FORMATION OF BROMO-SUBSTITUTED IMIDAZO[1,2-a]PYRIDINES AND THEIR AZA AND THIA ANALOGS WHEN THE CHICHIBABIN REACTION IS CARRIED OUT IN DIMETHYL SULFOXIDE

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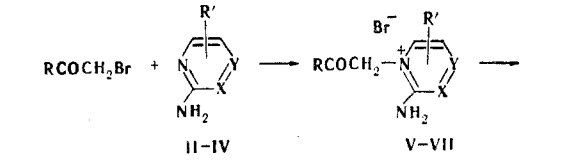
The reactions of bromomethyl ketones with 2-aminopyridine, 2-aminopyrimidine, 2-aminothiazole, and 2-aminobenzothiazole in dimethyl sulfoxide lead to bromo-substituted (with respect to the α position of the imadozole ring) imidazo[1,2-a]pyridines, imidazo[1,2-a]pyrimidines, imidazo[2,1-b]thiazoles, and imidazo[2,1-b]-benzothiazoles.

We have previously shown [1] that in dimethyl sulfoxide (DMSO) 2-amino-N-(β-oxoethyl)pyridinium (V), 2-amino-N-(β-oxoethyl)pyrimidinium (VI), and 2-amino-N-(β-oxoethyl)thiazolium (VII) bromides not only undergo cyclization to, respectively, imidazo[1,2-a]pyridine (VIII), imidazo[1,2-a]pyrimidine (IX), and imidazo[2,1-b]thiazoles (X) but are also brominated in the α position of the imidazole ring. According to [2], bromination occurs as a result of the formation of bromine by oxidation by DMSO of the hydrogen bromide evolved in the cyclization step. The formation of bromo-substituted compounds directly from α-bromomethyl ketones I and the corresponding hetarylamines II-IV, which are incapable of halogenation, has also been noted.



II, V, VIII XI Y=X=CH=CH; III, VI, IX, XII Y=X=N=CH; IV, VII, X, XIII Y=X=S; R and R′ (see Table 1)

In the present communication we present the results of a further study of the possibility of the synthesis of VIII-X and their bromo-substituted derivatives XI-XIII and XV in DMSO.

It was established that the only (or predominant) products in the reaction of keto ammonium bromides V-VII with DMSO at room temperature for 1-2 days are unbrominated VIII-X (Table 1, method A). When the reaction mixtures are allowed to stand for a longer time at room temperature, the amounts of bromo-substituted XI-XIII increase, and in time they become the only products.

Heating salts V-VII in DMSO on a boiling-water bath (method B) promotes both cyclization and bromination, particularly when electron-acceptor groups are present. In the case of 2-amino-1-(2-furoylmethyl)pyrimidinium bromide heating for 30 min led to a mixture of equal amounts of 2-(2-furyl)imidazo[1,2-a]pyrimidine and its 3-bromo derivative.

Instead of bromides V-VII one can use equimolar amounts of bromomethyl ketones I and the corresponding hetarylamines II-IV; the positions that are capable of halogenation should not necessarily be substituted in the latter. In these cases the theoretically permissible transformations of the α-bromomethyl ketones in DMSO to monosubstituted glyoxylic acids [3] or mix-

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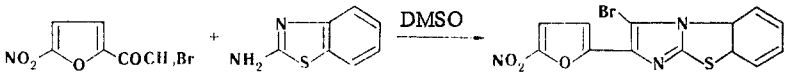
TABLE 1. Results of Reactions Carried out in DMSO

X–Y	R	R′	Reaction conditions			Reaction products								
						unbrominated					bromine-substituted			
									mp, °C				mp, °C	
			method	temp., °C	time, h	yield, %	R_f^1	R_f^2	found	literature data	yield, %	R_f^1	R_f^2	found	literature data
CH=CH	2-C_4H_3O[a]	6-I	A	20—25	48	60[b]	0,70	0,47	187—188	186—188[6]	0	—	—	—	—
CH=CH	5-NO_2-2-C_4H_2O	H	C	20—25	24	37	0,26	0,40	255	254—255[7]	5	0,46	0,52	257—258	248—249[11]
			D	95—100	0,5	16					33			253—254	
			E	95—100	1	0	—	—	—	—	70			256—257	
CH=CH	5-NO_2-2-C_4H_2O	6,8-Br_2	C	20—25	24	52	0,58	0,77	273—275	273—275	0	—	—	—	—
CH=CH	4-$NO_2C_6H_4$	H	B	95—100	2	0	—	—	—	—	58	0,47	0,63	231	223—225[12]
			D	95—100	0,5	0	—	—	—	—	100				
N=CH	2-C_4H_3O	H	B	95—100	0,5	40	0,09	0,13	212—214	—	40	0,49	0,54	161	—
N=CH	5-NO_2-2-C_4H_2O	H	C	20—25	24	60	0,28	0,27	>300	>300[7]	0	—	—	—	—
			C	20—25	48	48					6	0,09	0,12	>300	—
			D	95—100	0,5	0	—	—	—	—	40				
N=CH	4-$NO_2C_6H_4$	H	A	20—25	24	50	0	0	>300	—	3	0,37	0,31	>300	—
			D	95—100	0,5	0	—	—	—	>300(разл.)[8]	52				
S	5-NO_2-2-C_4H_2O	H	A	20—25	720	4	0,39	0,44	220—221	220—221[9]	70	0,49	0,60	241—242	240—242[13]
			B	95—100	2	43					32			240—242	
			D	95—100	0,5	0	—	—	—	—	100			242—243	
S	5-NO_2-2-C_4H_2O	3-(2-C_4H_3O)	D	95—100	5	0	—	—	—	—	96	0,63	0,41	>300	—
S	5-Br-2-C_4H_2O	2-CH_3	A	20—25	240	0	—	—	—	—	57	0,52	0,72	158—163	170—171[14]
S	4-$NO_2C_6H_4$	H	B	95—100	0,5	5	0,46	0,55	290—291	300—301[10]	76	0,60	0,73	231—234	—

[a]The furyl group is indicated by C_4H_3O. [b]In the form of the hydrobromide monohydrate, with mp 275-279°C.

tures of glyoxals and methylthio esters of glyoxylic acids [4] are outstripped by the formation of quaternary salts V-VII and their subsequent transformations. As shown in Table 1, if the reaction mixture is not heated (method C), in the first 2 days the only (or major) reaction products are imidazo compounds VIII-X. Heating accelerates not only the formation of quaternary salts and their cyclization but also the formation of bromine *in statum nascendi*, as a result of which bromo-substituted XI-XIII are obtained in high and sometimes quantitative yields after only 30 min (method D).

It is known that prolonged heating (up to 30 h) in alcohol is necessary for the preparation of imidazo[2,1-b]benzothiazoles via the Chichibabin reaction [5], and heating 5-nitro-2-bromoacetylfuran (XIV) with 2-aminobenzothiazole (XV) in DMSO for 1 h gave 3-bromo-2-(5-nitro-2-furyl)imidazo[2,1-b]benzothiazole (XVI) in 35% yield.

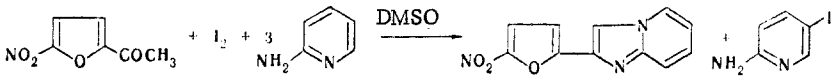


XIV XV XVI

When 2-(5-nitro-2-furyl)imidazo[1,2-a]pyridine hydrobromide (XVII) was heated in DMSO (method E), the 3-bromo derivative (XVIII) was also obtained.

XVII XVIII

It is interesting to note that 2-amino-5-iodopyridine (XX), rather than iodo derivative XIX, is formed along with 2-(5-nitro-2-furyl)imidazo[1,2-a]pyridine (XIX) in the reaction of 5-nitro-2-acetylfuran with iodine and 2-aminopyridine in DMSO for 3 days at room temperature.



XIX XX

The corresponding bromo-substituted compounds were obtained to monitor the course of the reactions and to identify the products by bromination of imidazo compounds VIII-X. With the same end in mind, 3-(2-furyl)-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole (XXI) was synthesized

TABLE 2. Characteristics of the New Compounds

Compound	mp, °C	Found, %			Empirical formula	Calc., %			Yield, %
		C	H	N		C	H	N	
3-Bromo-2-(5-nitro-2-furyl)imidazo[1,2-a]-pyrimidine	>300	38,5	1,6	18,1	$C_{10}H_5BrN_4O_3$	38,8	1,6	18,1	76
3-Bromo-2-(4-nitrophenyl)imidazo[1,2-a]-pyrimidine	>300	45,5	2,5	18,0	$C_{12}H_7BrN_4O_2$	45,1	2,2	17,6	86
5-Bromo-6-(4-nitrophenyl)imidazo[2,1-b]thiazole	231—234	40,4	1,8	12,3	$C_{11}H_6BrN_3O_2S$	40,7	1,8	12,9	87
5-Bromo-3-(2-furyl)-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole	>300	40,6	2,0	10,6	$C_{13}H_6BrN_3O_4S$	41,0	1,6	11,1	96
3-Bromo-2-(5-nitro-2-furyl)imidazo[2,1-b]benzothiazole	285—287	42,6	1,5	11,0	$C_{13}H_6BrN_3O_3S$	42,9	1,7	11,5	35
6-Iodo-2-(2-furyl)imidazo[1,2-a]pyridine hydrobromide hydrate[a]	295—297	32,3	2,1	6,4	$C_{11}H_5IN_2O \cdot HBr \times \times H_2O$	32,4	2,0	6,9	60

[a] IR spectrum: 1660 ($-C=\overset{+}{N}<$), and 2600-2800 cm^{-1} ($\overset{+}{N}H$).

by reaction of 5-nitro-2-bromoacetylfuran with 2-amino-4-(2-furyl)thiazole. The characteristics of the new compounds are presented in Table 2.

EXPERIMENTAL

Chromatographic monitoring was accomplished on Silufol UV-254 plates in benzene–dioxane–acetic acid (20:4:1) (R_f^1) and acetone–chloroform (1:5) (R_f^2) systems. The melting points were determined with a Boetius microheating apparatus and were not corrected. The IR spectra of Nujol (1500-2000 cm^{-1}) and hexachlorobutadiene (2000-3400 cm^{-1}) suspensions of the compounds were recorded with a UR-20 spectrometer.

Imidazo Compounds VIII-X and Their Bromo Derivatives XI-XIII (Table 1). A) A solution of 10 mmole of the bromide (V-VII) in 50 ml of DMSO was allowed to stand at room temperature for several days, after which the precipitated bromo derivative (XI-XIII) was removed by filtration, washed with DMSO and water, and, where necessary, recrystallized from dimethylformamide (DMF). Water (50 ml) was added to the filtrate, and the unbrominated compounds (VIII-X) containing traces of the bromo derivatives were removed by filtration and recrystallized from DMF.

B) A solution of 10 mmole of the bromide (V-VII) in 50 ml of DMSO was allowed to stand on a boiling-water bath for 0.5-2 h, after which the mixture was worked up as described above.

C) A mixture of 10 mmole of bromomethyl ketone (I), 10 mmole of hetarylamine (II-IV), and 50 ml of DMSO was allowed to stand at room temperature for the length of time indicated in Table 1, after which it was worked up as described in method A.

D) A mixture of 10 mmole of bromomethyl ketone (I), 10 mmole of the hetarylamine (II-IV), and 50 ml of DMSO was allowed to stand on a boiling-water bath for 0.5-2 h, after which it was worked up as described in method A.

E) A mixture of 0.52 g (1.7 mmole) of 2-(5-nitro-2-furyl)imidazo[1,2-a]pyridine hydrobromide (XVII) and 5 ml of DMSO was heated on a boiling-water bath for 1 h, after which it was cooled and filtered to give 0.34 g of 3-bromo-2-(5-nitro-2-furyl)imidazo[1,2-a]pyridine (XVIII). Dilution of the filtrate with water precipitated an additional 0.04 g of the bromo derivative. The overall yield was 0.38 g (70%).

Bromo-Substituted Imidazo Compounds (XI-XIII). A solution of 5 mmole of bromine in 20 ml of chloroform was added gradually to a solution of 5 mmole of imidazo compound (VIII-X) in 80 ml of chloroform, the mixture was allowed to stand for 2 h, and the precipitate was removed by filtration and recrystallized from DMF.

3-Bromo-2-(5-nitro-2-furyl)imidazo[2,1-b]benzothiazole (XVI). This compound was obtained by method D from bromo ketone XIV and amine XV by heating the mixture for 1 h.

Reaction of 5-Nitro-2-acetylfuran with Iodine and 2-Aminopyridine in DMSO. A mixture of 1.55 g (10 mmole) of 5-nitro-2-acetylfuran, 2.82 g (30 mmole) of 2-aminopyridine, 2.54 g (10 mmole) of iodine, and 25 ml of DMSO was allowed to stand at room temperature for 3 days, after which 25 ml of water was added, and the precipitated 2-(5-nitro-2-furyl)imidazo[1,2-a]-pyridine (XIX) was removed by filtration to give 1.14 g (50%) of a product with R_f^1 0.26, R_f^2 0.40, and mp 255°C (from DMF). Found: C 57.9; H 3.0; N 17.9%. $C_{11}H_7N_3O_3$. Calculated: C 57.6; H 3.1; N 18.3%. The filtrate was extracted with ether, and the ether was evaporated from the extract to give 1.1 g of 2-amino-5-iodopyridine (XX) with mp 128-129°C (from benzene). According to thin-layer chromatography (TLC), the product was identical to an authentic sample. Found: C 27.1; H 2.2; N 12.5%. $C_5H_5IN_2$. Calculated: C 27.3; H 2.3; N 12.7%.

3-(2-Furyl)-6-(5-nitro-2-furyl)imidazo[2,1-b]thiazole (XXI). A mixture of 1.66 g (10 mmole) of 2-amino-4-(2-furyl)thiazole, 2.34 g (10 mmole) of 5-nitro-2-bromoacetylfuran, and 50 ml of DMF was heated on a water bath for 5 h, after which 150 ml of water was added, and the precipitate was removed by filtration to give 2.83 g (95%) of a product with mp > 300°C (from DMF). Found: C 51.3; H 2.6; N 13.8%. $C_{13}H_7N_3O_4S$. Calculated: C 51.8; H 2.3; N 13.9%.

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INTRAMOLECULAR HYDROGEN BONDING IN 1-NITRO-5,10-DIHYDROPHENAZINE DERIVATIVES

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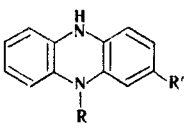
The formation of free radicals only for derivatives with a nitro group in the 1 position was observed in the oxidation of a number of 5-substituted 5,10-dihydrophenazines with lead dioxide. A long-wave absorption band was observed in the electronic spectra of the derivatives with a nitro group in the 1 position. The assumption of the formation of an intramolecular hydrogen bond in dihydrophenazines with a nitro group in the 1 position was confirmed by quantum-chemical modeling of the three structures of the 1,3-dinitro-5-phenyl-5,10-dihydrophenazine molecule. By comparison of the integral intensities of the bands of the stretching vibrations of the N–H bond in 5-substituted dihydrophenazines it was concluded that this bond is depolarized in derivatives with an intramolecular hydrogen bond.

In the oxidation of substituted 5,10-dihydrophenazines Ia-e and IIa-e with lead dioxide generation of phenazyl radicals was observed only for compounds with a nitro group in the 1 position. It was assumed that an intramolecular hydrogen bond is formed in these molecules [1, 2]. A similar hypothesis was expressed in [3].



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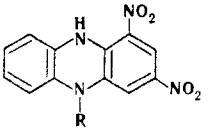

II

I a) R=CH_3, R′=H; b) R=$COCH_3$, R′=H; c) R=COC_6H_5, R=H; d) R=CO-(4-$NO_2C_6H_4$), R′=H; e) R=C_6H_5, R′=NO_2. II a) R=CH_3; b) R=C_6H_5; c) R=4-CH_3-C_6H_4; d) R=2,4-$(NO_2)_2$-C_6H_3; e) R=2,4,6-$(NO_2)_3$-C_6H_2

During a comparison of the electronic spectra of dihydrophenazines Ia-e and IIa-e we observed that a long-wave band with λ_{max} 530-565 nm is characteristic only for the second group

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