and the precipitated XXI was removed by filtration and washed with water. Compounds XVI, XVII, and XX (light-brown), XVIII (orange), XIX (light-yellow), and XXI (red) were obtained as crystalline substances and were purified for analysys by crystallization from glacial acetic acid (XVI-XIX) 50% acetic acid (XX), or dimethylformamide (DMF) (XXI).

1-Phenyl-3-(p-dimethylaminophenylimino)-6,8-dimethylimidazolino[1,2-f]xanthin-2-one (XXII, Table 2). A 1.5-g (0.01 mole) sample of p-nitrosodimethylaniline and two to three drops of piperidine were added to a suspension of 3.11 g (0.01 mole) of XV in 80 ml of ethanol, and the mixture was refluxed for 24 h. The solvent was removed by distillation to dryness, and the residue was washed with ether and purified by reprecipitation from ethanol solution by the addition of ether.

3-Arylazo-6,8-dimethylimidazoline[1,2-f]xanthin-2-ones (XXIII-XXV, Table 2). A mixture of 0.01 mole of XIII or XV, 2.5-3.5 g of anhydrous sodium acetate, and 0.011 more of arendediazonium tetrafluoroborate in 25-40 ml of glacial acetic acid was heated on a boiling-water bath for 20-30 min, after which it was cooled and diluted with 60-80 ml of water. The precipitated azo compounds (XXIII-XXV) were removed by filtration and washed with water and methanol.

Crystalline XXIII and XXV (yellow) and XXIV (orange) were purified for analysis by crystallization from glacial acetic acid (XXIV) and DMF (XXIII) or by reprecipitation from DMF by the addition of water (XXV).

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RESEARCH ON RIBOFLAVIN ANALOGS

VIII.* 7-TRIFLUOROMETHYL-8-CHLOROISOALLOXAZINES

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A number of 7-trifluoromethyl-8-chloro-10-R-isoalloxazines (where R = H, CH_3, CH_2CH_2OH, ribityl, galactyl, sorbityl, and rhamnityl) and 7-trifluoromethyl-8-(β-hydroxyethyl)aminoisoalloxazines with substituents such as ribityl and β-hydroxyethyl in the 10 position were synthesized.

Replacement of the hydrogen atoms in a metabolite molecule by fluorine atoms or replacement of a methyl group by a chlorine atom, which have quite close van der Waals radii, is one of the proven methods for modification of metabolite molecules.

We have previously reported the synthesis of 7- or 8-mono- and 7,8-bis(trifluoromethyl) analogs of riboflavin [1]. The aim of the present research was the synthesis of 7-trifluoromethyl-8-chloro derivatives of

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* See [1] for communication VII.

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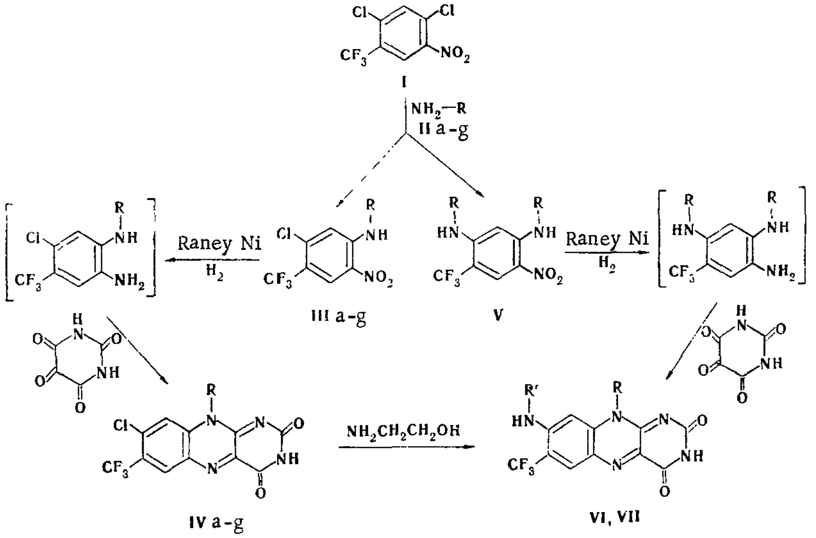
isoalloxazine, which are new analogs of riboflavin and well-known antagonists of riboflavin [2-4], as well as a study of the possibility of the use of the reactive chlorine atom in 7-trifluoromethyl-8-chloroisoalloxazine for the synthesis of a number of 8-amino derivatives of isoalloxazine, the interest in which is due to data on the high antivitamin activity of 8-amino- and 8-ribitylamino-8-norriboflavin [5].

The synthesis was carried out via the scheme presented below:



II—IV a $R=H$; b $R=CH_3$; c $R=CH_2CH_2OH$; d R= ribityl; e R=galactyl; f R=sorbitol; g R=rhamnityl; V $R=CH_2CH_2OH$; VI $R'=R=CH_2CH_2OH$; VII R=ribityl, $R'=CH_2CH_2OH$

Only the chlorine atom in the 4 position undergoes replacement in the reaction of 2,4-dichloro-5-nitro-1-trifluoromethylbenzene I [6] with ammonia or alkylamines under mild conditions to give nitroanilines III (Table 1), reduction of which and subsequent condensation with alloxan gives 7-trifluoromethyl-8-chloroisoalloxazines IV (Table 2).

Replacement of the chlorine atoms in I by a β-hydroxyethylamine residue under more severe conditions leads to diamine V.

In an attempt to synthesize 8-alkylamino-substituted isoalloxazines via the scheme presented above starting from V we obtained a complex mixture of reaction products, from which a small amount of 7-trifluoromethyl-8-(β-hydroxyethyl)amino-10-(β-hydroxyethyl)isoalloxazine (VI) was isolated by thin-layer chromatography (TLC).

The UV spectra of IVa-g, VI, and VII are characterized by three absorption bands (Table 2). As one should have expected, a hypsochromic shift of the middle band due to the introduction of the electron-acceptor CF_3 group is observed in the spectra of 7-trifluoromethyl-8-chloroisoalloxazines as compared with the spectra of riboflavin. The introduction of an alkylamino group into the isoalloxazine molecules leads to deepening of the color and bathochromic shift of the long-wave absorption bands (451 nm for riboflavin) [7].

EXPERIMENTAL

The UV spectra of alcohol solutions of the flavins were recorded with a Perkin–Elmer 402 spectrophotometer. Thin-layer chromatography (TLC) was carried out on Silufol UV-254 in the following systems: A) water-saturated butyl alcohol; B) propyl alcohol–0.2 N NH_4OH (3 : 1).

2-Chloro-4-amino-5-nitro-1-trifluoromethylbenzene (IIIa). A solution of 1 g (4 mmole) of I in 10 ml of ethanol saturated with ammonia was heated at 150° for 8 h, after which it was cooled, and the alcohol was partially evaporated. The residue was diluted with water, and the resulting precipitate was removed by filtration and dried. Recrystallization from aqueous alcohol gave yellow plates.

2-Chloro-4-methylamino-5-nitro-1-trifluoromethylbenzene (IIIb). A stream of methylamine was bubbled through an ince-cooled solution of 1 g (4 mmole) of 2,4-dichloro-5-nitro-1-trifluoromethylbenzene in 10 ml of ethanol. A precipitate began to form after a short time. Methylamine was bubbled through the mixture for another 20 min, after which the precipitate was removed by filtration. Dilution of the filtrate with water yielded an additional amount of nitro amine IIIb. Recrystallization from aqueous methanol gave plates of IIIb.

TABLE 2. Isoalloxazines

Compound	mp, °C (dec.)	R_f values in systems		Empirical formula	Found, %			Calculated, %			λ_{max}, nm (lg ε)	Yield, %
		A	B		Cl	F	N	Cl	F	N		
IVa	346—347	0,82	0,73	$C_{11}H_4ClF_3N_4O_2$	11,2	17,9	17,6	11,2	18,0	17,7	410(4,03)*; 390(4,18); 375(4,12)*; 308(3,93); 260(4,45)*; 250(4,57)	63
IVb	325—326	0,60	0,71	$C_{12}H_6ClF_3N_4O_2$	11,2	17,4	16,4	10,7	17,3	16,9	430(3,99); 332(3,78); 273(4,57)	85
IVc	265—266	0,63	0,74	$C_{13}H_8ClF_3N_4O_3$	10,0	16,1	15,7	9,9	15,8	15,5	430(3,99); 333(3,74); 273(4,49)	85
IVd	244—246	0,58	0,60	$C_{16}H_{14}ClF_3N_4O_6$	8,0	13,0	12,7	7,9	12,7	12,5	430(3,96); 335(3,82); 270(4,50)	77
IVe	233—234	0,52	0,79	$C_{17}H_{16}ClF_3N_4O_7$	7,6	11,7	11,5	7,4	11,9	11,6	430(3,97); 334(3,81); 272(4,48)	80
IVf	227—229	0,57	0,79	$C_{17}H_{16}ClF_3N_4O_7$	7,8	12,0	11,8	7,4	11,9	11,6	430(3,98); 335(3,84); 271(4,52)	84
IVg	246—247	0,64	0,67	$C_{17}H_{16}ClF_3N_4O_6$	7,5	12,8	12,1	7,6	12,3	12,1	430(4,02); 335(3,84); 272(4,56)	67
VI	Above 350	0,32	0,51	$C_{15}H_{14}F_3N_5O_4$	—	15,3	17,8	—	14,8	18,2	462(4,75); 318(4,18); 257(4,84)	84
VII	272—273	0,31	0,13	$C_{18}H_{20}F_3N_5O_7$	—	12,3	14,3	—	12,0	14,7	463(4,53); 318(3,95); 258(4,32)	90

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* Shoulder.

TABLE 1. Substituted Trifluoromethylbenzenes

Compound	mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
			Cl	F	N	Cl	F	N	
IIIa	114—115	$C_7H_4ClF_3N_2O_2$	15,0	24,1	11,8	14,8	23,7	11,6	82
IIIb	116—117	$C_8H_6ClF_3N_2O_2$	14,2	22,3	10,8	13,9	22,4	11,0	72
IIIc	122—124	$C_9H_8ClF_3N_2O_3$	12,9	19,7	10,3	12,5	20,0	9,9	78
IIId	195—196	$C_{12}H_{14}ClF_3N_2O_6$	9,8	14,6	8,0	9,5	15,2	7,5	87
IIIe	234—236	$C_{13}H_{16}ClF_3N_2O_7$	8,8	14,8	7,1	8,8	14,9	6,9	81
IIIf	209—210	$C_{13}H_{16}ClF_3N_2O_7$	8,6	15,1	6,9	8,8	14,9	6,9	95
IIIg	173—175	$C_{13}H_{16}ClF_3N_2O_6$	9,0	14,5	7,4	9,2	14,7	7,2	84
V	149—150	$C_{11}H_{14}F_3N_3O_4$	—	13,6	17,8	—	13,6	18,1	46

2-Chloro-4-(β-hydroxyethyl)amino-5-nitro-1-trifluoromethylbenzene (IIIc). A solution of 0.5 g (8 mmole) of monoethanolamine in 3 ml of methanol was added to a solution of 1 g (4 mmole) of dichloro-1-trifluoromethylbenzene I in 7 ml of methanol, and the mixture was refluxed for 10 min. It was then diluted with 20 ml of water, and the resulting precipitate was removed by filtration and dried. Recrystallization from aqueous ethanol gave plates of IIIc.

Trifluoromethylbenzenes (IIId-g). A mixture of 5 mmole of I and 10 mmole of the appropriate glycamine in 30 ml of ethanol was refluxed for 5 h, and the resulting precipitate was removed by filtration. The alcohol was vacuum evaporated to one-fourth of the original volume of the mixture, and the residue was diluted with water to give an additional amount of the nitro amine. Compounds IId, f were crystallized from aqueous ethanol, and IIIe, g were crystallized from ethanol.

2,4-Bis(β-hydroxyethyl)amino-5-nitro-1-trifluoromethylbenzene (V). A solution of 3.2 g (50 mmole) of monoethanolamine in 15 ml of butanol was added to a solution of 2.6 g (10 mmole) of trifluoromethylbenzene I in 15 ml of butanol, and the mixture was refluxed for 6 h. The solvent was partially evaporated, and the residue was diluted with water. The resulting precipitate was removed by filtration and crystallized from methanol to give a mixture of V and IIIc, which were separated through their different solubilities in ethanol. Workup gave 1.43 g of V and 0.6 g of IIIc.

7-Trifluoromethyl-8-chloroisoalloxazines (IVa-g). A solution of 2 mmole of nitro amines IIIa-g in 50 ml of acetic acid was reduced in the presence of Raney nickel. The solution was filtered to remove the catalyst, and the solution of the o-phenylenediamine was added to a suspension of 6 mmole of alloxan and 6 mmole of boric acid in 50 ml of acetic acid. The resulting solution was heated at 60° for 6 h in the case of IVa and at 25° for 1-2 days in the case of flavins IVb-g. The solvent was vacuum evaporated to dryness, and the residue was washed with ether until the odor of acetic acid vanished. Isoalloxazines IVa-b were crystallized from alcohol–water–acetic acid (1 : 1 : 1), and IVc-g were crystallized from water and water–acetic acid.

7-Trifluoromethyl-8-alkylaminoisoalloxazines (VI, VII). A mixture of 1 mmole of 8-chloroisoalloxazines IVc, d and 2.5 mmole of monoethanolamine in 15 ml of dimethylformamide (DMF) was heated with vigorous stirring at 120° for 5 h. The DMF was removed by vacuum distillation, and the residue was crystallized from methanol and ethanol. The physical constants, spectral characteristics, and yields of VI and VII are represented in Table 2.

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