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Pharmacology of Some Saligenin Derivatives.

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One of the authors reported the remarkable antispasmodic properties of benzyl benzoate and of the benzyl esters for smooth muscle,[1] and the local anesthetic properties of benzyl alcohol.[2] Numerous attempts were made by different investigators to prepare and study analogous benzyl esters and derivatives of benzyl alcohol, with the object of improving the therapeutic value of the original substances. Thus, Hirschfelder[3] pointed out that hydroxy-benzyl alcohol, or saligenin, also produced local anesthesia and was water-soluble. While phenmethylol and saligenin were both potent local anesthetics they had also a mildly relaxant or antispasmodic effect on smooth muscle preparations. Starting with saligenin, we synthesized a series of halogenated and other derivatives, and studied them especially as to their local anesthetic properties and their antispasmodic effects on smooth muscle.

The following compounds were prepared: amido saligenin, nitro saligenin, nitroso saligenin, mono-chlor saligenin, di-chlor saligenin, mono-brom saligenin, di-brom saligenin, mono-iodo saligenin, di-iodo saligenin, chlor-brom saligenin, brom-iodo saligenin, brom-nitro saligenin, nitro saligenin benzoate and saligenin nitro benzoate. All these compounds are solids and the majority are soluble in water only to a limited extent. Di-iodo saligenin is a very poorly soluble substance, saturated solutions of which give concentrations of only 1 : 20,000.

The local anesthetic effects of these compounds were studied on sensory nerve endings of frogs' legs, on the conjunctivæ of cats and rabbits and by the wheal method in guinea pigs. Minimal concentrations of the drugs, as well as the duration of the anesthesia, were taken into consideration when comparing the relative efficiency of the different compounds. Beginning with the most potent, the relative local anesthesia produced by the series, in concentrations of 1 : 1,000, was as follows: mono-iodo saligenin, di-brom saligenin,

[1] Macht, PROC. SOC. EXP. BIOL. AND MED., 1918, **15**, 63.

[2] Macht, *J. Pharmacol. and Exp. Therap.*, 1918, **11**, 263.

[3] Hirschfelder, *J. Pharmacol. and Exp. Therap.*, 1920, **15**, 261.

mono-brom saligenin, mono-chlor saligenin, brom-iodo saligenin, chlor-brom saligenin, di-chlor saligenin, nitro saligenin, and saligenin itself. Amido saligenin produced very little anesthesia; the other compounds produced no local anesthetic effect. When applied in solid form to the tongue and mucous membranes of the mouth, di-iodo saligenin produced definite anesthesia. The di-iodo saligenin being very insoluble, however, no quantitative comparison of this compound could be made with the others.

The effect of these compounds was studied on isolated surviving muscle preparations of the uterus, intestine, urinary bladder, gall bladder, fallopian tubes, ureters, vasa deferentia, and seminal vesicles of the rat, guinea pig, rabbit and cat. While saligenin itself produced only very mild relaxation of smooth muscle, all the halogenated derivatives were much more antispasmodic than either saligenin or benzyl alcohol. This was particularly true in regard to their action on isolated intestinal and uterine preparations. Beginning with the most potent, the relative relaxant, antispasmodic efficiency of the various compounds was as follows: di-brom saligenin, mono-brom saligenin, mono-iodo saligenin, mono-chlor saligenin, di-chlor saligenin, amido saligenin, and saligenin itself. These compounds produced relaxation of smooth muscle without killing it, as proved by response to a subsequent dose of pilocarpine hydrochloride. The di-iodo saligenin, although very insoluble, produced complete relaxation of intestinal muscle in concentrations as dilute as 1 : 20,000; di-brom saligenin, in concentrations of 1 : 10,000; mono-brom saligenin, in concentrations of 1 : 8,000; mono-iodo saligenin, in concentrations of 1:6,000; and the chlor-brom saligenin in concentrations of 1 : 15,000. Nitro saligenin produced a markedly depressant effect but killed the muscle. Brom-nitro saligenin was mild in its antispasmodic action, while chlor-brom and brom-iodo saligenin acted synergistically, the effect produced by them being greater than that effected by mixtures of either mono-iodo, mono-brom, or mono-chlor saligenin. Nitroso saligenin, nitro saligenin benzoate and saligenin nitro benzoate had no effect on smooth muscle. The halogenated compounds of the series were the most interesting. They were of low toxicity, 200 to 250 mg. per kilo weight of any of them, administered by stomach tube to rabbits, producing no harmful effects. The minimal lethal doses for the bromine and iodine derivatives was 0.5 gm. per kilo weight of rabbit when given by stomach.

With the exception of the di-iodo saligenin, most of the compounds are soluble *in vitro* and physiological saline to the extent of

1 : 1,000, and even more; and, as such, were studied on intravenous injection in cats and rabbits. Intravenous injection of doses of 10 mg., and more, in cats produced a mild fall in blood pressure. Large doses, 50 mg., or more, depressed the respiration; and lethal doses (200 mg., and more) paralyzed the respiratory center. Even large doses of the drugs (200 mg. per kilo) *fed* to rabbits produced no appreciable impairment of either kidney or liver function. Because of their low toxicity, anesthetic properties, and antispasmodic effect on smooth muscle, carefully controlled clinical experiments with these compounds have been begun and are in progress.

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Prevention and Cure of Rickets in Rats and Antirachitic Activation of Ergosterol by Cold Quartz Mercury Lamp.*

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The cold quartz mercury lamp has certain definitely advantageous physical and mechanical features not possessed by other sources of ultraviolet rays.[1] One of the most striking is the fact that the heat radiation is very slight. The emission spectrum of the cold quartz mercury lamp has a limited range from about 185 mμ to about 436 mμ with its maximum intensity at about 254 mμ. By means of a balanced thermocouple and filter method of ultraviolet radiometry, Coblentz and collaborators[2, 3] measured the intensity of the radiations from a cold quartz mercury lamp. They found that the relative intensities of the cold quartz emission lines at 254 mμ, 297 mμ, and 313 mμ were 865, 14, and 45, respectively, and that over 95% of all wave lengths emitted, including the line at 313 mμ, was contained in the resonance emission line of mercury vapor at 254 mμ. By a less accurate method (a sodium photo-electric cell and filters) Hibben[1] studied the energy transmission of the grid type of cold

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[1] Hibben, J. S., *Arch. Phys. Therapy, X-Ray, Radium*, 1931, **12**, 645, 675.

[2] Coblentz, W. W., Stair, R., and Hogue, J. M., *Bureau of Standards J. Res.*, 1931, **7**, 723.

[3] Coblentz, W. W., Stair, R., and Hogue, J. M., *Bureau of Standards J. Res.*, 1932, **8**, 759.