SYNTHESIS OF UNSATURATED ANALOGS OF PHENOXYMETHYLPENICILLIN

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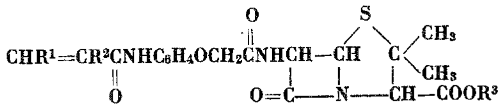
In order to obtain penicillins, capable of homo- and copolymerization, we undertook the synthesis of a number of unsaturated phenoxymethylpenicillin derivatives with an active vinyl group in the side acyl radical. For the synthesis we employed acylaminophenoxyacetic acids that contain the acryloyl, methacryloyl or crotonoyl group. The acids were obtained by the alkylation of the corresponding phenols [1] or by the acylation of aminophenoxyacetic acids with the acid chlorides or the anhydrides of acrylic, methacrylic, and crotonic acids [2]. For the acylation of 6-aminopenicillanic acid the unsaturated phenoxyacetic acids were converted to the mixed anhydrides by treatment with $ClCOOC_2H_5$ in the presence of triethylamine. The acylation was run in aqueous dioxane medium and the penicillins were isolated as the K salts (Table 2). For convenience of identification, in some cases the penicillins were converted to the methyl esters by reactions with CH_2N_2, or they were isolated as the acids (Table 1).

The structure of the penicillins was confirmed by the IR spectra: 1765-1770 cm^{-1} ($\nu_{C=O}$ of β-lactam ring), 1670-1680 cm^{-1} ($\nu_{C=O}$, amide I), and 1610-1590 cm^{-1} ($\nu_{C=C}$ of vinyl group and of benzene ring). A band at 1735 cm^{-1} ($\nu_{C=O}$ of ester) was observed in the IR spectra of the methyl esters.

The synthesized penicillins are active toward gram-positive microorganisms and are inactive toward gram-negative microorganisms. The values of the minimum concentration, which suppresses the growth of microbes (MSC), were determined by the method of series dilutions in meat peptone bouillon at a microbe charge of 10^5 cells/ml. The value of the MSC against Staphylococcus aur. 209P depends on the position of the substituent in the benzene ring (see Table 1). The o-substituted penicillin (II) proved to be the least active, while the m-substituted penicillin (III) was the most active. It should be mentioned that the

TABLE 1. Unsaturated Acylaminophenoxymethylpenicillins



Compound	R¹	R²	R³	Yield %	Mp, °C	Isomer	λ_{max}, nm	Found, %				Empirical formula	Calculated, %				$\varepsilon \cdot 10^3$,* liter/mole·cm	R_f †	$[\alpha]_D^{20}$
								C	H	N	S		C	H	N	S			
(I)	H	H	H	79,0	164--165	p	254	53,97	5,26	10,32	7,54	$C_{19}H_{21}N_3O_6S$	54,40	5,10	10,01	7,64	13,2	0,71	+164 (C 1,0, H_2O)
(II)	H	CH_3	CH_3	30,4	144—145	p	266	56,85	5,68	9,82	7,17	$C_{20}H_{25}N_3O_6S$	54,40	5,60	9,34	7,16	9,76	0,85	+117 (C 0,8, $CHCl_3$)
(III)	CH_3	H	CH_3	34,0	143—144	p	278	56,30	5,43	8,98	7,02	$C_{20}H_{25}N_3O_6S$	56,40	5,60	9,34	7,16	5,37	0,90	+148 (C 0,5, C_2H_5OH)
(IV)	H	CH_3	CH_3	17,0	76—77	m	254	56,80	6,05	9,40	6,87	$C_{20}H_{25}N_3O_6S$	56,40	5,60	9,34	7,16	20,25	0,95	+134 (C 1,46, DMF)

*Determined on an SF-4A spectrophotometer.
† Chromatographed in a thin layer of KSK silica gel in the system: 14: 4.5: 4.5: 5 n-butanol-ether-acetone-water.

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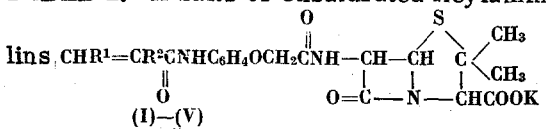
TABLE 2. K Salts of Unsaturated Acylaminophenoxymethylpenicillins



(I)–(V)

K salt of compound	R^1	R^2	Isomer	Mp, °C	Iodometric activity, μg/mg	Value of MSC relative to Staphylococcus aur. 209 P, μg/ml
(I)	H	H	*p*	229–231	1000	0,12
(II)	H	CH_3	*o*	200–201	1000	0,50
(III)	H	CH_3	*m*	211–212	1000	0,03–0,08
(IV)	H	CH_3	*p*	219–220	1000	0,25
(V)	CH_3	H	*p*	215–216	980	0,05–0,10

TABLE 3. Rate Constants of Inactivation of Unsaturated Acylaminophenoxymethylpenicillins and Inactivation by Penicillinase of Bacillus licheniformis 749/c

Compound	k, units/ml·min	
	pH 2,0; 35°	[Bacillus licheniformis 749/c] = 20 units/ml; 37°; pH 6.8
(I)	3,1±0,1	10,6±0,3
(II)	3,3±0,1	15,8±0,2
(III)	3,0±0,1	8,4±0,4
(IV)	3,5±0,2	11,8±0,2
(V)	3,8±0,2	6,1±0,1
Phenoxymethylpenicillin	3,3±0,1	16,9±0,2

nature of the unsaturated carboxylic acid has little effect on the activity. The values of the MSC for (I), (IV), and (V) are close. To check the effect of the unsaturated acylamino group on the acid resistance of the penicillins and their sensitivity to penicillinase we studied the inactivation rate of the penicillins in acid medium, and also inactivation by the penicillinase of Bacillus licheniformis 749/c (Table 3).

From Table 3 it can be seen that the insertion of an acylamino group is practically without effect on the sensitivity of the penicillins toward acids, whereas the sensitivity toward penicillinase is noticeably reduced for the penicillins that have an unsaturated acylamino group in the m- or p-position. The only exception is (II), the rate constant for the inactivation of which by penicillinase is nearly the same as for phenoxymethylpenicillin, although a greater resistance could be expected for this derivative due to the presence of a substituent in the o-position. The existence of additional interaction or of steric conformity in the formation of the enzyme-substrate complex during the inactivation of the antibiotic by the penicillinase can be assumed here.

EXPERIMENTAL METHOD

Potassium Salts of Penicillins. To 0.01 mole of the unsaturated acylaminophenoxyacetic acid in a mixture of 20 ml of dioxane and acetone was added 0.01 mole of triethylamine, the mixture was stirred for 30 min, then 0.01 mole of $ClCOOC_2H_5$ in 10 ml of dioxane was added, the mixture was stirred at 0-5° for 1 h, after which 0.075 mole of 6-aminopenicillanic acid in a mixture of 15 ml of water and 1 ml of triethylamine was added. The mixture was stirred for 3 h, with a gradual increase in the temperature from 0 to 10-15°. The reaction mixture was diluted with 30 ml of 1% $NaHCO_3$ solution, washed twice with 20 ml of ether, and acidified with 1 N H_2SO_4 solution to pH 2.0. The penicillin was extracted with 50 ml of chloroform, the solution was washed twice with 15 ml of water, dried over Na_2SO_4, 6 ml of a 1.2 N butanol solution of CH_3COOK was added, and with stirring the whole was poured into 500 ml of absolute acetone. The precipitated K salt of the penicillin was separated on a filter and washed with acetone. The yield was 70-90%.

Methyl Esters of Penicillins. A solution of 0.005 mole of the K salt of the penicillin in 30 ml of water was acidified with 1 N H_2SO_4 solution to pH 2.0 and then extracted with 25 ml of chloroform. The solution was washed with water, dried over anhydrous Na_2SO_4, and filtered. To the filtrate was added 45 ml of 1 N CH_2N_2 solution in ether. When the gas evolution had ceased the solvent was vacuum-distilled, while the residue was recrystallized from a 1:25 ethyl acetate—petroleum ether mixture. The yield was 17-34%.

The rate of inactivation in acid medium and by penicillinase was studied as described in [3, 4].

CONCLUSIONS

Some unsaturated acylaminophenoxymethylpenicillins and their methyl esters were synthesized and characterized. The antimicrobial properties of these compounds and their sensitivity toward penicillinase depend on the position of the unsaturated acylamino group in the benzene ring.

LITERATURE CITED

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3. E. F. Panarin and M. V. Solovskii, Antibiotiki, 1970, 426.
4. E. F. Panarin and M. V. Solovskii, Antibiotiki, 1971, 882.