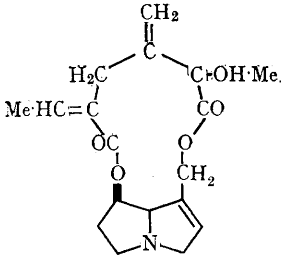
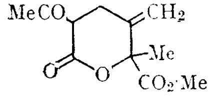
Senecio Alkaloids: The Total Synthesis of Seneciphyllic Acid

By J. D. EDWARDS, JR., TSUNAO HASE, and NOBUTAKA ICHIKAWA
(*Department of Chemistry, Lamar State College of Technology, Beaumont, Texas,* 77704, *U.S.A.*)

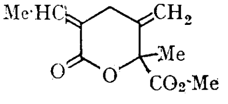
THE structure of the *Senecio* alkaloid seneciphylline[1] has been formulated as (I) and the necic acid derived from this alkaloid has been studied in several laboratories.[2,3,4] We now report the synthesis of *cis*- and *trans*-seneciphyllic acid.[5,6] The cyanohydrin (66% yield, b.p. 57—59°/1·5 mm.) of 3-methylbut-3-en-2-one was converted by the Pinner reaction into the orthomethyl ester (43%, b.p. 95—100°/10 mm., m.p. 51—52°) which gave methyl 2-hydroxy-2, 3-dimethylbut-3-enoate (95%, b.p. 64—65°/10 mm.) on hydrolysis. Treatment of this ester with *N*-bromosuccinimide gave the corresponding allyl bromide (50%, b.p. 54—55°/0·25 mm.). Alkylation of methyl acetoacetate (CH_3ONa) with this halide gave the δ-lactone[7] (II) (32%, b.p. 90—113°/0·10 mm., m.p. 96—97°). The selective reduction of the β-oxo-group in (II) was possible with morpholine borane[8] [48% reduction, 52% recovery of (II)]. Dehydration of this reduction product (sublimation apparatus, trace H_3PO_4, 145—150°/20 mm.) and separation on a silica-gel column gave[5] 7% of *cis*-(III), 41% of *trans*-(III) and 14% of the βγ-unsaturated isomer. On hydrolysis with aqueous barium hydroxide, *cis*-(III) gave *cis*-(±)-seneciphyllic acid (m.p. 97—98°) and *trans*-(III) gave *trans*-(±)-seneciphyllic acid (m.p. 161—162°). The infrared spectra ($CHCl_3$) of these racemates were identical with those of the seneciphyllic acids prepared from the alkaloid. Resolution of synthetic *cis*-(±)-seneciphyllic acid was accomplished by means of cinchonidine and gave the diastereomers (IV), m.p. 165—167°, $[\alpha]_D$ −92° and (V), m.p. 192—194°, $[\alpha]_D$ −87°. The acid,



(I)



(II)



(III)

---

[1] For a review see N. J. Leonard, "The Alkaloids," Ed. R. H. F. Manske, Academic Press, New York, 1960, Vol. VI, pp. 89—92.

[2] R. Konovalova and A. Danilova, *Zhur. obshchei Khim.*, 1948, **18**, 1198.

[3] R. Adams and M. Gianturco, *J. Amer. Chem. Soc.*, 1957, **79**, 174.

[4] S. Masamune, *Chem. and Ind.*, 1959, 21.

[5] Nomenclature of M. Kropman and F. L. Warren, *J. Chem. Soc.*, 1950, 700.

[6] Analyses and spectra are consistent with the structures given. All optical rotations were in ethanol at 27°.

[7] Only one racemate was isolated.

[8] The steric requirements of this reagent are high. For example, if (II) is first reduced at the double bond by catalytic hydrogenation, it is not possible to reduce the β-oxo-group with this reagent.

m.p. 114—116°, recovered from (IV) was identical (m.m.p. and infrared spectrum in KBr) with *cis*-seneciphyllic acid, and (V) yielded the other enantiomer, m.p. 112—114°. Resolution of synthetic *trans*-(±)-seneciphyllic acid in the same way gave the diastereomers (VI), m.p. 199—200°, $[\alpha]_D$ −80° and (VII), m.p. 161—162°, $[\alpha]_D$ −68°. From (VI) an acid, m.p. 144—146°, was obtained, identical with *trans*-seneciphyllic acid and (VII) gave the other enantiomer, m.p. 144—145°. The cinchonidine salts (IV) and (VI) were also shown to be identical (m.m.p. and infrared) with those prepared from *cis*- and *trans*-seneciphyllic acid.

(*Received, June* 14*th*, 1965; *Com.* 368.)