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STUDIES ON 1-CARBADETHIACEPHEMS, PART III: SYNTHESIS OF 2,3-DIFUNCTIONALISED 1-CARBADETHIACEPHEM DERIVATIVES[1]

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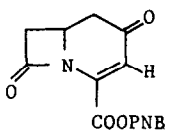
ABSTRACT. A novel C(3) chlorination of p-nitrobenzyl 1-carbadethia-2-oxocephem 4-carboxylate 1 with sulphur dichloride is described. Reaction of the resulting 3-chloro-compound 8 with various thiols, and modifications at C(2) provided the title compounds.

In Part I[2] of this series we presented our rationale for the study of C(2)-substituted 1-carbadethiacephems having sulphur-linked C(3) substituents, and we described practical syntheses[1,2] of p-nitrobenzyl ester 1. We now report the conversion of 1 into novel 1-carbadethiacephems of our target class. Our strategy was to functionalise 1 at C(3) with a group which subsequently would be displaced with an appropriate sulphur nucleophile. The displacement step has precedent in other β-lactam systems[3], but this work is the first which employs a direct functionalisation at an unsubstituted position to introduce a displaceable group.

Our initial approach involved C(3) addition of thiol, and a suitable substrate for this was prepared as follows. Sodium borohydride reduction of 1 gave exclusively the β-alcohol 2[4,5] ($NaBH_4$, aq. THF, -20°, 76%, m.p. 167-168°) which gave 3 on acetylation (Ac_2O, 4-dimethylaminopyridine, RT, 71%). Addition of thiophenol to 2 and 3 (DBN, EtOAc, 0-20°) gave 4 (75%) and 5 (95%) respectively.[7] Acetylation of 4 gave 5 (97%). Reintroduction of the Δ3 olefin was achieved by chlorination at C(3) of 5 using sulphuryl chloride-pyridine (CH_2Cl_2, -10°, 78%) followed by elimination of hydrogen chloride, to give 6 (DBN, CH_2Cl_2, 20°, 85%). The use of iodobenzene dichloride, which was employed[8] for a related transformation, gave lower yields in the chlorination step. The 2-methoxyethanethiol derivative 7 was similarly prepared (59% from 3). An alternative preparation of 7, which employed a C(3) substitution reaction, involved sulphoxidation of 6 (mCPBA, CH_2Cl_2, RT, 88%) followed by displacement of sulphenate with 2-methoxyethanethiol (DBN, CH_2Cl_2, -15°, 75%).



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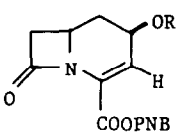

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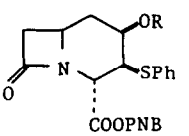
3 R=Ac



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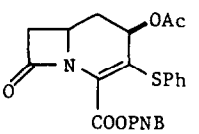

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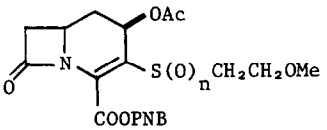
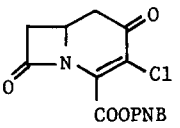


7 n=0

7a n=1

7b n=2



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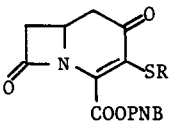
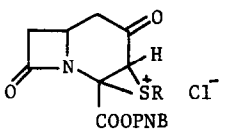


9 R=CH_2CH_2NHAc

10 R=CH_2CH_2OH

11 R=CH_2COOMe



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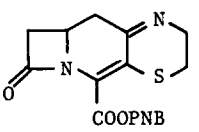

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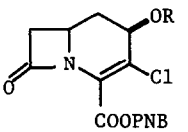
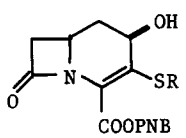


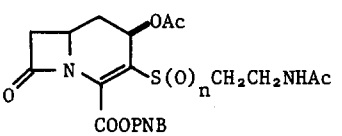
14 R=H

15 R=Ac



16 R=CH_2CH_2NHAc

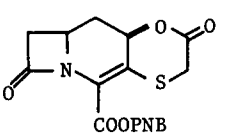
17 R=CH_2CH_2OMe



18 n=0

18a n=1

18b n=2



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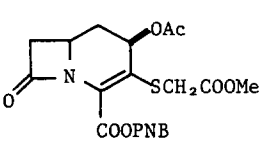

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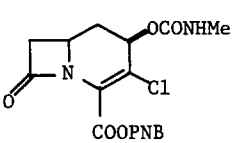

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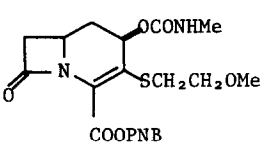

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Although these methods gave examples of our target systems, they were not ideal for our purposes since thiols failed to add to 1, and therefore 2-oxo systems were not conveniently prepared. Furthermore, the introduction of the C(3) leaving group was lengthy, so a direct functionalisation method was sought.

Chlorination of 1 with sulphuryl chloride gave 8 (SO_2Cl_2, pyridine, CH_2Cl_2, -30^o, 50%). In an investigation of alternative chlorination reagents, it was found that sulphur dichloride was a superior reagent[9] for this purpose, giving 8 in 62% yield from 1 (SCl_2, 10 equiv., pyridine, 20 equiv., CH_2Cl_2, RT, 1 hr.). To our knowledge, sulphur dichloride has not been previously used for the simple α-chlorination of enones. Thus, chloroketone 8 was readily available and it was used as a key intermediate as detailed in the following sections. (Chloroketone 8, m.p. 136-137°, ν max (CH_2Cl_2) 1788, 1744, 1695cm^{-1}, δ ($CDCl_3$, 100MHz) 2.9-3.2 (3H, m, C(1)-H`s and C(7)-H), 3.54 (H, dd, J=17, 5.5, C(7)-H´), 4.2-4.5 (H, m, C(6)-H), 5.52 (2H, s), 7.62 (2H, d, J=9), 8.26 (2H, d, J=9). Found: C, 51.54; H, 3.22; N, 7.99%. $C_{15}H_{11}ClN_2O_6$ requires: C, 51.35; H, 3.14; N, 7.99%.)

1-Carbadethia-2-oxocephem Derivatives

Reaction of 8 with N-acetylcysteamine gave 9 (DBN, THF, -78^o, 31%, ν max (CH_2Cl_2) 1785cm^{-1}). Similarly, 10 and 11 were produced using the appropriate thiols (25 and 40% respectively). From some of these reactions, enone 1 was also isolated. For example, reaction of 8 with methyl thioglycollate gave both 11 and 1 (40% and 26% isolated yields respectively). A possible explanation of this unusual reduction involves thiol addition at C(4) followed by formation of thiiranium cation 12 which gives 1 on reaction with excess thiol[10]. Reaction of 8 with cysteamine gave the tricyclic product 13 (94%).

1-Carbadethia-2-hydroxycephem Derivatives

Reduction of 8 gave the β-alcohol 14 ($NaBH_4$, aq. THF, -20^o, 91%) which was acetylated as before, giving 15 (97%). The β-stereochemistry was assigned by analogy with 2. Alcohol 14 was an excellent substrate for displacement reactions with thiols. Thus, compounds 16 and 17 were prepared from 14 by the thiol displacement route (DBN, THF, -78^o, 86 and 93% respectively). Acetylation of 16 and 17 gave 18 and 7 (96 and 93% respectively). When this sequence was applied to methyl thioglycollate, the product was the lactone 19 (83%); the desired product 20 was prepared by reaction of 15 with methyl thioglycollate (89%) under the usual conditions. Carbamate derivatives were prepared by reaction of 14 with methyl isocyanate to give chlorocarbamate 21 (Et_3N, EtOAc, 80^o, 94%) which gave 22 with 2-methoxyethanethiol (DBN, CH_2Cl_2, RT, 10 min, 75%.).

Representative sulphides 7 and 18 were oxidised to their sulphoxides 7a and 18a with m-chloroperbenzoic acid (88% and 96% respectively). Further m-chloroperbenzoic acid oxidation gave the corresponding sulphones 7b and 18b (58% and 90% respectively). Representative β-lactam i.r. absorptions are 7, 1776 cm^{-1}; 7a, 1778cm^{-1}; 7b, 1786cm^{-1}; 11, 1784cm^{-1}; 15, 1773cm^{-1} (CH_2Cl_2).

Deprotections

Using the above methodology, a varied range of 1-carbadethiacephem derivatives having moderately to highly activated β-lactams (as judged by i.r. absorption frequencies) was prepared. Samples of free carboxylic acids were obtained by hydrogenation of the following p-nitrobenzyl esters: 2-5, 7, 7a, 7b, 8-11, 14-17, 19-22, (EtOAc or THF, H_2/Pd-C). Sodium salts were obtained by hydrogenation of the following p-nitrobenzyl esters in the presence of base: 1, 6, 18, 18a, 18b (EtOAc-aq. $NaHCO_3$, H_2/Pd-C). None of these deprotected compounds showed a useful level of antibacterial activity.

Acknowledgement

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2. C.W. Greengrass and D.W.T. Hoople, Tetrahedron Letters, 22, 5535 (1981).
3. R. Scartazzini, P. Schneider and H. Bickel, Helv. Chim. Acta, 58, 2437 (1975). M. Sletzinger, T. Liu, R.A. Reamer and I. Shinkai, Tetrahedron Letters, 21, 4221 (1980) and references therein.
4. Sodium borohydride reduction of 7-azido-4-t-butyloxycarbonyl-1-carbadethia-2-keto-3-methyl-cephem has been shown[5] to afford the 2β-alcohol. The t-butyl ester corresponding to 3 was prepared as described for 3 and gave NMR signals for C(2)-H in good agreement with the values quoted[5] for the 7-azido derivative. Compound 3 (t-butyl ester analogue) δ($CDCl_3$, 200 MHz) (C(2)-H), 5.58; ddd; J=6Hz [C(2)-H-C(1)-H], J=11Hz [C(2)-H-C(1)-H'], J=2.2Hz [C(2)-H-C(3)-H]. Compound 3 (p-nitrobenzyl ester) δ($CDCl_3$, 100 MHz) (C(2)-H), 5.62, ddd, J=6.5, 10.5, 2.2Hz.
5. A. Martel, T.W. Doyle and B-Y. Luh, Can. J. Chem., 57, 614 (1979).
6. All new compounds had satisfactory spectral properties.
7. Stereochemical assignments were made using the corresponding t-butyl ester series: 5 (t-butyl ester analogue) δ($CDCl_3$, 250 MHz), 4.10 (dd; J=1.7, 3.8; C(3)-H), 4.55 (d; J=1.7; C(4)-H), 5.19 (ddd; J=3.8, 3.8, 12; C(2)-H). These couplings are in accord with the C(3)- and C(4)-stereochemistry depicted. The stereochemistry of the p-nitrobenzyl ester analogues was assigned by analogy with the corresponding t-butyl esters.
8. J.H. Bateson, P.M. Roberts, T.C. Smale and R. Southgate, J. Chem. Soc. Chem. Commun., 185 (1980).
9. Other reagents tried (with yields) were: Cl_2/py (23%), tBuOCl/py (35%), S_2Cl_2/py (0%), FSO_2Cl/py (0%).
10. The chemistry of thiiranium cations has recently been reviewed by C.J.M. Stirling, The Chemistry of the Sulphonium Group, Part 2, in The Chemistry of Functional Groups, Ed. S. Patai, Wiley, 1981.

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