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SYNTHESIS OF DITERPENE INDOLES FROM CYCLOPENTENONEPIMARIC ACID

E. V. Tret'yakova, O. B. Flekhter, F. Z. Galin, L. V. Spirikhin, and G. A. Tolstikov

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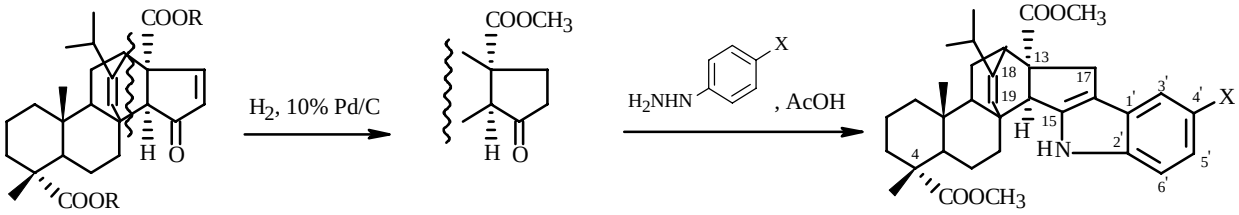
Diterpene indoles were prepared by the Fischer reaction from cyclopentenonepimaric acid. The structures of the synthesized compounds were confirmed by IR and NMR spectroscopies.

Key words: quinopimaric acid, cyclopentenonepimaric acid, Fischer reaction, diterpene indoles.

Levo-pimaric acid is found in pine resin and readily forms adducts with several dienophiles [1, 2] including benzoquinones [3-6]. We have found that 18-isopropyl-4,10-dimethyl-4,13-dicarboxy-8,12-etheno-cyclopenteno-perhydrophenanthrene (**1**), for which we propose the name cyclopentenonepimaric acid, is prepared from quinopimaric acid epoxide by Favorskii rearrangement [7, 8] and can be used to synthesize the diterpene heterocycles **4** and **5**.



1: R = H
2: R = CH_3

3

4: X = H
5: **X** = CH_3

Catalytic hydrogenolysis reduces only the conjugated double bond of the dimethyl ester of **2** to give the dihydro derivative **3** in quantative yield according to ^{1}H NMR. A Fischer reaction of **3** with phenyl- and tolylhydrazines in acetic acid forms diterpene indoles **4** and **5** in yields of 68 and 71%, respectively. The structures of the synthesized compounds were established using spectra.

Thus, ^{1}H NMR spectra of **4** and **5** exhibit signals for aromatic protons 3′-H—6′-H in the range 6.91-7.27 ppm. Signals for C-1′—C-6′ in the ^{13}C NMR resonate in the range 111.2-140.7 ppm. However, the signals for C-15 undergo strong-field shifts (δ 142.9 and 142.6 ppm); for C-16, weak-field shifts (δ 118.0 and 118.6 ppm) in the spectra of **4** and **5** compared with starting **3**.

The IR spectra of **4** and **5** in the range 3360-3592 and 1590-1610 cm^{-1} have bands characteristic of NH and aromatic stretches.

EXPERIMENTAL

IR spectra were recorded in mineral oil on Specord M80 and UR-20 spectrometers. ^{13}C and ^{1}H NMR spectra were

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, Ufa, pr. Oktyabrya, 71, fax (3472) 35 60 66, e-mail: obf@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 206-208, May-June, 2002. Original article submitted April 10, 2002.

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recorded on a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively) in $CDCl_3$ with TMS internal standard. Melting points were measured on a Boetius microstage.

TLC was performed on Silufol (Chemapol, Czech Rep.) plates using $CHCl_3$—CH_3OH (20:1). Compounds were developed using phosphotungstic acid in ethanol (10%) with subsequent heating at 100-120°C for 2-3 min.

Elemental analyses agreed with those calculated.

18-Isopropyl-4,10-dimethyl-4,13-dicarboxy-8,12-ethenocyclopentenoperhydrophenanthrene (cyclopentenonepimaric acid) (1) was prepared by the literature method [7]. ^{1}H NMR spectrum (δ, ppm, J/Hz): 0.53 (s, 3H, 23-H), 0.92 (d, J = 6.8, 3H, 21-H/22-H), 0.93 (d, J = 6.8, 3H, 22-H/21-H), 1.00 (m, 1H, 1-H_{ax}), 1.10 (m, 1H, 11-Hβ), 1.15 (s, 3H, 24-H), 1.23 (m, 1H, 6-H_{eq}), 1.30-1.51 (m, 2H, 2-H), 1.34 (m, 1H, 1-H_{eq}), 1.47 (m, 1H, 3-H_{eq}), 1.53 (m, 1H, 6-H_{ax}), 1.59 (m, 1H, 11-Hα), 1.78 (m, 1H, 3-H_{ax}), 1.90 (m, 1H, 9-H), 2.11 (sept, J = 6.8, $J_{19,11}$ = 1.2, 20-H), 2.30-2.51 (m, 3H, 7-H, 5-H), 2.55 (br.s, 1H, 12-H), 2.61 (br.s, 1H, 14-H), 5.19 (br.s, 1H, 19-H), 6.05 (d, J = 6, 1H, 16-H), 7.35 (d, 1H, 17-H), 7.75 (br.s, 1H, OH).

^{13}C NMR spectrum: 38.2 (C-1), 17.0 (C-2), 36.7 (C-3), 46.9 (C-4), 49.1 (C-5), 21.9 (C-6), 32.8 (C-7), 41.8 (C-8), 53.1 (C-9), 37.4 (C-10), 25.4 (C-11), 40.8 (C-12), 61.4 (C-13), 58.2 (C-14), 208.5 (C-15), 136.7 (C-16), 162.2 (C-17), 145.3 (C-18), 124.5 (C-19), 29.6 (C-20), 20.9 (C-21), 20.4 (C-22), 15.5 (C-23), 16.4 (C-24), 185.3 (C-25), 178.4 (C-26).

18-Isopropyl-4,10-dimethyl-4,13-dimethoxycarbonyl-8,12-ethenocyclopentenoperhydrophenanthrene (2) was prepared by methylation of **1** with the calculated amount of diazomethane in ethyl ether. ^{1}H NMR spectrum (δ, ppm, J/Hz): 0.53 (s, 3H, 23-H), 0.92 (d, J = 6.8, 3H, 21-H/22-H), 0.93 (d, J = 6.8, 3H, 22-H/21-H), 1.00 (m, 1H, 1-H_{ax}), 1.10 (m, 1H, 11Hβ), 1.15 (s, 3H, 24-H), 1.23 (m, 1H, 6p-H_{eq}), 1.30-1.51 (m, 2H, 2-H), 1.34 (m, 1H, 1-H_{eq}), 1.47 (m, 1H, 3-H_{eq}), 1.53 (m, 1H, 6-H_{ax}), 1.59 (m, 1H, 11-Hα), 1.78 (m, 1H, 3-H_{ax}), 1.90 (m, 1H, 9-H), 2.11 (sept, J = 6.8, $J_{19,11}$ = 1.2, 20-H), 2.30-2.51 (m, 3H, 7-H, 5-H), 2.55 (br.s, 1H, 12-H), 2.61 (br.s, 1H, 14-H), 3.60 (s, 3H, 27-H), 3.65 (s, 3H, 28-H), 5.19 (br.s, 1H, 19-H), 6.05 (d, J = 6, 1H, 16-H), 7.35 (d, 1H, 17-H).

^{13}C NMR spectrum: 38.2 (C-1), 17.0 (C-2), 36.6 (C-3), 47.1 (C-4), 51.8 (C-5), 21.7 (C-6), 34.5 (C-7), 41.7 (C-8), 52.6 (C-9), 37.4 (C-10), 25.3 (C-11), 40.7 (C-12), 61.4 (C-13), 53.0 (C-14), 208.2 (C-15), 136.5 (C-16), 162.1 (C-17), 145.3 (C-18), 124.4 (C-19), 32.8 (C-20), 20.9 (C-21), 20.3 (C-22), 16.7 (C-23), 15.5 (C-24), 179.2 (C-25), 172.9 (C-26), 49.2 (C-27), 58.4 (C-28).

18-Isopropyl-4,10-dimethyl-4,13-dimethoxycarbonyl-8,12-ethenocyclopentanoperhydrophenanthrene (3). A solution of **2** (0.46 g, 1 mmole) in absolute ethylacetate (75 mL) containing Pd/C (10%, 50 mg) at room temperature was purged with H_2 until absorption was complete. The catalyst was filtered off. The solvent was removed in vacuum by a water aspirator. Yield 0.42 g, 91%, mp 75-80°C.

IR spectrum (ν, cm^{-1}): 770, 827, 860, 890, 920, 1010, 1045, 1072, 1098, 1129, 1156, 1210, 1260, 1385, 1480, 1640, 1735, 1740, 2390, 2680.

^{1}H NMR spectrum (δ, ppm, J/Hz): 0.53 (s, 3H, 23-H), 0.92 (d, J = 6.8, 3H, 21-H/22-H), 0.93 (d, J = 6.8, 3H, 22-H/21-H), 1.00 (m, 1H, 1-H_{ax}), 1.10 (m, 1H, 11-Hβ), 1.15 (s, 3H, 24-H), 1.23 (m, 1-H, 6-H_{eq}), 1.30-1.51 (m, 2H, 2-H), 1.34 (m, 1H, 1-H_{eq}), 1.47 (m, 1H, 3-H_{ax}), 1.53 (m, 1H, 6-H_{ax}), 1.59 (m, 1H, 11-Hα), 1.78 (m, 1H, 3-H_{ax}), 1.90 (m, 1H, 9-H), 2.11 (sept, J = 6.8, $J_{19,11}$ = 1.2, 20-H), 2.30-2.51 (m, 3H, 7-H, 5-H), 2.55 (br.s, 1H, 12-H), 2.61 (br.s, 1H, 14-H), 3.60 (s, 3H, 27-H), 3.65 (s, 3H, 28-H), 5.19 (br.s, 1H, 19-H).

^{13}C NMR spectrum: 37.9 (C-1), 16.9 (C-2), 36.5 (C-3), 47.0 (C-4), 51.8 (C-5), 21.7 (C-6), 34.5 (C-7), 41.1 (C-8), 52.2 (C-9), 37.4 (C-10), 25.9 (C-11), 39.4 (C-12), 61.8 (C-13), 52.9 (C-14), 218.1 (C-15), 30.5 (C-16), 42.0 (C-17), 147.3 (C-18), 126.0 (C-19), 33.9 (C-20), 20.8 (C-21), 20.0 (C-22), 16.7 (C-23), 15.4 (C-24), 179.1 (C-25), 176.9 (C-26), 49.1 (C-27), 54.6 (C-28).

General Synthetic Method for 4 and 5. A solution of **3** (0.46 g, 1 mmole) in acetic acid (20 mL) was treated with phenyl- or tolylhydrazine hydrochloride (3.5 mmole) and refluxed for 18-20 h with TLC monitoring. The reaction mixture was poured into water (100 mL). The precipitate was filtered off, washed with water, and dried. The solid was chromatographed over a silica-gel column with elution by benzene.

15,16-Indolo-18-isopropyl-4,10-dimethyl-4,13-dimethoxycarbonyl-8,12-ethenocyclopentenoperhydrophenanthrene (4). Yield 0.31 g, 68%, R_f 0.87, mp 128-130°C.

IR spectrum (ν, cm^{-1}): 770, 827, 855, 890, 950, 1020, 1085, 1190, 1156, 1210, 1260, 1315, 1460, 1590, 1640, 1730, 1740, 3360.

^{1}H NMR spectrum (δ, ppm, J/Hz): 0.53 (s, 3H, 23-H), 0.92 (d, J = 6.8, 3H, 21-H/22-H), 0.93 (d, J = 6.8, 3H, 22-H/21-

H), 1.00 (m, 1H, 1-H_{ax}), 1.10 (m, 1H, 11-Hβ), 1.15 (s, 3H, 24-H), 1.23 (m, 1H, 6-H_{eq}), 1.31-1.50 (m, 2H, 2-H), 1.34 (m, 1H, 1-H_{eq}), 1.47 (m, 1H, 3-H_{eq}), 1.53 (m, 1H, 6-H_{ax}), 1.59 (m, 1H, 11-Hα), 1.78 (m, 1H, 3-H_{ax}), 1.90 (m, 1H, 9-H), 2.11 (sept, J = 6.8, $J_{19,11}$ = 1.2, 1H, 20-H), 2.30-2.51 (m, 3H, 7-H, 5-H), 2.55 (br.s, 1H, 12-H), 2.61 (br.s, 1H, 14-H), 2.81 (m, 2H, 17-H), 3.60 (s, 3H, 27-H), 3.65 (s, 3H, 28-H), 5.19 (br.s, 1H, 19-H), 6.91 (d, J = 7.2, 1H, 3′-H), 6.98 (t, J = 7.2, 1H, 4′-H), 7.15 (t, J = 7.2, 1H, 5′-H), 7.27 (d, J = 7.2, 1H, 6′-H), 7.85 (s, 1H, NH).

^{13}C NMR spectrum: 36.8 (C-1), 17.1 (C-2), 35.4 (C-3), 41.7 (C-4), 47.1 (C-5), 25.5 (C-6), 34.1 (C-7), 36.8 (C-8), 49.3 (C-9), 36.1 (C-10), 29.9 (C-11), 37.5 (C-12), 63.5 (C-13), 51.9 (C-14), 142.9 (C-15), 118.0 (C-16), 21.6 (C-17), 145.6 (C-18), 124.1 (C-19), 33.4 (C-20), 29.9 (C-21), 23.9 (C-22), 16.7 (C-23), 16.4 (C-24), 179.4 (C-25), 177.6 (C-26), 44.7 (C-27), 56.2 (C-28), 123.8 (C-1′), 140.7 (C-2′), 126.8 (C-3′), 120.6 (C-4′), 118.3 (C-5′), 111.2 (C-6′).

Found, %: C 76.99, H 8.21, N 2.86. $C_{34}H_{43}NO_4$. Calc., %: C 77.09, H 8.18, N 2.64.

Methyl-15,16-indolo-18-isopropyl-4,10-dimethyl-4,13-dimethoxycarbonyl-8,12-ethenocyclopentenoperhydrophenanthrene (5). Yield 0.33 g, 71%, R_f 0.87, mp 105-107°C.

IR spectrum (ν, cm^{-1}): 765, 821, 855, 890, 970, 1010, 1185, 1156, 1190, 1210, 1260, 1320, 1460, 1605, 1635, 1720, 1740, 3590.

^{1}H NMR spectrum (δ, ppm, J/Hz): 0.53 (s, 3H, 23-H), 0.92 (d, J = 6.8, 3H, 21-H/22-H), 0.93 (d, J = 6.8, 3H, 22-H/21-H), 1.00 (m, 1H, 1-H_{ax}), 1.10 (m, 1H, 11-Hβ), 1.15 (s, 3H, 24-H), 1.23 (m, 1H, 6-H_{eq}), 1.31-1.50 (m, 2H, 2-H), 1.34 (m, 1H, 1-H_{eq}), 1.47 (m, 1H, 3-H_{eq}), 1.53 (m, 1H, 6-H_{ax}), 1.59 (m, 1H, 11-Hα), 1.78 (m, 1H, 3-H_{ax}), 1.90 (m, 1H, 9-H), 2.11 (sept, J = 6.8, $J_{19,11}$ = 1.2, 1H, 20-H), 2.30-2.51 (m, 3H, 7-H, 5-H), 2.37 (s, 3H, 7′-H), 2.55 (br.s, 1H, 12-H), 2.61 (br.s, 1H, 14-H), 2.81 (m, 2H, 17-H), 3.60 (s, 3H, 27-H), 3.65 (s, 3H, 28-H), 5.19 (br.s, 1H, 19-H), 6.91 (d, J = 7.2, 1H, 3′H), 6.98 (t, J = 7.2, 1H, 5′-H), 7.27 (d, J = 7.2, 1H, 6′-H), 7.85 (s, 1H, NH).

^{13}C NMR spectrum: 37.9 (C-1), 17.1 (C-2), 36.8 (C-3), 47.2 (C-4), 51.9 (C-5), 21.9 (C-6), 35.5 (C-7), 41.8 (C-8), 52.2 (C-9), 37.2 (C-10), 25.5 (C-11), 42.4 (C-12), 63.5 (C-13), 53.9 (C-14), 142.6 (C-15), 118.7 (C-16), 35.6 (C-17), 145.6 (C-18), 125.5 (C-19), 34.1 (C-20), 21.2 (C-21), 19.9 (C-22), 16.7 (C-23), 15.7 (C-24), 179.4 (C-25), 177.6 (C-26), 49.3 (C-27), 56.3 (C-28), 123.3 (C-1′), 140.1 (C-2′), 121.4 (C-3′), 120.1 (C-4′), 119.3 (C-5′), 116.0 (C-6′), 16.7 (C-7′).

Found, %: C 77.09, H 8.28, N 2.60. $C_{35}H_{45}NO_4$. Calc., %: C 77.31, H 8.34, N 2.58.

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