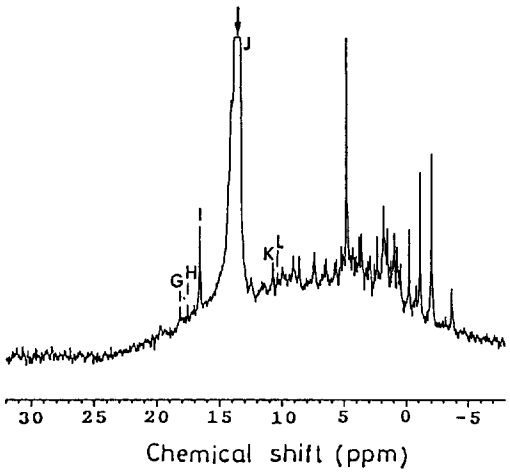


Figure 7. A spin-diffusion difference spectrum of ferricytochrome c_3. Signal J was irradiated for 5s. Otherwise, the conditions were same to the NOE difference spectra.

Since heme methyl groups represented by I, J, and K are located inside of the protein according to the assignment in Table 1, the spin diffusion from J to K is reasonable. However, heme methyl H is exposed to the solvent in the crystal structure. We checked the possibility of spill-over of the power by changing the power level of the irradition. But it was not the case. As can be seen in Figure 2b, heme methyl H is close to the β-methyl protons in the thioether bridge. This can provide a pathway of spin diffusion from the interior of the protein, because the structure of the bridge would be rigid.

Heme methyl G should be assigned to 5-CH_3 of either heme II or III in the crystal structure. While 5-CH_3 of heme II is exposed to the solvent, that of heme III is located in the interior of the protein. Moreover, 5-CH_3 of heme II has no rigid protons in the neighborhood in the crystal structure. Therefore, it is unlikely that there is a path of spin diffusion from J to G. It leads to a tentative assignment of signal G to 5-CH_3 of heme III. Therefore, we can tentatively assign hemes 2 and 4 in NMR spectra to those of III and II in crystal structure, respectively.

Acknowledgments. The authors are grateful to prof. H. Akutsu, Yokohama National University for his assistance.

References

1. J. R. Postgate, *The Sulphate-reducing Bacteria*, 2nd ed., Cambridge University Press, Cambridge, U. K., p. 76 (1984).
2. M. Pierrot, R. Haser, M. Frey, F. Payan, and J. P. Astier, *J. Biol, Chem.*, **257**, 14341-14348 (1982).
3. Y. Higuchi, M. Kusunoki, Y. Matsuura, N. Yasuoka, and M. Kakudo *J. Mol. Biol.*, **172**, 109-139 (1984).
4. M. Bruschi, M. Loutfi, P. Bianco, and J. Haladjian *Biochem. Biophys. Res. Commun.*, **120**, 384-389 (1984).
5. K. Niki, Y. Kawasaki, Y. Higuchi, and N. Yasuoka *Langmuir*, **3**, 982-986 (1987).
6. K. Fan, H. Akutsu, K. Niki, N. Higuchi, and Y. Kyogoku, *J. Electroanal. Chem.*, **278**, 295-306 (1990).
7. J. P. Gayda, T. Yagi, H. Benosaman, and P. Bertrand *FEBS Lett.*, **217**, 57-61 (1987).
8. K. Fan, H, Akutsu, Y. Kyogoku, and K. Niki, *Biochemistry*, **29**, 2257-2263 (1990).
9. A. Dolla, C. Cambillau, P. Bianco, J. Haladjian, and M. Bruschi, *Biochem. Biophys. Res. Commun.*, **147**, 818-823 (1987).
10. B. Guigliarelli, P. Bertrand, C. More, R. Haser, and J. P. Gayda *J. Mol. Biol.*, **216**, 161-166 (1990).
11. J. S. Park, M. Enoki, A. Ohbu, K. Fan, Y. Kygoku, K. Niki, and H. Akutsu, *J. Mol. Struct.*, **242**, 343-353 (1991).
12. S. Ramaprasad, R. D. Johnson, and G. N. La Mar *J. Am. Chem. Soc.*, **106**, 3632-3635 (1984).

Ring Transformations of Ethyl 4-Carbethoxy-5,6-dihydro-1-1-dioxo-2*H*-1,2,6-thiadiazin-5-ylethanoate into N-Alkyl-5-carbethoxy-2-pyridones

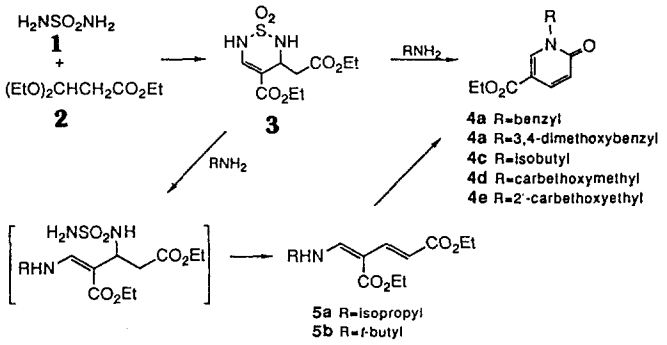
Chai-Ho Lee, Young Soo Chung, and Bong Young Chung*

Department of Chemistry, Won Kwang University, Chunbuk 570-749
**Department of Chemistry, Korea University, Seoul 136-701.* *Received May 6, 1993*

Treatment of ethyl 4-carbethoxy-5,6-dihydro-1,1-dioxo-2*H*-1,2,6-thiadiazin-5-ylethanoate (**3**) with alkylamines produced N-alkyl-5-carbethoxy-2-pyridones (**4**) in moderate yields.

Introduction

In recent years, we have been interested in the synthesis of some heterocycles containing sulfamide moiety[1] because they have been found to possess a wide range of biological activities such as anticonvulsant, hypoglycemic, antihypertensive, histamine-H_2-receptor antagonistic and herbicidal activities.[2] Unfortunately, little is known about the ring transfor-



Scheme 1.

mations of the unsaturated cyclic sulfamides by alkylamines. The early description of conversion of thiadiazines into pyrazoles by the action of hydrazine is the only example of this kind of conversion.[3] We now wish to report a new ring transformation reaction of ethyl 4-carbethoxy-5,6-dihydro-1,1-dioxo-2*H*-1,2,6-thiadiazin-5-ylethanoate (**3**) into N-alkyl-5-carbethoxy-2-pyridones (**4**).

Results and Discussion

Reaction of a trifluoroacetic acid solution of sulfamide (**1**) with ethyl 3,3-diethoxypropanoate (**2**) at room temperature produced the cyclic sulfamide **3**.[1d] Treatment of **3** with less hindered alkylamines in ethanol gave N-alkyl-5-carbethoxy-2-pyridones (**4**) in 33-66% yields. However, bulky alkylamines such as isopropylamine and *t*-butylamine afforded only ethyl 5-alkylamino-4-carbethoxy-2,4-pentadienoates (**5**), instead of the corresponding pyridones.

Compounds **4** have been assigned as N-alkyl-5-carbethoxy-2-pyridones on the basis of the ^{1}H- and ^{13}C-NMR spectral data. Distinctive signals were observed in the ^{1}H-NMR spectra for the methine protons of C-3 (δ 6.48-6.53 ppm), C-4 (δ 7.74-7.99 ppm), and C-6 (δ 8.05-8.31 ppm), and in the ^{13}C-NMR spectra for the carbonds of C-3 (δ 119.47-119.82 ppm), C-4 (δ 138.14-138.52 ppm), C-5 (δ 109.61-110.47 ppm), C-6 (δ 142.24-143.24 ppm), and the two carbonyl carbons (δ 162.00 -162.58 ppm and 163.89-164.22 ppm). The carbethoxy carbonyl and amide carbonyl stretching bands of **4** were also observed in their IR spectra at 1770-1710 cm^{-1}, respectively. However, employment of the bulky primary amines in this procedure afforded only ethyl 5-alkylamino-4-carbethoxy-2,4-pentadienoates (**5**). This result indicates that the reaction of compound **3** with primary alkylamines proceeds through the following reaction pathways as depicted in Scheme 1 : 1) attack of alkylamines to the C-5 of compound **3** to produce ethyl 5-alkylamino-4-carbethoxy-3-sulfamido-4-pentenoates as intermediates, 2) elimination of sulfamide (**1**) from the above intermediates to yield **5**, and 3) cyclization of **5** to give pyridones **4**. In the cases of bulky amines, the final step may be prohibited due to the steric hindrance.

Experimental

General. Infrared (IR) spectra were obtained on a Perkin Elmer 710B spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AC 100 (100 MHz) and JMN-EX 400 FT NMR spectrometer. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS. Reagents and solvents were used without further purification.

Preparation of Ethyl 4-Carbethoxy-1,1-dioxo-5,6-2*H*-1,2,6-thiadiazin-5-ylethanoate (3)[1d]

A trifluoroacetic acid (10 m*l*) solution containing sulfamide (**1**, 0.20 mmol) and ethyl 3,3-diethoxypropanoate (**2**, 0.40 mmol) was stirred at room temperature for 24 hr and concentrated to dryness. The flash column chromatography (chloroform) of the crude product **3** afforded the product **3** in 40% yield. IR (chloroform): 3285, 3220, 1720, 1700, 1360, 1145 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.14-1.20 (m, 6H), 2.6H (dd, 1H, J=2.80, 15.7 Hz), 2.98 (dd, 1H, J=11.20-15.70 Hz), 4.05-4.12 (m, 4H), 4.54-4.60 (m, 1H), 7.32 (s, 1H), 7.62 ppm (d, 1H, J=6.30 Hz, D_2O exchangeable). The remaining N-H signal was not detected; ^{13}C-NMR (DMSO-d_6): δ 4.16, 14.33, 37.04, 59.26, 59.90, 61.64, 100.21, 141,93, 165.42, 170.55 ppm.

General Procedures for the Preparation of N-Alkyl-5-carbethoxy-2-pyridones (4) or Ethyl 5-Alkylamino-4-carbethoxy-2,4-pentadienoates (5)

A solution of **3** (1.00 mmol) and alkylamine (1.00 mmol) in ethanol (20.0 m*l*) was refluxed for 30 hr and concentrated to dryness. The residue was purified by flash column chromatography (chloroform) to give the desired product **4** or **5**.

N-Benzyl-5-carbethoxy-2-pyridone (4a). Reaction of **3** with benzylamine gave **4a** as an oil in 62% yield. IR (chloroform): 1715, 1665 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H, J=7.20 Hz), 4.20 (q, 2H, J=7.20 Hz), 5.07 (s, 2H), 6.48 (d, 1H, J=9.50 Hz), 7.22-7.25 (m, 5H), 7.74 (dd, 1H, J=2.50, 9.50 Hz), 8.05 ppm (d, 1H, J=2.50 Hz); ^{13}C-NMR ($CDCl_3$): δ 14.21, 52.64, 60.98, 110.24, 119.82, 128.07, 128.26, 128.92, 135.45, 138.52, 142.50, 162.38, 164.08 ppm; Anal: Cacld for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.11; H, 5.79; N, 5.52.

N-(3,4-Dimethoxybenzyl)-5-carbethoxy-2-pyridone (4b):. Reaction of **3** with 3,4-diemethoxybenzylamine gave **4b** as an oil in 57% yield. IR (chloroform): 1715, 1665 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.25 (t, 3H, J=7.2 Hz), 3.79 (s, 6H), 4.21 (q, 2H, J=7.20 Hz), 5.02 (s, 2H), 6.49 (d, 1H, J=9.50 Hz), 6.78-6.96 (m, 3H), 7.76 (dd, 1H, J=2.30, 9.50 Hz), 8.10 ppm (d, 1H, J=2.30 Hz); ^{13}C-NMR ($CDCl_3$): δ 14.19, 52.38, 55.78, 55.84, 60.94, 110.24, 111.12, 11.52, 119.68, 120.81, 127.91, 138.45, 142.24, 149.07, 149.25, 162.43, 164.04 ppm.

N-Isobutyl-5-carbethoxy-2-pyridone (4c). Reaction of **3** with isobutylamine gave **4c** as an oil in 33% yield. IR (chloroform): 1721, 1670 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.93 (d, 6H, J=6.60 Hz), 1.33 (t, 3H, J=7.20 Hz), 2.15 (m, 1H), 3.77 (d, 2H, J=6.30 Hz), 4.23 (q, 2H, J=9.40 Hz), 6.51 (d, 1H, J=9.40 Hz), 7.88 (dd, 1H, J=2.40, 9.50 Hz), 8.08 ppm (d, 1H, J=2.4 Hz); ^{13}C-NMR ($CDCl_3$): δ 14.22, 19.62, 27.82, 30.82, 57.48, 60.94, 109.61, 119.59, 138.32, 143.03, 162.58, 164.22 ppm.

N-Carbethoxymethyl-5-carbethoxy-2-pyridone (4d). Reaction of **3** with glycine ethyl ethyl ester hydrochloride and triethylamine (1.1 mmol) gave **4d** as an oil in 66% yield. IR (chloroform): 1740, 1710, 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.26 (t, 3H, J=7.00 Hz), 1.33 (t, 3H, J=7.10 Hz), 4.14 (q, 2H, J=7.00 Hz), 4.34 (q, 2H, J=7.10 Hz), 4.67 (s, 2H), 6.55 (d, 1H, J=9.60 Hz), 7.99 (dd, 1H, J=2.30, 9.60 Hz), 8.22 ppm (d, 1H, J=2.30 Hz); ^{13}C-NMR ($CDCl_3$): δ 13.92, 14.16, 50.77, 60.97, 61.97, 110.18, 119.47, 139.14, 143.24, 162.00, 163.89, 166.98 ppm.

N-(2-Carbethoxyethyl)-5-carbethoxy-2-pyridone (4

e). Reaction of **3** with β-alanine ethyl ester hydrochloride and triethylamine (1.1 mmol) gave **4e** as an oil in 47% yield. IR (chloroform): 1735, 1720, 1665 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.23 (t, 3H, J=7.20 Hz), 1.35 (t, 3H, 7.10 Hz), 2.85 (t, 2H, J=6.20 Hz), 4.02-4.42 (m, 6H), 6.53 (d, 1H, J=9.50 Hz), 7.87 (dd, 1H, J=2.40, 9.50 Hz), 8.31 ppm (d, 1H, J=2.40 Hz); ^{13}C-NMR ($CDCl_3$): δ 14.04, 14.28, 32.79, 47.07, 59.91, 61.00, 109.90, 119.53, 138.94, 143.84, 162.40, 164.27, 170.96 ppm.

Ethyl 4-carbethoxy-5-isopropylamino-2,4-pentadienoate (5a). Reaction of **3** with isopropylamine gave **5a** as an oil in 65% yield. IR (chloroform): 3280, 1700, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.07-1.36 (m, 12H), 3.53 (m, 1H), 3.98-4.33 (m, 4H), 6.95 (d, 1H, J=16.90), 7.17-7.43 (m, 2H), 8.79-8.90 ppm (brd m, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.31, 23.45, 50.53, 59.39, 59.54, 94.06, 107.27, 143.42, 155.14, 168.80, 169.05 ppm.

Ethyl 5-*t*-Butylamino-4-carbethoxy-2,4-pentadienoate (5b). Reaction of **3** with *t*-butylamine gabe **5b** as an oil in 72% yield. IR (chloroform): 3260, 1700, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.31 (s, 9H), 1.13-1.48 (m, 6H), 4.05-4.35 (m, 4H), 6.99 (d, 1H, J=15.50 Hz), 9.15-9.30 ppm (brd m, 1H); ^{13}C-NMR ($CDCl_3$): δ 14.10, 14.37, 29.85, 52.90, 59.48, 59.60, 94.09, 107.15, 143.76, 153.05, 168.96, 169.14 ppm.

Conclusion

An expedient route has been developed for the preparation of N-alkyl-5-carbethoxy-2-pyridones from cyclic sulfamides and primary amines, which is a new example of ring transformation.

Acknowledgement. The present studies were supported by the Basic Science Research Institute Program, Ministry of Education, 1992, Project No. BSRI-92-334.

References

1. (a) C.-H. Lee, Y. H. Lee, W. S. Choi, and B. Y. Chung, *Bull. Korean Chem. Soc.*, **13**, 462 (1992); (b) C.-H. Lee, M. S. Lee, Y. H. Lee, and B. Y. Chung, *Bull. Korean Chem. Soc.*, **13**, 357 (1992); (c) C.-H. Lee, S. Y. Jin, Y. H. Lee, and B. Y. Chung, *Bull. Korean Chem. Soc.*, **13**, 8 (1992); (d) C.-H. Lee and H. Kohn, *J. Heterocyclic Chem.*, **27**, 2107 (1990); (e) C.-H. Lee and H. Kohn, *J. Org. Chem.*, **55**, 6097 (1990); (f) C.-H. Lee and Kohn, *J. Pharm. Sci.*, **79**, 716 (1990); (g) C.-H. Lee, J. D. Korp, and H. Kohn, *J. Org. Chem.*, **54**, 3077 (1989); (h) C.-H. Lee and H. Kohn, *Heterocycles*, **27**, 2581 (1988).
2. (a) P. Aeberli, J. Gogerty, and W. Houlihan, *J. Med. Chem.*, **10**. 636 (1967); (b) E. H. Weiseman, J. N. Pereira, K. F. Finger, and R. Pinson, *J. Med. Chem.*, **8**. 777 (1965); (c) H. Stegelmeier, E. Nimers, U. Rosentereter, A. Knorr, and B. Garthoff (Bayer AG), D.O.S. 3309655, Sept. 20, 1984; *Chem. Abstr.*, **102**, 24633 (1985); (d) A. M. Pietruszkiewicz and J. J. Baldwin, *J. Heterocyclic Chem.*, **20**, 821 (1983); (e) A. Zeidler, K. H. Konig, and D. Mangold, *Kem.-Kemi*, **9**, 590 (1974).
3. J. Elguero. P. Goya, and A. Martinez, *Heterocycles*, **29**, 245 (1989).

Effects of N-and C-Substituents on Protonation of 14-Membered Tetraaza Macrocycles and Formation of their Copper(II) and Nickel(II) Complexes

Shin-Geol Kang*, Mi-Seon Kim, Jang-Sik Choi, and Moon Hwan Cho†

Department of Chemistry, Taegu University, Kyungsan 713-714
†Department of Chemistry, Kangweon National University, Chuncheon 200-701
Received April 28, 1993

The protonation constants of the 14-membered tetraaza macrocycles A(3,14-dimethyl-2,6,13,17-tetraazatricyclo[16.4.0^{1,18}.0^{7,12}]docosane) and B(2,3,6,13,14,17-hexamethyl-2,6,13,17-tetraazatricyclo-[16.4.0^{1,18}.0^{7,12}]docosane) were measured by potentiometry. The formation constants of each of these ligands with copper(II) and nickel(II) were determined by an out-of-cell spectrophotometric method. The results indicate that the per-N-methylated macrocycle B exhibits much higher selectivity for complex formation with copper(II) over nickel(II) ion than A and other related 14-membered tetraaza macrocycles. The effects of the N-and C-substituents on the basicity and the metal ion selectivity of the ligands are discussed. The synthesis and properties of copper(II) and nickel(II) complexes of B are also described.

Introduction

There has been considerable interest in the synthesis of macrocyclic ligands which show high selectivity for a particular metal ion in the complex formation,[1-14] since such ligands can be used in the fields of biochemistry, waste treatment, and hydrometallurgy. Crown ethers often show some size-based selectivity toward IA or IIA metal ions.[1] However, most polyaza macrocyclic ligands form complexes with nickel(II) and copper(II) ions without showing considerable selectivity for one of the two.[5-13] Although it has been reported that D in the Chart 1 shows some selectivity for copper(II) over