TABLE 1. N-Chloroarenesulfonimides (I-VII)

Compound	Yield (in %)	mp (in °C)	Found (in %)				Empirical formula	Calculated (in %)			
			C	H	Cl	N		C	H	Cl	N
I	90—92	119—20	43,38	3,08	10,61	4,29	$C_{12}H_{10}ClNO_4S_2$	43,43	3,03	10,68	4,23
II	94—95	103—4	46,70	4,00	9,85	3,99	$C_{14}H_{14}ClNO_4S_2$	46,72	3,92	9,85	3,89
III	92—94	188—9	34,10	1,95	8,34	9,99	$C_{12}H_8ClN_3O_8S_2$	34,12	1,91	8,40	9,96
IV	88—90	86—7	39,11	2,26	9,61	3,86	$C_{12}H_8ClF_2NO_4S_2$	39,18	2,19	9,64	3,81
V	88—90	152—3	35,90	2,07	8,82	3,54	$C_{12}H_8Cl_3NO_4S_2$	35,96	2,01	8,84*	3,51
VI	90—92	165—6	29,41	1,70	7,20	2,90	$C_{12}H_8Br_2ClNO_4S_2$	29,43	1,65	7,24	2,86
VII	89—91	180—1	24,62	1,42	6,02	2,42	$C_{12}H_8ClI_2NO_4S_2$	24,69	1,38	6,07	2,40

*The calculation was performed for the one chlorine atom attached to nitrogen.

of the reaction mixture, which required 25-30 min. The precipitate formed was filtered off, carefully washed with cooled water, dried, and crystallized from carbon tetrachloride (free from carbon disulfide). Yield 88-95%.

The IR spectra were taken on a UR-10 spectrophotometer with a sodium chloride prism.

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INVESTIGATIONS IN THE FIELD OF SEMISYNTHETIC PENICILLINS.

IX. 6-AMINOPENICILLANIC DERIVATIVES OF p-ALKOXYPHENYL- AND p-ALKOXYBENZYLSUCCINIC ACIDS. MONOPENICILLINS

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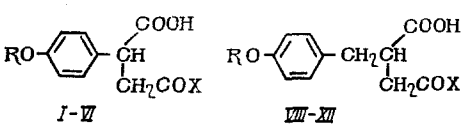
The work presented is a continuation of investigations on the synthesis and the study of the properties of 6-aminopenicillanic derivatives of p-alkoxyphenyl- and p-alkoxybenzylsuccinic acids [1] with the general structure



I-VI

VIII-XII

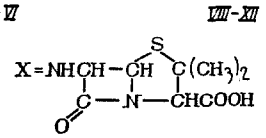


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TABLE 1. Penicillin Derivatives of p-Alkoxyphenylsuccinic Acids

Compound	R	Yield (in %)	mp (in °C)*	Found (in %)		Empirical formula	Calculated (in %)		R_f †
				N	S		N	S	
I	CH_3	45,5	106—9	6,21	7,35	$C_{19}H_{22}N_2O_7S$	6,63	7,58	0,72
II	C_2H_5	55,0	103—110	6,30	7,02	$C_{20}H_{24}N_2O_7S$	6,42	7,33	0,69
III	C_3H_7	65,0	116—122	6,01	7,48	$C_{21}H_{26}N_2O_7S$	6,22	7,11	0,76
IV	iso-C_3H_7	55,5	90—7	6,18	7,09	$C_{21}H_{26}N_2O_7S$	6,22	7,11	0,76
V	C_4H_9	56,0	118—125	5,69	7,18	$C_{22}H_{28}N_2O_7S$	6,03	6,89	0,77
VI	iso-C_4H_9	66,6	115—8	6,4	7,1	$C_{22}H_{28}N_2O_7S$	6,03	6,89	0,76

*Here and in Table 2: melt with decomposition.
†Here and in Table 2: butanol—water—acetone—ether (14:4.5:4.5:5) system.

To synthesize the penicillins we used the acylation of 6-aminopenicillanic acid (6-APA) by anhydrides of the corresponding acids [2], obtained by the reaction of the acids with acetic anhydride taken in twofold excess [3, 4].

The required initial dicarboxylic acids were obtained by published methods [3-5].

The purity and individuality of the penicillins obtained were checked by thin-layer chromatography [6] (Tables 1 and 2), and their structures were confirmed by elementary analysis and IR spectroscopy. Absorption bands were found at 1780, 1650, and 1720 cm^{-1} which are characteristic, respectively, for the carbonyl of a β-lactam ring and of amide and carboxy groups, and at 1600-1615 cm^{-1} for the corresponding substituents.

The penicillins were characterized in the form of the acids (see Tables 1 and 2). The investigations of their biological properties were performed on the sodium salts by generally adopted methods [7, 8].

The study of the antimicrobial action of the penicillins obtained showed that they act feebly on the growth of both Gram-positive and Gram-negative microorganisms. The minimum growth-inhibiting concentration for *E. coli*, *Bac. diphtheriae*, and *Salmonella typhosa* and Proteus varies from 62.5 to 500 μg/ml and more, and for *Streptococcus* and *Staphylococcus* it is 1.56-3.12 μg/ml. Penicillins (VIII) and (XXII) are exceptions. The are active on *Streptococcus* and *Staphylococcus* in concentrations of 0.39-0.78 μg/ml. The p-alkoxyphenyl- and p-alkoxybenzylmonopenicillin derivatives of succinic acid are more active than the unsubstituted monopenicillin derivative of the same acid [9], which retards the growth of the cocci mentioned in a concentration of 15.6 μg/ml.

Depending on the alkyl radical of the alkoxy group, the majority of the penicillins studied have an antibacterial action 8-32 times greater than that of benzylpenicillin in relation to β-lactamase-forming staphylococci. In view of this, the active penicillins were subjected to hydrolysis by the enzyme β-lactamase of *Bac. licheniformis* 749/c. All the hydrolyzed penicillins are decomposed more slowly than benzylpenicillin. Their hydrolysis under the action of one unit of β-lactamase for 1 h took place at the rate of from 26.5 (20.7-32.2) to 41.2 (39.6-42.8) units/h. Under similar experimental conditions, benzylpenicillin decomposes at the rate of 60 units/h. The penicillins studied are more resistant to the action of the β-lactamase of *Bac. licheniformis* than the bispenicillin derivatives of succinic acid with the same substituents [1].

The penicillins obtained are not acid-resistant, and their half-decomposition time in an aqueous ethanolic medium at pH 1.3 and a temperature of 37°C is 3-7 min.

All the penicillins have a low toxicity. Their tolerated dose on a single injection into mice intravenously is 150-300 mg/kg.

EXPERIMENTAL

The physical constants of the p-alkoxyphenyl- and p-alkoxybenzylsuccinic acids and their anhydrides that we obtained correspond to the figures given in the literature [3-5].

Monopenicillin Derivatives of p-Alkoxyphenylsuccinic Acids (I-VI). A suspension of 3.9 g (0.18 mole) of 6-APA in 14.5 ml of dimethylformamide and 10 ml of triethylamine was stirred

TABLE 2. Penicillin Derivatives of p-Alkoxybenzylsuccinic Acids

Compound	R	Yield (in %)	mp (in °C)	Found (in %)		Empirical formula	Calculated (in %)		R_f
				N	S		N	S	
VII	CH_3	58,1	99—102	6,28	6,84	$C_{20}H_{24}N_2O_7S$	6,42	7,33	0,81
VIII	C_2H_5	58,0	130—2	5,78	7,32	$C_{21}H_{26}N_2O_7S$	6,22	7,11	0,64
IX	C_3H_7	63,0	103—5	5,86	7,05	$C_{22}H_{28}N_2O_7S$	6,03	6,89	0,84
X	iso-C_3H_7	60,0	89—90	5,87	6,4	$C_{22}H_{28}N_2O_7S$	6,03	6,89	0,74
XI	C_4H_9	76,0	100—3	5,81	6,8	$C_{23}H_{30}N_2O_7S$	5,88	6,69	0,80
XII	iso-C_4H_9	61,0	118—23	5,89	6,99	$C_{23}H_{30}N_2O_7S$	5,88	6,69	0,78

at 0°C for 2 h, and then 0.018 mole of the anhydride of the appropriate dicarboxylic acid was added over 10 min, and the mixture was stirred at 0°C for 30 min and at room temperature for 2 h. About 50 ml of water was added to the reaction mixture and it was extracted with ether. The ether extract was discarded and the aqueous layer was cooled to 7°C, 100 ml of ether was added, and the mixture was acidified with 1 N hydrochloric acid to pH 2.0. The ether layer was separated off and the acidified aqueous layer was extracted with ether. The combined ethereal extracts were washed with ice water and were shaken with anhydrous sodium sulfate and carbon. The penicillin was isolated from the ethereal extract by the addition of an 8% aqueous solution of sodium bicarbonate to pH 6.5-7.0 in the aqueous layer. The latter was separated off, extracted with ether, and freeze-dried. The resulting crystalline residue was triturated with absolute ether. To determine some physicochemical constants, a small part of the sodium salt was reconverted into the penicillin acid. An ethereal extract was evaporated under reduced pressure and the residue was crystallized from petroleum ether (see Table 1).

The monopenicillin derivatives of p-alkoxybenzylsuccinic acids (VII-XII) were obtained similarly (see Table 2).

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