

the tryptophan content of this fibrin, calculated upon the basis of the humin nitrogen was 4.8%. The total tryptophan content would therefore be 5.05% which is in excellent agreement with the value obtained by the colorimetric method.

Summary

1. Some of the difficulties and errors in the methods used by various authors are pointed out.

2. The effect of temperature and time upon the reaction of *p*-dimethylaminobenzaldehyde in 20% hydrochloric acid has been studied. In this concentration of hydrochloric acid the reaction requires greater time for completion than is generally supposed. The higher the temperature, the greater the instability of the color produced.

3. Pure tryptophan in solution can be accurately determined by use of this method. The tryptophan content of proteins can also be accurately determined without previous hydrolysis of the protein, but from observations and from general considerations it seems that an enzyme-digested protein is better suited for this determination than is undigested protein.

4. There is excellent agreement between the figures for the tryptophan content of fibrin obtained by the "humin" formation method of Gortner and Holm⁸ and those obtained by the colorimetric method.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF H. A. METZ]

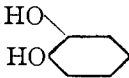
SOME NEW DERIVATIVES OF SYNTHETIC ADRENALINE (SUPRARENINE)

BY CASIMIR FUNK AND LOUIS FREEDMAN

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In the manufacture of synthetic adrenaline, and especially in its purification, we have observed the formation of certain derivatives which are of unusual chemical interest, and which may prove to have valuable pharmacological properties.

It has been found that the secondary alcohol group in the side chain

HO——CH(O—R)—CH₂NHCH₃, where R represents an alkyl radical. A derivative of adrenaline has been prepared by Mannich¹ in which the hydrogens of all 3 hydroxyl groups have been replaced by methyl groups, but so far as we are aware no derivatives have as yet been described in which only the secondary alcohol group has been converted into an ether.

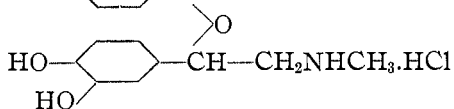
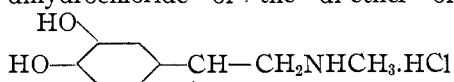
We have succeeded in preparing the methyl and ethyl ethers of this type, but have failed so far to prepare the purified propyl and benzyl

¹ Mannich, *Arch. Pharm.*, **248**, 127, 154 (1910).

derivatives. Large amounts of tarry residue, from which it is difficult to obtain the pure products, are formed with the higher homologs.

These new ethereal compounds differ from adrenaline in that they form soluble and easily oxidizable bases and, therefore, have to be isolated and purified as the hydrochlorides. We have as yet been unable to reconvert these ethers into adrenaline by hydrolysis; vigorous hydrolysis cannot be used because of the ease with which these compounds decompose.

In the preparations of the ethyl compound, when the reaction to form the ether is made more vigorous, another new compound, which has also been isolated and purified, is formed. This compound is probably the dihydrochloride of the di-ether of adrenaline with the structure



and is formed by the elimination

of water from 2 molecules of adrenaline.

None of the above compound was formed as a by-product in the preparation of the methyl ether, even though the reaction was carried out under higher temperature and pressure. Further work on the preparation of these compounds, and their pharmacologic action, is now being carried out.

Experimental Part

Preparation of the Hydrochloride of the Ethyl Ether of *r*-Adrenaline, *r*-3,4-Dihydroxy-phenyl Ethyl-ethanol-methyl Amine Hydrochloride.—Racemic adrenaline (synthetic) was heated with absolute ethyl alcohol containing various amounts of dry hydrogen chloride for various periods of time. We will describe only those experiments that gave the best results.

A solution of 4.4 g. (0.02 mole) of adrenaline hydrochloride in 44 cc. of absolute ethyl alcohol containing 0.02 mole of dry hydrogen chloride was refluxed for 1 hour on a water-bath. It was then filtered, the filtrate evaporated to half volume and the residue allowed to stand over sulfuric acid. On the next day, a crop of crystals was obtained which when filtered and washed with absolute alcohol, and dried, gave 2.4 g. of a white crystalline compound melting at 163° (with decomposition). After recrystallization from absolute alcohol, the material weighed 2.0 g. and melted at 165–166°. After 4 recrystallizations from absolute alcohol it melted at 169° (corr.); *r*-adrenaline hydrochloride melts at 157°. This new compound is soluble in 2.5 parts of absolute alcohol. It is readily soluble in water and its aqueous solution, on addition of ammonia, yields a soluble base which oxidizes very quickly in the presence of an excess of ammonia. The highest yield of the ethyl ether was obtained by using 1.5 molecular equivalents of hydrogen chloride and refluxing for 1/2 hour. Thus, from 22 g. of adrenaline hydrochloride, we obtained 16 g. (65% yield) of the hydrochloride of the ether.

In its color reactions it resembles adrenaline. With ferric chloride, it gives a dark green which turns to a maroon-red on standing or on addition of ammonia. It also gives an orange-red to a bright red color on addition of mercuric chloride and sodium acetate to its aqueous solution. These color reactions prove that the phenolic groups

in the ring are free, and that the secondary alcohol group can still give the sublimate reaction, even though the alcohol group is converted to an ether. On treatment with sodium nitrite in hydrochloric acid solution, the compound gives a yellow oil which shows the characteristic Liebermann nitrosamine reaction, proving the presence of a secondary amine and precluding the possibility of the addition of the ethyl group on the nitrogen.

*Analyses.*² Subs., 0.2788: 11.5 cc. of 0.1 *N* HCl. Subs., 0.0971: Cl, 0.0138; CO₂, 0.1212; H₂O, 0.0642. Calc. for C₁₁H₁₈O₃NCl: C, 53.36; H, 7.32; N, 5.65; Cl, 14.35. Found: C, 53.60; H, 7.34; N, 5.73; Cl, 14.21.

The hydrogen chloride can also be titrated directly with standard alkali, the formation of the easily oxidizable base giving a red color in excess alkali, thus acting as an indicator.

Preparation of Di-adrenaline-ether Dihydrochloride.—A solution of 45 g. of racemic adrenaline hydrochloride in 450 cc. of absolute ethyl alcohol containing 36.5 g. of dry hydrogen chloride (4 molecular equivalents) was refluxed for 1 hour. The product failed to crystallize at first, but after it had stood over sulfuric acid for several days a crop of crystals weighing 20 g. was obtained. This substance did not melt sharply and appeared to be a mixture. The bulk of it was practically insoluble in absolute alcohol, but was recrystallized from 70% alcohol, the more soluble ethyl ether hydrochloride remaining in solution while the di-adrenaline-ether dihydrochloride crystallized in clusters of thin rectangular prisms. The compound melted at 166–174° without decomposition, forming a yellow oil. It was triturated in a mortar with 95% alcohol, filtered and washed several times with 95% alcohol; m. p., 172–180°. On further recrystallizing and washing, the compound melted sharply at 180–183°. The final yield of the pure product was 3 g., the remaining material being the ethyl ether described in the previous experiments.

Color Reactions.—With ferric chloride it gives a deep green which passes to a reddish-violet and then to a violet on standing or on addition of ammonia. With mercuric chloride and sodium acetate, it gives a grayish-blue precipitate which darkens on standing. With ammonia alone it forms a gray precipitate which dissolves in an excess of ammonia, giving a purple solution. It is precipitated by phosphotungstic and phosphomolybdic acids, forming a grayish-white precipitate. The ethyl and methyl ethers are not precipitated by these reagents.

Analyses. Subs., 0.2779: 13.8 cc. of 0.1 *N* HCl. Subs., 0.1185: CO₂, 0.2243; H₂O, 0.0678; Cl, 0.0199. Calc. for C₁₅H₂₆O₅N₂Cl₂: C, 51.29; H, 6.22; N, 6.68; Cl, 16.83. Found: C, 51.67; H, 6.35; N, 6.8; Cl, 16.87.

Preparation of the Hydrochloride of Methyl Ether of Racemic Adrenaline. (*r*-3,4-Dihydroxy-phenyl-methyl-ethanol-methylamine Hydrochloride.)—A solution of 11 g. of racemic adrenaline hydrochloride in 110 cc. of absolute methyl alcohol containing 7.3 g. (4 molecular equivalents) of dry hydrogen chloride was refluxed for 1 hour. The methyl ether crystallized immediately as the reaction mixture cooled, forming thin rectangular prisms. The crude compound melts at 172–173° with effervescence. It is very soluble in absolute methyl alcohol but less soluble in absolute ethyl alcohol. On recrystallization from 5 parts of absolute ethyl alcohol, it separated in white rectangular prisms similar to the ethyl derivative; m. p., 175° (corr.); yield, 3 g. or about 26%. This methyl ether gives the same color reactions as does the ethyl derivative.

Analyses. Subs., 0.2536: 10.7 cc. of 0.1 *N* HCl. Subs., 0.0978: CO₂, 0.1863; H₂O, 0.0630; Cl, 0.0150. Calc. for C₁₀H₁₈O₃NCl: C, 51.37; H, 6.90; N, 5.99; Cl, 15.18. Found: C, 51.94; H, 7.15; N, 5.95; Cl, 15.33.

An attempt to form the di-adrenaline ether by means of this reaction, even by heating at higher temperatures in a sealed tube, failed. Only the methyl ether was obtained.

² All combustions were made by the Dennstedt method.

Summary

Racemic adrenaline hydrochloride is readily converted into ethers in which the hydrogen of the secondary alcohol group is replaced by an alkyl group, by treating it with the corresponding absolute alcohol containing dry hydrogen chloride. The methyl and ethyl ethers have thus far been obtained and described. In the formation of the ethyl ether we have isolated as a by-product what appears to be di-adrenaline ether, formed by the condensation of 2 molecules of adrenaline with the elimination of 1 molecule of water from the 2 secondary alcohol groups.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF WISCONSIN]

THE ACTION OF SELENIUM OXYCHLORIDE UPON ETHYLENE, PROPYLENE, BUTYLENE AND AMYLENE¹

BY CARL E. FRICK

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Preliminary experiments by Lenher² have shown that the oxychloride of selenium reacts with saturated paraffin hydrocarbons only very slowly at high temperatures, while with the unsaturated hydrocarbons of the aliphatic series, it unites directly, frequently with great evolution of heat. Mueller³ has reported that selenium oxychloride reacts with unsaturated hydrocarbons and ketones, producing substances that are very unstable in light and air. He gave no analytical results, however, nor any properties of the substances produced. The object of this investigation has been to make a quantitative study of the reactions taking place between selenium oxychloride and the olefins, ethylene, propylene, butylene and amylene; and to compare these reactions with those of selenium monochloride and the same olefins.

When selenium oxychloride reacts with ethylene, the dichloride of bis(β -chloro-ethyl)selenide is always produced, regardless of whether the ethylene or the oxychloride is in excess during the course of the reaction. With selenium monochloride and ethylene, Boord and Cope⁴ have pointed out that this reaction takes place in two stages and that bis(β -chloro-ethyl)selenide is produced when the ethylene is in excess, while the dichloride of bis(β -chloro-ethyl)selenide is always formed when the monochloride is in excess.

¹ This paper is constructed from a part of a thesis submitted by the author to the Graduate School of the University of Wisconsin in partial fulfilment of the requirements for the degree of Doctor of Philosophy, January, 1923.

² Lenher, *THIS JOURNAL*, **43**, 29 (1921).

³ Mueller; *Chem.-Ztg.*, **43**, 843 (1919).

⁴ Boord and Cope, *THIS JOURNAL*, **44**, 395 (1922).