SYNTHESIS OF 1-ARYLDIHYDRO URACILS AND 1-ARYL-2-THIODIHYDRO URACILS AND THEIR TRANSFORMATIONS.

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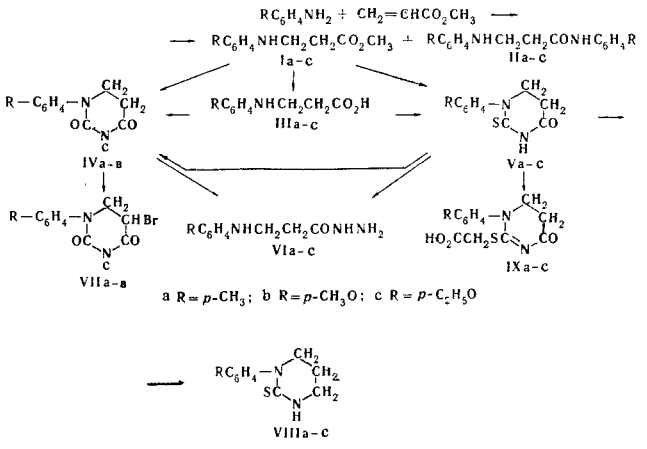
During the interaction of n-toluidine, n-anisidine, and n-phenetidine with methyl acrylate, the corresponding methyl esters of N-aryl-β-alanines and the corresponding N-aryl-β-alanines were obtained which were converted into 1-aryldihydro uracils and 1-aryl-2-thiodihydro uracils and then into 1-aryl-5-bromodehydrouracils, 1-aryl-2-thiohexahydropyrimidines, the hydrazides of N-aryl-β-alanines and 1-aryl-2-carboxymethylthio-4-oxo-1,4,5,6-tetrahydropyrimidines.

It has already been found that 1-substituted dihydro uracils and the 1-substituted 2-thiodihydro uracils may be used as stabilizers of polycaprolactam [1]. This work describes the synthesis and transformations of certain 1-aryldihydro uracils and 1-aryl-2-thiodihydro uracils.



a R = *p*-CH_3; b R = *p*-CH_3O; c R = *p*-C_2H_5O

The methyl esters of N-aryl-β-alanines (Ia–Ic) were obtained during the interaction between methyl acrylate [2–5] and the corresponding amines, and without preliminary extraction from the reaction mixture they were subjected to alkaline hydrolysis in aqueous solution. After hydrolysis the corresponding arylamides of N-aryl-β-alanines (IIa–IIc) separated from the reaction mixture as a precipitate. The N-aryl-β-alanines IIIa and IIIc [5, 6] were separated out by acidification of the alkaline filtrate with acetic acid. It was impossible to isolate N-(p-methoxyphenyl)-β-alanine [7] by this method.

The dihydro uracils IVa–IVc [8, 9] and thiohydro uracils Va–Vc were obtained both on heating the methyl esters of compounds Ia–Ic and also on heating the corresponding alanines of IIIa and IIIc or their hydrochlorides in glacial acetic acid with carbamide or ammonium thiocyanate in the presence of hydrochloric acid [10]. The hydro uracils of IVa–IVc and the thiohydro uracils of Va–Vc also were separated on heating the corresponding alanines of IIIa and IIIc and their hydrochlorides in aqueous solutions of carbamide or ammonium thiocyanate or on fusion with carbamide [1]. In addition the dihydro uracils of IVa–IVc were obtained on oxidation of thiodihydro uracils of Va–Vc in boiling glacial acetic acid with 30% hydrogen peroxide.

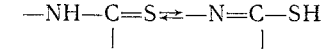
On heating the dihydro uracils of IVa–IVc and thiohydro uracils of Va–Vc with a 25% solution of hydrazine opening of the pyrimidine ring occurs and the corresponding hydrazides of VIa–VIc are formed which were also obtained from the methyl esters of Ia–Ic. One should note that opening of the ring proceeds more readily in the case of the dihydro uracils of IVa–IVc than with thiodihydro uracils of Va–Vc.

During the action of boiling acetic acid and bromine [11–13] on the dihydro uracils of IVa–IVc, the corresponding 1-aryl-5-bromohydro uracils of compounds VIIa–VIIc were obtained.

By the action of lithium aluminium hydride in an ethereal solution [1] on the thiodihydro uracils of Va–Vc, the latter were converted into the corresponding 1-aryl-2-thiohexahydropyrinidines of VIIIa [14], VIIIb, and VIIIc.

On boiling the thiodihydro uracils of Va–Vc in glacial acetic acid containing monochloroacetic acid [15, 16], high yields of 1-aryl-2-carboxymethylthio-4-oxo-1, 4, 5, 6-tetrahydropyrimidines of IXa–IXc were formed.

The formation of compounds IXa–IXc proceeded with the evolution of hydrochloric acid, which apparently was cleaved on enolisation of the thiodihydro uracils of Va–Vc



EXPERIMENTAL

The methyl ester of N-(n-tolyl)-β-alanine (Ia) was obtained according to a previously described method [3].

The methyl ester of N-(n-methoxyphenyl)-β-alanine (Ia) [4] was obtained according to the procedures described in the literature [3, 4].

The methyl ester of N-(n-ethoxyphenyl)-β-alanine (Ic) was prepared by a previously described method [5].

N-(n-Tolyl)-β-alanine (IIIa). Compound Ia was synthesized from 6.5 g (0.06 mole) n-toluidine according to the method of Sotwvick and Crouch [3], the benzene and excess methyl acrylate were removed by distillation, 25 ml of 30% KOH was added, and the mixture was heated at 60° C for 14 hr. After cooling, the n-toluidide of compound IIa (table) separated out from the reaction mixture and was removed by filtration. The filtrate was washed with ether, acidified with acid, and maintained for 24 hr at 0° C. The resulting precipitate of the alanine of compound IIIa was removed by filtration and crystallized twice from petroleum ether. Yield, 5 g (44% from original amine), mp 86.5–87° C. Found, %: N 7.87. Calculated for $C_{10}H_{13}NO_2$, %: N 7.80.

Characteristics of Compounds II–IX

Compound	Mp, °C	Solvent for recrystallization	Empirical formula	Found, %			Calculated, %			Yield, %
				C	H	N	C	H	N	
IIa	145—145.5	Benzene	$C_{17}H_{20}N_2O$	76.25	5.80	10.59	76.00	5.60	10.45	12.7
IIb	138—139.5	Benzene	$C_{17}H_{20}N_2O_3$	68.07	6.65	9.27	68.00	6.75	9.30	7.5
IIc	142.5—143	Ethanol	$C_{19}H_{24}N_2O_3$	69.55	7.42	8.33	69.50	7.40	8.55	11.0
IVa	192—193	Dioxane	$C_{11}H_{12}N_2O_2$	65.50	6.11	13.82	65.00	5.95	13.80	46.2***
IVb	205—206	Dioxane	$C_{11}H_{12}N_2O_3$	60.35	5.58	12.90	60.00	5.50	12.70	36.6***
IVc	206—206.5*	Dioxane	$C_{12}H_{14}N_2O_3$	61.60	6.03	12.02	61.50	6.00	12.00	24.6***
Va	259—260	Acetic acid	$C_{11}H_{12}N_2OS$	60.14	5.47	12.84	60.00	5.50	12.75	59.8
Vb	256.6—257.5	Acetic acid	$C_{11}H_{12}N_2O_2S$	55.90	5.00	11.85	56.00	5.10	11.80	58.00
Vc	247.5—248	Acetic acid	$C_{12}H_{14}N_2O_2S$	57.50	5.48	11.27	57.70	5.60	11.20	24.2
VIa	138—139	Benzene	$C_{10}H_{15}N_3O$	62.51	7.80	22.00	62.20	7.82	21.80	34.4
VIb	129—130	Ethanol	$C_{10}H_{15}N_3O_2$	57.78	7.17	20.18	57.50	7.20	20.10	78.0
VIc	116.5—117.5	Ethanol	$C_{11}H_{17}N_3O_2$			18.80			18.84	29.0
VIIa	167 (decomp.)	Ethanol	$C_{11}H_{11}BrN_2O_2$	Br 28.27		10.11	Br 28.80		9.88	47.0
VIIb	182 (decomp.)	Ethanol	$C_{11}H_{11}BrN_2O_3$	Br 26.76		9.50	Br 26.70		9.36	34.0
VIIc	165.5—167.5	Ethanol	$C_{12}H_{13}BrN_2O_3$	Br 25.85		9.05	Br 25.60		8.95	54.8
VIIIa	192—192.5**	Benzene	$C_{11}H_{14}N_2S$	64.15	7.01	13.67	64.10	6.85	13.58	56.0
VIIIb	177.5—179	Benzene	$C_{11}H_{14}N_2OS$	59.00	6.50	12.41	59.50	6.35	12.60	42.6
VIIIc	203—204	Ethanol	$C_{12}H_{16}N_2OS$	61.28	6.83	12.01	61.00	6.80	11.85	57.0
IXa	199—200.5	Dioxane	$C_{13}H_{14}N_2O_3S$	56.01	5.25	10.08	56.15	5.07	10.01	48.0
IXb	188—189	Dioxane	$C_{13}H_{14}N_2O_4S$	52.80	4.89	9.70	53.00	4.80	9.53	61.5
IXc	149—150	Dioxane	$C_{14}H_{16}N_2O_4S$	54.46	4.93	8.97	54.50	5.22	9.10	60.0

*According to data in the literature [8,9], mp 200-204 and 200-203° C.

**According to data in the literature [14], 188° C.

***Obtained according to method (A).

n-Anisidide of N-(n-methoxyphenyl)-β-alanine (IIb). The reaction was conducted in a manner similar to that for the preparation of compound IIIa. After cooling, the n-anisidide of compound IIb (table) separated out from the reaction mixture. On treatment of the filtrate a resin-like mass was obtained from which it was impossible to extract N-(n-methoxyphenyl)-β-alanine.

N-(n-Ethoxyphenyl)-β-alanine (IIIc) [5, 6]. This compound was obtained from n-phenetidine by a method analogous to that used for the preparation of compound IIIa. For hydrolysis of the ester the compound was heated with 20% KOH for 3 hr at 80–90° C. After cooling, the n-ethoxyanilide of compound IIc (table) separated out from the reaction mixture. The filtrate was washed with ether, acidified with acetic acid, and the resulting precipitate was twice crystallized from benzene, mp 103–104° C (108–110) [5]. Yield, 18.8 g (42.5%). Found, %: N 7.39 Calculated for $C_{11}H_{15}NO_3$, %: N 7.25.

1-Aryldihydro uracils (IVa–IVc, table). A) A mixture of 0.042 moles of the ester of compound I, 12 g (0.2 mole) of carbamide, and 15 ml of glacial acetic acid was boiled for 3 hrs, and 10 ml of conc HCl was added and the mixture was boiled for a further 2 hr. The reaction mixture was cooled and diluted in water (1 : 5). The precipitate which formed on standing was removed by filtration and twice recrystallized from dioxane. B) A 10 ml volume of 30% hydrogen peroxide was added over the course of 15 min into a boiling solution of 0.01 mole of the thiohydro uracil of compound V in 30 ml of glacial acetic acid, the mixture was boiled for 15 min and maintained at room temperature for 2 hr, after which the liquid fractions were distilled at 2–3 mm pressure. The remaining mass was diluted in water (1 : 5), and the resulting precipitate was removed by filtration and crystallized from ethanol. Yields: compound IVa, 41.6%; compound IVb, 35.8%; compound IVc, 44.8%.

Mixed samples of the dihydro uracils of compounds IVa–IVc, obtained by methods (A) and (B), do not produce depression of the melting point.

1-Aryl-2-thiodihydro uracils (Va–Vc, table). A mixture of 0.042 mole of the ester of compound I, 7.6 g (0.1 mole) ammonium thiocyanate, and 15 ml glacial acetic acid was heated for 2 hr at 100–105° C, 10 ml of HCl was added dropwise, and the mixture was heated for a further 3 hr. The reaction mixture was diluted with water (1:5), and the resulting precipitate was removed by filtration, washed with ethanol and ether, and crystallized from glacial acetic acid.

Hydrazides of N-aryl-β-alanines (VIa–VIc, table). A) A mixture of 0.015 mole dihydro uracil of compound IV, 25 ml of a 25% solution (0.097 mole) of hydrazine, and 10 ml of dioxane was boiled for 8 hr. After standing for 48 hr, the resulting precipitate was removed by filtration and twice crystallized from benzene.

B) The hydrazides of compound VIa, VIb, and VIc are obtained with yields of 85.5%, 70%, and 72%, respectively from 0.018 mole of the thiodihydro uracil of compound V, 25 ml of a 25% solution (0.097 mole) of hydrazine, and 10 ml of dioxane according to method (A).

C) A 0.02 mole quantity of the ester of compound I and 15 ml of a 25% solution (0.03 mole) of hydrazine were boiled for 3 hr, and cooled, and the resulting precipitate was removed by filtration and twice crystallized from benzene. The hydrazides of compounds VIa, VIb, and VIc were obtained with yields of 80%, 87.5%, and 78.5%, respectively.

The mixed samples of the hydrazides of compounds VIa–VIc obtained by methods (A–C) did not depress the melting point.

1-Aryl-5-bromodihydro uracils (VIIa–VIIc, table). A 0.088 mole quantity of the dihydro uracil of compound IV was dissolved on heating in 100 ml of glacial acetic acid a mixture of 45 ml glacial acetic acid and 3 ml (0.058 mole) bromine was added dropwise. The reaction mixture was then diluted with water (1:5). The resulting precipitate was removed by filtration and crystallized three times from ethanol.

1-Aryl-2-thiohexahydropyrimidines (VIIIa–VIIIc, table). A 0.036 mole quantity of the thiodihydrouracil of compound V was added over 2 hr to an ethereal solution of $LiAlH_4$, which had been prepared from 2 g (0.25 mole) lithium hydride, 17.4 g (0.065 mole) aluminium bromide, and 120 ml absolute ether. The reaction mixture was boiled for 24 hr. Excess of $LiAlH_4$ was decomposed with a mixture of ether and ethanol (1:1). The solvents were removed by distillation and the residue was extracted in the Soxhet apparatus with acetone. Acetone was removed by distillation, and the residue was washed with water and ether.

1-Aryl-2-Caboxymethylthio-4-oxo-1,4,5,6-tetrahydropyrimidines (IXa–IXc, table). A mixture of 0.015 mole of the thiodihydro uracil of compound V, 2.5 g (0.026 mole) monochloroacetic acid, and 25 ml glacial acetic acid was boiled for 5 hr. After standing for 24 hr the original product separated out and was removed by filtration, and the filtrate was evaporated under vacuum. The oily mass was treated with a mixture of acetone and water (1:2). The extracted product was crystallized three times from dioxane.

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