SYNTHESIS OF 1,11,11-TRIMETHYL-3,6-DIAZOTRICYCLO [6.2.1.$0^{2,7}$]UNDECA-2,6-DIENE AND 1,15,15-TRIMETHYL-3,10-DIAZOTETRACYCLO[10.2.1.$0^{2,11}$.$0^{4,9}$]PENTADECA-2,4(9),5,7,10-PENTAENE FROM CAMPHOROQUINONE ENANTIOMERS

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*Optically active camphordihydro-2,3-pyrazine and camphorquinoxaline were prepared from camphoroquinone enantiomers. It was shown that (1*S*,4*R*)-(+)-camphoroquinone was formed by oxidation of (1*S*,3*R*,4*R*)-(-)-3-bromocamphor and (1*R*,4*S*)-(-)-camphoroquinone from (1*R*,3*S*,4*S*)-(+)-3-bromocamphor, respectively. Camphor anhydride was a side product (6-10%) of the reaction.*

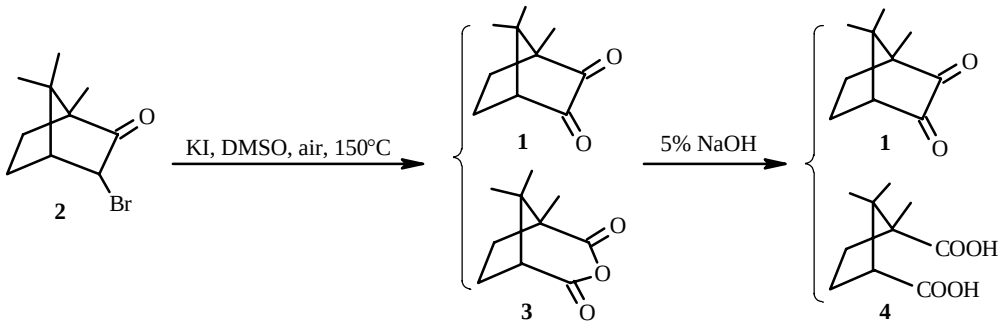
Key words: 3-*endo*-bromocamphor, camphoroquinone, camphor anhydride, camphordihydro-2,3-pyrazine, camphorquinoxaline.

Camphor and its derivatives are used as starting chiral compounds in various syntheses [1, 2] due largely to the availability of both enantiomers. Camphoroquinone is used not only as a simple precursor for preparing certain stereoisomeric diols, keto- and aminoalcohols, oximes, and other derivatives but also as a ligand in asymmetric catalysis [3, 4].

Methods that use electrophilic reagents with nitrogenous functionalities are very valuable for preparing N-containing camphor derivatives because they can immediately introduce nitrogen via an electrophilic addition reaction without forming any intermediates. Such reagents include 1,2-diamines, which are widely used to synthesize heterocyclic systems and as chelating agents in medicinal chemistry [5]. Moreover, their optically active derivatives are important for asymmetric synthesis of various compounds [6-8].

Many natural and synthetic biologically active molecules include a pyrazine ring. In particular, steroidal pyrazines that were recently isolated from marine worms *Cephalodiscus gilchristi* have high antitumor activity [9, 10]. Several studies on the synthesis and investigation of the biological activity of benzopyrazine derivatives have been published [11-13]. Therefore, the demand for optically active compounds containing a pyrazine moiety continues to grow.

Herein we report the synthesis of optically active 1,11,11-trimethyl-3,6-diazatricyclo[6.2.1.$0^{2,7}$]undeca-2,6-diene (camphordihydro-2,3-pyrazine) and 1,15,15-trimethyl-3,10-diazatetracyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2,4(9),5,7,10-pentaene (camphorquinoxaline) based on both enatiomers of camphoroquinone.



2 **1** **3** **1** **4**

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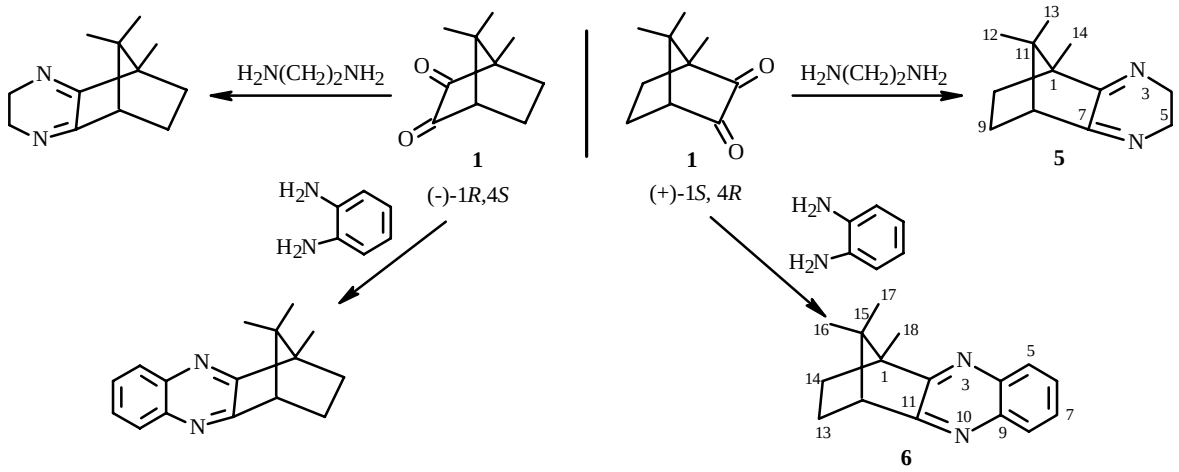
TABLE 1. Reaction Conditions for Camphorquinoxaline Synthesis

Solvent/catalyst	Reaction time, h	Reaction temperature, °C	Yield, %
MeOH/-	30	65	60-70
$MeOH/BF_3 \cdot Et_2O$	15	65	50-65
CH_3COOH	1	118	60-70

Camphoroquinone (**1**) can be prepared by several methods including oxidation of camphor by selenium dioxide [14, 15] and phenylselenous acid anhydride [16] and oxidation of 3-bromocamphor (**2**) by air in DMSO, DMF, or HMPA in the presence of NaI [17]. The last study confirmed that (+)-camphoroquinone was formed from (+)-3-*endo*-bromocamphor; (-)-camphoroquinone, from (-)-3-*endo*-bromocamphor in quantitative yields.

We found that this reaction is a good method for preparing camphoroquinone but that it also forms small quantities (6-10%) of camphor anhydride (**3**), which crystallizes with camphoroquinone. Compound **3** was isolated as white crystals by column chromatography over SiO_2 followed by crystallization from ether:hexane. Anhydrides are known to hydrolyze readily in acidic or basic medium into the corresponding acids. Therefore, treatment of a mixture of **1** and **3** with NaOH solution (5%) produced pure **1** in 74-76% yield and camphoric acid (**4**). The absolute configuration was determined by comparing optical rotations of **3** and **4** with literature data [18]. During the measurement of the specific rotation of **1**, it was observed that its sign reverses, i.e., (+)-camphoroquinone formed from (-)-3-*endo*-bromocamphor [19] and (-)-camphoroquinone, from (+)-3-*endo*-bromocamphor [19], which does not agree with previous results [17].

Reaction of camphoroquinone with ethylenediamine at a 1:2 molar ratio formed in good yield (84%) camphordihydro-2,3-pyrazine (**5**) (Scheme 1). The reaction occurs at room temperature in methanol in the presence of 4 Å molecular sieves over 7 h. Performing the synthesis in boiling methanol could shorten the reaction time to 1 h.



Scheme 1. Synthesis of camphordihydro-2,3-pyrazine (**5**) and camphorquinoxaline (**6**)

Under analogous conditions, cyclocondensation of camphorquinone and *o*-phenylenediamine at a 1:1 mole ratio formed camphorquinoxaline (**6**) after 30 h (Scheme 1). The reaction gave complete conversion of the camphoroquinone (TLC monitoring).

Using $BF_3 \cdot Et_2O$ as the catalyst shortened the reaction time to 15 h. However, the yield of camphorquionoxaline was reduced due to the formation of side products. The optimal conditions were boiling in glacial acetic acid where acetic acid is both the solvent and catalyst. Compound **6** was isolated by crystallization from hexane in 71% yield (Table 1).

We found that (+)-camphordihydro-2,3-pyrazine and (+)-camphorquinoxaline were formed from (-)-camphoroquinone and the (-)-forms of **5** and **6** from (+)-camphoroquinone.

The structures of **5** and **6** were confirmed by IR, NMR and mass spectroscopy and elemental analysis.

The optically active *N*-containing camphoroquinone derivatives are interesting as potential biologially active compounds.

EXPERIMENTAL

PMR and ^{13}C NMR spectra in $CDCl_3$ were recorded on a Bruker AM-400 spectrometer (working frequency 400.13 and 100.61 MHz, respectively). IR spectra were recorded on a Specord M-80 instrument in KBr disks. Specific rotation was measured using an SM-3 circular polarimeter. Mass spectra were obtained on a Finnigan SSQ-7000 GC—MS at 70 eV ionization energy using a DB-5MS column (30 m). GC was performed on a Kristall 2000 M instrument with a capillary column (60 m × 0.25 mm), HP-5MS phase, and He carrier gas. TLC was performed on Silufol plates with elution by diethylether:hexane and development by bromthymol blue (0.2%) in ethanol (95%) and vanillin solution [vanillin (3 g) + ethanol (95%, 100 mL) + conc. H_2SO_4 (0.5 mL)].

(+)-1*S*,4*R*-Camphoroquinone (1). $[\alpha]_D^{20}$ +108° (*c* 1.8, toluene), mp 200°C. IR spectrum (KBr, ν, cm^{-1}): 2976, 1776, 1760, 1452, 1400, 1380, 1328, 1200, 1168, 1108, 1056, 1008, 1000, 972, 912.

Mass spectrum (*m*/*z*, I_{rel}, %): 166 (20) $[C_{10}H_{14}O_2]^+$, 138 (30) $[M - CO]^+$, 123 (20), 110 (10) $[M - 2CO]^+$, 95 (100) $[C_7H_{11}]^+$, 83 (63), 69 (58), 67 (22), 55 (56).

PMR spectrum (400.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.94 (3H, s, Me), 1.07 (3H, s, Me), 1.11 (3H, s, Me), 1.64 (2H, m, H-6_{exo}, H-5_{endo}), 1.94 (1H, m, H-6_{endo}), 2.18 (1H, m, H-5_{exo}), 2.64 (1H, d, J = 5.1, H-4). ^{13}C NMR spectrum (100.62 MHz, $CDCl_3$): 204.7 (C-2), 202.7 (C-3), 58.5 (C-1), 57.9 (C-4), 42.5 (C-7), 29.8 (C-6), 22.2 (C-5), 21.0 (C-8), 17.3 (C-9), 8.6 (C-10).

(-)-1*R*,4*S*-Camphoroquinone. $[\alpha]_D^{20}$ -109° (*c* 1.6, toluene), mp 196°C.

(+)-1*S*,3*R*-1,2,2-Trimethylcyclopentan-1,3-dicarboxlic Anhydride (3). $[\alpha]_D^{20}$ +0.9° (*c* 1.8, $CHCl_3$), mp 221-221.5°C. IR spectrum (KBr, ν, cm^{-1}): 2980, 1812, 1768, 1460, 1400, 1392, 1376, 1326, 1316, 1282, 1252, 1224, 1214, 1184, 1152, 1132, 1112, 1046, 986, 984, 948. Mass spectrum (*m*/*z*, I_{rel}, %): 138 (31) $[M - CO]^+$, 123 (19), 110 (14) $[M - 2CO]^+$, 95 (100) $[C_7H_{11}]^+$, 83 (44), 69 (73), 67 (18), 55 (49).

(-)-(1*S*,3*R*)-1,2,2-Trimethylcyclopentan-1,3-dicarboxylic Acid (4). $[\alpha]_D^{20}$ -51.9° (*c* 4.0, EtOH), mp 181-182°C. IR spectrum (KBr, ν, cm^{-1}): 3500-2500, 1704, 1464, 1414, 1398, 1384, 1286, 1246, 1168, 1128, 948.

(+)-(1*R*,3*S*)-1,2,2-Trimethylcyclopentan-1,3-dicarboxylic Acid. $[\alpha]_D^{20}$ +50.7° (*c* 3.6, EtOH), mp 182°C.

Synthesis of (-)-1*S*,4*R*-1,11,11-Trimethyl-3,6-diazatricyclo[6.2.1.$0^{2,7}$]undeca-2,6-diene [(-)-camphordihydro-2,3-pyrazine] (5). A solution of (+)-camphoroquinone (0.5 g, 0.003 mol) in methanol (10 mL) was treated with ethylenediamine (0.4 mL, 0.006 mol) and refluxed with stirring in the presence of 4 Å molecular sieves for 1 h. After the reaction was complete, the mixture was cooled, extracted with Et_2O, washed with saturated NaCl solution, and dried over K_2CO_3. Solvent was removed. The solid was chromatographed over SiO_2 ($CHCl_3$:CH_3OH, 100:1) to afford **5** (0.48 g, 84%), $[\alpha]_D^{20}$ -11.6° (*c* 2.1, EtOH). IR spectrum (KBr, ν, cm^{-1}): 2968, 2856, 1656, 1480, 1448, 1396, 1376, 1340, 1234, 1212, 1116, 1084, 972, 920.

Mass spectrum (*m*/*z*, I_{rel}, %): 190 (100), 175 (74), 163 (46), 148 (54), 135 (39), 120 (74), 106 (12), 91 (19), 77 (23), 54 (44).

PMR spectrum (400.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.81 (3H, s, Me), 1.00 (3H, s, Me), 1.07 (3H, s, Me), 1.51 (2H, m, H-6_{exo}, H-5_{endo}), 1.82 (1H, m, H-6_{endo}), 2.04 (1H, m, H-5_{exo}), 2.42 (1H, d, J = 4.8, H-4), 3.48 (4H, m, H-11, H-12).

^{13}C NMR spectrum (100.62 MHz, $CDCl_3$): 168.7 (C-2), 167.1 (C-3), 52.6 (C-4), 46.4 (C-1), 46.3 (C-7), 44.6 (C-12), 44.5 (C-11), 31.8 (C-6), 24.2 (C-5), 20.1 (C-8), 17.3 (C-9), 9.3 (C-10).

(+)-1*R*,4*S*-1,11,11-Trimethyl-3,6-diazatricyclo[6.2.1.$0^{2,7}$]undeca-2,6-diene. [(+)-Camphordihydro-2,3-pyrazine] was prepared from (-)-camphoroquinone by the same method, $[\alpha]_D^{20}$ +9.4° (*c* 6.8, EtOH).

Synthesis of (-)-1*S*,4*R*-1,15,15-Trimethyl-3,10-diazatricyclo[10.2.1.$0^{2,11}$.$0^{4,9}$]pentadeca-2,4(9),5,7,10-pentaene [(-)-camphorquinoxaline] (6). A solution of (+)-camphoroquinone (0.5 g, 0.003 mol) in glacial acetic acid (8 mL) was treated with *o*-phenylenediamine (0.32 g, 0.003 mol) and refluxed for 1 h. After the reaction was complete, the mixture was cooled, extracted with Et_2O, washed with saturated NaCl solution, and dried over Na_2SO_4. Solvent was removed. Recrystallization from hexane afforded camphorquinoxaline (0.51 g, 71%), $C_{16}H_{18}N_2$, mp 69-70°C, lit. [5] mp 78°C, $[\alpha]_D^{20}$ -32.7° (*c* 2.2, EtOH). PMR spectrum (400.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.63 (3H, s, Me), 1.12 (3H, s, Me), 1.45 (3H, s, Me), 1.43 (2H, m, H-6_{exo}, H-5_{endo}), 2.06 (1H, m, H-6_{endo}), 2.30 (1H, m, H-5_{exo}), 3.06 (1H, d, J = 4.8, H-4), 7.64 (2H, m, H-13, H-16), 8.01 (2H, m, H-14, H-15).

^{13}C NMR spectrum (100.62 MHz, $CDCl_3$): 165.44 (C-2), 163.68 (C-3), 141.47 (C-12), 141.26 (C-11), 128.74 (C-16), 128.60 (C-13), 128.00 (C-14), 127.97 (C-15), 54.14 (C-1), 53.72 (C-7), 53.23 (C-4), 31.79 (C-6), 24.57 (C-5), 20.23 (C-8), 18.46 (C-9), 9.98 (C-10).

(+)-1*R*,4*S*-1,15,15-Trimethyl-3,10-diazatricyclo[10.2.1.0^{2,11}.0$^{4.9}$]pentadeca-2,4(9),5,7,10-pentaene. [(+)-Camphorquinoxaline] was prepared from (-)-camphoroquinone by the same method, $[\alpha]_D^{20}$ +33.0° (*c* 2.2, EtOH).

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