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A STEREOSELECTIVE SYNTHESIS OF α-ALKOXY-β-LACTAMS[1]

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The discovery of 7-methoxycephalosporin[2] which shows appreciable activity against gram-negative organisms has generated strong interest in α-alkoxy-β-lactams. The partial synthesis of a number of 7-alkoxycephalosporins and 6-alkoxypenicillins and analogs has been reported.[3] Deamination of 6-APA has led to the corresponding 6α-hydroxypenicillanic acid which has been isomerized.[4] Photocyclization of appropriate α-ketoamides has been shown to produce several products including α-hydroxy-β-lactams.[5] We present here a different route that constitutes a convenient and stereospecific synthesis of α-hydroxy-β-lactams which can be converted to various α-alkoxy-β-lactams.

We selected the readily available O-acetylmandelyl chloride (1) as a model reagent for the synthesis of α-hydroxy-β-lactams through annelation of imines. Benzalaniline (2) and 1 underwent ready reaction in presence of triethylamine to give 1,3,4-triphenyl-3-acetoxy-2-azetidinone (3) as a single isomer in 90-95% yield. Hydrolysis of 3 with refluxing 80% trifluoroacetic acid produced the desired α-hydroxy-β-lactam (4) which could be methylated to 5 with methyl iodide and silver oxide.

The thioimidate 6 also underwent facile reaction with 1 and triethylamine to give 1,3,4-triphenyl-3-acetoxy-4-methylthio-2-azetidinone (7) as a single isomer.[6] Hydrolysis of 7 with aqueous trifluoroacetic acid was unsatisfactory as cleavage of the β-lactam ring became a significant side reaction. Zinc chloride in aqueous methanol was eventually found to be a convenient reagent for the hydrolysis of 7 to 8. Methylation of 8 with methyl iodide and silver oxide produced the α-methoxy-β-lactam 9.

Assignment of the stereochemistry of β-lactam formation in reaction with (1) presented some problems. In an attempt to aid configuration determination Raney-nickel desulfurization[6b,7] was utilized to obtain the α-methoxy-β-lactam 10 from 9 and the cis β-lactam 11 from (8). Desulfurization of 7 gave 3 which had been synthesized previously from 1 and 2.

The hydroxy-β-lactams 4 and 8 were acetylated under mild conditions to produce 3 and 7, respectively.

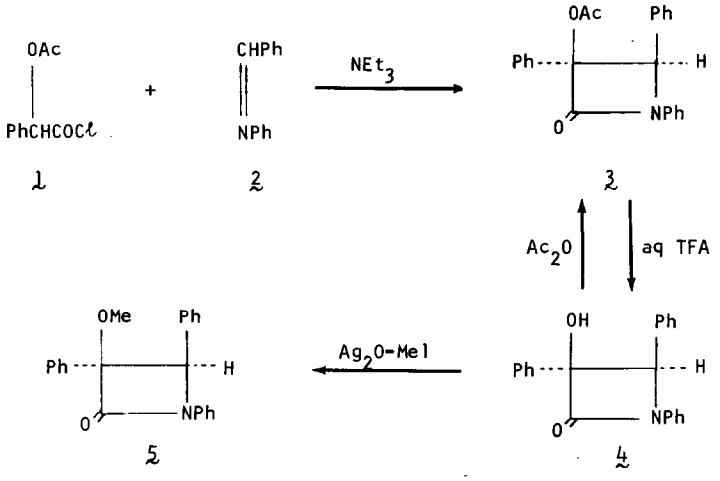
The β-lactams 5 and 10 proved to be isomeric. Configuration assignment could be made unequivocally on the basis of their pmr spectra; the isomer 5 with the higher chemical shift (τ 6.80) for the O-methyl group must have the 4-phenyl group and the 3-OMe group cis to each other. Since neither methylation nor acetylation should invert the stereochemistry of the α-hydroxy-β-lactam 4, the α-acetoxy-β-lactam can be assigned the Z configuration (see stereostructure 3). Because of their method of preparation one can deduce that 7, 8 and 9 must correspond to one another in configuration. It must be noted, however, that Ra-Ni desulfurization which is reported to proceed with retention of configuration,[6b,7] produces 10 from 9 and 3 from 7 and that 3 and 7 have been assigned the opposite configuration.

A study of the pmr spectra of the various β-lactams was made to obtain information on configuration. In the pmr spectrum of 3, the methyl resonance appears at τ 8.35 - a much higher value than observed for the corresponding resonance (τ 7.80) in 7. In chloroform solution -OMe and -SMe signals of 7 appear as one singlet, but they are resolved on the addition of $Eu(fod)_3$. We have assumed the OMe and SMe groups to be trans to the vicinal phenyl rings in 7 since their chemical shift appear to be at normal value. On this basis, the configuration shown by stereostructures 3 and 7 can be assigned. It is noteworthy that the phenyl groups are cis to each other in 7. Previously[6b] we have noted the strong directive influence exercised by the thioimidate group on the stereochemistry of β-lactam formation. The details of the mechanism of β-lactam formation are not well understood, however.

The inversion at C-4 during RaNi desulfurization of 7 to 3 is unusual. It is conceivable that this abnormality arises due to some type of anchimetric effect of the acetoxy group at C-3. In this connection the desulfurization of 8 to 11 is worth noting since under similar conditions the compound 4 was not reduced by Ra-Ni to 11. Probably the same anchimetric effect is involved in the reduction of 8 to 11. The size of the coupling between the vicinal protons at 11 establishes it to be cis-β-lactam.

The reactions described here can be used for the efficient synthesis of variously substituted 3-hydroxy-2-azetidinones in a stereoselective manner — the stereochemical outcome of the β-lactam formation from an imine can be reversed by first using a thioimidate in place of an imine and subsequent desulfurization.

The hydroxy group of course can be modified to produce diverse α-acyloxy or α-alkoxy-β-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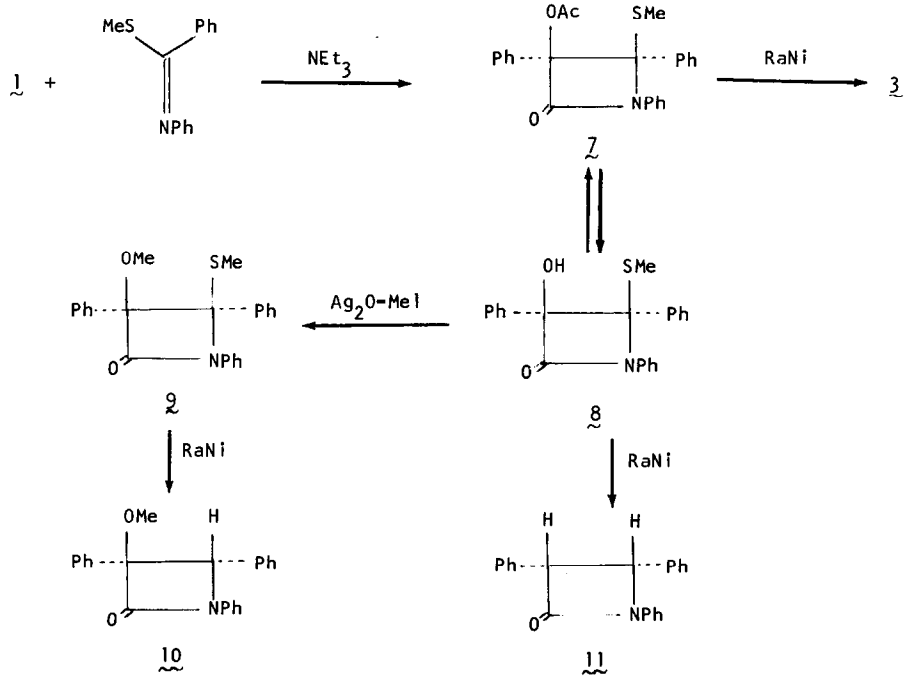
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lactams from the same intermediate. In view of a recent publication by Sheehan and Lo[8] there is added interest now in 6-acyloxypenams and analogs for their antibiotic potential.

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References

1. Part XXXIX in "Studies on β-Lactams. For Part XXXVIII, see A. K. Bose, M. Tsai, and J. C. Kapur, submitted for publication; for Part XXXVII, see A. K. Bose, M. S. Manhas, H. P. S. Chawla, and B. Dayal, Tetrahedron Lett., 0000 (1974).

2. R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark and J. G. Whitney, J. Amer. Chem. Soc., 93, 2308 (1971).

3. (a) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, J. Amer. Chem. Soc., 94, 1408 (1972).

   (b) W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, J. Org. Chem., 38, 943 (1973).

   (c) J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, J. Amer. Chem. Soc., 95, 2401 (1973).

   (d) G. A. Kopper and R. E. Koehler, ibid., 95, 2404 (1973).

   (e) W. A. Spitzer and T. Goodson, Tetrahedron Lett., 273 (1973).

4. D. Hauser and H. P. Sigg, Helv. Chim. Acta, 50, 1327 (1967).

5. B. Åkermark and N. G. Johanson, and B. Sjöberg, Tetrahedron Lett., 371 (1969); also see K. R. Henery-Logan and C. G. Chen, ibid., 1103 (1973).

6. Also see (a) M. D. Bachi and O. Goldberg, Chem. Comm., 319 (1972); (b) A. K. Bose, B. Dayal, H. P. S. Chawla, and M. S. Manhas, Tetrahedron Lett., 2823 (1972).

7. S. Wolfe and S. K. Hasan, Chem. Comm., 833 (1970).

8. (i) Y. S. Lo and J. C. Sheehan, J. Amer. Chem. Soc., 94, 8253 (1972); (ii) J. C. Sheehan and Y. S. Lo, J. Org. Chem., 38, 3227 (1973).