131. *Alkaloids of Senecio. Part III. Jacobine, Jacodine, and Jaconine.*

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THE alkaloidal content of *Senecio Jacobæa* L., the common ragwort, was first closely examined by Manske (*Canadian J. Res.*, 1931, **5**, 651), who described a crystalline alkaloid, jacobine, to which he assigned the formula $C_{18}H_{23}O_5N$; on hydrolysis he obtained retronecine, $C_8H_{13}O_2N$, and jaconecic acid, for which the formula $C_{10}H_{16}O_6$ was given with reserve. If all three formulæ were correct, hydrolysis would involve the addition of three molecules of water, whereas in the *Senecio* alkaloids hitherto examined, at most two have been required, one for the ester group and one for a lactone group in the acidic portion of the molecule. Manske's analytical results, moreover, do not agree closely with the formulæ assigned. Some years ago we found in *S. Jacobæa* two alkaloids which differ in rotation (not determined by Manske) but not much in solubility. One of them has since been isolated by Hosking and Brandt (*New Zealand J. Sci. Tech.*, 1936, **17**, 638), who assigned to it the formula $C_{18}H_{25}O_6N$ but no name. Lately, from material collected in August (instead of June and July as before), we obtained only one alkaloid, apparently identical with that of Hosking and Brandt. For the sake of simplicity we suggest the retention of Manske's name jacobine, for it is certainly the principal alkaloid in the plant. We have obtained analyses for it and for its fission products in agreement with the equation

$$C_{18}H_{25}O_6N + 2H_2O = C_8H_{13}O_2N + C_{10}H_{16}O_6$$

The basic fission product is, as Manske found, retronecine; the acid is isomeric with retronecic and isatinecic acids (cf. Blackie, *Pharm. J.*, 1937, **138**, 102) from South African species of *Senecio*, but whilst the latter acids contain two *C*-methyl groups and are cyclic dihydroxy-compounds, jaconecic acid contains three (or four?) *C*-methyl groups and is most likely an acyclic hydroxy-ketonic acid. Senecic acid ($C_{10}H_{14}O_4$, from senecionine) is an acyclic unsaturated lactonic acid.

In our earlier material jacobine was mixed with an alkaloid $C_{18}H_{25}O_5N$ (isomeric with senecionine and squalidine; J., 1936, 743) having a higher lævorotation, a smaller solubility in ethyl acetate, and forming a nitrate more soluble in alcohol than that of jacobine; for this alkaloid we suggest the name *jacodine*. Like senecionine, it is unsaturated, but its lævorotation and solubility in alcohol are much greater than those of senecionine. Evidently Manske's alkaloid was not pure and his analytical results are explained by a contamination with jacodine, which we found very difficult to separate from jacobine.

From the mother-liquors of jacobine and jacodine, obtained from material collected in July, 1934, we isolated a small quantity of a base, $C_{18}H_{25}O_8N,H_2O$, which is very soluble in alcohol, and may be called *jaconine*. We have failed to isolate it from later material, from which jacodine also was absent.

On account of the occurrence of *Senecio* poisoning of cattle in New Zealand (Winton disease), we examined a supply of *S. Jacobæa* collected there through the kindness of Dr. B. C. Aston, chief chemist of the Department of Agriculture, Wellington; for his help in this matter we tender him our hearty thanks. The alkaloidal content was the same (0·06%) as in the Scottish plant, and the same mixture (of jacobine and jacodine) appeared to be present. The greater incidence of poisoning in New Zealand is probably due to a greater abundance of *Senecio* in the pasture.

Jacobine is also the principal alkaloid in *S. cineraria*, D.C., a Mediterranean plant, which has established itself on the coast near Dublin, whence our material was obtained. Although very different in appearance from *S. Jacobæa*, *S. cineraria* seems to be a closely related species, for the two hybridize in Ireland (Colgan, "Flora of the County Dublin," Dublin, 1904, p. 112); such biological relationship is in accordance with the presence of the same alkaloid in both species. *S. cineraria* probably contains a small amount of another alkaloid with a lower rotation. Manske (*Canadian J. Res.*, 1936, **14**, 6), working with very little material, found this species practically devoid of alkaloid. We suggest that aureine (from *S. aureus* L.), described in the same paper, may be identical with senecionine, which, as we have previously shown (J., 1936, 743), Manske failed to obtain pure. The optical rotation of aureine (not recorded) would help to settle this point. We further suggest that the acid $C_{10}H_{16}O_4$, found by Manske in *S. mikanoides* (Walp) Otto, m. p. 64°, is in reality dimethylacrylic acid, previously isolated from *S. kæmpferi* D.C. by Shimoyama (*Apoth. Ztg.*, 1892, **7**, 453) and identified as such by Asahina (*Arch. Pharm.*, 1913, **251**, 355).

EXPERIMENTAL.

S. Jacobæa.—7 Kg. (dry), collected in June, 1934, yielded 2·1 g. (0·03%); 29 kg. (July, 1934), 16·6 g. (0·06%); 36 kg. (August, 1935), 18·19 g. (0·05%); and 3·3 kg., from New Zealand, 1·91 g. (0·06%)

S. cineraria.—2 Kg., collected at the end of June, 1936, near Dublin, yielded 1·05 g. (0·05%). The material was extracted by the method previously described (J., 1936, 743). Both batches in 1934 yielded a mixture of jacobine and jacodine; that collected in June had $[\alpha]_D^{16^\circ} - 62{\cdot}6^\circ$; that collected in July had $[\alpha]_D^{16^\circ} - 84{\cdot}2^\circ$; both melted at 212°; the former mixture gave C, 61·8; H, 7·3%, approximating fairly closely to $C_{18}H_{25}O_6N$, but, as indicated by the rotation, the latter mixture contained a considerable proportion of jacodine and it gave analytical results not in agreement with any simple formula. Crystallisation from alcohol had little effect in separating the second mixture, as shown by the rotation of the fractions; nor had a fractional extraction with hydrochloric acid from chloroform solution. Crystallisation of the nitrates from absolute alcohol was rather more effective; the least soluble nitrate yielded a base with C, 62·1; H, 6·9% (approximating to $C_{18}H_{25}O_5N$), but not yet quite pure.

Jacobine.—The alkaloid was only obtained pure from the 1935 and 1936 material. It crystallised from absolute alcohol in nacreous diamond-shaped plates, m. p. 219°; the alkaloid from *S. Jacobæa* had $[\alpha]_D^{17^\circ} - 46{\cdot}3^\circ$ (*c*, 1·51 in chloroform), and that from *S. cineraria*, $[\alpha]_D^{17^\circ} - 30{\cdot}5^\circ$ (*c*, 1·44 in chloroform); the lower value is probably due to contamination with another alkaloid of lower rotation. Jacobine is more soluble in absolute alcohol than senecionine (*ca.* 1 in 110), very soluble in chloroform, slightly in ether, and moderately readily in ethyl acetate (about twice as soluble as jacodine) (Found for alkaloid from *S. Jacobæa* : C, 62·1, 62·1; H, 7·1, 7·2; N, 4·1; for alkaloid from *S. cineraria* : C, 61·8; H, 7·2; N, 4·3. Calc. for $C_{18}H_{25}O_6N$: C, 61·5; H, 7·2; N, 4·0%). Jacobine contains two active hydrogen atoms (Found according to Zerewitinoff, 1·76, 1·71).

Jacobine nitrate, prepared by dissolving the base in the calculated quantity of 0·1*N*-acid and evaporating the solution, forms prisms from water and rhombic plates from alcohol, m. p. 234°, $[\alpha]_D^{17^\circ} - 28{\cdot}6^\circ$ (*c*, 1·68 in water) (Found for *S. Jacobæa* : C, 52·4, 52·6; H, 6·3, 6·1; for *S. cineraria* : C, 52·2, 52·1; H, 6·5, 6·4. $C_{18}H_{25}O_6N,HNO_3$ requires C, 52·2; H, 6·3%). The picrate is very soluble in cold water and crystallises from alcohol in needles, m. p. 180°. The methiodide forms stout prisms, m. p. 255°, from alcohol.

Hydrolysis (for method, see Part I, J., 1935, 13). Retronecine was obtained both from *S. Jacobæa* and from *S. cineraria*, m. p. 119° alone or with retronecine ($[\alpha]_D + 50{\cdot}8^\circ$) from *S. retrorsus*; $[\alpha]_D + 50{\cdot}5^\circ$, $+ 49{\cdot}9^\circ$ respectively.

Jaconecic Acid.—Like other acids from *Senecio* alkaloids, this acid was only obtained pure with difficulty, particularly from our earlier mixtures. On prolonged standing in a desiccator the syrup partly crystallised; an impurity could then be removed with *dry* ether, and the residue could be recrystallised from a concentrated solution in acetone by the addition of *dry* ether. From the pure alkaloid the acid was more readily obtained crystalline. It separated from dry ether in fine needles, m. p. 182° (Hosking and Brandt give m. p. 181° but no analysis); $[\alpha]_D^{15°} + 31{\cdot}7°$ (Found : C, 51·4; H, 7·1. Calc. for $C_{10}H_{16}O_6$: C, 51·7; H, 6·9%). Jaconecic acid from *S. cineraria* melted at 181°, alone or mixed with authentic material. *C*-Methyl estimation by Dr. H. Roth : Found, 3·10, 3·17.

Jacodine.—We have obtained this alkaloid analytically but perhaps not yet optically pure. The more soluble fraction of the mixed nitrates had a much higher lævorotation than jacobine nitrate; m. p. 215°, $[\alpha]_D^{17°} - 77{\cdot}4°$ (*c*, 1·33 in water). From this nitrate we obtained a *base*, which was recrystallised from ethyl acetate, in which it was less soluble than jacobine; it formed long plates pointed at both ends, m. p. 217°, $[\alpha]_D^{17°} - 109{\cdot}6°$ (*c*, 1·48 in chloroform) (Found : C, 64·3; H, 7·2; N, 4·3. $C_{18}H_{25}O_5N$ requires C, 64·4; H, 7·2; N, 4·3%). The picrate was very little soluble in water and formed needles, m. p. 171°, from alcohol.

Hydrolysis of the base yielded retronecine, m. p. 119° (not depressed by an authentic specimen), and an acid, which formed sphæro-crystals and needles, m. p. 136—137°, from chloroform (Found : equiv., 116. Calc. for a dibasic acid $C_{10}H_{16}O_5$: equiv. 108). The small amount of the material did not permit of complete purification.

Jaconine separated from the concentrated mother-liquors of the two previous alkaloids in prisms, m. p. 146°, very soluble in alcohol, moderately soluble in ethyl acetate, and somewhat soluble in water. The amount obtained was very small (Found for air-dried material purified from alcohol : C, 54·4; H, 6·9; N, 3·5; loss on drying at 50° in a high vacuum, 4·5. Found for anhydrous material: C, 56·8; H, 6·4. $C_{18}H_{25}O_8N,H_2O$ requires C, 53·9; H, 6·8; N, 3·5; H_2O, 4·5%. $C_{18}H_{25}O_8N$ requires C, 56·4; H, 6·6%).

In spite of the high oxygen content the alkaloid distilled at 180°/0·01 mm. without *apparent* decomposition; the vitreous solid crystallised in flat prisms when the tube was heated in a water-bath. The vapours evolved on heating with zinc dust coloured pine-wood red. It is not certain whether the distillate was identical with the material as first crystallised.

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