DIMETALATION OF BIS-CARBAMATE MEE-1 AND IN SILICO STUDY OF PHYSICOCHEMICAL PARAMETERS

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Abstract. This scientific work is devoted to the dimetalation of N,N'-hexamethylene bis-[(ortho-cresolyl)-carbamate] and the synthesis of N,N'-disodium, N,N'-hexamethylene bis-[(ortho-cresolyl)-carbamate] i.e. MEE-1b. As a result, distrium substituted bis-carbamate MEE-1b was obtained in high yield. *In silico* primary screenings were carried out to study the elemental composition, some physicochemical properties and biological activities. As a result, it was revealed that bis-carbamate MEE-1b can be used as an inhibitor and substrate of cytochrome. And also in the treatment of phobic disorders. Further study in real *in vitro* and *in vivo* analyzes is also recommended.

Key words: Bis-carbamate, pass online, screening, sodium, activity, inhibitor, substrate, phobic, cytochrome.

Introduction. Numerous studies in the field of carbamate and bis-carbamate derivatives carried out in present, caused not only by theoretical, but also by practical needs. With this points of view, derivatives of carbamates and bis-carbamates are of undoubted interest as substances with various technical, biological and pharmacological activities [1,4-6]. For example, in agriculture, carbamates and their derivatives are used as herbicides, pesticides, defoliants, fungicides, insecticides, nematicides, bactericides and many others etc. Of particular interest are the use of these class of compounds in medicine as antitumor, antidiabetic, lowering bad

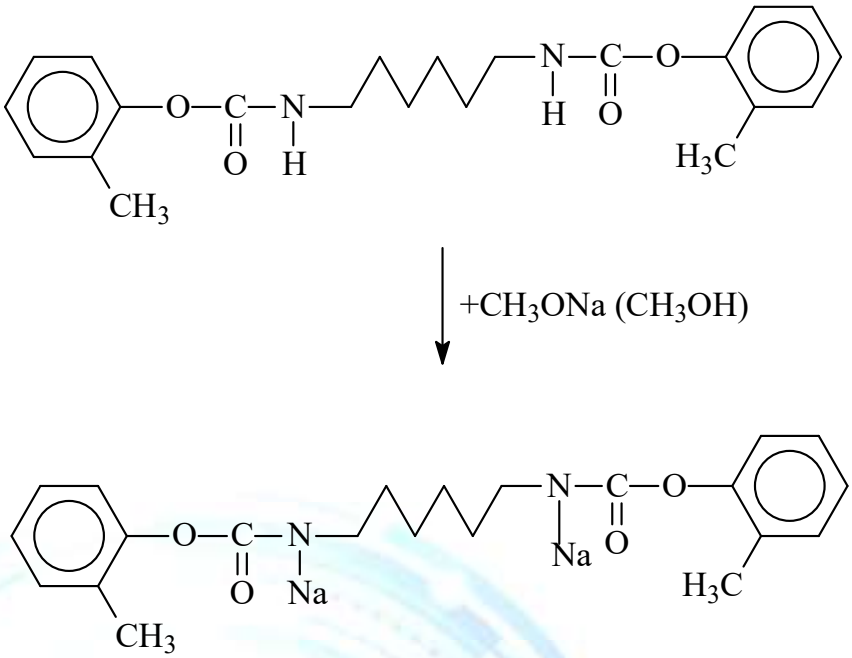
cholesterol, antiarrhythmic, anti-inflammatory and other drugs [2,3,7-12,15,17,19,24].

Due to the versatile use of bis-carbamates, the authors of this article synthesized bis-carbamates of the MEE-1,2,3 series [13,14,16,18]. Properties, parameters, structure have been studied and implemented in various areas of the chemical, oil and agricultural industries [20-23]. Continuing these studies, a resource-saving, economical, low-cost and environmentally friendly method for the synthesis of derivatives based on cresolyl carbamates was found. The purpose of this work is the synthesis of N,N'-disodium N,N' - hexamethylene bis [(ortho-cresolyl) - carbamate] i.e. MEE-1b and the study of some physical and chemical properties.

Materials and Methods. Synthesis of N,N'-disodium, N,N'-hexamethylene bis-[(ortho-cresolyl)-carbamate] i.e. MEE-1b: In 38.4 g (0.1 mol) N,N'-hexamethylene-bis-[(ortho-cresolyl)]-carbamate was mixed with 6.4 g (0.2 mol) of a concentrated solution of methyl alcohol with 0.2 mol of sodium methyl ether. The reaction mixture is stirred for 2.0 hours at a temperature of 38-45°C, the contents of the flask are transferred to a glass and water is added. The resulting precipitate is checked by TLC. After drying, a white powder is obtained; the product yield is 37.75 g (88.2% of theory).

Virtual screening of structural formulas based on "Structure-Activity" (SAR) relationship *PASS Online* http://way2drug.com/PassOnline/predict.php computer prediction program to find directions of practical use of new substances.

Results and Discussions. One of the metalation methods that can be carried out using N metalation is the replacement of hydrogen atoms in the N-H group by sodium with N′N′-hexamethylene bis-[(ortho-cresolilo)-carbamate] is subjected to directed metalation at N-H groups via CH_3ONa. N′N′-dimetalation reaction proceeds according to the following scheme:



After drying, a white powder is obtained; the product yield is 37.75 g (88.2% of theory).

For an initial study of the physicochemical parameters of the synthesized N,N'-disodium, N,N'-hexamethylene bis-[(ortho-cresolyl)-carbamate] i.e. MEE-1b, computer programs for *in silico* screening were used. To begin with, we received a MOL file of the bis-carbamate MEE-1b structure (Figure 1).

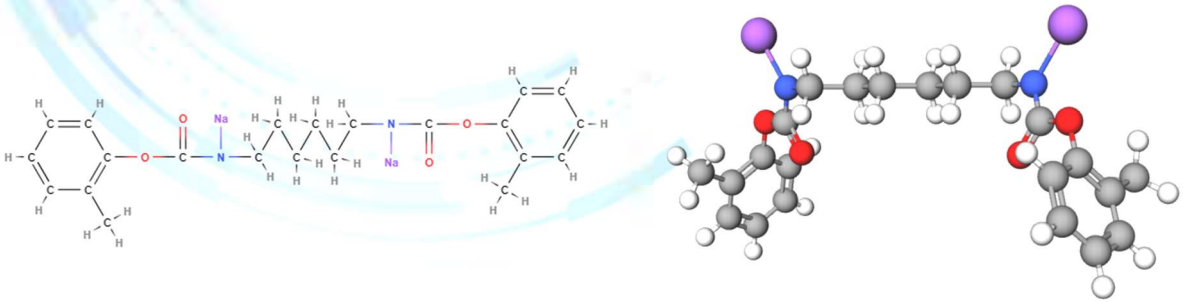


Figure 1. 2D and 3D structure of N,N'-disodium, N,N'-hexamethylene bis-[(ortho-cresolyl)-carbamate]

Next, we obtained data on elemental analysis (Table 1) and some physicochemical parameters (Table 2).

Table 1

Computer program calculations of MEE-1b bis-carbamate

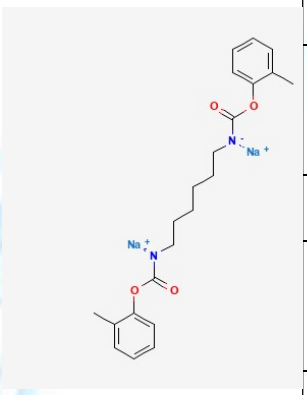
 Compound MEE-1b	Formula		$C_{22}H_{26}N_2Na_2O_4$
	Molecular mass		428.4379 u
	The number of donors of the hydrogen bond		0
	The number of hydrogen bond acceptors		4
	Percentage composition		
	C	12.0107 u × 22	61.675 %
	H	1.00794 u × 26	6.1168 %
	N	14.0067 u × 2	6.5386 %
	Na	22.989769 u × 2	10.732 %
	O	15.9994 u × 4	14.938 %

Table 2

Physicochemical parameters of MEE-1b

Property	Value	Property	Value
Molecular Formula	$C_{22}H_{26}N_2Na_2O_4$	Total Electrons	226
Empirical Formula	$C_{11}H_{13}NNaO_2$	Molecular Polarizability	37.32441 A^3

Molecular Mass	428.43127 amu	Molar Refractivity	107.75404 cm^3/mol
Monoisotopic Mass	428.16873 amu	Polar Surface Area	59.079998 A^2
Degree of Unsaturation	10	vdW Volume	418.8981 A^3
Hydrogen Bond Acceptors	6	logP	6.8299994
Hydrogen Bond Donors	0	Complexity	579.6055
Rotatable Bonds	11	-	-

The number of hydrogen bond acceptors in the MEE-1b molecule, as you can see in Tables 1 and 2, differs. Typically, hydrogen bond acceptors are oxygen, nitrogen, or fluorine atoms because they have a partial negative charge and are capable of accepting hydrogen bonds. The MEE-1b molecule contains two nitrogen atoms and four oxygen atoms, for a total of 6.

Virtual screening of structural formulas studied on PASS Online prediction program and we obtained the following predicted activities (Table 3).

Table 3

Predicted biological activity of MEE-1b - (Pa >70%)

Substance	Activities	Pa
MEE-1b	CYP2C12 substrate	0,817
	Venombin AB inhibitor	0,773
	1,4-Lactonase inhibitor	0,753
	CYP2J substrate	0,775
	Alkane 1-monooxygenase inhibitor	0,751
	Taurine dehydrogenase inhibitor	0,754
	Arginine 2-monooxygenase inhibitor	0,747
	Aspulvinone dimethylallyltransferase inhibitor	0,773
	Phobic disorders treatment	0,769
	Omptin inhibitor	0,713
	Ubiquinol-cytochrome-c reductase inhibitor	0,741
	CDP-glycerol glycerophosphotransferase inhibitor	0,730

**Note: Pa - The probability that an activity exists.*

As you can see, the substance MEE-1b can be used as an inhibitor venombin AB, 1,4-Lactonase, alkane 1-monooxygenase, taurine dehydrogenase, arginine 2-monooxygenase, aspulvinone dimethylallyltransferase, omptin, ubiquinol-cytochrome-c reductase, CDP-glycerol glycerophosphotransferase and substrate of CYP2C12, CYP2J. It can also be used to treat phobic disorders.

Conclusion. For the first time in the world, the N,N'-disodium, N,N'-hexamethylene bis-[(ortho-cresolyl)-carbamate] i.e. MEE-1b was synthesized in high yield and studied by *in silico* methods. Primary data will help reduce real and costly analyzes and will help with their implementation in any industry. For example, it has been revealed that this MEE-1b bis-carbamate can be used as an inhibitor and substrate in pharmacomedicine. Accordingly, these predictions need to be studied in vitro and in vivo studies.

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