Tetrahedron Letters,Vol.24,No.43,pp 4755-4756,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

AN UNUSUAL BOND MIGRATION DURING O-ACYLATION OF TETRAMIC ACIDS

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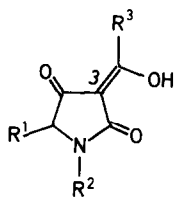
Summary The quaternary ammonium enolates of 5-substituted pyrrolidine-2,4-diones undergo isomerisation to the exocyclic $\Delta^{5,6}$-isomers during O-acylation.

The group of 3-acyl tetramic acids of general structure (1) are microbial metabolites of interest for their range of biological activities; an example is tirandamycin, the potent inhibitor of bacterial DNA-directed RNA polymerase.[1] As part of a synthetic programme in this area we have reported two methods for acylation of pyrrolidine-2,4-diones (2), either with acid chlorides and Lewis acids,[2] or using the reaction of vinyl-lithium reagents (3) with aldehydes.[3] Attempts at base-mediated acylation of diones (2) by others have led either to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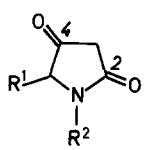
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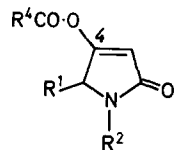
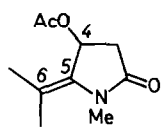

(4)

predominant 4-O-acylation, i.e. (4), or to low to moderate yields of the desired 3-C-acylation, i.e.(1), using various metal enolate derivatives and acid chlorides or fluorides,[4] or triethylamine and an active ester.[5] We wish to report our studies using a tetra-alkylammonium enolate of (2), that have uncovered an unexpected double-bond migration during acylation.

When 1-methyl-5-isopropylpyrrolidine-2,4-dione (2; R^1=$CHMe_2$, R^2=Me), the tetramic acid nucleus of the mould pigment erythroskyrine[6] and prepared from N-methyl-L-valine methyl ester,[3] was treated with acetyl chloride-triethylamine (CH_2Cl_2, reflux), the enol acetate (4; R^1=$CHMe_2$, R^2=R^4=Me)[7] was isolated (87%). In contrast, when the dione was treated with tetraethylammonium hydroxide solution (1 equiv.) and the dried tetraethylammonium salt was acylated with freshly distilled acetyl chloride (3 equiv., CH_2Cl_2, 25°C, 48 h), an alternative product, m.p. 64°C, was isolated (55%). This was identified as the 4-O-acetyl-$\Delta^{5,6}$-isomer (5) on the basis of analytical and spectroscopic data,[7,8]

for example the ^{1}H and ^{13}C n.m.r. spectra (with appropriate decoupling experiments) from which the $-CH(OR)CH_2-$ and $Me_2C{=}C$ fragments could be deduced. O-Acylation has thus been accompanied by a double-bond migration. To examine the generality of this isomerisation the 5-benzyl dione (2; $R^1{=}CH_2Ph, R^2{=}H$), available from other work in our laboratories,[2] was treated in the same way. Two crystalline products were obtained that were identified as the (E)- and (Z)-4-O-acetyl-$\Delta^{5,6}$-isomers (6a),[7] m.p. 97-98°C (60%), and (6b),[7] m.p. 129-131°C (20%), respectively, by spectroscopic methods including ^{1}H n.m.r. spectra and n.O.e. measurements. When the minor (Z)-isomer (6b) was recrystallised from chloroform-hexane the same 3:1 mixture of (6a) and (6b) was again formed.



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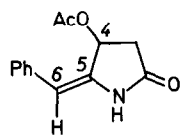
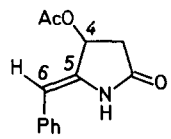
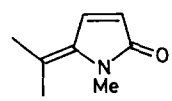


(6a)



(6b)



(7)

These double-bond shifts may be rationalised as a series of protonation-deprotonation steps catalysed by traces of acid present in the acylation reaction mixture, with the $\Delta^{5,6}$ location representing a thermodynamic minimum. No isomerisation of enol acetate (4; $R^1{=}CHMe_2, R^2{=}R^4{=}Me$) was observed on standing in acid-free dichloromethane for several days.

An attempt to deprotonate enamide (5) under kinetic conditions ($LiNPr^{i}_{2}$, -78°C) led, not surprisingly, to elimination of acetic acid and isolation of lactam (7),[7] whose properties are under investigation.

We thank SERC and Beecham Pharmaceuticals for a CASE studentship (to G.E.P) and Drs. A.G. Brown and M. Gilpin (Beecham) for helpful discussion.

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7. All new compounds gave spectra (IR, UV, NMR, MS) consistent with the assigned structure, and satisfactory accurate mass measurement or combustion analysis.
8. For (5): ν_{max}(Nujol) 1730, 1700, 1665 cm^{-1}; λ_{max}(EtOH) 231(ε12,650) nm; $\delta_H(CDCl_3)$ 1.75 and 1.95 (each 3H,s,$CH_3C{=}$), 2.75(3H, s, CH_3CO), 2.45(1H, d, J 18 Hz, CHH), 2.83(1H, d of d, J 18 and 6.5 Hz, CHH), 3.30(3H, s, NCH_3), and 5.80(1H, d, J 6.5 Hz, CHOAc); $\delta_C(CDCl_3)$ (with off-resonance multiplicities) 19.1, 20.9, 21.3, 31.1 (all q), 37.8 (t), 68.4(d), 112.1, 133.3 170.1, 173.7 (all s).

(Received in UK 24 August 1983)