SOME PECULIARITIES IN THE ACYLATION OF THE ISOMERIC 1,2,5-TRIMETHYL-4-PHENYL-4-PIPERIDOLS

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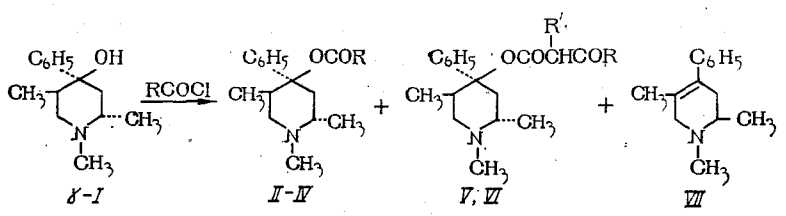
UDC 547.823

A rather large number of researches have been devoted to the preparation of esters of tertiary γ-piperidols, especially esters of 1,2,5-trimethyl-4-phenyl-4-piperidol (I) [1], and to the study of their pharmacological properties.

We have examined the acylation of the γ isomer of 1,2e,5e-trimethyl-4e-phenyl-4-piperidol (γ-I), as well as of a mixture of the isomers of this piperidol, with acid chlorides in the presence of triethylamine and also without it. As the acylating agents we used the acid chlorides of acetic, propionic, butyric, and benzoic acids.



II, V: R=C2H5, R'=CH3; III: R=C3H7-n; IV: R=C6H5; VI: R=CH3, R'=H

On reaction of the γ isomer of piperidol I with propionyl chloride in the presence of triethylamine, the β-oxo-α-methylvalerate V is formed in predominant amount, and the propionate (the base of promedol) (II) of this piperidol is formed in a considerably smaller amount. The fact that ester V is a crystalline substance with a rather high melting point for compounds of this type (100-101°C; the γ isomer of piperidol I has mp 107-108°) was somewhat unexpected. All the esters of piperidol I which had been prepared up until now were liquid, noncrystallizing substances which dissolved well in nonpolar solvents. Even in this respect, ester I behaves peculiarly; on heating it dissolved in petroleum ether, and then it separated out almost quantitatively, but only after extended storage of its solution at a reduced temperature. Ester V does not dissolve in petroleum ether without heating. Apparently the reason for the difference of properties of ester V from its numerous analogs consists in the fact that keto–enol transformations take place in its ester group. The presence of its enol form was confirmed by a ferric chloride test. The fact that ester V does not dissolve in petroleum ether without heating may be explained by the formation of intramolecular or intermolecular associates due to interaction of the hydrogen in the acidic and hydroxyl group with the basic nitrogen atom of the piperidine ring.

Ester V, which is the α-propionylpropionate of the γ isomer of piperidol I, i.e., an analog of promedol, is completely void of analgetic properties. On reaction of γ-I with acetyl chloride under similar conditions, only the β-oxobutyrate (VI) and the dehydration product of this piperidol (VII) were isolated in slight yield.

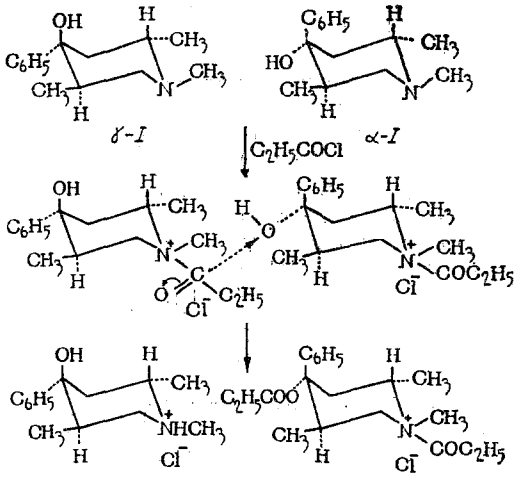
The formation of esters V and VI can be explained by the fact that under the conditions of the reactions given, ketenes and dimers of these should be readily formed from acetyl chloride and propionyl chloride. There is no doubt that esters V and VI are formed on reaction of piperidol I with the dimers of methylketene and ketene, respectively. On treatment of the γ isomer of piperidol I under the same conditions with butyryl chloride or benzoyl chloride, the butyrate (III) and benzoate (IV) were isolated, respectively.

The γ isomer, and also the α isomer (1,2e,5e-trimethyl-4a-phenyl-4-piperidol) of piper-

Patrice Lumumba Peoples' Friendship University, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 5, pp. 104-106, May, 1977. Original article submitted April 7, 1976.

 0091-150X/77/1105-0688$07.50

idol I is partially acylated with propionyl chloride in petroleum ether (without triethylamine), the extent of acylation depending on the ratio of piperidol to acid chloride and on the duration of the reaction. However, on treatment of a mixture of the γ and α isomers of piperidol I (formed on reaction of the 1,2,5-trimethyl-4-piperidone with phenyl lithium, and consisting approximately of 60% γ isomer and 40% α isomer) with propionyl chloride a quantitative acylation of the α isomer takes place, while the γ isomer is recovered unchanged. In this case a different ratio of reagents and duration of heating essentially do not effect the result of this reaction. Apparently in this case the steric features of the structure of the α and β isomers determine the direction of acylation.



Acylation of the α isomer of piperidone I takes place by reaction of its equatorial hydroxyl group with the acyl radical of the quaternary salt of the γ isomer of piperidol I, which is formed on the reaction of the piperidol with propionyl chloride. Acylation of the axial hydroxyl group of the γ isomer of piperidone I does not take place, due to steric shielding. The results obtained may present considerable interest as applicable to the acylation of isomeric tertiary γ-piperidols, which, by the way, is carried out under industrial conditions, and also may be used to solve some problems of their steric structure.

EXPERIMENTAL

Propionate (II) and β-Oxo-α-methylvalerate (V) of the γ Isomer of 1,2,5-Trimethyl-4-phenyl-4-piperidol. To a solution of 20 g (0.091 mole) of γ-I in 100 ml of absolute benzene and 28.9 g (0.286 mole) of triethylamine was gradually added 21.3 g (0.23 mole) of propionyl chloride. The mixture was kept at room temperature for 12 h, and then boiled for 7 h. The triethylamine hydrochloride (28.2 g) was filtered off and washed repeatedly with benzene. To the benzene solution were added 100 ml of water, 50 ml of 18% hydrochloric acid, and 100 ml of ether. The benzene–ether layer was separated, the water layer shaken with 50 ml of ether, and then it was treated with sodium carbonate. The organic bases were extracted with ether and the solution was dried with sodium sulfate. The residue (23.5 g) from the ether extract was refined on a column containing aluminum oxide (30 g, grade II activity, H = 6 cm, d = 2.8 cm, petroleum ether as solvent). The volume of petroleum ether solution collected was 500 ml; this was kept at –10° for 12 h. Ester V (10.8 g) separated. The mother liquor was evaporated to 40 ml, on cooling to –10° and keeping for 12 h, another 1.85 g of ester V separated. The petroleum ether was distilled from the mother liquor and the residue was distilled, collecting the fraction of bp 155-162° (2 mm) in an amount of 6.4 g, from which there was obtained 3.6 g (12.6%) of the hydrochloride of propionate II (promedol), mp 197-199°. The residue after distillation of the 3.2 g was dissolved in 30 ml of petroleum ether and passed through a column containing aluminum oxide (2 g); it was eluted with petroleum ether. The solution was evaporated down to 15 ml, and with addition of a little ester V it was kept for 12 h at –10°. Additional ester V separated (0.15 g). In all there was obtained 12.8 g of ester V (42.5%), mp 100-101° (from petroleum ether). In its IR spectrum the bands at 1745 cm^{-1} (present in the IR spectrum of propionate II) and at 1738 cm^{-1} pertain to the oxo groups of the ester function. Found, %: C 72.6; H 9.1; N 4.2. $C_{20}H_{29}NO_3$. Calculated, %: C 72.5; H 8.8; N 4.2. The picrate of V melts at 148.5-150.5° (from alcohol). Found, %: N 10.3. $C_{20}H_{29}NO_3 \cdot C_6H_3N_3O_7$. Calculated, %: N 10.0. The hydrochloride of V has mp 144-146° (from acetone). Found, %: Cl 9.3; N 3.8. $C_{20}N_{29}NO_3 \cdot HCl$. Calculated, %: Cl 9.7; N 3.8.

The γ isomer of I is obtained on alkaline hydrolysis of ester V.

β-Oxobutyrate (VI) of the γ Isomer of 1,2,5-Trimethyl-4-phenyl-4-piperidol. Into reaction were brought 5 g (0.023 mole) of γ-I, 7.2 g (0.071 mole) of triethylamine, 1.6 g (0.02 mole) of acetyl chloride, and 80 ml of benzene; the reaction was carried out as before. On chromatographic separation of the reaction products on aluminum oxide (using petroleum ether as eluent), 0.2 (7%) of the dehydration product VII, 0.5 g (10%) of ester VI, and 1.2 g of γ-I were successively isolated. The hydrochloride of ester VI had mp 167-170° (from acetone). IR spectrum: bands at 1745 and 1735 cm^{-1}, belonging to β-ketoester group. Found, %: Cl 10.7; N 4.2. $C_{18}H_{25}NO_3 \cdot HCl$. Calculated, %: Cl 10.5; N 4.1. Picrate of ester VI, mp 155-155.5° (from alcohol). Found, %: N 10.8. $C_{18}H_{25}NO_3 \cdot C_6H_3N_3O_7$. Calculated, %: N 10.5.

On acylation of piperidol I with butyryl chloride under analogous conditions, ester III was obtained in 8.7% yield, but in the acylation of γ = I with benzoyl chloride, the benzoate IV is formed in 84% yield. In the IR spectra of the hydrochlorides of esters III and IV, the band at 1745 cm^{-1} corresponds to the ester group.

Acylation of mixture of α- and γ-isomers of 1,2,5-trimethyl-4-phenyl-4-piperidol. To a solution of 35.6 g (0.16 mole) of a mixture of the α and γ isomers of piperidol I in 100 ml of benzene was gradually added 23 g (0.25 mole) of propionyl chloride. The mixture was boiled for 4 h. According to thin-layer chromatographic evidence, in the reaction product there were the γ isomer of piperidol I (R_f 0.36) and the propionate of the α isomer of this piperidol (R_f 0.55). The reaction mixture was treated with a sodium carbonate solution. The organic bases were extracted with benzene. The residue after distillation of the benzene (39 g) was separated by use of column chromatography on aluminum oxide (500 g of adsorbent, H = 54 cm, d = 3 cm). On elution with benzene (4 liters) there was isolated 18 g (49%, calculated on the starting mixture of isomers of piperidol I) of the propionate ester of II (α-promedol, which corresponds in characteristics to those reported in [1]). Then the column was eluted with ethanol (400 ml) and there was isolated 17.5 g (50%, based on starting isomer mixture) of the γ isomer of piperidol I, mp 107-108° [1].

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INFLUENCE OF DIFFERENT OINTMENT BASES ON THE ANTIMICROBIAL ACTIVITY OF ARENARIN

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UDC 615.457.615.281]:615.454.1

The new antimicrobial preparation of plant origin arenarin has proved its value in medical ophthalmological practice. It is supplied for the treatment of chemical and thermal burns of the eyes in the form of a 1% ointment in a petrolatum base.

The antibiotic is obtained from the flowers of the yellow everlasting (*Helichrysum arenarium* D. C.) and consists of a 5% solution of the active principle of the everlasting in 96% ethanol. According to Drobotskii, arenarin acts on Gram-positive pathogenic bacteria, including cocci, in a concentration of 20-40 μg/ml but does not affect the Gram-negative microflora. The preparation has an antiinflammatory action, stimulates regenerative processes in tissues, and raises the immunobiological reactivity of the macroorganism [2]. According to clinical trials, arenarin is an extremely effective agent for the treatment of burns to the eyes.

However, the results of the experiments show that petrolatum as the ointment base mixes poorly with the lachrymal fluid, releases the antibiotic slowly and insufficiently completely,

Khar'kov Pharmaceutical Institute. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 5, pp. 107-110, May, 1977. Original article submitted May 17, 1976.

 0091-150X/77/1105-0690$07.50