benzene was heated on a boiling-water bath for 2 h, after which it was cooled and neutralized with ammonium hydroxide. The precipitated IVa-d were removed by filtration and crystallized from isopropyl alcohol (IVa-c) or nitromethane (IVd).

Cyclization of III. An alcohol solution of 0.01 mole of III, 10 drops of concentrated HCl, and 12 drops of nitrobenzene was heated on a boiling-water bath for 2 h, after which it was cooled and filtered to remove the resinous precipitate, which was refluxed with ammonium hydroxide and triturated with water to give Va-c: R = H, mp 66-67°C (isopropyl alcohol) [1]; R = Br, mp 110-111°C (isopropyl alcohol). Found: C 65.7; H 4.6; Br 26.0; N 4.6%. $C_{17}H_{14}BrN$. Calculated: C 65.4; H 4.5; Br 25.6; N 4.5%; 65.4; R = F, mp 86-87°C (isopropyl alcohol). Found: N 5.1%. $C_{17}H_{14}FN$. Calculated: N 5.6%. Compounds Va-c were obtained in 15-20% yields. The mother liquor was evaporated to dryness, and the residue was treated with ammonium hydroxide and water. The solid material was dissolved in hot isopropyl alcohol, and the insoluble residue (VIb, c) was removed by filtration and crystallized from nitromethane to give VIb, c: R = Br, mp 227-228°C. Found: C 70.0; H 4.7; Br 12.9; N 4.6%. $C_{36}H_{29}BrN_2O_3$. Calculated: C 70.0; H 4.7; Br 12.9; N 4.5%. R = F, mp 270-271°C. Found: N 4.7%. $C_{36}H_{29}FN_2O_3$. Calculated: N 5.0%. Compounds VIb, c were obtained in $\sim$ 5-7% yields. The cooled isopropyl alcohol solutions were worked up to give IVa-d in 25-30% yields. Traces of 2-naphthylamine were removed by washing the precipitates with hot water.

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HALO-2-PYRONES IN THE ULLMANN REACTION. 1.

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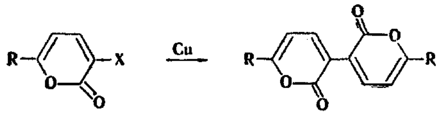
The Ullmann reaction was used for the first time for the synthesis of poly-2-pyrones. 3-Halo-2-pyrones were obtained by halogenation of the corresponding 6-aryl-2-pyrones. The Ullmann reaction was carried out by heating a mixture of the 3-halo-2-pyrone with activated copper in a stream of an inert gas. The reaction products were the previously undescribed bis-2-pyrones, in which the α-pyrone rings are interlinked by means of the 3-C atoms.

Continuing our search [1] for new biologically active substances in the pyrone series we obtained bis-2-pyrones that are directly interlinked in the 3 position. The Ullmann reaction, which consists in the reaction of a halo derivative of the pyrone with copper, was used for the first time for the synthesis of poly-2-pyrones.



I–V, VII X–XIII

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TABLE 1. Characteristics of the 3-Halo-6-aryl-2-pyrones

Compound	R	X	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
				C	H	X		C	H	X	
I	C_6H_5	Br	137—138	52,4	2,5	31,7	$C_{11}H_7O_2Br$	52,6	2,8	31,9	70
II	C_6H_5	I	160—161	45,8	2,5	43,9	$C_{11}H_7O_2I$	45,9	2,4	44,2	33
III	*p*-$CH_3C_6H_4$	Br	184—185	54,6	3,1	30,5	$C_{12}H_9O_2Br$	54,3	3,4	30,2	80
IV	*p*-$CH_3C_6H_4$	I	185—186	46,3	3,0	40,6	$C_{12}H_9O_2I$	46,2	2,9	40,7	30
V	*p*-$CH_3OC_6H_4$	Br	159—160	51,2	3,5	28,8	$C_{12}H_9O_3Br$	51,2	3,2	28,5	80
VI	2,5-$CH_3OC_6H_3$	Br	127—129	50,8	3,6	25,8	$C_{13}H_{11}O_4Br$	50,2	3,6	25,7	70
VII	2-Naphthyl	Br	186—187	59,5	3,1	26,5	$C_{15}H_9O_2Br$	59,8	3,0	26,6	75
VIII*	*p*-$NO_2C_6H_4$	Br	233—234	44,2	2,5	27,5	$C_{11}H_6O_4Br$	44,5	2,0	27,0	50
IX*	*m*-$NO_2C_6H_4$	Br	223—224	44,7	2,5	27,3	$C_{11}H_6O_4Br$	44,5	2,0	27,0	60

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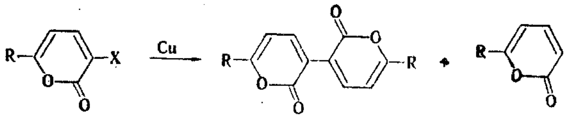
*The structure was confirmed by analysis for the N content.

TABLE 2. Ullmann Reaction for 3-Halo-6-aryl-2-pyrones



Starting compound	Time, h	Temp., °C	Reaction products											
			bis-2-pyrone								mono-2-pyrone			
			R	mp, °C	found, %		empirical formula	calculated, %		yield, %	R	empirical formula	mp, °C	yield, %
					C	H		C	H					
I	6	175	C_6H_5	300—302	77,1	4,3	$C_{22}H_{14}O_4$	77,2	4,1	35	C_6H_5	$C_{11}H_8O_2$[a]	67—68	26
II	2	165	C_6H_5	300—301	77,0	4,0	$C_{22}H_{14}O_4$	77,2	4,1	50	C_6H_5	$C_{11}H_8O_2$[a]	67—68	30
III	7	175	*p*-$CH_3C_6H_4$	310—312	77,6	4,7	$C_{24}H_{18}O_4$	77,8	4,9	32	*p*-$CH_3C_6H_4$	$C_{12}H_{10}O_2$[b]	102—102,5	30
IV	2	170	*p*-$CH_3C_6H_4$	310—311	77,8	5,1	$C_{24}H_{18}O_4$	77,8	4,9	47	*p*-$CH_3C_6H_4$	$C_{12}H_{10}O_2$[b]	102—103	40
V	15	185	*p*-$CH_3OC_6H_4$	296—297	71,3	4,2	$C_{24}H_{18}O_6$	71,6	4,5	10	*p*-$CH_3OC_6H_4$	$C_{12}H_{10}O_3$[c]	96—97	48
VII	18	195	2-Naphtyl	338—339	81,4	4,3	$C_{30}H_{18}O_4$	81,4	4,1	29	2-Naphthyl	$C_{15}H_{10}O_2$[d]	133—134	24

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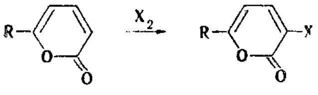
[a] This compound had mp 67-68°C [10]. [b] This compound had mp 102-103°C [11]. [c] This compound had mp 96-97°C [11]. [d] This compound had mp 133-134.5°C [11].

The 3-bromo and 3-iodo derivatives of 6-aryl-2-pyrones, which were obtained by halogenation of the corresponding 6-aryl-2-pyrones, were subjected to the reaction.

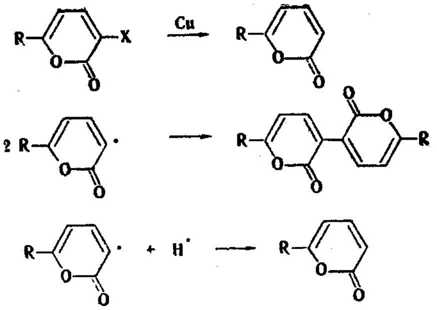


XIV–XX I–IX

The ease of the halogenation reaction depends to a great degree on the presence of electrophilic and nucleophilic substituents in the aromatic ring. 3-Bromo-6-phenyl-2-pyrone (I) was obtained in the bromination of 6-phenyl-2-pyrone (XIV). The bromination was carried out with bromine in chloroform and with dioxane dibromide. The bromination of 6-(p-tolyl)-2-pyrone (XV) proceeds more readily and gives the product in better yield than in the case of XIV. 6-(p-Methoxyphenyl)-2-pyrone (XVI) reacts very vigorously with bromine to give the 3-bromo derivative (V) in good yield. 6-(2,5-Dimethoxyphenyl)-2-pyrone is brominated considerably more slowly than XVI due to the steric factor. The bromination of 6-(2-naphthyl)-2-pyrone (XVIII) in the 3 position of the pyrone ring proceeds readily and gives the product in good yield. 6-(p-Nitrophenyl)-2-pyrone (XIX) and 6-(m-nitrophenyl)-2-pyrone (XX) undergo bromination with great difficulty. The reaction takes place only when the corresponding pyrone is refluxed with an equivalent amount of bromine. The yields of the reaction products do not exceed 60%, and pyrone XX reacts with bromine more rapidly than XIX.

The iodination of 6-aryl-2-pyrones [2] by the action of iodine in concentrated nitric acid leads to the formation of monoiodides, to which, in analogy with the products of bromination, 3-iodo structures were assigned. We found that two competitive reactions — iodination and nitration — take place in the oxidative iodination of 6-aryl-2-pyrones (with iodine in concentrated nitric acid). Despite the description of Shusherina and co-workers [2], we were unable to obtain only the 3-iodo derivative as a result of the reaction. We obtained 3-iodo and 3-nitro derivatives, which were isolated in pure form by means of chromatography. Data on the compounds obtained are presented in Table 1.

Finely dispersed copper was obtained by reaction of zinc with a saturated solution of cupric sulfate, and it was then activated [3]. The Ullmann reaction was carried out by heating the thoroughly ground powdered halo derivative and copper at 160-195°C in a stream of an inert gas. This method was used to obtain a number of 2-pyrone derivatives, data on which are presented in Table 2. It is known [4] that halo derivatives are arranged in the order RI > RBr > RCl with respect to their activity in the Ullmann reaction. Our data confirm this principle for 3-halo-2-pyrones. Thus 3-iodo-6-phenyl-2-pyrone (II) and 3-iodo-6-(p-tolyl)-2-pyrone (IV) react with copper more rapidly and give the product in better yield than in the case of I and III, respectively. Evidence for the free-radical mechanism of the Ullmann reaction has been presented by Nursten [5]. However, there is research [6] that shows that the Ullmann reaction proceeds through the formation of an intermediate organocopper compound. As a result of the Ullmann reaction, we obtained the corresponding mono-2-pyrones in addition to bis-2-pyrones, and this confirms a radical mechanism for this reaction in the case of 3-halo-2-pyrones.



The previously undescribed 3,3'-bis-2-pyrones are light-lemon-yellow or yellow crystalline substances that are only slightly soluble in most organic solvents and have high melting points. The IR spectra of X-XIII contain intense absorption bands at 1720-1740 and 1630-1650 cm^{-1}, which are the characteristic stretching vibrations used for the identification of the α-pyrone ring.

EXPERIMENTAL

Halogenation of 2-Pyrones

3-Bromo-6-phenyl-2-pyrone (I). A) A solution of 7.35 g (45.9 mmole) of bromine in 20 ml of chloroform was added at room temperature to 7.1 g (41.7 mmole) of 6-phenyl-2-pyrone (XIV) in 30 ml of chloroform, and the mixture was allowed to stand at room temperature for a day. The resulting precipitate was removed by filtration to give 7.35 g (71%) of cream-colored needles with mp 137-138°C (from alcohol) (mp 137°C [7]).

B) A solution of 3.8 g (13.5 mmole) of dioxane dibromide [8] in 10 ml of chloroform was added with vigorous stirring at room temperature to 2.6 g (13 mmole) of XIV in 20 ml of chloroform, and the mixture was stirred at 20°C for 16 h. The solvent was then removed by vacuum distillation, and the precipitated crystals were removed by filtration to give 1.8 g (60%) of I. The identical character of the reaction product and a sample of 3-bromo-6-phenyl-2-pyrone obtained previously was proved by thin-layer chromatography (TLC). No melting-point depression was observed for a mixture of the synthesized product with a sample of 3-bromo-6-phenyl-2-pyrone obtained by method A.

3-Iodo-6-phenyl-2-pyrone (II). A) A solution of 1.8 g of nitric acid (sp. gr. 1.49) in 15 ml of carbon tetrachloride and 5 ml of glacial acetic acid was added dropwise to a refluxing solution of 4.2 g (26 mmole) of XIV and 3.1 g (13 mmole) of iodine in 25 ml of glacial acetic acid and 15 ml of carbon tetrachloride, and the mixture was refluxed for 4 h. The solvents were removed by vacuum evaporation, and the residue was chromatographed with a column filled with activity II Al_2O_3 to give 2.45 g (33%) of II [mp 160-161°C (from alcohol) (mp 160-161°C [2]), elution with benzene] and 2.25 g (40%) of 3-nitro-6-phenyl-2-pyrone [mp 159-160°C (from alcohol) (mp 159-160°C [9]), elution with glacial acetic acid].

B) A solution of 8.22 g of nitric acid (sp. gr. 1.10) in 20 ml of glacial acetic acid was added in the course of 4 h to a refluxing solution of 5.2 g (30 mmole) of XIV in 50 ml of glacial acetic acid and 7.62 g (30 mmole) of iodine in 50 ml of carbon tetrachloride, and the mixture was refluxed for 4 h. It was then worked up as in method A to give 1.1 g (12%) of II and 1.4 g (22%) of 3-nitro-6-phenyl-2-pyrone.

3-Bromo-6-(p-tolyl)-2-pyrone (III). This compound was prepared by the method used to obtain I. According to the data in [2], it has mp 184.5-185°C.

3-Iodo-6-(p-tolyl)-2-pyrone (IV). This compound (mp 185.5-186°C [2]) was prepared by the method used to obtain II.

3-Bromo-6-(p-methoxyphenyl)-2-pyrone (V). A 16-g (100 mmole) sample of bromine was added in the course of 1 h to a cooled (with ice water) solution of 20.2 g (100 mmole) of 6-(p-methoxyphenyl)-2-pyrone (XVI) in 100 ml of chloroform, and the resulting precipitate was separated to give 20.7 g (82%) of yellow crystals of V with mp 159-160°C (from alcohol).

3-Bromo-6-(2,5-dimethoxyphenyl)-2-pyrone (VI). A solution of 3.2 g (20 mmole) of bromine in 15 ml of chloroform was added dropwise with vigorous stirring to 4.64 g (20 mmole) of 6-(2,5-dimethoxyphenyl)-2-pyrone (XVII) in 100 ml of chloroform, and the mixture was stirred at room temperature for 6 days. The solvent was then removed by distillation to give 4.3 g (69%) of light-lemon-yellow crystals of VI with mp 127-129°C (from benzene).

3-Bromo-6-(2-naphthyl)-2-pyrone (VII). A 16-g (100 mmole) sample of bromine was added to 11.1 g (50 mmole) of 6-(2-naphthyl)-2-pyrone (XVIII) in 75 ml of chloroform, and the resulting precipitate was stirred for 2 days. Workup gave 11.1 g (74%) of VII with mp 186-187°C (from alcohol).

3-Bromo-6-(p-nitrophenyl)-2-pyrone (VIII). A 3.5-g (22 mmole) sample of bromine was added to 3.5 g (17 mmole) of 6-(p-nitrophenyl)-2-pyrone (XIX) in 50 ml of chloroform, and the mixture was refluxed for 10 h. It was then cooled, and the precipitate was removed by filtration to give 2.35 g (50%) of yellow crystals of VIII with mp 233-234°C (from alcohol).

3-Bromo-6-(m-nitrophenyl)-2-pyrone (IX). A 4-g (25 mmole) sample of bromine was added to 4 g (18.5 mmole) of 6-(m-nitrophenyl)-2-pyrone (XX) in 50 ml of chloroform, and the mixture was refluxed for 10 h. The resulting precipitate was separated to give 3.3 g (62%) of yellow crystals of IX with mp 223-224°C (from alcohol).

Reaction of 3-Halo Derivatives of 2-Pyrones with Copper

3-Halo-6-aryl-2-pyrone and freshly activated copper in a ratio of 1 : 5 were triturated and stirrred in a stream of an inert gas. The prepared mixture was heated at 160-195°C for 2-18 h. The reaction was monitored by means of thin-layer chromatography. The fused mixture was pulverized and extracted with hot heptane to isolate the mono-2-pyrone and then with hot chloroform to isolate the bis-2-pyrone. Data on the reaction times and temperatures and the compounds obtained are presented in Table 2.

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