Preparation of Some 4-Hydroxyl-1-methyl-1*H*-2,1-benzothiazine-3-carboxanilide 2,2-Dioxides

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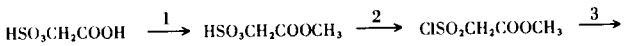
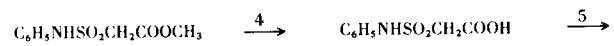
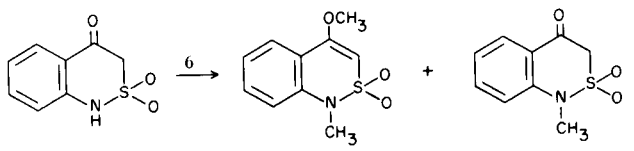
An improved, 3-step synthesis of 3,4-dihydro-1-methyl-1*H*-2,1-benzothiazin-4-one 2,2-dioxide has been developed. This general method offers a more facile entrance into the 2,1-benzothiazine 2,2-dioxide heterocyclic system than was heretofore available. Preparation of several 3-carboxanilides was accomplished by interaction of this ring system with various isocyanates. The resulting carboxanilides are moderately strong, enolic acids.

For a continuing study of the biological activity of β-keto amides, 3,4-dihydro-1-methyl-1*H*-2,1-benzothiazin-4-one 2,2-dioxide (II) was required. Since two separate groups, Loev, Kormendy and Snader (1,4) and Rossi and Pagani (2), had simultaneously reported the synthesis of II by virtually identical routes, several attempts were made to utilize the six-step technique. Thus, from sulfoacetic acid, after esterification (3) and preparation of the sulfonyl chloride (3), treatment with aniline was reported to give methyl *N*-phenylsulfamoylacetate. Hydrolysis was reported to give *N*-phenylsulfamoylacetic acid with various melting points of 115° (1), 167° (1) and 130° (2). Finally, cyclization with polyphosphoric acid was reported to yield 3,4-dihydro-1*H*-2,1-benzothiazin-4-one 2,2-dioxide (I) which on methylation (dimethyl sulfate) gave a mixture chromatographically separated (4) into the *O*,*N*-dimethylated product (III) and the desired *N*-methylated ketone II.

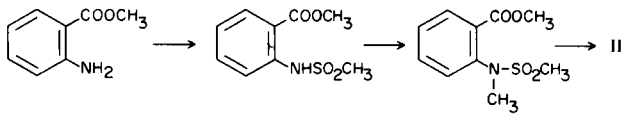




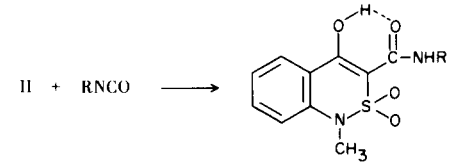


I III II

No reference to the yield in either steps 1 or 2 appear in the literature (*i.e.* references 1, 2 or 3). In our hands, great difficulty was experienced in reproducing the initial esterification (very low yields, black-tarry residues) as well as in handling the very reactive ester-sulfonyl chloride resulting from step 2. This experience, together with the reported (4) mixture resulting from methylation of I, prompted the development of a three-step, high-yield procedure for preparing II. Commercially available methyl anthranilate was treated with methane sulfonyl chloride and the resulting sulfonamide then *N*-methylated. Cyclization, employing sodium hydride, gave II in 95% yield. The ketonic II corresponded in melting point and in infrared spectrum to the material prepared by Loev and Snader (4).



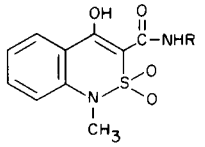
Combination of II with isocyanates in dimethyl sulfoxide solution yielded the carboxanilides (IV) summarized in Table I. A typical procedure is illustrated in the Experimental for compound **3**. All of the carboxanilides lack infrared absorption C=O bands below 6.0 μ and produce a red color with ferric chloride solution. This data, together with nmr spectral data, support the enol (*i.e.* 4-hydroxy) form for the carboxanilides.



IV

TABLE I

4-Hydroxy-1-methyl-1*H*-2,1-benzothiazine-3-carboxanilide 2,2-Dioxides



Compound Number	R	Yield %	M.p., °C	Crystn. Solvent (a)	Formula	Analyses Calcd., % C	H	N	Found, % C	H	N
1	C_6H_5 (b)	28	172-174	M	$C_{16}H_{14}N_2O_4S$	58.2	4.30	8.50	57.93	4.32	8.40
2	4-$CH_3OC_6H_4$	100	176-178	M-C	$C_{17}H_{16}N_2O_5S$	56.7	4.48	7.78	56.75	4.41	7.67
3	4-BrC_6H_4 (c)	69	213-215	E-C	$C_{16}H_{13}N_2O_4SBr$	47.0	3.20	6.82	47.28	3.20	6.90
4	3-ClC_6H_4	54	174-176	C	$C_{16}H_{13}N_2O_4SCl$	52.8	3.58	7.67	52.76	3.57	7.85
5	4-$NO_2C_6H_4$	69	237-238	C	$C_{16}H_{13}N_3O_6S$	51.3	3.53	11.2	51.11	3.55	11.49
6	4-$CH_3C_6H_4$	70	188-189	E	$C_{17}H_{16}N_2O_4S$	59.3	4.72	8.13	59.12	4.76	8.19
7	2-$CH_3OC_6H_4$	76	168-170	E	$C_{17}H_{16}N_2O_5S$	56.7	4.48	7.78	56.72	4.58	7.85
8	-$CH_2CH{=}CH_2$	51	91-92	I	$C_{13}H_{14}N_2O_4S$	53.2	4.78	9.52	52.95	4.90	9.49

(a) M = methanol; C = chloroform; B = benzene; E = ethanol; I = isopropanol. (b) Potentiometric titration of **1** in 2:1 dioxane-water solution using standard sodium hydroxide and a Beckman Model G *p*H meter indicated a pK_a (*p*H ½) of 4.96. (c) pK_a (2:1 dioxane-water) of 5.3.

It seems likely that hydrogen bond formation between the enol hydroxyl group and the anilide carbonyl favors the enol over the keto form for the carboxanilides. The carboxanilides were moderately acidic (pK_a approximately 5 in 2:1 dioxane-water solution) and all showed a tendency to form insoluble sodium salts in aqueous medium.

EXPERIMENTAL

All melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. A Varian A-60 spectrometer (TMS, standard) was used to measure nmr spectra. Infrared spectra were determined in potassium bromide pellets. Analyses were carried out by the Physical Measurements Laboratory of Pfizer, Inc.

Methyl *N*-Methylsulfonylanthranilate.

To 30.2 g. (0.20 mole) of methyl anthranilate in 30 ml. of ether was slowly added a solution of 11.4 g. (0.10 mole) of methanesulfonyl chloride in 10 ml. of ether. After 18 hours at room temperature, the resultant slurry was washed four times with water and the clear ether layer dried (calcium sulfate). Evaporation of all solvent followed by recrystallization from isopropanol gave white crystals which, after thorough trituration with water and drying, weighed 14.3 g. (62%), m.p. 91-92°; ir: 3.25 (NH), 5.93 (C=O), 7.63 and 8.65 μ (SO_2).

Anal. Calcd. for $C_9H_{11}NO_4S$: C, 47.2; H, 4.80; N, 6.12. Found: C, 47.15; H, 4.84; N, 6.14.

Methyl *N*-Methyl-*N*-methylsulfonylanthranilate.

To a suspension of 8.8 g. (0.184 mole) of hexane-washed 50% sodium hydride in mineral oil suspended in 100 ml. of dry dimethylformamide was added a solution of 35.0 g. (0.153 mole) of methyl *N*-methylsulfonylanthranilate in 50 ml. of dimethylformamide. After stirring the suspension for 45 minutes, a solution of 65.2 g. (0.46 mole) of iodomethane in 50 ml. of ether was added and the white suspension stirred for 1.5 hours. Pouring the reaction into 1200 ml. of 3 *N* hydrochloric acid produced a yellow suspension which was extracted six times with ether and the extracts dried (calcium sulfate). Evaporation of solvent and trituration of the residue with hexane gave 18.7 g. (48%) of white solid, m.p. 55.5-58°; ir: 5.78 (C=O), 7.50 and 8.75 μ (SO_2).

Anal. Calcd. for $C_{10}H_{13}NO_4S$: C, 49.4; H, 5.38; N, 5.76. Found: C, 49.42; H, 5.42; N, 5.58.

1-Methyl-3,4-dihydro-1*H*-2,1-benzothiazin-4-one 2,2-Dioxide (II).

To a suspension of 4.6 g. (0.096 mole) of hexane-washed 50% sodium hydride in mineral oil in 30 ml. of dry dimethylformamide was added a solution of 18 g. (0.074 mole) of methyl *N*-methyl-*N*-methylsulfonylanthranilate in 70 ml. of dry dimethylformamide. After 1 hour, the reaction was poured in a thin stream into 400 ml. of 3 *N* hydrochloric acid. The resultant solid was filtered, washed well with water and dried to give 14.8 g. (95%) of II, m.p. 119-121°; ir: 5.93 (C=O), 7.50 and 8.70 μ (SO_2), no peak at 3.0 μ. (Lit. m.p. 122-123° (4) and m.p. 117-118° (2)).

Carboxanilides.

All of the carboxanilides listed in Table I were prepared by the general technique illustrated below for the 4′-bromocarboxanilide (**3**). The requisite isocyanates are commercially available and were used as received.

4′-Bromo-4-hydroxy-1*H*-2,1-benzothiazine-3-carboxanilide 2,2-Dioxide (**3**).

A yellow solution of 2.0 g. (0.0096 mole) of 1-methyl-3,4-dihydro-1*H*-2,1-benzothiazin-4-one 2,2-dioxide, 2.3 g. (0.012 mole) of *p*-bromophenyl isocyanate and 1.2 g. (0.012 mole) of triethylamine in 60 ml. of dry dimethylsulfoxide was stirred at room temperature for 2 hours. After pouring the solution into 200 ml.

of 3 *N* hydrochloric acid, the resultant white solid was filtered, washed thoroughly with water, dried and recrystallized from ethanol-chloroform (3:1), yield 2.7 g. (69%), m.p. 213-215°; ir: 2.93 (NH), 6.18 and 6.2 (enol), 7.55 and 8.68 μ (SO_2); nmr (DMSO-d_6): τ -0.4 (broad, 1, OH), 1.9-2.7 (m, 8, aromatic protons), 3.59 (broad, NH), 6.57 (s, 3, CH_3). A sample of **3** gives a deep red color with dilute ferric chloride in methanol solution. Dilute sodium hydroxide dissolves **3** but rapidly redeposits the insoluble sodium salt.

See Table I for additional data on **3** and other related carboxanilides.

Acknowledgment.

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