzene, yielding 0.17 g., m.p. 175–177°; infrared bands at 3620, 3530, 1765, 1715, and 1665 cm.$^{-1}$. The analytical sample was recrystallized from ethyl acetate, n.m.r. signals at 6.08 d and 5.55 d (*J* = 1 c.p.s., exocyclic methylene), 4.54 t, d (*J* = 4, 2 c.p.s., H_8), 1.31 and 1.20 p.p.m. (C-4 and C-10 methyls). The substance gave a positive Zimmerman test.

Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.55; H, 7.62; O, 23.91.

Dehydrodihydromicrocephalin (5).—A solution of 1.4 g. of **4** in 30 ml. of acetic acid was allowed to stand in the refrigerator for 24 hr. with 1.00 g. of chromic acid in 80 ml. of acetic acid. The product was worked up as described in the previous paragraph (to remove chromium salts completely, it was necessary to pass the benzene solution through an alumina column), yielding 0.55 g. of **5**, m.p. 192–194° (from ethyl acetate); $[\alpha]^{26}D$ +2° (*c* 7.4, ethanol); infrared bands at 3500, 1770, and 1720 cm.$^{-1}$; n.m.r. signals at 4.52 t, d (*J* = 4, 2 c.p.s., H_8), 1.38 and 1.20 (C-4 and C-10 methyls), and 1.23 p.p.m. d (*J* = 7 c.p.s., C-11 methyl); rotatory dispersion curve in dioxane (*c* 0.85), $[\alpha]_{700}$ 0°, $[\alpha]_{589}$ +11.9°, $[\alpha]_{317}$ +477°, $[\alpha]_{312}$ +473°, $[\alpha]_{308}$ +479°, and $[\alpha]_{272}$° −8°.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.64; H, 8.33; O, 24.03. Found: C, 67.93; H, 8.28; O, 23.83.

This substance was also prepared in 75% yield by catalytic reduction (ethanol, 5% palladium on charcoal) of **6**. It gave a positive Zimmermann test but could not be induced to condense with piperonal.

Anhydrodihydromicrocephalin Mesylate (8).—To a chilled solution of 2 g. of **4** in 13 ml. of dry pyridine was added in small portions 9 ml. of methanesulfonyl chloride. The mixture was refrigerated overnight, poured onto crushed ice, and extracted with chloroform, and the chloroform layer was washed, dried, and evaporated. The residue was recrystallized from ethanol, yielding 1.25 g. (51%), m.p. 125–126° dec.; infrared bands at 1760 and 1640 cm.$^{-1}$; $[\alpha]^{20}D$ +59° (*c* 1.00); n.m.r. signals at 4.71 d and 4.58 d (*J* = 1 c.p.s., exocyclic methylene), 4.53 c (intensity two protons, H_1 and H_8), 3.04 (three protons, mesylate), 1.27 d (*J* = 7 c.p.s., C-11 methyl), and 0.88 p.p.m. (C-10 methyl).

Anal. Calcd. for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.36; O, 24.36. Found: C, 58.16; H, 7.32; O, 24.89.

Ozonolysis of 0.5 g. of the mesylate in 50 ml. of chloroform at −70° followed by steam distillation gave 29% of formaldehyde, isolated as the dimedone derivative. The aqueous mother liquor on evaporation furnished a yellow, water-soluble oil which could not be crystallized and gave a positive ferric chloride test. Ozonolysis of 0.2 g. of mesylate in 20 ml. of methanol at −70° for 1 hr., followed by catalytic reduction of the solution with 0.06 mg. of 5% palladium on charcoal at 20 lb./in.^{2}, filtration, evaporation, and chromatography of the residue over alumina (solvent and eluent, chloroform) furnished, after recrystallization from chloroform–petroleum ether (b.p. 35–60°) 0.065 g. of the norketone **9**, m.p. 137–139°, infrared bands (KBr) at 1775 and 1715 cm.$^{-1}$.

Anal. Calcd. for $C_{15}H_{22}O_6S$: C, 54.54; H, 6.71. Found: C, 54.62; H, 7.07.

Bisanhydrodihydromicrocephalin (11).—A mixture of 1 g. of **8** and 50 ml. of 2,6-lutidine was refluxed for 2 days, cooled, diluted with ice, neutralized, and filtered. The precipitate, 0.55 g., was taken up in hot methanol, treated with charcoal, filtered, and cooled. Additional recrystallizations from methanol furnished 0.25 g. of **11**, m.p. 162–166°, whose ultraviolet spectrum [λ_{max} 265 mμ (ε 112)] indicated the presence of a small amount of conjugated homoannular diene which could not removed by further recrystallization or chromatography; infrared bands at 1770 and 1650 cm.$^{-1}$; n.m.r. signals at 5.82 s (two protons, H_1 and H_2), 5.22 d and 4.92 d (*J* = 2 c.p.s., exocyclic methylene), 4.78 c (H_8), 3.0 (slightly broadened singlet, two protons, H_3), 1.32 d (*J* = 7 c.p.s., C-11 methyl), and 0.91 p.p.m. (C-10 methyl). A mixture melting point with a conjugated diene **12** of m.p. 159–161° from ivalin (*vide infra*) was 158–164°, but the two substances differed in ultraviolet spectrum, infrared spectrum, and gave two distinct spots on thin layer chromatography.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.77. Found: C, 77.50; H, 8.66; O, 13.63.

Tetrahydroalantolactone (7). **A.**—A solution of 0.159 g. of **11** in 5 ml. of ethanol was reduced in the presence of platinum oxide until hydrogen absorption ceased. Filtration, evaporation, and recrystallization of the residue from methanol furnished 0.118 mg. of tetrahydroalantolactone, m.p. and m.m.p. (with an authentic sample) 143–144°. The infrared spectra of the two samples were identical.

B.—A mixture of 0.5 g. of dehydrodihydromicrocephalin, 1.5 ml. of ethanedithiol, and 1.5 ml. of boron trifluoride etherate was allowed to stand at room temperature for 4 hr. The usual work-up furnished an oil which could not be induced to crystallize, presumably because it represented a mixture of double bond isomers (treatment of **5** with BF_3 etherate alone resulted in a mixture of dehydration products). The oil was dissolved in 50 ml. of absolute ethanol and refluxed with W-2 Raney nickel for 60 hr. Filtration and evaporation *in vacuo* followed by recrystallization from methanol furnished tetrahydroalantolactone, m.p. 140–142°, m.m.p. (with authentical material) 140–142°. The two samples were undistinguishable by infrared spectroscopy and thin-layer chromatography.

1-Epitetrahydromicrocephalin (13).—A solution of 0.59 g. of dehydrodihydromicrocephalin (**5**) in 50 ml. of methanol was refluxed with 0.5 g. of sodium borohydride for 3 hr., cooled, acidified with acetic acid, and evaporated *in vacuo*. The residue was extracted with hot ethyl acetate, the extract was evaporated *in vacuo*, and the product was recrystallized from chloroform–ether, yielding 0.253 g. (43%), m.p. 210–212°. The analytical sample had m.p. 214–215°; infrared bands at 3650, 3450, and 1770 cm.$^{-1}$; $[\alpha]^{23}D$ −25° (*c* 1.00). Thin-layer chromatography of the mother liquors revealed several spots; the intensity ratio of the spots corresponding to **13** and **4** was estimated to be greater than 4:1.

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.12; H, 9.02; O, 23.96. Found: C, 67.22; H, 9.10; O, 23.76.

Treatment of 0.131 g. of the above with 1 ml. of methanesulfonyl chloride and 1 ml. of pyridine and work-up in the usual manner resulted in 0.04 g. of a mesylate, m.p. 142–144°, unde-

pressed on admixture of the mesylate (**14a**) of dihydroasperilin (**14b**), m.p. 142–144°. Infrared spectra and rotations, $[\alpha]^{23}D$ +41 (*c* 1.00), were identical.

Formic Acid Dehydration of 5.—A mixture of 0.882 g. of **5** and 10 ml. of formic acid was refluxed for 4 hr., concentrated at reduced pressure, diluted with water, and extracted with ether. The ether extract was washed, dried, evaporated, and chromatographed over alumina (Alcoa F-20). The initial fractions were combined and weighed 0.468 g. The infrared spectrum exhibited bands at 1770, 1710, and 1670 cm.$^{-1}$; the n.m.r. spectrum showed that the eluate was a mixture (**15**) with the $\Delta^{4,5}$-isomer predominating—weak vinyl proton signals at 6.69, 6.55, 5.88, and 5.70 (total intensity one-half proton), 4.5 c (H_8), 1.73 (vinyl methyl singlet, intensity almost three protons), 1.30 (C-10 methyl singlet), and 1.22 d (*J* = c.p.s., C-11 methyl), with indications of a weak doublet at 1.13 p.p.m. due to the presence of another isomer.

A solution of 0.23 g. of **15** in 6 ml. of acetic acid was hydrogenated with platinum oxide. The oily product was dissolved in benzene and chromatographed over 9 g. of acid-washed alumina. From the benzene eluates was isolated 0.04 g. of somewhat impure dehydrotetrahydroasperilin (**17**), m.p. and m.m.p. 120–122°, infrared spectra superimposable. From the fractions eluted with chloroform there was isolated 0.015 g. of slightly impure tetrahydroasperilin (**16**), m.p. and m.m.p. 144–146°, infrared spectra superimposable.

Anhydrodihydroivalin (12).—Reaction of 0.45 g. of dihydroivalin (**10a**) with methanesulfonyl chloride in the usual manner furnished, after recrystallization from ethanol, 0.5 g. of the mesylate **10b**, m.p. 149–150° dec.; infrared bands at 1765 and 1640 cm.$^{-1}$; n.m.r. signals at 5.02 and 4.72 (exocyclic methylene, the second of these was superimposed on the H_2 resonance, complex multiplet centered at 4.72), 4.53 c (H_8), 2.90 (mesyl), 1.06 d (*J* = 7 c.p.s., C-11 methyl), and 0.735 p.p.m. (C-10 methyl).

Anal. Calcd. for $C_{16}H_{24}O_5S$: C, 58.51; H, 7.36. Found: C, 58.39; H, 7.55.

A solution of 0.8 g. of the mesylate in 50 ml. of lutidine was refluxed for 24 hr., poured onto crushed ice, neutralized with dilute sulfuric acid, and filtered. The solid was taken up in hot ethanol, treated with charcoal, concentrated, and allowed to cool. The colorless needles melted at 159–161° (m.m.p. 158–164° with **11**), but the infrared (bands at 1775, 1645, and 1610 cm.$^{-1}$) and ultraviolet spectra [λ_{max} 2300 mμ (ϵ 9850), heteroannular diene] clearly differentiated it from **11**. The n.m.r. spectrum could be interpreted most simply on the basis of formula **12**, with signals at 6 c (H_2), 5.44 s, and 4.84 s (exocyclic methylene), the latter partially superimposed on a complex signal centered at 4.7 (H_3), 4.45 c (H_8), 1.23 d (*J* = 7 c.p.s., C-10 methyl), and 0.83 p.p.m. d (*J* = 2 c.p.s., C-10 methyl).

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; O, 13.77. Found: C, 77.50; H, 8.77; O, 14.02.

Catalytic hydrogenation of **12** furnished tetrahydroalantolactone.

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Dithiolium Derivatives. I. 2-Dialkylamino-1,3-dithiolium Perchlorates[1]

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A convenient synthesis of some 4-substituted 2-dialkylamino-1,3-dithiolium perchlorates is described which employs mild conditions. A mechanism for the cyclization is proposed, and the structure of the products is discussed with reference to ultraviolet and n.m.r. spectra.

Leaver and Robertson have reported the synthesis of some 1,3-dithiolium salts by the cyclization of phenacyl carbodithioates (I) in ether saturated with hydrogen sulfide and hydrogen chloride.[3,4] We repeated the synthesis of 2,4-diphenyl-1,3-dithiolium chloride (III, R = R′ = Ph), but the yield was considerably less than previously reported. The reaction was found to be accompanied by an interesting color change. Phenacyl dithiobenzoate (I, R = R′ = Ph) was obtained as a brick red solid by the condensation of sodium dithiobenzoate and phenacyl chloride, while the dithiolium chloride product (III, R = R′ = Ph) obtained from it was pale green. A similar and almost instantaneous change was observed when 70% perchloric acid was added to phenacyl dithiobenzoate. The product proved to be 2,4-diphenyl-1,3-dithiolium perchlorate (III, R = R′ = Ph) and was identical with the perchlorate salt obtained *via* the hydrochloride. This mild method of cyclization of β-keto dithio esters into 1,3-dithiolium salts has been fully confirmed by the preparation of the compounds in Table I. The conditions, however, are in marked contrast to those of Leaver, Robertson, and McKinnon,[4] employing boiling mixtures of acetic and perchloric acids with hydrogen sulfide.

Under the latter conditions the reaction was considered to involve an initial conversion of the β-carbonyl group into a thiocarbonyl function either by the action of the hydrogen sulfide directly or by its generation *in situ* by decomposition of the starting material. Because the reaction has been shown to occur in high yields without the use of hydrogen sulfide, it may be regarded as a direct acid-catalyzed cyclization, I → II followed by dehydration to give the pseudoaromatic cation III[5] (see p. 1704).

To extend the yet limited range of known 1,3-dithiolium compounds,[3-9] preparation of 2-dialkylamino derivatives was investigated. Initial experiments to effect the ring closure of β-keto N,N-dialkyldithiocarbamates [I, R = $(CH_3)_2N$ or $(C_2H_5)_2N$] with hydrogen chloride and hydrogen sulfide did not meet with success. The use of 70% perchloric acid, however, readily gave insoluble perchlorate salts irrespective of the nature of the substituent attached to the ketone group.

(1) This research was supported by a grant from the Petroleum Research Fund administered by the American Chemical Society. We gratefully acknowledge this support.

(2) American Chemical Society Petroleum Research Fund Postdoctoral Fellow, 1962–1963.

(3) D. Leaver and W. A. H. Robertson, *Proc. Chem. Soc.*, 252 (1960).

(4) D. Leaver, W. A. H. Robertson, and D. M. McKinnon, *J. Chem. Soc.*, 5104 (1962).

(5) E. Klingsberg, *J. Am. Chem. Soc.*, **84**, 3410 (1962). (The term "pseudoaromatic," applied to the 1,3-dithiolium cation, seems well justified because the aromatic conjugation can only exist in the cation molecule, and, even in this state, there is incomplete delocalization of π-electrons.)

(6) W. R. H. Hurtley and S. Smiles, *J. Chem. Soc.*, 1821, 2263 (1926).

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