1,2-Benzothiazines. IV.[1] The Synthesis of 7,8-Dihydropyrido[1,2-*b*][1,2]benzothiazine-10,11(9H,10aH)-dione 5,5-Dioxides as 1,2-Benzothiazine Analogs of Partial Tetracycline Structures

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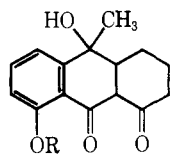
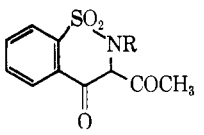
The preparation of 7,8-dihydropyrido[1,2-*b*][1,2]benzothiazine-10,11(9H,10aH)-dione 5,5-dioxide (**6a**) and its 8-methyl (**6b**) and 8-phenyl (**6c**) derivatives is described. Base-catalyzed cyclization of 3-acetyl-4-isopropyloxy-2H-1,2-benzothiazine-2-acetaldehyde 1,1-dioxide (**3a**) gave 7,8-dihydro-8-hydroxy-11-isopropyloxypyrido-[1,2-*b*]-[1,2]benzothiazin-10(9H)-one 5,5-dioxide (**4a**). The corresponding 8-methyl (**4b**) and 8-phenyl (**4c**) derivatives were formed by spontaneous cyclization of the isopropyl enol ethers (**3b** and **3c**) of 2-acetonyl- (**2b**) and 2-phenacyl-3-acetyl-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (**2c**), under the basic conditions of their formation. Compounds **4a–c** reacted with H_2SO_4 to give pyrido[1,2-*b*][1,2]benzothiazine-10,11(9H,10aH)-dione 5,5-dioxide (**5a**) and its 8-methyl (**5b**) and 8-phenyl (**5c**) derivatives, which were hydrogenated to form the target compounds **6**. Attempts to prepare **6a** by cyclization of 2-(3-carbomethoxypropyl)-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (**10a**) were unsuccessful. Reaction of N-(5-chloro-2-oxopentyl)saccharin (**14**) with 2 equiv of sodium ethoxide gave 2,3-dihydro-6H-oxepino[*c*][1,2]benzothiazin-5(4H)-one 7,7-dioxide (**15**) and the ethanolysis product N-(5-chloro-2-oxopentyl)-*o*-carbethoxybenzenesulfonamide; reaction with 3 equiv of sodium ethoxide gave **15** and 3-(1-cyclopropylcarbonyl)-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (**17**). Compounds **15** and **17** reacted with HBr–AcOH to give 3-(4-bromo-1-butyryl)-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (**19**). Attempts to prepare **6a** by cyclization of **19** resulted in O-alkylation to give **15** rather than the expected N-alkylation. Compounds **5** and **6** showed negligible antibacterial properties. Some antifungal activity was observed.

The antibacterial activity of the tetracyclines has been attributed to inhibition of protein synthesis resulting from the ability of the antibiotics to form metal chelates through their β-diketone moiety.[2,3] Shemyakin and co-workers[2] have reported that the relatively simple tricyclic β-diketones[4] **1a** and **1b** are $^1/_{20}$ as potent as the tetracyclines with respect to inhibition of growth of *Staphylococcus aureus*. These



1a, R = H
b, R = $CH_2C_6H_5$



2a, R = CH_2CHO
b, R = CH_2COCH_3
c, R = $CH_2COC_6H_5$
d, R = H
e, R = CH_3
f, R = $CH_2CH{=}NOH$
g, R = $CH_2CO_2CH_3$

results as well as the demonstrated antibacterial properties of 6-demethyl-6-dehydroxytetracycline[5] suggested that the phenolic hydroxyl,[2] tertiary alcohol,[5] and methyl[5] groups were not structural requirements for antibiotic activity in this series. In view of the ease of preparation[6] of **2d** from saccharin, it became of interest to elaborate it into tricyclic β-diketones of structure **6** to determine if these, too, were antibacterial agents.

Chemistry.—Reports by Hauser, *et al.*,[7] and Woodward, *et al.*,[8] of base-catalyzed condensations at the γ carbon of β-diketones suggested that compounds of structure **2a–c** could be cyclized directly to give the tricyclic skeleton. Accordingly, both **2b** and **2c**, prepared[6] by alkylation of **2d**, were treated with sodamide and lithium amide in liquid ammonia[7] and with sodium hydride in dimethylformamide.[8] However, these conditions were ineffective in promoting the desired cyclization. Attempts to use acid catalysis in the cyclization (with concentrated sulfuric acid at room temperature or hydrobromic acid at reflux) were equally unsuccessful.

In order to prevent conversion of the diketone to its anion under the conditions of base-catalyzed condensation, the β-diketone system was tied up by treatment of **2b** and **2c** with isopropyl iodide and potassium carbonate.[9] The resulting enol ethers, **3b** and **3c**, were not isolated as such since they cyclized spontaneously under these conditions to give the crystalline hydroxy compounds **4b** and **4c** (Chart I).[9,10] When **4b** and **4c** were dissolved in concentrated sulfuric acid at room temperature, dehydration and ether cleavage took place to give the corresponding unsaturated β-diketones **5b** and **5c**.[10]

Attempts to obtain **2a** by alkylation of **2d** were unsuccessful. Reaction of the sodium salt of **2d** with chloroacetaldoxime[11] afforded the oxime **2f**, but this could not be converted to the corresponding aldehyde by hydrolysis, exchange with benzaldehyde[12] or levu-

(1) Paper III of this series: H. Zinnes, R. A. Comes, and J. Shavel, Jr., *J. Org. Chem.*, **31**, 162 (1966).

(2) (a) M. M. Shemyakin and M. N. Kolosov, *Pure Appl. Chem.*, **6**, 305 (1963); (b) M. N. Kolosov, S. A. Popravko, and M. M. Shemyakin, *Ann.*, **668**, 86 (1963).

(3) W. A. Baker, Jr., and P. M. Brown, [*J. Am. Chem. Soc.*, **88**, 1314 (1966)] have recently presented evidence that chelation of metals by the tetracyclines may take place through the enol–ketoamide system of ring A.

(4) While the structures of the β-diketones discussed in this paper are illustrated in the diketone form, the infrared spectra indicate that they actually exist as one or a mixture of the two possible enols.

(5) J. R. D. McCormick, E. R. Jensen, P. A. Miller, and A. P. Doerschuk, *J. Am. Chem. Soc.*, **82**, 3381 (1960).

(6) H. Zinnes, R. A. Comes, F. R. Zuleski, A. N. Caro, and J. Shavel, Jr., *J. Org. Chem.*, **30**, 2241 (1965).

(7) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, **80**, 6360 (1958); R. B. Meyer, and C. R. Hauser, *J. Org. Chem.*, **25**, 158 (1960); R. J. Light and C. R. Hauser, *ibid.*, **26**, 1716 (1961).

(8) L. H. Conover, K. Butler, J. D. Johnston, J. J. Korst, and R. B. Woodward, *J. Am. Chem. Soc.*, **84**, 3222 (1962); R. B. Woodward, *Pure Appl. Chem.*, **6**, 561 (1963).

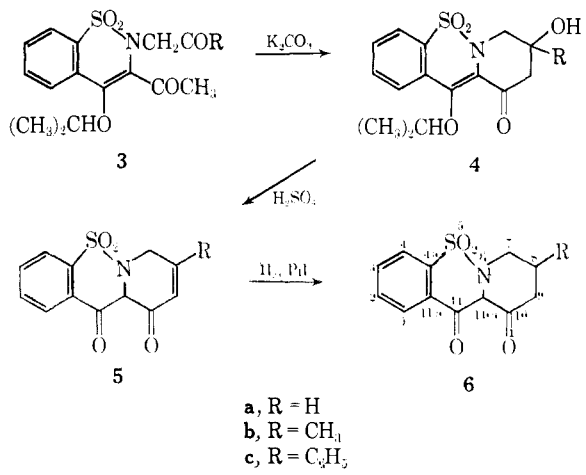
(9) This procedure has been used[6] to prepare the corresponding enol ether of **2e** which showed a ketone band at 1666 cm^{-1}.

(10) Spectral data supporting the structural assignments of the compounds described in this paper are given in the Experimental Section.

(11) R. W. L. Kimber and J. C. Parham, *J. Org. Chem.*, **28**, 3205 (1963).

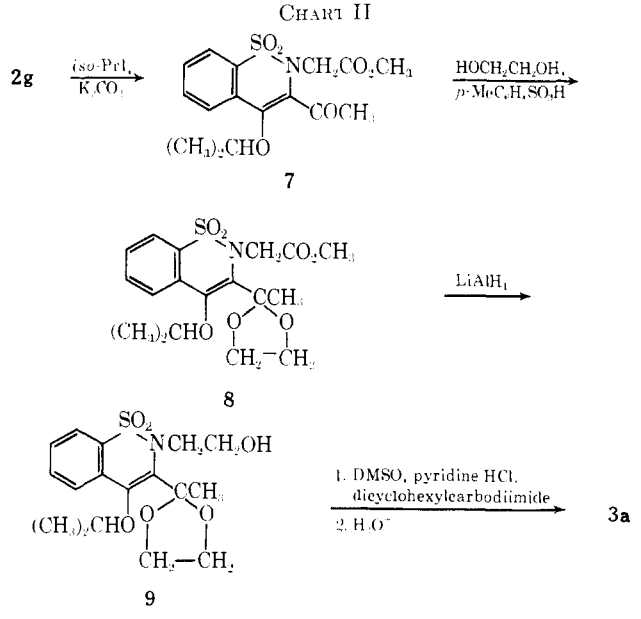
(12) T. Reichstein, A. Grussner, and R. Oppenauer, *Helv. Chim. Acta*, **17**, 510 (1934).

CHART I



linic acid,[13] or by treatment with nitrous acid.[14] However, the aldehyde–enol ether **3a**, required for the synthesis of **5a**, was successfully prepared as outlined in Chart II.

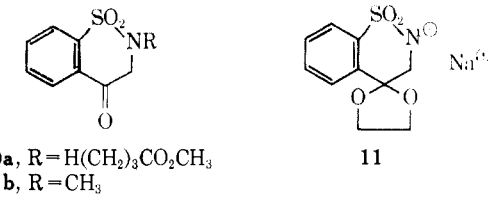
CHART II



Compound **2g**[6] was converted to the enol ether **7**. In this case, spontaneous cyclization did not occur so that **7** was isolated in crystalline form.[9,10] The crude ketal **8**, obtained by treatment of **7** with ethylene glycol and *p*-toluenesulfonic acid, was reduced to the alcohol **9** which was then oxidized by the method of Pfitzner and Moffatt[15] to the corresponding aldehyde. Cleavage of the ketal took place on acid treatment during the work-up procedure so that the product isolated was the desired **3a**.[10]

Cyclization of **3a** was achieved by refluxing with potassium carbonate in acetone. While the product resisted attempts at purification, it was apparent from the infrared spectrum that it was **4a**. Treatment of the crude **4a** with concentrated sulfuric acid resulted in the formation of **5a** which could be isolated in crystalline form. Hydrogenation of **5a–c** proceeded sluggishly to give target compounds **6a–c**, respectively.[10]

In the course of this work, we attempted to prepare **6a** by cyclization of **10a**. While we have previously reported[1] our inability to condense **10b** with esters, it was felt that an intramolecular condensation might be more favorable since it would involve a cyclization process. Compound **10a** was prepared by treatment of **11**[1] with methyl γ-iodobutyrate in refluxing 1,2-

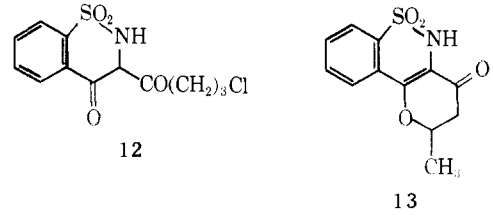


10a, R = $H(CH_2)_3CO_2CH_3$
b, R = CH_3

11

dimethoxyethane followed by acid hydrolysis of the ketal function.[16] Attempts to cyclize **10a** by the use of sodium hydride in benzene or dimethylformamide, sodium ethoxide in ethanol, or lithium amide in liquid ammonia met with the same lack of success encountered in our attempts[1] to condense **10b** with aliphatic esters.

Another approach to the synthesis of **6a** was suggested by our earlier observation[6] that N-methylation of **2d** took place preferentially to O-methylation. Thus it appeared that **6a** could be prepared by cyclization of **12**. Compound **14** was formed by alkylation of sodium



saccharin with 1,5-dichloro-2-pentanone.[17] When **14** was treated with 2 equiv of sodium ethoxide (Chart III), the expected **12** was not obtained. Purification of the crude product afforded crystalline **15**[10,18] in 8% yield and the spectra of the remaining amorphous residue suggested that it consisted largely of the ethanolysis product **16**. Considering our previously reported[6] observations concerning the mechanism of the rearrangement of N-acetonylsaccharin and assuming that 1 equiv of sodium ethoxide was consumed by a competing process, the reaction was carried out using 3 equiv of sodium ethoxide. In addition to **15**, isolated in 8% yield, there was obtained a second crystalline material in 40% yield, which was shown to have the structure **17**.[10,19] Alkylation with chloroacetone gave the 2-acetonyl derivative **18**.

(13) C. H. DePuy and B. W. Ponder, *J. Am. Chem. Soc.*, **81**, 4629 (1959).

(14) L. C. Keagle and W. H. Hartung, *ibid.*, **68**, 1608 (1946); A. C. Cope, H. L. Dryden, Jr., C. G. Overberger, and A. A. D'Addieco, *ibid.*, **73**, 3416 (1951).

(15) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **85**, 3027 (1963); **87**, 5661 (1965).

(16) Attempts to alkylate **11** (in aqueous alcohol or DMF at room temperature or in refluxing 1,2-dimethoxyethane) with the commercially available ethyl γ-bromobutyrate were unsuccessful. Methyl γ-iodobutyrate was prepared by the method of F. F. Blicke, W. B. Wright, Jr., and M. F. Zienty [*J. Am. Chem. Soc.*, **63**, 2488 (1941)].

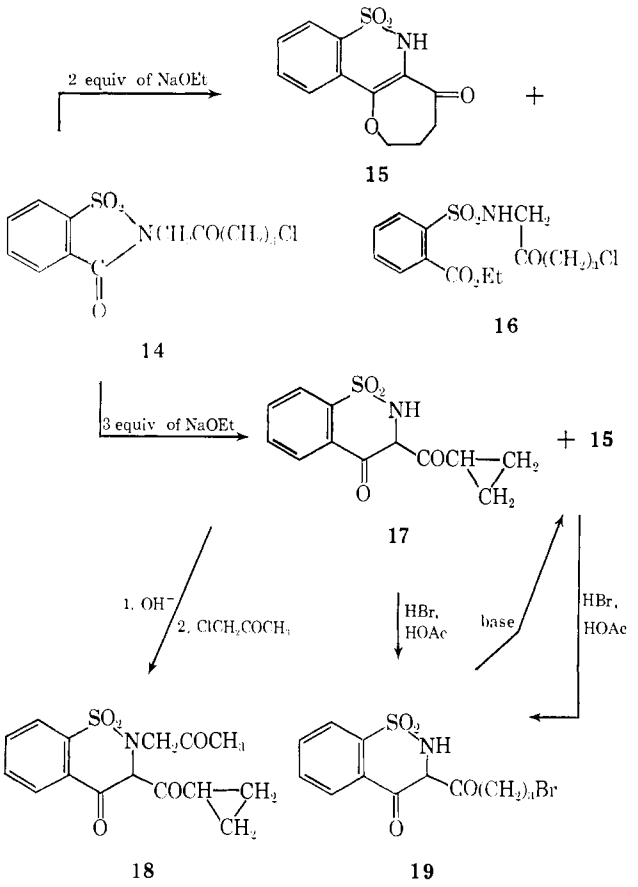
(17) H. Hart and G. Levitt, *J. Org. Chem.*, **24**, 1261 (1959).

(18) The six-membered ring compound **13** was ruled out by the absence of C-CH_3 resonance in the pmr spectrum.

(19) The difference in ultraviolet spectrum from that observed with **2d**[6] indicated conjugation of the β-dikecone system with an olefin or a cyclopropyl group. The choice of cyclopropyl over olefin was based on the pmr spectrum which showed the absence of olefinic protons as well as the presence of characteristic absorption which was similar to that given by methyl cyclopropanecarboxylate.[20]

(20) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Vol. 1, Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 112.

CHART III



The cyclopropane ring of **17** was cleaved by HBr in acetic acid to afford the crystalline bromo derivative **19**. Reaction of this substance with either sodium hydride in 1,2-dimethoxyethane or aqueous NaOH resulted in cyclization to give **15**. The latter was recovered unchanged after standing overnight at room temperature in methanolic aqueous HCl solution but was converted to **19** on treatment with HBr in acetic acid.

Thus it appears that rearrangement of **14** gave rise to **12** which underwent base-catalyzed cyclization to give **15** and **17**. While **17** could have arisen from N-cyclopropylcarbonylmethylsaccharin, which could have formed before the rearrangement, the isolation of **15** shows that at least some **12** was formed. The formation of **15** rather than **6a** from **12** or **19** was not expected since our previous experience[6] had indicated that N-alkylation would be favored over O-alkylation.

Microbiological Testing.—Minimum inhibitory concentrations (MIC) of compounds **5a–c** and **6a–c** against bacteria (*S. aureus*, *Escherichia coli*, and *Proteus vulgaris*) and fungi (*Trichophyton mentagrophytes*, *Candida albicans*, *Microsporum canis*, and *Sporotrichum schenkii*) were determined using serial dilution tests in broth; the concentrations ranged from 4 to 1000 μg/ml. Except for minimal activity (MIC 500–1000 μg/ml) of **5a** and **6a** against *S. aureus*, the compounds showed no antibacterial properties. Against *T. mentagrophytes*, **5a**, **5b**, **6a**, and **6c** showed MIC of 31, 31, 16, and 62 μg/ml, respectively, in the absence of serum and 250, 250, 62, and 500 μg/ml, respectively, in the presence of serum. Against *C. albicans*, **5a**, **5b**, and **6a** showed activity at 500 μg/ml in the absence of serum, but these were inactive at 1000 μg/ml in the presence of serum. Compounds **5a** and **6a** were active against *M. canis* at 250 μg/ml in both the absence and presence of serum. Compound **6a** showed MIC of 62 μg/ml against *S. schenkii* which increased to 125 μg/ml in the presence of serum.

Experimental Section[21]

7,8-Dihydro-8-hydroxy-11-isopropyloxy-8-methylpyrido[1,2-b][1,2]benzothiazin-10(9H)-one 5,5-Dioxide (4b).—A mixture of 86 g (0.28 mole) of **2b**,[6] 215 g of anhydrous K_2CO_3, 170 g (1.0 mole) of isopropyl iodide, and 2800 ml of acetone was refluxed with stirring for 113 hr. The acetone was distilled and the residue was partitioned between water and CH_2Cl_2. The dried organic solution was evaporated to give a semisolid. Trituration with a warm mixture of 125 ml of ethyl ether and 125 ml of isopropyl ether and standing at room temperature gave 63.5 g of a solid, mp 132–137°. This was extracted in a Soxhlet apparatus for 18 hr using a mixture of 200 ml of ethyl ether and 600 ml of isopropyl ether as the solvent. The solution, from which crystals had already begun to separate, was allowed to stand at room temperature to give 49.6 g of product, mp 147–149°, which gave a negative $FeCl_3$ test. Recrystallization from ethyl ether–isopropyl ether (1:1) gave an analytical sample: mp 147.5–148.5°; λ_{max} 246 mμ (ε 7400) and 324 (9450); ν_{max} 3380 (s, OH) and 1696 (s, C=O)[9] cm^{-1}; pmr, δ 4.43 and 1.29 (1 H heptet and 6 H doublet, respectively, J = 6 cps, isopropyl), 3.74 (2 H broad singlet, NCH_2),[22] 3.20 (1 H singlet, OH), 2.74 (2 H singlet, CH_2CO), 1.41 (3 H singlet, $-OCCH_3$).

Anal. Calcd for $C_{16}H_{19}NO_5S$: C, 56.96; H, 5.68; N, 4.15; S, 9.50. Found: C, 57.15; H, 5.56; N, 4.23; S, 9.68.

7,8-Dihydro-8-hydroxy-11-isopropyloxy-8-phenylpyrido[1,2-b][1,2]benzothiazin-10(9H)-one 5,5-Dioxide (4c).—The reaction was carried as in the previous experiment using 50 g (0.14 mole) of **2c**.[6] The CH_2Cl_2 solution was washed successively with cold 1 *N* NaOH and with water, dried, and evaporated to give a gummy residue. This was triturated with 40 ml of acetonitrile to give 14.4 g of product, mp 190–192°. Recrystallization from acetonitrile gave material: mp 191–194°; λ_{max} 246 mμ (ε 7400) and 324 (9450); ν_{max} 1686 (s, C=O)[9] and 3380 (s, OH) cm^{-1}; pmr, δ 7.40 (5 H multiplet, C_6H_5), 4.42 and 1.25 (1 H heptet and 6 H doublet, respectively, J = 6 cps, isopropyl), 3.92 (2 H broadened singlet, NCH_2), 3.26, 2.83 (two doublets, 1 H each, J = 17 cps, CH_2CO–); negative $FeCl_3$ test.

Anal. Calcd for $C_{21}H_{21}NO_5S$: C, 63.14; H, 5.30; N, 3.51; S, 8.03. Found: C, 63.43; H, 5.30; N, 3.53; S, 8.24.

8-Methylpyrido[1,2-b][1,2]benzothiazine-10,11(9H,10aH)-dione 5,5-Dioxide (5b).—A solution of 13.3 g of **4b** in 240 ml of concentrated H_2SO_4 was stirred at room temperature for 30 min. It was poured into 2400 ml of ice–water. The resulting yellow precipitate was collected by filtration, washed well with water, and dissolved in CH_2Cl_2. The dried solution was evaporated, and the residue was triturated with petroleum ether which gave 5.1 g of product (**5b**), mp 164–166° dec. Recrystallization from ethanol–CH_2Cl_2 gave material: mp 167–168° dec; λ_{max} 255 mμ (ε 14,900) and 394 (9200); ν_{max} 1644 (m), 1610 (m), 1580 (m), 1550 (m)[23] cm^{-1}; pmr, δ 13.2 (1 H broad singlet, enolic H), 6.13 (1 H triplet, J = 2 cps, C=CH), 4.40 (2 H broad singlet, NCH_2), and 2.05 (3 H singlet, CH_3), absence of isopropyl signals; positive $FeCl_3$ test.

Anal. Calcd for $C_{13}H_{11}NO_4S$: C, 56.31; H, 4.00; N, 5.05; S, 11.56. Found: C, 56.43; H, 3.78; N, 4.84; S, 11.55.

8-Phenylpyrido[1,2-b][1,2]benzothiazine-10,11(9H,10aH)-dione 5,5-Dioxide (5c).—The reaction was carried out as in the previous experiment using 12 g (0.03 mole) of **4c**. Trituration of the CH_2Cl_2 extract with petroleum ether gave 9.0 g of product, mp 172–175° dec. Recrystallization from ethanol–CH_2Cl_2 gave 7.8 g of material: mp 175–176° dec; λ_{max} 265 mμ (ε 11,300), 306

(21) Melting points were determined using the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DKI spectrophotometer and a Baird Model 455 double-beam instrument. Unless otherwise stated, the former were determined as solutions in 95% ethanol and the latter as Nujol mulls. The pmr spectra were determined with the Varian A-60 spectrometer using Me_4Si as an internal standard and unless otherwise stated in $CDCl_3$. The drying agent used throughout was Na_2SO_4 and the petroleum ether had bp 30–60°.

(22) On exchanging with D_2O the signal at δ 3.74 was resolved into doublets at δ 3.88 and 3.64 (J = 14 cps).

(23) This pattern of infrared absorption is characteristic for β-diketones in the 1,2-benzothiazine series.[6]

(12,800), and 411 (9700); ν_{max} 1624 (m), 1595 (m), 1585 (m), 1570 (m), 1554 (m)[23] cm^{-1}; pmr, δ 13.3 (1 H broad singlet, enolic H), 7.51 (5 H multiplet, C_6H_5), 6.66 (1 H triplet, J = 2 cps, >C=CH), 4.85 (2 H doublet, J = 2 cps, NCH_2), absence of isopropyl signals; positive $FeCl_3$ test.

Anal. Calcd for $C_{18}H_{13}NO_4S$: C, 63.70; H, 3.86; N, 4.13; S, 9.45. Found: C, 63.94; H, 3.68; N, 4.13; S, 9.55.

3-Acetyl-2H-1,2-benzothiazin-4(3H)-one-2-acetaldoxime 1,1-Dioxide (2f).—To a solution of 36 g (0.15 mole) of **2d**[6] in a mixture of 150 ml of 1 *N* NaOH, 115 ml of water, and 375 ml of ethanol was added 25.5 g (0.15 mole) of KI and 18.7 g (0.2 mole) of chloroacetaldoxime.[11] It was allowed to stir at room temperature for 2.5 hr and the resulting crystals were collected and washed with 50% aqueous ethanol to give 27.4 g of product, mp 158–159°. Dilution with water to 2000 ml gave 7.5 g of somewhat less pure second crop, mp 154–155°. Recrystallization of a portion of the first crop from isopropyl ether gave an analytical sample: mp 161–162°; λ_{max} 242 mμ (ϵ 6400) and 322 (10,300); ν_{max} 3300 (m), 1625 (m), 1592 (m), 1545 (m)[23] cm^{-1}.

Anal. Calcd for $C_{12}H_{12}N_2O_5S$: C, 48.64; H, 4.08; N, 9.45; S, 10.85. Found: C, 48.71; H, 4.26; N, 9.29; S, 10.96.

3-Acetyl-2-carbomethoxymethyl-4-isopropyloxy-2H-1,2-benzothiazine 1,1-Dioxide (7).—A mixture of 46.5 g (0.15 mole) of 2 g,[6] 127.5 g (0.75 mole) of isopropyl iodide, 115.5 g of anhydrous K_2CO_3, and 1500 ml of acetone was refluxed with stirring for 48 hr. The acetone was distilled and the residue was portioned between water and CH_2Cl_2. The CH_2Cl_2 extract was triturated with petroleum ether to give 32.5 g of product, mp 118–120°. Recrystallization from a mixture of isopropyl ether and ethyl ether gave material: mp 121–123°; λ_{max} 238 mμ (ϵ 6400), 297 infl (9500), and 315 (11,000); ν_{max} 1760 (s, ester) and 1666 (s, ketone)[9] cm^{-1}; negative $FeCl_3$ test.

Anal. Calcd for $C_{16}H_{19}NO_6S$: C, 54.38; H, 5.42; N, 3.96; S, 9.07. Found: C, 54.17; 5.39; N, 4.23; S, 8.99.

4-Isopropyloxy-3-(1-methyl-1,3-dioxolan-1-yl)-2H-1,2-benzothiazine-2-ethanol 1,1-Dioxide (9).—A mixture of 90 g (0.25 mole) of **7**, 89.1 g (1.25 mole) of ethylene glycol, 5.4 g of *p*-toluenesulfonic acid monohydrate, and 2000 ml of benzene was placed in a flask equipped with a Dean–Stark water separator and was refluxed with vigorous stirring for 72 hr. The solvent was removed, and the residue was stirred with 2000 ml of water and extracted with several 1000-ml portions of ether. The ether solution (containing **8**) was washed with water, dried, and concentrated to 1000 ml. It was then added to 31.5 g (0.83 mole) of $LiAlH_4$ in 3000 ml of ether, the temperature being maintained at 0 to −5°. The reaction mixture was stirred at this temperature for 1.5 hr, hydrolyzed, and filtered. The filtrate was evaporated, and the residue was triturated with 150 ml of isopropyl ether to give 47.9 g of crystalline product, mp 146–151°. Recrystallization of a portion from isopropyl ether gave an analytical sample: mp 155–156°; λ_{max} 273 mμ (ϵ 7055) and 300 (5840); ν_{max} at 3540 (s, OH), 1608, 1540 (w, aromatic and olefin) cm^{-1}; pmr, δ 4.4 and 1.24 (1 H multiplet and 6 H doublet, respectively, J = 6 cps, isopropyl), 4.1 (4 H broad multiplet, NCH_2CH_2O–), 3.51 (4 H singlet, –OCH_2CH_2O–), 2.38 (1 H broad signal, OH), and 1.78 (3 H singlet, >CCH_3).

Anal. Calcd for $C_{15}H_{23}NO_6S$: C, 55.27; H, 6.28; N, 3.79; S, 8.68. Found: C, 55.11; H, 6.32; N, 3.94; S, 8.73.

3-Acetyl-4-isopropyloxy-2H-1,2-benzothiazine-2-acetaldehyde 1,1-Dioxide (3a).—A mixture of 9.3 g (0.025 mole) of **9**, 15.7 g (0.075 mole) of dicyclohexylcarbodiimide, 1.5 g (0.0125 mole) of pyridine hydrochloride, and 130 ml of dimethyl sulfoxide (distilled from CaH_2) was stirred at room temperature for 18 hr and filtered. The filtrate was poured into 4000 ml of 0.02 *N* HCl and filtered, and the filtrate was extracted with ether. The ether solution was washed with water, dried, and evaporated, and the residue was dissolved in a minimum amount of CH_2Cl_2. Slow addition of petroleum ether and scratching caused precipitation of 5.4 g of product, mp 140–145°. A portion was dissolved in CH_2Cl_2 and reprecipitated by the addition of petroleum ether to give an analytical sample: mp 147–148°; λ_{max} 238 mμ (ϵ 5980), 300 sh (7860), 320 (9640); ν_{max} 1742 (s, aldehyde) and 1680 (s, ketone) cm^{-1}; pmr, δ 9.60, (1 H multiplet, J = 1 cps, CHO), 4.6 and 1.40 (1 H heptet and 6 H doublet, respectively, J = 6 cps, isopropyl), 4.0 (2 H doublet, J = 1 cps, NCH_2), 2.6 (3 H singlet, CH_3CO–); negative $FeCl_3$ test.

Anal. Calcd for $C_{16}H_{17}NO_5S$: C, 55.72; H, 5.30; N, 4.33; S, 9.92. Found: C, 55.64; H, 5.34; N, 4.27; S, 10.07.

Pyrido[1,2-*b*][1,2]benzothiazine-10,11(9H,10aH)-dione 5,5-Dioxide (5a).—A mixture of 20 g (0.062 mole) of **3a**, 40 g of anhydrous K_2CO_3, and 2000 ml of acetone was refluxed with vigorous stirring for 2.5 hr and then filtered. Evaporation of the filtrate gave a dark gum which was triturated with petroleum ether: ν_{max} 3400 (s, OH) and 1695 (s, C=O) cm^{-1}. The gum (**4a**) was dissolved in 340 ml of concentrated H_2SO_4, and the solution was maintained at room temperature for 15 min and then poured into 4500 ml of ice–water. The resulting yellow solid was collected, washed with water, and dissolved in CH_2Cl_2. The dried solution was evaporated and the residue (6.9 g) was recrystallized from 30 ml of ethanol to give 6.0 g of crystalline product: mp 155–156° dec; λ_{max} 255 mμ (ϵ 8600) and 391 (5650); ν_{max} 1634 (m), 1620 (m), 1584 (m), and 1550 (m)[23] cm^{-1}; pmr, δ 13.1 (1 H broad signal, enolic H), 7.00 (1 H as two triplets, J = 11 and 3 cps, NCCH=C), 6.36 (1 H as two triplets, J = 11 and 2 cps, COCH=C), 4.57 (2 H quartet, J = 2 and 3 cps, NCH_2); positive $FeCl_3$ test.

Anal. Calcd for $C_{12}H_9NO_4S$: C, 54.77; H, 3.45; N, 5.32; S, 12.18. Found: C, 54.62; H, 3.49; N, 5.25; S, 12.31.

7,8-Dihydropyrido[1,2-*b*][1,2]benzothiazine-10,11(9H,10aH)-dione 5,5-Dioxide (6a).—A slurry of 2.0 g (0.0076 mole) of recrystallized[24] **5a** in 200 ml of glacial acetic acid was hydrogenated for 6 hr at room temperature and atmospheric pressure using 200 mg of 10% Pd–C catalyst. The acetic acid was removed from the filtered solution at a maximum temperature of 35°, using a rotary flash evaporator. Trituration of the residue with water gave 1.7 g of tannish yellow solid which was recrystallized from isopropyl alcohol. Removal of the first crop of brownish material and concentration of the mother liquor gave 0.7 g of material, mp 118–131° dec, which was recrystallized from methanol. Removal of the first crop and concentration of the mother liquor gave 0.27 g of yellow crystalline product, mp 141–142° dec. Recrystallization from methanol gave an analytical sample: mp 141.5–142.5° dec; λ_{max} 258 mμ (ϵ 7800) and 378 (9300); ν_{max} 1620 (m), 1585 (m), and 1555 (m)[23] cm^{-1}; pmr, δ 14.2 (1 H broad signal, enolic H), 3.88 (2 H triplet, J = 6 cps, NCH_2), 2.68 (2 H triplet, J = 6 cps, $COCH_2$), and 2.19 (2 H multiplet, >CCH_2C<), absence of olefinic signals.[25]

Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.16; H, 4.24; N, 5.07; S, 12.05.

7,8-Dihydro-8-methylpyrido[1,2-*b*][1,2]benzothiazine-10,11-(9H,10aH)-dione 5,5-Dioxide (6b).—Hydrogenation of 1.9 g (0.0069 mole) of **5b**[24] was carried out as described above. The solid obtained on trituration of the residue with water was collected and dissolved in CH_2Cl_2. The dried solution was evaporated and the residue was triturated with petroleum ether to give 1.4 g of product, mp 135–136°; the pmr spectrum showed the absence of olefinic hydrogen. Recrystallization from a small amount of ethanol gave material: mp 138–139°; λ_{max} 258 mμ (ϵ 8200) and 380 (10,000); ν_{max} 1622 (w), 1580 (m), 1546 (m)[23] cm^{-1}; pmr, δ 14.3 (1 H broad signal, enolic H), 4.12 and 3.44 (two multiplets, 1 H each, NCH_2), 3.2–2.1 (3 H complex multiplet, MeCH< and $COCH_2$), and 1.18 (3 H doublet, J = 6 cps, CH_3).[25]

Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01; S, 11.48. Found: C, 56.09; H, 4.85; N, 4.95; S, 11.59.

7,8-Dihydro-8-phenylpyrido[1,2-*b*][1,2]benzothiazine-10,11-(9H,10aH)-dione 5,5-Dioxide (6c).—A slurry of 7.5 g (0.022 mole) of **5c**[24] and 300 mg of 10% Pd–C in 500 ml of ethanol was hydrogenated at atmospheric pressure for 6 hr during which reaction had ceased with only 40% of the required hydrogen uptake. Complete hydrogenation required the addition of two more 250-mg portions of catalyst during a total of 8 additional hr of reaction time. The catalyst was filtered off and washed well with ethanol and CH_2Cl_2. The filtrate was concentrated and the mixture was allowed to stand at room temperature. The resulting solid was collected and washed with ethanol to give 5.6 g of product, mp 155–160°. Recrystallization from ethanol–CH_2Cl_2 gave material: mp 161–162°; λ_{max} 258 mμ

(24) No hydrogen uptake was observed when the unrecrystallized olefins were used.

(25) Of particular interest is the difference between the pmr spectrum of **6a** and those of **6b** and **6c**. With **6a**, the NCH_2 protons appear together as a clearly defined triplet, whereas with **6b** and **6c** the signal given by the individual protons are separated by ca. 0.7 ppm and geminal coupling can be seen. The apparent magnetic equivalence of the NCH_2 protons of **6a** could be the result of conformational interconversion which would give rise to a time-averaged signal. In contrast, the presence of methyl or phenyl substituents in **6b** or **6c**, respectively, might be expected to cause these compounds to assume a preferred conformation, thus permitting the nonequivalent protons to be observed separately.

(ϵ 7300), 380 (9800); ν_{max} 1641 (m), 1590 (m), and 1550 (m)[23] cm^{-1}; pmr, δ 14.3 (broad signal, enolic H), 7.29 (5 H multiplet, C_6H_5), 4.37 (1 H quartet, J = 10 and 17 cps, NCH<), 3.75–3.25 (2 H complex multiplet, C_6H_5CH and the other NCH<), 3.0–2.76 (2 H complex multiplet, $COCH_2$), absence of olefinic signal.[25]

Anal. Calcd for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10; S, 9.39. Found: C, 63.07; H, 4.43; N, 3.84; S, 9.35.

N-(5-Chloro-2-oxopentyl)saccharin (14).—A mixture of 15.1 g (0.097 mole) of 1,5-dichloro-2-pentanone,[17] 27.5 g (0.13 mole) of sodium saccharin, and 100 ml of dimethylformamide was heated at 100° for 30 min and was poured into 1500 ml of ice–water. The resulting gum was solidified by trituration with several portions of water. The solid was collected and dissolved in CH_2Cl_2, and the dried solution was evaporated. The residue was triturated with petroleum ether and then crystallized from a minimal amount of ethanol to give 12.0 g of product, mp 82–84°. Recrystallization of a portion from ethanol gave an analytical sample: mp 91–92°; ν_{max} 1736 (s) and 1726 (s) cm^{-1}.

Anal. Calcd for $C_{12}H_{12}ClNO_4S$: C, 47.77; H, 4.01; Cl, 11.75; N, 4.64; S, 10.63. Found: C, 48.00; H, 4.09; Cl, 11.58; N, 4.87; S, 10.45.

3-(1-Cyclopropylcarbonyl)-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (17) and 2,3-Dihydro-6H-oxepino[c][1,2]benzothiazin-5-(4H)-one 7,7-Dioxide (15).—A solution of 0.36 mole of $NaOC_2H_5$ in 180 ml of ethanol was heated to 45° and 36 g (0.12 mole) of **14** was added all at once as the powder. The mixture was quickly heated to 50–55° and maintained at this temperature for 5 min. It was then quickly cooled to 25° and 240 ml of 9% HCl was added as rapidly as possible while maintaining the temperature at 30–35°. The resulting solid was collected, washed with 50 ml of 50% aqueous ethanol, and dried *in vacuo* at 60° to give 12.7 g of **17**, mp 160–165°. Recrystallization from 235 ml of methanol–water (2:1) gave 8.9 g of material: mp 171–172°; λ_{max} 247 mμ (ϵ 9200), 329 (13,760), and 341 (13,760); ν_{max} 3230 (s, NH), 1620 (m), 1604 (m), 1595 (m), 1559 (m)[23] cm^{-1}; pmr, δ 15.11 (1 H, enolic H), 6.30 (1 H, NH), 2.62 and 1.20 (1 H multiplet and 4 H multiplet, respectively, cyclopropyl);[19,20] positive $FeCl_3$ test.

Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.38; H, 4.21; N, 5.45; S, 12.04.

The original acidic aqueous ethanol filtrate was diluted to 2000 ml with water and the gummy material which separated on standing was collected and dissolved in CH_2Cl_2. The dried solution was evaporated and the residue was triturated with ether to give 2.5 g of **15**, mp 225–229° dec. Recrystallization from 2-butanone gave 1.4 g of material: mp 248–250° dec; λ_{max} 253 mμ (ϵ 9275) and 316 (10,200); ν_{max} 3140 (s, NH), 1648 (s, C=O) cm^{-1}; pmr (in deuterated DMSO), δ 4.46 (2 H triplet, J = 7 cps, $-OCH_2$), 3.28 (2 H triplet, J = 7 cps, $COCH_2$), 2.24 (2 H multiplet, >CCH_2C<);[18] negative $FeCl_3$ test.

Anal. Calcd for $C_{12}H_{11}NO_4S$; C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.58; H, 4.31; N, 5.04; S, 12.28.

Reaction of N-(5-Chloro-2-oxopentyl)saccharin (14) with 2 Equiv of Sodium Ethoxide.—The reaction was carried out as in the previous experiment using 0.02 mole of $NaOC_2H_5$, 3.0 g (0.01 mole) of **14**, and 20 ml of ethanol. The acidified (25 ml of 9% HCl) reaction mixture was diluted with 100 ml of water and extracted with CH_2Cl_2. The dried organic solution was evaporated to a residue which was successively triturated with petroleum ether and methanol to give 0.2 g of crystalline **15**, mp 232–240°, identified by its infrared spectrum. The residue obtained on evaporation of the methanol filtrate had infrared and ultraviolet spectra which were very similar to those of N-acetonyl-*o*-carbethoxybenzenesulfonamide.[6]

2-Acetonyl-3-(1-cyclopropylcarbonyl)-2H-1,2-benzothiazin-4-(3H)-one 1,1-Dioxide (18).—To a solution of 3.5 g (0.0133 mole) of **17**, in a mixture of 133 ml of 0.1 *N* NaOH, 42 ml of water, and 175 ml of ethanol was added 2.1 g (0.0133 mole) of KI and 4.9 g (0.053 mole) of chloroacetone. It was allowed to stand overnight at room temperature and 200 ml of water was added. The resulting precipitate was collected and dissolved in ether. The dried solution was evaporated to give 3.4 g of product, mp 150–151°. Recrystallization from ethanol gave an analytical sample: mp 151–152°; λ_{max} 245 mμ (ϵ 6750), 327 (11,250), 342 (10,700); ν_{max} 1733 (s, C=O), 1616 (m), 1594 (m), 1584 (m), 1546 (m)[23] cm^{-1}.

Anal. Calcd for $C_{15}H_{15}NO_5S$: C, 56.06; H, 4.71; N, 4.36; S, 9.98. Found: C, 55.86; H, 4.78; N, 4.31; S, 9.93.

3-(4-Bromo-1-butyryl)-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (19) A. From 17.—To 60 ml of glacial acetic acid, previously saturated with HBr, was added 3.3 g (0.0125 mole) of **17**. The mixture was stirred at room temperature for 6 hr and poured into 400 ml of water. The resulting solid was collected, washed well with water, and dissolved in ether. Evaporation of the dried ether solution gave 3.7 g of product, mp 122–124°. Recrystallization from a small amount of isopropyl ether gave material, mp 127–128, which gave a positive $FeCl_3$ test; ν_{max} 3220 (s, NH) 1625 (m), 1585 (m), 1550 (m)[23] cm^{-1}; pmr (deuterated DMSO), δ 14.1 (1 H very broad signal, enolic H), 8.89 (1 H singlet, NH), 3.60 (2 H triplet, J = 7 cps, $BrCH_2$), 3.00 (2 H triplet, J = 7 cps, $COCH_2$), 2.22 (2 H multiplet, >CCH_2C<).

Anal. Calcd for $C_{12}H_{12}BrNO_4S$: C, 41.63; H, 3.49; Br, 23.08; N, 4.05; S, 9.26. Found: C, 42.02; H, 3.65; Br, 22.80; N, 3.95; S, 9.21.

B. From 15.—To 10 ml of glacial acetic acid, previously saturated with HBr, was added 100 mg of **15**. The mixture was stirred overnight at room temperature and poured into 50 ml of water. The resulting solid was collected, washed well with water, and dissolved in CH_2Cl_2. Evaporation of the dried solution gave 50 mg of **19**, mp 122–125°, identified by mixture melting point and comparison of infrared spectra.

Reaction of 19 with Aqueous Alkali.—A mixture of 2.08 g (0.006 mole) of **19** and 120 ml of 0.05 *N* NaOH was stirred at room temperature. A precipitate was seen to form even before the starting material had completely dissolved. Stirring was continued overnight at room temperature and the precipitate was collected, washed well with water, and dissolved in CH_2Cl_2. Evaporation of the dried solution gave 1.4 g of **15**, mp 232–237°, identified by comparison of infrared spectra.

Reaction of 19 with Sodium Hydride in 1,2-Dimethoxyethane.—A solution of 1.0 g (0.0029 mole) of **19** in 25 ml of 1,2-dimethoxyethane was added to a suspension of 0.0030 mole of NaH[26] in 25 ml of 1,2-dimethoxyethane and the mixture was refluxed with stirring for 4 hr. It was poured into 300 ml of ice–water and the 1,2-dimethoxyethane was removed using a rotary flash evaporator (maximum temperature was 35°). Extraction with CH_2Cl_2 and evaporation of the organic solution gave 0.4 g of **15**, mp 230–235°.

2-(3-Carbomethoxypropyl)-2H-1,2-benzothiazin-4(3H)-one 1,1-Dioxide (10a).—To a slurry of 0.44 mole of NaH[26] in 120 ml of 1,2-dimethoxyethane was added a solution of 9.6 g (0.04 mole) of 2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide ethylene ketal in 120 ml of 1,2-dimethoxyethane and the mixture was refluxed with stirring for 1 hr. It was cooled to room temperature, a solution of 9.2 g (0.04 mole) of methyl γ-iodobutyrate in 40 ml of 1,2-dimethoxyethane was added, and refluxing was continued for 19 hr. The mixture was filtered and the filtrate was distilled *in vacuo* to give an oil which was converted to a gummy solid on trituration with petroleum ether; the infrared spectrum showed the absence of NH absorption. It was refluxed for 15 min with a mixture of 100 ml of methanol and 100 ml of 10% aqueous HCl, the methanol was distilled off, and the resulting mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extract was triturated with a small amount of isopropyl alcohol to give 3.9 g of product, mp 81–83°. Recrystallization from isopropyl alcohol gave an analytical sample: mp 85–86°; ν_{max} 1725 (s, ester), 1695 (s, ketone) cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_5S$: C, 52.52; H, 5.09; N, 4.71; S, 10.78. Found: C, 52.61; H, 5.18; N, 4.71; S, 10.62.

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(26) NaH was employed as a 53% dispersion in mineral oil.