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DIRECTED METALLATION OF TETRAMIC ACIDS: A NEW SYNTHESIS OF 3-ACYL TETRAMIC ACIDS

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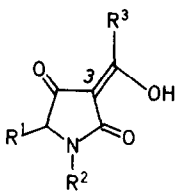
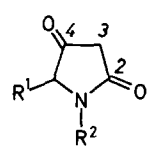
Summary:- 3-Acyl tetramic acids have been prepared by directed metallation at C-3 of the 4-O-methyl ethers of pyrrolidine-2,4-diones, reaction of the vinyl-lithium derivative with aldehydes, and oxidation and hydrolysis of the adducts.

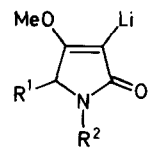
The 3-acyl tetramic acids (1), such as tirandamycin (2),[1] a potent inhibitor of bacterial DNA-directed RNA polymerase, and erythroskyrine (3)[2], a mould pigment, form a class of metabolites isolated from microorganisms and displaying a variety of biological properties. The heterocyclic nucleus (1) common to these natural products consists of a pyrrolidine-2,4-dione (4) acylated at C-3.[3] We have been interested in developing flexible syntheses of such systems applicable to targets including those having unsaturated groupings conjugated to the C-3 carbonyl substituent, such as the important 3-dienoyl tetramic acids [e.g. (2)], and have previously reported on the Lewis-acid promoted acylation of pyrrolidine-2,4-diones (4).[4] We wish now to disclose a complementary base-mediated approach, namely the reaction of vinyl-lithium derivatives (5), available from enol ethers of diones (4), with aldehydes and subsequent conversion of the adducts to 3-acyl tetramic acids.[5]



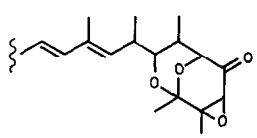
(1)

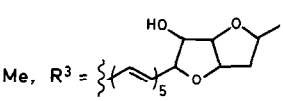


(4)



(5)

(2) $R^1 = R^2 = H$, $R^3 =$ 

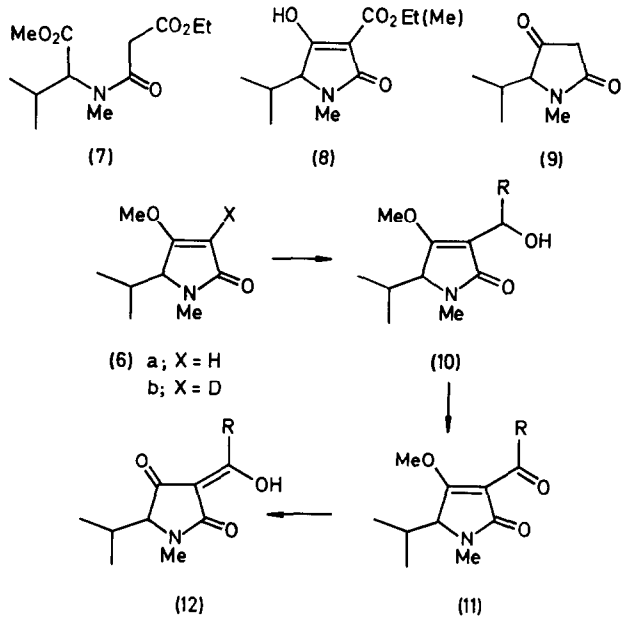
(3) $R^1 = CHMe_2$, $R^2 = Me$, $R^3 =$ 

Our studies were carried out on the 1-methyl-5-isopropyl compound (6a), related to erythroskyrine (3), which was prepared as follows. N-Methyl-L-valine methyl ester,[6] available from N-benzyloxycarbonyl-N-methyl-L-valine[7] (MeOH, reflux, 4 h; 81%), was condensed with ethyl hydrogen malonate (DCC, CH_2Cl_2; 70%) and the amide (7)[6] cyclised (NaOMe, MeOH) to give the 3-alkoxycarbonyl tetramic acid (8) as a mixture of ethyl and methyl esters (85-90%). Hydrolysis - decarboxylation proceeded efficiently (moist MeCN, reflux, 8 h; 95%) to afford dione (9),[6] m.p. 76-78°C, that was converted to the 4-O-methyl ether (6a),[6] m.p. 56-58°C, either by direct methylation (Me_2SO_4, K_2CO_3, acetone; 56%) or more efficiently by methylation of the dry tetrabutylammonium salt (Bu_4NOH aq. and drying; then Me_2SO_4, CH_2Cl_2; 84%).

Preliminary deprotonation studies showed that treatment of (6a) in a basic protic medium (CD_3ONa, 1 equiv., in CD_3OD) led to incorporation of deuterium rapidly at C-5 (seconds) and more slowly at C-3 (98% D by p.m.r. after 7 days). Deprotonation of (6a) by Bu^nLi (1.6 equiv., THF, -80°C for 30 min) occurred at C-3 as shown by quenching with CD_3OD to give the 3-deuterated derivative (6b) (> 80% D by p.m.r.). Metallation with an amide base ($LiNPr^i_2$, -80°C) followed by CD_3OD quenching led to only approx. 40% deuteration, in contrast to recent findings in the closely analogous tetronic acid series,[8] presumably indicating a lower acidity at C-3 in the tetramic acid series.

Acylation was accomplished at C-3 by the following sequence. Metallation of (6a) with Bu^nLi as above, followed by addition of an aldehyde (1.6 equiv., -80°C for 40 min., -50°C for 30 min) afforded, after column chromatography on silica, the hydroxy-adducts (10a-d)[6] (see Table) from benzaldehyde, heptanal, (E)-2-butenal, and (E,E)-2,4-hexadienal, respectively, in each case as a mixture of diastereomers that was not further separated; some (6a) was also recovered. Alcohols (10a-d) were not stored, but immediately oxidised (MnO_2, CH_2Cl_2, 25°C) to give, again after column separation, the corresponding keto-derivatives (11a-d)[6] (see Table). Oxidation of (10b) was somewhat slower than the other cases and some unchanged alcohol (11%) was isolated along with (11b) after 30 h; in contrast oxidation of (10c) was rapid, and extended reaction times led to decreased recoveries of (11c). The 4-O-methyl-3-acyl tetramic acids (11a-d) were easily converted by shaking with 1M NaOH aq. at 25°C into the free 3-acyl tetramic acids (12a-d)[6] (see Table), identical with samples prepared from dione (6a) by our Lewis-acid promoted acylation procedure.[4]

We are currently exploring the scope of this method,[9] which joins the complete 3-acyl side-chain to a tetramic acid nucleus, with a view to synthesis of naturally occurring tetramic acids and analogues. We thank S.E.R.C. and Beecham Pharmaceuticals for a CASE Studentship (G.E.P.) and Drs. A.G. Brown and M. Gilpin (Beecham) for helpful discussion.



(10) – (12) a; R = Ph
b; R = $(CH_2)_5Me$
c; R = CH=CHMe
d; R = $(CH=CH)_2Me$

TABLE : Preparation of 3-Acyl Tetramic Acids

R	Alcohols (10) Yield (%)[a]	Ketones (11) Rn.time; Yield (%)[a]	3-Acyl Tetramic Acids (12) Rn.time; Yield (%)[a]
Ph	70	18 h ; 90	24 h ; 85
$(CH_2)_5Me$	57	30 h ; 64	4 h ; 83
CH=CHMe	54	1 h ; 63	2 h ; 91
$(CH=CH)_2Me$	58	18 h ; 87	2 h ; 80

[a] isolated yields

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3. The 3-acyl tetramic acids represented in this Letter are drawn in the 3-exo-enol form found in the solid state, and as the major tautomer in solution for a number of cases: M.J. Nolte, P.S. Steyn, and P.L. Wessels, J.Chem.Soc., Perkin Trans.1, 1980, 1057.

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5. For other synthetic work on 3-acyl tetramic acids see; V.J. Lee, A.R. Branfman, T.L. Herrin, and K.L. Rinehart, J.Am.Chem.Soc., 1978, 100, 4225; R.K. Boeckman and A.J. Thomas, J.Org.Chem., 1982, 47, 2824; P. DeShong, N.E. Lowmaster, and O. Baralt, ibid., 1983, 48, 1149.

6. All new compounds gave spectra (IR, UV, NMR, MS) consistent with the assigned structure, and satisfactory accurate mass measurement or combustion analysis. Purity was assessed also by t.l.c. examination.

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9. For example, studies using lithiated (6a) and esters as acylating agents have to date proved unpromising. Compounds (11) were stable to mild acid treatment (1$\underline{N}$ HCl, THF, 25°C).

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