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Synthesis and antimicrobial and antifungal activity of derivatives of the diterpenoid isosteviol and the glycoside steviolbioside containing onium nitrogen atoms

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Abstract:

Previously unknown derivatives of the diterpenoid isosteviol and the glycoside steviolbioside containing onium nitrogen atoms were synthesized. The antimicrobial and antifungal activities of these compounds were studied.

Key words: Isosteviol, glycosides, steviolbioside, synthesis, antimicrobial and antifungal activity.

Full Text:

The main component of the glycosides from the plant *Stevia rebaudiana* Bertoni, the glycoside stevioside (I), which is used as a food sweetener [1], has hypotensive [2], insulinotropic, and antihyperglycemic [3] properties. Its hydrolysis products, i.e., the glycoside steviolbioside (II) (alkaline hydrolysis) [4] and the diterpenoid isosteviol (16-oxoent-beieran-19-oic acid) (I) (acid hydrolysis) [5] are also biologically active compounds. Compound II has hypoglycemic activity [6], while compound III has hypotensive activity [7]. Their derivatives, i.e., esters and amides of II [8, 9], as well as the lactone [10] and the mono- and diesters of III [11-13] in turn have biological activity.

We report here the synthesis of esters of compounds II and III (V-IX) containing quaternized nitrogen atoms, the addition of which should, as indicated by published data, [14, 15] confer antimicrobial activity.

Compounds V-VII were synthesized as follows. Reaction of III with excess thionyl chloride yielded the acid chloride, interaction of which with N,N-dimethylaminoethanol in C[Cl.sub.4] produced a mixture of products, chromatography of which on silica gel allowed extraction of compound IV. In the [¹H] NMR spectrum of this compound, the characteristic [16] signals from protons in the ent-beieran backbone, i.e., singlets at 0.63 ppm ([C.sub.20][H.sub.3]), 0.97 ppm ([C.sub.17][H.sub.3]), and 1.21 ppm ([C.sub.18][H.sub.3]), a doublet at 2.15 ppm ([C.sub.3][H.sub.eq]), and a doublet of doublets at 2.58 ppm ([C.sub.15][H.sub.α]), were supplemented by a multiplet at 4.6 ppm (C[H.sub.2]O) and a multiplet at 3.3 ppm (C[H.sub.2]N). The IR spectrum of compound IV contained absorption bands from the ester group (1160, 1180, 1240, and 1730 [cm.sup.-1]) along with absorption bands corresponding to the tertiary amine (2730, 2775, 2800 [cm.sup.-1]). Amine (IV) was uaternized by heating with C[H.sub.3]I, n-C[sub.3]H[sub.7]I, and PhC[H.sub.2]Br in absolute acetonitrile. In the [¹H] NMR spectra of compounds V-VII, signals from protons in the methylene group bound to the onium nitrogen atom were weakfield shifted (3.7 ppm) compared with the corresponding protons in the amine (IV) (3.3 ppm). Protons in the alkyl groups attached to the [N.sub.+] atoms of salts of V-VII also showed weakfield resonance shift (3.2 ppm).

Starting compound III was prepared by the same method [17], i.e., by acid hydrolysis of the sweetener SWETA, which is a mixture of glycosides from the plant *Stevia rebaudiana* Bertoni and the products of their enzymatic processing [18].

The product of the alkaline hydrolysis of I, i.e., glycoside II, was similarly alkylated with dibromopropane in KOH-DMSO medium [19]. The IR spectrum of the resulting bromide VIII, as compared with that of starting compound II, lacked the absorption band of the carboxyl group at 1690 [cm.sup.-1], this being replaced by absorption bands from the ester group (1726, 1237, 1200, 1170 [cm.sup.-1]), while the [¹H] NMR spectrum showed addition of a multiplet at 4.01-4.16 ppm, corresponding to the resonance of methylene protons bonded to the ester group (AB[X.sub.2] spin system). Interaction of compound VIII with triethylamine in methanol yielded a derivative of II with an onium nitrogen atom (compound IX), whose formation was indicated by the presence in the [¹H] NMR spectrum of a triplet at 1.29 ppm and a quartet at 3.05 ppm, corresponding to the resonance of the ethyl substituents at the uaternized nitrogen atom. The carbohydrate (sophorosyl) parts of the [¹H] NMR spectra of compounds VIII and IX were identical to that of the [¹H] NMR spectrum of II [9] and contained characteristic doublets from anomer protons at 4.47 and 4.53 ppm.

[ILLUSTRATION OMITTED]

CHEMICAL METHODS

IR spectra were recorded on a Bruker Vector 22 Fourier spectrometer over the range 400-4000 [cm.sup.-1]. Samples were examined as emulsions in Vaseline grease. Mass spectra were recorded using an MX-1310 instrument with an ionizing energy of 60 eV, an electron collector current of 30 μ A, and a system for direct injection of substances into the ion source at a temperature of 120[degrees]C. Ampoules and the evaporator were heated to 120-250[degrees]C. Exact ion masses were determined by comparison with reference peaks from perfluorokerosene.

Matrix-activated laser desorption/ionization (MALDI) mass spectra were obtained using a Dynamo Maldi TOF time-of-flight mass spectrometer (Finnegan, USA). [¹H] NMR spectra were recorded on Avance-600 and Bruker MSL-400 instruments. Reaction completeness and substance purity were monitored by thin layer chromatography on Silufol UV-254 plates eluted with petroleum ether and ethyl acetate (1:1). Spots were detected with iodine vapor.

Compounds I, II, and III were synthesized using previously described methods ([20], [4], and [17] respectively) and their constants were consistent with published values. The commercial sweetener SWETA was obtained from Stevia Corp. The physicochemical characteristics of newly synthesized compounds IV-IX are presented in Table 1. Elemental analysis data were consistent with calculated values. Compounds IV-IX were white or slightly yellow crystalline substances, partially soluble in water and with good solubility in organic solvents.

19-Nor-4[alpha]-(2-dimethylaminoethyloxycarbonyl)-16oxo-e"-beieran (IV). N,N-dimethylaminoethanol (0.9 ml; 8.9 mmol) was added to a solution of 0.5 g (1.4 mmol) of the acid chloride of III in absolute C[Cl.sub.4]. The reaction mix was heated at a bath temperature of 80[degrees]C for 24 h, washed with water (2 x 10 ml), and dried over Ca[Cl.sub.2]. The resulting precipitate was chromatographed on silica gel (eluted with chloroform). The IR spectrum, ν , [cm.sup.-1], was: 1160, 1180, 1240, 1730 (COO), 1740 (C=O), 2730, 2775, 2800 (C-N[(C[H.sub.3]).sub.2]). The [¹H] NMR spectrum (CD[Cl.sub.3]), δ , ppm (J, Hz), was: 0.67 (s, 3H, [C.sup.20][H.sub.3]); 0.97 (s, 3H, [C.sup.17][H.sub.3]); 1.21 (s, 3H, [C.sup.18][H.sub.3]); 2.15 (d, 1H, J 13.7, [C.sup.3][H.sub.eq]); 2.58 (dd, 1H, J 18.6, 3.7, [C.sup.15][H.sub.alpha]); 2.76 (s, 6H, N[(C[H.sub.3]).sub.2]); 13.18 (m, 2H, -C[H.sub.2]N); 4.50 (m, 2H, -OC[H.sub.2]-). The mass spectrum, m/z (MALDI), was: 389.75. [C.sub.24][H.sub.39]N[O.sub.3].

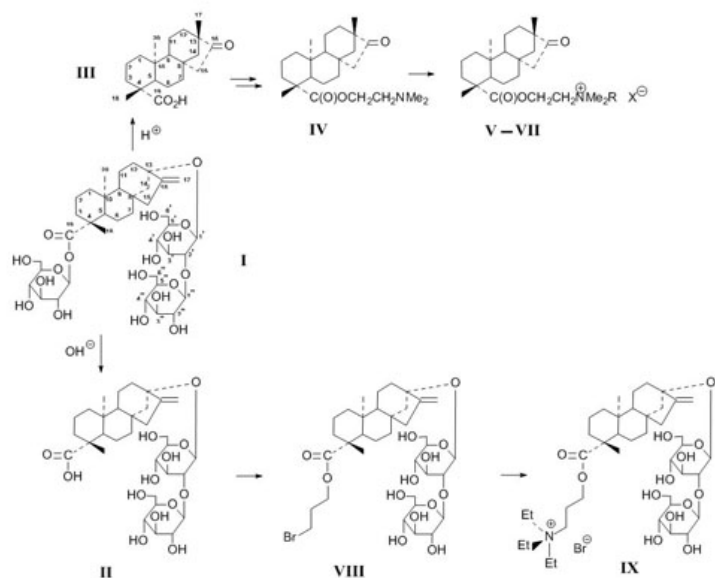
General method for preparation of quaternized derivatives of aminoketone (IV). Alkyl halide (0.04 ml; 0.6 mmol) was added to a solution of 0.24 g (0.6 mmol) of amine IV in 5 ml of absolute acetonitrile. The reaction mix was heated at a bath temperature of 80[degrees]C for 20 h. Solvent was evaporated at reduced pressure. The product was recrystallized from methanol.

19-Nor-4[alpha]-[2-(trimethylammonio)ethyloxycarbonyl]16-oxo-e"-beieran iodide (V). The IR spectrum, ν , [cm.sup.-1], was: 1128, 1140, 1730 (COO), 1735 (C=O). The [¹H] NMR spectrum (C[D.sub.3]OD), δ , ppm (J, Hz), was: 0.68 (s, 3H, [C.sup.20][H.sub.3]); 0.87 (s, 3H, [C.sup.17][H.sub.3]); 1.17 (s, 3H, [C.sup.18][H.sub.3]); 2.09 (d, 1H, J 13.7, [C.sup.3][H.sub.eq]); 2.53 (dd, 1H, J 18.6, 3.7, [C.sub.15][H.sub.alpha]); 3.16 (s, 9H, N[(C[H.sub.3]).sub.3]); 3.67 (m, 2H, -C[H.sub.2][N.sup.+]); 4.46 (m, 2H, -OC[H.sub.2]-). The mass spectrum, m/z (MALDI), was: 405 [[M-I].sup.+]. [C.sub.25][H.sub.42]N[O.sub.3].

19-Nor-4[alpha]-[2-(dimethyl-M-propylammonio)ethyloxycarbonyl]16-oxo-e"-beieran iodide (VI). The IR spectrum, ν , [cm.sup.-1], was: 1131, 1146, 1725 (COO), 1738 (C=O). The ¹H NMR spectrum (C[D.sub.3]OD), δ , ppm (J, Hz), was: 0.69 (s, 3H, [C.sup.20][H.sub.3]); 0.88 (s, 3H, [C.sup.17][H.sub.3]); 1.18 (s, 3H, [C.sup.18][H.sub.3]); 2.10 (s, 1H, J 13.7, [C.sup.3][H.sub.eq]); 2.54 (dd, 1H, J 18.6, 3.7 [C.sup.15][H.sub.alpha]); 3.11 (s, 6H, N[(C[H.sub.3]).sub.2]); 3.67 (m, 2H, -C[H.sub.2][N.sup.+]); 4.45 2H, -OC[H.sub.2]-). The mass spectrum, m/z (MALDI), was: 433 [[M-I].sup.+]. [C.sub.27][H.sub.46]N[O.sub.3].

19-Nor-4[alpha]-[2-(dimethylbenzylammonio)ethyloxycarbonyl]-16-oxo-e"-beieran iodide (VII). The IR spectrum, ν , [cm.sup.-1], was: 1133, 1148, 1213, 1716 (COO), 1730 (C=O). The [¹H] NMR spectrum (C[D.sub.3]OD), δ , ppm (J, Hz), was: 0.66 (s, 3H, [C.sup.20][H.sub.3]); 0.89 (s, 3H, [C.sup.17][H.sub.3]); 1.17 (s, 3H, [C.sup.18][H.sub.3]); 2.10 (d, 1H, J 13.7, [C.sup.3][H.sub.eq]); 2.51 (dd, 1H, J 18.6, 3.7, [C.sup.15][H.sub.alpha]); 3.07 (s, 6H, N[(C[H.sub.3]).sub.2]); 3.66 (m, 2H, -CH₂N); 4.54 (m, 2H, -OC[H.sub.2]-); 4.55 (s, 2H, -C[H.sub.2]Ph); 7.51 (m, 5H, arom.). The mass spectrum, m/z (MALDI), was: 481 [[M-Br].sup.+]. [C.sub.31][H.sub.46]BrN[O.sub.3].

19-Nor-4[alpha]-(3-bromo-w-propyloxycarbonyl)-13-O-([beta]-sophorosyl)-ent-kaurene (VIII). A mixture of 0.09 g of KOH and 15 ml of DMSO, mixed for 10 min at room temperature, was supplemented with 0.5 g (0.7 mmol) of II; mixing was continued for a further 30 min, after which 0.8 ml (7 mmol) of 1,3-dibromopropane was added dropwise and the reaction was mixed for a further 4 h. The reaction mix was then diluted with 30 ml of water and the resulting precipitate was collected by filtration, dried under reduced pressure, and recrystallized from methanol. The IR spectrum, ν , [cm.sup.-1], was: 1726 (COO), 1662 (C[H.sub.2]=), 640 (C-Br). The [¹H] NMR spectrum (CD[Cl.sub.3]), δ , ppm (J, Hz), was: 0.74 (s, 3H, [C.sup.20][H.sub.3]); 1.09 (s, 3H, [C.sup.18][H.sub.3]); 1.36-2.11 (14H, aglycone), 3.13-3.73 (m, 12H, [beta]-D-sophorosyl), 4.01-4.16 (m, C[O.sub.2]C[H.sub.2]C[H.sub.2]), 4.47 (d, 1H, J 7.6, [C.sup.1]H), 4.53 (d, 1H, J 7.6, [C.sup.1]H), 4.77 (s, 1H, [C.sup.17][H.sub.A]), 5.01 (s, 1H, [C.sup.17][H.sub.B]). The mass spectrum, m/z (MALDI), was: 785 [[M + Na].sup.+]. [C.sub.35][H.sub.55]Br[O.sub.13].



13-O-([beta]-D-sophorosyl)-19-nor-4[alpha]-[3-(triethylammonio)-n-propyloxycarbonyl]-ent-kaurene bromide (IX). A mixture of 0.17 g (0.22 mmol) of VIII bromide in 30 ml of absolute methanol was supplemented by dropwise addition of 0.04 ml (0.24 mmol) of triethylamine in 5 ml of methanol. The reaction mix was boiled with a reflux condenser for five days. Solvent and excess triethylamine were evaporated in vacuo (10 mmHg). The residue was recrystallized from methanol. The IR spectrum, ν , [cm.sup.-1], was: 1723 (COO), 1662 (C[H.sub.2]). The [sup.1]H NMR spectrum (CD[Cl.sub.3]), [delta], ppm (J, Hz), was: 0.74 (s, 3H, [C.sup.20][H.sub.3]), 1.09 (s, 3H, [C.sup.18][H.sub.3]), 1.29 (t, 9H, J 7.2, 3[N.sup.+]-C[H.sub.2]C[H.bar].sub.3]), 3.05 (q, 6H, J 7.2, 3[N.sup.+]-C[H.bar].sub.2C[H.sub.3]), 3.14-3.74 (m, 12H, [beta]-D-sophorosyl), 4.02-4.16 (m, C[O.sub.2]C[H.sub.2]C[H.sub.2]), 4.47 (d, 1H, J 7.8, [C.sup.1]H), 4.53 (d, 1H, J 7.8, [C.sup.1]H), 4.77 (s, 1H, [C.sup.17][H.sub.A]), 5.00 (s, 1H, [C.sup.17][H.sub.B]). The mass spectrum, m/z (MALDI), was: 785 [[M-Br].sup.+]. [C.sub.41][H.sub.70]Br[O.sub.13].

BIOLOGICAL METHODS

Bacteriostatic and fungistatic properties were studied by serial dilutions in liquid nutritive medium as described in [21, 22]. Test strains were *Staphylococcus aureus* 209-P, *Escherichia coli* F-50, *Bacillus cereus* 8035, *Pseudomonas aeruginosa* 9027, *Aspergillus niger* BKMF-1119, *Trichophyton metagrophytes* 1773, and *Candida albicans* 855-653. Lincomycin was used as reference agent.

L[D.sub.50] values were measured in experiments using mongrel white mice of both genders, weighing 19.0 [+ or -] 2.0 g, kept on a standard diet with a natural light regime at room temperature; substances were given i.p. Animals were randomized to form the experimental groups. Control mice (n = 10) received weights of distilled water equal to doses given to experimental mice. Experimental animals were observed for five days.

The most active substance against Gram-positive bacteria (*Staphylococcus aureus* 209-P and *Bacillus cereus* 8035) was compound VII (Table 2). None of the test compounds was active against Gram-negative bacteria (*Escherichia coli* F-50 and *Pseudomonas aeruginosa* 9027).

TABLE I. Physicochemical Properties of the Isosteviol (IV – VII) and Steviolbioside (VIII, IX) Derivatives Synthesized Here.

Compound	Yield, %	Melting temperature, °C	Atomic formula	Molecular weight
IV	45	230	C ₂₃ H ₃₀ NO ₂	389.58
V	78	263 – 265	C ₂₃ H ₃₂ INO ₃	531.52
VI	61	125 – 129	C ₂₃ H ₃₄ INO ₃	559.57
VII	70	215	C ₃₁ H ₄₆ BrNO ₃	560.62
VIII	77	147	C ₃₃ H ₅₀ BrO ₃	763.72
IX	61	115	C ₄₁ H ₇₀ BrNO ₃	864.91

Compound VII was also the most active substance against fungi (*Aspergillus niger* BKMF-1119, *Trichophyton metagrophytes* 1773, and *Candida albicans* 855-653).

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TABLE 2. Acute Toxicity and Antimicrobial and Antifungal Activities of compounds V-IX.

Compound	LD ₅₀ mg/kg	Minimal inhibitory concentration, µg/ml						
		<i>S.aureus</i> 209p	<i>B.cereus</i> 8035	<i>E.coli</i> F 50	<i>Ps.aureus</i> 9027	<i>Asp.niger</i>	<i>Trich. gypseum</i>	<i>Candida albicans</i>
V	75.0	250	500	> 10 ³	> 10 ³	> 10 ³	> 10 ³	125
VI	60.0	125	> 1000	> 1000	> 1000	> 1000	500	125
VII	60.4	31.25	250	> 1000	> 1000	500	62.5	31.25
IX	–	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000	> 1000
Lincomycin	–	10	500	inactive	inactive	–	–	–

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TABLE 1. Physicochemical Properties of the Isosteviol (IV-VII) and Steviolbioside (VIII, IX) Derivatives Synthesized Here. Compound Yield, Melting Atomic % temperature, formula [degrees]C IV 45 230 [C.sub.24][H.sub.39][O.sub.3] V 78 263-265 [C.sub.25][H.sub.42][O.sub.3] VI 61 125-129 [C.sub.27][H.sub.46][O.sub.3] VII 70 215 [C.sub.31][H.sub.46]BrN[O.sub.3] VIII 77 147 [C.sub.35][H.sub.55]Br[O.sub.3] IX 61 115 [C.sub.41][H.sub.70]BrN[O.sub.13] Compound Molecular weight IV 389.58 V 531.52 VI 559.57 VII 560.62 VIII 763.72 IX 864.91 TABLE 2. Acute Toxicity and Antimicrobial and Antifungal Activities of compounds V-IX. Compound L[D.sub.50], Minimal inhibitory concentration, mg/kg [micro]g/ml *S.aureus* *B.cereus* *E.coli* F 50 209p 8035 V 75.0 250 500 > [10.sup.3] VI 60.0 125 > 1000 > 1000 > 1000 VII 60.4 31.25 > 1000 > 1000 500 62.5 31.25 IX -- > 1000 > 1000 > 1000 Lincomycin 10 500 inactive Compound L[D.sub.50], Minimal inhibitory concentration,

mg/kg [micro]g/ml Ps.aureus 9027 Asp.niger V 75.0 > [10.sup.3] > [10.sup.3] VI 60.0 > 1000 > 1000 VII 60.4 > 1000 500 IX -- > 1000 > 1000 Lincomycin inactive -- Compound L[D.sub.50], Minimal inhibitory concentration, mg/kg [micro]g/ml Trich. gypseum Candida albicans V 75.0 > [10.sup.3] 125 VI 60.0 500 125 VII 60.4 62.5 31.25 IX -- >1000 > 1000 Lincomycin -- --

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