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Metal Derivatives of Diterpenoid Isosteviol

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Abstract—Metal salts (including transition metals salts) of chiral natural diterpenoid isosteviol and its hydrophosphoryl derivative were obtained for the first time. The compounds obtained can be used in pharmaceutics, metal catalysis, and also for creating new materials with magnetic properties.

Keywords: isosteviol, *ent*-16-oxobeyeran-19-oic acid salts, phosphites

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Recently chiral organometallic compounds attracted considerable attention of the chemists. These compounds often possess biological activity, catalytic action [1], and magnetic properties necessary for producing magnetic materials [2].

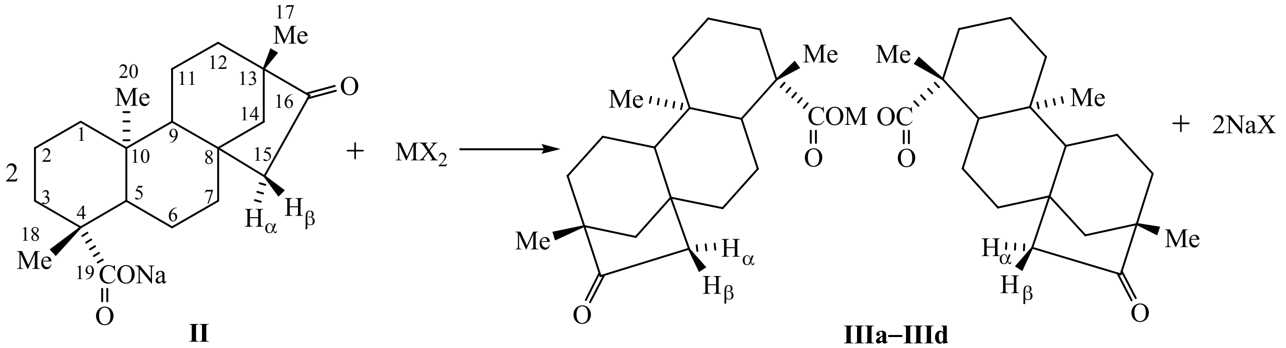
In this work tetracyclic diterpenoid isosteviol (*ent*-16-oxobeyeran-19-oic acid) **I** was chosen as the starting chiral compound for obtaining metal derivatives. Isosteviol was isolated from glycoside stevioside (*Stevia Rebaudiana Bertoni*) by acid hydrolysis [3].

Compound I is a natural carboxylic acid. Its sodium salt **II** was obtained by reaction with NaOMe in MeOH. Exchange reaction of the salt **II** with Ca and Fe(II) gluconates or Cu(II) and Ni chlorides were performed by mixing aqueous solutions of the reactants. After partial evaporation, the desired products **IIIa–IIId** precipitated from the solution. They were filtered off and washed with warm water (Scheme 1).

Structure and composition of the calcium salt **IIIa** were proved by ^{1}H NMR, IR spectroscopy and elemental analysis data. In the ^{1}H NMR spectra of compounds **IIIb–IIId** the proton signals suffered a strong broadening due to the magnetic properties of the metal. Thus the identification of these compounds was carried out only by elemental analysis and IR spectral data.

^{1}H NMR spectra (CDCl$_3$) of **I**, its sodium and calcium salts (**II**, **IIIa**) contain characteristic proton signals of Me^{20}, Me^{17}, Me^{18} groups, H$^3_\beta$ and H$^{15}_\alpha$ of

Scheme 1.



X = C$_6$H$_{12}$O$_7$, Cl; M = Ca (**a**), Fe (**b**), Cu (**c**), Ni (**d**).

similar multiplicity, but of different chemical shifts (detailed assignment of the proton signals in the spectrum of compound **I** was made in [4]).

In the IR spectrum of **I** there were two absorption bands corresponding to the carboxy (1693 cm^{-1}) and carbonyl (1740 cm^{-1}) groups. IR spectra of salts **II**, **IIIa–IIId** were characterized by insignificant shift of the absorption band of the carbonyl group (1733–1737 cm^{-1}) and the appearance of the absorption band of the fragment $C(O)O^-$ in the range of 1542–1573 cm^{-1} instead of 1693 cm^{-1}.

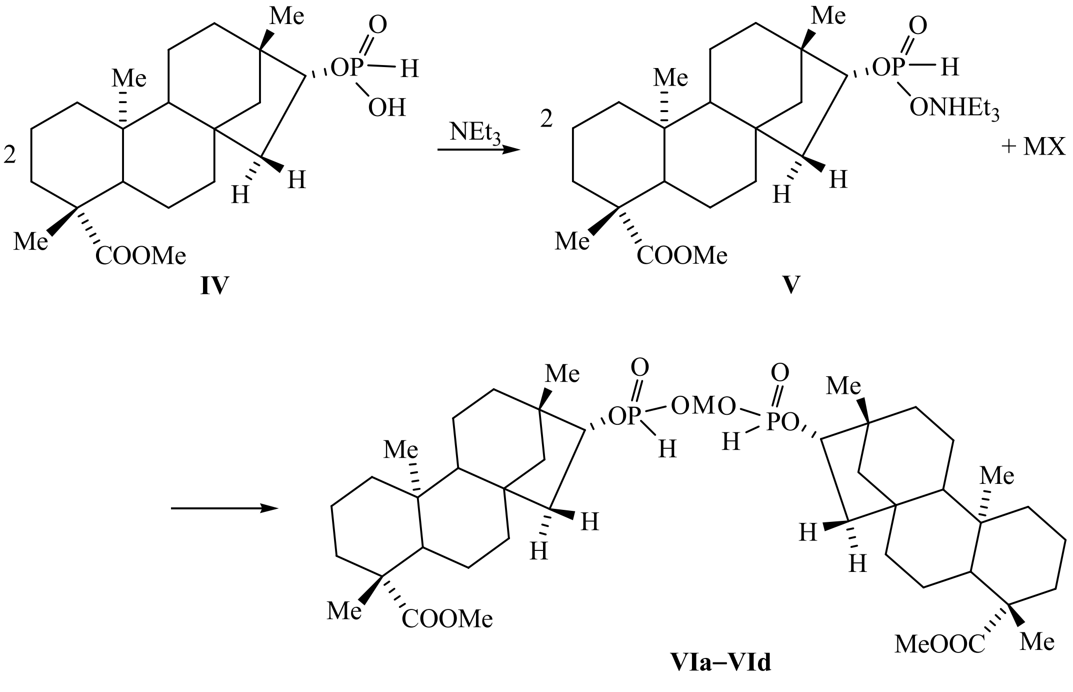
Previously [5] we have performed reducing carbonyl group in compound **I** followed by phosphorylation to obtain hydrophosphoryl derivative **IV**. The latter was converted into the triethylammonium salt V by reaction with NEt_3. This salt was used in the exchange reactions with Ca and Fe(II) gluconates, Cu(II) and Ni chlorides to obtain salts **VIa–VId** (Scheme 2).

^1H and ^{31}P NMR spectra of the calcium salt **VIa** differ from those of the respective compounds **IV** and **V**. Thus, the ^{31}P NMR spectra of **IV**, **V** were characterized by the presence of two doublets at 8.01 (J_{PH} 705.3, $^3J_{PH}$ 7.9 Hz) and 4.76 ppm (J_{PH} 606.6, $^3J_{PH}$ 10.2 Hz), respectively. The ^{31}P NMR spectrum of the calcium salt **VIa** contained a broad doublet at 3.79 (J_{PH} 655.3 Hz). In the ^1H NMR spectrum of **VIa** there were no signals of the methylene and methyl groups of NEt_3 observed in the spectrum of compound **V**. Compared with the spectra of compounds **IV** and **V** there was a change in the positions of all signals, their broadening and changed spin-spin coupling values for the signal of PH group.

The IR spectra of salts **V** and **VIa–VId** contained no absorption bands of the overtone of torsional vibrations of P(OH) group at 2310 and 2165 cm^{-1}, which were present in the spectra of compound **IV**. Also the spectra contained no broad absorption band at 1016 cm^{-1} corresponding to the stretching vibrations of P–OH group. In the spectra of salts V and **VIa–VId** the absorption band of PH group was shifted to the range of 2367–2418 cm^{-1} differing from that of compound **IV** (2430 cm^{-1}). Also position of the absorption band of carbonyl group changed when passing from **IV** to **V** and **VIa–VId**. In the IR spectra of metal salts **VIa–VId** there were no absorption bands of N^+–H group at 2492, 2677 and 2738 cm^{-1} characteristic for triethylammonium salts **V**.

Exchange processes at mixing triethylammonium salt **V** with the above metal salts as well as at mixing

Scheme 2.



X = $C_6H_{12}O_7$, Cl; M = Ca (**a**), Fe (**b**), Cu (**c**), Ni (**d**).

compound **IV** with metal gluconates were detected by mass spectrometry.

Mass spectrum (MALDI) of the starting acid **IV** contained molecular ions $[M\mathrm{H} + \mathrm{Na}]^+$ and $[M\mathrm{H} + \mathrm{K}]^+$ with *m*/*z* 421 and 437, respectively. In the mass spectrum of the copper salt **VIc** there was molecular ion $[M_2\mathrm{CuH}]^+$ with *m*/*z* 859. Along with the protonated ion, the mass spectrum contained the ions $[M_2\mathrm{Cu}_2]^+$ and $[M_2\mathrm{Cu}_3]^+$ with *m*/*z* 921 and 985, indicating a more complex structure than the salt **VIb**. Similar ions were detected in the MALDI mass spectra of compounds **VIc**, **VId**. Evidently, the transition metal atoms participate in coordination with the oxygen atoms of the P=O bonds. Crystal structure of the compounds obtained studied by means of X-ray diffraction will be published in the next report.

In summary, metal derivatives of diterpenoid isosteviol of two types have been obtained by the exchange reactions. Also their spectral and spectrometric data have been discussed.

EXPERIMENTAL

IR spectra were recorded on a Bruker Vector-22 instrument from KBr pellets or mull with mineral oil placed between KBr plates. ^{31}P NMR spectra were registered on a Bruker CXP-100 spectrometer (36.48 MHz), external rference 85% H_3PO_4. ^{1}H NMR spectra were taken on a Bruker Avance-600 spectrometer (600.13 MHz), residual proton signals of the deuterated solvent serving as internal reference. Mass spectra were obtained on a MALDI mass spectrometer Ultraflex III Bruker using *p*-nitroaniline as a matrix. Optical rotation angles were measured on a Perkin Elmer polarimeter (Model 341); specific rotation values were calculated by the formula $[\alpha] = \alpha 100/(c \cdot l)$, where *c* is the concentration (g/100 mL), *l* is the cell thickness (dm), *α* is the measured rotation angle (deg), [α] is the specific rotation (deg mL g^{-1} dm^{-1}).

Sodium *ent*-16-oxobeyeran-19-oate (II). To 0.01 g (0.43 mmol) of Na in 5 mL of MeOH was added 0.14 g (0.43 mmol) of compound **I**. The mixture was refluxed for 30 min. The solvent was evaporated, and the crystalline residue was washed with chloroform. Then the solvent was removed, and the residue was washed with hexane. Yield 0.11 g (77%), $[\alpha]_D^{20}$ –30 (*c* 0.10, H_2O). IR spectrum, ν, cm^{-1}: 1573 [C(O)O$^-$], 1733 (C^{16}=O). ^{1}H NMR spectrum, (D_2O), δ, ppm, (*J*, Hz): 0.77 s (3H, Me^{20}), 0.90 s (3H, Me^{17}), 0.99 s (3H, Me^{18}), 0.70–1.95 m (18H, beyerane structure protons), 2.03 d (1H, H_β^3, *J* 10.8), 2.61 d (1H, H_α^{15}, *J* 18.2). Found, %: C 71.08; H 8.93; Na 5.87. $C_{20}H_{29}O_3Na$. Calculated, %: C 70.54; H 8.60; Na 6.25.

Calcium *ent*-16-oxobeyeran-19-oate (IIIa). Preliminary heated on water bath aqueous solutions of 0.13 g (0.40 mmol) of compound **II** and 0.07 g (0.17 mmol) of calcium gluconate were mixed in a wide vessel. After partial evaporation, the formed precipitate was washed with warm water. Yield 0.10 g (86%), $[\alpha]_D^{20}$ –53 (*c* 0.13, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1542 [C(O)O$^-$], 1736 (C^{16}=O). ^{1}H NMR spectrum, (D_2O), δ, ppm, (*J*, Hz): 0.78 s (6H, 2Me^{20}), 0.98 s (6H, 2Me^{17}), 1.15 s (6H, 2Me^{18}), 0.60–1.95 m (36H, beyerane), 2.08 d (2H, 2H_β^3, *J* 8.2), 2.62 d (2H, H_α^{15}, *J* 17.9). Found, %: C 72.00; H 8.23; Ca 6.15. $C_{40}H_{58}O_6Ca$. Calculated, %: C 71.16; H 8.68; Ca 5.94.

Iron(II) *ent*-16-oxobeyeran-19-oate (IIIb) was obtained similarly from Fe(II) gluconate. Yield 82%, pale gray crystals, $[\alpha]_D^{20}$ –49 (*c* 0.31, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1542 [C(O)O$^-$], 1736 (C^{16}=O). Found, %: C 69.87; H 8.15; Fe 8.43. $C_{40}H_{58}O_6Fe$. Calculated, %: C 69.54; H 8.48; Fe 8.08.

Copper(II) *ent*-16-oxobeyeran-19-oate (IIIc). Aqueous solutions of 0.13 g (0.40 mmol) of compound **II** and 0.07 g (0.40 mmol) of $CuCl_2 \cdot 2H_2O$ were mixed in a wide vessel. The salt formed after partial evaporation was washed with warm water. Yield 0.13 g (92%), greenish-blue crystals, [$[\alpha]_D^{20}$ –73 (*c* 0.35, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1560 [C(O)O$^-$], 1737 (C^{16}=O). Found, %: C 68.35; H 9.37; Cu 9.02. $C_{40}H_{58}O_6Cu$. Calculated, %: C 68.77; H 9.22; Cu 9.10.

Nickel *ent*-16-oxobeyeran-19-oate (IIId) was obtained similarly from compound **II** and $NiCl_2 \cdot 6H_2O$. Yield 80%, yellowish crystals, $[\alpha]_D^{20}$ –21 (*c* 0.77, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1560 [C(O)O$^-$], 1736 (C^{16}=O). Found, %: C 69.85; H 8.13; Ni 8.77. $C_{40}H_{58}O_6Ni$. Calculated, %: C 69.25; H 8.44; Ni 8.47.

Calcium methyl-*ent*-16α-phosphitobeyeran-19-oate (VIa) was obtained similarly to **IIIa** from compound **V** and calcium gluconate. Yield 77%, $[\alpha]_D^{20}$ –47 (*c* 0.42, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1727 (C=O), 2384 (P–H). ^{1}H NMR spectrum, ($CDCl_3$), δ, ppm, (*J*, Hz): 0.72 br.s (6H, 2Me^{20}), 0.98 br.s (6H, 2Me^{17}), 1.17 br.s (6H, 2Me^{18}), 0.50–2.25 m (40H, beyerane structure protons), 3.35 br.s (6H, 2MeOOC), 4.28–4.42 m (2H, 2H^{16}), 6.76 br.d (2H, 2HP, J_{HP} 656.0). Found, %: C 60.11; H 8.43; Ca 4.65; P 7.19. $C_{42}H_{68}O_{10}CaP_2$. Calculated, %: C 60.40; H 8.22; Ca

4.80; P 7.42. ^{31}P NMR spectrum, δ_P, ppm, (*J*, Hz): 3.79 d (J_{PH} 655.3).

Iron methyl-*ent*-16α-phosphitobeyeran-19-oate (VIb) was obtained similarly from compound **V** and Fe(II) gluconate. Yield 80%, pale gray crystals, $[\alpha]_D^{20}$ –60 (*c* 0.16, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1727 (C^{16}=O), 2418 (P–H). Found, %: C 58.99; H 8.38; Fe 5.93; P 6.87. $C_{42}H_{68}O_{10}FeP_2$. Calculated, %: C 59.28; H 8.07; Fe 6.56; P 7.28.

Copper methyl-*ent*-16α-phosphitobeyeran-19-oate (VIc). Aqueous solutions of 0.20 g (0.40 mmol) of compound **V** and 0.07 g (0.40 mmol) of $CuCl_2\cdot 2H_2O$ were mixed. The precipitate was filtered off and washed with water. Yield 0.28 g (82%), greenish crystals. $[\alpha]_D^{20}$ –44 (*c* 0.38, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1726 (C^{16}=O), 2417 (P–H). Mass spectrum (MALDI), *m*/*z*: 859 $[M_2CuH]^+$, 921 $[M_2Cu_2]^+$, 983 $[M_2Cu_3]^+$. Found, %: C 56.99; H 6.86; Cu 7.57; P 7.39. $C_{42}H_{68}O_{10}CuP_2$. Calculated, %: C 57.54; H 8.06; Cu 7.25; P 7.07.

Nickel methyl-*ent*-16α-phosphitobeyeran-19-oate (VId) was obtained similarly from compound **V** and $NiCl_2\cdot 6H_2O$. Yield 89%, yellowish crystals, $[\alpha]_D^{20}$ –41 (*c* 0.56, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1726 (C^{16}=O), 2404 (P–H). Found, %: C 59.43; H 8.50; Ni 6.21; P 7.10. $C_{42}H_{68}O_{10}NiP_2$. Calculated, %: C 59.02; H 8.04; Ni 6.88; P 7.26.

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