

## Synthesis of 1,2,3-Thiadiazolo Terpenoids on the Basis of Cyclopentanonopimaric and Betulonic Acids

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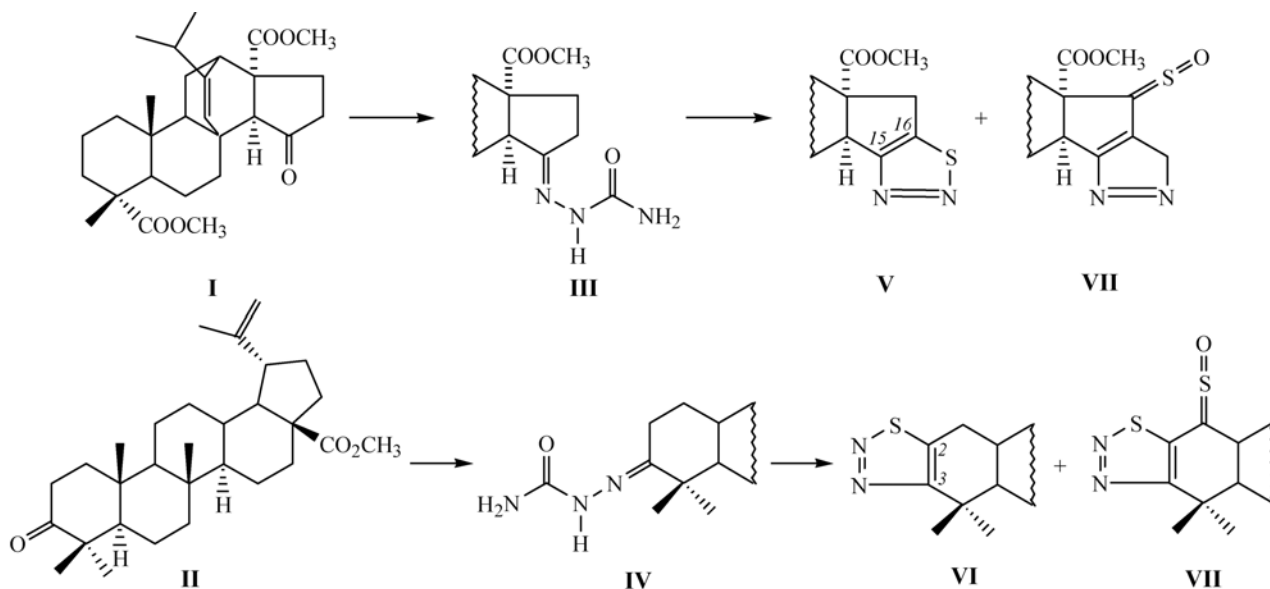
**Abstract**—The Hurd–Mori reaction with derivatives of cyclopentanonopimaric and betulonic acids afforded mostly the corresponding 1,2,3-thiadiazoles and small amounts of thioketone oxides.

Compounds containing a 1,2,3-thiadiazole fragment exhibit versatile biological activity. For example, a highly active cotton defoliant and a plant immune adjuvant were found among 1,2,3-thiadiazole derivatives [1]. In addition, some compounds of this series are key intermediates in the synthesis of other biologically active substances, e.g., cephalosporin antibiotics [2]. The use of the Hurd–Mori reaction for the synthesis of 1,2,3-thiadiazoles on the basis of naturally occurring compounds was reported only for *seco* derivatives of (+)-carene,  $\alpha$ -pinene [3], and an androstane steroid [4]. With the goal of obtaining new biologically active

substances, we made an attempt to introduce a 1,2,3-thiadiazole fragment into molecules of di- and triterpenoids.

As starting compounds we used methyl esters **I** and **II** derived from cyclopentanonopimaric and betulonic acids, respectively (Scheme 1) [5–7]. 1,2,3-Thiadiazolo derivatives **V** and **VI** were synthesized from semi-carbazones **III** and **IV**, respectively, and thionyl chloride. The products were isolated in 72–75% yield by column chromatography on aluminum oxide. Apart from the major products, we also isolated small amounts of thioketone oxides **VII** and **VIII**.

Scheme.



Semicarbazones **III** and **IV** were prepared in turn from terpenoids **I** and **II** and semicarbazide in aqueous ethanol (yield 70–75%). The  $^{13}\text{C}$  NMR spectra of **III** and **IV** contained additional signals from the carbonyl carbon atom in the semicarbazone moiety ( $\delta_{\text{C}}$  157.9 and 158.7 ppm, respectively), and the signal from the C=N carbon atom was observed at  $\delta_{\text{C}}$  158.7 and 159.4 ppm. Protons of the  $\text{NH}_2$  and NH groups appeared in the  $^1\text{H}$  NMR spectra as a multiplet or broadened singlet at  $\delta$  7.10–7.16 and 8.40–8.48 or 8.60 ppm, respectively. In the  $^{13}\text{C}$  NMR spectra of compounds **V** and **VI**, characteristic signals of the thiadiazole fragment were observed, respectively, at  $\delta_{\text{C}}$  153.1 and 145.1 ppm (=C–N=) and 171.7 and 165.3 ppm (=C–S–). Thioketone oxides **VII** and **VIII** showed in the  $^{13}\text{C}$  NMR spectra analogous signals from carbon atoms in the thiadiazole ring, and new signals belonging to the C=S=O group appeared at  $\delta_{\text{C}}$  190.2 and 194.9 ppm.

## EXPERIMENTAL

The IR spectra were recorded on a Specord M-80 spectrometer from samples dispersed in mineral oil. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were obtained on a Bruker AM-300 instrument at 300 and 75.5 MHz, respectively, using chloroform-*d* as solvent and tetramethylsilane as internal reference. The melting points were determined on a Boetius micro device. TLC analysis was performed on Silulfol plates (Chemapol, Czechia), using chloroform–methanol (25 : 1) as eluent. Spots were detected by treatment with a 10% solution of phosphotungstic acid in ethanol, followed by heating at 100–120°C for 2–3 min. Initial methyl esters **I** and **II** were synthesized by the procedures described in [5, 7].

### Semicarbazones **III** and **IV** (general procedure).

To a solution of 0.48 g (1 mmol) of compound **I** or 0.47 g (1 mmol) of compound **II** in 10 ml of ethanol we added with stirring 10 ml of a 1.2 M aqueous solution of semicarbazide hydrochloride and 0.5 g of sodium acetate trihydrate, and the mixture was stirred for 6 h at 40°C. The mixture was then poured into 100 ml of water, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol.

**Semicarbazone III.** Yield 0.37 g (70%), mp 128–130°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3460–3180, 1730, 1700, 1580, 1470, 1380, 1320, 1290, 1200, 1115, 1080, 1035, 975, 935, 850, 770, 730.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.52 s (3H, 23-H), 0.80 d (3H, 21-H/22-H,  $J$  = 6.8 Hz), 0.85 d (3H, 22-H/21-H,  $J$  = 6.8 Hz), 0.89–0.98 m (2H, 1- $\text{H}_{\text{ax}}$ , 11- $\text{H}_{\text{ax}}$ ), 1.05 s (3H, 24-H), 1.17–1.50 m (8H, 1- $\text{H}_{\text{eq}}$ , 2- $\text{H}_{\text{ax}}$ , 2- $\text{H}_{\text{eq}}$ , 3- $\text{H}_{\text{eq}}$ , 6- $\text{H}_{\text{ax}}$ , 6- $\text{H}_{\text{eq}}$ , 7- $\text{H}_{\text{ax}}$ , 7- $\text{H}_{\text{eq}}$ ), 1.51–1.72 m (4H,

3- $\text{H}_{\text{ax}}$ , 11- $\text{H}_{\text{eq}}$ , 9-H, 5-H), 1.81–1.97 m (4H, 16- $\text{H}_{\text{ax}}$ , 16- $\text{H}_{\text{eq}}$ , 17- $\text{H}_{\text{ax}}$ , 17- $\text{H}_{\text{eq}}$ ), 2.20 d.d.d (1H, 12-H,  $^4J_{12,19}$  = 1.6,  $^3J_{12,11-\text{ax}}$  = 2.2,  $^3J_{12,11-\text{eq}}$  = 13.2 Hz), 2.35 sept (1H, 20-H,  $J$  = 6.8 Hz), 2.85 br.s (1H, 14-H), 3.55 s (3H, 28-H), 3.65 s (3H, 27-H), 5.19 br.s (1H, 19-H), 8.40–8.48 m (3H, NH,  $\text{NH}_2$ ).  $^{13}\text{C}$  NMR spectrum,  $\delta_{\text{C}}$ , ppm: 15.3, 16.4, 16.7, 19.8, 20.5, 21.7, 25.6, 27.9, 33.6, 33.8, 34.8, 36.4, 37.1, 37.6, 41.1, 41.8, 46.8, 48.9, 51.5, 51.8, 52.5, 55.6, 58.9, 125.9 (CH=C), 146.2 (C=CH), 157.9 (NHCONH $_2$ ), 158.7 (C=N), 176.8 (COOCH $_3$ ), 178.9 (COOCH $_3$ ). Found, %: C 68.03; H 7.94; N 8.85.  $\text{C}_{29}\text{H}_{43}\text{N}_3\text{O}_5$ . Calculated, %: C 67.81; H 8.44; N 8.18.

**Semicarbazone IV.** Yield 0.39 g (75%), mp 143–145°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3400–3100, 1730, 1690, 1550, 1470, 1380, 1290, 1210, 1150, 1070, 1050, 980, 930, 880, 730.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.86 s, 0.94 s, 1.00 s, 1.18 s, 1.24 s, 1.43 s, and 1.67 s (18H, 6CH $_3$ ); 1.20–1.90 m (CH $_2$ , CH); 2.35–2.45 m (3H, 13-H, 16-H); 2.95–3.05 m (1H, 19-H); 3.65 s (3H, OCH $_3$ ); 4.60 br and 4.75 br (1H each, 29-H); 7.10–7.16 m (2H, NH $_2$ ), 8.60 br.s (1H, NH).  $^{13}\text{C}$  NMR spectrum,  $\delta_{\text{C}}$ , ppm: 14.6, 15.5, 15.8, 19.3, 19.5, 19.6, 20.9, 21.2, 23.4, 25.5, 28.2, 29.6, 30.5, 32.0, 33.6, 34.0, 36.9, 38.2, 40.6, 41.2, 42.4, 46.9, 49.4, 49.9, 51.2, 55.3, 56.5, 109.6 (C $^{29}$ ), 150.3 (C $^{20}$ ), 158.7 (NHCONH $_2$ ), 159.4 (C=N), 176.5. Found, %: C 77.35; H 10.10; N 7.71.  $\text{C}_{32}\text{H}_{51}\text{N}_3\text{O}_3$ . Calculated, %: C 73.10; H 9.77; N 7.99.

### Compounds **V** and **VI** (general procedure).

Freshly distilled thionyl chloride, 1.45 ml (20 mmol) was added in one portion under stirring to a suspension of 0.50 g (1 mmol) of compound **III** or 0.53 g (1 mmol) of compound **IV** in 20 ml of dry methylene chloride. The mixture was stirred for 6 h at room temperature and was left overnight, 20 ml of water was added, and the organic phase was separated and washed with a 10% solution of sodium carbonate (3  $\times$  20 ml) and water (3  $\times$  20 ml), dried over MgSO $_4$ , and evaporated under reduced pressure. The residue was subjected to chromatography on aluminum oxide using benzene as eluent to isolate compound **V** or **VI**. The subsequent elution with benzene–methanol (10 : 1) afforded minor product **VII** or **VIII**.

**Dimethyl (5*R*,9*R*,13*S*)-22-isopropyl-5,9-dimethyl-16-thia-17,18-diazahexacyclo-[10.8.2.0 $^{1,10}$ .0 $^{4,9}$ .0 $^{13,20}$ .0 $^{15,19}$ ]docosa-15(19),17,21-triene-5,13-dicarboxylate (V).** Yield 0.37 g (75%), mp 98–100°C. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 1730, 1650, 1500, 1460, 1380, 1320, 1255, 1115, 1085, 1030, 990, 945, 850, 740.  $^1\text{H}$  NMR spectrum,  $\delta$ , ppm: 0.55 s (3H, 23-H), 0.80 d (3H, 21-H/22-H,  $J$  = 6.8 Hz), 0.85 d (3H, 22-H/21-H,  $J$  = 6.8 Hz), 0.89–0.98 m (2H, 1- $\text{H}_{\text{ax}}$ , 11- $\text{H}_{\text{ax}}$ ), 1.05 s (3H, 24-H), 1.17–1.50 m (8H, 1- $\text{H}_{\text{eq}}$ , 2- $\text{H}_{\text{ax}}$ , 2- $\text{H}_{\text{eq}}$ , 3- $\text{H}_{\text{eq}}$ , 6- $\text{H}_{\text{ax}}$ ,

6- $H_{eq}$ , 7- $H_{ax}$ , 7- $H_{eq}$ ), 1.51–1.72 m (4H, 3- $H_{ax}$ , 11- $H_{eq}$ , 9-H, 5-H), 2.20 sept (1H, 20-H,  $J = 6.8$  Hz), 2.50 d.d.d (1H, 12-H,  $^4J_{12,19} = 1.6$ ,  $^3J_{12,11-ax} = 2.2$ ,  $^3J_{12,11-eg} = 13.2$  Hz), 2.85 br.s (1H, 14-H), 3.2 s (2H, 17- $H_{ax}$ , 17- $H_{eq}$ ), 3.55 s (3H, 28-H), 3.65 s (3H, 27-H), 5.20 br.s (1H, 19-H).  $^{13}C$  NMR spectrum,  $\delta_C$ , ppm: 15.7, 16.7, 17.1, 19.9, 21.2, 21.7, 25.2, 34.3, 35.2, 35.4, 36.3, 37.4, 38.0, 41.6, 43.1, 47.2, 49.4, 51.8, 52.5, 53.2, 54.8, 65.3, 126.6 (CH=C), 145.5 (C=CH), 153.1 (=CS), 171.7 (=CN=), 175.9 (COOCH<sub>3</sub>), 179.2 (COOCH<sub>3</sub>). Found, %: C 68.48; H 7.00; N 5.15; S 6.12. C<sub>28</sub>H<sub>38</sub>N<sub>2</sub>O<sub>4</sub>S. Calculated, %: C 67.44; H 7.68; N 5.62; S 6.43.

**Methyl 1-isopropenyl-5b,8,8,12a-tetramethyl-2,3,3a,4,5,5a,5b,6,7,7a,8,12,12a,12b,13,14,14a,14b-octadecahydro-1H-cyclopenta[7,8]chryseno-[2,3-d][1,2,3]thiadiazole-3a-carboxylate (VI).** Yield 0.37 g (72%), mp 108–110°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1720, 1680, 1560, 1480, 1380, 1300, 1220, 1170, 1080, 1050, 970, 920, 850, 710.  $^1H$  NMR spectrum,  $\delta$ , ppm: 0.74 s, 0.93 s, 0.94 s, 1.30 s, 1.42 s, and 1.60 s (18H, 6CH<sub>3</sub>); 1.00–1.90 m (CH<sub>2</sub>, CH); 2.20–2.30 m (3H, 13-H, 16-H); 2.90–3.00 m (1H, 19-H), 3.62 s (3H, OCH<sub>3</sub>); 4.55 br.s and 4.70 br.s (1H each, 29-H).  $^{13}C$  NMR spectrum,  $\delta_C$ , ppm: 14.4, 15.4, 15.8, 19.1, 19.2, 21.3, 23.4, 25.6, 29.5, 30.4, 31.0, 31.9, 33.1, 36.0, 36.6, 37.2, 38.0, 38.4, 40.6, 42.3, 46.7, 48.8, 49.1, 51.0, 52.3, 56.3, 109.5 (C<sup>29</sup>), 145.1 (=CS), 150.1 (C<sup>20</sup>), 165.3 (=CN=), 176.2. Found, %: C 73.05; H 8.85; N 5.30; S 5.98. C<sub>31</sub>H<sub>46</sub>N<sub>2</sub>O<sub>2</sub>S. Calculated, %: C 72.89; H 9.07; N 5.48; S 6.27.

**Dimethyl (5R,9R,13S)-22-isopropyl-5,9-dimethyl-14-sulfinyl-16-thia-17,18-diazahexacyclo-[10.8.2.0<sup>1,10</sup>.0<sup>4,9</sup>.0<sup>13,20</sup>.0<sup>15,19</sup>]docosa-15(19),17,21-triene-5,13-dicarboxylate (VII).** Yield 0.05 g (10%), mp 133–135°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1730, 1645, 1695, 1460, 1385, 1320, 1245, 1110, 1080, 1035, 990, 945, 840, 730.  $^1H$  NMR spectrum,  $\delta$ , ppm: 0.55 s (3H, 23-H), 0.80 d (3H, 21-H/22-H,  $J = 6.8$  Hz), 0.85 d (3H, 22-H/21-H,  $J = 6.8$  Hz), 0.89–0.98 m (2H, 1- $H_{ax}$ , 11- $H_{ax}$ ), 1.05 s (3H, 24-H), 1.17–1.50 m (8H, 1- $H_{eq}$ , 2- $H_{ax}$ , 2- $H_{eq}$ , 3- $H_{eq}$ , 6- $H_{ax}$ , 6- $H_{eq}$ , 7- $H_{ax}$ , 7- $H_{eq}$ ), 1.51–1.72 m (4H, 3- $H_{ax}$ , 11- $H_{eq}$ , 9-H, 5-H), 2.20 sept (1H, 20-H,  $J = 6.8$  Hz), 2.50 d.d.d (1H, 12-H,  $^4J_{12,19} = 1.6$ ,  $^3J_{12,11-ax} = 2.2$ ,  $^3J_{12,11-eg} = 13.2$  Hz), 2.85 br.s (1H, 14-H), 3.55 s (3H, 28-H), 3.65 s (3H, 27-H), 5.20 br.s (1H, 19-H).  $^{13}C$  NMR spectrum,  $\delta_C$ , ppm: 15.5, 16.8, 17.2, 19.9, 21.0, 21.8, 25.2, 35.2, 35.4, 36.3, 37.4, 38.0, 41.6, 43.1, 47.2, 49.4, 51.8, 52.5, 53.2, 54.8,

65.3, 126.9 (CH=C), 146.5 (C=CH), 153.3 (=CS), 170.9 (=CN=), 176.2 (COOCH<sub>3</sub>), 179.2 (COOCH<sub>3</sub>), 190.2 (C=S=O). Found, %: C 62.18; H 6.90; N 5.20; S 12.00. C<sub>28</sub>H<sub>36</sub>N<sub>2</sub>O<sub>5</sub>S<sub>2</sub>. Calculated, %: C 61.74; H 6.66; N 5.14; S 11.77.

**Methyl 1-isopropenyl-5b,8,8,12a-tetramethyl-12-sulfenyl-2,3,3a,4,5,5a,5b,6,7,7a,8,12,12a,12b,13,14,14a,14b-octadecahydro-1H-cyclopenta-[7,8]chryseno[2,3-d][1,2,3]thiadiazole-3a-carboxylate (VIII).** Yield 0.06 g (12%), mp 152–154°C. IR spectrum,  $\nu$ , cm<sup>-1</sup>: 1700, 1670, 1550, 1490, 1380, 1330, 1240, 1150, 1090, 1050, 950, 920, 860, 720.  $^1H$  NMR spectrum,  $\delta$ , ppm: 0.67 s, 0.85 s, 0.88 s, 1.25 s, 1.36 s, and 1.70 s (18H, 6CH<sub>3</sub>); 1.00–2.00 m (CH<sub>2</sub>, CH); 2.22–2.32 m (3H, 13-H, 16-H); 2.90–3.00 m (1H, 19-H); 3.65 s (3H, OCH<sub>3</sub>); 4.57 br.s and 4.73 br.s (1H each, 29-H).  $^{13}C$  NMR spectrum,  $\delta_C$ , ppm: 14.7, 15.7, 16.2, 19.3, 21.6, 23.6, 26.7, 29.8, 31.3, 32.4, 33.4, 36.4, 36.8, 37.5, 38.3, 38.7, 40.9, 42.6, 42.8, 46.6, 49.1, 50.1, 51.4, 52.6, 56.6, 109.8 (C<sup>29</sup>), 145.4 (=CS), 150.9 (C<sup>20</sup>), 165.6 (=CN=), 176.4, 194.9 (C=S=O). Found, %: C 67.05; H 8.15; N 5.23; S 11.29. C<sub>31</sub>H<sub>44</sub>N<sub>2</sub>O<sub>3</sub>S<sub>2</sub>. Calculated, %: C 66.80; H 7.96; N 5.03; S 11.50.

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