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BROMINATION OF δ-KETO AMIDES

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It is demonstrated that 3,5-dibromo-3,4-dihydropyridones are formed in the bromination of derivatives of δ-keto amides. The course of the bromination was investigated in the case of N-substituted and N-unsubstituted δ-keto amides. Dibromo-3,4-dihydropyridones were converted to the corresponding monobromopyridones. The stabilities of the compounds obtained were studied by subjecting them to thermal analysis. The structures of the compounds obtained were confirmed by their PMR, IR, and UV spectra.

We have previously shown that δ-keto amides I undergo intramolecular cyclization to dihydro-2-pyridone derivatives under the influence of acids or bases [1]. N-Alkyl-substituted δ-keto amides II do not form a dihydropyridone ring (III) under similar conditions because of steric hindrance. This paper is devoted to a study of the bromination of N-alkyl- and N-unsubstituted δ-keto amides in order to synthesize bromo derivatives of dihydro-2-pyridones.

The bromination of N-alkyl-δ-keto amides II with a twofold excess of bromine in chloroform or in acetic acid at room temperature leads to 1-alkyl-3,5-dibromo-3-(N-alkylcarbamoyl)-4,6-diphenyl-3,4-dihydro-2-pyridones (VIII). The UV and IR spectra of pyridones VIII (Table 1) are similar to those obtained for nitrogen-unsubstituted 3,4-dihydro-2-pyridones [1, 2], and this indicates that they have a dihydro structure. The PMR spectra of VIII (Table 2) contain, in addition to signals of protons of two phenyl and alkyl groups and an exocyclic amide group, singlets at 4.63-4.66 ppm, which correspond to the 4-H proton, and this confirms the presence of bromine in the 3 and 5 positions of the pyridone ring.

γ-Bromo-δ-keto amides IV are formed initially in the reaction of δ-keto amides II with 2 moles of bromine. This is confirmed by the bromination of amides II with an equivalent amount of bromine, as a result of which we obtained γ-butyrolactones V [3], which are capable of being formed only from γ-bromo-substituted δ-keto amide IV. The subsequent bromination of IV takes place in the α position to give α,γ-dibromo-substituted δ-keto amides VII, which, in contrast to IV, undergo cyclization to pyridones VIII. The bromine atom in the α position in amide VII promotes both spatial drawing together of the N-alkylamido and δ-carbonyl groups and hydrolysis of the N-alkylamido group. The spatial drawing together, which is responsible for the production of bromo derivatives of dihydropyridones VIII rather than lactones VI, which can be obtained only by bromination of lactone V, is the decisive factor in this case.

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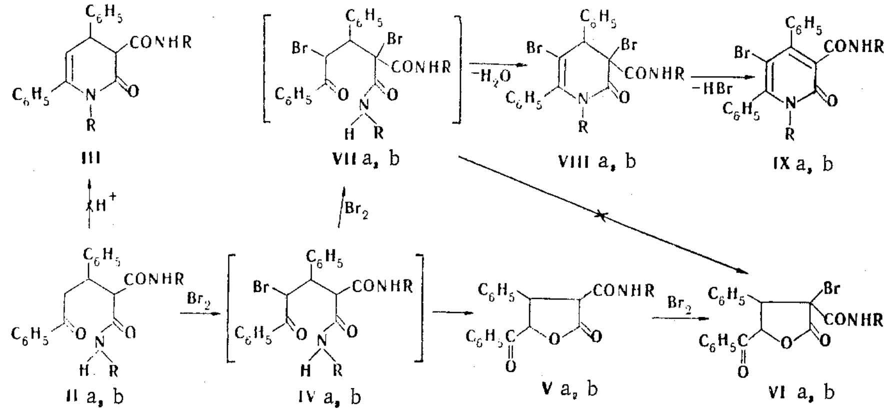
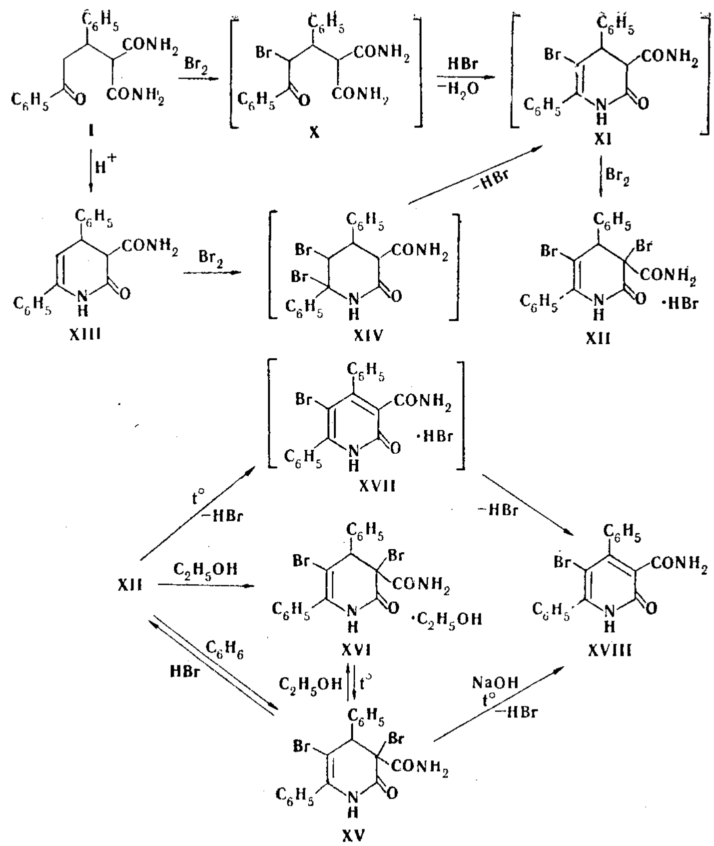


a $R=CH_3$; b $R=i\text{-}C_4H_9$

Dihydropyridones VIII in a slightly alkaline medium readily split out a molecule of HBr to give 5-bromo-2-pyridone derivatives IX. As compared with dihydro derivatives VIII, the signal of a 4-H proton is absent in the PMR spectra of pyridones IX (Table 2), a 70-nm bathochromic shift of the long-wave maximum is observed in the UV spectra, in connection with the formation of a pyridone ring, and a 30-38 cm^{-1} decrease in the frequencies of absorption of the endocyclic amide carbonyl groups is observed in the IR spectra (Table 1).



The bromination of N-unsubstituted δ-keto amides proceeds via a different pathway. Regardless of the amount of bromine (1:1 and 1:2) introduced into the reaction mixture, δ-keto amide I forms 3,5-dibromo-3,4-dihydro-2-pyridone, which is isolated in the form of hydrobromide salt XII. It is difficult to establish the sequence of the bromination and cyclization reactions in this case. It may be assumed that the initial product is γ-bromo-substituted X, which, under the influence of the liberated hydrogen bromide undergoes cyclization to 5-bromo-3,4-dihydro-2-pyridone (XI) and upon further reaction with bromine gives 3,5-dibromo-3,4-dihydro-2-pyridone (XII). α-Cyano-δ-keto amides are brominated similarly [4]. Compound XII is also formed by bromination of dihydropyridone XIII, which may be formed simultaneously with X under the influence of the liberated hydrogen bromide, since it is known that δ-keto amide I in an acidic medium readily forms a 3,4-dihydropyridone. In

TABLE 1. IR and UV Spectra of 2-Pyridones

Compound	IR spectra, ν, cm^{-1}			UV spectra, λ_{max}, nm ($\varepsilon \cdot 10^{-3}$)
	C=O (exo)	C=O (endo)	NH, NH_2	
VIIIa*	1650	1692	3335	203 (23,6); 225 i (13,6); 270 i (5,6)
VIIIb*	1645	1693	3300	203 (28,0); 225 i (13,6); 265 i (6,4)
IXa*	1645	1662	3300	205 (42,4); 245 i (15,0); 340 (9,6)
IXb*	1630	1655	3230	205 (39,4); 238 i (14,4); 335 (8,0)
XII	1660*	1692*	3100, 3160, 3260*	205 (36,0); 222 i (18,4); 272 (12,0)
	1695†	1720†	3220, 3410†	
XV	1655*	1708*	3270, 3365, 3430*	205 (32,0); 222 (18,4); 272 i (6,4)
	1680 i*			
	1695†	1720†	3230, 3410, 3510, 3570†	
XVI	1670*	1695*	3280, 3380*	203 (36,0); 221 i (19,2); 272 i (7,6)
	1695†	1720†	3230, 3410, 3500†	
XVIII*	1630	1672	3180, 3350	205 (50,0); 253 (26,0); 346 (13,2)

*The IR spectra were obtained from suspensions in Nujol.
†In dioxane.

TABLE 2. PMR Spectra of 2-Pyridones

Compound	Solvent	δ, ppm	
		4-H, s	other signals
VIIIa	$CDCl_3$	4,63	8,75 (1H, s, NH); 7,43 (5H, s, C_6H_5); 7,24 (5H, s, C_6H_5); 2,88 (3H, s, CH_3N); 2,60 (3H, d, J=5,0 Hz, CH_3NH)
VIIIb	$CDCl_3$	4,66	9,04 (1H, s, NH); 7,50 (5H, s, C_6H_5); 7,18 (5H, s, C_6H_5); 3,45 (2H, d, J=6,0 Hz, CH_2N); 2,88 (2H, t, J=6,0 Hz, CH_2NH); 1,61 (2H, m, CH); 0,65 (12H, m, CH_3)
IXa	$CDCl_3$	—	7,18—7,75 (10H, m, C_6H_5); 3,27 (3H, s, CH_3N); 2,67 (3H, d, J=6,0 Hz, CH_3NH)
IXb	$CDCl_3$	—	7,10—7,55 (10H, m, C_6H_5); 3,71 (2H, d, J=7,0 Hz, CH_2—N); 2,97 (2H, t, J=6,0 Hz, CH_2NH); 1,75 (2H, m, CH); 0,71 (12H, m, CH_3)
XII	$CDCl_3$	4,70	8,70 (1H, s, NH); 7,60 and 7,40 (2H, s, NH_2); 7,54 (5H, s, C_6H_5); 7,42 (5H, s, C_6H_5)
	DMSO	4,39	10,93 (1H, s, NH); 7,97 (1H, s, HBr); 8,25 and 7,72 (2H, s, NH_2); 7,47 (5H, s, C_6H_5); 7,35 (5H, s, C_6H_5)
XV	$CDCl_3$	4,70	8,52 (1H, s, NH); 7,60 and 7,40 (2H, s, NH_2); 7,55 (5H, s, C_6H_5); 7,41 (5H, c, C_6H_5)
	DMSO	4,36	10,95 (1H, s, NH); 8,22 and 7,68 (2H, s, NH_2); 7,43 (5H, s, C_6H_5); 7,32 (5H, s, C_6H_5)
XVI	$CDCl_3$	4,51	8,23 (1H, s, NH); 8,2 and 7,7 (2H, s, NH_2); 7,36 (5H, s, C_6H_5); 7,21 (5H, s, C_6H_5); 3,59 (2H, d, J=6,7 Hz, CH_2); 1,11 (3H, t, J=6,7, CH_3)
XVIII	DMSO	—	12,05 (1H, s, NH); 7,72 and 7,15 (2H, s, NH_2); 7,42 (5H, s, C_6H_5); 7,28 (5H, s, C_6H_5)

accordance with the literature data [5], we assume that in the bromination of dihydropyridone XIII bromine initially adds to the double bond to give dibromopiperidone XIV, which readily splits out hydrogen bromide. The resulting dihydro derivative XI upon further bromination gives salt XII. In contrast to the data in [5], we were unable to isolate dibromo derivative XIV in this case. The presence in salt XII of 1 mole of hydrogen bromide was established by potentiometric titration in a solution of 50% ethanol with sodium hydroxide. Salt XII is stable only in the crystalline state. During recrystallization from benzene it is converted to dihydropyridone XV. Adduct XVI is formed during crystallization of salt XII or dihydropyridone XV from ethanol.

The IR (in dioxane solution) and UV spectra (Table 1) of XII, XV, and XVI are almost identical and correspond to the dihydropyridone structure. In contrast to dihydropyridone XV, a signal at 7.97 ppm, which can be assigned to the HBr proton, appears in the PMR spectrum (in DMSO) of salt XII.

Like N-substituted dibromo derivatives VIII, N-unsubstituted dibromopyridone XV in an alkaline medium readily splits out a molecule of hydrogen bromide and undergoes oxidative debromination to 5-bromo-2-pyridone (XVIII). Adduct XVI, although it is chromatographically individual, does not have a sharp melting point. Thermal analysis of the latter with a derivatograph showed that this is associated with the thermal instability of adduct XVI. The thermoanalytical curves of XVI are presented in Fig. 1. Two steps corresponding to the two

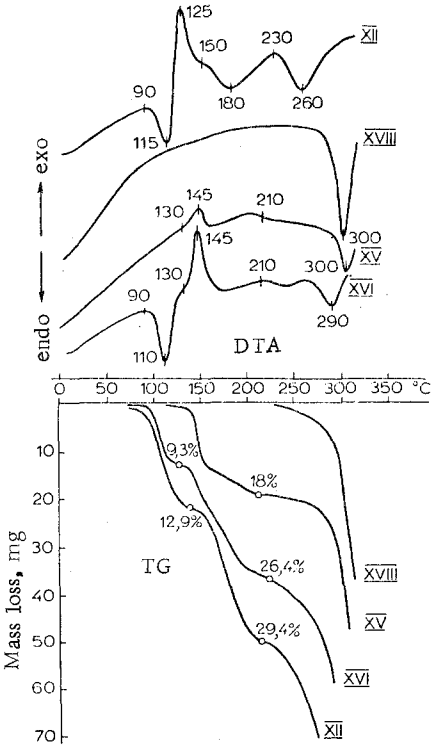


Fig. 1. Thermoanalytical curves (DTA and TG) of XII (sample weight 170 mg), XV (sample weight 100 mg), XVI (sample weight 140 mg), and XVIII (sample weight 90 mg).

stages in the thermal conversion of the substance are observed on the weight-change curve (TG). In the first step, which is accompanied by an endothermic effect (the DTA curve), the sample loses 9.3% of its weight at 90-130°C, and this corresponds to the removal of one molecule of C_2H_5OH and conversion of XVI to XV. An exothermic process with a mass loss of 17.1% occurs upon further heating at 130-210°C. This value is close to the calculated value (17.97%) for the removal of a molecule of HBr from XV. Consequently, oxidative dehydrobromination to give aromatic XVIII evidently takes place in the second stage of the transformation. At temperatures above 210°C XVIII begins to decompose with an endothermic effect at 290°C. Thus the thermal transformations of XVI evidently proceed via the scheme

$$\text{XVI} \xrightarrow[-C_2H_5OH]{90-130^\circ} \text{XV} \xrightarrow[-HBr]{130-210^\circ} \text{XVIII}.$$

This is completely confirmed by the thermal analysis of individual XV and XVIII. When XV is heated at 130-210°C, one observes an exothermic process with a mass loss of 18%, which corresponds to the removal of one molecule of HBr. No effects whatsoever are observed on the thermoanalytical curves of XVIII up to 210°C. A further increase in the temperature leads to decomposition of XVIII, which is accompanied by an endothermic effect at 300°C and a pronounced loss in weight.

The thermal transformation of XII is also a two-step process; however it differs in character from the process described above for XVI. Salt XII undergoes the following thermal transformations:

$$\text{XII} \xrightarrow[-HBr]{90-150^\circ} \text{XVII} \xrightarrow[-HBr]{150-230^\circ} \text{XVIII}$$

In the first stage at 90-150°C the sample sustains a loss in weight that is accompanied by an endothermic effect at 115°C and an exothermic effect at 125°C. The second stage takes

TABLE 3. Characteristics of the Compounds Obtained

Compound	mp, °C	Found, %				Empirical formula	Calc., %				R_f	Yield, %
		C	H	Br	N		C	H	Br	N		
VIa	157—158*	57,1	3,6	20,5	3,1	$C_{19}H_{16}BrNO_4$	56,7	4,0	19,9	3,5	0,66	54
VIIIa	153—155†	49,9	3,6	34,3	6,2	$C_{20}H_{18}Br_2N_2O_2$	50,2	3,8	33,4	5,9	0,76	56
VIIIb	122—124‡	55,1	5,2	29,3	4,8	$C_{26}H_{30}Br_2N_2O_2$	55,5	5,4	28,4	5,0	0,88	60
IXa	198—200†	60,1	4,2	19,7	6,7	$C_{20}H_{17}BrN_2O_2$	60,5	4,3	20,1	7,0	0,33	62
IXb	188—189*	64,7	6,1	17,4	5,6	$C_{26}H_{29}BrN_2O_2$	64,9	6,1	16,6	5,8	0,59	47
XII	147—150†	39,5	2,7	45,9	5,2	$C_{18}H_{15}Br_3N_2O_2$	40,7	2,8	45,1	5,3	0,40	94
XV	283—286**,††	48,7	3,0	34,8	6,1	$C_{18}H_{14}Br_2N_2O_2$	48,0	3,1	35,5	6,2	0,64	62
XVI	120—130†,††	48,3	3,9	33,0	6,0	$C_{20}H_{20}Br_2N_2O_3$	48,4	4,1	32,2	5,6	0,64	65
XVIII	298—300‡‡	57,9	3,7	22,2	7,3	$C_{18}H_{13}BrN_2O_2$	58,5	3,5	21,6	7,6	0,78	57

*In a mixture of ethanol with petroleum ether. †In ethanol. ‡In petroleum ether. **In benzene. ††At ~150°C the compound solidified, after which it remelted at ~285°C. ‡‡In a mixture of ethanol with acetic acid.

place at 150-230°C with heat absorption and is also associated with a loss in weight. The overall decrease in the weight of XII at 90-230°C is 29.4%, which corresponds to the removal of two molecules of HBr (the calculated value is 30.5%). The existence of an exothermic effect in the first stage makes it possible to assume that the first process involves oxidative dehydrobromination of salt XII to give hydrobromide salt XVII, which then loses one molecule of HBr and is converted to free base XVIII.

EXPERIMENTAL

The IR spectra of suspensions of the substances in paraffin oil and hexachlorobutadiene were recorded with a UR-20 spectrometer. The UV spectra of solutions ($2.5 \cdot 10^{-5}$ mole/liter) of the compounds in ethanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra were recorded with a Perkin-Elmer R-12A spectrometer (60 MHz) with tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was accomplished on Silufol UV-254 plates in an acetone–hexane system (1:1) with development in UV light. Thermal analysis was carried out with an OD-102 derivatograph (MOM, Hungary). A platinum flanged crucible with six flanges was used. The weights of the samples ranged from 90 to 170 mg. The heating rate in all of the experiments was 5 deg/min. The inert substance was α-Al_2O_3.

3,5-Dibromo-3-(N-methylcarbamoyl)-1-methyl-4,6-diphenyl-3,4-dihydro-2-pyridone (VIIIa). A) A 2-g (5.9 mmole) sample of amide IIa [6] was suspended in 10 ml of chloroform, 0.65 ml (12.5 mmole) of bromine was added, and the resulting solution was allowed to stand overnight at 20°C. The resulting oil was crystallized from ethanol to give 0.62 g (44%) of VIIIa (Table 3).

B) A 1-g (2.95 mmole) sample of amide IIa was suspended in 20 ml of acetic acid, 0.32 ml (6.24 mmole) of bromine was added, and the resulting solution was poured into water after 1 h. Workup gave 0.8 g (56%) of VIIIa.

3,5-Dibromo-3-(N-isobutylcarbamoyl)-1-isobutyl-4,6-diphenyl-3,4-dihydro-2-pyridone (VIIIb). A 0.13-ml (2.53 mmole) sample of bromine was added to a solution of 0.5 g (1.18 mmole) of amide IIb in 5 ml of acetic acid, and the resulting solution was poured into water after 3.5 h. The next day, the oil was separated and began to crystallize on treatment with alcohol, after which is was recrystallized (Table 3).

5-Bromo-3-(N-methylcarbamoyl)-1-methyl-4,6-diphenyl-2-pyridone (IXa). A 0.5-g (1.04 mmole) sample of dihydropyridone VIIIa was refluxed for 30 min in a 2.5% alcohol solution of sodium hydroxide, after which the reaction mixture was cooled and made weakly acidic, and the precipitate was separated (Table 3).

Pyridone IXb was similarly obtained.

3,5-Dibromo-3-carbamoyl-4,6-diphenyl-3,4-dihydro-2-pyridone Hydrobromide (XII). A) A 0.18-ml (3.50 mmole) sample of bromine was added to a suspension of 1 g (3.43 mmole) of amide I in 15 ml of chloroform. After 30 min, the clear solution was evaporated *in vacuo*, and the residue was crystallized from petroleum ether to give 0.6 g (35%) of salt XII.

B) This compound was similarly obtained from 1 g (3.43 mmole) of amide I and 0.36 ml (7.0 mmole) of bromine. The yield of salt XII was 0.85 g (50%).

C) A 1.18-ml (23 mmole) sample of bromine was added to a suspension of 2.92 g (10 mmole) of pyridone XIII [1] in 60 ml of chloroform, and the mixture was allowed to stand in a refrigerator for 3 h. The precipitate was removed by filtration and washed with petroleum ether to give 5 g (94%) of salt XII.

Recrystallization of salt XII from benzene gave dihydropyridone XV (Table 3), whereas recrystallization from ethanol gave XVI.

5-Bromo-3-carbamoyl-4,6-diphenyl-2-pyridone (XVIII). This compound was obtained from dihydropyridone XV by a method similar to that used to prepare IXa (Table 3).

α-Bromo-α-(N-methylcarbamoyl)-β-phenyl-γ-benzoyl-γ-butyrolactone (VIa). A 0.17-ml (3.31 mmole) sample of bromine was added to a suspension of 1 g (3.09 mmole) of lactone Va [3] in 20 ml of acetic acid. The next day, the solution was poured into water, and the precipitate was separated (Table 3). IR spectrum: 1665, 1695, 1788, and 3375 cm^{-1}. PMR spectrum (d_6-DMSO): 2.33 (CH_3), 4.34 (β-H), 6.46 (γ-H), and 7.2-8.0 ppm (aromatic protons, NH).

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SYNTHESIS OF HYDROGENATED HETEROCYCLIC COMPOUNDS FROM α-METHYLENE-1,5-DIKETONES.

5.* SYNTHESIS AND STEREOCHEMISTRY OF THE PRODUCTS OF ADDITION OF HYDRAZINES TO 2,4-DIBENZOYL-3-PHENYL-1,4-PENTADIENE

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UDC 547.828.829.07:541.63

The addition of phenyl- and 1,1-dimethylhydrazine to 2,4-dibenzoyl-3-phenyl-1,4-pentadiene leads to the formation of the corresponding 1-substituted 3,5-dibenzoyl-4-phenylpiperidines. 3-Benzoyl-4,6-diphenyl-1,7-diazabicyclo[3.2.1]oct-6-ene was obtained in the reaction with hydrazine.

We have previously reported [2] the addition of primary amines and hydroxylamine to 2,4-dibenzoyl-3-phenyl-1,4-pentadiene (I), which leads to the formation of the corresponding substituted piperidines. In the present paper we present data on the addition of phenylhydrazine, 1,1-dimethylhydrazine, and hydrazine to diketone I.

*See [1] for Communication 4.

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