

# 1,2-Benzothiazines. 6.<sup>1</sup> 3-Carbamoyl-4-hydroxy-2H-1,2-benzothiazine 1,1-Dioxides as Antiinflammatory Agents

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A variety of new 3-carbamoyl-4-hydroxy-2H-1,2-benzothiazine 1,1-dioxides of structure II was prepared and evaluated an antiinflammatory agents. Three synthetic methods were employed. Method A, consisting of base-catalyzed carbamoylation of ketone I by isocyanates, and method B, involving aminolysis of  $\beta$ -keto ester III, are modifications of previously described processes. In the completely new method C, the enamine IV, derived from ketone I, is reacted with phosgene to give the acid chloride V. The latter reacts with an amine to give enamine-amide VI which can be hydrolyzed to II. The prototype compound 2 has the same order of activity as phenylbutazone when evaluated against adjuvant-induced polyarthritis as well as carrageenin-induced edema. Its acute toxicity is less than that of phenylbutazone. The structural modifications described herein all resulted in decreased or complete loss of activity in the carrageenin test.

Our continuing studies<sup>1</sup> in 1,2-benzothiazine chemistry as well as our interest in the development of new antiinflammatory agents have resulted in the preparation of 3-carbamoyl-4-hydroxy-2H-1,2-benzothiazine 1,1-dioxides of structure II. Recent appearance of publications and patents<sup>2</sup> disclosing such compounds has prompted us to describe the results of our own experiments in this field.

Lombardino, *et al.*,<sup>2</sup> have described the synthesis of a number of substances of structure II as well as the results of their evaluation as antiinflammatory agents. Of those reported, compound 2 appeared to be of particular interest, since a paper describing its metabolism was published.<sup>3</sup> We have independently found compound 2 to be a potent antiinflammatory agent and have prepared a variety of derivatives in an effort to find more active compounds and perhaps define structure-activity relationships (Scheme I).

**Chemistry.** Lombardino, *et al.*,<sup>2</sup> have synthesized compound 2 and its derivatives II by the base-catalyzed reaction of ketones I<sup>4</sup> with a variety of isocyanates. Difficulties arising from base-catalyzed self-condensation<sup>4</sup> of I were overcome by the slow addition of a mixture of I and the isocyanate to a suspension of sodium hydride in DMF. We have prepared compounds 2-4, 14-19, and 21 by the same reaction but have employed a different experimental technique. The details, given in our Experimental Section, describe a convenient method for the preparation of the preformed anion of I with a minimum of self-condensation. This procedure<sup>†</sup> (designated method A) was also utilized with ethyl isothiocyanate and phenyl isothiocyanate to prepare the thioamides 34 and 35, respectively, but the same conditions employed with ethyl isocyanate failed to give more than trace amounts of 33. The latter was ultimately obtained in 78% yield by the use of method C, described below.<sup>‡</sup> See Tables I and II.

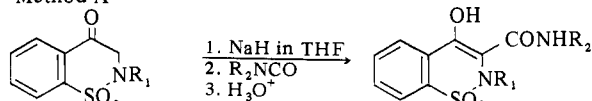
Compounds 20 and 23-27 were prepared by reacting ester IIIb<sup>5</sup> with an appropriate amine in refluxing xylene

<sup>†</sup>The method was also used for the preparation of a considerable number of aromatic substitution products (II, R<sub>2</sub> = substituted phenyl) as well as some 2-substituted derivatives (II, R<sub>1</sub> = ethyl, propyl, benzyl, etc.) which are not described herein since their preparation and properties are reported in ref 2.

<sup>‡</sup>Compound 33 was also obtained in 11% yield by the reaction of ethyl isocyanate with the bromomagnesium derivative, generated by treatment of Ia with isopropylmagnesium bromide.

## Scheme I

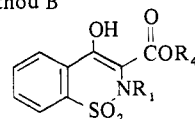
### Method A



Ia, R<sub>1</sub> = CH<sub>3</sub>  
b, R<sub>1</sub> = CH<sub>2</sub>CO<sub>2</sub>CH<sub>3</sub>  
c, R<sub>1</sub> = CH<sub>2</sub>CN

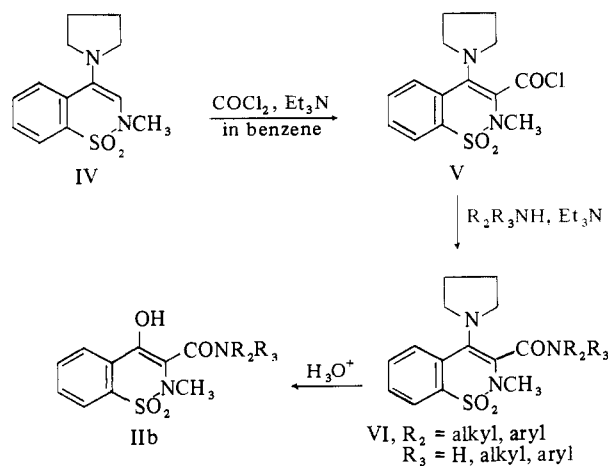
IIa, R<sub>2</sub> = aryl, heterocycle

### Method B



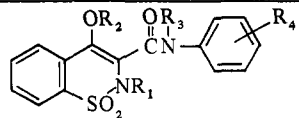
IIIa, R<sub>1</sub> = H; R<sub>4</sub> = C<sub>2</sub>H<sub>5</sub>  
b, R<sub>1</sub> = CH<sub>3</sub>; R<sub>4</sub> = C<sub>2</sub>H<sub>5</sub>  
c, R<sub>1</sub> = H; R<sub>4</sub> = CH<sub>3</sub>  
d, R<sub>1</sub> = R<sub>4</sub> = CH<sub>3</sub>




### Method C



(method B). This is essentially the method described by Lombardino, *et al.*,<sup>2</sup> except that we have employed 4A molecular sieve rather than a tedious intermittent distillation for the removal of the formed alcohol. The aforementioned authors<sup>2</sup> reported their inability to carry out aminolysis reactions with the 2-unsubstituted ester IIIc, though they did obtain the desired product, 1, by catalytic debenzyla-

Table I



Compd no.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Formula	Method	Yield, <sup>a</sup> %	Mp, °C	Activity <sup>f</sup>
1	H	H	H	H	C <sub>15</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub> S	B	61	261-268 dec <sup>c</sup>	MO
2	CH <sub>3</sub>	H	H	H	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub> S	A	60	217-218.5 <sup>d</sup>	MK
3	CH <sub>2</sub> CO <sub>2</sub> CH <sub>3</sub>	H	H	H	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>6</sub> S	A	53	238-239.5	IN
4	CH <sub>2</sub> CN	H	H	H	C <sub>17</sub> H <sub>13</sub> N <sub>2</sub> O <sub>4</sub> S	A	62	240-241	IN
5	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	H	H	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S	b	b	151-153	IN
6	CH <sub>3</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	C <sub>19</sub> H <sub>20</sub> N <sub>2</sub> O <sub>4</sub> S	b	b	199-200	IN
7	CH <sub>3</sub>	CH <sub>3</sub> CO	H	H	C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>5</sub> S	b	b	195-197	MO
8	CH <sub>3</sub>	H	OH	H	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>5</sub> S	C <sup>b</sup>	14	162-164	IN
9	CH <sub>3</sub>	H	CH <sub>3</sub>	H	C <sub>17</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> S	C	16	175-178 <sup>e</sup>	SL
10	CH <sub>3</sub>	H	C <sub>2</sub> H <sub>5</sub>	H	C <sub>18</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> S	C	46	150-152	IN
11	CH <sub>3</sub>	H	C <sub>6</sub> H <sub>5</sub>	H	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> S	C	22	186-189	IN
12	CH <sub>3</sub>	CH <sub>3</sub> CO	CH <sub>3</sub> CO	H	C <sub>20</sub> H <sub>18</sub> N <sub>2</sub> O <sub>6</sub> S	b	b	206-210	IN
13	CH <sub>3</sub>	C=O	CH <sub>3</sub> CO	H	C <sub>17</sub> H <sub>12</sub> N <sub>2</sub> O <sub>5</sub> S	b	b	262-263.5	IN
14	CH <sub>3</sub>	H	H	<i>o</i> -NO <sub>2</sub>	C <sub>16</sub> H <sub>13</sub> N <sub>2</sub> O <sub>6</sub> S	A	32	336.5-337.5	IN
15	CH <sub>3</sub>	H	H	<i>o</i> -CO <sub>2</sub> CH <sub>3</sub>	C <sub>17</sub> H <sub>13</sub> F <sub>3</sub> N <sub>2</sub> O <sub>4</sub> S	A	48	221-222.5	IN
16	CH <sub>3</sub>	H	H	<i>o</i> -C <sub>6</sub> H <sub>5</sub>	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> S	A	54	164-165	IN
17	CH <sub>3</sub>	H	H	<i>p</i> -C <sub>6</sub> H <sub>5</sub>	C <sub>22</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> S	A	25	262-262.5	IN
18	CH <sub>3</sub>	H	H		C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>6</sub> S	A	26	266-266.5	SL
19	CH <sub>3</sub>	H	H		C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> O <sub>6</sub> S	A	48	243-245	IN
20	CH <sub>3</sub>	H	H		C <sub>24</sub> H <sub>18</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	B	72	295-296 dec	IN

<sup>a</sup>With method C, this is the overall yield based on IV. <sup>b</sup>See Experimental Section. <sup>c</sup>Lit.<sup>2</sup> 253° dec. <sup>d</sup>Lit.<sup>2</sup> 213-215°. <sup>e</sup>Lit.<sup>2</sup> 162-165°. <sup>f</sup>MO = moderate activity; MK = marked activity; IN = insignificant activity; SL = slight activity.

tion of the corresponding 2-benzyl derivative. We have successfully employed method B for the direct conversion of IIIa to 1.

The *N*-methyl derivative 9 was obtained by alkylation of 2 using sodium hydride and dimethyl sulfate in tetrahydrofuran as well as by method C described below. Lombardino, *et al.*,<sup>2</sup> have described the preparation of 9 by aminolysis of IIIId with *N*-methylaniline but they reported their product, which melted 13° lower than ours, to give an infrared band at 6.00 μ (1660 cm<sup>-1</sup>) which is not present in the spectrum of our product. We have repeated their work and have obtained the same lower melting product displaying the extra absorption band. Since such a band is present in the spectrum of IIIId, it is apparent that their product was contaminated with unreacted starting ester.

Alkylation of 2 with *n*-propyl iodide and isopropyl iodide resulted in *O*-alkylation to give 5 and 6, respectively. Acetylation of 2, using acetic anhydride and pyridine, gave rise to the diacetyl derivative 12, which on treatment with dilute alkali lost the *N*-acetyl group to form 7. The cyclic diacyl derivative 13 was obtained from the reaction of 2 with phosgene.

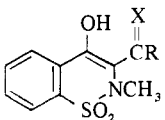
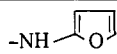
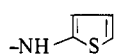
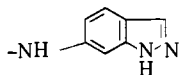
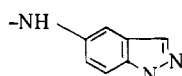
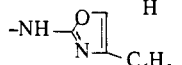
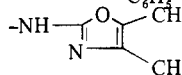
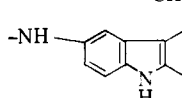


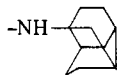

We have also developed a completely new method for the preparation of compounds of structure II. This procedure (method C) started with the enamine IV<sup>4</sup> which was formed from Ia. Reaction of IV with phosgene and triethylamine in benzene gave the acid chloride V. (The corresponding reaction with the enamine derived from cyclohexanone has been reported.<sup>6</sup>) This was allowed to react *in situ* with an appropriate amine to yield the enamineamide VI which was hydrolyzed to the desired IIb. Method C was employed to prepare 2, 22, 30, and 31 but was especially useful for the synthesis of 9-11, 28, and 29, which are β-ketoamides de-

rived from secondary aromatic amines. Such amides are difficult to obtain by other means. This process was the only one which gave satisfactory yields of 33. Table III lists those enamineamides VI which were isolated in crystalline form. The acid hydrolysis could be carried out using the crude VI as well as with pure enamineamide.

**Pharmacology.** The antiinflammatory activity of these compounds was determined by means of the *carrageenin-induced rat paw edema assay* described by Winter, *et al.*<sup>7</sup> Male rats (Charles River strain) were arranged in groups of 8-10. Test compounds were administered orally as aqueous suspensions and the phlogistic agent (0.05 ml of 1% carrageenin in 0.9% sterile sodium chloride solution) was injected 1 hr later into the plantar area of the left hind paw of each animal. The size of the injected and uninjected hind paws of the unanesthetized rat was determined 3 hr later by insertion into mercury to a previously positioned mark on the skin over the lateral malleolus. Differences in mercury displacement produced by the injected and noninjected paws were recorded and a statistical analysis of measurements with control and treated groups was obtained. The activities recorded in Tables I-III refer to the oral screening dose of 100 mg/kg. The results were evaluated as shown in Table IV.

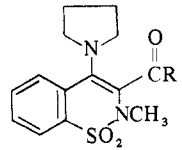



As can be seen in Tables I-III, all of the structural modifications of the prototype compound 2 resulted in a decrease in activity. Except for slight activity shown by 18, the aromatic substitution products 14-19 failed to exhibit significant antiedema properties. It is of interest that the 2-unsubstituted derivative 1 still retained considerable activity but that compounds with 2 substituents larger than methyl (compounds 3 and 4 as well as the corresponding 2-ethyl,<sup>2</sup> 2-propyl,<sup>2</sup> and 2-benzyl<sup>2</sup> derivatives) were com-

Table II

Compd no.	X	R						Yield, <sup>a</sup> %	Mp, °C	Activity <sup>c</sup>
			Formula	Method						
21	O		C <sub>14</sub> H <sub>12</sub> N <sub>2</sub> O <sub>5</sub> S	A	35	208-209	MO			
22	O		C <sub>14</sub> H <sub>12</sub> N <sub>2</sub> O <sub>4</sub> S <sub>2</sub>	C	10	250-252	SL			
23	O		C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> O <sub>4</sub> S	B	68	277-278 dec	IN			
24	O		C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> O <sub>4</sub> S	B	71	266-267 dec	IN			
25	O		C <sub>19</sub> H <sub>14</sub> N <sub>3</sub> O <sub>3</sub> S	B	11	225-227 dec	SL			
26	O		C <sub>15</sub> H <sub>14</sub> N <sub>3</sub> O <sub>3</sub> S	B	33	249-250 dec	IN			
27	O		C <sub>20</sub> H <sub>19</sub> N <sub>2</sub> O <sub>4</sub> S	B	65	260-263 dec	IN			
28	O		C <sub>18</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> S	C	17	200-202	IN			
29	O		C <sub>19</sub> H <sub>18</sub> N <sub>2</sub> O <sub>4</sub> S	C	41	173-174	IN			
30	O		C <sub>20</sub> H <sub>24</sub> N <sub>2</sub> O <sub>4</sub> S	C	33	251-253	IN			
31	O		C <sub>14</sub> H <sub>16</sub> N <sub>2</sub> O <sub>4</sub> S	C	60	220-222	IN			
32	O	-NH <sub>2</sub>	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O <sub>4</sub> S	<i>b</i>		244-248 dec	IN			
33	O	-NHC <sub>2</sub> H <sub>5</sub>	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub> S	C	78	194-196	IN			
34	S	-NHC <sub>2</sub> H <sub>5</sub>	C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> S <sub>2</sub>	A	46	221-222	IN			
35	S	-NHC <sub>2</sub> H <sub>5</sub>	C <sub>16</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> S <sub>2</sub>	A	51	235-237.5	IN			

<sup>a</sup>With method C, this is the overall yield from IV. <sup>b</sup>Prepared as described in ref 5. <sup>c</sup>See footnote *f*, Table I.

Table III

Compd no.	R						Yield, %	Mp, °C	Activity <sup>a</sup>
		Formula							
36	-NHC <sub>2</sub> H <sub>5</sub>	C <sub>20</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> S	51	207-209 dec	SL				
37	-N(C <sub>2</sub> H <sub>5</sub> )C <sub>6</sub> H <sub>5</sub>	C <sub>22</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> S	47	142-144	IN				
38		C <sub>22</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub> S	35	177-179 dec	IN				
39		C <sub>23</sub> H <sub>25</sub> N <sub>3</sub> O <sub>3</sub> S	45	182-185 dec	IN				
40		C <sub>18</sub> H <sub>23</sub> N <sub>3</sub> O <sub>3</sub> S	71	224-226 dec	IN				
41	-NH(1-adamanty1)	C <sub>24</sub> H <sub>31</sub> N <sub>3</sub> O <sub>3</sub> S	52	160-162 dec	IN				
42	-NHC <sub>2</sub> H <sub>5</sub>	C <sub>16</sub> H <sub>21</sub> N <sub>3</sub> O <sub>3</sub> S	81	185-187	IN				

<sup>a</sup>See footnote *f*, Table I.

Table IV

% inhibition of edema	Evaluation
<20	Statistically ( $P < 0.05$ )
	Insignificant activity (IN)
20-34	Slight activity (SL)
35-45	Moderate activity (MO)
>45	Marked activity (MK)

pletely inactive in our test system. Of the heterocyclic analogs of **2**, only the furyl (**21**) was moderately active. The 2-thienyl (**22**) and the 2-(4-phenyloxazole) (**25**) showed slight activity and the others were inactive.

The unsubstituted amide **32**<sup>5</sup> as well as the *N*-alkylamides **31** and **33** was found to be devoid of activity in our test system. The thioamides **34** and **35** were likewise inactive.

None of the acyl or alkyl derivatives of **2** were as active as the parent compound. Of these only the enol acetate **7** was moderately active. The *N*-methyl derivative **9** was slightly active but other substitution of the amide nitrogen (**8**, **10**, **11**, **28**, and **29**) resulted in complete loss of activity. The diacyl derivatives **12** and **13** as well as the enol ethers **5** and **6** were inactive. Of the enamines listed in Table III, only **36**, derived from **2**, showed some activity.

Compound **2** was found to be moderately active at 50 and 25 mg/kg and inactive at 10 mg/kg. As such, it was as active as phenylbutazone. Essentially the same results were obtained with adrenalectomized rats.<sup>8</sup>

Compound **2** also showed the same order of activity as phenylbutazone when evaluated against adjuvant-induced polyarthritis<sup>8</sup> in the rat. In these tests, the compound was administered orally at 25 mg/kg either at the time of injection of the adjuvant (prophylactic) or 14 days later when the polyarthritis was established (therapeutic). The oral ALD<sub>50</sub> of **2** in male rats was found to be greater than 5000 mg/kg as compared to an ALD<sub>50</sub> of 1000 mg/kg for phenylbutazone.

## Experimental Section

Melting points were determined using the Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DKI spectrophotometer and a Baird Model 455 double-beam instrument. The former were determined as solutions in 95% ethanol and the latter as Nujol mulls. The nmr spectra were determined with the Varian A-60 spectrometer using Me<sub>4</sub>Si as an internal standard. The abbreviations br, s, d, t, and m refer to broad, singlet, doublet, triplet, and multiplet, respectively. All compounds analyzed correctly for C, H, N, S, and halogen, if present.

2-Substituted 2*H*-1,2-Benzothiazin-4(3*H*)-one 1,1-Dioxides (I). The preparation of Ia<sup>4</sup> and Ib<sup>9</sup> by alkylation of the corresponding *N*-unsubstituted ketal followed by acid hydrolysis has been previously reported.

2-Cyanomethyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (Ic). The corresponding ketal<sup>4</sup> was hydrolyzed as in the previous examples. Methanol recrystallization gave material, mp 130°, which analyzed correctly for C<sub>10</sub>H<sub>8</sub>N<sub>2</sub>O<sub>3</sub>S, yield 63%.

2-Methyl-4-(1-pyrrolidinyl)-2*H*-1,2-benzothiazine 1,1-Dioxide (IV). The preparation of this compound was reported earlier<sup>4</sup> but its purification was not described. It has now been recrystallized from benzene-ether (1:9) to give material, mp 142-144°, which analyzed correctly for C<sub>13</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S. The unrecrystallized compound (obtained in 95% yield) was used as the starting material for method C.

Preparation of 4-Hydroxy-3-carbamoyl-2*H*-1,2-benzothiazine 1,1-Dioxides (II). Method A. A solution of 0.15 mol of 2-substituted 2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide (I) in 300 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) was added dropwise with stirring over a period of 45 min to a slurry of 0.17 mol of sodium hydride in 100 ml of tetrahydrofuran, the

temperature being maintained at 0 to -5°. When gas evolution had ceased, a solution of 0.34 mol of the appropriate isocyanate in 100 ml of tetrahydrofuran was added at such a rate that the temperature remained at -5°. It was then allowed to stand at room temperature for 24 hr and the solvent was removed *in vacuo* at room temperature, using a rotary flash evaporator. The residue was poured into 500 ml of ice-water, the mixture was filtered, and the filtrate was washed with ether. The aqueous solution was acidified with hydrochloric acid and the resulting precipitate was collected and dissolved in dichloromethane. This solution was washed with water, dried, and evaporated, and the solid residue was recrystallized. Compounds **2**, **3**, **14**, **15**, **34**, and **35** were recrystallized from ethyl acetate, **4** from tetrahydrofuran-dichloromethane, **16** from isopropyl alcohol, **17**, **18**, and **19** from acetonitrile, and **21** from 2-butanone.

Method B. A mixture of 0.02 mol of IIIb,<sup>5</sup> 0.025 mol of the appropriate amine, and 800 ml of xylene was refluxed for 24 hr in a Soxhlet apparatus, the thimble of which contained 10 g of Linde Type 4A molecular sieve. The mixture was cooled to 25° and the resulting crystalline precipitate was collected, washed with ether, and recrystallized. Compound **1** was recrystallized from methanol, **20** and **27** from dimethylformamide-water, **23** from 2-butanone, **24** from 1,4-dioxane-water, **25** from ethyl acetate, and **26** from dimethylformamide.

Method C. A solution of 6.0 g (0.06 mol) of phosgene in 55 ml of benzene was diluted with 30 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride) and cooled to -10°. To this was added, over a period of 30 min, a solution of 13.2 g (0.05 mol) of 2-methyl-4-(1-pyrrolidino)-2*H*-1,2-benzothiazine 1,1-dioxide (IV)<sup>4</sup> and 8.2 ml of triethylamine in 200 ml of tetrahydrofuran and the reaction mixture was stirred at room temperature for 3 hr. A solution of 0.068 mol of the appropriate amine and 8.2 ml of triethylamine in 50 ml of tetrahydrofuran was added at room temperature over a period of 10 min and stirring was continued for an additional 1 hr. The reaction mixture was refluxed for 16 hr, concentrated to half of its volume, treated with ice-water, and extracted with dichloromethane. Evaporation of the dichloromethane gave the crude enamineamide VI. This was hydrolyzed by refluxing with 200 ml of 3*N* hydrochloric acid for 1 hr. The reaction mixture was extracted with dichloromethane and the organic phase reextracted with 4% sodium hydroxide solution. Acidification gave a white solid which was collected and recrystallized. Compounds **9**, **10**, and **28** were recrystallized from methanol, **2**, **11**, and **29** from methanol-dichloromethane, **30** from tetrahydrofuran-methanol, **31** from dichloromethane-tetrahydrofuran, and **33** from dichloromethane-isopropyl ether. Compound **8** was purified as described below.

In the preparation of **31** the reflux time after addition of the pyrrolidine was only 1.5 hr. In the preparation of **33**, the tetrahydrofuran solution of ethylamine and triethylamine was added rapidly at -50°. The reaction mixture was then stirred at room temperature for 16 hr, refluxed for 3 hr, and worked up in the usual manner.

4-Hydroxy-2-methyl-*N*-phenyl-2*H*-1,2-benzothiazine-3-hydroxamic Acid 1,1-Dioxide (**8**). It was found necessary to employ a modification of method C. A solution of 6 g (0.055 mol) of *N*-phenylhydroxylamine and 13.1 g of triethylamine in 50 ml of tetrahydrofuran was added in one lot to the enamine-acid chloride at -5°. The reaction mixture was stirred at room temperature for 16 hr and refluxed for 2 hr. The usual work-up gave the crude enamineamide as an oil which was hydrolyzed by refluxing for 30 min with a mixture of 100 ml of methanol and 10 ml of concentrated hydrochloric acid. The mixture was diluted with ice-water, extracted with dichloromethane, and reextracted with 1*N* sodium hydroxide. The alkaline solution was acidified by careful addition of hydrochloric acid and extracted with dichloromethane. The dichloromethane solution was washed well with water, dried, and evaporated to a volume of 25 ml. Dilution with 50 ml of ether caused precipitation of a yellow solid, mp 206-215° dec. Fractional crystallization from a mixture of dichloromethane and methanol gave two products. The first fractions yielded 2.2 g of material, mp 214-218°, which was identified as **2**. The later fractions yielded 2.5 g of the desired **11**, mp 162-164°, which analyzed correctly for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O<sub>5</sub>S:  $\nu$  max 3050, 1595, 1180 cm<sup>-1</sup>;  $\lambda$  max 334  $\mu$ m (11,600).<sup>#</sup>

#The  $\beta$ -phenylhydroxylamine was prepared and recrystallized shortly before use. The formation of **2** implies the presence of an appreciable amount of aniline in the reaction mixture. Heller, Hughes, and Ingold<sup>10</sup> have reported that the conversion of  $\beta$ -phenylhydroxylamine to azoxybenzene and aniline occurs by a chain reaction which is initiated by short exposure to atmospheric oxygen. The melting point of **8** is considerably lower than the isomeric *o*-, *m*-, and *p*-hydroxy derivatives of **2**. These are reported<sup>2</sup> to be 205-208, 231-232, and 279-280° dec, respectively.

<sup>8</sup> Reference 2 reports compound **2** to have 2.1 times the anti-edema potency of phenylbutazone.

**Preparation of Pure Enamineamides VI.** Table III lists those enamineamides which were isolated and purified. In the preparation of 36 the crude enamineamide, obtained as described above, was triturated with 300 ml of ether to give a crystalline product which was recrystallized from tetrahydrofuran-methanol. In the preparation of 37-42, the crude product was stirred with 1000 ml of ether and filtered to remove insoluble polymeric material. Concentration of the filtrate to a small volume gave the crystalline enamineamide. Compound 36 was recrystallized from tetrahydrofuran-methanol, 37 from ether, 38 and 39 from tetrahydrofuran-ether, 40 from tetrahydrofuran-dichloromethane, 41 from ether-dichloromethane, and 42 from tetrahydrofuran-isopropyl ether. The spectral properties of 36 are typical of the series:  $\nu$  max 3190, 1615, 1583, 1180, 1165  $\text{cm}^{-1}$ ;  $\lambda$  max 236 (17,200), 266 sh (8800), 366  $\text{m}\mu$  (13,200); nmr ( $\text{CDCl}_3$ )  $\delta$  7.50 (9 H, m, aromatic), 3.40 (4 H, m,  $\alpha$  protons of pyrrolidine), 2.67 (3 H, s,  $\text{NCH}_3$ ), 1.87 (4 H, m,  $\beta$  protons of pyrrolidine).

**4-Hydroxy-2-N-dimethyl-2H-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (9) by Methylation of 2.** To a slurry of 0.05 mol (2.1 g of a 57% mineral oil dispersion) of sodium hydride in 50 ml of tetrahydrofuran was added a solution of 6.6 g (0.02 mol) of 2 in 150 ml of tetrahydrofuran, the temperature being maintained at 0-10° during the addition. A solution of 2.6 g (0.021 mol) of dimethyl sulfate in 10 ml of tetrahydrofuran was added; the reaction mixture was allowed to slowly warm to room temperature and then refluxed for 2 hr. Most of the solvent was removed and the residue was treated with ice-water. The mixture was filtered and the filtrate was acidified with dilute hydrochloric acid. The resulting crude precipitate was recrystallized from methanol to give 3.9 g of crystalline product, mp 175-178°, \*\* identical with the product obtained by method C:  $\nu$  max 1603, 1588, 1580, 1550, 1490, 1180, 1155  $\text{cm}^{-1}$ ;  $\lambda$  max 232 sh (12,800), 323  $\text{m}\mu$  (12,400); nmr ( $\text{CDCl}_3$ )  $\delta$  4.30 (1 H, s, exchangeable, endic H), 7.67 (4 H, m,  $\text{C}_6\text{H}_4$ ), 7.30 (5 H, m,  $\text{C}_6\text{H}_5$ ), 3.40 (3 H, s,  $\text{SO}_2\text{NCH}_3$ ), 2.33 (3 H, s,  $\text{CONCH}_3$ ).

**4-Isopropoxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (6).** A mixture of 7.75 g (0.025 mol) of 2, 40 ml (0.4 mol) of isopropyl iodide, 34.3 g (0.25 mol) of potassium carbonate, and 200 ml of acetone was refluxed for 44 hr and filtered, and the solvent was evaporated. The residue was partitioned between water and dichloromethane and the organic layer was evaporated. Recrystallization of the residue from ethyl acetate gave 6.6 g of crystalline product, mp 198-199.5°. Recrystallization gave an analytical sample: mp 199-200°;  $\nu$  max 3380, 1660, 1172, 1160  $\text{cm}^{-1}$ ;  $\lambda$  max 316  $\text{m}\mu$  (14,800); nmr ( $\text{CDCl}_3$ )  $\delta$  9.62 (1 H, br, exchangeable, NH), 7.78 (5 H, m,  $\text{C}_6\text{H}_5$ ), 7.33 (4 H, m,  $\text{C}_6\text{H}_4$ ), 4.42 (1 H, m,  $\text{OCHMe}_2$ ), 3.08 (3 H, s,  $\text{NCH}_3$ ), 1.35 (6 H, d,  $J = 7$  Hz,  $\text{C}(\text{CH}_3)_2$ ).

**2-Methyl-4-n-propoxy-2H-1,2-benzothiazine-3-carboxanilide 1,1-Dioxide (5).** This compound was prepared and isolated in the same manner as in the previous experiment except that acetonitrile was used as the solvent and the reflux time was 21 hr. Recrystallization of the dichloromethane extract from methanol gave 2.6 g of crystalline product, mp 151-153°.

**N-Acetyl-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide Acetate 1,1-Dioxide (12).** A solution of 8.25 g (0.025 mol) of 2 in 30 ml of pyridine was boiled with 15 ml of acetic anhydride for 40 min. The reaction mixture was cooled to room temperature and diluted with ether. The resulting precipitate was collected and

recrystallized from ethyl acetate to give 6.0 g of product: mp 206-208° dec;  $\nu$  max 1762, 1714, 1668, 1587, 1180, 1163  $\text{cm}^{-1}$ ;  $\lambda$  max 317  $\text{m}\mu$  (9700); nmr ( $\text{CDCl}_3$ )  $\delta$  7.40 (9 H, m, aromatic), 3.20 (3 H, s,  $\text{NCH}_3$ ), 1.50 (3 H, s,  $\text{COCH}_3$ ), 1.40 (3 H, s,  $\text{COCH}_3$ ).

**4-Hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxanilide Acetate 1,1-Dioxide (7).** When a solution of 4.1 g (0.01 mol) of 12 in 100 ml of dimethylformamide was diluted with 20 ml of 1 N aqueous sodium hydroxide, a dark reddish-purple color formed instantaneously. After standing for 5 min, the solution was diluted with water and acidified with dilute hydrochloric acid. The resulting precipitate, mp 195-198° dec, weighed 3.39 g. Recrystallization from acetonitrile gave an analytical sample: mp 195-197° dec;  $\nu$  max 3230, 1758, 1648, 1598, 1182, 1172, 1160  $\text{cm}^{-1}$ ;  $\lambda$  max 314 (11,200), 280 sh (9000), 230  $\text{m}\mu$  (14,000); nmr ( $\text{DMSO}$ )  $\delta$  10.33 (1 H, br, exchangeable, NH), 7.83 (9 H, m, aromatic), 3.10 (3 H, s,  $\text{NCH}_3$ ), 2.30 (s, 3 H,  $\text{COCH}_3$ ).

**3,4-Dihydro-5-methyl-3-phenyl-2H,5H-[1,3]oxazino[5,6-c]-1,2-benzothiazine-2,4-dione 6,6-Dioxide (13).** A solution of 0.03 mol of phosgene in 28 g of benzene was diluted with 30 ml of tetrahydrofuran. To this was added a mixture of 8.25 g (0.025 mol) of 2, 6.7 g (0.06 mol) of triethylamine, and 100 ml of tetrahydrofuran, the exothermic reaction being moderated with cooling during the addition. The reaction mixture was refluxed for 2.5 hr, poured into ice-water containing 0.05 mol of HCl, and extracted with dichloromethane. Evaporation of the dichloromethane gave a residue which was triturated with ether and then recrystallized from ethyl acetate to give 2.5 g of product, 262-263.5° dec, which analyzed correctly for  $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$ :  $\nu$  max 1793 and 1780 (d), 1708, 1692, 1640, 1287, 1170  $\text{cm}^{-1}$ ;  $\lambda$  max 314 (10,000), 293  $\text{m}\mu$  (9500).

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\*\*Lit.<sup>2</sup> reports mp 162-165°.