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STUDIES ON FUSED β-LACTAMS : SYNTHESIS OF NOVEL 1-AZA-ANALOGS OF CEPHAM

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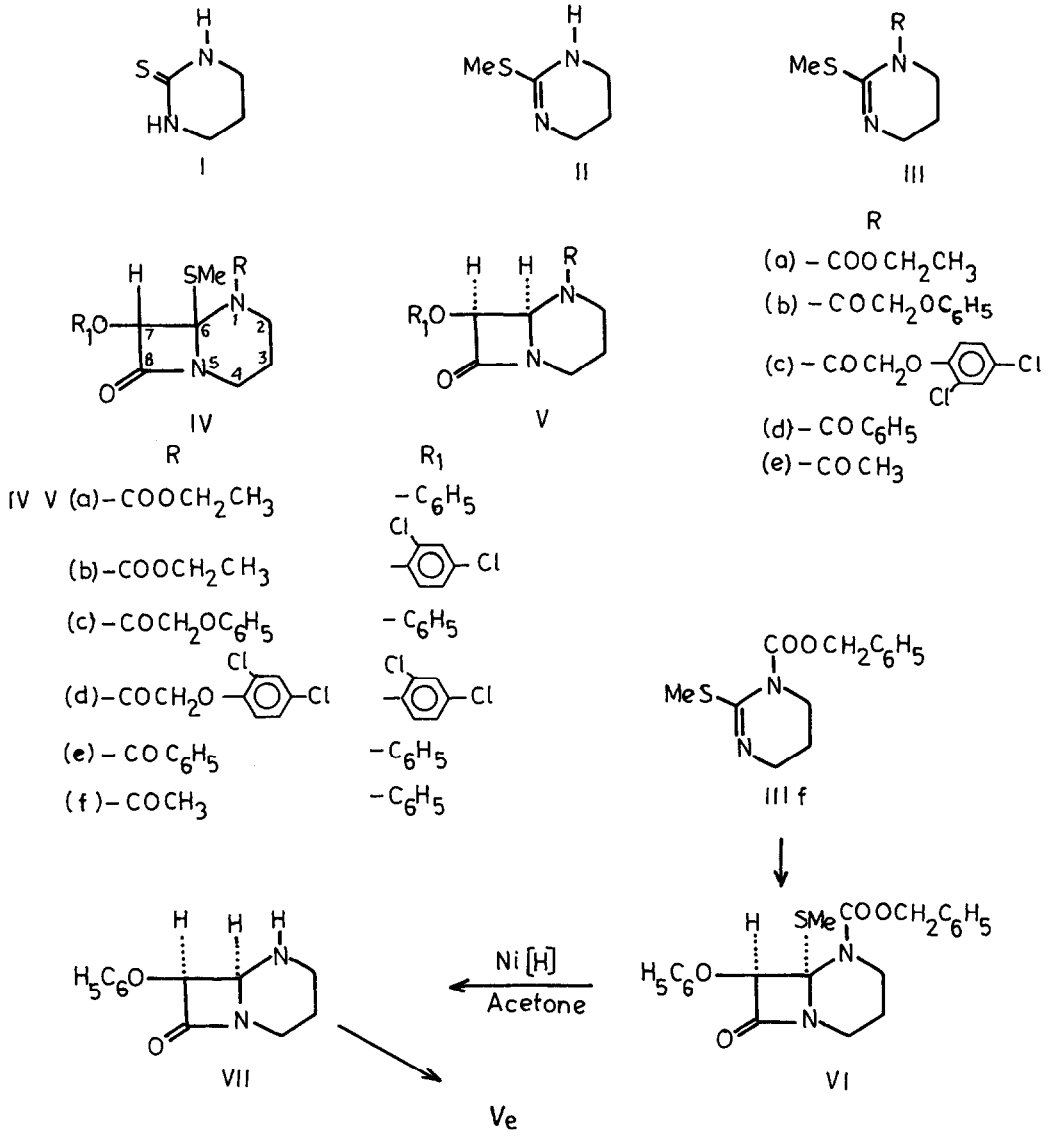
Abstract : Stereospecific synthesis of some 1-aza-analogs of cepham (V) have been accomplished using appropriate β-methylthio-β-lactams (IV) as precursors. The possible single step removal of the thiomethyl as well as benzyloxycarbonyl groups using Ni [H] converted VI into the novel 1-aza cepham (VII).

Numerous compounds have been prepared in recent years[1-6] incorporating one or more nitrogen atoms into the ring fused to the β-lactam. Among these the real 1-aza(NH) cepham was reported by Wolfe[1] et al with a trans-stereochemistry of the β-lactam ring. In continuation of our work on the synthesis of polycyclic cis-β-lactams[7,8], we wish to report here the first example of the preparation of novel 1-aza cepham (VII) with a cis-stereochemistry of the β-lactam ring. The strategy employed was the stereospecific formation of β-methylthio-β-lactams (IV).

2-Thio-hexahydropyrimidine (I)[9] was methylated with dimethylsulphate in methanol to obtain 2-methylthiotetrahydropyrimidine (II), which on acylation with appropriate acid halides produced the synthon III in excellent yields. Treatment of III with different acid chlorides in the presence of triethylamine gave the β-lactams (IV). The PMR data of these β-lactams exhibited 1H and 3H singlets for the C_7-H and the C_6-SCH_3 confirming thereby the formation of a single isomer[10] in each case.

Next, we subjected the β-methylthio-β-lactams (IV) to reductive desulphurisation which has been reported to proceed with retention of configuration[11]. This reaction using Raney-Ni in acetone converted IV to the cis-1-aza-cepham analogs (V) in good yields. The cis-stereochemistry was assigned on the basis of PMR spectra of these compounds.



The 90 MHz PMR ($CDCl_3$) spectrum (Fig.1) of the aza-cepham (Va) exhibited the β-lactam protons at δ 5.4 as a broad singlet, making it difficult to assign their stereochemistry. However, by adding a few drops of TFA to the $CDCl_3$ solution this signal could be split into a double doublet (C_6-H, J=3.0 and 1.5 Hz) and a doublet (C_7-H, J=3.0 Hz). Spin decoupling of the C_2-methylene protons converted the C_6-H signal into the expected doublet with J=3.0 Hz (coupling with C_7-H) indicating a long range coupling of C_6-H with one of the C_2-methylene protons.

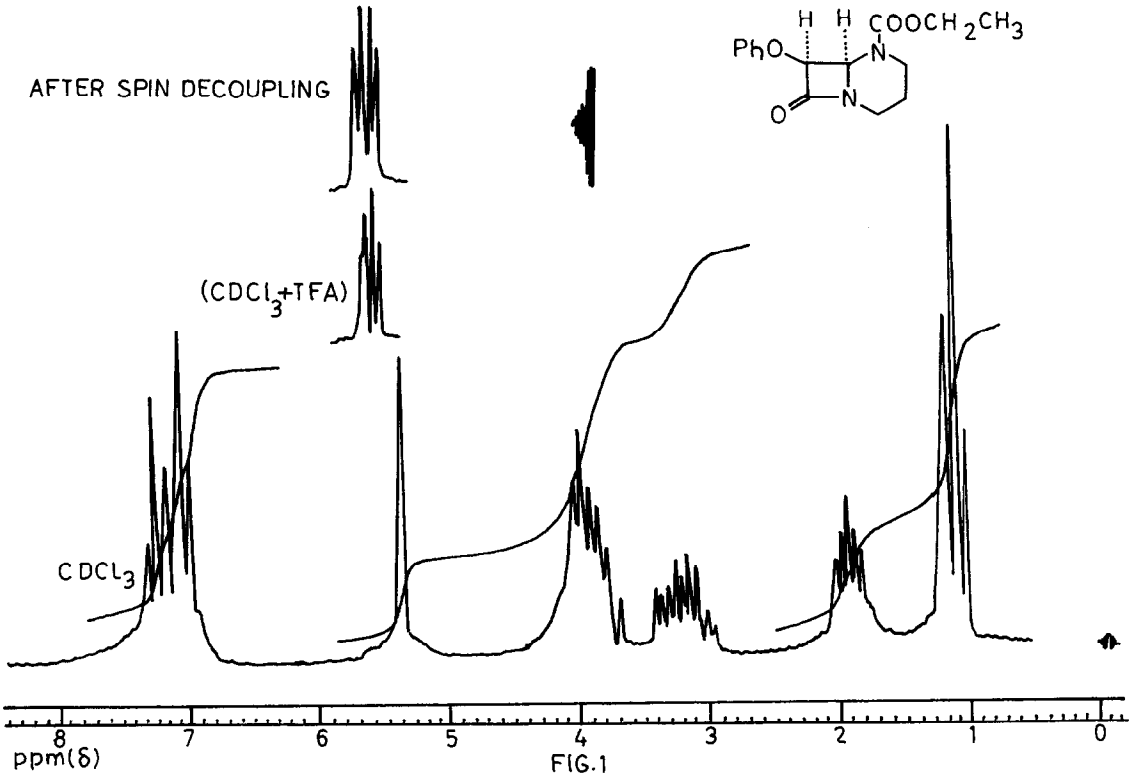


FIG.1

The PMR spectrum of Vb exhibited similar appearance for the β-lactam protons. However, no overlap of the β-lactam protons was observed in the PMR spectra of Vc-f in $CDCl_3$ solution. The C_6-H showed a long range coupling with C_2-H in all of these (Va-f) compounds and appeared as a double doublet. The coupling constant between the β-lactam protons was found to be between the range of 3.0-4.0 Hz confirming their cis-stereochemistry[12].

In order to prepare an 1-aza-cepham having the basic NH group as a C_1-substitute, we prepared the imine (III f) having a benzyloxycarbonyl function. Annelation with phenoxyacetylchloride converted IIIf into the β-methylthio-β-lactam VI from which we wanted to remove the thiomethyl as well as benzyloxycarbonyl groups to obtain the target compound VII.

It is interesting to note that the treatment of VI with Raney-Ni in acetone for about 3 hr. at reflux temperature converted it to the desired compound VII in 40% yield, m.p. 98-100°C. IR : 1760 (β-lactam CO) and 3250 cm^{-1}(N-H). The PMR of VII has all the resonances in the expected positions. The β-lactam protons are characterised by a pair of doublets at δ5.1 and 5.7 with the required cis-coupling (J=4.5 Hz). The N-H (exchangeable with D_2O) appeared as a broad peak at δ2.2. Unlike in the

N-acylated-aza-cephams (V), the C_6-H in VII shows no long range coupling with the C_2-H.

The compound VII is a novel 1-aza-cepham analog and it should be possible to convert it to any of the aza-cepham analogs (Va-f) by simple acylation with appropriate acid halide. Thus acylation of VII with benzoyl chloride in the presence of triethylamine produced a solid compound, m.p., 124-25°C and was, as expected, found to be identical in all respects to the N-benzoyl-aza-cepham (Ve). Removal of the amino protecting benzyloxycarbonyl group under mild conditions using Ni [H], as demonstrated in the present communication, shall be of immense utility in synthesis and more so in the case of sensitive β-lactam compounds.

The β-lactams reported here were obtained as crystalline solids except Va,b which remained as viscous liquids even after passing through neutral alumina columns. All the new compounds showed satisfactory elemental and spectral analysis.

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