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REACTION OF TETRAAMINOPYRIMIDINE WITH 1-ARYLSULFONYL-4-METHYL-IMIDAZOLIN-2-ONES

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Previously [1] it was established that in aqueous medium, in the presence of piperidine, tetraaminopyrimidine (I) reacts with the 1-(benzenesulfonyl)-, 1-tosyl-, and 1-(4'-chloro-benzenesulfonyl)-4-methylimidazolin-2-ones (IIa-c) to give mixtures of the 6- and 7-methyl-2,4-diaminopteridines (IIIa, b):



(IIa-i): $R = C_6H_5$ (a), $C_6H_4CH_{3-4'}$ (b), C_5H_4Cl-4' (c), $C_6H_1OCH_{3-4'}$ (d), C_6H_4F-4' (e), $C_6H_3Cl_2-2'$, 5' (f), $C_6H_3Br_2-2'$, 5' (g), C_6H_4Br-4' (h), $C_6H_1NO_2-4'$ (j).

In the present paper, in order to study the effect of the character of the substituents in the aromatic ring on the structural direction of this reaction, we condensed (I) with other 1-(arylsulfonyl)-4-methylimidazolin-2-ones (IId-i) (Tables 1 and 2).

As can be seen from Table 2, in their effect on the relative yield of the 7-methyl isomer (IIIb), substituents in the p-position of the aromatic ring of (IIa-i) fall into the following order: $Cl < CH_3O < F < CH_3 < Br < H < NO_2$. An examination of this series permits concluding that an electron-donor character of the substituent favors the formation of the 6-methyl isomer (IIIa), while an electron-acceptor character favors the formation of the 7-methyl isomer (IIIb). The observed rule can be explained if we start with the previously [1] expressed concepts regarding the mechanism for the reaction of (I) with (IIa-c), which consists in the prior hydrolytic cleavage of (IIa-c) to the N-arylsulfonylaminoacetone (IV) and the subsequent cyclocondensation of (IV) with (I). In the next step of the process ketone (IV) reacts with (I) to give an equilibrium mixture of two imines (Va, b), in which imine (Va) predominates due to the higher nucleophilicity of the amino group at C⁵.

The cyclization of imines (Va, b), with cleavage of the arylsulfamido moiety, and subsequent dehydrogenation of the intermediate dihydropteridines (VIa, b) by atmospheric oxygen, lead to the (IIIa, b) mixtures:



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Compound	Yield. %	mp, °C		μ τ ι	ound/calc.,	10		Empirical formula	TLF R _f (EA - benzene,
(IId-i)		(solvent)	U	H	z	so	Hal		3 ; 2) *
q	06	136138	<u>57.25</u> 56,95	$\frac{5.23}{5,09}$	8.52 8,57	$\frac{9.54}{9.81}$	I	$C_{11}H_{12}N_2O_4S \cdot 0,75C_6H_6$	0,22
Ð	87	162–163 (EA)	46.73	$\frac{3.57}{3,54}$	$\frac{11.33}{10,93}$	$\frac{12.45}{12.51}$	7.53 7,41	$C_{10}H_9N_2O_3SF$	0,34
ېې	56	198-199 (decomp.) (EA)	I	ł	9,33 9,12	$\frac{10.51}{10,44}$	<u>23,23</u> 23,08	$\mathrm{C}_{10}\mathrm{H_8N_2O_3SCl_2}$	0,53
50	75	217-218 (decomp.) (EA - alcohol. 8.1)	$\frac{30.65}{30,33}$	$\frac{2.03}{2.04}$	<u>70,7</u>	I	I	$\mathrm{G}_{10}\mathrm{H}_8\mathrm{N}_2\mathrm{O}_3\mathrm{SBr}_2$	0,46
, L	80	192-193 (EA - alcohol,	<u>38,16</u> 37,87	2.91	9,10 8,83	10,00	$\frac{24.96}{25,19}$	$\mathrm{C}_{\mathrm{t}0}\mathrm{H}_9\mathrm{N}_2\mathrm{O}_5\mathrm{SBr}$	0,45
j	80	0:1) 193-195 (decomp.)(alco- hol)	42,40	$\frac{3.17}{3,20}$	14.86	11,30	ł	C ₁₀ H ₉ N ₅ O ₅ S	0,50

TABLE 1. 1-(Arylsulfonyl)-4-methylimidazolin-2-ones (IId-i)

*The substances were detected in UV light.

						(,	
Starting (IIa-i)	Reac- tion time, h	Yield of re- action prod- ucts (IIIa)+ (IIIb), %	(IIIa): (IIIb) ratio	Starting (IIa-i)	Reac- tion time, h	Yield of re- action prod- ucts (IIIa) + (IIIb), %	(IIIa): (IIIb) ratio
a b c d e	$550 \\ 240 \\ 170 \\ 100 $	$74 \\ 65 \\ 65 \\ 70 \\ 60$	1,5 : 1 3 : 1 5,7 : 1 5,5 : 1 5,3 : 1	f g h i	170 170 290 170	64 55 70 50 (IIIb)	4,3 : 1 3,5 : 1 2,5 : 1 –

TABLE 2. Condensation of Tetraaminopyrimidine (I) with 1-(Arylsulfonyl)-4-methylimidazolin-2-ones (IIa-i)

Despite the lower concentration of imine (Vb) in the (Va, b) mixture, the tendency for cyclization is apparently greater for (Vb) due to the linear conjugation of the double bonds in (Vb), which enhances the electrophilicity of the CH_2 group. Consequently, when (I) is reacted with (IIa-h), besides (IIIa), noticeable amounts of the 7-methyl isomer (IIIb) are also formed. For the cyclization of imine (Vb) and the regioselective formation of the 7-methyl isomer (IIIb) it should be especially favorable to have a simultaneous withdrawal of the electrons from the CH_2 group both toward the conjugated bonds of (Vb) and toward the strong electron-acceptor $HNSO_2C_6H_4NO_2-4'$ moiety.

As a result, the insertion of various substituents into the aromatic ring of (IIa) permits varying the ratio of the (IIIa, b) isomers in a broad range when the (IIa-i) are reacted with (I) and also the synthesis of (IIIa, b) with a high degree of regioselectivity. The pure (IIIb), devoid of noticeable amounts of (IIIa), can be obtained by reacting (IIi) with (I). In contrast, the reaction of (I) with (IIc-e) gives a (IIIa, b) mixture with a sharp predominance of (IIIa) (∞ 80%). Compound (IIIa) can be purified by treating the (IIIa, b) mixture with KMnO4 to remove nonpteridine impurities and subsequent recrystallization of the desired product from DMSO.

EXPERIMENTAL

The UV spectra were taken in 0.1 N HCl solution on a Specord UV-Vis instrument, the IR spectra were taken as KBr pellets on a UR-20 instrument, and the PMR spectra were taken in 1 N KOH solution on a Varian DA-60-IL instrument, using TMS as the external standard. The TLC was run on Silufol UV-254.

The 1-(arylsulfonyl)-4-methylimidazolin-2-ones (IId-i) were obtained from 4-methylimidazolin-2-one and the appropriate arylsulfonyl chlorides in pyridine as described in [2]. Compound (IId) was isolated by diluting the reaction mixture with water, decantation of the aqueous pyridine solution from the obtained oil, treatment of the latter with benzene, and filtration of the obtained precipitate. The physicochemical characteristics of (IId-i) are given in Table 1.

The reaction of tetraaminopyrimidine (I) with 1-(arylsulfonyl)-4-methylimidazolin-2ones (IId-i) was run as described in [1]. The mixtures of the 6- and 7-methyl-2,4-diaminopteridines (IIIa, b) obtained from (IId-h) were identified via TLC and the UV and IR spectra, and also by hydrolytic deamination to mixtures of the 6- and 7-methylpterins (VIIa, b) [3]. The ratios of the structural isomers in the (IIIa, b) mixtures were determined from the integral intensities of the protons at C⁷ and C⁶ in the PMR spectra of (VIIa, b) [4, 5]. The reaction of (I) with (IIi) gave the pure (IIIb), which decomposes above 330°. Rf 0.65 (here and subsequently using the system i-PrOH-H₂O-NH₄OH, 7:2:1, and detection of the fluorescent spot in UV light). Ultraviolet spectrum: λ_{max} 243, 282, 332 nm, λ_{min} 265, 293 nm. Infrared spectrum (ν , cm⁻¹): 1180, 1230, 1290, 1354, 1380, 1455, 1490, 1508, 1550, 1585, 1615, 1630, 1660, 3225, 3330, 3420. The authentic (IIIb) had the same characteristics [3]. The alkaline hydrolysis of (IIIb) as described in [3] gave (VIIb) in nearly quantitative yield, which was identified via the UV, IR, and PMR spectra [4, 5].

<u>Preparation of Pure (IIIa).</u> A mixture of (IIIa, b) (0.74 g), isolated from the reaction of (I) with (IIc), was dissolved in 15 ml of aqueous AcOH (1:1), 0.25 g of finely ground KMnO₄ was added, the mixture was stirred for 2 h at $\sim 20^{\circ}$, filtered, made alkaline with aqueous NH₃ to pH ~ 8 , and the precipitate was filtered and recrystallized from DMSO. We obtained 0.38 g of (IIIa), which decomposes above 330°. R_f 0.65. Ultraviolet spectrum: λ_{max} 242, 282, 338 nm, λ_{min} 265, 297 nm. Infrared spectrum (v, cm⁻¹): 1205, 1360, 1380, 1445, 1565, 1590, 1630, 1665, 3120, 3215, 3320, 3462. The authentic (IIIa) had the same characteristics [3]. The alkaline hydrolysis of (IIIa) as described in [3] gave (VIIa) in nearly quantitative yield, which was identified via the UV, IR, and PMR spectra [4, 5].

CONCLUSIONS

When tetraaminopyrimidine is reacted with 1-arylsulfonyl-4-methylimidazolin-2-ones, the presence of an electron-donor substituent in the aromatic ring of the arylsulfamido moiety favors the formation of 6-methyl-2,4-diaminopteridine, while an electron-acceptor substituent favors the formation of the isomeric 7-methyl-2,4-diaminopteridine.

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