CHEMISTRY AND SYNTHESIS OF SOME DIHYDRO-2*H*-1,4-BENZOTHIAZINE DERIVATIVES

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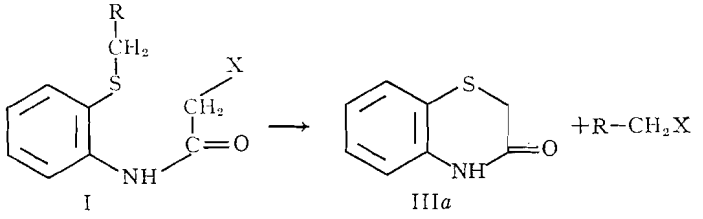
ABSTRACT

The formation of 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (III*a*) by cyclization of alkyl 2-haloacetamidophenyl sulfides (I) was investigated; it is proposed that the reaction proceeds via a six-membered sulfonium halide. The preparation of 4-alkyl derivatives of III*a* and of 4-alkyl and 4-acyl derivatives of its reduction product 3,4-dihydro-2*H*-1,4-benzothiazine (V*a*) is described. Acylation of V*a* was shown to proceed without opening of the thiazine ring. Preparation of the O-benzoyl, N-benzoyl, and O,N-dibenzoyl derivatives of 2-(β-hydroxyethylmercapto)aniline (VIII) has permitted clarification of the confusion in the literature with respect to the derivatives of V*a* and VIII. Compound XVIII, the 1,1-dioxide of III*a*, undergoes C-alkylation at the 2-position when treated with alkyl halides, rather than O-alkylation as previously suggested.

The formation of 3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine (III*a*) when the distillation of 2-(α-chloroacetamido)phenyl methyl sulfide (I*a*) was attempted was reported recently by Davis *et al.* (1). It was observed in this laboratory that the reaction is general for 2-(α-chloroacetamido)phenyl alkyl (and aralkyl) sulfides (Table I), and that when the

TABLE I



I III*a*

Compound No.	R	X	Method	% yield of products III*a*	% yield of products RCH_2X
I*a*	H	Cl	A	65*	—
I*b*	CH_3	Cl	A	61	—
I*c*	CH_3CH_2	Cl	A	30	—
I*d*	$CH_3CH_2CH_2$	Cl	A	26	—
I*e*	C_6H_5	Cl	A	64	76
I*f*	$C_6H_5CH_2$	Br	B	50	88
I*f*	$C_6H_5CH_2$	Br	C	51	43†
I*g*	$C_6H_5CH_2$	I	D	24	—
I*g*	$C_6H_5CH_2$	I	E	49	49
I*g*	$C_6H_5CH_2$	I	F	17	22
I*g*	$C_6H_5CH_2$	I	G	48	57
I*g*	$C_6H_5CH_2$	I	H	70	48

*See ref. 1.
†The halide that was isolated was phenethyl iodide.
NOTE: A, heating at 180–200 °C, under water aspirator pressure; B, heating at 140–180 °C, under water aspirator pressure (8 mm); C, refluxed for 3 h with an equivalent amount of sodium iodide in acetone; D, refluxed for 3 h in acetone only; E, refluxed for 3 h with an equivalent amount of sodium bromide in acetone; F, stirred at room temperatu re for 3 h in dimethyl sulfoxide; G, stirred in dimethyl sulfoxide at 60° for 3 h; H, stirre d in dimethyl sulfoxide at 60° for 3 h with an equivalent amount of sodium bromide.

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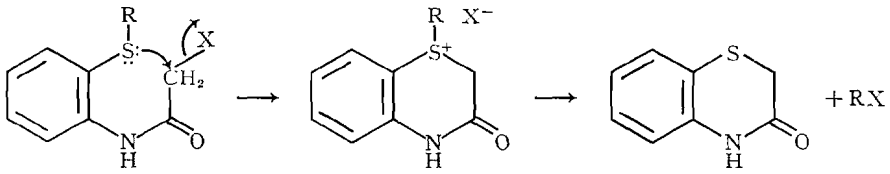
aralkyl group was benzyl or phenethyl, the corresponding halide was isolated in good yield. This suggests the possibility that the elimination of these halides proceeds through a six-membered cyclic sulfonium halide (II).



I II IIIa

Refluxing 2-(α-bromoacetamido)phenyl phenethyl sulfide (I*f*) with an equivalent amount of sodium iodide in acetone gave III*a* in 51% yield. Instead of phenethyl bromide, however, phenethyl iodide was obtained in 43% yield as the second product. 2-(α-Iodoacetamido)phenyl phenethyl sulfide was prepared in 78% yield by stirring the bromo compound with an equivalent amount of sodium iodide in acetone at room temperature for 20 min. The iodo derivative, when it was refluxed in acetone for 3 h, gave only a 20% yield of III*a*; however, when sodium bromide was added the yield was increased to 49%.

The reaction probably proceeds in two stages. In the slow or rate-determining step, the sulfonium ion (II) is formed. The rate of sulfonium ion formation appears to be dependent on the polarity of the solvent. Because charged moieties are being formed in the transition state, the addition of sodium bromide can be expected to accelerate the reaction by providing additional charge stabilization (2).

Distillation of 2-(α-chloroacetamido)anisole under similar conditions proceeded normally with no decomposition or elimination of methyl chloride, thus showing the lesser nucleophilic reactivity of oxygen compared with that of sulfur.

The 2-(α-haloacetamido)phenyl alkyl or aralkyl sulfides (I) were prepared according to the method of Davis *et al.* (1) from 2-alkyl- or 2-aralkyl-mercaptoanilines (Table II).

The 6-chloromethyl (3) and 6-trifluoromethyl (4) derivatives (III*b* and III*c*) were prepared by reductive cyclization of the corresponding *o*-nitrophenylthioglycolic acids (5, 6). It was found that the reduction was more conveniently performed with sodium hydrosulfite than with the other reagents previously described in the literature.

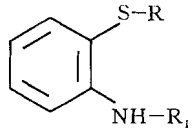
Treatment of III with alkyl or aralkyl halides in alcoholic potassium hydroxide or in dimethylformamide containing sodium hydroxide gave the new N-alkyl or N-aralkyl derivatives (IV) (Table III). When III*a* was allowed to react with ethyl chloroacetate, the use of sodamide gave better results than the standard method with sodium hydride.

The reduction of III*a* with $LiAlH_4$ in ether by the procedure of Angelini *et al.* (7) gave 3,4-dihydro-2*H*-1,4-benzothiazine (V*a*) in 80% yield, but was unsatisfactory for large-scale preparation because of the low solubility of III*a* in ether. The use of tetrahydrofuran according to the procedure of Hromatka *et al.* (8) repeatedly resulted in a violent and uncontrollable reaction towards the end of the addition period; when the addition was performed at reflux temperature, the reduction could be accomplished without difficulty. III*b* was reduced smoothly by $LiAlH_4$ in ether solution to V*b* (9). III*c* was more conveniently reduced with diborane in tetrahydrofuran solution to V*c*.

Several of the N-alkyl derivatives (IV) were reduced by $LiAlH_4$ in ether to give the N-alkyl dihydrobenzothiazines (VI) (Table IV). The carbethoxymethyl substituent in IV*d* was reduced during the reaction to a β-hydroxyethyl group (VI*c*).

TABLE II

o-Substituted aminophenyl sulfides

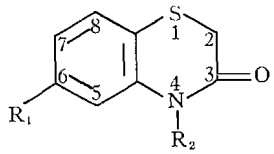


Compound No.	R	R_1	Melting, °C, or boiling, °C (mm), point	Solvent*	% yield	Formula	% analyses									
							Calcd.					Found				
							C	H	N	S	X†	C	H	N	S	X†
	i-C_3H_7	H	78–80 (0.55)‡	—	86	$C_9H_{13}NS$	64.62	7.83	8.38	—	—	64.68	7.98	8.46	—	—
	$CH_2CH_2C_6H_5$	H	150 (0.2)	—	81	$C_{14}H_{15}NS$	73.32	6.59	6.11	—	—	73.14	6.62	6.20	—	—
Ie	$CH_2C_6H_5$	$COCH_2Cl$	53–54	E + PE	63	$C_{15}H_{14}ClNOS$	61.73	4.84	4.80	—	12.15 (Cl)	61.79	4.85	4.96	—	12.17 (Cl)
If	$CH_2CH_2C_6H_5$	$COCH_2Br$	60–62	E + PE	61	$C_{16}H_{16}BrNOS \cdot \frac{1}{2}H_2O$	53.48	4.77	3.90	—	22.24 (Br)	53.93	4.94	4.47	—	22.24 (Br)
Ig	$CH_2CH_2C_6H_5$	$COCH_2I$	83–84	E + PE	78	$C_{16}H_{16}INOS$	48.37	4.06	3.53	—	31.94 (I)	48.50	4.09	3.72	—	32.22 (I)
Ih	CH_3	$COCH_2Br$	67–68.5	E + PE	45.6	$C_9H_{10}BrNOS$	41.55	3.88	5.39	12.32	30.72 (Br)	41.50	3.97	5.19	12.49	30.95 (Br)
Ii	CH_3	$COCH_2CH_2Cl$	70–71	E + PE	61	$C_{10}H_{12}ClNOS$	52.28	5.27	6.10	13.96	15.43 (Cl)	52.30	5.31	6.06	13.81	15.61 (Cl)
Ij	CH_3	$COCHCl_2$	96–97	E + PE	80	$C_9H_9Cl_2NOS$	43.21	3.63	5.60	12.82	28.34 (Cl)	43.10	3.65	5.68	12.56	28.46 (Cl)
X	CH_2CH_2OH	COC_6H_5	88.5–90§	E + M	68	$C_{15}H_{15}NO_2S$	65.90	5.53	5.13	11.73	—	65.97	5.37	4.92	11.67	—
XI	$CH_2CH_2OCOC_6H_5$	H	44.5–46	A + W	69.6	$C_{15}H_{15}NO_2S$	65.90	5.53	5.12	11.73	—	65.92	5.68	5.04	12.09	
			176–180			$C_{15}H_{16}NO_2S \cdot HCl$	58.14	5.21	4.32	10.35	11.45 (Cl)	58.23	5.28	4.42	10.59	11.15 (Cl)
XII	CH_2CH_2OH	$CONHC_6H_3Cl_2$	156–157	E	68.6	$C_{15}H_{14}Cl_2N_2O_2S$	50.42	3.95	7.84	8.97	19.85 (Cl)	50.72	4.08	8.07	8.99	19.74 (Cl)
XIII	$CH_2CH_2OCOC_6H_5$	$CONHC_6H_3Cl_2$	153–154	A	34.8	$C_{22}H_{18}Cl_2N_2O_3S$	57.28	3.93	6.07	6.95	15.37 (Cl)	57.01	4.25	5.87	6.76	15.30 (Cl)
XIV	$CH_2CH_2OCOCH_3$	$COCH_3$	184–186 (1.1)	—	96	$C_{12}H_{15}NO_3S$	56.89	5.97	5.53	12.66	—	56.85	5.91	5.63	12.88	—
XV	CH_2CH_2OH	$COCH_3$	176 (0.5)	—	96	$C_{10}H_{13}NO_2S$	56.85	6.20	6.63	15.18		57.07	6.43	6.70	15.01	

*Recrystallization solvents: E, ether; PE, petroleum ether (30–60°); A, ethanol; W, water; M, methanol.
†The particular halogen analyzed is indicated in parentheses.
‡n_D^{25} 1.5808.
§96% yield from IX and potassium hydroxide in dilute ethanol; lit. (14) m.p. 75°.

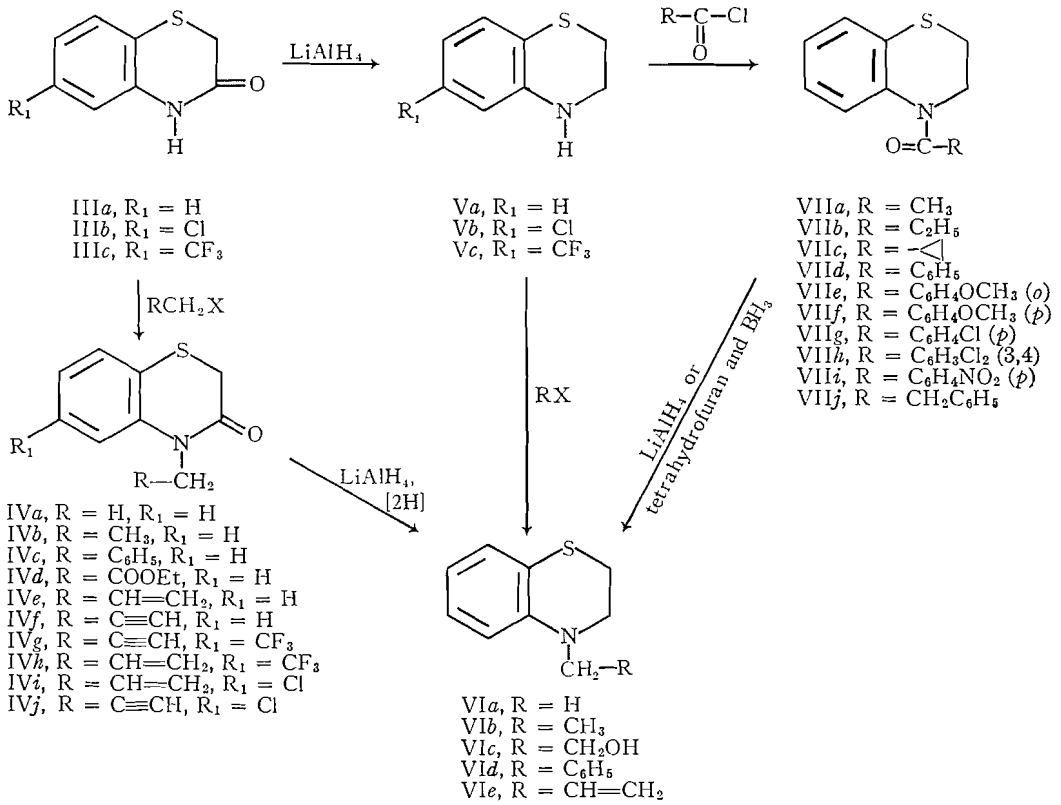
TABLE III

3,4-Dihydro-3-oxo-substituted-2*H*-1,4-Benzothiazines



Compound No.	R_1	R_2	Melting, °C, or boiling, °C (mm), point	% yield	Solvent*	Formula	% analyses: Calcd. C	H	N	S	X†	Found C	H	N	S	X†	Method
IV*b*	H	C_2H_5	182–190 (12)	54‡	—	—											B
IV*c*	H	$CH_2C_6H_5$	84.5–85.5	62§	A	$C_{15}H_{13}NOS$	70.55	5.13	5.59		—	70.66	5.24	5.58			A, B
IV*d*	H	$CH_2COOC_2H_5$	48.5–50.5	19	E + PE	$C_{12}H_{13}NO_3S$	57.35	5.21	5.58	—	—	57.24	5.28	5.75	—	—	A
IV*e*	H	$CH_2CH{=}CH_2$	124 (0.3)	63.5	—	$C_{11}H_{11}NOS$	64.36	5.40	6.83	—	—	64.40	5.37	7.07	—	—	A
IV*f*	H	$CH_2{-}C{\equiv}CH$	111–112	59	A + W	$C_{11}H_9NOS$	65.00	4.46	6.89	—	—	64.80	4.54	6.92	—	—	A
IV*g*	F_3C	$CH_2{-}C{\equiv}CH$	72–76	62	PE	$C_{12}H_8F_3NOS$	53.13	2.97	5.16	—	21.02 (F)	52.85	2.89	5.38	—	20.64 (F)	A
IV*h*	F_3C	$CH_2CH{=}CH_2$	124 (0.65)	82	—	$C_{12}H_{10}F_3NOS$	52.72	3.69	5.13	—	20.86 (F)	52.85	3.79	5.21	—	20.58 (F)	A
IV*i*	Cl	$CH_2CH{=}CH_2$	52–55	25	PE	$C_{11}H_{10}ClNOS$	55.11	4.21	5.84	—	14.80 (Cl)	54.95	4.01	5.87	—	15.24 (Cl)	A
IV*j*	Cl	$CH_2{-}C{\equiv}CH$	78.5–80.5	23	PE	$C_{11}H_8ClNOS$	55.58	3.39	5.89	—	14.92 (Cl)	55.37	3.07	6.00	—	14.82 (Cl)	A

*Recrystallization solvents: A, ethanol; E, ether; PE, petroleum ether (30–60°); W, water.
†The particular halogen analyzed is indicated in parentheses.
‡The distilled product was cloudy; hence it was reduced to VI*b* without elemental analysis.
§The yield varied depending on the method used: 42% by method A and 62% by method B.
‖The halide that was used was allyl or propargyl bromide.



REACTION SCHEME 1.

Treatment of the unsubstituted dihydrobenzothiazine (V*a*) with acyl halides and pyridine in ether gave a number of new N-acyl dihydrobenzothiazines (VII) (Table IV).

The N-benzoyl derivative (VII*d*) was reduced by diborane to the corresponding N-benzyl derivative (VI*d*). This reduction could not be effected by $LiAlH_4$, which caused cleavage of the benzoyl group (cf. Nystrom and Brown (10)).

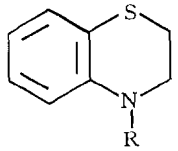
In contrast, the N-acetyl derivative (VII*a*) was readily converted by $LiAlH_4$ into the N-ethyl derivative (VI*b*).

An alternative approach to the N-alkyl derivatives (VI) was the direct alkylation of V*a*; this method was applied successfully in the preparation of the N-benzyl and N-methyl derivatives.

It is interesting to note that none of the acylation reactions of V*a* showed signs of thiazine ring opening. Acylation of several substituted 3,4-dihydro-2*H*-1,4-benzothiazines in an alkaline medium has also been reported by Lowrie (11) to occur without ring opening. The suggestion that the heterocyclic ring in dihydrobenzothiazines is readily opened (12, 13) would thus appear to be incorrect. Some of the confusion in the earlier literature arises from the reported synthesis of V*a* (Fusco and Palazzo (14)) from *o*-nitrochlorobenzene and 2-mercaptoethanol. Fusco and Palazzo isolated the dibenzoyl derivative (IX) when their product was benzoylated, and therefore concluded that ring cleavage had occurred; however, it has been shown (8, 15) that their initial product was, in fact, 2-(β-hydroxyethylmercapto)aniline (VIII). The interconversions of the O-benzoyl,

TABLE IV

3,4-Dihydro-4-substituted-2*H*-1,4-benzothiazines



Compound No.	R	Melting, °C, or boiling, °C (mm), point	% yield*	Solvent†	Formula	% analyses									
						Calcd.					Found				
						C	H	N	S	X‡	C	H	N	S	X‡
V*a*	H	37–38,§ 116–118 (0.5)	62		C_8H_9NS	63.53	6.00	9.26	21.21	—	63.36	6.06	9.13	21.37	—
				M + B	$C_8H_9NS\cdot HCl$‖	51.19	5.37	7.47	17.08	18.89 (Cl)	51.37	5.34	7.27	17.11	18.86 (Cl)
VI*a*	CH_3	100 (0.4)	65.5¶		$C_9H_{11}NS$**	65.42	6.71	8.48	19.40	—	65.36	6.70	8.71	19.72	—
VI*b*	C_2H_5	104 (0.17)	76.5		$C_{10}H_{13}NS$	66.99	7.31	7.81	17.89	—	67.27	7.10	7.73	17.63	—
VI*c*	CH_2CH_2OH	151 (0.4)	60		$C_{10}H_{13}NOS$	61.50	6.71	7.18	16.42	—	61.20	6.73	7.54	15.95	—
VI*d*	$CH_2C_6H_5$	96.5–97.5	80††	A + W	$C_{15}H_{15}NS$	74.64	6.27	5.81	13.29	—	74.80	6.20	5.67	13.39	—
VI*e*	$CH_2—CH=CH_2$	102–103 (0.3)	47		$C_{11}H_{13}NS$	69.06	6.85	7.32	—	—	68.72	6.62	7.73	—	—
VII*a*	$COCH_3$	55–57	59	E + PE	$C_{10}H_{11}NOS$	62.14	5.74	7.25	16.59	—	62.35	5.73	7.32	16.78	—
VII*b*	$COCH_2CH_3$	52–53	67	E + PE	$C_{11}H_{13}NOS$	63.73	6.32	6.76	15.47	—	63.90	6.44	6.78	15.76	—
VII*c*	CO—◁	70–71.5	62	M + W	$C_{12}H_{13}NOS$	65.72	5.97	6.39	14.62	—	65.67	5.87	6.47	14.44	—
VII*d*	COC_6H_5	88–89.5	74	E + PE	$C_{15}H_{13}NOS$	70.55	5.13	5.49	12.56	6.26 (O)	70.35	5.04	5.70	12.73	5.88 (O)
VII*e*	$COC_6H_4OCH_3$ (*o*)	141.5–142.5	61	A + W	$C_{16}H_{15}NO_2S$	67.34	5.30	4.91	11.24	—	67.11	5.38	5.11	11.25	—
VII*f*	$COC_6H_4OCH_3$ (*p*)	127–128	69	A + W	$C_{16}H_{15}NO_2S$	67.34	5.30	4.91	11.24	—	67.23	5.42	4.83	11.28	—
VII*g*	COC_6H_4Cl (*p*)	101–103	94	A + W	$C_{15}H_{12}ClNOS$	62.16	4.18	4.83	11.07	12.24 (Cl)	62.13	4.23	4.69	11.21	12.03 (Cl)
VII*h*	$COC_6H_3Cl_2$ (3,4)	101.5–103	72	A + W	$C_{15}H_{11}Cl_2NOS$	55.56	3.42	4.32	9.89	21.87 (Cl)	55.45	3.37	4.15	10.22	21.75 (Cl)
VII*i*	$COC_6H_4NO_2$ (*p*)	186.5–188.5	89	A + B	$C_{15}H_{12}N_2O_3S$	59.98	4.03	9.33	10.68	—	60.26	4.30	9.13	10.79	—
VII*j*	$COCH_2C_6H_5$	73–74	90	A + W	$C_{16}H_{15}NOS$	71.35	5.61	5.20	11.90	—	71.48	5.65	5.06	11.72	—
XXII*a*	$CONHC_6H_3Cl_2$ (3,4)	160–161	99	A	$C_{15}H_{12}Cl_2N_2OS$	53.10	3.57	8.26	9.45	20.90 (Cl)	53.41	3.50	8.17	9.28	20.43 (Cl)
XXII*b*	$CONHCH_3$	116–117.5	18	M + E	$C_{10}H_{12}N_2OS$	57.65	5.81	13.45	15.40	—	57.66	5.85	13.36	15.21	—
XXII*c*	$CONHC_2H_5$	81.5–82.5	27	E + PE	$C_{11}H_{14}N_2OS$	59.43	6.35	12.61	14.42	—	59.83	6.07	12.68	14.74	—
XXII*d*	$CONHC_6H_5$	110–111	65	PE	$C_{15}H_{12}N_2OS$	65.18	7.29	10.14	11.60	—	65.18	7.15	10.18	11.81	—
XXII*e*	$CONHC_{10}H_{17}$	171–172	94	B	$C_{19}H_{16}N_2OS$	71.22	5.03	8.75	10.00	—	70.96	4.86	8.72	10.18	—

*Yields given are those of the crude solid or the once-distilled liquid.

†Recrystallization solvents: A, ethanol; B, benzene; E, ether; M, methanol; PE, petroleum ether (30–60°); W, water.

‡The particular element analyzed is indicated in parentheses.

§For reported physical data, see refs. 7–9, 23, and 28.

‖The pinkish-white hydrochloride (m.p. 162–165 °C) was obtained from V*a* and dry HCl gas, in ether containing a little methanol. Fusco and Palazzo (14) report that the hydrochloride salt was hygroscopic and gave no melting point, etc.

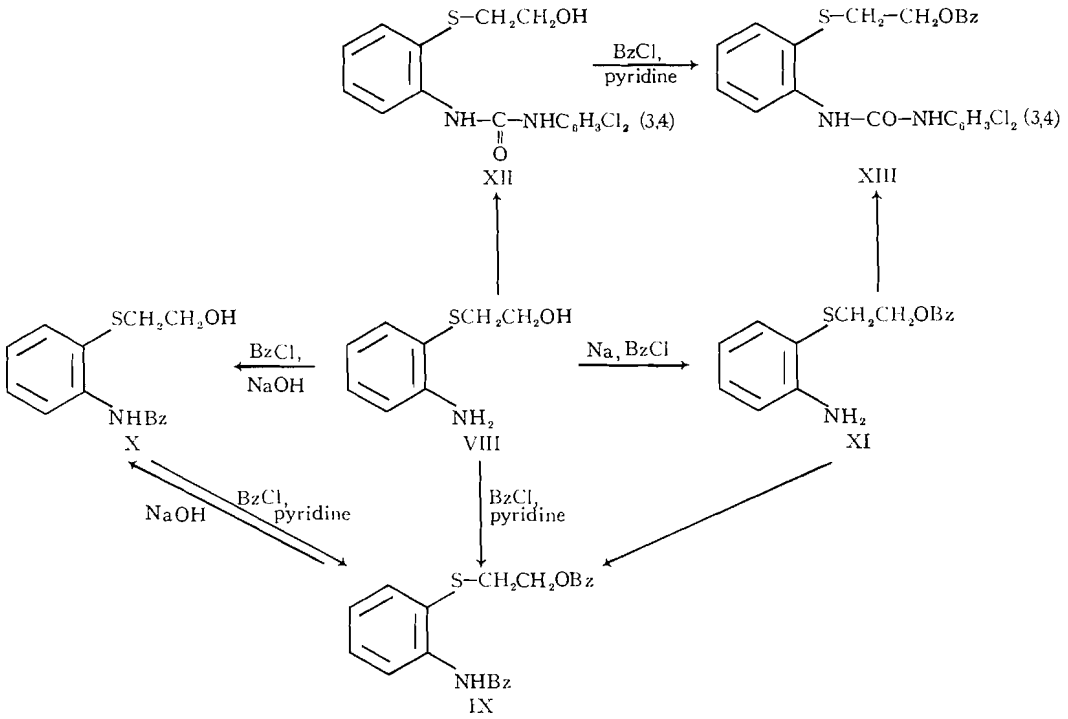
¶65.5% from IV*a* and $LiAlH_4$.

**Formed a picrate, m.p. 132–133° (decomp.) when crystallized from aqueous ethanol.

Anal. Calcd. for $C_9H_{11}NS\cdot C_6H_3N_3O_7$: C, 45.68; H, 3.58; N, 14.21. Found: C, 45.82; H, 3.79; N, 14.16.

††Yield varied from 0 to 80% depending on the method used: 80% from IV*c* and diborane; 70% from VII*d* and diborane; 0% from VII*d* and $LiAlH_4$; 52% from V*a*, benzyl chloride, and potassium iodide.

N-benzoyl, and O,N-dibenzoyl derivatives of VIII are shown in Reaction Scheme 2. The O-benzoyl derivative (XI) may be prepared by the gradual addition of 1 equivalent of benzoyl chloride to a suspension of the sodium salt of VIII in toluene.



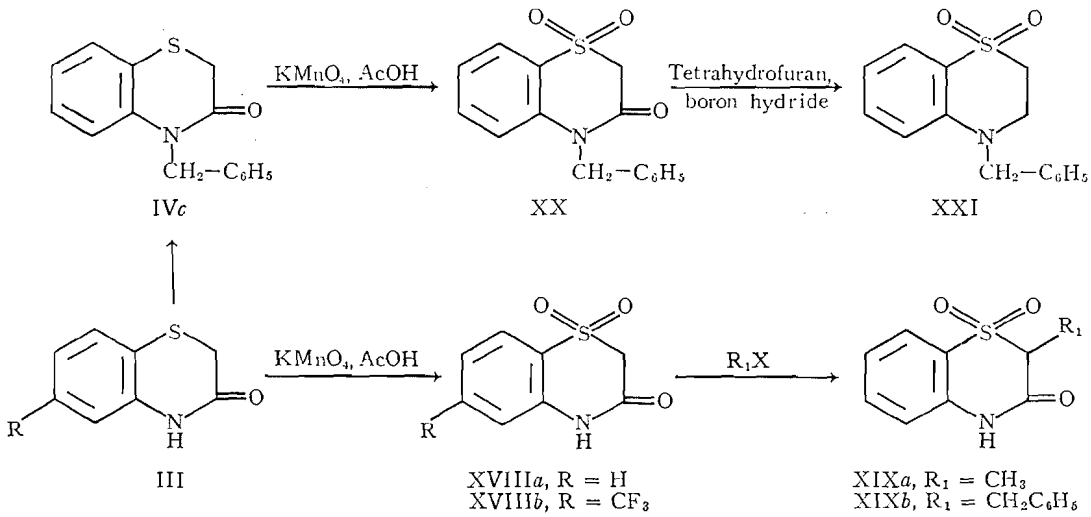
REACTION SCHEME 2.

Reaction of XI with 3,4-dichlorophenylisocyanate gives XIII, which could also be obtained from XII and benzoyl chloride. Refluxing VIII with acetic anhydride gave the N,O-diacetyl derivative (XIV) in a quantitative yield. The latter, when boiled with aqueous alcoholic potassium hydroxide for 5 min, gave 2-(β-hydroxyethylmercapto)-acetanilide (XV) in 96% yield.

Nitrosation of V*a* gave 3,4-dihydro-4-nitroso-2*H*-1,4-benzothiazine (XVI) as an oil, which was reduced to 4-amino-3,4-dihydro-2*H*-1,4-benzothiazine (XVII) (characterized as the hydrochloride). The two methylene groups of XVII gave signals centered at τ 6.36 and 6.85 in the nuclear magnetic resonance spectra (in dimethyl sulfoxide). This establishes that nitrosation of V*a* does not involve thiazine ring opening.

Oxidation of III*a* with potassium permanganate in glacial acetic acid gave the sulfone XVIII*a*, which was previously prepared by Claasz (16) by the reductive cyclization of 2-nitrobenzenesulfonylacetic acid. The compound shows strong infrared absorption bands at 3 300 and 1 700 cm^{-1}, which suggests the predominance of the oxo form (XVIII*a*). The sulfone could not be reduced by diborane or $LiAlH_4$. However, the 4-benzyl sulfone (XX) (prepared from IV*c* and potassium permanganate) could be reduced by diborane to 4-benzyl-3,4-dihydro-2*H*-1,4-benzothiazine-1,1-dioxide (XXI).

Benzylation of XVIII*a* in the presence of a base gave a benzyl derivative (XIX*b*) which was different from XX. Infrared absorption bands indicated the presence of NH (3 200 cm^{-1}) and C=O (1 680 cm^{-1}) groups in XIX*b*. The nuclear magnetic resonance spectrum



REACTION SCHEME 3.

(in deuteriochloroform) showed the expected singlet at low field (τ 0.25) for the NH hydrogen (which disappeared on treatment with deuterium oxide), and a typical ABX pattern with a quadruplet centered at τ 5.79 for a methine group and a multiplet centered at τ 6.64 for a methylene group. Thus benzylation of XVIII*a* caused substitution on the 2-carbon atom to give 2-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-1,1-dioxide (XIX*b*).

Methylation of XVIII*a* with methyl iodide in a basic medium produced the known (Claasz (17)) methyl derivative (XIX*a*). The infrared absorption spectrum of XIX*a* had peaks at 1 670 cm^{-1} (C=O) and 3 220 cm^{-1} (NH). Its nuclear magnetic resonance spectrum (in dimethyl sulfoxide) had a signal at τ 0.22 (NH) which disappeared when D_2O was added, as well as a quadruplet at τ 5.25 and a doublet at τ 8.50 which indicated the presence of a CH—CH_3 grouping.

On the basis of this evidence, the methylation product of XVIII*a* has the structure XIX*a*. The original suggestion by Claasz that the methylation of XVIII*a* gives the O-alkylated product, 3-methoxy-2*H*-1,4-benzothiazine-1,1-dioxide, is therefore incorrect.

EXPERIMENTAL

Melting points, determined with a Thomas Hoover capillary melting point apparatus, are corrected. Infrared spectra were obtained with a Beckman IR-8 spectrophotometer. Analyses were carried out by the Abbott Microanalytical Laboratory, Chicago, Illinois.

2-Phenethylmercaptoaniline

Phenethyl bromide (185.0 g, 1.0 mole) was added dropwise to a solution of 2-aminobenzenethiol (125.1 g, 1.0 mole) and sodium hydroxide (44.0 g, 1.1 moles) in 90% ethanol (700 ml) at a rate sufficient to maintain a gentle reflux. After the addition was complete the reaction mixture was refluxed for an additional hour. The solution was concentrated to half its volume, and the residue was diluted with water and extracted with ether. The ethereal extract was washed with water, dried, and distilled to give the product, b.p. 149–155° at 0.2 mm, yield 185.0 g (81%). The analytical sample distilled at 150° and 0.2 mm.

The above method was used for the preparation of 2-isopropylmercaptoaniline and the known 2-methylmercaptoaniline (1), 2-ethylmercaptoaniline (18), 2-*n*-propylmercaptoaniline (19), 2-*n*-butylmercaptoaniline (18), and 2-benzylmercaptoaniline (1, 20).

2-(α-Haloacetamido)phenyl Alkyl or Aralkyl Sulfides (I)

All compounds in this series were made according to the method of Davis *et al.* (1), and are recorded in Table II.

2-(α-Iodoacetamido)phenyl Phenethyl Sulfide (Ig)

A solution of sodium iodide (8.6 g, 0.057 mole) in acetone (200 ml) was stirred with a solution of I*f* (20.0 g, 0.057 mole) in acetone (70 ml) for 20 min at room temperature. The precipitated sodium bromide (5.6 g, 97%) was removed by filtration, and the filtrate was evaporated under reduced pressure in a bath at 30° to give the product melting at 82.5–84°. One crystallization from ether – petroleum ether (30–60°) gave the analytical sample, m.p. 83–84°.

6-Chloro-3-oxo-3,4-dihydro-2H-1,4-benzothiazine (IIIb)

Sodium hydrosulfite (15.6 g, 0.09 mole) was added in portions to a solution of 4-chloro-2-nitrophenylthioglycolic acid (7.4 g, 0.03 mole) (which was being stirred at 45°) in water (500 ml) containing sodium hydroxide (5.2 g, 0.13 mole). The reaction was exothermic and the temperature was held at 90° for 5 min after the addition of the hydrosulfite was complete. The hot reaction solution was treated with norite, filtered, and acidified while hot to give 4.0 g (66%) of the product, m.p. 205–206°; infrared absorption (Nujol mull): 3 200 cm^{-1} and 1 655 cm^{-1}.

4-Methyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine (IVa)

Method A, Table III

A solution of III*a* (40.0 g, 0.242 mole) (22–25), methyl iodide (52.0 g, 0.40 mole), and potassium hydroxide (13.6 g, 0.243 mole) in ethanol (400 ml) was refluxed for 5 h. The mixture was filtered and the filtrate was evaporated to dryness. The residue was extracted with ether (leaving some unchanged starting material), and the ether solution was washed with aqueous sodium thiosulfate, dried, and evaporated. The product was obtained by distillation, b.p. 119–122° at 0.5 mm, m.p. 53.5–55.5° (lit. (26) m.p. 55–56°).

4-Benzyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine (IVc)

Method B, Table III

A solution of III*a* (33.0 g, 0.2 mole) in dimethylformamide (200 ml) was added to a suspension of sodium hydride (9.6 g, 50% NaH, 0.2 mole) in dimethylformamide (100 ml) without external cooling, and the mixture was stirred for 90 min. A solution of benzyl chloride (25.3 g, 0.2 mole) in benzene (50 ml) was added dropwise without external cooling, and the temperature was held at 100° for 1 h.

The reaction mixture was diluted with water, and extracted with benzene (200 ml). The benzene extract was evaporated and crystallized from petroleum ether to give the product, m.p. 84–85°, yield 31.5 g (62%).

4-Carbethoxymethyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine (IVd)

A suspension of sodium amide (23.0 g, 0.623 mole) in toluene (1 300 ml) and a solution of III*a* (100 g, 0.605 mole) were mixed and refluxed for 17 h. Ethyl chloroacetate (85.5 g, 0.7 mole) was then added to the cooled reaction mixture, followed by further refluxing for 4.5 h.

The reaction mixture was cooled and diluted with water (500 ml). The organic layer was separated, washed with water, dried, and distilled to give 29.0 g (19%) of the product, b.p. 148–158° at 0.2–0.3 mm, which solidified on standing. The analytical sample was obtained by crystallization from ether – petroleum ether (30–60°), m.p. 48.5–50.5°.

3,4-Dihydro-2H-1,4-benzothiazine (Va)

The procedure of Hromatka *et al.* (8) was modified by performing the addition of the 3-oxo compound (III*a*) to the $LiAlH_4$ in tetrahydrofuran at reflux temperature instead of 0°, thereby preventing a violent reaction at the end of the addition period.

6-Trifluoromethyl-3,4-dihydro-2H-1,4-benzothiazine (Vc)

3-Oxo-6-trifluoromethyl-3,4-dihydro-2*H*-1,4-benzothiazine (III*c*, m.p. 200–202° (lit. (4) m.p. 185–186°)) was reduced with diborane by the procedure described below for the preparation of VI*d*, yield 67%, m.p. 88–89° when crystallized from petroleum ether.

Anal. Calcd. for $C_9H_8F_3NS$: C, 49.31; H, 3.65; N, 6.39. Found: C, 49.11; H, 3.57; N, 6.40.

4-(β-Hydroxyethyl)-3,4-dihydro-2H-1,4-benzothiazine (VIc)

IV*d* (21.7 g, 0.086 mole) in ether (200 ml) was added dropwise to a suspension of $LiAlH_4$ (7.27 g, 0.19 mole) in ether (500 ml) at a rate sufficient to maintain a gentle reflux. After the addition was complete (1 h), the mixture was refluxed for an additional 2 h, and cooled; then ethyl acetate (34 g, 0.38 mole) was added dropwise, followed by water (58 ml). The precipitate was filtered, and the filtrate dried and distilled to give the product, b.p. 125–143° at 0.15–0.18 mm, yield 13.3 g (79%). The analytical sample distilled at 151° and 0.4 mm.

Reduction of IV*a*, IV*b*, and IV*e* by the above procedure gave VI*a*, VI*b*, and VI*e*, respectively.

4-Benzyl-3,4-dihydro-2H-1,4-benzothiazine (VId)

A solution of IV*c* (12.75 g, 0.05 mole) in tetrahydrofuran (100 ml) was added dropwise to a 1 *M* diborane (27) solution (100 ml) in tetrahydrofuran, and the temperature was held at 0°. The reaction mixture was then refluxed for 1 h, cooled, hydrolyzed by 10% aqueous hydrochloric acid (60 ml), and concentrated to one-fourth of its volume. The residue was made strongly alkaline and extracted with chloroform. The chloroform

extract was washed with water, dried, and evaporated to give the product, m.p. 90–93°, yield 7.4 g (62%). Crystallization from ether – petroleum ether (30–60°) gave the analytical sample, m.p. 96.5–97.5°.

Another method for the preparation of VI*d* was by refluxing a mixture of V*a* (7.55 g, 0.05 mole), benzyl chloride (6.32 g, 0.05 mole), and potassium iodide (8.3 g, 0.05 mole) in absolute ethanol (200 ml) for 16 h, filtering the hot mixture, and evaporating the filtrate. The residue, on crystallization from ether–petroleum ether (30–60°), gave the product, yield 6.35 g (52%).

VI*a* was similarly obtained (66% yield, b.p. 104° at 0.17 mm) by refluxing V*a* (30.2 g, 0.2 mole), methyl iodide (42.63 g, 0.3 mole), and anhydrous potassium carbonate (15.2 g, 0.11 mole) in methanol (300 ml) for 4.5 h.

4-Benzoyl-3,4-dihydro-2H-1,4-benzothiazine (VIId)

Benzoyl chloride (14.1 g, 0.1 mole) in ether (50 ml) was added, with stirring, to a solution of V*a* (15.1 g, 0.1 mole) in ether (250 ml) containing pyridine (8.3 g, 0.105 mole) at −5°. After the reaction mixture was stirred for 4 h at room temperature, it was filtered and the filtrate washed with 10% aqueous hydrochloric acid and water. The dried ethereal extract was evaporated and the residue crystallized from ether – petroleum ether (30–60°) to give the product, m.p. 86–89°, yield 19.0 g (79%). One recrystallization from the same solvent gave the analytical sample, m.p. 88–89.5°; infrared absorption (Nujol mull): 1 645 cm^{-1} (C=O).

All other 4-acyl derivatives of V*a* were synthesized by this method, and all had the characteristic infrared absorption band in the 1 635 – 1 660 cm^{-1} region.

The 4-benzoyl derivative was also obtained under Schotten–Baumann conditions, but the yield was somewhat inferior.

Reduction of VIIa and VIId

VII*a* was reduced by $LiAlH_4$ in ether by the procedure described for the reduction of IV*d*. For the reduction of VII*d*, however, the procedure employing diborane, described for the reduction of IV*c*, had to be followed.

4-Amino-3,4-dihydro-2H-1,4-benzothiazine (XVII)

Sodium nitrite (13.8 g, 0.2 mole) in 20 ml water was added to V*a* (30.2 g, 0.2 mole) in 5% hydrochloric acid (250 ml) at −5°. The solution was basified and extracted with chloroform, and the chloroform solution was washed with water and saturated sodium chloride, dried, and evaporated. The nitrosated product (XVI) could not be distilled without decomposition; accordingly, it was reduced with $LiAlH_4$ in ether in the usual way. The 4-amino derivative thus obtained was treated with hydrogen chloride in ether to give the hydrochloride, m.p. 174° (decomp.) when crystallized from methanol.

Anal. Calcd. for $C_8H_{11}ClN_2S$: C, 47.37; H, 5.47; N, 13.83; S, 15.82; Cl, 17.49. Found: C, 47.81; H, 5.61; N, 13.27; S, 15.26; Cl, 17.63.

2-(β-Hydroxyethylmercapto)aniline (VIII) (9, 21)

Treatment of 2-aminobenzenethiol with ethylene oxide in the presence of alcoholic potassium hydroxide gave VIII in an almost quantitative yield. Culvenor *et al.* (21) claimed to have prepared V*a* by this reaction.

2-(β-Acetoxyethylmercapto)acetanilide (XIV)

A mixture of VIII (46.0 g, 0.275 mole) and acetic anhydride (100 ml) was slowly distilled for 2 h at atmospheric pressure in a bath at 150–170°. The residue was fractionally distilled to give the product, b.p. 184–186° at 1.1 mm, as a colorless liquid which slowly solidified on standing. The product, when refluxed with 5% dilute ethanolic potassium hydroxide, gave 2-(β-hydroxyethylmercapto)acetanilide (XV), b.p. 176° at 0.5 mm.

2-(β-Benzoxyethylmercapto)benzanilide (IX) (14)

Benzoyl chloride (13.3 g, 0.094 mole) was added dropwise to VIII (8.0 g, 0.047 mole) in pyridine (180 ml), and the mixture was stirred overnight at room temperature. Dilution with water yielded the crude product, which was purified by crystallization from methanol, m.p. 81–83°, yield 14.0 g (78%); infrared absorption (Nujol mull): 3 390 cm^{-1} (NH), 1 725 cm^{-1} (ester), and 1 685 cm^{-1} (C=O).

The same product was obtained by the reaction of either X or XI with benzoyl chloride in pyridine, as described above.

2-(β-Hydroxyethylmercapto)benzanilide (X)

Benzoyl chloride (8.3 g, 0.059 mole) was added to a stirred mixture of VIII (10.0 g, 0.059 mole) in 100 ml of 3.3% aqueous potassium hydroxide solution. After being stirred vigorously for 10–15 min, the mixture was extracted with ether. The ethereal extract was washed with water and evaporated, and the residue was crystallized from ether to give 11.0 g (68%) of the product, m.p. 88.5–90°; infrared absorption (Nujol mull): 3 430 cm^{-1}, 3 330 cm^{-1}, and 1 665 cm^{-1}.

2-(β-Benzoxyethylmercapto)aniline (XI)

A solution of VIII (17.0 g, 0.1 mole) in toluene (100 ml) was added to a vigorously stirred mixture of sodium (2.3 g, 0.1 mole) in 300 ml boiling toluene, under a dry nitrogen atmosphere. After the addition was complete (15 min), the mixture was refluxed for 1½ h and then cooled to room temperature, and benzoyl chloride (14.0 g, 0.1 mole) in toluene (50 ml) was slowly added. The mixture was stirred for another 30 min

at room temperature, and then 200 ml water was added at 15°. The organic layer was separated, washed with water, dried, and evaporated under reduced pressure in a bath below 40°. Part of the oily residue was dissolved in ether, and hydrogen chloride was added to give the product as the hydrochloride, m.p. 176–180°.

The free base was obtained from the hydrochloride as a viscous, honey-colored liquid which solidified (m.p. 43–46°) when it was allowed to stand overnight. Recrystallization from warm ethanol gave the analytical sample, m.p. 44.5–46°; infrared absorption (Nujol mull): 3 460 cm^{-1}, 3 360 cm^{-1} (primary sorpamine), and 1 710 cm^{-1} (ester).

N-(2-(β-Hydroxyethylmercaptophenyl))-N'-(3',4'-dichlorophenyl)urea (XII)

3,4-Dichlorophenylisocyanate (18.8 g, 0.1 mole) in ether (500 ml) was added to VIII (15.1 g, 0.1 mole) in ether (500 ml); after the mixture had been stirred for 1 h at room temperature, it was refluxed for over 2½ h. The crude product (24.5 g) was filtered off and crystallized from acetone–ether, m.p. 156–157°; infrared absorption (Nujol mull): 3 550 cm^{-1} (OH), 3 330 cm^{-1} (NH), and 1 700 cm^{-1} (C=O).

N-(2-(β-Benzoxyethylmercaptophenyl))-N'-(3',4'-dichlorophenyl)urea (XIII)

A solution of XI (2.0 g, 0.0073 mole) in ether was mixed with an equivalent amount (1.4 g) of 3,4-dichlorophenylisocyanate in ether. The clear solution was refluxed for 30 min and then left for 2 days at room temperature. The crystalline solid (1.7 g, 50%) was filtered off and crystallized from 15 ml absolute ethanol to give the product, yield 0.9 g, m.p. 153–154°; infrared absorption (Nujol mull): 3 350 cm^{-1} (NH), 3 280 cm^{-1} (NH), 1 720 cm^{-1} (ester), and 1 655 cm^{-1} (amide).

The same product (XIII) was also obtained from XII (10.0 g, 0.028 mole) and benzoyl chloride (3.9 g, 0.028 mole) in pyridine.

4-(3',4'-Dichlorophenylcarbamyl)-3,4-dihydro-2H-1,4-benzothiazine (XXIIa)

Equivalent amounts of V*a* and 3,4-dichlorophenylisocyanate in benzene were refluxed for 1½ h, and then the solvent was removed to give the product in a quantitative yield. One recrystallization from 360 ml boiling ethanol gave colorless needles, m.p. 159–161°; infrared absorption (Nujol mull): 3 260 cm^{-1} and 1 655 cm^{-1}. The mixed melting point of XXII with XII was 128–146°.

Other ureas (XXII*b*–XXII*e*) were similarly prepared by refluxing equivalent amounts of V*a* and the corresponding isocyanate for 1½ h in ether. The final products were isolated by the addition of petroleum ether (30–60°) to the reaction solution.

3-Oxo-3,4-dihydro-2H (4H) -1,4-benzothiazine-1,1-dioxide (XVIIIa)

A solution of III*a* (33.0 g, 0.2 mole) in glacial acetic acid (500 ml) was added to potassium permanganate (45 g, 0.28 mole) in water (1 000 ml) over a 15 min period. The temperature was allowed to rise to 42° during the addition. After 1.5 h at room temperature, sodium bisulfite (24.0 g, 0.23 mole) was added at 15–20°. The solution was concentrated to 200 ml under reduced pressure, and the product separated out when the concentrate was cooled, yield 31.9 g (81%), m.p. 195–202°. Recrystallization from methanol–benzene raised the melting point to 208–209° (lit. (16) m.p. 207–208°); infrared absorption (KBr pellet): 3 300 cm^{-1} (NH) and 1 700 cm^{-1} (C=O).

The 6-trifluoromethyl analogue (XVIIIb) was prepared in the same way, m.p. 256–257° (decomp.) when crystallized from acetone – petroleum ether, yield 60%.

Anal. Calcd. for $C_9H_6F_3NO_3S$: C, 40.75; H, 2.26; F, 21.50; S, 12.07. Found: C, 40.94; H, 2.53; F, 21.54; S, 12.29.

The 4-benzyl derivative (XX) was similarly prepared from IV*c*, m.p. 140–141° when crystallized from chloroform – petroleum ether, yield 64%.

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.71; H, 4.52; N, 4.87; O, 16.72. Found: C, 63.03; H, 4.66; N, 5.18; O, 16.37.

2-Benzyl-3-oxo-3,4-dihydro-2H-1,4-benzothiazine-1,1-dioxide (XIXb)

A solution of XVIII*a* (9.85 g, 0.05 mole) in 50% aqueous ethanol (50 ml) containing sodium hydroxide (2.0 g, 0.05 mole) was refluxed for 1 h. The cooled reaction mixture was extracted first with petroleum ether (to remove unreacted benzyl chloride) and then with ether. The ethereal extract was washed with water, dried, and evaporated. The residue was crystallized from ether – petroleum ether (30–60°) to give 9.0 g (62%) of the product, m.p. 144–147°. Two recrystallizations from the same solvent gave the analytical sample, m.p. 147–148°; infrared absorption (Nujol mull): 3 200 cm^{-1} and 1 685 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.71; H, 4.52; N, 4.77; S, 11.15. Found: C, 62.69; H, 4.50; N, 4.64; S, 11.31.

4-Benzyl-3,4-dihydro-2H-1,4-benzothiazine-1,1-dioxide (XXI)

Treatment of 4-benzyl-3-oxo-3,4-dihydro-2*H*-1,4-benzothiazine-1,1-dioxide with diborane in tetrahydrofuran as described for the preparation of VI*d* gave the product, m.p. 127–128° when crystallized from aqueous methanol, yield 60%.

Anal. Calcd. for $C_{15}H_{15}NO_2S$: C, 65.93; H, 5.49; N, 5.12; O, 11.72; S, 11.72. Found: C, 65.86; H, 5.31; N, 5.18; O, 11.94; S, 11.57.

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