[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, THE GEORGETOWN UNIVERSITY MEDICAL CENTER[1]]

SACCHARIN DERIVATIVES: 3-ALKYLAMINO- AND 3-DIALKYLAMINOALKYLAMINO-1,2-BENZISOSULFONAZOLES AND 2-DIALKYL- AMINOALKYL-*o*-BENZOIC SULFIMIDES

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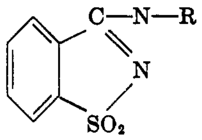
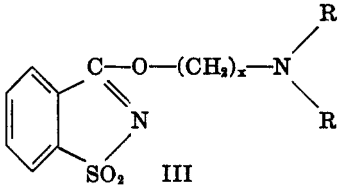
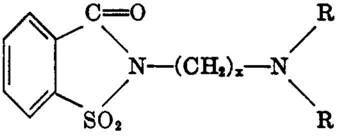
In continuation of our investigation of the chemistry of saccharin and its derivatives (1) we have prepared and wish to report at this time four new series of compounds derived from saccharin. Our present studies concern members prepared in the following series: 3-alkylamino-1,2-benzisosulfonazoles (I), 3-dialkylaminoalkylamino-1,2-benzisosulfonazoles (II), 3-dialkylaminoalkoxy-1,2-benzisosulfonazoles (III), and 2-dialkylaminoalkyl saccharins (IV).



I, R = Alkyl
II, R = Dialkylaminoalkyl



III



IV

The dialkylaminoalkyl derivatives, their simple and quaternary salts, types II, III, and IV, were investigated for pharmacological activity. Some of the members of these series possessed slight hypotensive activity and members in all three series possessed antihistaminic and bronchiodilatory activity in varying degrees.

Saccharin chloride, 3-chloro-1,2-benzisosulfonazole, was first prepared by Jesurum (2) while investigating the reaction of phosphorus pentachloride with saccharin. His method was modified and improved by Meadow and Reid (3). In our experience, derived from numerous preparations of this compound, the best yields are obtained by this method only if the reactants are intimately mixed and maintained at a temperature of 170–180° for an hour. We would also like to point out that saccharin chloride is a strong vesicant and can produce painful chemical burns and a very persistent dermatitis.

The reaction of saccharin chloride with alcohols was investigated by Meadow and Reid (3) who prepared a series of 3-alkoxy-1,2-benzisosulfonazoles employing an excess of the alcohol as reaction medium. In the present work we em-

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TABLE I

3-DIALKYLAMINOALKOXY-1,2-BENZISOSULFONAZOLE HYDROCHLORIDES

Substituent	Formula	M.p., °C.	Analyses							
			Carbon		Hydrogen		Nitrogen		Ionic chloride	
			Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
Dimethylaminoethyl	$C_{11}H_{15}ClN_2O_3S$	178–179	45.43	45.21	5.20	5.65	9.63	9.37	12.19	12.03
Diethylaminoethyl	$C_{13}H_{19}ClN_2O_3S$	144–145	48.97	48.95	6.01	5.91	8.79	8.79	11.12	11.36
γ-Diethylamino-propyl	$C_{14}H_{21}ClN_2O_3S$	186–187	52.74	52.50	6.64	6.76	8.79	8.57	10.66	11.02
β-Di-*n*-butylamino-propyl	$C_{18}H_{29}ClN_2O_3S$	135–137	55.58	55.57	7.52	7.56	7.20	7.00	9.16	8.86
γ-Di-*n*-butylamino-propyl	$C_{18}H_{29}ClN_2O_3S$	131–132	55.58	55.63	7.52	7.77	7.20	6.98	9.16	9.04
β-(2-Pyridylethyl)	$C_{14}H_{13}ClN_2O_3S$	156–157	51.77	51.90	4.03	3.89	8.63	8.44	10.92	11.08
δ-Diethylamino-pentyl-2	$C_{16}H_{25}ClN_2O_3S$	141–142	53.24	53.04	6.98	7.02	7.76	7.89	9.82	9.65
β-Di-*n*-butylamino-ethyl	$C_{17}H_{27}ClN_2O_3S$	130–131	54.46	54.71	7.26	7.23	7.47	7.47	9.46	9.23
Pyrrolidinoethyl	$C_{13}H_{17}ClN_2O_3S$	151–152	49.28	49.45	5.41	5.28	8.84	8.97	11.19	11.46
Piperidinoethyl	$C_{14}H_{19}ClN_2O_3S$	151–152	50.82	50.83	5.79	6.00	8.47	8.32	10.72	10.33
Morpholinoethyl	$C_{13}H_{17}ClN_2O_4S$	150–151	46.91	46.84	5.15	5.40	8.42	8.08	10.65	10.46

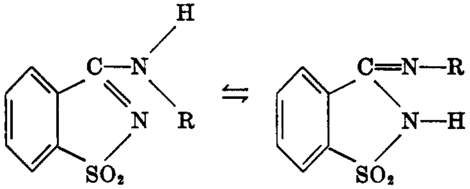
ployed the reaction of saccharin chloride and dialkylaminoalkanols in an inert solvent, usually acetone. The reaction proceeded rapidly and gave the product in almost quantitative yield as the hydrochloride salt. The 3-dialkylaminoalkoxy-1,2-benzisosulfonazoles, obtained as the crystalline hydrochloride salts, are listed in Table I together with pertinent data.

TABLE II

3-ALKYLAMINO-1,2-BENZISOSULFONAZOLES

Alkyl Substituent	Formula	M.p., °C.	Analyses					
			Carbon		Hydrogen		Nitrogen	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
Methyl	$C_8H_8N_2O_2S$	303–304	48.96	49.32	4.11	3.87	14.28	14.14
Ethyl	$C_9H_{10}N_2O_2S$	289–290	51.41	51.49	4.79	4.54	13.32	13.00
n-Propyl	$C_{10}H_{12}N_2O_2S$	223–224	53.55	53.54	5.39	5.39	12.49	12.67
n-Butyl	$C_{11}H_{14}N_2O_2S$	185–185.5	55.44	55.37	5.92	6.11	11.76	12.01
n-Amyl	$C_{12}H_{16}N_2O_2S$	163–164	57.12	57.15	6.39	6.45	11.10	10.93
n-Hexyl	$C_{13}H_{18}N_2O_2S$	177–178	58.62	58.90	6.81	6.60	10.52	10.79
n-Heptyl	$C_{14}H_{20}N_2O_2S$	165–165.5	59.97	60.29	7.19	6.98	9.99	10.34
n-Octyl	$C_{15}H_{22}N_2O_2S$	155–156	61.19	61.19	7.53	7.60	9.52	9.60
n-Nonyl	$C_{16}H_{24}N_2O_2S$	147–148	62.30	62.44	7.84	7.76	9.08	8.90
n-Decyl	$C_{17}H_{26}N_2O_2S$	149–150	63.32	63.37	8.13	7.99	8.69	8.86
n-Undecyl	$C_{18}H_{28}N_2O_2S$	148–149	64.25	63.87	8.39	8.23	8.33	8.52
n-Dodecyl	$C_{19}H_{30}N_2O_2S$	150–151	65.10	64.97	8.63	8.41	7.99	8.26

Saccharin chloride has been reacted with nitrogenous bases such as ammonia and aniline (2) and shown to yield 3-substituted amino-1,2-benzisosulfonazoles. The alkyl amines, methyl through dodecyl, yielded analogous products on reaction with saccharin chloride. The compounds thus prepared were all obtained as crystalline solids and are listed in Table II. The compounds, as would be expected from their structure, are tautomeric (4). Indeed the exocyclic nitrogen atom no longer behaves as an amino nitrogen but rather like an amido nitrogen. It does not form the hydrochloride or methiodide.



The 3-dialkylaminoalkylamino-1,2-benzisosulfonazoles were obtained by reacting equimolar quantities of the dialkylaminoalkylamines with saccharin chloride in either acetone or benzene. These are listed in Table III. If the hydrochlorides of the compounds in which R = dialkylaminoalkyl are boiled with excess alcoholic hydrogen chloride and precipitated with ether, the monohydrochloride (of the side chain amino group) is recovered unchanged in all cases.

We have previously detailed the use of dimethylformamide as a solvent for sodium saccharin and alkyl halides and pointed out its advantages as a reaction

TABLE III

3-DIALKYLAMINOALKYLAMINO-1,2-BENZISOSULFONAZOLE HYDROCHLORIDES

Substituent	Formula	M.p., °C.	Analyses							
			Carbon		Hydrogen		Nitrogen		Ionic chloride	
			Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
Dimethylamino-ethyl	$C_{11}H_{16}ClN_3O_2S$	260–262	45.59	45.80	5.57	5.49	14.50	14.30	12.24	12.50
γ-Dimethylamino-propyl	$C_{12}H_{18}ClN_3O_2S$	206–207	47.44	47.62	5.97	6.04	13.83	13.42	11.67	11.67
Diethylaminoethyl	$C_{13}H_{20}ClN_3O_2S$	165–166	49.12	49.21	6.34	6.57	13.22	13.39	11.16	11.00
γ-Diethylamino-propyl	$C_{14}H_{22}ClN_3O_2S$	210–212	50.67	50.99	6.68	6.56	12.66	12.90	10.68	10.69
δ-Diethylamino-butyl	$C_{15}H_{24}ClN_3O_2S$	199–200	52.08	52.06	6.99	7.27	12.15	11.96	10.25	10.12
ε-Diethylamino-amyl	$C_{16}H_{26}ClN_3O_2S$	glass	53.39	53.07	7.28	7.30	11.68	11.30	9.85	9.52
γ-Dibutylamino-propyl	$C_{18}H_{30}ClN_3O_2S$	186–187	55.72	55.61	7.79	7.98	10.83	10.57	9.14	8.97
Morpholinoethyl	$C_{13}H_{18}ClN_3O_3S$	269–271	47.05	47.21	5.47	5.39	12.66	12.60	10.69	10.77
Pyrrolidinoethyl	$C_{13}H_{18}ClN_3O_2S$	202–203	49.44	49.49	5.75	6.01	13.31	13.03	11.22	11.31

TABLE IV

2-DIALKYLAMINOALKYL SACCHARINS

No.	Substituent	Formula	B.p., °C.	Mm.	Analyses					
					Carbon		Hydrogen		Nitrogen	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
1	Diethylaminoethyl	$C_{13}H_{18}N_2O_3S$	144–154[a]	0.06	55.30	55.43	6.43	6.44	9.92	10.03
2	Morpholinoethyl	$C_{13}H_{16}N_2O_4S$	178–186[b]	0.10	52.69	52.72	5.44	5.53	9.45	9.14
3	Piperidinoethyl	$C_{14}H_{18}N_2O_3S$	160–163[c]	0.10	57.12	57.27	6.16	6.06	9.52	9.25
4	γ-Diethylamino-propyl	$C_{14}H_{20}N_2O_3S$	163–166	0.20	56.73	56.61	6.80	6.75	9.45	9.41
5	γ-Di-*n*-butylamino-propyl	$C_{18}H_{20}N_2O_3S$	175–185	0.10	61.33	61.27	8.01	8.03	7.95	8.15

No.	Hydrochloride				Methiodide			
	Formula	M.p., °C.	Analyses, ionic chloride		Formula	M.p., °C.	Analyses, ionic iodide	
			Calc'd	Found			Calc'd	Found
1	$C_{13}H_{19}ClN_2O_3S$	217–218[d]	11.12	11.25	$C_{14}H_{21}IN_2O_3S$	200–201	29.91	30.04
2	$C_{13}H_{17}ClN_2O_4S$	236	10.65	10.76	$C_{14}H_{19}IN_2O_4S$	259–260	28.96	29.06
3	$C_{14}H_{19}ClN_2O_3S$	252–254	10.72	10.68	$C_{15}H_{21}IN_2O_3S$	260–261	29.09	29.03
4	$C_{14}H_{21}ClN_2O_3S$	166–167[e]	10.65	10.74	$C_{15}H_{23}IN_2O_3S$	220–221	28.95	28.76
5	$C_{18}H_{29}ClN_2O_3S$	90–92	9.12	9.43	$C_{19}H_{31}IN_2O_3S$	150–152	25.67	25.62

[a] M.p., 61–63°, Hamor and Soine, *J. Am. Pharm. Assn.*, **43**, 120 (1954) reported m.p. 65.5–68.5°. [b] M.p. 103–104°. [c] M.p. 80–81°. [d] Reference a reported m.p. 213–215°. Reference a reported m.p. 167.5–169°.

medium in the preparation of N-substituted saccharins (1). The reaction of dialkylaminoalkyl chlorides with sodium saccharin in this medium proceeded readily at the reflux temperature. The bases were isolated by distillation at pressures below 1 mm. or were converted to the hydrochlorides. The bases, their hydrochloride salts and methiodides are listed in Table IV.

EXPERIMENTAL

The preparation of the various types of compounds will be illustrated by an example of each class.

3-Dialkylaminoalkoxy-1,2-benzisosulfonazole hydrochlorides. Table I. *3-Dimethylaminoethoxy-1,2-benzisosulfonazole hydrochloride.* Pseudosaccharin chloride (12 g., 0.06 mole) was dissolved with warming in 90 ml. of acetone and the theoretical quantity, 5.35 g. (0.06 mole) of dimethylaminoethanol in 30 ml. of acetone added slowly through the condenser. There was an instantaneous reaction and the product started to precipitate. The mixture was refluxed gently for 30 minutes, refrigerated and the product filtered off. After washing with acetone and ether, the product melted at 172–175°. Recrystallization from chloroform-ether gave a pure product, m.p. 176–177°.

In some cases the product did not crystallize from acetone on refrigeration. Ether was then added to induce crystallization.

3-Substituted amino-1,2-benzisosulfonazoles: Tables II and III. (*a*) *3-Propylamino-1,2-*

benzisosulfonazole. To a solution of 4 g. (0.02 mole) of pseudosaccharin chloride in benzene was added 0.9 g. (0.02 mole) of *n*-propylamine dissolved in 10 ml. of benzene. The mixture was refluxed 10 minutes, cooled, the product filtered off and washed with a little cold benzene. One recrystallization from acetone-water yielded a crystalline material with m.p. 223–224°.

(*b*) *3-Dimethylaminoethylamino-1,2-benzisosulfonazole hydrochloride.* To a solution of 4 g. of pseudosaccharin chloride (0.02 mole) in 50 ml. of acetone was added rapidly through the condenser a solution of 1.8 g. (0.02 mole) of dimethylaminoethylamine in 5 ml. of acetone. The hydrochloride precipitated out immediately. The mixture was refluxed 10 minutes, cooled, the product filtered off and washed with acetone and then with ether. Recrystallization from acetone-ether gave 5.5 g., 95%, of crystalline material, m.p. 261–263°.

2-Dialkylaminoalkyl saccharins: Table IV: *2-Diethylaminoethyl saccharin.* Sodium saccharin (20.5 g., 0.1 mole) was dissolved in 40 ml. of dimethylformamide with the aid of heat. After solution was effected 13.6 g. (0.1 mole) diethylaminoethyl chloride, dissolved in an equal volume of dimethylformamide, was slowly added through the condenser. The mixture was refluxed for four hours, cooled, and worked up further for the isolation of the free base or of its salts.

(*a*) *Hydrochloride salt.* To ½ of the above solution was added an equal volume of absolute ethanol and sufficient alcoholic hydrogen chloride to render the solution acid. Ether was added to the cooled solution until crystallization started. Refrigeration overnight yielded a crystalline product that was filtered off, washed with cold alcohol-ether mixture and recrystallized from methanol-ether. The recrystallized product melted at 217–218°.

(*b*) *Free base.* The other ½ of the solution was stripped of all solvent on the water-bath at reduced pressure. The oily residue that remained was filtered hot and distilled *in vacuo.* The product boiled between 144–154° at 0.06 mm. It solidified in the receiver and melted at 61–63°.

(*c*) *The methiodide:* The base (3 g.) dissolved in 25 ml. of acetone was mixed with 5 ml. (excess) of methyl iodide and allowed to stand overnight. A crystalline product was obtained which was filtered off and recrystallized from methanol, m.p. 200–201°.

SUMMARY

Four series of saccharin derivatives have been prepared and characterized. The 3-alkylamino- and 3-dialkylaminoalkylamino-1,2-benzisosulfonazoles have been obtained by the reaction of 3-chloro-1,2-benzisosulfonazole (pseudosaccharin chloride) with the corresponding alkyl amines and dialkylaminoalkylamines in an inert solvent. A series of 3-dialkylaminoalkoxy-1,2-benzisosulfonazoles was similarly obtained from saccharin chloride and dialkylaminoalkanols. Several members of the 2-dialkylaminoalkyl saccharin series have also been prepared by reaction of sodium saccharin with dialkylaminoalkyl halides in dimethylformamide. The dialkylaminoalkyl derivatives, types II, III, and IV, have been screened for pharmacological activity.

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