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THE PREPARATION OF 1-(2-FURYL)-2-AMINO-1,3-PROPANEDIOL AND DERIVATIVES

KENYON HAYES AND GABRIEL GEVER

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The work of Rebstock, *et al.* (1) elucidating the structure of chloramphenicol[1] was of interest to us since the antibacterial activities of various nitrofuran (2), nitropyrrole (3), nitrothiophene (3), and nitrobenzene (4) derivatives have been the subject of investigation in these laboratories for many years. We undertook the synthesis of some intermediates that might be useful for the preparation of *threo*-1-(5-nitro-2-furyl)-2-dichloroacetamino-1,3-propanediol, the nitrofuryl analog of chloramphenicol. The compound of primary interest in this regard was *threo*-1-(2-furyl)-2-amino-1,3-propanediol (IV).

Since Crooks (5) and Carrara and Weitnauer (6) have recently disclosed a synthesis of *threo*-1-phenyl-2-amino-1,3-propanediol, which we have observed independently, and which closely parallels the synthesis we have investigated in the furan series, we wish to present our findings.

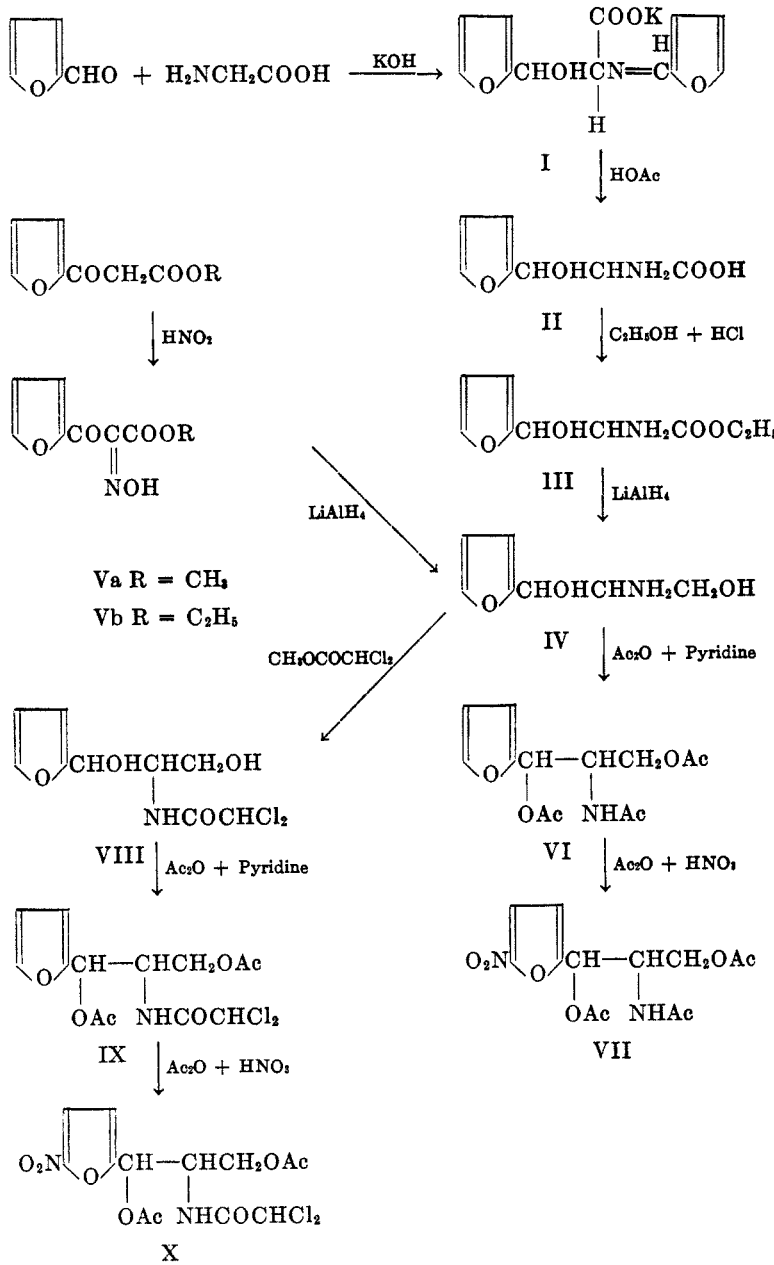
Our first approach to the preparation of 1-(2-furyl)-2-amino-1,3-propanediol was analogous to that used by Controulis, Rebstock, and Crooks (7) to prepare 1-phenyl-2-amino-1,3-propanediol. However, where they isolated a stable product from the condensation of benzaldehyde and 2-nitroethanol, we found that the reaction between 2-furaldehyde and 2-nitroethanol gave a hygroscopic, unstable product.

In view of the method of Karrer, *et al.* (8) for reducing amino esters to amino alcohols with lithium aluminum hydride, a search of the literature was made to see if β-(2-furyl)serine or its esters had been prepared. No reference was found, but the corresponding phenylserine had been prepared by the condensation of benzaldehyde with glycine in the presence of dilute alcoholic sodium hydroxide (9, 10). Furthermore, it was reported that this synthesis gave primarily one pair of optical isomers, the other stereoisomeric pair being present only in very small quantities (11).

In order to determine which isomer, *threo* or *erythro*, was produced by this synthesis, phenylserine was prepared, esterified, and reduced with lithium aluminum hydride. The 1-phenyl-2-amino-1,3-propanediol which was obtained melted at 86–87°, agreeing with the melting point reported by Controulis, *et al.* (7) for the desired *threo* isomer. The N-benzoyl derivative was also prepared, its melting point being in agreement with that of the corresponding compound prepared by Controulis (7). Carrara, *et al.* (6) have reported identical conclusions.

The condensation of benzaldehyde and glycine not only gives phenylserine but also yields varying amounts of 1,2-diphenyl-2-aminoethanol. The application of this reaction to other aldehydes and amino acids as a synthetic procedure for preparing either the substituted serines or the ethanolamines has been the

[1] Presented at the 115th American Chemical Society Meeting in San Francisco, March 27, 1949. Abstracts of papers—pages 9K, 10K.



subject of detailed investigation (12–24). However, these studies have led to no definite conclusions as to the general applicability of the reaction.

In addition to other aldehydes, Wilson and Reed (22) noted that 2-furaldehyde failed to react with glycine.[2] We found that 2-furaldehyde and glycine gave no

[2] Bergmann, Ensslin, and Zervas, *Ber.*, **58**, 1034 (1925) prepared the barium salt of N-furfurylideneglycine by condensing glycine and 2-furaldehyde in the presence of barium hydroxide in water.

β-(2-furyl)serine when dilute alcoholic sodium hydroxide or aqueous alkali was used, only decomposition taking place. When a cold mixture of 2-furaldehyde and glycine in alcohol was treated with a solution of potassium hydroxide in alcohol, complete solution resulted. When this solution was kept at 0–10° for one to three days, a solid (I) precipitated. A water solution of I when acidified with acetic acid gave an immediate precipitate of β-(2-furyl)serine with a concomitant liberation of furfural.

Analysis of the ethanol-insoluble intermediate (I) indicates that the reaction proceeds in an analogous manner to that of benzaldehyde and glycine (12).

When the reaction was run in methanol (in which I is very soluble), acidification with acetic acid gave no precipitate of furylserine. When the methanolic solution was diluted with twice its volume of isopropanol and allowed to stand in the refrigerator two more days the intermediate precipitated—although in much smaller yield. It was also observed that the longer the original reaction mixture stood the darker it became. The maximum yield was obtained after three-days' standing at a temperature of approximately 10°.

It is presumed that the furylserine obtained by this procedure belongs to the DL-*threose* series. This belief is based on the fact that the phenylserine obtained in this manner has been shown to belong to the DL-*threose* series.

The esterification of furylserine was accomplished by allowing the amino acid to stand at room temperature several days with alcoholic hydrogen chloride. Isolation of the amino ester hydrochloride by removing the solvent proved impracticable, since decomposition occurred readily. However, if the alcoholic amino ester hydrochloride solution was exactly neutralized with sodium alkoxide, the free amino ester was obtained in yields up to 73%. Ethyl furylserinate (III) is relatively stable, but does slowly decompose on standing, even in a desiccator. The oxalate salt is very stable, being unchanged after one-year's standing.

The purity of the furylserine, the concentration of the hydrogen chloride, the temperature of the esterification, and the period of time required for the isolation are all important factors in obtaining a good yield of the ester. In several runs where unrecrystallized furylserine was used, low yields of oily ester were obtained. When an alcoholic solution of furylserine was saturated with hydrogen chloride, decomposition occurred in a very short time. A satisfactory molar ratio of hydrogen chloride to amino acid was found to be 5:1. Several runs were made where the temperature of esterification was over 30° and no crystalline product was isolated.

The ethyl furylserinate (III) was reduced to 1-(2-furyl)-2-amino-1,3-propanediol (IV) in moderate yield by the method of Karrer, Portmann, and Suter (8). The aminodiol was isolated as the oxalate from which IV was obtained as a crystalline solid, m.p. 62.5–63.0°.

Prior to the development of the synthesis of IV *via* β-(2-furyl)serine, work was directed towards α-amination of furoylacetic acid esters, followed by reduction of the keto- and carbalkoxy-functions to hydroxyl groups. These are in part the syntheses of threonine from ethyl acetoacetate reported by Albertson, *et al.* (25) and Pfister, *et al.* (25a) applied to esters of furoylacetic acid. The yield of de-

sired furylaminopropanediol obtained by this method was so low that the procedure was abandoned, but a number of new furan derivatives were prepared for this work and they are reported here.

Ethyl 2-furoylacetate was treated with benzenediazonium chloride in buffered solution to yield ethyl α-phenylazofuroylacetate in excellent yield. This is essentially the method of Bülow and Neber (26) as applied to ethyl acetoacetate. Attempts to obtain ethyl α-acetaminofuroylacetate by reductive acetylation failed due to the difficulties of isolation in the presence of the by-product acetanilide.

Recourse was then made to oximation of ethyl furoylacetate, and also of the methyl ester, by the method of Wolff and Hall (27) for the preparation of ethyl α-oximinobenzoylacetate. The methyl (Va) and ethyl (Vb) oximinofuroylacetates were obtained in a state of analytical purity. On catalytic hydrogenation with palladium in acetic acid-acetic anhydride, Va readily absorbed two moles of hydrogen to give methyl α-acetaminofuroylacetate in good yield. This material was stable and readily purified.

Numerous attempts to hydrogenate selectively the ketonic carbonyl group of methyl α-acetaminofuroylacetate to yield methyl N-acetyl-β-furylserinate failed. Adams platinum oxide catalyst in various solvents was employed with careful control of the *p*H. This acetaminoketo ester readily absorbed two moles of hydrogen, rather than one, even when zinc and ferrous ions were used as catalyst inhibitors (28). The absorption of hydrogen did not proceed in a stepwise manner. No β-(2-furyl)alanine, which might result from complete reduction of the *beta*-carbonyl group, could be isolated after alkaline hydrolysis of the fully hydrogenated product.

It was thought it might be possible to reduce the esters of α-oximinofuroylacetate to the desired furylaminopropanediol by the action of lithium aluminum hydride. An ethereal solution of Vb was reduced with a large excess of lithium aluminum hydride and the reduction mixture worked up essentially by the procedure of Karrer, *et al.* (8) for reduction of serine esters. There was obtained a very small amount of an oxalate salt of melting point 226–227° (thrice recrystallized from water) which gave analytical results in close agreement with the anticipated oxalate of IV. This was identical with the material obtained by the reduction of ethyl furylserinate. Since the synthesis *via* furylserine showed greater promise at this time, no effort was made to improve this reduction of α-oximinofuroylacetic acid esters.

For introduction of the 5-nitro group in the furan nucleus of IV, protection of the oxidizable amino and hydroxyl functions of the side chain was deemed necessary. This was first done by N,O,O-triacetylation. Later, when difficulties were encountered on deacetylation of the nitrated product, the aminodiol was N-acylated with methyl dichloroacetate by the method of Controulis, Rebstock, and Crooks (7). This was then O,O-diacetylated to give a completely protected side-chain for nitration.

Nitration of both 1-(2-furyl)-2-acetamino-1,3-diacetoxypropane (VI) and 1-(2-furyl)-2-dichloroacetamino-1,3-diacetoxypropane (IX) went smoothly in good

yield employing the Kimel, Stillman, and Coleman (29) furan nitration procedure. Neither of the 5-nitro-2-furyl-derivatives could be induced to crystallize even after standing for six months. The viscous oils gave acceptable analytical data and showed ultraviolet absorption curves very closely related to the curves of a number of esters of 5-nitro-2-furfuryl alcohol (Figure 1).

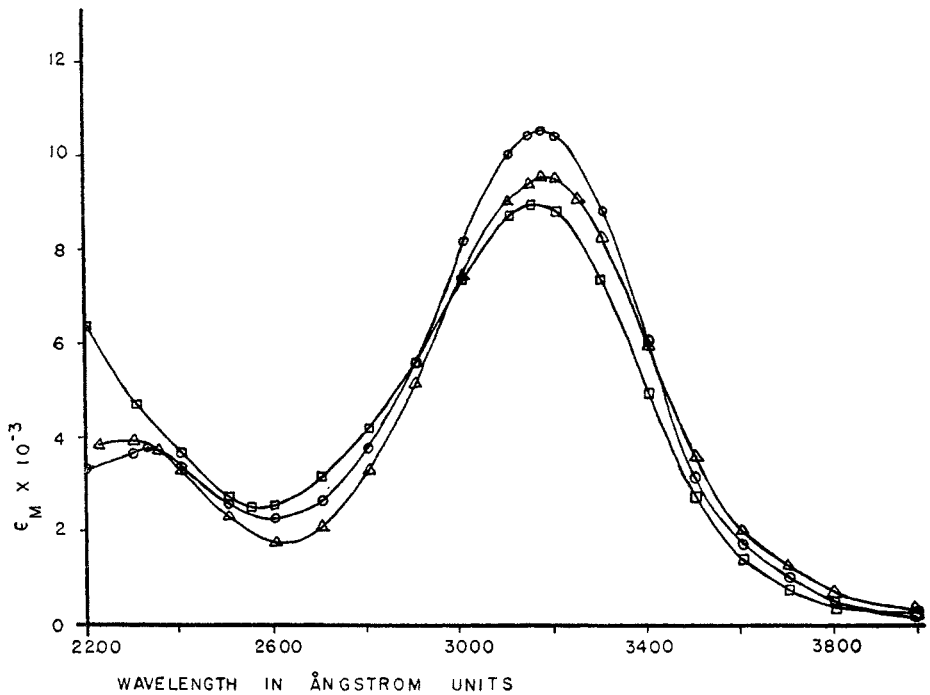


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA (in water) of 5-nitro-2-furfuryl acetate, —○—○—○—○—; and some *alpha*-substituted derivatives; VII, —△—△—△—△—; X, —□—□—□—□—

EXPERIMENTAL[3]

β-Phenylserine was prepared by the method of Erlenmeyer (9); yield, 42%; m.p. 194°.

Ethyl phenylserinate hydrochloride. Dry hydrogen chloride was passed into a refluxing suspension of 12.6 g. of anhydrous phenylserine in 70 ml. of absolute alcohol for three hours. The clear solution was left at room temperature for 18 hours and then cooled in an ice-bath. The crystals which separated were washed with ether. Concentration of the filtrate yielded more product. Total yield 15.5 g., 91%, m.p. 136–137°. Recrystallization from chloroform did not change the melting point.

Anal. Calc'd for $C_{11}H_{16}ClNO_3$: C, 53.76; H, 6.56; Cl, 14.44.

Found: C, 53.94; H, 7.02; Cl, 14.84.

1-Phenyl-2-amino-1,3-propanediol oxalate. A cooled solution of 0.33 g. (0.014 atom) of sodium in 10 ml. of methanol was slowly added to a cooled solution of 3.5 g. (0.014 mole) of ethyl phenylserinate hydrochloride in 10 ml. of methanol. The resulting precipitate of sodium chloride was filtered off and the methanolic filtrate concentrated to constant weight

[3] All melting points were taken on a Fisher-Johns apparatus. We are indebted to Messrs. J. Rigas, A. Caprio, and J. Corrado for the microanalyses.

in vacuo. The residue was taken up in 100 ml. of dry ether and filtered from a small amount of undissolved material. This filtrate was then added slowly to a refluxing solution of 1.8 g. (0.0426 mole assuming 90% purity) of lithium aluminum hydride in 75 ml. of dry ether. Refluxing was continued for 90 minutes and the mixture then was cooled and carefully treated with 8 ml. of water. The precipitate was thoroughly washed with ether. The solids were then extracted three times with 125-ml. portions of hot alcohol. Evaporation of the ethereal filtrate left a small amount of yellow oil. When a slight excess of alcoholic oxalic acid was added, 0.9 g. of a white precipitate was obtained. A similar treatment of the alcoholic filtrate yielded 0.5 g. of product. Total yield 1.4 g., 47%. When recrystallized from 50% alcohol the melting point was 217°.

Anal. Calc'd for $C_{10}H_{14}NO_4$: C, 56.59; H, 6.65.
Found: C, 56.33; H, 6.84.

1-Phenyl-2-amino-1,3-propanediol. A solution of 1.0 g. of 1-phenyl-2-amino-1,3-propanediol oxalate in 10 ml. of hot water was neutralized with 13.8 ml. of a 0.170 *M* solution of barium hydroxide. After the mixture was cooled and filtered, the filtrate was distilled *in vacuo* at room temperature to constant weight. The residue was taken up in 5 ml. of hot ethyl acetate, filtered, and the filtrate cooled. The 1-phenyl-2-amino-1,3-propanediol obtained weighed 0.48 g., 61%, m.p. 83–85°. Recrystallization from ethyl acetate raised the m.p. to 86–87°.

Anal. Calc'd for $C_9H_{13}NO_2$: C, 64.65; H, 7.83; N, 8.38.
Found: C, 64.32; H, 7.51; N, 8.60.

1-Phenyl-2-benzamino-1,3-propanediol. A solution of 1.0 g. (0.006 mole) of 1-phenyl-2-amino-1,3-propanediol in 10 ml. of water was mixed with 0.850 g. (0.006 mole) of benzoyl chloride. This mixture was adjusted to *p*H 12 by dropwise addition of a 20% sodium hydroxide solution. The solid which precipitated was recrystallized from chloroform and then from ethyl acetate, m.p. 165–166°.

Anal. Calc'd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16.
Found: C, 70.94; H, 5.94; N, 5.53.

β-(2-Furyl)serine (II). A mixture of 460 g. of redistilled 2-furaldehyde (4.8 moles), 180 g. (2.4 moles) of glycine, and 800 ml. of absolute alcohol (SDA #32[4]) was cooled to 3° in an ice-bath. A cold solution of 268 g. (4.8 moles) of potassium hydroxide (U.S.P.) in 1200 ml. of SDA #32 alcohol was added, with stirring, over a period of 70 minutes, keeping the temperature below 10°. The resulting pink solution was then allowed to remain at a temperature of 10° or lower for 24 hours. The precipitate which resulted was washed with alcohol. The filtrate, upon standing another 24 hours, deposited a little more solid. (In other runs it was necessary to let the reaction mixture stand for three days before complete precipitation occurred.) A sample of this intermediate dissolved in dry methanol and reprecipitated with absolute ethanol melted at 151–152° with decomposition. This compound rapidly absorbs carbon dioxide from the air.

Anal. Calc'd for $C_{12}H_{10}KNO_5$: C, 50.16; H, 3.51; N, 4.88; K, 13.61.
Found: C, 50.50; H, 3.43; N, 4.86; K, 13.43, 13.89.

This intermediate was dissolved in 750 ml. of water and acidified with 130 ml. of glacial acetic acid. The emuslion was diluted with 750 ml. of alcohol and cooled in an ice-bath for two hours. The precipitate which formed was washed with 250 ml. of alcohol; yield 196 g., 48%, m.p. 198–202°. Recrystallization from 50% alcohol raised the melting point to 207–208°.

Anal. Calc'd for $C_7H_9NO_4$: C, 49.12; H, 5.30; N, 8.19.
Found: C, 48.77; H, 5.01; N, 8.39.

2-Phenyl-4-furfurylidene-5-oxazalone. When furylserine was treated with benzoyl chloride in the presence of alkali (10) the azlactone was obtained, m.p. 170°.

Anal. Calc'd for $C_{14}H_9NO_3$: C, 70.29; H, 3.79; N, 5.86.
Found: C, 70.18; H, 3.65; N, 6.16.

[4] Absolute ethyl alcohol denatured with ether.

Ethyl β-(2-furyl)serinate (III). After many experiments involving effects of time of reaction, concentration, temperature, and purity of the starting material, the following procedure was selected as the most satisfactory.

A cold suspension of 51 g. (0.3 mole) of recrystallized furylserine in 650 ml. of SDA #32 alcohol was treated with 146 ml. of a 10.4 *N* solution of hydrogen chloride (1.5 moles) in SDA #32 alcohol and the reaction mixture was diluted to 850 ml. with SDA #32 alcohol. The acid dissolved rapidly and the solution was allowed to stand at room temperature for five days. It was then cooled in an ice-bath and neutralized with a cold solution of 35 g. (1.52 atoms) of sodium in 700 ml. of SDA #32 alcohol. The resulting precipitate of sodium chloride was removed and the filtrate concentrated to dryness at 4–5 mm., at a temperature not exceeding 35°. The residual solid was slurried with 100 ml. of dry ether and filtered. Yield 44.0 g., 73%, m.p. 75–76°. An analytical sample recrystallized from ether melted at 77–78°.

Anal. Calc'd for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03.
Found: C, 54.36; H, 6.40; N, 7.47.

The *oxalate* was prepared by mixing equimolar amounts of the ester and oxalic acid dissolved in absolute alcohol. Recrystallization from 75% alcohol gave a product melting at 141°.

Anal. Calc'd for $C_{11}H_{15}NO_8$: C, 45.67; H, 5.23; N, 4.84.
Found: C, 45.76; H, 5.23; N, 5.09.

1-(2-Furyl)-2-amino-1,3-propanediol (IV) *and oxalate.* Ethyl furylserinate (47.2 g.) was reduced with lithium aluminum hydride and the product was isolated as the oxalate in a manner analogous to that used with ethyl phenylserinate. Yield 23.7 g., 50%, m.p. 227–228°.

Anal. Calc'd for $C_8H_{12}NO_6$: C, 47.52; H, 5.98; N, 6.93.
Found: C, 47.83; H, 6.31; N, 6.67.

Treatment of the oxalate with the calculated amount of aqueous barium hydroxide, followed by filtration, evaporation of the filtrate, and recrystallization of the residual oil from ethyl acetate gave white crystals of IV, m.p. 62.5–63.0°.

Anal. Calc'd for $C_7H_{11}NO_3$: C, 53.51; H, 7.05; N, 8.91.
Found: C, 53.15; H, 6.86; N, 9.30.

Ethyl α-phenylazofuroylacetate. Ethyl 2-furoylacetate, b.p. 135–139° (12 mm.), prepared by the method of Barger, *et al.* (30), was treated at 0–5° with benzenediazonium chloride in an aqueous-alcoholic solution buffered with sodium acetate to give the phenylazo-derivative in 91% yield. Recrystallization from 1:2 aqueous ethanol raised the melting point to 67.0–67.5°.

Anal. Calc'd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93.
Found: C, 63.13; H, 5.49.

Methyl (Va) *and ethyl* (Vb) *α-oximinofuroylacetate.* Methyl 2-furoylacetate, b.p. 120–130° (8–9 mm.), prepared by the same method as the ethyl ester (30), was nitrosated by essentially the method Wolff and Hall (27) employed with ethyl benzoylacetate. Three-tenths mole (50.4 g.) of keto-ester in 150 ml. of acetic acid was cooled to 5–8° and treated with a solution of 21.5 g. of sodium nitrite in 30 ml. of water during one hour, keeping the temperature below 8°. The mixture was stirred with cooling for 1¾ hours after the addition and then poured into 500 ml. of ice-water and the product extracted with three portions of ether. After washing with water and drying, the ether was evaporated from the solution and the residual acetic acid removed by vacuum-distillation. The residual, orange oil was crystallized by stirring with 75 ml. of toluene. The solid was air-dried to constant weight, 44.5 g., 83%, m.p. 96–98°. This material, as well as the uncrystallized product, was of adequate purity for hydrogenation. For analysis a sample was recrystallized from ether-toluene and repeatedly from isopropyl ether to the constant melting point 125.0–125.5°.

Anal. Calc'd for $C_8H_7NO_5$: C, 48.73; H, 3.58; N, 7.11.
Found: C, 48.90; H, 3.47; N, 7.10.

The corresponding ethyl oximinoester was prepared by the same procedure. The crude,

oily product after removal of the extraction solvent was soluble in toluene so it was crystallized without a diluent. The ethyl α-oximinofuroylacetate was purified by decolorizing with charcoal in ether and precipitation with carbon tetrachloride; yield 59%, m.p. 133–135°. For analysis it was recrystallized from methanol-isopropyl ether (1:5), m.p. 133–135°.

Anal. Calc'd for $C_9H_9NO_5$: C, 52.18; H, 4.38; N, 6.76.

Found: C, 51.68, H, 4.70; N, 6.89.

Methyl α-acetaminofuroylacetate. Methyl α-oximinofuroylacetate (44.4 g., 0.225 mole) was dissolved in a mixture of 160 ml. of glacial acetic acid and 40 ml. of acetic anhydride. The oximino group was reductively acetylated, using 3.5 g. of Baker's 5% palladium-on-charcoal, employing the Parr-Burgess shaker at room temperature and 2–3 atmospheres of hydrogen. The hydrogen uptake tapered off at 95–105% of the theoretical two moles. The catalyst was filtered and the solvents removed by distillation *in vacuo*. The residual oil crystallized on stirring with 50 ml. of toluene to give 36 g. of white powder, m.p. 100–101°. Evaporation of the toluene followed by decolorization of the oil with charcoal in methyl acetate, and subsequent precipitation with toluene gave four more grams, m.p. 98–100°. Total crude yield was 79%. For analysis, the material was recrystallized from ethyl acetate-toluene (1:1), using Darco, to yield white needles, m.p. 103.0–103.5°. The mixture m.p. with unreduced oximino-ester was depressed. Further recrystallization from methanol-isopropyl ether (1:4), and from methyl acetate-isopropyl ether (1.5:2) raised the m.p. to 105.0–105.2°.

Anal. Calc'd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.93; N, 6.22.

Found: C, 53.33; H, 5.40; N, 5.89.

Lithium aluminum hydride reduction of ethyl α-oximinofuroylacetate. A large excess, because of polyfunctional reduction (31), of lithium aluminum hydride (12 g., 0.316 mole) was dissolved in 200 ml. of dry ether. Ethyl α-oximinofuroylacetate (10.6 g., 0.05 mole) was dissolved in 300 ml. of dry ether and added to the reducing agent during one hour. A solid precipitated and hydrogen was evolved. After refluxing for two hours the mixture was hydrolyzed and worked up essentially as was done by Karrer, *et al.* (8) in the reduction of serine esters. There was obtained a small amount (approx. 200 mg.) of a triply crystallized oxalate salt of m.p. 226–227° dec. This agreed in all respects with the oxalate obtained by reduction of furylserine ester. See above.

Anal. Calc'd for $C_8H_{12}NO_5$: C, 47.52; H, 5.98; N, 6.93.

Found: C, 47.47; H, 6.38; N, 6.82.

1-(2-Furyl)-2-benzamino-1,3-propanediol. For characterization purposes this amide was prepared. Shaking an aqueous solution of IV with a slight excess of benzoyl chloride and dilute sodium hydroxide gave a gummy solid. Extraction with chloroform and recrystallization from 15% ethyl acetate in isopropyl ether gave long white needles, m.p. 105–106°.

Anal. Calc'd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79; N, 5.36.

Found: C, 63.90; H, 5.48; N, 5.40.

1-(2-Furyl)-2-dichloroacetamino-1,3-propanediol (VIII). Unrecrystallized IV obtained from 9.05 g. (0.0488 mole) of its oxalate was heated at 90–100° with an excess of methyl dichloroacetate (12 ml.) for two hours, the liberated methanol being removed by distillation. The resultant brown solution was well shaken with two portions (100, 50 ml.) of low boiling petroleum ether which caused the product to crystallize. The tan crystals were extracted with 70 ml. of hot ethyl acetate-isopropyl ether (2:5), the extract decolorized with Norit, treated to incipient cloudiness while hot with isopropyl ether (20 ml.), cooled, and seeded. After collecting the first crop the filtrates were re-used to recrystallize the remainder of the crude amide. Yield 6.25 g., 52%, m.p. 84–86°. For analysis a sample was dissolved in an excess of chloroform, treated with Norit, and partially evaporated hot to give white crystals, m.p. 88.5–89.0°.

Anal. Calc'd for $C_9H_{11}Cl_2NO_4$: C, 40.32; H, 4.11; N, 26.45.

Found: C, 40.66; H, 4.17; N, 26.63.

1-(2-Furyl)-2-acetamino-1,3-diacetoxypropane (VI). The oxalate of 1-(2-furyl)-2-amino-1,3-propanediol (5.45 g., 0.027 mole) was converted to the free aminodiol as above. The

residual oil (4.24 g., 100% recovery) was treated with a warm mixture of 20 ml. of acetic anhydride and 20 ml. of pyridine. The temperature was held below 65° by cooling, after which the mixture stood for 11 hours, at which time it was heated on the steam-bath for two hours. The acetylating agents were removed by distillation *in vacuo*, leaving a light brown oil. The crude product crystallized after some time and was recrystallized by successive extractions with 200 ml. of ethyl acetate-isopropyl ether (1:20), yielding white crystals, 6.40 g., 83.5%, m.p. 91.5–92.5°. For analysis this material was recrystallized from ethyl acetate-isopropyl ether (1:5) using Norit; m.p. 92.0–92.5°.

Anal. Calc'd for $C_{13}H_{17}NO_6$: C, 55.11; H, 6.05; N, 4.95.

Found: C, 55.55; H, 5.90; N, 5.01.

1-(2-Furyl)-2-dichloroacetamino-1,3-diacetoxypropane (IX). 1-(2-Furyl)-2-dichloroacetamino-1,3-propanediol (2.68 g., 0.010 mole) was treated with a mixture of 5 ml. of acetic anhydride and 5 ml. of pyridine and heated at 100° for one hour. The acetylating materials were removed by vacuum-distillation and the product was crystallized by stirring with isopropyl ether. The crude product was recrystallized from chloroform-isopropyl ether (1:19), declorizing with Norit. Yield 2.85 g., 81%, m.p. 87.8–88.3°.

Anal. Calc'd for $C_{13}H_{15}Cl_2NO_6$: C, 44.33; H, 4.29; Cl, 20.14.

Found: C, 44.55; H, 4.50; Cl, 20.09.

1-(5-Nitro-2-furyl)-2-acetamino-1,3-diacetoxypropane (VII). 1-(2-Furyl)-2-acetamino-1,3-diacetoxypropane (8.5 g., 0.030 mole) was dissolved in 19 ml. of acetic anhydride. Meanwhile 22.5 ml. of acetic anhydride was cooled to 10° and 6.0 ml. of c.p. concentrated nitric acid (*d.* 1.42) was added slowly to the acetic anhydride with cooling to maintain the temperature below 25°. The first solution was then added to the nitrating agent during four minutes. The initial temperature was 15° but rose spontaneously and was kept at 40° by external cooling. The reaction was stirred at 40° for 30 minutes longer and was then cooled to 15°. Water (20 ml.) was added and the exothermic hydrolysis mixture was cooled. A 20% aqueous solution of trisodium phosphate was then added (190 ml.) to *p*H 3.90. Water (50 ml.) was added and the nitration intermediate was hydrolyzed by heating at 60° for one hour. After cooling, the nitrofuran was extracted with ethyl acetate (ten 50-ml. portions). The combined ethyl acetate extracts were washed with 20% sodium bicarbonate solution (four 30-ml. portions), then dried, and treated with Norit. The ethyl acetate was removed by distillation and the residual oil was pumped *in vacuo* at 80° for some hours.

The brown oil (5.8 g.) was extracted from a small amount of black tar by refluxing with ordinary ether (two 100-ml. portions). The yellow ethereal solution was treated with charcoal, the ether removed by distillation, and the yellow oil pumped *in vacuo* at 80–100° for one hour, yielding 3.75 g. Assayed by ultraviolet absorption, assuming a molecular weight of 328, $\epsilon^{3170\text{Å}}$ 9480.

The ether extraction was repeated using 400 ml. of absolute ether plus 12 ml. of absolute ethanol. The material could not be induced to crystallize; yield, 3.45 g. (29%) of a bright yellow, viscous oil, $\epsilon^{3170\text{A}}$ 9300.

Anal. Calc'd for $C_{13}H_{16}N_2O_8$: C, 47.56; H, 4.91; N, 8.53.

Found: C, 47.53; H, 5.15; N, 8.14.

1-(5-Nitro-2-furyl-2-dichloroacetamino-1,3-diacetoxypropane (X). 1-(2-Furyl)-2-dichloroacetamino-1,3-propanediol was nitrated and purified in the same manner as the triacetate above. The product could not be induced to crystallize. Assuming a molecular weight of 397, $\epsilon^{3170\text{Å}}$ 8930; yield 66–69%.

Anal. Calc'd for $C_{13}H_{14}Cl_2N_2O_8$: C, 39.31; H, 3.56; N, 7.05.

Found: C, 39.48; H, 3.69; N, 6.88.

SUMMARY

1. The synthesis of β-phenylserine by the condensation of benzaldehyde and glycine gives almost exclusively the *threose* form.

2. By condensing 2-furaldehyde and glycine in the presence of alcoholic po-

tassium hydroxide, β-(2-furyl)serine has been prepared for the first time. It, too, is presumed to belong to the *threose*-series. Esterification, followed by reduction with lithium aluminum hydride gave 1-(2-furyl)-2-amino-1,3-propanediol. The latter has been acylated and nitrated to give 1-(5-nitro-2-furyl)-2-acetamino-(and -2-dichloroacetamino)-1,3-diacetoxypropane.

3. Reduction of ethyl and methyl α-oximinofuroylacetate with lithium aluminum hydride also gave 1-(2-furyl)-2-amino-1,3-propanediol, but in poor yield.

NORWICH, NEW YORK

REFERENCES

(1) REBSTOCK, CROOKS, CONTROULIS, AND BARTZ, *J. Am. Chem. Soc.*, **71**, 2458 (1949).
(2) DODD AND STILLMAN, *J. Pharmacol. Exptl. Therap.*, **82**, 11 (1944).
(3) WARD AND DODD, *J. Bact.*, **56**, 649 (1948).
(4) Unpublished results.
(5) CROOKS, 2nd National Medicinal Chemistry Symposium, June 15, 1950, Notre Dame, Ind.; Abstracts, page 39.
(6) CARRARA AND WEITNAUER, *Gazz. chim. ital.*, **79**, 856 (1949) [*Chem. Abstr.*, **44**, 7268a (1950)].
(7) CONTROULIS, REBSTOCK, AND CROOKS, *J. Am. Chem. Soc.*, **71**, 2463 (1949).
(8) KARRER, PORTMANN, AND SUTER, *Helv. Chim. Acta*, **31**, 1617 (1948).
(9) ERLENMEYER, *Ber.*, **25**, 3445 (1892).
(10) ERLENMEYER AND FRÜHSTUCK, *Ann.*, **284**, 36 (1895).
(11) ERLENMEYER, *Ann.*, **307**, 70 (1899).
(12) ERLENMEYER, *Ann.*, **337**, 205 (1904).
(13) ERLENMEYER, *Ber.*, **28**, 1866 (1895).
(14) ERLENMEYER, *Ber.*, **29**, 295 (1896).
(15) ERLENMEYER, *Ber.*, **30**, 1525 (1897).
(16) ERLENMEYER, *Ber.*, **30**, 2896 (1897).
(17) ROSENMUND AND DORNSAFT, *Ber.*, **52**, 1734 (1919).
(18) ROSENMUND AND DORNSAFT, *Arb. pharm. Inst. Univ. Berlin*, **12**, 73 (1921).
(19) FORSTER AND RAO, *J. Chem. Soc.*, 1943 (1926).
(20) READ AND CAMPBELL, *J. Chem. Soc.*, 2674 (1930).
(21) GESELLSHAFT FÜR KÖHLENTECHNICK, German Patent 632,424 (1936).
(22) WILSON AND READ, *J. Chem. Soc.*, 1120 (1935).
(23) DALGLIESH AND MANN, *J. Chem. Soc.*, 658 (1947).
(24) DALGLIESH, *J. Chem. Soc.*, 90 (1949).
(25) ALBERTSON, TULLAR, KING, FISHBURN, AND ARCHER, *J. Am. Chem. Soc.*, **70**, 1150 (1948).
(25a) PFISTER, ROBINSON, SHABICA, AND TISHLER, *J. Am. Chem. Soc.*, **71**, 1101 (1949).
(26) BÜLOW AND NEBER, *Ber.*, **45**, 3732 (1912).
(27) WOLFF AND HALL, *Ber.*, **36**, 3612 (1903).
(28) BRAY AND ADAMS, *J. Am. Chem. Soc.*, **49**, 2101 (1927).
(29) KIMEL, STILLMAN, AND COLEMAN, U. S. Patent 2,490,006 (1949).
(30) BARGER, ROBINSON, AND SMITH, *J. Chem. Soc.*, 718 (1937).
(31) NYSTROM AND BROWN, *J. Am. Chem. Soc.*, **70**, 3738 (1948).