and developed in ascending fashion with isopropyl alcohol–ammonium sulfate (5% of each in water). Hypoxanthine (20 γ) was spotted as a control. The materials were located by visual inspection under ultraviolet light and the spots were eluted with water. The pertinent data are recorded in Table I.

Ultraviolet Absorption Spectra.—The ultraviolet absorption spectra were measured on a Beckman model DU spectrophotometer at a concentration of 10 mg. per l. For *p*H 1, 0.1 *N* hydrochloric acid was used, for *p*H 11, a Sørensen glycine–sodium hydroxide buffer.

TUCKAHOE, NEW YORK

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

The Alkaloids from *Senecio tomentosus*. Observations on the Alkaloid Jacobine and on the Structure of Jaconecic Acid

BY ROGER ADAMS, MAURIZIO GIANTURCO AND BENJAMIN L. VAN DUUREN

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Extraction of *Senecio tomentosus* affords a new alkaloid, $C_{19}H_{27}O_7N$, isomeric with the previously described otosenine. Hydrogenation with platinum or palladium as catalyst gives a tetrahydro derivative. Hydrolysis of the alkaloid yields an acid, $C_{10}H_{16}O_6$, identical with jaconecic acid first obtained by the hydrolysis of jacobine. Tomentosine with hydrochloric acid gives a chlorinated dehydrated jaconecic acid, presumably the same compound as that derived from otosenine by similar treatment. The structure of jaconecic acid is discussed in light of its physical and chemical properties. A synthetic approach to jaconecic acid involved the oxidation of isoseneciphyllic acid by perbenzoic acid. From the product, a pure dilactone and a mixture of isomeric dilactones were isolated. The first was reduced to two dihydro derivatives which were isolated in pure form. The second was reduced to a mixture of dihydro compounds. The dihydro compounds from the first were stable to thionyl chloride, the dihydro product from the second reacted with replacement of an hydroxyl with chlorine. The infrared spectrum of the resulting material is very similar to that of the product obtained by treatment of tomentosine with hydrochloric acid. The structures of the synthetic lactones are discussed.

Extraction of *Senecio tomentosus* with ethanol[1] yielded 0.006% of a mixture of two or possibly three alkaloids. By chromatography of the crude bases on Florisil and elution with carbon tetrachloride, a crystalline product was obtained. This was identified as senecionine by melting point, optical rotation, infrared spectrum and R_f value.[2,3] A chloroform fraction yielded a new alkaloid, m.p. 232°, $[\alpha]_D$ +14° ($CHCl_3$), picrate m.p. 251° dec. From analyses of the pure alkaloid and of its picrate, the empirical formula $C_{19}H_{27}NO_7$ for the alkaloid was deduced. An alkaloid with the same empirical formula, m.p. 218–219°, $[\alpha]_D$ +20.8° ($CHCl_3$), picrate m.p. 233–235° dec., has been isolated from *Senecio othonnae*[4] and *Senecio renardi*[5] and was named otosenine. Since the physical properties of otosenine and its picrate are so different from those of the alkaloid obtained from *Senecio tomentosus* and its picrate, these two alkaloids are assumed not to be identical. The name tomentosine is consequently suggested for the alkaloid isolated in the present investigation.

Tomentosine, on hydrogenation with a palladium–strontium carbonate catalyst, absorbed two moles of hydrogen to give tetrahydrotomentosine, $C_{19}H_{31}NO_7$, m.p. 157–158°, $[\alpha]_D$ −9.2° ($CHCl_3$). With platinum as catalyst, hydrogenation proceeded to an uptake of about 2.5 moles of hydrogen indicating perhaps the partial reduction of a ketone group. From the oily reaction product a small amount of tetrahydrotomentosine was all that could be isolated.

The infrared spectrum of tomentosine shows a band at 1745 cm.$^{-1}$ which may indicate a small ring ketone structure.[6] Zhdanovich and Menshikov[4] identified the presence of a ketone in the basic moiety from otosenine by the formation of an oxime of reduced otonecine. The spectrum of tomentosine shows other bands, an hydroxyl at 3540, an ester carbonyl at 1725 and a carboxyl (zwitterion) at 1612 cm.$^{-1}$. In addition, bands in the vicinity of 880, 1160, 1210 and 1260 cm.$^{-1}$ in the spectrum of the alkaloid are consistent with the assumption of the presence of an epoxide function in the molecule.[7] A band at 830 cm.$^{-1}$ corresponds to a CHR=CR′R″ type of carbon–carbon double bond. This band is present in the spectra of all Senecio alkaloids whose necine contains the $RCH{=}C(R')CH_2OH$ grouping.

Significant features of the absorption spectrum of the tetrahydrotomentosine (Table I) are: complete absence of an ester C=O and C=C bands and the presence of hydroxyl, keto C=O and carboxyl (zwitterion) bands as in tomentosine. The four bands from 880 to 1260 cm.$^{-1}$ previously discussed for tomentosine and assigned to an ethylene oxide function are also present in the spectrum of tetrahydrotomentosine. When tetrahydrotomentosine in aqueous sodium bicarbonate was continuously extracted with ether and the ether evaporated, an oil, which could not be crystallized, re-

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(1) The method employed was that described in a previous paper; R. Adams, K. E. Hamlin, C. F. Jelinek and R. F. Phillips, THIS JOURNAL, **64**, 2760 (1942). An earlier plant sample yielded 0.07% tomentosine unaccompanied by any other alkaloids.

(2) The determination of melting points alone is not a reliable guide for purity or identity of a Senecio alkaloid, since mixtures frequently melt at the same temperature as a single component.

(3) The carbon tetrachloride–chloroform fraction yielded more crystalline material, also identified as senecionine, together with a dark resinous material, from which, after chromatography, the picrate of a base isomeric with tomentosine was isolated (see Experimental).

(4) E. S. Zhdanovich and G. P. Menshikov, *J. Gen. Chem. U.S.S.R.*, **11**, 835 (1941).

(5) A. V. Danilova and R. A. Konovalova, *ibid.*, **20**, 1921 (1950).

(6) The frequencies of absorption of the carbonyl of cyclobutanone, cyclopentanone and cyclohexanone are 1775, 1740 and 1715 cm.$^{-1}$, respectively (R. S. Rasmussen "Progress in Chemistry of Natural Products," Vol. 5, Springer Verlag, Vienna, 1948, p. 331). 17-Ketosteroids show characteristic absorption around 1743 cm.$^{-1}$ (L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corp., New York, N. Y., 1949).

(7) J. E. Field, J. O. Cole and D. E. Woodford, *J. Chem. Phys.*, **18**, 1298 (1950).

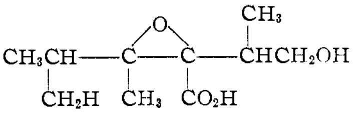
sulted. Its infrared spectrum had a band at 1732 cm.$^{-1}$, thus indicating the presence of a keto carbonyl group in the basic moiety of tetrahydrotomentosine and hence in the basic moiety of tomentosine.

Hydrolysis of tomentosine with aqueous barium hydroxide, followed by separation of the basic and acidic fragments, yielded a colorless crystalline acid, $C_{10}H_{16}O_6$, m.p. 183–184°, $[\alpha]^{25}\text{D}$ +28.1° (95% EtOH). From its melting point and rotation it appeared to be identical with jaconecic acid previously reported by various authors. The basic product was a brown resin which resisted crystallization and formation of crystalline derivatives.

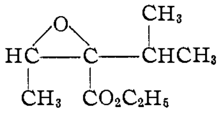
Jaconecic acid was first isolated by Manske by the hydrolysis of a mixture of alkaloids from *Senecio jacobea*, which contained the alkaloid jacobine.[8,9] The infrared spectrum of the acid obtained in this investigation was the same as that of an authentic sample kindly furnished by Dr. Manske. Barger and Blackie[10] also reported the isolation from *Senecio jacobea* L., *Senecio cineraria* D. C. and *Senecio paludosus*, of jacobine, which on hydrolysis with alkali gave jaconecic acid, m.p. 182°, $[\alpha]\text{D}$ +31.7°.[11] Hosking and Brandt[12] described an acid, m.p. 180–181°, obtained by hydrolysis of jacobine from *Senecio jacobea* L., which was undoubtedly jaconecic acid. Zhdanovich and Menshikov[4] hydrolyzed otosenine with alkali to obtain an acid, m.p. 180–182°, $[\alpha]\text{D}$ +30.6° (EtOH), which they believed identical with jaconecic acid.

The following properties[13] of jaconecic acid have been determined by Bradbury and have been confirmed in this Laboratory. It is dibasic.[4,13] It gives a yellow color with aqueous ferric chloride indicative[14] of an α-hydroxy acid. This grouping was confirmed by oxidation with lead tetraacetate, which yielded one mole-equivalent of carbon dioxide. It gives a monoacetate. A negative reaction with periodate reagent establishes the absence of a glycol structure.[15] The acid absorbs no hydrogen in presence of either platinum oxide or Raney nickel. The infrared spectrum indicates absence of a ketone C=O and a carbon–carbon double bond, but the presence of an alcoholic hydroxyl, carbon-methyl, an epoxide group[16] and two acid carbonyls, of which one corresponds to an α-hydroxy acid.[17] Barger and Blackie[10] reported that jaconecic acid contained three or more carbon-methyl groups, Bradbury[13] the presence of three such groups, and in this investigation three (2.3) were found.

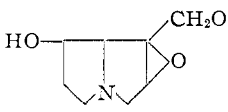
On the basis of these data Bradbury suggested formula I for jaconecic acid.



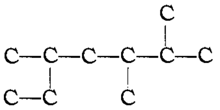
I



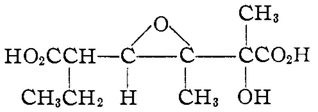
II



III



IV



V

Structure I, however, does not explain satisfactorily all the experimental data reported by Bradbury and confirmed in this investigation. A compound of structure I might be expected to exist as or to readily form a lactone.[18] Such a structure should not give a color with ferric chloride,[19] nor a molecule of carbon dioxide with lead tetraacetate, both of which are reactions characteristic of an α-hydroxy acid. In order to explain these two facts, it must be assumed that the epoxide linkage in structure I is opened by these reagents to an α-hydroxy acid. If this were the case, jaconecic acid should not be stable to aqueous hydrochloric acid and aqueous alkali as reported by Bradbury.[13]

The epoxide linkage in compound II, with a structure somewhat similar to I, is hydrolyzed easily by methanol in presence of a little sulfuric acid.[20] Moreover, structure I, which belongs to the general class of glycidic acids, should with acetic anhydride yield a triacetate and not a monoacetate.[21] It should, indeed, be hydrolyzed by boiling water to a glycol.[19] The degradation of glycidic acids to ketonic compounds and carbon dioxide by the action of alkali is well known[21] and consequently alkaline hydrolysis of the alkaloid to yield a compound of structure I is unlikely.

Some epoxy compounds such as epoxyretronecine (III) are extremely stable to both acid and alkaline hydrolysis and to hydrogenation. The epoxy

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[8] R. H. F. Manske, *Can. J. Research*, **5**, 651 (1931).

[9] R. Adams and M. Gianturco, THIS JOURNAL, **78**, 398 (1956); see also R. B. Bradbury and C. C. J. Culvenor, *Australian J. Chem.*, **7**, 378 (1954).

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

[11] The alkaloid from which these authors obtained the acid was probably impure as shown by subsequent investigations in this Laboratory[9] and in the Laboratory of Culvenor.[9]

[12] T. R. Hosking and C. W. Brandt, *New Zealand J. Sci. Technol.*, **17**, 638 (1936).

[13] R. B. Bradbury, *Chemistry & Industry*, 1021 (1954).

[14] A. Berg, *Bull. soc. chim.*, **11**, 882 (1894).

[15] R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N.Y., 1948, p. 115.

[16] Bradbury[7,13] accepts the presence of bands at 878, 1153, 1213 and 1266 cm.$^{-1}$ in the infrared spectrum of jaconecic acid as an indication of the presence in the molecule of an epoxide grouping. Jaconecic acid is the only one of the Senecio acids studied in this Laboratory that has all four of these bands.

[17] In α-isopropyl-α,β-dihydroxybutyric acid, previously synthesized in this Laboratory, the acid C=O band appears at 1691 cm.$^{-1}$; R. Adams and B. L. Van Duuren, THIS JOURNAL, **74**, 5349 (1952).

[18] The epoxide linkage should not prevent the formation of the lactone since methylene lactones have been found in nature [C. J. Cavallito and T. H. Haskell, THIS JOURNAL, **68**, 2332 (1946)] and have been synthesized [E. R. H. Jones, *J. Chem. Soc.*, 230 (1950); H. V. Pechmann, *Ber.*, **33**, 3336 (1900)].

[19] Glycidic acid does not give a color with ferric chloride; E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier Publishing Co., New York, N. Y., I^B, 1952, p. 1065.

[20] L. J. Dry and F. L. Warren, *J. Chem. Soc.*, 60 (1955).

[21] N. G. Darzens, *Compt. rend.*, **141**, 767 (1905).

TABLE I

INFRARED ABSORPTION FREQUENCIES OF TOMENTOSINE AND RELATED PRODUCTS

Compound	Alcoholic hydroxyl	Salt struct.	γ-Lactone C=O	Ketone C=O	Ester C=O	Acid C=O	C=C	—CO_2—	CH_3—C	$\overset{\diagup \mathrm{O} \diagdown}{\mathrm{C{-}C}}$
Tomentosine	3340[a] 3320 (doublet)			1745(S)			835(M)	1575(S)		878(M), 1157(M), 1210(W), 1262(M)
	3540(M)[b]	2400(M)		1752(S)	1725(S)		840(M)	1612(S)	1390(M) 1360(S)	
Tetrahydro-tomentosine	3300–3100 (broad)[a]			1745(S)		1705(W)		1615(S)		875(M), 1155(M), 1210(M), 1270(M)
	3500–3000[b]	2400(M)		1740(S)		1705(W)		1608(S)	1400(M) 1370(sh) 1360(M)	
Jaconecic acid	3270(S)[a]					1730(S) 1685(S)			1370 (broad)	878(M), 1153(S), 1213(S), 1266(S)
	3580[b] 3480 (doublet)					1745(S) 1716(S)				
Chlorojaconecic Lactone			1780(S)[b]						1400(S) 1390(sh)	
Lactone $C_{10}H_{12}O_5$ M.p. 182–183°	3470 (v. sharp)[a]		1785(S) 1750(S)				1668(S)			
Mixture of diastereoisomeric lactones $C_{10}H_{12}O_5$ M.p. 127–134°	3440 (broad)[b]		1760 (broad)				1668(S)			
Lactone $C_{10}H_{14}O_5$, M.p. 145°	3505 3400 (doublet)[a]		1802(S) 1765(S)							
Lactone $C_{10}H_{14}O_5$ M.p. 119–121°	3505 3400 (doublet)[a]		1788(S) 1765(S)							
Lactone $C_{10}H_{14}O_5$ (oil)	3400 (broad)[a]		1780 (broad)							
Product $C_{10}H_{13}ClO_4$ (oil)			1780(S)[b]						1390 (broad)	

Spectrum method: [a] Nujol mull. [b] 5% solution in $CHCl_3$.

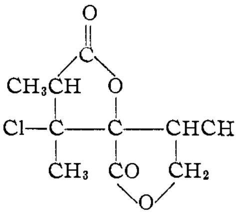
function in this molecule is unaffected by acetic anhydride.[22]

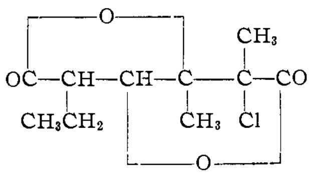
Since jaconecic acid is derived from several alkaloids of various Senecio species and since the skeleton IV is found in all the acids from the alkaloids senecionine, seneciphylline, retrorsine and riddelliine, it is not unreasonable to consider that jaconecic acid might also have this same skeleton. Jaconecic acid is now postulated to be an epoxide of dihydroisoseneciphyllic acid (V). Such a formula explains more satisfactorily than structure I certain of the chemical characteristics of this compound: the color with ferric chloride; the oxidation with lead tetraacetate; the greater stability to acid and alkali; the failure to undergo hydrogenation and triacetylation.

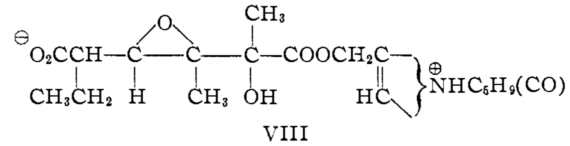
When Zhdanovich and Menshikov[4] hydrolyzed otosenine with 15% hydrochloric acid, they obtained a compound with the empirical formula $C_{10}H_{13}ClO_4$, m.p. 111–113°, $[\alpha]_D$ −25.2° ($CHCl_3$). This compound was apparently formed from the acid moiety of the alkaloid, by replacement of one hydroxyl group by chlorine and removal of one molecule of water. Bradbury[13] reported the same chloro compound by hydrolysis of jacobine with hydrochloric acid. The hydrolysis of tomentosine under the same conditions yielded a substance with the same empirical formula and melting point but different rotation, $[\alpha]_D$ −76° (95% EtOH). This difference in rotation probably is due to the solvent used.[23]

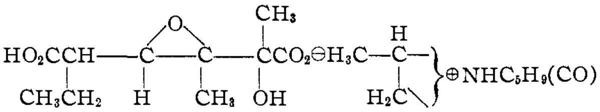
Bradbury[13] described the properties of the compound $C_{10}H_{13}ClO_4$. It is neutral; it behaves like a lactone on titration; on warming with excess alkali, two equivalents of alkali are utilized and jaconecic acid is recovered from the solution; it contains no active hydrogen; like jaconecic acid, it cannot be reduced with hydrogen and a catalyst. The infrared absorption spectrum[13] indicated no hydroxyl and no free acid C=O bands (Table I) while the C=O at 1785 cm.$^{-1}$ can be attributed to a γ-lactone. The compound $C_{10}H_{13}ClO_4$ from the action of hydrochloric acid on tomentosine has the same chemical properties and absorption spectrum as those found by Bradbury for the chloro compound from jacobine.

Bradbury proposed formula VI for his chloro compound. Formula VII, which is more closely related to the structure of jaconecic acid (V) as postulated in this Communication, is suggested as an alternative. The formation, transformations and properties of the chloro compound can be equally-well or better explained by formula VII. On the basis of these speculations tomentosine may be represented by formula VIII. This structure indicates its salt-like character as shown by the infrared spectrum, its allylic ester linkage susceptible to hydrogenolysis, the double bond and the ketone in the basic moiety. By the action of hydrogen in presence of a catalyst, tetrahydrotomentosine is formed which may be represented by IX. It is thus postulated as a salt of jaconecic acid and a base of unknown structure.


VI

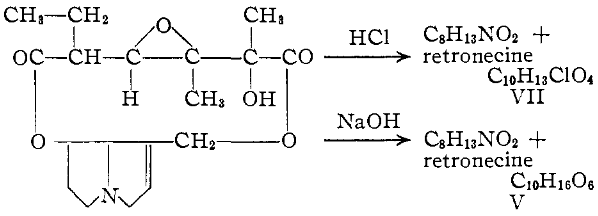

VII


VIII


IX

When tetrahydrotomentosine was treated with 15% hydrochloric acid, the same chloro compound as that obtained by similar treatment of tomentosine was isolated. Bradbury found that jaconecic acid was unaffected by boiling with hydrochloric acid. On the other hand, the alkaloid jacobine by similar treatment gave the chloro lactone. Apparently the presence of a base, set free during the hydrolysis of jacobine, tomentosine or tetrahydrotomentosine, acts as a catalyst for the hydrolysis of the epoxide, the replacement of the hydroxyl by chlorine and subsequent lactonization.

Jacobine, which from the infrared spectrum is a diester, may be represented by formula X.


X

Since only minute amounts of jaconecic acid and the chloro compound were available, further study of these structures had to be confined to a synthetic approach. Isoseneciphyllic acid (XI) was treated for several days with a chloroform solution of perbenzoic acid. The resulting mixture, after removal of benzoic acid, yielded upon crystallization two fractions. One was a pure substance, $C_{10}H_{12}O_5$, m.p. 182–183°, $[\alpha]_D$ −67.6° (EtOH–AcOEt, 1:1) or $[\alpha]_D$ −99° ($Cl_2CHCHCl_2$); the second was probably a mixture of stereoisomers, m.p. 127–134°, $[\alpha]_D$ +80° (95% EtOH); these constants remained unchanged after sublimation. The compound melting at 182–183° was hydro-

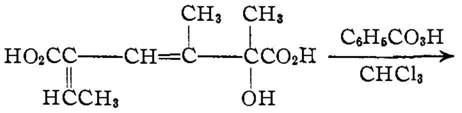
[22] L. J. Dry, M. J. Koekemoer and F. L. Warren, *J. Chem. Soc.*, **59**, (1955). See also B. H. Nicolet and T. C. Poulter, This Journal, **52**, 1186 (1930), who describe the slow rate of alkaline hydrolysis of the epoxides of oleic and elaidic acids. C. Doree and A. C. Pepper, *J. Chem. Soc.*, 477 (1942), report that heating at 170° with potassium hydroxide is necessary for the hydrolysis of the epoxides of brassidic and erucic acids.

[23] A large difference in specific rotation of oxidized isoseneciphyllic acid was observed between acetylene tetrachloride and 1:1 ethanol-ethyl acetate as solvent. At the time the rotation of the product obtained in this research was taken, it was not known that Zhdanovich and Menshikov had used chloroform as solvent. No more material was available for a redetermination in chloroform.

genated and one molecule of hydrogen was absorbed. If the reaction mixture was worked up immediately, a compound $C_{10}H_{14}O_5$, m.p. 144–145°, was obtained; if, instead, the solution of the hydrogenation compound was permitted to stand overnight over the catalyst in an atmosphere of hydrogen, an isomer, m.p. 119–121°, resulted.

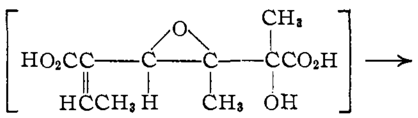
The low melting fraction, m.p. 127–134°, from the oxidation, was hydrogenated; it also absorbed one molecule of hydrogen but the product could not be induced to crystallize. The crude material analyzed for $C_{10}H_{14}O_5$. Salient data from the infrared spectra of these products are found in Table I.

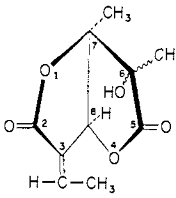
A possible interpretation of these results is shown in formulas XI-XIV. The analytical and infrared data conform to these structures.



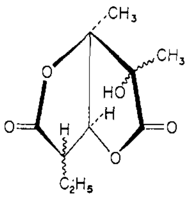
$$\underset{\underset{\displaystyle HCCH_3}{\|}}{HO_2CC}—CH=\overset{\overset{\displaystyle CH_3}{|}}{C}—\underset{\underset{\displaystyle OH}{|}}{\overset{\overset{\displaystyle CH_3}{|}}{C}}CO_2H \xrightarrow[CHCl_3]{C_6H_5CO_3H}$$

XI

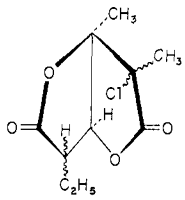




XII



XIII

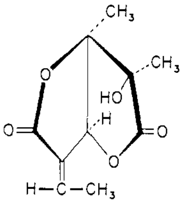


XIV

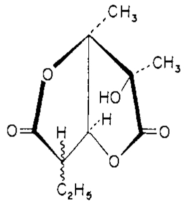
The *cis* configuration of the two rings in the dilactones XII, XIII and XIV may be assumed since two five-membered fused rings would normally have such a structure. In the optically active acid XI, the configuration of the groups about the asymmetric carbon atom must be fixed, but how the methyl and hydroxyl groups are arranged in the lactones XII is uncertain. The strong carbon-carbon double bond bands in the infrared spectrum of the dilactones XII indicate that they have the same geometrical arrangement about the carbon-carbon double bond as found in integerrinecic acid and integerrinecic acid lactone. To the latter the *trans* geometrical structure was assigned on the basis of a comparison of their spectral characteristics with those of tiglic and angelic acids.[24]

The reaction of the hydrogenation products with thionyl chloride has provided evidence for the existence of isomerism about carbon atom 6. The two hydrogenation products of the unsaturated lactone XII, m.p. 182–183°, were both resistant to the action of thionyl chloride alone or with pyridine. On the other hand, the hydrogenation product of the stereochemical mixture of unsaturated lactones, m.p. 127–134°, yielded, after short boiling with thionyl chloride, material which was subjected to sublimation in a high vacuum and then consisted of oil with a few crystals. As these could not be separated, the mixture was analyzed; the results checked closely for the formula $C_{10}H_{13}O_4Cl$.

The two lactones of structure XII and the three hydrogenated lactones of structure XIII exhibit in their infrared spectra different types of hydroxyl bands. Those for the compound m.p. 182–183° and its hydrogenation products are very sharp, similar to the band found for an hydroxyl in molecules capable of single bridge intramolecular hydrogen bonding; those for the compound m.p. 127–134° and its hydrogenation product are broad. These facts, along with the difference in capability of replacement of the hydroxyl by chlorine, permit speculation regarding the stereochemical structures of the lactones. It is likely that the unsaturated lactone XII, m.p. 182–183°, and its hydrogenation products have the configuration at carbon 6 shown in XV and XVI, respectively.

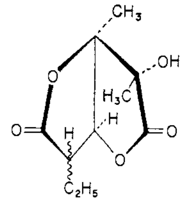


XV



XVI

The two hydrogenation products XVI from the high-melting unsaturated lactone may differ from each other in the configuration of the groups on carbon 3. On the other hand, the liquid mixture of hydrogenated lactones from the unsaturated lactone, m.p. 127–134°, which reacts with thionyl chloride, probably has the hydroxyl group on carbon 6 in the more exposed and reactive position as shown in XVII [25]



XVII

The infrared spectra of the synthetic chloro compound and the one from natural sources differ in the region of smaller wave numbers below 1200 cm.$^{-1}$. This difference may be due to different configurations on carbon atom 3.

Acknowledgments.—The authors are indebted to Mr. J. Nemeth, Mrs. Lucy Chang and Mrs. M.

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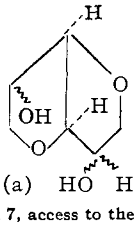
[24] R. Adams and B. L. Van Duuren, THIS JOURNAL, **75**, 4631 (1953).

[25] A. C. Cope (private communication) has found that in compounds of type (a) only the endo hydroxyl groups can be easily replaced by chlorine atoms by the action of thionyl chloride in pyridine. This reaction appears to proceed by an S_N2 type of mechanism, requiring backside approach of a nucleophilic reagent. Access to the rear of the carbon atoms bearing the hydroxyl groups is less hindered when the latter are in the endo positions. However, construction of Fisher–Taylor–Hirschfelder models of compounds of the general structure XIII showed that, due to the presence of two methyl groups on carbon atoms 6 and 7, access to the rear of carbon atom 6 is more hindered when the hydroxyl group has the endo rather than the exo configuration.



(a)

Benassi for the microanalyses and to Mr. J. Brader for the infrared spectra.

Experimental[26]

Isolation of the Alkaloids.—Extraction of *Senecio tomentosus* by the usual procedure[1] gave a 0.006% yield of crude alkaloids. A paper chromatogram of the crude material with butanol–acetic acid showed two spots, R_f 0.40 and 0.62. All the paper chromatograms in this investigation were run on Whatman No. 1 paper by the descending technique at a temperature of 24 ± 1°.

Separation of the Alkaloids: Chromatographic Procedure.—About 70 g. of Florisil was packed into a 2 × 80 cm. Pyrex glass column as a slurry in light petroleum ether. A solution of 2 g. of crude alkaloidal material in 20 ml. of chloroform was poured on top of the column. Elution was performed first with 100 ml. of light petroleum ether–carbon tetrachloride (1:1), followed by 100 ml. of carbon tetrachloride, 100 ml. of carbon tetrachloride–chloroform (1:1), 100 ml. of chloroform–ethanol (20:1). Eluates of 10 ml. were collected; each fraction was evaporated at room temperature in front of a fan, and the R_f values were determined. The fractions yielded the following results: 1–13, no material; 14–20, crystalline material of R_f 0.62; 21–23, no material; 24–32, mixture of crystalline and dark resinous material, R_f 0.40, 0.62; 33–40, an amorphous product, R_f 0.40. Nothing further could be eluted with more polar solvents. The dark material adsorbed on the top part of the column could not be eluted by methanol. Fractions 14–20 were combined and material weighing 0.7 g. was crystallized from benzene. The product consisting of white crystals, m.p. 245° (sealed evac. tube), weighed 0.5 g.; rotation: 0.070 g. made up to 2.0 ml. with chloroform at 25° gave α_D $-1.92°$, l 1; $[\alpha]^{22}_D$ $-54.8°$. The infrared spectrum of this compound was identical with that of an authentic sample of senecionine.

Anal. Calcd. for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 64.70; H, 7.61; N, 4.60.

Fractions 24–32 yielded 0.2 g. of product which was washed with cold methanol to dissolve the resinous material. White crystals, weighing 0.05 g., were left undissolved and proved to be senecionine. The methanol-soluble material was then chromatographed through a column filled with 30 g. of Celite previously moistened with 12 ml. of phosphate buffer of *p*H 4. By eluting with chloroform, 20 mg. of senecionine was obtained first, followed by a glassy material R_f 0.42, which could not be induced to crystallize. A picrate obtained from this material was crystallized from ethanol, m.p. 245–246°.

Anal. Calcd. for $C_{19}H_{27}NO_7 \cdot C_6H_3N_3O_7 \cdot C_2H_5OH$: C, 49.39; H, 5.48; N, 8.53. Found: C, 49.34; H, 5.46; N, 8.45.

All attempts to eliminate a molecule of ethanol from the picrate failed. The base had an R_f value practically identical with that of tomentosine, which gives, however, an unsolvated picrate. The product may be a stereoisomer of tomentosine. The amount available was too small for further study.

Fractions 33–40 yielded 0.6 g. of material purified by crystallization from benzene, m.p. 232° (sealed evac. tube), which was called tomentosine; rotation: 0.016 g. made up to 1.6 ml. with chloroform at 25° gave $[\alpha]_D$ $+0.140°$, l 1; $[\alpha]^{25}_D$ $+14.0°$. Its picrate was made in and purified from ethanol, m.p. 251° dec.

Anal. Calcd. for $C_{19}H_{27}NO_7$: C, 59.83; H, 7.14; N, 3.67. Found: C, 60.12; H, 7.17; N, 3.62.

Anal. Calcd. for $C_{19}H_{27}NO_7 \cdot C_6H_3N_3O_7$: C, 49.18; H, 4.91; N, 9.18. Found: C, 49.19; H, 5.09; N, 9.27.

Aqueous Alkaline Hydrolysis of Tomentosine.—The alkaloid was hydrolyzed with aqueous barium hydroxide by the usual method[1] and the acid and basic fragments isolated: (a) the basic hydrolysis product was a resinous substance which rapidly darkened on standing and could not be converted to a crystalline hydrochloride or picrate; (b) the ether extract of the hydrolysate in acid solution yielded, on crystallization from ether jaconecic acid, white needles, m.p. 183–184°; rotation: 0.0078 g. made up to 1.60 ml. with 95% ethanol at 25° gave α_D $+0.135°$, l 1; $[\alpha]^{25}_D$ $+28.1°$. The acid gave no depression of melting point on admixture with an authentic sample of jaconecic acid obtained by Manske[8] upon hydrolysis of the alkaloidal material from *Senecio jacobea*.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.72; H, 6.94. Found: C, 51.51; H, 6.84; C-Me, 2.31.

Tetrahydrotomentosine.—A solution of 0.50 g. of tomentosine in 50 ml. of 90% ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 0.10 g. of palladium-on-strontium carbonate catalyst (6%). Two mole-equivalents of hydrogen were absorbed. The solution was filtered, washed with ethanol and evaporated to dryness. The oily residue was crystallized from acetone to give 0.35 g. (70%) of needle clusters, m.p. 157–158°. The mother liquors from the crystallization yielded 0.15 g. of an oil which resisted crystallization; rotation: 0.0087 g. made up to 1.60 ml. with chloroform at 37° gave α_D $-0.050°$, l 1; $[\alpha]^{37}_D$ $-9.2°$.

Anal. Calcd. for $C_{19}H_{31}NO_7$: C, 59.48; H, 8.05; N, 3.63. Found: C, 59.51; H, 8.14; N, 3.65.

Hydrogenation of Tomentosine (PtO_2 Catalyst).—A solution of 0.25 g. of tomentosine in 30 ml. of 90% ethanol was hydrogenated at room temperature and atmospheric pressure using 10 mg. of platinum oxide catalyst. Two mole equivalents of hydrogen were rapidly absorbed, and then during the course of 24 hr. additional hydrogen reacted. The solution was filtered, taken to dryness and the resultant oil crystallized from acetone. Colorless needles weighing 0.09 g. (33%) separated, m.p. 157–158°. The product gave no depression of melting point on admixture with tetrahydrotomentosine. The oil obtained from the mother liquors could not be crystallized.

Hydrochloric Acid Hydrolysis of Tomentosine.—A solution of 0.5 g. of tomentosine in 10 ml. of 15% hydrochloric acid was boiled under reflux for 15 hr. The crystalline solid that separated on cooling was filtered off and the aqueous solution extracted with ether. The ether extract was dried with anhydrous magnesium sulfate, filtered, and the solvent removed. The residue and the product that crystallized from the aqueous solution were combined, and the resulting 0.25 g. (83%) recrystallized from ether and finally purified by vacuum sublimation at 100° and 0.5 mm.; colorless needles, m.p. 111–112°; rotation: 0.0089 g. made up to 1.60 ml. with 95% ethanol at 36° gave α_D $-0.042°$; l 1; $[\alpha]^{36}_D$ $-76.0°$. Evaporation of the aqueous acid solution to dryness under reduced pressure left an oily product.

Anal. Calcd. for $C_{10}H_{13}ClO_4$: C, 51.61; H, 5.66. Found: C, 51.83; H, 5.70.

Acid Hydrolysis of Tetrahydrotomentosine.—Acid hydrolysis of 0.25 g. of tetrahydrotomentosine by the method described above gave 0.12 g. (82%) of the chloro lactone, m.p. 111°, undepressed on admixture with a sample from the previous experiment.

Lead Tetraacetate Oxidation of Jaconecic Acid.—To a solution of 0.23 g. of jaconecic acid in 5 ml. of water saturated with sodium chloride, 0.40 g. of lead tetraacetate was added. The carbon dioxide that was liberated was collected over a saturated sodium chloride solution. After 1 hr. at room temperature and 10 minutes at 60°, no more carbon dioxide was evolved; calcd. for one mole of carbon dioxide from $C_{10}H_{16}O_6$: 22.4 ml. at S.T.P., found, 16.2 ml. at S.T.P. (72.3%).

The aqueous solution was steam distilled into a saturated aqueous solution of dimedone. No crystalline product was obtained. The residue in the distillation flask was extracted with ether. Upon evaporating the ether a small amount of an oily product resulted.

Isoseneciphyllic Acid (α-Longinecic Acid).—The source of isoseneciphyllic acid for synthetic purposes was the crude alkaloidal material from *Senecio carthamoides*. Table II shows the constants of pure isosenecionine and seneciphylline in comparison with those of the total alkaloids and also the constants of pure senecic and isoseneciphyllic acid in comparison with those of the crude hydrolytic mixture.

Papergrams were run with the following solvents: for the alkaloids, the upper layer obtained by shaking equal volumes of *n*-butyl alcohol with 5% aqueous acetic acid; for the necic acids, *n*-propyl alcohol–water–pyridine (6:2:1). The alkaloidal mixture from *Senecio carthamoides* was that obtained directly from the plant extraction. It was approximately an equal mixture of senecionine and seneciphylline (α-longilobine). The seneciphylline was obtained pure

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[26] All melting points are corrected.

TABLE II

	M.p., °C.	$[\alpha]_D$	Rf		Analyses, % Carbon	Hydrogen	Nitrogen
Alkaloidal mixture from *Senecio carthamoides*	222–224	−96°	0.58	0.62	64.97	7.07	4.48
Senecionine	245	−56	.62		64.46	7.51	4.18
Seneciphylline	217	−139	.58		64.85	6.95	4.20
Mixed acids by hydrolysis of *Senecio carthamoides*	110–112	−1.0	.46	0.49	55.66	6.72	
Senecic acid	146	+10.95	.49		55.54	7.46	
Isoseneciphyllic acid	114–115	−13.25	.46		56.07	6.59	

by the chromatographic procedure previously described.[9] The mixture of acids obtained by hydrolysis of the crude *Senecio carthamoides* alkaloids was chromatographed through a column of Celite wetted with 40% of its weight of phosphate buffer of *p*H 4. By elution with chloroform, the bulk of the senecic acid was obtained pure; after this, chloroform containing increasing amounts of *n*-butyl alcohol was used as eluent and isoseneciphyllic acid of good grade resulted. It still contained small amounts of senecic acid as ascertained by paper chromatograms and by determination of the optical rotation of the various fractions.

Reaction of Isoseneciphyllic Acid with Perbenzoic Acid.—A solution of 0.77 g. of isoseneciphyllic acid, containing traces of senecic acid, in a little ether in a 20-ml. volumetric flask was cooled by acetone Dry Ice mixture and 9 ml. of a chloroform solution of perbenzoic acid containing 76 g. of oxidant per liter was added. The solution was made up to 20 ml. and allowed to stand at room temperature for several days. The reaction was interrupted when the rate of consumption of perbenzoic acid slowed down considerably as ascertained by frequent titrations of aliquots of the reaction mixture by the standard procedure. The organic solvents were eliminated at room temperature, the residue was washed with cold water and the benzoic acid which was insoluble was separated. The aqueous solution was taken to dryness at room temperature and the process repeated until all of the benzoic acid had been removed. The material was then chromatographed through Celite, buffered with phosphate, in a fashion similar to that used for the separation of senecic and isoseneciphyllic acids. The first fractions contained a neutral crystalline material, followed by small amounts of unidentified acidic products. Fractional crystallization of the neutral fractions from ethyl acetate–petroleum ether afforded the products whose constants are recorded in Table III. The constants were not changed by further crystallization and sublimation.

Hydrogenation of Fraction I.—A solution of 0.136 g. of fraction I, m.p. 182–183°, in 9 ml. of 95% ethanol was hydrogenated over 0.05 g. of platinum oxide. The equivalent of one mole of hydrogen was absorbed very rapidly. Evaporation of the solvent under reduced pressure yielded 0.120 g. of white material. It was purified by sublimation at 110° (0.5 mm.); white crystals, m.p. 144–145°.

TABLE III

Fraction	M.p., °C.	$[\alpha]°_D$	Calcd. for $C_{10}H_{12}O_5$ Carbon, % 56.60	Hydrogen, % 5.70
I	182–183	-67.6^a -99^b	56.69	5.74
II	127–134	$+80^c$	56.61	5.74

[a] *c* 1.42 in EtOH–AcOEt (1:1). [b] *c* 0.50 in $Cl_2CHCHCl_2$. [c] *c* 5.31 in 95% EtOH.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.07; H, 6.58.

When the experiment was repeated under the same conditions but the solution was left overnight under hydrogen in the presence of platinum catalyst, a different product was obtained. It was purified by sublimation, m.p. 119–121°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.11; H, 6.67.

When either of the two above products was refluxed overnight with thionyl chloride, thionyl chloride and pyridine or acetyl chloride, only starting material was recovered without substantial loss of product.

Hydrogenation of Fraction II.—A solution of 0.150 of fraction II, m.p. 127–134°, was hydrogenated under conditions identical with those used for fraction I. The equivalent of one mole of hydrogen was rapidly absorbed. Evaporation of the solvent left a semi-solid material which could not be induced to crystallize.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 55.84; H, 6.29.

When the above material was heated under reflux for a short time with thionyl chloride, the excess reagent eliminated and the residue submitted to sublimation, an oil mixed with a few crystals was obtained. All attempts to separate the few crystals from the oil failed. The mixture of crystals and oil was submitted for analysis. The results agreed closely with the formula $C_{10}H_{13}ClO_4$.

Anal. Calcd. for $C_{10}H_{13}ClO_4$: C, 51.61; H, 5.66. Found: C, 51.80; H, 6.05.

URBANA, ILLINOIS