The Total Synthesis of Senecic and Integerrinecic Acids[1]

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RECEIVED NOVEMBER 9, 1960

The total synthesis of senecic and integerrinecic acids, the esterifying acids present in the pyrrolizidine alkaloids senecionine and integerrimine, is described. Methyl 2-methylene-3-acetoxybutanoate and ethyl methylacetoacetate were condensed to give a mixture of cis- and trans-5-methyl-2-hepten-6-one-3-carboxylic acids. Hydrolysis of the cyanohydrin of the trans isomer gave (+)-integerrinecic acid, which was resolved by means of the brucine salts. Integerrinecic acid lactone was converted photochemically into the previously unknown senecic acid lactone, which was hydrolyzed to give (+)-senecic acid, identical with the natural acid.

Senecionine (I), the cyclic diester of retronecine and senecic acid, is the most widely occurring alkaloid in the genus *Senecio*.[3] As a preliminary to the study of the biogenesis of senecionine and related alkaloids, the total synthesis of senecic acid was undertaken, partly to provide a final
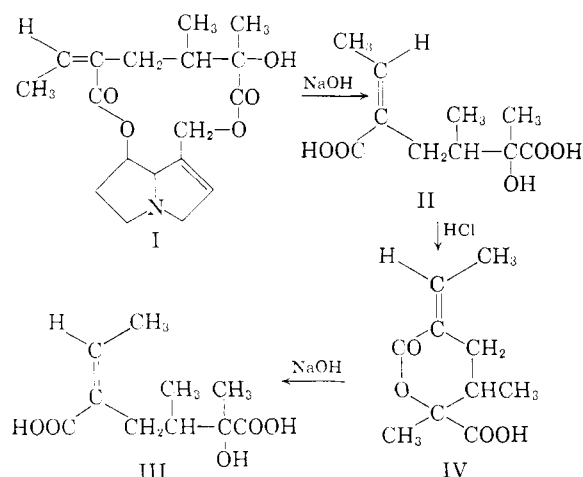
proof of the structure of this acid, partly to afford a means of preparing the isotopically-labeled com-

quent hydrolysis gives the geometric isomer, integerrinecic acid (III). The lactone formed by heating senecic acid in mineral acid is identical with the lactone of integerrinecic acid (IV). The configurations shown in II, called *cis*, and III, called *trans*, were first assigned on the basis only of relative stability and the fact that senecic acid has the lower melting point. An indication that *cis* acids of this type (*i.e.*, methyl group *cis* to the carboxyl) have a somewhat lower extinction coefficient at this ultraviolet absorption maximum was amplified by Adams and van Duuren,[5] who assigned configurations to some related compounds on this basis. Recent investigations by Nair and Adams[6] have now put these configurational assignments on a firm ground. Studies of the nuclear magnetic resonance spectra of a number of substituted *cis* and *trans* substituted crotonic acids and esters have made it possible to accept the configurations of senecic and integerrinecic acids as II and III, respectively.

The first objective of the present work was the ketoacid VIII; it is a degradation product of senecic acid, as will be shown in the sequel, and its cyanohydrin was expected to lead to the desired dicarboxylic acids by hydrolysis. The following course proved successful
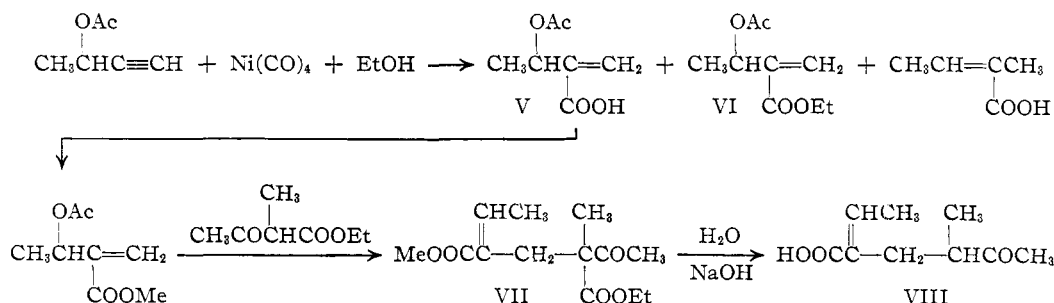
pound for projected studies. There have been no previous reports of attempts to synthesize the C_{10}-acids of the senecic acid type.

The structure of senecic acid (II) was first determined by Kropman and Warren,[4a,b] who showed that the carbon–carbon double bond is in the less stable configuration since lactonization and subse-

3-Acetoxy-2-methylenebutanoic acid (V)[7] was prepared by the reaction of 3-acetoxy-1-butyne with nickel carbonyl, according to the general procedure of Jones and his co-workers.[8] The desired acid V was obtained in about 25% yield, along with its ethyl ester (10%) and tiglic acid (5%). The ethyl ester is an expected product, but the formation of tiglic acid involves a reduction for which there does

(1) Presented at the I.U.P.A.C. Symposium on Natural Products, Melbourne, Austral., August, 1960.

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(3) F. L. Warren, *Progr. Chem. Nat. Prod.*, **12**, 198 (1955).

(4) (a) M. Kropman and F. L. Warren, *J. Chem. Soc.*, 2852 (1949); (b) 700 (1950).

(5) R. Adams and B. L. van Duuren, *J. Am. Chem. Soc.*, **75**, 4631 (1953).

(6) M. D. Nair and R. Adams, *ibid.*, **82**, 3786 (1960).

(7) A specimen of this acid was prepared earlier by Dr. M. C. Whiting in connection with another investigation. It has not heretofore been described in the literature. The corresponding 3-hydroxy-2-methylenebutanoic acid has been described as an oily compound: W. Reppe, German Patent 855,110 (1952); *C. A.*, **50**, 10132 (1956).

(8) E. R. H. Jones, T. Y. Shen and M. C. Whiting, *J. Chem. Soc.*, 230 (1950); 48 (1951).

not appear to be a precedent in this type of reaction. The preparation of the methyl ester VI was accomplished in good yield with the use of one molecular proportion of diazomethane.

The condensation of VI with ethyl methylacetoacetate is a Michael addition of the type for which a catalytic amount of sodium ethoxide in the absence of solvent has been recommended.[9] Under these conditions an equimolar mixture of VI and ethyl methylacet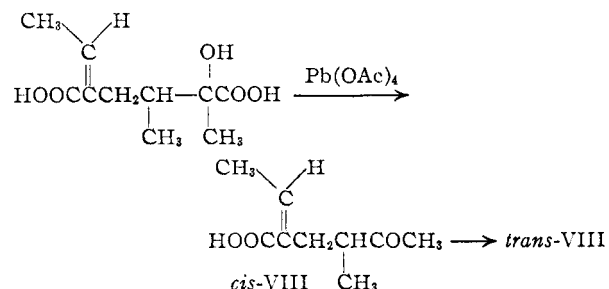oacetate remained largely unreacted. When the reactants were heated at 100° with 0.2 mole of piperidine, VI was converted in high yield into 1-vinyl-3-cyclohexene-1,4-dicarboxylic acid ("mikanecic acid")[10] (IX), probably by the pathway (B: is piperidine)

$$\underset{\substack{| \\ \text{CHOAc} \\ |}}{\overset{\text{CH}_2}{}} \quad \underset{\substack{| \\ \text{CHCH}_3}}{\overset{\text{CHCH}_3}{}}$$

MeOOCC=CH$_2$ + :B $\longrightarrow$ OAc$^-$ + MeOOCCHCH$_2$B $\xrightarrow{\text{B:}}$

B:H + $\underset{\substack{\text{MeOOCC=CH}_2}}{\overset{\text{CH=CH}_2}{}}$ $\longrightarrow$

CH=CH$_2$

COOMe

COOMe

and

CH=CH$_2$

COOH

COOH
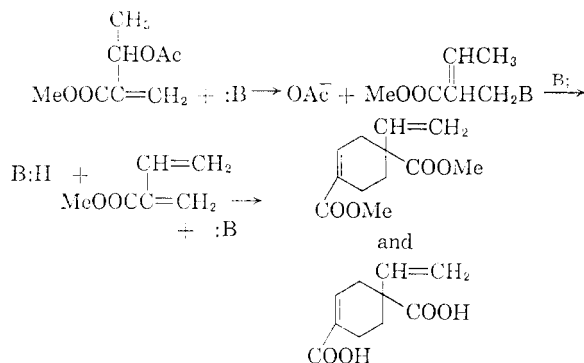
The desired condensation was effected smoothly by the use of a molar proportion of sodium ethoxide. Reaction took place rapidly at room temperature with the separation of sodium acetate. Hydrolysis and decarboxylation of the product gave, on distillation, a mixture of the cis and trans forms of the ketoacid (VIII). $C_9H_{14}O_3$, together with a small amount of a compound (X), $C_9H_{12}O_2$, m.p. 160°, and, as the non-volatile residue, a dicarboxylic acid (XI), $C_8H_{12}O_4$.

The trans-ketoacid (VIII) crystallized from the mixture as a low-melting solid, while the cis-ketoacid, isolated by chromatography on cellulose, is an oil. The isomers were identified by comparison with the authentic compounds prepared by lead tetraacetate oxidation of senecic acid
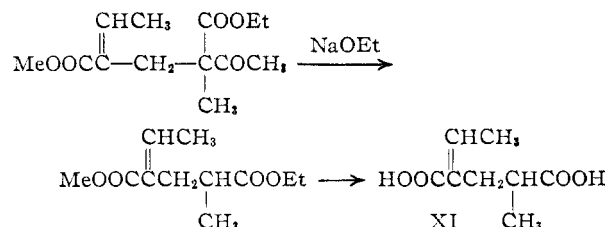
$$\underset{\text{CH}_3}{\overset{\text{H}}{}}\text{C}$$

HOOCCH$_2$CH—CCOOH $\xrightarrow{\text{Pb(OAc)}_4}$
| |
CH$_3$ CH$_3$

OH

CH$_3$\ /H
C
‖
HOOCCH$_2$CHCOCH$_3$ $\longrightarrow$ trans-VIII
|
cis-VIII CH$_3$

The initial product of this reaction is the (−)-cis-ketoacid, an oil with $[\alpha]D^{-27°}$ (ethanol), whose infrared spectrum in solution was identical with that of the oily synthetic cis-VIII. In alkaline solution this optically-active acid was rapidly racemized. This racemate (and also the (−)-cis-

acid) gave a 2,4-dinitrophenylhydrazone, m.p. 191–192°, undepressed on admixture with the derivative of the same melting point prepared from the oily synthetic acid.
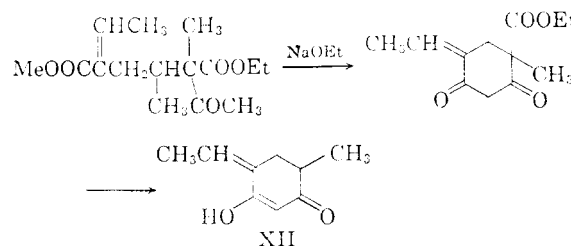
The racemic cis-ketoacid (from senecic acid), when heated in hydrochloric acid solution, gave the (±)-trans-ketoacid, m.p. 50–51°, identical with the crystalline synthetic material. Similar lead tetraacetate oxidations of dihydrosenecic[3] and isoseneciphyllic[11] acids have been described, but the reaction has not been reported previously for senecic acid.

The dicarboxylic acid, XI, $C_8H_{12}O_4$, melted over a range (highest value 143–147°) and is almost certainly a mixture of the cis and trans forms of 2-hexene-3,5-dicarboxylic acid, which would be formed in the initial Michael condensation of the cleavage of the initial condensation product by sodium ethoxide

$$\underset{\text{CHCH}_3}{\overset{}{}} \quad \underset{\text{COOEt}}{\overset{}{}}$$

MeOOCC—CH$_2$—CCOCH$_3$ $\xrightarrow{\text{NaOEt}}$
|
CH$_3$

CHCH$_3$ CHCH$_3$

MeOOCCCH$_2$CHCOOEt $\longrightarrow$ HOOCCCH$_2$CHCOOH
| |
CH$_3$ XI   CH$_3$

Its ultraviolet and infrared spectra were in accord with this structure (λ_{max} 215 mμ, ϵ 11000; infrared peaks at 1700, 1688 (shoulder) and 1635 cm.$^{-1}$). The optically-active cis and trans forms of XI have been prepared[12] as degradation products of isatinecic and retronecic acids, respectively.

The compound X remains unidentified. Its ultraviolet absorption in ethanol (λ_{max} 288, ϵ 21000; λ_{max} 285, ϵ 17700, in the presence of a trace of HCl) indicates the presence of a conjugated dienone system (infrared peaks at 1720, 1688, 1620, 1575 cm.$^{-1}$). It is acidic and gives no ferric chloride color. These properties suggest a cyclic β-diketone, and indicate the structure XII for the substance

$$\underset{\substack{\text{CHCH}_3 \\ \text{CH}_3}}{\overset{}{}}$$

MeOOCCCH$_2$CHCCOOEt $\xrightarrow{\text{NaOEt}}$
|
CH$_3$COCH$_3$

COOEt
CH$_3$CH
CH$_3$
O   O

CH$_3$CH   CH$_3$

$\longrightarrow$

HO   O

XII

It would, however, be expected that XII would isomerize the corresponding resorcinol.

The (±)-trans-ketoacid VIII and sodium cyanide reacted readily in aqueous solution to give an oil whose infrared spectrum was consistent with the expected cyanohydrin XIII. Hydrolysis of the cyanohydrin in concentrated hydrochloric acid gave a mixture from which three crystalline products were isolated. The major product, $C_{10}H_{14}O_4$, m.p. 142–143°, was (±)-integerrinecic acid lactone

(9) C. F. Koelsch, J. Am. Chem. Soc., 65, 437 (1943).

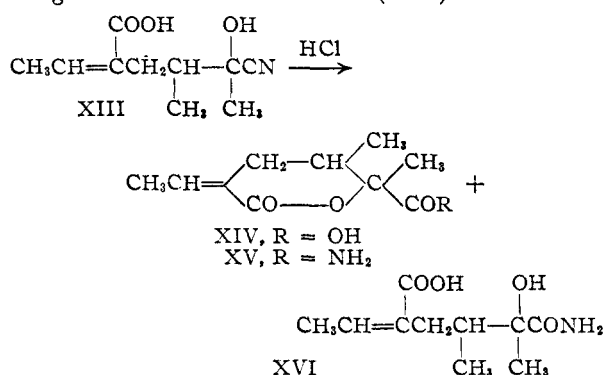(10) C. C. J. Culvenor and T. A. Geissman, Chemistry & Industry, 366 (1959).

(11) R. Adams, T. R. Govindachari, J. H. Looker and J. D. Edwards, J. Am. Chem. Soc., 74, 700 (1952).

(12) S. M. H. Christie, M. Kropman, L. Novellie and F. L. Warren, J. Chem. Soc., 1703 (1949).

(XIV); its infrared spectrum was identical with that of (+)-integerrinecic acid lactone prepared from senecic acid. The other two compounds had compositions and properties that indicated their identities as integerrinecic lactone amide (XV) and integerrinecic acid monoamide (XVI).

$$\underset{\text{XIII}}{CH_3CH=\overset{\overset{\displaystyle COOH}{|}}{C}CH_2\overset{\overset{\displaystyle OH}{|}}{C}H-\overset{\overset{\displaystyle}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}\overset{}{\underset{\underset{\displaystyle CH_3}{|}}{C}}N} \xrightarrow{HCl}$$

$$CH_3CH=\underset{XIV, R = OH}{\underset{XV, R = NH_2}{\left\langle\begin{array}{c}CH_2-CH\\ \\CO\text{---}O\end{array}\right\rangle}}\overset{CH_3}{\underset{COR}{C}}\overset{CH_3}{\diagdown} +$$

$$\underset{XVI}{CH_3CH=\overset{\overset{\displaystyle COOH}{|}}{C}CH_2\overset{\overset{\displaystyle OH}{|}}{C}H-\overset{}{\underset{\underset{\displaystyle CH_3}{|}}{C}}\underset{\underset{\displaystyle CH_3}{|}}{C}ONH_2}$$

Crystalline (±)-integerrinecic acid lactone comprises about one-half of a crude fraction of which the other half is believed to be the second possible racemate of XIV; it has not yet been obtained as a crystalline substance.

Resolution of (±)-integerrinecic acid lactone was accomplished readily by means of the brucine salts. The salt of the (+)-isomer, m.p. 235°, crystallized readily from alcohol; that of the (−)-form, m.p. 221–222°, was obtained by recrystallization of the remaining material from acetone. The acids recovered from the salts had m.p. 153°, [α]D + 40° (ethanol), and m.p. 153°, [α]D −40° (ethanol). Admixture of the (+)-form with natural (+)-integerrinecic acid lactone left the melting point of the latter undepressed, while a mixture of the natural (+)-acid and the synthetic (−)-enantiomer melted at 142°, the melting point of the synthetic racemate. The reported constants of the lactone from senecic or integerrinecic acid have been reported as m.p. 154°, [α]D +39° (ethanol),[13] and m.p. 156°.[14]

To complete a formal synthesis of senecic acid, two possibilities were open: (1) a repetition of the cyanohydrin synthesis, starting with the (±)-cis-ketoacid and using conditions for the hydrolysis which would permit retention of the configuration around the double bond; and (2) isomerization of integerrinecic acid (or its lactone) to senecic acid (or its lactone). Since hydrolysis of the cis-cyanohydrin without isomerization appeared unpromising, the second course was chosen. Irradiation of an alcoholic solution of integerrinecic acid with a strong source of ultraviolet light emitting wave lengths down to 2350 Å. gave approximately 50% conversion to the cis configuration after about 12 hours, as judged by paper chromatographic comparison with authentic integerrinecic and senecic acids. However, isolation of pure senecic acid was accomplished more readily by irradiating integerrinecic acid lactone. The conversion into the cis form proceeded to about the same extent as in the case of the acid itself. The cis- and trans-lactones were separated by chromatography on

(13) R. H. F. Manske, *Can. J. Res.*, **17B**, 1 (1939).
(14) M. F. Richardson and F. L. Warren, *J. Chem. Soc.*, 452 (1943).

silicic acid. Hydrolysis of the pure cis-lactone gave senecic acid. The cis-lactone, for which the name senecic acid lactone is appropriate, has not previously been prepared since methods heretofore used for the lactonization of senecic acid have given integerrinecic acid lactone. We have now found that senecic acid can be lactonized with partial retention of the configuration of the double bond by keeping in 60% sulfuric acid at room temperature for ten hours. By this means, senecic acid lactone, identical with that formed from its isomer by irradiation, was isolated. An attempt to achieve this conversion into the cis-lactone by vacuum sublimation failed; senecic acid sublimed unchanged at 125° (0.1 mm.). This observation is in contrast with the report[5] that usaramoensenecic acid is converted under these conditions (at 120°) into integerrinecic acid lactone.

Experimental[15]

Ethyl methylacetoacetate was prepared by a standard procedure and separated from unsubstituted and disubstituted ethyl acetoacetate by the method of Arndt, *et al.*[16]; ethyl methylacetoacetate had b.p. 84–86° (26 mm.).

3-Acetoxy-1-butyne.—3-Butyn-2-ol (100 g.), acetic anhydride (170 ml.) and pyridine (135 ml.) were mixed, kept overnight and poured into dilute sulfuric acid. The organic layer, diluted with ether, was washed with more sulfuric acid, then with sodium bicarbonate and finally with water. Distillation gave 3-acetoxy-1-butyne (62 g.), b.p. 121–122°. Petrow[17] gives b.p. 37.5–38°(20 mm.) and Reppe,[18] b.p. 124–126°.

3-Acetoxy-2-methylenebutanoic Acid.—Apparatus similar to that described by Jones, *et al.*,[8] was used, with an ice-water mixture in the condenser rather than Dry Ice which caused the nickel carbonyl to solidify in the condenser. 3-Acetoxy-1-butyne (22.6 g.), ethanol (70 ml.), glacial acetic acid (8.1 ml.) and water (4.5 ml.) were mixed and heated to 65°. A small portion (2–3 ml.) of a solution of nickel carbonyl (15 ml.) in ethanol (20 ml.) was run in from a dropping funnel and when reaction began (darkening of color, heat evolution) the remainder was added fairly rapidly to prevent a fall in temperature and yet allow it to be kept below 75°. The mixture was refluxed from a steam-bath for 1 hour (liquid at 60°), cooled slightly, and then ether (60 ml.) added and distilled off to remove excess nickel carbonyl. The ethanol was removed under reduced pressure, the residue poured into water, acidified to congo red with sulfuric acid and extracted first with chloroform and then with ether. The chloroform solution was divided into acidic and neutral fractions by extracting with aqueous sodium bicarbonate and recovering acids from the bicarbonate, after acidification, with chloroform and finally with ether. This and the earlier ether extract yielded mostly acetic acid, but when water was added to the residue, 1-vinyl-3-cyclohexene-1,4-dicarboxylic acid (22 mg.), R_f 0.04 in butanol–ammonia, m.p. 234°, undepressed on admixture with authentic material,[10] was obtained. The chloroform-extracted neutral product (3–4 ml.) did not give a constant-boiling fraction on distillation. The acidic product from chloroform (17.5 g.) was refluxed gently at 0.1 mm. pressure (bath temp. 105°) until no more crystals collected in the condenser above the level of reflux. The crystals (2.0 g.) were removed and crystallized from water to give tiglic acid, m.p. 63–64°, undepressed on admixture with authentic material prepared by shaking an ethanolic solution of tiglaldehyde in oxygen.

Anal. Calcd. for $C_5H_8O_2$: C, 60.0; H, 8.1. Found: C, 60.0; H, 8.3.

(15) Melting points are uncorrected. Solvents used for paper chromatography are (1) butanol–acetic acid, the upper phase resulting from shaking butanol with an equal volume of 5% acetic acid; (2) butanol–ammonia–water (30:2:4); (3) ethanol–ammonia–water (8:1:1).
(16) F. Arndt, L. Loewe and B. Beyer, *Ber.*, **74**, 1460 (1941).
(17) A. A. Petrow, *Zhur. obshchei. Khim.*, **23**, 1101 (1955); *C. A.*, **50**, 4002 (1956).
(18) W. Reppe and co-workers, *Ann.*, **596**, 1 (1955).

The acid product, thus freed from tiglic acid (which otherwise sublimes over with the first part of the main product), was distilled to give an oil (6.4 g.), b.p. 100–110° (0.05 mm.), which solidified when cooled to 0°. This oil was dissolved in a small volume of pentane at room temp. and cooled to 0°, when 3-acetoxy-2-methylenebutanoic acid separated as long needles, m.p. 38°.

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.1; H, 6.4. Found: C, 53.2; H, 6.5.

After storage at 0° for 6 months, a sample supplied by Dr. M. Whiting had m.p. 31°; a mixture with the above acid melted at 34–36°. The infrared spectrum (chloroform solution) shows carbonyl peaks at 1724 (broad) and 1693 cm.$^{-1}$ a double bond peak at 1625 cm.$^{-1}$, and a strong methylene peak at 960 cm.$^{-1}$ (Jones, Whitham and Whiting[19] give 935–950 cm.$^{-1}$ as the range for the corresponding peak in a series of α-methylenecarboxylic acids).

In a second series of runs, similarly performed except that the reaction temperature was kept at 70–75° and maintained for only 10 min. after the nickel carbonyl had been added, 3-acetoxy-1-butyne (75 g., in 3 batches of 25 g.) gave tiglic acid (4–5 g.); 3-acetoxy-2-methylenebutanoic acid (23.2 g.), b.p. 95–105° (0.1 mm.); and from the neutral product fraction, ethyl 3-acetoxy-2-methylenebutanoate (6.9 g.), b.p. 42° (0.05 mm.), infrared absorption in chloroform at 1738 (acetyl), 1718 (α,β-unsaturated ester), 1630 and 950 cm.$^{-1}$ (C=C).

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.1; H, 7.5. Found: C, 58.0; H, 7.8.

Methyl 3-Acetoxy-2-methylenebutanoate.—3-Acetoxy-2-methylenebutanoic acid (17.1 g.) was treated at 0° in ether with a 5% excess of a standard solution of diazomethane in ether. The color of the reagent was discharged rapidly until the addition was almost complete when the color discharge became noticeably slower. The second phase probably represents addition of diazomethane to the double bond. Solvent was removed and the product distilled to give methyl 3-acetoxy-2-methylenebutanoate (15.7 g.), b.p. 56° (0.5 mm.).

Anal. Calcd. for $C_8H_{12}O_4$: C, 55.8; H, 7.0. Found: C, 55.8; H, 7.2.

Reaction of Methyl 3-Acetoxy-2-methylenebutanoate with Ethyl Methylacetoacetate. (I).—A mixture of methyl 3-acetoxy-2-methylenebutanoate (1.7 g.), ethyl methylacetoacetate (1.5 g.) and piperidine (2 drops) was heated at 100° for 10 hr. The mixture developed an acrid odor. It was taken up in chloroform and the solution washed with dilute sulfuric acid, then with water, dried and the solvent removed. The residue was heated at 60° (0.1 mm.) to remove unchanged reactants and then shaken with 1 N sodium hydroxide (20 ml.) for 8 hr. The alkaline solution was washed with chloroform and acidified to give a flocculent precipitate of 1-vinyl-3-cyclohexene-1,4-dicarboxylic acid (1.05 g.), m.p. 236°, mixed m.p. 237° with authentic material.[20]

(II).—Methyl 3-acetoxy-2-methylenebutanoate (1.7 g.) and ethyl methylacetoacetate (1.5 g.) were mixed and treated with a solution of sodium (0.24 g.) in dry ethanol (5 ml.). A precipitate of sodium acetate formed immediately and the temperature of the solution rose 10–15°. After 1.5 hr. at room temperature, a drop of acetic acid was added to make the solution acidic and the alcohol was removed under reduced pressure. The residue was shaken with 1 N sodium hydroxide (30 ml.) for 5 hr., then acidified and extracted with ether to give an oil which was distilled from a bulb-tube. The distillate (1.13 g.) collected at 0.05 mm. with bath temperature 100–105°. When recrystallized from benzene–light petroleum, a small yield of needles, m.p. 159–160°, was obtained. This compound is responsible for the spot of R_f 0.65 which on papers printed with ninhydrin appears as a yellow streak.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.0; H, 8.0. Found: C, 71.0; H, 8.0.

The mother liquor, containing the bulk of the product, was evaporated and the residue taken up in pentane (about 30–40 ml.). On cooling the solution to 0°, the *trans*-racemate of 5-methyl-2-hepten-6-one-3-carboxylic acid (VIII) separated as long needles, m.p. 47–51°, undepressed

on admixture with the compound, m.p. 50–51°, prepared from the product of oxidation of senecic acid with lead tetraacetate (see below). Infrared absorption peaks were at 1700, 1683 and 1635 cm.$^{-1}$. It has R_f 0.42 in butanol–ammonia.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.5; H, 8.3. Found: C, 63.7; H, 8.2.

The acid of R_f 0.38, the *cis*-racemate of 5-methyl-2-hepten-6-one-3-carboxylic acid, was isolated by chromatography on cellulose powder of the residues from crystallization of the *trans*-ketoacid. The residues (0.5 g., from the above and similar runs) were applied to a column (90 × 2.2 cm., containing 200 g. of cellulose) and eluted with butanol–ammonia (d. 0.88)–water (30:2:4). Fractions of 11 ml. were collected and evaporated. Fractions 26–47, showing only the acid R_f 0.38, were combined and the acid recovered and distilled from a bulb-tube at 90–100° (0.08 mm.). The infrared spectrum of the product in chloroform solution was identical with that of *cis*-5-methyl-2-hepten-6-one-3-carboxylic acid derived from senecic acid (see below). The acid formed a 2,4-dinitrophenylhydrazone, m.p. 190–191° from ethanol, undepressed on admixture with the 2,4-dinitrophenylhydrazone of the (−)-*cis*- or that of the (±)-*cis*-ketoacid from senecic acid (see below).

(III).—In another experiment, employing 5 times the above amounts of reactants, the initial condensation product, after hydrolysis with dilute sodium hydroxide and acidification, was extracted with chloroform (which yielded the keto-acid) and then with ether. The ether extract, on evaporation and treatment of the residue with a little benzene, gave a solid (2.3 g.), R_f 0.03 in butanol–ammonia. More of this dicarboxylic acid was obtained from the nonvolatile residues from the distillation of the ketoacid. Recrystallization from ethyl acetate gave needles, m.p. 143–147°. This acid is a mixture of *cis* and *trans* forms of 2-hexene-3,5-dicarboxylic acid (XII). The ultraviolet spectrum had max. absorption at 215 mμ (ϵ 11,000); infrared peaks were at 1700, 1688 (shoulder) and 1635 cm.$^{-1}$.

Anal. Calcd. for $C_8H_{12}O_4$; C, 55.8; H, 7.0; equiv. wt. (for 2 CO_2H), 86. Found: C, 56.2; H, 7.0; equiv. wt., 86.

Oxidation of Senecic Acid with Lead Tetraacetate.—Lead tetraacetate (1.2 g.) was added to a solution of senecic acid (0.5 g.) in dry benzene (100 ml.). The solution was warmed to 50°, and shaken for 1 hr. Excess oxidant was destroyed with ethylene glycol (2 drops), the solution filtered, and the benzene removed. The residue was dissolved in hot water, the solution treated with dilute sulfuric acid, filtered from lead sulfate and extracted with ether. The product distilled from a bulb-tube at 100–105° (0.05 mm.) to give (−)-*cis*-5-methyl-2-hepten-6-one-3-carboxylic acid (0.25 g.), R_f 0.38, [α]D −27° (c 2.9, ethanol).

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.5; H, 8.3. Found: C, 62.9; H, 8.1.

The non-volatile residue from the distillation (0.13 g.) was unchanged senecic acid, m.p. 137–140° from ethyl acetate–light petroleum, mixed m.p. 138–141°. The (−)-*cis*-ketoacid formed a 2,4-dinitrophenylhydrazone, m.p. 191–192° from ethanol.

Anal. Calcd. for $C_{15}H_{19}O_6N_4$: C, 51.3; H, 5.4; N, 15.9. Found: C, 51.5; H, 5.3; N, 15.8.

A solution of the optically active ketoacid in 1 N sodium hydroxide was inactive by the time it had clarified sufficiently to observe its activity. Recovered from this solution after 3 hr., the ketoacid showed no optical rotation in ethanol although its infrared spectrum was unchanged. The racemic ketoacid formed a 2,4-dinitrophenylhydrazone, m.p. 189–190°, undepressed on admixture with that of the active ketoacid.

The (−)-*cis*-ketoacid was heated for 30 min. at 100° in concd. hydrochloric acid and recovered with ether after addition of water. The product was taken up in pentane, cooled to 0° and seeded with the crystalline synthetic ketoacid to give needles of the (±)-*trans*-ketoacid, m.p. 50–51°, R_f 0.42. The 2,4-dinitrophenylhydrazone crystallized from 95% ethanol in irregular prisms, m.p. 145–146°.

Anal. Calcd. for $C_{15}H_{19}O_6N_4$: C, 51.3; H, 5.4; N, 15.9. Found: C, 51.5; H, 5.4; N, 16.1.

(±)-Integerrinecic Acid Lactone.—The (±)-*trans*-ketoacid (0.85 g.) was added to a solution of sodium cyanide

(19) E. R. H. Jones, G. H. Whitham and M. C. Whiting, *J. Chem. Soc.*, 1865 (1954).

(20) C. C. J. Culvenor and T. A. Geissman, unpublished results.

(0.4 g.) in water (2 ml.). Heat was evolved. The solution was cooled, left for 40 min., and poured into concd. hydrochloric acid (15 ml.). This mixture (some precipitation, presumably of sodium chloride, occurs) was heated at 100° for 3 hr., cooled, diluted and extracted with ether to give a brown gum (0.94 g.), R_f 0.42. Continuous ether extraction gave an additional 10–20 mg., R_f 0.23, which crystallized from benzene in needles, m.p. 152–154°. From solubility and R_f value, this compound is considered to be one of the two possible diastereoisomers of *trans*-3-carboxy-5-methyl-2-hepten-6-ol-6-carboxamide (XVIII).

The main product did not crystallize so was taken up in aqueous sodium bicarbonate and the solution washed with chloroform. The chloroform yielded the amide XVI of (±)-integerrinecic acid lactone or its diastereoisomer (0.10 g.), crystallizing from benzene in needles, m.p. 160–162°. The infrared spectrum in chloroform showed peaks at 1705 (unsaturated δ-lactone), 1685 (amide carbonyl), 1570 (NH₂ deformation) and at 3470, 3390 cm.⁻¹ (NH₂ stretching).

Anal. Calcd. for $C_{10}H_{15}O_3N$: C, 60.9; H, 7.7. Found: C, 61.0; H, 7.6.

The bicarbonate solution was acidified and extracted with ether to give a clear gum (0.76 g.). From benzene this gave (±)-integerrinecic acid lactone (0.24 g.) as prisms, m.p. 135–139°. Recrystallization gave large prisms, m.p. 142–143°. The infrared spectrum in chloroform was identical with that of integerrinecic acid lactone prepared from senecic acid.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 60.7; H, 7.0.

Resolution of (±)-Integerrinecic Acid Lactone.—The racemate (198 mg.) and brucine (394 mg.) were dissolved in ethanol (5 ml.). Cooling gave crystals (307 mg.) which were filtered and recrystallized from ethanol to give essentially pure brucine salt of (+)-integerrinecic acid lactone (255 mg.) as needles, m.p. 233°. Further recrystallization raised the melting point to 236°.

Anal. Calcd. for $C_{10}H_{14}O_4 \cdot C_{23}H_{26}O_4N_2$: N, 4.7. Found: N, 4.7.

The mother liquors gave no additional crystals on concentration so the ethanol was removed and the residue taken up in acetone. Addition of ether precipitated a solid (273 mg.), m.p. 211–215°. Two recrystallizations from acetone gave the brucine salt of (−)-integerrinecic acid as prisms, m.p. 221–222°.

Anal. Calcd. for $C_{10}H_{14}O_4 \cdot C_{23}H_{26}O_4N_2$: C, 66.9; H, 6.8; N, 4.7. Found: C, 66.7; H, 6.8; N, 5.3.

The brucine salt of m.p. 236° was dissolved in dilute sulfuric acid and the solution extracted with ether. Evaporation of the extract and crystallization of the residue from benzene gave (+)-integerrinecic acid lactone as needles, m.p. 153°, $[\alpha]^{25}$D + 40° (c, 0.94, ethanol).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 60.8; H, 7.3.

The lactone derived from natural integerrinecic acid or senecic acid has m.p. 154°, $[\alpha]$D + 39° (ethanol). A mixture of the lactone obtained from senecic acid and the synthetic (+)-lactone melted undepressed.

The second brucine salt, m.p. 221–222°, was treated similarly and the derived acid lactone crystallized from benzene to give (−)-integerrinecic acid lactone as fine needles, m.p. 153°, $[\alpha]^{25}$D −40° (c 1.20, ethanol).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 60.6; H, 7.1.

Equal weights of this compound and the (+)-lactone from senecic acid were dissolved in hot benzene and cooled to give needles of the racemic lactone, m.p. 142°, undepressed on admixture with the synthetic (±)-integerrinecic acid lactone.

Ultraviolet Irradiation of Integerrinecic Acid.—A solution of integerrinecic acid (100 mg.) in 95% ethanol (5 ml.) in a quartz cell was irradiated at a distance of 6″ from the unscreened arc of a Hanovia S-500 lamp. Paper chromatograms (ethanol–ammonia) showed that after 12 hours illumination, the mixture contained about 50% each of integerrinecic acid, R_f 0.66, and senecic acid, R_f 0.60.

An additional 5 hr. illumination did not appreciably alter the proportion, indicating that equilibrium had been reached. The acids, recovered by evaporation, could not be induced to crystallize, and an attempt to separate them by chromatography on cellulose in ethanol–ammonia–water (80:4:16) failed.

Ultraviolet Irradiation of Integerrinecic Acid Lactone.— A solution of integerrinecic acid lactone (300 mg.) in 95% ethanol (4 ml.) was irradiated for 10 hr. with a Hanovia 420 lamp. A paper chromatogram, run in butanol–ammonia, showed 2 spots of about equal intensity at R_f's 0.40, 0.46 (integerrinecic acid, R_f 0.40). An additional 3-hr. illumination did not appear to alter the composition of the mixture. The solution was evaporated and the residue crystallized from benzene to give the slightly impure *trans*-lactone (95 mg.), m.p. 144–148°, R_f 0.40. Since it was known (see above) that the brucine salt of integerrinecic acid lactone was not very soluble in cold ethanol, and since a test preparation of the brucine salt of the *cis*-lactone (see below) failed to crystallize from ethanol, separation of the lactones by this method was attempted. The residual material from the above crystallization was converted into brucine salts (with 400 mg. of brucine) which were dissolved in ethanol (6 ml.) and seeded with the salt of the *trans*-lactone. The crystals obtained (31 mg. apparently a mixture) melted about 135° with apparent evolution of solvent. The filtrate was evaporated and the lactone recovered from the residue by extraction from dilute sulfuric acid with ether. Crystallization of the lactone from 50:50 benzene–light petroleum gave a solid (99 mg.), m.p. 93–102°. This was chromatographed on silicic acid (24 g., moistened with 16 ml. 0.5 N sulfuric acid), with collection of 5-ml. fractions. Fractions 8–24, eluted with benzene, gave a solid (27 mg.) showing only one spot, R_f 0.46. Crystallization from benzene–light petroleum gave needles m.p. 129–130°, of *cis*-senecic acid lactone.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.1. Found: C, 60.9; H, 7.3.

Fractions 32–40, eluted with benzene–chloroform (50:50), gave pure *trans*-integerrinecic acid lactone, m.p. and mixed m.p. 153–154°.

Hydrolysis of *cis*-Senecic Acid Lactone.—The *cis*-lactone was warmed in 1 N sodium hydroxide at about 60° for 1 hr. The solution was acidified, saturated with sodium chloride and extracted with ether to give a gum which after sublimation at 125° (0.1 mm.) and crystallization from benzene, gave senecic acid as needles, m.p. 142–143°, mixed m.p. 143–144°. The infrared spectrum (KBr disk) of this product was completely identical with that of senecic acid.

Vacuum Sublimation of Senecic Acid.—Under a pressure of 0.1 mm., senecic acid sublimed readily at about 125° to give a glassy deposit. This was taken up in a small amount of ethyl acetate, benzene added, and the solution concentrated and cooled to give needles of unchanged senecic acid, m.p. and mixed m.p. 146–147°. The mother liquor, spotted on a paper chromatogram (butanol–ammonia), showed senecic acid (R_f 0.04) but no lactone (R_f either 0.40 (*trans*) or 0.46 (*cis*)). Identity of the recovered senecic acid was checked by means of its infrared spectrum.

Lactonization of Senecic Acid in 60% Sulfuric Acid.— Senecic acid (900 mg.) was shaken with 60% sulfuric acid (10 ml.) until dissolved and then left for 10 hr. at room temperature. The solution was cooled to 0°, diluted with water, R_f 0, 0.37, 0.44, for the *trans*- and *cis*-lactones, respectively.

Senecic Acid.—Senecic acid was obtained by hydrolysis of senecionine isolated from *Senecio triangularis*.[21] Recrystallization from ethyl acetate gave needles, m.p. 145–146°.

Integerrinecic Acid Lactone.—Senecic acid (0.2 g.) was heated in concd. hydrochloric acid at 100° for 3 hr. Dilution with water and extraction with ether gave a residue which was crystallized from benzene to give integerrinecic acid lactone (63 mg.), m.p. 149–151°. Paper chromatography in butanol–ammonia showed this product to contain a little dicarboxylic acid (integerrinecic acid, R_f 0.04; integerrinecic acid lactone, R_f 0.37). Incomplete lactoniza-

(21) One of several *Senecio* species examined recently in this Laboratory; the sample, from Gothic, Colo., contained nearly 2% senecionine.

Cyanocarbon Chemistry. XVIII.[1] Tricyanovinylation of Hydrazones and Other Nucleophilic Substances

BY J. R. ROLAND AND B. C. McKUSICK

The strongly electrophilic nature of tetracyanoethylene is shown by its reaction with the wide range of nucleophilic substances represented by aromatic hydrazones, azulene, pyrrocoline and 2-methylfuran. The condensation that occurs introduces a tricyanovinyl group at one of the positions of high electron density. Tricyanovinyl chloride complements tetracyanoethylene as a tricyanovinylation agent in showing increased reactivity and condensing with sterically hindered compounds. The tricyanovinyl aromatic compounds are new classes of dyes.

Tetracyanoethylene reacts with aromatic amines to give N-tricyanovinylamines or p-tricyanovinylarylamines, depending on the structure of the aromatic amine.[2] The present paper describes related reactions of tetracyanoethylene with other types of nucleophilic compounds.

p-Tricyanovinylphenylhydrazones.—The class of compounds most investigated was the p-tricyanovinylphenylhydrazones. Examination of I suggests that electrophilic substitution might occur at any of the starred atoms. The general order of re-

$$\text{Ia, X} = -CH=CH-$$
$$\text{b, X} = NH$$
$$\text{c, X} = S$$
$$\text{d, X} = O$$

activity toward tetracyanoethylene was found to be position 4 for the strongly nucleophilic heterocycles Ib and Id, position 2 for Ia and Ic, position 3 for compounds having positions 2 and 4 substituted, and finally position 1. The p-tricyanovinylphenylhydrazones were prepared by two general methods: (A) stirring a phenylhydrazone with tetracyanoethylene in a strongly polar solvent such as dimethylformamide at 20–60° (eq. 1) and (B) refluxing a carbonyl compound with 1-formyl-2-p-tricyanovinylphenylhydrazine in aqueous alcoholic solution containing hydrogen chloride (eq. 2).

R = alkyl, aryl

The condensation products are crystalline solids that range in color from red to green and give red to blue solutions (Table I). The presence of strong

(1) Paper XVII, Tricyanoethylene and Tricyanovinyl Chloride, C. L. Dickinson, D. W. Wiley and B. C. McKusick, J. Am. Chem. Soc., 82, 6132 (1960).
(2) B. C. McKusick, R. E. Heckert, T. L. Cairns, D. D. Coffman and H. F. Mower, ibid., 80, 2806 (1958).

chromophores is shown by molecular extinction coefficients that range from 19,000 to 53,000, mostly above 30,000. The visible spectra strongly support the structures assigned, and infrared spectra confirm conclusions based on the visible spectra. Chemical evidence for the structures is based on the hydrolytic reaction (eq. 3), hydrazine interchanges (eq. 4, 5), the identity of products prepared by both methods A and B, and the behavior toward aqueous alkali.

$$C_6H_5CH=NNHC_6H_4C(CN)=C(CN)_2 \xrightarrow{\text{NaOH}}$$
$$\text{III}$$

$$[C_6H_5CH=NNHC_6H_4\overset{O^{\ominus}}{C}=C(CN)_2]Na^+$$

$$\text{acid} \downarrow$$

$$C_6H_5CH=NNHC_6H_4C(OH)=C(CN)_2 \quad (3)$$

$$\text{III} \xrightarrow[H_2NNHC_6H_4NO_2]{HCl} C_6H_5CH=NNH\overset{NO_2}{\underset{NO_2}{\bigcirc}} \quad (4)$$

$$\text{III} + (CH_3)_2NC_6H_4CHO \xrightarrow{HCl}$$
$$(CH_3)_2NC_6H_4CH=NNHC_6H_4C(CN)=C(CN)_2 \quad (5)$$

The products of this group react reversibly with aqueous alkali to cause large bathochromic shifts in absorption maxima whereas N-substituted compounds (Table I, no. 12) are instantly and irreversibly bleached by alkali. This behavior is explained by the formation of a stable anion through loss of a proton (eq. 6). Compounds that have no removable proton undergo hydrolysis according to eq. 3 to yield colorless or pale yellow products.

$$\text{III} \underset{H^+}{\overset{OH^\ominus}{\rightleftharpoons}} \bigcirc -CH=NN=\bigcirc=C-C=C=N^\ominus \quad (6)$$
$$\overset{red}{} \qquad\qquad\qquad \overset{blue}{CN\ CN}$$

Tricyanovinylation of Furfural and 2-Pyrrolecarboxaldehyde Hydrazones. Table IIA.—These strongly nucleophilic heterocycles yield blue products on tricyanovinylation. The structure IV is assigned primarily on spectral evidence since