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

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The preparation of 2-acetylcylopent-1-en-1-ylamine type enamino es from terpenic compounds is described.

Enaminones of various structures, including enamino es, are of great interest both as intermediates for the synthesis of organic compounds of various classes and from the point of view of their potential biological activity. 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 enamine synthesis are available, such intermediates have previously been known in the isoprenoid series. Some enamino es (2-acetylcylopent-1-en-1-ylamine derivatives) have proved to be readily obtainable by heating terpenic 1,6-ketonitriles with an alkali. This reaction is an analog of the known intramolecular condensation reaction of 1,5-ketonitriles to give aminocyclohexenone derivatives. Using the available natural terpenic compounds limonene 1, 3-carene 4 and δ-cadinol 7 as substrates, we have synthesized, via the corresponding ketonitriles 2, 5 and 8, enamino es 3, 6 and 9, yellowish crystalline substances which decompose upon storage in air (Scheme 1).

Our preparation of enamino es 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.O (30 ml) and extracted with EtO (20, 10 ml). The combined etheral solutions are treated with 1 mol dm⁻¹ HCl(15, 10 ml) and the combined aqueous solutions are washed with EtO (10 ml) and neutralized with concentratedaq. NH₄ (5 ml), followed by extraction with EtO (20, 10 ml). The combined etheral solutions are washed with brine (10 ml) and dried over MgSO₄ (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 enamino es were purified via water-soluble hydrochlorides by treatment of the crude material with 1 mol dm⁻¹ HCl to give the water-soluble fraction (enamine 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 13C NMR (Scheme 2)). The 'neutral' fractions, isolated in poor yields, are complex mixtures of by-products having a nitrite group absorption (2100 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 a to the nitrite and cyclization onto.

Scheme 1. Reagents and conditions: 1, see ref. 7, ii, NaOH-EtOH reflux

† Characterization data for (3Z,2-acety1)-4-(1-methylethenyl)cylopent-1-en-1-ylamine 6: 83%, mp. 62-64°C (pentane-toluene) [α]₂₅ = +59° (c 1.45, CHCl₃) IR (1% in CCl₄) ν/cm⁻¹: 3565, 3300, 1645, 1605, 1520, UV (EtOH) λmax/nm (log ε 4.16): MS m/z: 165 (M⁺, 53%), 150 (M⁺-Me, 100), 122 (M⁺-MeCO₂), 108 (M⁺-MeCO₂, 44), 80 (15); 1H NMR δH ppm: 2.03 (3H, 1-Ha), 2.31 (1d, J=18.5 Hz, 1-Hb), 5.1 (5-Ha, 2.68 (dd, J=18.5 and 7.5 Hz, 1H), 1.80 (ds, J=7.5 and 1.5 Hz, 1H), 0.73 (3H, 9-Ha, 0.99 (3H, 9-Hb)); 13C NMR δC ppm: 80.80 (q, C-1), 195.24 (s, C-2), 107.59 (s, C-3), 156.04 (s, C-4), 33.70 (t, C-5), 22.22 (d, C-6), 34.25 (d, C-7), 21.50 (s, C-8), 13.37 (q, C-9), 23.95 (q, C-10).

(1S,2R,5S,6S)-6-Acetyl-7-amino-2-hydroxy-2-methyl-5-methylthienyl-bicyclo(3.3.0) octane 7, see ref. 9, 88%, mp. 153-155°C (MeOH) solvate with one molecule of MeOH [α]₂₅ = -180°(c 1.76, CHCl₃) IR (1% in CHCl₃) ν/cm⁻¹: 3560 (EtOH), 3680, 3500, 2925, 1660, 1580, 1500, 1038, UV (EtOH) λmax/nm (log ε 4.28): MS m/z: 251 (M⁺, 22%), 236 (M⁺-Me, 53), 233 (M⁺-CO₂), 208 (M⁺-MeCO₂, 110), 119 (M⁺-H₂O-MeCO₂, 59), 124.50, 375.11, 552.73, 851.00, 472.19, 494 (9); 1H NMR δH ppm: 1.97 (3H, 1-Ha), 0.76 (ds, J=7.3 Hz, 1H), 1.14 (s, 3H, 1-Hb, 1.35 (s, 2H, 2-Ha), 3.35 (s, 3H, Me₃), 1H NMR δC ppm: 17.56 (q, C-1), 145.06 (s, C-2a), 103.9 (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 (C-7), 27.81 (d, C-9), 15.44 (q, C-10), 21.39 (q, C-11), 20.79 (c, C-12), 32.84 (c, C-13), 70.74 (c, C-14), 28.25 (q, C-15), 30.00 (MeOH).

* Transformation of ketonitrile 8 into enamino es is conducted in the same manner, but double portions of KOH, HCl and NH₄ are used owing to the hydrolysis of the acetate.
the ketone. The predominant formation of compounds 3, 6 and 9 seems to reflect the relative stability of the anion pair [eqn. (1)]

\[ \text{MeCOCH}^+ - (\text{C})\text{CH}_2\text{CN} \cong \text{MeCOCH}_2\text{C} = \text{CN} \]  

It should be noted that enamines 3 and 6 are the amino-substituted analogues of the methylcyclopentenyketones formed on intramolecular condensation of ketoaldehydes, which are structurally related to ketonitriles 2 and 5.

References

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