The Alkaloids of *Cacalia floridana*

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Four closely related alkaloids have been isolated from *Cacalia floridana*. These include the known pyrrolizidine-derived base, otosenine, and three new alkaloids, named florosenine, floricaline, and floridanine. Structures for the new alkaloids are proposed on the basis of chemical interconversions and spectral evidence.

The genus *Cacalia* (*Compositeae*) has received little phytochemical attention; chemical constituents of only two species have been recorded. The Mexican species, *Cacalia decomposita* A. Gray, contains a number of interesting furonaphthalene derivatives;[1,2] no mention has been made of the occurrence of alkaloids in this plant. The species *C. hastata*, which is native to the Soviet Union, contains an alkaloid of undetermined structure, named hastacine, ($C_{18}H_{27}O_5N$, mp 171°); it is interesting to note that *C. hastata* is said to be synonymous with *Senecia sagittatus* Sch. bip.[3]

The close relationship which exists between the genera *Cacalia* and *Senecio* implied that members of the *Cacalia* species, like those of the extensively investigated genus *Senecio*,[4] might be sources of new pyrrolizidine-type alkaloids. This supposition was confirmed in the case of the American species described below.

Extraction of *Cacalia floridana*, commonly known as Indian plantain (whole plants), yielded a mixture of four tertiary bases. These were separated by a combination of crystallization and chromatography. No other alkaloids were present in appreciable amount as N-oxides, since reductive treatment of a sample of the crude base mixture, followed by chromatography, afforded only the same four compounds.

The major alkaloid of *C. floridana* is otosenine (**1**).[5,6] Otosenine, which is formally derived from the amino alcohol otonecine (**2**),[5] is almost certainly biogenetically derived from the well-known Senecio-type base jacobine (**3**)[4] *via* jacobine N-oxide. Other members of the small group of otonecine-derived alkaloids include retusamine,[6-8] senkirkine (renardine),[9-11] O-acetylsenkirkine,[11] onetine,[12] and crosemperine.[13]

The remaining three bases from *C. floridana* are new alkaloids which were named florosenine, floricaline, and floridanine. Florosenine and floricaline were crystallized only as benzene solvates, and floridanine was crystallized only as a chloroform solvate. However, the molecular weights of all three alkaloids were verified by mass spectrometry.

The composition of florosenine ($C_{21}H_{29}O_8N$) differs from that of otosenine ($C_{19}H_{27}O_7N$) in that it contains the elements of ketene (C_2H_2O). This difference suggested that florosenine might be the O-acetyl derivative of otosenine; this hypothesis was also supported by the spectral data presented below (see Table I). Indeed, acetylation of otosenine with acetyl chloride yielded florosenine; conversely, otosenine was obtained from florosenine by very mild alkaline hydrolysis. Florosenine is therefore represented by structure **4**.

TABLE I

NUCLEAR MAGNETIC RESONANCE VALUES (δ)

	N-CH_3	C-2[b]	C-9[d]	C-11	C-12[e]	C-14[f]	C-18	C-19
Otosenine (1)	2.05	6.16	5.50 4.36	1.36		1.14	2.98[g]	1.24[i]
Florosenine (4)	2.05	6.16	5.28 4.35	1.68	2.05	1.14	2.95[g]	1.24[i]
Floricaline (7)	2.03[c]	6.08	5.04 4.45	1.63	2.07[c]	1.27	1.96[h]	1.27[j]
Floridanine (5)[a]	2.78	6.35		1.45	1.90	~1.0		~1.0

[a] Spectrum in CF_3COOH. [b] Unresolved multiplet. [c] Assignments may be interchanged. [d] J = 11 cps. [e] Value for acetoxy substituent. [f] Doublet, J = 6.5 cps. [g] Quartet, J = 5 cps. [h] Value for acetoxy substituent. [i] Doublet, J = 5 cps. [j] Doublet, J = 6 cps.

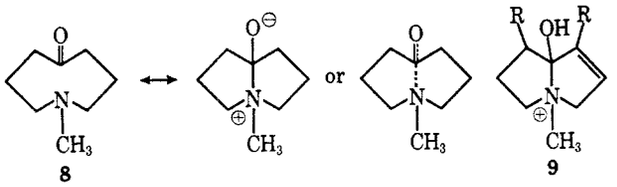
The composition of floridanine ($C_{21}H_{31}O_9N$) corresponds to that of florosenine with a molecule of water added, suggesting structure **5** for floridanine, a hypothesis in accord with the spectral data presented in the following sections. Florosenine (**4**) and floridanine (**5**) would then form a pair of related bases analogous to the previously known pair otosenine (**1**) and onetine (**6**).[5] The composition of floricaline ($C_{23}H_{33}O_{10}N$) suggested that it might be a monoacetyl derivative of floridanine. Indeed, floricaline was converted into floridanine by mild, partial alkaline hydrolysis. Conversely, floricaline was obtained from floridanine by acetylation with acetic anhydride in pyridine at room temperature. Under these latter conditions, acetylation of the secondary alcohol function of **5** should be favored. As expected, the related tertiary alcohol, otosenine, did not react with acetic anhydride in pyridine on standing at room temperature for 2 days; structure **7** is therefore suggested for floricaline. It should be emphasized that the above arguments do not offer unambiguous proof for the structures of floridanine and floricaline. However, the assigned structures (**5**

(1) J. Romo and P. Joseph-Nathan, *Tetrahedron*, **20**, 2331 (1964).
(2) J. Correa and J. Romo, *ibid.*, **22**, 685 (1966).
(3) V. S. Konovalov and G. P. Menshikov, *J. Gen. Chem. USSR*, **15**, 328 (1945); *Chem. Abstr.*, **40**, 3760 (1946).
(4) N. J. Leonard in "The Alkaloids," Vol. VI, Manske and Holmes, Ed., Academic Press, New York, N. Y., 1960.
(5) E. S. Zhdanovich and G. P. Menshikov, *J. Gen. Chem. USSR*, **11**, 835 (1941).
(6) J. A. Wunderlich, *Chem. Ind.* (London), 2089 (1962).
(7) C. C. J. Culvenor and L. W. Smith, *Aust. J. Chem.*, **10**, 464 (1957).
(8) C. C. J. Culvenor, G. M. O'Donovan, and L. W. Smith, *ibid.*, **20**, 801 (1967).
(9) L. H. Briggs, J. L. Mangan, and W. E. Russell, *J. Chem. Soc.*, 1891 (1948).
(10) A. V. Danilova, N. I. Koretskaya, and L. M. Utkin, *Zh. Obshch. Khim.*, **31**, 3815 (1961); *J. Gen. Chem. USSR*, **31**, 3560 (1961).
(11) L. H. Briggs, R. C. Cambie, B. J. Candy, G. M. O'Donovan, R. H. Russell, and R. N. Seelye, *J. Chem. Soc.*, 2492 (1965).
(12) A. V. Danilova, N. I. Koretskaya, and L. M. Utkin, *Zh. Obshch. Khim.*, **32**, 647 (1962); *J. Gen. Chem. USSR*, **32**, 638 (1962).
(13) C. K. Atal, C. C. J. Culvenor, R. S. Sawhney, and L. W. Smith, *Aust. J. Chem.*, **20**, 805 (1967).

and **7**) receive added support from the spectral considerations presented below (see Table I).

The infrared spectra of florosenine, floridanine, and floricaline, like that of otosenine, show the presence of a carbonyl group at unusually long wavelengths. This type of absorption is characteristic of the ring carbonyl of otonecine-derived alkaloids;[6,11] it is attributable to the same strong interaction between the carbonyl and the basic nitrogen which has been found in the case of the parent compound, 1-methyl-1-azacyclooctan-5-one (**8**).[14]

Appreciable differences exist in the positions of the ketonic carbonyl band in otosenine (6.33 μ), florosenine (6.18 μ), and floricaline (6.18 μ). These are probably due to variations in the geometry of the eight-membered ring and differing degrees of hydrogen bonding. In floridanine, the ketonic carbonyl appears only as a very diffuse band beyond 6 μ.



8 **9**

The most significant features of the nmr spectra of three *Cacalia* bases, **1**, **4**, and **7** in $CDCl_3$, are summarized in Table I. Values for floridanine (**5**) are included, although these are of limited usefulness since only a rather poorly resolved spectrum of this alkaloid in trifluoroacetic acid could be obtained. The nmr spectrum of otosenine (**1**) is practically identical with the published spectrum of jacobine (**3**);[15] the only significant difference is the N-methyl signal at δ 2.05 in the otosenine spectrum. The N-methyl signal appears at essentially the same position in the spectra of florosenine (**4**) and floricaline (**7**). This same function appears at much lower field (δ 2.78) in the spectrum of floridanine, due to the strongly acidic solvent (CF_3COOH) employed; in this case, the N-methyl is undoubtedly part of a true quaternary carbinolamine system (**9**). The nmr spectrum of florosenine (**4**) differs from that of otosenine in two ways: the acetoxy methyl of **4** is clearly visible at 2.05, and the C-11 methyl of **4** is somewhat deshielded (1.68), compared with the same methyl (1.36) of otosenine (**1**).[16]

The absence of the strained epoxide ring in floricaline (**7**) causes minor conformational changes in the macrocyclic diester system of **7** as compared to that of florosenine (**4**), and these changes are reflected in its nmr spectrum. Thus, the protons at C-2, C-9, C-11, and C-14 in the spectrum of **7** appear at slightly different positions from those in the spectrum of **4**; in addition, the new methyl at δ 1.96 is assigned to the second acetoxy group of floricaline.

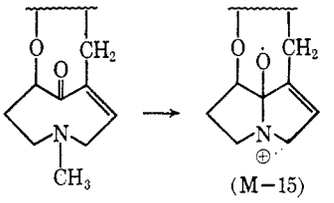
The mass spectra of the *Cacalia* bases (**1**, **4**, **7**, and **5**) confirm their molecular weights and also show some significant breakdown patterns; only the most obvious features of the spectra are presented here.

(14) N. J. Leonard, R. C. Fox, M. Oki, and S. Chiavarelli, *J. Amer. Chem Soc.*, **76**, 630 (1954).

(15) C. C. J. Culvenor, *Aust. J. Chem.*, **17**, 233 (1964).

(16) A similar deshielding effect is observed on comparing the nmr spectra of senkirkine and its O-acetyl derivative; see ref 11.

(a) All of the bases show an M − 15 peak, attributable to loss of the N-methyl group as shown below.

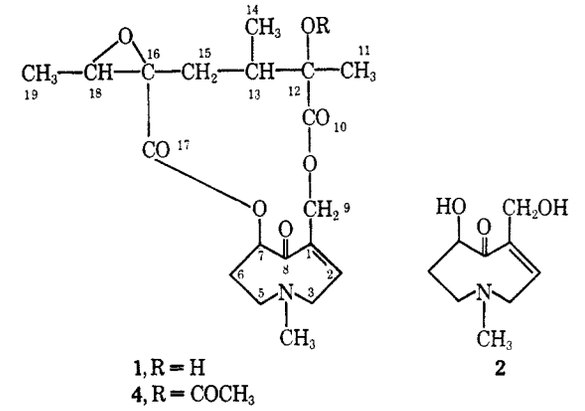


(M−15)

(b) Only otosenine (**1**) shows an M − 17 peak (loss of OH); the other three bases instead show peaks at M − 59 (loss of CH_3CO_2). Since not only **1** but also **7** and **5** bear one or more OH groups in the 12-membered ring, apparently only the loss of OH at C-12 is important enough to be observed as an M − 17 peak.

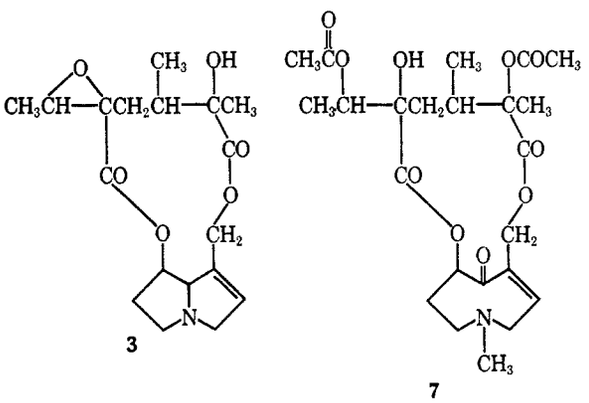
(c) Only **7** and **5** shows peaks at M − 18 (loss of water). Direct dehydration is apparently important only when C-16 bears a hydroxyl group.

(d) All four bases show M − 44 peaks (loss of CO_2). Removal of CO_2 involves loss of the lactone carbonyl at C-10 rather than at C-17, by analogy with the pre-



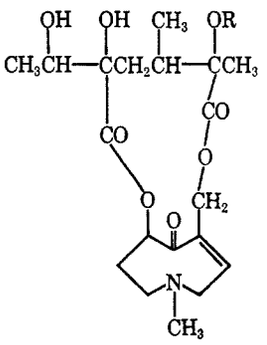
1, R = H
4, R = $COCH_3$

2



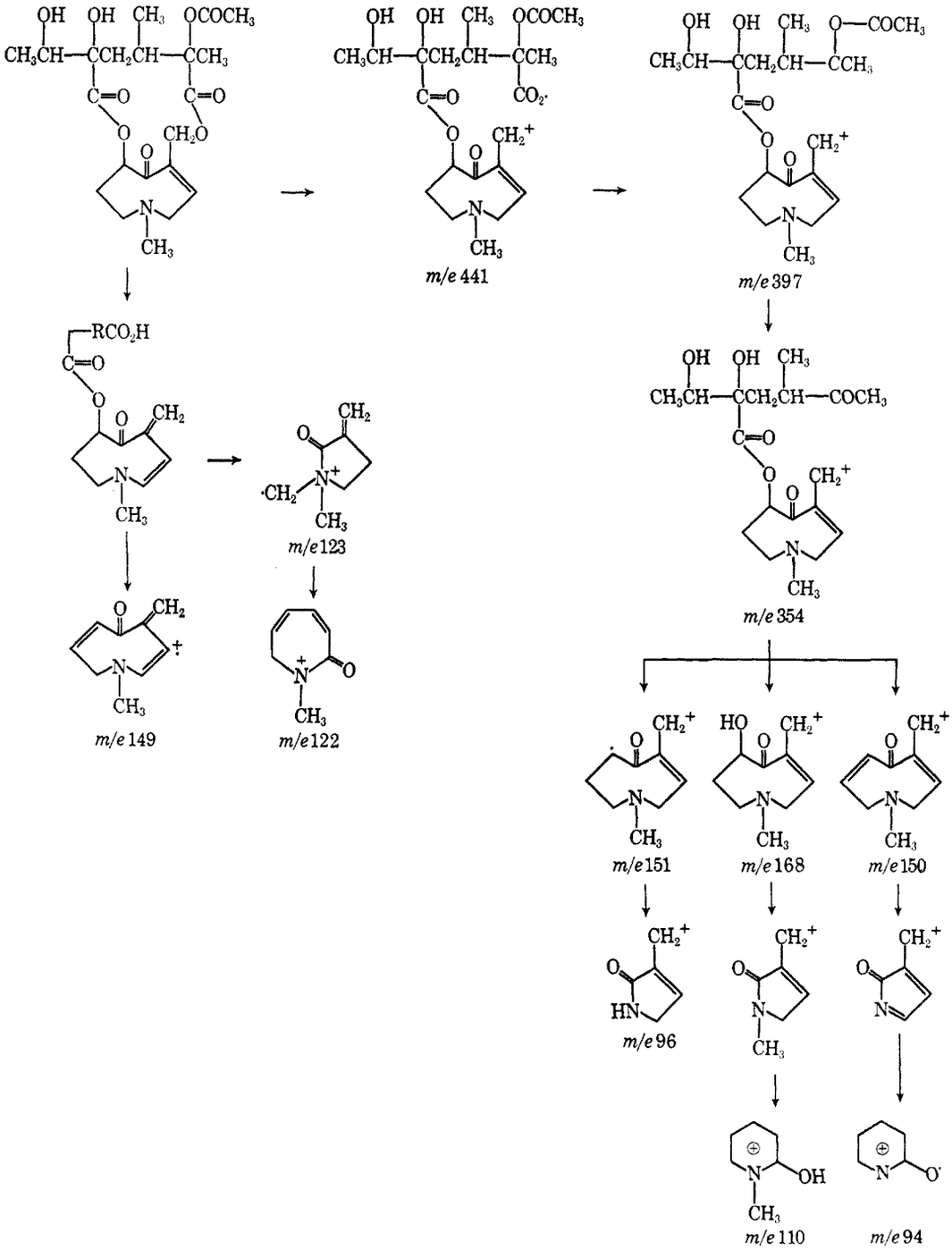
3

7



5, R = $COCH_3$
6, R = H

SCHEME I
FRAGMENTATION OF FLORIDANINE



viously described cracking patterns for the Senecio-type bases, monocrotaline[17] and senecionine.[18]

(e) All four bases show a certain number of common fragments in the mass range below 169. The fragments at *m/e* 168, 151, 150, 149, 123, 122, 110, 96, and 94 are among the most characteristic of those attributable to the common otonecine portion of the alkaloids; suggested structures for these ions are given below.

The fragmentation sequences in Scheme I are proposed for origin of most of the important peaks in the spectrum of floridanine (**5**). The scheme proposed is in general accord with those deduced for some closely related pyrrolizidine lactone alkaloids.[17,18]

Our initial attempts to effect a direct chemical correlation between otosenine and floridanine by means of hydrolysis have been unsuccessful. Further experiments in this direction are planned when additional supplies of the alkaloids are accumulated.

Experimental Section

All melting points are uncorrected. Optical rotations were measured in chloroform at room temperature. Ir spectra were determined in KBr disks, uv spectra were run in 95% ethanol, and nmr spectra were taken in $CDCl_3$. Microanalyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind.

(17) N. Neuner-Jehle, H. Nesvadba, and G. Spiteller, *Monatsh. Chem.*, **96**, 321 (1965).

(18) C. K. Atal, K. K. Kapur, C. C. J. Culvenor, and L. W. Smith, *Tetrahedron Lett.*, 537 (1966).

Extraction of *Cacalia floridana*.—In a typical extraction, 3.2 kg of dried, ground plant[19] were extracted in a Soxhlet-type apparatus with 95% ethanol until the supernatant no longer gave a positive test (Mayer's reagent) for alkaloids. The alcohol was removed *in vacuo* to provide a semisolid, viscous mass. This was extracted with weakly ammoniacal ethyl acetate at reflux for 1 hr. The cooled mixture was filtered and the solution was extracted with six 250-ml portions of 5% sulfuric acid. The aqueous portion was made alkaline (pH 10) with ammonia and extracted with chloroform. After being dried (Na_2SO_4) and concentrated *in vacuo*, the total nonquaternary bases (22.7 g) were obtained as a white foamy solid.

Isolation of the Alkaloids. A. Without Reduction.—The crude bases (20.7 g) were dissolved in 2 *N* H_2SO_4 and any nonalkaloidal material present was removed by chloroform extraction. The aqueous solution was basified with ammonia, and the water-soluble bases were thoroughly extracted with chloroform. Evaporation of the solvent yielded a colorless gum (11.8 g) which crystallized partially from benzene; this solid (4.8 g) was then washed with acetone. The white solid showed a single spot on thin layer chromatography over neutral alumina using benzene–chloroform–methanol (5:94:1) as the solvent; it was visualized with iodine vapor. Further crystallization of this solid from acetone yielded pure otosenine as colorless needles: mp 218–219°; $[\alpha]D$ +16.5° (*c* 1.12) (lit.[5] mp 221°; $[\alpha]D$ +20.8°).

Anal. Calcd for $C_{19}H_{27}O_7N$: C, 59.83; H, 7.14; N, 3.67; mol wt, 381. Found: C, 59.82; H, 7.23; N, 3.99; mol wt (by mass spectrometry), 381.

The infrared spectrum of this material was identical with that of an authentic specimen of otosenine.

The mother liquors from the crystallization of otosenine were evaporated to dryness, and the residue (7 g) in benzene solution was chromatographed over neutral grade III alumina. Elution of the column with benzene and benzene–chloroform (9:1) gave a gum which, on crystallization from cyclohexane–benzene, furnished colorless flakes (1.0 g) of florosenine: mp 100–103°; $[\alpha]D$ +31.9° (*c* 1.38).

Anal. Calcd for $C_{21}H_{29}O_8N \cdot C_6H_6$: C, 64.65; H, 7.03; N, 2.79; mol wt, 423. Found: C, 64.70; H, 7.35; N, 2.88; mol wt (by mass spectrometry), 423.

The compound showed a single spot on tlc and exhibited no characteristic uv absorption.

Elution of the column with benzene–chloroform (1:1) afforded a gum, which crystallized from benzene to give colorless prisms (1.8 g) of floricaline, mp 120–122°.

Anal. Calcd for $C_{23}H_{33}O_{10}N \cdot C_6H_6$: C, 62.02; H, 7.00; N, 2.49. Found: C, 62.12; H, 7.29; N, 2.66.

After extended drying, floricaline lost most of its benzene of crystallization and was obtained as a microcrystalline solid: mp 177–178°; $[\alpha]D$ +74.3° (*c* 1.1).

Anal. Calcd for $C_{23}H_{33}O_{10}N \cdot {}^1/_6C_6H_6$: C, 58.06; H, 6.85; N, 2.82; mol wt, 483. Found: C, 58.44; H, 7.01; N, 3.09; mol wt (by mass spectrometry), 483.

(19) The material used in this investigation was collected by Dr. R. K. Godfrey and Dr. S. McDaniel, Florida State University, Tallahassee, Fla. A voucher specimen is maintained at that institution under no. S. McDaniel 4776. We gratefully acknowledge this assistance in the collection and identification of the plant.

Further elution of the column with chloroform and crystallization of the residue from acetone furnished otosenine (250 mg), mp 220–221°.

Elution of the column with chloroform–methanol (19:1) afforded a brown gum which could not be crystallized. It was rechromatographed in chloroform solution over neutral Grade IV alumina, the column being eluted with the same solvent. Crystallization from chloroform furnished colorless prisms (175 mg) of floridanine: mp 195–196°; $[\alpha]D$ +66.5° (*c* 0.8).

Anal. Calcd for $C_{21}H_{31}O_9N \cdot {}^1/_3CHCl_3$: C, 51.16; H, 6.51; N, 2.91; mol wt, 441. Found: C, 51.09; H, 6.38; N, 2.83; mol wt (by mass spectrometry), 441.

B. After Reduction.—The crude bases (2 g) in 2 *N* H_2SO_4 (50 ml) were stirred with an excess of zinc dust for 5 hr. The solution was filtered and, after the nonalkaloidal material was removed by chloroform extraction, the aqueous layer was basified and then extracted with chloroform. Buffer extraction of the chloroform extract with McIlvaine buffer solutions of pH 7.6 and 6.6 yielded otosenine, mp 218°. Chromatography of the bases not extracted by pH 7.6 and 6.6 buffers (neutral alumina) yielded only florosenine, floricaline, and floridanine.

Acetylation of Otosenine to Florosenine.—Otosenine (300 mg) was heated with acetyl chloride (5 ml) under reflux for 10 min; at the end of this time, the solid had dissolved completely. After allowing the reaction mixture to stand at room temperature for 3 hr, it was evaporated to dryness *in vacuo*. The residue was taken up in ice-cold 0.5 *N* H_2SO_4, basified with ammonia, and extracted exhaustively with chloroform. Evaporation of the solvent left a gum, which crystallized from cyclohexane–benzene to yield colorless flakes (137 mg) of florosenine, mp and mmp 100–103° (also tlc and ir comparison).

Alkaline Hydrolysis of Florosenine to Otosenine.—Ten milliliters of 0.1 *N* aqueous KOH were added to a solution of florosenine (150 mg) in ethanol (10 ml). The mixture was allowed to stand at room temperature for 3 hr, and the alcohol was then distilled *in vacuo* on a steam bath.

The reaction mixture was diluted with water and repeatedly extracted with chloroform. Evaporation of the solvent left a residue which crystallized from benzene to give microcrystalline needles of otosenine (27 mg), mp and mmp 220–222° (also tlc and ir comparison).

Acetylation of Floridanine to Floricaline.—Floridanine (130 mg) was dissolved in a mixture of acetic anhydride (3 ml) and pyridine (1 ml) at room temperature. After 24 hr, the reaction mixture was evaporated to dryness. The residue crystallized from benzene to give colorless prisms; after drying, these melted at 177–178°. Mixture melting point, tlc, and ir comparison showed the product to be identical with floricaline.

Alkaline Hydrolysis of Floricaline to Floridanine.—A solution of floricaline (500 mg) in ethanol (10 ml) was diluted with 25 ml of 0.1 *N* aqueous KOH at room temperature. After 3 hr, the reaction mixture was extracted directly with chloroform and the solvent was removed, leaving a solid residue (180 mg). Crystallization from chloroform yielded colorless prisms, mp 195–196°, identical with floridanine (mmp, tlc, and ir comparison).

Registry No.—**1**, 16958-29-5; **4**, 16958-30-8; **5**, 16957-31-9; **7**, 16958-32-0.