8-α-AMIDO-5-AZANONAM-1,3-DIENES POTENTIAL β-LACTAM ANTIBIOTICS.

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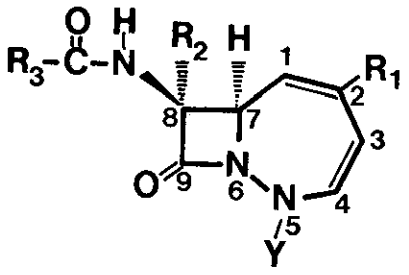
1,2-Diazepines 2 react stereospecifically with phtalimidoacetyl chloride in the presence of base to give the corresponding diazepino-β-lactams in high yield. Treatment of such an azetidinone (5) with sodium hydroxide and then with dicyclohexylcarbodiimide gave isoimide 7 which hydrolysed easily yo the corresponding 8-amino-5-azanonam-1,3-diene 8 in high overall yield. Acylation gave the 5-azanonam-1,3-dienes 9 which are the immediate precursors of the cephalosporin analogues 1.

Altering the structure of natural products, in order to induce specific modifications of their pharmacological spectrum, is a general trend in modern drug research[1]. In the particular case of β-lactam antibiotics, the thiazoline and thiazine moieties of penicillins and cephalosporins respectively have been replaced by other heterocycles[2]. For example specific pharmacological properties have been found with 1-oxa and 1-carba-cephalothins which have been prepared by various total synthetic methods[3]. Along these lines we undertook the total synthesis of cephalosporin analogues, of general formula 1, bearing a seven-membered ring fused to the β-lactam moiety.



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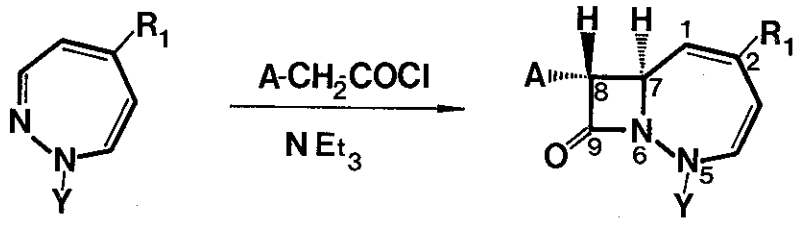
According to the nomenclature proposed by Bose[4] we shall name type 1 compounds 8-substituted 5-azanonam-1,3-dienes. In formula 1 R_3 would be identical with one of the many substituents encountered in the penam and in the cepham series; R_2 is a hydrogen atom or a methoxy group, R_1 a hydrogen atom or an alkyl moiety and Y

an acid bearing substituent. The Δ^1 double bond in 1 is thought to replace the sulfur atom of the cepham antibiotics.

1,2-Diazepines 2, which are readily prepared by U.V.irradiation of 1-iminopyridinium ylides[5], react easily with derivatives of acetic acid chloride in the presence of a base and lead stereospecifically to the corresponding β-lactams 3[6]. With respect to all the known β-lactam antibiotics, adducts 3 have the wrong



2 3

configuration at C-8 as shown by NMR[6] and by X-ray analysis[7].

Our first objective was to introduce an amido function at C-8 bearing one of the substituents R_3 known to occur with β-lactam antibiotics. The most effective way to achieve this goal was by using the sequence described below.

1-Ethoxycarbonyl-5-methyl-1,2-diazepine 4 reacts with a fourfold excess of phtalimidoacetyl chloride in the presence of triethylamine according to Sheehan's method[8] and leads in 91% to nonam-1,3-diene 5 m.p. 145°; IR ($CHCl_3$) ν (C=O) 1800 and 1720 cm^{-1} U.V. (EtOH) λ_{max} 277 nm (ε:9,900); ^1H NMR ($CDCl_3$) δ 4.90 (H-7 and H-8; m); 5.03 (H-3; d; $J_{3,4}$=9,5 Hz); 5.80 (H-1; m) and 6.85 ppm (H-4; d; $J_{3,4}$=9,5 Hz); ^{13}C NMR ($CDCl_3$) δ 56.3 (C-7; d); 63.5 (C-8; d); 110.8 (C-3; d); 124.6 (C-1; d); 128.3 (C-4; d); 131.8 (C-2, s); 158.1 ppm (C-9, s).[9]

Selective saponification of 5 with NaOH N/10 gives the nonam-1,3-diene 6 in 90% yield, m.p. 158°; IR (KBr) ν (N-H) 3320, ν (O-H) 3100 cm^{-1}, ν (C=O) 1795, 1735 and 1670 cm^{-1}; U.V. (MeOH) λ_{max}

275 nm (ε 10000); the ^{1}H NMR shows in particular with D_2O exchangable OH and NH (J=7 Hz) groups and H-7 (δ 4.55 ppm) and H-8 (δ 4.70 ppm) atoms in a trans configuration ($J_{7,8}$=1 Hz)[10]. Intramolecular cyclisation of 6 with dicyclohexylcarbodiimide leads in 90% yield to isoimide 7, m.p.165°; IR ($CHCl_3$) ν (C=O) 1800, 1735 cm^{-1}; ν (C=N) 1705 cm^{-1}; U.V. (MeOH) λ_{max} 276 nm (ε 12,600); ^{1}H NMR ($CDCl_3$) δ 4.62 (H-7; m); 4.82 ppm (H-8, d, $J_{7,8}$=1,5 Hz). Treatment of 7 with methylhydrazine at -78°[11] leads to the desired 8-α-amino-5-azanonam-1,3-diene 8 in 84% yield, IR ($CHCl_3$) ν (C=O) 1790, 1735 cm^{-1}; UV (MeOH) λ_{max} 278 nm (ε:7,800). This rather unstable compound[12] is immediately acylated with the usual acetic acid derivatives using dicyclohexylcarbodiimid as a dehydrating agent[13]. The corresponding 2-methyl-5-ethoxycarbonyl-8-α-amido-5-azanonam-1,3-dienes 9a to 9d are thus obtained in excellent yields (Table 1) as stable compounds. Spectroscopic data fit with the proposed structures 9a to 9d (Table 1). As a typical example let us quote the ^{1}H and ^{13}C NMR spectra of β-lactam 9c: ^{1}H NMR ($CDCl_3$) δ 4.50 (H-7; m); 4.66 (H-8; dd; $J_{7,8}$=1.5 and $J_{NH,8}$=7 Hz); 5.00 (H-3; d; $J_{3,4}$=9 Hz); 5.90 (H-1; m) and 6.73 ppm (H-4; d; $J_{3,4}$=9 Hz); ^{13}C NMR ($CDCl_3$) δ 58.3 (C-7; d); 66.3 (C-8; d); 111.3 (C-3; d); 125.8 (C-1; d); 127.5 (C-4; d); 131.2 (C-2; s) and 160.3 ppm (C-9; s).

The overall yield for the 5-step synthesis of compound 9c is 57%. Alternative syntheses of 8-α-amino-5-azanonam-1,3-dienes, starting for example from azidoacetic acid chloride, proved to be less interesting in terms of preparative organic synthesis. Therefore we believe that the aforementioned approach to the total synthesis of compounds having structure 1 is a promising one.

Configurational inversion of C-8 and introduction of an acid bearing group Y in formula 1 will be our next goal.

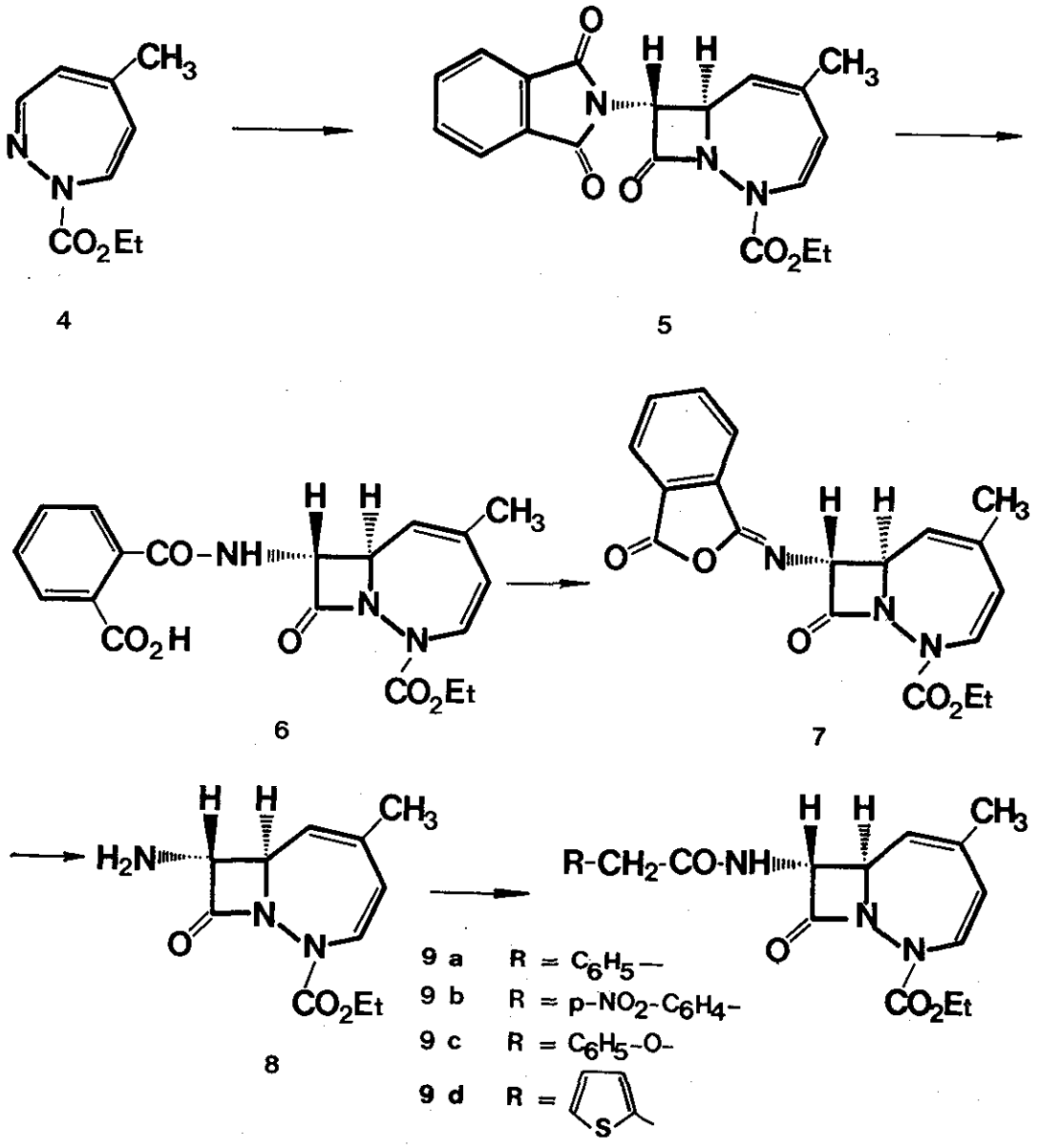


Table 1 8-α-amido-5-azanonam-1,3-dienes 9 obtained by acylation of the unstable 8-α-aminononamdiene 8

	m.p.	yield	IR ($CHCl_3$)				U.V. (MeOH) λ_{max} (ε)
			ν(N-H)	ν(C=O) lactam	ν(C=O) ester	ν(C=O) amide	
9a	50°	93%	3410	1790	1725	1670	275(7,900)
9b	oil	77%	3360	1780	1735	1680	272(16,300)
9c	151°	92%	3310	1780	1735	1670	269(10,250) 275(10,400)
9d	137°	92%	3400	1790	1730	1675	274(9,200)

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