121. *The* Senecio *Alkaloids. Part I. Rosmarinine.*

By (Miss) Margaret F. Richardson and Frank L. Warren.

Rosmarinine, isolated originally from *Senecio rosmarinifolius* Linn., has now been found in other *Senecio* species. *S. hygrophilus* R. A. Dyer and C. A. Sm. is conspecific with " *S. adnatus* " DC. of de Waal and Tiedt, who isolated platyphylline; but the alkaloid content varies: rosmarinine, platyphylline, and an *alkaloid* $C_{18}H_{27}O_6N$, m. p. 176°, have been isolated as sole constituents or as mixtures, depending on stage of growth, season and district.

Rosmarinecine, now obtained crystalline, is assigned a structure (II or III). Senecic acid, found free in the plant and obtained by hydrolysis of platyphylline and rosmarinine, is isolated as its open-chain form and as the monolactone. The identity of platynecic acid and senecic acid is confirmed.

During investigations on the *Senecio* alkaloids we have isolated rosmarinine, first obtained from *S. rosmarinifolius* Linn. by de Waal (*Onderstepoort J. Vet. Sci. and An. Ind.*, 1940, **15**, 241), from *S. brachypodus* DC., *S. pauciligulatus* R. A. Dyer and C. A. Sm., and *S. hygrophilus* R. A. Dyer and C. A. Sm. (descriptions of the last two to appear in *J. South African Bot.*). The last named is conspecific with specimens erroneously identified as *S. adnatus* DC. (Nat. Herb. Nos. 27,025 and 27,026), from which de Waal and Tiedt (*ibid.*, p. 251) isolated platyphylline, one of the alkaloids originally isolated from *S. platyphyllus* DC. (Orékhov and Tiedebel, *Ber.*, 1935, **68**, 650).

In view of the discrepancy the *S. hygrophilus* was collected over a wide area and at different stages of growth. de Waal collected his material in 1939 near Mount Ayliff, East Griqualand. From material collected at Weza, E. Griqualand, we also isolated only platyphylline; but from plants growing in the environs of Pietermaritzburg, two alkaloids were usually found, and in one district rosmarinine alone was found. These findings are summarised in the table, in the obtaining of which a standard procedure was adopted for the extraction of at least one kilogram, and the results are reproducible to the accuracy given.

Date, 1941.	District.	Growth stage.	Platyphylline, %.	Rosmarinine, %.
Oct. 5th	G	Pre-budding	0·8	0·3
Oct. 31st	G	Budding	0·15	0·1
Oct. 31st	M	Budding	0·2	0·03
Oct. 31st	M	Budding (shade)	0·5	trace
Nov. 12th	M	Flowering	0·1	0·05
Nov. 21st	D	Flowering	none	1·5
Dec. 22nd	W	Flowering	0·5	none

G, Greenhill, near Richmond, Natal; M, between Nel's Rust and Greenhill; D, Duncairn, Pietermaritzburg; W, Weza, between Harding and Kokstad, East Griqualand.

It will be noted that the plant is richest in alkaloid prior to budding, as was observed for " *S. latifolius* " by Watt (J., 1909, **95**, 466), and when growing in the shade. Variations of the alkaloidal content with the season are recorded for the *Senecio* species by Barger and Blackie (J., 1936, 743; 1937, 584).

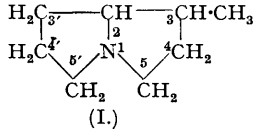
Material collected in 1940 from Duncairn yielded a new *alkaloid*, $C_{18}H_{27}O_6N$, m. p. 176°; but as the season advanced, the amount of this alkaloid diminished and finally gave way to small quantities of rosmarinine. The new alkaloid crystallised from benzene with two molecules of solvent of crystallisation, which were lost on standing. This power of forming a molecular compound with benzene is not shared by either platyphylline or rosmarinine. There was, however, a possibility of a combination similar to that of " homoquinone " (cupreine–quinine); but even after prolonged boiling of equimolecular portions of the two alkaloids with benzene none of the new alkaloid was isolated, whereas the two individuals were separated quantitatively.

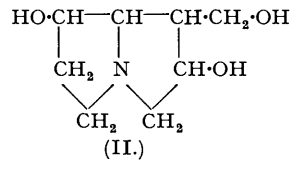
Senecic acid was found free in the plant, and the accumulation of material from these investigations has permitted a more careful study of its properties. It has been isolated now as a hydroxy-dicarboxylic acid as well as the lactone, both of which show considerable stability (cf. Barger and Blackie, J., 1936, 744). Evaporation with a drop of hydrochloric acid converts the acid into the lactone. The differences in the recorded melting points and the difficulties in purification (Manske, *Canadian J. Res.*, 1939, **17**, 1) may have been due to the mixture. We failed to detect any fumaric acid as recorded for several species by Manske (*ibid.*, 1936, **14**, 6).

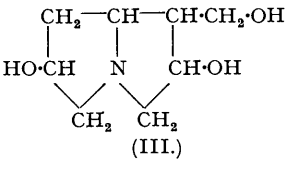
Rosmarinine was characterised by hydrolysis to senecic acid and rosmarinecine, the latter of which, previously isolated as an oil even after regeneration from the picrate (de Waal, *Onderstepoort J. Vet. Sci. and An. Ind.*, 1941, **16**, 157), has now been obtained as a crystalline solid, m. p. 171—172° (corr.). Platyphylline gives platynecine and senecic acid as shown by de Waal (*loc. cit.*), the platynecic acid of Orékhov and Tiedebel (*loc. cit.*) being identical with senecic acid lactone.

Rosmarinecine, $C_8H_{15}O_3N$, is a tertiary amine, and readily forms a *methiodide*, m. p. 189° (corr.). It is saturated in that it is not reduced by sodium amalgam or catalytically in the presence of Adams's catalyst. The existence of a methylpyrrolizidine nucleus (I) for several *Senecio* alkaloids would indicate that rosmarinecine is a trihydroxy-derivative of methylpyrrolizidine, with which the formula, $C_8H_{12}N(OH)_3$, agrees. The hydroxy-groups cannot occupy the 2-, 5- or 5′-positions. A hydroxy-group in position 2 might be expected to be reduced by a type of Emde degradation (cf. Briggs, Newbold, and Stone, J., 1942, 7), and a system containing hydroxyl groups in position 5 or 5′ would be capable of anionotropic change similar to cotarnine, and would be reducible. Furthermore, it does not form *O*-alkyl compounds when heated with alcohols (cf. Blount and Robinson, J., 1932, 2305) and does not condense with nitromethane (cf. Hope and Robinson, J., 1911, **99**, 2119). In addition, rosmarinecine is not oxidised by periodic acid; therefore no two hydroxy-groups are on neighbouring carbon atoms.

This leaves only two possibilities, (II) and (III), of which that with the hydroxy-group in the 3′-position (II) is favoured, since this shows a close connection between the modified formulæ of platynecine and retronecine (Adams, Carmack, and Mahan, *J. Amer. Chem. Soc.*, 1942, **64**, 2593; Adams and Hamlin, *ibid.*, p. 2597). Thus rosmarinecine is probably 3′ : 4-*dihydroxy*-3-*hydroxymethylpyrrolizidine* (II), and such a


(I.)


(II.)


(III.)

formula would represent rosmarinecine as hydroxyplatynecine, a conclusion that would find support in the close association in the plant of rosmarinine and platyphylline, which are esters of senecic acid with rosmarinecine and platynecine respectively. Dehydration between positions 3 and 4 would give retronecine.

Experimental.

On account of the confusion that has arisen in the identification of South African *Senecio* species, the National Herbarium Number and the Collector's Number will always be quoted in this series of papers.

Extraction.—The dried, ground plant material (2 kg.) was extracted (Soxhlet) with 95% alcohol, the extract concentrated to 2 l., a solution of citric acid (15 g.) in water (250 c.c.) added, and the alcohol removed in a vacuum. The black viscous mass was diluted to 1 l. and kept for 3 days, and the fatty material collected. The addition of the citric acid solution before the complete removal of the alcohol causes the fatty material to become granular, and facilitates the removal of the alkaloid. If this procedure were not adopted, the alcohol was only difficultly removed from the intractable sticky mass. The filtrate was extracted many times with ether to remove acids, the dissolved ether removed by bubbling air rapidly through the solution, and this then extracted with chloroform, which caused copious precipitation of gummy material. The filtered material was made alkaline with ammonia and extracted with chloroform. The chloroform extract was evaporated to a small bulk, a few drops of methanol added, and the residual solvent blown off. The solidification of the alkaloid was facilitated by the addition of a few drops of acetone. Only occasionally was it necessary to redissolve the material in citric acid and regenerate it. The ethereal solution gave the necic acid.

S. hygrophilus R. A. Dyer and C. A. Sm. (Nat. Herb. No. 26,456 and 26,457; Warren 84 and 163).—The crude alkaloid was stirred to a thick paste with acetone and filtered. The solid was reshaken with cold acetone, collected, and crystallised from acetone or ethanol to give shining laminæ of rosmarinine, m. p. 209° (corr.), $[\alpha]_D^{24°}$ — 91·5° (1% in methanol) (Found : C, 61·3; H, 7·5; N, 4·1. Calc. for $C_{18}H_{27}O_6N$: C, 61·2; H, 7·7; N, 4·0%). de Waal (*Onderstepoort J. Vet. Sci. and An. Ind.*, 1940, **15**, 245) gives m. p. 208° (corr.), $[\alpha]_D^{20°}$ — 94°. The acetone washings gave platyphylline, which separated from ethanol in rhombic crystals, m. p. 129° (corr.), and showed no depression on admixture with a specimen supplied by de Waal (Found : N, 4·3. Calc. for $C_{18}H_{27}O_5N$: N, 4·2%). Orékhov and Tiedebel (*loc. cit.*) give m. p. 124°; de Waal 129° (corr.). The perchlorate had m. p. 226° (corr.); Orékhov and Tiedebel give 222—223°.

Flowering plant material collected in 1940 gave an *alkaloid* which separated from acetone in rhombic crystals, m. p. 175—176° (corr.), $[\alpha]_D^{25°}$ — 62·4° (1½% in methanol) (Found : C, 61·4; H, 7·6; N, 4·3. $C_{18}H_{27}O_6N$ requires C, 61·2; H, 7·7; N, 4·0%). Flowering aerial portion gave 0·1% yield calculated on dried material. Crystallisation from benzene gave stout prisms containing $2C_6H_6$, which were given up on standing to leave an amorphous powder (Found : loss at 40° in a vacuum, 28·7. Calc. for $C_{18}H_{27}O_6N,2C_6H_6$: loss, 30·6%).

Ethereal extract gave 0·03% of senecic acid.

S. pauciligulatus R. A. Dyer and C. A. Sm. (Warren 128A in Nat. Herb., Pretoria).—This gave 1% of pure rosmarinine,

m. p. 209° (corr.) (Found: C, 61·2; H, 7·8; N, 4·2. Calc. for $C_{18}H_{27}O_6N$: C, 61·2; H, 7·7; N, 4·0%). Ethereal extract gave 0·3% of senecic acid.

S. brachypodus D.C. (Nat. Herb. No. 26,502; Warren 199).—This gave rosmarinine, m. p. 209° (corr.), showing no depression with the specimens above (Found: N, 4·0%). Roots gave 0·24%, flowering aerial portion 0·36%, calculated on dried material. Ethereal extract gave 0·17% of senecic acid.

Hydrolysis of Rosmarinine.—Rosmarinine (10 g.; 1 mol.) was refluxed with hydrated barium hydroxide (14 g.; 1·6 mols.) and water (200 ml.) for 1 hour. The solution was filtered and made just acid to phenolphthalein with 25% sulphuric acid, and the barium sulphate separated centrifugally. The solution was evaporated to dryness, and the residue exhaustively extracted with absolute alcohol. The extract was evaporated to dryness, the gum taken up in water, 25% sulphuric acid added drop by drop till all traces of barium had been precipitated, and the filtered solution evaporated on a water-bath to leave a pale yellow gum which partly crystallised on standing. The whole was taken up in a little dry pyridine, and the solid frozen out at − 10° and recrystallised from pyridine to give rosmarinecine in stout prisms, m. p. 171—172° (corr.), $[\alpha]_D^{25°}$ − 118·5° (Found: C, 55·5; H, 8·8; N, 8·2. Calc. for $C_8H_{15}O_3N$: C, 55·45; H, 8·7; N, 8·1%). The picrate had m. p. 175° (corr.); de Waal gives m. p. 175° (corr.) (Found: N, 14·1. Calc. for $C_8H_{15}O_3N,C_6H_3O_7N_3$: N, 13·9%).

The solid after extraction with alcohol was worked up as described by de Waal (*Onderstepoort J. Vet. Sci. and An. Ind.*, 1941, **16**, 157) to give *senecic acid*, m. p. 151° (corr.) (to a turbid liquid), $[\alpha]_D^{25°}$ + 11·8° (2% in ethanol) (Found: C, 55·5; H, 7·5; equiv., 109. $C_{10}H_{16}O_5$ requires C, 55·5; H, 7·5%; equiv., 108). The dibasic acid was evaporated twice to dryness with dilute hydrochloric acid, and the resulting solid crystallised from benzene to give fine silky needles of senecic acid lactone, m. p. 156° (corr.) (Found: equiv., 202. Calc. for $C_{10}H_{14}O_4$: equiv., 198). Manske (*Canadian J. Res.*, 1939, **17**, 1) gives for the lactone m. p. 154°.

Rosmarinecine Methiodide.—Rosmarinecine (1·2 g.) in methanol was heated with excess of methyl iodide for 20 mins., the solvent removed in a vacuum, and the residue crystallised from methanol to which a little dry ether was added to give colourless needles of *rosmarinecine methiodide*, m. p. 195° (corr.) (Found: N, 4·4. $C_8H_{15}O_3N,CH_3I$ requires N, 4·4%).

Attempted Oxidation.—Rosmarinecine (0·1 g.) in water (10 ml.) was left for 90 mins. with 0·1M-periodic acid (10 ml.); iodometric estimation of periodic acid then showed no change in concentration. A repetition at 40° similarly showed no oxidation.

Attempted Condensation.—Rosmarinecine (0·1 g.), ethanol (1 ml.), and nitromethane (5 drops) were kept for one hour and heated. The product gave a picrate from alcohol, m. p. 175° (corr.), not depressed by rosmarinecine picrate.

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NATAL UNIVERSITY COLLEGE (UNIVERSITY OF SOUTH AFRICA),
PIETERMARITZBURG.

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