# SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME ALKYL-N-(NITROPHENYL)CARBAMATES

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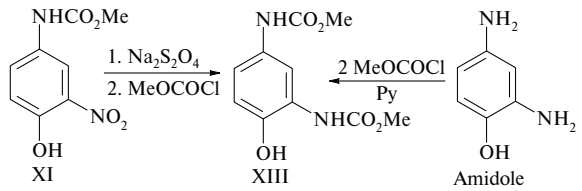
Some polyfunctional derivatives of N-aryl-substituted carbamates [1, 2], for example, 2-nitrophenyl derivatives [3], possess a broad spectrum of antimicrobial activity. In the search for new antibacterial preparations, we have synthesized a series of N-arylcarbamates with a nitro group in the benzene nucleus, which are described by the general formula

$$R'XC_6H_3NHCO_2R$$

I – XII

R = Me, R′ = H, X = 2-$NO_2$ (I); R = Et, R′ = H, X = 4-$NO_2$ (II); R = $CHMe_2$, R′ = H, X = 4-$NO_2$ (III); R = *cyclo*-$C_6H_{11}$, R′ = H, X = 4-$NO_2$ (IV); R = $CH_2Ph$, R′ = H, X = 4-$NO_2$ (V); R = Me, R′=4-Me, X = 2-$NO_2$ (VI); R = Me, R′ = 4-OMe, X = 2-$NO_2$ (VII); R = Me, R′ = 2-$NHCO_2Me$, X = 4-$NO_2$ (VIII); R = Me, R′ = 3-$NHCO_2Me$, X = 4-$NO_2$ (IX); R = Me, R′ = 4-$NHCO_2Me$, X = 2-$NO_2$ (X); R = Me, R′ = 4-OH, X = 3-$NO_2$ (XI); R = Me, R′ = 4-OMe, X = 3-$NO_2$ (XII).

Compounds I and X were obtained by nitrating the corresponding core-substituted alkyl-N-phenylcarbamates according to the Menke method [4]. Nitro compounds II – V and IX were synthesized by nitrosation of the corresponding N-arylcarbamates with nitrosylsulfuric acid in glacial acetic acid at a temperature below 20°C, followed by oxidation of the nitroso group to nitro group with 20% aqueous nitric acid. N-Nitroarylcarbamates VI – VIII and XII were isolated as the main products of direct carbamate nitrosation [5]. 4-Hydroxy-3-methyl-N-(4-hydroxy-3-nitrophenyl)carbamate (XI) was obtained by nitrosation of methyl-N-(4-hydroxyphenyl)carbamate [6] with nitrous acid.

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The position of the nitro group in compound XI was checked by conducting sequential reduction and acylation reactions, which converted this group into a methoxycarboxamide group. The product is identical to 4-hydroxy-1,3-di(methoxycarboxamido)benzene (XIII) obtained by coutersynthesis from amidole.

## EXPERIMENTAL CHEMICAL PART

The IR absorption spectra were recorded on an IKS-29 spectrophotometer using samples prepared as nujol mulls. Purity of the reaction products was checked by TLC on Silufol UV-254 plates (Czech Republic) eluted in an ether – chloroform system (2 : 1) and developed by exposure to iodine vapors.

The synthesis of compounds I – X and XII was described and their characteristic presented elsewhere [4, 5]. Methyl-N-(4-hydroxyphenyl)carbamate was obtained by a modified method [6] using sodium hydrocarbonate (instead of an aqueous alkaline solution) as the hydrogen chloride acceptor.

**Methyl-N-(4-hydroxy-3-nitrophenyl)carbamate (XI)**. To a solution of 1.67 g (0.01 mole) of methyl-N-(4-hydroxyphenyl)carbamate in 3 ml of glacial acetic acid were added 5 ml of water and then sodium acetate to pH 4.2. To this mixture was added a solution of 1.7 g (0.025 mole) of sodium nitrite in 5 ml of water. The reaction mixture was held for 8 h at 20°C and poured into 50 ml of ice-cold water. The precipitated crystalline product was separated by filtration, dried in air, and recrystallized from hexane to obtain 1.4 g (67%) of compound XI in the form of yellow crystals; m.p., 142°C; $C_8H_8N_2O_5$; IR spectrum ($\nu_{max}$, $cm^{-1}$): 3300 – 3430 (NH, OH), 1720 (C=O), 1620, 1585 (C–$C_{arom}$), 1535, 1295 ($NO_2$).

**4-Hydroxy-1,3-di(methoxycarboxamido)benzene (XIII)**. M e t h o d A . To an solution of 12.4 g (0.1 mole) of amidole in in 75 ml of anhydrous pyridine, cooled on ice, was added dropwise with stirring 20 ml (0.26 mole) of methyl chloroformate. The reaction mixture was held for 3 h in cold and allowed to stand overnight at 20°C. Then the mixture

**TABLE 1.** Antimicrobial Properties of N-Arylcarbamates I–XII

| Compound | Diameter of retarded microbial growth zone, mm | | | |
|---|---|---|---|---|
| | *St. aureus* 209 | *Micrococcus*[1] | *E. coli* O18 | *E. coli*[1] |
| I | … | … | 14.0 ± 1.7** | 13.8 ± 2.0** |
| II | 12.0 ± 0.5* | 0 | 0 | 5.5 ± 0.1* |
| III | 13.0 ± 0.8** | 0 | 0 | 0 |
| IV | 18.0 ± 1.6** | 24.8 ± 3.2*** | 0 | 0 |
| V | 19.8 ± 0.05** | 22.4 ± 0.01*** | 2.4 ± 0.2* | 0 |
| VI | 17.0 ± 0.08** | 25.0 ± 0.05*** | 16.6 ± 2.75** | … |
| VII | 30.0 ± 0.1*** | 21.0 ± 0.05** | 0 | 10.0 ± 0.05* |
| VIII | 10.5 ± 0.1* | 18.0 ± 0.1** | 0 | 22.4 ± 0.5*** |
| IX | 20.0 ± 0.1** | 22.1 ± 0.09*** | 11.5 ± 3.8* | 0 |
| X | 27.1 ± 0.1*** | 25.5 ± 1.4*** | 8.7 ± 0.8* | 2.2 ± 0.3* |
| XI | 7.8 ± 0.1* | 14.0 ± 0.1** | 15.0 ± 1.09** | 9.8 ± 1.08* |
| XII | 12.8 ± 0.08* | 12.0 ± 0.03* | … | … |
| Gentamicin | 38.6 ± 0.08*** | 36.2 ± 0.06*** | 18.0 ± 1.5** | … |

**Notes**: [1] Microbes isolated from a patient with acute respiratory viral disease; rated microbe resistance: (0) stable growth, (*) low sensitivity, (**) medium sensitivity, (***) high sensitivity.

was poured into 25 ml of ice-cold water, carefully acidified with concentrated hydrochloric acid to an acid reaction, and extracted with chloroform (2 × 250 ml). Then the solvent was distilled off in a rotor evaporator; during this process, the residue exhibits crystallization. Finally the product is recrystallized from ethanol to obtain 14.6 g (61%) of compound XIII in the form of a white powder; m.p., 126°C; $C_{10}H_{12}N_2O_5$; IR spectrum ($\nu_{max}$, $cm^{-1}$): 3300 – 3420 (NH, OH), 1715 (C=O), 1620, 1575 (C–C arom).

M e t h o d B . To 1.5 g (7 mmole) of nitro compound XI in 20 ml of methanol, cooled on ice, was added by portions with stirring 4 g (23 mmole) of sodium dithionite in 20 ml of a 7% aqueous ammonium hydroxide solution. When the solution discolored, a small amount (0.05 g) of sodium dithionite was added and the reaction mixture was stirred for 0.5 h and allowed to stand in the cold for 1 h. The precipitate was separated by filtration, washed with water, dried, and acylated with methyl chloroformate in an aqueous sodium hydrocarbonate solution. This yielded a crystalline product with m.p. = 126°C, identical to the substance obtained by method A.

## EXPERIMENTAL BIOLOGICAL PART

The antimicrobial activity of N-arylcarbamates I – XII was determined by testing with standard staphylococcal strains of *St. aureus* 209 and *E. coli* $O_{18}$ and with cultures of these microbes isolated from humans. The resistance of the cultures of conditionally-pathogenic human microflora with respect to the synthesized compounds was studied by direct diffusion into a nutrient medium (meat-infusion broth) and by the method of paper disks in Petri dishes preliminarily inoculated with suspensions of the isolated microorganisms (diluted to $1 \times 10^5$ microbial cells per ml). Compounds I – XII were introduced in 25 μl aliquots into wells with nutrient medium, starting with a concentration of 1 mg/ml (solvent, DMSO). The samples of microbe cultures with tested compounds were incubated at 37°C.

The microbe sensitivity to the drugs was evaluated by measuring the diameter (in mm) of the zone of retarded microbial growth around each well (with allowance for the well diameter) [7]. The observations made every two days over a period of two weeks gave a pattern of stable or suppressed microbial growth and the dynamics of decrease in the activity of compounds. The reference drug was gentamicin. In addition, the drug resistance of the microbial cultures studied was assessed and rated according to the conventional classification [8].

It was established that a most pronounced antimicrobial activity in the series of compounds studied is inherent in compounds VI, VII, IX, and X containing nitro groups in *ortho* positions relative to the carbamate group. The activity of compounds VI, VII, IX, and X correlates with the σ-constants of substituents (Me, OMe, H, $NHCO_2Me$) in *para* positions to the carbamate fragment [9].

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