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BROMINATION OF 5-SUBSTITUTED 3H-FURAN-2-ONES AND 3H-PYRROL-2-ONES

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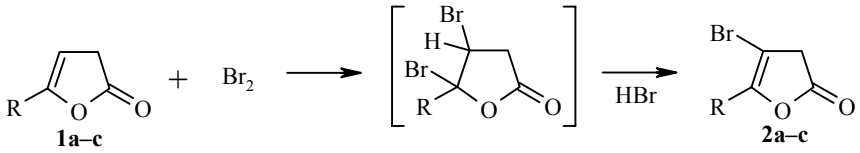
The bromination of 5-alkyl(aryl)-3H-furan-2-ones and 5-alkyl(aryl)-3H-pyrrol-2-ones and also their derivatives takes place at the ethylene bond with the formation of 4-monobromo derivatives. N-Phenyl-3H-pyrrol-2-ones are brominated simultaneously at the ethylene bond of the heterocycle and at the phenyl substituent at the nitrogen atom.

Keywords: 5-alkyl(aryl)-3H-pyrrol-2-ones, 5-alkyl(aryl)-3H-furan-2-ones, N-phenyl-3H-pyrrol-3-ones, bromination.

Five-membered 2-carbonyl-containing O- and N-heterocycles are chemically active compounds containing several reaction centers. We studied the reactivity of the methylene group and reaction at the ester fragment earlier [1, 2], and we also studied the reaction at the ethylene bond for the case of the reaction with dichlorocarbene under conditions of phase-transfer catalysis [3].

In the present work we present results on the bromination of 5-alkyl(aryl)-3H-furan-2-ones and 5-alkyl(aryl)-3H-pyrrol-2-ones and also their arylidene derivatives, the halogenation of which had not been studied before. It seemed of interest to study the regioselectivity of bromination in order to functionalize the obtained bromine derivatives further.

The bromination of 5-alkyl(aryl)-3H-furan-2-ones **1a-c** was carried out with various brominating agents (with a solution of bromine in acetic acid and with dioxane dibromide). The reaction was conducted under mild conditions at 18-20°C with the reagents in an equimolar ratio.



1, **2 a** R = C_5H_{11}, **b** R = C_6H_{13}, **c** R = Ph

It was shown on the basis of elemental analysis and ^{1}H NMR spectroscopy that bromination with bound bromine (dioxane dibromide) and with a solution of bromine in acetic acid leads to 5-alkyl(aryl)-4-bromo-3H-furan-2-ones **2a-c**, the formation of which is possible through a stage involving addition followed by dehydrobromination of the intermediate dibromide, which is transformed into the required products with a yield of up to 61%.

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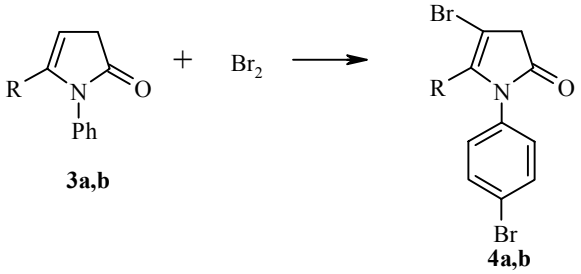
TABLE 1. The ^{1}H NMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm		
	R, m	$C(3)H_2$ / C(4)H, s	=CH–Ar, s
2a	0.85-1.94 (11H)	4.12 (2H)	—
2b	0.82-2.01 (13H)	4.15 (2H)	—
2c	7.50-7.75 (5H)	4.20 (2H)	—
4a	0.82-2.00 (9H)	3.95 (2H)	—
4b	0.82-2.02 (9H)	3.94 (2H)	—
4c	7.30-7.72 (9H)	3.95 (2H)	
4d	0.82-1.95 (9H)	4.05 (2H)	—
8a	7.40-7.72 (10H)	—	6.05
8b	7.30-7.70 (10H)	—	6.10
8c	7.45-7.75 (9H)	—	6.16
8d	7.40-7.75 (7H)	4.35 (1H)	6.65

The ^{1}H NMR spectra of compounds **2a-c** do not contain a signal for the vinylic proton. At 4.12-4.20 ppm there is a singlet for the methylene protons at C-3, and at 0.82-2.01 ppm there is a series of signals for the protons of the alkyl substituent at position 5 of the heterocycle (Table 1).

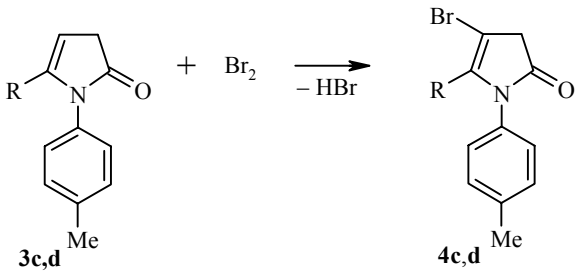
Analogous bromination conditions were used to study the reactivity of the ethylene bond in the nitrogen-containing analogs – 1,5-disubstituted 3H-pyrrol-2-ones **3a-c**. It was shown that the structure of the reaction products depends on the nature of the substituent at the nitrogen atom of the heterocycle. Thus, during the bromination of 5-alkyl-1-phenyl-3H-pyrrol-2-ones **3a**,**b** both addition of bromine at the ethylene bond of the heterocycle, followed by dehydrobromination, and electrophilic substitution in the phenyl fragment at the nitrogen atom occur. The obtained 5-alkyl-4-bromo-1-(4-bromophenyl)-3H-pyrrolones **4a**,**b** were isolated with yields of up to 65%.



3a,b **4a,b**

3, **4 a** R = Bu, **b** R = *i*-Bu

5-Alkyl(aryl)-1-(4-methylphenyl)-3H-pyrrol-2-ones **3c**,**d** were also brought into bromination. Their bromination with a solution of bromine in benzene under mild conditions led to the production of 5-alkyl(aryl)-4-bromo-1-(4-methylphenyl)-3H-pyrrol-2-ones **4c**,**d** with a yield of 52%.



3c,d **4c**,**d**

3, **4 c** R = Ph, **d** R = Bu

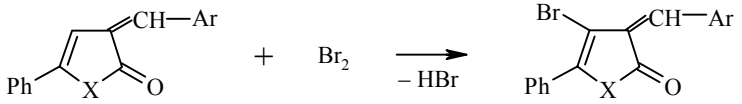
The IR spectra of compounds **4a-d** contain absorption bands for the lactam carbonyl in the region of 1680-1675 cm^{-1}, for the C=C double bond in the region of 1620-1610 cm^{-1}, and for the C–Br bond at 516-510 cm^{-1}. In the ^1H NMR spectra of compounds **4a-d** the signal for the vinylic proton at position 4 is absent, but there are signals for the protons of the methylene group at position 3 at 3.95-4.05 ppm and the methyl group of the aryl substituent at 2.14 ppm. In the downfield region there are a series of signals for the protons of the aromatic substituent at 7.34-7.45 ppm.

To confirm that the reaction can indeed occur at the phenyl fragment at the nitrogen atom the N-phenylamides of the 4-oxoalkanoic acids **5a**,**b**, which are intermediate products in the production of the 1,5-disubstituted 3H-pyrrol-2-ones and do not contain an ethylene bond, were also brought into bromination. Their reaction with bromine under mild conditions led to the formation of N-(bromophenyl)amides of 4-oxoalkanoic acids **6a**,**b** with yields of up to 70%.

5a,b **6a,b**

5, **6 a** R = Ph, **b** R = C_5H_{11}

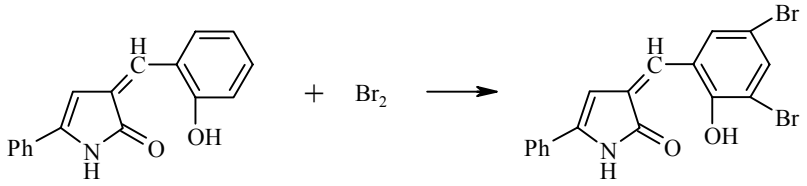
We also extended the bromination to the arylidene derivatives of furan-2-ones and pyrrol-2-ones, which contain two ethylene bonds. The concurrent formation of the products from addition of bromine either at the ethylene bond of the heterocycles or at the exocyclic ethylene bond could be expected for these compounds.



7a–c **8a–c**

7, **8 a**,**b** Ar = Ph, **c** Ar = C_6H_4–NO_2-3; **a** X = O, **b**,**c** X = NH

It should be noted that somewhat more drastic reaction conditions, i.e., heating at 45-50°C, are required in this case. It was found that the reaction of compounds **7a-c** with bromine leads to the formation of monobromine-containing products **8a-c** with yields of up to 53%.



7d **8d**

An exception is 3-(2-hydroxybenzylidene)-5-phenyl-3H-pyrrol-2-one (**7d**), the bromination of which takes place at the arylidene substituent at position 3, and this is due to the ease of halogenation of the benzene ring activated by the hydroxyl group. The ethylene bond of the ring in this case is not affected. We isolated 3-(3,5-dibromo-2-hydroxybenzylidene)-5-phenyl-3H-pyrrol-2-one (**8d**) with a yield of 42%. Its structure was confirmed by the ^1H NMR spectrum. In the spectrum of this compound the singlet of the vinylic proton of the heterocycle is retained at 4.35 ppm, and there is also a singlet for the proton of the exocyclic sp^2-hybridized carbon atom at 6.65 ppm and a series of signals for the protons of the aromatic substituents lie in the downfield region at 7.40-7.75 ppm.

TABLE 2. The Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	n_D^{20}	Yield, %
		C	H	N	Br			
2a	$C_9H_{13}BrO_2$	46.62 / 46.35	5.05 / 5.58		33.40 / 34.33		1.5020	60
2b	$C_{10}H_{15}BrO_2$	49.04 / 48.62	6.25 / 6.12		31.80 / 32.35		1.5050	54
2c	$C_{10}H_7BrO_2$	50.45 / 50.21	3.04 / 2.93		33.67 / 33.47		1.5120	61
4a	$C_{14}H_{15}Br_2NO$	45.10 / 45.04	3.95 / 4.02	3.60 / 3.75	43.10 / 42.89	266-268	—	63
4b	$C_{14}H_{15}Br_2NO$	45.15 / 45.04	3.96 / 4.02	3.65 / 3.75	43.05 / 42.89	262-264	—	65
4c	$C_{17}H_{14}BrNO$	62.31 / 62.19	4.31 / 4.27	4.40 / 4.27	24.52 / 24.39	72-73	—	51
4d	$C_{15}H_{18}BrNO$	58.74 / 58.44	5.96 / 5.84	4.72 / 4.54	26.70 / 25.97	75-76	—	52
6a	$C_{16}H_{14}BrNO_2$	58.10 / 57.83	4.35 / 4.22	4.53 / 4.22	24.54 / 24.09	130-131	—	68
6b	$C_{15}H_{20}BrNO_2$	55.35 / 55.21	6.23 / 6.13	4.10 / 4.29	24.35 / 24.54	125-126	—	72
8a	$C_{17}H_{11}BrO_2$	62.45 / 62.38	3.30 / 3.36		25.00 / 24.46	158-159	—	52
8b	$C_{17}H_{12}BrNO$	62.70 / 62.57	3.52 / 3.68	4.09 / 4.29	24.85 / 24.54	>200 (dec.)	—	53
8c	$C_{17}H_{11}BrN_2O_3$	60.38 / 60.17	3.41 / 3.24	7.85 / 8.26	24.05 / 23.59	>230 (dec.)	—	53
8d	$C_{17}H_{11}Br_2NO_2$	48.52 / 48.45	2.20 / 2.61	3.21 / 3.32	33.52 / 33.00	>250 (dec.)	—	42

Thus, the bromination of 5-alkyl(aryl)-3H-furan-2-ones and 5-alkyl(aryl)-3H-pyrrol-2-ones and their derivatives is realized under mild conditions at the ethylene bond of the heterocycle and leads to the formation of monobromo-substituted products. N-Phenyl-3H-pyrrol-2-ones are brominated simultaneously at the ethylene bond of the heterocycle and at the phenyl substituent.

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 instrument. The ^{1}H NMR spectra were obtained on a Varian FT-80A instrument at 80 MHz with TMS as internal standard. The yields and characteristics of the compounds are given in Tables 1 and 2.

5-R-3H-Furan-2-ones (1a-c) and 3-Arylidene-5-phenyl-3H-furan(pyrrol)-2-ones (7a-d). The compounds were obtained by the method in [1]. The 1-Ar-5-R-3H-pyrrol-2-ones **3a-d** and the amides of the 4-oxo acids **5a**,**b** were obtained by the method in [2].

5-Alkyl(aryl)-4-bromo-3H-furan-2-ones (2a-c). To a solution of the compound **1a-c** (6 mmol) in dioxane with cooling to 0°C we added 6 mmole of dioxane dibromide. The reaction mixture was then poured into cold water (30 ml), neutralized with sodium carbonate, and extracted with chloroform. The extract was dried over calcium chloride. The product was purified on a column of aluminum oxide with hexane as eluent.

5-Alkyl(aryl)-4-bromo-1-(4-bromophenyl)-3H-pyrrol-2-ones (4a,b). To a solution of the compound **3a**,**b** (30 mmol) in dioxane with cooling to 0°C we added dioxane dibromide (30 mmol). The mixture was kept for 30 min. The crystals that separated were recrystallized from 2-propanol.

5-Alkyl(aryl)-4-bromo-1-(4-methylphenyl)-3H-pyrrol-2-ones (4c,d). The compounds were obtained similarly to compounds **4a**,**b**. The products were recrystallized from chloroform.

N-(4-Bromophenyl)amides of 4-Oxo Acids (6a,b). The compounds were obtained similarly to compounds **4a-d**. The products were recrystallized from a 3:1 mixture of 2-propanol and hexane.

3-Arylidene-4-bromo-5-phenyl-3H-furan(pyrrol)-2-ones (8a-d). To a solution of the compound **7a-d** (5 mmol) in chloroform we added an equimolar amount of bromine. The mixture was heated on a water bath (45-50°C) for 30 min. The crystals that separated on cooling were recrystallized from hexane.

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