# SYNTHESIS OF CERTAIN DERIVATIVES OF 6-AMINOPENICILLANIC ACID BASEC ON N-SUBSTITUTED MONOAMIDES OF MALEIC ACID

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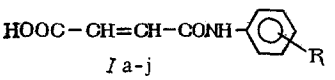
After the discovery of 6-aminopenicillanic acid (6-APA) a large number of semisynthetic penicillins were synthesized [1-3]. For the purpose of searching for new antibiotic preparations we synthesized certain semisynthetic penicillins containing N-substituted monoamides of maleic acid as the actyl radical.

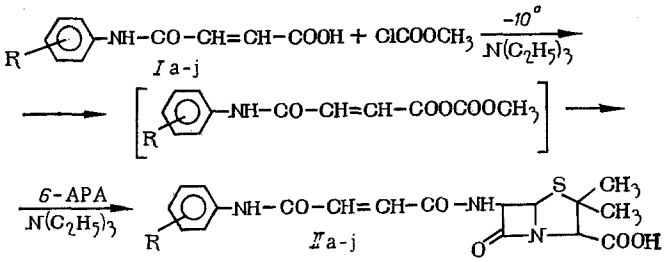
The carboxylic acids based on maleic anhydride and substituted aromatic amines were synthesized by the known method [4-6].



*I* a-j

a) R=H, f) R=*m*-$NO_2$
b) R=*o*-$CH_3O$, g) R=*n*-$NO_2$
c) R=*m*-$CH_3O$, h) R=*o*-Br
d) R=*n*-$CH_3O$, i) R=*m*-Br
e) R=*o*-$NO_2$, j) R=*n*-Br

N-Substituted monoamides of maleic acid were introduced into reaction with 6-APA as mixed anhydrides [7, 8], obtained with the methyl or isobutyl ester of chlorocarbonic acid.



Derivatives of 6-APA (IIa-j) were isolated as sodium salts by lyophilization of their aqueous solutions, prepared using sodium bicarbonate, or by their precipitation from organic solvent with 1 N sodium alkoxide in butanol (Table 1).

The second method makes it possible to obtain derivatives of 6-APA as crystalline salts. The degree of purity was determined by iodometric titration. The structure was confirmed by elemental analysis data and IR spectroscopy, from which the presence of β-lactam and thiazolidine rings in the synthesized derivatives of 6-APA could be judged (characteristic frequencies of the carbonyl group of the β-lactam ring in the region of 1770-1790 $cm^{-1}$, the amide group in the region of 1680-1690 $cm^{-1}$, ionized carboxyl group in the region of 1600-1610 $cm^{-1}$). Characteristic frequencies of the nitro group in the region of 1350 and 1520 $cm^{-1}$ are present in nitro derivatives of 6-APA. Characteristic frequencies of deformation vibrations of aromatic ring protons are presented in the region of 700-900 $cm^{-1}$ as a function of position of the substituent.

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TABLE 1. Semisynthetic Penicillins

| Compound | R | Yield (%) | mp (deg) * | Found (%) | | | Empirical formula | Calculated (%) | | | MSC (μg/ml) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | C | H | N | | C | H | N | Staph. aureus 340 | Staph. aureus 0394 | E. coli 60 |
| IIa | H | 37,5 | 189—92 | 52,85 | 5,44 | 10,05 | $C_{18}H_{19}N_3O_5S \cdot H_2O$ | 53,06 | 5,21 | 10,31 | 3,1 | 1, 5 | 50 |
| IIb | *o*-$CH_3O$ | 44 | 157—60 | 52,48 | 5,59 | 9,35 | $C_{19}H_{21}N_3O_6S \cdot H_2O$ | 52,16 | 5,31 | 9,61 | 10 | 6 | 50 |
| IIc | m-$CH_3O$ | 34 | 172—5 | 52,34 | 5,64 | 9,24 | $C_{19}H_{21}N_3O_6S \cdot H_2O$ | 52,16 | 5,31 | 9,61 | 6 | 12 | 25 |
| IId | p-$CH_3O$ | 40 | 184—6 | 51,85 | 5,48 | 9,43 | $C_{19}H_{21}N_3O_6S \cdot H_2O$ | 52,16 | 5,31 | 9,61 | 6 | 6 | 50 |
| IIe | *o*-$NO_2$ | 21 | 164—7 | 48,07 | 4,78 | 12,14 | $C_{18}H_{18}N_4O_7S \cdot H_2O$ | 47,79 | 4,46 | 12,38 | 12 | 6 | 25 |
| IIf | m-$NO_2$ | 23 | 178—81 | 47,95 | 4,65 | 12,45 | $C_{18}H_{18}N_4O_7S \cdot H_2O$ | 47,79 | 4,46 | 12,38 | 6 | 12 | 25 |
| IIg | p-$NO_2$ | 18 | 196—9 | 48,12 | 4,32 | 12,21 | $C_{18}H_{18}N_4O_7S \cdot H_2O$ | 47,79 | 4,46 | 12,38 | 3,1 | 6 | 25 |
| IIh | *o*-Br | 35 | 161—3 | 44,78 | 4,48 | 8,35 | $C_{18}H_{18}BrN_3O_5S \cdot H_2O$ | 44,46 | 4,15 | 8,63 | 1,5 | 1,5 | 25 |
| IIi | m-Br | 24 | 170—3 | 44,82 | 4,37 | 8,41 | $C_{18}H_{18}BrN_3O_5S \cdot H_2O$ | 44,46 | 4,15 | 8,63 | 6 | 12 | 50 |
| IIj | p-Br | 20 | 192—4 | 44,65 | 4,29 | 8,56 | $C_{18}H_{18}BrN_3O_5S \cdot H_2O$ | 44,46 | 4,15 | 8,63 | 6 | 6 | 25 |
| Benzyl-penicillin | | | | | | | | | | | 50 | 50 | 50 |
| Oxacillin | | | | | | | | | | | 0,7 | 0,7 | 50 |
| Methicillin | | | | | | | | | | | 1,5 | 1,5 | 50 |

*All materials melt with decomposition.

TABLE 2. Spectrum of Antibacterial Effect of Semisynthetic Penicillins (IIa) and (IIh)

| Microorganism | MSC (μg/ml) | | |
|---|---|---|---|
| | IIa | IIh | benzyl-penicil-lin |
| Staph. aureus * 0394 | 1,5 | 1,5 | 50 |
| 370 | 1,5 | 3,1 | 50 |
| Sarcina lutea 152 | 0,8 | 0,4 | 0,4 |
| Bacillus subtilis 3 | 0,4 | 0,4 | 0,4 |
| Enterococcus 16 | 3,8 | 3,8 | 1,9 |
| Micrococcus lysodeicticus 13 | 0,4 | 0,8 | 0,1 |
| Proteus vulgaris 247 | 50 | 50 | 50 |
| " rettgari 52 | 50 | 50 | 50 |
| Ps. aeruginosa 0387 | 50 | 50 | 50 |
| E. coli 60 | 50 | 25,0 | 50 |
| Klebsiella pneumoniae 102 | 50 | 50 | 50 |
| Aerobacter aerogenes 62 | 50 | 50 | 50 |

*Strains stable to benzylpenicillin.

The antimicrobic activity of the new semisynthetic penicillins was studied in experiments *in vitro* by the method of two serial dilutions in liquid nutriment (see Table 1). It was established that the investigated materials possess expressed antibacterial effect in relation to penicillin-resistant strains of *Staphylococcus aureus*; their biological activity was 4-33 times greater in comparison with the activity of benzylpenicillin. The most inhibiting effect was shown by (IIa) and (IIh). The minimum suppressing concentration (MSC) of these materials was close to or exceeded slightly the MSC of methicillin. However, oxacillin was 2-4 times more active than the indicated derivatives. In this connection the antimicrobic activity of (IIa) and (IIh) was studied in relation to a broader group of microorganisms (Table 2). The preparations were effective in action on Gram-positive bacteria, while Gram-negative (*Escherichia, Proteus, Pseudomonad, Klebsiella*) were stable to the named materials.

## EXPERIMENTAL

IR spectra were taken on an IKS-22 instrument in KBr.

N-Substituted Monoamides of Maleic Acid (Ia-j). To a solution of 0.1 mole of maleic anhydride in 160 ml of acetone was added with intense stirring 0.12 mole of the corresponding substituted or unsubstituted aniline in 100 ml of acetone. The reaction was carried out for 1.5-2 h at a temperature of 50-60°. Then the reaction mixture was cooled and poured into 800 ml of 0.01 N hydrochloric acid. The precipitate was filtered, washed with water, then suspended in 1 liter of water, and a 30% sodium hydroxide solution was added with intense stirring to pH 7.0-8.0. The undissolved portion was filtered and the filtrate was acidified to pH 2.5-3.0. The precipitate was filtered, washed with water, and dried. Yield was 70-92%; mp corresponded to literature data [4-6].

Semisynthetic Penicillins (IIa-j). To a solution of 0.01 mole of N-substituted maleic acid monoamide in 50 ml of tetrahydrofuran cooled to −10° with stirring was added 0.01 mole of triethylamine in 10 ml of tetrahydrofuran, the mixture was stirred for 30 min, 0.01 mole of the isobutyl ester of chlorocarbonic acid in 10 ml of tetrahydrofuran was added gradually, and the mixture was stirred for 30 min at a temperature of −10°. Then 0.01 mole of 6-APA in a mixture of 20 ml of cold water and 1.4 ml of triethylamine were added in one portion.

The reaction mixture was stirred for 40 min at −10° and for 2 h at 30°, 50 ml of water was added, and the mixture was cooled to 0°.

The obtained solution was washed with ether (2 × 40 ml), the pH of the aqueous layer was brought to 3.0 with 6 N sulfuric acid, and the liberated derivative of 6-APA was extracted with 50 ml of chloroform.

The extract was washed with water (3 × 30 ml) and dried with magnesium sulfate. The dried extract was filtered, a threefold volume of dry ether was added to it, and the sodium salt of the 6-APA derivative was separated by adding 1 N sodium alkoxide in butanol to pH 7.0. The precipitated product was filtered, washed with dry ether, and dried.

Samples for elemental analysis were subjected to additional purification: The sodium salt of the 6-APA derivative was precipitated from methanol with ether and then transformed two times from the Na form to the H form. Derivatives of 6-APA were subjected to elemental analysis in the H form.

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