previous case employing recrystallized succinimide (7.7 g.) and freshly redistilled crotonaldehyde (5.8 g.) and the reaction temperature increased from 28 to 34°. Concentration *in vacuo* yielded 12.8 g. of crude reaction product.

The crude aldehydo compound was converted to the 2,4-dinitrophenylhydrazone (40%) which melted at 165–166° after crystallization from an ethyl acetate–acetone solution.

Anal. Calcd. for $C_{14}H_{15}O_6N_5$: C, 48.13; H, 4.32; N, 20.06. Found: C, 48.35; H, 4.38; N, 20.32.

Preparation of β-Succinimidopropionic Acid, IX.—The crude β-succinimidopropionaldehyde (15.5 g., viscous oil) was dissolved in 30 cc. of warm water. Approximately 1.5 cc. of 10% aqueous sodium hydroxide solution was added, and the resulting solution was cooled to 8°. An aqueous solution of potassium permanganate consisting of 300 cc. of water and 10.5 g. of permanganate was added in portions. The temperature increased rapidly to 14° but was maintained at approximately 10° by continued cooling. After the oxidation was complete, the manganese dioxide was removed by filtration, and the excess permanganate was destroyed with dilute sodium bisulfite solution. The clear reaction solution was concentrated *in vacuo* yielding a viscous oil. The residual oil was extracted with ether, and after drying over anhydrous sodium sulfate the ether was removed by distillation. The residual oil rapidly crystallized on cooling and the crystalline product melted at 124–128°. Further extraction of the syrup with ethyl acetate gave additional crude product. The total yield (2.15 g.) was low. Recrystallization from absolute ethanol yielded needle-like crystals melting at 131–132°.

Anal. Calcd. for $C_7H_9O_4N$: C, 49.12; H, 5.30; N, 8.18; neut. equiv., 171. Found: C, 49.03; H, 5.34; N, 8.00; neut. equiv., 177.

Conversion of β-Phthalimidopropionaldehyde to β-Alanine Hydrochloride.—The crude β-phthalimidopropionaldehyde I was oxidized by permanganate essentially as discussed in the previous case. Concentration *in vacuo* yielded a white crystalline material which was collected by filtration, washed with water and dried. The N-phthalyl-β-alanine VIII thus obtained melted at 139–141°. Recrystallization from absolute ethanol increased the melting point to 141–142°. When the N-phthalyl-β-alanine was recrystallized from water, it melted at 149.5–151°. The melting point of the N-phthalyl-β-alanine was not depressed when mixed with an authentic sample.[7]

Two and five-tenths grams of the recrystallized N-phthalyl-β-alanine was refluxed with 25 cc. of 20% hydrochloric acid for a period of eighteen hours. Upon cooling, the phthalic acid crystallized from the reaction solution, and after filtration the filtrate was evaporated *in vacuo* to yield a crystalline residue. Recrystallization from isopropyl alcohol yielded β-alanine hydrochloride (0.51 g.) as fine needles melting at 120–121.5°. An additional crystallization increased the melting point to 121.5–123°.

Summary

1. The 1,4 addition of cyclic imides, such as phthalimide and succinimide, to acrolein, methacrolein and crotonaldehyde has been described.

2. A new synthesis of β-alanine, using β-phthalimidopropionaldehyde as the starting material, has been described.

(7) Schöberl, *Ann.*, **542**, 274 (1939).

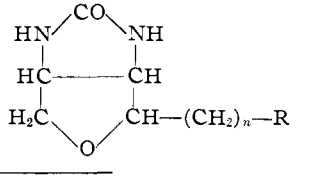
MINNEAPOLIS, MINNESOTA RECEIVED JULY 19, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Furan and Tetrahydrofuran Derivatives. X.[1] The Synthesis of the Sulfonic Acid Analogs of Oxybiotin and Homoöxybiotin

BY KLAUS HOFMANN, ANNA BRIDGWATER AND A. E. AXELROD[2]

In connection with our studies on the relationships of chemical structure and biological activity in the biotin and oxybiotin series,[3] it seemed desirable to replace the carboxyl group in *dl*-oxybiotin (I) by a sulfonic acid moiety and to test the biological activity of the resulting compound. Recently we have shown that *dl*-homoöxybiotin (II) has the ability to antagonize the growth-promoting effects of *dl*-oxybiotin for yeast. It was of interest to determine whether the sulfonic acid analog (IV) would possess greater antagonistic potency than homoöxybiotin (II). This communication describes the synthesis of the two sulfonic acids (III and IV). A brief account of the biological activities of these acids and of several of the intermediates obtained during their preparation will also be presented.



	n	R
(I)	4	COOH
(II)	5	COOH
(III)	4	SO_3H
(IV)	5	SO_3H

The methods used to prepare *dl*-hexahydro-2-oxo-4-(4-hydroxybutyl)-1-furo-(3,4)-imidazole (XIII), the key intermediate in the synthesis of III, were those recently developed in this Laboratory for the preparation of similar compounds.[3,4,5,6] Starting material for the present study was 2-furanpropanol (V)[3] which was transformed into 2-furanpropyl chloride (VI) by a modification of the procedure of Gilman.[7] This chloride, on treatment with potassium cyanide followed by hydrolysis, was converted into 2-furanbutyric acid (VII), which was then esterified. The resulting ethyl 2-furanbutyrate (VIII), upon reduction with sodium and alcohol, yielded the desired 2-furanbutanol (IX). Condensation of IX with diethylacetylenedicarboxylate, followed by partial hydrogenation and thermal decomposi-

(1) A preliminary report of some of the work herein described has appeared in THIS JOURNAL, **69**, 1550 (1947).

(2) The authors wish to express their appreciation to Ciba Pharmaceutical Products, Inc., Summit, New Jersey, and to the Buhl Foundation for their generous support of this study.

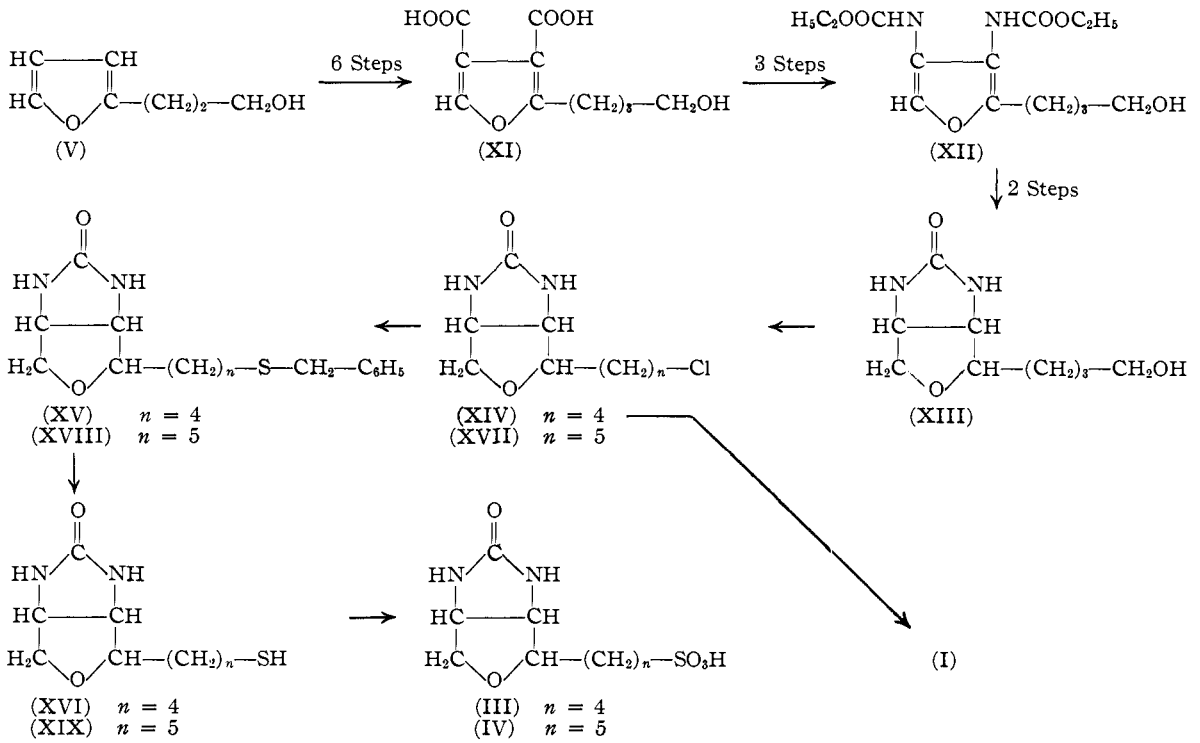
(3) Hofmann, Chen, Bridgwater and Axelrod, THIS JOURNAL, **69**, 191 (1947).

(4) Hofmann, *ibid.*, **67**, 421 (1945).

(5) Hofmann and Bridgwater, *ibid.*, **67**, 1165 (1945).

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

(7) Gilman and Hewlet, *Rec. trav. chim.*, **51**, 93 (1932).



tion,[4,8] gave 3,4-dicarbethoxy-2-furanbutanol which was transformed into 3,4-dicarboxy-2-furanbutanol (XI) by alkaline hydrolysis. The acetate of XI, by a modified Curtius degradation,[6] was converted into 3,4-dicarbethoxyamino-2-furanbutanol (XII).

It should be noted that the transformation of a tri-substituted furan such as XII into the corresponding tetrahydro derivative creates three assymetric carbon atoms within the molecule, and four racemic 3,4-diamino-2-tetrahydrofuranbutanols may theoretically be expected. Stereochemically this situation parallels that of the 3,4-dicarbethoxyamino-2-tetrahydrofuranpentanols.[9] Catalytic hydrogenation of XII resulted in the formation of a mixture of reduction products, which were separated into an ether-soluble and an ether-insoluble fraction. The ether-insoluble material, containing the desired *cis*-3,4-dicarbethoxyamino-2-tetrahydrofuranbutanol, upon treatment with barium hydroxide[5] yielded a hexahydro-2-oxo-4-(4-hydroxybutyl)-1-furo-(3,4)-imidazole (XIII) which on the basis of evidence presented below has the same spatial configuration as *dl*-oxybiotin (I).

Treatment of XIII with thionyl chloride[3] gave the corresponding chloride (XIV), which upon reaction with potassium cyanide and hydrolysis was transformed into *dl*-oxybiotin (I). Therefore, derivatives which are prepared from XIII by modification of the side chain also have the same stereochemical configuration as *dl*-oxybiotin. Condensation in absolute alcohol of the chloride (XIV) with sodiobenzylmercaptide gave the benzyl thioether (XV), which upon reduction with sodium and alcohol was converted into the mercaptobutanol (XVI). Attempts to cleave the thioether (XV) with sodium in liquid ammonia failed, probably because of the insolubility of the compound in the liquid ammonia. Oxidation with dilute barium permanganate of the mercaptobutanol (XVI) gave the desired sulfonic acid (III) in excellent yield. Oxidation of XVI with bromine according to Levene[10] gave the same sulfonic acid in poor yields.

A similar series of reactions was used in the preparation of the sulfonic acid (IV). *dl*-Hexahydro-2-oxo-4-(5-chloropentyl)-1-furo(3,4)-imidazole (XVII),[3] through the benzyl thioether (XVIII), was converted into the mercaptopentanol (XIX), which on oxidation with barium permanganate yielded the desired sulfonic acid (IV). Both sulfonic acids were characterized in the form of their crystalline barium salts.

The microbiological activity of compounds III, IV, XV, XVI, XVIII and XIX was determined with *Lactobacillus arabinosus* and *Saccharomyces cerevisiae* as the test organisms. In conformity with earlier observations which showed that the substitution of carboxyl groups by sulfonic acid groups in biologically active molecules led to antagonists, the sulfonic acid analog of oxybiotin (III) was also found to possess antagonistic activity against *d*-biotin and *dl*-oxybiotin (molar-inhi-

(8) Hofmann, THIS JOURNAL, **66**, 51 (1944).
(9) Hofmann, *ibid.*, **71**, 164 (1949).
(10) Levene, Mori and Mikeska, *J. Biol. Chem.*, **75**, 347 (1927).

bition ratio[11] toward *d*-biotin and *dl*-oxybiotin for *S. cerevisiae* = 1,500,000 and 16,000, respectively).

Two intermediates in the synthesis of the sulfonic acid (III), namely, the benzyl thioether (XV) and the mercaptobutanol (XVI), proved to be rather active antagonists. Thus, compound XV possessed a molar-inhibition ratio toward *d*-biotin and *dl*-oxybiotin of 740,000 and 9,300, respectively, when *S. cerevisiae* was used as the test organism.

In contrast to *dl*-homoöxybiotin (II), which is an effective oxybiotin antagonist for yeast, the corresponding sulfonic acid analog (IV) possessed slight growth-stimulating activity both for *L. arabinosus* and *S. cerevisiae*. Compounds XVIII and XIX also had stimulatory activity for *L. arabinosus*. They were inhibitory, however, when tested with *S. cerevisiae*.

A complete description of the biological activities of the above compounds, especially their inhibitory action toward pathogenic organisms, will be published elsewhere.

Experimental[12,13]

2-Furanbutyric Acid (VII).—To a three-neck flask, equipped with a dropping funnel and a stirrer with a mercury seal, were added 300 g. of 2-furanpropanol (V)[8] and 312 g. of dimethylaniline. The flask was cooled in an ice–salt-bath, and 306 g. of thionyl chloride in 180 cc. of dry chloroform was added dropwise with stirring. The inside temperature was kept at 0–10° throughout the operation. The mixture was stirred for one hour, poured on crushed ice, and extracted with chloroform. The chloroform extracts were washed with 2 *N* hydrochloric acid, water and 2 *N* potassium carbonate, and were dried over sodium sulfate. The solvent was removed *in vacuo*, and the residue on distillation yielded 218 g. (63% of the theoretical yield) of 2-furanpropyl chloride (VI) as a colorless liquid which boiled at 80–92° at 13 mm. To a solution of 71 g. of (VI) in 700 cc. of 95% alcohol, 36 g. of potassium cyanide dissolved in 75 cc. of water were added, and the mixture refluxed for twenty-two hours. The solution was concentrated to one-third of its volume, 215 cc. of 5 *N* potassium hydroxide was added, and refluxing was continued for nine hours. Most of the alcohol was removed by distillation and the solution was extracted with ether. It was then acidified with 18 *N* sulfuric acid to congo red and re-extracted with ether. The ether extracts were washed with water, dried over sodium sulfate, and the ether removed on the steam-bath. The residue, on distillation, yielded 46 g. (60% of the theoretical yield) of 2-furanbutyric acid as a colorless liquid which boiled at 94–117° at 0.03 mm.

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.31; H, 6.54. Found: C, 62.53; H, 6.71.

Anilide of 2-Furanbutyric Acid.—A mixture of 3.0 g. of the above acid and 6.0 g. of freshly distilled aniline was heated to 170–175° for seventeen hours. The anilide was isolated in the usual manner, and was sublimed at 140° and 0.02 mm. Recrystallization of the sublimate from a mixture of petroleum ether and ether yielded shiny white crystals which melted at 62–64°.

Anal. Calcd. for $C_{14}H_{15}O_2N$: C, 73.31; H, 6.59; N, 6.11. Found: C, 72.81; H, 6.90; N, 6.03.

(11) The ratio of the molar concentration of the antagonist to that of *d*-biotin or *dl*-oxybiotin, at which *complete* inhibition of growth results.

(12) All melting points are corrected.

(13) The microanalyses were performed in our Microanalytical Laboratory by Mr. George L. Stragand.

2-Furanbutanol (IX).—The furanbutyric acid (VII) (175 g.) was esterified with cold ethanolic hydrochloric acid and the ester isolated in the usual manner; 179 g. (87% of the theoretical yield) of ethyl 2-furanbutyrate (VIII), which boiled at 119–122° and 23 mm. was obtained. The ester (VIII) (60 g.) was reduced with sodium and ethanol as described previously,[4] and 36 g. (78% of the theoretical yield) of 2-furanbutanol was obtained as a colorless liquid which boiled at 115–117° at 18 mm.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.62. Found: C, 68.50; H, 8.25.

α-Naphthylurethan of 2-Furanbutanol.—This derivative was prepared in the usual manner and following recrystallization from a mixture of petroleum ether (b. p. 30–60°) and ether melted at 71–73°.

Anal. Calcd. for $C_{19}H_{19}O_3N$: C, 73.80; H, 6.19; N, 4.53. Found: C, 73.82; H, 6.16; N, 4.71.

3,4-Dicarboxy-2-furanbutanol (XI).—Fifty grams of 2-furanbutanol (IX) and 67 g. of diethylacetylene dicarboxylate were heated on the steam-bath overnight. The cooled mixture was dissolved in 300 cc. of ethyl acetate and hydrogenated at room temperature and atmospheric pressure in the presence of 8 g. of a palladium-on-barium sulfate catalyst[14] until one mole of hydrogen had been absorbed. The catalyst was removed by filtration, the ethyl acetate was evaporated *in vacuo*, and the residue heated to 190–200° at 16 mm. until the evolution of ethylene had ceased, and distilled *in vacuo;* 86.8 g. (86% of the theoretical yield), of 3,4-dicarbethoxy-2-furanbutanol (X) was obtained, which boiled at 156–161° at 0.02 mm. Saponification of the above material with a mixture of 500 cc. of methanol and 250 cc. of 5 *N* potassium hydroxide followed by acidification gave 67.3 g. (96% of the theoretical yield) of 3,4-dicarboxy-2-furanbutanol (XI) which was recrystallized from a mixture of methanol and ethyl acetate; m. p. 126–127°.

Anal. Calcd. for $C_{10}H_{12}O_6$: C, 52.63; H, 5.31. Found: C, 52.59; H, 5.54.

3,4-Dicarboxy-2-furanbutanol Acetate.—To 57.5 g. of 3,4-dicarboxy-2-furanbutanol (XI) in 235 cc. of dry pyridine was added slowly 150 cc. of acetic anhydride. After standing overnight, the solvents were removed *in vacuo*, the residue was dissolved in ethyl acetate, and the solution washed with 2 *N* hydrochloric acid and water, and extracted with several portions of 10% sodium bicarbonate. The combined bicarbonate extracts were acidified with concentrated hydrochloric acid to congo red and the desired compound re-extracted with ethyl acetate. The combined ethyl acetate extracts were washed with water, dried over sodium sulfate, and the solvent removed *in vacuo*. The crystalline residue of 3,4-dicarboxy-2-furanbutanol acetate was repeatedly washed with petroleum ether (b. p. 30–60°) and dried over phosphorus pentoxide; 61.3 g. (90% of the theoretical yield) of crystals was obtained, which upon recrystallization from ether melted at 89–90°.

Anal. Calcd. for $C_{12}H_{14}O_7$: C, 53.35; H, 5.22. Found: C, 53.04; H, 4.99.

3,4-Dicarbethoxyamino-2-furanbutanol (XII).—To a suspension of 50 g. of the above acetate in 250 cc. of dry ether was added, in small amounts, with cooling and shaking, a total of 87 g. of phosphorus pentachloride. Shaking was continued until most of the phosphorus pentachloride had disappeared, and the ether was removed *in vacuo* at a bath temperature of 95–100°. Dry benzene (100 cc.) was added to the residue with subsequent removal, and this procedure was repeated twice more. The residue was dissolved in 500 cc. of ether and stirred vigorously in an ice-bath for two hours with a solution of 48 g. of sodium azide in 130 cc. of water. The ether layer was separated, the aqueous layer reëxtracted with fresh ether, and the combined ether extracts washed with 10% sodium bicarbonate and water and finally dried over freshly desiccated sodium sulfate. The dried solution was filtered through a fluted

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

filter filled with sodium sulfate, and the ether was removed *in vacuo* at a bath temperature of 20°. The resulting oily azide was dissolved in 500 cc. of absolute alcohol and decomposed under nitrogen as described in a previous communication.[15] The resulting solution was cooled to 0° and 370 cc. of *N* sodium hydroxide was added with stirring. After standing overnight the alcohol was removed *in vacuo*, the residue was diluted with water and extracted with ether. The ether extracts were washed with three 100-cc. portions of water, dried over sodium sulfate, and the solvent evaporated on the steam-bath. The oily residue crystallized on standing and gave 30 g. (52% of the theoretical yield) of ether-washed crystals which melted at 77–79°. No further purification was necessary for the next step. A sample for analysis was recrystallized from ether.

Anal. Calcd. for $C_{14}H_{22}O_6N_2$: C, 53.49; H, 7.05; N, 8.90. Found: C, 53.31; H, 6.75; N, 9.26.

***dl*-Hexahydro-2-oxo-4-(4-hydroxybutyl)-1-furo-(3,4)-imidazole (XIII).**—A solution of 50 g. of (XII) in 800 cc. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure in the presence of 75 g. of a palladium-on-barium sulfate catalyst[14] until 2 moles of hydrogen had been absorbed (reaction complete in approximately two hours). The catalyst was removed by filtration, the glacial acetic acid was evaporated *in vacuo*, and the residual oil dissolved in 100 cc. of ether. Washing of the ethereal solution with 100 cc. of 10% sodium bicarbonate resulted in the separation of an oily layer which contained the desired *cis* isomer of 3,4-dicarbethoxyamino-2-tetrahydrofuranbutanol. This oil was separated, dissolved in ethyl acetate, the solution dried over sodium sulfate, and the ethyl acetate removed *in vacuo*. A 10% solution of $Ba(OH)_2 \cdot 8H_2O$ (2.8 liters) was added to the residue and the mixture stirred at 90° for four hours. Isolation in the usual manner[3,6] gave 12 g. of crystals of XIII (37% of the theoretical yield) which upon recrystallization from dioxane melted at 156–157°.

Anal. Calcd. for $C_9H_{16}O_3N_2$: C, 53.98; H, 8.05; N, 13.99. Found: C, 54.12; H, 7.81; N, 13.80.

***dl*-Hexahydro-2-oxo-4-(4-chlorobutyl)-1-furo-(3,4)-imidazole (XIV).**—The butanol (XIII) (2 g.) was placed in a round-bottomed flask surrounded with ice, 5 cc. of ice-cold thionyl chloride was added at once and the solution was kept at room temperature for approximately twelve hours. The reaction product was isolated in the usual manner[3] and recrystallized from ethyl acetate; 1.33 g. (61% of the theoretical yield) of prisms melting at 124–126° was obtained.

Anal. Calcd. for $C_9H_{15}O_2N_2Cl$: C, 49.38; H, 6.90; N, 12.80; Cl, 16.22. Found: C, 49.16; H, 6.84; N, 12.54; Cl, 16.27.

***dl*-Oxybiotin (I).**—To a solution of 3.5 g. of the above chloride (XIV) in 100 cc. of 95% alcohol a solution of 2 g. of potassium cyanide in 4 cc. of water was added, and the mixture refluxed for twenty-four hours. The solvents were removed *in vacuo*, 1 *N* sodium hydroxide (100 cc.) was added to the residue, and refluxing continued for twelve hours. A slow stream of carbon dioxide was passed into the solution for thirty minutes and the resulting precipitate of silica removed by filtration through a layer of Filter-Cel. The clear filtrate was concentrated to a small volume *in vacuo* and was then acidified to congo red with concentrated hydrochloric acid. The resulting *dl*-oxybiotin (2.1 g.) (69% of the theoretical yield) was purified by crystallization from water. The compound was by mixed melting point and biological activity identical with *dl*-oxybiotin prepared by another method.[6]

***dl*-Hexahydro-2-oxo-4-(4-benzylthiobutyl)-1-furo-(3,4)-imidazole (XV).**—A stock solution of sodiobenzylmercaptide was prepared by dissolving 1.2 g. of sodium in a mixture of 19 cc. of absolute ethanol and 6 cc. of benzyl mercaptan.

To a solution of 442 mg. of the chloride (XIV) in 10 cc. of absolute ethanol 1.1 cc. of the above sodiobenzylmercaptide solution was added, and the mixture refluxed for two hours. The ethanol was removed *in vacuo*, the residue dissolved in ethyl acetate, and the solution washed with several portions of water, dried over sodium sulfate, and the ethyl acetate removed *in vacuo*. The oily residue solidified on standing, and the crystals were washed with ether and purified by recrystallization from dilute methanol; 410 mg. (66% of the theoretical yield) of silky needles were obtained which melted at 76–79°.

Anal. Calcd. for $C_{16}H_{22}O_2N_2S$: C, 62.73; H, 7.24; N, 9.14; S, 10.46. Found: C, 62.54; H, 6.96; N, 9.31; S, 10.32.

Sulfone of XV.—To a solution of 100 mg. of (XV) in 2 cc. of glacial acetic acid, 1 cc. of 30% hydrogen peroxide (Superoxol) was added, and the mixture kept at room temperature for twelve hours. The solvents were removed and the crystalline residue dried over potassium hydroxide *in vacuo*. Recrystallization of the substance from absolute ethanol gave 90 mg. (82% of the theoretical yield) of prisms melting at 189–190°.

Anal. Calcd. for $C_{16}H_{22}O_4N_2S$: C, 56.80; H, 6.55; N, 8.27; S, 9.48. Found: C, 57.03; H, 6.64; N, 7.95; S, 9.22.

Recrystallization of the sulfone from aqueous methanol gave needles of the half hydrate melting at 95–100°.

Anal. Calcd. for $C_{16}H_{22}O_4N_2S \cdot {}^1/_2H_2O$: C, 55.32; H, 6.62. Found: C, 55.11; H, 6.64.

***dl*-Hexahydro-2-oxo-1-furo-(3,4)-imidazole-4-(4-butane Sulfonic Acid) (III).**—To 4 g. of sodium which was placed in a round-bottomed flask, a solution of 500 mg. of the above thioether (XV) in 50 cc. of absolute ethanol was added at once and the mixture refluxed until all of the sodium had dissolved. Absolute alcohol (200 cc.) was then added and carbon dioxide was passed into the solution for one hour. The sodium carbonate was removed by filtration and the filter cake was repeatedly washed with absolute ethanol. The combined filtrate and washings were evaporated to dryness *in vacuo* in a stream of carbon dioxide, and the residue extracted with three 25-cc. portions of hot ethyl acetate. The combined ethyl acetate extracts were filtered and evaporated to dryness *in vacuo* under carbon dioxide. The resulting crystalline *dl*-hexahydro-2-oxo-4-(4-mercaptobutyl)-1-furo-(3,4)-imidazole (XVI), 185 mg. (52% of the theoretical yield), was used for the next step without further purification. The compound gave a strong nitroprusside test. To a solution of the above thiopentanol (XVI) (390 mg.) in 39 cc. of water which was cooled in an ice-bath, a 0.01 *M* solution of barium permanganate was added slowly with stirring until the pink color remained for twenty minutes. (Approximately 174 cc. of the solution was required.) The mixture was heated on the steam-bath, and 2 cc. of methanol was added in order to decompose the excess of permanganate. The manganese dioxide was removed by filtration and the clear filtrate was concentrated to dryness *in vacuo*. The crystalline residue was suspended in hot 95% alcohol and water was added until all of the barium salt had dissolved. Upon the addition of more hot 95% alcohol, the barium salt of the sulfonic acid crystallized; 485 mg. (81% of the theoretical yield) of colorless needles were obtained, which were purified by recrystallization from dilute ethanol.

Anal. Calcd. for $C_9H_{15}O_5N_2SBa/2$: C, 32.53; H, 4.55; N, 8.44: S, 9.66; Ba, 20.69. Found: C, 32.58; H, 4.74; N, 8.18; S, 9.43; Ba, 20.33.

***dl*-Hexahydro-2-oxo-4-(5-benzylthiopentyl)-1-furo-(3,4)-imidazole (XVIII).**—To a solution of 538 mg. of *dl*-hexahydro-2-oxo-4-(5-chloropentyl)-1-furo(3,4)imidazole (XVII)[3] in 5 cc. of absolute ethanol, 1.3 cc. of the above-mentioned sodiobenzylmercaptide solution was added and the mixture was refluxed for two hours. The benzyl thioether was isolated as described for the preparation of the lower homolog (XV). Recrystallization from dilute methanol yielded 639 mg. (86% of the theoretical yield) of needles which melted at 66–68°.

Anal. Calcd. for $C_{17}H_{24}O_2N_2S$: C, 63.73; H, 7.55;

(15) Hofmann and Bridgwater, THIS JOURNAL, **67**, 738 (1945).

N, 8.74; S, 10.00. Found: C, 63.24; H, 7.36; N, 8.89; S, 10.30.

Sulfone of (XVIII).—A sample of the thioether (XVIII) (200 mg.) was oxidized with Superoxol as described for the preparation of the lower homolog. Recrystallization from methanol gave 190 mg. (87% of the theoretical yield) of needles melting at 169–170°.

Anal. Calcd. for $C_{17}H_{24}O_4N_2S$: C, 57.95; H, 6.86; N, 7.94; S, 9.10. Found: C, 57.79; H, 6.59; N, 7.93; S, 9.17.

***dl*-Hexahydro-2-oxo-4-(5-mercaptopentyl)-1-furo-(3,4)-imidazole (XIX).**—Five hundred milligrams of the above thioether (XVIII) were cleaved with sodium in absolute ethanol as described for the lower homolog (XV); 250 mg. (70% of the theoretical yield) of the desired material, m. p. 92–94°, was obtained which was purified by recrystallization from ethyl acetate. The substance gave a strong nitroprusside test.

Anal. Calcd. for $C_{10}H_{18}O_2N_2S$: C, 52.15; H, 7.88; N, 12.15; S, 13.90. Found: C, 52.35; H, 7.58; N, 11.82; S, 14.67.

***dl*-Hexahydro-2-oxo-1-furo-(3,4)-imidazole-4-(5-pentane Sulfonic Acid) (IV).**—To an ice-cold solution of 200 mg. of the above thiopentanol (XIX) in 10 cc. of water and 1 cc. of acetone, a 0.01 *M* solution of barium permanganate was slowly added with stirring until the solution remained pink for thirty minutes (approximately 76 cc.). The excess of permanganate was destroyed by the addition of 2 cc. of methanol and heating on the steam-bath, and the solution was filtered and concentrated to dryness *in vacuo*. The residue was dissolved in a small amount of water, acetone was added until the solution became cloudy and the barium salt of the sulfonic acid crystallized out. Two hundred fifteen milligrams (71% of the theoretical yield) of the crystalline salt was obtained. The compound was purified by recrystallization from dilute acetone.

Anal. Calcd. for $C_{10}H_{17}O_5N_2SBa/2$: C, 34.70; H, 4.95; N, 8.09; S, 9.27; Ba, 19.86. Found: C, 34.37; H, 5.20; N, 8.14, S, 9.30; Ba, 19.60.

Summary

1. The sulfonic acid analogs of oxybiotin and homoöxybiotin have been prepared.

3. These compounds, as well as several intermediates in their synthesis, were capable of antagonizing the growth-promoting activity of biotin and oxybiotin for several microörganisms.

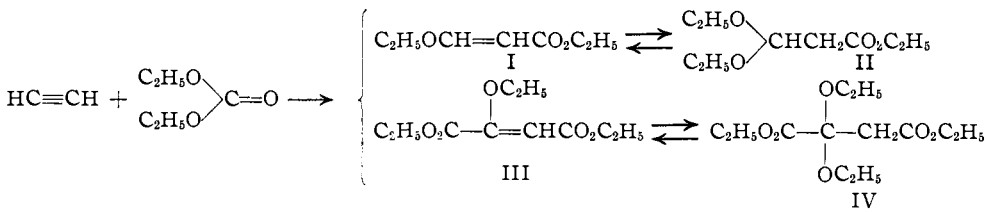
PITTSBURGH, PA. RECEIVED JULY 15, 1948

[CONTRIBUTION FROM ROHM & HAAS COMPANY]

Condensation of Acetylenes. Acetylene and Alkyl Carbonates

BY W. J. CROXALL AND H. J. SCHNEIDER

Although alkyl carbonates in the presence of strong bases have been successfully used to introduce the carbalkoxy group into the anions of esters,[1,2,3] ketones[4] and nitriles[5,6] there appears to be no record of the acylation of an acetylene with an alkyl carbonate. This paper describes the results obtained with acetylene and alkyl carbonates.



Preliminary work demonstrated that when ethyl carbonate in the presence of alcohol-free sodium ethoxide was contacted with acetylene at 80° and two to five psi gage pressure, absorption of acetylene occurred over a period of six to eight hours. After neutralization with aqueous acetic acid, distillation of the reaction mixture gave two fractions. The main fraction was a mixture of ethyl β-ethoxyacrylate (I) and ethyl β,β-diethoxypropionate (II). The higher boiling fraction was mostly ethyl α,α-diethoxysuccinate (IV) containing a small amount of ethyl ethoxymaleate (III). The over-all reaction may be represented schematically as follows:

Excess of ester was found to give higher yields of the products and when a twenty to one molar ratio of ethyl carbonate to sodium ethoxide was used, the yields (calculated as mole per cent.) varied between 55–60% based on the ethyl carbonate and acetylene and 175–200% based on the sodium ethoxide. Lower ratios of carbonate to ethoxide gave progressively poorer yields so that when a two to one ratio was used only traces of the products were obtained along with a large amount of non-distillable residue.

Further investigation showed that basic agents other than sodium ethoxide (Method A) were suitable as condensation agents. Sodium acetylide (Method C), disodium acetylide (Method D), and benzyltrimethylammonium ethoxide (Method E) were successfully employed in this reaction with various alkyl carbonates. Table I lists the experiments using these agents with various alkyl carbonates. In all the experiments the yield values

(1) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2056 (1941).
(2) Hauser, Abramovitch and Adams, *ibid.*, **64**, 2714 (1942).
(3) Walker, Levine, Kibler and Hauser, *ibid.*, **68**, 672 (1946).
(4) Wallingford, Homeyer and Jones, *ibid.*, **63**, 2252 (1941).
(5) Wallingford, Jones and Homeyer, *ibid.*, **64**, 576 (1942).
(6) Levine and Hauser, *ibid.*, **68**, 760 (1946).