71 (1818)

The pharmacological action of some ethers and esters of saligenin.[1]

By ARTHUR D. HIRSCHFELDER and HERMAN H. JENSEN.

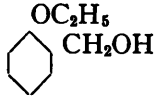
[*From the Department of Pharmacology, University of Minnesota, Minneapolis, Minn.*]

Benzyl alcohol saligenin and other aromatic alcohols have been shown to possess local anesthetic and antispasmodic action (Macht; Hirschfelder; Hjort). Hirschfelder and Quigley have also demonstrated that the local anesthetic action of benzyl alcohol and its derivatives is diminished when one of the inactive hydrogens (*i.e.*, in the CH_2 of the CH_2OH carbinol group) is substituted by another radical; or, in other words, that the secondary aromatic alcohols are not as good local anesthetics as the primary, and that substitutions for both the CH_2 hydrogens (tertiary alcohols) causes complete loss of local anesthetic action.

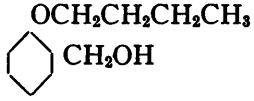
Although Hirschfelder, Lundholm and Norrgard had demonstrated that methyl and ethyl substitutions on the phenolic hydroxyl of saligenin rendered the substances more irritating than saligenin, a more extensive study of this type of substitution products was desirable, particularly on account of the fact that they furnished some alcohols homologous with acetyl-salicylic acid.

The substances studied may be devided into three groups:

I. Ethers of saligenin with substitution on the phenolic hydroxyl: *i.e.*, the ethyl, *n*-butyl, iso-amyl and benzyl ethers.

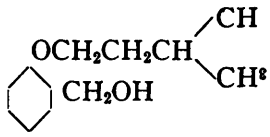


I.
Ethyl saligenin.

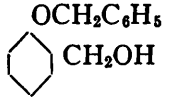


II.
N-Butyl saligenin.

[1] The substances used in this research were prepared by Merrill C. Hart as by-products of an investigation of the phenolic alcohols and their derivatives as antiseptics and for the chemotherapy of the venereal diseases, with the aid of funds furnished by the United States Interdepartmental Social Hygiene Board. Their preparation has already been described elsewhere (M. C. Hart and A. D. Hirschfelder, *Jour. Am. Chem. Soc.*, 1921, July).

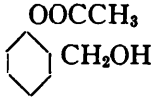


III.
Iso-amyl saligenin.

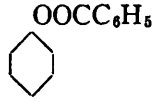


IV.
Benzyl saligenin.

II. Esters of saligenin with substitution on the phenolic hydroxyl (acetyl and monobenzoyl saligenin).

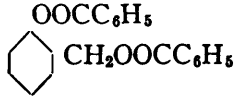


V.
Acetyl saligenin.



VI.
Benzoyl saligenin.

III. An ester with substitution on both hydroxyls (dibenzoyl saligenin).



VI.
Dibenzoyl saligenin.

All of these esters and ethers except the dibenzoyl compound are oily liquids, and the latter is a solid; and all are practically insoluble in water but soluble in the usual organic solvents and in olive oil. Their pharmacological properties were therefore studied by dissolving the substances in olive oil and emulsifying this with acacia by the Continental method.

Toxicity tests, made by determining the dose which was lethal for frogs in twenty-four hours, gave the following results: For the ethers, ethyl saligenin 0.5 mg. per gram frog, *n*-butyl 0.25 mg., iso-amyl 0.12, benzyl 0.36 to 4 mg.; for the esters, acetyl saligenin 0.9 mg., benzoyl 1.0 mg., dibenzoyl 2.0 to 3.0 mg. All of these compounds are therefore more toxic than saligenin itself.

The local anesthetic action was tested by dipping the frog's foot into the emulsion and then into one per cent. sulphuric acid. Two per cent. emulsions were used. Anesthetic action set in from two to five minutes after exposure to the drug and lasted

from ten to twenty-five minutes, except in the case of the normal butyl ether which was more prolonged and lasted from one to two hours, thus being more prolonged than that of saligenin. With the dibenzoyl ester no anesthesia whatever was obtained, even after thirty minutes' exposure to a five per cent. emulsion. This corresponds to the results which have been obtained with benzyl benzoate and other benzyl esters by Macht and others.

All these substances are, however, very irritating. On the tongues of human beings they give rise to a bitter taste and an intense burning sensation which is most marked with the normal butyl, and least marked with the dibenzoyl ester.

Upon the contractions of excised segments of rabbits' duodenum in 400 mils of aërated Ringer-Langendorff solution at 38–39 the addition of 2.5 mils of ethyl saligenin decreased the amplitude, slowed the rate, and finally caused complete inhibition. 1.5 mils of *n*-butyl, 0.5 mil of iso-amyl, 1.0 mil of benzoyl ester, and 10.0 mils of the dibenzoyl ester produced the same effects; but only 0.8 mil of the benzyl ether was required to produce complete inhibition, accompanied by a very marked lowering of tone. This lowering of tone was also striking with the iso-amyl but not with the other ethers. In the case of the acetyl ester there was at first an increased amplitude (probably due to acetic acid from hydrolysis) with slowing of the rate, gradually followed by inhibition.

When injected intravenously into starved rabbits, anaesthetized with ether, no visible effect upon the contractions of the exposed small intestine could be observed through a glass window in the abdominal wall after the ethyl and the iso-amyl ethers, but the *n*-butyl, the benzyl, the benzoyl and the dibenzoyl compounds all caused a definite inhibition of peristalsis and a well-marked dilatation of the intestine. Contrary to the findings of Mason and Piek, and in accord with the experiments of Macht, we also observed this inhibition after the injection of benzyl benzoate. When applied locally to the rabbit's intestine, all our compounds, with one exception, caused inhibition and dilatation. The acetic ester, however, on intravenous injection augmented the peristalsis, and when applied locally produced spastic contractions.

All the emulsions, on intravenous injection, caused a fall of blood pressure, which varied from a sudden transitory fall in the

case of the ethyl, *n*-butyl and iso-amyl ethers to a more gradual and more prolonged fall after the acetyl, benzoyl and dibenzoyl esters. The benzyl ether caused a sudden and more prolonged fall, which lasted four to five minutes. Control emulsions, injected at the same slow rate, gave no effect whatever. Perfusion of the frog's circulatory system gave a marked vaso constrictor effect, in striking contrast to the vasodilation obtained with emulsions of saligenin and benzyl benzoate. This constriction is probably due to irritation of the arterial walls.