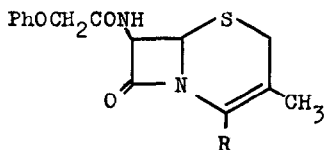


CYCLOADDITION REACTIONS OF CEPHALOSPORIN COMPOUNDS I.
THE CYCLOADDITION OF DIAZOMETHANE TO THE CEPHEM NUCLEUS.

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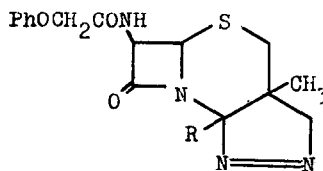
(received in UK 25 September 1973; accepted for publication 10 October 1973)

The cycloaddition of diazomethane to methyl 7-methoxy-carbamido-cephalosporanate in dichloromethane was reported by Archer and Kitchell¹. They isolated the resulting compound by column chromatography and found it to have a 2-pyrazoline structure. In this field no further results have been published up till now. Our investigation deals with the cycloaddition of diazomethane to C₃-methyl-cephem compounds.



I

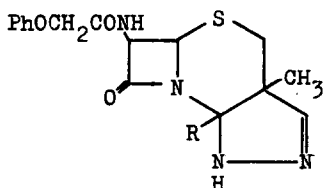
- a, R = $-\text{COOCH}_2\text{C}_6\text{H}_4\text{-p-NO}_2$
b, R = $-\text{COOCH}_2\text{CCl}_3$
c, R = $-\text{COOCH}_3$
d, R = $-\text{H}$



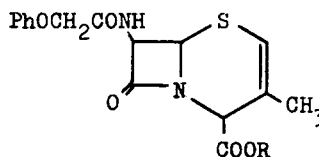
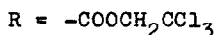
II

Ia-c were allowed to stand with excess of diazomethane in dichloro-methane-ether solution at room temperature for one week. IIa-c precipitated in crystalline form². In spite of this we found unreactivity in the case of Id.

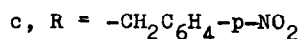
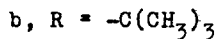
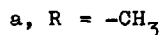
The cephem Δ^3 -double bond having dipolarophile role is a homoconjugated π -system and it is influenced by the interaction with the nitrogen lone-pair electrons and π and p orbitals of the ester carbonyl group. Moreover, the allyl sulphide properties of the dihydrothiazine ring must also be taken into consideration. In the nmr spectra of Iia-c there was only one signal exchangeable with D_2O (δ 9.1 doublet), due to the C_7 -NH proton. The singlet assigned to the C_3 -methyl group occurred at δ 0.96 vs δ 2.18 for Ia. A new triplet showing the presence of two further protons was observed (δ 3.01 and 2.85, $J=15.5$ cps) and assigned to the $-CH_2-$ group of the pyrazoline ring. According to these facts and the uv spectra, the compounds are 1-pyrazolines³. In spite of the results of Archer and Kitchell¹ there is a λ_{max} at 325 nm ($\epsilon=400, 248, 286$ for Iia-c, respectively) due to the $n \rightarrow \pi^*$ transition characteristic of the azo group⁴. The lack of the λ_{max} at 285 nm also supports this structure¹. In addition to the parent peak (M^+ at m/e 525) a peak of significant intensity occurs at m/e 497 ($M-28$) in the mass spectrum of Iia⁵. Unfortunately, the ir spectra do not give any information about the presence of the $N=N$ bond because of its low intensity, but the appearance of the C-N stretching at 1274 and 1290 cm^{-1} is consistent with the expected structure.



III



IV



We could prepare, however, the corresponding 2-pyrazolines (III) if the reactions were carried out in dimethylformamide in lieu of dichloromethane. The structure of III was confirmed by its nmr spectrum showing the same general patterns as II but instead of the two protons at $\sim\delta$ 2.9 two new signals appeared corresponding to one proton respectively, at δ 7.0 and δ 7.67. The lower field proton was exchangeable with D₂O. Moreover, the mass spectrum does not show any significant loss of nitrogen.

Although the orientation effect on the cycloaddition in the case of allyl sulphides⁶ and different acrylic acid derivatives⁷ is similar (i.e. the diazo carbon becomes attached to the δ - and β -positions, respectively), in Δ^3 -cephems the products obtained show the more dominant influence of the ester group.

Knowing the 1,3-dipolar cycloadditional reactions of vinyl sulphides with diazoalkanes, we attempted to prepare the corresponding derivatives of Δ^2 -cephem. Having prepared IVa-c from the corresponding Δ^3 -cephem methyl ester in the usual way⁸, we could not observe any reactions providing new products under the above mentioned conditions in dichloromethane-ether solution. These facts can be explained by the loss of conjugation energy causing the decrease of reaction enthalpy, i.e. the increase of transition state energy in the course of cycloaddition⁹.

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REFERENCES AND FOOTNOTES

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5. The mass spectral investigation was carried out in the Central Research Institute of Chemistry, Budapest, by Dr. J. Tamás to whom the authors are indebted.
6. K.Kondo and I.Ojima, *Chem. Letters* 711 (1972)
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9. The stereochemical aspects of this reaction including the addition of diazoalkanes to S-oxidized derivatives will be the subject of a following paper.