140. *The* Senecio *Alkaloids. Part VI. The Isomerisation of Senecic Acid to* trans-*Senecic* (*Integerrinecic*) *Acid, and the General Structure of the " Necic " Acids.*

By MEYER KROPMAN and FRANK L. WARREN.

The lactone obtained from senecic acid is hydrolysed to give *trans*-senecic acid which is identical with integerrinecic acid, obtained by Manske by hydrolysis of integerrimine. The structural change is proved to involve geometrical isomerism.

The geometrical isomerism of senecic and integerrinecic acids parallels that found for isatinecic (*cis*-hydroxysenecic) and retronecic (*trans*-hydroxysenecic) acids. A general formula for these " necic " acids is advanced and represents a class of monoterpenes with a new irregular isoprene chain. The identity of integerrimine and squalidine is indicated.

THE structure of senecic acid has been advanced previously by us (*J.*, 1949, 2852), and we have now prepared its geometrical isomeride. The lactone, m. p. 156°, obtained from senecic acid (cf. Richardson and Warren, *J.*, 1942, 452) was boiled with sodium hydroxide to open the lactone ring and then acidified to give trans-*senecic acid*, m. p. 150°. When this was mixed with a specimen of integerrinecic acid, m. p. 150°, kindly sent to us by Dr. R. H. F. Manske (*Canad. J. Res.*, 1939, **17**, 8) the melting-point was unchanged, but when it was mixed with senecic acid, m. p. 147°, the melting-point was depressed to 128°. The lactone obtained from *trans*-senecic acid was found to be identical with that from senecic acid. Since both acids give the same lactone and the *trans*-acid is regenerated from it the previously reported senecic acid lactone is actually *trans*-senecic (integerrinecic) acid lactone.

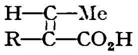
trans-Senecic acid was smoothly reduced catalytically to an oily acid which was converted into *bis*-p-*phenylphenacyl dihydrointegerrinecate*, m. p. 98°, which was identical with the bis-*p*-phenylphenacyl ester prepared from dihydrosenecic acid. The isomerism involved in the formation of integerrinecic acid must therefore involve the double bond. That the ethylenic linkage had not moved was proved by ozonolysis of *trans*-senecic acid, whereby acetaldehyde, identified as the octahydroxanthen derivative, was obtained.

Since senecic acid has the lower melting point and is the less stable form, senecic and integerrinecic acids are assigned *cis*- and *trans*-configurations, respectively, corresponding to isatinecic and retronecic acids (cf. Christie, Kropman, Novellie, and Warren, *J.*, 1949, 1703; Kropman and Warren, *loc. cit.*).

The ultra-violet extinction curve for *trans*-senecic acid showed a maximum in accordance with the αβ-unsaturated carboxylic grouping. The maxima observed for *cis*- (cf. Kropman and Warren, *loc. cit.*) and *trans*-senecic acid are of interest when compared with those for isatinecic and retronecic (*trans*-isatinecic) acids (cf. Christie, Kropman, Leisegang, and Warren, *J.*, 1949, 1700), and may be of significance in assigning geometrical configuration when only one form of other " necic " acids has been isolated:

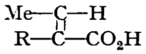
cis-Acids.			*trans*-Acids.		
	$\lambda_{max.}$, mμ.	$\varepsilon_{max.}$		$\lambda_{max.}$, mμ.	$\varepsilon_{max.}$
Senecic	215	4100	Integerrinecic	218	9333
Isatinecic	215	4500	Retronecic	218	9400
	218	4720			

The four " necic " acids whose constitutions have been determined conclusively may now be represented as *cis*- (I) and *trans*- (II) forms of a general formula with relationships as shown below.



$$\begin{array}{c} \mathrm{H{-}C{-}Me} \\ \| \\ \mathrm{R{-}C{-}CO_2H} \end{array}$$

(I.)



$$\begin{array}{c} \mathrm{Me{-}C{-}H} \\ \| \\ \mathrm{R{-}C{-}CO_2H} \end{array}$$

(II.)

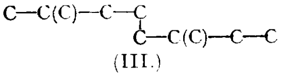
(Ia.) Senecic acid, m. p. 147°.
(Ib.) Isatinecic acid, m. p. 148·5°.

(IIa). Integerrinecic acid, m. p. 150°.
(IIb.) Retronecic acid, m. p. 181°.

Where R = $CH_2X{\cdot}C(OH)(CO_2H){\cdot}CHMe{\cdot}CH_2{\cdot}$ (Ia and IIa; X = H). (Ib and IIb; X = OH).

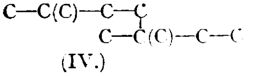
Confirmation of this concept is afforded by the isolation by Konovalova and Danilova (*J. Gen. Chem. Russia*, 1948, **18**, 1198) of seneciphyllic acid, m. p. 144—145°, and *iso*seneciphyllic acid, m. p. 105—108°, by hydrolysis of seneciphylline with alcoholic and aqueous alkali, respectively. The two acids are reported as geometrical isomers and the *iso*-acid is the less stable form. On our nomenclature the *iso*-acid is *cis*-seneciphyllic acid (type I) and the seneciphyllic acid has the *trans*-configuration (type II). Therefore it is the *cis*-form in which the acid occurs in the alkaloid, and the *trans*-acid is formed by isomerisation with alcoholic alkali or hydrochloric acid. The conditions which permit this isomerisation are those which effect lactone formation when this is possible. The isolation of the lactones of *trans*-senecic and retronecic acid from *cis*-senecic and isatinecic acid, respectively, is readily understood (cf. Christie, Kropman, Leisegang, and Warren, *loc. cit.*).

Schinz and Bourquin (*Helv. Chim. Acta*, 1946, **25**, 1599) formulated nine irregular, as contrasted with the regular (III), isoprene chains for the monoterpenes. Two only were known in Nature, namely (IV), represented by artemisia ketone, and (V), by lavandulol. The " necic " acids of known constitution represent a new class of monoterpenes with one (VI) of the remaining irregular chains.



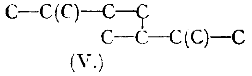
$$\begin{array}{l} C{-}C(C){-}C{-}C \\ \qquad\qquad\quad C{-}C(C){-}C{-}C \end{array}$$

(III.)



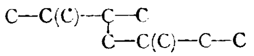
$$\begin{array}{l} C{-}C(C){-}C{-}C \\ \qquad\qquad C{-}C(C){-}C{-}C \end{array}$$

(IV.)



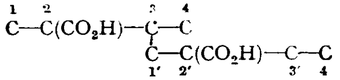
$$\begin{array}{l} C{-}C(C){-}C{-}C \\ \qquad\qquad\quad C{-}C{-}C(C){-}C \end{array}$$

(V.)



$$\begin{array}{l} C{-}C(C){-}C{-}C \\ \qquad\qquad C{-}C(C){-}C{-}C \end{array}$$

(VI.)



$$\begin{array}{l} \overset{1}{C}{-}\overset{2}{C}(CO_2H){-}\overset{3}{C}{-}\overset{4}{C} \\ \qquad\qquad\quad \underset{1'}{C}{-}\underset{2'}{C}(CO_2H){-}\underset{3'}{C}{-}\underset{4}{C} \end{array}$$

(VII.)

It is of significance that senecioic (2-methylprop-1-ene-1-carboxylic) acid possesses the *iso*pentane unit, and it is not improbable that all the " necic " acids possess the same carbon skeleton (VI). It may be of importance in considering biological synthesis that the two carboxylic groups appear in the butane units at the $C_{(2)}$ and $C_{(2')}$ atoms (VII) which are the positions normally occupied by methyl groups in the terpenes.

Manske (*loc. cit.*) found that integerrimine, $C_{18}H_{25}O_5N$, m. p. 172—172·5°, was hydrolysed to retronecine and integerrinecic acid, whilst Barger and Blackie (*J.*, 1939, 743) record that hydrolysis of squalidine, $C_{18}H_{25}O_5N$, m. p. 169°, gives retronecine and squalinecic acid. Squalinecic acid, m. p. 129°, was twice distilled, and was crystallised by inoculation with senecic acid but was not obtained pure. It contained three *C*-alkyl groups and the recorded analysis for carbon and hydrogen would indicate that " squalinecic " acid was a mixture of an acid, $C_{10}H_{16}O_5$, and its lactone, $C_{10}H_{14}O_4$. Furthermore a mixed melting-point determination on integerrinecic acid and its lactone carried out by us showed a melting point of 128°. It would seem to us that integerrimine is identical with squalidine, and in this connection it is of interest that both these alkaloids have only been found in small quantities associated with senecionine. A close relationship between *Senecio* alkaloids found together in the plant has been demonstrated previously (cf. Richardson and Warren, *J.*, 1943, 452; Christie *et al.*, *loc. cit.*).

Senecionine and integerrimine (squalidine) may now be formulated as *cis*- and *trans*-senecic esters of retronecine. Integerrimine is the first *Senecio* alkaloid in which the acid moiety has been found to occur in the *trans*-form, and may have been formed during isolation.

EXPERIMENTAL.

Micro-analyses by Drs. Weiler and Strauss, Oxford.

Senecic Acid.—Rosmarinine (7 g.), hydrated barium hydroxide (9·8 g.), and water (140 ml.) were heated under reflux for 1 hour. Carbon dioxide was passed through the hot solution, which was then filtered and the filtrate made acid to Congo-red with 5N-hydrochloric acid. Exhaustive extraction of the acid solution with ether gave the crude acid (4·2 g., 0·98 mol.) which, recrystallised from ethyl acetate, gave needles of senecic acid, m. p. 147° (uncorr.). *Bis*-p-*phenylphenacyl senecate* separated from ethanol as a white amorphous solid, m. p. 100—101° (Found: C, 75·3; H, 6·1. $C_{38}H_{36}O_7$ requires C, 75·5; H, 6·0%).

trans-*Senecic Acid.*—The lactone, m. p. 154° (Found: equiv., 194·4. Calc. for $C_{10}H_{14}O_4$: equiv., 198), (150 mg.) prepared from senecic acid, was heated for 1 hour on a water-bath with 2·5N-sodium hydroxide (10 ml.). On cooling, the solution was acidified to Congo-red with 5N-hydrochloric acid and extracted with ether. The ethereal solution gave a white solid which, after three crystallisations from water, gave trans-*senecic acid* as clusters of needles, m. p. 150°, $[\alpha]_D^{21}$ *ca.* +18° (*c*, 1·7 in ethanol) (Found: C, 55·9; H, 7·5%; equiv., 112·2. $C_{10}H_{16}O_5$ requires C, 55·6; H, 7·4%; equiv., 108). The melting point was undepressed when the *trans*-acid was mixed with integerrinecic acid whereas a mixture of senecic and *trans*-senecic acids had a melting point 128°. *Bis*-p-*phenylphenacyl* trans-*senecate* (*integerrinecate*) separated from ethanol as an amorphous white solid, m. p. 144—145° (Found: C, 75·0; H, 6·0. $C_{38}H_{36}O_7$ requires C, 75·5; H, 6·0%).

trans-*Senecic Acid Lactone.*—*trans*-Senecic acid (30 mg.) was treated several times with dilute hydrochloric acid and the hydrochloric acid evaporated each time. The product when recrystallised from ethyl acetate gave *trans*-senecic acid lactone, m. p. 152—154°, undepressed on admixture with the lactone from senecic acid.

Hydrogenation of Senecic and trans-*Senecic Acids.*—Senecic acid (168 mg.) was hydrogenated in the presence of platinic oxide to yield the oily dihydrosenecic acid. *Bis*-p-*phenylphenacyl dihydrosenecate* separated from ethanol as a white amorphous solid, m. p. 98° (Found: C, 74·9; H, 6·4. $C_{38}H_{38}O_7$ requires C, 75·3; H, 6·3%). Catalytic hydrogenation of *trans*-senecic acid (150 mg.) gave a colourless oily acid which could not be induced to crystallise, and which gave a bis-*p*-phenylphenacyl ester, m. p. 98°, undepressed when mixed with the corresponding ester of dihydrosenecic acid.

Ozonolysis.—*trans*-Senecic acid (250 mg.) was dissolved in dry ethyl acetate and a stream of dry ozone passed through at 0° for ½ hour. The viscous, yellow, pungent ozonide was treated with water and warmed in a stream of carbon dioxide. The issuing acetaldehyde was passed into water and treated with dimedon; a flocculent precipitate was obtained which, when heated under reflux with one drop of hydrochloric acid in 80% ethanol (4 ml.) and cooled, gave flat crystals, m. p. 175—176°, undepressed on mixing with the octahydroxanthen derivative of acetaldehyde.

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