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Studies on Benzothiazoline Derivatives. III.[1] Reactions of 2,2-Disubstituted Benzothiazolines with Haloacyl Halides or Acid Anhydrides[2]

MIKIO HORI, TADASHI KATAOKA, HIROSHI SHIMIZU, and YUTAKA IMAI

Gifu College of Pharmacy[3]

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A new ring transformation of benzothiazolines to 3-oxo-2,3-dihydro-4*H*-1,4-benzothiazines or benzothiazoles was found in the reactions of 2,2-disubstituted benzothiazolines (3—5) with haloacyl halides. N,S-Bis(haloacyl) *o*-aminobenzenethiols were key intermediates of the reactions. In the case of benzothiazoline (1) and 2-methylbenzothiazoline (2), N-acylated products were obtained.

Reactions with acid chlorides or acid anhydrides gave the N-acylated compounds in good yields.

Keywords——benzothiazoline; 2,3-dihydro-4*H*-1,4-benzothiazine; haloacyl halide; N,S-bis(haloacyl) *o*-aminobenzenethiol; ring transformation; benzothiazole; acid anhydride; N-acylation

Previous papers from this laboratory have described the synthesis of benzothiazolines by the reaction of benzothiazolium salts with $LiAlH_4$ or Grignard reagents, together with their pharmacological activity,[1] and the mechanism of the oxidative ring-opening reaction in the course of their synthesis.[4]

Ring transformation of thiazolium salts has been reported by some research groups.[5] Takamizawa *et al.* reported the ring expansion of benzothiazolium salts to 3-oxo-2,3-dihydro-4*H*-1,4-benzothiazines by the use of diethyl acylphosphonate,[5c] but the mechanism of the reaction was entirely different from that of the reactions described in the present paper. In this paper we report a new ring transformation of benzothiazolines to benzothiazines or benzothiazoles, found in the reaction of 2,2-disubstituted benzothiazolines with haloacyl halides or acid anhydrides.

The reactions of benzothiazolines and chloroacetyl chloride are shown in Chart 1.

Benzothiazoline (**1**) and 2-methylbenzothiazoline (**2**) formed N-chloroacetylated products **6** (96%) and **7** (49%), respectively. In contrast, 2,2-dimethylbenzothiazoline (**3**) yielded ring-expanded products, 3-oxo-2,3-dihydro-4*H*-1,4-benzothiazines **9** (11%) and **10** (9%), and 2-chloromethylbenzothiazole (**11**, 47%) along with **8** (17%). The reaction of 2-methyl-2-phenylbenzothiazoline (**4**) gave **10** (36%), **11** (25%) and acetophenone (**12**, 58%). Under the same conditions, 2,2,3-trimethylbenzothiazoline (**5**) afforded only the ring-expanded product **13** (57%). Results obtained from the reaction of compounds **1**, **3** and **4** with chloroacetyl chloride are summarized in Table I.

These results show that the bulkier the substituents at the C_2 position of compounds **1**—**5**, the more easily the benzothiazoline ring is opened.

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[3] Location: *5-6-1 Mitahora-Higashi, Gifu 502, Japan.*

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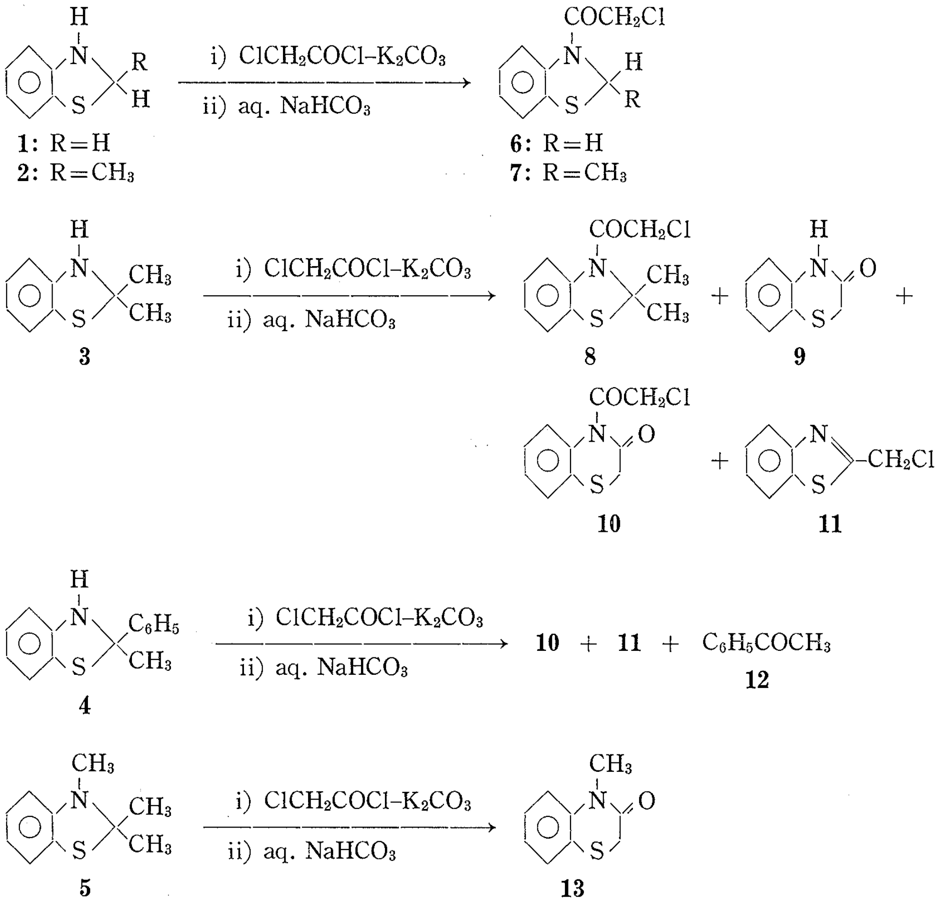

Chart 1

Table I. Product Distribution in the Reaction of Benzothiazolines with Chloroacetyl Chloride

Compounds	Products and product ratio[a]		
	Molar ratio of benzothiazoline to $ClCH_2COCl$		
	2 : 1	1 : 1.5	1 : 5
1	**1**(1), **6**(1)	**6**	**6**
3	**3**(10.6), **8**(1), **11**(6.7)	**3**(9.7), **8**(1), **11**(6.5)	**3**(0.2), **8**(1), **10**(0.94),[b] **11**(2.4)
4	**4**(1.76), **11**(1)	**10**(0.65), **11**(1)	**10**(2.6), **11**(1)

[a] The product distribution was measured by NMR spectroscopy.

[b] Although the reaction of **3** afforded **9**, as depicted in Chart 1, **9** was not detected as a product here. The difference between two reactions is due to the treatment of the product by TLC on silica gel followed by exposure to iodine. Treatment of an authentic sample of **10** on silica gel TLC plates with iodine caused dechloroacetylation to give **9** quantitatively.

We next investigated the reactions of **3** with various haloacyl halides; the results are shown in Chart 2 and Table II. A solution of **3** in ether or benzene was allowed to react with an excess of haloacyl halides (3—5 mol) in the presence of a base and then treated with aq. $NaHCO_3$. On treatment with α- or β-bromoacyl chloride, **3** yielded a ring expansion product such as **14**, **15** or **16**. On the other hand, the reaction with trichloroacetyl chloride afforded 2-trichloromethylbenzothiazole (**20**) in 96% yield, and the reaction with ethyl chloroformate gave 3-ethoxycarbonyl-2,2-dimethylbenzothiazoline (**17**) together with the disulfide **21**. Moreover, in the case of acetyl or propionyl chloride **3** produced only the N-acylated benzothiazoline **18** or **19**.

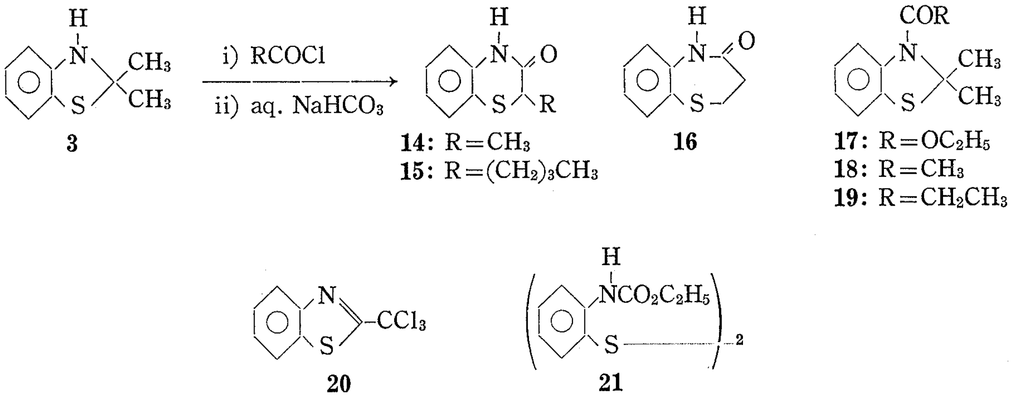

Chart 2

TABLE II. Products of the Reaction of 3 with Acyl Halides

Reagents	Products (% yield)
$CH_3\overset{Br}{C}HCOCl$	**14**(22)
$CH_3(CH_2)_3\overset{Br}{C}HCOCl$	**15**(18)
$BrCH_2CH_2COCl$	**16**(16)
Cl_3CCOCl	**20**(96)
$ClCO_2C_2H_5$	**17**(55), **21**(34)
CH_3COCl	**18**(96)
CH_3CH_2COCl	**19**(62), **3**(22)

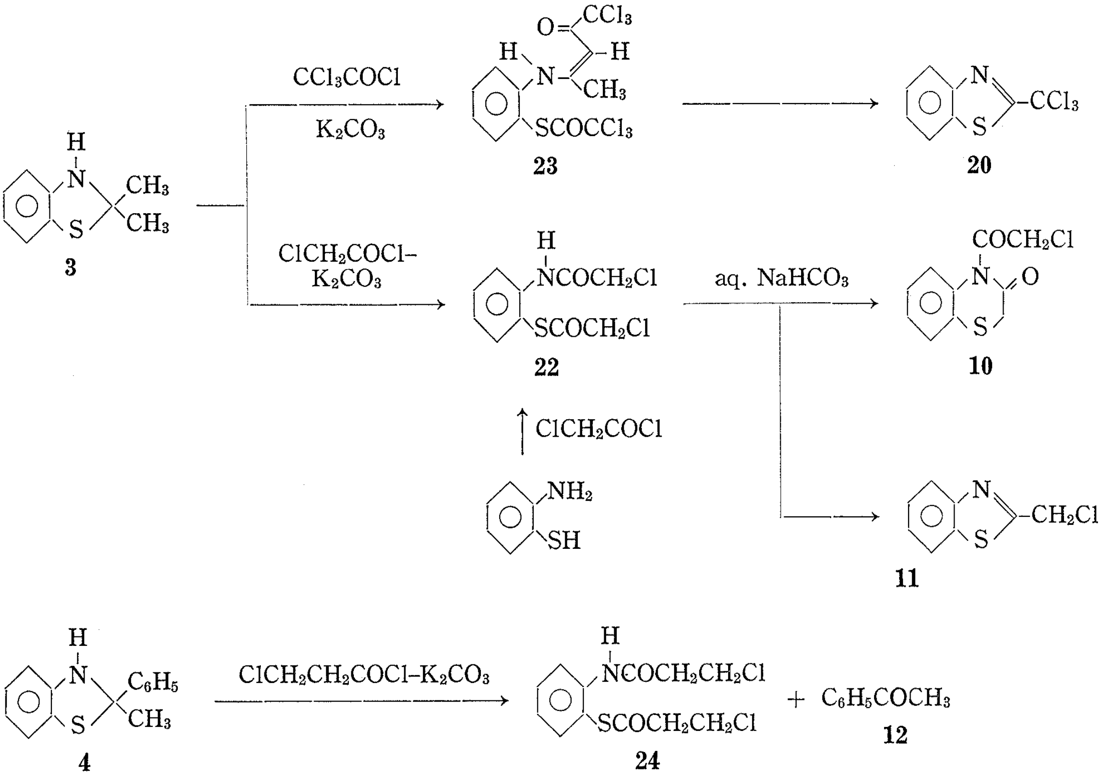

Chart 3

The results obtained from the reactions in Chart 2 show that haloacyl halides cause the ring transformation of benzothiazolines to benzothiazines or benzothiazoles.

To obtain mechanistic information on this ring transformation the following reactions were examined further.

When the reaction mixture was worked up without aq. $NaHCO_3$, N,S-bis(chloroacyl) *o*-aminobenzenethiol, **22** (64%) or **24** (76%) was obtained from the reaction of **3** or **4** with chloroacyl chlorides, respectively. Compound **22** was identical with an authentic sample synthesized from *o*-aminobenzenethiol and chloroacetyl chloride. Treatment of **22** with aq. $NaHCO_3$ resulted in the formation of **10** (24%) and **11** (72%). The nuclear magnetic resonance (NMR) spectrum of the reaction mixture of **3** and chloroacetyl chloride (5 mol) in $CDCl_3$ showed peaks at δ 2.43 (3H, s, $=-CH_3$), 2.94 (3H, s, $=-CH_3$), 4.43 (2H, s, CH_2) of S-(2-isopropylideneaminophenyl)thiochloroacetate (**25**) hydrochloride, and these peaks disappeared on addition of aq. $NaHCO_3$. In contrast, the reaction of **3** and trichloroacetyl chloride gave the enaminoketone **23** (15%) which was hydrolyzed quantitatively to 2-trichloromethylbenzothiazole (**20**) on standing.

On the basis of the results described above, we propose that the mechanism of the reaction of 2,2-dimethylbenzothiazoline (**3**) and chloroacetyl chloride, as an example of the reaction of benzothiazoline and haloacyl chloride, is as shown in Chart 4.

Compound **8** was inert to acyl halide. Consequently it is not associated with the ring transformation.

Tautomerism between benzothiazolines and Schiff's bases has been discussed in several reports. Goetz has reported that 2-acylbenzothiazolines behave as the closed ring tautomer under the conditions of infrared (IR) and ultraviolet (UV) measurement in the solid state

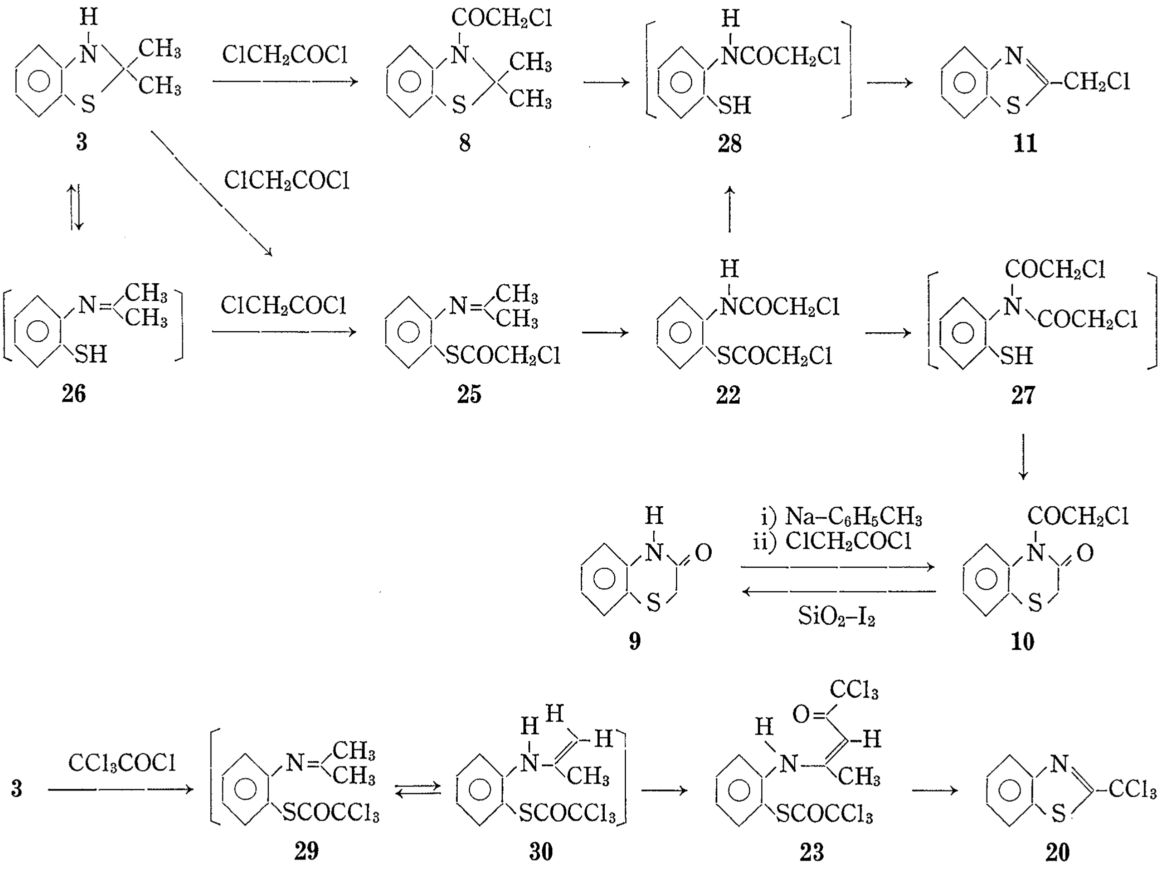

Chart 4

or in solution, but they were easily ring-opened by reaction with potassium *t*-butoxide.6) On the other hand, Braithwaite *et al.* and Uhlemann *et al.* found that benzothiazolines were ring-opened to Schiff's bases in their reactions with metallic salts.7) Tautomerization of **3** yields the Schiff's base **26**, which is acylated to **25** by chloroacetyl chloride. Acylation and hydrolysis of **25**8) yields **22**, which yields **27** by S→N acyl migration in competition with the hydrolysis of the thiol ester to **28**.9) Compound **27** cyclizes to **10**, which is acylated to **9** during thin-layer chromatography (TLC) on silica gel and successive exposure to iodine. On the other hand, cyclization of **28** yields **11**.

A mechanistic interpretation of the reaction of **3** with trichloroacetyl chloride is also shown in Chart 4. The initial intermediate **29** isomerizes to the enamine **30**, which is further acylated **23**. The enaminoketone **23** decomposes to **20** on standing. This reaction did not yield benzothiazine derivatives, but the benzothiazole derivative **20**.

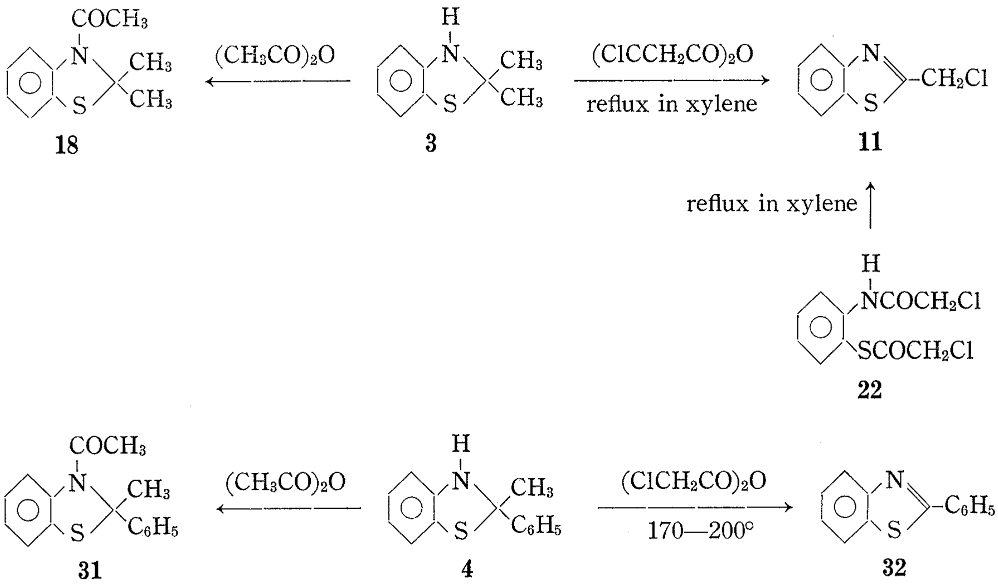

Chart 5

Anticipating ring transformation, we also investigated the reaction of **3** or **4** with acid anhydrides as shown in Chart 5. The acylated products **18** (93%) and **31** (81.8%) were obtained by the reaction of **3** and **4** with acetic anhydride, respectively. However, the reaction with chloroacetic anhydride gave **11** (94.1%) and 2-phenylbenzothiazole (**32**, 43.7%). Compound **22** was thought to be an intermediate of the reaction of **3** and chloroacetic anhydride. In fact, when **22** was refluxed in toluene for 4 hr, it was transformed into **11** in a yield of 87%. Heating of **4** with chloroacetic anhydride resulted in the formation of **32** with elimination of methane.10)

Experimental

Melting points were measured on a Yanagimoto micromelting point apparatus and are uncorrected. Infrared (IR) spectra were determined on a JASCO IRA-1 machine. Nuclear magnetic resonance (NMR) spectra were determined on a Hitachi R-20B spectrometer; chemical shifts are given in parts per million

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relative to tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a Hitachi RMU-6E spectrometer at an ioning voltage of 70 eV.

Reaction of Benzothiazoline (1) with Chloroacetyl Chloride——Chloroacetyl chloride (6.746 g, 60 mmol) in dry ether was added to a suspension of **1**[11] (1.637 g, 12 mmol) and K_2CO_3 (12.358 g, 90 mmol) in dry ether and the mixture was stirred for 24 hr at room temperature then filtered. The filtrate was washed with aq. $NaHCO_3$, dried and evaporated down. The residue was recrystallized from hexane to give 3-chloroacetylbenzothiazoline (**6**) (2.454 g, 96%) as colorless prisms, mp 118—120°. *Anal.* Calcd. for C_9H_8ClNOS: C, 50.58; H, 3.78; N, 6.56. Found: C, 50.56; H, 3.75; N, 6.75. IR ν_{max}^{KBr} cm^{-1}: 1660 (CO). NMR ($CDCl_3$) δ: 4.26 (2H, s, $COCH_2Cl$), 5.35 (2H, s, S–CH_2–N), 6.70—7.70 (3H, m, ArH), 7.70—8.30 (1H, m, ArH).

Reaction of 2-Methylbenzothiazoline (2) with Chloroacetyl Chloride——Chloroacetyl chloride (2.732 g, 25 mmol) in dry ether was added to a suspension of **2**[12] (0.731 g, 5 mmol) and K_2CO_3 (5 g, 36 mmol) in dry ether. The mixture was stirred for 17 hr at room temperature and filtered. The filtrate was washed with aq. $NaHCO_3$, dried and evaporated down. 2-Chloromethylbenzothiazole (**11**) and 4-chloroacetyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazine (**10**) were not present in the residue as determined from the NMR spectrum. The residue was chromatographed on silica gel using benzene as an eluent to give 3-chloroacetyl-2-methylbenzothiazoline (**7**). This was recrystallized from ether–pet. ether as colorless needles (0.54 g, 49%), mp 79—81°. *Anal.* Calcd. for $C_{10}H_{10}ClNOS$: C, 52.74; H, 4.43; N, 6.15. Found: C, 53.01; H, 4.46; N, 6.21. IR ν_{max}^{KBr} cm^{-1}: 1680 (CO). NMR ($CDCl_3$) δ: 1.61 (3H, d, $J=7.5$ Hz, CH_3), 4.26 (2H, AB q, $J_{AB}=12.5$ Hz, $\Delta\nu_{AB}=6.3$ Hz), 5.95 (1H, broad q, $J=7.5$ Hz, C_2–H), 6.90—7.90 (4H, m, ArH).

Reaction of 2,2-Dimethylbenzothiazoline (3) with Chloroacetyl Chloride——A mixture of **3**[10] (0.825 g, 5 mmol), K_2CO_3 (3.45 g, 25 mmol) and chloroacetyl chloride (2.825 g, 25 mmol) in dry ether was stirred for 8 hr at room temperature. After removal of the inorganic material the filtrate was washed with aq. $NaHCO_3$, dried and evaporated down. A mixture of EtOH-pet. ether was added to the residue and the crystals formed were collected by filtration. Recrystallization from EtOH–hexane gave 4-chloroacetyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazine (**10**) (0.113 g, 9%) as colorless needles, mp 112—113°. *Anal.* Calcd. for $C_{10}H_8ClNO_2S$: C, 49.69; H, 3.34; N, 5.80. Found: C, 49.44; H, 3.40; N, 5.59. IR ν_{max}^{KBr} cm^{-1}: 1690 (CO). NMR ($CDCl_3$) δ: 3.48 (2H, s, S–CH_2CO), 4.85 (2H, s, $COCH_2Cl$), 7.00—7.65 (4H, m, ArH). This sample was identified by comparison of its IR and NMR spectra with those of an authentic sample synthesized from **9** and chloroacetyl chloride and by mixed melting point determination. An oily residue from the filtrate of a mixture of EtOH–pet. ether was separated by preparative TLC on silica gel developing with benzene into 3 products, 3-chloro-2,2-dimethylbenzothiazoline (**8**) (0.201 g, 17%), 2-chloromethylbenzothiazole (**11**) (0.436 g, 47%) and 3-oxo-2,3-dihydro-4*H*-1,4-benzothiazine (**9**) (0.093 g, 11%). Compound **8** was recrystallized from EtOH as colorless prisms, mp 104—106°. *Anal.* Calcd. for $C_{11}H_{12}ClNOS$: C, 54.65; H, 5.00; N, 5.79. Found: C, 54.64; H, 5.09; N, 5.85. IR ν_{max}^{KBr} cm^{-1}: 1660 (CO). NMR ($CDCl_3$) δ: 1.95 (6H, s, $C(CH_3)_2$), 4.29 (2H, s, CH_2), 7.05—7.35 (4H, m, ArH). Compound **11** was a colorless oil, bp 118—120° (1.15 mmHg). NMR ($CDCl_3$) δ: 4.92 (2H, s, CH_2), 7.20—7.70 (2H, m, ArH), 7.70—8.25 (2H, m, ArH). The sample was identical with an authentic sample[13] with regard to the IR and NMR spectra. Compound **9** was recrystallized from EtOH as colorless needles, mp 183—184°. *Anal.* Calcd. for C_8H_7NOS: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.09; H, 4.14; N, 8.39. IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1650 (CO). NMR (CF_3CO_2H) δ: 3.63 (2H, s, CH_2), 6.90—7.60 (4H, m, ArH), 9.95 (1H, broad s, NH). The sample was identical with an authentic sample[14] on the basis of IR and NMR spectra and mixed melting point determination.

4-Chloroacetyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazine (10)——Sodium metal (0.345 g, 15 mmol) was added to a solution of **9** (1.65 g, 10 mmol) in dry xylene and the mixture was heated for 3 hr. A solution of chloroacetyl chloride (1.695 g, 15 mmol) in dry xylene was added in the cold, and the mixture was stirred for 9 hr at room temperature. Aq. $NaHCO_3$ was added and the organic layer was separated. The aqueous layer was extracted with ether. The extract was combined with the organic layer, which was then dried and evaporated down. Crystals obtained were recrystallized from EtOH–hexane to give colorless needles (0.995 g, 41%), mp 112—113°. *Anal.* Calcd. for $C_{10}H_8ClNO_2S$: C, 49.69; H, 3.34; N, 5.80. Found: C, 49.61; H, 3.30; N, 5.75. IR ν_{max}^{KBr} cm^{-1}: 1690 (CO). NMR ($CDCl_3$) δ: 3.48 (2H, s, $COCH_2S$), 4.85 (2H, s, $COCH_2Cl$), 7.00—7.65 (4H, m, ArH).

Dechloroacetylation of 10 to 9 by Chromatography on Silica Gel——A solution of **10** (0.100 g) in $CHCl_3$ was subjected to preparative TLC on silica gel (Wakogel B-10), developing with benzene, and the TLC plates were exposed to iodine for 10 min. The product was extracted with $CHCl_3$ and identified as 3-oxo-2,3-dihydro-4*H*-1,4-benzothiazine (**9**) (0.065 g, 95.5%). Compound **10** was also decomposed by column chromatography on silica gel (Wakogel C-200).

Reaction of 2-Methyl-2-phenylbenzothiazoline (4) with Chloroacetyl Chloride——K_2CO_3 (10.35 g, 75 mmol) and an ethereal solution of chloroacetyl chloride (5.65 g, 50 mmol) were added to an ethereal solution

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of 4[10] (2.27 g, 10 mmol). After stirring for 24 hr at room temperature, the reaction mixture was filtered and the filtrate was treated with aq. $NaHCO_3$ for 1 hr. The organic layer was separated, dried and evaporated down. The NMR spectrum of the residue indicated the presence of **10**, **11** and acetophenone (**12**). The residue was treated with EtOH–pet. ether to give crystals of **10** (0.88 g, 36%). The filtrate was evaporated to dryness and separated by preparative TLC on silica gel using benzene to give **11** (0.451 g, 25%) and **12** (0.697 g, 58%). These 3 products were identical with authentic samples as regards IR and NMR spectra.

Reaction of 2,2,3-Trimethylbenzothiazoline (5) with Chloroacetyl Chloride——Chloroacetyl chloride (3 g, 25 mmol) in dry ether was added to a suspension of 5[15] (0.895 g, 5 mmol) and K_2CO_3 (5 g, 37.5 mmol) in dry ether and the mixture was refluxed for 4 hr with stirring. The cooled mixture was filtered and the filtrate was dried and evaporated down. The residue was purified by column chromatography on silica gel using ether–pet. ether (1 : 1) as an eluent and recrystallized from EtOH–hexane to give 4-methyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazine (**13**) (0.51 g, 57%) as colorless prisms, mp 53—54°. *Anal.* Calcd. for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.82. Found: C, 60.13; H, 5.02; N, 8.12. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1670 (CO). NMR ($CDCl_3$) δ: 3.37 (2H, s, C_2–H), 3.42 (3H, s, N–CH_3), 6.86—7.52 (4H, m, ArH).

NMR Measurement of the Products from Reactions of Benzothiazolines (1, 3 and 4) with Chloroacetyl Chloride——A solution of chloroacetyl chloride in dry ether was added to a suspension of benzothiazoline and K_2CO_3 (5 eq.) in dry ether. The resulting mixture was stirred for 18 hr at room temperature and excess K_2CO_3 was filtered off. The filtrate was washed with aq. $NaHCO_3$, dried and evaporated down. The residue was dissolved in $CDCl_3$ and subjected to NMR measurement. Peaks used for the measurement were ($CDCl_3$) δ: **1**: 4.83 (CH_2); **3**: 1.72 ($C(CH_3)_2$); **4**: 2.02 (CH_3); **6**: 4.24 ($COCH_2Cl$), 5.32 (NCH_2S); **8**: 1.95 ($C(CH_3)_2$), 4.29 ($COCH_2Cl$); **10**: 3.43 (SCH_2CO), 4.85 ($COCH_2Cl$); **11**: 4.93 (CH_2Cl). The results are listed in Table I.

Reaction of 3 with *α*-Bromopropionyl Chloride——A solution of α-bromopropionyl chloride (5.145 g, 30 mmol) in dry acetone was added to a mixture of **3** (1.65 g, 10 mmol) and Et_3N (4.545 g, 45 mmol) in dry acetone. The mixture was stirred for 8 hr at room temperature. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and aq. $NaHCO_3$ was added. The resulting mixture was stirred for 1 hr at room temperature. The organic layer was separated, dried and evaporated down. The residue was separated by preparative TLC on silica gel using ether-pet. ether (1 : 6) as an eluent. 2-Methyl-2-oxo-2,3-dihydro-4*H*-1,4-benzothiazine (**14**) was obtained as colorless needles (0.394 g, 22%), mp 132—133° by recrystallization from pet. ether. *Anal.* Calcd. for C_9H_9NOS: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.54; H, 5.11; N, 7.80. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3300 (NH), 1660 (CO). NMR ($CDCl_3$) δ: 1.49 (3H, d, $J=7.0$ Hz, C_2–CH_3), 3.57 (2H, q, $J=7.0$ Hz, C_2- H), 6.80—7.50 (4H, m, ArH), 9.95 (1H, broad s, NH).

Reaction of 3 with *α*-Bromohexanoyl Chloride——An ethereal solution of α-bromohexanoyl chloride (6.405 g, 30 mmol) was added to a suspension of **3** (1.65 g, 10 mmol) and K_2CO_3 (6.21 g, 45 mmol) in dry ether and the mixture was refluxed for 8 hr. The inorganic material was filtered off and aq. $NaHCO_3$ was added to the solution. The mixture was stirred for 1 hr at room temperature. The ether layer was separated, dried and evaporated down. Chromatography on silica gel developing with ether–pet. ether (1 : 1) gave 2-*n*-butyl-3-oxo-2,3-dihydro-4*H*-1,4-benzothiazine (**15**) as colorless needles (0.399 g, 18%), mp 96—97° by recrystallization from pet. ether. *Anal.* Calcd. for $C_{12}H_{15}NOS$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.02; H, 6.86; N, 6.07. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3300 (NH), 1650 (CO). NMR ($CDCl_3$) δ: 0.60—2.40 (9H, m, $(CH_2)_3CH_3$), 3.20—3.65 (1H, m, C_2–H), 6.70—7.55 (4H, m, ArH), 10.05 (1H, broad s, NH).

Reaction of 3 with *β*-Bromopropionyl Chloride——A mixture of **3** (1.65 g, 10 mmol), β-bromopropionyl chloride (8.575 g, 50 mmol) and K_2CO_3 (9.7 g, 70 mmol) in dry ether was stirred for 24 hr at room temperature. After removal of the inorganic material the filtrate was treated with aq. $NaHCO_3$ for 1 hr at room temperature. The organic layer was separated, dried and evaporated down. The residue was purified by column chromatography on silica gel developing with benzene. 4-Oxo-2,3-dihydro-5*H*-1,5-benzothiazepine (**16**) obtained was identical with an authentic sample[16] by comparison of their IR and NMR spectra and mixed melting point determination.

Reaction of 3 with Ethyl Chloroformate——K_2CO_3 (3.5 g, 25 mmol) and then an ethereal solution of ethyl chloroformate (2.713 g, 25 mmol) was added to an ethereal solution of **3** (0.825 g, 5 mmol). The mixture was allowed to react for 6 hr at room temperature, but the reaction scarcely proceeded. It was then refluxed for 3 hr, but the reaction proceeded only to the extent of about 7.5%. Therefore, an excess of Et_3N was added to the mixture. The resulting reaction mixture was refluxed for 6 hr at room temperature and then filtered. The filtrate was concentrated under reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was stirred with aq. $NaHCO_3$ for 0.5 hr, separated, dried and evaporated down. The residue was chromatographed on silica gel using benzene to give 3-ethoxycarbonyl-2,2-dimethylbenzothiazoline (**17**) (0.65 g, 55%) and *o*-(N-ethoxycarbonylamino)phenyl disulfide (**21**) (0.335 g, 34%). Compound **17** was a colorless oil, bp 118—120° (2 mmHg). *Anal.* Calcd. for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90. Found: C, 61.15; H, 6.52; N, 5.66. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1710 (CO). NMR ($CDCl_3$) δ: 1.39 (3H, t, $J=7$ Hz, CH_2-

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15) A.I. Kiprianov and V.A. Portnyagina, *Zhur. Obshchei Khim.*, **25**, 2257 (1955) [*C.A.*, **50**, 9378*h* (1956)].

16) W.H. Mills and J.B. Whitworth, *J. Chem. Soc.*, **126**, 2738 (1927).

CH_3), 1.94 (6H, s, $C(CH_3)_2$), 4.29 (2H, q, $J=7$ Hz, CH_2CH_3), 6.75—7.15 (3H, m, ArH), 7.50—7.80 (1H, m, ArH). Compound **21** was recrystallized from pet. ether as colorless needles, mp 95—96°. *Anal.* Calcd. for $C_{18}H_{20}N_2O_4S_2$: C, 55.08; H, 5.14; N, 7.14. Found: C, 55.04; H, 5.15; N, 7.11. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3360 (NH), 1740, 1700 (CO). NMR ($CDCl_3$) δ: 1.30 (3H, t, $J=7$ Hz, CH_3), 4.19 (2H, q, $J=7$ Hz, CH_2), 6.75—7.15 (1H, m, ArH), 7.20—7.80 (3H, m, ArH), 8.10—8.36 (2H, m, ArH). MS *m/e*: 392 (M^+), 151 (100).

Reaction of 3 with Acetyl Chloride——Acetyl chloride (1.57 g, 20 mmol) in dry ether was added to a suspension of **3** (1.65 g, 10 mmol) and K_2CO_3 (4.2 g, 30 mmol) in dry ether. The mixture was refluxed for 24 hr, cooled and filtered. The filtrate was washed with aq. $NaHCO_3$, dried and evaporated down. The residue was distilled *in vacuo* to give 3-acetyl-2,2-dimethylbenzothiazoline (**18**) as a colorless oil (1.98 g, 96%), bp 118—120° (1 mmHg), which solidified and was recrystallized from pet. ether as colorless prisms, mp 49—51°. *Anal.* Calcd. for $C_{11}H_{13}NOS$: C, 63.73; H, 6.31; N, 6.74. Found: C, 63.57; H, 6.13; N, 6.56. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1670 (CO). NMR ($CDCl_3$) δ: 1.95 (6H, s, $C(CH_3)_2$), 2.37 (3H, s, $COCH_3$), 6.95—7.30 (4H, m, ArH).

Reaction of 3 with Propionyl Chloride——Propionyl chloride (4.7 g, 50 mmol) in dry ether was added dropwise to an ice-cold suspension of **3** (1.65 g, 10 mmol) and K_2CO_3 (11 g, 75 mmol) in dry ether. The resulting mixture was refluxed for 12 hr and filtered. The precipitate was washed with dry acetone. The filtrate and the washings were combined and concentrated under reduced pressure. The residue was dissolved in dry ether and the insoluble solid was collected by filtration. It was recrystallized from a mixture of dry acetone and dry ether to afford 2,2-dimethylbenzothiazoline hydrochloride (0.441 g, 22%) as colorless needles, mp 137° (dec.). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3000—2200 (NH_2^+). NMR ($CDCl_3$) δ: 2.05 (6H, s, $C(CH_3)_2$), 7.00—7.40 (3H, m, ArH), 7.40—7.70 (1H, m, ArH), 9.83 (2H, broad s, NH_2^+). It was hydrolyzed very easily by water to form acetone. The filtrate was concentrated and distilled *in vacuo* to give 2,2-dimethyl-3-propionylbenzothiazoline (**19**) (1.365 g, 62%) as a colorless oil, bp 104—106° (0.8 mmHg). The oil solidified on standing and melted at 30—31°. *Anal.* Calcd. for $C_{12}H_{15}NOS$: C, 65.12; H, 6.83; N, 6.33. Found: C, 65.23; H, 6.76; N, 6.25. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1670 (CO). NMR ($CDCl_3$) δ: 1.24 (3H, t, $J=7.5$ Hz, $CH_2\underline{CH_3}$), 1.95 (6H, s, $C(CH_3)_2$), 2.65 (2H, q, $J=7.5$ Hz, $\underline{CH_2}CH_3$), 6.95—7.30 (4H, m, ArH).

Reaction of 3 with Trichloroacetyl Chloride——K_2CO_3 (4.14 g, 30 mmol) and then trichloroacetyl chloride (2.73 g, 15 mmol) were added to a solution of **3** (0.825 g, 5 mmol) in dry benzene. The mixture was refluxed for 8 hr, cooled and filtered. The filtrate was stirred with aq. $NaHCO_3$ for 0.5 hr, separated, dried and evaporated down. The residue was chromatographed on silica gel, developing with benzene–hexane (1:2), to give 2-trichloromethylbenzothiazole (**20**). Compound **20** was distilled *in vacuo* as a colorless oil, bp 133—135° (1 mmHg) (1.208 g, 96%). *Anal.* Calcd. for $C_8H_4Cl_3NS$: C, 38.04; H, 1.60; N, 5.55. Found: C, 38.33; H, 1.60; N, 5.96. NMR (CCl_4) δ: 7.25—7.80 (2H, m, ArH), 7.80—8.30 (2H, m, ArH).

Reaction of 3 with Chlroacetyl Chloride without aq. $NaHCO_3$ Treatment——Chloroacetyl chloride (5.5 g, 50 mmol) was added to a suspension of **3** (1.65 g, 10 mmol) and K_2CO_3 (9 g, 65 mmol) in dry ether. The resulting mixture was stirred for 8 hr at room temperature and then for 0.5 hr under reflux. The cooled mixture was filtered and the filtrate was concentrated to dryness. The residual solid was recrystallized from EtOH–hexane to give N,S-bis(chloroacetyl) *o*-aminobenzenethiol (**22**) (1.782 g, 64%) as colorless prisms, mp 80—81°. *Anal.* Calcd. for $C_{10}H_9Cl_2NO_2S$: C, 43.18; H, 3.26; N, 5.04. Found: C, 43.26; H, 3.25; N, 5.02. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3300 (NH), 1690 (CO). NMR ($CDCl_3$) δ: 4.18 (2H, s, CH_2), 4.30 (2H, s, CH_2), 7.00—7.75 (3H, m, ArH), 8.20—8.50 (1H, m, ArH), 8.85 (1H, broad s, NH).

N,S-Bis(chloroacetyl) *o*-Aminobenzenethiol (22)——K_2CO_3 (9 g, 65 mmol) and then chloroacetyl chloride (5.6 g, 50 mmol) were added to a solution of *o*-aminobenzenethiol (1.25 g, 10 mmol) in dry ether. After stirring for 15 hr at room temperature the mixture was filtered to remove the inorganic materials and the filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOH–hexane to give colorless prisms (2.3 g, 83%), mp 80—81°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3300 (NH), 1690 (CO). NMR ($CDCl_3$) δ: 4.18 (2H, s, CH_2), 4.30 (2H, s, CH_2), 7.00—7.25 (3H, m, ArH), 8.20—8.50 (1H, m, ArH), 8.85 (1H, broad s, NH).

Hydrolysis of 22——A solution of **22** (1.15 g) in ether was stirred with aq. $NaHCO_3$ (*ca.* 5%). After evolution of carbon dioxide had ceased, the organic layer was separated and the aqueous layer was extracted with ether. The organic layer and the extract were combined, dried and evaporated down. The NMR spectrum of the residue showed that it was a mixture of **10** and **11** in a ratio of 1:3. A mixture of EtOH–pet. ether was added to it and crystals formed were collected by filtration. The crystals were **11** (0.545 g, 72%). From the filtrate, **10** (0.24 g, 24%) was obtained.

Reaction of 3 with Trichloroacetyl Chloride without aq. $NaHCO_3$ Treatment——A solution of trichloroacetyl chloride (2.73 g, 15 mmol) in dry ether was added to a suspension of **3** (0.825 g, 5 mmol) and K_2CO_3 (4.14 g, 30 mmol) in dry ether, and the resulting mixture was refluxed for 8 hr. Inorganic material was removed by filtration and the filtrate was concentrated. The residue was recrystallized from pet. ether to give S-[*o*-(5,5,5-trichloro-2-methyl-4-oxo-2-penten-2-ylamino)phenyl] thiotrichloroacetate (**23**) (15%) as colorless prisms, mp 134—135°. *Anal.* Calcd. for $C_{13}H_9Cl_6NO_2S$: C, 34.24; H, 1.99; N, 3.07. Found: C, 34.23; H, 1.95; N, 3.13. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3260—2800 (NH), 1710 (CO), 1580 (C=C–CO). NMR ($CDCl_3$) δ: 2.10 (3H, broad s, $=\!-CH_3$), 5.86 (1H, broad s, $=\!-H$), 7.20—7.80 (4H, m, ArH), 12.00 (1H, broad s, NH). MS *m/e*: 453 (M^+), 163 (100). On standing **27** changed into **15**, which was identical with an authentic sample.

Reaction of 4 with β-Chloropropionyl Chloride without aq. $NaHCO_3$ Treatment——K_2CO_3 (5.175 g, 37.5 mmol) and then a solution of β-chloropropionyl chloride (3.175 g, 25 mmol) in dry ether were added to a solution of **4** (1.135 g, 5 mmol) in dry ether. The reaction mixture was stirred for 24 hr at room temperature and then cooled. After removal of the inorganic material, the filtrate was added to water and the resulting mixture was stirred for 0.5 hr at room temperature. The organic layer was dried and evaporated down. The residual oil was solidified by trituration with EtOH–pet. ether. Crystals were collected by filtration and recrystallized from EtOH to give N,S-bis(β-chloropropionyl) *o*-aminobenzenethiol (**24**) (0.543 g, 36%) as colorless needles, mp 139—140°. The filtrate in EtOH-pet. ether was concentrated and then subjected to column chromatography on silica gel using benzene as an eluent. Acetophenone (**12**) (0.454 g, 76%) and **24** (0.421 g, 28%) were obtained. *Anal.* Calcd. for $C_{12}H_{13}Cl_2NO_2S$: C, 47.07; H, 4.28; N, 4.57. Found: C, 47.09; H, 4.21; N, 4.51. IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1690 (CO). NMR ($CDCl_3$) δ: 2.82 (2H, t, $J=7$ Hz, $CONH_2$), 3.14 (2H, t, $J=7$ Hz, $COCH_3$), 3.87 (4H, t, $J=7$ Hz, CH_2Cl), 7.00—8.05 (3H, m, ArH), 7.85 (1H, broad s, NH), 8.20—8.55 (1H, m, ArH).

Reaction of 3 with Acetic Anhydride——A mixture of **3** (1.65 g, 10 mmol) and acetic anhydride (4.08 g, 40 mmol) was refluxed for 4 hr. Aq. K_2CO_3 was added and the resulting mixture was stirred for 0.5 hr. The organic layer was separated, dried and evaporated down. The residue was distilled *in vacuo* to give **21** (1.93 g, 93%) as a colorless oil, bp 118—120° (1 mmHg), which solidified and was recrystallized from pet. ether as colorless prisms, mp 49—51°. This was identical with an authentic sample obtained from **3** and acetyl chloride as regards IR and NMR spectra.

Reaction of 3 with Chloroacetic Anhydride——A solution of **3** (1.65 g, 10 mmol) and chloroacetic anhydride (6.84 g, 40 mmol) in dry xylene was refluxed for 8 hr. After cooling, aq. $NaHCO_3$ was added. The resulting mixture was stirred for 1 hr at room temperature. The organic layer was separated and the aqueous layer was extracted with chloroform. The organic layer and the $CHCl_3$ extract were combined, dried and evaporated down. The residual oil was distilled *in vacuo* to give 2-chloromethylbenzothiazole (**11**) (1.727 g, 94.1%), which was identical with an authentic sample on the basis of their NMR and IR spectra.

Thermolysis of 22——A solution of **22** (0.556 g, 20 mmol) in dry toluene was refluxed for 20 hr. A part of the mixture was concentrated and the residue was checked by NMR spectroscopy. The NMR spectrum showed the formation of **8**. Aq. $NaHCO_3$ was added to the solution, which was then stirred for 1 hr at room temperature. The organic layer was separated, dried and evaporated down. The residue was distilled *in vacuo* to give **11** (0.320 g, 87%), which was identical with an authentic sample.

Reaction of 4 with Acetic Anhydride——A mixture of **4** (2.27 g, 10 mmol) and acetic anhydride (4.08 g) was refluxed for 4 hr and concentrated under reduced pressure. The oily residue was dissolved in CH_2Cl_2 and treated with aq. $NaHCO_3$ at room temperature. The organic layer was dried and evaporated down. Distillation of the residue gave 3-acetyl-2-methyl-2-phenylbenzothiazoline as a colorless oil (2.191 g, 81.8%), bp 165—168° (1 mmHg), which soon solidified. The solid was recrystallized from pet. ether as colorless prisms, mp 117—118°. *Anal.* Calcd. for $C_{16}H_{15}NOS$: C, 71.33; H, 5.61; N, 5.20. Found: C, 71.06; H, 5.68; N, 4.97. IR ν_{max}^{KBr} cm^{-1}: 1650 (CO). NMR ($CDCl_3$) δ: 2.08 (3H, s, C_2–CH_3), 2.35 (3H, s, $COCH_3$), 7.00—7.85 (9H, m, ArH).

Reaction of 4 with Chloroacetic Anhydride——A mixture of **4** (2.27 g, 10 mmol) and chloroacetic anhydride (2.6 g, 15 mmol) was heated for 8 hr at 170—200° with stirring, then cooled. The reaction mixture was dissolved in CH_2Cl_2 and aq. $NaHCO_3$ was added. It was stirred for 1 hr at room temperature. The CH_2Cl_2 layer was separated, dried and evaporated down. The residue was purified by column chromatography on silica gel using benzene to give 2-phenylbenzothiazole (**32**) (0.922 g, 43.7%), which was recrystallized from EtOH as colorless prisms, mp 112—113°. The sample was identified from the IR and NMR spectrum and by mixed melting point determination with an authentic sample.