## Synthesis of 2-(Diethylcarbamoyl)- and 2-(Diethylthiocarbamoyl)saccharin, and Related Compounds

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Because acylurea and carbamate groups are associated with various pharmacological activities, a number of saccharin and 6-nitrosaccharin derivatives containing these groups were synthesized for pharmacological screening. The compounds prepared were: 2-(diethylcarbamoyl)saccharin; 2-(diethylcarbamoyl)-6-nitrosaccharin; 2-(diethylthiocarbamoyl)saccharin; and 2-carbethoxysaccharin. Also isolated from the reaction of the N,N-dialkylcarbamoyl chlorides and sodium saccharin (or sodium 6-nitrosaccharin) were compounds whose analyses corre-sponded to the following structures: 3-(diethylamino)-1,2-benzisothiazole-1,1-dioxide; 3-(diethylamino)-6-nitro-1,2-benzisothiazole-1,1-dioxide; and 3-(di-methylamino)-1,2-benzisothiazole-1,1-dioxide. Preliminary pharmacological testing has indicated that 2-(diethylcarbamoyl)saccharin; 2-carbethoxysaccharin; and 3-(diethylamino)-1,2-benzisothiazole-1,1-dioxide possess a low degree of sedative and central nervous system depressant activity, and have no significant anticonvulsant, antitumor, or diuretic activity.

MANY COMPOUNDS containing carbamate or acylurea groups exhibit various types of medicinal activity including those of anticonvulsant, antifungal, antitumor, diuretic, and sedative (1). The purpose of this work was the preparation of some saccharin and nitrosaccharin derivatives containing carbamate and acylurea groups for pharmacological testing.

The compounds prepared have the following general formula (A), and are listed and their properties given in Table I.



These saccharin derivatives were prepared by refluxing sodium saccharin or sodium 6-nitrosaccharin with N,N-diethylcarbamoyl chloride, N,N-diethylthiocarbamoyl chloride, or ethyl chloroformate in such solvents as chloroform, benzene, or a carbon tetrachloride-water mixture.

Also isolated, in many cases, from the reaction of the N,N-dialkylcarbamoyl chlorides and sodium saccharin (in addition to the expected dialkylcarbamoylsaccharins) were other, highermelting compounds. The elemental analyses

and the infrared absorption spectra of these compounds correspond to structures of the following general formula (B). These substances are listed and their properties given in Table II.



Preliminary pharmacological testing has indicated that 2-(diethylcarbamoyl)saccharin; 2carbethoxysaccharin; and 3-(diethylamino)-1,2benzisothiazole-1,1-dioxide possess a low degree of sedative and central nervous system depressant activity and have no significant anticonvulsant, antitumor,1 or diuretic activity.2 Of interest here may be the work of Whitehead and Traverso reporting the synthesis of N-monosubstituted 3amino-1,2-benzisothiazole-1,1-dioxides for evaluation as diuretic or hypoglycemic agents (2).

## **EXPERIMENTAL**

2-(Diethylcarbamoyl)saccharin(I).<sup>3</sup>-To a mixture of 24.12 Gm. (0.1 mole) of powdered sodium saccharin and 100 ml. of dry chloroform contained in a 250-ml. flat-bottomed flask provided with a reflux condenser was added 15.0 Gm. (0.11 mole) of N,N-diethylcarbamoyl chloride. The mixture was refluxed for eighteen hours with occasional stirring and then filtered while hot. Evaporation of chloroform from the filtrate gave a thick, viscous, almost transparent, semisolid mass. Recrystal-

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National Institutes of Health, Public Health Service, Be-thesda, Md. <sup>2</sup> The authors are indebted to Smith Kline and French Laboratories, Philadelphia, Pa., for pharmacological testing. <sup>3</sup> Chem. Abstr. nomenclature: 2-(diethylcarbamoyl)-1,2-benzisothiazolin-3-one-1,1-dioxide.

|                         | %<br>Found                              | 11.38  | •<br>•  | 21.29  | •<br>•                              | Reported   | %<br>Found<br>13.44  |
|-------------------------|---|--|---|--|-------------------------------------|--|--|
| X S <sup>2</sup><br>N-R | Sulfur,<br>Caled.                       | 11.40  | ÷   | 21.50  | :                                   | acorrected.  | Sulfur,<br>Calcd.<br>13.48   |
|                         | en, % Nitrogen, %<br>Found Calcd. Found | 66.6   | :   | 9.32   | :                                   | and are ut   | n, %<br>Found<br>11.67   |
|                         |   | 9.95   | . <u>.</u>  | 9.40   | :                                   | apparatus  | Nitroge<br>Caled.<br>11.76   |
|                         |   | 5.05   | 4.08  | 5.03<br>5.05   | 3.67                                | ting point :   | m, %<br>Found<br>5.89<br>4.77  |
|                         | Hydrog<br>Calcd.                        | 5.00   | 4.03  | 4.73   | 3.55                                | Johns mel  | Hydroge<br>Calcd.<br>5.92<br>4.62<br>4.80  |
|                         | , %<br>Found                            | 51.26  | 44.06   | 50.53<br>49.89   | 47.26                               | with Fisher<br>ERIVATIVH                             | Found<br>55.60<br>51.24  |
|                         | Carbon<br>Calcd.                        | 51.10  | 44.03   | 48.32  | 47.17                               | were taken<br>JIOXIDE D:<br>R                        | Carbon<br>Caled.<br>55.42<br>46.63<br>51.47  |
|                         | Vield,                                  | 40   | 63  | 28   | 65                                  | ting points  | $egin{array}{c} { m Yield}, & \ \% & \ 51 & \ 67 & \ 9 & \ 9 & \ 9 & \ 9 & \ 9 & \ 1 & \ $ |
|                         | Recrystal-<br>lizing<br>Solvent         | EtOH-H2O   | EtOH  | EtOH   | EtOH                                | eles, Calif. <sup>6</sup> Mel<br>2-BENZISOTHIA2<br>X | Recrystal-<br>lizing<br>Solvent<br>EtOH<br>Acetone<br>EtOH   |
|                         | M. P., <sup>b</sup>                     | 117–118  | 172-173   | 140–141  | 136°                                | tories, Los Ang<br>ABLE II.—1,                       | M. P. <sup>b</sup><br>°C.<br>206–207<br>256–257<br>273–274   |
|                         | Formula                                 | $C_{12}H_{14}N_2O_4S$                                | C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> O <sub>6</sub> S | C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> S <sub>2</sub> | C <sub>10</sub> H,NO <sub>5</sub> S | o Analytical Labora<br>T                             | $\begin{array}{c} {}^{Formula}\\ C_{JJ}H_{14}N_2O_2S\\ C_{IJ}H_{18}N_3O_4S\\ C_9H_{10}N_2O_2S \end{array}$   |
|                         | ×<br>0                                  | $-\overset{\ }{\overset{C}{C}} - N(C_2H_{\delta})_2$ | $-c-N(C_2H_5)_2$  | $-c - N(C_2 H_5)_2$  | COC₂H₅                              | srformed by Elek Micr<br>3).                         | ${}^{R}_{M} = {}^{N}_{N} (C_{2}H_{5})_{2} - {}^{N}_{N} (C_{2}H_{5})_{2} - {}^{N}_{N} (CH_{3})_{2} - {}^{N}_{N} (CH_{3}) - {}^{N}_{N} (CH_$ |
|                         | ×                                       | Н  | $NO_2$  | Н  | Н                                   | es were pe<br>int 136° (3                            | X<br>H<br>NO <sub>2</sub>  |
|                         | No.                                     | I  | II  | III  | IV                                  | a Analy<br>melting po                                | No.<br>V<br>U<br>U<br>U<br>U<br>U  |



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TABLE I.—SACCHARIN DERIVATIVES<sup>4</sup>

lization of this solid from ethanol gave as a first crop 2.5 Gm. of a white crystalline product which was a mixture of two compounds, one melting at  $110-115^{\circ}$  (the desired compound), and the other melting in the range of 200-205° [corresponding to 3-(diethyl-amino) - 1,2 - benzisothiazole - 1,1 - dioxide]. To the ethanolic mother liquor from the above first crop was added distilled water, resulting in the formation of a copius white precipitate. After standing four hours at room temperature the mixture was filtered and, after repeated recrystallization from ethanol-water, gave 12.5 Gm. (40%) of white, crystalline 2-(diethylcarbamoyl)saccharin melting at 117-118°.

**3** - (Diethylamino) - 1,2 - benzisothiazole - 1,1 - dioxide(V).—The above reaction was repeated using the same materials, but the reflux period was lengthened to sixty-four hours. At the end of the sixty-four-hour period the hot chloroformic reaction mixture was filtered. The insoluble residue (8.5 Gm.) contained some unreacted saccharin and sodium chloride. Evaporation of the filtrate to saturation point, cooling, and filtering gave 12.5 Gm. of a white, crystalline product melting in the range of 200-205°. Recrystallization from ethanol gave 11.5 Gm. (46.9%) of the compound analyzing for 3- (diethylamino)-1,2-benzisothiazole-1,1-dioxide and melting at 206-207°.

2-(Diethylthiocarbamoyl)saccharin(III).—A mixture of 24.12 Gm. (0.1 mole) of powdered sodium saccharin and 18.0 Gm. (0.12 mole) N,N-diethylthiocarbamoyl chloride was refluxed in 100 ml. dry chloroform for six hours. The hot solution was Upon evaporation the filtrate gave a filtered. red-colored soft material which was dissolved in hot ethanol and decolorized by activated charcoal. The ethanol solution, on standing one day at room temperature and then filtering, yielded 9.0 Gm. (30%) of light yellow-colored crystals melting at 140-141°. While the analytical values found for carbon differ by approximately 1.5% from the calculated values (as shown in Table I), the nitrogen and sulfur determinations agreed closely with the calculated values. Also, the infrared spectra of this compound (as determined using the Perkin-Elmer model 137 Infracord, with the sample prepared in a Nujol mull) showed two moderately strong absorption bands in the carbonyl region of 5.76 and  $5.90\mu$ , corresponding to the expected structure.

Another run of identical materials was refluxed for twenty-four hours. From this reaction, 8.0 Gm. (34%) of a white, crystalline substance melting at  $206-207^{\circ}$  was isolated. This compound gave the same elemental analysis as was obtained for 3-(diethylamino)-1,2-benzisothiazole-1,1-dioxide. A mixed melting point of the two compounds gave no depression, therefore they were judged to be identical. A run using a reaction medium of watercarbon tetrachloride gave a similar yield of this higher-melting compound.

2 - (Diethylcarbamoyl) - 6 - nitrosaccharin(II).— A mixture of 2.3 Gm. (0.008 mole) sodium 6-nitrosaccharin (3) and 1.4 Gm. (0.01 mole) N,N-diethylcarbamoyl chloride was refluxed in 50 ml. of dry chloroform for twenty hours. Filtration of this hot mixture followed by complete evaporation of chloroform from the filtrate gave a soft solid. Recrystallization from ethanol yielded 1.9 Gm. (73%) of white, needle crystals melting at 172–173°.

3 - (Diethylamino) - 6 - nitro - 1,2 - benziso-

thiazole-1,1-dioxide(VI).—Three grams (0.012 mole) of sodium 6-nitrosaccharin was refluxed with 1.5 Gm. (0.012 mole) of N,N-diethylthiocarbamoyl chloride in 50 ml. of dry chloroform for eighteen hours. The resultant product was purified and recrystallized from acetone, giving 2.0 Gm. (67%) of the desired light yellow-colored compound, m. p.  $256-257^{\circ}$ .

**3** - (Dimethylamino) - 1,2 - benzisothiazole - 1,1 dioxide(VII).—A mixture of 4.8 Gm. (0.02 mole) powdered sodium saccharin, 2 ml. chloroform, and 1.5 Gm. (0.02 mole) N,N-dimethylcarbamoyl chloride was heated in a flask equipped with a reflux condenser on an electric hot plate at 150-160° for one hour. After cooling the flask 25 ml. of chloroform was added and the mixture was refluxed for twenty-four hours, with occasional manual stirring. The desired product was isolated in a manner similar to that used for the preceding compounds and recrystallized from ethanol to give 0.5 Gm. (9%) of white, crystalline compound, m. p. 273-274°.

**2-(Carbethoxy)saccharin(IV).**—Magidson and Garbschow (4) prepared this compound, but did not fully describe the procedure. A mixture of 24.12 Gm. (0.1 mole) powdered saccharin, 10.8 Gm. (0.1 mole) ethyl chloroformate, and 50 ml. of dry benzene was refluxed for sixteen hours. The hot reaction mixture was then filtered; the insoluble residue (8.5 Gm.) contained some unreacted saccharin and sodium chloride. After cooling the filtrate, filtering, and recrystallizing the resultant solid, 22.5 Gm. (65%) of white, crystalline compound, m. p. 136° (reported m. p. 136°) (4) was obtained.

## DISCUSSION

When N.N-diethylcarbamoyl chloride is refluxed with sodium saccharin in chloroform two products are obtained. The lower-melting compound (m. p. 117-118°) is the expected 2-(diethylcarbamoyl)saccharin. The higher-melting compound (m. p. 206–207°) has the empirical formula  $C_{11}H_{14}N_2O_2S$ . It was observed that at least sixteen but not over eighteen hours were required in order to obtain a maximum yield (40%) of 2-(diethylcarbamoyl)saccharin. On the other hand, if the refluxing time for the reaction mixture was prolonged to more than eighteen hours, the proportion of the yield of the higher-melting compound gradually increased, and that of the lower-melting compound decreased. At the end of sixty-four hours, the reaction mixture was found to contain a preponderance of the product of  $C_{11}H_{14}N_2O_2S$  (47% yield).

The refluxing of sodium 6-nitrosaccharin with N,N-diethylcarbamoyl chloride in chloroform for twenty hours gave only 2-(diethylcarbamoyl)-6-nitrosaccharin. Longer heating periods were not tried.

The reaction of sodium saccharin with N,Ndiethylthiocarbamoyl chloride in chloroform was very similar to the reaction of sodium saccharin and N,N-diethylcarbamoyl chloride. With shorter reaction periods (six to eight hours) a mixture of two compounds was obtained. Fractional crystallization gave a lower-melting substance (m. p. 140–141°) which was the expected 2-(diethylthiocarbamoyl)saccharin, and a higher-melting compound (206– 207°) which was identical with the product of C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S (obtained by the reaction of N,Ndiethylcarbamoyl chloride with sodium saccharin), as shown by no depression of a mixed melt of the two. Refluxing the mixture for twenty-four hours, instead of the six to eight-hour reaction time, gave a yield of 34% of the higher-melting compound. Similarly, stirring a mixture of sodium saccharin and N,N-diethylthiocarbamoyl chloride in water-carbon tetrachloride for one hour at room temperature yielded 34% of the higher melting compound.

When sodium 6-nitrosaccharin was refluxed with N,N-diethylthiocarbamoyl chloride in chloroform for eighteen hours, only a high-melting compound (m. p. 256-257°) of C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S could be isolated. Likewise, when sodium saccharin was refluxed with N,N-dimethylcarbamoyl chloride in chloroform for twenty-four hours, only a high-melting compound (m. p. 273-274°) of C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>S could be obtained.

The infrared absorption spectra of 2-(diethylcarbamoyl)saccharin, the higher-melting product of C11H14N2O2S, 2-(diethylthiocarbamoyl)saccharin, and the high-melting compound C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S were determined for comparison purposes. The two saccharin derivatives each show two moderately strong absorption bands in the carbonyl region of 5.76 and 5.90 $\mu$  which are absent in the two highmelting compounds (5). The products of C<sub>11</sub>H<sub>14</sub>-N<sub>2</sub>O<sub>2</sub>S and C<sub>11</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S show moderately strong absorption at  $6.24\mu$  which is absent in the two saccharin derivatives.4 The absorption at 6.24µ is in the region that could correspond to the --C=-N (conjugated or cyclic) grouping.

2-(diethylcarbamoyl)saccharin Refluxing in chloroform for periods of up to seventy-two hours resulted in recovery of the unchanged starting materials. This indicates that the 2-substituted saccharins are not intermediates in the formation of the higher-melting compounds and that the latter compounds are not then simply results of rearrangement of the former compounds.

The above experimental facts along with the elemental and infrared analyses suggest that these higher-melting compounds have the 3-(dialkylamino)-1,2-benzisothiazole-1,1-dioxide structure as shown in Table II. The following series of reaction equations involving sodium saccharin and N,Ndiethylcarbamoyl chloride may offer an explanation for the occurrence of both the lower-melting 2substituted saccharins and the higher-melting 3substituted 1,2-benzisothiazole-1,1-dioxides.



Evidence for the possibility of the above series of reactions is given by Ayca who has shown that solid saccharin is in the lactam form which gives the N-substituted derivatives; while in solution, saccharin is partly rearranged into the lactim form which gives the O-substituted derivatives (6). Evidence for the rearrangement may be seen in work of Norris on the reaction of dialkycarbamoyl chlorides with silver nitrate (7). Here, R2NCOCl and AgNO<sub>3</sub> gave the corresponding R<sub>2</sub>NNO<sub>2</sub> and R<sub>2</sub>NNO, CO<sub>2</sub>, and a little dialkylammonium nitrate. The reactions presumably proceeded through the O2NOCONR2 unstable intermediates and ONOCONR<sub>2</sub>, respectively.

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