described. Analysis of the rotations of various 11-keto-20-hydroxypregnanes by the "Method of Molecular Rotation Differences" shows certain regularities independent of the presence of oxygen functions at the C-17 or C-21 positions.

RAHWAY, N. J. RECEIVED OCTOBER 20, 1948

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Senecio Alkaloids: α- and β-Longilobine from *Senecio longilobus*

BY ROGER ADAMS AND T. R. GOVINDACHARI

The investigations[1] on *Senecio* alkaloids, of which nearly forty have been isolated so far, have brought to light the striking similarities of many members belonging to this group. Essentially, most of these alkaloids are alkamine esters, in which a pyrrolizidine base carrying two hydroxyls is esterified with aliphatic acids either on one or both hydroxyls. While the heterocyclic component has proved to be retronecine in a large number of cases, the acid fragments exhibit a bewildering variety. These necic acids, although many of them are isomeric, differ widely in melting point, optical rotation, etc., and only in a few cases has the acid moiety been found to be common to two different alkaloids.

The work presented here comprises an investigation of the alkaloids of *Senecio longilobus*, a plant to which a large percentage of the West Texas cattle losses may probably be attributed rather than to the loco plant. Manske[2] was the first to isolate a product from this source which he designated as longilobine. It became apparent very early in the course of the work that longilobine was not a single entity, but a mixture of at least two components. It has been known for a long time that many species of *Senecio* elaborate more than one alkaloid and several alkaloids have been isolated from the same species by fractional crystallization procedures.[3,4] In some instances, however, the attempts at separation of such mixtures have failed completely.[5,6]

Manske has reported longilobine to be $C_{18}H_{23}O_5N$ and the acid obtained by hydrolysis $C_{10}H_{14}O_5$, although his analytical data did not agree satisfactorily with these empirical formulas. The analysis of a sample of longilobine prepared in this Laboratory suggested the same formula as proposed by Manske but likewise was not as close to the theoretical as might be expected of a pure product. In spite of several crystallizations a constant melting point and specific rotation were not reached and the values obtained did not coincide with those reported by Manske.

It has been suggested[3a,6] that these alkaloids are difficult to burn and often gave low values for carbon. It seemed more likely that some other alkaloid with lower carbon content was associated with the $C_{18}H_{23}O_5N$ alkaloid and that this could not be effectively removed by crystallization.

The use of chromatographic adsorption methods for the separation and purification of alkaloids has been a well-established procedure but no application of chromatography has been made so far in the case of the *Senecio* alkaloids. The chromatography of colorless substances presents a difficult problem and many ingenious ways have been devised to locate the invisible zones.[7] Mention may be made of the use of the ultraviolet lamp,[8] the brush method,[9] the use of fluorescent adsorbents[10] and the use of total reflection on a thick glass plate[11] for the detection of boundaries.

They proved unsatisfactory for the separation of the constituents of the crude alkaloid from *Senecio longilobus* for various reasons. Preliminary tests indicated that the "brush method" might have been successfully applied if a further careful study had been undertaken. Investigations along these lines were abandoned when it was found that two main fractions corresponding to $C_{18}H_{23}O_5N$ and $C_{18}H_{25}O_6N$ could be separated easily on a column of alumina by a simple empirical procedure. The criterion of purity was set as a constant optical rotation, which did not change or lead to fractions having higher and lower optical rotations on further adsorption and fractional elution. The liquid chromatogram method, combined with the examination of the column cut into portions arbitrarily, proved sufficiently useful for the purpose.

An initial treatment of the crude alkaloid with alumina was used for effecting a preliminary separation of products before the usual chromatographic procedure. Longilobine with a specific

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[1] For a detailed discussion, the following papers may be consulted: (a) Adams and Rogers, THIS JOURNAL, **61**, 2815 (1939); (b) Adams, Hamlin, Jelinek and Phillips, *ibid.*, **64**, 2760 (1942); (c) Adams, Carlin and Rogers, *ibid.*, **64**, 571 (1942). The authors also had access to a chapter on *Senecio* alkaloids contributed by Dr. N. J. Leonard, University of Illinois, to a forthcoming monograph on alkaloids, under the editorship of Dr. R. H. F. Manske.

[2] Manske, *Can. J. Res.*, **17B**, 1 (1939).

[3] (a) de Waal and Onderstepoort, *J. Vet. Sci. Animal Ind.*, **16**, 149 (1941); (b) **12**, 155 (1939).

[4] Barger and Blackie, *J. Chem. Soc.*, 584 (1937).

[5] Barger and Blackie, *ibid.*, 743 (1936).

[6] Manske, *Can. J. Res.*, **14B**, 8 (1936).

[7] Zechmeister, *Annals New York Academy of Sciences*, **49**, 149 (1948).

[8] Karrer and Schöpp, *Helv. Chim. Acta*, **17**, 693 (1934); Winterstein and Schön, *Z. physiol. Chem.*, **230**, 139 (1939).

[9] Zechmeister. Cholnoky and Ujhelyi. *Bull. soc. chim. Biol.*, **18**, 1885 (1936).

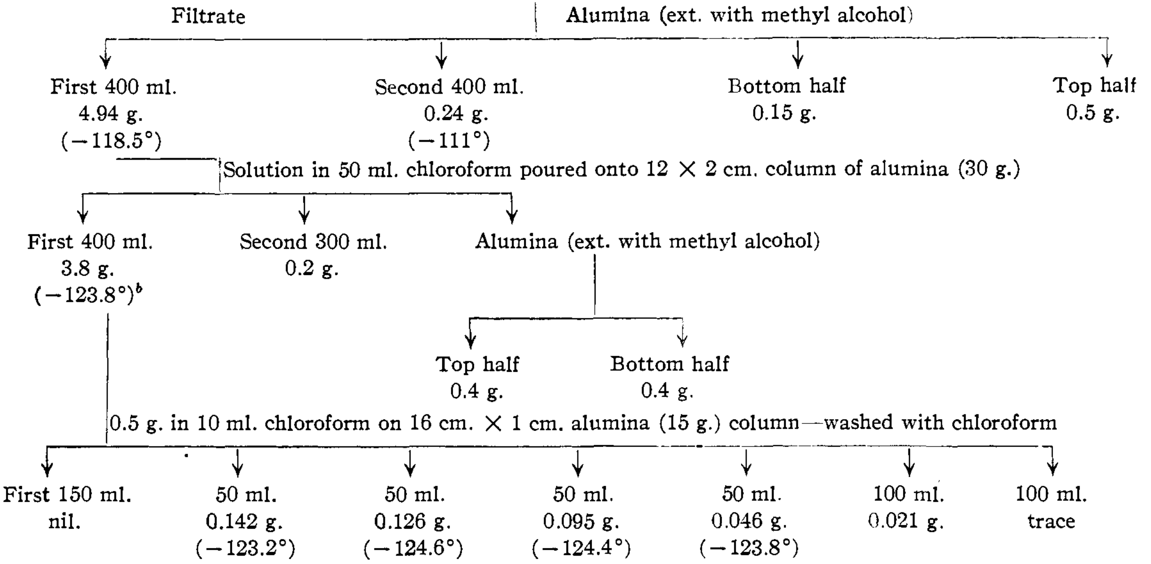
[10] Brockmann and Volpers, *Ber.*, **80**, 77 (1947).

[11] Claesson, *Nature*, **159**, 708 (1947).

TABLE I

PURIFICATION OF α-LONGILOBINE[a]

6 g. of α-fraction (2.8 g. of sp. rot. −116° and 3.2 g. of sp. rot. −110°) in 150 ml. chloroform was poured onto 12 × 2 cm. column of alumina (30 g.) and the alumina washed with 800 ml. of chloroform



Filtrate | Alumina (ext. with methyl alcohol)

First 400 ml. 4.94 g. (−118.5°)
Second 400 ml. 0.24 g. (−111°)
Bottom half 0.15 g.
Top half 0.5 g.

Solution in 50 ml. chloroform poured onto 12 × 2 cm. column of alumina (30 g.)

First 400 ml. 3.8 g. (−123.8°)[b]
Second 300 ml. 0.2 g.
Alumina (ext. with methyl alcohol)
- Top half 0.4 g.
- Bottom half 0.4 g.

0.5 g. in 10 ml. chloroform on 16 cm. × 1 cm. alumina (15 g.) column—washed with chloroform

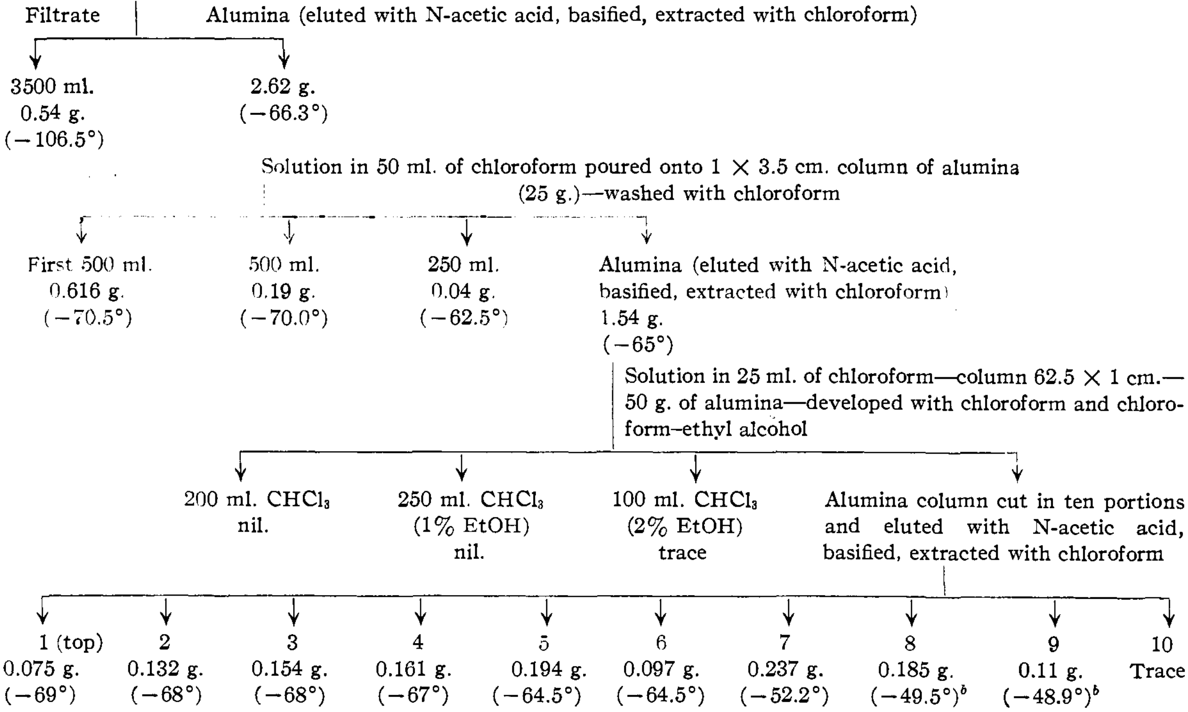
First 150 ml. nil.
50 ml. 0.142 g. (−123.2°)
50 ml. 0.126 g. (−124.6°)
50 ml. 0.095 g. (−124.4°)
50 ml. 0.046 g. (−123.8°)
100 ml. 0.021 g.
100 ml. trace

[a] Figures in parentheses denote the specific rotation of the sample in chloroform. [b] This product was crystallized twice from ethanol. The product had a rotation in chloroform $[\alpha]^{25}D$ −125.2°. Further chromatographing of this fraction was employed to demonstrate a constant optical rotation.

TABLE II

PURIFICATION OF β-LONGILOBINE[a]

4 g. of β-fraction (1.8 g. of sp. rot. −66.5° and 2.2 g. of sp. rot. −72.5°) in 100 ml. chloroform was poured onto 7.5 × 4.5 cm. column of alumina (100 g.) and the alumina washed with 3500 ml. of chloroform



Filtrate | Alumina (eluted with N-acetic acid, basified, extracted with chloroform)

3500 ml. 0.54 g. (−106.5°)
2.62 g. (−66.3°)

Solution in 50 ml. of chloroform poured onto 1 × 3.5 cm. column of alumina (25 g.)—washed with chloroform

First 500 ml. 0.616 g. (−70.5°)
500 ml. 0.19 g. (−70.0°)
250 ml. 0.04 g. (−62.5°)
Alumina (eluted with N-acetic acid, basified, extracted with chloroform) 1.54 g. (−65°)

Solution in 25 ml. of chloroform—column 62.5 × 1 cm.—50 g. of alumina—developed with chloroform and chloroform–ethyl alcohol

200 ml. $CHCl_3$ nil.
250 ml. $CHCl_3$ (1% EtOH) nil.
100 ml. $CHCl_3$ (2% EtOH) trace
Alumina column cut in ten portions and eluted with N-acetic acid, basified, extracted with chloroform

1 (top)	2	3	4	5	6	7	8	9	10
0.075 g.	0.132 g.	0.154 g.	0.161 g.	0.194 g.	0.097 g.	0.237 g.	0.185 g.	0.11 g.	Trace
(−69°)	(−68°)	(−68°)	(−67°)	(−64.5°)	(−64.5°)	(−52.2°)	(−49.5°)[b]	(−48.9°)[b]	

[a] Figures in parentheses denote the specific rotation of the sample in chloroform. [b] A mixture of samples 8 and 9 were combined and recrystallized from ethanol. The product had a rotation in chloroform $[\alpha]^{28}D$ −48.6°.

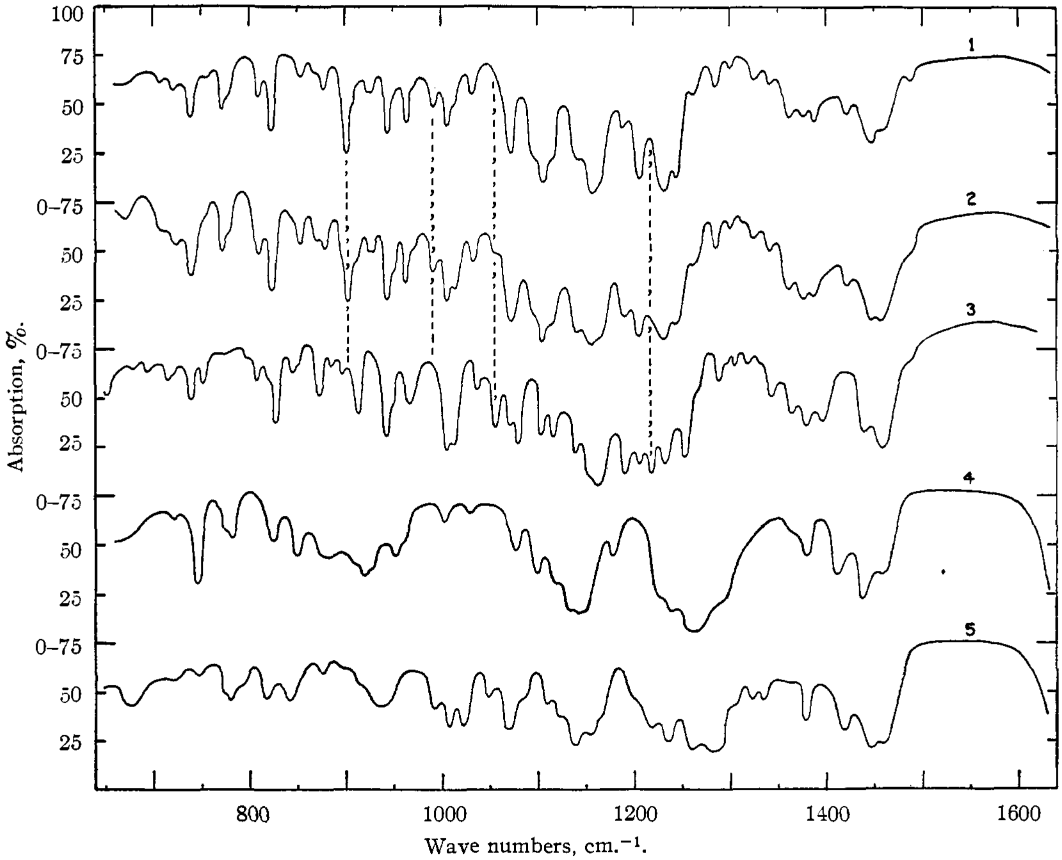


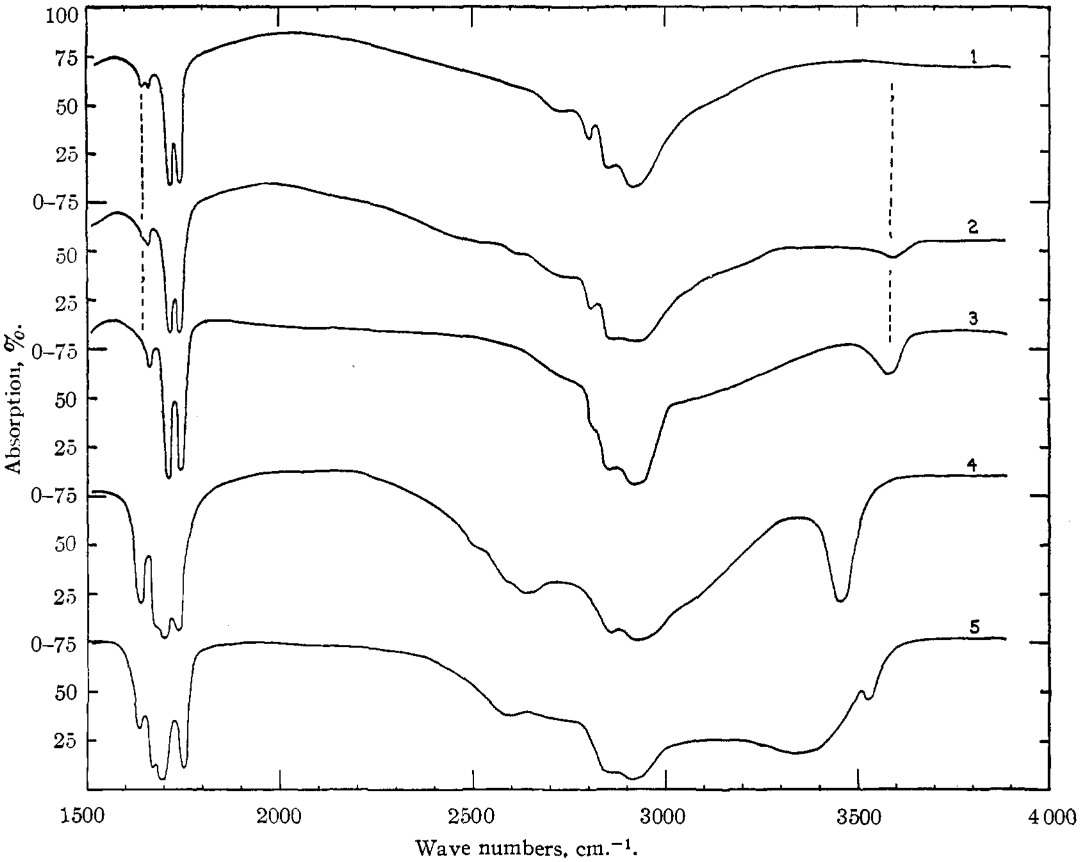
Fig. 1.—Infrared absorption spectra; all spectra are of crystalline solids ground up in Nujol between rock salt plates: 1, α-longilobine; 2, crude longilobine; 3, β-longilobine; 4, α-longinecic acid; 5, β-longinecic acid.

rotation of −91° was stirred with chloroform and alumina for thirty minutes. The filtrate from the alumina had a specific rotation in chloroform of −116°. The alumina was eluted with ether and the solvent was found to contain very little product. This was followed by elution with methanol from which solvent material of specific rotation −66.5° was obtained.

The purification of the higher rotating fraction designated as α-longilobine was achieved by two passages of a solution in chloroform through alumina columns. The α-longilobine passed with the solvent into the filtrate and the impurities were retained on the adsorbent. The pure α-longilobine was obtained by evaporation of the chloroform and after crystallization from ethanol had a specific rotation of −125.2° in chloroform at 28°. It melted at 217–218° and the analysis was in good agreement with the empirical formula $C_{18}H_{23}O_5N$.

The lower rotating fraction, called β-longilobine, was also chromatographed several times, first through short columns then through a long narrow alumina column in chloroform as solvent. The first operation eliminated practically all of the α-longilobine. The subsequent operations served for the isolation of β-longilobine in optically pure state. A certain amount of a third alkaloid was obviously present (probably riddelliine) which was more strongly adsorbed than β-longilobine. As a consequence, the optically pure product was usually obtained from the lower quarter of the column. Pure β-longilobine had a specific rotation of −48.6° in chloroform. It melted at 207–208° and analyzed correctly for $C_{18}H_{25}O_6N$.

The infrared spectra of α- and β-longilobine were complementary and when combined were essentially identical with that of crude longilobine. They are shown in Chart I. Both α- and β-longilobine show the same two frequencies at 1740 cm.$^{-1}$ and 1717 cm.$^{-1}$ indicating that the molecules must have virtually identical carbonyl linkages. The former is in the region where normal esters, six-membered lactones, cyclopentanones and some acids are found. The latter lies in the region where conjugated esters or six-membered lactones, ketones and acids are found. Both the alkaloids contain the carbon–carbon double bond absorptions at about 1664 cm.$^{-1}$. In addition, α-longilobine has a second absorption at 1645 cm.$^{-1}$. Certain absorptions appearing in the low frequency region and common to both seem to be due to the retronecine part of the



molecule, *e.g.*, those at 738 cm.$^{-1}$, 824 cm.$^{-1}$, and 1006 cm.$^{-1}$. The characteristic bands used in identification of α-longilobine were those at 992 cm.$^{-1}$ and 902 cm.$^{-1}$ and of β-longilobine at 1055 cm.$^{-1}$ and the hydroxyl band at 3590 cm.$^{-1}$.

Crude longilobine on hydrolysis furnished retronecine and an acid which was difficult to purify. Pure α-longilobine on hydrolysis yielded retronecine and an acid melting at 114–115° which analyzed correctly for $C_{10}H_{14}O_5$. The acid was dibasic and on heating *in vacuo* was converted to a glassy mass, possibly by lactonization. β-Longilobine gave on hydrolysis retronecine and an acid melting at 146–147°, which analyzed correctly for $C_{10}H_{16}O_6$. On direct titration two carboxyls were indicated.

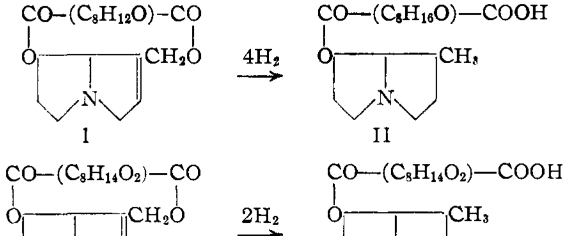
The infrared spectra of the two acids (Chart I) show many similarities and differences. Both contain the same strong absorption band between 1675 cm.$^{-1}$ and 1700 cm.$^{-1}$, which could be due to acid or keto carbonyl absorption. In addition, the α-acid shows another carbonyl absorption at 1735 cm.$^{-1}$ and the β-acid at 1750 cm.$^{-1}$. These two bands could be due to the carbonyl of an acid, ester, or lactone. The carbon–carbon double bond stretching frequency at 1637 cm.$^{-1}$ appears in both spectra.

The α-acid shows a single strong hydroxyl frequency at 3452 cm.$^{-1}$. The β-acid appears to have two hydroxyl frequencies, one at 3350 cm.$^{-1}$ and the other at 3525 cm.$^{-1}$. The latter corresponds to the hydroxyl frequency found in β-longilobine itself at 3585 cm.$^{-1}$. The consistently high frequency of this band (above 3500 cm.$^{-1}$) both in β-longilobine and in β-longinecic acid probably indicates that the hydroxyl group is in a hindered position, preventing inter-molecular and intra-molecular bonding. It seems unlikely that these hydroxyl absorptions could be due to an acid hydroxyl group, since few cases are known in which a solid acid gives an absorption in this region. Structural work on α- and β-longinecic acids are under way.

On hydrogenation in the presence of Raney nickel catalyst, α-longilobine furnished a single product in quantitative yield, taking up two mole equivalents of hydrogen. This tetrahydro-α-longilobine is a crystalline compound possessing the physical properties of an amino acid and on hydrolysis furnished retronecanol and an acid identical with α-longinecic acid obtained by direct hydrolysis of the alkaloid with barium hydroxide. It is, therefore, evident that hydrogenation in the presence of Raney nickel as catalyst cleaves one ester linkage in the alkaloid and saturates the retronecine double bond, but leaves the unsaturation in the acid part of the molecule unaffected.

On the other hand, when α-longilobine was hydrogenated in the presence of platinum-oxide catalyst, four mole equivalents of hydrogen were taken up and a single product was obtained in excellent yield. This product was amorphous and could not be crystallized. It showed the physical properties of an amino acid and on hydrolysis yielded retronecanol and an acid which could not be induced to solidify. The additional two moles of hydrogen taken up in the presence of platinum-oxide catalyst must therefore be accounted for by unsaturation in the acid moiety of the alkaloid. The intermediates obtained in the hydrogenation with either catalyst were certainly amino acids and there is a striking similarity in the behavior of α-longilobine on hydrogenation to riddelliine.[1b] With the structure of retronecine and retronecanol established[12] the general structural formula for α-longilobine may be indicated as I and the reduction product resulting from the absorption of four moles of hydrogen as II.

β-Longilobine in the presence of platinum-oxide catalyst absorbs merely two mole equivalents of hydrogen to give a single product in excellent yield. This product like those from α-longilobine appears to be an amino acid, since it is easily soluble in water and ethanol but insoluble in ether and other non-polar solvents. It was amorphous and could not be crystallized. On hydrolysis, retronecanol was obtained and an acid, m.p. 146°, identical with that from β-longilobine by hydrolysis with baryta. The two moles of hydrogen have obviously been used in hydrogenolysis and saturation of the retronecine double bond. The acid portion is saturated or contains no easily reduced unsaturation. The formula for β-longilobine may be designated as III and its reduction product as IV.



The authors are grateful to Mrs. J. L. Johnson for determination and interpretation of infrared spectra.

Experimental

Extraction of Longilobine from Senecio longilobus.—The powdered plant material (whole plant) was extracted continuously in a Soxhlet for twenty-four to thirty hours with ethanol. The alkaloid was isolated as previously described for riddelliine.[1b] The residue from the chloroform extract was once recrystallized from methanol. The yield of longilobine from 27 lb. of dried material was 29.8 g. (0.24%). The product melted at 203–204° (cor.) with sintering from 197°. It was recrystallized thrice from absolute ethanol and then melted at 209–210° (cor.). This was the sample analyzed.

Rotation: (once recrystallized product) 0.2819 g. made up to 10 ml. in chloroform at 30° gave α_D −2.565°; *l*, 1; $[\alpha]^{30}_D$ −91°.

Anal. Calcd. for $C_{18}H_{23}O_5N$: C, 64.86; H, 6.91; N, 4.2. Found: C, 63.88; H, 7.12; N, 3.98.

Hydrolysis of Crude Longilobine.—One gram of crude longilobine (once crystallized) was refluxed with 2 g. of barium hydroxide octahydrate in 7 ml. of water for one hour. The necine and necic acid portions were isolated as in the case of riddelliine.[1b] Retronecine·hydrochloride in yield of 0.41 g. was obtained. Crystallization from ethanol gave a product, m.p. 162–163° (cor.), which did not depress the melting point of an authentic specimen of retronecine hydrochloride from monocrotaline.[1a]

Anal. Calcd. for $C_8H_{13}O_2N \cdot HCl$: C, 50.11; H, 7.36; Cl, 18.51. Found: C, 50.24; H, 7.16; Cl, 18.49.

The retronecine was also identified by conversion to diacetylretronecine picrate prepared from the base according to the directions of Barger, *et al.*[12a] The m.p. was 143° (cor.).

Anal. Calcd. for $C_{12}H_{17}O_4N \cdot C_6H_3O_7N_3$: N, 11.95. Found: N, 11.91.

The necic acid portion weighed 0.61 g. and was an amber-colored oil which could not be induced to crystallize.

Chromatographic Procedure.—Alumina[13] was used exclusively as the adsorbent in these experiments. The columns were packed dry with the adsorbent and washed with pure solvent before introducing the substance. Chloroform was found to be the ideal solvent. The α-longilobine was eluted from the column by washing with chloroform or with a mixture of chloroform and ethanol (one to two per cent.). In many early experiments, the β-longilobine was eluted by extracting the alumina residue with methanol. A purer product was obtained in better yield by stirring the alumina, after removal from the column, with fifteen to twenty parts of normal acetic acid, filtering from the alumina, basifying the filtrate with ammonia and extracting with chloroform. This was the preferred procedure in all later experiments.

The chloroform extract of the several "cuts," either from the filtrate or from the alumina, was distilled and the residue was made up to a known volume in pure chloroform. An aliquot portion was transferred to a tared watch glass and the amount of material in each fraction determined by evaporation. Another portion was utilized for determining the rotation. From these data, the specific rotation of each fraction was calculated.

Preliminary Separation of α- and β-Longilobine.—A solution of 5 g. of crude longilobine ($[\alpha]^{30}_D$ −91°) in 150 ml. of dry chloroform was stirred for thirty minutes with 10 g. of freshly ignited alumina. The alumina was allowed to settle and the chloroform was decanted off through a filter paper. The process was repeated with two 150-ml. portions of chloroform (filtrate A).

The alumina was stirred with a total of 500 ml. of absolute ether in three lots and the ether decanted off (filtrate B).

The alumina was then stirred with a total of 500 ml. of methanol in five portions (filtrate C).

Filtrate A gave 2.9 g. of material. *Rotation:* 0.0521 g. made up to 2 ml. in chloroform at 30° gave α_D −3.02°; *l*, 1; $[\alpha]^{30}_D$ −116°.

Filtrate B gave 0.1 g. of material. This was discarded.

Filtrate C gave 1.8 g. of material. *Rotation:* 0.0694 g. made up to 2 ml. in chloroform at 30° gave α_D −2.3°; *l*, 1; $[\alpha]^{30}_D$ −66.2°.

Further purification of the two main fractions from

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[12] Adams and Leonard, This Journal, **66**, 257 (1944).

[12a] Barger, *et al.*, *J. Chem. Soc.*, 11 (1935).

[13] Activated alumina, Grade F 20, made by Aluminum Ore Co., East St. Louis, Illinois, was found to be quite satisfactory.

filtrates A and C was achieved as shown in Tables I and II.

α-Longilobine.—From absolute ethanol, m. p. 217–218° (cor.). *Rotation:* 0.0412 g. made up to 2 ml. in chloroform at 25° gave α_D −2.58°; *l*, 1; $[\alpha]^{25}_D$ −125.2°.

Anal. Calcd. for $C_{18}H_{23}O_5N$: C, 64.86; H, 6.91; N, 4.2. Found: C, 65.21; H, 7.00; N, 4.37.

α-Longilobine Methiodide.—The methiodide was prepared by warming the alkaloid in chloroform solution with an excess of methyl iodide. After removing the chloroform, the product was twice recrystallized from ethanol with the addition of a few drops of water; white crystals, m. p. 240° (cor.).

Rotation: 0.0151 g. made up to 1 ml. in water at 28° gave α_D −1.06°; *l*, 1; $[\alpha]^{28}_D$ −70.1°.

Anal. Calcd. for $C_{18}H_{23}O_5N \cdot CH_3I$: C, 48.0; H, 5.48; N, 2.95; I, 26.4. Found: C, 47.92; H, 5.64; N, 3.17; I, 26.51.

β-Longilobine.—From absolute ethanol, m. p. 207–208° (cor.). *Rotation:* 0.0367 g. made up to 2 ml. in chloroform at 28° gave α_D −0.89°; *l*, 1; $[\alpha]^{28}_D$ −48.6°.

Anal. Calcd. for $C_{18}H_{25}O_6N$: C, 61.5; H, 7.12; N, 3.98. Found: C, 61.41; H, 7.28; N, 4.15.

β-Longilobine Methiodide.—This was prepared in the same manner as the α-longilobine derivative. After two recrystallizations from ethanol containing water, the product melted at 256° (cor.).

Rotation: 0.0168 g. made up to 1 ml. in water at 28° gave α_D −0.40°; *l*, 1; $[\alpha]^{28}_D$ −23.8°.

Anal. Calcd. for $C_{18}H_{25}O_6N \cdot CH_3I$: C, 46.25; H, 5.68; N, 2.88. Found: C, 46.02; H, 5.93; N, 2.81.

α-Longinecic Acid.—A mixture of 0.5 g. of α-longilobine, 1 g. of barium hydroxide octahydrate and 7 ml. of water was refluxed for one hour. The necine and necic acid portions were isolated by the usual procedure. The yield of retronecine hydrochloride was 0.205 g. (72%), m. p. 163–164° (cor.).

The yield of α-longinecic acid was 0.289 g. (80%). This was recrystallized from absolute ether, with addition of petroleum ether to incipient turbidity. The product melted at 114–115° (cor.). By titration it was shown to be dibasic.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.08; H, 6.54; neut. equiv., 107. Found: C, 56.16; H, 6.34; neut. equiv., 103.9.

Rotation: 0.0249 g. made up to 1 ml. in water at 28° gave α_D −0.33°; *l*, 1; $[\alpha]^{28}_D$ −13.25°.

On heating α-longinecic acid, water was evolved and a glassy product resulted which could possibly be a lactone. It could not be purified.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.12. Found: C, 59.77; H, 6.58.

β-Longinecic Acid.—From 0.5 g. of β-longilobine by a similar hydrolysis, 0.19 g. (66.5%) of retronecine hydrochloride, m. p. 163–164°, was obtained. The yield of β-longinecic acid was 0.26 g. (78.6%). The acid was less soluble in absolute ether than α-longinecic acid. It was recrystallized by dissolving in a large volume of ether, concentrating to a small volume, adding a few drops of petroleum ether and rubbing with a glass rod. The recrystallized acid melted at 146–147° (cor.). Direct titration of β-longinecic acid indicated dibasicity. By adding excess of alkali, permitting to stand overnight and back titrating with standard hydrochloric acid, three carboxyls were indicated (Calcd. 77.3. Found 83.9).

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.8; H, 6.95; neut. equiv., 116. Found: C, 51.58; H, 7.00; neut. equiv., 115.9.

Rotation: 0.0298 g. made up to 1 ml. in water at 28° gave α_D −0.27°; *l*, 1; $[\alpha]^{28}_D$ −9.06°.

Hydrogenolysis of α-Longilobine (Raney Nickel Catalyst). Tetrahydro-α-longilobine.—A solution of 0.4 g. of α-longilobine in 15 ml. of ethanol and 2.5 ml. of water was hydrogenated at slightly over atmospheric pressure in the presence of approximately 0.5 g. of Raney nickel. A total of two mole equivalents of hydrogen were absorbed during three hours, after which no more hydrogen was taken up. The catalyst was filtered off and the solvent removed *in vacuo*. The residue was a colorless crystalline solid in a yield of 0.4 g. It was fairly soluble in water, more soluble in ethanol and acetic acid and insoluble in ether. It was best crystallized from a small volume of water, m. p. 190–191° (cor.). *Rotation:* 0.0187 g. made up to 2 ml. with water at 28° gave α_D −0.61°; *l*, 1; $[\alpha]^{28}_D$ −65.2°.

Anal. Calcd. for $C_{18}H_{27}O_5N$: C, 64.10; H, 7.81. Found: C, 63.95; H, 7.96.

Hydrolysis of Tetrahydro-α-longilobine.—A mixture of 0.2 g. of tetrahydro-α-longilobine and 0.5 g. of barium hydroxide octahydrate in 5 ml. of water was refluxed for one hour and cooled. After saturating with carbon dioxide, the solution was filtered and made acid to congo red. Continuous extraction with ether for twenty-four hours and removal of solvent yielded an oil which solidified on rubbing. Recrystallization from ether–petroleum ether (b. p. 30–60°) gave a solid which melted at 114°. The melting point of a mixture of this product with α-longinecic acid gave no depression.

The aqueous solution remaining after ether extraction was made alkaline with sodium hydroxide and extracted with ether. After drying the ether extract with anhydrous magnesium sulfate and distilling the ether, a solid remained which was converted to a picrate with aqueous picric acid. The picrate, after recrystallization from water, melted at 211° and was identical with an authentic specimen of retronecanol picrate.

Hydrogenolysis of α-Longilobine (Platinum Oxide Catalyst).—A solution of 0.5 g. α-longilobine in 15 ml. of absolute ethanol and 1.5 ml. of acetic acid was hydrogenated at slightly over atmospheric pressure in the presence of 0.05 g. of platinum oxide catalyst. A total of four mole equivalents of hydrogen was absorbed. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was a glassy mass which could be broken down to a brittle powder; yield, 0.51 g. (quant.). If the acetic acid was omitted, the residue was an amorphous solid in nearly the same yield. Attempts to crystallize the product were unsuccessful. Accurate analysis was not possible because of the extreme hygroscopicity of the material.

A solution of 0.5 g. of the above material in 20 ml. of a 10% aqueous solution of sodium hydroxide was refluxed for one hour and cooled. The solution was repeatedly extracted with ether, the ether extract dried over anhydrous magnesium sulfate and the ether distilled. The residue was an oil which solidified on keeping in the desiccator. On recrystallization from petroleum ether (b. p. 30–60°), a white crystalline solid was obtained, m. p. 95–96° (cor.) identical with an authentic specimen of retronecanol.

The aqueous layer in acidification and continuous extraction with ether gave 0.25 g. of an amber-colored liquid which did not solidify.

Hydrogenolysis of β-Longilobine.—When 0.5 g. of β-longilobine was similarly hydrogenated in the presence of 0.05 g. of platinum oxide catalyst, only two mole equivalents of hydrogen were taken up. After filtration of catalyst and removal of solvent, a glassy mass was left behind which was converted to an amorphous powder on treatment with ether. This material (0.45 g.) was insoluble in ether and easily soluble in water and ethanol. On dissolving in absolute ethanol and adding absolute ether, the material separated as an oil which solidified on rubbing. This solid melted at 55–60°, forming a voluminous foam. Attempts to purify the material for analysis were unsuccessful.

A solution of 0.4 g. of the above material in 4 ml. of water was refluxed for one hour with one gram of barium hydroxide octahydrate. The acid portion was isolated by saturating with carbon dioxide, filtering the barium carbonate, acidifying the filtrate and extracting continuously with ether; yield, 0.21 g. After two recrystallizations from ether–petroleum ether mixture, the acid melted at 146° (cor.) and was identical with β-longinecic acid, obtained by direct hydrolysis of β-longilobine. The basic portion was isolated in the usual way and proved to be retronecanol identified conveniently as the picrate, m. p. 211°.

Summary

1. The alkaloid from *Senecio longilobus*, first isolated by Manske, has been shown to be a mixture of two components designated as α- and β-longilobine, whose empirical formulas are $C_{18}H_{23}O_5N$ and $C_{18}H_{25}O_6N$, respectively. The separation was achieved by an empirical chromatographic procedure, combining the liquid chromatogram method and examination of the column. The course of the chromatogram was followed by determining the specific rotations of the different fractions and the two main components were rechromatographed until a constant specific rotation was attained.
2. On hydrolysis α-longilobine gives one molecule of retronecine and one molecule of a crystalline dibasic acid $C_{10}H_{14}O_5$, designated as α-longinecic acid.
3. Similarly β-longilobine gives one molecule of retronecine and one molecule of a crystalline dibasic acid $C_{10}H_{16}O_6$, designated as β-longinecic acid.
4. On reduction with hydrogen and Raney nickel, α-longilobine absorbs two moles of hydrogen to form tetrahydro-α-longilobine which has the properties of an amino acid and on hydrolysis yields retronecanol and α-longinecic acid. With platinum oxide as catalyst four moles of hydrogen are absorbed, yielding an amorphous product which gives on saponification retronecanol and an oily acid which was not purified.
5. β-Longilobine absorbs only two moles of hydrogen in the presence of platinum oxide as catalyst, yielding an amorphous product which gives on hydrolysis retronecanol and β-longinecic acid.
6. Both α- and β-longilobine are shown to be cyclic diesters, from one mole of retronecine and one mole of a dibasic acid, each of the two hydroxyls in retronecine being utilized.

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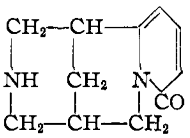
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Condensation Reactions of N-Substituted Pyridones[1]

BY ROGER ADAMS AND ANTHONY W. SCHRECKER

A consideration of possible methods for the synthesis of cytisine[2] (I) leads to the necessity of further knowledge of the activity of a 6-methyl group in N-substituted 2-pyridones. This communication is devoted primarily to the description of the reactivity of the ring-substituted methyl group in 1,6-dimethyl-2-pyridone. It includes also the results of a similar study of 1,4-dimethyl-2-pyridone. 6-Methyl-2-pyridone-1-β-propionitrile and ethyl 6-methyl-2-pyridone-1-acetate were synthesized and preliminary experiments on pyridocoline formation were attempted. The activity of the methyl group in 2-acetamido-6(and 4)-methylpyridine is also described.



I

The ability of such compounds as 2-picoline to undergo condensation reactions with carbonyl compounds has been attributed to the double bond linking the nitrogen with the carbon atom carrying the methyl group.[3] A molecule carrying such a structural unit can undergo an electromeric shift permitting formation of a carbanion and subsequent condensation with a carbonyl group.[4] No such double bond appears in the formula of a compound such as 1,6-dimethyl-2-pyridone (IIa). If N-alkylpyridones are, however, resonance hybrids of an uncharged and a betaine (IIb) structure, as postulated by Arndt and Kalischek,[5] and the carbanion (III) is stabilized by resonance, then the requirement for base-catalyzed condensation reactions should be fulfilled. Replacement of the 6-methyl group by a carbethoxymethyl group would render the compound somewhat similar in its behavior to a β-keto ester and replacement by a cyanomethyl group similar to a β-carbonylated nitrile, such as ethyl cyanoacetate. Such compounds should form sodium enolates which react with alkyl and acyl halides. These predictions have been realized experimentally.

The predictions were supported by the experiments of Kaslow and Cook[6] who demonstrated the reactivity of the 4-methyl group in 1,4-dimethylcarbostyril toward ethyl oxalate. The condensation product was readily transformed into 1-methyl-4-carbostyrilacetonitrile, which underwent condensation with benzaldehyde.

The starting materials, 1,6-dimethyl-2-pyridone

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[1] From a thesis presented by Anthony W. Schrecker to the Graduate College of the University of Illinois, August, 1948, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Späth and Galinovsky, *Ber.*, **66**, 1338 (1933).

[3] Mills and Smith, *J. Chem. Soc.*, **121**, 2724 (1922).

[4] Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 130.

[5] Arndt and Kalischek, *Ber.*, **63**, 587 (1930).

[6] Kaslow and Cook, THIS JOURNAL, **67**, 1969 (1945).