[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Senecio Alkaloids: The Alkaloids of *Senecio Brasiliensis*, *Fremonti* and *Ambrosioides*

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The total alkaloids of *Senecio brasiliensis, fremonti* and *ambrosioides* have been subjected to partition chromatography and the components separated. The first proved to be a mixture of senecionine, seneciphylline and jacobine; the second, senecionine and seneciphylline; the third, senecionine, seneciphylline and retrorsine.

Owing to the difficulty of separation of the pyrrolizidine alkaloids from one another and to the rather widespread though erroneous assumption that these alkaloids do not give exact analytical values on combustion, the reported list of the pyrrolizidine alkaloids is excessively long. In recent years, the use of more refined methods has permitted the separation and identification of individual alkaloids from total plant alkaloids previously reported as pure entities. Thus, carthamoidine, douglasine, eremophiline,[1] hieracifoline[2,3] and pterophine[4,5] have been shown to be mixtures of two or more of the following alkaloids: senecionine, seneciphylline, retrorsine and riddelliine. The alkaloids from *Senecio ampullaceus*, *parksii* and *vulgaris* are also mixtures of two or more of these same alkaloids.[1] In addition, Manske's "jacobine" has been found[3,6] to be composed of senecionine, seneciphylline and a third alkaloid, identical with Bradbury and Culvenor's jacobine[7]; aureine[8] is identical[9] with senecionine, while jacobine is seneciphylline.[7,10]

This Communication is concerned with the composition of the alkaloidal material from *Senecio brasiliensis, fremonti* and *ambrosioides*.

The Alkaloids of *Senecio brasiliensis*.—Novelli and de Valera[11] reported the isolation from *Senecio brasiliensis* of a new alkaloid, m.p. 232–234° dec., $[\alpha]^{20}\text{D}$ $-66.8°$ ($CHCl_3$) to which they assigned the formula $C_{18}H_{25}NO_5$ on the basis of satisfactory analytical data for the alkaloid itself and for its derivatives: methiodide, m.p. 243° dec.; picrate, m.p. 189.5°, and aurichloride, m.p. 182°. The alkaloid yielded on hydrolysis retronecine and a dextrorotatory acid $C_{10}H_{16}O_5$, m.p. 141–142°, for which, however, the value of the specific rotation was not reported.

Senecio brasiliensis was later investigated by Fonseca[12] who reported the isolation from the plant of a new alkaloid, designated as brasilinecine,[13] that was presumed to be different from Novelli's alkaloid. Fonseca described derivatives as follows: methiodide, m.p. 235–237° dec., and picrate, m.p. 191–192°. The material on hydrolysis gave retronecine and an acid, m.p. 141–143°, for which the analysis and rotation were not reported.

Dr. Novelli kindly provided the authors with three samples of his material corresponding to various stages of purification of his total alkaloid by fractional extraction with solvents. The physical properties of these samples as determined in this Laboratory are reported in Table I, together with those of senecionine, seneciphylline and jacobine.

The physical properties of sample C indicated its identity with senecionine; this was confirmed by comparison of their infrared spectra and by a determination of the melting point of a mixture of the two. The infrared spectra of samples A and B, even though very similar to that of sample C, contained some additional bands at 902 cm.$^{-1}$ (strong) and 992 cm.$^{-1}$ (weak) that are found in the spectrum of seneciphylline. A third additional band (shoulder) at 1094 cm.$^{-1}$ was present in the spectrum of sample A and is found also in the spectrum of jacobine.

Sample A which was the total alkaloid from *Senecio brasiliensis* was then subjected to partition chromatography; only a few fractions of pure senecionine and seneciphylline were obtained, due to the relatively high load used for the column, but jacobine was separated completely from the other two alkaloids to the extent of about 3% of the total material. With the approximate percentage of jacobine known and the values for the optical rotations of pure senecionine, seneciphylline, jacobine and Novelli and de Valera's total alkaloid from *Senecio brasiliensis* also known, the approximate composition of the total alkaloid was calculated as senecionine (74%), seneciphylline (23%) and jacobine (3%). The dextrorotatory acid, $C_{10}H_{16}O_5$, m.p. 141–142°, obtained by Novelli and de Valera was undoubtedly somewhat impure senecic acid.[14]

Since the alkaloidal content of plants yielding pyrrolizidine alkaloids has often been reported as varying in the quantity and ratio of the various alkaloids, it seems very likely that Fonseca's alkaloid consisted of a mixture of senecionine, seneciphylline and jacobine. Unfortunately, a sample of Fonseca's product was not available for comparison.

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(1) R. Adams and T. R. Govindachari, THIS JOURNAL, **71**, 1956 (1949).

(2) R. H. F. Manske, *Can. J. Research*, **17B**, 8 (1939).

(3) R. Adams and M. Gianturco, THIS JOURNAL, **78**, 398 (1956).

(4) H. L. deWaal, *Onderstepoort J. Vet. Sci. Animal Ind.*, **16**, 149 (1941).

(5) C. C. J. Culvenor and L. W. Smith, *Chemistry & Industry*, 1386 (1954).

(6) R. H. F. Manske, *Can. J. Research*, **15**, 651 (1931).

(7) R. B. Bradbury and C. C. J. Culvenor, *Chemistry & Industry*, 1021 (1954).

(8) R. H. F. Manske, *Can. J. Research*, **14B**, 6 (1936).

(9) N. J. Leonard, The Senecio Alkaloids in "The Alkaloids," Vol. I, Academic Press, Inc., New York, N. Y., 1949, p. 107.

(10) G. Barger and J. J. Blackie, *J. Chem. Soc.*, 584 (1937).

(11) A. Novelli and A. P. G. de Valera, *An. Assoc. Quim. Argentina*, **33**, 176 (1945).

(12) E. de Camargo Fonseca, *Anais faculd. farm. odontol. Univ. Sao Paulo*, **9**, 85 (1951).

(13) This is an unfortunate name since the suffix necine has always been used to designate the bases obtained by hydrolysis of the pyrrolizidine alkaloids.

(14) Pure senecic acid has m.p. 146° and $[\alpha]\text{D}$ $+10.95°$ (ethanol); see ref. 15.

TABLE I

PHYSICAL PROPERTIES OF *Senecio brasiliensis* ALKALOID FRACTIONS

Compound	M.p., °C.	$[\alpha]_D$	*Rf* (BuOH–AcOH)	Found C	H	N	M.p., °C. Methiodide	Aurichloride	Picrate
Sample A	232–236	−74.8	0.44, 0.58, 0.62	64.37	7.33	4.10			
Sample B	239–242	−62.0	0.58, .62	64.82	7.52	4.07			
Sample C	243–244	−57.0	.62	64.55	7.21	3.99			
				Calculated					
Senecionine	245	−56.0	0.62	64.46	7.51	4.18	243–245[15]	186	190–191
Seneciphylline	217	−139.0	.58	64.85	6.95	4.20	231–232[16]	162–163	182–183
Jacobine	225	−38.0	.44	61.52	7.17	3.98			

The Alkaloids of *Senecio fremonti*.—*Senecio fremonti* Torr. and Gray yielded a crude, slightly colored, material, m.p. 214–217°, $[\alpha]^{27}\mathrm{D}$ −92.7° (ethanol). It gave a poor analysis for $C_{18}H_{23}NO_5$; a paper chromatogram indicated it to be a mixture (*R*f 0.58, 0.62) and the infrared spectrum showed the probable components to be senecionine and seneciphylline. This was confirmed when the two alkaloids were obtained in the pure state by partition chromatography. The ratio of senecionine to seneciphylline was found to be about 1:1.

The Alkaloids of *Senecio ambrosioides*.—The crude alkaloidal material extracted from *Senecio ambrosioides*, m.p. 212–220°, $[\alpha]^{27}\mathrm{D}$ −71.6° (ethanol), analyzed for $C_{18}H_{25}NO_5$; a paper chromatogram indicated the presence of a mixture composed of two alkaloids, *R*f 0.58, 0.62, accompanied by a small amount of a third one, *R*f 0.44. The infrared spectrum indicated that senecionine and seneciphylline were probably the main components of the mixture. Retrorsine was also present as indicated by a weak band (shoulder) at 1055 cm.$^{-1}$, which has been used for determining the presence of this alkaloid in mixtures containing also senecionine, seneciphylline and riddelliine. The composition of the crude alkaloidal material as senecionine, seneciphylline and retrorsine was confirmed by partition chromatography. From the values of the optical rotations of senecionine, seneciphylline, retrorsine and of the total alkaloid from *Senecio ambrosioides*, and the approximate percentage of retrorsine determined, the approximate composition of the total alkaloid was estimated to be senecionine (72%), seneciphylline (20%) and retrorsine (8%).

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Experimental[17]

Paper Chromatography.—The method and the solvent system previously successfully adopted[3] were used throughout the present investigation; however, in order to detect the minor alkaloids, like jacobine in Novelli and de Valera's total alkaloid from *Senecio brasiliensis* or retrorsine in the total alkaloid from *Senecio ambrosioides*, unusually high amounts of alkaloid (150–250 γ) were brought on the paper strip. Under these conditions, the senecionine and seneciphylline were not separated.

Partition Chromatography of Sample A of Novelli and de Valera's Extract from *Senecio brasiliensis*.—A portion of 90 g. of Celite 545 was ground in a mortar with 50% of its weight of a molar solution of $NaH_2PO_4 \cdot H_2O$ and then enough solvent, 3:1 carbon tetrachloride–chloroform saturated with molar phosphate solution, was added to give a freely moving slurry. The material was packed into a glass column (2.2 × 54 cm.) using a close fitting perforated plunger. A solution of 0.70 g. of sample A in 40 ml. of chloroform was poured onto 3 g. of Pyrex glass powder and the solvent was eliminated at reduced pressure. The glass powder was then packed on top of the chromatographic column. Elution was begun with the same solvent mixture of carbon tetrachloride and chloroform (3:1). The first thirty 5-ml. fractions contained no dissolved material. Fractions 31–34 contained pure senecionine (130 mg.) which, after one crystallization from benzene, had the following constants: m.p. 243–245°; rotation, 0.030 g. made up to 2.0 ml. in chloroform at 25° gave $\alpha\mathrm{D}$ −0.85°, *l* 1; $[\alpha]^{25}\mathrm{D}$ −56.7°. *Anal.* Found: C, 64.70; H, 7.61. Fractions 44–89 (480 mg.) contained mixtures of senecionine and seneciphylline; the latter fractions were richer in seneciphylline as judged by the determination of *R*f values, infrared spectra and optical rotations. Fractions 90–94 yielded pure seneciphylline (30 mg.). They were crystallized from benzene; m.p. 216–217°; rotation, 0.0165 g. made up to 1.5 ml. in chloroform at 25° gave $\alpha\mathrm{D}$ −1.52°, *l* 1; $[\alpha]^{25}\mathrm{D}$ −138°. Fractions 95–97 contained no dissolved material. The elution was then continued with pure chloroform, and pure jacobine (20 mg.) was obtained from fractions 99–104; m.p. 223–225°; rotation, 0.0150 g. made up to 1.5 ml. in chloroform at 25° gave $\alpha\mathrm{D}$ −0.38°, *l* 1; $[\alpha]^{25}\mathrm{D}$ −38.0°.

Isolation of Total Alkaloids of *Senecio fremonti* **Torr. and Gray.**—The alkaloids were obtained by ethanolic extraction of the whole plant of *Senecio fremonti* Torr. and Gray and isolated in the usual manner.[18] The crude, slightly colored, crystalline alkaloid had the following constants: m.p. 214–217°; rotation, 0.0180 g. made up to 1.6 ml. in chloroform at 27° gave $\alpha\mathrm{D}$ −1.04°, *l* 1; $[\alpha]^{27}\mathrm{D}$ −92.7°; *R*f 0.58, 0.62. *Anal.* Found: C, 65.06; H, 7.51; N, 4.20.

Partition Chromatography of Crude Extract from *Senecio fremonti*.—A chromatographic column similar to that just described was assembled from 50 g. of Celite 545. On top of the column by the usual procedure was placed 100 mg. of crude extract. Elution was performed with mixtures of carbon tetrachloride and chloroform as follows: 4:1 for fractions 1–26; 2:1 for fractions 26–45; chloroform alone was used for fractions 46–60. The results are indicated in Table II.

TABLE II

PARTITION CHROMATOGRAPHY OF *Senecio fremonti* EXTRACT

Fractions	*Rf* value	Residue, mg.	M.p., °C.
1–20	..	None	
21–28	0.62	42	244–245
29–31	..	None	
32–39	0.58	40	216–217
40–60		None	

Fractions 21–28 were combined and crystallized from benzene. The infrared spectrum of the product was identical with that of pure senecionine. Fractions 32–39 were combined and crystallized from benzene. The material thus obtained was pure seneciphylline.

Isolation of Total Alkaloids of *Senecio ambrosioides*.—The alkaloids were obtained by ethanolic extraction of the whole plant of *Senecio ambrosioides* and isolated in the usual manner.[18] The crude, crystalline material had the follow-

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[15] R. Adams and T. R. Govindachari, THIS JOURNAL, **71**, 1953 (1949).

[16] A. Orekhov and V. Tiedebel, *Ber.*, **68**, 650 (1935).

[17] All the melting points are corrected.

[18] R. Adams and E. F. Rogers, THIS JOURNAL, **61**, 2815 (1939).

TABLE III

PARTITION CHROMATOGRAPHY OF *Senecio ambrosioides* EXTRACT

Fractions	R_f value	Residue, mg.	M.p., °C.
1–32		None	
33–37	0.62	65	243–245
38	.58, 0.62	15	
39–43	.58	10	215–217
44–47		None	
48–54	.44	8	207–208

ing constants; m.p. 212–220°; rotation, 0.0296 g. made up to 2.2 ml. in chloroform at 27° gave α_D −0.96°, *l* 1; $[\alpha]^{27}_D$ −71.6°; R_f 0.44, 0.58, 0.62. *Anal.* Found: C, 64.37; H, 7.74; N, 4.13.

Partition Chromatography of Crude Extract from *Senecio ambrosioides*.—A chromatographic column using 60 g. of Celite 545 and 100 mg. of crude extract prepared in the usual way was placed on top of the column. Elution was performed with mixtures of carbon tetrachloride and chloroform as follows: 4:1 for fractions 1–30; 3:2 for fractions 32–38; 2:3 for fractions 39–45; pure chloroform for fractions 46–60. The results are indicated in Table III.

The product from fractions 33–37 was identified as senecionine. Fractions 39–43 contained seneciphylline and fractions 48–54 retrorsine. These were all recognized by determination of melting points and comparison of the infrared spectra with those of authentic samples.

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[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Bitter Principles of Plants. I. Columbin: Preliminary Structural Studies[1]

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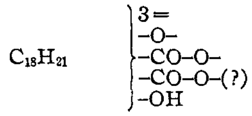
The major bitter principle of columbo root, columbin, and a number of its transformation products have been investigated. On the basis of spectral and hydrogenation studies a number of conclusions have been reached concerning the nature of the functional systems in the columbin molecule and their interrelations.

Among the chemical compounds present in the root of the columbo tree, *Jateorrhiza palmata*, is the nitrogen-free bitter principle columbin (I). Although first isolated by Wittstock in 1830,[2] it was only in 1936 that a pure sample was reported by Wessely,[4c] who determined its molecular formula to be $C_{20}H_{22}O_6$. A series of papers by Feist[3] and by Wessely[4] contain the major previous contributions to the study of the columbin molecule.

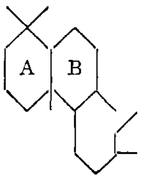
The most important results of the earlier work may be summarized briefly as follows. Columbin (I), $C_{20}H_{22}O_6$, is isomerized easily by base to isocolumbin (II), $C_{20}H_{22}O_6$. Both columbin and isocolumbin are acetylated by vigorous treatment with sodium acetate in acetic anhydride to the same monoacetyl derivative, acetylisocolumbin (III), $C_{22}H_{24}O_7$. A methylation product, methylisocolumbin (IV), $C_{21}H_{24}O_6$, is produced[5] by methyl sulfate and alkali treatment of columbin or isocolumbin. Although compounds I–IV are all *neutral* substances, they possess the remarkable property of losing carbon dioxide upon melting to give, respectively, decarboxycolumbin (V), $C_{19}H_{22}O_4$, decarboxyisocolumbin (VI), $C_{19}H_{22}O_4$, decarboxyacetylisocolumbin (VII), $C_{21}H_{24}O_5$, and decarboxymethylisocolumbin (VIII), $C_{20}H_{24}O_4$. Columbin and decarboxycolumbin, as well as their iso derivatives, absorb four moles of hydrogen on catalytic reduction to give saturated monocarboxylic acids, *e.g.*, columbin gives octahydrocolumbic acid (IX), $C_{20}H_{30}O_6$. Equivalent weight titrations indicated that the carboxyl group of the octahydro acids arose from hydrogenolysis of a lactone ring.[4a] A second difficultly opened lactone ring was at first suspected in the undecarboxylated compounds, but this hypothesis was later rejected.[4c] In addition, the sixth oxygen atom of columbin was assumed to be present as part of a stable ether ring. These results may be summarized in the partial structure for columbin (Ia)

(Ia)



$$C_{18}H_{21}\left\{\begin{array}{l} 3= \\ -O- \\ -CO-O- \\ -CO-O-(?) \\ -OH \end{array}\right.$$

Zinc dust distillation of columbin gave 1,2,5-trimethylnaphthalene, strongly suggesting that columbin is a member of the class of diterpenes possessing the sclareol type skeleton X



X

Our examination of columbin began with a study of its infrared spectrum. The difficultly acetylatable hydroxyl appeared at 2.86 μ; in addition, two carbonyls (5.73 and 5.80 μ) were observed. As the subsequent arguments will show, both carbonyls represent lactone rings, which we shall designate as lactones L-1 and L-2, respectively.

When columbin is completely reduced to octahydrocolumbic acid (XI), lactone L-1 (5.73 μ) is unchanged. It must represent, both before and after reduction, an unconjugated δ-lactone.[6] The possibility of attributing this carbonyl to a cyclopentanone structure is discounted by the absence of a weak saturated ketone band in the ultraviolet in

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[1] From the Ph.D. Dissertation of E. J. Soboczenski, The Ohio State University, 1956.

[2] Wittstock, *Poggendorfs Ann.*, **19**, 298 (1830).

[3] K. Feist, *et al.*, (a) *Ann.*, **517**, 119 (1935); (b) **519**, 124 (1935); (c) **521**, 184 (1935); (d) **522**, 185 (1936); (e) **523**, 289 (1936); (f) **534**, 41 (1938).

[4] F. Wessely, *et al.*, (a) *Monatsh.*, **66**, 87 (1935); (b) *Ann.*, **522**, 41 (1936); (c) *Monatsh.*, **68**, 313 (1936); (d) **70**, 30 (1937).

[5] The yield of methylisocolumbin is low, water-soluble salts and unreacted isocolumbin being the major reaction products.

[6] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.