

SYNTHESIS OF 2, 5-DIMETHYL- AND 1, 2, 5-TRIMETHYL-4-DIMETHOXY-PHOSPHINYLPYPERID-4-OLS

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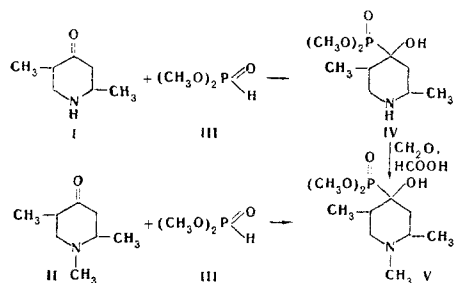
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Dimethyl phosphite is condensed with 2, 5-dimethyl- and 1, 2, 5-trimethylpiperid-4-ones in the presence of alkali metal alkoxides. It is shown that 2, 5-dimethyl- and 1, 2, 5-trimethyl-4-dimethoxyphosphinyl-piperid-4-ols are formed in both cases in the same stereoisomeric forms and in high yields. Methylation of the piperidol isomer which was not substituted at the nitrogen atom indicated that the two piperidols formed had the same configuration.

α -Hydroxyalkylphosphonic esters comprise an important category of organophosphorous compounds. A large number of physiologically active compounds occur in this series, some of which are useful in agriculture, as insecticides, [1-5]. Others are important as drugs [2, 6]. Continuing work on the production of organophosphorus insecticides [7-10], we turned to the synthesis of dialkyl α -hydroxyphosphonic esters of the piperidine series. Our aim was to study the influence of the above cyclic system on the insecticidal properties of this series of compounds. Because of the presence of various reactive centers, these substances are useful subjects for further study and reactions, with a view to the preparation of a whole series of promising physiologically active substances.

The starting compounds were 2, 5-dimethyl- (I), 1, 2, 5-trimethylpiperid-4-ones [11] (II), and dimethyl phosphite [12] (III). 2, 5-Dimethyl- and 1, 2, 5-trimethyl-4-dimethoxyphosphinyl-piperid-4-ols (IV and V, respectively) were obtained in high yield by the condensation of I and II with III in the presence of sodium methoxide as described previously [13, 14].

The individuality of compounds IV and V was shown by their layer chromatography in alumina. It was evident that the addition of III to the carbonyl groups of I and II proceeded stereospecifically to form a single stereoisomeric alcohol in each case.



The above reactions are energetic and are accompanied by significant heat evolution. The addition of III to the piperidone I proceeds readily and rapidly. If the temperature is allowed to rise significantly during catalyst addition, resinification of IV occurs. Consequently the reaction mixture was strongly cooled.

The alcohol IV, which is not substituted at the nitrogen atom, was methylated in order to establish the

configurational similarities between IV and V. The isomer synthesized by this method proved to be identical with the piperidol isomer prepared by direct condensation of II with III. The structures of the new piperidols containing phosphorus [15] were confirmed by their IR spectra.

EXPERIMENTAL

2, 5-Dimethyl-4-dimethoxyphosphinylpiperid-4-ol (IV). A freshly prepared saturated solution of sodium methoxide in methanol was added dropwise, with cooling, to a mixture of 3.17 g (0.025 mole) of the piperidone I and 2.75 g (0.025 mole) of III at such a rate that the temperature did not rise above 20-25° C. Sodium methoxide was added until heat evolution from the reaction mixture ceased. The mixture was left overnight. The colorless crystals which were formed were filtered off and were washed with ethanol, acetone, and ether. Yield 5.4 g (83%) of the piperidol IV, mp. 165° C (decomp). TLC showed a single spot: R_f 0.49 (alumina, activity II, benzene-dioxane-methanol, (4 : 4 : 1). IR spectrum: 1200 cm^{-1} (P=O), 1145 cm^{-1} (P-O-CH₃). Found, %: N 5.70; P 13.52. Calculated for C₉H₂₀NO₄P, %: N 5.90; P 13.05. The hydrochloride of IV was prepared by adding an ethereal solution of dry HCl to an ethereal solution of 0.47 g (0.002 mole) of the base. Yield 0.5 g (92%); mp 266-267° C (from ethanol). Found, %: N 5.07. Calculated for C₉H₂₀NO₄P · HCl, %: N 5.12.

1, 2, 5-Trimethyl-4-dimethoxyphosphinylpiperid-4-ol (V).

a) A methanolic solution of sodium methoxide was added slowly, dropwise, to a mixture of 35.7 g (0.25 mole) of II and 27.5 g (0.25 mole) of III. The temperature of the reaction mixture rose from 18° C to 60° C. The viscous mass which formed crystallized on cooling. Yield 49.2 g (78%) of the piperidol V, mp 113-114° C (from ligroin). TLC showed a single spot: R_f 0.77 [alumina activity, II, benzene-dioxane-methanol, (4 : 4 : 1)]. IR spectrum: 1245 cm^{-1} (P=O), (P-O-CH₃). Found, %: N 5.53; P 12.27. Calculated for C₁₀H₂₂NO₄P, %: N 5.57; P 12.32. 0.53 g (94%) of the hydrochloride, mp 185-187° C (highly hygroscopic), was prepared from 0.5 g (0.002 mole) of the base. Found, %: N 4.87. Calculated for C₁₀H₂₂NO₄P · HCl, %: N 5.30.

b) A mixture of 0.9 g (0.0038 mole) of the piperidol IV, 0.6 g (0.013 mole) formic acid, and 0.4 g (0.013 mole) of 33% formalin solution was heated on a water bath for 4 hr. The reaction mixture was neutralized with sodium carbonate solution and extracted several times with ether. The extract was dried with KOH. The ether was distilled off and the residue crystallized on cooling. Yield 0.56 g (61%) of the piperidol V, mp 113-114° C (from ligroin). A sample mixed with the material described above, gave an undepressed melting point.

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