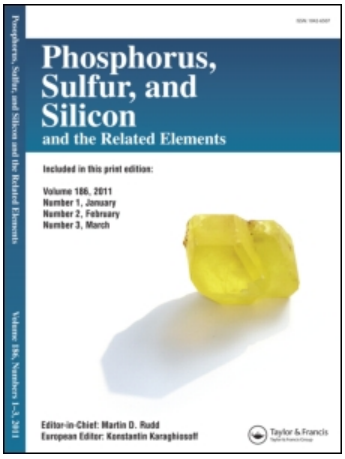

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Młochowski, Jacek , Kloc, Krystian , Syper, Ludwik and Inglot, Anna D.(1991) 'RECENT DEVELOPMENTS IN THE CHEMISTRY AND BIOLOGY OF DISELENIDES, BENZISOSELENAZOLONES AND SELENINIC ACIDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 59: 1, 267 — 270
To link to this Article: DOI: 10.1080/10426509108045739
URL: http://dx.doi.org/10.1080/10426509108045739

Phosphorus, Sulfur, and Silicon, 1991, Vol. 59, pp. 267-270
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RECENT DEVELOPMENTS IN THE CHEMISTRY AND BIOLOGY OF DISELENIDES, BENZISOSELENAZOLONES AND SELENINIC ACIDS

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Abstract Syntheses of various groups of organoselenium compounds such as aryl and heteroaryl diselenides (1), bis(2-carbamoyl)phenyl diselenides (2), 1,2-benzisoselenazol-3(2H)-ones (3), their 1-oxides (4) and seleninic acids (5) are reported. Some of them manifest potent biological activity as immunomodulators (compounds 1-3) and cytostatics (compounds 5)

INTRODUCTION

In recent decade many exciting research results indicated that selenium can influence the mammalian metabolism. A number of selenium compounds, particularly organoselenium ones, were reported as potentially useful chemotherapeutic agents. Several examples of anti-infective, anticancer and antiinflammatory agents were reported.[1-5] Working on chemistry and biology of the synthetic immunostimulants, we pointed out that, although numerous compounds stimulating immunological response in mammalia have been known, only a few of them are effective in human cells.[6,7] The work presented here was inspired with information that some of benzisoselenazolones (ebselen), 2,2--diselenobis(benzamides) and carbamoylphenylselenylyl sulfides, exhibit the glutathione peroxidase-like activity[3-5] and with report that other oxidase, namely galactose oxidase induced interferon.[8] It prompted us to study

chemistry and biology of the aromatic and azaaromatic diselenides (1,2) benzisoselenazolones (3), their 1-oxides (4) and seleninic acids (5) and the results obtained are briefly reported in this paper.

RESULTS

Aromatic and azaaromatic diselenides 1 were synthesized from haloarenes, haloazines or diazonium derivatives according to the general method elaborated earlier in our laboratory.[9] It was based on the nucleophilic substitution of the halogen atom or diazonium ion with the diselenide group by the action of lithium diselenide, formed in situ from elemental selenium and lithium in the presence diphenylacetylene as catalyst.

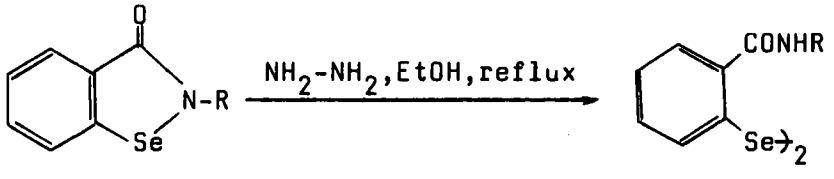
$$2\ Ar\text{-}X \xrightarrow[\text{or/and HMPT}]{Li_2Se_2,\ THF} Ar\text{-}SeSe\text{-}Ar + 2\ LiX$$

1 32-78%

Ar = p-C_6H_4-Y (Y=$COCH_3$,$CONH_2$,$CONHC_{12}H_{25}$,$CONHC_{18}H_{37}$,COOH), 2-, 3-pyridyl, 2-(6-methylpyridyl), 2-, 3-quinolyl

X = Cl, Br, $N_2^{\oplus}$

N-Substituted bis(2-carbamoyl)phenyl diselenides 2 were obtained in high yields by the reductive ring cleavage of 1,2-benzisoselenazol-3(2H)-ones 3 with hydrazine.

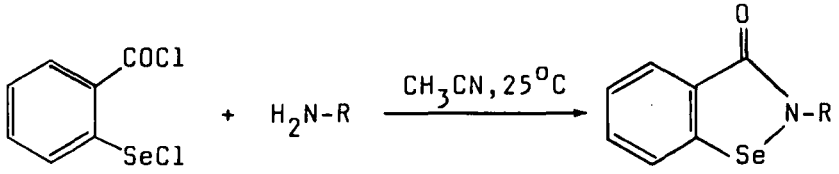


3 2 71-100%

R = H, alkyl, aryl, 2-, 3-pyridyl, 2-pyrimidynyl, acetyl

Studying the reaction of 2-(chloroseleno)benzoyl chloride with various compounds having amino group, we found that

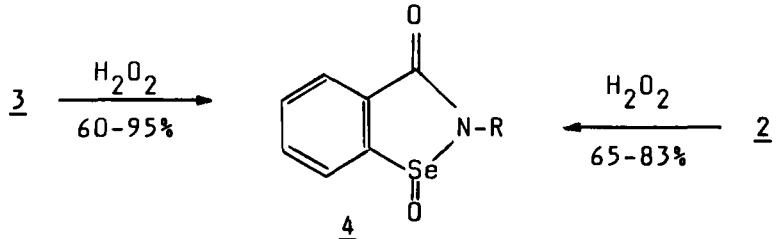
most of them reacted in usual way giving benzisoselenazol-3(2H)-ones (3) although some exception were observed (e.g. formation of 3H-2,1-benzoxaselenolones from 8-aminoquinolines).



3 62-96%

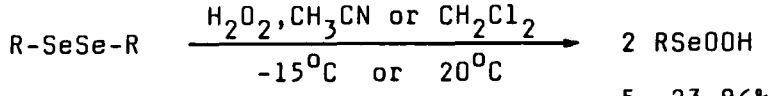
R = H, alkyl, aryl, azaaryl, carboxyalkyl, carboxamid, acetyl.

1,2-Benzisoselenazol-3(2H)-one 1-oxides (4) were obtained in two alternative ways by the oxidation of compounds 3 or by oxidative cyclisation of diselenides 2.



4

It was observed that oxidative cyclisation tooks place only when aryl diselenides were o-substituted with the carboxamide group or with its precursor. In other cases, areneseleninic acids were formed which could be subsequently oxidized to peroxyseleninic acids when excess of hydrogen peroxide was used. Alkyl diselenides were smoothly oxidized to alkaneseleninic acids 5 using stoichiometric amount of 30% hydrogen peroxide according to the method reported earlier.[10]



5 23-96%

R = alkyl, aryl

The ability to induce cytokines, such as interferon gamma (IFN-γ) and tumor necrosis factor (TNF) in human peripheral blood leucocytes of compounds synthesized was established. Some of then, particularly diselenides 1,2 2-(6-methylpyridyl) diselenide, bis[2-(N-phenylcarbamoyl)] diselenide and its pyridine analog gave maximal response TNF$>$500 U$\cdot$ml^{-1} and IFN$>$300 U$\cdot$ml^{-1} which made them the most potent known low-molecular-weight immunomodulators. Cytotoxicity of these compounds was also investigated and it was revealed that acids 5, particularly methaneseleninic acid and buthaneseleninic acid manifested high activity against experimental tumor KB cells (ID_{50}= 3.6$\cdot$10^{-3} and 11$\cdot$10^{-3} μM$\cdot$ml^{-1}).

ACKNOWLEDGEMENTS

This work was supported by the Polish Academy of Sciences Grants CPBP 01.13 and CPBR 3.13.

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