acetate–petroleum ether produced desacetyldihydroisotenulin; it had m.p. 196–198°; a mixed melting point with authentic material was 199–202°; infrared: 3520, 1760, 1740 cm.$^{-1}$.

Dehydrodesacetyldihydroisotenulin.—The method of Herz and Mitra[9] was used. Needles (30%) were obtained from ethyl acetate–petroleum ether: m.p. 146–147°; infrared: 1755–1760, 1730, 1697 cm.$^{-1}$ (lit.,[9] m.p. 144–146°; infrared: 1778, 1758, 1710 cm.$^{-1}$).

N.m.r. spectra were obtained at 60 Mc. in deuteriochloroform, with tetramethylsilane as internal standard. The following tabulation describes the peaks observed, in cycles per second.

Bigelovin: 72, singlet, 3H (C-5 methyl); 73, 83, doublet, 3H (C-10 methyl); 87–108, multiplet (CH_2, CH); 118, singlet, 3H (acetyl methyl); 177–200, multiplet (allylic C-1, C-7 protons); 268, 271, 278, 281, 290, 293, split triplet, 1H (C-8 proton); 334, 342, doublet, 1H (C-6 proton); 364, 367, 370, 373, split doublet, 1H (C-3 proton); 354, 357, 372, 375, split doublet, 2H (C-13 protons, exocyclic methylene); 469, 472, 463, 465, split doublet, 1H (C-2 proton).

Dihydrobigelovin[28]: 63, 64, 68, 70, 73, multiplet (methyl); 65, singlet, 3H (C-5 methyl); 77–106, multiplet (CH_2, CH); 118, singlet, 3H (acetyl methyl); 170–195, 133–158, multiplets (protons at C-3, C-7); 260–263, 271, 274, 281, 284, split triplet, 1H (C-8 proton); 327, 335, 317, 326, two doublets (C-6 proton); 351, 354, 372, 375, split doublet, 2H (C-13 protons, exocyclic methylene).

Tetrahydrobigelovin: 63, 67, 74, multiplet (methyl); 66, singlet, 3H (C-5 methyl); 80–112, multiplet (CH_2, CH); 117, singlet, 3H (acetyl methyl); 130–170, multiplet (C-3, C-11 protons); 260, 262, 270, 272, 282, 284, split triplet, 1H (C-8 proton); 318, 316, doublet, 1H (C-6 proton).

Acknowledgment.—The n.m.r. spectra were obtained by Dr. N. S. Bhacca of Varian Associates, who was helpful in their interpretation. One of us (B.A.P.) is grateful for a National Science Foundation Predoctoral Fellowship, 1956–1961.

(28) Some contamination with the tetrahydro compound, as revealed by comparison of the n.m.r. spectra. The data are gived to show the absence of the C-2 and C-3 vinyl protons and the presence of the exocyclic methylene group.

Angularine, a New Pyrrolizidine Alkaloid from *Senecio angulatus* L.

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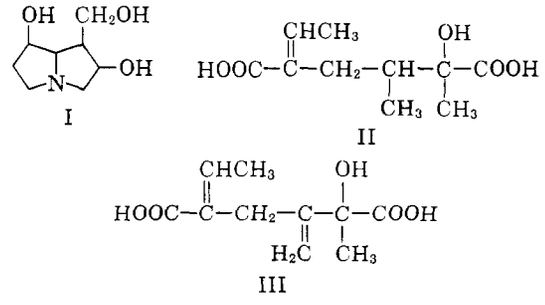
Received July 27, 1962

Rosmarinine, the senecic acid ester of rosmarinecine, and a new alkaloid, angularine, the corresponding seneciphyllic acid ester, have been isolated from *Senecio angulatus* L.

Assays of a number of hitherto unexamined species of the genus *Senecio* led to the observation that *Senecio angulatus* L., an ornamental plant native to South Africa and cultivated in Southern California, yields up to 1.5% (dry basis) of crystalline alkaloid. The crude alkaloid, isolated by the usual methods, showed variable melting point behavior from one preparation to another, and gave analytical results that agreed with a molecular formula within the limits of $C_{18}H_{25-27}NO_6$. On paper chromatograms the substance showed an elongated spot which, by comparison with the well defined spots given under the same conditions by specimens of other, known, *Senecio* alkaloids, appeared to consist of two components.

Hydrolysis of the unresolved alkaloid mixture gave the known pyrrolizidine base, rosmarinecine (I),[1,2] identified by comparison with an authentic specimen and the preparation of its triacetate picrate, dibenzoate, anhydro base picrate, and anhydro base acetate picrate. These were identified by their properties and by direct comparison with authentic specimens.[3]

The other product from the hydrolysis of the alkaloid mixture was a crystalline acid that was at first regarded as a single compound and which was at length found to be a mixture. Its melting point was 114–116° when first isolated, but this altered upon repeated recrystallization, eventually broadening to about 116–129°. Separation of the mixture into senecic (II) and seneciphyllic (III) acids was achieved by partition chromatography on a silicic acid column.



I

II

III

Comparison of the infrared absorption spectrum of a mixture of equal parts of senecic and seneciphyllic acids, with that of the crude mixture of acids obtained from the unresolved alkaloid gave an indication that the plant contains roughly equal amounts of the corresponding alkaloids. The n.m.r. spectrum of the methyl esters of the acid mixture could be interpreted on the same grounds: the methyl groups of the ester groupings gave sharp 3H

(1) M. Richardson and F. L. Warren, *J. Chem. Soc.*, 452 (1943).

(2) L. J. Dry, M. J. Koerkemoer, and F. L. Warren, *ibid.*, 59 (1955).

(3) We are grateful to Prof. F. L. Warren for specimens of rosmarinecine and the picrate of tri-O-acetylrosmarinecine.

singlets at 6.46 and 6.50 τ and the methylene group of the seneciphyllic ester produced a doublet at 5.03 and 5.38 τ. Peaks (3H each) at 8.54 and 8.93 τ were due to the methyl groups on the hydroxyl-bearing carbon atoms of the seneciphyllic and senecic acid esters, respectively; and a doublet of reduced intensity is found at 9.16 τ, representing the CH—CH_3 (methyl) group of the senecic ester component of the mixture. Finally, the vinyl hydrogen atom of the ethylidene group (present in both acids) produced a signal (multiplet, 1H) at 4.26 τ, and the allylic methyl group gave a doublet at 8.09 τ.

Separation of the crude alkaloid into the two pure components was at length accomplished by partition chromatography on a buffered Celite column. Elution with carbon tetrachloride–chloroform mixtures yielded, in earlier fractions, pure rosmarinine, identified by its properties and direct comparison (mixed melting point, infrared spectrum) with an authentic specimen; and, in later fractions, the new alkaloid, angularine. Angularine differs but little from rosmarinine in physical properties (melting point, optical rotation, chromatographic behavior), but the two compounds were clearly distinguished by elemental analysis, infrared absorption spectra, and by a large depression in the mixed melting point.

A specimen of the crude, crystalline alkaloid mixture from *S. angulatus* was tested for hepatotoxic activity by Dr. K. K. Chen, Eli Lilly and Co., who reported that it produced no evidence of liver damage in experimental animals. This result agrees with that of a test performed earlier by Dr. Chen and his colleagues[4] using a sample of pure rosmarinine supplied by Prof. F. L. Warren, and indicates that angularine, like rosmarinine, is devoid of hepatotoxic activity.

Experimental

Infrared spectra were determined in potassium bromide disks. Concentrations given for measurements of optical rotations are in g. per ml. Melting points were determined on a Fisher–Johns block.

Extraction of Alkaloids.—Fresh *Senecio angulatus* (4.16 kg.) was cut into small pieces, soaked in methanol overnight, and then ground in a Waring Blendor. The mixture was filtered and the plant residue was extracted (Soxhlet) with methanol. The combined methanolic extracts were evaporated in a flash evaporator, the final solution being adjusted to a 2-l. aqueous solution made 2 *N* in hydrochloric acid. Zinc dust was added and the mixture stirred for 24 hr. to reduce any N-oxides that might be present. The filtered solution was first washed with chloroform, then made alkaline with ammonia and extracted with chloroform. The dried chloroform extract was evaporated to give 51 g. of crude alkaloid. Recrystallized from ethyl acetate, the alkaloid mixture had m.p. 180–182°. On a paper chromatogram (1-butanol–5% acetic acid) it gave an elongated spot at R_f about 0.45.

Separation of Alkaloid Mixture.—A mixture of 1100 g. of Celite and 200 ml. of 1 *M* phosphate buffer, pH 4.0, was homogenized with carbon tetrachloride in a Waring Blendor. A column was prepared by allowing this mixture to settle to a height of 50 cm. in a 5-cm. tube, and a solution of 1.0 g. of the alkaloid mixture, dissolved in chloroform, was added to the column. Elution was carried out with a carbon tetrachloride (80%)–chloroform (20%) mixture, with the collection of 50-ml. fractions. Rosmarinine was eluted first (fractions 43–49), followed by angularine.

Rosmarinine, m.p. 195–200°, as recovered from the column, was recrystallized from ethyl acetate, after which it melted at 205–208° and had $[\alpha]^{25}D$ −90.2 (*c*, 0.0193, ethanol). Reported[2] m.p. 209°, $[\alpha]^{24}D$ −91.5° (1%, methanol). The alkaloid showed no depression in melting point when mixed with an authentic sample of rosmarinine.[3]

Anal. Calcd. for $C_{18}H_{27}NO_6$: C, 61.15; H, 7.70. Found: C, 61.38; H, 7.87.

Angularine, m.p. 175–185° as recovered from the column, was recrystallized from ethyl acetate, when it had m.p. 200–201°, $[\alpha]^{25}D$ −98.0 (*c*, 0.0223, ethanol). A mixture of angularine and rosmarinine melted at 185–195°.

Anal. Calcd. for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17. Found: C, 61.69; H, 7.40.

Hydrolysis of Alkaloid.—Five grams of the original alkaloid mixture was hydrolyzed with a solution of 10 g. of barium hydroxide octahydrate in 50 ml. of water with refluxing for 2 hr. After cooling, the solution was saturated with carbon dioxide and the barium carbonate removed by filtration. The filtrate was acidified to congo red with hydrochloric acid and extracted thoroughly with ether.

The combined ether extracts were dried and evaporated to dryness *in vacuo* to yield about 2.5 g. of crystalline acid, m.p. 114–116°. After several recrystallizations from ethyl acetate–petroleum ether (b.p. 60–80°) the melting point was 116–129°, and no improvement in the melting point was obtained by further recrystallization. The rotation of this mixture was $[\alpha]^{25}D$ −9°, and the analytical figures were inconclusive.

Anal. Calcd. for $C_{10}H_{14}O_6$: C, 56.07; H, 6.59. Calcd. for $C_{10}H_{16}O_6$: C, 55.54; H, 7.46. Found: C, 55.64; H, 6.80.

A paper chromatogram of this mixture showed only a single spot, and the infrared spectrum was closely similar to those of both senecic and seneciphyllic acids, and nearly identical to the spectrum of an equal mixture of these two acids.

After extraction of the acid component, the hydrolysis solution was made basic with sodium hydroxide and evaporated to dryness *in vacuo*. The residue was extracted with boiling absolute ethanol and the filtered extract evaporated to dryness to yield the base as a glass which slowly crystallized. Recrystallization from methanol–acetone afforded rosmarinecine, m.p. 171–172°, $[\alpha]^{25}D$ −116.5° (*c*, 0.0106, ethanol) (reported,[2] m.p. 171–172°, $[\alpha]D$ −118°).

Anal. Calcd. for $C_8H_{15}NO_4$: C, 55.47; H, 8.73. Found: C, 55.32; H, 8.96.

The base was characterized by the preparation of the following derivatives, as described by Dry, *et al.*[2]:

Rosmarinecine triacetate (picrate): m.p. 142–143°; $[\alpha]^{25}D$ −9.1° (*c*, 0.0070, chloroform); (reported[2] m.p. 138–139.5°). A mixed melting point with an authentic sample[3] was undepressed. The infrared spectrum was identical with that of the authentic compound.

Anal. Calcd. for $C_{20}H_{24}N_4O_{13}$: C, 45.45; H, 4.59. Found: C, 45.65; H, 4.58.

Rosmarinecine dibenzoate: m.p. 179.5–180.5°, $[\alpha]^{25}D$ −9.2° (*c*, 0.0111, ethanol); (reported,[2] m.p. 179–180°).

Anal. Calcd. for $C_{22}H_{23}NO_6$: C, 69.27; H, 6.08. Found: C, 69.48; H, 6.36.

Anhydrorosmarinecine (picrate): m.p. 186–189° (reported[2] m.p. 183–185°).

Anal. Calcd. for $C_{14}H_{16}N_4O_9$: C, 43.75; H, 4.20. Found: C, 43.53; H, 4.34.

(4) C. L. Rose, P. N. Harris, and K. K. Chen, *J. Pharmacol. Exp. Therap.*, **126**, 179 (1959).

Anhydrorosmarinecine acetate (picrate): m.p. 192–194° (reported,[2] m.p. 190–192°).

Anal. Calcd. for $C_{16}H_{18}N_4O_{10}$: C, 45.07; H, 4.26. Found: C, 44.92; H, 4.25.

Separation of the Acids: Senecic and Seneciphyllic Acids.—A silicic acid column (5 × 50 cm.) was prepared with a slurry of the adsorbent in chloroform. A solution of 1.0 g. of the mixed acids (from hydrolysis of the unresolved alkaloid) in a little acetone was placed on the column, and elution was carried out with an acetone (20%)–chloroform (80%) mixture, with the collection of 50-ml. fractions. **Senecic acid** appeared in fractions 45–51, m.p. 141–143°. Purified by recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°) it had m.p. 144–147° (reported, m.p. 145–146°,[5] 151°,[2]), and $[\alpha]^{25}D$ +19.6° (*c*, 0.0138, ethanol).

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 55.54; H, 7.46. Found: C, 55.37; H, 7.31.

Seneciphyllic acid, which appeared in fractions 52–60, m.p. 105–110°, was purified by recrystallization from ethyl acetate–petroleum ether (b.p. 60–80°), when it had m.p. 115–117° (reported,[6] m.p. 118–119°), and $[\alpha]^{25}D$ −9.0 (*c*, 0.0333, ethanol).

Anal. Calc. for $C_{10}H_{14}O_6$: C, 56.07; H, 6.59. Found: C, 56.32; H, 6.88.

Acknowledgment.—This work was part of a study supported by a National Science Foundation research grant, G-8821, and a U.S. Public Health Service research grant, RG-6457.

(5) C. C. J. Culvenor and T. A. Geissman, *J. Am. Chem. Soc.*, **83**, 1647 (1961).

(6) S. Masamune, *Chem. Ind.* (London), 21 (1959).

The Homoallylic Rearrangement in the Synthesis of Amitriptyline and Related Systems

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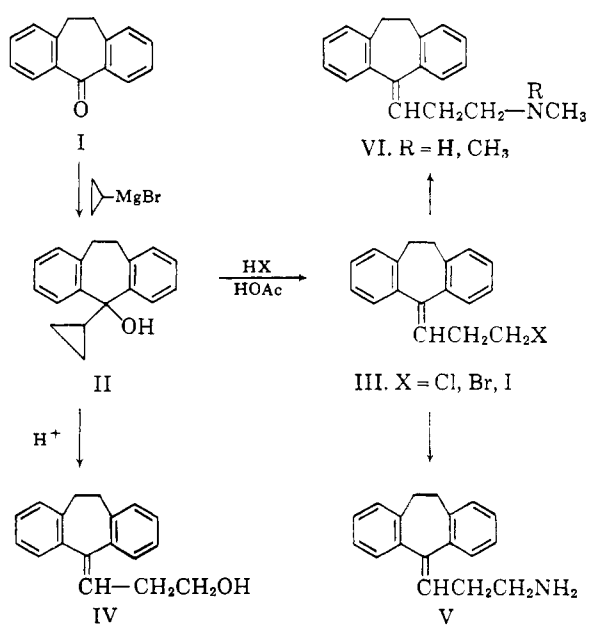
Received July 9, 1962

A novel synthesis of 5-(γ-dimethylaminopropylidene)-5H-dibenzo[*a,d*]-10,11-dihydrocycloheptene and related systems based on the homoallylic rearrangement is presented.

The effective psychotherapeutic drug amitriptyline (ELAVIL®) has been synthesized heretofore by the reaction between the Grignard reagent derived from γ-dimethylaminopropylchloride and 5H-dibenzo[*a,d*]-10,11-dihydro-5-cyclohepten-5-one.[1,4] The growing importance of an alternative approach to amitriptyline, which would likewise provide versatility in the synthesis of γ-functionally related systems, constituted the basis for the present work.

The condensation of 5H-dibenzo[*a,d*]-10,11-dihydrocyclohepten-5-one (I) with the Grignard reagent derived from cyclopropyl bromide[2] afforded the crystalline cyclopropylcarbinol (II), m.p. 73–74°, in high yield. The latter, on treatment with hydrogen chloride or hydrogen bromide in acetic acid solution, rearranged quantitatively to the corresponding γ-halopropenylcycloheptenes (III).[3,4] The corresponding iodo derivative (III. X = I) was produced from the bromide (III. X = Br) with sodium iodide in refluxing actone. The halo derivatives (III) were all highly crystalline individuals exhibiting characteristic absorption in the ultraviolet at 240 mμ (ε 14,000–17,000).

Rearrangement of the derived cyclopropylcarbinol (II) with dilute perchloric acid in dioxane at



25° proceeded smoothly with formation of the primary carbinol (IV) presumably by way of the

(1) (a) Belgian Patent, 584,061, Merck & Co., Inc.; *cf.* E. Jucker, *Chimia* (*Aarau*), **15**, 267 (1961); (b) British Patent, 858,187, 858,188, Hoffmann-LaRoche, A.G.; Belgian Patent, 609,095, Kefalas A/S; (c) M. Protiva, V. Hněvsová-Seidlová, Z. J. Vejdelek, F. Jerkovsky, Z. Votava, and J. Metysöva, *J. Med. Pharm. Chem.*, **4**, 411 (1961); (d) See also F. J. Villani, C. A. Ellis, C. Teichman, and C. Bigos, *ibid.*, **5**, 373 (1962); and South African Patent, R61/1889, Kefalas A/S.

(2) The authors are indebted to Professor H. Hart of Michigan State University for pertinent information concerning organometallic derivatives of cyclopropane.

(3) For examples of the rearrangement of cyclopropylcarbinols compare: O. Wallach, *Ann*, **360**, 82 (1908); T. A. Favorskaya and S. A. Fridman, *J. Gen. Chem. USSR*, **15**, 421 (1945); P. Bruylants and A. Dewael, *Bull. acad. roy. med. Belg.* (5), **14**, 140 (1928); M. Julia, S. Julia, and R. Guegan, *Compt. rend.*, **248**, 820 (1959). M. Julia, S. Julia, and S. Y. Tchen, *Bull. soc. chim. France*, 1849 (1961); M. S. Julia and B. S. Bourdillor, *Compt. rend.*, 951 (1961); M. Hanack, *Angew. Chem.*, **74**, 116 (1962).

(4) Since the completion of this work III (X = Br), prepared by another method, was reported by S. O. Winthrop, M. A. Davis, G. S. Meyers, J. G. Gavin, R. Thomas, and R. Barber, *J. Org. Chem.*, **27**, 230 (1962).