of this value with the corresponding increment from 80 to 298.16° yields for the molal entropy of the liquid $S^{\circ}_{298.16}$ = 262.5 (±2.6) e. u. from the study at Stanford.

Discussion

As shown in Fig. 2, the heat capacity measurements on liquid 11-*n*-decylheneicosane at The Pennsylvania State College are not reproducible. A similar phenomenon has been observed in The Pennsylvania State College laboratory in the case of liquid isopentane[7] and questioned by Guthrie and Huffman,[8] who obtained perfect reproducibility on the same sample. No adequate explanation of this situation has yet been found and the results obtained at The Pennsylvania State College are still believed to be valid.[9] The lack of reproducibility in the case of 11-*n*-decylheneicosane is 0.6%, which is several times the estimated accuracy of the determination. In view of the complicated nature of the compound and the large amount of impurity present, it is useless to speculate on the cause of the phenomenon.

This lack of reproducibility in the liquid region was not observed at the Stanford Laboratory as is to be expected since the accuracy is only 0.7%. If the lack of reproducibility in The Pennsylvania State College data is due to calorimetric errors, no reasonable cause for such errors has been discovered.

(7) Aston and Schuman, THIS JOURNAL, **64**, 1034 (1942).
(8) Guthrie and Huffman, *ibid.*, **65**, 1139 (1943).
(9) Aston, *ibid.*, **65**, 2041 (1943).

Acknowledgment.—We wish to thank Project 42 of the American Petroleum Institute for supplying the sample and for aiding financially the work of The Pennsylvania State College.

Summary

1. The heat capacity of solid and liquid 11-*n*-decylheneicosane has been measured from 12.27 to 295.74°K. at The Pennsylvania State College, and from 80.3 to 297.4°K. at Stanford University.

2. The results at The Pennsylvania State College indicated that the liquid heat capacities are not reproducible.

3. The equilibrium temperatures of the fusion, together with the heat of fusion, have been determined in both laboratories.

4. From The Pennsylvania State College measurements the mole per cent. impurity, on the basis of the melting point lowering from 50–100% was calculated to be 3.52% and the melting point of the *pure* material to be 282.34 ± 0.05°K. The corresponding Stanford data were 3.4% impurity and a melting point of 282.2 ± 0.1°K.

5. The molal entropy of the liquid at 298.16°K. as determined from the thermal data at The Pennsylvania State College is 259.60 e. u. The data at Stanford yield a corresponding value of 262.5 e. u., based on the use of an approximate extrapolation method below 80°K.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

A Simple Synthesis of *dl*-Desthiobiotin and Related Substances

BY ROBERT DUSCHINSKY AND L. ALLEN DOLAN

Imidazolone derivatives carrying appropriate substituents in the 4- and 5-positions of the nucleus were believed to be promising starting materials for the synthesis of biotin and related substances. The present paper describes, as a first step toward this goal, a general method of introducing side chains into the 5-position of 4-methylimidazolone-2 (II), as well as the hydrogenation of the obtained imidazolone derivatives. The new method is illustrated by the formulas I–VIII, which represent the synthesis of the biologically important 4-methyl-5-(ω-carboxyamyl)-imidazolidone-2 or *dl*-desthiobiotin (VI).

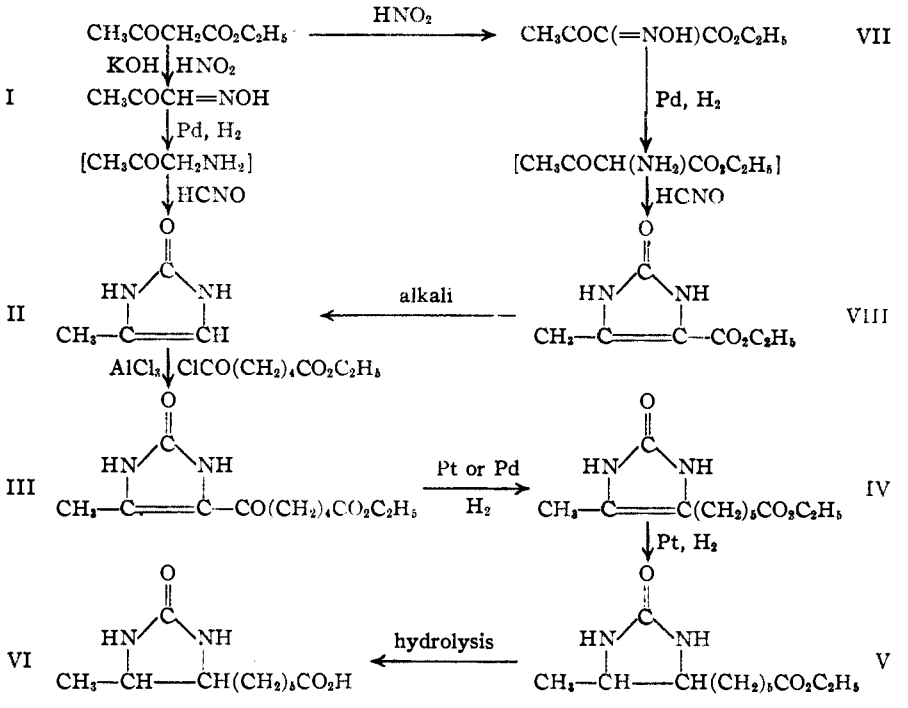
A synthesis of desthiobiotin has already been reported by Wood and du Vigneaud.[1] Our synthesis is quite different in approach, and was completed prior to this publication. It is based on the observation that 4-methylimidazolone-2 (II) undergoes Friedel–Crafts condensations, the acyl group being introduced in position 5.

(1) Wood and du Vigneaud, THIS JOURNAL, **67**, 210 (1945).

The hitherto unknown 4-methylimidazolone-2 (II) became accessible by alternative methods from ethyl acetoacetate, *i. e.*, *via* oximinoacetone (I) or *via* ethyl α-oximinoacetoacetate (VII). The oximino compounds were converted by hydrogenation to the corresponding amino compounds, which were not isolated but directly condensed with cyanic acid. When the ester (VIII), first described by Gabriel and Posner,[2] was saponified by alkaline reagents, the decarboxylated substance II was isolated instead of the expected free acid. Like all imidazolone derivatives, the substances VIII and II give a deep red ferric chloride reaction, indicating the presence of an enolic hydroxy group. This reaction is suppressed when one or two acetyl groups are introduced into the nucleus by treatment with acetic anhydride.

4-Carboxy-imidazolone-2[3] and 4-methyl-5-car-

(2) Gabriel and Posner, *Ber.*, **27**, 1144 (1894).
(3) Hilbert, THIS JOURNAL, **54**, 3414 (1932).



boxy-imidazole[4] are not decarboxylated upon treatment with alkali. It was therefore assumed that the combined influence of the substituents in position 2 and 4 was responsible for the observed spontaneous decarboxylation of 4-methyl-5-carboxy-imidazolone-2, because these substituents tend to increase the electron density on carbon atom 5 of the nucleus.[5] Consequently, it was thought that the 5-position in 4-methylimidazolone-2 should be easily attacked by electrophilic reagents and, as a matter of fact, the substance was found to undergo Friedel–Crafts reactions with acyl halides.[6]

The condensation products thus obtained were stable toward hot normal alkali or acid,[7] but were decomposed by boiling 20% hydrochloric acid, whereby the previously introduced acyl group was recovered as acid. The possibility of an N or O acylation, however, was definitely excluded because the condensation products showed ferric chloride reaction and formed oximes, and because by treatment with acetic anhydride two acetyl groups were introduced into the compounds.[8]

4 - Methyl - 5 - (ω - carbethoxyvaleryl) - imidazolone-2 (III) was prepared from 4-methylimidazolone - 2 by condensation with ω - carbethoxyvaleryl chloride in the presence of aluminum chloride with a yield of more than 60%.

Hydrogenation of compound III with Adams platinum catalyst in acetic acid at room temperature resulted in a rapid uptake of 2 moles of hydrogen and reduction of the keto group to methylene, since 4-methyl-5-(ω-carbethoxyamyl) - imidazolone-2 (IV) could be isolated. A third mole of hydrogen was absorbed more slowly, yielding desthiobiotin ethyl ester (V), and, by subsequent saponification, desthiobiotin (VI). Steps III to VI were advantageously performed in one operation, thus giving desthiobiotin with an over-all yield of 80–90%, based on the Friedel–Crafts product III, and of 25%, based on ethyl acetoacetate.

The synthetic *dl*-desthiobiotin melted at 163°, its methyl ester at 72°. For *Saccharomyces cerevisiae str. 139*, it showed, on a weight basis, a growth-promoting activity equal to 53% of that of biotin, and for *Lactobacillus casei* a molar inhibition ratio of 17,000.[9]

In view of the microbiological activity of the synthetic compound, there is no doubt that the diastereomer, related to *dl*-biotin, was obtained.[10]

7,8-Diaminopelargonic acid dihydrochloride[11] was obtained from the synthetic desthiobiotin by refluxing with hydrochloric acid. The diaminopelargonic acid was then reconverted with phosgene by a method comparable to that of Melville[12] to yield desthiobiotin which was identical in physical, chemical, and biological properties with the original synthetic *dl*-desthiobiotin.

Wood and du Vigneaud[1] hydrogenated 4-

(4) Gerngross, *Ber.*, **45**, 522 (1912).

(5) Compare the decarboxylation mechanism suggested for aromatic hydroxy acids by Fieser and Fieser, "Organic Chemistry," 1944. p. 674.

(6) The activation by the methyl group alone appears insufficient, since Ochiai, *J. Pharm. Soc., Japan*, **60**, 55 (1940); *C. A.*, **34**, 5450 (1940), found that 4-methylimidazole does not undergo Friedel–Crafts condensations. A similar situation prevails for the thiazole nucleus where according to Ochiai and Nagasawa, *Ber.*, **72**, 1470 (1939), 4-methylthiazole fails to react in contrast to 4-methylthiazolone-2.

(7) Only saponification of ester groups takes place.

(8) The question whether the diacetyl compounds formed are O,N or N,N derivatives remains undecided.

(9) Rubin, Drekter and Moyer, *Proc. Soc. Exp. Biol. Med.*, **58**, 352 (1945). We submitted to Dr. V. du Vigneaud, upon publication of his paper,[1] a sample of our *dl*-desthiobiotin. Dr. du Vigneaud kindly checked the yeast growth-promoting activity and found a potency of 53%.

(10) *dl*-Desthiobiotin of 50% activity was obtained from synthetic biotin by Harris, Mozingo, Wolf, Wilson, Arth and Folkers, THIS JOURNAL, **66**, 1800 (1944). *dl-allo*-Desthiobiotin was found to be inactive.

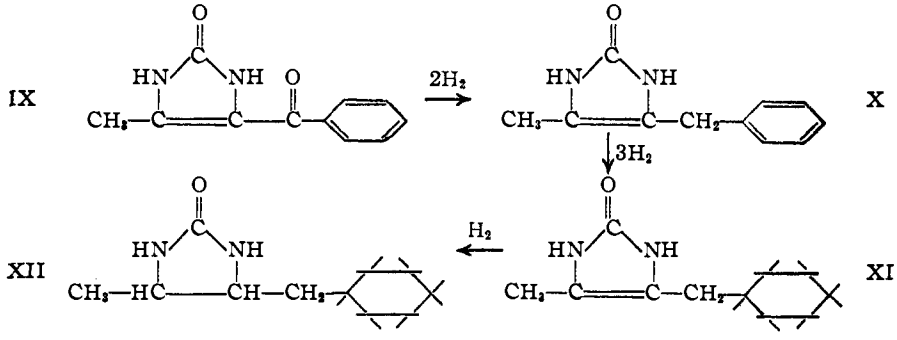
(11) The substance was tested by Dr. V. du Vigneaud and Dr. K. Dittmer and found close to 50% as active in promoting yeast growth as the diaminopelargonic acid sulfate derived from *d*-biotin.

(12) Melville, THIS JOURNAL, **66**, 1422 (1944).

methyl-(ω-carboxyamyl)-imidazolone-2 with Raney nickel and obtained a mixture of the *cis*- and *trans*-isomers of desthiobiotin which were difficult to separate. The hydrogenations with platinum catalyst, as described n the present paper, however, yielded sterically almost uniform material, very probably the *cis*-form.

Table I in the experimental part reviews Friedel–Crafts reactions with other acyl halides and Table II hydrogenations of various imidazolone derivatives. In particular, 4-methyl-5-(ω-carboxypropyl)-imidazolidone-2 and 4-methyl-5-(ω-carboxyoctyl)-imidazolidone-2 were prepared as homologs of desthiobiotin. The latter compound inhibited biotin at a molar ratio of 200,000 in *Saccharomyces cerevisiae* and of 1,000,000 in *Lactobacillus casei*. The former compound as well as 4-methylimidazolidone-2, 4,5-dimethylimidazolidone-2, and 4-methyl-5-ethylimidazolidone-2, were found to have only a very small, if any, growth-promoting or inhibiting activity toward both micro-organisms.

The hydrogenation of 4-methyl-5-benzoylimidazolone-2 (IX), prepared by Friedel–Crafts reaction of II with benzoyl chloride, is represented by the following formulas (IX–XII), showing that the imidazolone nucleus is more resistant to hydrogenation than the benzene ring.



4 - Methyl - 5 - hexahydrobenzyl - imidazolidone-2 (XII) showed no growth-promoting or inhibiting activity for *Lactobacillus casei* and a molar inhibition ratio of 370,000 for *Saccharomyces cerevisiae*.

Experimental[13]

4-Methyl-5-carbethoxyimidazolone-2 (VIII).—Ethyl α-oximino-acetoacetate was prepared in a yield of 72% from ethyl acetoacetate according to Adkins and Reeve.[14] For the hydrogenation and subsequent cyclization, according to Ochiai and Ikuma,[15] 477 g. (3 moles) oximino ester, m. p. 54–56°, dissolved in a mixture of 1430 cc. ethanol and 6000 cc. of 0.5 *N* hydrochloric acid, were shaken at 50 atm. hydrogen pressure with 48 g. of moist 2.5% palladium charcoal as catalyst. The theoretical amount of 2 moles of hydrogen was taken up in twenty minutes and was accompanied by a temperature rise from 33 to 52°.[16] Three hundred cc. of 5 *N* hydrochloric acid and a solution of 365 g. potassium cyanate (4.5 moles) in 1400 cc. of water were added to the filtered mixture and the temperature raised to 65° within ten minutes. The crystallization of the ester (VIII) began readily and was completed by cooling; yield, 417 g. (81.5%); m. p. 225–226°. It gives a red ferric chloride reaction.

Mono- and Diacetyl Derivatives.—The ester VIII (4.25 g.) was refluxed for a half hour with 40 cc. of acetic anhydride. After distilling off *in vacuo ca.* 15 cc. of the anhydride and cooling, white needles separated which were washed with ether; yield, 2 g.; m. p. 172–173°. The product was sublimed at 0.3 mm. and 140° (bath). The analysis shows that the substance is a monoacetyl derivative.

Anal. Calcd. for $C_9H_{12}O_4N_2$: C, 50.94; H, 5.70; N, 13.20. Found: C, 50.97; H, 5.60; N, 13.54, 13.47.

After further concentration of the acetic anhydride mother liquor and separation of 0.1 g. of unsharp melting material, the residue was heated *in vacuo* at 100°. Thus 1.7 g. of crystalline material remained which, after distillation at 0.1 mm. and 110° (bath), melted at 53–56° and proved to be a diacetyl derivative.

Anal. Calcd. for $C_{11}H_{14}O_5N_2$: C, 51.96; H, 5.55; N, 11.02. Found: C, 52.29; H, 5.64; N, 10.80.

Neither the mono- nor diacetyl derivative gives a ferric chloride reaction.

4-Methylimidazolone-2 (II): Method A.—Ester VIII was saponified and decarboxylated either by heating with 1 mole of *N* sodium hydroxide to 60° for sixty to seventy hours, followed by acidification with hydrochloric acid, or better in the following way.

To a solution of 340 g. (2 moles) of VIII in 1450 cc. of water and 840 cc. of ethanol, which was kept refluxing with continuous stirring, a hot solution of 680 g. (2.15 moles) of crystallized barium hydroxide in 2800 cc. of water, was added gradually within two hours. Too fast addition of the barium hydroxide results in a bulky precipitate which disintegrates with difficulty. Heating and stirring was then continued for four to six hours, until the precipitation of the heavy, fast-settling barium carbonate was complete. After filtering the hot solution, the small residual amount of barium was eliminated by addition of *ca.* 250 cc. of *N* sulfuric acid. Evaporation gave a crystallizing sirup which was dissolved in 50 cc. of boiling water and cooled. A bulky crystalline, slightly yellowish mass resulted, which was sucked dry and washed with a little ice-cold water; yield, 140–150 g. (71.5–76.5%); m. p, 185–188°. The crude material is directly suitable for Friedel–Crafts reactions.

For the analysis it was recrystallized from 2 volumes of boiling water and sublimed at 140–160° (0.2 mm.); m. p. 202–204° (*in vacuo*). Soluble in water, ethanol, acetone, hot dioxane, butyl alcohol and nitrobenzene; insoluble in ether and petroleum ether.

Anal. Calcd. for $C_4H_6ON_2$: C, 48.97; H, 6.16; N, 28.56. Found: C, 49.19; H, 6.09; N, 82.89.

Method B.—Oximinoacetone (I) was prepared from ethyl acetoacetate with a yield of 65%[17]; 8.7 g. (m. p. 63–65°) was dissolved in a mixture of 50 cc. of 2 *N* hydrochloric acid and 50 cc. of alcohol and hydrogenated during a half hour with 1.5 g. of 2.5% palladium charcoal at 50 atm. hydrogen pressure and 30–45°. Two moles of hydrogen was taken up. After filtering off the catalyst, 10 cc. of 5 *N* hydrochloric acid and 12.5 g. of potassium

(13) Melting points were determined with an uncalibrated set of Anschütz thermometers.

(14) Adkins and Reeve, THIS JOURNAL, 60, 1329 (1938).

(15) Ochiai and Ikuma, *Ber.*, 69, 1147 (1936).

(16) Too high temperature is detrimental to the yield.

(17) Fischer–Orth, "Die Chemie des Pyrrols," Vol. I, 1934, p. 408.

cyanate, dissolved in 40 cc. of water, were added and the mixture heated to 100° for *ca.* five minutes. The slightly yellow solution was concentrated to a small volume until crystals separated; yield, 4.4 g. (45%); m. p. 194–198°; after sublimation 200–202°.

The **diacetyl derivative** was obtained in 80% yield by short refluxing with 10 vols. of acetic anhydride, the excess of which was distilled off, first at ordinary pressure and then *in vacuo*. The process was repeated with the residue: white needles from cold ether, subliming at 100–110° (1 mm.); m. p. 78–80°.

Anal. Calcd. for $C_8H_{10}O_3N_2$: C, 52.74; H, 5.53; N, 15.38. Found: C, 52.99; H, 4.94; N, 15.56.

In an attempted Friedel–Crafts reaction, with the preceding diacetyl derivative and acetyl chloride, **monoacetyl-4-methylimidazolone-2** was isolated in 50% yield. It was purified by sublimation *in vacuo* at 150° and recrystallized from a small amount of water; m. p. 175°. The substance gave no ferric chloride reaction, and was reconverted into the diacetyl derivative by treatment with acetic anhydride, showing that no C acetylation had taken place.

Anal. Calcd. for $C_6H_8O_2N_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.76; H, 5.48; N, 20.09.

Ethyl hydrogen adipate was prepared according to Fourneau and Sabetay[18] by refluxing for ten hours equimolecular quantities of adipic acid and ethyl adipate. The half ester was separated by fractionation; b. p. 160–161° (10 mm.); m. p. 27°; yield, *ca.* 35%, not counting the recovered starting materials.

ω-Carbethoxyvaleryl chloride was obtained according to Blaise and Koehler[19] by refluxing the ethyl hydrogen adipate with 1.5 moles of thionyl chloride; b. p. 120–121° (13 mm.); yield, 95–97.5%.

4-Methyl-5-(ω-carbethoxyvaleryl)-imidazolone-2 (III).—To a solution of 46.3 g. of 4-methylimidazolone-2 (II) and 92 g. of carbethoxyvaleryl chloride in 275 cc. of nitrobenzene was added portion-wise with stirring and cooling 190 g. (3 moles) of anhydrous aluminum chloride. After heating the mixture for five hours at 65°, the hydrochloric gas evolution had practically stopped. The brown viscous oil was poured on 1 kg. of an ice and water mixture containing 70 g. of sodium carbonate. After addition of 500 cc. of ether the keto ester (III) crystallized in yellowish needles. They were washed with water and ether, and recrystallized from 1200 cc. of 50% ethanol; m. p. 173–174°; yield 74.4 g. (61.9%). It was soluble in acetic acid, less so in alcohol and insoluble in water and ether. The alcoholic solution gives a red ferric chloride reaction.

Anal. Calcd. for $C_{12}H_{18}O_4N_2$: C, 56.68; H, 7.14; OC_2H_5, 18.60. Found: C, 56.87, 56.98; H, 7.10; OC_2H_5, 18.69.

The **diacetyl derivative** of the keto ester (III) was obtained by twice refluxing with 5 vols. of acetic anhydride and crystallizing the reaction product from alcohol; yield, *ca.* 90%; m. p. 74–75°. It sublimes at 0.6 mm. and 160° (bath), and is soluble in most organic solvents, except petroleum ether.

Anal. Calcd. for $C_{16}H_{22}O_6N_2$: C, 56.79; H, 6.55; N, 8.28; $(C_2H_3O)_2O$, 25.45. Found: C, 57.04; H, 6.57; N, 8.97; $(C_2H_3O)_2O$, 27.53.

A **monobenzoyl derivative** was obtained by refluxing keto ester III for ten minutes with 2 moles of benzoyl chloride in pyridine and pouring the mixture on ice. The substance crystallized from ether, was recrystallized from carbon tetrachloride, and melted at 127–128°.

Anal. Calcd. for $C_{19}H_{22}O_5N_2$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.53; H, 6.05; N, 7.71.

4-Methyl-5-(ω-carboxyvaleryl)-imidazolone-2.—Three hundred and sixty mg. of ester III and 6 cc. of *N* sodium hydroxide were heated on a boiling water-bath for one hour. After acidification with 6 cc. of *N* hydrochloric acid, the free acid crystallized in white needles, melting at 210–212°; yield, 315 mg. (98%). The same product was obtained by refluxing with *N* sulfuric acid. It was soluble in hot alcohol and water; insoluble in most organic solvents.

Anal. Calcd. for $C_{10}H_{14}O_4N_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.01; H, 6.03; N, 11.63.

Sometimes this acid crystallized with one mole of water which caused melting at lower temperature with subsequent resolidification.

Anal. Calcd. for $C_{10}H_{14}O_4N_2 \cdot H_2O$: C, 49.14; H, 6.60; N, 11.47. Found: C, 49.19; H, 6.59; N, 11.35.

Acid Hydrolysis of 4-Methyl-5-(ω-carboxyvaleryl)-imidazolone-2.—Two hundred and ten mg. of the preceding keto acid was refluxed one hour with 2 cc. of 20% hydrochloric acid. After dilution of the pink solution with 10 cc. of water, 120 mg. (57%) of recovered starting material crystallized. The mother liquor was extracted with ether. The extract gave on evaporation 60 mg. (22%) of adipic acid melting at 149–151°. It was identified by mixed melting point.

Oxime of 4-Methyl-5-(ω-carboxyvaleryl)-imidazolone-2.—Keto ester III (2.4 g.) was heated with 15 cc. of *N* sodium hydroxide on a boiling water-bath for five minutes; 1.1 g. of hydroxylamine hydrochloride was added and the heating continued for half an hour, when white needles separated. A second crop of oxime crystallized upon heating the mother liquor with 10 cc. of *N* NaOH and 700 mg. of hydroxylamine hydrochloride, followed by acidification with acetic acid; total yield was 2.03 g. (84%). The product decomposes at 227°. It is soluble in alkali; insoluble in organic solvents, and can be recrystallized from 400 parts of boiling water.

Anal. Calcd. for $C_{10}H_{15}O_4N_3$: C, 49.78; H, 6.27; N, 17.42. Found: C, 49.94; H, 6.07; N, 17.78.

Friedel–Crafts condensations of 4-methylimidazolone-2 with other acyl halides are reviewed in Table I. Most of the examples were run only once, therefore the optimum conditions were not determined. About 10 volumes of nitrobenzene based on the methylimidazolone weight was used as solvent, and 2 moles of aluminum chloride as condensation agent, except in reaction 5, where 3 moles was used. The reaction temperature was 60–65°, and the end-point was determined by titrating the hydrogen chloride driven over with dry air. After pouring on ice, the condensation products were washed with ether, except in reaction 1 where the nitrobenzene was eliminated by steam distillation. In reaction 3, the free 4-methyl-5-oxalylimidazolone-2 was obtained, instead of the expected ethyl ester.

Solvent and Catalyst for Hydrogenations.—The acetic acid used as solvent was purified by distillation over chromium trioxide. The platinum oxide was prehydrogenated, the acid decanted, and replaced in order to wash out soluble inorganic material from the catalyst. When not stated otherwise the hydrogenations were carried out at room temperature and atmospheric pressure.

4-Methyl-5-(ω-carbethoxyamyl)-imidazolone-2 (IV).—The keto ester III (5.08 g.) dissolved in 50 cc. acetic acid, was hydrogenated with 2 g. of Adams platinum catalyst for thirty minutes until 977 cc. of hydrogen was taken up (calcd. for 2 moles, 975 cc. at 24°). After filtering off the catalyst, the acetic acid was evaporated and the residue treated with ethanol. On cooling, white needles separated which were washed with cold ethanol and ether; yield, 3.36 g. (70%); m. p. 194–196°. The ester can be recrystallized from 15 volumes of ethanol and sublimed at 0.4 mm. and 200° (bath). It is fairly soluble in ethanol and acetic acid, and little soluble in ether. The alcoholic solution gives a very strong purple ferric chloride reaction.

Anal. Calcd. for $C_{12}H_{20}O_3N_2$: C, 59.98; H, 8.39; N, 11.66. Found: C, 60.03; H, 8.44; N, 12.02.

The same substance was obtained when 2.54 g. of keto ester III dissolved in 35 cc. of ethanol was hydrogenated with 4 g. of palladium charcoal catalyst (2.5%) at 140° and 90 atm. pressure; yield, 1.13 g. (47%).

The **diacetyl derivative** of the preceding ester IV was obtained by twice refluxing with acetic anhydride and evaporating to dryness. It is a colorless oil distilling at

(18) Fourneau and Sabetay, *Bull. soc. chim.*, [4] **43**, 859 (1928).

(19) Blaise and Koehler, *ibid.*, [4] **7**, 219 (1910).

TABLE I

FRIEDEL-CRAFTS REACTIONS

Reaction no.			1	2	3	4	5	6
Reactants	II, g.		1.96	4.9	9.8	4.9	3.8	9.8
	cpd.	name	AcBr	ClAcCl	EtO_2CCOCl[a]	$MeO_2C(CH_2)_2COCl$[b]	$EtO_2C(CH_2)_7COCl$[c]	BzCl
		g.	1.35	6.2	14.65	8.8	9.1	15
Time, hr.			5	6	3½	3	4½	5½
Prod., 4-Me-5-R-imidazolone-2, R=			$-OCCH_3$[d,e]	$-OCCH_2Cl$	$-OCCO_2H$	$-OC(CH_2)_2CO_2CH_3$	$-OC(CH_2)_7CO_2C_2H_5$	$-OCC_6H_5$
Yield, %			50	59	24	39	42	79
M. p., °C.			322	248–250	dec. *ca.* 260	215	169	258
Cryst. from	solvent		water	water	50% ethanol	10% ethanol	50% ethanol	50% ethanol
	parts of		50	160	300	30	25	25
Formula			$C_6H_8O_2N_2$	$C_6H_7O_2N_2Cl$	$C_9H_{12}O_4N_2$	$C_9H_{12}O_4N_2$	$C_{15}H_{24}O_4N_2$	$C_{11}H_{10}O_2N_2$
Anal., %	carbon	calcd.	51.42		42.39	50.94	60.79	
		found	51.22		50.94	51.29	60.95	
	hydrogen	calcd.	5.75	Cl, 20.31	3.56	5.70	8.16	
		found	5.53	Cl, 20.09	3.48	5.78	8.20	
				20.45				
	nitrogen	calcd.	19.99	16.05	16.47	13.20	9.45	13.86
		found	19.92	16.01	16.10	13.37	9.57	13.71

[a] Weygand, "Organisch-chemische Experimentierkunst," 1938, p. 231. [b] Robinson and Robinson, *J. Chem. Soc.* **127**, 180 (1925). [c] Robinson and Robinson, *J. Chem. Soc.*, 2206 (1926). [d] *Oxime* by refluxing one hour with hydroxylamine hydrochloride and sodium acetate; yield 90%, m. p. 298° (dec.). Recrystallized from 170 parts water. *Anal.* Calcd. for $C_6H_9O_2N_3$: C, 46.46; H, 5.85; N, 27.09. Found: C, 46.00; H, 5.24; N, 26.95. [e] *Diacetyl derivative* by twice refluxing and evaporating with acetic anhydride. Distilled at 0.5 mm. and 110–115° (bath); m. p. 72–73°. Soluble in organic solvents. *Anal.* Calcd. for $C_{10}H_{12}O_4N_2$: C, 53.96; H, 5.00; N, 12.50. Found: C, 53.54; H, 5.16; N, 12.97. [f] *Diacetyl derivative* with acetic anhydride as above. Recrystallized from 7 volumes of ethanol; m. p. 121–123°, yield 79%. *Anal.* Calcd. for $C_{18}H_{14}O_4N_2$: C, 62.92; H, 4.93; N, 9.79. Found: C, 62.97; H, 4.75; N, 10.27.

0.4 mm. and *ca.* 170° (bath); $n^{24}D$ 1.4971; soluble in organic solvents, and gives no ferric chloride reaction.

Anal. Calcd. for $C_{16}H_{24}O_5H_2$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.26; H, 7.41; N, 8.79.

4-Methyl-5-carboxyamylimidazolone-2.—Four hundred and eighty mg. of ester IV was refluxed one-fourth of an hour with 3 cc. of *N* sodium hydroxide. Upon acidification with 3 cc. of *N* hydrochloric acid, the free acid crystallized in colorless needles, which were washed with water, alcohol and ether. The yield was 230 mg. (46%). The substance was recrystallized from 8 cc. of water; m. p. 169–170°. Wood and du Vigneaud reported a m. p. of 168°.[1]

Anal. Calcd. for $C_{10}H_{16}O_3N_2$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.43; H, 7.64; N, 13.11.

4-Methyl-5-(ω-carbethoxyamyl)-imidazolidone-2; *dl*-Desthiobiotin Ethyl Ester (V).—Three hundred and sixty mg. of ester IV dissolved in 7 cc. of acetic acid was hydrogenated to complete saturation with 400 mg. of Adams platinum catalyst. Uptake was 36.5 cc. hydrogen in two hours and twenty minutes at 23° (theoret. for 1 mole was 38.5 cc.). After filtering off the catalyst and evaporating the solvent, the residue was distilled at 0.5–0.7 mm. and 200–220° (bath). A forerun was separated and 220 mg. (60%) of an oil, solidifying to a crystalline mass, was obtained. After redistilling, the substance melted at 54–56°. It is insoluble in water, and soluble in organic solvents, except petroleum ether.

Anal. Calcd. for $C_{12}H_{22}O_3N_2$: C, 59.48; H, 9.15; N, 11.56. Found: C, 59.39; H, 9.15; N, 11.64.

By saponification of the crude, not distilled, ester V with *N* sodium hydroxide, desthiobiotin was obtained. It was, however, more advantageous to proceed directly from keto ester III in a one-step hydrogenation followed by saponification.

4-Methyl-5-(ω-carboxyamyl)-imidazolidone-2; *dl*-Desthiobiotin (VI).—A solution of 67 g. of keto ester III in 670 cc. of acetic acid was shaken for twenty hours with 16.5 g. of Adams platinum catalyst under a slight hydrogen pressure. The liquid filtered from the catalyst was evaporated *in vacuo* and the last traces of acetic acid were eliminated by distillation with ethanol. The resulting colorless sirup was dissolved in 50 cc. of ethanol, 500 cc. of *N* sodium hydroxide was added and the mixture kept for thirty minutes at 50°. After acidifying with 100 cc. of 5 *N* hydrochloric acid, desthiobiotin crystallized in colorless needles, which were filtered and washed chlorine-free with water. The yield was 51.1 g. (91%); m. p. 159.5–161.5°. Recrystallization from 650 cc. of boiling water yielded 46.8 g., melting at 162.5–163°; a second recrystallization did not raise the melting point. The substance is soluble in *ca.* 13 volumes of boiling, and *ca.* 1000 volumes of cold water; it is more soluble in ethanol and acetic acid. Concentrated aqueous solutions are obtained by addition of one equivalent of alkali. The ferric chloride reaction is negative.

Anal. Calcd. for $C_{10}H_{18}O_3N_2$: C, 56.05; H, 8.47; N, 13.08. Found: C, 56.02; H, 8.25; N, 12.84.

The **methyl ester** was obtained by treatment with diazomethane. It was purified by distillation at 0.5 mm. and 170° (bath) and melted at 72°.

Anal. Calcd. for $C_{11}H_{20}O_3N_2$: C, 57.87; H, 8.83; N, 12.27. Found: C, 58.00; H, 8.73; N, 12.09.

7,8-Diaminopelargonic Acid Sulfate.—*dl*-Desthiobiotin (428 mg.) was refluxed for two hours under nitrogen with 1 cc. of 48% hydrobromic acid and a few grains of red phosphorus. Concentration *in vacuo* gave a semi-crystalline mass, which was taken up with 2 cc. of boiling water. From the filtered (aqueous) solution 35 mg. of desthiobiotin was recovered melting at 160–162°. The bromine was eliminated with silver acetate from the mother liquor, the solution was reconcentrated and the residual sirup neutralized to congo paper with sulfuric acid, when 305 mg. (53%) sulfate crystallized. This was recrystallized by dissolving in 2 cc. of water and adding 8 cc. of methanol; m. p. 241–245°.

Anal. Calcd. for $C_9H_{22}O_6N_2S$: C, 37.75; H, 7.75; N 9.78. Found: C, 37.54; H, 7.65; N, 9.62.

7,8-Diaminopelargonic Acid Dihydrochloride.—A solution of 428 mg. of *dl*-desthiobiotin in 10 cc. of concentrated hydrochloric acid was refluxed for six hours. Concentration *in vacuo* and drying over sodium hydroxide yielded a crystalline material which was washed with 5 cc. of ethanol; yield, 380 mg. (73%), m. p. 206–208°. It was recrystallized by dissolving in 8 cc. of methanol and precipitation with 12 cc. of ether, giving 330 mg. of substance of the same melting point.

Anal. Calcd. for $C_9H_{22}N_2O_2Cl_2$: C, 41.38; H, 8.49; Cl, 27.15. Found: C, 41.66; H, 8.42; Cl, 26.79.

Reconversion into *dl*-Desthiobiotin.—To a solution of 261 mg. of recrystallized diaminopelargonic acid dihydrochloride in 10 cc. of water were added portionwise with stirring 8.1 cc. of *N* sodium hydroxide and 10 cc. of *ca.*

TABLE II

HYDROGENATION

Reaction no.			1	2	3	4	5
4-Methyl-5-R-imidazolone-2, R =			—H	—CH_3	—$COCH_3$	—$CO(CH_2)_3CO_2CH_3$	—$CO(CH_2)_7CO_2C_2H_5$
Amt. taken, mg.			980	560	80	424	1.19
PtO_2, mg.			500	100	40	200	600
Time, hr.			1½	24	1½	2½	4
Hydrogen uptake	cc. per		245	111	41	151	305
	mole		1	1	3	3	3
4-Methyl-5-R-imidazolidone-2, R =			—H	—CH_3	—C_2H_5	—$(CH_2)_3CO_2H$	—$(CH_2)_8CO_2H$
Yield, %			32	...	68	*ca.* 50	92
M. p., °C.			120–122.5	191–196	167–171	139–140	155–156.5
Purification	treat.		Subl., 0.5 mm.	Subl., 0.4 mm.	Subl., 0.4 mm.	Recryst.	Recryst.
	temp., bath; °C.		100–110	150	150	5 vol. H_2O	1600 vol. H_2O
Formula			$C_4H_5ON_3$	$C_5H_7ON_3$	$C_6H_{11}ON_3$	$C_8H_{14}O_2N_2$	$C_{13}H_{24}O_4N_2$
Anal., %	carbon	calcd.	47.98	52.61	56.22	51.60	60.91
		found	48.31	53.01	56.20	51.39	61.42
							61.49
	hydrogen	calcd.	7.95	8.83	9.44	7.58	9.44
		found	7.80	8.64	9.35	7.27	8.90
							9.11
	nitrogen	calcd.	27.98	24.54	21.86	15.05	10.93
		found	28.01	24.02	21.81	15.17	11.05
			27.67				

3.5% phosgene solution in xylene, so that the *p*H was maintained around 8. After separation of the xylene and acidification with hydrochloric acid, 160 mg. (75%) of desthiobiotin crystallized, melting at 162°, and after recrystallization at 163°. Activity for *Saccharomyces cerevisiae* was 50% of that of biotin.

4-Methyl-5-benzylimidazolone-2 (X).—A solution of 1.1 g. of 4-methyl-5-benzoylimidazolone-2 (IX) in 10 cc. of acetic acid was hydrogenated with 0.5 g. of platinum catalyst. Uptake was 248 cc. (*ca.* 2 mols) in forty minutes. Evaporation of the filtered reaction mixture gave a white crystalline mass, which was recrystallized from 10 cc. of water, yielding 990 mg. of unsharp melting material. The product was twice recrystallized from 50% ethanol and finally sublimed at 0.6 mm. and 220–235° (bath). The purified substance decomposed at *ca.* 270° as reported in the literature[20] and melted in an evacuated capillary tube at 290°. With palladium charcoal as catalyst the pure product was obtained in 87% yield.

Anal. Calcd. for $C_{11}H_{12}ON_2$: N, 14.88. Found: N, 14.77.

4-Methyl-5-hexahydrobenzyl-imidazolone-2 (XI).—A solution of 1.1 g. of IX in 10 cc. of acetic acid was hydrogenated with 0.5 g. of platinum catalyst until 640 cc. (*ca.* 5 mols) was taken up in one hundred and forty minutes. Crystallization occurred during the hydrogenation. The product was separated from the catalyst by extraction with hot acetic acid. The filtrate of 20 cc. gave upon addition of 10 cc. of water a white precipitate weighing 1.12 g. The product was purified by recrystallization from 100 cc. of ethanol and sublimation at 0.7 mm. and 230° (bath). In an evacuated capillary tube, it melted at 358–360° without decomposition.

Anal. Calcd. for $C_{11}H_{18}ON_2$: C, 68.00; H, 9.34; N, 14.42. Found: C, 68.39; H, 9.19; N, 14.66.

4-Methyl-5-hexahydrobenzyl-imidazolidone-2 (XII).—When 1.1 g. of ketone IX was hydrogenated under the previously described conditions, the uptake came to a standstill at 740 cc. (*ca.* 6 mols) in eight hours. After evaporation of the acetic acid, the residue was recrystallized from 25 cc. of 50% ethanol, yielding 690 mg. of white needles melting at 138–140°. The substance is soluble in alcohol, insoluble in water and ether, and can be sublimed at 0.4 mm. and 150° (bath). A hydrogenation at 20 atm. pressure of 7.7 g. of IX gave 5.15 g. (75.5%) of the same compound.

Anal. Calcd. for $C_{11}H_{20}ON_2$: C, 67.33; H, 10.27; N, 14.27. Found: C, 67.09; H, 9.96; N, 13.97.

The imidazolone derivatives IX, X and XI give ferric chloride reaction, the imidazolidone derivative XII does not.

Further hydrogenation experiments with 5-substituted 4-methylimidazolone derivatives are presented in Table II. Although the hydrogenation curves showed the already observed stepwise uptake, when a keto group was present, only complete hydrogenation to the corresponding imidazolidones was carried out and no intermediates were isolated. About 10 volumes of glacial acetic acid was used in these experiments as solvent. 4,5-Dimethylimidazolone-2 used in reaction 2 was prepared according to Biltz.[21] In reaction 4 the ester obtained after hydrogenation was saponified with barium hydroxide, in reaction 5 with sodium hydroxide.

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Summary

4-Methylimidazolone-2 was prepared from ethyl acetoacetate by two methods. The compound underwent Friedel–Crafts condensations with acyl halides in 5-position of the nucleus as illustrated in a number of examples.

Hydrogenation of the imidazolone derivatives with Adams platinum catalyst yielded imidazolidone derivatives, the keto groups in α-position to the nucleus undergoing hydrogenolysis.

Application of these methods gave *dl*-desthiobiotin (25% yield from ethyl acetoacetate), as well as the homolog 4-methyl-5-(ω-carboxypropyl)-imidazolidone-2 and 4-methyl-5-(ω-carboxyoctyl)-imidazolidone-2.

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