SYNTHESIS OF PYRIDINE AND PYRIMIDINE DERIVATIVES BY REACTION OF PYRYLIUM SALTS WITH UREAS, THIOUREAS, AND ISOTHIOUREAS

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UDC 547.495'2.496'3.812.821'3.853'4.07

2,4,6-Triphenylpyrylium perchlorate is converted to 2,4,6-triphenylpyridine in reactions with urea and N-acetyl- and N,N-dimethylureas, whereas it is converted to 1,2,4,6-tetraphenylpyridinium perchlorate on reaction with N,N'-diphenylurea. The reaction of pyrylium perchlorates with thiosemicarbazide and semicarbazide leads to 1-thiocarbamido- and 1-carbamidopyridinium salts. The latter reacts with 2,4,6-triphenylpyrylium perchlorate to give 1-aminopyridinium salts, which were acylated with acetic anhydride. Difficult-to-obtain 2-alkylthio-4,6-diarylpyrimidines were synthesized in 40-93% yields by the reaction of 2,4,6-triarylpyrylium salts with S-alkylisothioureas.

A method for the preparation of pyrimidines from pyrylium salts and amidines was recently described [1]. The formation of a pyrimidine ring can also be expected in the reaction of the indicated salts with urea, thiourea, and their derivatives. We have found that 2,4,6-triphenylpyridine (II) is formed when 2,4,6-triphenylpyrylium perchlorate (I) is refluxed with urea, thiourea, and N-acetyl- and N.N-dimethylureas in dimethylformamide (DMF), whereas 1,2,4,6-tetraphenylpyridinium perchlorate is formed with N,N'-diphenylurea.

The reaction of pyrylium salts with semicarbazide and thiosemicarbazide, i.e., with N-aminourea and N-aminothiourea, also leads to pyridine derivatives. 1-Carbamido-2,4,6-triphenylpyridinium perchlorate (IVa, 28%) and 1,3,5-triphenylpentene-1,5-dione semicarbazone (68%) are formed from semicarbazide (IIIa) and salt Ia in ethanol. We also obtained 1,3,5-triphenylpentene-1,5-dione semicarbazone by alternative synthesis by the method in [2]. The reaction of aryl-substituted pyrylium salts Ia,d with thiosemicarbazide leads to perchlorates IVd,g in higher yields:



The reaction of alkyl-substituted pyrylium salts with semicarbazide was previously studied [3] and led to betaines, which were isolated in the form of 1-carbamidopyridinium picrates. Under our conditions, products of the reaction at the amino group of the hydrazine fragment (IVb,c,e,f) are also isolated in the reactions

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 324-328, March, 1979. Original article submitted March 1, 1978; revision submitted September 20, 1978.

Com- pound	mp, deg C <sup>a</sup>	IR spectrum cm <sup>-1</sup>	Found, %					Empirical	Calculated, %					- g
			с	н	CI	N	s	formu <b>la</b>	с	н	CI	N	s	Yie %
IV <sup>a</sup>	225-226,5	1110, 1590, 1625, 1690, 3200, 3320,	62,2	4,6	7,3	8,6		C <sub>24</sub> H <sub>20</sub> ClN <sub>3</sub> O <sub>5</sub>	61,9	4,3	7,6	9,0		28
IVP	197	3440 1100, 1570, 1600, 1630, 1700, 3200, 3300 3420	56,9	4,7	8,7			C19H18CIN3O5	56,5	4,5	8,8	_	_	70
IV <sup>c</sup>	197—199	1090, 1590, 1640, 1690, 3280, 3300,	38,9	5,1	12,3			$C_9H_{14}CIN_3O_5$	38,7	5,0	12,7	—	-	80
IV <sup>d</sup>	170—171	1090, 1570, 1600, 1630, 3220, 3330, 3440	60,3	4,4		8,5	6,2	$C_{24}H_{20}C1N_3O_4S$	59,8	4,2	<sup>`</sup> 7,4	8,7	6,6	75
IV <sup>e</sup> IV <sup>f</sup> IVg	141—143 171—172 196—198	1100, 1590, 1633, 3215, 3360, 3480 1100, 1585, 1640, 3200, 3320, 3430 1105, 1355, 1530, 1570, 1605, 1630,	$54,0 \\ 36,9 \\ 54,4$	4,5 5,1 3,9			7,2 10,4 6,0	C19H18CIN3O4S C9H14CIN3O4S C24H19CIN4O6S	54.4 36,6 54,7	4,3 4,8 3,6	8,4 12,0 6,7		7,6 10,8 6,1	92 71 59
Va Vb Vla Vl <sup>b</sup> Vl <sup>c</sup>	$\begin{array}{c} 161-163^{b} \\ 144-145 \\ 183-184^{c} \\ 251-252 \\ 225-226 \\ 168-169 \end{array}$	1100, 1550, 1580, 1625, 3355 1100, 1583, 1637, 3365, 3550 1090, 1560, 1615, 1643, 3285, 3370 1100, 1570, 1610, 1630, 1730, 3195 1110, 1573, 1605, 1630, 1730, 3220 1100, 1580, 1640, 1750, 3190	65,2 60,3 40,8 64,1 59,6 43,5	4,7 5,1 5,4 4,4 4,8 5,7	8,7 9,9 14,8 7,2 8,5 13,0	.		$\begin{array}{c} C_{23}H_{19}CIN_{2}O_{4}\\ C_{18}H_{17}CIN_{2}O_{4}\\ C_{8}H_{13}CIN_{2}O_{4}\\ C_{25}H_{21}CIN_{2}O_{5}\\ C_{20}H_{18}CIN_{2}O_{5}\\ C_{10}H_{15}CIN_{2}O_{5}\\ \end{array}$	65,3 59,9 40,6 64,6 59,8 43,1	4,5 4,8 5,5 4,6 4,5 5,4	8,4 9,8 15,0 7,6 8,8 12,7			98 93 49 72 86 93

TABLE 1. Characteristics of the Synthesized Pyridinium Perchlorates (IV-VI)

a) The following solvents were used for crystallization: acetic acid for IVa,b, Vb, and VIb, water for IVc, ethanol for IVd,f,g, methanol for Va,c and VIc, and chloroform with ether for VIa.b) This compound had mp 160-162 deg C [8]. c) This compound had mp 185 deg C [9].

of 2-methyl-4,6-diphenyl- (Ib) and 2,4,6-trimethylpyrylium (Ic) perchlorates with semicarbazide and thiosemicarbazide. 1-Phenylthiosemicarbazide reacts with salt Ia in DMF to give pyridine II in high yield. Thus the reaction proceeds only at one amino group under the investigated conditions with semicarbazide and thiosemicarbazide.

The reaction of IVa-c, which are also N-substituted ureas, with perchlorate Ia was also studied; pyridine II and the corresponding 1-aminopyridinium perchlorates (Va-c), which in view of their low basicities do not form bisperchlorates but are readily acetylated to give VIa-c, are formed in this case. The transformation found in this research can be regarded as a method for the preparation of 1-aminopyridinium salts from pyrylium perchlorates and semicarbazide. Thus pyrylium salts do not form pyrimidine derivatives with urea and thiourea derivatives.

In contrast to them, S-substituted isothioureas react with 2,4,6-triarylpyrylium salts to give pyrimidine derivatives. Thus 1-methyl- and 2-benzylthio-4,6-diarylpyrimidines (VIII) were obtained from S-methyland S-benzylisothioureas (VII):



I **a** R=H, **d**  $R=NO_2$ , **e**  $R=OCH_3$ ; VII **a**  $R'=CH_3$ , **b**  $R'=CH_2C_6H_5$ ; VIII **a** R=H,  $R'=CH_3$ ; **b**  $R=NO_2$ ,  $R'=CH_3$ ; **c**  $R=OCH_3$ ,  $R'=CH_3$ ; **d** R=H,  $R'=CH_2C_6H_5$ ; **e**  $R=NO_2$ ,  $R'=CH_2C_6H_5$ ; **f**  $R=OCH_3$ ,  $R'=CH_2C_6H_5$ 

The structure of pyrimidines VIII was confirmed by data from IR and PMR spectroscopy (see the experimental section). In addition, VIIId was identical to the compound described in [4]. It should be emphasized that the expected intermediate ketone IX, in contrast to the reaction of pyrylium salts with hydrazine [5], was not isolated. We also found that pyrylium salts Ib,c with one or several alkyl substituents do not form pyrimidines with S-benzylisothiourea under similar conditions but rather are converted to the corresponding pyridines.

TABLE 2. Characteristics of the Synthesized Pyrimidines VIII

-un	mp,°C	Found, %			,	Empirical	Ca	ılcu	lated	<b>,</b> %	IR spectrum cm <sup>-1</sup>			
9 2 2	ethanol)	с	н	N	s	TOrmuta	С	н	N	s	in spectrum, em	Yie		
<b>a</b> b	155 164—165 <b>a</b>	73,3 63,3	5,2 4,0	9,7 12,6	11,2 9,4	C <sub>17</sub> H <sub>14</sub> N <sub>2</sub> S C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S	73,4 63,1	5,1 4,1	10,1 13,0	11,5 9,9	1255, 1530, 1575, 1605 1250, 1355, 1540, 1580,	73 89		
$c^{b}$	98- <b></b> 99	69,8	5,6	8,9	1 <b>0</b> ,0	C₁8H₁6№2OS	70,1	5,2	9,1	10,4	1610 1240, 1250, 1530, 1578,	40		
d	147148 <sup>C</sup>	77,7	5,5	7,5	8,9	$C_{23}H_{18}N_2S$	77,9	5,1	7,9	9,0	1240, 1265, 1520, 1570, 1605	87		
e	149—150	69,2	4,3	10,3	8,2	C <sub>23</sub> H <sub>17</sub> N <sub>3</sub> O <sub>2</sub> S	69,2	4,3	10,5	8,0	1240, 1265, 1362, 1548, 1580, 1615	93		
f	9899	75,4	5,4	7,1	8,0	C24H20N2OS	75,0	5,2	7,3	8,3	1240, 1265, 1520, 1578, 1615	87		

a) From heptane. b) PMR spectrum: 2.65 (s,  $CH_3S$ ), 3.7 (s,  $CH_3O$ ), and 6.7-8.0 ppm (m, aromatic and heteroaromatic protons). c) This compound had mp 147-148 deg C [4].

We obtained the difficult-to-prepare 2-methyl(benzyl)thio-4,6-diarylpyrimidines for the first time in rather high yields from pyrylium salts and isothioureas. The only previously described member of this series (VIIId) was synthesized from  $\alpha$ , $\beta$ -dibromochalcone and S-benzylisothiourea in 5% yield [4].

## EXPERIMENTAL

The PMR spectrum in  $CCl_4$  was recorded with a Tesla BS 487C spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of the compounds in mineral oil were recorded with a UR-20 spectrometer. The purity of the compounds was monitored by thin-layer chromatography (TLC) on aluminum oxide in a heptane-ethyl acetate system (9:1) or in chloroform.

<u>Reaction of Perchlorate Ia with N,N-Dimethylurea.</u> A mixture of 1.02 g (2.5 mmole) of perchlorate Ia and 0.44 g (5.0 mmole) of N,N-dimethylurea was refluxed in 5 ml of DMF for 1 h, after which it was cooled and diluted with ether, and the ether solution was washed with water and dried. The ether was removed by distillation, and the residue was recrystallized from ethanol to give 0.55 g (72%) of 2,4,6-triphenylpyridine (II) with mp 137-138 deg C (137.5 deg [6]). A mixture of this product with the genuine compound had the same melting point.

The reaction of N-acetylurea, 1-phenylthiosemicarbazide, and N,N'-diphenylurea with perchlorate Ia was accomplished similarly. In the latter case the reagents were refluxed for 1.5 h, after which the mixture was cooled and treated with ether, and the precipitate was separated and dissolved in acetone. A few drops of 25% ammonium hydroxide were added, and the mixture was heated and treated with ether to precipitate 1,2,4, 6-tetraphenylpyridinium perchlorate (42%) with mp 264-265 deg C (265-266 deg [7]). IR spectrum: 1100, 1560, 1600, and 1630 cm<sup>-1</sup>. Found: C 71.2; H4.9; Cl 7.4%. C<sub>29</sub>H<sub>22</sub>ClNO<sub>4</sub>. Calculated: C 71.9; H 4.6; Cl 7.3%.

Reaction of the Pyrylium Salts with Semicarbazide. An aqueous solution of 10 mmole of NaOH and 5 mmole of perchlorate Ia-c was added gradually to 10 mmole of semicarbazide hydrochloride in ethanol, and the mixture was refluxed for 30 min. It was then cooled with ice, and the precipitated perchlorate IVc was removed by filtration. To isolate perchlorate IVb the solvent was removed by evaporation, the residue was treated with acetone, and IVb was precipitated from the acetone solution by the addition of ether. In the case of perchlorate IVa the residue after evaporation of the ethanol was treated with hot benzne, and the undissolved perchlorate IVa was precipitated by recrystallization from acetic acid. 1,3,5-Triphenylpentene-3-dione semicarbazone, with mp 191-191.5 deg C (from ethanol), was extracted in 68% yield from the benzene solution. IR spectrum: 1350, 1593, 1695, 3150, 3205, 3280, 3350, 3480 cm<sup>-1</sup>. Found: C 75.6; H 5.7; N 11.2%. Cal-C<sub>24</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub>. Found: C 75.2; H 5.5; N 11.0%.

The reaction of the pyrylium salts with thiosemicarbazide was carried out under the same conditions in a ratio of 1:1.2. Perchlorates IVd-g crystallized out of solution when the mixtures were cooled; prior filtration of the hot reaction mixture was necessary for the isolation of perchlorate IVg, while removal of a portion of the solvent was necessary for the isolation of IVd.

Reaction of Salts IVa-c with Perchlorate Ia. Perchlorates IV and Ia were used in a ratio of 1.2:1 and were refluxed in DMF for 1 h. The oil that separated when the cooled mixture was treated with ether was

washed with ether, after which a small amount of acetone was added, and 1-amino-2,4,6-trimethylpyridinium perchlorate (Vc) or 1-amino-2-methyl-4,6-diphenylpyridinium perchlorate (Vb) was removed by filtration; 1-amino-2,4,6-triphenylpyridinium perchlorate (Va) was precipitated with water.

The acylation of perchlorates Va-c was carried out in refluxing acetic anhydride for 30 min. 1-Acetamido-2,4,6-trimethylpyridinium (VIc) and 1-acetamido-2,4,6-triphenylpyridinium (VIa) perchlorates were precipitated by the addition of ether to the cooled reaction mixtures, whereas 1-acetamido-2-methyl-4,6diphenylpyridinium perchlorate (VIb) crystallized out from the reaction mixture. Data on perchlorates IV-VI are presented in Table 1.

Reaction of the Pyrylium Salts with Isothioureas. A solution of sodium, obtained from 4 mg-atom of sodium, was added with ice cooling to a suspension of 4 mmole of the salt of the corresponding isothiourea in absolute ethanol, 15 min after which, 2 mmole of perchlorate Ia,d,e was added, and stirring was continued for 4 h. The reaction mixture was allowed to stand in a refrigerator for 20 h, and the resulting precipitate was removed by filtration and treated with boiling heptane to extract pyrimidines VIIIa-f (Table 2). In the case of pyrimidine VIIIb the reaction was complete after 4 days.

The reaction of perchlorates lb,c with S-benzylisothiourea was accomplished similarly. At the end of the reaction, the precipitated NaCl was removed by filtration, the filtrate was evaporated, and the residue was washed with ether and recrystallized from water and acetic acid to give S-benzylisothiourea perchlorate (97%) with mp 179-180 deg C. IR spectrum: 1100, 1660, 3185, 3235, 3340, 3410 cm<sup>-1</sup>. Found: C 36.5; H 4.2; N 10.2; S 11.7%. C<sub>8</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>4</sub>S. Calculated: C 36.0; H 4.2; N 10.5; S 12.0%. The ether solution gave 2,4,6-trimethylpyridine picrate (40%) with mp 155-156 deg C (from ethanol, mp 155-156.5 deg C [10]). Found: N 15.8%. C<sub>8</sub>H<sub>11</sub>N · C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>. Calculated: N 16.0%. 2-Methyl-4,6-diphenylpyridine picrate, with mp 211-212 deg C (from acetic acid, mp 212-213 deg C (10)), was obtained in 47% yield. Found: C 60.7: H 4.0; N 12.1%. C<sub>18</sub>H<sub>15</sub>N · C<sub>6</sub>H<sub>3</sub>N<sub>3</sub>O<sub>7</sub>. Calculated: C 60.8; H 4.0; N 11.8%.

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