SYNTHESIS OF 2-ARYL-3,4,5,6-BIS(TRIMETHYLENE)PYRYLIUM SALTS AND THE CORRESPONDING PYRIDINE BASES

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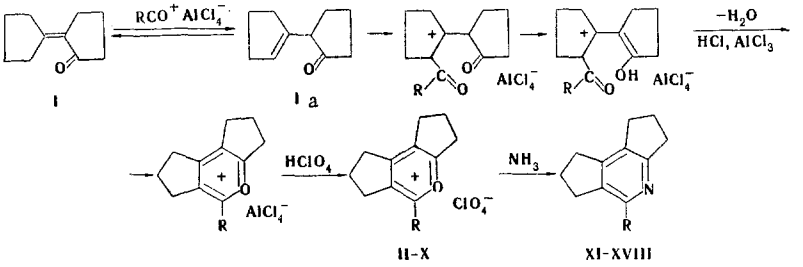
UDC 542.953.2:547.816'836.3.07

2-Aryl-3,4,5,6-bis(trimethylene)pyrylium perchlorates were obtained by acylation of cyclopentylidenecyclopentanone with aromatic acid chlorides in the presence of anhydrous aluminum chloride with subsequent treatment with 70% perchloric acid. The synthesized salts were converted to the corresponding pyridine bases.

2-Alkyl-3,4,5,6-bis(trimethylene)pyridines [1], which display biological activity [2], are formed in the acylation of cyclopentylidenecyclopentanone with aliphatic acid chlorides in the presence of 70% perchloric acid with subsequent treatment of the reaction products with 22% ammonium hydroxide. However, the intermediates – 2-alkyl-3,4,5,6-bis(trimethylene)pyrylium perchlorates – have not been isolated.

In order to isolate the 3,4,5,6-bis(trimethylene)pyrylium salts, we studied the acylation of cyclopentylidenecyclopentanone (I) with aromatic acid chlorides in the presence of anhydrous aluminum chloride via a previously developed method [3].

Under the reaction conditions, I undergoes partial rearrangement to Ia, which is then acylated via a known scheme [3,4].



It is known [5] that the characteristic bands in the IR spectra of pyrylium salts are those at 1610-1650 cm^{-1} (8a) and 1530-1560 cm^{-1} (8b), which are affiliated with the symmetrical and asymmetrical stretching vibrations of the heteroring, and the broad intense absorption band of the ClO_4^- ion at 1090-1100 cm^{-1} (see [6]). The spectra of the compounds that we synthesized contain these absorption bands, and this confirms the presence of the pyrylium structure.

When the salts obtained are treated with excess concentrated ammonium hydroxide, they are readily converted in high yield to the corresponding 2-aryl-3,4,5,6-bis(trimethylene)pyridines.

It was recently demonstrated [7] that depression of the analeptic and sedative action is observed when the methyl group is replaced by a phenyl group in the hydrochloride of a 2-substituted 3,4,5,6-bis(trimethylene)pyridine. In a pharmacological investigation of the hydrochlorides of 2-(p-methoxyphenyl)- and 2-(o-methoxyphenyl)-3,4,5,6-bis(trimethylene)pyridines that we synthesized, we detected a distinctly expressed neuroleptic effect and a capacity for prolongation of hexanal narcosis, while 2-styryl-3,4,5,6-bis(trimethyl-

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1461-1463, November, 1972. Original article submitted October 15, 1971.

TABLE 1. 2-Aryl-3,4,5,6-bis(trimethylene)pyrylium Salts (II-X)

Comp.	R	mp, °C	Empirical formula	Found, %			Calc., %			Yield, %	Characteristic bands in the IR spectrum, cm^{-1}
				C	H	Cl	C	H	Cl		
II	C_6H_5	168	$C_{17}H_{17}ClO_5$	60,6	5,0	10,6	30,1	4,9	10,1	43	1610, 1565, 1098
III	p-ClC_6H_4	148	$C_{17}H_{16}Cl_2O_5$	54,2	4,2	19,0	55,0	4,3	19,1	31	1608, 1562, 1094
IV	o-$CH_3OC_6H_4$	136	$C_{18}H_{19}ClO_6$	58,5	5,3	9,3	58,9	5,2	9,7	61	1610, 1564, 1090
V	m-$CH_3OC_6H_4$	151	$C_{18}H_{19}ClO_6$	59,2	5,6	9,4	58,9	5,2	9,7	41	1610, 1582, 1100
VI	p-$CH_3OC_6H_4$	102	$C_{18}H_{19}ClO_6$	58,5	5,4	9,4	58,9	5,2	9,7	65	1610, 1570, 1095
VII	p-$CH_3C_6H_4$	204	$C_{18}H_{19}ClO_5$	61,3	5,8	9,9	31,6	5,5	10,0	45	1610, 1572, 1090
VIII	$CH{=}CHC_6H_5$	187	$C_{19}H_{19}ClO_5$	62,5	5,4	9,5	52,9	5,3	9,5	38	1610, 1570, 1095
IX	3,4-$(CH_3O)_2C_6H_3$	131	$C_{19}H_{21}ClO_7$	57,5	5,3	8,9	56,9	5,6	9,2	27	1610, 1575, 1098
X	3,4-$(CH_3O)_2C_6H_3CH_2$	89	$C_{20}H_{23}ClO_7$	58,4	5,5	8,2	59,0	5,6	8,6	35	1612, 1578, 1100

TABLE 2. 2-Aryl-3,4,5,6-bis(trimethylene)pyridines (XI-XVIII)

Comp.	R	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				C	H	C	H	
XI	C_6H_5	81	$C_{17}H_{17}N$	86,5	7,1	86,8	7,3	94
XII	p-ClC_6H_5	105	$C_{17}H_{16}ClN$	73,2	6,1	73,5	5,9	92
XIII	p-$CH_3OC_6H_4$	96	$C_{18}H_{19}NO$	81,1	7,1	81,5	7,2	98
XIV	m-$CH_3OC_6H_4$	Oil*	—	—	—	—	—	—
XV	o-$CH_3OC_6H_4$	83	$C_{18}H_{19}NO$	81,3	7,1	81,5	7,2	89
XVI	p-$CH_3C_6H_4$	94	$C_{18}H_{19}N$	86,6	7,7	86,7	7,7	95
XVII	3,4-$(CH_3O)_2C_6H_3$	78	$C_{19}H_{21}NO_2$	76,9	6,3	77,4	6,7	92
XVIII	$CH{=}CHC_6H_5$	88	$C_{19}H_{19}N$	87,0	7,0	87,3	7,3	89

*The picrate had mp 130°. $C_{24}H_{22}O_8$. Found: C 58.9; H 4.8%. $C_{18}H_{19}NO \cdot C_6H_3N_3O_7$. Calculated: C 58.5; H 4.5%.

ene)pyridine hydrochloride prevents the onset of narcosis (L. V. Poddubnaya and L. B. Olekhnovich, Rostov-on-Don Medical Institute).

EXPERIMENTAL

General Method for the Synthesis of 2-Aryl-3,4,5,6-bis(trimethylene)pyrylium Perchlorates. Mixing of 9 mmole of aromatic acid chloride and 7.5 mmole of anhydrous aluminum chloride gave an acylating complex, to which 3 mmole of I was added. The mixture was heated on a boiling-water bath for 45 min and allowed to stand at room temperature for 1.5 h. It was then poured into a mixture of 10 g of ice and 5 ml of concentrated hydrochloric acid. The resulting aqueous emulsion was extracted twice with ether, and the aqueous solution was acidified with 1 ml of 70% perchloric acid. The resulting crystals were removed by filtration, washed with ether, and dried. The salts obtained by this method (Table 1) were crystallized from glacial acetic acid (II, III, and V-VIII) or 25% acetic acid (IV).

2-(3,4-Dimethoxyphenyl)-3,4,5,6-bis(trimethylene)pyrylium Perchlorate (IX). This compound was similarly obtained. The dark oil that formed after the reaction mixture was poured over ice was extracted with chloroform, and the salt was precipitated by the addition of ether. The precipitated hygroscopic crystals, which deliquesced rapidly in air, were removed by filtration in a box filled with dry air (dried with P_2O_5), and were stored in a vacuum desiccator over phosphorus pentoxide. Salt X was similarly obtained.

2-Aryl-3,4,5,6-bis(trimethylene)pyridines (Table 2). A 1.2-mmole sample of 2-aryl-3,4,5,6-bis-(trimethylene)pyrylium perchlorate was treated with excess 22% ammonium hydroxide, and the mixture was allowed to stand for 3 days. The resulting crystalline product was removed by filtration, washed with water, and dried. The product was purified by chromatography with a column filled with aluminum oxide [elution with chloroform–benzene (3 : 2)].

2-Aryl-3,4,5,6-bis(trimethylene)pyridine Hydrochlorides. An ether solution containing 8 mmole of 2-aryl-3,4,5,6-bis(trimethylene)pyridine was saturated with dry hydrogen chloride. The resulting dark oil was dissolved in acetone and precipitated by the addition of ether. The hydrochlorides were purified by reprecipitation of the salts from acetone solution by the addition of ether. The hydrochloride of pyridine XV was obtained in 79% yield and had mp 108°. Found: C 71.1; H 6.5; Cl 11.2%. $C_{18}H_{19}NO \cdot HCl$. Calculated: C 71.7; H 6.7; Cl 11.8%. The hydrochloride of pyridine XIII was obtained in 74% yield and had mp

209°. Found: C 71.1; H 6.2; Cl 11.3%. $C_{18}H_{19}NO \cdot HCl$. Calculated: C 71.7; H 6.7; Cl 11.8%. The hydrochloride of pyridine XVIII was obtained in 72% yield and had mp 119°. Found: C 76.2; H 6.2; Cl 11.4%. $C_{19}H_{19}N \cdot HCl$. Calculated: C 76.5; H 6.8; Cl 11.9%.

The IR spectra of mineral oil suspensions of the pyrylium salts were recorded with a UR-20 spectrophotometer at 700-1800 cm^{-1}.

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