Senecio Alkaloids. Synthesis of Necic Acids

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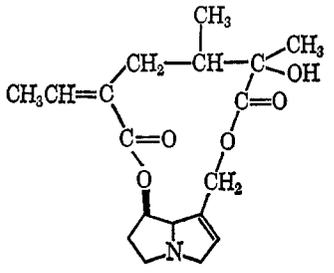
The compound methyl 5-aceto-2-hydroxy-2-methyl-3-methylenehexanedioate 2(δ)-lactone made in the synthesis of seneciphyllic acid has been used to prepare senecic and integerrinecic acids. Morpholine borane was used to selectively reduce the β-keto group of this lactone.

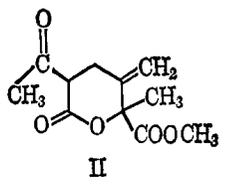
The decanecic acids, integerrinecic and senecic, differ only in the configuration at the double bond and are formed along with the alkanolamine, retronecine, by the hydrolysis of the *Senecio* alkaloids[3] (I), integerrimine and seneciomine.



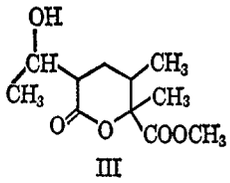
I

The synthesis of the more stable *trans*[4] acid, integerrinecic, has been reported by Culvenor and Geissman.[5] These authors also report the photochemical isomerization of integerrinecic acid to senecic acid.

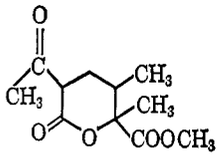
During the synthesis of *cis*- and *trans*-seneciphyllic acid,[6] the ester lactone II was prepared and this compound has now been used to realize a synthesis of senecic and integerrinecic acids.



II



III



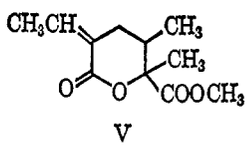
IV

The synthesis of these necic acids from II required the reduction of the two unsaturated centers to yield III. Catalytic hydrogenation at room temperature was first tried with a highly active Adams catalyst[7] and with Raney nickel W-2[8] and W-6,[9] but reduction of only the olefinic group occurred to give IV, even at 100 atm. This is apparently due to the steric inaccessibility of the β-keto group since ethyl acetoacetate is easily reduced[10,11] with Raney nickel. When alkali[12] was added to the Raney nickel reduction, cleavage or condensation resulted.

With sodium or potassium borohydride, the β-keto group in II could not be selectively reduced in the presence of the lactone group. Depending upon the conditions, either no reduction occurred or both groups were reduced. With the more basic hydride reducing agents, enolization and undesirable reduction took place.

The successful conversion of II to III was accomplished by first selectively reducing the β-keto group of II with morpholine borane[13] under forcing conditions. The remaining double bond was resistant to hydrogenation and required several exposures to Adams catalyst for complete conversion to III. It was also found that if the olefinic bond in II was first hydrogenated (IV) it was not possible to reduce the β-keto group with morpholine borane. For compounds containing carbonyl groups in sufficiently different steric environments, it should be possible by choice of reaction conditions to selectively reduce the least hindered with this reagent.

The mixture of stereomers III was dehydrated by heat in the presence of phosphoric acid and the crude product mixture was sublimed. Chromatography on silica gel gave approximately 5% of the β,γ-unsaturated ester lactone, 10% of *cis*-V, and 30% of *trans*-V.[4]



V

The two racemates of the *trans*-V fraction were separated on silica gel and gave about equal amounts of the *trans*-VA[14] and *trans*-VB racemates. The identity of the *trans*-VA racemate and integerrinecic acid lactone methyl ester was established by infrared and mixture melting point. The resolution of the acid lactone racemate derivable from *trans*-VA has been reported.[5] Hydrolysis of the *trans*-VB racemate gave the diastereomeric racemate of integerrinecic acid.

(1) Robert A. Welch Foundation Postdoctoral Fellow.

(2) Robert A. Welch Foundation Scholar.

(3) N. J. Leonard, "The Alkaloids," Vol. VI, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1960, Chapter 3.

(4) *cis* and *trans* refer to the methyl and carboxyl arrangement at the double bond.

(5) C. C. J. Culvenor and T. A. Geissman, *J. Am. Chem. Soc.*, **83**, 1647 (1961). For later studies on the synthesis of (±)-integerrinecic acid lactone, see N. K. Kochetkov, A. E. Vasil'ev, and S. N. Levchenko, *Zh. Obshch. Khim.*, **35** (1), 190 (1965), and references therein. For stereochemical assignments, see N. I. Koretskaya, A. V. Danilova, and L. M. Utkin, *ibid.*, **32**, 3823 (1962).

(6) J. D. Edwards, Jr., T. Hase, and N. Ichikawa, *Chem. Commun.*, 364 (1965).

(7) V. L. Frampton, J. D. Edwards, Jr., and H. R. Henze, *J. Am. Chem. Soc.*, **73**, 4432 (1951).

(8) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 181.

(9) H. R. Billica and H. Adkins, ref 8, p 176.

(10) L. W. Corvert and H. Adkins, *J. Am. Chem. Soc.*, **54**, 4116 (1932).

(11) R. Mozingo, C. Spencer, and K. Folkers, *ibid.*, **66**, 1859 (1944).

(12) R. Schroter, "Newer Methods of Preparative Organic Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1948, p 83.

(13) The use of this reagent for the selective reduction of certain β-ketocarbonyl compounds under essentially neutral or acidic conditions will be reported in another article.

(14) The *trans*- and *cis*-VA racemates gave integerrinecic and senecic acids on hydrolysis.

The *cis*-V mixture of racemates was less stable and more difficult to separate than the *trans*. Even with a 1200:1 ratio of silica gel to sample, only a 10% yield of the *cis*-VA and *cis*-VB racemates was possible because of band overlap. For this reason, the *cis*-V mixture of racemates was hydrolyzed and the resulting dicarboxylic acid racemates were separated by fractional crystallization. One of these racemates was shown by mixture melting point to be racemic senecic acid. Resolution of this synthetic senecic acid racemate was accomplished with cinchonidine and the diastereomer isolated gave, on decomposition, an acid identical with senecic acid.

The geometric configuration of the ester lactones (V) can be assigned by infrared. The *trans* isomers have a strong C=C stretching vibration at 1635 cm^{-1}, whereas the *cis* isomers have weak absorption at this position. These assignments are confirmed by the symmetrical methyl group bending. In the *cis* isomers where steric interaction is significant, this band is split and found at 1362 and 1383 cm^{-1} with decreased intensity. In the *trans* isomers it is found at 1374 cm^{-1}. The β-keto groups in II and IV absorb at 1790 cm^{-1} and this band in II disappears on reduction with morpholine borane. The lactone and ester carbonyls of II and IV are located at 1730 and 1725 cm^{-1}. In III and the morpholine borane reduction product of II, these carbonyls are found as a single band at 1725 cm^{-1}. The terminal methylene group absorption in II and the morpholine borane reduction product is at 913–915 cm^{-1} and disappears on hydrogenation. The frequencies of the different lactone carbonyls indicate that these δ lactones are probably in the half-chair conformation.[15]

Experimental Section[16]

Reduction of II.—To a mixture of morpholine borane (4.0 g, 0.04 mole) and II (9.0 g, 0.04 mole) in 270 ml of methanol, there was added dropwise with stirring at 22°, 85.5 ml of 5% hydrochloric acid. After standing for 48 hr at room temperature, during which time some evolution of hydrogen occurred, the mixture was added to 2.2 l. of water and extracted four times with 450 ml of ether. After drying and evaporation, the ether phase gave 4.5 g of recovered II. The aqueous phase was evaporated to dryness under reduced pressure to give a borate residue. Methanolysis was found to be the best procedure to decompose this borate. To the borate residue there was added 1.0 l. of methanol and, after slow distillation, the pale green residue was extracted three times with boiling ether. Evaporation of the ether gave 4.4 g of an oil. Infrared analysis indicated complete reduction of the β-keto group in II.

The morpholine borane reduction product (6.9 g, 0.03 mole) was hydrogenated in an apparatus[7] which allowed prereduction of the Adams catalyst (0.5 g) with methanol as the solvent. The reduction was carried out at atmospheric pressure and after absorption of hydrogen had stopped, the mixture was filtered and the solvent was evaporated under reduced pressure. The hydrogenation of this sample was repeated three times in the same manner using 0.5 g of fresh catalyst each time after which the calculated volume of hydrogen had been absorbed. Evaporation of the solvent gave 6.9 g of III.

Dehydration of III.—After heating 3.45 g of III in a sublimation apparatus to 60° in an oil bath, there was added with stirring 30 drops of 85% phosphoric acid. The temperature was raised to 145° and after 30 min the small amount of water which had condensed on the cold finger was removed. The mixture was then heated at 145–150° (35 mm) for a period of 12 hr. During this time the sublimate was removed from the cold finger 16 times by washing with ether. By this procedure, 2.3 g of sublimate was obtained. The infrared spectrum of this product showed no hydroxyl group absorption and a strong C=C band.

Chromatography of Sublimate.—A 4 cm × 7.5 in. column was prepared from 110 g of silica gel (E. Merck AG) (0.08 mm) suspended in purified chloroform.[17] To this was added 1.1 g of the above sublimate and a flow of 125 ml/hr of chloroform was maintained by air pressure (see Table I).

TABLE I

Fraction	Ml	Material (mg)
1–18	1260	Forerun discarded (18)
19–57	390	β,γ isomer (55)
58–73	280	*cis*-V (100)
74–77	120	*cis*-V and *trans*-VA (30)
78–81	130	*trans*-VA (58)
82–87	250	*trans*-V mixture (120)
88–89	250	*trans*-VB (133)

Fractions 78–81 on evaporation and several recrystallizations from ether–petroleum ether (bp 30–60°) gave the *trans*-VA racemate: mp 64–66°.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.03; H, 7.52.

Fractions 88–89 were evaporated and recrystallized from ether–petroleum ether to give the *trans*-VB racemate: mp 54.5–55°.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.93; H, 7.40.

A mixture melting point of *trans*-VA and *trans*-VB was 35–40°. Further quantities of *trans*-VA and *trans*-VB were realized by chromatography of fractions 82–87.

Integerrinecic Acid Lactone Methyl Ester.—Integerrinecic acid lactone (mp 155.5–156.5°, 39.8 mg) in 0.5 ml of ether was cooled in an ice bath and 1 ml of an etheral diazomethane solution (10% excess) was added dropwise with stirring. After the addition, the solution was allowed to stand at 0° for 15 min and then evaporated to dryness under vacuum. The residue, 42.5 mg, was recrystallized from ether–petroleum ether to give crystals: mp 93–94°, $[\alpha]^{27}D$ +42.0° (*c* 0.233, C_2H_5OH). The infrared spectrum ($CHCl^3$) was identical with that of *trans*-VA. A mixture melting point with *trans*-VA was 64–75°.

Hydrolysis of *trans*-VB.—*trans*-VB (132.7 mg, 0.625 mmole), 1.0 ml ethanol, 494 mg of barium hydroxide octahydrate, and 8.0 ml of water were refluxed for 1.5 hr. Carbon dioxide was then passed through the solution and the precipitate was filtered and washed with water. The filtrate was concentrated under vacuum to 1 ml and 5% hydrochloric acid was added dropwise until acid to congo red paper. This solution was evaporated to dryness under vacuum and the precipitate was recrystallized several times from ether–petroleum ether to give 91 mg of colorless crystals: mp 162–164°.

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.37; H, 7.38.

Hydrolysis of *cis*-V Mixture.—Hydrolysis of 150 mg of the *cis*-V mixture of racemates by barium hydroxide as described above gave 150 mg of a semisolid residue. This was recrystallized from ether–petroleum ether and gave 105 mg of colorless crystals: mp 138–147°. (The filtrate from this crystallization contained racemic senecic acid, see below.) After seven recrystallizations this gave 34 mg of colorless crystals of constant mp 160–162°. This is the racemate of the diastereomer of senecic acid. A mixture melting point with senecic acid, mp 145–147°, was 132–140°.

(±)-Senecic Acid.—The filtrate from the above first crystallization was evaporated and the precipitate was crystallized from ether–petroleum ether to yield 18 mg of colorless crystals: mp 145–148°. After seven recrystallizations there was obtained 5 mg of colorless crystals: mp 163–165°. A mixture melting point with senecic acid, mp 147–149°, was 147–149°.

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.74; H, 7.40.

Resolution of (±)-Senecic Acid.—A solution of 19.3 mg of *cis*-VA dicarboxylic acid racemate and 52.5 mg of cinchonidine

(15) K. K. Cheung, K. H. Overton, and G. A. Sim, *Chem. Commun.*, 634 (1965).

(16) All analyses by Huffman Analytical Laboratories, Wheatridge, Colo. Melting points are uncorrected and were done on a Fisher-Johns apparatus.

(17) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p 283.

in 8 drops of methanol was heated to boiling and 1 ml of ethyl acetate was added. After standing in the refrigerator for 1 day, this gave 25 mg of crystals: mp 133–137°. This was recrystallized four times to give 9.5 mg of constant mp 136–138° (no depression in melting point when admixed with the cinchonidine salt prepared from senecic acid: mp 136–138°). The infrared (KBr) spectra of the two samples were identical. The synthetic cinchonidine salt was dissolved in dilute hydrochloric acid and extracted with ether. Evaporation of the extract and crystallization from ether–petroleum ether gave crystals, mp 146–148°, and no depression resulted when admixed with senecic acid. The infrared (KBr) spectra of the synthetic sample and senecic acid were identical in every respect.

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Indole-3-alkylamine Bases of *Desmodium pulchellum*

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The isolation and identification of seven indole-3-alkylamine bases derived from tryptophan in *Desmodium pulchellum* are described. Rearrangement of N,N-dimethyl tryptamine oxide and 5-methoxy-N,N-dimethyltryptamine oxide, obtained from this species, has been studied and its implication in the light of alkaloid biosynthesis is appraised.

Previously, the occurrence of seven indolealkylamine bases in *Desmodium pulchellum* Benth *ex* Baker (family *Leguminosae*) has been reported.[2] The present paper describes the experimental details of the isolation and identification of these compounds. In addition, the results of rearrangement of two tertiary amine oxides, *viz.*, N,N-dimethyltryptamine oxide and its 5-methoxy analog, isolated from this plant, are now reported. These results indicate the pathway of tryptophan metabolism and support a recent suggestion[3] that the formation of amine oxides and their rearrangement to carbinol amine bases may be important stages in the biosynthesis of certain group of alkaloids.

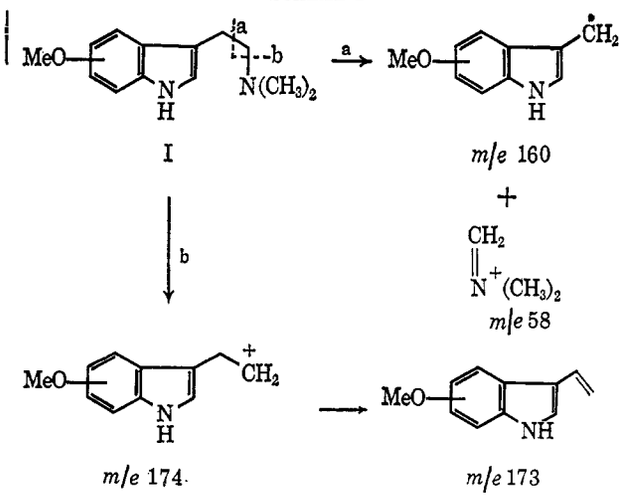
The alkaloids were extracted from the defatted plant material with alcohol containing acetic acid and the mixture of crude bases obtained in the usual way was separated into the following three main components by column chromatography on Brockmann alumina. Elution with benzene gave the major base while the minor components, less and more polar, migrated out as brown gum upon washing of the column with ether–methyl alcohol and methyl alcohol, respectively. The more polar compounds were finally purified by column chromatography on cellulose powder.

The total alkaloids from the plant showed with *p*-dimethylaminobenzaldehyde or with vanillin in presence of concentrated hydrochloric acid purple and blue colors and exhibited ultraviolet absorption characteristic of 3-alkyl indoles. Four of the seven compounds mentioned here were isolated in quantities sufficient for complete characterization, and for the remaining three minor bases the general procedure for identification involved paper and thin layer chromatographic determinations. The mixture of minor components was submitted to preparative paper chromatography and the distinct zones obtained were eluted with ethyl alcohol. The ethyl alcohol eluates were chromatographed separately and in mixture with a reference compound. The pure components from separate chromatographic runs were used for ultraviolet absorption spectra determinations and for preparation of picrates.

The major alkaloid, mp 69°, which crystallizes from ether–petroleum ether is a tertiary base as it readily forms a methiodide and an N-oxide. Elemental analysis of the alkaloid and its derivatives are consistent with the molecular formula $C_{13}H_{18}N_2O$ for the parent base.

The molecular formula of the base was further verified with the help of mass spectrometry (M = 218). Aside from the molecular ion peak, there are certain important peaks at *m/e* 174, 173, 160, 159, 158, 145,and 58 (strongest) in the mass spectrum of this alkaloid. The two peaks at *m/e* 160 and 174 seem to represent a methoxy indole grouping with one and two CH_2 groups, respectively, attached to the β position of the indole. The peaks at *m/e* 145 and 159 presumably arise from the loss of a methyl group (−15) from *m/e* 160 and 174, respectively. The genesis of the strongest peak at *m/e* 58 and other significant peaks can be best explained by assuming a skeleton (I) present in this alkaloid (see Scheme I).

SCHEME I



The above evidences together with the pmr spectral data of the alkaloid in $CDCl_3$ [one-proton singlet at τ 1.58 (NH), three-proton singlet at τ 6.08 (OCH_3), and

(1) Department of Pure Chemistry, University College of Science, Calcutta, India.

(2) S. Ghosal and B. Mukherjee, *Chem. Ind.* (London), 794 (1965).

(3) A. Chatterjee and S. Ghosal, *J. Indian Chem. Soc.*, **42**, 123 (1965), and references cited therein.