[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

The Preparation of 1-(3,4-Dihydroxyphenyl)-2-amino-1-butanol[1]

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In the prolonged search that has been made for sympathomimetic amines, which possess pharmacological actions similar to but more desirable than epinephrine, 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol has aroused considerable interest. Under the names ethylnorsuprarenin and ethylnoradrenalin it has been tested in several laboratories and a number of papers have been published on the pharmacology of this compound by Tainter and co-workers,[2] Raymond-Hamet,[3] and Bacq.[4] Unpublished work by Tainter, Cameron, and Whitsell indicates that it is equally as effective as epinephrine in the relief of acute asthmatic attacks in doses one-half larger, and this relief is accompanied by fewer side effects; that it is approximately one one-hundredth as toxic as epinephrine; that it neither excites the central nervous system nor raises systolic blood pressure, but instead lowers diastolic pressure and increases the pulse rate, thus improving circulation without a proportionate rise in cardiac work.

There is little doubt that the compound tested pharmacologically was 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol, but a thorough search of the literature has thus far failed to reveal any description of its synthesis or physical constants. Consequently its synthesis was attempted in these laboratories, and successfully completed. A new process was used which may have a general application.

In a search for a suitable means of obtaining this amine the usual methods of introducing a primary amino group proved unsatisfactory. Although Hartung[5] has described α-isonitroso-3,4-dihydroxybutyrophenone, our attempts to nitrosate both 3,4-dihydroxybutyrophenone and 3,4-dibenzyloxybutyrophenone were unsuccessful. Treatment of α-bromo-3,4-dibenzyloxybutyrophenone with ammonia was unsatisfactory as a synthetic method. The reaction of the bromoketone with hexamethylenetetramine was too slow to be practical.

In the present investigation the possibility of forming a primary amine by hydrogenolysis of a secondary amine has been studied. Since the catalytic hydrogenolysis of a tertiary benzylmethylamino compound has been generally used for producing a methylamino compound, it was believed that a high molecular weight secondary amine might behave similarly to produce a primary amine. It was found that a benzhydryl group could be removed readily by hydrogenation in the presence of a palladium catalyst. Benzhydrylamine was allowed to react with a bromoketone and the benzhydrylamino compound successfully reduced to the desired primary amine.

3,4-Dihydroxybutyrophenone has been prepared by the Fries isomerization of catechol dibutyrate and guaiacol butyrate in nitrobenzene or carbon disulfide.[6,7,8] The methods either gave low yields or required a high reaction temperature and tedious manipulation. Catechol was treated with *n*-butyryl chloride and aluminum chloride in chlorobenzene to give a 68% yield of 3,4-dihydroxybutyrophenone with no difficulties encountered. The product was benzylated readily with benzyl chloride and the 3,4-dibenzyloxybutyrophenone obtained in excellent yield. α-Bromo-3,4-dibenzyloxybutyrophenone has been previously prepared,[9] but has not been characterized. The dibenzyloxyketone was brominated without difficulty and its identity was established. The bromoketone was treated with benzhydrylamine and the resulting α-benzhydrylamino-3,4-dibenzyloxybutyrophenone hydrochloride was hydrogenated to yield 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol.

Experimental

3,4-Dihydroxybutyrophenone.—To 165 g. (1.5 moles) of catechol in 660 ml. of dry chlorobenzene was added 200 g. (1.87 moles) of *n*-butyryl chloride and the mixture heated at 50° for thirty minutes. It was then cooled and 426 g. (3.2 moles) of anhydrous aluminum chloride added in small portions. Then the temperature of the mixture was gradually raised to 110° and held there for three hours. The mixture was hydrolyzed in ice and hydrochloric acid, and the chlorobenzene removed by steam distillation. While still warm, 75 ml. of concentrated hydrochloric acid and 125 ml. of toluene were added. After thorough cooling, the product was filtered and washed well with water and toluene. When recrystallized from water it melted at 146–146.5°. It is reported to melt at 146–147°.[6] The yield of 3,4-dihydroxybutyrophenone was 68% of the theoretical. A small amount of 4-chlorobutyrophenone, m. p. 34–35°, was isolated from the toluene washings.

3,4-Dibenzyloxybutyrophenone.—A mixture of 184.5 g. (1.023 moles) of 3,4-dihydroxybutyrophenone, 278.5 g. (2.2 moles) of benzyl chloride, 187 g. (1.35 moles) of anhydrous potassium carbonate, 13.5 g. (0.09 mole) of sodium iodide in 500 ml. of alcohol and 8 ml. of water was refluxed and stirred five hours, when all effervescence had ceased. The alcohol was distilled and any unreacted benzyl chloride removed by steam distillation. The warm mixture was poured into dilute sodium hydroxide, cooled, filtered, and

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(2) Tainter, *et al.*, *Arch. intern. pharmacodynam.*, **46**, 192 (1933); *J. Pharmacol.*, **51**, 371 (1934); **55**, 242 (1935); **57**, 152 (1936); **62**, 318 (1938); **63**, 340 (1938); **66**, 146 (1939); **67**, 56 (1939); **71**, 62 (1941); *Am. J. Med. Sci.*, **197**, 796 (1939); *J. Physiol.*, **98**, 263 (1940).

(3) Raymond-Hamet, *Bull. sci. pharmacol.*, **41**, (36) 481–489 (1934); *Compt. rend.*, **202**, 690 (1936); *Compt. rend. soc. biol.*, **128**, 827 (1938).

(4) Bacq, *Arch. intern. pharmacodynam.*, **55**, 190 (1937); Heirman and Bacq, *Arch. intern. physiol.*, **50**, 100 (1940).

(5) Hartung, U. S. Patent 1,995,710.

(6) Rosenmund and Lohfert, *Ber.*, **61B**, 2601 (1928).

(7) Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930).

(8) Miller, Hartung, Rock and Crossley, THIS JOURNAL, **60**, 7 (1938).

(9) Bockmühl, Ehrhart & Stein, U. S. Patent 2,083,001.

washed with water until neutral to litmus. Recrystallization from alcohol gave a 90% yield of 3,4-dibenzyloxybutyrophenone, m. p. 86–87°. It is reported to melt at 88°.[10]

α-Bromo-3,4-dibenzyloxybutyrophenone.—This bromoketone was prepared by the procedure of Bockmühl, Ehrhart and Stein,[9] who prepared and used the compound without isolating and characterizing it. To 335.5 g. (0.93 mole) of 3,4-dibenzyloxybutyrophenone dissolved in 1500 ml. of methylene chloride was added 110 g. (1.1 moles) of powdered calcium carbonate and then 149 g. (0.93 mole) of bromine in 400 ml. of methylene chloride. The excess calcium carbonate was dissolved with dilute hydrochloric acid, the methylene chloride layer separated, washed with water, and dried over sodium sulfate. After removing the solvent under reduced pressure the residue was recrystallized from alcohol. A 70% yield of cream-colored crystals, m. p. 100–101° was obtained.

Anal. Calcd. for $C_{24}H_{23}O_3Br$: C, 65.61; H, 5.28. Found: C, 65.48; H, 5.14.

α-Benzhydrylamino-3,4-dibenzyloxybutyrophenone Hydrochloride.—To 57.1 g. (0.13 mole) of α-bromo-3,4-dibenzyloxybutyrophenone in 175 ml. of absolute alcohol was added 47.7 g. (0.26 mole) of benzhydrylamine and the mixture refluxed three hours. The alcohol was completely removed under reduced pressure and 400 ml. of dry ether added. The precipitated benzhydrylamine hydrobromide was filtered and washed with dry ether. The ether solutions were combined and thoroughly shaken with 10% hydrochloric acid. An oil separated which slowly crystallized. It was filtered off, washed with water and with ether to remove traces of color. A 75% yield of cream-colored needles, m. p. 175–176° dec., was obtained.

(10) I. G. Farbenind. A. G., British Patent 457,824.

Anal. Calcd. for $C_{37}H_{36}O_3NCl$: N, 2.42; Cl, 6.13. Found: N, 2.38; Cl, 6.09.

1-(3,4-Dihydroxyphenyl)-2-amino-1-butanol Hydrochloride.—To 28.9 g. (0.1 mole) of α-benzhydrylamino-3,4-dibenzyloxybutyrophenone hydrochloride, dissolved in 150 ml. of absolute alcohol, was added 0.5 g. of palladium sponge catalyst.[11] It was shaken at 55–70° under fifty pounds pressure until three equivalents of hydrogen had been used. After the alcohol was removed the residue was dissolved in water and the toluene and diphenylmethane removed by extracting with ether. The aqueous solution was boneblacked and further hydrogenated until the fourth equivalent of hydrogen had been used. The catalyst was removed and the solution taken to dryness under reduced pressure. The residue was boneblacked in absolute alcohol, an equal volume of acetone added and then dry ether until precipitation was complete. A 60% yield of colorless material was obtained. When completely dry it melted with decomposition at 199–200° (uncor.).

Anal. Calcd. for $C_{10}H_{16}O_3NCl$: N, 5.99; Cl, 15.17. Found: N, 6.17; Cl, 15.08.

Summary

1. The synthesis and characterization of 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol has been described.

2. It has been shown that the intermediate benzhydrylaminoketone readily undergoes hydrogenolysis to the desired primary amine.

(11) Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 123 (1921).

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The Chemistry of Allergens. IX. Isolation and Properties of an Active, Carbohydrate-Free Protein from Castor Beans[1]

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The method of isolation, amino acid content and chemical and immunological properties of a non-toxic, allergenic, protein-polysaccharidic fraction, CB-1A, from castor beans were recorded in a previous publication.[1b]

The importance of the role of carbohydrate in the immunological specificity of pneumococcus organisms[2] and recognition of a possible analogous relationship in allergenic specificity[3] led to the isolation and chemical characterization of an essentially carbohydrate-free protein (CS-60C) from cottonseed.[4]

To determine similarly the significance of the polysaccharidic portion of the castor bean allergen, an attempt was made to isolate a carbohydrate-free protein from CB-1A, by electrophoresis, analogously to the previously described fractionation of CS-1A from cottonseed.[4,5] However, the final cathodic fraction, CB-60C, so obtained, contained 0.47% carbohydrate. Therefore, CB-1A was subjected to a varied and prolonged series of procedures involving chromatographic adsorption of the picrate, electrophoretic recovery of the protein from the picrate, electrophoresis of the protein, and solvent fractionation. The final active fraction, CB-65A, contained only a trace of carbohydrate as shown by chemical tests. The present paper describes the isolation of CB-60C and CB-65A and compares their chemical and immunological properties with those of CS-60C from cottonseed.

Experimental

Apparatus.—The high voltage electrophoresis apparatus described and illustrated in papers IV[6] (Fig. 1) and VI[4] of this series was used except that 250, 125, 50 or 25 ml. cells

(1) (a) Not copyrighted. (b) For Article VIII of this series see Spies and Coulson, THIS JOURNAL, **65**, 1720 (1943).

(2) First demonstrated by Heidelberger and Avery, *J. Exptl. Med.*, **38**, 73 (1923).

(3) The possible non-protein nature of allergens is discussed by Coca, Walzer and Thommen, "Asthma and Hay Fever in Theory and Practice," Charles C. Thomas, Baltimore, 1931, pp. 734 *et seq*; also Vaughn, "Practice of Allergy," C. V. Mosby Co., St. Louis, Mo., 1939, p. 607.

(4) Spies and Umberger, THIS JOURNAL, **64**, 1889 (1942).

(5) Spies, Bernton and Stevens, *ibid.*, **63**, 2163 (1941).