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2-METHYLENEPENAMS: A NEW SYNTHESIS

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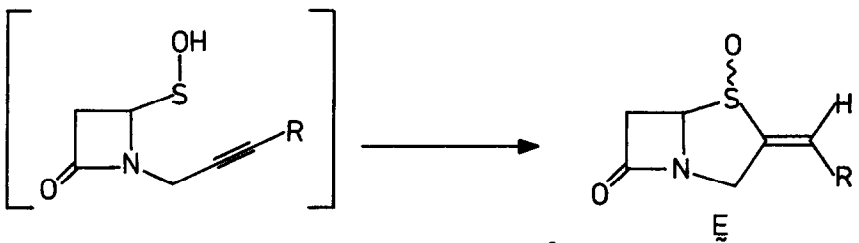
SUMMARY. The synthesis of the 2-methylenepenam nucleus by an intramolecular trapping of a sulphenic by an appropriately orientated acetylenic bond is described.

A recent publication from the Beecham Laboratories[1] concerning the synthesis of 2-methylenepenam derivatives has prompted us to report our own stereospecific synthesis of the parent 2-methylenepenam nucleus and some of its derivatives.

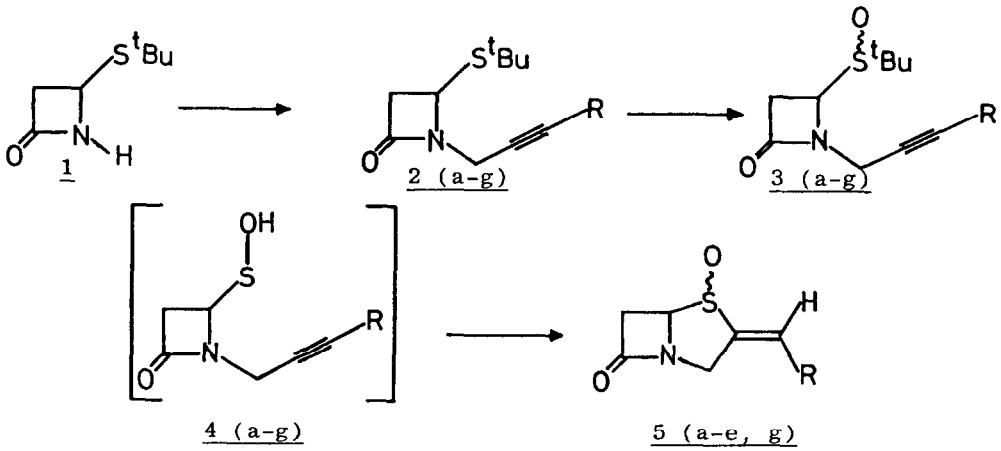


E

4-t-Butylthioazetid-2-one 1 (m.p. 114-116°C), obtained in 67% yield from 4-acetoxyazetid-2-one and excess t-butylthiol in the presence of sodium carbonate, was N-metallated with potassium t-butoxide in DMF, and alkylated by addition to a DMF[2] solution of propargyl bromide at 0°C to afford 2a (m.p. 60-64°C) in 90% yield. Sodium periodate oxidation (aq. methanol) of 2a gave mixed sulphoxides 3a (93%, m.p. 83-89°C). Thermolysis[3] of the mixture 3a in dry toluene at reflux temperature under a N_2 atmosphere gave 2-methylenepenam-1-oxide 5a as a single sulphoxide isomer (not assigned) in 40% yield. Similarly thermolysis of the sulphoxides 3b-e gave good yields (>50%) of the 2-methylenepenam-1-oxides 5b-e exclusively as their E isomers (vide infra).

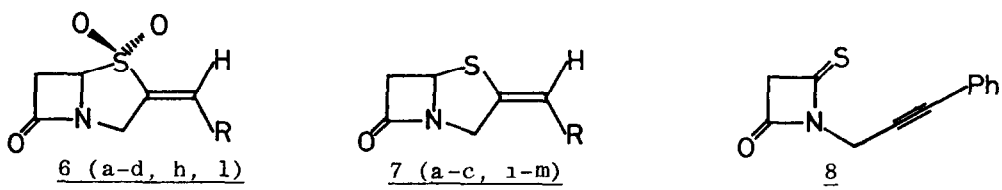
The sulphoxides 5a-e were oxidised with m-chloroperbenzoic acid in chloroform to the 2-methylenepenam sulphones 6a-e (>80%). Reduction of the sulphoxides 5b-e to the sulphides 7b-e proceeded quantitatively using phosphorous tribromide in DMF. However no satisfactory method of reducing 5a to 7a was discovered.

Deprotection of the esters 6b-d and 7b-d was achieved only for 7d, where dithionite reduction gave an unstable gum having spectral properties consistent with those expected for 7f. In all other cases concomitant destruction of the β-lactam nucleus occurred.



1 2 (a-g) 3 (a-g)

4 (a-g) 5 (a-e, g)



6 (a-d, h, l) 7 (a-c, 1-m) 8

R = a) H
b) C_6H_4-2-(CO_2Et)
c) C_6H_4-2($CO_2CH_2CH_2Si(CH_3)_3$
d) C_6H_4-2($CO_2CH_2C_6H_4$-4'-NO_2)
e) $CH_2OSi(CH_3)_2$
f) C_6H_4-2-CO_2H
g) CH_2OH
h) CH_2SCOCH_3
1) CH_2SCN
j) $CH_2SCH_2CO_2CH_2C_6H_4$-4-NO_2
k) N_3
l) CHO
m) $CH{=}CHCO_2CH_2C_6H_4$-4-NO_2
n) Ph

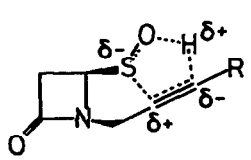


Fig 1

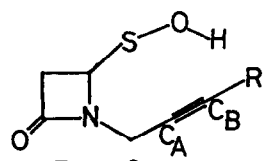


Fig 2

Net Charge C_A	C_B	Compound	Yield of 5 from 3
-0.003	+0 003	n	0%
0 0	0 0	a	40%
+0.011	-0 001	b	57%

The N-2-hydroxyethylidene side chain was formed by tetra-n-butylammonium fluoride deprotection of 6e (70%) and 7e (78%) [lower yields were obtained using either the diphenyl-t-butylsilyl (47%) or tetrahydropyranyl (5%) protecting groups]. Modification of the side chain hydroxyl group was achieved through mesylation (mesyl chloride/triethylamine, DMF, $0^{o}C$) and displacements with sulphur nucleophiles (7h-j, average yield 40%) and nitrogen nucleophiles (6k and 7k, average yield 60%). The stereochemistry of the double bond remained E for all displacement reactions with the exception of 6k where an isomerisation to an E/Z mixture (1:1) occurred under the reaction conditions. Attempted mesylate displacements with carbon nucleophiles resulted in β-lactam cleavage, and iodide displacement gave a hydrolytically unstable product.

Oxidation of 7g with pyridinium dichromate gave the unsaturated aldehyde 7l (80%) which reacted with 4-nitrobenzyloxycarbonylmethylenetriphenylphosphorane to give the E,E diene ester 7m (20%).

The ring closure reaction presumably occurs via the intermediary of a sulphenic acid 4 to give 5 as a single isomer which was shown to have the E configuration by x-ray crystallographic analysis[4] of the sulphone 6b (m.p. 142-143.5^{o}C). The only compound which failed to ring close was the sulphoxide 3n. In this example the product isolated in 81% yield was the mono-thiomalonimide 8.[5] The E configuration in the products 5 is consistent with the pericyclic ring closure mechanism for a sulphenic acid and acetylenic triple bond proposed by Jones.[7] The transition state for the ring closure shows the partial carbon-sulphur bond to be polarised such that the carbon atom C_A has some cationic character (Fig. 1). Simple Hückel M.O. calculations[8] showed that in the ground state the acetylenic triple bond in 3n was unfavourably polarised (Fig. 2) for ring closure to occur and as a result the observed product 8 was formed by dehydration of the sulphenic acid 4n.

^{1}H N.m.r. spectra of these 2-methylenepenams showed the C-5 and C-6 protons as an ABX system in both the sulphoxide and sulphides. However in the sulphones, due to overlapping signals for the C-6 protons, this was simplified to an AA'X pattern.[9]

The biological activity of these compounds as antibacterials, β-lactamase inhibitors (synergistically with ampicillin) or fungicides was not significant.

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References

1. E.G. Brain, N.J.P. Brown and R.I. Hickling, J.Chem.Soc.Perkin Trans 1 892 (1981).

2. D. Davies and M.J. Pearson, Recent Advances in β-Lactam Antibiotics, p.89, Ed. G.I. Gregory, Royal Society of Chemistry Special Publications No. 38 (1981).

3. A.C. Kaura, C.D. Maycock and R.J. Stoodley, J.Chem.Soc.Chem.Commun., 34 (1980) and refs. therein.

4. Carried out by Dr. D.J. Williams, Imperial College, London.

5. Compound 8 m.p. 52-58°C; i.r. (bromoform) 1805 cm^{-1}, n.m.r. ($CDCl_3$) 3.73 (2H,S), 4.51 (2H,S), 7.34 (5H,m). Compare ref. 6.

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9. Selected Data from 100 M. Hz ^1H N.m.r. spectra recorded in $CDCl_3$.

Compound	C-6-H (J,Hz)	C-5-H (J,Hz)	Vinylic (J,Hz)
5a	3.34 dd (17,2) 3.63 dd (17,4)	4.50 dd (4,2)	6.06 (2)
6a	3.52 d (3)	4.44 t (3)	5.93 ddd (2,2,2) 6.27 ddd (2,2,2)
5b	3.36 (17,2) 3.66 (17,4)	4.54 br.t [a]	7.32 br.s
6b	3.46 d (3)	4.37 t [a]	7.30 br.s
7b	3.10 dd (24,2) 3.64 dd (24,2)	5.12 dd (4,2)	7.18 br.d
5g	3.28 dd (17,2) 3.67 dd (17,4)	4.46 [b]	6.40
6g	3.48 d (3)	4.37 t (3)	6.75 m
7g	3.10 dd (16,1.5) 3.63 dd (16,3)	5.12 dd (3,1.5)	5.76 m

a signal overlaps with ester methylene.

b signal overlaps with side chain methylene.

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