to obtain white crystals of maximum m. p. 188–189° (cor.). No retention of solvent was observed.

Anal. Calcd. for $C_{28}H_{25}N$: C, 89.56; H, 6.71; N, 3.73. Found: C, 89.41; H, 6.56; N, 4.00.

N-Phthaloyl-4-(biphenylene-*o*-tolylmethyl)-2,5-dimethylaniline.—A solution of 2.34 g. of 4-(biphenylene-*o*-tolylmethyl)-2,5-dimethylaniline and 0.92 g. of phthalic anhydride in 150 ml. of dry benzene was refluxed for thirty minutes, cooled and the flocculent white precipitate collected on a filter. The yield was 2.59 g. (79%). The compound had no definite melting point; upon heating above 130° it slowly melted with the evolution of water vapor with ring closure to the imide structure taking place. The sample for analysis was recrystallized three times from benzene and dried *in vacuo* at 60° for three hours.

Anal. Calcd. for $C_{36}H_{39}NO_3$: C, 82.58; H, 5.58; N, 2.68. Found: C, 83.08; H, 5.66; N, 2.70.

N-[4-(Biphenylene-*o*-tolylmethyl)-2,5-dimethylphenyl]-phthalimide.—A mixture of equivalent amounts of 4-(biphenylene-*o*-tolylmethyl)-2,5-dimethylaniline and phthalic anhydride was melted and maintained at 180° for thirty minutes. After cooling, the solidified melt was broken up and boiled with 20 ml. of 95% ethanol for ten minutes. After cooling, the cream-colored product was collected on a filter and dried. The yield was 90%. Two recrystallizations from a 3:1 mixture of absolute ethanol and benzene gave microscopic white crystals, m. p. 232–234° (cor.).

Anal. Calcd. for $C_{36}H_{27}NO_2$: C, 85.51; H, 5.38. Found: C, 85.27; H, 5.50.

Attempted Resolution of N-Phthaloyl-4-(biphenylene-*o*-tolylmethyl)-2,5-dimethylaniline with Quinine.—A solution of 0.50 g. of N-phthaloyl-4-(biphenylene-*o*-tolylmethyl)-2,5-dimethylaniline and 0.361 g. of quinine trihydrate in 7.5 ml. of hot benzene was allowed to stand at room temperature for thirty-six hours. The resulting precipitate of white "warty" crystals was collected on a filter and washed with a few ml. of benzene. The yield was 0.67 g. (83%). The salt decomposed with evolution of water vapor over the range 150–160°.

Rotation: 0.0270 g. made up to 2 ml. with 95% ethanol at 25° gave α_D $-$ 0.92°; l, 1; $[\alpha]^{25}_D$ $-67°$.

The salt was recrystallized four times from benzene to yield 0.19 g. of material. The rotation of the salt after each recrystallization was identical with that of the original salt within experimental error. The final product was hydrolyzed at 0° by stirring with 5 ml. of ethanol–water (1:1) containing a few drops of concd. hydrochloric acid. The resulting free acid showed no rotation in ethanol. Both the quinine salt and the free acid dissolved too slowly to determine if immediate mutarotation occurred.

Anal. Calcd. for $C_{56}H_{53}N_3O_5$: C, 79.31; H, 6.30; N, 4.96. Found: C, 79.27; H, 6.59; N, 4.95.

N-Camphoryl-4-(biphenylene-*o*-tolylmethyl)-2,5-dimethylaniline.—A mixture of 3.00 g. of 4-(biphenylene-*o*-tolylmethyl)-2,5-dimethylaniline and 1.45 g. of *d*-camphoric anhydride was melted and the melt maintained at 150° for fifteen minutes. After cooling, the melt was taken up in 30 ml. of hot benzene and the resulting dark orange solution placed in the ice box overnight. The light tan precipitate was collected on a filter and washed with a few ml. of benzene; 2.75 g. (62%). The product decomposed with foaming over the range 155–185°. Twelve hours of drying *in vacuo* at 100° did not change the decomposition range.

Rotation: 0.0229 g. made up to 2 ml. with absolute ethanol at 25° gave α_D + 0.34°; l, 1; $[\alpha]^{25}_D$ + 30°.

Three recrystallizations from benzene gave 0.70 g. of white product with a constant rotation, decomposing over the range 160–190°.

Rotation: 0.0400 g. made up to 3 ml. with absolute ethanol at 25° gave α_D + 0.32°; l, 1; $[\alpha]^{25}_D$ + 16°.

The initial filtrate was evaporated to dryness by a current of air and the brown gummy residue recrystallized from carbon tetrachloride with the use of Darco to afford 0.90 g. of light tan product.

Rotation: 0.0299 g. made up to 2 ml. with absolute ethanol at 25° gave α_D + 0.39°; l, 1; $[\alpha]^{25}_D$ + 26°. Three further recrystallizations from carbon tetrachloride gave a product identical with that obtained by recrystallization from benzene; $[\alpha]^{25}_D$ + 16°. The product dissolved too slowly to determine if immediate mutarotation occurred.

Anal. Calcd. for $C_{38}H_{39}NO_3$: C, 81.83; H, 7.05; N, 2.51. Found: C, 82.03; H, 7.30; N, 2.70.

Summary

1. A number of tetraarylmethanes containing the fluorene nucleus have been prepared by condensing 9-hydroxy-9-*o*-tolyfluorene with phenol, aniline, *o*-toluidine and *p*-xylidine.

2. The attempted resolutions of 4-(biphenylene-*o*-tolylmethyl)-2-methylaniline and 4-(biphenylene - *o* - tolylmethyl) - 2,5 - dimethylaniline failed.

URBANA, ILLINOIS RECEIVED JULY 5, 1949

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

Synthesis of Viridifloric Acid

BY ROGER ADAMS* AND WERNER HERZ

A program of research has been undertaken in this Laboratory to elucidate the structures of the acid moieties in the alkaloids of the type occurring in various *Senecio* species. These alkaloids are esters of retronecine, or of a closely related pyrrolizidine derivative, with dibasic acids usually containing ten carbon atoms. Alkaloids of this general type are not restricted, however, to the genus *Senecio*, but have been isolated from several other genera of plants. Monocrotaline[1] from *Crotalaria spectabilis* and *retusa* is an ester of retronecine with monocrotalic acid, a monobasic acid of formula $C_8H_{12}O_5$. In the genera *Heliotropium, Trachelanthus, Cynoglossum* and *Lindelofia,* the alkaloids are esters of a pyrrolizidine derivative with various seven-carbon monobasic acids.

This communication concerns viridifloric acid obtained by hydrolysis of the alkaloid viridiflorine[2] found in *Cynoglossum viridiflorum.* It is a stereoisomer of trachelanthic acid obtained by hydrolysis of trachelanthamine found in *Trachelanthus korolkovi*[3]; more recently the latter was

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* Harvard University Ph.D. 1912.

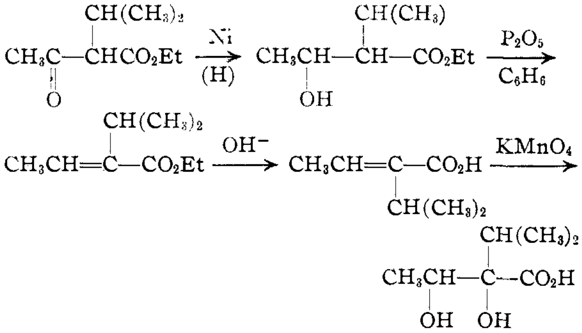
(1) Adams and Rogers, THIS JOURNAL, **61**, 2815 (1939).

(2) Menshikov, *Zhur. Obshchei Khim.*, **18**, 1736 (1948).

(3) (a) Menshikov, *ibid.*, **17**, 343 (1947); (b) Menshikov and Borodina, *ibid.*, **11**, 209 (1941); (c) **15**, 225 (1945); (d) Menshikov, *ibid.*, **16**, 1311 (1946); (e) Gurevitch and Menshikov, *ibid.*, **17**, 1714 (1947).

isolated by hydrolysis of lindelofine, an alkaloid of *Lindelofia anchusoides.*[4] Heliotrinic acid, resulting from the hydrolysis of heliotrine, occurring in *Heliotropium lasiocarpum,*[5] differs from it only in being optically active and containing a methoxyl group in place of a hydroxyl.[6] Menshikov has deduced from degradation studies that the structures of trachelanthic and viridifloric acid are represented by the two stereoisomeric forms of α-isopropyl-α,β-dihydroxybutyric acid.

The synthesis of viridifloric acid has now been achieved as outlined in the scheme



The product which resulted has a melting point of 119°. The melting point of viridifloric acid, as reported by Menshikov,[2] is 119–123° while trachelanthic acid melts more than twenty degrees lower.[3a] It is not possible to say at this time whether viridifloric acid possesses the *threo* or *erythro* configuration.

Catalytic reduction of ethyl isopropylacetoacetate gave ethyl α-isopropyl-β-hydroxybutyrate in excellent yield.[7] Dehydration of this ester resulted in what appeared to be a mixture of α,β- and β,γ-unsaturated esters which could not be separated by fractional distillation. Evidence for the presence of a mixture is the appearance of two peaks in the infrared spectrum at 1718 and 1736 cm.$^{-1}$, the former attributable to a conjugated ester grouping, the latter characteristic of a normal ester, as well as the results obtained on hydrolysis. Similar mixtures have been obtained on dehydration of other alkyl-substituted β-hydroxybutyric esters.[8]

Saponification of the ester mixture gave rise to a solid and a liquid fraction, each having the expected empirical formula. The solid acid, m. p. 54.5°, was identified as α-isopropylcrotonic acid (*cis* or *trans*) by reduction to the known α-isopropylbutyric acid[9] and by ozonolysis. The liquid fraction also gave α-isopropylbutyric acid on reduction, indicating that the carbon skeleton had been retained. Ozonolysis furnished a mixture of volatile aldehydes isolated by means of methone from which the methone derivative of formaldehyde could be separated by treatment with acid. Hence at least part of the liquid fraction consisted of 2-isopropyl-3,4-butenoic acid. Since acetone was not detected, the presence of another possible dehydration product, β,β-dimethyl-α-ethylacrylic acid,[10] was excluded. The other geometric isomer of α-isopropylcrotonic acid, if present, could not be isolated.

A number of attempts were made to improve the yield of α-isopropylcrotonic acid. Dehydration of α-isopropyl-β-hydroxybutyric acid with acetic anhydride resulted in a small amount of the unsaturated acid, the largest portion of the product being α-isopropyl-β-acetoxybutyric acid. Treatment of the β-hydroxy ester with phosphorus pentachloride, followed by hydrolysis of the resulting mixture of unsaturated and β-chlorobutyric esters,[11] gave only a 16% yield of α-isopropylcrotonic acid, lower than could be achieved by the first method.

Oxidation of isopropylcrotonic acid with potassium permanganate furnished the α-isopropyl-α,β-dihydroxybutyric acid, m. p. 119°, which is the same as that of viridifloric acid.

Efforts to hydroxylate α-isopropylcrotonic acid in such a manner as to give trachelanthic acid, using performic or peracetic acid prepared with 90% hydrogen peroxide[12] or perbenzoic acid in a chloroform–water mixture[13] have not been successful, the products being more highly oxygenated compounds of uncertain composition, although α-ethylcrotonic acid, the lower homolog, underwent these reactions fairly smoothly.

Experimental

Ethyl α-Isopropyl-β-hydroxybutyrate.—A solution of 67 g. of redistilled ethyl isopropylacetoacetate in 100 ml. of ethanol was treated with one-half of one tablespoon of Raney nickel and reduced at 1800 lb. and 100°.[14] The solution was filtered and distilled *in vacuo*, 60.5 g. of a fraction boiling at 65–73° (0.5 mm.) being collected. Redistillation did not alter the boiling point, n^{20}D (average of three runs) 1.4298.

Anal.[15] Calcd. for $C_9H_{18}O_3$: C, 62.05; H, 10.41. Found: C, 61.85; H, 10.32.

The *p*-nitrobenzoate, recrystallized from ethanol, melted at 62°.

Anal. Calcd. for $C_{16}H_{21}NO_6$: C, 59.44; H, 6.55. Found: C, 59.21; H, 6.61.

Dehydration of Ethyl α-Isopropyl-β-hydroxybutyrate.—To a mixture of 60 g. of phosphorus pentoxide in 150 ml. of benzene was slowly added 49 g. of the hydroxy ester. After three hours at reflux and subsequent cooling, water was added cautiously. The benzene layer was separated and the water layer was extracted with ether until the extracts were colorless. The combined benzene and ether

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[4] Menshikov, *ibid.*, **18**, 1836 (1948).

[5] Menshikov, *Ber.*, **65**, 974 (1932).

[6] Menshikov, *Zhur. Obshchei Khim.*, **9**, 1851 (1939).

[7] Mazurewitsch, *J. Russ. Phys.-Chem. Soc.*, **41**, 1319 (1909), obtained a very poor yield of this compound from the Reformatsky reaction.

[8] For two recent articles on this subject, see Huston and Goerner, THIS JOURNAL, **68**, 2504 (1946); Huston, Goerner and György, *ibid.*, **70**, 389 (1948).

[9] Fischer, Rohde and Brauns, *Ann.*, **402**, 375 (1914).

[10] Kon, Smith and Thorpe, *J. Chem. Soc.*, **127**, 567 (1925).

[11] Blaise, *Bull. soc. chim.*, [3] **29**, 327 (1903); Spiegelberg, "Festschrift Emil C. Barell," 212 (1936).

[12] English and Gregory, THIS JOURNAL, **69**, 2120 (1947).

[13] Braun, *ibid.*, **51**, 228 (1929).

[14] Adkins, Connor and Cramer, *ibid.*, **52**, 5192 (1930).

[15] Analyses by Mrs. Jane Wood and Miss Emily Davis. Infrared spectra were determined by Miss Elizabeth Peterson.

extracts were dried and distilled. Two fractions were collected, one boiling at 62-70° (20 mm.) (wt. 22.5 g., n^{20}_D 1.4265), the second boiling at 70-75° (20 mm.) (7.5 g., n^{20}_D 1.4337). Since subsequent work showed that hydrolysis of both fractions gave the same mixture, they were combined and redistilled, b. p. 58-62° (13 mm.).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 69.09; H, 10.27.

α-Isopropylcrotonic Acid.—Ten grams of the mixed esters was saponified with 130 ml. of 85% ethanol containing 13 g. of potassium hydroxide. The alkaline mixture was concentrated *in vacuo*, cooled, acidified and chilled. Part of the water-insoluble layer solidified. The solid was collected by filtration, washed with a little water and pressed dry. It weighed 3.1 g. and was purified further by steam distillation and recrystallization from water. The white needles melted at 54.5°. Their infrared spectrum had bands at 1685 cm.$^{-1}$ (conjugated carboxyl) and at 1630 cm.$^{-1}$ (conjugated double bond).

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.83; H, 9.45.

The filtrate contained a considerable quantity of oil from which additional amounts of isopropylcrotonic acid could be separated by virtue of the relative insolubility of the sodium salt. The oil was taken up in ether and extracted with 5% sodium bicarbonate solution. The ether layer was evaporated on the steam-bath and yielded 0.6 g. of sirup which solidified on seeding with isopropylcrotonic acid. The basic extract was acidified and extracted with ether. The ether extract yielded 3.2 g. of an oil which did not solidify in a freezing mixture, b. p. 200-203°(745 mm.)[16] The infrared spectrum had bands at 1693 and 1642 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.64; H, 9.75.

Reduction of α-Isopropylcrotonic Acid.—A solution of 1 g. of the solid acid in 25 ml. of ethanol was reduced in the presence of 20 mg. of platinum oxide. The solvent was removed *in vacuo;* the residue boiled at 200-202° (746 mm.) and was identified as α-isopropylbutyric acid by conversion to the amide, m. p. 136°, and the anilide, m. p. 115°, through the acid chloride.[9]

Reduction of 2.5 g. of the oil gave 2.2 g. of α-isopropylbutyric acid, boiling at the same temperature and yielding the same derivatives.

Ozonolysis of α-Isopropylcrotonic Acid.—A solution of 0.5 g. of the solid acid in 10 ml. of glacial acetic acid was ozonized with 2-3% ozone for fifteen minutes. The solution of the ozonide was diluted with water and steam distilled, the receiver being chilled in a freezing mixture. The first 50 ml. of distillate was filtered from 35 mg. of unozonized α-isopropylcrotonic acid, treated with 50 ml. of an aqueous solution of methone, warmed and allowed to stand. The precipitate melted at 140° and did not depress the melting point of an authentic sample of the methone derivative of acetaldehyde.

Ozonolysis of one gram of the liquid acid followed by steam distillation gave a methone derivative melting unsharply in the range 165-175°. The product was dissolved in 25 ml. of dilute ethanol containing a few drops of concd. hydrochloric acid and was refluxed for five minutes. On cooling there separated long white needles of the methone derivative of formaldehyde, m. p. 188°, giving no depression on admixture of an authentic sample.

α-Isopropyl-α,β-dihydroxybutyric Acid (Viridifloric Acid).—The procedure of Fittig[17] for the oxidation of α-ethylcrotonic acid was followed. A solution of 5 g. of solid α-isopropylcrotonic acid in 400 ml. of water containing 2 g. of sodium hydroxide was cooled in an ice-bath and 310 ml. of a 2% aqueous solution of potassium permanganate was added at 0° with stirring. This required about an hour. The mixture was filtered; the filtrate was concentrated to 50 ml., cooled, acidified and thoroughly extracted with ether. The ether extracts were concentrated on the steam-bath and the residue was subjected to steam distillation. The distillate deposited 0.8 g. of unoxidized α-isopropylcrotonic acid. The aqueous residue was treated with 10 g. of calcium carbonate, boiled for one hour to remove oxalic acid, cooled, filtered and concentrated to very small volume *in vacuo*. The residue was acidified with concd. hydrochloric acid and the acid was isolated by extraction with ether. Removal of ether followed by drying in a vacuum desiccator and stirring with petroleum ether yielded 0.96 g. of product. After purification from chloroform–*n*-pentane the crystals melted at 119°. The compound gave a positive test with periodic acid reagent.

Anal. Calcd. for $C_7H_{14}O_4$: C, 51.83; H, 8.70. Found: C, 51.65; H, 8.60.

Performic Acid Oxidation of α-Ethylcrotonic Acid.—Following the procedure of English and Gregory,[12] 2 g. of α-ethylcrotonic acid[18] was added to a mixture of 9 g. of 98-100% formic acid, 2 g. of 90% hydrogen peroxide and two drops of concd. sulfuric acid which had been allowed to stand at room temperature for twenty minutes. The mixture was stirred vigorously at a temperature of 50-55° for two hours. The temperature was then raised to 95° for one-half hour; the solvents were removed *in vacuo* and the residue was hydrolyzed by heating with 30 ml. of 10% sodium hydroxide solution for one-half hour on the steam-bath. The acidified mixture was extracted with ten 50-ml. portions of ether and the ether was dried and removed on the steam-bath. The solid residue weighed 0.71 g., and, after recrystallization from ether-petroleum ether (b. p. 30-50°), melted at 145°. The m. p. of the dihydroxy acid obtained by potassium permanganate oxidation of α-ethylisocrotonic acid is 144.5-145.5°.[19]

Anal. Calcd. for $C_6H_{12}O_2$: C, 48.63; H, 8.17. Found: C, 48.87; H, 8.31.

Summary

Viridifloric acid, the necic acid of viridiflorine, an alkaloid found in *Cynoglossum viridiflorum*, has been synthesized.

URBANA, ILLINOIS RECEIVED JULY 22, 1949

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[16] Crossley and LeSueur, *J. Chem. Soc.*, **77**, 83 (1900), give 203-204° as the b. p. of a mixture of α-isopropylcrotonic and β,β-dimethyl-α-ethylacrylic acids obtained by dehydrohalogenation of ethyl α-bromo-α-isopropylbutyrate which could not be separated into its constituents.

[17] Fittig, *Ann.*, **268**, 1 (1892).

[18] Blaise and Bagard, *Ann. chim.*, [8] **11**, 127 (1907).

[19] Fittig, Borstelmann and Lurie, *Ann.*, **334**, 101 (1904).