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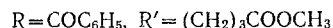
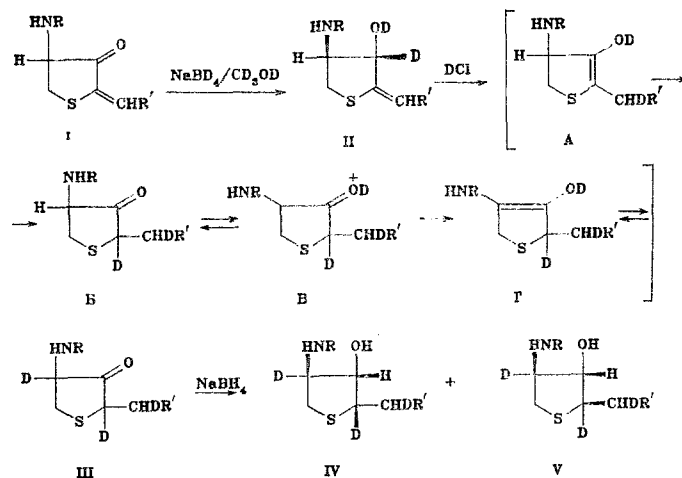
REDUCTIVE DEUTERATION OF 4-BENZAMIDO-3-OXO-2-(4-METHOXYCARBONYL-BUTYLIDENE)TETRAHYDROTHIOPHENE TO GIVE THE 3-DEUTEROXY DERIVATIVE AND ITS PROTOTROPIC ISOMERIZATION

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The prototropic rearrangement of a deuterated 3-hydroxytetrahydrothiophene with a  $\beta,\gamma$ -exocyclic double bond is accompanied by deuterium migration along the double bond. Thus 4-r-benzamido-3-t-deuteroxy-3-c-deutero-2-(4-methoxycarbonylbutylidene)tetrahydrothiophene gives *cis*- and *trans*-4-r-benzamido-3-oxo-2-(4-methoxycarbonylbutyl)tetrahydro-2,4,4'-d<sub>3</sub>-thiophene, which, as a result of reduction with sodium borohydride, gives two isomers, viz., 4-r-benzamido-3-t-hydroxy-2-t- and -2-c-(4-methoxycarbonylbutyl)tetrahydrothiophenes that are deuterated in the 2, 4, and 4' positions.

We have previously observed the ability of a 3-hydroxytetrahydrothiophene with a  $\beta,\gamma$ -exocyclic double bond in the 2 position to undergo prototropic isomerization [1]. It was of interest to follow the character of this reaction under deuteration conditions.



We obtained 4-r-benzamido-3-t-deuteroxy-3-c-deutero-2-(4-methoxycarbonylbutylidene)-tetrahydrothiophene (II) from 4-benzamido-3-oxo-2-(4-methoxycarbonylbutylidene)tetrahydrothiophene (I) [2] by reduction with sodium borodeuteride in deuterated methanol at 0°C. The fact that two deuterium atoms enter the 3 position in the reductive deuteration follows from an examination of the <sup>1</sup>H NMR spectrum of II and a comparison of this spectrum with the spectrum of nondeuterated analog III. In the <sup>1</sup>H NMR spectrum of II the 3-H signal ( $\delta$  4.60-4.95 ppm) is almost absent, whereas the multiplicity of the 4-H signal (4.82 ppm), correspondingly, is lower than in the spectrum of its nondeuterated analog, which constitutes evidence for deuteration in the 3 position of the tetrahydrothiophene

ring. The degree of deuteration of II determined from the ratio of the integral intensities of the overall signal, which includes the residual signal of the 3-H proton and the signals of the 4- and 4'-H protons (5.80 ppm), is ~85%. The  $^1\text{H}$  NMR spectrum of II, like the spectrum of its nondeuterated analog [3], retains the characteristic peculiarities of the spectra of the trans-3,4 isomers:  $\Delta\delta_{\text{5-H}', \text{5-H''}} = 0.39$  ppm and  $\Sigma^3J_{4,5} = 12.0$  Hz. Consequently, II is the trans-3,4 isomer.

We subjected deuterated amino alcohol II to prototropic isomerization under the influence of a solution of deuterium chloride in benzene at 30°C, as a result of which deuterium migrated to the 2 and 4' positions, the 4-H proton was replaced by deuterium, and 4-benzamido-3-oxo-2-(4-methoxycarbonylbutyl)tetrahydro-2,4,4'- $\text{d}_3$ -thiophene (III) was formed. As we established in [1], oxotetrahydrothiophene III is produced in the form of a mixture of cis and trans isomers in the isomerization of amino alcohol II. As compared with the spectrum of its nondeuterated analog (see the experimental section), the 4-H signal (4.45 ppm) almost vanishes in the  $^1\text{H}$  NMR spectrum of III, and the multiplicities of the 5-H' (3.22 ppm) and 5-H'' (2.76 ppm) signals decrease: Each of these signals is converted from a doublet of doublets to a doublet (an AB system) with  $J = 10.7$  Hz. This constitutes evidence for deuteration in the 4 position of the tetrahydrothiophene ring. The degree of deuteration determined with respect to the integral intensities of the residual 4-H signal and the 5-H' and 5-H'' signals (2H) is 85%. The integral intensities of the overall signals at 1.08-2.45 [-(CH<sub>2</sub>)<sub>4</sub>-] and 2.75-3.65 ppm (5- and 2-H, OCH<sub>3</sub>) decrease simultaneously; this is evidently a consequence of deuteration in the 2 and 4' positions. The degree of deuteration in these positions, which was found from the ratio of the integral intensities of the two signals indicated above and the signal of the protons of the benzoyl group (5H, 7.05-7.85 ppm), is 80-90%.

This mixture of isomeric tetrahydrothiophenes was not separated, and amino alcohol II was reduced, without isolation, with sodium borohydride in methanol at 0°C. As a result of the reaction, we isolated two cis- and trans-isomeric tetrahydrothiophenes IV and V. To separate the isomers we used the different solubilities of their complexes with sodium borohydride in methanol. The positions of the deuterium atoms in IV and V were proved by  $^1\text{H}$  NMR spectroscopy. In the  $^1\text{H}$  NMR spectra of V and IV the signal of the 3-H proton (4.22 and 4.65 ppm, respectively) is virtually a singlet. The signal of the 4-H proton (4.82 and 4.92 ppm) is of low intensity, and the intensity of the group of signals at 3.20-3.75 ppm, which includes the signal of the 2-H proton, is decreased appreciably. This constitutes evidence for deuteration in the 2 and 4 positions of the tetrahydrothiophene ring. A comparison of the integral intensities of the signal of the 3-H proton, the residual signal of the 4-H proton, and of the group of signals at 2.40-3.60 ppm (2- and 5-H and CH<sub>3</sub>O) gives a degree of deuteration in the 4 and 2 positions of no less than 90%. In addition, the relative intensity of the complex signal of the protons attached to the C(2'), C(3'), and C(4') atoms (1.20-2.00 ppm) is decreased in the  $^1\text{H}$  NMR spectra of V and IV. This makes it possible to assume that deuteration takes place in the 4' position. In fact, not only the C(2) and C(4) signals but also the C(4') signal have low peak intensities in the  $^{13}\text{C}$  NMR spectra with suppression of the spin-spin coupling with the protons (due to a decrease in the spin-lattice relaxation  $T_1$  as a result of coupling with the deuterium nuclei, which have an appreciable electric quadrupole moment) (Table 1).

An estimate of the degree of deuteration from the ratios of the integral intensities of the signals in the  $^1\text{H}$  NMR spectra gives a value of no less than 90%. The spin-spin coupling constants (SSCC) for IV and V are the same as for the nondeuterated analogs, and this makes it possible to unambiguously determine their configurations [3]. The deuterium atom in the 4' position in IV and V is evidently introduced as a result of prototropic rearrangement, after which the resulting enol form (A) undergoes rearrangement to the oxo form, and a deuterium atom enters the 2 position of the tetrahydrothiophene ring (B); in acidic media the oxo form is capable of keto-enol tautomerism, which also leads to deuteration at the C(4) atom (E).

It should be noted that deuterium does not enter the 2 and 4' positions as a result of prototropic isomerization of 4-r-benzamido-3-t-hydroxy-2-(4-methoxycarbonylbutylidene)-tetrahydrothiophene under the same reaction conditions; however, as in the case of oxotetrahydrothiophene III, deuterium replaces the proton in the 4 position.

TABLE 1.  $^{13}\text{C}$  Chemical Shifts of IV and V (in  $\text{d}_5$ -Pyridine)

Compound	$\delta$ , ppm					
	$\text{C}_{(2)}$	$\text{C}_{(3)}$	$\text{C}_{(4)}$	$\text{C}_{(5)}$	$\text{C}_{(4')}$	$\text{C}_{(1')}, \text{C}_{(2')}, \text{C}_{(3')}$
IV(non-deuterated)	50,6	77,5	60,5	33,9	30,9	33,1, 28,7, 25,2
IV	50,2	77,4	60,2	33,8	30,2	22,8, 28,3, 25,1
V(non-deuterated)	50,1	81,1	59,3	33,8	35,1	30,1, 28,0, 25,0
V	50,2	81,2	59,7	33,9	35,3	30,3, 27,8, 25,0

## EXPERIMENTAL

The  $^1\text{H}$  NMR spectra of solutions of the compounds in deuteropyridine (II, IV, and V) and in deuteriochloroform (III) were recorded with a Hitachi R-20A spectrometer with tetramethylsilane as the internal standard. The  $^{13}\text{C}$  spectra were obtained with Bruker WP-80 and WH-360 spectrometers with carbon-nuclei operating frequencies of 20.1 and 20.5 MHz, respectively; the chemical shifts were measured with an accuracy of 0.1 ppm, and the SSCC constants were measured with an accuracy of 0.5 Hz.

4-r-Benzamido-3-t-deuteroxy-3-c-deutero-2-(4-methoxycarbonylbutylidene)tetrahydrothiophene (II). A 0.17-g (4.1 mmole) sample of sodium borodeuteride was added at  $0^\circ\text{C}$  to a solution of 2 g (6 mmole) of amino ketone I in 15 ml of deuterated methanol at  $0^\circ\text{C}$ , and the mixture was stirred at  $18$ – $20^\circ\text{C}$  for 2 h. It was then cooled to  $0^\circ\text{C}$  and acidified to pH 1–2 with deuterated hydrochloric acid (diluted to twice its original volume with heavy water), and the mixture was maintained at  $0$ – $3^\circ\text{C}$  for 18 h. The precipitate was removed by filtration and washed with heavy water to give 1.7 g (85%) of a product with mp  $124$ – $125^\circ\text{C}$  (from deuterated methanol).  $^1\text{H}$  NMR spectrum: 3.12, 3.51 (2H, m,  $^3J_{4,5} = 5.0$ ,  $^3J_{4,5} = 7.0$ ,  $^2J_{5,5''} = 10.9$  Hz; 5-H', 5-H''); 4.78 (1H, m, 4-H); 5.80 ppm (1H, m, 4'-H). Found: S 9.1%.  $\text{C}_{17}\text{H}_{19}\text{D}_2\text{NO}_4\text{S}$ . Calculated: S 9.5%.

4-r-Benzamido-3-t-hydroxy-2-t-(4-methoxycarbonylbutyl)tetrahydro-2,4,4- $\text{d}_3$ -thiophene (IV) and 4-r-Benzamido-3-t-hydroxy-2-c-(4-methoxycarbonylbutyl)tetrahydro-2,4,4'- $\text{d}_3$ -thiophene (V). Deuterium chloride (obtained by the reaction of deuterated hydrochloric and sulfuric acids) was passed at  $30^\circ\text{C}$  through a suspension of 1.5 g (4.5 mmole) of II in 9 ml of benzene for 1 h, after which the resulting solution was concentrated to dryness *in vacuo*, and the residue was identified as III in the form of a mixture of cis and trans isomers with respect to the 2 position.  $^1\text{H}$  NMR spectrum: 1.05–2.45 (7H, m, 1'-, 2'-, 3'-, and 4'-H); 2.76 and 3.22 ppm (2H, AB system,  $^2J_{5,5''} = 10.7$  Hz; 5-H', 5-H'').  $^1\text{H}$  NMR spectrum of nondeuterated III: 1.05–2.45 (8H, m, 1'-, 2'-, 3'-, and 4'-H); 2.75 and 3.21 (2H, m,  $^3J_{4,5'} = 7.5$ ,  $^3J_{4,5''} = 11.0$ ,  $^2J_{5,5''} = 10.7$  Hz; 5-H', 5-H''); 4.45 (1H, m, 4-H); 7.05–7.85 ppm (5H, m,  $\text{C}_6\text{H}_5$ ). Compound III was dissolved in 12 ml of methanol, 0.2 g (4.7 mmole) of sodium borohydride was added at  $0^\circ\text{C}$ , and the mixture was stirred at  $18$ – $20^\circ\text{C}$  for 2 h and maintained at  $0$ – $3^\circ\text{C}$  for 16–18 h. The precipitate was removed by filtration and mixed with 3 ml of water, and the aqueous mixture was acidified to pH 1–2 at  $0^\circ\text{C}$  with 2 N hydrochloric acid. The precipitate was removed by filtration and washed with water to give 0.3 g (20%) of IV with mp  $105$ – $106^\circ\text{C}$  (from alcohol).  $^1\text{H}$  NMR spectrum: 1.20–1.90 (5H, 3'-, 2'-, and 4'-H); 2.95 and 3.33 (2H, AB system,  $^2J_{5,5''} = 11.0$  Hz; 5-H', 5-H''); 4.22 ppm (1H, s, 3-H). The methanol and aqueous filtrates were combined and acidified with 2 N hydrochloric acid, and the acidic mixture was extracted with chloroform. The extracts were washed with water and dried with  $\text{MgSO}_4$ , and the chloroform was removed *in vacuo*. Methanol was added to the residue, and the mixture was maintained at  $0$ – $3^\circ\text{C}$  for 16–18 h. The precipitate was removed by filtration and washed with methanol–ether (1:1) to give 0.7 g (47%) of V with mp  $137$ – $138^\circ\text{C}$  (from methanol).  $^1\text{H}$  NMR spectrum: 1.20–1.90 (5H, m, 3'-, 2'-, and 4'-H); 2.85 and 3.51 ppm (2H, AB system,  $^2J_{5,5''} = 10.3$  Hz; 5-H', 5-H'').

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