[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Isoquinoline Derivatives

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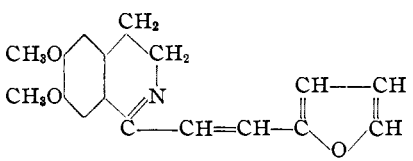
In initiating a study of the effect of various groups on the pharmacological action of isoquinoline derivatives, the introduction of the furan nucleus into position 1 was considered to be of special interest. Of the various methods recommended for synthesizing isoquinolines, that of Bischler and Napieralski[2] involving the ring-closure of acyl β-arylethylamines is the most satisfactory and was used in this research. The variation in the group substituted in the isoquinoline nucleus is thus accomplished by the incorporation of the required acyl group in the amide used as the starting point.

Of the few available acid chlorides containing the furan nucleus, furylacryloyl chloride seemed the most suitable for the present work. This acid chloride was accordingly condensed in the usual manner with homoveratrylamine to form N-(3,4-dimethoxyphenylethyl)-furylacrylamide. The latter, upon treatment with phosphorus oxychloride in boiling toluene, underwent ring-closure to form 1-furylvinyl-6,7-dimethoxy-3,4-dihydroisoquinoline I.



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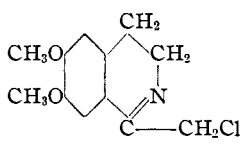

II

This new isoquinoline exhibits certain peculiarities in the formation of its salts. The picrate is normal in composition while an acid sulfate and two definite hydrochlorides are formed. Of the latter one is a normal monohydrochloride, while in the second the chlorine content corresponds most closely to the complex formula $3C_{17}H_{17}NO_3 \cdot 4HCl$. These various salts are all convertible into the same picrate. Attempts by various means to reduce the isoquinoline derivative I to 1-furylethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline were unsuccessful. We obtained no definite product of reduction nor could the original isoquinoline compound be recovered.

Because of the difficulties involved in the preparation of homoveratrylamine, it seemed advisable to carry out an analogous synthesis using the more easily available β-phenylethylamine. The study of the reaction might thus be facilitated by the larger quantities which could be obtained. N-(β-Phenylethyl)-furylacrylamide was accordingly prepared. Attempts to bring about ring closure, however, by any of the known methods to form

(1) E. R. Squibb and Sons Organic Chemistry Research Fellow, 1932–1933.

(2) Bischler and Napieralski, *Ber.*, **26**, 1903 (1893).

the required 1-furylvinyl-3,4-dihydroisoquinoline were without success. Similar failures in the attempted ring closure of amides of unsubstituted β-phenylethylamine have been noted by previous workers.[3]

As an alternate method for the introduction of new groups into position 1 of the isoquinoline nucleus the possible use of a halogen substituted derivative was investigated. Child and Pyman[4] attempted to combine 1-chloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline II with ammonia, and salts of phthalimide and malonic ester, but were unable to isolate any definite products. These authors were successful, however, in the introduction of the cyano group in place of chlorine, giving a nitrile which upon reduction yielded 1-(β-aminoethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline.

It seemed possible that a chloroisoquinoline such as II might form a Grignard reagent which in turn might react with a variety of substances. N-(β-Phenylethyl)-chloroacetamide was accordingly prepared and the ring closed by means of phosphorus pentoxide in boiling xylene to form 1-chloromethyl-3,4-dihydroisoquinoline. This chloroisoquinoline compound proved to be extremely unstable. All attempts to replace the chlorine by hydroxyl or ester groupings were unsuccessful.

Experimental Part

Homoveratrylamine $(CH_3O)_2C_6H_3CH_2CH_2NH_2$ was prepared according to the general procedure of Buck and Perkin.[5] A number of improvements in technique are recorded below.

Methylvanillin.—In the methylation of vanillin it was found necessary to use considerably more sodium hydroxide than indicated by Buck and Perkin. A hot mixture of 200 g. of vanillin and 265 g. of sodium hydroxide (20% solution) was stirred vigorously and treated with 360 g. of dimethyl sulfate added through a dropping funnel. An additional 320 g. of sodium hydroxide (20%) was added in small portions from time to time to keep the solution just alkaline. The product was extracted with ether and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 200–206 g. of material which melted at 42–43° (92-94%).

3,4-Dimethoxycinnamic Acid.—This compound was prepared by the condensation of methylvanillin with ethyl acetate as described by Buck and Perkin. The ethyl acetate was purified before using by distillation over phosphorus pentoxide. The cinnamic acid was purified by dissolving in boiling alcohol and then concentrating the solution to incipient crystallization. A yield of 84 g. of material melting at 180–181° was obtained (67%).

3,4-Dimethoxyhydrocinnamic Acid.—3,4-Dimethoxycinnamic acid was dissolved in 75% alcohol by the addition of just sufficient concentrated ammonium hydroxide. This solution was then hydrogenated at about 3 atmospheres pressure using Adams platinum oxide catalyst. After removal of the alcohol the remaining solution was diluted with water, cooled in an ice-bath and acidified. Yields of 90–92% of pure acid melting at 98–99° were obtained.

3,4-Dimethoxyhydrocinnamamide.—The preparation of this compound when car-

(3) Mannich and Walther, *Arch. Pharm.*, **265**, 1 (1927); Child and Pyman, *J. Chem. Soc.*, 2010 (1929).

(4) Child and Pyman, *J. Chem. Soc.*, 36 (1931).

(5) Buck and Perkin, *ibid.*, **125**, 1678 (1924).

ried out at a lower temperature (190–200°) than that of Buck and Perkin resulted in a product of higher purity. After one crystallization from benzene the amide melted at 120–121° (yield, 70–75%).

Homoveratrylamine.—This amine was obtained in slightly higher yields (73–75%) when a 15% excess of potassium permanganate, based on the amide used, was employed in the preparation of the sodium hypochlorite solution.

N-(3,4-Dimethoxyphenylethyl)-furylacrylamide.—To a cold mixture of 12 g. of homoveratrylamine and 67 cc. of sodium hydroxide (10%) was added a chloroform solution of 11.5 g. of furylacryloyl chloride. The addition was made in several portions with shaking and cooling. After standing for a few minutes the lower layer was separated and diluted with several volumes of petroleum ether. A dark oil separated which solidified upon shaking. This material was filtered and washed with water. Upon crystallization from benzene with addition of norite 15.2 g. of amide melting at 106–108° was obtained (75%). Recrystallization raised the melting point to 108–109°.

Anal. Calcd. for $C_{17}H_{19}NO_4$: N, 4.65. Found: N, 4.54, 4.55.

1-Furylvinyl-6,7-dimethoxy-3,4-dihydroisoquinoline I.—To 12.5 g. of the above amide in 60 cc. of dry toluene was added 25 cc. of phosphorus oxychloride. The mixture was boiled under reflux on the oil-bath for one and one-half hours. Upon cooling, a mass of crystals separated, which were filtered, washed with toluene and petroleum ether, and dried. This crude material in 75 cc. of warm water was treated with about 150 cc. of 50% sulfuric acid. A mass of yellow crystals of the sulfate formed which were filtered and thoroughly washed with dry acetone (yield 80%). After crystallization from 50% alcohol the salt melted at 243.5–244°.

Anal. Calcd. for $C_{17}H_{17}NO_3.H_2SO_4$: S, 8.41. Found: S, 8.20, 8.35, 8.25.

Picrate.—After recrystallization from alcohol this salt melted at 210–211°.

Anal. Calcd. for $C_{23}H_{20}N_4O_{10}$: C, 53.88; H, 3.94; N, 10.94. Found: C, 53.65; H, 3.89; N, 11.26, 11.14.

1-Furylvinyl-6,7-dimethoxy-3,4-dihydroisoquinoline when precipitated from aqueous solution by the addition of alkali separated as an oil which gradually solidified. This solid was filtered, washed with water and dried in vacuum over calcium chloride. The compound softened at 90° and melted at 94–96°. The free base darkened rapidly in contact with the air and no attempt at purification was made.

Hydrochlorides.—A portion of the free base was dissolved in a little absolute alcohol and treated with a slight excess of concentrated hydrochloric acid. Upon dilution with dry ether a yellow precipitate separated. Crystallization of this material from 1:1 alcohol–benzene yielded bright yellow crystals which melted with effervescence at 135–136°.

Anal. Found: Cl, 9.47, 9.49, 9.50.

When this product (m. p. 135–136°) was recrystallized from acetone, yellow crystals melting at 183–184° were obtained.

Anal. Calcd. for $C_{17}H_{17}NO_3 \cdot HCl$: Cl, 11.11. Found: Cl, 10.80.

One gram of the sulfate was dissolved in a little warm water and treated with several volumes of concentrated hydrochloric acid. A mass of fine crystals formed which was filtered on a hardened filter paper and washed with acetone (0.7 g.). This hydrochloride was suspended in boiling acetone and dissolved by the addition of just sufficient absolute alcohol. Upon cooling, bunches of orange crystals slowly separated from the solution. These began to sinter at 160° and effervesced at 167.5–168.5°.

Anal. Calcd. for $3C_{17}H_{17}NO_3 \cdot 4HCl$: Cl, 14.27. Found: Cl, 14.48, 14.49, 14.51.

Attempts to bring about reduction of (I) were made using zinc and dilute sulfuric acid, sodium amalgam and aluminum amalgam. No definite product could be isolated

in any case. Upon treatment with picric acid amorphous precipitates were obtained which could not be crystallized.

Upon catalytic hydrogenation of the isoquinoline sulfate in aqueous solution using platinum oxide, six molecules of hydrogen were absorbed. Evaporation of the solution yielded a clear colorless sirup which failed to crystallize. The picrate prepared from this sirup was a yellow oil which could not be crystallized.

N-(β-Phenylethyl)-furylacrylamide.—This compound was prepared from β-phenylethylamine and furylacryloyl chloride in the same manner as the dimethoxy compound. After crystallization from benzene the amide melted at 124–125° (yield 76%).

Anal. Calcd. for $C_{15}H_{15}NO_2$: N, 5.81. Found: N, 5.68.

Attempts to bring about ring closure in this compound with phosphorus oxychloride according to the method of Buck and Perkin, with phosphorus pentoxide by the method of Pictet and Kay,[6] with phosphorus pentachloride and aluminum chloride by the method of Decker and Kropp[7] and with thionyl chloride were entirely unsuccessful. In every case the product was a dark oil without basic properties and which could not be crystallized.

N-(β-Phenyl)-chloroacetamide.—This compound was prepared by the method of Child and Pyman. The yield was 83% and the product melted at 62–64°.

1-Chloromethyl-3,4-dihydroisoquinoline.—Twenty-seven grams of N-(β-phenylethyl)-chloroacetamide was dissolved in 100 cc. of boiling xylene. To the solution was added 54 g. of phosphorus pentoxide in three portions at ten-minute intervals. The mixture was boiled for a total time of forty-five minutes. The hot xylene was decanted and the residue washed with xylene and allowed to cool. The mass was then treated with about 300 cc. of water and the insoluble material extracted with ether. Upon making alkaline with ammonium hydroxide the free isoquinoline was precipitated from the solution as an oil. This was extracted with ether and the ether then washed with 75 cc. of 2-normal hydrochloric acid. Evaporation of this aqueous solution yielded a sirupy residue which was treated with acetone and allowed to stand. Large dark red crystals gradually formed. These were filtered and washed with acetone. Concentration of the filtrate yielded a second crop. The total yield was 9.4 g. of product which melted at 161–164° (38% yield). After crystallization from absolute alcohol this hydrochloride melted at 164–165°.

The picrate of 1-chloromethyl-3,4-dihydroisoquinoline was crystallized from alcohol and melted at 173–174°.

Anal. Calcd. for $C_{16}H_{13}ClN_4O_7$: Cl, 8.68. Found: Cl, 8.54, 8.56.

The free base was an oil which rapidly turned dark red and finally solidified to a non-basic, water-soluble mass upon standing overnight.

Attempts were made to convert the chloroisoquinoline into the corresponding alcohol or esters of the alcohol. Potassium acetate in both absolute alcohol and acetic acid solutions and a mixture of sodium benzoate and benzoic acid were used. The chlorine could be replaced but the amounts of reaction products were extremely small and the reaction appeared to be impractical.

Summary

1. The Bischler and Napieralski isoquinoline reaction has been applied successfully with homoveratrylamine and furylacryloyl chloride with the formation of 1-furylvinyl-6,7-dimethoxy-3,4-dihydroisoquinoline. Attempts to apply an analogous reaction with phenylethylamine were unsuccessful.

(6) Pictet and Kay, *Ber.*, **42**, 1973 (1909).

(7) Decker and Kropp, *ibid.*, **42**, 2075 (1909)

2. N-(β-Phenylethyl)-chloroacetamide was dehydrated by the action of phosphorus pentoxide giving 1-chloromethyl-3,4-dihydroisoquinoline.

NEW HAVEN, CONNECTICUT RECEIVED JANUARY 6, 1933
PUBLISHED JUNE 6, 1933

[CONTRIBUTION NO. 88 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Preparation of Certain Disubstituted Fluorenones by the Action of Heat upon the Corresponding Substituted Diphenic Acids or their Derivatives

BY E. H. HUNTRESS AND I. S. CLIFF

The number of substituted fluorenones containing substituents in the positions ortho to the carbonyl linkage is so small as to excite interest. Of the few instances reported in the literature[1] some could not be duplicated in other laboratories and others are obtainable only by tedious processes or from very difficultly accessible sources.[2] In connection with certain studies of the phenanthridone series now in progress in this Laboratory it was desired to obtain from readily accessible sources fluorenones which should contain substituents in the 1- or the 1,8-positions. This result has now been obtained by extending to certain dichlorodiphenic acids the method of preparation used in making fluorenone from diphenic acid.[3]

The two ketones with which we are here mainly concerned are 1,8- and 1,6-dichlorofluorenone. Both substances are obtained by operating upon suitable derivatives of the hitherto unknown 3,3'-dichlorodiphenic acid (I). The 1,8-dichlorofluorenone (III) is smoothly obtained in quantitative yield by the action of heat upon 3,3'-dichlorodiphenic anhydride (II), none of the 1,6-ketone being formed. The 1,6-dichlorofluorenone (V) is obtained in 55% yield by the action of heat upon 1,6-dichlorofluorenone-5-carboxylic acid (IV) (the keto acid corresponding to 3,3'-dichlorodiphenic acid), none of the 1,8-ketone being formed.

(1) *Cf.* Huntress and Cliff, THIS JOURNAL, **54**, 826 (1932). In this earlier note we accidentally omitted mention of fluorenone-1-carboxylic acid, long known, but recently synthesized and studied by Mayer and Freitag, *Ber.*, **54**, 347–357 (1921), and by Sieglitz, *ibid.*, **57**, 316–7 (1924).

(2) During the progress of this work we have encountered several further cases of ortho substituted fluorenones. Fieser [THIS JOURNAL, **51**, 2485 (1929)] has reported 1,4,6-trimethoxyfluorenone from the sulfuric acid ring closure of 2,5,5'-trimethoxy-2'-carboxybiphenyl. The same worker also prepared 1,6-dimethoxyfluorenone-4-carboxylic acid by similar ring closure of 5,5'-dimethoxydiphenic acid but reported no attempt to isolate the corresponding dimethoxy ketone. Finally von Braun and Manz [*Ann.*, **496**, 170–196(1932)] have reported an impressive list of 1-substituted fluorenones obtained as degradation products of fluoranthene derivatives: *e. g.*, fluorenone-1-propionic acid and its 2-amino-, 2-acetylamino-, 6-amino- and 6-acetylamino- derivatives; fluorenone-1,6-dicarboxylic acid; fluorenone-1,2-dicarboxylic acid and its anhydride, dimethyl ester, and acid methyl ester; 2-nitrofluorenone-1-carboxylic acid; 2-bromofluorenone-1-carboxylic acid; fluorenonehydrindone; and certain other fluorenone-1-carboxylic acids containing also the anthraquinone nucleus.

(3) Huntress, Hershberg and Cliff, THIS JOURNAL, **53**, 2720–2724 (1931).