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Enaminones of the 2-Acetylcyclopent-1-en-1-ylamine Type Derived from the Terpenic Compounds Limonene, 3-Carene and δ-Cadinol

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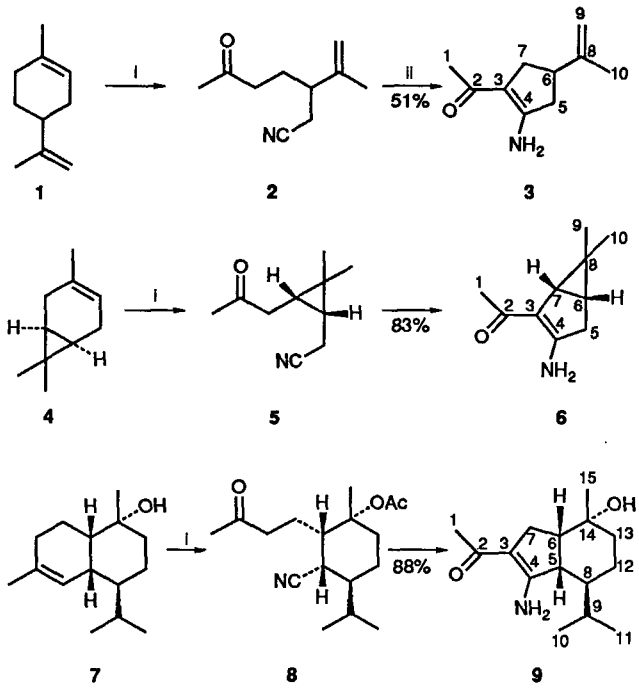
The preparation of 2-acetylcyclopent-1-en-1-ylamine type enaminones from terpenic compounds is described.



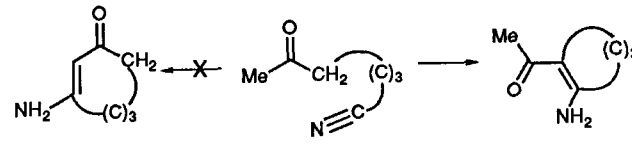
Scheme 1 *Reagents and conditions*: i, see ref. 7; ii, NaOH–EtOH–reflux

Enamines of various structures, including enaminones, are of great interest both as intermediates for the synthesis of organic compounds of various classes[1–3] and from the point of view of their potential biological activity.[4] At the same time, the lower isoprenoids (mono- and sesqui-terpenoids) are used extensively as chiral substrates in the synthesis of many useful organic compounds. Although many methods of enaminone synthesis are available,[5] such intermediates have previously been unknown in the isoprenoid series. Some enaminones (2-acetylcyclopent-1-en-1-ylamine derivatives) have proved to be readily obtainable by heating terpenic 1,6-ketonitriles with an alkali. This reaction is an analogue of the known intramolecular condensation reaction of 1,5-ketonitriles to give aminocyclohexenone derivatives.[6] Using the available natural terpene compounds limonene **1**, 3-carene **4** and δ-cadinol **7** as substrates, we have synthesized, *via* the corresponding ketonitriles **2**, **5** and **8**,[7] enaminones **3**, **6** and **9**, yellowish crystalline substances which decompose upon storage in air (Scheme 1).

Our preparation of enaminones **3** and **6** is carried out as follows. Ketonitrile **2** or **5** (10 mmol) is added to a stirred solution of KOH (0.56 g, 10 mmol) in 95% aq. EtOH (10 ml). The reaction mixture is heated to boiling point and allowed to reflux for 15 min, then it is diluted with H_2O (30 ml) and extracted with Et_2O (20, 10 ml). The combined ethereal solutions are extracted with 1 mol dm^{-3} HCl (15, 10, 5 ml), and the combined aqueous solutions are washed with Et_2O (10 ml) and neutralized with concentrated aq. NH_3 (5 ml), followed by extraction with Et_2O (20, 10 ml). The combined ethereal solutions are washed with brine (10 ml) and dried over $MgSO_4$ (2 g). The solvent is evaporated at reduced pressure to give a crystalline product which is then purified by crystallization from an appropriate solvent to give compounds **3**, **6** or **9** in good yields.†‡

In all cases, the resultant enaminones were purified *via* water-soluble hydrochlorides by treatment of the crude materials with 1 mol dm^{-3} HCl to give the water-soluble fraction (enaminone hydrochloride) and a fraction containing 'neutral' compounds. Only derivatives of the cyclopentenylamine type were detected in the water-soluble fractions, and no detectable amount of the isomeric cycloheptenylamine derivatives was found (TLC, ^1H and ^{13}C NMR (Scheme 2)).

The 'neutral' fractions, isolated in poor yields, are complex mixtures of by-products having a nitrile group absorption (2210 cm^{-1}) in the IR spectra and showing no carbonyl absorption. The formation of cyano-containing by-products may be a result of anion formation α to the nitrile and cyclization onto



Scheme 2

† *Characterization data* for (±)-2-acetyl-4-(1-methylethen-1-yl)cyclopent-1-en-1-ylamine **3**: 51%, m.p. 74–75.5°C (aq. MeOH); IR (1% in CCl_4) ν/cm^{-1} 3452, 3300, 3090, 1645, 1590, 1510, 915, 890; UV (EtOH) λ_{max}/nm 315 (log ε 4.19); MS *m/z* 165 (M^+, 90%), 150 ($M^+ - Me$, 58), 124 ($M^+ - MeC{=}CH_2$, 31), 122 ($M^+ - MeCO$, 100), 105(26), 80(20); ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.96 (s, 3H, 1-H_3), ~2.4 (m, 3H) and ~2.7 (m, 2H) (5-H_2, 6-H, 7-H_2), 4.65 (br s, 2H, 9-H_2), 1.66 (br s, 3H, 10-H_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 27.73 (q, C-1), 194.74 (s, C-2), 104.61 (s, C-3), 162.46 (s, C-4), 35.42 (t) and 38.67 (t) (C-5 and C-7), 42.40 (d, C-6), 146.89 (s, C-8), 109.13 (t, C-9), 20.18 (q, C-10).

For (1*R*,5*R*)-2-Acetyl-3-amino-6,6-dimethylbicyclo[3.1.0]hex-2-ene **6**: 83%, m.p. 62–64°C (pentane–toluene), $[\alpha]_{580}^{24}$ +59° (*c* 1.45, $CHCl_3$); IR (1% in CCl_4) ν/cm^{-1} 3505, 3300, 1645, 1605, 1520; UV (EtOH) λ_{max}/nm 330 (log ε 4.16); MS *m/z* 165 (M^+, 53%), 150 ($M^+ - Me$, 100), 122 ($M^+ - MeCO$, 23), 108 ($M^+ - MeCMe_2$, 44), 80(15); ^1H NMR δ_H 2.03 (s, 3H, 1-H_3), 2.31 (d, *J* 18.5 Hz, $W_{1/2}$ 5 Hz, 1H, 5-Hα), 2.68 (dd, *J* 18.5 and 7.5 Hz, 1H, 5-Hβ), ~1.0 (m, 1H, 6-H), 1.80 (dd, *J* 7.5 and 1.5 Hz, 1H, 7-H), 0.75 (s, 3H, 9-H_3), 0.99 (s, 3H, 10-H_3); ^{13}C NMR δ_C 28.00 (q, C-1), 195.24 (s, C-2), 107.59 (s, C-3), 165.04 (s, C-4), 33.70 (t, C-5), 22.21 (d, C-6), 34.25 (d, C-7), 21.50 (s, C-8), 13.37 (q, C-9), 25.95 (q, C-10).

(1*S*,2*R*,5*S*,6*S*)-8-Acetyl-7-amino-2-hydroxy-2-methyl-5-(methylethyl)bicyclo[4.3.0]non-7-ene **9**: 88%, m.p. 153–155°C (MeOH, solvate with one molecule of MeOH); $[\alpha]_{580}^{24}$ −100° (*c* 1.76, $CHCl_3$); IR (1% in $CHCl_3$) ν/cm^{-1} 3640 (MeOH), 3608, 3500, 3295, 1660, 1580, 1500, 1030; UV (EtOH) λ_{max}/nm 322 (log ε 4.28); MS *m/z* 251 (M^+, 22%), 236 ($M^+ - Me$, 3), 233 ($M^+ - H_2O$, 2), 208 ($M^+ - MeCO$, 11), 190 ($M^+ - H_2O - MeCO$, 39), 150(8), 124(50), 87(14), 85(73), 83(100), 47(12), 43(19); ^1H NMR δ_H 1.97 (s, 3H, 1-H_3), 0.76 (d, *J* 7 Hz, 3H, 10-H_3), 0.84 (d, *J* 7 Hz, 3H, 11-H_3), 1.18 (s, 3H, 15-H_3), 1.5 (s, 2H, O—H), 3.35 (s, 3H, MeOH); ^{13}C NMR δ_C 27.56 (q, C-1), 195.66 (s, C-2), 103.94 (s, C-3), 168.14 (s, C-4), 42.18 (d) and 48.28 (d) and 49.41 (d) (C-5, C-6, C-8), 29.42 (t, C-7), 27.01 (d, C-9), 15.44 (q, C-10), 21.39 (q, C-11), 20.79 (t, C-12), 34.84 (t, C-13), 70.74 (s, C-14), 28.25 (q, C-15), 50.00 (MeOH).

‡ Transformation of ketonitrile **8** into enaminone **9** is conducted in the same manner, but double portions of KOH, HCl and NH_3 are used owing to the hydrolysis of the acetate.

Mendeleev Commun., 1992, 2(4), 161–162

the ketone. The predominant formation of compounds **3**, **6** and **9** seems to reflect the relative stability of the anion pair [eqn. (1)]

$$MeCOCH^{-}—(C)_3CH_2CN \leftrightharpoons MeCOCH_2(C)_3CH^{-}—CN \quad (1)$$

It should be noted that enaminones **3** and **6** are the amino-substituted analogues of the methylcyclopentenylketones formed on intramolecular condensation of ketoaldehydes,[8–10] which are structurally related to ketonitriles **2** and **5**.

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