7-CHLORO-8-TRIFLUOROMETHYL-10-(1'-GLYCITYL)ISOALLOXAZINES*

Z. V. Pushkareva, N. A. Plashkina,
V. I. Troitskaya, and L. M. Yagupol'skii

UDC 547.865.7'821'221

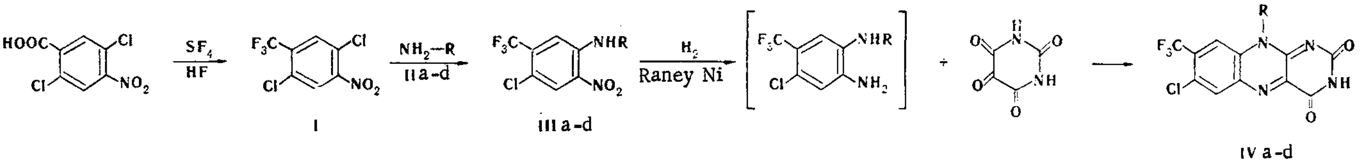
7-Chloro-8-trifluoromethylisoalloxazines with D-ribityl, D-galactyl, D-sorbityl, and L-rhamnityl substituents in the 10 position were obtained. The effect of the trifluoromethyl group on the electronic spectra of flavins containing a trifluoromethyl group was studied.

The presence of an o-7,8-dimethyl grouping in the riboflavin molecule is one of the structural factors that insure its vitamin activity. Replacement of the methyl groups by other substituents leads to the production either of riboflavin antagonists [2] or compounds with reduced vitamin activity [3], as well as substances that have antitumorigenic activity [4].

Replacement of one of the methyl groups in the riboflavin molecule by a trifluoromethyl group leads to the production of vitamin B_2 antagonists that inhibit the growth of the lactate bacteria Lactobacillus casei. The analog containing a trifluoromethyl group in the 8 position [7-methyl-8-trifluoromethyl-10-(1'-D-ribityl)-isoalloxazine] [5] has the maximum inhibiting effect.

The present paper is devoted to the synthesis of 8-trifluoromethylisoalloxazines, potential riboflavin antagonists in which additional modification of the vitamin molecule by replacement of a second methyl group by a chlorine atom is realized.

The 7-chloro-8-trifluoromethylisoalloxazines were synthesized by the scheme presented below:



II—IV a R=D-ribityl; b R=D-galactyl; c R=D-sorbityl; d R=L-rhamnityl

2,5-Dichloro-4-nitrobenzotrifluoride (I) was obtained by reaction of 2,5-dichloro-4-nitrobenzoic acid [6] with sulfur tetrafluoride in anhydrous HF. Condensation of I with polyhydroxyalkylamines II leads to substituted nitroanilines III. 7-Chloro-8-trifluoromethylisoalloxazines IV were obtained by condensation of alloxan with o-phenylenediamines — products of reduction of nitro amines III.

The preparation of a series of riboflavin analogs containing a trifluoromethyl group has been accomplished by synthesis of isoalloxazine 7-chloro-8-trifluoromethyl derivatives [1, 7].

---

*Communication IX from the series "Investigation of a Number of Riboflavin Analogs", see [1] for communication VIII.

S. M. Kirov Ural Polytechnic Institute, Sverdlovsk. Institute of Organic Chemistry, Academy of Sciences of the Ukrainian SSR, Kiev. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1686-1689, December, 1976. Original article submitted December 2, 1975.

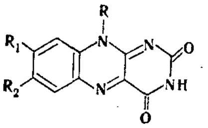
TABLE 1. UV Spectra of the Trifluoromethyl Analogs of Riboflavin (in Alcohol)

Compound	R_2	R_1	λ_{max}, nm	lg ε	Compound	R_2	R_1	λ_{max}, nm	lg ε
Va	CH_3	CH_3	449 362 270 223	4,0 3,93 4,49 4,43	IVa	Cl	CF_3	450 321 270 221	3,98 3,81 4,57 4,49
Vb	CH_3	CF_3	450 325 270 218	3,89 3,78 4,48 4,32	Vd	CF_3	Cl	430 335 272 228	4,06 3,89 4,55 4,52
Vc	CF_3	CH_3	430 339 270 225	4,01 3,82 4,48 4,36	Ve	CF_3	CF_3	432 320 276 221	3,91 3,54 4,49 4,28

TABLE 2. 2-Chloro-4-nitro-6-polyhydroxyalkylaminobenzotrifluorides (IIIa-d)

Compound	R	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
				Cl	F	N	Cl	F	N	
IIIa	Ribityl	161—162	$C_{12}H_{14}ClF_3N_2O_6$	9,8	15,1	7,8	9,5	15,2	7,5	81
IIIb	Galactyl	198—200	$C_{13}H_{16}ClF_3N_2O_7$	9,1	14,2	6,9	8,8	14,1	6,9	67
IIIc	Sorbityl	178—180	$C_{13}H_{16}ClF_3N_2O_7$	8,7	13,9	7,2	8,8	14,1	6,9	80
IIId	Rhamnityl	153—154	$C_{13}H_{16}ClF_3N_2O_6$	9,7	14,2	7,2	9,2	14,7	7,2	80

This made it possible to establish how the position of the trifluoromethyl group in the isoalloxazine ring affects the electronic spectra of the compounds of this series. We investigated the UV spectra of compounds of the general formula V:



Va-e

V R=ribityl; a $R_1=R_2=CH_3$; b $R_1=CF_3$, $R_2=CH_3$; c $R_1=CH_3$, $R_2=CF_3$; d $R_1=Cl$, $R_2=CF_3$; e $R_1=R_2=CF_3$

as compared with the spectral data of the IVa obtained by us in the present research. The UV spectra of the investigated compounds are presented in Table 1. It is evident from Table 1 that replacement of the methyl group in the 8 position of the riboflavin molecule by a trifluoromethyl group does not affect the visible portion of the spectrum (V, Vb, and VIa), whereas the long-wave absorption band in the UV region undergoes a considerable hypsochromic shift. The introduction of a trifluoromethyl group in the 7 position of the isoalloxazine ring leads to a hypsochromic shift of both long-wave bands (Va, c, e). Replacement of the methyl group by a chlorine atom both in the 7 position and in the 8 position (Vb and IVa, and Vc and IVe) does not affect the absorption spectrum substantially. The introduction of two trifluoromethyl residues in the riboflavin molecule leads to a more profound shift of both long-wave absorption bands to the short-wave region.

The $-N_1=C-C=N_5$ system, which determines the biological activity of riboflavin and its analogs [8], is responsible for the $\pi-\pi^*$ transition of the long-wave absorption band. Thus the introduction of a trifluoromethyl group in the 7 position of flavin molecules has the most substantial effect on the catalytic system of riboflavin analogs.

EXPERIMENTAL

The UV spectra of flavins IVa-d were recorded with a Perkin–Elmer 402 spectrophotometer. Chromatography was carried out on Silufol UV-254 plates in the following solvent systems: A) butyl alcohol–acetic acid–water (4 : 1 : 1) and B) propanol–0.25 N NH_4OH (3 : 1).

2,5-Dichloro-4-nitrobenzotrifluoride (I). A mixture of 7.08 g (0.03 mole) of 2,5-dichloro-4-nitrobenzoic acid, 16.2 g (0.15 mole) of SF_4, and 20 ml of anhydrous HF was heated in an autoclave at 110° for 10 h, after which the reaction product was extracted with benzene. The extract was washed with 5% sodium carbonate

TABLE 3. 7-Chloro-8-trifluoromethyl-10-R-isoalloxazines (IVa-d)

Compound	R	mp, °C (dec.)	R_f in systems		Empirical formula	Found, %			Calculated, %			λ_{max}, nm (lg ε)	Yield, %
			A	B		Cl	F	N	Cl	F	N		
IVa	Ribityl	235—236	0,73	0,82	$C_{16}H_{14}ClF_3N_4O_6$	8,1	12,9	12,7	7,9	12,7	12,5	450 (3,98); 321 (3,81); 270 (4,57); 221 (4,49)	94
IVb	Galactyl	225—226	0,72	0,82	$C_{17}H_{16}ClF_3N_4O_7$	6,9	11,7	11,1	7,4	11,9	11,6	450 (3,90); 321 (3,75); 270 (4,44); 220 (4,41)	67
IVc	Sorbityl	226—227	0,71	0,82	$C_{17}H_{16}ClF_3N_4O_7$	7,4	11,4	11,6	7,4	11,9	11,6	449 (3,99); 322 (3,73); 269 (4,43); 219 (4,35)	81
IVd	Rhamnityl	256—257	0,74	0,84	$C_{17}H_{16}ClF_3N_4O_6$	7,7	12,8	12,2	7,6	12,3	12,1	451 (3,95); 322 (3,79); 271 (4,61); 222 (4,50)	75

solution and water and dried with $MgSO_4$ containing NaF. The benzene was removed by distillation, and benzotrifluoride I was distilled to give 6.3 g (81%) of a product with bp 115° (13 mm). The product began to crystallize on standing to give a solid mp 30-32°. Found: Cl 27.2; F 22.4; N 5.2%. $C_7H_2Cl_2F_3NO_2$. Calculated: Cl 27.3; F 21.9; N 5.4%.

2-Chloro-4-nitro-5-polyhydroxyalkylaminobenzotrifluorides (IIIa-d). A 0.01-mole sample of I was refluxed in alcohol with 0.03 mole of glycamines IIa-d, after which the solvent was vacuum evaporated, and the residue was refluxed in benzene. The solid was removed by filtration and crystallized successively from alcohol–benzene (3 : 1) and aqueous alcohol (Table 2).

7-Chloro-8-trifluoromethylisoalloxazines (IVa-d). An acetic acid solution of o-phenylenediamine, obtained as a result of reduction of 2 mmole of N-substituted nitroanilines IIIa-d, was added to a suspension of 6 mmole of alloxan and 6 mmole of boric acid in glacial acetic acid, and the mixture was allowed to stand at room temperature for 2 days. The acetic acid was vacuum evaporated, and the residue was washed with ether and crystallized from water. The properties of the compounds obtained are presented in Table 3.

LITERATURE CITED

1. N. A. Plashkina, V. I. Troitskaya, Z. V. Pushkareva, and T. P. Ryapsova, Khim. Geterotsikl. Soedin., No. 8, 1136 (1976).
2. R. Barlow, J. Chem. Soc., 2225 (1951).
3. P. Karrer and T. Quibell, Helv. Chim. Acta, 19, 1034 (1936).
4. C. Shunk. F. Koniuszy, and K. Folkers, J. Am. Chem. Soc., 74, 4251 (1952).
5. G. M. Shavlovskii, and V. P. Senchina, Mikrobiologiya, 7, 367 (1972).
6. H. Goldstein and R. Jaunin, Helv. Chim. Acta, 34, 1860 (1951).
7. N. A. Plashkina, V. I. Troitskaya, L. M. Yagupol'skii, and Z. V. Pushkareva, Khim. Geterotsikl. Soedin., No. 11, 1567 (1975).
8. L. S. Tul'chinskaya and V. M. Berezovskii, Zh. Obshch. Khim., 40, 1252 (1970).