14. *The* Senecio *Alkaloids. Part VIII. The Occurrence and Preparation of the* N-*Oxides. An Improved Method of Extraction of the* Senecio *Alkaloids.*

By MATTHEUS J. KOEKEMOER and FRANK L. WARREN.

The preparation and properties of the *N*-oxides of platyphylline, platynecine, and rosmarinine are described.

The occurrence of the *Senecio* alkaloids as *N*-oxides, or their tautomeric forms, is indicated. An improved method of isolation of the alkaloids involving their reduction before isolation is developed to give yields several times greater than those previously reported.

ISATIDINE, first isolated from *Senecio isatideus* (Blackie, *Pharm. J.*, 1937, **138**, 102), and since found associated with retrorsine in various *Senecio* species (de Waal, *Onderstepoort J. Vet. Sci. and Animal Ind.*, 1939, **12**, 155; de Waal and Pretorius, *ibid.*, 1941, **17**, 181), has been shown by Christie, Kropman, Leisegang, and Warren (*J.*, 1949, 1700; cf. also Leisegang and Warren, *J.*, 1949, 486; 1950, 702) to be retrorsine *N*-oxide. Isatidine is insoluble in chloroform, which is the solvent usually employed for the extraction of the *Senecio* alkaloids, and its initial detection and later isolation in smaller quantities from the other species were facilitated by its ready crystallisation from aqueous concentrates.

The aqueous solutions left after removal of the chloroform-soluble alkaloids from several *Senecio* species investigated in these laboratories have always given pronounced tests for alkaloids. The evaporation, however, of the aqueous moiety was always associated with extensive decomposition, and butanol extraction gave only gummy products. Retrorsine is the only *Senecio* alkaloid which is known to exist as its *N*-oxide (isatidine), and the authors set out to find whether the other alkaloids also occurred in the oxidised form in the plant.

To facilitate this study the *N*-oxides of platyphylline, platynecine, and rosmarinine were prepared by oxidation of the bases with hydrogen peroxide (cf. Christie *et al.*, *loc. cit.*); platyphylline *N*-oxide, m. p. 180—184°, and platynecine *N*-oxide, m. p. 217—218°, were crystalline solids, whilst rosmarinine *N*-oxide was obtained only as an amorphous powder. The structures of these compounds follow from the summary of the structures of the *Senecio* alkaloids given by Leisegang and Warren (*J.*, 1950, 702). That these *N*-oxides of platyphylline and rosmarinine have not been isolated previously from the plant is readily understood in view of their insolubility in chloroform whilst their hygroscopic nature prevents crystallisation from the aqueous mother-liquors. The isolation by way of the phosphotungstate, employed successfully by de Waal and Pretorius (*loc. cit.*) for the isolation of small quantities of retrorsine *N*-oxide, is not practicable in view of the difficulty of crystallisation, particularly of mixtures with the amorphous rosmarinine *N*-oxide. On the other hand, these *N*-oxides in dilute hydrochloric acid were readily reduced (cf. Leisegang and Warren, *loc. cit.*) by zinc dust to give the original alkaloids in quantitative yield.

In view of these findings, the alkaloids in a number of *Senecio* species were re-investigated. For this purpose, the usual alcohol extraction was effected in glass apparatus, and the chloroform-soluble alkaloids were first completely removed. The residual aqueous solution was then reduced with zinc dust in acid solution, made alkaline again, and re-extracted with chloroform. The results from a representative number of extractions are shown in the table, which gives the percentages of impure and purified alkaloids based on the dried plant material.

In all the *Senecio* species investigated, the chloroform extract after reduction gave alkaloids in purer form, as revealed by the quantity of pure alkaloids obtained from the impure base, and in considerably larger yield than the first chloroform extraction. When no alkaloids were obtained in the first chloroform extract, none were obtained after reduction, *e.g.*, in *S. pandurifolius*; and the same alkaloids were obtained before and after reduction. These findings indicate that the *Senecio* alkaloids exist in the plant mainly as the *N*-oxide form but seemingly always associated with a smaller quantity of unoxidised alkaloid.

For the routine isolation of alkaloids, the reduction of the defatted aqueous solutions can be effected directly and the total alkaloids extracted in one operation. The enormous increase in yield by this new method should greatly facilitate constitutional studies which have been limited by availability of material. *S. coronatus* yielded only traces of alkaloid soluble in chloroform; but the new method of reduction before isolation has now given increased yields of alkaloid commensurate with its toxic nature.

Plant.	Alkaloid.	Before reduction.	After reduction.
S. isatideus D.C. (ii)	Crude	0·2—0·4%	4—5%
	retrorsine	0·1—0·2	3·5—4
S. adnatus D.C. (i)	Crude	0·63	3·2
	rosmarinine	0·25	2·2
S. hygrophilus D. and S. (i)	Crude	1·0	2·7
	rosmarinine	0·2	0·55
	platyphylline	0·2—0·4	1·5—1·7
S. brachypodus D.C. (i)	Crude	0·3	1·0
	rosmarinine	0·15	0·7

For original identification of the alkaloids from these plants cf. (i) Richardson and Warren, *J.*, 1943, 453, (ii) Blackie, *loc. cit.*

This widespread occurrence of the alkaloid *N*-oxides in the *Senecio* species (Compositæ) probably has its counterpart in the other genera, *Cynoglossum, Heliotropium, Trichodesma* (Boraginaceæ), and *Crotalaria* (Leguminosæ–Papilionaceæ) which contain similar pyrrolizidine alkaloids (cf., respectively, Menschikov, *J. Gen. Chem. Russia*, 1948, **18**, 1736; *Ber.*, 1932, **65**, 974; Menschikov and Borodina, *J. Gen. Chem. Russia*, 1945, **15**, 225; Adams and Rogers, *J. Amer. Chem. Soc.*, 1939, **61**, 2815, *et seq.*). The recent isolation by Galinovski, Goldberger, and Pohm (*Monatsh.*, 1949, **80**, 550) of laburnine, hydroxymethylpyrrolizidine, from *Cytisus laburnum* (Leguminosæ–Papilionaceæ) connects these tertiary amines with the lupinane group of alkaloids, and the natural occurrence of *N*-oxides, or their tautomeric forms, is probably more widespread than previously envisaged.

EXPERIMENTAL.

Analyses are by Drs. Weiler and Strauss, Oxford. All m. p.s are uncorrected.

Preparation of N-*Oxides*.—The alkaloid was oxidised by hydrogen peroxide as previously reported for the conversion of retronecine into isatinecine (Leisegang and Warren, *J.*, 1949, 486; cf. also Christie, Kropman, Leisegang, and Warren, *J.*, 1949, 1700). The excess of hydrogen peroxide was destroyed by platinum as described by Cope, Foster, and Towle (*J. Amer. Chem. Soc.*, 1949, **71**, 3929).

Platyphylline N-*oxide*. The product, crystallised from alcohol–acetone by cooling the solution to 0° or by the addition of ether, gave *platyphylline* N-*oxide* as fine, silky needles, m. p. 180—184° (decomp.), $[\alpha]_D^{18}$ −59° ($c = 0{\cdot}9$ in water), which appear to lose solvent of crystallisation on being heated. The very hygroscopic crystals were dried at 78° in a high vacuum for analysis (Found : C, 60·9; H, 7·9; N, 4·0. $C_{18}H_{27}O_6N$ requires C, 61·2; H, 7·7; N, 4·0%). Reduction of platyphylline *N*-oxide with zinc and hydrochloric acid, and extraction of the alkaline solution with chloroform gave platyphylline, m. p. 124—126° undepressed when mixed with authentic specimen (cf. the reduction of isatidine, Christie, Kropman, Leisegang, and Warren, *J.*, 1949, 1700).

Platynecine N-*oxide*. The product, crystallised from alcohol–acetone, gave *platynecine* N-*oxide* in stout, monoclinic, hygroscopic prisms, m. p. 217—218° (decomp.), which were dried at 78° in a high vacuum for analysis (Found : Loss of weight on heating, 23·1. $C_8H_{15}O_3N,2\frac{1}{2}H_2O$ requires H_2O, 20·6. $C_8H_{15}O_3N,C_2H_5OH$ requires C_2H_5OH, 21·1%) (Found : C, 53·7; H, 8·6; N, 7·9. $C_8H_{15}O_3N$ requires C, 55·5; H, 8·7; N, 8·1%). The *picrate* crystallised from absolute alcohol in needles, m. p. 160—162° (Found : C, 42·05; H, 4·6; N, 13·6. $C_{14}H_{18}O_{10}N_4$ requires C, 41·8; H, 4·5; N, 13·9%). Platynecine *N*-oxide was reduced as above, and the solution made alkaline with sodium carbonate, filtered, evaporated to dryness in a vacuum, and extracted with chloroform; this gave platynecine, m. p. 146—148° undepressed when mixed with authentic specimen.

Rosmarinine N-*oxide*. This was obtained as a syrup which in a vacuum gave a hygroscopic, amorphous solid which could not be induced to crystallise and decomposed in a vacuum at 169°. The picrate was amorphous. Reduction of rosmarinine *N*-oxide, as described for platyphylline *N*-oxide, gave rosmarinine, m. p. 204—206° undepressed when mixed with authentic specimen.

Extraction of Alkaloids.—The dried ground plant material (1 kg.) was refluxed with alcohol (3 l.), the solution decanted, and the residue pressed out. This operation was repeated twice more. The alcohol was evaporated under reduced pressure, water (300 ml.) added, and the residual alcohol removed under reduced pressure. The concentrate was treated with 17% aqueous citric acid (200 ml.), the fats filtered off, and the filtrate extracted with ether. The aqueous solution was made alkaline with ammonia solution and extracted with chloroform (8 × 150 ml.). The solution was made acid with 11N-hydrochloric acid (200 ml.) and treated with zinc dust (30 g.), and the solution filtered, made alkaline with 14N-ammonia (200 ml.), and re-extracted with chloroform (8 × 150 ml.).

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DEPARTMENT OF CHEMISTRY AND CHEMICAL TECHNOLOGY,
UNIVERSITY OF NATAL, PIETERMARITZBURG, S. AFRICA.

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