[CONTRIBUTION FROM ABBOTT LABORATORIES]

Partial *para*-Migration in the Allylic Rearrangement of *o*-Acetamidophenyl Allyl Ether and of *o*-Aminophenyl Allyl Ether

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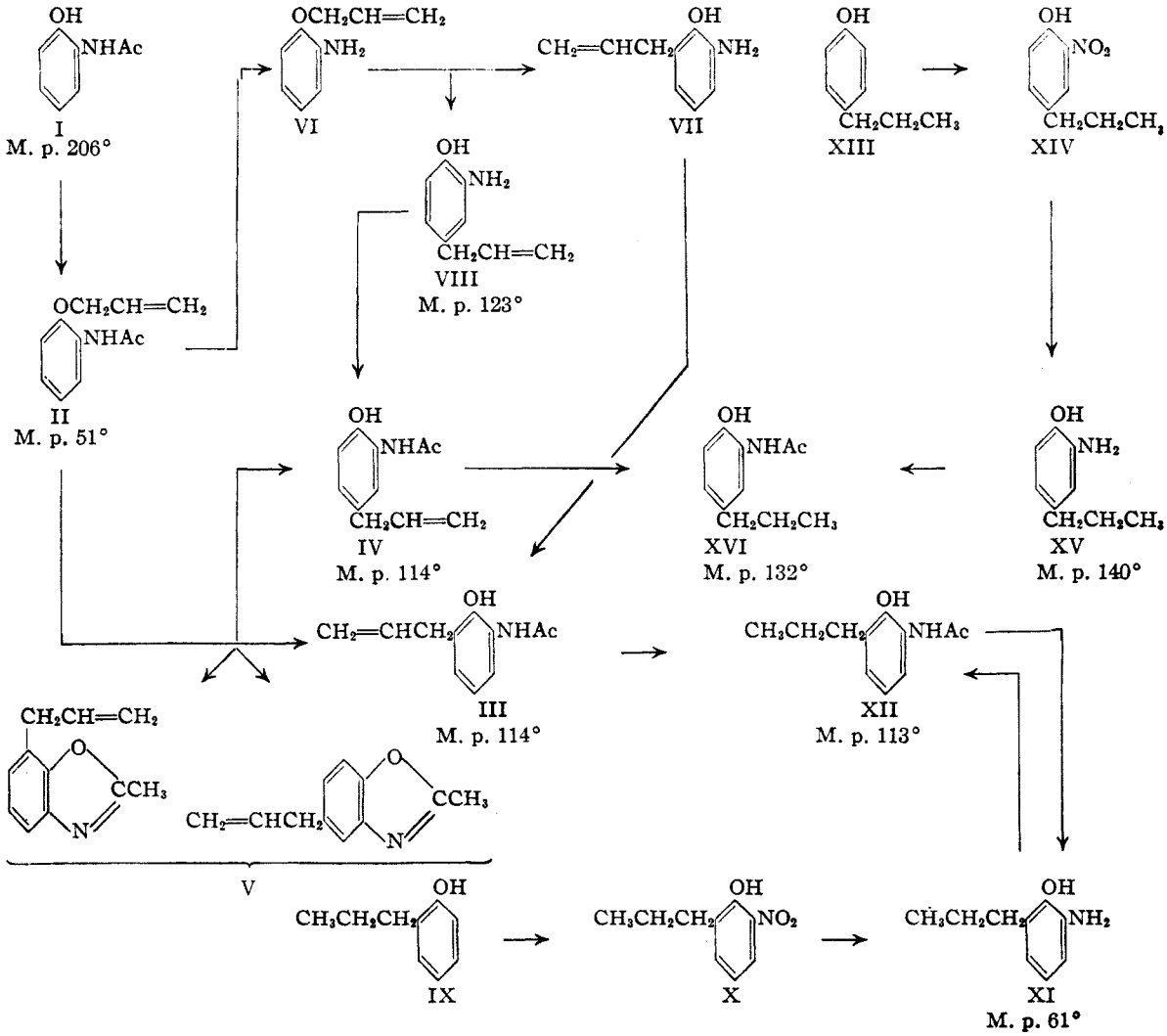
In the rearrangement of allyl ethers of phenolic compounds, the allyl group usually migrates exclusively to the *ortho* position if one is free, and the product is obtained generally in good yield.[2] The allylic rearrangement seemed, therefore, to provide a likely avenue for the synthesis of 2-amino-6-propylphenol (XI) which was required in connection with another problem. It was found, however, that the rearrangement of both *o*-acetamidophenyl allyl ether (II) and *o*-aminophenyl allyl ether (VI) gave products which were mixtures of the *ortho*- and *para*-rearranged isomers. Other examples of partial rearrangement to the *para* position are known[2] and it may be significant that each of these involves compounds containing strongly *ortho–para* directing groups, adjacent to the hydroxyl.

When *o*-acetamidophenyl allyl ether (II) was heated in dimethylaniline at 190° for thirty minutes, it was possible to isolate 50% of 2-acetamido-6-allylphenol (III) and 7.6% of the *para* isomer (IV) (*o* to *p* ratio = 6.5:1). Treatment of the acetamido compound at such elevated temperatures, however, also caused the loss of at least 10% of the product, probably by cyclization to 2-methyl-5-allyl-benzoxazole and/or the 7-allyl isomer (V).



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(2) Tarbell, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 8.

To avoid the loss through cyclization when the acetyl group was present, *o*-aminophenyl allyl ether (VI) was rearranged. When it was heated in diphenyl ether at 190° for forty minutes and the resulting mixture of aminophenols acetylated, 42% of III and 21% of IV were isolated (*o* to *p* ratio = 2:1). The acetylation of the amino group before the separation of the isomers could be carried out was made necessary by the extreme sensitivity of the aminophenols to air oxidation.

The isomeric acetamido allylphenols (III) and (IV) were reduced to their corresponding propyl derivatives (XII) and (XVI) and the structures of these two compounds proved by synthesis. *o*-Propylphenol (IX) was nitrated *ortho* to the hydroxyl to give X. The nitro group was reduced and the resulting aminophenol (XI) acetylated. The product was shown by mixed m. p. determinations to be identical with XII prepared through the allylic rearrangement. The same procedure beginning with *p*-propylphenol was used to confirm the structure of 2-acetamido-4-propylphenol (XVI).

Acknowledgments.—The author is indebted to Doctors M. A. Spielman and W. J. Close for their assistance and encouragement and to Mr. M. Freifelder for the hydrogenations reported. Furthermore, he wishes to thank Mr. E. F. Shelberg, Mrs. Jane Wood, and Messrs. B. F. Claeboe and R. H. Berg of the Microanalytical Laboratory for their coöperation in providing he microanalytical data.

Experimental Part

o-Acetamidophenyl Allyl Ether (II).—A mixture of 125 g. (0.82 mole) of *o*-acetamidophenol (I), 116 g. (0.82 mole) of anhydrous potassium carbonate, and 300 ml. of acetone was stirred vigorously to ensure intimate mixing. Then 100 g. (0.82 mole) of allyl bromide was added cautiously with stirring at a gentle reflux temperature. Refluxing and stirring was continued eight hours. About 800 ml. of water was added and the resulting mixture extracted with ether. The ether extract was washed with 10% aqueous sodium hydroxide, rinsed with water, dried, and concentrated to yield 156 g. (100%) of brown oil which crystallized completely, m. p. 49–51°. A sample recrystallized from pentane yielded white chalky crystals, m. p. 50–51.5°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.57; N, 7.24.

2-Acetamido-6-allylphenol (III) and 2-Acetamido-4-allylphenol (IV). Method A. Rearrangement of *o*-Acetamidophenyl Allyl Ether.—A solution of 95.5 g. (0.50 mole) of *o*-acetamidophenyl allyl ether (II) in 200 ml. of dimethylaniline was heated at 190° for thirty minutes.[3] The reaction mixture was dissolved in ether and extracted with excess 20% aqueous sodium hydroxide. The alkaline extract was neutralized and extracted with ether. The ether extract was washed with dilute hydrochloric acid, rinsed with water, treated with Norit, dried, and evaporated under reduced pressure. A light brown solid weighing 69.1 g. resulted. By repeated fractional recrystallization from benzene about 35 g. of III, m. p. 112–114°, was obtained. The filtrates were concentrated, seeded with IV and allowed to crystallize slowly. The solution yielded a mixture of dense granular crystals (IV) dispersed among light fluffy needles (III). These were collected, dried, mixed with pentane, and shaken vigorously. The needles (III) were largely held in suspension and were decanted from the denser crystals (IV). Shaking and decanting was repeated several times. The whole process was repeated until the separation of III and IV was essentially complete.

A total of 47.5 g. (50%) of III, m. p. 112–114°, was obtained. Recrystallization from benzene yielded fine white needles, m. p. 113–114°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.17; H, 7.01; N, 7.25.

A total of 7.3 g. (7.6%) of IV, m. p. 112–114°, was obtained. Treatment with Norit and recrystallization from 2:1 benzene–cyclohexane yielded white platelets, m. p. 113–114°; mixed m. p. with III, 85–100°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.15; H, 6.54; N, 7.33.

By fractionating the oil isolated from the original ether solution, 8.4 g. (10%) of material boiling at 94–96° (1.7 mm.), $n^{25}D$ 1.5444, was obtained. The analysis suggested that this was **2-methyl-5-allylbenzoxazole** and/or the **7-allyl isomer.**

Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.41; N, 8.10. Found: C, 76.07; H, 6.40; N, 8.29.

Method B. Rearrangement of *o*-Aminophenyl Allyl Ether (VI).—A solution of 14.9 g. (0.100 mole) of freshly distilled *o*-aminophenyl allyl ether (VI) (see below) in 30 ml. of diphenyl ether was heated to 190° in an oil-bath during fifteen minutes and maintained at 190–195° for thirty minutes under nitrogen. The reaction mixture was then dissolved in ether, extracted with 120 ml. of 1 *N* hydrochloric acid, and rinsed with water. The acid solution was treated with Norit, filtered and placed in a 1-liter three-necked flask equipped with a mechanical stirrer, two dropping funnels and a thermometer. With stirring and cooling to 20–25°, 15.3 g. (14.2 ml., 0.150 mole) of acetic anhydride and a solution of 17.6 g. (0.13 mole) of sodium acetate trihydrate in 20 ml. of water were added simultaneously over fifteen minutes so that the acetic anhydride was always in excess. Stirring was continued thirty minutes. The precipitate was collected, dissolved in ether, extracted with 40 ml. of 10% aqueous sodium hydroxide, and rinsed with water. The alkaline solution was made strongly acid and the brown oil which separated was extracted with ether. The ether solution was treated with Norit, dried, concentrated, diluted with Skelly B, and the precipitate collected. When dried it weighed 14.8 g. (77%). The two isomeric products were isolated in a manner similar to that described in Method A.

A total of 8.0 g. (42%) of III, m. p. 112–114°, was obtained. Recrystallization from benzene gave fine white needles, m. p. 113–114° and mixed m. p. with III from Method A, 113–114°.

A total of 4.1 g. (21%) of IV, m. p. 112–114°, was obtained. Treatment with Norit and recrystallization from 2:1 benzene–cyclohexane gave white platelets, m. p. 113–114° and mixed m. p. with IV from Method B, 113–114°.

***o*-Aminophenyl Allyl Ether** (VI).—A mixture of 114.6 g. (109.5 ml., 0.600 mole) of *o*-acetamidophenyl allyl ether (II) and 120 ml. of 6 *N* hydrochloric acid was refluxed for seventy minutes. The resulting solution was made alkaline with 20% sodium hydroxide solution and the red oil which separated was extracted with benzene. The benzene extract was washed with 10% sodium hydroxide solution, rinsed with water, dried, concentrated and fractionated to yield 81 g. (91%) of colorless oil, b. p. 84–85° at 0.6 mm., $n^{25}D$ 1.5628, which darkened on standing.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.44; N, 9.40. Found: C, 72.57, 72.70; H, 6.91, 6.99; N, 9.52.

2-Amino-4-allylphenol (VIII).—A solution of 18.0 g. (0.120 mole) of freshly distilled *o*-aminophenyl allyl ether (VI) in 100 ml. of diphenyl ether was heated at 185–190° for six hours under nitrogen. The precipitate which formed on cooling was collected and recrystallized repeatedly from an ether–Skelly B mixture. Only about 1 g. of product, m. p. 121.5–123°, was obtained. It was very sensitive to air oxidation.

(3) Water distilled out during this heating period. Such a loss of water supports the structure proposed for V.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H, 7.44; N, 9.40. Found: C, 72.80; H, 7.34; N, 9.54.

The acetyl derivative of VIII was prepared in the usual manner. Its m. p. was 112–113°, its mixed m. p. with III was 85–100°, and its mixed m. p. with IV was 112–113°.

2-Acetamido-6-propylphenol (XII).—To 19.1 g. (0.100 mole) of 2-acetamido-6-allylphenol (III) in 250 ml. of 95% ethanol was added 0.2 g. of platinum oxide. The mixture was reduced in twenty minutes at 25° and 2 atmospheres pressure, filtered, diluted with 800 ml. water and the product, 18 g. (94%), collected. Recrystallized from 50% ethanol, its m. p. was 112–113° and its mixed m. p. with XII prepared by the acetylation of 2-amino-6-propylphenol was 112–113°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.36; H, 7.69; N, 7.24.

2-Acetamido-4-propylphenol (XVI).—About 0.02 g. of platinum oxide in 75 ml. of 95% ethanol was reduced to platinum black. Then 1.91 g. (0.010 mole) of 2-acetamido-4-allylphenol was added and reduced in thirty minutes at 25° and 2 atmospheres pressure. The reaction mixture was filtered and evaporated to dryness and the residue was recrystallized from benzene, 1.6 g. (83%), m. p. 129–131°. Recrystallized from 60% ethanol, it yielded white needles, m. p. 130.5–132°.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.82; N, 7.25. Found: C, 68.42; H, 7.78; N, 7.16.

2-Amino-6-propylphenol (XI).—A mixture of 1.93 g. (0.010 mole) of 2-acetamido-6-propylphenol (XII) in 3 ml. of 6 *N* hydrochloric acid was refluxed for ninety minutes and the product worked up in the usual manner to yield 1.45 g. (77%) of pink platelets of the hydrochloride. The free base was liberated from 0.50 g. of the hydrochloride yielding 0.40 g. (99%) of white platelets, m. p. 60–61°, after recrystallization from ether and Skelly B. The product was very sensitive to air oxidation and was collected under nitrogen.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.54; H, 8.67; N, 9.27. Found: C, 71.48; H, 8.50; N, 9.47.

2-Nitro-6-propylphenol (X).—A solution of 20.4 g. (0.150 mole) of *o*-propylphenol in 20.4 g. (0.34 mole) of glacial acetic acid was added to a mixture of 40.8 g. (0.46 mole) of nitric acid (d. 1.42) and 61.2 g. (1.02 mole) of glacial acetic acid at −4 to −6° with stirring over a period of two hours. The reaction mixture was immediately poured with stirring onto 300 g. of ice. It was then extracted with benzene and the extract washed with water, 5% sodium bicarbonate, and finally with water. The brown benzene solution was steam distilled and the 3 liters of distillate extracted with benzene, dried, concentrated and vacuum distilled twice. The product was an orange oil, 7.0 g. (39%), b. p. 84–89° at 1.2 mm., $n^{25}D$ 1.5542.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.74. Found: C, 59.80; H, 6.03; N, 7.66.

2-Amino-6-propylphenol Hydrochloride (XIa).—A solution of 7.0 g. of 2-nitro-6-propylphenol in 150 ml. of absolute ethanol was hydrogenated over 1.5 g. of Raney nickel in one hour at 2 atmospheres pressure and at room temperature. The product was isolated in the usual manner. It weighed 6 g. (83%), m. p. 208° (dec.). A sample was converted in 91% yield to 2-acetamido-6-propylphenol (XII), m. p. 111–112°. The mixed m. p. with XII prepared by the reduction of 2-acetamido-6-allylphenol (III) was 111–112°.

2-Acetamido-4-propylphenol (XVI).—To a solution of 9.4 g. (0.050 mole) of 2-amino-4-propylphenol hydrochloride[4] in 15 ml. of water, 6.1 g. (0.060 mole) of acetic anhydride and a solution of 7.5 g. (0.055 mole) of sodium acetate trihydrate in 9 ml. of water, were added simultaneously over five minutes with stirring and cooling. Stirring was continued ten minutes and the product, 9.4 g. (97%), m. p. 130–133°, was collected and dried. A sample recrystallized several times from 60% ethanol melted at 131–132°. Its mixed m. p. with XVI prepared by the reduction of 2-acetamido-4-allylphenol (IV) was 130.5–132°.

Summary

1. The thermal rearrangement of *o*-acetamidophenyl allyl ether has been shown to yield 2-acetamido-6-allylphenol and 2-acetamido-4-allylphenol in the ratio of 6.5 to 1.

2. The thermal rearrangement of *o*-aminophenyl allyl ether has been shown to yield 2-amino-6-allylphenol and 2-amino-4-allylphenol in the ratio of 2 to 1.

3. Several *o*-amino and *o*-acetamido alkyl phenols have been prepared and their structures proved by synthesis.

(4) Baranger, *Bull. soc. chim.*, [4] **49**, 1213 (1931).

NORTH CHICAGO, ILLINOIS RECEIVED SEPTEMBER 8, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

The Synthesis of D-Fructomethylose by Biochemical Oxidation[1]

BY LAURENS ANDERSON[2] AND HENRY A. LARDY

Two organisms of the genus *Acetobacter*, *A. xylinum* and *A. suboxydans*, have been widely used in the carbohydrate field for the oxidation of the grouping —CHOHCHOHCH$_2$OH to —CHOHCOCH$_2$OH. By this method a considerable number of ketose sugars have been prepared from the corresponding alcohols. As is the case with many biochemical procedures the application of the method is limited to compounds of proper steric makeup. According to "Bertrand's rule,"[3] *A. xylinum* will attack those alcohols in which the configurations about carbons two and three are the same. Hann, Tilden and Hudson[4] suggested that *A. suboxydans* is specific in its ability to oxidize polyalcohols of D-configuration. While these generalizations appear to hold for "normal" sugar alcohols ($C_nH_{n+2}(OH)_n$) of five or more carbon atoms, the results obtained with alcohols having a terminal methyl group have been anomalous. Thus Votoček, Valentin and Rác[5] were unable to oxidize L-rhamnitol (I) with *A. xylinum*, and Müller and Reichstein[6] obtained only slight oxi-

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. This work was supported in part by the Research Committee of the Graduate School from funds supplied by the Wisconsin Alumni Research Foundation.

(2) Wisconsin Alumni Research Foundation Fellow, 1946–1947.

(3) Bertrand, *Compt. rend.*, **126**, 762 (1898); *Ann. chim. phys.*, [8] **8**, 181 (1904).

(4) Hann, Tilden and Hudson, THIS JOURNAL, **60**, 1201 (1938).

(5) Votoček, Valentin and Rác, *Coll. Czech. Chem. Commun.*, **2**, 402 (1930).

(6) Müller and Reichstein, *Helv. Chim. Acta*, **21**, 271 (1938).