fractions except possibly a small amount in that prepared at the extreme temperature of 460°.

Isolation of the Cyclic Dimer.—For the precise isolation of the cyclic dimer, liquid reaction product (909 g.) made from isobutylene in the presence of added nitrogen at 430–440° under 4700 maximum lb./sq. in. for one hour[19] was fractionated through a 45-plate column to obtain a 100-ml. middle fraction from the plateau material boiling at 105° (760 mm.). This fraction was filtered through silica gel several times to remove unsaturated components. The saturated product obtained (54 ml.) was further purified by fractionating it through a 62-plate column at 740 mm. (reflux ratio 40:1) to obtain ten 5-ml. fractions and a residue. All of the fractions, except the first two and last, boiled at the same temperature and had the same refractive index, indicating the isolation of a pure compound. The sixth and seventh fractions were combined and taken as the isolated compound. The properties of this composite are shown in Table I for the cyclic dimer.

Estimation of Cyclic Dimer Formation.—For the routine estimation of cyclic dimer formation under any particular set of reaction conditions employed, the crude dimeric fraction of the liquid was analyzed. The analysis consisted of estimating the saturates present from the bromine number, assuming that the unsaturates contained had a molecular weight of 112. The unsaturates were then removed from the crude dimer and the cyclic dimer content of the saturated product obtained was determined by comparing its density (d^{20}_4) with that of 1,1,3-trimethylcyclopentane and an average value (0.7051) for octanes. Olefin removal was accomplished by treating the crude dimeric product with thioglycolic acid,[18] and filtering the acid-treated product (*ca.* 35 ml.), which still contained traces of unsaturates, through a column (diameter 15 mm.) of 20 g. of 100–200 mesh silica gel, and recovering as much saturated product as possible by displacing it from the gel with water.[17] Some separation of mixtures of paraffins and naphthenes is caused by silica gel filtration; however, by refiltering the saturated products obtained, it was determined that the amount of such separation was not sufficient to affect the essential validity of the analytical results given.

(19) This product is not described in the text, but a large amount was available as a result of preliminary work. Its distillation curve and properties indicated that it was substantially identical to the product, described in Table II, made at 430° under 2025 maximum lb./sq. in. in one hour. In the two reactions virtually the same amount of isobutylene reacted; the extra pressure of nitrogen apparently had little effect.

Acknowledgment.—The authors wish to thank Dr. W. A. Gruse and Dr. R. L. Wakeman of the Mellon Institute for suggestions made relative to this investigation and for their interest in it.

Summary

1. A study of the thermal polymerization of isobutylene was made at temperatures of from 370 to 460°, maximum pressures of from 540 to 5350 lb./sq. in., and times of from one-half to four hours. Under these conditions a cyclic dimer, 1,1,3-trimethylcyclopentane, is the main reaction product. It amounts to as much as 45.9% of the total liquid product when the reaction is carried out at 400° under 540 maximum lb./sq. in. for one hour.

2. Mechanisms are proposed to explain the formation of 1,1,3-trimethylcyclopentane from isobutylene.

3. A conventional synthesis of the trimethylcyclopentane, which resulted in the identification of the cyclic dimer, is described. During the synthesis, a new substance, optically inactive 1-chloro-1,3-dimethylcyclopentane, was prepared.

PITTSBURGH, PA. RECEIVED FEBRUARY 12, 1945

[CONTRIBUTION NO. 568 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Furan and Tetrahydrofuran Derivatives. VI. The Total Synthesis of *dl*-Oxybiotin[1]

BY KLAUS HOFMANN

Although a number of biological studies[2,3,4] of biotin derivatives have been described and have led to most interesting results, further progress in this field depends largely on the synthesis of new biotin analogs. It seemed of interest to prepare a number of such analogs in order to investigate further the relationships of chemical structure to biotin activity.

In a recent communication[5] the synthesis of hexahydro-2-oxo-1-furo[3,4]imidazole-4-valeric acid, an oxygen analog of biotin, was announced, and microbiological studies[6] have demonstrated a high degree of biotin activity for this compound. In view of this comparable biological activity, as well as the close structural similarity to biotin, we have proposed the name *dl*-oxybiotin for this new compound.

The present report describes in detail the final phases of the oxybiotin synthesis. The different steps of the complete synthesis may be summarized as follows: 2-furanpentanol (I), the starting material, was prepared from furfural by conventional methods, and was condensed with diethyl acetylene-dicarboxylate according to the Alder–Rickert procedure. Saponification of the resulting 3,4-dicarbethoxy-2-furanpentanol gave 3,4-dicarboxy-2-furanpentanol (II) which was acetylated and transformed into the acid chloride (III).[7] Compound (III) was subjected to a modified Curtius degradation and the resulting 3,4-diaminocarbethoxy-2-furanpentanol acetate was partially hydrolyzed to give 3,4-diaminocarbeth-

(1) The author wishes to express his appreciation to Ciba Pharmaceutical Products, Inc., and to the Buhl Foundation for their generous support of this study.

(2) du Vigneaud, Dittmer, Hofmann and Melville, *Proc. Soc. Exptl. Biol. Med.*, **50**, 374 (1942).

(3) Melville, Dittmer, Brown and du Vigneaud, *Science*, **98**, 497 (1943).

(4) Dittmer, du Vigneaud, György and Rose, *Arch. Biochem.*, **4**, 229 (1944).

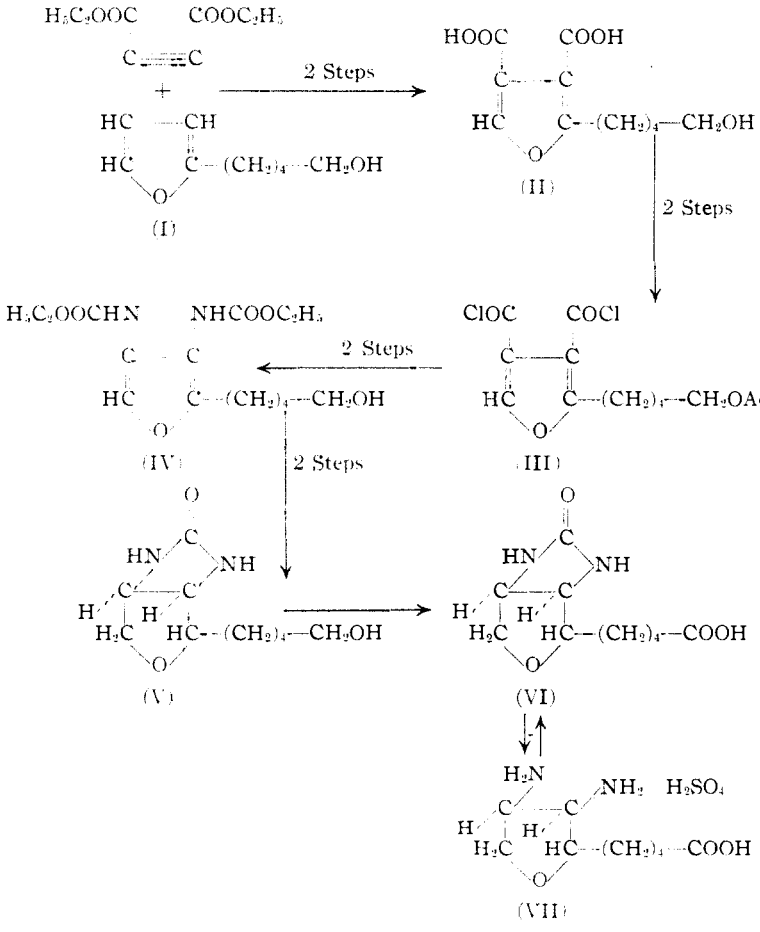
(5) Hofmann, THIS JOURNAL, **67**, 694 (1945).

(6) Pilgrim, Axelrod, Winnick and Hofmann, *Science*, **102**, 35 (1945).

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

oxy-2-furanpentanol (IV).[8] The transformation of (III) into (IV) was carried out originally in two separate steps, first to the acetate of (IV), which was isolated, and then partially hydrolyzed to give (IV). This procedure gave rather low yields, and it was therefore modified. As may be seen in the experimental section, the two steps were combined into one operation, thus simplifying the synthesis and improving the yield.

Recently[9] it was observed that 3,4-diaminocarbethoxy-2-methylfuran on low-pressure hydrogenation absorbed two moles of hydrogen and was transformed into a mixture of 3,4-diaminocarbethoxy-2-methyltetrahydrofurans. Compound (IV) was subjected to the same treatment and afforded a mixture of stereoisomeric 3,4-diaminocarbethoxy-2-tetrahydrofuranpentanols.



This lability of the 3,4-diaminofuranurethans is in contrast to the behavior of the corresponding 3,4-dicarboxyfurans, which are remarkably resistant toward catalytic hydrogenation.[10,11]

Whereas substitution of the furan nucleus with carboxyl groups enhances its "aromatic" properties, the introduction of aminocarbethoxy groups labilizes the ring system and renders it more "olefin-like" in character.

It seems probable that the 3,4-diaminofuranurethans are tautomeric systems of the amino form (VIII) or the imino form (IX) and that the existence of this type of tautomerism could account for the behavior of these compounds.[12]

From structural considerations, it would appear that only *cis*-3,4-diaminotetrahydrofurans can undergo ring closure to form hexahydro-2-oxo-1-furo[3,4]-imidazoles, for *trans* ring closure involves too much strain. The reduction of (IV) was therefore carried out in glacial acetic acid, since reduction in acidic solvents is known to favor the formation of *cis* isomers (von Auwers and Skita rule).[13]

In a previous study from this Laboratory,[9] a new method was described for the synthesis of hexahydro-2-oxo-1-furo[3,4]imidazoles which involved treatment of *cis*-3,4-diaminocarbethoxy-2-tetrahydrofurans with dilute aqueous barium hydroxide. The *cis*-3,4-diaminocarbethoxy-2-tetrahydrofuranpentanol present in the above-mentioned mixture of hydrogenation products of (IV) could be expected to cyclize in an analogous manner to give the bicyclic urea derivative (V). This crude mixture was subjected to the barium hydroxide treatment and *dl*-hexahydro-2-oxo-1-furo-[3,4]imidazole-4-pentanol (V) was obtained in good yield. Oxidation of the primary alcohol group in compound (V) with alkaline potassium permanganate yielded *dl*-oxybiotin (VI) which melted at 206–208°.

Although the method of synthesis proves the structure of oxybiotin, additional confirmatory experiments were carried out with the material.

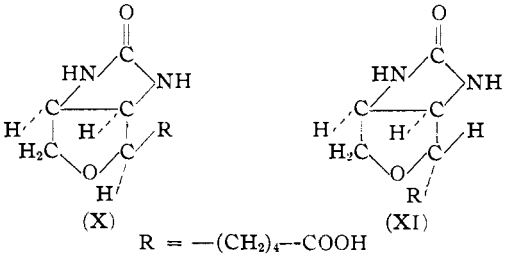
The presence of the carboxyl group was demon-

(8) Hofmann and Bridgwater, THIS JOURNAL, **67**, 738 (1945).
(9) Hofmann and Bridgwater, *ibid.*, **67**, 1165 (1945).
(10) Hofmann, *ibid.*, **66**, 157 (1944).
(11) Archer and Pratt, *ibid.*, **66**, 1656 (1944).
(12) For a detailed discussion of the tautomerism of β-aminofurans, see Stevenson and Johnson, *ibid.*, **59**, 2525 (1937).
(13) For a detailed discussion, see Linstead, Doering, Davis, Levine and Whetstone, *ibid.*, **64**, 1985 (1942).

strated by esterification and a water soluble methyl ester melting at 114–116° was obtained.

The cyclic urea portion of the molecule was established in the customary manner.[14] Hydrolysis of compound (VI) with barium hydroxide at 140° resulted in the formation of *cis*-3,4-diamino-2-tetrahydrofuranvaleric acid which was isolated as the crystalline sulfate (VII). *dl*-Oxybiotin was regenerated when (VII) was treated with phosgene.

The type of ring closure used in the present synthesis is unquestionable proof for the *cis* configuration of the two rings, and oxybiotin therefore must possess either structure (X) or (XI).



(X) (XI)

R = —$(CH_2)_4$—COOH

These structures differ in the spatial arrangement of the valeric acid side chain, which in compound (X) is attached in the *cis* position with respect to the nitrogen in position 3,[15] and occupies the opposite *trans* configuration in compound (XI). Whether *dl*-oxybiotin has structure (X) or structure (XI) cannot be decided at the present time.

The striking microbiological activity of *dl*-oxybiotin, which for certain organisms equals that of *dl*-biotin, justifies some conclusions as to the stereochemical relationships between these two compounds. It seems likely that oxybiotin and biotin have identical spatial configurations and that the two compounds differ from one another only in the nature of one of the hetero atoms.

The high yeast growth activity of desthiobiotin[3] has been attributed[16,17] to a transformation of this compound into biotin by the yeast cell. It was of interest to determine whether oxybiotin is active as such or whether it exerts its activity as a result of conversion into biotin.

Recently[18] we have developed a differential assay procedure for oxybiotin and biotin and by its use were able to demonstrate that yeast (*S. cerevisiae*) utilizes the oxybiotin molecule as such, and does not transform it into biotin. A detailed description of these studies will be presented elsewhere.

Experimental[19,20]

Modified Procedure for the Preparation of 3,4-Diaminocarbethoxy-2-furanpentanol (IV).—A solution of 32.7 g. of the acid chloride (III)[7] in 300 cc. of ether was stirred vigorously for two hours in an ice-bath with a solution of 30 g. of sodium azide in 80 cc. of water. Sixty cc. of a 40% sodium hydroxide solution was then added and stirring was continued for an additional hour. The ether layer was separated, the aqueous solution was re-extracted with ice cold ether and the combined ether extracts were dried for approximately thirty minutes over desiccated sodium sulfate. The dried solution was filtered through a fluted filter filled with sodium sulfate and the ether was removed *in vacuo* at room temperature. The colorless oily azide was dissolved in 300 cc. of absolute alcohol and was decomposed under nitrogen as described in a previous communication.[8]

The resulting solution containing the acetate of (IV) was cooled to 0° and 102 cc. of 1 *N* sodium hydroxide was added slowly with stirring. The solution was kept at room temperature overnight, the alcohol was removed *in vacuo* and the residue was dissolved in ether. The ether solution was washed with three portions of 2 *N* hydrochloric acid, one portion of 10% sodium bicarbonate, was dried over sodium sulfate and the ether was removed on the steam-bath. The resulting oil was suspended in a mixture of one part of ether and two parts of petroleum ether (b. p. 30–60°). This suspension was heavily seeded and worked with a spatula until it crystallized. The crystalline mass was collected, washed with additional amounts of the above ether–petroleum ether mixture and was dried *in vacuo* over phosphorus pentoxide; 19.1 g. (57.2% of the theoretical yield based on the acid chloride) of crystals was obtained, which melted at 75–80°. Recrystallization from 60% aqueous methanol (90 cc.) gave material melting at 79–81° which was identical with the compound described in an earlier communication.[8]

***dl*-Hexahydro-2-oxo-1-furo[3,4]imidazole-4-pentanol (V).**—A solution of 6.6 g. of (IV) in 200 cc. of glacial acetic acid was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 6.6 g. of a palladium on barium sulfate catalyst.[21] Two moles of hydrogen was absorbed within sixty to eighty minutes. The catalyst was removed by filtration, the glacial acetic acid was evaporated *in vacuo* and the reduction products were dissolved in ethyl acetate. The ethyl acetate solution was washed with 10% sodium bicarbonate, dried over sodium sulfate, and the solvent was removed *in vacuo*. Four hundred cc. of a 10% aqueous solution of $Ba(OH)_2 \cdot 8H_2O$ was added to the residue and the mixture was heated on the steam-bath for two hours. The mixture was frequently shaken and the organic material dissolved completely after a short time of heating. A slow stream of carbon dioxide was then passed into the hot solution for approximately thirty minutes and the precipitate of barium carbonate was removed by filtration through filter-cel. The clear yellow filtrate was concentrated to dryness *in vacuo* and the residue was extracted with three 50-cc. portions of boiling dioxane. The dioxane extracts were combined, filtered, and concentrated to a small volume on a hot-plate. On cooling, 1.9 g. (44.1% of the theoretical yield) of (V) was obtained in silky needles. The compound, which was highly water soluble, was purified by recrystallization from hot dioxane and melted at 153–154°.

Anal. Calcd. for $C_{10}H_{18}O_3N_2$: C, 56.07; H, 8.47; N, 13.07. Found: C, 56.06; H, 8.18; N, 12.90.

***dl*-Oxybiotin Hexahydro-2-oxo-1-furo[3,4]imidazole-4-valeric Acid (VI).**—To a solution of 2.14 g. of (V) in 100 cc. of 0.1 *N* sodium hydroxide 63 cc. of a 5% solution of potassium permanganate was added slowly with stirring. The solution was kept at room temperature overnight and 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 filtrates and washings were acidified to congo red with concentrated hydrochloric acid and were concentrated to a volume of 15 to 20 cc. *in vacuo*. The solution was placed in the refrigerator overnight and the crystalline *dl*-oxybiotin was collected, washed with a small amount

(14) Hofmann, Melville and du Vigneaud, *J. Biol. Chem.*, **141**, 211 (1941).

(15) For the numbering of the hexahydro-2-oxo-1-furo[3,4]imidazole ring system see ref. 9.

(16) Dittmer, Melville and du Vigneaud, *Science*, **99**, 203 (1944).

(17) Stokes and Gunness, *J. Biol. Chem.*, **157**, 121 (1945).

(18) Hofmann and Winnick, *ibid.*, in press.

(19) The microanalyses were performed by the Microchemical Laboratory, California Institute of Technology, Pasadena, California.

(20) All melting points are corrected.

(21) Schmidt, *Ber.*, **52**, 409 (1919).

of ice water and was dried *in vacuo* at 100° over phosphorus pentoxide; 1.1 g. (48.2% of the theoretical yield) of crystals was obtained which melted at 200–205°. Several recrystallizations from hot water to a constant microbiological activity gave silky needles which melted at 206–208°.

Anal. Calcd. for $C_{10}H_{16}O_4N_2$: C, 52.63; H, 7.07; N, 12.27. Found: C, 52.62; H, 7.43; N, 12.12.

Methyl Ester: A. By Esterification with Methanol and Hydrochloric Acid.—A solution of 100 mg. of (VI) in 10 cc. of dry methanol was saturated with dry hydrogen chloride and the solution was refluxed for one hour. The methanol was removed *in vacuo* and two 10-cc. portions of fresh methanol were added to the residue and successively removed by evaporation *in vacuo*. The oily residue was then dissolved in two cc. of ice water, the solution was layered with 10 cc. of ethyl acetate, and solid potassium carbonate was added to bind most of the water. The ethyl acetate solution was decanted from the solid residue, filtered through a layer of potassium carbonate and the solvent was removed on the steam-bath. The resulting crystalline ester was purified by recrystallization from a mixture of dioxane and ether, and melted at 114–116°.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: C, 54.52; H, 7.49; N, 11.55; OCH_3, 12.81. Found: C, 54.39; H, 7.39; N, 12.10; OCH_3, 13.20.

B. By Treatment of the Acid Chloride of Oxybiotin with Methanol.—*dl*-Oxybiotin (100 mg.) was dissolved in two cc. of thionyl chloride and the solution was kept at room temperature for one hour. The thionyl chloride was removed *in vacuo* and the residue was refluxed for thirty minutes with 5 cc. of methanol. The methanol was removed *in vacuo* and the ester was isolated and purified as described under A.

Anal. Calcd. for $C_{11}H_{18}O_4N_2$: C, 54.52; H, 7.49; N, 11.55. Found: C, 54.37; H, 7.31; N, 11.90.

***cis-dl*-3,4-Diamino-2-tetrahydrofuranvaleric Acid Sulfate (VII).**—A mixture of 600 mg. of *dl*-oxybiotin, 12 g. of $Ba(OH)_2 \cdot 8H_2O$ and 60 cc. of water was heated in a sealed tube to 140–150° for twenty hours, and 522 mg. (66.1% of the theoretical yield) of the sulfate (VII) was isolated in the usual manner.[14] The compound was purified by recrystallization from dilute methanol and melted at 252–255° with decomposition.

Anal. Calcd. for $C_9H_{18}O_3N_2 \cdot H_2SO_4$: C, 36.00; H, 6.71; N, 9.32; S, 10.68. Found: C, 35.76; H, 6.63; N, 9.00; S, 10.77.

***dl*-Oxybiotin (VI) by Phosgene Treatment of (VII).**—A solution of 100 mg. of (VII) was dissolved in two cc. of a 10% solution of sodium bicarbonate, was cooled in an ice-bath and a slow stream of phosgene was passed into the solution until it became acid to congo red. The *dl*-oxybiotin, which crystallized, was collected and recrystallized from a small amount of water; 46 mg. (60.5% of the theoretical yield) of needles melting at 205–207° was obtained which did not depress the melting point of an authentic sample of *dl*-oxybiotin.

Anal. Calcd. for $C_{10}H_{16}O_4N_2$: C, 52.63; H, 7.07; N, 12.27. Found: C, 52.78; H, 7.32; N, 12.40.

Acknowledgment.—The author wishes to express his thanks to Mrs. Florence Baker and to Miss Anna Bridgwater for their valuable assistance throughout this work.

Summary

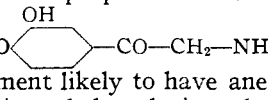
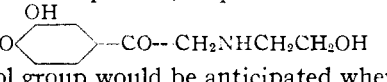
The total synthesis of *dl*-oxybiotin (hexahydro-2-oxo-1-furo[3,4]imidazole-4-valeric acid) has been described.

PITTSBURGH, PENNSYLVANIA RECEIVED MAY 26, 1945

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Amines Related to Epinephrine. II. Some More Amines of the "Eprocaine" Type

BY RALPH HILL[1] AND GARFIELD POWELL

Looking further into the properties of compounds of the type  where —NHR is a fragment likely to have anesthetic activity,[2] we anticipated that the introduction of $C_6H_5COO(CH_2)_x$— as R, or this group with aryl substituents, would produce compounds having anesthetic activity and possibly also pressor activity.[3] Such compounds should give salts with appreciable water solubility, and would be closely related to procaine when the aryl substituent is —NH_2. For the preparation of such compounds, a preferential benzoylation of  on the alcohol group would be anticipated when the benzoylating agent reacts with a salt of the amine.[3,4] This method, in fact, was successfully employed with *p*-nitrobenzoyl chloride but did not work out, with benzoyl chloride. The N-benzoyl derivative, however, was easily obtained. Though the rearrangement of N derivatives to O derivatives is less commonly observed than the reverse rearrangement, it has been effected, by the use of alcoholic hydrogen chloride, in at least two instances.[5] On attempting this method, which would give the compounds sought, with N-benzoyl-(3,4-dihydroxyphenacylamino)-ethanol we obtained what we believe to be a dihydroparoxazine and its salt. Such dihydroparoxazines occurring not as a part of a fused ring system have hitherto not been described in the literature.

Comparable behavior with acids to give a dihydroparoxazine was not shown with the unbenzoylated amine.

Experimental

β-Aminoethyl Benzoate Hydrochloride.—β-Chloroethylamine hydrochloride was prepared by treating ethanolamine hydrochloride with thionyl chloride.[6] The N-benzoyl derivative was prepared and converted to β-

(1) From a dissertation submitted in partial fulfillment of the requirements for the Ph.D. degree in Columbia University.

(2) Ralph Hill and G. Powell, THIS JOURNAL, **66**, 742 (1944).

(3) See Coles and Lott, *ibid.*, **58**, 1939 (1936).

(4) Rubin and Day, *J. Org. Chem.*, **5**, 54 (1940).

(5) Kanao, *J. Pharm. Soc. Japan*, **48**, 1074 (1928); Immediata and Day, *J. Org. Chem.*, **5**, 512 (1940).

(6) Ward, THIS JOURNAL, **57**, 914 (1935).