

[CONTRIBUTION FROM THE PEDIATRIC RESEARCH LABORATORY OF THE JEWISH HOSPITAL OF BROOKLYN]

Synthesis of Derivatives of Diphenylethane Related to Materials Occurring Naturally. IV. Stilbene-2-acetic Acid

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In an earlier communication^{1a} the authors indicated the relationship between benzalphthalide and benzyloquinoline. In order to continue the study of this series, it was necessary to convert the previously synthesized stilbene-2-aldehyde to stilbene-2-acetic acid ($C_6H_5CH=CHC_6H_5CH_2COOH$).

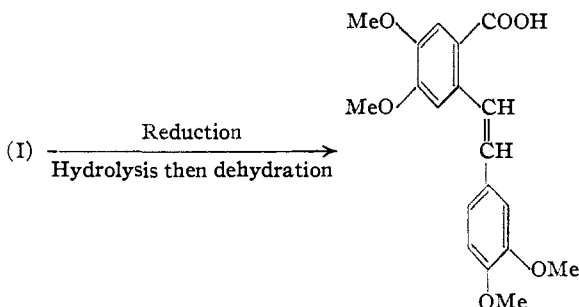
At first this was accomplished by the condensation of the aldehyde with hippuric acid, and the hydrolysis and oxidation of the resulting azlactone.

While studying the method for the hydrolysis of the azlactone, it was observed that the intermediate, *o*-styryl- α -benzamido cinnamic acid could be obtained in excellent yield with dilute barium hydroxide. This compound could be hydrolyzed and oxidized to stilbene-2-acetic acid by boiling with sodium hydroxide solution and then treating the resultant solution with hydrogen peroxide.

The yields of stilbene-2-acetic acid from the aldehyde through the azlactone were unsatisfactory. It was decided, therefore, to devise an alternate method of synthesis. The aldehyde was converted to the alcohol, then to the corresponding chloride and the latter to the cyanide. The cyanide yielded, on hydrolysis, stilbene-2-acetic

acid and some stilbene-2-acetamide. Although this process is lengthier, the over-all yield is better. Stilbene-2-acetamide hydrolyzes to stilbene-2-acetic acid and the amount of this material obtained depends upon the length of time of the hydrolysis.

In anticipation of the application of this method to the preparation of papaverine, itself, *m*-hemipinic anhydride was condensed with homoveratric acid to yield tetramethoxybenzalphthalide (I). Reduction of (I), hydrolysis and dehydration yielded tetramethoxystilbene-2-carboxylic acid.



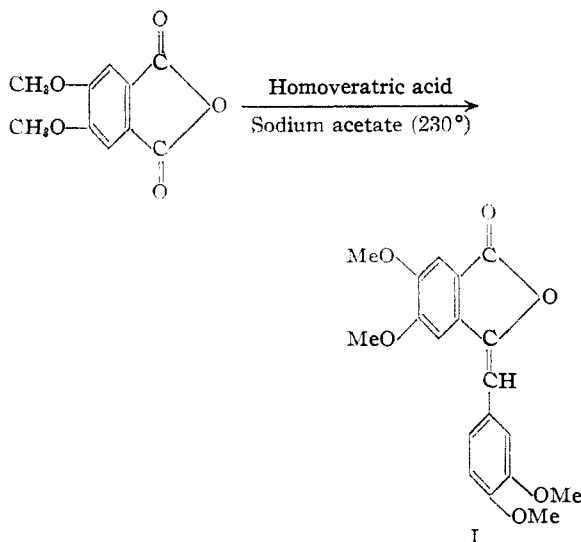
Preliminary attempts to convert stilbene-2-acetic acid to the lactone and then to the imide were unsuccessful. This imide, if obtained, could be converted to benzyloquinoline by reduction and dehydration. Attempts in this direction are being maintained.

Experimental

Stilbene-2-aldehyde.—This compound is prepared, essentially by the procedure described previously^{1a} with this improvement. 2-Stilbene-carboxylic hydrazide is prepared in about 60% yield by refluxing stilbene-2-carboxylic ester with 85% hydrazine hydrate (10% excess) with mechanical stirring for twenty hours. Any unreacted ester is recovered by extracting the reaction mixture with benzene. The residue is the hydrazide. On evaporating the benzene, the ester is recovered.

Before the 2-stilbene-carboxylic hydrazide is condensed with toluenesulfonyl chloride, it is made anhydrous by drying with benzene using a distillation trap of the type employed in determining moisture content of materials.

Stilbene-2-methyl Alcohol.—0.2 mole (41.6 g.) of stilbene-2-aldehyde is added to 1 liter of molar aluminum isopropylate in anhydrous isopropyl alcohol. The mixture is refluxed for one-half hour and slowly distilled until the distillate shows no test for acetone with 2,4-dinitrophenylhydrazine. The residue is poured into 1000 cc. of 10%



(1) Now in the armed forces of the U. S. A.

(1a) Natelson and Gottfried, *THIS JOURNAL*, **63**, 487 (1941).

sulfuric acid. The alcohol, which crystallizes in pearly plates, is filtered off, and recrystallized from dilute alcohol; yield 40 g.; m. p. 92–93°.

Anal. Calcd. for $C_{18}H_{14}O$: C, 85.71; H, 6.67. Found: C, 85.32; H, 6.72.

Stilbene-2-methyl Chloride.—Forty grams of stilbene-2-methyl alcohol is dissolved in 80 cc. of ether and 160 cc. of thionyl chloride (large excess) is added slowly with stirring and cooling. The mixture is refluxed for one-half hour; the ether and thionyl chloride are removed under vacuum. The residue is picked up in ether and washed well with water and dilute sodium bicarbonate. The mixture is dried over anhydrous sodium sulfate and vacuum distilled; yield 32 g., b. p. 170–185° (15 mm.).

Anal. Calcd. for $C_{18}H_{18}Cl$: Cl, 15.51. Found: Cl, 15.10, 15.30.

Stilbene-2-acetonitrile.—Seventeen grams of stilbene-2-methyl chloride, 4.5 g. of sodium cyanide dissolved in a minimum quantity of water, and 25 cc. of ethyl alcohol are refluxed for eight hours. The mixture is thrown into 200 cc. of water and extracted with ether. The ether is washed with water, dried over anhydrous sodium sulfate, and vacuum distilled, collecting from 200–210° (fifteen minutes). The distillate crystallizes; yield 10 g., m. p. 81–82°.

Anal. Calcd. for $C_{18}H_{13}N$: N, 6.39. Found: N, 6.38, 6.27.

Stilbene-2-acetic Acid. Method 1.—Ten grams of stilbene-2-acetonitrile is refluxed with 100 cc. of glacial acetic acid, containing 40 cc. of concentrated hydrochloric acid, for four hours. The mixture is poured into water and extracted with ether. The ether is extracted with sodium bicarbonate solution. The bicarbonate solution is then acidified. The precipitated acid is recrystallized from ligroin. White needles are obtained; yield 7 g., m. p. 105–106°.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 80.67; H, 5.93; neut. equiv., 238. Found: C, 80.24; H, 6.04; neut. equiv., 245.

Stilbene-2-acetamide.—The ether extract of the sodium bicarbonate solution was evaporated to dryness, and the residue treated with hot 10% sodium hydroxide to remove traces of the acid. The alkali insoluble portion was recrystallized from alcohol to yield white leaflets (2 g.), m. p. 152–153°. Hydrolysis of this product with glacial acetic acid and concentrated hydrochloric acid, as described for the nitrile, yielded stilbene-2-acetic acid.

Anal. Calcd. for $C_{18}H_{15}ON$: N, 5.90. Found: N, 5.83, 5.79.

Stilbene-2-acetic Acid. Method 2.—Twenty grams of sodium hydroxide in 200 cc. of water is added to 10 g. of stilbene-2-(benzamido)-acrylic acid. The solution is refluxed for eight hours, and treated at 0° with 10 cc. of 30% hydrogen peroxide (excess). The mixture is allowed to stand overnight in the refrigerator. It is then acidified and the mixture of stilbene-2-acetic acid and benzoic acid is recrystallized from dilute alcohol to remove the benzoic acid. The residue of stilbene-2-acetic acid is further recrystallized from benzene or ligroin; yield 2 g.; m. p. 105–106° (mixed m. p. with the product from method 1 showed no depression).

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 80.67; H, 5.93; neut. equiv., 238. Found: C, 80.48; H, 6.01; neut. equiv., 242.

***o*-Styryl- α -benzamidocinnamic Acid.**—2-Phenyl-4-*o*-styrylbenzylidene-5(4)-oxazolone (20 g.) from hippuric acid and stilbene-2-aldehyde (1), is mixed with 1000 cc. of water and 250 g. of hydrated barium hydroxide and heated at 85° with stirring for eight hours. The white barium salt is filtered off and washed several times with warm water. The free acid is obtained by boiling the barium salt with 100 cc. of alcohol and 20 cc. of concentrated hydrochloric acid mixture. The mixture is cooled, filtered, and the precipitate washed well with water. The acid is recrystallized from alcohol to yield a pale yellow crystalline powder; yield 13.6 g.; m. p. 199–202°.

Anal. Calcd. for $C_{24}H_{19}O_3N$: C, 78.03; H, 5.14; N, 3.79; neut. equiv., 369. Found: C, 78.41; H, 5.47; N, 3.90, 4.01; neut. equiv., 370, 376.

Tetramethoxybenzaldehyde.—Ten grams of *m*-hemipinic anhydride and 10 g. of homoveratric acid were mixed with 0.5 g. of anhydrous sodium acetate. The mixture was heated at 230° for two hours in an open flask. The mixture was cooled, broken up, dissolved in hot alcohol and filtered. The alcohol was allowed to cool, yield 10 g. of yellow crystals, m. p. 179–180°; soluble in glacial acetic, slightly soluble in hot alcohol, almost insoluble in cold alcohol.

Anal. Calcd. for $C_{19}H_{18}O_6$: C, 66.67; H, 5.26. Found: C, 67.01; H, 5.39.

Tetramethoxybenzylphthalide.—Ten grams of the tetramethoxybenzaldehyde was dissolved in 100 cc. of hot 20% sodium hydroxide and then diluted to a liter with water. The solution was cooled to room temperature, 2 g. of sodium, dissolved in 60 g. of mercury was added and the mixture was vigorously stirred for four hours. The solution was acidified and the separated tetramethoxybenzylphthalide was recrystallized from alcohol; yield 9.5 g., m. p. 146–148°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.28; H, 5.81. Found: C, 66.01; H, 6.00.

Tetramethoxystilbene-2-carbonic Acid.—Ten grams of tetramethoxybenzylphthalide was dissolved in 200 cc. of ethyl alcohol containing 3 g. of potassium hydroxide. The mixture was slowly evaporated to dryness on a hot-plate. The temperature was raised to 180° and kept there for one hour. The residue was dissolved in water, filtered and acidified. The tetramethoxystilbenecarbonic acid obtained was recrystallized from alcohol, m. p. 209–211°; yield, 7 g.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.28; H, 5.81. Found: C, 66.47; H, 5.97.

Summary

Stilbene-2-acetic acid and tetramethoxystilbenecarbonic acid, proposed intermediates for the preparation of benzylisoquinoline and papaverine, respectively, have been prepared.