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

Senecio Alkaloids: The Isolation of Senecionine from *Senecio Cineraria* and Some Observations on the Structure of Senecionine

BY ROGER ADAMS AND T. R. GOVINDACHARI

Senecio cineraria DC (synonyms[1]: *Cineraria maratima* Linn.; *Senecio acanthifolius* Hort.) commonly known as Dusty Miller is a herbaceous perennial, flourishing in all seasons in favorable climates. Manske[2] found that *Senecio cineraria* contained a recognizable amount of alkaloid but did not characterize the product. Barger and Blackie[3] reported jacobine, $C_{18}H_{25}O_6N$, to be the principal alkaloid of *Senecio cineraria*, associated with another alkaloid with a lower specific rotation.

Seeds of *Senecio cineraria* obtained from Holland were extracted in this Laboratory, yielding approximately 0.1% of a crude alkaloidal fraction. The material was easily purified and the products from the third and fourth recrystallizations were identical in melting point and specific rotation. The analysis of the pure alkaloid corresponded closely to the empirical formula $C_{18}H_{25}O_5N$. It was evident that the alkaloid could not be jacobine, a conclusion confirmed by comparison of its infrared spectrum with that of an authentic specimen of jacobine. The result was somewhat surprising, in view of Barger and Blackie's[3] findings, but there are several instances among *Senecio* species in which the alkaloidal constituents and content vary[2,3,4,5] with the stage of growth, season of collection and location.

The identity of our alkaloid with senecionine[2,3,5,6,7] was established by the melting point determination of a mixture with an authentic specimen and by the identity of the infrared spectra. The alkaloid senecionine has been isolated from several species of *Senecio*. It has been reported to yield on hydrolysis[5,6,7] retronecine and a lactonic monocarboxylic acid, $C_{10}H_{14}O_4$.[8] Senecionine was therefore assumed to be an ester of senecic acid lactone with one of the two hydroxyls in retronecine. A Zerewitinoff determination of the alkaloid indicated one active hydrogen which was ascribed by Barger and Blackie[5] to the unesterified hydroxyl of the retronecine part of the molecule.

Evidence is now presented to prove definitely that senecionine is a cyclic diester formed from one molecule of a dibasic acid, senecic acid, with one molecule of retronecine, both the hydroxyl groups of the latter being involved in ester formation. On hydrolysis with baryta, followed by removal of barium as carbonate, acidification and continuous extraction with ether, senecionine yielded a dibasic acid. On evaporating to dryness an aqueous solution of this acid with a few drops of hydrochloric acid, senecic acid lactone was obtained,[4] which has been reported by earlier investigators to be the necic acid from senecionine. It is of interest in this connection that Richardson and Warren[4] obtained senecic acid by the hydrolysis of rosmarinine, while deWaal[6] had reported senecic acid lactone as the product of hydrolysis of the same alkaloid. These differences are certainly due to slight changes in experimental procedure in the isolation of the easily lactonizable senecic acid.

Senecic acid absorbed one molecule of hydrogen in the presence of platinum oxide catalyst. Dihydrosenecic acid was a sirupy liquid, which on evaporating to dryness in aqueous solution with a few drops of hydrochloric acid yielded dihydrosenecic acid lactone, identical with the product obtained by direct reduction of senecic acid lactone. Senecic acid is therefore an unsaturated hydroxy dibasic acid, with the hydroxyl group present presumably in the γ-position with respect to one of the carboxyls.

Although this experimental evidence would permit senecionine to be a mono ester of senecic acid lactone with retronecine, on the assumption that the lactone ring was opened up by the alkaline hydrolytic reagent, hydrogenation experiments of the alkaloid confirm the formulation of senecionine as a cyclic diester. Senecionine absorbed two mole equivalents of hydrogen in the presence of Raney nickel as catalyst, yielding a single product in quantitative yield. This tetrahydrosenecionine is a crystalline compound possessing the properties of an amino acid and yielded on hydrolysis retronecanol and senecic acid. Thus the two mole equivalents of hydrogen have been utilized in cleaving one ester linkage in the alkaloid and saturating the retronecine double bond, the acid portion of the molecule being unaffected. Tetrahydrosenecionine was easily converted to a crystalline methyl ester with diazomethane. While tetrahydrosenecionine showed a strong absorption at 1600 cm.$^{-1}$, characteristic of a zwitterion, this absorption was absent in the methyl ester.

When senecionine was hydrogenated in the presence of platinum oxide catalyst, three mole equivalents of hydrogen were taken up and a single product was obtained in quantitative yield. The absorption of the third equivalent of hydro-

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(1) Bailey, "Manual of Cultivated Plants," Macmillan, 1924, p. 784; Bailey, "The Standard Cyclopaedia of Horticulture," The Macmillan Co., New York, N. Y., 1947, Vol. III, p. 3152.

(2) Manske, *Can. J. Res.*, **14B**, 6 (1936).

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

(4) Richardson and Warren, *ibid.*, 452 (1943).

(5) Barger and Blackie, *ibid.*, 743 (1936).

(6) deWaal, *Onderstepoort J. Vet. Sci. Animal Ind.*, **16**, 149 (1941).

(7) Manske, *Can. J. Res.*, **17**, 1 (1939).

(8) There has been some confusion in naming this acid, but it will be referred to as senecic acid lactone in this paper.

Chart I

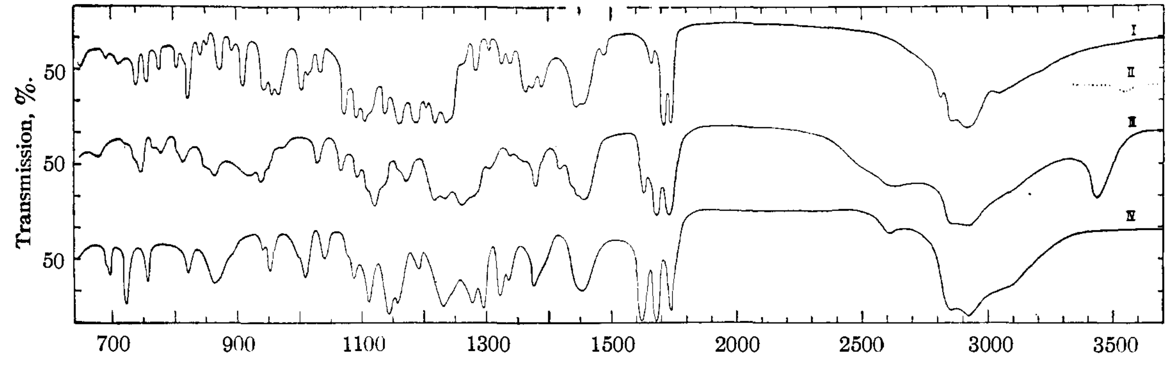
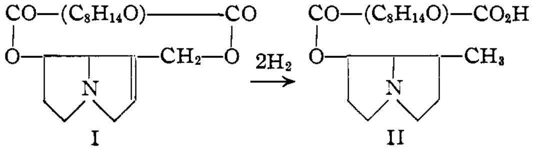


Fig. 1.—Curve I, senecionine in Nujol suspension; II, part of the spectrum of senecionine in carbon tetrachloride solution, showing hydroxyl absorption at 3552 cm.$^{-1}$; III, senecic acid in Nujol suspension; IV, senecic acid lactone in Nujol suspension.

gen was extremely slow, indicating that the double bond in the acid portion of the alkaloid is probably hindered. Attempts to purify the crude hexahydrosenecionine or its methyl ester were unsuccessful. It showed however the properties of an amino acid and there was a characteristic zwitterion absorption at 1601 cm.$^{-1}$. On hydrolysis, it yielded retronecanol and dihydrosenecic acid. The third mole of hydrogen must therefore have been taken up in the acid part of the molecule.

With the structure of retronecine and retronecanol established[9] the general structural formula for senecionine may be indicated as I and of tetrahydrosenecionine as II. The active hydrogen



found in senecionine by Barger and Blackie[5] may be accounted for by the hydroxyl in the acid moiety of the molecule.

An interesting feature of the infrared spectrum of senecionine is that the fundamental hydroxyl frequency is absent when the determination is carried out in Nujol suspension; a characteristic hydroxyl absorption at 3552 cm.$^{-1}$ appears when the determination is made in carbon tetrachloride solution. These differences must be due to strong inter-molecular bonding which is broken up in solution. The infrared spectra of senecionine in Nujol suspension and carbon tetrachloride solution and of senecic acid and senecic acid lactone are shown in Chart I.

The authors are very grateful to Dr. R. H. F. Manske for supply of authentic specimens of jacobine and senecionine and to Mrs. J. L. Johnson for determination and interpretation of infrared spectra.

Experimental

Extraction of Senecionine from *Senecio Cineraria* DC.—Extraction of 43 lb. of the ground seeds of *Senecio cineraria* with 95% ethanol was continued during forty-eight hours. The alkaloid was isolated by the same procedure as that previously described for riddelliine.[10] The yield of senecionine after one recrystallization from absolute ethanol was 19 g. (0.1%). The material darkened from 210° and melted with decomposition at 225° (cor.). After the third crystallization a constant melting point of 236° (with decomposition) was reached as well as a constant rotation.

Rotation: 0.0341 g. made up to 1 ml. in chloroform at 25° gave α −1.88°; l, 1; $[\alpha]^{25}\text{D}$ −55.1°.

Anal. Calcd. for $C_{18}H_{25}O_5N$: C, 64.48; H, 7.52; N, 4.17. Found: C, 64.72; H, 7.52; N, 4.44.

Barger and Blackie[5] reported m. p. 232°, $[\alpha]\text{D}$ −54.6 and −55.4°; Manske,[7] m. p. 237°, $[\alpha]^{28}\text{D}$ −51.1°; Manske,[2] m. p. 238°; deWaal,[6] m. p. 232°; Konawalowa and Orekhov,[11] m. p. 232–233°, $[\alpha]\text{D}$ −56.34°.

Senecionine Methiodide.—This was prepared by addition of excess methyl iodide to a chloroform solution of the alkaloid. After removal of chloroform, the product was recrystallized from absolute ethanol, with the addition of a few drops of water. Colorless crystals resulted, m. p. 243–245° (cor.). Barger and Blackie[5] reported m. p. 249°.

Anal. Calcd. for $C_{19}H_{28}O_5NI$: C, 47.80; H, 5.91; N, 2.94. Found: C, 47.91; H, 6.27; N, 3.07.

Senecionine Picrate.—This was prepared from an aqueous acid solution of the alkaloid and was insoluble in water. After two recrystallizations from absolute ethanol, the picrate melted at 190–191° (cor.). Barger and Blackie[5] reported m. p. 191°.

Anal. Calcd. for $C_{18}H_{25}O_5N{\cdot}C_6H_3O_7N_3$: C, 51.06; H, 4.99; N, 9.92. Found: C, 51.13; H, 5.04; N, 10.21.

Senecic Acid.—A mixture of 1 g. of senecionine, 2 g. of barium hydroxide octahydrate and 14 ml. of water was refluxed for one hour. The solution was then saturated with carbon dioxide and the barium carbonate removed by filtration. The filtrate was made slightly acid to congo red with dilute hydrochloric acid and continuously extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and on evaporation yielded 0.64 g. of the crude crystalline acid (99%). By repeated crystallization from ethyl acetate with addition of petroleum ether (b. p. 40–60°) the melting point was raised to a constant value of 146° (cor.). By titration it was shown to be dibasic.

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(9) Adams and Leonard, THIS JOURNAL, **66**, 257 (1944).

(10) Adams, Hamlin, Jelinek and Phillips, *ibid.*, **64**, 2760 (1942).

(11) Konawalowa and Orekhov, *Bull. soc. chim. France*, [5] **4**, 1285 (1937).

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 55.54; H, 7.46; neut. equiv., 108. Found: C, 55.87; H, 7.37; neut. equiv., 109.9.

Rotation: 0.0321 g. made up to 1 ml. in absolute ethanol at 25° gave $\alpha + 0.35°$; l, 1; $[\alpha]^{25}_D + 10.95°$.

Richardson and Warren[4] reported m. p. 151°; $[\alpha]_D +$ 11.8° in ethanol.

From the aqueous solution left after ether extraction retronecine hydrochloride was isolated in the usual way. The yield was 0.48 g. (84%), m. p. 160–161° (cor.).

When senecionine was hydrolyzed by addition of powdered potassium hydroxide to an ethanolic solution or by a *N* ethanolic solution of potassium hydroxide, the acid isolated by the procedure described above, was a gelatinous solid which could not be crystallized. This could however be lactonized by evaporating to dryness with a few drops of aqueous hydrochloric acid to senecic acid lactone, identical in melting point and specific rotation with senecic acid lactone to be described in a subsequent section. A melting point of the mixture showed no depression.

Hydrolysis of 200 mg. of an authentic sample of senecionine (from *Senecio integerrimus*) with barium hydroxide as previously described resulted in a yield of 102 mg. of acid. The acid solidified readily, but with the small quantity available repeated crystallization to raise the melting point to 146° was not possible. A product melting at 141° was obtained, which had the same solubility characteristics and infrared spectrum as the product from the alkaloid of *Senecio cineraria*. The acid was lactonized by the usual procedure yielding senecic acid lactone, m. p. 154°. On mixing with a specimen of senecic acid lactone obtained by us (m. p. 156°), the mixture melted at 154°.

Senecic Acid Dimethyl Ester.—A solution of 200 mg. of senecic acid (not recrystallized) in 10 ml. of absolute ether was treated with an excess of an ethereal solution of diazomethane. After standing for twelve hours, the ether was removed and the product purified by two distillations; n^{20}_D 1.4710. The yield was 180 mg. (83%).

Anal. Calcd. for $C_{12}H_{20}O_6$: C, 58.99; H, 8.25. Found: C, 58.71; H, 8.23.

Dihydrosenecic Acid.—A solution of 0.25 g. of pure senecic acid (m. p. 146°) in 10 ml. of absolute ethanol was reduced in the presence of 50 mg. of platinum oxide catalyst. Exactly one mole equivalent of hydrogen was absorbed during the course of two hours. The catalyst was filtered off and the solvent removed *in vacuo*. The residue was a heavy transparent viscous oil, which could not be induced to solidify. The yield was 0.26 g.

Esterification of 0.2 g. of this product with diazomethane resulted in the dimethyl ester, purified by distillation at 0.1 mm.; n^{20}_D 1.4533.

Anal. Calcd. for $C_{12}H_{22}O_6$: C, 58.55; H, 9.01. Found: C, 58.76; H, 9.12.

Senecic Acid Lactone.—To a solution of 200 mg. of senecic acid in 3 ml. of water, a few drops of dilute hydrochloric acid were added and the solution evaporated to dryness on a steam-bath. The operation was repeated once more. The sticky residue was taken up in boiling ethyl acetate, filtered to remove insoluble material, and the clear filtrate treated with petroleum ether (b. p. 40–60°) to incipient turbidity. The crystals that separated were filtered and washed with a mixture of ethyl acetate and petroleum ether (1:1). The yield was 0.1 g. After two recrystallizations from benzene, the product melted at 156° (cor.). Direct titration indicated monobasicity. By adding excess alkali, refluxing for fifteen minutes and back titrating, two carboxyls were indicated (Calcd.: 99. Found: 96.7).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12; neut. equiv., 198. Found: C, 60.59; H, 7.33; neut. equiv., 197.6.

Rotation: 0.0148 g. made up to 1 ml. in absolute ethanol at 25° gave $\alpha +0.54°$; l, 1; $[\alpha]^{25}_D +36.5°$.

Barger and Blackie[5] reported 153°; $[\alpha]_D +41.8°$; Orekhov and Tiedebel,[12] m. p. 154–155°, $[\alpha]_D +37.9°$; Manske,[7] m. p. 154°, $[\alpha]_D +38.9°$; de Waal,[8] m. p. 156°; deWaal,[13] m. p. 154–155°; $[\alpha]_D +45°$; Richardson and Warren,[4] m. p. 156°.

Dihydrosenecic Acid Lactone.—A solution of 0.2 g. of senecic acid lactone in 15 ml. of absolute ethanol was reduced in the presence of 50 mg. of platinum oxide catalyst. One mole of hydrogen was taken up during two hours. The yield of the crude product was 0.19 g. This could not be directly crystallized. The material was distilled at 0.3 mm. pressure and the waxy crystalline distillate was recrystallized from absolute ether with addition of petroleum ether (b. p. 40–60°). The pure product melted at 87° (cor.).

A solution of 20 mg. of the product (m. p. 87°) in 0.5 ml. of absolute ether was diluted to 12 ml. with petroleum ether (b. p. 40–60°). The solution remained clear, but on scratching colorless feathery crystals separated which melted at 118–120° (cor.). This is presumably an isomorph of the product, m. p. 87°. Unless the conditions described were rigidly observed it was difficult to obtain this higher melting form of dihydrosenecic acid lactone. The infrared spectra of the two forms were similar but had distinct differences when the determination was conducted in Nujol suspension. The spectra in carbon tetrachloride solution were identical.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.99; H, 8.06. Product, m. p. 87°. Found: C, 59.95; H, 7.95. Product, m. p. 118–120°. Found: C, 59.95; H, 8.25.

Barger and Blackie[5] reported m. p. 106°; deWaal,[8] m. p. 120°.

Dihydrosenecic Acid Lactone by Lactonization of Dihydrosenecic Acid.—An aqueous solution of 0.12 g. of dihydrosenecic acid was evaporated to dryness after addition of a few drops of hydrochloric acid. The operation was repeated thrice. The gummy residue of lactone was transferred to a small subliming apparatus and distilled at 0.1 mm. pressure. The distillate was a sticky semisolid. It was repeatedly extracted with boiling petroleum ether (b. p. 80–100°). On concentrating the ligroin solution to a small volume and scratching, crystals separated. Another recrystallization from ether-petroleum ether mixture gave crystals, m. p. 87° (cor.), identical in every respect with the dihydrosenecic acid lactone obtained by the direct reduction of senecic acid lactone. The yield was 30 mg. By employing the same procedure as described earlier, the higher melting form (m. p. 118–120°) was also obtained.

Hydrogenolysis of Senecionine (Raney Nickel Catalyst); Tetrahydrosenecionine.—A solution of 0.25 g. of senecionine in 15 ml. of absolute ethanol was hydrogenated at slightly over atmospheric pressure in the presence of approximately a third of a small spoonful of Raney nickel. Two moles of hydrogen were absorbed during four hours, after which no more hydrogen was taken up. The catalyst was removed by filtration and on removal of the solvent *in vacuo*, a yellowish crystalline solid remained. The yield was 0.23 g. (92%). The product was recrystallized twice from absolute ethanol to constant m. p. 196–197° (cor.). It formed colorless crystals sparingly soluble even in hot ethanol and insoluble in other common organic solvents.

Anal. Calcd. for $C_{18}H_{29}O_5N$: C, 63.70; H, 8.61; N, 4.13. Found: C, 63.93; H, 8.68; N, 4.32.

Tetrahydrosenecionine Methyl Ester.—A solution of 0.05 g. of tetrahydrosenecionine in 1 ml. of methanol was treated with 20 ml. of an ethereal solution of diazomethane (from 0.2 g. of nitrosomethyl urea). The clear solution was left for twenty-four hours at room temperature and the ether then removed in an air draft. The oily material was extracted with four 10-ml. portions of boiling benzene. The benzene extract was concentrated to a small volume, but the product did not crystallize. The benzene was completely removed yielding 45 mg. of a solid residue. This was insoluble in cold water, but easily soluble in all

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(12) Orekhov and Tiedebel, *Ber.*, **68**, 1886 (1935).

(13) deWaal and Tiedt, *Onderstepoort J. Vet. Sci. Animal Ind.*, **15**, 251 (1940).

organic solvents. It was recrystallized from water containing a few drops of methanol. The crystallization was very slow and had to be induced by scratching. After another recrystallization from the same solvent, the product melted at 113° (cor.).

Anal. Calcd. for $C_{19}H_{31}O_5N$: C, 64.57; H, 8.84. Found: C, 64.39; H, 8.79.

Hydrolysis of Tetrahydrosenecionine.—A solution of 0.13 g. of tetrahydrosenecionine in 2 ml. of water was hydrolyzed by refluxing with 0.25 mg. of barium hydroxide octahydrate for one hour. The acid and basic portions were isolated by the usual procedure.

Acid Portion.—A yield of 60 mg. of the crude acid was obtained. The crystallization proved difficult and the acid was therefore lactonized to the more easily crystallized senecic acid lactone which was purified by two recrystallizations from benzene. The product, m. p. 155–156° (cor.), was identical with that obtained by direct hydrolysis of senecionine, followed by lactonization.

Hydrogenolysis of Senecionine (Platinum Oxide Catalyst).—A solution of 0.2 g. of senecionine in 15 ml. of absolute ethanol was hydrogenated in the presence of 0.2 g. of platinum oxide catalyst. The first two mole equivalents of hydrogen were taken up in less than thirty minutes, after which the reduction slowed down considerably. The total volume of hydrogen absorbed after a further period of ten hours was 39 ml. (N. T. P.), the volume required by theory for three mole equivalents being 40.1 ml. After filtering off the catalyst, the solvent was removed *in vacuo*, leaving 200 mg. of a glassy transparent mass, which could be reduced to a powder. The product was extremely hygroscopic and was easily soluble in water and ethanol, but insoluble in all non-polar solvents. Attempts to crystallize this material or the product obtained from it by the action of diazomethane were unsuccessful.

A solution of 0.35 g. of this reduction product was hydrolyzed by refluxing in 8 ml. of water with 1 g. of barium hydroxide octahydrate for one hour. The acid portion isolated in the usual way was a colorless oil. The yield was 0.18 g. This was methylated by diazomethane and the ester purified by distillation at 0.1 mm. pressure, n^{20}_D 1.4595. The infrared spectrum contained all the absorption bands characteristic of dihydrosenecic acid dimethyl ester, but there were a few extraneous absorptions which could be accounted for only by impurities.

Anal. Calcd. for $C_{12}H_{22}O_6$: C, 58.55; H, 9.01. Found: C, 58.71; H, 8.84.

Summary

1. The alkaloid isolated from *Senecio cineraria* in this Laboratory from seeds obtained from Holland has been shown to be senecionine.

2. On hydrolysis with baryta senecionine gives one molecule of retronecine and one molecule of a dibasic acid $C_{10}H_{16}O_5$, senecic acid.

3. Senecic acid was easily lactonized to a crystalline lactonic monobasic acid, $C_{10}H_{14}O_4$, senecic acid lactone, reported by previous investigators as the necic acid from senecionine.

4. On reduction with hydrogen in the presence of Raney nickel, senecionine absorbs two moles of hydrogen to form tetrahydrosenecionine which has the properties of an amino acid and yields on hydrolysis retronecanol and senecic acid. The methyl ester of this compound was also characterized. In the presence of platinum oxide catalyst, senecionine absorbs three moles of hydrogen, yielding an amorphous product, which gives on hydrolysis retronecanol and dihydrosenecic acid.

5. Senecionine is therefore a cyclic diester from one molecule of retronecine and one molecule of a dibasic acid, each of the two hydroxyls in retronecine being involved in ester formation.

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Senecio Alkaloids: The Alkaloids of *Senecio Douglasii, Carthamoides, Eremophilus, Ampullaceus* and *Parksii*

BY ROGER ADAMS AND T. R. GOVINDACHARI

In a previous communication,[1] the isolation of two alkaloids, designated as α- and β-longilobine from *Senecio longilobus* by application of a chromatographic procedure, was described. The β-longilobine fractions from the chromatograms were contaminated with another alkaloid, which was not isolated in a pure condition but tentatively identified as riddelliine on the basis of its infrared spectrum.

In the course of work carried out in this laboratory over a period of years, several *Senecio* alkaloids had been isolated. Of these, the alkaloids from *Senecio douglasii, carthamoides, eremophilus* and *ampullaceus* had specific rotations ranging from −86 to −109° and melting points ranging from 212 to 218°. The analytical values on these alkaloids corresponded roughly to the molecular formula $C_{18}H_{23}O_5N$, but satisfactory values were not obtained, even after repeated crystallization. All these alkaloids gave infrared spectra which were essentially identical with that of the total alkaloid from *Senecio longilobus* before separation into its constituents. A sample of senecionine from *Senecio vulgaris*,[2] kindly supplied by Dr. R. H. F. Manske, also gave the same infrared spectrum. The slight differences among these spectra were such as would be expected when the proportions of the components of a mixture were varied. The infrared spectra were not changed in any way by repeated crystallization. It was evident that these alkaloids were mixtures which could not be separated into the components by mere crystallization procedures. It was considered that the chromatographic method applied successfully in the isolation of α- and β-longilobine could profitably be extended to these other alkaloids. As a result of this work, it has been established that in addition to varying amounts of the three alkaloids

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[1] Adams and Govindachari, THIS JOURNAL, **71**, 1180 (1949).

[2] Manske, *Can. J. Res.*, **14B**, 8 (1936).