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SYNTHETIC STUDIES ON β-LACTAM ANTIBIOTICS. 18.[1]
CONVENIENT, STEREOCONTROLLED SYNTHESIS OF 3-METHYL 7α-METHOXY-1-OXACEPHEMS

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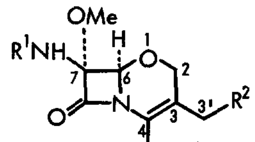
Summary: Alcohols **4** and **8**, prepared from **3**, underwent completely stereospecific etherification to give 1-oxacephams **5** and **10**, which were converted into the 1-oxacephem nucleus **1b** via **6** and **1c**. Functionalization at C-3' in **6** and **1c** was unsuccessful.

Since 7α-methoxy-1-oxacephem **1a** (6059-S) was found to be a highly active β-lactam antibiotic of a new type,[2] we have been concerned for exploring efficient synthetic routes to 7α-methoxy compounds **1** from abundant penicillins. A previous synthesis,[3] though stereocontrolled and convenient on small scales, has a disadvantage of removing three carbon atoms of the starting penicillin which, if properly functionalized, are usable for constructing the 1-oxacephem skeleton. Our recent finding[4] that azetidinone-epioxazoline **3** can be easily prepared from 6-epipenicillin S-oxide **2** has prompted us to examine new, stereocontrolled synthetic routes to **1** starting from this useful intermediate **3** and retaining all the carbon atoms of penicillins. We now report a convenient synthesis of the 3-methyl 7α-methoxy-1-oxacephem nucleus **1b** and attempted functionalization at C-3' of 3-methyl Δ^3-1-oxacephem derivatives.



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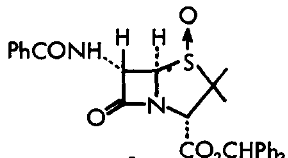

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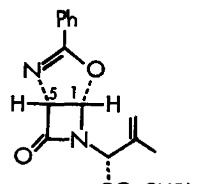

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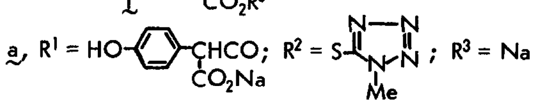
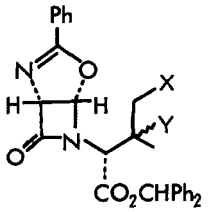


b, $R^1 = R^2 = H$; $R^3 = CHPh_2$

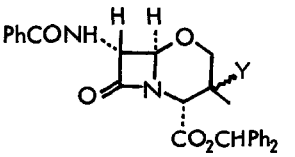
c, $R^1 = PhCO$; $R^2 = H$; $R^3 = CHPh_2$

Treatment of **3** with $KClO_3$/catalytic OsO_4 in THF-H_2O at 60 °C gave an isomeric mixture of diols **4**,[5] which were used for the next step without separation. Cyclization of **4** was effected by treatment with a catalytic amount of $BF_3 \cdot Et_2O$ in Et_2O-CH_2Cl_2 at 25 °C to give, after column chromatography,[6] 3α-hydroxycepham **5a**,[7] its 3β-epimer **5b**, and a mixture of **5a** and **5b** in 37, 25, and 8% overall yields from **3**, respectively. No undesired 6,7-cis isomers were isolated. This result indicates that the above intramolecular etherification proceeds in a completely

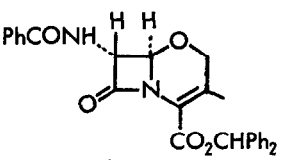
stereospecific manner in contrast to the intermolecular etherification in our previous synthesis[3] which gave an undesired cis by-product in ~5% yield. The configuration of the 3-hydroxy group in cephams 5 is assigned from the following dehydration result. Dehydration of 5a with $SOCl_2$/pyridine in CH_2Cl_2 (25 °C, 0.5 hr) proceeded smoothly to give 1-oxa-3-cephem 6[8] (67%),[6] whereas the reaction of 5b with $SOCl_2$/pyridine/catalytic DMF in CH_2Cl_2 (25 °C, 5 hr) afforded a 1:2 mixture of 6 and Δ^2-isomer 7[9] as judged from the NMR spectrum of the crude product. Reasonably, the hydrogen at C-4 and the hydroxy group at C-3 are trans in 5a which was dehydrated to Δ^3-isomer more easily than the other epimer 5b.[10] When a crude cyclization product containing 5a and 5b was dehydrated ($SOCl_2$/pyridine/CH_2Cl_2, 0 °C, 1.3 hr; then 25 °C, 2.3 hr), 6 and 7 were obtained in 25 and 11% overall yields from 3,[6] respectively. Interestingly, either 6 or 7 gave, on treatment with NEt_3 in $(CH_2Cl)_2$ at 25 °C, an equilibrium mixture of 6 and 7 in a 4:6 NMR ratio.



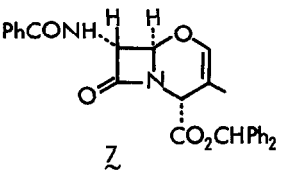
4, X = Y = OH
8, X = OH; Y = Br
9, X = Br; Y = OH
11, X-Y = O
12, X = Cl, Y = OH



5a, Y = α-OH
5b, Y = β-OH
10, Y = Br



6



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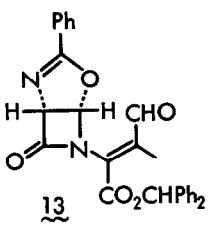
Alternatively, reaction of 3 with N-bromosuccinimide (NBS) in aqueous acetone at 15 °C gave bromohydrin 8[11] (40%) as a crystalline single epimer and isomers 9[12] (30%) as an unseparable epimeric mixture.[6] Intramolecular etherification of 8 (catalytic $BF_3 \cdot Et_2O$, AcOEt-CH_2Cl_2, 25 °C) was completely stereospecific as in the reaction of 4, giving 3-bromo-1-oxacepham 10[13] (~100%), which was converted (1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), CH_2Cl_2, -20 °C) into 1-oxa-3-cephem 6 (97%). On the other hand, epoxidation of 3 (m-chloroperbenzoic acid, CH_2Cl_2, 25 °C, 2 days) to an unseparable epimeric mixture (49%)[6] of epoxides 11 followed by ring cleavage (conc HCl, CH_2Cl_2, 0 °C) gave only an epimeric mixture (74%)[6] of undesired chlorohydrins 12.

Methoxylation of 7-epi-1-oxacephem 6 by the conventional method[14] (t-BuOCl, LiOMe, CH_2Cl_2, -40°C) gave 7α-methoxy-7β-amide 1c[15] (79%),[6] which underwent the side chain cleavage (PCl_5, pyridine, CH_2Cl_2, 25 °C; MeOH, -20 °C; Et_2NH, -10 °C) without noticiable epimerization at C-7[1,3] to afford methoxy amine 1b[16] (53%).[6] This amine 1b is an important intermediate for preparing various 7β-acylamino-7α-methoxy-3-methyl-1-oxa-3-cephem-4-carboxylic acids whose antibacterial activity will be published in the near future.

Since 3-substituted methyl 1-oxacephems including 1a are β-lactam antibiotics of a more

important class, we have attempted to functionalize the 3-methyl group in 1-oxacephems 6 and 1c. These compounds on treatment with NBS/2,2'-azobisisobutyronitrile (AIBN)[17] in refluxing CCl_4 respectively gave aldehyde 13 (15% as an only isolatable product)[6] and non-β-lactam products. The aldehyde 13 may be formed via the 2-bromo derivative of 6. Compounds 6 and/or 1c were essentially inert to N-chlorosuccinimide (NCS)/AIBN, DBU/Br_2[18] (THF, ~25 °C), NCS/hν (CH_2Cl_2-AcOH, 0 °C), or SeO_2[19] (AcOH, ~30 °C). Reaction of 6 with DBU/NCS gave 14, whereas that with NBS/hν (CH_2Cl_2-AcOH, 0 °C)[20] resulted in β-lactam cleavage.



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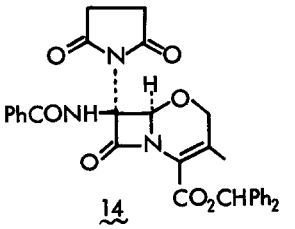

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(5) 4: foams; IR ($CHCl_3$) 3500 (br), 1770 (br), 1742, 1636 cm^{-1}; NMR ($CDCl_3$) δ, Epimer A: 1.20 or 1.22 (s, 3, C(OH)CH_3), 3.52 (s, 2, CH_2OH), 4.63 (s, 1, $CHCO_2$-), 5.40 and 6.30 (each d, 1, J = 3 Hz, C_1 H and C_5 H), 7.00 (s, 1, $CHPh_2$), 7.2-8.1 (m, 15, ArH). Epimer B: 1.20 or 1.22 (s, 3, CH(OH)CH_3), 3.58 (s, 2, CH_2OH), 4.57 (s, 1, $CHCO_2$-), 5.40 and 6.17 (each d, 1, J = 3 Hz, C_1 and C_5 H), 7.00 (s, 1, $CHPh_2$), 7.2-8.1 (m, 15, ArH).

(6) The product(s) were separated or purified by chromatography (silica gel, C_6H_6-AcOEt), when necessary, followed by crystallization.

(7) 5a: foams; IR (Nujol) 3385 (br), 1755, 1740, 1648 cm^{-1}; NMR (DMSO-d_6) δ 1.40 (s, 3, C(OH)CH_3), 3.42 and 3.85 (ABq, 2, J = 11.5 Hz, C_2 H), 4.35 (s, 1, C_4 H), 4.75 (d, 1, J = 8 Hz, C_7 H), 5.27 (s, 1, C_6 H), 5.67 (s, 1, OH), 6.77 (s, 1, $CHPh_2$), 7.1-7.9 (m, 15, ArH), 9.08 (d, 1, J = 8 Hz, NH). 5b: mp 207-209 °C; $[\alpha]_D^{22}$ +45.3 ° (c 1.050, dioxane); IR (Nujol) 3530, 3320, 1783, 1753, 1745, 1723, 1638 cm^{-1}; NMR (DMSO-d_6) δ 0.83 (s, 3, C(OH)CH_3), 3.47 (s, 1, C_2 H), 4.30 (s, 1, C_4 H) 4.88 (d, 1, J = 8 Hz, C_7 H), 5.25 (s, 1, C_6 H), 5.62 (s, 1, OH), 6.80 (s, 1, $CHPh_2$), 7.1-7.9 (m, 15, ArH), 9.07 (d, 1, J = 8 Hz, NH).

(8) 6: mp 144-146 °C; $[\alpha]_D^{22}$ 0.0° (c 1.028, $CHCl_3$); $[\alpha]_{365}^{22}$ +132.2° (c 1.028, $CHCl_3$); IR ($CHCl_3$)

3440, 1782, 1722, 1663 cm^{-1}; NMR ($CDCl_3$) δ 1.92 (s, 3, C_3 H), 4.23 (s, 2, C_2 H), 4.90 (s, 1, C_6 H), 5.07 (d, 1, J = 8 Hz, C_7 H), 6.88 (s, 1, $CHPh_2$), 7.1-8.0 (m, 16, ArH and NH).

(9) 7: foams; IR ($CHCl_3$) 3440, 1782, 1745, 1676, 1663 (sh) cm^{-1}; NMR ($CDCl_3$) δ 1.55 (d, 3, J = 1 Hz, C_3, H), 4.65 (br s, 1, C_4 H), 5.02 (d, 1, J = 7 Hz, C_7 H), 5.32 (s, 1, C_6 H), 6.27 (br s, 1, C_2 H), 6.90 (s, 1, $CHPh_2$), 7.1-7.9 (m, 16, ArH and NH).

(10) The structural assignments are consistent with the ^1H NMR NOE and decoupling data on both epimers 5a and 5b. The NMR study will be published in a separate paper.

(11) 8: mp 159-160 °C (decomp.); $[\alpha]_D^{23}$ +53.8° (c 1.024, $CHCl_3$); IR (Nujol) 3200 (br), 1788, 1733, 1633 cm^{-1}; NMR ($CDCl_3$) δ 1.70 (s, 3, $CBrCH_3$) 3.79 (br s, 3, CH_2OH), 4.90 (s, 1, $CHCO_2$-) 5.47 and 6.63 (each d, 1, J = 3 Hz, C_1 H and C_5 H), 7.03 (s, 1, $CHPh_2$), 7.2-8.0 (m, 15, ArH).

(12) 9: foams; IR ($CDCl_3$) 3370 (br), 1780, 1743 (sh), 1634 cm^{-1}; NMR ($CDCl_3$) δ 1.37 + 1.46 (each s, total 3, $C(OH)CH_3$), 3.33 (s) + 3.50 and 3.61 (ABq, J = 5.5 Hz) (total 2, CH_2Br), 4.66 + 4.77 (each s, total 1, $CHCO_2$-), 5.38 + 5.44 (each d, total 1, J = 3 Hz, C_1 or C_5 H), 5.90 + 6.14 (each d, total 1, J = 3 Hz, C_1 or C_5 H), 6.88 + 6.98 (each s, total 1, $CHCO_2$-), 7.2-8.2 (m, 15, ArH).

(13) 10: foams; IR ($CHCl_3$) 3450, 1793, 1749, 1673 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (s, 3, $CBrCH_3$), 3.82 and 4.52 (ABq, 2, J = 11 Hz, C_2 H), 4.77 (s, 1, C_4 H), 5.05 (d, 1, J = 8 Hz, C_7 H), 5.47 (s, 1, C_6 H), 6.93 (s, 1, $CHPh_2$), 7.1-7.9 (m, 16, ArH and NH).

(14) G. A. Koppel and R. E. Koehler, Tetrahedron Lett., 1943 (1973).

(15) 1c: foams; IR ($CHCl_3$) 3430, 1788, 1728, 1688 cm^{-1}; NMR ($CDCl_3$) δ 1.95 (s, 3, C_3, H) 3.63 (s, 3, OCH_3), 4.25 (s, 2, C_2 H), 5.22 (s, 1, C_6 H), 6.98 (s, 1, $CHPh_2$), 7.2-8.1 (m, 16, ArH and NH).

(16) 1b: mp 114-116 °C; $[\alpha]_D^{25}$ -50.7° (c 0.420, $CHCl_3$); IR ($CHCl_3$) 3415, 3335, 1777, 1723 cm^{-1}; NMR ($CDCl_3$) δ 1.90 (s, 3, C_3, H), 2.18 (br s, 2, NH_2), 3.48 (s, 3, OCH_3), 4.22 (s, 2, C_2 H), 4.78 (s, 1, C_6 H), 6.86 (s, 1, $CHPh_2$), 7.1-7.6 (m, 10, ArH).

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