Summary[12]

Six straight-chain 1-olefins, namely, 1-octene, 1-decene, 1-dodecene, 1-tetradecene, 1-hexadecene and 1-octadecene, were hydroxylated with hydrogen peroxide in formic acid solution (performic acid is the oxidizing agent) and gave good yields of the corresponding 1,2-glycols. Only 1.025 to 1.05 moles of hydrogen peroxide was required for each mole of olefin. 1,2-Octanediol, 1,2-decanediol, 1,2-dodecanediol and 1,2-tetradecanediol were prepared for the first time.

The same olefins were epoxidized with peracetic acid in acetic acid solution but gave only fair yields of the corresponding 1,2-epoxides. 1,2-Epoxyoctane, 1,2-epoxytetradecane and 1,2-epoxyoctadecane were prepared for the first time.

(12) Presented at the 109th meeting of the American Chemical Society, Division of Organic Chemistry, April 8–12, 1946, at Atlantic City, New Jersey.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL UNIVERSITY MEDICAL COLLEGE]

α-Isopropyl-5-methyl-2-oxo-4-imidazolidinepropionic Acid, A Structural Isomer of Desthiobiotin[1,2]

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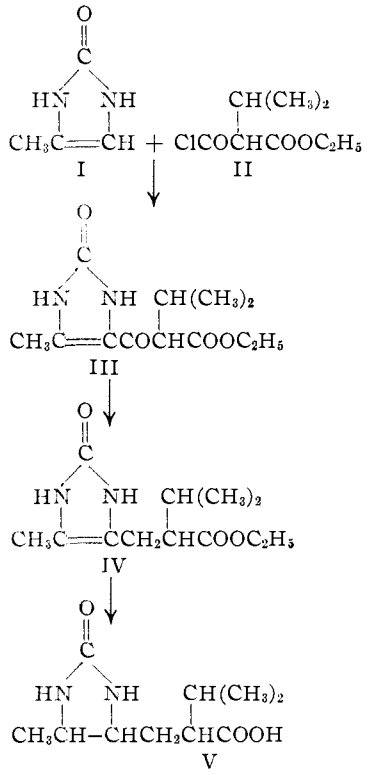
The synthesis of a structural isomer of desthiobiotin, namely, α-isopropyl-5-methyl-2-oxo-4-imidazolidinepropionic acid (V), has been accomplished. This isomer of desthiobiotin corresponds to that which would be derivable from the revised structure of the "egg-yolk biotin," or "α-biotin" as proposed by Kögl and Borg.[3] The condensation of 4-methylimidazolone-2 (I) and ethyl α-chloroformylisovalerate (II), was carried out by the method of Duschinsky and Dolan,[4] followed by the stepwise reduction of the resulting ketone (III).



The final reduction of IV was carried out over both platinum and over Raney nickel catalysts. The reduction of a similar imidazolone over platinum led[4] to a preferential *cis* reduction and the production of *dl*-desthiobiotin, while over Raney nickel[5] the same imidazolone yielded both the *dl* and *allo* isomers of desthiobiotin. With the additional asymmetric center in the present molecule these two methods of reduction could be expected to lead, respectively, to two and four racemic isomers. One crystalline form of V has been obtained in reasonable yield from the reduction over platinum and the same form has been obtained in small yield from the reduction over Raney nickel.

The crystalline form of V as well as the unfractionated products from the reductions over each catalyst were assayed in biotin-deficient media with *Saccharomyces cerevisiae*[6] and *Lactobacillus casei*.[7] No growth-promoting activity was found. They were also tested for antibiotin activity for *L. casei* and no inhibition of growth was observed.

Experimental[8]

Ethyl α-Chloroformylisovalerate (II).—A solution of 320 g. of ethyl malonate in 1 liter of absolute ethanol containing 46 g. of sodium was alkylated with 246 g. of isopropyl bromide. The conversion of this ester to the mono acid and mono acid chloride was accomplished by the method used by Staudinger and Bereza[9] for the ethyl analog.

(1) The authors wish to express their appreciation to Lederle Laboratories, Inc., for a research grant which has aided greatly in this work.

(2) The authors also wish to thank Mrs. Mary McKee for assistance with the yeast assays and Dr. J. R. Rachele for the microanalyses reported here.

(3) Kögl and Borg, *Z. physiol. Chem.*, **281**, 65 (1944).

(4) Duschinsky and Dolan, THIS JOURNAL, **67**, 2079 (1945).

(5) Wood and du Vigneaud, *ibid.*, **67**, 210 (1945).

(6) Biotin and desthiobiotin have equal growth-promoting activities for yeast; Melville, Dittmer, Brown and du Vigneaud, *Science*, **98**, 497 (1943).

(7) Desthiobiotin inhibits the growth of *L. casei* and this inhibition may be reversed by sufficient biotin; (a) Dittmer, Melville and du Vigneaud, *ibid.*, **99**, 203 (1944); (b) Lilly and Leonian, *ibid.*, **99**, 205 (1944).

(8) Melting points were determined on a micro melting point block.

(9) Staudinger and Bereza, *Ber.*, **42**, 4908 (1909).

The solution of the di-ester was filtered from the precipitated sodium bromide and 118 g. of potassium hydroxide in 1.5 liter of ethanol was added during three hours. The alcohol was then distilled at reduced pressure with a bath temperature of 40°. The thick paste was dissolved in 1 liter of water and the solution was washed twice with ether. The aqueous solution was then added to 500 cc. of ice and water containing 53 cc. of concentrated sulfuric acid and was extracted with four 400-cc. portions of ether. The ether was dried over sodium sulfate and was concentrated at a low temperature. The 230 g. of residue was dissolved in 500 cc. of dry ether, the solution was cooled in an ice-bath, and 275 g. of phosphorus pentachloride was added. After fifteen hours, the solution was rapidly distilled in a short-neck distilling apparatus and the fraction distilling between 50 and 80° at 8 mm. was fractionated using an 8-in. Widmer column. The fraction distilling at 70–74° at 8 mm. amounted to 107 g. (29%).

Anal. Calcd. for $C_8H_{13}O_3Cl$: Cl, 18.4. Found: Cl, 17.0.

One gram of the acid chloride was added over a period of fifteen minutes to 15 cc. of concentrated ammonium hydroxide, and 0.4 g. of potassium hydroxide was then added. After the solution had stood overnight, it was concentrated *in vacuo* to remove most of the ammonia. An aliquot was cooled and crystals of the potassium salt of α-carbamylisovaleric acid, m. p. 215°,[10] separated. The main portion was acidified with hydrochloric acid and 0.7 g. of α-carbamylisovaleric acid, m. p. 158°,[11] was obtained.

Ethyl 2,3-Dihydro-α-isopropyl-5-methyl-β,2-dioxo-4-imidazolepropionate (III).—To a cooled solution of 6.4 g. of 4-methylimidazolone-2[4] and 12.7 g. of ethyl α-chloroformylisovalerate in 40 cc. of nitrobenzene was slowly added 26 g. of aluminum chloride. The solution was stirred at room temperature for one hour and at 55–65° for 3 hours. It was then poured onto 100 g. of ice and water containing 9.5 g. of sodium carbonate. The addition of 500 cc. of hexane brought about separation of a third phase which solidified when the mixture was stirred and cooled. The product was dissolved in 100 cc. of hot 20% ethanol, and was clarified with Darco. When the solution was cooled, 6.4 g. (40%) of needles separated, m. p. 120–121°. The product was recrystallized once or twice from aqueous ethanol before reduction.

Anal. Calcd. for $C_{12}H_{18}O_4N_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.72; H, 7.32; N, 10.93.

The absorption of III in 95% ethanol, determined with a Beckman spectrophotometer (Model DU), showed a maximum at 307 mμ, ε = 20,000. 2,3-Dihydro-2-oxo-4-imidazolecarboxylic acid shows[12] a single maximum at 253 mμ of ε = 9,000.

Ethyl 2,3-Dihydro-α-isopropyl-5-methyl-2-oxo-4-imidazolepropionate (IV).—A solution of 2.54 g. of the above ketone in 12.5 cc. of acetic acid, which had been distilled from boron triacetate, was hydrogenated over 500 mg. of pre-reduced platinum oxide[13] for five hours when 480 cc. of hydrogen had been consumed (theory for 2 moles, 484 cc. at 21°). The catalyst was separated, the acetic acid was evaporated and the residue was dissolved in 15 cc. of 10% ethanol, treated with charcoal and filtered. The solution was kept at 5° for eighteen hours, when 1.4 g. (58%) of product, m. p. 118–120°, was collected.

Anal. Calcd. for $C_{12}H_{20}O_3N_2$: N, 11.67. Found: N, 11.51.

A solution of IV in 95% ethanol showed only end absorption, rising from ε = 350 at 250 mμ to ε = 3400 at 230 mμ. An ethanol solution of the compound gave the red ferric chloride test characteristic of imidazolones.

α-Isopropyl-5-methyl-2-oxo-4-imidazolidinepropionic Acid (V), (a) Hydrogenation of the Imidazolone over Platinum.—A preliminary reduction of 240 mg. of IV in 5 cc. of acetic acid, using 300 mg. of pre-reduced platinum oxide, resulted in the consumption of 22.8 cc. of hydrogen in nine hours (calcd. 24 cc.). All attempts to crystallize the resulting oily ester were unsuccessful. The ester was saponified and a crystalline acid was obtained from chloroform–hexane. After recrystallization from ethanol–water and then from ethanol a few mg., m. p. 208–210°, was obtained.

In another preparation 1.0 g. of IV in 10 cc. of acetic acid was hydrogenated under 28 pounds pressure for twenty hours. The catalyst was separated and the acetic acid was evaporated. The ester was saponified in 8 cc. of warm *N* sodium hydroxide, and the solution was acidified with 8 cc. of *N* hydrochloric acid and seeded. After two days, the product was collected and recrystallized successively from 5 cc. of 70% ethanol and 9 cc. of 40% ethanol; 144 mg., m. p. 208–210°, was obtained.

Anal. Calcd. for $C_{10}H_{18}O_3N_2$: C, 56.05; H, 8.45; N, 13.03. Found: C, 56.24; H, 8.25; N, 13.05.

An additional 53 mg. was obtained after long cooling of the mother liquors, making the total yield 21%.

A solution of V in 95% ethanol showed only end absorption, rising from ε = 55 at 250 mμ to ε = 900 at 230 mμ. An ethanol solution of this compound does not give a red ferric chloride test.

(b) **Hydrogenation of the Imidazolone over Raney Nickel.**—The saponification of 1.2 g. of IV was carried out by gentle warming with 5 cc. of *N* sodium hydroxide. An additional 2 cc. of sodium hydroxide was added, and after two hours 1.6 g. of Raney nickel was added and the *p*H was adjusted to 7.5 by the addition of carbon dioxide. The solution was diluted to 20 cc. and hydrogenated at 100° and 2000 lb. pressure for thirty hours. It was then filtered and the *p*H of 8.0 was adjusted to 5.5 and the solution was diluted to 50 cc. After removal of an aliquot for assay, the remainder was acidified and continuously extracted with ether for six hours. The ether extract yielded 700 mg. of a glass. An aliquot of this material was taken for assay. The main portion of the product was dissolved in 5 cc. of chloroform and 5 cc. of hexane was added. After four days, the crystals and oil which had separated were washed with hexane and recrystallized from ethanol–water. The 16 mg. of crystalline product obtained melted at 208–210° and the m. p. was not depressed by admixture with the product described above.

Biological Assays.—Solutions of the crystalline compound containing up to 180 γ per tube; of the crude platinum reduction product containing up to 400 γ per tube; and of the crude nickel reduction product containing up to 400 γ per tube were assayed[14] for their ability to replace biotin in stimulating the growth of *Saccharomyces cerevisiae*. The last mentioned solution showed the greatest stimulation, corresponding on a weight basis to 0.004% of the activity of biotin, but this was reduced over tenfold by one treatment at room temperature with Darco. These solutions also failed to inhibit[7a] the growth of *Lactobacillus casei*. In addition, solutions containing 5 mg. per cc. of the crystalline product and 4 mg. per cc. of the nickel reduction product failed to inhibit or to stimulate[15] the growth of *L. casei*. These concentrations would be capable of detecting biotin antagonistic activity up to a molar inhibition ratio[16] of 35,000,000.

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Summary

The synthesis of α-isopropyl-5-methyl-2-oxo-4-imidazolidinepropionic acid is described.

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