7171 P

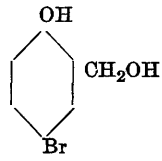
Experimental Pharmacological Study of Mono-Brom-Hydroxy-Benzyl Alcohol.

DAVID I. MACHT AND FITZGERALD DUNNING.

From the Chemical and Pharmacological Research Laboratories, Hynson, Westcott & Dunning, Inc., Baltimore

Macht, Dunning and Stickels[1] described the preparation and some of the pharmacological properties of a large number of derivatives of hydroxy-benzyl alcohol, commonly known as saligenin. Further investigation of the compounds pointed to the mono-brom-hydroxy-benzyl alcohol as being the most interesting of the series, and a more intensive and extensive study of that compound was accordingly begun.

Mono-brom-hydroxy-benzyl alcohol, named *bromsalizol* for convenience, is a white crystalline compound, melting at 107.5°-109°C., which on tasting, produces a numbness of the mucous membranes of the mouth and tongue. Its formula is



with the bromine in the para-position. The analogous compounds with halogen atoms in the ortho- and meta-positions in the benzene ring have also been prepared in our laboratories. Bromsalizol is soluble in water to the extent of 0.5% and is freely soluble in alcohol and olive oil.

When studied on lower and higher animals, the toxicity of bromsalizol was found to be quite low. The minimal lethal dosage for some of the higher animals is shown in Table I. Doses of from 5 to 10 grains (0.3 to 0.6 gm.) have been repeatedly ingested by a large number of men without any discomfort or untoward effect.

The two salient pharmacodynamic properties exhibited by bromsalizol, even when employed in small doses or low dilutions, are (1) its antispasmodic or relaxant effect on smooth muscle tissues and organs, and (2) its local anesthetic effect. Its action on smooth muscle was studied *in situ* on intestines of cats, rabbits and rats, and much more extensively on all kinds of smooth muscle preparations from excised organs of the cat, rabbit, guinea pig, rat, bear, wood-

[1] Macht, Dunning and Stickels. PROC. SOC. EXP. BIOL. AND MED., 1932, **30**, 378.

TABLE I.
Toxicity of Bromsalizol.

Animals*	Method of Administration	Dose per kilo, gm.	Result
Dog (3)	by stomach tube	1.0	fatal
" (3)	intravenous injection	0.25	"
Cat (10)	" "	0.25	"
Rabbit (6)	by mouth	0.5	"
" (6)	intravenous injection	0.25	"
" (3)	" "	0.1	mild stupor; recovery
Guinea pig (6)	intraperitoneal injection	1.0	fatal
Guinea pig (6)	" "	0.2	mild depression; recovery
White rat (10)	" "	0.4	fatal
White rat (10)	" "	0.15	coma; recovery
White mouse (10)	" "	0.5	fatal
White mouse (10)	" "	0.2	coma; recovery

*No. of experiments indicated in parentheses.

chuck and other animals. Experiments on excised muscle strips from the intestines, uterus, gall bladder, urinary bladder, fallopian tubes, ureters and other organs showed that the drug in dilutions of from 1:10,000 to 1:50,000 lowered the tonus of smooth muscle and slowed or completely inhibited the rhythmic contractions without killing the tissue, however, as could be proven by subsequent application of a suitable pharmacological stimulus. (Fig. 1.)

The local anesthetic effects of mono-brom-hydroxy-benzyl alcohol in aqueous or saline solutions were studied by the following methods: (1) instillation into the eyes of rabbits, (2) reflex action of preparations of frogs' legs, (3) the wheal method in guinea pigs, (4) direct application to nerve trunks tested with electric stimuli, and (5) infiltration in different tissues and subsequent surgical operations on the areas infiltrated. It was found that bromsalizol is from 3 to 4 times more efficacious as a local anesthetic than the mother substance, hydroxy-benzyl alcohol, or saligenin.

Action on Vital Functions. Injections of from 5 to 10 mg. of bromsalizol per kilo weight into cats under ether produced no effect on respiration or blood pressure. Doses of from 10 to 25 mg. per kilo weight produced a slight lowering of the blood pressure. Repeated doses of from 25 to 50 mg. of bromsalizol produced marked lowering of blood pressure and a slowing of the respiration, while lethal doses induced death through primary paralysis of the respiratory center. The lowering of blood pressure after moderately large but not lethal doses of the drug is due for the most part to its direct peripheral action, producing vasodilatation. This was established by perfusion experiments and by tests on surviving arterial rings.

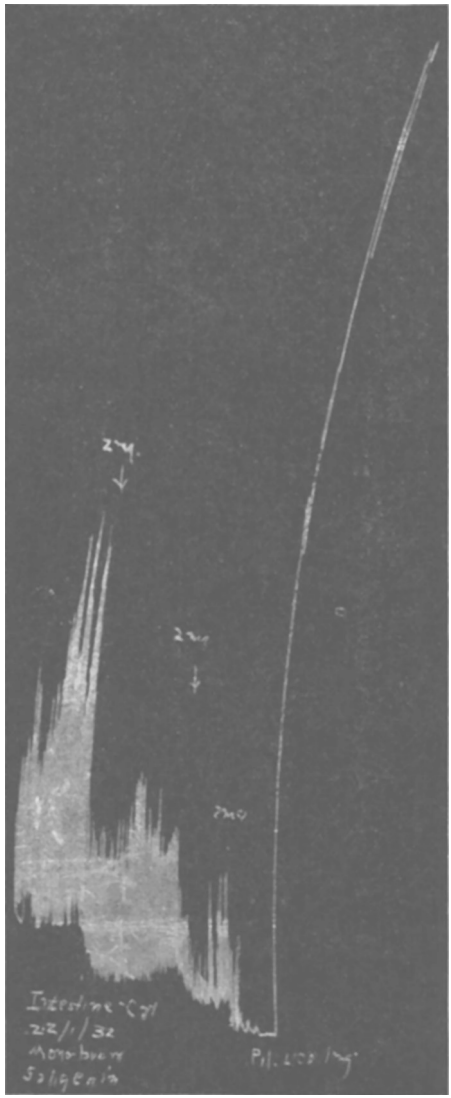


FIG. 1. Loop of small intestine of cat.

Note that 2 mg. of monobrom saligenin relax tonus, and that 6 mg. completely inhibit contractions without killing the preparation, as proven by its subsequent response to 1 mg. of pilocarpine.

Studies on kidney function by the Rowntree-Geraghty phenolsulphonphthalein test and on the liver function by Rosenthal's bromsulphalein method, as well as studies on blood chemistry, after prolonged feeding of the drug to rabbits, indicated that these organs

were not injured in any way by even large quantities of the substance.

After having established the maximum tolerated dosage and the toxic or lethal dosage of the compound and after having studied its action on the vital functions of the body, and in consideration of the wide margin of safety between the minimal effective pharmacodynamic and the toxic doses of the drug, carefully controlled clinical observations were made by a number of well-known physicians. Their preliminary reports indicated that the drug was efficacious in relieving spastic conditions, particularly of the gastro-intestinal organs and of the uterus (spastic dysmenorrhea). It was furthermore found by a number of surgeons to be a satisfactory local anesthetic for the performance of minor operations. The favorable preliminary results obtained with the drug render a further and more extensive clinical therapeutic study of the compound very desirable. Full data will be published elsewhere.

7172 C

Ergotoxine Excitement.

ALFRED GILMAN. (Introduced by H. G. Barbour.)

From the Department of Pharmacology and Toxicology, Yale University.

The attention of investigators has been so centered on the peripheral effects of ergotoxine that the central action of this drug has received scant notice. Most of the studies of ergotoxine have been conducted upon anesthetized animals. In these its depressant action upon the respiratory center has been repeatedly reported. There have been few references, however, to central stimulation. Barger and Dale,[1] after intramuscular injection of ergotoxine in cats, observed vomiting and "hyperexcitability". They have recorded similar findings including fever in rabbits. Githens[2] considered this fever to be of central origin. Rothlin[3] found clonic and tonic convulsions 3 hours after large intravenous doses of ergotamine in rabbits. Koppanyi and Evans[4] reported vomiting and defecation of

[1] Barger, G., and Dale, H. H., *Biochem. J.*, 1907, **2**, 240.

[2] Githens, T. S., *J. Pharm. and Exp. Therap.*, 1917, **10**, 327.

[3] Rothlin—Cited by Barger, G. Ergot and Ergotism, Gurney and Jackson, London.

[4] Koppanyi, T., and Evans, E., PROC. SOC. EXP. BIOL. AND MED., 1932, **29**, 1181, 1183.