Proton Magnetic Resonance Spectra of Penicillin and Cephalosporin Derivatives

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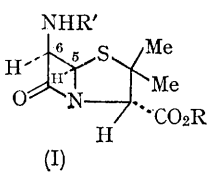
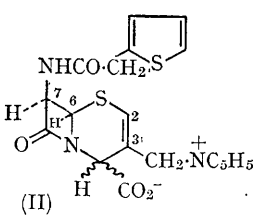
WHEN examined at 60 Mc./sec., the pattern of the proton magnetic resonance (p.m.r.) peaks for the two β-lactam protons of benzylpenicillin esters [*e.g.* (I; R = *p*-C_6H_4·NMe_2, R′ = CO·CH_2Ph)] in deuterochloroform and of pyridinium derivatives of 7β-acylamidoceph-2-em-4-carboxylic acids [*e.g.*, (II)] in deuterium oxide solution differed from those of other penicillin and cephalosporin derivatives and appeared to be anomalous.[1] These anomalies have been resolved by p.m.r. measurements conducted at 100 Mc./sec. and by measurements on solutions in other solvents.



(I)



(II)

In our original interpretation[1] of the 60 Mc./sec. spectrum of the *p*-dimethylaminophenyl ester of benzylpencillin (I; R = *p*-C_6H_4·NMe_2, R′ = CO·CH_2Ph),[2] we assigned a sharp singlet at τ 4·43 to the 5-proton and a pair of doublets of equal intensity centred at τ 4·28 and 4·47 (J = 4 c./sec.) to the 6-proton. The 100 Mc./sec. spectrum, however, reveals that the 6- and 5-protons give, respectively, a normal double doublet centred at τ 4·35 (J = 4 and 9 c./sec.) and a single doublet centred at τ 4·45 (J = 4 c./sec.). On deuteration, the double doublet for the 6-proton collapses to give a single doublet.

A p.m.r. study (60 Mc./sec.) of the *p*-chlorophenyl ester of benzylpenicillin (I; R = *p*-C_6H_4Cl, R′ = CO·CH_2Ph)[2] in a range of solvents (see Table) supports these assignments. Thus, in deuterochloroform, acetone, and dimethyl sulphoxide solutions the peaks for the two β-lactam protons overlap, but in benzene and pyridine solutions they are widely separated. The 6-proton is deshielded in pyridine (*cf.* the 7-proton of cephalosporanic acids and esters in pyridine solution[1]), but the 5-proton is shielded in benzene solution. These solvent shifts show that the anomalous patterns observed in deuterochloroform solution must be attributed to the chance equivalence of the chemical shifts for the two β-lactam protons.

Measurements at 100 Mc./sec. (deuterium oxide solution) have caused us to revise our original assignments[1] for the exocyclic methylene and β-lactam protons in the pyridinium derivatives of 7β-acylamidoceph-2-em-4-carboxylic acids [*e.g.*, (II).][3] Two single-proton doublets centred at τ 4·45 and 4·74 (J = 14 c./sec.) are now attributed to the AB system associated with the exocyclic 3-methylene group, and a sharp two-proton singlet at τ 4·70 is assigned to the 6- and 7-protons. The

other assignments are as given previously.[1] The two doublets for the exocyclic 3-methylene group of (II) are centred at the same positions as, and have similar coupling constants to, those for cephaloridin, the corresponding Δ^3-derivative (τ 4·40 and 4·70, J = 15 c./sec.; see Table 4 in Ref. 1), thus confirming that the double bond in (II) is in the ring and is at C-2. If the double bond was exocyclic, the 2-methylene group would have given an AB system consisting of two doublets (J = 18 c./sec.) with centres at about τ 6·4 and 6·9.

TABLE

Proton-resonance lines (τ-values) for β-lactam protons of the p-*chlorophenyl ester of benzylpenicillin* (I; R = *p*-C_6H_4Cl, R′ = $CO{\cdot}CH_2Ph$) *in different solvents* (J-*values in c./sec. in parentheses*)

Solvent	5-H	6-H
$CDCl_3$	4·48 (4)	4·35* (4, 8)
Acetone	4·40 (4)	4·30* (4, 8)
Me_2SO	4·33 (4)	4·40* (4, 8)
Benzene	4·83 (4)	4·38* (4, 8·5)
Pyridine	4·20 (4)	3·86* (4, 8)

* Two doublets with the J-values given

These assignments for the pyridinium derivatives of 7β-acylamidoceph-2-em-4-carboxylic acids were supported by measurements at 60 Mc./sec. on a solution of (II) in deuterated dimethyl sulphoxide. The imino-proton gave a doublet (J = 9 c./sec.) centred at τ 0·83, the 7-proton a double doublet (J = 4 and 9 c./sec.) centred at τ 4·72, the 6-proton a doublet (J = 4 c./sec.) centred at τ 4·63, and the 3-methylene protons two doublets (J = 14 c./sec.) centred at τ 4·23 and 4·60. On deuteration, the doublet for the imino-proton disappeared, and the multiplet for the 6- and 7-protons collapsed to a singlet.

The anomalous patterns of the β-lactam protons in the 60 Mc./sec. p.m.r. spectra of these penicillin and cephalosporin derivatives are caused by both β-lactam protons accidentally having similar chemical shifts. Similar effects are shown by the β-lactam protons of ampicillin [I; R = H, R′ = D-$CO{\cdot}CH(NH_2)Ph$][1] and the 12-protons of certain 11-oxo-steroids,[4] which give two-proton singlets at τ 4·49 and 7·70—7·73, respectively.

It is noteworthy that the β-lactam protons in these compounds, like those discussed previously,[1] have vicinal coupling constants of 4 c./sec., indicating that the β-lactam protons are *cis*; *trans*-β-lactam protons show coupling constants of about 2 c./sec.[5]

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