INVESTIGATION OF RIBOFLAVIN ANALOGS

IV. Riboflavin Analogs Containing a Trifluoromethyl Group*

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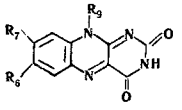
Trifluoromethyl derivatives of riboflavin, galactoflavin, and 9-(β-hydroxyethyl) isoalloxazine have been synthesized for biological tests.

As is well known, the synthesis of analogs of natural riboflavin using various methods for modifying its structure has led to the preparation of a number of substances capable of the "competing inhibition" of enzymatic reactions (antimetabolites), among which have been found compounds capable of inhibiting the growth of tumors in animal experimentation [2].

One of the proven routes for modifying the molecules of metabolites is the replacement of hydrogen atoms by fluorine atoms, which does not disturb the geometry of the molecule but has a marked influence on the electron-density distribution. Thus, 5-fluorouracil has found practical use in oncological practice, and in the fluoromethyl derivatives of benzimidazole possess a considerable activity against a number of bacteria and viruses.

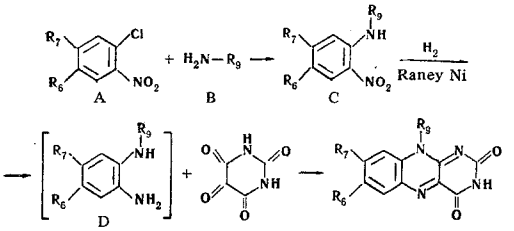
The present work was devoted to a systematic study of one of the methods of modifying the riboflavin molecule, comprising the replacement of the methyl group in the isoalloxazine ring by a trifluoromethyl group. It is just this modification, which has not been used previously in the isoalloxazine series, which permits the maximum retention of the geometry of the riboflavin molecule.

For this purpose we selected the following series of compounds of the general formula (Table 2):



Compounds I, II, and III were intended to elucidate the influence of a CF_3 group on biological activity with the retention of a methyl group in position 7 of the isoalloxazine ring and with its absence while retaining a ribityl residue at $N_{(3)}$. Compounds IV, V, and VI have a similar structure, but in this case the CF_3 group is not in the riboflavin skeleton but in the molecule of an antimetabolite, galactoflavin. Compounds VII, VIII, and IX are constructed on the same principle but with a simplified hydroxyalkyl residue (β-hydroxyethyl).

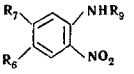
The synthesis was carried out by the following route:



*For part III, see [1].

The initial o-chloronitrobenzotrifluorides (A) were obtained by published methods [4–6]. 1-Amino-1-deoxygalactitol was obtained by the reduction of galactose phenylhydrazone as described by Wolfrom et al. [7]. The synthesis of 1-amino-1-deoxyribitol was carried out similarly but it was not isolated in the form of the Schiff's base with salicylaldehyde; the aqueous solution after reduction was treated repeatedly with benzene, the water distilled off in vacuum, and the residual sirupy product was used in the reactions with the o-chloronitrobenzotrifluorides. The replacement of the halogen in compounds A by amino alcohols took place under roughly the same conditions: by boiling in pyridine or in higher alcohols (amyl or butyl alcohol) for from 8–12 hr. The nitroamines C produced consisted of yellow or orange substances crystallizing well from water or ethanol. The physical constants, yields, and elementary analyses of the intermediate nitroamines are given in Table 1.

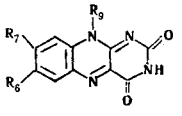
Table 1



R_6	R_7	R_9	Mp, °C	Empirical formula	Found, %			Calculated, %			Yield, %
					C	H	N	C	H	N	
CF_3	CH_3	d-Ribityl	179	$C_{13}H_{17}F_3N_2O_6$	44.30	4.79	7.88	44.01	4.70	7.96	40
H	CF_3	d-Ribityl	173	$C_{12}H_{15}F_3N_2O_6$	42.61	4.64	8.35	42.35	4.41	8.20	21
CF_3	H	d-Ribityl	161	$C_{12}H_{15}F_3N_2O_6$	42.73	4.67	8.00	42.35	4.41	8.20	37
CF_3	CH_3	d-Galactyl	250	$C_{14}H_{18}F_3N_2O_7$	43.42	5.03	7.40	43.75	4.94	7.29	23
H	CF_3	d-Galactyl	223	$C_{13}H_{17}F_3N_2O_7$	42.23	4.96	7.49	42.16	4.61	7.57	14
CF_3	H	d-Galactyl	209	$C_{13}H_{17}F_3N_2O_7$	42.55	4.72	7.48	42.16	4.61	7.57	44
CF_3	CH_3	CH_2CH_2OH	136	$C_{10}H_{11}F_3N_2O_3$	45.80	4.14	10.65	45.41	4.18	10.61	91
H	CF_3	CH_2CH_2OH	109	$C_9H_9F_3N_2O_3$	43.50	3.72	11.70	43.20	3.61	11.20	84
CF_3	H	CH_2CH_2OH	76	$C_9H_9F_3N_2O_3$	43.31	3.55	11.50	43.20	3.61	11.20	75

The reduction of compounds C was carried out catalytically in acetic acid and after the separation of the catalyst the acetic acid solution of the o-diamine D was used for the condensation with alloxan, which was performed in the presence of boric acid. The isoalloxazines sythesized consisted of bright yellow substances crystallizing well from water or acetic acid and melting with decomposition. 9-(1'-d-Galactyl)-7-trifluoromethylisoalloxazine could not be synthesized by this method. The physical constants, yields, and elementary analyses of the isoalloxazines obtained are given in Table 2.

Table 2



Compound	R_6	R_7	R_9	Decomp. p., °C	Empirical formula	Found, %			Calculated, %			Yield,* %
						C	H	N	C	H	N	
I	CF_3	CH_3	d-Ribityl	244—245	$C_{17}H_{17}F_3N_4O_6$	47.16	4.27	13.14	47.44	3.96	13.02	52
II	H	CF_3	d-Ribityl	236—238	$C_{16}H_{15}F_3N_4O_6$	45.64	3.97	13.50	46.15	3.60	13.46	39
III	CF_3	H	d-Ribityl	240—242	$C_{16}H_{15}F_3N_4O_6$	45.91	3.70	13.18	46.15	3.60	13.46	40
IV	CF_3	CH_3	d-Galactyl	238—240	$C_{18}H_{19}F_3N_4O_7$	46.29	4.28	12.26	46.96	4.13	12.17	41
VI	CF_3	H	d-Galactyl	241—242	$C_{17}H_{17}F_3N_4O_7$	45.25	4.00	12.86	45.86	3.81	12.55	35
VII	CF_3	CH_3	CH_2CH_2OH	285—288	$C_{14}H_{11}F_3N_4O_3$	49.13	3.40	16.39	49.41	3.24	16.47	58
VIII	H	CF_3	CH_2CH_2OH	279—281	$C_{13}H_9F_3N_4O_3$	47.78	2.97	17.10	47.85	2.77	17.18	49
IX	CF_3	H	CH_2CH_2OH	297—281	$C_{13}H_9F_3N_4O_3$	47.95	2.85	17.34	47.85	2.77	17.18	53

*Figures calculated on the intermediate nitroamine.

EXPERIMENTAL

N-(1'-d-Ribityl)-5-methyl-2-nitro-4-trifluoromethylaniline (X). A mixture of 1 g (0.0042 mole) of 4-chloro-6-methyl-3-nitrobenzotrifluoride (XI) and 2.5 g (0.016 mole) of 1-amino-1-deoxyribitol in 8 ml of amyl alcohol was boiled for 12 hr. The hot dark red solution was decanted from the unchanged d-ribamine and cooled. The yellow precipitate that deposited was filtered off, washed with ether, and crystallized from water.

N-(1'-d-Ribityl)-2-nitro-4-trifluoromethylaniline and N-(1'-d-ribityl)-2-nitro-5-trifluoromethylaniline. These were obtained in a similar manner to X.

5-Methyl-9-(1'-d-ribityl)-6-trifluoromethylisoalloxazine (I). Raney nickel was added to a mixture of 0.5 g (0.0014 mole) of X and 20 ml of acetic acid, and hydrogenation was carried out at atmospheric pressure and room temperature for 8 hr. The catalyst was filtered off and the resulting faintly greenish solution of the o-diamine was added to a suspension of 0.25 g (0.0017 mole) of alloxazine and 0.3 g of boric acid in 25 ml of acetic acid. The reaction mixture was kept at 50° C for 1 hr and at room temperature for 1 day. The acetic acid was evaporated in vacuum, the residue was triturated with ether, and the substance was twice crystallized from 10% acetic acid.

Compounds II, III, IV, and VI were obtained similarly to I and were crystallized from water.

N-(1'-d-Galactyl)-5-methyl-2-nitro-4-trifluoromethylaniline (XII). A mixture of 1.5 g (0.0063 mole) of XI, 2.7 g (0.01 mole) of 1-amino-1-deoxygalactitol hydrobromide, and 1.6 g (0.02 mole) of anhydrous sodium acetate was boiled in pyridine for 12 hr. The hot solution was filtered, the pyridine was evaporated off in vacuum, and the residue was treated with petroleum ether several times and was then boiled in water. After cooling, the yellow-orange precipitate was filtered off and crystallized from ethanol.

N-(1'-d-galactyl)-2-nitro-4-trifluoromethylaniline and N-(1'-d-galactyl)-2-nitro-5-trifluoromethylaniline. These were obtained in a similar manner to XII and were crystallized from water.

N-(β-Hydroxyethyl)-5-methyl-2-nitro-4-trifluoromethylaniline (XIII). A mixture of 0.9 g (0.004 mole) of XI and 0.85 g (0.0014 mole) of monoethanolamine was boiled in butanol for 8 hr. The butanol was distilled off in vacuum, the residue was treated with water and the bright yellow substance was filtered off and crystallized from aqueous methanol.

N-(β-Hydroxyethyl)-2-nitro-4-trifluoromethylaniline and N-(β-hydroxyethyl)-2-nitro-5-trifluoromethylaniline. These were obtained in a similar manner to XIII. In the latter case the nitroamine separated out in the crystalline form when the butanol was distilled off.

9-(β-Hydroxyethyl)-7-methyl-6-trifluoromethylisoalloxazine (VII). Compound XIII (1 g; 0.0038 mole) was hydrogenated in acetic acid solution as described above. Then the acetic acid solution of the o-diamine was poured into a mixture of 0.9 g (0.0064 mole) of alloxan and 0.95 g of boric acid in 20 ml of acetic acid. The reaction mixture was kept in the boiling water bath for 2 hr 30 min, the acetic acid was evaporated in vacuum to 1/4 of its original volume, the residue was poured into water and the yellow precipitate that deposited was filtered off, washed with water and with ethanol, and crystallized from 70% acetic acid.

Compounds VIII and IX were obtained in a similar manner to VII.

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