$[\alpha]^{25}D$ −13.4° (*c* 2.4, 2.5 *N* hydrochloric acid); ir, 1125 and 1135 (sulfone), weak at 1025 cm^{-1}.[12]

Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.56; H, 6.32; N, 6.76. Found: C, 40.5; H, 6.24; N, 6.76.

The mother liquor yielded an additional 250 mg of **2b**. This compound did not form a stable hydrochloride salt.

The aqueous mother liquor, after removal of **2b**, was taken to dryness and crystallized from 80–90% ethanol to yield three fractions (total 1.81 g, 36%). Additional product was obtained by converting the mother liquor into the hydrochloride salt. Crystallization from 2 ml of water and 30 ml of acetone yielded 530 mg of a crystalline hemihydrochloride (9.7%). These last three fractions and the hydrochloride were shown to be substantially pure **3b** isomer. A part of these three fractions (1.23 g) was recrystallized from 20 ml of water to yield 851 mg as coarse rectangular plates of **3b**, **3-(*R*)-carboxy-5-(*S*)-ethyl-1,4-thiazane *S*-dioxide**: mp 256° dec; ir, 1133 cm^{-1} (sulfone), no sulfoxide absorption.

Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.56; H, 6.32; N, 6.76. Found: C, 40.6; H, 6.22; N, 6.80.

The hydrochloride was prepared from this fraction and shown to be identical with the salt previously isolated. A solution of 585 mg of **3b** in 30 ml of 2 *N* hydrochloric acid was concentrated *in vacuo* to dryness and crystallized from a solvent mixture of 1 ml of water and 25 ml of acetone to yield 600 mg of the hemihydrochloride of **3b**: mp 238° dec; $[\alpha]^{25}D$ −7.0° (*c* 2.1, 2 *N* hydrochloric acid).

Anal. Calcd for $C_7H_{13}NO_4S \cdot 0.5HCl$: C, 37.28; H, 6.03; N, 6.21; Cl, 7.86. Found: C, 36.9; H, 5.94; N, 6.09; Cl, 7.91.

Cyclization of *cis*-*S*-(β-Styryl)-L-cysteine *S*-Dioxide (1c) to 2c and 3c.—A solution of 2.17 g (0.00851 mol) of *cis*-*S*-(β-styryl)-L-cysteine *S*-dioxide (**1c**) in 400 ml of 2 *N* ammonium hydroxide (free of oxygen) was allowed to stand for 5 days at 25° under nitrogen, and the solution was then concentrated *in vacuo* to a white solid. This was digested with 100 ml of water at 80° for 5 min and refrigerated overnight. Filtration yielded 1.01 g (47%) of white solid (**2c**). The aqueous filtrate was reduced *in vacuo* to a dry solid which was stirred with 100 ml of methanol. Only a trace of material was insoluble. The methanol-soluble material tended to gel on concentration and could not be crystallized. It was converted into the hydrochloride by addition of hydrochloric acid, and the solution was concentrated *in vacuo* to a crystalline solid (hydrochloride of **3c**).

The first fraction (water and methanol insoluble) was purified by solution in 125 ml of normal ammonium hydroxide followed by concentration *in vacuo* to 40 ml, addition of 100 ml of water, and concentration again to 40 ml. A yield of 0.44 g of crystalline **2c**, **3-(*R*)-carboxy-5-(*R*)-phenyl-1,4-thiazane *S*-dioxide**, was obtained. Concentration of the mother liquor to 10 ml yielded a second crop, 0.424 g. The compound is rather insoluble in 2 *N* hydrochloric acid (<0.5%) but moderately soluble in 6 *N* acid. Removal of acid *in vacuo* yielded the starting material. The compound had mp 288° dec; $[\alpha]^{26}D$ +8.3° (*c* 2, 5 *N* hydrochloric acid); ir, 1140 (sulfone) and no absorption in 1000–1060-cm^{-1} region.

Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.3; H, 5.12; N, 5.49.

The methanol-soluble fraction (hydrochloride) was dissolved in 50 ml of hot methanol and concentrated *in vacuo* to *ca.* 20 ml (crystallization). Acetone (20 ml) was added, and the mixture was crystallized overnight in the refrigerator. A yield of 848 mg (34%) of delicate needles was obtained. A second fraction was recovered by concentration of the mother liquor to 5 ml and addition of 20 ml of acetone, 294 mg (12%). The compound analyzed as the hydrochloride of **3c**, **3-(*R*)-carboxy-5-(*S*)-phenyl-1,4-thiazane *S*-dioxide**: mp 248° dec; $[\alpha]^{26}D$ −13.4° (*c* 1.3, *N* hydrochloric acid); ir, 1760 (unionized carboxyl) and 1110 and 1155 cm^{-1}, no absorption in the sulfoxide region.

Anal. Calcd for $C_{11}H_{13}NO_4S \cdot HCl$: C, 45.28; H, 4.84; Cl, 12.15. Found: C, 45.7; H, 4.91; Cl, 11.8.

Registry No.—**1a**, 17190-47-5; **1b**, 17190-48-6; **1c**, 7732-30-1; **2a**, 17190-58-8; **2b**, 17190-50-0; **2c**, 17190-51-1; **3a**, 17190-59-9; **3a** HCl, 17190-52-2; **3a** hemihydrochloride, 17190-53-3; **3b**, 17190-54-4; **3b** hemihydrochloride, 17190-55-5; **3c** hydrochloride, 17190-56-6; *trans*-5-(1-butenyl)-L-cysteine, 17190-57-7.

Acknowledgment.—We thank Mr. L. M. White and Miss Geraldine Secor for elemental analysis and Mrs. Nancy Bennett for technical assistance in nmr spectroscopy.

3-Epiisotelekin from *Gaillardia Aristata* Pursh. and the Structure of Farinosin[1,2]

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The structure of a minor sesquiterpene lactone isolated from *Gaillardia aristata* Pursh. has been shown to be 3-epiisotelekin (**2a**). In the course of the structure proof evidence has been accumulated which requires revision of the structure of farinosin, a sesquiterpene lactone from *Encelia farinosa* Gray, to **13**.

As part of our systematic study of *Helenium* and related species we reported recently[1] the isolation and structure determination of the pseudoguaianolide spathulin (**1**) from a collection of *Gaillardia aristata* Pursh. made in Colorado. A minor constituent found in this species was an unidentified sesquiterpene lactone which we called aristalin.

In an effort to secure more aristalin for structure investigation, we have now examined a collection of *G. aristata* from Alberta, Canada. This resulted in the isolation of a new sesquiterpene lactone, shown to be 3-epiisotelekin (**2a**) by means of reactions which also led to the revision of the structure of farinosin, a lactone isolated by one of us recently from *Encelia farinosa* Gray.[6]

Gaillardia aristata Pursh., collected near Calgary, Alberta,[7] after the usual work-up[1] and chromatography over silicic acid afforded two crystalline compounds. One of them, mp 258–260°, was identical with spathulin in accordance with our previous report.[1] The second compound was not identical with aristalin, however, and must be formulated as 3-epiisotelekin (**2a**) for the following reasons.

(1) Constituents of Gaillardia Species. VI. Previous paper: W. Herz, S. Rajappa, M. V. Lakshmikantham, D. Raulais, and J. J. Schmid, *J. Org. Chem.*, **32**, 1042 (1967).

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

(3) To whom correspondence should be addressed.

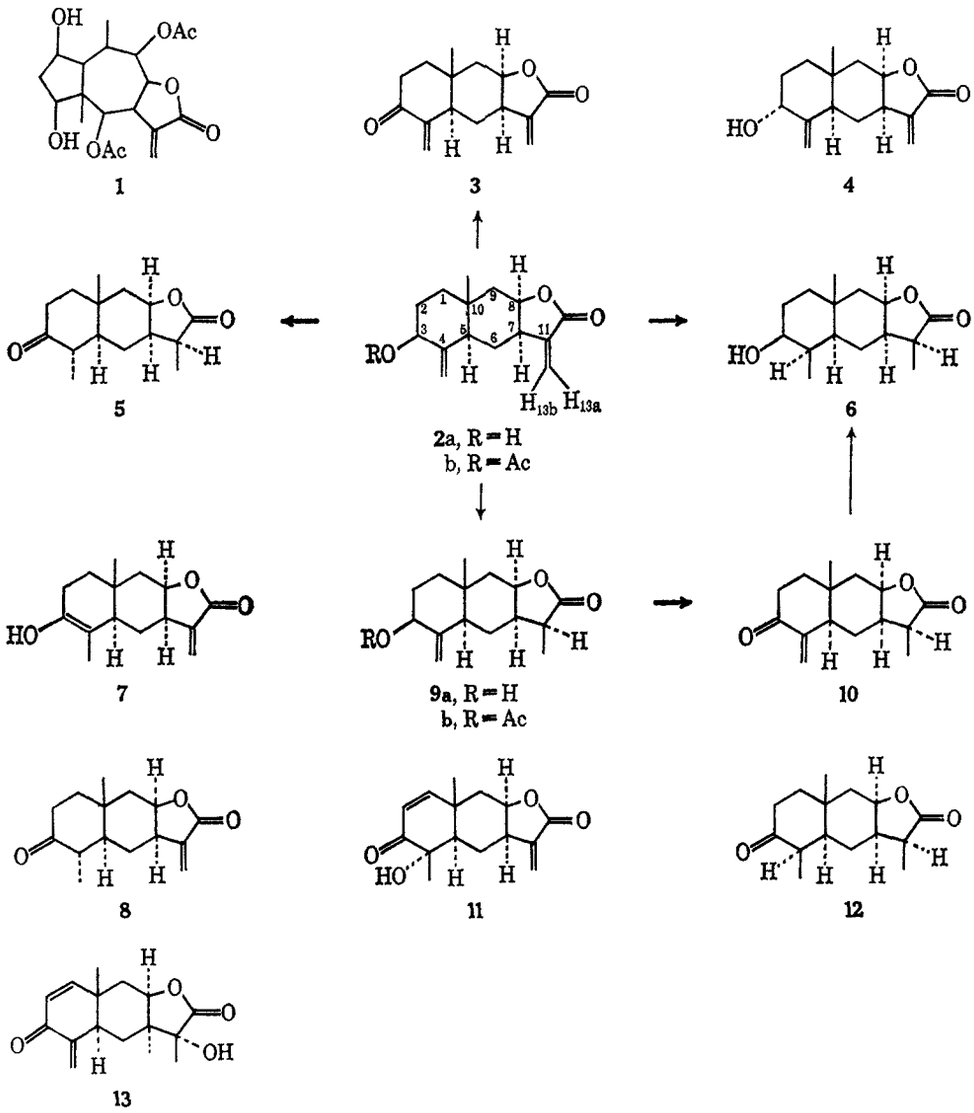
(4) The Florida State University.

(5) University of California at Los Angeles.

(6) T. A. Geissman and R. Mukherjee, *J. Org. Chem.*, **33**, 656 (1968).

(7) We are grateful to Dr. F. W. Bachelor for providing us with this material.

SCHEME I



3-Epiisotelekin (**2a**), mp 176°, $[\alpha]^{26}D$ + 156.6°, had the formula $C_{15}H_{20}O_3$. The presence of a hydroxyl group was revealed by an infrared band at 3600 cm^{-1}, disappearance of a signal (intensity 1 H) at 2.22 ppm in the nmr spectrum of **2a** on treatment with D_2O, and the formation of a monoacetate (**2b**). Infrared bands at 1760 and 1669 cm^{-1} and strong end absorption in the ultraviolet spectrum indicated the presence of an α,β-unsaturated lactone chromophore. Besides these, there must also be present another double bond because of a second infrared band at 1650 cm^{-1} in the double-bond region. The new compound was therefore bicyclic.

The nmr spectrum of **2a** delineated further these and other structural features. The spectrum exhibited two narrowly split doublets at 5.65 and 6.18 ppm characteristic of an exocyclic methylene group conjugated with a lactone function; the proton under the lactone oxygen appeared at 4.53 as a triplet of doublets requiring lactone closure as in **2a**. The proton under the hydroxyl group was a broad multiplet centered at 4.17 ppm; on acetylation this signal shifted downfield to 5.16 ppm indicating the secondary nature of the hydroxyl group. Besides the above signals, there were also present a pair of narrowly split multiplets at 4.66 and 5.18 ppm, assignable to two isolated exocyclic methylene protons, and a sharp singlet (3 H) at 0.82 ppm, characteristic of a quaternary methyl group.

Oxidation of **2a** with Jones reagent gave a conjugated ketone (**3**) [mp 145–147°; $[\alpha]^{26}D$ +149.5°; λ_{max} 207 mμ (ϵ 38,850)] whose infrared spectrum showed a new carbonyl band at 1692 cm^{-1}. Of the two double-bond absorptions at 1669 and 1650 cm^{-1} present in **2a**, the former was retained, but the latter now appeared at 1615 cm^{-1} as a medium intensity band (cisoid double bond conjugated with a carbonyl in a six- or higher membered ring). As would be expected, the signals assigned to the unconjugated methylene group of **2a** were now shifted downfield to 5.05 and 5.82 ppm.[8] The hydroxyl group of **2a** must therefore be allylic; this fact was corroborated by the facile oxidation of **2a** to **3** by manganese dioxide (Scheme I).

A search of the literature revealed that isotelekin (**4**), a eudesmanolide isolated from *Telekia speciosa* (Schreb.) Baumg.,[9] embodies all the structural details

(8) These signals now appeared less complex, as doublets (J = 2 cps) split further narrowly, as would be expected in going from 3-epiisotelekin (**2a**) to **3**.

(9) V. Benesova, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 1350 (1961).

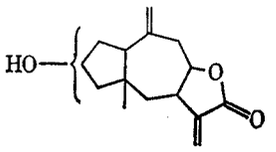
enumerated above for the compound from *G. aristata*.[10] However, since the physical constants of our substance were markedly different from those reported for **4**, we tentatively formulated it as the C-3 epimer of isotelekin, *i.e.*, **2a**. Indeed the published infrared spectrum[9] of isotelekin was very similar to that of **2a**, and their nmr spectra[11] were virtually identical except for the signals due to the C-3 proton. In the spectrum of isotelekin, the proton under the hydroxyl appeared at 4.28 ppm as a narrow multiplet ($W_{1/2}$ = 6 cps) whereas in **2a** this proton was a broad multiplet ($W_{1/2}$ = 11 cps) centered at 4.17 ppm which would be the case if the hydroxyl group were axial (H-3 equatorial) in **4** and equatorial (H-3 axial) in the new substance.[12,13]

In an effort to correlate **2a** with one of the 3-oxotetrahydroalantolactones,[13] **2a** was reduced with 10% Pd–C in ethyl acetate at atmospheric pressure. Hydrogen uptake ceased after an absorption corresponding to only *ca.* 1.4 mol and gave a mixture of two products which were separated by preparative tlc. The major product was the previously known saturated ketone **5**: mp 170–171°; $[\alpha]^{26}D$ −30.9°;[14] λ_{max} 280 mμ (ε 110); ir bands at 1765 and 1701 cm^{-1} (for nmr signals, *vide* Table I); dinitrophenylhydrazone mp 240–241° [λ_{max} 364 mμ (ε 15,700)]; identical in all respects with an authentic sample.[15] The minor reduction product was the expected saturated alcohol **6**: mp 162–164°; $[\alpha]^{26}D$ −19.1;[16] ir bands at 3600 and 1768 cm^{-1} (for nmr signals, *vide* Table I). Through correlation of its hydrogenation products with compounds of established structure and stereochemistry,[17,18] the new lactone from *G. aristata*, by its structure and stereochemistry, is therefore firmly established as **2a**, the first eudesmanolide to be found in a *Gaillardia* species. More significantly, the isolation of a "normal" sesquiterpene lactone and a pseudoguaianolide from one and the same plant collection is without precedent[19] and provides the first indication in support of the supposition that methyl migration leading to pseudoguaianolides occurs past the cyclization stage.

The allylic alcohol–ketone isomerization observed during the catalytic hydrogenation of **2a** also requires comment.[20] Since allylic migration of double bonds, where hydrogenation is sterically impeded, is well documented,[21] we initially postulated that **5** was formed by ketonization of an intermediate enol **7** which in turn was produced by migration of the double bond of **2a** under the influence of the catalyst. However, the hypothesis was invalidated by an experiment involving treatment of **2a** with a catalyst in the absence of hydrogen, in the course of which **2a** was largely recovered and only about 5–6% ketonic material was obtained. The ketonic product was not the expected **8** but proved to be identical with the manganese dioxide oxidation product **3**. Use of prereduced catalyst resulted in increased yields of **3**, but no **8**. Such heterogeneous oxidation of an allylic alcohol in the presence of palladium–charcoal catalyst does not appear to have been reported previously.[22]

Partial reduction of **2a** with 5% Pd–$CaCO_3$ gave the dihydro derivative **9a** (mp 179–180°; $[\alpha]^{26}D$ +23.0°; no uv absorption; ir bands at 3600, 1770, and 1650 cm^{-1}; acetate mp 147–148°, $[\alpha]^{24}D$ +3.0°) in which only the exocyclic methylene group conjugated with the lactone function had been reduced. This was borne out by its nmr spectrum in which the two narrow doublets of **2a** (at 5.65 and 6.18 ppm) had been replaced by a new methyl doublet at 1.22 ppm (J = 7 cps) but which still exhibited the two signals at 4.62 and 5.1 ppm. Oxidation of **9a** gave the α,β-unsaturated ketone **10** {mp 271–274°; $[\alpha]^{24}D$ 18.8°; λ_{max} 222 mμ (ε 3300); ir bands at 1769, 1692, and 1618 cm^{-1}, the high intensity of the last indicating a cisoid chromophore}. As would be expected in going from **9** to **10**, the protons of the exocyclic methylene group had undergone a downfield shift and now appeared at 5.10 and 5.85 ppm;[23] other significant signals were found at

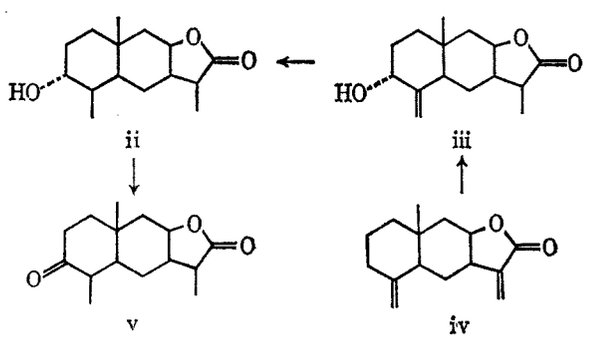
(10) Although it was tempting to formulate **2a** as a pseudoguaianolide (*i.e.*, i), such a structure was incompatible with the nmr data and the oxidation results.



i

(11) We are indebted to Dr. V. Herout for an authentic sample of isotelekin.

(12) The conclusion[9] that the C-3 hydroxyl group of isotelekin is axial is based on the correlation of isotelekin with ii which in turn had previously[13] been prepared from dihydroisoalantolactone (iv) by oxidation with selenium dioxide to iii and catalytic reduction. Oxidation[13] of ii to v followed by sodium borohydride reduction furnished a new alcohol different from ii. Hence the hydroxyl group of ii and iii was presumed to be axial; this conclusion is now verified by the nmr spectra.



ii iii v iv

(13) K. Tanabe, *Chem. Pharm. Bull.* (Tokyo), **7**, 218 (1958).

(14) Tanabe[13] reported mp 170–171° and $[\alpha]^{23}D$ −34.8° for **5** and $[\alpha]^{23}D$ −22.5° and mp 189–191° for the epimeric ketone v. Recently Geissman and Mukherjee[6] reported $[\alpha]^{28}D$ −31.8° and mp 173–174° for **5**.

(15) Kindly provided by Dr. Y. Y. Lin who prepared it from dihydroisoalantolactone according to the literature[13] method.

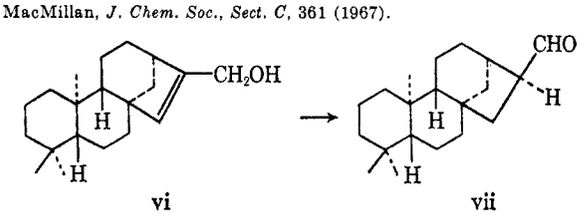
(16) Tanabe[13] reported mp 165–166° and $[\alpha]^{23}D$ −19.2° for this alcohol and mp 143–144° and $[\alpha]^{23}D$ −0.8° for its epimer ii.

(17) The absolute configuration of the C-11 methyl group of tetrahydroalantolactone has been shown to be β.[18]

(18) W. Cocker and M. A. Nisbet, *J. Chem. Soc.*, 534 (1963).

(19) W. Herz, Pseudoguaianolides in *Compositae*, in "Recent Advances in Phytochemistry," T. J. Mabry, R. E. Alston, and V. C. Runeckles, Ed., Appleton-Century Crofts, New York, N. Y., 1968.

(20) An analogous rearrangement, vi → vii, has recently been reported during the hydrogenation of the kaurene derivative vi: M. F. Barnes and J. MacMillan, *J. Chem. Soc., Sect. C*, 361 (1967).



vi vii

(21) (a) J. McQuillin in "Techniques of Organic Chemistry," Vol. IX, A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1963, p 498; (b) J. F. Biellmann and M. J. Jung, *J. Amer. Chem. Soc.*, **90**, 1673 (1968).

(22) W. F. Pickering, *Rev. Pure Appl. Chem.*, **16**, 185 (1966).

(23) For an article citing nmr spectra of compounds analogous to **9** and **10**, see H. Hikino, K. Aota, and T. Takemoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1929 (1967).

TABLE I

NMR SPECTRA OF 3-EPIISOTELEKIN DERIVATIVES[a]

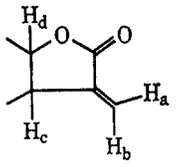
Compd	H-3	H-8	H-13$_{a,b}$	H-14$_{a,b}$	C-4 Me	C-10 Me	C-11 Me	Miscellaneous
2a	4.17 c	4.53 td	5.65 d (1) 6.18 d (1)	4.66 nm 5.18		0.82		3.0 c;[b] 2.22[c]
2b	5.16 c	4.50 td	5.60 d (1) 6.12 d (1)	4.60 nm 4.95 nm		0.85		3.0 c;[b] 2.12[d]
4	4.28 c	4.53 td	5.53 d (1) 6.07 d (1)	4.53 nm 4.93 nm		0.81		2.98 c;[b] 1.75[c]
3		4.50 td	5.58 d (1) 6.10 d (1)	5.05 db (2) 5.82 db (2)		0.99		3.0 c[b]
5		4.58 td			1.07 d (6.5)	1.20	1.23 d (7.0)	
6	3.8 c	4.52 td			0.88 d (6.5)	1.0	1.21 d (6.5)	
8		4.50 td	5.56 d (1) 6.10 d (1)		1.05 d (7.0)	1.20		
9a	3.95 c	4.43 td		4.62 nm 5.10 nm		0.80	1.22 d (7)	2.7 c;[b] 2.10[c]
9b	5.10 c	4.42 td		4.57 nm 4.92 nm		0.82	1.20 d (7)	2.72 c;[b] 2.10[d]
10		4.50 td		5.10 db (2.5) 5.85 db (2.5)		0.97	1.23 d (7)	

[a] Spectra were determined in deuteriochloroform solution on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are quoted in parts per million, signals being denoted in the usual way: d, doublet; db, doublet broadened; td, triplet of doublets; c, complex signal whose center is given; nm, narrow multiplet. Singlets are unmarked. Figures in parentheses denote line separations in cycles per second. H_3, H_8, $H_{13a,b}$, and $H_{14a,b}$ each integrated for one proton. Methyl signals had three-proton intensities. [b] Apparently due to H_7. [c] Hydroxyl proton disappears with D_2O. [d] Acetate signal intensity three protons.

0.97 (singlet, C-10 methyl) and 1.02 ppm (doublet, C-11 methyl).

The properties of **10** were at variance with the properties of a substance of presumably identical structure, which one of us (T. A. G.) had encountered earlier[6] in the course of work on the structure of farinosin, one of the sesquiterpene lactones of *Encelia farinosa* Gray. Farinosin had been formulated as **11** because of its spectral properties and because of its transformation to **5** by the following route. Zinc–acetic acid reduction of farinosin yielded a tetrahydro derivative (postulated formula **12**) whose dehydration with phosphorus oxychloride–pyridine furnished anhydrotetrahydrofarinosin: mp 218–219°; $[\alpha]^{28}D$ +52.2°; λ_{max} 210 mμ (11,640); nmr signals at 6.21 and 5.70 (exocyclic methylene), 1.26 (methyl singlet), and 1.02 ppm (methyl doublet). Anhydrotetrahydrofarinosin could be reduced to **5** and was therefore assigned formula **10**. To account for the marked differences in the physical properties of dehydrodihydroisotelekin (A) and anhydrotetrahydrofarinosin (B) we initially contemplated the possibility of a difference in stereochemistry at C-11, since A had not yet been converted into **5** and might conceivably have had an α- rather than a β-oriented C-11 methyl group. However, that the configuration of the C-11 methyl group in **9** and in A was β was shown by the solvent-induced shifts[24] of the C-11 methyl signals of A and of **9**. The $\delta_{CDCl_3}-\delta_{C_6H_6}$ values were of the order of 0.25 ppm which indicates the pseudo-equatorial conformation, hence β configuration, of the C-11 methyl group. This point was further corroborated by catalytic reduction of A with platinum oxide[25] which gave in our hands the saturated alcohol **6** whose stereochemistry at C-11 is the same as that in tetrahydroalantolactone.[13] Hence A was indeed properly represented by expression **10**, a finding which required revision of the structure of anhydrotetrahydrofarinosin (B) and therefore that of farinosin itself.

Reexamination of the spectral properties of farinosin and of B revealed that their structures should be changed from **11** and **10** to **13** and **8**, respectively. The key evidence which favored this revision was the chemical shift and multiplicity of nmr signals previously[6] assigned to the C-11 methylene protons of farinosin (in formula **11**) and the C-4 methylene protons of B (in **10**). Although the chemical shifts fall within the acceptable range for these assignments, their appearance and their multiplicity invalidate it. Thus in all sesquiterpene lactones which incorporate partial structure C, the signals due to the exocyclic methylene



C

protons H_a and H_b appear as a pair of sharp doublets with J on the order of 1–3 cps.[26,27] In farinosin and farinosin acetate the corresponding signals appear as a pair of narrow multiplets ($W_{1/2}$ = 5 cps) exhibiting at least two couplings, which would be accommodated by the C-4 methylene protons of the revised structure **13** and not by the C-11 methylene protons of the old

(24) C. R. Narayanan and N. K. Venkatasubramanian, *Tetrahedron Lett.*, 5865 (1966).

(25) This essentially duplicated the condition of ref 6.

(26) We have shown[1,27] by double irradiation experiments that this splitting is due to allylic coupling of H_a and H_b with H_c and not to geminal coupling. This is also true of **8** where H-13a (at 6.12 ppm) and H-13b (at 5.68) are both coupled to H-7 (at 3.00), which in turn is coupled to H-8 at 4.50. The methylene signals at 5.82 and 5.05 ppm, on the other hand, are not coupled to the signal at 3 ppm which confirms the structure assigned to this substance.

(27) W. Herz, S. Rajappa, M. V. Lakshmikantham, and J. J. Schmid, *Tetrahedron*, **22**, 693 (1966); W. Herz, S. Rajappa, S. K. Roy, J. J. Schmid, and R. N. Mirrington, *ibid.*, **22**, 1907 (1966); W. Herz, V. Sudarsanam, and J. J. Schmid, *J. Org. Chem.*, **31**, 3232 (1966); W. Herz, H. Chikamatsu, N. Viswanathan, and V. Sudarsanam, *ibid.*, **32**, 682 (1967); W. Herz, P. S. Santhanam, P. S. Subramaniam, and J. J. Schmid, *Tetrahedron Lett.*, 3115 (1967); W. Herz, Y. Sumi, V. Sudarsanam, and D. Raulais, *J. Org. Chem.*, **32**, 3658 (1967).

structure **11**. The appearance of these signals is virtually identical with the shape of the C-4 methylene protons of **3** and **10** but quite different from the C-11 methylene signals of **3** whose identity was established by spin decoupling.[26] Furthermore, in going from tetrahydrofarinosin to the anhydro derivative B, the nmr signals of the newly introduced exocyclic methylene protons H-13a and H-13b appear at 5.64 and 6.16 ppm (J = 1.2 cps) as a pair of sharp doublets incompatible with the old structure **10** but completely in accord with the new formula **8**. The reported[6] ultraviolet maximum of anhydrotetrahydrofarinosin [λ_{max} 210 mμ (ϵ 11,640)] further supports the revised structure, since it is consonant with an α,β-unsaturated lactone, but not with that of an α,β-unsaturated, cross-conjugated ketone.

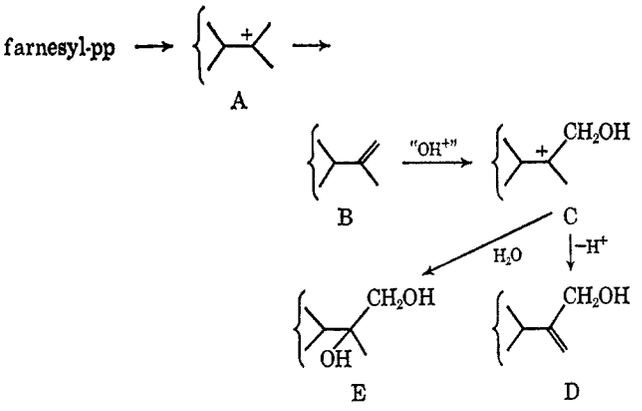
That the structure of anhydrotetrahydrofarinosin is indeed **8** and that of farinosin **13** was demonstrated conclusively as follows. Treatment of **2a** with methanolic hydrogen chloride[28] under reflux gave a mixture from which the ketone **8** (mp 214–217°; ir bands at 1760, 1708, 1668, and 1450 cm^{-1}) was isolated as the major product. Its nmr spectrum was identical with that of anhydrotetrahydrofarinosin.

The configuration of the hydroxyl group of farinosin, now located at C-11, must be α because H-8 of farinosin is deshielded relative to H-8 of those compounds in which the hydroxyl group is acetylated or absent.[6] The model also shows that an α-hydroxyl group should experience relatively little hindrance toward acetylation compared with a β-oriented hydroxyl group; this circumstance explains the facile acetylation of farinosin's tertiary hydroxyl.[29,30]

The α-hydroxylactone system of farinosin is so far quite uncommon among naturally occurring sesquiterpene lactones.[31,32] In view of the frequent cooccurrence of C-11,13-unsaturated lactones and their C-11,13-dihydro derivatives,[33–35] the appearance of a C-11 hydroxylated compound such as farinosin could conceivably be attributed to oxidation of the corresponding saturated lactones, in analogy with the conversion of santonin to α-hydroxysantonin in animal organisms. Less likely, we think, is a biological hydration of the exocyclic methylene group in the chemically "wrong" sense.

A plausible alternative which has the advantage of relating the formation of α-hydroxylactones more directly to the biosynthetic pathway to compounds embodying other oxidation stages (*i.e.*, the costol–costal–costic acid series and the lactones) is shown in Scheme II, where A is the initial cyclodecadiene and

SCHEME II



where further transformations of C can proceed in the usual manner to lead eventually, not only to the α,β-unsaturated lactones, but also to α-hydroxylactones exemplified by farinosin. It is evident that C or E (or the corresponding epoxide) could, by obvious steps, furnish a saturated aldehyde, further transformations of which could account for the simultaneous presence of C-11 methylene and C-11 methyl lactones in the plant. This is much more palatable than the requirement for either a dehydrogenation or a hydrogenation step which is otherwise needed to explain cooccurrence of the two types of lactones.

Experimental Section[36]

Isolation of 3-Epiisotelekin and Spathulin from *Gaillardia aristata* Pursh.—Above-ground plant material (wt 18 lb) collected by Dr. F. W. Bachelor near Calgary, Canada, in the flowering season during Aug and Sept 1966, was ground, extracted with chloroform, and worked up in the usual manner. This gave 127 g of gum which was dissolved in the minimum amount of 1:1 benzene–chloroform and adsorbed over a chromatographic column containing 1.1 kg of silicic acid (Mallinckrodt, 100 mesh), set in benzene. The column was eluted in the following sequence, and 500-ml fractions were collected. Fractions 1–16 (benzene), 17–26 (benzene–chloroform 4:1), 27–38 (benzene–chloroform 3:2), and 39–54 (benzene–chloroform 1:1) eluted practically nothing. Fractions 55–57 (benzene–chloroform 2:3) eluted a gum showing several spots on tlc and were discarded. Fractions 58–72 (benzene–chloroform 2:3) eluted solid material. These were combined on the basis of tlc and allowed to stand overnight in the minimum amount of methylene chloride. The deposited crystals were freed of the solvent, washed with a mixture of 1:1 methylene chloride–petroleum ether, and dried to give 1.8 g of almost pure 3-epiisotelekin (**2a**).

Fractions 73–78 (benzene–chloroform 2:3) and 79–88 (benzene–chloroform 1:3) eluted small amounts of impure **2a**. These were combined with the mother liquors from fractions 58–72 and rechromatographed over 60 g of silicic acid. Elution with 1:1 benzene–chloroform afforded 0.75 g of fairly pure **2a**.

Fractions 89–91 (benzene–chloroform 1:3) eluted practically nothing. Fractions 92–95 (benzene–chloroform 1:3) eluted considerable amount of dark green gelatinous gum. The presence of spathulin (**1**) in these fractions was indicated by tlc. On being left in an acetone–hexane solution for 2 days at room temperature, the gum deposited colorless crystalline material

(28) For recent leading references to this acid-induced allyl alcohol–methyl ketone isomerization, see ref 20 and S. W. Pelletier and P. C. Parthasarathy, *J. Amer. Chem. Soc.*, **87**, 777 (1965).

(29) The nmr spectrum of α-hydroxysantonin which is also easily acetylated has been interpreted on a similar basis.[30]

(30) J. T. Pinhey and S. Sternhell, *Aust. J. Chem.*, **18**, 543 (1965).

(31) α-Hydroxybalchanolide[32] has been isolated from a plant source, but α-hydroxysantonin[30] is an animal metabolite of santonin and has so far not been found in plants.

(32) V. Herout, M. Suchý, and F. Šorm, *Collect. Czech. Chem. Commun.*, **26**, 2612 (1961).

(33) For recent examples, see mikanolide and dihydromikanolide[34] and parthenin and coronopilin.[35]

(34) W. Herz, P. S. Santhanam, P. S. Subramaniam, and J. J. Schmid, *Tetrahedron Lett.*, 3111 (1967).

(35) T. J. Mabry, W. Renold, H. E. Miller, and H. B. Kagan, *J. Org. Chem.*, **31**, 681 (1966); H. E. Miller and T. J. Mabry, *ibid.*, **32**, 2929 (1967); L. Farkas, M. Nogradi, V. Sudarsanam, and W. Herz, *ibid.*, **31**, 3228 (1966).

(36) Melting points were taken in capillaries and are uncorrected. Unless otherwise specified, rotations were run in chloroform; ultraviolet spectra, in 95% ethanol; infrared spectra, in chloroform; and nmr spectra, in deuteriochloroform. Thin layer chromatograms were carried out on microslides coated with silica gel G. The plates were developed with chloroform–methanol (6:0.3), and the spots were detected by spraying with concentrated sulphuric acid followed by heating. Since R_f values varied from plate to plate, they are not quoted. Plates coated with silica gel $PF_{254+366}$ were used for preparative tlc and developed with chloroform–methanol (95:5). The bands were detected with ultraviolet light. Petroleum ether boiled at 30–60°. Analyses were by Dr. F. Pascher, Bonn, Germany.

which was freed from the dark green supernatant solution, washed with acetone–hexane mixture, and dried. Two crystallizations from acetone gave 2.1 g of spathulin, mp and mmp 258–261°; the ir spectrum (Nujol) and tlc mobility were identical with those of authentic material.

The polar fractions 96–106 (chloroform), 107–116 (chloroform–ether 95:5), 117–126 (chloroform–ether 90:10), 127–132 (chloroform–methanol 95:5), and 133–137 (chloroform–methanol 90:10) either did not elute anything or eluted only small amounts of gummy material showing several spots in tlc, from which no solid material could be isolated.

3-Epiisotelekin (2a), upon recrystallization from methylene chloride and *n*-pentane or acetone–isopropyl ether, formed colorless needles: mp 176–177°; $[\alpha]^{26}D$ +156.6° (*c* 2.02); and ir bands at 3600, 1760, 1669, 1650, 970, 950, and 900 cm^{-1}. In the uv spectrum it showed only end absorption, 210 mμ (ε 10,590).

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; O, 19.33. Found: C, 72.31; H, 8.35; O, 19.18.

3-Epiisotelekin Acetate (2b).—A mixture of 60 mg of 3-epiisotelekin, 1 ml of pyridine, and 1 ml of acetic anhydride was heated on the steam bath for 2 hr, and evaporated *in vacuo*. The residue was treated with ice water, and the product was isolated with chloroform. Removal of the solvent gave a crystalline material, which on being crystallized from isopropyl ether–pentane formed colorless plates (48 mg): mp 132–133°; $[\alpha]^{26}D$ +93.24° (*c* 2.2); ir bands at 1760, 1722, 1668, 1650, 970, 950, 905, and 880 cm^{-1}.

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64; O, 22.04. Found: C, 70.71; H, 7.74; O, 21.85.

3-Oxoisoalantolactone (3). A.—To an ice-cooled, stirred solution of 105 mg of 3-epiisotelekin in 6 ml of reagent-grade acetone was added dropwise 0.4 ml of Jones reagent. The reaction mixture was stirred at ice temperature for 10 min and then at room temperature for 20 min. Excess of the reagent was destroyed by the careful addition of a few drops of methanol. The mixture was diluted with ice–water and extracted thoroughly with chloroform. The chloroform solution was washed with brine water and dried over anhydrous sodium sulfate, and the solvent was evaporated *in vacuo* to give a syrup which eventually solidified. It was passed through a small column of silicic acid (4 g) set in benzene–chloroform (1:1) and crystallized from acetone–isopropyl ether three times to give colorless long needles (42 mg): mp 145–147°; $[\alpha]^{26}D$ +149.5° (*c* 2.2); λ_{max} 207 mμ (ε 38,850); ir bands at 1668, 1692, 1670 (w), 1615 (s), 915, 950, and 880 cm^{-1}.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37; O, 19.49. Found: C, 73.02; H, 7.59; O, 19.43.

The nmr spectrum of **3** is given in Table I. The following double irradiation experiments were performed by Mr. J. J. Schmid. Irradiation at 3.00 ppm (H-7) simplified the signal at 4.50 (H-8) to a triplet and collapsed the signals at 6.12 (H-13a) and 5.68 (H-13b) to sharp singlets. Irradiation at 2.5 ppm (H-5) simplified the multiplets at 5.9 and 5.1 to broad singlets, indicating that H-14a and H-14b were allylically coupled to H-5. Irradiation at 5.1 (H-14a) simplified the signal at 5.9 (H-14b) to a doublet (J = 2.4 cps) indicating that *gem* coupling was small.

B.—A solution of 100 mg of 3-epiisotelekin in 30 ml of reagent grade chloroform was stirred with 1.0 g of active manganese dioxide[37] for 36 hr at room temperature. It was filtered with suction; the precipitate was washed thoroughly with warm chloroform, and the filtrate was evaporated *in vacuo* to give a crystalline residue. As judged from tlc, it was a mixture of the ketonic product and the starting material. Preparative tlc gave 62 mg of ketone **3** from the higher R_f band and 14 mg of starting material (**2a**) from the lower R_f band.

Catalytic Hydrogenation of 3-Epiisotelekin.—A solution of 248 mg (1 mmol) of 3-epiisotelekin in 40 ml of ethyl acetate was hydrogenated in the presence of 248 mg 10% palladized charcoal catalyst at atmospheric pressure. Uptake of hydrogen was complete in 45 min, the absorption amounting to *ca.* 1.4 mol. Prolonged reduction for 6 hr more did not result in any further uptake of hydrogen. Evaporation of the filtered solution *in vacuo* gave a crystalline product which showed two spots in tlc. The mixture was separated by preparative tlc.

The higher R_f band gave 152 mg of 3-oxo-4Hβ-tetrahydroalantolactone (**5**), which after two crystallizations from acetone–petroleum ether melted at 170–171°, undepressed on admixture with an authentic specimen: $[\alpha]^{26}D$ −30.9° (*c* 2.4); λ_{max} 280 mμ (ε 110); ir bands at 1765, 1700, and 1450 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 72.02; H, 8.89; O, 18.85.

The 2,4-dinitrophenylhydrazone prepared in the usual way was crystallized three times from methanol to give yellow needles: mp 240–241°; λ_{max} 364 mμ (ε 15,700).

Anal. Calcd for $C_{21}H_{26}O_6N_4$: C, 58.59; H, 6.09; N, 13.02. Found: C, 59.29; H, 6.32; N, 12.59.

The lower R_f band gave 46 mg of 3-β-hydroxytetrahydroalantolactone (**6**) which crystallized from isopropyl ether–petroleum ether as colorless plates: mp 162–164°; $[\alpha]^{26}D$ −19.13° (*c* 1.8); ir bands at 3600, 1768, and 962 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.23; H, 9.68; O, 19.00.

Treatment of 3-Epiisotelekin with 10% Pd–C.—To 100 mg of prereduced 10% palladized charcoal catalyst in 16 ml of ethyl acetate was added 100 mg of 3-epiisotelekin. The mixture was stirred at room temperature for 24 hr, filtered, and washed with warm ethyl acetate; the solvent was removed *in vacuo*. The colorless crystalline residue showed two spots in tlc. The mixture was separated by preparative tlc. The higher R_f band gave 18 mg of product, which after crystallization from acetone–isopropyl ether had mp 145–147° and was identical in all respects (mixture melting point, ir and nmr spectra, tlc) with 3-oxoisoalantolactone (**3**). The lower R_f band gave 63 mg of starting material (**2a**). Repetition of this experiment with 10% palladized charcoal which was *not* prereduced gave only 5 mg of **3** from 100 mg of **2a**.

Dihydro-3-epiisotelekin (9a).—A solution of 124 mg (0.5 mmol) of 3-epiisotelekin in 18 ml of ethyl acetate was hydrogenated in the presence of 80 mg of 5% palladium on calcium carbonate catalyst at atmospheric pressure. The reduction was stopped after an uptake of hydrogen equivalent to 1 mol (13 min) and worked up in the usual way. The crude product was purified by preparative tlc and was crystallized from acetone–isopropyl ether giving colorless tiny needles (86 mg). For analysis it was crystallized three times from the same solvent system: mp 178–180° (softening around 170°); $[\alpha]^{26}D$ +22.95° (*c* 2.6); no uv maximum; ir bands at 3590, 1768, 1650, 970, 910, and 880 cm^{-1}.

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86; O, 19.17. Found: C, 71.61; H, 8.94; O, 19.31.

Dihydro-3-epiisotelekin Acetate (9b).—A mixture of 48 mg of dihydro-3-epiisotelekin, 1 ml of pyridine, and 1 ml of acetic anhydride was allowed to stand at room temperature overnight. Standard work-up gave 36 mg of the acetate after crystallization from isopropyl ether–petroleum ether: mp 147–148°; $[\alpha]^{24}D$ +3.0° (*c* 1.0).

Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27; O, 21.89. Found: C, 69.45; H, 8.39; O, 22.32.

3-Oxodihydroisoalantolactone (10).—A mixture of 100 mg of dihydro-3-epiisotelekin, 1.0 g of active manganese dioxide, and 25 ml of reagent grade chloroform was stirred at room temperature for 36 hr. Standard work-up followed by separation by preparative tlc gave 67 mg of the ketone and 12 mg of the starting material. Recrystallization from acetone–isopropyl ether gave colorless plates: mp 271–274°; $[\alpha]^{24}D$ +18.82° (*c* 1.2); λ_{max} 222 mμ (ε 3307); ir bands at 1769, 1692, 1618, 970, 950, and 875 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12; O, 19.33. Found: C, 72.29; H, 8.27; O, 19.51.

Catalytic Reduction of 3-Oxodihydroisoalantolactone.—A solution of 31 mg (0.25 mmol) of **10** in 10 ml of ethyl acetate was hydrogenated in the presence of 14 mg of platinum oxide, at atmospheric pressure until hydrogen uptake ceased. Evaporation of the filtered solution *in vacuo* gave a colorless crystalline product which showed practically a single spot in tlc. Recrystallization from isopropyl ether–petroleum ether gave 22 mg of colorless needles, mp 162–164°, undepressed on admixture with **6**. Their ir and nmr spectra were identical.

Acid-Catalyzed Isomerization of 3-Epiisotelekin.—A solution of 100 mg of 3-epiisotelekin in 25 ml of reagent grade methanol was treated with 4.5 ml of concentrated hydrochloric acid and refluxed for 14 hr.[38] The mixture was concentrated *in vacuo* and treated with ice water. On standing the product crystal-

(37) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(38) Control experiments indicated that practically no isomerization took place when the reaction mixture was left at room temperature overnight, and only partial isomerization was effected by heating under reflux for 2 hr. The amount of rearranged product increased with longer durations of reflux.

lized as colorless thin needles. It was extracted with chloroform; the chloroform solution was washed with aqueous bicarbonate solution followed by water, dried over anhydrous sodium sulfate, and evaporated *in vacuo*. The crude solid product showed one major spot and at least three other minor spots of varying intensities. The mixture was separated by preparative tlc; work-up of the major band gave 58 mg of crude ketone **8**, which showed a melting point range of 198–204° after one crystallization from acetone–isopropyl ether. Four more recrystallizations from the same solvent system raised the melting point to 214–217°. The product showed a single spot in tlc; $[\alpha]^{24}D$ +52.84° (*c* 1.19); λ_{max} 210 mμ (ε 7200); ir bands at 1760, 1708, 1668, 1450, 990, 950, and 880 cm^{-1}.

Registry No.—**2a**, 17322-81-5; **2b**, 17230-63-6; **3**, 17230-64-7; **4**, 17322-82-6; **5**, 17230-66-9; 2,4-dinitrophenylhydrazone of **5**, 17230-67-0; **6**, 17230-68-1; **8**, 17230-69-2; **9a**, 17230-70-5; **9b**, 17230-71-6; **10**, 17322-83-7.

Novel Alkaloids Containing the [2]Benzopyrano[3,4-*c*]indole Nucleus[1-3]

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Five new Amaryllidaceae alkaloids containing the [2]benzopyrano[3,4-*c*]indole nucleus have been isolated, and their structures were established. The structures and stereochemistry of haemanthidine (**5a**) and macronine (**4b**) are completely defined. Evidence is presented that tazettine (**1a**, R = H) and criwelline (**1b**, R = H) may be rearrangement artifacts.

Although the total number of Amaryllidaceae alkaloids is close to 150, only three alkaloids have been found to contain the [2]benzopyrano[3,4-*c*]indole nucleus. Tazettine is one of the most abundant alkaloids of this family.[4,5] Structural studies on this base began in 1934[6] and culminated in the assignment of structure (**1a**, R = H) in 1966.[7] Criwelline (**1b**, R = H), the C_3 epimer of tazettine, was first isolated from *Crinum powellii* Hort. var. *album* in 1956.[8] It was related structurally to 6-hydroxycrinamine (**5b**) and tazettine in 1959.[9] Macronine was isolated in 1964 from *Crinum macrantherum* Engl., and its functional groups were determined.[10] In the same year it was assigned structure **4b**,[11] but the stereochemistry at C_{6a} was not defined.

The advent of thin and thick layer chromatography has made possible the isolation of pure material from mixtures which were previously inseparable. Using this powerful technique, several Amaryllidaceae species have been reinvestigated to study other alkaloids that have escaped previous detection.

Alkaloid Isolation from *Sprekelia formosissima* L. (Herb.) and *Ismene calithina* (Nichols).—Tazettine, haemanthamine, haemanthidine, and ismine have been reported to occur in *Sprekelia formosissima*.[12,13] In a recent reexamination of the alkaloids in this plant, using procedures which avoided strongly basic conditions (including chromatography on alumina), the alkaloid fraction appeared devoid of tazettine by tlc criteria. *Ismene calithina*, reported to contain galanthamine, homolycorine, lycorine, nerinine, and tazettine,[14] when processed under similar conditions, was also found by tlc to contain no tazettine.

The major alkaloid in each case was identified as pretazettine ($C_{18}H_{21}NO_5$). Although the base defied crystallization, crystalline hydrochloride and hydrobromide salts have been obtained. Pretazettine is converted readily into tazettine under a variety of basic conditions. Chromatography on basic alumina or treatment with 0.1 *N* sodium hydroxide at 25° for 1 hr affords a quantitative conversion into tazettine. Pretazettine is unstable as the free base in solution and gradually rearranges to tazettine upon standing. An aqueous solution of pretazettine is converted at 70° into tazettine in less than 1 hr. Under dilute acidic conditions, however, pretazettine appears to be stable. This facile rearrangement suggests that the true alkaloid in the plant is pretazettine. The tazettine isolated by previous workers probably arises from this rearrangement which has occurred during routine alkaloid isolation conditions.[15]

The chemical and physical properties of pretazettine (as well as its salts) are in good agreement with those reported by Proskurnina[16] for isotazettine, although a direct comparison has not been possible. The name isotazettine should not be continued because it introduces confusion with the existing references to isotazettine (criwelline), tazettinol, and isotazettinol. These are all C_{6a} hydroxy derivatives of the [2]benzopyrano[3,4-*c*]indole nucleus but vary in stereochemistry of the substituent at C_3.

Comparison of the ir and nmr spectra of tazettine and pretazettine indicates that the bases have many structural features in common. A difference between

(1) Supported by a grant, HE 7503, from the National Institutes of Health.

(2) For the preliminary communication, see W. C. Wildman and D. T. Bailey, *J. Amer. Chem. Soc.*, **89**, 5514 (1967). Subsequent to our initial communication, comparable results have been reported by W. Döpke and P. W. Jeffs, *Tetrahedron Lett.*, 1307 (1968).

(3) Taken from the dissertation of D. T. Bailey submitted in partial fulfillment of the requirements for the Ph.D. degree, Iowa State University, 1968.

(4) W. C. Wildman, *Alkaloids*, **6**, 372 (1960).

(5) H.-G. Boit. "Ergebnisse der Alkaloid-Chemie bis 1960," Akademie-Verlag, Berlin, p 410.

(6) E. Späth and L. Kahovec, *Ber.*, **67**, 1501 (1934).

(7) (a) R. J. Highet and P. F. Highet, *Tetrahedron Lett.*, 4099 (1966). Other papers on the structure of tazettine are (b) W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 2962 (1955); (c) T. Ikeda, W. I. Taylor, Y. Tsuda, S. Uyeo, and H. Yajima, *ibid.*, 4749 (1956); (d) T. Ikeda, W. I. Taylor, Y. Tsuda, and S. Uyeo, *Chem. Ind.* (London), 1088 (1955); (e) T. Ikeda, W. I. Taylor, Y. Tsuda, and S. Uyeo, *ibid.*, 411 (1956); (f) R. J. Highet and W. C. Wildman, *ibid.*, 1159 (1955); (g) H. Irie, Y. Tsuda, and S. Uyeo, *J. Chem. Soc.*, 1446 (1959); (h) Y. Tsuda and S. Uyeo, *ibid.*, 2485 (1961); and (i) R. D. Haugwitz, P. W. Jeffs, and E. Wenkert, *ibid.*, 2001 (1965).

(8) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **89**, 2093 (1956).

(9) H. M. Fales, D. H. S. Horn, and W. C. Wildman, *Chem. Ind.* (London), 1415 (1959).

(10) H. Hauth and D. Stauffacher, *Helv. Chim. Acta*, **47**, 185 (1964).

(11) C. F. Murphy and W. C. Wildman, *Tetrahedron Lett.*, 3857 (1964).

(12) H.-G. Boit and H. Ehmke, *Chem. Ber.*, **88**, 1590 (1955).

(13) R. J. Highet, *J. Org. Chem.*, **26**, 4767 (1961).

(14) H.-G. Boit and W. Döpke, *Naturwissenschaften*, **45**, 315 (1958).

(15) W. C. Wildman and Carol J. Kaufman, *J. Amer. Chem. Soc.*, **76**, 5815 (1954).

(16) N. F. Proskurnina, *Zh. Obshch. Khim.*, **23**, 3365 (1957).