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STEREOSPECIFIC SYNTHESIS OF ALL OF THE POSSIBLE ISOMERS OF 4-UREIDO-3-HYDROXY-2-(5'-ALKOXYCARBONYLBUTYL)THIOPHAN

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All four possible isomers of 4-ureido-3-hydroxy-2-(5'-alkoxycarbonylbutyl)-thiophan were synthesized by the action of potassium isocyanate on the corresponding hydrochlorides (or hydrobromides) of the stereoisomers of 4-amino-3-hydroxy-2[5'-methoxy(or ethoxy)carbonylbutyl]thiophans, which were obtained by several methods. The configurations of the compounds obtained were proved by PMR spectroscopy.

As a further development of our earlier research [1-3] in the present study we accomplished the stereospecific synthesis of all four isomers of 4-ureido-3-hydroxy-2-substituted thiophans, which are of interest for the synthesis of biologically active compounds.

We synthesized all four isomers (the cis, epi, allo, and epiallo configurations) of 4-ureido-3-hydroxy-2-(5'-alkoxycarbonylbutyl)thiophan (XI-XIV) by the action of potassium isocyanate on the corresponding hydrochlorides (or hydrobromides) of the stereoisomers of 4-amino-3-hydroxy-2-(5'-alkoxycarbonylbutyl)thiophans (VII-X), which were obtained by several methods.

r-4-Benzamido-t-3-hydroxy-c(and t)-2-(5'-methoxycarbonylbutyl)thiophans (III and VI) were converted to r-4-benzamido-c-3-hydroxy-c(and t)-2-(5'-methoxycarbonylbutyl)thiophans (I and IV) by cleavage of the intermediate oxazoline derivatives [2] by heating in an aqueous pyridine medium; these compounds were previously obtained by the method in [1]. r-4-Benzamido-t-3-chloro-c(and t)-2-(5'-methoxycarbonylbutyl)thiophans (II and V) were also obtained from III and VI by the method in [2].

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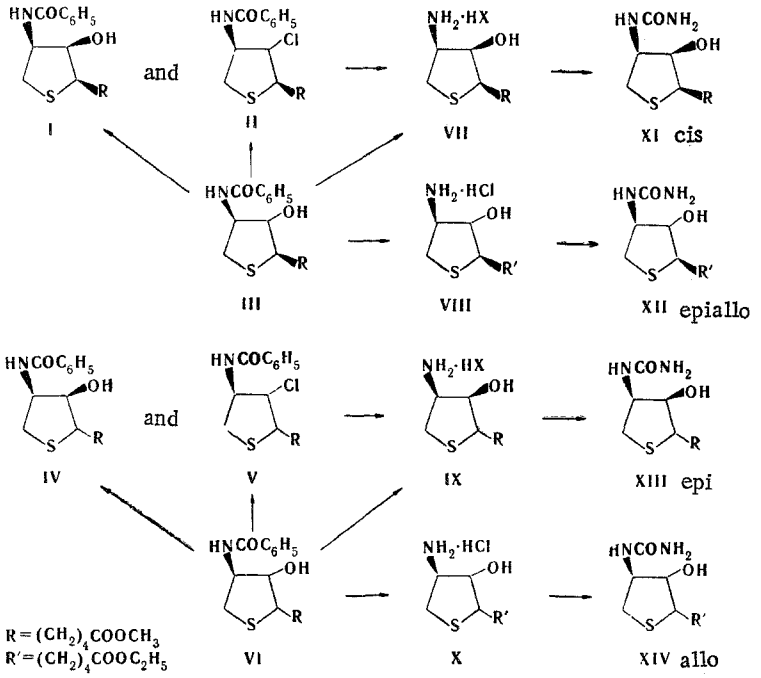

Alkaline hydrolysis in an aqueous methanol medium or hydrolysis in hydrobromic acid of I and IV takes place without a change in the configuration and leads to the corresponding hydrohalides of r-4-amino-c-3-hydroxy-c(and t)-2-(5'-methoxycarbonylbutyl)thiophans (VII and IX). In the case of II and V under acid hydrolysis conditions, in addition to removal of the benzoyl protective group, the chlorine atom in the 3 position is replaced by a hydroxy group with inversion of the trans configuration; this leads to the production of the corresponding thiophans VII and IX. Compounds III and VI can be converted directly to thiophans VII and IX under acid hydrolysis conditions, during which the trans configuration of the hydroxy group undergoes inversion to the cis configuration through the intermediate formation of an oxazoline derivative [3].

The corresponding hydrochlorides of r-4-amino-t-3-hydroxy-c(and t)-2-(5'-ethoxycarbonylbutyl)thiophan (VIII and X) were isolated from III and VI by alkaline hydrolysis in an aqueous ethanol medium with simultaneous transesterification. The four stereoisomeric trisubstituted amino hydroxy thiophans VII-X were obtained in this way.

The corresponding epiallo-r-4-ureido-t-3-hydroxy-c-2-(5'-ethoxycarbonylbutyl)thiophan (XII) and allo-r-4-ureido-t-3-hydroxy-t-2-(5'-ethoxycarbonylbutyl)thiophan (XIV) were obtained by the action of potassium isocyanate in an aqueous medium on thiophans VIII and X. We were unable to introduce a ureido group in thiophans VII and IX with cis-oriented substituents in the 3 and 4 positions in an aqueous medium. We accomplished this reaction in pyridine at 80-100°C and obtained the corresponding ureido derivatives: cis-r-4-ureido-c-3-hydroxy-c-2-(5'-methoxycarbonylbutyl)thiophan (XI) and epi-r-4-ureido-c-3-hydroxy-t-2-(5'-methoxycarbonylbutyl)thiophan (XIII).

The structures of the new compounds VIII and X-XIV were established on the basis of chemical transformations and the results of elementary analysis. The configurations of XI-XIV were established by PMR spectroscopy.

The parameters of the PMR spectra of XI-XIV are presented in Table 1. To assign the signals to definite protons we used magnetic double resonance, analysis of the ratios of the integral intensities of the signals, and the data in [3]. To determine the configurations of the substituents in the investigated compounds we studied the temperature dependences of the vicinal spin–spin coupling constants [3]. It should be noted that the signal of the proton attached to C_3 in the spectra of all of the compounds is close to a triplet (the $J_{2H,3H}$ and $J_{3H,4H}$ constants are almost identical), and we therefore studied the temperature dependence of the sum of the vicinal $J_{2H,3H}$ and $J_{3H,4H}$ constants. It can be seen that the temperature dependences of the cis- ($J_{4H,5H''}$, Fig. 1a) and trans-vicinal ($J_{4H,5H''}$, Fig. 1b) constants, which characterize the $4CH-5CH_2$ fragment, differ: the cis-vicinal constant is virtually independent of the temperature, while the trans constant changes appreciably with the temperature ($J_{4H,5H''}$ = 0.32 Hz when Δt = 91.5°C). The change in the sum

TABLE 1. Parameters of the PMR Spectra of Solutions of XI-XIV in Deuteropyridine*

Compound	Chemical shifts, δ, ppm					Spin-spin coupling constants, J, Hz				
	2H	3H	4H	5H′	5H″	2H, 3H	3H, 4H	4H, 5H′	4H, 5H″	5H′, 5H″
XII	3,20—3,63	4,10	4,70	3,39	2,87	$\Sigma J=15,6$		6,7	8,5	10,3
XIV	3,58—3,95	4,61	4,90	3,79	2,77	$\Sigma J=7,3$		5,2	2,2	10,5
XI	3,17—3,60	4,22	4,52	2,75—3,30		3,2	3,2	$\Sigma J_{4,5}=17,6$		
XIII	2,85—3,35	4,01	4,48	3,02	2,88	$\Sigma J=7,6$		6,3	8,0	10,4

*The spectra of XII and XIV were recorded at 34°C, while the spectra of XI and XIII were recorded at 70°C.

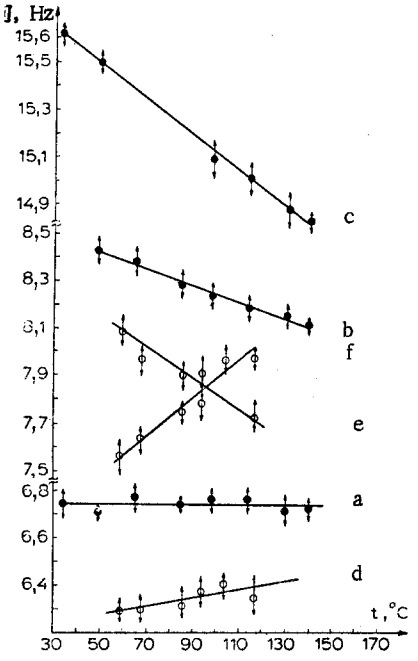

Fig. 1

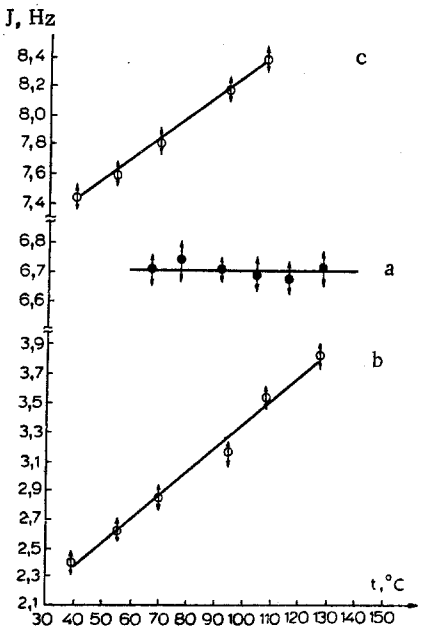

Fig. 2

Fig. 1. Temperature dependences: a) $J_{4H,5H'}$; b) $J_{4H,5H''}$; c) sum of $J_{2H,3H}$ and $J_{3H,4H}$ for XII; d) $J_{4H,5H'}$; e) $J_{4H,5H''}$; f) sum of $J_{2H,3H}$ and $J_{3H,4H}$ for XIII.

Fig. 2. Temperature dependences: a) sum of $J_{2H,3H}$ and $J_{3H,4H}$ for XI; b) $J_{4H,5H''}$; c) sum of $J_{2H,3H}$ and $J_{3H,4H}$ for XIV.

of the vicinal $J_{2H,3H}$ and $J_{3H,4H}$ constants (Fig. 1c) with the temperature is greater by a factor of approximately two than the change in the known trans-vicinal $J_{4H,5H''}$ constant ($\Sigma J_{2H,3H}$ and $J_{3H,4H}$ = 0.67 Hz when Δt = 91.5°C). It follows from this that both of the constants that enter into the investigated sum are trans-vicinal constants, whereas XII is r-4-ureido-c-3-hydroxy-c-2-(5'-ethoxycarbonylbutyl)thiophan.

The sum of $J_{2H,3H}$ and $J_{3H,4H}$ for XI remains virtually unchanged as the temperature changes (Fig. 2a). This makes it possible to assign both vicinal constants to the cis series and to identify XI as r-4-ureido-c-3-hydroxy-c-2-(5'-methoxycarbonylbutyl)thiophan. The temperature dependence of the sum of $J_{2H,3H}$ and $J_{3H,4H}$ is similar to the temperature dependence of trans-vicinal constant $J_{4H,5H''}$ for both XIV ($\Delta J_{4H,5H''}$ = 1.14 Hz, $\Delta\Sigma J_{2H,3H}$ and $J_{3H,4H}$ = 0.96 Hz when Δt = 68°C, Fig. 2, dependences b and c) and for XIII ($\Delta J_{4H,5H''}$ = −0.37 Hz, $\Delta\Sigma J_{2H,3H}$ and $J_{3H,4H}$ = 0.41 Hz when Δt = 58°C, Fig. 1, dependences e and f). One trans-vicinal constant consequently enters into the investigated sum for both compounds, and each of these compounds can have either an allo or epi configuration. A choice between the two configurational variants becomes possible if one takes into account the fact that in the case of XIV the difference in the chemical shifts of the protons attached to C_5 is much greater than in XIII ($\Delta\delta^{XIV}_{5H',5H''}$ = 1.02 ppm, $\Delta\delta^{XIII}_{5H',5H''}$ = 0.18 ppm; Table 1).

It is known from an analysis of the previously investigated PMR spectra of trisubstituted thiophans [1, 3] that a larger $\Delta\delta_{5}H',_{5}H''$ value is characteristic for the allo configuration, whereas in the case of the epi configuration the chemical shifts of the protons attached to C_5 either coincide or differ only slightly. On the basis of this XIV is r-4-benzamido-t-3-hydroxy-t-2-(5'-ethoxycarbonylbutyl)thiopan, and XIII is r-4-benzamido-c-3-hydroxy-t-2-(5'-methoxycarbonylbutyl)thiophan.

EXPERIMENTAL

The proton NMR spectra of solutions of the compounds in deuteropyridine were recorded with a Hitachi R-20A spectrometer with tetramethylsilane as the internal standard.

r-4-Benzamido-c-3-hydroxy-c-2-(5'-methoxycarbonylbutyl)thiophan (I). A solution of 3 g (8.5 mmole) of 2-phenyl-c-6-(5'-methoxycarbonylbutyl)-cis-3a,4,6,6a-tetrahydrothieno-[3,4-d]oxazoline hydrochloride [6] in 10 ml of pyridine and 30 ml of water was refluxed for 6 h, after which it was cooled and extracted with chloroform. The chloroform extracts were washed with a 2.5 N solution of hydrochloric acid and water and dried over $MgSO_4$. The chloroform was removed in vacuo, the residue was dissolved in 5 ml of methanol, and the solution was maintained at 3°C for 16-18 h. The resulting precipitate was removed by filtration to give 2.4 g (85%) of colorless plates with mp 131-132°C (from CH_3OH). No melting-point depression was observed for a mixture of this product with a genuine sample.

r-4-Benzamido-c-3-hydroxy-t-2-(5'-methoxycarbonylbutyl)thiophan (IV). This compound was obtained from 3 g (8.5 mmole) of 2-phenyl-t-6-(5'-methoxycarbonylbutyl)-cis-3a,4,6,6a-tetrahydrothieno[3,4-d]oxazoline hydrochloride [1] by the method used to prepare I. Workup gave 2.65 g (90%) of colorless prisms with mp 101-102°C (from CH_3OH). No melting-point depression was observed for a mixture of this compound with a genuine sample.

r-4-Amino-c-3-hydroxy-c-2-(5'-methoxycarbonylbutyl)thiophan Hydrochloride (VIIa). A 12-ml sample of a 10 N solution of sodium hydroxide was added to a solution of 2.4 g (7.2 mmole) of I in 12 ml of methanol, and the mixture was refluxed for 11 h. It was then cooled and acidified to pH 1-2 with hydrochloric acid, and the benzoic acid was extracted with benzene. The aqueous solution was evaporated, and the residue was extracted with methanol (three 7-ml portions). The extract was concentrated in vacuo to 5 ml, and the residue was separated to give 1.8 g (67%) of colorless needles with mp 208-209°C (from CH_3OH) [3].

r-4-Amino-c-3-hydroxy-t-2-(5'-methoxycarbonylbutyl)thiophan Hydrochloride (IX). This compound was similarly obtained from 2 g (6.0 mmole) of IV [1]. Workup gave 1.5 g (95%) of colorless plates with mp 173-174°C (from CH_3OH) [3].

r-4-Amino-c-3-hydroxy-c-2-(5'-methoxycarbonylbutyl)thiophan Hydrobromide (VIIb). A solution of 3 g (8.9 mmole) of I in 40 ml of hydrobromic acid was refluxed for 7 h, after which it was cooled and extracted with benzene. The extract was evaporated and 20 ml of methanol was added to the residue. The methanol solution was treated with activated charcoal and concentrated to 5 ml. The concentrate was maintained at 0-3°C for 16 h, and the precipitate was removed by filtration to give 2.5 g (89.5%) of colorless prisms with mp 159-160°C (from CH_3OH) [3].

r-4-Amino-t-3-hydroxy-c-2-(5'-ethoxycarbonylbutyl)thiophan Hydrochloride (VIII). The reaction of 12 g (35.5 mmole) of r-4-benzamido-t-3-hydroxy-c-2-(5'-methoxycarbonylbutyl)-thiophan (III) [1] under conditions similar to those in the preparation of VIIa, except that ethanol was used in place of methanol, gave 9.2 g (90.5%) of VIII as colorless prisms with mp 150-151°C (from C_2H_5OH). Found: C 46.0; H 7.9; N 5.2; Cl 12.9%. $C_{11}H_{21}NO_3S\cdot HCl$. Calculated: C 46.6; H 7.8; N 4.9; Cl 12.5%.

r-4-Amino-t-3-hydroxy-t-2-(5'-ethoxycarbonylbutyl)thiophan Hydrochloride (X). This compound was obtained from 10 g (30 mmole) of r-4-benzamido-t-3-hydroxy-t-2-(5'-methoxycarbonylbutyl)thiophan (VI) [1] under conditions similar to those described for VIII. Workup gave 8.2 g (97%) of X as colorless plates with mp 86-87°C (from C_2H_5OH). Found: C 46.3; H 7.6; N 5.1; Cl 12.7%. $C_{11}H_{21}NO_3S\cdot HCl$. Calculated: C 46.6; H 7.8; N 4.9; Cl 12.5%.

r-4-Ureido-t-3-hydroxy-c-2-(5'-ethoxycarbonylbutyl)thiophan (XII). A 2.6-g (36.1 mmole) sample of potassium isocyanate was added at 18-20°C in the course of 15 min (during which a precipitate formed) to a solution of 0.8 g (2.75 mmole) of VIII in 5 ml of water, after which the mixture was stirred at 30°C for 1 h. It was then cooled and filtered, and

the filtrate was washed with water and worked up to give 0.6 g (72.3%) of colorless needles with mp 138-139°C (from C_2H_5OH). Found: C 49.2; H 7.6; N 10.0%. $C_{12}H_{22}N_2O_4S$. Calculated: C 49.6; H 7.6; N 10.0%.

r-4-Ureido-t-3-hydroxy-c-2-(5'-ethoxycarbonylbutyl)thiophan (XIV). This compound was obtained from III under conditions similar to those described for X. Workup gave colorless plates (80%) with mp 157-158°C (from alcohol). Found: C 49.7; H 7.6; N 9.8%. $C_{12}H_{22}N_2O_4S$. Calculated: C 49.6 H 7.6; N 10.0%.

r-4-Ureido-c-3-hydroxy-c-2-(5'-methoxycarbonylbutyl)thiophan (XI). A solution of 0.7 g (2.6 mmole) of VIIa in 7 ml of pyridine was heated to 90-100°C, after which 2.5 g of potassium isocyanate was added in the course of an hour, and the mixture was stirred at the same temperature for 1 h. It was then cooled, and the precipitate was removed by filtration. The filtrate was evaporated, 3 ml of methanol was added to the residue, and the mixture was maintained at 0°C for 16-18 h. The resulting precipitate was removed by filtration to give 0.55 g (77%) of colorless needles with mp 147-149°C. Found: C 47.2; H 7.0; N 10.1%. $C_{11}H_{20}N_2O_4S$. Calculated: C 47.8; H 7.3; N 10.1%.

r-4-Ureido-c-3-hydroxy-t-2-(5'-methoxycarbonylbutyl)thiophan (XIII). The reaction of 1 g (3.8 mmole) of IXa under similar conditions gave 0.7 g (94%) of XIII as colorless plates with mp 163-164°C (from CH_3OH). Found: C 47.3; H 7.3; N 10.0%. $C_{11}H_{20}N_2O_4S$. Calculated: C 47.8; H 7.3; N 10.1%.

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MESOIONIC COMPOUNDS WITH A BRIDGED NITROGEN ATOM.

4.* THIAZOLO[3,2-a]QUINOLINIUM 1-OXIDE DERIVATIVES

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It is shown that diverse 2-substituted thiazolo[3,2-a]quinolinium 1-oxides can be obtained from 2-quinolylmercaptoacetic acids. The structures of the synthesized compounds were confirmed by the PMR and mass spectra.

Up until recently it was assumed [2, 3] that thiazolo[3,2-a]quinolinium 1-oxides (IIa,b) are formed by the action of acetic anhydride on 2-quinolylmercaptoacetic acids (Ia,b). It was not until 1978 that it was observed [4] that the melting point of the product formed in the reaction of acid Ia and acetic anhydride depends on the conditions under which the reaction is carried out and ranges from 162 to 182°C (according to the data in [3], IIa melts at 194°C). Samples obtained under different conditions also differ with respect to the absorption frequency of the CO group in the IR spectra. On the basis of the data from the PMR spectrum, it was assumed that the isolated compound has the IIIa structure, although the ratio of the intensities of the signals of the protons of the methylene group and the heterorings (1:8) did not correspond to this structure.

*See [1] for communication 3.

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