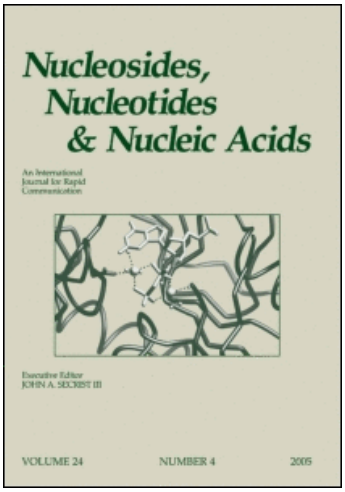

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As-Triazine Derivatives with Potential Therapeutic Action XXVII. Synthesis of 5-[Alkyl-(ethoxycarbonyl)methyl]mercapto-6-azauridines

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AS-TRIAZINE DERIVATIVES WITH POTENTIAL THERAPEUTIC ACTION XXVIII.[1] SYNTHESIS OF 5-[ALKYL-(ETHOXYCARBONYL)METHYL] MERCAPTO-6-AZAURIDINES

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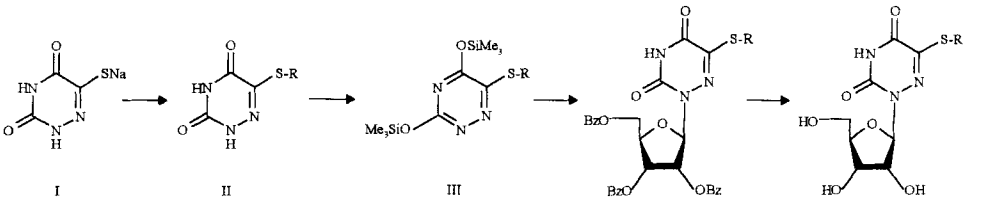
ABSTRACT: 5-Mercapto-6-azauracil (I) reacted in aqueous medium with ethyl α-halo-alkanoates giving 5-[alkyl-(ethoxycarbonyl)methyl]mercapto-6-azauracils (II). Their 2,4-bis(trimethylsilyloxy) derivatives (III) were condensed with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose in the presence of anhydrous stannic chloride to afford the corresponding blocked nucleosides (IV). Under the action of sodium methoxide, the derivatives IV were debenzoylated with the formation of the title compounds (V).

The research on 5-[alkyl-(ethoxycarbonyl)methyl]mercapto-6-azauridines (V) was undertaken in an attempt to find substances with improved pharmacological and therapeutic properties as compared to 5-mercapto-6-azauracil. The study was stimulated by the assumption that the carbethoxyalkyl group may favorably effect the transport of a substance of this type in the organism, especially through the cellular membrane.

We have investigated the synthesis of these nucleosides by applying the Friedel-Crafts-catalyzed silyl-Hilbert-Johnson reaction.[2] 5-mercapto-6-azauracil[3] (I) reacts in aqueous medium with ethyl α-halo-alkanoates leading to 5-[alkyl-(ethoxycarbonyl) methyl]mercapto-6-azauracils (II a-e). Treatment of II with hexamethyldisilazane in the presence of traces of trimethylchlorosilane, under reflux, afforded the corresponding 2,4-bis(trimethylsilyloxy) derivatives (III a-e). Condensation of III with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose in dry 1,2-dichloroethane, at room temperature, in the presence of anhydrous stannic chloride, gives only the N-glycosides in 80-85% yield. The resulting

blocked nucleosides (IV a-e) were deacylated by methoxide-catalyzed transesterification to yield the 5-[alkyl-(ethoxycarbonyl)methyl]mercapto-6-azauridines (V a-e).



I II III IV V

a.) R = -CH(CH_3)-$COOC_2H_5$
b.) R = -CH(C_4H_9)-$COOC_2H_5$
c.) R = -CH(C_6H_{11})-$COOC_2H_5$
d.) R = -CH(C_8H_{17})-$COOC_2H_5$
e.) R = -CH($C_{10}H_{21}$)-$COOC_2H_5$

The assignment of the carbohydrate moiety to the N^1 position of the 5-substituted-6-azauracil ring is based on the fact that the nucleosides (V) exhibit a hypsochromic shift of the absorption maximum in the ultraviolet spectrum by passing from acidic to basic media. This is a typical behavior for N^1-ribosylated 6-azauracils.[4] The anomeric protons of the nucleosides IV and V appear in ^{1}H-NMR spectra as doublets at δ = 6.05-6.66 ppm., with a coupling constant of 2-3.2 Hz, fact which indicates that the nucleosides are β-anomers by comparison with the ^{1}H-NMR spectra of other nucleosides of this type.[5-7]

The elemental analysis results for the compounds II a-e, IV a-e, and V a-e were within ± 0.4% of the theoretical values for C, H, and N.

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