(m, $W_{1/2}$ = 8 Hz, H-4).

Anal. Calcd for $C_{20}H_{32}$: C, 88.2; H, 11.8. Found: C, 88.3; H, 11.7.

Hydroboration of *D*-Homoandrost-4-ene and Subsequent Oxidation. Diborane was bubbled into a solution of 500 mg of alkene in 15 ml of tetrahydrofuran during 1.5 hr. After the excess reagent was destroyed with ice, oxidation (as of **7c**) produced 480 mg of oil separated by plc into *D*-homo-5β-androstan-4-one (**29a**, 78 mg): mp 154–159° from methanol; ν_{max} 1700 cm^{-1}; nmr τ 9.18 (CH_3-18), 8.88 (CH_3-19); a portion sublimed for analysis had mp 166–167° (*Anal.* Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: 83.0; H, 11.2) and *D*-homo-5α-androstan-4-one (**29b**, 105 mg), recrystallized from methanol: mp 122–124°; nmr τ 9.27 (CH_3-19), 9.18 (CH_3-18); ν_{max} 1710 cm^{-1} (*Anal.* Calcd for $C_{20}H_{32}O$: C, 83.3; H, 11.2. Found: C, 83.5; H, 11.2).

Borohydride Reduction of the Title Ketones and Acetylation of the Alcohols. Similar reduction conditions to those of the first experiment were employed. Except for the 1-ketone which yielded the 1α-alcohol **7a**, all gave mixtures, separated by plc into the components shown in Table I. The acetates were formed under standard conditions, and their properties together with those of the alcohols are presented in Table II. All were recrystallized from methanol.

Registry No.—**1a**, 29220-43-7; **1b**, 42548-29-8; **1c**, 481-29-8; **1d**, 53-43-0; **4a** isomer A, 51057-06-8; **4a** isomer B, 51057-07-9; **4b** isomer A, 51057-08-0; **4b** isomer B, 51057-09-1; **4c** isomer A, 51057-10-4; **4c** isomer B, 4503-01-9; **4d** isomer A, 847-74-5; **4d** isomer B, 847-75-6; **6a** 17-one, 51057-11-5; **6a** 17A-one, 51057-12-6; **6b** 17-one, 51057-13-7; **6b** 17A-one, 51057-14-8; **6c** 17-one, 51057-15-9; **6c** 17A-one, 26729-16-8; **6d** 17-one, 3278-90-8; **6d** 17A-one, 3278-99-7; **9**, 10455-05-7; **10**, 51153-08-3; **11**, 7417-23-4; **12** isomer A, 51057-16-0; **12** isomer B, 51057-17-1; **13**, 39851-65-5; **14**, 51057-18-2; **15**, 51057-19-3; **16**, 51057-20-6; **17**, 51057-21-7; **18**, 51057-22-8; **19**, 51057-23-9; **3α-20**, 51057-24-0; **3β-20**, 51057-25-1; **3α-21**, 51057-26-2; **3β-21**, 51057-27-3; **22**, 39851-67-7; **23**, 39851-68-8; **24**, 51057-28-4; **25**, 51057-29-5; **26**, 51057-30-8; **27**, 51057-31-9; **29a**, 51057-32-0; **29b**, 51057-33-1.

References and Notes

(1) (a) We are indebted to the Consejo Nacional de Investigaciones Cientificas y Tecnológicas, and the Consejo de Desarollo U. C. V. for financial support (respective projects DFS1-0121 and 305). This work has been partly presented at the Asovac conference, Maracaibo 1972, and 7th Caribbean conference, Puerto Rico 1973. (b) Author to whom correspondence should be addressed at 28 Parker St., Oxford, OX4 ITD, England.

(2) Among others, (a) S. Popov, G. Eaden, and C. Djerassi, *J. Org. Chem.*, **37**, 155 (1972); (b) D. N. Kirk, W. Klyne, C. M. Peach, and M. A. Wilson, *J. Chem. Soc. C*, 1454 (1970).

(3) D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier, New York, N. Y., 1968, p 294.

(4) M. W. Goldberg and E. Wydler, *Helv. Chim. Acta*, **20**, 1142 (1943). N. L. Wendler, D. Taub, and H. L. Slates, *J. Amer. Chem. Soc.*, **77**, 3559 (1955).

(5) D. N. Kirk and M. A. Wilson, *J. Chem. Soc. C*, 414 (1971).

(6) L. H. Sarrett, M. Feurer, and K. Folkirs, *J. Amer. Chem. Soc.*, **73**, 1777 (1951).

(7) L. Marquez, tesis de grado, Universidad Central 1972.

(8) J. M. Evans, D. Marcano, and L. Marquez, *Acta Cient. Venezolana*, **23**, 172 (1972).

(9) M. Fetizon and M. Golfier, *C. R. Acad Sci.*, **267**, 900 (1965).

(10) During manuscript preparation Hugo Rojas (unpublished work) has observed preferential oxidation at C(17) in 4,17-diols.

(11) H. Powell, D. H. Williams, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **86**, 2623 (1964).

(12) J. E. Bridgeman, C. E. Butchers, E. R. H. Jones, A. Kasal, G. D. Meakins, and P. D. Woodgate, *J. Chem. Soc. C*, 244 (1970).

(13) L. E. Contreras, J. M. Evans, and D. Marcano, *Acta Cient. Venezolana*, **23**, 89 (1972).

(14) J. Broome, B. R. Brown, A. Roberts, and A. M. S. White, *J. Chem. Soc.*, 1406 (1960).

(15) J. Gutzwiller and C. Djerassi, *Helv. Chim. Acta*, **49**, 2108 (1966).

(16) W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Amer. Chem. Soc.*, **78**, 2579 (1956).

(17) We thank J. Costa, D. Evans, and L. Guttierez for technical assistance.

(18) We are extremely grateful to Professor E. R. H. Jones, Oxford, for permission to use the plans of his small-scale applicator, to construct our machine in the U. C. V. workshops.

(19) H. Obermann, M. Spiteller-Friedmann, and G. Spiteller, *Chem. Ber.*, **103**, 1497 (1970).

(20) L. Rizicka, V. Prelog, and P. Meister, *Helv. Chim. Acta*, **28**, 1651 (1945).

3-Acyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxides. I. Alkylation, Amination, and Ethoxycarbonylation

C. R. Rasmussen

Department of Chemical Research, McNeil Laboratories, Inc., Fort Washington, Pennsylvania 19034

Received September 18, 1973

Preparation of ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**2c**) is described. Treatment of **2c** with ammonia gave carboxamide **8**, whose reactions with ethyl chloroformate could be directed to afford either 3-(ethoxycarbonyl)carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**22**), ethyl 3-(ethoxycarbonyl)-carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine-2-carboxylate 1,1-dioxide (**25**), or 2*H*,5*H*-1,3-oxazino[5,6-c][1,2]benzothiazine-2,4(3*H*)-dione 6,6-dioxide (**24a**). Alkylation reactions of **2c** with methyl iodide and 1,2-dibromoethane are compared with those of 3-acetyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2b**). Mass spectral evidence is presented for the assignment of structure **13** to the products of **2b** with ammonia and primary amines.

In 1956, Abe, Yamamoto, and Matsui[1] reported the base-induced rearrangement of *N*-phenacylsaccharin **1a** to 3-benzoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**2a**) (Scheme I). Since then, rearrangements of a wide variety of *N*-β-keto-substituted saccharins have been studied.[2a,b]

Our interest in the chemistry of ring system **2** was stimulated by its apparent polydentate character, which offered potential versatility for preparation of a variety of novel derivatives for pharmacological testing.

We wish to report here and in an accompanying paper[3] our findings with some alkylation and amination reactions carried out on the known 3-acetyl derivative **2b** and the previously unreported ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**2c**).[4]

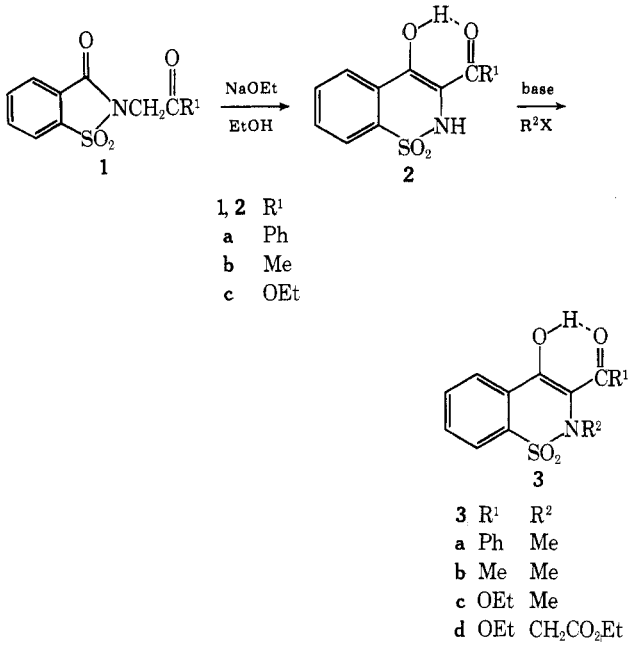
Results and Discussion

Synthesis of ester **2c** was carried out analogously to that reported for ketones **2a**[1] and **2b**;[2a] however, higher base concentration and longer reaction times were required to achieve satisfactory yields.[5]

Conventional alkylation reactions of **2a** and **2b** have been shown to occur preferentially at sulfonamide nitrogen.[2a] Ester **2c** behaves similarly, providing alkylated products **3c** and **3d**[6] upon treatment with methyl iodide and ethyl bromoacetate, respectively (Scheme I).

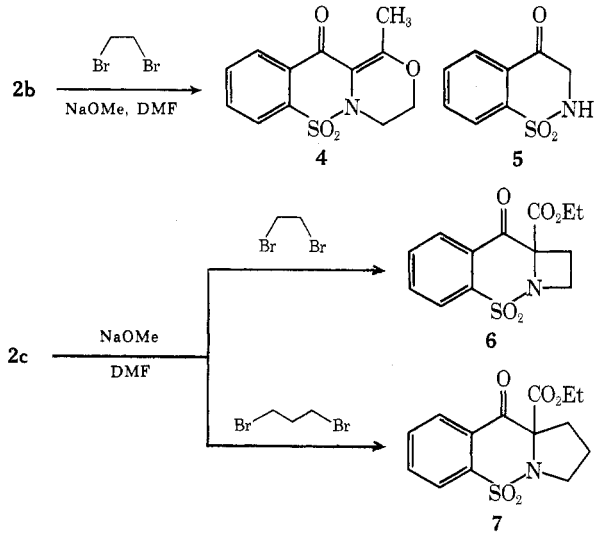
Ketone **2b** and ester **2c** both undergo cycloalkylation when treated with 1,2-dibromoethane. However, the course of these reactions differs, as illustrated in Scheme II. Formation of oxazine **4** from **2b** and azetidine **6** from **2c**

Scheme I



reflects the enhanced nucleophilic character of the 3-keto oxygen atom as compared to that of the ester carbonyl. When **2c** was allowed to react with 1,3-dibromopropane, pyrrolidine **7**, analogous to **6**, was obtained. Both products **6** and **7** gave negative ferric chloride tests and their uv spectra, unlike that of **4** (Table II), were virtually identical with the published spectrum of 2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide (**5**).[7]

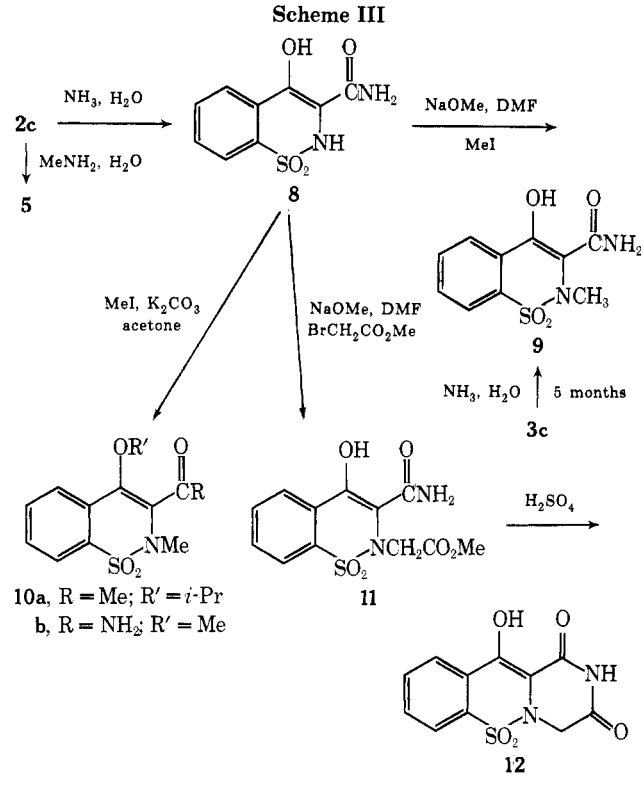
Scheme II



Reaction of ester **2c** with aqueous ammonia gave 3-carboxamide **8** in 90% yield (Scheme III). Treatment of **8** with methyl iodide gave in 56% yield 2-methyl derivative **9**, whose structure was confirmed by ammonolysis of 2-methyl-3-carboxylate **3c**. Reaction of **3c** with ammonia was largely incomplete after 5 months, indicating severe steric hindrance caused by the 2-methyl substituent. When allowed to stand in the presence of excess aqueous methylamine, ester **2c** gave only ketone **5**[7] in poor yield along with unchanged starting material.

Employing the conditions of Zinnes[2a] for the conversion of **2b** to isopropyl ether **10a**, amide **8** gave, in 35% yield, methoxyamide **10b** (negative ferric chloride test). Treatment of **8** in 1,2-dimethoxyethane with 2 equiv of diazomethane gave amide **9** in 20% yield. No enol ether **10b** was isolated.

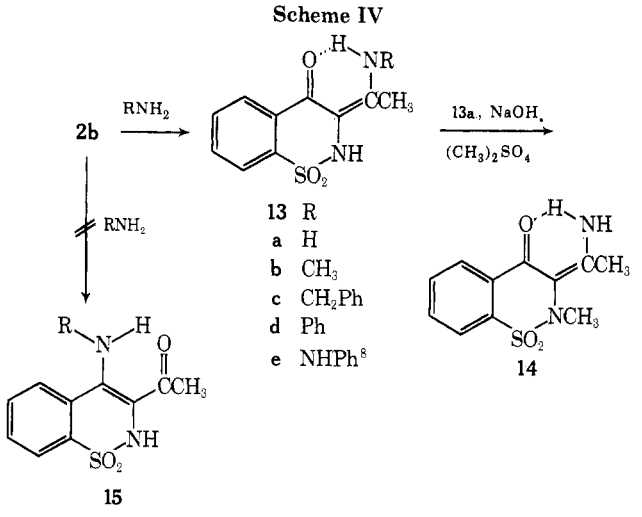
Scheme III



Alkylation of amide **8** with methyl bromoacetate afforded 2-acetate **11**, whose cyclization to imide **12** was effected in warm sulfuric acid.

Aqueous solutions of ammonia, methylamine, and benzylamine were found to react with **2b** in excellent yields, affording vinylogous amides **13a-c**. Aniline failed to react with **2b** under aqueous conditions; however, **13d** was obtained in 60% yield upon warming **2b** neat with excess amine (Scheme IV). Compounds **13a-d** were intensely yellow, generally retained solubility in dilute aqueous alkali, and gave negative ferric chloride tests.

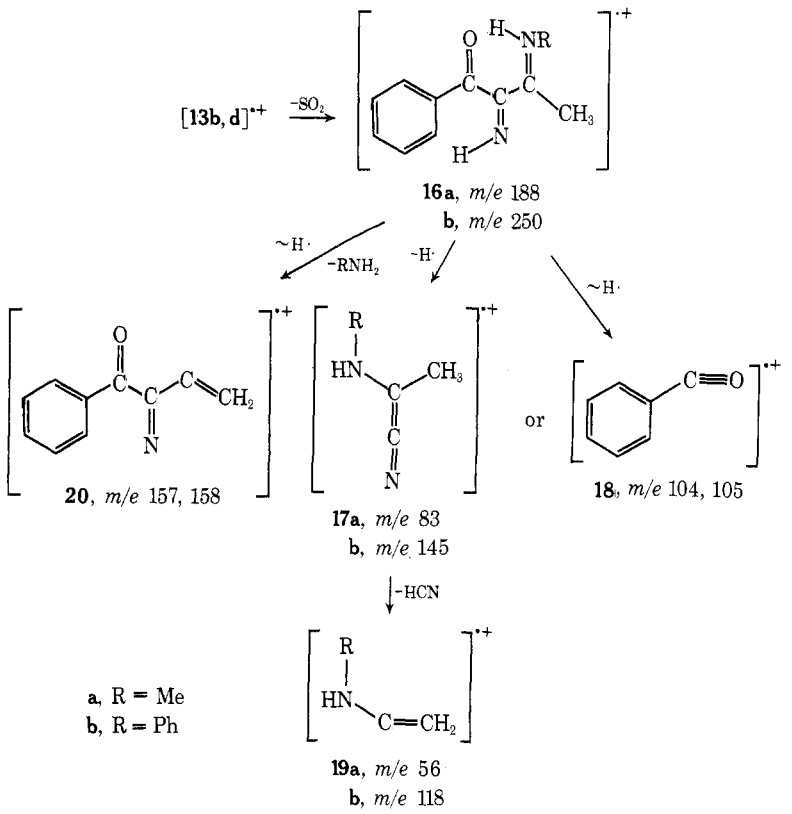
Scheme IV



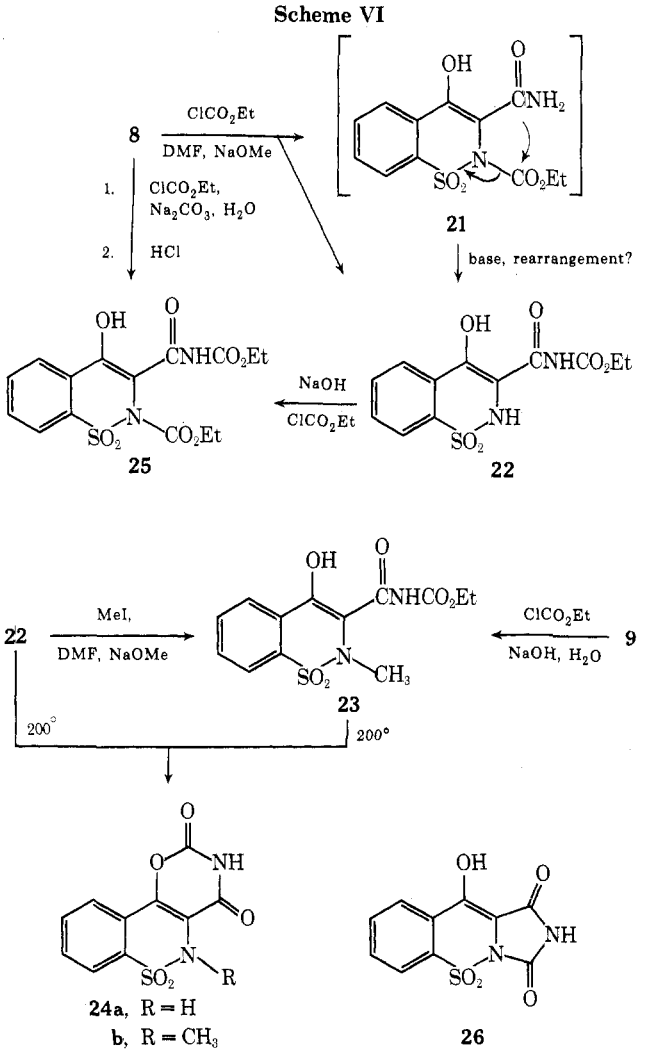
Phenylhydrazone **13e** has been reported[8] but no structure proof was given. Published uv data for **13e** are compared with those of **13a-d** and 2-methyl derivative **14** in Table I.

Alternate structure **15**, which could have conceivably arisen from the reaction of **2b** with primary amines, was ruled out by mass spectroscopic examination of represen-

Scheme V



Scheme VI



tative compounds **13b** and **13d**. The salient features of these results are shown in Scheme V and Table II.

Relatively abundant ions common to both **13b** and **13d** were observed at *m/e* 157 and 158, indicating structural similarity. In accordance with Spiteller's observations,[9] **13b** and **13d** primarily undergo loss of SO_2.

We, therefore, favor structure **13** over **15** because (1) ions assigned structures **17a** and **17b** are base and 89% of base peaks, respectively, and (2) no significant peak at *m/e* 43, corresponding to loss of CH_3CO^+, was observed in either spectrum. It is expected that such a fragment would be relatively abundant if **15** were the correct structure.[10]

Ethoxycarbonylation of amide **8** was carried out in DMF containing 1 equiv of sodium methoxide in an attempt to obtain 2-ethoxycarbonyl-3-carboxamide **21** (Scheme VI). The only product isolated from this reaction in poor yield was the 3-*N*-ethoxycarbonylamide **22**. The structure of **22** was confirmed by the transformations **9** → **23** and **22** → **23**.

At temperatures near 200°, **22** and **23** decomposed to give new compounds. These decomposition products were assigned oxazinedione structures **24a** and **24b** on the basis of negative ferric chloride tests, solubility in aqueous alkali, uv spectra, and elemental analyses. Imide **26**, which could have conceivably arisen from **23**, was ruled out because of the negative ferric chloride test.[5]

Treatment of aqueous alkaline solutions of either **8** or **22** with excess ethyl chloroformate gave the *N,N'*-diethoxycarbonyl derivative **25** as a sodium salt which separated from the reaction medium at pH values of *ca.* 8–10. Similarly, 2-methylamide **9** afforded **23** as a sodium salt. Excess chloroformate and concentrated sodium hydroxide effected direct conversion of **8** to **24a** in 70% yield.

Although occurring in the presence of substituted sulfonamide nitrogen (**9** → **23**), ethoxycarbonylation of 2-unsubstituted amide **8** may, like alkylation, take place at the 2 position, affording intermediate **21**. Under basic

Table I[e]
Physical Data of Vinylogs 4, 13a–e, and 14

Compd	Mp, °C[a]	R	Yield, %	ν NH, cm^{-1}[b]	ν C=O, cm^{-1}	λ_{max} (MeOH), nm (ε)	Formula
4	157.5–158.5		35		1660	256 (8,450) 330 (6,100)	$C_{12}H_{11}NO_4S$
13a	259–261 dec	H	91	3380, 3140 (KBr)	1615 (KBr)	249 (9,800) 358 (11,300)	$C_{10}H_{10}N_2O_3S$
14	199–201		42	3475, 3400	1610	245 (10,500) 351 (11,000)	$C_{11}H_{12}N_2O_3S$
13b	235–236 dec	CH_3	81	3300	1605	252 (9,800) 370 (13,700)	$C_{11}H_{12}N_2O_3S$
13c	196–199	CH_2Ph	73	3305, 3220	1602	253 (11,100) 372 (15,000)	$C_{17}H_{16}N_2O_3S$
13d	163–165	Ph	63	3350	1608	256 (13,600) 382 (17,100)	$C_{16}H_{14}N_2O_3S$
13e	175–170[c]	NHPh				239 (12,000)[d] 387 (13,500)	

[a] Uncorrected. [b] Chloroform unless otherwise specified. [c] Data taken from ref 8. [d] EtOH (95%). [e] Satisfactory analytical values (±0.3% for C, H, N, S) were reported for all compounds in table: Ed.

Table II
Fragmentation of 3-[(1-Methylamino)- and -(1-anilino)ethylidene]-2*H*-1,2-benzothiazine-4(3*H*)-one 1,1-Dioxides at 70 eV

Assignment	13b *m/e* (intensity)[a]		13d *m/e* (intensity)[a]	
M^+	252 (31)		314 (100)	
13 − HCN	225 (3)	m* 140.3[b]		m* 199.0[b]
13 − CH_2N	224 (2)			
16 (**13** − SO_2)	188 (13)		250 (38)	
16 − H	187 (<5)	m* 155.5[b]	249 (24)	m* 217.2[b]
16 − CH_3 and/or NH	173 (16)		235 (12)	
16 − NH_3	171 (8)		233 (18)	
16 − RNH	158 (11)		158 (11)	
20	157 (26)		157 (45)	
20 − CH_3	132 (15)		132 (<5)	
17	83 (100)	m* 83.5[b]	145 (89)	
19	56 (51)		118 (46)	
18 + C_7H_7N	105 (75)		105 (51)	
18 − H + C_7H_6N + C_7H_4O	104 (8)		104 (12)	
$PhNH_2$			93 (33)	
Ph	77 (22)		77 (59)	
19 − CH_2 + **18** − H	42 (31)		104 (12)	
CH_3CO	43 (1.4)[c]		43 (1.7)[c]	

[a] Expressed as per cent of base peak. [b] Metastable peaks were observed for the transitions indicated. [c] See discussion.

conditions, rearrangement of the 2-ethoxycarbonyl group to the 3-carboxamide nitrogen atom as a contributing pathway leading to the formation of **22** can be envisioned. Several unsuccessful experiments avoiding excess base were carried out in an effort to obtain **21**. Thin layer chromatograms of the reaction mixtures indicated materials other than those attributable to **8**, **22**, and **25**. The presence of **21** in these mixtures remains speculative.

Experimental Section

Melting points were obtained on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 521 grating instrument. Uv spectra were obtained from a Cary 14 spectrophotometer. Nmr spectra were recorded on a modified Varian A-60. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane as internal standard. Mass spectra were obtained at 70 eV from Morgan-Shaffer Corp., Montreal, Canada, and from a Perkin-Elmer Hitachi RMU-6E. Elemental analyses were obtained from Scandinavian Microanalytical Laboratories, Herlev, Denmark. Thin layer chromatograms were generally carried out on silica gel GF plates with benzene–acetone mixtures as developing solvents.

Starting Materials. 1b. This compound was prepared according to the method of Eckenroth and Klein in 82% yield, mp 142–144° (lit.[11] mp 143°).

1c. The preparation was carried out according to the method of Eckenroth and Koerppen[12a] in 82% yield, mp 104–106° (lit.[12a] mp 104°, lit.[12b] mp 107°).

2b. Synthesis of **2b** was carried out essentially as reported in 92% yield, mp (155) 157–158.5° (lit.[2a] mp 158–159°).

Ethyl 4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (2c). To a solution of 57.5 g (2.5 g-atoms) of sodium in 1 l. of absolute EtOH was added 271 g (1.01 mol) of **1c**. The rapidly stirred mixture was warmed to 57–62° and maintained at these temperatures for 2 hr. The orange slurry was poured onto ice-concentrated HCl (260 ml). Extraction with methylene chloride (5 × 1 l.), drying (Na_2SO_4), solvent removal *in vacuo*, and trituration of the residue with benzene gave 188 g (69%) of product (two crops). Recrystallization from acetone–benzene afforded the analytical sample: mp 139.5–141°; ir ($CHCl_3$) 3350, 3240 (OH, NH), 1660, 1608 cm^{-1} (HOC=CC=O); nmr ($CDCl_3$) δ 11.45 (s, enol, OH or NH), 6.67 (broad singlet, NH or OH), 4.40 (q, J = 7 Hz, $-OCH_2-$), 1.38 (t, J = 7 Hz, CH_2CH_3); uv max (MeOH)[13] 241 nm (ε 4800), 284 (inflection, 3700), 301 (shoulder, 4800), 322 (6600).

Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20; S, 11.91. Found: C, 49.12; H, 4.18; N, 4.88; S, 11.89.

Conventional alkylation procedures gave the following derivatives of **2c**.

Ethyl 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-Dioxide (3c). Reaction of **2c** with methyl iodide in DMF containing NaOMe gave, after recrystallization from EtOH (95%)–H_2O, pure **3c** in 71% yield, mp 136–138°.

Ethyl 3-Ethoxycarbonyl-4-hydroxy-2*H*-1,2-benzothiazine-2-acetate 1,1-Dioxide (3d).[6] This compound was prepared in 72% yield by reaction of ethyl bromoacetate with **2c** in ethanolic NaOEt. After recrystallization from EtOH (95%), the melting point was 97–98°.

Anal. Calcd for $C_{15}H_{17}NO_7S$: C, 50.70; H, 4.82; N, 3.94. Found: C, 50.50; H, 4.61; N, 4.09.

3,4-Dihydro-1-methyl-11*H*-1,4-oxazino[4,3-*b*][1,2]benzothiazin-11-one 6,6-Dioxide (4). To a solution of 2.3 g (0.1 g-atom) of

sodium in MeOH (150 ml) was added 23.9 g (0.1 mol) of **2b** and 60 ml of DMF. Most of the MeOH was removed *in vacuo*. To the residue was added 75.2 g (0.4 mol) of ethylene dibromide and the mixture was warmed on the steam bath for 2 hr. Addition of H_2O threw down the crude product, which was treated with aqueous NaOH (10%) to remove base-soluble materials. Recrystallization of the base-insoluble residue from acetone–MeOH gave 9.36 g (35%) of pure **4**, nmr ($CDCl_3$) A_2B_2 pattern at δ 4.38 (m, 2, $-OCH_2-$) and 3.87 (m, 2, $-CH_2N$) and 2.51 (s, 3, CH_3). See Table II for the other physical data.

Since this reaction was run only once, it is assumed that use of 2 equiv of base would substantially improve the yield.

Ethyl 9,9a-Dihydro-9-oxoazetidino[1,2-*b*][2*H*]-1,2-benzothiazine-9a-carboxylate 4,4-Dioxide (6). To a solution of 5.75 g (0.25 g-atom) of sodium in 100 ml of MeOH was added 100 ml of DMF. The mixture was concentrated *in vacuo* to *ca.* 75 ml. A solution of **2c** in 100 ml of DMF was then added and the orange solution was cooled to 10°. 1,2-Dibromoethane (23.5 g, 0.125 mol) was added in one portion with swirling. After heating on the steam bath for 2 hr, most of the solvent was removed *in vacuo*. After addition of 500 ml of H_2O, the brown oil was extracted into ether (4 × 250 ml). The combined extracts were washed with aqueous Na_2CO_3 (10%, 5 × 50 ml) and aqueous NaOH (1 *N*, 2 × 50 ml). Drying ($MgSO_4$) and solvent removal *in vacuo* gave 15.3 g (52%) of a syrup. Fresh ether (100 ml) was added to the residue. Cooling and scratching gave crystals contaminated with yellow oil. Several recrystallizations from ether gave 7.6 g (26%) of pure **6**: mp 86.5–88.5°; uv max (MeOH) 251 nm (ϵ 9660), 289 (1800), and 295 (inflection, 1540); ir ($CHCl_3$) 1736 (ester C=O) and 1684 cm^{-1} (aromatic C=O); nmr ($CDCl_3$) δ 4.35 (q, 2, J = 7 Hz, $-OCH_2-$), 4.0 (m, 2, NCH_2), 3.4 (m, 1, H_b),[14] 2.28 (m, 1, H_a), and 1.30 (t, 3, J = 7 Hz, $-CH_2CH_3$).

Anal. Calcd for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44; N, 4.74; S, 10.86. Found: C, 53.07; H, 4.41; N, 4.89; S, 10.88.

Ethyl 10,10a-Dihydro-10-oxopyrrolidino[1,2-*b*][2*H*]-1,2-benzothiazine-10a-carboxylate 5,5-Dioxide (7). The preparation was carried out on a 0.05-mol scale in a manner analogous to that described for **6**. Several recrystallizations from ether gave 5.3 g (34%) of pure **7**: mp 80.5–83°; uv max (MeOH) 246 nm (ϵ 9250), 288 (1880), and 296 (shoulder, 1540); ir ($CHCl_3$) 1735 (ester C=O) and 1690 cm^{-1} (aromatic C=O); nmr ($CDCl_3$) δ 4.28 (q, 2, J = 7 Hz, OCH_2), 4.0–3.3 (m, 2, NCH_2), 2.72 (m, 2, H_a, H_b),[14] 2.5–1.6 (m, 2, $CH_2CH_2CH_2$), 1.25 (t, 3, J = 7 Hz, OCH_2CH_3).

Anal. Calcd for $C_{14}H_{15}NO_5S$: C, 54.36; H, 4.89. Found: C, 54.24; H, 4.93.

4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (8). A solution of 53.85 g (0.2 mol) of **2c** in 2 pints of aqueous NH_3 (58%) was allowed to stand at room temperature for 2 days. Removal of most of the excess NH_3 *in vacuo*, pouring into ice–HCl, and recrystallization of the resulting solid from acetone–MeOH gave 43 g (90%) of **8**: mp 244–247° dec; uv max (MeOH) 226 nm (ϵ 8000), 297 (shoulder, 6100), 313 (7300), and 361 (shoulder, 1450); ir (KBr) 3485 (NH), 1653 and 1645 cm^{-1} (HOC=C-$CONH_2$).

Anal. Calcd for $C_9H_8N_2O_4S$: C, 45.00; H, 3.36; N, 11.66; S, 13.35. Found: C, 45.10; H, 3.32; N, 11.64; S, 13.35.

4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (9). Method A. The preparation was carried out by reaction of methyl iodide (7.8 g, 0.055 mol) with 12.0 g (0.055 mol) of amide **8** in the presence of NaOMe (0.055 mol) in DMF. Conventional work-up and recrystallization from acetone gave 7.1 g (56%) of pure product, mp 240–245° dec.

Anal. Calcd for $C_{10}H_{10}N_2O_4S$: C, 47.24; H, 3.96. Found: C, 47.22; H, 4.08.

Method B. Ester **3c** (2.82 g, 0.01 mol) was dissolved in 100 ml of aqueous NH_3 (28%), tightly stoppered, and allowed to stand for 5 months. Acidic work-up and recrystallization from acetone gave **9** identical in all respects with that obtained from method **A.**

4-Methoxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (10). A solution of 12.0 g (0.05 mol) of **8** and 71 g (0.5 mol) of methyl iodide in 500 ml of acetone was allowed to reflux for 6 hr in the presence of 85 g of anhydrous K_2CO_3. After standing overnight, filtration and solvent removal *in vacuo* gave a semisolid gum. Trituration with H_2O followed by MeOH gave 6.2 g (46%) of crystals (two crops). Recrystallization from acetone gave 4.7 g (35%) of pure **10**: mp 208–218°; ir (KBr) 3445, 3335, 3260 (NH), 1675–1670 ($CONH_2$), and 1590 cm^{-1} (C=C); uv max (MeOH) 230 nm (inflection, ϵ 8450), 281 (shoulder 9000), 287 (9300), and 306 (8800); nmr (DMSO-d_6) δ 3.75 (s, 3, OCH_3) and 2.97 (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_4S$: C, 49.24; H, 4.51; N, 10.44; S, 11.95. Found: C, 49.31; H, 4.59; N, 10.20; S, 11.92.

Methyl 3-Carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine-2-acetate 1,1-Dioxide (11). A solution of 1.55 g (0.067 g-atom) of sodium in absolute MeOH was evaporated to near dryness *in vacuo*. To the residue was added 60 ml of dry DMF followed by 16.05 g (0.067 mol) of amide **8**. To the resulting solution was added, with stirring, 10.4 g (0.067 mol) of methyl bromoacetate over 5 min. After stirring overnight at ambient temperature, the solvent was removed *in vacuo* and the residue was treated with H_2O. Recrystallization of the resulting solid from acetone gave 15.5 g (74%) of pure **11** as colorless crystals: mp 223–225° dec; ir (KBr) 1750 (CH_2CO_2Me), 1655 and 1607 cm^{-1} (HOC=C$CONH_2$).

Anal. Calcd for $C_{12}H_{12}N_2O_6S$: C, 46.12; H, 3.87; N, 8.97; S, 10.27. Found: C, 46.30; H, 4.00; N, 8.88; S, 10.23.

1,2,3,4-Tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazine-1,3-dione 6,6-Dioxide (12). A mixture of 13.08 g (0.042 mol) of **11** and *ca.* 8 ml of concentrated H_2SO_4 (98%) was warmed on the steam bath with stirring until solution was complete. Heating was continued for 1 hr, during which time the mixture crystallized (sometimes scratching with a glass rod was necessary). The reaction was quenched by pouring into ice water. Recrystallization from acetone gave 6.6 g (56%) of pure product: mp 234–238° dec; uv max (MeOH) 242 nm (ϵ 7950), 254 (shoulder, 6600), and 350 (10,800); ir (KBr) 3450 (broad), 3225, 1755 (shoulder), 1728, and 1650 cm^{-1}; nmr (DMSO-d_6) δ 12.3–11.6 (broad, *ca.* 1, OH and/or NH) and 4.47 ppm (s, 2, NCH_2). A dilute ethanolic solution of **12** gave a deep green ferric chloride test.

Anal. Calcd for $C_{11}H_8N_2O_5S$: C, 47.14; H, 2.88; N, 10.00. Found: C, 47.06; H, 3.00; N, 9.85.

Preparation of 13a–d. The physical data for these compounds are shown in Table I. Reaction conditions, work-up, and the solvents used for recrystallization are described below.

3-[(1-Amino)ethylidene]-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (13a). A solution of 10.7 g (0.045 mol) of **2b** in 110 ml of concentrated aqueous NH_3 was allowed to stand for 2 days at room temperature, during which time amber crystals formed. Removal of most of the excess NH_3 and H_2O *in vacuo* gave the crude solid, which was collected, dried, and recrystallized from acetone.

The 2-methyl derivative **14** was prepared by the action of dimethyl sulfate in aqueous NaOH (10%). The alkali-insoluble product was recrystallized from acetone–EtOH.

3-[(1-Methylamino)ethylidene]-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (13b). A solution of 2.39 g (0.01 mol) of **2b** in 11 ml of aqueous $MeNH_2$ (30%) was allowed to stand for 1 day at room temperature. The work-up was essentially the same as for **13a** except that aqueous HCl was employed to remove the remaining $MeNH_2$. The solid which was obtained after trituration with MeOH was recrystallized from acetone.

3-[(1-Benzylamino)ethylidene]-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (13c). A mixture of 2.39 g (0.01 mol) of ketone **2b** and 3.21 g (0.03 mol) of benzylamine in 10 ml of H_2O was stirred until **2b** dissolved. The resulting mixture was allowed to stand for 1 day at room temperature. Work-up was identical with that described for **13b.** Recrystallization from acetone–MeOH gave pure **13c.**

3-[(1-Anilino)ethylidene]-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide (13d). A mixture of 12.0 g (0.05 mol) of **2b** and 14.0 g (0.15 mol) of aniline was heated on the steam bath overnight. Excess aniline was removed *in vacuo*. Trituration of the red oil with EtOH and recrystallization from acetone gave pure **13d.**

3-(Ethoxycarbonyl)carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide (22). A solution of 2.76 g (0.12 g-atom) of sodium in 50 ml of absolute EtOH was evaporated to near dryness *in vacuo;* then 75 ml of DMF was added followed by 24.0 g (0.1 mol) of amide **8.** When solution had occurred, 12.96 g (0.12 mol) of ethyl chloroformate was added dropwise with stirring and cooling. The color of the solution changed to light yellow. After stirring at room temp for 1 hr, most of the DMF was removed *in vacuo*. The oily residue was treated with H_2O and allowed to stand until crystallization occurred. Recrystallization from acetone–H_2O gave the pure product: mp 192–193° dec (dependent on rate of heating); ir (KBr) 3350, 3120, 1745, and 1640 cm^{-1}; uv (MeOH, freshly prepared) 234 nm (shoulder, ϵ 9150), 236 (9200), and 325 (10,000); uv (MeOH, standing overnight) 251 nm (ϵ 5600), 252 (shoulder, 5600), and 285 (shoulder 2000) (see footnote 13). This preparation gave erratic yields of **22.**

Anal. Calcd for $C_{12}H_{12}N_2O_6S$: C, 46.15; H, 3.87; N, 8.97; S, 10.27. Found: C, 46.00; H, 3.88; N, 8.57, 9.11; S, 10.19.

3-(Ethoxycarbonyl)carbamoyl-4-hydroxy-2-methyl-2*H*-1,2-

benzothiazine 1,1-Dioxide (23). A. To a vigorously stirred solution of 7.62 g (0.03 mol) of amide **9** in 25 ml of aqueous NaOH (10%) was added 6 ml of ethyl chloroformate. Repeated additions of ethyl chloroformate and NaOH solution were carried out maintaining the pH at 8–9 (pH paper) until solid no longer appeared to be forming. Addition of brine (saturated), filtration, and washing with brine gave the crude sodium salt, which was taken up in warm H_2O and acidified with HCl. Recrystallization of the resulting solid from dioxane gave 5.0 g (39%) of pure product: mp (195) 196–197° dec (dependent on rate of heating); uv (MeOH, freshly prepared) 235 nm (ϵ 10,900) and 325 (10,900); ir (KBr) 3330, 1770–1760, 1730 (shoulder), 1650 (shoulder), and 1644–1640 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}N_2O_6S$: C, 47.85; H, 4.32. Found: C, 47.87; H, 4.49.

B. *Via* **22.** To a solution of 0.34 g (0.005 mol) of NaOEt in 10 ml of DMF was added 1.2 g (3.84 mmol) of **22**. After solution was complete, 2 ml of methyl iodide was added and the reaction mixture was allowed to stir for 1 hr at room temperature. Addition of H_2O threw down a solid which was recrystallized as above, mp 201–202° dec (dependent on rate of heating). The ir and uv spectra of the product indicated identity with **23** prepared *via* procedure A. A mixture decomposition point of both products was undepressed.

2*H*,5*H*-1,3-Oxazino[5,6-*c*][1,2]benzothiazine-2,4(3*H*)-dione 6,6-Dioxide (24a). A. A test tube containing 1 g (3.2 mmol) of **22** was heated in an oil bath (preheated to *ca.* 200°) until gas evolution ceased. Trituration with acetone gave 0.4 g (47%) of crude product. Recrystallization from acetone gave the analytical sample: mp 292–294° dec (dependent on rate of heating); uv (MeOH) 255 nm (broad, ϵ 6000) and 360 (7600); uv (MeOH + 1 drop of 0.1 *N* HCl) 237 nm (ϵ 9000), 300 (shoulder, 8200), and 320 (11,200) (traces of acid sometimes present in MeOH gave uv spectra which appeared to be mixtures of both protonated and unprotonated **24a**); ir (KBr) 3410, 3240, 1740, 1710 (shoulder), 1700, and 1630 cm^{-1}.

Anal. Calcd for $C_{10}H_6N_2O_5S$: C, 45.12; H, 2.27; S, 12.04. Found: C, 45.28; H, 2.50; S, 11.96.

B. *Via* **8.** A solution of 12.0 g (0.05 mol) of amide **8** in 100 ml of aqueous NaOH was treated with excess ethyl chloroformate (*ca.* 2–3 ml added at 5–10-min intervals over 1 hr). The solution became warm and some cooling was necessary (H_2O bath). Aqueous NaOH (50%) was added as needed [in order to maintain a pH >10 (pH paper)]. Two crops of sodium salt were removed by filtration. The mother liquors were poured into excess ice–HCl. The combined crops of sodium salt were dissolved in H_2O and acidified. The resulting solid was combined with that obtained by acidification of the alkaline filtrate, taken up in hot THF–dioxane (1:1, *ca.* 200 ml), filtered through a pad of Filter-aid, and concentrated *in vacuo* to *ca.* 100 ml. Addition of acetone (100 ml) followed by 500 ml of H_2O gave 9.35 g (70%) of pure **24a** which was identical with that prepared by procedure A by melting point, ir, and uv.

5-Methyl-2*H*,5*H*-1,3-oxazino[5,6-*c*][1,2]benzothiazine-2,4(3*H*)-dione 6,6-Dioxide (24b). Fusion of 8.4 g (0.026 mol) of **23** at 195–205° in the manner described for **24a** (method A) gave 3.64 g (50.5%) of pure product (from acetone): mp (262) 264–267°; uv 231 nm (shoulder, ϵ 7700), 241 (shoulder, 7100) 284 (shoulder 7000), 292 (7950), and 314 (9100) (the uv solutions of **24b** did not undergo significant change in the 314-nm region upon either acidification or basification); ir (KBr) 3230, 3180, 1781 (shoulder), 1779, 1744, 1705 (shoulder), 1700, 1692, and 1610 cm^{-1}.

Anal. Calcd for $C_{11}H_8N_2O_5S$: C, 47.14; H, 2.88; N, 10.00; S, 11.44. Found: C, 47.15; H, 2.92; N, 9.82; S, 11.55.

Ethyl 3-(Ethoxycarbonyl)carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine-2-carboxylate 1,1-Dioxide (25). A solution of 4.8 g (0.02 mol) of amide **8** in 25 ml of aqueous Na_2CO_3 (10%) was treated with excess ethyl chloroformate (*ca.* 2-ml portions added at intervals of 10–15 min over 1 hr). Aqueous NaOH (10%) was added in sufficient amounts to maintain a pH of *ca.* 8–10 (pH paper). Brine (saturated) was added and the resulting sodium salt was collected, washed with brine, and recrystallized from acetone–EtOH (95%): mp 182.5–184° dec; uv (MeOH) 240 nm (shoulder, ϵ 9900), 266 (shoulder, 3600), and 350 (8900).

Anal. Calcd for $C_{15}H_{15}NaN_2O_8S \cdot H_2O$: C, 42.45; H, 4.05; N, 6.61; S, 7.55. Found: C, 42.43; H, 4.08; N, 6.45; S, 7.30.

The above sodium salt was dissolved in warm water and acidified with a slight excess of concentrated HCl. The resulting oil crystallized upon scratching and cooling. Recrystallization from acetone–MeOH gave 4.5 g (59%) of pure product: mp 159–160°; uv (MeOH) 232 nm (broad, ϵ 11,500), 266 (shoulder, 4000), and 337 (9000); ir ($CHCl_3$) 3415, 1775–1770, 1750 (shoulder), 1660–1650, and 1606 cm^{-1}. The nmr spectra of the sodium salt (*vide supra*) and the conjugate acid **25** (DMSO-d_6) indicated the presence of two nonequivalent ethyl groups.

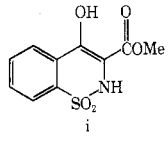
Anal. Calcd for $C_{15}H_{16}N_2O_8S$: C, 46.87; H, 4.20. Found: C, 46.72; H, 4.27.

Acknowledgment. The author gratefully acknowledges the technical assistance of Dr. David L. Shaw for some of the synthetic work, Mrs. Mary C. Christie for the ir, uv, and nmr spectra, and Dr. H. R. Almond, Jr., for assistance in the interpretation of nmr and mass spectral data.

Registry No.—**1c,** 24683-20-3; **2b,** 51015-24-8; **2c,** 24683-21-4; **3c,** 24683-26-9; **3d,** 20566-30-7; **4,** 51015-25-9; **6,** 24802-31-1; **7,** 24802-32-2; **8,** 24683-22-5; **9,** 24683-25-8; **10b,** 27222-93-1; **11,** 27321-37-5; **12,** 51015-26-0; **13a,** 24196-95-0; **13b,** 24196-96-1; **13c,** 24196-97-2; **13d,** 24196-98-3; **14,** 24196-99-4; **22,** 24683-23-6; **23,** 24683-24-7; **24a,** 24683-27-0; **24b,** 24683-28-1; **25,** 27222-95-3; **25** Na salt, 51015-27-1.

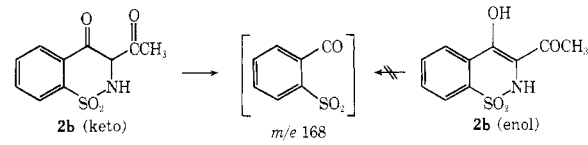
References and Notes

(1) K. Abe, S. Yamamoto, and K. Matsui, *Yakugaku Zasshi,* **76,** 1058 (1956); *Chem. Abstr.,* **51,** 3499 (1957).
(2) (a) H. Zinnes, R. A. Comes, F. R. Zuieski, A. N. Caro, and J. Shavel, Jr., *J. Org. Chem.,* **30,** 2241 (1965); (b) A. Kraaljeveld and M. Akkerman, U. S. Patent 3,284,450 (1966).
(3) C. R. Rasmussen and D. L. Shaw, *J. Org. Chem.,* **39,** 1560 (1974).
(4) During preparation of this paper, synthesis of methyl ester i in DMSO solution was published: J. G. Lombardino, E. H. Wiseman, and W. M. McLamore, *J. Med. Chem.,* **14,** 1171 (1971). Ester i could not be obtained in satisfactory yield under methanolic sodium methoxide conditions. We verify this observation.



i

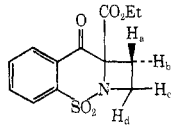
(5) All enolizable dicarbonyl compounds of this and our subsequent paper appear to be completely enolic by nmr. Each of these enolic compounds shows a positive ferric chloride test. We prefer the "4-hydroxy" of Abe[1] rather than the "4(3*H*)-one" nomenclature of Zinnes *et al.*[2a] A. R. Katritzky, *Chem. Ind. (London),* 334 (1965).
(6) Diester **3d** has been found to be a potent inducer of ventricular fibrillation. The potential use of this compound as a pharmacological tool is reported elsewhere: T. P. Pruss, *Toxicol. Appl. Pharmacol.,* **14,** 1 (1969).
(7) H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.,* **31,** 162 (1966).
(8) J. Shavel, Jr., and H. Zinnes, U. S. Patent 3,346,572 (Oct 10, 1967).
(9) G. Spiteller, *Advan. Heterocycl. Chem.,* **7,** 373 (1966).
(10) F. W. McLafferty, *Advan. Chem. Ser.,* **40,** 8 (1963). We have also recorded the mass spectrum of **2b** at 70 eV and have found an abundant *m/e* 43 peak.
(11) H. Eckenroth and K. Klein, *Chem. Ber.,* **29,** 329 (1896).
(12) (a) H. Eckenroth and G. Koerppen, *Chem. Ber.,* **30,** 1267 (1897); (b) O. J. Magidson and S. W. Gorbatshaw, *ibid.,* **56,** 1816 (1923).
(13) Freshly prepared alcoholic solutions of **2a, 2b,** and **2c** were found to be mandatory for consistent uv spectra. The uv characteristics of these solutions underwent marked deterioration above 300 nm upon standing. Acetonitrile solutions of these compounds were stable. In an effort to understand these observations, a methanolic solution of **2b** (50 mg/100 ml), which had been allowed to stand for 1 week, was evaporated in the cold (N_2). This residue (negative ferric chloride test) and untreated **2b** were examined by mass spectroscopy at 70 eV. The methanol-treated sample showed a significant *m/e* 168 peak (structure ii) while untreated **2b** did not. Both samples gave identical molecular ions. We interpret these results as differences in the fragmentation patterns of enol **2b** and keto **2b,** since it is known that polar solvents favor the keto form of β-dicarbonyl compounds: E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 380.



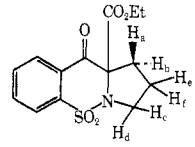
ii

(14) It was not clear from molecular Dreiding models why the proton we

ascribe to be H_b in **6** appears at such low field (δ 3.4). Protons which we assign to H_a and H_b in **7** appear as a two-proton multiplet centered at δ 2.72. Protons assigned H_c and H_d in both molecules are observed at δ 4.0–3.5, which appears to be consistent with adjacency to the electronegative nitrogen atom. It seems difficult to invoke primary deshielding effects on H_b in **6** by the aromatic carbonyl group (H_b in **6** and H_b in **7** both approach coplanarity with the aromatic carbonyl group) because the same large effect (deshielding of H_b) is not observed in **7**. If our analysis of the molecular models is correct, H_b in **6** is about 0.8 Å closer to the nearest sulfonamide oxygen than H_b in **7** which may account for its appearance at lower field. Because the conformational preferences of **6** and **7** are not known, these chemical shift assignments should be regarded as tentative.



6



7

3-Acyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxides. II.[1] Reaction with Aziridines. Nucleophilic Displacements on (1,2,3,4-Tetrahydro-11-hydroxy-1-oxopyrazino[1,2-*b*][1,2]benzothiazin-2-yl)ethyl Methanesulfonate 6,6-Dioxide

C. R. Rasmussen* and David L. Shaw

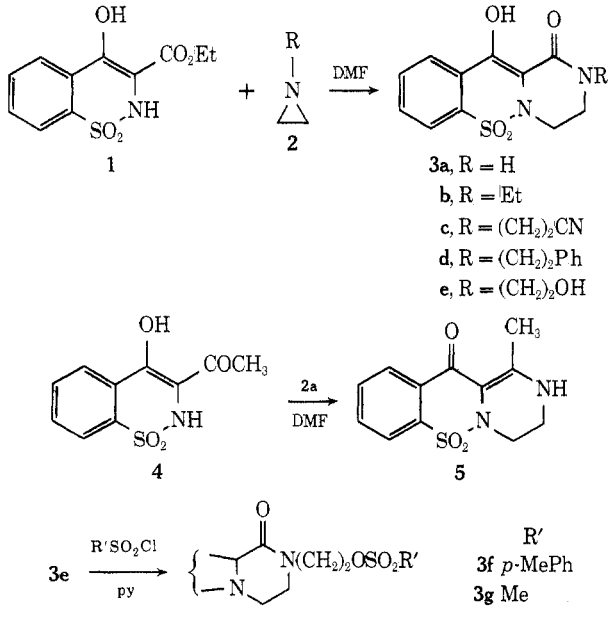
Department of Chemical Research, McNeil Laboratories, Inc., Fort Washington, Pennsylvania 19034

Received September 18, 1973

Ethyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**1**) reacts with aziridines **2** to give 1,2,3,4-tetrahydro-11-hydroxypyrazino[1,2-*b*][1,2]benzothiazin-1(2*H*)-one 6,6-dioxides (**3**) in 60–95% yields. Reactions of 2-ethyl methanesulfonate **3g** with various sulfur and nitrogen nucleophiles have been shown to proceed *via* the intermediate 2,3,5,6-tetrahydro-13*H*-oxazolo[2′,3′:3,4]pyrazino[1,2-*b*][1,2]benzothiazin-13-one 8,8-dioxide (**6**). The different reaction pathways taken by either **3g** or **6** with primary and secondary amines are described in terms of a postulated mechanism.

Aziridines (ethylenimines) are known to undergo autocatalytic ring-opening reactions with a variety of acidic nucleophiles.[2] The availability of carboxylate **1** in these laboratories prompted us to explore the apparently little-investigated reactions of acidic sulfonamides[3,4] with ethylenimines **2**.

Scheme I

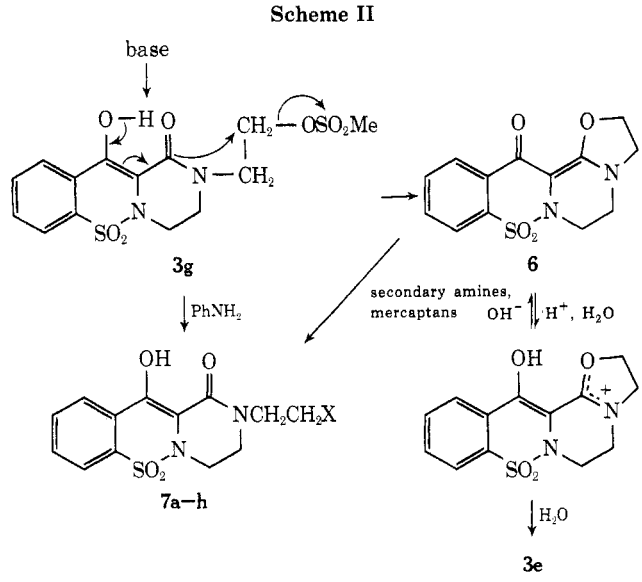


Treatment of ester **1** in DMF solution with **2** gave novel piperazines **3** in 60–90% yields (Scheme I, Table I). These compounds were acidic and completely enolic (nmr). Reaction of 3-acetylbenzothiazine **4**[5] with ethylenimine (**2a**) afforded piperazine **5** in only 8% yield. Treatment of **4** with other aziridines was not attempted.

Further work was centered on reactions of ethanol **3e** and its sulfonate esters **3f**[6] and **3g**.

Treatment of **3g** with either dimethylamine or sodium methyl mercaptide led to isolation of a bright yellow product which was assigned structure **6**. The latter reaction also afforded the expected product **7f** in 28% yield. Methanolic triethylamine, used preparatively, gave **6** in 83% yield. The uv spectrum of **6** showed a reversible 21-nm hypsochromic shift in acid, indicating oxazolinium ion formation (Scheme II). Dilute aqueous hydrochloric acid converted **6** to alcohol **3e**.

Scheme II



Formation of **7f** in the reaction of **3g** with methyl mercaptide led us to investigate the possibility that **6** might