A Simplified Method for the Preparation of N-Acetylphenylalanines

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synthetic Among various preparations of phenylalanine and its nuclearsubstituted derivatives the Erlenmeyer's azlactone method^{1,2}) seems to be the most accepted one. During the course of the study on the synthesis of aromatic amino acids by this method, a simple and practical procedure has been found in a step of the reductive cleavage of the azlactone ring to yield N-acetylphenylalanines. The application of this method to several azlactones is described in this communication.

It is well-known that benzoyl- or acetylglycine, when heated with aromatic aldehyde in acetic anhydride in the presence of fused sodium acetate as condensing catalyst, yields 2-phenyl- or 2-methyl-4benzal-5-oxazolone respectively. The route to N-acetylphenylalanines from the azlactones that has ever been utilized is as follows: neutral, alkaline or acidic hydrolysis of azlactones and subsequent hydrogenation of the resulting acetylaminocinnamic acids to acetylphenylalanines. The reducing agents which have been used for this conversion are: 1. Sodium^{3,4}) or sodium amalgam and water or ethanol. 2. Catalytic hydrogenation (Pt, Pd⁵⁾ or Raney nickel⁶⁾).

Since N-acetylphenylalanines were found to be susceptible to optical resolution^{7,8)} it seemed worthy to study to find a good and simple preparative method for these compounds.

Oxazolones were found to be easily reduced in a dilute aqueous solution of an equivalent amount of sodium hydroxide under pressure using Raney nickel catalyst. The reduction proceeded very smoothly at lower temperature and at the same time the cleavage of the azlactone ring occurred to form sodium salts of N-acetylphenylalanines during the course of hydrogenation. The reduction of the C=Cdouble bond may be facilitated by the presence of alkali which also naturally acts as hydrolyzing agent. By acidification of the reduction mixture with conhydrochloric acid N-acetylcentrated phenylalanines were readily obtained.

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TABLE I	
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N-ACETYL-B-(SUBSTITUTED PHENYL)-	-ALANINES
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Substituted Group	Yielda), %	m.p.b , $^{\circ}C$	Formula	C d Calcd.	% Found	H Calcd.	% Found	N Calcd.	% Found
none	98	144	$C_{11}H_{13}O_3N$	63.77	63.56	6.28	5.91	6.76	6.62
p -methyl	99	164	$C_{12}H_{15}O_{3}N$	65.16	65.65	6.79	6.81	6.33	6.04
p -methoxy	96	150	$C_{12}H_{15}O_4N$	60.76	60.71	6.33	6.29	5.91	5.69
3, 4-methylenediox	y 92	164—6	$C_{12}H_{13}O_5N$	57.37	57.31	5.18	5.17	5.58	5.51

a) Yields are based upon weight of crude product since in general no purification was required before hydrolysis or resolution.

b) Melting point of the analytical sample.

Four azlactones prepared from acetylglycine, benzaldehyde, tolualdehyde, anisaldehyde and piperonal by usual method were all converted in to the corresponding Nacetylphenylalanines in almost quantitative yield by the procedure described above. The results are summarized in Table I.

It was also found that 2-phenyl-5-oxazolone was very resistant to this hydrogenation unlike 2-methyl-5-oxazolone.

From the standpoint of preparation, the above procedure is characterized by excellent yield and readiness of operation.

Experimental

2-Methyl-4-benzal-5-oxazolone.—This azlactone was prepared according to Herbst's procedure⁵⁾.

2-Methyl-4-(p-methylbenzal)-5-oxazolone.— By analogous procedure given for 2-methyl4benzal-5-oxazolone this compound was prepared. The experimental conditions are as follows: a mixture of 165 g. of acetylglycine, 97.5 g. of fused sodium acetate, 250g. of freshly distilled p-methylbenzaldehyde, and 380 g. of 90 % acetic anhydride was warmed until the solution was complete. The resulting solution was then heated for one hour under reflux, cooled and placed in a refrigerator overnight. The brown solid mass obtained was digested with cold water. The yellow crystals melting at 133—135°C weighed 188 g. An analytical sample was obtained by recrystallization from chloroform and petroleum ether.

Anal. Found: C, 71.54; H, 5.42; N, 6.83%. Calcd. for $C_{12}H_{11}O_2N$: C, 71.64; H, 5.47; N, 6.96%.

2-Methyl-4-(*p*-methoxybenzal)-5-oxazolone. —A mixture of 54.4 g. of anisaldehyde, 38.6 g. of acetylglycine and 19.7 g. of anhydrous sodium acetate in 82 ml. of acetic anhydride was treated in the same manner. Thirty grams of yellow crystals with melting point of 114°C was obtained. The azlactone was recrystallized from chloroformpetroleum ether.

Anal. Found: C, 66.65; H, 5.26; N, 6.34%. Calcd. for $C_{12}H_{11}O_3N$: C, 66.36; H, 5.07; N, 6.45%.

2-Methyl-4-(3', 4'-methylenedioxybenzal)-5oxazolone.— With 37.5 g. of piperonal, 23.4 g. of acetylglycine, 12.3 g. of sodium acetate and 52ml. of acetic anhydride, 46.2 g. of the azlactone was obtained as yellowish crystals melting at 176— 180°C. An analytical sample was obtained by recrystallization from acetic acid and petroleum ether.

Anal. Found: N, 5.77%. Calcd. for $C_{12}H_9O_4N$: N, 6.06%.

General Procedure of Preparation of N-Acetylphenylalanines.-Four azlactones prepared as described above were all converted into the corresponding N-acetylphenylalanines in the following manner: one mole of the crude benzaloxazolone, an about five per cent. aqueous solution of an equivalent amount of sodium hydroxide and Raney nickel catalyst (as alloy, one tenth or one twentieth of the oxazolone used, by weight) were placed in a stainless steel autoclave. An initial hydrogen pressure of 40-70 atm. was applied and the apparatus was shaken at room temperature or, if necessary, at a higher temperature of 30-50°C. Hydrogen was absorbed rapidly in most cases. When, after 0.2-2 hours, one mole of hydrogen had been absorbed, the reaction was stopped and the catalyst was removed by filtration. The pH of the clear orangeyellow filtrate was adjusted to 2-3 with concentrated hydrochloric acid. After being kept overnight in an ice-box, the crystals were collected and washed with water. The crude products thus obtained could be recrystallized from hot water. Table I shows the results of yield, melting point and elementary analysis of four N-acetylphenylalanines.

Summary

A simple and practical procedure is described of preparing N-acetylphenylalanines by hydrogenation of the corresponding unsaturated azlactones in an aqueous sodium hydroxide solution with Raney nickel under pressure. By this method N-acetyl derivatives of phenylalanine, p-methylphenylalanine, p-methoxyphenylalanine and 3,4-methylenedioxyphenylalanine were synthesized in good yield.

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