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Dedicated to Full Member of the Russian Academy of Sciences I.P. Beletskaya on her jubilee

Synthesis of 2-Mono- and 2,2-Bis[2-(1*H*-tetrazol-5-yl)ethyl] Derivatives of Dipterocarpol

E. I. Rodionov[a], A. A. Kovaleva[a], A. D. Zorina[b], G. L. Starova[b], and R. E. Trifonov[b]*

[a] *St. Petersburg State Institute of Technology, Moskovskii pr. 26, St. Petersburg, 190013 Russia*

[b] *St. Petersburg State University, Universitetskaya nab. 7/9, St. Petersburg, 199034 Russia*
**e-mail: rost_trifonov@mail.ru*

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Abstract—The azidation of 2,2-bis(2-cyanoethyl)-20-hydroxydammar-24-en-3-one afforded new tetrazole derivatives of natural dipterocarpol, 2-(2-cyanoethyl)-2-[2-(1*H*-tetrazol-5-yl)ethyl]-20-hydroxydammar-24-en-3-ones, 2,2-bis[2-(1*H*-tetrazol-5-yl)ethyl]-20-hydroxydammar-24-en-3-one, and 2,2-bis[2-(1*H*-tetrazol-5-yl)-ethyl]-3-oxo-25,26,27-trinordammaran-(20*S*),24-olide. The structure of the final and intermediate products was determined by NMR spectroscopy and X-ray analysis.

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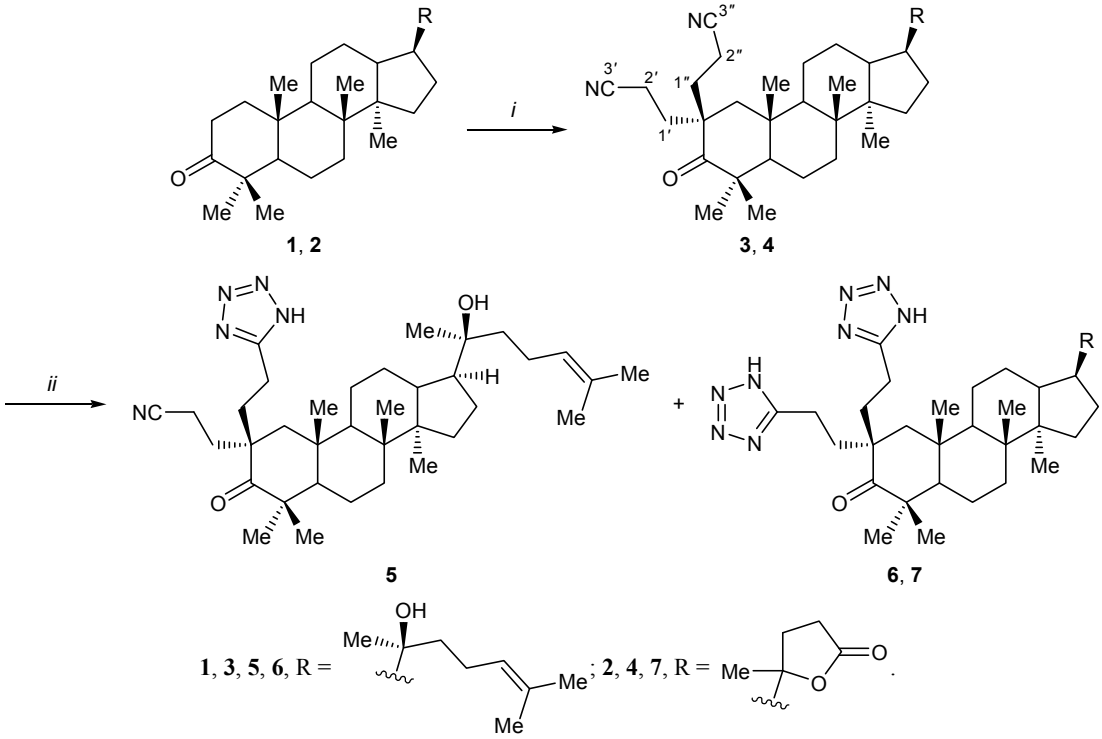
Dammarane triterpenoids, including dipterocarpol (**1**) isolated from a number of tropical plants, are widespread in nature, and they exhibit various pharmacological activities [1–3]. Chemical modification of compounds of plant origin is a known synthetic approach that makes it possible to obtain substances with improved pharmacological profile and create new medicinal agents. Introduction of nitrogen-containing heterocycles such as azoles and azines into a triterpene skeleton afforded a number of compounds with high anti-inflammatory, antitumor, antiviral, and other kinds of activity and simultaneously reduced side effects intrinsic to some unmodified natural triterpenoids [4–6]. Taking into account that tetrazolyl fragment is a metabolically stable analog of carboxy and *cis*-amide groups, which is capable of effectively participating in various intermolecular interactions and acting as an acid or base, the synthesis of tetrazolyl derivatives of natural triterpenoids seems an important problem [7, 8]. However, until now published data on the synthesis and properties of such derivatives remain very limited. We previously described the synthesis and properties of two series of tetrazolyl derivatives of dammarane triterpenoids, 3-[2-(1*H*-tetrazol-5-yl)-ethoxy]dammaranes and 3-[2-(1*H*-tetrazol-5-yl)-ethoxyimino)dammaranes, in which the tetrazolethyl fragment is linked to the triterpene skeleton through an oxygen atom [9, 10].

Herein we report the synthesis of 2,2-bis[2-(1*H*-tetrazol-5-yl)ethyl]dipterocarpol derivative and the corresponding lactone via 1,3-dipolar cycloaddition of dimethylammonium azide to 2,2-bis(2-cyanoethyl) derivatives **3** and **4** which were prepared by Michael addition of acrylonitrile to dipterocarpol (**1**) and lactone **2** in the presence of a quaternary ammonium base (Pr_4NOH, Scheme 1). The reaction was selective, and both cyanoethyl groups entered the 2-position of the dammarane skeleton. Analogous regioselectivity was observed previously for other triterpenoids [11, 12].

The IR spectra of cyanoethyl derivatives **3** and **4** showed absorption bands at 2249 and 1690 cm^{-1} due to stretching vibrations of the CN and C^3=O carbonyl groups. The ^1H and ^{13}C NMR spectra of **3** and **4** contained signals from protons of the cyanoethyl substituents (δ 1.6–2.3 ppm), $C^{2''}$ and $C^{2'}$ methylene carbon atoms [δ_C 12.34, 12.54 (**3**), 12.33, 12.53 ppm (**4**)], $C^{1'}$ and $C^{1''}$ [δ_C 31.6, 37.50 (**3**), 31.10, 37.42 ppm (**4**)], carbon atoms of the cyano groups [δ_C 118.6 (**3**, $C^{3''}$), 119.5 ppm (**4**, $C^{3'}$), and all protons and carbons of the dammarane skeleton. The structure of **4** was also confirmed by X-ray analysis (Fig. 1). The X-ray diffraction data indicated nonequivalence of the cyanoethyl

Scheme 1.



Reagents and conditions. *i*: CH_2=CHCN, $Pr_4N^+OH^-$, KOH, dioxane, 2 h; *ii*: $Me_2NH_2^+N_3^-$, DMF, 154°C, 15 h.

groups: the β-oriented cyanoethyl group is more sterically accessible than the α-cyanoethyl group which appears closer to the methyl group on C^4. Therefore, it was the β-oriented cyanoethyl group which was expected to react with azides first.

The azidation of **3** and **4** was carried out under different conditions. The reactions of **3** and **4** with various ammonium azides in toluene or DMF at a temperature below 140°C led to the formation of only monotetrazolyl derivatives in low yields. We succeed-

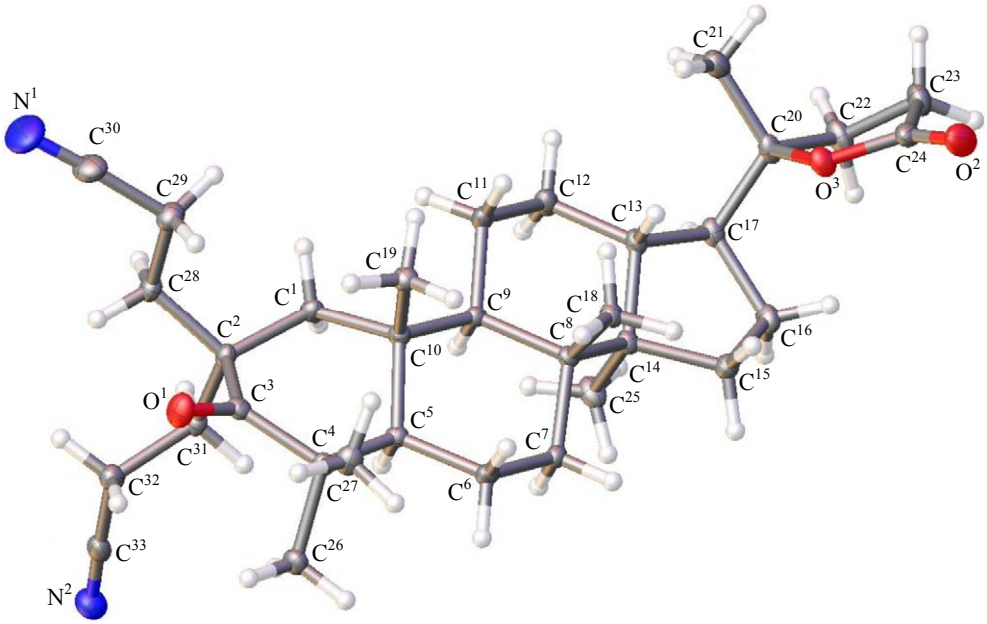


Fig. 1. Structure of the molecule of 2,2-bis(2-cyanoethyl)-3-oxo-25,26,27-trinordammaran-(20*S*),24-olide (**4**) according to the X-ray diffraction data.

ed in obtaining acceptable yields of bis(tetrazolylethyl) derivatives **6** and **7** only by using excess azidating agent at a temperature approaching the boiling point of DMF and prolonged reaction time (18 h). The low rate of azidation of **3** and **4** may result from their steric crowding. According to published data [13], this factor significantly hinders 1,3-dipolar cycloaddition of azides to nitriles in the synthesis of tetrazoles. Tetrazolylethyl derivatives **5**–**7** were isolated from the reaction mixtures by column chromatography.

In the azidation of **3**, we succeeded in isolating appreciable amounts of both bis(tetrazolylethyl) and mono(tetrazolylethyl) derivatives **6** and **5**. The $C^{2''}$ signal of **5** is located in a weaker field (δ_C 23.17 ppm) than that of dinitrile **1**, the signal of $C^{3'}$ of the 2α-cyanoethyl group is observed at δ_C 120.5 ppm, and the $C^{3''}$ atom (tetrazole ring) resonated at δ_C 154 ppm. These data suggest that the azidation of **3** initially involves 2β-cyanoethyl group with formation of compound **5** and that further azidation of the latter yields bis(tetrazolylethyl) derivative **6**. Analogous reaction sequence could be inferred for dinitrile **4**; however, we did not isolate the corresponding monotetrazolyl derivative. The IR spectra of **6** and **7** lacked C≡N stretching band, and no signal assignable to cyano group was observed in their ^{13}C NMR spectra (δ_C 118–119 ppm in the spectra of **3** and **4**). In going from nitriles **3** and **5** to bis-tetrazole **6**, signals from methylene carbon atoms of the ethylene linker shifted downfield (δ_C 24.17 and 24.79 ppm), and signals of C^5 in the tetrazole rings appeared at δ_C 156.33 and 157.06 ppm.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Perkin Elmer Spectrum BX spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III-400 spectrometer at 400.13 and 100.61 MHz, respectively; the chemical shifts were measured relative to the residual proton and carbon signals of the deuterated solvent. The mass spectra were obtained on a Bruker MaXis instrument. Silufol plates were used for thin-layer chromatography (eluent hexane–ethyl acetate, 4:1 or 2:1); spots were visualized by spraying with a 5% solution of 4-methoxybenzaldehyde in ethanol acidified with sulfuric acid, followed by heating at 100–120°C for 2–3 min. The melting points were determined with a Wägetechnik Rapido PHMK micro hot stage.

Dipterocarpol (**1**) was isolated from the *Dipterocarpus alatus* latex [14]. Lactone **2** was synthesized by oxidation of **1** with chromium(VI) oxide according to the procedure described in [15].

The X-ray diffraction data for compound **4** were collected on a Rigaku SuperNova diffractometer (HyPix-3000 detector, 100 K). The structure was solved by the direct method using Superflip program [16] and was refined by the least-squares method in anisotropic approximation for non-hydrogen atoms using SHELXL [17] and Olex2 [18]. Single crystals of **4** were obtained by crystallization from ethyl acetate; $C_{33}H_{48}N_2O_3$, *M* 520.73; orthorhombic crystal system, space group $P2_12_12_1$; unit cell parameters at 100(2) K: a = 10.1708(2), b = 14.6410(3), c = 19.2303(4) Å; V = 2863.60(11) Å^3; Z = 4; $-13 \le h \le 10$, $-18 \le k \le 19$, $-21 \le l \le 24$. Total of 15888 reflection intensities were measured, including 6545 independent reflections (R_{int} = 0.0326, R_σ = 0.0471) used for all calculations. Final divergence factors: R_1 = 0.0401 [reflections with $I > 2\sigma(I)$], wR_2 = 0.0850; R_1 = 0.0484, wR_2 = 0.0900 (all independent reflections). Residual electron density: ρ_{min}/ρ_{max} = 0.25/–0.21 $\bar{e}$/Å^3; F = 0.1(5). CCDC entry no. 1811742.

3,3′-[(20*S*)-20-Hydroxy-3-oxodammar-24-ene-2,2,-diyl]dipropanenitrile (3). A mixture of 2.3 mmol of compound **1**, 0.04 mol of acrylonitrile, 1.25 mL of tetrapropylammonium hydroxide, and 1.5 mL of 30% aqueous potassium hydroxide in 10 mL of dioxane was stirred for 24 h at room temperature. The mixture was poured into 100 mL of an ice–water mixture containing 3 mL of aqueous HCl. The precipitate was filtered off, washed with water until neutral washings, dried in air, and purified by silica gel column chromatography using hexane–ethyl acetate (2:1) as eluent. Yield 1.0 g (81%), colorless crystals, mp 230–233°C. IR spectrum, ν, cm^{-1}: 3528 (OH), 2249 (CN), 1688 (C^3=O). ^1H NMR spectrum ($CDCl_3$), δ_C, ppm: 0.73 s (3H, $C^{30}H_3$), 0.89 s (3H, $C^{19}H_3$), 0.93 s (3H, $C^{18}H_3$), 0.99 s (3H, $C^{28}H_3$), 1.11 s (3H, $C^{21}H_3$), 1.17 s (3H, $C^{28}H_3$), 1.65 s (3H, $C^{26}H_3$), 1.71 s (3H, $C^{27}H_3$), 1.72 m (1H, 1′-H), 1.96 m (2H, 1′-H, 1″-H), 2.02–2.20 m (2H, 2H, 2″-H), 2.25–2.37 m (3H, 1″-H, 2′-H, 2″-H), 5.15 t (1H, 24-H, J = 6.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.34 ($C^{2''}$), 12.54 ($C^{2'}$), 14.10, 16.29, 17.70, 21.02, 22.63, 23.06, 25.72, 26.5, 30.11, 31.60 ($C^{1'}$), 36.74, 37.50 ($C^{1''}$), 40.15, 40.50, 42.27, 46.18, 48.23, 49.93, 50.27, 51.55, 51.85, 73.98, 75.28, 118.63 ($C^{3''}$), 119.50 ($C^{3'}$), 124.62 (C^{24}), 131.69 (C^{25}), 218.64 (C^3). Mass spectrum (ESI): m/z 571.42 $[M + Na]^+$. $C_{36}H_{56}N_2O_2$. Calculated: *M* 548.4341.

2,2-Bis(2-cyanoethyl)-3-oxo-25,26,27-trinordammaran-(20*S*),24-olide (4) was synthesized in a similar

way. Yield 67%, colorless crystals, mp 233–235°C. IR spectrum, ν, cm^{-1}: 2248 (CN), 1767 (C=O, lactone), 1687 (C^3=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.73 s (3H, $C^{30}H_3$), 0.95 s (3H, C^{19}), 0.99 s (3H, $C^{18}H_3$), 1.11 s (3H, $C^{28}H_3$), 1.17 s (3H, $C^{29}H_3$), 1.39 s (3H, $C^{21}H_3$), 1.64 m (1H, 1′-H), 1.89–1.95 m (2H, 1′-H, 1″-H), 1.98–2.05 m (1H, 2″-H), 2.08–2.27 m (3H, 2′-H, 2″-H), 2.27–2.72 m (2H, 1″-H, 2′-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.33 ($C^{2''}$), 12.53 ($C^{2'}$), 14.66, 16.10, 17.01, 18.84, 19.51, 21.02, 23.05, 26.78, 29.11, 30.12, 31.10, 32.27, 33.64, 36.73, 37.42, 40.14, 43.19, 46.17, 48.22, 49.22, 49.82, 50.17, 51.50, 51.55, 65.92, 89.87 (C^{20}), 118.63 ($C^{3''}$), 119.49 ($C^{3'}$), 176.63 (C^{24}), 218.53 (C^3). Mass spectrum (ESI): *m*/*z* 543.3564 $[M + Na]^+$. $C_{33}H_{48}N_2O_3$. Calculated: *M* 520.7458.

Compounds 5 and 6. A mixture of 0.0017 mol of dinitrile **3**, 0.034 mol of dimethylamine hydrochloride, and 0.034 mol of sodium azide in 12 mL of DMF was heated for 18 h at 154°C. The mixture was cooled, poured into 50 mL of an ice–water mixture, and acidified to pH 2. The precipitate was filtered off, washed with water, and dried, and the products were isolated by silica gel column chromatography. Compound **5** was eluted with hexane–ethyl acetate (1:1), and compound **6**, with ethyl acetate.

3-{(20*S*)-20-Hydroxy-3-oxo-2β-[2-(1*H*-tetrazol-5-yl)ethyl]dammar-24-en-2*α*-yl}propanenitrile (5). Yield 0.325 g (30%), colorless crystals, mp 116–117°C. IR spectrum, ν, cm^{-1}: 3458 (OH), 2249 (CN), 1690 (C^3=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.74 s (3H, $C^{30}H_3$), 0.92 s (3H, $C^{19}H_3$), 0.99 s (3H, $C^{18}H_3$), 1.12 s (3H, $C^{28}H_3$), 1.20 s (3H, $C^{21}H_3$), 1.64 s (3H, $C^{26}H_3$), 1.71 s (3H, $C^{27}H_3$), 1.25–1.57 m (12H, CH, CH_2), 1.79–2.09 m (2H, 1′-H, 1″-H), 2.27–2.51 m (3H, 1″-H, 2′-H), 2.69 m (1H, 1″-H), 2.97 m (1H, 2″-H), 5.14 t (1H, 24-H, *J* = 6.7 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 12.40 ($C^{2'}$), 14.17, 14.66, 16.29, 17.72, 20.17, 22.57, 23.17 ($C^{2''}$), 25.58, 25.73, 27.49, 30.02, 31.05, 32.6 ($C^{1'}$), 33.68, 36.80, 39.03, 40.14, 40.23, 42.31, 46.28, 48.41, 49.73, 49.79, 50.28, 51.18, 52.33, 60.51, 75.93, 120.56 ($C^{3'}$), 124.51 (C^{24}), 131.78 (C^{25}), 156.30 ($C^{3''}$), 218.64 (C^3). Mass spectrum (ESI): *m*/*z* 614.4582 $[M + Na]^+$. $C_{36}H_{57}N_5O_2$. Calculated: *M* 591.8792.

(20*S*)-20-Hydroxy-2,2-bis[2-(1*H*-tetrazol-5-yl-ethyl)dammar-24-en-3-one (6). Yield 0.561 g (57%), colorless crystals, mp 160–163°C. IR spectrum, ν, cm^{-1}: 3444 (OH), 1690 (C^3=O). ^{1}H NMR spectrum (CD_3OD), δ, ppm: 0.83 s (3H, $C^{30}H_3$), 0.95 s (3H, $C^{19}H_3$), 1.04 s (3H, $C^{18}H_3$), 1.12 s (3H, $C^{27}H_3$), 1.13 s (3H, $C^{28}H_3$), 1.19 s (3H, $C^{21}H_3$), 1.61 s (3H, $C^{26}H_3$), 1.67 s (3H, $C^{27}H_3$), 1.32–1.59 m (12H, CH, CH_2), 2.02–2.18 m (2H, 1′-H, 1″-H), 2.33 m (1H, 2″-H), 2.97 m (2H, 2″-H), 5.12 t (1H, 24-H, *J* = 6.6 Hz). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 14.07, 15.76, 17.26, 18.25, 22.49, 22.55, 24.18 ($C^{2''}$), 24.79 ($C^{2'}$), 27.74, 29.42, 31.15, 33.94, 36.90, 38.94, 40.31, 41.27, 42.54, 47.90, 51.52, 52.43, 74.90, 78.37, 124.87 (C^{24}), 130.85 (C^{25}), 156.33 ($C^{3''}$), 157.06 ($C^{3'}$), 219.92 (C^3). Mass spectrum (ESI), *m*/*z*: 635.4757 $[M + H]^+$, 657.4564 $[M + Na]^+$. $C_{36}H_{58}N_8O_2$. Calculated: *M* 634.4683.

3-Oxo-2,2-bis[2-(1*H*-tetrazol-5-yl)ethyl]-25,26,27-trinordammaran-(20*S*),24-olide (7) was synthesized as described above for compound **6**; reaction time 48 h. Yield 78%, colorless crystals, mp 154–156°C. IR spectrum, ν, cm^{-1}: 1766 (C=O, lactone), 1690 (C^3=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.72 s (3H, $C^{30}H_3$), 0.89 s (3H, $C^{19}H_3$), 0.94 s (3H, $C^{18}H_3$), 1.14 s (3H, $C^{28}H_3$), 1.16 s (3H, $C^{29}H_3$), 1.39 s (3H, $C^{21}H_3$), 1.32–1.59 m (12H, CH, CH_2), 1.80–2.18 m (2H, 1′-H, 1″-H), 2.40 m (1H, 1″-H), 2.75 m (2H, 2′-H), 3.05 m (2H, 2″-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.19, 14.62, 16.13, 17.01, 17.60, 18.92, 19.49, 20.05, 21.04, 23.21, 25.97, 29.12, 30.03, 31.10, 32.34, 33.70, 36.78, 37.12, 40.11, 43.34, 46.17, 48.64, 49.18, 49.71, 50.17, 51.48, 60.40, 91.18 (C^{20}), 157.43 ($C^{3''}$), 158.33 ($C^{3'}$), 178.10 (C^{24}), 220.32 (C^3). Mass spectrum (ESI): *m*/*z* 629.3924 $[M + Na]^+$. $C_{33}H_{50}N_8O_3$. Calculated: *M* 606.4006.

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