Anal. Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.46. Found: C, 49.21; H, 6.81; N, 11.25.

Resolution of *l*(+)-Arginine Salts of *dl*-Biotin.—A mixture of 1.44 g. of *dl*-biotin and 1.15 g. (10% excess) of *l*(+)-arginine was dissolved in 20 ml. of water and the solution was diluted with isopropyl alcohol. Crystallization was allowed to proceed in the refrigerator overnight. The crystals were collected on a filter and washed with acetone; m. p. 214–218° (micro-block); $[\alpha]^{25}D$ +49.09° (*c*, 1.039 in water); yield 1.13 g. (92%). The *l*(+)-arginine salt of biotin when pure had the following properties: m. p. 228–230° (micro-block); $[\alpha]^{25}D$ +59.9° (*c*, 1.37 in water).

Anal. Calcd. for $C_{16}H_{30}N_6O_5S$: C, 45.91; H, 7.23. Found: C, 46.25; H, 7.51.

One and nine-hundredths grams of the crude *l*(+)-arginine salt was recrystallized twice from aqueous isopropyl alcohol; $[\alpha]^{25}D$ +57.2° (*c*, 1.747 in water). The purified salt was dissolved in 10 ml. of water and acidified with dilute hydrochloric acid. The crystalline biotin was collected on a filter, washed with water and dried; m. p. 229–231° (micro-block); a mixture of this sample with biotin of natural origin melted without depression; $[\alpha]^{25}D$ +88.8° (*c*, 1.025 in 0.1 *N* sodium hydroxide); yield 0.51 g. (80%). Further purification was accomplished by suspending the biotin in 20 ml. of hot water, adding just enough dilute sodium hydroxide solution to dissolve the solid, then acidifying with hydrochloric acid. The pure crystalline biotin melted at 229–231°; $[\alpha]^{25}D$ +90.4° (*c*, 1.87 in 0.1 *N* sodium hydroxide); yield 0.44 g. (64% overall).

Anal. Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.16; H, 6.60; N, 11.46. Found: C, 49.07, 49.35; H, 6.46, 6.47; N, 11.42.

Acknowledgment.—The authors wish to express their thanks to Messrs. D. F. Hayman, R. N. Boos, Leonard Rosalsky and Edward Thornton for carrying out the microanalyses.

Summary

dl-Biotin has been resolved by three independent methods.

The fractional crystallization of the *d*(−)-mandelic acid esters of *dl*-biotin led to the isolation of biotin. From the *l*(+)-mandelic acid esters, *l*-biotin was obtained.

Quinidine methohydroxide was found to be a satisfactory reagent for the separation of *l*-biotin from its enantiomorph. Biotin was obtained from the mother liquor salts.

The *l*(+)-arginine salt of biotin crystallized as the less soluble salt from the mixed *dl*-biotin salts of *l*(+)-arginine. Decomposition of the salt gave biotin. This resolution of *dl*-biotin is the most satisfactory one.

RAHWAY, NEW JERSEY RECEIVED AUGUST 17, 1945

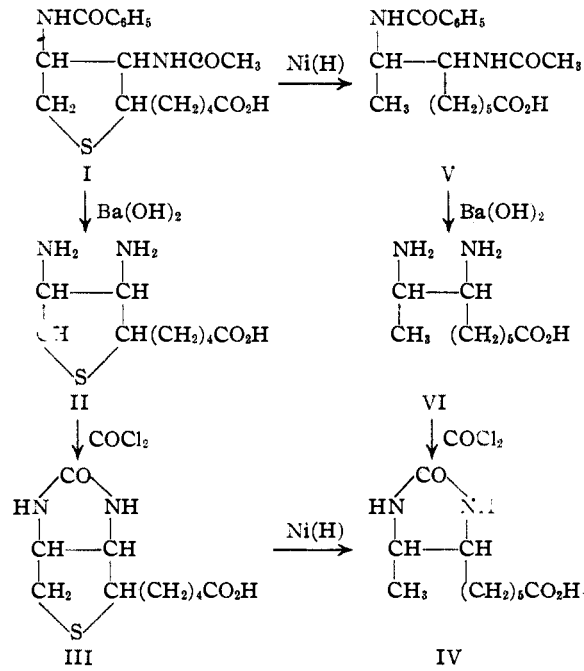
[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK AND CO., INC.]

Biotin. VII. A Stereochemical Correlation of *dl*-Biotin, *dl*-Allobiotin and *dl-epi*-Allobiotin

BY STANTON A. HARRIS, RALPH MOZINGO, DONALD E. WOLF, ANDREW N. WILSON AND KARL FOLKERS

A stereochemical correlation of *dl*-biotin, *dl*-allobiotin and *dl-epi*-allobiotin[1] and of the three intermediate racemic methyl esters of 3-acetamido - 4 - benzamidotetrahydro - 2 - thiophenevaleric acid[2] has been accomplished. This was effected by the use of the sulfur hydrogenolysis reaction[3,4] with Raney nickel catalyst. The application of this reaction is illustrated by reactions III → IV and I → V.

A tetrahydrothiophene which is substituted in the 2, 3 and 4 positions could exist in eight stereoisomeric forms. Four of these forms are represented by formulas VIIId, f, g and h in Diagram I; the other four forms are enantiomorphic to the ones shown and do not need to be illustrated for the purpose of this discussion. If the sulfur atom were replaced by hydrogen atoms, the asymmetry about carbon atom 2 would be lost. Two of these forms are represented by formulas IXj and k; the other two enantiomorphic forms are not illustrated. The racemates as well as the individual isomers may be used to show these



relationships. Thus, the four possible racemates corresponding to formulas VIIId, f, g and h should yield two desthio racemates corresponding to

(1) Harris, Mozingo, Wolf, Wilson, Arth and Folkers, THIS JOURNAL, **66**, 1800 (1944).

(2) Harris, Wolf, Mozingo, Arth, Anderson, Easton and Folkers, *ibid.*, **67**, 2096 (1945).

(3) Mozingo, Wolf, Harris and Folkers, *ibid.*, **65**, 1013 (1943).

(4) du Vigneaud, Melville, Folkers, Wolf, Mozingo, Keresztesy and Harris, *J. Biol. Chem.*, **146**, 475 (1942); Melville, Dittmer, Brown and du Vigneaud, *Science*, **98**, 497 (1943).

formulas IXj and k. The determination of the pairs of racemic tetrahydrothiophenes which will give a common desthio derivative would furnish a correlation of the arrangement of the nitrogen atoms with respect to each other in these molecules. The results of these reactions combined with the results of stability studies on the ureides, III and IV, have made it possible to show the spatial arrangement of the nitrogen atoms with respect to each other in biotin and its isomers.

Two of the four racemic tetrahydrothiophenes must have the *cis* arrangement of their amino groups which should allow the formation of a practically strain-free bicyclic ring system. The other two racemates must have the *trans* arrangement of their amino groups which could allow only the formation of a strained bicyclic ring system. Since three racemates[2] related to biotin have been obtained synthetically, one or two of these racemates must have rings fused in the *trans* manner. These relationships are shown by formulas VIIId, f, g and h in Diagram I (where the R's = —CO—).

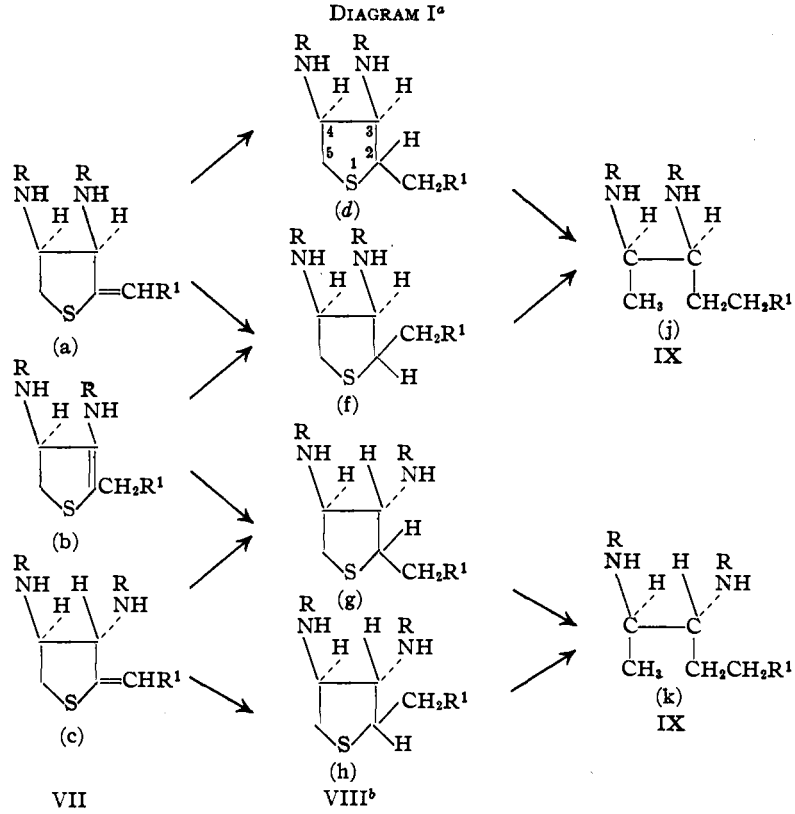
Starting with the three known *dl*-3-acetamido-4-benzamidotetrahydro-2-thiophenevaleric acids,[2] I, (diamido acids) two independent series of reactions (I→II→III→IV and I→V→VI→IV) gave the same desthio ureides. In the first sequence of reactions (I→II→III→IV) the *dl*-allodiamido acid,[2] I, and the *dl-epi*-allodiamido acid,[2] I, yielded *dl*-allobiotin, III, and *dl-epi*-allobiotin, III, respectively. These two racemates, when treated with Raney nickel catalyst, yielded the same desthio derivative, m. p. 165–166°, which is called *dl*-desthioallobiotin, IV. By the same sequence of reactions[2] the *dl*-biotin was formed and converted into *dl*-desthiobiotin, m. p. 165–166°. The melting point of a mixture of the *dl*-desthio derivatives derived from *dl*-allobiotin and *dl-epi*-allobiotin showed no depression. However, when *dl*-desthioallobiotin was mixed with *dl*-desthiobiotin the melting point was depressed to 144°.

In the second sequence of reactions (I→V→VI→IV) the three racemic diamido acids, I, were first treated with Raney nickel catalyst to yield *dl*-diamidopelargonic acids, V. The *dl*-allodiamido acid and the *dl-epi*-allodiamido acid yielded the same *dl*-allodiamidopelargonic acid, V, m. p. 169–170°. The *dl*-diamido acid yielded *dl*-diamidopelargonic acid, m. p. 192°. After hydrolysis and treatment with phosgene,[5] the *dl*-allodiamidopelargonic acid yielded *dl*-desthiobiotin, IV.

dl-Desthiobiotin was found to be one-half as active[6] as desthiobiotin by yeast assay while *dl*-desthioallobiotin was inactive in this assay. The observation that *dl*-desthiobiotin has one-half the activity of desthiobiotin for yeast growth and also that the latter is optically active is evidence that the steric arrangement of the nitrogen atoms about the carbon atoms is not disturbed by the hydrogenolysis reaction.

Since *dl*-allobiotin and *dl-epi*-allobiotin gave the same desthio derivative, their nitrogen atoms must have the same steric relationship. They differ by being epimeric at carbon 2 where the side chain is attached; therefore, the name *dl-epi*-allobiotin. *dl*-Biotin, which gave a different desthio derivative, must have a different arrangement of its nitrogen atoms. The fourth racemate, which should yield *dl*-desthiobiotin and is un-

DIAGRAM I[a]



[a] The enantiomorphs are omitted from this diagram for simplicity: R = C_6H_5CO—, CH_3O, H, or —CO—; $R^1 = (CH_2)_3CO_2H$. [b] The configuration of the side chain has not been established.

(5) Recently desthiobiotin has been hydrolyzed to the *d*-diaminopelargonic acid with barium hydroxide and reconverted to desthiobiotin with phosgene [Melville, THIS JOURNAL, **66**, 1422 (1944)].

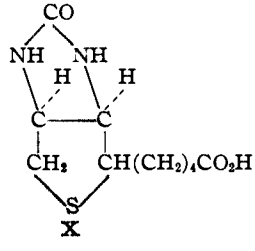
(6) These assays were kindly carried out by Dr. Jacob L. Stokes and Misses Marion Gunness and Muriel Caswell of this Laboratory: see also, Stokes and Gunness, *J. Biol. Chem.*, **157**, 121 (1945). For the activity of *d*-desthiobiotin, see Melville, Dittmer, Brown and du Vigneaud, *Science*, **98**, 497 (1943).

known, would be epimeric with *dl*-biotin at carbon atom 2. This fourth racemate by this system of nomenclature would be called *dl-epi*-biotin.

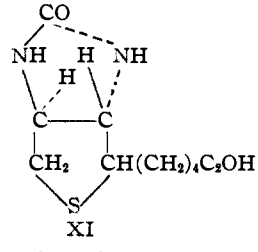
dl-Biotin[2] has been synthesized from the *dl*-diamino acid in excellent yield just as biotin was resynthesized[7] in nearly theoretical yield by treating the diaminocarboxylic acid with phosgene. *dl*-Allobiotin and *dl-epi*-allobiotin[2] were not obtained in such good yields apparently because they were not stable to recrystallization from water. This observation was supported by the fact that *dl*-allobiotin was hydrolyzed in an aqueous solution containing one mole of sulfuric acid to the corresponding *dl*-allodiamino acid sulfate and carbon dioxide by boiling for a few minutes. Under the same conditions *dl*-biotin liberated no carbon dioxide and was recovered unchanged from the reaction mixture. Both *dl*-desthioallobiotin and *dl*-desthiobiotin were found to be stable under these conditions which indicated that the instability of the —NHCONH— group in *dl*-allobiotin and *dl-epi*-allobiotin was due to the strained *trans* fusion of the two rings.

dl-Allobiotin could not be esterified by the use of methyl alcohol and sulfuric acid. However, the ester was made by the use of diazomethane. A molecular weight determination on the methyl ester showed that the compound was monomeric. The monomeric nature of *dl-epi*-allobiotin was demonstrated by the fact that it yielded *dl*-desthioallobiotin, the methyl ester of which was found also to be monomeric by molecular weight determination.

These experiments indicated that biotin and *dl*-biotin have the *cis* arrangement of their nitrogen atoms as illustrated by formula X and that *dl*-allobiotin and *dl-epi*-allobiotin have the *trans* arrangement of their nitrogen atoms as illustrated by formula XI.

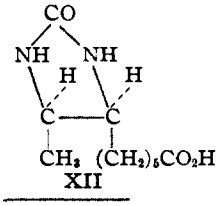


X

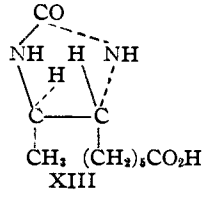


XI

Since *dl*-biotin undoubtedly has the *cis* arrangement of its nitrogen atoms, it then follows that the configuration of *dl*-desthiobiotin is represented by formula XII and that of *dl*-desthioallobiotin is represented by formula XIII.



XII



XIII

(7) Melville, Hofmann and du Vigneaud, *Science*, **94**, 308 (1941).

It was indicated that the methyl ester of 4-benzamido - 3 - oximino - $\Delta^{2,5}$ - tetrahydro - 2-thiophenevaleric acid was reduced with zinc dust in acetic acid–acetic anhydride mixture to give a mixture of two isomeric dehydro compounds. These are represented by formulas VIIb and VIIc in Diagram I. In one compound the double bond is in the ring between positions 2 and 3 (3-acetamido-4-benzamido-4,5-dihydro-2-thiophenevaleric acid methyl ester, or the *dl-iso*-dehydro ester, VIIb), and in the other it is between the side chain and the ring (3-acetamido-4-benzamido - $\Delta^{2,5}$ - tetrahydro - 2 - thiophenevaleric acid methyl ester, or the *dl*-allodehydro ester, VIIc). The *dl-iso*dehydro ester, VIIb, yielded two series of tetrahydrothiophene derivatives[2] after hydrogenation over a palladium catalyst. One of these series of compounds was composed of the *dl*-diamido acid and ester (3-acetamido - 4 - benzamidotetrahydro - 2 - thiophenevaleric acid and its methyl ester), the sulfate of the *dl*-diamino acid (sulfate of 3,4-diaminotetrahydro-2-thiophenevaleric acid), *dl*-biotin, and finally *dl*-desthiobiotin. The second series of compounds from the *dl-iso*dehydro ester, VIIb, was composed of the *dl*-allodiamido acid and ester, the sulfate of the *dl*-allodiamino acid, *dl*-allobiotin and, finally, *dl*-desthioallobiotin. This last series of *dl*-allo compounds[2] was also obtained from the *dl*-allodehydro ester, VIIc, along with the series of compounds composed of the *dl-epi*-allodiamido acid and ester, the sulfate of the *dl-epi*-allodiamino acid, *dl-epi*-allobiotin and finally *dl*-desthioallobiotin. The steric structure of the *dl*- series of compounds is represented by formula VIIIf in Diagram I, the *dl*-allo series is represented by formula VIIIg and the *dl-epi*-allo series is represented by formula VIIIh.

Since the *dl*-compounds and the *dl*-allo compounds have the *cis* and the *trans* arrangements of their nitrogen atoms, respectively, they must have been derived from the dehydro compound having the double bond in the nucleus as represented by formula VIIb. Of the three possible positions for the double bond in the nucleus, that in formula VIIb appears to be most probable since it would result from a 1,4 addition of hydrogen. Therefore, the *dl-iso*dehydro ester probably is 3 - acetamido - 4 - benzamido - 4,5 - dihydro - 2-thiophenevaleric acid methyl ester. If random hydrogenation of the *dl-iso*dehydro ester had taken place, then all four of the *dl*-diamido esters should have been obtained. Since only two isomers have been obtained,[2] it is assumed that hydrogenation took place essentially in one direction. We have no indication whether this hydrogenation took place in the *cis* or the *trans* manner. Since different conditions effect different modes of hydrogen addition,[8] the configuration of the side chain in respect to the adjacent nitrogen atom is not known.

(8) Linstead, Doering, Davis, Levine and Whetstone, THIS JOURNAL, **64**, 1985 (1942).

Since the *dl*-allodehydro ester gave the *dl*-allo compounds and the *dl-epi*-allo compounds, both of which have the *trans* arrangement of their nitrogen atoms, this dehydro compound must have the *trans* arrangement also or structure VIIc. Therefore, the *dl*-allodehydro ester appears to be 3 - acetamido - 4 - benzamido - $\Delta^{2,5}$ - tetrahydro-2-thiophenevaleric acid methyl ester, VIIc.

So far no evidence has been obtained for *cis* and *trans* isomerism around the double bond in the dehydro esters and therefore this type of isomerism has not been considered in the above discussion. The *dl*-dehydro compound VIIa and the series of tetrahydrothiophenes, VIIId, ending with *dl-epi*-biotin have not been identified from any reaction mixture.

Experimental

Stability of *dl*-Allobiotin, XI, and *dl*-Biotin, X, toward Hydrolysis.—A solution of 0.25 g. of *dl*-allobiotin in 20 cc. of 0.1 *N* sulfuric acid was refluxed while a slow stream of nitrogen was passed through the solution. The exit gases were passed through a clear solution of barium hydroxide. A copious evolution of carbon dioxide took place as soon as refluxing commenced. The solution was allowed to reflux for one-half hour; after this time, no more carbon dioxide was being eliminated. The solution was concentrated to dryness under reduced pressure and the residue was taken up in a few drops of aqueous ethyl alcohol. When this solution was left in a refrigerator, the sulfate of the *dl*-allodiamino acid crystallized; yield 0.3 g. (93%); m. p. 231–232°. When this compound was mixed with an authentic sample of the sulfate of *dl*-allodiamino acid, the melting point was not depressed.

Anal. Calcd. for $C_8H_{20}N_2O_6S_2$: C, 34.16; H, 6.37; N, 8.85. Found: C, 34.32; H, 5.98; N, 8.75.

dl-Biotin was treated in the same way and there was no evolution of carbon dioxide over a period of one-half hour. The *dl*-biotin was recovered without any change in its melting point of 231°.

Stability of *dl*-Desthioallobiotin, XIII, and *dl*-Desthiobiotin, XII, toward Hydrolysis.—*dl*-Desthioallobiotin (100 mg.) was refluxed with 9 cc. of 0.1 *N* sulfuric acid for one-half hour. No carbon dioxide was liberated during this time and the starting material was recovered in 80% yield. *dl*-Desthiobiotin was treated in the same way with the same results.

***dl*-Allobiotin Methyl Ester.**—A solution of 0.3 g. of *dl*-allobiotin in 10 cc. of methyl alcohol was treated with an excess of diazomethane in ether solution. After five minutes the excess diazomethane was expelled by heating and the solvent was allowed to evaporate slowly, leaving a solid residue, m. p. 146–148°. After recrystallization from methyl alcohol, the *dl*-allobiotin methyl ester was washed with methyl alcohol and ether. The melting point was 150–151°.

Anal. Calcd. for $C_{11}H_{18}N_2O_3S$: C, 51.14; H, 7.02; N, 10.85. Found: C, 50.89; H, 7.21; N, 10.93.

The molecular weight, determined cryoscopically in ethylene bromide, was found to be 291; calcd., 258.

The *dl*-Allodiamidopelargonic Acid (*dl*-ζ-Acetamido-η-benzamidopelargonic Acid) from *dl*-Allodiamido Acid.—A solution of 3.7 g. of *dl*-allodiamido acid,[3] m. p. 195°, in 1110 cc. of 0.5% sodium carbonate solution was heated to 75° and treated with about 40 g. of Raney nickel catalyst.[4] The mixture was stirred well for fifteen minutes at 75°, was cooled and the catalyst was removed by centrifuging. The catalyst was washed twice with 150-cc. portions of 0.5% sodium carbonate solution and once with 150 cc. of water. The combined liquors were neutralized to litmus with sulfuric acid after which the precipitate of aluminum hydroxide which formed was removed by filtration through supercel. The clear filtrate was acidified further to congo red and concentrated to about 400 cc. The crystalline precipitate was filtered and washed. After recrystallization from boiling water, the melting point of the *dl*-ζ-acetamido-η-benzamidopelargonic acid was constant at 169–170°; yield, 2.5 g.

Anal. Calcd. for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.99, 64.89; H, 8.25, 8.48; N, 8.61.

The *dl*-Allodiamidopelargonic Acid from *dl-epi*-Allodiamido Acid.—From 0.5 g. of *dl-epi*-allodiamido acid, m. p. 192°, 1.5 g. of the *dl*-ζ-acetamido-η-benzamidopelargonic acid, m. p. 169–170°, was obtained by the same process as described above. The melting point of a mixture of this compound with that obtained from the *dl*-allodiamido acid showed no depression.

Anal. Calcd. for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.57; H, 7.81; N, 8.88.

The *dl*-ζ-Acetamido-η-benzamidopelargonic Acid from *dl*-Diamido Acid.—The *dl*-diamido acid, m. p. 230–231°, was desulfurized by the same procedure. In this case the *dl*-diamidopelargonic acid melted at 192°.

Anal. Calcd. for $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.65; N, 7.87; N, 8.88, 8.93.

***dl*-Desthioallobiotin, XII, from *dl*-Allobiotin.**—One-half gram of *dl*-allobiotin, m. p. 194–195°, when treated with Raney nickel catalyst by the same method as described above, yielded 0.24 g. of *dl*-desthioallobiotin, m. p. 166°.

Anal. Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 55.86; H, 8.25; N, 12.76, 12.73.

***dl*-Desthioallobiotin from *dl-epi*-Allobiotin.**—*dl-epi*-Allobiotin (70 mg.) was treated with Raney nickel catalyst as described above and 40 mg. of *dl*-desthioallobiotin, m. p. 164–165°, was obtained. There was no depression of the melting point when this product was mixed with the product obtained from *dl*-allobiotin.

Anal. Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 55.92; H, 8.62; N, 12.93.

***dl*-Desthioallobiotin from *dl*-Allodiamidopelargonic Acid.**—*dl*-Allobiotin and *dl-epi*-allobiotin were shown above to yield the same *dl*-allodiamidopelargonic acid, m. p. 169–170°. This acid (0.5 g.) was hydrolyzed with 25 g. of hydrated barium hydroxide in 100 cc. of water for fifteen hours at 140°. The solution was acidified with sulfuric acid and the barium sulfate removed. The solution was concentrated to dryness to obtain the diaminopelargonic acid sulfate. Without further purification this product was treated with phosgene in the usual way. The *dl*-desthioallobiotin melted at 164°. The melting point of a mixture of this *dl*-desthioallobiotin with that obtained directly from *dl*-allobiotin showed no depression.

Anal. Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 56.48; H, 8.26; N, 13.31.

***dl*-Desthiobiotin, XII, from *dl*-Biotin.**—*dl*-Biotin was desulfurized in the same manner to yield *dl*-desthiobiotin, m. p. 166°. The melting point of a mixture of *dl*-desthiobiotin with *dl*-desthioallobiotin was 144° showing that these compounds were not the same. These compounds were found also to be different by assay with yeast which showed *dl*-desthiobiotin to be one-half as active as *d*-desthiobiotin while *dl*-desthioallobiotin was inactive.[7]

Anal. Calcd. for $C_{10}H_{18}N_2O_3$: C, 56.05; H, 8.47; N, 13.08. Found: C, 56.04; H, 8.52; N, 13.22, 12.92.

***dl*-Desthiobiotin from *dl*-Diamidopelargonic Acid.**—The *dl*-diamidopelargonic acid, m. p. 192°, was hydrolyzed in the usual way and treated with phosgene to give *dl*-desthiobiotin, m. p. 165–166°.

***dl*-Desthioallobiotin Methyl Ester.**—*dl*-Desthioallobiotin in an ether–methanol suspension was methylated with diazomethane. The *dl*-desthiobiotin methyl ester was recrystallized from ether to a constant melting point of 77°.

Anal. Calcd. for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27; mol. wt., 228.3. Found: C, 57.75; H, 8.74; N, 12.44; mol. wt. 250 (Rast).

Acknowledgments.—The authors wish to acknowledge Messrs. R. N. Boos, L. Rosalsky,

M. K. Humphrey, E. Thornton and M. Mc Gregor, and Mrs. Edith Meiss for the microanalyses reported in this paper.

Summary

dl-Biotin has been converted by the Raney nickel hydrogenolysis reaction into *dl*-desthiobiotin. *dl*-Allobiotin and *dl-epi*-allobiotin have been converted to a common desthio derivative, *dl*-desthioallobiotin, which differs from *dl*-desthiobiotin. These desthio derivatives were obtained also by an alternative series of reactions starting with the 3-acetamido-4-benzamidotetrahydro-2-thiophenevaleric acid methyl esters which were treated with Raney nickel catalyst to give the ζ-acetamido-η-benzamidopelargonic acids. These acids were hydrolyzed and treated with phosgene to yield *dl*-desthiobiotin and *dl*-desthioallobiotin.

dl-Biotin was stable toward boiling dilute sulfuric acid while *dl*-allobiotin was quickly hydrolyzed to give the corresponding diamino acid sulfate and carbon dioxide.

These results indicate that *dl*-biotin has the *cis* configuration in respect to its nitrogen atoms, and that *dl*-allobiotin and *dl-epi*-allobiotin both have the *trans* configuration in respect to their nitrogen atoms.

RAHWAY, NEW JERSEY RECEIVED AUGUST 18, 1945

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Rearrangement in the Reaction of α-Halogenonaphthalenes with Lithium Diethylamide

BY HENRY GILMAN, N. N. CROUNSE, S. P. MASSIE, JR., R. A. BENKESER AND S. M. SPATZ

It has been shown that sodamide in liquid ammonia reacts with aryl halides, in which the halogen is *ortho* to an ether[1] or sulfide[2] linkage, to give a rearrangement product in which the amino group is *meta* to the oxygen or sulfur group.

$$o\text{-}ClC_6H_4OCH_3 + NaNH_2 \longrightarrow m\text{-}H_2NC_6H_4OCH_3 + NaCl$$

In extension of those studies it has been observed[3] that related rearrangements occur with lithium dialkylamides in ether solution.

$$o\text{-}IC_6H_4OCH_3 + LiN(C_2H_5)_2 \longrightarrow m\text{-}(C_2H_5)_2NC_6H_4OCH_3 + LiI$$

However, from the particular reaction just given as an illustration there was isolated 22% of anisole. This suggested that a halogen–metal interconversion reaction may have been responsible for most of the anisole.

$$o\text{-}IC_6H_4OCH_3 + LiN(C_2H_5)_2 \longrightarrow o\text{-}LiC_6H_4OCH_3 \xrightarrow{HOH} C_6H_5OCH_3$$

It appeared that one of the better ways of establishing the possibility of a halogen–metal interconversion reaction was by means of α-bromonaphthalene, for α-bromonaphthalene is known[4] to undergo the halogen–metal interconversion reaction with *n*-propyllithium almost quantitatively (97%). Any intermediately formed α-naphthyllithium could be readily characterized by carbonation to α-naphthoic acid.

$$\alpha\text{-}C_{10}H_7Br + LiN(C_2H_5)_2 \longrightarrow \alpha\text{-}C_{10}H_7Li \xrightarrow[HOH]{CO_2} \alpha\text{-}C_{10}H_7CO_2H$$

Only a trace of acidic material was isolated from these reactions, and α-naphthoic acid has not as yet been identified. However, the basic fraction was found to be composed largely of β-diethylaminonaphthalene. This demonstrated that rearrangements with alkali amide types are not confined to aryl halides in which the halogen is *ortho* to an oxygen or sulfur linkage.

A rearrangement reaction of this type is not novel, for Bergstrom and Urner[5] obtained a good yield of β-naphthylamine from reaction of α-chloronaphthalene with an excess of potassium amide in liquid ammonia. However, the same authors observed no rearrangement in a corresponding reaction with α-fluoronaphthalene from which α-naphthylamine was isolated. Accordingly, this suggested an examination of the reaction of lithium diethylamide in ether with α-fluoronaphthalene and with α-chloronaphthalene. We have found that these two halonaphthalenes, as well as the α-bromonaphthalene, undergo rearrangement. There appear, then, to be significant differences between the reactions of simple alkali amides in liquid ammonia from those of the alkali dialkylamides in ether.

The reaction of lithium dialkylamides with RX compounds proceeds quite satisfactorily in some cases.[6] However, direct reaction of the RX compound with the secondary amine may be preferred at times. For example, we have shown that 2-dimethylaminoquinoline is obtainable in 91% yield by reaction of dimethylamine with 2-chloroquinoline. By contrast, the reaction of 2-chloroquinoline with potassium amide in liquid ammonia gave largely tars.[6] It seemed of interest to determine whether the reaction of 2-chloroquinoline with lithium dimethylamide in ether

(1) Gilman and Avakian, THIS JOURNAL, **67**, 349 (1945).
(2) Gilman and Nobis, *ibid.*, **67**, 1479 (1945).
(3) Unpublished studies by R. H. Kyle.
(4) Gilman and Moore. THIS JOURNAL, **62**, 1843 (1940).
(5) Unpublished results privately communicated by Dr. F. W. Bergstrom.
(6) Unpublished studies by E. C. Horning. See Bergstrom and Fernelius, *Chem. Rev.*, **20**, 437 (1937).