STUDIES ON RIBOFLAVIN ANALOGS

VI. 7-Trifluoromethylisoalloxazines*

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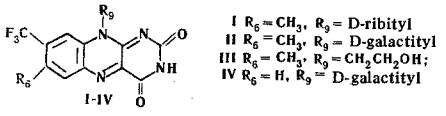
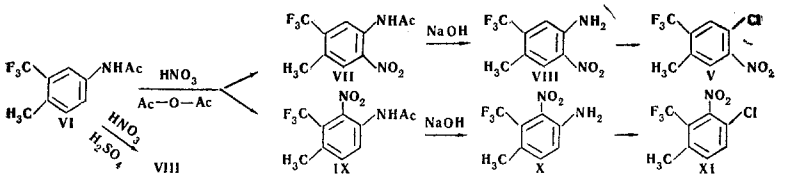
New trifluoromethyl analogs of riboflavin have been synthesized for biological tests. The synthesis of the intermediate products – 5-chloro-2-methyl-4-nitrobenzotrifluoride and 3-chloro-6-methyl-2-nitrobenzotrifluoride – has been developed.

Studying one of the methods for the modification of the riboflavin molecule, namely the replacement of one of its methyl groups by a trifluoromethyl group, we previously prepared 6-trifluoromethyl-, 7-methyl-6-trifluoromethyl-, and 7-trifluoromethylisoalloxazines with various substituents on N_9 [2]. In order to study the interrelationship of structure and properties, including biological activity, the necessity arose for synthesizing, in addition to the trimethyl derivatives of isoalloxazine mentioned, the 7-trifluoromethyl riboflavin analogs isomeric with them having the following formulas:



The present paper describes the synthesis of 6-methyl-9-(D-ribit-1'-yl)-7-trifluoromethylisoalloxazine (I), which has been reported briefly previously [3], and of 9-(D-galactit-1'-yl)-6-methyl-7-trifluoromethyl-, 6-methyl-9-(β-hydroxyethyl)-7-trifluoromethyl, and 9-(D-galactit-1'-yl)-7-trifluoromethylisoalloxazines (II), (III), and (IV). The synthesis of compounds I-IV was effected by a method similar to that for the preparation of the flavins [2], consisting in the replacement of the chlorine in 5-chloro-2-methyl-4-nitrobenzotrifluoride (V) or in 3-chloro-4-nitrobenzotrifluoride [2] by an amino alcohol residue, the reduction of the resulting nitroamine to a primary-secondary o-diamine, and the condensation of the latter with alloxan. Compound V was obtained in the following way, starting from 5-acetylamino-2-methylbenzotrifluoride (VI) [3].



The nitration of VI with acetyl nitrate leads to two isomeric o-nitroamines: 5-amino-2-methyl-4-nitrobenzotrifluoride (VIII) and 3-amino-6-methyl-2-nitrobenzotrifluoride (X). Their structures were confirmed by reduction to the o-diamines and the diazotization of the latter. In this process the nitroamine VIII gave a benzotriazole identical with the 6-methyl-5-trifluoromethylbenzotriazole described in the literature [4], and the nitroamine X gave the previously unknown 5-methyl-4-trifluoromethylbenzotriazole (XII). Compound VIII was obtained fairly unambiguously by the nitration of VI with nitrating mixture.

Compounds VIII and X, after diazotization and the replacement of the diazonium group by chlorine, gave, respectively, 5-chloro-2-methyl-4-nitrobenzotrifluoride (V) and 3-chloro-6-methyl-2-nitrobenzotrifluoride (XI). The latter was of interest for the synthesis of trifluoromethyl analogs of isoriboflavin, but the chlorine in this compound could not be replaced by any amine residue.

*For part V, see [1].

Table 1. 7-Trifluoromethylisoalloxazines

Compound	R_6	R_9	Mp, °C*	Empirical formula	Found, %		Calculated, %		Yield, %†
					N	F	N	F	
I	CH_3	D-Ribityl	236—237	$C_{17}H_{17}F_3N_4O_6$	13,2	13,0	13,0	13,1	55
II	CH_3	D-Galactityl	232—233	$C_{18}H_{19}F_3N_4O_7$	11,7	12,3	12,2	12,4	51
III	CH_3	CH_2CH_2OH	>300	$C_{14}H_{11}F_3N_4O_3$	16,6	17,2	16,4	16,8	65
IV	H	D-Galactityl	227—228	$C_{17}H_{17}F_3N_4O_7$	12,3	13,2	12,6	12,8	41

*Melts with decomposition; I, II, and IV were recrystallized from water, and III from 70% AcOH.
†Calculated on the intermediate nitroamines.

EXPERIMENTAL

Nitration of 5-acetylamino-2-methylbenzotrifluoride (VI). A) The nitration of VI with acetyl nitrate was carried out in a similar manner to the nitration of 3-acetylaminobenzotrifluoride [5]. During the reaction, the 3-acetylamino-6-methyl-2-nitrobenzotrifluoride (IX), mp 146°C (from aqueous ethanol) deposited from the reaction mixture. Found %: N 10.7; F 21.7. $C_{10}H_9F_3N_2O_3$. Calculated %: N 10.7; F 21.8. To separate the 5-amino-2-methyl-4-nitrobenzotrifluoride (VIII) and the 3-amino-6-methyl-2-nitrobenzotrifluoride (X), gaseous HCl was passed through their benzene solution. The flocculent precipitate of the hydrochloride of X that deposited was filtered off and treated with aqueous ammonia, and the X was crystallized from petroleum ether, mp 73°C. Found %: N 13.2. $C_8H_7F_2N_2O_2$. Calculated %: N 12.7. After the benzene had been blown off and the residue had been crystallized from aqueous ethanol, VIII was obtained with mp 108°C. Found %: N 12.6; F 25.8. $C_8H_7F_3N_2O_2$. Calculated %: N 12.7; F 25.9. The yield of each isomer was 45%.

B) At 0°C, 3 g (14 mM) of VI was added in small portions to a nitrating mixture consisting of 1 ml of HNO_3 (d 1.5) and 3 ml of H_2SO_4 (d 1.84), and the mixture was kept at 0°C for 2 hr and was then poured onto ice and made strongly alkaline with 20% NaOH solution, and the VIII was distilled off with steam; mp 108°C (from aqueous ethanol). Yield 2.2 g (80%).

5-Methyl-4-trifluoromethylbenzotriazole (XII). This was obtained in a similar manner to 6-methyl-5-trifluoromethylbenzotriazole [4]; colorless substance readily subliming at 160-180°C, mp 213°C (from aqueous ethanol). Found %: N 21.2. $C_8H_6F_3N_3$. Calculated %: N 20.9.

5-Chloro-2-methyl-4-nitrobenzotrifluoride (V). At 15-20°C, a solution of 5 g (23 mM) of VIII in 10 ml of glacial acetic acid was added slowly to a solution of 1.75 g (25 mM) of $NaNO_2$ in 12 ml of H_2SO_4, d 1.84, and the mixture was kept for 30 min; the resulting diazonium solution was poured into a solution of 2.5 g (25 mM) of cuprous chloride in 10 ml of conc. HCl and the mixture was heated in the water bath for 20 min and then diluted with water, and the product was extracted with ether. The ethereal extracts were washed with water, with 20% sodium carbonate, and with water again and were dried with $CaCl_2$, the ether was evaporated off, and the V was distilled in vacuum, bp 109-110°C (8 mm), mp 45°C (from aqueous ethanol). Yield 4.4 g (81%). Found %: N 6.2; Cl 15.0. $C_8H_5ClF_3NO_2$. Calculated %: N 5.8; Cl 14.8.

3-Chloro-6-methyl-2-nitrobenzotrifluoride (XI). This was obtained in a similar manner to V. After dilution of the reaction mixture with water, the light yellow precipitate of XI was filtered off and washed with 10% HCl and with water; mp 78°C (from aqueous ethanol). Yield 77%. Found %: N 6.2; Cl 14.7. $C_8H_5ClF_3NO_2$. Calculated %: N 5.8; Cl 14.8.

4-Methyl-2-nitro-N-(D-ribit-1-yl)-5-trifluoromethylaniline (XIII). A mixture of 2 g (8.4 mM) of V and 4.5 g of 80% 1-amino-1-deoxyribitol was boiled in isoamyl alcohol for 16 hr, the solution was decanted from the resin, and cooled, and the XIII was filtered off, mp 156°C (from water). Yield 0.95 g (32%). Found %: N 8.0; F 16.1. $C_{13}H_{17}F_3N_2O_6$. Calculated %: N 7.9; F 16.0.

N-(D-Galactit-1-yl)-4-methyl-2-nitro-5-trifluoromethylaniline (XIV). This was obtained in a similar manner to XIII. Yield 28%. Mp 226°C (from aqueous ethanol). Found %: N 6.7; F 15.2. $C_{14}H_{19}F_3N_2O_7$. Calculated %: N 7.3; F 14.8.

N-β-Hydroxyethyl)-4-methyl-2-nitro-5-trifluoromethylaniline (XV). A mixture of 1 g (4.2 mM) of V and 0.92 g (15 mM) of ethanolamine was boiled in butanol for 12 hr. The butanol was distilled off in vacuum, the residue was washed with water, and the red crystals of XV were filtered off. Yield 0.8 g (73%), mp 131°C (from petroleum ether). Found %: N 10.9; F 21.2. $C_{10}H_{11}F_3N_2O_3$. Calculated %: N 10.6; F 21.6.

6-Methyl-9-(D-ribit-1-yl)-7-trifluoromethylisoalloxazine (I). In 20 ml of ethanol in the presence of Raney nickel, 0.7 g (2 mM) of XIII was reduced with hydrazine hydrate, the catalyst was filtered off, the alcohol was evaporated in vacuum, and the residue was washed with water. The white precipitate of the o-diamine was filtered off, dried, and dissolved in 5 ml of acetic acid, and the solution was added to a mixture of 0.45 g (3.2 mM) of alloxan and 0.47 g of boric acid in 30 ml of acetic acid. The mixture was kept at 40°C for 1 hr and at room temperature for 2 days. The highly fluorescent solution was filtered and evaporated in vacuum to dryness, the residue was treated with ether, the yellow-brown precipitate was filtered off and dissolved in the minimum amount of ethanol (in the cold), and the I was precipitated with ether. Compounds II, III, and IV* were obtained similarly. The physical constants, elementary analyses, and yields of the flavins I-IV are given in the table.

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*For the synthesis of N-(D-galactit-1-yl)-2-nitro-5-trifluoromethylaniline, see [2].