SYNTHESIS OF 6-UNSUBSTITUTED OLIVANIC ACID ANALOGUES AND THEIR ANTIBACTERIAL ACTIVITIES

Sir:

Since the discovery of the olivanic acids and thienamycins several methods have been developed by us[1~5] and others[6~11] for the synthesis of these compounds and related analogues. As part of a program directed towards the investigation of the structural features necessary for antibacterial activity we have synthesized a range of 6-unsubstituted analogues of the olivanic acids. We now wish to report the results of these studies.

The synthesis of simple analogues* possessing no substituent at position 3 (*e.g.* **2a**) was found to be possible[1,7] using **1a** and an intramolecular WITTIG reaction to form the [2, 3] double bond. Extension of this basic method led to the preparation of aryl thioethers[2] of type **2b** and those containing a 3-(2-acetamidoethenylthio)ether substituent (**2d**) from the corresponding thioethers (**1b**) and (**1c**)[4]. Compounds having a saturated

Scheme 1.

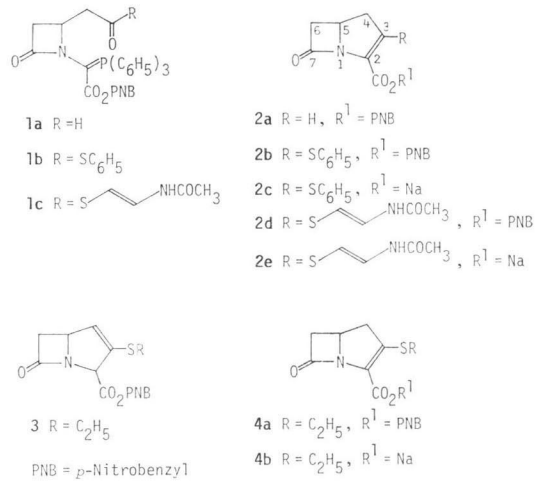
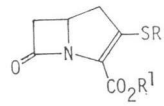


Table 1. Minimum inhibitory concentrations



No.	1	2	3	4	5	6	7
R	$-CH_3$	$-C_2H_5$	$-(CH_2)_2OCH_3$	$-(CH_2)_2CO_2CH_3$	$-(CH_2)_2OCOCH_3$	$-(CH_2)_2$-OCONHCH$_3$	$-(CH_2)_2$-NHCOCH$_3$
R^1	Na	Na	Na	Na	Na	Na	Na
C. f[a]	1.6	2.5	3.1	1.6	2.5	1.6	5.0
E. c[b]	3.1	2.5	3.1	1.6	1.2	0.8	5.0
E. c[c]	6.2	—	6.2	6.2	5.0	6.2	25
K. p[d]	3.1	1.0	1.6	1.6	0.5	0.4	5.0
P. m[e]	25	10	6.2	12.5	5.0	1.6	50
P. m[f]	25	10	50	25	>50	12.5	50
Ps. a[g]	>50	>100	>100	>50	>50	>50	>50
S. t[h]	3.1	2.5	3.1	3.1	1.2	0.8	12.5
S. m[i]	3.1	10	12.5	25	12.5	6.2	12.5
S. a[j]	6.2	5.0	6.2	12.5	1.2	1.6	12.5
S. a[k]	12.5	10.0	25	50	12.5	12.5	50
S. f[l]	>50	100	50	>50	50	25	>50
S. p[m]	<0.2	1.0	<0.2	<0.2	≤0.1	<0.2	—

M.I.C. values are in mcg/ml and were determined in D.S.T. agar (Oxoid). Inoculum 10^8 c.f.u.

a) *Citrobacter freundii* E8 b) *Escherichia coli* 0111 c) *Escherichia coli* R_{TEM} d) *Klebsiella* h) *Salmonella typhimurium* CT10 i) *Serratia marcescens* US20 j) *Staphylococcus aureus* Oxford

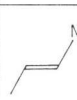
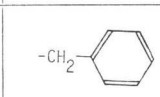
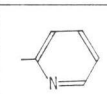
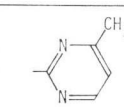
* All compounds are racemic mixtures.

alkylthio substituent at the 3-position were unobtainable using the intramolecular WITTIG reaction and an alternative sequence was developed[3,5]. This involved base-catalysed addition of a thiol to the azabicycloheptene (**2a**) followed by oxidation to the Δ-3 compounds (*e.g.* **3**). These were then isomerised using 1,5-diazabicyclo [5.4.0]undec-5-ene (DBU) to provide an equilibrium mixture of Δ-2 (**4a**) and Δ-3 isomers (**3**) which were separable by chromatography. Removal of the protecting group (*e.g.* in **2b**, **2d** or **4a**) was carried out by catalytic hydrogenolysis using 10% palladium on charcoal in aqueous dioxan and addition of one equivalent of sodium bicarbonate to provide the sodium salts of the acids (*e.g.* **2c**, **2e** or **4b**).

Table 1 shows a range of analogues prepared using the methods described above. Compounds (**9**, **10**, **11**, **13** and **14**) were synthesised *via* the thioester cyclisation and compounds (**1**~**8** and **12**) using the thiol addition method. For examples (**1**~**7** and **9**~**12**; Table 1) addition of one equivalent of sodium bicarbonate provided the sodium salts of the acids. The zwitterions (**8**, **13** and **14**) were obtained by hydrogenolysis of the appropriate *p*-nitrobenzyl ester in the presence of 0.05 M phosphate buffer. All compounds were tested as aqueous solutions and the concentrations assayed by ultraviolet absorption of the characteristic olivanic acid chromophore at λ_{max} 297 to 305 nm.

All of the analogues showed a moderate level of antibacterial activity and the indications were that the nature of the 3-substituent did not dramatically effect the breadth of spectrum. Most of the compounds containing an alkyl or alkenyl thioether 3-substituent were similar in activity. The introduction of an aromatic nucleus (*e.g.* **11** or **12**) led to a slight diminution of activity, but this activity was regained in the pyridine or pyrimidine examples (**13**) and (**14**). In common with other analogues of this type[12], the amino-

of 6-unsubstituted olivanic acid analogues.

8	**9**	**10**	**11**	**12**	**13**	**14**
$-(CH_2)_2NH_2$						
H	Na	Na	Na	Na	H	H
3.1	3.1	12.5	>50	25	25	25
3.1	1.6	3.1	5.0	6.2	3.1	1.6
1.6	3.1	12.5	—	50	25	25
1.6	0.8	3.1	5.0	6.2	3.1	1.6
25	12.5	6.2	16.0	50	12.5	3.1
25	12.5	>25	>50	50	50	25
6.2	12.5	>25	>50	>50	>50	>25
3.1	3.1	3.1	16.0	6.2	3.1	1.6
6.2	6.2	25	>50	50	12.5	6.2
0.8	3.1	1.6	5.0	6.2	3.1	3.1
3.1	12.5	12.5	5.0	6.2	12.5	6.2
25	25	25	>50	>50	>50	>25
0.2	0.4	0.2	—	<0.2	<0.1	0.1

pneumoniae e) *Proteus mirabilis* C977 f) Indole positive *Proteus* g) *Pseudomonas aeruginosa* A k) *Staphylococcus aureus* Russell l) *Streptococcus faecalis* I m) *Streptococcus pneumoniae* CN33

ethyl compound (**8**) possessed significant anti-*Pseudomonas* activity and together with the acetamidoethenyl compound (**9**) were the only compounds to show this property. Many of the compounds were less active against β-lactamase producing organisms indicating some instability to β-lactamases although the degree of this instability was variable.

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