Organic Syntheses

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of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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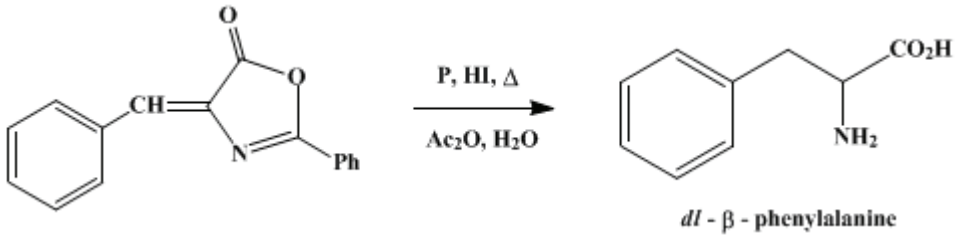
Organic Syntheses, Coll. Vol. 2, p.489 (1943); Vol. 19, p.67 (1939).

dl-β-PHENYLALANINE

[Alanine, β-phenyl-, *dl*-]

[(*A*) (*From the Azlactone of α-Benzoylaminocinnamic Acid*)]



dl - β - phenylalanine

Submitted by H. B. Gillespie and H. R. Snyder.
Checked by W. W. Hartman and J. B. Dickey.

1. Procedure

In a 1-l. three-necked, round-bottomed flask fitted with a reflux condenser, a mechanical stirrer, and a dropping funnel (Note 1) are placed 25 g. (0.1 mole) of the azlactone of α-benzoylaminocinnamic acid (Note 2) and (Note 3), 20 g. (0.64 gram atom) of red phosphorus, and 135 g. (125 cc.) of acetic anhydride. During a period of about one hour 195 g. (125 cc., 0.76 mole) of 50 per cent hydriodic acid (sp. gr. 1.56) is added with stirring (Note 4). The mixture is refluxed for three to four hours and, after cooling, is filtered with suction. The unreacted phosphorus is washed on the filter with two 5-cc. portions of glacial acetic acid, and discarded. The filtrate and washings are evaporated to dryness, under reduced pressure, in a 500-cc. Claisen flask heated in a water bath. A 250-cc. distilling flask cooled in ice is used as a receiver, and the distillate is reserved for a second reduction (Note 5).

To the dry residue in the Claisen flask 100 cc. of water is added, and the evaporation to dryness is repeated. The second distillate is discarded. To the residue in the flask 150 cc. of water and 150 cc. of ether are added, and the mixture is shaken until solution is complete. The aqueous layer is separated and extracted three times with 100-cc. portions of ether. The ether extracts are discarded; the water solution is heated on a steam bath with 2–3 g. of Norite and a trace of sodium sulfite until all dissolved ether has been removed. The solution is filtered, and the filtrate is heated to boiling and neutralized to Congo red with 15 per cent ammonia (sp. gr. 0.94). Usually about 25 cc. of ammonia is required. The phenylalanine separates in colorless plates which, when cold, are filtered and washed thoroughly on the filter with two 30-cc. portions of cold water. The yield is 10.5–11 g. (63.6–67 per cent of the theoretical amount) of a product which decomposes at 284–288°(corr.) (Note 6).

2. Notes

1. Clean corks protected by tin foil should be used.
2. This azlactone is prepared readily from benzaldehyde according to the procedure given for the azlactone of α-benzoylamino-β-(3,4-dimethoxyphenyl) acrylic acid (p. 55). From 53 g. (0.5 mole) of benzaldehyde, 89.5 g. (0.5 mole) of hippuric acid (p. 328), 41 g. of fused sodium acetate, and 153 g. of acetic anhydride there is obtained 78–80 g. (62–64 per cent yield) of an almost pure product melting at 165–166° (corr.). This material is sufficiently pure for use in the preparation of phenylalanine. By crystallization from 150 cc. of benzene a product melting at 167–168° (corr.) is obtained.
3. The reduction may be carried out by the same procedure starting from α-benzoylaminocinnamic acid, and in this way slightly higher yields are obtained. The azlactone may be converted into the free acid in the following way.
In a 12-l. flask fitted with a mechanical stirrer, 62.3 g. (0.25 mole) of the azlactone is suspended in 6 l. of water, and 11 g. (0.275 mole) of sodium hydroxide is added as a 10 per cent solution. The mixture is heated on the steam bath with stirring until solution is complete. This requires three to four hours. The

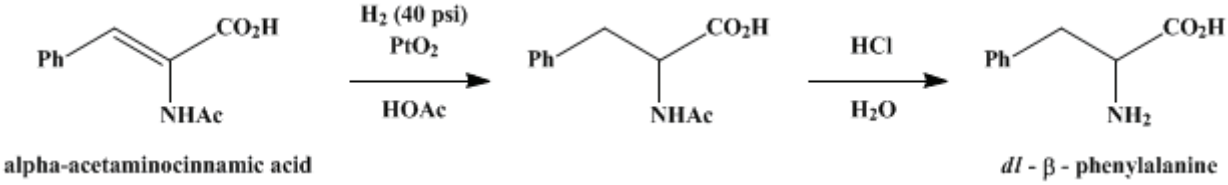
hot solution is filtered and acidified with hydrochloric acid. The α-benzoylaminocinnamic acid separates as white prisms in the hot solution, and when cold it is filtered. The yield is 55.5–64.5 g. (83–96.5 per cent) of almost pure product melting with decomposition over a two-degree range between the limits 224° and 236° (corr.). The crude acid can be recrystallized from alcohol, but its melting point remains unchanged.

4. During the addition the reaction mixture may solidify. If this occurs the stirrer is stopped and one or two portions of about 5 cc. of the hydriodic acid solution are stirred into the cake with a glass rod. The mass then becomes sufficiently fluid to permit use of the mechanical stirrer.

5. For a second run the distillate is placed in a 1-l. flask with 4 cc. of water, 25 g. of the azlactone, and 20 g. of red phosphorus. The mixture is refluxed for three to four hours and treated according to the above procedure. The yield is practically the same as in the first run.

6. The decomposition temperature is extremely variable and depends upon the rate of heating. The temperatures reported here were obtained by immersing the melting-point tube in a bath preheated to 200°, and then heating rapidly.

[(*B*) (*From α-Acetaminocinnamic Acid*)]



alpha-acetaminocinnamic acid

dl - β - phenylalanine

Submitted by R. M. Herbst and D. Shemin.
Checked by Reynold C. Fuson and E. A. Cleveland.

1. Procedure

A solution of 20.5 g. (0.1 mole) of α-acetaminocinnamic acid (p. 1) in 150 cc. of glacial acetic acid (Note 1) is placed in the bottle of a Burgess-Parr reduction apparatus, 0.5 g. of platinum oxide catalyst (Org. Syn. Coll. Vol. I, **1941**, 463) is added, and the mixture is shaken in an atmosphere of hydrogen under an initial pressure of 40 lb. per sq. in. until the calculated amount of gas is taken up; usually about two hours is required (Note 2) and (Note 3). When the reduction is complete, the catalyst is removed by suction filtration and washed with a little water. The combined filtrate and washings are evaporated to dryness under diminished pressure on a water bath.

The crystalline residue (Note 4) is taken up in 400 cc. of 1 *N* hydrochloric acid, transferred to a 1-l. flask fitted with a reflux condenser, and boiled for ten hours (Note 5). The resulting solution is evaporated to dryness under diminished pressure on the water bath; to the residue 100 cc. of water is added slowly through a dropping funnel at about the same rate as that at which it distils, in order to remove the excess hydrochloric acid as completely as possible. The residue is then taken up in 30–40 cc. of boiling water, and the *p*H of the solution is adjusted until it is basic to Congo red, but still acid to litmus, by careful addition of concentrated ammonia and acetic acid (Note 6). Then two volumes of 95 per cent alcohol is added to aid in the separation of the phenylalanine. The mixture is placed in the refrigerator for a day, after which the product is transferred to a Büchner funnel, and washed first with three 25-cc. portions of ice-cold water and then with alcohol. The yield is 14.5 g. The filtrate is evaporated to dryness under reduced pressure on the water bath, and the residue is extracted with about 70 cc. of ice-cold water in three or four portions. The insoluble material, after washing with 95 per cent alcohol, is added to the main fraction of phenylalanine. The total yield is 16 g. (Note 7).

The combined fractions weighing about 16 g. are dissolved in a minimum amount of boiling water (Note 8), two volumes of 95 per cent alcohol is added, and the flask is placed in a refrigerator overnight to complete crystallization. The phenylalanine is transferred to a Büchner funnel, washed with several small portions of ice-cold water, and finally with alcohol. The yield is 10.5–11 g. By concentrating the filtrate and washings further, 3–3.5 g. of product can be obtained conveniently. The total yield is 14–14.3 g. (85–86 per cent of the theoretical amount) of analytically pure phenylalanine.

2. Notes

1. It may be necessary to warm the mixture in order to dissolve the acetaminocinnamic acid completely in this amount of acetic acid. If so the solution should be allowed to cool to room temperature before it is placed in the reduction apparatus.
2. When the calculated amount of hydrogen is taken up, the catalyst is no longer colloidal and the rate of hydrogen uptake becomes very slow.
3. With freshly prepared and moist catalyst the benzene ring may also be reduced and N-acetylhexahydrophenylalanine formed. When this occurs, the hydrogen uptake continues at a rapid rate even after the amount required for hydrogenation of the side chain has been taken up. After recrystallization from water or dilute alcohol, the hexahydro compound forms needles melting at 178°.
4. Pure N-acetylphenylalanine can be obtained by recrystallizing the residue from hot water or from hot dilute alcohol; it forms colorless needles melting at 150–151°.
5. Hydrolysis with 1 *N* hydrochloric acid is not complete if less than ten hours is allowed. With higher acid concentrations the hydrolysis can be completed more rapidly.
6. When the solution is made just basic to Congo red, the product separates in an almost solid mass; addition of alcohol facilitates the testing of the *p*H by disintegrating the mass and also decreases the solubility of the product.
7. This product contains about 2.5 per cent of ammonium chloride; allowing for this the yield of phenylalanine is 94 per cent. Unless absolutely pure phenylalanine is required, the subsequent recrystallization can be omitted.
8. Phenylalanine dissolves rather slowly in boiling water. It is therefore convenient to start with an excess of water and to concentrate the solution over a free flame until crystals begin to separate from the hot solution.

3. Discussion

dl-Phenylalanine has been prepared by the action of ammonia and hydrogen cyanide on phenylacetaldehyde;[1] by the reduction of the oxime[2] or the phenylhydrazone[3] of phenylpyruvic acid; by the reduction of phenylpyruvic acid in alcoholic-ammoniacal solution;[4] by the reduction of α-aminocinnamic acid or its derivatives;[5] and by the action of ammonia on α-bromo-β-phenylpyruvic acid[6]—a procedure for which detailed directions are given in Org. Syn. **21**, 99.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 3, 705
- Org. Syn. Coll. Vol. 4, 80

References and Notes

1. Erlenmeyer and Lipp, Ann. **219**, 194 (1883).
2. Erlenmeyer, ibid. **271**, 169 (1892); Knoop and Hoessli, Ber. **39**, 1479 (1906); Shemin and Herbst, J. Am. Chem. Soc. **60**, 1951 (1938).
3. Feofilaktov and Vinogradova, Compt. rend. acad. sci. U.R.S.S. **24**, 759 (1939) [C. A. **34**, 1971 (1940)]; J. Gen. Chem. (U.S.S.R.) **10**, 255 (1940) [C. A. **34**, 7283 (1940)].
4. Knoop and Oesterlin, Z. physiol. Chem. **148**, 311 (1925).
5. Plöchl, Ber. **17**, 1623 (1884); Erlenmeyer, Ann. **275**, 15 (1893); Bergmann, Stern, and Witte, ibid. **449**, 280 (footnote) (1926); Harington and McCortney, Biochem. J. **21**, 854 (1927); Lamb and Robson, ibid. **25**, 1234 (1931).
6. Fischer, Ber. **37**, 3064 (1904).

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

red phosphorus

Congo red

azlactone of α-benzoylamino-β-(3,4-dimethoxyphenyl) acrylic acid

Azlactone of α-Benzoylaminocinnamic acid

alcohol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ammonia (7664-41-7)

Benzene (71-43-2)

ether (60-29-7)

acetic anhydride (108-24-7)

ammonium chloride (12125-02-9)

sodium acetate (127-09-3)

hydrogen (1333-74-0)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

hydrogen cyanide (74-90-8)

PHOSPHORUS (7723-14-0)

platinum oxide

benzaldehyde (100-52-7)

Norite (7782-42-5)

hydriodic acid (10034-85-2)

Hippuric acid (495-69-2)

α-Acetaminocinnamic acid,

acetaminocinnamic acid (5469-45-4)

Phenylpyruvic acid (156-06-9)

α-Benzoylaminocinnamic acid (1155-48-2)

phenylalanine (63-91-2)

N-Acetylhexahydrophenylalanine

N-Acetylphenylalanine (2018-61-3)

phenylacetaldehyde (122-78-1)

α-aminocinnamic acid

α-bromo-β-phenylpyruvic acid (42990-49-8)

DL-β-Phenylalanine,
Alanine, β-phenyl-, dl-,
DL-Phenylalanine (150-30-1)