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FREE-RADICAL ANNELATION IN THE SYNTHESIS OF BICYCLIC β-LACTAMS. 3.[1] SYNTHESIS OF 1-OXACEPHEM AND 1-OXAHOMOCEPHEM DERIVATIVES.[2]

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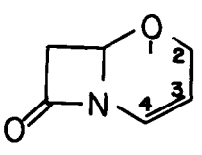
Abstract: The synthesis of *tert*-butyl 3-benzyl-1-oxa-Δ^3-cephem-4-carboxylate (16) and other bicyclic β-lactams is described.

The biological activity of the β-lactam antibiotics has been correlated with the enhanced chemical reactivity of their β-lactam function, which is considerably higher than that of simple non-fused 2-azetidinones. In compounds like the cephalosporins, in which the β-lactam system is fused to an unsaturated six-membered ring, the increased chemical reactivity seems to be associated with the presence of a double bond in conjugation with the nitrogen atom of the β-lactam ring.[3] A similar relationship exists in the new family of synthetic β-lactam antibiotics which derive from 1-oxacephem 1.[4] In a recent communication[5] we have described the synthesis of saturated 1-oxacephams 2 and 1-oxahomocephams 3 by a new method which is based on the intramolecular addition of a free-radical center to a double bond in intermediate β-lactams of type 4. Since compounds 2 and 3 are lacking the unsaturation in the six or seven membered ring, we have now extended the aforementioned synthetic method to the preparation of 1-oxacephem and 1-oxahomocephem systems. To achieve this goal, the intramolecular free-radical addition, with acetylenic rather than with ethylenic compounds was studied.



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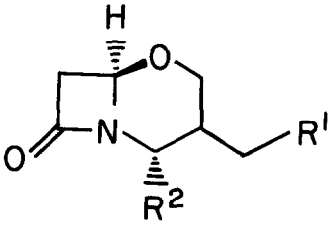

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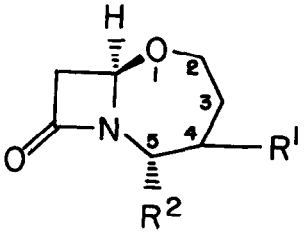

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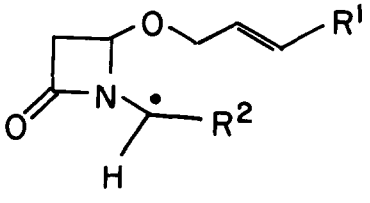

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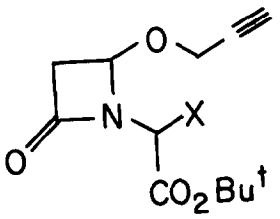
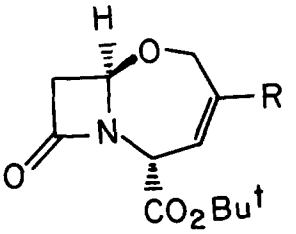
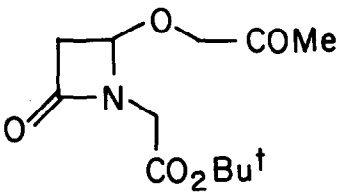


5, X=Cl
6, X=H
7, X=unpaired electron



8, R=H
9, R=Ph
10, R=unpaired electron



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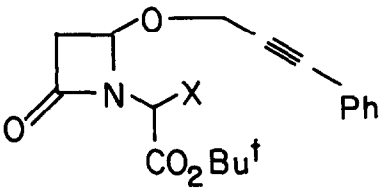
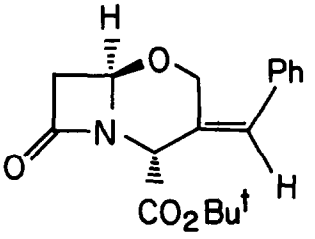
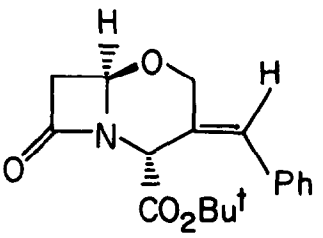


12, X=Cl
13, X=H
14, X=unpaired electron

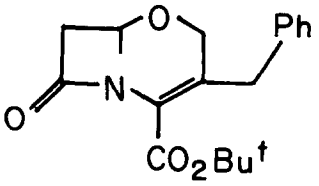


Z

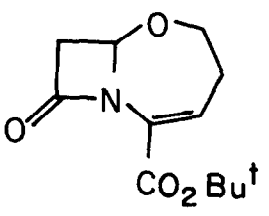


E

15



16



17

Treatment of a 0.02 M solution of the acetylenic chlorolactam 5[6] in benzene with 1.1 equivalent of tri-n-butyltin hydride and 2-4 molar % azobisisobutyronitrile for 44 h, at 80°C, followed by chromatography, led to the isolation of a 2:1 mixture[7] of the non-fused β-lactam 6 and the 1-oxahomocephem 8 (49%), as well as a small amount (ca. 3%) of the bicyclic β-lactam 9[8] (mp 107-109°C). While a pure sample of 6[8] crystallized out from the mixture of 6 and 8,[9] purification of 8 was achieved by an additional chromatography after the selective hydration[10] of the accompanying acetylenic β-lactam 6 into the more polar acetonyloxy derivative 11. The annelation of the acetylenic chloro-compound 5 evidently proceeds through the intermediacy of the free-radical 7[11] which either abstracts a hydrogen atom to give the non-fused β-lactam 6, or undergoes an intramolecular endo-addition to give the bicyclic radical 10. This reactive vinylic radical either abstracts a hydrogen atom to give the major product 8, or reacts with benzene to give the minor product 9.

Access to the 1-oxacephem system required the diversion of the annelation course from the observed endo addition mode yielding a seven-membered ring, to the exo addition mode, leading to the desired six-membered ring. For this purpose compound 5, in which the triple bond occupies a terminal position, was replaced by compound 12, in which the triple bond is substituted by a phenyl group.[12] Compound 12 was prepared from 4-acetoxy-2-azetidinone and 3-phenyl-2-propyn-1-ol by the usual method.[5,6] Treatment of 12 with tri-n-butyltin hydride, under the conditions described above for the annelation of 5, afforded the 3-benzylidene-1-oxacepham 15 (64%), as a 1.3:1 mixture of the corresponding E and Z isomers,[7,8,13] and the non-fused β-lactam 13[8] (18%). The annelation of the intermediate free-radical 14 proved to be highly stereospecific with respect to the relative orientation of the *tert*-butyl ester and the bridgehead hydrogen atom in the resulting bicyclic products 15-Z and 15-E.

To obtain the Δ^3-oxacephem 16, the mixture of the E-and Z-isomers of 15 was treated with 4-dimethylaminopyridine (room temperature, 40 h). Under these conditions only the Z-isomer of 15 underwent migration of the double bond from the exocyclic position into conjugation with the ester group, to give *tert*-butyl 3-benzyl-1-oxa-Δ^3-cephem-4-carboxylate 16 (76%,[14] mp 102-103°C), while the E-isomer of 15 (mp 117-118°C)[8,15] was recovered almost quantitatively.[14] Similarly, treatment of the non-conjugated 1-oxahomocephem 8 with pyridine (60°C, 2 days), afforded *tert*-butyl-1-oxa-Δ^4-homocephem-5-carboxylate 17 (mp 102°C).[8]

We are presently investigating the application of the free-radical annelation to the synthesis of new bicyclic β-lactam systems.

Acknowledgements: We thank Professor Y. Kishi for useful discussions. This research was supported by a grant from the United-States-Israel Binational Science Foundation (BSF), Jerusalem, Israel.

References and Notes

1. Part 2, M.D. Bachi and C. Hoornaert, Tetrahedron Lett., 22, 2693 (1981).
2. The numbering system used in the area of the β-lactam antibiotics is employed throughout this paper.
3. R.M. Sweet in "Cephalosporins and Penicillins: Chemistry and Biology, E.H. Flynn, Ed., Academic Press, New York, N.Y., 1972, p. 280.
4. H. Otsuka, W. Nagata, M. Yoshioka, M. Narisada, T. Yoshida, Y. Harada, and H. Yamada, Medicinal Research Reviews, 1, 217 (1981).
5. M.D. Bachi and C. Hoornaert, Tetrahedron Lett., 22, 2689 (1981).
6. Prepared according to the procedure described by C.L. Branch, J.H.C. Nayler and M.J. Pearson, J.Chem.Soc.,Perkin Trans.I, 1450 (1978).
7. Determined by means of NMR spectral data.
8. Satisfactory ^{1}H NMR and IR spectra, as well as high resolution mass spectra (HMS) or elemental microanalyses were obtained for all new compounds.
9. Compound 6 crystallized out (ether-hexane) at -20°C and melted at room temperature.
10. The acetylene 6 was hydrated by treatment with mercuric sulfate and aqueous sulfuric acid in boiling methanol.
11. The homolysis of the carbon to chlorine bond under these conditions is well documented. See: H.G. Kuivila, Synthesis, 499 (1970).
12. It was anticipated that the phenyl group will favour the exo-cyclization on the ground of both thermodinamic and kinetic factors. See: A.L.J. Beckwith and K.U. Ingold in "Rearrangements in Ground and Excited States", P. de Mayo, Ed., Academic Press Inc., 1980, Vol. 1, p. 161.
13. Hydrogenation of 15 (5% Pd/C, EtOH, 4 Atm.) afforded a 85:15 mixture respectively of 3α-benzyl and 3β-benzyl-1-oxa-cepham-4-butyloxycarbonyl (2, R^1=Ph, R^2=CO_2Bu^t, 73%) identical to authentic samples prepared according to reference 5.
14. The yield was calculated on basis of the original amount in the mixture of 15-Z and 15-E.
15. The geometry of double bond of the E-isomer of 15 was corroborated by Nuclear Overhauser Effect (NOE), thus, irradiation of the protons at position-2 resulted in an increase (ca. 15%) of the intensity of the vinylic proton signal.

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