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

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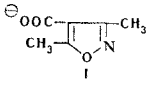
We have studied the isotope exchange of hydrogen in the CH_3 groups of the 3,5-dimethylisoxazole-4-carboxylate anion (I) with D_2O in the presence of OD^-. By back-exchange with H_2O, samples of 3,5-dimethylisoxazole-4-carboxylic acid (II) containing deuterium only in the CH_3 groups were obtained.



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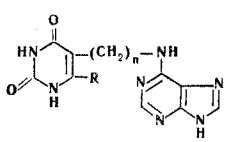
In the search for substances with antitumoral activity, among the covalently-bound nucleic bases [1, 2] we have synthesized the $N_{(NH_2)}$-[ω-(5-uracilyl)alkyl]-adenines (Ia-c).



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;

H 4.79. Calculated for $C_{12}H_{13}N_7O_2$, %: C 50.17; H 4.56. IR spectrum: 3370, 3233, 3128, 1708, 1673, 1629, 1603, 1553, 1466, 1416, 1378, 1358, 1336, 1318, 1257, 1192, 1162, 1128, 1108, 1053, 1000, 948, 863, 798, 773, 740 cm^{-1}. After recrystallization from formamide, a sample of Ic had a somewhat different IR spectrum: 3460, 3380, 3290, 1726, 1650, 1631, 1605, 1542, 1466, 1405, 1380, 1358, 1332, 1308, 1255, 1202, 1168, 1151, 1110, 1070, 1000, 955, 906, 870, 825, 800, 780, 740 cm^{-1}.

The IR spectra were taken in paraffin oil on a UR-10 spectrometer in the physical chemistry laboratory (Director B. S. Kikot). The microanalyses were carried out in the analytical laboratory of the Institute (Director A. D. Chinaeva).

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SOME REACTIONS BASED ON 4,4-DICHLORO-2,6-PYRANDICARBOXYLIC ACID

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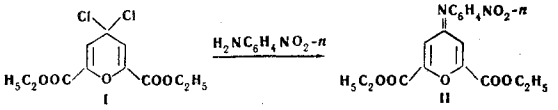
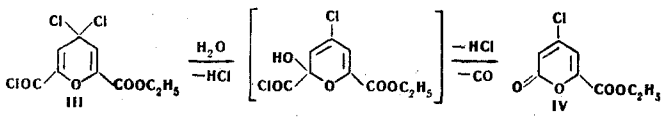
It has been shown, with the reaction of p-nitroaniline with 2,6-diethoxycarbonyl-4, 4-dichloropyran (I) as an example, that, as in the case of the reaction of 4,4-dichlorobenzopyrans with aromatic amines [1], in this gem-dichloropyran system no allyl rearrangement takes place.



Conversely, the reaction of 4,4-dichloro-2-chloroformyl-6-ethoxycarbonylpyran (III) with water is accompanied by an allyl rearrangement and subsequent decarbonylation with the formation of 4-chloro-6-ethoxycarbonyl-2-pyrone (IV).



Consequently, the conversion of 4,4-dichloro-2-chloroformylchromenes into 4-chlorocoumarins observed previously [2] is not specific for benzopyrans and can be extended to monocyclic systems as well.

A mixture of 2.4 g (0.01 mole) of diethyl chelidonate and 20 ml of $SOCl_2$ was heated for 10 hr, the excess of $SOCl_2$ was distilled off in vacuum, the residue was dissolved in 20 ml of benzene, and the resulting solution was treated with a hot solution of 1.38 g of p-nitroaniline in 70 ml of benzene. The reaction mixture was left for 3 hr and was then heated to the boil and the hydrochloride of the imine II was filtered off. By treatment with aqueous bicarbonate solution, the hydrochloride was converted into the base II, yield 2.5 g (72%), mp 150.5–151° C (from ethanol). Found, %: C 56.88, 56.89; H 4.64, 4.57; N 7.94, 7.95. Calculated for $C_{17}H_{16}N_2O_7$, %: C 56.66; H 4.48; N 7.78.

A mixture of 4.9 g of monoethyl chelidonate and 50 ml of $SOCl_2$ was boiled for 10 hr, after which distillation yielded 2.5 g of III, bp 128–130° C (1 mm), to which water was added; after 18 hr, the mixture was treated with $NaHCO_3$ and extracted with benzene to give 0.68 g (38%) of substance IV, mp 59.5–60° C (it sublimed at 100° C at 20 mm). Found, %: C 47.52, 47.39; H 3.36, 3.44; Cl 17.44, 17.28. Calculated for $C_8H_7ClO_4$, %: C 47.42; H 3.38; Cl 17.50. IR spectrum (CCl_4): 1760, 1736 cm^{-1} (ester and pyrone carbonyls). The NMR spectra confirms the structure IV.

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