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METALLATION OF 3-ACETYLTETRAMIC ACIDS : A NEW SYNTHESIS OF 3-DIENOYL- AND 3-TRIENOYL-TETRAMIC ACIDS

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<u>Summary</u>: 3-Acetyltetramic acids have been metallated, and the trilithio-derivatives condensed with aldehydes to afford 3-dienoyl- and 3-trienoyl-tetramic acids.

The 3-acyltetramic acids (1) constitute a class of microbial natural products, within which the 3-dienoyltetramic acids, exemplified by tirandamycin A (2), form an important sub-group of six structurally related metabolites possessing a variety of biological properties.<sup>1</sup> Tirandamycin A (2), which has antibacterial properties and is an inhibitor of bacterial DNA-directed RNA polymerase, has attracted much recent synthetic interest.<sup>2</sup> A common strategy in these syntheses is the linkage of the acyltetramic acid moiety to the remainder of the molecule by condensation using the dianion of the 3-phosphonoacetyltetramic acid (3).<sup>2a-c,3</sup> As part of a continuing synthetic programme with acyltetramic acids,<sup>4</sup> we report now a method for the generation of nucleophilic reactivity, and hence for the construction of 3-dienoyltetramic acids and their vinylogues, directly from 3-acetyltetramic acids (4) carrying neither activation at C-7 nor protection at N-1.



(3)  $R^1 = H$ ,  $R^2 = 2.4$  - dimethoxybenzyl,  $R^3 = CH_2P(O)(OEt)_2$ 

(4)

The 3-acetyl compounds are amongst the most readily accessible 3-acyltetramic acids, being very efficiently prepared from an  $\alpha$ -amino-ester and diketene.<sup>5</sup> Thus, for example, <u>L</u>-valine ethyl ester was converted to <u>N</u>-(3-oxobutanoyl)-<u>L</u>-valine ethyl ester (diketene, EtOH, -20°C + 20°C; 94%) which was cyclised to 3-acetyl-5-isopropylpyrrolidine-2,4-dione (5a)<sup>6</sup> (NaOEt, EtOH, reflux; 93%), <u>i.e</u>. 86% overall from <u>L</u>-valine. Deuteriation studies with CD<sub>3</sub>ONa-CD<sub>3</sub>OD indicated (<sup>1</sup>H n.m.r. spectrum) rapid exchange of the OH and NH protons followed more slowly by deuteriation at C-7 (the acetyl group) and (slowest) at C-5. Kinetic deprotonation (n-butyl-lithium, 3.5 equiv., THF, -78°C), however, followed by quenching with D<sub>2</sub>O and work-up in H<sub>2</sub>O, afforded the desired 7-monodeuterio-derivative (5b) in quantitative yield.



For reaction with aldehyde electrophiles, the 3-acetyltetramic acid (5a) was lithiated (n-BuLi, 3.2 equiv., THF,  $-78^{\circ}$ C) and the orange suspension of the (presumed)trilithio-derivative, one representation of which is (6),<sup>7</sup> was quenched with an aldehyde (1.4 equiv.,  $-78^{\circ}$ C  $\rightarrow 20^{\circ}$ C) to afford quantitative yields of hydroxy-adducts (7a-e) from (<u>E</u>)-but-2-enal, (<u>E</u>)-2-methylbut-2-enal, (<u>E</u>)-3-phenylpropenal, (<u>E</u>,<u>E</u>)-hexa-2,4-dienal, and butanal, respectively, that were used directly without further purification. Dehydration of the adducts (7a-d), formed from unsaturated aldehydes, was best accomplished by saturation of a solution in chloroform (approx. 0.2 M) with HCl (g.) to yield, after 24 h at 20°C, the dienoyltetramic acids (8a) (54%), (8b) (49%), and (8c) (48%), and the trienoyltetramic acid  $(8d)^8$  (73%), after purification by crystallisation.<sup>6</sup>,<sup>9</sup> The elimination could be easily monitored by U.V. spectroscopy; for example, the hydroxy-adduct (7a) has  $\lambda_{max}$ .<sup>279</sup> nm, whereas the dienoyltetramic acid (8a) exhibits  $\lambda_{max}$ .<sup>355</sup> nm.

The elimination was also performed using phosphorus oxychloride in chloroform, or with boron trifluoride etherate in dichloromethane. In the latter case the acyltetramic acids were isolated as their boron difluoride complexes<sup>4b</sup> from which they were liberated by treatment with methanol. The hydroxy adduct (7e), from addition to butanal, underwent dehydration extremely slowly with the above reagents, even at elevated temperature, and with some consequent decomposition.

We are currently exploring the scope of the 'trianion' protocol, which constitutes a direct approach for the elaboration of an easily accessible acyltetramic acid to the important 3-dienoyl derivatives.<sup>10,11</sup> We thank S.E.R.C. for a studentship (A.D.B.).

## References and Notes

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- For four total syntheses of tirandamycin A, see : (a) R.H. Schlessinger,
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- 4. (a) R.C.F. Jones and A.D. Bates (<u>Tetrahedron Lett</u>., 1986, <u>27</u>, 5285;
  (b) R.C.F. Jones and G.E. Peterson, <u>ibid</u>., 1983, <u>24</u>, 4751, 4755, 4757;
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- 6. All new compounds gave spectra (i.r., u.v., n.m.r., m.s.) consistent with the assigned structure, and satisfactory accurate mass measurement or combustion analysis. Purity was also assessed by t.l.c. examination.
- 7. The trilithio-derivative is drawn as (6) for convenience; we have no further structural information. The sequence of metallation (0,N-1,C-7) is supported by the treatment of (5a) with BuLi (2 equiv., -80°C) and iodomethane to afford the N-methyl derivative.
- 8. Only one previous example of a 3-trienoyltetramic acid has been reported.<sup>3</sup>
- The recoveries of spectroscopically satisfactory material before crystallisation were very good.
- 10. Metallation-condensation studies on the boron difluoride complex (i)<sup>4D</sup> were hampered by partial loss of boron in the presence of organolithium or amide bases; attempted "trianion" formation from the hydrazone (ii)<sup>6</sup> was unsuccessful.



11. The base-catalysed reaction of benzaldehyde with 3-acetyltetramanilide has been reported to give a mixture of the products of condensation at C-5 and C-7; T. Yamaguchi, K. Saito, K. Kiso, M. Takeshita, T. Tsujimoto, and H. Yuki, <u>Yakugaku Zasshi</u>, 1976, <u>96</u>, 927.

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