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The Synthesis of Seneciphyllic Acid (1)

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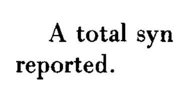
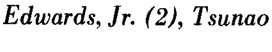
A total synthesis of seneciphyllic acid, the necic acid of the *Senecio* alkaloid seneciphylline, is reported.

The structure of the *Senecio* alkaloid, seneciphylline, has been formulated (4-7) as I and studies relating it to other alkaloids have been reported (7,8). Seneciphyllic acid, the necic acid derived from this alkaloid, can exist in the *cis* and *trans* configurations (9). When dilute aqueous alkali is used in the hydrolysis step (4), the *cis* acid (II) is formed whereas the *trans* isomer is produced with alcoholic potassium hydroxide. On heating with dilute hydrochloric acid, the *cis* acid is converted to the *trans* isomer. The original geometric assignments were later confirmed (5) by nuclear magnetic resonance spectroscopy. Studies on the reduction of seneciphylline with lithium aluminum hydride indicate (7) that the acid has the *cis* configuration in the alkaloid. To confirm the structures assigned to these acids (II and III), (R)-2-hydroxy-3-methylene-5-heptene-2,5-dicarboxylic acid, the following synthesis was carried out.

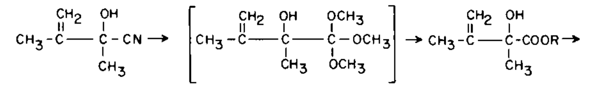


I



II cis

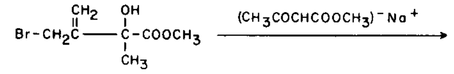
III trans



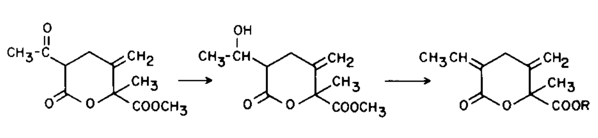
IV

V R=CH$_3$

VI R=H



VII



VIII

IX

X R=CH$_3$

XI R=H

The reaction of the cyanohydrin IV, prepared from 3-methyl-3-buten-2-one, with methanol-anhydrous hydrogen chloride gave the ortho ester. This compound could not be obtained solvent free and the structure was assigned on spectroscopic data and on hydrolysis to the ester V. Saponification of V gave the β,γ-unsaturated acid VI. Halogenation of the ester V with *N*-bromosuccinimide gave VII and the alkylation of methyl acetoacetate either through the enolate anion or the enamine with this allyl bromide gave the δ-lactone, VIII. The selective reduction of the β-keto group in VIII to give IX has been reported (13). With the common selective basic metal hydride reducing agents, for example sodium borohydride, VIII enolized and no reduction of the β-keto group occurred. Dehydration of IX gave a mixture of the racemates *cis*-X (7%) and *trans*-X (41%). These geometric ester lactone racemates were separated by cloumn chromatography and gave on hydrolysis the racemates of *cis*- and *trans*-seneciphyllic acid. Both acid racemates were resolved with cinchonidine and in each case the diastereomeric salts were isolated. Decomposition of the cinchonidine salts afforded *cis*- and *trans*-seneciphyllic acid (II and III) and the corresponding enantiometers. Also carried out was the vacuum sublimation of (±)-*trans*-seneciphyllic acid at 90° to give the (±)-*trans*-acid lactone (XI).

EXPERIMENTAL (14)

2-Hydroxy-2,3-dimethyl-3-butenenitrile (IV).

The general directions of Tanaka and Murata (15) were used. To 100 g. (1.19 mole) of 3-methyl-3-buten-2-one was added dropwise with stirring at -5° a solution of 36 g. (1.33 mole) of hydrogen cyanide in 36 ml. of methanol after which 3.2 ml. of 20% potassium carbonate solution was added dropwise. The mixture was stirred at

-5° for one hour and neutralized with 2.2 ml. of 20% sulfuric acid. The methanol was removed by water pump vacuum and the residue was added to 100 ml. of water and extracted with ether. The dried ether was evaporated on a steam bath and the cyanohydrin distilled, b.p. 57-59° (1.5 mm.), 88 g. (66%). The infrared spectrum (liquid film) showed absorption at 3400, 1145 (OH), and 2247w cm^{-1} (CN).

Anal. Calcd. for C_6H_9NO: C, 64.84; H, 8.16; N, 12.60. Found: C, 65.10; H, 8.25; N, 12.29.

Methyl 2,3-Dimethyl-2-hydroxy-3-butenoate (V).

To a cold (0°) stirred solution of 40.5 g. (0.365 mole) of the cyanohydrin and 29 ml. (0.723 mole) of methanol in 32 ml. of anhydrous ether was added 16 g. of anhydrous hydrogen chloride. The pale yellow solution was allowed to stand at this temperature overnight and then neutralized with a saturated solution of potassium carbonate. This was extracted with ether and after drying and distillation of the ether, the fraction boiling at 95-100° (10 mm.) was collected, 30 g. On standing, this cut solidified and was recrystallized first from petroleum ether (90-120°) and then from benzene, to give colorless crystals, m.p. 51-52° (Found: C, 57.50; H, 8.84; N, 0.00). The infrared spectrum (chloroform) had a strong band at 1650 cm^{-1} and others of diagnostic use at 3546, 3280 and 912 cm^{-1}. Nmr, (carbon tetrachloride): doublet at δ 4.9 and singlets at δ 3.7, 1.7 and 1.5. Areas indicated the product was contaminated with ether or alcohol. This material sublimed at room temperature and atmospheric pressure. This apparent ortho ester (37 g.) was stirred with a sulfuric acid solution (25 g. in 225 ml. water) at 50° for 2 hours and then extracted with ether. After drying, distillation gave a 95% yield of the ester, b.p. 90-95° (15 mm.). The product was redistilled, b.p. 64-65° (10 mm.). The infrared spectrum (liquid film) showed absorption at 3500 (OH), 1730 (C=O), and 1645, 908 cm^{-1} (C=C).

Anal. Calcd. for $C_7H_{12}O_3$: C, 58.31; H, 8.39; mol. wt. 144. Found: C, 58.35; H, 8.73; mol. wt. 134.

2,3-Dimethyl-2-hydroxy-3-butenoic Acid (VI).

To 1 g. of barium hydroxide octahydrate in 12 ml. of water, there was added 1 g. of the above ester and the mixture was refluxed for one hour. Carbon dioxide was passed through the mixture until it was basic to litmus. After filtration the solution was made acid to Congo red paper by the addition of 5% hydrochloric acid and continuously extracted for 3 hours with ether. After drying, the ether was removed on a steam bath to give 0.5 g. of colorless crystals, m.p. 75-77°. After several recrystallizations from cyclohexane, the melting point was 87-88°. The infrared spectrum (chloroform) showed absorption at 1700 (C=O) and 1642, 910 cm^{-1} (C=C) with a typical COOH absorption in the 2500-3600 cm^{-1} range. Nmr spectrum (deuterochloroform): singlet at δ 7.52; quartets at δ 5.22 and 5.03; double doublet at δ 1.82 and singlet at δ 1.59.

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75; neut. eq., 130. Found: C, 55.41; H, 7.69; neut. eq. 133.

Methyl 3-Bromomethyl-2-hydroxy-2-methyl-3-butenoate (VII).

To a solution of 25 g. (0.174 mole) of methyl 2,3-dimethyl-2-hydroxy-3-butenoate in 150 ml. of carbon tetrachloride, there was added 30.9 g. (0.174 mole) of *N*-bromosuccinimide and 0.3 g. of benzoyl peroxide. After stirring under reflux for 3 hours, the succinimide was filtered and the carbon tetrachloride removed under reduced pressure. The product distilled, b.p. 53-65° (0.35 mm.), 19 g. (46%). On redistillation, this gave a material with b.p. 54-55° (0.25 mm.), n_D^{20} 1.4920. The infrared spectrum (liquid film) showed absorption at 3500 (OH), 1730 (C=O) and 1643, 930 cm^{-1} (C=C). Nmr spectrum (carbon tetrachloride): singlet at δ 1.56, singlet at δ 3.78, quartet at δ 4.08, and singlet at δ 5.48.

Anal. Calcd. for $C_7H_{11}BrO_3$: C, 37.69; H, 4.97; mol. wt., 223. Found: C, 38.06; H, 4.74; mol. wt., 246.

Methyl 5-Aceto-2-hydroxy-2-methyl-3-methylenehexanedioate, 2(δ)-Lactone (VIII).

To 0.09 mole of sodium methoxide in 78 ml. of methanol, there was added dropwise with stirring 11.6 g. (0.1 mole) of methyl acetoacetate. After stirring at room temperature for 30 minutes, 18 g. (0.08 mole) of the bromo compound dissolved in 42 ml. of methanol was added with stirring and then refluxed for 4 hours. The methanol was removed at room temperature under vacuum and the residue was added to water. This was extracted with ether and after drying, the ether was removed on a steam bath. The fraction, b.p. 90-135° (0.15 mm.), was collected and on standing crystallized to give 5.8 g. (32%). Recrystallization from methanol or *n*-heptane gave colorless crystals, m.p. 96-97°. This compound has no absorption in the ultraviolet. Nmr spectrum (carbon tetrachloride): the three methyl groups all gave sharp singlets (3H) at δ 1.48, 1.63 and 3.65 and the multiplicities and coupling constants for the vinyl protons (2H), δ 5.01 and 5.09 were as expected. The other three hydrogens gave the most complex pattern, δ 2.6-2.75 and 2.8-2.9 (3H) and appears to be an ABC pattern.

Anal. Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24; mol. wt., 226. Found: C, 58.30; H, 6.12; mol. wt., 218.

An active hydrogen determination with lithium aluminum hydride gave after equilibrium at 70° for 1 hour, 0.86 moles/mole.

The sodium salt of the corresponding hydroxy acid was prepared from the lactone by adding one mole of 0.5 *N* sodium hydroxide to a methanol solution and allowing it to stand overnight at room temperature. Evaporation of the solvent gave the sodium salt which was soluble in chloroform. The infrared spectrum (chloroform) showed absorption at 3400 (OH) and 1600 (COO^-) cm^{-1}. From this sodium salt the benzyl ester was prepared and used for selective reduction studies.

The alkylation of methyl acetoacetate by this allyl bromide was also studied using the enamide procedure (16) with dimethylamine and pyrrolidine. Both gave lower yields than the above procedure.

Methyl 5-Ethylidene-2-hydroxy-2-methyl-3-methylenehexanedioate 2(δ)-Lactone (X).

The product (0.74 g.) obtained (13) from the morpholine borane reduction of VIII was placed in a sublimation apparatus and 8 drops of 85% phosphoric acid was added. This was heated at 145-150° for 1 hour at atmospheric pressure to give 38 mg. of sublimate. From the infrared spectrum this appeared to be the β,γ-isomer. Further heating for 4 hours at 20 mm. at the same temperature gave 472 mg. of sublimate. This was dissolved in 2 ml. of ether and 4-5 ml. of petroleum ether (30-60°) were added. After standing in the refrigerator for 48 hours, the 230 mg. of crystals, m.p. 63-64.5°, were filtered and recrystallized from ether-petroleum ether, m.p. 65-66°. The infrared spectrum (chloroform) had absorption at 1742, 1721 (C=O) and at 1634 cm^{-1} (C=C). This was (±)-*trans* X and slowly decomposed on standing at room temperature.

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.14; H, 6.56.

The above filtrate was evaporated to dryness and residue (230 mg.) chromatographed on a 25 g. silica gel (E. Merck AG, 0.08 mm.) column, and eluted with purified chloroform.

TABLE I

Fraction	Ml	Material (mg.)
1-8	240	β,γ-isomer (60)
9-14	120	*cis* (X) (47)
15-17	46	*cis* and *trans* (X) (8)
18-25	280	*trans* (X) (90)

The *cis* ester-lactone (X) was an oil and the infrared spectrum (chloroform) had absorption at 1740 (C=O) and a weak band at 1613 cm^{-1} (C=C). The symmetrical methyl group bending absorption is split (1358 and 1374 cm^{-1}) in the *cis* isomer because of steric interaction, whereas this absorption in the *trans* isomer is stronger and found at 1372 cm^{-1}. Similar results were reported (13) for senecic and integerrinecic acid lactone methyl esters.

(±)-*trans*-Seneciphyllic Acid (III).

To a solution of 200 mg. of *trans*-X (m.p. 63-64.5°) in 1 ml. of ethanol, there was added 0.6 g. of barium hydroxide octahydrate and 5 ml. of water. This mixture was refluxed for 1.5 hours and then saturated with carbon dioxide gas. After filtration the aqueous phase was acidified to Congo red with 5% hydrochloric acid and evaporated to dryness under reduced pressure at room temperature. The residue was refluxed with ether several times and on evaporation of the ether, the residue crystallized, m.p. 156-158°, 191 mg. (94%). This was recrystallized from ether-petroleum ether to give colorless crystals, m.p. 161-162°. A mixture melting point with *trans*-seneciphyllic acid (m.p. 144-145°) was 145-147°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.94; H, 6.54.

(±)-*trans*-Seneciphyllic Acid Lactone (XI).

In a small sublimation apparatus, there was placed 48 mg. of (±)-*trans*-seneciphyllic acid and this was heated to 160° for a few minutes to melt the crystals. It was then cooled to 90° and kept at 0.1 mm. for 3 hours. The sublimate was removed by ether and on evaporation gave 36 mg. (75%) of crystals. These were recrystallized twice from benzene and twice from ether-petroleum ether to give colorless crystals, m.p. 151-152°. A mixture melting point with that prepared (m.p. 145-147°) from seneciphyllic acid 149-150°. The infrared spectra (chloroform) were identical.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.49; H, 6.17.

Resolution of (±)-*trans*-Seneciphyllic Acid.

A mixture of 0.16 g. (0.75 mmole) of synthetic (±)-*trans*-seneciphyllic acid and 0.22 g. (0.75 mmole) of cinchonidine was dissolved in 25 drops of methanol and heated to the boiling point and 4.8 ml. of ethyl acetate were added. After thorough stirring and heating, the solution was placed in a refrigerator and after 2 days the crystals were filtered and washed with ethyl acetate, 230 mg., m.p. 181-184°. After 4 recrystallizations from methanol-ethyl acetate, the melting point was 199-200°, $[\alpha]_D^{27^\circ}$, -80° (c. 1.067 ethanol). A mixture melting point with the cinchonidine salt (m.p. 196-198°) of *trans*-seneciphyllic acid was 198-199°. The infrared spectra (potassium bromide) of these two salts were identical.

Anal. Calcd. for $C_{29}H_{36}N_2O_6$: C, 68.48; H, 7.14; N, 5.51. Found: C, 68.53; H, 7.04; N, 5.23.

The filtrate from the above crystals (m.p. 181-184°) was evaporated to dryness under reduced pressure to give a residue of 140 mg. On recrystallization from acetone, 80 mg. of colorless crystals, m.p. 158-161°, were obtained and after three recrystallizations, the melting point was 161-162° (50 mg.); $[\alpha]_D^{27^\circ}$ -68° (c. 0.801, ethanol).

Anal. Calcd. for $C_{29}H_{36}N_2O_6$: C, 68.48; H, 7.14; N, 5.51. Found: C, 68.49; H, 7.17; N, 5.35.

trans-Seneciphyllic Acid (III).

(a) The cinchonidine salt, m.p. 199-200° (40 mg.) was dissolved in 5 ml. of 5% hydrochloric acid and extracted three times with 4 ml. of ether. After washing with water and drying, the ether was evaporated to give 11 mg. of crystals, m.p. 144-146°. Two recrystallizations from ether-petroleum ether, 30-60°, gave 8 mg. of colorless crystals, m.p. 145-146°. A mixture melting point with seneciphyllic acid (m.p. 144-145°) was 145-146°. The infrared spectra (potassium bromide) were identical.

(b) In the same way, 20 mg. of the cinchonidine salt, m.p. 161-162°, gave 5 mg. of an acid, m.p. 144-145°; $[\alpha]_D^{25^\circ}$ +9.0° (c. 1.021, ethanol). Equal amounts of this acid and the above enantiomer were dissolved in ether. After evaporation of the ether, the crystals had a m.p. 158-160°. A mixture melting point with the racemate (m.p. 161-162°) was 160-162°.

(±)-*cis*-Seneciphyllic Acid.

This racemate (45.9 mg.) was prepared from the (±)-*cis*-X (45 mg.) in the same way as the above *trans* racemate. After several recrystallizations from ether-petroleum ether, the colorless crystals had a m.p. 97-98°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.13; H, 6.60.

Resolution of (±)-*cis*-Seneciphyllic Acid.

To a solution prepared by heating a mixture of 41.2 mg. of cinchonidine in 8 drops of methanol, there was added 0.7 ml. of ethyl acetate and 0.6 ml. of ether. After standing in the refrigerator for 6 days, the crystals, 43 mg. m.p. 160-165°, were filtered and recrystallized several times from acetone, 22 mg., m.p. 165-167°; $[\alpha]_D^{27^\circ}$ -92° (c. 1.016, ethanol). A mixture melting point with the cinchonidine salt of *cis*-seneciphyllic acid (m.p. 165-167°) was undepressed.

Anal. Calcd. for $C_{29}H_{36}N_2O_6 \cdot CH_3COCH_3$: C, 67.82; H, 7.47; N, 4.94. Found: C, 68.06; H, 7.46; N, 5.01.

The above filtrate was evaporated to dryness and the residue dissolved in 20 ml. of ether by refluxing. This solution was condensed to 2 ml. and placed in a refrigerator to give 25 mg. of crystals. After three recrystallizations from water, the melting point was 151-153°. On standing *in vacuo* for 24 hours, the melting point was 184-187° and on recrystallization from acetone, 192-194°; $[\alpha]^{26^\circ}$ -87° (c. 0.937, ethanol).

Anal. Calcd. for $C_{29}H_{36}N_2O_6$: N, 5.51. Found: N, 5.27.

cis-Seneciphyllic Acid (II).

(a) From 14 mg. of the cinchonidine salt, m.p. 165-167°, there was obtained in the same way as from the *trans*-cinchonidine salts, 5.2 mg. of crude *cis*-acid. Recrystallization from ether-petroleum ether, 30-60°, gave colorless crystals, m.p. 114-116°. A mixture melting point with *cis*-seneciphyllic acid (m.p. 114-115°) was undepressed. The infrared spectra (potassium bromide) were identical.

(b) From 20 mg. of the cinchonidine salt, m.p. 190-192°, there was in the same way obtained 4.2 mg. of the crude *cis*-acid. Recrystallization from ether-petroleum ether gave crystals, m.p. 112-114°. A 1:1 mixture of these two enantiomeric acids gave on crystallization the racemate, m.p. 94-96°.

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(9) *Cis* and *trans* refer to the methyl and carboxyl arrangement at the double bond. This acid is also reported in the literature as α-longinecic acid (10), isoseneciphyllic acid (11), and seneciphyllic acid (4). We have used the nomenclature of Kropman and Warren (12) and the thermodynamically more stable geometrical isomer III would be *trans*-seneciphyllic acid.

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