Syntheses of novel chiral quinoxaline derivatives from seco-derivatives of monoterpene hydrocarbons 3-carene and α-pinene

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The preparation of substituted quinoxaline derivatives bearing a terpenoid substituent in the quinoxaline nucleus has been described, using (1*R*,3*S*)-2,2-dimethyl-3-(2-oxopropyl)cyclopropaneacetonitrile and (±)-(1*S**,3*S**)-2,2-dimethyl-3-acetylcyclobutaneacetonitrile as starting materials.

The quinoxalines (benzopyrazines) are well-known heterocyclic compounds. The quinoxaline fragment is a constituent of some intricate, biologically-active molecules such as riboflavin (vitamin B_2) and quintomycine A. A number of drugs used for the treatment of acute infection are quinoxaline derivatives (quinoxidine, dioxidine). The goal of the present work is the synthesis of new chiral quinoxaline derivatives from commercially available monoterpenes – (+)-3-carene and α-pinene. Previously we described the transformation of the above hydrocarbons to the seco-derivatives – (1*R*,3*S*)-2,2-dimethyl-3-(2-oxopropyl)cyclopropaneacetonitrile **1** and (±)-(1*S**,3*S**)-2,2-dimethyl-3-acetylcyclobutaneacetonitrile **7b**.[1]

The traditional methods of quinoxaline backbone formation include condensation of *o*-diaminoarenes with 1,2-bifunctional intermediates such as α-dicarbonyl derivatives[2] and α-halogenoketones.[3]

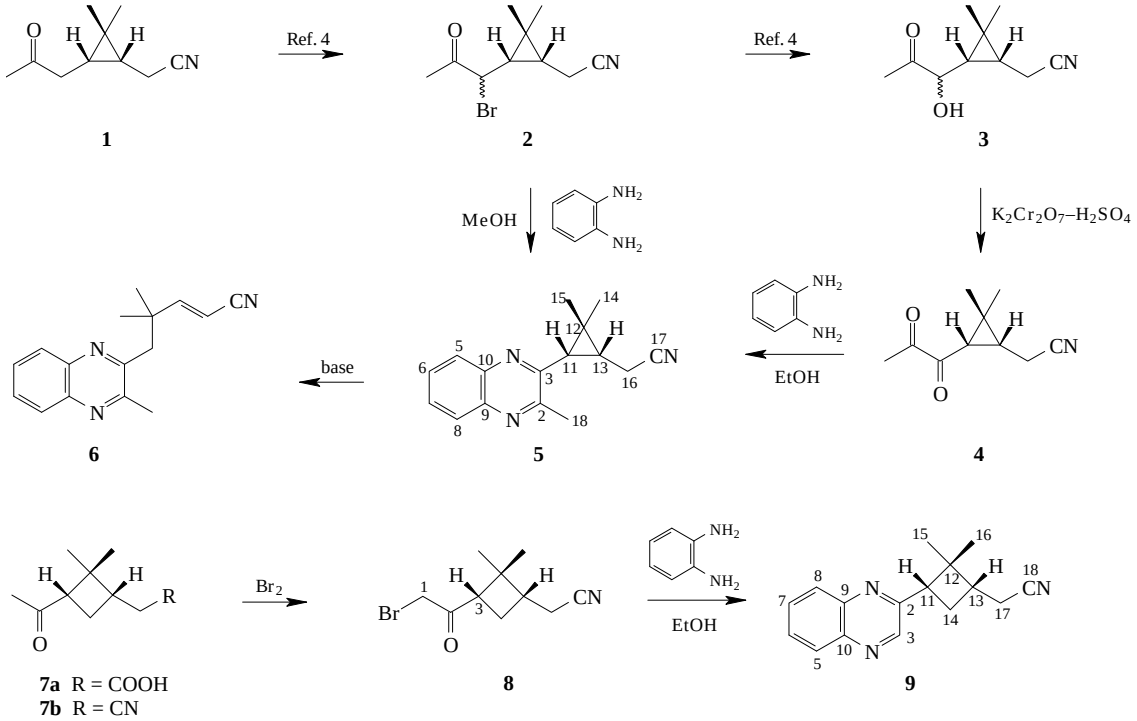
Conversion of ketonitrile **1** to a mixture of epimeric α-hydroxy derivatives **3** (without isolation of unstable bromides **2**) in > 90% total yield is a known procedure.[4] Oxidation of an epimeric mixture of alcohols **3** with Jones reagent in an acetone solution at room temperature gives diketone **4** that was condensed with *o*-phenylenediamine in ethanolic solution to form quinoxaline **5**[†] (39% yield from ketonitrile **1**). So, an oxidative mixture (30.2 g of $K_2Cr_2O_7$, 23 ml of 95% H_2SO_4 and 150 ml of H_2O) was added dropwise to a stirred solution of crude hydroxyketone **3** (prepared as previously described[4]) at 25–35 °C. The reaction mixture was diluted with water (100 ml) and extracted with ether (2×50, 30 ml). The combined ethereal extracts were washed with brine (2×50 ml), dried over anhydrous Na_2SO_4 and concentrated in vacuum to give diketone **4** as a brown oil (35.4 g).[‡] This crude product was used without further purification for preparation of quinoxaline **5** according to the following procedure. A solution of *o*-phenylenediamine (13.0 g, 0.120 mol) and diketone **4** (35.4 g, 0.198 mol) in 95% aqueous ethanol (130 ml) was kept for 18 h at room temperature, the solvent was removed under reduced pressure *in vacuo*, the residue was dissolved in ether (200 ml), and the ethereal solution was washed successively with 1 M HCl (75 ml), water (50 ml), brine (2×50 ml) and dried over anhydrous Na_2SO_4 and percolated through Al_2O_3. Evaporation of the eluate gave quinoxaline **5** (19.7 g) as a viscous dark oil that solidified spontaneously at room temperature.

A mixture of epimeric bromides **2** can also be used for the preparation of quinoxaline **5**. However, in such a case the reaction should be carried out under carefully controlled conditions due to the instability of the bromides. If the reaction is carried out under non optimised conditions, it is accompanied by an accumulation of by-products to a considerable extent. The best result was obtained using the following procedure. Bromine (0.94 ml, 0.018 mol) was added dropwise to a stirred solution of ketonitrile **1** (2.75 g, 0.0167 mol) in dichloromethane (15 ml) at 10 °C. The reaction mixture was stirred at 10 °C for an additional 20 min. The solvent, excess bromine and the resulting HBr were removed under reduced pressure at a temperature not exceeding 15 °C. The residue was dissolved in CH_2Cl_2 (15 ml) and the resulting solution was added dropwise with stirring to a suspension of *o*-phenylenediamine (3.78 g, 0.0350 mol) in methanol (25 ml) at 5 °C. The reaction mixture was allowed to warm to room temperature and was kept at ambient temperature for 24 h. The solvent was removed in vacuum and the residue was treated with ether and water. The ethereal layer was separated, washed with 1 M HCl, brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum to yield quinoxaline **5** (2.12 g, 51%) identical with the sample prepared from diketone **4**.

Bromination of seco-pinane compounds have been described previously.[5] So, bromination of pinonic acid **7a** with a dioxane–bromine complex gives a separable mixture of monosubstituted derivatives (≈58 : 41 of C-1 bromide to C-3 bromide). Bromination of ketonitrile **7b** under the same reaction conditions resulted in a complex mixture of monobromides. It was shown by NMR spectroscopy that the major components of that mixture were bromide **8**, its C-3 epimer and the product of C-3 bromination. Treatment of the above mixture with *o*-phenylenediamine in ethanol or acetic acid led to quinoxaline **9** in not more than 10% yield (from ketonitrile **7b**). Bromination of ketonitrile **7b** in methanolic solution gave exclusively C-1 bromides (*cis* : *trans* ≈ 3:1), and reaction of the C-1 bromides with *o*-phenylenediamine provided quinoxaline **9** in 36% yield. This is demonstrated by the following experiment. An ethereal solution of bromine (2.9 ml, 0.056 mol, in 5 ml of ether) was added dropwise to a stirred solution of ketonitrile **7b** (7.78 g, 0.0471 mol) in methanol (25 ml) at 20 °C. The solvent was evaporated in vacuum and the residue was dissolved in CH_2Cl_2 (50 ml). The resulting solution was washed with water to neutralize the reaction, then with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum to yield bromoketone **8** (13.8 g) as a light yellow oil. A solution of the bromoketone (9.37 g) and *o*-phenylenediamine (9.12 g, 0.0845 mol) in methanol (30 ml) was refluxed for 20 h. Solvent was removed and the reaction mixture was treated as described above for quinoxaline **5**,

[†] (1*R*,3*S*)-2,2-Dimethyl-3-(3-methylquinoxalin-2-yl)cyclopropylacetonitrile **5**. Mp 91–93 °C (MeOH), $[\alpha]^{16}$ + 131° (*c* = 0.87, $CHCl_3$). Found: C 76.5, H 7.1, N 16.6; calc. for $C_{16}H_{17}N_3$: C 76.46, H 6.82, N 16.72%; MS (*m*/*z*, %): 251.14213 (10, M^+, calc. for $C_{16}H_{17}N_3$: 251.14224), 211 (100), 209 (5), 196 (30), 195 (14), 102 (6), 77 (7), 76 (8); IR (ν_{max}/cm^{-1}, 0.25% in KBr) 2235; UV (λ_{max}/nm, ε, EtOH) 210 (22200), 243 (25600), 333 (8600). ^{1}H NMR (200 MHz, $CDCl_3$): 0.98 (s, 3H, H-14), 1.41 (s, 3H, H-15), 1.55 (ddd, *J* = 8.5, 8.5 and 7.0 Hz, 1H, H-13), 2.10 (d, *J* = 8.5 Hz, 1H, H-11), 2.68 (s, 3H, H-18), 3.01 (dd, *J* = 17.5, 8.5 Hz, 1H, H-16a), 3.20 (dd, *J* = 17.5, 7.0 Hz, 1H, H-16b), 7.58 (m, 2H, H-5 and H-8), 7.86 (m, 2H, H-6 and H-7); ^{13}C NMR (50 MHz, $CDCl_3$): 14.2 (C-14), 14.3 (C-16), 22.9 (C-18), 23.5 (C-12), 27.0 (C-13), 28.4 (C-15), 29.8 (C-11), 119.9 (C-17), 128.3, 128.5, 128.6 and 128.7 (C-5, C-6, C-7 and C-8), 140.0 and 140.2 (C-9 and C-10), 153.9 and 154.2 (C-2 and C-3).

[‡] (1*R*,3*S*)-2,2-Dimethyl-3-(2-oxopropionyl)cyclopropylacetonitrile **4** is decomposed on heating (90–100 °C) or column chromatography on SiO_2 or Al_2O_3. ^{1}H NMR (200 MHz, C_6D_6–CCl_4): 1.13 (s, 3H), 1.24 (s, 3H), 1.59 (ddd, *J* = 8.0, 7.6, 7.3 Hz, 1H), 2.22 (s, 3H), 2.59 (ddd, *J* = 17.0, 7.6, 7.3 Hz, 2H), 2.69 (d, *J* = 8.0 Hz, 1H).



affording quinoxaline **9** (2.89 g, 36%) as a dark yellow oil that solidified spontaneously at room temperature.[§]

Quinoxaline derivatives **5** and **9** with terpenoid substituents are highly crystalline, light yellow compounds. Derivative **5** is unstable under basic conditions, forming compound **6**.[¶]

The authors thank the Competitive Centre on Natural Sciences at St. Petersburg University (grant no. 95-0-9.4-102) and the Russian Foundation for Basic Research (grant no. 96-03-33222) for financial support of this work.

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§ (±)-(1*S**,3*S**)-2,2-Dimethyl-3-(quinoxalin-2-yl)cyclobutylacetonitrile **9**, mp 84–84.5 °C (petroleum ether–C_6H_6). Found: C 76.3, H 7.0, N 16.5; calc. for $C_{16}H_{17}N_3$: C 76.46, H 6.82, N 16.72%; MS (*m*/*z*, %): 251.14337 (12, M^+, calc. for $C_{16}H_{17}N_3$: 251.14224), 211 (62), 183 (15), 157 (77), 156 (100), 129 (22), 103 (11), 76 (16); IR (ν_{max}/cm^{-1}, 25% in KBr) 2239; UV (λ_{max}/nm, ε, EtOH) 209 (15400), 239 (26700), 332 (7100). ^{1}H NMR (200 MHz, $CDCl_3$): 0.64 (s, 3H, H-15), 1.37 (s, 3H, H-16), 2.3–2.7 (m, 5H, H-13, H-14 and H-17), 3.45 (m, 1H, H-11), 7.64 (m, 2H, H-6 and H-7), 8.00 (m, 2H, H-5 and H-8), 8.53 (s, 1H, H-3); ^{13}C NMR (50 MHz, $CDCl_3$): 17.32 (C-15), 17.38 (C-17), 24.18 (C-14), 29.92 (C-16), 38.29 (C-13), 43.66 (C-12), 47.14 (C-11), 118.48 (C-18), 128.73, 128.86, 128.92 and 129.54 (C-5, C-6, C-7 and C-8), 141.11 (C-10), 141.97 (C-9), 145.11 (C-3), and 154.49 (C-2).

¶ 4,4-Dimethyl-5-(3-methylquinoxalin-2-yl)pent-2-enenitrile **6**, mp 82–83 °C (petroleum ether–toluene). Found: C 76.7, H 6.8, N 16.9; calc. for $C_{16}H_{17}N_3$: C 76.46, H 6.82, N 16.72%; MS (*m*/*z*, %): 251.14310 (61, M^+, calc. for $C_{16}H_{17}N_3$: 251.14224), 236 (54), 211 (78), 196 (11), 183 (13), 158 (100), 157 (63), 156 (12), 117 (12), 89 (20), 77 (13), 76 (19); IR (ν_{max}/cm^{-1}, 0.25% in KBr) 2220; UV (λ_{max}/nm, ε, EtOH) 205 (35000), 238 (29500), 320 (7900). ^{1}H NMR (200 MHz, $CDCl_3$): 1.18 (s, 6H, H-14 and H-15), 2.68 (s, 3H, H-18), 3.02 (s, 2H, H-11), 5.10 (d, *J* = 16.7 Hz, 1H, H-16), 6.97 (d, *J* = 16.7 Hz, 1H, H-13), 7.62 (m, 2H, H-5 and H-8), 7.92 (m, 2H, H-6 and H-7); ^{13}C NMR (50 MHz, $CDCl_3$): 23.30 (C-18), 26.11 (C-14 and C-15), 39.39 (C-12), 45.53 (C-11), 96.36 (C-16), 117.81 (C-17), 128.07, 128.51, 128.78 and 129.14 (C-5, C-6, C-7 and C-8), 140.56 and 140.22 (C-9 and C-10), 152.55 and 152.82 (C-2 and C-3), 163.55 (C-13).

Received: Moscow, 10th January 1997
Cambridge, 21st March 1997; Com. 7/00345E