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Allyl Derivatives of Sympathomimetic Amines[1]

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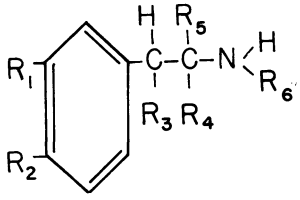
Abstract. The allyl group was substituted on the side chains of benzedrine and ephedrine in the belief that these derivatives would antagonize the parent compounds. Their antagonistic effect was clearly demonstrated; the action was believed to be due to reaction at the receptors in the muscles.

Sympathomimetic amines are those which produce effects similar to those which occur when the sympathetic nervous system is excited. That is, they stimulate heart muscle, constrict certain arterioles, and cause inhibition of smooth (visceral) muscles. The combination of these mechanisms probably causes the rise in blood pressure, always prominent in their effect.

The sympathomimetic amines studied in this research were benzedrine, also called amphetamine, and ephedrine. These are similar in action and structure to adrenaline (epinephrine), a naturally occurring amine in the body.



Adrenaline: $R_1, R_2, R_3 = OH$
$R_4, R_5 = H$
$R_6 = CH_3$
Benzedrine: $R_1, R_2, R_3, R_5, R_6 = H$
$R_4 = CH_3$
Ephedrine: $R_1, R_2, R_5 = H$
$R_4, R_6, = CH_3$
$R_3 = OH$

Their action is believed by Ohta (1946) and others to be due to

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an indirect action on adrenaline. Amine oxidase, which occurs in the kidney, brain, and lungs, acts on secondary amines of the adrenaline type, converting them to aldehydes. Thus, once adrenaline combines with amine oxidase it loses it potency but releases the amine oxidase, permitting it to act on more adrenaline.

When drugs such as benzedrine are introduced into the system they are so similar to adrenaline that they combine with the amine oxidase. However, this combination is irreversible, the α-methyl group preventing the oxidation of the amine. The oxidase is thus prevented from acting on adrenaline, and the increased amount of adrenaline in the system causes the stimulation.

The allyl derivatives of these sympathomimetic amines, benzedrine and ephedrine, were prepared in our laboratory in the belief that the substitution would reduce the action of the drug. That is, it would act as a depressant, or antagonize the parent compound. Substitution on the amino group on the side chain of an aromatic nucleus nearly always reduces the action. The allyl derivative of morphine has been found to be a powerful antagonist to the action of morphine (Barlow, 1955). Working in the light of these data, we substituted the allyl group on the side chains of benzedrine and ephedrine.

Experimental

Diallyl benzedrine was prepared following the work of Brauchli and Cloetta (1928) in synthesizing diallyl β-tetrahydronaphthylamine at the University of Zurich.

The benzedrine sulfate, dissolved in hot water, was neutralized with a slight excess of potassium hydroxide. The free benzedrine oil separated as a light layer. A calculated excess of allyl bromide was added. This solution was heated for thirty minutes and the orange oil which separated in the bottom of the flask was taken up in ether. The amine oil was dissolved in benzene, and dry HBr was bubbled through the solution. White crystals appeared, and these were purified in an alcohol-ether mixture. The HBr salt was analyzed by a potentiometric titration with silver nitrate, and the per cent bromide was found to be 26.84 per cent as compared to 26.97 per cent calculated for diallyl benzedrine hydrobromide. Carbon-hydrogen analysis of the compound showed it to contain 60.50 per cent carbon as compared to 60.81 per cent calculated, and 7.82 per cent hydrogen compared to 7.48 per cent calculated. Melting point is 147-148° C.

An attempt was made to synthesize a mono-allyl benzedrine using the free benzedrine with allyl alcohol and allyl bromide in the presence of sodium allyloxide. So far, these attempts have been

unsuccessful, though they had proved satisfactory in the preparation of mono-O-allyl ephedrine. The difficulty is probably due to formation of interfering compounds, notably diallyl ether, formed by a Williamson synthesis from allyl bromide and sodium allyloxide.

The mono-O-allyl ephedrine was most successfully prepared by refluxing the ephedrine with sodium in toluene, removing the excess sodium, and adding an equimolar amount of allyl bromide. Sodium bromide precipitated as a white salt and the remaining amine oil was hydrobrominated. The amine salt was analyzed potentiometrically with silver nitrate and found to contain 27.34 per cent bromine, as compared to 27.90 per cent calculated for mono-allyl ephedrine. A carbon-hydrogen analysis gave 54.30 per cent carbon, 54.55 per cent calculated, and 6.74 per cent hydrogen, 7.04 calculated. Infrared analysis showed a NH band at 3.1μ and the absence of the OH group at 2.8μ. This showed that the allyl group had replaced the hydrogen of the hydroxy group, rather than the hydrogen on the nitrogen. The decomposition range of this compound is 190-195° C.

Discussion

The difficulty with which the allyl group is attached to the benzedrine and ephedrine may be explained by the mechanism of the reaction. If it proceeds by S_{N2} mechanism, the nucleophilic nitrogen attacking the allyl carbon, the steric hindrance in the amine would be a factor limiting the reaction. In the case of S_{N1} mechanism, the allyl carbonium ion would be more free to attack the amine nitrogen. The difficulty with which the second allyl group is attached to ephedrine is probably explained by the "umbrella" effect of the allyl group on the oxygen, sterically preventing an attack on the amine nitrogen.

Certain pharmacological data point up the antagonistic effect of the allyl compounds. Brauchli and Cloetta (1928) demonstrated the antagonistic action of diallyl ephedrine on ephedrine, working with dogs. The ephedrine caused a sharp rise in the blood pressure. Injection of the allyl ephedrine antagonized this effect, resulting in a rate lower than normal.

The drugs and their allyl derivatives were also tested on live specimens in our laboratory. A goldfish, anaesthetized in chlorotone, was wrapped in moist cotton and mounted on a glass slide. Under low power of the microscope, the circulation in the tail was clearly visible. A drop of the drug, benzedrine or ephedrine, produced a noticeable retardation of circulation. Application of the allyl derivative restored the circulation to normal, clearly indicating an antagonistic effect.

The reason for the antagonistic action of the allyl derivative is

not clear. Attempts have been made to relate its effects to a quickened action of amine oxidase, so it would destroy adrenaline at a rate faster than normal. However, this explanation is unsatisfactory since the derivative must work in the presence of the parent compound, which is complexed with the amine oxidase.

Coret and van Dyke (1949), explaining the depressant action of the isopropyl homologue of adrenaline, considered the muscles affected by the adrenaline. They believed that vascular smooth muscle has reaction sites which are excitatory and others which are inhibitory. Antagonistic action would then be due to competition at these reaction sites. Adrenaline normally reacts primarily at the excitatory sites and it is believed that a drug such as benzedrine would react equally at both sites. However, if the allyl derivative were injected into the system, it would react at the excitatory sites, producing no stimulation, but preventing the action of adrenaline at that site. Thus the total effect produced would be inhibitory. In the light of what is now known about the action of adrenaline, this seems the most satisfactory explanation.

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