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Reaction of *N*,*N*-Dialkylcarboxamides with Halogens

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Abstract—*N*,*N*-Dialkylcarboxamides react with halogens in the absence of water to form complexes which are likely to have an ionic structure with the Hlg^+ ion coordinated at the carbonyl oxygen atom. These products can be isolated as individual compounds. Complexes with bromine undergo further transformations to afford bis-dialkylamide hydrogen tribromide and the corresponding α-bromo amide. When the reaction is carried out in the presence of water, the products are only bis-dialkylamide hydrogen tribromides; here, the *N*-alkyl groups act as a source of protons.

The reaction of *N*,*N*-dialkylcarboxamides with halogen was the subject of numerous studies. According to Gur'yanova *et al.* [1], such reaction in weakly polar media is reversible, and it yields 1:1 molecular complexes. The complex formation constants of dimethylformamide (DMF) [2], dimethylacetamide (DMA) [3], tetramethylurea [4], and *N*,*N*-dimethylbenzamide [5] with iodine in carbon tetrachloride at 25°C range from 2 to 7 l/mol. Bromine is a less active complexing agent than iodine toward DMF, whereas iodine chloride is more active [6]. It is assumed that the site of halogen coordination is the carbonyl oxygen atom [2]. In a more polar solvent, methylene chloride, the complex formation constant of iodine with DMF [7] and DMA [8] is slightly smaller than in carbon tetrachloride; in less polar heptane the complex formation constant of iodine with tetramethylurea [9] is somewhat greater than in CCl_4 (19 l/mol). Judging by the K_{ass} values, bromine and iodine form fairly weak complexes with *N*,*N*-dialkylcarboxamides. This is clearly seen when comparing with their thio analogs, *N*,*N*-dimethyl(thioacetamide) [10] and *N*,*N*,*N*′,*N*′-tetramethylthiourea [9] whose K_{ass} values for complex formation with iodine in CCl_4 [10] and heptane [9] exceed those found for amides [3, 4] by 2–3 orders of magnitude.

The conclusion that the above complexes are weak contradicts published data according to which complexes of dialkylcarboxamides with halogens can be isolated as individual compounds. For example, the isolation of DMF–bromine [11], DMF–chlorine [12], DMA–chlorine [12], DMA–bromine [13], and HMPA–bromine complexes [14] has been reported. The complexes DMF–Br_2 and DMF–Cl_2 were characterized by UV, IR, and ^{1}H NMR spectra [13]; ^{31}P NMR spectra and results of conductomertric measurements were reported for the complex HMPA–Br_2 [14]. These complexes were assigned [11–14] ionic structure with a $[-O-Br]^+ \cdot Br^-$ fragment.

Halogen complexes with amides can be used in organic synthesis. The bromine complex with DMA was used to brominate isoxazolidinones [15], and the HMPA–Br_2 complex was used to convert an alcohol–aldehyde mixture into the corresponding ester [16]. In the two cases, neither the complexes were isolated nor their structure was discussed. More frequently, the possibility for complex formation of dialkylcarboxamides with halogens is merely neglected, e.g., in the halogenation of poorly soluble compounds in dialkylamides as media possessing a strong dissolving power. Sometimes, the processes were carried out under fairly severe conditions. For instance, the chlorination of pyrazines was performed in DMF at 45–80°C [17], 4-nitroimidazoles were brominated in DMF at 60–70°C [18], and imidazo[2,1-*b*]thiazoles, at 80°C [19]. There are a number of examples which suggest as if dialkylcarboxamides are relatively stable toward halogens and their interaction is limited to formation of complexes without rupture of existing covalent bonds and formation of new bonds. However, polarographic study of bromine solutions in DMF [20] has shown that even at room temperature

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the total amount of bromine is gradually reduced to Br_3^- ion. It was presumed that dimethylformamide molecule is thus oxidized to radical cation whose further transformations were not examined. Later on, Mikhailov [21] found that the reaction of DMF with bromine is accompanied by profound transformations of the former and that the reaction course and product composition depend on the presence or absence of water in the system. Analogous products are formed in the reaction of DMF with iodine trichloride [22]. Profound transformations were also observed in the reactions of DMA with bromine [23, 24] and iodine chloride [25] and of HMPA with chlorine [26] and bromine [27]. Our experience shows that these reactions are strongly exothermic and that the main difficulty is not to initiate the process but to keep its quiet running.

We can conclude that there is a large divergence in published data on the reaction of halogens with *N*,*N*-dialkylcarboxamides:

(1) The interaction is such a weak that it could be neglected, and dialkylamides can be used as solvents for halogenation reactions;

(2) Formation of weak molecular complexes;

(3) Formation of stable isolable complexes in which the carboxamide skeleton remains unchanged;

(4) Vigorous reaction leading to essential transformation of the amide structure.

A plausible explanation is that halogen complexes (or adducts) with dialkylamides are actually formed but they are only intermediates in further transformations. Then, the stability of intermediate complexes can be considered in two aspects: first, as a high degree of association of halogen and dialkylamide. In this case, the greater the nucleophilicity (or basicity, or donor number) of amide and the greater the electrophilicity of halogen, the stronger is the complex (its formation constant is greater, and the degree of dissociation into initial components is lower). The other aspect is a weak ability of the complex to undergo further transformations; this process may be governed by other factors, e.g., ready elimination of hydrogen. The number of such assumptions is unlimited unless fine details of the structure of complexes and mechanism of their further transformations are known. Clearly, the role of halogen–dialkylamide complexes as possible intermediates may be substantiated by (1) isolation of halogen–dialkylamide complexes which are stable under standard conditions and (2) by performing their further transformations.

With the goal of obtaining relatively stable but reactive complexes we examined the behavior of a number of *N*,*N*-dialkylcarboxamides toward bromine and of some dialkylamides toward iodine and interhalogen compounds. The results of previous studies led us to conclude that complexes of amides with iodine and interhalogen compounds are stronger than those with bromine (here, the lower degree of dissociation is meant). Therefore, complexes with iodine and interhalogen compounds should be isolable *a priori*, provided that the corresponding complex with bromine is stable. The reactions of dialkylamides with halogens were carried out as follows. To a solution of appropriate amide in a thoroughly dehydrated inert solvent (the reactions with liquid amides were sometimes carried out without a solvent) we added a solution of halogen (bromine was added with no solvent), in some cases at reduced temperature. The product was separated, and the concentration of halogen and hydrogen halide was determined by iodometric titration. Obviously, a stable complex should be characterized by a concentration of halogen close to stoichiometric and zero concentration of hydrogen halide. The details are given in Experimental, and the results, in Table 1.

Among the examined amides, compounds **I** and **II** are the most nucleophilic; they are characterized by the greatest proton affinities (judging by the *PA* values from [28, 29]), the strongest ability to form hydrogen bonds (K_{HB} [30]), and high heat of mixing with bromine [31]. Amides **I** and **II** react with Br_2 at room (or even lower) temperature to afford red–orange viscous oily products which differ visually from the initial amides and bromine. The products contain a lot of hydrogen bromide. Presumably, the amide–Br_2 complex (if it is formed) undergoes fast further transformations. Less basic amides **III**–**VII** [32] behave similarly. A reason for fast transformations of the complexes may be liquid state of the primary adduct. *N*-Methylpyrrolidinone (**VIII**) gives a solid product with bromine, but it contains a lot of HBr. DMF (**IX**) and DMA (**X**) react with bromine at low temperature in solution (or without a solvent) to afford a red–orange solid low-melting product

Scheme 1.

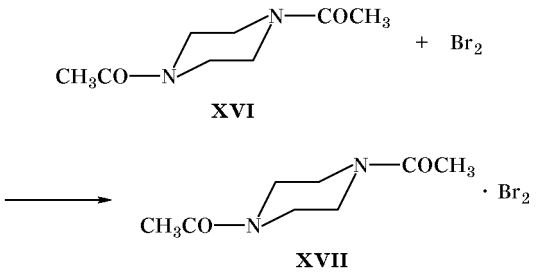


Table 1. Reaction of bromine with dialkylamides

Dialkylamide	Reaction conditions		Aggregate state of the product	Concentration, %		Isolation procedure[a]
	solvent	temperature, °C		Br_2	HBr	
N,*N*,*N*′,*N*′-Tetramethylurea (**I**)	–	–15	Liquid	42–46	9–18	*f*
	CCl_4	–30		35	7.0	*c*
HMPA (**II**)	–	1	Liquid	25	12.0	*f*
	Heptane	–20		30	9.8	*c*
N,*N*-Dimethylpivalamide (**III**)	–	–10	Liquid	46	1.5	*f*
N-Acetylpiperidine (**IV**)	–	–20	Liquid[b]	45	4.4	*f*
N-Acetylmorpholine (**V**)	Chloroform	–5	Liquid	34	11.0	*a*
N,*N*-Dimethylbenzamide (**VI**)	–	20	Liquid	39	3.7	*f*
	Chloroform	–10		38	1.5	*a*
N-Benzoylpiperidine (**VII**)	–	20	Liquid	35	3.0	*f*
	Chloroform	–15		32	1.5	*a*
N-Methylpyrrolidinone (**VIII**)	–	–15	Solid	41	11.0	*d*
DMF (**IX**)	–	–10	Low-melting solid	59	2.4	*f*
	Chloroform	–60		50	0.5	*a*
DMA (**X**)	–	–15	Glassy material	53	0.2	*f*
	Chloroform	–40		49	0.1	*a*
	CCl_4	–30		45	0.5	*a*
N,*N*′-Diformylpiperazine (**XI**)	Chloroform	20	Solid	35	16.0	*d*
	Chloroform	–20		45	0.8	*e*
N,*N*′-Dipropionylpiperazine (**XII**)	Chloroform	20	Solid	32	14.0	*d*
	Chloroform	–35		43	0.4	*e*
N,*N*′-Dipivaloylpiperazine (**XIII**)	Chloroform	20	Solid	37	6.6	*d*
N,*N*′-Bis(dimethylcarbamoyl)piperazine (**XIV**)	Chloroform	20	Solid	34	13.0	*d*
N,*N*′-Dibenzoylpiperazine (**XV**)	Chloroform	20	Solid	6.2	0	*e*
N,*N*′-Diacetylpiperazine (**XVI**)	Chloroform	20	Solid	46	0	*e*

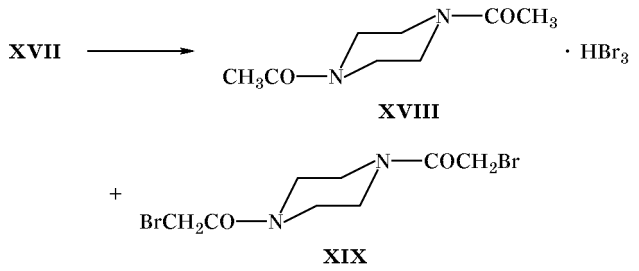
[a] See Experimental.

[b] Solidifies on storage as a result of further transformations.

(DMF) or a glassy material (DMA) with a high concentration of bromine and low concentration of HBr. The concentration of hydrogen bromide rapidly increases on storage at room temperature. Encouraging results were obtained in the series of *N*,*N*′-bisacylated piperazine derivatives. All *N*,*N*′-diacylpiperazines **XI**–**XVI** gave solid products in reaction with bromine.

The data in Table 1 show that at least one of the examined dialkylamides, *N*,*N*′-diacetylpiperazine (**XVI**), forms complex **XVII** with bromine, which is stable at room temperature (Scheme 1). On keeping in carbon tetrachloride or chloroform, complex **XVII** undergoes the same transformations as does DMA in the reaction with bromine [24]: It is converted into tribromide **XVIII** and *N*,*N*′-bis(bromoacetyl)piperazine (**XIX**) (Scheme 2). Structurally related *N*,*N*′-dipropionylpiperazine (**XII**) forms with bromine less stable complex **XX**; but the latter undergoes analogous transformations (Scheme 3). The yield of compound **XXI** was low, and it was not isolated as individual product. The ^{1}H NMR spectrum of the residue obtained by evaporation of the extract (after washing of the reaction mixture with chloroform) contained signals from the initial amide and α-bromo derivative.

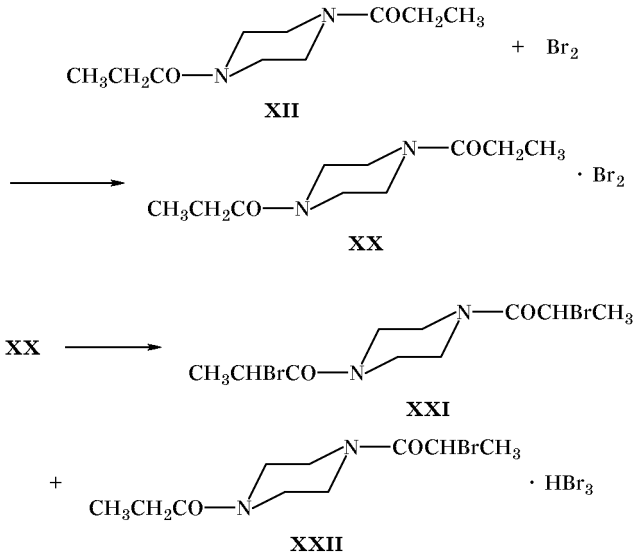
Scheme 2.



XVIII

XIX

Scheme 3.



XII

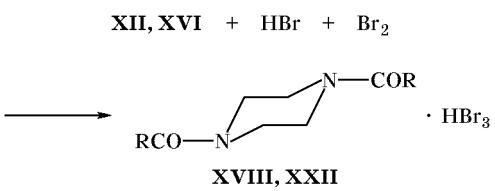
XX

XXI

XXII

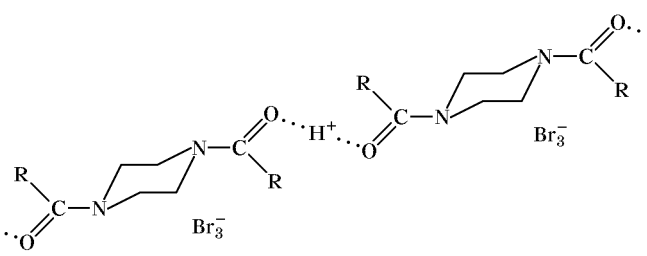
H-Complexes **XVIII** and **XXII** were also synthesized by independent procedure from the corresponding amide, hydrogen bromide, and bromine (Scheme 4).

Scheme 4.



XVIII, XXII

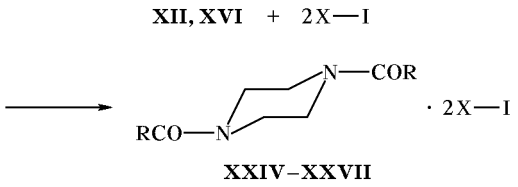
XVI, **XVIII**, R = Me; **XII**, **XXII**, R = Et.



The extremely low solubility of complexes **XVIII** and **XXII** suggests that they have a polymeric ionic structure (see above).

As expected, amides capable of forming stable complexes with bromine also give stable complexes with iodine and interhalogen compounds. Diacetylpiperazine **XVI** and iodine form 1:1 complex **XXIII**. The latter loses halogen on heating before melting. Interhalogen compounds, iodine chloride and iodine bromide react with amide **XVI** to form 2:1 complexes. *N*,*N*′-Bispropionylpiperazine (**XII**) reacts in a similar way (Scheme 5).

Scheme 5.



XXIV–**XXVII**

XXIV, R = Et, X = Cl; **XXV**, R = Et, X = Br; **XXVI**, R = Me, X = Cl; **XXVII**, R = Me, X = Br.

Table 2 lists the yields, physical properties, and elemental analyses of compounds **XVII**, **XVIII**, and **XXII**–**XXVII**. Hassel and Romming [33] noted an analogous difference in the stoichiometry of complexes formed by a difunctional nucleophile (dioxane) with bromine, iodine, and interhalogen compounds.

The IR spectrum of **XVII** in Nujol resembles that of the free ligand with the difference that the carbonyl stretching vibration band of the complex is displaced toward lower frequencies. The main IR absorption bands of complex **XVII**, diacetylpiperazine **XVI**, and tribromide **XVIII** are compared in Table 3. We previously showed [24] that bis(dimethylacetamide)–hydrogen tribromide, which is structurally related to **XVIII**, is protonated at the carbonyl oxygen atom, which is typical for carboxamides [34]. Presumably, the proton in **XVIII** is also coordinated at the carbonyl group. As a result, the C=O stretching vibration band shifts to lower frequencies, as compared to the nonprotonated amide. A similar shift of the carbonyl band is observed in the IR spectrum of **XVII**.

Complex **XVIII** shows in the IR spectrum a broad diffuse band typical of compounds having a short symmetrical –O···H···O– bond. An analogous band was observed in the IR spectrum of bis(dimethylacetamide)–hydrogen tribromide complex. Probably, vibrations in the above fragment are anharmonic [35].

The ^{1}H and ^{13}C NMR spectra of **XVII** in chloroform (Table 4) differ from those of parent amide **XVI**

Table 2. Yields, melting points, colors, and elemental analyses of compounds **XVII**, **XVIII**, and **XXII**–**XXVII**

Comp. no.	Yield, %	mp, °C	Color	Found, %				Formula	Calculated, %			
				C	H	N	Hlg[a]		C	H	N	Hlg
XVII	70	[b]	Yellow–orange	27.49	4.56	8.51	48.66 (48.45)	$C_6H_{14}Br_2N_2O_2$	29.12	4.28	8.49	48.42
XXIII	69	[b]	Violet	22.73	3.42	6.80	59.75 (60.00)	$C_8H_{14}I_2N_2O_2$	22.66	3.33	6.61	59.86
XXVI	70	120–122	Light yellow	19.48	2.92	5.66	65.62 (65.82)	$C_8H_{14}Cl_2I_2N_2O_2$	19.41	2.85	5.66	65.61
XXVII	56	100–102	Orange	16.47	2.51	4.75	70.85 (70.87)	$C_8H_{14}Br_2I_2N_2O_2$	16.46	2.42	4.80	70.85
XXIV	84	81–83	Light yellow	22.95	3.59	5.37	61.93 (62.08)	$C_{10}H_{18}Cl_2I_2N_2O_2$	22.97	3.47	5.36	62.09
XXV	93	60–62	Orange	19.93	3.19	4.50	66.84 (66.88)	$C_{10}H_{18}Br_2I_2N_2O_2$	19.63	2.97	4.58	67.60
XVIII[c]	72	183–184	Yellow–orange	23.85	3.75	6.85	57.81 (37.70)	$C_8H_{15}Br_3N_2O_2$	23.38	3.68	6.82	58.33
XXII[d]	64	168–170	Yellow–orange	27.40	4.48	6.03	54.70 (36.00)	$C_{10}H_{19}Br_3N_2O_2$	27.36	4.36	6.38	54.61

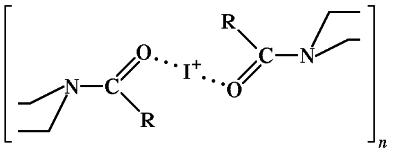
[a] Total halogen; in parentheses is given the active halogen concentration.
[b] Loses halogen on heating.
[c] Found, %: HHlg 19.95.
[d] Found, %: HHlg 18.50.

Table 3. IR spectra of complexes **XVII** and **XVIII** and free ligand **XVI**

Comp. no.	ν, cm^{-1}												
XVI	1650 (C=O)	1281	1250	–	–	–	1006	980	727	624	590	539	458
XVII	1635 (C=O)	1283	1252	–	–	–	1005	984	727	627	589	540	454
XVIII	1655 (C=O)	1285	–	1170	1095	1033	1009	945	–	631	571	–	–

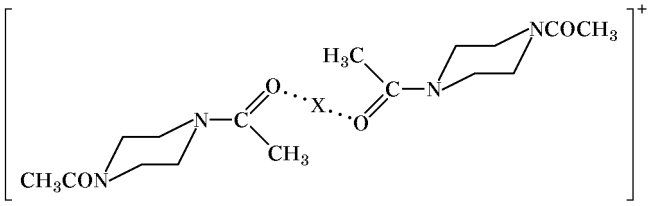
by a slight downfield shift of all signals. On storage of a solution of complex **XVII** in acetonitrile (even specially purified from reducing impurities), hydrogen bromide accumulates in the mixture at an appreciable rate. This process strongly hampers UV spectroscopic and conductometric studies of **XVII** in solution. Stable complexes of dipropionylpiperazine with iodine bromide (**XXV**) and iodine chloride (**XXIV**) are much better soluble. The equivalent electric conductivity of solutions of complex **XXV** in acetonitrile in the range of concentrations from 10^{-2} to 10^{-3} M is about 8 $\Omega\,cm^2\,mol^{-1}$, and it shows a weak concentration dependence. These data indicate that complexes **XXIV** and **XXV** in solution exist as ionic species. The UV spectra of acetonitrile solutions contain absorption bands at λ 227 (**XXIV**) and 256 nm (**XXV**). Their position differs from the position of bands of initial interhalogen compounds and amides but is typical of $[ICl_2^-]$ and $[IBr_2^-]$ ions [36]. Counterions are likely to be iodine cations coordinated to two carbonyl groups of two dipropionylpiperazine molecules. The color of the solid complexes corresponds to the color of salts having ICl_2^- and IBr_2^- anions. In addition, diacetylpiperazine complexes with iodine chloride and iodine bromide are very poorly soluble in most moderately polar solvents. In this respect, they resemble the corresponding H-complexes of diacylpiperazines. An analogous stoichiometry and low solubility of the 1,4-diazabicyclo[2.2.2]octane complex with bromine [37] and of the 4,4-bipyridine

complex with iodine chloride [38] were previously interpreted as factors indicating an ionic polymeric structure of these hypervalent compounds. We can conclude that solid complexes **XXIV**–**XXVII** exist as ionic crystals in which one iodine cation is surrounded by two "halves" of two different diacylpiperazine molecules as shown below:



XXIV–XXVII

Complexes of diacetylpiperazine with bromine and iodine (compounds **XVII** and **XXIII**) have a different stoichiometry, but their color resembles the color of salts formed by Br_3^- and I_3^- ions. Presumably, complexes **XVII** and **XXIII** have an analogous structure in which the halogen cation coordinates to two "whole" diacylpiperazine molecules. Taking into account that compounds **XVII** and **XXIII** have no sharp melting point but lose the halogen on heating to give the initial amide, molecular structure of these complexes is also possible. In this case, polymeric molecular structure with bridging halogen atoms can be assumed (like that described by Hassel for the dioxane–bromine complex [33]):



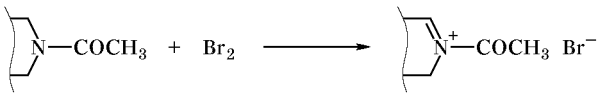
$\cdot$ [X—X—X]$^-$

XVII, XXIII

XVII, X = Br; **XXIII**, X = I.

Naturally, the available data are insufficient to unambiguously choose between the molecular and ionic structure of diacylpiperazine complexes with halogens; the problem calls for a special investigation. However, it is clear that dialkylamide complexes with halogens do exist and that under certain conditions they can be isolated as individual compounds. It is also clear that the halogen atom coordinates at the carbonyl oxygen atom and that just these complexes are intermediates in the bromination of amide at the acyl moiety. When the formation of complexes with an O···Br bond is hindered or impossible, the reaction with bromine follows a different pathway. Complex **XVII** cannot be obtained by reaction of diacetylpiperazine with bromine in the presence of water. Here, the carbonyl group is deactivated due to hydrogen bonding with water molecules. Nevertheless, the reaction with bromine does occur, and the major product is diacetylpiperazine–hydrogen tribromide complex **XVIII** which is formed in high yield. The yields of the other products are very small, so that they can be neither isolated nor characterized. The ^{1}H NMR spectrum of the oily residue obtained by washing of the reaction mixture with chloroform and subsequent evaporation of the extract contains no signals assignable to bromoacetyl group protons. Also, there are no signals typical of piperazine ring which is likely to decompose giving rise to protons. Under these conditions, the first (or one of the first) stage of oxidation of an organic substrate is the same as in the halogenation of acyclic dialkylcarboxamides [24], which involves intermediate formation of iminium salt (Scheme 6).

Scheme 6.

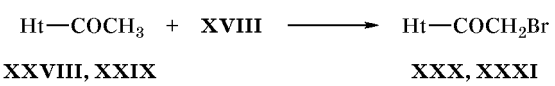


Its further transformations remain unclear. The extremely low yield of organic products in the bromination in the presence of water indicates that the most probable reaction path is profound decomposition of the piperazine ring via oxidation and hydrolysis. Halogen binding to the carbonyl group may also be hindered for steric reasons, as, e.g., in the case of *N*,*N*′-dipivaloylpiperazine (**XIII**). Pivalamides are characterized by reduced barrier to rotation about the C–N bond [34] and reduced conjugation between the lone electron pair on the nitrogen and double C=O bond. As a result, pivalamides behave largely as amines rather than amides (i.e., as N-nucleophiles rather than O-nucleophiles). Therefore, the reaction of *N*,*N*′-dipivaloylpiperazine with bromine leads to fast decomposition of the piperazine ring.

N,*N*′-Diacetylpiperazine–hydrogen tribromide complex **XVIII** is a convenient reagent for acid-catalyzed bromination of acidophobic compounds due to high concentration of active bromine, stability on prolonged storage, safe handling, and low solubility in most organic solvents. The reactions of complex **XVIII** with acetyl-substituted furan and thiophene derivatives **XXVIII** and **XXIX** smoothly afforded the

corresponding bromoacetyl-substituted compounds **XXX** and **XXXI** (Scheme 7).

Scheme 7.

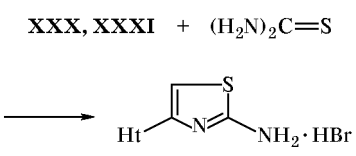


XXVIII, XXIX **XXX, XXXI**

XXVIII, **XXX**, Ht = 4-methyl-2-furyl;
XXIX, **XXXI**, Ht = 2-thienyl.

The structure of bromoketones **XXX** and **XXXI** was proved by the ^1H and ^{13}C NMR spectra and by their transformation into aminothiazoles via reaction with thiourea (Scheme 8).

Scheme 8.



XXXII, XXXIII

XXX, **XXXII**, Ht = 4-methyl-2-furyl;
XXXI, **XXXIII**, Ht = 2-thienyl.

EXPERIMENTAL

Spectrophotometric data were obtained using Specord UV-Vis, Specord M40, and SF-26 spectrophotometers. The IR spectra were measured on a UR-20 spectrometer. The ^1H NMR spectra were recorded on Tesla BS-467 (60 MHz) and Varian Gemini-200 (200 MHz) instruments; the ^{13}C NMR spectra were run on a Gemini-200 spectrometer at 50.3 MHz; tetramethylsilane or hexamethyldisiloxane was used as internal reference.

The concentration of water in liquid amides was monitored by GLC on an LKhM-8MD chromatograph equipped with a thermal conductivity detector; carrier gas helium, 3×2000-mm column packed with Versamide 900 on Inerton N-AW (0.16–0.20 mm). The bromination products were identified by HPLC using a GPTs chromatograph equipped with an RIDK-102 differential refractometer as detector; 3×150-mm column packed with Separon C18; eluent methanol–water, 7 : 3. The concentrations of active halogen and acids were determined by iodometric titration using a 0.01 M solution of $Na_2S_2O_3$.

Acetonitrile was purified by the known procedure [27]. Chloroform was washed with concentrated sulfuric acid, a saturated solution of sodium carbonate, and water, dried over calcium chloride, and distilled over phosphoric anhydride. Carbon tetrachloride was distilled over P_2O_5. Only freshly distilled solvents were used. Acetyl chloride, benzoyl chloride, dioxane, methanol, ethanol, and ethyl acetate were purified by simple distillation. Dimethylformamide, dimethylacetamide, tetramethylurea, dimethylpivalamide, triethylamine, piperidine, morpholine, and pivalic acid were purified by distillation through a 20-cm Vigreaux column. Hexamethylphosphoramide and *N*-methylpyrrolidinone were distilled under reduced pressure. Tertiary benzamides, as well as cyclic amides, namely *N*-acetylpiperidine, *N*-acetylmorpholine, *N*,*N*′-diacetylpiperazine, *N*,*N*′-dipropionylpiperazine, *N*,*N*′-dipivaloylpiperazine, *N*,*N*′-dibenzoylpiperazine, and *N*,*N*′-bis(dimethylcarbamoyl)piperazine (mp 130–132°C [39]) were synthesized by acylation of the corresponding amines according to standard procedures [40].

Iodine bromide and iodine chloride were prepared by known methods [41]. Molecular bromine of chemically pure grade was distilled over P_2O_5. Initial crystalline ligands were kept for 1 h under reduced pressure (0.1 mm) near melting point prior to reaction with bromine. Liquid organic nucleophiles were distilled just before use.

The possibility for formation of a stable complex was checked as follows. A flask was charged with an amide, appropriate solvent was added (if necessary), and bromine was added dropwise (1.1 equiv). The product was separated and analyzed for bromine and hydrogen bromide. The products were isolated by the procedures given below (cf. Table 1): (*a*) the solvent was removed under reduced pressure (water-jet pump); (*b*) the solvent was partially distilled off, and the precipitate was filtered off; (*c*) liquid adduct was separated using a separatory funnel and was dried under reduced pressure (water-jet pump); (*d*) the precipitate was filtered off and dried under reduced pressure; (*e*) the precipitate was filtered off but was not dried; and (*f*) when the reaction was carried out without a solvent, the reaction mixture was directly analyzed by iodometric titration. Table 1 summarizes the reaction conditions, product isolation procedure, and also the concentrations of active bromine and hydrogen bromide in the adduct.

***N*,*N*′-Diacetylpiperazine–bromine complex (XVII).** To a solution of 8.5 g (50 mmol) of anhydrous diacetylpiperazine in 50 ml of chloroform we added dropwise 5.2 ml (100 mmol) of bromine. Chloroform was partially distilled off (until a solid precipitated) under reduced pressure (water-jet pump), and the precipitate was filtered off. Yield 11.5 g (70%). The product was a 1 : 1 complex. We failed

to obtain a 2:1 complex of bromine with diacetylpiperazine, stable under standard conditions.

***N*,*N*′-Diacetylpiperazine–iodine complex (XXIII).** To a solution of 0.25 g (1.5 mmol) of diacetylpiperazine in 2 ml of methanol we added a solution of 0.37 g (1.5 mmol) of iodine in methanol. The solvent was removed under reduced pressure (water-jet pump) to obtain 0.43 g (69%) of complex **XXIII** as violet crystals. Like the bromine complex, the product lost halogen on heating and became colorless before melting.

N,*N*′-Diacetylpiperazine reacted with interhalogen compounds to form 1:2 complexes. Our attempts to obtain 1:1 complex by the above procedure gave a mixture of the 1:2 complex and the initial amide, which precipitated from the chloroform solution.

***N*,*N*′-Diacetylpiperazine–iodine chloride complex (XXVI).** To a solution of 0.5 g (2.9 mmol) of *N*,*N*′-diacetylpiperazine in 3 ml of chloroform we added a solution of 0.942 g (5.8 mmol) of iodine chloride in 4 ml of chloroform. A yellow solid precipitated immediately and was filtered off and dried on a filter. Yield 1 g (70%).

The complex of iodine bromide with *N*,*N*′-diacetylpiperazine (**XXVII**) was synthesized in a similar way.

***N*,*N*′-Dipropionylpiperazine complexes with iodine chloride and iodine bromide XXIV and XXV** were synthesized in a similar way, but to isolate the products it was necessary to remove the solvent almost to dryness, for the complexes are much more readily soluble in chloroform.

***N*,*N*′-Diacetylpiperazine–hydrogen tribromide complex (XVIII).** To a solution of 1 g (5.9 mmol) of amide **I** in 5 ml of water we added a mixture of 0.83 ml of 41% hydrobromic acid (5.8 mmol) and 0.3 ml (5.8 mmol) of bromine. The precipitate was filtered off, washed, and dried. We isolated 1.75 g (73%) of a yellow finely crystalline product with mp 183–184°C, which was poorly soluble in most moderately polar organic solvents.

***N*,*N*′-Dipropionylpiperazine–hydrogen tribromide complex (XXII)** was obtained in a similar way.

The yields, properties, amd elemental analyses of the newly synthesized complexes of *N*,*N*′-diacetyl- and *N*,*N*′-dipropionylpiperazine with halogens, as well as of the corresponding H-complexes, are given in Table 2. The chemical shift of the bridging proton in the ^{1}H NMR spectra of the complexes depends on the concentration and solvent preparation procedure; its signal is usually observed as a narrow singlet in the region δ 14.5–18.0 ppm.

Further transformations of the *N*,*N*′-diacetylpiperazine–bromine complex (XVII). A mixture of 11.5 g (34.9 mmol) of complex **XVII** with carbon tetrachloride was stirred for 5 days. The precipitate was filtered off, washed with chloroform, and dried. Yield of complex **XXII** 7.6 g. Its physical properties, elemental composition, and spectroscopic data coincided with those of a product obtained from *N*,*N*′-diacetylpiperazine, HBr, and bromine. The filtrate was evaporated on a rotary evaporator to isolate 2.65 g of *N*,*N*′-bis(bromoacetyl)piperazine (**XIX**). It was washed with water and recrystallized from benzene; colorless prisms, mp 156–158°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.3–4.0 m (8H, NCH_2CH_2), 3.86 s (4H, $COCH_2Br$). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.42, 41.88, 46.24. Found, %: C 28.25; H 3.51; Br 49.81; N 8.21. $C_8H_{12}Br_2N_2O_2$. Calculated, %: C 29.29; H 3.69; Br 48.72; N 8.54.

When the reaction of *N*,*N*′-diacetylpiperazine with bromine was carried out at a reactant ratio of 2:3 or 1:2, as well as on increasing the reaction time and using chloroform as solvent, the yield of compound **XIX** did not increase considerably, but the yield of H-complex **XXVIII** slightly increased.

Reaction of *N*,*N*′-diacetylpiperazine (XVI) with bromine in the presence of water. To a solution of 5.25 g (30.9 mmol) of amide **XVI** in 35 ml of water-saturated chloroform we added 2.45 ml (46.3 mmol) of bromine, and the mixture was kept for 2 days at 20°C. The first portion of product **XVIII** (6.58 g) was filtered off and, after 3 days, the second portion (4.15 g) was separated. The filtrate was evaporated on a rotary evaporator. The residue (0.45 g) was a mixture of an oily material containing some crystals of amide **XVI**. ^{1}H NMR spectrum of the oily product ($CDCl_3$), δ, ppm: 0.92–1.12 m, 1.86 s, 1.96 s, 1.98 s, 3.20–3.55 m, 4.73 s, 5.95 s, 6.00 s.

Reaction of bromine with *N*,*N*′-dipropionylpiperazine (XII). To a solution of 8.5 g (43 mmol) of dipropionylpiperazine in 50 ml of chloroform we added dropwise with stirring over a period of 30 min 3 ml (57 mmol) of bromine. The mixture was stirred for 7 days at room temperature, and the precipitate of complex **XXII** was filtered off and dried. Yield 12.8 g, yellow finely crystalline substance with mp 168–170°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.96 t (6H, $COCH_2CH_3$, ^3J = 7.56 Hz), 2.30 q (4H, $COCH_2CH_3$, ^3J = 7.5 Hz), 3.27–3.61 m (8H, NCH_2CH_2), 10 br.s (1H, HBr). UV spectrum: λ_{max} 270 nm (absorption of Br_3^- ion). Concentration of active bromine 35% (calculated 36.86%), HBr 18.50% (calculated 18.44%). The filtrate was evaporated on a rotary evaporator to obtain 0.8 g of an oily

Table 4. ^{1}H and ^{13}C NMR spectra of *N*,*N*′-diacetylpiperazine (**XVI**) and its complexes **XVII** and **XVIII**

Comp. no.	δ, ppm		δ_C, ppm					
	CH_3CO	NCH_2	CH_3CO	NCH_2				CH_3CO
XVI	2.02	3.32–3.58 m	21.17	40.90	41.11	45.72	45.99	169.04
XVII	2.10	3.40–3.70 m	21.24	41.01	41.22	45.81	46.07	169.22
XVIII[a]	2.00	3.26–3.59 m	–	–	–	–	–	–

[a] The ^{1}H NMR spectrum of complex **XVIII** was recorded in DMSO-d_6.

substance containing 1.40% of acid (HBr) and 5.48% of active bromine. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 t (*J* = 7.7 Hz), 1.82 d (*J* = 7.7 Hz), 2.44 q (*J* = 7.7 Hz), 3.23–4.01 m, 4.52 q (*J* = 7.7 Hz).

2-Bromoacetyl-5-methylfuran (XXX). To a solution of 5.3 g (42.7 mmol) of 2-acetyl-5-methylfuran in 25 ml of methanol we added 18 g (43 mmol) of compound **XVIII**, and the mixture was heated with stirring to 40°C. The undissolved red–orange precipitate of **XVIII** turned colorless, indicating that the reaction came to completion. The mixture was diluted with 25 ml of water and extracted with ether (4 × 20 ml), and the extract was dried over anhydrous calcium chloride. The extract was evaporated on a rotary evaporator to leave a dark oily residue which crystallized on storage. Yield 7.2 g (83%). The product contained no less than 87% of the main substance; the major impurities were unchanged initial compound **XXVIII** (6%) and, assumingly, 2-dibromoacetyl-5-methylfuran (7%). The product was distilled under reduced pressure (71–73°C/0.1 mm; oil pump with a trap cooled by liquid nitrogen) to obtain a yellow viscous liquid which crystallized on storage to afford light yellow crystals with mp 56–58°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.41 s (3H, CH_3), 4.26 s (2H, CH_2Br), 6.22 d (1H, 4-H, ^3J = 3.4 Hz), 7.50 d (1H, 3-H, ^3J = 3.4 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 13.80, 29.66, 109.44, 120.97, 148.74, 158.81, 179.21.

2-Bromoacetylthiophene (XXXI) was synthesized in a similar way using acetic acid as solvent. Light yellow liquid, yield 95%, bp 120–124°C (1 mm); published data [42]: bp 95–98°C (1 mm). The product crystallized on storage; yellow crystals, mp 33–35°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 4.41 s (2H, CH_2Br), 7.07–7.15 m (1H, 4-H), 7.70 d (1H, 5-H), 7.78 d (1H, 3-H). Compound **XXXI** was not analyzed for elemental composition because of its high volatility and strong lacrimatory properties.

The structure of compounds **XXX** and **XXXI** as α-bromo ketones was confirmed by their transformation into 2-aminothiazoles according to Hantzsch (via reaction with thiourea).

2-Amino-4-(2-thienyl)thiazole hydrobromide monohydrate (XXXIII). To a solution of 0.8 g (10.5 mmol) of thiourea in 10 ml of methanol we added 1.7 g (8.3 mmol) of 2-bromoacetylthiophene. After 24 h, methanol was distilled off from the mixture, and the residue was recrystallized from 5 ml of water. Yield 1.6 g (73%); bright yellow crystals, mp 104–106°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 7.07 s (1H, thiazole), 7.2 t (1H, 4-H, $^3J_{(1)}$ = 3.7, $^3J_{(1)}$ = 5.0 Hz), 7.6 d (1H, 5-H, ^3J = 3.7, ^4J = 1 Hz), 7.7 d (1H, 3-H, ^3J = 5.06, ^4J = 1 Hz). Found, %: C 29.87; H 3.24; Br 27.62; N 9.61; S 22.89. $C_7H_9BrN_2OS_2$. Calculated, %: C 29.89; H 3.22; Br 28.42; N 9.96; S 22.80.

2-Amino-4-(4-methyl-2-furyl)thiazole hydrobromide monohydrate (XXXII) was synthesized in a similar way. Light brown crystals (from water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.34 s (3H, CH_3), 6.25 d (1H, 4-H, ^3J = 1.5 Hz), 6.8 d (1H, 3-H, ^3J = 1.5 Hz), 6.9 s (1H, thiazole). Found, %: C 34.82; H 3.44; Br 28.03; N 10.33; S 11.24. $C_8H_{11}BrN_2O_2S$. Calculated, %: C 34.42; H 3.97; Br 28.60; N 10.03; S 11.49.

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