SYNTHESIS OF β-CHLOROETHYLAMINO DERIVATIVES IN THE 1,3,4-THIADIAZOLE SERIES. I

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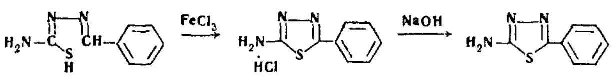
A study is made of the hydroxyethylation of some 2-amino-5-aryl-1,3,4-thiadiazoles and replacement of the hydroxyl group in the hydroxyethylation products by chlorine, as well as of condensation of p-[di(β-chloroethyl)amino]phenylacetyl chloride with the 2-amino-5-aryl-1,3,4-thiadiazoles.

In view of the interest in β-chloroalkyl derivatives of various heterocyclic compounds in connection with their action on malignant tumors, we have synthesized for biological testing some derivatives of 2-amino-1,3,4-thiadiazole. It has been shown that the later [1] hinders growth of some tumors (Melanoma S-91, lymphosarcoma, etc), and its action is supressed by nicotinamide. Positive actions are also exhibited by 2-alkyl and 2-acyl derivatives of this heterocyclic compound [2,3,4].

Our starting object is 2-amino-5-phenyl-1,3,4-thiadiazole, synthesized [5] by oxidizing benzaldehyde thiosemicarbazone with ferric chloride in aqueous solution, the equation being

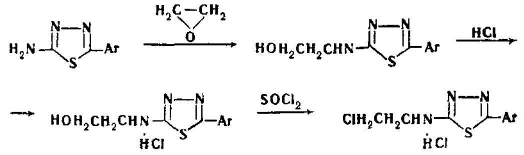


It should be mentioned that due to hydrolysis by the acid solution arising from the $FeCl_3 \cdot 6H_2O$, yields are lowered, but that, as we showed, a 65% yield of amine is obtained by boiling in ethanol. The melting point of the resultant amine (227–228°) agreed with that given in the literature. Hydroxyethylation of it in the presence of 12% acetic acid and methanol, for 48 hours, gives the 2-monohydroxyethyl derivative, mp 111–113°, in 84% yield, and the hydrochloride of the latter melts at 186.5–187.5°.

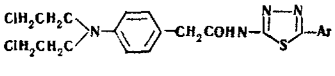
The hydrochloride of 2-(β-chloroethylamino)-5-phenyl-1,3,4-thiadiazole is obtained by reacting the hydrochloride of the corresponding 2-(β-hydroxyethylamino)-5-phenyl-1,3,4-thiadiazole with excess thionyl chloride, prolonged boiling in chloroform solution being used, and after recrystallizing from dry ethanol it had melting point 206–208°.

The other 2-amino-5-aryl-1,3,4-thiadiazoles viz. 2-amino-5-p-nitrophenyl-1,3,4-thiadiazole (mp 256°) [6], 2-amino-5-styryl-1,3,4-thiadiazole (mp 233–235°) [7,8], and 2-amino-5-p-methoxyphenyl-1,3,4-thiadiazole (mp 185–187°) [9], all obtained by ferric chloride oxidation, were subjected to the same reactions.

The following are, in general, the equations for the synthesis of β-chloroethyl derivatives of 2-amino-5-aryl-1,3,4-thiadiazole



Regarding 2-acylamino derivatives, the behavior of p-[di-(β-chloroethyl)amino] phenylacetyl chloride [10] towards 2-amino-5-aryl-1,3,4-thiadiazoles was investigated. The examples of the latter used were those mentioned above, and in the absence of a hydrogen chloride acceptor they gave good yields of the corresponding p-[di(β-chloroethyl)amino]phenylacetyl derivatives of the following structure:

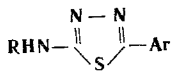


EXPERIMENTAL

2-(β-Hydroxyethylamino)-5-phenyl-1,3,4-thiadiazole. 3 g (0.017 mole) 2-amino-5-phenyl-1,3,4-thiadiazole, 15 ml 12% AcOH, 10 ml (0.2 mole) ethylene oxide, and 20 ml MeOH were left together in a tightly sealed flask for 48 hr, with occasional shaking. After filtering, excess ethylene oxide and MeOH were vacuum distilled off, and after cooling, and filtering again, the mixture was brought to pH 9 by adding a 5% solution (universal indicator). On cooling and scratching the walls of the vessel with a glass rod, 1.4 g (84% based on the amine which entered into reaction) reaction product separated, as minute crystals, soluble in hot water and EtOH, slightly soluble in benzene; from $CHCl_3$ it separated as silky needles, mp 111–113°. Found: N 18.98; 19.07; S 14.62; 14.81%. Calculated for $C_{10}H_{11}N_3OS$: N 18.99; S 14.48%.

2-(β-Hydroxyethylamino)-5-phenyl-1,3,4-thiadiazole hydrochloride. 0.88 g (0.004 mole) 2-(β-hydroxyethylamino)-5-phenyl-1,3,4-thiadiazole was dissolved in 30 ml of a mixture of equal amounts of dry EtOH and ether, and dry HCl gas passed in for an hour. The precipitate was filtered off and recrystallized from dry EtOH, yield 0.6 g product (60%), glistening

Derivatives of 1,3,4-thiadiazole*



No.	R	Ar	Mp, °C	Solvent	Formula	Found, %			Calculated, %			Yield, %
						Cl	N	S	Cl	N	S	
1	$-CH_2CH_2OH$	$C_6H_4NO_2$-*p*	148—149	Dry EtOH	$C_{10}H_{10}N_4O_3S$	—	21.48 21.55	11.81 11.94	—	21.04	12.03	83
	Hydrochloride		188.5—190	" "	$C_{10}H_{10}N_4O_3S \cdot HCl$	11.56 11.70	18.19 18.13	10.50 10.40	11.71	18.51	10.59	58
2	" "	$-CH{=}CH-C_6H_5$	125—127	Toluene	$C_{12}H_{13}N_3OS$	—	17.17 17.20	12.91 12.74	—	16.99	12.96	80
	Hydrochloride		225—227	Dry EtOH	$C_{12}H_{13}N_3OS \cdot HCl$	12.40 12.53	14.95 15.04	10.91 11.00	12.49	14.80	11.29	63
3	" "	$C_6H_4OCH_3$-*p*	130—132	" "	$C_{11}H_{13}N_3O_2S$	—	16.81 16.89	12.94 12.96	—	16.72	12.76	88
	Hydrochloride		170.5—172.5	" "	$C_{11}H_{13}N_3O_2S \cdot HCl$	12.20 12.26	14.51 14.54	11.15 10.86	12.31	14.60	11.14	67
4	$-CH_2CH_2Cl$	$C_6H_4NO_2$-*p* (hydrochloride)	211—213 (decomp.)	" "	$C_{10}H_9ClN_4O_2S \cdot HCl$	21.52 21.75	17.78 18.02	9.83 9.79	22.03	17.44	9.98	50
5	" "	$-CH{=}CH-C_6H_5$ (hydrochloride)	199—201 (decomp.)	" "	$C_{12}H_{12}ClN_3S \cdot HCl$	23.73 23.66	14.17 14.37	10.29 10.65	23.46	13.90	10.60	48
6	" "	$C_6H_4OCH_3$-*p* (hydrochloride)	192—194	" "	$C_{11}H_{12}ClN_3OS \cdot HCl$	23.23 23.27	14.01 14.15	10.15 10.21	23.16	13.72	10.47	57
7	$\begin{matrix}ClH_2CH_2C\\ ClH_2CH_2C\end{matrix}\rangle N-C_6H_4-CH_2CO$-*p*	$C_6H_4NO_2$-*p*	213—213.5	Glacial AcOH	$C_{20}H_{19}Cl_2N_5O_3S$	14.50 14.54	14.36 14.33	6.68 6.42	14.76	14.57	6.67	81
8	" "	$-CH{=}CH-C_6H_5$	230—231	"	$C_{22}H_{22}Cl_2N_4OS$	15.42 15.61	12.34 12.26	7.11 7.20	15.37	12.13	6.95	85
9	" "	$C_6H_4OCH_3$-*p*	198—199 (decomp.)	"	$C_{21}H_{22}Cl_2N_4O_2S$	15.07 15.37	11.90 11.86	6.74 6.79	15.24	12.03	6.89	80

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*The table does not give the properties of compounds described in the experimental part.

needles, mp 186.5–187.5°. Found: Cl 13.90; 13.59; N 16.57; 16.56; S 12.48 12.31%. Calculated for $C_{10}H_{11}N_3OS \cdot HCl$: Cl 13.76; N 16.30; S 12.44%.

2-(β-Chloroethylamino)-5-phenyl-1,3,4-thiadiazole hydrochloride. 10 ml (0.14 mole) $SOCl_2$ was added, in small portions, and with shaking, to a suspension of 1.39 g (0.005 mole) 2-(β-hydroxyethylamino)-5-phenyl-1,3,4-thiadiazole in 5 ml $CHCl_3$, and the resultant transparent solution was heated in a flask under reflux on a water-bath for 3 hr. After vacuum-distilling off excess $SOCl_2$ plus $CHCl_3$, the tarry residue was dissolved in 20 ml dry EtOH, and an equal volume of dry ether, added. The precipitate was filtered off, and recrystallized from dry EtOH, yield 0.8 g (53%) slightly yellowish minute crystals, soluble in water, mp 206–208°. Found: Cl 25.54; 25.51; N 15.56; 15.73; S 11.56; 11.44%. Calculated for $C_{10}H_{10}ClN_3S \cdot HCl$: Cl 25.67; N 15.22; S 11.61%.

2-{p-[Di (β-chloroethyl)amino] phenyl} acetylamino-5-phenyl-1, 3, 4-thiadiazole. 0.29 g (0.001 mole) p-[di(β-chloroethyl)]aminophenylacetyl chloride and 0.18 g (0.001 mole) 2-amino-5-phenyl-1,3,4-thiadiazole were heated together in a flask with a reflux condenser in 40 ml dry benzene for 4 hr. The precipitate was filtered off, and refluxed for 10 min with 50 ml 5% HCl. The residue insoluble in the acid was filtered off, washed on the filter with hot water, and after drying, recrystallized from glacial AcOH, yield 0.34 g (80%), white crystalline power mp 199–201°. Found: Cl 16.54; 16.05; N 12.69; 12.78; S 7.31; 7.27%. Calculated for $C_{20}H_{20}Cl_2N_4OS$: Cl 16.29; N 12.86; S 7.36%.

The other compounds were prepared by the methods described above. The table gives their properties.

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