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A SYNTHESIS OF 3-ACYL-5-ALKYL TETRAMIC ACIDS

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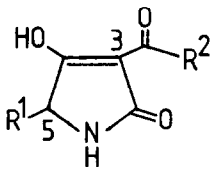
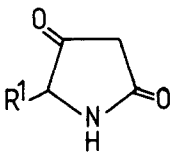
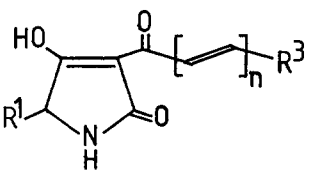
Pyrrolidine-2,4-diones (tetramic acids) acylated at the 3-position (1) constitute a growing class of antibiotics and pigments isolated from microorganisms.[1] Prior to the commencement of our work synthetic studies in this area were largely limited to construction of 3-acetyl derivatives by base-catalysed cyclisation of N-acetoacetyl α-aminoesters.[2]



(1)



(2)



(3)

Recent renewed activity in this field[1] prompts us to report our approach to compounds of type (1), namely the Lewis-acid catalysed acylation of appropriate pyrrolidine-2,4-diones (2),[3] which allows for the insertion of various acyl residues at the 3-position. Many of the naturally occurring tetramic acids have a polyunsaturated grouping conjugated to the C-3 carbonyl substituent (3), and we wish to report the first synthesis of tetramic acids containing such unsaturation.

The 5-benzyl dione (2a) was chosen for our studies (as we required it for another programme in our laboratories) and was prepared as follows.[4] The methyl ester of L-phenylalanine was acylated with ethoxycarbonylacetyl chloride to the ester-amide (4),[5] 65%, m.p. 54-58°, which was not purified

further but cyclised directly with sodium ethoxide in benzene-ethanol to the 3-ethoxycarbonyl tetramic acid (5),[5] 40%, m.p. 120-121°, $[\alpha]_D$-125°. Hydrolysis-decarboxylation could be achieved either by short-period treatment of (5) in boiling water, or, better, by reaction with a glacial acetic-trifluoroacetic acid mixture at reflux[6], to provide (2a),[5] 61 and 95% respectively, m.p. 136-140°.

Dione (2a) was acetylated using acetyl chloride in the presence of BF_3-etherate at 70°C to give 3-acetyl-5-benzyl tetramic acid (1a),[5] 55%, m.p. 148-153°, identical with a sample independently prepared from base-mediated cyclisation of N-acetoacetyl-L-phenylalanine ethyl ester.[7] Acylation with heptanoyl chloride-BF_3 similarly yielded 3-heptanoyl compound (1b),[5] 63%, m.p. 114-115°.

The corresponding reaction between (2a) and trans-but-2-enoyl chloride was unsatisfactory using BF_3 as the Lewis acid. Use of $SnCl_4$ gave no improvement, but (1c),[5] 52%, m.p. 220-224°, could be smoothly prepared by employing $TiCl_4$ in nitrobenzene at 50-55°. Two double bonds conjugated to the C-3 carbonyl substituent were introduced by use of trans,trans-hexa-2,4-dienoyl chloride and either the BF_3 or the $TiCl_4$ reagent system to produce (1d),[5] 20 and 33% respectively, m.p. 190-197°.

This work represents the first synthesis of the chromophores of some naturally occurring tetramic acids, and the Table shows a comparison of our U.V. data for (1c) with that published for ikarugamycin (6),[8] and for (1d) with that reported for streptolydigin (7)[9] and tirandamycin (8).[10]

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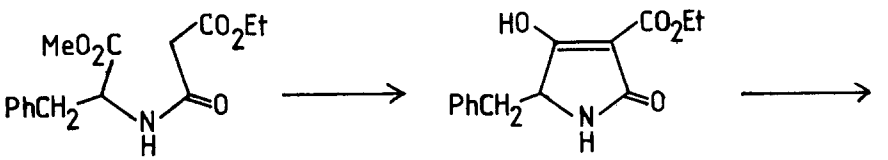
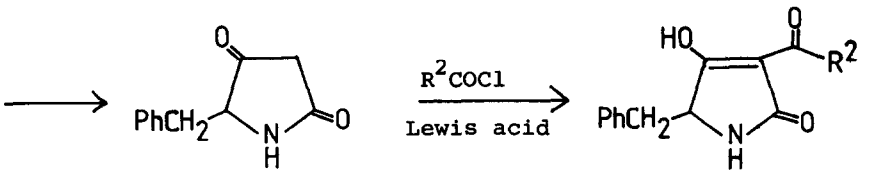
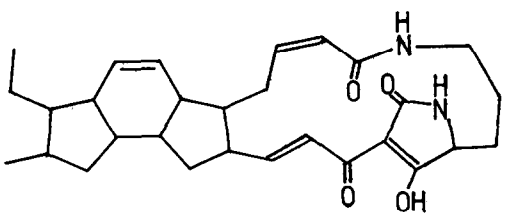


(4) (5)

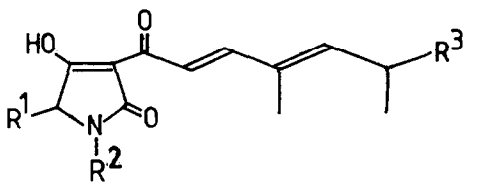


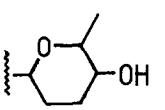
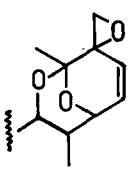
(2a)

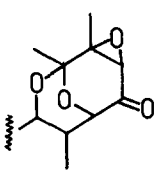
(1) a; R^2=CH_3
b; R^2=C_6H_{13}
c; R^2=CH=CH.CH_3
d; R^2=CH=CH.CH=CH.CH_3



(6)



(7) R^1=CH(CH_3)CONHCH_3; R^2=  ; R^3= 

(8) R^1=R^2=H; R^3= 

TABLE

	λ_{max} nm. (ε_{max} x 10^{-3})	
1c	241 (16.7),313 (14.75)	0.01M ethanolic KOH
	226 (10.7),318 (18.65)	" " H_2SO_4
6	243 (21.4),321 (13.3)	0.1M methanolic NaOH
	227 (20.7),327 (17.3)	methanol
1d	258 (17.2),283 (18.55),333 (20.3)	0.01M ethanolic KOH
	354 (30.5),368 shoulder (26.5)	" " H_2SO_4
7	262, 291, 335	" " KOH
	357, 370	" " H_2SO_4
8	287, (16.2),331 (16.7)	" " KOH
	353, (32.7),366 shoulder (30.0)	" " H_2SO_4

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3. S.V. Bhat, H. Kohl, B.N. Ganguli and N.J. De Souza, Eur. J. Med. Chem.-Chim. Ther., 1977, 12, 53, have prepared some 5-ethylidene-3-acyl tetramic acids (as analogues of the antibiotic magnesidin) in this way, and an example of base-catalysed acylation has been recently disclosed (ref. 1). J.L. Bloomer and F.E. Kappler, J.C.S. Perkin I, 1976, 1845, have used this methodology to prepare 3-acyl tetronic acids, the O-heterocyclic analogues of (1).
4. cf. T.P.C. Mulholland, R. Foster and D.B. Haycock, J.C.S. Perkin I, 1972, 2121.
5. All new compounds gave spectra (IR, UV, NMR, MS) consistent with the assigned structures. Satisfactory combustion analyses were also obtained on these materials (with the exception of (4), which was not fully purified).
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7. We thank Dr. M. Ahmed for this preparation.
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