3. *Alkaloids of* Senecio. *Part I. Retrorsine.*

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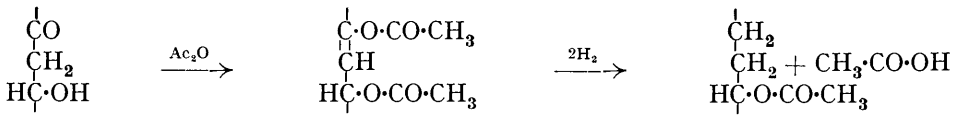
The genus *Senecio*, with 1250 species, is the largest of the *Compositae* and has provided more alkaloids than all the other genera combined. A number of its species are responsible for cattle poisoning, particularly in South Africa; this led to the investigation by one of us (Watt, J., 1909, **95**, 466) of material considered at the time to be *S. latifolius* D.C., from which two alkaloids, senecifoline and senicifolidine, were isolated; Cushny (*J. Pharm. Exp. Ther.*, 1911, **2**, 531) showed them to produce the liver degeneration characteristic of the intoxication. More recently botanists have divided *S. latifolius* into several species and the source of the above alkaloids is uncertain; perhaps the botanical material was not homogeneous (see Steyn, " The Toxicology of Plants in S. Africa," Central News Agency Ltd., S. Africa, 1934; J. M. Watt and Breyer-Brandwyk, " The Medicinal and Poisonous Plants of Southern Africa," Edinburgh, 1932). Before this was realised we received a further supply of so-called *S. latifolius* which yielded neither of the two alkaloids previously isolated, but a third closely related base, which we have since also obtained from accurately identified *S. retrorsus* D.C. It is identical with the retrorsine of Manske (*Canadian J. Res.*, 1931, **5**, 651). Since other species have yielded still further alkaloids, to be described later,

and all are hydrolysed to closely related acids and bases, we consider Manske's nomenclature of " necines " and " necic acids " very suitable, *e.g.*,

$$\underset{\text{retrorsine}}{C_{18}H_{25}O_6N} + 2H_2O = \underset{\text{retronecine}}{C_8H_{13}O_2N} + \underset{\text{retronecic acid}}{C_{10}H_{16}O_6}$$

We established this equation some ten years ago and were at first at a loss to explain the discrepancy with the older results (H. E. W.). There is, however, also great similarity; indeed the hydrolytic product senecifolinine (J., 1909, **95**, 473) is perhaps identical with retronecine (see experimental part); its parent alkaloid is certainly different, and the other fission product, senecifolic acid, differs in melting point and rotation from retronecic acid, with which it is isomeric. Retronecine contains neither *O*-methyl nor *N*-methyl groups, does not react with nitrous acid, forms a quaternary iodide by the addition of methyl iodide, and is evidently a tertiary base; the nitrogen atom may belong to two rings (probably pyridine and pyrrolidine). The base contains two reactive hydrogen atoms (Zerewitinoff) and on boiling with acetic anhydride yields a diacetyl derivative. Manske obtained, at a lower temperature, only a monobenzoyl derivative and concluded, from the coloration formed with piperonal and alkali, that a $CH_2{\cdot}CO$ group is present. We have quite failed to demonstrate a ketone group in the molecule. It is conceivable that the group $CH_2{\cdot}CO$, if present, reacts in the enolic form with acetic anhydride. The diacetyl derivative is peculiar in losing one acetoxy-group on catalytic reduction, four hydrogen atoms being taken up; after hydrolysis the net result is the change from $C_8H_{13}O_2N$ to $C_8H_{15}ON$; the mechanism may be illustrated as follows:



The base $C_8H_{15}ON$ is the monohydroxy-derivative of a hypothetical isomeride of tropane, $C_8H_{15}N$, which we propose to call retronecane (perhaps identical with piperolidine of Löffler and Kaim, *Ber.*, 1909, **42**, 96, and octahydropyrrocoline of Clemo and Ramage, J., 1932, 2970). Retronecine might then be retronecanolone; the base $C_8H_{15}ON$ can be called retronecanol, etc. We have compared the catalytic reduction of retrorsine, retronecine, and diacetylretronecine. With platinum oxide of Adams and Shriner, all three bases took up four hydrogen atoms rather rapidly; with palladium and hydrogen at two atmospheres the result was similar for the first and the third base (both acyl derivatives), but retronecine was reduced much more slowly, and after two hydrogen atoms had been taken up a substance resulted which was transformed by traces of mineral acid into an analogue of pyrrole-red. (A new " necine " to be reported on later, shows the same extreme sensitiveness to acids even before reduction.) On further reduction with palladium the stable retronecanol was obtained, which can be distilled with steam. On oxidation with chromic acid it yielded an amphoteric substance, which was esterified with ethyl alcohol; the ester was distilled and converted into a crystalline methiodide, $C_9H_{12}O_2NI$, which is therefore presumably derived from an acid $C_5H_4N{\cdot}CO_2H$ (picolinic?). We hope to identify it when more material is available.

Retronecic acid is a dihydroxydicarboxylic acid, $C_{10}H_{16}O_6$ (isomeric with dihydroxycamphoric), and yields a lactone acid, $C_{10}H_{14}O_5$. Apart from this, our older experiments mostly yielded negative results; since then dehydrogenation by selenium has come into vogue and recent experiments indicate that this method furnishes a promising degradation of the acid. Retronecine and retronecic acid may be combined in retrorsine by two or by one ester linking; in the latter case the second molecule of water used up in hydrolysis would hydrolyse a lactone group. Retrorsine does not react with diazomethane, gives a *monophenylcarbamate*, and gives off two molecules of methane with the Grignard reagent. One of the active hydrogens must belong to a hydroxyl group in the acidic moiety; the other is either in the second hydroxyl or, if in a lactone group, there must be an active hydrogen in the basic moiety.

Experimental.

Retrorsine is readily soluble in alcohol and in chloroform, slightly in water, acetone, and ethyl acetate, hardly in ether. Water does not precipitate it from alcoholic solution, but when the alcohol is boiled off and the solution concentrated, it suddenly separates in leaflets. It is conveniently recrystallised from ethyl acetate or from 13 parts of boiling methyl ethyl ketone; m. p. 212° (Manske, 214—215° corr.) (Found : C, 61·6; H, 7·1. Calc. for $C_{18}H_{25}O_6N$: C, 61·5; H, 7·1%). In ethyl alcohol ($l = 1$, $c = 1·99$), $\alpha_D^{18°} - 0·35°$, $[\alpha]_D^{18°} - 17·6°$.

0·1613 G. in anisole, treated at 120—125° for 15 minutes with excess of methylmagnesium iodide, gave 23·0 c.c. of methane (equiv. to 2·2 reactive hydrogen atoms). Nitrous acid and diazomethane were without action.

Retrorsine Monophenylcarbamate.—The alkaloid (0·5 g.) and phenyl *iso*cyanate (1·5 c.c.) were boiled in chloroform (10 c.c.) for 2 hours, and the solvent and excess of the reagent then removed in a vacuum at 100°. The brown viscous residue was washed with cold benzene and extracted with warm dilute hydrochloric acid. The *carbamate*, precipitated by ammonia, was extracted with ether; it separated from the dried and concentrated solution as prismatic needles, m. p. 200—202° (Found : C, 64·2; H, 6·5; N, 6·2. $C_{25}H_{30}O_7N_2$ requires C, 63·8; H, 6·4; N, 6·0%).

Retrorsine nitrate, prepared by addition of nitric acid to a concentrated solution of the alkaloid in absolute alcohol and recrystallised from alcohol–ether, formed prisms, m. p. 145° (Found : loss in a vacuum at 100°, 5·4. $C_{18}H_{25}O_6N,HNO_3,\frac{1}{2}C_2H_5{\cdot}OH$ requires $C_2H_5{\cdot}OH$, 5·3%).

Retrorsine methiodide crystallised from 50% methyl alcohol in prisms, m. p. 260° (Manske, 266° corr.), readily soluble in water, sparingly in alcohol (Found : C, 45·9; H, 5·6; I, 25·7. Calc. for $C_{19}H_{28}O_6NI$: C, 46·2; H, 5·7; I, 25·8%).

Retrorsine Perbromide.—When a 2% solution of bromine was dropped into one of the base, in chloroform, four atomic proportions were used up and orange-yellow prisms separated, which were recrystallised from methyl alcohol (Found : Br, 41·2. $C_{18}H_{25}O_6NBr_2,HBr$ requires Br, 40·5%). On treatment with sulphurous acid retrorsine was recovered. The hydrogen bromide doubtless results from partial conversion into a bromo-derivative remaining in the mother-liquor.

Hydrolysis of Retrorsine.—The alkaloid is slowly hydrolysed by boiling concentrated hydrochloric acid; with *N*-sodium hydroxide, 2 hours' boiling suffices. Owing to the solubility relations of the fission products, the following process is very suitable. The alkaline solution is made acid to Congo-red, evaporated almost to dryness, mixed with plaster of Paris, and exhaustively extracted with dry ether (Soxhlet; about 30 hours). Retronecic acid crystallises from the boiling ether in the receiver. When alcoholic sodium hydroxide is used (as Watt did for senecifoline), the ethereal mother-liquor leaves a syrup (ester ?), from which more acid can be recovered after a second hydrolysis. After extraction with ether, the plaster of Paris is freed from ether by exposure to the air, well ground with anhydrous sodium carbonate (20 g. for 10 g. of alkaloid), returned to the Soxhlet apparatus, and extracted with chloroform (16 hours). The oily residue of retronecine, left on evaporation, crystallises in a vacuous desiccator. It is recrystallised from acetone, forming stout prisms which may be an inch long. With half the above quantity of sodium carbonate a fraction very sparingly soluble in acetone is obtained and identified as the hydrochloride. The yield of retronecine and of retronecic acid is almost quantitative.

Retronecine, m. p. 121—122° (Found : C, 61·5; H, 8·3. Calc. for $C_8H_{13}O_2N$: C, 61·9; H, 8·4%), shows in ethyl alcohol ($l = 1$, $c = 1·83$) $\alpha_D + 0·93°$, $[\alpha]_D + 50·2°$. 0·07179 G. in anisole gave with methylmagnesium iodide 20·6 c.c. of methane (equiv. to 2·0 reactive hydrogen atoms). Retronecine is very readily soluble in water and in alcohol, moderately in acetone and in chloroform, slightly in ether. An aqueous solution, strongly alkaline to litmus, does not yield a precipitate with picric acid, potassium mercuric iodide, or potassium bismuth iodide, but does with phosphotungstic acid. On distillation with zinc dust the vapours give the pyrrole reaction on pinewood. There is no reaction with nitrous acid. The Schotten–Baumann reaction gives a neutral, and phenyl *iso*cyanate a basic, product; both are soluble in ether, and neither could be crystallised. No *p*-nitrophenylhydrazone could be obtained, and no phenylosazone; Fehling's solution is not reduced. No benzylidene compound could be isolated, whether alcoholic sodium hydroxide or hydrogen chloride was used as condensing agent; there merely resulted a dark solution, as reported by Manske.

Retronecine hydrochloride forms prisms from absolute alcohol, m. p. 161° (Manske, 164°

corr.) (Found : C, 49·9; H, 7·2. Calc. for $C_8H_{13}O_2N$,HCl : C, 50·1; H, 7·3%). In ethyl alcohol ($l = 1$, $c = 1{\cdot}50$) $\alpha_D^{15°} - 0{\cdot}24°$, $[\alpha]_D^{15°} - 16°$ (another preparation and another observer : m. p. 162—163°, $[\alpha]_D^{15°} - 13{\cdot}7°$). Watt gives for senecifolinine hydrochloride, m. p. 168°, $[\alpha]_D^{20°} - 12{\cdot}6°$. His analysis, calculated for $C_8H_{11}O_2N$,HCl, agrees better with $C_8H_{13}O_2N$,HCl. His aurichloride had m. p. 150°; we found for retrorsine aurichloride, m. p. 146°. The two bases are evidently very similar, but identity cannot be established without a direct comparison.

Diacetylretronecine.—When retronecine was boiled with acetic anhydride for ½ hour, the solution darkened and became fluorescent. After removal of the excess of acetic anhydride in a vacuum, distillation with water, and addition of aqueous picric acid, a *picrate* rapidly crystallised (yield, 80%), which formed prisms from water, m. p. 146° (Found : C, 46·1; H, 4·4. $C_{18}H_{20}O_{11}N_4$ requires C, 46·2; H, 4·3%).

On evaporation of its aqueous solution, the acetate of the free base remained as a syrup, which was mixed with plaster of Paris and sodium carbonate; after continuous extraction with chloroform the liquid residue distilled at 125° in a high vacuum; the distillate showed a strong green fluorescence, but nevertheless gave the same picrate. It readily reacted with methyl iodide; the *methiodide* was crystallised from alcohol–ether, m. p. 118—120° (Found : I, 33·0. $C_{13}H_{20}O_4NI$ requires I, 33·3%).

Reduction of Retronecine.—Boiling for several hours with zinc dust and acetic acid, or in alcoholic solution with the addition of 12 atomic proportions of sodium, had no effect; after mixing with plaster of Paris and extraction with chloroform, unchanged retronecine was recovered almost quantitatively. Reduction in 33% acetic acid, with palladium and hydrogen under 2 atmospheres, proceeded slowly and gave, after absorption of 1 mol. of hydrogen, a slightly coloured syrup with an odour of acetamide, transformed by traces of mineral acids into an insoluble red resin. With platinum oxide (according to Willstätter and Waldschmidt-Leitz, later according to Adams and Shriner) two molecules of hydrogen were rapidly taken up and the product yielded a picrate of retronecanol, m. p. 208° (see below).

Reduction of Retrorsine.—This starts rapidly in dilute acetic or alcoholic solution, both with palladium and with platinum oxide; ultimately some 6 hours may be required under atmospheric pressure. Two molecules of hydrogen are taken up. The reduced alkaloid is very soluble in chloroform, and is precipitated by ether as a white amorphous powder. It is extremely soluble in water, much more than the parent alkaloid, and could not be crystallised. It did not react with diazomethane nor could a free carboxyl group be demonstrated by esterification with alcohol and hydrogen chloride. In contradistinction to retrorsine, the hydrogenated alkaloid is precipitated by aqueous picric acid, but neither the picrate nor the methiodide could be obtained pure. On hydrolysis, as described for retrorsine, unchanged retronecic acid was obtained, together with a new base, retronecanol, which was volatile with steam. The distillate was acidified and evaporated. After grinding with dry potassium carbonate, the residue was extracted with ether; the syrupy base so obtained gave the same *picrate*, m. p. 208°, as that mentioned above. It formed prisms from water and from alcohol (Found : C, 45·7, 45·8; H, 4·8, 4·8. $C_8H_{15}ON$,$C_6H_3O_7N_3$ requires C, 45·5; H, 4·9%).

Acetylretronecanol.—Reduction of diacetylretronecine, like that of retrorsine, proceeds with palladium more readily than the reduction of retronecine itself. The product was isolated as *picrate*, m. p. 176°, which crystallised from 95% alcohol in long prisms (Found : C, 46·6; H, 4·8; N, 13·6. $C_{10}H_{17}O_2N$,$C_6H_3O_7N_3$ requires C, 46·6; H, 4·9; N, 13·6%). The same picrate was obtained by acetylating retronecanol (above). Acetylretronecanol, regenerated from this picrate, was slowly extracted from alkaline aqueous solution by chloroform. After drying, it distilled at 107°/12 mm. but did not crystallise in the ice chest. The oily base reacts violently with methyl iodide, with considerable decomposition; it should be diluted. The *methiodide* formed stout prisms from alcohol, m. p. 207—208° (Found : C, 41·0; H, 6·1; I, 40·3. $C_{11}H_{20}O_2NI$ requires C, 40·6; H, 6·2; I, 39·1%).

Oxidation of Retronecanol.—The base (1 g.) was dissolved in water (4 c.c.) and sulphuric acid (0·4 g.), and heated with a mixture of chromic acid (1 g.), sulphuric acid (1·4 g.), and water (20 g.). After 1 hour an equal quantity and after another hour half the quantity of chromic acid were added, making in all 5 oxygen atom equivalents. After 4 hours, when no more chromic acid was being used up, the excess was reduced by sulphur dioxide. The solution was nearly neutralised with barium hydroxide, and the precipitate boiled with water. The remaining sulphuric acid was removed from the combined filtrates by barium carbonate. The neutral solution, containing a soluble sulphate, was evaporated, and the residue extracted with alcohol. After repeated esterification with hydrogen chloride, the ester was liberated with potassium carbonate, extracted by ether, and distilled at about 140°/10 mm. The pale brown distillate

did not yield a crystalline picrate, but in acetone solution a colourless *methiodide* was formed, which crystallised from alcohol in rhombohedral plates, m. p. 292—295° (Found : C, 36·9; H, 4·2; I, 43·3. $C_9H_{12}O_2NI$ requires C, 36·9; H, 4·1; I, 43·3%).

Retronecic Acid.—This acid is best crystallised from a little boiling water, or from ethyl acetate; it forms narrow prisms, m. p. 177° (Found : C, 51·7; H, 6·9; equiv., by titration, 117. Calc. for $C_{10}H_{16}O_6$: C, 51·7; H, 6·9%; equiv., 116). In ethyl alcohol ($l = 1$, $c = 1·32$), α_D − 0·15°, $[\alpha]_D$ − 11·36°. The acid is not oxidised by ammoniacal silver nitrate, or reduced catalytically by hydrogen, nor does it decolorise bromine water. A lactone group is absent (back titration). The silver salt crystallises in needles from hot water. The methyl ester is syrupy and distils at about 200° in a high vacuum. Boiling concentrated hydrobromic acid did not attack the acid, but at 150—160° in a sealed tube it charred it completely. When retronecic acid was heated with anhydrous oxalic acid for some hours at 120—130°, formic acid was given off. The reaction mixture was freed from oxalic acid by boiling with calcium carbonate; on concentration the calcium salt of another acid crystallised. After acidification, mixing with plaster of Paris, and extraction with ether, this acid was obtained in plates, m. p. 181—183°; it is doubtless identical with Manske's lactone acid, m. p. 186° (corr.) [Found : C, 56·1; H, 6·6; equiv., by direct titration, 217; by back titration (a) in the cold, 205, (b) after boiling with sodium hydroxide, 104. Calc. for $C_{10}H_{14}O_5$: C, 56·1; H, 6·5%; equiv., as monobasic acid, 214].

We gratefully acknowledge a research grant from the Carnegie Trust for the Universities of Scotland, and are greatly indebted to the Director of Veterinary Services of the Department of Agriculture of the Union of South Africa for a supply of material.

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[*Received, October 29th,* 1934.]