Onderstepoort Journal of Veterinary Science and Animal Industry, Volume 16, *Numbers* 1 *and* 2, *January and April*, 1941.

Printed in the Union of South Africa by the
Government Printer, Pretoria.

South African Senecio Alkaloids. Part 5.—Notes on Isatidine, Rosmarinine and Pterophine, and on the Structure of their Necines and Necic Acids.

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In previous publications of this series it was mentioned that besides retrorsine, isatidine was isolated from *S. isatideus* and *S. retrorsus* (Part I, 1939). Subsequently the isolation of senecionine, retrorsine and a new alkaloid pterophine ($C_{18}H_{23}O_5N$) from the "bread-poisoning" variety *S. ilicifolius* was recorded as well as a new alkaloid rosmarinine $C_{18}H_{27}O_6N$ from *S. rosmarinifolius* (Part III, 1940). Finally the author with Tiedt (1940) described the isolation of platyphylline from *S. adnatus*. Previous to the isolation of pterophine from *S. ilicifolius* Thunb. the writer isolated this alkaloid from another member of the same Rigidi-group (Flora Capensis, 1894) viz., *Senecio pterophorus* D.C.; hence the name pterophine for this new alkaloid. Recently another new Senecio alkaloid, viz., graminifoline, probably $C_{18}H_{23}O_5N$, was isolated besides retrorsine, from *S. graminifolius* Jacq.

As far as can be ascertained from the literature Table 1 gives a complete list of the well-defined Senecio alkaloids isolated by the various workers in this field of research.

Toxic Alkaloids.

From preliminary toxicological experiments it appears that rosmarinine is not markedly physiologically active (rats) and as *S. rosmarinifolius* contains this one alkaloid only, the toxicity of this plant may meanwhile be considered doubtful. No experimental evidence is as yet available on the toxicity of platyphylline and graminifoline. The other alkaloids isolated from South African species of Senecio, viz., pterophine, senecionine, isatidine and retrorsine are all very toxic. Fatal results have occurred from liver-cirrhosis in all cases where these alkaloids have been injected subcutaneously into rats and in addition where isatidine and retrorsine have been dosed to horses by the stomach tube.

Table 1.

Constants of known Senecio Alkaloids.

Alkaloid.	Formula.	MP °C.	Spec. Rot.°	Nitrates.	
				MP °C.	Spec. Rot.° (H_2O).
1. Longilobine	$C_{18}H_{23}O_5N$	217–8*	−79·2 (EtOH)	—	—
2. Spartioidine	$C_{18}H_{23}O_5N$	178*	—	—	—
3. Graminifoline	$C_{18}H_{23}O_5N$	236*	—	—	—
4. Pterophine	$C_{18}H_{23}O_5N$	226–7*	−88·5 ($CHCl_3$)	208*	−69·9
5. Seneciphylline	$C_{18}H_{23}O_5N$	217–8	−128·0 ($CHCl_3$)	—	—
6. Senecionine	$C_{18}H_{25}O_5N$	237*	−56·0 ($CHCl_3$)	218*	−34·2
7. Squalidine	$C_{18}H_{25}O_5N$	169	−26·9 ($CHCl_3$)	204	−8·65
8. Jacodine	$C_{18}H_{25}O_5N$	217	−109·6 ($CHCl_3$)	215	−77·4
9. Integerrimine	$C_{18}H_{25}O_5N$	171–2*	+4·3 (EtOH)	—	—
10. Platyphylline	$C_{18}H_{27}O_5N$	129*	−56·0 ($CHCl_3$)	—	—
11. Ridelline	$C_{18}H_{23}O_6N$	196*	—	—	—
12. Retrorsine	$C_{18}H_{25}O_6N$	216–7*	−18 (EtOE)	145*	−36·1
13. Jacobine	$C_{18}H_{25}O_6N$	223–4*	−46·3 ($CHCl_3$)	234	−28·6
14. Rosmarinine	$C_{18}H_{27}O_6N$	209*	−120·0 ($CHCl_3$)	218*	−93·75
15. Isatidine	$C_{18}H_{25}O_7N$	138–145*	−8·25 (H_2O)	130*	−23·0
16. Jaconine	$C_{18}H_{25}O_8N$	146*	—	—	—
17. Senecifoline	$C_{18}H_{27}O_8N$	194–5	+28·8 (EtOH)	240	−15·48
18. Mikanioidine	$C_{21}H_{29}O_6N$	Amorph	—	—	—

* All melting-points corrected (Kofler micromeltingpoint apparatus).

1, 2, 5, 6, 9, 11, 12, 13, 18: Manske (1931, 1939).
3, 4, 6, 10, 12, 14, 15: de Waal (1939, 1940 and this paper).
5, 10: Orechoff and Konowalowa (1935, 1936).
6, 7, 8, 15, 16: Barger and Blackie (1936, 1937).
17: Watt (1909).

The Necines and Necic Acids.

The following equations have been established for the hydrolysis of most of the above alkaloids as far as their hydrolytic products have been isolated and identified by the various workers:—

1. $C_{18}H_{23}O_5N + 2H_2O(KOH) = C_8H_{13}O_2N + C_{10}H_{14}O_5$.
   longilobine — retronecine — longinecic acid

2. $C_{18}H_{23}O_5N + 2H_2O(KOH) = C_8H_{13}O_2N + C_{10}H_{14}O_5$.
   seneciphylline — retronecine — seneciphyllic acid

3. $C_{18}H_{23}O_5N + H_2O(KOH) \rightarrow C_8H_{13}O_2N + C_{10}H_{16}O_6$.
   pterophine — retronecine — Pterophenecic lactone

4. $C_{18}H_{25}O_5N + H_2O(KOH) = C_8H_{13}O_2N + C_{10}H_{14}O_4$.
   senecionine — retronecine — senecic acid

5. $C_{18}H_{25}O_5N + 2H_2O(KOH) = C_8H_{13}O_2N + C_{10}H_{16}O_5$.
   integerrimine — retronecine — integerrinecic acid

6. $C_{18}H_{27}O_5N + H_2O(KOH) = C_8H_{15}O_2N + C_{10}H_{14}O_4$.
   platyphylline — platynecine — platynecic acid

7. $C_{18}H_{25}O_6N + 2H_2O(NaOH) = C_8H_{13}O_2N + C_{10}H_{16}O_6$.
jacobine — retronecine — jaconecic acid

8. $C_{18}H_{25}O_6N + 2H_2O(KOH) = C_8H_{13}O_2N + C_{10}H_{16}O_5$.
retrorsine — retronecine — retronecic acid

9. $C_{18}H_{27}O_6N + H_2O(BaO_2H_2) = C_8H_{15}O_3N + C_{10}H_{14}O_4$.
rosmarinine — rosmarinecine — senecic acid

10. (*a*) $C_{18}H_{27}O_6N + 2H_2O\ (BaO_2H_2) = C_8H_{13}O_3N + C_{10}H_{16}O_6$.
isatidine — isatinecine — isatinecic acid

(*b*) $C_{18}H_{27}O_6N + 2H_2O(KOH) = C_8H_{13}O_3N + C_{10}H_{16}O_6$.
isatidine — isatinecine — dewalinic acid

11. $C_{21}H_{29}O_6N_2 + H_2O(KOH) = C_8H_{15}O_2N + C_{13}H_{16}O_5$.
mikanioidine — mikanecine — mikanecic acid.

In Table 2 some of the best-known properties of the five "necine" bases and in Table 3 of the ten "necic" acids are tabulated.

TABLE 2.

Constants of the Bases (Alkanolamines).

Name.	Formula.	Form.	Corr. M.P.°C.	Spec. Rot.°	Corr. M.P.°C. (Picrate).
Retronecine(1)	$C_8H_{13}O_2N$	Cryst	121	+ 50 (EtOH)	142
Platynecine(1)	$C_8H_{15}O_2N$	Cryst	149	− 56·8 ($CHCl_3$)	189
Mikanecine(2)	$C_8H_{15}O_2N$	Oil	—	—	186
Isatinecine(1)	$C_8H_{13}O_3N$	Cryst	215	+ 22·5 (H_2O)	147
Rosmarinecine(1)	$C_8H_{15}O_3N$	Oil	—	—	175

TABLE 3.

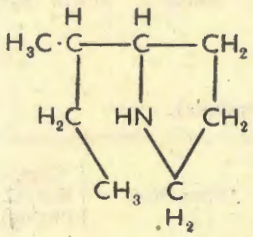
Constants of the "Necic" Acids.

Name.	Formula.	M.P. °C. (Corr.).	Spec. Rot.°
Senecic(1)	$C_{10}H_{14}O_4$	156	+ 41·8 (EtOH) + 45·0 ($CHCl_3$)
Platynecic(1) identical with senecic acid.			
Longinecic(2)	$C_{10}H_{14}O_5$	126–9	—
Seneciphyllic(2)	$C_{10}H_{14}O_5$	140–1	± 0
Integerrinecic(2)	$C_{10}H_{16}O_5$	151	—
Pterophnecic(1)	$C_{10}H_{16}O_6$	166·5	− 17·7 (H_2O)
Retronecic(1)	$C_{10}H_{16}O_6$	179·180	−11·36 (EtOH)
Jeconecic(3)	$C_{10}H_{16}O_6$	181 (uncorr.)	+ 31·7 (H_2O)
Isatinecic(1)	$C_{10}H_{16}O_6$	148·5	+ 88·2 (H_2O)
Dewalinic(1)	$C_{10}H_{16}O_6$	181	+ 56·0 (H_2O)
Mikanecic(2)	$C_{13}H_{16}O_5$	240	—

(1) Constants by de Waal (1939, 1940 and this paper).
(2) Constants by Manske (1931, 1936, 1939).
(3) Constants by Barger and Blackie (1937).

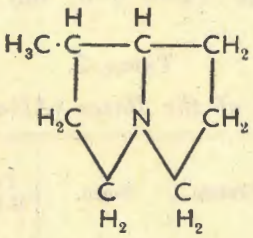
Structure of the Bases.

Menschikoff (1932) isolated from a Borraginaceae species, *Heliotropium lasiocarpum*, an alkaloid heliotrine ($C_{16}H_{27}O_5N$) which can be hydrolized to a base heliotridine ($C_8H_{13}O_2N$) and heliotrinic acid ($C_8H_{16}O_4$). From heliotridine Menschikoff prepared the saturated desoxygenated base heliotridane ($C_8H_{15}N$, 1933, 1935). Hofmann degradations of the latter by the same author, followed by catalytic hydrogenation, led to the isolation, at the second stage of the degradation process of △-dimethylamino-γ-methylheptane (Formula I, cited by Henry, 1939). He then proposed the methylpyrollizidine structure for heliotridane (II). The correctness of this formula was confirmed by the synthesis from 2-sec.-butyl-pyrrolidine (III) of methyl-pyrrollizidine (II), which was found to be identical with dl-heliotridane prepared from the basic fission product of the alkaloid heliotrine (1937, cited from Henry, 1939).



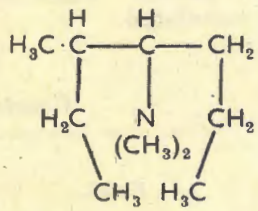
III.

($C_8H_{17}N$)



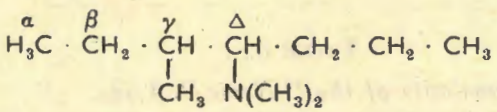
II.

($C_8H_{15}N$)



I.

Formula I can also be written :



i.e. △ — dimethylamino — γ — methylheptane.

From another alkaloid trichodesmine (from *Trichodesma incanum*, also a Borraginaceae species) Menschikoff obtained upon its hydrolysis the well-known Senecio base retronecine (1935), which is isomeric but not identical with heliotridine. Retronecine, which has one olefenic double bond and two hydroxyl groups, can be reduced similarly to heliotrine to the oxygen free base heliotridane (see Henry, 1939). The latter was finally also prepared by Orechoff and Konowalowa (1936), of the same Institute from platynecine. Provided the two saturated senecio bases rosmarinecine and mikanecine can also be reduced to heliotridane then four of the Senecio bases will have the same underlying pyrrolizidine structure. The fifth base, isatinecine however radically differs in its properties from those of the other four Senecio bases and must, therefore have a different structure.

Structure of Isatinecine.

In the second paper of this series (1940) the author recorded the ready consumption of four molecules of hydrogen by isatidine when this alkaloid was catalytically hydrogenated. The resulting reduced compound had the formula $C_{18}H_{31}O_6N$ and on hydrolysis yielded the base tetrahydro-isatinecine ($C_8H_{17}O_3N$) which is also obtained when isatinecine is catalytically hydrogenated (see experimental part). In the light of recent investigations this phenomenon can now be explained as follows. In isatidine the base isatinecine, containing two ethylenic double bonds, is esterified with isatinecic acid which has one ethylenic double bond and one peroxygen atom. The latter acid is a peracid and has one peroxygen atom in one percarboxylic group (R. CO. O. OH) and in addition it has one ordinary carboxylic group (R. CO. OH). When isatidine is, therefore, hydrogenated three molecules of hydrogen go to saturate two double bonds in the basic part of the molecule (isatinecine) and one double bond in the acidic part of the molecule (isatinecic acid).

(1) $C_{18}H_{25}O_7N + 4H_2 \xrightarrow[-O]{} C_{18}H_{31}O_6N + H_2O$.
isatidine — Hexahydro-desoxy-isatidine.

(2) $C_{18}H_{25}O_7N + 2H_2O = C_8H_{13}O_2N + C_{10}H_{16}O_6$.
isatidine — isatinecine — isatinecic acid.

(3) $C_{18}H_{31}O_6N + H_2O \rightarrow C_8H_{17}O_3N$.
hexahydro-desoxy-isatidine — tetrahydro-isatinecine.

(4) $C_8H_{13}O_3N + 2H_2 = C_8H_{17}O_3N$.
isatinecine — tetrahydro-isatinecine.

This result together with the previous structural results obtained for isatinecine (Part II, 1940) may now be summarized as follows:—

(1) Isatinecine has *two* olefenic double bonds.

(2) Isatinecine has *no* C-CH_3 group.

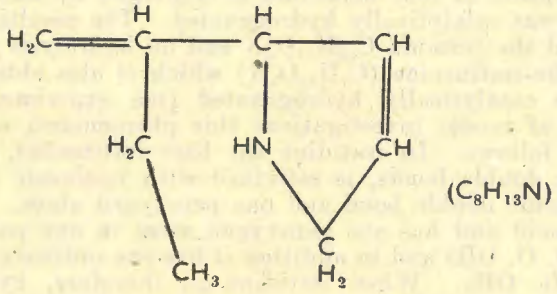
(3) Isatinecine has no N-CH_3 group.

(4) Neither isatinecine nor isatidine yields a methiodide derivative with methyliodide and has, therefore not a tertiary N-atom (contradictory to the other known senecio alkaloids).

(5) Both isatidine and isatinecine give positive tests for a pyrrole nucleus (a property similar to that possessed by all the other known senecio alkaloids).

These results prove beyond any doubt that the methylpyrrolizidine or pyrrolizidine structure is not present in isatinecine. Due to the absence of a tertiary N-atom in the molecule and the presence of a pyrrole ring and two olefenic double bonds the only explanation is, that the bicyclic ring system has been opened at the point of intersection where the N-atom is situated to form a monocyclic pyrrole-ringstructure. Such an arrangement will provide for the

introduction of the necessary amount of hydrogen atoms in the molecule and the presence of a secondary amino-group. A proposed structure as basis for isatinecine may thus be formulated as follows:—



IV.

Thus far we have been unable to determine the number of hydroxyl-groups in isatinecine. Retronecine and platynecine are dihydroxy-bases and if we assume that isatinecine has three hydroxyl-groups, then such three oxygen atoms can readily be introduced into the above formula. Such a hypothetical structure for isatinecine may explain why some of the properties exhibited by this base differ so radically from those shown by the other four senecio bases. Isatinecine, as well as its parent alkaloid isatidine, is readily soluble in water and insoluble in chloroform. Whereas all the other senecio alkaloids thus far isolated can be extracted from an alkaline solution with chloroform, isatidine remains dissolved in the aqueous alkaline solution.

Work is being continued on the structure of isatinecine with a view to the final elucidation of its structure.

The Peroxide Nature of Isatidine.

Another very remarkable difference in the properties of isatidine as compared with those of the other known senecio alkaloids is the presence of one peroxygen atom in the molecule which, as already stated, is easily removed upon the catalytic hydrogenation of isatidine.

$$C_{18}H_{25}O_7N \underset{-O}{+4H_2} \rightarrow C_{18}H_{31}O_6N \text{ (see Part II, 1940).}$$

This peroxygen atom is present in isatinecic acid as a free percarboxylic grouping (R. CO. O. OH). This peracid immediately liberates iodine from potassium iodide solution even in the presence of sodium carbonate. The acid slowly decomposes in air and readily forms a monolactone when isatidine is hydrolyzed under an excess of heat. In isatinecic monolactonic mono-carboxylic acid the percarboxylic group has lactonized and iodine is only liberated from acidified KI solution. The same applies to the alkaloid isatidine in which both the percarboxylic and ordinary carboxylic group must therefore be esterified apparently with two hydroxylgroups of the

base, isatinecine. When isatidine is hydrolyzed with alcoholic KOH, a migration of the peroxygen atom apparently takes place, since dewalinic acid thus obtained is an ordinary dicarboxylic acid.

Identity of Platynecic and Senecic Acid.

Orechoff (1935) isolated from *S. platyphyllus* the alkaloid platyphylline which can be hydrolyzed into platynecine and platynecic acid ($C_{10}H_{14}O_4$). The author and Tiedt (1940) isolated from *S. adnatus* the same alkaloid platyphylline and from this also prepared the same base platynecine and the same acid platynecic acid. In this paper the results of the hydrolysis of rosmarinine (isolated from *S. rosmarinifolius*, Part III, 1940) are recorded. The hydrolysis of rosmarinine yields a new base rosmarinecine ($C_8H_{15}O_3N$) and an acid, $C_{10}H_{14}O_4$, identical with platynecic acid, obtained from platyphylline above (ex *S. adnatus*).

Barger and Blackie (1936) and again Manske (1939) hydrolyzed pure senecionine and isolated from this alkaloid the base retronecine and an acid, senecic acid, $C_{10}H_{14}O_4$. A comparison of the properties of platynecic acid and senecic acid as found by these independent authors are as follows:—

	Senecic Acid. (Barger and Blackie, Manske).	Platynecic Acid. (Orechoff).	Platynecic Acid. (de Waal).
Formula	$C_{10}H_{14}O_4$	$C_{10}H_{14}O_4$	$C_{10}H_{14}O_4$
M.P. °C	153–4 (ether)	154–5 (benzol)	156* (benzol). 156* (water)
Spec. Rot	+ 41·9 (EtOH)	+ 37·9 (EtOH)	+ 41·8 (EtOH) + 45·0 ($CHCl_3$)
C–CH_3	3	—	—
—COOH	1	1	1
Lactone	1	—	1
—OH	Nil	1	Nil

* M.P. corrected.

Dr. Manske was kind enough to furnish the author with a specimen of senecic acid, which upon recrystallization from (*a*) water and (*b*) benzol gave no melting point depressions when mixed with pure specimens of platynecic acid prepared from platyphylline or rosmarinine and crystallized from either water or benzol. The acid is not obtained pure when crystallized from ether.

The identity of senecic and platynecic acid was further established by the catalytic hydrogenation of platynecic acid (author's specimen). The consumption of hydrogen immediately stopped when one molecule of hydrogen had been consumed and the isolated product had all the properties of dihydro-senecic acid (Barger and Blackie, 1936). As the latter authors admit that their hydro-senecic acid was impure (micro-hydrogenation) 1·5 gm. of pure dihydro-senecic acid, which was found to melt at 120° C., was prepared.

We suggest that the name " platynecic " acid should not be used in future but *senecic* acid, as the latter was obtained previous to " platynecic " acid by the hydrolysis of senecionine.) Orechoff described his acid as a monohydroxymonocarboxylic acid of which the function of the fourth oxygen atom was not known. This should be corrected to a monolactonic-monocarboxylic acid for senecic acid, of which the function of all the four oxygen atoms are therefore known.

Experimental Part.

Rosmarinine.

(1) Rosmarinine (see Part III, 1940) readily formed a methiodide when a solution of the alkaloid in hot chloroform and methanol was treated with an excess of methyl-iodide. As the reaction mixture cooled down crystals of rosmarinine-methiodide were deposited, which when recrystallized from alcohol melted at 251° C. (decomp).

*Micro-analysis :**

3·455 mgm. : 5·830 mgm. CO_2 and 1·828 mgm. H_2O.
Calc. for $C_{18}H_{27}O_6N$. CH_3J : C 46·07%; H 6·10%.
Found : C 46·02%; H 5·92%.

(2) Rosmarinine did not form a picrate.

(3) Rosmarinine gave positive tests for a pyrrole.

(4) 5·2 gm. Rosmarinine dissolved in 120 ml. decinormal HCl readily consumed one molecule of hydrogen only upon catalytic hydrogenation.

Theory for 1 mol. H_2 330 m.l. H_2 at N.T.P.
Found 340 m.l. H_2 at N.T.P.

Hydrolysis of Rosmarinine.

Rosmarinine can be hydrolyzed with either alcoholic KOH or aqueous bariumhydrate but the hydrolysis with bariumhydrate gave better results.

8 gm. Rosmarinine suspended in 150 ml. of water was refluxed for 4 hours with 6·5 gm. bariumhydrate ($BaO_2H_2 \cdot 8\,H_2O$). The filtrate was neutralized against phenolphthalein with H_2SO_4 ($1:4H_2O$), the $BaSO_4$ centrifuged off and the clear supernatant liquid evaporated to dryness on a waterbath.

(*a*) *Isolation of the Base, Rosmarinecine.*

The dry residue was extracted three times with hot ethanol which removed the base. All attempts to isolate a crystalline base failed. The base, however, readily formed a picrate. The alcoholic solution was, therefore, again evaporated to dryness and the dry residue again extracted with warm ethanol. To the warm filtrate a slight excess of a solution of picric acid in ethanol was added. Yellow needles immediately separated. After the crystallization had completed the crystalline mass was filtered off, dried and recrystallized from alcohol. Rosmarinine-picrate melted sharply at 175°.

* Micro-analyses by Dr. O. G. Backeberg, University, Johannesburg.

Micro-analysis:

3·414 mgm.: 5·319 mkm. CO_2 and 1·360 mgm. H_2O.

3·301 mgm.: 0·491 ml. N_2 at 23° C. and 625 mm. Hg.

Cal. for $C_8H_{15}O_3N.C_6H_3N_3O_7$:

C = 41·80%; H = 4·50%; N = 13·92%.

Found:

C = 42·29%; H = 4·46%; N = 13·47%.

The free base has, therefore the formula $C_8H_{15}O_3N$ and could be regenerated from the picrate but was again obtained only as an oily substance. It did not form a nitrate or a hydrochloride.

(*b*) *Isolation of Senecic Acid.*

After the removal of the base with ethanol the residue was dissolved in a small volume of water, the solution acidified with H_2SO_4 (1 : 4 H_2O) until it was just acid to congo-red, the $BaSO_4$ centrifuged off and the clear supernatant evaporated to dryness on a waterbath.

The dry residue was repeatedly stirred with dry ether until no more substance was dissolved. The combined ether extracts were allowed to evaporate at room temperature in an open dish. The crystalline residue can be recrystallized either from benzol or from water, yielding prismatic crystals or fine silkish needles respectively. The melting-point in either case was 156° and the acid is a monolactonic, monocarboxylic acid identical with platynecic acid obtained from platyphylline (Part IV, 1940) and senecic acid supplied by Dr. Manske and obtained from senecionine (1939).

Micro-analysis:

3·652 mgm.: 8·090 mgm. CO_2 and 2·292 mgm. H_2O.

Calc. for $C_{10}H_{14}O_4$: C = 60·60%; H = 7·07%.

Found: C = 60·41%; H = 7·02%.

Hydrogenolysis of Rosmarinine.

A solution of 4 gm. of rosmarinine in 60 ml. 0·5 N HCl was hydrogenated in the presence of 100 mgm. PtO_2 as catalyst. After $2\frac{1}{2}$ hours the hydrogen consumption was completed with an absorption of 1 mol. of hydrogen. The hydrochloride of dihydrorosmarinine did not crystallize, did not form a crystalline nitrate and similar to rosmarinine did not form a picrate.

The acid filtrate, after the hydrogenation, was, therefore, neutralized with solid $Ba(OH)_2 \cdot 8H_2O$ and 1·2 mol. of this alkali added in excess. After the solution had been refluxed for 4 hours the filtrate was titrated with H_2SO_4 (1: 4 H_2O) until it was just acid to phenolphthalein. The $BaSO_4$ was centrifuged off, the supernatant decanted and evaporated on a waterbath and the dry residue extracted with ethanol. From the ethanol solution *rosmarinecine-picrate* was prepared and isolated as described above. The basic part of the alkaloid molecule, therefore, remained unchanged during the hydrogenation and rosmarinine is, therefore, a saturated necine base.

From the residue after the extraction of the base dihydro-senecic acid was isolated following the process described further above and was found to be identical with the dihydrosenecic acid obtained upon the hydrogenation of senecic acid. In addition the hydrogenated acid exhibited all the properties of dihydrosenecic acid described by Barger and Blackie (1936). The m.p. of the pure acid (from ether) is 120° and not 106° (as recorded by the above authors for the impure acid).

Fig. 1.—Senecic acid (benzol)×14. M.P. 156° C.

Pterophine.

(*a*) *The isolation from* S. pterophorus D.C.

This plant grows abundantly in the whole of the Transkei and further west to East London. The plants used in this investigation were gathered near the Centuli Location (Umtata district, Transkei), in the pre-flowering and again in the flowering stages in October, and November, 1939, respectively.

6·5 Kg. of the dried and ground plantmaterial was filled into linen bags, introduced into the large extractor (see Fig. 3) and extracted on the Soxhlett-principle with 96 p.c. alcohol for about 4 days.

The alcohol was then distilled off and the last traces of alcohol removed under reduced pressure on a steambath. The residue was acidified with an aqueous solution of citric acid, shaken and the precipitate allowed to settle down. The filtrate was then thoroughly shaken with ether, the ether discarded and the residual ether expelled from the clear acid filtrate by a current of air. Ammonium hydrate (5 p.c. solution) was then added until the solution was positively

alkaline and the alkaline solution thoroughly and repeatedly shaken with chloroform. The chloroform dissolved two alkaloids and an investigation of the ammoniacal liquors proved the absence of any chloroform-insoluble alkaloids.

The chloroform solution was washed with water once, and allowed to evaporate before a fan at room temperature, the crystalline residue dried and washed with cold acetone. The colourless crystalline residue (about 12 gm.) was crystallized from approximately 500 ml. ethanol. The m.p. of the crystals was not sharp (215-220°). It was a mixture of retrorsine and a new alkaloid pterophine in the proportion of approximately 1 : 70 (determined by the preparation of their nitrates, their separation followed by their weight determinations).

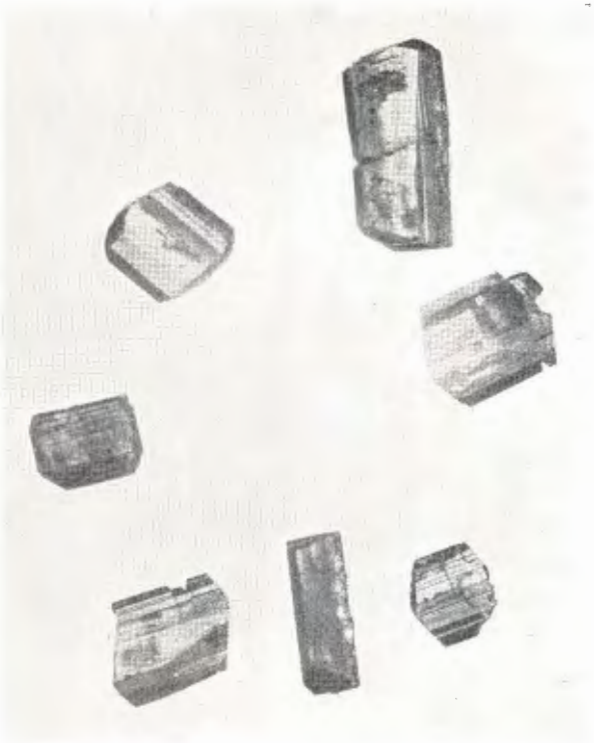


Fig. 2.—Senecic acid (water)×15. M.P. 156° C.

Pure pterophine was obtained free from admixed retrorsine by at least six fractional recrystallizations from ethanol. It can also be obtained pure very conveniently by the titration of the alkaloid mixture with decinormal nitric acid until just acid to Congo-red. The faintly acid solution was evaporated before the fan and the crystalline residue dissolved in hot ethanol. Ether was then cautiously added to the alcoholic solution until a final addition would just allow the turbidity caused to disappear on gentle shaking. The

nitrates of the two alkaloids crystallized from this solution. Retrorsine nitrate crystallized in fine silkish needles and pterophine nitrate in heavy monoclinic prisms. The former could be readily washed away from the latter with ether in which retrorsine nitrate floated about and could thus be decanted from the heavier and much larger amount of pterophine (Ratio approx. 1 : 70). The m.p. of pure pterophine was 227-8° (decomp) and of its nitrate 208° (decomp). Retrorsine nitrate $\cdot\frac{1}{2}$ C_2H_5OH melted at 110° and decomposed at 145°.

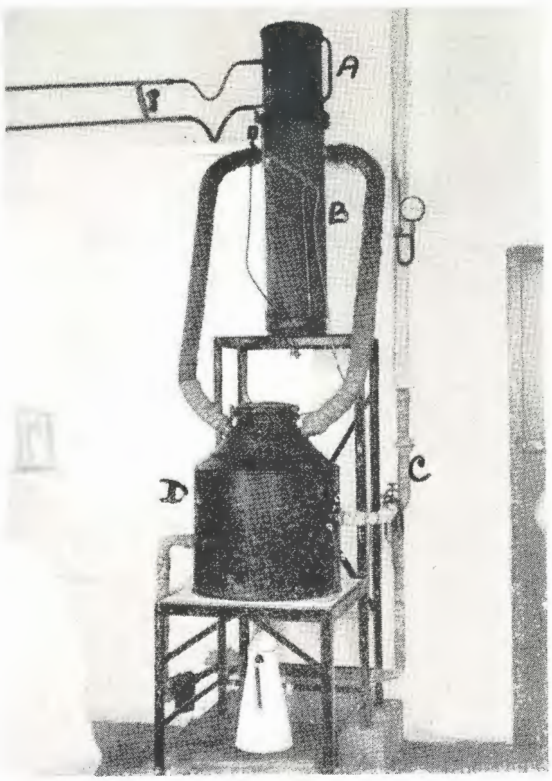


Fig. 3.

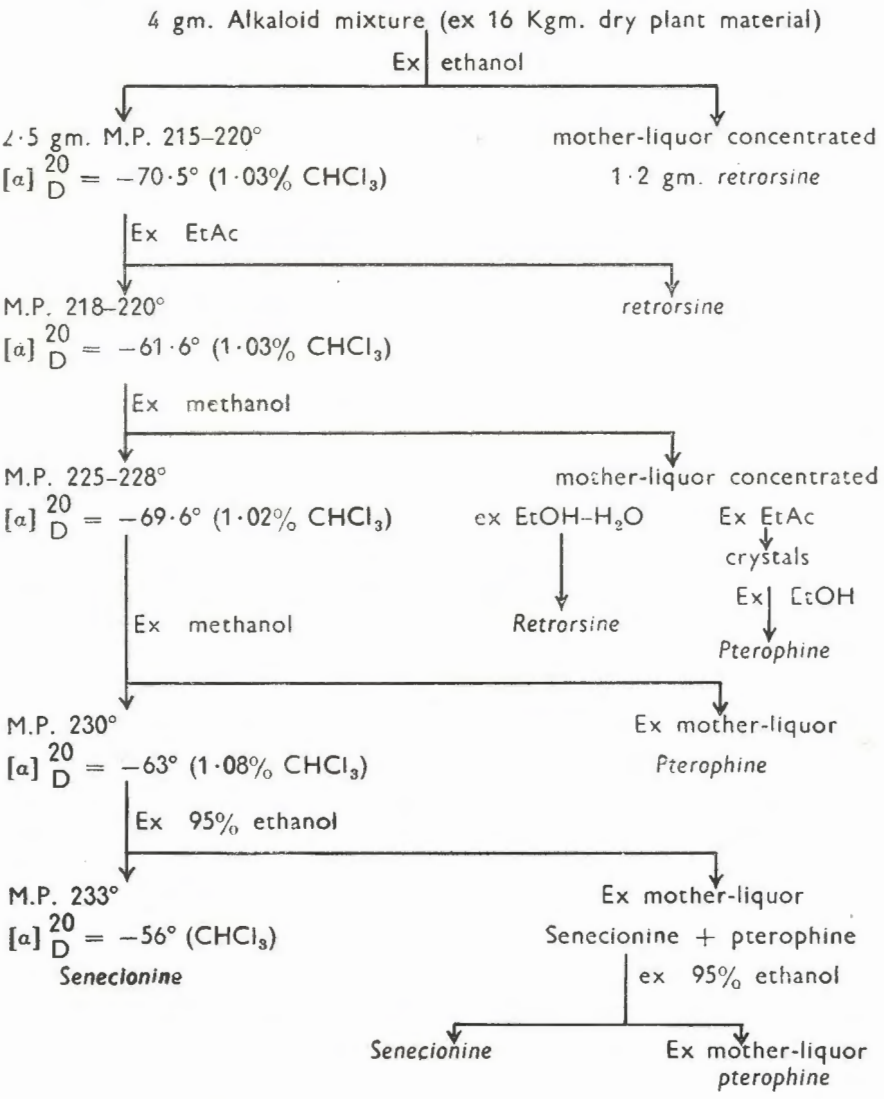
A=Chilled water condensor.
B=Plant container.
C=Steampipe.
D=Solvent container.

(*b*) *The Isolation from* S. ilicifolius *Thunb.*

This plant is the cause of breadpoisoning in the Cape South Western districts and was collected in the post-flowering stage in December, 1938.

7·0 Kgm. of dried and ground plantmaterial was filled in bags and extracted with 96 p.c. alcohol in the large extractor. The isolation of the alkaloids from the alcohol-free extract was similar to that applied in the case of *S. pterophorus*. Either 3 p.c. hydrochloric acid or citric acid can be used as a solvent.

Chloroform removed three alkaloids whilst there were no alkaloids present in the ammoniacal solution after its thorough extraction with chloroform. The alkaloids are retrorsine, senecionine and pterophine which were separated as follows:—



Properties of Pterophine.

(1) Pterophine is a new senecio alkaloid and gives positive tests with the usual alkaloidal reagents. It is very bitter and when injected subcutaneously in quantities of 25 mgm. into rats caused their death within 24 hours from acute liver cirrhosis.

(2) Pterophine decolourizes soda-alkaline potassium-permanganate solution.

(3) Pterophine melts with decomposition at 227-8°. The resulting melt gives a positive test for the pyrrole nucleus, an indication that a hydro- or hydroxy-pyrrole is present in the parent base.

(4) Pterophine dissolves colourless in conc. H_2SO_4 and other mineral acids. It is sparingly soluble in cold water. It is soluble in methanol, ethanol, ethyl acetate, chloroform and benzol; it is slightly soluble in acetone and ether and insoluble in petroleum-ether.

(5) *Specific Rotation* :—

$[\alpha]_D^{18}$ 88·5° (1·875% in chloroform).

(6) *Micro-analysis* :—

(*a*) 3·575 mgm.: 8·429 mgm. CO_2 and 2·194 mgm. H_2O.
3·191 mgm.: 0·149 ml. N_2 at 22·5° C. and 625 mm. Hg.

(*b*) 3·397 mgm.: 8·009 mgm. CO_2 and 2·058 mgm. H_2O.
2·959 mgm.: 0·135 ml. N_2 at 20° C. and 627 mm. Hg.

Calc. for $C_{18}H_{23}O_5N$: C 64·85%; H 6·96%; N 4·20%.

Found (*a*): C 64·30%; H 6·87%; N 4·42%.

Found (*b*): C 64·30%; H 6·78%; N 4·44%.

$\therefore$ $C_{18}H_{23}O_5N$.

The alkaloid is isomeric with seneciphylline, longilobine, spartioidine and graminifoline.

(7) Pterophine has no peroxygen structure and does not react with diazomethane or phenyl-isocyanate.

Properties of Derivatives of Pterophine.

(1) *Pterophine-picrate*, was obtained when the ethanolic solutions of the two components were mixed. Crystals were soon deposited which when recrystallized from methanol (yellow needles) melted at 190°.

Micro-analysis :

3·685 mgm.: 6·946 mgm. CO_2 and 1·513 mgm. H_2O.

3·569 mgm.: 0·389 ml. N_2 at 23° C. and 626 mm. Hg.

Calc. for $C_{18}H_{23}O_5N$. $C_6H_3N_3O_7$:
C 51·25%; H 4·65%; N 9·96%.

Found:
C 51·41%; H 4·59%; N 10·35%.

(2) *Pterophine-nitrate* melted at 208° and has an $[\alpha]_D^{20} = -69·9°$ (1·21% in water).

Micro-analysis :

(*a*) 3·655 mgm.: 7·284 mgm. CO_2 and 1·911 mgm. H_2O.

(*b*) 3·504 mgm.: 7·008 mgm. CO_2 and 1·900 mgm. H_2O.

Calc. for $C_{18}H_{23}O_5N$. HNO_3: C 54·54%; H 6·10%.

Found (*a*): C 54·35%; H 5·85%.

Found (*b*): C 54·54%; H 6·17%.

(3) *Pterophine-methiodide.*—To a warm solution of pterophine in chloroform an excess of methyliodide was added. The solution, which after 24 hours contained a few crystals of the desired product, was evaporated in front of a fan and the crystalline residue recrystallized from 95 p.c. ethanol. The colourless prismatic crystals melted at 260° (decomp).

Micro-analysis:

(*a*) 3·759 mgm.: 6·609 mgm. CO_2 and 1·858 mgm. H_2O.

(*b*) 3·563 mgm.: 6·252 mgm. CO_2 and 1·761 mgm. H_2O.

3·292 mgm.: 0·114 ml. N_2 at 23·5° C. and 625 mm. Hg.

Calc. for $C_{18}H_{23}O_5N.CH_3J$:

C = 48·00%; H = 5·52%; N = 2·95%.

Found (*a*): C = 47·95%; H = 5·53%.

Found (*b*): C = 47·86%; H = 5·53%; N = 3·30%.

Hydrolysis of Pterophine.

To a solution of 2·2 gm. pterophine in 100 ml. hot ethanol a solution of 1 gm. KOH in 2 ml. water was added. The mixture was refluxed for 1½ hours and the solvent then evaporated on a waterbath.

(*a*) *Isolation of the Base, Retronecine.*—The dry residue was extracted several times with a small volume of acetone until the acetone extract gave no turbidity on the addition of petroleum-ether. The acetone solution was evaporated to dryness and the dry residue washed with cold ethyl-acetate followed by ether. The remaining crystalline material was recrystallized from acetone. M.p. 121°. The base was retronecine and showed no melting point depression when admixed with an authentic sample of retronecine.

Micro analysis:

3·266 mgm.: 7·424 mgm. CO_2 and 2·290 mgm. H_2O.

3·359 mgm.: 0·324 ml. N_2 at 22·5° C. and 625 mm. Hg.

Calc. for $C_8H_{13}O_2N$: C = 61·92%; H = 8·44%; N = 9·02%.

Found: C = 61·99%; H = 7·85%; N = 9·16%.

(*b*) *Isolation of Pterophnecic Lactone.*—The residue after the base had been extracted with acetone was dissolved in a small volume of water and the solution acidified with conc. HCl (1 : 1) until it was just acid to Congo-red. The precipitate was centrifuged off and the clear supernatant liquid evaporated in front of a fan. The residue was dried in a vacuous desiccator over conc. H_2SO_4. The dry residue was then extracted with ethyl-acetate (five times) until the solution gave no turbidity on the addition of petroleum-ether. The ethyl-acetate solution was concentrated when the lactone crystallized. Recrystallized from equal volumes of ethanol and ether the lactone melted sharply and colourless at 166·5°. Upon a second hydrolysis of pterophine it was found more convenient to extract the lactone with ethanol.

Properties of Pterophnecic Lactone.

The acid fission product of pterophine thus obtained has one lactone group which can be saponified with decinormal alcoholic KOH and back titrated with decinormal HCl. It has no free carboxyl-radicle, does not taste acid but has a bitterish taste. It has $[\alpha]_D^{20} = -17{\cdot}7$ (1·0% in water).

Micro-analysis:

(*a*) 3·438 mgm.: 6·318 mgm. CO_2 and 2·189 mgm. H_2O.

(*b*) 3·508 mgm.: 6·476 mgm. CO_2 and 2·176 mgm. H_2O.

Calc. for $C_{10}H_{16}O_6$: C=51·67%; H=6·94%.

Found (*a*): C=50·21%; H=7·13%.

Found (*b*): C=50·35%; H=6·94%.

The formula and nature of this lactone is still doubtful and will be verified as soon as more material becomes available.

Senecio graminifolius Jacq.

This senecio plant occurs frequently in the Griqualand East and Transkeian areas. It contains two alkaloids, retrorsine and a new alkaloid graminifoline (probably $C_{18}H_{23}O_5N$). The yield of retrorsine is 0·5 per cent. (calculated on the dried and ground plantmaterial, pre-flowering stage) but the yield of graminifoline is very small, approximately 0·0005 per cent. The composition and properties of the latter alkaloid is still uncertain and awaits further identification. Meanwhile *S. graminifolius* can be considered a poisonous senecio variety if only on account of the large amount of the toxic alkaloid retrorsine present in this plant.

Summary.

1. Isatinecine has a pyrrole nucleus and has no tertiary nitrogen atom. It must, therefore have a secondary aminogroup. The pyrrollizidine structure applicable to the two senecio bases retronecine and platynecine is, therefore, not present in isatinecine and, therefore, also not in isatidine (no tert. N-atom).

2. Isatinecine has two double bonds, the introduction of which into the pyrrolizidine molecule is not compatible with the empiric formula for isatinecine. In agreement with these properties a basic structure for isatinecine is proposed, in which the pyrrolizidine bicyclic system has opened at the point of intersection where the N-atom is situated.

3. Isatidine has one peroxygen atom which is present in the esterifying acid, isatinecic acid, which is a free peracid with one percarboxylgroup (R. CO. O. OH) which readily lactonizes.

4. The isolation of a new alkaloid pterophine is described. It has the formula $C_{18}H_{23}O_5N$, m.p. 227 – 8° C. and $[\alpha]_D^{18} = -88{\cdot}5$ (1·875% in $CHCl_3$). The alkaloid is present in both *S. pterophorus* and *S. ilicifolius* and is toxic.

5. Pterophine has a pyrrole nucleus and a tertiary N-atom which readily forms a methiodide. The nitrate and the picrate of the alkaloid have also been prepared.

6. Upon the hydrolysis of pterophine with alcoholic potash it yields the well-known senecio base retronecine and a new acid lactone (probably $C_{10}H_{16}O_6$).*

7. The hydrolysis with bariumhydrate of the new senecio alkaloid rosmarinine is described. The fission products are a new base rosmarinecine ($C_8H_{13}O_3N$) and senecic acid, $C_{10}H_{14}O_4$. Rosmarinine has a tertiary N-atom, which forms a methiodide and has the pyrrole nucleus.

8. Platynecic acid (the necic acid of platyphylline) is identical with senecic acid (the necic acid of senecionine and rosmarinine).

9. Besides retrorsine, *S. graminifolius* contains a new alkaloid, graminifoline (probably $C_{18}H_{23}O_5N$) in very small amounts.

10. Retrorsine is also present in *S. pterophorus* and *S. ilicifolius*.

ACKNOWLEDGMENT.

In conclusion I wish to express my sincere thanks to Dr. T. J. Wilken-Jorden, Chief Chemist of the South African Iron and Steel Corporation, Ltd., Pretoria, for his keen interest and constructive criticism.

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* *Author's note.*—Since this article had been submitted to the press it was found that this acid exhibits a dualism, one form of which is most likely identical with seneciphyllic acid, $C_{10}H_{14}O_4$.

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