acid, the barium sulfate being subsequently filtered from the hot solution. After concentration of the filtrate, a precipitate of the imino dibasic acid, tyrosine-N-acetic acid, was obtained. This substance was identified by conversion into its characteristic hydrochloride, m. p. 212–213° with evolution of a gas, by treatment with 1:1 hydrochloric acid.[8]

Summary

Tyrosine-N-acetic acid, an unsymmetrical imino dibasic acid, will react with phenyl isocyanate to form a phenylureido dibasic acid which appears to be stable only in the form of its salts or esters. The free phenylureido acid undergoes spontaneous ring closure in cold aqueous solutions to give a trisubstituted hydantoin. Although the phenylureido derivative of tyrosine-N-acetic acid may theoretically undergo cyclization to give either of two isomeric hydantoins, only one of these isomers was obtained under the conditions studied.

NEW HAVEN, CONN. RECEIVED AUGUST 18, 1938

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

The Synthesis of 1,4-Di-(3',4'-dimethoxyphenyl)-butanone-2 (Veratrylhomoveratryl Ketone)[1]

BY RICHARD CARROLL AND PAUL E. SPOERRI

The importance of a new general synthesis of the papaverine type of alkaloid was pointed out by Allen and Buck[2] in 1930. The published methods for the synthesis of papaverine itself involve the preparation of homoveratroylhomoveratrylamine[3–5] through the condensation of homoveratrylamine with homoveratric acid. No attempt has been made to prepare homoveratroylhomoveratrylamine from the oxime of 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2 by means of a Beckmann rearrangement.[6]

It was felt that the synthesis of this tetramethoxy ketone would furnish a new approach to the preparation of a benzylisoquinoline alkaloid as illustrated by the following equations

$$\begin{array}{l}\rm (CH_3O)_2C_6H_3CH_2COCH_2CH_2C_6H_3(OCH_3)_2 \longrightarrow \\ \rm (CH_3O)_2C_6H_3CH_2C({=}NOH)CH_2CH_2C_6H_3(OCH_3)_2 \longrightarrow \\ \qquad \rm (CH_3O)_2C_6H_3CH_2CONHCH_2CH_2C_6H_3(OCH_3)_2\end{array}$$

In a first attempt to prepare this ketone, 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2, a Friedel–Crafts reaction between 1-chloro-4-(3',4'-dimethoxyphenyl)-butanone-2 and veratrole was studied. The chloro ketone was made from 3,4-dimethoxydihydrocinnamoyl chloride by means of the Nierenstein[7] reaction. The desired coupling, as shown by the following equation, did not take place and the method was abandoned.

$$\begin{array}{l}\rm (CH_3O)_2C_6H_3CH_2CH_2COCH_2Cl + C_6H_4(OCH_3)_2 \longrightarrow \\ \qquad \rm (CH_3O)_2C_6H_3CH_2CH_2COCH_2C_6H_3(OCH_3)_2\end{array}$$

The ketone was finally prepared by the following series of reactions

$$\begin{array}{l}\rm (CH_3O)_2C_6H_3CH_2CN + (CH_3O)_2C_6H_3CH_2CH_2COOC_2H_5 \longrightarrow \\ \rm (CH_3O)_2C_6H_3CH(CN)COCH_2CH_2C_6H_3(OCH_3)_2 \longrightarrow \\ \rm (CH_3O)_2C_6H_3CH(CONH_2)COCH_2CH_2C_6H_3(OCH_3)_2 \longrightarrow \\ \qquad \rm (CH_3O)_2C_6H_3CH_2COCH_2CH_2C_6H_3(OCH_3)_2\end{array}$$

Ethyl 3,4-dimethoxydihydrocinnamate was condensed with 3,4-dimethoxybenzylcyanide to give 1-cyano-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2. This ketonitrile was hydrolyzed to 1-carbamyl-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2. This was further hydrolyzed and decarboxylated to yield 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2.

The hydrolysis of the ketonitrile, 1-cyano-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2, presented some difficulty. It was finally accomplished by prolonged treatment of the material with an acetic–hydrochloric acid solution. The resulting amide, 1-carbamyl-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2, was decarboxylated to 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2 by means of dilute hydrochloric acid.

During the course of attempts to hydrolyze the above-mentioned ketonitrile, a product, melting at 209°, was obtained whose analysis corresponded to the calculated values for 1-(3',4'-dimethoxy-

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(1) Presented before the Division of Organic Chemistry of the American Chemical Society at the Dallas meeting, April, 1938. This paper is an abstract of the thesis submitted by Richard Carroll to the Graduate Faculty of the Polytechnic Institute of Brooklyn in partial fulfilment of the requirements for the degree of Doctor of Philosophy in June, 1938.

(2) Allen and Buck, THIS JOURNAL, **52**, 310 (1930).

(3) Kindler and Peschke, *Arch. Pharm.*, **272**, 236 (1934).

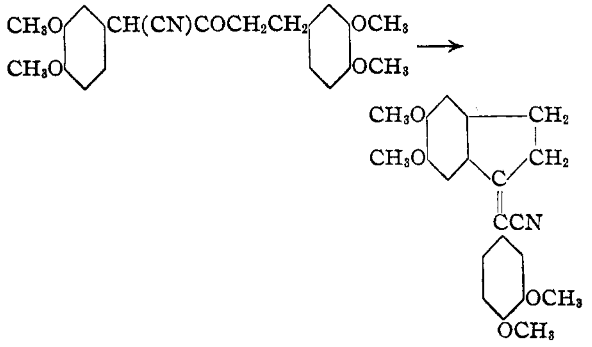
(4) Buck, Haworth and Perkin, *J. Chem. Soc.*, **125**, 2183 (1924).

(5) Sugasawa and Tsuda, *J. Pharm. Soc., Japan*, **55**, 194 (1935), *C. A.*, **31**, 6664 (1937), reduced dihomoveratroylamide.

(6) This reaction was suggested in a thesis by Ivey Allen, Jr., under J. S. Buck at Duke University, 1929.

(7) Bradley and Schwarzenbach, *J. Chem. Soc.*, 2904 (1928).

α-cyanobenzylidene)-5,6-dimethoxyindane. This material resulted from treatment of the ketonitrile with sulfuric acid. It could be formed in accordance with the following reaction



Experimental

3,4-Dimethoxydihydrocinnamoyl Chloride.—Thirteen grams of 3,4-dimethoxydihydrocinnamic acid[8] was treated with 6 g. of thionyl chloride. After standing for fifteen minutes the mixture was heated on a steam-bath for one hour and then distilled. The fraction boiling at 138–142° at 0.5 mm. was collected and redistilled. It solidified to a white solid melting at 40°[9,10] which was identified by conversion to the amide, melting at 121°.

1 - Chloro - 4 -(3′,4′ - dimethoxyphenyl) - butanone - 2.—Forty-eight cc. of nitrosomethylurethan was converted to diazomethane by the method of von Pechmann[11] and as used by Bradley and Robinson.[12]

To the ethereal solution (400 cc.) of diazomethane, cooled by ice, 27 g. of 3,4-dimethoxydihydrocinnamoyl chloride in 75 cc. of absolute ether was added slowly. There was a vigorous evolution of nitrogen during the addition. The solution was then placed in an ice chest overnight. After standing, dry hydrogen chloride was passed into the solution until the evolution of nitrogen ceased.

The solution was then evaporated to constant weight and allowed to stand. The chloro ketone crystallizes in rosets and has strong lachrymatory and vesicant properties. It can be recrystallized from alcohol and melts at 53°.

Anal. Calcd. for $C_{12}H_{15}ClO_3$: C, 59.38; H, 6.23; Cl, 14.60. Found: C, 59.04, 59.15; H, 6.14, 6.02; Cl, 14.71.

1-Cyano-1,4-di-(3′,4′-dimethoxyphenyl)-butanone-2.—Twenty-three grams of 3,4-dimethoxybenzyl cyanide, prepared by the method of Pfeiffer, Quehl and Tappermann,[13] was added to 32 g. of ethyl 3,4-dimethoxydihydrocinnamate and heated to 60°. This mixture was added to a warm solution of 3.1 g. of sodium in 50 cc. of absolute alcohol.[14]

The reaction mixture was refluxed[15] on a steam-bath for three hours and then allowed to stand for two days. During the heating, yellow colored crystals appeared. After standing, the solid material (sodio derivative of 1-cyano-1,4-di-(3′,4′-dimethoxyphenyl)-butanone-2) was removed by filtration, washed with absolute alcohol and air dried. It was then dissolved in 400 cc. of water and the solution was extracted with ether. The aqueous layer was then placed under a vacuum to remove the dissolved ether. This was followed by the addition of 25 cc. of hydrochloric acid. The heavy gum which precipitated, crystallized in a few hours; yield 39 g. It was recrystallized from a dilute alcoholic solution and melted at 76°.[16]

Anal. Calcd. for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.27; N, 3.79. Found: C, 67.72, 67.60; H, 6.05, 6.14; N, 3.80, 3.86.

1-Carbamyl-1,4-di-(3′,4′-dimethoxyphenyl)-butanone-2.—Fifteen grams of 1-cyano-1,4-di-(3′,4′-dimethoxyphenyl)-butanone-2 was dissolved in a mixture of 112 cc. of glacial acetic acid and 112 cc. of concentrated hydrochloric acid contained in a glass-stoppered flask. After standing for four days between 15 and 20°, the solution was poured into 1800 cc. of water and allowed to stand for twenty-four hours. A gum separated which clung to the walls of the beaker (if a crystal is added at the time of dilution a solid is obtained). The water layer was removed and the residue was dissolved in hot alcohol and filtered. The filtrate was evaporated to 10 cc. The product crystallized very slowly in buff colored plates. It gives a violet coloration with ferric chloride and dissolves in aqueous sodium hydroxide. It can be recrystallized from alcohol and melts at 123°; yield 4 g.

Anal. Calcd. for $C_{21}H_{25}NO_6$: C, 65.10; H, 6.50; N, 3.61. Found: C, 65.08, 65.18; H, 6.41, 6.58; N, 3.80.

1,4 - Di - (3′,4′ - dimethoxyphenyl) - butanone - 2.—Two grams of 1 - carbamyl - 1,4 - di - (3′,4′ - dimethoxyphenyl)-butanone-2 was added to 120 cc. of a solution of 12 cc. of concentrated hydrochloric acid in 138 cc. of water. This mixture was boiled for two hours. After cooling, the water solution was decanted and the remaining gum was dissolved in hot alcohol. This solution was filtered and evaporated to 4 cc. Buff colored crystals were deposited on standing; yield 0.90 g. The material was recrystallized from alcohol and melted at 76°.

Anal. Calcd. for $C_{20}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.45, 69.85; H, 7.04, 7.13.

Dinitro Derivative.—Nitration in acetic acid yields a dinitro derivative which can be recrystallized from acetic acid, and melts at 195°.

Anal. Calcd. for $C_{20}H_{22}N_2O_9$: C, 55.30; H, 5.10; N, 6.45. Found: C, 54.92, 55.09; H, 4.89, 5.03; N, 6.34, 6.27.

Compound Melting at 209°.—One-fifth gram of 1-cyano - 1,4 - di - (3′,4′ - dimethoxyphenyl) - butanone-2 was added to 5 cc. of a sulfuric acid solution (3 volumes H_2SO_4:2 volumes H_2O) and warmed on a steam-bath for ten minutes.

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[8] Perkin and Robinson, *J. Chem. Soc.*, **91**, 1080 (1907).

[9] After standing several weeks the material changed to a dark gummy paste.

[10] Pictet and Finkelstein, *Ber.*, **42**, 1985 (1909), prepared this chloride by using phosphorus pentachloride.

[11] Von Pechmann, *Ber.*, **28**, 856 (1895).

[12] Bradley and Robinson, *J. Chem. Soc.*, 1545 (1928).

[13] Pfeiffer, Quehl and Tappermann, *Ber.*, **63**, 1301 (1930).

[14] Pfeiffer, Quehl and Tappermann[13] used an alcoholic solution of sodium ethoxide for this type of condensation, while Haworth and co-workers, *J. Chem. Soc.*, 1426 (1934), employed a suspension of potassium ethoxide in benzene.

[15] All of the glassware was previously dried and the solution protected from moisture by a calcium oxide tube.

[16] A portion of this material was recrystallized after standing several months. It then melted at 122° and gave the following analytical results: C, 68.49, 68.66; H, 6.11, 6.05; N, 3.92, 4.04.

The solid first dissolved, this was followed by the appearance of yellow colored needles. After cooling, the solution deposited a curdy yellow precipitate. The solid was recrystallized from ethyl acetate and melted at 209°; yield 0.12 g.

Anal. Calcd. for $C_{21}H_{21}NO_4$: C, 71.78; H, 6.02; N, 3.99. Found: C, 71.76, 72.15; H, 5.85, 6.14; N, 4.32, 4.24.

Summary

1. Methods have been described for the preparation of 1-cyano-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2, 1-carbamyl-1,4-di-(3',4'-dimethoxyphenyl)-butanone-2 and 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2.
2. Attempts to prepare 1,4-di-(3',4'-dimethoxyphenyl)-butanone-2 by means of a Friedel–Crafts reaction were unsuccessful.

BROOKLYN, N. Y. RECEIVED AUGUST 17, 1938

[CONTRIBUTION NO. 175 FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, AND FROM THE CHEMICAL LABORATORY OF MCGILL UNIVERSITY]

The Influence of Branched Chains on Optical Activity. The Configuration of Propyl-*t*-butylcarbinol, with a Note on the Relation between Rotatory Power and Chemical Character

BY PHILIP G. STEVENS, W. EDWARD HIGBEE[1] AND ROBERT T. ARMSTRONG[2]

In a previous paper on this subject[3] the configuration of dextro methyl-*t*-butylcarbinol, as determined by Freudenberg's displacement rule, was found to be the same as dextro methyl-*n*-butylcarbinol. It was therefore apparent from their molecular rotations, +7.8° and +12.0°, respectively, that the *t*-butyl group did not cause as great a shift in the rotation as the isopropyl (+4.7°), or the cyclohexyl (+7.4°) group. This result was unexpected as it was felt that, if branching of the chain were responsible for the observed shift, the completely branched *t*-butyl group would cause a greater shift. Therefore the suggestion was made that the real effect of the singly branched group was due to the presence of a tertiary hydrogen atom. According to the theories advanced by Kuhn and Freudenberg,[6] this hydrogen atom might well bring about a shift in the rotation, since it represents another center of chemical reactivity close to the asymmetric carbon atom.

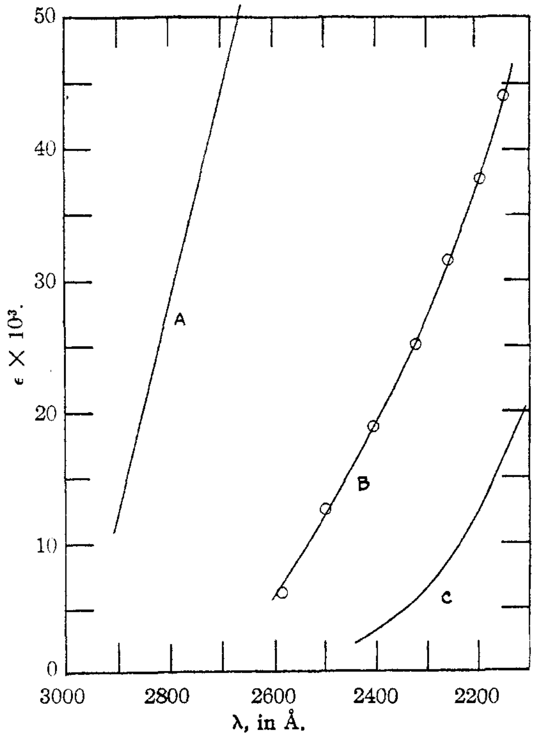

Fig. 1.—A, *n*-Butyl alcohol[4]; B, pinacolyl alcohol; C, ethyl alcohol.[5]

On the other hand, something may be abnormal about the *t*-butyl group. However, methyl-*t*-butylcarbinol shows no anomalous absorption bands in the near ultraviolet, and is similar to other carbinols as shown in Fig. 1. The high transmission of this carbinol as compared with other carbinols with a fewer number of carbon atoms may possibly be attributed to the high purity of the sample used.

Anomalous properties are often found in the lowest member of various series. This has been found to be true for the rotations of the isopropyl series.[7] A determination of the configuration of

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(3) Stevens, THIS JOURNAL, **55**, 4237 (1933).

(4) Bielecki and Henri, *Ber.*, **45**, 2819 (1912).

(5) Harris, *ibid.*, **66**, 1940 (1933).

(6) Kuhn, *Trans. Faraday Soc.*, **26**, 293 (1930); Kuhn, Freudenberg and Wolf, *Ber.*, **63**, 2367 (1930).

(7) Stevens, *ibid.*, **54**, 3732 (1932); Levene and Marker, *J. Biol. Chem.*, **101**, 413 (1933).