2-METHOXYCARBONYLPHENOXY-(α,α-DIALKYL)METHYLPENICILLINS AND -CEPHALOSPORINS, NOVEL ANALOGS OF PHENOXYMETHYLPENICILLIN

Sh. L. Mndzhoyan, M. S. Kramer,
M. M. Grigoryan, Yu. Z. Ter-Zakharyan,
and R. V. Agababyan

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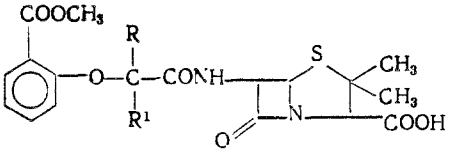
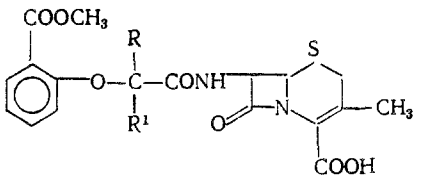
Continuing earlier on semisynthetic phenoxymethylpenicillins [2, 3], some novel penicillins (I-VII) containing the biologically active methyl salicylate moiety in the acyl fragment have been synthesized and examined.



I—VIII R = H (I), Et (II, III), Pr (IV, V), Bu (VI, VII), iso-Bu (VIII); R^1 = H (I), Et (II), iso-Pr (III), Pr (IV), Bu (V, VI), iso-Bu (VII, VIII)

Compounds (I-VIII) were synthesized by the mixed anhydride method, by acylating 6-aminopenicillinic acid (6-APA) with 2-methyoxycarbonylphenoxy-(α,α-dialkyl)acetic acids [5], obtained by condensing methyl salicylate [6] with α,α-dialkylbromoacetic acids [1].

In order to study the relationship between structure and antibacterial activity, the cephalosporin derivatives (IX-XVI) containing similar acyl substituents in the 7-position of the cephem ring, were also synthesized, by acylating 7-aminodesoxycephalosporanic acid 7-ADCA) by the mixed anhydride method:



IX—XVI

R = H (IX), Et (X, XI), Pr (XII, XIII), Bu (XIV, XV), iso-Bu (XVI); R^1 = H (IX), Et (X), iso-Pr (XI), Pr (XII), Bu (XIII, XIV), iso-Bu (XV, XVI)

The desired products (I-XVI) were isolated as their sodium salts, the purity and homogeneity which was checked by TLC. The structures of the products, as the free acids, were confirmed by elemental analysis, the results of which were in agreement with the calculated values, and the IR spectra, in which absorption was present at 1750-1780 cm^{-1} (β-lactam CO), 1710-1725 cm^{-1} (carboxyl CO), 1640-1660 cm^{-1} (amide CO), and 3300-3400 cm^{-1} (NH).

EXPERIMENTAL (CHEMISTRY)

IR spectra were obtained on a UR-20 spectrometer (East Germany) as a paste in Vaseline grease, or in KBr disks. TLC was carried out on Silufol UV-254 plates (Czech SSR), in the system propanol—water, 3:1, visualized with iodine vapor.

2-Methoxycarboxylphenoxy-(α,α-dialkyl)methylpenicillins (I-VIII). To a solution of 0.01 mole of the appropriate 2-methoxycarbonyl-(α,α-dialkyl)acetic acid in 25 ml of dry acetone was added with stirring at 0°C a solution of 2.4 g (0.024 mole) of triethylamine and 3 g (0.028 mole) of ethyl chloroformate in 20 ml dry acetone. The mixture was stirred at this temperature for 30 min, and for 2 h at room temperature. The solid was filtered off, and the

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TABLE 1. Properties of Penicillins (I-VIII) and Cephalosporins (IX-XVI)

Compound	Yield, %	mp, °C (decomp.)	R_f	Empirical formula
I	51,0	104—105	0,60	$C_{18}H_{20}N_2O_7S$
II	65,4	99—100	0,67	$C_{22}H_{28}N_2O_7S$
III	45,0	95—96	0,58	$C_{23}H_{30}N_2O_7S$
IV	53,2	92—93	0,78	$C_{24}H_{32}N_2O_7S$
V	56,0	102—103	0,74	$C_{25}H_{34}N_2O_7S$
VI	40,5	111—112	0,65	$C_{26}H_{36}N_2O_7S$
VII	58,8	132—133	0,60	$C_{26}H_{36}N_2O_7S$
VIII	62,0	101—102	0,68	$C_{26}H_{36}N_2O_7S$
IX	68,4	150—151	0,65	$C_{18}H_{19}N_2O_7S$
X	55,0	113—114	0,70	$C_{22}H_{26}N_2O_7S$
XI	60,4	129—130	0,68	$C_{23}H_{28}N_2O_7S$
XII	45,5	118—119	0,64	$C_{24}H_{30}N_2O_7S$
XIII	48,0	94—95	0,75	$C_{25}H_{32}N_2O_7S$
XIV	56,5	145—146	0,72	$C_{26}H_{34}N_2O_7S$
XV	50,2	159—160	0,67	$C_{26}H_{34}N_2O_7S$
XVI	53,5	160—161	0,60	$C_{26}H_{31}N_2O_7S$

TABLE 2. Antibacterial Activity of Penicillins (I-VIII)

Compound	MIC, μg/ml					
	Staphylococci			Flexner dysentery bacillus	Typhoid bacillus	Proteus vulgaris
	sensitive strains		resistant strains			
	209/P	Smith				
I	0,9	0,9	15,6	31,2	15,6	31,2
II	0,48	0,24	15,6	15,6	31,2	31,2
III	0,9	0,48	15,6	15,6	31,2	62,5
IV	0,9	0,9	15,6	15,6	31,2	31,2
V	0,9	0,48	15,6	31,2	31,2	31,2
VI	1,9	1,9	15,6	62,5	62,5	125
VII	0,9	1,9	15,6	31,2	62,5	62,5
VIII	0,9	1,9	15,6	31,2	31,2	62,5
PMP	0,024	0,048	62,5	15,6	7,8	62,5

filtrate added to a mixture of a solution of 5.6 g (0.062 mole) of 6-APA in 100 ml of acetone and 200 ml of 3% sodium bicarbonate solution. The mixture was stirred for 4 h, and extracted with ether. The aqueous layer was separated, acidified with 1 N HCl at 6-7°C to pH 2.0, and the acid which separated was extracted with ether. The extract was with ice water, shaken with calcined sodium sulfate and charcoal, and filtered. To the filtrate was added 8% sodium bicarbonate solution to pH 7.0-7.5. The aqueous layer was separated, washed with ether, and lyophilized. To determine the physical properties, a small portion of the sodium salt was converted into the acid (Table 1).

2-Methoxycarbonylphenoxy-(α,α-dialkyl)methylcephalosporins (IX-XVI) were obtained similarly, from 5.56 g (0.026 mole) of 7-ACDA, except that the solvent used in working up was ethyl acetate rather than ether (Table 1).

EXPERIMENTAL (BIOLOGY)

The antibacterial activity of the penicillins and cephalosporins (I-XVI) (as the sodium salts) was examined by twofold dilution on meat peptone broth (pH 7.2-7.4) with a microbial of $2 \cdot 10^6$ microbial bodies per ml of medium. The tests were carried out with Gram-positive (sensitive international strains of Staphylococcus 209p and Smith and the penicillinase producing strain 5) and Gram-negative (Flexner dysentery 6858, typhoid bacllus, and Proteus vulgaris) bacilli. For comparison, and as controls, each test included, in addition to the test compound, the minimum inhibitory concentration (MIC) of phenoxymethylpenicillin (PMP) and cephalexin.

The maximum tolerated dose (MID) was found in acute tests with mongrel white mice of both sexes weighing 19-20 g by the intravenous route, observation of the animals being continued for five days. A total of 85 animals was employed in the tests.

Penicillins (I-VIII) showed antibacterial activity against sensitive staphylococci (Table 2) inferior to that of PMP. The MIC values of these compounds were in the range 0.24-1.9 μg/ml. Like PMP, they were inactive against penicillinase-forming staphylococci. Gram-negative organisms showed low sensitivity to these penicillins. Against the dysentry bacillus and Proteus vulgaris, the MIC values were similar to those of PMP, but with the typhoid bacillus the MIC value was greater.

These novel semisynthetic penicillins are nontoxic. Intravenous administration of doses of 2000 mg/kg did not result in any visible changes in the behavior or condition of the animals. No deaths occurred during the whole period of observation. Higher doses of the compounds were not tested. The MIC of PMP is 250 mg/kg, so that these penicillins (I-VIII) are some eight times less toxic than PMP.

The stability to acid of the penicillins most active against staphylococci (II-V) was assessed. Acid deactivation was carried out in aqueous alcohol at pH 1.3 and a temperature of 37°C. Their stability was assessed by their half-breakdown times ($\tau/2$) in minutes [4]. All the penicillins tested showed high stability to acid. The half-breakdown period of the most acid-resistant penicillin (IV) was 163 min, this compound being more stable than PMP, the value for which under these conditions was 132 min. The stability of the penicillin (II) (half-breakdown period 118 min) was the same as for PMP. Penicillins (III) and (V), although less acid-resistant than (II) and (IV), also showed definite stability to acid, the half-breakdown times being 68 and 43 min respectively.

Examination of the cephalosporins (IX-XVI) showed them to possess antibacterial activity against the test organisms. Their MIC values were greater than those of the corresponding penicillins (I-VIII). The MIC values for (IX-XVI) against sensitive staphylococci ranged from 1.9 to 62.5 μg/ml, while against the penicillinase-forming strain and the Gram-negative bacilli they were greater than 125 μg/ml. Like their penicillin analogs, compounds (IX-XVI) were nontoxic.

These novel analogs of PMP have thus been found to include nontoxic semisynthetic penicillins with high resistance to acids and activity against sensitive staphylococci.

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