# SYNTHESIS OF SOME NEW ESTERS OF 1-n-BUTYL-2,5-DIMETHYL-4-ETHYNYL (ETHYL)-AND 1-ALLYL-2,5-DIMETHYLPIPERID-4-OLS

A. Sh. Sharifkanov, T. G. Sarbaev, K. B. Erzhanov, and K. S. Pishchulina

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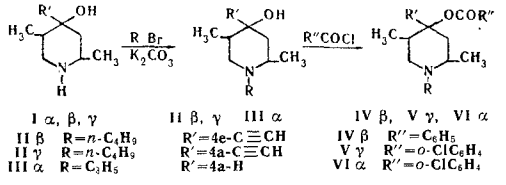
The following are synthesized: 1-n-butyl-2e,5e-dimethyl-4e-ethynylpiperid-4a-yl benzoate (β isomer), 1-n-butyl-2e,5e-dimethyl-4a-ethynyl (ethyl) piperid-4e-yl o-chlorobenzoate (γ isomers), 1-allyl-2e,5e-dimethylpiperid-4e-yl o-chlorobenzoate (γ isomer).

Previous papers [1–5] described 1-n-butyl-2e,5e-dimethyl-4a-ethylpiperid-4e-yl (γ isomer) and 1-allyl-2e,5e-dimethylpiperid-4e-yl (α isomer) benzoates. In the present work the following are synthesized: 1-n-butyl-2e,5e-dimethyl-4e-ethylpiperid-4a-yl benzoate (β isomer) (IVβ), 1-n-butyl-2e,5e-dimethyl-4a-ethynyl (ethyl) piperid-4e-yl o-chlorobenzoates (γ isomers) (Vγ, VIIγ), and 1-allyl-2e,5e-dimethyl-piperid-4e-yl-o-chlorobenzoate (α isomer) (VIα). The purpose was to ascertain the effects of the steric structure of the starting piperidol and of the chlorine atom ortho in the acyl part on the pharmacological properties of the compounds. The starting 1-alkyl (alkenyl) piperid-4-ols (IIβ, IIγ, IIIα) were obtained from the individual 2e,5e-dimethyl-4e(4a)ethynyl-piperid-4a(4e)-ols (Iβ, Iγ) [2–4] and 2e,5e-dimethyl-piperid-4e-ol (Iα) [6–8], by treatment, as required, with n-butyl bromide or allyl bromide in dry acetone in the presence of ignited powdered potassium carbonate [9, 10].




Esterification of the piperidols IIβ, IIγ, and IIIα with acid chlorides gave the corresponding esters IVβ, Vγ, VIα.

Exhaustive hydrogenation of the ethynyl group of ester Vγ, using Raney nickel catalyst gave ester VIIγ.

## EXPERIMENTAL

**1-n-Butyl-2e,5e-dimethyl-4e-ethynylpiperid-4a-yl benzoate (IVβ) hydrochloride.**

a) 3 g n-BuBr in 30 ml acetone was added dropwise, over a period of 30 min, to a stirred mixture of 3 g Iβ (mp 131–132°) [2,4] and 7 g powdered anhydrous $K_2CO_3$ in 70 ml dry acetone at 50–55°. The mixture was heated for 5 hr at 60–70°. After cooling, the solid ($K_2CO_3$ and KBr) was filtered off, washed with acetone, and the acetone distilled off from the filtrate. The residue was dissolved in dry ether, and the solution made acid to Congo Red with ethereal hydrogen chloride. After washing with dry ether the salt which came out was recrystallized from absolute EtOH. Yield 3.9 g (79%) of hydrochloride of IIβ, mp 200–201°, identical with a specimen previously prepared by a different method [1]. Found: Cl 14.62; 14.66; N 5.82; 5.88, calculated for $C_{13}H_{23}NO \cdot HCl$, Cl 14.44; N 5.69%.

b) A mixture of 2.45 g IIβ hydrochloride and 7 g benzoyl chloride in 10 ml dry pyridine was heated for 10 hr at 135–140°. After cooling 50 ml dry ether was added, and the whole left overnight. The precipitate was filtered off, the reaction product extracted from the solid with hot benzene (500 ml), the benzene extract evaporated to 80 ml, and the solid filtered off and recrystallized twice from benzene (once using active charcoal) then from acetone–EtOH (5:1). Yield 0.7 g IVβ hydrochloride, mp 212–213°. Mixed mp with the hydrochloride of the starting piperidol IIβ 170–180°; with the hydrochloride of the benzoate of the γ isomer of this piperidol (mp 194–195°) [1], mp 175–187°. Found: H 8.29; 8.44; Cl 10.42; 10.47; N 4.00; 4.02%, calculated for $C_{20}H_{27}NO_2 \cdot HCl$ : C 68.66; H 8.07; Cl 10.13; N 4.00%.

**1-n-Butyl-2e,5e-dimethyl-4a-ethylpiperid-4e-yl o-chlorobenzoate (Vγ) hydrochloride.**

a) 15.3 g Iγ (mp 93–94°) [2,4], 15 g n-BuBr, 28 g anhydrous powdered $K_2CO_3$, and 200 ml dry acetone gave, similarly to IIβ, 20.4 g (85%) hydrochloride IIγ, mp 206–207°. Undepressed mixed mp with a specimen prepared as described in [1].

b) A mixture of 2.45 g IIγ hydrochloride and 10.5 g o-chlorobenzoyl chloride (bp 110–111°/15 mm) in 10 ml dry pyridine was heated for 10 hr at 135–140°. Then the pyridine and excess acid chloride were distilled off under a water pump vacuum on a water bath. The residue was rubbed with dry ether, then extracted with boiling benzene (600 ml). The benzene extracts were evaporated to small volume, the crystals which came out filtered off and recrystallized thrice from acetone–EtOH (5:1). Yield 2.4 g Vγ hydrochloride, mp 183°–184°. Mixed mp with the hydrochloride of the starting piperidol (mp 206°–207°), mp 165°–173°. Found: C 62.58; 62.85; H 7.45; 7.47; Cl (ionic) 9.33; 9.47; N 3.62; 3.58%, calculated for $C_{20}H_{26}ClNO_2 \cdot HCl$: C 62.48; H 7.09; Cl (ionic) 9.23; N 3.64%.

**1-Allyl-2e,5e-dimethylpiperid-4e-yl (VIα) hydrochloride.** A mixture of 2.5 g IIIα [5, 8] in 5 ml dry benzene and 7 g o-chlorobenzoyl chloride was heated for 10 hr at 105–110°. The benzene and excess acid chloride were then distilled off on a water bath under a water pump vacuum. The residue was washed a few times with dry ether to remove residual acid chloride, and then left under ether in a refrigerator. The solid was recrystallized thrice from benzene (once using active charcoal). Yield 3.4 g (65.9%) VIα hydrochloride, mp 149–150°. Found: C 59.45; 59.58; H 6.95; 7.04; N 4.22; 4.25; Cl (ionic) 10.36; 10.40%, calculated for $C_{17}H_{22}ClNO_2 \cdot HCl$: C 59.30; H 6.73; N 4.06; Cl (ionic) 10.30%.

**1-n-Butyl-2e,5e-dimethyl-4a-ethylpiperid-4a-yl o-chlorobenzoate (VIIγ) hydrochloride.** 0.8 g Vγ hydrochloride in 30 ml dry EtOH was hydrogenated in the presence of Raney Ni (1 g) at 20° and 688.5 mm, until 89.6 ml hydrogen had been absorbed. Then the catalyst was filtered off, washed with EtOH, the EtOH distilled off from the filtrate, and the residue crystallized from acetone–ether. Yield 0.5 g (64.7%) VIIγ hydrochloride mp 125–126°, mixed mp with the hydrochloride of the starting ester Vγ 106–131°. Found: C 61.70; 61.70; H 8.41; 8.42; Cl (ionic) 9.28; 9.33; N 3.71; 3.82, calculated for $C_{20}H_{30}ClNO_2 \cdot HCl$: C 61.85; H 8.06; Cl (ionic) 9.12; N 3.60%.

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