

New pyrazole-, isoxazole- and *N*-acylpyrazoline derivatives with a pinane carbon frame

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Syntheses of new 1,2-azole-type fused heterocycles based on the α -pinene molecule are described.

New cyclic systems with the pyrazole heterocyclic moiety are of interest from the viewpoint of their biological activity¹ as well as applications in the preparation of chiral catalysts for enantioselective organic synthesis.² Pyrazole-type fused heterocycles based on terpene molecules are known in the *p*-menthane,³ bornane⁴ and modified carane⁵ series. Now we report the syntheses of new pyrazole derivative of α -pinene **1** as well as the corresponding isoxazole and *N*-acylpyrazoline derivatives. α -Pinene **1** was transformed to pinocarvone oxime **2**[†] by nitroschlorination–dehydrochlorination as described in ref. 6, and the latter compound was used as a starting material for the syntheses of the heterocycles.

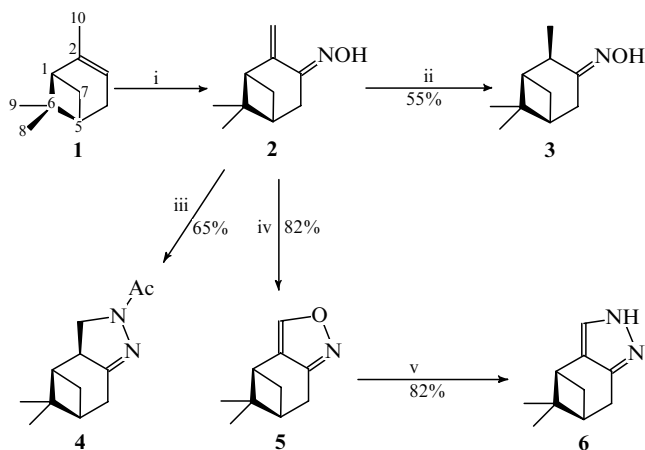
Reaction of oxime **2** with hydrazine hydrate is greatly dependent on the reaction conditions. When carried out in the open air, the reaction leads to isopinocampone oxime **3**. Thus, 80% aqueous hydrazine hydrate (20 ml, \approx 0.33 mol) was added dropwise to a solution of pinocarvone oxime (**2**, 1.00 g, 6.1 mmol) in a mixture of ethanol (10 ml) and acetic acid (2 ml, 35 mmol) and the mixture was allowed to reflux for 14 h without special protection from the atmospheric oxygen. The mixture was diluted with water (50 ml) and extracted with Et₂O (3 \times 40 ml). The combined ethereal extracts were washed

with 1 M aq. HCl, 0.5 M aq. Na₂CO₃ and brine and then dried (MgSO₄). The crude product (0.92 g) was chromatographed on a silica gel column followed by crystallization from MeCN to give 0.55 g (55%) of isopinocampone oxime **3**[‡] with mp 88–90 °C (lit.,⁷ 88–89 °C). The use of 0.033 mol of hydrazine hydrate under the same reaction conditions resulted in 45% yield of oxime **3**. The reaction does not take place in the absence of oxygen. This transformation is similar to the reduction of α - and β -pinenes with diimide generated *in situ* from hydrazine hydrate by the action of atmospheric oxygen⁸ (Scheme 1).

In the presence of excess acetic acid under an inert atmosphere, the reaction leads to *N*-acylpyrazoline **4** as the main product, the corresponding pyrazole **6** being only the by-

[†] (±)-Pinocarvone *E*-oxime **2** with mp 131–133 °C (petroleum ether).

[‡] (±)-Isopinocampone oxime **3**. ¹H NMR (200 MHz, CDCl₃): 0.88 s (3H, H-8), 0.95 d (*J* = 10.3 Hz, 1H, H-7a), 1.22 s (3H, H-9), 1.27 d (*J* = 7.3 Hz, 3H, H-10), 1.88 ddd (*J* = 6.3, 6.0 and 2.3 Hz, 1H, H-1), 1.97 dddd (*J* = 6.3, 6.0, 3.0 and 3.0 Hz, 1H, H-5), 2.42 dddd (*J* = 10.3, 6.3, 6.3 and 2.7 Hz, 1H, H-7b), 2.58 dd (*J* = 18.8 and 3.0 Hz, 1H, H-4a), 2.80 qdd (*J* = 7.3, 2.3 and 2.3 Hz, 1H, H-2), 2.89 dddd (*J* = 18.8, 3.0, 2.7 and 2.3 Hz, 1H, H-4b), 9.7 br.s (1H, =NOH); ¹³C NMR (50 MHz, CDCl₃): 45.91 (C-1), 41.29 (C-2), 161.98 (C-3), 30.58 (C-4), 37.84 (C-5), 38.86 (C-6), 33.23 (C-7), 21.63 (C-8), 27.15 (C-9), 19.32 (C-10).



Scheme 1 Reagents and conditions: i, (a) NOCl; (b) NaOH; ii, $\text{NH}_2\text{NH}_2\text{-AcOH}$ (9:1), EtOH/ O_2 , reflux, 14 h; iii, $\text{NH}_2\text{NH}_2\text{-AcOH}$ (1:6), EtOH, reflux for 7 h, under argon; iv, $\text{I}_2\text{-KI-NaHCO}_3$, THF- H_2O (dark), reflux, 3 h; v, $\text{NH}_2\text{NH}_2\text{-AcOH}$, 150°C , 60 h.

product. Thus, 80% aqueous hydrazine hydrate (0.5 ml, 8.2 mmol) was added dropwise to a solution of pinocarvone oxime (**2**, 0.50 g, 3 mmol) in a mixture of ethanol (3 ml) and glacial acetic acid (3 ml, 53 mmol) and the mixture was allowed to reflux for 7 h under argon. The solvent was removed under reduced pressure and the resulting mixture was diluted with water (50 ml) and extracted with Et_2O (3×15 ml). The combined ethereal extracts were dried (MgSO_4) and concentrated *in vacuo*. The residue was percolated through a silica gel column ($\text{Et}_2\text{O-MeCN}$) to give 0.54 g of a light brown solid which was a mixture of five pinane derivatives in the ratio 73:13:6:5:3 (according to ^1H NMR), the first two components being *N*-acylpyrazoline **4** (65% yield) and pyrazole **6** (15% yield). *N*-Acylpyrazoline **4**[§] is rather stable to oxidation and is not transformed to the pyrazole either under the reaction conditions or during the isolation procedure and after purification. In contrast, for oxime **2**, treatment of the corresponding α,β -unsaturated ketone (pinocarvone) with hydrazine hydrate resulted in 50% yield of a chromatographically homogeneous mixture of four components ($\approx 1:1:1:1$, ^1H NMR).[¶]

The configuration of the C-2 atom in compound **4** was determined by comparison of the experimental values of the vicinal proton-proton couplings with calculated ones for both $2\alpha\text{H-4}$ and $2\beta\text{H-7}$ derivatives.⁹ The geometry of the models was specified by semi-empirical calculations (PM3, AM1, MNDO). Calculations of the vicinal spin-spin couplings were carried out using the equation $^3J_{\text{H-H}} = 5.8 - 1.2 \cos \phi +$

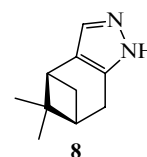
Table 1 Experimental and calculated J values.

$^3J_{\text{H-H}}$	Experimental ^a	Calculated 4	Calculated 7
$\text{H}^1\text{-H}^2$	2.1	2.3	2.1
$\text{H}^5\text{-}\alpha\text{H}^4$	2.3	2.6	4.7
$\text{H}^5\text{-}\beta\text{H}^4$	4.0	4.1	2.2

^a ± 0.1 Hz.

$3.9 \cos 2\phi$ which was deduced from the Karplus' equation in respect of deformation of carbon-carbon bonds and valence angles H-C-C in the pinane ring system. According to the data shown in Table 1, the *N*-acylpyrazoline derivative **4** belongs to the configuration series of isopinocamphe oxime **3**.

Pyrazole **6** is formed in good yield in the reaction of isoxazole **5** with hydrazine hydrate according to the following procedure. A mixture of isoxazole **5** (0.50 g, 3.1 mmol), hydrazine hydrate (1.00 g, 20 mmol) and glacial acetic acid (3 ml) was heated in a sealed tube at 150°C for 60 h. Column chromatography of the crude product (0.49 g) afforded 0.13 g of the starting material and 0.30 g (82%) of pyrazole **6**.⁺ Formation of pyrazole derivatives from the corresponding isoxazoles is well known.¹⁰



Pyrazole **6** seems to have one predominant tautomeric form like other derivatives of this group. Semi-empirical calculations show the derivative **6** to be $0.1\text{--}2.7 \text{ kcal mol}^{-1}$ more stable than isomer **8**: $H_f^0 = 0.1$ (PM3), 1.2 (MINDO/3), 1.8 (AM1), 2.7 (MNDO). Semi-empirical methods were shown to predict correctly the relative stability of the tautomeric fused pyrazole derivatives having five- and six-membered carbocycles condensed with the pyrazole fragment.¹¹ It should be stressed that isomer **6** could be predicted as the predominant tautomer according to the Mills-Nixon effect.¹¹ At the same time, due to the strain in the bicyclic pinane-type carbon moiety of the compound, the experimental values of the carbon chemical shifts for the pyrazole fragment correlate with the calculated ones¹² neither for tautomer **6** nor for tautomer **8**.

Isoxazole **5** was prepared in excellent yield by treatment of pinocarvone oxime **2** with $\text{I}_2\text{-KI}$ ^{13,14} as follows. A solution of NaHCO_3 (1.00 g, 9.4 mmol) in H_2O (9 ml) was added in the dark to a solution of pinocarvone oxime (**2**, 0.50 g, 3.0 mmol) in THF (15 ml) followed by addition of a solution of I_2 (0.82 g, 3.2 mmol) and KI (1.76 g, 10.6 mmol) in water (7 ml). The reaction mixture was allowed to reflux for 3 h in the dark, diluted with water (50 ml) and extracted with Et_2O (3×40 ml). The combined ethereal extracts were washed with 0.5 M aq. Na_2CO_3 and brine and then dried (MgSO_4). The crude

[§] (\pm)-(1*S**,2*R**,4*S**)-7,8-Diaza-8-acyl-3,3-dimethyltricyclo[4.3.0.1^{2,4}]-dec-6-ene **4**. Mp $113\text{--}114^\circ\text{C}$ (toluene-petroleum ether); MS (m/z , %): 206.1427 (76, M^+ , calc. for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$ 206.1419), 165 (100), 152 (12), 149 (33), 135 (10), 126 (13), 121 (27), 120 (26), 110 (28), 95 (43), 82 (23), 81 (24), 69 (17), 67 (18), 55 (12), 53 (13), 43 (53); IR (ν_{max} /cm⁻¹, 3% in CHCl_3): 1635, 1610, 1460, 1420; ^1H NMR (400 MHz, C_6D_6): 0.49 d ($J = 10.5$ Hz, 1H, H-7a), 0.68 s (3H, H-8), 0.89 s (3H, H-9), 1.46 ddd ($J = 6.0$, 6.0 and 2.0 Hz, 1H, H-1), 1.62 dddd ($J = 6.0$, 5.5, 4.0 and 2.5 Hz, 1H, H-5), 2.16 dddd ($J = 10.5$, 6.5, 6.5 and 2.5 Hz, 1H, H-7b), 2.25 ddd ($J = 16.5$, 2.3 and 2.3 Hz, 1H, H-4b), 2.37 s (3H, CH_3CON), 2.62 dddd ($J = 16.5$, 4.0, 2.3 and 2.0 Hz, 1H, H-4a), 2.65 dddd ($J = 13.5$, 11.5, 2.3, 2.3 and 2.3 Hz, 1H, H-2), 3.28 dd ($J = 13.5$ and 11.5 Hz, 1H, H-10b), 4.12 dd ($J = 11.5$ and 11.5 Hz, 1H, H-10a); ^{13}C NMR (50 MHz, CDCl_3): 40.58 (C-1 or C-5), 51.92 (C-2), 162.43 (C-3), 31.45 (C-4), 40.91 (C-5 or C-1), 40.02 (C-6), 35.25 (C-7), 20.93 (C-8), 27.75 (C-9), 49.15 (C-10), 21.01 (CH_3CON), 168.82 (CH_3CON).

[¶] The numbering of the C-atoms shown on the scheme does not coincide with the numbering of the system according to IUPAC. This numbering scheme is usual for the pinane-type monoterpenoids and is given for NMR interpretation only.

⁺ (\pm)-(2*S**,4*S**)-7,8-Diaza-3,3-dimethyltricyclo[4.3.0.1^{2,4}]deca-1(9),6-diene **6**. Mp $120\text{--}122^\circ\text{C}$ (after sublimation *in vacuo*). Found: C 73.8, H 8.7, N 17.1; calc. for $\text{C}_{10}\text{H}_{14}\text{N}_2$: C 74.03, H 8.70, N 17.27%; MS (m/z , %): 162.1157 (22, M^+ , calc. for $\text{C}_{10}\text{H}_{14}\text{N}_2$ 162.1156), 147 (30), 133 (10), 120 (19), 119 (100), 118 (20), 94 (13), 92 (14); UV (λ_{max} /nm, in EtOH): 230 (ϵ 3400); IR (ν_{max} /cm⁻¹, 1% in CCl_4): 3489 and 3150 (N-H), 3075(=CH), 1580, 1464, 1392, 1379, 1363, 955; ^1H NMR (200 MHz, CDCl_3): 0.61 s (3H, H-8), 1.26 d ($J = 9.0$ Hz, H-7a), 1.35 s (3H, H-9), 2.25 ddt ($J = 6.0$, 6.0 and 2.7 Hz, 1H, H-5), 2.64 ddd ($J = 9.0$, 6.0 and 6.0 Hz, 1H, H-7), 2.70 dd ($J = 6.0$ and 6.0 Hz, 1H, H-1), 2.88 d ($J = 2.7$ Hz, 2H, H-4a,b), 7.12 s (1H, H-10), 11.2 br.s (1H, NH); ^{13}C NMR (50 MHz, CDCl_3): 41.09 (C-1), 125.29 (C-2), 145.57 (C-3), 27.17 (C-4), 38.88 (C-5), 41.60 (C-6), 34.13 (C-7), 21.35 (C-8), 26.56 (C-9), 124.07 (C-10).

product (0.48 g) was distilled at reduced pressure to give 0.40 g (82%) of isoxazole **5**.*

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*(±)-(2*S**,4*S**)-7-Aza-8-oxa-3,3-dimethyltricyclo[4.3.0.1^{2,4}]deca-1(9),6-diene **5**. Bp 107–109 °C/7–8 mmHg. Found: C 73.4, H 8.0, N 8.3; calc. for C₁₀H₁₃NO: C 73.59, H 8.03, N 8.58%; MS (*m/z*, %): 163 (16, M⁺), 148 (13), 135 (24), 134 (26), 122 (16), 120 (63), 119 (12), 104 (15), 95 (21), 94 (18), 93(19), 92 (11), 77 (15), 69 (71), 67 (38), 65 (13), 53 (17), 43 (10), 42 (10), 41 (100), 39(36); UV (λ_{max} /nm, in EtOH): 228 (ϵ 5000), 261 (ϵ 700); IR (ν_{max} /cm⁻¹, neat): 3137 (=C–H), 1634 (C=C), 1475, 1405, 1268, 1089, 1078, 845; ¹H NMR (200 MHz, CDCl₃): 0.66 s (3H, H-8), 1.22 d (*J* = 10.0 Hz, 1H, H-7a), 1.36 s (3H, H-9), 2.27 dddd (*J* = 6.0, 5.0, 3.5 and 3.5 Hz, 1H, H-5), 2.70 ddd (*J* = 10.0, 6.0 and 6.0 Hz, 1H, H-7b), 2.81 dd (*J* = 6.0 and 5.0 Hz, 1H, H-1), 2.96 d (*J* = 3.5, 2H, H-4), 7.90 s (1H, H-10); ¹³C NMR (50 MHz, CDCl₃): 40.17 (C-1), 124.06 (C-2), 154.14 (C-3), 25.75 (C-4), 37.51 (C-5), 41.34 (C-6), 33.07 (C-7), 21.16 (C-8), 26.06 (C-9), 148.84 (C-10).

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