indicating that the N-alkylated complexes maintain the diamagnetic square-planar geometry even in the coordinating solvents.

Cyclic voltammograms for the Ni(II) complexes of N-Me_2**A**, N-Et_2**A**, and N-Me_2**B** indicate that the complexes exhibit two one-electron waves corresponding to Ni(III)/Ni(II) and Ni(II)/Ni(I) processes. The cyclic voltammetry data in Table 1 show that the introduction of N-alkyl substituents results in anodic shifts in both of the oxidation and the reduction potentials compared with the complexes of parent ligand systems. That is, N-alkylation makes attainment of Ni(I) state easier and Ni(III) state more difficult. The methyl and the ethyl groups have similar effects on the redox potentials. This anodic shift of redox potentials may be attributed to the weaker Ni-N interactions in the N-alkylated complexes. The weaker Ni-N interaction for the tertiary amine results in stabilization of antibonding σ-orbitals of the Ni(II) complex, and this makes addition of an electron more favorable while removal of an electron less favorable.[1,2,4]

The present study shows that introduction of alkyl substituents at the secondary amine donors in the polyaza macrotricyclic Ni(II) complexes, which already contain two tertiary nitrogen donors, results in the decrease in the ligand field strength as well as an anodic shift in both of the oxidation and the reduction potentials.

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Conversion of 1,3-Thiazolidines to Dihydro-1,4-thiazine by Chlorinolysis

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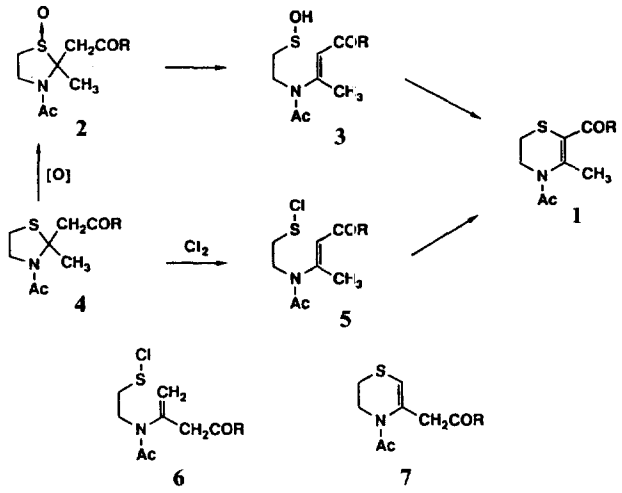
The ring expansion of 1,3-thiazolidines **4** derived from β-ketoacid derivatives to the corresponding dihydro-1,4-thiazines **1** by using the action of chlorine on **4** has been achieved. In the chlorinolysis unisolable sulfenyl chlorides **5** may be formed from chlorosulfonium ions **11** by β-elimination involving carbonyl activated methylene hydrogens. Addition of sulfenyl chloride to the internal double bond appears to form probable thiiranium ions **14**, which in turn gave **1** with loss of acidic proton. Imminium ions **15** could be hydrolyzed easily to give enol **8**. As a side reaction, dihydrothiazine that was formed was further chlorinated to produce dichlorides **16** which were rearranged readily to the chloromethyl compounds **10**.

Introduction

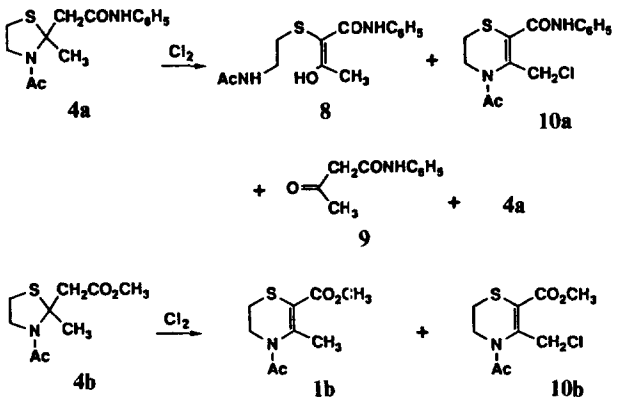
Recently we reported the synthesis of dihydro-1,4-thiazines **1** by rearrangement of 1,3-thiazolidine sulfoxides **2** involving sulfenic acid[1] **3**. As an extension of this work, we now report the synthesis of **1** by chlorinolysis of 1,3-thiazolidines **4** involving sulfenyl chloride **5**.

An important feature of the 1,3-thiazolidines[1] **4** is the pre-



R=a : HNC_6H_5, b : OCH_3

Scheme 1.



Scheme 2.

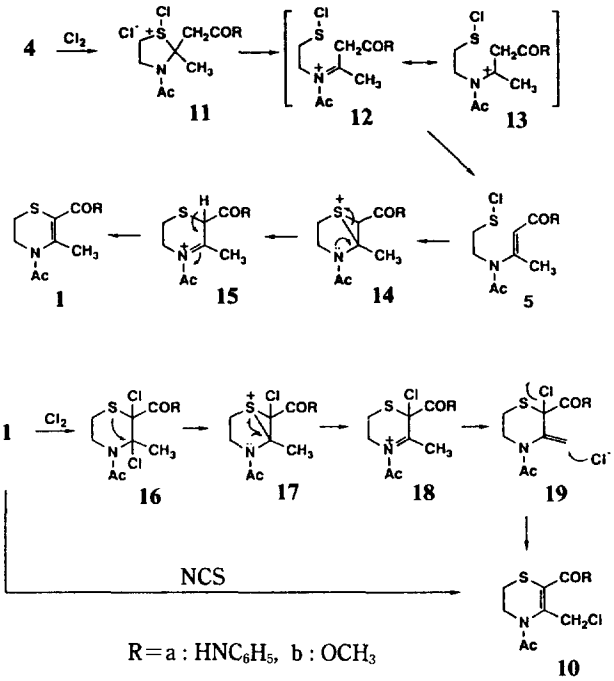
sence of both carbonyl activated methylene and unactivated methyl protons β to the C-S bond being ruptured.

In the rearrangement of the sulfoxides **2**, normal dihydrothiazines **1** or isomeric thiazines **7** resulted depending on the geometry of the molecule and the reaction conditions (Scheme 1). Thus, in considering the chlorinolysis approach, it seemed to be interesting to compare the results with those of previous series.

Results

The starting 1,3-thiazolidines **4** were prepared by the previously reported method. The chlorinolysis reactions were carried out in the methylene chloride solution at −60~−20℃. When thiazolidine **4a** was allowed to react with one equivalent of chlorine, we obtained a 85 : 9 : 3 : 3 mixture of 2-(N-acetylaminoethylthio)acetanilide enol **8**, acetoacetanilide **9**, starting material **4a** and chloromethyl compound **10a**, respectively. The same reaction for the thiazolidine ester **4b** gave a 93 : 7 mixture of dihydro-1,4-thiazine **1b** and chloromethyl compound **10b** and a small amount of starting material **4b**. The results are summarized in Scheme 2.

It seems likely that chloromethyl compounds **10** arose by further chlorination of the dihydro-1,4-thiazines **1**. In fact,



R=a : HNC_6H_5, b : OCH_3

Scheme 3.

the compounds **10** were obtained when dihydro-1,4-thiazines **1** were treated with 1 equivalent of chlorine under the same conditions. The chloromethyl compound **10a** was also prepared by N-chlorosuccinimide chlorination of the 2-methyl group of **1a**.

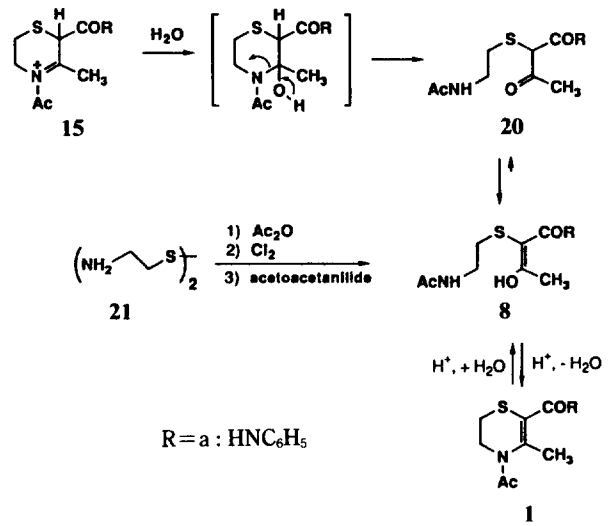
Discussion

The ring expansion reaction comprises the formation of sulfenyl chlorides **5** as key intermediates from chlorosulfonium salts[2] **11** and cyclization of **5** to dihydro-1,4-thiazines **1**. The ring opening of **11** would occur either by a concerted β-elimination involving the carbonyl activated methylene hydrogen to produce **5** or by stepwise mechanism to form carbocation **13** followed by loss of acidic proton to give **5**.

In view of previously observed carbocation **13** intemediacy in the acid catalyzed rearrangement of 1,3-thiazolidine sulfoxide[1] **2**, the stepwise ring opening involving **13** seems more probable. The sulfenyl chloride **5** now undergoes a nucleophilic attack at the sulfur atom by the internal double bond to form most likely thiiranium ion[3] **14**, which would spontaneously open to the low energy imminium ion **15**. This could then lose the acidic proton to produce the dihydro-1,4-thiazine **1b** (Scheme 3)[4].

An alternative ring opening of chlorosulfonium salts **11** involving 2-methyl hydrogens to form sulfenyl chloride **6** did not occur. If that happened, isomeric thiazine **7** would be produced. Thus, only the carbonyl activated methylene hydrogens were involved in the ring expansion.

As indicated earlier, dichlorides **16** were most likely formed by addition of chlorine to dihydro-1,4-thiazine **1**. A proposed mechanism for the formation of **10** from dichloride **16** is shown in Scheme 3. The sulfur atom may attack the anomeric 3-halocarbon of **16** to give a thiiranium ion **17** which would be converted to more stable imminium ion **18**. The removal of a methyl hydrogen may produce the exo methy-



Scheme 4.

lene compound **19**, followed by the allylic chlorination to give the chloromethyl compound **10**. Formation of analogous dichlorides and chloromethyl compounds have previously observed in the chlorinolysis of oxathiolanes[4].

In the chlorinolysis of thiazolidine amide **4a**, the formation of enol **8** was unexpected. As shown in Scheme 4, it is likely that the imminium ion **15** was attacked by water present in the reaction medium[5] to produce keto compound **20** which exists almost exclusively as enol form[6] **8**. The structure of enol **8** follows from spectral data. NMR spectrum showed a singlet at δ 15.42 ppm, characteristic of the enol proton; IR spectrum showed a strong peak at 3090 cm^{-1}, indicative of OH stretching; Mass spectrum fitted empirical formula $C_{14}H_{18}O_3N_2S$ giving molecular ion (M^+) at m/e 294. The structure of **8** was further confirmed by independent synthesis involving sulfenylation of acetoacetanilide **9** with sulfenyl chloride formed by action of chlorine on disulfide[8] **21** (Scheme 4). The dihydrothiazine **1a** and the enol **8a** were easily interconverted by acid catalyzed hydrolysis and dehydration[9].

Interestingly, the corresponding enol compound **8b** did not form in the ring expansion reaction of thiazolidine ester **4b**. This difference is attributable to the stronger electron withdrawal by ester carbonyl group compared with the amide carbonyl[4]. Thus, in ester **15b** a proton α to the carbonyl group, much more acidic than that of amide **15a**, is lost before water attack to produce dihydrothiazine **1b**.

It was also noted that while acetoacetanilide **9a** was produced in the ring expansion reaction of sulfide amide **4a**, the corresponding parent ketone **9b** was not formed in the case of sulfide ester **4b**. Thus, acetoacetanilide **9a** was formed by water attack on the carbocation **13a**. However, due to the stronger electron withdrawing effect of ester carbonyl group in **13b** a proton was released before reacting with water.

Experimental

General procedure

All melting points were obtained with an Electro thermal melting point apparatus and corrected. Infrared spectra were recorded on an Analect Model FX-6160 FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian Model EM 360 (60 MHz) or a Varian Gemini 300 (300 MHz) using Me_4Si as an internal standard and all are reported in δ. Elemental analyses of new compounds are within 0.4% of the theoretical values unless otherwise noted. All chromatographic isolations were accomplished by preparative thin-layer or column chromatography, using Silica gel 60 (230-400 mesh ASTM). All solvents were freshly distilled and stored under nitrogen atmosphere. Acetoacetanilide, methyl acetoacetate and 2-aminoethanthiol were purchased from Aldrich Chemicals. A chlorine solution in methylene chloride (2% (v/v)) was prepared by the following method: to a pre-cooled (−20℃) methylene chloride (98 m*l*, dried over CaH_2) was added a cylinder which was filled with a liquidified chlorine (2 m*l*) prepared by the liquefaction of chlorine gas under aceton-dry ice bath (−78℃). This solution was stored in a refregerator and used without titration.

Synthesis of 3-Acetyl-2-methyl-1,3-thiazolidine-2-acetic Acid Methyl ester 4b

After a solution of methyl acetoacetate **9b** (34.8 m*l*, 0.3 mol), 2-aminoethanethiol (23.1 g, 0.3 mol) and *p*-toluenesulfonic acid monohydrate (2.85 g) in benzene (300 m*l*) was refluxed for 5 h with a Dean-Stark water separator, it was cooled room temperature. The reaction mixture was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* to give an yellow oily residue (46.8 g, 89.0 %). This residue was dissolved in acetic anhydride (76 m*l*) and stirred for 20 h at room temperature. A solution of potassium carbonate (102.3 g, 0.74 mol) in water (200 m*l*) was added dropwise for 30 min to the reaction mixture at room temperature. The product was extracted with methylene chloride (400 m*l*), dried (Na_2SO_4) and concentrated to give an yellow oily residue (54.4 g), which was purfied by distillation under reduced pressure to afford **4b** (28.0 g, 43.0%). bp: 178-180℃/3 mmHg; ^{1}H-NMR (60 MHz) ($CDCl_3$) δ 1.87 (s, 3H, 3-$COCH_3$), 2.12 (s, 3H, 2-CH_3), 3.67 (s, 3H, 2-OCH_3), 2.91 and 3.16 (2d, 2H, J=16.8 Hz, 2-CH_2), 2.86 (t, 2H, J=6 Hz, 5-CH_2), 3.82 (t, 2H, J=6Hz, 4-CH_2); IR (NaCl): 1710 (C=O), 1650 (C=O) cm^{-1}.

Synthesis of 3-Acetyl -2-methyl-2-(N-phenyl carbamoylmetryl)-1,3-thiazolidine 4a

A solution of acetoacetanilide **9** (13 g, 73 mmol), 2-aminoethanthiol (6.2 g, 80 mmol), and *p*-tolunenesulfonic acid monohydrate (0.7 g) in benzene (75 m*l*) was refluxed for 16 h with a Dean-Stark water separator and then cooled to room temperature. The reaction mixture was washed with water and dried (Na_2SO_4). The solvent was removed *in vacuo* to give an yellow oily liquid (16.8 g, 98%). This oily residue was dissolved in acetic anhydride and stirred for 4 h at room temperature. The white precipitate was filtered off to give **4a** (18.1 g, 91%), mp. 191-204℃ (dec); ^{1}H-NMR (300 MHz) ($CDCl_3$) δ 1.81 (s, 3H, 3-$COCH_3$), 2.12 (s, 3H, 2-CH_3), 2.92-3.09 (m, 2H, 5-CH_2S), 3.12-3.36 (m, 2H, 2-CH_2), 3.89 (t, 2H, J=6.12 Hz, 4-CH_2N), 7.09-7.52 (m, 5H, ArH), 7.76 (br, s, H, NH); IR (KBr): 1680 (C=O), 1630 (C=O) cm^{-1}; ms (70 eV) m/e 278 (M^+).

Preparation of 4-Acetyl-3-methyl-5,6-dihyro-1,4-thiazine-2-carboxylic Acid Methyl ester 1b

To a solution of 1,3-thiazolidine **4b** (0.3 g, 1.38 mmol) in methylene chloride (20 m*l*) cooled in an acetone-dry ice bath at −20℃ was added dropwise a solution of chlorine (0.104

g, 1.47 mmol) in methylene chloride (3.4 m*l*) for 1 min. The cooling bath was then removed and the reaction mixture was allowed to reach ambient temperature (20℃) while being stirred for about 30 min. The solvent was evaporated to give an oily residue, which was dissolved in methylene chloride (30 m*l*), washed with cold water and dried ($MgSO_4$). The solvent was removed to give a pale yellow oily residue (0.28 g), which was an about 93 : 7 mixture of dihydro-1,4-thiazine **1b**, and chloromethyl compound **10b** by ^{1}H-NMR spectroscopy. This mixture was separated by preparative TLC using 1 : 1 (v/v) *n*-hexane-ethyl acetate as an eluent. The second band (R_f 0.4) was extracted with a 3 : 1 mixture of chloroform and methanol to give dihydro-1,4-thiazine **1b**. Recrystallzation from ethyl ether gave white needles **1b** (0.19 g, 63.3 %), mp. 74-76℃; ^{1}H-NMR (300 MHz) ($CDCl_3$) δ 2.16 (s, 3H, CH_3 CO), 2.45 (s, 3H, 3-CH_3) 3.06-3.13 (m, 2H, 6-CH_2S), 3.81 (s, 3H, $COOCH_3$), 3.75-3.83 (m, 2H, 5-CH_2N); IR (KBr) 1710 (C=O), 1660 (C=O) cm^{-1}; Anal. Caclcd. for $C_9H_{13}O_3NS$ C, 50.21; H, 6.09; N, 6.51. Found: C, 50.4; H, 6.19; N, 6.43.

Chlorinolysis of 3-Acetyl-2-methyl-2-(N-phenylcarbamoyl)-1,3-thiazolidine 4a

To a stirred solution of 1,3-thiazolidine **4a** (1.06 g, 4 mmol) in methylene chloride (400 m*l*) cooled in an acetone-dry ice bath at −20℃ was added a solution of chlorine (0.312 g, 4.4 mmol) in methylene chloride (10 m*l*) for 60 sec. The cooling bath was then removed and the reaction mixture was allowed to reach ambient temperature (25℃), while being stirred for about 1 h. The reaction mixture was washed with ice-cold water and dried ($MgSO_4$). Evaporation of the solvent yielded an oily residue (0.86 g) as a 85 : 9 : 3 : 3 mixture of 2-(N-acetylaminoethylthio)acetoacetanilide enol **8**, acetoacetanilide **9**, 1,3-thiazoldine **4a** and chloromethyl compound **10a** respectively (by ^{1}H-NMR spectrum and TLC). From this mixture, 1,3-thiazoldine **4a** and chloromethyl compound **10a** by preparative TLC using 7 : 3 (v/v) benzene-ethylacetate as an eluent were separated. The 2-(N-acetylaminoethylthio) acetoacetanilide enol **8** (0.240 g, 28.6 %) and acetoacetanilide **9** (0.02 g) were separated by preparative TLC with a 9 : 1 (v/v) *n*-hexane-ethyl acetate mixture.

For **8**; mp. 124-125℃; ^{1}H-NMR (300 MHz) ($CDCl_3$) δ 1.94 (s, 3H, $COCH_3$), 2.35 (s, 3H, CH_3), 2.69 (m, 2H, CH_2S), 3.41-3.45 (m, 2H, CH_2N), 6.00 (br, s, H, NH), 7.11-7.54 (m, 5H, ArH), 9.11 (s, H, NH), 15.42 (br, s, H, OH); IR (KBr) 3090 (OH), 1633 (C=O) cm^{-1}; ms: (70 eV) m/e (relative intensity) 294 (M^+, 6.9), 276 (1.0), 177 (5.6), 118 (4.6), 93 (base peak).

Synthesis of 4-Acetyl-3-chloromethyl-5,6-dihydro-1,4-thiazine-2-carboxylic Acid Methyl Ester 10b

Method A. To a stirred solution of 1,4-thiazine **1b** (0.125 g, 1 mmol) in methylene chloride (20 m*l*) cooled in an acetone-dry ice bath at −20℃ was added a chlorine (71 mg, 1 mmol) gas for 27 sec. When the addition was complete, the solvent was removed under reduced pressure at 10℃ to obtain an oily residue **10b** (0.241 g, 96.5%), ^{1}H-NMR (60 MHz) ($CDCl_3$) δ 2.36 (s, 3H, CH_3CO) 3.17-3.73 (m, 2H, 6-CH_3), 4.03 (s, 3H, $COOCH_3$), 3.84-4.12 (m, 2H, 5-CH_2), 5.10 (s, 2H, 3-CH_2Cl).

Method B. The reaction was carried out by using 1, 3-thiazolidine **4b** as the starting meterial and 2 moles of chlorine to obtain the same compound as in method A.

Synthesis of 4-Acetyl-3-chloromethyl-5,6-dihydro-1,4-thiazine-2-carboxamide 10a

To a warmed solution of 1,4-thiazine **1a** (1.0 g, 3.6 mmol) in carbon tetrachloride (300 m*l*) was added N-chlorosuccinimide (NCS) (0.53 g, 3.9 mmol) and benzoyl peroxide (44 mg). The reaction mixture was stirred and heated to reflux under nitrogen atomsphere for 2 h. The white precipitate succinimide at room temperature was filtered off. The filtrate was dried ($MgSO_4$) and concentrated to yield the crude product as a viscose oil. It was crystallized from methylene chloride, benzene and petroleum ether to give chloromethyl compound **10a** (0.46 g, 46%), mp. 99-101℃; ^{1}H-NMR (60 MHz) ($CDCl_3$) δ 2.20 (s, 3H, $COCH_3$), 3.1-3.4 (m, 2H, CH_2S), 3.73-4.03 (m, 2H, CH_2N), 4.85 (s, 2H, CH_2Cl), 7.16-8.83 (m, 5H, ArH), 8.43 (s, H, NH); IR (KBr) 1670 (C=O) cm^{-1}.

Independent synthesis of 2-(N-acetylaminoethylthio)acetoacetanilide enol 8

Step 1. Preparation of N,N′-diacetylcystamine. A solution of cystamine **21** (2.0 g, 13.14 mmol) in acetic anhydride (10 m*l*) was stirred at room temperature for 30 min. An excess of acetic anhydride was quenched by the addition of a potassium carbonate (15.2 g) in water (30 m*l*) at 20℃. The product was extracted with methylene chloride, washed with water and dried (Na_2SO_4). The solvent was evaporated at room temperature under reduced pressure to obtain a white solid residue (2.91 g). Crystallization from methylene chloride and petroleum ether gave colorless crystalline needles (1.84 g, 59.3%), mp. 91-93℃; ^{1}H-NMR (60 MHz) ($CDCl_3$) δ 1.90 (s, 3H, CH_3CO), 2.58-2.85 (m, 2H, CH_2S), 3.27-3.73 (m, 2H, CH_2N), 7.30 (br, s, 1H, NH).

Step 2. Preparation of 2-(N-acethylaminoethylthio) acetoacetanilide enol 8. To an ice-cooled solution of N,N′-diacetylcystamine (1.74 g, 7.37 mmol) in carbon tetrachloride (20 m*l*) at 10℃ was added chlorine gas (0.53 g, 7.7 mmol) over 3 min and stirred at the same temperature for 30 min. The solvent was removed under reduced pressure to obtain a dark brown oily residue (2.26 g). A solution of this crude sulfenyl chloride in chloform (30 m*l*) was treated by a solution of acetoacetanilide **9** (1.772 g, 0.01 mol) in chloroform (40 m*l*) at room temperature for 30 min. The brown precipitates were filtered off and the filtrate was washed with cold water and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a light brown oily residue (2.24 g). Crystallization from methylene chloride and petroleum ether gave a colorless needle **8** (0.7 g, 28%). This compound was identical with the compound **8** obtained by the chlorinolysis of 1,3-thiazolidine in ^{1}H-NMR and IR spectra.

Hydrolysis of 4-Acetyl-5,6-dihydro-3-methyl-N-phenyl-1,4-thiazine-2-carboxamide 1a

Method A. A mixture of dihydro-1,4-thiazine-2-carboxamide **1a** (50 mg, 0.18 mmol) and concentrated hydrochloric acid (0.5 m*l*) in methylene chloride (5 m*l*) was stirred at room temperature for 20 h. The organic phase was washed with cold water and dried (Na_2SO_4). Evaporation of the solvent gave an yellow foamy solid **8** (49 mg, 92%). This compound has identical ^{1}H-NMR and IR spectra with those of **8** prepared by the previous method.

Method B. To a solution of 1,4-thiazine **1a** (100 mg, 0.31 mmol) in methylene chloride (10 m*l*) cooled in an acetone -dry ice bath at −20℃ was added hydrogen chloride (34 mg, 0.93 mmol) over 25 sec. The reaction mixture was allowed to reach ambient temperature (25℃), while being

stirred. After workup, an oily residue **8**, (70 mg, 66.3%) was obtained.

Dehydration of 2-(N-acetylaminoethylthio)acetoacetanilide enol 8

A solution of 2-(N-acetylaminoethylthio)acetoacetanilide enol **8** (1.0 g, 3.4 mmol) and *p*-toluenesulfonic acid (32 mg) in benzene (250 m*l*) was refluxed for 25 h with a Dean-Stark water trap. The reaction mixture was cooled, washed with cold water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to give an yellow foamy residue (640 mg). Crystallization from ethyl acetate and petroleum ether gave **1a** (490 mg, 52%) as a light yellow needle, mp. 91-93℃; ^{1}H-NMR (300 MHz) ($CDCl_3$) δ 2.17 (s, 3H, CH_3CO), 2.40 (s, 3H, 3-CH_3), 3.18 (t, 2H, J=6.0 Hz, 6-CH_2S), 3.79 (t, 2H, J=6.0 Hz, 5-CH_2N), 7.15 (t, 1H, J=8.1 Hz, *p*-ArH), 7.35 (t, 2H, J=7.5 Hz, *m*-ArH), 7.57 (d, 2H, J=7.7 Hz, *o*-ArH), 8.35 (br, s, H, NH).

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5. Because the chlorine solution in methylene chloride used in chlorinolysis could not be dried absolutely (see the experimental section), the small amount of water was in the reaction medium.
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The Application of NMR Techniques to the Structural Confirmation of *O*-Substituted 3,4-Dihydroxyphenylacetic Acid Derivatives

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The structures of the compounds, **1**, **2**, **3**, and **4**, which were precursors of analgesics, were confirmed by modern NMR techniques. The complete ^{13}C-NMR assignments of these systems were established by applying COLOC (COrrelated spectroscopy for LOng range Couplings), HETCOR (HETeronuclear CORrelated spectroscopy), RCT (Relay Coherence Transfer), and NOE difference spectroscopy. The limitation of COLOC approach which has been widely used recently is discussed.

Introduction

Capsaicinoid is a pungent principle of red pepper.[1] Red pepper has been used as food additivies and folk medicine for a long Time. Capsaicinoid was found to be responsible for analgesic activity. Structural elucidation by Bennett and Kirby concluded that it was a mixture of at least five analogous amides including capsaicin [*N*-(4-hydroxy-3-methoxybenzyl)-*trans*-8-methyl-6-nonenamide].[2]

In the course of our continuing study on analgesic activity of capsaicinoids,[3] we became interested in the synthesis of 3-hydroxy analogs. The synthesis required partial alkylation of phenolic hydroxy group of 3,4-dihydroxyphenylacetic acid derivatives. Unfortunately, selective demethylation of 4-alkoxy-3-methoxyphenylacetamide was not successful. No selectivity was observed when monobenzylation was attempted and the products were separated by MPLC.[4] In confirming the substitution patterns, the ^{1}H-NMR spectra were not distinguishable because of the inherently low dispersion of ^{1}H substituent chemical shift as it can be predicted. Although ^{13}C-NMR spectroscopy has been used to determine the structures of substituted aromatic systems based on theoretical treatment and empirical data, the former still has the lack of flexibility and restriction on the range fof application and the latter has the limited tabulations. Furthermore, signal assignment between hydroxylated and *O*-alkylated carbons based on chemical shift calculations is not reliable because the substituent effect of OH, OR^1, and OR^2 groups are very