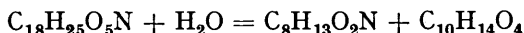


169. Alkaloids of *Senecio*. Part II. *Senecionine* and *Squalidine*.

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THE first alkaloid of this genus was discovered long ago by Grandval and Lajoux (*J. Chim. Pharm.*, 1895, 2, 15) in *S. vulgaris*, the common groundsel, and named senecionine. We have of late examined nearly every British species of *Senecio* and find that they mostly contain two or three very similar alkaloids which are sometimes difficult to separate, partly because of their scarcity. It seems essential that purification should be checked by optical activity, a point neglected by some previous workers; the melting point is no adequate criterion of purity. We are unable to confirm either Grandval and Lajoux's formula $C_{18}H_{25}O_6N$ or that of Manske, $C_{18}H_{23}O_5N$ (*Canadian J. Res.*, 1936, 14, 8). In both investigations impure preparations seem to have been analysed (see experimental part). We ourselves remained in doubt as to the exact number of hydrogen atoms in senecionine as long as we worked with the summer alkaloids of that species. From *S. viscosus* and *S. squalidus* we, however, at once obtained pure senecionine of higher melting point and constant rotation, and found that in April and September the very small amount of alkaloid in *S. vulgaris* (0.02% or less) is also pure senecionine. In the summer it is temporarily accompanied by another base, but we have been unable to separate the mixture. Our pure senecionine gave accurate analyses for $C_{18}H_{25}O_5N$ and this formula is confirmed by those of the fission products formed according to the equation



The basic fission product is, as Manske surmised, retronecine, first obtained from retrorsine of *S. retrorsus*. We find also an identical rotation. Manske did not succeed in purifying the acid for analysis, nor could we as long as we worked with impure senecionine, but later we were able to characterise it completely and suggest the name *senecic acid*. It is an unsaturated lactonic acid; it is reduced to *dihydrosenecic acid*, $C_{10}H_{16}O_4$, and must be acyclic. Retronecic acid, $C_{10}H_{16}O_6$, and a similar acid obtained from the alkaloids of South African species are saturated dihydroxydicarboxylic acids which must be monocyclic. The difference between these two kinds of acids is further shown by a determination of C-alkyl groups by Dr. H. Roth of Heidelberg, according to the oxidation method with chromic acid worked out by him. The results indicate that senecic acid furnishes three, but retronecic acid only two, equivalents of acetic acid, and we consider that retronecic acid has a five-membered ring, as has camphoric acid. The numerous acid fission products of the *Senecio* alkaloids, which vary much more than the basic moiety, are evidently examples of terpene acids, not hitherto observed in nature. Senecic acid on oxidation with nitric acid (presumably at the double bond) readily yields an acid $C_6H_8O_4$ in which the lactone group of senecic acid still survives. We are attempting to identify this acid.

Senecionine contains one reactive hydrogen atom present in the unesterified hydroxyl group of retronecine. In retrorsine the second hydroxyl is presumably in the acid moiety, the lactone acid corresponding to retronecic acid.

In *S. viscosus* we found no subsidiary alkaloid. In *S. vulgaris* one is present, which we could not separate, nor have we as yet obtained the very bitter ether-soluble senecine of Grandval and Lajoux, of which they only obtained a few milligrams and did not give any other properties. From *S. squalidus* we obtained a minute quantity of a new alkaloid, *squalidine*, isomeric with senecionine and having a lower melting point and great solubility in alcohol. Like senecionine, squalidine is an ester of retronecine, but the acid, squalinecic acid, is different, although, like senecic acid, it is unsaturated and therefore acyclic. We had not enough material to characterise it completely.

EXPERIMENTAL.

Senecionine from *S. viscosus*.—27 Kg. (dry) of this not very common species were collected in July, 1934, on a newly made embankment near Cockburnspath, mixed with 5% of calcium hydroxide, and percolated with 90% alcohol. After evaporation, the extract was mixed with dilute hydrochloric acid; the filtered acid solution was washed with ether, basified with ammonia,

and extracted with chloroform. After a second passage through acid, the second chloroform extract left a crystalline residue, which was recrystallised from alcohol; yield, 16.2 g. (0.06%). 370 G. collected early in the summer gave 0.28 g. (0.075%).

The alkaloid was pure senecionine and crystallised in rhomb-shaped plates, m. p. 232°, $[\alpha]_D - 54.6^\circ$ and $- 55.6^\circ$ from two separate batches (*c* 1.63 and 4.60, respectively, in chloroform) (Found: C, 64.4; H, 7.5; N, 4.2. Calc. for $C_{18}H_{25}O_5N$: C, 64.5; H, 7.5; N, 4.2%).

Senecionine from S. vulgaris.—2.7 Kg. (dry) collected in April, 5.5 kg. collected in June, and 20 kg. collected in September gave 0.4 g. (0.015%), 3.3 g. (0.06%), and 3.1 g. (0.015%), respectively. The April and the September alkaloid had m. p. 232° and $[\alpha]_D - 55.6^\circ$ (*c* 4.91, chloroform) and were therefore pure senecionine, but the higher content in June is accounted for, at least in part, by the appearance of another alkaloid which again disappears during the summer. The mixture of June alkaloids had m. p. 220°, $[\alpha]_D - 80.9^\circ$. The rotation is almost identical with that given by Grandval and Lajoux ($- 80.5^\circ$), who seem to have had a similar mixture. Our material had a homogeneous appearance and did not change much on repeated crystallisation from alcohol, but the melting point remained low and the analyses were not sharp (Found: C, 63.8, 64.3, 64.4, 64.2; H, 7.3, 7.1, 7.1, 7.2; N, 4.1, 4.2. Calc. for $C_{18}H_{25}O_5N$: C, 64.5; H, 7.5; N, 4.2%. Calc. for $C_{18}H_{23}O_5N$: C, 64.9; H, 7.0; N, 4.2%). Grandval and Lajoux quote one analysis agreeing closely with the formula $C_{18}H_{25}O_6N$, which is certainly wrong. Manske's single analysis gives the carbon 1.8% low for his formula $C_{18}H_{23}O_6N$; his hydrogen (7.2%) is the mean quoted above for our mixture and his m. p. 222° is very similar. The alkaloid accompanying senecionine must have a higher levorotation and probably less hydrogen than senecionine, but we were unable to isolate either it or pure senecionine from the mixture.

Senecionine from S. squalidus.—13.75 Kg. (dry) of this species, collected in July, 1935, from the station yard at Oxford (the only place in Britain where it is plentiful), yielded 8.2 g. (0.06%) of mixed alkaloids consisting almost entirely of senecionine, which was readily obtained pure, and 0.7 g. (0.005%) of a much more soluble new alkaloid, *squalidine*, having $[\alpha]_D - 26.9^\circ$ (see below). After the first crystallisation the rotation of the senecionine was accordingly somewhat low ($- 52.3^\circ$ instead of $- 55^\circ$).

Properties and Salts (m. p., rotation, analyses, see above).—Senecionine dissolves in *ca.* 340 parts of absolute alcohol at 15°, is hardly soluble in water and ether, but readily in chloroform. The solubility in water is so slight that it tastes less bitter than other *Senecio* alkaloids, but its salts are intensely bitter. It sublimes slowly at 130—140°/0.2 mm., rapidly at 190°, without decomposition. It has one hydroxyl group instead of two in retrorsine, which latter is accordingly more soluble in water and alcohol and less volatile. Active hydrogen (Zerewitinoff), 0.89, 0.90 equivalent. Senecionine readily decolorises alkaline permanganate (owing to a double bond in the acidic moiety). *Senecionine nitrate*, prepared by dissolving the base in the calculated quantity of 0.1*N*-acid and evaporating the solution, crystallises from water in prisms, and from absolute alcohol in rhombic plates, m. p. 214°, $[\alpha]_D - 34.2^\circ$ (*c* 1.14 in water) (Found: C, 54.4; H, 6.5. $C_{18}H_{25}O_5N \cdot HNO_3$ requires C, 54.3; H, 6.5%). The picrate forms fine needles, m. p. 191°, from dilute solution; the methiodide is sparingly soluble in absolute alcohol, much more soluble in 80% alcohol, and forms prisms, m. p. 249°; the aurichloride forms needles, m. p. 186°.

Hydrolysis.—This was effected as in the case of retrorsine, the plaster of Paris method described in Part I (J., 1935, 13) being used for the separation of the fission products. The base obtained was retronecine, $[\alpha]_D + 52.1^\circ$ (*c* 2.5 in absolute alcohol) (from *S. viscosus*), $+ 52.2^\circ$ (*c* 2.05) (from *S. vulgaris*); the m. p. in both cases and also of a mixture with retronecine from *S. retrorsus* was 118°. The purification of *senecic acid* was much more difficult. Although the acid crystallised on spontaneous evaporation of the ethereal extract of the plaster of Paris, it could not readily be recrystallised. By distillation at 180°/0.1 mm. we obtained a gum; its solution in chloroform was greatly concentrated, and addition of light petroleum then produced a semi-solid mass of aggregates of needles. This was filtered off, drained on porous plate, and washed with ether-petroleum (1 : 5) (light petroleum alone made it viscous); m. p. 147°. Ultimately, by spontaneous evaporation of the solution in *dry* ether we obtained needles, m. p. 153°, subliming without decomposition in a high vacuum, soluble in about 100 parts of cold water and crystallising from hot water in flat prisms, $[\alpha]_D + 41.8^\circ$ (*c* 1.29 in absolute alcohol) (Found: C, 60.5, 60.6; H, 7.1, 7.2. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%). The equiv. by titration with 0.1*N*-sodium hydroxide in the cold was 198; at 100°, only slightly more alkali was neutralised; heated with a total of 3 mols. of 0.1*N*-sodium hydroxide at 100° for some minutes, the acid neutralised 2 proportions; hence equiv., 99. A lactone acid $C_{10}H_{14}O_4$ requires 198 and 99. The lactone group seems to be unusually stable, and is not readily re-formed,

for on heating with 3 equivs. of alkali, addition of 3 equivs. of hydrochloric acid, and keeping at room temperature for 10 days, the solution still neutralised 2 equivs. of alkali, so that both carboxyl groups were still free. After strong acidification with hydrochloric acid, and continuous extraction with ether, a small yield of the original lactone acid, m. p. 153°, was obtained.

Senecic acid reduced alkaline permanganate and apparently contains three C-alkyl groups (Found : acetic acid after oxidation with chromic acid, 2.90, 2.88 equivs.; Dr. H. Roth).

Dihydrosenecic Acid.—Senecic acid (99 mg.) in a mixture of methyl alcohol, water, and a little acetic acid, shaken with platinum oxide, took up about 1 equiv. of hydrogen in $\frac{1}{2}$ hour. After filtration and evaporation, the product did not crystallise; it was therefore distilled (at 180°/0.2 mm.). The gummy distillate was dissolved in benzene; it crystallised, on scratching and gradual addition of 2 vols. of petroleum, in long slender needles (20 mg.), m. p. 106° (Found : C, 59.5; H, 8.2. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.1%).

Oxidation of Senecic Acid.—460 Mg. of the crude acid, repeatedly evaporated on the water-bath with concentrated nitric acid, yielded 107 mg. of an oxidation product, crystallising from water; recrystallised from ethyl acetate with petrol, a first fraction (30 mg.) was obtained, m. p. 142° (Found : C, 49.7; H, 5.2. Found after sublimation : C, 49.9; H, 5.5; equiv. in the cold, 144 ± 5 . $C_6H_8O_4$ requires C, 50.0; H, 5.6%; equiv., 144). The substance contains apparently two C-alkyl groups (Found : 1.68, 1.69 equivs. of acetic acid; Dr. H. Roth). Synthetic $\alpha\beta$ -dimethylmalic acid similarly yielded 1.90, 1.91 equivs. of acetic acid; the oxidation product of senecic acid does not appear to be its lactone.

Squalidine from S. squalidus.—A minute quantity (0.005% of the dry plant) remained in the mother-liquor from the crystallisation of senecionine. It is much more soluble in alcohol than the latter alkaloid and separates on concentration in crystals, of a very bitter taste, m. p. 169°, $[\alpha]_D^{25} - 26.9^\circ$ (*c* 1.45, chloroform) (Found : C, 64.3, 64.5; H, 7.9, 7.6; N, 4.4. $C_{18}H_{25}O_5N$ requires C, 64.5; H, 7.5; N, 4.2%). The alkaloid is therefore isomeric with senecionine. It is distinctly volatile in a high vacuum at 70°, over one-third being lost when the specimen was dried for analysis. The nitrate crystallised from absolute alcohol; m. p. 204°, $[\alpha]_D^{16} - 8.65^\circ$ (*c* 2.08 in water). The picrate formed needles, m. p. 203°, from dilute alcohol. On hydrolysis squalidine yielded a base, which was distilled in a high vacuum; m. p. 115°. The mixture with retronecine (m. p. 119°) melted at 115°; the base is almost certainly retronecine.

Squalinecic Acid.—The acid differs from senecic acid, to which it is, however, probably closely related. It was first obtained as a syrup, twice distilled in a high vacuum (bath at 130°), and crystallised by inoculation with senecic acid. Recrystallisation from benzene by addition of petroleum gave slender needles, m. p. 129°; it was, however, not pure (Found : C, 57.1; H, 7.2. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%. $C_{10}H_{16}O_5$ requires C, 55.6; H, 7.4%). Like senecic acid, squalinecic acid reduces alkaline permanganate and is therefore acyclic. Like senecic acid, it contains 3 C-alkyl groups (Found : 2.75, 2.77; calc. for $C_{10}H_{16}O_5$).

We gratefully acknowledge a research grant from the Carnegie Trust for the Universities of Scotland.

DEPARTMENT OF MEDICAL CHEMISTRY, UNIVERSITY OF EDINBURGH. [Received, May 1st, 1936.]