SYNTHESIS AND USE OF 4-AZIDOHEXAHYDROPYRIMIDIN-2-THIONES AS EFFICIENT AMIDOALKYLATING REAGENTS

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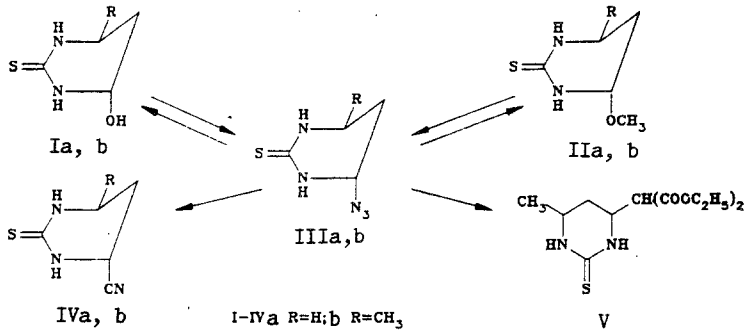
4-Hydroxy- or 4-alkoxyhexahydropyrimidin-2-thiones in acid or basic media readily react with certain O- and S-nucleophiles to form the corresponding 4-substituted hexahydropyrimidin-2-thiones [1, 2]. In addition, on account of the low nucleophilicity of the hydroxy and alkoxy groups of the indicated compounds, they prove to be inactive in amidoalkylation reactions of C-nucleophiles. This has encouraged us to synthesize novel amidoalkylating agents containing good leaving groups at the C_4 atom of the hexahydropyrimidin-2-thione molecules.

We have shown that 4-azidohexahydropyrimidin-2-thiones are efficient amidoalkylating reagents and can be formed readily and in high yield by treating 4-hydroxy(alkoxy) hexahydropyrimidin-2-thiones with hydrazoic acid in aqueous media. Thus reaction of the 4-hydroxy or 4-methoxy derivatives Ia, b and IIa, b with an aqueous solution of hydrazoic acid (obtained in situ from sodium azide and hydrochloric acid) gives in greater than 90% yield the corresponding 4-azido-hexahydropyrimidin-2-thione IIIa (mp 129-130°C (decomp.)) or trans-4-azido-6-methylhexahydropyrimidin-2-thione IIIb (mp 155.5-156°C (decomp., from ethyl acetate)).



Compounds IIIa, b are stable in the cold to hydrolysis or alcoholysis but, upon heating with water at 95°C or refluxing with methanol, are rapidly and quantitatively converted to the corresponding 4-hydroxy- (Ia, b) or 4-methoxypyrimidines (IIa, b).

It has been found that treatment of azidopyrimidines IIIa, b with sodium cyanide at 20°C in DMF or acetonitrile for several hours gives 4-cyanohexahydropyrimidin-2-thione (IVa, mp 158.5-159.5°C, from alcohol) or trans-6-methyl-4-cyanohexahydropyrimidin-2-thione (IVb, mp 235-237°C, decomp., from alcohol) in 70-85% yields. In the same way the azidopyrimidine IIIb reacts with sodium diethylmalonate in various solvents to give up to 96% yield of 6-methyl-4-[bis(carbethoxy)methyl] hexahydropyrimidin-2-thione (V) as a mixture of the cis- and trans- isomers with the latter predominating. The stereoselectivity depends signficantly on the nature of the solvent being 74% in alcohol.

The structures of III-V were confirmed by IR, UV, and PMR spectra and by elemental analytical data.

It should also be mentioned that the high nucleophilicity of the azido group situated alpha to nitrogen in cyclic ureas is of a general nature and will be the subject of a subsequent publication.

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UNUSUAL RECYCLIZATION OF 5-METHYL-2, 4-DIPHENYL-6-(2-N, N-DIMETHYL-AMINOVINYL)-3-AZAPYRILIUM PERCHLORATE

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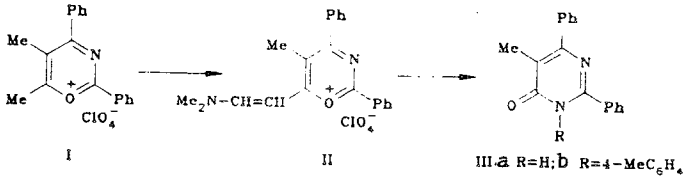
We have discovered a previously unknown recyclization of 3-azapyrilium salts which accompanies splitting of an exocyclic C—C bond. The 3-azapyrilium salt II, obtained by a Vilsmeier reaction from 5,6-dimethyl-2, 4-diphenyl-3-azapyrilium perchlorate (I) [1], reacts with ammonium acetate or with p-toluidine upon refluxing in acetic acid to split off the N, N-dimethylaminovinyl group and to form the 4(3H)-pyrimidones IIIa, b.



2-(2-N, N-Dimethylaminovinyl)-5-methyl-4, 6-diphenyl-3-azapyrilium perchlorate (II, $C_{21}H_{21}ClN_2O_5$). Yield 50 %, mp 26°C (from acetic acid). IR spectrum (Vaseline mull): 1627 (C=C), 1608 (3-azapyrilium cation), 1080 cm^{-1} (ClO_4). PMR spectrum (nitrobenzene-d_5): 2.22 (3H, s, $5CH_3$); 3.49 and 3.78 (each 3H, s, NCH_3); 5.75 and 8.63 (each 1H, d, j = 11 Hz, =CH); 7.20-8.35 ppm (10H, m, arom.).

5-Methyl-2, 6-diphenylpyrimidin-4(3H)-one (IIIa). Yield 32 %, mp 260°C [2].

5-Methyl-3-(p-tolyl)-2, 6-diphenylpyrimidin-4(3H)-one (IIIb, $C_{24}H_{20}N_2O$). Yield 41%, mp 228°C (from benzene). IR spectrum (vaseline mull): 1647 cm^{-1} (C=C). PMR spectrum ($CDCl_3$): 2.13 and 2.19 (each 3H, s, CH_3); 6.80-7.70 ppm (14H, m, arom.). M^+ 352.

Elemental analytical data agreed with those calculated.

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