Summary

1. A simple general procedure for the preparation of volatile acid chlorides is described, involving the distillation of the desired acid chloride from a mixture of benzoyl chloride and an organic acid.

2. The procedure has been used in the preparation of twelve aliphatic acid chlorides with yields of 70–90%.

3. The mechanism of the reaction is discussed. No definite conclusions concerning the mechanism could be reached.

CHICAGO, ILLINOIS RECEIVED MARCH 24, 1938

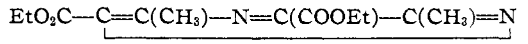
[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

A Synthesis of *dl*-Threonine

BY HOMER ADKINS AND E. WILKINS REEVE[1]

Rose and associates, after isolating *dl*-threonine from the hydrolysate of fibrin, showed the compound to be one of the stereoisomeric α-amino-β-hydroxybutyric acids.[2] West and Carter have synthesized these acids by adding mercuric acetate to crotonic acid in methanol, then brominating the product to give $CH_3CH(OCH_3)CHBr$-$COOH$. The latter compound was then ammonolyzed and hydrolyzed to $CH_3CHOHCHNH_2$-$COOH$.[3]

It appeared that the α-amino-β-hydroxybutyric acids could be made by nitrosating acetoacetic ester and then hydrogenating the resulting oximino-acetoacetic ester. However, when Winans[4] attempted to do this he obtained a pyrazine,



$$EtO_2C{-}C{=}C(CH_3){-}N{=}C(COOEt){-}C(CH_3){=}N$$

The formation of a pyrazine in the hydrogenation of an α-oximino ketone probably involves the reaction of an imino group. Whether an imine is formed in the hydrogenation of an oxime depends upon whether the first mole of hydrogen cleaves the oxygen to nitrogen linkage to give $R_2C{=}NH$, or adds to the carbon to nitrogen double bond to give $R_2CHNHOH$. There is evidence that the first reaction with an oxime is hydrogenolysis rather than hydrogenation. It seemed possible that if the ether, $R_2C{=}NOEt$, rather than the oxime were submitted to hydrogenation, the order of these reactions would be reversed.[5] Therefore the ethyl ether of α-oximino-acetoacetic ester was prepared and submitted to hydrogenation over Raney nickel. The reaction proceeded smoothly and rapidly to give ethyl α-amino-β-hydroxybutyrate without the formation of a detectable amount of the pyrazine.

The practicality of the method outlined above is indicated by the following facts. Acetoacetic ester was converted in over 65% yield to oximino-acetoacetic ester. The oximino ester was ethylated with diethyl sulfate to give a 40% yield of the ether, $CH_3C(O)C{=}(NOEt)COOEt$. The ether was hydrogenated within twenty minutes at 90–100°. The resulting hydroxyamino ester may be isolated by distillation, but better yields of the desired acids were obtained by hydrolyzing with boiling water the product of hydrogenation. The yield of α-amino-β-hydroxybutyric acids was 75%. The *dl*-threonine, m. p. 228°, then may be separated in over 50% yield from the stereoisomeric *dl-allo*-threonine, m. p. 252°, through the use of water and alcohol.

After the completion of the experiments referred to above, it was discovered that the proportions of products to be obtained by the hydrogenation of oximino-acetoacetic ester over Raney nickel, were determined by the pressure of hydrogen. For example when a hydrogenation was carried out at an initial pressure of 120 atmospheres, 2.2 moles of hydrogen per mole of oximino-acetoacetic ester was absorbed within about fifteen minutes, while with an initial pressure of 320 atmospheres, 2.8 moles of hydrogen was absorbed within ten minutes. These time intervals refer to the period from the beginning of a reasonably rapid hydrogenation, at about 40°, to the completion of reaction at about 70°. Similar comparisons were made for a maximum temperature of 80 and 90°.

The product isolated from the hydrogenation at the lower pressure was a pyrazine as observed by Winans. However, when the reaction product

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[1] This investigation was supported in part by a grant from the Wisconsin Alumni Research Foundation.

[2] McCoy, Meyer and Rose, *J. Biol. Chem.*, **112**, 283 (1935); Meyer and Rose, *ibid.*, **115**, 721 (1936).

[3] West and Carter, *ibid.*, **119**, 103 (1937).

[4] Winans and Adkins, THIS JOURNAL, **55**, 4169 (1933).

[5] Jones and Major [*ibid.*, **52**, 669 (1930)] obtained O-alkyl substituted hydroxylamines hydrochloride by the hydrogenation of O-alkyl substituted oximes over Adams platinum catalyst.

from the hydrogenation at the higher pressure was hydrolyzed with boiling water a 37% yield of α-amino-β-hydroxybutyric acid was obtained. More than a 50% yield of *dl*-threonine was obtained from this mixture of stereoisomers.

The difference between the products obtained at the two pressures is not due to the conversion of the pyrazine to the hydroxyamino ester at the higher pressure, because this reaction does not take place. The difference apparently depends upon the fact that in the more rapid hydrogenation, at the higher pressure, there is not sufficient time for the reaction of the intermediate imino ketone with another molecule before it is further hydrogenated to the hydroxyamino ester.

There is little difference, in over-all yield or purity of product, between the two methods given for the preparation of *dl*-threonine. The method in which oximino-acetoacetic ester is hydrogenated requires a higher pressure of hydrogen and necessitates submitting to hydrogenation almost twice as much material. It is probably not so satisfactory for the preparation of larger quantities of the amino acid for this reason and because the temperature control in the hydrogenation of large quantities of an oxime is difficult. The hydrogenation of oximes usually gives very poor yields of amines if the temperature is not maintained within narrow limits. However, the direct hydrogenation of the oxime has the advantage of avoiding the ethylation of oximino-acetoacetic ester. A purer grade of oximino-acetoacetic ester is needed for the direct hydrogenation than if it is to be converted to the ethyl ether before hydrogenation.

Ethyl Oximino-acetoacetate.—In a five-liter, three-necked flask, fitted with a thermometer, reflux condenser, and a mechanical stirrer, were placed 730 ml. (750 g., 5.8 mols.) of commercial ethyl acetoacetate, and 840 ml. of glacial acetic acid. The flask was cooled in an ice–salt bath, and a solution of 450 g. of 95% sodium nitrite in a liter of water was added over a period of approximately one hour, the temperature being kept at 25 to 35°. The mixture was then stirred for a half hour at 25°, three liters of water added, and stirring continued for two hours.

One quarter of the reaction mixture was placed in a two-liter separatory funnel and shaken with 350 ml. of ether. The bottom aqueous layer was run off and the next quarter of the reaction mixture placed in the separatory funnel and extracted with the same ether. This was repeated until all was extracted. This cycle was repeated twice using 200 ml. of ether each time. The ether extracts were combined, washed once with water, four times with sodium bicarbonate solution, and once more with water. The addition of sodium chloride was occasionally necessary to cause the layers to separate promptly. After drying the ether solution with sodium sulfate, the solvent was distilled off on a steam-bath at atmospheric pressure, and then for two hours at about 35 mm. The brown, liquid, impure ethyl oximino-acetoacetate, weighed 650 to 700 g.

The crude product was dissolved using 120 ml. of toluene per 100 g. of crude material and filtered. On cooling to −13 to −15° with stirring for one-half hour, crystals settled out. They were filtered, washed with a little cold toluene, and air dried overnight. A yield of 550 to 600 g., m. p. 57.5–58°, 63%, was obtained.[6] This material may be crystallized again from toluene, but 180 ml. of toluene should be used per 100 g. of material. From 100 g. there was obtained 90 g. of pure white material, m. p. 58–58.5°. If the toluene was distilled off on a hot-plate at atmospheric pressure, the oximino compound decomposed, sometimes violently. The mother liquor can be used for crystallizing the next batch of crude material or most of the toluene can be distilled off under reduced pressure on a steam-bath, and 50–60 g. more of material, m. p. 56°, obtained on cooling.

Ethyl O-Ethyl-oximino-acetoacetate.—A mixture of 477 g. (3 moles) of crystalline ethyl oximino-acetoacetate (m. p. above 55°), 462 g. (3 moles) of commercial diethyl sulfate, and 150 ml. of dioxane was stirred at room temperature (one-half hr.) until the ethyl oximino-acetoacetate had dissolved.

In a five-liter, three-necked flask fitted with an efficient reflux condenser, a thermometer, and an efficient stirrer were placed 150 ml. of water and 60 ml. of a solution of 120 g. of sodium hydroxide in a total volume of 600 ml. of water. This was heated to 90°, and then one-tenth of the oximino-acetoacetate solution was poured down the reflux condenser. The reaction was vigorous but the temperature was maintained easily at 75–90° by means of a water-bath which could be raised or lowered as required. The reaction was over in less than a minute and then another 60 ml. of the sodium hydroxide solution and one-tenth of the oximino-acetoacetic ester solution was added. Again there was a short vigorous reaction. This method of addition was kept up until 40% of each solution had been added, after which the respective materials were added in twice the former amounts. The total time of addition was ten minutes. After all was added, it was heated to refluxing with a free flame or by introducing steam directly into the reaction mixture, and refluxed three minutes. It was then cooled rapidly by adding 500 ml. of cold water and immersing the flask in cold water. The top layer was separated and washed once with a liter of cold water. Three hundred forty ml. was obtained, which on steam distillation gave 280 ml. of fairly pure product, which, however, still contained traces of diethyl sulfate and oximino-acetoacetic ester.

The 280 ml. of material was washed three times with cold 2% sodium hydroxide, cooling the mixture under cold tap water if necessary so it would not become warm. The alkali insoluble material (255 ml.) was refluxed with mechanical agitation with five times its volume of water for one-half hour. After cooling to room temperature and separating the layers, 244 ml. of material remained. This

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[6] Bouveault and Wahl, *Bull. soc. chim.*, [3] **33**, 559 (1905), report a melting point of 56° from pet. ether and ether.

was steam distilled, 228 ml. being obtained. The suspended water was allowed to settle out overnight, the bottom layer of ester drawn off and fractionated through a Widmer column. There was obtained 228 g., b. p. 96–98° (7–8 mm.), the yield being 40% of the theoretical. The ethyl O-ethyl-oximino-acetoacetate so obtained had the following properties: b. p. 110 (16 mm.), 97–98 (8 mm.); n^{25}D 1.4402; d^{25} 1.050; mol. ref. obsd. 46.96, calcd. 45.29; anal. for N_2, found 7.48 to 7.58, calcd. 7.49.

The semicarbazone melted at 160–160.5° (from alcohol or toluene), anal. for N_2 22.9 to 23.1%, calcd. 22.9%. Apparently the disemicarbazone of α,β-diketobutyrate is formed also but is separated easily because of its insolubility.

Hydrogenations.—The hydrogenations[7] were carried out in a steel vessel having a void of 270 ml., over 2 to 3 g. of Raney nickel. In general 25 g. of the oximino ester or 35 g. of its ether was dissolved in three times its volume of dry ethanol. Hydrogen was admitted to the vessel to a pressure of about 300 atm. and the vessel heated with shaking to 90° within about fifteen minutes. Reaction was complete with the oximino ester after about five minutes at 90°, while the ether required about twenty minutes at 90 to 100°. A somewhat longer time was required for reactions at lower pressures or temperatures. The vessel was then cooled to room temperature, the pressure released, and the catalyst removed by centrifuging. The reaction mixture was then worked up as indicated below for various compounds.

Ethyl α-Amino-β-hydroxybutyrate.—After the hydrogenation of 35 g. of ethyl O-ethyl-β-oximino-acetoacetate the alcohol was removed at 30–50 mm. and the desired ester distilled from a Claisen flask at 73–76° (1 mm). The yield was 75% of the theoretical. If distillation was not carried out rapidly at the lowest pressure available, using an oil-bath kept below 100°, then a considerable quantity of the corresponding diketopiperazine was formed. The ester may be obtained in a 37% yield in a similar fashion from the hydrogenation of the oximino-acetoacetic ester.

The ester so obtained was soluble in water, alcohol and benzene, and had the following properties: n^{25}D 1.4505; d^{25} 1.089; mol. ref. obsd. 36.31, calcd. 36.64; anal. for N_2, found 9.62, 9.65, calcd. 9.55. The material solidified to give the diketopiperazine on standing for a few weeks.

α-Amino-β-hydroxybutyric Acid.—The alcoholic solution obtained by the hydrogenation of the oximino ester or its ether (or the ethyl α-amino-β-hydroxybutyrate which had been separated by distillation) was added to 600 ml. of distilled water and boiled gently for four hours without a reflux condenser. The volume of the brown solution was then about 200 ml. It was cooled and any oil which separated out was discarded. The water was then removed by distillation at 30–35 mm. from a steam-bath until the weight of the residue was 30 to 40 g., depending upon whether 25 g. of the oximino ester or 35 g. of its ether had been hydrogenated. Dry ethanol (90 ml.) was then added slowly and the material stirred and allowed to stand for an hour at room temperature. If crystals did not separate immediately, the solution was cooled for a few minutes in an ice-bath and then allowed to stand for an hour at room temperature. The solid acid was then filtered off, washed with dry ethanol and dried in air. From 25 g. of the oximino ester was obtained 7 g. yellow crystals, m. p. 226° dec., a yield of 37% based upon the oximino-acetoacetic ester. From 35 g. of the ether of the oximino ester was obtained 16–17 g. of white crystals, m. p. 228–229° dec., a yield of about 75% based upon the ether of the oximino ester or 30% based upon the oximinoacetoacetic ester from which the ether was prepared in 40% yield.

Separation of *dl*-Threonine from *dl*-*allo*-Threonine.—Fifteen grams of the crude α-amino-β-hydroxybutyric acid in 25 ml. of water was heated on the steam-bath with occasional stirring for ten minutes. The mixture was cooled to room temperature and allowed to stand with occasional stirring for ten minutes, after which it was filtered on a Büchner filter and washed twice, each time with 1 ml. of water. The wash water was added to the main solution. By adding 100 ml. of dry alcohol slowly and with stirring to the filtrate, there was precipitated nearly pure *dl*-threonine. After standing for an hour in an ice-bath with occasional stirring, it was filtered off, washed with absolute alcohol, and dried. There was obtained 9 g. of white crystals, m. p. 228–229°, dec. The filtrate was discarded. *dl*-Threonine is about twice as soluble in warm water as is *dl*-*allo*-threonine.

The material which was insoluble in the water was mostly *dl*-*allo*-threonine. Five grams of crude material was obtained, m. p. 245 to 250°, dec. It was treated with 20 ml. of water and heated on a steam-bath for five minutes. Traces of insoluble material were filtered off, and the filtrate cooled, first to room temperature, and then in an ice-bath for several hours, during which time pure *dl*-*allo*-threonine slowly crystallized out. It was filtered, washed with 50% alcohol, and air dried. There was obtained 1.5 to 2 g., m. p. 252–3°, dec. The filtrate can be concentrated and more *allo*-threonine, slightly impure, obtained, and the crude α-amino-β-hydroxybutyric acid left in the filtrate thrown out with alcohol, and again submitted to purification. In the synthesis of West and Carter the two racemic mixtures were separated as the formyl derivatives of β-methoxy-α-aminobutyric acid.

The neutral equivalent of various samples of *dl*-threonine, m. p. 228–229°, and *dl*-*allo*-threonine, m. p. 250–252° (titrated in the presence of formaldehyde), varied from 121 to 120 as compared with a calculated value of 119.

2,5-Dimethyl-3,6-dicarbethoxypyrazine.—The mixture of products in alcohol of the hydrogenation of oximino-acetoacetic ester (25 g.) at 100–125 atm. at 80° was allowed to stand in air until the dark red color changed to yellow. (This oxidation of the dihydropyrazine to pyrazine may be brought about quickly by the addition of 9 g. of 30% hydrogen peroxide.) When the solution was cooled to −15° about 5 g. of the pyrazine, m. p. 84–85°,[8] separated out; after recrystallization from alcohol the m. p. was 87°.

Summary

A synthesis of *dl*-threonine has been described in which acetoacetic ester was nitrosated to oximino-acetoacetic ester, then ethylated and hy-

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(7) Adkins, "Reactions of Hydrogen," etc., University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 20, 31.

(8) Wleügel, *Ber.*, **15**, 1051 (1882).

drogenated to give a mixture of stereoisomeric α-amino-β-hydroxy acids which were separated into *dl*-threonine and *dl*-*allo*-threonine.

It has been found that oximino-acetoacetic ester reacts with hydrogen at 100 atm. to give a dihydropyrazine, while at 300 atm. pressure ethyl α-amino-β-hydroxybutyrate is the chief product.

The methods given make it possible to obtain *dl*-threonine in a 12 to 14% yield based on acetoacetic ester.[9]

[9] The freedom of *dl*-threonine from *dl*-*allo*-threonine is not adequately indicated by the m. p. of a sample. The complete separation and estimation of the proportion of the stereo-isomers can be made only through the use of biological assays.

MADISON, WISCONSIN RECEIVED APRIL 11, 1938

[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

Synthesis of Polycyclic Compounds from Dicyclohexenyl

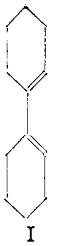
BY CH. WEIZMANN, ERNST BERGMANN AND T. BERLIN

Dicyclohexenyl (I), which is easily accessible through dehydration of cyclohexanone–pinacol, has been used for diene syntheses by Gruber and Adams[1] and by Barnett and Lawrence.[2] Further applications of this synthetic method are reported herein. The condensation product between (I) and maleic anhydride could be dehydrogenated to form phenanthrene-9,10-dicarboxylic acid anhydride,[3] while lead tetraacetate effected dehydrogenation of the middle ring exclusively, giving 1,2,3,4,5,6,7,8-octahydrophenanthrene-9,10-dicarboxylic acid anhydride.[4] With phenylmagnesium bromide, phenanthrene-9,10-dicarboxylic acid anhydride reacted normally, yielding 9-benzoylphenanthrene-10-carboxylic acid.[5] It is isomeric with the *o*-(9-phenanthroyl)-benzoic acid, described by Weizmann and co-workers.[6] Both substances could be cyclized to form the same 1,2,3,4-dibenzanthraquinone (II), when their acid chlorides were heated in decahydronaphthalene solution in the presence of traces of phosphoric oxide.[7] The quinone proved identical with the substance obtained by Clar[8] in a more tedious manner.

Cinnamic acid, on heating with dicyclohexenyl (I), formed the condensation product (III). This, when treated with selenium, was converted into 9-phenylphenanthrene, while dehydrogenation with sulfur resulted in 9-phenylphenanthrene-10-carboxylic acid, which had been obtained before by Koelsch.[9] It is known that selenium in the course of dehydrogenation reactions tends to remove carboxyl groups more than sublimed sulfur.[10]

For the preparation of 9-phenylphenanthrene, the above method seems to be much more convenient than those described by Koelsch[9] and by E. and F. Bergmann.[11]

The reaction of dicyclohexenyl (I) and quinone[2] or α-naphthoquinone, was reinvestigated, our results being slightly different from those of previous authors. The condensation with quinone, carried out in a sealed tube at 140°, gave the true addition product (IV) and a second substance, containing two (or four) hydrogen atoms less (*e. g.*, V). The hydrogen has been transferred to quinone molecules which could be recovered in the form of hydroquinone. The same holds true for the case of α-naphthoquinone. Besides α-naphthohydroquinone, two products have been ob-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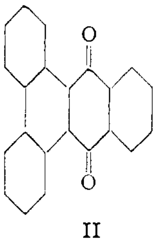

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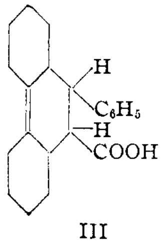

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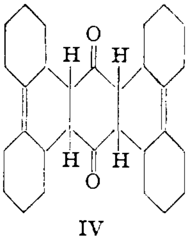

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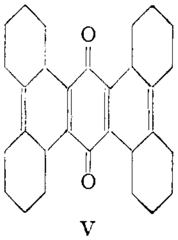

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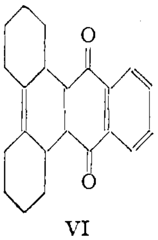

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(1) Gruber and Adams, THIS JOURNAL, **57**, 2555 (1935).

(2) Barnett and Lawrence, *J. Chem. Soc.*, 1104 (1935).

(3) The same product has been obtained recently through another method by Jeanes and Adams, THIS JOURNAL, **59**, 2608 (1937).

(4) Haworth and Richardson, *J. Chem. Soc.*, 633 (1935); 348 (1936); Haworth and Sheldrick, *ibid.*, 636 (1935); Haworth and Kelly, *ibid.*, 998 (1936).

(5) It has been described recently by Jeanes and Adams.[3]

(6) Weizmann and co-workers, *J. Chem. Soc.*, 1367 (1935).

(7) This method has been used before by Busso, Thesis, Berlin, 1930.

(8) Clar, *Ber.*, **62**, 350 (1929).

(9) Koelsch, THIS JOURNAL, **56**, 480 (1934).

(10) Compare Linstead, "Annual Reports," 1936, pp. 296, 304.

(11) E. and F. Bergmann, THIS JOURNAL, **59**, 1443 (1937).