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Furan and Tetrahydrofuran Derivatives. IX. On *epi*-Oxybiotin and the Four Racemic 3,4-Diamino-2-tetrahydrofuran Valeric Acids[1]

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In recent communications[3,4] the first total synthesis of *dl*-oxybiotin has been described. The key to this synthesis was the catalytic hydrogenation of 3,4-dicarbethoxyamino-2-furanpentanol (II) to a *cis*-3,4-dicarbethoxyamino-2-tetrahydrofuranpentanol. Hydrogenation of a tri-substitution product of furan such as II creates three asymmetric carbon atoms in the molecule, and four racemic tetrahydrofurans, V, VI, VII, and VIII, may be expected. Two of these, V and VI, have a *trans*, and the others, VII and VIII, a *cis*-configuration of the carbethoxyamino groups. The isomers in each pair differ in the spatial configuration of the side chain R′. They may be designated as the *trans*, *cis* V, the *trans*, *trans* VI, the *cis*, *cis* VII and the *cis*, *trans* VIII isomers, respectively. All of the theoretically possible racemic 3,4-diamino-2-tetrahydrofuran valeric acids, XV, XVI, XVII and XVIII, have been prepared. Their synthesis and some of their properties will be described in this communication. In the last analysis, this work represents a study of the catalytic hydrogenation of 3,4-dicarbethoxy-2-furanpentanol (I) and of 3,4-dicarbethoxyamino-2-furanpentanol (II).

Attempts to reduce compound I or the corresponding free dicarboxylic acid in glacial acetic acid over a platinum oxide catalyst were unsuccessful. This observation is in agreement with the work of Archer and Pratt,[5] who also were unable to effect reduction of methyl-3,4-dicarboxy-2-furan acetate under similar conditions. Substitution of the furan nucleus with carboxyl groups endows this otherwise labile ring system with an unusual stability which reflects itself in resistance toward catalytic hydrogenation and stability toward strong mineral acids.[5,6]

These observations may be explained by the resonance concept. In addition to the obvious structures which contribute to the resonance hybrid of furan, additional structures such as A and B may be written for the furan dicarboxylic acids. They are the result of a conjugation between the unsaturation of the ring and the carboxyl groups. The electron-attracting carboxyl groups tend to remove electrons from the ring, thus lowering its affinity for electrophilic reagents and increasing its stability. The fact that resonance tends to bring the carboxyl groups into planarity with the ring may explain the finding that furan-3,4-dicarboxylic acids do not undergo intramolecular anhydride formation.[7,8] The failure of (I) to undergo hydrogenation under the above-mentioned conditions led us to investigate other reduction procedures. It was observed that the compound was smoothly reduced when subjected to high-pressure hydrogenation over a Raney nickel catalyst. A mixture of reduction products was obtained which on treatment with hydrazine hydrate yielded two crystalline isomeric hydrazides $C_{11}H_{22}O_4N_4$ of m. p. 208–210° and m. p. 177–180°.

Based on experimental evidence which will be presented later, we have assigned the *trans*, *cis*-structure III to the higher, and the *trans*, *trans*-configuration IV to the lower melting isomer.

Degradation of these hydrazides by the Curtius procedure with ethanol as the solvent for the decomposition of the corresponding azides yielded two isomeric urethans, V and VI, which on oxidation with chromic acid gave the corresponding 3,4-dicarbethoxyamino-2-tetrahydrofuran valeric acids XI and XII. These compounds were hydrolyzed with aqueous barium hydroxide and the resulting 3,4-diamino-2-tetrahydrofuran valeric acids, XV and XVI, were isolated as the crystalline sulfates and characterized as the dibenzoates and the dibenzoylmethyl esters. Treatment of these diaminocarboxylic acids with phosgene under a variety of experimental conditions did not result in the formation of the corresponding hexahydro-2-oxo-1-furo-(3,4)-imidazoles. Both compounds, therefore, must have a *trans* configuration of the amino groups.

Hydrolysis of the hydrazide (III) with aqueous barium hydroxide at 120° resulted in the formation of an acid. This material was esterified and the dimethyl ester reacted with hydrazine hydrate. Instead of the original hydrazide (III), the isomeric hydrazide (IV) was thus obtained. This was further substantiated by transformation of the isomerized hydrazide into the urethan (VI). The hydrazide (III) was then hydrolyzed with 2 *N* hydrochloric acid, and the hydrazide re-

(A) (B)

(1) A preliminary report on some of the experiments herein described has appeared in THIS JOURNAL, **66**, 157 (1944).

(2) We wish to express our thanks to Ciba Pharmaceutical Products, Inc., and to the Buhl Foundation for their generous support.

(3) Hofmann, THIS JOURNAL, **67**, 694 (1945).

(4) Hofmann, *ibid.*, **67**, 1459 (1945).

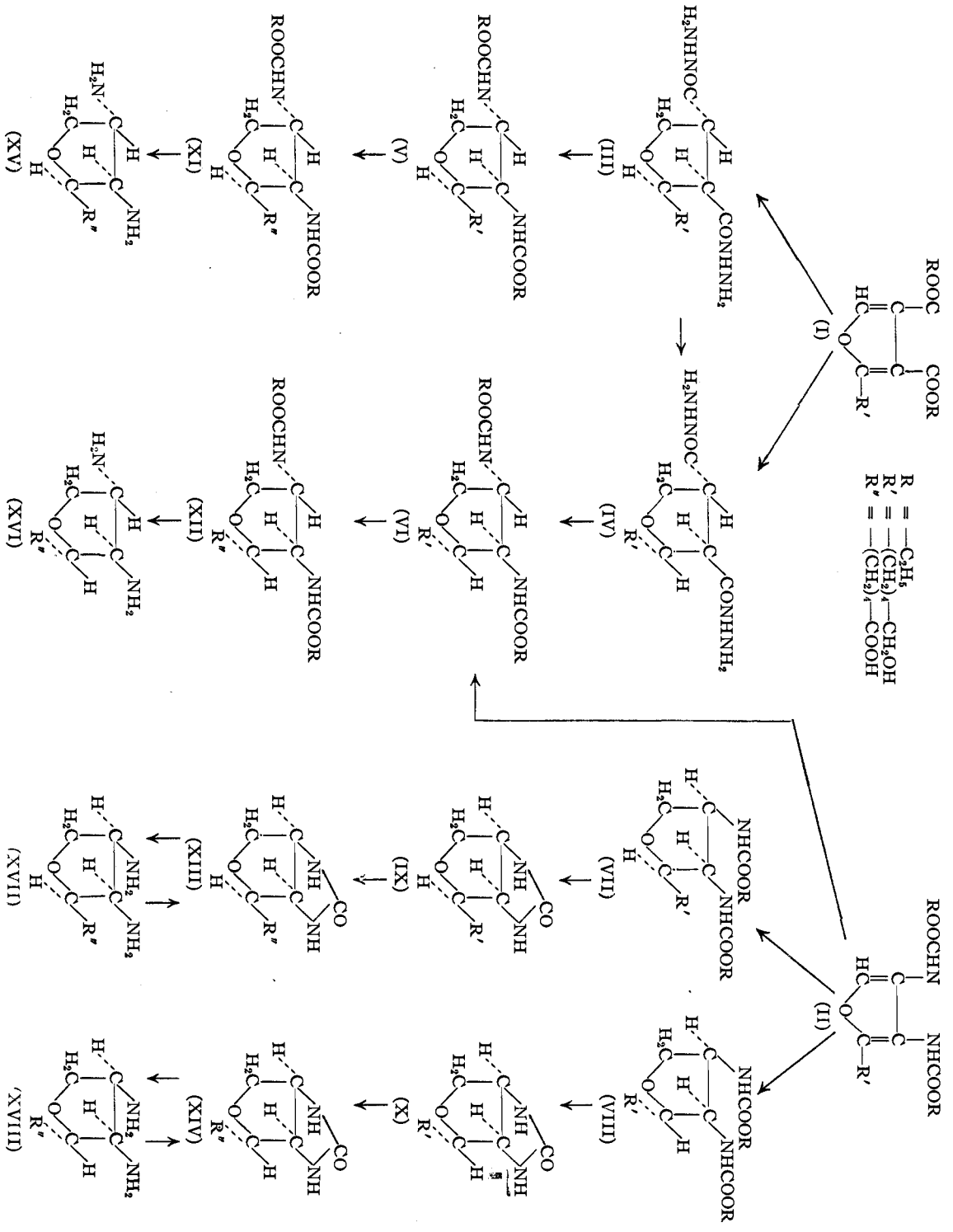
(5) Archer and Pratt, *ibid.*, **66**, 1656 (1944).

(6) Reichstein, *Helv. Chim. Acta*, **16**, 276 (1933).

(7) Alder and Rickert, *Ber.*, **70**, 1354 (1937).

(8) Hofmann, THIS JOURNAL, **67**, 421 (1945).

generated from the resulting dicarboxylic acid. No rearrangement occurred under these conditions since III was obtained. Therefore, the barium hydroxide treatment must have racemized the molecule. In pairs of stereoisomers it is usually the *cis*-oid compound which has the higher energy content and the lower stability, and it seems logical to assume that the hydrazide (III) has the *trans, cis*- and the hydrazide (IV) the *trans, trans*-configuration. The rearrangement which occurs during the barium hydroxide treatment must involve positions 3 and 4, since the asymmet-



ric center at position 2 is stereochemically stable. These observations, in conjunction with the established *trans*-configuration of the substituents in positions 3 and 4 for both isomers, provide strong evidence for the correctness of the assigned stereo structures. The finding that two different diaminocarboxylic acids, XV and XVI, resulted from the degradation of the hydrazides, III and IV, indicated that no rearrangement had occurred during these transformations. Consequently, the configuration of the diaminocarboxylic acids also is established.

The 3,4-dicarbethoxyaminofurans are less "aromatic" than the 3,4-dicarboxyfurans, and undergo hydrogenation at room temperature and atmospheric pressure in the presence of a palladium-on-barium sulfate catalyst. Thus far, this has been demonstrated for 3,4-dicarbethoxyamino-2-furanpropanol,[9] -butanol,[10] and -pentanol.[3,4]

A careful study of the hydrogenation products of (II) revealed the presence of three isomeric 3,4-dicarbethoxyamino-2-tetrahydrofuranpentanols, VI, VII and VIII. During the development of the oxybiotin synthesis[3,4] these hydrogenation products were treated with barium hydroxide and no attempts were made to isolate the different isomeric urethans. It has now been possible to isolate the *trans*-isomer (VI) from this mixture. Its identity with the urethan obtained from the hydrazide (IV) was definitely established by degradation through the 3,4-dicarbethoxyamino-2-tetrahydrofuran valeric acid (XII) to the diaminocarboxylic acid (XVI). Therefore, hydrogenation of II under conditions which favor a *cis*-addition of hydrogen gave a mixture of hydrogenation products containing approximately 24% of the *trans,trans*-isomer (VI). Although the *cis*-3,4-dicarbethoxyaminotetrahydrofurans, VII and VIII, have not been isolated, their presence among the hydrogenation products was conclusively demonstrated by their transformation into cyclic urea derivatives. This has already been demonstrated[3,4] for the isomer which on treatment with barium hydroxide yielded a hexahydro-2-oxo-4-(5-hydroxypentyl)-1-furo-(3,4)-imidazole of melting point 153–154°. Because the spatial position of the side chain has not yet been established, this compound may have structure IX or X. It could be expected that the mother liquors from the above pentanol might contain its epimer with the opposite configuration of the side chain. These fractions have now been subjected to a chromatographic fractionation and it was possible to isolate a hexahydro-2-oxo-4-(5-hydroxypentyl)-1-furo-(3,4)-imidazole of melting point 104–106° which for reasons presented below must be the epimer of the derivative of m. p. 153–154° (structure IX or X). Oxidation of this material, followed by esterification, gave *epi*-oxybiotin methyl ester. *epi*-Oxybiotin was obtained upon hydrolysis of the ester, and on drastic hydrolysis was transformed into a *cis*-3,4-diamino-2-tetrahydrofuran valeric acid, XVII or XVIII. This substance also was characterized as its dibenzoate and its dibenzoyl methyl ester. Treatment of the above diaminocarboxylic acid with phosgene resulted in the regeneration of *dl-epi*-oxybiotin. This series of reactions establishes the constitution of *epi*-oxybiotin as XIII or XIV beyond any question.[11]

The experiments herein described have led to the isolation of three out of the four theoretically possible racemic 3,4-diamino-2-tetrahydrofuran valeric acids. The fourth isomer, namely, the one which stereochemically corresponds to oxybiotin, has already been described.[4] This compound has now been transformed into its dibenzoate and the dibenzoylmethyl ester. It is of considerable interest to compare the reactions of these substances with those of the corresponding 3,4-diamino-2-tetrahydrothiophenevaleric acids which became known as a result of synthetic studies on biotin. In contrast to our tetrahydrofurans where only the isomers with a *cis*-configuration of the amino groups are capable of ring formation, the *trans*-3,4-diaminotetrahydrothiophenevaleric acids form bicyclic urea derivatives on treatment with phosgene.[12] This suggests fundamental differences between the two ring systems. One would conclude from this preliminary evidence that stereochemically the tetrahydrothiophene ring resembles the cyclohexane ring in contrast to the tetrahydrofuran ring which behaves more like cyclopentane. The suggested stereochemical differences between these two ring systems will be further investigated. Work is also in progress to establish the spatial arrangement of the side chain in oxybiotin and *epi*-oxybiotin.

Experimental[13,14,15]

Hydrogenation of 3,4-Dicarbethoxy-2-furanpentanol (I).—3,4-Dicarbethoxy-2-furanpentanol[16] (20 g.) was dissolved in 120 cc. of grain alcohol and hydrogenated for three hours at an initial pressure of 1800 lb./sq. in. and a temperature of 180° over a Raney nickel catalyst prepared from 10 g. of the alloy. The catalyst was removed by filtration through Filter-Cel, the alcohol removed *in vacuo*, and the resulting oil dissolved in ether. The ethereal solution was washed with 2 *N* sodium carbonate and water and dried over sodium sulfate; the ether was removed on the steam-bath. The residue on distillation yielded 15.7 g. (78%) of hydrogenated esters which boiled at 175–180° at 0.02 mm.

(9) Hofmann, Chen, Bridgwater and Axelrod, THIS JOURNAL, **69**, 191 (1947).

(10) Hofmann, Bridgwater and Axelrod, *ibid.*, **69**, 1550 (1947).

(11) When tested with *L. arabinosus*, *dl-epi*-oxybiotin was found to possess 0.1% of the growth-promoting activity of *d*-biotin. It seems very likely that this activity is due to contamination with *dl*-oxybiotin.

(12) Harris, Mozingo, Wolf, Wilson and Folkers, THIS JOURNAL, **67**, 2102 (1945).

(13) The microanalyses were performed in our microanalytical laboratories by Mr. George L. Stragand.

(14) All melting points were determined with short stem Anschütz thermometers and are not corrected.

(15) The tetrahydrofuran derivatives described in this paper are *dl*-forms.

(16) Hofmann, THIS JOURNAL, **67**, 421 (1945).

Anal. Calcd. for $C_{15}H_{26}O_6$: C, 59.58; H, 8.66; OC_2H_5, 29.8. Found: C, 59.64; H, 8.42; OC_2H_5, 26.7.

3,4-Dicarboxy-2-tetrahydrofurandihydrazide of m. p. 208–210° (III).—A mixture of 15 g. of the above hydrogenated esters and 15 g. of hydrazine hydrate was refluxed for two hours and then placed in a refrigerator for twelve hours. The resulting crystals were collected, washed with absolute ethanol, and dried over concentrated sulfuric acid *in vacuo*. Recrystallization from dilute ethanol gave 3.2 g. of needles (24%) which melted at 208–210°.

Anal. Calcd. for $C_{11}H_{22}O_4N_4$: C, 48.16; H, 8.08; N, 20.41. Found: C, 48.15; H, 7.85; N, 20.18.

3,4-Dicarboxy-2-tetrahydrofurandihydrazide of m. p. 177–180° (IV).—The combined mother liquors from the preparation of III were concentrated *in vacuo* to a thick sirup which was kept over concentrated sulfuric acid for several days. The material was then dissolved in a small amount of absolute ethanol and the solution placed in a refrigerator for two days. The resulting crystals were collected, washed with a small amount of ice-cold ethanol, and purified by several recrystallizations from the same solvent; 1.5 g. (11%) of crystals melting at 177–180° was obtained.

Anal. Calcd. for $C_{11}H_{22}O_4N_4$: C, 48.16; H, 8.08; N, 20.41. Found: C, 48.01; H, 7.95; N, 20.27.

Transformation of the Hydrazide (III) into the Isomer (IV).—A solution of 6 g. of III, 15 g. of barium hydroxide octahydrate, and 80 cc. of water was heated to 120° for five hours in a sealed tube. A slow stream of carbon dioxide was passed into the hot solution and the resulting barium carbonate removed by filtration through Filter-Cel. The filtrate was concentrated to a small volume *in vacuo*, acidified to congo red with concentrated hydrochloric acid, and extracted with five 20-cc. portions of ethyl acetate. The combined ethyl acetate extracts were washed with a small amount of water, dried over sodium sulfate, and concentrated to dryness *in vacuo*. The resulting oily acid, 4.48 g. (83%), was esterified with diazomethane, and the methyl ester distilled *in vacuo*. Treatment of 656 mg. of this ester with 600 mg. of hydrazine hydrate gave 312 mg. (48%) of IV melting at 177–179°. Degradation of this hydrazide by the method given below yielded the urethan (VI) of melting point 128–130°.

Hydrolysis of (III) with Hydrochloric Acid.—A solution of 1.37 g. of III in 15 cc. of 2 *N* hydrochloric acid was refluxed overnight, and then evaporated to dryness *in vacuo*. The resulting acid was isolated and esterified as described above, and the methyl ester transformed into the hydrazide; 490 mg. of the ester gave 260 mg. (53%) of III melting at 207–209°. Degradation of this hydrazide by the method given below yielded the urethan (V) of melting point 108–110°.

3,4-Dicarbethoxyamino-2-tetrahydrofuranpentanol of m. p. 108–110° (V).—A solution of 1.1 g. of (III) in 10 cc. of 2 *N* hydrochloric acid was cooled in an ice-bath, and 6 cc. of a 10% solution of sodium nitrite was slowly added with vigorous stirring. Stirring was continued for an additional ten minutes and the resulting oily azide extracted with ice-cold ether. The ethereal solution was washed with ice-cold 2 *N* sodium carbonate and water, dried over sodium sulfate and filtered. Absolute alcohol (40 cc.) was then added and the solution slowly heated until the ether had evaporated. The resulting alcoholic solution was refluxed for one hour, and evaporated to dryness *in vacuo*. The residue was recrystallized from ethyl acetate; 523 mg. (40%) of V, melting at 108–110° was obtained.

Anal. Calcd. for $C_{15}H_{28}O_6N_2$: C, 54.21; H, 8.49; N, 8.42. Found: C, 53.92; H, 8.09; N, 8.57.

3,4-Dicarbethoxyamino-2-tetrahydrofuran-pentanol of m. p. 128–130° (VI). a. From the Hydrazide (IV).—The hydrazide (IV) (3.2 g.) was transformed into the corresponding urethan (VI) as described above. Crystallization from ethyl acetate gave 1.3 g. (34%) of needles melting at 128–130°.

Anal. Calcd. for $C_{15}H_{28}O_6N_2$: C, 54.21; H, 8.49; N, 8.42. Found: C, 53.84; H, 8.19; N, 8.64.

b. **From 3,4-Dicarbethoxyamino-2-furanpentanol (II).**—The hydrogenation products obtained from 61.2 g. of (II) as previously described[4] were seeded with a small amount of the above urethan and kept at room temperature overnight. The resulting crystals were collected, washed with ice-cold ethyl acetate, and recrystallized from the same solvent; 15 g. (24%) of needles was obtained which melted at 130–131°. No depression of the melting point was observed when this sample was mixed with a sample of the urethan prepared according to a above.

Anal. Calcd. for $C_{15}H_{28}O_6N_2$: C, 54.21; H, 8.49; N, 8.42. Found: C, 53.99; H, 8.20; N, 8.62.

3,4-Dicarbethoxyamino-2-tetrahydrofuran Valeric Acid of m. p. 121–122° (XI).—To a solution of the urethan (V) (3.2 g.) in 50 cc. of glacial acetic acid, 100 cc. of a 2% solution of chromium trioxide in glacial acetic acid was slowly added. The mixture was kept at room temperature for twelve hours; methanol (1 cc.) was then added and the solution heated on the steam-bath for thirty minutes. The solvents were removed *in vacuo*, the green residue dissolved in ethyl acetate, and the ethyl acetate solution washed with water. The acidic oxidation products were extracted from the ethyl acetate solution with 2 *N* sodium carbonate, and the acids liberated by acidification and re-extraction with ethyl acetate. The extracts containing the acidic material were dried over sodium sulfate, the ethyl acetate removed *in vacuo* and the crystalline residue purified by recrystallization from ethyl acetate at −20°; 1.3 g. (40%) of crystals was obtained which melted at 121–122°.

Anal. Calcd. for $C_{15}H_{26}O_7N_2$: C, 52.02; H, 7.56; N, 8.08. Found: C, 52.10; H, 7.34; N, 8.60.

3,4-Dicarbethoxyamino-2-tetrahydrofuran Valeric Acid of m. p. 158–160° (XII).—Compound (VI) (664 mg.) was oxidized as described above and the resulting crystals purified by crystallization from ethyl acetate; 280 mg. (40%) of needles melting at 158–160° was obtained.

Anal. Calcd. for $C_{15}H_{26}O_7N_2$: C, 52.02; H, 7.56; N, 8.08. Found: C, 52.05; H, 7.14; N, 8.21.

Oxidation by the same procedure of one gram of the urethan (VI) obtained from the hydrogenation of (II) yielded 600 mg. (58%) of needles, melting at 160–161.5°, which did not depress the melting point of the above material.

Anal. Calcd. for $C_{15}H_{26}O_7N_2$: C, 52.02; H, 7.56; N, 8.08. Found: C, 51.85; H, 7.32; N, 8.25.

***epi*-Hexahydro-2-oxo-4-(5-hydroxypentyl)-1-furo(3,4)-imidazole (IX or X).**—The combined mother liquors from several preparations of the hexahydro-2-oxo-4-(5-hydroxypentyl)-1-furo(3,4)imidazole of m. p. 153–154°[4] were concentrated to dryness *in vacuo*. The oily residue (15 g.) was dissolved in 500 cc. of acetone and the solution poured on a column prepared from 300 g. of aluminum oxide (Fisher adsorption alumina). The column was then eluted with 250-cc. portions of each of the following solvent mixtures which removed the amounts of material indicated in parentheses: acetone (3.1 g. of oil); acetone 90, methanol 10 (0.7 g. of oil); acetone 80, methanol 20 (1.7 g. of oil); acetone 70, methanol 30 (3.7 g. of crystals); acetone 60, methanol 40 (3 g. of crystals); acetone 50, methanol 50 (0.7 g. of oil). The fractions containing crystalline material were combined and recrystallized several times from 95% ethanol at −20°; 1.5 g. of the *epi*-pentanol was thus obtained which melted at 104–106°.

Anal. Calcd. for $C_{10}H_{18}O_3N_2$: C, 56.07; H, 8.47; N, 13.07. Found: C, 56.12; H, 8.30; N, 13.31.

***epi*-Oxybiotin Methyl Ester.**—To a solution of the above *epi*-pentanol (760 mg.) in 35 cc. of 0.1 *N* sodium hydroxide, 25 cc. of a 5% solution of potassium permanganate was added slowly and the mixture kept at room temperature for twelve hours. The manganese dioxide was removed by filtration through Filter-Cel. The filter cake

of manganese dioxide was washed repeatedly with hot water and the combined filtrate and washings were acidified to congo red with concentrated hydrochloric acid, and concentrated to dryness *in vacuo*.

The dry residue was extracted with two 25-cc. portions of methanol and an ethereal solution of diazomethane was added to the combined extracts until the yellow color remained. The mixture was kept for ten minutes and was then evaporated to dryness and the residue extracted with ethyl acetate. The combined ethyl acetate extracts were filtered and evaporated to dryness *in vacuo*, leaving a semicrystalline residue. This material was dissolved in 20 cc. of acetone and the solution chromatographed on 10 g. of Fisher alumina. The column was eluted with several 10-cc. portions of a mixture containing 90% acetone and 10% methanol. All of the eluates containing crystalline material were combined and the substance recrystallized from ethyl acetate; 190 mg. (22%) of needles was obtained which melted at 104–106°.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: C, 54.52; H, 7.45; N, 11.55. Found: C, 54.67; H, 7.35; N, 11.64.

***epi*-Oxybiotin (XIII or XIV). a. From the Methyl Ester.**—A mixture of the above methyl ester (190 mg.), $Ba(OH)_2 \cdot 8H_2O$ (0.5 g.), and water (5 cc.) was heated to 100° for two hours in a sealed tube. Most of the barium was then precipitated with carbon dioxide and the resulting solution acidified to congo red with 2 *N* sulfuric acid. The barium sulfate was removed by filtration and the filtrate concentrated to a small volume *in vacuo*. The resulting *epi*-oxybiotin was collected and recrystallized from hot water; 150 mg. (83%) of prismatic crystals was obtained which melted at 185–186°.

Anal. Calcd. for $C_{10}H_{16}O_4N_2$: C, 52.63; H, 7.07; N, 12.27. Found: C, 52.91; H, 7.04; N, 12.23.

b. From the Corresponding Diaminocarboxylic Acid and Phosgene.—A solution of 50 mg. of the diaminocarboxylic acid prepared from *epi*-oxybiotin as described below, in 1 cc. of 10% sodium bicarbonate, was treated with phosgene in the usual manner.[4] The resulting *epi*-oxybiotin (25 mg.) (66%) melted at 183–184°. No depression of the melting point was observed when this material was mixed with a sample of *epi*-oxybiotin prepared according to a above.

***trans*-3,4-Diamino-2-tetrahydrofuran Valeric Acid (XV).**—A solution of 1.32 g. of (XI), 8 g. of $Ba(OH)_2 \cdot 8H_2O$ and 40 cc. of water was heated to 110° for three hours in a sealed tube. The crystalline sulfate of (XV) (870 mg.) (75%) was isolated in the usual manner.

Dibenzoate of XV.—A sample of the sulfate was benzoylated with benzoyl chloride and 5 *N* potassium hydroxide, and the dibenzoate recrystallized from dilute methanol. The substance melted at 215–217°.

Anal. Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.15; H, 6.23; N, 6.96.

Dibenzoyl Methyl Ester of XV.—A sample of the dibenzoate was esterified with diazomethane and the resulting ester recrystallized from a mixture of methanol and ether. The substance melted at 183–185°.

Anal. Calcd. for $C_{24}H_{28}O_5N_2$: C, 67.89; H, 6.64; N, 6.60. Found: C, 67.87; H, 6.38; N, 6.62.

***trans*-3,4-Diamino-2-tetrahydrofuran Valeric Acid (XVI).**—Compound XII (720 mg.) was hydrolyzed with barium hydroxide as described above; 465 mg. (74%) of the sulfate of (XVI) was obtained.

Dibenzoate of XVI.—A sample of the sulfate was benzoylated and the dibenzoate recrystallized from dilute methanol. The substance melted at 194–195°.

Anal. Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.57; H, 6.52; N, 6.76.

Dibenzoyl Methyl Ester of (XVI).—This derivative was prepared from the dibenzoate with diazomethane and was recrystallized from a mixture of ethanol and ether. The substance melted at 171–173°.

Anal. Calcd. for $C_{24}H_{28}O_5N_2$: C, 67.89; H, 6.64; N, 6.60. Found: C, 67.96; H, 6.31; N, 6.68.

***cis*-3,4-Diamino-2-tetrahydrofuranvaleric Acid from Oxybiotin.**—A sample of oxybiotin was hydrolyzed with barium hydroxide and the sulfate of the diamino carboxylic acid isolated as previously described.[4]

Dibenzoate.—A sample of the sulfate was benzoylated. The dibenzoate after recrystallization from a mixture of methanol and ethyl acetate melted at 230–231°.

Anal. Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.17; H, 6.36; N, 6.83.

Dibenzoyl Methyl Ester.—This derivative was prepared from the dibenzoate with diazomethane. After recrystallization from methanol the material melted at 148–150°.

Anal. Calcd. for $C_{24}H_{28}O_5N_2$: C, 67.89; H, 6.64; N, 6.60. Found: C, 67.86; H, 6.35; N, 6.54.

***cis*-3,4-Diamino-2-tetrahydrofuranvaleric Acid from *epi*-Oxybiotin.**—A sample of *epi*-oxybiotin (100 mg.) was hydrolyzed with 1.5 g. of $Ba(OH)_2 \cdot 8H_2O$ in 7.5 cc. of water as described.[4] The resulting sulfate of the diaminocarboxylic acid (70 mg., 53%) melted at 233–234° with decomposition.

Dibenzoate.—This derivative was prepared in the usual manner and after recrystallization from dilute methanol melted at 188–189°.

Anal. Calcd. for $C_{23}H_{26}O_5N_2$: C, 67.30; H, 6.38; N, 6.82. Found: C, 67.52; H, 6.56; N, 6.67.

Dibenzoyl Methyl Ester.—This derivative, prepared from the dibenzoate with diazomethane, after recrystallization from methanol, melted at 162–165°.

Anal. Calcd. for $C_{24}H_{28}O_5N_2$: C, 67.89; H, 6.64; N, 6.60. Found: C, 67.49; H, 6.46; N, 6.98.

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Summary

The four theoretically possible racemic 3,4-diamino-2-tetrahydrofuran valeric acids have been prepared and characterized. Only the two isomers with a *cis*-configuration of the amino groups were found to form bicyclic urea derivatives on treatment with phosgene. Definite stereo structures have been assigned to the two *trans*-isomers. *epi*-Oxybiotin has been prepared and its structure partially established. Differences between the 3,4-diamino-2-tetrahydrothiophenevaleric acids and the corresponding tetrahydrofurans have been discussed.

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