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SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. PART 11.[1]
COMPLETELY STEREOCONTROLLED SYNTHESIS OF 7α-UNSUBSTITUTED 1-OXACEPHEMS FROM PENICILLINS

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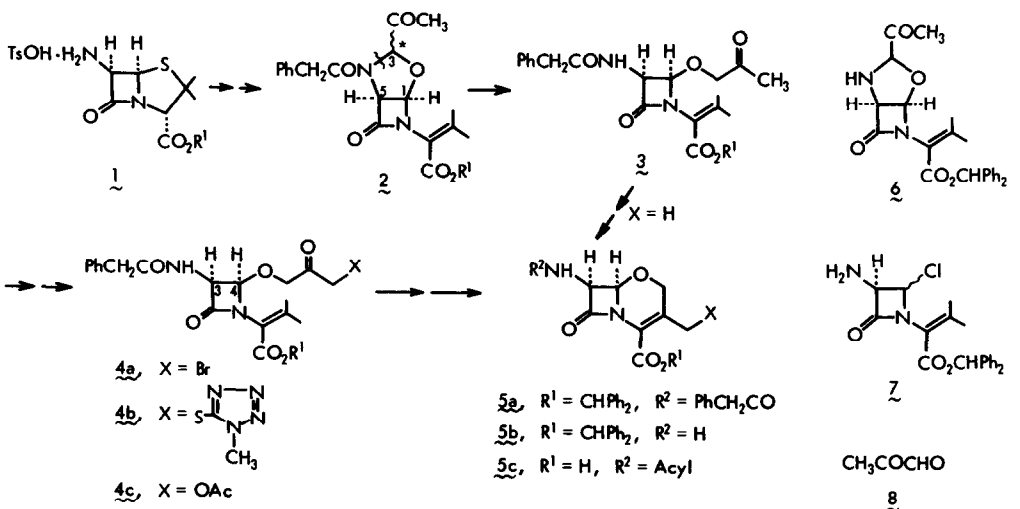
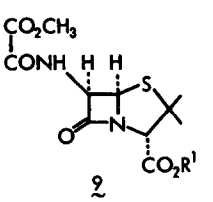
Summary: A cis intermediate 3 was obtained by novel reductive cleavage of 2, prepared from 1 in 6 steps including a new ester to ketone conversion. Regioselective bromination of 3 followed by substitution and known conversions gave 1-oxacephems 5.

Despite recent increasing interest in 1-oxacephem[2] antibiotics having much higher antibacterial activity than that of the 1-thia congeners, cephalosporins,[1,3,4] development of 7α-unsubstituted 1-oxacephems 5c as potent antibiotics has been hindered by the lack of a stereocontrolled synthesis of the 1-oxacephem nucleus which is not naturally occurring. All known total or partial syntheses of 1-oxacephems involve intra- or intermolecular etherification of 4-chloroazetidinones with concomitant or sole formation of undesired α-oxa (trans-oxa) epimers.[3-5] Quite recently, a stereocontrolled synthetic route leading specifically to 7α-methoxy-1-oxacephems was reported from our laboratories.[6] We wish to report here the first stereocontrolled synthesis of 7α-unsubstituted 1-oxacephems 5c from 6-aminopenicillanates 1.

Our synthetic strategy consists of conversion of 6-aminopenicillanate 1 into acetyloxazolidine-azetidinone 2, its reductive cleavage to intrinsically cis acetonyl ether 3 as a key reaction, and its functionalization at the terminal methyl to give versatile intermediates 4. Transformation of 3 and 4 to 1-oxacephems 5c can be done by applying known processes.[1,3]



To obtain the compound 2, direct preparation of the acetyloxazolidine nucleus 6 was attempted unsuccessfully by reaction (N-methylmorpholine, THF, 0°C or -50°C; $ZnCl_2$ or $AgBF_4$)[7] of 4-chloroazetidinone 7[3] with aldehyde 8 (a complex mixture formed). This first difficulty in our synthesis was overcome by our finding that the desired compound 2 could be practically prepared by selective reduction of oxazoline 11 having a carbomethoxy group, which is less reactive than acetyl but still capable of activating the C=N bond, to oxazolidine 12 followed by conversion of carbomethoxy into acetyl. Thus, acylation (CH_3O_2CCOCl, NEt_3, THF or CH_2Cl_2, 3°C or -8°C) of 1 ($R^1 = CH_2Ph$;[8a] $R^1 = CHPh_2$[8b]) to oxalyl amides 9, chlorination (Cl_2, CH_2Cl_2, -20°C) to 4-chloroazetidinones 10, cyclization ($ZnCl_2$, NEt_3, THF) to oxazolines 11, and selective reduction [Al amalgam, THF-H_2O (5-10%), 20-40°C (exothermic)] gave the carbomethoxy-oxazolidines 12[9] ($R^1 = CH_2Ph$, mp 114-116°C, 51%; $R^1 = CHPh_2$, mp 128.5-130.5°C, 54% overall yield from 1) as crystals. Purification of intermediates 9-11 was not necessary. Phenyl-acetylation ($C_6H_5CH_2COCl$, pyridine, toluene, 0°C) of 12 gave amides 13a, which without purification were converted into the acetyloxazolidines 2[9,10] ($R^1 = CH_2Ph$,[11] 72%; $R^1 = CHPh_2$, mp 122.5-123.5°C, 59% overall yield from 12) by conventional five-step process [NaOH, aq acetone, 0°C; $(COCl)_2$, DMF, C_6H_6; CH_2N_2, CH_2Cl_2, 0°C; HCl, Et_2O; Zn, AcOH] via 13b-13e.[9] In an alternative, much improved one-step process,[12] the esters 13a were treated with methyl-magnesium bromide or iodide and triethylamine in toluene-Et_2O at -35°C to give the ketones 2 ($R^1 = CH_2Ph$, 59%; $R^1 = CHPh_2$, 70% overall yield from 12). Significantly, this Grignard reaction in the presence of the amine could achieve not only the direct ester-to-ketone conversion, but also highly selective conversion of the methoxycarbonyl group into acetyl despite the presence of the butenoic ester and the reactive β-lactam ring.



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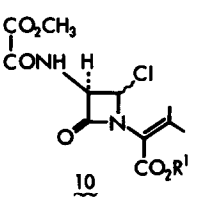

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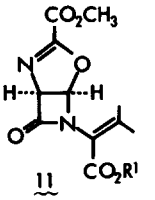

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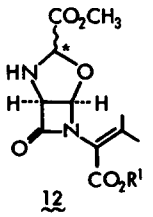

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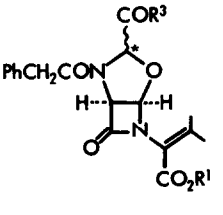
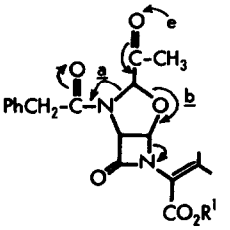


13a, $R^3 = OCH_3$
13b, $R^3 = OH$
13c, $R^3 = Cl$
13d, $R^3 = CHN_2$
13e, $R^3 = CH_2Cl$

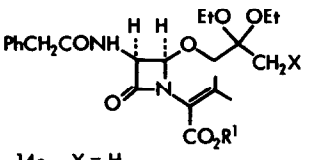


A

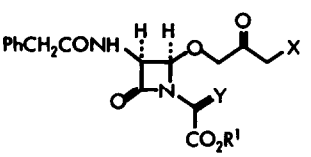
The critical step in this synthetic route is conversion of the acetyloxazolidines 2 thus prepared into the acetonyloxy compounds 3 by reductive cleavage, since, to our knowledge, the reaction of this type has not been reported in the literature. There would be two possible paths, a and b, as shown in formula A, and the key is to increase the selectivity of path a and to prevent further reduction of the desired product 3. The best conditions found after extensive study are slow addition of an ethereal solution of HCl to a mixture of 2, an excess of activated zinc, t-BuOH, and C_6H_6 or CH_2Cl_2[13] until over-reduction by-products become

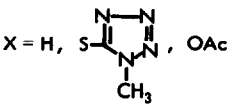
noticeable on TLC. It is essential to stop the reaction before the substrate 2 is consumed. After simple chromatography (C_6H_6-AcOEt, silica gel), there were isolated the known cis-acetonyl ethers 3 ($R^1 = CH_2Ph$,[14] 40-50%; $R^1 = CHPh_2$,[3] 48-51%) and the unchanged starting materials ($R^1 = CH_2Ph$ 11-25%; $R^1 = CHPh_2$, 38-45%).

Completely regioselective bromination of ketones 3 at the terminal methyl was achieved by reaction with $CuBr_2$[15]/$HC(OEt)_3$/ EtOH/40-60°C to give α-bromo ketals 14b, which were subsequently hydrolyzed with $HClO_4$/aq acetone/50°C to bromo ketones 4a[16] in good yields. Intermediacy of ketals 14a in this bromination is apparent from their isolation in an early stage and will favor the terminal bromination.[17] The reactive bromides 4a can undergo facile nucleophilic substitution as exemplified by conversion [1-methyl-1H-tetrazole-5-thiol, triethylamine, 0°C, aq acetone;[18] AcONa, DMF; chromatography (C_6H_6-AcOEt, silica gel)] into tetrazolthio compound 4b ($R^1 = CH_2Ph$,[14] 53% overall yield from 3) and acetates 4c ($R^1 = CH_2Ph$,[14] 45%; $R^1 = CHPh_2$,[1] 39% overall yield from 3).



14a, X = H
14b, X = Br





15a, Y = O
15b, Y = H, OH
15c, Y = H, Cl
15d, Y = PPh_3

The ethers 3, 4b, and 4c synthesized above were easily converted into various 1-oxacephem antibiotics 5c according to the general method reported from our laboratories[1,3,6] consisting of ozonolysis (15a), reduction (15b), chlorination (15c), reaction with triphenylphosphine (15d), intramolecular Wittig reaction (5a), side-chain cleavage (5b), and acylation with useful side-chain components.

The present route provides the first, practical, stereocontrolled synthesis of 7α-unsubstituted 1-oxacephem antibiotics 5c. Antibacterial activity of some of 5c, superior to that of the 1-thia congeners, has been reported.[19]

References and Notes

(1) Part 10: M. Narisada, T. Yoshida, H. Onoue, M. Ohtani, T. Okada, T. Tsuji, I. Kikkawa, N. Haga, H. Satoh, H. Itani, and W. Nagata, J. Med. Chem. 22, 757 (1979).

(2) The trivial name of 1-oxacephem(s) is used for 1-oxa-1-dethiacephalosporin(s); see ref 1.

(3) M. Narisada, H. Onoue, and W. Nagata, Heterocycles 7, 839 (1977).

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(5) (a) L. D. Cama, and B. G. Christensen, J. Am. Chem. Soc., 96, 7582 (1974); (b) S. Wolfe, J. B. Ducep, K. C. Tin, and S. L. Lee, Can. J. Chem. 52, 3996 (1974); (c) C. U. Kim, and D. N. McGregor, Tetrahedron Lett. 409 (1978); (d) E. G. Brain, C. L. Branch, A. J. Eglington, J. H. C. Nayler, N. F. Osborne, M. J. Pearson, T. C. Smale, R. Southgate, and P. Tolliday, "Recent Advances in the Chemistry of β-lactam Antibiotics", Elks, J., Ed.,

The Chemical Society, Burlington House, London, 1977, p 204.

(6) S. Uyeo, I. Kikkawa, Y. Hamashima, H. Ona, Y. Nishitani, K. Okada, T. Kubota, K. Ishikura, Y. Ide, K. Nakano, and W. Nagata, J. Am. Chem. Soc. 101, 4403 (1979).

(7) Under similar conditions trichloroacetaldehyde reacted with 7 to give the trichloroacetyloxazolidine nucleus (CCl_3 instead of CH_3 in 6) in 48% yield.

(8) (a) E. G. Brain, I. McMillan, J. H. C. Nayler, R. Southgate, and P. Tolliday, J. Chem. Soc., Perkin Trans. I 562, 1975; (b) M. Murakami, I. Isaka, and T. Kashiwagi, Japan. Patent 7,126,501 (1971); Chem. Abstr. 76, 3848n (1972).

(9) The stereochemistry at the asterisked carbon was not determined. Each of these compounds was obtained as a single epimer.

(10) Compounds 2 can be used for the next step without purification. Shown are isolated yields of materials purified by chromatography (C_6H_6-AcOEt, silica gel).

(11) Obtained as foams: IR ($CHCl_3$) 1785, 1727, 1703, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 and 2.18 (each s, 3 H, propylidene methyl), 2.28 (s, 3 H, acetyl), 3.92 (s, 2 H, N-side chain methylene), 5.15 and 6.03 (each d, 1 H, J = 4 Hz, C_1 and C_5 H), 5.23 (ABq, 2 H, J = 14, 13 Hz, benzyl ester methylene), 6.15 (s, 1 H, C_3 H), 7.38 and 7.42 (each s, 5 H, phenyl).

(12) This Grignard process can be generally applied to conversion of esters to ketones: I. Kikkawa and T. Yorifugi, to be published.

(13) The benzene or dichloromethane was added to dissolve the substrate. Aluminum amalgam/CF_3CO_2H/t-BuOH also was effective, though yields of 3 were slightly lower.

(14) Authentic samples of these benzyl esters were prepared from the corresponding diphenylmethyl esters[1,3] by deblocking (CF_3COOH-anisole, CH_2Cl_2, 0°C) followed by reesterification ($PhCH_2Br$-NEt_3, acetone).

(15) L. C. King, G. K. Ostrum, J. Org. Chem. 29, 3459 (1964).

(16) Spectral data of 4a, $R^1 = CH_2Ph$: IR ($CHCl_3$) 1780, 1730, 1685 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 and 2.25 (each s, 3 H, propylidene methyl), 3.62, 3.68, and 4.12 (each s, 3 H, phenylacetyl and bromoacetonyl methylenes), 5.1-5.5 (m, 4 H, benzyl ester methylene, C_3 H, and C_4 H), 6.73 (d, 1 H, J = 7 Hz, amide H), 7.4 (two s, 10 H, phenyl); $R^1 = CHPh_2$: IR ($CHCl_3$) 1780, 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.97 and 2.25 (each s, 3 H, propylidene methyl), 3.60 (s, 4 H) and 4.02 (s, 2 H) (phenylacetyl and bromoacetonyl methylenes), 5.12 (d, 1 H, J = 4 Hz, C_4 H), 5.30 (dd, 1 H, J = 8, 4 Hz, C_3 H), 6.72 (d, 1 H, J = 8 Hz, amide H), 6.97 (s, 1 H, diphenylmethyl ester methine), ~7.3 (m, 15 H, phenyl).

(17) M. Gaudry, A. Marquet, Bull. Soc. Chim. France 4169 (1969).

(18) The reagents were added to the preceding hydrolysis mixture.

(19) T. Yoshida, The Royal Society Discussion Meeting "Penicillin 50 years after Fleming", London, May 1979, The Chemical Society, London; Abstr. p 10. A full account will appear soon in Philosophical Transactions of the Royal Society.

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