Tetrahedron Letters No. 23, pp 2345 - 2348, 1972. Pergamon Press. Printed in Great Britain.

# A NEW REACTION IN CEPHALOSPORIN DERIVATIVES. A NUCLEOPHILIC SUBSTITUTION OF 2-(4-CARBOXY-7-ACYLAMINOCEPH-3-EM-3-YLMETHYLTHIO)PYRIDINE N-OXIDE DERIVATIVES IN THE PRESENCE OF COPPER(II) SALTS.

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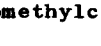
(Received in Japan 17 April 1972; received in UK for publication 2 May 1972)

Reactions under mild conditions are the essential requirement for the chemical manipulations of cephalosporanic acid derivatives. We now report a new and facile nucleophilic substitution reaction of 2-[4-carboxy-7-(2-thienylacetamido)ceph-3-em-3-ylmethylthio]pyridine N-oxide (Ia).

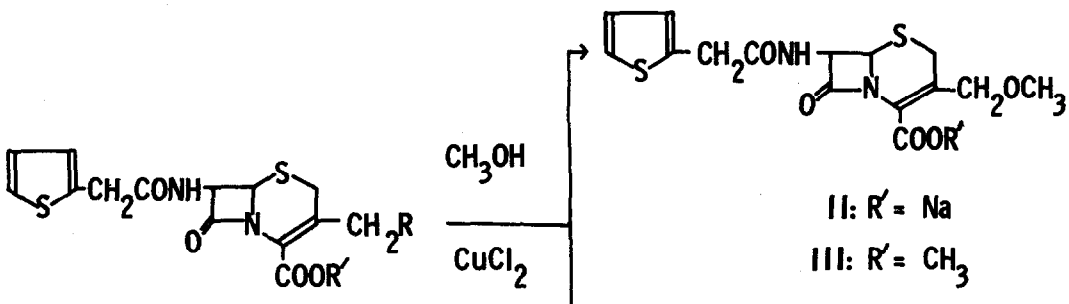
The starting material Ia was obtained in 94% yield by the reaction of sodium 7-(2-thienylacetamido)cephalosporanate and sodium salt of 2-pyridinethiol N-oxide in water (24 hr at 50°C). When a methanolic solution of Ia was stirred for 48hr at room temperature in the presence of 0.5 mole equivalent of $CuCl_2$ a mixture of 3-methoxymethylcephem derivative (II)[1] and 3-methylenecepham derivative (IV) was obtained in 75% yield (II:IV= 50:50) along with the copper salt (VI). IV: mp 166-168°C, C, 43.90; H, 3.92; N, 6.68%, $C_{15}H_{15}O_5N_2S_2Na \cdot H_2O$ requires C, 44.10; H, 4.19; N, 6.85%, IR (KBr); 1755 $cm^{-1}$(β-lactam), NMR ($\delta$, 100 Mc, $D_2O$); 3.61 (singlet, 3H, 4-$OCH_3$), 3.75 (AB quartet, 2H, 2-$CH_2$), 5.35 (doublet, 1H, 6-CH), 5.52 (doublet, 1H, 7-CH), and 5.60 (singlet, 2H, C=$CH_2$).

When Ia was stirred with 2 mole equivalents of $CuCl_2$ in methanol for

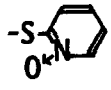
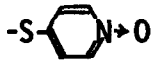
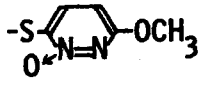
30 min at room temperature II was obtained exclusively in 49% yield. The methyl ester (Ib) gave III upon treatment with 2-3 mole equivalents of $CuCl_2$ in methanol. III: mp 178-180°C, C, 50.10; H, 4.78; N, 7.71%, $C_{16}H_{18}O_5N_2S_2$ requires C, 50.24; H, 4.74; N, 7.32%, IR ($CHCl_3$); 1785 $cm^{-1}$ (β-lactam), NMR (δ, 100 Mc, $CDCl_3$); 3.32 (singlet, 3H, 3-$CH_2OC\underline{H}_3$), 3.47 (singlet, 2H, 2-$C\underline{H}_2$), 3.82 (singlet, 3H, 4-$COOC\underline{H}_3$), 4.26 (singlet, 2H, 3-$C\underline{H}_2OCH_3$), 4.92 (doublet, 1H, 6-C$\underline{H}$), 5.78 (quartet, 1H, 7-C$\underline{H}$), and 6.43 (doublet, 1H, N$\underline{H}$).

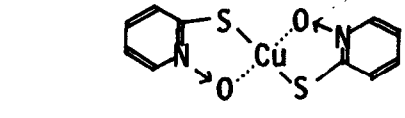
The observation that Ic and Id failed to afford II and IV while the pyridazine derivative (Ie) gave II and IV, together with the afore-mentioned isolation of the copper salt (VI), strongly suggests a participation of VII in the present reaction. The reaction also proceeded in the presence of other copper(II) and mercury(II) salts but less satisfactorily. Reaction with other alcohols and phenols gave similar results. As an extension of the present reaction Ia was treated with sulfanilamide in the presence of $CuCl_2$ in DMF to give 3-aminomethylcephem derivative (I, R=NH-  -$SO_2NH_2$, R'=Na): mp>280°C, C, 44.58; H, 3.84%, $C_{20}H_{19}O_6N_4S_3Na\cdot\frac{1}{2}H_2O$ requires C, 44.51; H, 3.73%, IR (KBr); 1760 $cm^{-1}$(β-lactam), NMR (δ, 100 Mc, $D_2O$); 3.27 (AB quartet, 2H, 2-$C\underline{H}_2$), 4.25 (AB quartet, 2H, 3-$C\underline{H}_2$), 5.05 (doublet, 1H, 6-C$\underline{H}$), 5.72 (doublet, 1H, 7-C$\underline{H}$), 6.90 and 7.81 (two doublets, 4H, phenyl protons).

The nmr study of IV in $DCl/CD_3OD$ indicated that the isomerization of IV to II proceeded with incorporation of a $CD_3O$ group at the 3-position.[2] This isomerization is somewhat worthy of note because it gives not only a biologically active 3-methoxymethylcephem derivative (II)[1] but also provides other possible utilities as exemplfied by the formation of a 3-ethoxymethylcephem derivative (VIII) from V by the reaction with ethanol containing 3% of hydrogen chloride. VIII: mp 176-178°C, C, 50.54; H, 4.90; N, 6.91% $C_{17}H_{20}O_5N_2S_2\cdot\frac{1}{2}H_2O$ requires C, 50.35; H, 5.22; N, 6.90%, NMR (δ, 100 Mc, $CDCl_3$); 1.16 (triplet, 3H, $-CH_2C\underline{H}_3$), 3.42 (quartet, 2H, $-C\underline{H}_2CH_3$), 3.46 (singlet, 2H, 2-$C\underline{H}_2$), 3.78 (singlet, 3H, 4-$COOC\underline{H}_3$), 4.88 (doublet, 1H, 6-C$\underline{H}$), 5.72 (quartet, 1H, 7-C$\underline{H}$), and 6.76 (doublet, 1H, N$\underline{H}$).

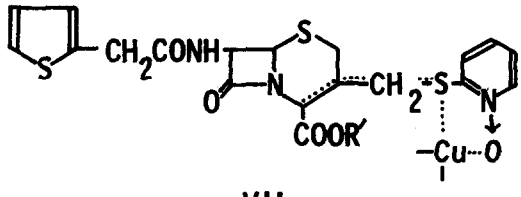



I

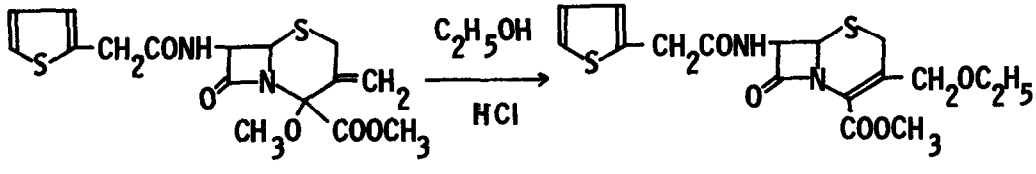
| | R | R′ |
|---|---|---|
| Ia: |  | Na |
| b: | 〃 | $CH_3$ |
| c: |  | Na |
| d: |  | 〃 |
| e: |  | 〃 |



VI



VII




V VIII

The present reaction of 2-(4-carboxy-7-acylaminoceph-3-em-3-ylmethylthio)pyridine N-oxide derivative with O or N nucleophiles in the presence of copper(II) salts provides an alternative[1,3] and convenient method for the preparation of 3-(substituted methyl)-3-cephem derivatives.

Furthermore the reaction suggests that a combination of an azine-2-thiol 1-N-oxide and copper(II) salts may have a versatile and promising utility in the synthetic organic chemistry. Further application of the present reaction and the study of the stereochemistry at the 4-position of the 3-methylenecepham derivatives are under way in this laboratory.

Acknowledgements The authors are grateful to Drs. S. Tatsuoka, K. Morita and K. Masuda for their encouragement throughout this work.

## References

1. J. A. Webber, G. W. Huffman, R. E. Koehler, C. F. Murphy, C. W, Ryan, E. M. Van Heyningen, and R. T. Vasileff, J. Med. Chem. 14, 113 (1971).
2. Nmr spectrum of the isomerized compound was identical with II except the absence of the peak due to 3-$CH_3O$ group.
3. Glaxo Laboratories Ltd., BE Patents 719,710-719,712 (basic No. 36,338-36,340), Aug. 20, 1968.