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Synthesis of 2-Amino-4-aryl-3-cyano-4*H*-pyrano and 2-Amino-3-cyanothieno Derivatives of Cyclopentanonopimaric Acid

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

Institute of Organic Chemistry, Ufa Research Center, Russian Academy of Sciences, pr. Oktyabrya 71, Ufa, 450054 Bashkortostan, Russia
e-mail: obf@anrb.ru

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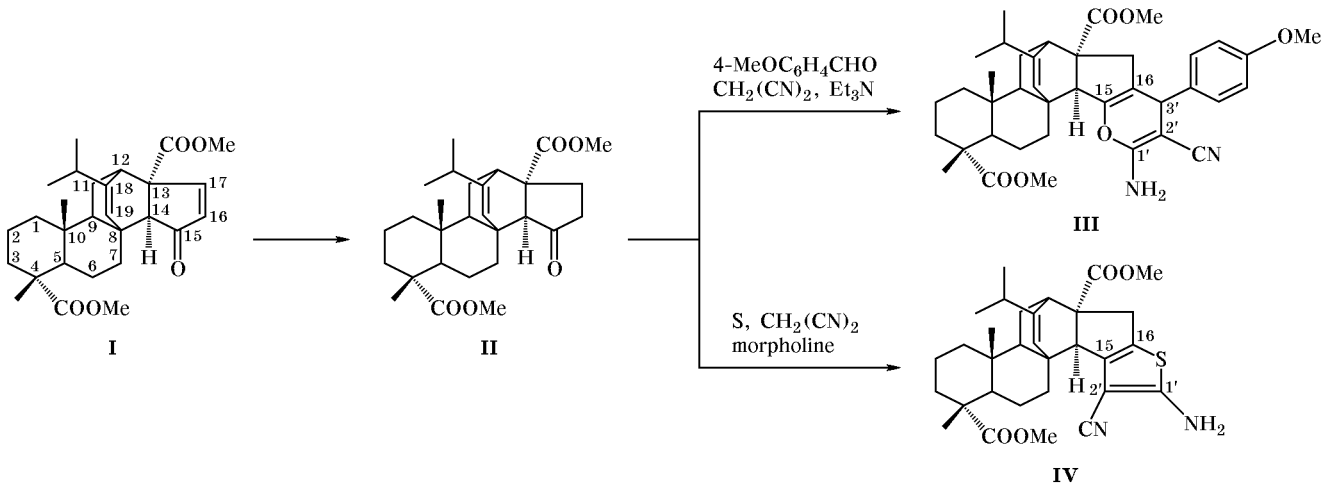
Abstract—Condensation of cyclopentanonopimaric acid with malononitrile in the presence of *p*-methoxybenzaldehyde or elemental sulfur gave the corresponding fused 2-amino-3-cyano-4-(4-methoxyphenyl)-4*H*-pyrano and 2-amino-3-cyanothieno derivatives.

Derivatives of rosin acids of the abietane series exhibit a wide spectrum of biological activity [1, 2]. Heterocyclic compounds derived from dehydroabietic acid were recently shown to possess a strong antibacterial and fungicide activity [3].

We have synthesized fused pyrano and thieno derivatives **III** and **IV** from cyclopentanonopimaric acid which is readily available from quinopimaric acid [4]. Catalytic hydrogenation of dimethyl ester **I** was successfully performed over both Pd/C and Raney nickel. The reduction involved only the conjugated $C^{16}=C^{17}$ double bond, which was confirmed by the ^1H NMR data. The ^1H and ^{13}C signals in the spectra of diterpenoids **I** and **II** were assigned on the basis of calculations by the additivity schemes [5].

Reactions of carbonyl compounds with α,β-unsaturated nitriles provide a convenient method of synthesis of heterocycles [6]. The pyran ring in **III** was built up via condensation of diester **II** with *p*-methoxybenzaldehyde and malononitrile in ethanol in the presence of triethylamine (Scheme 1), following the procedure reported in [7]. The yield of **III** was 65%. Its structure was established on the basis of spectral data. The presence of a conjugated cyano group in **III** is indicated by high intensity of the corresponding IR band at 2220 cm^{-1}. In addition, the IR spectrum of **III** contains absorption bands due to vibrations of the amino group (3390 and 1640 cm^{-1}) and C–O–C fragment of the pyran ring (1130 cm^{-1}). Aromatic proton signals appear in the ^1H NMR

Scheme 1.



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spectrum at δ 6.80–7.39 ppm. In the ^{13}C NMR spectrum, the CN signal is located at δ_C 112.6 ppm, the signal from $C^{1'}$ is observed at δ_C 158.8 ppm, and aromatic carbon signals occupy the δ_C range from 110.4 to 156.9 ppm. The formation of a cyclic adduct is confirmed by the chemical shifts of C^{15} and C^{16} (δ_C 151.3 and 95.3 ppm, respectively).

Fused 2-amino-3-cyanothieno derivative **IV** was synthesized in 53% yield by reaction of compound **II** with malononitrile and elemental sulfur [8] in MeOH containing a catalytic amount of morpholine at 60°C. The IR spectrum of **IV** contains absorption bands at 2230 cm^{-1} (C≡N) and at 3240 and 1650 cm^{-1} (NH_2). The chemical shifts of C^{15} and C^{16} are δ_C 153.9 and 146.1 ppm, respectively. The signals from the thiophene carbon atoms $C^{1'}$ and $C^{2'}$ appear at δ_C 166.0 and 98.2 ppm, respectively, and the cyano group gives a signal at δ_C 112.5 ppm.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in mineral oil. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 spectrometer at 300 and 75.5 MHz, respectively, using tetramethylsilane as internal reference. The optical rotations were measured on a Perkin–Elmer MC-241 polarimeter from solutions in chloroform. The melting points were determined on a Boetius microdevice. Silufol plates (Chemapol, Czechia) were used for TLC analysis; eluent chloroform–methanol, 20:1; spots were visualized by treatment with a 10% solution of phosphotungstic acid in ethanol and subsequent heating for 2–3 min at 100–120°C.

Dimethyl (17*S*)-19-isopropyl-5β,9β-dimethyl-16-oxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]nonadeca-14,18-diene-5α,13α-dicarboxylate (I) was prepared by the procedure reported in [4]. mp 68–70°C, $[\alpha]_D^{20}$ = –24.20 (*c* = 0.1, $CHCl_3$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.49 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.8], 0.85 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.8], 0.89–0.98 m (2H, 1-H_{ax}, 11-H_{ax}), 1.05 s (3H, 4-CH_3), 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}, 5-H, 9-H, 11-H_{eq}), 2.00 sept [1H, C**H**(CH$_3$)$_2$, *J* = 6.8], 2.35 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), 2.85 br.s (1H, 14-H), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.19 br.s (1H, 19-H), 5.89 d (1H, 16-H, *J* = 6.0), 7.21 d (1H, 17-H, *J* = 6.0). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 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**H(CH$_3$)$_2$], 20.9 [CH(**C**H$_3$)$_2$], 20.3 [CH(**C**H$_3$)$_2$], 16.7 (CH_3), 15.5 (CH_3), 179.2 (**C**OOCH$_3$), 172.9 (**C**OOCH$_3$), 49.2 (OCH_3), 58.4 (OCH_3).

Dimethyl (17*S*)-19-isopropyl-5β,9β-dimethyl-16-oxopentacyclo[10.5.2.0^{1,10}.0^{4,9}.0^{13,17}]nonadec-18-ene-5α,13α-dicarboxylate (II). A solution of 0.45 g (1 mmol) of compound **I** in 75 ml of anhydrous methanol was hydrogenated in the presence of 135 mg (20%) of Raney nickel. The catalyst was filtered off, and the solvent was distilled off from the filtrate under reduced pressure. Yield 0.44 g (90%), mp 79–80°C; published data [9]: mp 75–80°C; $[\alpha]_D^{20}$ = 13.20 (*c* = 0.1, $CHCl_3$). IR spectrum, ν, cm^{-1}: 770, 830, 860, 890, 920, 1010, 1045, 1070, 1098, 1160, 1210, 1260, 1385, 1480, 1640, 1735, 1740 ($COOCH_3$), 2390, 2680. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.50 s (3H, 10-CH_3), 0.80 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.8], 0.86 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.8], 0.88–0.97 m (2H, 1-H_{ax}, 11-H_{ax}), 1.05 s (3H, 4-CH_3), 1.15–1.50 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}), 1.52–1.70 m (4H, 3-H_{ax}, 5-H, 9-H, 11-H_{eq}), 1.81–1.97 m (4H, 16-H_{ax}, 16-H_{eq}, 17-H_{ax}, 17-H_{eq}), 2.05 sept [1H, C**H**(CH$_3$)$_2$, *J* = 6.8], 2.35 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), 2.85 br.s (1H, 14-H), 3.55 s (3H, $COOCH_3$), 3.65 s (3H, $COOCH_3$), 5.20 br.s (1H, 19-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 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**H(CH$_3$)$_2$], 20.8 [CH(**C**H$_3$)$_2$], 20.0 [CH(**C**H$_3$)$_2$], 16.7 (CH_3), 15.4 (CH_3), 179.1 (**C**OOCH$_3$), 176.9 (**C**OOCH$_3$), 49.1 (OCH_3), 54.6 (OCH_3).

Dimethyl (21*S*)-18-amino-17-cyano-23-isopropyl-16-(4-methoxyphenyl)-5β,9β-dimethyl-19-oxahexacyclo[10.9.2.0^{1,10}.0^{4,9}.0^{13,21}.0^{15,20}]tricosa-15(20),-17,22-triene-5α,13α-dicarboxylate (III). A mixture of equimolar amounts (1 mmol) of compound **II** (0.47 g), *p*-methoxybenzaldehyde (0.14 g), and malononitrile (0.05 g) in 50 ml of ethanol containing 2–3 drops of triethylamine was heated for 20 min under reflux with stirring. The mixture was cooled and poured into water, and the precipitate was filtered off, dried, and purified by column chromatography on aluminum oxide using chloroform as eluent. Yield

0.57 g (65%), mp 169–170°C. IR spectrum, ν, cm^{-1}: 740, 770, 850, 870, 900, 940, 980, 1040, 1070, 1095, 1130 (C–O–C), 1200, 1270, 1295, 1350, 1380, 1400, 1460, 1480, 1505, 1580, 1620, 1640 (NH_2), 1740 ($COOCH_3$), 2220 (CN), 2390, 2675, 3390 (NH_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.60 s (3H, 10-CH_3), 0.89–0.98 m (2H, 1-H_{ax}, 11-H_{ax}), 0.99 d [3H, $CH(CH_3)_2$, *J* = 6.8], 1.03 d [3H, $CH(CH_3)_2$, *J* = 6.8], 1.05 s (3H, 4-CH_3), 1.19–1.55 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}), 1.57–1.78 m (4H, 3-H_{ax}, 5-H, 9-H, 11-H_{eq}), 2.50 br.s (2H, 17-H_{ax}, 17-H_{eq}), 2.25 sept [1H, $CH(CH_3)_2$, *J* = 6.8], 2.45 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), 2.80 br.s (1H, 14-H), 3.30 s (3H, OCH_3), 3.65 s (3H, OCH_3), 3.72 s (1H, 3′-H), 3.80 s (3H, OCH_3), 5.49 br.s (1H, 19-H), 6.80–7.11 m and 7.20–7.39 m (4H, H_{arom}), 7.47 br.s (2H, NH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 40.9 (C^1), 16.8 (C^2), 37.2 (C^3), 46.9 (C^4), 51.7 (C^5), 21.5 (C^6), 36.3 (C^7), 41.5 (C^8), 52.5 (C^9), 39.3 (C^{10}), 30.3 (C^{11}), 41.2 (C^{12}), 61.3 (C^{13}), 52.8 (C^{14}), 151.3 (C^{15}), 95.3 (C^{16}), 32.4 (C^{17}), 135.9 (C^{18}), 147.2 (C^{19}), 158.8 ($C^{1'}$), 52.8 ($C^{2'}$), 37.7 ($C^{3'}$), 33.8 [$CH(CH_3)_2$], 25.8 [$CH(CH_3)_2$], 20.6 [$CH(CH_3)_2$], 16.5 (CH_3), 15.3 (CH_3), 178.9 ($COOCH_3$), 176.9 ($COOCH_3$), 49.0 ($COOCH_3$), 55.2 ($COOCH_3$), 112.6 (CN), 122.4, 131.1, 130.0, 120.7, 110.4, 156.9 (C_{arom}), 61.7 (OCH_3). Found, %: C 72.99; H 7.33; N 4.21. $C_{39}H_{48}N_2O_6$. Calculated, %: C 73.10; H 7.55; N 4.37.

Dimethyl (20*S*)-17-amino-18-cyano-22-isopropyl-5β,9β-dimethyl-16-thiahexacyclo[10.8.2.$0^{1,10}$.$0^{4,9}$.$0^{13,20}$.$0^{15,19}$]docosa-15(19),21-diene-5α,13α-dicarboxylate (IV). A mixture of equimolar amounts (1 mmol) of compound **II** (0.47 g), powdered sulfur (0.03 g), and malononitrile (0.05 g) in 50 ml of methanol containing 2–3 drops of morpholine was stirred for 2 h at 60°C. The mixture was cooled and poured into water, and the precipitate was filtered off, dried, and purified as described above for compound **III**. Yield 0.33 g (53%), mp 128–130°C. IR spectrum, ν, cm^{-1}: 740, 830, 870, 920, 960, 985, 1055, 1120, 1205, 1260, 1320, 1395, 1480, 1550, 1610, 1650 (NH_2), 1670, 1740 ($COOCH_3$), 2230 (CN), 2400, 2680, 3240 (NH_2). ^1H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 0.60 s (3H, 10-CH_3), 0.89–0.98 m (2H, 1-H_{ax}, 11-H_{ax}), 0.99 d [3H, $CH(CH_3)_2$, *J* = 6.8], 1.03 d [3H, $CH(CH_3)_2$, *J* = 6.8], 1.05 s (3H, 4-CH_3), 1.19–1.55 m (8H, 1-H_{eq}, 2-H_{ax}, 2-H_{eq}, 3-H_{eq}, 6-H_{ax}, 6-H_{eq}, 7-H_{ax}, -H_{eq}), 1.57–1.78 m (4H, 3-H_{ax}, 5-H, 9-H, 11-H_{eq}), 2.50 br.s. (2H, 17-H_{ax}, 17-H_{eq}), 2.25 sept [1H, $CH(CH_3)_2$, *J* = 6.8], 2.45 d.d.d (1H, 12-H, $^4J_{12,21}$ = 1.6, $^3J_{12,11\text{-}ax}$ = 2.2, $^3J_{12,11\text{-}eq}$ = 13.2), 2.80 br.s (1H, 14-H), 3.65 s (3H, $COOCH_3$), 3.80 s (3H, $COOCH_3$), 5.49 br.s (1H, 19-H), 6.90 br.s (2H, NH_2). ^{13}C NMR spectrum (acetone-d_6), δ_C, ppm: 38.1 (C^1), 16.7 (C^2), 36.5 (C^3), 46.7 (C^4), 50.6 (C^5), 21.4 (C^6), 34.5 (C^7), 41.9 (C^8), 51.1 (C^9), 37.3 (C^{10}), 25.0 (C^{11}), 40.6 (C^{12}), 61.4 (C^{13}), 53.1 (C^{14}), 153.9 (C^{15}), 146.1 (C^{16}), 36.6 (C^{17}), 149.8 (C^{18}), 123.9 (C^{19}), 166.0 ($C^{1'}$), 98.2 ($C^{2'}$), 32.6 [$CH(CH_3)_2$], 20.3 [$CH(CH_3)_2$], 19.9 [$CH(CH_3)_2$], 16.2 (CH_3), 15.0 (CH_3), 178.1 ($COOCH_3$), 171.4 ($COOCH_3$), 49.2 (OCH_3), 59.2 (OCH_3), 112.5 (CN). Found, %: C 70.10; H 7.61; N 5.36; S 6.05. $C_{31}H_{42}N_2O_4S$. Calculated, %: C 69.11; H 7.86; N 5.20; S 5.95.

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