SYNTHESIS OF 8-TRIFLUOROMETHYLPURINES

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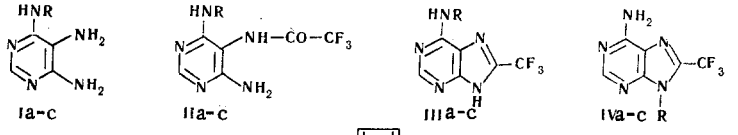
The corresponding N_4-trifluoromethylpyrimidines, which are cyclized to 8-trifluoromethylpurines at 160-185°C, are obtained by the reaction of N_4-substituted 4,5,6-triaminopyrimidines with trifluoroacetic anhydride.

8-Trifluoromethylpurines have not been described in the literature. We have synthesized 6-benzyl- and 6-furfurylamino-8-trifluoromethylpurines (IIIa, b) for a comparison of their physiological activity with that of the corresponding 8-methylpurines.

Triaminopyrimidines I are not cyclized by heating with trifluoroacetic anhydride and orthotrifluoroacetic ester. Acyl derivatives II were obtained by refluxing I in a benzene solution with trifluoroacetic anhydride. The cyclization of these compounds could not be carried out by the known methods for the cyclization of 4-amino-5-acylaminopyrimidines [1-4]. The products of the cyclization (III and IV) are formed as the result of cleavage of water on heating IIa-c above their melting points (see Table 1).



a $R = CH_2C_6H_5$; b $R = CH_2$–(furfuryl); c $R = m\text{-}ClC_6H_4$

Isomers III and IV are separated by dissolving III in 2-N NaOH. In all cases, III is obtained in higher yields than IV. The basicity of the secondary amino group does not affect the direction of the cyclization reaction, as confirmed by the same yields obtained for IIIa and IIIc.

Compounds IIa-c have two melting points – the higher melting point corresponds to the cyclization products.

EXPERIMENTAL

4-Amino-5-trifluoroacetamido-6-benzylaminopyrimidine (IIa), and 4-Amino-5-trifluoroacetamido-6-furfurylaminopyrimidine (IIb). A mixture of 0.015 mole of Ia or 0.015 mole of Ib, 0.015 mole of trifluoroacetic anhydride, and 50 ml of absolute benzene was refluxed for 2 h. The precipitate was filtered and dissolved in 2-N NaOH. The solution was filtered with charcoal and treated with acetic acid to precipitate 90-95% of II. Colorless silky needles of IIa with mp 171-172° (decomp.) were obtained by recrystallization

TABLE 1. 8-Trifluoromethylpurines

Compound	Mp, °C	Crystallization solvent	Empirical formula	Found %		Calc. %		Yield, %
				F	N	F	N	
IIIa	256—257	Benzene	$C_{13}H_{10}F_3N_5$	19,42	23,78	19,43	23,88	53
IVa	178—179	Ethanol	$C_{13}H_{10}F_3N_5$	19,44	23,90	19,43	23,88	14
IIIb	238—240	Chloroform	$C_{11}H_8F_3N_5O$	20,21	24,85	20,12	24,73	66
IVb	185—187	Chloroform	$C_{11}H_8F_3N_5O$	20,33	25,06	20,12	24,73	18
IIIc	266—267	Methanol	$C_{12}H_7ClF_3N_5$	18,18	22,23	18,11	22,25	51
IVc	176—178	Benzene	$C_{12}H_7ClF_3N_5$	18,17	22,33	18,11	22,25	23

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from chloroform. Found %: F 18.04; N 22.45. $C_{13}H_{12}F_3N_5O$. Calculated %: F 18.31; N 22.50. Compound IIb had mp 181-182° (decomp.). Found %: F 18.69; N 23.02. $C_{11}H_{10}F_3N_5O_2$. Calculated %: F 18.92; N 23.25. Compounds II do not melt sharply since cyclization begins near their melting points, and the final melting points of isomers III are observed.

4-Amino-5-trifluoroacetamido-6-(m-chlorophenylamino)pyrimidine (IIc). This was similarly obtained but was not purified by recrystallization since it partially cyclizes on heating and gives analytical results that are too high. The product had mp 150-152° and was identified by cyclization to IIIc and IVc.

Cyclization of IIa-c. Compounds II (0.05 mole) were heated on an oil bath for 15-20 min at 160-185°. Water evolution was observed. After cooling, the reaction mass was treated with 2-N NaOH (three 10-ml portions). The alkaline filtrates were neutralized with acetic acid, and the precipitated III were filtered and recrystallized. Compounds IV, which are insoluble in NaOH, were washed with water and recrystallized. Compounds III and IV crystallized in the form of fine, colorless needles.

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