For economy of space in publication, the details of the isolation and identification of the hydrogenation products have not been submitted. A brief outline of the method follows.

When nickel was used for the hydrogenation of aryl esters, part of the acid formed reacted with nickel and was recovered from the salt by alkaline extraction, followed by acidification.

The hydrogenation products were separated with a Widmer column containing a glass helix 11 cm. in length with nine turns. Small fractions were in some cases further purified by redistillation through a column 19 cm. long with an inside diameter of 0.5 cm. and with a nichrome wire helix (two turns per cm.) fitted snugly inside the column. Both columns were jacketed.

All of the products except esters and saturated hydrocarbons were identified by the preparation of known solid derivatives and the determination of mixed melting points with authentic samples. The saturated hydrocarbons were identified by boiling points, densities and refractive indices. The esters were identified by saponification equivalents, densities, refractive indices and the preparation of known solid derivatives of the hydrolytic products.

The yields quoted in Table I include not only the pure product isolated, but also the amount present in intermediate fractions. For example, in a fraction containing acid and ester, the identity of the components was shown by the preparation of solid derivatives of the hydrolytic products. The amounts of acid and ester were then determined by neutralization and saponification equivalents and these data included in calculating the total yield. These results were usually checked by refractive indices, which were also useful in the examination of the hydrocarbon fractions.

Summary

The esters of phenol ($RCOOC_6H_5$) are converted to alcohols (RCH_2OH) and cyclohexanol over copper chromite. Over nickel, three reactions may occur: (1) formation of cyclohexyl esters ($RCOOC_6H_{11}$), (2) cleavage in a different manner than that observed over copper chromite, giving an acid (RCOOH) and cyclohexane, and (3) cleavage similar to that obtained over copper chromite. Of these, the last was unimportant except in the case of a lactone and of phenyl benzoate. The formation of cyclic ethers from coumarins previously reported cannot be attributed to the character of coumarins as aryl esters.

PHILADELPHIA, PENNA. RECEIVED NOVEMBER 12, 1940

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

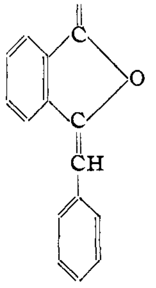
Synthesis of Derivatives of Symmetrical Diphenylethane Related to Materials Occuring Naturally. III. The Relationship between Benzalphthalide and the Benzylisoquinoline Alkaloids

BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED

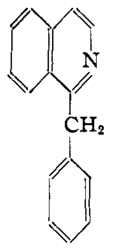
While studying the structure of benzalphthalide in the further attempt to use it as a starting material in the synthesis of biologically important compounds, it became apparent that certain derivatives of benzalphthalide, in addition to being related to the sterols, are also structurally linked to the benzylisoquinoline alkaloids. With this relationship in view, it was decided to attempt to prepare various derivatives of benzylisoquinoline, and eventually papaverine itself.

An examination of the structure of benzalphthalide shows that its conversion to a benzylisoquinoline derivative involves adding one more carbon to the five-membered heterocycle and replacing the oxygen by nitrogen.

This can be accomplished in two ways: first by building up the carbon chain and replacing the oxygen by nitrogen, second by replacing the oxygen by nitrogen and then building up the carbon chain. Both methods were attempted.



Benzalphthalide



Benzylisoquinoline

In the first method, the benzalphthalide was converted to 2-stilbene carboxylic acid by reduction and dehydration, applying and improving the method of Gabriel.[1] This procedure was described in the first paper of this series.[2] The method of Sonn and Müller[3] which was used to prepare *o*-β-phenethylbenzaldehyde (2) was found

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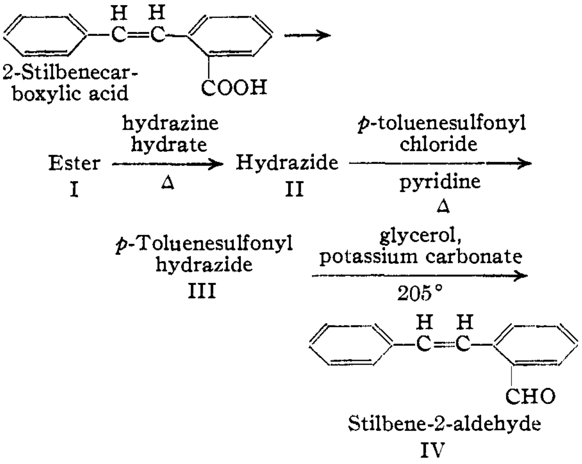
[1] Gabriel and Posner, *Ber.*, **27**, 2506 (1894).

[2] Natelson and Gottfried, THIS JOURNAL, **58**, 1432 (1936).

[3] Sonn and Müller, *Ber.*, **52**, 1927 (1919).

to be inapplicable in the case of the attempted reduction of 2-stilbene carboxylic acid to stilbene-2-aldehyde, the double bond evidently interfering. This readily reducible double bond also interfered with other standard methods of converting an acid to an aldehyde.

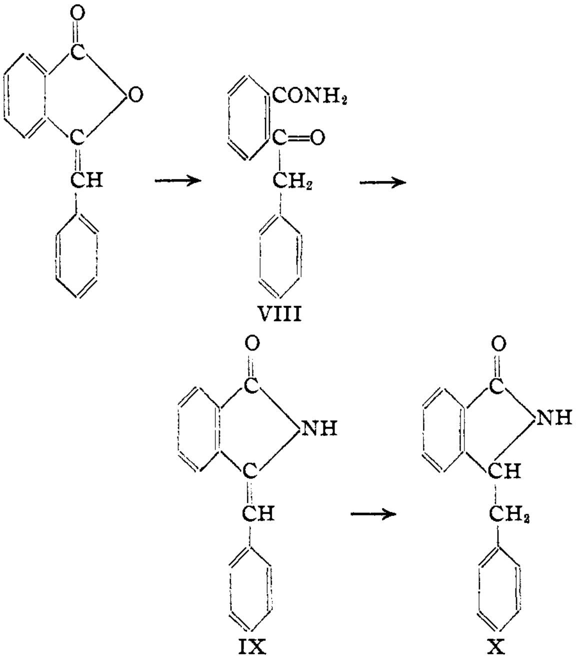
Finally the method of MacFadyen and Stevens[4] was employed with slight modifications. The latter consisted of the use of *p*-toluenesulfonyl chloride instead of benzenesulfonyl chloride, and glycerol instead of glycol as the solvent in the final conversion of the *p*-toluenesulfonyl hydrazide to the aldehyde. The introduction of these modifications made it possible to obtain a much better yield of the aldehyde.



Stilbene-2-aldehyde was characterized by the preparation of three derivatives, the phenylhydrazone (V), the condensation product with hippuric acid (VI), and the condensation product with rhodanine (VII). With the aldehyde now available in good yields, it is planned to convert it to 2-stilbene-acetic acid, the lactone of which would have the required structure for conversion to benzylisoquinoline.

In the second method, benzalphthalide was treated with ammonia according to the method of Gabriel[5] except that the reaction was carried out in an autoclave. This resulted in a much improved yield. The benzalphthalamide (VIII) formed was converted to benzalphthalimide (IX) through the elimination of water with acetic anhydride. Gabriel[6] employed glacial acetic acid as the dehydrating agent. However, the latter gave poor yields of the benzalphthalimide. Substitution of acetic anhydride greatly increased the yields.

An attempt to convert the benzalphthalimide to benzylphthalimide, (X), according to the method of Gabriel,[6] met with no apparent success. However, by means of catalytic hydrogenation, the benzal derivative was easily reduced to the benzyl compound in quantitative yields. In addition, the benzylphthalimide obtained by this method melted 20° higher than the product reported by Gabriel.



It is intended to attempt to convert compound X to a benzylisoquinoline according to the second proposed method.

Experimental Method

2-Stilbenecarboxylic Ester.—2-Stilbenecarboxylic acid (100 g.) is suspended in 1 liter of absolute ethyl alcohol and dry hydrogen chloride is bubbled in for four hours. The mixture is then refluxed for one hour. The alcohol is removed by distillation and the residue is vacuum distilled. Most of the ester distilled at 215° at 15 mm.

2-Stilbenecarboxylic Hydrazide.—A mixture of 150 g. of 2-stilbenecarboxylic ester, 150 g. of 50% hydrazine hydrate, and 150 cc. of ethyl alcohol is heated in an autoclave at 110° for fifteen hours. The resulting mixture is cooled and crystallization of the mass occurs. The resulting white solid is then recrystallized from dilute ethyl alcohol; yield 85 g.; m. p. 132°. When the hydrazide is recrystallized from benzene, the m. p. is found to be 135°.

Anal. Calcd. for $C_{15}H_{14}ON_2$: N, 11.76. Found: N, 11.81, 11.80.

If *n*-butyl alcohol is substituted for ethyl alcohol, the hydrazide can be obtained by refluxing from ten to fifteen

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[4] MacFadyen and Stevens, *J. Chem. Soc.*, 584–587 (1936).

[5] Gabriel and Michael, *Ber.*, **11**, 1628 (1878).

[6] Gabriel and Michael, *ibid.*, **11**, 1682 (1878); Gabriel, *ibid.*, **18**, 1262 (1885).

hours. However, the yield is not as good as when ethyl alcohol and an autoclave are used.

1 - *o* - Styrylbenzoyl - 2 - *p* - toluenesulfonylhydrazine.—2-Stilbenecarboxylic hydrazide (62 g.), 200 cc. of anhydrous pyridine, and 60 g. of toluenesulfonyl chloride are thoroughly mixed in a 500 cc. Erlenmeyer flask equipped with a calcium chloride drying tube. The mixture is heated in an oven at 100° for two hours, and then allowed to stand overnight at room temperature. The mixture is poured onto crushed ice containing sufficient hydrochloric acid so that the resulting mixture is acid. The white crystalline product which separates is filtered off and recrystallized from benzene; yield 68 g.; m. p. 190°.

Anal. Calcd. for $C_{22}H_{20}O_3N_2S$: N, 7.14. Found: N, 7.10, 7.06.

Stilbene-2-aldehyde.—A mixture of 21 g. of 1-*o*-styrylbenzoyl-2-*p*-toluenesulfonylhydrazine, 17 g. of potassium carbonate, and 100 cc. of glycerol is heated slowly in a liter Erlenmeyer flask to 205° in an oil-bath. Foaming takes place, and an oil rises to the top of the reaction mixture. The latter is cooled, and 600 cc. of water is added. The mixture is extracted with ether; the ether layer is dried over anhydrous sodium sulfate, and then evaporated to dryness. The resulting residue crystallizes on standing. On recrystallization from dilute ethyl alcohol, yellow crystals are obtained; yield 8.8 g.; m. p. 83°.

1 - *o* - Styrylbenzoyl - 2 - phenylhydrazine.—Phenylhydrazine hydrochloride (1 g.) and 1.5 g. of sodium acetate are dissolved in 8 cc. of water. To this is added a solution of 1 g. of stilbene-2-aldehyde in 10 cc. of ethyl alcohol. The resulting mixture is heated for a few minutes and then cooled. The white crystals which separate are filtered off and recrystallized from ethyl alcohol; m. p. 138°.

Anal. Calcd. for $C_{21}H_{18}ON_2$: N, 9.36. Found: N, 9.28, 9.20.

2 - Phenyl - 4 - *o* - styrylbenzylidene - 5(4) - oxazolone.—Stilbene-2-aldehyde (5 g.), 4.3 g. of hippuric acid, 7.8 g. of acetic anhydride, and 2 g. of anhydrous sodium acetate in a 125-cc. Erlenmeyer flask equipped with a calcium chloride tube are heated in a boiling water-bath for eight hours. On cooling and adding 15 cc. of ethyl alcohol, yellow crystals separate; these are filtered off and recrystallized from ethyl alcohol; yield 3.5 g.; m. p. 141°.

Anal. Calcd. for $C_{24}H_{17}O_2N$: N, 4.00. Found: N, 3.98, 4.03.

5-*o*-Styrylbenzylidene Rhodanine.—Stilbene-2-aldehyde (15 g.), 9.5 g. of rhodanine, 50 cc. of glacial acetic acid, and 18 g. of fused sodium acetate are thoroughly mixed in a 125-cc. Erlenmeyer flask. The mixture is refluxed for one-half hour, the condenser being protected by a calcium chloride tube. The reaction mixture is cooled and poured into 3 liters of water. The yellow crystalline solid which separates is filtered off, and recrystallized from acetone; yield 13 g.; m. p. 195–196°.

Anal. Calcd. for $C_{18}H_{13}ONS_2$: N, 4.33. Found: N, 4.19, 4.30.

Benzalphthalimide.—A mixture of 100 g. of benzalphthalide, 70 cc. of concentrated ammonium hydroxide, and 100 cc. of ethyl alcohol is heated in an autoclave at 90° for one hour. The mixture is cooled and an equal volume of water is added. The white solid which separates is filtered off, washed with water, and recrystallized from dilute ethyl alcohol; yield 101 g.; m. p. 168°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.88. Found: N, 5.89, 5.80.

Benzalphthalimide.—A mixture of 100 g. of benzalphthalamide, 100 cc. of acetic anhydride, and 100 cc. of glacial acetic acid is refluxed for one-half hour, the condenser being protected by a calcium chloride tube. The mixture is cooled and poured into water. The yellow solid which separates is filtered off and recrystallized from ethyl alcohol; yield 80 g.; m. p. 180°.

Anal. Calcd. for $C_{15}H_{11}ON$: N, 6.36. Found: N, 6.36, 6.28.

Benzylphthalimide.—Benzalphthalimide (10 g.) is suspended in 100 cc. of glacial acetic acid in a pressure bottle. To this is added 0.5 g. of platinum oxide. Hydrogen is pumped in to a pressure of fifty pounds, and the reaction mixture is shaken vigorously until complete reduction has taken place. It is then poured into water. The white crystalline solid which separates is filtered off and recrystallized from dilute ethyl alcohol; yield 9 g.; m. p. 157°.

Anal. Calcd. for $C_{15}H_{13}ON$: N, 6.31. Found: N, 6.30, 6.19.

Summary

1. The relationship between benzalphthalide and the benzylisoquinoline alkaloids is pointed out.

2. Two possible routes are indicated for the conversion of benzalphthalide derivatives to benzylisoquinoline derivatives.

3. Stilbene-2-aldehyde, a valuable intermediate is prepared.

4. A good method for the preparation of benzylphthalimide is described.

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