SYNTHESIS OF PYRIMIDINE DERIVATIVES BY REACTION OF PYRYLIUM SALTS WITH GUANIDINE AND COMPOUNDS OF THE GUANIDINE SERIES

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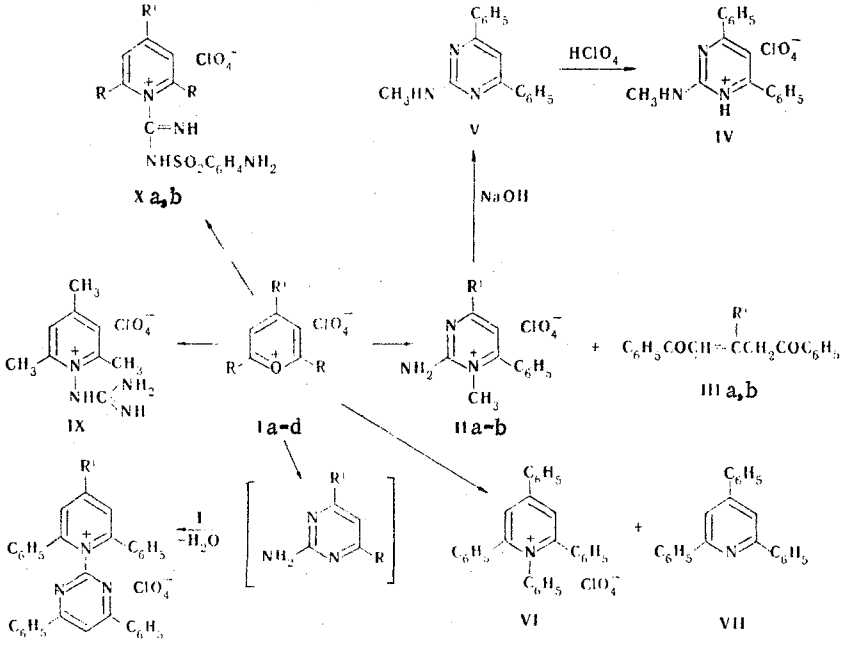
UDC 547.495.9'812.3'853.4

2,4,6-Triphenylpyrylium perchlorate reacts with methylguanidine to give 1-methyl-2-amino-4,6-diphenylpyrimidinium perchlorate, which undergoes the Dimroth rearrangement to give 2-methylamino-4,6-diphenylpyrimidine. 2,4,6-Triarylpyrylium perchlorates react with guanidine to give N-pyrimidinylpyridinium salts. Pyrylium salts react with aminoguanidine, sulfanilylguanidine, and symmetrical diphenylguanidine at one amino group to give the corresponding pyridinium salts.

We have described the reaction of pyrylium salts with 2-aminobenzimidazoles [1], amidines [2], and isothioureas [3], which leads to the synthesis of pyrimidines. In the present research we examined the reactions of the indicated salts with compounds of the guanidine series in order to synthesize pyrimidine derivatives.

1-Methyl-2-amino-4,6-diphenylpyrimidinium perchlorate (IIa) is formed in 43% yield when 2,4,6-triphenylpyrylium perchlorate (Ia) is refluxed with methylguanidine in ethanol. In addition to the principal reaction, the pyrylium ring is opened under the influence of the highly basic methylguanidine, and 1,3,5-triphenyl-2-pentene-1,5-dione (IIIa) is formed in 46% yield. The yield of IIIa may also be higher if the reaction is carried out without heating. One might have expected the formation of the isomeric (with respect to IIa) 2-methylamino-4,6-diphenylpyrimidinium perchlorate (IV) or a mixture of the latter with salt IIa in this transformation. According to the results of chromatography, both salt IIa and the base isolated from it are individual substances. We expected to obtain IV by replacement of



I a $R=R^1=C_6H_5$; b $R=C_6H_5$, $R^1=p$-$CH_3OC_6H_4$; c $R=C_6H_5$, $R^1=p$-$NO_2C_6H_4$; d $R=R^1=CH_3$; II, III a $R^1=C_6H_5$; b $R^1=p$-$CH_3OC_6H_4$; VIII a $R^1=C_6H_5$; b $R^1=p$-$CH_3OC_6H_4$; c $R^1=p$-$NO_2C_6H_4$; X a $R=R^1=C_6H_5$; b $R=R^1=CH_3$

Rostov State University. Scientific-Research Institute of Physical and Organic Chemistry, Rostov-on-Don 344006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 748-752, June, 1980. Original article submitted April 5, 1979; revision submitted November 20, 1979.

 0009-3122/80/1606-0574$07.50

a chlorine atom by a methylamino group in 2-chloro-4,6-diphenylpyrimidine. Unfortunately, this transformation does not take place when the starting compounds are heated in an ampul for 3 h. It is also known that 2-amino-4,6-diphenylpyrimidine is not methylated by methyl iodide [4]. Thus it also does not seem possible to obtain IIa by alternative synthesis.

However, the data from the IR and PMR spectra confirm the IIa structure. Three bands of stretching vibrations of a partially associated primary amino group at 3260, 3350, and 3460 cm^{-1} and a band of deformation vibrations of this amino group at 1665 cm^{-1} are present in the IR spectrum. The PMR spectrum of perchlorate IIa in trifluoroacetic acid contains a singlet at δ 3.45 ppm (protons of the N–CH_3 group) and a multiplet from NH and the aromatic protons at δ 7.1-7.7 ppm. The ratio of the integral intensities of the indicated signals is 3:14. Trifluoroacetic acid evidently protonates IIa. A definite confirmation of the formation of perchlorate IIa in the reaction of salt Ia with methylguanidine is provided by Dimroth rearrangement [5] of this compound with the isolation of 2-methylamino-4,6-diphenylpyrimidine (V), which, in contrast to the unstable 1-methyl-2-iminodihydropyrimidine, can be purified by column chromatography. The broad signal centered at δ 5.5 ppm in the PMR spectrum of V in chloroform corresponds to an amino proton, while the signal of the N–CH_3 group is split into a doublet by the NH proton with J ~ 5 Hz and δ 2.95 ppm. The ratio of the integral intensities of the indicated signals is 1:3. The PMR spectrum of its perchlorate (IV) in trifluoroacetic acid contains a singlet of the protons of the N–CH_3 group with δ 2.9 ppm and a multiplet of NH and the aromatic protons with δ 7.1-7.7 ppm. The ratio of the integral intensities of the indicated signals is 3:14; trifluoroacetic acid evidently also protonates this compound. In addition, we converted perchlorate IIa to the free base and then to the picrate by the rapid successive action of equimolar amounts of alkali and picric acid. The picrate depresses the melting point of the picrate of the 2-methylamino-4,6-diphenylpyrimidinium salt.

Thus, the results constitute evidence that attack on the α position of the pyrylium salt is realized primarily by the methylamino group of methylguanidine, the basicity of which is higher. 2,6-Diphenyl-4-(p-anisyl)pyrylium perchlorate (Ib) behaves similarly in the reaction with methylguanidine and gives the 1-methyl-2-amino-4-(p-anisyl)-6-phenylpyrimidinium salt (IIb) in 69% yield.

A pyrimidine is not formed in the reaction of perchlorate Ia with N,N'-diphenylguanidine. When salt Ia is refluxed in ethanol, it is converted to diketone IIIa; in dimethylformamide (DMF) 1,2,4,6-tetraphenylpyridinium perchlorate (VI) is formed in 25% yield, and 2,4,6-triphenylpyridine (VII) is formed in 50% yield. The existence of two reaction products can be explained by the fact that attack on the α position of the pyrylium salt is realized by both the amino group and the phenylamino group of N,N'-diphenylguanidine.

An N-pyrimidinylpyridinium salt (VIIIa) is formed in 63% yield when salt Ia is refluxed with guanidine in DMF. In addition, guanidine perchlorate is isolated. Some of the starting salt is converted to diketone IIIa. Perchlorate VIIIa can also be obtained in ethanol but only in 12% yield. 2-Amino-4,6-diphenylpyrimidine was not isolated from the reaction mixture; however, traces of it were detected by chromatography in an experiment that was carried out without heating and produced primarily the diketone. The structure of perchlorate VIIIa was proved by IR spectroscopic data and alternative synthesis from 2-amino-4,6-diphenylpyrimidine and salt Ia. Other 2,4,6-triarylpyrylium perchlorates (Ib, c) also react similarly with guanidine. 2,4,6-Trimethylpyrylium perchlorate (Id) does not form pyrimidine derivatives with guanidine.

As in the case of the reaction with simicarbazide [3], pyrylium salt Id reacts with aminoguanidine only at one amino group to give pyridinium salt IX. Perchlorates Ia, d react with sulfanilylguanidine at one amino group of the guanidine fragment; salt Ia reacts only when it is refluxed in DMF. Compounds X contain a primary aromatic amino group (according to a qualitative reaction with an alkali solution of sodium hypochlorite).

Thus, N,N'-diphenylguanidine, aminoguanidine, and sulfaguanidine do not form pyrimidine structures with pyrylium salts. We synthesized the difficult-to-obtain salts of 2-methylamino- (IV) and N-methyl-2-aminopyrimidines (IIa, b) with aromatic substituents in the 4 and 6 positions, as well as N-pyrimidinylpyridinium salts (VIIIa-c), for the first time by recyclization of pyrylium salts.

TABLE 1. Characteristics of the Synthesized Perchlorates

Compound	mp, deg C[a]	IR spectra, cm^{-1}	Found, %			Empirical formula	Calc., %			Yield, %
			C	H	Cl		C	H	Cl	
IIa	222—222,5	1085, 1510, 1570, 1610, 1625, 1660, 3260, 3350, 3460	56,5	4,3	9,4	$C_{17}H_{16}ClN_3O_4$[b]	56,4	4,5	9,8	43
IIb	214—214,5	1110, 1260, 1510, 1570, 1600, 1620, 1650, 3280, 3365, 3450	55,0	4,8	9,2	$C_{18}H_{18}ClN_3O_5$[c]	55,2	4,6	9,1	69
IV	234—235	1100, 1495, 1565, 1610, 1645, 3390	56,1	4,3	9,5	$C_{17}H_{16}ClN_3O_4$	56,4	4,5	9,8	89
VIIIa	300—301	1100, 1510, 1560, 1575, 1590, 1620	73,2	4,6	5,8	$C_{39}H_{28}ClN_3O_4$[d]	73,4	4,4	5,6	63
VIIIb	269—270	1095, 1250, 1510, 1575, 1590, 1630	70,8	5,1	5,5	$C_{41}H_{32}ClN_3O_6$	70,5	4,6	5,1	55
VIIIc	244—246	1100, 1350, 1500, 1530, 1560, 1600, 1630	64,7	4,1	5,0	$C_{39}H_{26}ClN_5O_8$	64,3	3,6	4,9	35
IX	179—180	1100, 1570, 1595, 1650, 3180, 3245, 3360, 3435	38,9	5,5	13,0	$C_9H_{15}ClN_4O_4$	38,9	5,4	12,7	57
Xa	269—271	1075, 1250, 1290, 1560, 1600, 1640, 3200, 3360, 3460	59,4	4,2	—	$C_{30}H_{25}ClN_4O_6S$[e]	59,6	4,2	5,9	89
Xb	233—234	1100, 1285, 1305, 1555, 1600, 1655, 3170, 3430, 3470	43,5	4,8	—	$C_{15}H_{19}ClN_4O_6S$[f]	43,0	4,6	8,5	97

[a]The compounds were recrystallized: IIa, b, IV, and VIIIa, c from acetic acid, VIIIb from methanol—acetonitrile, IX from acetone, Xa from ethanol—acetonitrile, and Xb from water. [b]Found %: N 11.4. Calculated %: N 11.6. [c]Found %: N 10.7. Calculated %: N 10.7. [d]Found %: N 6.7. Calculated %: N 6.6. [e]Found %: S 4.8%. Calculated %: S 5.3. [f]Found %: S 7.3. Calculated %: S 7.7.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were obtained with a BS-487C spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard. The individuality of the compounds was monitored by thin-layer chromatography (TLC) on Al_2O_3 or Silufol UV-254 plates (elution with chloroform). The characteristics of all of the perchlorates obtained are presented in Table 1.

1-Methyl-2-amino-4,6-diphenylpyrimidinium Perchlorate (IIa). A solution of 0.68 g (4.8 mmole) of methylguanidine nitrate in absolute ethanol was mixed with a solution of sodium ethoxide, prepared from 0.11 g (4.8 mg-atom) of sodium, after which 1.64 g (4 mmole) of perchlorate Ia was added, and the mixture was refluxed for 2 h. It was then filtered, and the filtrate was evaporated without cooling to 5-8 ml. The concentrate was cooled, and 0.62 g (43%) of perchlorate IIa was removed by filtration. The filtrate was diluted with ether, and the ether solution was separated and washed with water. The solvent was evaporated, and the residue was recrystallized from ethanol or heptane to give 0.30 g (46%) of diketone IIIa with mp 116-118°C [6].

1-Methyl-2-amino-4-(p-anisyl)-6-phenylpyrimidinium perchlorate (IIb) was similarly obtained.

1-Methyl-2-amino-4,6-diphenylpyrimidinium Picrate. A mixture of 0.36 g (1 mmole) of perchlorate IIa, 10 ml of aqueous NaOH solution (an equimolar amount), and 15 ml of ether was stirred at 20°C until the solid dissolved completely. The ether layer was separated, washed with water, and mixed with an ether solution of picric acid. The precipitate was removed by filtration to give the picrate with mp 224-225°C (from acetic acid). Found %: C 56.4; H 3.6; N 17.1. $C_{23}H_{18}N_6O_7$. Calculated %: C 56.3; H 3.7; N 17.1.

1-Methyl-2-amino-4-(p-anisyl)-6-phenylpyrimidinium picrate was similarly obtained and had mp 190-191°C (from acetic acid). Found %: C 55.6; H 3.6; N 16.0. $C_{24}H_{20}N_6O_8$. Calculated %: C 55.4; H 3.9; N 16.1.

2-Methylamino-4,6-diphenylpyrimidine (V). A suspension of 0.72 g (2.0 mmole) of perchlorate IIa in 30 ml of 1 N NaOH solution was stirred on a boiling-water bath for 30 min, after which it was cooled, and treated with acetic acid until the aqueous layer had pH 5-6. The product was extracted with ether, and the ether solution was placed in a column filled with aluminum oxide and eluted with chloroform. The first fraction was collected and worked up to give 0.18 g (35%) of a colorless crystalline pyrimidine V with mp 106-107°C (from heptane). Found %: C 78.3; H 5.9. $C_{17}H_{15}N_3$. Calculated %: C 78.1; H 5.8. IR spectra, cm^{-1}: 3375, 1590, 1550, 1500, 1350.

2-Methylamino-4,6-diphenylpyrimidinium Perchlorate (IV). An equimolar amount of 70% $HClO_4$ was added to a solution of pyrimidine V in acetic acid, and ether was added to precipitate salt IV (89%) with mp 234-235°C (from acetic acid).

2-Methylamino-4,6-diphenylpyrimidinium Picrate. This compound was obtained by mixing ether solutions of pyrimidine V and picric acid and had mp 234-235°C (from acetic acid).

2-Methylamino-4,6-diphenylpyrimidinium Picrate. This compound was obtained by mixing ether solutions of pyrimidine V and picric acid and had mp 234-235°C (from acetic acid). This product depressed the melting point of 1-methyl-2-amino-4,6-diphenylpyrimidinium picrate (the mixture had mp 205°C). Found %: C 56.6; H 3.9; N 17.3. $C_{23}H_{18}N_6O_7$. Calculated %: C 56.4; H 3.7; N 17.1.

Reaction of Perchlorate Ia with N,N'-Diphenylguanidine. A mixture of 0.82 g (2 mmole) of perchlorate Ia, 0.50 g (2.4 mmole) of N,N'-diphenylguanidine, and 4 ml of DMF was refluxed for 30 min, after which it was cooled and treated with ether. The mixture was stirred thoroughly, the ether layer was separated, and 1-2 ml of acetic acid was added to the residue. The precipitate was removed by filtration to give 0.23 g (25%) of perchlorate VI with mp 262-264°C (from acetic acid) (mp 265-266°C [7]). The ether solution was washed with water, the solvent was evaporated, and the residue was recrystallized from heptane to give 0.18 g (52%) of pyridine VII with mp 136-137°C.

1-(4,6-Diphenyl-2-pyrimidinyl)-2,4,6-triphenylpyridinium Perchlorate (VIIIa). A) A mixture of perchlorate Ia, guanidine hydrochloride, and fused potassium acetate in a ratio of 1:1.2:1.2 was refluxed in DMF for 20 min, after which the KCl was removed by filtration. The filtrate was treated with ether to precipitate a colorless product, which was washed with ethanol to remove guanidine perchlorate and give perchlorate VIIIa in 63% yield. The ether solution was washed with water, the ether was removed by distillation, and the residue was recrystallized from ethanol to give 0.2 g (30%) of diketone IIIa.

B) A mixture of perchlorate Ia and 2-amino-4,6-diphenylpyrimidine, obtained by the method in [8], in a ratio of 1:1.2 was refluxed in DMF for 45 min, after which it was cooled, and the liberated oil, which crystallized, was identified as perchlorate VIIIa (94%).

1-[4-Phenyl-6-(p-anisyl)-2-pyrimidinyl]-2,6-diphenyl-4-(p-anisyl)-pyridinium (VIIIb) and 1-[4-Phenyl-6-(p-nitrophenyl)-2-pyrimidinyl]-2,6-diphenyl-4-(p-nitrophenyl)pyridinium Perchlorate (VIIIc). These compounds were similarly obtained.

1-Guanidino-2,4,6-trimethylpyridinium Perchlorate (IX). This compound was obtained by the method presented for perchlorate IIa by refluxing the starting components for 1 h in methanol. Salt IX was precipitated by means of ether.

1-Sulfanilamidino-2,4,6-triphenylpyridinium Perchlorate (Xa). A mixture of perchlorate Ia and sulfanilylguanidine in a molar ratio of 1:1.2 was refluxed in DMF for 30 min, after which perchlorate Xa was precipitated by the addition of ether.

1-Sulfanilamidino-2,4,6-trimethylpyridinium Perchlorate (Xb). This compound was similarly obtained by refluxing the starting compounds in ethanol for 1 h.

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ACTION OF ACIDIC AND ALKALINE AGENTS ON DIOXONAPHTHOFURAN DERIVATIVES

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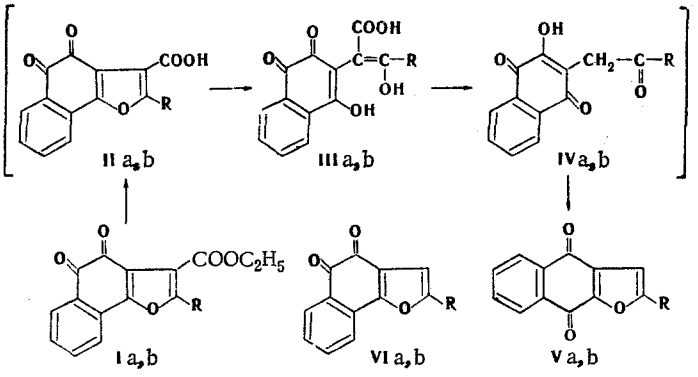
UDC 547.728.2:542.938

The action of sulfuric and polyphosphoric acids and sodium hydroxide on 3-carbethoxy-4,5-dioxonaphthofuran derivatives was studied. 2-Methyl- and 2-phenyl-3-carboxy-4,5-dioxonaphthofurans were obtained by the action of sulfuric acid on the indicated compounds. The action of alkali on 2-methyl- and 2-phenyl-3-carbethoxy-4,5-dioxonaphthofurans and 2-phenyl-4,9-dioxonaphthofurans leads to the formation of 2-hydroxy-3-acetonyl- and 2-hydroxy-3-phenacyl-1,4-dioxonaphthalenes.

In connection with the interest in diverse quinones as potential antiviral agents [1] we studied the transformations of quinones in the naphthofuran series. During an attempt to decarbethoxylate 3-carbethoxy-4,5-dioxonaphthofurans Ia, b via the method described for derivatives of other classes [2] we observed only hydrolysis of the ester group and the formation of the corresponding acids.

In an attempt to carry out decarbethoxylation by the action of polyphosphoric acid (PPA) on Ia, b, instead of the expected 2-methyl- and 2-phenyl-4,5-dioxonaphthofurans, we obtained the previously described [3] 4,9-dioxonaphthofuran derivatives Va, b. The reaction evidently proceeds through a step involving the formation of IIa, b. The formation of 4,9-dioxonaphthofurans Va, b can be explained by opening of the furan ring in IIa, b by decarboxylation of the resulting carboxylic acids IIIa, b and cyclization of the resulting intermediate hydroxynaphthoquinone derivatives IVa, b. We obtained hydroxynaphthoquinones IVa, b [3] by the action of alkali on 4,5-dioxonaphthofuran derivatives Ia, b. 4,9-Dioxonaphthofurans Va, b were isolated by the action of PPA on IVa, b at 170°C. When this reaction is carried out at 60°C, 4,5-dioxonaphthofuran derivatives VIb are formed along with Va, b.



I-V a $R=CH_3$; I-VI b $R=C_6H_5$

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 753-754, June, 1980. Original article submitted January 4, 1980.

 0009-3122/80/1606-0578$07.50