SYNTHESIS OF 5-PHENYLAMINO DERIVATIVES OF OROTIC ACID

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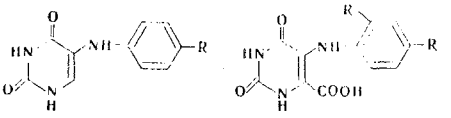
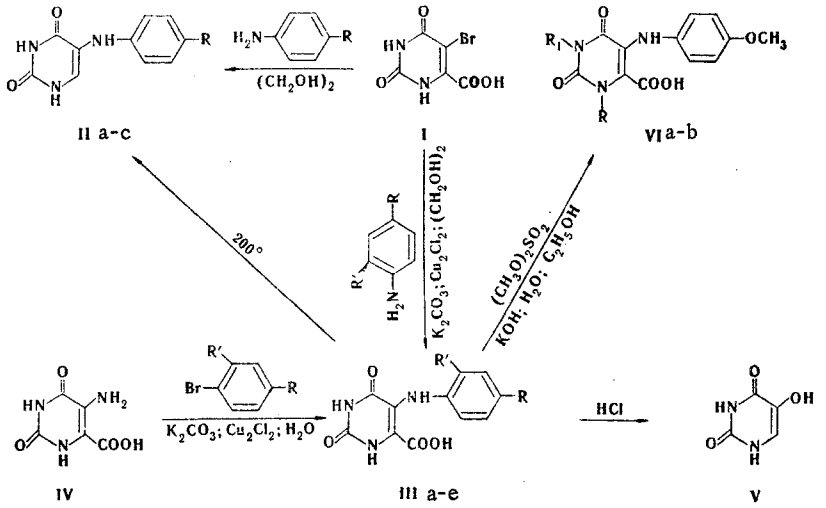
The possibility of nucleophilic substitution of bromine in 5-bromoorotic acid by aromatic amines was studied. 5-Phenylamino derivatives of uracil and 5-phenylamino derivatives of orotic acid were synthesized.

This paper is devoted to the study of the possibility of nucleophilic substitution of bromine in 5-bromoorotic acid (I) by aromatic amines. 5-Phenylamino-substituted orotic acids may be of interest as derivatives of orotic acid – the precursor in the biosynthesis of pyrimidine bases.



II a-c III a-e

When I is heated with anisidine, aniline, and p-chloroaniline in ethylene glycol at high temperatures, bromine is substituted nucleophilically, and the compound undergoes decarboxylation to give 5-phenylamino derivatives of uracil (IIa-c). We were able to retain the carboxyl group and obtain 5-phenylamino derivatives of orotic acid (IIIa-d) by the Ullmann reaction of I with aromatic amine in ethylene glycol. The possi-



II a-c I VI a-b

IV III a-e V

II a R=OCH_3; b R=H; c R=Cl; III a R′=H, R=OCH_3; b R′=R=H; c R′=H, R=Cl; d R′=H, R=$COOCH_3$; e R′=R=NO_2; VI a R=R_1=CH_3; b R=H, R_1=CH_3

*Deceased.

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TABLE 1

Comp.	R	R′	mp, °C (dec.)*	Empirical formula	Found, %					Calc., %					Yield, %
					C	H	Cl	N	H_2O	C	H	Cl	N	H_2O	
IIa	OCH_3	—	313	$C_{11}H_{11}N_3O_3$	57,0	4,9	—	18,4	—	56,6	4,7	—	18,0	—	55,0
IIb	H	—	310	$C_{10}H_9N_3O_2$	59,6	4,6	—	20,5	—	59,1	4,5	—	20,7	—	58,6
IIc	Cl	—	318	$C_{10}H_6ClN_3O_2$	50,3	3,3	14,8	17,4	—	50,5	3,4	14,9	17,7	—	56,0
IIIa	OCH_3	H	312	$C_{12}H_{11}N_3O_5 \cdot 0{,}5H_2O$	50,3	4,3	—	14,7	3,0	50,0	4,1	—	14,7	3,1	58,6
IIIb	H	H	320	$C_{11}H_9N_3O_4 \cdot H_2O$	49,6	3,9	—	15,4	6,5	49,8	4,1	—	15,8	6,8	64,0
IIIc	Cl	H	336	$C_{11}H_8ClN_3O_4 \cdot 0{,}5H_2O$	45,5	3,2	11,8	14,8	2,8	45,4	3,1	12,2	14,4	3,2	38,5
IIId	$COOCH_3$	H	>330	$C_{13}H_{11}N_3O_6 \cdot H_2O$	48,4	4,1	—	13,2	5,1	48,3	4,0	—	13,0	5,5	14,5
IIIe	NO_2	NO_2	288	$C_{11}H_7N_5O_8$	39,4	2,3	—	20,7	—	39,1	2,1	—	20,8	—	51,0

*Compounds IIa-c were recrystallized from aqueous dimethylformamide, while IIIa-e were recrystallized from water.

bility of carrying out the reaction and the yields of the compounds obtained (see Table 1) depend on the character of the substituent in the aromatic amine used. Compounds IIIc and IIId were obtained in low yield in the reaction of I with p-chloroaniline and ethyl aminobenzoate, while I did not undergo reaction at all with p-nitroaniline or anthranilic acid (i.e., when strong electron-acceptor substituents were introduced into the aromatic ring). However, we were able to obtain 5-(2',4'-dinitrophenylamino)orotic acid (IIIe) by the Ullmann reaction [2] of 5-aminoorotic acid (IV) with 2,4-dinitrochlorobenzene. In a study of the properties of 5-phenylamino derivatives of orotic acid, we established that IIIa and IIIb undergo decarboxylation to IIa and IIb on heating to 200°. When IIIa is refluxed in hydrochloric acid, it undergoes both decarboxylation and hydrolysis of the phenylamino group to give isobarbituric acid (V). 1,3-Dimethyl-5-(p-methoxyphenylamino)orotic acid (VIa) is formed in the reaction of IIIa with dimethyl sulfate at 12-15° in aqueous alcohol in the presence of alkali; a monomethyl derivative of 5-(p-methoxyphenylamino)orotic acid (VIb) was isolated at a reaction temperature of 305°. It is known [3-6] that methylation of orotic acid leads primarily to 3-methyl-substituted orotic acid, and the 3-methyl-5-(p-methoxyphenylamino)orotic acid structure is therefore the most probable one for monomethyl derivative VIb.

EXPERIMENTAL

5-Phenylamino Derivatives of Uracil (IIa-c). These derivatives were obtained by heating I [1] in ethylene glycol (1 : 1) with 2.5 moles of anisidine, aniline, or, respectively, p-chloroaniline at 180° for 1.5 h. The mixture was diluted with water, and the resulting II was separated by filtration.* Compounds IIa and IIb were also formed in 70% yield by heating IIIa and IIIb at a bath temperature of 200° for 8 h in the absence of a solvent.

5-(p-Methoxyphenylamino)orotic Acid (IIIa). A mixture of 36 g (0.13 mole) of IV and 11.28 g (0.2 mole) of potassium carbonate was heated at 120° for 30 min in 120 ml of ethylene glycol, after which 34 g (0.27 mole) of p-anisidine and 0.18 g of cuprous chloride were added to the solution, and the mixture was heated at 150° for 2 h. The cooled mixture was treated with 80 ml of dilute (1 : 1) hydrochloric acid, and the resulting IIIa was removed by filtration and reprecipitated from aqueous alkali solution by the addition of hydrochloric acid. Compounds IIIb-d† were similarly obtained.

5-(2',4'-Dinitrophenylamino)orotic Acid (IIIe). A mixture of 1.5 g (8.7 mmole) of IV, 1.2 g (8.7 mmole) of potassium carbonate, 2.4 g (18.5 mmole) of 2,4-dinitrochlorobenzene, and 0.02 g of cuprous chloride in 25 ml of water was refluxed for 24 h. The resulting IIIe was removed by filtration and reprecipitated from aqueous alkaline solution by the addition of hydrochloric acid.

Isobarbituric Acid (V). A 0.5-g sample of IIIa was heated at 80-90° for 30 min in 10 ml of concentrated hydrochloric acid. The mixture was then cooled, and the precipitated V was removed by filtration and crystallized from water to give 0.15 g (67%) of a product with mp 330° (dec.). UV spectrum, λ_{max}, nm (ε): 278 (6700), 210 (7900). According to [7], λ_{max} 278, 210 nm at pH 7.4.

1,3-Dimethyl-5-(p-methoxyphenylamino)orotic Acid (VIa). A 7.2-g (25.2 mmole) sample of IIIa was dissolved in 60 ml of aqueous alcohol (1 : 1) containing 5.4 g (96.4 mmole) of potassium hydroxide. Dimethyl sulfate [12 ml (0.13 mole)] was added in the course of an hour to the cooled (12-15°)

*The physical constants and yields of II are presented in Table 1.

†The physical constants and yields of III are presented in Table 1.

solution with stirring. The pH was maintained at 9-10 while 3 g (53.5 mmole) of potassium hydroxide dissolved in 10 ml of aqueous alcohol (1 : 1) was added gradually. The solution was then stirred for 1 h and acidified with 18 ml of concentrated hydrochloric acid. The VIa was removed by filtration to give 2.7 g (35%) of a product with mp 191° (dec., from water) and R_f 0.50.* Found,%: C 54.8; H 4.8; N 13.9. $C_{14}H_{16}N_3O_5$. Calculated,%: C 55.1; H 4.9; N 13.8.

3-Methyl-5-(p-methoxyphenylamino)orotic Acid (VIb). A 7.2-g (25.2 mmole) sample of IIIa was dissolved in 60 ml of aqueous alcohol (1 : 1) containing 6 g (0.11 mole) of potassium hydroxide. A total of 12 ml (0.13 mole) of dimethyl sulfate was added to the solution in the course of 20 min at 3-5°, after which it was stirred for another 30 min and acidified with 18 ml of concentrated hydrochloric acid. The resulting VIb was removed by filtration to give 2.65 g (37%) of a product with mp 234° (dec., from water) and R_f 0.63.* Found,%: C 53.8; H 4.5; N 14.3. $C_{13}H_{13}N_3O_5$. Calculated,%: C 53.6; H 4.5; N 14.4.

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*A butanol–acetic acid–water system (4 : 1 : 5) was used for paper chromatography.