Synthesis and Properties of 2-Cyanoethoxy Derivatives of Dammarane Triterpenoids

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Abstract—Cyanoethylation of dammaran-3 β -ols and 3-oxime dammarene, semisynthetic derivatives of the natural dipterocarpol, afforded a series of new dammarane triterpenoids containing 2-cyanoethoxy fragment at the carbon atom in the position 3 of the tetracyclic scaffold. A notable antiviral activity was found in 20(*S*)-3-[(2-cyanoethoxy)imino]-dammar-24-en-20-ol and 20(*S*)-3-O-(2-cyanoethyl)-25,26,27-trinor-20,24-olide-dammarane.

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Naturally occurring triterpenoids of oleanane and lupane family as well as their semisynthetic derivatives exhibit various types of biological activity and are utilized in development of new drugs, in particular, antiviral means [1, 2]. Lately the antiviral action was studied of glycyrrhetic acid and betulin. It was shown that the introduction of substituents of various electronic nature resulted in formation of new metabolically stable candidate substances. For instance, the succinate of 18 β -glycyrrhetic acid [3], as well as dimethyl succinate and dimethyl glutarate (at C³ and C²⁸) of betulin proved to be promising compounds with a high anti-HIV action. Betulinic acid dimethyl succinate became the basic compound of antiviral pharmaceutical bevirimat used in the treatment of AIDS and enteroviruses [2, 3]. It is also known that amides, hydrazones, hydrazides, oxazoles, cyanalkyl

and other nitrogen-containing betulin and oleanane acids derivatives are capable to suppress the reproduction of viruses of influenza, papilloma, enterovirus ECHO6, and herpes [4–13].

According to published information natural triterpenoids of dammarane series exhibit a wide range of biologic action [14–17], yet few data on preparation and properties of semisynthetic derivatives of this series are reported. We showed formerly that the dammarane triterpenoid alninkanone [20(*S*),24(*R*)-20,24-epoxy-24-methyldammaran-3-one] **1** exhibited a pronounced inhibiting activity with respect to influenza viruses of types A (H3N2) and B (Hong Kong flu) [18].

2,3- and 3,4-Seco acids obtained from alninkanone **1** proved to be active against type A flu virus (protection index 60%) [19].

Scheme 1.

In continuation of research on looking for new biologically active semisynthetic derivatives of natural dipterocarpol (20*S*-hydroxydammaran-24-en-3-one) **2** and its analogs we obtained in this study a series of 2-cyanoethoxy-substituted dammarane triterpenoids and their antiviral activity was tested.

In the first stage we synthesized dammarane triterpenoid **3** containing a lactone fragment in the position 17 by oxidation of dipterocarpol **2** with chromic anhydride along procedure [20, 21] (Scheme 1). Further the reduction of 20(*S*)-25,26,27-trinor-20,24-olidedammaran-3-one **3** with boron trifluoride etherate and sodium tetrahydroborate afforded 20(*S*)-25,26,27-trinor-20,24-epoxydammaran-3 β -ol **4** [21].

Cyanoethylation of epoxy compound **4** with acrylonitrile in dioxane in the presence of tetrapropylammonium hydroxide at room temperature led to the formation of cyanoethyl derivative of epoxydammarane **5** in a good yield (Scheme 1). The structure of 20(*S*)-3-*O*-(2-cyanoethyl)-25,26,27-trinor-20,24-epoxydammarane **5** was confirmed by the presence of an absorption band of the stretching vibrations of CN group at 2252 cm⁻¹ in the IR spectrum, by the signals of the methylene protons of the cyanoethyl fragment at δ 2.59, 3.57, 3.77 ppm in the ¹H NMR spectrum, of carbon atom of cyano group at δ 118.2 ppm in the ¹³C

NMR spectrum, and also by chromatographic and spectral data.

The syntheses of 3-cyanoethoxy derivatives of dammarane **7** (Scheme 2) and **9** (Scheme 3) we succeeded to perform in two stages. In the first stage the keto group at C³ of triterpenoid **2** and lactone **3** was reduced to the 3 β -hydroxy group with sodium tetrahydroborate in ethanol to obtain dammaranediol **6** (Scheme 2) and 3 β -hydroxylactone **8** (Scheme 3). The structure of compounds **6** and **8** was confirmed by the presence of the signal of the proton H^{3a} at 3 β -hydroxyl [δ 3.20 ppm (1H, C³H)]. Further in similar conditions 20(*S*)-3-*O*-(2-cyanoethyl)dammar-24-en-20-ol **7** and 20(*S*)-3-*O*-(2-cyanoethyl)-25,26,27-trinor-20,24-olide-dammarane **9** were synthesized.

The structures of compounds **7** and **9** were confirmed by the presence of the absorption band of the cyano group stretching vibrations at 2250 cm⁻¹ in the IR spectra, by characteristic signals of the methylene protons of the cyanoethyl fragment at δ 2.58, 3.55, 3.72 ppm in the ¹H NMR spectrum, and by the signal of the carbon atom of the cyano group at δ 118.2 ppm in the ¹³C NMR spectra. The reaction of compound **6** occurred selectively at the secondary hydroxy group at the atom C³ not affecting the tertiary hydroxyl at the atom C²⁰.

Scheme 2.

Scheme 3.

Yields of compounds **5**, **7**, and **9** were 45, 22, and 81% respectively. We failed to increase the yields by varying the reaction duration and the other conditions. Besides the target products the reaction mixture contained the initial hydroxy derivatives **4**, **6**, and **8** due apparently to the reversibility of Michael reaction. The individual cyanoethoxy derivatives were isolated by column chromatography.

We also synthesized 2-cyanoethoxy derivative of dipterocarpol **10**, where the cyanoethyl group is attached to the oxygen atom of the oxime fragment involving the atom C³. According to published data the triterpene oximes showed often a high biologic activity; for instance, oxime of betulonic acid turned out to be more active than the acid proper with respect to viruses of flu type A and herpes [8, 9]. Oxime of dipterocarpol **10** was obtained in a good yield by

boiling substrate **2** with hydroxylamine hydrochloride in pyridine (Scheme 4). In the ¹³C NMR spectrum of 3-oxime **10** the signal of the carbonyl carbon atom at δ 218.03 ppm is absent, and a signal of the C=NOH group appears at 167.24 ppm. The cyanoethylation of compound **10** in the above described conditions led to the formation in a good yield of 20(*S*)-3-*N*-(2-cyanoethoxyimino)dammar-24-en-20-ol **11** (Scheme 4).

The structure of 20(*S*)-3-(2-cyanoethoxyimino)dammar-24-en-20-ol **11** was confirmed by the presence of the absorption band of CN group in the IR spectrum, and also by the signals of protons of the methylene groups at δ 3.72 and 4.23 ppm in the ¹H NMR spectrum and by the only carbon atom signal in the downfield region at 118.00 ppm in the ¹³C NMR spectrum. No splitting of the CN group signal in the

Scheme 4.

^{13}C NMR spectrum, and also published data on the formation of exclusively *E*-isomer at the $\text{C}=\text{N}$ bond in oximes and cyanoethoxyimines at C^3 in the A ring of lupane and oleanane triterpenoids [13], made it possible to ascribe to the structure of compound **11** just *E*-configuration.

All compounds synthesized in this study were tested for antiviral activity with respect to influenza virus A/Puerto Rico/8/34 (H1N1) on MDCK cells. Among the cyanoethoxy derivatives of dammarane triterpenoids a considerable activity was shown by lactone **9** (selectivity index SI 10) and cyanoethoxyimine **11** (selectivity index SI 9).

EXPERIMENTAL

TLC was performed on Silufol plates, eluent hexane (petroleum ether)–ethyl acetate, 4 : 1 and 2 : 1; the development by spraying with a 5% solution of anisaldehyde and sulfuric acid in ethanol followed by heating to 100–120°C for 2–3 min. Melting points were measured on a small heating block PHMK VEB Wagetechnik Rapido. IR spectra were recorded on a spectrophotometer Perkin Elmer Spectrum BX from pellets with KBr. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker Avance II 400 (operating frequencies 400 and 100 MHz respectively). Mass spectra were obtained on an instrument maXis Bruker. Rotation angles were measured on an Automatic polarimeter AA-55.

Dipterocarpol **2** was obtained by extraction with ethyl acetate from latex of *Dipterocarpus alatus* followed by recrystallization from a mixture ethyl acetate–hexane [20].

20(*S*)-3-O-(2-Cyanoethyl)-25,26,27-trinor-20,24-epoxydammarane (5). A mixture of 0.52 g (0.0013 mol) of 20(*S*)-25,26,27-trinor-20,24-epoxydammaran-3 β -ol **4**, 1.71 mL (0.026 mol) of acrylonitrile, 0.65 mL of tetrapropylammonium hydroxide, and 1.7 mL of 30% KOH solution in 10 mL of dioxane was stirred at room temperature in an argon atmosphere for 2 h. Then the reaction mixture was poured in a beaker containing 100 mL of ice and 1 mL of 15% hydrochloric acid. The precipitate was filtered off, washed with water till neutral washings, and dried in air. The reaction product was purified by flash-chromatography on silica gel. Eluent hexane–ethyl acetate. Yield 0.42 g (81%), mp 193–195°C, $[\alpha]_{\text{D}}^{23.5} +48.7^\circ$ (*c* 1.0, CHCl_3). ^1H NMR spectrum (CDCl_3), δ , ppm: 0.80 s (3H, C^{30}H_3), 0.90 s

(3H, C^{19}H_3), 0.89 s (3H, C^{18}H_3), 0.98 s (3H, C^{28}H_3), 1.01 s (3H, C^{29}H_3), 1.14 s (3H, C^{21}H_3), 1.11–1.62 m (12H, CH, CH_2), 1.63–1.95 m (1H, C^{13}H), 1.96–2.04 m (8H, CH, CH_2), 2.05–2.11 m (4H, CH, CH_2), 2.57 t (2H, C^2H_2 , *J* 6.5 Hz), 3.57 m (1H, C^1H_2), 3.78 m (1H, C^1H_2), 3.81 m (2H, C^{24}H_2). ^{13}C NMR spectrum (CDCl_3), δ , ppm: 15.52, 15.89, 16.05, 16.12, 16.20, 19.28 (C^2), 21.63, 22.98, 24.94, 25.78, 26.47, 26.95, 28.09, 31.22, 35.04, 35.28, 37.08, 38.82, 38.99, 40.40, 43.08, 49.81, 49.96, 50.72, 56.29, 64.16 (C^1H_2), 66.75, 85.96 (C^{20}), 87.73 (C^3H), 118.19 (CN). Mass spectrum (ESI), *m/z* (*I*_{rel}, %): 478.3682 [*M* + Na]⁺. $\text{C}_{30}\text{H}_{49}\text{NO}_2$. Calculated *M* 455.3763.

20(*S*)-Dammar-24-en-20,3 β -diol (6). To 4 g (0.009 mol) of 20(*S*)-hydroxydammar-24-en-3-one **2** dissolved in 70 mL of ethanol was added 470 mg (0.012 mol) of sodium tetrahydroborate, and the mixture was refluxed for 24 h at 80°C. Then the reaction mixture was diluted with water and acidified to pH 2. The precipitate was filtered off, washed, dried, and recrystallized from a mixture petroleum ether–ethyl acetate. Yield 2.4 g (60%), mp 132–134°C (134–135°C [16]).

20(*S*)-25,26,27-Trinor-20,24-olidedammaran-3 β -ol (8) was obtained from lactone **3** analogously to compound **6**. Reduced lactone **8** melted at 200–201°C (203–206°C [21]). No depression was observed at melting a mixed sample with an authentic compound. The spectral data were consistent with the published information [21].

20(*S*)-3-O-(2-Cyanoethyl)-dammar-24-en-20-ol (7) was obtained similarly to compound **5**. Yield 1.24 g (45%), mp 251–253°C, $[\alpha]_{\text{D}}^{22.7} +53.7^\circ$ (*c* 1.0, CHCl_3). ^1H NMR spectrum (CDCl_3), δ , ppm: 0.78 s (3H, C^{30}H_3), 0.86 s (3H, C^{19}H_3), 0.88 s (3H, C^{18}H_3), 0.96 s (3H, C^{28}H_3), 0.98 s (3H, C^{29}H_3), 1.15 s (C^{21}H_3), 1.63 s (3H, C^{26}H_3), 1.69 s (3H, C^{27}H_3), 1.10–1.19 m (8H, CH, CH_2), 1.20–1.60 m (11H, CH, CH_2), 1.63–1.83 m (1H, C^{13}H), 1.98–2.20 m (5H, CH, CH_2), 2.55 t (2H, C^2H_2 , *J* 6.6 Hz), 3.55 m (1H, C^1H_2), 3.71 m (1H, C^1H_2), 5.20 t (1H, C^{24}H , *J* 6.7 Hz). ^{13}C NMR spectrum (CDCl_3), δ , ppm: 16.11, 16.20, 16.42, 17.70, 18.17, 18.40, 19.05 (C^2H_2), 21.55, 22.54, 22.96, 24.08, 25.38, 25.73, 27.52, 28.08, 31.16, 35.22, 37.05, 38.78, 38.98, 40.40, 40.48, 42.25, 49.84, 50.27, 50.63, 56.28, 64.15 (C^1H_2), 75.39, 87.70 (C^3H), 118.19 (CN), 124.73 (C^{24}H), 131.54 (C^{25}). Mass spectrum (ESI), *m/z* (*I*_{rel}, %): 520.4146 [*M* + Na]⁺, $\text{C}_{33}\text{H}_{55}\text{NO}_2$. Calculated *M* 497.4232.

20(S)-3-O-(2-Cyanoethyl)-25,26,27-trinor-20,24-olidedammarane (9) was obtained similarly to compound **5**. Yield 0.108 g (22%), mp 197–199°C, $[\alpha]_D^{22.8} +208.32^\circ$ (c 1.0, CHCl_3). ^1H NMR spectrum (CDCl_3), δ , ppm: 0.79 s (3H, C^{30}H_3), 0.86 s (3H, C^{19}H_3), 0.90 s (3H, C^{18}H_3), 0.97 s (3H, C^{28}H_3), 1.00 s (3H, C^{29}H_3), 1.38 s (3H, C^{21}H_3), 1.11–1.62 m (12H, CH, CH_2), 1.63–1.83 m (1H, C^{13}H), 1.84–2.04 m (8H, CH, CH_2), 2.05–2.20 m (4H, CH, CH_2), 2.59 t (2H, C^2H_2 , J 6.4 Hz), 3.56 m (1H, C^3H_2), 3.81 m (1H, C^3H_2). ^{13}C NMR spectrum (CDCl_3), δ , ppm: 15.48, 16.05, 16.11, 16.17, 16.22, 19.28 (C^2H_2), 21.44, 22.94, 25.05, 25.48, 26.8, 28.09, 29.20, 31.02, 31.18, 35.19, 37.06, 38.78, 38.99, 49.35, 40.41, 43.17, 50.16, 50.57, 56.27, 64.15 (C^1H_2), 87.67 (C^3H), 90.12 (C^{20}), 118.17 (CN), 176.73 (C^{24}). Mass spectrum (ESI), m/z (I_{rel} , %): 492.3459 [$M + \text{Na}$] $^+$. $\text{C}_{30}\text{H}_{47}\text{NO}_3$. Calculated M 469.35559.

Oxime of 20(S)-hydroxydammar-24-en-3-one (10).

In 10 mL of pyridine was dissolved 4 g (0.009 mol) of 20(S)-hydroxydammar-24-en-3-one **2**, 2.4 g (0.0345 mol) of hydroxylamine hydrochloride, and the mixture was boiled for 2 h, cooled, poured in 50 mL of water, and acidified to pH 2. The separated precipitate was filtered off, washed with water till neutral reaction, and purified by chromatography (eluent hexane–ethyl acetate), then recrystallized from ethyl acetate. Yield 3.71 g (93%), mp 185–186°C. ^1H NMR spectrum, δ , ppm: 0.88 s (3H, CH_3), 0.96 s (3H, CH_3), 1.00 s (3H, CH_3), 1.08 s (3H, CH_3), 1.16 s (3H, CH_3), 1.21–1.60 m (11H, CH, CH_2), 1.64 s (3H, CH_3), 1.70 s (3H, CH_3), 1.71–1.89 m (11H, CH, CH_2), 2.01–2.12 m (2H, CH, CH_2), 2.20–2.39 m (1H, CH), 5.12 t (1H, C^{24}H , J 6.9 Hz), 7.69 br.s (1H, NOH). ^{13}C NMR spectrum (CDCl_3), δ , ppm: 15.40, 15.87, 16.33, 17.32, 17.71, 19.04, 21.80, 22.56, 22.86, 24.78, 25.42, 25.74, 27.35, 27.52, 31.17, 34.82, 37.18, 39.05, 40.39, 40.47, 42.31, 42.61, 49.70, 50.25, 50.27, 56.03, 75.43 (C^{20}), 124.71 (C^{24}H), 131.57 (C^{25}), 167.24 (C^3).

20(S)-3-(2-Cyanoethoxyimino)dammar-24-en-20-ol (11). A mixture of 1.16 g (0.0025 mol) of compound **10**, 3.34 mL (0.05 mol) of acrylonitrile, 1.27 mL of tetrapropylammonium hydroxide, and 1.7 mL of 30% solution of KOH was stirred in 10 mL of dioxane for 2 h, the reaction product was isolated as described for compounds **5**, **7**, and **9**, and recrystallized from ethyl acetate. Yield 1.04 g (90%), mp 124–125°C, $[\alpha]_D^{23.1} +138.93^\circ$ (c 1.0, CHCl_3). ^1H NMR spectrum (CDCl_3), δ , ppm: 0.89 s (3H, C^{30}H_3), 0.94 s (C^{19}H_3), 1.00 s (C^{18}H_3), 1.06 s (C^{28}H_3), 1.15 s (C^{21}H_3), 1.16 s (C^{29}H_3), 1.64 s (C^{26}H_3), 1.71 s (C^{27}H_3), 1.20–1.58 m (12H, CH,

CH_2), 1.59–1.75 m (8H, CH, CH_2), 1.80–2.11 m (4H, CH, CH_2), 2.25–2.33 m (1H, C^{13}H), 3.71 t (2H, C^1H_2 , J 6.5 Hz), 4.23 t (2H, C^2H_2 , J 6.4 Hz), 5.14 t (1H, C^{24}H , J 6.8 Hz). ^{13}C NMR spectrum (CDCl_3), δ , ppm: 15.36, 15.48, 16.20, 16.35, 17.71, 18.03, 18.38 (C^2H_2), 19.04, 21.81, 22.56, 24.79, 25.44, 25.75, 27.48, 27.52, 31.13, 34.78, 37.06, 39.01, 40.44, 40.48, 40.51, 42.32, 49.80, 50.19, 50.29, 55.93, 67.29 (C^1H_2), 75.36, 118.00 (CN), 124.71 (C^{24}H), 131.60 (C^{25}), 168.27 (C^3). Mass spectrum (ESI), m/z (I_{rel} , %): 533.4103 [$M + \text{Na}$] $^+$. $\text{C}_{33}\text{H}_{54}\text{N}_2\text{O}_2$. Calculated M 510.41853.

Examination of cytotoxicity *in vitro*. The cytotoxicity of compounds was estimated in experiments on cell culture MDCK that was incubated for 48 h at 37°C in a carbon dioxide incubator in an atmosphere of 5% of CO_2 . From the studied compounds a double dilution series was prepared of concentrations from 500 to 3 $\mu\text{g/mL}$ in supporting medium Eagle MEM and the microtetrazolium (MTT) test was carried out on 96-well plate templates [22]. The cells were twice washed with physiological solution (0.9% NaCl), and in each well was added 100 of MTT solution [3-(4,5-dimethylthiazole-2)-2,5-diphenyltetrazolium bromide] in a concentration 0.5 $\mu\text{g/mL}$ in physiological solution. The templates were incubated for 1 h at 37°C, then the liquid was removed, and in each well was added 0.1 mL of dimethyl sulfoxide. The optical density of cells was measured on a spectrophotometer Victor 2 1440 at the wavelength of 535 nm. From the findings obtained the concentration of the compound destructing 50% of cell in the culture (CND_{50}) was calculated.

Estimation of antiviral activity *in vitro*. The monolayer culture of MDCK cells was infected by the following procedure: in each well of the templates was added 100 μL of the tested compound dissolved in supporting medium, and the incubation was carried out for 1 h at 37°C in a carbon dioxide incubator in an atmosphere of 5% of CO_2 . Then into each well was added 100 μL of 10-fold (10^{-1} – 10^{-7}) dilutions of virus and all was left for 2 days at 37°C in the atmosphere of 5% of CO_2 . After 48 h 100 μL of the culture fluid was sampled from each well, transferred to the plate template for immunological reaction, and the hemagglutination assay was performed. To this end in the wells with sampled culture fluid was added an equal amount of 1% suspension of hen erythrocytes in physiological solution. The results were estimated after 40 min incubation at room temperature. As infectious titre of the virus the reciprocal value was regarded of the maximum virus dilution that caused complete

agglutination of erythrocytes. The titre was expressed in logarithm of the 50% of the infective dose ($\log ID_{50}$). The antiviral activity of a compound was estimated from the decreased infective titre of the virus. From the data obtained the 50% effective concentration was calculated, or the concentration of the compound which caused the two-fold reduction of the virus titre (by $0.3 \log ID_{50}$) (EC_{50}), and then the selectivity index SI was calculated (the ratio CTD_{50}/EC_{50}).

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