4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2*H*-1,4-benzothiazine and Related Compounds. A New Class of Antiinflammatory Agents[1]

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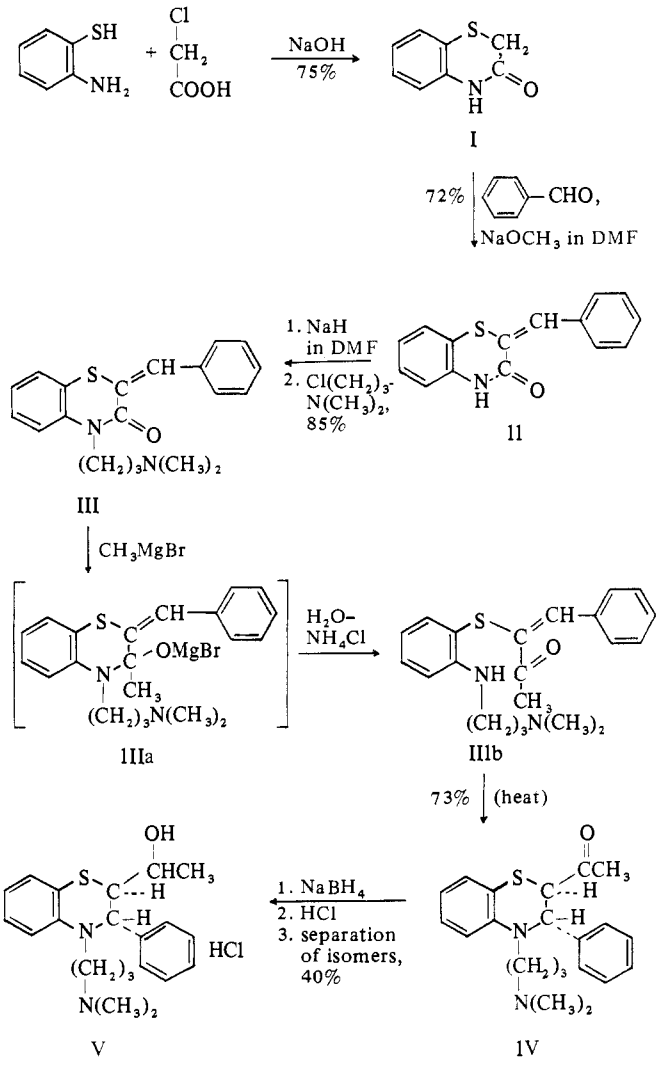
The synthesis and antiinflammatory activity of the title compound **20** and 22 related products are described. The intermediate ketone for **20** was unexpectedly obtained by the interaction of 2-benzylidene-4-(3-dimethylaminopropyl)-1,4-benzothiazin-3-one with methylmagnesium bromide. The mechanism for this novel rearrangement is discussed.

As part of a program to evaluate a variety of benzothiazines as potential medicinal agents,[2-4] we prepared the compounds shown on Scheme I. Interaction of III with methylmagnesium bromide in THF at room temperature rapidly gave the insoluble complex IIIa. The mixture was poured onto a cold aqueous solution of NH_4Cl to give the hydrolysis product IIIb. The latter slowly cyclized at room temperature, and this conversion to IV was completed by heating on a steam bath. After crystallization from hexane, IV was obtained in 73% yield. The ir spectral data (Figure 1) provided the evidence for the interpretation of this novel rearrangement. The absence of the amido band (6.1 μ in III) and the presence of a CO group at 5.95 μ in IIIb indicated that the major reaction of III with the Grignard reagent took place on the amido group with a minor reaction on the double bond. The completion of the conversion of IIIb to IV is indicated by the appearance of a strong CO band at 5.8 μ and disappearance of both the CO band at 5.9 μ and the NH band at 2.9 μ. The structure assigned to IV was confirmed by nmr spectral data. It was expected that the ring closure of IIIb to IV would yield the less sterically hindered isomer in which the phenyl and acyl groups would be in a trans configuration. The latter assumption was confirmed by X-ray analysis of the MeI salt of **20**, one of the isomeric alcohols of V (Figure 2).†

Most of the ketones listed in Table I were prepared by interaction of the intermediates of Table II with the appropriate Grignard reagent. Compound **4** was obtained by use of phenyllithium in place of a Grignard reagent. The ketones were purified as oxalic acid salts prior to their conversion to the HCl salts. The compounds of Table II are products of the alkylation of arylidenes of Table III with the appropriate basically substituted alkyl halide. Compound **17** was obtained from the reaction of 4-(4-dimethylaminobutyl)-1,4-benzothiazin-3-one with benzaldehyde. The compounds of Table III were obtained by condensation of benzothiazin-3-ones with aromatic aldehydes. Several of these products had previously been prepared by a different and less satisfactory synthetic route.[5] A practical synthesis of I is also described in the Experimental Section.

Reduction of IV with $NaBH_4$ in MeOH gave a mixture of isomeric alcohols **20** and **21** (method A). Treatment of the HCl of IV in MeOH with an aqueous solution of $NaBH_4$ yielded only isomer **20** (method B). The latter was assigned the threo configuration based on the dihedral angle measurements of the MeI salt of **20** (Figure 2).† Acetylation of **20** with Ac_2O gave the acetyl derivative **22**. The tertiary alcohols **19** and **23** were obtained by interaction of the appropriate ketone and Grignard reagent. In contrast to the

Scheme I



product of the interaction of III with methylmagnesium bromide, the more bulky phenylmagnesium bromide reacted with III to give the expected 2-diphenylmethyl derivative.

Structure-Activity Relationships. Compounds of this series were evaluated as antiinflammatory agents in the carrageenin-induced edema procedure and these results are shown in Table I. The initial modification of the lead compound **1** consisted in variation of the acyl group in the 2 position (**2-4**) and the replacement of the phenyl group in the 3 position (**5-10**). With the exception of the 4-pyridyl substitution (**9**), these modifications resulted in compounds with lower activity. Increasing the length of the basic side chain at the 4 position from ethylene to trimethylene gave the highly active compound **13**, whereas increasing the length to tetramethylene yielded a slightly more active ma-

† Single-crystal X-ray analysis was performed on material crystallized from MeOH (triclinic, space group P_1^-) with cell constants: a = 7.81 Å, b = 14.57 Å, c = 22.05 Å, and α = 108°, β = 93° 43', γ = 93° 21'. Crystal density = 1.437 g/cm^3.

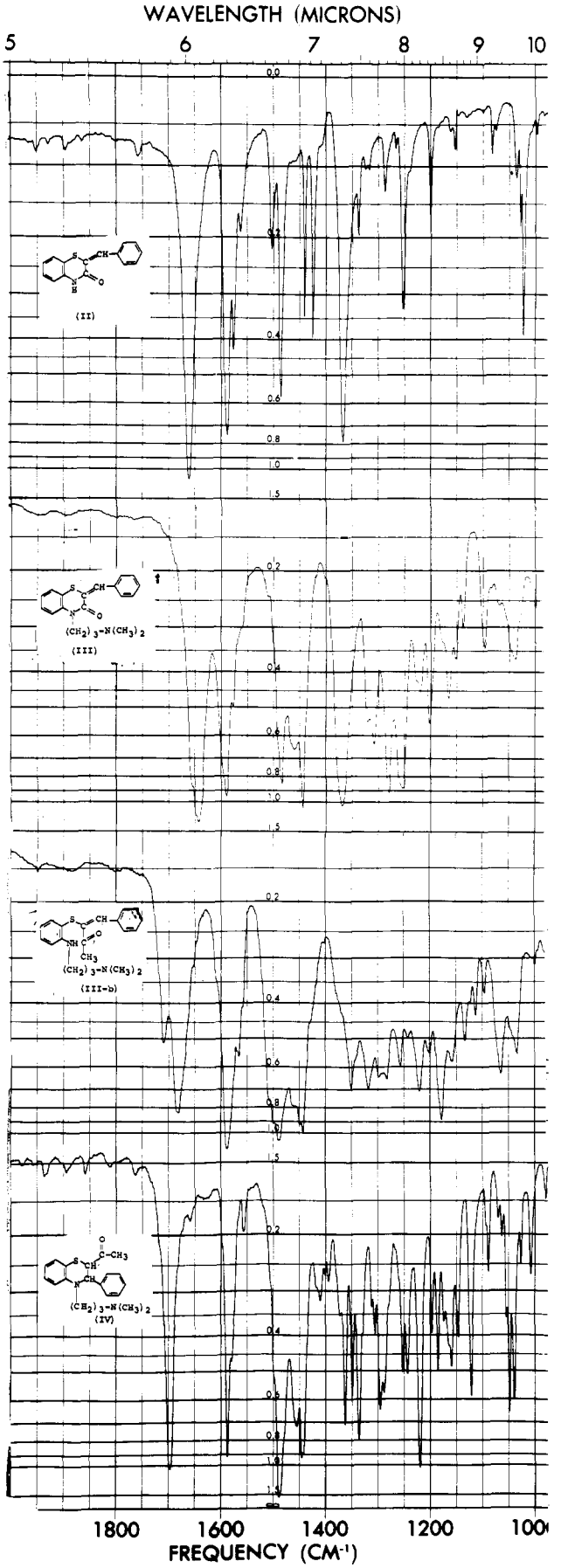


Figure 1. Ir spectral data for II, III, IIIb, and IV.

terial **17**. Further modifications of **1**, in which the dimethylamino group was replaced by diethylamino or morpholino, yielded the less active analogs **11** and **12**. Reduction of the

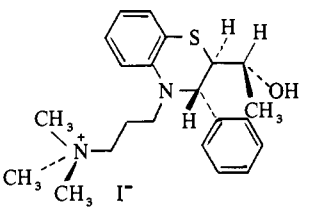


Figure 2. Configuration of the MeI salt of the title compound **20**.

keto group of **13** with $NaBH_4$ or $LiAlH_4$ gave a mixture of alcohols **20** and **21**. Essentially all of the activity resided in the higher melting, less soluble isomer **20**. The latter was about twice as active as phenylbutazone in our test procedure. The acetyl derivative of **20** (**22**) and the tertiary alcohols **19** and **23** were less active than **20**. The most active compounds of Table I, **20** and **13**, were subjected to extensive biological evaluations. The results of these studies will be reported in the following paper.[6]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were determined with a Perkin-Elmer IR-621 spectrometer and the nmr spectra with a Varian XL-100-15 spectrometer. All compounds gave ir spectra similar to those shown in Figure 1. Where analyses are indicated only by the symbols of elements, analytical results obtained for these elements were within 0.4% of the theoretical values.

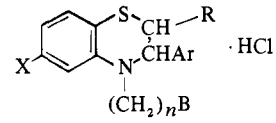
1,4-Benzothiazin-3(4*H*)-one (I). A solution of 220.0 g (5.5 mol) of NaOH in 1.5 l. of H_2O (in a 5-l. flask equipped with a stirrer and condenser) was cooled to 15° and treated portionwise with 670.0 g (5.3 mol) of 2-aminobenzenethiol while the temperature was maintained below 30°. The resulting solution was then treated with a solution of 530.0 g (5.6 mol) of chloroacetic acid in 800 ml of H_2O while the temperature was kept below 40°. An oil separated from the solution, and this mixture was stirred and refluxed for 4 hr, during which time the oil changed to a granular solid. After the mixture had been allowed to stand overnight at room temperature, the solid was filtered and washed with cold H_2O. The liquid was pressed out of the filter cake, and the latter was triturated with 1.0 l. of MeCN on the filter funnel. After 30 min, the solvent was drawn through the filter cake and the latter was then dissolved in 650 ml of hot DMF. When the warm solution was diluted with 2.0 l. of warm MeCN, a solid rapidly crystallized. After being kept at room temperature for several hours, the mixture was cooled overnight. The product was filtered and washed with MeCN to give 662 g (75%) of colorless product, mp 177–179° (reported[7] mp 176°).

2-Benzylidene-2*H*-1,4-benzothiazin-3(4*H*)-one (II). A solution of 400 g (2.4 mol) of I and 400 ml (4.0 mol) of benzaldehyde in 2 l. of DMF was treated with 160 g (3.0 mol) of NaOMe (in one portion). The temperature rose spontaneously to 60°. After the exothermic reaction had subsided, the orange-red solution was stirred and refluxed for 3 hr (a yellow solid separated). The mixture was cooled to 25°, poured onto 10 l. of H_2O, and allowed to stand in the cold overnight. The yellow solid was filtered, washed with H_2O and then with EtOH, and air-dried to give 570 g of material, mp 200–202° (s. 190°). It was dissolved in 1.5 l. of hot DMF, and the resulting solution was diluted with 3.0 l. of hot EtOH. The solution was cooled and the product was filtered and dried. The yellow solid weighed 444 g (72%), mp 202–204° (compound a, Table III). This material had previously been prepared by a different method,[5] mp 200–202°

Most of the compounds of Table III were prepared in the above manner. In the case of c and g, Ac_2O–NEt_3 was used in place of DMF–NaOMe.

2-Benzylidene-4-[3-(dimethylamino)propyl]-2*H*-1,4-benzothiazin-3(4*H*)-one (III). A stirred suspension of 480.0 g (1.9 mol) of II in 1.9 l. of DMF was treated portionwise with 98 g (2.0 mol) of NaH (50% oil dispersion) while the temperature was maintained below 50°. After the temperature had dropped below 40°, the mixture was warmed to 70°, cooled to 25°, and then treated with 1.25 l. of a 2.4 *N* solution of 3-dimethylaminopropyl chloride (3.0 mol) in toluene and 20 g of NaI. This mixture was heated at 100–105° for 3 hr, cooled to 25°, and poured into 10 l. of cold H_2O. Et_2O (1.8 l.) was added, the mixture was shaken, and the layers were allowed to separate. The organic phase was removed and the aqueous phase was twice extracted with Et_2O (1.2 l.). The organic

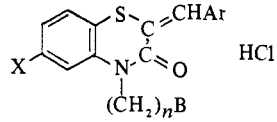
Table I



No.	X	R	Ar	n	B	Mp, °C[a]	Yield, %[b]	Formula[c]	Reversal of carrageen-in-induced edema ID_{50}, mg/kg, oral[e]
1	H	$-COCH_3$	C_6H_5	2	$-N(CH_3)_2$	185-186	71	$C_{20}H_{24}N_2OS \cdot HCl$	150
2	H	$-COCH_2CH_3$	C_6H_5	2	$-N(CH_3)_2$	188-190	34	$C_{21}H_{26}N_2OS \cdot HCl$	>150
3	H	$-CO(CH_2)_2CH_3$	C_6H_5	2	$-N(CH_3)_2$	200-202	49	$C_{22}H_{28}N_2OS \cdot HCl$	>150
4	H	$-COC_6H_5$	C_6H_5	2	$-N(CH_3)_2$	213-215	57	$C_{25}H_{26}N_2OS \cdot HCl$	>150
5	H	$-COCH_3$	$4-(Cl)C_6H_4$	2	$-N(CH_3)_2$	192-194	48	$C_{20}H_{23}ClN_2OS \cdot HCl$	>150
6	H	$-COCH_3$	$4-(OCH_3)C_6H_4$	2	$-N(CH_3)_2$	203-205	78	$C_{21}H_{26}N_2O_2S \cdot HCl$	>150
7	H	$-COCH_3$	2-Pyridyl	2	$-N(CH_3)_2$	173-175	64	$C_{19}H_{23}N_3OS \cdot HCl$	>150
8	H	$-COCH_3$	3-Pyridyl	2	$-N(CH_3)_2$	208-210	45	$C_{19}H_{23}N_3OS \cdot HCl$	>150
9	H	$-COCH_3$	4-Pyridyl	2	$-N(CH_3)_2$	189-191	53	$C_{19}H_{23}N_3OS \cdot HCl$	130
10	H	$-COCH_3$	2-Thienyl	2	$-N(CH_3)_2$	127-130	42	$C_{18}H_{22}N_2OS_2 \cdot HCl$	>150
11	H	$-COCH_3$	C_6H_5	2	$-N(C_2H_5)_2$	201-203	48	$C_{22}H_{28}N_2OS \cdot HCl$	>150
12	H	$-COCH_3$	C_6H_5	2	Morpholino	184-186	29	$C_{22}H_{26}N_2O_2S \cdot HCl \cdot H_2O$	>150
13	H	$-COCH_3$	C_6H_5	3	$-N(CH_3)_2$	183-185	73	$C_{21}H_{26}N_2OS \cdot HCl$	65
14	H	$-COCH_3$	$4-(Cl)C_6H_4$	3	$-N(CH_3)_2$	187-189	68	$C_{21}H_{25}ClN_2OS \cdot HCl$	>150
15	Cl	$-COCH_3$	C_6H_5	3	$-N(CH_3)_2$	197-199	54	$C_{21}H_{25}ClN_2OS \cdot HCl$	150
16	H	$-COCH_3$	C_6H_5	3	Morpholino	183-185	28	$C_{23}H_{28}N_2O_2S \cdot HCl$	160
17	H	$-COCH_3$	C_6H_5	4	$-N(CH_3)_2$	165-167	68	$C_{22}H_{28}N_2OS \cdot HCl$	125
18	H	$-CH(OH)CH_3$	C_6H_5	2	$-N(CH_3)_2$	195-197	65	$C_{20}H_{26}N_2OS \cdot HCl$	125
19	H	$-C(OH)(CH_3)_2$	C_6H_5	2	$-N(CH_3)_2$	107-110	72	$C_{21}H_{28}N_2OS \cdot HCl$	100
20	H	$-CH(OH)CH_3$	C_6H_5	3	$-N(CH_3)_2$	223-225	40	$C_{21}H_{28}N_2OS \cdot HCl$	55
21	H	$-CH(OH)CH_3$	C_6H_5	3	$-N(CH_3)_2$	204-206	9	$C_{21}H_{28}N_2OS \cdot HCl$	>150
22	H	$-CH(OCOCH_3)CH_3$	C_6H_5	3	$-N(CH_3)_2$	192-194	63	$C_{23}H_{30}N_2O_2S \cdot HCl$	>150
23	H	$-C(OH)(CH_3)C_6H_5$	C_6H_5	3	$-N(CH_3)_2$	76-78	78	$C_{27}H_{32}N_2OS \cdot C_6H_8O_7$[d]	>150
		Phenylbutazone							120

[a] Crystallization solvents: *i*-PrOH, **1-3, 13, 15, 22**; EtOH, 4, 8, 11; CH_3CN, **5-7, 9, 12, 14, 16, 18, 21**; Me_2CO-Et_2O, **10**; $CHCl_3$-EtOH, 17, 19; DMF, **20**; CH_3OH-Et_2O, **23**. [b] Yields of ketones **1-17** are based on the purified oxalic acid salts crystallized from the following solvents (mp): DMF, **1** (198-200°), **2** (210-212°), **3** (210-212°), 4 (213-215°), **5** (190-192°), **12** (162-164°), **16** (183-185°); CH_3CN, **6** (135-137°), **10** (124-127°), 14 (82-84°), **15** (108-110°), 17 (124-126°); EtOH, 7 (170-172°), 11 (158-160°); MeOH, 8 (189-191°); **13** was purified as the free base. [c] Analyzed for Cl and S except **23** (N, S). [d] $C_6H_8O_7$ = citric acid. [e] All compounds were dissolved or suspended in 1% aqueous Na CMC and administered orally. Dose-response curves were obtained using seven rats at each of three dose levels (150, 75, and 37.5 mg/kg), and the median inhibition dose (ID_{50}) was calculated. See the following paper[6] for the detailed procedure.

Table II



No.	X	Ar	n	B	Mp, °C[a]	Yield,[b] %	Formula[c]
A	H	C_6H_5	2	$N(CH_3)_2$	234-236	56	$C_{19}H_{20}N_2OS \cdot HCl$
B	H	$4-(Cl)C_6H_4$	2	$N(CH_3)_2$	224-226	46	$C_{19}H_{19}ClN_2OS \cdot HCl$
C	H	$4-(OCH_3)C_6H_4$	2	$N(CH_3)_2$	193-195	44	$C_{20}H_{22}N_2O_2S \cdot HCl$
D	H	2-Pyridyl	2	$N(CH_3)_2$	237-239	68	$C_{18}H_{19}N_3OS \cdot HCl$
E	H	3-Pyridyl	2	$N(CH_3)_2$	223-225	37	$C_{18}H_{19}N_3OS \cdot HCl$
F	H	4-Pyridyl	2	$N(CH_3)_2$	225-227	40	$C_{18}H_{19}N_3OS \cdot HCl$
G	H	2-Thienyl	2	$N(CH_3)_2$	214-216	38	$C_{17}H_{18}N_2OS_2 \cdot HCl$
H	H	C_6H_5	2	$N(C_2H_5)_2$	169-171	52	$C_{21}H_{24}N_2OS \cdot HCl$
I	H	C_6H_5	2	Morpholino	198-200	53	$C_{21}H_{22}N_2O_2S \cdot HCl \cdot H_2O$
J	H	C_6H_5	3	$N(CH_3)_2$	191-193	70	$C_{20}H_{22}N_2OS \cdot HCl$
K	H	$4-(Cl)C_6H_4$	3	$N(CH_3)_2$	230-232	65	$C_{20}H_{21}ClN_2OS \cdot HCl$
L	Cl	C_6H_5	3	$N(CH_3)_2$	180-182	62	$C_{20}H_{21}ClN_2OS \cdot HCl$
M	H	C_6H_5	3	Morpholino	180-182	68	$C_{22}H_{24}N_2O_2S \cdot HCl$
N	H	C_6H_5	4	$N(CH_3)_2$	172-174	72	$C_{21}H_{24}N_2OS \cdot C_2H_2O_4$[d]

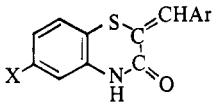
[a] Crystallization solvents: CH_3CN, B, H, I, N; the others from EtOH. [b] Based on the purified salt. Melting point of base: **B**, 122-124°; C, 100-102°; D, 95-97°; E, 103-105°; F, 92-94°; G, 84-86°; I, 128-130°; K, 82-84°. Materials crystallized from CH_3CN except D and G (hexane). [c] Compounds analyzed for Cl and S except N (C, S). [d] $C_2H_2O_4$ = oxalic acid.

phases were combined and extracted with a cold solution of 300 ml of concentrated HCl in 4.0 l. of H_2O and then with 500 ml of H_2O. These aqueous phases were combined, extracted with 300 ml of Et_2O, cooled, and treated portionwise with 600 g of K_2CO_3. The liberated base was extracted with 1.2 l. of Et_2O (three times), the organic phases were combined and dried ($MgSO_4$), and the solvent was evaporated to give 543.0 g (85%) of an oily base.

A similar procedure was used to obtain most of the other compounds of Table II. In the case of B, G, and H, the reaction was carried out in toluene and $NaNH_2$ was used in place of NaH. The HCl salts were prepared by treating a solution of the base in EtOH or Et_2O with 1 equiv of HCl in EtOH.

2-Acetyl-4-[3-(dimethylamino)propyl]-2,4-dihydro-3-phenyl-2*H*-1,4-benzothiazine (IV). A stirred solution of 34.0 g (0.1 mol) of III in 300 ml of THF was treated rapidly with 50 ml (0.15 mol) of 3 *M* ethereal MeMgBr. The temperature of the solution rose to 42° and a precipitate of the complex began to separate in about 20 min. After being stirred for 4 hr at room temperature, the mixture was poured

Table III



No.	X	Ar	Mp, °C[a]	Yield, %	Formula
a	H	C_6H_5	202-204	72	$C_{15}H_{11}NOS$[b]
b	H	4-(Cl)C_6H_4	248-250	77	$C_{15}H_{10}ClNOS$[b]
c	H	4-(OCH_3)C_6H_4	201-203	32	$C_{16}H_{13}NO_2S$[b]
d	H	2-Pyridyl	240-242	74	$C_{14}H_{10}N_2OS$[c]
e	H	3-Pyridyl	220-222	59	$C_{14}H_{10}N_2OS$[c]
f	H	4-Pyridyl	262-264	35	$C_{14}H_{10}N_2OS$[c]
g	H	2-Thienyl	234-236	50	$C_{13}H_9NOS_2$[c]
h	Cl	C_6H_5	240-242	61	$C_{15}H_{10}ClNOS$[c]

[a]Crystallized from DMF-EtOH except f (EtOH). [b]Reference 5. [c]*Anal.* N, S.

onto a cold solution of 15 g of NH_4Cl in 150 ml of H_2O. The organic phase was separated and the aqueous layer was extracted with 300 ml of ether (in two portions). The organic layers were combined, dried ($MgSO_4$), and filtered, and the solvent was evaporated to give 36.0 g of oily residue. After it had stood overnight at room temperature, it was heated on a steam bath for 1 hr and then crystallized from 200 ml of hexane to give 26.0 g (73%) of pale-yellow product, mp 87-89°.

A solution of 142.0 g of IV in 700 ml of *i*-PrOH was treated with 1 equiv of HCl in EtOH to give 142.0 g of **13**: mp 182-184°; recrystallized from *i*-PrOH; λ_{max} (Nujol) 3.9, 4.1, 5.9, 6.4 μ; nmr (DMSO-d_6) τ 4.79 (m, 2 H, J = 1 Hz), 5.92 (d, 3 H, J = 2 Hz), 7.32 (s, Me_2N), 7.73 (s, $COCH_3$).

The hexane filtrate of IV was evaporated to give a red oil which was adsorbed on alumina and developed with PhH. The **4-[3-(dimethylamino)propyl]-2-(α-methylbenzyl)-2*H*-1,4-benzothiazin-3(4*H*)-one** was eluted with PhH-Me_2CO (4:1). The oily base (1.6 g) gave 1.3 g (3%) of the HCl: mp 130-133° ($CHCl_3$-Et_2O); λ_{max} (Nujol) 3.8, 4.0, 6.0, 6.3 μ. *Anal.* ($C_{21}H_{26}N_2OS \cdot HCl$) Cl, S.

4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2*H*-1,4-benzothiazine Hydrochloride (V). Method A (20 and 21). A stirred solution of 31.0 g (0.088 mol) of IV in 350 ml of MeOH was treated portionwise with 9.0 g (0.24 mol) of $NaBH_4$ while the solution had been maintained below 40°. After being stirred for 2 hr at room temperature, the solvent was removed on a rotary evaporator, and the cooled residue was shaken with 100 ml of H_2O and 150 ml of Et_2O. The layers were separated, and the aqueous phase was extracted with 300 ml of Et_2O (in three portions). The organic phases were combined, washed with 50 ml of H_2O (twice), dried ($MgSO_4$), and filtered, and the solvent was evaporated to give 31.0 g of a viscous base. The latter was dissolved in 150 ml of MeCN and treated with 13.5 ml of 6.7 *N* ethanolic HCl. A crystalline salt rapidly separated from the solution. After the solution had stood overnight at room temperature, the solid was filtered and washed with cold MeCN and Et_2O to give a nearly colorless solid weighing 22.0 g, mp 205-208° (s. 180°). This material was added to 220 ml of hot DMF (100°), and the resulting solution was allowed to stand at room temperature overnight. The colorless solid, **20**, was filtered, washed with DMF and Et_2O, and dried: wt 13.7 g (40%); mp 223-225°; λ_{max} (Nujol) 3.05, 3.8, 6.3 μ.

The other isomer, **21**, was obtained by concentration of the MeCN filtrate to about 200 ml to give 2.3 g of material, mp 194-196°. After recrystallization from 30 ml of MeCN, the colorless product weighed 1.6 g (9%); mp 204-206°; λ_{max} (Nujol) 3.04, 3.8, 6.3 μ.

4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-hydroxyethyl)-3-phenyl-2*H*-1,4-benzothiazine Hydrochloride (V). Method B (20). A stirred solution of 35.0 g (0.1 mol) of IV in 350 ml of MeOH was cooled and treated with a solution of 8.0 ml of concentrated HCl in 50 ml of H_2O. To the resulting mixture was added 7.2 g (0.2 mol) of $NaBH_4$ in 35 ml of H_2O during a 15-min period while the mixture was maintained at 20-25°. After being stirred for 1 hr at room temperature, the solution was poured into 500 ml of ice-water and the gum-like product was extracted with 400 ml of $CHCl_3$ (in three portions). The organic phases were combined, dried ($MgSO_4$), and filtered, and the solvent was evaporated to give 40.0 g of viscous residue. The latter was converted to the HCl salt as described in method A to give 29.2 g (75%) of **20**, mp 220-223°. This product was added to 300 ml of hot DMF (100°) and the resulting solution was allowed to cool overnight at room temperature to give 26.2 g (68%) of colorless product, mp 223-225°. Plate chromatography of this material on silica gel using a mixture of PhH-EtOAc-EtOH-AcOH-H_2O as the solvent system (assay developed by H. R. Roberts and his staff of these laboratories) showed the absence of isomer **21**. Compound **20**, prepared by method A, was found to contain a small quantity of isomer **21**.

The MeI of **20** was prepared by treating a solution of 5.0 g (0.014 mol) of **20** in 50 ml of MeOH with 4.2 g (0.028 mol) of MeI. After the mixture had stood overnight, it was diluted with Et_2O and filtered, and the product was recrystallized from *i*-PrOH: yield 5.4 g (77%); mp 157-159°; λ_{max} (Nujol) 2.95, 6.3 μ. *Anal.* ($C_{22}H_{31}IN_2OS$) I, S.

4-[3-(Dimethylamino)propyl]-3,4-dihydro-2-(1-acetoxyethyl)-3-phenyl-2*H*-1,4-benzothiazine Hydrochloride (22). A mixture of 8.0 g (0.02 mol) of **20**, 40 ml of Ac_2O, and 8 ml of pyridine was refluxed for 30 min and then cooled; the solution was diluted with 300 ml of Et_2O to give 8.5 g of product, mp 141-143°. After crystallization from 60 ml of MeCOEt, the colorless solid weighed 5.7 g (63%): mp 152-154°; λ_{max} (Nujol) 3.9, 4.0, 5.76, 6.4 μ.

4-[4-(Dimethylamino)butyl]-2*H*-1,4-benzothiazin-3(4*H*)-one. Alkylation of 31 g (0.019 mol) of I with 41 g of $Cl(CH_2)_4Br$ by the procedure used in obtaining III gave 31 g of the intermediate chloro compound, bp 180-185° (0.2 mm). The latter was treated with NaI and excess $HNMe_2$ in benzene to give 15.3 g (31%) of product: bp 170-173° (0.2 mm); λ_{max} 6.0, 6.3 μ. *Anal.* ($C_{14}H_{20}N_2OS$) N. Interaction of this material with benzaldehyde, according to the conditions used in the preparation of II, gave compound N of Table II.

4-[3-(Dimethylamino)propyl]-2-(diphenylmethyl)-2*H*-1,4-benzothiazin-3(4*H*)-one Oxalate. Interaction of 17.0 g (0.05 mol) of III with 25 ml (0.075 mol) of PhMgBr in THF, according to the method used in preparing IV, gave 23.0 g of the base. An Et_2O solution of the base was treated with 4.5 g of oxalic acid in Et_2O to give 25.9 g (100%) of the oxalate, mp 81-84° (s. 60°). After crystallization from MeCN-Et_2O, the nearly colorless solid weighed 19.3 g (76%), mp 90-93° (s. 85°). *Anal.* ($C_{28}H_{30}N_2O_5S$) C, H, N, S. The free base liberated from the purified oxalate and the unpurified base showed identical ir spectra: λ_{max} 6.0, 6.3 μ.

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