Novel Synthesis of the 7-oxo-1,3-diazabicyclo[3.2.0]heptane and 8-oxo-1,3-diazabicyclo[4.2.0]octane Ring Systems

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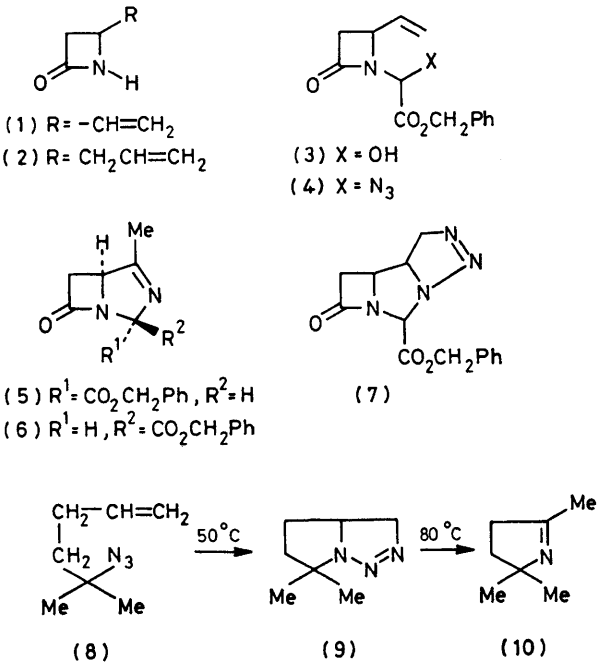
Summary 4-Vinyl- and 4-allyl-azetidin-2-ones (**1**) and (**2**) have been converted into the imines (**5**) and (**19**) respectively, while use of azetidin-2-ones in which the double bond was substituted with a methoxycarbonyl group allowed the synthesis of the enamines (**13**) and (**21**).

As a continuation of our studies[1] concerned with the preparation of fused β-lactams by intramolecular cycloaddition reactions, we now report the synthesis of the 7-oxo-1,3-diazabicyclo[3.2.0]hept-3-ene and -heptane ring systems. The homologous 4,6-ring systems have also been obtained. All compounds in the following report are (±) mixtures, but in some instances only one enantiomer is depicted for convenience.

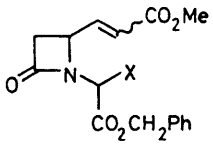
Condensation of 4-vinylazetidin-2-one (**1**)[2] with benzyl glyoxylate afforded the α-hydroxy-ester (**3**)† which was converted into the azide (**4**)† by established procedures.[3] When (**4**) was heated in refluxing toluene (1 mg ml^{-1}, under argon), the two imines (**5**)† (35%), δ 5·95 (2-H) and (**6**)† (23%), m.p. 76—77 °C, δ 5·23 (2-H) were isolated.‡ The intermediate 1,2,3-triazoline (**7**) is assumed to undergo ready loss of nitrogen to form the isolated products. Heating[4] (**8**) has been shown to give (**10**), the reaction proceeding *via* the isolable triazoline (**9**).



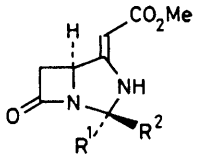
† Satisfactory elemental analysis and/or accurate mass data were obtained.

‡ In all cycloadditions described, both C(2) epimers are formed. However, epimerisation to the epimer possessing the natural penicillin stereochemistry at C(2) was achieved by treatment of the mixture with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in methylene dichloride at −20 °C.

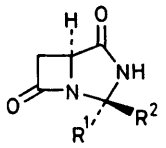
Ozonolysis of (**3**), followed by addition of methoxycarbonylmethylenetriphenylphosphorane provided the $\alpha\beta$-unsaturated ester (**11**)† as an inseparable mixture of *E*- and *Z*-isomers. The azide (**12**)† was then prepared and heated in toluene at 110 °C for 23 h to give a mixture of enamines (**13**)† (24%), m.p. 154·5—156 °C, δ 5·54 (2-H) and (**14**)† (15%), m.p. 137—139·5 °C, δ 5·02 (2-H). The olefinic proton of each epimer appeared at δ *ca.* 4·7, a chemical shift consistent with an enamine structure. Although the azido-olefin (**12**) was a mixture of geometric isomers, each enamine epimer was a single olefinic isomer. An *X*-ray study of the epimer with the natural penicillin stereochemistry at C(2) showed that the double bond had the *Z*-configuration. Presumably the *Z*-olefin is favoured owing to stabilisation *via* hydrogen bonding between the enamine N–*H* and the carbonyl of the methyl ester. Ozonolysis of (**13**) and (**14**) in ethyl acetate at −76 °C provided (**15**),† m.p. 147·5—148·5 °C, δ 5·42 (2-H) and (**16**),† m.p. 154·5—155·5 °C, δ 5·07 (2-H), respectively.



(**11**) X = OH
(**12**) X = N_3

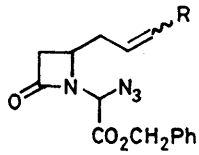


(**13**) R^1 = CO_2CH_2Ph, R^2 = H
(**14**) R^1 = H, R^2 = CO_2CH_2Ph

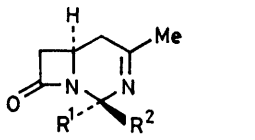


(**15**) R^1 = CO_2CH_2Ph, R^2 = H
(**16**) R^1 = H, R^2 = CO_2CH_2Ph

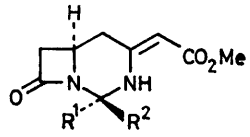
We have also demonstrated the cyclisation process in the homologous series. Thus 4-allylazetidin-2-one (**2**)[5] was converted into the azide (**17**),§ which was heated in toluene at reflux for 7 h. Treatment of the crude product¶ with DBU afforded the imine (**19**)† (30%), m.p. 94·5—95 °C, δ($CDCl_3$) 2·03 (s, CH_3) and 5·72 (br. s, 2-H), possessing the natural penicillin stereochemistry at C(2).



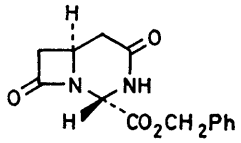
(**17**) R = H
(**18**) R = CO_2Me



(**19**) R^1 = CO_2CH_2Ph, R^2 = H
(**20**) R^1 = H, R^2 = CO_2CH_2Ph



(**21**) R^1 = CO_2CH_2Ph, R^2 = H
(**22**) R^1 = H, R^2 = CO_2CH_2Ph



(**23**)

The azide (**18**)§ was also prepared and cyclised (refluxing toluene, 5½ h) to give a mixture of enamines (**21**) and (**22**), from which (**21**)† (20%), m.p. 149—150 °C, δ($CDCl_3$) 4·66 (br. s, =CH) and 5·53 (d, *J* 1·7 Hz, 2-H), λ_{max}(EtOH) 283 nm (ϵ 18,700), could be crystallised. Purification of the mother liquors on 'Florisil' gave a further quantity of material (30%) which was an inseparable mixture of epimers (**21**) and (**22**) in a ratio of 1 : 4. The latter showed δ($CDCl_3$) 4·68 (br. s, =CH) and 5·15 (dd, *J* 1·7 and 4 Hz, 2-H). The *Z*-geometry of the double bond in each epimer is assigned by analogy with the corresponding 5-membered ring derivatives. Ozonolysis of (**21**) in methylene dichloride containing methanol (*ca.* 2%) gave the amide (**23**)† (87%), m.p. 141—142 °C, δ 5·61 (2-H). All compounds showed the expected spectroscopic properties; none of the bicyclic esters or corresponding free acids showed any antibacterial activity.

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§ Azides in this series were unstable oils, and were generally used immediately after preparation.

¶ In this case the epimer (**20**) with the proton α at C(2) was unstable to chromatography and could not be selectively crystallised from the mixture.

[1] M. J. Pearson, *J. Chem. Soc., Perkin Trans.* 1, submitted for publication.
[2] T. Durst and M. J. O'Sullivan, *J. Org. Chem.*, 1970, **35**, 2043.
[3] M. J. Pearson, *J. Chem. Soc., Perkin Trans* 1, 1977, 189.
[4] A. L. Logothetis, *J. Am. Chem. Soc.*, 1965, **87**, 749.
[5] A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1979, 236.