

Senecio Alkaloids—Part III.

Chemical Investigations upon the Senecio Species Responsible for "Bread-poisoning." The Isolation of Senecionine from *Senecio ilicifolius* Thunb. and a New Alkaloid "Rosmarinine" from *Senecio rosmarinifolius* Linn.

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In the South-Western districts of the Cape Province, especially in the Knysna, George, Riversdale and Mossel Bay districts, certain species of the Senecio plants (Fam. Compositae) grow abundantly. The following are found as "weeds" on cultivated wheat-lands: *Senecio ilicifolius* (abundant), *S. burchellii* (abundant), *Senecio rosmarinifolius* (fairly common) as well as certain other species which do not occur so abundantly.

It is very well known that *S. ilicifolius* is the cause of "bread-poisoning" in human beings, and the other two species are also suspected poisonous plants. Chemical investigations already carried out by certain workers on various species of Senecio led to the isolation of the toxic principles namely alkaloids. [See Steyn (1934); de Waal (1939, 1940); Barger and Blackie (1936, 1937); Manske (1931, 1936, 1939); Orechoff *et al* (1935)]. The toxic alkaloids present in these plants cause the typical chronic cases of liver-cirrhosis in human beings as well as in animals, e.g., horses ("Dunsiekte", "Horse-Staggers", "Walking" disease, "Poisonous ragwort", "Winton" disease, etc.), sheep and cattle.

In the Cape South-Western districts where animal husbandry plays a minor rôle in farming, animal losses due to Senecio poisoning, are not so frequent. Moreover, there is sufficient other green grazing during spring and the early summer months when the young Senecio plants sprout. As these Senecio species grow freely and abundantly on cultivated grain lands, contamination of the threshed wheat easily takes place with the seeds and pieces of the stem of these plants. The

plants are harvested with the wheat and deficient winnowing and sieving appliances of the threshing machines readily pass the seed and pieces of the stem into the wheat bag, mainly into the third-class wheat. Steyn (1934) recorded the results of his investigations and described how specimens of wheat used for human consumption contained sticks of these plants up to two inches long. Even with the very best winnowing appliances seeds and sticks of at least the same size as the wheat grains will pass through the wheat. It may be pointed out here that chemical investigation proved that the toxic principle was present in the seeds as well as in the leaves and stems of *S. ilicifolius*.

The abundance of these plants on many of these wheat-lands, ready for harvesting, must be very alarming to the consumers of bread manufactured from such wheat (especially the third-class wheat) and to those families where the main diet consists of bread.

When the author visited the George district at the end of November, 1938 to collect Senecio plants for chemical investigation he witnessed the abundance of *S. ilicifolius* Thunb. on wheat-lands. Its predominance all along the coastal districts as far east as East London is also very well known. *Senecio rosmarinifolius* Linn. and *S. burchelli* D.C. are also very common in these parts, the former being frequently found here while the latter has a very wide distribution throughout South Africa.

THE TOXICITY OF SENECIO PLANTS.

From information obtained from the Government Extension Officer at George, four cases of "bread-poisoning" in human beings occurred in the Knysna district during 1937. Steyn (1934) recorded a natural case of chronic seneciosis in a horse on a farm where seven cases of "bread-poisoning" had occurred. On investigation, a corner of the land on which the wheat for household purposes was grown was found heavily overgrown with *Senecio burchellii* D.C.

In this article the results of the chemical investigation upon *S. ilicifolius* Thunb. and *S. rosmarinifolius* Linn. for their toxic principles are described. About six miles outside George the author gathered on 30.11.1938 forty bags of *S. ilicifolius* in the post-flowering stage (i.e., the stage in which it is harvested with the wheat) on a small area of less than an acre of cultivated land. The plants were three to five feet high and grew so profusely that the field had the appearance of a cultivated Senecio land.

When Dr. D. G. Steyn and the author investigated the problem of Senecio poisoning in stock, especially prevalent in horses and sheep in the Transkeian and East London areas, in September and again in November, 1939, the same phenomenon was observed with *S. pterophorus* D.C.

This species closely resembles *S. ilicifolius* and belongs to the same Senecio group: Rigidi. Both *S. ilicifolius* and *S. pterophorus* spread very easily and rapidly so that their occurrence has become alarmingly abundant. On account of the fact that these Senecio

plants are allowed to grow freely and densely it has become impossible to plough them under completely. In fact when the Senecio are in flower in summer such fields have the appearance of huge yellow flowering gardens.

The other species collected for this investigation was *S. rosmarinifolius* Linn. which occasionally appeared in thick patches in valleys or on pasture lands. The author collected ten bags of this plant in the flowering stage in the Mt. Pleasant locality on 1.12.1938, about 25 miles from George. A year later 40 more bags of this plant in the flowering stage were received from the same locality.

The toxic principles of both these Senecio species are two stable alkaloids with high melting-points (208° and 232° C.) and are not decomposed when exposed to light, air or moderate heat. They are not decomposed during the baking of bread from flour ground from Senecio-contaminated wheat. Both alkaloids are also very sparingly soluble in water. The only remedy must therefore be to eradicate these plants completely in the pre-flowering stage on infested farms. For this purpose the Union Government and every farmer will have to co-operate in perfect harmony to ensure the complete destruction of such poisonous Senecio plants.

EXPERIMENTAL PART.

The Isolation of the toxic Alkaloid Senecionine from S. ilicifolius Thunb.

Five kilograms of the dried and ground plant material was extracted with 96 per cent. alcohol in a large extraction apparatus (Soxhlett principle) for two days. The alcohol was distilled off under reduced pressure and the watery residue treated with four litres of 4 per cent. hydrochloric acid and allowed to stand for about 3 days. The clear tawny-coloured supernatant was then decanted or filtered from the heavy tarry deposit and repeatedly shaken with commercial ether until the ether layer was practically colourless (about five shakings). Air was then drawn through the clear brown solution to expel the ether.

The clear acid solution was made alkaline with 5 per cent. ammonium hydrate and then thoroughly shaken with successive quantities of technical chloroform until no more alkaloid was removed. The ammoniacal solution on evaporation left no traces of any alkaloid.

The chloroform solution was washed with water only once and then allowed to evaporate in front of a fan at room temperature. The residue was dissolved in 3 per cent. hydrochloric acid, again shaken with ether, made alkaline with ammonia, shaken with chloroform, the chloroform solution washed and allowed to evaporate. A crystalline residue resulted, which was washed with a little cold acetone, followed by ether, dried and recrystallized from 90 per cent. alcohol.

After three recrystallizations the prismatic colourless crystals (see Fig. 1) melted with decomposition at $232\text{--}3^{\circ}\text{C}$. (corr.)* The yield was 1 gm. of alkaloid, i.e., 0.02 per cent.

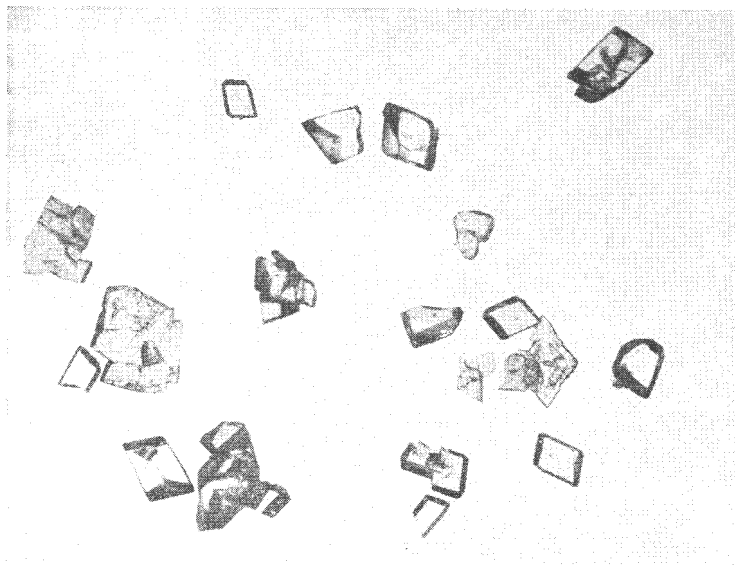


Fig. 1.—Senecionine $\times 24$.

Micro-analysis.†

- (i) 3.550 mgm. : 8.444 mgm. CO_2 and 2.414 mgm. H_2O .
4.124 mgm. : 0.201 c.c. N_2 at 621 m.m. and 25°C .
- (ii) 3.395 mgm. : 8.065 mgm. CO_2 and 2.261 mgm. H_2O .
4.062 mgm. : 0.194 c.c. N_2 at 621 m.m. and 25°C .

Found—

- (i) C = 64.87 per cent. ; H = 7.61 per cent. ; N = 4.61 per cent.
- (ii) C = 64.79 per cent. ; H = 7.45 per cent. ; N = 4.58 per cent.

Calculated for $\text{C}_{18}\text{H}_{25}\text{O}_5\text{N}$:

C = 64.50 per cent. ; H = 7.51 per cent. ; N = 4.20 per cent.

Solubility.

The substance dissolved very readily in chloroform and was also soluble in acetone, methyl- and ethyl-alcohol. It was sparingly soluble in cold water, but dissolved in hot water. It was insoluble in ether, petroleum-ether and benzene.

* All melting-points recorded with the Kofler micro-melting point apparatus and are therefore corrected.

† All micro-analyses by Dr. O. G. Backeberg, of the University of the Witwatersrand, Johannesburg.

Chemical Properties.

The substance proved to be an alkaloid. It tasted very bitter (typical of the other Senecio alkaloids) and decolorized soda-alkaline potassium permanganate solution. It dissolved readily in dilute mineral acid solutions and gave positive reactions with the alkaloidal reagents, viz., Wagner's, Dragendorf's and Mayer's reagents, phosphotungstic and picric acid solutions.

Specific Rotation.

weight = 50.0 mgm.

volume = 8.0 c.c. chloroform.

$$\theta = -0.35^\circ.$$

$$\begin{aligned} [a]_D^{20} &= \frac{-0.35 \times 1000 \times 8}{1 + 50}^\circ \\ &= -56.0^\circ. \end{aligned}$$

The properties of Senecionine (Barger and Blackie, 1936, and Manske, 1936) are identical with those of the isolated substance. The formula of Senecionine is $C_{18}H_{25}O_5N$, its melting-point is $232^\circ C.$, its specific rotation is -55.6 (chloroform), its alkaloid reactions, its solubility and other chemical properties are all identical with those of the isolated substance.

Therefore the toxic principle isolated from *S. ilicifolius* Thunb. is the alkaloid *Senecionine*.* This alkaloid is responsible for "bread-poisoning" and was found to be present in the seeds, leaves and stems of the plant.

*Isolation of a new Alkaloid "Rosmarinine" from
Senecio rosmarinifolius Linn.*

Approximately 7.0 kilograms of dried and ground *S. rosmarinifolius* was introduced into the large extractor and the extraction and working up of the material was carried out exactly similar to that described for *S. ilicifolius* Thunb. (above). As in the case of *S. ilicifolius* no trouble with emulsions was experienced when the ammoniacal liquid was shaken with chloroform. From the chloroform solution, on evaporation, a new alkaloid was isolated for which the name *rosmarinine* is proposed. No other alkaloid was found to be present in the resultant ammoniacal solutions after the treatment with chloroform.

The crystalline residue after the evaporation of the chloroform was washed with cold acetone with the addition of a small volume of ethanol to effect complete solution. The substance rapidly crystallized in a pure state and almost quantitatively. The pure substance crystallized in small, shining, snow-white, squarish flakes with a constant melting-point of $208^\circ C.$ From 20 per cent. ethanol it crystallizes in pyramidal columns (see Fig. 2). A substantial yield of 0.1 per cent. alkaloid, calculated on the dried and ground plant material, was obtained.

* Since this article had been submitted to the Press two more alkaloids have been isolated from this species, viz., *retrorsine* and a new alkaloid *ptero-phine* ($C_{15}H_{25}O_5N$) so that *S. ilicifolius* contains three very toxic alkaloids.

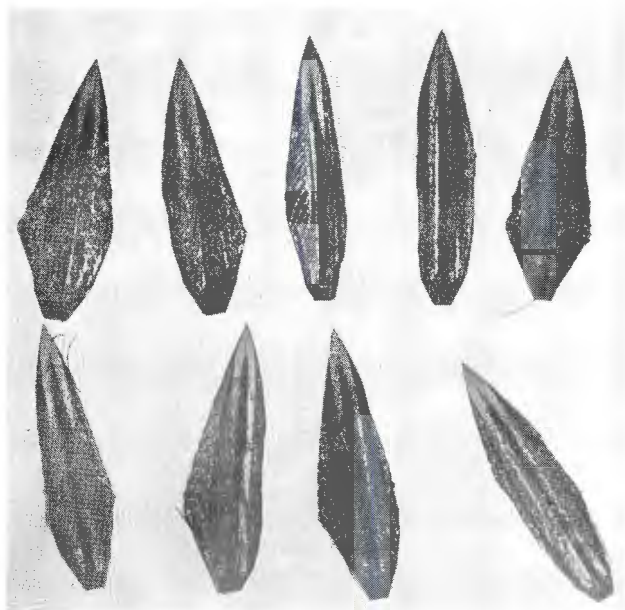


Fig. 2.—Rosmarinine $\times 15$.

Micro-analysis.

- (i) 3.559 mgm.: 8.024 mgm. CO_2 and 2.261 mgm. H_2O .
 3.508 mgm.: 0.159 c.c. N_2 at 621 m.m. and 25.5°C .
 (ii) 3.740 mgm.: 8.400 mgm. CO_2 and 2.604 mgm. H_2O .
 3.749 mgm.: 0.167 c.c. N_2 at 625 m.m. and 23.5°C .

Found—

- (i) C = 61.49 per cent.; H = 7.51 per cent.; N = 4.24 per cent.
 (ii) C = 61.25 per cent.; H = 7.79 per cent.; N = 4.22 per cent.

Calculated for $\text{C}_{18}\text{H}_{27}\text{O}_6\text{N}$:

C = 61.18 per cent.; H = 7.70 per cent.; N = 4.0 per cent.

Therefore formula is $\text{C}_{18}\text{H}_{27}\text{O}_6\text{N}$.

Specific rotation:

- (a) weight = 50.0 mgm.
 volume = 10.0 c.c. ethanol.
 $\theta = -0.47^\circ$.
 $[\alpha]_D^{20} = -94^\circ$ (ethanol).
 (b) weight = 50.0 mgm.
 volume = 8.0 c.c. chloroform.
 $\theta = -0.75^\circ$.
 $[\alpha]_D^{20} = -120.0^\circ$ (chloroform).

Chemical Properties.

The alkaloid gave positive alkaloidal reactions with Wagner's and Dragendorff's reagents and with phosphotungstic and picric acid solutions. It gave *no* precipitate with Mayer's reagent.

The alkaloid tasted extremely bitter and dissolved readily in methanol, ethanol and chloroform; it dissolved sparingly in cold and hot acetone and dissolved in boiling water and ethyl-acetate. It was insoluble in ether and petroleum-ether. It dissolved readily in dilute mineral acid solutions and slowly decolourized soda-alkaline potassium permanganate solution.

Rosmarinine Nitrate.

400 mgm. Rosmarinine was dissolved in the calculated quantity of decinormal nitric acid and the solution allowed to evaporate in front of a fan at room temperature. The crystalline residue was recrystallized from absolute alcohol-ether and the colourless prismatic crystals melted sharply with decomposition at 218° C. (corr.).

Micro-analysis:

3·508 mgm. : 6·760 mgm. CO₂ and 2·103 mgm. H₂O
found: C = 52·49 per cent.; H = 6·71 per cent.

Calculated for C₁₈H₂₇O₆N.HNO₃:

C = 51·92 per cent.; H = 6·77 per cent.

Specific rotation:

weight = 100·0 mgm.; Vol. = 7·5 c.c. H₂O; $\theta = -1·22^\circ$.

$$[a]_D^{20} = \frac{-1·22 \times 7·5 \times 1000^\circ}{1 \times 100}$$

$$= -91·5^\circ \text{ (conc. 1·33 per cent. H}_2\text{O)}.$$

In a further publication in this journal, the hydrolysis and other structural results of this alkaloid will be dealt with.

List of Some of the Properties of the More Well-known and Established Senecio Alkaloids.

Name of Alkaloid.	Formula.	M.P. ° C.	[α] _D .	M.P. of Nitrate.	[α] _D of Nitrate.
Senecionine.....	C ₁₈ H ₂₅ O ₅ N	232°	— 56·0 (CHCl ₃)	214°	—34·2 (water).
Retrorsine.....	C ₁₈ H ₂₅ O ₆ N	214°	— 17·6 (C ₂ H ₅ OH)	110°	—36·1 (water).
Isatidine.....	C ₁₈ H ₂₅ O ₇ N	138°	— 8·25 (water)	130°	—23·3 (water).
Platyphylline....	C ₁₈ H ₂₇ O ₅ N	129°	— 45·0 (CHCl ₃)	—	—
Rosmarinine....	C ₁₈ H ₂₇ O ₆ N	208°	—120·0 (CHCl ₃) — 94·0 (C ₂ H ₅ OH)	218°	—91·5 (water).

These alkaloids have now all been isolated from certain species of *Senecio* in this laboratory. Rosmarinine, a new alkaloid, has so far been isolated from *S. rosmarinifolius* Linn. only. In addition to the isolation of Senecionine from *S. ilicifolius* Thunb. it has also been obtained from:—

Senecio vulgaris (Manske, 1936, Barger and Blackie, 1936).

Senecio viscosus (Manske, 1936, Barger and Blackie, 1936).

Senecio squalidus (Manske, 1936, Barger and Blackie, 1936).

Senecio aureus (Manske, 1939).

Platyphylline will be dealt with in due course.

SUMMARY.

I. Two of the main *Senecio* species responsible for "bread-poisoning" in human beings in the Cape South-Western districts, viz., *S. ilicifolius* Thunb. and *S. rosmarinifolius* Linn., have been chemically examined for their toxic principles.

II. From *S. ilicifolius* Thunb. a known alkaloid, Senecionine, $C_{18}H_{25}O_5N$, previously isolated by other workers from *S. vulgaris*, *S. viscosus*, *S. squalidus* and *S. aureus*, has been obtained.

III. Senecionine is a stable alkaloid with m.p. 232° and very sparingly soluble in water. The alkaloid will not be destroyed during the baking of bread from flour of contaminated wheat.

IV. *S. rosmarinifolius* Linn. contains a new alkaloid for which the name "Rosmarinine" is proposed. It has the formula $C_{18}H_{27}O_6N$, the melting-point 208° , it is extremely bitter and very sparingly soluble in water. It must be considered a dangerous poison when wheat becomes contaminated with *S. rosmarinifolius* or when animals graze on this plant.

V. Rosmarinine has a specific rotation of -120.0° in chloroform and -94.0° in ethanol. Its nitrate has a melting-point of $218^\circ C.$ and a specific rotation of -91.5° in water.

VI. As a result of this chemical investigation and the nature of the toxic principles, the author urges the complete eradication of these *Senecio* plants which unfortunately occur very abundantly. This is considered the only remedy to prevent human deaths due to "bread-poisoning" and animal losses from chronic liver-cirrhosis.

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