

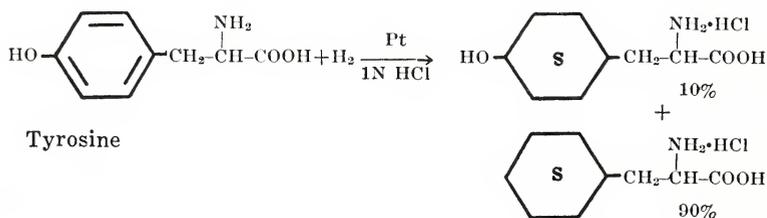
The Catalytic Hydrogenation of Tyrosine¹

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In connection with another research project we became interested in the catalytic reduction of tyrosine.

It was shown by Waser (2-6) and Karrer (1) that tyrosine could be hydrogenated by means of a platinum catalyst to produce a mixture of hexahydrotyrosine and β -cyclohexylalanine which is extremely difficult to separate.

Since we were interested in preparing β -cyclohexylalanine, the experiments of Waser and Karrer were repeated with the confirmation of their results. However, we were able to complete the hydrogenation in about an hour or less as compared to the two or three days as described by Waser (4). This difference was probably due to a difference in the activity of the two catalysts.



Because of the difficulty involved in obtaining pure β -cyclohexylalanine by the aforementioned procedure, a thorough study of the reaction was made. From this investigation a method was developed whereby both L(-)- or DL- β -cyclohexylalanine can be made quantitatively in a two hour period.

The fundamental difference between the two procedures is that Waser and Karrer used a 1 N. hydrochloric acid solution as the reaction medium whereas we employed a solution consisting of a 1.5-2 N. hydrochloric acid and ethyl alcohol.

The difference in the results may be due to the fact that the β -cyclohexylalanine hydrochloride, which is formed in the reaction, is insoluble in the hydrochloric acid solution while it is soluble in the alcohol-hydrochloric acid mixture. In the former case the amino acid salt probably precipitates on the surface of some of the platinum catalyst and as a consequence affects the efficiency of the catalyst.

Table I shows some of the experiments that were performed and the results that were obtained under various conditions.

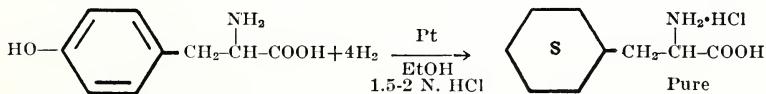
1. Contribution No. 624 from the Chemistry Department, Indiana University.

TABLE I

Moles of Tyrosine	Solvents Used	Theoretical Moles of H ₂	Actual Moles of H ₂	Time in Minutes	Type of Catalyst
0.055	155 ml. 1 N HCl	0.236	0.288	85	2 g. fresh PtO ₂
0.055	105 ml. 1.7 N HCl	0.229	0.220	70	1.1 g. fresh moist PtO ₂
0.044	138 ml. 1.1 N HCl	0.189	0.180	75	1.5 g. fresh moist PtO ₂
0.027	158 ml. 0.45 N HCl	0.118	0.106	25	0.75 g. fresh moist PtO ₂
0.055	50 ml. water 30 ml. 95% ETOH, 15 ml. Conc. HCl	0.227	0.227	120	0.75 g. fresh moist PtO ₂
0.083	100 m. water 50 ml. 95% EtOH 20 ml. Conc. HCl	0.3455	0.341	120	1.5 g. moist fresh catalyst

The theoretical moles of hydrogen are based on the hydrogen needed to reduce the tyrosine and the platinum oxide catalyst.

One of the major difficulties encountered in the synthesis of amino acids is that they are generally produced in the form of their hydrochloride salt from which they must be isolated. This is frequently one of the most troublesome steps of the synthesis when one is interested in securing a high yield. The β -cyclohexylalanine was no exception to the general rule. After trying the numerous methods customarily used for this purpose, with little success, a new approach was used in which lithium carbonate was employed to remove the hydrochloric acid.



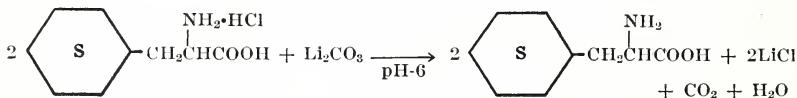
The advantage of the latter method is that the removal of the hydrochloric acid is quantitative due to the fact that the lithium chloride which is formed in the reaction mixture may be extracted with organic solvents leaving behind the precipitated amino acid free of any salts. In this manner a 95-98 per cent yield of the free amino acid can be obtained from the hydrochloric acid salt.

Numerous organic solvents were tried for this purpose including n-butyl alcohol, n-amyl alcohol, isoamyl alcohol, isopropyl alcohol, ethyl alcohol, and methyl alcohol. Of all those tried, a fifty per cent ethyl alcohol-water mixture was found to be the most effective.

The N-acetyl, N-benzoyl and N-phthalyl derivatives of L- β -cyclohexylalanine were prepared for characterization purposes. However, in many instances complete racemization occurred during the preparation of the benzoyl derivative.

Experimental

L- β -Cyclohexylalanine hydrochloride:—A solution consisting of 15 grams (0.083 moles) of L-tyrosine, 100 ml. of water, 50 ml. of 95% ethyl alcohol and 20 ml. of concentrated hydrochloric acid was prepared in a citrate bottle. One and twenty-five hundredths grams of moist platinum oxide was added and the mixture hydrogenated at 40-20 pounds per square inch. When the theoretical amount of hydrogen was absorbed the solution was decanted from the catalyst and evaporated to dryness at forty millimeters pressure between 60°C. and 70°C. The residue was treated with 100 ml. of water and again evaporated to dryness as before. The dried amino acid hydrochloride was placed in a vacuum desiccator over sodium hydroxide at one mm. pressure. The dried crude amino acid hydrochloride weighed 17.3 grams. No attempt was made to further purify this product.



L(+)- β -cyclohexylalanine:—Fifteen grams of the crude amino acid hydrochloride was dissolved in 200 ml. of 50 per cent ethyl alcohol-water solution which was heated to 95°C. The stoichiometric quantity of lithium carbonate was added to the vigorously stirred solution. The mixture was cooled slowly to room temperature and then placed in a refrigerator. The precipitate was filtered and washed with water until no test for the chloride ion could be obtained. When dried the β -cyclohexylalanine weighed 12.4 grams or 96.8 per cent of the theoretical amount. This product showed a rotation of $\alpha_{\text{D}}^{20} = +13.48$ when 1 g. of it was dissolved in 15 ml. of ethyl alcohol and 10 ml. of 4% hydrochloric acid. Anal. Calc'd for $\text{C}_6\text{H}_{11}\text{O}_2\text{N}$: N, 8.19% Found: N, 8.18%.

L(-)-*N*-Acetyl- β -cyclohexylalanine:—Ten grams (0.0585 moles) of 1- β -cyclohexylalanine was added to 100 ml. of twenty per cent sodium hydroxide in a 500 ml. flask at five degrees centigrade. Twenty-five milliliters of acetic anhydride was added to one half milliliter portions. The mixture was stirred mechanically, while the temperature was kept below ten degrees centigrade. Concentrated hydrochloric acid was added while the temperature was maintained below 10°C. until the pH of the solution was four. The precipitated acetyl derivative when filtered and dried at 100°C. weighed ten grams. Purified by recrystallization from ethyl alcohol it melted at 205-206° Corr. N. E. Calc'd: 213, Found 213. One gram dissolved in twenty milliliters of 95% ethyl alcohol at 25°C. gave an optical rotation of $\alpha_{\text{D}}^{25} = -3.68^\circ$.

L(-)-*N*-benzoyl- β -cyclohexylalanine:—Two grams of the 1- β -cyclohexylalanine was dissolved in 20 ml. of 1.0 N sodium hydroxide at 50°C.

Five grams of benzoyl chloride was added and the mixture stirred for twenty-five minutes. Thirty milliliters of 20 per cent sodium hydroxide was slowly added while the temperature of the solution was maintained at five degrees. The solution was acidified with hydrochloric acid and the residue filtered. The product was recrystallized from alcohol and water and melted at 122-124°C. Corr. Karrer (1) reported that the L(-) isomer melted at 124-125°. N. E. Calc'd 275, Found 278. Anal. Calc'd for $C_{16}H_{21}O_2N$, Found 5.14 nitrogen, Calc'd 5.10.

L(-)-N-Phthalyl-β-cyclohexylalanine:—Two grams of 1-β-cyclohexylalanine (0.117 moles) was mixed with 1.85 grams of phthalic anhydride in a test tube. The tube was inserted in an oil bath at 185°C. and the melt stirred with a glass rod. When bubbling ceased, the mixture was cooled and the solid removed from the test tube. The solid was recrystallized twice from a mixture of alcohol and water and dried over phosphorus pentoxide at 76°C. in vacuum. The melting point was 157-158°C. Corr. N. E. Calc'd 301, Found 301.

Summary

L-Tyrosine has been successfully hydrogenated to L-β-cyclohexylalanine hydrochloride, in quantitative yields using platinum as the catalyst. The time required was two hours as compared to several days by previous methods.

The L-β-cyclohexylalanine hydrochloride has been converted to the free amino acid in 96 per cent yields by the use of lithium carbonate and organic solvents.

L(-)-N-Acetyl-β-cyclohexylalanine, L(-)-N-benzoyl-β-cyclohexylalanine and L(-)-N-phthalyl-β-cyclohexylalanine were also prepared. The acetyl and the phthalyl derivatives have not been reported previously in the literature.

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