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The Photolysis of Phenylglycine and the Synthesis of α-Deuterated m-Anisaldehyde

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THE PHOTOLYSIS OF PHENYLGLYCINE

and

THE SYNTHESIS OF α-DEUTERATED m-ANISALDEHYDE

by

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is approved by

Alan L. Maycock

ABSTRACT

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The Photolysis of Phenylglycine.

Attempts were made to produce mandelic acid by irradiating phenylglycine in both acidic and basic aqueous solutions but no mandelic acid was detected.

The Synthesis of α-Deuterated m-Anisaldehyde.

Meta-methoxy-α-deutero-benzaldehyde was synthesized from m-methoxy benzaldehyde. The yield was quite low and only about 40% of the product was deuterated.

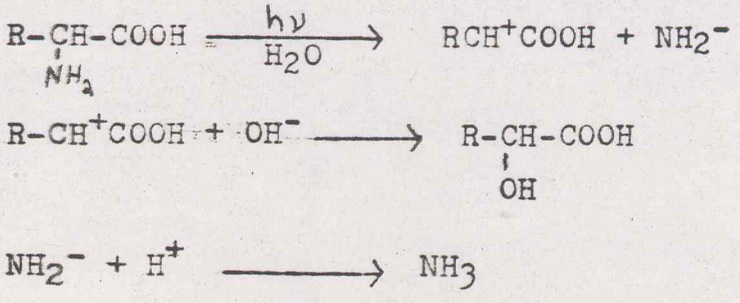
CONTENTS

Part I:

The Photolysis of Phenylglycine

INTRODUCTION

Weizmann, Hirshberg, and Bergmann(1) suggested that amino acids undergo photolysis in aqueous solutions according to the following mechanism:



$$R\text{-}\underset{NH_2}{CH}\text{-}COOH \xrightarrow[H_2O]{h\nu} RCH^+COOH + NH_2^-$$

$$R\text{-}CH^+COOH + OH^- \longrightarrow R\text{-}\underset{OH}{CH}\text{-}COOH$$

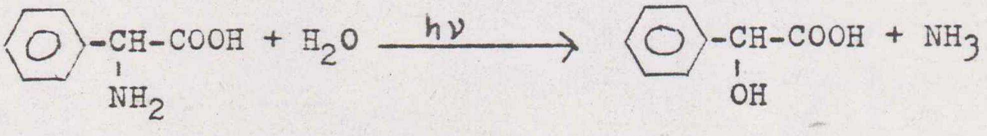
$$NH_2^- + H^+ \longrightarrow NH_3 \qquad (1)$$

They then verified this mechanism by showing that the photolysis of optically active aspartic acid produces a racemic mixture of 2-hydroxy-succinic acid.

Ground state studies on optically active 2-bromo-propanoic acid (2) have shown that this compound undergoes hydrolysis with retention in neutral solution, and hydrolysis with inversion in acidic or basic solution. Our work examines the photolysis of phenylglycine to determine whether it follows the mechanism suggested for amino acids, or the mechanism of the ground state hydrolysis of 2-bromo-propanoic acid.

DISCUSSION

We chose to investigate the photochemical solvolysis of phenylglycine in neutral, basic, and acidic aqueous solutions.



Phenylglycine Mandelic Acid

Although phenylglycine is not appreciably soluble in a neutral solution it is somewhat soluble in both acidic and basic solutions.

Weizmann, Bergmann, and Hirshberg (1) show that the photolysis rate of amino acids depends upon pH and is a minimum in neutral solutions. In a subsequent paper (3) they mention that phenylglycine undergoes photolysis in aqueous solutions (they do not specify products), but side reactions eventually lead to an insoluble coating on the quartz walls which blocks further reaction. However, in our study no mandelic acid was found in either the acidic or the basic solution.

From photolysis I (phenylglycine in a basic solution) the photolysis mixture was extracted with a mixture of $HCCl_3$ and toluene. The residue from this extract was tested by column and thin layer chromatography and was and was found to contain at least nine separate products, none of which were identified.

The photolysis mixture was neutralized in order to precipitate out any unreacted phenylglycine (there was none) and extracted with ether to remove any mandelic acid. The IR spectrum of the ether residue showed no carbonyl absorption.

In photolysis II (phenylglycine in acid solution) an unidentified black suspension (about 1 g) was formed during the reaction; however, this suspension could not have been mandelic acid, because mandelic acid is soluble in acid. The mixture was neutralized and unreacted phenylglycine was recovered. The photolysis mixture was extracted with ether to remove any mandelic acid, but the residue from the ether extraction was so small that an IR spectrum could not be taken. Since mandelic acid was not detected the project was abandoned.

CONCLUSION

The photolysis of phenylglycine in either acidic or basic solutions does not lead to the production of mandelic acid.

EXPERIMENTAL

Photolysis I-

Six and one half g (.043 mole) of phenylglycine dissolved in 240 ml of a .25M NaOH solution was irradiated in a quartz vessel using a Rayonet Photochemical Reactor containing a circular bank of 16 lamps emitting maximum radiation at 254 nm. After 46 hr the entire mixture was extracted with $HCCl_3$ and toluene. The residue from this extraction was tested by column chromatography (ether over silicic acid) and by TLC (ether, CCl_4, $HCCl_3$, MeOH, EtOH over silica gel 7G) and was found to contain at least 9 separate compounds.

The photolysis mixture was acidified with HCl to pH=8, but no phenylglycine was recovered. Finally the solution was extracted with ether. The IR spectrum from the ether residue showed no carbonyl absorption.

Photolysis II-

Approximately 2 g (.013 mole) of phenylglycine dissolved in 300 ml of HCl (pH<1) were irradiated at 254 nm for 44 hr. The mixture became dark brown and had a smell similar to cinimaldehyde.

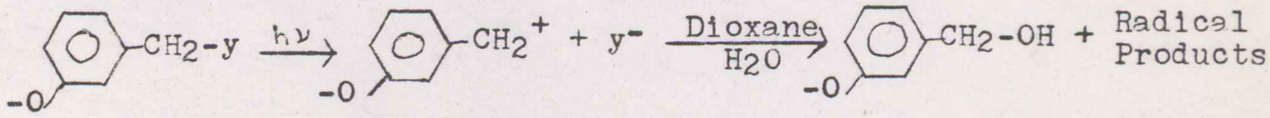
An unidentified black ppt was filtered off and the orange solution was treated with NaOH to pH~7.5. Phenylglycine (identity verified by IR) precipitated out and was removed by filtration. The solution was extracted with ether, and only a minute residue (not enough for an IR) was obtained upon evaporation of the ether layer.

Part II:

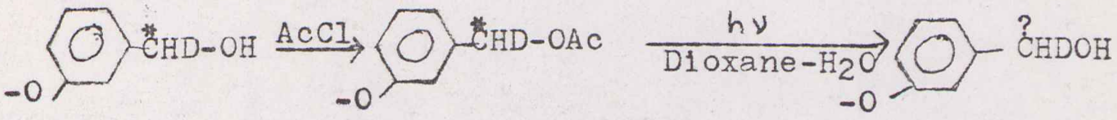
The Synthesis of α-Deuterated m-Anisaldehyde

INTRODUCTION

It was demonstrated by Zimmerman and Sandel (4) that benzyl derivatives bearing m-methoxy groups underwent photochemical solvolysis reactions. In contrast with ground state solvolysis, this reaction is aided by the m-methoxy group in the excited state (excited by hν).



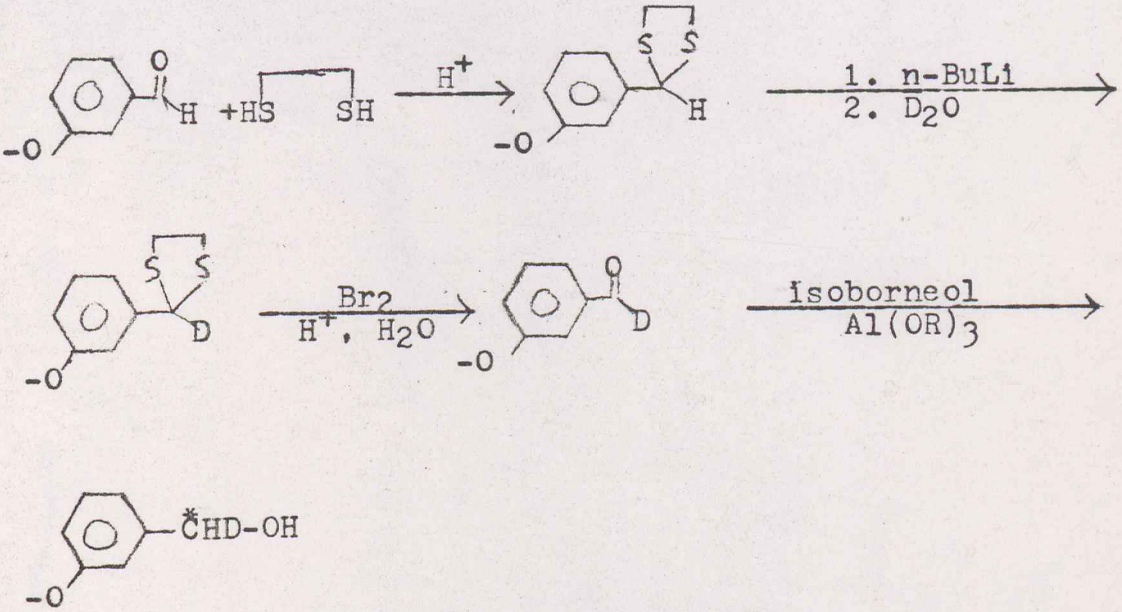
Zimmerman and Sandel theorized that this reaction proceeded via a carbonium ion intermediate. The proposed mechanism can be tested by photochemically solvolyzing optically active m-methoxy-α-deutero-benzyl acetate (II) to m-methoxy-α-deutero-benzyl alcohol (III) and then comparing the optical rotation of (III) to that of the optically active m-methoxy-α-deutero-benzyl alcohol (I).



I II III

DISCUSSION

In order to test Zimmerman and Sandel's mechanism we required optically active m-methoxy-α-deutero-benzyl alcohol. This study involves trying to synthesize that compound by the following sequence:



Upon treating the dithioketal with n-butyllithium (5) and then D_2O only 40-50% of it became deuterated (by NMR analysis). Two unsuccessful attempts were made to hydrolyze the dithioketal. Neither refluxing it in acidic water and ethanol, nor in dioxane, methanol, H_2O, and conc. HCl effected hydrolysis. After hydrolysis was completed through the Br_2 reaction (6), attempts were made to purify the deuterated aldehyde through formation of the bisulfite addition product, a process which was unsuccessful and which drastically reduced the yield. The recovered aldehyde showed only 25-35% deuterium incorporation (by NMR analysis).

The project has been completed up to the point where the m-methoxy-α-deutero-benzaldehyde has been synthesized.

EXPERIMENTAL

Preparation of the dithioketal of *m*-anisaldehyde-

Two hundred g (1.47 moles) of *m*-anisaldehyde, 142 g (1.51 mole) of ethanedithiol, and a few grams of *p*-toluene sulfonic acid were refluxed in benzene for 6 hr. The benzene was washed with aqueous NaOH (a small amount of CH_3OH and NaCl was used to aid in separating the layers) and then the aqueous layers were extracted with ether. The organic layers were combined, and dried with anhydrous $MgSO_4$. The solvents were removed and the product was distilled at 145-155°(1mm) to give 247 g (80%) of dithioketal as clear pale yellow oil; IR (neat): 775,s; 690,s; NMR (CCl_4-δ): 6.5-7.2 (4,m); 5.50 (1,s); 3.65 (3,s); 3.15-3.25 (4,d); Mass Spec (m/e): 212 (100), 184 (35), 183 (33), 169 (14), 153 (88), 152 (43), 151 (77), 149 (10), 121 (12), 109 (12), 108 (25), 105 (10), 77 (16), 65,(17), 63 (10), 51 (10), 45 (18).

Preparation of the dithioketal of *m*-methoxy-α-deutero-benzaldehyde-

The dithioketal (232 g, 1.1 mole) was dissolved in dry THF and cooled to -45° in an N_2 atmosphere. The reaction mixture was kept at -30 to -50° while 84 g (1.3 mole) of *n*-butyllithium (90% in hydrocarbon) was added dropwise. Thirty minutes after the evolution of gas had ceased, 36 g (1.8 mole) of D_2O was added at -10°. After sitting for a day the reaction mixture formed two layers. The top layer was removed and the solvent was evaporated. The bottom layer was extracted with ether, and then all organic materials were combined and washed will 4N NaOH followed by salt water. The ether was dried and removed to give about 200 g of 50% deuterated dithioketal (undistilled); IR (neat): essentially identical to IR of undeuterated dithioketal except for minor impurities; NMR (CCl_4-δ): essentially identical to NMR of undeuterated dithioketal except for minor impurities; the 5.50 singlet was about half its original size.

Preparation of m-Methoxy-α-deutero-benzaldehyde-

The dithioketal was combined with 500 cc of acedic acid, 200 cc of H2O, and 230 cc of conc. HCl. The mixture was heated to 45° whereupon 92 cc of Br2 dissolved in 400 cc of acedic acid was added dropwise. Then 200 cc of H_2O was added and the reaction was allowed to sit for a week at room temperature. The solution was treated with NaCl and extracted first with $HCCl_3$ and then with ether. The extractions were washed with base and dried. Finally, the partially deuterated m-anisaldehyde was distilled at 55-59° (1 mm) to give 14 g (11%); IR: identical to m-anis-aldehyde; NMR: identical to m-anis-aldehyde except that the 10.7 singlet was 2/3 to 3/4 its original size.

FOOTNOTES

1. Weizmann, Ch., *etal.*, "The Photochemical Deamination of Amino Acids in Water Solution. Part I," *Journal of the American Chemical Society 58*, 1675-1678 (1936).

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3. Weizmann, Ch., *etal.*, "The Photochemical Deamination of Amino Acids in Water Solution II," *Journal of the American Chemical Society 60*, 1799-1801 (1938).

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6. Weygand, F., Bestman, H., "Homologe α-Ketaldehyde Aus Carbonsauren," *Chemische Berichte 90*, 1230-1234 (1957).