SEMISYNTHETIC PENICILLINS.

XVIII. NEW PHENOXYMETHYLPENICILLIN ANALOGS

Sh. L. Mndzhoyan, N. D. Marukhyan, Yu. Z. Ter-Zakharyan, É. V. Kazaryan, and V. S. Sakanyan

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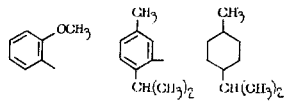
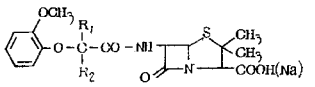
Phenoxymethylpenicillin is widely used in medicine. It is the only preparation of this type which is stable to acid and therefore can be given orally. However, it is somewhat toxic, insoluble in water, and unstable to penicillinase-forming organisms.

With the aim of obtaining new phenoxymethylpenicillin analogs that are soluble in water, nontoxic, and active against benzylpenicillin-resistant organisms, penicillin derivatives of trisubstituted acetic acids with the general formula (RO)R'R"CCOOH were prepared,

where R =  R', R" = CH_3–C_4H_9

with different combinations of iso-structural groups.

In this paper we report the synthesis and study of compounds with R' and R" as given above



The trisubstituted acetic acids used as starting materials were prepared by condensing guaiacol with the appropriate α,α-dialkylbromoacetic acid [1]. The structures of the products were confirmed by elemental analysis and physical data; IR and NMR spectra confirmed the presence of a carboxyl carbonyl group and an ether linkage (Table 1).

TABLE 1. Properties of the 2-Methoxyphenoxy-α,α-dialkylacetic Acids

Compound	R'	R''	Yield, %	bp, °C (mm)	Found, %		Empirical formula	Calculated, %	
					C	H		C	H
Ia*	H	H	—	—	—	—	—	—	—
IIa	CH_3	CH_3	59,0	87—8 (3)	62,99	6,94	$C_{11}H_{14}O_4$	62,85	6,67
IIIa	CH_3	C_2H_5	62,9	85—9 (2)	63,86	7,46	$C_{12}H_{16}O_4$	64,28	7,43
IVa	CH_3	C_3H_7	51,0	95—100 (1)	65,26	7,43	$C_{13}H_{18}O_4$	65,54	7,56
Va	CH_3	iso-C_3H_7	57,9	75—8 (2)	65,66	7,78	$C_{13}H_{18}O_4$	65,54	7,56
VIa	CH_3	C_4H_9	65,0	85—8 (2)	66,20	7,83	$C_{14}H_{20}O_4$	66,67	7,93
VIIa	CH_3	iso-C_4H_9	65,7	78—82 (2)	67,04	7,50	$C_{14}H_{20}O_4$	66,67	7,93
VIIIa	C_2H_5	C_2H_5	56,5	75—8 (2)	65,65	8,01	$C_{13}H_{18}O_4$	65,54	7,56
IXa	C_2H_5	C_3H_7	58,5	72—4 (1)	67,11	7,92	$C_{14}H_{20}O_4$	66,67	7,93
Xa	C_2H_5	iso-C_3H_7	57,2	85—90 (2)	66,66	8,34	$C_{14}H_{20}O_4$	66,67	7,93
XIa	C_2H_5	C_4H_9	55,0	125—7 (1)	68,00	8,80	$C_{15}H_{22}O_4$	67,66	8,27
XIIa	C_2H_5	iso-C_4H_9	61,2	88—90 (2)	67,79	8,61	$C_{15}H_{22}O_4$	67,66	8,27
XIIIa	C_3H_7	C_3H_7	57,2	84—8 (2)	68,12	7,45	$C_{15}H_{22}O_4$	67,66	8,27
XIVa	C_3H_7	iso-C_3H_7	58,1	95—7 (2)	67,71	8,03	$C_{15}H_{22}O_4$	67,66	8,27
XVa	C_3H_7	iso-C_4H_9	60,0	71—5 (2)	68,61	9,02	$C_{16}H_{24}O_4$	68,57	8,57
XVIa	iso-C_3H_7	iso-C_3H_7	59,5	69—73 (2)	66,13	7,72	$C_{15}H_{22}O_4$	67,66	8,27
XVIIa	iso-C_3H_7	C_4H_9	60,0	110—5 (1)	69,08	8,24	$C_{16}H_{24}O_4$	68,57	8,57
XVIIIa	iso-C_3H_7	iso-C_4H_9	55,8	75—80 (1)	68,11	8,03	$C_{16}H_{24}O_4$	68,57	8,57
XIXa	C_4H_9	C_4H_9	61,6	72—6 (2)	69,88	8,11	$C_{17}H_{26}O_4$	69,38	8,85
XXa	C_4H_9	iso-C_4H_9	64,5	88—90 (2)	69,43	8,67	$C_{17}H_{26}O_4$	69,38	8,85
XXIa	iso-C_4H_9	iso-C_4H_9	59,0	76—8 (2)	70,00	8,35	$C_{17}H_{26}O_4$	69,38	8,85

*Reported in [3].

Note. Subsequently, R' and R" will correspond to the number of the compound.

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan.
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TABLE 2. Properties of 2-Methoxyphenoxy-α,α-dialkylmethylpenicillins

Compound	Yield, %	mp. °C *	R_f	† τ1/2, min	Minimum concentration suppressing microorganism growth μg/ml							Maximum tolerable dose, mg/kg
					Strept. hemolyticus	Staph. aureus 209P	Staph. Smith	Staph. 4–0	Staph. albus	benzylpenicillin-resistant staphylococcus 18b	benzylpenicillin-resistant staphylococcus 39	
I	68,0	85–6	0,88	128,6 (98,6–158,6)	0,12	0,09	0,09	0,09	0,024	1000	500	2000
II	53,5	86–7	0,78	115,0 (115,0–115,0)	0,09	0,09	0,39	0,19	0,19	500	125	2000
III	59,5	58–60	0,89	109,2 (94,6–106,0)	0,024	1,56	0,78	0,39	0,39	1000	1000	2000
IV	67,5	96–7	0,81	165,1 (147,5–182,7)	0,024	0,39	0,39	0,19	0,78	500	500	3000
V	58,0	82–3	0,80	231,0 (231,0–231,0)	0,012	0,39	0,39	0,39	0,39	1000	1000	3000
VI	58,2	79–82	0,89	166,9 (139,1–194,7)	0,012	0,19	0,19	0,048	0,09	125	125	2000
VII	55,0	78–80	0,87	96,4 (85,2–107,6)	0,09	0,19	0,19	0,19	0,09	125	250	2500
VIII	59,0	74–5	0,79	173,1 (172,6–173,5)	0,09	1,56	0,39	0,39	1,56	500	250	2500
IX	51,0	70–2	0,87	104,5 (80,9–128,5)	0,012	3,12	3,12	0,39	0,09	250	500	2500
X	55,2	88–9	0,80	165,2 (147,9–182,2)	0,012	0,78	0,39	0,39	0,78	250	250	2500
XI	53,0	69–71	0,83	138,2 (137,2–139,1)	0,048	0,19	0,19	0,09	0,19	500	500	2500
XII	62,1	72–5	0,80	124,0 (111,1–136,9)	0,024	3,12	1,56	1,56	0,39	500	500	3000
XIII	53,0	75–7	0,85	70,7 (66,3–75,0)	0,09	0,78	3,12	3,12	0,19	500	500	2500
XIV	52,0	80–2	0,81	142,2 (124,2–160,2)	0,09	0,09	0,19	0,09	0,19	250	250	2500
XV	60,7	70–1	0,87	173,9 (173,2–174,6)	0,048	1,56	1,56	0,78	0,78	500	125	1500
XVI	58,8	72–4	0,80	198,0	0,048	1,56	0,78	0,19	0,39	62,5	125	2500
XVII	57,0	81–3	0,79	173,3 (173,3–173,3)	0,09	0,39	0,19	0,09	0,09	125	500	3000
XVIII	60,0	94–6	0,81	71,0 (63,6–78,4)	0,048	0,39	0,39	0,39	0,78	250	500	2500
XIX	56,0	95–6	0,83	138,0 (138,0–138,0)	0,024	1,56	1,56	0,09	0,78	500	500	3000
XX	56,0	80–1	0,80	210,0 (210,0–210,0)	0,012	0,39	0,19	0,39	0,39	500	500	3000
XXI	56,5	85–7	0,86	174,5 (173,7–175,3)	0,024	1,56	1,56	1,56	0,39	125	500	1000
phenoxymethylpenicillin		—	—	123,0 (109,0–137,0)	0,006	0,024	0,048	0,012	0,024	2000	2000	250

*Melts with decomposition.

†n-Butanol–ether–acetone–water (14 : 4.5 : 4.5 : 5).

Note. Limits of experimental error are given in parentheses; conditions: pH 1.3, 37°C.

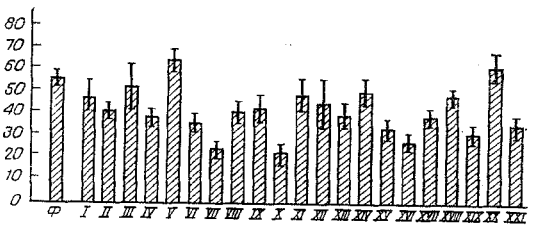

Fig. 1. Inactivation of penicillins after 1 h under the action of one unit of β-lactamase from Bac. licheniformis. Compounds are plotted along the abscissa: φ) phenoxymethylpenicillin; I-XXI) 2-methoxyphenoxy (α,α-dialkyl) methylpenicillins; amount of inactivated penicillin (ED) is plotted along the ordinate. Vertical lines give the confidence intervals.

The dialkylacetic acids were obtained from disubstituted malonic esters, and the dialkylbromoacetic acids by bromination of the dialkylacetic acids by the Volhard–Zelinsky method [2].

The penicillins were obtained by acylation of 6-aminopenicillinic acid (6-APA) with mixed anhydrides of the corresponding acids [3].

The structures of the compounds were confirmed by elemental analysis and by IR spectra, which indicated the presence of β-lactam and thiazolidine rings, amide, carboxyl groups, and other substituents. The purity of the preparations was checked by TLC [4]. The penicillins were characterized as the acids.

The properties of the sodium salts of the penicillins were compared with those of phenoxymethylpenicillin in tests performed under the same experimental conditions.

The acute toxicity of the compounds was determined by means of single intravenous injection into white mice (178 animals). With the exception of XV and XXI, the maximum tolerable dose of the penicillins was about

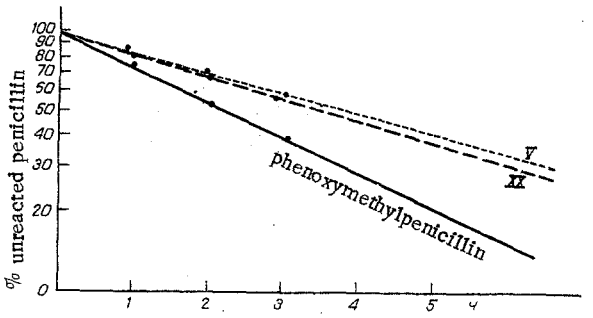

Fig. 2. Acid inactivation of penicillins V, XX, and phenoxymethylpenicillin. Inactivation time (in h) is plotted along the abscissa; amount of residual penicillin (in %) is plotted along the ordinate.

2000-3000 mg/kg, i.e., on the average, they were less toxic than phenoxymethylpenicillin by a factor of 10 (Table 2).

The antimicrobial activity of the penicillins was determined by the standard method of double serial dilution using meat-peptone broth. They were found to be active against gram-positive microorganisms; the minimum concentrations which suppressed the growth of Streptococcus hemolyticus and Staphylococcus are given in Table 2. For Streptococcus faecalis and hay bacillus, the minimum concentrations are in the range 1.56-12.5 μg/ml; for phenoxylmethylpenicillin, the corresponding figure is 1.56 μg/ml. Against gram-negative organisms (E. coli, dysenteric bacillus, Salmonella typhosa), they like phenoxymethylpenicillin, showed weak activity. Against benzylpenicillin-resistant staphylococci (strains 18b and 39, isolated at the clinic) these penicillins were 4-8 times as active as phenoxymethylpenicillin.

The rate at which the penicillins were split by β-lactamase from Bac. licheniformis was determined iodometrically [5-7]. Under our experimental conditions, phenoxymethylpenicillin was hydrolyzed at a rate of 56.2 (53.3-59.1) units/h (Fig. 1). Penicillins VII and X were hydrolyzed at 25.4 (22.4-28.4) and 25.5 (17-4-27.6) units/h respectively, i.e., they were twice as stable ($\alpha > 0.999$) to the action of the enzyme as phenoxymethylpenicillin. Penicillins II, IV, VI, VIII, IX, XIII, XV-XVIII, and XIX-XXI were also more stable than phenoxymethylpenicillin. The difference between the arithmetic means for all the penicillins and phenoxymethylpenicillin is statistically reliable and lies within the limits $\alpha > 0.99$ to $\alpha > 0.999$. Thus, the majority of the penicillins studied are somewhat more stable to the action of β-lactamase than is phenoxymethylpenicillin, and this is consistent with their antibacterial activity toward penicillinase-producing strains of staphlococci (18b and 39).

Acid inactivation of the penicillins was carried out in aqueous-alcoholic solution at pH 1.3 and 37°C. Their stability was expressed as the half decay period (τ/2) in minutes [7].

All the penicillins were reasonably stable to acid; IV-VI, VIII, X, XI, IV-XVIII, and XIX-XXI were more stable than phenoxymethylpenicillin. The difference between the arithmetic means for the penicillins and for phenoxymethylpenicillin is statistically reliable and lies in the range $\alpha > 0.98$ to $\alpha > 0.999$. Compounds V and XX are the most stable to acid. Figure 2 shows the inactivation of these two penicillins. In the time taken to hydrolyze 50% of the phenoxymethylpenicillin (130 min), V and XX were hydrolyzed by 34% and 36% respectively.

Thus, we have synthesized some new active semisynthetic penicillins which are less toxic and more stable to acid than phenoxymethylpenicillin, but unlike the latter are readily soluble in water and fairly stable to lactamase.

EXPERIMENTAL (CHEMICAL)

The physical constants of the α,α-dialkylbromoacetic acids prepared agree with those given in the literature [8].

o-Methoxyphenoxy-α,α-dialkylacetic Acids (Ia-XXIa). A solution of 9.67 g (0.078 mole) of guaiacol in 22.5 ml of 20% aqueous sodium hydroxide was added to a solution of 0.06 mole of α,α-dialkylbromoacetic acid in 22.5 ml of 20% sodium hydroxide, and the mixture refluxed on the water bath for 10-12 h. After cooling,

the mixture was extracted with ether and the aqueous layer acidified with hydrochloric acid. The resulting dark brown oil was separated, the aqueous layer extracted with ether, and the ether extracts added to the oil and dried over magnesium sulfate. The ether was evaporated and the residue distilled in vacuum (Table 1).

2-Methoxyphenoxy(α,α-dialkyl)methypenicillins (I-XX). To a solution of 0.01 mole of the starting acid in 25 ml of absolute acetone at 0° was added with mixing a solution of 2,4 g (0.024 mole) of triethylamine in 25 ml of absolute acetone and 3 g (0.028 mole) of ethyl chlorocarbonate in 20 ml of absolute acetone. Mixing was continued for 30 min at 0° and for 2 h at room temperature. The precipitated material was added to a mixture of a solution of 5.6 g (0.026 mole) of 6-APA in 100 ml of absolute acetone and 200 ml of a 2.5% solution of sodium bacarbonate, stirred for 4 h, and extracted with ether. The aqueous layer was separated, acidified to pH 2.0 with 1 N hydrochloric acid at 6-7°, and the acid formed extracted with ether. The ether extract was washed with ice water, shaken with sodium sulfate and charcoal, and filtered. The filtrate was brought to pH 7.0-7.5 by the addition of 8% aqueous sodium bicarbonate, the aqueous layer separated, washed with ether, and lyophilized (see Table 2).

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COMPLEXES OF PLATINUM(II) AND PALLADIUM(II) WITH 2-ALKYL-N-(β-AMINOETHYL)PYRROLIDINES – NEW BIOLOGICALLY ACTIVE COMPOUNDS

V. I. Bystrenina, A. D. Shebaldova,
A. I. Idelevich, L. K. Kulikova,
M. K. Krasheninnikova, and T. K. Nelyubova

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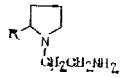
The increased interest in complexes of platinum(II) and other platinum-group metals with organic ligands containing an amino group is largely due to their observed antitumor activity [1]. In view of the fact that the nature of the amino compound has a substantial effect on the antitumor properties of the complexes [2], the possibility arises of a search for new active compounds of this type by varying the organic ligand containing the amino group.

As ligands for the synthesis of such potentially biologically active compounds, it appeared to us desirable to utilize 2-alkyl-N-(β-aminomethyl)pyrrolidines (L):



R = C_4H_9 (I); iso-C_5H_{11} (II),

which have not hitherto been examined in this respect. Meanwhile, it follows from the structures of these compounds that they are powerful complexing agents as a result of the presence of the donor nitrogen atoms of the amino-group and the heterocycle.

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