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STUDY OF THE REACTION OF PRODUCTS OF N-CHLOROACETYLATION OF ISOMERIC AMINOPHENOLS WITH PSEUDOEPHEDRINE

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Аннотация: Мақолада псевдоэфидрин алколоидининг изомер аминофенолларни N- холрацителаш маҳсулотлари билан реакцияларини ўрганиш натижалари келтирилган. Реакцияларнинг боришига таъсир этувчи омиллар тадқиқ этилган.

Калит сўзлар: хлорацетилхлорид, псевдоэфидрин, 2-хлоро-N-(2-гидроксифенил)ацетамид, 2-хлоро-N-(3-гидроксифенил)ацетамид.

Аннотация: В статье представлены результаты реакции продуктов N-хлорацетилирования изомерных аминофенолов с алколоидом псевдоэфедрин. Исследованы факторы, влияющие на протекание реакции.

Ключевые слова: хлорацетилхлорид, псевдоэфидрин, 2-хлоро-N-(2-гидроксифенил)ацетамид, 2-хлоро-N-(3-гидроксифенил)ацетамид.

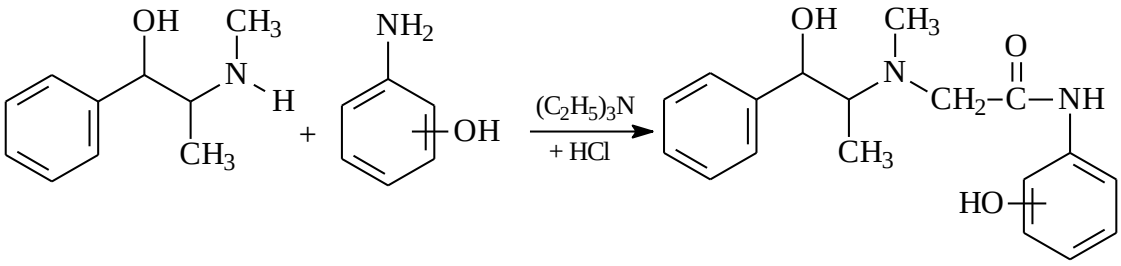
Abstract: The article presents the results of the reaction of the products of N-chloroacetylation of isomeric aminophenols with the alcoloid pseudoephedrine. The factors influencing the course of the reaction have been investigated.

Keywords: chloroacetyl chloride, pseudoephedrine, 2-chloro-N- (2-hydroxyphenyl) acetamide, 2-chloro-N- (3-hydroxyphenyl) acetamide

Introduction. As a part of the program to develop new antifungal agents, a series of fluconazole analogues were designed and synthesized wherein one of the triazole moieties in fluconazole were replaced with 2H-1,4-benzothia- zin-3(4H)-one or 2H-1,4-benzoxazin-3(4H)-one moiety. The new chemical entities thus synthesized were screened against various fungi and they were observed that the result compounds are potent inhibitors of Candida strains [1]. Studied describes the synthesis of 2-(9-oxoacridin-10(9H)-yl)-N-phenyl acetamide derivatives through condensation of 2-chloro-N-phenyl acetamides with acridone molecule. All the

synthesized compounds were screened for their anti-cancer activity against three diverse cell lines including breast (MCF-7), cervical (HeLa) and lung adenocarcinoma (A-549) employing standard MTT assay [2]. Three series of novel AHL analogs were synthesized and evaluated for their in vitro cytotoxic activity against four human cancer cell lines. The SARs investigation indicated that AHLs with a terminal phenyl group, especially those with the chalcone scaffold had remarkably enhanced cytotoxicity than those with the hydrophobic side chains [3]. A series of acetaminophen (APAP) analogs, 2-(1,1-dioxido-3-oxo-1,2-benzisothiazol-2-(3H)-yl)-N-(4-hydroxyphenyl)alkane-carboxamides, bearing a heterocyclic moiety linked to the p-acylaminophenol fragment, were prepared in a general project to develop APAP analogs with modulated pharmacokinetic profiles. Unexpectedly, the products described maintained the in vivo analgesic profile, while the characteristic hepatotoxicity of APAP was consistently reduced. One of the products, it was studied in vivo in comparison with APAP. Compound 5a displayed an analgesic efficacy comparable to that of APAP [4,5]. Some cancers, like acute myeloid leukemia (AML), they use reactive oxygen species to endogenously activate cell proliferation and angiogenic signaling cascades. Thus many cancers display increases in reactive oxygen like hydrogen peroxide concentrations. To translate this finding into a therapeutic strategy we designed new hydrogen peroxide-activated agents with two key molecular pharmacophores. The first pharmacophore is a peroxide-acceptor, the second is a pendant amine [6,7]. Additionally, other work describes the synthesis of few hydroxylated amide derivatives as melanogenesis inhibitors. In vitro, in vivo and computational studies proved that compound is a highly potent melanogenesis inhibitor compared to standard kojic acid. [8,9].

Analysis and results. The reaction of chlorocytolation of isomeric aminophenols with chloroacetyl chloride, N-chloroacetyl products were obtained [10]. The reactions of nucleophilic substitution of the obtained products with the alcoloid pseudoephedrine were carried out and also the role of solvents in the reaction was studied.



Obtained products:

The used solvents were DMF, acetone, 1,4-dioxane, which are widely used in nucleophilic assays. Triethylamine was used as a proton acceptor. The reactions were carried out at the boiling point of the solvents acetone and 1,4-dioxane. There are two different temperatures in DMF 20^0C, 40^0C. The table shows the results of the behavioral reactions**.**

Results of the reaction of N-chloroacetyl products of isomeric aminophenols with the alcoloid pseudoephedrine.

1- table

	Reaction mixture	Solvents	Reaction temperatures, ^{0}C.	The duration of the reaction, hours.	Outputs %.
1	2-chloro-N- (2-hydroxyphenyl) acetamide, pseudoephedrine, triethylamine. 1:1:1.	Acetone	56	6	70
2		1,4- Dioxan	101	4	72
3		DMF	20	5	75
4		DMF	40	3	75
5	2-chloro-N- (3-hydroxyphenyl) acetamide, pseudoephedrine, triethylamine. 1:1:1.	Acetone	56	5	92
6		1,4- Dioxan	101	2	90
7		DMF	20	3	94
8		DMF	40	1	90
9	2-chloro-N- (4-hydroxyphenyl) acetamide, pseudoephedrine, triethylamine. 1:1:1.	Acetone	56	4,5	91
10		1,4- Dioxan	101	2	89
11		DMF	20	2,5	96
12		DMF	40	1	95

It was known that the yields of the reaction with 2-chloro-N- (2-hydroxyphenyl) acetamide are lower than the rest due to the side reaction of intramolecular rearrangement in the presence of polar solvents.

Result and discussion. In a round-bottomed flask equipped with a reflux condenser, the reagent was added: chloroacetyl product: pseudoephedrine: triethiamine 1: 1: 1 mol ratio. The reactions with 1,4-dioxane and acetone solvents were carried out at the boiling point of the solvents. With a solvent DMF the reactions were carried out at temperatures of 200 C and 400 C. The reaction times were verified by TLC every 10 minutes. The reaction products with 1,4-dioxane and acetone were purified by the following methods. The solvents were evaporated from the reaction mixture, and the reaction products were recrystallized with absolut ethanol. To purify the reaction product with DMF, the reaction mixture was added with water and extracted twice with chloroforum. Chloroforum was evaporated and the reaction products were obtained.

Conclusion. Carried out the reactions of pseudoephedrine with the products of the chloro-citlation of isomeric aminophenols: 2-chloro-N- (2-hydroxyphenyl) acetamide, 2-chloro-N- (3-hydroxyphenyl) acetamide, 2-chloro-N- (4-hydroxyphenyl) acetamide. The effect of the reaction solvents has been studied. The structure of the products obtained has been proven by IR and Mass spectroscopy.

References:

[1]. Hanumant B. Boratea and others. Fluconazole analogues containing 2H-1,4-benzothiazin-3(4H)-one or 2H-1,4-benzoxazin-3(4H)-one moieties, a novel class of anti-Candida agents. // Bioorganic & Medicinal Chemistry Letters 20 (2010) 722–725.

[2]. Rajesh Kumara and others. Synthesis, cytotoxic study and docking based multidrug resistance modulator potential analysis of 2-(9-oxoacridin-10(9H)-yl)-N-phenyl acetamides. // European Journal of Medicinal Chemistry 80 (2014) 83-91.

[3]. Jing-Li Ren and others. Discovery of novel AHLs as potent antiproliferative agents. // European Journal of Medicinal Chemistry 93 (2015) 321-329.
[4]. Anthony L. Vaccarino and others. Synthesis and in vivo evaluation of non-hepatotoxic acetaminophen analogs. // Bioorganic & Medicinal Chemistry 15 (2007) 2206–2215.
[5]. Anish K. Vadukoot and others. Design of a hydrogen peroxide-activatable agent that specifically targets cancer cells // Bioorganic & Medicinal Chemistry 22 (2014) 6885–6892.
[6]. Qamar abbas and others. Development of highly potent melanogenesis inhibitor by in vitro, in vivo and computational studies. // Drug Design, Development and Therapy 2017:11 2029–2046.
[7]. Liu X.H., Cui P., Song B.A., Bhadury P.S., Zhu H.L., Wang S.F. Synthesis, structure and antibacterial activity of novel 1-(5-substituted-3-substituted-4,5-dihydropyrazol-1-yl)ethanone oxime ester derivatives. // Bioorgan. Med. Chem. 2008, 16, -P. 4075–4082.
[8]. Riyadh S.M., Farghaly T.A., Abdallah M.A., Abdalla M.M., El-Aziz M.R. New pyrazoles incorporating pyrazolylpyrazole moiety: Synthesis, anti-HCV and antitumor activity. // Eur. J. Med. Chem. 2010, 45, -P. 1042–1050.
[9]. Huang K.H., Veal J.M., Fadden P.R., Rice J.W., Eaves J., Strachan J.P., Barabasz A.F., Foley B.E., Barta T.E., Discovery of Novel 2-Aminobenzamide Inhibitors of Heat Shock Protein 90 as Potent, Selective and Orally Active Antitumor Agents. // J. Med. Chem. 2009, 52, -P. 4288–4305.
[10]. A.K. Abdushukurov, M.S. Yusufov Study of the reaction of isomeric aminophenols with chloroacetyl chloride // Universum: Technical sciences: electron. nauchn. jurn. 2020. № 3 (72). URL: http://7universum.com/ru/tech/archive/item/9096