CARBOCYCLIC ANALOGUES OF PENICILLINS

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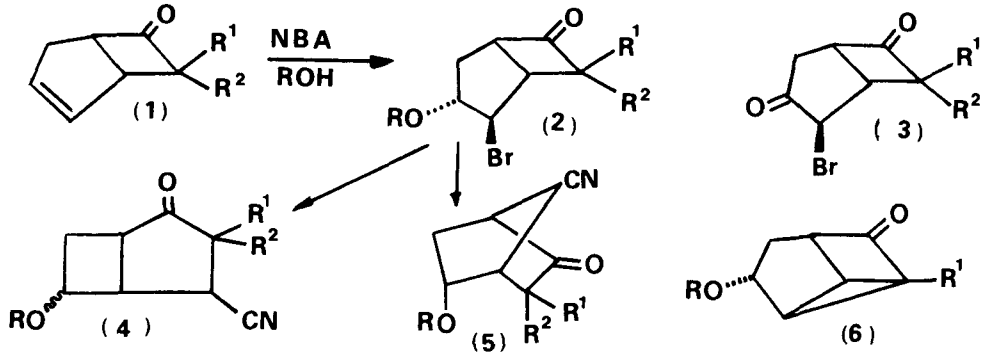
The role of β-lactamase inhibitors such as clavulanic acid to deal with micro-organisms resistant to penicillins has dramatically improved both the range and understanding of penicillin action. Furthermore the search for new inhibitors amongst penicillin related structures has grown significantly. We envisaged that replacement of the heteroatoms of the penicillin ring system by carbon functions would lead to potential β-lactamase inhibitors (Lowe 1985).

This communication describes the synthesis of a selection of carbocyclic analogues of penicillin by cycloaddition of ketenes to cyclopentadiene to give 7-mono and 7,7-disubstituted bicyclo[3.2.0]hept-2-en-6-ones (1) (Rey 1970). Treatment with N-bromoacetamide gave the 2-exo-bromo-3-endo-methoxy (or benzyloxy) 7-substituted bicyclo[3.2.0]heptan-6-ones (2) (Schemel). A novel 2-exo-bromo-7,7-disubstituted bicyclo[3.2.0]heptan-3,6-dione product(3, R^1=Me, Et R^2 = Me, Cl) was also isolated in this reaction {3, R^1 = R^2 = Me, ν(c=o) 1735, 1785 cm^{-1}}. Subsequent nitrile mediated rearrangement of the 7,7-disubstituted bicyclo[3.2.0] heptan-6-ones (2, R^1, R^2=Cl, Me, Et, Ph, Bz, R=Me, Bz) afforded 6-exo-benzyloxy-4-cyano-3,3-disubstituted bicyclo[3.2.0]heptan-3-ones (4, R^1, R^2=Cl,Me, Et, Ph, Bz, R=Me, Bz) (Meth-Cohn, 1982) {For (4) R=Me, R^1=Cl, R^2=CH_3, ν(c=o) 1780 cm^{-1}. δ($CDCl_3$) 4.20 (s, H-2), 4.03 (m, H-3), 3.42 (m, H-5), 3.25 (m, H-1), 3.15 (s, OCH_3), 2.10 - 2.35 (m, H-4), 1.58 (s, $-CH_3$), yield = 88%}.

We have investigated the influence of the substituents R^1 and R^2 on the rearrangement step and have observed the formation of a 7 - anti-cyanonorbornan-2-one type product {5 R=Me, Bz, R^2=H, R^1=Me, Cl, Ph, Bz, Et} from 2-exo-bromo-3-endo-methoxy (or benzyloxy)-7-monosubstituted bicyclo[3.2.0]heptan-6-ones (2, R=Me, Bz, R^2=H, R^1=Me, Et, Cl, Ph, Bz {for (5) R=Me, R^1=Et, R^2=H, ν(c=o) 1730 cm^{-1}. δ($CDCl_3$)4.19 (m, H-5) 3.65 (s, OCH_3) 3.67 (m, H-4), 3.57 (s, OCH_3 , 3.35 (m, H-7) 3.12 (m, H-1),2.40 (m, H-6 exo),2.20 (m, H-3 endo),1.30 (m, H-6 endo),1.35 - 0.80 (m, CH_2CH_3)}.

Similar results were obtained for the rearrangement of 2-exo-bromo-3-endo-methoxy-7-mono and 7,7-disubstituted bicyclo[3.2.0]heptan-6-ones (2) with methoxide as nucleophile. Isolation of the proposed tricyclo[3.2.0] heptan-6-one intermediate (6 R=Me, R^1= Et) in this rearrangement was achieved by treatment of the 2 exo-bromo-3-endo-methoxy-7-ethylbicyclo[3.2.0]heptan-6-one (2, R=Me, R^2=H, R^1=Et) with the strong base n-butyl lithium.



Scheme 1: R^1=Cl, Me, H; R^2=Me, Et, Ph, Bz; R=Bz, Me.

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Meth-Cohn, O. et al (1982) J. Chem. Soc. Chem. Commun. 90-92
Lowe, G., Swan, S. (1985) J. Chem. Soc. Perkin Trans 1, 391-398