Azetidinone Intermediates for the Synthesis of Cephem Ring Systems. Part 1. Chemical Shift Non-equivalence of the Allylic Methylene Protons

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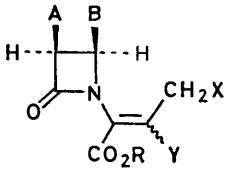
The chemical shift non-equivalence of the allylic methylene groups CH_2Br and CH_2SPh, present in some azetidinone intermediates useful for the synthesis of cephem ring systems, affords a valuable criterion for establishing the stereochemistry of the double bond. The synthetic procedures used for the preparation of the compounds examined are described.

We have recently described the chemical properties of some new β-lactam derivatives, versatile intermediates for the synthesis of cephem ring systems.[1] We now report a study on the chemical shift non-equivalence of the methylene protons, CH_2X, in azetidinone derivatives (1). Experimental details of the syntheses are also described.



(1)

It is known [2] that diastereotopic groups, such as CH_2X, are potentially anisochronous, but the extent of the chemical shift non-equivalence may not always be large enough to be noticed. In particular, the chemical shift non-equivalence of the corresponding methylene protons is not observable (or small) when X = Br or S–Ph for compounds having the CH_2X grouping *Z* with respect to the β-lactam nitrogen atom, whereas non-equivalence is relevant when CH_2X is *E* to the nitrogen atom. On the contrary, no observable splitting of the methylene protons is detected both for *E* and *Z* isomers when X is OMe, OBu^t, or OAc. The ^1H n.m.r. data related to compounds with X = Br or S–Ph are shown in the Table.

As the factors determining chemical shift non-equivalence are differences in conformational populations and intrinsic asymmetry,[2] it follows that the various substituents introduced in place of X affect mainly the first term, which is generally considered the more important. The influence of the different substituents on chemical shift non-equivalence cannot be related to their conformational energy values as determined in a substituted cyclohexane.† In fact, on this basis, bromine would be less effective than OMe or OAc in determining differences of conformational populations. Therefore, these conformational energy values cannot be applied when the substituents are bonded to the acyclic moieties of the derivatives herein examined.

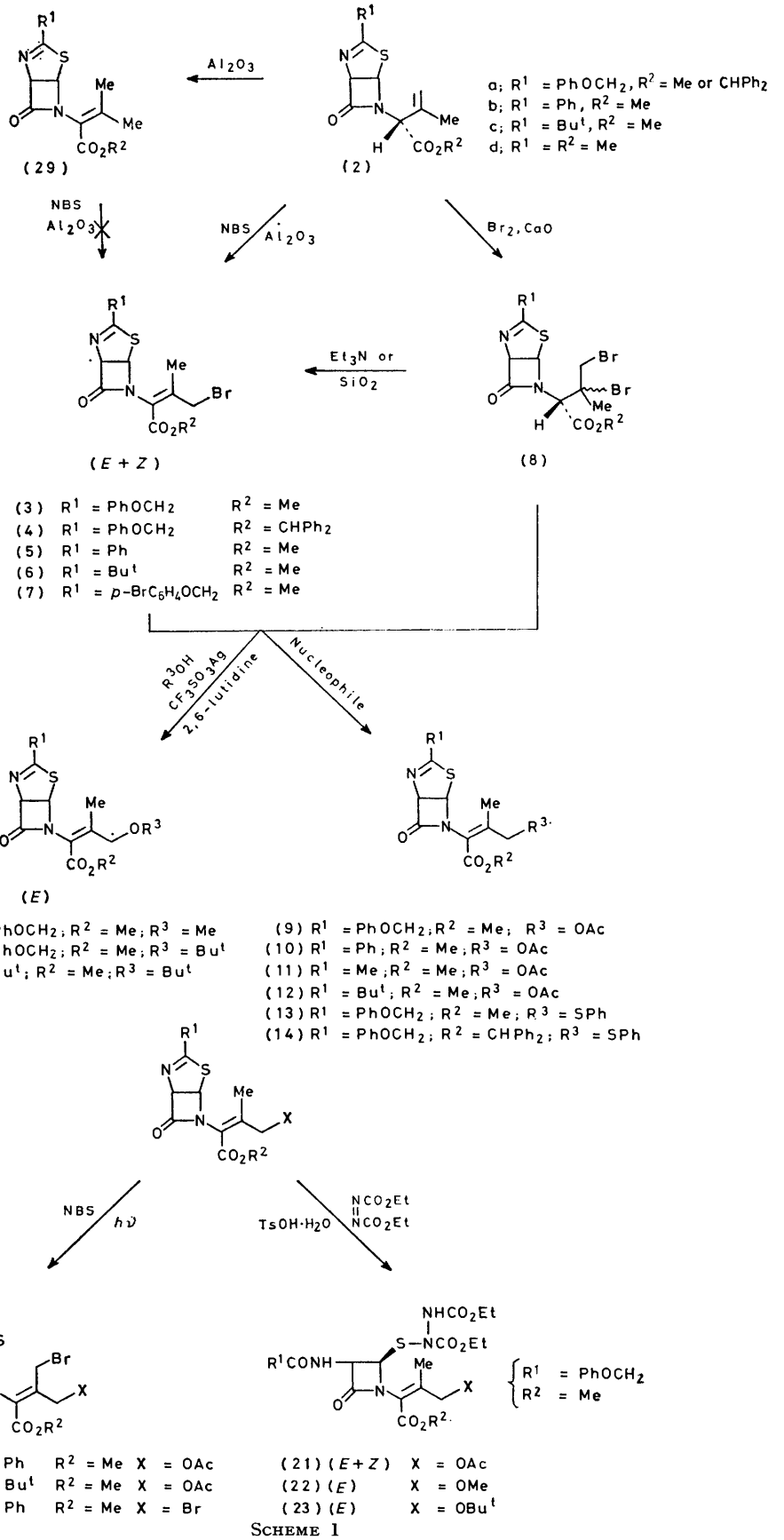
In compounds (3)—(7) having a CH_2Br geminal to a methyl group, the chemical shift non-equivalence has high values for *E* isomers (Δδ 0.28—0.36 p.p.m.), whereas among the *Z* isomers, only (5) displays a slight non-equivalence (Δδ 0.09 p.p.m.). When two geminal CH_2Br groups are present, as in compound (20), only *E* methylene protons show non-equivalence. Compounds (26) and (28), having a CH_2Br group geminal to a methoxy group, show a chemical shift non-equivalence (Δδ 0.10 and 0.14 p.p.m.) for *Z* isomers only. Comparison of compounds (*Z*)-(26) and (*Z*)-(28) with (*E*)-(3)—(*E*)-(7) allows the influence of the group geminal to CH_2Br to be evaluated; a methyl group is more effective than a methoxy group in differentiating conformational populations. It is still not clear to us why chemical shift non-equivalence is not apparent for compound (*E*)-(18). One working hypothesis appears to be an accidental equivalence of the environments of the CH_2Br protons in the different conformations.

For the thiomethyl derivatives (13) and (14), chemical

^1H n.m.r. data (δ, p.p.m. and *J*, Hz) of the CH_2–X group (obtained for solutions in deuteriochloroform (5—10% w/v; Me_4Si as internal reference)

	CH_2Br			CH_2OAc	CH_2SPh		
Compound	δ	*J*	Δδ	δ	δ	*J*	Δδ
(*E*)-(3)	4.73	9.5	0.28				
	4.45	9.5					
(*Z*)-(3)	4.03						
(*E*)-(4)	4.57	9.5	0.33				
	4.24	9.5					
(*Z*)-(4)	3.90						
(*E*)-(5)	4.65	9.0	0.28				
	4.37	9.0					
(*Z*)-(5)	4.03	10.0	0.09				
	3.94	10.0					
(*E*)-(6)	4.70	9.5	0.35				
	4.35	9.5					
(*Z*)-(6)	3.98						
(*E*)-(7)	4.65	9.5	0.36				
	4.29	9.5					
(*Z*)-(7)	3.90						
(*E*)-(13)					4.75	13.5	0.22
					4.53	13.5	
(*Z*)-(13)					4.14		
(*E*)-(14)					4.77	13.0	0.20
					4.57	13.0	
(*Z*)-(14)					4.12		
(*E*)-(18)	4.53			4.83			
(*Z*)-(18)	4.13			5.22			
(*Z*)-(19)	4.58			4.83			
(20) (*E*)	4.73	10.0	0.23				
	4.50	10.0					
(*Z*)	4.21						
(*E*)-(26)	4.25						
(*Z*)-(26)	4.73	11.5	0.10				
	4.63	11.5					
(*E*)-(28)	4.42						
(*Z*)-(28)	4.82	11.0	0.14				
	4.68	11.0					

† Hirsch [3] reports the following values for $-\Delta G$/kcal mol^{-1}: Br 0.38, OAc 0.60, OMe 0.60, SPh 0.8; that for OBu^t is expected to be ⩾0.6.

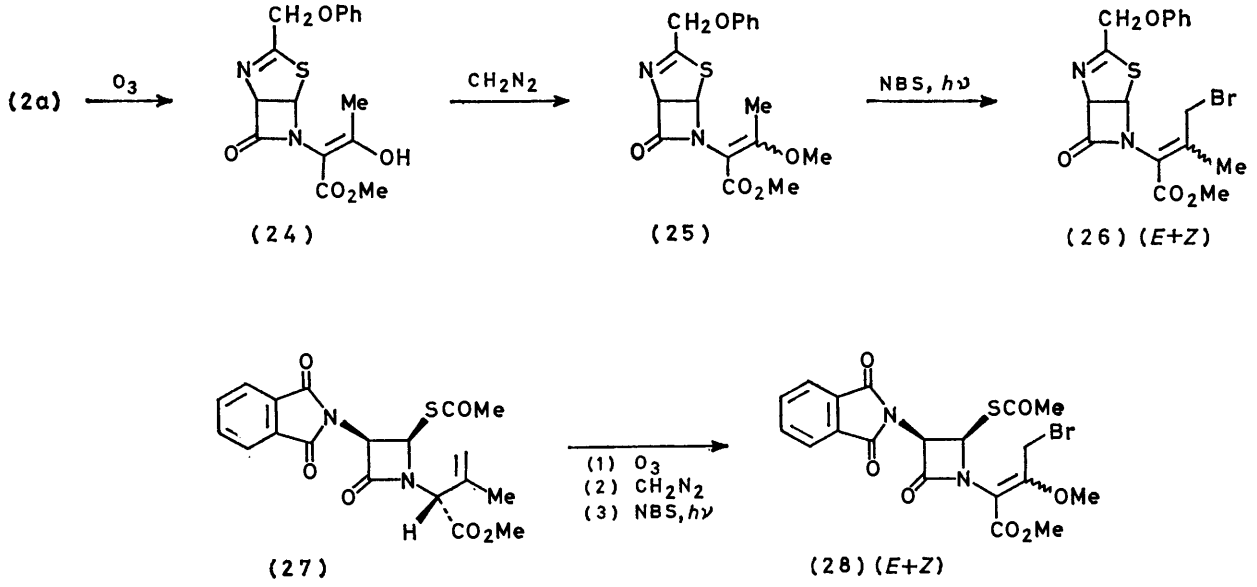

a; R1 = PhOCH2, R2 = Me or CHPh2
b; R1 = Ph, R2 = Me
c; R1 = But, R2 = Me
d; R1 = R2 = Me
(29)
(2)
Al2O3
NBS
Al2O3
NBS / Al2O3
Br2, CaO
Et3N or
SiO2
(E + Z)
(8)
(3) R1 = PhOCH2 R2 = Me
(4) R1 = PhOCH2 R2 = CHPh2
(5) R1 = Ph R2 = Me
(6) R1 = But R2 = Me
(7) R1 = p-BrC6H4OCH2 R2 = Me
R3OH
CF3SO3Ag
2,6-lutidine
Nucleophile
(E)
(15) R1 = PhOCH2; R2 = Me; R3 = Me
(16) R1 = PhOCH2; R2 = Me; R3 = But
(17) R1 = But; R2 = Me; R3 = But
(9) R1 = PhOCH2; R2 = Me; R3 = OAc
(10) R1 = Ph; R2 = Me; R3 = OAc
(11) R1 = Me; R2 = Me; R3 = OAc
(12) R1 = But; R2 = Me; R3 = OAc
(13) R1 = PhOCH2; R2 = Me; R3 = SPh
(14) R1 = PhOCH2; R2 = CHPh2; R3 = SPh
NBS
hν
TsOH·H2O
NCO2Et
NCO2Et
(18) (E+Z) R1 = Ph R2 = Me X = OAc
(19) (E+Z) R1 = But R2 = Me X = OAc
(20) R1 = Ph R2 = Me X = Br
(21) (E+Z) X = OAc
(22) (E) X = OMe
(23) (E) X = OBut

SCHEME 1

shift non-equivalence is also observed for *E* isomers ($\Delta\delta$ 0.22 and 0.20 p.p.m.).

The effect of the different ester groups on the non-equivalence of the *E*-CH_2Br groups is not very large [see compounds (*E*)-(3)—(*E*)-(4) and (*E*)-(13)—(*E*)-(14)].

Indeed, the above results afforded a valuable criterion for the determination of the configuration of the groups CH_2Br (geminal to Me or OMe) and CH_2SPh (geminal to Me) on the double bond, which has been established on the basis of its chemical shifts.[4] The assignment based on the chemical shift non-equivalence appears to be more reliable than that based on the chemical shift values of the substituents on the double bond; in fact, for compound (28) the assignment based on the chemical shifts of the CH_2Br and OMe groups gives opposite results.[4] The synthetic pathways are summarized in Schemes 1 and 2.



SCHEME 2

β-Lactam thiazolines (2) [5] gave, almost quantitatively, monobromides (3)—(6) as a 70 : 30 *E* : *Z* mixture, on treatment with *N*-bromosuccinimide (NBS) and aluminium oxide.[1] The mechanism of this bromination, which we believe to be the first example of bromination of (2a), involves the initial abstraction of the α-proton by alumina and concerted attack of a positive bromine with concomitant shift of the double bond, affording the conjugated esters (3)—(6). Indeed, compounds (2) were converted with aluminium oxide into the corresponding isomeric conjugated esters (29), which in turn were recovered unchanged after subsequent treatment with NBS and aluminium oxide. On the other hand (2) did not react with NBS alone. Alternatively, bromine added across the isopropenyl double bond of (2) in methylene chloride in the presence of calcium oxide to give the dibromides (8) as a 1 : 1 mixture of diastereoisomers. These were quantitatively converted into the monobromides (3)—(6) by treatment with triethylamine or simply by passing through silica gel. In the same reaction conditions, starting from (2a) and using mercuric oxide in carbon tetrachloride,* dibromide (7) was obtained after chromatography on silica gel.

Both the monobromides (3)—(6) and the dibromides (8) were transformed into their monoacetates (*E*) + (*Z*)-(9)—(12) by nucleophilic displacement with potassium acetate in acetone (1 h; 40 °C). The single isomers were separated either by chromatography or by fractional crystallisation. Compounds (13) and (14) were similarly obtained by treatment with potassium thiophenoxide.

The alkoxymethyl ethers (15)—(17) were prepared by treating the bromides (3)—(6) or dibromides (8) in the suitable alcohols, with silver trifluoromethanesulphonate in the presence of 2,6-lutidine (30 min at 0—20 °C).

Photochemical bromination of the acetates (9) and (12) (performed either on the single isomer or on the *E*–*Z* mixture), gave compounds (18) and (19) in 40—60% yield. Moreover, bromination of the bromo-compound (5) afforded the dibromide (20).

Acid-catalysed oxidative ring opening [1] of compounds (9), (15), and (16) using diethyl azodicarboxylate (excess) and toluene-*p*-sulphonic acid (1 equiv.) in acetone containing 2% water (6 h; 20 °C) afforded the hydrazinothioazetidinones (21)—(23) in 70% yield.

Additionally, compounds (26) and (27) (*E* + *Z*) were obtained in moderate yield by an accurate allylic NBS bromination of the corresponding enol ethers [7] previously prepared by ozonolysis of (2a) and (27).[8]

EXPERIMENTAL

Reactions were monitored by t.l.c. on Merck silica gel GF_{254} with benzene–light petroleum–ethyl acetate as solvent. Light petroleum refers to the fraction of boiling range 68—80 °C. Only general preparations are given. Ful

* It is known [6] that bromine and mercuric oxide constitute a very reactive brominating agent effecting nuclear bromination by means of a free radical chain process.

experimental details are available as Supplementary Publication No. SUP 22354 (12 pp.).*

Bromination Procedures.—(*a*) *N*-Bromosuccinimide (7 g) and aluminium oxide were added to a solution in benzene (200 ml) of 6-(1-methoxycarbonyl-2-methylprop-2-enyl)-3-phenoxymethyl-4-thia-2,6-diaza-*cis*-bicyclo[3.2.0]hept-2-en-7-one (2a) (8 g) and the mixture was stirred at room temperature for 20 h. After filtering off insoluble material, the solvent was removed *in vacuo* and the residue taken up with carbon tetrachloride. After further filtration and evaporation, the resulting brown oil was chromatographed on silica gel (benzene–ethyl acetate 95 : 5) yielding 6-(1-methoxycarbonyl-2-bromomethylprop-1-enyl)-3-phenoxymethyl-4-thia-2,6-diaza-*cis*-bicyclo[3.2.0]hept-2-en-7-one (3) (8.2 g) (70 : 30 *E* : *Z*).

(*b*) Bromine was added dropwise over 30 min to a vigorously stirred solution at room temperature of the thiazoline (2a) (3.46 g) in methylene chloride (200 ml) containing calcium oxide (5 g). The inorganic material was filtered off and the solvent evaporated *in vacuo* to give the oily dibromide (8a) (4 g) as a 1 : 1 inseparable mixture of diastereoisomers. The product was then quantitatively transformed into the monobromide (3 *E* + *Z*) by passing through silica gel or by mild treatment with triethylamine.

Nucleophilic Displacements.—A mixture of the bromide (3) (7 g) and fused potassium acetate (10 g) in dry acetone (70 ml) was stirred at room temperature for 24 h. The inorganic material was filtered off and the solvent evaporated *in vacuo* to give a solid residue (6.2 g) consisting of the two diastereoisomeric acetates 6-[1-methoxycarbonyl-2-(acetoxymethyl)prop-1-enyl]-3-phenoxymethyl-4-thia-2,6-diaza-*cis*-bicyclo[3.2.0]hept-2-en-7-one (9). The isomers were separated by crystallization from ethyl ether. The *E* isomer had m.p. 76—77 °C, δ 1.75 (3 H, s, MeC=), 2.05 (3 H, s, MeCO), 3.78 (3 H, s, MeO), 4.99 (2 H, d, *J* 1.0 Hz, CH_2OPh), 5.13 (2 H, s, CH_2OAc), 5.88 (1 H, d, *J* 4.0 Hz, 5-H), 6.07 (1 H, two t, *J* 4.0 and 1.0 Hz, 1-H), and 6.85—7.55 (5 H, m, Ph). The *Z* isomer showed δ 2.04 (3 H, s, MeCO), 2.21 (3 H, s, MeC=), 3.81 (3 H, s, MeO), 4.63 (2 H, s, CH_2OAc), 5.02 (2 H, d, *J* 1.0 Hz, CH_2OPh), 5.90 (1 H, d, *J* 4.0 Hz, 5-H), 6.10 (1 H, two t, *J* 4.0 and 1.0 Hz, 1-H), and 6.8—7.5 (5 H, m, Ph).

Alkoxymethyl Ethers.—To a solution of the bromide (3) (1.3 g) in t-butyl alcohol (15 ml) and 2,6-lutidine (0.36 ml), silver trifluoromethanesulphonate in diethyl ether (50 ml) was added dropwise at room temperature. After stirring for 1 h the inorganic material was filtered off and the solvent evaporated off *in vacuo*. Chromatography (silica gel) of the oily residue (95 : 5 benzene–ethyl acetate) afforded mainly 6-[1-methoxycarbonyl-2-(t-butoxymethyl)prop-1-enyl]-3-phenoxymethyl-4-thia-2,6-diaza-*cis*-bicyclo[3.2.0]hept-2-en-7-one (16) as single *E* isomer (70% yield), δ 1.20 (9 H, s, Bu^t), 1.86 (3 H, s, MeC=), 3.78 (3 H, s, MeO), 4.50 (2 H, s, $=CCH_2O$), 5.00 (2 H, d, *J* 1.0 Hz, CH_2OPh), 5.90 (1 H, d, *J* 4.0 Hz, 5-H), 6.10 (1 H, 2 t, *J* 4.0 and 1.0 Hz, 1-H), and 6.85—7.55 (5 H, m, Ph).

Reaction of Functionalized Thiazolines with Diethyl Azodicarboxylate.—Diethyl azodicarboxylate (2 ml) followed by toluene-*p*-sulphonic acid monohydrate (0.9 g) were added to the thiazoline (9; *E*-isomer) (2 g) dissolved in 98% acetone–water (40 ml) and the resultant solution was left at room temperature for 4 h. The ice-cooled mixture was then neutralized ($NaHCO_3$), the solvent removed *in vacuo*, and the residue taken up with ethyl acetate and water. The organic layer was washed several times with water, dried (Na_2SO_4), and evaporated. Rapid chromatography on a short column (silica gel, benzene–ethyl acetate 80 : 20) gave 1-(3-acetoxy-1-methoxycarbonyl-2-methylprop-1-enyl)-4-(1,2-bisethoxycarbonylhydrazinothio)-3-phenoxyacetamidoazetidin-2-one (21; *E*-isomer) (2.1 g) as a solid, δ 1.24 (6 H, t, CH_3CH_2), 2.10 (3 H, s, MeCO), 2.15 (3 H, s, MeC=), 3.82 (3 H, s, MeO), 4.18 (4 H, q, CH_2Me), 4.59 (2 H, s, PhOCH_2), 5.17 (1 H, dd, *J* 5.5 and 8.0 Hz, 3-H), 5.24 (2 H, s, CH_2OAc), 5.95 (1 H, d, *J* 5.5 Hz, H-4), and 6.8—7.6 (7 H, m, NH and aromatic protons). Similarly starting from the *Z*-isomer (9), the corresponding (*Z*)-hydrazinothioazetidinone (21) could be obtained, δ 1.23 (6 H, t, CH_3CH_2), 2.09 (3 H, s, MeCO), 2.23 (3 H, s, MeC=), 3.82 (3 H, s, MeO), 4.17 (4 H, q, CH_2Me), 4.57 (2 H, s, PhOCH_2), 5.02 (2 H, s, CH_2OAc), 5.25 (1 H, dd, *J* 5.5 and 8.0 Hz, 3-H), 5.93 (1 H, d, *J* 5.5 Hz, 4-H), and 6.8—7.75 (7 H, m, NH and aromatic protons).

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* See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1978, Index issue.

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