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JAUNU 2-HETEROARIL-3,5,6-TRIHLOR-1,4-BENZOHINONU SINTĒZE

Promocijas darba kopsavilkums

SYNTHESIS OF NEW 2-HETEROARYL-3,5,6-TRICHLORO-1,4-BENZOQUINONES

Summary of Doctoral Theses

Zinātniskie
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ABSTRACT

Synthesis of new 2-heteroaryl-3,5,6-trichloro-l,4-benzoquinones. Gulbis J., supervizors: Dr.habil.chem., prof. R. Valters, Dr. chem. G. Karlivāns. Dissertation, 74 pages, 2 tables, 118 literature references, 1 appendix. In Latvian.

2,5-DIHYDROXY-3,4,6,7-TETRACHLORO-2,3-DIHYDROBENZO[b]FURAN, HETEROARYLSUBSTITUTED TRICHL0R0-l,4-BENZ0QUIN0NES, THIO-SEMICARBAZIDE, SUBSTITUTED DERIVATIVES OF THIOSEMICARBAZIDE

The aim of present work is to find new ways of the synthesis of heteroarylsubstituted trichloro-l,4-benzoquinones, where heteroarylsubstituent would be related to benzo-quinone. The reactions of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with thiosemicarbazide and miscellaneous substituted derivatives of thiosemicarbazi-de were investigated.

Introduction

This work is devoted to the synthesis of novel derivatives of heteroarylsubstituted 1,4-benzoquinones.

Quinones and their derivatives provoke scientific interests as reversible systems of oxidation-reduction processes. The studies of such processes are important for better understanding of the functioning of living organisms, as well as the structure of biological materials. In nowadays, safety and high efficiency are the main requirements for pharmaceutical products. The search for new products includes the extraction of active compounds from plants that have been known for centuries to possess healing properties. In this way many highly active quinones-containing natural products have come into medical practice. Such drugs give evidence of the importance of benzoquinones in biochemical processes proceeding in plants and animals.

For a long time heterocyclic derivatives of 1,4-benzoquinones have caught attention of pharmaceutists, because series of novel potentially very perspective medicines (mitomicines, asterriquinones) are discovered among them.

Material scientists and physicists are continuously searching for materials possessing unique physical and electrochemical properties. Since 1973, when the first organic compound (radical cation salt of tetrathiafulvalene) possessing electrical conductivity was discovered, the search for novel electroconducting organic materials is still in progress. The derivatives of fulvalenes (as electron donor) and tetracyanoquinodimethane or another quinoide compound possessing strong electronacceptor properties (as electron acceptor) are commonly used as radical ions. The compounds where both components are connected covalently and form triad of A-D-A or D-A-D types (A - acceptor group; D - donor group) have drawn attention recently. 1,4-Benzoquinone is used as electronacceptor moiety in this type of compounds. These compounds are possessing interesting electrophysical properties.

The aim of the work

At the beginning the main aim of the work was to synthesize a compound bearing heterocycle as the electrondonor part and trichloro-l,4-benzoquinone as the electronacceptor moiety in a single molecule. The methodology developed at Riga Technical Uni-

versity was used for synthesis of this type of compounds. Up to now the reactions of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with various thio- and seleno-ureas were investigated leading to the formation of 2-amino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)thiazoles and selenazoles. These hydroquinone group containing products were subsequently oxidized, and the corresponding (2-aminothiazol-5-yl)- and (2-amino-selenazol-5-yl)substituted trichloro-l,4-benzoquinones were obtained.

The aim of present work was to find new ways of the synthesis of heteroarylsubstituted trichloro-l,4-benzoquinones containing other heterocycles. Therefore, we investigated the reactions of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with thiosemicarbazide and various substituted derivatives of thiosemicarbazide.

Conclusions

1. In the reactions of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with the unsubstituted and variously substituted thiosemicarbazides recyclization proceeds and various 2-heteroarylsubstituted 3,5,6-trichlorohydroquinones form. The structure of heterocycle in the obtained 2-heteroaryl-3,5,6-trichlorohydroquinone depends on the reaction conditions and on substituents in thiosemicarbazide:

a) the corresponding 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)substituted 2-(isopropylidenhydrazino)thiazole and 2-(isopropylidenhydrazino)-3-phenyl(or methyl)thiazole hydrochlorides form as the major products in the reactions of unsubstituted or 4-monosubstituted thiosemicarbazide in acetone solution;

b) 3-phenylamino-5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-2-iminothiazoline hydrochloride form in the reaction with 1-phenylthiosemicarbazide in acetone, but in ethanol - 2-amino-4-phenyl-6-(2,5-dihydroxy-3,4,6-trichlorophenyl)-4H-1,3,4-thiadiazine and the derivative of 2-aminothiazole as side product were formed. The formation of the last product could be explained by the cleavage of N-N bond;

c) 3-dialkylamino-4-(2,5-dihydroxy-3,4,6-trichlorophenyl)pyrazoles form in the reaction with 4,4-dialkylthiosemicarbazides as the result of sulfur extrusion from the unisolated intermediate - 2-dialkylamino-6-(2,5-dihydroxy-3,4,6-trichlorophenyl)-4H-1,3,4-thiadiazine.

2. Removing of isopropylidene group and the recyclization of heterocycle to the derivative of 3-amino-2-methyl(phenyl)iminothiazoline hydrochloride occurs with derivatives of 2-isopropylidenhydrazinothiazole and 2-isopropylidenazinothiazoline at the presence of hydrochloric acid.
3. 2-Heteroaryl-3,5,6-trichlorol,4-benzoquinones form by the oxidation of obtained 2-heteroarylsubstituted 3,5,6-trichlorohydroquinones with ferric chloride in water-dimethylformamide solution. The oxidation of hydroquinone fragment of 3-amino-2-methyl(or phenyl)iminothiazoline to the corresponding 1,4-benzoquinone is accompanied by the recyclization of iminothiazoline to the derivative of 4H-l,3,4-thiadiazine that was not observed for other heterocycles.
4. The nucleophilic substitution of chlorine atom at the 3rd position and the formation of corresponding derivatives of 3-S-substituted 2,5-dihydroxy-4,6,7-trichloro-2,3-dihyd-

robenzo[b]furan occurs in the reaction of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with triethylammonium N-methyl or N-phenyldithiocarbamates, sodium N,N-diethyldithiocarbamate and tert-butyltrithiocarbonate.

5. In acidic media the reaction products of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with triethylammonium N-methyl or N-phenyldithiocarbamates recyclize to 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-3-methyl(or phenyl)thiazoline-2-thiones which are oxidized to the corresponding derivatives of 1,4-benzoquinones. In tramolecular addition of phenolic OH group to C=C bond of thiazolinethione is obser ved in acidic media: 5-(2,5-dihydroxy-3,4,6-trichlorophenyl)-3-methylthiazoline-2-thione $\rightarrow$ 7-hydroxy- 5,6,8-trichloro- 3-methyI-2,3,3a,8b-tetrahydrothiazolo[4,5-6]-benzo[d]furan-2-thione.
6. The reaction products of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with sodium N,N-diethyldithiocarbamate [2,5-dihydroxy-3,4,6-trichloro-3-(N,N-diethyldithiocarbamoyl)-2,3-dihydrobenzo[b]furan] or tert-butyltrithiocarbonate *[S-tert*-butyl-S -(2,5 -dihydroxy- 3,4,6-trichloro-2,3-dihydrobenzo[b]furan-3-yl)trithiocarbonate cyclize in acidic media and form tricyclic compounds - perchlorate of 7-hydroxy-5,6,8-trichloro-2-(N,N-diethylamino)-3a,86-dihydro-l,3-dithiolo[4,5-6]benzo[rf|furan or 7-hydroxy-5,6,8-trichIoro-3a,8b-dihydro-l,3-dithiolo[4,5-6]benzo[d]furan-2-thione, correspondingly.
7. N,N-Dialkylhydrazides of S-(4,6,7-trichIoro-2,5-dihydroxy-2,3-dihydrobenzo[b]furan-3-yl)dithiocarbonic acid are obtained in the reactions of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan with freshly prepared N,N-dialkylhydrazinium salts of N,N-dialkylhydrazides of dithiocarbonic acid. Their cyclization in ethanol in the presence of hydrochloric acid leads to the formation of 3-N,N-dialkylamino-5-(3,4,6-trichloro-2,5-dihydroxyphenyl)thiazoline-2-thiones, but in trifluoroacetic acid tricyclic 3-N,N-dialkylamino-5,6,8-trichloro7-hydroxy-2,3,3a,8b-tetrahydrothiazolo-[4,5-6]benzo[d]ruran-2-thiones were formed.
8. In the present work the synthetic possibilities to obtain 2-heteroaryl-3,5,6-trichloro-1,4-benzoquinones containing various heteroarylsubstituents are considerably enlar ged on the basis of 2,5-dihydroxy-3,4,6,7-tetrachloro-2,3-dihydrobenzo[b]furan's re actions with bifunctional sulfur containing nucleophilic agents.

Darba rezultāti atspoguļoti sekojošās publikācijas un tēzēs:
The results of this thesis have been presented in the following publications and papers:

1. Yu. V. Gulbis, M. F. Utinan, G. A. Karlivan, R. E. Valter - Preparation of 3- di-alkylamino-4-(3,5,6-trichloro-l,4-benzoquinon-2-yl)pyrazoles. -*Chem. Het. Comp.*, 1992, 28, pp. 357-358.
2. M. F. Utinan, Yu. V. Gulbis, R. E. Valter, G. A. Karlivan - Preparation of 3-sub-stituted 2-dimethylamino-5-(3,5,6-trichloro-l,4-benzoquinon-2-yl)thiazolium salts. -*Chem. Het. Comp.*, 1992,28, pp. 361-362.
3. Yu. V. Gulbis, R. E. Valter, G. A. Karlivan, M. F. Utinan - Synthesis of 3-substi-tuted 5-(3,5,6-trichloro-l,4-benzoquinon-2-yl)thiazoline-2-thiones. -*Chem. Het. Comp.*, 1994,30, pp. 99-102.
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7. J. Gulbis, R. Valters - Synthesis of 3-N,N-dialkylamino-5-(3,5,6-trichloro-l,4-benzoquinon-2-yl)thiazoline-2-thiones. - *Chem. Het. Comp.*, 2001, 37, pp. 1424-1428.

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2. R. Valters, G. Karlivans, J. Gulbis, M. Utinans, A. Bace - A general method for the synthesis of trichloro-l,4-benzoquinonylsubstituted sulfur containing he-

terocycles. —*Abstract book of the 16th International Symposium on the Organic Chemistry of Sulfur,* July 10-15, 1994, Merseburg (Germany), P.96.
3. R. Valters, G. Karlivans, J. Gulbis, M. Utinans, A. Bace - A general method for the synthesis of trichloro-l,4-benzoquinonylsubstituted heterocycles. - *Abstract book of the 15 th International Congress of Heterocyclic Chemistry,* August 6-11, 1995, Taipei (Hong Kong), P02-121.
4. R. Valters, G. Karlivans, J. Gulbis, A. Bace - Synthesis of trichloro-l,4-benzo-quinonylsubstituted heterocycles. -*Abstract book of the 18th International Symposium on the Organic Chemistry of Sulfur,* July 13-18, 1998, Florence (Italy), POC-11,p.83.
5. R. Valters, G. Karlivans, J. Gulbis, N. Batenko - Synthesis of trichloro- 1,4-benzo-quinonylsubstituted heterocycles and related compounds. -*Abstract book of the 17th International Congress of HeterocyclicChemistry,* August 1-6, 1999, Vienna (Austria), PO-279.
6. R. Valters, G. Karlivans, J. Gulbis, A. Bace - Synthesis of novel trichloro-1,4-benzoquinonylsubstituted heterocycles. - *Phosphorus, Sulfur and Silicon,* 1999, **153&154,** pp. 411-412.
7. R. Valters, J. Gulbis, N. Batenko, G. Karlivans- Synthesis of trichloro-l,4-benzo-quinonylsubstituted 3-dialkylaminothiazoline-2-thiones and related heterocycles. -*Abstract book of the 20th International Symposium on the Organic Chemistry of Sulfur,* July 14-19,2002, Northern Arizona University, Flagstaff, Arizona (USA), PR-1.