Figure 5 reports the self-heating rate and the pressure rise rate vs. temperature, as well as the pressure increase of *o*-nitrobenzyl bromide in a titanium bomb (*5*). The relevant data are reported in Table IV. Under adiabatic conditions the exothermicity of the first reaction is largely sufficient to raise the temperature above the starting temperature of the second reaction.

In the decomposition of *o*-nitrobenzyl bromide in a titanium bomb at least two exotherms take place. The titanium bomb, having a thermal inertia smaller than that of a Hastelloy C bomb, is more sensitive. Other runs on *o*-nitrobenzyl bromide with a higher degree of filling (0.15 g mL^{-1}) have shown, also in a titanium bomb, a behavior similar to that reported in Figure 3.

Discussion

The combined use of thermoanalytical techniques (TGA, DSC, ARC) under different experimental conditions—dynamic, isothermal, adiabatic (*17*)—has shown that all the nitrobenzyl halogenides tested decompose exothermally and violently, developing great amounts of gas. A scale of relative stability within this group of compounds can be based on the starting decomposition temperature from the DSC and ARC runs: (1) bromide derivatives are less stable than the corresponding chlorides; (2) ortho isomers are less stable than meta and para isomers; *m*-nitrobenzyl bromide is slightly less stable than *p*-nitrobenzyl bromide, while *p*-nitrobenzyl chloride is slightly less stable than *m*-nitrobenzyl chloride.

A regular correlation cannot be established of the stability of the isomers; this confirms the finding of other authors for the isomeric nitroanilines, nitrochlorobenzenes, nitrophenols, nitrotoluenes (*6*) and nitrobenzoyl chlorides (*18*).

ARC runs have recorded initial decomposition temperatures always lower than the DSC runs under dynamic conditions. This is justified by the higher sensitivity of the adiabatic calorimeter (0.4 W kg^{-1}) as related to the DSC (5 W kg^{-1}) (*17*) and by the fact that in the dynamic DSC runs the temperature of the thermal effect is a function of the heating rate (*9*).

The DSC 2-h isotherm runs after the ASTM (*10*) always gave starting decomposition temperatures very close to those from the ARC runs.

As for the decomposition mechanism, DSC runs under dynamic conditions show that *o*-nitrobenzyl bromide and chloride follow a first-order kinetics. The behavior of the other compounds apparently indicates a different, more complex kinetics. Further, *m*- and *p*-nitrobenzyl bromides decompose in two steps at least.

No kinetic information could be obtained from the ARC runs, due to the difficulty of maintaining the adiabaticity till the end of the decomposition process. Above a certain self-heating rate (10 °C min^{-1}) the system is not adiabatic; part of the reaction heat is transmitted to the surroundings. Therefore, the instrumental ΔT—and consequently the ΔH—from the ARC runs are surely smaller than those theoretically reached under strictly adiabatic conditions.

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Synthesis and Nuclear Magnetic Resonance Study of 2-Thiazolines

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A series of 5,5-dimethyl-2-thiazoline-4-carboxylates with a phenyl or methyl group at the 2-position of the ring were prepared from the corresponding methyl or ethyl ester of penicillamine and either methyl benzimidate or ethyl acetimidate. The free acid was obtained by the reaction of penicillamine with benzonitrile to produce 5,5-dimethyl-2-phenyl-2-thiazoline-4-carboxylic acid. Corresponding thiazolines were prepared from cysteine in the same manner. The nuclear magnetic resonance spectra of both series exhibit coupling of the methyl group at the 2-position with the hydrogen at the 4-position. The groups at the 5-position are nonequivalent and in the case of the cysteine series give rise to an ABX system. Further analysis confirms a concentration dependence for this splitting pattern.

Introduction

Recent studies (*1–6*) of copper complexes of the composition $[Cu^{II}_6Cu^{I}_8L_{12}Cl]^{Z\pm}$ where L = D-penicillamine, Z = 5- or L = 2,2-dimethylcysteamine, Z = 7+, have demonstrated the unique interactions of this class of chelate antidotes with copper. In the chronic form of copper intoxication known as Wilson's disease, the drug of choice has been the use of oral D-penicillamine. The intensely purple copper complexes of penicillamine and related ligands (*1–8*) have possible relevance to the treatment of Wilson's and other diseases (*9*, *10*). The stabilities of these very large mixed valence copper clusters appear to depend significantly on the structure of the ligand (*4*).

Attempts to prepare modified ligands from D-penicillamine (structure I, R_1 = Me, R_2 = H) require protection of the sulfur and nitrogen functional groups. A convenient direct method of

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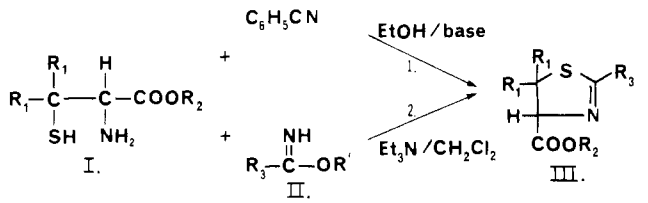
Table I. Nuclear Magnetic Resonance Chemical Shifts[a]

	substituents[c]						
compd[b]	R_1		H	R_2		R_3	
1	Me	1.47 (s), 1.75 (s)	5.00 (s)	H	12.53 (s)	Ph	7.37, 7.80 (m)
2[d]	Me	1.16 (s), 1.50 (s)	4.41 (q, 1.5)	Me	3.58 (s)	Me	2.05 (d, 1.5)
3	Me	1.19 (s), 1.47 (s)	4.97 (s)	Me	3.59 (s)	Ph	7.38, 8.00 (m)
4	Me	1.25 (s), 1.53 (s)	4.67 (q, 1.5)	Et	0.92 (t), 4.03 (q)	Me	1.90 (d, 1.5)
5	Me	1.52 (s), 1.83 (s)	4.98 (s)	Et	1.37 (t), 4.42 (q)	Ph	7.62, 8.06 (m)
6	H	3.75 (d)	5.45 (t)	H	10.55 (s)	Ph	7.52, 7.94 (m)
7[d]	H	3.41, 3.50[e]	4.99[f]	Me	3.51 (s)	Me	2.15 (d, 1.5)
8[d]	H	3.62, 3.71[e]	5.28[f]	Me	3.82 (s)	Ph	7.40, 7.85 (m)
9[d]	H	3.20, 3.29[e]	4.77[f]	Et	0.95 (t), 3.88 (q)	Me	1.90 (d, 1.5)
10[d]	H	3.20, 3.56[e]	5.20[f]	Et	0.91 (t), 4.09 (q)	Ph	7.52, 8.12 (m)
11	Me	1.40 (s), 1.47 (s)	4.25 (s)	Me	3.91 (s)		
12	Me	1.50 (s), 1.57 (s)	4.26 (s)	Et	1.28 (t), 4.46 (q)		

[a] Chemical shifts in ppm from Me_4Si; splitting patterns and J values in parentheses; J values in hertz; recorded at 60 MHz. [b] Satisfactory elemental analysis was obtained for each sample. [c] Refer to Scheme I, structure II (1-10), and structure I (11, 12). [d] Spectra also recorded at 100 MHz. [e] AB portion of ABX splitting pattern. [f] X portion of ABX splitting pattern.

Scheme I



providing the protecting group is to form the heterocyclic structure III, a 2-thiazoline. This approach (Scheme I) has previously been used to obtain larger heterocyclic systems in penicillin derivatives and also as a method for modifications of the group (R_3) at the 2-position on the ring (*11–19*). In this paper we are reporting the synthesis of 2-thiazolines which are potential intermediates to 2-mercaptoethylamine type chelates for copper(II).

Results

Two general condensation reactions (Scheme I) were employed in the synthesis of a variety of 2-thiazolines. The use of these "Type E syntheses" has appeared, in part, for several of the compounds (**3**, **5–9**) (*11–13*). However, the general utility of this approach has not been explored for both the penicillamine and cysteine derivatives. The thiazolines with the free acid functional group at the 4-position which were obtained directly (reaction 1) from the free acid starting materials and benzonitrile in ethanol (*19*) probably involve an intermediate benzimidate similar to the starting material (II) in reaction 2.

For the synthesis of thiazolines with the ester functional group at the 4-position, two penicillamine esters (**11** and **12**) were prepared. The esterification of penicillamine was conducted in the alcohol with thionyl chloride at room temperature for a period of 1 week; the esters were isolated as their hydrochloride salts. The condensation (reaction 2) between the β-thiol amino acid ester and the imidate takes place in methylene chloride at room temperature in the presence of triethylamine to produce the 2-thiazolines. Penicillamine esters (**11** and **12**) and cysteine esters (structure I, R_1 = H, R_2 = Me or Et) were used as starting materials along with methyl benzimidate hydrochloride or ethyl acetimide hydrochloride (II, R_3 = Ph, Me; R′ = Me, Et) for the synthesis of the heterocyclic systems under mild conditions.

Discussion

The nuclear magnetic resonance spectra of these thiazolines revealed some interesting characteristics and interactions in this heterocyclic ring system. Table I lists the chemical shifts (ppm) and coupling constants (J, Hz) observed at 60 MHz in all samples and confirmed at 100 MHz for five of the samples. The substituents R_2 produced the normal splitting patterns at the expected chemical shifts. A phenyl group, R_3, at the 2-position on the ring exhibits a multiplet in two sets of peaks while a methyl group appears as an unexpected doublet and will be discussed below. The *gem*-dimethyl resonances, R_1, of the penicillamine ester (**11** and **12**) occur at about 1.5 ppm with a difference in chemical shift of 0.07 ppm, whereas the same methyl groups at the 5-position on the thiazoline ring of the penicillamine derivatives (**1–5**) have a difference in chemical shift of about 0.3 ppm.

The hydrogen at the 4-position (the α-hydrogen of the original amino acid) is the most sensitive to structural changes. The chemical shift ranges from 4.41 ppm in **2** to the most deshielded at 5.45 ppm in **8**. The splitting patterns begin with a singlet in the penicillamine derivatives **3** and **5** when the 2-position of the ring is occupied by a phenyl group but become a pseudotriplet in the corresponding cysteine derivatives **8** and **10** as the X portion of an ABX pattern. The fortuitous overlap of the pair of doublets at the X resonance gives the 1:2:1 ratio of peak heights with the center peak somewhat broadened. This overlap is more clearly shown in the 2-methyl derivatives. When a methyl group, R_3, occupies the 2-position, long-range coupling with the 4-position hydrogen gives a quartet (J = 1.5 Hz) in the penicillamine derivatives **2** and **4** while the overlapping pair of doublets in the corresponding cysteine derivatives **7** and **9** are further split into quartets. The center region does not show a clean quartet but rather two overlapping quartets separated by about 0.02 ppm. The long-range interaction of the methyl group at the 2-position is confirmed by decoupling experiments on **7** and **9**. Analysis of these splitting patterns was confirmed by computer simulation of spectra (not including the ABX pattern) using a previously reported program (*20*).

Inconsistencies were found in the spectra of the cysteine derivatives **6–10** in examining the region assigned to the two hydrogens at the 5-position. Integration over the region gave the correct ratio for two hydrogens and interaction with the hydrogen at the 4-position would have required an eight-line pattern in the splitting of the four lines of this AB system. The nonequivalence was supported by the asymmetry at the 4-position and the difference in chemical shifts of the methyl groups at the 5-position in the penicillamine derivatives. However, it was observed that the pattern of the 5-position hydrogens even in the same compound varied from sample to sample, sometimes as two or three lines and other times as many as eight distinct lines.

Compound **10** was selected for further study of the ABX pattern. Because the variation in pattern just mentioned ap-

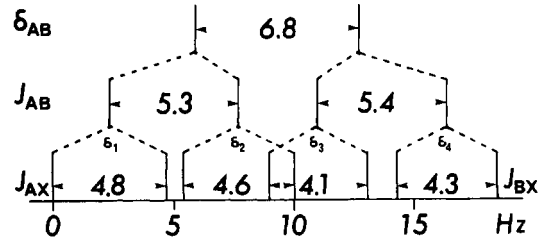


Figure 1. (Bottom) Eight-line ABX pattern in H^1 NMR of **10** after addition of 300 μL of benzene, J_{AX} and J_{BX} (Hz). (Center) Resolution to four lines δ_{1-4}, J_{AB} (Hz). (Top) Calculated difference in chemical shift of A and B, δ_{AB}. Note—intensities are not shown to scale, but the ratios were observed to correspond to the expected theoretical values.

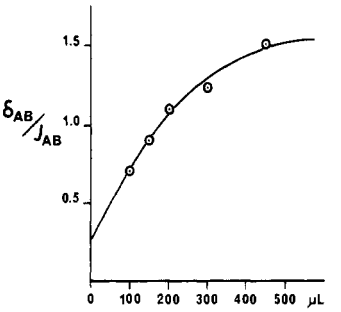


Figure 2. Dependence of δ_{AB}/J_{AB} on microliters of benzene added to a neat sample of **10**: δ_{AB} calculated for protons at 5-position; J_{AB} = 5.5 Hz determined from ABX pattern.

parently depends on the amount of solvent used, an NMR spectrum of 500 μl of the neat oil was first obtained. Only two peaks appear in the region of the hydrogens at the 5-position. To this sample was added successive 50-μL portions of benzene; after each addition the critical region of the NMR spectrum was recorded. The downfield peak was the first to separate into two peaks; at 200 μL of benzene added the eight-line pattern was clearly established; the center pair of peaks merged to form a single absorption after 400 μL of solvent had been added.

Mathematical analysis (*21*) was used to resolve the interaction in **10** at 100, 150, 200, 300, and 450 μL of benzene added to the sample. For each dilution as illustrated at 300 μL in Figure 1, the J_{AX} was taken as the average of the splitting between lines 1–2 and 3–5 of the pattern shown on the bottom line of Figure 1 and centers of these were assigned as δ_1 and δ_2, respectively. The J_{BX} was taken as the average of the splitting between lines 4–6 and 7–8 on the bottom of the figure and the centers were assigned as δ_3 and δ_4, respectively. The four-line AB pattern (δ_1, δ_2, δ_3, δ_4) is shown on the middle line of Figure 1. The coupling J_{AB} was the average of δ_1–δ_2 and δ_3–δ_4. The difference in the chemical shift of A and B (δ_{AB}) on the top line of Figure 1 which is of the same order as J_{AB} was calculated as $\delta_{AB} = ((\delta_1 - \delta_4)(\delta_2 - \delta_3))^{1/2}$. With the average values for the dilution series in the eight-line pattern, the 1–2 and 3–5 line interval was 4.8 Hz, assigned J_{AX}; the 4–6 and 7–8 line interval was 4.3 Hz, assigned J_{BX}. The centers of these pairs would form a four-line pattern with J_{AB} = 5.5 Hz. From this set of four lines the differences in the chemical shifts of A and B were calculated as 3.9, 5.0, 6.1, 6.8, and 8.2 Hz at 100, 150, 200, 300, and 450 μL, respectively. It can be seen that the difference in chemical shift increases with increasing volume of solvent. A plot of the ratio δ_{AB}/J_{AB} vs. microliters of solvent added (Figure 2) indicates that the ratio reaches a constant value at about 1.5 after approximately 450 μL of solvent has been added. An intercept other than zero suggests that the environments are never equivalent but that the difference in chemical shift may reach a minimum of about 1.4 Hz.

Experimental Section

Materials and Methods. Penicillamine, MSD, was used directly from 250-mg capsules supplied by Merck Sharp and Dohme; cysteine ethyl ester hydrochloride was obtained from Tridom Chemical Inc., cysteine methyl ester hydrochloride from Pfaltz and Bauer, Inc., and methyl benzimidate hydrochloride from Aldrich Chemical Co.; ethyl acetimidate hydrochloride and benzonitrile were obtained from Eastman Chemical Co.; cysteine hydrochloride and solvents from Fisher Scientific Co. were used as they were received. Deuterated solvents were obtained from Norell, Inc.

Infrared spectra were recorded in dried KBr matrix for solids or as a thin film on a KBr disk for oils by using a Beckman Acculab 10 spectrophotometer. Nuclear magnetic resonance spectra were obtained in solutions of $CDCl_3$ for **1**, **2**, and **5**–**9**, C_6H_5 for **3**, **4**, and **10**, and D_2O for **11** and **12** with chemical shifts measured from Me_4Si or the solvent as internal standard. They were recorded at 37 °C with a Varian EM-360 (60 MHz) spectrophotometer. Elemental analysis data obtained from Galbraith Laboratories Inc., Knoxville, TN, for each compound were supplied for review.

***2-Phenyl-5,5-dimethyl-2-thiazoline-4-carboxylic Acid* (1).** Benzonitrile (1.4 mL, 13 mmol) and penicillamine (2 g, 13 mmol) were refluxed in 80 mL of methanol for 30 min with $NaHCO_3$ (1.148 g, 13 mmol). The solution was cooled to room temperature and piperidine (1.4 mL, 13 mmol) was added dropwise to the mixture. The solution was again heated to reflux for 3 days and then evaporated to near dryness. The residue was dissolved in 80 mL of water, the pH adjusted to 10, and the solution extracted twice with 40 mL of ether. The aqueous phase was adjusted to pH 4 with acetic acid and again extracted with three 50-mL portions of chloroform. The chloroform extract was washed with water, dried over Na_2SO_4, and evaporated to a light pink solid: mp 111–115 °C.

***Methyl 5,5-Dimethyl-2-methyl-2-thiazoline-4-carboxylate* (2).** Penicillamine methyl ester hydrochloride, **11** (3.7 g, 18.5 mmol), and ethyl acetimidate hydrochloride (2.3 g, 18.5 mmol) were stirred in 50 mL of methylene chloride with 4 mL of triethylamine in a closed container at 25 °C for 48 h. Some solid is present during the entire reaction time. The solvent is removed under reduced pressure and the residue is refluxed for 1 h in ether. After filtration, to remove the hydrochloride salts, the ether is evaporated at reduced pressure. The oily residue is dissolved in benzene, charcoal is added to the mixture, and the suspension is filtered through alumina. Removal of the benzene under reduced pressure yields the product.

***Ethyl 5,5-Dimethyl-2-methyl-2-thiazoline-4-carboxylate* (4).** Penicillamine ethyl ester (solution from **12**) and ethyl acetimidate hydrochloride (3.31 g, 27 mmol) were stirred in a closed container with 4 mL of triethylamine at 25 °C for 48 h. Isolation was the same as for **2**. Compounds **3** and **5** were prepared in a manner similar to that for **2** and **4** using methyl benzimidate.

***Ethyl 5,5-Dihydro-2-phenyl-2-thiazoline-4-carboxylate* (10).** Cysteine ethyl ester hydrochloride (2.00 g, 11 mmol) and methyl benzimidate hydrochloride (1.85 g, 11 mmol) were stirred in 25 mL of methylene chloride with 2 mL of triethylamine in a closed container at 25 °C for 48 h. Isolation followed the same procedure as that for **2**. Compounds **7**–**9** were prepared and isolated in a similar manner.

***Penicillamine Methyl Ester* (11).** Penicillamine (4 g, 26.8 mol) in 20 mL of methanol with 2.4 mL of thionyl chloride was stirred at room temperature for 1 week, and the solvent was evaporated to near dryness. The residue was dissolved in 192 mL of 0.6 M HCl and extracted twice with 96 mL of $CHCl_3$. The chloroform solution was again extracted with 39 mL of 1 M HCl; the aqueous phases were combined and adjusted to pH 9.5 with Na_2CO_3. The product was isolated by extracting the aqueous solution with five 20-mL portions of chloroform which was dried

over $MgSO_4$. The solution was evaporated to $^1/_4$ volume and diluted with 75 mL of diethyl ether. Bubbling HCl gas into the cold solution yielded a white crystalline solid: mp 185–187 °C; IR (KBr) 1745 cm^{-1}. A solution of penicillamine methyl ester which can be used directly in the thiazoline synthesis was obtained when the basic aqueous phase was extracted 5 times with CH_2Cl_2. Penicillamine ethyl ester **12** was prepared and used in the same manner.

Acknowledgment

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Registry No. **1**, 55771-38-5; **2**, 89530-15-4; **3**, 55771-72-7; **4**, 89530-16-5; **5**, 89530-17-6; **6**, 62096-93-9; **7**, 2519-89-3; **8**, 3113-46-0; **9**, 89530-18-7; **10**, 89530-19-8; **11**, 34297-27-3; **12**, 63474-91-9; penicillamine, 52-67-5; cysteine ethyl ester hydrochloride, 868-59-7; benzonitrile, 100-47-0; ethyl acetimidate hydrochloride, 2208-07-3; methyl benzimidate hydrochloride, 5873-90-5.

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Structure of a New 1,4-Diphenyl-3*H*-2-benzopyran-3-one Derivative

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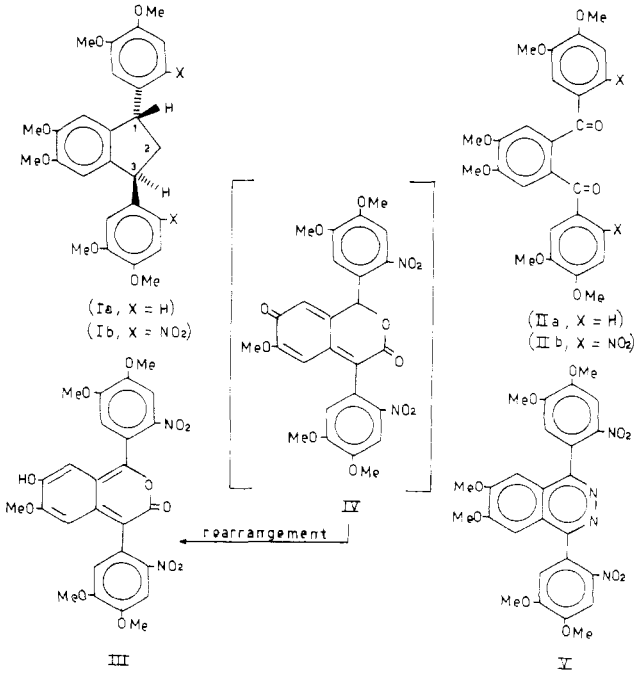
Diketone IIb and small amounts of 1,4-bis(3,4-dimethoxy-2-nitrophenyl)-7-hydroxy-6-methoxy-3*H*-2-benzopyran-3-one (III) were obtained by oxidation of *trans*-1,3-bis(4,5-dimethoxy-2-nitrophenyl)-5,6-dimethoxyindane (Ib) prepared by nitration of Ia. Compound IIb treated with hydrazine hydrate afforded the corresponding 1,4-diarylphthalazine V. The compounds were characterized by microanalysis and NMR, IR, and mass-spectral data.

In the present paper we report on studies of the oxidation of 1,3-bis(4,5-dimethoxy-2-nitrophenyl)-5,6-dimethoxyindane (Ib) obtained by nitration of Ia (*1*). On the basis of NMR spectral evidence, trans configurations must be assigned to both Ia and Ib because the protons of positions 2 are magnetically equivalent.

Compound Ib oxidized similarly to Ia (*1*) gave two products. The first one was identified as (4,5-dimethoxy-1,2-phenylene)-bis[(2-nitro-4,5-dimethoxyphenyl)methanone] (IIb), sparingly soluble in ethanol. For the second product, $C_{26}H_{22}N_2O_{12}$, soluble in ethanol as well as aqueous sodium hydroxide solution, we tentatively assign the structure of 1,4-bis(4,5-dimethoxy-2-nitrophenyl)-7-hydroxy-6-methoxy-3*H*-2-benzopyran-3-one (III). It probably is formed via the quinone intermediate IV (*2*).

By analogy with *o*-diaroylbenzenes which upon treatment with hydrazine hydrate give the corresponding 1,4-diarylphthalazines (*3*), the diketone IIb was transformed readily into 1,4-bis(2-nitro-4,5-dimethoxyphenyl)-6,7-dimethoxyphthalazine (V).



Experimental Section

General Methods. Melting points were determined on Thiele (Ib and IIb) and Kofler (III and V) apparatus and are uncorrected. Infrared spectra were recorded in Nujol mulls with a

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