A NEW TRIFLUOROMETHYL ANALOG OF RIBOFLAVIN

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In making a systematic study of one of the methods of modifying the molecule of riboflavin in order to obtain biologically-active compounds, we have previously obtained 7-methyl-6-trifluoromethyl-, 6-trifluoromethyl-, and 7-trifluoromethylisoalloxazines with various substituents on N_9 [1]. Substances closest in chemical structure to natural riboflavin are of the most interest. These include 7-methyl-9-(1'-d-ribityl)-6-trifluoromethylisoalloxazine, which exhibited a comparatively high toxicity in preliminary tests (G. N. Platonova). Its synthesis was recently described by L. M. Yagupol'skii et al. [2]. Here we report the synthesis of the isomeric 6-methyl-9-(1'-d-ribityl)-7-trifluoromethylisoalloxazine (**I**), obtained for a comparative study of biological activity and of the influence of the trifluoromethyl group on the redox properties of the isoalloxazines. The starting material was 2-methyl-5-nitrobenzotrifluoride, which was obtained as described by L. M. Yagupol'skii [3] and was reduced to the corresponding amine. The latter was converted with acetic anhydride into 5-acetylamino-2-methylbenzotrifluoride (**II**) and was nitrated with nitrating mixture. After deacylation, the amino group of the 5-amino-2-methyl-4-nitrobenzotrifluoride (**III**) was replaced by chlorine in the usual way via the diazonium compound, and 5-chloro-2-methyl-4-nitrobenzotrifluoride (IV) was obtained; on being boiled in isoamyl alcohol with d-ribitylamine, this gave 2-methyl-4-nitro-5-(1'-d-ribitylamino)benzotrifluoride (V). The latter was hydrogenated using Raney nickel in glacial acetic acid and, after the removal of the catalyst, the o-diamine formed, without isolation from the acetic acid solution, was subjected to condensation with alloxan in the presence of boric acid. Some characteristics of the newly-obtained compounds are given in the table.

Compound I consists of small yellow crystals soluble in acetic acid and sparingly soluble in water and ethanol.

Compound	Mp, °C	Solvent	Empirical formula	Found, %		Calculated, %		Yield, %
				N	F	N	F	
II	103	Aqueous ethanol	$C_{10}H_{10}F_3NO$	6.10	—	6.45	—	83
III	108	"	$C_8H_7F_3N_2O_2$	13.21	—	12.72	—	80
IV	45	"	$C_8H_5ClF_3NO_2$	6.10	23.11	5.85	23.75	81
V	156—7	Water	$C_{13}H_{17}F_3N_2O_5$	8.08	16.09	7.90	16.02	28
I	232—3 (decomp.)	"	$C_{17}H_{17}F_3N_4O_6$	13.30	13.01	13.04	13.12	57

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SYNTHESIS OF 2-(5'-NITRO-2'-FURYL)BENZIMIDAZOLES

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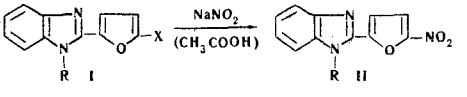
The high bactericidal activity of 2-(5'-nitro-2'-furyl)benzimidazole and its 1-methyl derivative, and also the extremely laborious method of its preparation due to the complexity of the synthesis of the initial hydrochloride of 5-nitrofuran-2-carbimidic ester [1, 2] induced us to search for a simpler route for the preparation of these compounds.

2-(5'-Nitro-2'-furyl)benzimidazoles (II)

Compound	R	Mp, °C (ethanol)	Empirical formula	N, % found	N, % calculated	Yield, %
IIa	H	230—231	$C_{11}H_7N_3O_3$	18.50	18.33	90
II_b	CH_3	212—213	$C_{12}H_9N_3O_3$	17.41	17.28	85
IIc	$CH_2C_6H_5$	160—161	$C_{18}H_{13}N_3O_3$	13.10	13.15	80

We have found that the action of 3 moles of sodium nitrite on solutions of 2-(5'-halo-2'-furyl)benzimidazoles (I) [3] in glacial acetic acid first at room temperature and then at the boil for 2-3 hr gives 2-(5'-nitro-2'-furyl)benzimidazoles (**II**) with a high degree of purity in yields of 80-90%.



R = H, CH_3, $CH_2C_6H_5$ X = Cl, Br

Compounds **IIa** and **IIc** and their methiodides were also obtained from **IIa** in a similar manner to the methods described previously [3].

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2 July 1968 Rostov-on-Don State University

BROMINE MOBILITY IN 2-ACETYL-3-BROMOFURAN

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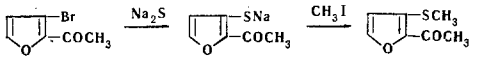
In preceding papers it was shown that the halogen atoms in the α-position of disubstituted furan derivatives readily undergo a nucleophilic substitution reaction with sodium sulfide [1], sodium thiosulfate [2], and mercaptides [3]. The mobility of the halogen atom in the β position of the furan ring has been studied only for monosubstituted halofurans. The investigations showed that halogen in the β position of furan is not active in substitution reactions.

Continuing investigations on the mobility of halogen in a furan ring, we have studied the substitution of the bromine in 2-acetyl-3-bromofuran (I) with sodium sulfide. The reaction takes place readily under conditions analogous for the replacement of the bromine in 5-acetyl-2-bromofuran:



Without being isolated, the resulting sodium salt of 2-acetyl-3-mercaptofuran was converted with methyl iodide into 2-acetyl-3-methylthiofuran (II), the structure of which was confirmed by its IR spectrum and the preparation of its oxime.

2-Acetyl-3-methylthiofuran (II). A mixture of 18.9 g of **I**, 24 g of sodium sulfide, and 100 ml of water was boiled for 4 hr. The dark solution formed was filtered and boiled for another 3 hr with 16 g of methyl iodide. The **II** that separated out was extracted with ether and crystallized from aqueous ethanol. Yield 46%. Mp 54° C. Found, %: C 53.36; H 5.03. Calculated for $C_7H_8O_2S$, %: C 53.44; H 5.13. **Oxime of II.** Mp 65.6–66° C. Found, %: N 8.01. Calculated for $C_7H_9NO_2S$, %: N 8.18.

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OPENING OF THE IMIDAZOLE RING IN IMIDAZO[1,2-a]BENZIMIDAZOLES

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Reduction of 9-methyl-3-nitro-2-phenylimidazo[1,2-a]benzimidazole (**Ia**) [1] with stannous chloride leads to a complex of a tin salt and the amine (**IIa**) from which it is impossible to liberate the free amine. We have established that boiling the complex with highly dilute alcohol causes the opening of the imidazole ring attached to the benzimidazole nucleus at the bond 3-4 with the formation of 2-(α-carboxybenzylamino)-1-methylbenzimidazole (**IIIa**), which separated from the reaction mixture in the form of the hydrochloride with a yield of 94%. Similar conversions are observed for the 9-benzyl derivative (**Ib**) also. Thus, in present case the imidazole ring opens in a different manner from that in the molecule of 9-methyl-2-phenylimidazo[1,2-a]benzimidazole methiodide, where the C=N bond at the "guanidine" carbon atom is cleaved.