STEREOSPECIFIC SYNTHESIS OF cis- AND trans-4-AMINO-3-HYDROXYTHIOPHANES

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The reduction of 4-benzoylamino- and 4-carbethoxyamino-3-ketothiophanes proceeds stereospecifically to form only trans-4-benzoylamino- and trans-4-carbethoxyamino-3-hydroxythiophanes, respectively, from which trans-4-amino-3-hydroxythiophane is obtained by alkaline hydrolysis. It was established that acid hydrolysis of trans-4-carbethoxyamino-3-hydroxythiophane leads only to trans-4-amino-3-hydroxythiophane, while acid hydrolysis of trans-4-benzoylamino-3-hydroxythiophane is accompanied by inversion to form cis-4-amino-3-hydroxythiophane. Derivatives of the cis- and trans- isomeric pairs of 4-amino-3-hydroxythiophanes were synthesized.

This investigation of the stereospecific synthesis of 4-amino-3-hydroxythiophanes involves the preparation of cis and trans derivatives and the conversion of the trans configuration of some compounds of this group to the cis configuration. To synthesize 4-amino-3-hydroxythiophane we started from 4-acylamino-3-ketothiophanes (I and II) in which the keto group was reduced with sodium borohydride. It is well known that a mixture of epimeric alcohols or one epimeric alcohol can be obtained, depending on the steric accessibility of the carbonyl group, the geometrical dimensions of the reducing agent, and the reduction conditions [1].

4-Carbethoxyamino-3-hydroxythiophane (IIIb) and 4-benzoylamino-3-hydroxythiophane (IVb) were obtained by the reduction of 4-carbethoxyamino-3-ketothiophane (I) [2] and 4-benzoylamino-3-ketothiophane (II), respectively, with sodium borohydride in methanol at 0 deg C. The formation of a hydroxyl group was confirmed by IR spectroscopy (the presence of a band at 3610 cm^{-1}). The reaction at 0 deg apparently led to the formation of one epimeric alcohol since repeated recrystallization of the reaction products did not change their melting points.

IIIb and IVb were subjected to alkaline hydrolysis with sodium hydroxide in aqueous alcohol; both compounds gave the same 4-amino-3-hydroxythiophane (Vb), which was isolated as the hydrobromide (Vb^{I}) or hydrochloride (Vb^{II}). It was found that Vb^{I} and Vb^{II} do not react with phosgene. Since the ability to form cyclic carbonates is used to determine the configuration of a hydroxyl group with respect to other substituents [3,4], we assigned the trans configuration to 4-amino-3-hydroxythiophane Vb.

The hydrobromides of the 4-amino-3-hydroxythiophanes (Vb^{I} and Va^{I}, respectively) were isolated by the hydrolysis of trans-acylamino alcohols IIIb and IVb with boiling concentrated hydrobromic acid; their melting points were close (120-121 deg and 122-123 deg), but a mixture of them gave a 30-35 deg melting-point depression. Different hydrochlorides of the 4-amino-3-hydroxythiophanes (Vb^{II} and Va^{II}, respectively) are also formed by deacylation of IIIb and IVb with hydrogen chloride in amyl alcohol at 100 deg.

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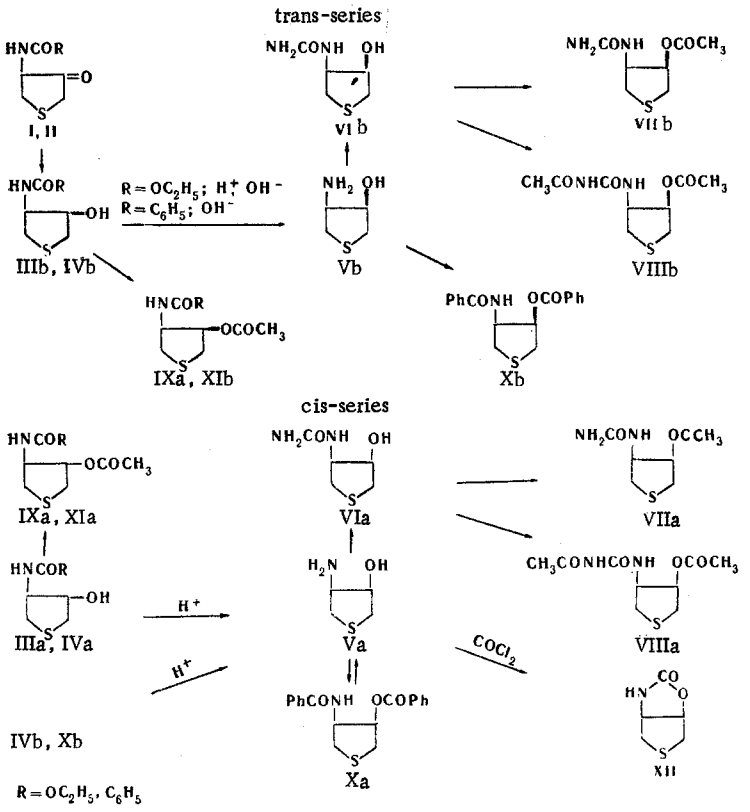


3,4-Carbamoylidothiophane (XII) was obtained from Va^{l} and Va^{II} by reaction with phosgene under the conditions presented above. The fact that Va reacts with phosgene to form a cyclic derivative attests to its cis configuration.

Thus the saponification of the benzoyl group of trans-4-benzoylamino-3-hydroxythiophane (IVb) by refluxing with hydrobromic acid or with amyl alcohol saturated with hydrogen chloride is accompanied by inversion of configuration to form cis-4-amino-3-hydroxythiophane (Va), while saponification of the carbethoxy group of trans-4-carbethoxyamino-3-hydroxythiophane (IIIb) does not change the configuration and gives trans-4-amino-3-hydroxythiophane (Vb). The ability of trans-4-benzoylamino-3-hydroxythiophane (IVb) to invert its configuration made it possible to obtain the parallel series of derivatives of cis-amino alcohol Va.

The cis- and trans-4-ureido-3-hydroxythiophanes (VIa and b), which have different melting points and acetylation capacities, were obtained from cis and trans-amino alcohols Va and Vb by reaction with potassium isocyanate in water at 0 deg. Thus, cis-ureido-3-acetoxythiophane (VIIa) and trans-4-acetylureido-3-acetoxythiophane (VIIIb), respectively, are formed from VIa and VIb by heating with acetic acid in the presence of hydrogen bromide; in both cases, refluxing in acetic anhydride gives diacetyl derivatives VIIIa and VIIIb. Monoacetyl derivative VIIb was obtained from VIb in acetic anhydride at 50-60 deg. The greater ease of acetylation of VIb as compared with VIa agrees with their trans and cis configurations, respectively.

The cis- and trans-4-carbethoxyamino-3-hydroxythiophanes (IIIa,b) were obtained from the amino alcohol hydrohalides (Va^{I}, a^{II}, b^{I}, b^{II}) by reaction with ethyl chlorocarbonate in water at 0 deg. The cis- and trans-4-carbethoxyamino-3-acetoxythiophanes (IXa,b) were synthesized by acetylation of IIIa and b with a mixture of acetic anhydride and acetyl chloride.

Schotten-Baumann benzoylation of Va^{I} and Vb^{II} gave cis- and trans-dibenzoyl derivatives Xa and Xb, from which the corresponding cis- and trans-4-benzoylamino-3-hydrothiophanes (IVa,b) are formed by selective saponification. IVb obtained in this way is identical to the compound from II. Acetylation gives cis-and trans-4-benzoylamino-3-acetoxythilophanes XIa and XIb, during which cis compound IVa requires more severe conditions.

TABLE 1. Characteristics of the Compounds Obtained

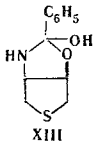
Compound	Form	Mp,* °C	Empirical formula	Found, % C	Found, % H	Found, % N	Calc., % C	Calc., % H	Calc., % N	Yield, %†
IIIa	Plates	71—72	$C_7H_{13}NO_3S$	43,7	6,9	6,9	44,0	6,8	7,3	66,0
IIIb	Plates	99—100		44,2	6,6	7,2				87,2
IVa	Prisms	154—155	$C_{11}H_{13}NO_2S$	59,1	5,8	6,2	59,2	5,9	6,3	97,2
IVb	Primss	129—130		59,1	5,9	6,1				96,4
Va	Plates	122—123	$C_4H_9NOS \cdot HBr$	24,1	4,9	6,5‡	24,0	5,0	7,0	81,4 (70,6)
Vb'	Plates	120—121		23,6	4,8	6,8‡				85,6 (82,6)
Va"	Prisms	206—207	$C_4H_9NOS \cdot HCl$	30,8	6,3	Cl 22,9	30,9	6,5	Cl 22,8	71,7 (33,6)
Vb"	Prisms	167—168		30,7	6,3	Cl 23,1				60,6 (12,3)
VIa	Plates	204—205	$C_5H_{10}N_2O_2S$	37,1	6,5	17,2	37,1	6,2	17,3	60,0
VIb	Plates	149—149,5		37,3	6,0	17,1				86,2
VIIa	Plates	164—165	$C_7H_{12}N_2O_3S$	41,2	6,2		41,2	5,9		18,2
VIIb	Plates	150—151		41,3	5,8					65,2
VIIIa	Prisms	146—147	$C_9H_{14}N_2O_4S$	43,6	5,8	11,0	43,9	5,7	11,4	66,6
VIIIb	Prisms	172—173		43,7	5,6	11,1				83,4
IXa	Needles	88—89	$C_9H_{15}NO_4S$	46,3	6,3	6,0	46,3	6,5	6,0	53,2
IXb	Needles	66—67		46,2	6,7	5,8				65,6
Xa	Needles	164—165	$C_{18}H_{17}NO_3S$	65,3	5,0	3,8	66,0	5,2	4,3	87,7
Xb	Needles	154—155		66,0	5,0	4,2				90,7
XIa	Prisms	150—151	$C_{13}H_{15}NO_3S$	58,8	5,6	5,1	58,8	5,7	5,3	62,5
XIb	Prisms	101—102		59,0	5,5	5,2				81,5
XII	Prisms	127—128	$C_5H_7NO_2S$	41,6	4,6	9,8	41,4	4,9	9,6	61,5

*IIIa was recrystallized from CCl_4-petroleum ether, VIIIa and b were recrystallized from methanol, and the remaining compounds were crystallized from alcohol.

†Alkaline hydrolysis yields; the acid hydrolysis yields are given in parenthesis.

‡Found %: Br 39.8 (Va'); 39.7 (Vb'). Calc. %: Br 39.9.

In addition to trans-4-benzoylamino-3-hydroxythiophane (IVb), its O-benzoyl derivative – trans-4-benzoylamino-3-benzoyloxythiophane (Xb), which is hydrolyzed to cis-4-amino-3-hydroxythiophane (Va) by heating with hydrobromic acid – also undergoes inversion of configuration. The inversion of IVb and Xb on heating acids is apparently accompanied by the initial formation of cyclic intermediate XIII with inversion of configuration. Similar cases are discussed in [5,6].



XIII

EXPERIMENTAL

trans-4-Benzoylamino-3-hydroxythiophane (IVb). A. Sodium borohydride [0.5 g (14.36 mmole)] was added in the course of 1 h to a solution of 3 g (13.56 mmole) of 4-benzoylamino-3-ketothiophane (II) in 10 ml of methanol at 0 deg, and the mixture was stirred for 8 h at 18-20 deg. Water (10 ml) was added, and the mixture was acidified to pH 2 with hydrochloric acid and extracted with chloroform. The solvent was removed to give 2.92 g of IVb.

B. A solution of 1.5 g (4.58 mmole) of trans-4-benzoylamino-3-benzoylxythiophane (Xb) in 5 ml of 2.5 N sodium hydroxide and 16 ml of alcohol was refluxed for 25 min and extracted with chloroform. The extract was washed with water, and the chloroform was removed to give 0.99 g (97.2%) of IVb.

trans-4-Carbethoxyamino-3-hydroxythiophane (IIIb). A. This was obtained in the same way as IVb from 4-carbethoxyamino-3-ketothiophane (I).

B. Ethyl chlorocarbonate [1.25 ml (13.07 mmole)] and 5 ml of 20% sodium acetate were added simultaneously to a solution of 2 g (9.99 mmole) of trans-4-amino-3-hydroxythiophane hydrobromide (Vb') in 5 ml of 2 N sodium hydroxide at 0 deg, and the mixture was stirred for 2 h at 18-20 deg. The mixture was then extracted with chloroform, the chloroform was removed, and alcohol was added to the residue to give 1.52 g (79.4%) of IIIb.

trans-4-Amino-3-hydroxythiophane Hydrohalides (Vb' and b"). A. Sodium hydroxide [7.5 ml (9 N)] was added to a solution of 2.5 g (11.2 mmole) of IVb in 27.5 ml of alcohol, and the mixture was refluxed for 2 h. It was then acidified to pH 2 with hydrobromic acid and extracted with benzene. The aqueous layer was evaporated to dryness, 3 ml of alcohol was added, and the solid was filtered to give 1.92 g of the hydrobromide (Vb'). The hydrochloride (Vb") was obtained under the same conditions by acidification with hydrochloric acid. Vb' and Vb" were obtained in 80% yield by the hydrolysis of Xb.

B. A solution of 10 g (52.29 mmole) of IIIb in 100 ml of concentrated HBr was refluxed for 5 h and evaporated to dryness. The residue was dissolved in 35 ml of alcohol, the solution was treated with activated charcoal and evaporated to 15-16 ml, 5 ml of ether was added, and the precipitate was filtered to give 8.65 g of Vb'.

C. Hydrogen chloride was passed through a solution of 1 g (5.23 mmole) of IIIb in 10 ml of amyl alcohol for 8 h at 100 deg. The amyl alcohol was removed and 3 ml of alcohol was added to the residue. The resulting solution was treated with activated charcoal, and held at 0 deg for 16-18 h, and the resulting solid was filtered to give 0.1 g of Vb".

cis-4-Amino-3-hydroxythiophane Hydrohalides (Va' and a"). A. A solution of 3 g (13.44 mmole) of IVb in 30 ml of concentrated HBr was refluxed for 5 h, cooled, and extracted with benzene to remove benzoic acid, and evaporated to dryness. The residue was dissolved in 200 ml of alcohol. The solution was treated with activated charcoal, evaporated to 70-75 ml, and kept at 0 to -3 deg for 16-20 h to give 1.9 g of the hydrobromide (Va'). Va' was also obtained in ~80% yield by hydrolysis of IIIa, IVa and Xb. A mixture of Va' and Vb' had mp 88-90 deg.

B. Hydrogen chloride was bubbled through a solution of 4 g (17.92 mmole) of IVb in 30 ml of amyl alcohol for 8 h at 100 deg, and the solution was allowed to stand at 0 deg for 16-18 h. The resulting precipitate was filtered and the filtrate was evaporated to give 1.35 g of IVb and 0.71 g of the hydrochloride (Va"). A mixture of Va" and Vb" had mp 145-147 deg.

C. Sodium hydroxide [1.5 ml (9 N)] was added to a solution of 1.5 g (4.58 mmole) of cis-4-benzoylamino-3-benzoyloxythiophane (Xa) in 5.5 ml of alcohol, and the mixture was refluxed for 2 h. It was then acidified to pH 2 with hydrobromic acid and extracted with benzene. The aqueous layer was evaporated to dryness to give 0.78 g (85.2%) of Va'. Va" was similarly obtained using hydrochloric acid.

3,4-Carbamoylidothiophane (XII). Hydrobromide Va' [1.3 g (6.49 mmole)] was added to 10 ml of 1 N sodium hydroxide, the mixture was stirred for 15 min, and 10 ml of 30% phosgene in toluene was added at 0 deg, and the mixture was stirred for 4 h. The mixture was then extracted with chloroform. The chloroforms was removed to give 0.58 g of XII [7]. XII was obtained in 60% yield under these conditions from hydrochloride Va".

cis-4-Carbethoxyamino-3-hydroxythiophane (IIIa). Ethyl chlorocarbonate [2.5 ml (25.93 mmole)] and 10 ml of 20% sodium acetate solution were added simultaneously to a solution of 4 g (19.99 mmole) of Va' in 10 ml of 2 N sodium hydroxide at 0 deg, and the mixture was stirred for 2 h at 18-20 deg. The mixture was extracted with chloroform, the solvent was removed from the extracts, and ether–petroleum ether (1:1) was added to the residue to give 2.52 g of IIIa. A mixture of IIIa and IIIb had mp 61-65 deg.

cis-4-Benzoylamino-3-hydroxythiophane (IV). Sodium hydroxide [9 ml (2.5 N)] was added to a solution of 3 g (9.16 mmole)] of Xa in 33 ml of alcohol, and the mixture was refluxed for 25 min, cooled, and extracted with chloroform. The chloroform was removed to give 1.98 g of IVa. A mixture of IVa and IVb had mp 119-123 deg.

cis-4-Ureido-3-Hydroxythiophane (VIa). A solution of 3.7 g (45.61 mmole) of potassium isocyanate in 6 ml of water at 18-20 deg was added to a solution of 2 g (9.99 mmole) of hydrobromide Va' in 6 ml of water. The mixture was stirred at 45-50 deg for 3 h, cooled, and the precipitate was filtered to give 0.97 g of VIa.

trans-4-Ureido-3-hydroxythiophane (Vb). This was obtained in the same way as VIa from hydrobromide Vb'.

cis-4-Ureido-3-acetoxythiophane (VIIa). A solution of 0.9 g (5.55 mmole) of VIa in 10 ml of 20% hydrogen bromide in acetic acid was refluxed for 4 h and evaporated to dryness. The residue was recrystallized from ether–alcohol (1:1) to give 0.2 g of VIIa.

trans-4-Ureido-3-acetoxythiophane (VIIb). A solution of 1.1 g (6.78 mmole) of VIb in 5 ml of acetic anhydride was stirred at 50-60 deg for 4 h, and the acetic anhydride was removed in vacuo to give 0.91 g of VIIb.

cis-4-Acetylureido-3-acetoxythiophane (VIIIa). A solution of 1.5 g (9.25 mmole) of VIa in 7 ml of acetic anhydride was refluxed for 4 h. The solution was evaporated to dryness, 2 ml of alcohol was added, and the solution was kept at 0-3 deg for 10-16 h to give 1.2 g of VIIIa.

trans-4-Acetylureido-3-acetoxythiophane (VIIIb). A This was obtained in the same way as VIIIa from VIb.

B. A solution of 1 g (6.17 mmole) of VIa in 13 ml of acetic acid saturated with hydrogen bromide was refluxed for 4 h. The solution was evaporated to dryness, and the residue was recrystallized from methanol to give 0.25 g (16.4%) of VIIIb.

cis-4-Carbethoxyamino-3-acetoxythiophane (IXa). Acetyl chloride (3 ml) was added to a solution of 1 g (5.23 mmole) of IIIa in 5 ml of acetic anhydride at 0 deg, and the mixture was stirred at 18-20 deg for 30 min. It was then evaporated to dryness, and 2 ml of methanol was added to the residue to give 0.66 g of IXa.

trans-4-Carbethoxyamino-3-acetoxythiophane (IXb). This was obtained in the same way as IXa from IIIb.

cis-4-Benzoylamino-3-benzoyloxythiophane (Xa). Benzoyl chloride [4 ml (34.68 mmole)] and 10 ml of 4 N sodium hydroxide were added simultaneously to a solution of 2 g (19.99 mmole) of hydrobromide Va' in a mixture of 8 ml of dioxane and 2.5 ml of water at 0-3 deg and pH 8-9, and the mixture was stirred at 18-20 deg for 1 h. The resulting precipitate was filtered and washed with water and benzene to give 2.87 g of Xa.

trans-4-Benzoylamino-3-benzoyloxythiophane (Xb). A. Pyridine [0.2 ml (2.48 mmole)] and 0.32 ml (2.77 mmole) of benzoyl chloride were added to a solution of 0.47 g (2.1 mmole) of IVb in 8 ml of chloroform at 0 deg, and the mixture was stirred at 30-35 deg for 2 h. Water (30 ml) was added, the chloroform layer was separated, the solvent was removed, and the residue was washed with ether to give 0.55 g (79.8%) of Xb.

B. This compound was obtained also in the same way as Xa from Vb'.

cis-4-Benzoylamino-3-acetoxythiophane (XIa). Compound IVa [0.5 g (2.24 mmole)] was dissolved in 3 ml of acetic anhydride, and 2 ml of acetyl chloride was added to this solution at 0 deg. The mixture was then stirred at 50 deg for 30 min, and the resulting precipitate was filtered and washed with benzene to give 0.37 g of XIa.

trans-4-Benzoylamino-3-acetoxythiophane (XIb). Acetyl chloride (8 ml) was added to a solution of 2 g (8.96 mmole) of IVb in 12 ml of acetic anhydride at 0 deg, and the mixture was stirred at 18 deg for 30 min. It was then evaporated to dryness, benzene was added to the residue, and the resulting solid was filtered to give 1.94 g of XIb.

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