s-TRIAZOLO [4,3-a] [1,3] DIAZACYCLOALKANS III[1]. A NOVEL SYNTHESIS OF 2-ARYL-3-OXO-2,3,5,6,7,8-HEXAHYDRO-s-TRIAZOLO [4,3-a] PYRIMIDINES

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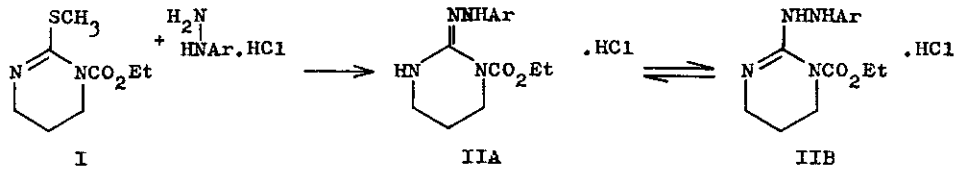
Abstract - A novel synthesis of s-triazolo [4,3-a] pyrimidines is described. Arylhydrazine hydrochlorides react easily with 1-ethoxycarbonyl-2-methylthio-1,4,5,6-tetrahydropyrimidine to form hydrochlorides of cyclic arylaminoguanidines, which are then cyclized in aqueous K_2CO_3 medium into s-triazolo [4,3-a] pyrimidines.

A wide spectrum of pharmacological activity is characteristic of the derivatives of guanidine [2-4]. In connection with that, our laboratory carries out the investigations concerning the synthesis of guanidine derivatives and of the compounds involving isothiourea radicals bioisosteric with the guanidine group in their molecules [5-7].

Recently, the derivatives of 3-oxo-2,3,5,6,7,8-hexahydro-s-triazolo [4,3-a] pyrimidines - the compounds involving a guanidine fragment in the cyclic system - were obtained as sole products from the reaction of 1-ethoxycarbonyl-2-methylthio-1,4,5,6-tetrahydropyrimidine (I) with hydrazine and arylhydrazines [1].

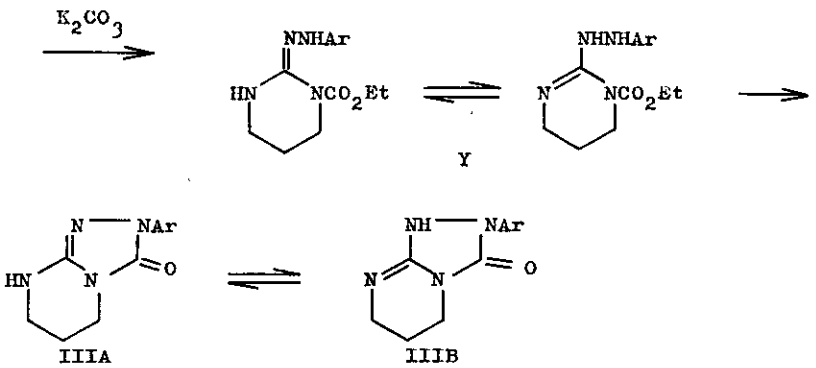
The concern of the present study is a novel method of the synthesis of the 2-aryl derivatives of s-triazolo [4,3-a] pyrimidine, with arylhydrazine hydrochlorides, readily accessible and more stable than free arylhydrazines. At the first stage the hydrochlorides of cyclic aminoguanidines (II) are isolated. (In the reaction of I with free hydrazines the products of type II have not been isolated).



I IIA IIB

The structure of compounds II has been confirmed by the data obtained from elemental and spectroscopic analysis. In the ^{1}H-NMR spectra of products II, the signal of the protons of the SCH_3 group disappered, with appearance of amine and aryl proton signals.

Compounds II in aqueous K_2CO_3 medium are immediately cyclized into the derivatives of s-triazolo[4,3-a]pyrimidine III.



Y IIIA IIIB

The fact, that the intermediate compounds Y have not been observed, proves an extraoridinarily strong tendency towards the formation of triazole system. Because of the presence of the amidine group in the molecules of compounds II and III these compounds can occur in two tautomeric forms A and B. From the signal of the CH_2-7 group (located on the pyrimidine ring) present in the ^{1}H-NMR spectra of the compound III as a sextet reduced to a triplet after adding D_2O to the sample, it may be stated that the 2-aryl derivatives of s-triazolo[4,3-a]pyrimidine III are present in the solutions of $CDCl_3$ and DMSO-d_6 mainly in the form A. In the case of compounds II the protons of CH_2-4 and CH_2-6 groups are shown in the ^{1}H-NMR spectrum as a multiplet (4H), so the spectral analysis cannot be the basis for conclusions concerning their

tautomeric structure.

Compounds III can be obtained in practice by treating the raw, uncrystallized product of the reaction of the compound I and arylhydrazine hydrochloride with the aqueous solution of K_2CO_3. The results of pharmacological investigations will be the subject of a forthcoming publication.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded on a Unicam SP-200 G spectrophotometer for KBr disks. ^{1}H-NMR spectra were recorded for solutions in $CDCl_3$ and DMSO-d_6 with Varian E = 360 (60 mHz) and Tesla BS 487 instruments; chemical shifts are reported in ppm downfields from internal tetramethylsilane. 1-Ethoxycarbonyl-2-methylthio-1,4,5,6-tetrahydropyrimidine was prepared according to the method described by Bose [8].

Hydrochlorides of 1-Ethoxycarbonyl-2-arylhydrazino-1,4,5,6-tetrahydropyrimidine II a-f (General procedure) - A mixture of I (5 mmol) and the corresponding arylhydrazine hydrochloride (5 mmol) was heated under reflux for an appropriate period (see Table 1) . The cooled solution was evaporated in vacuo. The resulting oil or solid was crystallized from the mixture of solvents EtOH-Et_2O.

2-Aryl-3-oxo-2,3,5,6,7,8-hexahydro-s-triazolo[4,3-a]pyrimidines III a-f (General procedure). - To a stirred aqueous solution containing an appropriate compound II (0.5 g in 10 ml of H_2O) was added dropwise over a 5 min period, the 20 %aqueous solution of K_2CO_3, until the base reaction of the litmus paper was obtained. The stirring was continued for 1 h. The precipitate was filtered, washed twice with water (2x10 ml), dried and crystallized from EtOH. The physical properties for samples II a-f and III a-f are presented in Tables 1 - 4.

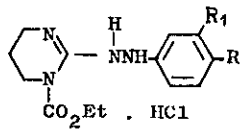


Table 1

1-Ethoxycarbonyl-2-arylhydrazino-1,4,5,6-tetrahydropyrimidine hydrochlorides (IIa-f)

No.	R	R_1	Molecular formula	Mp (°C)	Yield	Found (Calcd.) C	H	% N	Reaction time (h)
IIa	CH_3	H	$C_{14}H_{21}ClN_4O_2$	167-69	85	53.50 (53.76)	6.61 (6.77)	17.69 (17.91)	6
IIb	Cl	H	$C_{13}H_{18}Cl_2N_4O_2$	151-53	59	46.60 (46.86)	5.45 (5.40)	16.74 (16.81)	8
IIc	SO_2NH_2	H	$C_{13}H_{20}ClN_5O_4S$	211-13	75	41.21 (41.32)	5.27 (5.33)	18.39 (18.53)	8
IId	Br	H	$C_{13}H_{18}BrClN_4O_2$	207-09	72	41.19 (41.34)	4.69 (4.80)	14.57 (14.83)	6
IIe	Cl	Cl	$C_{13}H_{17}Cl_3N_4O_2$	144-45	75	42.31 (42.45)	4.59 (4.66)	15.01 (15.24)	6
IIf	H	H	$C_{13}H_{19}ClN_4O_2$	221-22	81	52.12 (52.26)	6.31 (6.41)	18.59 (18.75)	

Table 2

IR and ^{1}H-NMR data of the compounds II a-f

No	OCO	IR (cm^{-1}) NH, NH^+	^{1}H-NMR [a,b] (ppm)
IIa[a]	1735	3320, 3160 2900-2760	1.28 (t, 3H, CH_3), 1.68-2.03 (m, 2H, C-CH_2-C), 2.36 (s, 3H, Ar-CH_3), 3.02-3.54 (m, 4H, N-CH_2), 4.25 (q, 2H, O-CH_2), 7.04, 7.44 (d,d, 4H, Ph), 8.93 br s, 2H; 10.91 s, 1H, NH, NH^+
IIb[b]	1730	3320, 3150 2890, 2780	1.30 (t, 3H, CH_3), 1.63-2.12 (m, 2H, C-CH_2-C), 3.1-3.53 (m, 4H, N-CH_2), 4.28 (q, 2H, O-CH_2), 7.4-7.98 (m, 4H, Ph), 8.85 br s, 2H; 10.83, s, 1H, NH, NH^+
IIc[b]	1725	3360, 3300 3160, 2880-2790	1.24 (t, 3H, CH_3), 1.58-2.0 (m, 2H, C-CH_2-C), 3.0-3.45 (m, 4H, N-CH_2), 4.22 (q, 2H, O-CH_2), 7.28-7.95 (m, 4H, Ph), 8.8 br s, 2H; 10.8, s, 1H, NH, NH^+
IId[b]	1720	3320, 3240 2880 - 2800	1.30 (t, 3H, CH_3), 1.65-2.16 (m, 2H, C-CH_2-C), 3.12-3.68 (m, 2H, N-CH_2), 4.30 (q, 2H, O-CH_2), 7.6-7.85 (m, 4H, Ph), 8.92 br, s, 2H; 10.9, s, 1H, NH, NH^+
IIe[b]	1735	3330, 3160 2890 - 2760	1.23 (t, 3H, CH_3), 1.68-2.1 (m, 2H, C-CH_2-C), 3.16-3.85 (m, 4H, N-CH_2), 4.31 (q, 2H, O-CH_2), 7.42-8.01 (m, 3H, Ph), 8.94, br s, 2H; 10.91, s, 1H, NH, NH^+
IId[a]	1725	3315, 3170 2880 - 2800	1.28 (t, 3H, CH_3), 1.58-2.19 (m, 2H, C-CH_2-C), 3.04-3.7 (m, 4H, N-CH_2), 4.32 (q, 2H, O-CH_2), 7.09-7.8 (m, 5H, Ph), 8.92 br s, 2H; 10.92, s, 1H, NH, NH^+

Values for doublets (d), triplets (t) and quartet (q) refer to multiplet centres. a) Solution in $CDCl_3$.

b) Solution in DMSO-d_6.

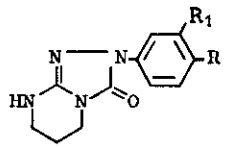


Table 3

2-Aryl-3-oxo-2,3,5,6,7,8-hexahydro-s-triazolo [4,3-a] pyrimidines

(III a-f)

No	R	R_1	Molecular formula	Mp (°C)	Yield	Found	(Calcd.)	%
IIIa	CH_3	H	$C_{12}H_{14}N_4O$	245-46	63	62.57 (62.60)	6.20 (6.13)	24.11 (24.33)
IIIb	Cl	H	$C_{11}H_{11}ClN_4O$	215-16	53	52.48 (52.70)	4.68 (4.42)	22.03 (22.35)
IIIc	SO_2NH_2	H	$C_{11}H_{13}N_5O_3S$	323-25	81	44.59 (47.75)	4.30 (4.44)	23.60 (23.72)
IIId	Br	H	$C_{11}H_{11}BrN_4O$	235-36	83	44.79 (44.76)	3.79 (3.76)	19.15 (18.98)
IIIe	Cl	Cl	$C_{11}H_{10}Cl_2N_4O$	246-48	79	46.27 (46.43)	3.41 (3.53)	19.38 (19.66)
IIIf	H	H	$C_{11}H_{12}N_4O_2$	176-78	82	61.01 (61.09)	5.53 (5.58)	25.81 (25.91)

Table 4

IR and ^{1}H-NMR data of the compounds III a-f

No	NCO	IR (cm^{-1}) NH	^{1}H-NMR[a,b] (ppm)
IIIa[a]	1710	3280	1.81-2.2 (m, 2H, C-CH_2-C), 3.09-3.41 (m, 2H, NH-CH_2), 3.52-2.8 (t, 2H, CH_2-NCO), 6.68 (br, s, 1H, NH), 7.2, 7.6 (d, d, 4H, Ph)
IIIb[b]	1715	3300, 3250	1.8-2.29 (m, 2H, C-CH_2-C), 3.15-3.45 (m, 2H, NH-CH_2), 3.51-3.8 (t, 2H, CH_2-NCO), 7.15 (br, s, 1H, NH), 7.29, 7.79 (d, d, 4H, Ph)
IIIc[b,d]	1690	3300, 3200	1.71-2.2 (m, 2H, C-CH_2-C), 3.16-3.4 (m, 2H, NH-CH_2), 3.52-3.88 (t, 2H, CH_2-NCO), 6.82-7.1 (br, s, 3H, SO_2NH_2, NH), 7.67-8.22 (m, 4H, Ph)
IIId[b]	1710	3300, 3240	1.60-2.11 (m, 2H, C-CH_2-C), 3.02-3.4 (m, 2H, NH-CH_2), 3.5-3.82 (t, 2H, CH_2-NCO), 7.15 (br, s, 1H, NH), 7.3-8 (m, 4H, Ph)
IIIe[b]	1700	3280	1.69-2.08 (m, 2H, C-CH_2-C), 3.1-3.42 (m, 2H, NH-CH_2), 3.53-3.88 (m, 2H, CH_2-NCO), 7.2 (br, s, 1H, NH), 7.4-8.03 (m, 3H, Ph)
IIIf[a,d]	1720	3300, 3260	1.85-2,42 (m, 2H, C-CH_2-C), 3.08-3.46 (sx, 2H, NH-CH_2), 3.53-3.9 (m, 2H, CH_2-NCO), 5.99-6,16 (br s, 1H, NH), 6.93-8.0 (m, 5H, Ar)

a) Solution in $CDCl_3$. b) Solution in DMSC-d_6. c) sx = sextet. d) The compounds IIIc and IIIf are identical with the products of the reaction of I with p-sulfamoylphenylhydrazine and phenylhydrazine [1b].

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