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Studies on Pyrimidine Derivatives and Related Compounds. XCIV.[1] On the Oxidation Products of 2-Substituted-2,3-dihydro-4H-1,4-thiazin-3-one Derivatives. (2)

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Hydrogen peroxide oxidation of 4-(4-amino-2-methylpyrimidin-5-yl)methyl-6-(2-hydroxyethyl)-2-(2-methoxyphenyl)-4-methyl-2,3-dihydro-4H-1,4-thiazin-3-one (**1c**) gave N-[(4-amino-2-methylpyrimidin-5-yl) methyl]-N-[1-(2-oxido-1,2-oxathiolan-3-yliden) ethyl] (2-methoxyphenyl)oxalamide (**3b**) and 2-oxido-1,2-oxathiolane-3-spiro-3′-[1′-(4-amino-2-methylpyrimidin-5-yl)methyl-4′-hydroxy-2′-methylene-4′-(2-methoxyphenyl)-tetrahydropyrrol-5′-one] (**6**). The former product (**3b**) was transformed into another product (**6**) under oxidative reaction conditions and **6** led to the known 1-(4-amino-2-methylpyrimidin-5-yl)methyl-4-hydroxy-3-(2-hydroxyethyl)-4-(2-methoxyphenyl)-2-methyl-Δ^2-pyrrolin-5-one (**4**) and 2-aza-2-(4-amino-2-methylpyrimidin-5-yl)methyl-4-hydroxy-4-(2-methoxyphenyl)-1-methyl-8-oxabicyclo[3.3.0]octan-3-one (**5**) on acid or alkali treatment. On the other hand, an oxalamide (**3d**) having a 2-anisyl substituent was recovered under the same reaction conditions. The same reaction with 2-aryl-4-benzyl-2,3-dihydro-4H-1,4-benzothiazin-3-ones (**12a—c**) afforded 2-aryl-4-benzyl-2-hydroxy-2,3-dihydro-4H-1,4-benzothiazin-3-ones (**13a—c**), bis-(2-aryloxalylaminophenyl)-1,1′-disulfide (**14a—b**) and 2-aryl-4-benzyl-3-oxo-2,3-dihydro-4H-1,4-benzothiazine-1,1-dioxide (**15a—c**), while 4-benzyl-2-methyl-2,3-dihydro-4H-1,4-benzothiazine-1,3-dioxide (**16b**) was mainly obtained in the oxidation of the 2-methyl derivative (**12d**), which was converted into 4-benzyl-2-hydroxy-2-methyl-2,3-dihydro-4H-1,4-benzothiazin-3-oxide (**13d**) *via* a Pummerer-type rearrangement. The reaction mechanism is discussed.

Keywords——1,4-thiazines; oxidation; substituent effect; α-ketoamido; 2-oxido-1,2-oxathiolane; desulfurization; Pummerer reaction

The reaction products obtained by hydrogen peroxide oxidation and subsequent alkaline treatment of 4-(4-amino-2-methylpyrimidin-5-yl)methyl (**1**) or 4-benzyl-6-(2-hydroxyethyl)-5-methyl-2-substituted-2,3-dihydro-4H-1,4-thiazine-3-ones have been reported.[3] Summarizing the results, the oxidation products were influenced markedly by 2-substituents, that is, the reaction afforded 4-(4-amino-2-methylpyrimidin-5-yl)methyl-2-hydroxy-6-(2-hydroxyethyl)-5-methyl-2-phenyl-2,3-dihydro-4H-1,4-thiazin-3-one (**2a**), N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-N-[1-(2-oxido-1,2-oxathiolan-3-ylidene)ethyl]-*o*-tolyloxalamide (**3a**), 1-(4-amino-2-methylpyrimidin-5-yl)methyl-4-hydroxy-3-(2-hydroxyethyl)-4-(2-methoxyphenyl)-2-methyl-Δ^2-pyrrolin-5-one (**4**) and 2-aza-2-(4-amino-2-methylpyrimidin-5-yl)methyl-4-hydroxy-4-(2-methoxyphenyl)-1-methyl-8-oxabicyclo[3.3.0]octan-3-one (**5**) in the cases of 2-phenyl (**1a**), 2-*o*-tolyl (**1b**) and 2-*o*-methoxyphenyl (**1c**) substituents, respectively.

As 2-hydroxy-1,4-thiazines having a hemithioketal moiety possess interesting reactivity and pharmacological action, we attempted to synthesize analogous compounds and to clarify the hydroxylation reaction mechanism.

Reinvestigation of the oxidation of 4-(4-amino-2-methylpyrimidin-5-yl)methyl-6-(2-hydroxyethyl)-2-(2-methoxyphenyl)-5-methyl-2,3-dihydro-4H-1,4-thiazin-3-one (**1c**) using an equimolar amount of hydrogen peroxide gave two kinds of 1,2-oxathiolan-2-oxides (**3b** and **6**)

1) Part XCIII: A. Takamizawa, Y. Matsushita, and H. Harada, *Chem. Pharm. Bull.*, **28**, 447 (1980).
2) Location: *Fukushima-ku, Osaka, 553, Japan.*
3) A. Takamizawa, H. Harada, and I. Makino, *Chem. Pharm. Bull.*, **26**, 722 (1978).

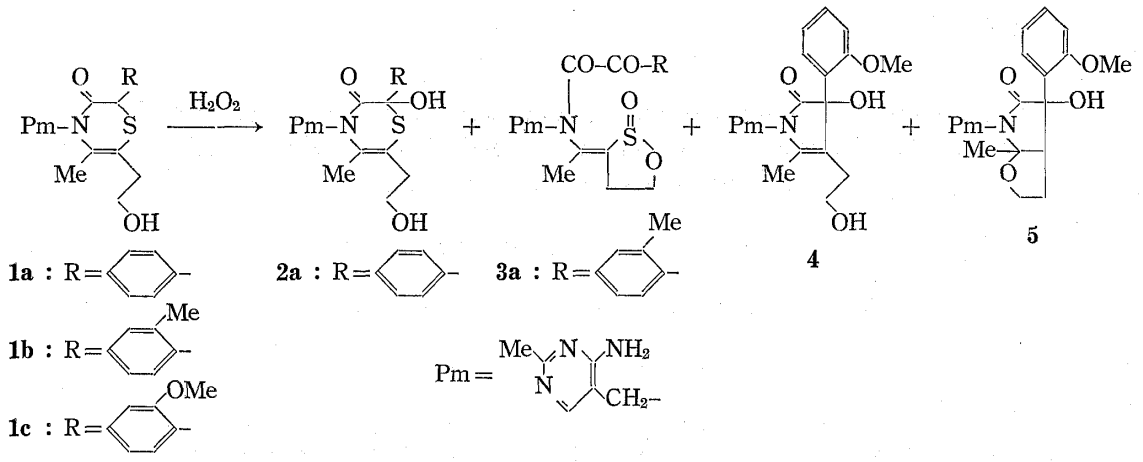


Chart 1

in 8.5 and 7% yields, respectively, in addition to the starting material (**1c**, 26%) and *o*-anisic acid (**7**, 19%). On oxidation using 2 mol of hydrogen peroxide, the yield of **6** rose to 44%. The structure of the first 1,2-oxathiolan-2-oxide (**3b**) was identified as N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-N-[1-(2-oxido-1,2-oxathiolan-3-ylidene)ethyl]-(2-methoxyphenyl)oxalamide, which had been obtained previously.[3] The first oxathiolane (**3b**) was slowly converted into the second oxathiolane (**6**) when left to stand in acetic acid at room temperature. The structure of this product was determined from the elemental analysis data and nuclear magnetic resonance (NMR) spectra of itself and its methylated derivative (**8**). The NMR spectra of both compounds showed peaks due to the pyrimidinylmethyl and 1,2-oxathiolane-2-oxide moieties, the exomethylene group (δ 4.23—4.93 in **6** and 4.10—5.00 in **8**) and a tertiary hydroxyl group in **6** (δ 7.27) or two methoxyl groups in **8** (δ 3.53 and 3.57). Catalytic reduction of **6** over a palladium–carbon catalyst as well as mineral acid treatment provided oxazabicyclo[3.3.0]octanone (**5**)[3] as a mixture of stereoisomers by desulfurization. Therefore, the second 1,2-oxathiolan-2-oxide (**6**) must have the pyrrolidin-2-one ring structure prior to desulfurization. Based on the above results, the structure of the second oxathiolane (**6**) was determined to be 2-oxido-1,2-oxathiolane-3-spiro-3′-[1′-(4-amino-2-methylpyrimidin-5-yl)methyl-4′-hydroxy-2′-methylene-4′-(2-methoxyphenyl)-tetrahydropyrrol-5′-one].

Stereoisomeric oxazabicyclo[2.2.0]octane derivatives (**5**) were obtained by acid or alkali treatment or catalytic reduction of **6**, and were separable by silica gel thin layer chromatography (TLC). The NMR spectrum of the compound (mp 263—266° from acetone, **5a**) having the higher *Rf* value showed a singlet due to 1-methyl protons at δ 1.42, while the other (mp 227—230° from acetone, **5b**) showed the same signal at δ 1.65. The 6a-methyl signals of 2,6a-dimethyl-11-alkyl or arylcarbamoyl-6a,8,9,9a,10,11-hexahydro-5H-furo[2,3-*h*]thiachromine (**9**)[4] and the 3a-methyl signals of 3-(4-amino-2-methylpyrimidin-5-yl)methyl-3a-methyl-2-substituted perhydrofuro[2,3-*d*]thiazoles (**10**)[5] appeared at δ 1.50—1.55 and δ 1.54—1.70, respectively. Accordingly, the stereochemical relationship between the 1-methyl and 4-*o*-methoxyphenyl groups in the compound having the higher methyl signal at δ 1.42, assuming shielding by the *o*-methoxyphenyl ring, may be *cis*-oriented.

Thus, the formation of **4** and **5** in the reaction of **1c** with hydrogen peroxide following alkali treatment, as reported in the previous paper,[3] can be explained as follows: the oxathiolane (**3b**) first formed by hydrogen peroxide oxidation underwent ring closure to afford

4) A. Takamizawa, K. Hirai, T. Ishiba, and I. Makino, *Chem. Pharm. Bull.*, **19**, 759 (1971); A. Takamizawa, I. Makino, and S. Yonezawa, *ibid.*, **22**, 286 (1974).

5) A. Takamizawa, K. Hirai, Y. Hamashima, S. Matsumoto, and T. Ishiba, *ibid.*, **16**, 1210 (1968); A. Takamizawa, K. Hirai, and Y. Hamashima, *ibid.*, **16**, 1758 (1968); A. Takamizawa, K. Hirai, Y. Hamashima, Y. Matsumoto, and S. Tanaka, *ibid.*, **16**, 1764 (1968).

the second oxathiolane (**6**) having a pyrrolidinone ring structure under the reaction conditions used, then expulsion of sulfur dioxide from the sulfinate (**11**), which was formed by alkaline hydrolysis of the 1,2-oxathiolane-2-oxide moiety, resulted in the formation of **4** and **5.**

This was not the case for the corresponding *p*-substituted derivatives (**1d** and **1e**). Hydrogen peroxide oxidation of **1d** and **1e** afforded N-[(4-amino-2-methylpyrimidine-5-yl)-methyl]-N-[1-(2-oxido-1,2-oxathiolan-3-ylidene)ethyl]-*p*-tolyl and anisyloxalamides (**3c** and **3d**) in 19 and 25% yields, respectively. The oxalamide (**3d**) was left to stand in an acetic acid solution at room temperature under the conditions adopted for the *o*-methoxyphenyl derivative (**3b**), but the corresponding pyrrolidinone derivative could not be isolated and only the crystalline starting material (**3d**) was recovered in 50% yield, although spots of small amounts of transformed compounds were observed on the TLC plates (Chart 2).

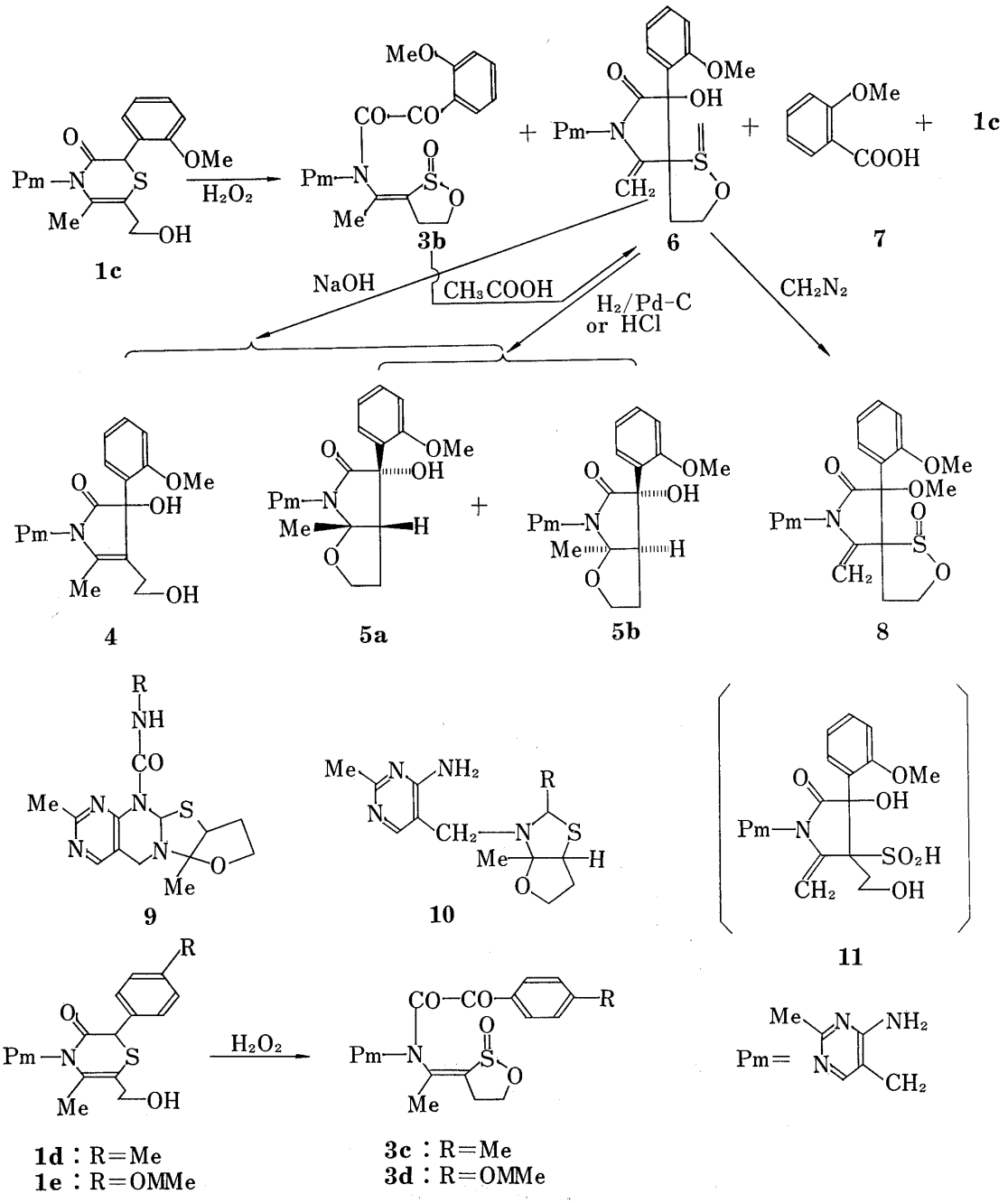
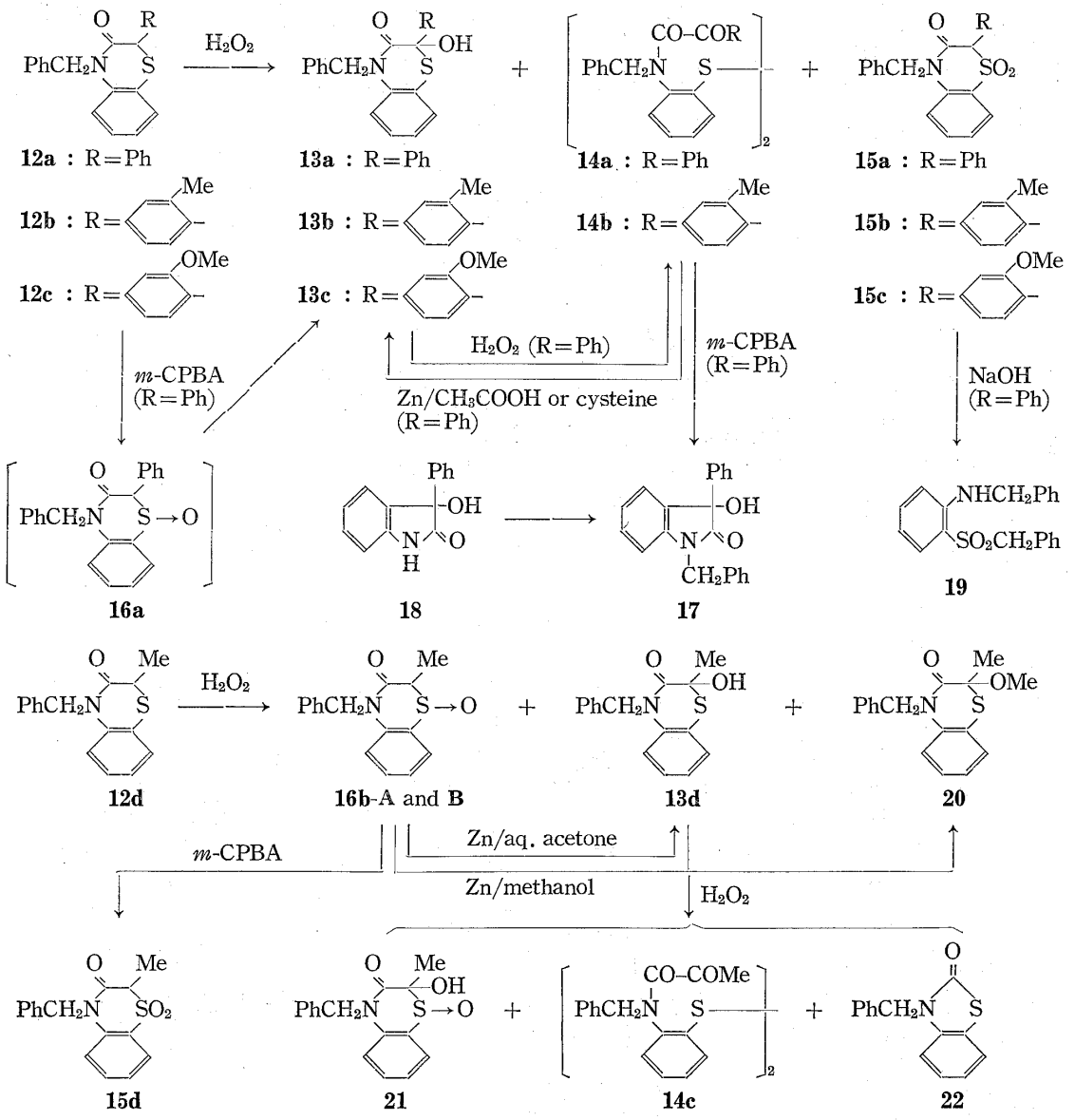


Chart 2

As described above, the use of phenyl, *o*-tolyl and *o*-methoxyphenyl groups as 2-substituents caused marked differences in the oxidation products. To study this hydroxylation reaction in detail, simpler substances such as 4-benzyl-2-substituted-2,3-dihydro-4H-1,4-benzothiazin-3-one (**12**) were chosen as model compounds.

Similar oxidation of the 2-phenyl derivative (**12a**) with an equimolar amount of hydrogen peroxide formed a 2-hydroxy derivative (**13a**) and a disulfide (**14a**) in 27 and 22% yields, respectively. These two products were interconvertible by hydrogen peroxide oxidation of **13a** and cysteine or zinc–acetic acid reduction of **14a**. In the oxidation using 2 moles of reagent, a new compound, the sulfone (**15a**), was obtained as the main product (33%) in addition to small quantities of **13a** and **14a**. In order to obtain an intermediate in this oxidation reaction, aprotic conditions using an equimolar amount of *m*-chloroperbenzoic acid (*m*-CPBA) were adopted. The formation of the sulfoxide (**16a**) was considered reasonable on the basis of the low *Rf* value on the TLC plate, but it could not be isolated, and only the 2-hydroxy compound (**13a**) was obtained in 51% yield. The sulfoxide was completely rearranged during the separation process using silica gel column chromatography. The same reaction using



Me: methyl, Ph: phenyl, *m*-CPBA: *m*-chloroperbenzoic acid

Chart 3

2 mol of *m*-CPBA afforded the sulfone derivative (**15a**) in almost quantitative yield. On the other hand, *m*-CPBA oxidation of the disulfide (**14a**) caused desulfurization to give 1-benzyl-3-hydroxy-3-phenyl-2,3-dihydro-1H-indolin-2-one (**17**), which was identical with the N-benzyl derivative of 3-hydroxy-3-phenyl-2,3-dihydro-1H-indolin-2-one (**18**).[6] Alkali treatment of the sulfone (**15a**) provided benzyl *o*-benzylaminophenylsulfone (**19**) by hydrolysis of the amide group with decarboxylation. Similar hydrogen peroxide oxidation of the 2-*o*-tolyl and 2-*o*-methoxyphenyl derivatives (**12b** and **12c**) led to similar results. The main products were the 2-hydroxylated derivatives (**13b** and **13c**) and the disulfide (**14b**) using equimolar amounts of hydrogen peroxide, and the sulfone derivatives (**15b** and **15c**) using 2 mol of oxidant. In the case of the compound (**12d**) having the 2-methyl substituent, the products were a stereoisomeric mixture of the sulfoxides (**16b-A** and **B**, 73%, **16b-A**/**16b-B**=2/3) and a small quantity of a 2-hydroxy compound (**13d**). When the separation took a long time, the yield of the sulfoxides decreased (6.7%) and the yields of the 2-hydroxy (**13d**, 14%) and methoxy (**20**, 3%) derivatives increased. The formation of 4-benzyl-2-methoxy-2-methyl-2,3-dihydro-4H-1,4-benzothiazin-3-one (**20**) was attributed to the use of methanol–chloroform for silica gel column chromatography. The sulfoxide (**16b**) was converted into 2-hydroxy and 2-methoxy derivatives (**13d** and **20**) on treatment with zinc–aqueous acetone and zinc–methanol. On oxidation with *m*-CPBA, the sulfoxide (**16b**) was oxidized to the sulfone (**15d**) in good yield. Furthermore, hydrogen peroxide oxidation of the 2-hydroxy derivative (**13d**) resulted in the formation of the 2-hydroxy sulfoxide (**21**), disulfide (**14c**) and benzothiazolone (**22**) in 17, 27 and 21% yields, respectively. The isolation of 2-hydroxysulfoxide (**21**) is interesting in relation to the formation of the oxalamide derivatives (**3a**, **b**) in the 4-(4-amino-2-methyl-

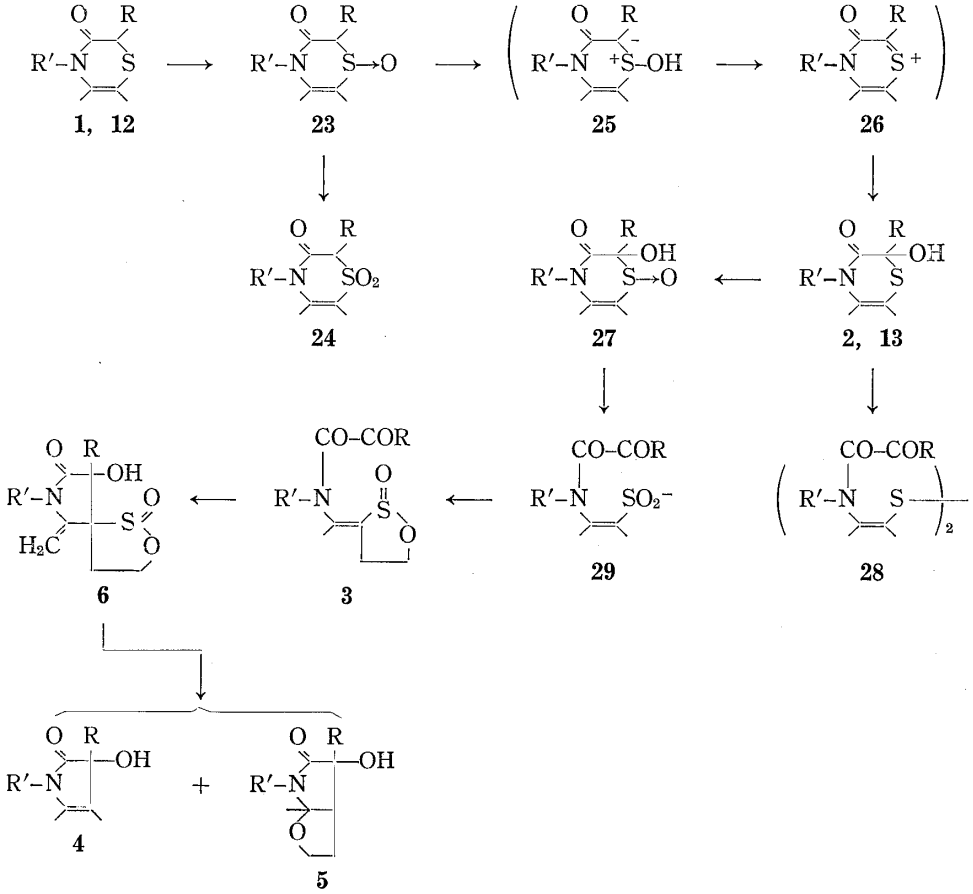


Chart 4

6) J.M. Bruce, *J. Chem. Soc.*, **1959**, 2366.

pyrimidin-5-yl)methyl-6-(2-hydroxyethyl)-5-methyl-2-substituted-2,3-dihydro-4H-1,4-thiazin-2-one series described above (Chart 3).

In the reaction of 1,4-benzothiazine derivatives, the initial step of the 2-hydroxylation reaction was S-oxidation and the resulting sulfoxides rearranged to form the 2-hydroxy compounds (Pummerer reaction). In the presence of excess reagents, further oxidation of the sulfoxides to sulfones predominated over the formation of the 2-hydroxy derivatives. However, no effect of the 2-substituents was observed in either the S-oxidation or the subsequent Pummerer reaction in these model experiments.

Chart 4 summarizes the reaction. The initial step in the oxidation reaction of 2,3-dihydro-4H-1,4-thiazin-3-one was formation of the sulfoxide (**23**) by S-oxidation. With the benzothiazine derivatives, these sulfoxides were fairly stable with respect to the rearrangement and were oxidized to the sulfone (**24**) in the presence of excess oxidant, while with the N-pyrimidinylmethylthiazine derivatives (**1**), the sulfoxides (**23**) were rapidly rearranged into the 2-hydroxy derivatives (**2**) and finally oxidized to 1,2-oxathiolane-2-oxide (**3**) through **29**. In the case of the compound having an *o*-methoxyphenyl substituent in the pyrimidinylmethyl series, further cyclization to **6** occurred (although the reason for this is not clear) and its desulfurization resulted in the formation of the pyrrolin-2-one (**4**) and furopyrrolidinone (**5**) derivatives described in the previous paper.[3]

Experimental[7]

4-(4-Amino-2-methylpyrimidin-5-yl)methyl-2-*p*-anisyl-6-(2-hydroxyethyl)-4-methyl-2,3-dihydro-4H-1,4-thiazin-3-one (1e)——**1e** was obtained according to Takamizawa *et al.*,[8] mp 123° (54%). *Anal.* Calcd for $C_{20}H_{24}N_4O_3S \cdot H_2O$: C, 57.39; H, 6.26; N, 13.39; S, 7.66. Found: C, 57.42; H, 5.77; N, 13.30; S, 7.99.

Oxidation of 4-(4-Amino-2-methylpyrimidin-5-yl)methyl-2,3-dihydro-6-(2-hydroxyethyl)-5-methyl-2-substituted-4H-1,4-thiazin-3-one (1c—e)——a) A stirred solution of 1 mmol of thiazine (**1c**)[8] in 10 ml of acetic acid was treated with 1 mmol of 30% hydrogen peroxide solution (H_2O_2) at room temperature. Stirring was continued for 5 hr then the solution was allowed to stand for 2 days. Evaporation under reduced pressure and extraction with methylene chloride (CH_2Cl_2) gave an oily yellow material, which was separated by preparative thin-layer chromatography (PLC) using 5—10% ethanol–chloroform. *o*-Anisic acid (**7**, 29 mg, 19%), the starting material (**1c**, 105 mg, 26%), and a mixture of **3b** and **6** were obtained. The mixture of **3b** and **6** was subjected to PLC separation using 30% acetone–ethyl acetate to give **3b**[3] (34 mg, 8.5%) and **6**, mp 229—232° (dec.), from ethanol (28 mg, 7%).

6, *Anal.* Calcd for $C_{20}H_{22}N_4O_5S$: C, 55.80; H, 5.15; N, 13.01; S, 7.45; mol. wt. 430.49. Found: C, 55.83; H, 5.08; N, 12.78; S, 7.43; mol. wt. 436.1. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3140, 1700, 1665, 1640, 1595, 1140, 1025. NMR δ ppm (DMSO-d_6): 1.42—2.2^m (2H, CH_2), 2.33^s [3H, pyrimidine (Pm)-2-CH_3], 3.60^s (3H, OCH_3), 4.23—4.93^m (6H, $>$=CH_2, CH_2O and Pm-5-CH_2), 6.83^b (2H, NH_2), 6.73—7.78^m [4H, benzene (Bz)], 7.27^s (1H, OH), 8.00^s (1H, Pm-6-H).

b) A stirred solution of 1 mmol of thiazine (**1c—e**) in 10 ml of acetic acid was treated with an equimolar amount of 30% H_2O_2, and after stirring for 2 hr, an additional equimolar amount of 30% H_2O_2 was added. Stirring was continued for 6 hr, then the solution was allowed to stand for 2 days. Extraction and purification were carried out as described above to give *o*-anisic acid (**7**, 27 mg, 18%), **3b** (12 mg, 3%) and **6** (176 mg, 44%) starting from **1c**, **3c** [mp 150° (from ethyl acetate–ether, 77 mg, 19%)] starting from **1d**,[9] and **3d** [mp 114° (from ethyl acetate–ether, 109 mg, 25%)] and *p*-anisic acid (16 mg, 10%) starting from **1e**.

3c, *Anal.* Calcd for $C_{20}H_{22}N_4O_4S$: C, 57.96; H, 5.35; N, 13.52; S, 7.74. Found: C, 57.81; H, 5.20; N, 13.23; S, 7.76. IR ν_{max}^{Nujol} cm^{-1}: 3390, 3330, 1665, 1635, 1600, 1175, 1120. NMR δ ppm ($CDCl_3$): 1.63—2.20^m (3H, ⫽CH_3), 2.23—3.00^m (2H, ⫽CH_2), 2.40 and 2.50$^{2\times s}$ (3H×2, Pm-2-CH_3 and Bz–CH_3), 4.07—5.37^m (4H, Pm-5-CH_2 and CH_2O), 6.43^b (2H, NH_2), 7.23 and 7.85^{ABq} (4H, J=7, Bz), 7.97^s (1H, Pm-6-H).

7) Melting points are uncorrected. NMR spectra were taken on a NEVA T-60 spectrometer in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ-values and coupling constants in Hz. Signal multiplicities are represented as singlet (s), doublet (d), triplet (t), quartet (q), broad (b) and multiplet (m). IR spectra were taken in a nujol mull or in chloroform solution on a Japan Spectroscopic Company IR-S spectrometer. Preparative layer chromatography, thin-layer chromatography and column chromatography were done using Kieselgel 60 GF nach Stahl, DC-Fertigplatten Kieselgel 60 F254 and Kieselgel 60 (Merck), respectively.

8) A. Takamizawa, H. Sato, and I. Makino, *Vitamins* (*Japan*), **49**, 177 (1975).
9) A. Takamizawa, *Vitamins* (*Japan*), **47**, 1 (1973).

3d, *Anal.* Calcd for $C_{20}H_{22}N_4O_5S$: C, 55.80; H, 5.15; N, 13.01; S, 7.45. Found: C, 55.69; H, 5.07; N, 12.79; S, 7.27. IR ν_{max}^{Nujol} cm^{-1}: 3385, 3320, 3125, 1635, 1595, 1165, 1115. NMR δ ppm ($CDCl_3$): 1.66—2.20^m (3H, $\diagup\!\!\diagdown CH_3$), 2.47^s (3H, Pm-2-$CH_3$), 2.33—3.10^m (2H, $\diagup\!\!\diagdown CH_2$), 3.85^s (3H, OCH_3), 4.23—5.33^m (4H, Pm-5-CH_2 and CH_2O), 6.45^b (2H, NH_2), 6.90 and 7.93^{ABq} (4H, J=9, Bz), 7.97^s (1H, Pm-6-H).

2-Oxido-1,2-oxathiolane-3-spiro-3′-[1′-(4-amino-2-methylpyrimidin-5-yl)methyl-4′-hydroxy-2′-methylene-4′-(2-methoxyphenyl)tetrahydropyrrol-5′-one] (6)——A solution of 22 mg of N-[(4-amino-2-methylpyrimidin-5-yl)methyl]-N-[1-(2-oxido-1,2-oxathiolan-3-ylidene)ethyl] (2-methoxyphenyl)oxalamide (**3b**) in 2 ml of acetic acid was allowed to stand for 2 days. Concentration under reduced pressure, extraction with chloroform and recrystallization from acetone gave 8 mg (36%) of colorless crystals, mp 227—229° (dec.), which were identical with **6** obtained in the oxidation reaction of **1c**.

2-Oxido-1,2-oxathiolane-3-spiro-3′-[1′-(4-amino-2-methylpyrimidin-5-yl)methyl-4′-methoxy-2′-methylene-4′-(2-methoxyphenyl)tetrahydropyrrol-5′-one] (8)——A stirred solution of 100 mg of **6** in 4 ml of methanol and 8 ml of chloroform was treated with 40 ml of diazomethane–ether solution. The solution was stirred for 4 hr and allowed to stand for a day. After removal of the ether under reduced pressure, the treatment with diazomethane was repeated. Evaporation and recrystallization from acetone–ethyl acetate gave 72 mg (70%) of colorless crystals, mp 194°.

8, *Anal.* Calcd for $C_{21}H_{24}N_4O_5S$: C, 56.74; H, 5.44; N, 12.60; S, 7.21. Found: C, 56.87; H, 5.47; N, 12.38; S, 7.49. IR ν_{max}^{Nujol} cm^{-1}: 3310, 3130, 1695, 1665, 1640, 1585, 1250, 1140, 1090. NMR δ ppm ($CDCl_3$): 1.53—2.37^m (2H, CH_2), 2.50^s (3H, Pm-2-CH_3), 3.53 and 3.57$^{2\times s}$ (3H×2, $OCH_3\times2$), 4.10—5.00^m (6H, >=CH_2, Pm-5-CH_2 and CH_2O), 6.25^b (2H, NH_2), 6.77—7.63^m (4H, Bz), 8.27^s (1H, Pm-6-H).

Catalytic Reduction of 6——A solution of 108 mg of **6** in a mixture of 20 ml of methanol and 8 ml of chloroform was hydrogenated over 100 mg of 5% palladium–carbon catalyst for 8 hr. After filtration, 100 mg of fresh catalyst was added to the solution, which was hydrogenated again for a further 8 hr. Removal of the catalyst by filtration, evaporation, and extraction with chloroform gave 21 mg (22%) of colorless crystals which were identified as a mixture of **5a** and **5b** in a 3: 2 ratio by NMR spectroscopy.

Acid Treatmcnt of 6——A solution of 43 mg of **6** in 4 ml of 10% hydrochloric acid was heated at 55° for 3 hr. Neutralization with ammonia, extraction with chloroform and recrystallization gave 22 mg (55%) of colorless crystals, mp 209—216°, which were identified as a mixture of **5a** and **5b** in a 3: 2 ratio by NMR spectroscopy.

Alkali Treatment of 6——A mixture of 20 mg of **6** and 0.5 ml of 5% sodium hydroxide was warmed over a water bath for 3 min and the resulting clear solution was allowed to stand for 1.5 hr. Carbon dioxide was passed into the solution, which was then adjusted to pH 4 with dilute hydrochloric acid and extracted with methylene chloride. The aqueous layer was made alkaline again with sodium hydroxide and extracted with methylene chloride. The extracts were combined, dried and concentrated under reduced pressure. The residue was subjected to TLC separation using 11% ethanol–chloroform to yield crude **4** (2 mg, 10%), **5a** (6 mg, 30%) and **5b** (5.5 mg, 27%), which were recrystallized from acetone, mp 263—266° and mp 227—230°, respectively.

5a, *Anal.* Calcd for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.77; H, 6.33; N, 14.81. IR ν_{max}^{Nujol} cm^{-1}: 3460, 3340, 3300, 3180, 1660, 1585. NMR δ ppm (DMSO-d_6): 1.42^s (3H, ), 1.6—2.3^m (2H, CH_2), 2.32^s (3H, Pm-2-CH_3), 3.5—4.0^m (2H, CH_2O), 3.68^s (3H, OCH_3), 4.32^b (2H, Pm-5-CH_2), 6.17^s (1H, OH), 6.85^b (2H, NH_2), 6.8—7.7^m (4H, Bz), 8.03^s (1H, Pm-6-H).

5b, *Anal.* Calcd for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.35; H, 6.58; N, 14.45. IR ν_{max}^{Nujol} cm^{-1}: 3260, 3200, 3100, 1680, 1600. NMR δ ppm (DMSO-d_6): 1.65^s (3H, ), 1.6—2.3^m (2H, CH_2), 2.33^s (3H, Pm-2-CH_3), 3.58^s (3H, OCH_3), 3.2—3.7^m (2H, CH_2O), 4.27^b (2H, Pm-5-CH_2), 6.13^s (1H, OH), 6.87^b (2H, NH_2), 6.8—7.7^m (4H, Bz), 8.03^s (1H, Pm-6-H).

Acetic Acid Treatment of N-[(4-Amino-2-methylpyrimidin-5-yl)methyl]-N-[1-(2-oxido-1,2-oxathiolan-3-ylidene)ethyl]-*p*-anisyloxalamide (3d)——A solution of 90 mg of **3d** in 2 ml of acetic acid was allowed to stand for 3 days at room temperature, then concentrated under reduced pressure. Extraction with chloroform and concentration gave 83 mg of a pale yellow material, which was subjected to TLC separation using 5% ethanol–chloroform, and 44 mg (50%) of the crystalline starting material was recovered.

4-Benzyl-2-(*o*-tolyl) and (2-Methoxyphenyl)-2,3-dihydro-4H-benzothiazin-3-one (12b and 12c)——**12b** and **12c** were prepared according to Takamizawa *et al.*[10] **12b**, mp 101° (46%). *Anal.* Calcd for $C_{22}H_{19}NOS$: C, 76.49; H, 5.54; N, 4.05; S, 9.28. Found: C, 76.77; H, 5.47; N, 3.78; S, 9.03. **12c**, mp 129° (20%). *Anal.* Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88; S, 8.87. Found: C, 72.95; H, 5.31; N, 3.62; S, 8.72.

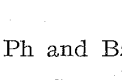
Hydrogen Peroxide Oxidation of 4-Benzyl-2-substituted-2,3-dihydro-4H-1,4-benzothiazin-3-one (12a—c)——General Procedure. A stirred solution of 1 mmol of benzothiazine (**12a—c**) in 5 ml of acetic acid was treated with an equimolar amount (or 2 mol) of 30% hydrogen peroxide at room temperature. Stirring was continued for 7.5 hr and the mixture was allowed to stand overnight. After concentration under reduced

10) A. Takamizawa, H. Sato, and Y. Sato, *Chem. Pharm. Bull.*, **20**, 592 (1972).

pressure, the residue was separated by TLC using benzene to give **12a**, 25 mg, 7.6%, **13a**, mp 159—161° from ether, 95 mg, 27% (14 mg, 4.0%). **14a**, amorph., 77 mg, 22% (26 mg, 7.5%), and **15a**, amorph., (131 mg, 33%) starting from **12a**,[10] **12b**, 27 mg, 7.8%, **13b**, amorph., 74 mg, 20% (16 mg, 4.0%), **14b**, mp 155°, 69 mg, 19% (17 mg, 4.8%), **15b**, mp 157° from ether (164 mg, 44%) starting from **12b**, and **12c**, 18 mg, 5.0%, **13c**, mp 175° from ethyl acetate–ether, 99 mg, 26% (42 mg, 11%), **15c**, amorph. (131 mg, 33%) starting from **12c**.

13a, *Anal.* Calcd for $C_{21}H_{17}NO_2S$: C, 72.60; H, 4.93; N, 4.03; S, 9.23. Found: C, 72.53; H, 4.84; N, 3.93; S, 9.39. IR ν_{max}^{Nujol} cm^{-1}: 1653. NMR δ ppm ($CDCl_3$): 5.09 and 5.46^{ABq} (2H, $J=16.4$, phenyl(Ph)-CH_2), 5.17^{s} (1H, OH), 6.80—7.57^{m} (14H, Ph and Bz).

14a, *Anal.* Calcd for $(C_{21}H_{16}NO_2S)_2$: C, 72.81; H, 4.66; N, 4.04; S, 9.26; mol. wt., 692.86. Found: C, 72.35; H, 4.56; N, 4.00; S, 8.96; mol. wt., 683.0. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1657, 1598, 1587. NMR δ ppm ($CDCl_3$): 4.23, 4.32, 5.70, $5.77^{2\times ABq}$ (4H, $J=14$, Ph-CH_2, two pairs of ABq in a ratio of 1:1), 6.33—7.93^{m} (28H, $4\times$Ph and $2\times$Bz).

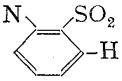
15a, *Anal.* Calcd for $C_{21}H_{17}NO_3S$: C, 69.40; H, 4.71; N, 3.85; S, 8.82. Found: C, 69.33; H, 4.78; N, 4.14; S, 8.63. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1325, 1160, 1130. NMR δ ppm ($CDCl_3$): 5.35^{s} (1H, CH), 5.42^{s} (2H, $PhCH_2$), 7.20—7.60^{m} (13H, $2\times$Ph and Bz), 7.93^{dd} (1H, $J=8.0$ and 2.0,  -H).

13b, *Anal.* Calcd for $C_{22}H_{19}NO_2S$: C, 73.10; H, 5.30; N, 3.88; S, 8.87. Found: C, 72.55; H, 5.68; N, 3.46; S, 8.69. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3650, 3560, 3385, 1650. NMR δ ppm ($CDCl_3$): 2.58^{s} (3H, CH_3), 5.17 and 5.45^{ABq} (2H, $J=16$, $PhCH_2$), 5.32^{s} (1H, OH), 6.52—7.37^{m} (13H, Ph and $2\times$Bz).

14b, *Anal.* Calcd for $(C_{22}H_{18}NO_2S)_2$: C, 73.31; H, 5.03; N, 3.89; S, 8.90; mol. wt., 720.92. Found: C, 73.48; H, 5.19; N, 3.72; S, 8.70; mol. wt., 720. IR ν_{max}^{Nujol} cm^{-1}: 1685, 1660. NMR δ ppm ($CDCl_3$): 2.15^{s} (6H, $2\times CH_3$), 4.25, 4.33, 5.78, $5.83^{2\times ABq}$ (4H, $J=15$, $2\times PhCH_2$, two pairs of ABq in a ratio of 1:1), 6.3—8.1^{m} (26H, $2\times$Ph and $4\times$Bz).

15b, *Anal.* Calcd for $C_{22}H_{19}NO_3S$: C, 70.01; H, 5.07; N, 3.71; S, 8.49. Found: C, 69.77; H, 5.21; N, 3.41; S, 8.45. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1325, 1170, 1140. NMR δ ppm ($CDCl_3$): 2.45^{s} (3H, CH_3), 5.40^{s} (2H, $PhCH_2$), 5.70^{s} (1H, CH), 7.07—8.03^{m} (13H, Ph and $2\times$Bz).

13c, *Anal.* Calcd for $C_{22}H_{19}NO_3S$: C, 70.01; H, 5.07; N, 3.71; S, 8.49. Found: C, 70.15; H, 5.13; N, 3.44; S, 8.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640, 3540, 3370, 1665. NMR δ ppm ($CDCl_3$): 3.68^{s} (3H, OCH_3), 5.12 and 5.43^{ABq} (2H, $J=16$, $PhCH_2$), 5.73^{s} (1H, OH), 6.67—7.83^{m} (13H, Ph and $2\times$Bz).

15c, *Anal.* Calcd for $C_{22}H_{19}NO_4S$: C, 67.16; H, 4.87; N, 3.56; S, 8.15. Found: C, 67.35; H, 4.97; N, 3.46; S, 8.09. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1330, 1170, 1140. NMR δ ppm ($CDCl_3$): 3.80^{s} (3H, OCH_3), 5.37^{s} (2H, $PhCH_2$), 6.15^{s} (1H, CH), 6.83—7.63^{m} (12H, Ph and $2\times$Bz), 7.93^{dd} (1H, $J=8.0$ and 1.8,  -H).

Bis[2-(N-benzyl-N-phenyloxalylamino)phenyl]-1,1′-disulfide (14a)——A stirred suspension of 347 mg of 4-benzyl-2-hydroxy-2-phenyl-2,3-dihydro-4H-1,4-benzothiazin-3-one (**13a**) in 5 ml of acetic acid was treated with 120 mg of 30% hydrogen peroxide and stirring was continued at room temperature until the solution became clear (about 6 hr). This was left to stand overnight then concentrated under reduced pressure. Extraction of the residue with chloroform gave 312 mg of oily material which was subjected to silica gel column chromatography using benzene, chloroform then 5% ethanol–chloroform as eluants. The 5% ethanol–chloroform eluate, 240 mg (69%), was identical with **14a** obtained in the oxidation reaction of **12a** (by NMR conparison).

4-Benzyl-2-hydroxy-2-phenyl-2,3-dihydro-4H-1,4-benzothiazin-3-one (13a)——a) A mixture of 40 mg of disulfide (**14a**), 2 ml of acetic acid and a small amount of zinc dust was stirred for 5 hr at room temperature. Addition of 50 ml of chloroform and washing with water gave 36 mg of chloroform extract, which was crystallized from ether. The collected crystals (17 mg, 42%) were identical with those of **13a** obtained in the oxidation reaction of **12a** (by IR comparison).

b) A suspension of 345 mg of **14a**, 244 mg of L-cysteine, 1 ml of water and 10 ml of methanol was warmed at 60° for 5 min, stirred for 3 hr at room temperature, then allowed to stand overnight. After filtration, the filtrate was concentrated under reduced pressure and extracted with chloroform. The chloroform extract was recrystallized from ethyl acetate–ether to give 253 mg (73%) of **13a**, which was identical with the oxidation product obtained above.

***m*-Chloroperbenzoic Acid (*m*-CPBA) Oxidation of 4-Benzyl-2-phenyl-2,3-dihydro-4H-1,4-benzothiazin-3-one (12a)**——a) A stirred solution of 331 mg of **12a** in 5 ml of chloroform was treated with 173 mg of *m*-CPBA and stirring was continued for 2 hr at room temperature. The solution was washed twice with aqueous potassium carbonate solution, then the organic layer was dried and concentrated. The residue (415 mg) was separated by PLC developed twice with 10% and 20% ethyl acetate–benzene. Products isolated from two different zones (*Rf* 0.7, 157 mg and 0.25, 19 mg) showed the same *Rf* value on a TLC plate (0.7) and both (176 mg, 51%) were identical with **13a** (by NMR comparison).

b) A stirred solution of 331 mg of **12a** in 5 ml of chloroform was treated with 350 mg of *m*-CPBA. Stirring was continued for 5 hr, then the mixture was allowed to stand overnight. The mixture was filtered and the filtrate was subjected to PLC separation, developing with 10% ethyl acetate–benzene, to give 331

mg (91%) of amorphous sulfone (**15a**), which was identical with the oxidation product (**15a**) obtained above.

1-Benzyl-3-hydroxy-3-phenyl-1,3-dihydro-2H-indol-2-one (17)——a) A stirred solution of 726 mg of disulfide (**14a**) in 15 ml of methylene chloride was treated with 414 mg of *m*-CPBA and stirring was continued for 20 hr. Dilution with methylene chloride followed by washing with 10% aqueous sodium hydroxide and saturated sodium chloride solution gave 735 mg of an oily material, which was separated by PLC using 7% ethyl acetate-benzene to yield 38 mg (5%) of **13a** and 63 mg (9.5%) of **17**, mp 150° from ether. **17**, *Anal.* Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44. Found: C, 79.84; H, 5.44; N, 4.39. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3560, 3380, 1720, 1614. NMR δ ppm ($CDCl_3$): 3.57^s (1H, OH), 4.80 and 5.15^{ABq} (2H, J=16, $PhCH_2$), 6.63—7.67^m 14H, 2×Ph and Bz).

b) A solution of 450 mg of 1,3-dihydro-3-hydroxy-3-phenyl-2H-indol-2-one[6] in 2 ml of ethanol and 350 mg of benzyl bromide was added to a stirred solution of sodium ethoxide prepared from 48 mg of sodium metal and 4 ml of ethanol, then the mixture was refluxed for 3 hr. Concentration and extraction with chloroform gave an oily residue which was subjected to PLC separation using 10% ethyl acetate–benzene. Recrystallization from ethyl acetate-ether gave 439 mg (70%) of colorless crystals; this material was identical with the oxidation product described above.

Alkaline Treatment of 4-Benzyl-2,3-dihydro-3-oxo-2-phenyl-4H-1,4-benzothiazine-1,1-dioxide (15a)——A suspension of 72 mg of **15a** in 5 ml of 10% sodium hydroxide was warmed at 90° for 4 hr with stirring, then the mixture was extracted with chloroform. The chloroform extract was passed through a short column of silica gel, then recrystallized from ether to yield 52 mg (78%) of **19**, mp 135—136°. **19**, *Anal.* Calcd for $C_{20}H_{19}NO_2S$: C, 71.19; H, 5.68; N, 4.15. Found: C, 71.24; H, 5.36; N, 4.43. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380, 1605, 1325, 1145, 1115. NMR δ ppm ($CDCl_3$): 4.30^d (2H, J=4, $PhCH_2$), 4.37^s (2H, SO_2CH_2), 6.40—7.57^m (15H, 2×Ph, Bz and NH).

Hydrogen Peroxide Oxidation of 4-Benzyl-2,3-dihydro-2-methyl-4H-1,4-benzothiazin-3-one (12d)[10]——a) A stirred solution of 3.305 g of **12d** in 40 ml of acetic acid was treated with 1.40 g of 30% hydrogen peroxide, and stirring was continued for 3 hr at room temperature. Concentration and extraction with chloroform left 3.8 g of an oily residue which was subjected to PLC separation using 10% ethyl acetate–benzene to yield 44 mg (1.3%) of **13d**, mp 125° from ether, and 2.56 g (73%) of amorphous sulfoxide (**16b**).

13d, *Anal.* Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.50; H, 5.34; N, 4.99; S, 11.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3430, 1653. NMR δ ppm ($CDCl_3$): 1.65^s (3H, CH_3), 4.23^s (1H, OH), 5.02 and 5.37^{ABq} (2H, J=16.2, $PhCH_2$), 6.87—7.40^m (9H, Ph and Bz).

16b, *Anal.* Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.24; mol. wt., 285.37. Found: C, 67.37; H, 5.14; N, 4.71; S, 11.04; mol. wt., 298.5. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1050. NMR δ ppm ($CDCl_3$): A: 1.43^d (3H, J=7, CH_3), 4.10^q (1H, J=7, >C<u>H</u>–CH_3), 5.17^s (2H, $PhCH_2$), 6.85—7.72^m (9H, Ph and Bz). B: 1.73^d (3H, J=7, CH_3), 3.73^q (1H, J=7, >C<u>H</u>–CH_3), 5.03 and 5.38^{ABq} (2H, J=16.2, $PhCH_2$), 6.85—7.72^m (9H, Ph and Bz), A/B=2/3.

b) A stirred solution of 2.69 g of **12d** in 30 ml of acetic acid was treated with 1.13 g of 30% hydrogen peroxide and stirring was continued for 8 hr at room temperature. After standing overnight, the mixture was concentrated then extracted with ethyl acetate. The resulting product was chromatographed on a silica gel column, eluting successively with benzene, 10% and 50% ethyl acetate–benzene and 5% methanol–chloroform. The 50% ethyl acetate–benzene and 5% methanol–chloroform eluates were each subjected to silica gel column chromatography, while the benzene and 10% ethyl acetate–benzene eluates were mixed, then separated by TLC, developing with 10% ethyl acetate–benzene, to yield **20**, mp 117° from ether, 94 mg (3.1%), **13d**, mp 125° from ether, 402 mg (14%) and **16b**, amorph., 190 mg (6.7%).

4-Benzyl-2,3-dihydro-2-methoxy-2-methyl-4H-1,4-benzothiazin-3-one (20)——A mixture of 15 mg of sulfoxide (**16b**), a small amount of zinc dust and 2 ml of methanol was stirred for a day at room temperature, then warmed at 45—55° for 1 hr. After concentration and extraction with methylene chloride, the extract was passed through a short column of silica gel with 5% ethanol–chloroform, then the eluate was recrystallized from ether to give **20**, 10 mg (66%), which was identical with the oxidation product described above.

20, *Anal.* Calcd for $C_{17}H_{17}NO_2S$: C, 68.20; H, 5.72; N, 4.68; S, 10.71. Found: C, 68.44; H, 5.60; N, 4.70; S, 10.98. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1670. NMR δ ppm ($CDCl_3$): 1.77^s (3H, CH_3), 3.13^s (3H, OCH_3), 4.78 and 5.55^{ABq} (2H, J=16.2, $PhCH_2$), 6.67—7.33^m (9H, Ph and Bz).

4-Benzyl-2,3-dihydro-2-hydroxy-2-methyl-4H-1,4-benzothiazin-3-one (13d)——A mixture of 15 mg of sulfoxide (**16b**), a small amount of zinc dust and 2 ml of 50% aqueous acetone was worked up as described above to give 8.5 mg (57%) of **13d**, which was identical with the above oxidation product.

4-Benzyl-2,3-dihydro-2-methyl-3-oxo-4H-1,4-benzothiazin-1,1-dioxide (15d)——A stirred solution of 570 mg of sulfoxide (**16b**) in 10 ml of chloroform was treated with 350 mg of *m*-CPBA and stirring was continued for 4 hr at room temperature. The mixture was diluted with chloroform, washed twice with aqueous sodium carbonate, then concentrated. The residue was chromatographed on a silica gel column and eluted with chloroform to yield 498 mg (81%) of oily sulfone (**15d**).

15d, *Anal.* Calcd for $C_{16}H_{15}NO_3S \cdot 1/2H_2O$: C, 61.92; H, 5.20; N, 4.51; S, 10.33. Found: C, 61.91; H, 4.90; N, 4.60; S, 10.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680, 1320, 1165, 1140. NMR δ ppm ($CDCl_3$): 1.67^d (3H, J=6.8, CH_3), 4.12^q (1H, J=6.8, >C<u>H</u>–CH_3), 5.22^s (2H, $PhCH_2$), 6.92—7.95^m (9H, Ph and Bz).

Hydrogen Peroxide Oxidation of 4-Benzyl-2,3-dihydro-2-hydroxy-2-methyl-4H-1,4-benzothiazin-3-one (16b)——A stirred solution of 285 mg of **13d** in 7 ml of acetic acid was treated with 217 mg of 30% hydrogen peroxide and stirring was continued for 5 hr at room temperature. Concentration under reduced pressure and extraction with methylene chloride gave 282 mg of oily material, which was separated by TLC, developing with 12% ethyl acetate–benzene. The highest zone was recrystallized from ether to give 51 mg (21%) of 3-benzyl-2-benzothiazolone (**22**), which was identical with an authentic sample. The second fraction of disulfide (**14c**, 96 mg) was separated repeatedly by TLC, developing with benzene, to yield 75 mg (27%) of pure oily disulfide (**14c**). The lower fraction (94 mg) was also purified repeatedly by TLC, developing with 5% ethanol–chloroform, to yield 50 mg (17%) of hydroxy sulfoxide (**21**). Another spot (17 mg, 5.6%) was found which had a slightly higher *Rf* value than **21** on the TLC plate; this may have been due to another stereoisomer of **21**, although this was not ascertained.

14c, *Anal.* Calcd for $(C_{16}H_{14}NO_2S)_2$: C, 67.58; H, 4.96; N, 4.93; S, 11.28; mol. wt., 568.72. Found: C, 67.78; H, 5.15; N, 4.73; S, 11.03; mol. wt., 532.0. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1650. NMR δ ppm ($CDCl_3$): 2.23^s (6H, $2\times CH_3$), 4.22, 4.27, 5.27, 5.35$^{2\times ABq}$ (4H, $J=14$, $2\times PhCH_2$, two pairs of ABq in a 1:1 ratio), 6.43—7.47^m (18H, $2\times$Ph, $2\times$Bz).

21, *Anal.* Calcd for $C_{16}H_{15}NO_3S$: C, 63.77; H, 5.02; N, 4.65. Found: C, 63.88; H, 5.38; N, 4.39. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640, 3570, 3460, 1685, 1075. NMR δ ppm ($CDCl_3$): 1.68^s (3H, CH_3), 4.78^b (1H, OH), 5.18^s (2H, $PhCH_2$), 6.83—7.88^m (9H, Ph and Bz).