Nucleophilic Displacement of 7α-Methoxy-7β-amino-1-oxacephem Derivatives: Synthesis of 7α-Substituted 1-Oxacephem Antibiotics

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Summary Acid-catalysed displacement of 7α-methoxy-7β-amino-1-oxacephem (**1**) with nucleophiles gave the 7α-substituted-7β-amino compounds (**5**—**8**), which were converted into the antibiotics (**13**—**16**).

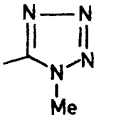
THE 7α-methoxy-7β-amino-1-oxacephem derivative (**1**), a key intermediate in syntheses of the clinically useful 7α-methoxy-1-oxacephem antibiotic [disodium salt of (**12**), code number 6059-S],[1] has been prepared by deacylation of the amide precursors (**2**)[2] and (**3**)[3] under conventional conditions (PCl_5–pyridine; MeOH). The observed formation of little of the 7β-methoxy epimer (**10**), in contrast to the predominant formation of 7β-methoxy-7α-amino derivatives in the deacylation of cephalosporins,[4] has been interpreted by assuming that acid-catalysed epimerisation at C-7 is very slow in the 1-oxa compound (**1**).[2]

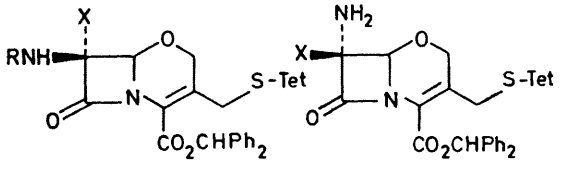
TABLE. Displacements of the methoxy-amine (**1**) (at room temperature).

Reagent	Solvent	Time	Product	Yield/%	M.p./°C
HCl–EtOH	CH_2Cl_2–EtOH	45 min	(**5**)	76·1	157—160
HCl–Bu^{t}OH	CH_2Cl_2–Bu^{t}OH	45 min	(**6**)	72·7	149—152
HCl–AcSH	CH_2Cl_2	16 h	(**7**)	80[a]	—
HCl–MeSH	CH_2Cl_2–MeOH	2 h	(**8**)	84·8[b]	165—171

[a] Crude yield of a single isomer. [b] Yield of a crystalline product containing about 10% of the 7β-methylthio epimer. After acylation, the products from these two isomers could be separated.

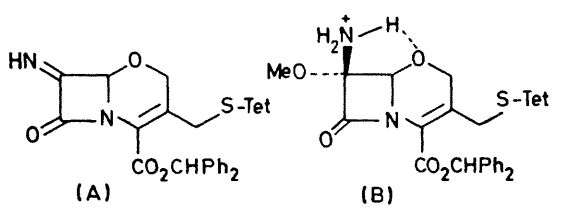
We found that the [$^2H_3$]methoxy amine (**4**) was obtained in 65% yield on deacylation of the amide (**3**) using [$^2H_4$]-methanol in place of methanol (PCl_5–pyridine, 25 °C; CD_3OD, 0 °C, 2 h; Et_2NH, −20 °C) and that acid-catalysed alcoholysis of (**1**) [CD_3OD–$CDCl_3$ (2:7), HCl (0·1 equiv.), 25 °C, 1 h] gave a 5:1 mixture of (**4**) and (**11**). These results clearly indicate that there is a rapid, acid-catalysed epimerisation (**1**)⇌(**10**) *via* intermediate (*A*) under the conventional deacylation conditions, and that the 7α-methoxy epimer (**1**) is the thermodynamically more stable of the two. This stability can be attributed to hydrogen-bonding, as shown in structure (*B*), which would be much weaker in the l-thia congener.

Tet =  throughout

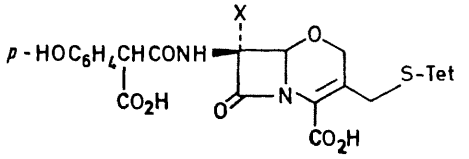


(**1**) R = H, X = OMe
(**2**) R = $PhCH_2CO$, X = OMe
(**3**) R = PhCO, X = OMe
(**4**) R = H, X = OCD_3
(**5**) R = H, X = OEt
(**6**) R = H, X = OBu^t
(**7**) R = H, X = SAc
(**8**) R = H, X = SMe
(**9**) X = SMe
(**10**) X = OMe
(**11**) X = OCD_3

This finding led us to examine a new method for preparing biologically interesting 7α-substituted l-oxacephems by performing acid-catalysed nucleophilic displacements of the abundant material (**1**) *via* the imine (*A*). The displacement reactions proceeded smoothly to give 7α-substituted 7β-amino derivatives in good yields (Table). The stereochemical assignments are based on an analogy with the methoxy-amine (**1**) for the alkoxy-amines (**5**) and (**6**), and on favourable α-side attack[5,6] for the thio-products (**7**) and (**8**) which are considered to be kinetically controlled products.

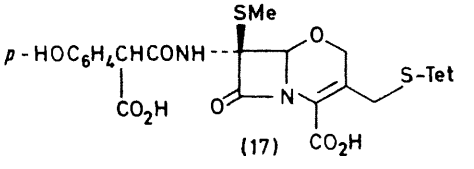


(A) (B)



(**12**) X = OMe
(**13**) X = OEt
(**14**) X = OBu^t
(**15**) X = SAc
(**16**) X = SMe

The 7β-amines (**5**)—(**8**) were converted into the corresponding 7α-substituted l-oxacephem antibiotics (**13**) (50%), (**14**) (60%), (**15**) (40%), and (**16**) (58%) by the known two-step process [4-(*p*-$MeOC_6H_4CH_2O$)$C_6H_4CH(CO_2CH_2C_6H_4$OMe-*p*)COCl, pyridine, CH_2Cl_2, −20 °C; CF_3CO_2H, anisole, CH_2Cl_2, 0 °C]. The antibacterial activities of products (**13**), (**14**), (**15**), and (**16**) were found to be approximately 1/10, 1/100, 1/200, and 1/300, respectively, of the activity of (**12**).



(**17**)

Compound (**17**), derived from the minor epimer (**9**) (separated after the acylation), did not show an *in vitro* antibacterial activity at a concentration of 100 μg/ml.

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