Anal. Calcd. for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37; N, 3.79. Found: C, 58.63; H, 7.26; N, 3.87.

In order to establish the stability of the tetrahydrograntianine to strong acid, the rotation solution was acidified with 0.1 ml. of concentrated hydrochloric acid and the rotation determined immediately, $[\alpha]^{27}D$ −54.0°. The rotation did not change after the solution stood at room temperature for 20 hr. A paper chromatogram of a sample of this solution, after treatment on the paper with ammonia vapors to set the base free, gave only one spot, R_f 0.29.

Reduction of a second sample of grantianine, which was permitted to remain in contact with hydrogen and the catalyst for 24 hr., gave the same product.

The picrate of tetrahydrograntianine was prepared from equivalent amounts of the base and picric acid in water. The product was purified from ethanol by addition of a little ether, m.p. 195–196°. *Anal.* Calcd. for $C_{18}H_{27}NO_7 \cdot C_6H_3N_3O_7$: C, 48.16; H, 5.01. Found: C, 48.36; H, 5.23.

Microtest for Character of Alkaloid Reduction Products. – Two types of reduction products have been obtained from pyrrolizidine alkaloids, dependent on the structure of the alkaloids. The one is represented by salts where both ester linkages have been cleaved; the second by intramolecular salts formed by cleavage of only one ester group.

A few mg. of the hydrogenated product is dissolved in 1–2 ml. of water and the *p*H of the solution is tested. The *p*H is tested again after a few mg. of Dowex 50 in the hydrogen phase is added. If the compound corresponds to the first type, the *p*H changes toward more acidic values; if it corresponds to the second type no change in *p*H is observed.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF PRETORIA AND THE POST GRADUATE MEDICAL SCHOOL, NEW YORK UNIVERSITY]

The Structure of Sceleratine, an Alkaloid from *Senecio sceleratus*

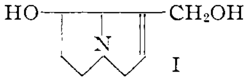
BY H. L. DE WAAL AND BENJAMIN L. VAN DUUREN[1]

RECEIVED FEBRUARY 9, 1956

Structural studies earlier conducted on sceleratine, sceleranecic dilactone and sceleratinic dilactone are re-evaluated. Sceleranecic dilactone is shown to be α,δ-dihydroxy-α-hydroxymethyl-γ-carboxy-β,γ-dimethylcaproic acid, γ,δ-dilactone (VI) and sceleratinic dilactone is the corresponding chloride X. Infrared data supporting these structures are discussed.

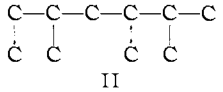
The toxic plant *Senecio sceleratus* which occurs in the Northern Transvaal region of South Africa has been known for many years to be responsible for cattle poisoning.[2] Chemical investigations revealed the presence of three alkaloids in this plant.[2] The structures of two of these alkaloids, retrorsine (β-longilobine) and its N-oxide isatidine have since been elucidated.[3] The third alkaloid, $C_{18}H_{27}O_7N$, was named sceleratine.

Aqueous alkaline hydrolysis of sceleratine gave retronecine (I) which is obtained by the hydrolysis of many pyrrolizidine alkaloids[3] and a new optically active substance, $C_{10}H_{14}O_5$, which was named sceleranecic dilactone. Hydrogenolysis of the alkaloid with platinum as catalyst gave the known base retronecanol (Ia) and the same dilactone. Sceleranecic dilactone was later found to occur as such in *Senecio sceleratus*, together with an apparently closely related compound, $C_{10}H_{13}O_4Cl$, which was named sceleratinic dilactone.[4]

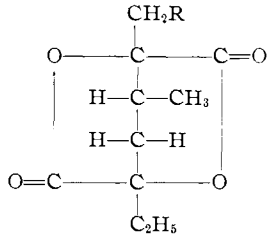


I

In previous studies of pyrrolizidine alkaloids only those alkaloids containing acid moieties with the same carbon skeletal structure were found in the same plant.[3] On this basis sceleranecic dilactone would be expected to have the same carbon skeleton, II, as retronecic acid, the acid moiety in the alkaloid retrorsine. Combining this assumption with the available experimental evidence, [2,4–6] structures IIIa and IIIb were suggested[6] for sceleranecic and sceleratinic dilactones, respectively.



II



IIIa, R = OH
b, R = Cl

Several objections can be raised to these structures. Thus an examination of the Kuhn–Roth carbon–methyl results[2,4–6] indicates the presence of three rather than two CH_3–C groups in IIIa and IIIb. It is known that these values are often too low.[7] In addition the behavior of sceleranecic and sceleratinic dilactones on neutralization with alkali cannot be satisfactorily accounted for by a structure containing two six-membered lactone groupings. Furthermore, the α,α′-dihydroxyadipic acid structure III would be expected to give, on oxidation with alkaline potassium permanganate or aqueous lead tetraacetate, a smaller molecule than the C-8 acid actually obtained from IIIa and IIIb by these oxidation procedures.

In view of these considerations it seemed desirable to re-evaluate the experimental results presented in the earlier papers without making any assumptions with respect to carbon-skeletal structure.

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[1] To whom inquiries should be sent at 550 First Avenue, New York 16, N. Y.

[2] H. L. de Waal and T. P. Pretorius, *Onderstepoort J. Vet. Sci. Animal Ind.*, **17**, 181 (1941).

[3] For a recent review see: R. Adams, *Angew. Chem.*, **65**, 433 (1953).

[4] H. L. de Waal and D. F. Louw, *Tydskrif vir Wetenskap en Kuns*, **10**, 171 (1950).

[5] H. L. de Waal and A. Crous, *J. S. African Chem. Inst.*, **1**, 23 (1948).

[6] H. L. de Waal, W. J. Serfontein and C. F. Garbers, *ibid.*, **4**, 115 (1951).

[7] E. J. Eisenbraun, S. M. McElvain and B. F. Aycock, THIS JOURNAL, **76**, 607 (1954).

Sceleranecic dilactone required two moles of alkali for neutralization.[1] The first mole of alkali was consumed on standing at room temperature. A second mole of alkali was neutralized only on refluxing the substance with an excess of alkali. A free dicarboxylic acid could not be isolated. This experiment indicates the absence of free carboxyl groups and the presence of two lactone groups which differ markedly in their stability. It is conceivable that a difference in the rate of hydrolysis of the two lactone groups may be due to a difference in the nature of the hydroxyl groups involved. However, it has been shown recently[8] that the rate of hydrolysis of lactones, especially γ-lactones, is not much affected by the nature of the hydroxyl groups. The most reasonable conclusion therefore is that sceleranecic dilactone contains one five-membered and one six-membered lactone grouping.

The presence of a primary hydroxyl group in sceleranecic dilactone was shown by the formation of a monobenzoate,[5] a monoacetate[5] and by the formation of a new acid, $C_{10}H_{12}O_6$, on oxidation of sceleranecic dilactone with nitric acid.[5] This new acid required three moles of alkali for neutralization. The first mole was neutralized instantaneously, a second mole of alkali was consumed on standing at room temperature and a third mole was used on refluxing the acid with an excess of alkali. This acid gave a monomethyl ester on treatment with diazomethane.[5] The $C_{10}H_{12}O_6$ acid therefore contains one free carboxyl group and the same two lactone groups present in sceleranecic dilactone. This acid then is derived from sceleranecic dilactone by oxidation of a primary hydroxyl group, which exists as such in sceleranecic dilactone, to a carboxyl group.

The reported results of carbon-methyl analyses[2,4-6] are listed in Table I. These results indicate that three CH_3–C groups are present in sceleranecic dilactone and the compounds derived from it.

TABLE I

CARBON-METHYL DETERMINATIONS

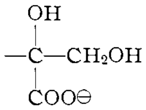
Compound	Calculated for 2 CH_3–C	Calculated for 3 CH_3–C	Found % CH_3–C	Found Number of CH_3–C groups
Sceleranecic dilactone	25.2	37.8	31.1	2.5
Sceleratinic dilactone	23.2	34.8	28.7	2.5
Acid, $C_{10}H_{12}O_6$	23.4	35.5	30.4	2.6

De Waal and Crous[5] reported that acetone could not be isolated from the chromic acid oxidation of sceleranecic dilactone. For this determination Rimington's oxidation procedure[9] was used. This result suggested the absence of *gem*-dimethyl groups.

Oxidation of dipotassium sceleranecate, obtained by the hydrolysis of sceleranecic dilactone, with an aqueous solution of lead tetraacetate gave formaldehyde identified as its 2,4-dinitrophenylhydrazone, carbon dioxide and a new optically active acid, $C_8H_{12}O_4$.[6] This acid required two moles of alkali for neutralization. The first mole of alkali was neutralized instantaneously and the second on refluxing the acid with an excess of alkali.[5] A Zerewitinoff determination on the $C_8H_{12}O_4$ acid showed the presence of one active hydrogen.[5] This acid therefore contains one free carboxyl group and one five-membered lactone grouping. The free hydroxy-dicarboxylic acid could not be isolated. The carbon-methyl analysis[5] gave 1.5 CH_3–C groups which is lower than that expected for the structure derived for this compound.

The same $C_8H_{12}O_4$ acid was also obtained by the aqueous alkaline potassium permanganate oxidation of sceleranecic dilactone, by the lead tetraacetate oxidation of sceleratinic dilactone and by the chromic acid oxidation of the $C_{10}H_{12}O_6$ acid discussed above.[5]

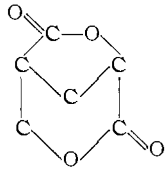
The formation of carbon dioxide and formaldehyde during the lead tetraacetate oxidation of sceleranecic dilactone is ascribed to the presence of the grouping



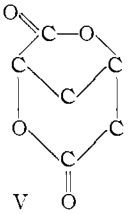
$$-\overset{\displaystyle OH}{\underset{\displaystyle COO^{\ominus}}{\overset{|}{\underset{|}{C}}}}-CH_2OH$$

in dipotassium sceleranecate.

Since sceleranecic dilactone evidently contains three CH_3–C groups and one hydroxymethyl group not involved in either of the two lactone structures, the dilactone structure must be accommodated by a skeleton containing six carbon atoms. Starting from either the γ- or the δ-lactone only two partial structures can be written for the dilactone in such a manner that one α-hydroxy acid grouping is present, *viz.*, IV and V.

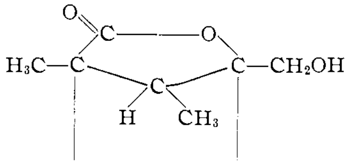


IV

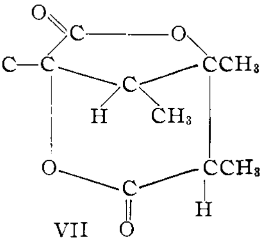


V

The hydroxymethyl group can be placed in only one position in each structure. This leaves only three possible positions for the three methyl groups, so that the two complete structures derived from IV and V are VI and VII, respectively.



VI



VII

Structure VII would be expected to give on oxidation with lead tetraacetate or alkaline permanga-

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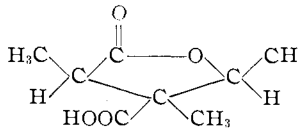
[8] C. M. Stevens and D. S. Tarbell, *J. Org. Chem.*, **19**, 1996 (1954).

[9] C. Rimington, *Onderstepoort J. Vet. Sci. Animal Ind.*, **4**, 80 (1935).

nate β-hydroxy-α,β,γ-trimethylglutaric acid. Since the acid actually obtained by these oxidations contains a stable lactone, structure VII is ruled out and structure VI becomes the only acceptable structural formula for sceleranecic dilactone.[10]

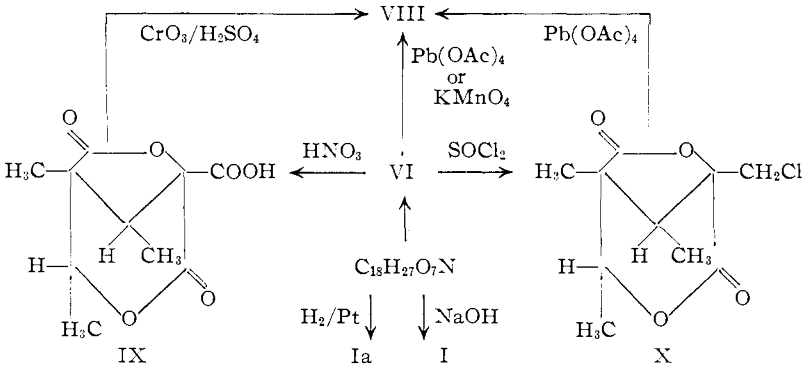
The $C_8H_{12}O_4$ acid therefore is α,β-dimethyl-β-carboxy-γ-valerolactone (VIII).



VIII

Sceleratinic dilactone which occurs in *Senecio sceleratus*[3] was obtained from sceleranecic dilactone by treatment with thionyl chloride or phosphorus pentachloride.[4] On neutralization with alkali this compound behaves the same as sceleranecic dilactone from which it is concluded that these two compounds contain the same dilactone structure. Oxidation of sceleratinic dilactone with lead tetraacetate gave VIII. Sceleratinic dilactone is therefore best represented by structure X (Chart I).

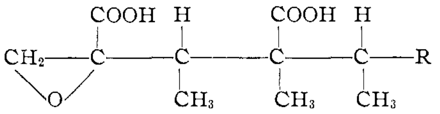
CHART I



The retention of the secondary hydroxyl group of the $C_{10}H_{12}O_6$ acid, IX, during its oxidation to VIII with chromic acid is not unlikely in view of the ready lactonization of the resultant γ-hydroxy acid.

Further confirmation of the above structures is provided by additional experiments reported earlier.[6] Thus it was found that treatment of sceleratinic dilactone with alkali gave a new acid, $C_{10}H_{16}O_6$. This acid contains two free carboxyl groups and is best represented as the corresponding epoxy acid, XIa. This experiment clearly indicates that the stable γ-lactone of sceleranecic dilactone is formed by lactonization at the tertiary hydroxyl group. The fact that a six-membered lactone did not form spontaneously from XIa is not surprising since δ-lactones are usually formed only on heating, either alone or in the presence of acid.

The dipotassium salt of XIa on treatment with thionyl chloride gave a new chloro acid, $C_{10}H_{15}O_5Cl$,[6] which was not further characterized but is probably correctly represented by structure XIb.



XIa, R = OH
b, R = Cl

Additional support for the structures presented in this paper was obtained from a study of the infrared absorption spectra. The pertinent bands and their probable assignments are given in Table II. In addition it was noticed that sceleratinic dilactone shows only minor peaks in the region 1000–1100 cm.$^{-1}$. Sceleranecic dilactone shows a strong band at 1050 cm.$^{-1}$. Absorption in this region is usually associated with the OH (primary) deformation mode.[11] The absorption spectrum of VIII shows no band in the region 1140–1160 cm.$^{-1}$. Sceleranecic dilactone, sceleratine and sceleratinic dilactone all show bands in the region 1140–1160 cm.$^{-1}$ which is indicative of the OH (tertiary) deformation mode.[11] A more detailed analysis of the 1300–1000 cm.$^{-1}$ region is complicated by the C–O stretching absorption of the lactone groups which occurs in this same region.

TABLE II

INFRARED ABSORPTION FREQUENCIES (CM.$^{-1}$)

Compound	Scelera-tine (XII)	Scelera-necic dilactone (VI)	Scelera-tinic dilactone (X)	$C_8H_{12}O_4$, VIII
O–H Stretching	3410	3500	. .	3500–2400
C–H Stretching	2950	2895	2910	. .
	2880	2800	2845	
C–O Stretching				
γ-Lactone	. .	1775	1765	1760
Ester	1715	. .	. .	. .
δ-Lactone	. .	1740	. .	. .
Acid	. .	. .	. .	1705
C–H Deformation	1475	1470	1470	1460
	1450	1450	1450	1450
	1375	1380	1380	1372
	1350	1350		1350

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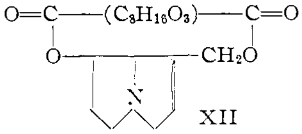
(10) It was pointed out by a referee that this structural assignment rests heavily on Kuhn–Roth carbon–methyl analyses. In this connection the following observations may therefore deserve consideration: of the four compounds analyzed for $\%\mathrm{CH_3{-}C}\!\begin{smallmatrix}/\\-\\\backslash\end{smallmatrix}$ three gave values of 2.5 or more $\mathrm{CH_3{-}C}\!\begin{smallmatrix}/\\-\\\backslash\end{smallmatrix}$ groups per molecule which is usually accepted as indicative of three $\mathrm{CH_3{-}C}\!\begin{smallmatrix}/\\-\\\backslash\end{smallmatrix}$ groups per molecule. In addition to the fact that acetone could not be isolated from the product of a chromic acid oxidation of sceleranecic dilactone, using a method specifically designed for this purpose, the values presented in Table 1 would seem to exclude any structures containing one $\mathrm{CH_3{-}C}\!\begin{smallmatrix}/\\-\\\backslash\end{smallmatrix}$ and one $\mathrm{(CH_3)_2{-}C}\!\begin{smallmatrix}/\\\backslash\end{smallmatrix}$ grouping. A structure containing these two groupings would be expected to yield at most two molecules of acetic acid. The results given in Table 1 would also be consistent with the presence of two $\mathrm{CH_3{-}C}\!\begin{smallmatrix}/\\-\\\backslash\end{smallmatrix}$ and one $\mathrm{(CH_3)_2{-}C}\!\begin{smallmatrix}/\\\backslash\end{smallmatrix}$ groupings. This would leave only five carbon atoms from which to construct the skeletal dilactone structure which is impossible.

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., p. 83.

The infrared absorption spectrum of sceleratine shows only one strong band in the 6 μ region, namely, at 1700 cm.$^{-1}$. From this observation it can be concluded that the acid moiety exists in the alkaloid as part of a cyclic diester XII.[12] Monocrotaline,


XII

which also contains a potential γ-lactone in the acid moiety has been shown to contain such a diester structure, rather than a monoester-monolactone structure.[13] The orientation of the acid moiety in sceleratine has not, as yet, been determined but can be expected to be similar to the acid moiety orientation of monocrotaline[13] and riddelline.[14]

Sceleranecic acid represents the first C-10 necic acid containing a substituted glutaric acid skeleton. All C-10 necic acids described up to now are substituted adipic acids. The related pyrrolizidine alkaloids from *Crotalaria species* of plants, *viz.*, monocrotaline[13] and dicrotaline,[15] give on hydrolysis substituted glutaric acids with less than ten carbon atoms. The structural relationships of these acids will be discussed in a separate report.[16]

Experimental

Infrared Absorption Spectra.—All spectra were obtained from 5 % solutions in chloroform using a Baird instrument equipped with rock salt optics. The compounds for which spectra are reported in this paper were prepared and purified as described in the earlier papers referred to above.

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[12] The two $-\mathrm{C}\langle{}^{\mathrm{O}}_{\mathrm{O}-}$ linkages in XII may also be referred to as lactone groupings. However, since these groupings occur in a large ring structure and exhibit infrared absorption in the region characteristic for normal esters, they are referred to as ester linkages in the present discussion.

[13] R. Adams, P. R. Shafer and B. H. Braun, THIS JOURNAL, **74**, 5612 (1952).

[14] R. Adams and B. L. Van Duuren, *ibid.*, **75**, 4638 (1953).

[15] R. Adams and B. L. Van Duuren, *ibid.*, **75**, 2377 (1953).

[16] B. L. Van Duuren, unpublished.

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[CONTRIBUTION FROM THE LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS, NATIONAL HEART INSTITUTE, NATIONAL INSTITUTES OF HEALTH, U. S. PUBLIC HEALTH SERVICE, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE]

The Structure of Pinidine

BY W. H. TALLENT AND E. C. HORNING

RECEIVED APRIL 18, 1956

dl-cis-2-Methyl-6-propylpiperidine was prepared by synthesis and found to have an infrared absorption spectrum identical with that of dihydropinidine. From the structure of the dihydro derivative, ozonolysis experiments and infrared absorption spectra data, pinidine was assigned the structure (—)-*cis*-2-methyl-6-(2-propenyl)-piperidine.

The isolation of a new alkaloid, pinidine, from *Pinus sabiniana* Dougl. was described recently.[1] It was found to be present in the leaves in moderate quantity (0.28%), and it was accompanied by D-(+)-α-pipecoline in lower amount (0.03%). Pinidine was also found to be a constituent of *P. jeffreyi* and *P. torreyana*, and the fact that these pines are unique in the respect that they do not contain α- or β-pinene may indicate a biosynthetic relationship between the formation of the alkaloid and the normal path of synthesis of pinenes. In order to continue the study of this new compound, its structure was investigated. Pinidine was determined to be one of the optically active forms of *cis*-2-methyl-6-(2-propenyl)-piperidine.

Degradative and infrared spectral evidence provided the initial clues to the structure of pinidine. A study of a high-resolution infrared absorption spectrum of pinidine in the 3–4 μ region indicated that a six-membered ring was present, and the occurrence of a sharp band at 3.31 μ was taken as evidence for a double bond in either a linear or a six-membered system.[2] Using a procedure related to that of Leonard and Gash,[3] it was established that this double bond was not α,β to the nitrogen atom, and ozonolysis experiments, leading to acetaldehyde, indicated that a $=\mathrm{CH}-\mathrm{CH}_3$ group was present. The amino group was secondary; this conclusion was based on analytical data showing the presence of one active hydrogen atom and the absence of an N-alkyl group, and by the presence of an N^+–H band in the infrared spectrum of the methiodide. Nevertheless, it was not possible to obtain acyl derivatives, and this was attributed to steric hindrance. A C-methyl determination showed that two such groups were present.[1]

A vapor-phase, high-temperature (400–500°) catalytic (Pd–C) dehydrogenation reaction led to a new compound which was recognized as a substituted pyridine by its infrared and ultraviolet absorption spectra. This compound was characterized as the chloroplatinate, and it was found to have an empirical formula $\mathrm{C}_9\mathrm{H}_{13}\mathrm{N}$. Since pinidine was known to have the formula $\mathrm{C}_9\mathrm{H}_{17}\mathrm{N}$, it was evident that no substituent groups were lost during the aromatization. A color test showed the presence of at least one α-substituent, and oxidation with potassium permanganate gave a pyridinecarboxylic acid. In view of the evidence pointing to 2,6-disubstitution in pinidine, it was considered that this material was probably pyridine-2,6-

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[1] W. H. Tallent, V. L. Stromberg and E. C. Horning, THIS JOURNAL, **77**, 6361 (1955). We have been advised that *P. pinceana* Gordon was obtained from northern Mexico rather than from California as reported. We regret the error and wish to thank Dr. N. T. Mirov for calling it to our attention.

[2] Effects in the C–H region due to ring size and unsaturation are discussed in W. H. Tallent and I. J. Siewers, *Anal. Chem.*, **28**, 953 (1956).

[3] N. J. Leonard and V. W. Gash, THIS JOURNAL, **76**, 2781 (1954).