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SYNTHESIS OF 4-ALKOXY-Δ^3-PYRROLIN-2-ONES AND TETRAMIC ACIDS[1]

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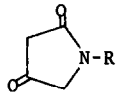
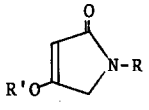
Abstract Acetoacetic ester is converted into 4-alkoxy-Δ^3-pyrrolin-2-ones which can be hydrolyzed to give tetramic acids.

The 2,4-pyrrolidinedione nucleus (1) is of great interest because of the



1

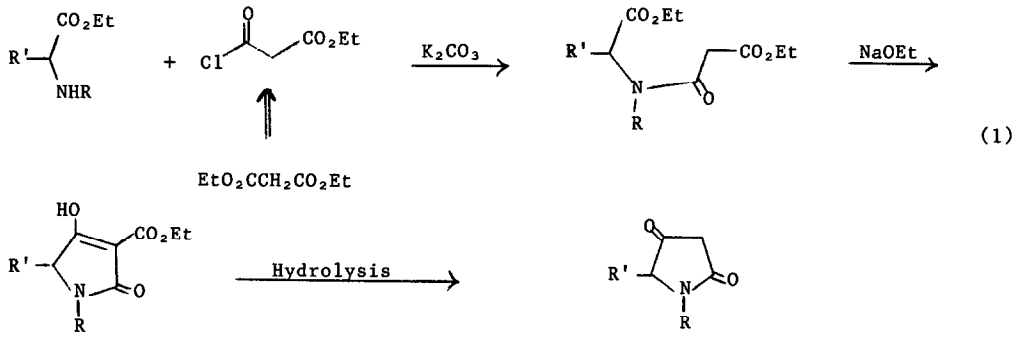
large number of physiologically active compounds containing this so-called tetramic acid unit. For example, streptolydigan and tirandamycin[2] are typical of the many 3-acyl tetramic acids which have antimicrobial activity as well as the ability to inhibit certain enzymes.[3] Other important compounds contain the corresponding enol ethers, 4-alkoxy-1-alkyl-Δ^3-pyrrolin-2-ones (2)[4] and recent work has resulted in



2

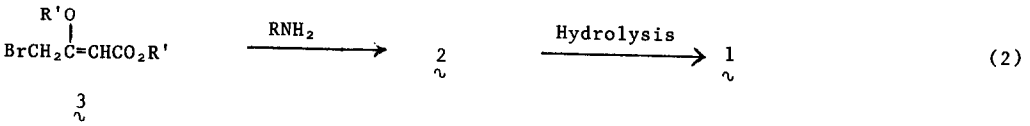
efficient methods for the acylation of these enol ethers.[5] In addition, a series of 5-oxotetramic acids are inhibitors of glycolic acid oxidase.[6] In short, the chemistry of tetramic acids is very "hot".

It is somewhat surprising that most of the synthetic efforts in this area have focused on tetramic acid derivatives rather than the parent molecules. In fact, there is essentially only one preparation of the tetramic acids themselves (eq 1).[7] This sequence involves several tedious steps which proceed in an overall yield for the three steps shown in eq 1 of 23% for R=CH_3 and R'=H.[8]



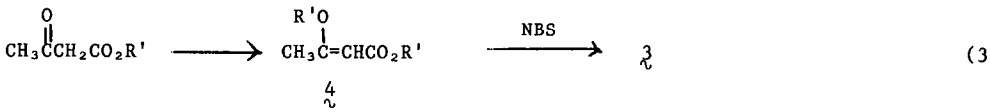
(1)

We wish to report a new synthesis of tetramic acids and the corresponding enol ethers which is simple and applicable to a wide range of compounds (eq 2). Thus, 4-bromo-3-alkoxy-2-butenoates (3) are allowed to react with primary amines and ammonia to give



3 → 2 → 1 (2)

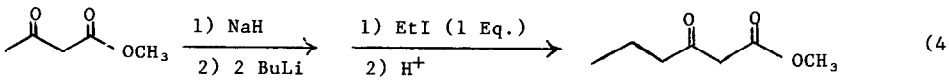
the alkoxypyrrolinones 2 which can be hydrolyzed to the tetramic acids 1. The bromo compounds 3 are prepared by the reaction of β-alkoxycrotonate esters 4, available from acetoacetic ester,[9] with N-bromosuccinimide (NBS) (eq 3).[10] Table I shows the alkoxy-



4 → 3 (3)

pyrrolinones which have been prepared. For example, when ethyl 4-bromo-3-ethoxy-2-butenoate was allowed to react with an excess of benzylamine, 1-benzyl-4-ethoxy-Δ^3-pyrrolin-2-one was obtained in 70% yield.

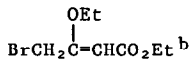
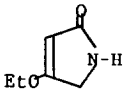
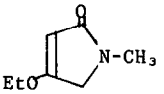
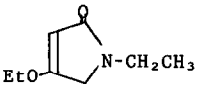
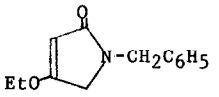
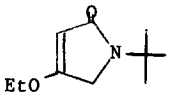
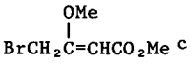
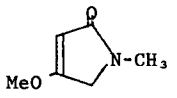
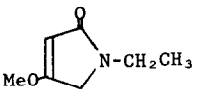
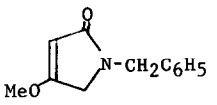
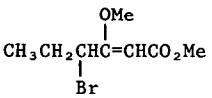
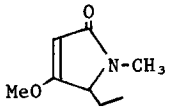
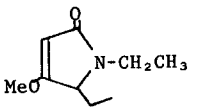
The versatility of this synthetic approach becomes apparent from simple modification of the starting acetoacetic ester. For example, the dianion of methyl acetoacetate[11] can be alkylated with one equivalent of ethyl iodide to give methyl 3-oxohexanoate (eq 4). This ketoester can be converted into the last two pyrrolinones of Table I.



(4)

Introduction of various functional groups at the 3 and 5 positions of the tetramic acid enol ethers is therefore readily accomplished.

TABLE I. Preparation of 4-Alkoxy-Δ^3-Pyrrolin-2-ones

Bromoester	Amine	Alkoxypyrrolinone	% Yield[a]
 [b]	NH_3		45-55
"	CH_3NH_2		55-70
"	$CH_3CH_2NH_2$		55
"	$C_6H_5CH_2NH_2$		70
"			45
 [c]	CH_3NH_2		49
"	$CH_3CH_2NH_2$		63
"	$C_6H_5CH_2NH_2$		42
	CH_3NH_2		63
"	$CH_3CH_2NH_2$		74

[a]All % yields are unoptimized and refer to pure, distilled products with satisfactory IR, ^1H NMR, ^{13}C NMR, mass spectra and/or elemental analysis.

[b]Available in 89% overall yield from ethyl acetoacetate.

[c]Prepared in 72% overall yield from methyl acetoacetate.

Hydrolysis of the alkoxypyrrolinones yields tetramic acids. For example, 1-benzyl-4-ethoxy-Δ^3-pyrrolin-2-one can be stirred with concentrated H_2SO_4 and CH_2Cl_2 for 20 min to give a 92% yield of 1-benzyl-2,4-pyrrolidinedione (1, R=$CH_2C_6H_5$).[12] Hydrolysis with 50% aqueous HBr gives similar results. Relatively unhindered tetramic acids are not easy to isolate.[7,13] For example, 4-ethoxy-1-methyl-Δ^3-pyrrolin-2-one upon treatment with aqueous HBr gives a high yield of a product with the correct mass spectral fragmentation but other analytical data indicates possible contamination with the corresponding "anhydro dimer."[13]

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References and Notes

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5. R. C. F. Jones and G. E. Peterson, Tetrahedron Lett., 4751, 4755, 4757 (1983). Unfortunately, these workers first prepared the tetramic acid and then converted it into the enol ether.
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7. T. P. C. Mulholland, R. Foster and D. B. Haydock, J. Chem. Soc., Perkin Trans. I, 2121 (1972). Many other workers have reported variations on this reliable although inefficient method.
8. This is the only case of three reported where the % yield is given for all three steps.
9. E. E. Smissman and A. N. Voldeng, J. Org. Chem., 29, 3161 (1964). The bromo compound apparently has the E geometry.
10. C. Piantadosi and V. G. Skulason, J. Pharm. Sci., 53, 902 (1964).
11. F. W. Sum and L. Weiler, J. Chem. Soc., Chem. Commun., 985 (1978).
12. Spectra data of this compound were identical with that reported by Rinehart.[2] The overall yield from ethyl acetoacetate is 80%.
13. Mulholland[7] indicates that the hydrolysis of eq 1 is very touchy in that a reaction time of 20 min as compared with 6 min leads to the formation of an "anhydro dimer" of N-methyltetramic acid. This matter is currently under investigation in our group.

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