SYNTHESIS OF BENZOIC AND PHENOXYACETIC ESTERS OF 1-ALLYL-2,4,5-TRIMETHYL-PIPERID-4-OL

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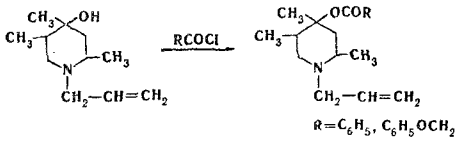
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 3, No. 5, pp. 872–873, 1967

UDC 547.823.07+541.69

Benzoic and phenoxyacetic esters of the γ isomer of 1-allyl-2, 4, 5-trimethylpiperid-4-ol are synthesized. Both esters have considerable anesthetic effect.

We previously synthesized various esters of 1-allyl-2,5-dimethyl-piperid-4-ol. Many of these esters exhibit a comparatively marked anesthetic action. The present paper describes the synthesis of the benzoic and phenoxyacetic esters of the γ isomer of 1-allyl-2,4,5-trimethylpiperid-4-ol, with a view to determining the effect of a methyl group at position 4 in the piperidine ring on the pharmacological properties of these compounds. The starting 1-allyl-2,4,5-trimethyl-piperid-4-ol was prepared [1] by condensing lithium methyl [2] with 1-allyl-2,5-dimethylpiperid-4-one [1,3]. The corresponding esters were obtained by treating the γ isomer of the piperidol with benzoyl chloride or phenoxyacetyl chloride.



Prof. M. D. Mashkovskii (VNIKhFI) carried out surface anesthesia tests on the hydrochlorides of both of these compounds, and found considerable activity. The data from the pharmacological studies will be published separately.

EXPERIMENTAL

1-Allyl-2, 4, 5-trimethylpiperid-4-yl benzoate. 7 g benzoyl chloride was added to a solution of 3 g of the γ isomer of 1-allyl-2, 4, 5-trimethylpiperid-4-ol (mp 29–30°) in 6 ml dry pyridine, and the mixture heated at 120–125° for 7 hr. Pyridine and excess acid chloride were vacuum distilled off on a water bath, and the residue washed with dry ether and left in a refrigerator under a fresh lot of ether. The resultant precipitate was filtered off, dissolved in benzene, boiled with active charcoal, filtered, part of the benzene distilled off, and ether added, to give 1.8 g crystalline material, which was crystallized twice from acetone–ether. Yield of benzoate of the γ isomer of 1-allyl-2, 4, 5-trimethylpiperid-4-ol, 1 g, mp 167–168°. Found: C 66.92; 66.79; H 7.98; 7.91; Cl 11.23; 11.20; N 4.62; 4.78%. calculated for $C_{18}H_{25}NO_2 \cdot HCl$: C 66.40; H 8.01; Cl 10.90; N 4.60%.

1-Allyl-2, 4, 5-trimethylpiperid-4-yl phenoxyacetate. 8.5 g phenoxyacetyl chloride 134–135° (4mm); n_D^{20} 1.5335) was added in small portions, with water cooling, to a mixture of 3.4 g of the γ isomer of 1-allyl-2, 4, 5-trimethylpiperid-4-ol in 6 ml dry toluene and 0.2 g Mg turnings, and the whole then heated at 90–95° for 3 hr and at 110–115° for 9 hr. The Mg was separated off, the solvent distilled off, along with excess acid chloride, the residue treated with Na_2CO_3 solution, the base extracted with ether, the extract dried over Na_2SO_4, the ether distilled off, and the residue distilled. Yield 1.3 g of the phenoxyacetate of the γ isomer of 1-allyl-2, 4, 5-trimethyl-4-ol, bp 156–160° (2mm), n_D^{20} 1.5080. Found: N 4.59; 4.67%, calculated for $C_{19}H_{27}NO_3$: N 4.41%. The hydrochloride was prepared from the base: mp 156–157.5° (ex acetone), found C 64.10, 64.46; H 7.97; Cl 10.01; N 3.72, 3.71%, calculated for $C_{19}H_{27}NO_3 \cdot HCl$: C 64.48; H 7.97; Cl 10.06; N 3.96%.

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31 January 1966

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