heated under reflux with a thermometer in the liquid. Heating was applied by a metal-bath. The material, at first in layers, became homogeneous at about 90°. The temperature of the liquid when it began to boil was 154° (b. p. of ethanolamine, 172°) and this temperature fell during twenty minutes to 144° where it remained during forty-five minutes more of gentle refluxing. The contents of the flask was then distilled at 16 mm.; 22 g. of ethanolamine came over at 82°. The residue, which was not extracted from aqueous solution by ether, was acidified with hydrochloric acid (12 cc. of concentrated acid), iced and treated with 10 g. of sodium nitrite and 5 cc. more of concentrated hydrochloric acid. After standing an hour, the solution was evaporated *in vacuo*, dissolved in a minimum of water and basified with 20% sodium hydroxide solution. Repeated extraction with ether removed a sirupy base leaving most of the color behind. The ethereal extracts were dried over potassium carbonate and poured into an excess of ethanolic hydrogen chloride solution. A sirupy layer separated and crystallized slowly. The yield of purified material was 7 g.

The salts described in Table I had no unusual solubilities but the lower melting members were most advantageously recrystallized from acetone with a trace of the esterifying alcohol and with addition of sufficient ether to saturate the solution to the liquid phase. The acid oxalates, V and VII, were prepared because the hydrochlorides could not be induced to crystallize. The hydrobromide III was obtained directly from the reaction mixture in which it was formed.

Intermediates.—The secondary amines leading to compounds I, III, IV and IX, phenethylmethylamine and homoveratrylmethylamine are familiar. The precursor of VIII, N-methyl-2,5-dimethoxyphenethylamine was described by Buck.[4] The intermediates for compounds V–VII are shown in Table I. Veratrylmethylamine (XII),[5] veratrylbutylamine (XIII) and anisylethylamine (X) were prepared by hydrogenation of the corresponding Schiff bases in acetic acid with Adams catalyst; the yields were 75–80%. N-Methyl-4-methoxy-3-bromobenzylamine (XI) was prepared by brominating X in aqueous solution as its hydrobromide; the yield of recrystallized hydrobromide was 76%.

Acknowledgment.—The microanalyses here reported were performed by Messrs. Walter S. Ide and Samuel Blackman to whom we wish to express our gratitude.

Summary

A group of N-phenethyl glycine and N-benzyl-β-alanine derivatives as well as two higher homologs have been prepared for study of their oxytocic properties.

[4] Buck, This Journal, **54**, 3661 (1932).

[5] Tiffeneau, *Bull. soc. chim.*, [4] **9**, 930 (1911), has characterized the base and its hydroiodide.

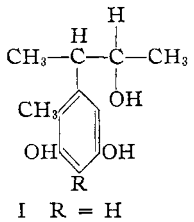
Tuckahoe 7, New York Received May 17, 1949

[Contribution from the Frick Chemical Laboratory, Princeton University]

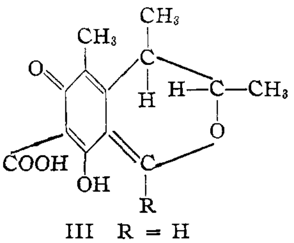
The Synthesis of Dihydrocitrinin and Citrinin

By H. H. Warren, Gregg Dougherty and Everett S. Wallis

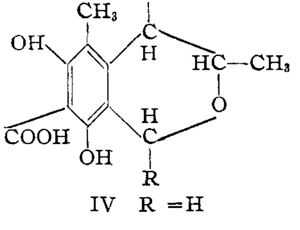
The synthesis of citrinin by Cartwright, *et al.*,[1] from the phenolic degradation product A (I), and the synthesis of the racemic form of A corroborates the structure, III, for citrinin advanced by Brown and co-workers.[2] In this Laboratory we have accomplished the synthesis of dihydrocitrinin (IV) from I by the cyclization of the carboxylic acid derivative, II, with methylal. The dihydrocitrinin thus prepared (m. p. 169.5–170.5° dec.) was readily converted to citrinin by oxidation with bromine in accordance with a method essentially the same as that recently published by Schwenk, Schubert and Stahl.[3]



I R = H
II R = COOH



III R = H



IV R =H

Preliminary observations from investigations now in progress on the synthesis of homologs and analogs of dihydrocitrinin and of citrinin for the purpose of determining the effect of variation in structure on physiological activity indicate that the cyclization is of general applicability for the preparation of derivatives of III and IV where R is methyl, ethyl, benzyl, etc., or substituted radicals of various structures. The results of these experiments will be described in a later paper.

Experimental Part

Compound A.—Citrinin was hydrolyzed with ammonium hydroxide according to the method of Schwenk.[3] Compound A was obtained in excellent yields. Recrystallization from hot chloroform gave a pure product of m. p. 128–130°.

Carboxylic Acid Derivative of Compound A.—The method used was similar to that described by Cartwright.[1] A mixture of 0.50 g. of compound A, 1.00 g. of potassium bicarbonate and 1.00 g. of glycerol was heated under an atmosphere of carbon dioxide in an oil-bath at 150° for five hours. After cooling, the material was dissolved in twice its volume of water and was extracted four times with ether to remove glycerol. Careful acidification of the

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[1] Cartwright, Robertson and Whalley, *Nature*, **163**, 94 (1949).

[2] Brown, Cartwright, Robertson and Whalley, *ibid.*, **162**, 72 (1948); see also Frye, Wallis and Dougherty, *J. Org. Chem.*, **14**, 397 (1949).

[3] Schwenk, Schubert and Stahl, *Arch. Biochem.*, **20**, 220 (1949).

cold aqueous solution with dilute sulfuric acid yielded 0.38 g. of white crystalline material which, after three recrystallizations from ether and chloroform, melted at 178.3–179.8 (dec.).

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.97; H, 6.71. Found: C, 59.70; H, 6.80.

Dihydrocitrinin.—A suspension of 0.20 g. of the carboxylic acid derivative of compound A in a solution of 0.40 g. of methylal and 4.0 ml. of benzene saturated with dry hydrogen chloride at room temperature was heated in a sealed tube at 60° for six hours. After standing overnight the tube was opened and the clear, slightly yellow liquid was decanted from a very small amount of oil, decolorized with Darco and evaporated nearly to dryness in a stream of nitrogen. Petroleum ether was added dropwise until a tarry precipitate started to form. The clear solution was decanted from the tar and upon further addition of petroleum ether a white crystalline material separated. Four recrystallizations from hot carbon tetrachloride and cyclohexane yielded a product which melted at 169.5–170.5 (dec.).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.87; H, 6.39. Found: C, 61.54; H, 6.15.

Citrinin.—To a solution of 0.030 g. of dihydrocitrinin in one-half ml. of chloroform was added dropwise a molar solution of bromine in chloroform until the bromine color persisted. After standing for ten minutes the solvent was evaporated at low temperature, yielding a dark orange tar which was dissolved in a minimum amount of ethanol. Addition of hot water initiated the formation of a lemon-yellow crystalline material, which after cooling was filtered and recrystallized. Crystals were obtained which melted at 175.8–176.3° (dec.). No depression of the melting point was observed when a sample of this material was admixed with an authentic sample of citrinin.

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.24; H, 5.47.

Acknowledgment.—We wish to take this opportunity to express our thanks to The Schering Corporation, Bloomfield, N. J., for the citrinin used in the preparation of Compound A, and to Merck and Company, Inc., Rahway, N. J., for the analyses published in this paper. We also wish to express our appreciation to The Standard Brands Corporation, New York City, N. Y. for a grant-in-aid which made this work possible.

Summary

A synthesis of dihydrocitrinin and of citrinin has been described.

Preliminary observations indicate that the synthesis is applicable to homologs and analogs and to other derivatives of similar structure.

PRINCETON, NEW JERSEY RECEIVED APRIL 20, 1949

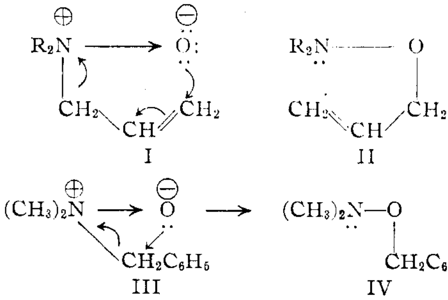
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Rearrangement of Allyldialkylamine Oxides and Benzyldimethylamine Oxide[1]

BY ARTHUR C. COPE AND PHILIP H. TOWLE

Meisenheimer has shown that allylmethylaniline oxide and allylethylaniline oxide rearrange to O-allyl-N-alkyl-N-phenylhydroxylamines on heating with aqueous sodium hydroxide, and that benzylmethylaniline oxide rearranges to O-benzyl-N-methyl-N-phenylhydroxylamine under the same conditions.[2,3] These reactions have been interpreted as intramolecular, thermal rearrangements, because crotylmethylaniline was observed to rearrange with inversion of the crotyl group, yielding O-methylvinylcarbinyl-N-methyl-N-phenylhydroxylamine.[4] The fact that the rearrangement products are formed in high yield in the presence of sodium hydroxide indicates that the oxygen–carbon bond is formed essentially at the same time that the nitrogen–carbon bond is broken, for otherwise appreciable amounts of allyl alcohol and benzyl alcohol should be formed by reaction of the migrating groups (if momentarily free as carbonium ions) with hydroxyl ions. According to this interpretation, the sodium hydroxide has no function in the rearrangement other than to liberate the amine oxides from their salts.

Meisenheimer[3] reported that allyldimethylamine oxide and allyldiethylamine oxide did not rearrange on heating with aqueous sodium hydroxide, but were recovered unchanged except for small amounts which were cleaved into dimethylamine and diethylamine, respectively, and unidentified decomposition products. If the driving force for the rearrangement is a nucleophilic attack of an unshared electron pair of oxygen on the allyl or benzyl group, or the attraction of the positively charged nitrogen of the amine oxide for the electron pair attaching it to the allyl or benzyl group, the rearrangement would be expected to proceed in the aliphatic series as indicated:



A possible explanation for the difference in behavior of allyldialkylamine oxides and allylalkylaniline oxides on heating is the greater tendency of aliphatic amine oxides to hydrate,[5] since combina-

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[1] Presented at the St. Louis meeting of the American Chemical Society, Division of Organic Chemistry, Sept. 7, 1948.

[2] Meisenheimer, *Ber.*, **52**, 1667 (1919).

[3] Meisenheimer, Greeske and Willmersdorf, *ibid.*, **55**, 513 (1922).

[4] Kleinschmidt and Cope, THIS JOURNAL, **66**, 1929 (1944).

[5] Sidgwick, "The Organic Chemistry of Nitrogen," revised by Taylor and Baker, University Press, Oxford, 1942, p. 167.