[CONTRIBUTION FROM THE CHEMICAL LABORATORIES, GENERAL MILLS, INC.]

1,4 Addition Reactions. III. The Addition of Cyclic Imides to α,β-Unsaturated Aldehydes. A Synthesis of β-Alanine Hydrochloride[1]

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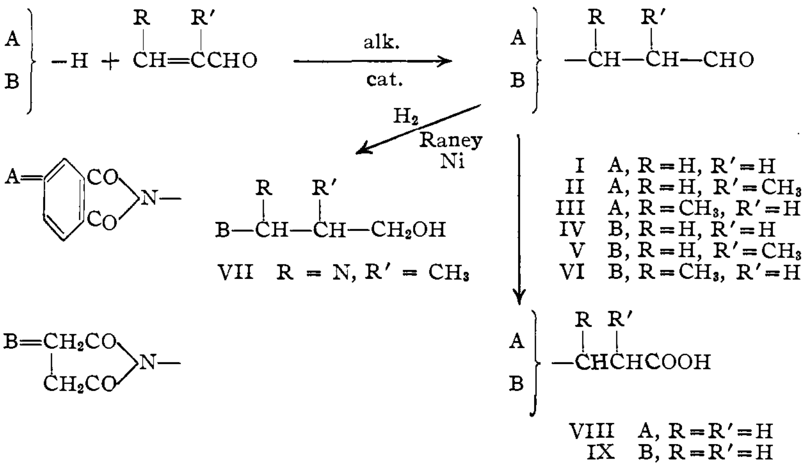
Previous publications[2,3] from this Laboratory have disclosed the 1,4 addition of malonate systems to acrolein. Since the 1,4 addition of imides to α,β-unsaturated aldehydes has not been reported, this paper describes the reaction of cyclic imides, such as phthalimide and succinimide with acrolein and alkyl substituted acroleins such as, methacrolein (α-methylacrolein) and crotonaldehyde.

The addition reactions involving phthalimide and acrolein, methacrolein and crotonaldehyde proceeded smoothly in the presence of a minute quantity of alkaline catalyst to yield the aldehydo compounds I, II and III, respectively. The adducts were characterized as the phenylhydrazones and the 2,4-dinitrophenylhydrazones.

Radde[4] attempted the preparation of phthalimidopropionaldehydes by the reduction of the corresponding acid chlorides. However, Radde observed that this reduction reaction was only applicable for the α-phthalimido acid chlorides and not for the β, γ and δ compounds.



The 1,4 addition of succinimide to acrolein, methacrolein and crotonaldehyde yielded the aldehydo compounds IV, V and VI, respectively.

The crude reaction products from the succinimide series were obtained in good yields, but they were liquids which resisted crystallization or distillation. Therefore, it was necessary to determine the proportion of the aldehydo compounds (1,4 addition products) by other methods. This was accomplished by means of derivative formation and reduction experiments. Some of the aldehydo derivatives were obtained in yields in excess of 80%. It was observed that the lowest yield of derivative occurred when crotonaldehyde was used as the unsaturated aldehyde.

If 1,2 addition had occurred, the presence of unsaturation in the reaction product could be readily determined by low pressure hydrogenation employing palladium on charcoal as the catalyst. In an experiment designed to determine this possibility (using methacrolein–succinimide reaction product) it was found that less than 5% of the theoretical amount of hydrogen had been consumed after one hour. However, when acetic acid, ethyl cyanoacetate and piperidine[5] were added to the same reaction mixture, and hydrogenation was resumed, 67% of the theoretical amount of hydrogen was taken up in one hour, indicating the predominant presence of the aldehydo compound.

The reduction of the crude α-methyl-β-succinimidopropionaldehyde in the presence of Raney nickel catalyst yielded 2-methyl-3-succinimido-1-propanol VII which in turn was characterized as the crystalline 3,5-dinitrobenzoate melting at 104–105°.

Oxidation by permanganate of β-phthalimidopropionaldehyde I yielded β-phthalimidopropionic acid VIII which was identical with an authentic sample. The substituted propionic acid was readily converted to β-alanine hydrochloride by means of acid hydrolysis.

Permanganate oxidation of β-succinimidopropionaldehyde IV yielded β-succinimidopropionic acid IX melting at 131–132°.

Experimental

β-Phthalimidopropionaldehyde, I.—Phthalimide (44.1 g.) was added to an alcoholic solution containing 110 cc. of absolute ethanol and 0.15 g. of sodium. The resulting reaction mixture was stirred at room temperature and the greater portion of the phthalimide remained suspended in the reaction mixture. A solution containing 25 cc. of acrolein and 15 cc. of absolute ethanol was added dropwise over a twenty-minute period and the reaction temperature increased to 51°. The reaction mixture was stirred for an additional half hour when a substantially clear solution resulted. After standing overnight, the re-

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[1] Paper No. 94, Journal Series, General Mills, Inc., Research Department.

[2] Moe and Warner, THIS JOURNAL, **70**, 2763 (1948).

[3] Warner and Moe, *ibid.*, **70**, 3470 (1948).

[4] Radde, *Ber.*, **55**, 3174 (1922).

[5] Alexander and Cope, THIS JOURNAL, **66**, 886 (1944).

action mixture was neutralized by the addition of the requisite quantity of glacial acetic acid. After filtration, the ethanol was removed by distillation under reduced pressure, yielding a viscous oil. Benzene (100 cc.) was added and the concentration *in vacuo* was repeated, yielding a semi-solid residue. The addition of benzene (100 cc.) yielded a pasty solid which was collected by filtration. Sixteen grams were obtained melting at 108–115°, and concentration of the filtrate yielded an additional quantity of solid which was not investigated further. Since this crude product proved difficult to purify by crystallization, a portion of it was placed in a round bottom flask and heated in an oil-bath under reduced pressure (15 mm.) until a clear melt was obtained. Fine needle-like crystals collected on the cool sides of the flask. These crystals melted at 119–120°.

Anal. Calcd. for $C_{11}H_9O_3N$: C, 65.02; H, 4.43; N, 6.90. Found: C, 65.20; H, 4.34; N, 7.03.

The phenylhydrazone melted at 121.5–122.5° after crystallization from ethanol.

Anal. Calcd. for $C_{17}H_{15}O_2N_3$: C, 69.60; H, 5.15; N, 14.33. Found: C, 69.41; H, 5.15; N, 14.73.

The 2,4-dinitrophenylhydrazone melted at 209–210° after crystallization from aqueous acetone.

Anal. Calcd. for $C_{17}H_{13}O_6N_5$: C, 53.26; H, 3.42; N, 18.28. Found: C, 53.24; H, 3.55; N, 18.33.

α-Methyl-β-phthalimidopropionaldehyde.—Phthalimide (14.7 g.) was suspended in an alcoholic solution consisting of 110 cc. of absolute ethanol and 0.04 g. of sodium. Methacrolein (7.4 g.) was added dropwise with no apparent increase in the reaction temperature. Reaction mixture was heated at 40–50° for a period of two hours when a substantially clear solution resulted. After neutralization, the ethanol was removed by concentration *in vacuo* and 21.3 g. of the reaction product resulted as an oil.

The crude phenylhydrazone was obtained in 80% yield and melted at 116–119°. An analytical sample was prepared by crystallization from ethanol and it melted at 119–121°.

Anal. Calcd. for $C_{18}H_{17}O_2N_3$: C, 70.35; H, 5.58; N, 13.68. Found: C, 69.88; H, 5.38; N, 13.63.

The crude 2,4-dinitrophenylhydrazone (70%) melted at 184–187°. An analytical sample which melted at 193–194° was prepared by crystallization from ethanol-acetone (50–50).

Anal. Calcd. for $C_{18}H_{15}O_6N_5$: N, 17.63. Found: N, 17.68.

β-Methyl-β-phthalimidopropionaldehyde.—This reaction was accomplished essentially as described in the previous case employing recrystallized phthalimide (29.4 g.) and freshly redistilled crotonaldehyde (15.66 g.). The reaction product (42 g.) was a brown pasty solid melting at 93–103°. A portion of this solid was recrystallized three times from Skelly C and melted at 105–108°.

Anal. Calcd. for $C_{12}H_{11}O_3N$: C, 66.36; H, 5.1; N, 6.4. Found: C, 66.62; H, 5.1; N, 6.6.

The crude phenylhydrazone (45%) melted at 98–100°. Purification by crystallization from ethanol yielded an analytical sample melting at 98–99°.

Anal. Calcd. for $C_{18}H_{17}O_2N_3$: C, 70.35; H, 5.58; N, 13.68. Found: C, 70.21; H, 5.60; N, 13.88.

The crude 2,4-dinitrophenylhydrazone (40%) melted at 170–172°. Recrystallization from acetone yielded an analytical sample melting at 180.5–181°.

Anal. Calcd. for $C_{18}H_{15}O_6N_5$: C, 54.4; H, 3.8; N, 17.6. Found: C, 54.63; H, 3.9; N, 17.84.

β-Succinimidopropionaldehyde, II.—Succinimide[6] (29.7 g.) was added to an alcoholic solution containing 50 cc. of absolute ethanol and 0.05 g. of sodium. The resulting suspension was cooled to 6° in an ice-bath. The cooling bath was removed and acrolein (16.8 g.) was added dropwise. The reaction temperature increased very rapidly to 31° and this temperature was maintained by varying the rate of addition of the acrolein. After the addition of the aldehyde was complete, the reaction mixture was stirred for an additional thirty-five minute period when a clear, water-white solution resulted. After standing for two and a half hours, the reaction mixture was neutralized with glacial acetic acid. Concentration *in vacuo* yielded a very viscous oil (44.3 g.) which resisted crystallization.

A portion of the crude aldehydo compound yielded a semicarbazone (75%) melting at 189–193°. An analytical sample was prepared by two crystallizations from aqueous ethanol and it melted at 201–202.5°.

Anal. Calcd. for $C_8H_{12}O_3N_4$: C, 45.3; H, 5.7; N, 26.4. Found: C, 45.34; H, 5.56; N, 26.64.

The *p*-nitrophenylhydrazone (61%) melted at 213–215°. After purification by crystallization from ethanol–acetone, it melted at 221–223°.

Anal. Calcd. for $C_{13}H_{14}O_4N_4$: C, 53.8; H, 4.8; N, 19.3. Found: C, 53.5; H, 4.8; N, 19.45.

The 2,4-dinitrophenylhydrazone (60% crude) melted at 183.5–184.5° after crystallization from 50 volume % ethanol–acetone solution.

Anal. Calcd. for $C_{13}H_{13}O_6N_5$: C, 46.56; H, 3.9; N, 20.89. Found: C, 47.05; H, 4.34; N, 20.68.

α-Methyl-β-succinimidopropionaldehyde, V.—Succinimide (9.9 g.) was added to an alcoholic solution containing 55 cc. of absolute ethanol and 0.05 g. of sodium. Methacrolein (7.04 g.) was added dropwise and the reaction temperature increased from 20 to 31°. The resulting clear reaction mixture was stirred for three hours and then neutralized with glacial acetic acid. Concentration *in vacuo* yielded 15.8 g. of an oily product which resisted crystallization.

The 2,4-dinitrophenylhydrazone which was obtained in 86% yield melted at 196.5–197° after crystallization from acetone.

Anal. Calcd. for $C_{14}H_{15}O_6N_5$: C, 48.13; H, 4.32. Found: C, 48.52; H, 4.59.

The *p*-nitrophenylhydrazone (80%) melted at 184–185° after crystallization from acetone.

Anal. Calcd. for $C_{14}H_{16}O_4N_4$: C, 55.26; H, 5.3; N, 18.42. Found: C, 55.22; H, 5.3; N, 18.42.

Low Pressure Reduction of Reaction Product, V.—The above crude reaction product (15.4 g.) was dissolved in 60 cc. of ethanol. Palladium on charcoal (0.5 g.) was added and the reduction was carried out at initial pressure of 32.5 pounds of hydrogen. After one hour, less than 5% of the theoretical amount of hydrogen had been consumed. The attempted reduction was interrupted at this point and 1 cc. of glacial acetic acid, 11.3 g. of ethyl cyanoacetate and 0.4 g. of piperidine were added. The reduction was again resumed at 32 pounds pressure. After one hour, 67% of the theoretical amount of hydrogen had been consumed. No attempt was made to characterize this simultaneous condensation–reduction product.

2-Methyl-3-succinimido-1-propanol, VII.—The crude β-methyl-β-succinimidopropionaldehyde (12.5 g.) was dissolved in 75 cc. of absolute ethanol. Raney nickel catalyst was added and the reduction was carried out at 70–80° at an initial pressure of 800 pounds of hydrogen. When the reduction was complete, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. A light yellow viscous oil resulted. The crude carbinol (1.9 g.) was mixed with 3,5-dinitrobenzoylchloride in a conventional manner. The resulting 3,5-dinitrobenzoate (0.93 g.) melted at 104–105° after crystallization from ethanol.

Anal. Calcd. for $C_{15}H_{15}O_8N_3$: C, 49.32; H, 4.14; N, 11.50. Found: C, 49.84; H, 4.23; N, 11.76.

β-Methyl-β-succinimidopropionaldehyde, VI.—This reaction was accomplished essentially as described in the

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[6] The 1,4 addition reactions involving Eastman Kodak Co. White Label succinimide did not proceed under the reaction conditions described. This may be due possibly to the presence of acidic components; hence recrystallized succinimide was employed in all experiments.

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).

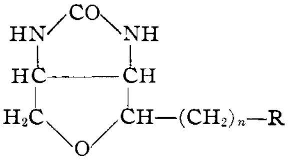
MINNEAPOLIS, MINNESOTA RECEIVED JULY 19, 1948

[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-

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(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).