Saccharin Derivatives VIII. Hypotensive Agents

By GLENN H. HAMOR

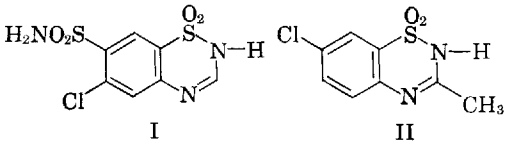
Saccharin analogs of chlorothiazide have been reported to possess diuretic activity. This paper relates the synthesis of 6-chloro-2-methylsaccharin, which is structurally similar to 7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide (diazoxide), a non-diuretic, hypotensive benzothiadiazine. The 6-chloro-2-methylsaccharin along with some 9 related saccharin derivatives, which had been synthesized earlier in a continuing study of saccharin chemistry, were screened for pharmacological activity. Preliminary results indicate hypotensive effects in cats and dogs, with little diuretic response. In fact, 2-ethyl-4-nitrosaccharin showed antidiuretic properties. In addition to producing a moderate transient hypotension in the anesthetized dog, 6-chloro-2-methylsaccharin produced CNS stimulation in rats.

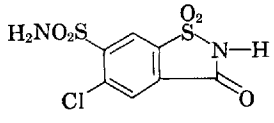
THE DIURETIC activity of compounds related to 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxide (chlorothiazide) (I) is well known (1). Certain of them also show hypotensive activity and are used clinically in the treatment of mild hypertension (2). Several recent papers describe closely related substances lacking the sulfamoyl group, exemplified by 7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide (diazoxide) (II), as possessing antihypertensive but not diuretic activity (3–6).

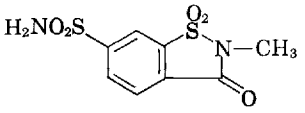
The saccharin analogs, 5-chloro-6-sulfamoylsaccharin (III) (7) and 2-methyl-6-sulfamoylsaccharin (IV) (8), are reported to exhibit diuretic activity.[1] This paper relates the results of preliminary pharmacological testing of some 9 saccharins corresponding to the hypotensive 1,2,4-benzothiadiazines in not containing an extranuclear sulfamoyl group. The synthesis of 6-chloro-2-methylsaccharin (V) is described. The remaining 8 saccharin derivatives had been prepared earlier in a continuing study of saccharin chemistry (9–11).

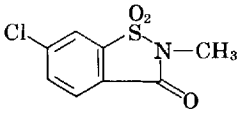
Because Topliss *et al.* (4) had reported most of the hypotensive activity of the benzothiadiazines to be retained if the chlorine at position 7 were replaced by nitro, various nitrosaccharins and related compounds were selected for testing (Table I). The 6-chloro-2-methylsaccharin was synthesized by chlorosulfonation of 4-chlorotoluene, followed by treatment with aqueous ammonia, which gave 4-chlorotoluene-2-sulfonamide. Oxidation of this compound succeeded by a Williamson reaction of the resulting 6-chlorosaccharin with methyl iodide gave the desired 6-chloro-2-methylsaccharin.

Preliminary pharmacological results[2] indicate these compounds to possess hypotensive effects, on intravenous injection in cats and dogs, of primarily a transient nature. The 4-nitro-2-*n*-propylsaccharin (compound *4*) shows some evidence of autonomic ganglionic blocking. These substances possess little diuretic response. In fact, 2-ethyl-4-nitrosaccharin (compound *3*) showed antidiuretic properties. In contrast, 2-methyl-6-sulfamoylsaccharin (IV), the diuretic compound, produced transient pressor effects in the cat after doses of 0.5–10.0 mg./Kg. intravenously. In addition to producing a moderate transient hypotension following administration of 5 and 10 mg./Kg. i.v. in the dog, 6-chloro-2-methylsaccharin (V) caused CNS stimulation in rats orally at 300 mg./Kg. It may be of interest to note that this saccharin compound (V) is tasteless, as have been other *N*-substituted saccharins in our experience.









EXPERIMENTAL

6-Chloro-2-methylsaccharin (V).[3]—In a 200-ml. round-bottom flask fitted with a reflux condenser and heating mantle were placed 5.0 Gm. (0.023 mole) of 6-chlorosaccharin,[4] m.p. 217° [reported m.p. 218° (12)], 1.3 Gm. (0.012 mole) of sodium carbonate, and 100 ml. of dimethylformamide. To this was added 7.3 Gm. (0.051 mole) of methyl iodide. The solution was refluxed for 1 hr. and then poured into approximtely 700 ml. of ice water. The mixture was cooled for 30 min., then filtered and washed with 2 portions of cold water to give 3.2 Gm. (60%) of white solid, m.p. 174–175.5°.[5] Recrystallization

Received December 29, 1965, from the School of Pharmacy, University of Southern California, Los Angeles.
Accepted for publication February 26, 1966.
Presented to the (Pharmaceutical Sciences) Section (Np), American Association for the Advancement of Science, Berkeley, Calif., meeting, December 1965.
Previous paper: Hamor, G. H., *J. Pharm. Sci.*, **52**, 603 (1963).

[1] However, deStevens reports III to be inactive as a diuretic. (See *Reference 1*, p. 113.)

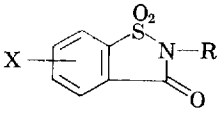
[2] The author is indebted to Smith Kline & French Laboratories, Philadelphia, Pa., for pharmacological testing.

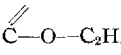
[3] *Chemical Abstracts* nomenclature, 6-chloro-2-methyl-1,2-benzisothiazolin-3-one 1,1-dioxide.

[4] The author thanks Bernard L. Reavlin for synthesis of the sample of 6-chlorosaccharin.

[5] Melting points were determined by the open capillary tube method and are uncorrected.

TABLE 1.—SACCHARIN DERIVATIVES



Compd.	X	R	M.p., °C.[a]	Ref.
IV	6-SO_2NH_2	CH_3	230–232	(8)
V	6-Cl	CH_3	180–181	This paper
1	6-NO_2	*n*-C_3H_7	120–121	(9)
2	6-NO_2	*i*-C_3H_7	148	(14)
3	4-NO_2	C_2H_5	184.5–185.5	(10)
4	4-NO_2	*n*-C_3H_7	138–139.5	(10)
5	H	*i*-C_3H_7	62–64	(14, 15)
6	H		136	(11, 13)
7	H	$OCH(CH_3)_2$	136–137	(14, 15)
8	H	$N(C_2H_5)_2$	206–207	(11)

[a] Melting points were determined either with a Fisher-Johns melting point apparatus or by the capillary tube method and are uncorrected.

from acetone–water gave white needle crystals, m.p. 180–181°.

Anal.[6]—Calcd. for $C_8H_6ClNO_3S$: C, 41.50; H, 2.61. Found: C, 41.60; H, 2.73.

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[6] Analyses were performed by Elek Microanalytical Laboratories, Torrance, Calif.

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Thin-Layer Chromatography of Cardiac Glycosides

By EUGENE J. JOHNSTON and ALLEN L. JACOBS

A rapid thin-layer chromatographic procedure for the separation and identification of the common cardiac glycosides is presented. A benzene–ethanol solvent is used for development and a perchloric acid spray for visualization.

THIN-LAYER chromatography has proven to be more rapid and sensitive than paper chromatography for the identification and purity determination of many drugs. A number of solvent systems and sprays useful for cardiac glycosides have been published (1–4). This paper reports the development of a relatively simple technique which has certain advantages over these approaches.

Received January 10, 1966, from the Analytical Research Department, Sandoz Pharmaceuticals, Hanover, N. J.
Accepted for publication February 21, 1966.

EXPERIMENTAL

Thin-Layer Plates.—A 0.25-mm. layer of Silica Gel G (E. Merck, Darmstadt) is applied to the plates. The plates are air dried for 10 min., then heated in an oven for 45 min. at 120°. The plates are stored in a desiccator and used without further activation.

Solvent System.—Benzene–95% ethanol (7:3 v/v).

Spray Reagent.—Fifteen milliliters of 70% perchloric acid added to 100 ml. of water.

Preparation of Samples.—The substances are dissolved in a suitable solvent, usually methanol. For purity studies, 100 mcg. of substance is spotted on