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Synthesis of Adrenochrome Alkyl Ethers *

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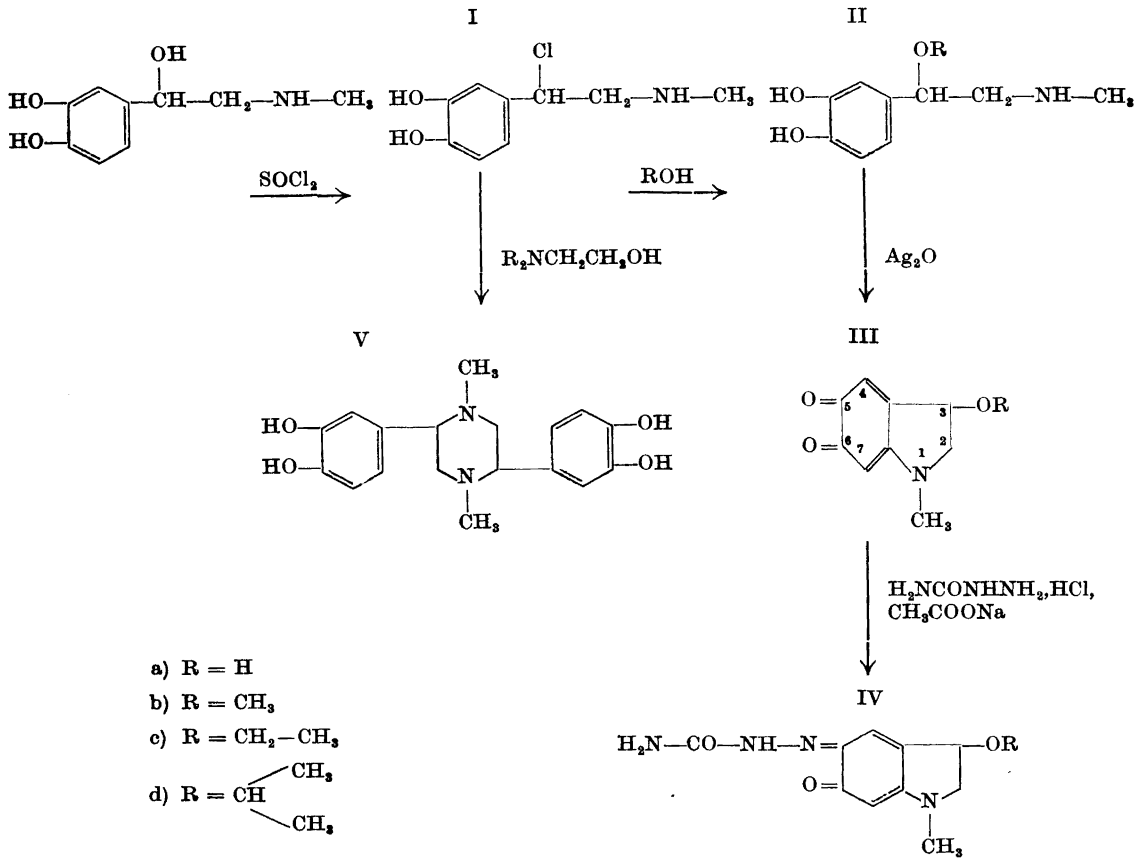
From adrenaline, its alkyl ethers (methyl, ethyl and *iso*propyl) were prepared through a common intermediate, methylaminomethyl-3,4-dihydroxyphenylchloromethane. On oxidation with silver oxide, these ethers were converted into those of adrenochrome and isolated as their monosemicarbazones.

Adrenochrome (III a), the quinoid oxidation product of adrenaline, is a well-known hemostatic agent. But, being an *ortho*-quinone, it readily deteriorates in aqueous solution. Several stable derivatives have been prepared from it, one of which, the monosemicarbazone (IV a), is commercially available under the name of adrenoxyl. Some homologs of adrenochrome, noradrenochrome [1], N-*iso*propylnoradrenochrome [2] and 2-ethylnoradrenochrome [2] have been reported. Two halogen substitution products, 2-iodo- [3] and 2-bromoadrenochrome [3], are described in the literature. Recently N-[β-hydroxyethyl]-noradrenochrome [4] has been synthesized. Most of the above compounds have been prepared as their monosemicarbazones.

The present paper is concerned with the synthesis of adrenochrome ethers. Owing to the instability of the adrenochrome molecule, direct etherification was not attempted. Instead, a circuitous route, starting from the corresponding adrenaline ethers, was chosen.

A methyl and an ethyl ether of adrenaline (II b and II c) have previously been prepared by Funk and Freedman [5] by passing dry hydrogen chloride into a boiling solution of adrenaline in the appropriate alcohol. The present method made use of an intermediate, methylaminomethyl-3,4-dihydroxyphenylchloromethane hydrochloride (I), which is readily formed from adrenaline with excess of thionyl chloride. It proved to be a crystalline compound, only stable if kept in the refrigerator and protected from light and moisture. It could not be recrystallized for analysis. The correctness of the above formula is shown by the formation of the following reaction products. It readily formed adrenaline hydrochloride with water. Heating with methanol or ethanol at 60° led to the formation of ethers identical with the corresponding ones pre-

* From the thesis for the M. A. degree of Niilo Seppäläinen, University of Helsinki, 1955.

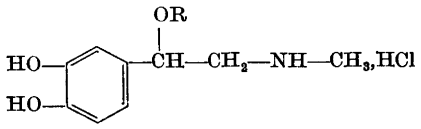


pared by the method of Funk and Freedman [5]. The former etherification method was used throughout in this work. An *iso*propyl ether of adrenaline was also synthesized. Some data on the adrenaline ethers, which were all obtained as hydrochlorides, are presented in Table 1.

When the synthesis of amino alkyl ethers of adrenaline was attempted by the above method, complications arose. A high-melting compound was formed in all cases, irrespective of the amino alcohol used. By analysis and melting point determination it was shown to be identical with the dimolecular ring condensation product obtained by Bretschneider [6] from methylaminomethyl-3,4-diacetoxyphenylchloromethane hydrochloride with diethylamine. Obviously the ring condensation reaction predominates under the strongly alkaline conditions produced by the amino alcohols. A structural formula of 2,5-bis(3,4-dihydroxyphenyl)-1,4-dimethylpiperazine (V) was suggested for this compound by Bretschneider.

The oxidation methods used for converting the adrenaline ethers into the corresponding adrenochrome ethers were essentially analogous with the famil-

Table 1. Adrenaline ethers.

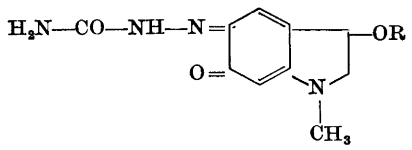


R	Formula	Yield %	M. P., °C	
			Found	In literature [5]
Methyl	$C_{10}H_{15}NO_3$, HCl	70	175	175
Ethyl	$C_{11}H_{17}NO_3$, HCl	82	169	169
*Iso*propyl	$C_{12}H_{19}NO_3$, HCl	35	177–8	—

iar ones employed in the synthesis of adrenochrome from adrenaline. Oxidation with silver oxide in methanol acidified with formic acid proved the best. The resultant adrenochrome ethers were isolated as the monosemicarbazones. All these were dark red, glistening, crystalline compounds. They were crystallized from aqueous pyridine, from which they were obtained without water of crystallization. The data for the ethers are presented in Table 2. For further characterization of these new compounds ultraviolet absorption spectra were made both of these and of the unetherified adrenochrome monosemicarbazone (adrenoxyl). The curves obtained are presented in Fig. 1. As can be seen, the general shape of the curves of the three ethers and the position of their maxima and inflection points are fully coincident with those of the curve of adrenoxyl.

As would be expected, the solubility of the monosemicarbazones of adrenochrome ethers in water is even poorer than that of adrenoxyl. In order to improve the solubility of adrenoxyl, its ability to form salts was studied. A bright yellow crystalline hydrochloride of adrenoxyl could readily be ob-

Table 2. Adrenochrome ethers (as monosemicarbazones).*



R	Formula	Yield %	M.P. °C	Analyses					
				Calc.			Found		
				C	H	N	C	H	N
Methyl	$C_{11}H_{14}N_4O_3$	56	217–18	52.79	5.64	22.39	52.71	5.44	22.43
Ethyl	$C_{12}H_{16}N_4O_3$	71	214–15	54.55	6.10	21.10	55.15	6.30	21.46
*Iso*propyl	$C_{13}H_{18}N_4O_3$	57	206– 7	56.10	6.52	20.13	55.52	6.51	20.03

* New features disclosed in this paper are covered by pending Finnish patent application.

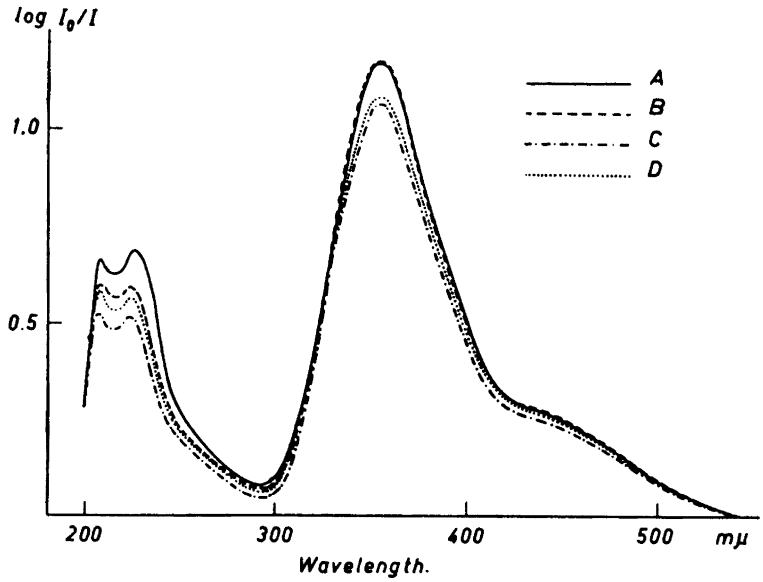


Fig. 1. Ultraviolet absorption spectra of the monosemicarbazones of A) adrenochrome, B) adrenochrome methyl ether, C) adrenochrome ethyl ether and D) adrenochrome *iso*propyl ether.

tained with a nearly quantitative yield. This was shown by analysis to be a monohydrochloride containing one molecule of water of crystallization. The salt is distinctly more soluble in water than adrenoxyl, but unfortunately it readily decomposes in solution, especially in the light. That the compound really was a salt of adrenoxyl was proved by liberating the base with pyridine. The base was shown to be identical with the starting adrenoxyl by melting point determination and ultraviolet absorptium spectrum. Whether the salt-forming ability of adrenoxyl is to be ascribed to the tertiary ring-nitrogen atom or to the semicarbazone side chain, was not investigated. The former possibility was taken into account by Ramirez and Ostwalden[7] when they studied the structure of adrenoxyl in the light of ultraviolet absorption spectra.

EXPERIMENTAL

All melting points are uncorrected. Microanalyses were performed by the Microanalytisches Laboratorium im Max-Planck-Institut für Kohlenforschung, Mülheim, Germany. Ultraviolet data, from the Analytical Laboratory of Lääketehdas Orion Oy, are for solutions in absolute methanol (concentration 0.01 g per liter).

Starting materials. The adrenaline used was an Uclaf product, m. p. 207—208.5°. The adrenoxyl was from Labaz, for parenteral use, m. p. 206—207°.

Methylaminomethyl-3,4-dihydroxyphenylchloromethane hydrochloride (I). To 70 g of thionyl chloride in an Erlenmeyer flask of 500 ml capacity was added 10 g of adrenaline after removal of the air with nitrogen. In about one minute a vigorous reaction set in, resulting in the formation of a clear solution. The gaseous reaction products were swept

off by passing in a continual stream of nitrogen. After about half an hour crystals began to separate from the liquid. When crystallization was complete, the product was filtered off and washed, first with benzene, then with ether. The yield of the colorless material was 13 g (99 %), m. p. 90—100° (decomp.). It could not be recrystallized, owing either to its insolubility in or to its reactivity with the usual solvents. It darkened rapidly in daylight but could be kept for some days in the refrigerator when protected from light and moisture.

Adrenaline ethers (II). A mixture of 2 g of methylaminomethyl-3,4-dihydroxyphenylchloromethane hydrochloride in 20 ml of the appropriate alcohol was refluxed for 1 h, the temperature of the boiling reaction mixture being kept at 60° by means of ether added through the condenser. The resulting solution was evaporated *in vacuo* almost to dryness. After addition of 25 ml of acetone the mixture was allowed to stand in the refrigerator overnight. The crystals deposited were filtered off, washed with acetone and dried in a desiccator. The ethers so obtained were sufficiently pure for oxidation to adrenochromes. For purification of an ether it was dissolved in hot absolute ethanol and as much acetone was added as possible without causing turbidity. The mixture was allowed to stand in the refrigerator overnight to ensure complete crystallization. No analysis of the ethers was made. Their constitution was confirmed by analyzing the corresponding adrenochrome ether monosemicarbazones prepared from them.

2,5-Bis(3,4-dihydroxyphenyl)-1,4-dimethylpiperazine hydrochloride (V). When dimethylaminoethanol was used as the alcohol component in the above etherification reaction, a high-melting (m. p. 303°) compound was the only product that could be isolated. The same compound was also obtained by allowing methylaminomethyl-3,4-dihydroxyphenylchloromethane hydrochloride to react with conc. aqueous ammonia. (Found: C 53.39; H 6.16; N 6.78. Calc. for $C_{18}H_{22}N_2O_4$, 2HCl: C 53.59; H 6.00; N 6.94.)

Adrenochrome ether monosemicarbazones (IV). The appropriate adrenaline ether hydrochloride (0.027 mole) was dissolved in a mixture of 2 ml of formic acid (99—100 %) and 100 ml of dry methanol. Freshly precipitated dry silver oxide (0.108 mole) was added. The mixture was shaken vigorously for 2—4 min at about 40° and filtered by suction into a solution previously prepared by dissolving semicarbazide hydrochloride (0.027 mole) and sodium acetate (0.073 mole) in 40 ml of distilled water. After washing with 10 ml of dry methanol the combined dark red filtrates were allowed to stand for 10 min at room temperature and then overnight at 0°. The dark red, glistening crystals were filtered, washed with water and dried in a desiccator.

Adrenoxyl hydrochloride. 3 g of adrenoxyl was placed in an Erlenmeyer flask, from which the air had been displaced with nitrogen and 120 ml of 2 % hydrochloric acid was added. The stoppered flask was shaken at room temperature until all the adrenoxyl had dissolved. Almost immediately a bright yellow crystalline compound began to separate. After separation had been completed in the refrigerator, the crystals were filtered off, washed with acetone and dried in a desiccator (without vacuum). The yield of the hydrochloride was almost quantitative. Upon crystallization from 2 % hydrochloric acid it melted at about 150° (decomp.). (Found: C 41.41; H 5.40; N 19.04; Cl 12.09. Calc. for $C_{10}H_{12}N_4O_3$, HCl, H_2O: C 41.31; H 5.20; N 19.27; Cl 12.20.)

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