RESEARCH ON RIBOFLAVIN ANALOGS

VII.* SYNTHESIS OF 7,8-BIS(TRIFLUOROMETHYL)ISOALLOXAZINES

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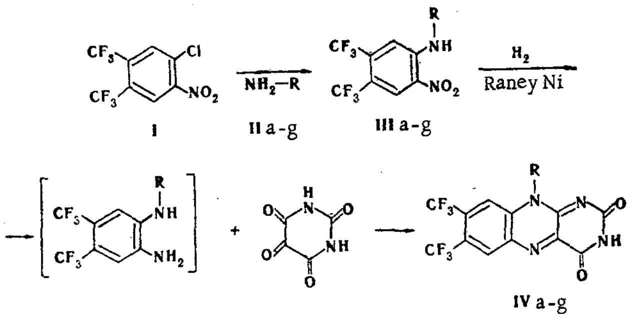
A number of 7,8-bis(trifluoromethyl)derivatives of isoalloxazine with the following substituents in the 10 position of the ring were synthesized: H, methyl, β-hydroxyethyl, ribityl, galactyl, sorbityl, and rhamnityl.

The synthesis and systematic study of monotrifluoromethyl derivatives of isoalloxazine, which are analogs of riboflavin with a slightly distorted geometry of the substituents attached to the phenyl ring, have been previously reported [1-4]. Replacement of the methyl group in the 7 or 8 position of the heteroring by a trifluormethyl substituent leads to compounds that are competitive antagonists of riboflavin [5].

In our development of systematic studies of the interrelationship of the chemical structures, physicochemical properties, and biological activities in a number of riboflavin analogs, we have synthesized a number of 7,8-bis(trifluoromethyl) derivatives (IV) of isoalloxazine. The introduction of two trifluoromethyl groups in the flavin molecule does not give rise to substantial changes in the geometry of the molecule. At the same time, the electron-acceptor character of the introduced substituent may effect the electron density distribution in the molecule to a greater extent than in the case of the monotrifluoromethyl analogs of riboflavin.

Compounds IVa-g were synthesized by the scheme presented below.



II—IV a R=H; b R=CH_3; c R=CH_2CH_2OH; d R=d-ribityl; e R=d-galactyl; f R==d-sorbityl; g R=L-rhamnityl

Substituted o-nitroanilines, obtained by reaction of nitrochlorobenzene I with amines II, were catalytically reduced by acetic acid to o-phenylenediamines, which were used, without isolation from the reaction mixture, in the condensation with alloxan.

Inasmuch as it is known [6] that the formation of products of incomplete condensation with splitting out of one water molecule – alloxan anils – is possible in the condensation of substituted o-phenylenediamine with alloxan, the electronic spectra of the synthesized analogs were recorded to confirm their iso-

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*See [1] for communication VI.

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TABLE 1. 4,5-Bis(trifluoromethyl)-2-nitroanilines (IIa-g)

Compound	R	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
				C	H	F	N	C	H	F	N	
IIIa	H	89—90	$C_8H_4F_6N_2O_2$	35,4	1,7	41,8	10,6	35,0	1,5	41,6	10,2	92
IIIb	CH_3	124—125,5	$C_9H_6F_6N_2O_2$	37,6	2,2	40,2	9,9	37,5	2,1	39,6	9,7	92
IIIc	CH_2CH_2OH	123,5—125	$C_{10}H_8F_6N_2O_3$	38,2	2,4	35,3	8,8	37,8	2,6	35,8	8,6	88
IIId	Ribityl	118—120	$C_{13}H_{14}F_6N_2O_6$	38,0	3,8	27,4	7,1	38,2	3,4	27,9	6,9	93
IIIe	Galactyl	158—161	$C_{14}H_{16}F_6N_2O_7$	38,0	3,4	25,5	6,4	38,3	3,6	26,0	6,4	78
IIIf	Sorbityl	174—175,5	$C_{14}H_{16}F_6N_2O_7$	38,6	3,6	25,9	6,5	38,3	3,6	26,0	6,4	81
IIIg	Rhamnityl	187—189	$C_{14}H_{16}F_6N_2O_6$	40,2	4,0	26,9	7,0	39,8	3,8	27,0	6,6	70

TABLE 2. 7,8-Bis (trifluoromethyl)isoalloxazines (IV)

Compound	R	mp, °C (dec.)	R_f in systems		Empirical formula	Found, %				Calculated, %				λ_{max}, nm (lg ε)	Yield, %
			A	B		C	H	F	N	C	H	F	N		
IVa	H	313—315	0,76	0,85	$C_{12}H_4F_6N_4O_2$	41,1	1,2	32,5	15,9	41,1	1,1	32,6	16,0	392 (3,53)*; 376 (3,57); 308 (3,49)*; 255 (4,20); 214 (4,24)	62
IVb	CH_3	287—288	0,68	0,84	$C_{13}H_6F_6N_4O_2$	43,1	1,8	31,0	15.3	42,9	1,6	31,3	15,4	430 (3,87); 317 (3,65); 276 (4,50); 220 (4,44)	64
IVc	CH_2CH_2OH	284,5—285	0,76	0,87	$C_{14}H_8F_6N_4O_3$	42,3	2,2	28,2	14,4	42,6	2,0	28.9	14,2	430 (3,92); 318 (3,64); 277 (4,54); 221 (4,42)	58
IVd	Ribityl	223,5—225	0,71	0,79	$C_{17}H_{14}F_6N_4O_6$	41,8	2.8	23.1	11,4	42,1	2,9	23,5	11,6	434 (3,92); 320 (3,60); 277 (4,55); 222 (4,35);	59
IVe	Galactyl	249—251	0,64	0,77	$C_{18}H_{16}F_6N_4O_7$	41,9	3,2	22,1	10,9	41.6	3,1	22,2	10,9	433 (3,90); 319 (3,60); 277 (4,53); 222 (4,36)	62
IVf	Sorbityl	222—224	0,68	0,77	$C_{18}H_{16}F_6N_4O_7$	42,0	3,5	22,1	11,2	41.6	3,1	22,2	10,9	434 (3,84); 317 (3,73); 276 (4,49); 221 (4,41)	68
IVg	Rhamnityl	255—256	0,65	0,69	$C_{18}H_{16}F_6N_4O_6$	43,1	3,4	22,4	11,1	43,4	3,2	22,9	11,2	433 (3,95); 315 (3,78); 278 (4,49); 222 (4,37)	57

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*Shoulder

alloxazine structure. As in the case of riboflavin [7], the UV spectra of all of the compounds obtained are characterized by four absorption bands (Table 2). In this case one should note the hypsochromic shift of the long-wave absorption bands in the spectra of the bis(trifluoromethyl) derivatives as compared with the spectra of riboflavin and its monitrifluoromethyl analogs [8]; this is associated with the effect of two strong electron-acceptor trifluoromethyl groups on the π-electron system of the molecule.

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 and B) propyl alcohol–0.2 N NH_4OH (3 : 1). 4,5-Bis(trifluoromethyl)-2-nitrochlorobenzene (I) was obtained by the method in [9]. 1-Amino-1-deoxyribitol (IId), 1-amino-1-deoxygalactitol (IIe), 1-amino-1-deoxysorbitol (IIf) and 1-amino-1-deoxyrhamnitol (IIg) were obtained as syrups by reduction of the phenylhydrazones of the corresponding sugars [10, 11].

4,5-Bis(trifluoromethyl)-2-nitroaniline (IIIa). A solution of 3 g (0.01 mole) of I in 20 ml of ammonia-saturated ethanol was heated in an autoclave at 150° for 12 h, after which the mixture was cooled, half of the alcohol was removed by evaporation, and the residual solution was diluted with water. The resulting precipitate was removed by filtration and dried to give needles with mp 89-90° (from aqueous ethanol) (in agreement with the literature melting point [9]).

4,5-Bis(trifluoromethyl)-2-nitro-N-methylaniline (IIIb). A stream of gaseous methylamine was bubbled through an ice-cooled solution of 2 g (7 mmole) of nitrochlorobenzene I in 13 ml of ethanol. A precipitate began to form after a certain time, after which methylamine was bubbled through the solution for another 30 min. The precipitate was removed by filtration and crystallized from aqueous alcohol.

4,5-Bis(trifluoromethyl)-2-nitro-N-(β-hydroxyethyl)aniline (IIIc). A solution of 3 g (0.01 mole) of I in 25 ml of ethanol was refluxed with 2 g (0.03 mole) of monoethanolamine for 8 h, after which the alcohol was evaporated until the volume of the mixture was reduced to one third that of the starting solution. The residual solution was diluted with water, and the resulting yellow-orange precipitate was removed by filtration and crystallized from aqueous methanol to give prisms of IIIc.

Nitroanilines (IIId-g, Table 1). A 3-mmole sample of nitrochlorobenzene (I) and 10 mmole of the appropriate amino alcohol were heated in 50 ml of butanol at 100° for 12 h, after which the hot solution was decanted from the resin, and the solvent was vacuum evaporated. The residue was treated with hexane, and the precipitated nitroamines were crystallized – IIId from hexane–ethanol–acetic acid (1 : 1 : 1), IIIe from alcohol (with the addition of benzene), IIIf from aqueous ethanol, and IIIg from aqueous methanol. Compounds IIId-g formed gels during purification with the indicated solvents.

7,8-Bis(trifluoromethylisoalloxazines (IVa-g, Table 2). A solution of 3 mmole of the nitroamine in 50 ml of 98% acetic acid was subjected to reduction in the presence of one fourth of a teaspoon of an alcoholic suspension of Raney nickel. A solution of the resulting o-phenylenediamine was added to a suspension of 10 mmole of the alloxan and 10 mmole of boric acid in 50 ml of acetic acid (heated to 60°), and the reaction mixture was heated at 90° for 1-2 days in the case of flavines IVa-c and at 30° in the case of IVd-g. The acetic acid was vacuum evaporated to dryness, and the residue was washed with ether until the odor of acetic acid had vanished. Compounds IVa-c were crystallized from aqueous alcohol–acetic acid, and IVd-g were crystallized from water.

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SYNTHESIS OF 3-AMINOBENZO-1,2,4-TRIAZINE 4-OXIDES

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o-Quinone monooxime guanylhydrazones, obtained from copper complexes of o-nitrosophenols, are cyclized to give the previously unknown 3-aminobenzo-1,2,4-triazine 4-oxides.

1,2-Naphthoquinone oxime guanylhydrazones, obtained from α-nitroso-β-naphthol or β-nitroso-α-naphthol and aminoguanidines, are readily cyclized to the corresponding 2-aminonaphtho[1,2-*l*]-1,3,4-triazine 1-oxides and 3-aminonaphtho[2,1-*l*]-1,2,4-triazine 4-oxides [1]. Compounds of this sort were not formed from o-nitrosophenol and 4-nitrosoresorcinol. However, we did synthesize o-benzoquinone monooxime guanylhydrazones from copper complexes of o-nitrosophenols [2]. These guanylhydrazones were easily converted to the previously undescribed 3-aminobenzo-1,2,4-triazine 4-oxides (I-IV, Table 1). Compound V was obtained from the readily accessible potassium salt of 2-nitroso-4-methylphenol and aminoguanidine sulfate without isolation of o-toluquinone monooxime guanylhydrazone, which is unstable at high temperatures.

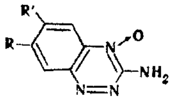
The IR spectra of triazines I-V contain intense absorption bands of the triazine C = N bond (1620-1650 cm^{-1} [3] and the N→O bond of heterocyclic compounds (1350-1370 cm^{-1}) [4]. Bands of an NH_2 group are present at 3000-3400 cm^{-1} [4].

The slow conversion of the stable copper complexes to the less stable free o-nitrosophenols, which react with excess aminoguanidine, promotes the formation of the guanylhydrazones.

EXPERIMENTAL

3-Aminobenzo-1,2,4-triazine 4-Oxides (I-IV). A 10-mmole sample of the copper complex of o-nitrosophenol was shaken at room temperature for 100 h with 70 ml of water, 40 ml of alcohol, 10 ml of 56%

TABLE 1. 3-Aminobenzo-1,2,4-triazine 4-Oxides



Compound	R	R′	mp, °C (aqueous ethanol)	Empirical formula	Found, %		Calc., %		λ_{max}, nm	lg ε	Yield, %
					N	hal	N	hal			
I	H	Cl	214—215	$C_7H_5N_4ClO$	28,4	17,8	28,4	18,1	260	4,70	75
II	CH_3	Cl	215	$C_8H_7N_4ClO$	26,5	16,9	26,6	16,9	260	4,68	92
III	H	Br	222—223	$C_7H_5N_4BrO$	23,1	32,7	23,2	33,1	260	4,59	73
IV	CH_3	Br	225	$C_8H_7N_4BrO$	21,6	31,5	21,9	31,4	265	4,66	80
V	H	CH_3	211	$C_8H_8N_4O$	31,9	—	31,8	—	255	4,71	76

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