BIOACTIVE COMPOUNDS: BIOTRANSFORMATION AND BIOLOGICAL ACTION

Edited by I.N. Todorov, G.E. Zaikov, and I.A. Degterev

BIOACTIVE COMPOUNDS: BIOTRANSFORMATION AND BIOLOGICAL ACTION

Edited by I.N. Todorov, G.E. Zaikov, and I.A. Degterev Art Director: Christopher Concannon

Graphics: Elenor Kallberg and Maria Ester Hawrys Book Production: Michael Lyons, June Martino,

Tammy Sauter, and Michelle Lalo

ISBN 1-56072-075-1

Bioactive compounds: biotransformation and biological action / I.N. Todorov, G.E. Zaikov and I.A. Degterev, editors.

p. cm.

Includes bibliographical references and index.

ISBN 1-56072-075-1:\$87.00

- 1. Bioactive compounds--Metabolism.
- 2. Biotransformation (Metabolism) I. Todorov, I.N.
- II. Zaikov, Gennadii Efremovich. III. Degterev, I.A.

QP517/B44B56 1993 93-2339

615'.7--dc20 CIP

© 1993 Nova Science Publishers, Inc. 6080 Jericho Turnpike, Suite 207 Commack, New York 11725 Tele. 516-499-3103 Fax 516-499-3146 E Mail Novasci1@aol.com

All rights reserved. No part of this book may be reproduced, stored in a retrieval system or transmitted in any form or by any means: electronic, electrostatic, magnetic, tape, mechanical, photocopying, recording or otherwise without permission from the publishers.

Printed in the United States of America

PREFACE

Advances made in chemotherapy are due to the operation of mechanisms of drug action at molecular and cellular levels. Biotransformation is one of the most significant aspects of mechanisms of drug action, it involves any drug-induced alterations occurring in organisms, cells, and model systems, including enzymatic transformations, namely metabolism, as well as spontaneous chemical reactions which are not mediated by enzymes. Biotransformation may result in activation or inactivation of different systems. In both cases, biotransformation may lead to an increase or decrease in therapeutic and/or adverse effects. In this context a search for ways of influencing or regulating the drug biotransformation seems to be essential.

The book includes a number of reviews covering the studies biotransformation of different classes of synthetic, natural, and endogenous compounds. Special attention is given, where possible, to the biological consequences of biotransformation reactions and to the possibility to affect biotransformation by showing more favorable pharmacological effects.

The choice of subjects of the analysis is due to the interest shown by the authors of the present manuscript and reflected the directions of investigations made in the Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics, Russian Academy of Sciences.

A major portion of the drugs considered here have been synthesized, tested or approved for use in Russia and we would like to attract the attention of a wider range of researchers and investigators to the study and application of the compounds in question.

Editors

Prof. Igor N. Todorov, Dr.Sci. (Molecular Biology), Head of Laboratory

Prof. Gennadii E. Zaikov, Dr.Sci. (Chemistry), Head of Laboratory

Igor A. Degterev, Dr. Sci. (Biochemical Pharmacology), Head of Research Group

CONTRIBUTORS

- Igor A. Degterev, Dr.Sci. (Biochemical Pharmacology), Head of research group.

 Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics Academy of Science, RUSSIA, 117334 Moscow, Kosygina 4, RUSSIA.
- V.S. Dombrovsky, Ph.D. (Organic Chemistry), Senior Researcher. Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics Academy of Science, RUSSIA, 117334 Moscow, Kosygina 4, RUSSIA.
- Elena Yu. Leonova, Researcher (Biochemical Pharmacology).

 Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics Academy of Science, RUSSIA, 117334 Moscow, Kosygina 4, RUSSIA.
- Victor G. Kartsev, Dr.Sci. (Organic Chemistry), Head of Laboratory.

 Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics Academy of Science, RUSSIA, 117334 Moscow, Kosygina 4, RUSSIA.
- Victor G. Sharf, Researcher (Biochemical Pharmacology).

 Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics Academy of Science, RUSSIA, 117334 Moscow, Kosygina 4, RUSSIA.
- Nadezhda K. Tatarskaya, Researcher (Biochemical Pharmacology).
 Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics Academy of Science, RUSSIA, 117334 Moscow, Kosygina 4, RUSSIA.
- Igor N. Todorov, Prof. Dr.Sci. (Molecular Biology), Head of Laboratory.

 Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics Academy of Science, RUSSIA, 117334 Moscow, Kosygina 4, RUSSIA.
- Gennadii E. Zaikov, Prof. Dr. Sci. (Chemistry), Head of Laboratory.

 Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics Academy of Science, RUSSIA, 117334 Moscow, Kosygina 4, RUSSIA.

All contributors work in Department of Kinetics of Chemical and Biological Processes, Institute of Chemical Physics of RUSSIA, Academy of Sciences, 117334 Moscow, Kosygina 4, RUSSIA.

Contents

Preface	X1
Contributors	111

Mechanism of Antistress and Anabolic Actions of Eleutherococcus Senticosus Maximum Extracts The Key Role of Biogenesis Modulation

The Key Role of Biogenesis Modulation of Corticosteroids

I.N. Todorov

Int	roductio	n	1
		al and Physicochemical Properties	
	of Eleu	therococcus	3
	1.1	Chemical Composition of Eleutherococcus	
		Extracts. Structure of Eleutherosides	3
	1.2	Conformation of Eleutherosides	5
	1.3	Fluorescence-Absorption Characteristics	
		of Eleutherosides	9
2.	Pharma	acological Properties of Eleutherococcus	
		S	12
	2.1	Eleutherococcus, A Preventative Agent	12
	2.2	- CO1 1 1 0	15
	2.3	Decrease in Morbidity Rates	15
	2.4		16
3.	Biologi	cal Activity of Eleutherococcus Extract	
Ο.	and Its	Eleutherosides	17
	3.1	Systemic Anabolic Effect	17
	3.2	Biosynthesis of Proteins and Nucleic Acids	18
	3.3	Immunogenesis	20
	3.4	Interferon Biosynthesis	21
	3.5	Carbohydrate Metabolism	22
	3.6	Lipid Metabolism	28
	3.7	Antimutagenic and Antiteratogenic Effects	28
	3.8	Antistress Action	30
	0.0		

4.	Study o	f the Pharmacokinetics and the Mechanism	
		n of Eleutherococcus Glycosides	32
	4.1	Incorporation of Tritium in Eleutheroside B.	
		Kinetics of its Accumulation and Elimination	
		from the Animal Body	32
	4.2	Distribution of Eleutheroside B in Organs	
		and Subcellular Fractions	38
	4.3	Metabolism and Kinetics of Binding to Blood	
		Serum Components	44
	4.4	Effect of Extract and Individual Glycosides	
		on Protein Biosynthesis in vitro	50
	4.5	In Vivo Effects of Eleutherococcus Extract	
		on Protein Metabolism and Biosynthesis	
		in Some Organs and Tissues	56
	Referen	ces	67
	Riolo	gical Activity of Diazoketones.	
F	an Ana	alytical Review of The Literature	
		From 1954 to 1989	
	Victo	or G. Kartsev and V.S. Dombrovsky	
	V ULL		
T	J -4!		79
		on	
Int	Monodi	azoketones	79
	Monodi 1.1	nazoketones	79 79
	Monodi 1.1 1.2	nazoketones Biological Activity	79 79 85
	Monodi 1.1 1.2 1.3	azoketones Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones	79 79 85 87
	Monodi 1.1 1.2 1.3 1.4	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis	79 85 87
	Monodi 1.1 1.2 1.3 1.4 1.5	n	79 85 87 89
	Monodi 1.1 1.2 1.3 1.4 1.5 1.6	Diazoketones	79 85 87 89 90
	Monods 1.1 1.2 1.3 1.4 1.5 1.6 1.7	Diazoketones Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Teratogenesis Mechanism of Resistance	79 85 87 89 90
	Monodi 1.1 1.2 1.3 1.4 1.5 1.6	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Teratogenesis Mechanism of Resistance Transport of Diazoketones into a Cell	79 85 87 89 90
	Monods 1.1 1.2 1.3 1.4 1.5 1.6 1.7	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Teratogenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport	
	Monodi 1.1 1.2 1.3 1.4 1.5 1.6 1.7	Diazoketones Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Teratogenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes	
	Monods 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	Diazoketones Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Teratogenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes Effect of Diazoketones on Cell Adhesion	
	Monods 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Teratogenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes Effect of Diazoketones on Cell Adhesion Effect of Diazoketones on the Immunosystem	
	Monods 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Teratogenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes Effect of Diazoketones on Cell Adhesion Effect of Diazoketones on the Immunosystem Inhibition of Enzymes in vitro and in vivo	
	Monodi 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes Effect of Diazoketones on Cell Adhesion Effect of Diazoketones on the Immunosystem Inhibition of Enzymes in vitro and in vivo by Diazoketone Inhibition of Purines	
	Monodi 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes Effect of Diazoketones on Cell Adhesion Effect of Diazoketones on the Immunosystem Inhibition of Enzymes in vitro and in vivo by Diazoketone Inhibition of Purines de nova Synthesis	
	Monodi 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes Effect of Diazoketones on Cell Adhesion Effect of Diazoketones on the Immunosystem Inhibition of Enzymes in vitro and in vivo by Diazoketone Inhibition of Purines	
	Monods 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Teratogenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes Effect of Diazoketones on Cell Adhesion Effect of Diazoketones on the Immunosystem Inhibition of Enzymes in vitro and in vivo by Diazoketone Inhibition of Purines de nova Synthesis Diazoketones as Inhibitors of Some Enzymes	
	Monods 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	Biological Activity Antitumor Activity Pharmacokinetics of Diazoketones Cancerogenesis Mutagenesis Mechanism of Resistance Transport of Diazoketones into a Cell and its Relation to the Active Transport of Amino Acids through Cell Membranes Effect of Diazoketones on Cell Adhesion Effect of Diazoketones on the Immunosystem Inhibition of Enzymes in vitro and in vivo by Diazoketone Inhibition of Purines de nova Synthesis Diazoketones as Inhibitors of Some Enzymes	

II.	Bisdiaz	oketones	107
	II.14	Mutageneous Properties	
		of Bisdiazoketones	.107
	II.15	Toxicity and Antitumor Activity of Diazine	.109
Co	nclusion	1S	.119
Rei	ferences	,	.119

Kinetics and Mechanisms of Microsomal Metabolism of Nitroheterocyclic Compounds-5Nitrofuran and 1-Nitroacridine Derivatives and Relationship with Biological Activity of These Compounds

Igor A. Degterev, Nadezhda K. Tatarskaya and Gennadii E Zaikov

Introduction	155
Biological Activity of 5-Nitrofuran and 1-Nitroacridine	
Derivatives and the Role of Metabolic Activation	156
Effect of the Structure of Furan and Acridine Derivatives	
on the Kinetic Parameters of their Metabolism in Liver	
and Tumor Microsomes	164
Relationship Between Biological Activity of 5-Nitrofuran	
and 1-Nitroacridine Derivatives and Their Structure	179
Mechanisms of Metabolic Transformation of 5-Nitrofuran	
and 1-Nitroacridine Derivatives in Microsomes of Liver	
and Tumor Cells	182
Differences in Xenobiotic-Metabolizing Activity	
of Microsomes of Liver and Tumor	189
Conclusion	190
References	191

Fundamental Possibilities of Modulating Microsomal Metabolism of Nitroheterocyclic Compounds: Prospects for Controlling Their Therapeutic Effects.

Igor A. Degterev, Elena Yu. Leonova, and Gennadii E. Zaikov

Introduction	201
The Effect of Ascorbic Acid (AA) and Glutathione (GSH)	
on Biological Action of NHCC	202
Effect of AA and GSH on Microsomal Metabolism	
of NHCC	204
The Effect of Blocking of NHCC Microsomal	
Metabolism in the Presence of Adrenalin	
and Related Compounds	213
Induction of Xenobiotic-Metabolizing Enzymes of Animal	
Liver by Food Antioxidant BHT Leads to the Change	
in NHCC Microsomal Metabolism	220
Conclusion	
References	226

Mechanism of Microsomal Oxidation of Adrenalin

Igor A. Degterev, Elena Yu. Leonova, and Nadezhda K. Tatarskaya

5
5
6
7
9
2
2
-

Biotransformation of Antitumor Alkylnitrosoureas

Victor G. Sharf

Introduction	257
Introduction	258
Hydrolytic Decomposition Mechanisms and Kinetics	258
Active Intermediates	2.64
Active Intermediates	265
Metabolic Transformations	266
Hydroxylation	200
Denitrosation	267
Other Metabolic Pathways	274
Acknowledgement	276
References	276

MECHANISM OF ANTISTRESS AND ANABOLIC ACTIONS OF ELEUTHEROCOCCUS SENTICOSUS MAXIMUM EXTRACTS

THE KEY ROLE OF BIOGENESIS MODULATION OF CORTICOSTERIODS

I.N. Todorov

Department of Kinetics of Chemical and Biological Processes Institute of Chemical Physics Academy of Sciences Russia, 117334 Moscow, Kosygina 4, Russia

"Such agents as ginseng (Panax) and Elutherococcus have recently aroused a great interest especially in RUSSIA. Many known clinical and experimental studies suggest that these agents produce nonspecific antistress effects. Further studies are, however, required before these assumptions receive greater recognition."

H. Selye. In: The new aspects in hormones and mechanism of their action.—Kiev: Naukova Dumka, 1977, p. 50.

INTRODUCTION

Search for an effective substitute of ginseng (Panax ginseng C.A. Mey), a celebrated medicinal agent of the ancient east, led to studies of the plants most related to ginseng among those of the same genus Araliaceae. The comparative examinations of ginseng and other Araliaceae types, which were initiated by I.I. Brekhman and his pupils as early as the mid-1950's at the Department of Pharmacology, the Far East Research Center, USSR Academy of Sciences, indicated that Eleutherococcus senticosus Maxim was the most promising substitute for ginseng. The findings that Eleutherococcus has the pharmacological potency comparable to that of ginseng as shown by some tests stimulated active studies of the action of Eleutherococcus extract and its components on the human and animal body not only in Russia, but in other countries as well. Enormous natural reserves of the plant available in the Far East, Russia, Sakhalin, Korea, Japan, and some Chinese provinces are also an important factor that contributes to the general interest in Eleutherococcus as a drug. Moreover, studies of cultured Eleutherococcus demonstrated that the plant can be grown from seeds and grafts. Eleutherococcus grows much faster than ginseng and it is more adaptable to the environment.

Great interest in this plant-derived agent was expressed at the First International Symposium on Eleutherococcus (Hamburg, 1980) and the Second International Symposium on Eleutherococcus (Moscow, 1984). These symposia

2 I.N. Todorov

were attended by Soviet investigators together with those from the USA, the UK, Bulgaria, India, Switzerland, Sweden, FRG, Yugoslavia, Korea, and Japan.

It is widely believed that Eleutherococcus belongs to a group of drugs by the general name "adaptogens." N.R. Faransworth et al. [1], Health Research Center, University of Chicago, believe that adaptogens should have three pronounced properties. The first property of an adaptogen is lack of toxicity. Eleutherococcus extracts were tested in many animal species and it was shown that the lethal dose of a dried extract given per dose was over 30 g/kg. Numerous investigations (more than 6.000 observations) of the effects of the Eleutherococcus extracts on human activity have been conducted. None of them has revealed any significant toxic effects of the agent. The second aspect of adaptogens is their nonspecific action. The ability of Eleutherococcus to artificially simulate stress under various stress conditions (heat, cold, excessive exercise, hypokinesis, etc.) and its favorable effect on various human functions (visual acuity, color differentiation, hearing, fatigability, thinking in association with motor activity, etc.) indicate a wide range of unspecific action of the drug. The third property of an adaptogen is its capacity of displaying a normalizing effect regardless of physiological abnormalities caused by damaging influences (e.g., normalization of blood pressure in patients with both elevated or lowered pressure or normalization of blood sugar levels in hyper- or hypoglycemia following Eleutherococcus treatment).

The evidence for the adaptogenic nature of Eleutherococcus extracts is vast, however, the mechanism of its adaptogenic action requires further studies. In the past 30 years, some 1,500 papers dealing with various directions in Eleutherococcus investigations have been published mainly in Russia. A wealth of knowledge of various aspects in the action of Eleutherococcus on the human body stimulated its application in medicine. The credit for introducing Eleutherococcus as an adaptogen into medical practice is given to Prof. I. Brekhman and his school [2–6].

Since the main purpose of our paper is to review the results of the studies of the mechanism of biological action of Eleutherococcus extracts and its basic active components, glycosides (or "eleutherosides" as generally called in special literature), we shall briefly outline the data on 1) chemical and physicochemical properties of eleutherosides and some of their pharmacological properties, including those on higher biological resistance of man and animals under unfavorable environmental factors, 2) on the use of the drug in preventive and clinical medicine, 3) on a wide adaptogenic spectrum of Eleutherococcus, mainly its protective properties under deteriorating ecological factors, etc., as there are detailed reviews made by I. Brekhman [5,6], I. Dardymov [7], G. Barenboim and N. Kozlova [8]. Primary emphasis will be focussed on reviewing the data on the biological activity of Eleutherococcus and its glycosides; on its total anabolic effect; impact on protein and nucleic acid biosynthesis, immunogenesis; effects on interferon biosynthesis, carbohydrate and lipid metabolism; antistress action, etc. The paper will present the complete results from a series of studies made at the

laboratory of Molecular Biology, Institute of Chemical Physics, Russian Academy of Sciences, under the guidance of the author of the present review. The studies were undertaken to examine the pharmacokinetics of eleutheroside B (the major Eleutherococcus glycoside) and the mechanism of antistress and anabolic actions of the eleutheroside and Eleutherococcus extracts on higher animals.

1. CHEMICAL AND PHYSICOCHEMICAL PROPERTIES OF ELEUTHEROCOCCUS

1.1. Chemical Composition of Eleutherococcus Extracts. Structure of Eleutherosides

A glycoside fraction was isolated from the methanol extract of the eleutherococcus root, which displayed 7 glycosides designated as eleutherosides A, B, B_1 , C, D, E, and F. The eleutherosides are in a ratio of 8:30:10:12:24:2:1. Later minor glycosides B_2 , B_3 , B_4 and others were detected. In addition to eleutheroside, the Eleutherococcus contains glucose, saccharose, starch, polysaccharides, pectin and many other compounds [7,9–15]. The majority of Eleutherococcus glycosides were isolated as crystals, which enabled the determination of their chemical structure (Figure 1). The first group (eleutherosides B, B_1 , D, E) includes glycosides having genins of an aromatic nature. Eleutheroside B was identified with syringin and represents a monoglucoside of 4- β -glucoside of sinapis alcohol.

 B_1 is a 7- α -glucoside of isofraxidine. Its aglycone is a 6-,7-,8-trioxycoumarin derivative, eleutherosides D and E are syringaresinole diglucosides, they vary in solubility in water and organic solvents and they seem to have a slightly different configuration. Figure 1 shows that eleutherosides D and E are close in structure. Eleutheroside D is known to represent a eleutheroside B dimer. This is like to apply to eleutheroside E. The scheme given below, illustrates the process of eleutheroside B dimerization:



I.L. Shamovsky et al. [16,17] suggested the mechanism of eleutheroside B dimerization which was based on the assumption that early in the reaction, two eleutherosides B are arranged by means of an enzyme or another cell matrix so that the planes of their conjugated systems coincide. There may be two cases of hydroxyl group arrangement: on either side of the plane. These different mutual

Figure 1. Structural formulas of eleutheroside A—eleutheroside A (daucosterol); B—eleutheroside B (Syringine); B₁—eleutheroside B₁ (7- α D-glycoside of isofraxidine); C—eleutheroside C (ethyl- α -D-galactoside); D—eleutheroside D (di- β -D-glycoside (-) syringaresion); E—eleutheroside E (hypothetical structure).

arrangements of hydroxyl groups are believed to be responsible for various configurations of dimerization products, i.e., eleutherosides D and E that arise from further reactions.

The second group involves eleutheroside A identified with daucosterol and eleutheroside C which is an ethyl- α -D-galactoside. As seen from Figure 1, the glycosides in question are mono- or bi-sides. The monosaccharide residues entering the side chain are terminal. All eleutherosides, except eleutheroside C, contain glucose residues, while eleutherioside C contains galactose. All the glucosides have methoxyl groups. Glycosides or their aglycones are highly labile.

The Eleutherococcus glycosides are not unique, they occur in many other plants that do not belong to the genus Araliaceae. On the other hand eleutherosides bear no resemblance to panaxosides (ginseng glycosides), though they belong to the same genus and have similar activity [7]. The principal work on the chemistry of Eleutherococcus was made in the 1960-1970's in the Russia. Later the results of these investigations were made evident by Wagner et al. [18] who, using thin-layer chromatography and high performance liquid chromatography, showed the presence of eleutherosides B₁, B, E, chlorogenic acid, β-sitosterol, carophylline, isofraxidine, syringaresinole, cesamine, ethyl ether of caffeic acid, and coniferol aldehydein Eleutherococcus extracts. Eleutheroside B was found by the authors in the Eleutherococcus root from Russia and Southern Korea, but it was absent in the plant material obtained from China. The noticeable variability in composition as indicated by N.R. Farnsworth et al. [1] may significantly affect the biological activity of Eleutherococcus extracts, which increases the need for chemical standardization of plant extracts before their biological evaluation.

1.2. Conformation of Eleutherosides

On the basis of the detailed knowledge of eleutheroside configurations (Figure 1), detected by various physical and chemical methods [9–12], I.L. Shamovsky et al. [17] theoretically calculated the conformations of eleutherosides with the method of atom—atom potentials. The choice of this method was due to the great complexity of the tested compounds, but on the other hand, the structural variety of eleutheroside molecules made their additional application and quantum chemical techniques justifiable. Thus, the Huckel method of molecular orbitals was used to calculate the length of chemical bonds and parameters for flexibility of conjugated systems, and the conformations were calculated by minimizing the energy of molecular tension in the atom—atom approximation [19].

Initial results i.e., the set of internal or external (Decartes) coordinates of all atoms of the calculated molecules, were displayed by the authors as the projections of eleutheroside molecules on two orthogonal planes. One of the projections was chosen so that it should retain most of the information about the three-dimensional structure of the molecules, i.e., the projections of atoms should be scattered over the outline plane at a maximum and not prevent from seeing the

