ISOTOPE EXCHANGE OF HYDROGEN IN 3, 5-DIMETHYLISOXAZOLE-4-CARBOXYLIC ACID

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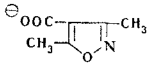
We have studied the isotope exchange of hydrogen in the CH_3 groups of the 3, 5-dimethylisoxazole-4-carboxylate anion (I) with D_2O in the presence of OD^-. By back-exchange with H_2O, samples of 3, 5-dimethylisoxazole-4-carboxylic acid (II) containing deuterium only in the CH_3 groups were obtained.



I

For such samples, the rate constant of the reaction at 50°C is 3.1×10^{-5} sec $^{-1}$. In the NMR spectrum of the initial acid II at a frequency of 40 MHz ($CHCl_3$, hexamethyldisiloxane as internal standard) there are two singlet signals from methyl groups with $\delta = 2.37$ ppm (CH_3 group in position 3) and $\delta = 2.62$ ppm (CH_3 group in position 5) with respect to $(CH_3)_4Si$. The assignment of the peaks is unambiguous on the basis of literature data on the NMR spectra of isomeric substituted 3- and 5-methylisoxazoles [1, 2]. In the spectra of the deuterated samples recorded at the same concentration, there is a decrease in the peaks with $\delta = 2.62$ ppm, which rigidly shows the position of entry of the deuterium and disproves the existing opinion [3] of the isotopic exchange of hydrogen in the CH_3 group attached to C-3 of the anion I. Consequently, in the anion I in an alkaline medium protonation of the hydrogen atoms is favored only in the CH_3 group in position 5. The selectivity of the activation of the CH_3 group on the C-5 atom in isoxazoles containing electron-accepting substituents in position 4 is also shown by the high reactivity in condensation reactions of such a group in 3, 5-dimethyl-4-nitroisoxazole [4].

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SYNTHESIS OF $N_{(NH_2)}$ -[ω-(5-URACILYL)ALKYL]ADENINES

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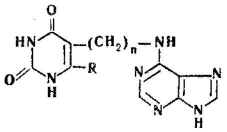
In the search for substances with antitumoral activity, among the covalently-bound nucleic bases [1, 2] we have synthesized the $N_{(NH_2)}$-[ω-(5-uracilyl)alkyl]-adenines (Ia–c).



a n = 1, R = H
b n = 2, R = H
c n = 2, R = CH_3

The compounds obtained are crystalline substances insoluble in the usual organic solvents and very sparingly soluble in water and they decompose without melting on being heated above 400° C. The samples for analysis were dried over P_2O_5 at 130° C in a vacuum of 0.1 mm Hg.

$N_{(NH_2)}$-(5-uracilylmethyl)adenine (Ia). A solution of 0.88 g (5.7 mM) of 6-chloropurine [obtained with the participation of student E. M. Rudakova], 1 g (5.7 mM) of 5-aminomethyluracil hydrochloride [3], and 0.75 g (13.4 mM) of KOH in 15 ml of water was boiled for 3 hr. The precipitate of Ia was filtered off and was purified by reprecipitation from alkaline solution with hydrochloric acid. Found, %: C 46.50; H 3.66. Calculated for $C_{10}H_9N_7O_2$, %: C 46.33; H 3.50. IR spectrum: 3539, 3250, 3100, 1729, 1664, 1629, 1607, 1535, 1464, 1414, 1380, 1325, 1247, 1179, 1139, 1071, 1007, 957, 859, 799, 767 cm^{-1}.

$N_{(NH_2)}$-[β-(5-uracilyl)ethyl]adenine (Ib). This was obtained in a similar manner to Ia from 6-chloropurine and 5-(β-aminoethyl)uracil hydrobromide [4]. Found, %: C 48.51; H 4.08. Calculated for $C_{11}H_{11}N_7O_2$, %: C 48.35; H 4.06. IR spectrum: 3380, 3280, 3120, 1708, 1677, 1630, 1600, 1545, 1460, 1416, 1380, 1340, 1315, 1292, 1250, 1223, 1158, 1137, 1114, 1026, 1000, 940, 895, 844, 800, 770, 743 cm^{-1}.

$N_{(NH_2)}$-[β-(6-methyl-5-uracilyl)ethyl]adenine (Ic). This was obtained in a similar manner to Ia from 6-chloropurine and 5-(β-aminoethyl)-6-methyluracil hydrobromide [4]. Found, %: C 49.84;